Development of Metal-Catalyzed Decarboxylative Cross-Coupling Reactions

by

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ABSTRACT

Carboxylic acids are a ubiquitous class of molecules in the field of organic chemistry and represent versatile building blocks in synthetic chemistry. Methods that enable the formation of new carbon–carbon or carbon–heteroatom bonds from carboxylic acids via the extrusion of carbon dioxide can present complementary reactivity and chemoselectivity to alternative cross-coupling reactions that use preformed organometallics reagents. While most carboxylic acids are typically considered stable, several strategies have been developed to promote decarboxylation and subsequent functionalization. This thesis describes the development of new methods for the decarboxylative functionalization of aliphatic carboxylic acids, using Cu, Ir, and Pd-catalysis.

PREFACE

The research conducted for this thesis was performed in collaboration with Prof. Rylan Lundgren.

The Cu-promoted oxidative coupling of malonate derivatives described in Chapter 2.1 was published as Patrick J. Moon, Heather M. Halperin, Rylan J. Lundgren *Angew. Chem. Int. Ed*. **2016**, *55*, 1984. Reaction optimization and scope studies are my original work. Heather Halperin assisted with substrate synthesis and scope studies. Nathan Paisley conducted preliminary reaction development work.

The Cu-catalyzed decarboxylative arylation of malonate half-esters described in Chapter 2.3 was published as Patrick J. Moon, Shengkang Yin, Rylan J. Lundgren *J. Am. Chem. Soc.* **2016**, *138*, 13826. Reaction discovery, optimization and scope studies are my original work. Scope studies with heteroaryl boron reagents were conducted by Shengkang Yin.

The Cu-catalyzed decarboxylative arylation of aryl acetate salts with aryl boron reagents described in Chapter 3 was published as Patrick J. Moon, Anis Fahandej-Sadi, Wenyu Qian, Rylan J. Lundgren *Angew. Chem. Int. Ed.* **2018**, *57*, 4612. Reaction discovery, optimization and scope studies are my original work. Anis Fahandej-Sadi and Wenyu Qian assisted with scope studies.

The Pd-catalyzed decarboxylative arylation of aryl acetate salts with aryl halides described in Chapter 4 was published as Duanyang Kong, Patrick J. Moon, Wenyu Qian, Rylan J. Lundgren *Chem. Commun.* **2018**, *54*, 6835. Reaction discovery, preliminary

optimization and mechanistic studies are my original work. Duanyang Kong conducted additional optimization and scope studies. Wenyu Qian assisted with scope studies.

The enantioselective decarboxylative benzylation of allylic electrophiles using aryl acetic acids described in Chapter 5 was published as Patrick J. Moon, Zhongyu Wei, Rylan J. Lundgren *J. Am. Chem. Soc.* **2018**, *42* 13826. Reaction discovery, mechanistic studies and scope studies and the synthesis of the core structures of Taranabant and Elacestrant are my original work. Zhongyu Wei conducted optimization and scope studies.

The Cu-catalyzed decarboxylative amination of aryl acetic acids described in Chapter 6 has been deposited to ChemRxiv (DOI: 10.26434/chemrxiv.8279432.v1). Mechanistic studies are my original work. Reaction discovery, optimization and scope studies were conducted by Duanyang Kong. Product functionalization studies were conducted by Odey Bsharat. The results pertaining to the direct $^{13}CO_2$ exchange reaction of carboxylic acids derivatives are subject to a manuscript in preparation.

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Finalement, j'aimerais remercier ma famille; votre support a été inébranlable non seulement au cours des cinq dernières années, mais tout au long de mes études.

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Å	Ångström
acac	acetylacetone
aq.	aqueous
°C	degrees Celsius
Ar	generic aryl moiety
Ac	Acetyl
Atm	atmosphere
Bn	benzyl
BINAP	(1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine)
Bu	Butyl
B(neop)	neopentyl glycol boronic ester
Boc	*tert*-butyloxycarbonyl
BOX	bisoxazoline
B(pin)	pinacol boronic ester
bpy	2,2’-bipyridine
cat.	catalytic stoichiometry
CEL	Chan-Evans-Lam
CFL	compact fluorescent lamp
cin	cinnamyl
COD	cyclooctadiene
Cy	cyclohexyl
δ	chemical shift
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
dba	dibenzylideneacetone
dtbbpy	4,4′-Di-tert-butyl-2,2′-dipyridyl
D^{i}PPF	1,1'-Bis(di-isopropylphosphino)ferrocene
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
DCM	dichloromethane
DMS	dimethyl sulfide

DMA	*N*,*N*-dimethylacetamide
DMF	*N*,*N*-dimethylformamide
DMAP	dimethylaminopyridine
DMSO	dimethylsulfoxide
dme	1,2-dimethoxyethane
EDCl	*N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
equiv.	equivalents
EPR	electron paramagnetic resonance
Et	ethyl
FC	Friedel-Crafts
GH-II	Grubbs-Hoveyda catalyst, second generation
Hex	hexane (mixture of isomers)
hv	light
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
HRMS	high resolution mass-spectrometry
*i*Pr	iso-propyl
IPr	1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene
L	generic ligand
LG	generic leaving group
[M]	generic metal complex
Me	methyl
MeCN	acetonitrile
Ms	methylsulfonyl
MTBE	Methyl tert-butyl ether
NEt_3	triethylamine
NFSi	*N*-fluorobenzenesulfonamide
NMR	nuclear magnetic resonance
NMP	*N*-methylpyrrolidine
OAc	acetate
OTf	triflate
PEPPSI	pyridine-enhanced precatalyst preparation stabilization and initiation

Ph	phenyl
Phen	phenanthroline
Piv	pivalate
ppy	2-phenylpyridyl
rac	racemic
R	generic group
rt	room temperature
S_NAr	bimolecular nucleophilic aromatic substitution
*t*Bu	*tert*-butyl
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TFA	trifluoroacetate
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
TBHP	tert-butyl hydroperoxide
TMS	trimethylsilyl
Tol	tolyl
Ts	4-toluenesulfonyl
UV	ultraviolet
X^-	generic anion
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

CHAPTER 1 – Introduction

1.1 General Introduction

Catalysis is fundamental to the development of modern sustainable chemical processes. The controlled cross-coupling of complex molecular fragments via selective metal-catalyzed carbon-carbon or carbon-heteroatom bond-formation is of paramount importance, with direct application in the preparation of novel pharmaceuticals, fine chemicals and modern materials.[1] In the context of pharmaceutical drug discovery for example, metal-catalyzed cross-coupling is the leading method to form C–C bonds.[2] While tremendous progress has been achieved in the field, the development of new selective catalytic processes stands to complement established reactions and directly impact the practice of chemical synthesis.

A traditional metal-catalyzed cross-coupling reaction involves C–C bond-formation from an electrophilic partner and a nucleophilic partner. The electrophilic partner is typically an organic (pseudo)halide while the nucleophilic partner is an organometallic reagent such as organo boron, tin, magnesium, zinc, silicon, etc. Despite Pd-catalysis historically dominating the field,[3] a number of other metals can be used with particular emphasis in recent years on the development of base-metal-catalyzed processes.[4-6] Ancillary ligands are typically employed to modulate catalyst activity and selectivity by binding to the metal center.[7] A general Pd-catalyzed catalytic cycle between an electrophilic aryl halide and a nucleophilic organometallic reagent is outlined in **Fig. 1-1**. Oxidative addition of an aryl halide at Pd^0, subsequent transmetalation of an organometallic reagent, and product-forming reductive elimination constitute three

fundamental steps in most transition-metal catalyzed cross-coupling reactions. An inherent limitation with this classical cross-coupling approach is that electrophilic functional groups (for example other aryl/alkyl halides present on the molecule) will typically be reactive under these conditions.

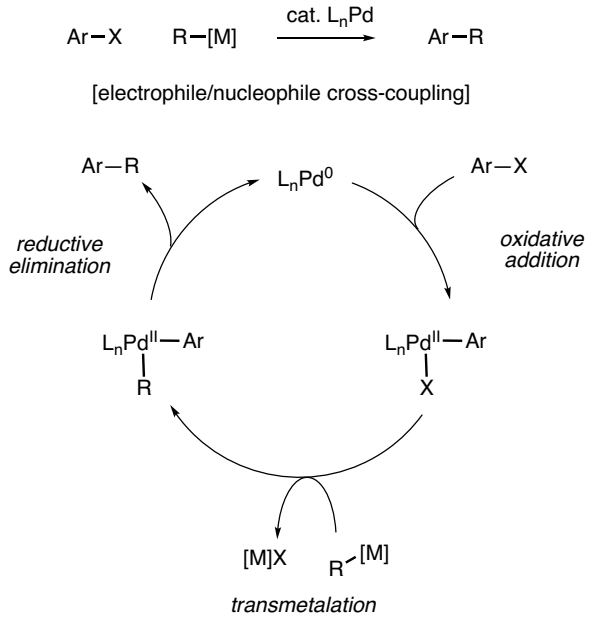


Fig. 1-1 Traditional Pd-catalyzed cross-coupling cycle

An alternative to traditional electrophile/nucleophile cross-couplings is the oxidative coupling of two nucleophilic partners.[8-9] A general example using Pd-catalysis is outlined in **Fig. 1-2**. Sequential transmetalation steps to a Pd^{II} catalyst, followed by reductive elimination will generate coupling product and a reduced Pd^{0} catalyst. Oxidation of Pd^{0} to Pd^{II} by an external oxidant closes the cycle. A number of alternative metals can also be used.[8-9] In this reaction manifold, the main challenge is to promote selective cross-coupling of the two different nucleophilic partners over non-productive homocoupling. As these reactions are conducted under oxidative conditions, non-

productive substrate or product overoxidation can also be challenging. Despite these obstacles, the judicious choice of catalyst and oxidant can lead to productive reactions that often tolerate electrophilic groups, thus complementing traditional electrophile/nucleophile cross-coupling.

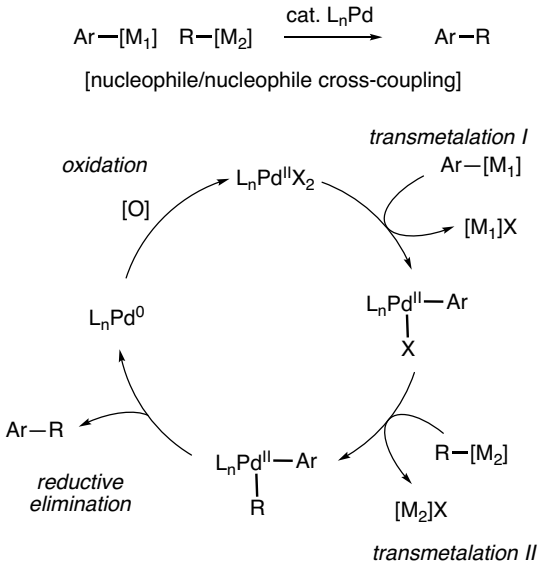


Fig. 1-2 General oxidative cross-coupling cycle

In recent years, significant effort has been dedicated to the development of decarboxylative cross-coupling reactions, wherein a new carbon-element bond is formed with concomitant extrusion of CO_2.[10] Depending on the conditions and catalyst system used, carboxylic acids can serve as organometallic or radical precursors, making them highly versatile building blocks as they can tap into a plethora of established cross-coupling manifolds.[11-12] From a practical standpoint, carboxylic acids are found in a number of bench-stable and commercially available molecules, which make them highly desirable cross-coupling partners. In comparison, many organometallic reagents are not commercially available and require additional preparative steps. Finally, contrasting

conventional cross-couplings that generate stoichiometric waste using preformed organometallic reagents (B, Si, Sn, Mg, Zn, etc.), decarboxylative couplings of carboxylic acids generate benign carbon dioxide as the sole by-product.

In the context of this introductory chapter and of this thesis as a whole, reactions will be broadly classified by the mechanism in which they operate. First, the carboxylic acid can undergo initial decarboxylation, either via an ionic or radical pathway, followed by metal-catalyzed bond-formation (**Fig 1-3, path A**). Alternatively, the carboxylic acid can act as an activating or directing group that first enables the formation of a new bond, followed by protodecarboxylation to form product (**Fig. 1-3, Path B**).

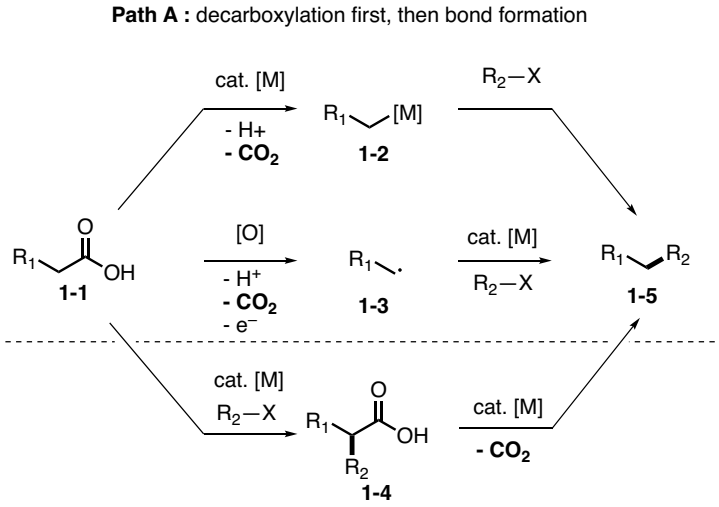


Fig. 1-3 Potential decarboxylative cross-coupling pathways

1.2 Decarboxylative Cross-Coupling Reactions Triggered by an Initial Decarboxylation Step

1.2.1 Enzymatic and Organocatalytic Decarboxylative Addition Reactions

The generation and trapping of enolates is a fundamental process in organic chemistry. Conventional approaches involve the stoichiometric generation of an enolate using a strong base under cryogenic conditions, followed by trapping with an appropriate electrophile.[13] Nature uses a different approach to access these reactive intermediates, as is the case for polyketide and fatty acid biosynthesis.[14-15] Polyketide synthases promote the decarboxylation of malonyl-CoA (**1-5**) and transiently stabilize a thioester enolate intermediate (**1-6**) which can undergo subsequent Claisen condensation with an acylated cysteine residue **1-7** (**Fig. 1-4**). These reactions proceed under physiological conditions (near neutral pH) in the presence of a variety of protic functionality, which is remarkable considering the generation of a highly basic enolate intermediate.

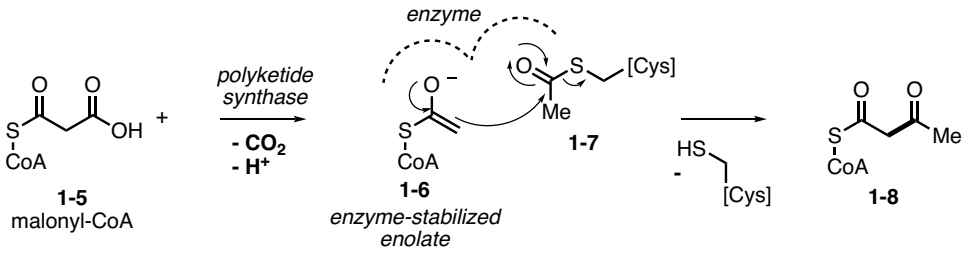


Fig. 1-4 Enzymatic process for Claisen condensation of malonate half-thioesters

Based on Nature's approach for decarboxylative enolate generation and trapping, a number of biomimetic processes have been developed via organocatalysis. For example, the group of Wennemers reported the enantioselective decarboxylative addition

of malonate half-thioesters (**1-9**) to nitroolefins (**1-10**) using a urea-functionalized cinchona alkaloid organocatalyst **1-12** (**Fig. 1-5**).[16] A bifunctional mode of activation is likely operational in this reaction as simple urea catalysts do not promote the desired coupling. The urea motif is suggested to activate the carbonyl oxygen of malonate half-thioester, while the tertiary ammonium engages the nitroolefin in hydrogen bonding. Moderate to good yields and enantioselectivities are obtained across a range of products, including addition products with protic functionality such as **1-14**.

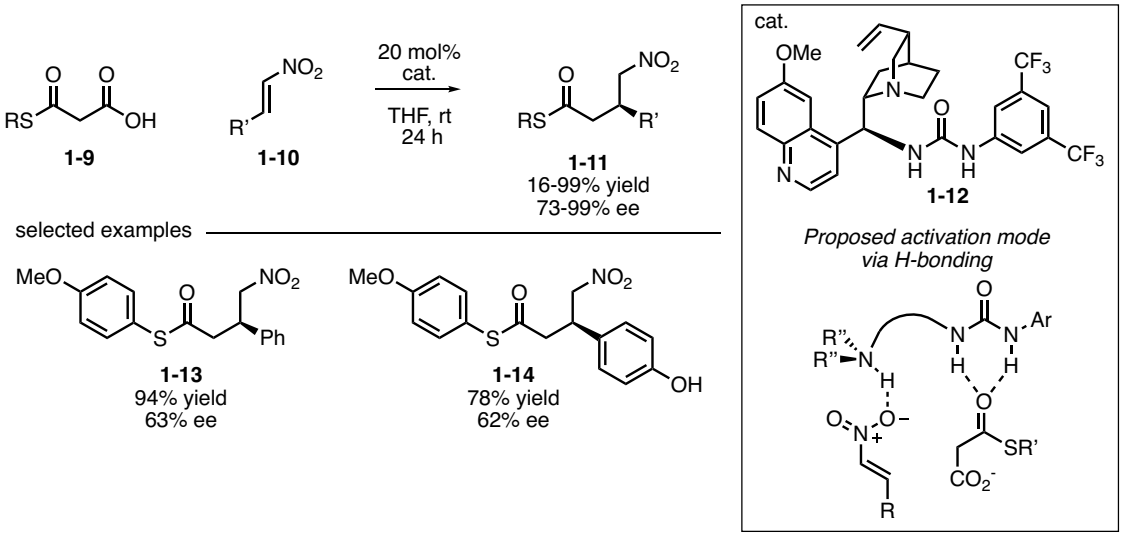


Fig. 1-5 Organocatalytic decarboxylative Michael addition to nitroolefins

In addition to Michael acceptors such as nitroolefins, a number of carbonyl electrophiles such as aldehydes, ketones and imines have also been reported as competent electrophiles using this strategy.[17] While this biomimetic strategy has been extensively explored, it is not clear in all cases whether decarboxylation proceeds as the first step to form a reactive enolate, or whether C−C coupling occurs first, followed by protodecarboxylation.[18] Section 1.3.1 will discuss decarboxylative aldol reactions of

malonate half-ester derivatives wherein C–C bond formation occurs first, followed by protodecarboxylation.

1.2.2 Metal-Catalyzed Coupling of C(sp^2) Carboxylic Acid Derivatives

The use of benzoic acids as surrogates to aryl organometallic reagents in transition metal-catalyzed cross-coupling reactions is highly attractive since a number of stable benzoic acid precursors are commercially available. However, their high stability typically necessitates forcing conditions to promote decarboxylative carbometalation. Once generated, the transiently formed organometallic intermediate (**1-16**) must be selectively intercepted to form product and avoid non-productive quenching (**Fig. 1-6**). Considering this challenge, it is not surprising that reports of metal-catalyzed protodecarboxylation of benzoic acids predate related cross-coupling processes.[19-20] Controlling and matching the rates of decarboxylation and subsequent cross-coupling steps are crucial to achieving a productive reaction.

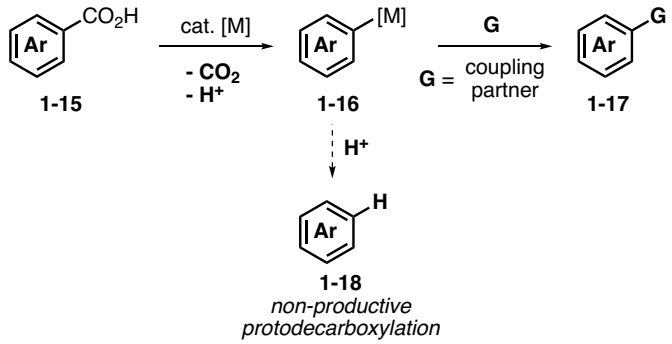


Fig. 1-6 Decarboxylative cross-coupling and non-productive protodecarboxylation of benzoic acid

While early work by Nilsson showed that stoichiometric Cu could promote the decarboxylative coupling of benzoic acids with excess aryl-iodides[21], it was not until the development of systems with Pd that more efficient catalytic processes were developed. In a seminal paper, Myers and coworkers reported a decarboxylative oxidative Heck reaction that was proposed to proceed via Pd-mediated decarboxylative metalation of benzoic acids, followed standard Heck-type mechanism: migratory insertion with an olefin, β-H elimination and reduction of a Pd–H to Pd^0 (**Fig. 1-7**).[22] Ag_2CO_3 is proposed to act both as a base and as the terminal oxidant to regenerate Pd^{II}. It is likely that Ag^I also promotes decarboxylation under these conditions since Ag salts are common additives in related protodecarboxylation or decarboxylative coupling reactions.[19-20]

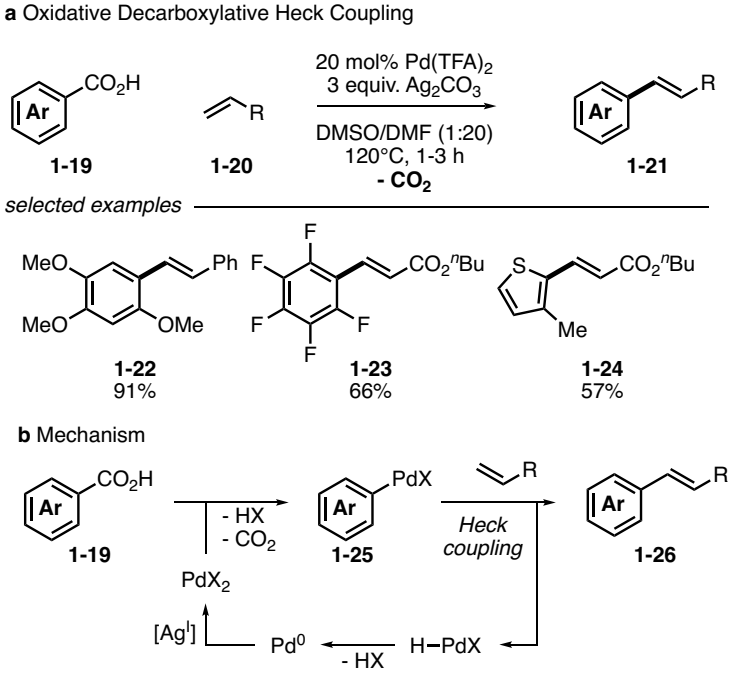


Fig. 1-7 Pd-catalyzed decarboxylative Heck coupling using benzoic acids

In another pioneering example, Goossen and coworkers described the decarboxylative coupling of benzoic acids and aryl halides using a bimetallic Pd/Cu catalyst system (**Fig. 1-8**).[23] A Cu-mediated decarboxylation is proposed to occur to form an aryl–Cu intermediate (**1-37**), which transmetallates to Pd^{II}–Aryl **1-33**, followed by reductive elimination to form biaryl product **1-29**. While this process is largely limited to electron-deficient 2-nitro-substituted benzoic acids, this study provided groundwork for a number of related metal-catalyzed decarboxylative coupling processes using $C(sp^2)$-carboxylic acids as precursors.[19-20, 24]

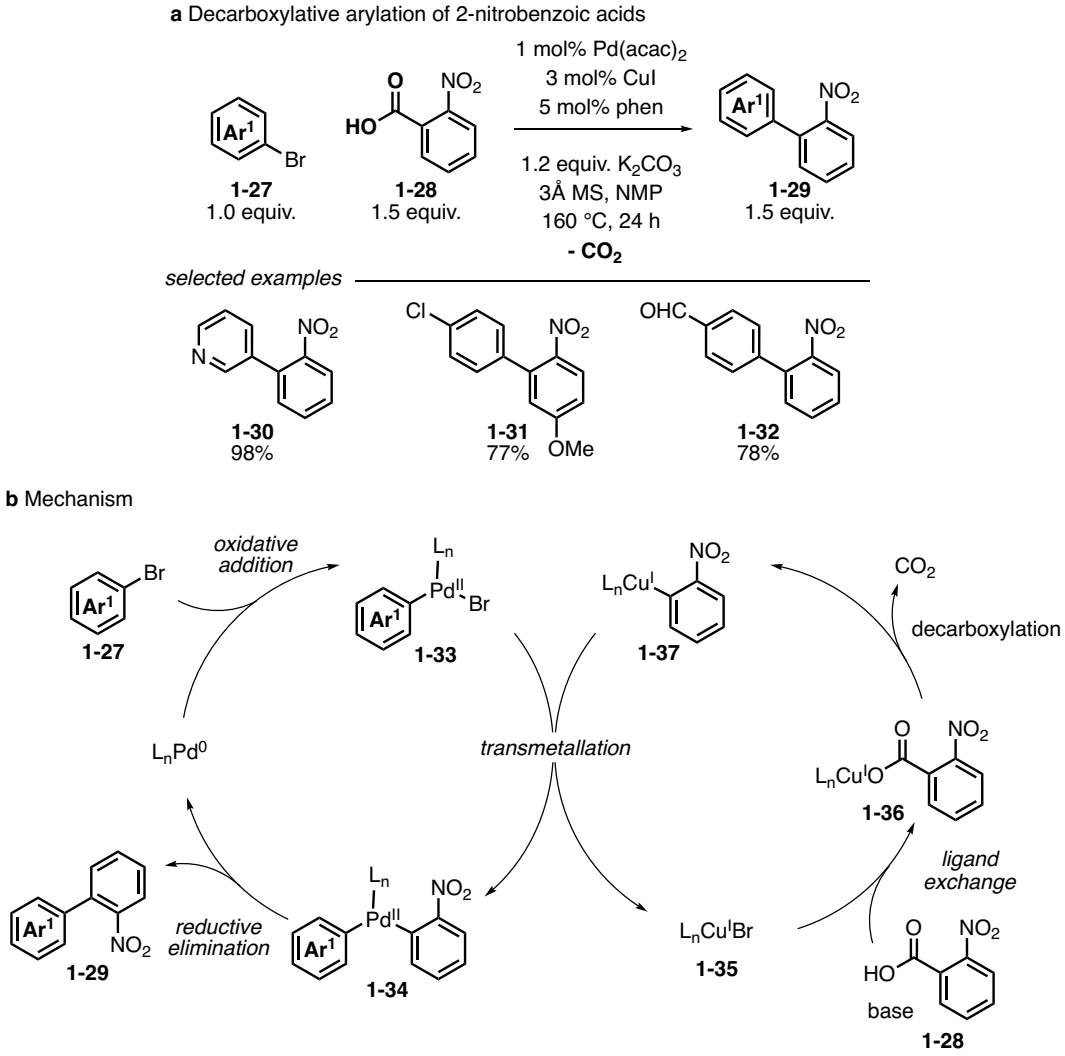


Fig. 1-8 Pd-catalyzed decarboxylative arylation of benzoic acids

1.2.3 Metal-Catalyzed Coupling of C(sp^3) Carboxylic Acids

Aliphatic carboxylic acids have also been reported to undergo decarboxylative coupling reactions via ionic decarboxylation pathways. Electronic activation (by way of an adjacent electron-withdrawing group) is required in order to enable the initial decarboxylation step. A number of intramolecular decarboxylative benzylations or allylations reactions have been developed by the groups of Tunge,[25] Stoltz,[26] Trost,[27] and others[12] whereby oxidative addition into an allylic or benzylic fragment and subsequent

decarboxylation directly leads to an organometallic species which can readily reductively eliminate to form product. For example, Tunge and coworkers reported the decarboxylative allylation of electron-deficient allylic nitroaryl acetates (**Fig. 1-9**).[25] Decarboxylation is proposed to occur at high temperatures via a Pd-carboxylate intermediate.

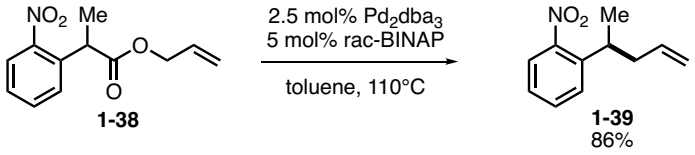


Fig. 1-9 Tunge's decarboxylative intramolecular allylation of allylic nitroaryl acetates

Contrasting intramolecular decarboxylative couplings of preformed benzylic or allylic esters, Liu and coworkers reported the intermolecular decarboxylative cross-coupling of potassium heteroaryl acetate salts with aryl (pseudo)halides to form diarylmethane products (**Fig. 1-10**).[28] Extension of this work to electron-deficient nitroaryl acetate salts was also accomplished.[29] Both processes require high temperatures (>100°C), presumably due to a difficult decarboxylation step. In the case of 2-pyridyl substrates, theoretical calculations suggested that coordination of the pyridine nitrogen to Pd^{II} lowers the barrier for ionic decarboxylation, leading to a Pd-benzyl species. In the case of nitroaryl acetates, which lack a basic nitrogen, decarboxylation is proposed to proceed from a Pd-carboxylate intermediate. Decarboxylation is the first step in this reaction since α,α-disubstituted nitroaryl acetates (which lack α-C–H bonds) are efficiently arylated (**1-48**, **Fig. 1-10**). This strategy was further extended by the group of Zhu to achieve decarboxylative vinylation using vinyl triflates, though the aryl acetate

scope remained restricted to electron-deficient nitroaryl acetates.[30] Related strategies have also been reported for the decarboxylative arylation of activated carboxylate salts derived from cyanoacetic acid[31] or malonate half-esters.[32]

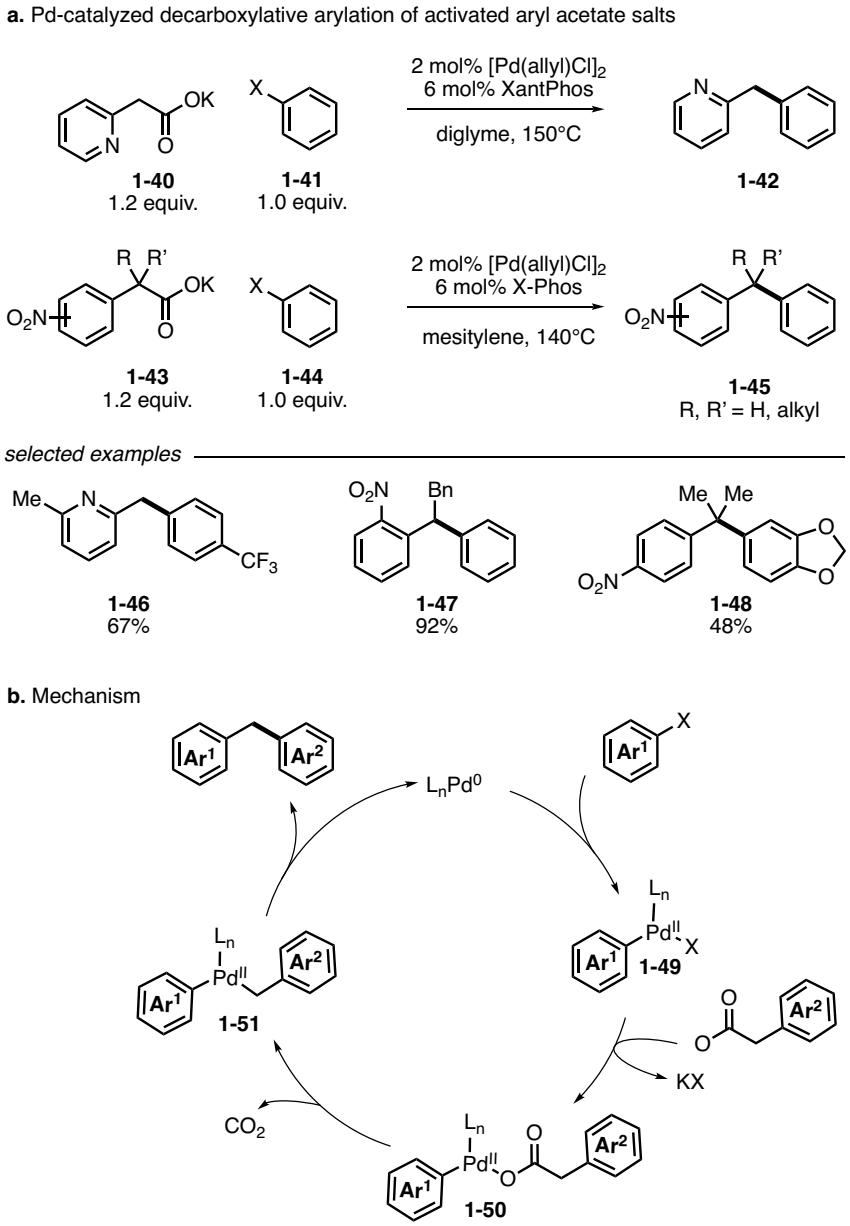


Fig. 1-10 Pd-catalyzed decarboxylative arylation of activated aryl acetate salts

1.2.4 Metal-catalyzed Oxidative Coupling of Aliphatic Carboxylic Acids via Oxidative Decarboxylation

Another mode of activation for the decarboxylation of carboxylic acids is by an oxidative pathway. Single electron oxidation of an aliphatic carboxylate (**1-52**) forms a carboxyl radical (**1-53**) which readily decarboxylates to form carbon centered radical **1-54** (**Fig. 1-11**). This radical can undergo a number of different processes, including trapping by a radical acceptor or interception by an appropriate transition metal catalyst and coupling partner, to achieve net decarboxylative cross-coupling. One of the oldest C–C bond forming reactions is the electrochemical oxidative decarboxylative dimerization of carboxylic acids, the Kolbe electrolysis.[33] This section will focus on key cross-coupling strategies that employ transition metal catalysts to intercept carbon-centered radicals formed from aliphatic carboxylic acids.

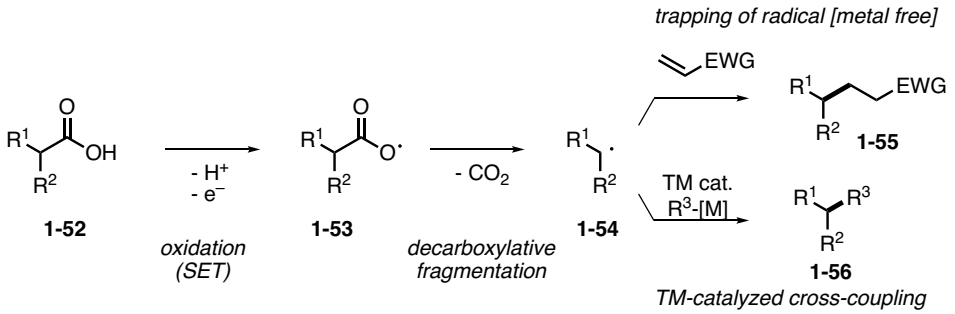


Fig. 1-11 Oxidative decarboxylation and trapping of radical intermediates

In 2014, the groups of Doyle and MacMillan reported the decarboxylative arylation of α-heteroatom substituted secondary carboxylic acids with aryl halides via the merger of Ni and photoredox catalysis (**Fig. 1-12**).[34] Single-electron oxidation and decarboxylation of the native carboxylic acid by a photoexcited Ir^{III} catalyst (**1-64**) would

generate a carbon-centered radical **1-67** and reduced Ir^{II} species **1-65**. The Ni^0 catalyst could undergo oxidative addition with an aryl iodide or bromide to form a Ni^{II}–aryl species **1-69**, which could intercept the previously generated carbon-centered radical **1-67** and undergo reductive elimination from Ni^{III} intermediate **1-70** to form product **1-72**. Reduction of Ni^I to Ni^0 by the reduced Ir^{II}-species would close both catalytic cycles.

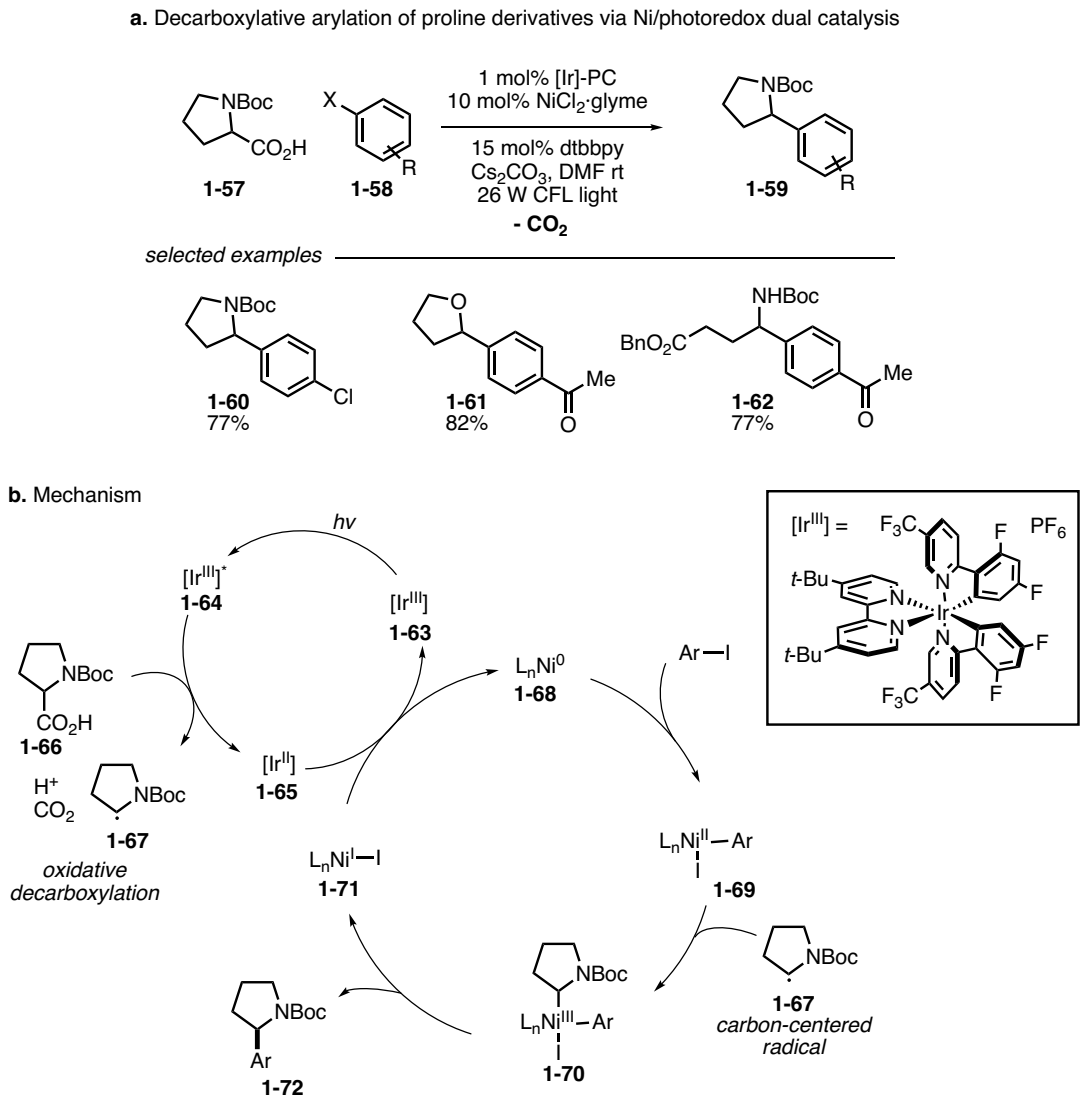


Fig. 1-12 Decarboxylative arylation of α-heteroatom substituted carboxylic acids via Ni and photoredox catalysis

A related approach that has seen tremendous attention in the past few years is the use of 'redox-active' NHPI-esters (N-hydroxyphthalimide) as radical precursors for various cross-couplings. Prior to their recent resurgence in the field of metal-catalyzed cross-coupling, these esters and related derivatives were known to generate radical species via photosensitization.[35-36] Baran and coworkers first reported the use of NHPI-esters (N-hydroxyphthalimide) as suitable partners for the decarboxylative arylation with arylzinc reagents via Ni-catalysis (**Fig. 1-13**).[37-38] Standard peptide coupling reagents such as DCC (dicyclohexylcarbodiimide) are used to first activate aliphatic acids, which inherently lowers overall step-economy despite being simple protocols. Contrasting established photomediated decarboxylative fragmentations of these activated esters, this reaction proceeds without light suggesting an alternative mechanism. The authors propose transmetalation of an arylzinc to Ni^{I}–Cl **1-83** to form a Ni–aryl **1-79** which can reduce by one electron the NHPI-ester to form a Ni^{II}-aryl species **1-82** and an NHPI-ester radical anion **1-80**. Fragmentation of this radical anion releases CO_2, a phthalimide anion, and the corresponding secondary alkyl radical **1-81**. This radical is intercepted by the Ni^{II}–aryl species **1-82** to form Ni^{III} species **1-83**, which reductively eliminates to form product **1-85**. Enantiopure redox-active esters provided racemic arylated product, while cyclopropyl functionalized substrates provided the ring-opened arylated product. These control experiments are consistent with the intermediacy of a carbon-centered radical. This strategy has since been extended to enable a number of other decarboxylative bond forming reactions including arylation, alkenylation, alkynylation, borylation, and amination.[39-40]

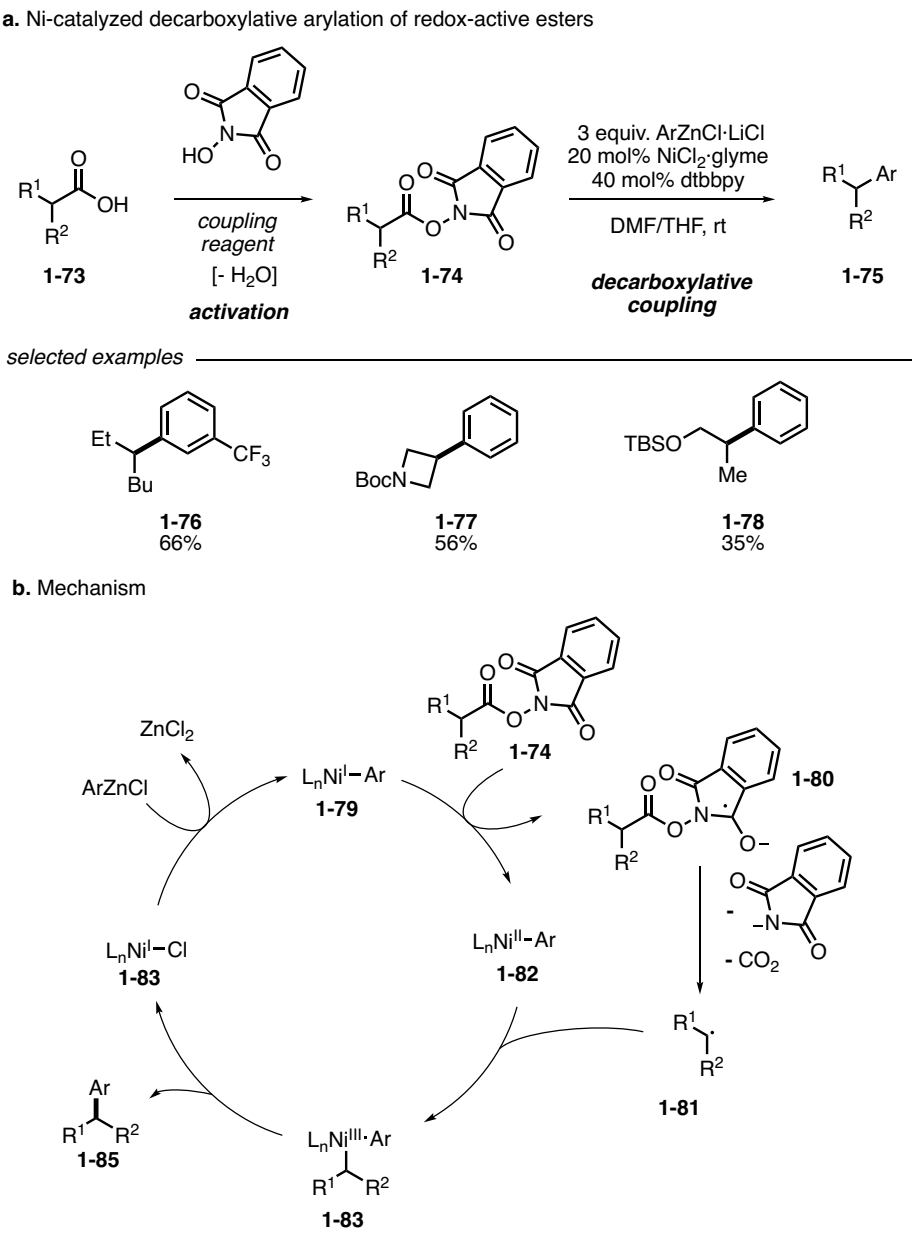


Fig. 1-13 Ni-catalyzed decarboxylative coupling of redox-active NHPI esters with aryl-zinc reagents

1.3 Decarboxylative Cross-Coupling via Post-Coupling Decarboxylation

Decarboxylative cross-coupling reactions can also proceed via an initial bond-forming event, followed by protodecarboxylation. In this case, the carboxylic acid can either activate α-C–H bonds by increasing its acidity, or direct reactivity at a different site of the molecule via coordination to a metal catalyst. In both cases, the free carboxylic acid must not interfere with the bond-forming step in order to have a productive reaction.

1.3.1 Decarboxylative Coupling via Initial Functionalization of α-C–H Bonds

In 2003, Shair and coworkers reported the Cu-catalyzed decarboxylative aldol reaction of malonate half-thioesters and aldehydes (**Fig. 1-14**).[41] The reaction was developed to be highly diastereoselective and enantioselective with the use of a chiral bisoxazoline type ligand.[42] This reaction tolerated a range of protic groups such as free alcohols (**1-90**) and other electrophiles such as ketones (**1-91**). A combination of kinetic studies, cross-over experiments and deuterium/^{13}C-labelling studies were consistent with a mechanism in which addition of malonate half-thioester Cu-enolate **1-93** to an aldehyde occurs first to form **1-94**, followed by decarboxylation to form **1-95**, and finally diastereoselective protonation to form **1-97**.[43] This contrasts with the proposed biosynthetic mechanisms (discussed in section 1.2.1) wherein decarboxylation occurs first, followed by addition to an electrophile.

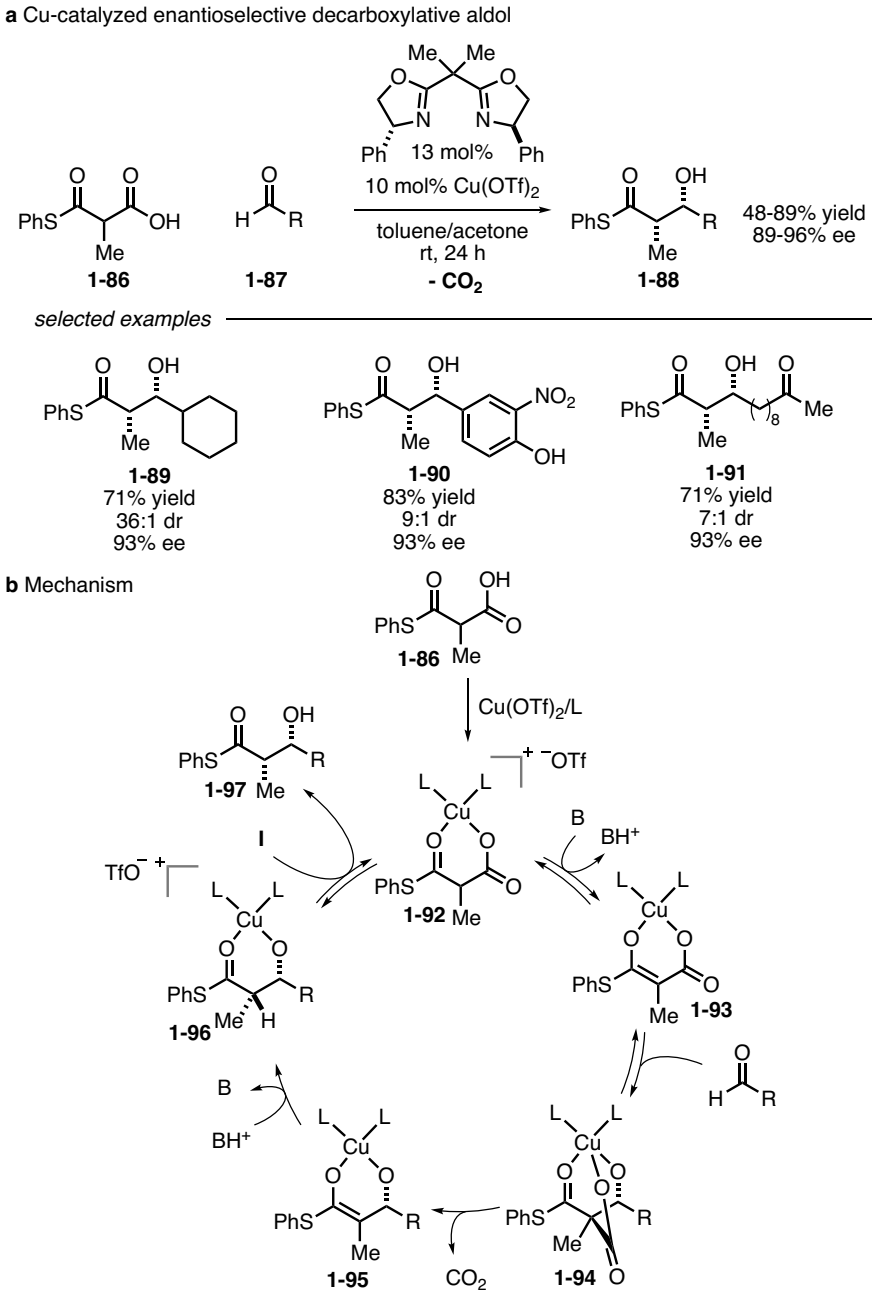


Fig. 1-14 Shair's Cu-catalyzed enantioselective decarboxylative aldol reaction

In 2009, Fagnou and coworkers studied the mechanism of a related decarboxylative aldol reaction of malonate half-esters with ketones using catalytic triethylamine (**Fig. 1-15**).[18] This reaction proceeded without metal catalyst, contrasting Shair's work with malonate half-thioesters. A post-ketone addition/pre-decarboxylation

intermediate **1-100** was observed and characterized by ^{1}H NMR, which supports a post-coupling decarboxylation mechanism.

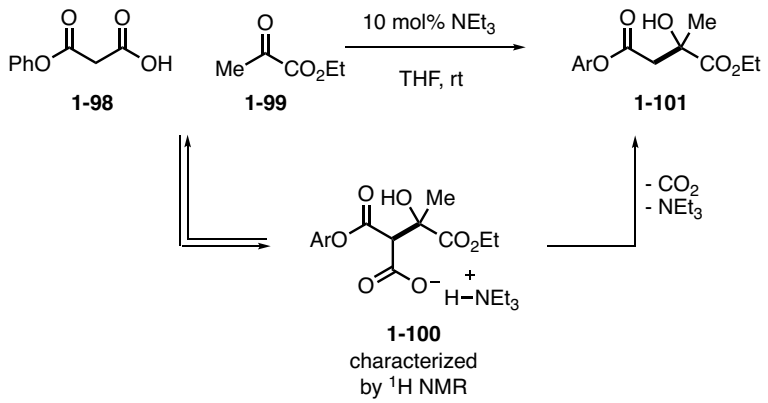


Fig. 1-15 Metal-free decarboxylative ketone aldol with malonate half-esters

1.3.2 Carboxylic Acids as Traceless Directing Groups

In the past twenty years, the field of C–H functionalization has matured beyond simple academic curiosity to become a relevant and useful strategy in synthesis.[44] For the direct functionalization of aromatic C–H bonds, directing groups are often used to direct the metal catalyst to react a given C–H bond, typically at the ortho position. The main drawback is that the directing group must be installed in a prior step, and removed in a subsequent step, lowering overall step- and atom-economy. Carboxylic acids can be used as 'traceless' activating groups in cases where they act as directing groups in a transition metal catalyzed functionalization, and are subsequently removed via protodecarboxylation in the same step (**Fig. 1-16**).[45] The net process provides products of formal C–H meta-functionalization, which remains a challenge in the field despite recent progress.[46-48]

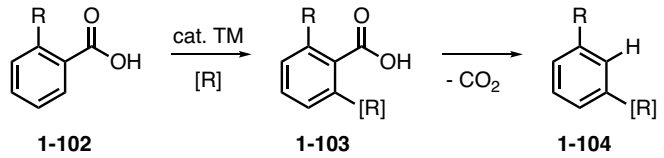


Fig. 1-16 Benzoic acids as traceless directing groups

Early work by Miura and coworkers showed that benzoic acids could be used as traceless activating groups for the one-pot Rh-catalyzed C–H olefination, Ag-catalyzed protodecarboxylation sequence to access meta-substituted arenes (**Fig. 1-17**).[49] Despite being a one-pot process, the addition of additional silver salt and base in a second step at higher temperature is required to induce protodecarboxylation. Various meta-substituted arenes could be obtained by this method (**1-108** to **1-110**).

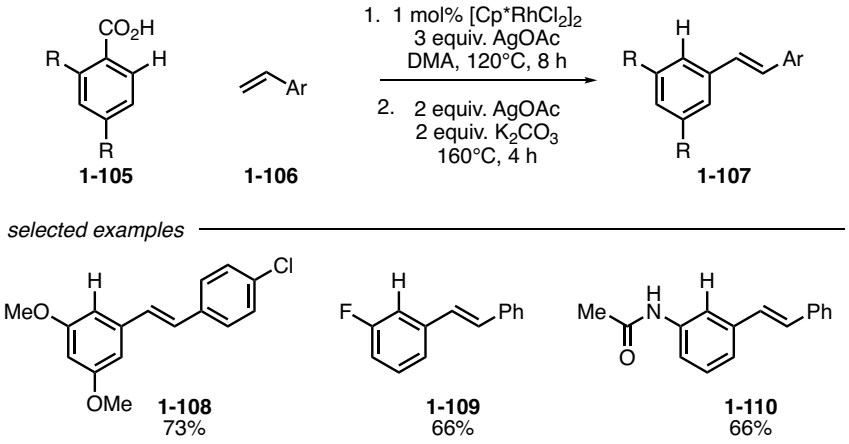


Fig. 1-17 Rh-catalyzed olefination using a traceless carboylic acid directing group

Later work by the group of Larrosa reported a striking example where in a one-pot process, the carboxylic acid directing group is installed on a phenol, directs an ortho-selective arylation, and undergoes protodecarboxylation to yield meta-substituted phenol

derivatives (**Fig. 1-18**).[50] This strategy overrides the inherent electronic bias of phenols for ortho/para substitution.

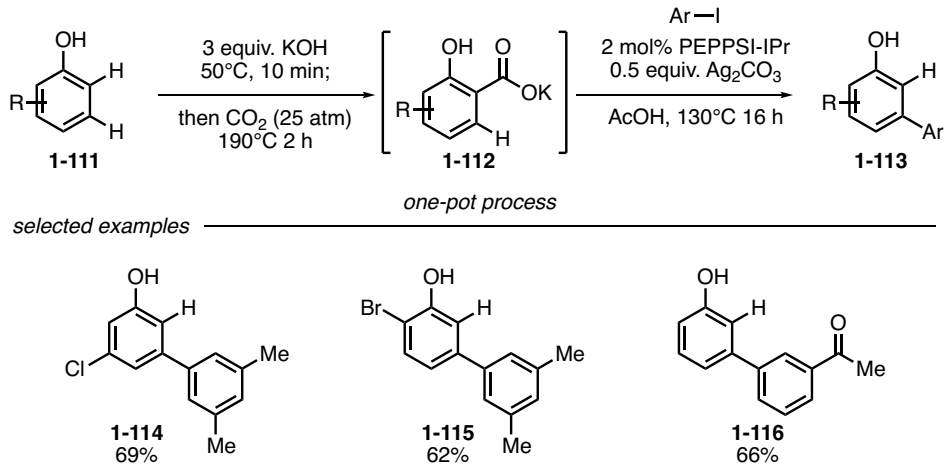


Fig. 1-18 Meta-selective arylation of phenols using a transient carboxylate directing group

This general strategy is not strictly limited to benzoic acid, as alkenyl carboxylic acids also undergo formally similar reactions though via a different mechanism. Maiti and coworkers reported that cinnamic acids undergo formal decarboxylative arylation with simple arene in a dehydrogenative process to form branched alkenes (**Fig. 1-19**).[51] A variety of branched arylated olefins could be accessed (**1-120** to **1-122**), though the process requires the arene partner to be the solvent. The authors propose this process proceeds via initial migratory insertion of the cinnamic acid into a Pd–Ar bond, followed by β-H elimination. Cu-promoted protodecarboxylation of arylated intermediate **1-129** would yield branched olefin product **1-130**. Control experiments showed that arylated cinnamic acid **1-123** decarboxylates under the reaction conditions, while cinnamic acid **1-125** does not decarboxylate, thus excluding a decarboxylation-first mechanism.

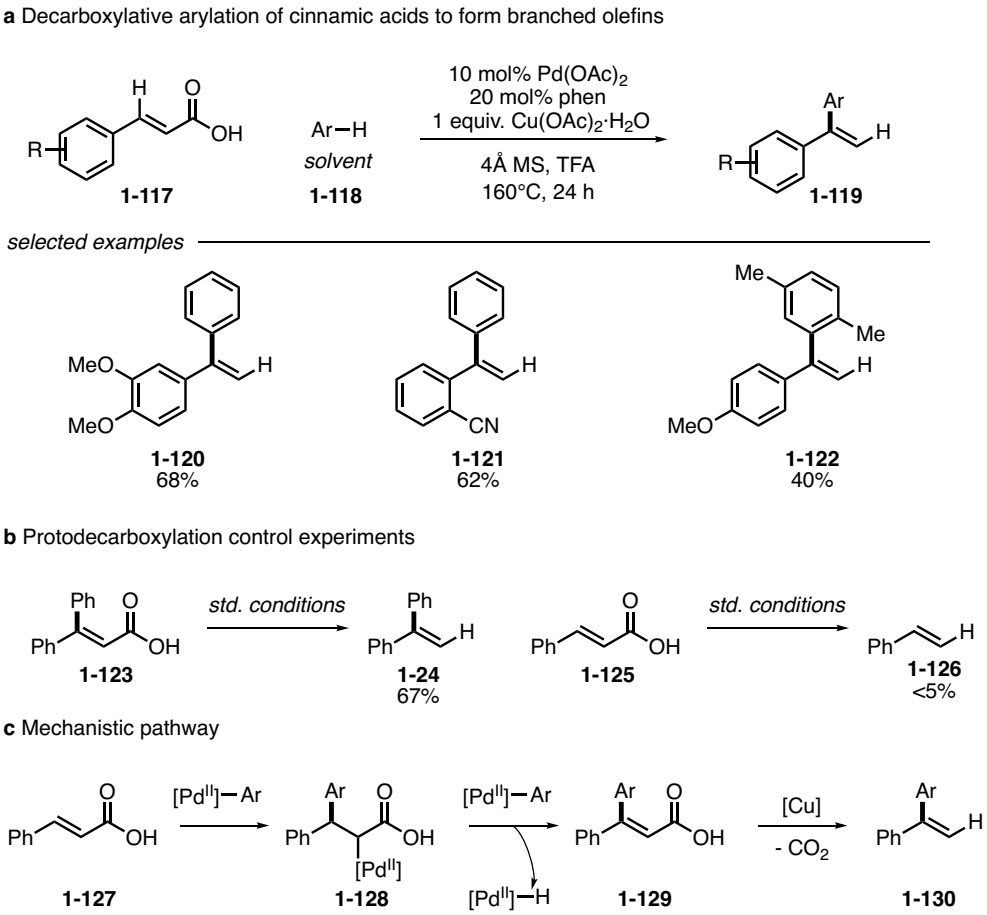


Fig. 1-19 Decarboxylative arylation of cinnamic acids to form branched olefins

1.4 Overview of Thesis

This thesis describes the discovery, optimization, and application of new decarboxylative coupling reactions. Mechanistic studies of these processes were conducted, with particular focus to elucidate the nature of the decarboxylation steps.

Chapter 2 discusses the development of the Cu-mediated oxidative coupling of activated methylene compounds and aryl boron reagents. This served as a proof-of-concept for the development of the decarboxylative arylation of malonate half-ester derivatives with aryl boronic esters. This reaction proceeds under ambient conditions

with catalytic amounts of $Cu(OTf)_2$. Arylation is proposed to proceed first, followed by protodecarboxylation.

Chapter 3 discusses the development of the Cu-catalyzed decarboxylative oxidative arylation of electron-deficient aryl acetate salts using aryl boronic esters to access diarylmethanes. Mechanistic control experiments suggest decarboxylation occurs first to form a benzylic nucleophile, which is then arylated. The metal cation (Cu, Zn) was found to play a key role in stabilizing the aryl acetate salt, and controlling the liberation of reactive benzylic nucleophile.

Chapter 4 discusses the development and mechanistic studies of the Pd-catalyzed arylation of moderately electron-deficient aryl acetate salts with aryl halides. Experiments suggest that initial decarboxylation generates a catalytic base which leads to the formation of a dienolate intermediate, followed by dienolate arylation, and decarboxylation of a diarylacetate intermediate.

Chapter 5 discusses the development of Ir- or Pd-catalyzed decarboxylative benzylation of allylic electrophiles using aryl acetic acids. This reaction displays broad tolerance for other protic and electrophilic groups. The reaction proceeds via initial allylation, followed by protodecarboxylation.

Chapter 6 discusses the development of the Cu-catalyzed decarboxylative amination of aryl acetic acid derivatives. This reaction proceeds under ambient conditions without pre-activation of the carboxylic acid. Mechanistic studies showed that aryl acetate salts reversibly decarboxylate in polar aprotic solvent to form a benzyl anion intermediate. The reversible generation of reactive nucleophile is likely key in achieving selective $C(sp^3)$–N bond formation over non-productive quenching.

CHAPTER 2 – Cu-Promoted Oxidative Coupling of Organoboron Reagents and C(sp^3) Nucleophiles

2.1 Introduction

Oxidative cross-coupling reactions between two distinct nucleophilic partners have emerged as valuable transformations that display reactivity and selectivity orthogonal to classical metal-catalyzed couplings of electrophiles with nucleophiles.[8-9] Oxidative coupling reactions often proceed under exceptionally mild conditions, employ base-metal mediators or catalysts, and in ideal cases, tolerate electrophilic functionality useful for subsequent transformations. The Cu-mediated union of aryl boronic acids and heteroatom nucleophiles exemplifies the power of such coupling manifolds.[52-53] As first reported by Chan and Lam,[54-55] and Evans,[56] functionalized aniline and phenol derivatives can be prepared from aryl boron species at room temperature by employing simple Cu-salts and mild organic bases (**Fig. 2-1**). In addition to N- and O-based nucleophiles, sulfur, selenium, tellurium, and halogen nucleophiles are also suitable partners in these reactions.[52-53, 57-64] Thus, the Chan-Evans-Lam reaction has emerged as a valuable synthetic alternative to traditional Cu-catalyzed Ullmann or Pd-catalyzed Buchwald-Hartwig couplings between aryl (pseudo)halides and heteroatom nucleophiles.[65]

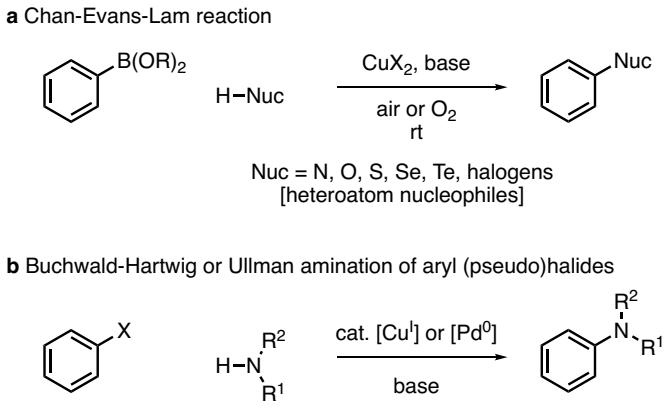


Fig. 2-1 The Chan-Evans-Lam reaction and Buchwald-Hartwig/Ullman reactions

A general catalytic cycle for the Chan-Evans-Lam reaction is outlined in **Fig**. **2-2**. Initial coordination and ligand exchange of a heteroatom nucleophile at a $Cu^{II}X_2$ center would generate nucleophile-bound Cu^{II} species. Subsequent transmetalation of the aryl boron species would lead to aryl-Cu species. Disproportionation with another Cu^{II} center would generate a high valent Cu^{III} intermediate that readily reductively eliminates to generate product. Aerobic re-oxidation of Cu^{I} to Cu^{II} closes the catalytic cycle. Studies by Stahl and coworkers on the Cu-catalyzed oxidative methoxylation of aryl boronic acids are consistent with a disproportionation step leading to a high valent Cu^{III} intermediate.[66-67]

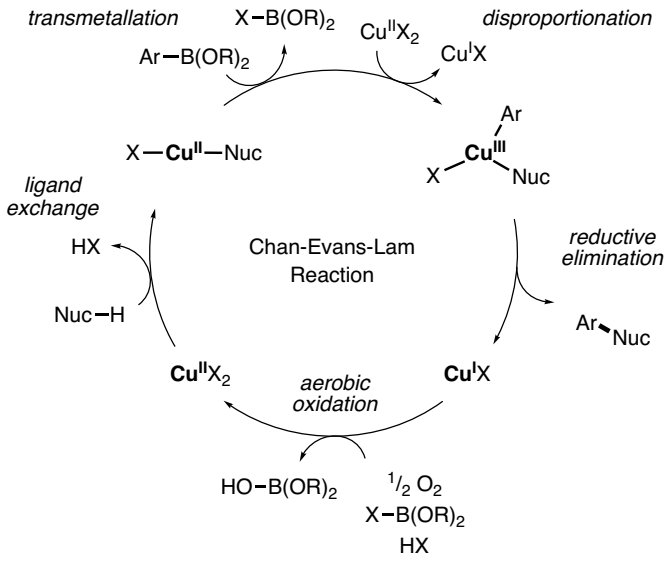


Fig. 2-3 General catalytic cycle for the Chan-Evans-Lam reaction

Despite the success of Chan-Evans-Lam type reactions in carbon–heteroatom bond construction processes, as well as an increasing appreciation for the mechanism of these transformations,[68] a general method for the Cu-mediated arylation of stabilized sp^3-carbon-based nucleophiles with organoboron reagents has not been established. This is particularly noteworthy in light of the importance of these compounds in synthetic organic and medicinal chemistry and the considerable body of literature concerning transition-metal-based methods for carbonyl α-arylation with sp^2-electrophiles.[69-71] Strategies for the α-arylation of stabilized enolates such as malonate derivatives include conventional redox-neutral S_NAr or state-of-the-art metal-catalyzed Hurtley or Hartwig-Buchwald cross-couplings using aryl (pseudo)halides (**Fig. 2-4**).[6, 72-74]

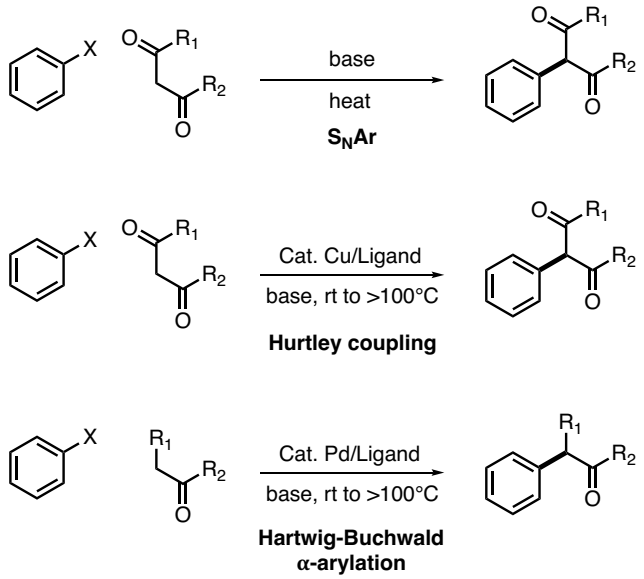


Fig. 2-4 Redox-neutral strategies for the α-arylation of enolates

An 'enolate' Chan-Evans-Lam reaction would complement alternative enolate arylation methods since electrophilic functionality such as aryl halides would likely be tolerated (**Fig. 2-5**). Since the Chan-Evans-Lam reaction typically works for a range of heteroatom nucleophile partners, but particularly good for relatively acidic heteroatom nucleophiles such as phenols, amides, or anilines (pKa ~13-31 in DMSO) oxidative arylation of activated methylene compounds such as malonates (pKa ~ 16 in DMSO) should be possible.

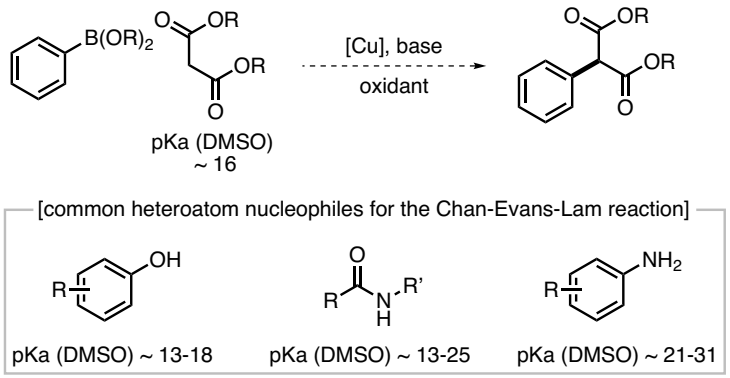


Fig. 2-5 Proposed 'enolate' Chan-Evans-Lam reaction

In comparison to heteroatom nucleophiles, reports of Cu-promoted C–C bond forming reactions with aryl boron reagents and C(sp) or C(sp^3)-nucleophiles under oxidative conditions remain sparse. Examples of cyanation,[75-76] alkynylation,[77-79] or trifluoromethylation[80-82] of aryl boron derivatives have been reported under a range of different conditions. To the best of our knowledge, enamine annulation[83] and vinylation[84] represent the closest known reports towards an enolate Chan-Evans-Lam reaction (**Fig. 2-6**).

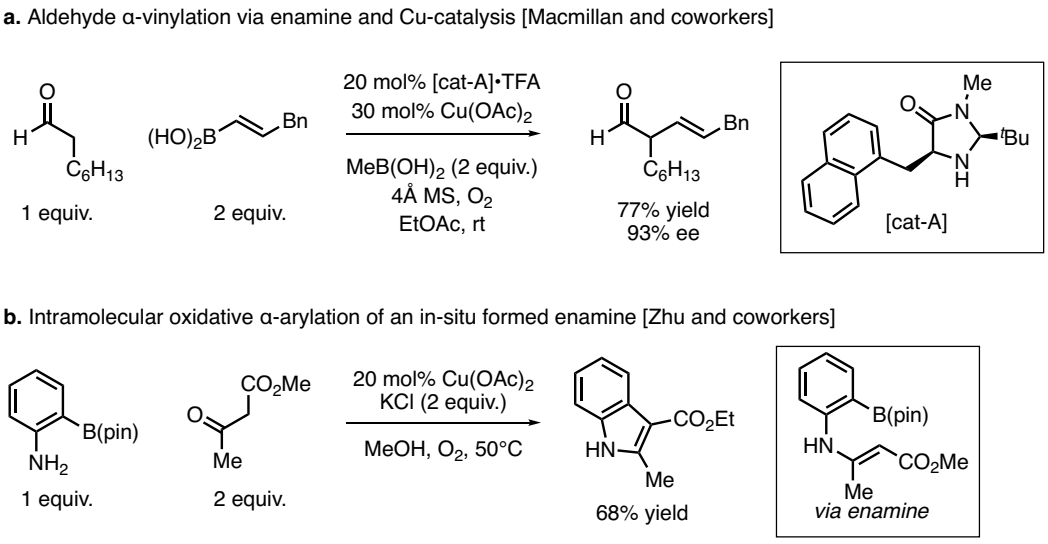


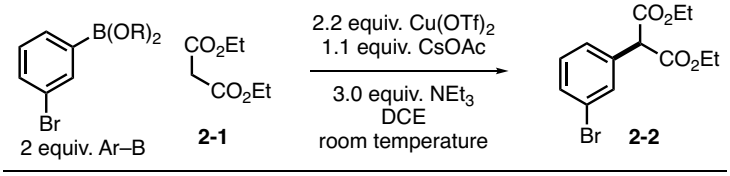
Fig 2-6 Oxidative vinylation and arylation of in-situ formed enamines

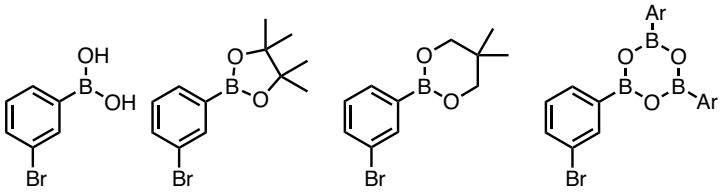
Motivated by this methodological gap and the opportunity to access compound classes not easily prepared by existing protocols, Section 2.2 describes the development of the first Cu-mediated oxidative coupling reactions between aryl boroxines or boronic esters and *in-situ* formed enolates to generate α-aryl carbonyl compounds. Section 2.3 describes the development of a decarboxylative variant of this reaction to access α-aryl acetates using malonic acid derivatives.

2.2 Development of a Cu-Promoted Oxidative Coupling of Aryl Boron Reagents with Activated Methylene Compounds

With the aim of developing Cu-mediated oxidative C–C bond formation between an aryl boron species and an activated C(sp^3)-nucleophile, reaction conditions similar to those employed for analogous heteroatom arylations were investigated, generally without success. Typical side products arising from protodeborylation, aryl-aryl homocoupling and acetoxylation were observed under variations of standard Chan-Evans-Lam conditions.[54-56, 84] The use of aryl boronic anhydrides (boroxines) however, provided a breakthrough in reactivity. **Fig. 2-7** is illustrative; under standard reaction conditions, aryl boronic acids or pinacol boronic esters provided only trace conversion to the desired arylated malonate product (2% and 7% respectively), while the aryl boroxine provided excellent yields (86%) and minimal side product formation. The corresponding neopentyl boronic ester also provided lower, but acceptable conversion to the product (68%). The transformation proceeded smoothly at room temperature with no observable side-reactions at the electrophilic aryl bromide site. $Cu(OTf)_2$ is the preferred Cu source, as the use of other reagents provided lower yields and increased amounts of protodeborylation (entries 2–4). Triethylamine was essential to the reaction, as other bases were not effective (entries 5–7). Acetate salts provided acceleration in reaction rate, but were not essential to product formation (entries 8 and 9). Water had a deleterious effect on the reaction, providing some insight into the poor reactivity observed with aryl boronic acids, which are in equilibrium with the anhydride form and water (entry 10).

A. Effect of Boron Group





4% conv. 2% yield **76% Ar–H**	20% conv. 7% yield <1% Ar–H	91% conv. 68% yield 8% Ar–H	**92% conv. 86% yield** 3% Ar–H [0.67 equiv]

B. Effect of Cu-Source and Reaction Parameters

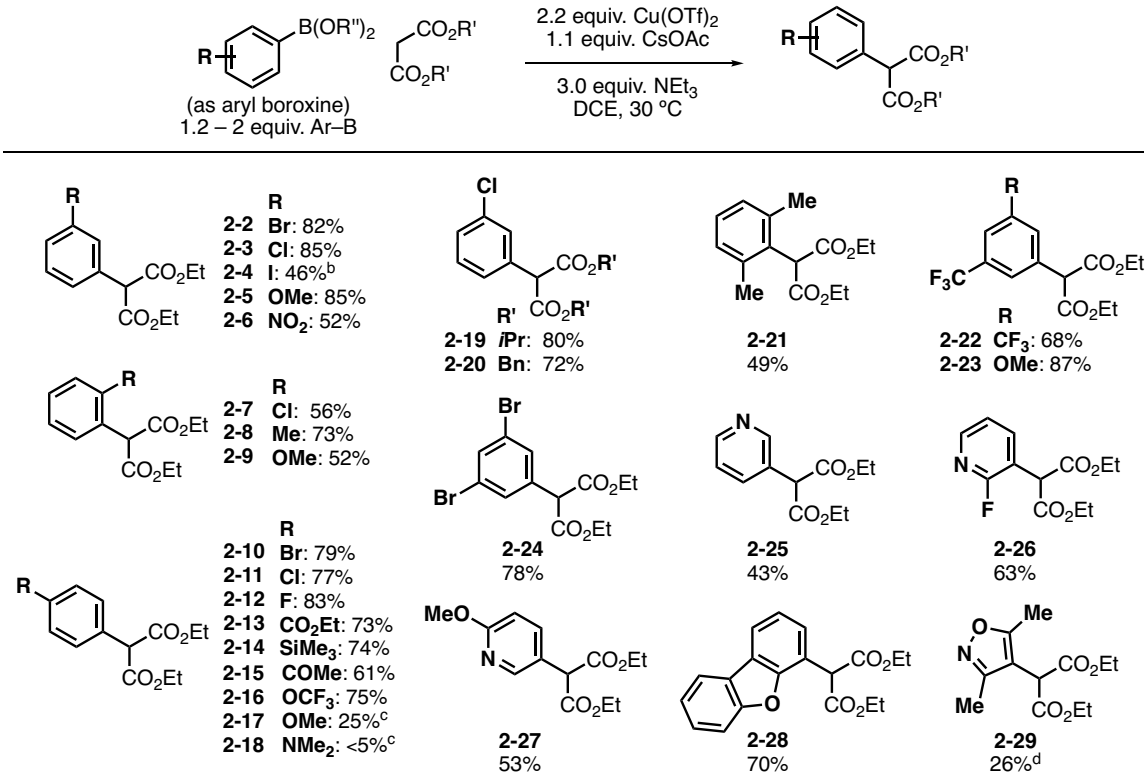
entry	deviation from above	conv. (%)	yield (%)	Ar-H (%)
1	**none**	**92**	**86**	**3**
2	$Cu(OAc)_2$ instead of $Cu(OTf)_2$	30	11	61
3	$Cu(OMe)_2$ instead of $Cu(OTf)_2$	15	13	84
4	$CuSO_4$ instead of $Cu(OTf)_2$	5	0	30
5	pyridine instead of NEt_3	3	0	92
6	K_2CO_3 instead of NEt_3	5	0	104
7	no NEt_3	0	0	104
8	NaOAc instead of CsOAc	86	78	6
9	no CsOAc	71	48	2
10	6 equiv. of H_2O	17	15	43

[a] Conversions (based on malonate) and yields determined by calibrated GC using dodecane as the internal standard, 0.2 M 48 h. Ar = 3-C_6H_4Br

Fig. 2-7 The Enolate Chan-Evans-Lam Reaction: effect of aryl boron reagent and reaction parameters

The scope of the Cu-mediated oxidative coupling of aryl boroxines and malonate esters is demonstrated in **Table 2-1**. Aryl fluorides, chlorides, bromides, and highly reactive iodides (**2-4**) were tolerated under the standard reaction conditions. In traditionally employed malonate arylation methods, such as S_NAr or Pd-catalyzed cross-coupling, these functional groups are typically reactive. Substitution at the 2- or 3-position with electron-withdrawing nitro or chloro groups (**2-3, 2-6, 2-7**) or donating methyl or methoxy groups (**2-5, 2-8, 2-9**) led to moderate to excellent yields of product.

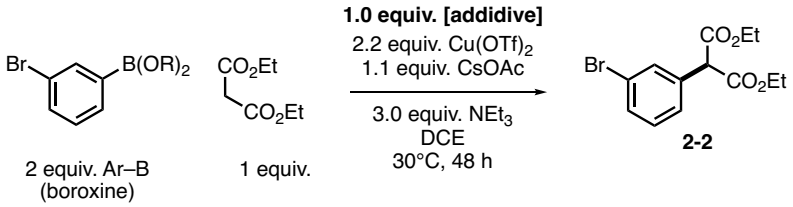
The reaction tolerated aryl boroxines with potentially reactive ester (**2-13**), ketone (**2-15**), and silyl functionality (**2-14**), as well as CF_3 (**2-22, 2-23**) and OCF_3 (**2-16**) substitution. For electron-rich, 4-substituted aryl boroxines, low yields were observed as the arylated malonate products undergo further oxidative coupling reactions with malonate (**2-17, 2-18**). These electron-rich arene derivatives however can be readily accessed from bromo-containing substrates in >60% overall yield via sequential oxidative coupling/Pd-catalyzed cross-coupling protocols.[85] Iso-propyl or benzyl malonate esters (**2-19, 2-20**), polysubstituted aryl boroxines (**2-22 to 2-24**), and bulky 2,6-disubstituted (**2-21**) reagents could be employed under the standard reaction conditions to give consistently high yields of product. Heterocycles such as substituted pyridines (**2-25** to **2-27**), dibenzofuran (**2-28**), and isoxazole (**2-29**) could also be oxidatively coupled to malonate derivatives.

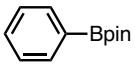
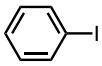
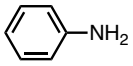
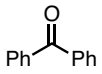
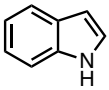
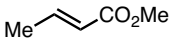
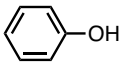
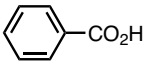
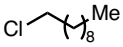
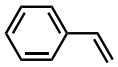
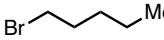
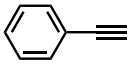
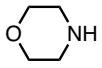
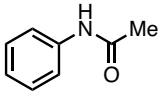
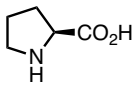
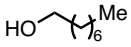
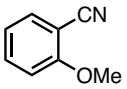
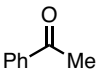
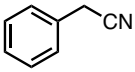


[a]0.20 M in DCE, 19 – 48 hours. Unless noted, yields are of isolated material using 2.0 equiv of aryl boron reagent (0.67 equiv. boroxine). 0.5 mmol scale [b]1.2 equiv of Ar–B at rt. [c]Yield determined by calibrated ^{1}H NMR, >95% conversion of malonate.[d] At 40 °C.

Table 2-1 Scope of the aryl boron reagent

A robustness screen conducted as outlined by Glorius[86] demonstrated that a secondary alkyl amine, a pinacol boronic ester, an alkene, an internal alkyne, a primary alkyl chloride or bromide, and an α,β-unsaturated ester were tolerated under the standard reaction conditions (>75% product yield, **Table 2-2**). Acidic pro-nucleophiles such as phenol, aniline, and phenylacetylene were not tolerated.

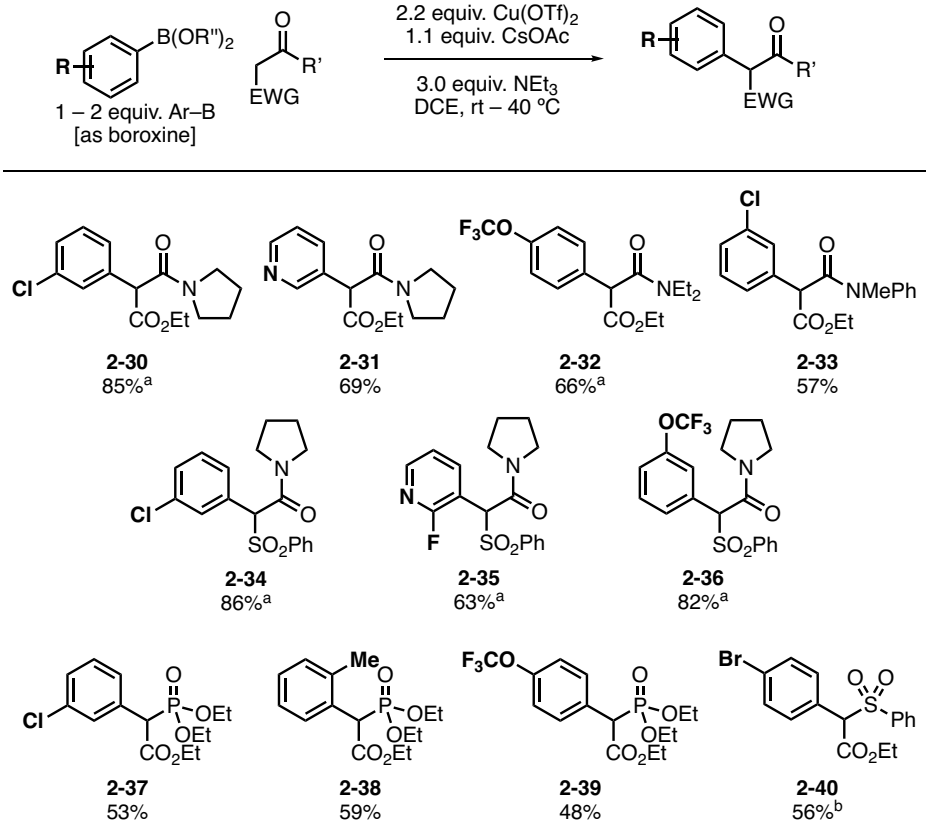


entry	Additive	yield of **2-2** (%)	Additive remaining (%)	Malonate remaining (%)	entry	Additive	yield of **2-2** (%)	Additive remaining (%)	Malonate remaining (%)
1	none	93 ✓	n.d.	<5	**12**		84 ✓	>95 ✓	11
2		78 ✓	83 ✓	12	**13**		18 ✗	46 –	79
3		69 ✓	>95 ✓	30	**14**		18 ✗	21 ✗	79
4		>95 ✓	>95 ✓	<5	**15**		20 ✗	91 ✓	78
5		35 ✗	77 ✓	66	**16**		93 ✓	n.d.	7
6		>95 ✓	>95 ✓	<5	**17**		90 ✓	>95 ✓	7
7		>95 ✓	84 ✓	<5	**18**		26 ✗	21 ✗	69
8		90 ✓	87 ✓	6	**19**		86 ✓	76 ✓	10
9		43 –	18 ✗	65	**20**		70 ✓	n.d.	31
10		76 ✓	n.d.	n.d.	**21**		90 ✓	91 ✓	<5
11		93 ✓	80 ✓	<5	**22**		89 ✓	>95 ✓	<5

Reactions performed on 0.10 mmol scale according to the general procedure (glovebox), with an additional 1.0 equivalent of additive. Yields determined by calibrated GC using dodecane as internal standard. 0.2 M 48 h. General accessment of product yield and additive recovery based on : 100–75% (good ✓), 74–40% (mediocre –), 40–0% (poor ✗). n.d. not determined

Table 2-2 Robustness Screen for the Cu-promoted oxidative arylation of malonate

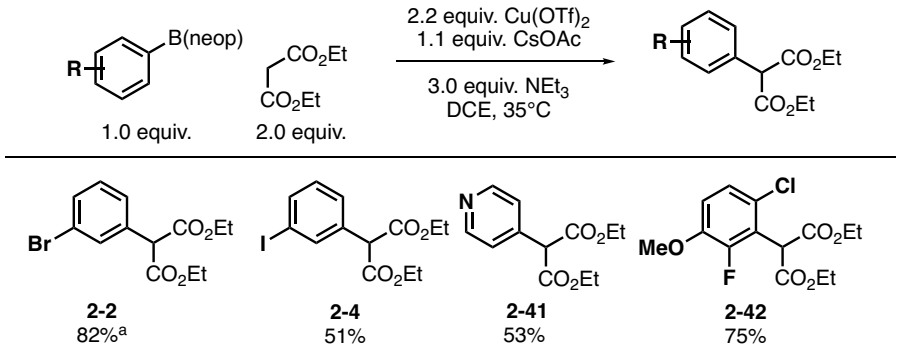
This methodology can be applied to activated methylene substrates that have not been reported to undergo Hurtley-type arylation under mild conditions (<70 °C), such as stabilized amides, sulfonyls, and phosphonyls (**Table 2-2**).[87-88] Both cyclic and acyclic alkyl 1,3-amido esters (**2-30** to **2-32**) and aryl/alkyl 1,3-amido esters (**2-33**) can be used as reaction partners, as well as 1,3-sulfonyl amides (**2-34** to **2-36**). In all cases, halogenated and heterocyclic boroxines were smoothly alkylated in high yield under mild conditions (rt – 30 °C). 1,3-Phosphonyl esters (**2-37** to **2-39**) and a sulfonyl ester (**2-40**) undergo oxidative coupling with similar efficiency to 1,3-diesters. Complementing this study, 1,3-ketoesters and cyanoesters are privileged substrates for low temperature (<70 °C) Hurtley coupling,[6] however these substrates are not suitable reaction partners under our standard conditions. 1,3-Ketoesters (pKa ~ 14 in DMSO) and cyanoesters (pKa ~13 in DMSO) have more acidic methylene C–H bonds than corresponding malonate derivatives (pKa ~16 in DMSO), and as such their corresponding enolates are less nucleophilic. Interplay between C–H acidity and nucleophilicity of the corresponding enolate for a given substrate class is likely important in achieving a productive coupling. Moreover, in the absence of external ancillary ligand under standard conditions, the substrate itself is likely the ligand on the Cu-center. It is therefore not necessarily surprising that certain substrate classes display poor reactivity, as the steric environment and electronic properties at Cu are likely different. While these substrate classes did not work under our standard conditions, significant effort was not invested in optimizing these reactions.



0.20 M in DCE, 2.5 – 72 hours, Unless noted yields are of isolated material using 2.0 equiv. of aryl boron reagent (0.67 equiv. boroxine) at 30 °C. 0.5 mmol scale a[b] 1.2 equiv. of Ar–B at rt. b[c] 1.5 equiv. Ar–B at 40 °C.

Table 2-3 Scope of the (sp^3)-nucleophile

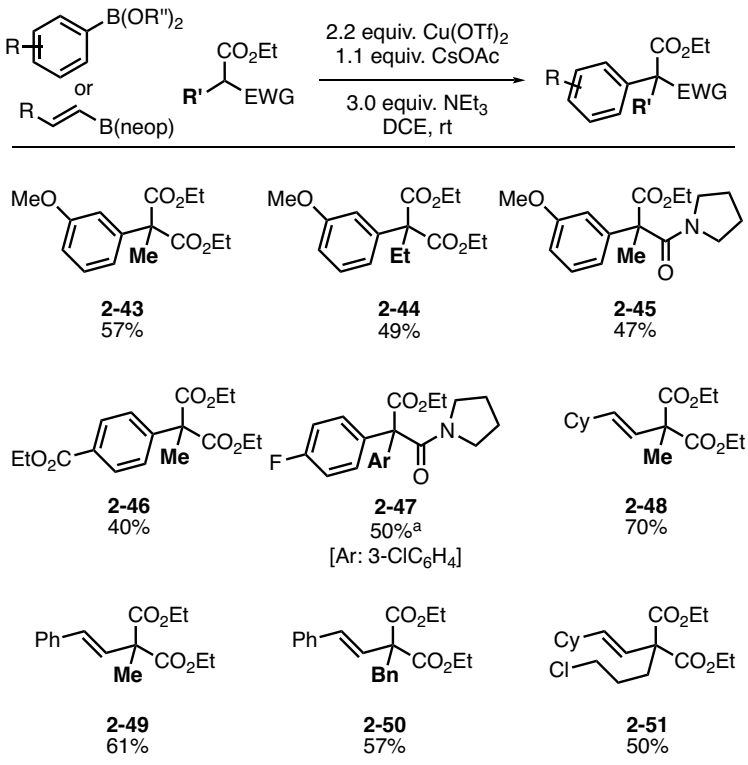
Under the standard reaction conditions, two equivalents of the aryl boron reagent were generally employed, which could be considered a drawback if the arylating reagent is particularly valuable. To address this issue, it was found that under modified conditions, aryl or heteroaryl neopentyl boronic esters could be used as the limiting reagent to afford good yields of the desired oxidative coupling product (**Table 2-4**). Examples of successful aryl groups include bromide and iodide containing substrates (**2-2, 2-4**), a pyridine (**2-41**), and a polyfunctionalized trisubstituted aryl partner (**2-42**).



0.20 M in DCE, 2.5 – 72 hours, Unless noted yields are of isolated material, 0.5 mmol scale
[a] Calibrated GC yield

Table 2-4 Oxidative arylation using aryl boronic ester as the limiting reagent

This oxidative coupling strategy also allowed for the generation quaternary carbon centers by arylation of tertiary C(sp^3)-nucleophiles under mild conditions (**Table 2-5**) Preliminary experiments with both substituted malonate esters and 1,3-amido esters demonstrated the ability of functionalized aryl boroxines to undergo Cu-mediated C–C bond formation under similar conditions to those described above, including compounds containing electrophilic aryl and alkyl chlorides (**2-47** and **2-51**).



0.20 M in DCE, 25 – 72 hours, using 3.0 equiv. Ar–B at room temperature.
[a] 40 ºC, 1.2 equiv Ar–B. b using 1.0 equiv. vinyl–B(neop), 2 equiv. malonate at 35°C.

Table 2-5 Cu-mediated oxidative arylation to form quaternary carbon centers

To the best of our knowledge this transformation is not possible by Hurtley coupling, despite reported failed attempts to arylate tertiary malonates.[89-90] Ma has developed ortho-directing group enabled Hurtley reactions to generate methylated quaternary centers from keto esters.[91-92] Tertiary cyanoacetates can also be arylated with CuI at ≥60 °C.[90, 92]

The major limitation of this reaction is the requirement for superstoichiometric copper loadings. Efforts to use catalytic amount of Cu salts in the presence of various terminal oxidants (pure O_2, O_2/N_2 mixtures, peroxides, etc.) did not provide synthetically useful yields of arylated product. Side-products arising from product and aryl boron

reagent overoxidation were observed. While not initially successful, achieving a catalytic process should be feasible provided re-oxidation of Cu^{I} to Cu^{II} is selective. In this regard, electrochemical conditions that enable the selective tuning of electrode potential could provide a breakthrough.

2.3 Decarboxylative Arylation of Malonic Acids Derivatives with Aryl Boron Reagents via Oxidative Cu-Catalysis

Following the proof-of-concept work described in section 2.2 using stabilized methylene compounds, we aimed to extend this oxidative α-arylation strategy to access simple mono-aryl acetate derivatives. Attempts to achieve the Cu-promoted oxidative coupling of non-stabilized enolates (generated via *in-situ* deprotonation or the use of pre-formed silyl ketene acetals) with aryl boron reagents were not successful (**Fig. 2-8**). These results highlight an inherent difficulty in oxidative coupling reactions,[93] as the use of preformed enolates resulted in exclusive formation of homocoupling products derived from both reaction partners without detectable cross-coupling.

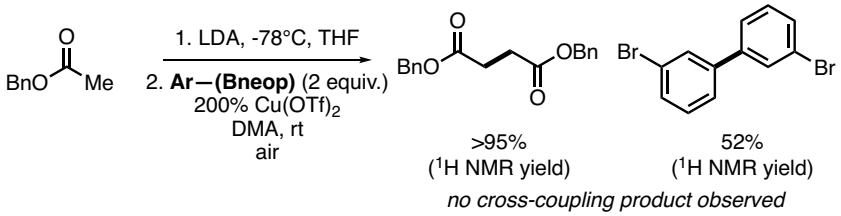
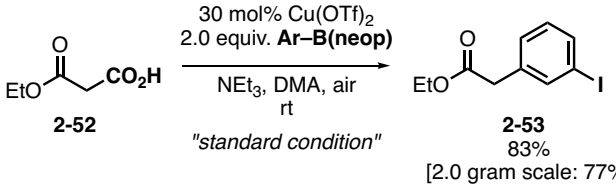


Fig. 2-8 Preliminary attempts at oxidative arylation of non-stabilized enolates

Monoethyl malonate, however, was observed to engage in highly selective catalytic decarboxylative cross-coupling with 3-iodophenyl boronic neopentyl ester [B(neop)] in air at room temperature with $Cu(OTf)_2$ to give the desired product in 83% yield (**Table 2-6**). No cross- or homo-coupling at the reactive electrophilic aryl iodide site, or competing arylation of the carboxylic acid was observed. This was somewhat surprising considering the potential difficulties associated with realizing an oxidative decarboxylative arylation reaction involving malonic acids, particularly as carboxylic acids themselves are viable

partners for copper-catalyzed O-arylation[60] and that irreversible decarboxylation or protodeborylation would result in unreactive substrates. The process can be scaled up to deliver gram quantities of aryl acetate product by using an uncapped round bottom flask (77% yield, 1.6 grams of product). To briefly describe key experimental parameters in reaction development, neopentyl glycol derived boronic esters were superior to pinacol ester, boroxine, or free boronic acid forms. Alternative Cu(II) salts performed poorly, but Cu(I) species, such as $Cu(MeCN)_4PF_6$ or CuI could be used as catalysts, in these cases a significant induction period was observed. These results suggest that the nature of the ligand on the Cu (pre)catalyst influences reactivity more than initial oxidation state. An excess of aryl boron reagent provides the best results; however only a slight excess (1.2 equiv) is required for good yields (74% vs 83% with 2 equiv).

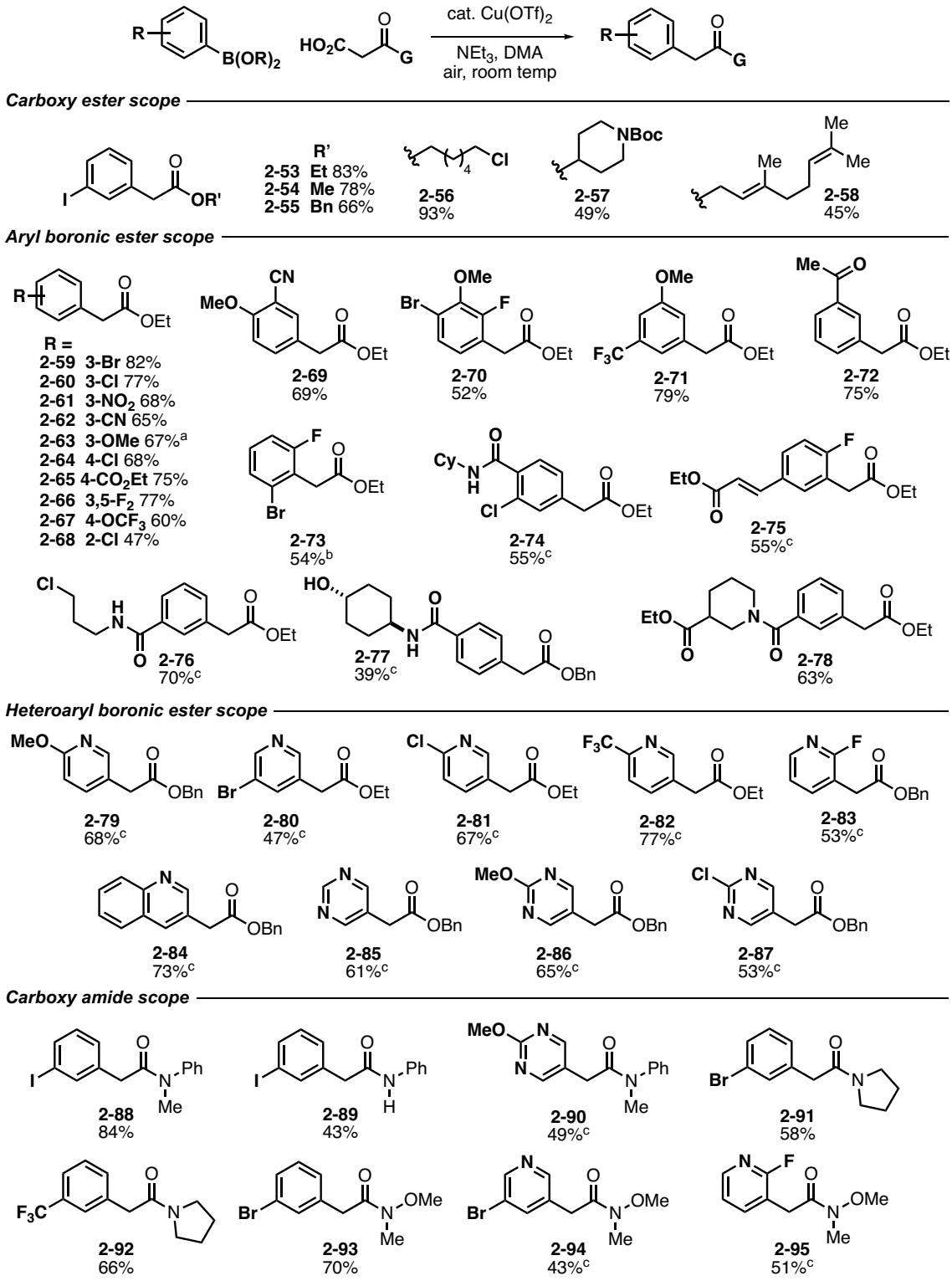


entry	deviation from above	conv. (%)	yield (%)
1	boroxine instead of Ar—B(neop)	98	68
2	boronic acid instead of Ar—B(neop)	59	19
3	Ar—Bpin instead of Ar—B(neop)	99	40
4	$Ar—BF_3K$ instead of Ar—B(neop)	42	0
5	$Cu(OAc)_2$ instead of $Cu(OTf)_2$	74	14
6	$CuSO_4$ instead of $Cu(OTf)_2$	42	20
7	$Cu(MeCN)_4PF_6$ instead of $Cu(OTf)_2$	99	73
8	CuI instead of $Cu(OTf)_2$	99	70
9	O_2 instead of ambient air	99	31
10	K-salt instead of free acid	39	36
11	no NEt_3	0	0
12	1.2 equiv. Ar—B(neop)	99	74

0.3 M in DMA, 30 mol% $Cu(OTf)_2$, 2.0 equiv. aryl boronic ester, in ambient air, rt. 48 h

Table 2-6 Overview of reaction discovery and optimization.

Due to the mild, ambient nature of the transformation, the oxidative decarboxylative α-arylation reaction is amenable to coupling of substrates containing a host of functional groups that would be potentially complicating with established methods (**Table 2-7**). The reaction tolerates alkyl halides (**2-56**, **2-76**), aryl halides (**2-53** to **2-60**, **2-64**, **2-66**, **2-68**, **2-70**, **2-73**), enolizable ketones (**2-72**) and esters (**2-78**), Michael acceptors (**2-75**), electron-rich olefins (**2-58**), nitriles (**2-62, 2-69**) as well as protic nitrogen (**2-74, 2-76, 2-77**) and oxygen (**2-77**) groups. The ester moiety can range from relatively simple, easy to dealkylate groups, such as methyl or benzyl, to more complex functional group-containing species (**2-56 to 2-58**). Heteroaryl boronic esters such as substituted pyridines (**2-79** to **2-83**), quinolines (**2-84**), and pyrimidines (**2-85** to **2-87**), including halogenated examples, are smoothly cross-coupled to give heteroaryl acetate adducts. Malonic monoamides undergo decarboxylative (hetero)arylation under standard conditions, including NH-amides (**2-89**), aryl-alkyl (**2-88, 2-90**) and dialkyl amides (**2-91, 2-92**). While beta-keto acids are not currently viable cross-coupling partners, Weinreb amides, versatile ketone surrogates, can be employed with both halogenated arenes and pyridines (**2-93** to **2-95**).



0.3 M in DMA or DCE, 24–72 h, 30 mol % $Cu(OTf)_2$, 1.5–2.0 equiv aryl boronic ester, in air at rt; [a]100 mol% Cu; [b]3 equiv ArB(neop); [c] 50 mol % Cu. The rest of the malonate half-ester mass balance is typically unaccounted for, likely due to the formation of side-products from oxidative degradation.

Table 2-7 Scope of the decarboxylative arylation of malonate half-ester derivatives

A large range of aryl boronic acids and esters are commercially available, however in cases where the aryl boron reagent is not immediately available, the oxidative coupling can be conducted in tandem with an arene borylation step (**Fig. 2-9**). Aryl halide **2-96** can be subjected to Pd-catalyzed borylation[94] to generate the corresponding aryl–B(neop) reagent **2-97** that can be used after extractive workup without chromatographic purification to give **2-98**. Ir- catalyzed C–H borylation[95] can be used to generate products of formal carbonyl α-C–H arylation (**2-101**). Leveraging the combined power of metal-catalyzed borylation and Cu-catalyzed decarboxylative malonate arylation, regiocontrolled alkylation of substituted aromatics such chloroarene **2-102** can be achieved in a straightforward and predictable manner to give two distinct compounds (**2-104** and **2-106**) from a common starting material.

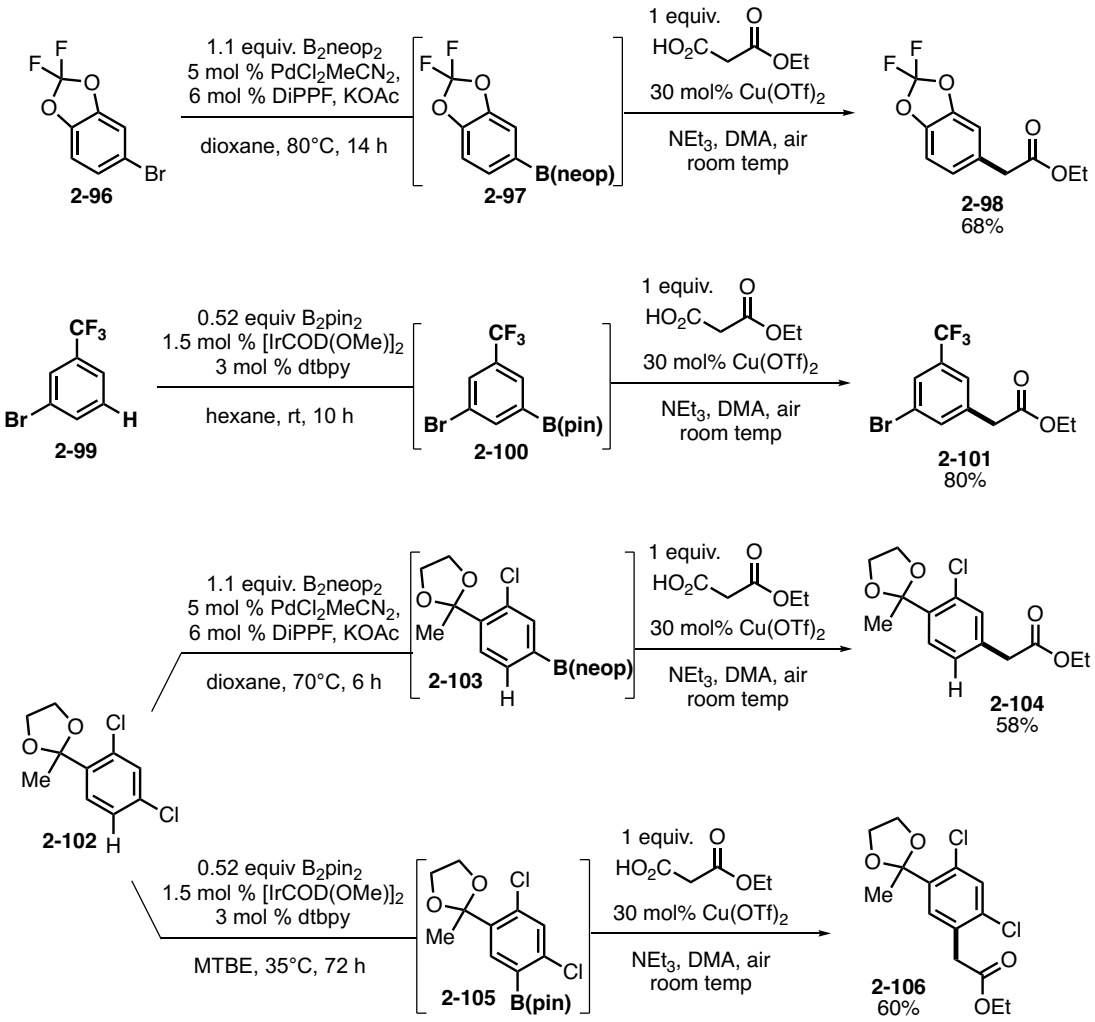


Fig. 2-9 Sequential arene borylation/decarboxylative coupling reactions

The applicability of this new copper-catalyzed decarboxylative arylation reaction was demonstrated in the preparation of the α-aryl cyclopropyl ketone core of Prasugrel (**Fig 2-10a**, **2-109**), which was synthesized in 54% yield in two steps via decarboxylative arylation of the Weinreb amide derivative **2-107** followed by treatment with cyclopropyl Grignard reagent. The arylated core of Lumacaftor was prepared by coupling the PMP-protected pyridyl α-carboxy amide **2-110** and a functionalized aryl B(neop) reagent **2-111** (**Fig 2-10b**) to deliver the target product **2-112** in 74% yield.

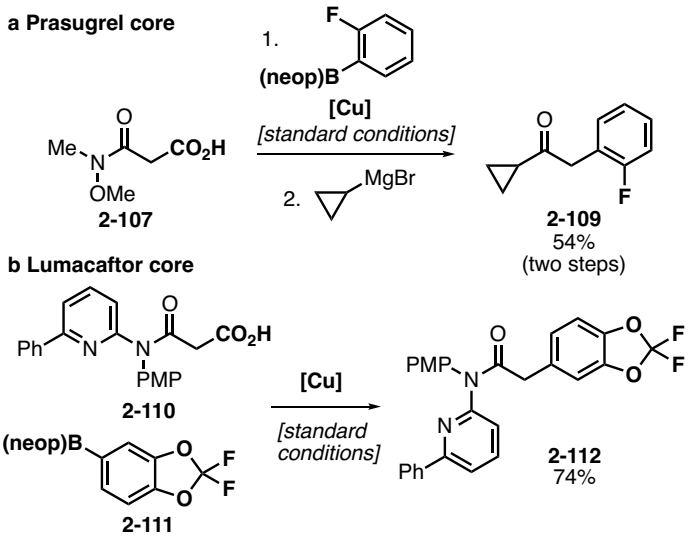


Fig. 2-10 Synthesis of the core structures of Prasugrel and Lumacaftor

The potential to functionalize complex molecules using this ambient decarboxylative strategy was tested on a variety of arene-containing drug molecules (**Fig. 2-11**). The complex alkaloid Nicergoline (**2-113**) could be borylated quantitatively and cross-coupled to monoethyl malonate in 57% yield (**2-115**). NBoc-Paroxetine (**2-116**) could be selectively alkylated at one of the five aryl C–H positions to deliver **2-118** via an Ir-catalyzed diborylation/mono-deborylation strategy[96] followed by decarboxylative cross-coupling. Indometacin ethyl ester (**2-119**) could be diversified into two unique derivatives by employing either Pd-catalyzed aryl chloride borylation followed by oxidative coupling (**2-121**), or Ir-catalyzed C–H borylation followed by oxidative coupling (**2-123**) to give the aryl acetate derivatives in synthetically useful yields (63% and 53% oxidative coupling yield respectively). These results support the prospect that malonic half esters may be used as two carbon units to synthesize and diversify drug-like molecules in medicinal chemistry campaigns by employing the reactivity platform described herein.

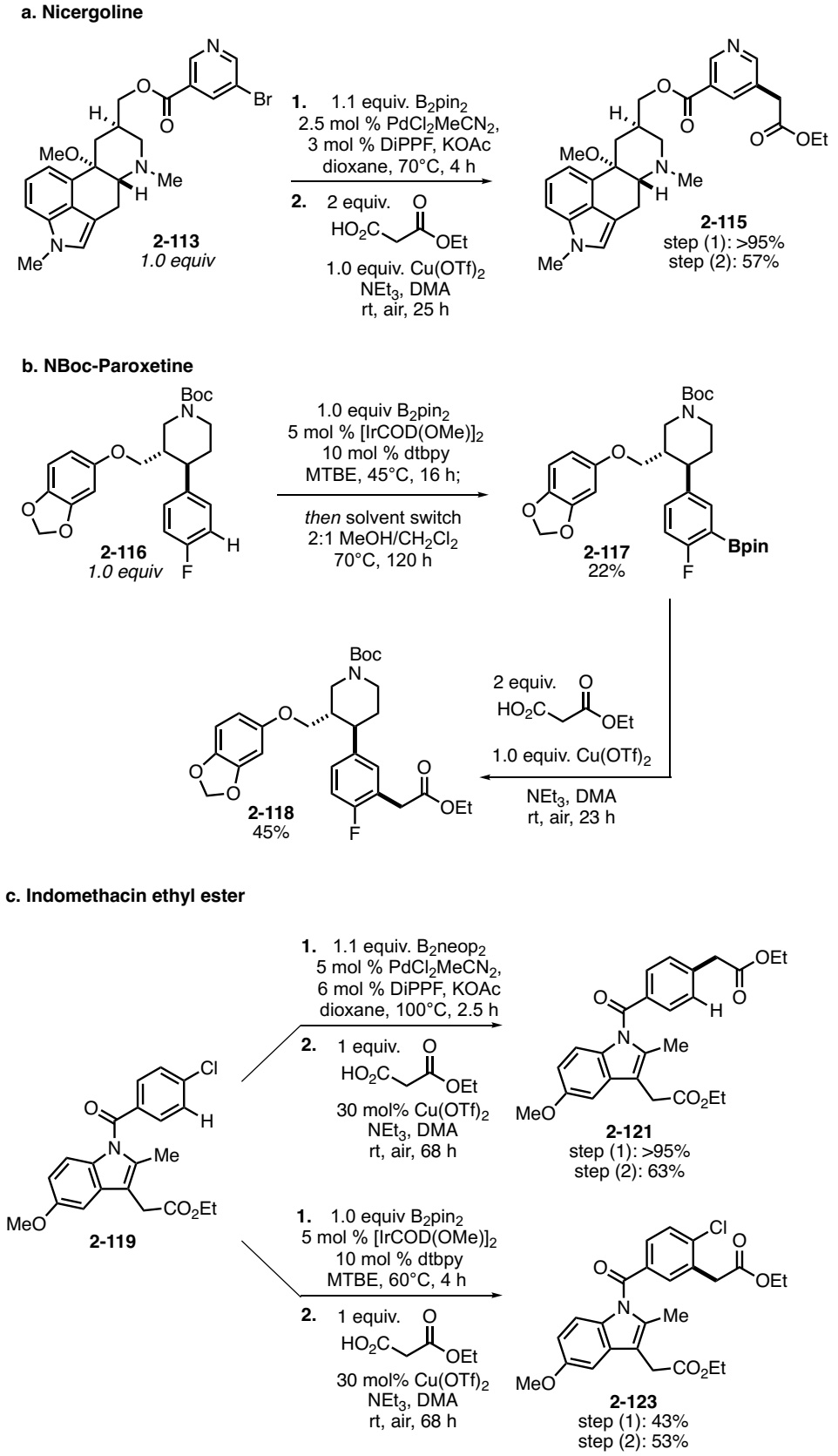


Fig. 2-11 Late-stage modification of Nicergoline, Paroxetine, and Indomethacin

With regards to the sequence in which decarboxylation and C–C bond formation are occurring, two potential mechanistic pathways could be occurring (**Fig. 2-12a**). Initial decarboxylation of **2-124** to form Cu-enolate **2-125** followed by oxidative arylation would form mono-aryl acetate product **2-126** (path A). Alternatively, oxidative arylation of a potential intermediate **2-127** would lead to arylated carboxylate **2-128,** which could undergo protodecarboxylation to generate product **2-126** (path B). To assess which pathway is operational, arylated carboxylate **2-129** was synthesized independently and was found to undergo rapid protodecarboxylation as a solution in DMA, but remained intact as solution in DCE (**Fig. 2-12b**). However, a solution of **2-129** in DCE in the presence of triethylamine showed protodecarboxylation to form mono-aryl acetate **2-59**. Subjecting malonate half-ester **2-52** to the standard conditions (in DCE) provided mono-aryl acetate product **2-59**, but intermediate **2-129** could be observed as an intermediate during the reaction (**Fig. 2-12c**). These experiments are consistent with oxidative arylation occurring first, followed by protodecarboxylation (path B, **Fig. 2-12a**). Considering that $Cu(OTf)_2$ mediates the oxidative coupling of malonates and aryl boron reagents (as described in Chapter 2.2), it is not unexpected that malonate half-esters can also be directly arylated via a similar mechanism. Once generated, the arylated malonate half-ester intermediate likely protodecarboxylates rapidly to the corresponding stable mono-aryl acetate terminal product.

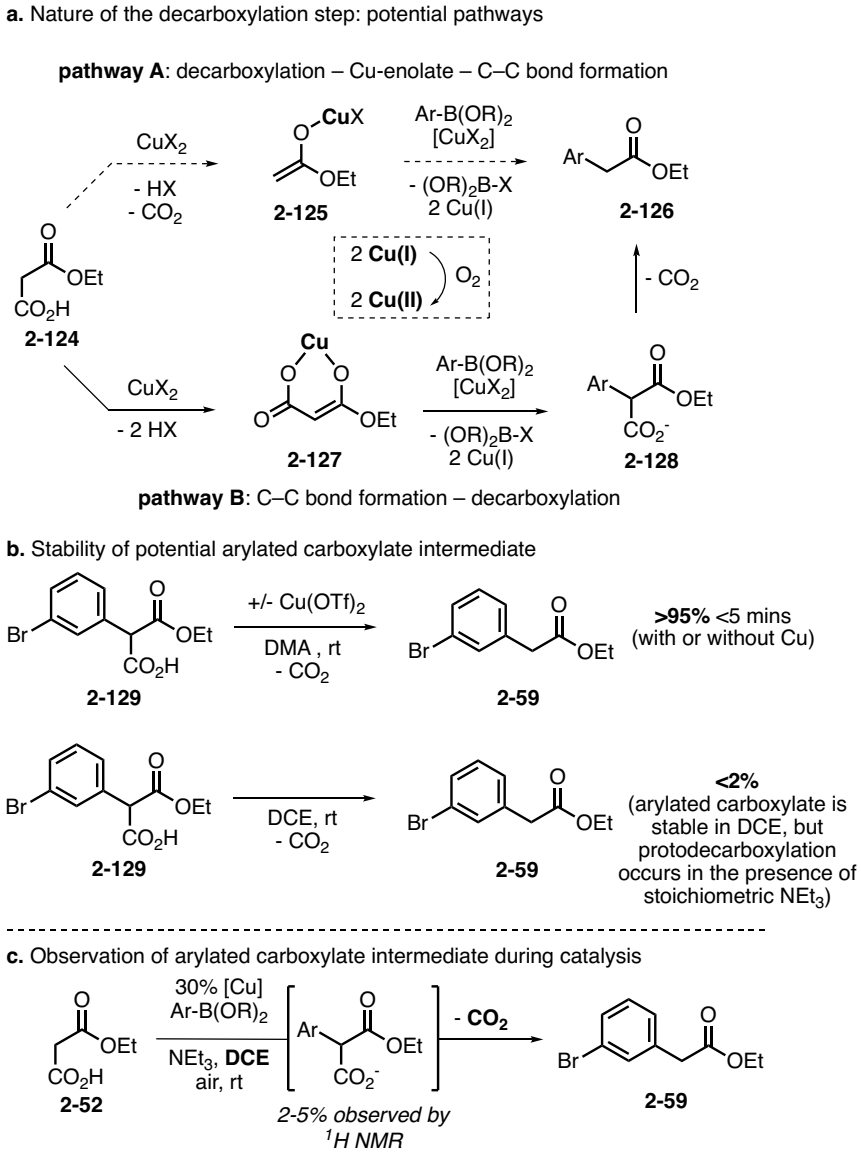


Fig. 2-12 Potential mechanism and nature of the decarboxylation step

2.4 Summary and Conclusions

In summary, we have reported a new strategy for the arylation of activated C(sp^3)-nucleophiles via Cu-mediated oxidative coupling. This enolate Chan-Evans-Lam reaction allows for installation of sensitive and densely functionalized aryl units under mild reaction conditions from readily available aryl boron species. Given the broad scope of reactivity, ability to form quaternary centers, and tolerance of electrophilic groups, this methodology is positioned to find broad appeal as an alternative to traditional cross-coupling or S_NAr reactions of aryl electrophiles with activated methylene species.

The decarboxylative α-arylation of malonic half esters and amides with aryl boronic esters was also developed to access mono-aryl acetate derivatives. This reaction proceeds at room temperature, in air, under mildly basic conditions, and employs a simple copper catalyst. In contrast with existing enolate arylation chemistry, this oxidative strategy is compatible with protic and electrophilic functional groups, facilitating applications in late-stage functionalization. We have demonstrated that biomimetic decarboxylative trapping of malonate derivatives can provide new routes to the core of drug molecules and should find use in the preparation of aryl acetates and related derivatives in the context of functional molecule synthesis.

2.5 Procedures and Characterization

General Considerations:

Unless noted, all reactions were conducted under inert atmosphere employing standard schlenk technique or by the use of a N2-filled glovebox. All glassware was oven-dried prior to use. Flash chromatography was performed using SiliaFlash P60 (40-63μm, 60A silica gel, Silicycle) or by automated flash chromatography (Isolera, HP-SIL or Ultra SNAP silica cartridges, Biotage). Analytical thin-layer chromatography was performed using glass plates pre-coated with silica (SiliaPlate G TLC - Glass-Backed, 250μm, Silicycle). TLC plates were visualized by UV light and/or staining with aqueous basic potassium permanganate. NMR spectra (^{1}H, ^{13}C, ^{19}F) were obtained on an Agilent VNMRS 700 MHz, Varian VNMRS 600 MHz, Varian VNMRS 500 MHz, or Varian 400 MHz spectrometer. The chemical shifts are given as parts per million (ppm) and were referenced to the residual solvent signal (CDCl3: δH = 7.26 ppm, δC = 77.16 ppm). Unless otherwise noted, quantitative ^{1}H NMR yields were determined from crude reaction mixtures using durene as an internal standard. Optical rotation data were obtained using a Perkin Elmer 241 Polarimeter at 589 nm and 25° C, using a 10 cm path-length cell. Unless otherwise noted, all reagents were obtained from commercial vendors and used as supplied.

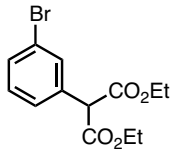
2.5.1 General Procedures and Characterization for Section 2.2

General Procedure A: Using Arylboroxines In an atmosphere controlled glovebox, $Cu(OTf)_2$ (398 mg, 1.10 mmol, 2.20 equiv.), arylboroxine (0.330 mmol, 0.670

equiv.), and CsOAc (106 mg, 0.550 mmol, 1.10 equiv.) were added sequentially to a 2 dram vial charged with a stir bar. The sp^3-carbon nucleophile (0.500 mmol, 1.00 equiv.) and triethylamine (0.210 mL, 1.50 mmol, 3.00 equiv.) were added as a solution in anhydrous 1,2-DCE (1.20 mL). Additional 1,2-DCE (2 x 0.5 mL) was used to quantitatively transfer the solution to the reaction mixture. The vial was sealed with a PTFE-lined cap and stirred outside the glovebox at 30 °C. Reaction progress was generally monitored by GC-FID using *n*-dodecane as an internal standard. Unless otherwise noted, reactions were quenched after 36 – 48 hours, when >95% conversion of sp^3-carbon nucleophile was reached. The reaction was quenched with 5 mL of brine and extracted with EtOAc (4 x 10 mL). The organic layer was then washed with 5 mL brine and dried with Na_2SO_4, filtered, and the solvent was removed by vacuum. The crude residue was purified by flash silica gel chromatography. Note: the order of addition of reagents is important for achieving optimal yields.

General Procedure B: using Neopentylboronic Esters In an atmosphere controlled glovebox, $Cu(OTf)_2$ (2.20 equiv.), neopentyl boronic ester (1.00 equiv.) if a solid, and CsOAc (1.10 equiv.) were sequentially added to a 2 dram vial charged with a stir bar. The sp^3-carbon nucleophile (2.00 equiv.), neopentyl boronic ester (1.00 equiv.) if a liquid, and triethylamine (3.00 equiv.) were added as a solution in dry 1,2-DCE (1.2 mL). Additional 1,2-DCE (2 x 0.5 mL) was used to quantitatively transfer the solution to the reaction mixture. The vial was sealed with a PTFE-lined cap and stirred outside the glovebox at 35 °C. The reaction was quenched with ~5 mL of brine and extracted with EtOAc (4 x 10 mL). The organic layer was then washed with 5 mL brine and dried with

Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The crude residue was purified by flash silica gel chromatography.



2-2 Prepared according to the General Procedure A from the corresponding arylboroxine (183 mg, 0.330 mmol, 2.00 equiv. Ar–B) and diethyl malonate (80 mg, 0.50 mmol, 1.0 equiv.), 37 h. Isolated as a colorless oil in 82% yield after purification by column chromatography (10:1 Hex/EtOAc).

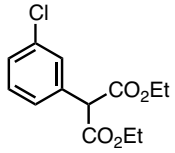
Prepared according to the General Procedure B from the corresponding neopentyl boronic ester (135 mg, 0.500 mmol, 1.00 equiv.) and diethylmalonate (160 mg, 1.00 mmol, 2.00 equiv.), stirred at 35 °C, 48 h. Calibrated GC yield of 87% obtained using dodecane as internal standard.

[Gram Scale Reaction in Air] To a 4 dram vial open to air was added diethyl malonate (0.961 g, 6.00 mmol, 1.00 equiv.), triethylamine (2.51 mL, 18.0 mmol, 3.00 equiv.), and dry 1,2-DCE (14.0 mL). To a 100 mL round bottom flask was added $Cu(OTf)_2$ (4.77 g, 13.2 mmol, 2.20 equiv.), arylboroxine (2.19 g, 12.0 mmol, 2.00 equiv.), and CsOAc (1.27 g, 6.6 equiv., 1.10 equiv.). The malonate solution was quantitatively transferred to the flask using additional 1,2-DCE rinses (2 x 6 mL). The reaction mixture was sealed under air with a rubber septa and stirred at 30 °C for 44 h. Isolated as a colorless oil in 74% yield (1.40 g) after purification by column chromatography (10:1 to 15:1 Hex/EtOAc). Note: CsOAc is hydroscopic and care should be taken to ensure the reagent is anhydrous prior to use.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.57 (m, 1H), 7.47 (m, 1H), 7.35 (m, 1H), 7.24 (m, 1H), 4.56 (s, 1H), 4.26 – 4.19 (m, 4H), 1.28 – 1.26 (t, *J* = 7.0 Hz, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.7, 135.0, 132.5, 131.5, 130.2, 128.1, 122.6, 62.2, 57.6, 14.1;

HRMS (LCMS ESI): calcd for $C_{13}H_{16}BrO_4$ $[M+H]^+$: 315.0226. Found 315.0233.

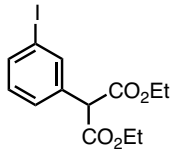


2-3 Prepared according to the General Procedure A from the corresponding arylboroxine (138 mg, 0.330 mmol, 2.00 equiv. Ar–B) and diethyl malonate (80 mg, 0.50 mmol, 1.00 equiv.), 21 h. Isolated as a colorless oil in 85% yield after purification by column chromatography (10:1 Hex/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42 (m, 1H), 7.33 – 7.29 (m, 3H), 4.57 (s, 1H), 4.28 – 4.17 (m, 4H), 1.27 (t, *J* = 7.2 Hz, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.7, 134.7, 134.5, 129.9, 129.7, 128.6, 127.7, 62.2, 57.7, 14.1;

HRMS (LCMS ESI): calcd for $C_{13}H_{16}ClO_4$ $[M+H]^+$: 271.0732. Found 271.0737.



2-4 Prepared according to the General Procedure A from the corresponding arylboroxine (138 mg, 0.200 mmol, 1.2 equiv. Ar–B) and diethyl malonate (80 mg, 0.50

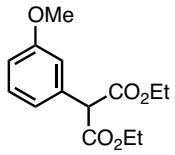
mmol, 1.0 equiv.), stirred at room temperature, 19 h. Isolated as a colorless oil in 46% yield after purification by column chromatography (20:1 to 10:1 Hex/EtOAc).

Prepared according to the General Procedure B from the corresponding neopentyl boronic ester (79 mg, 0.25 mmol, 1.0 equiv.) and diethyl malonate (80 mg, 0.50 mmol, 2.0 equiv.), stirred at 30°C, 44 h. Isolated as a colorless oil in 51% yield after purification by column chromatography (20:1 to 10:1 Hex/EtOAc).

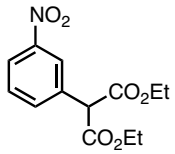
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.75 (m, 1H), 7.67 (m, 1H), 7.40 (m, 1H), 7.11 (m, 1H), 4.52 (s, 1H), 4.27 – 4.17 (m, 4H), 1.28 – 1.25 (t, *J* = 7.5 Hz, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.7, 138.3, 137.5, 135.0, 130.4, 128.7, 94.3, 62.2, 57.5, 14.1;

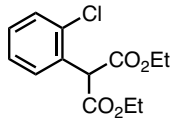
HRMS (LCMS ESI): calcd for $C_{13}H_{16}IO_4$ $[M+H]^+$: 363.0088. Found 363.0089.



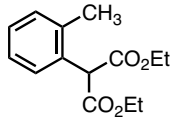
2-5 Prepared according to the General Procedure A from the corresponding arylboroxine (134 mg, 0.330 mmol, 2.00 equiv. Ar–B) and diethyl malonate (80 mg, 0.50 mmol, 1.00 equiv.), 20 h. Isolated as a pale yellow oil in 85% yield after purification by column chromatography (10:1 to 4:1 Hex/EtOAc). ^{1}H and ^{13}C NMR data agreed with literature data. HRMS matched the molecular formula.



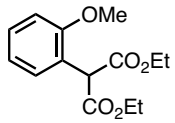
2-6 Prepared according to the General Procedure A from the corresponding arylboroxine (149 mg, 0.33 mmol, 2.00 equiv. Ar–B) and diethyl malonate (80 mg, 0.50 mmol, 1.00 equiv.), 48 h. Isolated as a pale yellow oil in 52% yield after purification by column chromatography (4:1 Hexane/CH_2Cl_2 to 100% CH_2Cl_2). ^1H and ^{13}C NMR data agreed with literature data. HRMS matched the molecular formula.



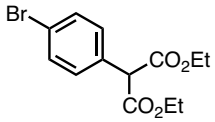
2-7 Prepared according to the General Procedure A from the corresponding arylboroxine (156 mg, 0.330 mmol, 2.00 equiv. Ar–B) and diethyl malonate (80 mg, 0.50 mmol, 1.0 equiv.), 42 h. Isolated as a colorless oil in 56% yield after purification by column chromatography (10:1 to 1:1 Hex/EtOAc). ^1H and ^{13}C NMR data agreed with literature data. HRMS matched the molecular formula.



2-8 Prepared according to the General Procedure A from the corresponding arylboroxine (118 mg, 0.330 mmol, 2.00 equiv. Ar–B) and diethyl malonate (80 mg, 0.50 mmol, 1.0 equiv.), 48 h. Isolated as a pale yellow oil in 73% yield after purification by column chromatography (10:1 to 4:1 Hex/EtOAc). ^1H and ^{13}C NMR data agreed with literature data. HRMS matched the molecular formula.



2-9 Prepared according to the General Procedure A from the corresponding arylboroxine (134 mg, 0.330 mmol, 2 equiv. Ar–B) and diethyl malonate (80 mg, 0.50 mmol, 1.0 equiv.), 48 h. Isolated as a colorless oil in 52% yield after purification by column chromatography (10:1 to 1:1 Hex/EtOAc). ^{1}H and ^{13}C NMR data agreed with literature data. HRMS matched the molecular formula.

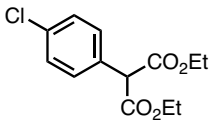


2-10 Prepared according to the General Procedure A from the corresponding arylboroxine (183 mg, 0.330 mmol, 2.0 equiv. Ar–B) and diethyl malonate (80 mg, 0.50 mmol, 1.0 equiv.), 33 h. Isolated) as a colorless oil in 79% yield after purification by column chromatography (10:1 to 4:1 Hex/EtOAc.

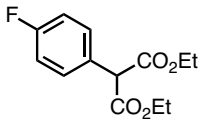
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.50 – 7.48 (m, 2H), 7.30 – 7.28 (m, 2H), 4.56 (s, 1H), 4.25 – 4.17 (m, 4H), 1.26 (t, *J* = 7.5, 6H)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.8, 131.93, 131.89, 131.1, 122.6, 62.1, 57.5, 14.2;

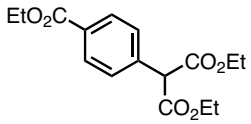
HRMS (LCMS ESI): calcd for $C_{13}H_{16}BrO_4$ $[M+H]^+$: 315.0226. Found 315.0227.



2-11 Prepared according to the General Procedure A from the corresponding arylboroxine (138 mg, 0.330 mmol, 2 equiv. Ar–B) and diethyl malonate (80 mg, 0.50 mmol, 1.0 equiv.), 48 h. Isolated as a colorless oil in 77% yield after purification by column chromatography (10:1 Hex/EtOAc). ^{1}H and ^{13}C NMR data agreed with literature data. HRMS matched the molecular formula.



2-12 Prepared according to the General Procedure A from the corresponding arylboroxine (122 mg, 0.330 mmol, 2 equiv. Ar–B) and diethyl malonate (80 mg, 0.50 mmol, 1.0 equiv.), 44 h. Isolated as a colorless oil in 83% yield after purification by column chromatography (10:1 to 4:1 Hex/EtOAc). ^{1}H and ^{13}C NMR data agreed with literature data. HRMS matched the molecular formula.

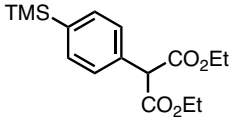


2-13 Prepared according to the General Procedure A from the corresponding arylboroxine (176 mg, 0.330 mmol, 2.00 equiv. Ar–B) and diethyl malonate (80 mg, 0.50 mmol, 1.0 equiv.), 31 h. Isolated as a colorless oil in 73% yield after purification by column chromatography (10:1 to 4:1 Hex/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.05 – 8.03 (m, 2H), 7.49 – 7.47 (m, 2H), 4.66 (s, 1H), 4.38 (q, *J* = 7.5 Hz, 2H), 4.27 – 4.17 (m, 4H), 1.39 (t, *J* = 1.39 Hz, 3H), 1.26 (t, *J* = 7.26 Hz, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.7, 166.4, 137.7, 130.5, 129.9, 129.5, 62.2, 61.2, 58.1, 14.5, 14.1

HRMS (LCMS ESI): calcd for $C_{16}H_{21}O_6$ $[M+H]^+$: 309.1333. Found 309.1334.

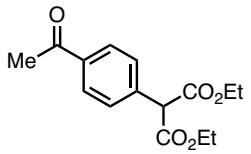


2-14 Prepared according to the General Procedure A from the corresponding arylboroxine (176 mg, 0.330 mmol, 2.00 equiv. Ar–B) and diethyl malonate (80 mg, 0.50 mmol, 1.0 equiv.), 48 h. Isolated a colorless oil in 74% yield after purification by column chromatography (10:1 to 4:1 Hex/EtOAc) as.

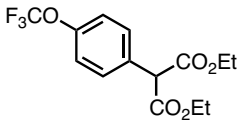
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52 – 7.51 (m, 2H), 7.39 – 7.37 (m, 2H), 4.60 (s, 1H), 4.26 – 4.16 (m, 4H), 1.27 (t, *J* = 7.2 Hz, 6H), 0.26 (s, 9H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.3, 140.6, 133.8, 133.3, 128.7, 61.9, 58.1, 14.2, -1.03;

HRMS (LCMS ESI): calcd for $C_{16}H_{25}O_4Si$ $[M+H]^+$: 309.1517. Found 309.1519.



2-15 Prepared according to the General Procedure A from the corresponding arylboroxine (90 mg, 0.20 mmol, 1.2 equiv. Ar–B) and diethyl malonate (80 mg, 0.50 mmol, 1.0 equiv.), 48 h. Isolated as a colorless oil in 61% yield after purification by column chromatography (4:1 to 1:1 Hex/EtOAc). ^{1}H and ^{13}C NMR data agreed with literature data. HRMS matched the molecular formula.



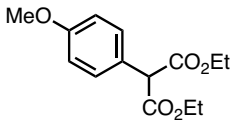
2-16 Prepared according to the General Procedure A from the corresponding arylboroxine (188 mg, 0.330 mmol, 2.0 equiv. Ar–B) and diethyl malonate (80 mg, 0.50 mmol, 1.0 equiv.), 26 h. Isolated as a colorless oil in 75% yield after purification by column chromatography (10:1 to 4:1 Hex/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.46 – 7.44 (m, 2H), 7.22 – 7.20 (m, 2H), 4.62 (s, 1H), 4.26 – 4.18 (m, 4H), 1.27 (t, J = 7.4 Hz, 6H);

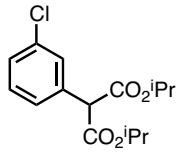
^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.9, 149.3, 131.6, 131.0, 121.1, 120.6 (q, J = 256 Hz), 62.2, 57.4, 14.1;

^{19}F NMR ($CDCl_3$, 469 MHz) δ -57.8

HRMS (LCMS ESI): calcd for $C_{14}H_{16}F_3O_5$ $[M+H]^+$: 321.0944. Found 321.0944.



2-17 Prepared according to the General Procedure A from the corresponding arylboroxine (134 mg, 0.33 mmol, 2.00 equiv. Ar–B) and diethyl malonate (80 mg, 0.5 mmol, 1.0 equiv.), 16h. >95% conversion of malonate, 25% desired product as determined by ^{1}H NMR analysis of the crude reaction mixture using dibenzyl ether as internal standard.

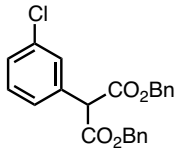


2-19 Prepared according to the General Procedure A from the corresponding arylboroxine (138 mg, 0.330 mmol, 2.0 equiv. Ar–B) and diisopropyl malonate (94 mg, 0.50 mmol, 1.0 equiv.), 48 h. Isolated as a pale yellow oil in 80% yield after purification by column chromatography (10:1 to 4:1 Hex/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41 (m, 1H), 7.31 – 7.29 (m, 3H), 5.07 (m, 2H), 4.50 (s, 1H), 1.27 (d, *J* = 6.7 Hz, 6H), 1.24 (d, *J* = 6.7 Hz, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.3, 134.9, 134.4, 129.8, 129.7, 128.5, 127.7, 69.8, 58.1, 21.8;

HRMS (LCMS ESI): calcd for $C_{15}H_{20}ClO_4$ $[M+H]^+$: 299.1045. Found 299.1044.

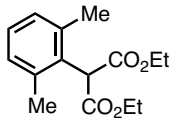


2-20 Prepared according to the General Procedure A from the corresponding arylboroxine (138 mg, 0.330 mmol, 2.0 equiv. Ar–B) and dibenzyl malonate (142 mg, 0.50 mmol, 1.0 equiv.), 48 h. Isolated as a pale yellow oil in 72% yield after purification by column chromatography (10:1 to 4:1 Hex/EtOAc).

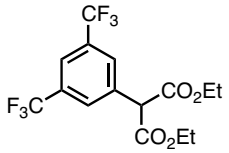
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41 (br, 1H), 7.33 – 7.28 (m, 7H), 7.28 – 7.25 (m, 6H), 5.21 – 5.14 (m, 4H), 4.68 (s, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.4, 135.2, 134.6, 134.3, 130.0, 129.7, 128.8, 128.7, 128.6, 128.3, 127.8, 67.8, 57.5;

HRMS (LCMS ESI): calcd for $C_{23}H_{23}ClNO_4$ $[M+NH_4]^+$: 412.1316. Found 412.1325.



2-21 Prepared according to the General Procedure A from the corresponding arylboroxine (132 mg, 0.330 mmol, 2.0 equiv. Ar–B) and diethyl malonate (80 mg, 0.50 mmol, 1.0 equiv.), 48 h. Isolated as a pale yellow oil in 49% yield after purification by column chromatography (10:1 to 4:1 Hex/EtOAc). ^{1}H and ^{13}C NMR data matched the literature data. HRMS matched the molecular formula.



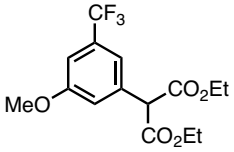
2-22 Prepared according to the General Procedure A from the corresponding arylboroxine (240 mg, 0.330 mmol, 2.0 equiv. Ar–B) and diethyl malonate (80 mg, 0.50 mmol, 1.0 equiv.), 48 h. Isolated as a colorless oil in 68% yield after purification by column chromatography (10:1 to 4:1 Hex/EtOAc).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90 (br, 2H), 7.87 (br, 1H), 4.73 (s, 1H), 4.30 – 4.21 (m, 4H), 1.29 (t, *J* = 7.0 Hz, 6H)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.0, 135.2, 132.0 (q, *J* = 34 Hz), 129.98 (d, *J* = 2.8 Hz), 123.3 (q, *J* = 271 Hz), 122.5 (m), 62.7, 57.5, 14.1;

^{19}F NMR ($CDCl_3$, 377 MHz) δ -62.9

HRMS (LCMS ESI): calcd for $C_{15}H_{15}F_6O_4$ $[M+H]^+$: 373.0869. Found 373.0879.



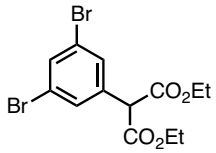
2-23 Prepared according to the General Procedure A from the corresponding arylboroxine (202 mg, 0.330 mmol, 2.0 equiv. Ar–B) and diethyl malonate (80 mg, 0.50 mmol, 1.0 equiv.), 48 h. Isolated as a colorless oil in 87% yield after purification by column chromatography (10:1 to 4:1 Hex/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.23 (br, 1H), 7.17 (br, 1H), 7.10 (br, 1H), 4.62 (s, 1H), 4.27 – 4.19 (m, 4H), 3.85 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.6, 160.0, 135.2, 132.1 (q, *J* = 32 Hz), 123.9 (q, *J* = 271 Hz), 118.7, 188.61, 110.9 (m), 62.3, 57.8, 55.8, 14.1;

^{19}F NMR ($CDCl_3$, 377 MHz) δ -62.7

HRMS (LCMS ESI): calcd for $C_{15}H_{18}F_3O_5$ $[M+H]^+$: 335.1101. Found 335.1107.

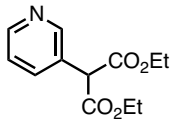


2-24 Prepared according to the General Procedure A from the corresponding arylboroxine (262 mg, 0.330 mmol, 2.0 equiv. Ar–B) and diethyl malonate (80 mg, 0.50 mmol, 1.0 equiv.), 24 h. Isolated as a colorless oil in 78% yield after purification by column chromatography (10:1 to 4:1 Hex/EtOAc).

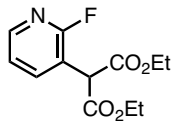
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65 (m, 1H), 7.51 (m, 2H), 4.51 (s, 1H), 4.29 – 4.18 (m, 4H), 1.28 (t, *J* = 7.2 Hz, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.2, 136.3, 134.2, 131.4, 123.0, 62.4, 57.1, 14.1;

HRMS (LCMS ESI): calcd for $C_{13}H_{15}Br_2O_4$ $[M+H]^+$: 392.9332. Found 392.9340.



2-25 Prepared according to the General Procedure A from the corresponding arylboroxine (105 mg, 0.330 mmol, 2.0 equiv. Ar–B) and diethyl malonate (80 mg, 0.50 mmol, 1.0 equiv.), 48 h. Isolated as a pale yellow oil in 43% yield after purification by column chromatography (1:1 to 1:3 Hex/EtOAc). ^{1}H and ^{13}C NMR data agreed with literature data. HRMS matched the molecular formula.



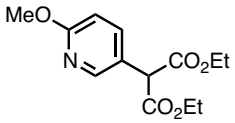
2-26 Prepared according to the General Procedure A from the corresponding arylboroxine (123 mg, 0.330 mmol, 2.0 equiv. Ar–B) and diethyl malonate (80 mg, 0.50 mmol, 1.0 equiv.), 48 h. Isolated as a pale yellow oil in 63% yield after purification by column chromatography (10:1 to 1:1 Hex/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.20 (m, 1H), 7.99 (m, 1H), 7.23 (m, 1H), 4.93 (s, 1H), 4.30 – 4.20 (m, 4H), 1.28 (t, *J* = 7.2 Hz, 6H);

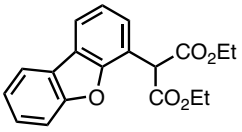
^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.0, 161.3 (d, *J* = 238 Hz), 147.6 (d, *J* = 15 Hz), 141.6 (d, *J* = 3.8 Hz), 121.8 (d, *J* = 4.5 Hz), 115.8 (d, *J* = 29 Hz), 62.5, 50.42 (d, *J* = 1.5 Hz), 14.1;

^{19}F NMR ($CDCl_3$, 377 MHz) δ -72.53 (d, *J* = 9.6 Hz)

HRMS (LCMS ESI): calcd for $C_{12}H_{15}FNO_4$ $[M+H]^+$: 256.098 Found: 256.0982



2-27 Prepared according to the General Procedure A from the corresponding arylboroxine (135 mg, 0.330 mmol, 2.0 equiv. Ar–B) and diethyl malonate (80 mg, 0.50 mmol, 1.0 equiv.), 24 h. Isolated as a pale yellow oil in 53% yield after purification by column chromatography (10:1 to 4:1 Hex/EtOAc). ^{1}H and ^{13}C NMR data agreed with literature data. HRMS matched the molecular formula.

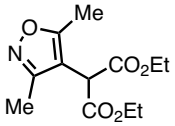


2-28 Prepared according to the General Procedure from the corresponding arylboroxine (194 mg, 0.330 mmol, 2.0 equiv. Ar–B) and diethyl malonate (80 mg, 0.50 mmol, 1.0 equiv.), 48 h. Isolated as a pale yellow oil in 69% yield after purification by column chromatography (10:1 Hex/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.95 (d, *J* = 7.5 Hz, 1H), 7.92 (dd, *J* = 1.5, 7.5 Hz, 1H), 7.60 – 7.57 (m, 2H), 7.46 (m, 1H), 7.39 – 7.33 (m, 2H), 5.39 (s, 1H), 4.30 – 4.22 (m, 4H), 1.28 (t, *J* = 7.5 Hz, 6H)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.9, 156.2, 154.4, 127.44, 127.42, 124.51, 124.47, 123.12, 123.06, 120.9, 120.7, 117.3, 112.0, 62.1, 51.7, 14.2;

HRMS (LCMS ESI): calcd for $C_{19}H_{19}O_5$ $[M+H]^+$: 327.1227 Found: 327.1232

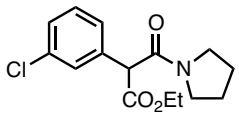


2-29 Prepared according to the General Procedure A from the corresponding arylboroxine (123 mg, 0.330 mmol, 2.0 equiv. Ar–B) and diethyl malonate (80 mg, 0.50 mmol, 1.0 equiv.), stirred at 40 °C, 48 h. Isolated as a pale yellow oil in 26% yield after purification by column chromatography (4:1 to 1:1 Hex/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.41 (s, 1H), 4.27 – 4.20 (m, 4H), 2.39 (s, 3H), 2.26 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 6H)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.9, 167.2, 159.6, 107.2, 62.3, 47.6, 14.2, 11.8, 10.6;

HRMS (LCMS ESI): calcd for $[M+H]^+$: 255.1107 Found: 255.1102

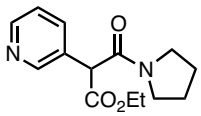


2-30 Prepared according to the General Procedure A from the corresponding arylboroxine (83 mg, 0.20 mmol, 2.00 equiv. Ar–B) and amido ester (93 mg, 0.50 mmol, 1.0 equiv.), stirred at room temperature, 3 h. Isolated as a colorless oil in 85% yield after purification by column chromatography (4:1 to 1:3 Hex/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41 (m, 1H), 7.33 – 7.28 (m, 3H), 4.66 (s, 1H), 4.27 – 4.17 (m, 2H), 3.59 – 3.42 (m, 3H), 3.25 – 3.20 (m, 1H), 1.97 – 1.80 (m, 4H), 1.26 (t, J = 7.2 Hz, 3H)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.3, 165.7, 135.2, 134.5, 129.9, 129.8, 128.4, 127.9, 62.0, 57.4, 47.0, 46.5, 26.2, 24.4, 14.2;

HRMS (LCMS ESI): calcd for $C_{15}H_{19}ClNO_3$ $[M+H]^+$: 296.1048. Found 296.1050.



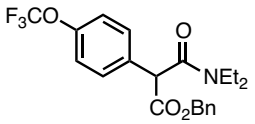
2-31 Prepared according to the General Procedure A from the corresponding arylboroxine (105 mg, 0.330 mmol, 2.0 equiv. Ar–B) and amido ester (93 mg, 0.50 mmol, 1.0 equiv.), 23 h. Isolated as an orange oil in 69% yield after purification by column chromatography (2% to 10% MeOH/CH_2Cl_2, treated with ~1% NH_4OH).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.53 (dd, J = 1.6, 5.0 Hz, 1H), 8.48 (d, J = 1.7 Hz, 1H), 7.91 (dt, J = 2.0, 8.0 Hz, 1H), 7.28 (dd, J = 5.0, 8.0 Hz, 1H), 4.69 (s, 1H), 4.21 –

4.14 (m, 2H), 3.56 – 3.51 (m, 2H), 3.40 (m, 1H), 3.27 (m, 1H), 1.95 – 1.79 (m, 4H), 1.23 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.0, 165.2, 150.3, 149.4, 137.5, 129.5, 123.6, 62.0, 54.8, 47.0, 46.5, 26.1, 24.3, 14.1;

HRMS (LCMS ESI): calcd for $C_{14}H_{19}N_2O_3$ $[M+H]^+$: 263.1396. Found 263.1392.



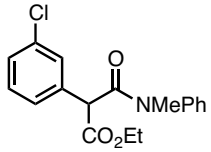
2-32 Prepared according to the General Procedure A from the corresponding arylboroxine (113 mg, 0.200 mmol, 1.2 equiv. Ar–B) and amido ester (125 mg, 0.50 mmol, 1.0 equiv.), stirred at room temperature, 5 h. Isolated as an off-white solid in 66% yield after purification by column chromatography (4:1 to 1:1 Hex/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.45 – 7.44 (m, 2H), 7.34 – 7.30 (m, 5H), 7.21 – 7.19 (m, 2H), 5.24 – 5.17 (m, 2H), 4.85 (s, 1H), 3.44 – 3.33 (m, 2H), 3.27 – 3.22 (m, 2H), 1.10 (t, *J* = 7.5 Hz, 3H), 1.06 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.6, 166.5, 149.1 (d, *J* = 1.5 Hz), 135.7, 132.4, 131.0, 128.6, 128.4, 128.2, 121.1, 120.6 (q, *J* = 256 Hz), 67.5, 55.3, 42.7, 40.9, 14.3, 12.8;

^{19}F NMR ($CDCl_3$, 377 MHz) δ -57.8

HRMS (LCMS ESI): calcd for $C_{21}H_{23}F_3NO_4$ $[M+H]^+$: 410.1574 Found: 410.1577

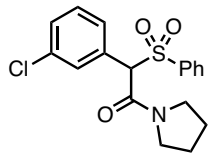


2-33 Prepared according to the General Procedure A from the corresponding arylboroxine (138 mg, 0.330 mmol, 2.0 equiv. Ar–B) and amido ester (111 mg, 0.50 mmol, 1.0 equiv.), 2.5 h. Isolated as a colorless oil in 57% yield after purification by column chromatography (4:1 to 1:1 Hex/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44 – 7.39 (m, 3H), 7.25 (m, 1H), 7.19 (m, 1H), 7.12 – 7.04 (m, 4H), 4.55 (s, 1H), 4.19 – 4.14 (m, 2H), 3.28 (s, 3H), 1.25 (t, *J* = 7.0, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.4, 167.4, 143.3, 135.6, 134.1, 130.1, 129.8, 129.6, 128.7, 128.2, 128.0, 127.9, 61.9, 55.5, 38.0, 14.2;

HRMS (LCMS ESI): calcd for $C_{18}H_{19}ClNO_3$ $[M+H]^+$: 332.1048. Found 332.1047.

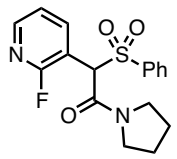


2-34 Prepared according to the General Procedure A from the corresponding arylboroxine (83 mg, 0.20 mmol, 1.2 equiv. Ar–B) and sulfonyl amide (127 mg, 0.50 mmol, 1.0 equiv.), stirred at room temperature, 48 h. Isolated as a white solid in 86% yield after purification by column chromatography (3:1 to 1:3 Hex/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62 – 7.57 (m, 3H), 7.42 – 7.39 (m, 2H), 7.36 (m, 1H), 7.33 – 7.32 (m, 1H), 7.29 (m, 1H), 7.20 (m, 1H), 5.19 (s, 1H), 3.61 (m, 1H), 3.55 (m, 1H), 3.39 (m, 1H), 3.26 (m, 1H), 1.96 – 1.78 (m, 4H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.3, 136.1, 134.6, 134.2, 130.81, 130.78, 130.7, 129.81, 129.80, 128.9, 128.3, 73.8, 47.3, 46.6, 26.2, 24.4;

HRMS (LCMS ESI): calcd for $C_{18}H_{19}ClNO_3S$ $[M+H]^+$: 364.0769. Found 364.0769.



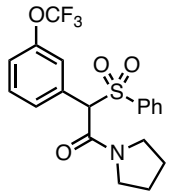
2-35 Prepared according to the General Procedure A from the corresponding arylboroxine (74 mg, 0.20 mmol, 1.2 equiv. Ar–B) and sulfonyl amide (127 mg, 0.50 mmol, 1.0 equiv.), stirred at room temperature, 48 h. Isolated as a white solid in 63% yield after purification by column chromatography (1:1 Hex/EtOAc to 100% EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.50 (m, 1H), 8.17 (m, 1H), 7.69 – 7.62 (m, 3H), 7.49 – 7.46 (m, 2H), 7.18 (m, 1H), 5.62 (d, *J* = 1.3 Hz, 1H), 3.72 (m, 1H), 3.55 (m, 1H), 3.50 – 3.39 (m, 2H), 2.00 – 1.64 (m, 4H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.2 (d, *J* = 237 Hz), 160.8, 148.5 (d, *J* = 15 Hz), 143.5 (d, *J* = 2.5 Hz), 136.9, 134.6, 129.7, 129.1, 121.8 (d, *J* = 4.25 Hz), 112.1 (d, *J* = 28 Hz), 63.8 (d, *J* = 2.5 Hz), 47.6, 46.9, 26.1, 24.4;

^{19}F NMR ($CDCl_3$, 469 MHz) δ -74.3 (d, *J* = 9.2 Hz)

HRMS (LCMS ESI): calcd for $C_{17}H_{18}FN_2O_3S$ $[M+H]^+$: 349.1017. Found 349.1017.



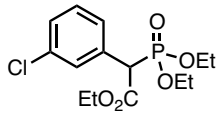
2-36 Prepared according to the General Procedure A from the corresponding arylboroxine (113 mg, 0.20 mmol, 1.2 equiv. Ar–B) and sulfonyl amide (127 mg, 0.50 mmol, 1.0 equiv.), stirred at room temperature, 48 h. Isolated as a white solid in 82% yield after purification by column chromatography (4:1 Hex/EtOAc to 100% EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.60 – 7.57 (m, 3H), 7.43 – 7.38 (m, 3H), 7.32 (m, 1H), 7.24 (br, 1H), 7.20 (m, 1H), 5.24 (s, 1H), 3.70 (m, 1H), 3.58 (m, 1H), 3.40 (m, 1H), 3.30 (m, 1H), 1.99 (m, 1H), 1.91 – 1.81 (m, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.2, 149.2 (d, J = 1.5 Hz), 136.0, 134.2, 131.2, 130.7, 129.9, 129.4, 128.4, 123.2, 122.1, 120.4 (q, J = 257 Hz), 73.7, 47.4, 46.7, 26.2, 24.4;

^{19}F NMR ($CDCl_3$, 469 MHz) δ -57.7

HRMS (LCMS ESI): calcd for $C_{19}H_{19}F_3NO_4S$ $[M+H]^+$: 414.0981. Found 414.0983.

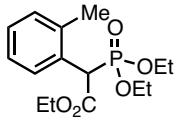


2-37 Prepared according to the General Procedure A from the corresponding arylboroxine (138 mg, 0.330 mmol, 2.00 equiv. Ar–B) and phosphonyl ester (112 mg, 0.500 mmol, 1.00 equiv.), 40 h. Isolated as a yellow oil in 53% yield after purification by column chromatography (4:1 to 1:3 Hex/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.53 (m, 1H), 7.42 (m, 1H), 7.31 – 7.28 (m, 2H), 4.28 – 4.18 (m, 3H), 4.13 – 4.00 (m, 4H), 1.30 – 1.26 (m, 6H), 1.23 (t, *J* = 5.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.3 (d, *J* = 4.0 Hz), 134.4 (d, *J* = 2.8 Hz), 133.1 (d, *J* = 8.5 Hz), 129.8 (overlapping doublets), 128.3 (d, *J* = 2.8 Hz), 128.0 (d, *J* = 6.3 Hz), 63.7 (d, *J* = 6.8 Hz), 63.4 (d, *J* = 7.3 Hz), 62.2, 52.0 (d, *J* = 134 Hz), 16.4 (overlapping doublets), 14.2;

HRMS (LCMS ESI): calcd for $C_{14}H_{21}ClO_5P$ $[M+H]^+$: 335.0815. Found 335.0812.

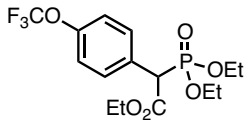


2-38 Prepared according to the General Procedure A from the corresponding arylboroxine (118 mg, 0.330 mmol, 2.00 equiv. Ar–B) and phosphonyl ester (112 mg, 0.500 mmol, 1.00 equiv.), 48 h. Isolated as a yellow oil in 59% yield after purification by column chromatography (4:1 Hex/EtOAc to 100% EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.76 (m, 1H), 7.20 – 7.14 (m, 3H), 4.52 (d, *J* = 26.0 Hz, 1H), 4.22 – 4.01 (m, 5H), 3.92 (m, 1H) 2.37 (s, 3H), 1.23 (m, 6H), 1.14 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.9 (d, *J* = 2.9 Hz), 136.7 (d, *J* = 7.8 Hz), 130.5 (d, *J* = 2.0 Hz), 129.6 (d, *J* = 8.0 Hz), 129.4 (d, *J* = 4.9 Hz), 127.9 (d, *J* = 2.9 Hz), 126.2 (d, *J* = 2.9 Hz), 63.3 (d, *J* = 6.3 Hz), 63.0 (d, *J* = 7.0 Hz), 61.8, 47.5 (d, *J* = 138 Hz), 20.1, 16.3 (d, *J* = 5.9 Hz), 16.2 (d, *J* = 5.9 Hz), 14.1;

HRMS (LCMS ESI): calcd for $C_{15}H_{24}O_5P$ $[M+H]^+$: 315.1356. Found 315.1356.



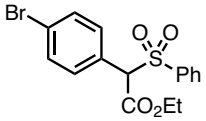
2-39 Prepared according to the General Procedure A from the corresponding arylboroxine (188 mg, 0.330 mmol, 2.00 equiv. Ar–B) and phosphonyl ester (112 mg, 0.500 mmol, 1.00 equiv.), 48 h. Isolated as a pale yellow oil in 48% yield after purification by column chromatography (4:1 Hex/EtOAc to 100% EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.57 – 7.55 (m, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 4.28 – 4.18 (m, 3H), 4.12 – 4.04 (m, 3H), 4.02 (m, 1H), 1.30 – 1.26 (m, 6H), 1.20 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.4 (d, *J* = 3.8 Hz), 149.1, 131.3 (d, *J* = 6.3 Hz), 129.9 (d, *J* = 8.5 Hz), 121.0, 120.6 (q, *J* = 256 Hz), 63.6 (d, *J* = 6.8 Hz), 63.4 (d, *J* = 7.0 Hz), 62.2, 51.7 (d, *J* = 133 Hz), 16.4 (overlapping doublets), 14.2;

^{19}F NMR ($CDCl_3$, 377 MHz) d -57.9

HRMS (LCMS ESI): calcd for $C_{15}H_{21}F_3O_6P$ $[M+H]^+$: 385.1022. Found 385.1023.

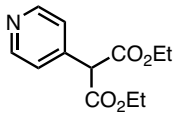


2-40 Prepared according to the General Procedure A from the corresponding arylboroxine (137 mg, 0.250 mmol, 1.50 equiv. Ar–B) and sulfonyl ester (114 mg, 0.500 mmol, 1.00 equiv.), stirred at 40 °C, 72 h. Isolated as an white solid in 56% yield after purification by column chromatography (20:1 to 10:1 Hex/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.66 – 7.62 (m, 3H), 7.49 – 7.43 (m, 4H), 7.27 – 7.24 (m, 2H), 5.04 (s, 1H), 4.26 – 4.14 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.6, 136.4, 134.5, 131.99, 131.95, 130.1, 128.9, 127.0, 124.5, 74.8, 62.9, 14.0;

HRMS (LCMS ESI): calcd for $C_{16}H_{16}BrO_4S$ $[M+H]^+$: 382.9947. Found 382.9954.

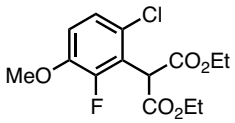


2-41 Prepared according to the General Procedure B from the corresponding neopentyl boronic ester (48 mg, 0.25 mmol, 1.0 equiv.) and diethyl malonate (80 mg, 0.50 mmol, 2.0 equiv.), stirred at 35 °C, 44 h. Isolated as a white solid in 53% yield after purification by column chromatography (5% MeOH/CH_2Cl_2, treated with ~0.5% NH_4OH).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.61 (br, 2H), 7.33 (br, 2H), 4.57 (s, 1H), 4.26 – 4.17 (m, 4H), 1.25 (t, J = 9.0 Hz, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.0, 150.1, 141.4, 124.5, 62.4, 57.4, 14.1;

HRMS (LCMS ESI): calcd for $C_{12}H_{16}NO_4$ $[M+H]^+$: 238.1074. Found 238.1074.



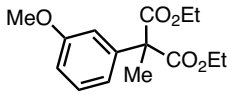
2-42 Prepared according to the General Procedure B from the corresponding neopentyl boronic ester (136 mg, 0.500 mmol, 1.00 equiv.) and diethyl malonate (160 mg, 1.00 mmol, 2.00 equiv.), stirred at 35 °C, 48 h. Isolated as an off-white solid in 75% yield after purification by column chromatography (10:1 to 4:1 Hex/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.14 (dd, *J* = 2.2, 8.7 Hz, 1H), 6.90 (t, *J* = 9.0 Hz, 1H), 5.12 (s, 1H), 4.26 (q, *J* = 7.5 Hz, 4H), 3.88 (s, 3H), 1.28 (t, *J* = 7.5 Hz, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.8, 151.7 (d, *J* = 250 Hz), 147.2 (d, *J* = 11 Hz), 126.0 (d, *J* = 4.25 Hz), 124.6 (d, *J* = 4.0 Hz), 121.6 (d, *J* = 14.5 Hz), 113.8 (d, *J* = 2.3 Hz), 62.3, 56.7, 51.6, 14.1;

^{19}F NMR ($CDCl_3$, 376 MHz) δ -129.6 (d, *J* = 9.0 Hz)

HRMS (LCMS ESI): calcd for $C_{14}H_{17}ClFO_5$ $[M+H]^+$: 319.0743. Found 319.0745.

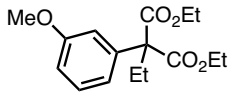


2-43 Prepared according to the General Procedure A from the corresponding arylboroxine (201 mg, 0.500 mmol, 3.0 equiv. Ar–B) and diethyl methylmalonate (87 mg, 0.50 mmol, 1.0 equiv.), stirred at room temperature, 72 h. Isolated as a colorless oil in 57% yield after purification by column chromatography (10:1 to 4:1 Hex/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26 (t, *J* = 10 Hz, 1H), 6.96 – 6.94 (m, 2H), 6.84 (m, 1H), 4.28 – 4.19 (m, 4H), 3.80 (s, 3H), 1.85 (s, 3H), 1.26 (t, *J* = 7.5 Hz, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.6, 159.5, 140.0, 129.2, 120.0, 114.1, 112.8, 61.8, 58.9, 55.4, 22.6, 14.1;

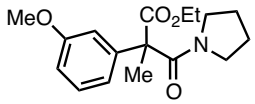
HRMS (LCMS ESI): calcd for $C_{15}H_{21}O_5$ $[M+H]^+$: 281.1384. Found 281.1386.



2-44 Prepared according to the General Procedure A from the corresponding arylboroxine (201 mg, 0.500 mmol, 3.0 equiv. Ar–B) and diethyl ethylmalonate (94 mg,

0.50 mmol, 1.0 equiv.), stirred at room temperature, 72 h. Isolated as a colorless oil in 49% yield after purification by column chromatography (15:1 to 10:1 Hex/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28 (m, 1H), 7.06 – 7.02 (m, 2H), 6.85 (dd, *J* = 2.3, 8.13 Hz, 1H), 4.25 (m, 4H), 3.83 (s, 3H), 2.36 (q, *J* = 7.5 Hz, 2H), 1.27 (t, *J* = 7.0 Hz, 6H), 0.92 (t, *J* = 7.5 Hz, 3H);

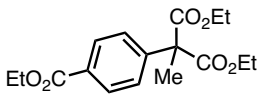


2-45 Prepared according to the General Procedure A from the corresponding arylboroxine (101 mg, 0.250 mmol, 3.0 equiv. Ar–B) and amido ester (50 mg, 0.25 mmol, 1.0 equiv.), stirred at room temperature, 72 h. Isolated as a colorless oil in 47% yield after purification by column chromatography (4:1 to 2:3 Hex/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.22 (t, *J* = 8.0 Hz, 1H), 7.03 (t, *J* = 2.0 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.79 (dd, *J* = 2.0, 8.0 Hz, 1H), 4.23 (q, *J* = 7.0 Hz, 2H), 3.78 (s, 3H), 3.58 – 3.54 (m, 2H), 2.89 (m, 1H), 2.73 (m, 1H), 1.78 (s, 3H), 1.75 – 1.61 (m, 4H), 1.27 (t, *J* = 7.5 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.0, 169.5, 159.7, 141.4, 129.5, 119.5, 113.3, 112.4, 61.6, 59.4, 55.3, 47.5, 47.1, 26.50, 26.48, 23.6, 14.2;

HRMS (LCMS ESI): calcd for $C_{17}H_{24c}NO_4$ $[M+H]^+$: 306.1700. Found 306.1701.



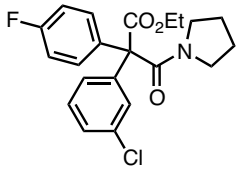
2-46 Prepared according to the General Procedure A from the corresponding arylboroxine (264 mg, 0.500 mmol, 3.0 equiv. Ar–B) and diethyl methylmalonate (87

mg, 0.50 mmol, 1.0 equiv.), stirred at room temperature, 72 h. Isolated as a colorless oil in 40% yield after purification by column chromatography (10:1 to 7:1 Hex/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.01 (m, 2H), 7.44 (m, 2H), 4.36 (q, *J* = 7.5 Hz, 2H), 4.26 – 4.19 (m, 4H), 1.86 (s, 3H), 1.37 (t, *J* = 8.5 Hz, 3H), 1.24 (t, *J* = 7.0 Hz, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.1, 166.3, 143.3, 129.8, 129.4, 127.6, 62.0, 61.1, 59.0, 22.4, 14.4, 14.0;

HRMS (LCMS ESI): calcd for $C_{17}H_{23}O_6$ $[M+H]^+$: 323.1489. Found 323.1487.



2-47 Prepared according to the General Procedure A from the corresponding arylboroxine (37 mg, 0.30 mmol, 1.2 equiv. Ar–B) and amido ester (74 mg, 0.25 mmol, 1.0 equiv.), stirred at 40 °C, 25 h. Isolated as a colorless oil in 46% yield after purification by column chromatography (4:1 Hex/EtOAc to 100% EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.43 (br, 1H), 7.36 – 7.33 (m, 2H), 7.28 – 7.21 (m, 3H), 7.02 – 6.99 (m, 2H), 4.31 (q, *J* = 7.0 Hz, 2H), 3.61 (t, *J* = 7.0 Hz, 2H), 2.85 (t, *J* = 6.5 Hz, 2H), 1.82 – 1.78 (m, 2H), 1.71 – 1.66 (m, 2H), 1.29 (t, *J* = 7.0 Hz, 3H);

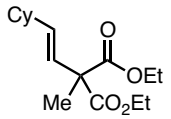
^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.9, 167.5, 162.2 (d, *J* = 247 Hz), 140.7, 134.1, 131.3 (d, *J* = 8.0 Hz), 129.7, 129.3, 128.1, 127.9, 127.8, 115.1 (d, *J* = 22 Hz), 67.7, 62.4, 47.7, 47.1, 26.4, 23.6, 14.1;

^{19}F NMR ($CDCl_3$, 377 MHz) δ -114.5

HRMS (LCMS ESI): calcd for $C_{21}H_{22}ClFNO_3$ $[M+H]^+$: 390.1267. Found 390.1273.

^{13}C NMR ($CDCl_3$, 125 MHz) d 170.8, 159.4, 138.4, 129.1, 120.6, 114.6, 112.7, 63.2, 61.5, 55.4, 29.2, 14.2, 9.5;

HRMS (LCMS ESI): calcd for $C_{16}H_{23}O_5$ $[M+H]^+$: 295.1540. Found 295.1541.

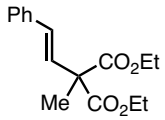


2-48 Prepared according to the General Procedure B from the corresponding neopentyl boronic ester (44.4 mg, 0.200 mmol, 1.00 equiv.) and diethyl methylmalonate (69.7 mg, 0.400 mmol, 2.00 equiv.), stirred at 35 °C, 72 h. Isolated as a colorless oil in 70% yield after purification by column chromatography (20:1 to 15:1 Hex/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.86 (dd, *J* = 1.4, 16 Hz, 1H), 5.50 (dd, *J* = 6.8, 16 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 4H), 1.98 (m, 1H), 1.74 – 1.67 (m, 4H), 1.62 (m, 1H), 1.50 (s, 3H), 1.29 – 1.20 (m, 8H), 1.15 (m, 1H), 1.10 – 1.02 (m, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.7, 137.9, 125.8, 61.5, 55.5, 40.8, 32.8, 26.3, 26.1, 20.6, 14.1;

HRMS (LCMS ESI): calcd for $C_{16}H_{27}O_4$ $[M+H]^+$: 283.1904. Found 283.1899.

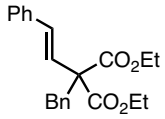


2-49 Prepared according to the General Procedure B from the corresponding neopentyl boronic ester (43.2 mg, 0.200 mmol, 1.00 equiv.) and diethyl methylmalonate (69.7 mg, 0.400 mmol, 2.00 equiv.), stirred at 35 °C, 48 h. Isolated as a colorless oil in 61% yield after purification by column chromatography (toluene).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42 – 7.40 (m, 2H), 7.33 – 7.30 (m, 2H), 7.26 m (1H), 6.70 (d, *J* = 16 Hz, 1H), 6.51 (d, *J* = 16 Hz, 1H), 4.26 – 4.20 (m, 4H), 1.68 (s, 3H), 1.27 (t, *J* = 7.5 Hz, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.2, 136.7, 130.9, 128.7, 128.0, 127.8, 126.7, 61.8, 55.8, 20.5, 14.2;

HRMS (LCMS ESI): calcd for $C_{16}H_{21}O_4$ $[M+H]^+$: 277.1434. Found 277.1430.

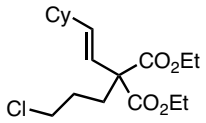


2-50 Prepared according to the General Procedure B from the corresponding neopentyl boronic ester (43.2 mg, 0.200 mmol, 1.00 equiv.) and diethyl benzylmalonate (100 mg, 0.400 mmol, 2.00 equiv.), stirred at 35 °C, 48 h. Isolated as a white solid in 57% yield after purification by column chromatography (toluene).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 – 7.34 (m, 2H), 7.34 – 7.28 (m, 2H), 7.28 – 7.21 (m, 4H), 7.15 – 7.13 (m, 2H), 4.24 (q, *J* = 7.0 Hz, 4H), 3.50 (s, 2H), 1.26 (t, *J* = 7.0 Hz, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.3, 136.7, 135.9, 131.5, 130.3, 128.7, 128.3, 128.0, 127.09, 127.08, 126.7, 61.8, 60.9, 42.8, 14.1;

HRMS (LCMS ESI): calcd for $C_{22}H_{25}O_4$ $[M+H]^+$: 353.1747. Found 353.1745.



2-51 Prepared according to the General Procedure B from the corresponding neopentyl boronic ester (44.4 mg, 0.200 mmol, 1.00 equiv.) and diethyl 2-(3-chloropropyl)malonate (94.7 mg, 0.400 mmol, 2.00 equiv.), stirred at 35 °C, 72 h. Isolated as a colorless oil in 50% yield after purification by column chromatography (20:1 to 15:1 Hexane/EtOAc).

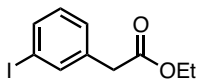
^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.89 (dd, *J* = 16 Hz, 1.5 Hz, 1H), 5.52 (dd, *J* = 16 Hz, 7.0 Hz, 1H), 4.21 – 4.14 (m, 4H), 3.49 (t, *J* = 6.5 Hz, 2H), 2.15 – 2.12 (m, 2H), 2.0 (br, 1H), 1.72 – 1.61 (m, 7H), 1.27 – 1.21 (m, 8H), 1.19 – 1.03 (m, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8, 139.0, 123.9, 61.5, 58.7, 45.0, 40.9, 32.9, 32.7, 27.8, 26.2, 26.0, 14.1;

HRMS (LCMS ESI): calcd for $C_{18}H_{30}ClO_4$ $[M+H]^+$: 345.1827. Found 345.1823.

2.5.2 General Procedures and Characterization for Section 2.3

General Procedure A: $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.30 equiv.) and arylboronic ester (1.00 mmol, 1.20 to 2.00 equiv.) were added sequentially to a 1 dram vial charged with a stirbar. The carboxylic acid (0.500 mmol, 1.00 equiv.) was added as a solution in anhydrous DMA (0.6 mL). Additional DMA (2 x 0.3 mL) was used to quantitatively transfer the solution to the reaction mixture. The solution was stirred until a homogeneous pale blue solution was formed (approximately 2 minutes, partially heterogeneous mixtures obtained when using increased Cu loadings), followed by the addition of triethylamine (0.42 mL, 3.0 mmol, 6.0 equiv.). The vial was sealed with a PTFE-lined cap, exposed to air via a needle, and gently stirred at room temperature. Upon completion of the reaction (24 to 72 h), the reaction mixture was diluted with EtOAc (40 mL), and washed sequentially with NH_4Cl (15 mL), 0.5 M NaOH (2 x 20 mL), and brine (15 mL). The organic layer was dried with Na_2SO_4, filtered, concentrated *in vacuo,* and purified by silica gel chromatography. No difference was observed if reactions were prepared in an atmosphere-controlled glovebox, then exposed to ambient air.



2-53 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (316 mg, 1.00 mmol, 2.00 equiv.) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 71 h.

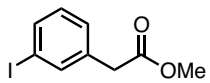
Isolated as a colorless oil in 83% yield after purification by column chromatography (15:1 Hexane/EtOAc).

[Gram Scale Reaction] To a 50 mL pear-shaped round bottomed flask in air was added $Cu(OTf)_2$ (942 mg, 2.16 mmol, 0.30 equiv.), 3-iodophenyl neopentyl boronic ester (4.55 g, 14.4 mmol, 2.0 equiv.), DMA (18 mL) and mono-ethyl malonate (951 mg, 7.2 mmol, 1.0 equiv.). The mixture was stirred for 10 minutes to generate a suspension to which NEt_3 (6.0 mL, 43 mmol, 6 equiv.) was added. After 24 hours the reaction was diluted with saturated aqueous NH_4Cl and EtOAc, the organic layer was extracted, washed with aqueous KOH and brine, dried with Na_2SO_4, filtered, and concentrated *in vacuo* and purified by silica gel chromatography (Hexane/EtOAc gradient). The product **2-53** was obtained as a colorless oil in 76% (run 1) and 78% (run 2) yield.

^{1}H NMR ($CDCl_3$, 500 MHz) d 7.65 (m, 1H), 7.61 (m, 1H), 7.26 (m, 1H), 7.06 (m, 1H), 4.16 (q, J = 7.0 Hz, 2H), 3.55 (s, 2H), 1.26 (t, J = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) d 171.1, 138.4, 136.5, 136.3, 130.3, 128.7, 94.5, 61.2, 40.9, 14.3;

HRMS (LCMS ESI): calcd for $C_{10}H_{11}INaO_2$ $[M+Na]^+$: 312.9696. Found 312.9696.



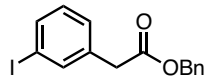
2-54 Prepared according to the General Procedure from the corresponding neopentyl boronic ester (316 mg, 1.00 mmol, 2.00 equiv.) and mono-methyl malonate (59.0 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.),

66 h. Isolated as a light yellow oil in 78% yield after purification by column chromatography (Hexane/EtOAc gradient).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.65 (m 1H), 7.61(m, 1H), 7.25 (m, 1H) 7.06 (t, *J* = 6.3 Hz, 1H), 3.70 (s 3H), 3.57 (s, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 171.5, 138.4, 136.4, 136.3, 130.4, 128.7, 94.5, 52.3, 40.7;

HRMS (EI): calcd for $C_9H_9IO_2$ M^+: 275.9647. Found 275.9649.

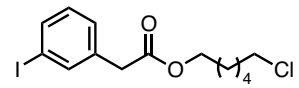


2-55 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (316 mg, 1.00 mmol, 2.00 equiv.) and mono-benzyl malonate (97.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 48 h. Isolated as a colorless oil in 66% yield after purification by column chromatography (20:1 to 10:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65 (m, 1H), 7.61 (m, 1H), 7.30 – 7.38 (m, 5H), 7.25 (m, 1H), 7.06 (m, 1H), 5.14 (s, 2H), 3.61 (s, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.7, 138.3, 136.3, 136.1, 135.7, 130.3, 128.7, 128.6, 128.4, 128.2, 94.4, 66.9, 40.7;

HRMS (LCMS ESI): calcd for $C_{15}H_{13}INaO_2$ $[M+Na]^+$: 374.9852 Found 374.9854.

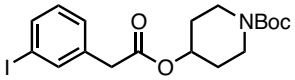


2-56 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (316 mg, 1.00 mmol, 2.00 equiv.) and mono-1-chlorohexyl malonate (120 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 60 h. Isolated as a colorless oil in 93% yield after purification by column chromatography (40:1 to 5:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65 (m, 1H), 7.61 (m, 1H), 7.25 (m, 1H), 7.06 (m, 1H), 4.10 (t, J = 6.5 Hz, 2H), 3.55 (s, 2H), 3.52 (t, J = 6.7 Hz, 2H), 1.78 – 1.74 (m, 2H), 1.66 – 1.61 (m, 2H), 1.46 – 1.42 (m, 2H), 1.36 – 1.31 (m, 2H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 171.0, 138.3, 136.4, 136.2, 130.3, 128.6, 94.4, 65.0, 45.0, 40.9, 32.5, 28.4, 26.5, 25.2;

HRMS (LCMS ESI): calcd for $C_{14}H_{18}ClINaO_2$ $[M+Na]^+$: 402.9932. Found 402.9932.

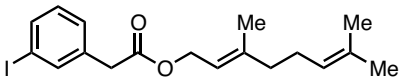


2-57 Prepared according to the General Procedure from the corresponding neopentyl boronic ester (316 mg, 1.00 mmol, 2.00 equiv.) and mono-4-NBoc piperidyl malonate (143.6 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 66 h. Isolated as a colorless oil in 49% yield after purification by column chromatography (4:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.65 (m 1H), 7.61(m, 1H), 7.25 (m, 1H) 7.06 (t, *J* = 7.7 Hz, 1H), 4.94 (m, 1H), 3.62 (br, 2H), 3.55(s, 2H), 3.23 (m, 2H), 1.81 (br, 2H), 1.58 (br, 2H), 1.46 (s, 9H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.3, 154.8, 138.3, 136.4, 136.3, 130.4, 128.6, 94.5, 79.9, 70.6, 41.2, 41.1(br), 30.6, 28.6;

HRMS (LCMS ESI): calcd for $C_{18}H_{24}INNaO_4$ $[M+Na]^+$: 468.0642. Found 468.0641.

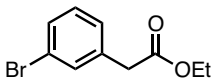


2-58 Prepared according to the General Procedure from the corresponding neopentyl boronic ester (316 mg, 1.00 mmol, 2.00 equiv.) and mono-geranyl malonate (8:1 mixture of *E*/*Z* isomers, 120 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 73 h. Isolated as a colorless oil (mixture of *E*/*Z* isomers [8:1] as in the geraniol starting material) in 45% yield after purification by column chromatography (Hexane/EtOAc gradient).

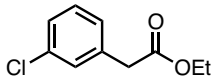
^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.65 (m, 1H), 7.60 (m, 1H), 7.25 (d, *J* = 8.5 Hz, 1H) 7.05 (t, *J* = 7.8 Hz, 1H), 5.33 (m, 1H), 5.08 (m, 1H), 4.62 (d, *J* = 7.0 Hz, 2H, *E* isomer), 4.60 (d, *J* = 7.3 Hz, 2H, *Z* isomer), 3.56 (s, 2H), 2.13 – 2.07 (m, 2H), 2.07 – 2.02 (m, 2H), 1.70 (m, 6H), 1.60 (s, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.1, 142.9, 138.4, 136.5, 136.3, 132.0, 130.3, 128.7, 123.9, 118.1, 94.5, 62.1, 40.9, 40.0, 26.4, 25.8, 17.9, 16.7;

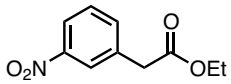
HRMS (LCMS ESI): calcd for $C_{18}H_{23}INaO_2$ $[M+Na]^+$: 421.0635. Found 421.0635.



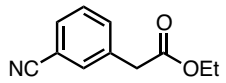
2-59 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (268 mg, 1.00 mmol, 2.00 equiv.) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 72 h. Isolated as a colorless oil in 82% yield after purification by column chromatography (15:1 Hexane/EtOAc). Spectroscopic data agreed with that reported.



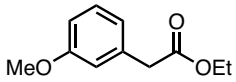
2-60 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (197 mg, 0.880 mmol, 2.00 equiv.) and mono-ethyl malonate (58.1 mg, 0.440 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (47.7 mg, 0.132 mmol, 0.300 equiv.), 62 h. Isolated as a colorless oil in 77% yield after purification by column chromatography (20:1 to 10:1 Hexane/EtOAc). Spectroscopic data agreed with that reported.



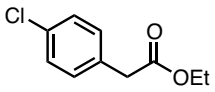
2-61 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (235 mg, 1.00 mmol, 2.00 equiv.) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 67 h. Isolated as a colorless oil in 68% yield after purification by column chromatography (10:1 to 1:1 Hexane/EtOAc). Spectroscopic data agreed with that reported.



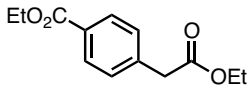
2-62 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (215 mg, 1.00 mmol, 2.00 equiv.) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 60 h. Isolated as a light beige solid in 65% yield after purification by column chromatography (4:1 Hexane/EtOAc). Spectroscopic data agreed with that reported.



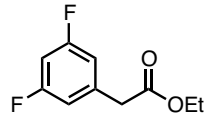
2-63 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (220 mg, 1.00 mmol, 2.00 equiv.) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (181 mg, 0.500 mmol, 1.00 equiv.), 50 h. Isolated as a colorless oil in 67% yield after purification by column chromatography (50:1 to 4:1 Hexane/EtOAc). Spectroscopic data agreed with that reported.



2-64 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (225 mg, 1.00 mmol, 2.00 equiv.) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 72 h. Isolated as a colorless oil in 68% yield after purification by column chromatography (15:1 Hexane/EtOAc). Spectroscopic data agreed with that reported.



2-65 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (262 mg, 1.00 mmol, 2.00 equiv.) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 70 h. Isolated as a colorless oil in 75% yield after purification by column chromatography (15:1 Hexane/EtOAc). Spectroscopic data agreed with that reported.



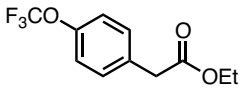
2-66 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (226 mg, 1.00 mmol, 2.00 equiv.) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 42 h. Isolated as a colorless oil in 77% yield after purification by column chromatography (10:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.84 – 6.80 (m, 2H), 6.72 (m, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.59 (s, 2H), 1.27 (t, J = 7.1 Hz, 3H);

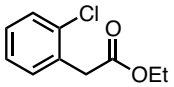
^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.4, 163.0 (dd, J = 249, 12.9 Hz), 137.6, 112.4, 102.7, 61.3, 41.0, 14.2;

^{19}F NMR ($CDCl_3$, 469 MHz) δ -110.0 (t, J = 8.2 Hz);

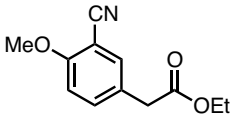
HRMS (EI): calcd for $C_{10}H_{10}O_2F_2$ $[M]^+$: 200.0649. Found 200.0647.



2-67 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (274 mg, 1.00 mmol, 2.00 equiv.) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 60 h. Isolated as a colorless oil in 60% yield after purification by column chromatography (50:1 to 4:1 Hexane/EtOAc). Spectroscopic data agreed with that reported.



2-68 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (225 mg, 1.00 mmol, 2.00 equiv.) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 42 h. Isolated as a colorless oil in 47% yield after purification by column chromatography (10:1 Hexane/EtOAc). Spectroscopic data agreed with that reported.

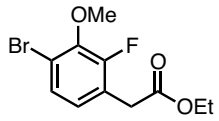


2-69 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (245 mg, 1.00 mmol, 2.00 equiv.) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 62 h. Isolated as a white solid in 69% yield after purification by column chromatography (2:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.46 (m, 2H), 6.92 (m, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.92 (s, 3H), 3.55 (s, 2H), 1.26 (t, J = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.9, 160.4, 135.4, 134.4, 126.8, 116.3, 111.5, 102.0, 61.2, 56.2, 39.9, 14.2;

HRMS (LCMS ESI): calcd for $C_{12}H_{13}NNaO_3$ $[M+Na]^+$: 242.0788. Found 242.0789.



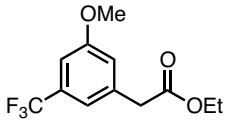
2-70 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (317 mg, 1.00 mmol, 2.00 equiv.) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 62 h. Isolated as a light yellow oil in 52% yield after purification by column chromatography (10:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 (m, 1H), 6.87 (m, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.95 (s, 3H), 3.62 (s, 2H), 1.26 (t, J = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.1, 154.7 (d, J = 251 Hz), 145.5 (d, J = 13 Hz), 127.8 (d, J = 41 Hz), 126.2 (d, J = 41 Hz), 122.7 (d, J = 14.7 Hz), 116.4 (d, J = 3.0 Hz), 61.5 (d, J = 4.3 Hz), 61.3, 34.4 (d, J = 3.6 Hz), 14.2;

^{19}F NMR ($CDCl_3$, 377 MHz) δ -130.6;

HRMS (LCMS ESI): calcd for $C_{11}H_{12}BrFNaO_3$ $[M+Na]^+$: 312.9846. Found 312.9842.



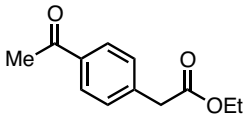
2-71 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (288 mg, 1.00 mmol, 2.00 equiv.) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 48 h. Isolated as a colorless oil in 79% yield after purification by column chromatography (10:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.13 (m, 1H), 7.02 (m, 2H), 4.17 (q, *J* = 7.0 Hz, 2H), 3.84 (s, 3H), 3.63 (s, 2H), 1.26 (t, *J* = 7.1 Hz, 3H);

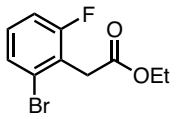
^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8, 159.9, 136.5, 132.0 (q, *J* = 34 Hz), 123.9 (q, *J* = 271 Hz), 118.6, 118.4, 109.5, 61.2, 55.5, 41.2, 14.2;

^{19}F NMR ($CDCl_3$, 377 MHz) δ -62.7;

HRMS (EI): calcd for $C_{12}H_{13}F_3O_3$ $[M]^+$: 262.0817. Found 262.0814.



2-72 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (232 mg, 1.00 mmol, 2.00 equiv.) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 67 h. Isolated in 75% yield after purification by column chromatography (6:1 to 1:1 Hexane/EtOAc) as a white solid. Spectroscopic data agreed with that reported.



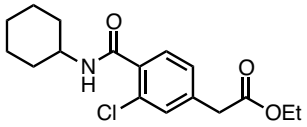
2-73 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (430 mg, 1.50 mmol, 3.00 equiv.) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 61 h. Isolated as a colorless oil in 54% yield after purification by column chromatography (30:1 to 4:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 (m, 1H), 7.15 (m, 1H), 7.04 (m, 1H), 4.19 (q, *J* = 7.4 Hz, 2H), 3.86 (d, *J* = 1.9 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.6, 161.4 (d, *J* = 244 Hz), 129.6 (d, *J* = 9.4 Hz), 128.4 (d, *J* = 4.4 Hz), 126.0 (d, *J* = 4.4 Hz), 123.0 (d, *J* = 18.9 Hz), 114.6 (d, *J* = 23.4 Hz), 61.3, 34.7, 14.2;

^{19}F NMR ($CDCl_3$, 469 MHz) δ -111.3;

HRMS (LCMS ESI): calcd for $C_{10}H_{10}BrFNaO_2$ $[M+Na]^+$: 282.9740. Found 282.9743.

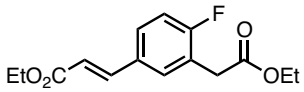


2-74 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (262 mg, 0.750 mmol, 1.50 equiv.) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (90.4 mg, 0.250 mmol, 0.500 equiv.), 54 h. Isolated as a white solid in 55% yield after purification by column chromatography (4:1 to 1:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.59 (m, 1H), 7.31 (m, 1H), 7.21 (m, 1H), 6.08 (br, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.99 (m, 1H), 3.58 (s, 2H), 2.05 – 1.97 (m, 2H), 1.77 – 1.68 (m, 2H), 1.63 (m, 1H), 1.48 – 1.36 (m, 2H), 1.31 – 1.15 (m, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 165.4, 137.7, 134.4, 131.0, 130.7, 130.4, 128.2, 61.3, 49.0, 40.8, 33.0, 25.6, 24.8, 14.3;

HRMS (LCMS ESI): calcd for $C_{17}H_{22}ClNNaO_3$ $[M+Na]^+$: 346.1180. Found 346.1185.



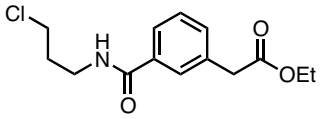
2-75 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (230 mg, 0.750 mmol, 1.50 equiv.) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 60 h. Isolated as a colorless oil in 55% yield after purification by column chromatography (30:1 to 4:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62 (d, J = 16 Hz, 1H), 7.45 – 7.42 (m, 2H), 7.07 (m, 1H), 6.35 (d, J = 16 Hz, 1H), 4.26 (q, J = 7.2 Hz, 2H), 4.18 (q, J = 7.2 Hz, 2H), 3.67 (s, 2H), 1.33 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.3, 166.9, 162.2 (d, J = 260 Hz), 143.2, 131.4, 130.9, 128.9, 122.3, 118.3, 116.2, 61.3, 60.6, 34.5, 14.4, 14.2;

^{19}F NMR ($CDCl_3$, 469 MHz) δ -113.9;

HRMS (LCMS ESI): calcd for $C_{15}H_{17}FNaO_4$ $[M+Na]^+$: 303.1003. Found 303.1005.

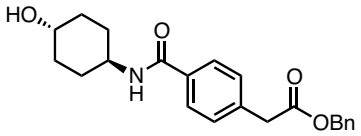


2-76 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (232 mg, 0.750 mmol, 1.50 equiv.) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (90.4 mg, 0.250 mmol, 0.500 equiv.), 61 h. Isolated as a colorless oil in 70% yield after purification by column chromatography (3:2 to 2:3 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.69 (m, 1H), 7.65 (m, 1H), 7.45 – 7.38 (m, 2H), 6.33 (br, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.68 – 3.60 (m, 6H), 2.13 (quint, J = 6.4 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.2, 167.5, 134.8 (2C), 132.6, 128.9, 127.9, 125.6, 61.1, 42.7, 41.2, 37.7, 32.1, 14.2;

HRMS (LCMS ESI): calcd for $C_{14}H_{18}ClNNaO_3$ $[M+Na]^+$: 306.0867. Found 306.0866.

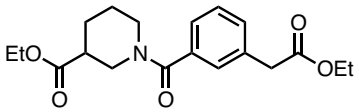


2-77 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (218 mg, 0.750 mmol, 1.50 equiv.) and mono-benzyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (90.4 mg, 0.250 mmol, 0.500 equiv.), 48 h. Crude NMR shows 54% NMR yield using trimethoxybenzene as internal standard. Isolated as a white solid in 39% yield after purification by column chromatography (6% to 7% $MeOH/CH_2Cl_2$).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 – 7.69 (m, 2H), 7.37 – 7.30 (m, 7H), 5.85 (br, 1H), 5.13 (s, 2H), 3.97 (m, 1H), 3.71 (s, 2H), 3.66 (m, 1H), 2.16 – 2.09 (m, 2H), 2.06 – 2.0 (m, 2H), 1.6 – 1.4 (m, 3H), 1.35 – 1.25 (m, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8, 166.6, 137.4, 135.7, 133.8, 129.6, 128.6, 128.4, 128.3, 127.2, 69.9, 66.9, 48.1, 41.2, 34.1, 31.0;

HRMS (LCMS ESI): calcd for $C_{22}H_{25}NNaO_4$ $[M+Na]^+$: 390.1676. Found 390.1674.

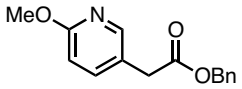


2-78 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (280 mg, 0.750 mmol, 1.50 equiv.) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 67 h. Isolated as a colorless oil in 63% yield after purification by column chromatography (4:1 Hexane/EtOAc to EtOAc).

^{1}H NMR (DMSO-d_6, 400 MHz, 120 °C) δ 7.34 (m, 1H), 7.30 (m, 1H), 7.20—7.25 (m, 2H), 4.01 – 4.11 (m, 4H), 3.98 (m, 1H), 3.67 (m, 1H), 3.64 (s, 2H), 3.22 (dd, J = 10 Hz, 13.2 Hz, 1H), 3.09 (m, 1H), 2.51 (m, 1H), 1.95 (m, 1H), 1.61—1.72 (m, 2H), 1.45 (m, 1H), 1.12 – 1.17 (m, 6H);

^{13}C NMR (DMSO- d_6, 100 MHz, 120 °C) δ 171.7, 169.9, 168.6, 135.9, 134.1, 129.4, 127.6, 126.8, 124.5, 59.6, 59.3, 45.3, 44.2, 40.2, 26.0, 23.1, 13.3, 13.2 (one peak missing, obscured by solvent signal);

HRMS (LCMS ESI): calcd for $C_{19}H_{25}NNaO_5$ $[M+Na]^+$: 370.1625. Found 370.1631.

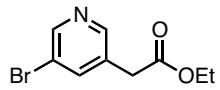


2-79 Prepared according to the General Procedure from the corresponding neopentyl boronic ester (165.8 mg, 0.75 mmol, 1.50 equiv.) and mono-benzyl malonate (97.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (90.4 mg, 0.250 mmol, 0.500 equiv.), 46h. Isolated as a colorless oil in 68% yield after purification by column chromatography (4:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.05 (d, J = 2.1 Hz, 1H), 7.52 (dd, J = 9.1, 2.1 Hz, 1H), 7.29 –7.38 (m, 5H), 6.72 (d, J = 9.1 Hz, 1H), 5.14 (s, 2H), 3.92 (s, 3H), 3.59 (s, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 171.2, 163.6, 147.1, 139.8, 135.8, 128.7, 128.5, 128.4, 122.4, 110.9, 67.0, 53.6, 37.7;

HRMS (LCMS ESI): calcd for $C_{15}H_{16}NO_3$ $[M+H]^+$: 258.1125. Found 258.1127.

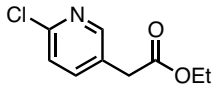


2-80 Prepared according to the General Procedure from the corresponding neopentyl boronic ester (202.4 mg, 0.75 mmol, 1.50 equiv.) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (90.4 mg, 0.250 mmol, 0.500 equiv.), 70 h. Isolated as a colorless oil in 47% yield after purification by column chromatography (2:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.60 (br s, 1H), 8.44 (br s, 1H), 7.81 (t, J = 2.1 Hz, 1H), 4.18 (q, J = 7.0 Hz, 2H), 3.60 (s, 2H), 1.27 (t, J = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.2, 149.8, 148.6, 139.6, 131.6, 120.8, 61.6, 38.1, 14.3;

HRMS (LCMS ESI): calcd for $C_9H_{11}BrNO_2$ $[M+H]^+$: 243.9968. Found 243.9965.

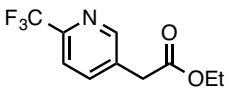


2-81 Prepared according to the General Procedure from the corresponding neopentyl boronic ester (169.1 mg, 0.75 mmol, 1.50 equiv.) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (90.4 mg, 0.250 mmol, 0.500 equiv.), 70 h. Isolated as a colorless oil in 67% yield after purification by column chromatography (4:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.29 (s, 1H), 7.62 (dd, *J* = 8.4, 3.2 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H) 4.17 (q, *J* = 7.0 Hz, 2H), 3.60 (s, 2H), 1.26 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.4, 150.5, 150.2, 139.8, 128.9, 124.2, 61.5, 37.8, 14.3;

HRMS (LCMS ESI): calcd for $C_9H_{11}ClNO_2$ $[M+H]^+$: 200.0473. Found 200.0469.



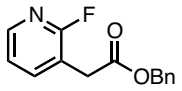
2-82 Prepared according to the General Procedure from the corresponding neopentyl boronic ester (194.3 mg, 0.75 mmol, 1.50 equiv.) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (90.4 mg, 0.25 mmol, 0.500 equiv.), 44 h. Isolated as a colorless oil in 77% yield after purification by column chromatography (4:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.64 (s, 1H), 7.83 (m, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 3.71(s, 2H), 1.27 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.0, 150.7, 147.2 (q, *J* = 34.8 Hz), 138.3, 133.3, 121.7 (q, *J* = 274.5 Hz) 120.4, 61.7, 38.4, 14.3;

^{19}F NMR ($CDCl_3$, 377 MHz) d -68.00;

HRMS (LCMS ESI): calcd for $C_{10}H_{11}F_3NO_2$ $[M+H]^+$: 234.0736. Found 234.0737.



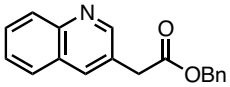
2-83 Prepared according to the General Procedure from the corresponding neopentyl boronic ester (156.8 mg, 0.75 mmol, 1.50 equiv.) and mono-benzyl malonate (97.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (90.4 mg, 0.250 mmol, 0.500 equiv.), 53 h. Isolated as a colorless oil in 53% yield after purification by column chromatography (4:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.15 (d, *J* = 4.9 Hz, 1H), 7.71 (m, 1H), 7.31 – 7.38 (m, 5H), 7.16 (m, 1H), 5.17 (s, 2H), 3.72 (s, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 169.8, 162.0 (d, *J* = 238.8 Hz), 146.8 (d, *J* = 14.8 Hz), 142.0 (d, *J* = 4.8 Hz), 135.5, 128.7, 128.5, 128.4, 121.6 (d, *J* = 4.4 Hz), 116.6 (d, *J* = 31.1 Hz), 67.2, 34.3(d, *J* = 1.9 Hz);

^{19}F NMR ($CDCl_3$, 376 MHz) δ -71.56;

HRMS (LCMS ESI): calcd for $C_{14}H_{13}FNO_2$ $[M+H]^+$: 246.0925. Found 246.0921.

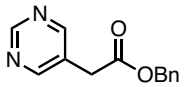


2-84 Prepared according to the General Procedure from the corresponding neopentyl boronic ester (180.8 mg, 0.75 mmol, 1.50 equiv.) and mono-benzyl malonate (97.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (90.4 mg, 0.250 mmol, 0.500 equiv.), 51 h. Isolated as a white solid in 73% yield after purification by column chromatography (Hexane/EtOAc gradient with 6% NEt_3).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.85 (d, *J* = 2.1 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 8.07 (br s, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.70 (m, 1H) 7.55 (m, 1H), 7.30 – 7.37 (m, 5H), 5.17 (s, 2H), 3.86 (s, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.7, 151.8, 147.5, 136.0, 135.6, 129.5, 129.4, 128.8, 128.6, 128.5, 128.0, 127.7, 127.0, 126.9, 67.2, 38.8;

HRMS (LCMS ESI): calcd for $C_{18}H_{16}NO_2$ $[M+H]^+$: 278.1176. Found 278.1171.

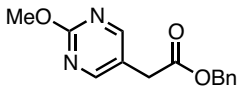


2-85 Prepared according to the General Procedure, with the modification of using 1,2-DCE as the solvent, from the corresponding neopentyl boronic ester (144.0 mg, 0.75 mmol, 1.50 equiv.) and mono-benzyl malonate (97.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (90.4 mg, 0.250 mmol, 0.500 equiv.), 31h. The solvent was removed *in vacuo.* The crude residue was purified by silica gel chromatography (25:1 DCM/MeOH). Isolated as a colorless oil in 61% yield.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 9.14 (s, 1H), 8.680 (s, 2H), 7.38 – 7.32 (m, 5H), 5.16 (s, 2H), 3.67 (s, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.0, 157.8, 157.5, 135.3, 128.8, 128.7, 128.5, 127.9, 67.5, 36.0;

HRMS (LCMS ESI): calcd for $C_{13}H_{13}N_2O_2$ $[M+H]^+$: 229.0972. Found 229.0972.

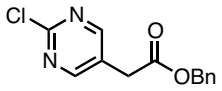


2-86 Prepared according to the General Procedure from the corresponding neopentyl boronic ester (166.5 mg, 0.75 mmol, 1.50 equiv.) and mono-benzyl malonate (97.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (90.4 mg, 0.250 mmol, 0.500 equiv.), 48 h. Isolated as a colorless oil in 65% yield after purification by column chromatography (1:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.44 (s, 2H), 7.32 – 7.37 (m, 5H), 5.15 (s, 2H), 4.00 (s, 3H), 3.59 (s, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.3, 165.1, 159.8, 135.4, 128.8, 128.7, 128.5, 120.8, 67.4, 55.1, 35.1;

HRMS (LCMS ESI): calcd for $C_{14}H_{15}N_2O_3$ $[M+H]^+$: 259.1077. Found 259.1080.

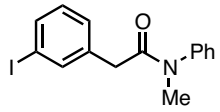


2-87 Prepared according to the General Procedure from the corresponding neopentyl boronic ester (169.9 mg, 0.75 mmol, 1.50 equiv.) and mono-benzyl malonate (97.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (90.4 mg, 0.250 mmol, 0.500 equiv.), 48 h. Isolated as a pale yellow solid in 53% yield after purification by column chromatography (10:1 CH_2Cl_2/Et_2O).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.57 (s, 2H), 7.32 – 7.39 (m, 5H), 5.17 (s, 2H), 3.67 (s, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 169.3, 160.6, 160.2, 135.1, 128.9, 128.9, 128.6, 126.4, 67.7, 35.2;

HRMS (LCMS ESI): calcd for $C_{13}H_{12}ClN_2O_2$ $[M+H]^+$: 263.0582. Found 263.0578.

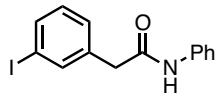


2-88 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (316 mg, 1.00 mmol, 2.00 equiv.) and 3-(methyl(phenyl)amino)-3-oxopropanoic acid (96.6 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 61 h. Isolated as a colorless oil in 84% yield after purification by column chromatography (4:1 to 2:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52 (m, 1H), 7.44 – 7.35 (m, 3H), 7.32 (m, 1H), 7.12 – 7.10 (m, 2H), 7.06 (m, 1H), 6.97 (m, 1H), 3.39 (s, 2H), 3.27 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.3, 143.8, 138.1, 137.7, 135.7, 130.0, 129.8, 128.4, 128.2, 127.7, 94.2, 40.6, 37.7;

HRMS (LCMS ESI): calcd for $C_{15}H_{14}INNaO$ $[M+Na]^+$: 374.0012. Found 374.0015.

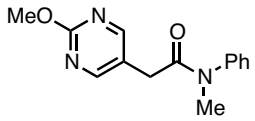


2-89 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (237 mg, 0.750 mmol, 1.50 equiv.) and 3-oxo-3-(phenylamino)propanoic acid (89.6 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 63 h. Isolated as a white solid in 43% yield after purification by column chromatography (6:1 to 4:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72 (m, 1H), 7.69 (m, 1H), 7.48 – 7.44 (m, 2H), 7.36 – 7.30 (m, 3H), 7.17 – 7.10 (m, 3H), 3.68 (s, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.2, 138.4, 137.5, 136.8, 136.7, 130.8, 129.1, 128.7, 124.7, 120.0, 95.0, 44.2;

HRMS (LCMS ESI): calcd for $C_{14}H_{12}INNaO$ $[M+Na]^+$: 359.9856. Found 359.9858.

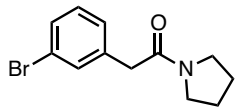


2-90 Prepared according to the General Procedure from the corresponding neopentyl boronic ester (166.5 mg, 0.75 mmol, 1.50 equiv.) and 3-(methyl(phenyl)amino)-3-oxopropanoic acid (96.6 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (90.4 mg, 0.150 mmol, 0.500 equiv.), 43 h. Isolated as a white solid in 49% yield after purification by column chromatography (1:4 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.23 (s, 2H), 7.46 – 7.48 (m, 2H), 7.40 – 7.42 (m, 1H), 7.18 (d, J = 7.7 Hz, 2H), 3.97 (s, 3H), 3.33 (s, 2H), 3.28 (s, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 169.7, 164.8, 159.7, 143.6, 130.3, 128.6, 127.6, 122.2, 55.0, 37.8, 34.8;

HRMS (LCMS ESI): calcd for $C_{14}H_{16}N_3O_2$ $[M+H]^+$: 258.1237. Found 258.1237.

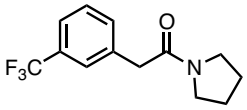


2-91 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (269 mg, 1.00 mmol, 2.00 equiv.) and 3-oxo-3-(pyrrolidin-1-yl)propanoic acid (78.6 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 70 h. Isolated as a light yellow oil in 58% yield after purification by column chromatography (0% to 10% MeOH/EtOAc).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 (m, 1H), 7.35 (m, 1H), 7.22 – 7.12 (m, 2H), 3.59 (s, 2H), 3.48 – 3.39 (m, 4H), 1.95 – 1.79 (m, 4H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.6, 137.2, 132.0, 130.0, 129.8, 127.7, 122.5, 46.9, 46.1, 14.6, 26.2, 24.4;

HRMS (LCMS ESI): calcd for $C_{12}H_{14}BrNNaO$ $[M+Na]^+$: 290.0151. Found 290.0155.



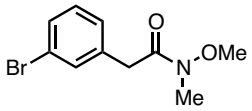
2-92 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (258 mg, 1.00 mmol, 2.00 equiv.) and 3-oxo-3-(pyrrolidin-1-yl)propanoic acid (78.6 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 72 h. Isolated as a light yellow solid in 66% yield after purification by column chromatography (EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52 – 7.49 (m, 3H), 7.43 (m, 1H), 3.70 (s, 2H), 3.50 (t, J = 7.0 Hz, 2H), 3.45 (t, J = 6.8 Hz, 2H), 1.96 (quint, J = 6.8 Hz, 2H), 1.86 (quint, J = 7.0 Hz, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.6, 136.0, 132.7, 130.8 (q, J = 32 Hz), 129.0, 125.9, 124.1 (q, J = 272 Hz), 123.7, 47.0, 46.1, 41.7, 26.2, 24.4;

^{19}F NMR ($CDCl_3$, 377 MHz) δ -62.6;

HRMS (LCMS ESI): calcd for $C_{13}H_{14}F_3NNaO$ $[M+Na]^+$: 280.0920. Found 280.0919.

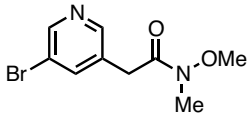


2-93 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (269 mg, 1.00 mmol, 2.00 equiv.) and 3-(methoxy(methyl)amino)-3-oxopropanoic acid (73.6 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 68 h. Isolated as a light yellow oil in 70% yield after purification by column chromatography (4:1 to 1:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 (m, 1H), 7.36 (m, 1H), 7.23 – 7.13 (m, 2H), 3.72 (s, 2H), 3.62 (s, 3H), 3.18 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.5, 137.1, 132.3, 129.92, 129.89, 128.0, 122.4, 61.3, 38.7, 32.2;

HRMS (LCMS ESI): calcd for $C_{10}H_{12}BrNNaO_2$ $[M+Na]^+$: 279.9944. Found 279.9949.

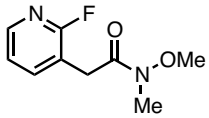


2-94 Prepared according to the General Procedure from the corresponding neopentyl boronic ester (202.4 mg, 0.75 mmol, 1.50 equiv.) and 3-(methoxy(methyl)amino)-3-oxopropanoic acid (73.6 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (90.4 mg, 0.250 mmol, 0.500 equiv.), 44h. Isolated as a colorless oil in 43% yield after purification by column chromatography (Hexane/EtOAc gradient with 1% NEt_3).

^{1}H NMR ($CDCl_3$, 700 MHz) d 8.57 (d, *J* = 2.1 Hz, 1H), 8.42 (s, 1H), 7.82 (m, 1H), 3.75 (s, 2H) 3.70 (s, 3H), 3.21 (s, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) d 170.7, 149.6, 148.8, 139.8, 132.4, 120.7, 61.6, 35.9, 32.5;

HRMS (LCMS ESI): calcd for $C_9H_{12}BrN_2O_2$ $[M+H]^+$: 259.0077. Found 259.0079.



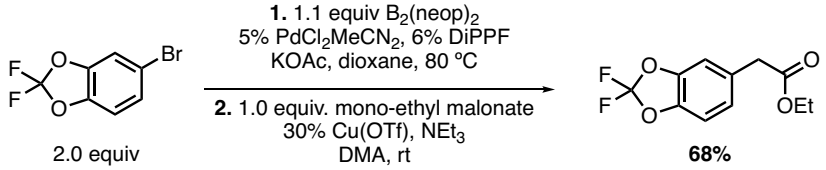
2-95 Prepared according to the General Procedure from the corresponding neopentyl boronic ester (159.8 mg, 0.75 mmol, 1.50 equiv.) and 3-(methoxy(methyl)amino)-3-oxopropanoic acid (73.6 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (90.4 mg, 0.250 mmol, 0.500 equiv.), 48 h. Isolated as a colorless oil in 51% yield after purification by column chromatography (Hexane/EtOAc gradient with 1% NEt_3).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.12 (d, *J* = 3.5 Hz, 1H), 7.74 (t, *J* = 8.1 Hz, 1H), 7.15 – 7.17 (m, 1H), 3.80 (s, 2H), 3.73 (s, 3H), 3.22 (s, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.3, 161.2 (d, *J* = 237.7 Hz), 146.3 (d, *J* = 15.0 Hz), 142.3 (d, *J* = 5.1 Hz), 121.6 (d, *J* = 3.7 Hz), 117.4 (d, *J* = 31.0 Hz), 61.4, 32.3, 31.8;

^{19}F NMR ($CDCl_3$, 376 MHz) -72.52;

HRMS (LCMS ESI): calcd for $C_9H_{12}FN_2O_2$ $[M+H]^+$: 199.0877. Found 199.0879.



2-98 Step 1. In a N_2-filled glovebox, $PdCl_2(MeCN)_2$ (25.9 mg, 0.100 mmol, 0.0500 equiv.), 1,1′-bis(diisopropylphosphino)ferrocene (56.9 mg, 0.120 mmol, 0.0600 equiv.), B_2neop_2 (497 mg, 2.20 mmol, 1.10 equiv.), KOAc (588 mg, 6.00 mmol, 3.00 equiv.) and dioxane (6.0 mL) were added to a 4-dram vial charged with a stir bar. The vial was sealed with a PTFE-lined cap and brought outside glovebox, at which point the corresponding aryl bromide (474 mg, 2.0 mmol, 1.0 equiv.) was added. The reaction was heated at 80°C for 14 h. The reaction mixture was diluted in hexanes (5.0 mL) and passed through a short pad of silica, washing with CH_2Cl_2, and then concentrated *in vacuo* to afford the corresponding crude aryl neopentyl ester which was used in the next step without further purification.

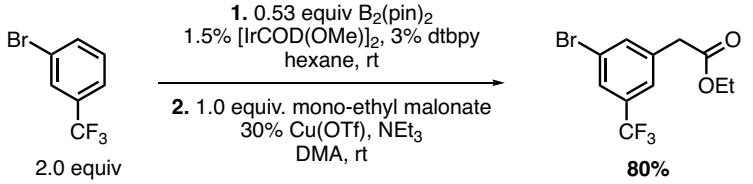
Step 2. Reaction conducted according to the General Procedure A from the corresponding crude neopentyl arylboronic ester (1.00 mmol, 2.00 equiv., half the material from step 1) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 42 h. Isolated as a light yellow oil in 68% yield after purification by column chromatography (10:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.04 (m, 1H), 7.00 – 6.97 (m, 2H), 4.16 (q, J = 7.2 Hz, 2H), 3.59 (s, 2H), 1.26 (t, J = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.1, 143.9, 142.9, 131.7 (t, J = 256 Hz), 130.1, 124.5, 110.7, 109.3, 61.2, 41.0, 14.2;

^{19}F NMR ($CDCl_3$, 469 MHz) δ -50.0;

HRMS (EI): calcd for $C_{11}H_{10}F_2O_4$ $[M]^+$: 244.0547. Found 244.0551.



2-101 Step 1. In a N_2-filled glovebox, $[Ir(COD)(OMe)]_2$ (10.0 mg, 0.0150 mmol, 0.0150 equiv.) and 4,4′-di-tert-butyl-2,2′-dipyridyl (7.9 mg, 0.030 mmol, 0.030 mmol, 0.030 equiv.) were added to a 1-dram vial charged with a stir bar. Hexanes (2.0 mL) was added and stirred at room temperature for 10 minutes, at which point arene (225 mg, 1.00 mmol, 1.00 equiv.) and B_2pin_2 (135 mg, 0.530 mmol, 0.530 equiv.) were sequentially added. The vial was sealed with a PTFE-lined cap and stirred at room temperature outside the glovebox. After 10 h, the crude mixture was filtered through a plug of silica and then concentrated *in vacuo* to afford the corresponding crude aryl pinacol boronic ester which was used in the next step without further purification.

Step 2. Reaction conducted according to the General Procedure A from the crude pinacol boronic ester (2.00 equiv.) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 18 h. Isolated as a light

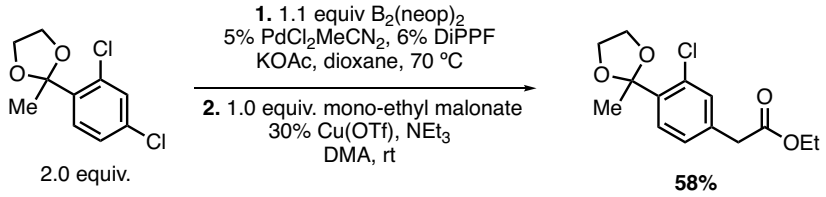
yellow oil in 80% yield after purification by column chromatography (15:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.68 (s, 1H), 7.64 (s, 1H), 7.49 (s, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.64 (s, 2H), 1.27 (t, J = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 137.1, 135.9, 132.5 (q, J = 33 Hz), 127.3, 125.0, 123.1 (q, J = 274 Hz), 122.8, 61.4, 40.6, 14.1;

^{19}F NMR ($CDCl_3$, 469 MHz) δ -62.8;

HRMS (EI): calcd for $C_{11}H_{10}BrF_3O_2$ $[M]^+$: 309.9816. Found 309.9816.



2-104 Step 1. In a N_2-filled glovebox, $PdCl_2(MeCN)_2$ (13 mg, 0.050 mmol, 0.050 equiv.), 1,1′-bis(diisopropylphosphino)ferrocene (28 mg, 0.060 mmol, 0.060 equiv.), and dioxane (3.0 mL) were added to a 4-dram vial charged with a stir bar. The corresponding aryl chloride (233 mg, 1.00 mmol, 1.00 equiv.), B_2neop_2 (270 mg, 1.20 mmol, 1.20 equiv.), and KOAc (294 mg, 3.00 mmol, 3.00 equiv.) were sequentially added. The vial was sealed with a PTFE-lined cap and heated at 70 °C outside the glovebox for 6 h. The reaction mixture was diluted with EtOAc and washed sequentially with sat. aq. $NaHCO_3$ and brine. The organic layer was dried with Na_2SO_4, filtered over celite and concentrated *in vacuo* to afford the corresponding crude neopentyl ester which was used in the next step without further purification.

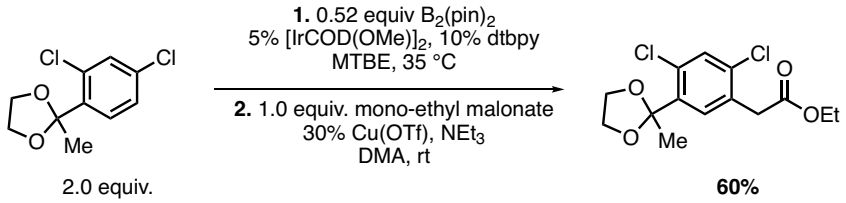
Step 2. Reaction conducted according to the General Procedure A from the corresponding crude neopentyl arylboronic ester (1.00 mmol, 2.00 equiv.) and mono-

ethyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 28 h. Isolated as a thick colorless oil in 58% yield after purification by column chromatography (10:1 to 2:1 pentane/Et_2O).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.58 (m, 1H), 7.32 (m, 1H), 7.15 (m, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.06 (m, 2H), 3.78 (m, 2H), 3.57 (s, 2H), 1.79 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 171.0, 138.4, 135.6, 132.2, 132.0, 127.9, 127.5, 108.4, 64.5, 61.2, 40.5, 25.3, 14.2;

HRMS (LCMS ESI): calcd for $C_{14}H_{17}ClNaO_4$ $[M+Na]^+$: 307.0708. Found 307.0706.



2-106 Step 1. In a N_2-filled glovebox, $[Ir(COD)(OMe)]_2$ (33.2 mg, 0.0500 mmol, 0.0500 equiv.) and 4,4′-di-tert-butyl-2,2′-dipyridyl (26.8 mg, 0.100 mmol, 0.100 equiv.) were added to a 1-dram vial charged with a stir bar. MTBE (2.0 mL) was added and stirred at room temperature for 10 minutes, at which point arene (233 mg, 1.00 mmol, 1.00 equiv.) and B_2pin_2 (132 mg, 0.520 mmol, 0.520 equiv.) were sequentially added. The vial was sealed with a PTFE-lined cap and stirred at 35 °C outside the glovebox. After 72 h, the crude mixture was diluted in EtOAc and sequentially washed with sat. aq. $NaHCO_3$, sat. aq. NaOAc, and brine. The organic layer was dried with Na_2SO_4, filtered

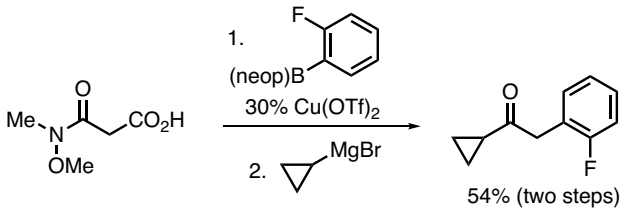
over celite and concentrated *in vacuo* to afford the corresponding crude pinacol boronic ester, which was used in the next step without further purification.

Step 2. Reaction conducted according to the General Procedure A from the crude pinacol boronic ester (2.00 equiv.) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 24 h. Isolated as a colorless oil in 60% yield after purification by column chromatography (10:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56 (s, 1H), 7.43 (s, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 4.09 – 4.03 (m, 2H), 3.82 – 3.75 (m, 2H), 3.73 (s, 2H), 1.77 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 138.5, 134.6, 131.8, 131.5, 131.0, 130.5, 108.1, 64.5, 61.2, 38.7, 25.3, 14.2;

HRMS (LCMS ESI): calcd for $C_{14}H_{16}Cl_2NaO_4$ $[M+Na]^+$: 341.0318. Found 341.0316.



2-108 Step 1. The decarboxylative coupling was conducting according to the General Procedure A from the corresponding neopentyl boronic ester (312 mg, 1.50 mmol, 3.00 equiv.) and 3-(methoxy(methyl)amino)-3-oxopropanoic acid (73.6 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 80 h. Isolated as a light yellow oil in 65% yield after purification by column chromatography (3:2 Hexane/EtOAc).

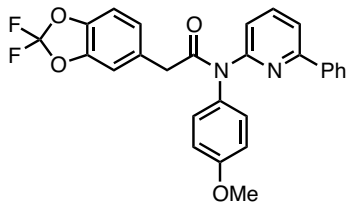
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33 – 7.24 (m, 2H), 7.14 – 7.05 (m, 2H), 3.83 (s, 2H), 3.70 (s, 3H), 3.23 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ; 171.4, 161.0 (d, J = 249 Hz), 131.4, 128.6, 124.0, 122.2, 115.2, 61.2, 32.2 (2C);

^{19}F NMR ($CDCl_3$, 377 MHz) δ -117.7;

HRMS (LCMS ESI): calcd for $C_{10}H_{13}FNO_2$ $[M+H]^+$: 198.0925. Found 198.0926.

2-109 Step 2 To a 1-dram vial sealed with a PTFE-lined cap under N_2 was added cyclopropyl magnesium bromide (1.37 mL, 0.365 M in THF, 2.2 equiv.). The corresponding weinreb amide (46.0 mg, 0.230 mmol, 1.0 equiv.) was added as a solution in THF (0.17 mL), using additional THF rinces (0.30 mL). The solution was heated at 45°C for 1 hour. The mixture was cooled to 0°C and quenched with 1 M HCl solution (1.0 mL). Additional water (5 mL) was added and then the reaction was extracted with EtOAc (3 x 10 mL EtOAc). The organic layer was washed with brine (5 mL) and water (5 mL), then dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was passed through a plug of silica, washing with 10:1 hexane/EtOAc, then concentrated to afford the title compound (83% yield) as a light yellow oil. Spectroscopic data agreed with that reported.



2-112 Prepared according to the General Procedure A from the corresponding neopentyl boronic ester (108 mg, 0.400 mmol, 2.00 equiv.) and 3-((4-methoxyphenyl)(6-

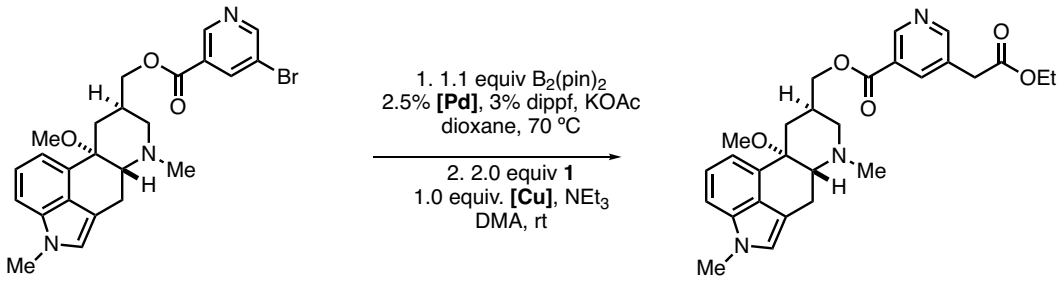
phenylpyridin-2-yl)amino)-3-oxopropanoic acid (85.3 mg, 0.200 mmol, 1.00 equiv., 85% pure (w/w)) using $Cu(OTf)_2$ (36.3 mg, 0.100 mmol, 0.500 equiv.), 44 h. Isolated as a light yellow oil in 74% yield after purification by column chromatography (65:35 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.90 – 7.87 (m, 2H), 7.71 (m, 1H), 7.59 (m, 1H), 7.45 – 7.37 (m, 3H), 7.30 – 7.20 (m, 3H), 6.95 – 6.90 (m, 4H), 6.80 (m, 1H), 3.84 (s, 3H), 3.78 (s, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.4, 159.0, 156.1, 154.8, 143.7, 142.6, 138.6, 138.2, 134.3, 131.6 (t, J = 254 Hz), 131.2, 129.8, 129.3, 128.7, 126.7, 124.4, 119.0, 117.6, 114.5, 110.7, 109.0, 55.5, 42.2;

^{19}F NMR ($CDCl_3$, 469 MHz) δ -49.9;

HRMS (LCMS ESI): calcd for $C_{27}H_{20}F_2N_2NaO_4$ $[M+Na]^+$: 497.1283. Found 497.1294.



2-115 step 1. In a N_2-filled glovebox, $PdCl_2(MeCN)_2$ (3.6 mg, 0.014 mmol, 0.025 equiv.), 1,1′-Bis(diisopropylphosphino)ferrocene (7.0 mg, 0.017 mmol, 0.030 equiv.), and dioxane (1.5 mL) were added to a 1-dram vial charged with a stir bar. The corresponding aryl bromide (271 mg, 0.560 mmol, 1.00 equiv.), B_2pin_2 (156 mg, 0.620 mmol, 1.10 equiv.), and KOAc (165 mg, 1.68 mmol, 3.00 equiv.) were sequentially added. The vial was sealed with a PTFE-lined cap and heated at 70°C outside the

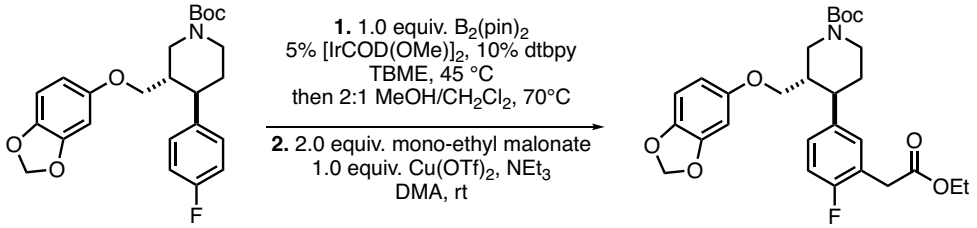
glovebox for 4 h. The reaction mixture was passed through a plug of celite, washing with toluene (50 mL). The organic layer was sequentially washed with sat. $NaHCO_3$ (20 mL) and brine (3 x 20 mL), and then dried with $NaSO_4$. The solvent was removed *in vacuo* to afford the corresponding pinacol arylboronic ester as a pale brown solid, 97% yield.

Step 2. Prepared according to the General Procedure A from the corresponding pinacol arylboronic ester (66.4 mg, 0.125 mmol, 1.00 equiv.) and mono-ethyl malonate (33.0 mg, 0.250 mmol, 2.00 equiv.) using $Cu(OTf)_2$ (45.2 mg, 0.125 mmol, 1.00 equiv.) and Et_3N (0.17 mL, 1.25 mmol, 10 equiv.), 25 h. Isolated as a colorless oil in 57% yield after purification by column chromatography (4% to 6% MeOH in CH_2Cl_2/MeCN/Hexanes (2:1:1), 1% NH_4Cl additive).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.15 (s, 1H), 8.70 (s, 1H), 8.25 (m, 1H), 7.24 (m, 1H), 7.20 (m, 1H), 7.05 (m, 1H), 6.80 (s, 1H), 4.40 (m, 1H), 4.30 (m, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 3.69 (s, 2H), 3.26 – 3.19 (m, 2H), 3.06 – 2.96 (m, 5H), 2.65 (br, 1H), 2.49 (s, 3H), 2.39 (br, 1H), 2.13 (br, 1H), 1.39 (t, *J* = 13 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 165.1, 154.2, 149.6, 137.9, 135.2, 130.0, 129.6, 126.3, 125.9, 123.3, 121.5, 115.0, 110.2, 109.0, 73.6, 70.1, 68.1, 61.5, 60.6, 49.6, 43.9, 38.2, 32.8, 31.5, 30.2, 22.3, 14.2;

HRMS (LCMS ESI): calcd for $C_{28}H_{34}N_3O_5$ $[M+H]^+$: 492.2493. Found 492.2494.



2-118 Step 1. In a N_2-filled glovebox, $[Ir(COD)(OMe)]_2$ (15 mg, 0.023 mmol, 0.050 equiv.) and 4,4′-di-tert-butyl-2,2′-dipyridyl (12 mg, 0.045 mmol, 0.10 equiv.) were added to a 1-dram vial charged with a stir bar. MTBE (1.5 mL) was added and stirred at room temperature for 10 minutes, at which point arene (195 mg, 0.450 mmol, 1.00 equiv.) and B_2pin_2 (114 mg, 0.450 mmol, 1.0 equiv.) were sequentially added. The vial was sealed with a PTFE-lined cap and stirred at 45 °C outside the glovebox. After 16 h, the crude mixture was concentrated, dissolved in 6 mL 2:1 MeOH/CH_2Cl_2, and heated at 70 °C. After 120 h, the crude mixture was concentrated. Isolated as a white solid in 22% yield (38% yield based on recovered arene) after purification by column chromatography (10:1 to 4:1 Hexane/EtOAc).

Step 2. Prepared according to the General Procedure A from the corresponding pinacol arylboronic ester (48 mg, 0.086 mmol, 1.00 equiv.) and mono-ethyl malonate (23 mg, 0.17 mmol, 2.00 equiv.) using $Cu(OTf)_2$ (31 mg, 0.086 mmol, 1.00 equiv.) and Et_3N (0.12 mL, 0.86 mmol, 10 equiv.), 23 h. Isolated as a colorless oil in 45% yield (76% yield based on recovered arene) after purification by column chromatography (10:1 to 4:1 Hexane/EtOAc).

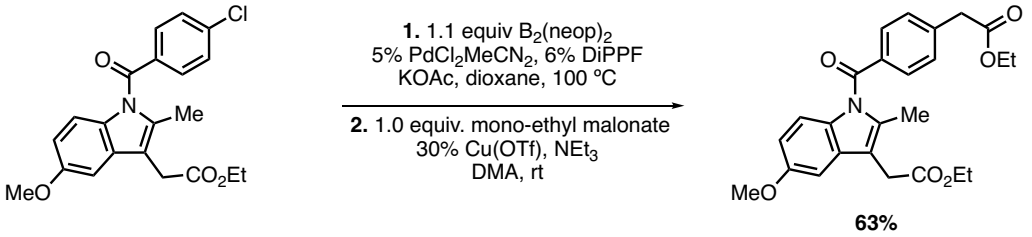
^{1}H NMR ($CDCl_3$, 500 MHz, 65 °C) δ 7.09 – 7.04 (m, 2H), 6.97 (t, J = 9.2 Hz, 1H), 6.61 (d, J = 8.6 Hz, 1H), 6.35 (m, 1H), 6.16 (m, 1H), 5.86 (s, 2H), 4.43 (m, 1H), 4.24 (m, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.64 (m, 1H), 3.60 (s, 2H), 3.49 (m, 1H), 2.84 – 2.76 (m,

2H), 2.65 (m, 1H), 2.01 (m, 1H), 1.81 (m, 1H), 1.71 (m, 1H), 1.50 (s, 9H), 1.23 (t, J = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 500 MHz, 65 °C) δ 170.5, 160.0 (d, J = 244 Hz), 154.9, 154.6, 148.4, 142.0, 139.4 (d, J = 3.6 Hz), 130.5 (d, J = 4.1 Hz), 127.8 (d, J = 8.1 Hz), 121.9 (d, J = 16 Hz), 115.5 (d, J = 22 Hz), 108.0, 106.3, 101.2, 98.4, 79.7, 69.4, 61.0, 47.5, 44.5, 44.4, 42.1, 34.6 (d, J = 2.9 Hz), 34.1, 28.6, 14.2;

^{19}F NMR ($CDCl_3$, 468 MHz, 65 °C) δ -120.3;

HRMS (LCMS ESI): calcd for $C_{28}H_{34}FNNaO_7$ $[M+Na]^+$: 538.2212. Found 538.2212.



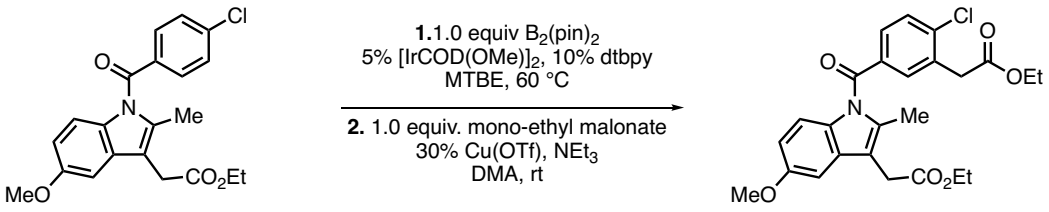
2-121 Step 1. In a N_2-filled glovebox, $PdCl_2(MeCN)_2$ (13 mg, 0.050 mmol, 0.050 equiv.), 1,1′-bis(diisopropylphosphino)ferrocene (28 mg, 0.060 mmol, 0.060 equiv.), and dioxane (3.0 mL) were added to a 4-dram vial charged with a stir bar. Indometacin ethyl ester (386 mg, 1.00 mmol, 1.00 equiv.), B_2neop_2 (249 mg, 1.10 mmol, 1.10 equiv.), and KOAc (294 mg, 3.00 mmol, 3.00 equiv.) were sequentially added. The vial was sealed with a PTFE-lined cap and heated at 100°C outside the glovebox for 2.5 h. The reaction mixture was diluted with EtOAc and washed sequentially with sat. aq. $NaHCO_3$ and brine. The organic layer was dried with Na_2SO_4, filtered over celite and concentrated *in vacuo.* Azeoptropical removal of trace water with toluene afforded the corresponding crude aryl neopentyl ester which was used in the next step without further purification.

Step 2. The reaction was conducted according to the General Procedure A from the corresponding crude neopentyl boronic ester (1.00 mmol, 2.00 equiv.) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (54.3 mg, 0.150 mmol, 0.300 equiv.), 68 h. Isolated as an off-white solid in 63% yield after purification by column chromatography (7:3 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.69 – 7.67 (m, 2H), 7.41 – 7.39 (m, 2H), 6.97 (m, 1H), 6.90 (m, 1H), 6.65 (m, 1H), 4.21 – 4.14 (m, 4H), 3.84 (s, 3H), 3.71 (s, 2H), 3.65 (s, 2H), 2.37 (s, 3H), 1.28 – 1.24 (m, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.0, 170.7, 169.2, 156.0, 139.4, 136.0, 134.4, 131.0, 130.6, 130.1, 129.7, 115.1, 112.4, 111.6, 101.2, 61.2, 61.0, 55.8, 41.5, 30.5, 14.3, 14.2, 13.4;

HRMS (LCMS ESI): calcd for $C_{25}H_{27}NNaO_6$ $[M+Na]^+$: 460.1731. Found 460.1731.



2-123 Step 1. In a N_2-filled glovebox, $[Ir(COD)(OMe)]_2$ (9.9 mg, 0.015 mmol, 0.050 equiv.) and 4,4′-Di-tert-butyl-2,2′-dipyridyl (8.0 mg, 0.030 mmol, 0.10 equiv.) were added to a 1-dram vial charged with a stir bar. MTBE (1.0 mL) was added and stirred at room temperature for 10 minutes, at which point arene (116 mg, 0.300 mmol, 1.00 equiv.) and B_2pin_2 (76.2 mg, 0.300 mmol, 1.0 equiv.) were sequentially added. The vial was sealed with a PTFE-lined cap and stirred at 60°C outside the glovebox. After 4

h, the crude mixture was concentrated and passed through a short silica column (4:1 to 1:1 Hexane/EtOAc). Isolated as a pale yellow oil in 43% yield.

Step 2. The reaction was conducting according to the General Procedure A from the corresponding pinacol arylboronic ester (123 mg, 0.24 mmol, 2.00 equiv.) and mono-ethyl malonate (15.9 mg, 0.120 mmol, 1.00 equiv.) using $Cu(OTf)_2$ (13.0 mg, 0.0360 mmol, 0.300 equiv.), 40 h. Isolated as a light yellow oil in 53% yield after purification by column chromatography (4:1 to 2:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.67 (m, 1H), 7.61 (m, 1H), 7.53 (m, 1H), 6.99 (m, 1H), 6.96 (m, 1H), 6.70 (m, 1H), 4.21 – 4.16 (m, 4H), 3.86 (s, 3H), 3.82 (s, 2H), 3.67 (s, 2H), 2.39 (s, 3H), 1.30 – 1.25 (m, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.9, 169.8, 168.2, 156.1, 139.5, 135.9, 134.3, 133.6, 132.8, 130.9, 130.7, 130.0, 129.9, 115.1, 112.8, 111.8, 101.3, 61.3, 61.0, 55.7, 39.1, 30.5, 14.3, 14.2, 13.4;

HRMS (LCMS ESI): calcd for $C_{25}H_{26}ClNNaO_6$ $[M+Na]^+$: 494.1341. Found 494.1345

CHAPTER 3 – Decarboxylative Oxidative Arylation of Aryl Acetate Salts with Aryl Boron Reagents

3.1 Introduction

Oxidative cross-coupling reactions can enable selective bond-formation between two distinct nucleophilic partners.[8-9, 29, 97] The inherent compatibility towards electrophilic functional groups displayed by oxidative coupling processes provides a significant benefit in comparison to traditional cross-coupling reactions. The Cu-promoted coupling of aryl boronic acids and N- or O-heteroatom nucleophiles (the Chan-Evans-Lam reaction) illustrates the power and practical utility of oxidative coupling reactions, finding widespread use in synthetic and medicinal chemistry.[52-56]

The previous chapter described the Cu-promoted oxidative arylation of activated methylenes compounds such as malonates using organoboronic esters (**Chapter 2.2**).[85, 98] Under related conditions, malonic half-esters are also oxidatively arylated to form an arylated carboxylic acid intermediate, which can protodecarboxylate to form mono-aryl acetate products (**Chapter 2.3**).[99-100] In the context of developing new aerobic Cu-catalyzed coupling processes of carboxylic acids, we were inspired by the work of Tunge,[25] Lui,[29] and Zhu[30] who demonstrated that nitroaryl acetates could be decarboxylatively trapped with allyl, aryl, and alkenyl electrophiles under Pd-catalysis at high temperatures (100–150 °C) (**Fig. 3-1**). We hypothesized that similar nitroaryl acetate substrates could be arylated with aryl boron reagents at lower temperatures via aerobic Cu-catalysis. This proposal was based on estimated similar C–H acidities of aryl acetates and malonate derivatives (pKa ~ 16 in DMSO), in addition to the reported mild ionic protodecarboxylation of nitrophenyl acetate salts in polar aprotic solvent.[101-102]

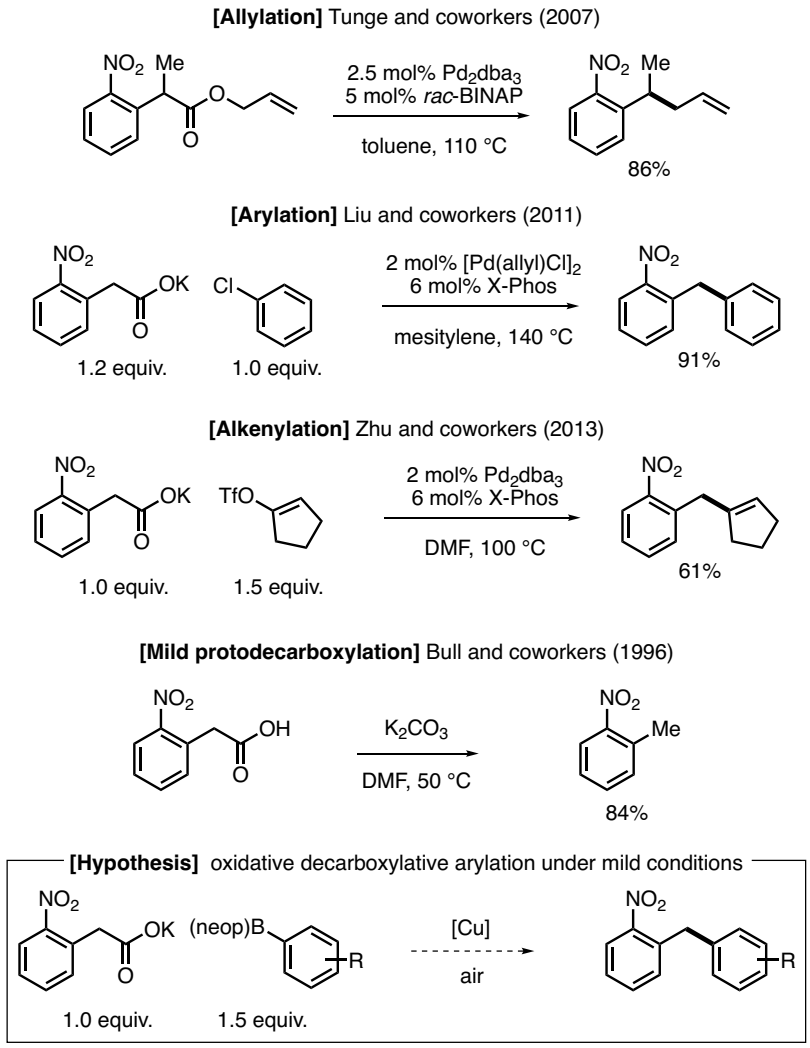


Fig. 3-1 Decarboxylative cross-coupling and protodecarboxylation reactivity of nitroaryl acetic acid derivatives

A mild oxidative method to prepare diarylmethane structures[103] from aryl acetic acids could provide a useful alternative strategy to Friedel-Crafts,[104-106] electrophile/nucleophile cross- coupling,[107-110] and radical benzylations (**Fig. 3-2**).[111-114]

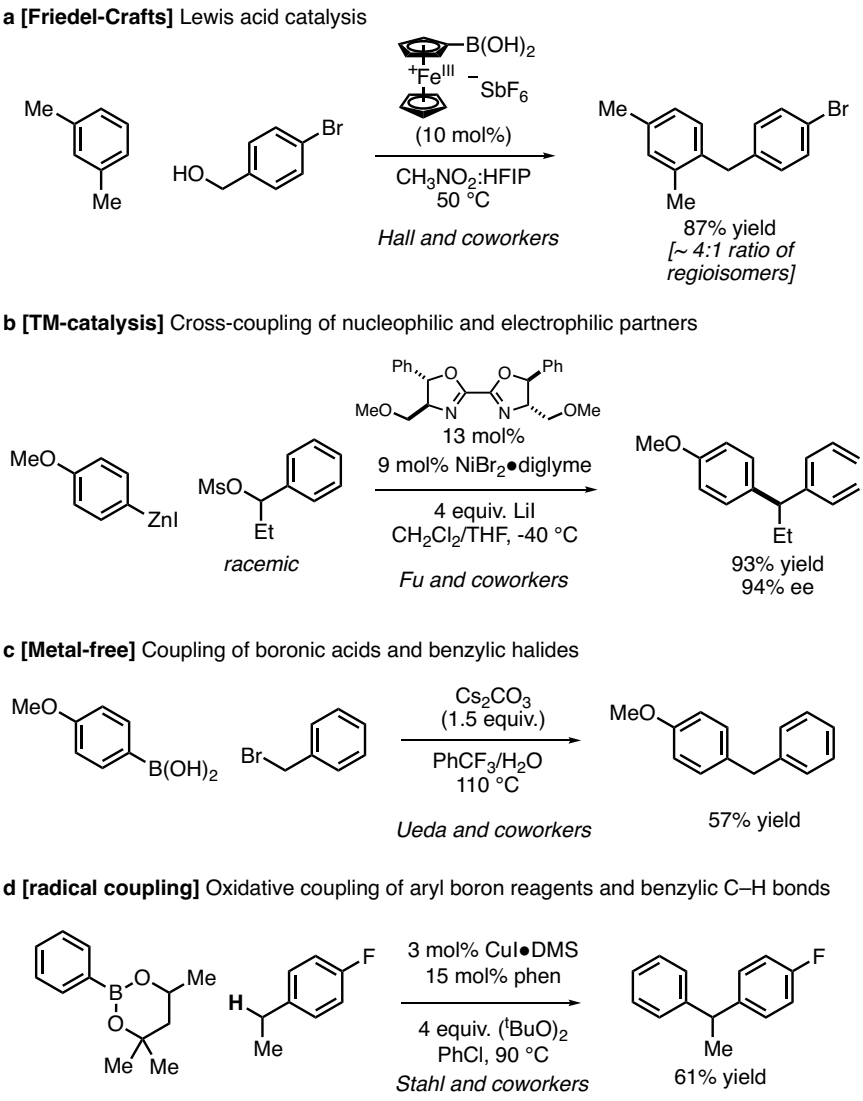


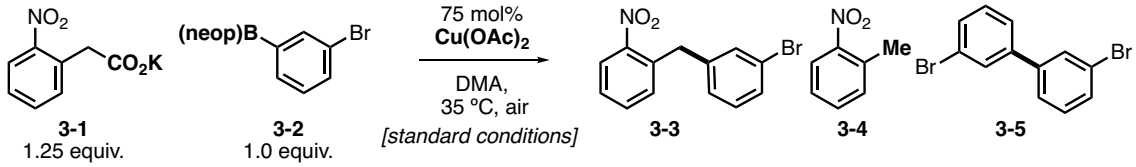
Fig. 3-2 Overview and selected examples of state-of-the-art strategies for diarylmethane synthesis

Chapter 3 discusses the development of an oxidative coupling reaction between aryl or alkenyl boronic esters and nitrophenyl acetates to generate functionalized diarylmethane products. The decarboxylation event precedes oxidative C–C bond formation, with the Cu catalyst assuming a dual role in mediating the oxidative coupling process and stabilizing substrate in DMA solvent. The mechanistic insights gained from

this work led to the discovery and development of other metal-catalyzed coupling reactions using aryl acetic acid derivatives as benzyl anion surrogates (see Chapter 4, 5, and 6).

3.2 Developement of the Decarboxylative Oxidative Arylation of Aryl Acetate Salts with Aryl Boron Reagents

Reaction development studies focused on enabling the oxidative cross-coupling of 2-nitrophenyl acetate (**3-1**) and 3-bromophenylboronic acid derivatives (**Table. 3-1**). Optimal conditions were achieved using the K-aryl acetate salt and neopentyl boronic ester, with 75 mol % $Cu(OAc)_2$ in DMA under air to yield the desired diarylmethane **3-3** in 75% yield (entry 1). Under other conditions, considerable hydrodecarboxylation of the acid was observed to form nitrotoluene **3-4**. This was surprising in light of the aggressive reaction conditions typically used to promote decarboxylation from electron-poor aryl acetates (100-150°C).[29-30] Use of the K-carboxylate salt was essential; when the free acid was used in combination with NEt_3 or K_2CO_3, or when reduced amounts of $Cu(OAc)_2$ were employed, formation of nitrotoluene outpaced product formation (entries 3, 4, and 9). Under anaerobic conditions, less than one turnover of Cu catalyst was observed (entry 7, 25% yield **3-3**). $Cu(OAc)_2$ dramatically outperformed $Cu(OTf)_2$ (entry 8), while other metal(II) acetates (Pd, Co, Ni, Fe and Zn) were completely ineffective in promoting the coupling process, with varying amounts of non-productive substrate decarboxylation observed (entry 13). Under optimized conditions, cross-coupling was observed exclusively at the aryl boron site over the aryl bromide.



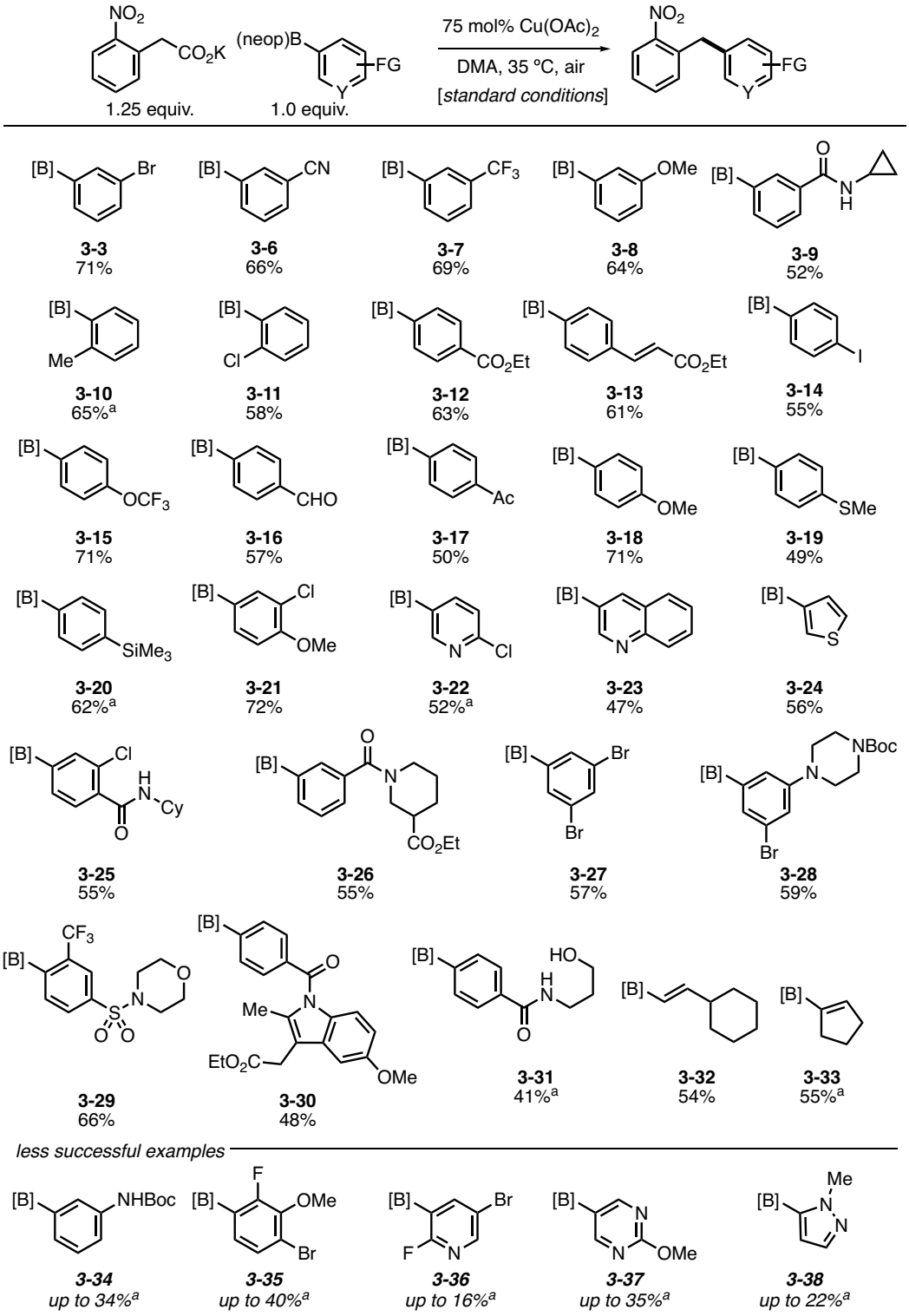
3-1 1.25 equiv. **3-2** 1.0 equiv. **3-3** **3-4** **3-5**

entry	deviation from standard conditions	conv. **3-1** (%)	conv. **3-2** (%)	**3-3** (%)	**3-4** (%)	**3-5** (%)
1	**none**	**113**	**>98**	**75**	**31**	**13**
2	acid instead of K-salt	<2	<2	0	0	0
3	acid instead of K-salt, 3 equiv. NEt_3	30	15	<2	26	0
4	acid instead of K-salt, 1.5 equiv. K_2CO_3	>123	>98	29	96	18
5	Li-salt instead of K-salt	78	>98	35	23	52
6	rt instead of 35 °C	65	>98	32	9	55
7	under N_2 instead of air	93	30	25	36	<2
8	$Cu(OTf)_2$ instead of $Cu(OAc)_2$	<2	33	<2	<2	22
9	30% $Cu(OAc)_2$ instead of 75%	>123	76	27	51	51
10	Ar–B(pin) instead of Ar–B(neop)	>123	62	31	38	<2
11	boroxine instead of Ar–B(neop)	113	61	47	39	5
12	1.25 equiv. Ar–B(neop), 1.0 equiv. K-salt	76	>123	48	21	63
13	Pd, Co, Ni, Fe, or Zn instead of Cu	31-119	20-98	<2	23-76	-

0.20 mmol scale, 0.2 M, 21 h, yields and conv. determined by calibrated ^{1}H NMR. conv. of **3-1** determined out of 125%. yields of **3-5** determined based on aryl unit mass balance.

Table 3-1 Reaction development: effect of general reaction parameters.

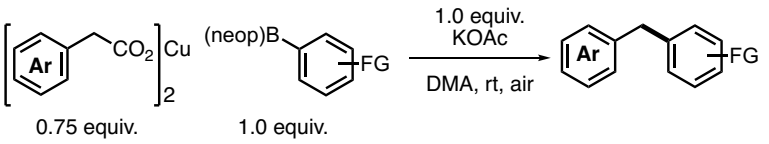
The oxidative benzylation process tolerates electronically diverse aryl boronic ester partners and a host of reactive functional groups that would be poorly compatible with traditional cross-coupling manifolds or thermally-driven decarboxylation processes (**Table 3-2**). Diarylmethanes featuring aryl bromides (**3-3, 3-27, 3-28**) and iodides (**3-14**), nitriles (**3-6**), NH-amides (**3-9, 3-25**), alcohols (**3-31**), esters (**3-12, 3-26**), ketones (**3-17**), aldehydes (**3-16**), and Michael acceptors (**3-13**) can be smoothly generated under the standard conditions. Substrates with Lewis-basic nitrogen-heterocycles (**3-22, 3-23**) or those featuring multiple functional groups (**3-21, 3-28, 3-30**) can be used without significant complication. Decarboxylative alkenylation of the aryl acetate can also be achieved using vinyl boronic ester partners (**3-32, 3-33**). Less sussessful examples include substrates that feature Boc-protected anilines (**3-34**), ortho-fluorine groups (**3-35**, **3-36**), or alternative pyrimidine or pyrazole heterocyles (**3-37**, **3-38**).

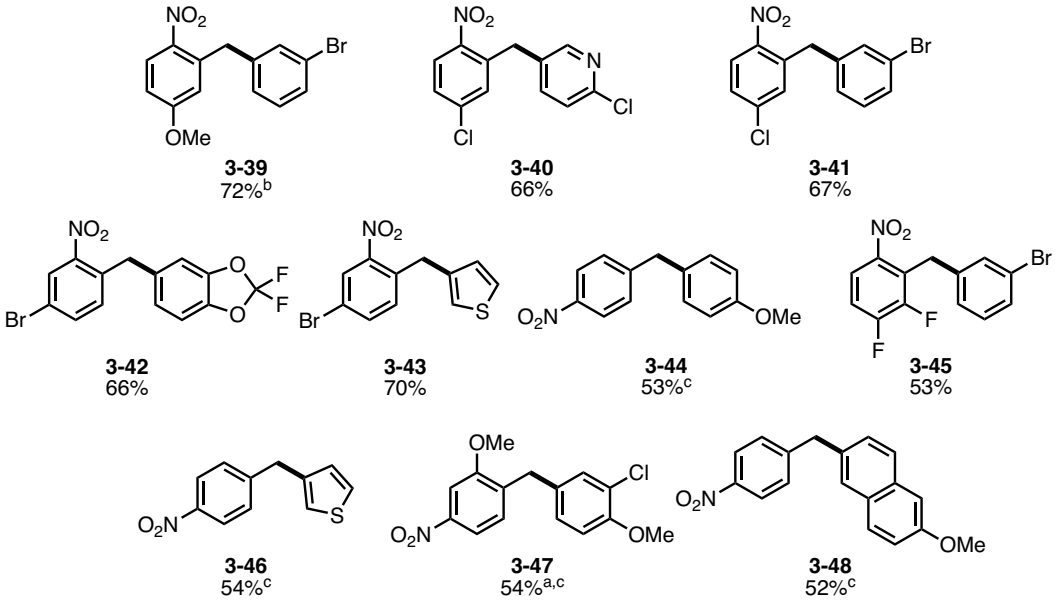


0.20-0.5 mmol scale, 0.2 M, 21 h. [a]calibrated ^{1}H NMR yield. The rest of the mass balance typically includes protodecarboxylation byproduct and aryl boron homocoupling byproduct, both of which are seperable from the desired diarylmethane product. [B] designates neopently boronic ester [B(neop)].

Table 3-2 Scope of aryl/alkenyl boronic esters

A range of substituted 2- and 4-nitrophenyl acetates engage in productive cross-coupling reactions (**3-39** to **3-48**, **Table 3-3**). For these substrates, it was more convenient and economical to employ the corresponding Cu bis(carboxylate) salts with KOAc additives. The copper bis(carboxylate) reagents can be isolated by simple filtration from $CuSO_4 \bullet H_2O$ and the corresponding aryl acetic acid, and are less hydrolytically sensitive than the corresponding potassium species. Under mild conditions, a series of polysubstituted diarylmethanes can be generated featuring electron-donating and withdrawing groups, including bromides, chlorides, and fluorides, as well as nitrogen and sulfur-containing heterocycles.





0.20-0.5 mmol scale, 0.2 M, 21 h. [a]calibrated ^{1}H NMR yield. [b]at 40°C. [c]0.5 equiv. carboxylate, 1.5-2.0 equiv. Ar—B(neop), 0.5 equiv. KOAc.The rest of the mass balance typically includes protodecarboxylation byproduct and aryl boron homocoupling byproduct, both of which are seperable from the desired diarylmethane product.

Table 3-3 Scope of nitroaryl acetate

Two general potential pathways for the decarboxylative arylation exist. One path consists of nitrophenyl acetate oxidative arylation followed by decarboxylation (Path I, **Fig. 3-3**). An alternative pathway involves a decarboxylation event to generate a benzylic nucleophile which undergoes subsequent oxidative trapping (Path II, **Fig. 3-3**).

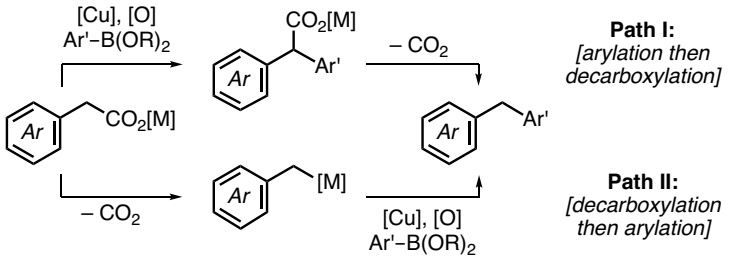


Fig. 3-3 Potential pathways for decarboxylation and C–C bond formation

We found both nitrophenyl acetate decarboxylation and arylation to be dependent on the nature of the cation and solvent polarity. In DMA at 35 °C, the free acid or the corresponding Cu(II) salts were stable, while rapid decarboxylation was observed for the K-salt (**Fig. 3-4**). The corresponding lithium, sodium and cesium carboxylate salts undergo decarboxylation and arylation under similar conditions. No decarboxylation or cross-coupling was observed in less polar solvents (THF, toluene). Decarboxylation from the K-carboxylate was not impeded by the addition of $Cu(OAc)_2$, however $Cu(OTf)_2$ completely suppressed reactivity, as did $Zn(OTf)_2$ and to a lesser extent $Zn(OAc)_2$ (**Fig. 3-4**).

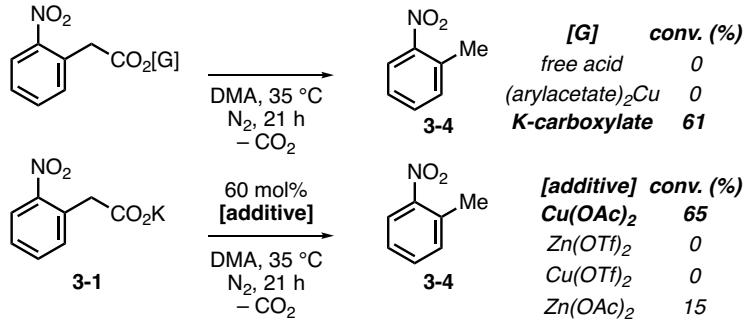


Fig. 3-4 Cation effects on arylacetate decarboxylation

It is likely that stable Cu-carboxylates are in equilibrium with reactive K-carboxylates under the standard reaction conditions and that decarboxylation precedes C–C bond formation (**Fig. 3-5**). We propose a benzylic nucleophile is generated and trapped by Cu in the presence of aryl boronic ester in a series of steps similar to those in the Chan-Evans-Lam reaction.[52-56]

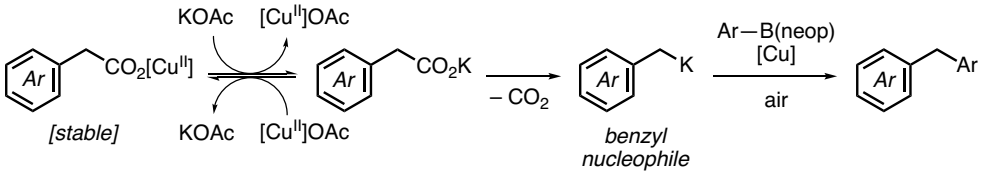


Fig. 3-5 Proposed pre-equilibrium leading to the decarboxylation step

No product formation or decarboxylation is observed when a Cu(carboxylate)$_2$ salt of the standard substrate is added to aryl boronic ester, providing evidence that such species cannot access productive intermediates in the reaction (**Fig. 3-6**). The addition of KOAc to mixtures of Cu(carboxylate)$_2$ and aryl boronic ester induces product formation with increasing rate and reaction productivity as KOAc loading is increased. Pivalate salts displayed a similar effect as acetate salts.

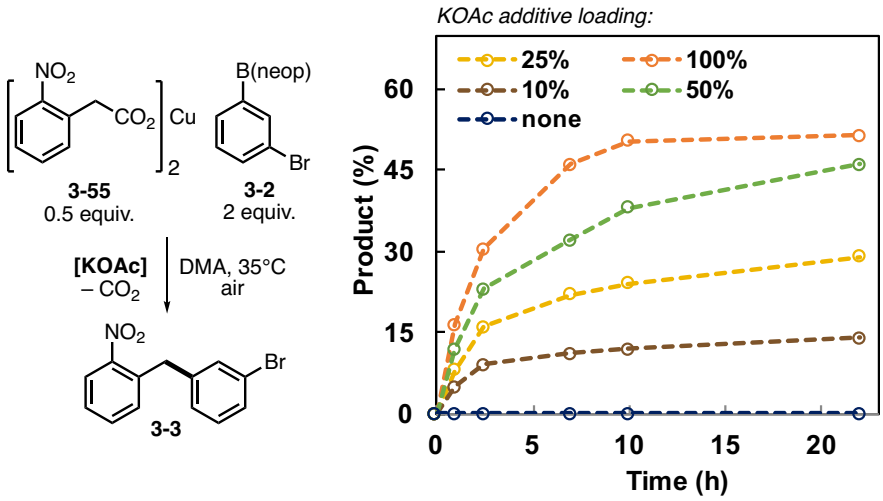


Fig. 3-6 Effect of KOAc additive on the decarboxylative arylation of Cu-carboxylate salts

When diarylmethyl carboxylate **3-56** is subjected to the standard conditions oxidative dimerization is dominant over diarylmethane product formation (**Fig. 3-7**). Since such homocoupling products are not observed under standard conditions, this result indicates it is unlikely diarylated acids are formed under standard condition, as depicted in path I in **Fig. 3-3**.

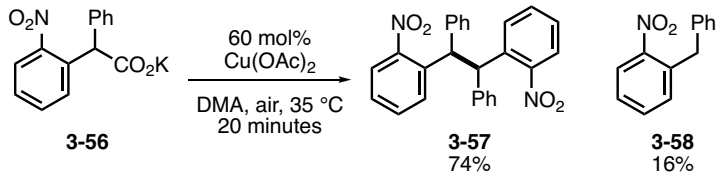


Fig. 3-7 Rapid oxidative homocoupling of diarylacetate salts

Finally, D-labelling studies of the nitrophenyl acetate also supports a decarboxylation event prior to C–C coupling (**Fig. 3-8)**. A competition experiment under standard conditions between D-labelled and H-labelled **3-1** provided product **3-3** (77% yield) with <10% exchange of the H/D labels. Should arylation of **3-1** occur first to from a dienolate species and followed by protodecarboxylation, complete scrambling of the deuterium and proton labels should occur. Since this does not occur, this would suggest initial arylation, followed by protodecarboxylation is not occurring. Over the course of this reaction, the H/D labels of the starting material slowly exchange (likely via a dienolate intermediate) which likely accounts for the small amount of 'HD'-labelled product that is observed.

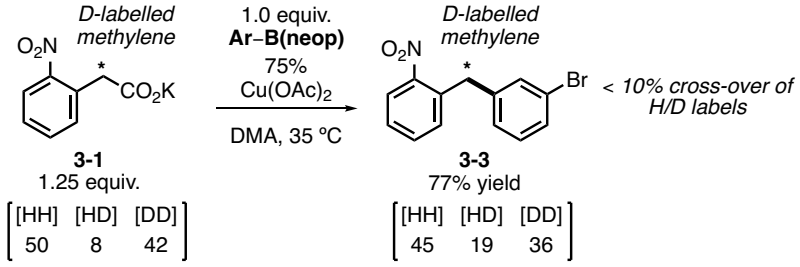


Fig. 3-8 Deuterium labeling study

Given that $Cu(OAc)_2$ plays a dual role, both enabling aerobic oxidative coupling and stabilizing the reactive nitrophenyl acetate substrate, the necessity for high Cu-loadings (75 mol %) becomes less surprising. At 25 mol % $Cu(OAc)_2$ a terminal yield of <25% is observed under otherwise standard conditions due to non-productive decarboxylation of the nitrophenyl acetate (**Fig. 3-9**). A reduction in Cu catalyst could be achieved by simply adding Zn salts to modulate the rate of substrate decarboxylation. The

use of 25% $Cu(OAc)_2$ in combination with 50% $Zn(OAc)_2$ closely mirrored reactions using 75 mol% $Cu(OAc)_2$, a dramatic improvement to reactions conducted with similar $Cu(OAc)_2$ loading in the absence of Zn. Redox-inactive metal co-catalysts have been previously reported by Stahl and coworkers for the oxidative homocoupling of simple arenes.[115] In line with the proposal that acetate is also vital to enable the exchange of metal carboxylates, the use of $Zn(OTf)_2$ with 25% $Cu(OAc)_2$ provided no diarylmethane product, as with $Zn(OAc)_2$ alone.

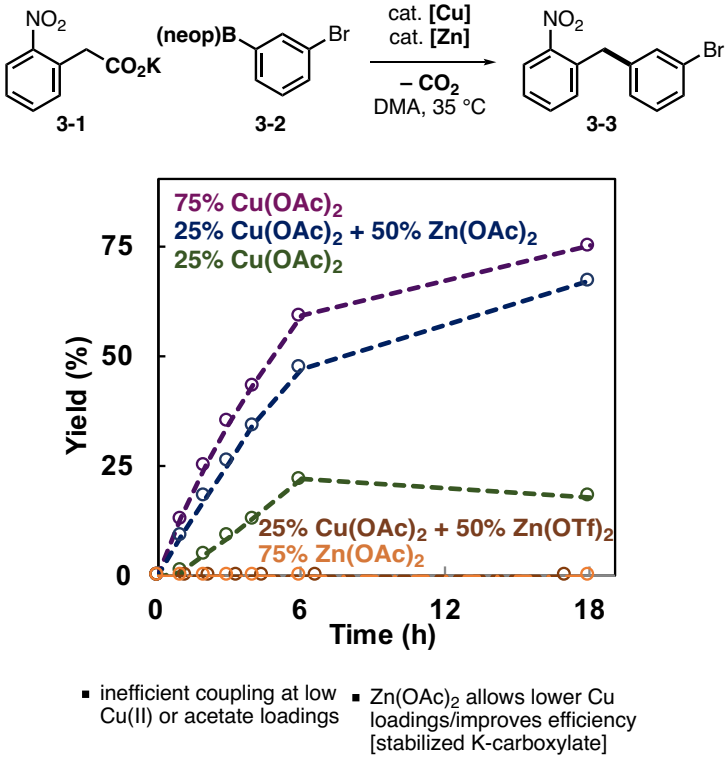


Fig. 3-9 Improved reaction efficiency at reduced Cu-loadings with $Zn(OAc)_2$

The proposed effect of $Zn(OAc)_2$ is to slow the liberation of benzylic nucleophile via the reversible formation of stable Zn-carboxylate species (**Fig. 3-10**). Lower loadings of $Cu(OAc)_2$ can therefore be used productively to mediate the oxidative arylation steps.

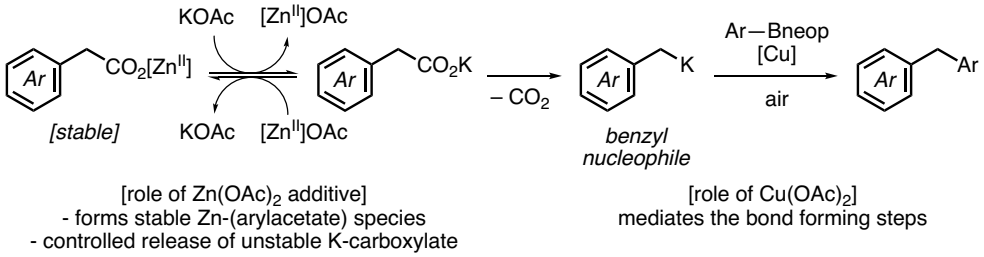


Fig. 3-10 Proposed role of $Zn(OAc)_2$ additive at low Cu-loadings

3.3 Summary and Conclusions

In conclusion, a Cu-catalyzed oxidative cross-coupling of nitrophenyl acetates and sp^2-organoboronic esters has been developed. Diarylmethanes containing a number of potentially reactive electrophilic groups can be prepared via this method. The nitro functional group of the benzylic partner can be readily modified to gain access to a diverse range of arylated products difficult to obtain directly by established cross-coupling or substitution manifolds. Process optimization and mechanistic studies uncovered an important relationship between reaction solvent and metal cations with aryl acetate decarboxylation. The mechanistic insights gained through this work laid the ground-work and served as inspiration for the related transition metal catalyzed cross-coupling reactions described in Chapters 4-6, all of which feature ionic decarboxylation from aryl acetic acid derivatives.

3.3 Procedures and Characterization

General Considerations:

Unless noted, all reactions were conducted under inert atmosphere employing standard schlenk technique or by the use of a N2-filled glovebox. All glassware was oven-dried prior to use. Flash chromatography was performed using SiliaFlash P60 (40-63μm, 60A silica gel, Silicycle) or by automated flash chromatography (Isolera, HP-SIL or Ultra SNAP silica cartridges, Biotage). Analytical thin-layer chromatography was performed using glass plates pre-coated with silica (SiliaPlate G TLC - Glass-Backed, 250μm, Silicycle). TLC plates were visualized by UV light and/or staining with aqueous basic potassium permanganate. NMR spectra (^{1}H, ^{13}C, ^{19}F) were obtained on an Agilent VNMRS 700 MHz, Varian VNMRS 600 MHz, Varian VNMRS 500 MHz, or Varian 400 MHz spectrometer. The chemical shifts are given as parts per million (ppm) and were referenced to the residual solvent signal (CDCl3: δH = 7.26 ppm, δC = 77.16 ppm). Unless otherwise noted, quantitative ^{1}H NMR yields were determined from crude reaction mixtures using durene as an internal standard. Optical rotation data were obtained using a Perkin Elmer 241 Polarimeter at 589 nm and 25° C, using a 10 cm path-length cell. Unless otherwise noted, all reagents were obtained from commercial vendors and used as supplied.

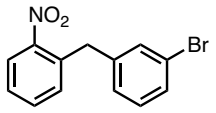
General Procedure A (using potassium aryl acetate salts – 0.5 mmol scale): To a 1 dram vial was added $Cu(OAc)_2$ (68.1 mg, 0.375 mmol, 0.75 equiv.), arylboronic neopentyl ester (0.50 mmol, 1.0 equiv.), and potassium nitrophenyl acetate (0.625 mmol,

1.25 equiv.), and charged with a stir-bar. Anhydrous DMA (2.5 mL) was added, and the solution was stirred 2 minutes until mostly homogeneous. The vial was sealed with a PTFE-lined cap and pierced with an 18 gauge needle, then gently stirred at 35°C. Upon reaction completion as monitored by ^{1}H NMR (12 to 48 h), the reaction mixture was diluted with EtOAc, and washed with saturated aqueous NH_4Cl, 0.1M aqueous KOH, and brine. The organic layer was dried with Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica gel chromatography. For some reactions, additional KOH (0.1M, aq.) and deionized water washes were used to remove remaining arylboronic ester and diol respectively. *Select reactions were conducted on 0.2 mmol scale instead of 0.5 mmol scale, using a 0.5 dram vial instead of a 1 dram vial.*

General Procedure B (using Cu(II) arylacetate salts): To a 0.5 dram vial was added Cu(II) arylacetate salt (0.15 mmol, 0.75 equiv.), arylboronic neopentyl ester (0.20 mmol, 1.0 equiv.), and potassium acetate (19.6 mg, 0.2 mmol, 1.0 equiv.), and charged with a stir-bar. Anhydrous DMA (1.0 mL) was added, and the solution was stirred 2 minutes. The vial was sealed with a PTFE-lined cap and pierced with an 18 gauge needle, then gently stirred at the indicated temperature (rt–40°C). Upon reaction completion as monitored by ^{1}H NMR (12 to 48 h), the reaction mixture was diluted with EtOAc, and washed with saturated aqueous NH_4Cl, 0.1M aqueous KOH, and brine. The organic layer with dried with Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica gel chromatography.

General Procedure C (using Cu(II) arylacetate salt as the limiting reagent): To a 0.5 dram vial was added Cu(II) arylacetate salt (0.1 mmol, 0.5 equiv.), arylboronic neopentyl ester (1.5 – 2.0 equiv.), and potassium acetate (9.8 mg, 0.1 mmol, 0.5 equiv.), and charged with a stir-bar. Anhydrous DMA (1.0 mL) was added, and the solution was stirred 2 minutes. The vial was sealed with a PTFE-lined cap and pierced with a 16 gauge needle, then gently stirred at 35°C. Upon reaction completion as monitored by ^{1}H NMR (12 to 48 h), the reaction mixture was diluted with EtOAc, and washed with saturated aqueous NH_4Cl, 0.1M aqueous KOH, and brine. The organic layer with dried with Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica gel chromatography.

General Procedure for the Synthesis of Copper(II) Arylacetate Salts: Carboxylic acid (1 equiv.) and 1M aq. NaOH (1 equiv) are combined and sonicated until mostly homogeneous (2-3 minutes). $CuSO_4 \bullet 5H_2O$ (0.5 equiv.) is added in one portion as a 1M aqueous solution. A precipitate immediately forms, and the mixture is gently stirred by agitation. The mixture is left to stand at least 30 minutes, at which point the precipitate is isolated by filtration. The obtained copper(II) arylacetate hydrate was dried under vaccum at 110°C for at least 2 hours to provide anhydrous copper(II) arylacetate in near quantitative yield (>90%).



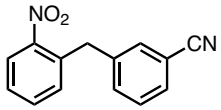
3-3 Prepared according to the General Procedure A from the corresponding arylboronic neopentyl ester (135 mg, 0.50 mmol, 1.0 equiv.) and nitrophenylacetate salt

(137 mg, 0.625 mmol, 1.25 equiv.), 20 h. Isolated as a light yellow oil in 71% yield after purification by silica gel chromatography (13:1 hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 498 MHz) δ 7.97 (m, 1H), 7.55 (m, 1H), 7.42 (m, 1H), 7.36 (m, 1H), 7.31 – 7.26 (m, 2H), 7.16 (m, 1H), 7.09 (m, 1H), 4.28 (s, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.3, 141.2, 134.9, 133.3, 132.6, 132.0, 130.3, 129.9, 127.9, 127.8, 125.2, 122.8, 38.2;

HRMS (EI): calcd for $C_{13}H_{10}BrNO_2$ $[M]^+$: 290.9895. Found 290.9885.

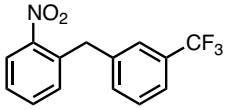


3-6 Prepared according to the General Procedure A from the corresponding arylboronic neopentyl ester (108 mg, 0.50 mmol, 1.0 equiv.) and nitrophenylacetate salt (137 mg, 0.625 mmol, 1.25 equiv.), 23 h. Isolated as a light yellow oil in 66% yield after purification by silica gel chromatography (20:1 to 2:1 hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.00 (dd, J = 8.2, 1.2 Hz, 1H), 7.59 (td, J = 7.6, 1.3 Hz, 1H), 7.51 (m, 1H), 7.46 (m, 1H), 7.42 – 7.37 (m, 3H), 7.30 (m, 1H), 4.34 (m, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 149.1, 140.3, 134.0, 133.5, 133.3, 132.6, 132.2, 130.4, 129.4, 128.2, 125.3, 118.7, 112.7, 38.2;

HRMS (EI): calcd for $C_{14}H_9N_2O_2$ $[M\text{-}H]^+$: 237.0664. Found 237.0666.



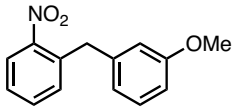
3-7 Prepared according to the General Procedure A from the corresponding arylboronic neopentyl ester (129 mg, 0.50 mmol, 1.0 equiv.) and nitrophenylacetate salt (137 mg, 0.625 mmol, 1.25 equiv.), 26 h. Isolated as a light-yellow oil in 69% yield after purification by silica gel column chromatography (40:1 to 10:1 Hexane:EtOAc, 5% toluene additive).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.01 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.59 (td, *J* = 7.5, 1.4 Hz, 1H), 7.51 (m, 1H), 7.48 – 7.41 (m, 3H), 7.36 (m, 1H), 7.31 (m, 1H), 4.39 (s, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.2, 139.7, 134.6, 133.2, 132.4, 132.3, 131.1 (q, *J* = 32.6 Hz), 129.0. 127.9, 125.5 (q, *J* = 3.9 Hz), 125.1, 124.0 (q, *J* = 272.5 Hz), 123.5 (q, *J* = 3.9 Hz), 38.2;

^{19}F NMR ($CDCl_3$, 376 MHz) δ -62.6 (s);

HRMS (EI): calcd for $C_{14}H_9F_3NO_2$ $[M-H]^+$: 280.0585. Found 280.0586.

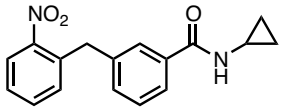


3-8 Prepared according to the General Procedure A from the corresponding arylboronic neopentyl ester (110 mg, 0.50 mmol, 1.0 equiv.) and nitrophenylacetate salt (137 mg, 0.625 mmol, 1.25 equiv.), 19h. Isolated as a light yellow oil in 64% yield after purification by silica gel chromatography (30:1 to 20:1 hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 498 MHz) δ 7.95 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.53 (td, *J* = 7.5, 1.4, 1H), 7.40 (m, 1H), 7.30 (m, 1H), 7.23 (t, *J* = 8.1 Hz, 1H), 6.79 (m, 1H), 6.76 (m, 1H), 6.72 (m, 1H), 4.31 (s, 2H), 3.79 (s, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 159.8, 149.3, 140.2, 135.5, 132.9, 132.3, 129.6, 127.4, 124.8, 121.4, 114.9, 111.8, 55.2, 38.3;

HRMS (EI): calcd for $C_{14}H_{13}NO_3$ $[M]^+$: 243.0895. Found 243.0889.

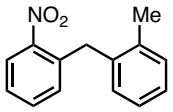


3-9 Prepared according to the General Procedure A from the corresponding arylboronic neopentyl ester (54.6 mg, 0.20 mmol, 1.0 equiv.) and nitrophenylacetate salt (54.8 mg, 0.25 mmol, 1.25 equiv.), 25h. Isolated as a yellow solid in 52% yield after purification by silica gel chromatography (1:1 hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.94 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.55 – 7.53 (m, 2H), 7.52 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.39 (m, 1H), 7.33 (t, *J* = 8.1 Hz, 1H), 7.28 – 7.25 (m, 2H), 6.15 (bs, 1H), 4.33 (s, 2H), 2.87 (m, 1H), 0.87 – 0.83 (m, 2H), 0.61 – 0.58 (m, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 168.8, 149.2, 139.3, 135.0, 134.9, 133.2, 132.5, 132.0, 128.8, 127.7, 127.6, 125.0, 124.9, 38.3, 23.2, 6.8;

HRMS (ESI): calcd for $C_{17}H_{16}N_2O_3Na$ $[M+Na]^+$: 319.1053. Found 319.1057.

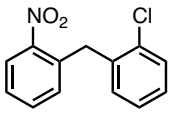


3-10 Prepared according to the General Procedure A from the corresponding arylboronic neopentyl ester (102 mg, 0.50 mmol, 1.0 equiv.) and nitrophenylacetate salt (137 mg, 0.625 mmol, 1.25 equiv.), 26 h. 65% yield by ^{1}H NMR using durene as internal standard.

^{1}H NMR ($CDCl_3$, 498 MHz) δ 7.99 (dd, *J* = 8.1, 1.4, 1H), 7.48 (td, *J* = 7.6, 1.3 Hz, 1H), 7.4 (m, 1H) 7.24 – 7.14 (m, 3H), 7.07 – 7.04 (m, 1H), 6.99 (m, 1H), 4.32 (s, 2H), 2.23 (s, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.5, 136.8, 136.7, 135.4, 133.0, 131.4, 130.5, 129.7, 127.2, 127.0, 126.3, 124.7, 35.9, 19.5;

HRMS (EI): calcd for $C_{14}H_{13}NO_2$ $[M]^+$: 227.0946. Found 227.0946.

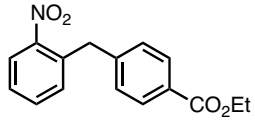


3-11 Prepared according to the General Procedure A from the corresponding arylboronic neopentyl ester (112 mg, 0.50 mmol, 1.0 equiv.) and nitrophenylacetate salt (137 mg, 0.625 mmol, 1.25 equiv.), 19 h. Isolated as a light yellow oil in 58% yield after purification by silica gel chromatography (40:1 hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 498 MHz) δ 8.00 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.61 (td, *J* = 7.6, 1.4 Hz, 1H), 7.44 – 7.39 (m, 2H), 7.27 – 7.19 (m, 2H), 7.13 (m, 1H), 7.08 (m, 1H), 4.45 (s, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.4, 136.5, 134.5, 134.4, 133.1, 131.7, 130.9, 129.7, 128.3, 127.5, 127.1, 124.8, 36.1;

HRMS (EI): calcd for $C_{13}H_{10}ClNO_2$ $[M]^+$: 247.0400. Found 247.0396.

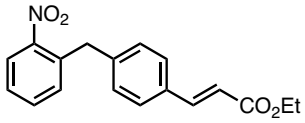


3-12 Prepared according to the General Procedure A from the corresponding arylboronic neopentyl ester (131 mg, 0.50 mmol, 1.0 equiv.) and nitrophenylacetate salt (137 mg, 0.625 mmol, 1.25 equiv.), 24 h. Isolated as a light yellow oil in 63% yield after purification by silica gel chromatography (10:1 Hexane:EtOAc, 2% toluene).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.00 – 7.97 (m, 3H), 7.56 (td, J = 7.6, 1.3 Hz, 1H), 7.43 (m, 1H), 7.31 – 7.29 (m, 1H), 7.25 – 7.22 (m, 2H), 4.39 (s, 2H), 4.38 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.4, 149.3, 143.9, 134.8, 133.1, 132.5, 129.9, 129.0, 128.9, 127.8, 125.0, 60.9, 38.5, 14.3;

HRMS (EI): calcd for $C_{16}H_{15}NO_4$ $[M]^+$: 285.1001. Found 285.0995.



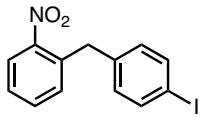
3-13 Prepared according to the General Procedure A from the corresponding arylboronic neopentyl ester (57.6 mg, 0.20 mmol, 1.0 equiv.) and nitrophenylacetate salt (54.8 mg, 0.25 mmol, 1.25 equiv.), 15h. 61% by ^{1}H NMR using durene as internal

standard. Isolated as a yellow solid in 48% (>90% pure, diaryl ether side-product present) yield after purification by silica gel chromatography (50:1 to 4:1 hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 498 MHz) δ 7.98 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.67 (d, *J* = 16.1 Hz, 1H), 7.56 (td, *J* = 7.6, 1.3 Hz, 1H), 7.49 – 7.45 (m, 2H), 7.43 (m, 1H), 7.31 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.21 – 7.11 (m, 2H), 6.42 (d, *J* = 16.0 Hz, 1H), 4.35 (s, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 167.0, 149.3, 144.1, 141.1, 135.0, 133.1, 132.9, 132.5, 129.4, 128.3, 127.7, 125.0, 118.0, 60.5, 38.3, 14.3;

HRMS (EI): calcd for $C_{18}H_{17}NO_4$ $[M]^+$: 311.1158. Found 311.1155.

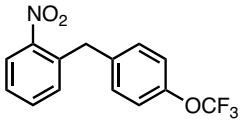


3-14 Prepared according to the General Procedure A from the corresponding arylboronic neopentyl ester (158 mg, 0.50 mmol, 1.0 equiv.) and nitrophenylacetate salt (137 mg, 0.625 mmol, 1.25 equiv.), 23 h. Isolated as a light yellow oil in 55% yield after purification by silica gel chromatography (40:1 to 10:1 hex:EtOAc, 2% toluene additive).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.94 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.61 – 7.58 (m, 2H), 7.52 (td, *J* = 7.6, 1.2 Hz, 1H), 7.40 – 7.38 (m, 1H), 7.26 – 7.24 (m, 1H), 6.90 – 6.88 (m, 2H), 4.24 (s, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 149.2, 138.4, 137.7, 135.0, 133.1, 132.4, 130.9, 127.7, 124.9, 91.9, 38.0;

HRMS (EI): calcd for $C_{13}H_{10}INO_2$ $[M]^+$: 338.9756. Found 338.9751.



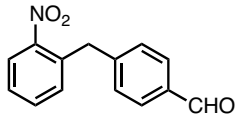
3-15 Prepared according to the General Procedure A from the corresponding arylboronic neopentyl ester (137 mg, 0.50 mmol, 1.0 equiv.) and nitrophenylacetate salt (137 mg, 0.625 mmol, 1.25 equiv.), 26 h. Isolated as a clear, light-yellow oil in 71% yield after purification by silica gel chromatography (20:1 Hexane:EtOAc, 2% toluene additive).

^{1}H NMR ($CDCl_3$, 498 MHz) δ 7.96 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.55 (dd, *J* = 7.59, 1.3 Hz, 1H), 7.44 – 7.39 (m, 1H), 7.30 – 7.27 (m, 1H), 7.19 – 7.11 (m, 4H), 4.31 (s, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.2, 147.9 (d, *J* = 1.3 Hz), 137.4, 135.1, 133.2, 132.4, 130.2, 127.8, 125.0, 121.1, 120.4 (q, *J* = 257.2 Hz), 37.6;

^{19}F NMR ($CDCl_3$, 376 MHz) δ -58.0 (s);

HRMS (EI): calcd for $C_{14}H_9F_3NO_3$ $[M-H]^+$: 296.0535. Found 296.0533.

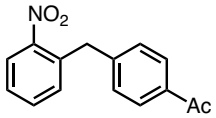


3-16 Prepared according to the General Procedure A from the corresponding arylboronic neopentyl ester (109 mg, 0.50 mmol, 1.0 equiv.) and nitrophenylacetate salt (137 mg, 0.625 mmol, 1.25 equiv.), 19h. Isolated as a light yellow oil in 57% yield after purification by silica gel chromatography (19:1 to 1.5:1 Hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.98 (s, 1H), 8.00 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.83 – 7.79 (m, 2H), 7.57 (td, *J* = 7.6, 1.3 Hz, 1H), 7.43 (m, 1H), 7.34 – 7.29 (m, 3H), 4.40 (s, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 191.8, 149.2, 145.9, 135.0, 134.4, 133.3, 132.6, 130.1, 129.5, 128.0, 125.1, 38.8;

HRMS (EI): calcd for $C_{14}H_{10}NO_4$ $[M-H]^+$: 240.0661. Found 240.0659.

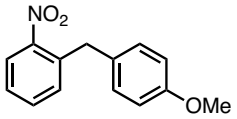


3-17 Prepared according to the General Procedure A from the corresponding arylboronic neopentyl ester (116 mg, 0.5 mmol, 1.0 equiv.) and nitrophenylacetate salt (137 mg, 0.625 mmol, 1.25 equiv.), 20h. Isolated as a colorless oil in 50% yield after purification by silica gel chromatography (4:1 to 1:1 Hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.91 – 7.86 (m, 2H), 7.56 (td, *J* = 7.5, 1.2 Hz, 1H), 7.43 (m, 1H), 7.30 (m, 1H), 7.26 – 7.22 (m, 2H), 4.37 (s, 2H), 2.57 (s, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.7, 149.2, 144.3, 135.6, 134.6, 133.2, 132.6, 129.1, 128.7, 127.9, 125.1, 38.5, 26.6;

HRMS (EI): calcd for $C_{15}H_{13}NO_3$ $[M]^+$: 285.0895. Found 285.0889.

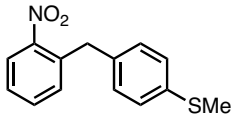


3-18 Prepared according to the General Procedure A from the corresponding arylboronic neopentyl ester (110 mg, 0.50 mmol, 1.0 equiv.) and nitrophenylacetate salt (121 mg, 0.55 mmol, 1.1 equiv.), 34 h. Isolated as a light yellow oil in 71% yield after purification by silica gel chromatography (20:1 to 10:1 hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 498 MHz) δ 7.92 (m, 1H), 7.51 (m, 1H), 7.37 (m, 1H), 7.28 (m, 1H), 7.11—7.06 (m, 2H), 6.87 – 6.82 (m, 2H), 4.26 (s, 2H), 3.80 (s, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 158.5, 149.5, 136.4, 133.0, 132.4, 130.8, 130.2, 127.4, 124.8, 114.2, 55.4, 37.6;

HRMS (EI): calcd for $C_{14}H_{13}NO_3$ $[M]^+$: 243.0895. Found 243.0889.

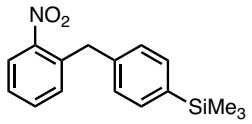


3-19 Prepared according to the General Procedure A from the corresponding arylboronic neopentyl ester (118 mg, 0.50 mmol, 1.0 equiv.) and nitrophenylacetate salt (137 mg, 0.625 mmol, 1.25 equiv.), 19h. Isolated as a light yellow oil in 49% yield after purification by silica gel chromatography (99:1 to 9:1 hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.92 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.50 (td, *J* = 7.6, 1.3 Hz, 1H), 7.37 (m, 1H), 7.26 (m, 1H), 7.19 – 7.17 (m, 2H), 7.08 – 7.05 (m, 2H), 4.25 (s, 2H), 2.45 (s, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.3, 136.6, 135.63, 135.61, 133.0, 132.3, 129.5, 127.5, 127.0, 124.8, 37.8, 16.0;

HRMS (EI): calcd for $C_{14}H_{13}NO_2S$ $[M]^+$: 259.0667. Found 259.0667.

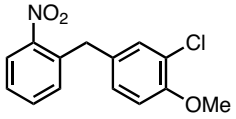


3-20 Prepared according to the General Procedure A from the corresponding arylboronic neopentyl ester (131 mg, 0.50 mmol, 1.0 equiv.) and nitrophenylacetate salt (137 mg, 0.625 mmol, 1.25 equiv.), 50h. 61% yield by ^{1}H NMR using durene as internal standard. Isolated as a light yellow oil in 42% yield after purification by silica gel chromatography (30:1 Hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.52 (td, *J* = 7.6, 1.4 Hz, 1H), 7.46 – 7.43 (m, 2H), 7.38 (m, 1H), 7.29 (m, 1H), 7.16 – 7.13 (m, 2H), 4.30 (s, 2H), 0.25 (s, 9H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.3, 139.2, 138.5, 135.6, 133.7, 132.9, 132.5, 128.4, 127.4, 124.8, 38.3, -1.1;

HRMS (EI): calcd for $C_{16}H_{19}NO_2Si$ $[M]^+$: 285.1185. Found 285.1179.

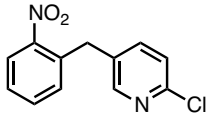


3-21 Prepared according to the General Procedure A from the corresponding arylboronic neopentyl ester (50.9 mg, 0.20 mmol, 1.0 equiv.) and nitrophenylacetate salt (54.8 mg, 0.25 mmol, 1.25 equiv.), 12h. Isolated as a light yellow oil in 70% yield after purification by silica gel chromatography (50:1 to 19:1 Hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.93 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.52 (td, *J* = 7.6, 1.3 Hz, 1H), 7.38 (m, 1H), 7.26 (m, 1H), 7.14 (d, *J* = 2.2 Hz, 1H), 7.01 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 4.22 (s, 2H), 3.86 (s, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 153.7, 149.2, 135.4, 133.1, 132.3, 131.8, 130.6, 128.3, 127.6, 124.9, 122.5, 56.2, 37.3;

HRMS (ESI): calcd for $C_{14}H_{11}ClNO_3$ $[M-H]^-$: 276.0433. Found 276.0429.

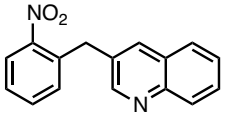


3-22 Prepared according to the General Procedure A from the corresponding arylboronic neopentyl ester (45 mg, 0.20 mmol, 1.0 equiv.) and nitrophenylacetate salt (55 mg, 0.25 mmol, 1.25 equiv.), 7 h. 52% yield by ^{1}H NMR using durene as internal standard. Isolated as a light yellow oil in 58% yield after purification by silica gel chromatography (4:1 hexane:EtOAc) (90% pure, pyridyl homocoupling side-product present).

^{1}H NMR ($CDCl_3$, 498 MHz) δ 8.25 (m, 1H), 8.02 (m, 1H), 7.60 (m, 1H), 7.49 – 7.43 (m, 2H), 7.32 (m, 1H), 7.26 (m, 1H), 4.31 (s, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.88, 149.86, 139.1, 137.0, 134.0, 133.5, 133.3, 132.4, 128.2, 125.3, 124.2, 35.2;

HRMS (ESI): calcd for $C_{12}H_{10}ClN_2O_2$ $[M+H]^+$: 248.0353. Found 248.0353.



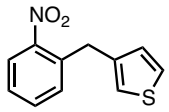
3-23 Prepared according to the General Procedure A from the corresponding arylboronic neopentyl ester (48.2 mg, 0.20 mmol, 1.0 equiv.) and nitrophenylacetate salt

(54.8 mg, 0.25 mmol, 1.25 equiv.), 9h. Isolated as a light yellow solid in 47% yield after purification by silica gel chromatography (2:1 to 1:1 Hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.80 (d, *J* = 2.4 Hz, 1H), 8.08 (m, 1H), 8.01 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.87 (m, 1H), 7.72 (m, 1H), 7.67 (m, 1H), 7.57 (td, *J* = 7.7, 1.4 Hz, 1H), 7.51 (m, 1H), 7.42 (m, 1H), 7.35 (m, 1H), 4.50 (s, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 151.7, 149.1, 147.0, 135.1, 134.5, 133.4, 132.5, 131.6, 129.2, 129.2, 128.0, 128.0, 127.5, 126.9, 125.2, 36.0;

HRMS (ESI): calcd for $C_{16}H_{13}N_2O_2$ $[M+H]^+$: 265.0972. Found 265.0970.

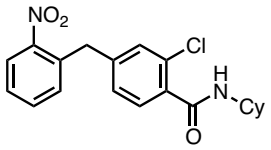


3-24 Prepared according to the General Procedure A from the corresponding arylboronic neopentyl ester (98.0 mg, 0.50 mmol, 1.0 equiv.) and nitrophenylacetate salt (137.0 mg, 1.25 mmol, 1.25 equiv.), 24h. Isolated as a light yellow oil in 56% yield after purification by prep plate (20:1 to 15:1 hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.92 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.64 (td, *J* = 7.6, 1.2 Hz, 1H), 7.37 (m, 1H), 7.31 (m, 1H), 7.25 (m, 1H), 6.96 (m, 1H), 6.90 (dd, *J* = 5.0, 1.2 Hz, 1H), 4.30 (s, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.2, 138.8, 135.5, 133.1, 132.1, 128.3, 127.5, 125.9, 124.8, 122.2, 33.2;

HRMS (EI): calcd for $C_{11}H_9NO_2S$ $[M]^+$: 219.0354. Found 219.0351.

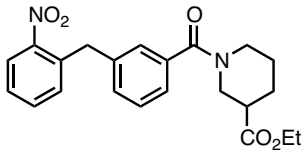


3-25 Prepared according to the General Procedure A from the corresponding arylboronic neopentyl ester (69.9 mg, 0.20 mmol, 1.0 equiv.) and nitrophenylacetate salt (54.8 mg, 0.25 mmol, 1.25 equiv.), 8h. Isolated as a yellow solid in 55% yield after purification by silica gel chromatography (2:1 Hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.99 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.56 (td, *J* = 7.6, 1.3 Hz, 1H), 7.42 (m, 1H), 7.27 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.15 (m, 1H), 7.09 (m, 1H), 6.02 (d, *J* = 7.5 Hz, 1H), 4.30 (s, 2H), 4.09 (m, 1H), 2.04 – 1.99 (m, 2H), 1.75 – 1.70 (m, 2H), 1.62 (m, 1H), 1.45 – 1.38 (m, 2H), 1.28 – 1.18 (m, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 165.3, 149.1, 142.5, 134.2, 133.8, 133.4, 132.6, 130.7, 130.4, 130.3, 128.1, 127.6, 125.2, 48.9, 38.0, 32.9, 25.6, 24.7;

HRMS (ESI): calcd for $C_{20}H_{21}ClN_2O_3Na$ $[M+Na]^+$: 395.1133. Found 395.1135.



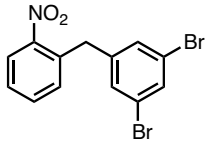
3-26 Prepared according to the General Procedure A from the corresponding arylboronic neopentyl ester (93.3 mg, 0.25 mmol, 1.0 equiv.) and nitrophenylacetate salt (68.5 mg, 0.313 mmol, 1.25 equiv.), 18h. Isolated as a thick light yellow oil in 55% yield after purification by silica gel chromatography (2:1 to 1:1 hexane:EtOAc).

^{1}H NMR (DMSO-d_6, 120 ^{o}C, 400 MHz) δ 7.87 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.61 (td, *J* = 7.6, 1.3 Hz, 1H), 7.49 – 7.42 (m, 2H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.19 – 7.15 (m, 2H),

7.07 (m, 1H), 4.25 (s, 2H), 4.03 (qd, J = 7.0, 1.5 Hz, 2H), 3.93 (m, 1H), 3.61 (m, 1H), 3.18 (dd, J = 12.8, 9.3 Hz, 1H), 3.03 (m, 1H), 2.46 (m, 1H), 1.94 (m, 1H), 1.65 (m, 2H), 1.40 (m, 1H), 1.13 (t, J = 7.0 Hz, 3H);

^{13}C NMR ($DMSO\text{-}d_6$, 120 °C, 101 MHz) δ 172.7, 169.7, 150.0, 139.7, 137.1, 134.6, 133.5, 132.9, 129.9, 128.9, 128.4, 127.2, 125.2, 124.7, 60.4, 46.2, 45.3, 41.2, 37.5, 27.0, 24.1, 14.3;

HRMS (ESI): calcd for $C_{22}H_{25}N_2O_5$ $[M+H]^+$: 397.1758. Found 397.1750.

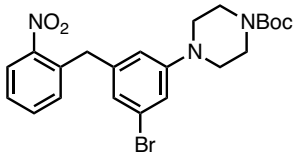


3-27 Prepared according to the General Procedure A from the corresponding arylboronic neopentyl ester (174 mg, 0.50 mmol, 1.0 equiv.) and nitrophenylacetate salt (137 mg, 0.625 mmol, 1.25 equiv.), 17 h. 57% yield by ^{1}H NMR using durene as internal standard. Isolated as puffy white solid in 39% yield after purification by silica gel chromatography (hexane to 16:1 hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 498 MHz) δ 8.03 (dd, J = 8.3, 1.1 Hz, 1H), 7.60 (td, J = 7.6, 1.3 Hz, 1H), 7.55 (m, 1H), 7.46 (m, 1H), 7.30 (m, 1H), 7.25 – 7.23 (m, 2H), 4.27 (s, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.0, 142.7, 133.9, 133.5, 132.6, 132.4, 130.7, 128.2, 125.3, 123.1, 37.9;

HRMS (EI): calcd for $C_{13}H_9Br_2NO_2$ $[M]^+$: 368.9000. Found 368.9007.

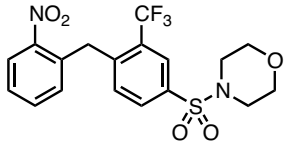


3-28 Prepared according to the General Procedure A from the corresponding arylboronic neopentyl ester (91 mg, 0.20 mmol, 1.0 equiv.) and nitrophenylacetate salt (54 mg, 0.25 mmol, 1.25 equiv.), 26 h. Isolated as a light yellow oil in 59% yield after purification by silica gel chromatography (4:1 to 1:1 hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (m, 1H), 7.52 (m, 1H), 7.38 (m, 1H), 7.26 (m, 1H), 6.87 (m, 1H), 6.74 (m, 1H), 6.62 (m, 1H), 4.19 (s, 2H), 3.54 – 3.48 (m, 4H), 3.11 – 3.03 (m, 4H), 1.45 (s, 9H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 154.8, 152.7, 149.4, 141.6, 135.0, 133.3, 132.5, 127.9, 125.1, 123.5, 123.3, 117.6, 115.9, 80.2, 49.0, 38.4, 28.6;

HRMS (ESI): calcd for $C_{22}H_{27}BrN_3O_4$ $[M+H]^+$: 476.1179. Found 476.1190.



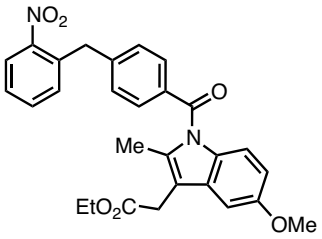
3-29 Prepared according to the General Procedure A from the corresponding arylboronic neopentyl ester (81.4 mg, 0.20 mmol, 1.0 equiv.) and nitrophenylacetate salt (54.8 mg, 0.25 mmol, 1.25 equiv.), 8h. Isolated as a yellow solid in 66% yield (95% purity, 5% protodeborylation side-product present) after purification by silica gel chromatography (10:1 to 1:4 Hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.11 (dd, *J* = 8.1, 1.3 Hz, 1H), 8.09 (m, 1H), 7.79 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.63 (td, *J* = 7.6, 1.3 Hz, 1H), 7.53 (m, 1H), 7.19 (m, 1H), 7.15 (m, 1H), 4.61 (s, 2H), 3.79 – 3.76 (m, 4H), 3.06 – 3.03 (m, 4H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.2, 143.4 (q, *J* = 1.3 Hz), 134.5, 133.7, 132.9, 132.8, 131.4, 131.1 (q, *J* = 1.1 Hz), 129.9 (q, *J* = 31.2 Hz), 128.6, 125.7 (q, *J* = 6.0 Hz), 125.4, 123.5 (q, *J* = 274.6 Hz), 66.0, 45.9, 35.3 (q, *J* = 2.6 Hz);

^{19}F NMR ($CDCl_3$, 376 MHz) d -60.7 (s)

HRMS (ESI): calcd for $C_{18}H_{16}F_3N_2O_5S$ $[M-H]^-$: 429.0738. Found 429.0732.

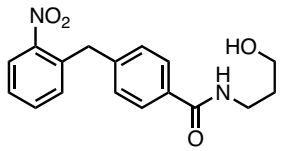


3-30 Prepared according to the General Procedure A from the corresponding arylboronic neopentyl ester (96.4 mg, 0.20 mmol, 1.0 equiv.) and nitrophenylacetate salt (54.8 mg, 0.25 mmol, 1.25 equiv.), 10h. Isolated as a yellow solid in 48% yield after purification by silica gel chromatography (16:1 to 1:1 Hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.99 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.66 – 7.63 (m, 2H), 7.59 (td, *J* = 7.6, 1.3 Hz, 1H), 7.45 (m, 1H), 7.34 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.28 – 7.25 (m, 2H), 6.98 (d, *J* = 2.6 Hz, 1H), 6.89 (d, *J* = 9.0 Hz, 1H), 6.68 (dd, *J* = 9.2, 2.6 Hz, 1H), 4.43 (s, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 3.66 (s, 2H), 2.37 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 170.9, 169.2, 155.9, 149.3, 144.0, 136.0, 134.5, 134.0, 133.2, 132.6, 131.0, 130.6, 130.1, 129.2, 128.0, 125.1, 115.0, 112.4, 111.6, 101.2, 61.0, 55.7, 38.7, 30.5, 14.3, 13.4;

HRMS (ESI): calcd for $C_{28}H_{27}N_2O_6$ $[M+H]^+$: 487.1864. Found 487.1857.

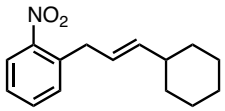


3-31 Prepared according to the General Procedure B from the corresponding arylboronic neopentyl ester (58.2 mg, 0.20 mmol, 1.0 equiv.) and copper arylacetate salt (63.6 mg, 0.15 mmol, 0.75 equiv.), 10h. 41% yield by ^{1}H NMR using durene as internal standard. Isolated as a yellow solid in 20% yield after purification by silica gel chromatography (19:1 CH_2Cl_2:MeOH).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.96 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.70 – 7.67 (m, 2H), 7.54 (td, *J* = 7.60, 1.34 Hz, 1H), 7.41 (m, 1H), 7.27 (m, 1H), 7.22 – 7.20 (m, 2H), 6.52 (m, 1H), 4.35 (s, 2H), 3.70 (q, *J* = 5.4 Hz, 2H), 3.62 (q, *J* = 6.16 Hz, 2H), 2.93 (t, *J* = 5.96 Hz, 1H), 1.78 (pent, *J* = 5.71 Hz, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 168.2, 149.2, 142.6, 134.9, 133.2, 132.6, 132.5, 129.1, 127.8, 127.3, 125.0, 59.8, 38.4, 37.2, 32.2;

HRMS (ESI): calcd for $C_{17}H_{17}N_2O_4$ $[M-H]^-$: 313.1194. Found 313.1194.

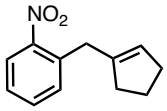


3-32 Prepared according to the General Procedure A from the corresponding vinylboronic neopentyl ester (111 mg, 0.50 mmol, 1.0 equiv.) and nitrophenylacetate salt (153 mg, 0.70 mmol, 1.4 equiv.), 17 h. Isolated as a yellow oil in 54% yield after purification by column chromatography (8:2 Hexane:Toluene).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.87 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.51 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.38 – 7.32 (m, 2H), 5.51 – 5.47 (m, 2H), 3.62 – 3.59 (m, 2H), 1.94 (m, 1H), 1.73 – 1.66 (m, 4H), 1.63 (m, 1H) 1.30 – 1.00 (m, 5H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.5, 139.6, 136.0, 132.8, 131.7, 127.1, 124.5, 123.7, 40.7, 35.9, 33.0, 26.2, 26.1;

HRMS (EI): calcd for $C_{15}H_{19}NO_2$ $[M]^+$: 245.1416. Found 245.1409.

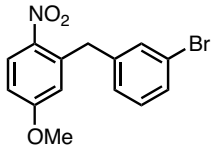


3-33 Prepared according to a modified General Procedure A from the corresponding vinylboronic neopentyl ester (54 mg, 0.30 mmol, 1.5 equiv.), nitrophenylacetate salt (44 mg, 0.2 mmol, 1.0 equiv.), and $Cu(OAc)_2$ (18 mg, 0.1 mmol, 0.5 equiv.), 23 h. 55% yield by ^{1}H NMR using durene as internal standard.

^{1}H NMR ($CDCl_3$, 499 MHz) δ 7.88 (d, *J* = 8.6 Hz, 1H), 7.52 (m, 1H), 7.38 – 7.32 (m, 2H), 5.22 (m, 1H), 3.71 (s, 2H), 2.32 – 2.26 (m, 2H), 2.26 – 2.19 (m, 2H), 1.86 (quint, *J* = 7.6 Hz, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.7, 141.7, 135.1, 132.8, 132.3, 127.3, 126.6, 124.7, 35.4, 34.6, 32.6, 23.6;

HRMS (ESI): calcd for $C_{12}H_{14}NO_2$ $[M+H]^+$: 203.0946. Found 203.0943.

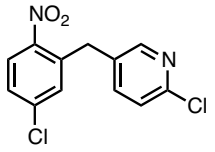


3-39 Prepared according to the General Procedure B from the corresponding arylboronic neopentyl ester (54 mg, 0.20 mmol, 1.0 equiv.) and copper arylacetate salt (73 mg, 0.15 mmol, 0.75 equiv.), 40°C, 9 h. Isolated as a colorless oil in 72% yield after purification by silica gel chromatography (10:1 Hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.12 (d, *J* = 9.2 Hz, 1H), 7.36 (m, 1H), 7.30 (m, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 7.10 (m, 1H), 6.86 (dd, *J* = 9.0, 2.8 Hz, 1H), 6.71 (m, 1H), 4.33 (s, 2H), 3.86 (s, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 163.4, 142.1, 141.2, 138.3, 132.0, 130.2, 129.9, 128.2, 127.8, 122.8, 118.1, 112.3, 56.0, 39.1;

HRMS (EI): calcd for $C_{14}H_{12}NO_3Br$ $[M]^+$: 321.0001. Found 321.0001.



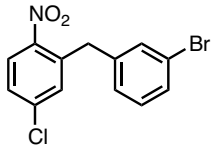
3-40 Prepared according to the General Procedure B from the corresponding arylboronic neopentyl ester (45 mg, 0.20 mmol, 1.0 equiv.) and copper arylacetate salt

(74 mg, 0.15 mmol, 0.75 equiv.), room temperature, 12 h. Isolated as a light yellow oil in 66% yield after purification by silica gel chromatography (13:1 to 4:1 Hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25 (m, 1H), 8.00 (d, *J* = 8.8 Hz, 1H), 7.45–7.40 (m, 2H). 7.30–7.25 (m, 2H), 4.28 (s, 2H);

^{13}C NMR ($CDCl_3$, 151 MHz) δ 150.3, 149.9, 147.2, 140.0, 139.1, 136.1, 132.5, 132.3, 128.5, 126.9, 124.4, 35.1;

HRMS (APPI): calcd for $C_{12}H_9N_2O_2Cl_2$ $[M+H]^+$: 281.9963. Found 281.9958.

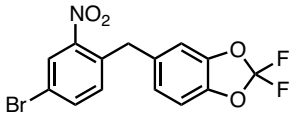


3-41 Prepared according to the General Procedure B from the corresponding arylboronic neopentyl ester (54 mg, 0.20 mmol, 1.0 equiv.) and copper arylacetate salt (74 mg, 0.15 mmol, 0.75 equiv.), room temperature, 13 h. Isolated as a light yellow oil in 67% yield after purification by silica gel chromatography (40:1 to 20:1 Pentane:Et_2O).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.96 (d, *J* = 8.5 Hz, 1H), 7.40–7.37 (m, 2H), 7.30 (m, 1H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 7.09 (m, 1H), 4.27 (s, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 147.4, 140.1, 139.7, 137.0, 132.3, 132.0, 130.4, 130.2, 128.1, 127.7, 126.6, 122.9, 38.0;

HRMS (EI): calcd for $C_{13}H_8NO_2BrCl$ $[M-H]^+$: 323.9427. Found 323.9429.



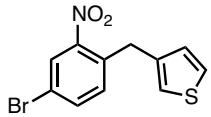
3-42 Prepared according to the General Procedure B from the corresponding arylboronic neopentyl ester (54 mg, 0.20 mmol, 1.0 equiv.) and copper arylacetate salt (87 mg, 0.15 mmol, 0.75 equiv.), room temperature, 10 h. Isolated as a colorless oil in 66% yield after purification by silica gel chromatography (30:1 pentane:Et_2O).

^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.10 (m, 1H), 7.66 (m, 1H), 7.21 (m, 1H), 6.99 (m, 1H), 6.91 (m, 2H), 4.27 (s, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.5, 144.1, 142.7, 136.3, 134.1, 134.0, 133.7, 131.67 (*t*, *J* = 256 Hz), 128.0, 124.0, 121.0, 110.2, 109.5, 37.8;

^{19}F NMR ($CDCl_3$, 469 MHz) δ -49.9 (s)

HRMS (EI): calcd for $C_{14}H_9NO_4F_2Br$ $[M]^+$: 370.9605. Found 370.9599.

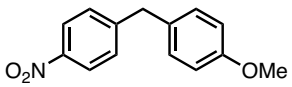


3-43 Prepared according to the General Procedure B from the corresponding arylboronic neopentyl ester (39 mg, 0.20 mmol, 1.0 equiv.) and copper arylacetate salt (87 mg, 0.15 mmol, 0.75 equiv.), room temperature, 8 h. Isolated as a light yellow oil in 70% yield after purification by silica gel chromatography (30:1 pentane:Et_2O).

^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.08 (d, *J* = 2.0 Hz, 1H), 7.64 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.28 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 6.97 (m, 1H), 6.88 (m, 1H), 4.25 (s, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.6, 138.2, 136.2, 134.7, 133.5, 128.3, 127.8, 126.4, 122.6, 120.5, 32.9;

HRMS (EI): calcd for $C_{11}H_8NO_2SBr$ $[M]^+$: 296.9459. Found 296.9454.

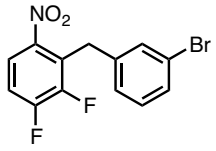


3-44 Prepared according to General Procedure C from the corresponding arylboronic neopentyl ester (66 mg, 0.30 mmol, 1.5 equiv.) and copper arylacetate salt (42 mg, 0.10 mmol, 0.5 equiv.), 35°C, 7.5 h. Isolated as a light yellow oil in 53% yield after purification by silica gel chromatography (15:1 to 10:1 Hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 498 MHz) δ 8.17 – 8.12 (m, 2H), 7.35 – 7.31 (m, 2H), 7.12 – 7.08 (m, 2H), 6.89 – 6.85 (m, 2H), 4.03 (s, 2H), 3.81 (s, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 158.6, 149.5, 146.6, 131.4, 130.1, 129.7, 123.9, 114.4, 55.4, 41.0;

HRMS (EI): calcd for $C_{14}H_{13}NO_3$ $[M]^+$: 243.0895. Found 243.0893.



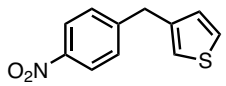
3-45 Prepared according to the General Procedure B from the corresponding arylboronic neopentyl ester (54 mg, 0.20 mmol, 1.0 equiv.) and copper arylacetate salt (74 mg, 0.15 mmol, 0.75 equiv.), room temperature, 13 h. Isolated as a light yellow oil in 53% yield after purification by silica gel chromatography (20:1 to 10:1 Hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.88 (ddd, *J* = 9.2, 4.6, 2.2 Hz, 1H), 7.36 (m, 1H), 7.33 (m, 1H), 7.26 (q, *J* = 8.8 Hz, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.12 (m, 1H), 4.37 (s, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 153.4 (dd, *J* = 259.6, 14.2 Hz), 149.2 (dd, *J* = 251.0, 13.3 Hz), 145.0, 139.4, 131.3, 130.2, 130.1, 127.1, 126.4 (d, *J* = 16.0 Hz), 122.7, 121.8 (dd, *J* = 8.1, 4.1 Hz), 115.8 (d, *J* = 19.0 Hz), 30.3;

^{13}F NMR ($CDCl_3$, 376.145 MHz) δ –126.1 (ddd, *J* = 4.7 Hz, *J* = 8.7 Hz, *J* = 20.3 Hz), –134.6 (m);

HRMS (EI): calcd for $C_{13}H_7NO_2BrF_2$ $[M]^+$: 326.9706. Found 326.9698.

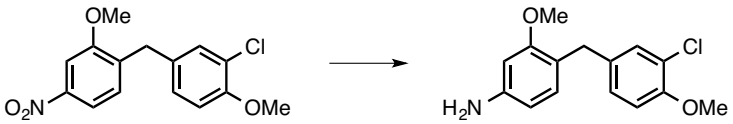


3-46 Prepared according to General Procedure C from the corresponding arylboronic neopentyl ester (78 mg, 0.40 mmol, 2.0 equiv.) and copper arylacetate salt (42 mg, 0.10 mmol, 0.5 equiv.), 35°C, 8.5 h. Isolated as a colorless oil in 54% yield after purification by silica gel chromatography (40:1 to 20:1 Hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 498 MHz) δ 8.18 – 8.13 (m, 2H), 7.38 – 7.33 (m, 2H), 7.30 (m, 1H), 6.97 (m, 1H), 6.89 (m, 1H), 4.09 (s, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 148.4, 146.8, 139.4, 129.6, 128.2, 126.5, 123.9, 122.2, 36.5;

HRMS (EI): calcd for $C_{11}H_9NO_2S$ $[M]^+$: 219.0354. Found 219.0351.



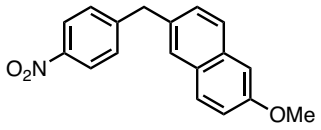
[reduced to facilitate purification]

3-47 Prepared according to General Procedure C from the corresponding arylboronic neopentyl ester (102 mg, 0.40 mmol, 2.0 equiv.) and copper arylacetate salt (48 mg, 0.10 mmol, 0.5 equiv.), 35°C, 13 h. 54% yield by ^{1}H NMR using durene as internal standard. Due to difficulties in separation, a mixture of product and aryl homocoupling, the mixture was reduced to yield aniline products using the same conditions as reported for the synthesis of **3-40**. Reported below is the characterization data of the corresponding aniline.

^{1}H NMR ($CDCl_3$, 498 MHz) δ 7.19 (m, 1H), 7.03 (m, 1H), 6.85 – 6.79 (m, 2H), 6.26 – 6.21 (m, 2H), 3.86 (s, 3H), 3.77 (s, 2H), 3.76 (s, 3H), 3.61 (s, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 158.3, 153.1, 146.4, 135.4, 131.0, 130.6, 127.9, 122.1, 119.6, 112.1, 107.1, 98.8, 56.3, 55.4, 34.3;

HRMS (ESI): calcd for $C_{15}H_{17}ClNO_2$ $[M+H]^+$: 278.0942. Found 278.0948.



3-48 Prepared according to General Procedure C from the corresponding arylboronic neopentyl ester (81 mg, 0.30 mmol, 1.5 equiv.) and copper arylacetate salt (42 mg, 0.10 mmol, 0.5 equiv.), 35°C, 7.5 h. Isolated as a white solid in 52% yield after purification by silica gel chromatography (15:1 to 10:1 hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 498 MHz) δ 8.18 – 8.13 (m, 2H), 7.73 – 7.67 (m, 2H), 7.57 (s, 1H), 7.40 – 7.36 (m, 2H), 7.25 (m, 1H), 7.17 (m, 1H), 7.14 (m, 1H), 4.21 (s, 2H), 3.93 (s, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 157.8, 149.1, 146.7, 134.4, 133.5, 129.8, 129.2, 128.7, 127.9, 127.5, 127.4, 123.9, 119.3, 105.8, 55.5, 41.8;

HRMS (EI): calcd for $C_{18}H_{15}NO_3$ $[M]^+$: 293.1052. Found 293.1047.

CHAPTER 4 – Mechanistic Study of Pd-Catalyzed Decarboxylative Benzylation of Aryl Halides Using Aryl Acetate Salts

4.1 Introduction

The abundance and stability of carboxylic acids make decarboxylative cross-coupling reactions valuable complements to traditional coupling manifolds.[10, 12, 20, 24, 116] The inherent kinetic stability of most carboxylates requires that activation strategies be considered when using these substrates in metal-catalyzed C–C bond forming processes.[11, 24] The arylation of aryl acetates has been established by Lei[29] and Zhu,[30] who developed Pd-catalyzed decarboxylative benzylation reactions of nitroaryl acetates (**Fig. 4-1a**). While these methods allow for the formation of sp^2–sp^3 C–C bonds from carboxylic acids without chemical activation or oxidation, reactivity is limited to highly stabilized nitrophenylacetate substrates, restricting broader applications in synthesis.[117-118] The previous chapter described the development of the oxidative decarboxylative benzylation of aryl boron reagents via aerobic catalysis using potassium nitroaryl acetate salts. This reaction proceeded under ambient conditions (<30°C) and was proposed to proceed via the initial ionic decarboxylation of the aryl acetic acid to form a benzylic anion nucleophile in polar aprotic solvent (DMA). As an extension of this work, we hypothesized that this nucleophilic benzylic intermediate should be arylated efficiently at room temperature with the appropriate choice of aryl halide and Pd/ligand catalyst system (**Fig. 4-1b**). This would stand in stark contrast to the aggressive conditions (140 °C) developed by Lei Liu for the same reaction. Gratifyingly, either 2- or 4-nitrophenyl

acetate potassium salts undergo smooth arylation with chlorobenzene in DMA using $[Pd(cin)Cl]_2$/XPhos as the catalyst system (**Fig. 4-1c**).[119]

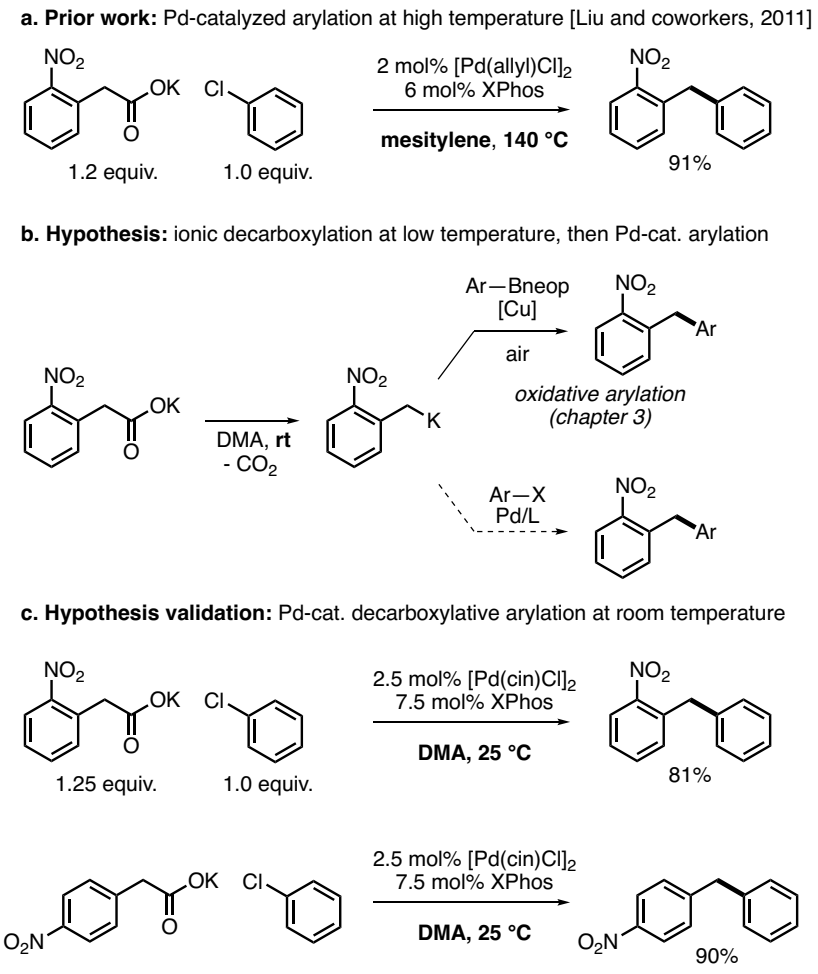
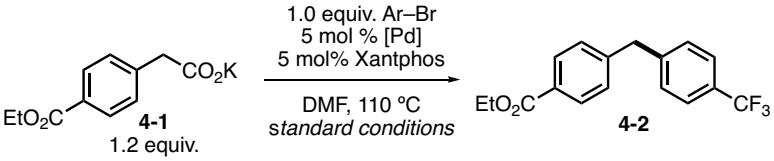


Fig. 4-1 Decarboxylative arylation of nitrophenyl acetate salts at room temperature

To further explore the limits of this reaction with respect to the electronic activation on the aryl acetate partner, various reaction parameters were investigated in depth by postdoctoral fellow Duanyang Kong and undergraduate student Wenyu Qian. An overview of key reaction parameters and representative scope examples are included in **Fig. 4-2**. Aryl acetate partners that have stronger electron-withdrawing groups could be

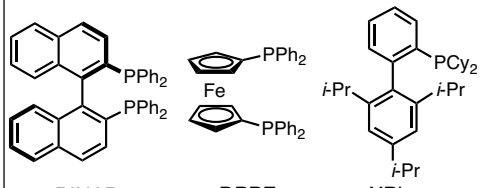
arylated at lower temperature. Hammett parameters (σ_p^-) provided a reasonable metric to gauge the level of activation of a given aryl acetate substrate, and estimate the temperature at which a productive decarboxylative arylation would occur.

a. Key reaction parameters



change from std. cond.	conv. **4-1** / Ar–Br	**4-2**
none	**101 / 100**	**87**
toluene instead of DMF	0 / 8	0
dioxane instead of DMF	6 / 2	0
90 °C instead of 110 °C	13 / 18	10
acid instead of carboxylate[b]	97 / 91	34
$NiCl_2$dme instead of [Pd]	82 / 1	0
Ar–Cl instead of Ar–Br	105 / 91	66
no ligand	81 / 70	15

Other Ligands (selected)

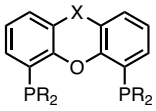


BINAP: 64 / 44 c; 13% y

DPPF: 59 / 50 c; 5% y

XPhos: 60 / 46 c; 8% y

Xantphos Ligands



Xantphos [R = Ph, X = $C(CH_3)_2$] 101 / 100 c; 87% y

DEA-Xantphos [R = NEt_2] 109 / 100 c; 94% y

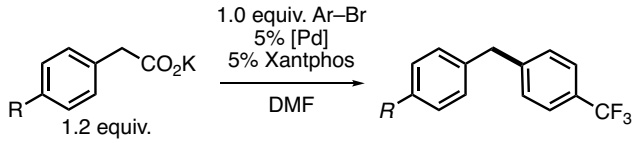
N-Xantphos[a] [R = Ph, X = NH] 105 / 100 c; 82% y

3,5-CF_3-Xantphos [R = 3,5-$CF_3C_6H_3$] 112 / 100 c; 57% y

t-Bu-Xantphos [R = *t*-Bu] 31 / 28 c; 1% y

4-1 (0.12 mmol), Ar–X (0.1 mmol), DMF (0.5 mL), 2.5 h, conv. and yield determined by calibrated ^{1}H NMR (max conv. of **4-1** is 120%), [Pd] = Pd(cinnamyl)Cl, Ar = 4-$CF_3C_6H_4$. [a] 6 h. [b] 120 mol% KO*t*-Bu added.

b. overview of aryl acetate scope



carboxylate R	σ_p^-	*[temp]*	*conv. (%) carboxylate*	*yield (%) product*
SO_2Me	1.13	90 °C	109	79 **(4-3)**
CN	1.00	100 °C	96	76 **(4-4)**
COMe	0.84	110 °C	110	72 **(4-5)**
$CONEt_2$	0.70	135 °C	120	60 **(4-6)**[a]
CF_3	0.65	125 °C	107	66 **(4-7)**[a,b]

carboxylate (0.6 mmol), Ar–Br (0.5 mmol), DMF (0.2 M), 8–14 h, conv. determined by ^{1}H NMR (max conv. of carboxylate is 120%), yields are of purifed material. [Pd] = Pd(cinnamyl)Cl, Ar = 4-$CF_3C_6H_4$. [a] DEA-Xantphos. [b] NMR yield.

Fig. 4-2 Overview of reaction parameters and scope with electron-deficient aryl acetates

The use of carboxylic acids as (pro)nucleophiles in metal-catalyzed cross-coupling reactions leads to the question of which species is the active nucleophile in the bond-forming process and at which stage of the reaction does decarboxylation occurs. For the Pd-catalyzed decarboxylative arylation of aryl acetate salts, two general mechanistic pathways could be operational (**Fig 4-3**). One involves the generation of a benzylic nucleophile via decarboxylation of aryl acetate (path A). Palladium may or may not be involved in this step, but ultimately a Pd(aryl)(benzyl) species is formed which can undergo product-forming reductive elimination. An alternative mechanism involves the generation of a dienolate species (path B). Here, aryl acetate decarboxylation generates a basic benzyl potassium which can deprotonate another aryl acetate partner. After Pd-catalyzed arylation, the corresponding diaryl carboxylate could undergo decarboxylation and abstract a proton from another equivalent of aryl acetate. As both Pd-catalyzed cross-coupling of benzylic nucleophiles[120] and dienolates[121] have been reported, we investigated the process to gain insight into the fundamental steps involved in the decarboxylative benzylation reaction.

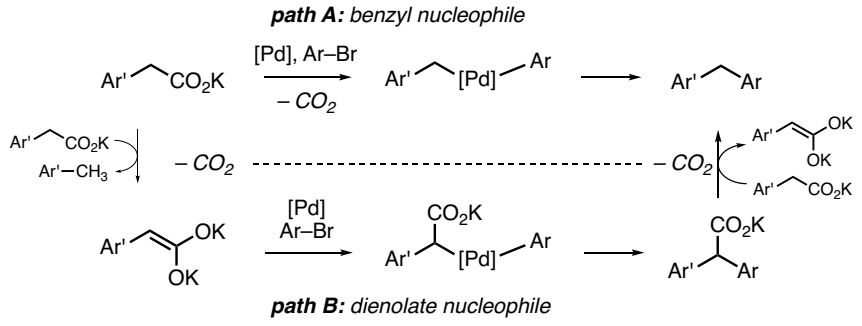


Fig. 4-3 Potential mechanistic pathways for the Pd-catalyzed decarboxylative benzylation of aryl halides

4.2 Mechanistic Studies

Subjecting aryl acetate **4-8** to standard reaction conditions without catalyst or aryl bromide leads to substrate decarboxylation (**Fig. 4-4**). The decarboxylation stops at ~50% toluene (**4-10**, **Tol**) formation, quenching with D_2O demonstrates the proto-decarboxylation occurs *in-situ*, suggesting against the accumulation of benzyl anion and instead the generation of a dienolate (**4-9**) in solution which would be resistant to spontaneous extrusion of CO_2.

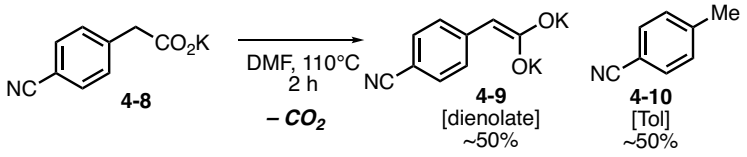


Fig. 4-4 Speciation of aryl acetate salt to form dienolate

The initial rate of formation of toluene **4-10** in the absence of Pd/ArBr is similar to that of product formation (**4-4**) under standard conditions (**Fig 4-5**). A small amount of non-productive aryl acetate protodecarboxylation (**4-10**) is observed under catalytic conditions. Since the intial rate for toluene **4-10** formation in the absence of Pd/ArBr closely mirrors the rate of product **4-4** formation under catalytic conditions (i.e. with Pd/ArBr), both processes likely share a common rate-determining-step which would potentially be decarboxylation of aryl acetate **4-8**.

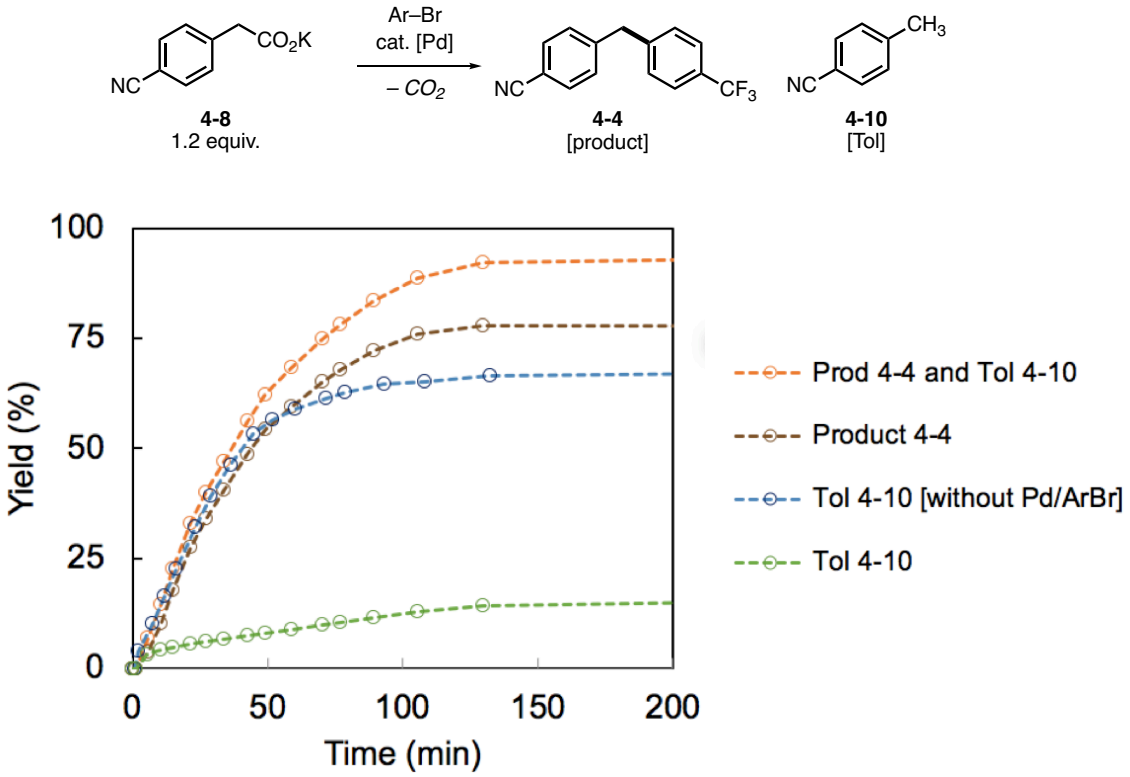


Fig. 4-5 Kinetic profile of protodecarboxylation and diarylmethane product formation

A crossover experiment in which a 1:1 ratio of aryl acetate and D_2-aryl acetate lead to rapid H/D exchange at the methylene position (**Fig 4-6**). This observation was mirrored in catalytic reactions, where the diarylmethane product was generated with approximately the statistic mixture of H_2/HD/D_2 labelled products (~1:2:1). These results are consistent with a dienolate arylation mechanism (Path B, **Fig. 4-3**) where significant H/D cross-over in the product is expected due to the methylene deprotonation and protonation steps involved. However, a direct benzyl nucleophile arylation mechanism (Path A, **Fig. 4-3**) cannot be ruled out because the H/D scrambling observed in the product could be due to background non-productive dienolate formation.

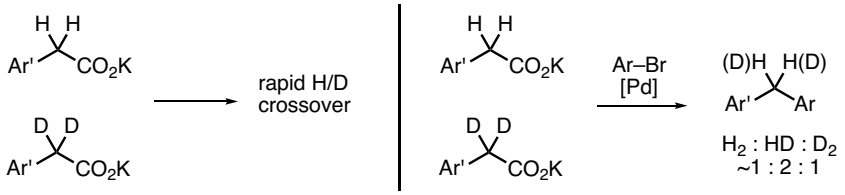


Fig. 4-6 Deuterium labelling experiment to probe the exchange of aryl acetate methylene protons

Finally, for aryl acetate that has been allowed to decarboxylate in the absence of catalyst and aryl bromide (reaching ~50% toluene formation), D_2O quenching does not form D-labelled toluene derivative, but instead generates methylene D-labelled aryl acetic acid. Under the same conditions, introduction of catalyst and aryl bromide after a 2 hour preheating incubation period leads to diarylmethane product formation without change in the amount of toluene derivative (**Fig. 4-7**). A small amount of triarylmethane product **4-11** was also observed. Collectively these experiments are consistent with a pathway in which an initial decarboxylation event generates a catalytic base, which can lead to the formation of a dienolate nucleophile (Path B, **Fig. 4-3**).

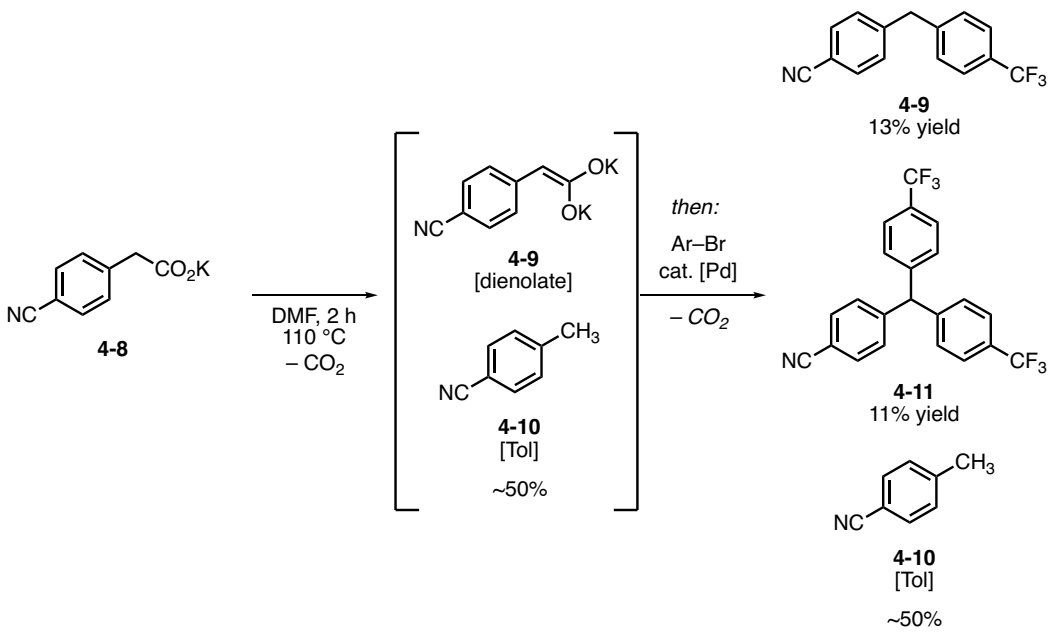


Fig. 4-7 Pd-catalyzed decarboxylative arylation of arylacetate after a preheating incubation period

4.3 Summary and Conclusions

In summary, the mechanistic understanding that electronically activated aryl acetate salts undergo decarboxylation at low temperatures in the appropriate polar aprotic solvent has allowed a significant improvement in the scope of Pd-catalyzed decarboxylative benzylations of aryl halides. Given that decarboxylation occurs from otherwise stable precursors by mild heating, this simple protocol should be of value for preparing functionalized diarylmethanes. Mechanistic experiments point towards the formation of a dienolate species being the active nucleophile, which should guide the development related decarboxylative coupling of poorly-activated acids.

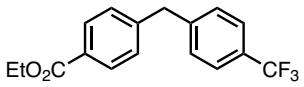
4.4 Procedures and Characterization

General Considerations:

Unless noted, all reactions were conducted under inert atmosphere employing standard schlenk technique or by the use of a N2-filled glovebox. All glassware was oven-dried prior to use. Flash chromatography was performed using SiliaFlash P60 (40-63μm, 60A silica gel, Silicycle) or by automated flash chromatography (Isolera, HP-SIL or Ultra SNAP silica cartridges, Biotage). Analytical thin-layer chromatography was performed using glass plates pre-coated with silica (SiliaPlate G TLC - Glass-Backed, 250μm, Silicycle). TLC plates were visualized by UV light and/or staining with aqueous basic potassium permanganate. NMR spectra (^{1}H, ^{13}C, ^{19}F) were obtained on an Agilent VNMRS 700 MHz, Varian VNMRS 600 MHz, Varian VNMRS 500 MHz, or Varian 400 MHz spectrometer. The chemical shifts are given as parts per million (ppm) and were referenced to the residual solvent signal (CDCl3: δH = 7.26 ppm, δC = 77.16 ppm). Unless otherwise noted, quantitative ^{1}H NMR yields were determined from crude reaction mixtures using durene as an internal standard. Optical rotation data were obtained using a Perkin Elmer 241 Polarimeter at 589 nm and 25° C, using a 10 cm path-length cell. Unless otherwise noted, all reagents were obtained from commercial vendors and used as supplied.

General Procedure: Xantphos or DEA-Xantphos ligand (0.050 equiv.), potassium aryl acetate (1.2 equiv.) and aryl bromide (1.0 equiv.) were added sequentially

to a 1-dram vial charged with a stir bar. [Pd(cinnamyl)Cl]$_2$ dimer (0.025 equiv.) was then added as a solution in anhydrous DMF (0.0050 M). The vial was sealed with a PTFE-lined cap under inert atmosphere, removed from the glovebox and heated while stirring. ^{1}H NMR analysis of small aliquots (~5 mL) was used to follow reactions to completion (1–24 hours), afterwhich the mixture was diluted in ethyl acetate (80 mL) and washed sequentially with saturated NH_4Cl (20 mL) and brine (20 mL). For reactions using heteroaryl bromides, Na_2CO_3 (1 M, 20 mL) was used instead of NH_4Cl. The organic layer was dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified by flash column chromatography.



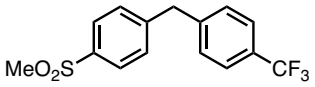
4-2 Prepared according to the General Procedure from the corresponding aryl bromide (113 mg, 0.50 mmol, 1.0 equiv.), potassium aryl acetate (148 mg, 0.60 mmol, 1.2 equiv.), [Pd(cinnamyl)Cl]$_2$ (6.5 mg, 0.0125 mmol, 0.025 equiv.), and XantPhos (14.5 mg, 0.025 mmol, 0.050 equiv.) in 2.5 mL DMF, 110 °C. Isolated as a light yellow solid in 73% yield after purification by silica gel chromatography (20:1 hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 498 MHz) δ 7.99 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 4.37 (q, *J* = 7.2 Hz, 2H), 4.09 (s, 2H), 1.38 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.4, 145.1, 144.3, 130.0, 129.3, 128.9 (2), 128.8 (q, *J* = 27.3 Hz) 127.4 (q, *J* = 272.6 Hz), 125.5 (q, *J* = 3.7 Hz), 60.9, 41.7, 14.4;

^{19}F NMR ($CDCl_3$, 469 MHz) δ -62.4;

HRMS (EI): calcd for $C_{17}H_{15}F_3O_2$ $[M]^+$: 308.1024. Found 308.1023.



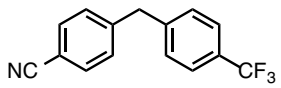
4-3 Prepared according to the General Procedure from the corresponding aryl bromide (68 mg, 0.30 mmol, 1.0 equiv.), potassium aryl acetate (91 mg, 0.36 mmol, 1.2 equiv.), $[Pd(cinnamyl)Cl]_2$ (3.9 mg, 0.0075 mmol, 0.025 equiv.), and XantPhos (8.7 mg, 0.015 mmol, 0.050 equiv.) in 1.5 mL DMF, 90 °C. Isolated as a light yellow solid in 79% yield after purification by silica gel chromatography (4:1 hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 498 MHz) δ 7.89–7.87 (m, 2H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 4.13 (s, 2H), 3.04 (s, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 146.4, 143.4, 138.8, 129.8, 129.3, 129.1 (q, *J* = 32.5 Hz), 127.8, 126.2 (q, *J* = 272.7 Hz), 125.7 (q, *J* = 4.3 Hz), 44.5, 41.5;

^{19}F NMR ($CDCl_3$, 469 MHz) δ -62.5;

HRMS (EI): calcd for $C_{15}H_{13}F_3O_2S$ $[M]^+$: 314.0588. Found 314.0586.

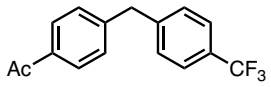


4-4 Prepared according to the General Procedure from the corresponding aryl bromide (113 mg, 0.50 mmol, 1.0 equiv.), potassium aryl acetate (120 mg, 0.60 mmol, 1.2 equiv.), $[Pd(cinnamyl)Cl]_2$ (6.5 mg, 0.0125 mmol, 0.025 equiv.), and XantPhos (14.7 mg, 0.025 mmol, 0.050 equiv.) in 2.5 mL DMF, 100 °C. Isolated as a light yellow oil in 76% yield after purification by silica gel chromatography (20:1 to 10:1 hexane:EtOAc). Spectroscopic data agreed with that reported.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62–7.57 (m, 4H), 7.30–7.27 (m, 4H), 4.11 (s, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 145.5, 143.3, 132.5, 129.6, 129.3, 129.1 (q, J = 32.4 Hz), 125.7 (q, J = 3.8 Hz), 124.1 (q, J = 271.5 Hz), 118.8, 110.6, 41.7;

^{19}F NMR ($CDCl_3$, 469 MHz) δ -62.5.

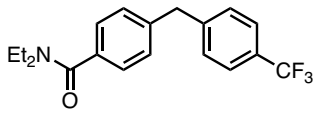


4-5 Prepared according to the General Procedure from the corresponding aryl bromide (45 mg, 0.20 mmol, 1.0 equiv.), potassium aryl acetate (52 mg, 0.24 mmol, 1.2 equiv.), $[Pd(cinnamyl)Cl]_2$ (2.6 mg, 0.005 mmol, 0.025 equiv.), and XantPhos (5.8 mg, 0.01 mmol, 0.050 equiv.) in 1.0 mL DMF, 110 °C. Isolated as a light yellow oil in 72% yield after purification by silica gel chromatography (8:1 hexane:EtOAc). Spectroscopic data agreed with that reported.

^{1}H NMR ($CDCl_3$, 498 MHz) δ 7.91–7.89 (m, 2H), 7.55 (d, *J* = 7.5 Hz, 2H), 7.29–7.26 (m, 4H), 4.09 (s, 2H), 2.58 (s, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.6, 145.5, 144.0, 135.6, 129.2, 129.1, 128.9 (q, *J* = 32.6 Hz), 128.7, 125.5 (q, *J* = 3.9 Hz), 124.2 (q, *J* = 273.0 Hz), 41.6, 26.6;

^{19}F NMR ($CDCl_3$, 469 MHz) δ -62.4.



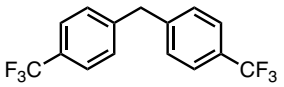
4-6 Prepared according to the General Procedure from the corresponding aryl bromide (45 mg, 0.20 mmol, 1.0 equiv.), potassium aryl acetate (66 mg, 0.24 mmol, 1.2 equiv.), $[Pd(cinnamyl)Cl]_2$ (2.6 mg, 0.005 mmol, 0.025 equiv.), and DEA-XantPhos (5.6 mg, 0.01 mmol, 0.050 equiv.) in 1.0 mL DMF, 135 °C. Isolated as a light yellow solid in 60% yield after purification by silica gel chromatography (2:1 hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 498 MHz) δ 7.54 (d, *J* = 8.1 Hz, 2H), 7.32-7.26 (m, 4H), 7.19 (d, *J* = 8.1 Hz, 2H), 4.04 (s, 2H), 3.38 (br, 4H), 1.17 (br, 6H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.1, 144.6, 141.0, 135.5, 129.2, 128.9, 128.7 (q, *J* = 33.8 Hz), 126.8, 125.4 (q, *J* = 4.2 Hz), 124.3 (q, *J* = 271.3 Hz), 43.3, 41.5, 39.3, 14.2, 12.9;

^{19}F NMR ($CDCl_3$, 469 MHz) δ -62.3;

HRMS (ESI): calcd for $C_{19}H_{21}F_3NO$ $[M+H]^+$: 336.1570. Found 336.1571.

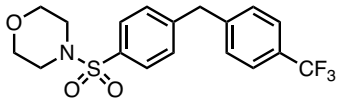


4-7 Prepared according to the General Procedure from the corresponding aryl bromide (113 mg, 0.50 mmol, 1.0 equiv.), potassium aryl acetate (145 mg, 0.60 mmol, 1.2 equiv.), $[Pd(cinnamyl)Cl]_2$ (6.5 mg, 0.0125 mmol, 0.025 equiv.), and DEA-XantPhos (14 mg, 0.025 mmol, 0.050 equiv.) in 2.5 mL DMF, 125 °C. 66% yield by ^{1}H NMR using durene as internal standard (53% isolated yield). Spectroscopic data agreed with that reported.

^{1}H NMR ($CDCl_3$, 498 MHz) δ 7.56 (d, J = 8.2 Hz, 4H), 7.29 (d, J = 8.2 Hz, 4H), 4.09 (s, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 143.9, 129.2, 128.9 (q, J = 33.8 Hz), 125.6 (q, J = 4.2 Hz), 124.1 (q, J = 271.3 Hz), 41.5;

^{19}F NMR ($CDCl_3$, 469 MHz) δ -62.4.



4-8 Prepared according to the General Procedure from the corresponding aryl bromide (23 mg, 0.10 mmol, 1.0 equiv.), potassium aryl acetate (39 mg, 0.12 mmol, 1.2 equiv.), $[Pd(cinnamyl)Cl]_2$ (1.3 mg, 0.0025 mmol, 0.025 equiv.), and XantPhos (2.9 mg, 0.005 mmol, 0.050 equiv.) in 0.5 mL DMF, 100 °C. Isolated as a yellow solid in 75% yield after purification by silica gel chromatography (8:1 to 2:1 hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 4.12 (s, 2H), 3.74 (t, *J* = 4.8 Hz, 4H), 2.99 (m, 4H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 145.7, 143.4, 133.3, 129.6, 129.3, 129.1 (q, *J* = 33.3 Hz), 128.3, 125.7 (q, *J* = 3.5 Hz), 124.0 (q, *J* = 271.3 Hz), 66.1, 45.9, 41.4;

^{19}F NMR ($CDCl_3$, 469 MHz) δ -62.4;

HRMS (ESI): calcd for $C_{18}H_{18}F_3NO_3SNa$ $[M+Na]^+$: 408.0852. Found 408.0851.

CHAPTER 5 – Enantioselective Benzylation Directly from Aryl Acetic Acids

5.1 Introduction

Carboxylic acids are stable and abundant chemical feedstocks, making them ideal starting materials in chemical synthesis.[11] The extrusion of CO_2 from organic acids and their derivatives is a key mechanistic step in both classical and emerging bond-forming methodologies used in the preparation of functional molecules.[10, 12, 17, 24, 40, 122] Unmodified carboxylic acids are typically directly engaged in catalytic enantioselective processes through mechanistic pathways initiated by decarboxylation to generate a reactive intermediate. Ionic decarboxylation leads to a carbanion intermediate which can be intercepted stereoselectively with electrophiles (**Fig. 5-1**).[123-126] Alternatively, single electron oxidation leads to the loss of CO_2 by homolysis, generation of a radical species, and stereoselective trapping with a chiral catalyst and a suitable reaction partner.[127-129]

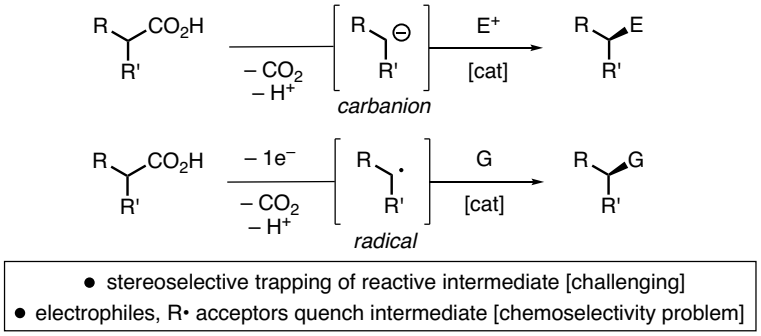


Fig. 5-1 Cross-couplings featuring ionic or radical decarboxylation as the initial step

In both these reaction manifolds, acid substrates that are otherwise recalcitrant towards decarboxylation can be covalently modified by fragments that can undergo

oxidative insertion[12, 26-27] or those that induce homolysis[130-131] in order to initiate reactivity. These indirect acid coupling strategies decrease overall process economy and efficiency. An illustrative example is the Pd-catalyzed enantioselective decarboxylative allylation of prochiral allyl enol carbonates reported by Stoltz and coworkers (**Fig. 5-2**).[26] Oxidative addition and subsequent decarboxylation leads to a Pd^{II}[allyl][enolate] intermediate, which can undergo C–C bond forming reductive elimination to generate the α-carbonyl quaternary carbon center.

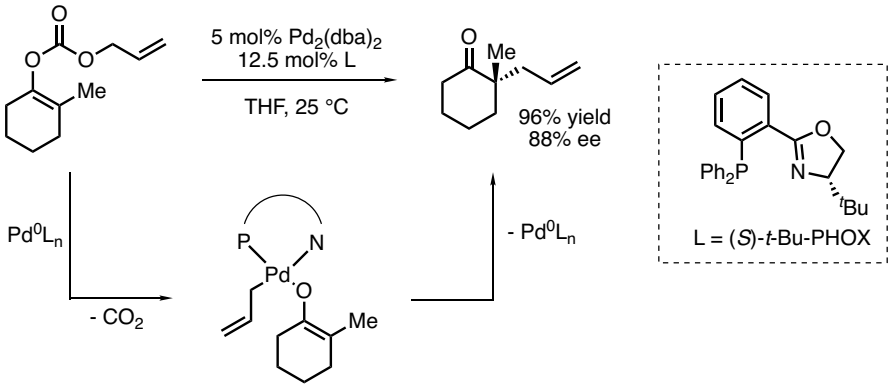


Fig. 5-2 Pd-catalyzed enantioselective decarboxylative allylation from allyl enol carbonates

A third mechanistic framework involves a stereoselective bond-forming event *prior* to decarboxylation (**Fig. 5-3**).[42] As the selectivity-determining bond forming event is separate from the decarboxylation step, this pathway has distinct potential advantage over methods relying upon the irreversible generation and trapping of reactive intermediates. Functionality that would quench highly nucleophilic species (protic groups, electrophiles) or intercept radicals (π-systems, weak abstractable CH bonds) could be tolerated in this

pathway, providing broad chemoselectivity and functional group compatibility – hallmarks of enabling synthetic methodologies.[86, 132]

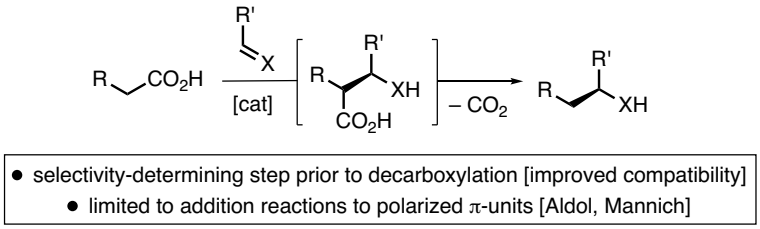


Fig. 5-3 Decarboxylation after stereodetermining step.

The ability to induce an enantioselective metal-catalyzed cross-coupling event adjacent to a free carboxylate unit without irreversible interference from the acid itself however, presents a major difficulty. Efforts to exploit this type of reactivity have been restricted to the use of malonic half esters and related β-carboxy carbonyl substrates in aldol or Mannich reactions and additions to π-electrophiles,[17, 42, 133] thus their larger potential in selective synthesis remains unrealized.

In considering new transformations that could leverage the advantage of pre-decarboxylative coupling of acids in enantioselective catalysis, we questioned whether aryl acetic acids could be used as benzylating reagents in metal-catalyzed asymmetric coupling reactions. In particular, we sought to develop the stereocontrolled benzylation of allylic electrophiles,[25, 29-30, 119, 134-137] owing to the diverse utility of chiral allylated products and the known ability of transition metals to affect nucleophile allylation processes.[26, 138-140] This approach would contrast methods that require stoichiometric strong base and Lewis acid additives to generate highly reactive benzylic anions from 2-pyridinyl and related electronically activated heteroaromatic substrates (**Fig. 5-4**).[141-144]

With these methods, coordination of the heteroaromatic with the BF_3 lewis acid is proposed to increase the acidity of the benzylic C–H bonds and stabilize the benzylic nucleophile formed after deprotonation.

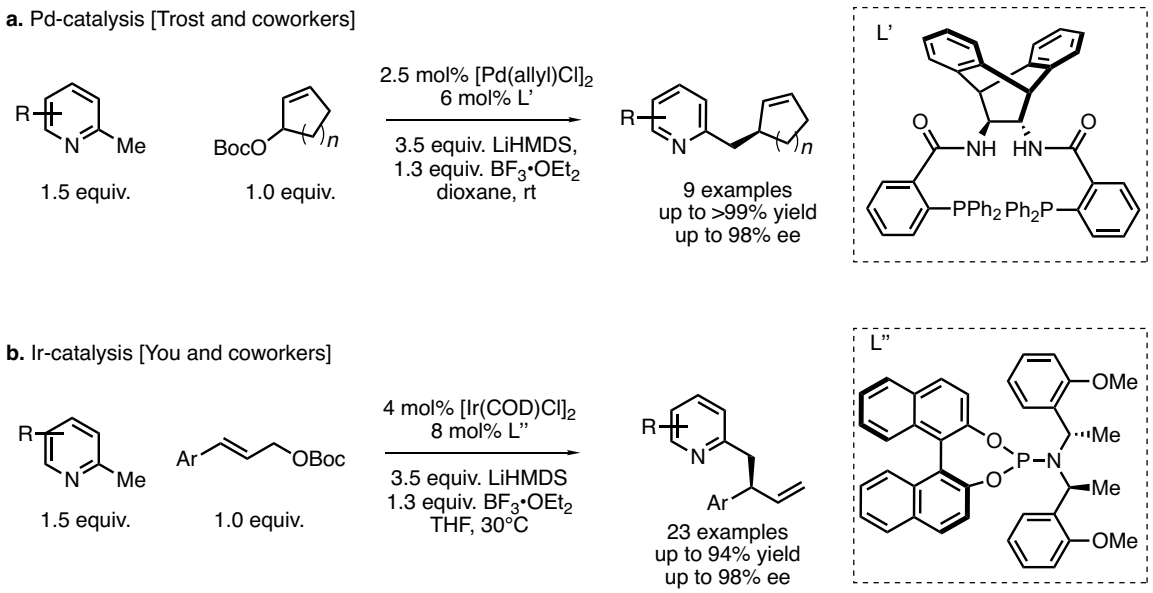


Fig. 5-4 Pd- or Ir-catalyzed benzylation of allylic electrophiles under strongly basic conditions

A feasible pathway for the decarboxylative benzylation would involve reversible metal-catalyzed carboxylate O-allylation from an allylic electrophile to generate an allyl aryl acetate (**5-1** in **Fig. 5-5**). The ester species could then undergo a second metal-catalyzed allylic substitution at the enolate position to form a new carbon–carbon bond (**5-2**). Catalytic and reversible O-deallylation via oxidative insertion would generate a new metal-allyl fragment for re-entry into the catalytic cycle and liberate the functionalized carboxylic acid (**5-3**). At this stage, the decarboxylation event would generate the benzylated $C(sp^3)$–$C(sp^3)$ coupled product (**5-4**).

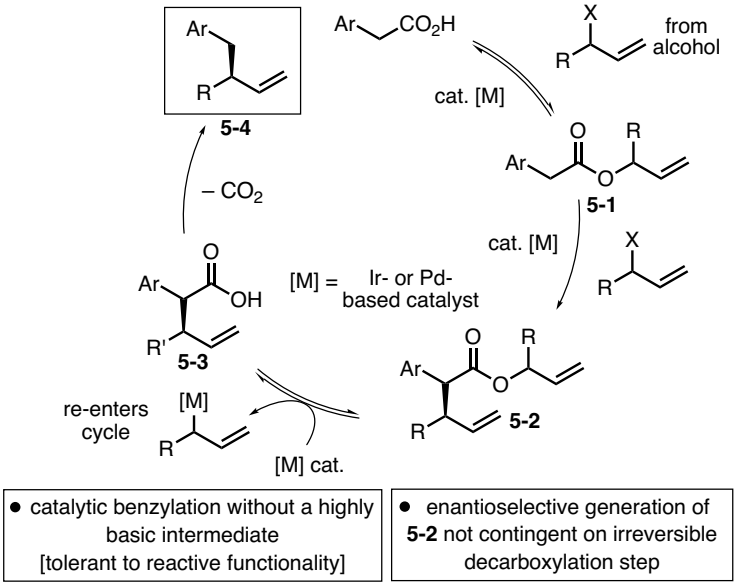


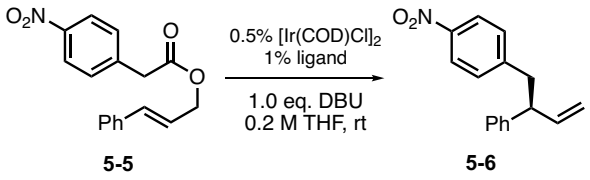
Fig. 5-5 Potential mechanism for decarboxylative benzylation

As the key stereocenter is generated prior to decarboxylation, substrates less prone to CO_2 extrusion could be subjected to reaction conditions to enable product formation without impacting the selectivity determining step. Heating the reaction mixture would be the simplest approach. This strategy would allow for enantioselective benzylation to occur without the generation of a strongly basic, functional group-intolerant benzyl anion, enabling the reaction to occur in the presence of protic and electrophilic groups. Such an approach would parallel alternative reductive coupling strategies pioneered by Krische that circumvents the use of preformed organometallics.[145] Furthermore, the process has the potential to be highly chemoselective for benzylic acids in the presence of other carboxylic acid groups typically employed in radical- or ionic-decarboxylative cross-coupling reactions, should O-allylation be reversible over the course of the reaction. Buoying our hope for a highly enantioselective process were recent reports that aryl acetic esters similar in structure to proposed intermediate **5-1** (**Fig. 5-5**) are suitable

nucleophiles in metal-catalyzed enantioselective allylic alkylations.[146-147] During our studies, Kanai and co-workers demonstrated that allylic esters can undergo Pd/B dual catalyzed fragmentation and recombination to generate chiral homoallylic carboxylic acids (analogous to the conversion of intermediate **5-1** to **5-3** with linear allylic substitution).[148]

5.2 Development of the Enantioselective Benzylation of Allylic Electrophiles Directly using Aryl Acetic Acids

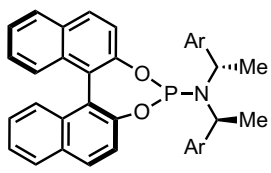
Cinnamyl aryl acetate **5-5** was initially investigated to screen Ir/phosphoramidite catalyst systems (**Table 5-1**) which have previously been described for related Ir-catalyzed asymmetric allylic alkylation of other nucleophiles.[149] High enantioselectivity (>95% ee) of product **5-6** was observed with ligands L1 and L2, as compared to ligands L3, L4, and L5 which provided lower yield and enantioselectivity.



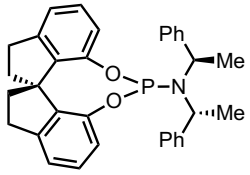
5-5 **5-6**

entry	ligand	conv. (%)	yield (%)	e.e. (%)	4-nitrotoluene(%)
1	L1	100	37	96	29
2	**L2**	**100**	**80**	**99**	**14**
3	L3	87	20	26	32
4	L4	27	<3	nd	8
5	L5	25	<3	nd	12

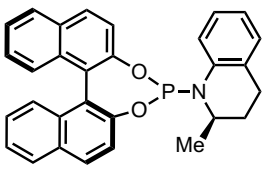
Reactions performed on 0.10 mmol scale. Yields determined by calibrated ^{1}H NMR using durene as internal standard.



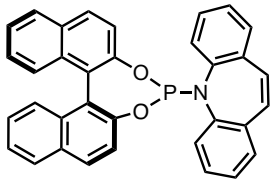
(S_a, S)-L1: Ar = Ph
(S_a, S)-L2: Ar = o-MeOPh



(S_a, R)-L3



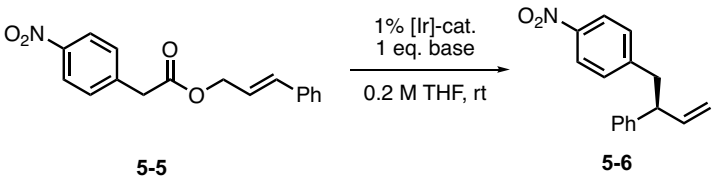
(S_a, R)-L4



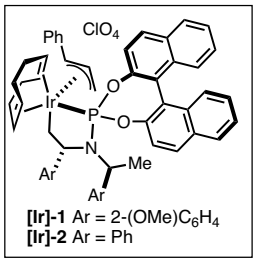
(S_a)-L5

Table 5.1 Reaction development: screen of chiral phosphoramidite ligands

It was later discovered that the cyclometallated Ir/phosphoramidite complexes [Ir]-1 and [Ir]-2[150-152] provided higher yields with similar enantioselectivity compared to *in situ* formed catalyst mixtures (Table **5-2**). These cyclometallated Ir-complexes are easily prepared in one step from $[Ir(COD)Cl]_2$ and are believed to be the active catalyst in related Ir-catalyzed asymmetric allylic alkylation reactions.[140, 151] Alternative bases such as *t*-BuOK, NEt_3, DIPEA or DBN proved inferior to DBU.



5-5 **5-6**



[Ir]-1 Ar = 2-(OMe)C_6H_4
[Ir]-2 Ar = Ph

entry	catalyst	base	conv. (%)	yield (%)	e.e. (%)	4-nitrotoluene(%)
1	**[Ir]-1**	**DBU**	**100**	**85**	**99**	**-**
2	**[Ir]-2**	**DBU**	**100**	**88**	**98**	**12**
3	[Ir]-2	DBN	100	76	98	23
4	[Ir]-2	t-BuOK	100	<3	nd	<3
5	[Ir]-2	NEt_3	65	<3	nd	<3
6	[Ir]-2	DIPEA	55	<3	nd	<3

Reactions performed on 0.10 mmol scale. Yields determined by calibrated ^1H NMR using durene as internal standard.

Table 5-2 Reaction development: effect of base

Fig. 5-6 provides an example of the exquisite site-selectivity observed in this enantioselective decarboxylative benzylation of allylic electrophiles. In the presence of Ir-catalyst [Ir]-1 and DBU, the diacid substrate **5-7** undergoes enantioselective coupling exclusively at the benzylic position to generate **5-9** (88%, 99% ee) without interference from the benzoic acid unit.

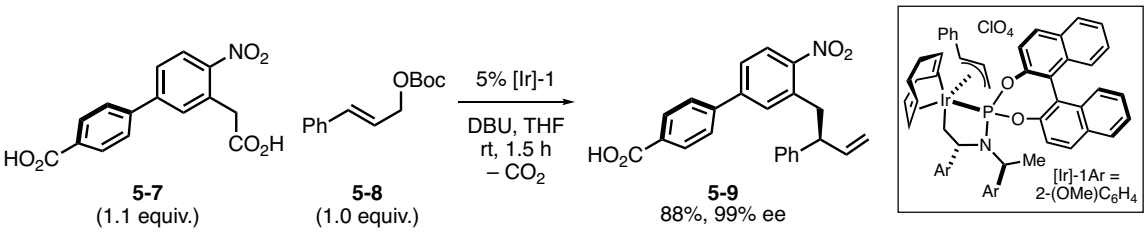


Fig. 5-6 Site-selective Ir-catalyzed enantioselective decarboxylative coupling

Monitoring of the reaction of cinnamyl aryl acetate **5-10** using [Ir]-2 as catalyst clearly showed the rapid generation of C,O-bis-allylic ester **5-11** which slowly O-deallylates to C-allylic acid **5-12** that is formed as an ultimately inconsequential mixture of diastereomers with high enantioselectivity at the benzylic position (**Fig. 5-7**). These observations are in line with the mechanistic hypothesis outlined in **Fig. 5-5**.

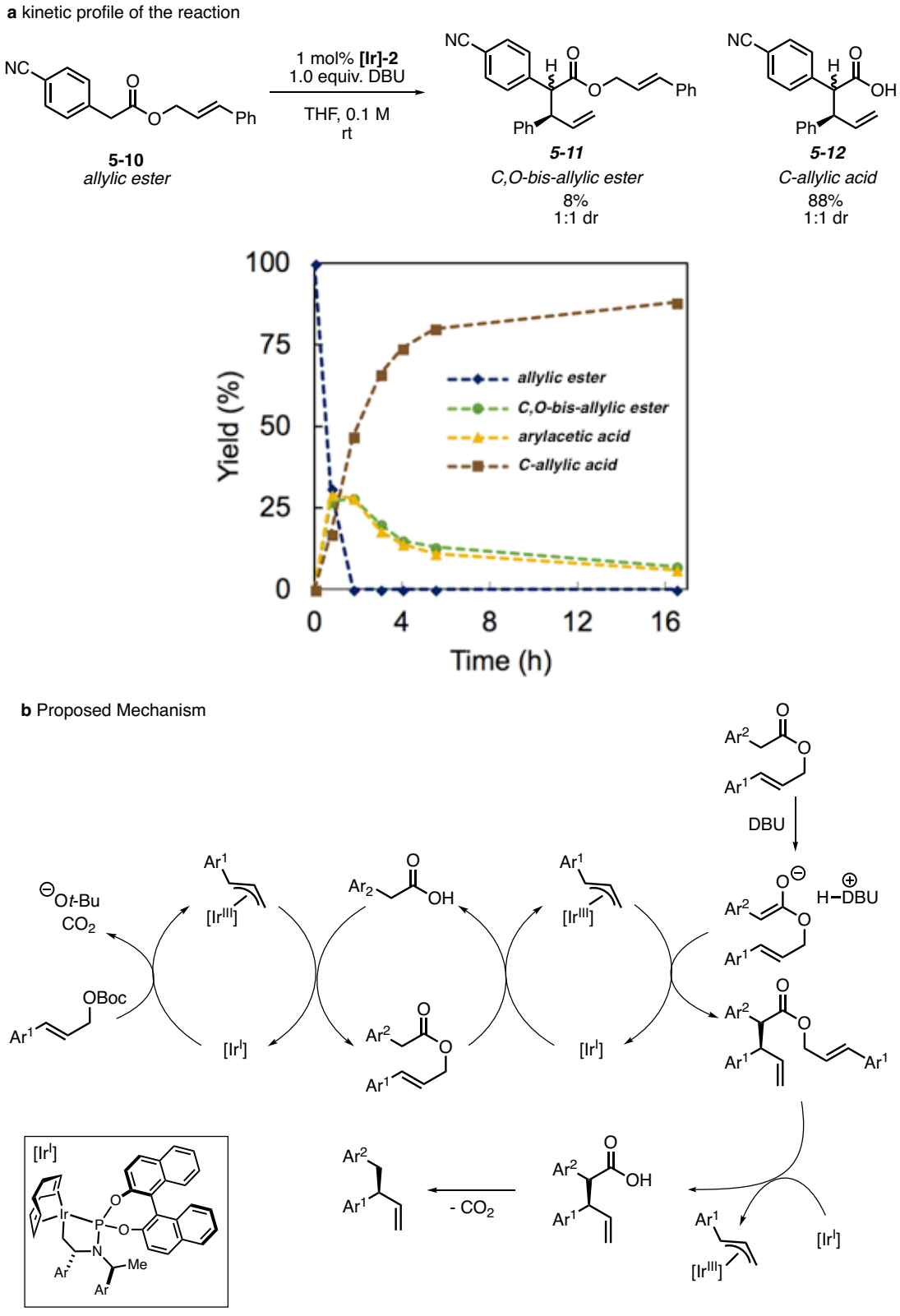


Fig. 5-7 Kinetic profile of the Ir-catalyzed enantioselective benzylation reaction and proposed mechanism

A cross-over experiment was conducted to rule out a potential mechanism that would involve a [3,3]-sigmatropic rearrangement (**Fig. 5-8**). Differentially substituted allylic aryl acetates **5-13** and **5-14** were subjected to standard conditions to yield a mixture of all four possible benzylation products. **5-15** and **5-17** would be expected as exclusive products should a sigmatropic rearrangement mechanism be operational.

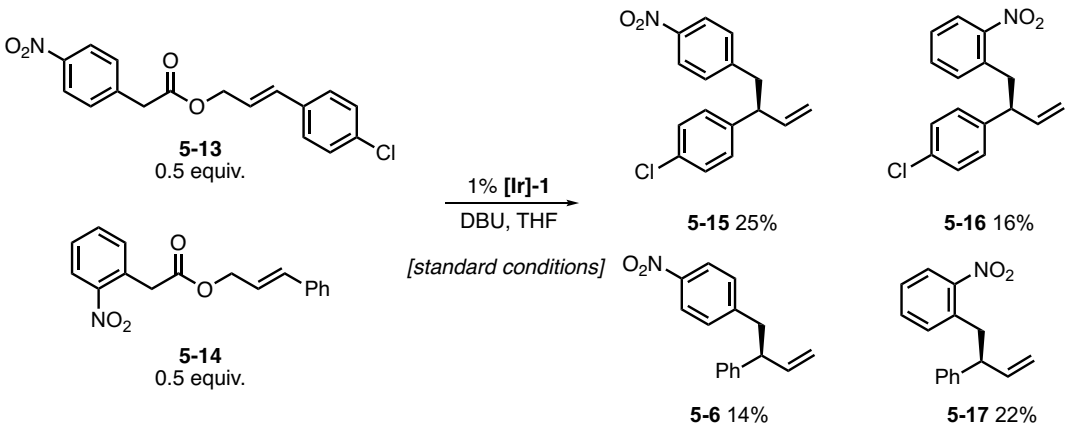


Fig. 5-8 Cross-over experiment

In cases where decarboxylation is not spontaneous at room temperature, heating the reaction at 70–90 °C for short periods of time delivers product with high yield and no impact on enantioselectivity (**5-18 to 5-23**, **Fig. 5-9**). A comprehensive intermolecular functional group compatibility survey showed the reaction proceeded with similar yields and enantioselectivities in the presence of both electrophilic and protic groups (aldehyde, ketone, free NH-groups, alkyl chloride, N-Boc amino acid, alkyl alcohol, phenol, alternative carboxylic acids, conjugate acceptors, N-heterocycle). The majority of these groups would protonate or undergo other reactions with organometallic benzyl

nucleophiles, or species generated upon single-electron oxidation conditions, highlighting the advantage of the current approach.

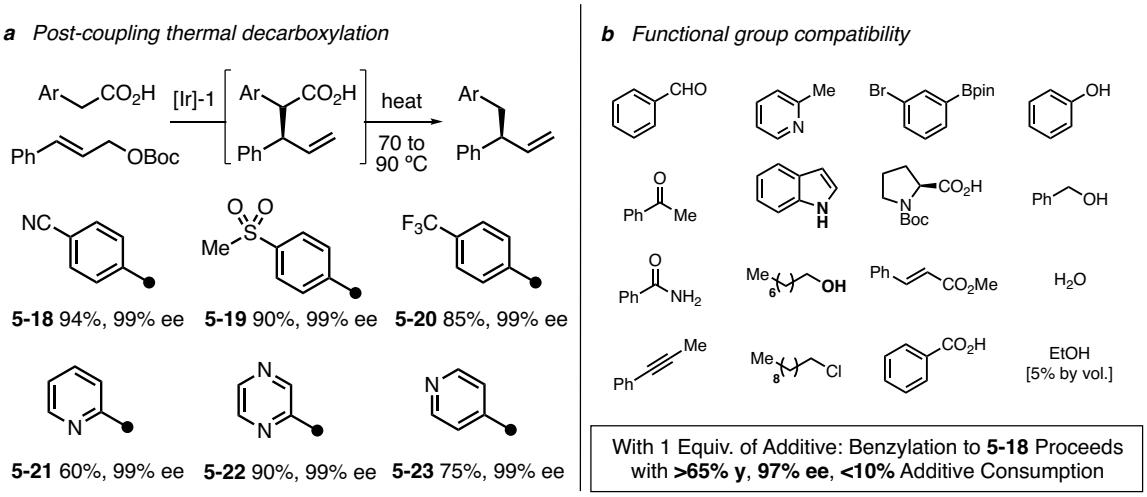
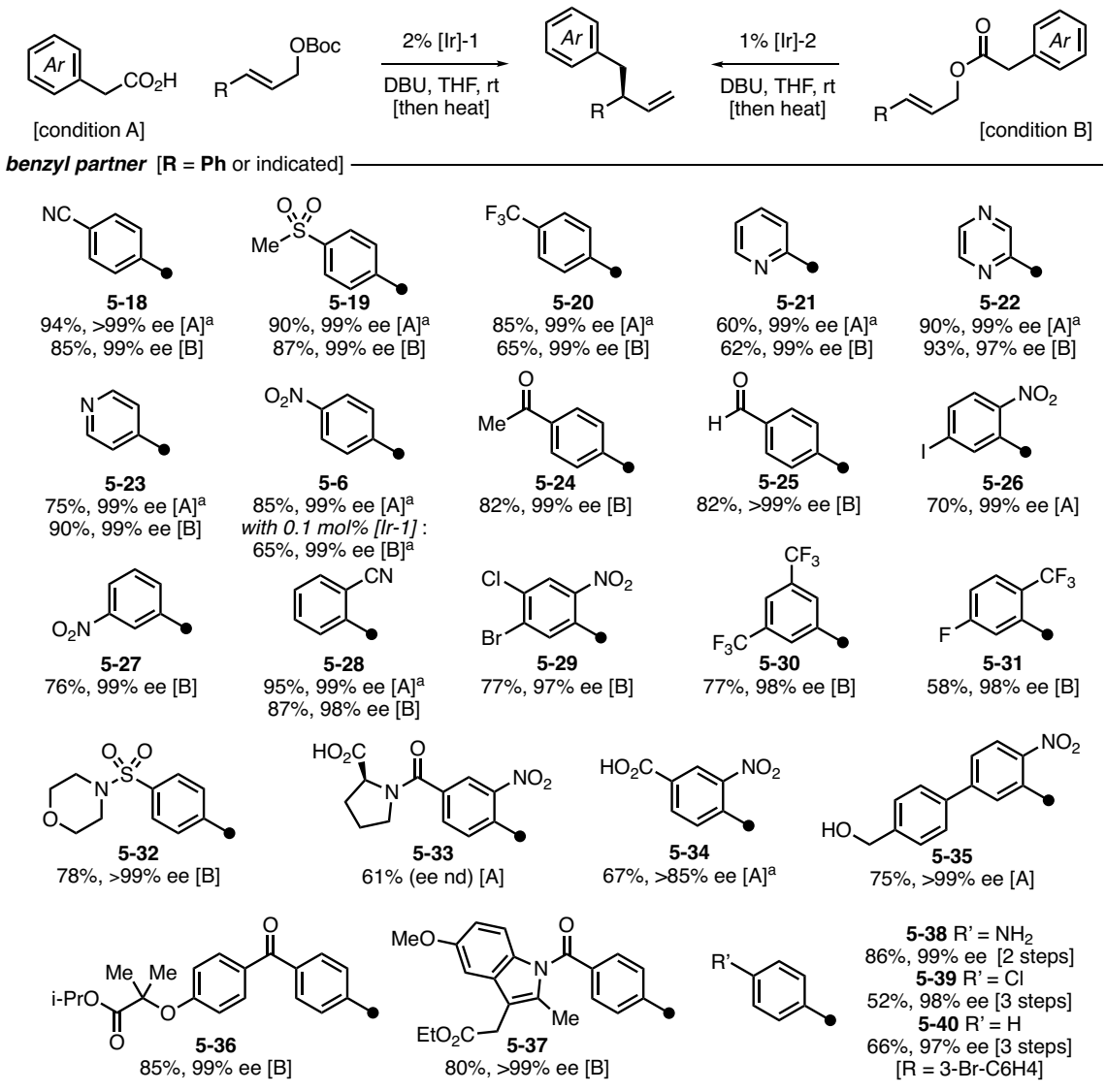


Fig 5-9 Post-coupling decarboxylation and functional group compatibility

The scope of the enantioselective benzylation is demonstrated in **Table 5-3**. Either a combination of aryl acetic acid and allylic carbonate or allyl aryl acetate esters can be used as substrate components. The alcohol activation step (carbonate vs ester) differentiates these methods and provides additional flexibility in substrate preparation. In the case of Ir-catalyzed reactions, uniformly high enantioselectivies (97–99% ee) are observed across a range of benzyl partners, including N-heterocycles (**5-21** to **5-23**), substrates bearing potentially reactive electrophilic or protic functionality (**5-24** to **5-26, 5-33** to **5-35**) including aryl iodides, aldehydes, other carboxylic acid groups, and polysubstituted reagents. Catalyst loadings as low as 0.1 mol% can be employed in some cases (**5-6**). Products derived from aryl acetic acid substrates that are resistant to decarboxylative coupling under the standard conditions can be easily accessed in

reasonable overall yields and excellent enantioselectivities by way of simple nitro group manipulations (52–86% yield, 97–99% ee, **5-38** to **5-40**).

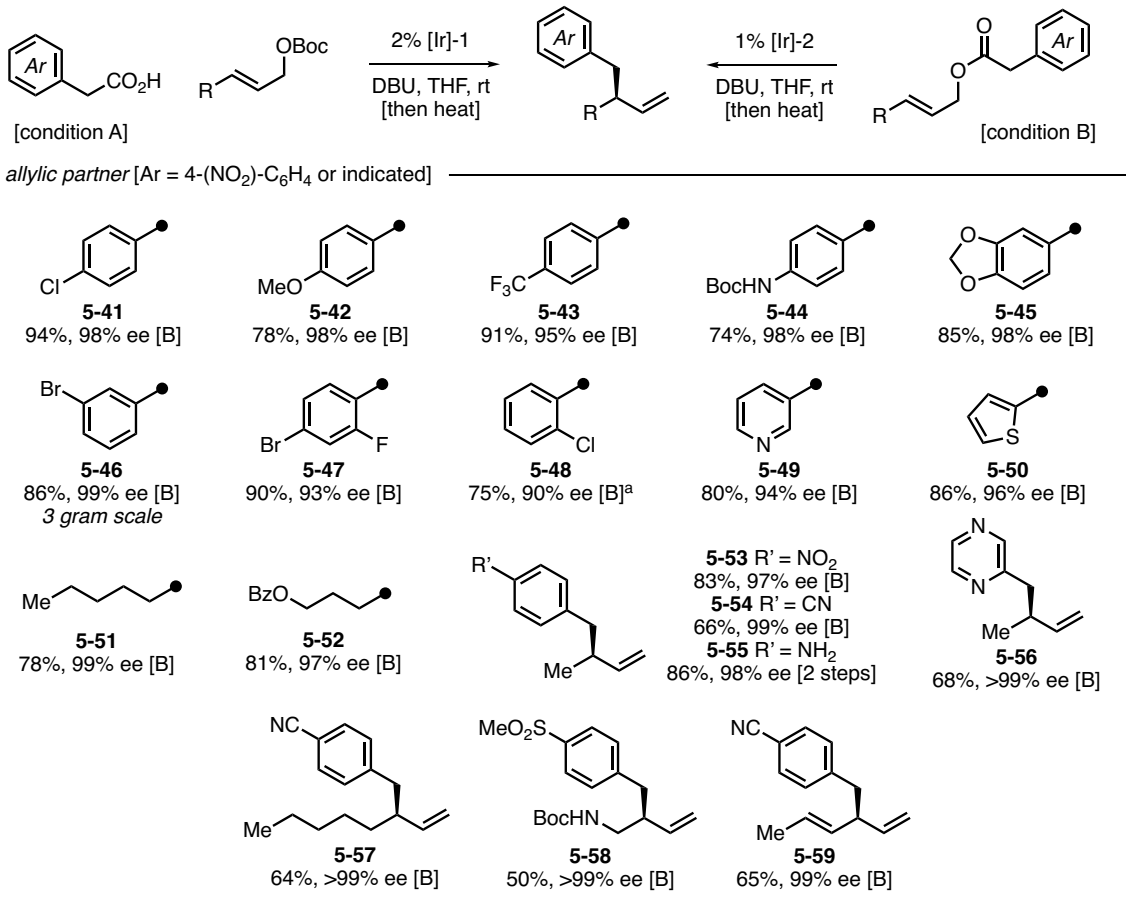


[a]Yields determined by ^{1}H NMR using an internal standard.

Table 5-3 Scope of arylacetic acid partner

The allyl fragment can vary in structure and also host a number of potentially reactive functional groups without significant change to process efficiency (halogens,

NH-groups, N- and S-heterocycles, 90–99% ee, **Table 5-4**). Alkyl-substituted allylic electrophiles are competent partners, giving access to simple methyl (**5-53 to 5-56**), long-chain alkyl (**5-51, 5-57**), and heteroatom-substituted (**5-52**, **5-58**) chiral benzylated products. These results are significant because long chain-alkyl-substituted allylic fragments are uncommon partners in Ir-catalyzed enantioselective alkylation reactions.[153]

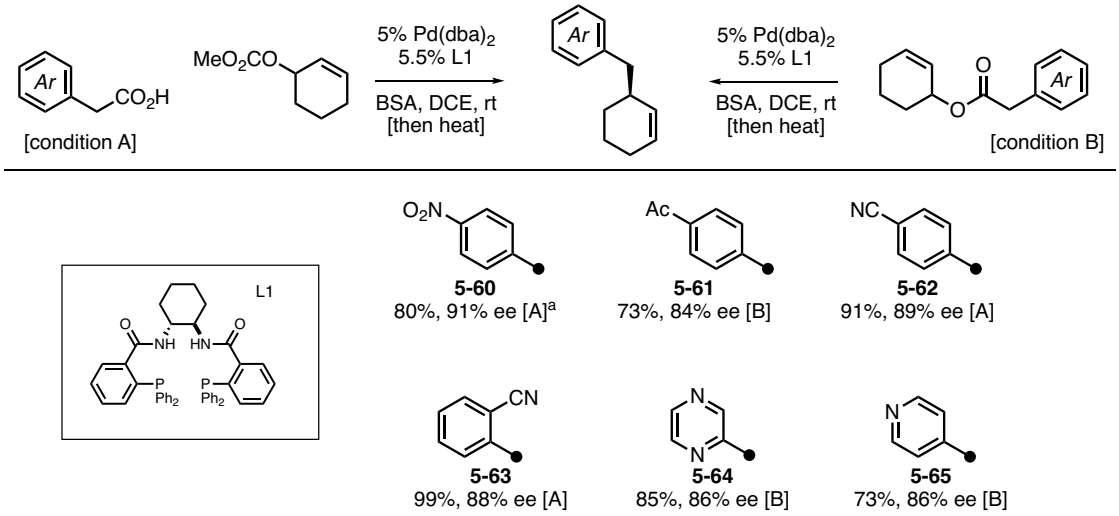


[a]Conducted at 0°C

Table 5-4 Scope of allylic partner

The generality of this approach is demonstrated with the benzylation of cyclic allylic electrophiles via Pd-catalysis using a Trost-type system and BSA as the base (**Table 5-5**).[154] Slightly lower selectivity (83–91% ee), but similarly broad scope of aryl

acetic acid partner from either allylic carbonates or allylic ester electrophiles was observed (**5-60 to 5-65**).



[a]Conducted at 0°C

Table 5-5 Pd-catalyzed decarboxylative benzylation

The utility of this reaction concept to access high-value, chiral benzylated intermediates of importance to human health was demonstrated by the expedient preparation of the core fragments of Elacestrant and Taranabant (**Fig. 5-10**). Briefly, condensation between aryl acetic acids and suitably functionalized allylic alcohols, followed by Ir-catalyzed enantioselective decarboxylative benzylation gives effectively single-enantiomer products (**5-68, 5-46,** both 99% ee) primed for conversion to bioactive targets, including at multi-gram scale. Ring-closing metathesis, hydrogenation, and Sandmeyer hydroxylation converts **5-68** to cyclic product **5-70** which bears the chiral core of Elacestrant.[155] Conversion of the nitro group in **5-46** to chlorine, followed by

ketone-selective Wacker oxidation[156] and diasteroselective reduction gives product **5-74**, which can be converted to (*ent*)-Taranabant via an established route.[157]

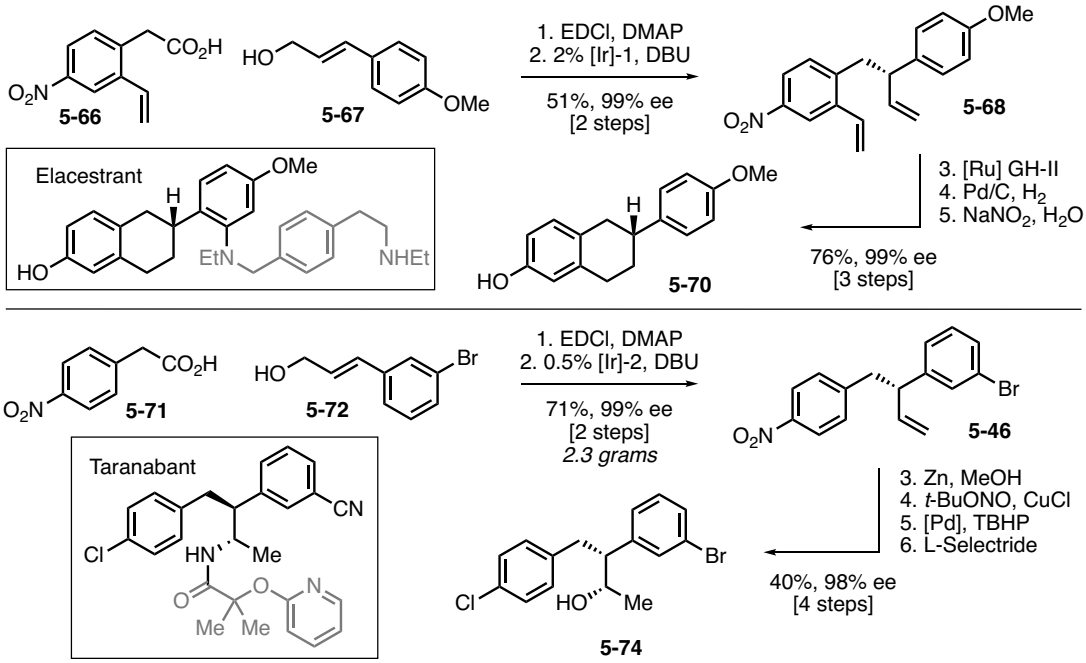


Fig. 5-10 Synthesis of the core structures of Elacestrant and Taranabant

A few limitations were uncovered for this decarboxylative benzylation reaction (**Fig. 5-11**). Substitution on the cinnamyl fragment (tertiary olefins, **5-75**, **5-76**) results in low conversion of starting material, likely due to a difficult oxidative addition step. Electron-deficient cinnamyl fragments (**5-77**) also proved problematic due to isomerization of the terminal olefin in the product (**5-78**) to the thermodynamically more stable internal olefin (**5-79**). Poor reactivity was observed with α-substituted aryl acetate partners (**5-80**), perhaps due to inefficient trapping of an Ir-allyl with a more sterically hindered enolate. Finally, ortho-substituents on the cinnamyl fragment (**5-81**) resulted in

lowered enantioselectivities under standard conditions. This problem could be partially addressed with lowering of the temperature to 0°C (see **5-48**, **Table 5-4**).

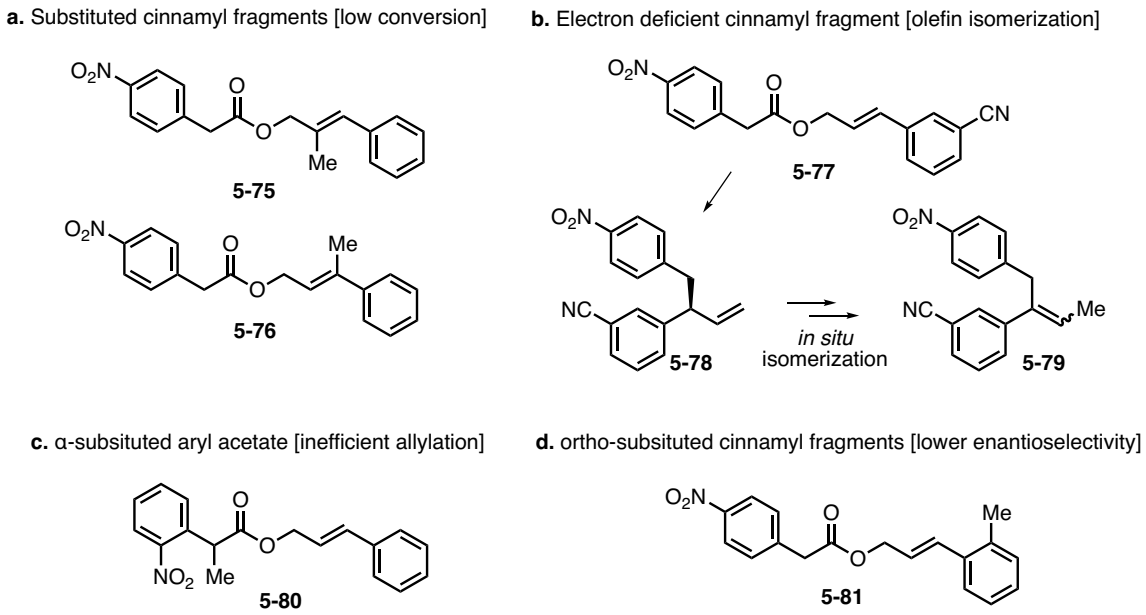


Fig. 5-11 Limitations and problematic substrates

5.3 Summary

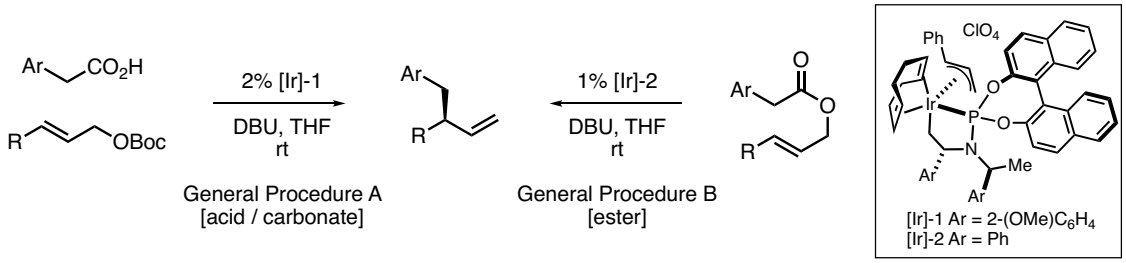
Reported is a new enantioselective benzylation of allylic electrophiles, directly from aryl acetic acids. The reaction proceeds via a pathway in which decarboxylation is the terminal event, occurring after a stereoselective carbon–carbon bond forming step. Compared to established methods, this process proceeds under mildly basic conditions and tolerates a broad range of protic and electrophilic functionality, thus highlighting its potential in complex molecule synthesis. Collectively, these studies show that the use of carboxylic acids as reagents in metal-catalyzed coupling reactions in which decarboxylation occurs as a terminating step has value in generating carbon–carbon bonds with high levels of enantio- and chemoselectivity.

5.4 Procedures and Characterization

General Considerations:

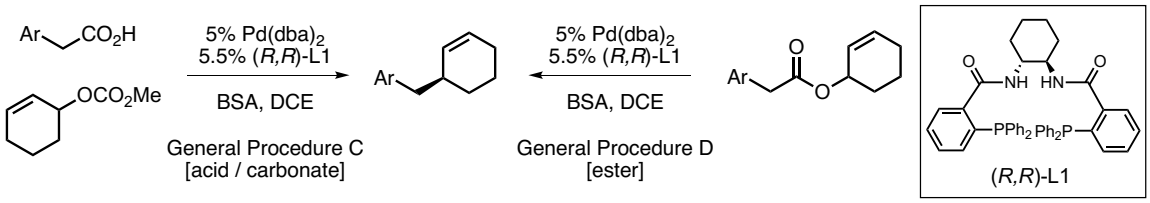
Unless noted, all reactions were conducted under inert atmosphere employing standard schlenk technique or by the use of a N2-filled glovebox. All glassware was oven-dried prior to use. Flash chromatography was performed using SiliaFlash P60 (40-63μm, 60A silica gel, Silicycle) or by automated flash chromatography (Isolera, HP-SIL or Ultra SNAP silica cartridges, Biotage). Analytical thin-layer chromatography was performed using glass plates pre-coated with silica (SiliaPlate G TLC - Glass-Backed, 250μm, Silicycle). TLC plates were visualized by UV light and/or staining with aqueous basic potassium permanganate. HPLC analysis was accomplished on an Agilent 1290 system with Daicel CHIRALPAK IA, IB, IC or IG columns (4.6 x 150 mm, 5 μm particle size), or Regis Whelk O-1 column (4.6 x 250 mm, 5 μm particle size). NMR spectra (^{1}H, ^{13}C, ^{19}F) were obtained on an Agilent VNMRS 700 MHz, Varian VNMRS 600 MHz, Varian VNMRS 500 MHz, or Varian 400 MHz spectrometer. The chemical shifts are given as parts per million (ppm) and were referenced to the residual solvent signal (CDCl3: δH = 7.26 ppm, δC = 77.16 ppm). Unless otherwise noted, quantitative ^{1}H NMR yields were determined from crude reaction mixtures using durene as an internal standard. Optical rotation data were obtained using a Perkin Elmer 241 Polarimeter at 589 nm and 25° C, using a 10 cm path-length cell. Unless otherwise noted, all reagents were obtained from commercial vendors and used as supplied.

5.4.1 General Procedures for the Decarboxylative Benzylation of Allylic Alcohol Derivatives



General Procedure A: In an atmosphere controlled glovebox, (*S,S,S*)-[Ir]-1 (2.2 mg, 0.002 mmol, 0.02 equiv.), aryl acetic acid (1.00 – 1.20 equiv.), cinnamyl carbonate (23.4 mg, 0.10 mmol, 1.00 equiv.) and durene internal standard were sequentially added to a 1-dram vial charged with a stir bar. THF (0.5 mL) was added and the mixture was stirred until homogeneous (approx. 1 minute), followed by the addition of DBU (1.00 – 1.20 equiv.). The vial was sealed with a PTFE-lined cap, removed from the glovebox and gently stirred at room temperature. Upon completion of the reaction (14–24 h), the yield was determined by ^{1}H NMR using durene as internal standard. For products that undergo spontaneous decarboxylation at room temperature, the reaction mixture was concentrated *in vacuo* and purified by preparative TLC. For products that do not undergo spontaneous decarboxylation at room temperature, the reaction mixture was diluted with an equal volume of DMF (0.5 mL), then heated (70 to 90 °C to induce decarboxylation (1 – 5 h, time not optimized). The yield was determined by ^{1}H NMR using durene as internal standard. The mixture was diluted with 12 mL EtOAc, washed with 1 mL 1 M HCl and 2 x 2 mL brine. The organic layer was dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified by silica gel chromatography. The use of a glovebox is not required to achieve optimal results, see **2h** for example.

General Procedure B: In an atmosphere controlled glovebox, (*S,S,S*)-[Ir]-1 or (*S,S,S*)-[Ir]-2 (0.005 mmol, 0.01 equiv.), allylic aryl acetate (0.5 mmol, 1.00 equiv.), and durene internal standard were sequentially added to a 1-dram vial charged with a stir bar. THF (2.5 mL) was added and the mixture was stirred until homogeneous (approximately 1 minute), followed by the addition of DBU (76.1 mg, 0.50 mmol, 1.0 equiv.). The vial was sealed with a PTFE-lined cap, removed from the glovebox and gently stirred at room temperature. Upon completion of the reaction (2 – 24 h) as determined by ^{1}H NMR using durene as internal standard, the reaction mixture was concentrated *in vacuo* and purified by silica gel chromatography. For products that do not undergo spontaneous decarboxylation at room temperature, the reaction mixture was transferred to a 4-dram vial, and diluted with an equal volume of DMF (2.5 mL). The vial was sealed with a PTFE-lined cap and flushed with N_2 for 5 min. The solution was then heated (70 to 90 °C) to induce decarboxylation (1 –19 h, time not optimized). Upon completion of the reaction, the mixture was diluted with 60 mL EtOAc, washed with 5 mL 1 M HCl and 2 x 10 mL brine. The organic layer was dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified by silica gel chromatography.

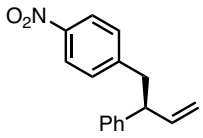


General Procedure C: In an atmosphere controlled glovebox, $Pd(dba)_2$ (2.9 mg, 0.005 mmol, 0.05 equiv.) and (*R,R*)-DACH-phenyl Trost ligand L1 (3.8 mg, 0.0055 mmol, 0.055 equiv.) were sequentially added to a 0.5-dram vial charged with a stir bar. DCE (0.1 mL) was added and the mixture was stirred for 10 minutes. In a separate 0.5-dram vial charged with a stir bar, aryl acetic acid (0.15 mmol, 1.5 equiv.), cyclohex-2-enyl methyl carbonate (15.6 mg, 0.10 mmol, 1.0 equiv.) and durene internal standard were added. The Pd/ligand solution was transferred to the vial with DCE rinses (2 x 0.2 mL). The reaction mixture was stirred for another 10 minutes, followed by the addition of BSA (61.0 mg, 0.30 mmol, 3.0 equiv.). The vial was sealed with a PTFE-lined cap, removed from the glovebox and gently stirred at room temperature. Upon completion of the reaction (14 – 48 h) as determined by ^{1}H NMR using durene as internal standard, the reaction mixture was treated with diethylamine (150 μL) and stirred for 1 h. The mixture was then concentrated *in vacuo*, dissolved in EtOAc and concentrated *in vacuo* again to fully remove DCE. The crude mixture was transferred to a 4-dram vial with DMF rinses (0.5 mL) and DBU (50 μL) was added. The vial was sealed with a PTFE-lined cap and flushed with N_2 for 5 min. The solution was then heated (rt – 140 °C) to induce decarboxylation (1 – 2 h, time not optimized). Upon completion of the reaction, the mixture was diluted with 10 mL EtOAc, washed with 1 mL 1 M HCl and 2 x 2 mL brine. The organic layer was dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified by silica gel chromatography.

General Procedure D: In an atmosphere controlled glovebox, $Pd(dba)_2$ (6.9 mg, 0.012 mmol, 0.05 equiv.) and (*R,R*)-DACH-phenyl Trost ligand L1 (9.1 mg, 0.0132 mmol, 0.055 equiv.) were sequentially added to a 1-dram vial charged with a stir bar. DCE (0.4 mL) was added and the mixture was stirred for 10 minutes. In a separate 1-dram vial charged with a stir bar, 2-cyclohexenyl aryl acetate (0.24 mmol, 1.0 equiv.) and durene internal standard were added. The Pd-ligand solution was transferred to the vial with DCE rinses (2 x 0.2 mL), followed by the addition of BSA (53.7 mg, 0.264 mmol, 1.1 equiv.). The vial was sealed with a PTFE-lined cap, removed from the glovebox and gently stirred at room temperature. Upon completion of the reaction (22 – 50 h) as determined by ^{1}H NMR using durene as internal standard, the reaction mixture was treated with diethylamine (125 μL) and stirred for 1 h. The mixture was then concentrated *in vacuo*, dissolved in EtOAc and concentrated *in vacuo* again to fully remove DCE. The crude mixture was transferred to a 4-dram vial with DMF rinses (1.0 mL) and DBU (50 μL) was added. The vial was sealed with a PTFE-lined cap and flushed with N_2 for 5 min. The solution was then heated (rt – 100 °C) induce decarboxylation (1 – 6 h, time not optimized). Upon completion of the reaction, the mixture was diluted with 30 mL EtOAc, washed with 3 mL 1 M HCl and 2 x 5 mL brine. The organic layer was dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified by silica gel chromatography.

In both General Procedures C and D, it is beneficial to ensure removal of DCE prior to inducing decarboxylation at high temperature.

General Procedure E: [product derivatization via cross-metathesis for HPLC analysis] To a vial under N_2 containing the appropriate terminal olefin product (0.02 mmol, 1 equiv.) and methyl acrylate (0.2 mmol, 10 equiv.) was added a stock solution of 0.1 M Grubbs-Hoveyda catalyst in CH_2Cl_2 (0.2 mL, 0.002 mmol, 0.10 equiv.). The reaction was stirred at room temperature until full consumption of the starting material was observed by ^{1}H NMR. The mixture was passed through a plug of silica (washing with 4:1 Hexane/EtOAc), concentrated *in vacuo* to remove excess methyl acrylate and analyzed by HPLC.



5-6 Prepared according to the General Procedure A from 4-nitrophenylacetic acid (21.7 mg, 0.12 mmol, 1.2 equiv.), 24 h. 85% yield, determined by ^{1}H NMR using durene as internal standard, 99% ee.

Prepared according to the General Procedure B from the corresponding allylic aryl acetate (149 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-2** (5.3 mg, 0.005 mmol, 0.01 equiv.), 18 h. Isolated as a yellow oil in 88% yield, 98% ee after purification by silica gel chromatography (2:1 hexane:toluene).

Prepared according to the General Procedure B with 0.1 mol% catalyst from the corresponding allylic aryl acetate (297 mg, 1.0 mmol, 1.0 equiv.) and **[Ir]-1** (1.1 mg, 0.001 mmol, 0.001 equiv.), 15 h. 65% yield determined by ^{1}H NMR using durene as internal standard, 99% ee.

Prepared according to the General Procedure B *without the use of a glove-box*. Under ambient atmosphere, the corresponding allylic aryl acetate (149 mg, 0.5 mmol, 1.0 equiv.), **[Ir]-2** (5.3 mg, 0.005 mmol, 0.01 equiv.) and durene internal standard were sequentially added to a 1-dram vial charged with a stirbar. The vial was sealed with a PTFE-lined cap and evacuated/backfilled with N_2 three time. The solids were dissolved in THF (2.5 mL) and stirred 2 minutes, followed by the addition of DBU (75 μL, 0.50 mmol, 1.0 equiv.). Upon completion of the reaction, the yield was determined by ^{1}H NMR using durene as internal standard. 92% yield as determined by ^{1}H NMR using durene as internal standard, 98% ee.

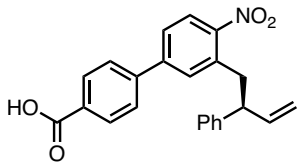
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.06 (d, *J* = 8.4 Hz, 2H), 7.28 (m, 2H), 7.20 (m, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 7.0 Hz, 2H), 6.02 (m, 1H), 5.07 (d, *J* = 10.3 Hz, 1H), 5.00 (d, *J* = 17.2 Hz, 1H), 3.58 (q, *J* = 7.6 Hz, 1H), 3.16 (m, 1H), 3.09 (m, 1H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 148.0, 146.5, 142.5, 140.5, 130.0, 128.7, 127.7, 126.8, 123.4, 115.4, 51.3, 42.1;

HRMS (EI): calcd for $C_{16}H_{15}NO_2$ $[M]^+$: 253.1103. Found 253.1099.

Chiral HPLC: ChiralPak IG column (1% IPA in hexane, 1.5 mL/min), t_r = 3.9 min (minor), t_r = 4.4 min (major).

$[\alpha]_D^{25}$ -91.2 (c = 0.76, $CHCl_3$)



5-9 Prepared according to General Procedure A from the corresponding aryl acetic acid (36.2 mg, 0.12 mmol, 1.1 equiv.), and **[Ir]-1** (6.1 mg, 0.005 mmol, 0.05 equiv.), 0.15 M in THF/DMA (3:1), 1.5 h. 88% yield determined by ^{1}H NMR using durene as internal standard. Isolated as a white solid in 92% yield (contains 10% protodecarboxylation impurity), 99% ee after purification by silica gel chromatography (EtOAc).

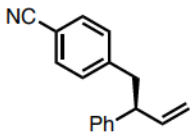
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.17 (d, *J* = 8.3 Hz, 2H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.54 (dd, *J* = 1.9, 8.5 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.34 – 7.29 (m, 2H), 7.25 (m, 1H), 7.20 – 7.17 (m, 2H), 7.14 (m, 1H), 6.15 (m, 1H), 5.12 (m, 1H), 5.07 (m, 1H), 3.73 (q, *J* = 7.2 Hz, 1H), 3.56 (m, 1H), 3.28 (m, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.3, 148.9, 144.0, 143.8, 142.7, 140.3, 135.8, 132.2, 130.8, 129.0, 128.6, 128.0, 127.4, 126.7, 125.9, 125.5, 115.5, 50.6, 39.8;

HRMS (ESI): calcd for $C_{23}H_{18}NO_4$ $[M-H]^-$: 372.1241. Found 372.1234;

Chiral HPLC: Chiralpak IC column (5% IPA in hexane, 1.5 mL/min), t_r = 6.9 min (major), t_r = 9.2 min (minor);

$[\alpha]_D^{25}$ 45.8 (c = 0.54, $CHCl_3$)



5-18 Prepared according to the General Procedure A from 4-cyanophenylacetic acid (16.1 mg, 0.10 mmol, 1.0 equiv.), 14 h. Subsequent decarboxylation was achieved at 70° C, 2h. 94% yield determined by ^{1}H NMR using durene as internal standard, >99% ee.

Prepared according to the General Procedure B from the corresponding allylic aryl acetate (139 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-2** (5.3 mg, 0.005 mmol, 0.01 equiv.), 21 h. Subsequent decarboxylation was achieved at 70° C, 3h. Isolated as a white solid in 85% yield, 99% ee after purification by silica gel chromatography (99:1 to 9:1 hexane:EtOAc).

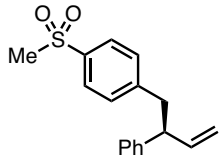
^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.50 – 7.47 (m, 2H), 7.29 – 7.26 (m, 2H), 7.20 (m, 1H), 7.14 – 7.09 (m, 4H), 6.01 (m, 1H), 5.06 (dt, *J* = 1.2, 10.2 Hz, 1H), 4.98 (dt, *J* = 1.2, 17.0 Hz, 1H), 3.55 (q, *J* = 8.2 Hz, 1H), 3.11 (m, 1H), 3.04 (m, 1H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 145.8, 142.6, 140.6, 131.9, 130.0, 128.6, 127.7, 126.7, 119.1, 115.3, 109.9, 51.3, 42.3;

HRMS (EI): calcd for $C_{17}H_{15}N$ $[M]^+$: 233.1205. Found 233.1207.

Chiral HPLC: ChiralPak IG column (1% IPA in hexane, 1.5 mL/min), t_r = 4.5 min (minor), t_r = 4.8 min (major).

$[\alpha]_D^2$ -107.6 (c = 0.89, $CHCl_3$)



5-19 Prepared according to the General Procedure A from 4-(methylsulfonyl)phenyl acetic acid (21.4 mg, 0.10 mmol, 1.0 equiv.), 14 h. Subsequent decarboxylation was achieved at 70° C, 3h. 90% yield determined by ^{1}H NMR using durene as internal standard, 99% ee.

Prepared according to the General Procedure B from the corresponding allylic aryl acetate (173 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-2** (5.3 mg, 0.005 mmol, 0.01 equiv.), 22 h. Subsequent decarboxylation was achieved at 70° C, 1h. Isolated as white solid in 87% yield, 99% ee after purification by silica gel chromatography (19:1 to 3:2 hexane:EtOAc).

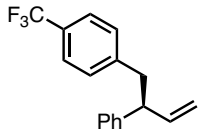
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.80 – 7.75 (m, 2H), 7.31 – 7.17 (m, 5H), 7.15 – 7.10 (m, 2H), 6.02 (m, 1H), 5.06 (dt, *J* = 1.3, 10.5 Hz, 1H), 4.98 (dt, *J* = 1.3, 17.1 Hz, 1H), 3.58 (q, *J* = 7.4 Hz, 1H), 3.17 – 3.05 (m, 2H), 3.02 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.7, 142.6, 140.6, 138.2, 130.2, 128.6, 127.7, 127.2, 126.7, 115.3, 51.3, 44.6, 42.1;

HRMS (EI): calcd for $C_{17}H_{18}O_2S$ $[M]^+$: 286.1028. Found 286.1026.

Chiral HPLC: ChiralPak IB column (10% IPA in hexane, 1.5 mL/min), t_r = 6.2 min (major), t_r = 6.8 min (minor).

$[\alpha]_D^{25}$ -69.9 (c = 1.12, $CHCl_3$)



5-20 Prepared according to the General Procedure A from 4-(trifluoromethyl)phenyl acetic acid (24.5 mg, 0.12 mmol, 1.2 equiv.), 16 h. Subsequent decarboxylation was achieved at 90° C, 19 h. 85% yield determined by ^{1}H NMR using durene as internal standard, >99% ee.

Prepared according to the General Procedure B from the corresponding allylic aryl acetate (160 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-2** (10.6 mg, 0.010 mmol, 0.02 equiv.), 25 h. Subsequent decarboxylation was achieved at 90° C, 19h. Isolated as a colorless oil in 65% yield after purification by silica gel chromatography (hexane), 99% ee after derivatization according to General Procedure E.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.46 – 7.44 (m, 2H), 7.29 – 7.25 (m, 2H), 7.19 (m, 1H), 7.15 – 7.12 (m, 4H), 6.01 (m, 1H), 5.04 (dt, *J* = 1.2, 10.3 Hz, 1H), 4.97 (dt, *J* = 1.2, 17.1 Hz, 1H), 3.56 (q, *J* = 8.0 Hz, 1H), 3.11 – 3.02 (m, 2H);

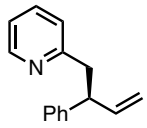
^{13}C NMR ($CDCl_3$, 176 MHz) δ 144.2, 143.0, 140.8, 129.5, 128.6, 128.3 (q, *J* = 34.1 Hz), 127.8, 126.6, 125.0 (q, J = 4.0 Hz), 124.3 (q, *J* = 277 Hz), 115.1, 51.4, 42.0;

^{19}F NMR ($CDCl_3$, 376 MHz) δ - 62.5 (s);

HRMS (EI): calcd for $C_{17}H_{15}F_3$ $[M]^+$: 276.1126. Found 276.1125.

Chiral HPLC: Derivatized to the corresponding cross-metathesis product according to General Procedure E. Whelk-O1 column (10% IPA in hexane, 1.5 mL/min), t_r = 6.6 min (minor), t_r = 7.4 min (major).

$[\alpha]_D^{25}$ -50.2 (c = 1.39, $CHCl_3$)



5-21 Prepared according to the General Procedure A from 2-pyridylacetic acid • HCl (17.4 mg, 0.10 mmol, 1.0 equiv.) and an additional equivalent DBU (30 mL, 0.20 mmol, 2.0 equiv.), 18 h. Subsequent decarboxylation was achieved at 70° C, 1h. 60% yield determined by ^{1}H NMR using durene as internal standard, >99% ee (second enantiomer not detected).

Prepared according to the General Procedure B from the corresponding allylic aryl acetate (25.3 mg, 0.10 mmol, 1.0 equiv.) and **[Ir]-1** (2.2 mg, 0.002 mmol, 0.02 equiv.), 20 h. Subsequent decarboxylation was achieved at 70° C, 1h. A modified workup was used, washing with saturated NH_4Cl instead of 1 M HCl. Isolated as a colorless oil in 61% yield, >99% ee (second enantiomer not detected) after purification by silica gel chromatography (1:1 hexane:EtOAc).

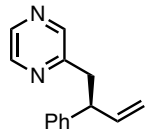
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.53 (m, 1H), 7.48 (dt, *J* = 1.9, 7.6 Hz, 1H), 7.27 – 7.25 (m, 2H), 7.19 – 7.16 (m, 3H), 7.06 (m, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.04 (m, 1H), 5.00 (dt, *J* = 1.2, 10.2 Hz, 1H), 4.97 (dt, *J* = 1.2, 17.0 Hz, 1H), 3.90 (q, *J* = 7.8 Hz, 1H), 3.22 (m, 1H), 3.16 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 160.6, 149.3, 143.4, 141.1, 136.0, 128.4, 127.8, 126.4, 123.9, 121.1, 114.8, 49.9, 44.4;

HRMS (ESI): calcd for $C_{15}H_{16}N$ $[M+H]^+$: 210.1277. Found 210.1275.

Chiral HPLC: Whelk-O1 column (1% IPA in hexane, 1.5 mL/min), t_r = 10.6 min (major), t_r = 12.1 min (minor).

$[\alpha]_D^{25}$ -54.4 (c = 0.26, $CHCl_3$)



5-22 Prepared according to the General Procedure A from 2-pyrazine acetic acid (13.8 mg, 0.10 mmol, 1.0 equiv.), 22 h. Subsequent decarboxylation was achieved at 70° C, 1h. 90% yield determined by ^{1}H NMR using durene as internal standard, 99% ee.

Prepared according to the General Procedure B from the corresponding allylic aryl acetate (127.2 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-1** (5.3 mg, 0.005 mmol, 0.01 equiv.), 15 h. Subsequent decarboxylation was achieved at 70° C, 2h. A modified workup was used, washing with saturated NH_4Cl instead of 1 M HCl. Isolated as a yellow oil in 93% yield, 97% ee after purification by silica gel chromatography (1:1 hexane:EtOAc).

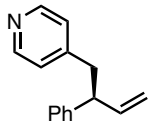
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.49 (dd, *J* = 1.6, 2.4 Hz, 1H), 8.35 (d, *J* = 2.5 Hz, 1H), 8.22 (d, *J* = 1.4 Hz, 1H), 7.29 – 7.26 (m, 2H), 7.20 – 7.16 (m, 3H), 6.04 (m, 1H), 5.04 (dt, *J* = 1.2, 10.2 Hz, 1H), 4.99 (dt, *J* = 1.2, 17.0 Hz, 1H), 3.89 (q, *J* = 7.8 Hz, 1H), 3.25 (m, 1H), 3.18 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 155.7, 145.3, 144.1, 142.7, 142.3, 140.5, 128.7, 127.7, 126.7, 115.3, 49.6, 41.4;

HRMS (EI): calcd for $C_{14}H_{14}N_2$ $[M]^+$: 210.1157. Found 210.1152.

Chiral HPLC: Chiralpak IC column (5% IPA in hexane, 1.5 mL/min), t_r = 3.2 min (major), t_r = 3.4 min (minor).

$[\alpha]_D^{25}$ -75.4 (c = 0.86, $CHCl_3$).



5-23 Prepared according to the General Procedure A from 4-pyridylacetic acid • HCl (17.4 mg, 0.10 mmol, 1.0 equiv.) and an additional equivalent DBU (30 mL, 0.20 mmol, 2.0 equiv.), 18 h. Subsequent decarboxylation was achieved at 70° C, 1h. 75% yield determined by ^{1}H NMR using durene as internal standard, 99% ee.

Prepared according to the General Procedure B from the corresponding allylic aryl acetate (126.7 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-2** (5.3 mg, 0.005 mmol, 0.01 equiv.), 17 h. Subsequent decarboxylation was achieved at 70° C, 1h. A modified workup was used, washing with saturated NH_4Cl instead of 1 M HCl. Isolated as a yellow oil in 90% yield, 99% ee after purification by silica gel chromatography (1:1 hexane:EtOAc).

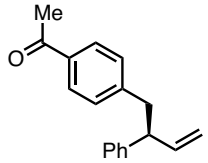
^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.42 (m, 2H), 7.28 (m, 2H), 7.20 (m, 1H), 7.13 (m, 2H), 6.97 (d, *J* = 5.9 Hz, 2H), 6.07 (m, 1H), 5.06 (dt, *J* = 1.2, 10.2 Hz, 1H), 4.99 (dt, *J* = 1.2, 17.0 Hz, 1H), 3.57 (q, *J* = 7.8 Hz, 1H), 3.04 (m, 1H), 2.99 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.6, 149.0, 142.7, 140.6, 128.6, 127.7, 126.7, 124.6, 115.3, 50.7, 41.4;

HRMS (EI): calcd for $C_{15}H_{15}N$ $[M]^+$: 209.1205. Found 209.1203.

Chiral HPLC: Chiralpak IC column (5% IPA in hexane, 1.5 mL/min), t_r = 9.5 min (minor), t_r = 10.6 min (major).

$[\alpha]_D^{25}$ -54.9 (c = 0.84, $CHCl_3$)



5-24 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (147 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-2** (5.3 mg, 0.005 mmol, 0.01 equiv.), 25 h. Subsequent decarboxylation was achieved at 70° C, 3h. Isolated as white solid in 82% yield, 99% ee after purification by preparatory TLC (10:1 pentane/Et_2O).

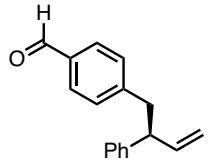
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.84 – 7.80 (m, 2H), 7.31 – 7.26 (m, 2H), 7.21 (m, 1H), 7.17 – 7.13 (m, 4H), 6.04 (m, 1H), 5.05 (dt, *J* = 1.3, 10.4 Hz, 1H), 4.98 (dt, *J* = 1.3, 17.1 Hz, 1H), 3.60 (1, *J* = 7.7 Hz, 1H), 3.14 – 3.04 (m, 2H), 2.57 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.9, 145.9, 143.0, 140.9, 135.1, 129.4, 128.5, 128.2, 127.7, 126.5, 115.0, 51.3, 42.1, 26.5;

HRMS (EI): calcd for $C_{18}H_{18}O$ $[M]^+$: 250.1358. Found 250.1351.

Chiral HPLC: Whelk-O1 column (1% IPA in hexane, 2.0 mL/min), t_r = 19.8 min (minor), t_r = 20.9 min (major).

$[\alpha]_D^{25}$ -87.8 (c = 1.02, $CHCl_3$)



5-25 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (28 mg, 0.10 mmol, 1.0 equiv.) and **[Ir]-1** (1.1 mg, 0.001 mmol, 0.01 equiv.), 4 h. Subsequent decarboxylation was achieved at 70° C, 0.5 h. Isolated as a colorless oil

in 82% yield, >99% ee (second enantiomer not detected) after purification by silica gel chromatography (99:1 to 10:1 pentane:Et_2O).

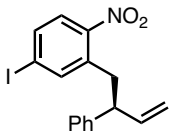
^{1}H NMR ($CDCl_3$, 700 MHz) δ 9.93 (s, 1H), 7.72 (d, *J* = 8.7 Hz, 2H), 7.28 – 7.24 (m, 2H), 7.21 – 7.17 (m, 3H), 7.14 – 7.11 (m, 2H), 6.02 (m, 1H), 5.04 (d, *J* = 10.4 Hz, 1H), 4.97 (d, J = 17.2 Hz, 1H), 3.59 (q, *J* = 7.5 Hz, 1H), 3.14 – 3.04 (m, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 192.0, 147.5, 142.8, 140.7, 134.6, 129.9, 129.6, 128.5, 127.7, 126.6, 115.1, 51.3, 42.3;

HRMS (EI): calcd for $C_{17}H_{16}O$ $[M]^+$: 236.1201. Found 236.1203.

Chiral HPLC: Whelk-O1 column (1% IPA in hexane, 2.0 mL/min), t_r = 22.2 min (major), t_r = 23.5 min (minor).

$[\alpha]_D^{25}$ -109.9 (c = 0.70, $CHCl_3$)



5-26 Prepared according to General Procedure A from the corresponding aryl acetic acid (36.9 mg, 0.12 mmol, 1.2 equiv.), 20 h. Isolated as a yellow oil in 70% yield, 99% ee after purification by silica gel chromatography (20:1 pentane/Et_2O).

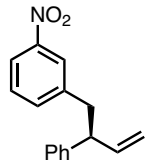
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (m, 1H), 7.59 (m, 1H), 7.41 (d, *J* = 1.7 Hz, 1H), 7.29 (m, 2H), 7.22 (m, 1H), 7.14 – 7.12 (m, 2H), 6.03 (m, 1H), 5.06 (m, 1H), 4.96 (m, 1H), 3.59 (q, *J* = 7.7 Hz, 1H), 3.34 (m, 1H), 3.20 (m, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.2, 142.5, 142.1, 139.8, 136.9, 136.4, 128.7, 127.6, 126.9, 126.0, 115.9, 99.7, 50.6, 39.1;

HRMS (EI): calcd for $C_{16}H_{13}NOI$ $[M\text{-}OH]^+$: 362.0042. Found 362.0037;

Chiral HPLC: Chiralpak IA column (1% IPA in hexane, 1.5 mL/min), t_r = 3.7 min (minor), t_r = 4.9 min (major);

$[\alpha]_D^{25}$ 2.8 (c = 1.19, $CHCl_3$)



5-27 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (60 mg, 0.2 mmol, 1.0 equiv.) and **[Ir]-1** (2.2 mg, 0.002 mmol, 0.01 equiv.), 25 h. Subsequent decarboxylation was achieved at 100° C, 9 h. Isolated as a colorless oil in 76% yield, >99% ee after purification by silica gel chromatography (pentane to 16:1 pentane:Et_2O) (contains 9% of the internal alkene isomerization byproduct).

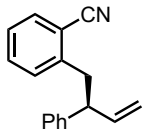
^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.03 (m, 1H), 7.95 (s, 1H), 7.39 – 7.26 (m, 4H), 7.22 (m, 1H), 7.17 – 7.12 (m, 2H), 6.04 (m, 1H), 5.08 (m, 1H), 5.00 (m, 1H), 3.60 (q, *J* = 7.6 Hz, 1H), 3.20 – 3.08 (m, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.1, 142.5, 142.0, 140.4, 135.5, 128.9, 128.6, 127.7, 126.7, 124.0, 121.2, 115.4, 51.4, 41.8;

HRMS (EI): calcd for $C_{16}H_{15}O_2N$ $[M]^+$: 253.1103. Found 253.1096.

Chiral HPLC: Chiralpak IB column (1% IPA in hexane, 1.5 mL/min), t_r = 4.7 min (major), t_r = 4.9 min (minor).

$[\alpha]_D^{25}$ -55.1 (c = 0.55, $CHCl_3$).



5-28 Prepared according to the General Procedure A from 2-cyanophenylacetic acid (16.1 mg, 0.10 mmol, 1.0 equiv.), 14 h. Subsequent decarboxylation was achieved at 70° C, 5h. 95% yield determined by ^{1}H NMR using durene as internal standard, 99% ee.

Prepared according to the General Procedure B from the corresponding allylic aryl acetate (139 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-2** (5.3 mg, 0.005 mmol, 0.01 equiv.), 20 h. Subsequent decarboxylation was achieved at 70° C, 3h. Isolated as a colorless oil in 87% yield, 98% ee after purification by silica gel chromatography (99:1 to 9:1 hexane:EtOAc).

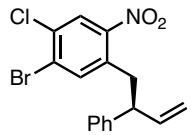
^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.58 (m, 1H), 7.41 (m, 1H), 7.29 – 7.24 (m, 3H), 7.22 – 7.18 (m, 3H), 7.13 (m, 1H), 6.07 (m, 1H), 5.05 (dt, *J* = 1.2, 10.2 Hz, 1H), 4.97 (dt, *J* = 1.2, 17 Hz, 1H), 6.68 (q, J = 7.8 Hz, 1H), 3.28 (m, 1H), 3.21 (m, 1H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 144.1, 142.6, 140.1, 132.7, 132.3, 130.5, 128.6, 127.7, 126.70, 126.67, 118.3, 115.6, 112.9, 51.2, 40.9;

HRMS (EI): calcd for $C_{17}H_{15}N$ $[M]^+$: 233.1205. Found 233.1206.

Chiral HPLC: ChiralPak IG column (1% IPA in hexane, 1.5 mL/min), t_r = 5.3 min (minor), t_r = 6.0 min (major).

$[\alpha]_D^{25}$ -39.0 (c = 1.12, $CHCl_3$)



5-29 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (85 mg, 0.20 mmol, 1.0 equiv.) and **[Ir]-2** (2.1 mg, 0.002 mmol, 0.01 equiv.), 24 h. Isolated as pale yellow oil in 77% yield, 97% ee after purification by preparatory TLC (40:1 pentane/Et_2O).

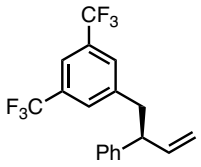
^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.01 (s, 1H), 7.34 – 7.29 (m, 3H), 7.24 (m, 1H), 7.17 – 7.12 (m, 2H), 6.04 (m, 1H), 5.09 (dt, *J* = 1.2, 10.3 Hz, 1H), 4.99 (dt, *J* = 1.2, 17.1 Hz, 1H), 3.59 (q, *J* = 7.8 Hz, 1H), 3.36 (m, 1H), 3.23 (m, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.4, 142.1, 139.6, 137.7, 134.9, 133.3, 128.7, 127.6, 127.5, 126.9, 126.2, 116.0, 50.6, 38.8;

HRMS (ESI): calcd for $C_{16}H_{13}BrCl_2NO_2$ $[M+Cl]^-$: 399.9512. Found 399.9512.

Chiral HPLC: ChiralPak IG column (1% IPA in hexane, 1.5 mL/min), t_r = 2.8 min (minor), t_r = 3.1 min (major).

$[\alpha]_D^{25}$ -18.6 (c = 0.30, $CHCl_3$)



5-30 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (194 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-2** (5.3 mg, 0.005 mmol, 0.01 equiv.), 21 h. Subsequent decarboxylation was achieved at 90° C, 1h. Isolated as a colorless oil in 77% yield after purification by silica gel chromatography (99:1 to 9:1 hexane:EtOAc), 98% ee after derivatization according to General Procedure E.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.68 (s, 1H), 7.44, (s, 2H), 7.32 – 7.28 (m, 2H), 7.23 (m, 1H), 7.14 – 7.10 (m, 2H), 6.05 (m, 1H), 5.11 (dt, *J* = 1.2, 10.4 Hz, 1H), 5.03 (dt, *J* = 1.2, 17.1 Hz, 1H), 3.56 (q, J = 7.36 Hz, 1H), 3.22 – 3.08 (m, 2H);

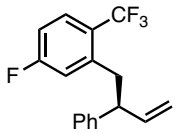
^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.4, 142.2, 140.0, 131.2 (q, *J* = 33.2 Hz), 129.4, 128.6, 127.6, 126.9, 123.4 (q, *J* = 272 Hz), 120.0, 115.6, 51.3, 41.9;

^{19}F NMR ($CDCl_3$, 376 MHz) δ - 63.1 (s);

HRMS (EI): calcd for $C_{18}H_{14}F_6$ $[M]^+$: 344.1000. Found 344.1004.

Chiral HPLC: Derivatized to the corresponding cross-metathesis product according to General Procedure E. Whelk O-1 column (1% IPA in hexane, 1.5 mL/min), t_r = 5.3 min (minor), t_r = 6.0 min (major).

$[\alpha]_D^{25}$ -41.6 (c = 1.05, $CHCl_3$)



5-31 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (169 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-2** (5.3 mg, 0.005 mmol, 0.01 equiv.), 21 h. Subsequent decarboxylation was achieved at 70° C, 3h. Isolated) as a colorless oil in 58% yield after purification by silica gel chromatography (99:1 to 13:1 hexane:EtOAc, 98% ee after derivatization according to General Procedure E.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62 (m, 1H), 7.34 – 7.30 (m, 2H), 7.24 (m, 1H), 7.20 – 7.17 (m, 2H), 6.95 (m, 1H), 6.75 (m, 1H), 6.05 (m, 1H), 5.06 (dt, *J* = 1.2, 10.2 Hz, 1H), 4.97 (dt, *J* = 1.2, 17.1 Hz, 1H), 3.63 (q, *J* = 7.94 Hz, 1H), 3.28 – 3.12 (m, 2H);

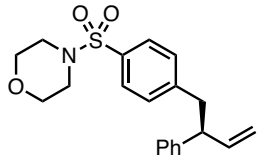
^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.9 (d, *J* = 252 Hz),142.9, 141.9 (d, *J* = 8.7 Hz), 140.4, 128.6, 128.3 (m), 127.7, 126.7, 124.9 (q, *J* = 30.3 Hz), 124.4 (q, *J* = 273 Hz), 118.9 (d, *J* = 23.6 Hz), 115.5, 113.1 (d, *J* = 21.2 Hz), 50.7, 38.7;

^{19}F NMR ($CDCl_3$, 376 MHz) δ - 58.6 (s), -108.9 (m);

HRMS (EI): calcd for $C_{17}H_{14}F_4$ $[M]^+$: 294.1032. Found 294.1029.

Chiral HPLC: Derivatized to the corresponding cross-metathesis product according to General Procedure E. Whelk-O1 column (10% IPA in hexane, 1.5 mL/min), t_r = 5.5 min (minor), t_r = 6.7 min (major).

$[\alpha]_D^{25}$ -29.0 (c = 1.37, $CHCl_3$)



5-32 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (80 mg, 0.20 mmol, 1.0 equiv.) and **[Ir]-1** (2.2 mg, 0.002 mmol, 0.01 equiv.), 14 h. Subsequent decarboxylation was achieved at 70° C, 2h. Isolated as a white solid in 78% yield, >99% ee after purification by silica gel chromatography (19:1 to 3:2 hexane:EtOAc).

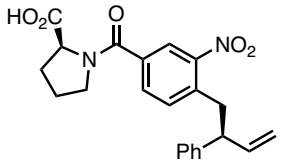
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.61 – 7.57 (m, 2H), 7.31 – 7.25 (m, 2H), 7.23 – 7.18 (m, 3H), 7.13 – 7.09 (m, 2H), 6.04 (m, 1H), 5.08 (d, *J* = 10.4 Hz, 1H), 5.01 (d, *J* = 17.2 Hz, 1H), 3.76 – 3.72 (m, 4H), 3.57 (q, *J* = 7.6 Hz, 1H), 3.18 – 3.04 (m, 2H), 2.99 – 2.93 (m, 4H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.0, 142.6, 140.5, 132.5, 129.9, 128.5, 127.7, 127.6, 126.65, 115.2, 66.1, 51.4, 46.0, 42.0;

HRMS (ESI): calcd for $C_{20}H_{24}NO_3S$ $[M+H]^+$: 358.1471. Found 358.1472.

Chiral HPLC: ChiralPak IA column (10% IPA in hexane, 1.5 mL/min), t_r = 5.5 min (major), t_r = 6.6 min (minor).

$[\alpha]_D^{25}$ -64.7 (c = 0.48, $CHCl_3$)



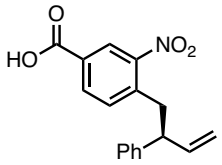
5-33 Prepared according to General Procedure A from the corresponding aryl acetic acid (19 mg, 0.06 mmol, 1.2 equiv.), and **[Ir]-1** (5.6 mg, 0.005 mmol, 0.10 equiv.), 21 h. Isolated as a white solid in 61% yield after purification by silica gel chromatography (3% MeOH in CH_2Cl_2, 1% AcOH). Analytical limitations, likely due to amide rotation, prevented ee determination in this case.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.09 (d, *J* = 1.5 Hz, 1H), 7.60 (dd, *J* = 1.5 Hz, 1H), 7.27 (m, 2H), 7.19 (m, 1H), 7.14 – 7.09 (m, 3H), 6.03 (m, 1H), 5.04 (d, *J* = 10.3 Hz, 1H), 4.95 (d, *J* = 16.7 Hz, 1H), 4.71 (t, *J* = 7.1 Hz, 1H), 3.65 – 3.51 (m, 3H), 3.42 (m, 1H), 3.28 (m, 1H), 2.29 (q, J = 6.8 Hz, 2H), 2.07 (m, 1H), 1.94 (m, 1H); (9:1 ratio of amide rotamers)

^{13}C NMR ($CDCl_3$, 176 MHz) δ 173.8, 168.2, 149.2, 142.4, 139.9, 137.6, 134.4, 133.4, 131.1, 128.6, 127.6, 126.8, 123.7, 115.8, 59.9, 50.5, 50.3, 39.3, 28.5, 25.3; (mixture of amide rotamers)

HRMS (ESI): calcd for $C_{22}H_{21}N_2O_5$ $[M-H]^-$: 393.1456. Found 393.1455;

$[\alpha]_D^{25}$ -75.0 (c = 0.29, $CHCl_3$)



5-34 Prepared according to General Procedure A from the corresponding aryl acetic acid (54 mg, 0.24 mmol, 1.2 equiv.), and **[Ir]-1** (11.2 mg, 0.01 mmol, 0.05 equiv.), 0.15 M in THF/DMA (3:1), 4 h. 67% yield determined by ^{1}H NMR using durene as internal standard, >85% ee, peak broadening on HPLC analysis prevents a more precise ee determination. Isolated as a white solid in 45% yield (contains 10% substrate protodecarboxylation impurity).

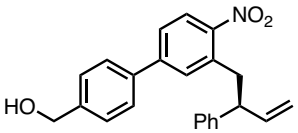
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.58 (s, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.32 – 7.26 (m, 2H), 7.24 – 7.13 (m, 4H), 6.06 (m, 1H), 5.07 (d, *J* = 10.3 Hz, 1H), 4.98 (d, *J* = 16.9 Hz, 1H), 3.66 (q, *J* = 7.5 Hz, 1H), 3.48 (m, 1H), 3.34 (m, 1H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 169.5, 149.7, 142.2, 140.7, 139.8, 133.9, 133.5, 133.2, 128.6, 127.6, 126.8, 126.4, 115.8, 50.5, 39.5;

HRMS (ESI): calcd for $C_{17}H_{14}NO_4$ $[M-H]^-$: 296.0928. Found 296.0924;

Chiral HPLC: Chiralpak IC column (5% IPA in hexane, 1.5 mL/min), t_r = 2.5 min (major), t_r = 3.4 min (minor);

$[\alpha]_D^{25}$ -50.7 (c = 0.78, $CHCl_3$)



5-35 Prepared according to the General Procedure A from the corresponding aryl acetic acid (34.5 mg, 0.12 mmol, 1.2 equiv.) and **[Ir]-1** (5.6 mg, 0.005 mmol, 0.05 equiv.), 0.1 M in THF, 18 h. Isolated as a yellow oil (contains 7% protodecarboxylation

impurity) in 74% yield, >99% ee (second enantiomer not detected) after purification by silica gel chromatography (2:1 pentane:THF).

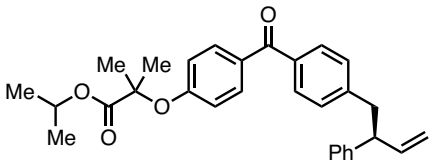
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00 (d, *J* = 8.3 Hz, 1H), 7.48 (dd, *J* = 1.9, 8.2 Hz, 1H), 7.45 – 7.36 (m, 4H), 7.31 – 7.17 (m, 5H), 7.13 (d, *J* = 1.9 Hz, 1H), 6.12 (m, 1H), 5.08 (dt, *J* = 1.2, 10.2 Hz, 1H), 5.03 (dt, *J* = 1.2, 17.0 Hz, 1H), 4.76 (d, *J* = 6.0 Hz, 2H), 3.71 (q, *J* = 8.2 Hz, 1H), 3.52 (m, 1H), 3.28 (m, 1H), 1.70 (t, *J* = 6.0 Hz, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 148.3, 144.9, 142.9, 141.4, 140.4, 138.2, 135.7, 131.9, 128.6, 128.0, 127.5 (2), 126.7, 125.6, 125.5, 115.5, 64.9, 50.7, 39.9;

HRMS (EI): calcd for $C_{23}H_{21}NO_3$ $[M]^+$: 359.1521. Found 359.1522.

Chiral HPLC: ChiralPak IC column (5% IPA in hexane, 1.5 mL/min), t_r = 11.9 min (major), t_r = 12.8 min (minor).

$[\alpha]_D^{25}$ 53.6 (c = 0.79, $CHCl_3$)



5-36 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (100 mg, 0.20 mmol, 1.0 equiv.) and **[Ir]-2** (2.1 mg, 0.002 mmol, 0.01 equiv.), 24 h. Subsequent decarboxylation was achieved at 70° C, 1h. Isolated as a colorless oil in 85% yield, 99% ee after purification by silica gel chromatography (49:1 to 4:1 hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.74 – 7.71 (m, 2H), 7.65 – 7.61 (m, 2H), 7.31 – 7.27 (m, 2H), 7.21 (m, 1H), 7.18 – 7.14 (m, 4H), 6.89 – 6.84 (m, 2H), 6.05 (m, 1H), 5.13 –

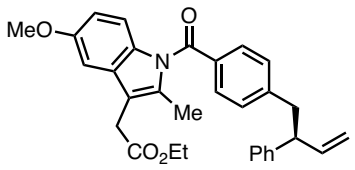
5.04 (m, 2H), 5.00 (dt, *J* = 1.4, 17.2 Hz, 1H), 3.62 (q, *J* = 7.4 Hz, 1H), 3.17 – 3.05 (m, 2H), 1.67 (s, 6H), 1.21 (d, *J* = 6.4 Hz, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 195.3, 173.2, 159.4, 144.7, 143.1, 140.9, 135.8, 131.9, 130.9, 129.8, 129.0, 128.5, 127.8, 126.5, 117.2, 115.0, 79.4, 69.3, 51.3, 42.2, 25.4, 21.5;

HRMS (ESI): calcd for $C_{30}H_{33}O_4$ $[M+H]^+$: 457.2373. Found 457.2375.

Chiral HPLC: ChiralPak IA column (3% IPA in hexane, 1.5 mL/min), t_r = 4.6 min (major), t_r = 5.5 min (minor).

$[\alpha]_D^{25}$ -47.0 (c = 1.16, $CHCl_3$)



5-37 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (105 mg, 0.20 mmol, 1.0 equiv.) and **[Ir]-1** (2.2 mg, 0.002 mmol, 0.01 equiv.), 20 h. Subsequent decarboxylation was achieved at 70° C, 0.5 h. Isolated as a pale-yellow oil in 80% yield, >99% ee after purification by silica gel chromatography (20:1 to 1:1 pentane/Et_2O).

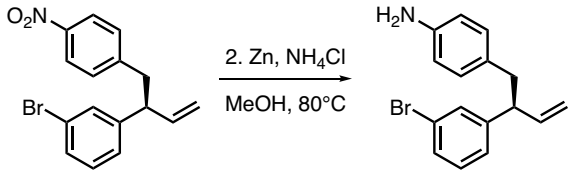
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.57 – 7.53 (m, 2H), 7.31 – 7.27 (m, 2H), 7.21 (m, 1H), 7.17 – 7.12 (m, 4H), 6.97 (m, 1H), 6.78 (m, 1H), 6.64 (m, 1H), 6.06 (m, 1H), 5.08 (dt, *J* = 1.2, 10.3 Hz, 1H), 5.02 (dt, *J* = 1.2, 17.2 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 3.66 (s, 2H), 3.61 (q, *J* = 7.64 Hz, 1H), 3.20 – 3.05 (m, 2H), 2.36 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.0, 169.5, 155.8, 145.6, 142.8, 140.8, 136.0, 133.2, 131.0, 130.5, 129.6 (2), 129.59, 128.5, 127.8, 126.6, 115.0, 122.2, 111.5, 101.2, 61.0, 55.7, 51.6, 42.3, 30.5, 14.3, 13.2;

HRMS (ESI): calcd for $C_{31}H_{32}NO_4$ $[M+H]^+$: 482.2326. Found 482.2320.

Chiral HPLC: ChiralPak IA column (10% IPA in hexane, 1.5 mL/min), t_r = 4.6 min (major), t_r = 5.2 min (minor).

$[\alpha]_D^{25}$ -78.3 (c = 0.71, $CHCl_3$)



5-38 *Step 1.* See procedure and characterization for the gram-scale synthesis of **5-46**. *Step 2.* To an 8-dram vial charged with a stir bar was added **5-46** (1.0 g, 3.0 mmol, 1.0 equiv.), zinc powder (1.5 g, 23 mmol, 7.5 equiv.), and NH_4Cl (0.32 g, 6.0 mmol, 2.0 equiv.) and 22 mL MeOH. The reaction was heated to 80° C for 0.5 h, then cooled to room temperature. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was passed through a silica plug, washing with EtOAc, and the filtrate was concentrated *in vacuo*. Isolated as a thick yellow oil in quantitative yield, 86% over two steps, 99% ee.

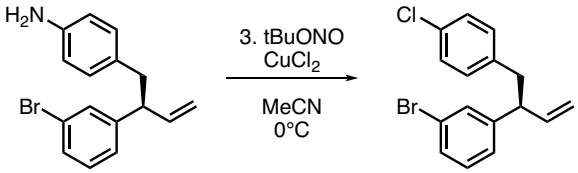
^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.34 – 7.31 (m, 2H), 7.14 (m, 1H), 7.06 (m, 1H), 6.86 – 6.82 (m, 2H), 6.60 – 6.56 (m, 2H), 5.99 (m, 1H), 5.06 (dt, *J* = 1.4, 10.4 Hz, 1H), 4.97 (dt, *J* = 1.4, 17.2 Hz, 1H), 3.59 – 3.46 (m, 3H), 2.96 – 2.85 (m, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.2, 143.8, 140.7, 130.9, 130.1, 130.0, 129.9, 129.3, 126.6, 122.4, 115.4, 115.2, 51.5, 41.3;

HRMS (EI): calcd for $C_{16}H_{16}NBr$ $[M]^+$: 301.0466. Found 301.0462.

Chiral HPLC: ChiralPak IC column (10% IPA in hexane, 1.5 mL/min), t_r = 3.9 min (major), t_r = 4.6 min (minor).

$[\alpha]_D^{25}$ -73.7 (c = 0.73, $CHCl_3$)



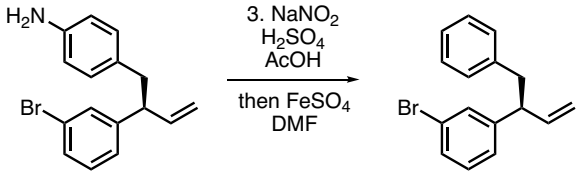
5-39 *Step 1-2.* See for procedure and characterization for the gram-scale synthesis of **5-46** and **5-38**. *Step 3.* To a 2-dram vial with PTFE lined cap containing $CuCl_2$ (32.3 mg, 0.24 mmol, 1.2 equiv.) and a stir-bar was evacuated and backfilled with N_2 three times, then anhydrous MeCN (1mL) was added, followed by *tert*-butyl nitrite (36 µl, 0.30 mmol, 1.5 equiv.). The suspension was cooled to 0° C, followed by the slow addition of aniline **5-38** (60.4 mg, 0.2 mmol, 1.0 equiv.) as a solution in MeCN (0.8 mL) over 5 minutes. Additional MeCN rinses (2 x 0.2 mL) were used to ensure a quantitative transfer. The suspension was stirred at 0° C for 2h. The reaction was diluted with Et_2O (15 mL) and washed with 1M HCl. The organic layer was dried with Na_2SO_4, filtered and concentrated in vacuo. Isolated as a colorless oil in 61% yield after purification by silica gel chromatography (hexane to 19:1 hexane/EtOAc), 52% over three steps, 98% ee after derivatization to **5-74** (See procedure and characterization for the synthesis of **5-74**).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35 – 7.30 (m, 2H), 7.22 – 7.18 (m, 2H), 7.14 (m, 1H), 7.04 (m, 1H), 6.99 – 6.95 (m, 2H), 5.97 (m, 1H), 5.08 (m, 1H), 4.98 (m, 1H), 3.50 (q, *J* = 7.7 Hz, 1H), 3.03 – 2.91 (m, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.6, 140.1, 137.9, 131.9, 130.8, 130.5, 130.0, 129.6, 128.3, 126.5, 122.5, 115.6, 51.2, 41.3;

HRMS (EI): calcd for $C_{16}H_{14}BrCl$ $[M]^+$: 319.9967. Found 319.9968.

$[\alpha]_D^{25}$ -67.8 (c = 0.69, $CHCl_3$)



5-40 *Step 1-2.* See procedure and characterization for the gram-scale synthesis of **5-46** and **5-38**. *Step 3.* To a ½-dram vial charged with a stir bar was added aniline **5-38** (60.4 mg, 0.20 mmol, 1.0 equiv.), H_2SO_4 (16 µl, 0.30 mmol, 1.5 equiv.) and AcOH (0.36 ml). The mixture was cooled to 5° C, followed by the slow addition of a 0.55 M aq. solution of $NaNO_2$ (0.40 mL, 0.22 mmol, 1.1 equiv.) over 15 minutes. The reaction was warmed to room temperature and stirred 15 minutes. In a separate 4-dram vial was added $FeSO_4$•$7H_2O$ (56 mg, 0.20 mmol, 1.0 equiv.) and DMF. The dark red diazonium solution was added to the $FeSO_4$/DMF suspension, open to air, and the reaction was stirred until gas evolution ceased (5 minutes). The reaction was quenched with water (8 ml), and extracted with EtOAc (3 x 70 ml). The organic layer was washed sequentially with water (4 x 75 ml), dried with Na_2SO_4, filtered and concentrated *in vacuo*. Isolated as a colorless oil in 77% yield after purification by silica gel chromatography (20:1 pentane:Et_2O), 66% over three steps, 97% ee after derivatization.

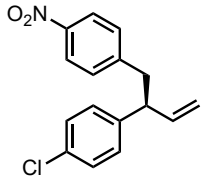
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 – 7.31 (m, 2H), 7.26 – 7.22 (m, 2H), 7.20 – 7.12 (m, 2H), 7.09 – 7.04 (m, 3H), 6.00 (m, 1H), 5.07 (dt, *J* = 1.3, 10.3 Hz, 1H), 4.98 (dt, *J* = 1.3, 17.1 Hz, 1H), 3.56 (q, J = 7.7 Hz, 1H), 3.08 – 2.95 (m, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.0, 140.5, 139.5, 130.9, 129.9, 129.4, 129.2, 128.2, 126.6, 126.1, 122.5, 115.4, 51.2, 42.0;

HRMS (EI): calcd for $C_{16}H_{15}Br$ $[M]^+$: 286.0357. Found 286.0362.

Chiral HPLC: 5-34 was derivatized to the corresponding epoxide **5-34'.** To a solution of **5-34** (10mg, 0.035 mmol) in $CDCl_3$ (1 mL) in a half-dram vial, was added excess mCPBA (20mg, 4.7 equiv.), and the mixture was stirred at rt for 16 h. Crude NMR showed full conversion to the corresponding epoxides (1.4:1 d.r.). ChiralPak IC column (1% IPA in hexane, 1.5 mL/min), major diastereomer, t_r = 7.4 min (major), t_r = 9.8 min (minor).

$[\alpha]_D^{25}$ -50.9 (c = 0.31, $CHCl_3$)



5-41 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (165.9 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-2** (5.3 mg, 0.005 mmol, 0.01 equiv.), 15 h. Isolated as a yellow solid in 94% yield, 98% ee after purification by silica gel chromatography (20:1 hexane:EtOAc).

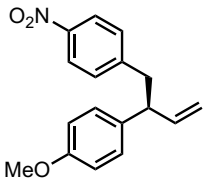
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.07 (m, 2H), 7.24 (m, 2H), 7.12 (m, 2H), 7.04 (m, 2H), 5.98 (m, 1H), 5.09 (dt, *J* = 1.2, 10.3 Hz, 1H), 5.00 (dt, *J* = 1.3, 17.1 Hz, 1H), 3.56 (q, *J* = 7.8 Hz, 1H), 3.15 (m, 1H), 3.04 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 147.5, 146.6, 140.9, 140.0, 132.5, 130.0, 129.1, 128.8, 123.5, 115.8, 50.6, 41.9;

HRMS (EI): calcd for $C_{16}H_{14}NO_2Cl$ $[M]^+$: 287.0713. Found 287.0718.

Chiral HPLC: Chiralpak IG column (1% IPA in hexane, 1.5 mL/min), t_r = 4.4 min (minor), t_r = 5.1 min (major).

$[\alpha]_D^{25}$ -114.7 (c = 0.93, $CHCl_3$)



5-42 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (163.7 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-2** (5.3 mg, 0.005 mmol, 0.01 equiv.), 15 h. Isolated as a yellow solid in 78% yield, 98% ee after purification by silica gel chromatography (20:1 hexane:EtOAc).

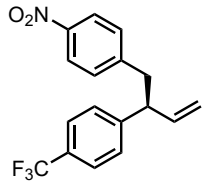
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.06 (d, *J* = 9.3 Hz, 2H), 7.16 (d, *J* = 8.5 Hz, 2H), 7.02 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 6.00 (m, 1H), 5.05 (d, *J* = 10.9 Hz, 1H), 4.98 (d, *J* = 17.3 Hz, 1H), 3.78 (s, 3H), 3.53 (q, *J* = 7.5 Hz, 1H), 3.13 (m, 1H), 3.04 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 158.4, 148.1, 146.5, 140.9, 134.5, 130.0, 128.7, 123.4, 115.0, 114.0, 55.3, 50.5, 42.1;

HRMS (EI): calcd for $C_{17}H_{17}NO_3$ $[M]^+$: 283.1209. Found 283.1211.

Chiral HPLC: Chiralpak IG column (1% IPA in hexane, 1.5 mL/min), t_r = 5.8 min (minor), t_r = 6.8 min (major).

$[\alpha]_D^{25}$ -115.5 (c = 0.69, $CHCl_3$)



5-43 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (182.7 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-2** (10.6 mg, 0.01 mmol, 0.02 equiv.), 2 h. The reaction mixture was passed through a pad of silica to remove DBU before concentrating *in vacuo*. Isolated as a white solid in 91% yield, 95% ee after purification by silica gel chromatography (20:1 hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.08 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.9 Hz, 2H), 7.24 (d, *J* = 7.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.00 (m, 1H), 5.12 (d, *J* = 10.3 Hz, 1H), 5.01 (d, *J* = 16.7 Hz, 1H), 3.66 (q, *J* = 7.5 Hz, 1H), 3.19 (m, 1H), 3.09 (m, 1H);

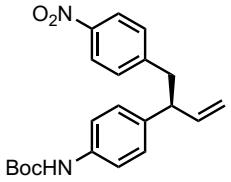
^{13}C NMR ($CDCl_3$, 126 MHz) δ 147.2, 146.7, 146.6, 139.5, 130.0, 129.2 (q, *J* = 31.8 Hz), 128.1, 125.6 (q, *J* = 3.6 Hz), 124.1 (q, *J* = 270.7 Hz), 123.6, 116.3, 51.1, 41.8;

^{19}F NMR ($CDCl_3$, 376 MHz) d –62.5 (s);

HRMS (EI): calcd for $C_{17}H_{14}NO_2F_3$ $[M]^+$: 321.0977. Found 321.0977.

Chiral HPLC: Chiralpak IG column (3% IPA in hexane, 1.5 mL/min), t_r = 2.4 min (minor), t_r = 2.6 min (major).

$[\alpha]_D^{25}$ -76.9 (c = 1.11, $CHCl_3$)



5-44 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (206.2 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-2** (5.3 mg, 0.005 mmol, 0.01 equiv.), 20 h. Isolated as a light yellow solid in 74% yield, 98% ee after purification by silica gel chromatography (4:1 pentane:Et_2O).

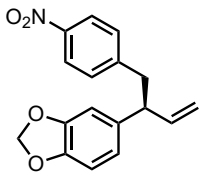
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.06 (d, *J* = 8.8 Hz, 2H), 7.26 (m, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.02 (d, *J* = 8.1 Hz, 2H), 6.40 (br, 1H), 5.99 (m, 1H), 5.05 (dt, *J* = 1.2, 10.1 Hz, 1H), 4.97 (dt, *J* = 1.2, 17.0 Hz, 1H), 3.53 (q, *J* = 7.8 Hz, 1H), 3.13 (m, 1H), 3.04 (m, 1H), 1.51 (s, 9H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 156.9, 152.7, 147.9, 146.4, 140.6, 136.9, 130.0, 128.2, 123.3, 118.6, 115.1, 80.6, 50.6, 42.0, 28.4;

HRMS (ESI): calcd for $C_{21}H_{24}N_2NaO_4$ $[M+Na]^+$: 391.1628. Found 391.1622.

Chiral HPLC: Chiralpak IA column (15% IPA in hexane, 1.5 mL/min), t_r = 3.3 min (major), t_r = 3.7 min (minor).

$[\alpha]_D^{25}$ -109.5 (c = 0.60, $CHCl_3$)



5-45 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (170.7 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-2** (5.3 mg, 0.005 mmol, 0.01

equiv.), 14 h. Isolated as a yellow oil in 85% yield, 98% ee after purification by silica gel chromatography (10:1 hexane:EtOAc).

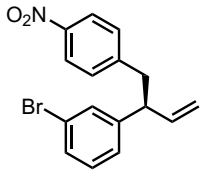
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.07 (m, 2H), 7.18 (m, 2H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.64 (d, *J* = 1.6 Hz, 1H), 6.52 (dd, *J* = 1.7, 8.0 Hz, 1H), 5.97 (m, 1H), 5.93 (m, 2H), 5.06 (dt, *J* = 1.2, 10.2 Hz, 1H), 4.99 (dt, *J* = 1.2, 17.1 Hz, 1H), 3.50 (q, *J* = 7.8 Hz, 1H), 3.12 (m, 1H), 3.03 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 147.9, 147.8, 146.5, 146.3, 140.6, 136.3, 130.0, 123.4, 120.8, 115.2, 108.3, 107.9, 101.0, 50.9, 42.1;

HRMS (EI): calcd for $C_{17}H_{15}NO_4$ $[M]^+$: 297.1001. Found 297.0999.

Chiral HPLC: Chiralpak IG column (1% IPA in hexane, 1.5 mL/min), t_r = 8.2 min (minor), t_r = 8.8 min (major).

$[\alpha]_D^{25}$ -139.5 (c = 0.62, $CHCl_3$)



5-46 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (188.1 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-2** (5.3 mg, 0.005 mmol, 0.01 equiv.), 17 h. Isolated as a yellow oil in 87% yield after purification by silica gel chromatography (20:1 pentane:Et_2O).

[Gram-Scale] Prepared according to the General Procedure B from the corresponding allylic aryl acetate (3.0 g, 8.0 mmol, 1.0 equiv.), **[Ir]-2** (42 mg, 0.04 mmol, 0.005 equiv.), and DBU (1.2 ml, 8.0 mmol, 1.0 equiv.), 24 h. Isolated in 86% yield (2.3 g) after purification by silica gel chromatography (20:1 pentane:Et_2O) as a yellow oil, 99% ee

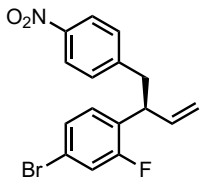
after derivatization to **5-32** (See procedure and characterization for the gram-scale synthesis of **5-32**).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.09 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.30 (s, 1H), 7.19 (d, *J* = 8.6 Hz, 2H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 5.97 (m, 1H), 5.10 (d, *J* = 10.1 Hz, 1H), 5.00 (d, *J* = 17.0 Hz, 1H), 3.55 (q, *J* = 7.8 Hz, 1H), 3.14 (m, 1H), 3.07 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 147.4, 146.6, 144.9, 139.6, 130.7, 130.2, 130.0, 129.9, 126.5, 123.5, 122.8, 116.1, 50.9, 41.8;

HRMS (EI): calcd for $C_{16}H_{14}NO_2Br$ $[M]^+$: 331.0208. Found 331.0208.

$[\alpha]_D^{25}$ -97.4 (c = 1.08, $CHCl_3$)



5-47 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (197.1 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-2** (5.3 mg, 0.005 mmol, 0.01 equiv.), 23 h. Isolated as a yellow oil in 90% yield, 93% ee after purification by silica gel chromatography (10:1 hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.10 (m, 2H), 7.31 – 7.29 (m, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 6.87 (dd, *J* = 8.3, 9.5 Hz, 1H), 5.98 (m, 1H), 5.13 (dt, *J* = 1.2, 10.2 Hz, 1H), 5.04 (d, *J* = 17.4 Hz, 1H), 3.89 (q, *J* = 7.8 Hz, 1H), 3.15 (m, 1H), 3.07 (m, 1H);

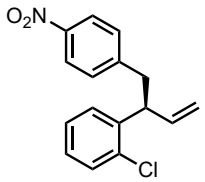
^{13}C NMR ($CDCl_3$, 126 MHz) δ 159.6 (d, *J* = 245.8 Hz), 147.0, 146.7, 138.0, 131.9 (d, *J* = 16.8 Hz), 131.8 (d, *J* = 4.6 Hz), 131.3 (d, *J* = 8.6 Hz), 129.9, 123.6, 117.5 (d, *J* = 24.6 Hz), 116.9, 116.8, 44.3, 40.8 (d, *J* = 1.2 Hz);

^{19}F NMR ($CDCl_3$, 376 MHz) d -119.9 (m);

HRMS (EI): calcd for $C_{16}H_{13}NO_2FBr$ $[M]^+$: 349.0114. Found 349.0109.

Chiral HPLC: Chiralpak IG column (1% IPA in hexane, 1.2 mL/min), t_r = 4.6 min (minor), t_r = 4.8 min (major).

$[\alpha]_D^{25}$ -87.4 (c = 0.80, $CHCl_3$)



5-48 Modified conditions were required to obtain high ee. In an atmosphere controlled glovebox, **[Ir]-1** (5.6 mg, 0.005 mmol, 0.05 equiv.), the corresponding allylic aryl acetate (33.2 mg, 0.10 mmol, 1.00 equiv.), and durene internal standard were sequentially added to a 1-dram vial charged with a stir bar. DME (0.5 mL) was added and the mixture was stirred until homogeneous (approx. 1 minute). The vial was sealed with a PTFE-lined cap, removed from the glovebox and gently stirred at 0° C for 10 min, followed by the addition of DBU (15.2 mg, 0.10 mmol, 1.0 equiv.). Upon completion of the reaction (40 h) as determined by ^{1}H NMR using durene as internal standard, the reaction mixture was warmed to room temperature to induce decarboxylation (3 h). Then the reaction mixture was concentrated *in vacuo* and purified by silica gel chromatography (20:1 pentane:Et_2O). Isolated as a colorless oil in 75% yield, 90% ee.

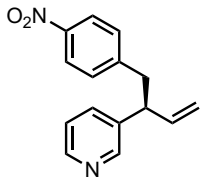
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.08 (d, *J* = 8.9 Hz, 2H), 7.32 (dd, *J* = 0.9, 8.0 Hz, 1H), 7.28 – 7.23 (m, 4H), 7.15 (m, 1H), 6.00 (m, 1H), 5.12 (d, *J* = 10.3 Hz, 1H), 5.03 (d, *J* = 17.3 Hz, 1H), 4.23 (q, *J* = 7.7 Hz, 1H), 3.12 (d, *J* = 7.2 Hz, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 147.5, 146.6, 140.1, 138.7, 133.8, 130.0, 129.9, 128.5, 127.9, 127.1, 123.4, 116.5, 46.5, 41.1;

HRMS (EI): calcd for $C_{16}H_{14}NO_2Cl$ $[M]^+$: 287.0713. Found 287.0710.

Chiral HPLC: Chiralpak IG column (1% IPA in hexane, 1.5 mL/min), t_r = 3.5 min (major), t_r = 3.8 min (minor).

$[\alpha]_D^{25}$ -32.1 (c = 1.50, $CHCl_3$)



5-49 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (29.8 mg, 0.10 mmol, 1.0 equiv.) and **[Ir]-2** (2.1 mg, 0.002 mmol, 0.02 equiv.), 2 h. The reaction mixture was passed through a pad of silica to remove DBU before concentrating *in vacuo*. Isolated as a brown oil in 80% yield, 94% ee after purification by silica gel chromatography (20:1 DCM:MeOH).

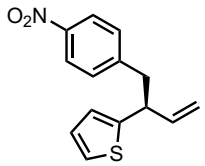
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.46 (dd, *J* = 1.4, 4.8 Hz, 1H), 8.37 (d, *J* = 2.1 Hz, 1H), 8.07 (d, *J* = 8.6 Hz, 2H), 7.43 (dt, *J* = 2.0, 7.8 Hz, 1H), 7.21 (dd, *J* = 4.6, 7.9 Hz, 1H), 7.18 (d, *J* = 8.3 Hz, 2H), 6.00 (m, 1H), 5.13 (d, *J* = 10.1 Hz, 1H), 5.02 (d, *J* = 17.0 Hz, 1H), 3.62 (q, *J* = 7.8 Hz, 1H), 3.19 (m, 1H), 3.07 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.5, 148.4, 147.0, 146.7, 139.3, 137.8, 135.1, 130.0, 123.6, 123.5, 116.5, 48.7, 41.7;

HRMS (EI): calcd for $C_{15}H_{14}N_2O_2$ $[M]^+$: 254.1055. Found 254.1055.

Chiral HPLC: Whelk-O1 column (30% IPA in hexane, 1.5 mL/min), t_r = 11.9 min (major), t_r = 13.2 min (minor).

$[\alpha]_D^{25}$ -79.4 (c = 0.54, $CHCl_3$)



5-50 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (151.7 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-2** (5.3 mg, 0.005 mmol, 0.01 equiv.), 6 h. Isolated as a yellow solid in 86% yield, 96% ee after purification by silica gel chromatography (10:1 hexane:EtOAc).

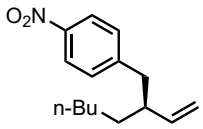
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.10 (m, 2H), 7.24 (d, *J* = 8.6 Hz, 2H), 7.17 (dd, *J* = 1.1, 5.1 Hz, 1H), 6.91 (dd, *J* = 3.5, 5.1 Hz, 1H), 6.73 (m, 1H), 5.96 (m, 1H), 5.08 (dt, *J* = 1.2, 10.2 Hz, 1H), 5.03 (dt, *J* = 1.2, 17 Hz, 1H), 3.88 (q, *J* = 7.8 Hz, 1H), 3.19 (m, 1H), 3.14 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 147.3, 146.7, 146.1, 139.8, 130.1, 126.8, 124.2, 123.9, 123.5, 116.0, 46.6, 43.0;

HRMS (EI): calcd for $C_{14}H_{13}NO_2S$ $[M]^+$: 259.0667. Found 259.0668.

Chiral HPLC: Chiralpak IG column (1% IPA in hexane, 1.5 mL/min), t_r = 5.5 min (major), t_r = 6.0 min (minor).

$[\alpha]_D^{25}$ -32.7 (c = 0.85, $CHCl_3$)



5-51 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (29.1 mg, 0.10 mmol, 1.0 equiv.) and **[Ir]-1** (1.1 mg, 0.001 mmol, 0.01 equiv.), 12 h. Isolated as a colorless oil in 78% yield after purification by silica gel chromatography (20:1 pentane:Et_2O), 99% ee after derivatization according to General Procedure E.

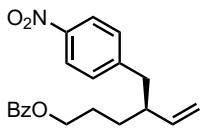
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.12 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 5.54 (m, 1H), 4.94 (dd, *J* = 1.5, 10.3 Hz, 1H), 4.82 (m, 1H), 2.79 (m, 1H), 2.65 (m, 1H), 2.30 (m, 1H), 1.42 – 1.20 (m, 8H), 0.87 (t, *J* = 7.9 Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 148.8, 146.4, 141.4, 130.1, 123.4, 115.5, 45.7, 41.7, 34.5, 31.9, 26.8, 22.6, 14.1;

HRMS (EI): calcd for $C_{15}H_{21}NO_2$ $[M]^+$: 247.1572. Found 247.1576.

Chiral HPLC: Derivatized to the corresponding cross-metathesis product according to General Procedure E. Chiralpak IA column (5% IPA in hexane, 1.5 mL/min), t_r = 2.7 min (major), t_r = 3.0 min (minor).

$[\alpha]_D^{25}$ -11.3 (c = 0.67, $CHCl_3$)



5-52 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (115.0 mg, 0.30 mmol, 1.0 equiv.) and **[Ir]-1** (3.3 mg, 0.003 mmol, 0.01

equiv.), 15 h. Isolated as a colorless oil (contains 8% linear allylation product) in 81% yield, 97% ee after purification by silica gel chromatography (10:1 hexane:EtOAc).

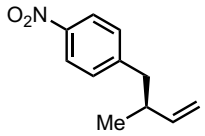
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (m, 2H), 7.97 (dd, *J* = 1.2, 8.3 Hz, 2H), 7.55 (tt, *J* = 1.4, 7.4 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 2H), 7.26 (d, *J* = 8.8 Hz, 2H), 5.56 (m, 1H), 5.00 (dd, *J* = 1.4, 10.3 Hz, 1H), 4.89 (m, 1H), 4.29 (m, 2H), 2.79 (m, 1H), 2.71 (m, 1H), 2.37 (m, 1H), 1.87 – 1.82 (m, 1H), 1.73 – 1.68 (m, 1H), 1.61 – 1.56 (m, 1H), 1.44 – 1.39 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.6, 148.3, 146.5, 140.7, 133.0, 130.3, 130.0, 129.5, 128.4, 123.5, 116.3, 64.6, 45.3, 41.7, 30.5, 26.4;

HRMS (ESI): calcd for $C_{20}H_{21}NNaO_4$ $[M+Na]^+$: 362.1363. Found 362.1359;

Chiral HPLC: Chiralpak IB column (5% IPA in hexane, 1.5 mL/min), t_r = 3.2 min (minor), t_r = 3.9 min (major);

$[\alpha]_D^{25}$ -23.0 (c = 0.93, $CHCl_3$)



5-53 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (117.6 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-2** (5.3 mg, 0.005 mmol, 0.01 equiv.), 14 h. Isolated as a light yellow oil in 83% yield after purification by silica gel chromatography (10:1 hexane:EtOAc), 97% ee after derivatization according to General Procedure E.

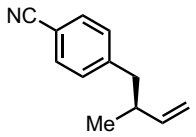
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.13 (m, 2H), 7.28 (m, 2H), 5.72 (m, 1H), 4.94 – 4.89 (m, 2H), 2.74 (m, 1H), 2.66 (m, 1H), 2.48 (m, 1H), 1.02 (d, *J* = 6.7 Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 148.7, 146.5, 142.7, 130.0, 123.5, 113.8, 43.0, 39.3, 19.6;

HRMS (EI): calcd for $C_{11}H_{13}NO_2$ $[M]^+$: 191.0946. Found 191.0942.

Chiral HPLC: Derivatized to the corresponding cross-metathesis product according to General Procedure E. Chiralpak IG column (5% IPA in hexane, 1.5 mL/min), t_r = 6.4 min (major), t_r = 6.8 min (minor).

$[\alpha]_D^{25}$ 14.4 (c = 0.72, $CHCl_3$)



5-54 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (107.7 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-2** (5.3 mg, 0.005 mmol, 0.01 equiv.), 22 h. Subsequent decarboxylation was achieved at 70° C, 3h. Isolated) as a colorless oil in 66% yield after purification by silica gel chromatography (10:1 hexane:EtOAc, 99% ee after derivatization according to General Procedure E.

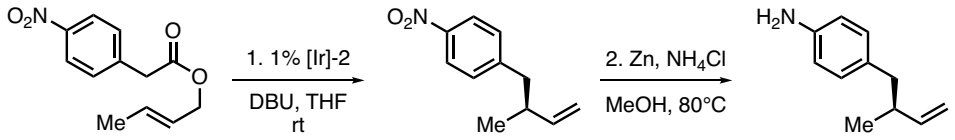
^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.56 (m, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 5.73 (m, 1H), 4.94 – 4.90 (m, 2H), 2.71 (m, 1H), 2.61 (m, 1H), 2.46 (m, 1H), 1.01 (d, *J* = 6.9 Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 146.4, 142.9, 132.0, 130.0, 119.2, 113.7, 109.8, 43.3, 39.2, 19.6;

HRMS (EI): calcd for $C_{12}H_{13}N$ $[M]^+$: 171.1048. Found 171.1044.

Chiral HPLC: Derivatized to the corresponding cross-metathesis product according to General Procedure E. Chiralpak IG column (10% IPA in hexane, 1.5 mL/min), t_r = 4.8 min (major), t_r = 5.1 min (minor).

$[\alpha]_D^{25}$ 18.4 (c = 0.87, $CHCl_3$)



5-55 *Step 1* Prepared according to the General Procedure B from the corresponding allylic aryl acetate (235.2 mg, 1.00 mmol, 1.0 equiv.) and **[Ir]-2** (10.6 mg, 0.01 mmol, 0.01 equiv.), 14 h. Isolated in 187.3 mg with 10% 4-nitrotoluene side-product after purification by silica gel chromatography (20:1 hexane:EtOAc) as a light yellow oil. *Step 2* To a 1-dram vial charged with a stir bar was added crude **5-53** (81.5 mg, from *Step 1*), zinc powder (202.9 mg, 3.20 mmol, 7.5 equiv.), and NH_4Cl (46.0 mg, 0.86 mmol, 2.0 equiv.) and 3 mL MeOH. The reaction was heated to 80° C for 1 h, then cooled to room temperature. The reaction mixture was passed through a silica plug, washing with EtOAc, the filtrate was concentrated *in vacuo*. Isolated as a light yellow oil, 86% over two steps after purification by silica gel chromatography (4:1 hexane:EtOAc), 98% ee after derivatization according to General Procedure E.

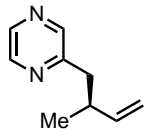
^{1}H NMR ($CDCl_3$, 700 MHz) δ 6.94 (d, *J* = 8.1 Hz, 2H), 6.62 (m, 2H), 5.79 (m, 1H), 4.93 (dt, *J* = 1.3, 17.2 Hz, 1H), 4.90 (m, 1H), 3.54 (br, 2H), 2.58 (m, 1H), 2.43 – 2.35 (m, 2H), 0.97 (d, *J* = 6.4 Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 144.3, 144.2, 130.9, 130.0, 115.1, 112.5, 42.4, 39.5, 19.3;

HRMS (EI): calcd for $C_{11}H_{15}N$ $[M]^+$: 161.1205. Found 161.1207.

Chiral HPLC: Derivatized to the corresponding cross-metathesis product according to General Procedure E. Whelk-O1 column (20% IPA in hexane, 1.5 mL/min), t_r = 11.4 min (minor), t_r = 12.4 min (major).

$[\alpha]_D^{25}$ 20.0 (c = 1.02, $CHCl_3$)



5-56 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (96.1 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-1** (5.3 mg, 0.005 mmol, 0.01 equiv.), 14 h. A modified workup was used, washing with saturated NH_4Cl instead of 1 M HCl. Subsequent decarboxylation was achieved at 80° C, 2h. Isolated as a light yellow oil in 68% yield, >99% ee after purification by silica gel chromatography (1:1 hexane:EtOAc).

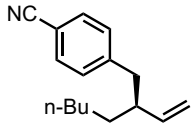
^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.50 (dd, *J* = 1.4, 2.2 Hz, 1H), 8.41 (d, *J* = 1.4 Hz, 1H), 8.39 (d, *J* = 2.5 Hz, 1H), 5.77 (m, 1H), 4.94 – 4.90 (m, 2H), 2.86 – 2.68 (m, 3H), 1.06 (d, *J* = 6.7 Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 156.4, 145.3, 144.1, 142.8, 142.3, 113.7, 42.5, 38.1, 19.8;

HRMS (EI): calcd for $C_9H_{12}N_2$ $[M]^+$: 148.1001. Found 148.0998.

Chiral HPLC: Chiralpak IG column (1% IPA in hexane, 1.5 mL/min), t_r = 5.5 min (major), t_r = 6.2 min (minor).

$[\alpha]_D^{25}$ 14.6 (c = 0.85, $CHCl_3$)



5-57 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (135.7 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-1** (11.1 mg, 0.01 mmol, 0.02 equiv.), 15 h. Subsequent decarboxylation was achieved at 70° C, 6h. Isolated as a light yellow oil in 64% yield after purification by silica gel chromatography (20:1 hexane:EtOAc), >99% ee after derivatization according to General Procedure E.

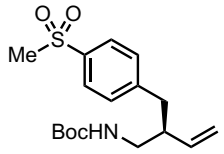
^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.55 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 5.53 (m, 1H), 4.93 (dd, *J* = 1.6, 10.4 Hz, 1H), 4.81 (m, 1H), 2.73 (m, 1H), 2.61 (m, 1H), 2.28 (m, 1H), 1.40 – 1.18 (m, 8H), 0.87 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 146.6, 141.5, 131.9, 130.1, 119.2, 115.3, 109.7, 45.6, 42.0, 34.4, 31.9, 26.8, 22.6, 14.1;

HRMS (EI): calcd for $C_{16}H_{21}N$ $[M]^+$: 227.1674. Found 227.1674.

Chiral HPLC: Derivatized to the corresponding cross-metathesis product according to General Procedure E. Chiralpak IA column (5% IPA in hexane, 1.0 mL/min), t_r = 4.2 min (major), t_r = 4.5 min (minor).

$[\alpha]_D^{25}$ -8.9 (c = 0.83, $CHCl_3$)



5-58 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (38.3 mg, 0.10 mmol, 1.0 equiv.) and **[Ir]-2** (1.1 mg, 0.001 mmol, 0.01 equiv.), 16 h. Subsequent decarboxylation was achieved at 70° C, 4h. Isolated as a light yellow oil in 50% yield (9:1 ratio of amide rotamers), >99% ee after purification by silica gel chromatography (1:1 hexane:EtOAc).

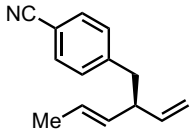
^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.84 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 5.58 (m, 1H), 5.09 (d, *J* = 10.5 Hz, 1H), 4.98 (d, *J* = 17.0 Hz, 1H), 4.57 (br, 1H), 3.31 (m, 1H), 3.04 (s, 3H), 3.00 (m, 1H), 2.83 (m,1 H), 2.68 (m, 1H), 2.54 (m, 1H), 1.44 (s, 9H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 155.9, 146.3, 138.5, 138.4, 130.2, 127.5, 117.9, 79.5, 45.8, 44.6, 44.1, 38.7, 28.4;

HRMS (ESI): calcd for $C_{17}H_{25}NNaO_4S$ $[M+Na]^+$: 362.1397. Found 362.1395.

Chiral HPLC: Chiralpak IG column (20% IPA in hexane, 1.5 mL/min), t_r = 8.1 min (minor), t_r = 9.1 min (major).

$[\alpha]_D^{25}$ -10.3 (c = 1.58, $CHCl_3$)



5-59 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (120.7 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-2** (5.3 mg, 0.005 mmol, 0.01 equiv.), 20 h. Subsequent decarboxylation was achieved at 70° C, 3h. Isolated as a

colorless oil in 65% yield, 99% ee after purification by silica gel chromatography (20:1 pentane:Et_2O).

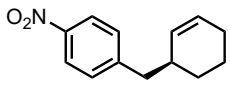
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 5.72 (m, 1H), 5.41 – 5.30 (m, 2H), 4.98 (d, *J* = 10.2 Hz, 1H), 4.92 (dt, *J* = 1.4, 17.1 Hz, 1H), 2.96 (m, 1H), 2.75 (d, *J* = 7.5 Hz, 2H), 1.63 (d, *J* = 4.7 Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 146.0, 140.3, 132.2, 131.9, 130.2, 126.3, 119.2, 114.9, 109.8, 48.1, 41.7, 18.0;

HRMS (EI): calcd for $C_{14}H_{15}N$ $[M]^+$: 197.1205. Found 197.1206.

Chiral HPLC: Chiralpak IG column (1% IPA in hexane, 1.5 mL/min), t_r = 3.7 min (major), t_r = 3.9 min (minor).

$[\alpha]_D^{25}$ -25.7 (c = 0.57, $CHCl_3$)



5-60 Prepared according to General Procedure C from 4-nitrophenylacetic acid (27.2 mg, 0.15 mmol, 1.5 equiv.), 48 h. The reaction mixture was stirred under 0° C for 1 h before adding BSA and conducted at 0° C. Subsequent decarboxylation was achieved at rt, 1h. 80% yield, determined by ^{1}H NMR using 1,3,5-trimethoxybezene as internal standard, 91% ee.

Prepared according to General Procedure D from the corresponding 2-cyclohexenyl aryl acetate (62.7 mg, 0.24 mmol, 1.0 equiv.), 50 h. Subsequent decarboxylation was achieved at rt, 1h. Isolated in 77% yield, 90% ee after purification by silica gel chromatography (10:1 pentane/Et_2O) as a yellow oil.

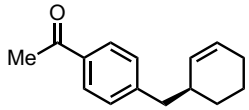
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 5.73 (m, 1H), 5.51 (m, 1H), 2.74 (m, 1H), 2.66 (m, 1H), 2.42 (m, 1H), 1.99 (m, 2H), 1.71 (m, 2H), 1.52 (m, 1H), 1.26 (m, 1H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 148.9, 146.5, 130.2, 129.9, 128.4, 123.5, 42.6, 37.0, 28.8, 25.3, 21.2;

HRMS (EI): calcd for $C_{13}H_{15}NO_2$ $[M]^+$: 217.1103. Found 217.1105.

Chiral HPLC: Derivatized to the corresponding epoxide**.** To a solution of olefin (10mg, 0.035 mmol) in $CDCl_3$ (1 mL) in a half-dram vial, was added excess mCPBA (20mg, 4.7 equiv.), and the mixture was stirred at rt for 16 h. Crude NMR showed full conversion to the corresponding epoxides (~2:1 d.r.). Whelk-O1 column (10% IPA in hexane, 1.5 mL/min), minor diastereomer, t_r = 11.0 min (major), t_r = 12.4 min (minor).

$[\alpha]_D^{25}$ -41.7 (c = 0.75, $CHCl_3$)



5-61 Prepared according to the General Procedure D from the corresponding 2-cyclohexenyl aryl acetate (62.0 mg, 0.24 mmol, 1.0 equiv.), 48 h. Diethylamine treatment was not applied during work-up. Subsequent decarboxylation was achieved at 100° C, 1h. Isolated as a colorless oil in 73% yield, 84% ee after purification by silica gel chromatography (10:1 pentane/Et_2O).

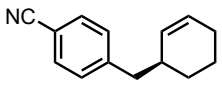
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.89 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 7.9 Hz, 2H), 5.71 (m, 1H), 5.53 (m, 1H), 2.69 (m, 1H), 2.60 (m, 1H), 2.59 (s, 3H), 2.41 (m, 1H), 1.99 (m, 2H), 1.71 (m, 2H), 1.51 (m, 1H), 1.26 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.9, 146.9, 135.2, 130.8, 129.4, 128.4, 127.9, 42.7, 37.0, 28.9, 26.6, 25.3, 21.2;

HRMS (EI): calcd for $C_{15}H_{18}O$ $[M]^+$: 214.1358. Found 214.1359.

Chiral HPLC: ChiralPak IG column (1% IPA in hexane, 1.5 mL/min), t_r = 8.8 min (major), t_r = 9.8 min (minor).

$[\alpha]_D^{25}$ -35.5 (c = 0.83, $CHCl_3$)



5-62 Prepared according to the General Procedure C from 4-cyanophenylacetic acid (24.2 mg, 0.15 mmol, 1.5 equiv.), 19 h. Subsequent decarboxylation was achieved at 120° C, 2h. Isolated as a colorless oil in 91% yield, 89% ee after purification by silica gel chromatography (10:1 hexane/EtOAc).

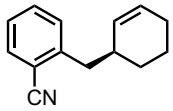
^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.57 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 5.72 (m, 1H), 5.50 (m, 1H), 2.69 (m, 1H), 2.60 (m, 1H), 2.39 (m, 1H), 1.99 (m, 2H), 1.70 (m, 2H), 1.51 (m, 1H), 1.23 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 146.9, 132.0, 130.3, 129.9, 128.2, 119.1, 109.7, 42.8, 36.9, 28.8, 25.2, 21.1;

HRMS (EI): calcd for $C_{14}H_{15}N$ $[M]^+$: 197.1205. Found 197.1208.

Chiral HPLC: derivatized to the corresponding epoxide**.** To a solution of olefin (10mg, 0.035 mmol) in $CDCl_3$ (1 mL) in a half-dram vial, was added excess mCPBA (20mg, 4.7 equiv.), and the mixture was stirred at rt for 16 h. Crude NMR showed full conversion to the corresponding epoxides (~2:1 d.r.). ChiralPak IC column (10% IPA in hexane, 1.5 mL/min), major diastereomer, t_r = 6.7 min (major), t_r = 7.9 min (minor).

$[\alpha]_D^{25}$ -49.3 (c = 0.76, $CHCl_3$)



5-63 Prepared according to the General Procedure C from 2-cyanophenylacetic acid (24.2 mg, 0.15 mmol, 1.5 equiv.), 14 h. Subsequent decarboxylation was achieved at 140° C, 1h. Isolated as a light-yellow oil in 99% yield, 88% ee after purification by silica gel chromatography (10:1 hexane/EtOAc).

Prepared according to the General Procedure D from the corresponding 2-cyclohexenyl aryl acetate (57.9 mg, 0.24 mmol, 1.0 equiv.), 21 h. Subsequent decarboxylation was achieved at 140° C, 1h. Isolated in 79% yield, 83% ee after purification by silica gel chromatography (10:1 hexane/EtOAc) as a light-yellow oil.

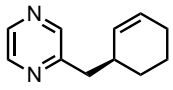
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62 (dd, *J* = 1.0, 7.5 Hz, 1H), 7.51 (dt, *J* = 1.3, 7.7 Hz, 1H), 7.32 – 7.28 (m, 2H), 5.73 (m, 1H), 5.54 (m, 1H), 2.87 (m, 1H), 2.80 (m, 1H), 2.49 (m, 1H), 2.00 (m, 2H), 1.73 (m, 2H), 1.52 (m, 1H), 1.34 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 145.0, 132.9, 132.5, 130.4, 130.2, 128.3, 126.5, 118.3, 113.0, 41.0, 36.8, 28.7, 25.3, 21.1;

HRMS (EI): calcd for $C_{14}H_{15}N$ $[M]^+$: 197.1205. Found 197.1208.

Chiral HPLC: derivatized to the corresponding epoxide**.** To a solution of olefin (10mg, 0.035 mmol) in $CDCl_3$ (1 mL) in a half-dram vial, was added excess mCPBA (20mg, 4.7 equiv.), and the mixture was stirred at rt for 16 h. Crude NMR showed full conversion to the corresponding epoxides (~2:1 d.r.). ChiralPak IC column (10% IPA in hexane, 1.5 mL/min), major diastereomer, t_r = 5.0 min (major), t_r = 5.6 min (minor).

$[\alpha]_D^{25}$ -53.1 (c = 0.74, $CHCl_3$)



5-64 Prepared according to the General Procedure D from the corresponding 2-cyclohexenyl aryl acetate (52.4 mg, 0.24 mmol, 1.0 equiv.), 24 h. Subsequent decarboxylation was achieved at 100° C, 1h. A modified workup was used, washing with saturated NH_4Cl instead of 1 M HCl. Isolated as a light-yellow oil in 84% yield, 86% ee after purification by silica gel chromatography (1:1 pentane/Et_2O).

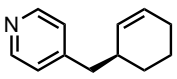
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.51 (m, 1H), 8.44 (s, 1H), 8.40 (d, *J* = 2.4 Hz, 1H), 5.73 (m, 1H), 5.54 (m, 1H), 2.83 (m, 1H), 2.75 (m, 1H), 2.64 (m, 1H), 2.00 (m, 2H), 1.72 (m, 2H), 1.53 (m, 1H), 1.32 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 156.6, 145.3, 144.2, 142.2, 130.4, 128.2, 42.0, 35.7, 28.8, 25.3, 21.1;

HRMS (EI): calcd for $C_{11}H_{14}N_2$ $[M]^+$: 174.1157. Found 174.1157.

Chiral HPLC: ChiralPak IG column (5% IPA in hexane, 1.5 mL/min), t_r = 2.9 min (major), t_r = 3.2 min (minor).

$[\alpha]_D^{25}$ -37.6 (c = 0.74, $CHCl_3$)



5-65 Prepared according to the General Procedure D from the corresponding 2-cyclohexenyl aryl acetate (52.2 mg, 0.24 mmol, 1.0 equiv.), 22 h. Subsequent decarboxylation was achieved at 70° C, 6h. A modified workup was used, washing with

saturated NH_4Cl instead of 1 M HCl. Isolated as a colorless oil in 73% yield, 86% ee after purification by silica gel chromatography (1:1 hexane/EtOAc).

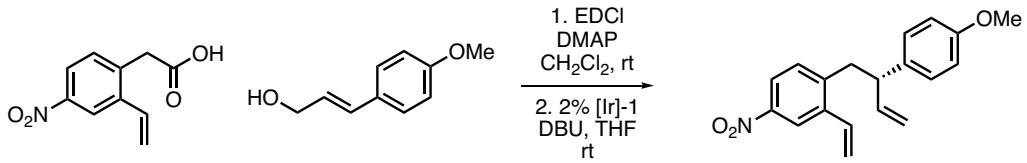
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.49 (m, 2H), 7.10 (m, 2H), 5.72 (m, 1H), 5.51 (m, 1H), 2.62 (m, 1H), 2.54 (m, 1H), 2.41 (m, 1H), 1.99 (m, 2H), 1.71 (m, 2H), 1.51 (m, 1H), 1.26 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.9, 149.6, 130.4, 128.2, 124.7, 42.0, 36.4, 28.8, 25.3, 21.2;

HRMS (EI): calcd for $C_{12}H_{15}N$ $[M]^+$: 173.1205. Found 173.1206.

Chiral HPLC: ChiralPak IG column (2% IPA in hexane, 1.5 mL/min), t_r = 8.7 min (major), t_r = 9.1 min (minor).

5.4.2. Synthesis of Elacestrant and Taranabant Cores



5-68 *Step 1.* To a flask charged with stir bar and purged with N_2 was added EDCl (288mg, 1.5 mmol, 1.5 equiv.), DCM (5 ml), cinnamyl alcohol (246 mg, 1.5 mmol, 1.5 equiv.) and DMAP (24 mg, 0.2 mmol, 0.2 equiv.). The solution was cooled to 0° C and aryl acetic acid (207 mg, 1.0 mmol, 1.0 equiv.) was added in one portion. The mixture was warmed to room temperature and stirred overnight. Upon completion of the reaction, the mixture was washed sequentially with 1 M HCl and water. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The corresponding cinnamyl aryl acetate was isolated as a white solid in 87% yield after purification by silica gel chromatography (19:1 to 3:2 hexane/EtOAc) which was used directly in the next step.

Step 2. Prepared according to the General Procedure B from the corresponding cinnamyl aryl acetate (353 mg, 1.0 mmol, 1.0 equiv.) and **[Ir]-1** (22 mg, 0.02 mmol, 0.02 equiv.), 22 h. Isolated as a colorless oil, 51% over two steps, 99% ee after after purification by silica gel chromatography (99:1 to 16:1 pentane/Et_2O).

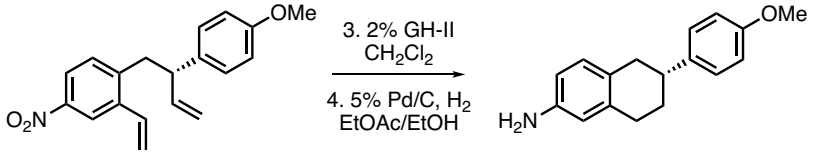
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.30 (d, *J* = 2.5 Hz, 1H), 7.90 (dd, *J* = 2.5, 8.4 Hz, 1H), 7.02 – 6.97 (m, 3H), 6.90 (dd, *J* = 11.4, 17.6 Hz, 1H), 6.82 – 6.78 (m, 2H), 6.01 (m, 1H), 5.78 (d, *J* = 17.4 Hz, 1H), 5.47 (d, *J* = 11.2 Hz, 1H), 5.04 (m, 1H), 4.96 (m, 1H), 3.78 (s, 3H), 3.50 (q, *J* = 7.6 Hz, 1H), 3.19 (m, 1H), 3.05 (m, 1H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 158.4, 146.8, 145.0, 140.6, 138.3, 134.5, 132.9, 131.6, 128.6, 121.8, 120.9, 118.6, 115.0, 114.0, 55.3, 49.5, 39.6;

HRMS (ESI): calcd for $C_{19}H_{19}NNaO_3$ $[M+Na]^+$: 332.1257. Found 332.1258.

Chiral HPLC: ChiralPak IG column (1% IPA in hexane, 1.5 mL/min), t_r = 5.6 min (major), t_r = 6.4 min (minor).

$[\alpha]_D^{25}$ -140 (c = 0.72, $CHCl_3$)



5-69 *Step 3.* To a solution of diene (93 mg, 0.30 mmol, 1.0 equiv.) in CH_2Cl_2 (3 ml) in a 4-dram vial was added 2nd Generation Hoveyda-Grubbs catalyst (3.8 mg, 0.0060 mmol, 0.02 equiv.) as a solution in CH_2Cl_2 (1.3 ml). The reaction was stirred at room temperature for 2 hours, until full conversion was observed by 1H NMR. The reaction mixture was passed through a pipette plug of silica (5 cm), washing with 10:1

hexane/EtOAc to separate the non-polar RCM product from the catalyst (green band). The pipette was flushed with CH_2Cl_2, and concentrated. This residue was subjected to a second identical silica plug. The combined product fractions were combined and concentrated to obtain the RCM product as a white solid (>95% crude yield), which was used directly in the next step. *Step 4.* In a 4-dram vial, the crude RCM product was dissolved in 4:1 EtOH/EtOAc (3.75 ml). Pd (10%) on activated carbon (16 mg, 0.015 mmol, 0.05 equiv.) was added and the vial was sealed with a PTFE-lined cap. The headspace was purged with H_2 for 5 minutes, an H_2 balloon was installed, and the reaction was stirred at room temperature for 16 h. The mixture was filtered over celite, and concentrated. Isolated as an off-white solid, 84% over two steps, 99% ee after purification by silica gel chromatography (19:1 to 3:2 hexane/EtOAc).

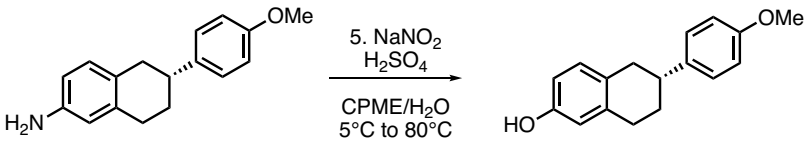
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.21 – 7.17 (m, 2H), 6.91 – 6.84 (m, 3H), 6.52 – 6.47 (m, 2H), 3.80 (s, 3H), 3.52 (s, 2H), 2.94 – 2.72 (m, 5H), 2.07 (m, 1H), 1.87 (m, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.9, 144.1, 139.1, 137.1, 129.8, 127.7, 127.0, 115.1, 113.8, 113.3, 55.3, 40.2, 37.2, 30.7, 29.9;

HRMS (ESI): calcd for $C_{17}H_{20}NO$ $[M+H]^+$: 254.1539. Found 254.1539.

Chiral HPLC: ChiralPak IB column (10% IPA in hexane, 1.5 mL/min), t_r = 6.7 min (major), t_r = 7.5 min (minor).

$[\alpha]_D^{25}$ 73.1 (c = 0.20, $CHCl_3$)



5-70 *Step 5.* To a 2-dram vial charged with a stir bar was sequentially added aniline **5-69** (30 mg, 0.12 mmol, 1.0 equiv.), ice (624 mg, 35 mmol, 289 equiv.). Concentrated H_2SO_4 (0.19 ml, 3.6 mmol, 30 equiv.) was slowly added and the mixture was stirred at room temperature for 5 minutes, open to air. CPME (1.5 mL) was then added to form a biphasic mixture, which was cooled to 5° C in an ice bath (5 minutes). Aqueous $NaNO_2$ (0.34 ml, 0.39 M, 0.13 mmol, 1.1 equiv.) was added via syringe pump over 10 minutes, keeping the temperature at 5° C. Upon completion of the addition, the mixture was sealed with a PTFE cap and pierced with a 22g needle, then heated to 80° C for 15 minutes. A yellow color forms in the top organic layer. The mixture was cooled to rt, extracted with EtOAc (2 x 30 ml), dried with Na_2SO_4, filtered and concentrated *in vacuo*. Isolated as an off-white solid, 91% yield, 99% ee after purification by silica gel chromatography (19:1 to 3:2 hexane/EtOAc).

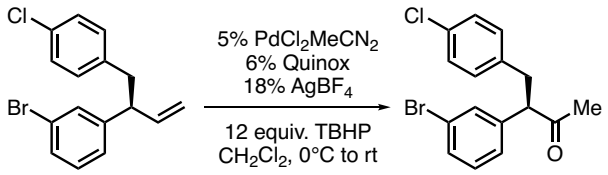
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.22 – 7.17 (m, 2H), 6.97 (m, 1H), 6.91 – 6.86 (m, 2H), 6.66 – 6.59 (m, 2H), 4.53 (s, 1H), 3.82 (s, 3H), 2.99 – 2.76 (m, 5H), 2.09 (m, 1H), 1.89 (m, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.0, 153.4, 138.9, 137.7, 130.0, 129.0, 127.7, 115.0, 113.9, 113.0, 55.3, 40.1, 37.2, 30.5, 29.9;

HRMS (ESI): calcd for $C_{17}H_{17}O_2$ $[M-H]^-$: 253.1234. Found 253.1232.

Chiral HPLC: ChiralPak IC column (5% IPA in hexane, 1.5 mL/min), t_r = 5.6 min (minor), t_r = 6.1 min (major).

$[\alpha]_D^{25}$ 53.8 (c = 0.12, $CHCl_3$)



5-73 In an atmosphere-controlled glovebox, $AgBF_4$ (8.9 mg, 0.046 mmol, 0.18 equiv.) and durene internal standard (5.1 mg, 0.038 mmol, 0.15 equiv.) were added to a 2-dram vial charged with a stirbar, and taped with electrical tape such as to be in the dark. Quinox ligand (3.0 mg, 0.015 mmol, 0.06 equiv.) was added as a stock solution in CH_2Cl_2 (0.075 M), followed by $PdCl_2MeCN_2$ (3.3 mg, 0.013 mmol, 0.05 equiv.) which was added as a stock solution in CH_2Cl_2 (0.064 M). The solution was diluted with CH_2Cl_2 (0.60 ml), sealed with a PTFE-lined cap and stirred at room temperature for 5 minutes outside the glove box. 70% aq. TBHP (0.29 ml, 3.0 mmol, 12 equiv.) was added and the mixture was stirred at room temperature another 10 minutes. The mixture was then cooled to 0° C (15 minutes), followed by the addition of the olefin **5-33** (82 mg, 0.25 mmol, 1.0 equiv.) as a solution in CH_2Cl_2 (0.5 ml, then 2 x 0.5 ml rinses). The reaction was kept at 0° C for 5 minutes, then warmed to room temperature. The reaction was monitored by ^1H NMR using durene as internal standard. After 16 h, the reaction was quenched with sat. aq. Na_2SO_3 (5 ml) and extracted with hexanes (3 x 50 ml). The combined organic layers were washed with H_2O and brine, the dried with Na_2SO_4, filtered, and concentrated in vacuo. Isolated) as a colorless oil in 71% yield (81% based on recovered starting material) after purification by silica gel chromatography (49:1 to 4:1 pentane:Et_2O, 98% ee after derivatization to **5-74** (See procedure and characterization for the synthesis of **5-74**).

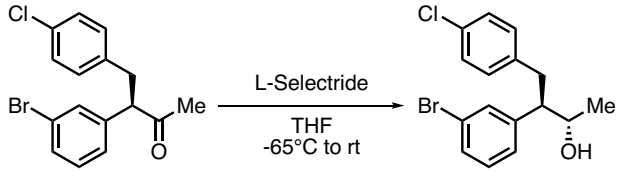
^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.43 (m, 1H), 7.35 (m, 1H), 7.22 – 7.18 (m, 3H), 7.10 (m, 1H), 7.00 – 7.96 (m, 2H), 3.84 (t, *J* = 7.9 Hz, 1H), 3.37 (dd, *J* = 7.5, 13.9 Hz, 1H), 2.86 (dd, *J* = 7.5 , 14.2 Hz, 1H), 2.05 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.5, 140.3, 137.6, 132.2, 131.2, 130.8, 130.5, 130.3, 128.5, 127.0, 123.0, 60.9, 37.7, 29.7;

HRMS (EI): calcd for $C_{16}H_{14}OBrCl$ $[M]^+$: 335.9917. Found 335.9912.

Chiral HPLC: Chiralpak IB column (5% IPA in hexane, 1.5 mL/min), t_r = 2.9 min (major), t_r = 3.2 min (minor).

$[\alpha]_D^{25}$ -286.0 (c = 0.88, $CHCl_3$).



5-74 To half-dram vial containing ketone **5-73** (34 mg, 0.10 mmol, 1.0 equiv.) in THF (0.5 ml) at -65° C was added L-Selectride (0.15 ml, 1.0 M in THF, 0.15 mmol, 1.5 equiv.). The reaction was stirred at -65° C for 1.5 h, after which it was warmed to -40° C and quenched with 3M NaOH (0.15 mL) and 30% aq. H_2O_2 (80 μl). The mixture was warmed to 0° C and stirred for 1 h. The mixture was diluted with EtOAc (20 mL), washed sequentially with sat. aq. $Na_2S_2O_3$ and brine, dried with Na_2SO_4, filtered, and concentrated *in vacuo*. Isolated as a colorless oil in 94% yield, 98% ee after purification by silica gel chromatography (30:1 to 2:1 hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42 – 7.36 (m, 2H), 7.21 – 7.10 (m, 4H), 7.03 – 6.98 (m, 2H), 4.00 (m, 1H), 3.14 (m, 1H), 2.90 (m, 1H), 2.77 (m, 1H), 1.29 (m, 1H), 1.17 (d, *J* = 6.4 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.8, 138.3, 132.0, 131.8, 130.4, 130.0, 129.9, 128.4, 127.9, 122.5, 69.2, 54.8, 37.9, 21.8;

HRMS (ESI): calcd for $C_{16}H_{16}BrClNaO$ $[M+Na]^+$: 360.9965. Found 360.9970.

Chiral HPLC: Chiralpak IB column (5% IPA in hexane, 1.5 mL/min), t_r = 2.9 min (major), t_r = 3.2 min (minor).

$[\alpha]_D^{25}$ -101.3 (c = 1.29, $CHCl_3$).

CHAPTER 6 – Mechanistic Studies for the Catalytic Oxidative Benzylation of Amines Enabled by Reversible Ionic Decarboxylation

6.1 Introduction

The strategic formation of C(sp^3)–N bonds is of paramount importance for the synthesis of functional molecules.[158] The benzylic amine fragment is a particularly significant unit found in a diverse array of pharmaceuticals and clinical candidates, including Imatinib, Abemaciclib, Lacosamide, Clopidogrel, among many others (**Fig. 6-1**).[159]

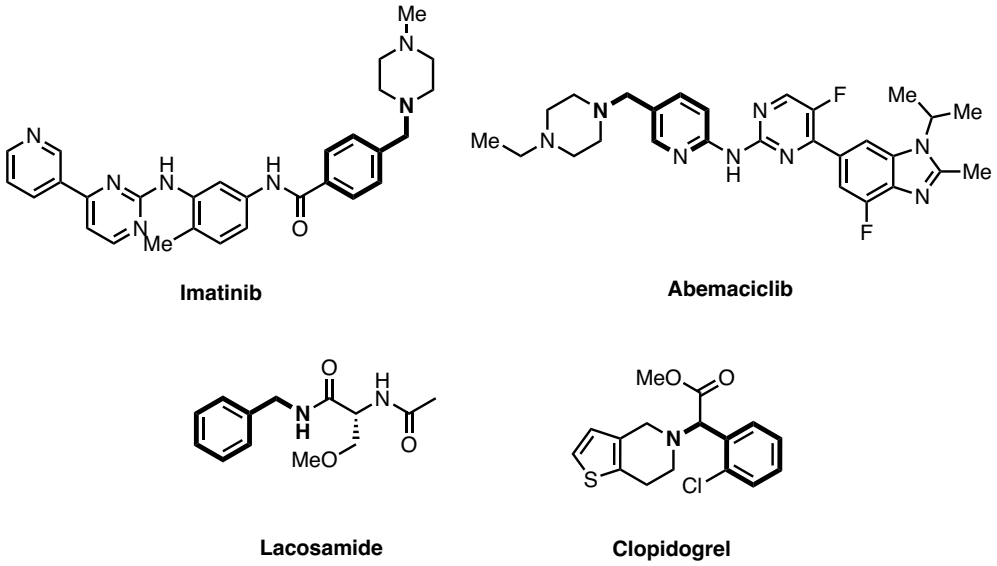


Fig. 6-1 Selected biologically active molecules containing the benzylic amine motif

Standard approaches to the preparation of benzyl amines include nucleophilic substitution between a nitrogen nucleophile and a benzylic (pseudo)halide or by the reductive amination of carbonyl compounds (**Fig. 6-2**). These textbook reactions remains widely used in drug discovery, comprising nearly 10% of all transformations reported in

synthetic medicinal chemistry journals in 2008.[2] Alkyl electrophiles used to generate benzylic amines can be tedious to prepare and exhibit modest stability. Nucleophilic substitution of these species by nitrogen nucleophiles can be complicated by the presence of other protic or electrophilic functional groups, limiting utility in the synthesis of polyfunctionalized targets. Thus, the development mechanistically distinct methods using alternative N-benzylating reagents stand to directly impact the preparation of complex nitrogen-containing molecules. Alternative approaches to alkyl amine synthesis include reductive amination,[160] hydroamination,[161] nitrenoid rearrangements,[162] among others.[163-169]

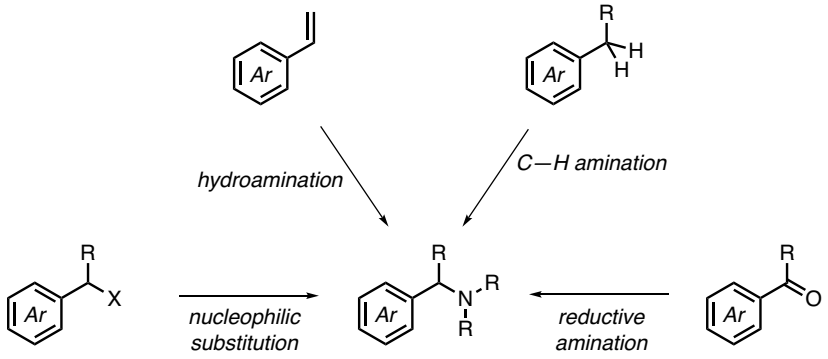


Fig. 6-2 Overview of common strategies to access benzylic amines

Decarboxylative C(sp^3)–N coupling strategies using readily available, bench-stable aliphatic carboxylic acids can increase versatility in the synthesis of complex amines by circumventing the preparation and use of electrophilic N-alkylating reagents. Studies have described decarboxylative N-alkylation processes that proceed via C–carboxyl homolysis to form carbon-centered radicals (**Fig 6-3, path I**).[170-174] These indirect methods require the stoichiometric modification of the carboxylic acid with high

molecular weight activators like N-hydroxyphthalimide (NHPI)[172, 174] or hypervalent iodine reagents[170-171, 173] (**A*** in **Fig 6-3**), hampering process step- and atom-economy. The *irreversible* radical decarboxylation step must be paired with a selective amination step in order to avoid non-productive quenching of the radical intermediate. A mechanistically distinct, but unknown, amination approach involves the direct ionic decarboxylation and trapping of native carboxylic acids, which would bypass stoichiometric carboxylate activation and streamline alkyl amine synthesis (**Fig. 6-3, path II**).

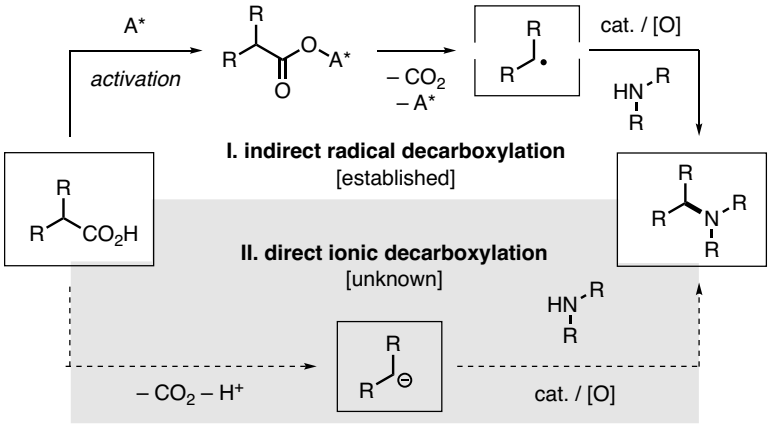


Fig. 6-3 Pathways for decarboxylative amination

In principle, control over the generation of the nucleophilic intermediate in combination with an appropriate catalyst/oxidant system would allow for selective amination in the presence of other reactive functionality. We describe such an approach herein using unmodified electron-poor aryl acetic acids as selective N-benzylating reagents. (**Fig. 6-4**). This work stems from our previous work on decarboxylative arylation or allylations using aryl acetic acids or corresponding carboxylate salts

(Chapters 3, 4, and 5).[119, 175-176] This method leverages *reversible* ionic decarboxylation to enable the controlled generation of benzylic nucleophiles, contrasting the established paradigm in the decarboxylative cross-coupling chemistry literature whereby irreversible decarboxylation is invoked.[10-11] The mechanistic steps of the oxidative amination likely parallels those established for the Cu-catalyzed coupling of amines and aryl boronic acid nucleophiles (the Chan–Evans–Lam reaction) to engender broad functional group compatability.[52, 54-56, 177, 67]

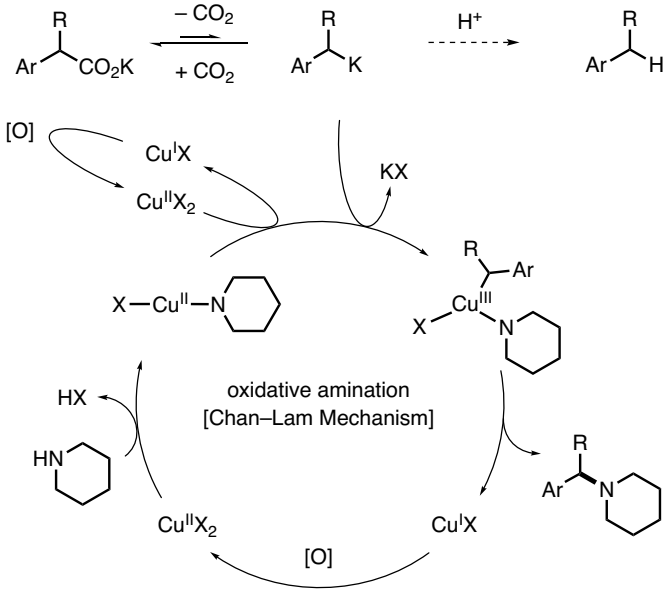
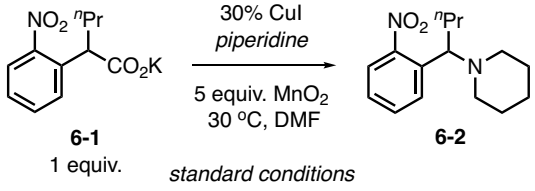


Fig 6-4 Mechanistic hypothesis for the direct oxidative amine benzylation via reversible decarboxylation of aryl acetic acids

Reaction development and scope studies were conducted by postdoctoral fellow Dr. Duanyang Kong, with the assistance of graduate student Odey Bsharat. Optimization studies culminated in conditions that allowed the decarboxylative amination of aryl acetate **6-1** with piperidine to give **6-2** in 92% yield using 30 mol% CuI and MnO_2 as the

oxidant (**Table 6-1**). The free aryl acetic acid could also be used under similar conditions with the addition of carbonate base (94% yield). The cost-effective nature of MnO_2 (~$0.10/g) made it an attractive oxidant, reactions conducted under air gave reasonable product yields (50%), while the use of pure O_2 gave effectively no product. A number of Cu-based catalysts afforded **6-2** in good yield, including CuI, $Cu(OAc)_2$ and $Cu(OTf)_2$. Other transition metal salts including Pd, Ni, Co, or Fe-species were inferior to CuI but still afforded some benzylated amine product. A number of amine partners could be successfully aminated, including examples that contained other protic or electrophilic groups such as anilines, alcohols and aldehydes.

a. *reaction development and key parameters*



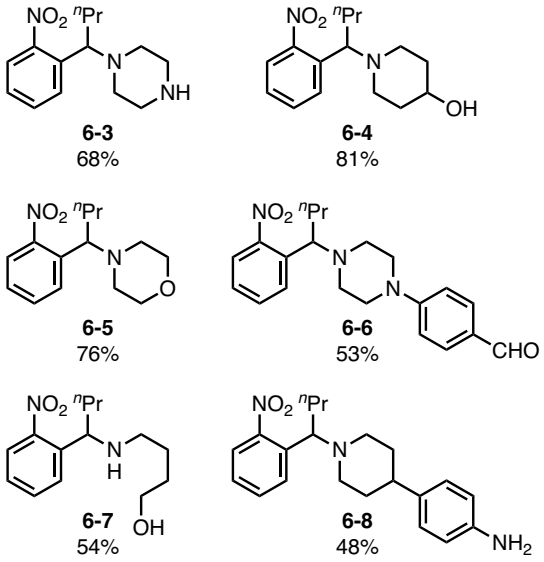
6-1
1 equiv.

standard conditions

6-2

deviation from std. cond.	conv. **6-1** (%)	**6-2** (%)
none	>99	92
free acid + 1 equiv. K_2CO_3	>99	94
air instead of MnO_2	>99	50
O_2 instead of MnO_2	80	<2
catalyst system		
$Cu(OAc)_2$	>99	91
$Cu(OTf)_2$	65	60
$Pd(OAc)_2$	>99	40
NiI_2, CoI_2, or $Fe(OAc)_2$	63–99	<15

b. *selected scope examples under standard conditions*



6-3
68%

6-4
81%

6-5
76%

6-6
53%

6-7
54%

6-8
48%

Table 6-1 Overview of reaction development and selected scope examples

6.2 Mechanistic Studies for the Cu-catalyzed Decarboxylative Amination of Aryl Acetic Acids

The nature of the decarboxylation step was explored by subjecting an olefin-tethered aryl acetate substrate (**6-3**) to the standard conditions (**Fig. 6-5**). Only direct amine coupling product was observed (**6-4**, 64% yield) along with a small amount of proto-decarboxylated material (**6-5,** 27% yield). Radical cyclization products were not observed, likely excluding the intermediacy of a benzylic radical formed from homolytic decarboxylation of a carboxyl radical or oxidation of a benzylic anion.[178]

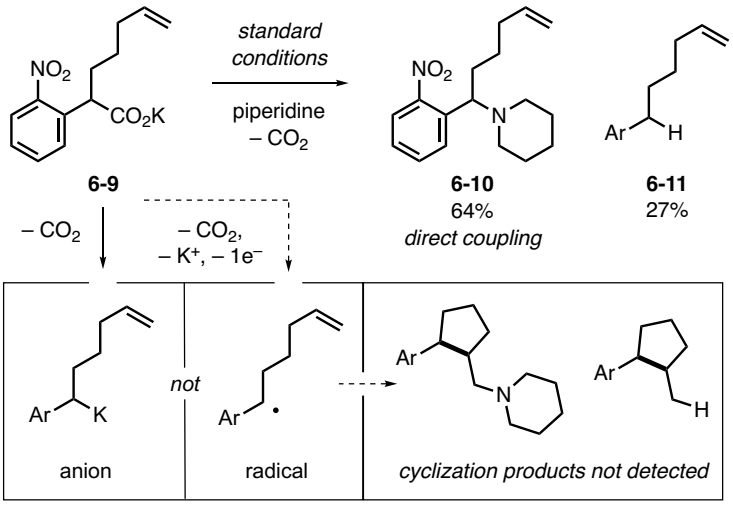


Fig. 6-5 Radical vs carbanion intermediate: Radical clock experiment

To further support the hypothesis for the generation of a benzyl nucleophile via ionic decarboxylation, substrate **6-1** was found to add to aldehyde electrophiles to generate homobenzylic alcohol **6-7** in the absence of catalyst or oxidant (**Fig. 6-6**). Carbonyl compounds are generally considered to be poor intermolecular radical traps.[179] An atmosphere of CO_2 inhibits this addition process, clearly indicated by the kinetic plots

in **Fig. 6-6**, consistent with competitive carboxylation of a putative benzyl anion intermediate. Additional control experiments demonstrated that Cu-salts *decreased* the rate of decarboxylation, suggesting that nucleophile generation and oxidative amination likely occur as separate mechanistic events (**Fig. 6-7**).

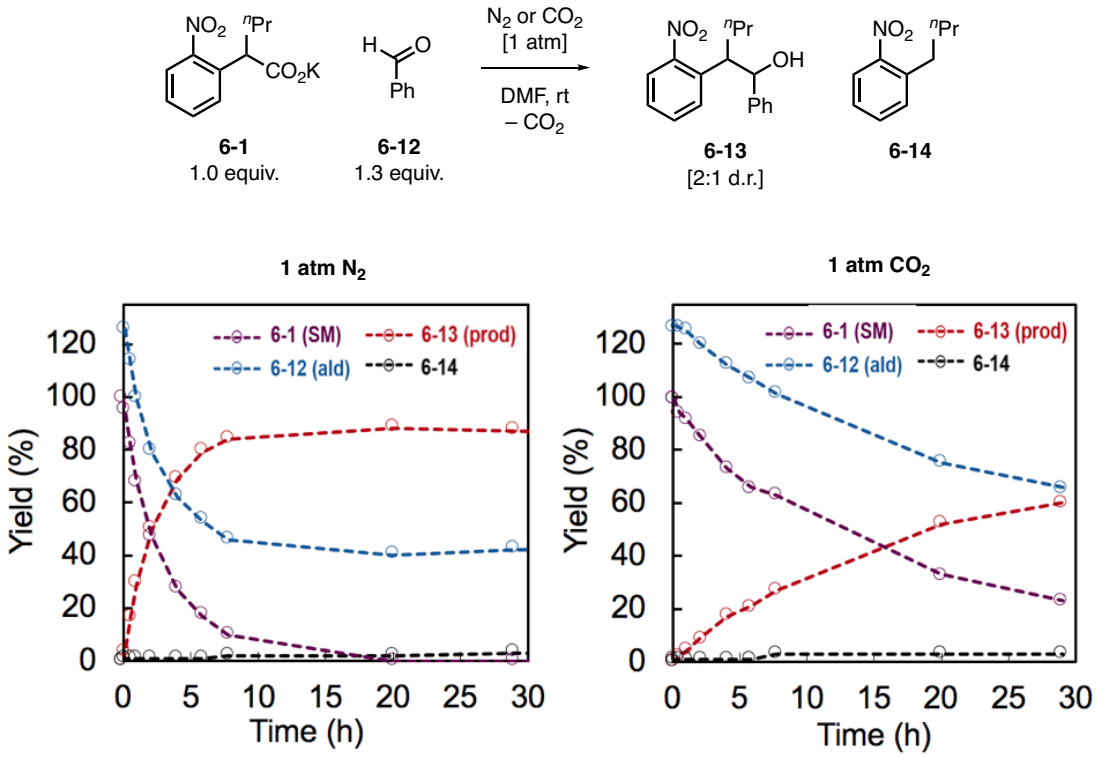


Fig. 6-6 Decarboxylative trapping with external electrophile and inhibition by CO_2

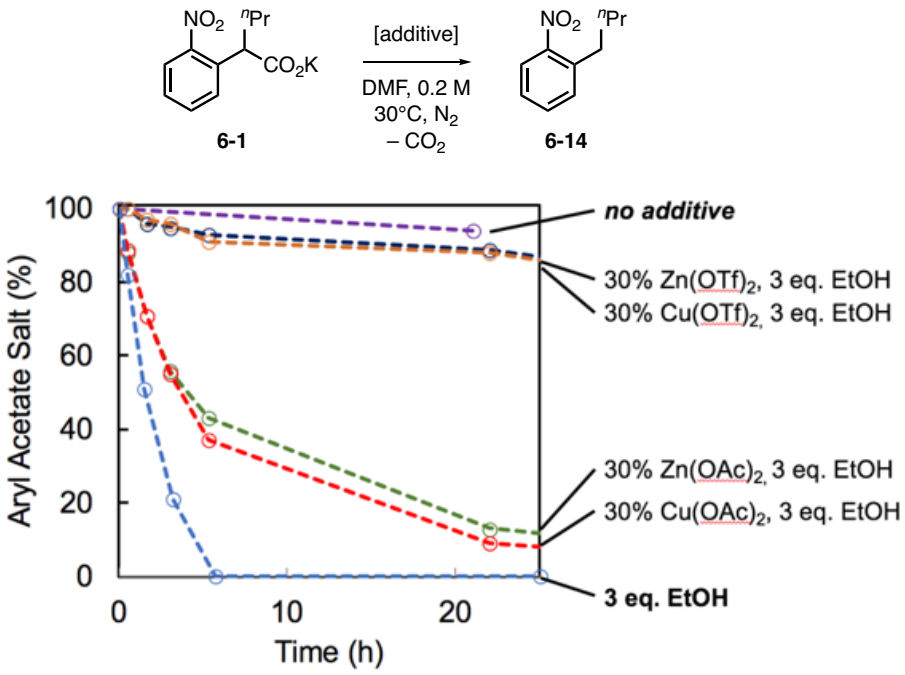


Fig. 6-7 Effect of protic and metal additives on the kinetics of protodecarboxylation

The behavior of aryl acetate **6-1** in the presence of an atmosphere of ^{13}C-labelled CO_2 established that the decarboxylation step is readily reversible at room temperature. Near quantitative $^{13}CO_2/^{12}CO_2$ exchange was observed in less than 5 hours in DMF at room temperature (**Fig. 6-8**).

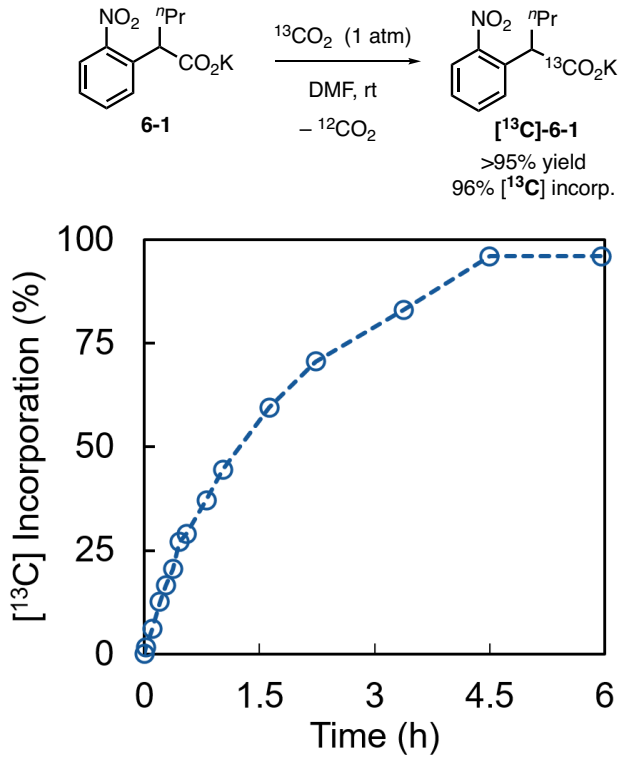
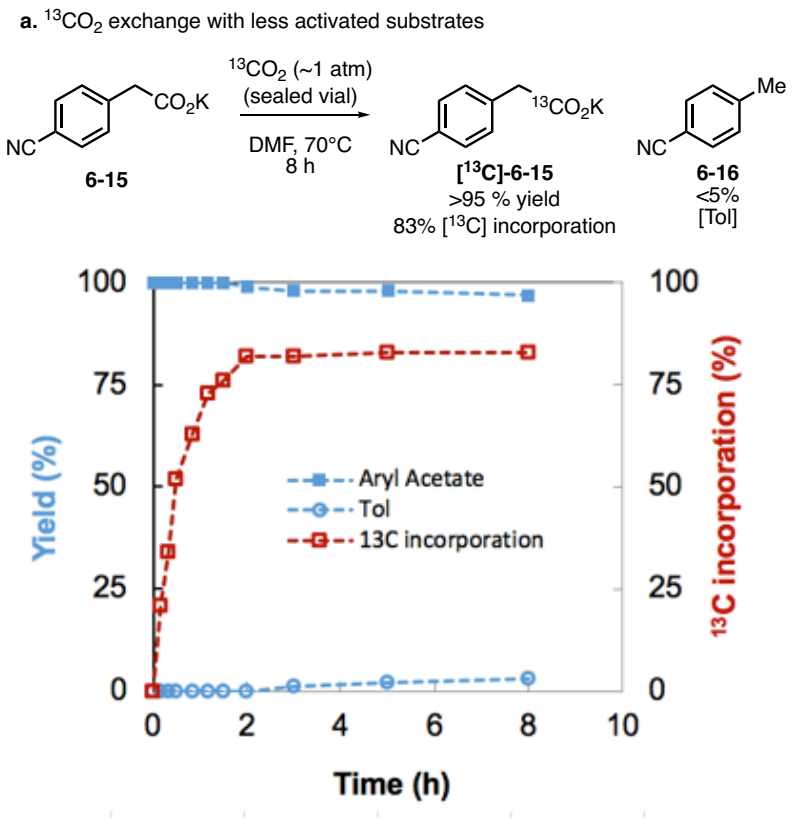


Fig. 6-8 Labelled $^{13}CO_2$ exchange experiment

The $^{13}CO_2$ exchange process also proceeds for less activated 4-cyano aryl acetate **6-15** at higher temperatures 70 °C (**Fig. 6-9a**). Very little protodecarboxylation is observed and the aryl acetate reaches >80% ^{13}C incorporation within two hours. This process proved to be general with a number of other aryl acetate or activated carboxylate substrates undergoing smooth ^{13}C incorporation (**6-18 to 6-23, Fig. 6-9b**). Along with postdoctoral fellows Duanyang Kong and Erica Liu and graduate student Odey Bsharat, the scope and mechanism of this $^{13}CO_2$ exchange process are being investigated.



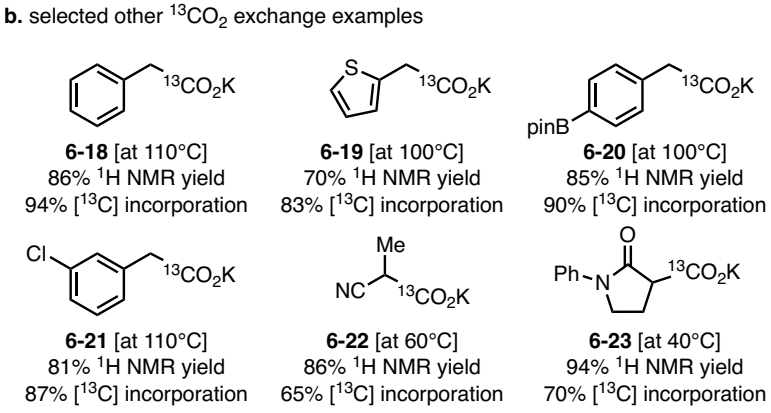


Fig. 6-9 Direct $^{13}CO_2$ exchange reaction with less activated carboxylates

In the context of the decarboxylative amination process these results are consistent with the reversible ionic decarboxylation of the potassium carboxylate substrate to form an anionic intermediate, which is readily quenched in the presence of an electrophile or can undergo Cu-catalyzed amination (**Fig. 6-10**). Selectivity for

interception of the nucleophilic benzyl intermediate by an appropriate Cu-species in the presence of external electrophiles (protic groups, carbonyls as in **Table 6-1**) is striking given the reactive nature of this species. The reversible generation of the reactive intermediate species is likely key to engendering the desired reactivity.

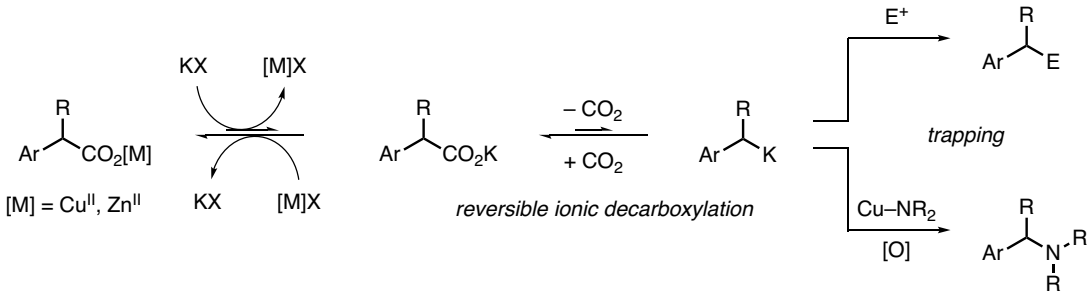


Fig. 6-10 Proposed reversible ionic decarboxylation and trapping pathway

Mechanistic controls further support a pathway in which decarboxylation occurs prior to C–N bond formation via a Cu-promoted Chan–Evans–Lam cycle (**Fig 6-11**). Both ester substrate **6-24** and amino carboxylate **6-26** do not generate product under the standard conditions and are recovered in high yield. These observations rule out a dienolate carbonyl α-amination pathway,[159] which would mirror the proposed mechanism for the Pd-catalyzed decarboxylative arylation of aryl acetic acids.[175] Consistent with a direct oxidative amination mechanism, stoichiometric deprotonation with KH at the benzylic position of the ethyl-substituted nitroarene **6-25** under standard conditions provided the amination product low, but observable yield (~10%). Decomposition of the benzyl nucleophile intermediate is observed under these conditions, highlighting the importance of a controlled release of organometallic species to achieve efficient cross-coupling.

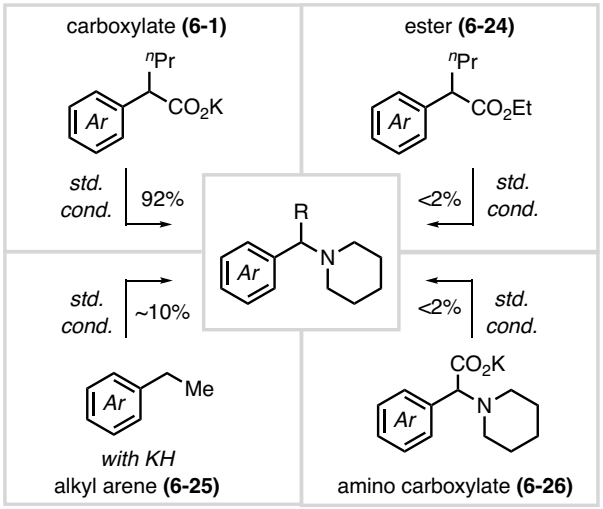


Fig. 6-11 Mechanistic control experiments

Various loadings of $Cu(OAc)_2$ deliver product with less than 0.5 turnover number (TON) in the absence of an external oxidant. (**Fig. 6-12)**. This is consistent with two equivalents of Cu(II) being required to form one equivalent of product, analogous to the Chan-Evans-Lam mechanism outlined by Stahl and co-workers.[67] Under catalytic conditions, MnO_2 or O_2 likely serve to re-oxidize the Cu(I) generated in the bond forming process.[180]

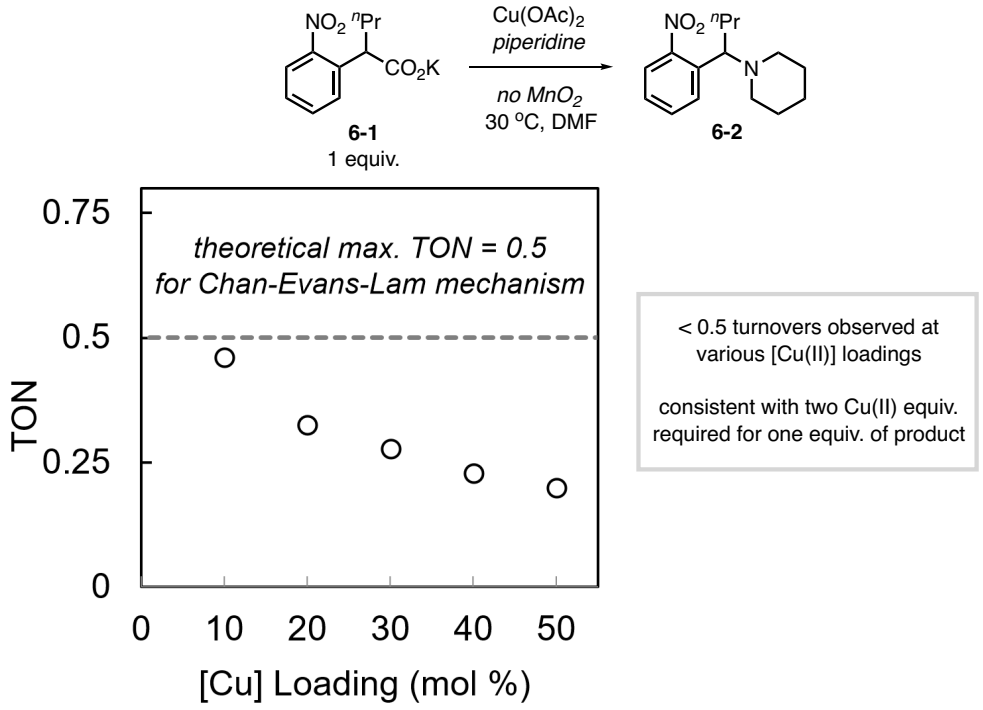


Fig. 6-12 TON at various $Cu(OAc)_2$ loadings in the absence of terminal MnO_2 oxidant

6.3 Summary and Conclusions

In summary, the Cu-catalyzed decarboxylative amination of aryl acetic acids has been developed. Chemoselective N-benzylation can be achieved directly from native carboxylic acids in the presence of protic or electrophilic functionality. A reversible ionic decarboxylation pathway is supported by $^{13}CO_2$ exchange experiments and is a unique mechanistic feature, which likely enables the controlled liberation of anionic benzylic nucleophiles. This stands in contrast to the established paradigm in decarboxylative cross-coupling chemistry, in which *irreversible* decarboxylation is invoked. Efforts are currently underway in our group to apply this concept in the development of novel ionic decarboxylative cross-coupling reactions as well as ^{13}C labelling methodologies.

6.4 Procedures and Characterization

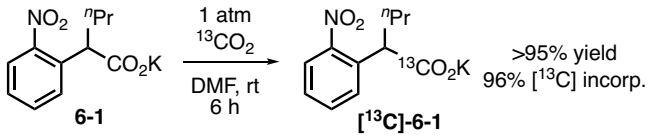
General Considerations:

Unless noted, all reactions were conducted under inert atmosphere employing standard schlenk technique or by the use of a N2-filled glovebox. All glassware was oven-dried prior to use. Flash chromatography was performed using SiliaFlash P60 (40-63μm, 60A silica gel, Silicycle) or by automated flash chromatography (Isolera, HP-SIL or Ultra SNAP silica cartridges, Biotage). Analytical thin-layer chromatography was performed using glass plates pre-coated with silica (SiliaPlate G TLC - Glass-Backed, 250μm, Silicycle). TLC plates were visualized by UV light and/or staining with aqueous basic potassium permanganate. NMR spectra (^{1}H, ^{13}C, ^{19}F) were obtained on an Agilent VNMRS 700 MHz, Varian VNMRS 600 MHz, Varian VNMRS 500 MHz, or Varian 400 MHz spectrometer. The chemical shifts are given as parts per million (ppm) and were referenced to the residual solvent signal (CDCl3: δH = 7.26 ppm, δC = 77.16 ppm). Unless otherwise noted, quantitative ^{1}H NMR yields were determined from crude reaction mixtures using durene as an internal standard. Optical rotation data were obtained using a Perkin Elmer 241 Polarimeter at 589 nm and 25° C, using a 10 cm path-length cell. Unless otherwise noted, all reagents were obtained from commercial vendors and used as supplied.

General Procedure A (from potassium aryl acetate salt): In a glovebox filled with N_2, Cu salts (0.3 equiv.), MnO_2 (5.0 equiv), potassium aryl acetate (1.0 equiv.), $Zn(OAc)_2$ (0 – 1.0 equiv.), amine or NaN_3 (1.5 - 3.0 equiv) and anhydrous DMF (0.2 M)

or DMF/DCE (1:1, 0.2 M) were added sequentially to a 1 dram vial charged with a stir bar. The vial was sealed with a PTFE-lined cap, removed from the glovebox and stirred at the corresponding temperature. ^{1}H NMR analysis of small aliquots (~5 mL) was used to follow reactions to completion, afterwhich the mixture was diluted in ethyl acetate (80 mL) and washed sequentially with saturated $NaHCO_3$ (20 mL x 2) and brine (20 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified by flash column chromatography.

General Procedure B (from aryl acetic acid): In a glovebox filled with N_2, Cu salts (0.3 equiv.), MnO_2 (5.0 equiv), aryl acetic acid (1.0 equiv.), K_2CO_3 (0 - 1 equiv.), amine or NaN_3 (1.5 - 3.0 equiv) and anhydrous DMF (0.2 M) or DMF/DCE (1:1, 0.2 M) were added sequentially to a 1 dram vial charged with a stir bar. The vial was sealed with a PTFE-lined cap, removed from the glovebox and stirred at the corresponding temperature. ^{1}H NMR analysis of small aliquots (~5 mL) was used to follow reactions to completion, afterwhich the mixture was diluted in ethyl acetate (80 mL) and washed sequentially with saturated $NaHCO_3$ (20 mL x 2) and brine (20 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified by flash column chromatography.



General Procedure for the $^{13}CO_2$ exchange experiment of 6-1: In a glovebox filled with N_2, potassium aryl acetate (106 mg, 0.41 mmol, 1.0 equiv.), trimethoxybenzene (0.2 equiv.) and anhydrous DMF (2.03 mL) were added sequentially to a 1-dram vial charged with a stir bar. A homogeneous light red solution forms upon stirring. The vial was sealed with a PTFE-lined cap, removed from the glovebox. The solution is sparged ~30 sec with a balloon of $^{13}CO_2$, then the balloon is installed as to maintain a $^{13}CO_2$-saturated headspace. The light red homogeneous solution immediately becomes light yellow upon exposure to $^{13}CO_2$. Collection of 5 uL crude aliquots are collected over 6 hours, and immediately diluted with 0.5 mL H_2O for LCMS analysis. [^{13}C] incorporation was quantified using the observed relative isotopic mass abundances for the $[M+NH_4]^+$ and $[M\text{-}OH]^+$. After 6 hours, near quantitative [^{13}C] incorportation is observed by LCMS and <5% protodecarboxyation side-product is observed by ^{1}H NMR using trimethoxybenzene as internal standard. The reaction is diluted with EtOAc (40 mL) and quenched with 1M HCl (3 mL). The organic layer is washed with brine, dried with Na_2SO_4, filtered, and concentrated *in vacuo* to obtain a light yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.87 (m, 1H), 7.60 – 7.51 (m, 2H), 7.41 (m, 1H), 4.19 (m, 1H), 2.14 (m, 1H), 1.82 (m, 1H), 1.43 – 1.21 (m, 2H), 0.90 (t, J = 7.6 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.3 ($^{13}CO_2H$), 149.6, 133.2, 133.0, 130.1, 128.1, 124.7, 55.3, 34.7, 20.9, 13.8;

HRMS (ESI): calcd for [^{13}C]$C_{10}H_{17}N_2O_4$ $[M+NH_4]^+$: 242.1216. Found 242.1218.

General Procedure for the $^{13}CO_2$ exchange (using sealed vials): In a 4-dram vial, potassium carboxylate (0.10 mmol, 1.0 equiv.) and trimethoxybenzene (~ 0.2 - 0.5 equiv.) were dissolved in anhydrous DMF (1.0 mL) and the vial is sealed with a PTFE-lined cap (complete dissolution can take a few minutes). Outside the glovebox, the reaction headspace is evacuated (~ 300 mTorr, via a 25g needle). The headspace is carefully refilled with ~ 1 atm $^{13}CO_2$ through the PTFE cap using a 25g needle. The PTFE lined cap is covered with electrical tape and stirred at the indicated temperature. Reaction progress is monitored by ^{1}H NMR using trimethoxybenzene as internal standard. [^{13}C]-incorporation was quantified either by ^{1}H NMR or by HRMS. *Note that this procedure also works outside the glovebox, using standard schlenk techniques.*

CHAPTER 7 – Conclusions and Future Work

7.1 Conclusions

The decarboxylative functionalization of carboxylic acid represents a versatile strategy to form new carbon-carbon or carbon-heteroatom bonds in organic synthesis. This thesis describes the development of new decarboxylative cross-coupling reactions using malonic acid and aryl acetic acid derivatives. An approach in which reactions were concurrently discovered, optimized, mechanistically studied enabled the development of new metal-catalyzed decarboxylative arylation, allylation, and amination reactions.

Under certain conditions, carboxylic acids can act as activating groups that enable the functionalization of acidic α-C–H bonds (i.e. arylation, allylation), followed by subsequent decarboxylation. Reactions that proceed via this mechanistic pathway can display exquisite chemoselectivity profiles as bond-formation does not rely on the interception of a reactive and basic organometallic intermediate. Examples of this type of pathway are described in this thesis in the Cu-catalyzed decarboxylative arylation of malonate half-esters (Chapter 2) and in the Ir- or Pd-catalyzed enantioselective benzylation of allylic electrophiles using aryl acetic acids (Chapter 5). In a related pathway, initial decarboxylation can generate a catalytic base that allows the decarboxylative arylation of aryl acetic acids via dienolate intermediates (Chapter 4).

Reactions can also proceed via initial decarboxylation to form a reactive intermediate, which can then be intercepted by a metal catalyst to form a new bond. Such pathways rely on compatible conditions that enable both substrate decarboxylation and efficient trapping of the reactive intermediate. Examples of this type of reactivity are

described in the decarboxylative arylation or amination of aryl acetic acids via oxidative Cu-catalysis (Chapter 3 and 6). In these reactions the Cu-catalyst is proposed to play a dual role in 1) mediating the bond-forming steps, and 2) controlling the liberation of benzylic nucleophile via the formation of stable Cu-carboxylate species. The reversible decarboxylation of aryl acetic acetate species was also discovered and likely also plays a role under cross-coupling conditions for the controlled release of benzylic nucleophile species (chapter 6).

7.2 Future Work

The work described in this thesis provides a foundation for future exploration of new decarboxylative coupling reactions. Particularly interesting would be to further exploit decarboxylative processes in the context of asymmetric catalysis.

The work described in Chapter 5 on Ir- and Pd-catalyzed enantioselective decarboxylative benzylation of allylic fragments using aryl acetic acids was limited to the use of non-2-substituted aryl acetic acids. Extension of this methodology to access products with two contiguous stereogenic centers, with control over enantioselectivity and diastereoselectivity should be possible (**Fig. 7-1**). Initial decarboxylative benzylation would provide intermediate **7-3** with high enantioselectivity at the allylic position, but inconsequentially poor diasteroselectivity. In a second step, a chiral-base-catalyzed protodecarboxylation would provide **7-4** in high enantioselectivity and diastereoselectivity.

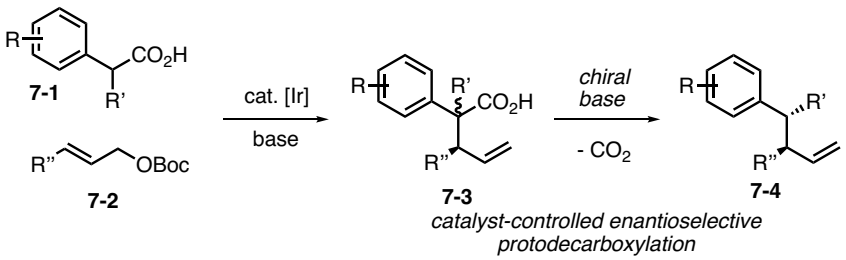


Fig. 7-1 Proposed union of enantioselective allylation and protodecarboxylation processes

The work described in chapters 3 to 6 show that under appropriate conditions (polar aprotic solvents), suitably activated aryl acetic acetate salts will undergo decarboxylation. The proposed benzylic anion intermediate could theroretically get trapped enantioselectively, where selectivity is controlled by a chiral cation catalyst. In this regard, a chiral phase-transfer catalysis strategy could be used (**Fig. 7-2**). Under conditions where the aryl acetate salt is insoluble, anion exchange with a chiral ammonium catalyst could solubilize the aryl acetate substrate. Provided a close-contact ion pair is formed upon decarboxylation, the nucleophilic benzylic anion could be trapped enantioselectively with an appropriate electrophile (ie. alkyl halide, aldehyde). Potential challenges that may arise are the suppression of pathways leading to racemic products. Background uncatalyzed decarboxylation processes or in situ racemization of the product would decrease overall selectivity for the process. Despite these potential pitfalls, appropriate screening of solvent, catalyst and cation effects could provide a breakthrough.

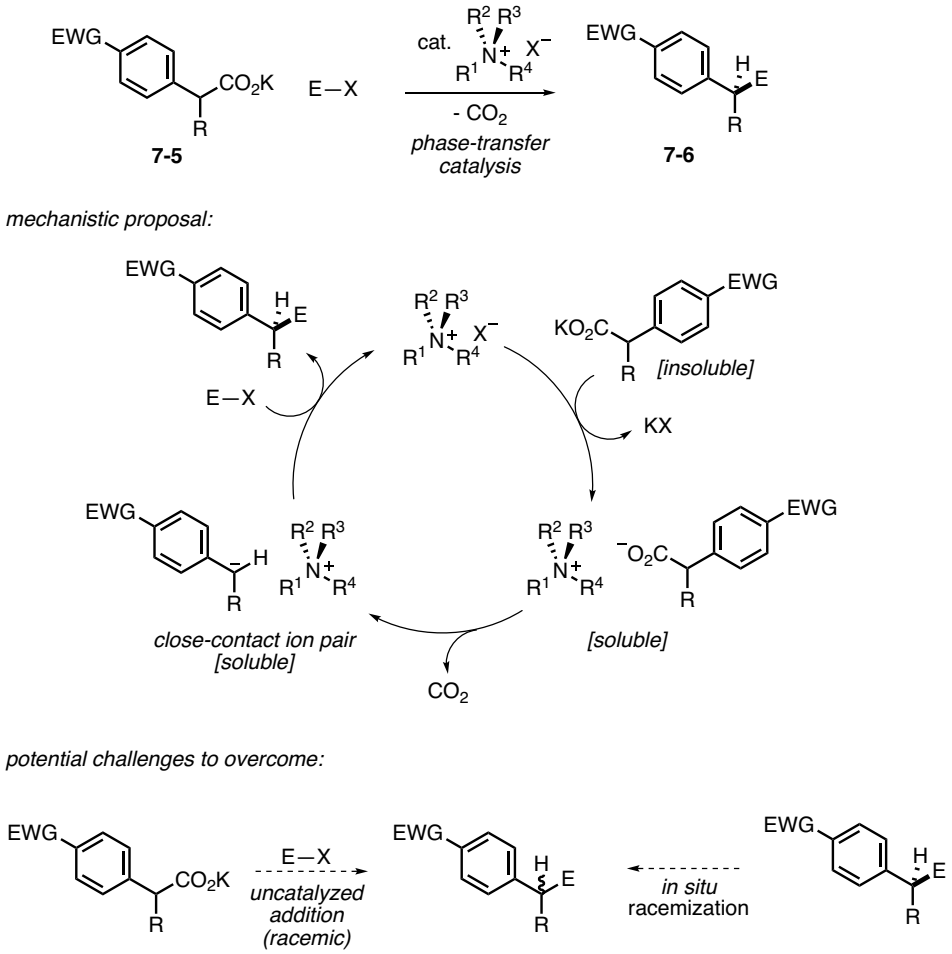


Fig. 7-2 Proposed enantioselective decarboxylative addition processes proceeding via chiral phase transfer catalysis

Chapters 3 and 4 describe the decarboxylative arylation of malonate half-ester and aryl acetate derivatives via oxidative Cu-catalysis. While the reaction worked well for these substrate classes, a general solution across a range of activated carboxylic acid substrates has not yet been achieved. A more in depth study surveying the reactivity of various 1,3-ketoacids, sulfonylacids and cyanoacids would be valuable. Insights into the mechanisms for decarboxylation and C–C bond formation in each of these cases would

likely accelerate the successful generalization of this reaction across new substrate classes.

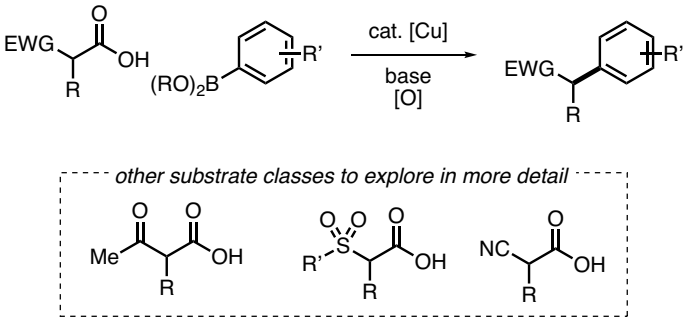


Fig. 7-3 A general reactivity platform for the decarboxylative arylation of carboxylic acids via oxidative Cu-catalysis

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