Development of Ir- and Rh-Catalyzed Deoxygenation and Carbene Cross Coupling Reactions of Allylic Carbonates

by

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Abstract

Transition metal-catalyzed allylic substitution reactions are widely used for the selective formation of new bonds. This class of reaction has been extensively studied with a variety of nucleophiles and under optimized conditions that will furnish product in high yield and with high chemo-, regio- and enantioselectivity. However, there remain opportunities for established catalyst systems to facilitate new transformations through the interception of metal π-allyl complexes with novel partners. This thesis describes two reactions of transition metal π-allyl species.

The selective deoxygenation of alcohols is a persistent challenge in organic synthesis and a host of methods have been developed to address this problem. The use of $[Ir(COD)Cl]_2$ (COD = 1,5 cyclooctadiene) and $[Rh(COD)Cl]_2$ precatalysts in the presence of a diazene transfer agent, *N*-isopropylidene-*N*'-2-nitrobenzenesulfonyl hydrazine (IPNBSH), facilitated the reductive transposition of allylic carbonates with high regioselectivity and good to excellent yield. The reaction proceeded under mild conditions and was highly chemoselective. $[Ir(COD)Cl]_2$ was effective for the deoxygenation of both alkyl and aryl monosubstituted allylic carbonates, including substituents potentially susceptible to decomposition by the transition metal. 1,3-Disubstituted allylic carbonates, including α,β–unsaturated esters, were reduced by $[Rh(COD)Cl]_2$ and $P(OPh)_3$.

Interception of a π-allyl fragment by a diazo-generated carbene intermediate gave the net cross coupling 1,3-dieneoate products in good yield, and in some cases, with high selectivity for the thermodynamically disfavored *E,Z* isomer. Only a single, Ir precatalyst, which has not previously been reported to interact with diazo compounds, gave acceptable yield of product. This observation potentially represents a new mode of activity for a well understood catalyst system.

Preface

All of the research conducted for this thesis was performed in collaboration with Rylan Lundgren. Chapter 1 has been published as Lundgren, R. J.; Thomas, B. N., "Chemo- and regioselective reductive transposition of allylic alcohol derivatives via iridium or rhodium catalysis" Chem. Commun., **2016**, *52*, 958—961. The substrate synthesis, a small number of the scope reactions in chapter 1 and the compilation of the supporting information are my original work.

Initial discovery and preliminary optimization work in chapter 2 were carried out by Rylan Lundgren. The remaining work, including finalizing optimized conditions, substrate preparation, scope investigation and mechanistic studies are my original work.

Chris Godwin assisted with the synthesis of a number of starting materials for the deoxygenation chemistry. Shengkang Yin synthesized some of the starting materials for the diazo cross coupling reactions.

Acknowledgments

I would like to extend my sincere thanks to the past and present members of the Lundgren group, including Anis Fahandej-Sadi, Raphael Dada, Jenner Lakusta, Nathan Paisley, Ping Shen and Chris Godwin. Patrick Moon and Shengkang Yin are owed individual thanks for their willingness to act as a sounding board for new ideas, as well as Morgan MacInnis for his mentorship early in my program. My experiences with the other students and post-doctoral fellows throughout the department have been unfailingly positive and far too numerous to thank everyone individually, so a blanket thank you will have to suffice.

Acknowledgment is made to Dr. Angelina Morales-Izquiedrdo for collection of mass-spectrometry data and Mark Miskolzie for assistance with NMR experiments. Mark's eagerness to share not only his knowledge of the instruments but also systems that keep them running made for many interesting and educational conversations. I would like to thank the members of my committee, Dr. Eric Rivard and Dr. Todd Lowary. All of the chemistry department support staff are acknowledged for making possible everything we do.

I would like to thank Rylan Lundgren for his patient guidance throughout the past three years. His mentorship made this an interesting and enjoyable experience for which I will always be grateful.

Special thanks are extended to my family, who have supported me in all of my endeavors and to my long suffering partner Kim. Thank you for putting up with the long hours and weekends. Your patience and encouragement made this possible.

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Abbreviations

°C	degrees Celsius
Ar	generic aryl moiety
Bn	benzyl
BPin	pinacol boronic ester
Bu	normal-butyl
COD	1,5-cyclooctadiene
Cp*	1,2,3,4,5-pentamethylcyclopentadiene
Cy	cyclohexyl
δ	chemical shift
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
Dioxane	1,4-dioxane
DMA	*N*,*N*-dimethylacetamide
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
equiv.	equivalents
Et	ethyl
GHII	(1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(o-isopropoxyphenylmethylene)ruthenium (Grubbs-Hoveyda 2nd generation)
Hex	hexane (mixture of isomers)
hν	light
HRMS	high resolution mass-spectrometry
IPNBSH	*N*-isopropylidene-*N*′-2-nitrobenzenesulfonyl hydrazine
IMes	1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene

iPr	iso-propyl
L	generic ligand
[M]	generic metal complex
Me	methyl
Mes	mesityl
MeCN	acetonitrile
NBSH	2-nitrobenzenesulfonylhydrazide
NEt_3	triethylamine
NHC	*N*-heterocyclic carbene
NMP	*N*-methylpyrrolidine
NMR	nuclear magnetic resonance
OAc	acetate
OBoc	*tert*-butyl carbonate
p-ABSA	4-acetamidobenzenesulfonyl azide
PCy_3	tricyclohexyl phosphine
Ph	phenyl
ppy	2-phenylpyridyl
R	generic group
rt	room temperature
tBu	*tert*-butyl
Tf	trifluoromethylsulfonyl
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
Tol	tolyl
Ts	4-toluenesulfonyl
X^-	generic anion

Chapter 1 – Chemo- and regioselective reductive transposition of allylic alcohol derivatives via iridium or rhodium catalysis

1.1 Introduction

Deoxygenation reactions of alcohols (Figure 1-1) are important in the synthesis of biologically active molecules[1] as well as the conversion of highly oxygenated biomass into fuels[2] and fine chemical feedstocks.[3, 4]

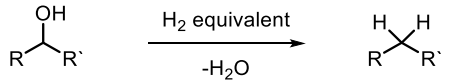
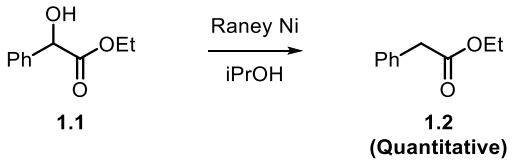


Figure 1-1 Schematic deoxygenation reaction

Chemoselective deoxygenation under mild conditions remains a problem in synthetic organic chemistry with no general solution. Delivery of a hydride equivalent across a C─O sigma bond selectively over other reducible functionalities such as C=O, C=C and C─X bonds is a major barrier to the development of mild deoxygenation strategies because commonly employed metal hydride reductants react preferentially with those groups.[5, 6] The accessible π* orbitals of polarized multiple bonds makes them susceptible to reduction by a hydride transfer mechanism.[7] Reduction of alcohols cannot proceed by the same type of mechanism because there are no available π* orbitals and alcohols are poor leaving groups under hydride reduction conditions, precluding nucleophilic displacement.[8] Conversely, the relatively low strength of C─X bonds facilitates facile nucleophilic displacement by metal hydrides.[9] A survey highlighting the strengths and limits of modern chemoselective alcohol deoxygenation techniques is presented below.

Direct hydrogenolysis of alcohols by transition metal catalysts under forcing conditions has been known since 1933[10] but the high temperatures and pressures of H_2 described in the original report are not broadly accessible due to the need for equipment capable of safely handling

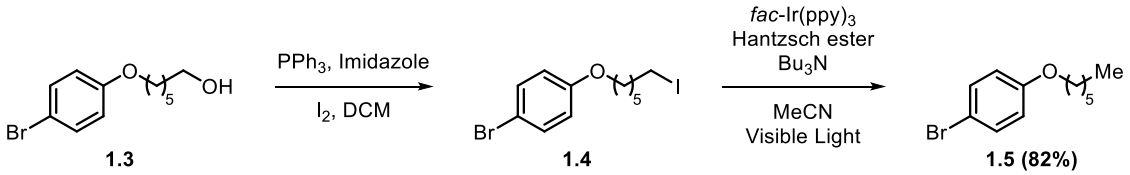
the necessary pressure. Progress towards a mild analogue was made with the development of a transfer hydrogenation reaction, using 2-propanol as a hydrogen source over Raney nickel or Raney cobalt catalysts (Figure 1-2) and is effective for the direct deoxygenation of simple α-aryl alcohols (**1.1**) to benzyl compounds (**1.2**).[11] Under similar conditions Raney nickel will also reduce nitro groups, [12] aldehydes[13] and aromatic rings.[14] The small reported scope and tendency to over-reduce sensitive functional groups limit the synthetic utility of this protocol.



1.1 **1.2 (Quantitative)**

Figure 1-2 Nickel-catalyzed transfer hydrogenation of a simple benzyl alcohol

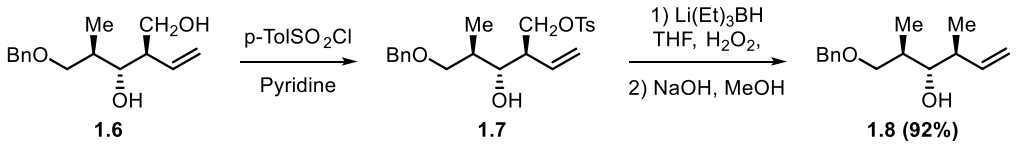
Conversion of alcohols to halides by phosphorous trihalides, hydrogen halides and thionyl halides are well-established transformations.[15] Reductive dehalogenation of the product is a similarly well-established reaction, which typically proceeds by a radical mechanism[16, 17] or hydride displacement,[18, 19, 20] furnishing the alkyl product. Net deoxygenation is achieved by sequential halogenation, followed by dehalohydrogenation (Figure 1-3). Drawbacks of this methodology include the potential sensitivity of the halogenated intermediates to light-induced radical decomposition, nucleophilic displacement of the halide and elimination to the olefin.[21] Additionally, organohalogen waste often requires special disposal procedures.



1.3 **1.4** **1.5 (82%)**

Figure 1-3 Representative radical deiodination reaction

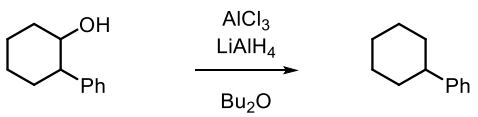
Displacement of sulfonic esters, including mesylate[19] and tosylate[19, 22, 23, 24] by nucleophilic hydrides is an effective strategy for the deoxygenation of 1° and 2° alcohols with good tolerance towards steric hinderance.[24] Derivatization of the alcohol (**1.6**) to the sulfonic ester (**1.7**) proceeds under mild conditions. However, displacement of the functionalized alcohol (**1.7**) to the alkyl product (**1.8**) requires a nucleophilic hydride source such as $LiEt_3BH$, which would readily reduce sensitive functional groups including ketones[25] and esters,[26] limiting the applicability of this method to relatively robust substrates (Figure 1-4).



1.6 **1.7** **1.8 (92%)**

Figure 1-4 Displacement of a tosylated alcohol by $LiEt_3BH$

In the absence of an activator, common hydrides such as $NaBH_4$ are not sufficiently nucleophilic to displace alcohols. However, in the presence of an acid, 2° and 3° alkyl alcohols can be converted to alkanes by $NaBH_4$ with high efficiency.[27] $LiAlH_4$ is also minimally reactive with 2° (**1.9**) and 3° alcohols (1° alcohols are unreactive) unless a Lewis acid is present, in which case the reaction proceeds with moderate to good yield (**1.10**) (Figure 1-5).[28] The same principle has shown promise in the conversion of biologically sourced polyols to synthetically valuable chiral feedstocks.[29] However, the utility of these methodologies is inherently limited by the preferential reaction of hydrides with C-X and C=O bonds over activated C-O bonds.[17, 30]



1.9 **1.10 (50%)**

Figure 1-5 Lewis acid-catalyzed deoxygenation

SmI_2 was first described as a versatile, non-hydridic, single electron reductant in 1980 and has since become a common reagent in deoxygenation chemistry.[31] The original paper by Kagan *et al.* reported the reduction of bromides, iodides and tosylates. More recent work has shown SmI_2 to also be a competent reductant of *p*-toluate[32] (**1.12**) (Figure 1-6), acetate, benzyl carbonate and TMS ether.[33] While SmI_2 is an effective reductant for a broad range of functionalized alcohols, it will also readily reduce aldehydes, esters, ketones and nitro groups.[33]

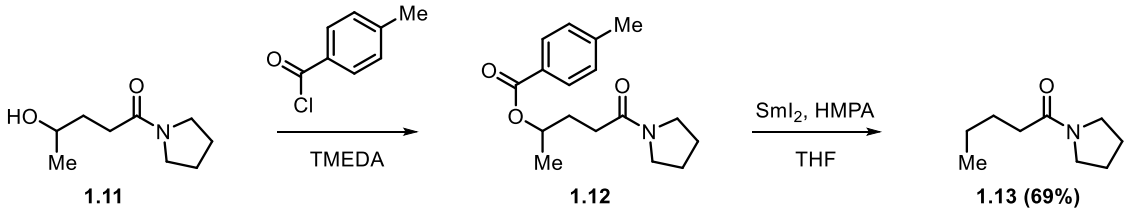


Figure 1-6 SmI_2 reduction of a *p*-tolyl-functionalized alcohol

Electrochemical reduction of functionalized alcohols, including *p*-toluates (**1.15**) to alkanes (**1.16**) is conceptually appealing because the reduction potential applied to the cell can be precisely controlled and it is free from the need for stoichiometric reductants, although stoichiometric additives are often required (Figure 1-7).[34, 35] Functionalities susceptible to reduction by hydride reductants and SmI_2 such as esters and epoxides are tolerated.[36] However, in order to complete the necessary electrical circuit, a conductive solvent is needed, requiring the addition of a salt such as Bu_4NBF_4 to non-conductive solvents.[37] The need for an electrochemical reaction cell and power source, which are not universally available, can be an impediment.

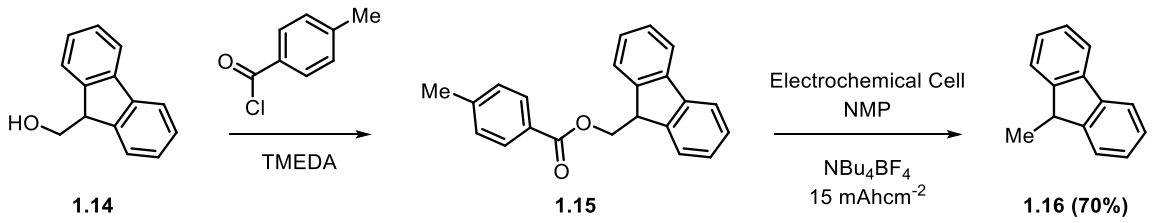


Figure 1-7 Electrochemical deoxygenation of a *p*-toluate functionalized alcohol

As a result of the limitations of the above reactions, classical methods that make use of stoichiometric activators continue to see widespread use. The Barton-McCombie reaction is well established as a mild deoxygenation method with broad functional group tolerance.[38, 39] In order for that reaction to proceed, the alcohol (**1.17**) must be converted to a thionoester (**1.18**) which then undergoes a free-radical chain reaction with tributyltin hydride, reducing the thionoester to an alkane (**1.19**) (Figure 1-8). A major drawback to this chemistry is the need for stoichiometric radical initiator, as well as tributyltin hydride, which is toxic, light sensitive and difficult to remove from the reaction mixture.[40]

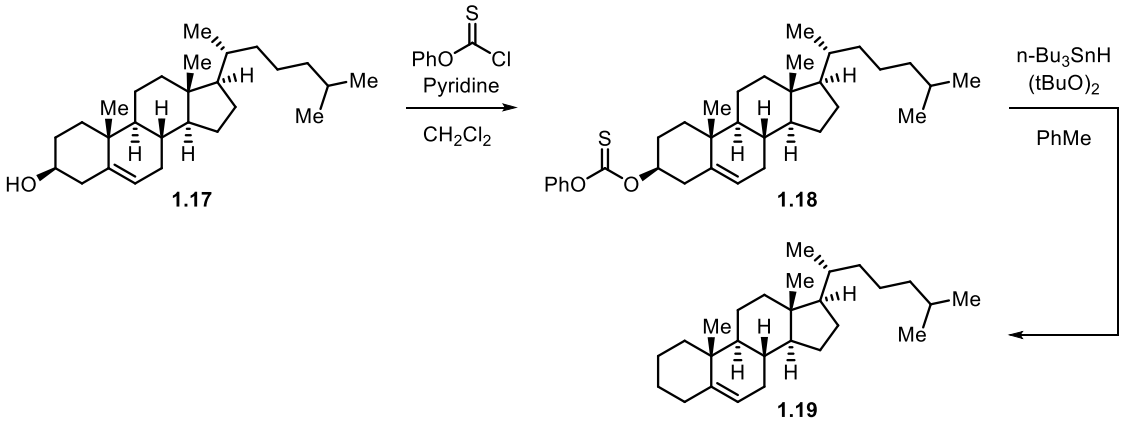


Figure 1-8 Barton-McCombie deoxygenation of a secondary alcohol

A common alternative to Barton-McCombie chemistry is the reductive Mitsunobu reaction, which employs triphenylphosphine-activated DEAD (diethyl azodicarboxylate), to facilitate the displacement of alcohols (**1.20**) by diazene precursors NBSH or IPNBSH (Figure 1-9).[41, 42, 43, 44] Subsequent elimination of 2-nitrobenzenesulfinic acid under thermal or acidic aqueous conditions gives an alkyl diazene (**1.22**), which then liberates dinitrogen *via* a free radical pathway, giving the deoxygenated product (**1.23**).[41] In addition to its toxicity, DEAD is sensitive to light and shock. It also has a tendency to explode when heated neat, making it expensive to transport

and hazardous to handle. Because of this, methods which catalytically activate the alcohol without the need for DEAD are desirable.

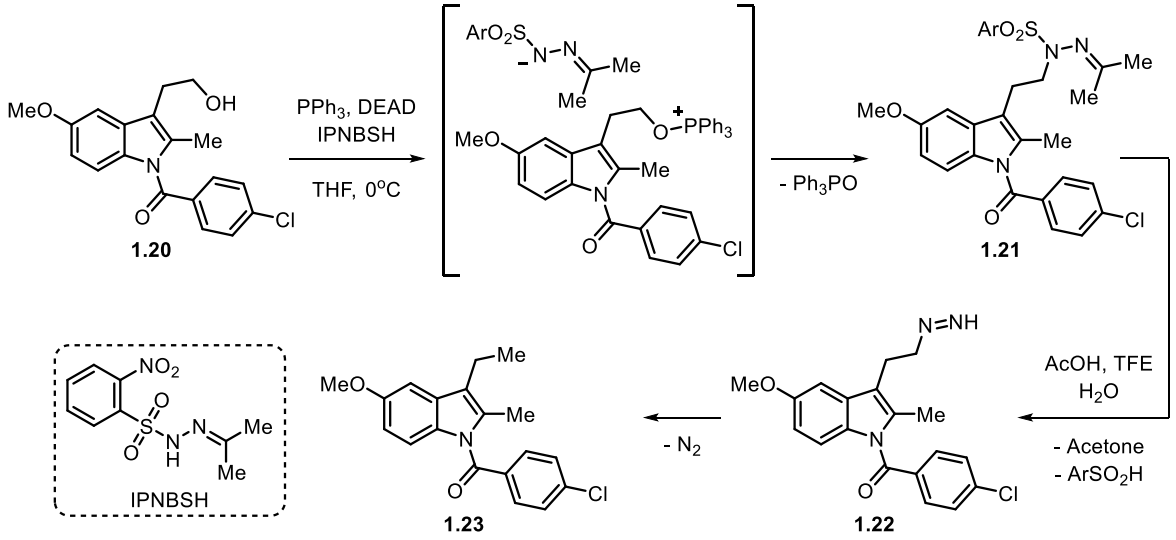


Figure 1-9 Diazene-mediated deoxygenation of a primary alcohol

Deoxygenation of allylic (**1.24**)[41, 44] and propargylic[41, 43] substrates by Mitsunobu-type chemistry have been the subject of additional study as those substrates are not reduced by the same radical mechanism as their alkyl counterparts. Instead of a radical mechanism, the resulting *N*-alkyl *N*-sulfonyl hydrazone (**1.25**) furnishes an allylic diazene, which undergoes a [1,5]-sigmatropic rearrangement, transposing the olefin to the neighboring position (**1.26**) (Figure 1-10).[45]

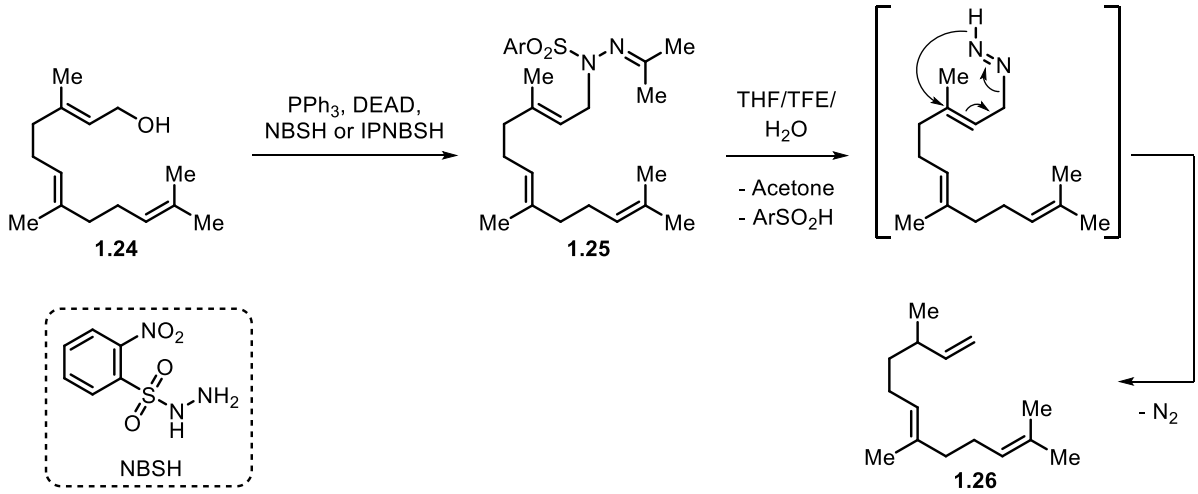


Figure 1-10 Stoichiometric Mitsonobu reduction of allylic alcohol with olefin transposition upon sigmatropic rearrangement

In addition to enabling olefin transposition, allylic substrates also present an opportunity to address some of the shortcomings of traditional selective deoxygenation reactions through the exploitation of existing metal-allyl chemistry. π-Allyl complexes of transition metals are well established electrophiles in allylic substitution reactions; metals including Mo,[46] Ru,[47] Ir,[48] Rh[49] and Pd[50] have been demonstrated to form these complexes. Displacement of an alcohol or easily prepared alcohol derivative (**1.27**/**1.28**) by a transition metal facilitates amination of the resulting π-allyl complex by a diazene precursor and eliminates the need for stoichiometric activators. Product regiochemistry is also influenced by the identity of the metal chosen, potentially enabling the selective product formation (**1.29**/**1.30**) from a single substrate isomer (Figure 1-11).

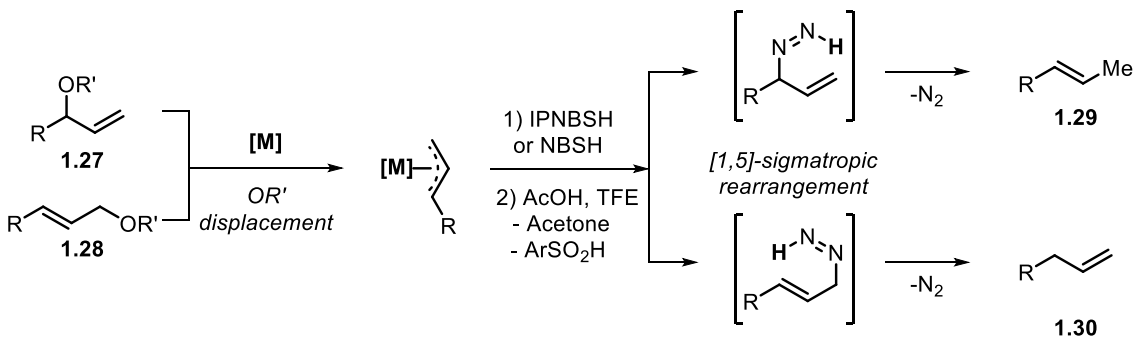


Figure 1-11 Metal-π-allyl complex formation and [1-5]-sigmatropic rearrangement of resulting diazene

The first transition metal catalyzed, diazene-mediated reduction of allylic alcohols was developed by Movassaghi and co-workers in 2008.[51] This Pd-catalyzed, IPNBSH-mediated method alleviates the need for DEAD or tin hydrides.[51] Conversion of the alcohol to a carbonate (**1.31**) renders the resulting species reactive towards Pd and makes possible the generation of a π-allyl complex, which can then be aminated by IPNBSH under basic conditions (**1.32**). Following elimination of the aminated product to a monoalkyl diazene, reductive sigmatropic rearrangement can take place, extruding dinitrogen and transposing the C=C bond (**1.33**) (Figure 1-12).

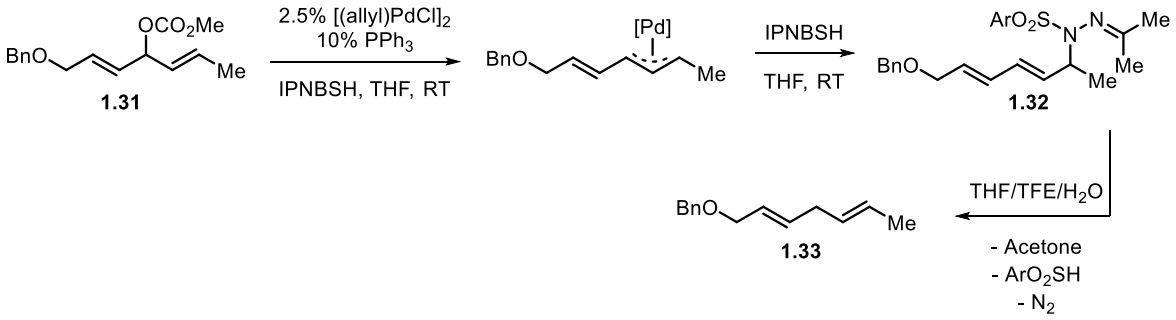


Figure 1-12 Palladium-catalyzed reduction of allylic carbonate by IPNBSH

Under Pd-catalyzed conditions, the expected regiochemical outcome is determined by substrate steric control over the amination of the Pd-allyl species.[52] In the case of mono-substituted allylic carbonates, both linear (**1.34**) and branched (**1.35**) substrates give the terminal olefin product (**1.36**) following sigmatropic rearrangement. In the case of internal allylic substrates (**1.37**), both formal S_N2 (**1.38**) and S_N2' (**1.39**) displacement is observed depending on the identities of R^1 and R^2 (Figure 1-13). Pd-catalysis is unable to furnish the internal product (**1.42**) from the linear (**1.40**) or branched methyl carbonate (**1.41**).

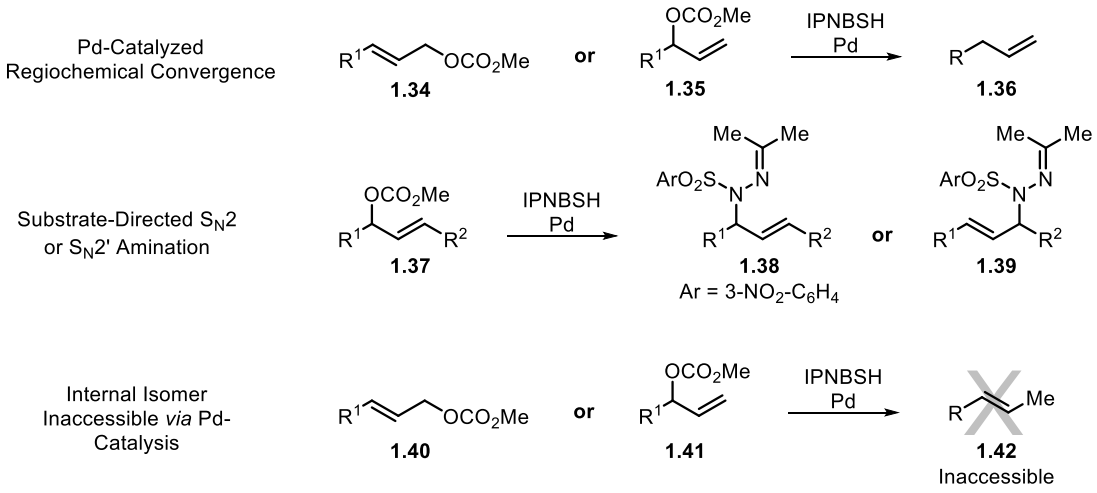


Figure 1-13 Regiochemical outcomes of the palladium-catalyzed reduction of allylic carbonates with IPNBSH

Pd-catalyzed reductions of allylic carbonates by formate furnish comparable products to diazene-mediated reductions, but do so at elevated temperature (40–90 °C).[53, 54, 55, 56] The product distribution of most formate reduction reactions is largely subject to the same substrate control as their NBSH and IPNBSH-mediated counterparts; however, a high degree of regioselectivity can be exerted over the product isomer in a specific class of 5 to 8 membered *N*-heterocycles, although the demonstrated substrate scope is limited.[57]

In a related reaction, a tertiary alkylphosphine catalyst efficiently hydrodebrominates allylic bromides (**1.43**), transposing the olefin with a high degree of regiocontrol (Figure 1-14).[58] However, in order for the reaction to proceed, excess $LiAlH(OtBu)_3$ is required, which inherently limits the functional group tolerance of the reaction. Allylic bromides are typically accessed from the allylic alcohol in a similar manner to allylic carbonates[59, 60] but organobromides tend to be less stable than allylic carbonates due to their propensity for light-induced decomposition.[21] High yield and regioselectivity are observed in most reported cases, though the reported scope is small and unlike carbonate substrates, the resulting halogenated waste requires special handling and treatment.[58]

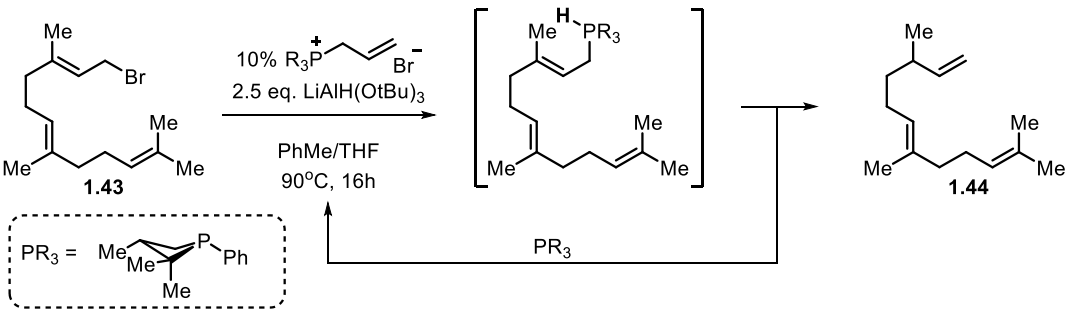


Figure 1-14 Phosphine-catalyzed reduction of allylic bromides with highly controlled olefin transposition

The method described below represents the first catalytic alternative to existing stoichiometric Mitsunobu chemistry for the selective, reductive deoxygenation of functionalized allylic alcohols (Figure 1-15).[61] The reaction proceeds by the formation of a metal π-allyl complex from the ionization of a methyl carbonate (**1.45**). Amination of the metal complex by IPNBSH gives an *N*-alkyl *N*-sulfonyl hydrazine, (**1.46**) which eliminates 3-nitrophenylsulfinic acid and acetone under acidic conditions, rendering an alkyl diazene. This intermediate then spontaneously rearranges, liberating N_2 and the product (**1.47**).

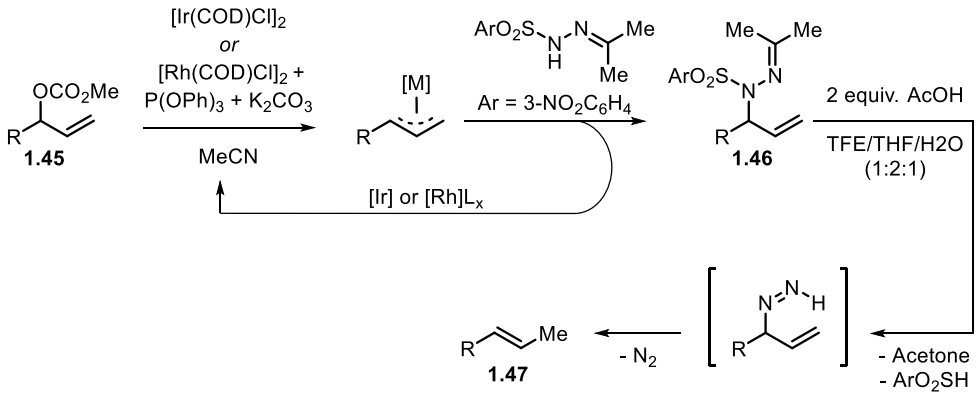


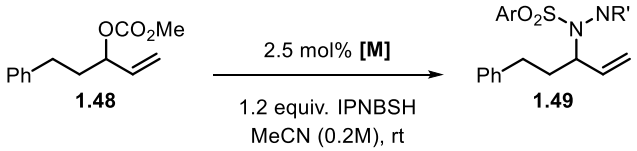
Figure 1-15 Proposed pathway for the Ir/Rh catalyzed reductive transposition of allylic methyl carbonates

1.2 Optimization of Precatalyst, Solvent and Leaving Group

A series of optimization reactions revealed two effective catalyst systems for the reductive deoxygenation of allylic carbonates. $[Ir(COD)Cl]_2$, without additives, was found to be an effective precatalyst for the deoxygenation of monosubstituted allylic carbonates. In the case of disubstituted substrates, $[Ir(COD)Cl]_2$ proved to be unsuitable, but the reaction proceeded smoothly in the presence of $[Rh(COD)Cl]_2$ with added phosphite ligand and carbonate base. Solvent, precatalyst and carbonate identity all had significant influence over the effectiveness of the reaction.

A series of reactions screening a monosubstituted alkyl allylic carbonate (**1.48**) against several precatalysts revealed $[Ir(COD)Cl]_2$ to give the highest yield of the desired branched aminated product (**1.49**). Rh exhibited low reactivity and Ru favored the undesired linear aminated product (Table 1-1).

Table 1-1 Effect of precatalyst on the amination of a simple alkyl-substituted allylic carbonate with IPNBSH

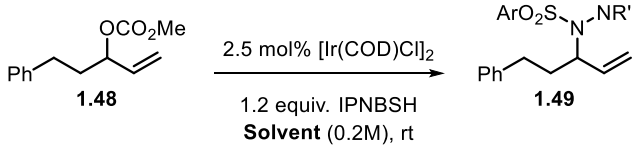


Entry	Deviation from standard conditions	Conv.	Yield (%)
1	**None**	**>98**	**91**
2	$[Rh(COD)Cl]_2$	8	<2
3	$[Rh(CO)_2Cl]_2$	10	<2
4	$RhCl(PPh)_3$	<2	<2
5	$RuCp^*(MeCN)_3PF_6$	>98	94 (14:80 b/l)

0.05-0.10 mmol scale, 24h reaction time, conversions and yields determined by ^1H NMR using Bn_2O as internal standard. b/l = branched:linear ratio.

Solvent effects are pronounced in this chemistry, with all tested solvents resulting in high conversion of the allylic methyl carbonate (**1.48**), but only acetonitrile gives the desired product (**1.49**) in both high yield and selectivity (Table 1-2).

Table 1-2 Effect of solvent on the amination of a simple alkyl-substituted allylic carbonate with IPNBSH



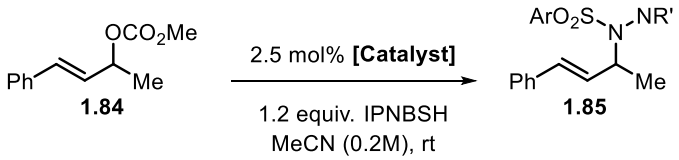
Entry	Solvent	Conv.	Yield (%)	(b/l)
1	**MeCN**	**94**	**91**	>20:1
2	THF	>98	25	>10:1
3	CH_2Cl_2	>98	40	>10:1
4	EtOH	>98	<5	nd

0.05-0.10 mmol scale, 24h reaction time, conversions and yields determined by ^1H NMR using Bn_2O as internal standard. b/l = branched:linear ratio.

$[Ir(COD)Cl]_2$ was an ineffective pre-catalyst for the amination of a simple disubstituted allylic carbonate (**1.84**) with IPNBSH, resulting in low yield and low conversion of the substrate. Screening against a variety of catalysts revealed $[Rh(COD)Cl]_2$, in the presence of 10 mol%

$P(OPh)_3$ and excess carbonate base, to give the highest yield of aminated product (**1.85**) (Table 1-3).[62, 63] In the absence of ligand or base, no tested pre-catalyst gave acceptable product yield.

Table 1-3 Effect of precatalyst on the amination of a simple disubstituted allylic carbonate with IPNBSH

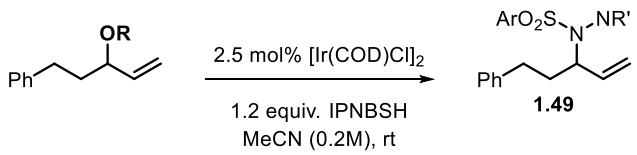


Entry	Catalyst	Conv.	Yield (%)	(b/l)
1	$[Ir(COD)Cl]_2$	18	17	>95:5
2	$[Ir(COD)Cl]_2$ + 10% $P(OPh)_3$	16	11	>95:5
3	$[Rh(COD)Cl]_2$	<2	<2	nd
4	$[Rh(CO)_2Cl]_2$	<2	<2	nd
5	$Rh(COD)_2BF_4$	<2	<2	nd
6	**$[Rh(COD)Cl]_2$ +10% $P(OPh)_3$**	**75**	**68**	**>95:5**

0.05-0.10 mmol scale, 24h reaction time, conversions and yields determined by ^1H NMR using Bn_2O as internal standard.

Leaving group identity was shown to play an important role in the amination of allylic substrates, with bulkier OR groups leading to reduced substrate conversion and yield of aminated product (**1.50**). All tested carbonates exhibit similarly high regioselectivity, independent of conversion. A phosphonate ester was also tested and although conversion and yield were high, selectivity was relatively poor (Table 1-4, Entry 4). Methyl carbonate was identified as the most effective leaving group for this reaction (Table 1-4, Entry 1).

Table 1-4 Effect of leaving group on amination of a monosubstituted allylic carbonate by IPNBSH

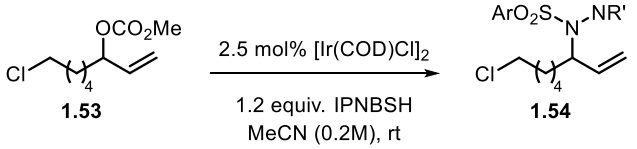


Entry	Leaving Group (OR)	Conv.	Yield (%)	(b/l)
1	**OCO_2Me**	**94**	**91**	**>20:1**
2	OCO_2Et	87	70	>20:1
3	OCO_2tBu	29	22	>20:1
4	$OP(O)(OEt)_2$	>98	80	7:1

0.05-0.10 mmol scale, 24h reaction time, conversions and yields determined by ^1H NMR using Bn_2O as internal standard.

Further optimization studies were performed on a primary alkyl chloride-substituted allylic carbonate (**1.53**), which exhibited behavior similar to that described above (Table 1-5). A primary allylic chloride could be susceptible to radical reactions under Barton-McCombie conditions, displacement by PPh_3 under Mitsunobu conditions, or elimination of the chloride to generate the terminal olefin. The observed high yield of aminated product (**1.54**) under the optimized conditions indicates that little undesirable reactivity is taking place, although under alternative conditions other side products, such as chloride elimination, are formed.

Table 1-5 Effect of various parameters on the amination of a primary alkyl chloride-substituted allylic carbonate with IPNBSH



Entry	Deviation from standard conditions	Conv.	Yield (%)
1	**None**	**>98**	**91**
2	$[Rh(COD)Cl]_2$	8	<2
3[a]	$RuCp^*(MeCN)_3PF_6$	94	10
4	THF in place of MeCN	74	15
5	CH_2Cl_2 in place of MeCN	61	12
6	NBSH in place of IPNBSH	23	10
7	CO_2tBu in place of CO_2Me	61	44

0.05-0.10 mmol scale, 24h reaction time, conversions and yields determined by ^1H NMR using Bn_2O as internal standard. [a] 5% [Ru].

Also of note and consistent with existing literature reports, the identity of the diazene precursor had a significant effect, with the free hydrazide (NBSH) being far less effective than the protected IPNBSH (Figure 1-5).[41] The use of ammonium formate as a reductant in place of NBSH or IPNBSH, which has been demonstrated to be effective under conditions catalyzed by Pd,[55] resulted in non-selective consumption of the substrate and was not pursued further.

Conditions for the decomposition of the aminated products (**1.54**) to the free alkyl diazene (**1.55**), developed by Movassaghi,[51] proved to be effective for the products of this chemistry. A model reaction, employing the optimized Ir-catalyzed system gave substrate (**1.53**) conversion of over 98% and a yield of the desired *N*-alkyl *N*-sulfonyl hydrazone (**1.54**) of 91%. Following diazene deprotection, sigmatropic rearrangement proceeded smoothly, yielding the desired olefin (**1.63**) in 71% isolated yield and 92:8 *E/Z* ratio (Figure 1-16).

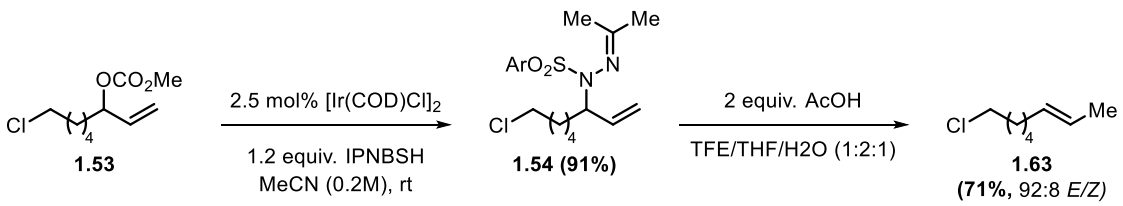


Figure 1-16 Amination and deoxygenation yields of a simple primary alkyl chloride-substituted allylic methyl carbonate with IPNBSH

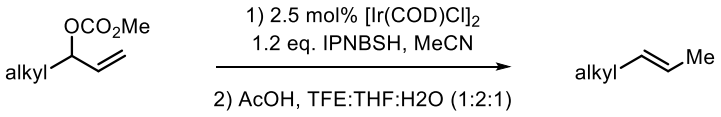
1.3 Reaction Scope

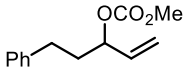
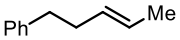
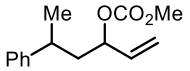
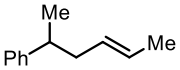
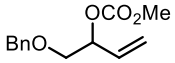
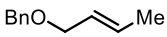
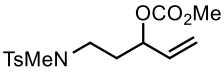
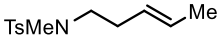
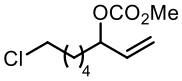
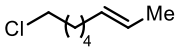
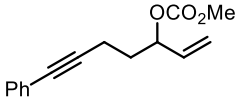
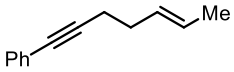
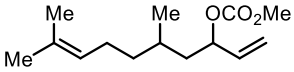
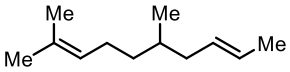
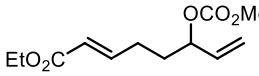
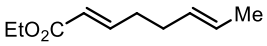
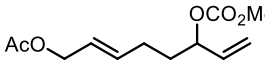
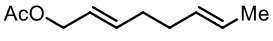
1.3.1 Scope of Monosubstituted Alkyl Allylic Carbonates

The optimized reaction tolerated a wide variety of sensitive functional groups without evidence of over-reduction. A variety of monosubstituted alkyl methyl carbonates were successfully deoxygenated, with good tolerance for a variety of potentially sensitive functional groups (Table 1-6). Notably, an allylic acetate (**1.58**), which would be subject to attack by Pd[50, 53]

under the Movassaghi conditions and by Ir at higher temperature,[64] was also tolerated, underscoring the high chemoselectivity of this method.

Table 1-6 Ir-catalyzed deoxygenation of alkyl-substituted allylic methyl carbonates with the IPNBSH diazene precursor



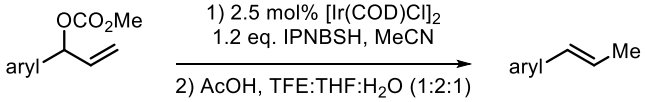
Entry	Substrate		Product		Yield (%)
1		**1.48**		**1.59**	84
2		**1.50**		**1.60**	68[a]
3[b]		**1.51**		**1.61**	71
4		**1.52**		**1.62**	88
5		**1.53**		**1.63**	71
6		**1.55**		**1.64**	74
7		**1.56**		**1.65**	57
8		**1.57**		**1.66**	75
9[c]		**1.58**		**1.67**	65[d]

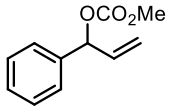
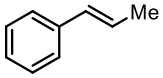
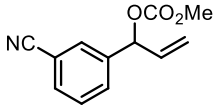
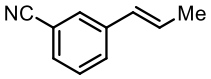
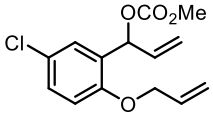
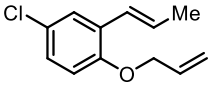
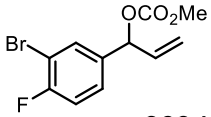
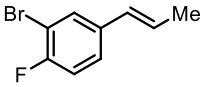
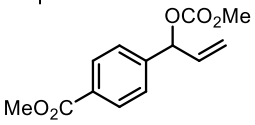
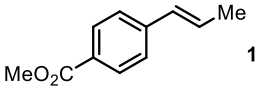
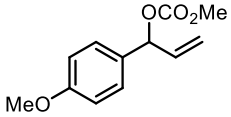
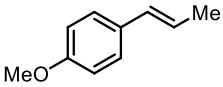
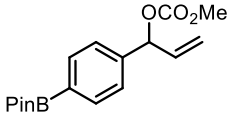
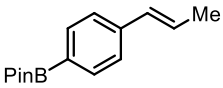
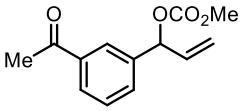
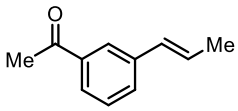
Isolated yields. Regioisomers ≥95:5 and E/Z ratios ≥92:8 in all cases. [a] 91:9 regiosiomer ratio. [b] 5 mol% $[Ir(COD)Cl]_2$. [c] Allylic Acetate E/Z 85:15 in starting material. [d] Allylic Acetate E/Z 85:15.

1.3.2 Scope of Monosubstituted Aryl Allylic Carbonates

Without altering the conditions, aryl-substituted allylic carbonates could readily be converted to substituted β-methyl styrenes (Table 1-7). β-Methyl styrenes are not always trivial to access and are frequently synthesized *via* Wittig chemistry or Heck coupling.[65, 66, 67] Both electron-rich and poor substrates were deoxygenated with similar efficiency. The aryl substrate scope included groups which could potentially be reduced under hydride or radical conditions; carbonyl, halide, allyl and cyano groups were tolerated, emphasizing the outstanding chemoselectivity of the reaction (**1.69**-**1.75**).[5, 6]

Table 1-7 Ir-catalyzed deoxygenation of aryl-substituted allylic methyl carbonates with IPNBSH diazene precursor



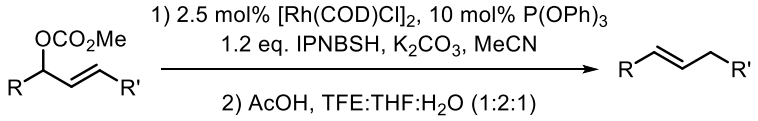
Entry	Substrate		Product		Yield (%)
1		**1.68**		**1.76**	69
2		**1.69**		**1.77**	63
3		**1.70**		**1.78**	71
4		**1.71**		**1.79**	94
5		**1.72**		**1.80**	56[a]
6		**1.73**		**1.81**	45
7		**1.74**		**1.82**	55
8		**1.75**		**1.83**	77

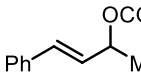
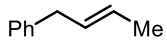
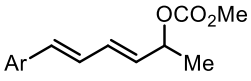
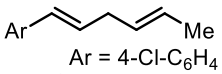
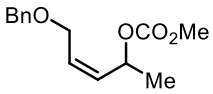
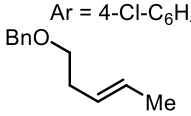
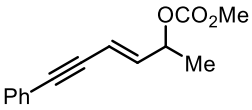
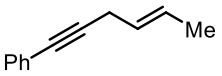
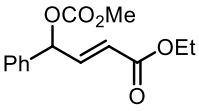
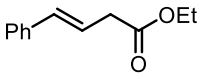
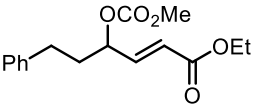
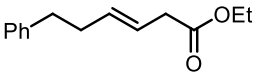
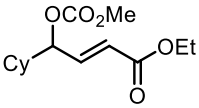
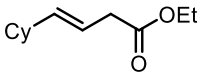
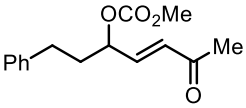
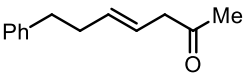
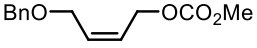
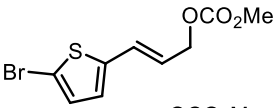
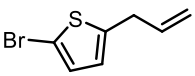
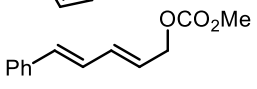
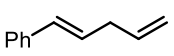
Isolated yields, 1.0-0.6 mmol scale. Regioisomers ≥97:3 and E/Z ratios ≥95:5 in all cases.
[a] 83:17 regiosiomer ratio.

1.3.3 Scope of 1,3-Disubstituted Allylic Carbonates

The optimized Rh-catalyzed deoxygenation conditions for 1,3-disubstituted allylic carbonates tolerated aryl, alkenyl, alkynyl and ethereal substituents (**1.94**, **1.86**, **1.88** and **1.87** respectively), providing a simple, mild method by which to access sensitive skipped dienes and enynes. In a demonstration of the high formal S_N2 selectivity of the amination step, linear substrates (**1.93, 1.94, 1.95**) were successfully deoxygenated to give the terminal olefin product. 1,4-Polyunsaturated compounds of this type are typically prepared *via* cross coupling[68, 69] or Wittig chemistry (Table 1-8).[70]

Table 1-8 Rh-catalyzed deoxygenation of 1,3-disubstituted allylic methyl carbonates with IPNBSH diazene precursor



Entry	Substrate		Product		Yield (%)
1[a]		**1.84**		**1.96**	62
2[a]		**1.86**	 Ar = 4-Cl-C_6H_4	**1.97**	57
3[a,b]		**1.87**		**1.98**	79
4		**1.88**		**1.99**	64
5		**1.89**		**1.100**	66
6		**1.90**		**1.101**	71
7[b]		**1.91**		**1.102**	69
8		**1.92**		**1.103**	56
9[b]		**1.93**		**1.104**	78
10[b]		**1.94**		**1.105**	52
11[b]		**1.95**		**1.106**	65

Isolated yields, 0.7-0.3 mmol scale. Regioisomer ratios ≥95:5 and E/Z ratios ≥94:6 in all cases. [a] reaction performed at 40°C. [b] 5 mol% $[Rh(COD)Cl]_2$ and 20 mol% $P(OPh)_3$.

The scalability of this methodology was demonstrated by the gram-scale preparation, without loss of yield or selectivity, of a dihalogenated β-methyl styrene (**1.79**) *via* the Ir-catalyzed protocol and a γ-unsaturated ester (**1.101**) via the Rh-catalyzed protocol (Figure 1-17).

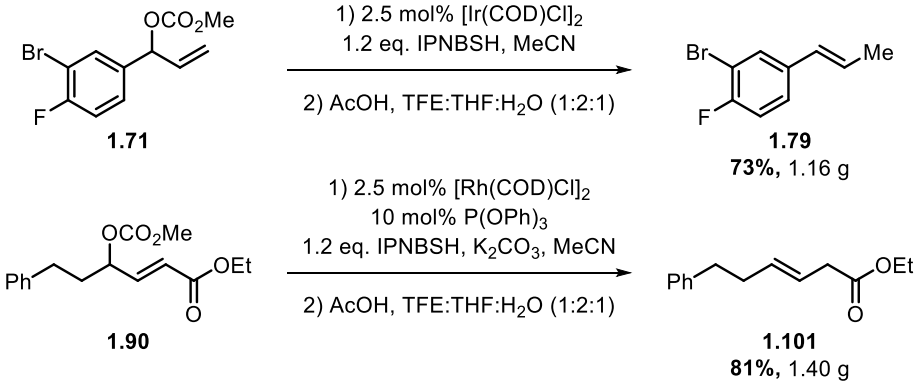


Figure 1-17 Gram-scale reactions of aryl and 1,3-disubstituted allylic carbonates under Ir and Rh-catalyzed conditions

Limitations of the Rh-catalyzed reaction are exemplified by **1.107**, **1.108** and **1.109** (Figure 1-18). Carbonates **1.107** and **1.108** were unreactive under the optimized conditions, whereas **1.109** gave primarily the elimination product (**1.110)** with no amination product observed. Although substrate **1.111** was successfully deoxygenated under the optimized Ir conditions, the regioselectivity of the amination step was low, giving a 2:1 mixture of product isomers (**1.112**, **1.113**) (Figure 1-18).

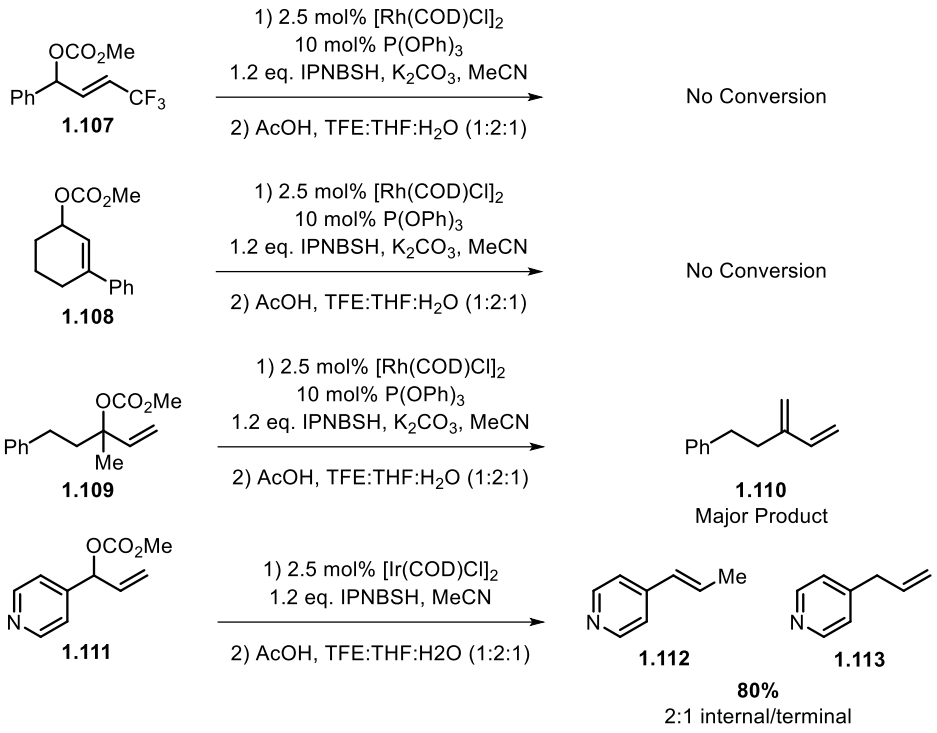


Figure 1-18 Selected allylic carbonates giving poor yield or selectivity

1.4 General Strategies for Allylic Carbonate Synthesis

Many of the allylic carbonates and their allylic alcohol precursors described above have previously been synthesized. Of those not previously reported, many were prepared by existing methodologies without modification. However, a number of substrates, particularly those prepared by cross-metathesis required the development of new protocols. The five general synthetic strategies employed are described below.

Allylic alcohols were synthesized by reaction with Grignard reagents from the corresponding aldehyde. If the aldehyde was not commercially available, the corresponding alcohol was oxidized *via* Swern or Des-Martin periodinane protocols to furnish the desired aldehyde. For aldehydes containing functional groups susceptible to undesirable reaction with Grignard reagents, vinylation was performed at − 78 °C to suppress side reactions.

More elaborate examples were prepared by cross-metathesis of the corresponding alcohol or aldehyde with the appropriate partner, followed by methyl carbonate installation or vinylation and carbonate installation respectively (Figure 1-19).

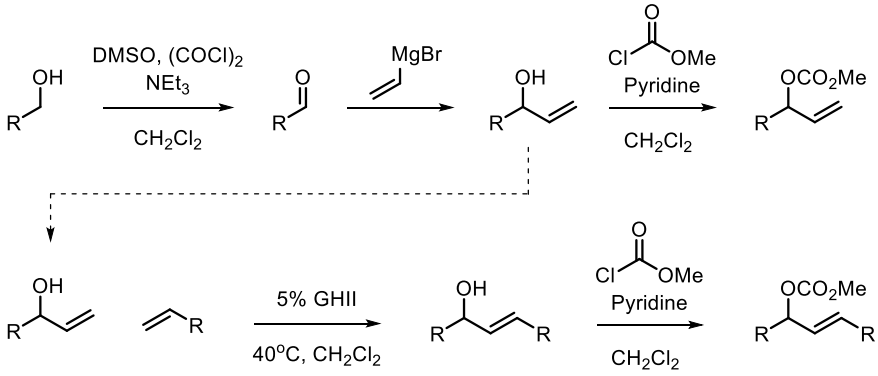


Figure 1-19 General strategy for the synthesis of allylic methyl carbonates

In the simplest synthetic case (Figure 1-20), the branched alcohol product of vinylation was converted to the methyl carbonate (**1.48**, **1.50**-**1.53**, **1.55**, **1.56**, **1.68**-**1.75**, **1.94**, **1.95**). Some substrates rearranged on purification over silica to give the linear product (**1.94**, **1.95**).

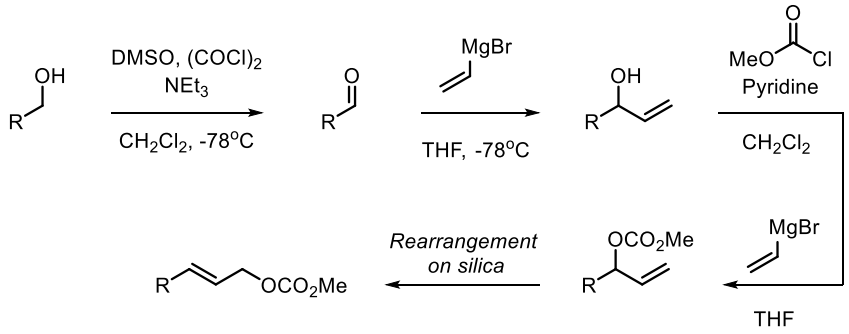


Figure 1-20 General synthetic scheme for the preparation of simple monosubstituted allylic methyl carbonates

Installation of α,β-unsaturated carbonyls could be accomplished through cross-metathesis between alkyl aldehydes bearing terminal olefins and α,β-unsaturated carbonyl compounds. Vinylation of the resulting aldehyde yielded a branched allylic alcohol which was then converted to the methyl carbonate (**1.57**; **1.89**-**1.92**) (Figure 1-21).

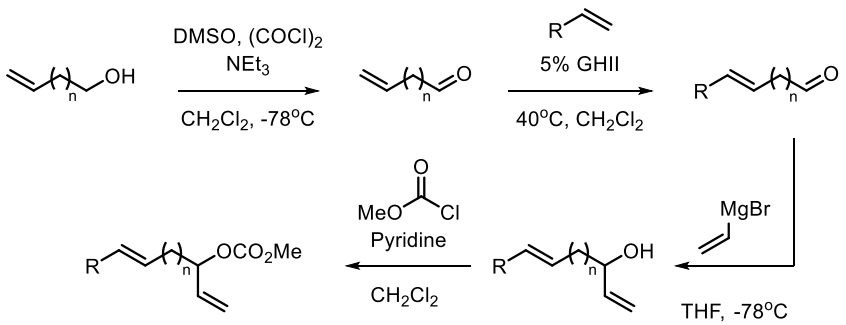


Figure 1-21 General synthetic scheme for substrates bearing α,β-unsaturated carbonyl groups: oxidation of alcohol preceding cross-metathesis

α,β-Unsaturated carbonyl and allyl acetate-containing substrates could also be prepared through cross-metathesis between alkyl alcohol and ω-unsaturated carbonyl compounds, followed by oxidation of the resulting alcohols with DMP. Vinylation of the resulting aldehyde at low temperature, yielded a branched allylic alcohol which was then converted to the methyl carbonate (**1.58**) (Figure 1-22).

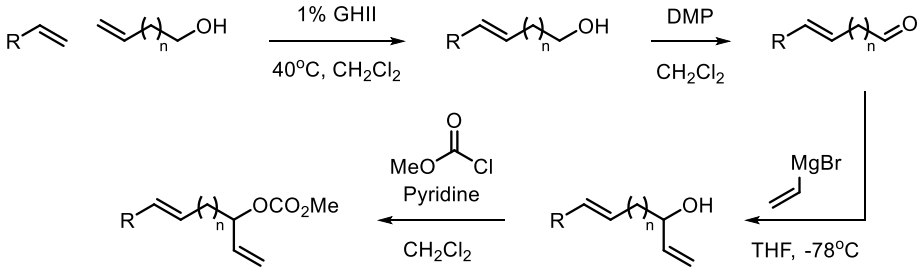


Figure 1-22 General synthetic scheme for substrates bearing α,β-unsaturated carbonyl groups: cross-metathesis preceding oxidation of alcohol

Substrate (**1.88**) was unique in its preparation because lithiated phenylacetylene was employed in place of a Grignard reagent. The resulting allylic alcohol which was then converted to the methyl carbonate. Upon purification by silica gel chromatography, the resulting methyl carbonate rearranged to a conjugated enyne (Figure 1-23).

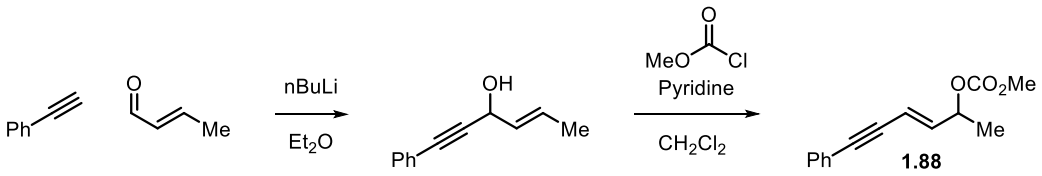


Figure 1-23 Scheme for the synthesis of substrate (**1.88**), with rearrangement of methyl carbonate upon silica column chromatography

The final synthetic strategy involved the addition of methylmagnesium bromide to an α,β-unsaturated aldehyde, furnishing an allylic alcohol, which was then converted to the methyl carbonate (**1.84**, **1.86**-**1.88**) (Figure 1-24).

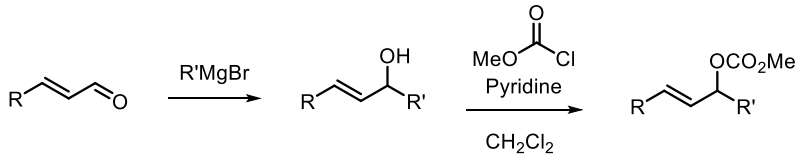


Figure 1-24 General synthetic scheme for the preparation of allylic methyl carbonates by Grignard addition to α,β-unsaturated aldehydes

1.5 Summary

A new catalytic method for the reductive transposition of allylic methyl carbonates, employing simple Rh and Ir precatalysts, has been developed. This strategy deoxygenates allylic alcohols activated with methylchloroformate, which is less hazardous than the tin hydride and DEAD employed in Mitsunobu and Barton-McCombie deoxygenations. The CO_2 and MeOH byproducts of ionization of the methyl carbonate also do not require extensive purification procedures.

The reaction tolerates functional groups potentially sensitive to reduction by less chemoselective methods. In a striking example of chemoselectivity, an allylic acetate which would be reactive under Pd-catalyzed conditions was tolerated by the Ir protocol. Unlike the equivalent Pd chemistry, where the regioselectivity of the amination step is under substrate control,[52] Ir and Rh give high formal S_N2 selectivity, giving access to skipped systems which can otherwise be difficult to prepare. Similar regioselectivity can be achieved with alternative phosphine-catalyzed methods; however, those have a small reported substrate scope and require metal hydrides as reductants, limiting the functional group tolerance.

Both mono and disubstituted allylic carbonates are readily deoxygenated by the simple Ir and Rh catalyst systems described above, which make use of common, commercially available metal complexes, a ubiquitous solvent and (in the case of Rh), an inexpensive ligand and base. Mild conditions and tolerance for a wide variety of reducible functionalities make this an appealing methodology for allylic deoxygenation, providing an alternate route for the preparation of valuable β-methyl styrenes as well as skipped dienes and enynes. Although the scope is not universal, it is broad and represents the first examples of regioselective Ir- and Rh-catalyzed allylic deoxygenation.

1.6 Procedures and Characterization

1.6.1 General Procedure for Allylic Alcohol Synthesis

To a nitrogen-purged round bottom flask equipped with a rubber septum and stir bar was added vinylmagnesium bromide as a 1.0M solution in THF (1.05 equiv) by syringe. The flask was cooled to 0 °C in an ice water bath. Solid aldehydes were added to a 4 dram (20 mL) vial equipped with a septum and placed under N_2 by evacuating/backfilling three times. The minimum quantity of dry THF required to dissolve the solid was then added by syringe. The aldehyde or aldehyde solution (1.0 equiv) was added dropwise by syringe. The reaction mixture was stirred at 0 °C for 10 minutes, at which time the cooling bath was removed and the reaction mixture was stirred until complete conversion of the aldehyde was observed by TLC. Upon completion, the reaction mixture was quenched by addition of saturated NH_4Cl and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. If necessary, the product was purified by column chromatography (Hex/EtOAc).

1.6.2 General Procedure for γ-hydroxy-α,β-Unsaturated Ester / Ketone Synthesis

The synthesis of γ-hydroxy-α,β-unsaturated esters and ketones **1.39** – **1.42** was achieved via cross-metathesis of ethyl acrylate or vinyl methyl ketone and the corresponding allylic alcohol in a procedure adapted from the literature.[71] To a nitrogen-purged round bottom flask equipped with a rubber septum and stir bar was added CH_2Cl_2, ethyl acrylate (or methyl vinyl ketone, 5 – 10 equiv.) and allylic alcohol (1.0 equiv.) by syringe. The catalyst (Grubbs–Hoveyda 2nd generation, 0.005 – 0.010 equiv.) was dissolved in dry CH_2Cl_2 under N_2 (2 to 4 mL/mmol) in a separate septum-capped vial and transferred to the reaction vessel via syringe (concentration 0.25 – 0.50 M). The reaction mixture was stirred at 40 °C until the alcohol was fully consumed, as

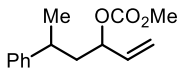
determined by TLC. The solvent was removed and the resulting crude mixture purified by flash chromatography (Hex/EtOAc).

1.6.3 General Procedure for Methyl Carbonate Synthesis

To a 4 dram (20 mL) vial was added allylic alcohol (1.0 equiv) and a stir bar. The vial was purged with N_2 by evacuating/backfilling three times and dry CH_2Cl_2 was added by syringe to make a ~1.0 M solution. Anhydrous pyridine (5.0 equiv) was added by syringe and the reaction mixture was stirred for 10 minutes at room temperature before being cooled to 0 °C in an ice water bath. Methyl chloroformate (2.4 equiv) was slowly added dropwise by syringe and the reaction mixture was stirred at 0 °C for 10 minutes, at which point the cooling bath was removed and the reaction stirred at room temperature until complete conversion of the alcohol was observed by TLC or 5 hours had elapsed. The reaction was quenched by addition of water, diluted with EtOAc and washed with 0.025% aqueous HCl. The organic layer was dried over Na_2SO_4 and if necessary, purified by column chromatography (Hex/EtOAc).

1.6.4 Methyl Carbonate Characterization

Substrates **1.1**,[72] **1.3**,[62] **1.19**,[62] **1.23**,[73] **1.35**[74] were prepared according to the General Procedure and spectroscopic data agreed with that reported.

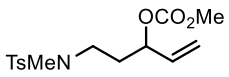


Substrate 1.50 Prepared according to the General Procedure from the corresponding alcohol (934 mg, 6.40 mmol). Isolated in 62% yield (mixture of diastereomers ~1:1) after purification by flash chromatography (Hex/EtOAc gradient) as a colorless oil.

^{1}H NMR ($CDCl_3$, 498 MHz) δ 7.33 – 7.27 (m, 2H), 7.23 – 7.14 (m, 3H), 5.77 (m, 1H), 5.28 – 5.13 (m, 2H), 4.96 (m, 0.5H), 4.83 (m, 0.5H), 3.77 (s, 1.5H), 3.74 (s, 1.5H), 2.84 (m, 1H), 2.11 (m, 0.5H), 2.00 (m, 0.5H), 1.83 (m, 1H), 1.29 (d, *J* = 1.5 Hz, 1.5H), 1.27 (d, *J* = 1.5 Hz, 1.5H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.2 (2), 146.3, 146.2, 136.3, 136.0, 128.7 (2), 127.1, 127.0, 126.5, 126.4, 118.2, 117.4, 77.8, 77.6, 54.8, 54.7, 42.9, 42.4, 36.3, 36.1, 22.6 (2);

HRMS (LCMS ESI): calcd for $C_{14}H_{18}NaO_3$ $[M+Na]^+$ 257.1148, found 257.1150.

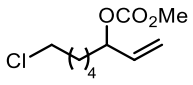


Substrate 1.52 Prepared according to the General Procedure from the corresponding alcohol (360 mg, 1.34 mmol). Isolated in 67% yield after purification by flash chromatography (Hex/EtOAc gradient) as a colorless oil.

^{1}H NMR ($CDCl_3$, 498 MHz) δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 5.81 (ddd, *J* = 17.2, 10.5, 6.6 Hz, 1H), 5.35 (m, 1H), 5.26 (m, 1H), 5.15 (m, 1H), 3.78 (s, 3H), 3.16 – 2.98 (m, 2H), 2.72 (s, 3H), 2.43 (s, 3H), 2.01 – 1.82 (m, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.1, 143.5, 135.1, 134.5, 129.8, 127.6, 118.3, 76.3, 54.9, 46.5, 35.3, 32.6, 26.6;

HRMS (LCMS ESI): calcd for $C_{15}H_{21}NNaO_5S$ $[M+Na]^+$ 350.1033, found 350.1032.

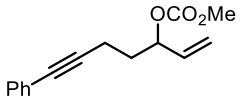


Substrate 1.53 Prepared according to the General Procedure from the corresponding alcohol (1.16 g, 6.00 mmol). Isolated in 87% yield, with no purification necessary, as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 498 MHz) δ 5.79 (ddd, *J* = 17.2, 10.5, 6.7 Hz, 1H), 5.30 (m, 1H), 5.21 (m, 1H), 5.05 (m, 1H), 3.78 (s, 3H), 3.52 (t, *J* = 6.6 Hz, 2H), 1.82 – 1.68 (m, 3H), 1.63 (m, 1H), 1.52 – 1.32 (m, 4H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.4, 136.0, 117.7, 79.1, 54.8, 45.0, 34.2, 32.6, 26.7, 24.4;

HRMS (LCMS ESI): calcd for $C_{10}H_{21}ClNO_3$ $[M+NH_4]^+$ 238.1204, found 238.1206.

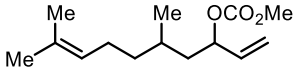


Substrate 1.55 Prepared according to the General Procedure from the corresponding alcohol (145 mg, 0.78 mmol). Isolated in 68% yield after purification by flash chromatography (Hex/EtOAc gradient) as a yellow oil.

^{1}H NMR ($CDCl_3$, 498 MHz) δ 7.42 – 7.37 (m, 2H), 7.31 – 7.26 (m, 3H), 5.84 (ddd, *J* = 10.5, 6.8, 3.7 Hz, 1H), 5.38 (m, 1H), 5.30 – 5.23 (m, 2H), 3.78 (s, 3H), 2.58 – 2.44 (m, 2H), 2.03 (m, 1H), 1.93 (m, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.3, 135.4, 131.7, 128.4, 127.9, 123.8, 118.2, 88.5, 81.5, 78.0, 54.9, 33.3, 15.6;

HRMS (LCMS ESI): calcd for $C_{15}H_{16}NaO_3$ $[M+Na]^+$ 267.0992, found 267.0992.

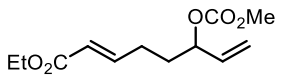


Substrate 1.56 Prepared according to the General Procedure from the corresponding alcohol (4.27 g, 23.5 mmol). Isolated in 64% yield (~1:1 mixture of diastereomers) after purification by flash chromatography (10:1 Hex/EtOAc) as a yellow oil.

^{1}H NMR ($CDCl_3$, 498 MHz) δ 5.78 (m, 1H), 5.30 (m, 1H), 5.23 – 5.04 (m, 3H), 3.77 (s, 1.5H), 3.77 (s, 1.5H), 2.06 – 1.87 (m, 2H), 1.83 – 1.11 (m, 11H), 0.93 (d, *J* = 2.6 Hz, 1.5H), 0.92 (d, *J* = 2.6 Hz, 1.5H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.5, 155.3, 136.7, 136.3, 131.5 (2), 124.7, 124.6, 117.8, 117.2, 78.1, 77.5, 54.7 (2), 41.7, 41.4, 37.4, 37.0, 28.9, 28.8, 25.8, 25.5, 25.4, 19.8, 19.5, 17.8 (2);

HRMS (LCMS ESI): calcd for $C_{14}H_{24}NaO_3$ $[M+Na]^+$ 263.1618, found 263.1617.

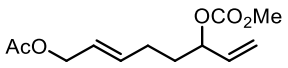


Substrate 1.57 Prepared according to the General Procedure from the corresponding alcohol (240 mg, 1.32 mmol). Isolated in 76% yield after purification by flash chromatography (4:1 Hex/EtOAc) as a colorless oil.

^{1}H NMR ($CDCl_3$, 498 MHz) δ 6.93 (dt, *J* = 15.7, 6.9 Hz, 1H), 5.86 – 5.74 (m, 2H), 5.32 (m, 1H), 5.25 (m, 1H), 5.07 (m, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 2.34 – 2.22 (m, 2H), 1.87 (m, 1H), 1.78 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.6, 155.2, 147.5, 135.5, 122.2, 118.2, 78.3, 60.4, 54.9, 32.6, 27.8, 14.4;

HRMS (LCMS ESI): calcd for $C_{12}H_{18}NaO_5$ $[M+Na]^+$ 265.1046, found 265.1051.

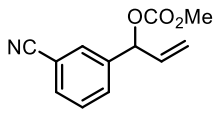


Substrate 1.58 Prepared according to the General Procedure from the corresponding alcohol (500 mg, 2.70 mmol, 85:15 *E/Z* mixture). Isolated in 43% yield after purification by flash chromatography (Hex/EtOAc gradient) as a colorless oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 5.82 – 5.72 (m, 2H), 5.59 (m, 1H), 5.30 (m, 1H), 5.22 (m, 1H), 5.06 (m, 1H), 4.50 (d, *J* = 6.4 Hz, 2H), 3.78 (s, 3H), 2.20 – 2.29 (m, 2H), 2.06 (s, 3H), 1.81 (m, 1H), 1.71 (m, 1H);

^{13}C NMR ($CDCl_3$, 176 MHz): δ 170.9, 155.3, 135.8, 134.7, 125.0, 117.9, 78.5, 65.1, 54.8, 33.4, 27.8, 21.1;

HRMS (LCMS ESI): calcd for $C_{12}H_{22}NaO_5$ $[M+Na]^+$ 265.1046 found 265.1041.

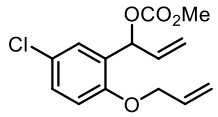


Substrate 1.69 Prepared according to the General Procedure from the corresponding alcohol (1.30 g, 8.10 mmol). Isolated in 52% yield after purification by flash chromatography (4:1 Hex/EtOAc) as colorless oil.

^{1}H NMR ($CDCl_3$, 498 MHz) δ 7.67 (m, 1H), 7.63 – 7.59 (m, 2H), 7.48 (m, 1H), 6.08 (d, *J* = 6.2 Hz, 1H), 5.98 (ddd, *J* = 10.3, 6.2, 4.2 Hz, 1H), 5.41 – 5.33 (m, 2H), 3.80 (s, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 154.9, 140.1, 134.8, 132.1, 131.5, 130.7, 129.6, 119.0, 118.5, 113.1, 79.0, 55.2;

HRMS (LCMS ESI): calcd for $C_{12}H_{11}NNaO_3$ $[M+Na]^+$ 240.0631, found 240.0630.

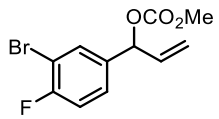


Substrate 1.70 Prepared according to the General Procedure from the corresponding alcohol (687 mg, 3.07 mmol). Isolated in 73% yield after purification by flash chromatography (Hex/EtOAc gradient with 1% NEt_3) as yellow oil.

^{1}H NMR ($CDCl_3$, 498 MHz) δ 7.37 (d, *J* = 2.6 Hz, 1H), 7.23 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 1H), 6.51 (m, 1H), 6.09 – 5.98 (m, 2H), 5.47 – 5.23 (m, 4H), 4.61 – 4.56 (m, 2H), 3.82 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.0, 154.0, 134.8, 132.8, 129.2, 129.0, 127.3, 126.2, 117.8, 117.3, 113.5, 74.1, 69.5, 55.0;

HRMS (LCMS ESI): calcd for $C_{14}H_{15}ClNaO_4$ $[M+Na]^+$ 305.0551, found 305.0552.



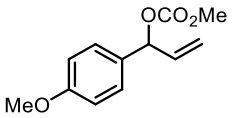
Substrate 1.71 Prepared according to the General Procedure from the corresponding alcohol (2.72 g, 11.8 mmol). Isolated in 69% yield after purification by flash chromatography (Hex/EtOAc gradient) as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 498 MHz) δ 7.58 (dd, *J* = 6.5, 2.3 Hz, 1H), 7.29 (m, 1H), 7.11 (m, 1H), 6.04 – 5.93 (m, 2H), 5.38 – 5.30 (m, 2H), 3.79 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.1 (d, J_{CF} = 248.2 Hz), 155.0, 135.9 (d, J_{CF} = 4.0 Hz), 135.1 (d, J_{CF} = 0.8 Hz), 132.5, 128.0 (d, J_{CF} = 7.5 Hz), 118.4, 116.7 (d, J_{CF} = 21.8 Hz), 109.4 (d, J_{CF} = 21.3 Hz), 78.8, 55.1;

^{19}F NMR ($CDCl_3$, 469 MHz) δ 107.5;

HRMS (LCMS ESI): calcd for $C_{11}H_{10}BrFNaO_3$ $[M+Na]^+$ 310.9690, found 310.9690.

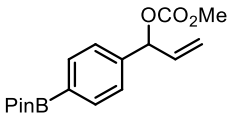


Substrate 1.73 Prepared according to the General Procedure from the corresponding alcohol (1.16 g, 7.04 mmol). Isolated in 77% yield as a pale yellow oil. The product is not stable to silica gel chromatography and will rearrange to the linear methyl carbonate.

^{1}H NMR ($CDCl_3$, 498 MHz) δ 7.31 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.10 – 5.98 (m, 2H), 5.36 – 5.23 (m, 2H), 3.80 (s, 3H), 3.77 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.9, 155.2, 136.0, 130.5, 128.8, 117.2, 114.1, 80.1, 55.4, 54.9;

HRMS (LCMS ESI): calcd for $C_{12}H_{14}NaO_4$ $[M+Na]^+$ 245.0784, found 245.0782.

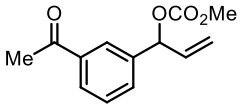


Substrate 1.74 The allylic alcohol was prepared via a modified procedure. To a round bottom flask was added aldehyde and a stir bar. The flask was then purged with nitrogen by evacuating and backfilling three times and anhydrous THF was added by syringe. The reaction vessel was then cooled to –78 °C in a dry ice/acetone bath, vinylmagnesium bromide was added dropwise while stirring and the reaction mixture was stirred for 1 hour at –78 °C. The reaction was allowed to stir for 30 minutes at room temperature, at which point it was quenched by the addition of saturated NH_4Cl. The resulting mixture was diluted with water (25 mL) and the aqueous layer washed three times with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. The methyl carbonate was prepared according to the General Procedure from the corresponding alcohol (783 mg, 3.00 mmol). Isolated in 83% yield with no purification as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 498 MHz) δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 6.08 (d, *J* = 6.4 Hz, 1H), 6.01 (ddd, *J* = 16.3, 10.3, 6.1 Hz, 1H), 5.34 (m, 1H), 5.27 (m, 1H), 3.77 (s, 3H), 1.34 (s, 12H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.1, 141.4, 135.8, 135.2, 126.4, 117.9, 84.0, 80.3, 55.0, 25.0 (2);

HRMS (LCMS ESI): calcd for $C_{17}H_{23}BNaO_5$ $[M+Na]^+$ 341.1531, found 341.1534.

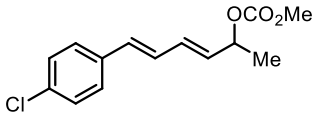


Substrate 1.75 The allylic alcohol was prepared via a modified procedure. To a round bottom flask was added aldehyde and a stir bar. The flask was then purged with nitrogen by evacuating and backfilling three times and 10 mL anhydrous THF was added by syringe. The reaction vessel was then cooled to –78 °C in a dry ice/acetone bath, vinylmagnesium bromide was added dropwise while stirring and the reaction mixture was stirred for 2 hours at –78 °C. After 2 hours the cooling bath was removed and 10 mL saturated NH_4Cl was added directly to the cold mixture. The resulting mixture was filtered and the white precipitate washed with three times with 10 mL of Et_2O. The aqueous layer was then washed three times with 10 mL of Et_2O. The methyl carbonate was prepared according to the general procedure from the alcohol (348 mg, 1.98 mmol). Isolated in 87% yield with no further purification as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 498 MHz) δ 7.95 (m, 1H), 7.91 (m, 1H), 7.58 (m, 1H), 7.47 (app. t, *J* = 7.7 Hz, 1H), 6.13 (d, *J* = 6.2 Hz, 1H), 6.03 (ddd, *J* = 16.9, 10.6, 6.1 Hz, 1H), 5.37 (m, 1H), 5.32 (m, 1H), 3.79 (s, 3H), 2.61 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.8, 155.1, 139.2, 137.7, 135.4, 131.8, 129.1, 128.5, 127.0, 118.3, 79.8, 55.1, 26.8;

HRMS (LCMS ESI): calcd for $C_{13}H_{14}NaO_4$ $[M+Na]^+$ 257.0784, found 257.0785.

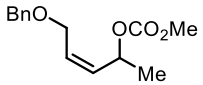


Substrate 1.86 Prepared according to the General Procedure from the corresponding benzyl alcohol (625 mg, 3.00 mmol), which undergoes quantitative isomerization upon methyl carbonate formation/silica gel chromatography. Isolated in 88% yield after purification by flash chromatography (Hex/EtOAc gradient) as a white solid.

^{1}H NMR ($CDCl_3$, 498 MHz) δ 7.34 – 7.24 (m, 4H), 6.70 (dd, *J* = 15.6, 10.6 Hz, 1H), 6.53 (d, *J* = 15.7 Hz, 1H), 6.43 (dd, *J* = 15.2, 10.4 Hz, 1H), 5.81 (dd, *J* = 15.4, 7.0 Hz, 1H), 5.29 (m, 1H), 3.78 (s, 3H), 1.42 (d, *J* = 6.6 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 155.3, 135.6, 133.5, 132.7, 132.6, 132.4, 129.0, 128.5, 127.7, 75.0, 54.8, 20.5;

HRMS (LCMS ESI): calcd for $C_{14}H_{15}ClO_3$ [M+Na] 289.0602, found 289.0603.

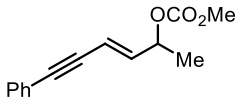


Substrate 1.87 Prepared according to the General Procedure from the corresponding alcohol (950 mg, 3.8 mmol). Isolated in 70% yield after purification by flash chromatography (Hex/EtOAc gradient) as a colorless oil.

^{1}H NMR ($CDCl_3$, 498 MHz) δ 7.37 – 7.32 (m, 4H), 7.29 (m, 1H), 5.74 (m, 1H), 5.57 (m, 1H), 5.46 (m, 1H), 4.53 (m, 2H), 4.23 – 4.15 (m, 2H), 3.76 (s, 3H), 1.34 (d, *J* = 6.6 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.2, 138.3, 131.7, 129.7, 128.5, 127.9, 127.8, 72.6, 71.2, 66.1, 54.7, 20.8;

HRMS (LCMS ESI): calcd for $C_{14}H_{18}NaO_4$ [M+Na] 273.1097, found 273.1098.

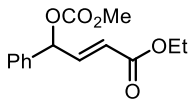


Substrate 1.88 Prepared according to the General Procedure from the corresponding alcohol (1.00 g, 5.81 mmol). Isolated a 5:1 mixture of product and propargylic methyl carbonate in 75% yield after purification by flash chromatography (Hex/EtOAc gradient) as a colorless oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.45 – 7.39 (m, 2H), 7.35 – 7.29 (m, 3H), 6.18 (dd, *J* = 15.9, 6.6 Hz, 1H), 5.98 (dd, *J* = 15.8, 1.1 Hz, 1H), 5.28 (m, 1H), 3.79 (m, 3H), 1.42 (d, *J* = 6.6 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 155.0, 140.9, 131.6, 131.5, 128.4, 128.3, 112.2, 91.1, 86.7, 74.7, 54.7, 20.0;

HRMS (LCMS ESI): calcd for $C_{14}H_{14}NaO_3$ [M+Na] 253.0835, found 253.0835.

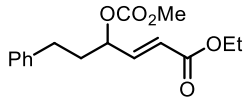


Substrate 1.89 Prepared according to the General Procedure from the corresponding alcohol (850 mg, 4.14 mmol). Isolated in 79% yield after purification by flash chromatography (Hex/EtOAc gradient) as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.41 – 7.32 (m, 5H), 7.01 (dd, *J* = 15.7, 5.1 Hz, 1H), 6.22 (dd, *J* = 5.1, 1.7 Hz, 1H), 6.09 (dd, *J* = 15.7, 1.7 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.79 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 165.9, 154.9, 143.9, 136.8, 129.2, 129.0, 127.5, 122.2, 78.2, 60.9, 55.2, 14.3;

HRMS (LCMS ESI): calcd for $C_{14}H_{16}NaO_5$ $[M+Na]^+$ 287.0890, found 287.0891.

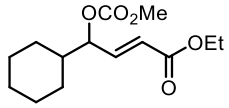


Substrate 1.90 Prepared according to the General Procedure from the corresponding alcohol (3.565 g, 16.3 mmol). Isolated in 63% yield after purification by flash chromatography (Hex/EtOAc gradient) as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.31 – 7.27 (m, 2H), 7.20 (m, 1H), 7.18 – 7.15 (m, 2H), 6.87 (dd, *J* = 15.7, 5.5 Hz, 1H), 6.02 (dd, *J* = 15.7, 1.5 Hz, 1H), 5.25 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 2.77 – 2.65 (m, 2H), 2.07 (m, 1H), 2.01 (m, 1H), 1.29 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 165.9, 155.2, 144.4, 140.7, 128.7, 128.5, 126.4, 122.5, 76.1, 60.8, 55.1, 35.6, 31.2, 14.3;

HRMS (LCMS ESI): calcd for $C_{16}H_{20}NaO_5$ $[M+Na]^+$ 315.1203, found 315.1204.

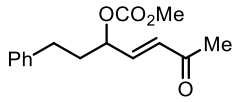


Substrate 1.91 Prepared according to the General Procedure from the corresponding alcohol (610 mg, 2.87 mmol). Isolated in 68% yield after purification by flash chromatography (Hex/EtOAc gradient) as a clear, colorless oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 6.84 (dd, *J* = 15.7, 5.9 Hz, 1H), 5.98 (dd, *J* = 15.7, 1.5 Hz, 1H), 5.05 (td, *J* = 6.0, 1.4 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.79 (s, 3 H), 1.81 – 1.63 (m, 6H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.27 – 1.01 (m, 5H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 166.0, 155.4, 143.8, 122.9, 80.8, 60.7, 55.0, 41.8, 28.6, 28.2, 26.2, 26.0, 26.0, 14.4;

HRMS (LCMS ESI): calcd for $C_{14}H_{22}NaO_5$ $[M+Na]^+$ 293.1359, found 293.1364.

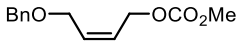


Substrate 1.92 Prepared according to the General Procedure from the corresponding alcohol (908 mg, 4.45 mmol). Isolated in 56% yield after purification by flash chromatography (Hex/EtOAc gradient) as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.29 (m, 2H), 7.20 (m, 1H), 7.17 (m, 2H), 6.66 (dd, *J* = 16.1, 5.5 Hz, 1H), 6.24 (dd, *J* = 16.0, 1.4 Hz, 1H), 5.26 (m, 1H), 3.81 (s, 3H), 2.78 – 2.66 (m, 2H), 2.25 (s, 3H), 2.09 (m, 1H), 2.02 (m, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.8, 155.1, 143.0, 140.6, 130.7, 128.7, 128.5, 126.4, 76.2, 55.2, 35.6, 31.3, 27.7;

HRMS (LCMS ESI): calcd for $C_{15}H_{18}NaO_4$ $[M+Na]^+$ 285.1097, found 285.1098.

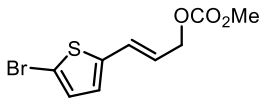


Substrate 1.93 Prepared according to the General Procedure from the corresponding alcohol (890 mg, 5.00 mmol). Isolated in 97% yield after purification by flash chromatography (Hex/EtOAc gradient) as a colorless oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.34 – 7.31 (m, 4H), 7.27 (m, 1H), 5.85 (m, 1H), 5.72 (m, 1H), 4.68 (d, *J* = 6.9 Hz, 2H), 4.50 (s, 2H), 4.12 (d, *J* = 6.2 Hz, 2H), 3.76 (s, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 155.6, 137.9, 131.4, 128.4, 127.8, 127.7, 126.0, 72.4, 65.6, 63.6, 54.8;

HRMS (LCMS ESI): calcd for $C_{13}H_{16}NaO_4$ $[M+Na]^+$ 259.0941, found 259.0942.

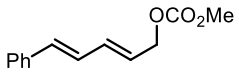


Substrate 1.94 Prepared according to the General Procedure from the corresponding branched allylic alcohol which undergoes isomerization upon methyl carbonate synthesis/silica gel column chromatography (1.19 g, 5.44 mmol). Isolated in 51% yield after purification by flash chromatography (Hex/EtOAc gradient) as a light brown solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 6.90 (d, *J* = 3.8 Hz, 1H), 6.71 (d, *J* = 3.8 Hz, 1H), 6.66 (m, 1H), 5.99 (dt, *J* = 15.6, 6.4 Hz, 1H), 4.70 (dd, *J* = 6.4, 1.3 Hz, 2H), 3.78 (s, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 155.5, 142.6, 130.3, 127.2, 127.0, 122.3, 112.1, 67.7, 54.9;

HRMS (LCMS ESI): calcd for $C_9H_9NaO_3S$ $[M+Na]^+$ 298.9348, found 298.9354.



Substrate 1.95 Prepared according to the General Procedure from the corresponding branched allylic alcohol, which undergoes isomerization upon methyl carbonate synthesis/silica gel column chromatography (1.21 g, 7.60 mmol). Isolated in 55% yield after purification by flash chromatography (10:1 Hex/EtOAc) as a white solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.40 (d, *J* = 7.9 Hz, 2H), 7.32 (t, *J* = 5.6 Hz, 2H), 7.25 (m, 1H), 6.77 (dd, *J* = 15.6, 10.5 Hz, 1H), 6.60 (d, *J* = 15.6 Hz, 1H), 6.49 (m, 1H), 5.89 (dt, *J* = 15.2, 6.5 Hz, 1H), 4.72 (d, *J* = 6.6, 1.1 Hz, 2H), 3.80 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.8, 137.0, 135.3, 134.4, 128.8, 128.1, 127.7, 126.7, 126.2, 68.3, 55.0;

HRMS (LCMS ESI): calcd for $C_{13}H_{14}NaO_3$ $[M+Na]^+$ 241.0835, found 241.0836.

1.7 Ir–Catalyzed Reductive Transposition of Allylic Carbonates

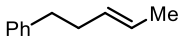
1.7.1 General Procedure (Glovebox) To a 4 dram (20 mL) vial containing a stirbar was added IPNBSH (230 mg, 0.90 mmol, 1.2 equiv.), the allylic carbonate (0.75 mmol, 1.0 equiv.) in MeCN (2 mL), $[Ir(COD)Cl]_2$ (13.0 mg, 0.019 mmol, 0.050 equiv. Ir) in MeCN (2 mL), and dibenzyl ether (14.5 μL, 0.075 mmol, 0.10 equiv.). The reaction mixture was stirred for 18 hours, over which time the solution turned from orange to purple to black. After 18 hours the solvent was removed by rotovap and ^{1}H NMR was used to judge the conversion of the allylic carbonate to the allylic sulfonyl hydrazone. The crude reaction mixture was then dissolved in THF (2 mL), and then water (1 mL), TFE (1 mL), and AcOH (110 μL, 2.5 equiv.) were added. The reaction mixture was stirred for 2 hours, after which hexane (50 mL) and saturated sodium bicarbonate (50 mL) was added (50 mL EtOAc was used for polar products). The organic layer was washed with brine,

dried with Na_2SO_4, concentrated, and purified by column chromatography (generally hexane/EtOAc, or pentane for volatile products). Conducting the reduction step without the removal of MeCN led to a slight reduction (10–15%) in product yield. Unless specifically noted, the *E/Z* and regioisomer ratios of the isolated products were ≥95:5.

1.7.2 General Procedure (No Glovebox) To separate 4 dram (20 mL) vials was added IPNBSH (230 mg, 0.90 mmol, 1.2 equiv.), allylic carbonate (0.75 mmol, 1.0 equiv.) and $[Ir(COD)Cl]_2$ (13.0 mg, 0.019 mmol, 0.050 equiv. Ir). Each vial was capped with a PTFE-lined septum cap and evacuated and backfilled with N_2 three times. Anhydrous MeCN (1.5 mL) was added to the vials containing the allylic carbonate and $[Ir(COD)Cl]_2$ via syringe. The MeCN solutions were then transferred to the vial containing IPNBSH via syringe. The remainder of the procedure is identical to that described above.

1.7.3 Gram Scale Reaction (No Glovebox), Figure 1-17. All glassware was rigorously dried under vacuum using an electric heat gun. To a 4 dram (20 mL) vial was added $[Ir(COD)Cl]_2$ (62 mg, 0.092 mmol, 0.025 equiv. Ir), the vial was capped and placed under N_2 and MeCN was added (10 mL). To a 100 mL round bottom flask under N_2 was added allylic carbonate (2.15 g, 7.4 mmol), followed by the $[Ir(COD)Cl]_2$ solution and an additional 25 mL of MeCN. The solution was stirred for 5 minutes before IPNBSH (2.18 g, 8.53 mmol) was added. The round bottom flask was placed under a positive pressure of N_2 via a balloon and the reaction mixture was stirred for 18 hours. The solvent was then removed and the crude reaction mixture was dissolved in THF (10 mL), TFE (5 mL) and water (5 mL) before adding AcOH (1 mL). The reaction mixture was stirred for 2 hours after which it was diluted with CH_2Cl_2 (100 mL), transferred to a separatory funnel, washed with saturated bicarbonate solution and water. The aqueous extracts where washed with EtOAc (3 x 10 mL), the organic extracts were combined, dried with Na_2SO_4, and concentrated. The product was

isolated in 73% yield (1.16 g, 5.4 mmol) after purification by column chromatography (40:1 Hex/EtOAc) as pale yellow oil.

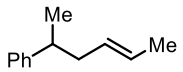


Product 1.59[75] Prepared according to the General Procedure from the corresponding methyl carbonate (165 mg, 0.75 mmol). Isolated in 84% yield after purification by column chromatography (pentane), *E*/*Z* = 93:7, colorless oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.30 – 7.26 (m, 3H), 7.20 – 7.18 (m, 2H), 5.49 – 5.47 (m, 2H), 2.67 (m, 2H), 2.32 – 2.30 (m, 2H), 1.67 – 1.65 (m, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 142.4, 130.8, 128.6, 128.4, 125.9, 125.6, 36.3, 34.4, 18.1;

HRMS (LCMS EI): calcd for $C_{11}H_{14}$ $[M]^+$ 146.1096, found 146.1098.

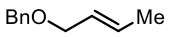


Product 1.60 Prepared according to the General Procedure from the corresponding methyl carbonate (175 mg, 0.75 mmol). Isolated in 68% yield after purification by column chromatography (40:1 Hex/EtOAc), *E*/*Z* = 92:8, 91:9 regioisomer ratio, colorless oil. The yield for a reaction on the same scale set up without a glovebox was 62%.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31 – 7.28 (m, 2H), 7.22 – 7.17 (m, 3H), 5.44 – 5.34 (m, 2H), 2.74 (m, 1H), 2.32 (m, 1H), 2.21 (m, 1H), 1.62 (dd, *J* = 6.2, 1.2 Hz, 3H), 1.24 (d, *J* = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 124 MHz) δ 147.6, 129.8, 128.4, 127.2, 126.5, 126.0, 41.6, 40.3, 21.6, 18.1;

HRMS (LCMS EI): calcd for $C_{12}H_{16}$ $[M]^+$ 160.1252, found 160.1250.

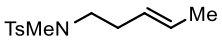


Product 1.61[76] Prepared according to the General Procedure from the corresponding methyl carbonate (177 mg, 0.75 mmol). Isolated in 71% yield after purification by column chromatography (20:1 Hex/EtOAc), colorless oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.36 – 7.33 (m, 4H), 7.30 – 7.26 (m, 1H), 5.74 (m, 1H), 5.64 (m, 1H), 4.50 (s, 2H), 3.97 (d, *J* = 6.3 Hz, 2H), 1.73 (d, *J* = 6.4 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 138.7, 129.8, 128.5, 127.9, 127.7 (2), 78.1, 71.1, 17.9;

HRMS (LCMS EI): calcd for $C_{11}H_{14}O$ $[M]^+$ 162.1045, found 162.1043.

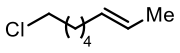


Product 1.62 Prepared according to the General Procedure from the corresponding methyl carbonate (98 mg, 0.30 mmol). Isolated in 88% yield after purification by column chromatography (4:1 Hex/EtOAc) as a viscous colorless oil, *E/Z* = 94:6.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.66 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 5.48 (m, 1H), 5.34 (m, 1H), 3.01 (t, *J* = 7.4 Hz, 2H), 2.72 (s, 3H), 2.42 (s, 3H), 2.21 (app. q, *J* = 7.8 Hz, 2H), 1.64 (d, *J* = 6.5 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz): δ 143.3, 135.0, 129.8, 127.9, 127.5, 127.1, 50.3, 34.9, 31.3, 21.7, 18.1;

HRMS (LCMS ESI): calcd for $C_{13}H_{19}NNaO_2S$ $[M+Na]^+$ 276.1029, found 276.1030.

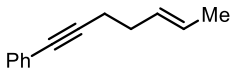


Product 1.63[77] Prepared according to the General Procedure from the corresponding methyl carbonate (499 mg, 2.27 mmol). Isolated in 71% yield after purification by column chromatography (pentane) as a colorless oil, *E/Z* = 92:8.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 5.50 – 5.33 (m, 2H), 3.53 (t, *J* = 6.8 Hz, 2H), 2.05 – 2.00 (m, 2H) 1.80 – 1.68 (m, 5H), 1.48 –1.36 (m, 4H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 131.2, 125.2, 45.3, 32.7, 32.5, 29.0, 26.6, 18.1;

HRMS (LCMS ESI): calcd for $C_8H_{15}Cl$ $[M]^+$ 146.0862, found 146.0863.

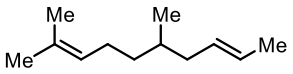


Product 1.64 Prepared according to the General Procedure from the corresponding methyl carbonate (100 mg, 0.40 mmol). Isolated in 74% yield after purification by column chromatography (Hex/EtOAc gradient) as a viscous colorless oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.41 – 7.38 (m, 2H), 7.30 – 7.24 (m, 3H), 5.59 – 5.51 (m, 2H), 2.45 (t, *J* = 7.2 Hz, 2H), 2.32 – 2.26 (m, 2H), 1.72 – 1.66 (m, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 131.7, 129.6, 128.3, 127.7, 126.5, 124.2, 90.1, 81.0, 32.1, 20.1, 18.1;

HRMS (LCMS ESI): calcd for $C_{13}H_{14}$ $[M]^+$ 170.1096, found 170.1093.

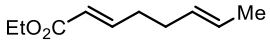


Product 1.65 Prepared according to the General Procedure from the corresponding methyl carbonate (180 mg, 0.75 mmol). Isolated in 57% yield after purification by column chromatography (pentane), colorless oil, *E/Z* = 94:6.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 5.41 – 5.39 (m, 2H), 5.10 (m, 1H), 2.01 – 1.94 (m, 3H), 1.85 – 1.78 (m, 1H), 1.67 (s, 3H), 1.66 – 1.65 (m, 3H), 1.59 (s, 3H), 1.44 (m, 1H), 1.33 (m, 1H), 1.12 (m, 1H), 0.85 (d, *J* = 6.8 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 131.2, 130.2, 126.0, 125.1, 40.2, 36.8, 32.9, 25.9, 25.8, 19.6, 18.0, 17.8;

HRMS (LCMS EI): calcd for $C_{12}H_{22}$ $[M]^+$ 166.1722, found 166.1722.

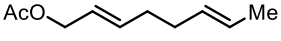


Product 1.66 Prepared according to the General Procedure from the corresponding methyl carbonate (73 mg, 0.30 mmol). Isolated in 75% yield after purification by column chromatography (10:1 Hex/EtOAc) as a thick, colorless oil, E/Z = 94:6.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 6.93 (dt, *J* = 15.7, 7.0 Hz, 1H), 5.80 (d, *J* = 15.7 Hz, 1H), 5.48 – 5.35 (m, 2H), 4.17 (q, *J* = 7.0 Hz, 2H), 2.23 (m, 2H), 2.12 (m, 2H), 1.62 (d, *J* = 6.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 166.7, 148.7, 129.6, 126.0, 121.5, 60.1, 32.2, 31.0, 17.8, 14.2;

HRMS (LCMS ESI): calcd for $C_{10}H_{16}NaO_2$ $[M+Na]^+$ 191.1043, found 191.1042.



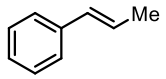
Product 1.67 Prepared according to the General Procedure from the corresponding methyl carbonate (145 mg, 0.60 mmol, 85:15 *E/Z* mixture). Isolated in 65% yield (85:15 *E/Z* of allylic

acetate alkene, >95:5 *E/Z* of newly formed alkene) after purification by flash chromatography (20:1 to 10:1 Hex/EtOAc) as a colorless oil.

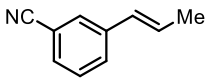
^{1}H NMR ($CDCl_3$, 498 MHz) δ 5.77 (m, 1H), 5.57, (m, 1H), 5.47 – 5.37 (m, 2H), 4.50 (d, *J* = 6.5 Hz, 2H), 2.18 – 2.03 (m, 7H), 1.64 (d, *J* = 5.8 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.0, 136.1, 130.5, 125.6, 124.2, 65.4, 32.4, 32.1, 21.2, 18.0;

HRMS (LCMS ESI): calcd for $C_{10}H_{16}NaO_2$ $[M+Na]^+$ 191.1040 found 191.1043.



Product 1.76[75] Prepared according to the General Procedure from the corresponding methyl carbonate (192 mg, 1.00 mmol). Isolated in 69% yield after purification by column chromatography (pentane). Spectroscopic data agrees with commercially available material.

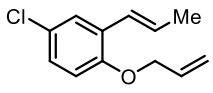


Product 1.77 Prepared according to the General Procedure from the corresponding methyl carbonate (163 mg, 0.75 mmol). Isolated in 63% yield after purification by column chromatography (Hex/EtOAc gradient), regioisomer ratio = 93:7.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.58 (s, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.38 (m, 1H), 6.38 – 6.29 (m, 2H), 1.91 (dd, *J* = 6.4, 1.4 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 139.3, 130.2 (2), 129.9, 129.4, 129.2, 129.0, 119.1, 112.8, 18.7;

HRMS (LCMS EI): calcd for $C_{10}H_9N$ $[M]^+$ 143.0735, found 143.0736.

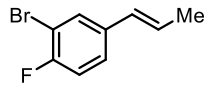


Product 1.78 Prepared according to the General Procedure from the corresponding methyl carbonate (212 mg, 0.75 mmol). Isolated in 71% yield after purification by column chromatography (10:1 Hex/EtOAc), regioisomer ratio = 94:6. The yield for a reaction set up without a glovebox was 64%.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.36 (d, J = 2.7 Hz, 1H), 7.09 (dd, J = 8.8, 2.7 Hz, 1H), 6.75 (d, J = 8.8 Hz, 1H), 6.68 (d, J = 16 Hz, 1H), 6.24 (m, 1H), 6.06 (m, 1H), 5.41 (m, 1H), 5.29 (m, 1H), 4.57 (m, 2H), 1.90 (dd, J = 1.7, 6.7 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 153.9, 133.3, 129.2, 128.0, 127.2, 126.3, 126.1, 124.6, 117.7, 113.7, 69.7, 19.1;

HRMS (LCMS EI): calcd for $C_{12}H_{13}OCl$ $[M]^+$ 210.0626, found 210.0634.

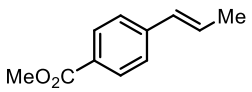


Product 1.79 Prepared according to the General Procedure from the corresponding methyl carbonate (292 mg, 1.01 mmol). Isolated in 94% yield after purification by column chromatography (10:1 Hex/EtOAc), colorless oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.50 (dd, J = 6.7, 2.1 Hz, 1H), 7.21 (m, 1H), 7.02 (app. t, J = 16.1 Hz, 1H), 6.29 (d, J = 15.8 Hz, 1H), 6.16 (dq, J = 16.1, 6.5 Hz, 1H), 1.87 (dd, J = 6.6, 1.7 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 158.6 (J_{CF} = 246 Hz), 135.8 (J_{CF} = 3.5 Hz), 130.7, 128.8 (J_{CF} = 0.7 Hz), 127.2 (J_{CF} = 2.3 Hz), 126.3 (J_{CF} = 6.9 Hz), 116.5 (J_{CF} = 22.3 Hz), 109.2 (J_{CF} = 21.3 Hz), 18.5;

HRMS (LCMS EI): calcd for C_9H_8FBr $[M]^+$ 215.9773, found 215.9770.

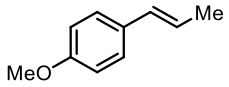


Product 1.80[78] Prepared according to the General Procedure from the corresponding methyl carbonate (176 mg, 0.70 mmol). Isolated in 56% yield after purification by column chromatography (Hex/EtOAc gradient) as a colorless solid, regioisomer ratio = 83:17.

^{1}H NMR ($CDCl_3$, 498 MHz) δ 7.99 – 7.96 (m, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 6.45 – 6.35 (m, 2H), 3.93 (s, 3H), 1.93 (dd, *J* = 6.3, 1.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.0, 142.5, 130.4, 129.9, 128.8, 128.2, 125.7, 52.0, 18.6;

HRMS (LCMS ESI): calcd for $C_{11}H_{12}NaO_2$ $[M+Na]^+$ 199.0730, found 199.0728.

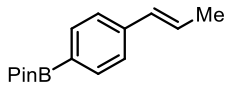


Product 1.81[78] Prepared according to the General Procedure from the corresponding methyl carbonate (167 mg, 0.75 mmol). Isolated in 45% yield after purification by column chromatography (10:1 Hex/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.27 – 7.25 (m, 2H), 6.85 – 6.83 (m, 2H), 6.34 (d, *J* = 15 Hz, 1H), 6.09 (dq, *J* = 16, 6.6 Hz, 1H), 3.80 (s, 3H), 1.86 (dd, *J* = 6.4, 1.8 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 158.8, 131.0, 130.5, 127.0, 123.7, 114.1, 55.4, 18.6;

HRMS (LCMS EI): calcd for $C_{10}H_{12}O$ $[M]^+$ 148.0888, found 148.0887.

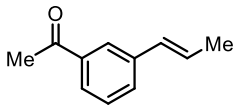


Product 1.82[79] Prepared according to the General Procedure from the corresponding methyl carbonate (200 mg, 0.63 mmol). Isolated in 55% yield after purification by column chromatography (20:1 pentane/Et_2O) as a yellow oil.

^{1}H NMR ($CDCl_3$, 498 MHz) δ 7.73 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 6.41 (m, 1H), 6.31 (m, 1H), 1.89 (dd, *J* = 6.4, 1.5 Hz, 3H), 1.34 (s, 12H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.8, 135.2, 131.3, 127.1, 125.3, 83.8, 25.0, 18.7;

HRMS (LCMS EI): calcd for $C_{15}H_{21}BO_2$ $[M]^+$ 244.1635, found 244.1636.



Product 1.83 Prepared according to the General Procedure from the corresponding methyl carbonate (176 mg, 0.75 mmol). Isolated in 77% yield after purification by column chromatography (2:1 pentane/Et_2O) as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 498 MHz): δ 7.90 (m, 1H), 7.77 (m, 1H), 7.52 (m, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 6.45 (m, 1H), 6.33 (m, 1H), 2.60 (s, 3H), 1.91 (dd, *J* = 6.5, 1.6 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 198.4, 138.6, 137.5, 130.4, 130.3, 128.8, 127.4, 126.8, 125.8, 26.8, 18.6;

HRMS (LCMS EI): calcd for $C_{11}H_{12}O$ $[M]^+$ 160.0888, found 160.0890.

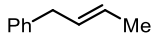
1.8 Rh–Catalyzed Reductive Transposition of Allylic Carbonates

1.8.1 General Procedure (Glovebox) To a 1 dram (5 mL) vial was added $[Rh(COD)Cl]_2$ (0.050 equiv. Rh), triphenylphosphite (0.10 equiv.) and MeCN (200 μL). The solution was stirred for five minutes. To a second 1 dram (5 mL) vial containing the allylic carbonate (1.00 equiv) was added the [Rh]/$P(OPh)_3$ solution and residual catalyst solution rinsed into the reaction vial with MeCN (100 μL). The solution was stirred for 15 minutes (NOTE: adequate pre-activation time is important). Then, to a 2 dram (10 mL) vial containing IPNBSH (1.2 equiv.) and K_2CO_3 (2.0 equiv.), the allylic carbonate/[Rh]/$P(OPh)_3$ solution was added, followed by an MeCN rinsing (to make a 0.30 M solution). The vial was capped with a PTFE-lined septum, removed from the glovebox and stirred at the indicated temperature. After 18 hours the solvent was removed and the crude reaction mixture was dissolved in THF (2 mL), water (1 mL), TFE (1 mL), and AcOH (220 μL, 5.0 equiv.) were added. The reaction mixture was stirred for 2 hours after which hexane (50 mL) and saturated bicarbonate (50 mL) was added (EtOAc was used for polar products). The organic layer was washed with brine, dried with Na_2SO_4, concentrated, and purified by column chromatography (generally hexane/EtOAc, or pentane for volatile products). Unless specifically noted, the E/Z and regioisomer ratios were ≥95:5.

1.8.2 General Procedure (No Glovebox) All glassware was rigorously dried under vacuum using a heat gun. To a 1 dram (5 mL) vial was added $[Rh(COD)Cl]_2$ (0.050 – 0.075 equiv. Rh; a slight increase in catalyst loading was required for the more slowly reacting substrate in Table 3, entry 1 to ensure >90% conversion and >85% yield of aminated product), the vial was capped with a PTFE lined septa cap and placed under N_2. MeCN (150 μL) and $P(OPh)_3$ (0.10 – 0.15 equiv.) was added via syringe and the solution was stirred for 5 minutes before being transferred to a vial containing allylic carbonate (1.0 equiv.) using MeCN (150μL). To a 1 dram (5 mL) vial was added

IPNBSH (1.2 equiv.) and K_2CO_3 (2.0 equiv.). The vial was then placed under N_2. The solution of catalyst and allylic carbonate was transferred to the IPNBSH-containing vial by syringe using 200μL MeCN after stirring for 15 minutes. The reaction mixture was stirred for 24 hours at 40 °C (Table 3, entry 1) or room temperature (Table 3, entry 6). The remainder of the procedure is identical to that described above.

1.8.3 General Procedure Gram Scale Reaction (No Glovebox), equation 3 To a 4 dram (20 mL) vial was added $[Rh(COD)Cl]_2$ (100 mg, 0.20 mmol, 0.05 equiv. Rh), the vial was capped with a PTFE lined septa cap and placed under N_2. MeCN (10 mL) and $P(OPh)_3$ (220 μL, 0.84 mmol) was added via syringe and the solution was stirred for 5 minutes before the allylic carbonate (2.30 g, 7.88 mmol) was added as a MeCN solution (5 mL). To a round bottom flask was under N_2 was added IPNBSH (2.28 g, 8.80 mmol) and K_2CO_3 (2.25 g, 16.3 mmol). The solution of catalyst and allylic carbonate was added via syringe after stirring for 15 minutes to the round bottom flask along with additional MeCN (20 mL). The reaction mixture was stirred under a positive pressure of N_2 for 24 hours, after which the reaction was diluted with CH_2Cl_2 (100 mL) and passed over a plug of Celite and concentrated. The crude reaction mixture was dissolved in THF/TFE/water (2:1:1, 30 mL total) and AcOH was added (1 mL). The reaction mixture was stirred for 2 hours after which CH_2Cl_2 (100 mL) was added along with saturated aqueous $NaHCO_3$. The organic layer was collected and the aqueous layer was washed with additional CH_2Cl_2 (2 x 50 mL). The combined organic fractions were dried with Na_2SO_4, concentrated and the product was isolated by column chromatography (20:1 to 10:1 Hex/EtOAc) in 81% yield (1.40 g) as a pale yellow oil.

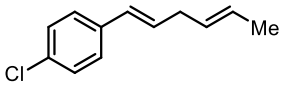


Product 1.96[75] Prepared according to the General Procedure from the corresponding methyl carbonate (165 mg, 0.70 mmol) at 40 °C. Isolated in 62% yield after purification by column chromatography (pentane) as a colorless oil, *E/Z* = 94:6.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.31 – 7.28 (m, 2H), 7.21 – 7.18 (m, 3H), 5.63 – 5.57 (m, 1H), 5.55 – 5.51 (m, 1H), 3.33 (d, *J* = 6.8 Hz, 2H), 1.70 (m, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 141.3, 130.2, 128.6, 128.5, 126.5, 126.0, 39.2, 18.0;

HRMS (LCMS EI): calcd for $C_{10}H_{12}$ $[M]^+$ 132.0939, found 139.0940.

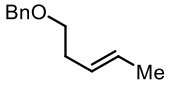


Product 1.97 Prepared according to the General Procedure from the corresponding methyl carbonate (106 mg, 0.40 mmol). Isolated in 57% yield after purification by column chromatography (40:1 pentane/Et_2O), *E/Z* = 94:6.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.25 – 7.22 (m, 4H), 6.31 (d, *J* = 15.9 Hz, 1H), 6.17 (dt, *J* = 15.8, 6.7 Hz, 1H), 5.50 – 5.47 (m, 2H), 2.87 – 2.85 (m, 2H), 1.68 (d, *J* = 5.1, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 136.4, 132.6, 130.2, 129.2, 128.8 (2), 127.4, 126.7, 36.1, 18.1;

HRMS (LCMS EI): calcd for $C_{12}H_{13}Cl$ $[M]^+$ 192.0706, found 192.0700.



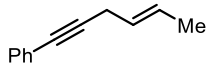
Product 1.98[80] Prepared according to the General Procedure from the corresponding methyl carbonate (100 mg, 0.40 mmol) at 40 °C with 5% $[Rh(COD)Cl]_2$ and 20% $P(OPh)_3$. Isolated in

79% yield after purification by column chromatography (20:1 Hex/EtOAc) as a colorless oil (*E/Z* = 94:6).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.35 – 7.32 (m, 4H), 7.28 (m, 1H), 5.57 – 5.42 (m, 2H), 4.52 (s, 2H), 3.48 (t, *J* = 6.9 Hz, 2H), 2.32 (m, 2H), 1.66 (dd, *J* = 8.1, 1.4 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 138.8, 128.5, 127.8, 127.7 (2), 127.1, 73.1, 70.4, 35.3, 18.2;

HRMS (LCMS EI): calcd for $C_{12}H_{16}O$ $[M]^+$ 176.1201, found 176.1200.

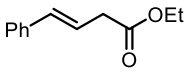


Product 1.99 Prepared according to the General Procedure from the corresponding methyl carbonate (161 mg, 0.70 mmol) at 40 °C with 5% $[Rh(COD)Cl]_2$ and 20% $P(OPh)_3$. Isolated in 64% yield after purification by column chromatography (Hex/EtOAc gradient).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.43 – 7.41 (m, 2H), 7.29 – 7.26 (m, 3H), 5.77 (m, 1H), 5.51 (m, 1H), 3.13 (m, 2H), 1.72 (m, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 131.7, 128.3, 127.8, 127.1, 125.2, 124.0, 87.8, 82.3, 22.8, 17.8;

HRMS (LCMS EI): calcd for $C_{12}H_{12}$ $[M]^+$ 156.0939, found 156.0942.

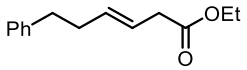


Product 1.100[81] Prepared according to the General Procedure from the corresponding methyl carbonate (106 mg, 0.40 mmol) at room temperature. Isolated in 66% yield after purification by column chromatography (pentane/Et_2O gradient) as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.38 (d, *J* = 7.4 Hz, 2H), 7.34 – 7.31 (m, 2H), 7.24 (m, 1H), 6.50 (d, *J* = 15.9 Hz, 1H), 6.31 (dt, *J* = 15.8, 7.0 Hz, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 3.24 (d, *J* = 7.7 Hz, 2H), 1.29 (q, *J* = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 171.8, 137.1, 133.5, 128.7, 127.7, 126.5, 122.1, 61.0, 38.7, 14.4;

HRMS (LCMS ESI): calcd for $C_{12}H_{14}NaO_2$ $[M+Na]^+$ 213.0886, found 213.0887.

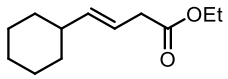


Product 1.101[82] Prepared according to the General Procedure from the corresponding methyl carbonate (117 mg, 0.40 mmol) at room temperature. Isolated in 71% yield after purification by column chromatography (10:1 Hex/EtOAc) as a light yellow oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.30 – 7.26 (m, 2H), 7.20 – 7.17 (m, 3H), 5.59 (m, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.02 (q, *J* = 6.1 Hz, 2H), 2.70 (t, *J* = 7.7 Hz, 2H), 2.37 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 172.3, 142.0, 133.9, 128.6, 128.5, 126.0, 122.5, 60.7, 38.3, 35.8, 34.4, 14.4;

HRMS (LCMS ESI): calcd for $C_{14}H_{18}NaO_2$ $[M+Na]^+$ 241.1199, found 241.1199.

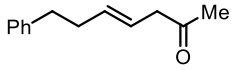


Product 1.102[83] Prepared according to the General Procedure from the corresponding methyl carbonate (190 mg, 0.68 mmol) at room temperature with 5% $[Rh(COD)Cl]_2$ and 20% $P(OPh)_3$. Isolated in 69% yield after purification by column chromatography (Hex/EtOAc gradient) as a colorless oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 5.52 – 5.46 (m, 2H), 4.13 (q, *J* = 7.0 Hz, 2H), 3.00 (d, *J* = 5.6 Hz, 2H), 1.95 (m, 1H), 1.74 – 1.56 (m, 6H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.19 – 1.02 (m, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 172.4, 140.6, 119.3, 60.5, 40.7, 38.3, 32.9, 26.2, 26.1, 14.3;

HRMS (LCMS ESI): calcd for $C_{12}H_{20}NaO_2$ $[M+Na]^+$ 219.1356, found 219.1357.

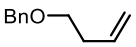


Product 1.103 Prepared according to the General Procedure from the corresponding methyl carbonate (176 mg, 0.60 mmol) at room temperature. Isolated in 56% yield after purification by column chromatography (10:1 Hex/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.30 – 7.26 (m, 2H), 7.20 – 7.16 (m, 3H), 5.62– 5.52 (m, 2H), 3.10 (d, *J* = 6.1 Hz, 2H), 2.70 (t, *J* = 7.4 Hz, 2H), 2.38 (m, 2H), 2.10 (s, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 207.6, 141.8, 134.6, 128.6, 128.5, 126.0, 122.7, 47.8, 25.8, 34.4, 29.5;

HRMS (LCMS EI): calcd for $C_{13}H_{16}O$ $[M]^+$ 188.1201, found 188.1203.

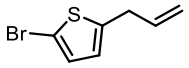


Product 1.104 Prepared according to the General Procedure from the corresponding methyl carbonate (142 mg, 0.60 mmol) at 40 °C with 5% $[Rh(COD)Cl]_2$ and 20% $P(OPh)_3$. Isolated in 78% yield after purification by column chromatography (Hex/EtOAc 40:1) as a colorless oil.

^{1}H NMR ($CDCl_3$, 498 MHz) δ 7.38 – 7.33 (m, 4H), 7.30 (m, 1H), 5.85 (m, 1H), 5.14 – 5.05 (m, 2H), 4.54 (s, 2H), 3.54 (t, *J* = 5.2 Hz, 2H), 2.41 – 2.38 (m, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.6, 135.4, 128.5, 127.8, 127.7, 116.5, 73.0, 69.7, 34.4;

HRMS (LCMS EI): calcd for $C_{11}H_{14}O$ $[M]^+$ 162.1045, found 162.1042.

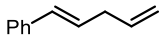


Product 1.105 Prepared according to the General Procedure from the corresponding methyl carbonate (83 mg, 0.30 mmol) at 40 °C with 5% $[Rh(COD)Cl]_2$ and 20% $P(OPh)_3$. Isolated in 52% yield after purification by column chromatography (Hex/EtOAc gradient) as a colorless oil.

^{1}H NMR ($CDCl_3$, 498 MHz) δ 6.87 (d, *J* = 3.7 Hz, 1H), 6.57 (dt, *J* = 3.7, 1.1 Hz, 1H), 5.93 (m, 1H), 5.19 – 5.10 (m, 2H), 3.50 (m, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.6, 135.6, 129.6, 125.0, 116.8, 109.6, 34.5;

HRMS (LCMS EI): calcd for C_7H_7SBr $[M]^+$ 203.9431, found 203.9431.



Product 1.106 Prepared according to the General Procedure from the corresponding methyl carbonate (131 mg, 0.60 mmol) at 40 °C with 5% $[Rh(COD)Cl]_2$ and 20% $P(OPh)_3$. Isolated in 65% yield after purification by column chromatography (Hex/EtOAc 40:1) as a colorless oil.

^{1}H NMR ($CDCl_3$, 498 MHz) δ 7.38 – 7.18 (m, 5H), 6.43 (d, *J* = 12.8 Hz, 1H), 6.24 (dt, *J* = 12.8, 5.2 Hz, 1H), 5.92 (m, 1H), 5.15 – 5.07 (m, 2H), 2.99 – 2.96 (m, 2H);

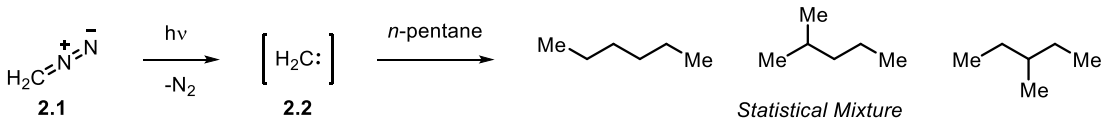
^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.8, 136.6, 131.0, 128.6, 128.3, 127.1, 126.2, 115.8, 37.1;

HRMS (LCMS EI): calcd for $C_{11}H_{12}$ $[M]^+$ 144.0939, found 144.0941.

Chapter 2 – Iridium-Catalyzed Cross-Coupling of Allylic Carbonates with α-Diazocarbonyl Compounds

2.1. Introduction

Carbenes are neutral, divalent carbon species bearing two non-bonding electrons that are highly reactive unless stabilized. Since early reports of indiscriminate reactivity,[84, 85] the use of carbene intermediates has been refined to a point of high selectivity and synthetic utility.[86, 87] Carbenes can be generated by the irradiation[84] or heating of diazo compounds.[88] However, the resulting free carbenes are highly reactive and exhibit little selectivity in bond forming processes. In Doering's original report of carbene insertion into alkane C–H bonds, diazomethane (**2.1**) was irradiated in the presence of pentane, producing a statistical mixture of isomers resulting from the insertion of CH_2 carbene (**2.2**) into each pentane C–H bond (Figure 2-1).[84] Development of techniques for the controllable generation and stabilization of carbenes has facilitated novel transformations; a survey of those important developments in the context of the Ir-catalyzed cross coupling chemistry developed in our lab follows.



2.1 2.2

Figure 2-1 Non-selective methylene insertion into pentane C-H bonds

In order for carbene intermediates to be synthetically useful, their reactivity must be controlled. This is typically done in one of two ways; persistent *N*-heterocyclic carbenes, first reported by Wanzlick in 1962[89] and isolated as the free carberne by Arduengo in 1991,[90] are stabilized by electronic as well as steric effects. Electronic stabilization occurs due to orbital overlap with the adjacent heteroatoms and steric protection arises from bulky groups installed on

those heteroatoms. Their high stability and strong σ-donating character makes NHCs common ancillary ligands in transition metal chemistry (Figure 2-2).

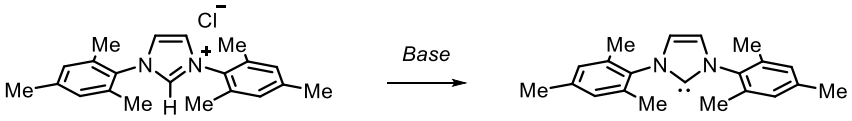


Figure 2-2 Deprotenation of HCl salt to give IMes NHC

Stabilization of carbenes can also be achieved through binding of the carbene directly to a metal center, as reported by Fischer in 1964.[91] What are likely the best known classes of metallocarbenes were highlighted by the awarding of the 2005 Nobel Prize in Chemistry to Grubbs, Schrock and Chauvin for the development of cross-metathesis (Figure 2-3).[92] In both Schrock and Grubbs catalysts, the active species is a metal alkylidene. Alkylidenes, also referred to as Schrock carbenes, form as the result of recombination of two triplet species and are distinct from singlet Fischer carbenes, which are viewed as being sigma-donors that also undergo π-backdonation. The naming conventions and distinctions between these species are still the subject of some debate.[93]

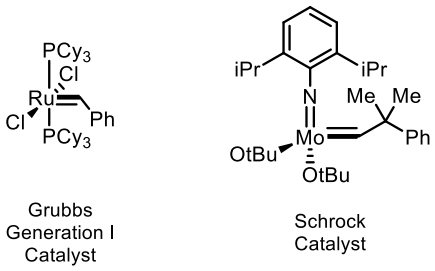


Figure 2-3 Representative Grubbs and Schrock metathesis catalysts bearing metal-stabilized carbenes

Metal-carbene complexes are typically derived *in-situ* from metal precatalysts and diazo compounds. The commonly accepted mechanism for metal-carbene complex formation from diazo compounds involves first, nucleophilic attack on the metal by the diazo (**2.3**), furnishing a zwitterionic metal alkyl complex (**2.4**), which then dediazotizes, liberating dinitrogen and forming a metal-carbene complex (**2.5**) (Figure 2-4).[94, 95]

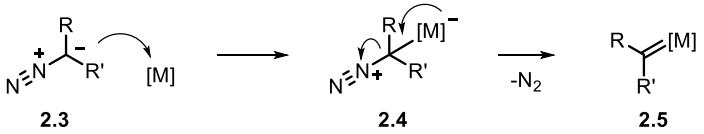


Figure 2-4 Schematic metal-carbene formation from a diazo compound

Generation of olefins (**2.8**) from α-alkyl carbenes (**2.7**) by way of a formal 1,2-hydride shift was first reported by Bamford and Stevens in 1952.[96] A diazo was generated *in-situ* from a *p*-toluene-sulfonylhydrazone (**2.6**) in the presence of an alkoxide base. Upon heat or light-induced dediazotization, the resulting carbene undergoes a 1,2-hydride shift, rendering the olefin product (Figure 2-5).[97, 98] If an alkyl lithium base is employed in place of an alkoxide base the net reaction is the same but it proceeds by a mechanism elucidated by Shapiro in 1967.[99, 100]

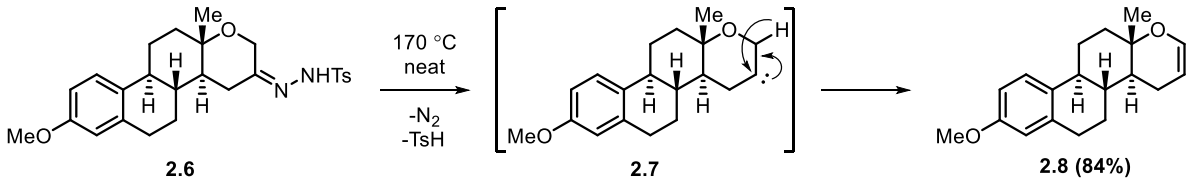


Figure 2-5 Bamford-Stevens olefination

Carbene insertions into E–H bonds (where E = O,[101] N,[102] S[103] or Si[104]) are well established transformations and commonly make use of transition metal catalysts to achieve controlled reactivity.[95, 105, 106] Rh, Cu, Ru, Fe and In have been shown to catalyze these reactions, with Rh

and Cu being most commonly used.[95, 107, 108] Ir has not been as widely reported to catalyze these reactions but has been shown to be effective for carbene intermediate insertions into Si–H bonds (Figure 2-6).[109] An Ir(salen) catalyst[110] effectively catalyzed the asymmetric insertion of α-aryl-α-diazoester-derived carbene intermediates into one Si–H bond of a disubstituted silane. High yield and enantioselectivity are achieved at low temperature across a small reported scope of substrates.

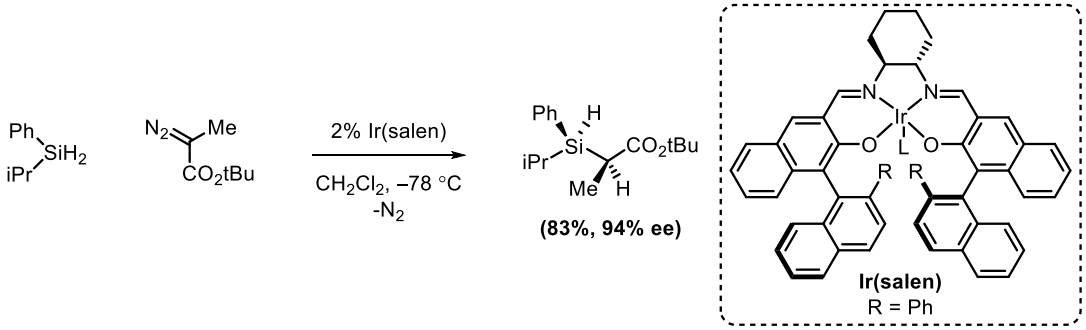


Figure 2-6 Ir(salen)-catalyzed carbene insertion into Si-H bond

Transition metal-catalyzed cyclopropanation reactions are well established chemical transformations[111, 112, 113] that often make use of diazo compounds as a carbene source. Fe, Mo, W, Pd, Cu and Rh have been reported to catalyze the reaction with varying degrees of efficiency.[114, 115] A small number of Ir-catalyzed variants have also been reported which employ bulky porphyrin and pincer ligands, giving moderate to good diasteroselectivity (Figure 2-7).[116, 117] The reported methodologies are generally limited to monosubstituted terminal alkenes and α-diazoesters, due to the low reactivity of α-aryl-α-diazoesters and internal olefins under the reaction conditions.

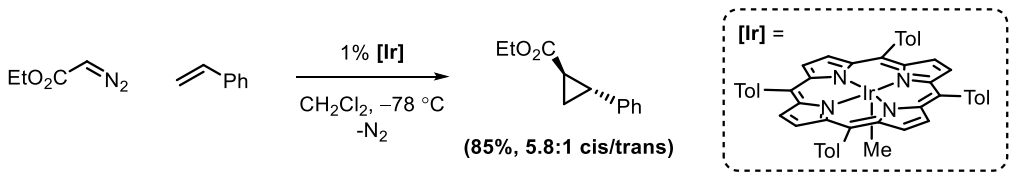


Figure 2-7 Ir-porphyrin-catalyzed olefin cyclopropanation

Controllable carbene insertion into C–H bonds by metal-carbene complexes is a well-established reaction.[118] The mechanism and factors influencing the reactivity of these reactions are well understood,[119, 120] which has enabled good chemo-,[121, 122] regio-,[123] diasetero-[124] and enantioselectivity[125] to be achieved. The majority of transition metal-catalyzed C–H insertions employ Rh and to a lesser extent, Cu.

A limited number of Ir-catalyzed C–H insertions of carbene and nitrene intermediates have been reported. Intramolecular C–H amination reactions employing aryl azides[126] and aryl sulfonyl azides[127] as nitrene precursors are high yielding but limited to an ortho-disubstituted aryl motif, although remote substitution on the ring is tolerated. Intermolecular amination reactions are less common, limited in scope and low yielding.[128] In the case of Ir-catalyzed carbene insertions into C–H bonds, the few reported reactions make use of complex porphyrin[116] and phebox[129] ligands. These reactions are generally high yielding and highly enantioselective, but the reported scope is limited. Only α-aryl, α-diazo esters have been reported to insert into the C-H bonds of THF, cycloheptatriene and substituted 1,4-cyclohexadiene. (Figure 2-8).

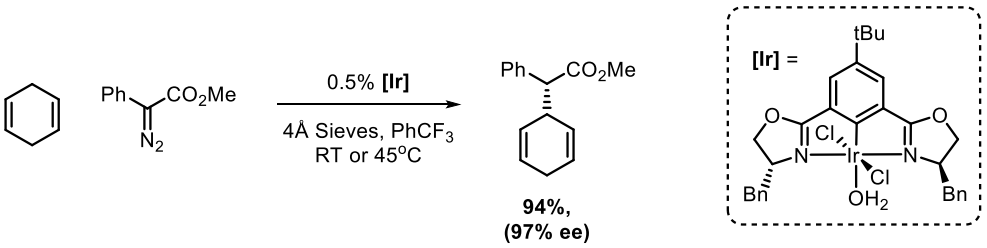


Figure 2-8 Enantioselective, Ir-catalyzed C-H carbene insertion

Carbene cross coupling reactions are not immediately recognizable as belonging to the same class of reactions as classical cross coupling reactions because they lack an obviously nucleophilic partner[130, 131] and mechanistic investigations have shown that, following the initial

oxidative addition step common to both reactions, they follow distinct pathways. Many diazo cross coupling reactions have been reported, most making use of Pd catalysts,[131, 132, 133] but a number of Cu,[134] Ni,[131] Rh,[131] and Ir-catalyzed[135] protocols have also been reported.

Of the various cross coupling protocols, the Heck reaction bears the greatest similarity to carbene cross coupling (Figure 2-9). Both reactions begin with the oxidative addition of an electrophile to the metal but after this step the mechanisms deviate. In the case of the Heck reaction,[136] complexation of an olefin (**2.9**) by the metal takes place, giving an η^2-olefin complex (**2.10**). Migratory insertion into the Pd–carbon bond gives a new Pd-carbon bond (**2.11**) and subsequent β-hydride elimination furnishes product (**2.12**).

In the case of carbene cross coupling, following oxidative addition to the metal center, a diazo compound (**2.14**) decomposes to give a metal-carbene complex (**2.15**). Migratory insertion gives compound **2.16**, which undergoes β-hydride elimination, regenerating the catalyst and giving product **2.17**.

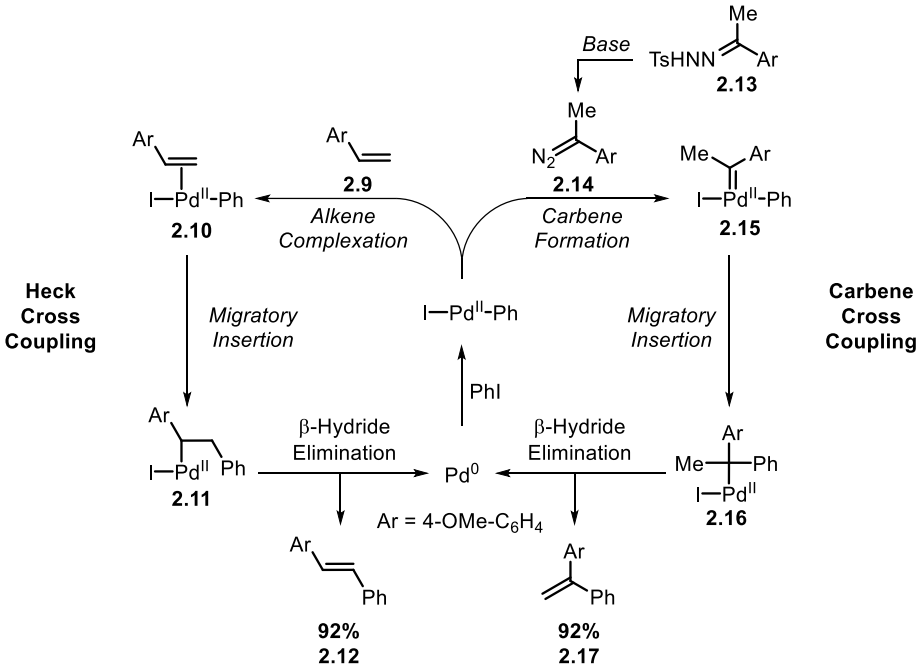


Figure 2-9 Comparison of Heck and carbene[137] cross coupling catalytic cycles

In an example of an Ir-catalyzed cross coupling type transformation (Figure 2-10), a pyrimidine-functionalized indoline (**2.18**) undergoes directed Ir C–H insertion, giving complex **2.19**. Binding of the diazo compound (**2.20**) to the Ir center (**2.21**) facilitates carbene formation and migratory insertion (**2.22**). Ethanolysis and decarboxylation occur in place of β-hydride elimination to regenerate the catalyst and give the alkylated indoline product (**2.23**).[135]

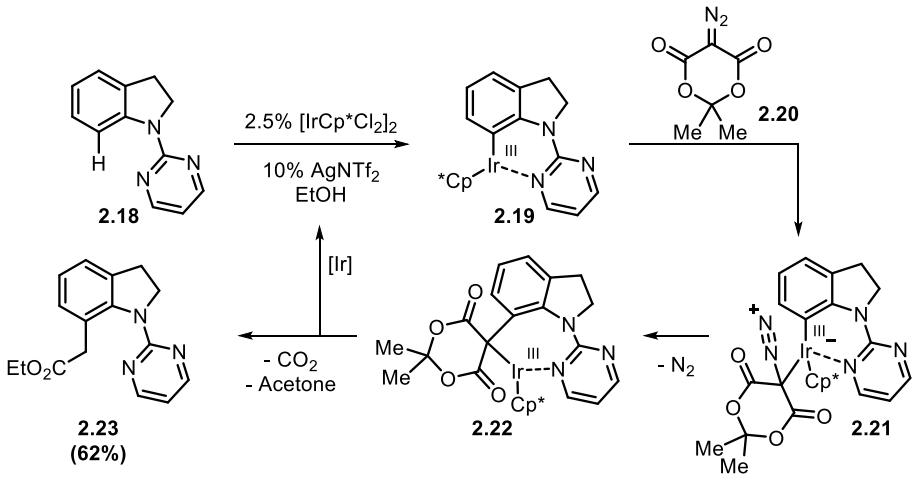


Figure 2-10 Ir-catalyzed, cross coupling of diazos and functionalized indoles by C–H activation

Cross coupling between allyl halides (**2.13**) and α-diazo carbonyl compounds (**2.14**) was achieved with a simple Pd catalyst at ambient temperature, forming a new C=C bond to give a 1,3-diene (**2.15**) (Figure 2-11).[138] High *E,E*-selectivity was achieved, although stringent control over the reaction time is necessary in order to achieve both high yield and selectivity. Diazo scope is limited to α-diazo, α-aryl carbonyl compounds. Allyl bromide is reported to react efficiently with diazo compounds bearing Me, OMe, Cl and Br-substituted aryl groups as well as a limited range of carbonyl functionality, primarily methyl ester and ketone. Two examples of allylic esters were also demonstrated. A limited range of 3-substituted allylic chlorides were explored, including three examples with 3,3-disubstitution, with moderate to good yield and high regioselectivity.

The authors propose three possible mechanistic pathways, all of which begin with the oxidative addition of an allyl chloride (**2.24**) to Pd, giving a π-allyl complex (Figure 2-11). Direct nucleophilic attack by the diazo (**2.25**) on the bound allyl fragment (Pathway A) or metal-catalyzed nucleophilic diazo (**2.25**) attack on the bound allyl fragment (Pathway B), would both give a free diazonium species that would decompose to give the observed product (**2.26)**. Pathway C is similar to that presented in Figure 2-9, where carbene formation from the diazo compound (**2.25**), followed by migratory insertion and β-hydride elimination also furnish product **2.26**. The precise mechanism of the reaction has not yet been established.

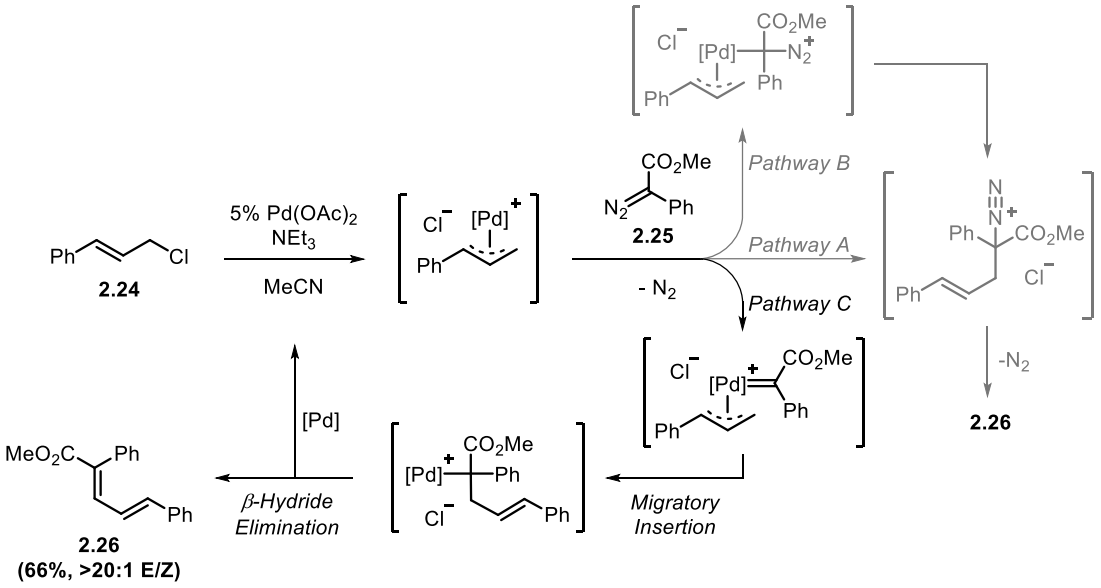


Figure 2-11 Proposed mechanistic pathways of Pd-catalyzed cross coupling between α-diazo esters and allyl halides

Repeating the reaction reported by Wang[138] (Figure 2-11) in our lab revealed it to be extremely sensitive to deviations from the reported procedure, particularly concentration and reaction time. The protocol presented in the published work was insufficiently detailed to successfully repeat the described results. The authors were contacted for a complete description of

the experimental protocol and following the more detailed procedure, the reported results were successfully replicated.

Our goal was to develop a complimentary method to the Pd-catalyzed systems reported by Wang,[138] which gives product regioisomers consistent with a mechanism under substrate steric control,[52] by leveraging the high selectivity for branched products inherent to Ir catalyzed systems (Figure 2-12).[139] It was predicted that an Ir-catalyzed analogue would yield the branched product (**2.28**). However, preliminary results revealed the Ir-catalysis to give exclusively linear product (**2.27**) and unlike the Pd-catalyzed reaction (**2.29**), to favor the thermodynamically disfavoured *Z*-*E*-diene. Only a single precatalyst (**2.30**), which has not previously been reported to interact with diazo compounds, gave an acceptable yield of product.

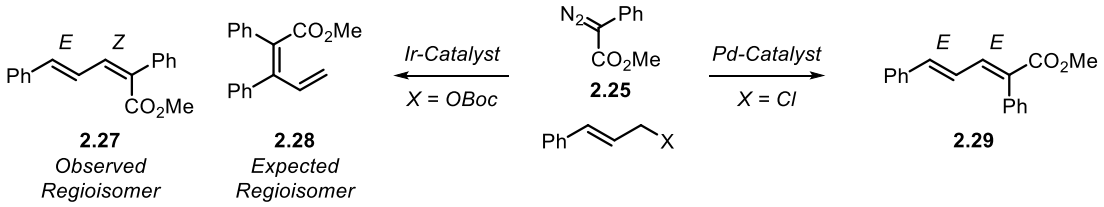


Figure 2-12 Comparison of expected and observed products of Ir and Pd-catalyzed carbene cross coupling with allylic partners

The method described below represents a new Ir-catalyzed method for the selective formation of *Z*,*E*-dienoates. Although the precise mechanism is unclear, we propose that the reaction proceeds as depicted in Figure 2-13. The precatalyst (**2.30**) is thought to be activated by the removal of the bound allyl fragment by the amine base, generating triethylammonium species **2.31** and Ir complex **2.33**. A unit of α-diazo ester (**2.25**) can interact with the resulting open coordination site, generating an Ir-carbene (**2.34**). Subsequent carbonate (**2.31** or **2.32)** ionization yields an η^1-bound allyl fragment instead of the typical η^3-allyl fragment as a result of the steric crowding of the system (**2.35**).[140] Migratory insertion of the nucleophilic allyl fragment into the

carbene (**2.36**) and subsequent β-hydride elimination liberate the product (**2.27 or 2.37**) and regenerate the catalyst (**2.33**).

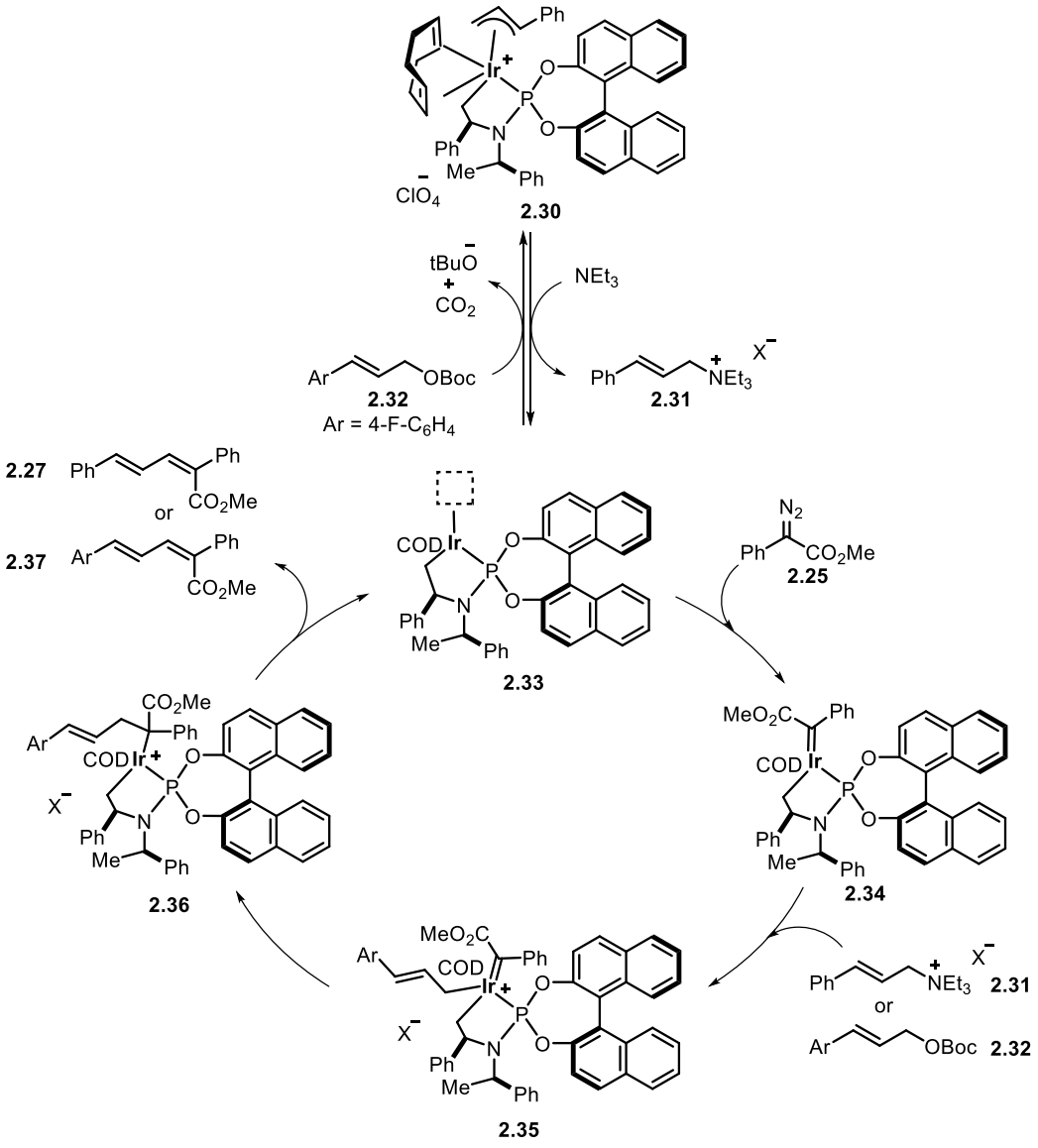


Figure 2-13 Proposed catalytic cycle for the Ir-catalyzed cross coupling of α-diazo esters and allylic carbonates

The origin of the *Z*-selectivity of this reaction remains unclear but there are indications that steric interactions between the catalyst and ester group of the diazo compound contribute. The *Z*-selectivity of the reaction increases with the steric bulk of the ester, from methyl (34:66 *E,E*/*Z,E*) to isopropyl (21:79 *E,E*/*Z,E*) to *tert*-butyl (14:86 *E,E*/*Z,E*), which is consistent with the established steric crowding of the catalyst system.[140]

2.2 Optimization Studies

2.2.1 Catalyst Optimization

Simple Ir and Rh precatalysts (**2.39** and **2.40**) were unsuitable for the cross coupling of α-diazo esters and allylic t-butyl carbonates, giving no more than trace yields and less than 10% conversion of the electrophile. Addition of a phosphite ligand had no effect (**2.41**).

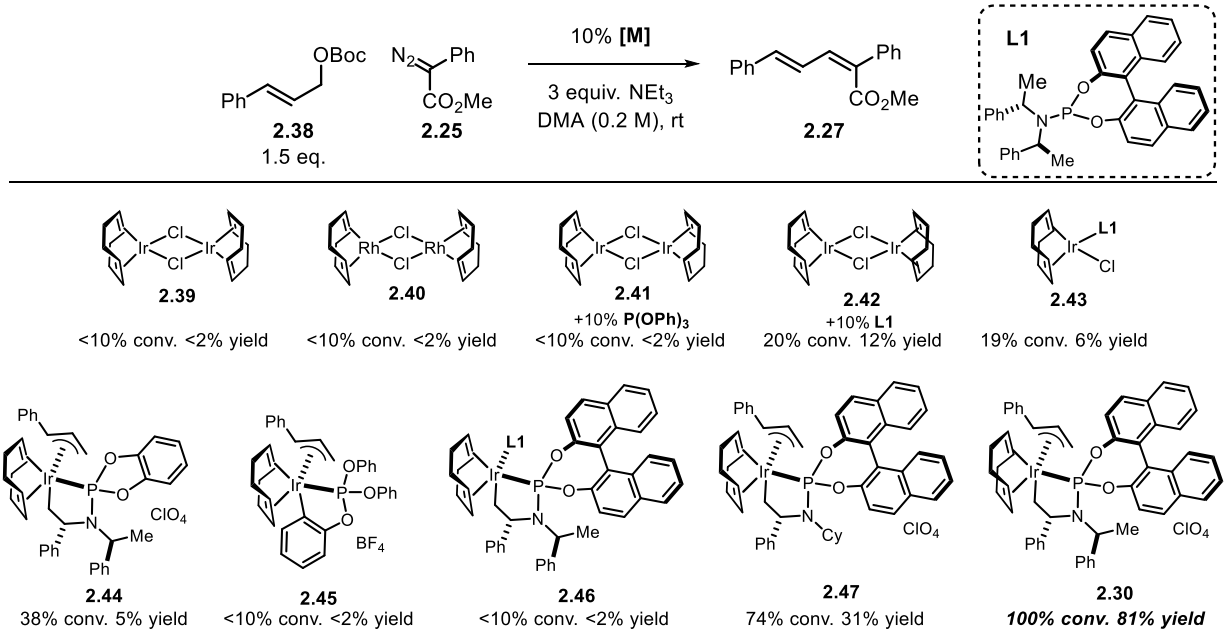
A series of cyclometallated catalysts were also tested. **2.44**, a simplified analogue of **2.30**, consumed electrophile unproductively and gave very little product. A simple cyclometallated complex (**2.45**), known to effectively form π-allyl complexes from allylic carbonates[141] was also unproductive under the tested conditions, giving less than 2% yield and 10% electrophile conversion (Table 2-1).

The optimal catalyst proved to a cycllometalated Ir species (**2.30**) originally developed for asymmetric, allylation[142] which was being studied in our lab for an unrelated transformation. Typically, the catalyst is formed in-situ from $[Ir(COD)Cl]_2$ and a phosphoramidite ligand in the presence of base,[143, 144] but the use of pre-formed catalysts has also been reported.[139] In-situ formation of **2.30** from $[Ir(COD)Cl]_2$ and **L1** (**2.42**) gave a greatly reduced yield compared to the pre-formed species. Two complexes (**2.43** and **2.46**) known to be a resting state of **2.30** in allylic substitution reactions[140] were similarly unproductive.

Replacement of the pendant phenethyl amine substituent, which has been shown not to have an effect on the effectiveness of the catalyst in amination reactions,[48] with a cyclohexyl group (**2.47**) had a dramatic, negative effect on the yield of carbene cross coupling reaction. An achiral cyclometalated species which was reported recently by Hartwig as an effective allylic allylation catalyst[141] was unreactive under these conditions. Of all the tested catalyst systems, only **2.30** gave acceptable yield of product.

Complex **2.30** is well established as a highly active catalyst for the asymmetric nucleophilic addition to allylic systems. Enantioselective allylation by C, N and O nucleophiles[142] have been the subject of intense study, particularly by the groups of Hartwig and Helmchen; as a result, the mechanism by which allylation takes place is very well understood.[143] The modular nature of the catalyst system enables derivatives to be readily synthesized and the reactivity tuned as a result. [48, 139, 145, 146, 147] In every case, branched products are strongly favored. There appear to be no reports of this type of catalyst system favoring linear products, generating carbenes, or forming new double bonds.

Table 2-1. Select precatalysts tested for the cross coupling of allylic carbonates and α-diazo esters

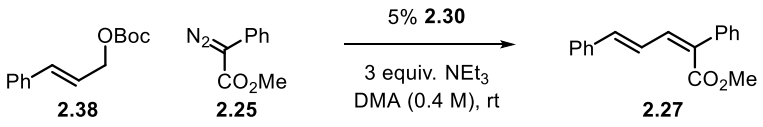


18 h. Conversions and yields determined by calibrated ^{1}H NMR, E/Z = 67:33

2.2.2 Solvent Optimization

A survey of solvents revealed a significant solvent effect, with DMA giving the highest yield and reproducibility (Table 2-2, Entry 1). Non-polar solvents were ineffective, largely due to low solubility of **2.30** (Table 2-2, Entries 5, 7, 8), and higher solvent polarity did not correlate with improved yield (Table 2-2, Entries 2-4, 9). Only DMA and DMF gave substantially higher yield that the other tested solvents. DMA was selected as the optimal solvent due to inconsistent yields obtained in DMF (Table 2-2).

Table 2-2. Effect of solvent on the Ir-catalyzed cross coupling of allyl carbonates and α-diazo esters



entry	Solvent	Remaining **2.38** (%)	yield (%)	*E,E* to *Z,E*
1	**DMA**	**67**	**26**	**36:64**
2	DCE	93	14	40:60
3	DMSO	106	2	ND
4	NMP	66	2	ND
5	PhCl	82	10	42:58
6	DMF	55	27	43:57
7	Dioxane	69	9	43:57
8	PhMe	64	9	47:53
9	DCM	94	12	47:53

150% electrophile, 18 h. Conversions and yields determined by calibrated ^{1}H NMR

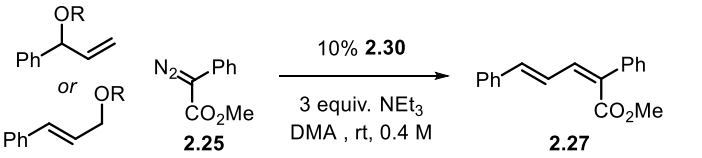
2.2.3 Leaving Group Optimization

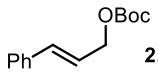
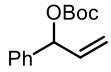
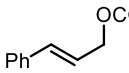
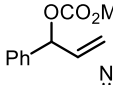
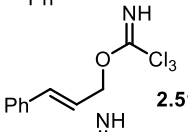
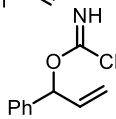
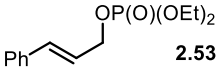
Examination of a selection of leaving groups (Table 2-3) revealed linear *tert*-butyl carbonates (**2.38**) to give the highest yield of all tested groups. Trichloroacetimidates (**2.51** and **2.52**) proved to be unsuitable under the tested conditions, giving less than 10% yield of the desired product, with most of the material decomposing unproductively. Phosphonate esters (**2.53**) were also prone to unproductive decomposition, resulting in significant side-product formation and reduced yield compared to carbonate electrophiles. *tert*-Butyl and methyl carbonates both resulted in greater product formation than other tested electrophiles but reactions with methyl carbonate electrophiles (**2.49**, **2.50**) produced significant side products, resulting from methoxide attack on the Ir-π allyl species, to form allylic ethers. In the case of *tert*-butyl carbonates, no such side products were detected.

Both branched (**2.48**, **2.50**) and linear (**2.38**, **2.49**) carbonate electrophiles were tested and it was determined that branched electrophiles rearranged *in situ* to the linear isomer under the reaction conditions. It is not clear whether branched electrophiles formed metal π-allyl species directly or if rearrangement to the linear isomer was required in order for oxidative addition to

proceed. Branched methyl and *tert*-butyl carbonate electrophiles both gave reduced yield relative to their respective linear isomers, leaving linear allylic *tert*-butyl carbonates as the optimal coupling partner.

Table 2-3. Effect of allylic partner identity on the Ir-catalyzed cross coupling of allylic substrates and α-diazo esters



entry	electrophile	conv. (%)	yield (%)	*E,E* to *Z,E*
1[a]	 **2.38**	**100**	**81**	**37:63**
2[a,b]	 **2.48**	150	72	36:64
3[c]	 **2.49**	>190	18[b]	46:54
4[d]	 **2.50**	86	46	54:46
5[e]	 **2.51**	200	<10	ND
6[e]	 **2.52**	200	<10	ND
7[d]	 **2.53**	150	35	70:30

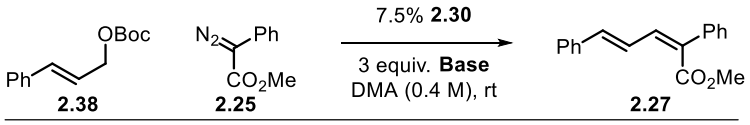
18 h. Conversions and yields determined by calibrated ^{1}H NMR. [a] 1.5 equiv. allylic substrate [b] Conversion to linear OBoc observed (42%). [c] 2 equiv. allylic substrate [d] 0.2 M, 1.5 equiv. allylic substrate. [e] 0.2 M, 5% **2.30**, 2 equiv. allylic substrate

2.2.4 Base Optimization

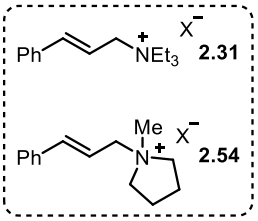
A series of common amine bases were surveyed and NEt_3 was observed to give the highest product yield (Table 2-4, Entry 1). *N*-methyl pyrrolidine also gave product but with reduced yield and selectivity (Table 2-4, Entry 3). Trace quantities of **2.31** and significant quantities of **2.48** were

observed as side products in the respective reactions. All other bases tested gave only trace product formation. Catalytic quantities of NEt_3 and *N*-methyl pyrrolidine base could be employed if K_2CO_3 was added as a terminal base but further studies were not undertaken because the additional complexity of a two-base system appeared to provide no advantages over the use of stoichiometric NEt_3.

Table 2-4. Effect of base on the Ir-catalyzed cross coupling of an allylic carbonate and α-diazo ester



entry	Base	conv. (%)	yield (%)	*E,E* to *Z,E*
1	**NEt_3**	**96**	**31**	**39:61**
2	$HNEt_2$	200	0	-
3	N-methyl pyrrolidine	200	20	58:42
4	Lutidine	124	<2	-
5	Pyridine	75	<2	-
6	DABCO	200	<2	-
7	DBU	200	<2	-

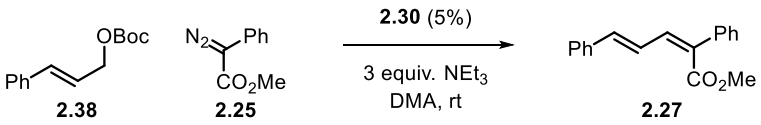


2 equiv. electrophile, 24 h. Conversions and yields determined by calibrated ^{1}H NMR.

2.2.5 Concentration Optimization

A significant concentration effect was observed in the optimized reaction. Product formation increased proportionally with reaction concentration between 0.1 M and 0.4 M (Table 2-5, Entries 2-4). Further increasing the concentration to 1.0 M gave only a slight increase in yield (Table 2-5, Entry 1). Above 0.4 M reagent handling becomes inconvenient, so 0.4 M was selected as the optimal balance between yield and convenience.

Table 2-5. Effect of reaction concentration on the Ir-catalyzed cross coupling of an allylic carbonate and α-diazo ester



2.38 **2.25** **2.27**

entry	Concentration (M)	conv. (%)	yield (%)	*E,E* to *Z,E*
1	1.0	80	47	34:66
2	0.4	80	41	35:65
3	0.2	74	23	35:35
4	0.1	54	12	40:60

2 equiv. electrophile, 21 h. Conversions and yields determined by calibrated ^{1}H NMR

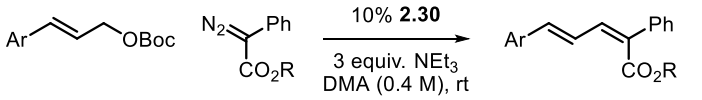
2.3. Reaction Scope

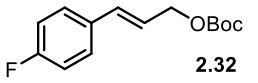
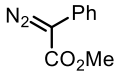
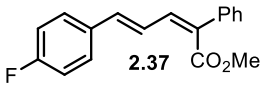
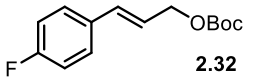
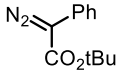
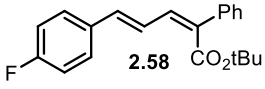
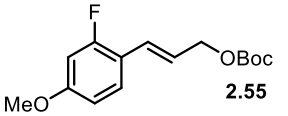
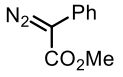
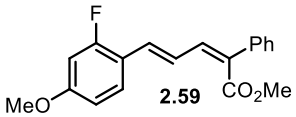
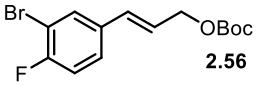
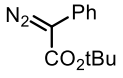
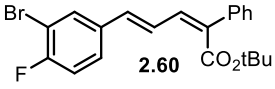
Under the optimized conditions, electron rich, neutral and deficient aryl substituents were tolerated on both the diazo and carbonate coupling partners. *Z*-Selectivity was strongly influenced by the steric bulk of the ester group, with bulkier groups giving higher selectivity. Reactions were very clean, with little side product observed.

2.3.1 Allylic Carbonates

A selection of allylic carbonates were investigated with two diazo coupling partners. Yields were generally high, with electron poor (**2.32**, **2.56**) aryl groups, as well as substrates bearing both electron withdrawing and donating substituents being tolerated (**2.55**) (Table 2-6).

Table 2-6. Ir-catalyzed cross coupling of functionalized allylic carbonates and simple α-diazo esters



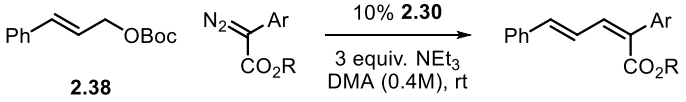
entry	Electrophile	Diazo	Product	Yield (%)	*E,E* to *Z,E*
1	 **2.32**	 **2.25**	 **2.37**	68	38:62
2	 **2.32**	 **2.57**	 **2.58**	72	19:81
3	 **2.55**	 **2.25**	 **2.59**	61	41:59
4	 **2.56**	 **2.57**	 **2.60**	69	28:72

1.5 equiv. electrophile, 21 h. Yields are of isolated material.

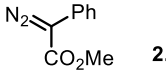
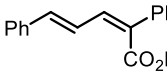
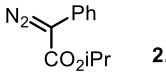
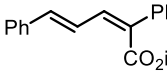
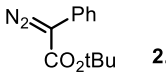
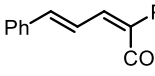
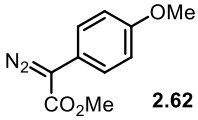
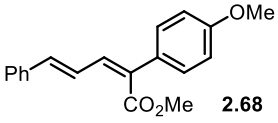
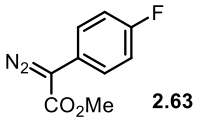
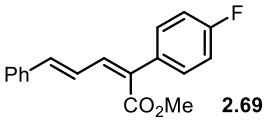
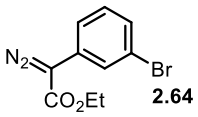
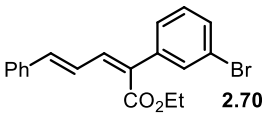
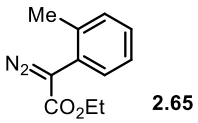
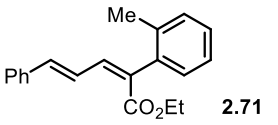
2.3.2 Diazo Compounds

A range of diazo compounds with varying substitution on both the ester and aryl groups were also investigated. The steric bulk of the ester group had little effect on the yield of the reaction, but was directly proportional to the *Z*-selectivity (Table 2-7, Entries 1-3). Electron rich diazo compounds exhibited similar steric sensitivity without significant effect on the yield of product (**2.62**). A fluorinated aryl group gave a good yield, although the selectivity was poor (**2.63**). Significantly, 3-bromo (**2.64**) and 2-methyl (**2.65**) substitution rendered the reaction non-selective, with 3-bromo substitution also resulting in a decrease in reactivity. Elevating the reaction temperature gave **2.70** in acceptable yield.

Table 2-7. Ir-catalyzed cross coupling of cinnamyl *tert*-butyl carbonate and functionalized α-diazo esters



2.38

entry	Diazo	Product	Yield (%)	*E,E* to *Z,E*
1	 **2.25**	 **2.27**	87	34:66
2	 **2.61**	 **2.66**	84	21:79
3	 **2.56**	 **2.67**	91	14:86
4	 **2.62**	 **2.68**	64	28:72
5	 **2.63**	 **2.69**	72	42:58
6	 **2.64**	 **2.70**	58	58:42
7	 **2.65**	 **2.71**	94[a]	55:45

1.5 equiv. electrophile, 21 h. Yields are of isolated material. [a] 35 °C

In many cases, the residual electrophile co-eluted with the product of the reaction upon purification by column chromatography. It was found that product loss due to contamination could be minimized by subjecting the product/electrophile mixture to additional catalyst and a simple 2° amine. This resulted in complete amination of the electrophile within four hours and an easily separable mixture without loss of product or degradation of selectivity (Figure 2-14).

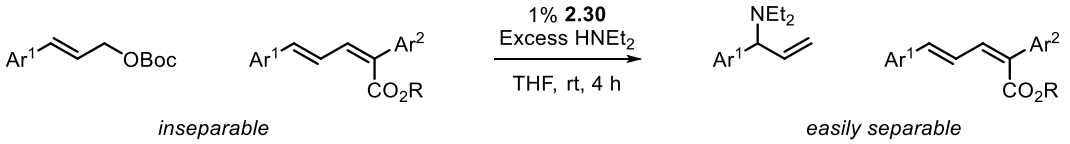
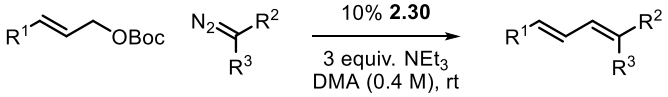


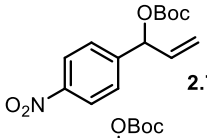
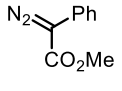
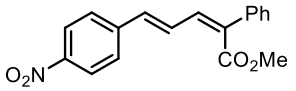
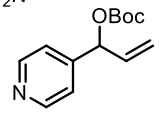
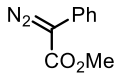
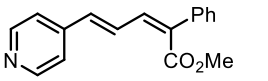
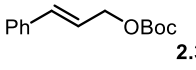
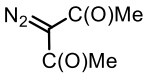
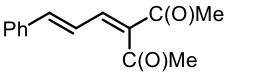
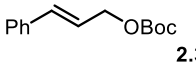
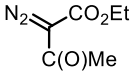
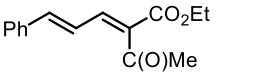
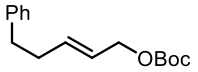
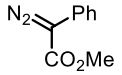
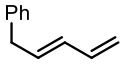
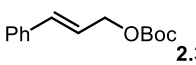
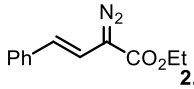
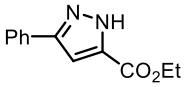
Figure 2-14 Excess carbonate removal by amination catalyzed by **2.30**

2.3.3 Incompatible Substrates

The reaction is not compatible with alkyl (**2.74**) and highly electron deficient allylic carbonates (**2.72**, **2.73**). Similarly, the only diazo substrates which furnished product bore both aryl and ester substitution. Diketone (**2.75**) and keto-ester (**2.76**) diazos were unreactive under the optimized conditions. An α,β-unsaturated diazo (**2.77**) primarily gave a known cyclization product (**2.8**), (Table 2-8).[148]

Table 2-8. Substrates currently incompatible with the Ir-catalyzed cross coupling of allylic carbonates and α-diazo esters



entry	Electrophile	Diazo	Product	Yield (%)
1	 **2.72**	 **2.25**	 **2.78**	6
2	 **2.73**	 **2.25**	 **2.79**	20
3	 **2.38**	 **2.75**	 **2.80**	0
4	 **2.38**	 **2.76**	 **2.81**	0
5	 **2.74**	 **2.25**	 **2.82**	Major Product
6	 **2.38**	 **2.77**	 **2.83**	Major Product

1.5 equiv. electrophile, 21 h. Yields determined by calibrated ^{1}H NMR

2.4 Stoichiometric Reactions

An equimolar reaction between catalyst **2.30** and diazo **2.25** in the absence of additional electrophile gave no detectable product, although base-induced decomposition of the catalyst was observed. Significant quantities of product formed in the presence of excess electrophile (**2.32**). The ratio of allylic carbonate (**2.32**) to precatalyst (**2.30**) in the reaction mixture is proportional to the observed ratio of products **2.27** and **2.37**. Addition of an allylic trialkyl ammonium species (**2.84**) in place of allylic carbonate gave significantly reduced yield. The low efficiency of this

coupling partner (Figrue 2-15) is inconsistent with the high yield of product derived from the bound catalyst alkyl fragment (**2.37**) when one equivalent of catalyst is present This suggests that the proposed mechanism (Figure 2-13) may not accurately reflect the true nature of the reaction.

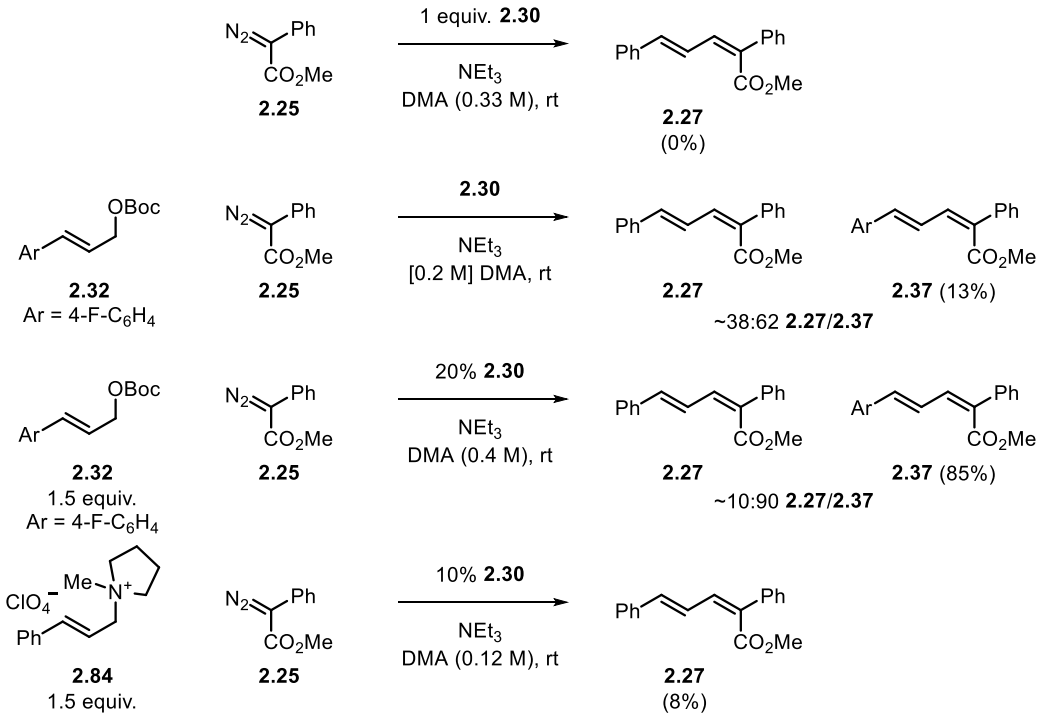


Figure 2-15 Stoichiometric reactions of **2.30** with diazo (**2.25**), allylic carbonate (**2.32**) and allylic trialkylammonium (**2.84**)

Further exploration of the reaction scope is warranted, including electron rich allylic carbonates (**2.85** and hindered α,β-unsaturated diazos (**2.86**), which may be less prone to side product formation (**2.83**). Substrates containing functionality potentially reactive with both carbene intermediates and **2.30** would be indicative of the selectivity of the method (**2.87**). Allylic carbonates with extended π systems (**2.87**) have not been explored and may facilitate the selective synthesis of *E*,*E*,*Z*-trienoates (Figure 2-16).

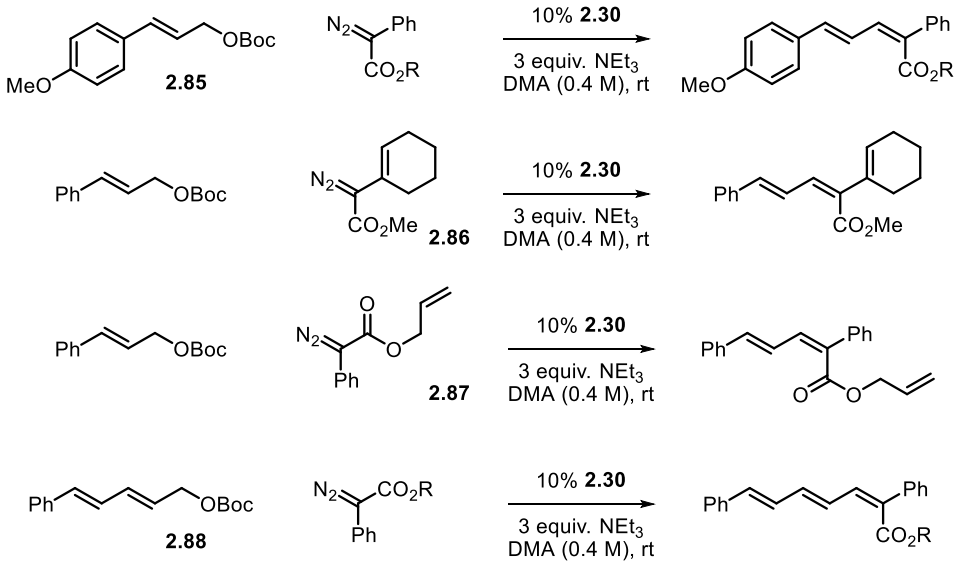


Figure 2-16 Select proposed future work

2.5 Summary

A *Z*-selective Ir-catalyzed cross coupling reaction between α-diazo esters and allylic carbonates has been developed. Electron rich, neutral and poor substrates are tolerated, furnishing *Z*,*E*-dienoates in moderate to good yield. Complimentary regioselectivity to that exhibited by Pd-catalysis is observed.[138] The reaction tolerates aryl substituents with a range of electron density on both the allylic carbonate and diazo, although ortho substituents on the diazo aryl ring have a negative effect on the selectivity of the reaction. Alkyl and highly electron deficient aryl allylic carbonates are currently incompatible with this methodology. The diazo coupling partner is also currently limited to substrates with both aryl and ester substituents.

Unlike the styrenyl substrates required for the acrylate olefination reported by Feng,[149] the easily prepared carbonate and diazo compounds employed in this chemistry may provide more convenient access to the same products.

The sole effective catalyst for this chemistry is well established for asymmetric addition of N, O and C nucleophiles to allylic electrophiles. It has not previously been reported to interact

with diazo compounds and has also not been reported to preferentially give linear product regioisomers. As such, the observed behavior is unprecedented for the catalyst system and warrants further study, with an aim to extend the chemistry of the Ir-mediated carbene coupling reaction.

2.6 Procedures and Characterization

2.6.1 General Procedure for Branched Allylic Alcohol Synthesis

Aldehydes were added to a flask equipped with a stir bar and placed under N_2 by evacuating/backfilling three time. 10 mL dry THF was then added by syringe and the reaction mixture cooled to – 78 °C in a dry ice/acetone bath. Vinylmagnesium bromide as a 1.0 M solution in THF (1.2 equiv.) was added dropwise by syringe. The reaction mixture was stirred until complete conversion of the aldehyde was observed by TLC, at which point the cooling bath was removed and 10 mL saturated NH_4Cl was added to quench the reaction. The aqueous layer was extracted three times with 10 mL EtOAc and the combined organic layers were washed with 20 mL brine before drying over Na_2SO_4. If necessary, the product was purified by column chromatography (Hex/EtOAc).

2.6.2 General Procedure for Rearrangement of Branched Allylic Alcohols[150]

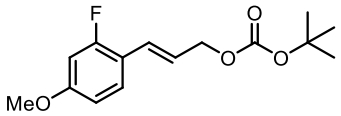
To a flask equipped with a stir bar was added branched allyic alcohol and a 4:1 mixture of THF and water (5 mL/mmol alcohol). Methanesulfonic acid (4 equiv.) was added dropwise while stirring and the mixture was stirred at 50 °C until complete conversion of the starting material was observed by TLC. If necessary, the product was purified by column chromatography (Hex/EtOAc).

2.6.3 General Procedure for Allylic *tert*-Butyl Carbonate Synthesis[151]

To a 4 dram (20 mL) vial was added allylic alcohol, Boc_2O (1.4 equiv), Bu_4NHSO_4 (0.03 equiv.) and a stir bar. CH_2Cl_2 (0.26 mL/mmol) was added and the vial was cooled to 0 °C in an ice

water bath while stirring. 0.3M NaOH (0.5mL/mmol) was added dropwise by syringe and the reaction mixture was stirred at 0 °C for 10 minutes, at which point the cooling bath was removed and the reaction mixture stirred at room temperature until complete conversion of the alcohol was observed by TLC or 24 hours had elapsed. The reaction was quenched by addition of saturated NH_4Cl and the aqueous layer extracted three times with EtOAc. The combined organic fractions were washed with brine and dried over Na_2SO4. The solvent was removed under vacuum and the crude product was stirred with imidazole (0.5 equiv.) in ethanol (1.0 mL/mmol) for 5 min. Upon removal of the ethanol under vacuum, the crude mixture was purified by silica plug (Hex/EtOAc).

Substrates **2.32**,[152] **2.38**,[153] **2.56**,[153] and **2.57**[153] were prepared according to General Procedure 1 and spectroscopic data agreed with that reported.



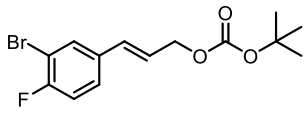
Substrate 2.55 Prepared according to the General Procedure 1 from the corresponding alcohol (336 mg, 1.2 mmol). Isolated in 46% yield after purification by flash chromatography (Hex/EtOAc gradient) as a clear colourless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35 (s, 1H), 6.73 (d, J = 16.0 Hz, 1H), 6.64 – 6.69 (m, 1H), 6.56 – 6.63 (m, 1H), 6.25 (dt, J = 16.1, 7.0 Hz, 1H), 4.67 – 4.75 (m, 2H), 3.80 (s, 3H), 1.50 (s, 9H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 161.1 (J_{CF} = 250 Hz), 160.6 (J_{CF} = 250 Hz), 153.4, 128.2 (J_{CF} = 5.4 Hz), 126.8 (J_{CF} = 2.8 Hz), 123.0 (J_{CF} = 4.9 Hz), 116.6 (J_{CF} = 12.6 Hz), 110.4 (J_{CF} = 3.1 Hz), 101.6 (J_{CF} = 25.8 Hz), 82.2, 67.8, 55.6, 27.8;

^{19}F NMR ($CDCl_3$, 377 MHz) δ −115.3;

HRMS (EI): calcd for $C_{15}H_{19}FO_4$ $[M]^+$ 282.1267, found 282.1269.



Substrate 2.56 Prepared according to the General Procedure 1 from the corresponding alcohol (831 mg, 2.5 mmol). Isolated in 89% yield after purification by flash chromatography (Hex/EtOAc gradient) as a white solid.

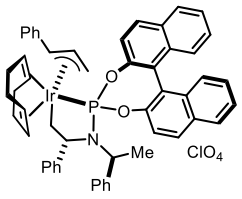
^{1}H NMR ($CDCl_3$, 400MHz) δ 7.57 (m, 1H), 7.28 (m, 1H), 7.06 (m, 1H), 6.56 (m, 1H), 6.22 (m, 1H), 4.70 (dd, J = 6.2, 1.4 Hz, 2H), 1.44 – 1.54 (s, 9H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 158.7 (J_{CF} = 248.7 Hz), 153.3, 134.0 (J_{CF} = 4.7 Hz), 131.7 (J_{CF} = 0.9 Hz), 131.5, 127.1 (J_{CF} = 7.2 Hz), 124.3 (J_{CF} = 2.5 Hz), 116.6 (J_{CF} = 22.4 Hz), 109.4 (J_{CF} = 21.7 Hz), 82.4, 67.0, 27.8;

^{19}F NMR ($CDCl_3$, 176 MHz) δ −108.2;

HRMS (EI): calcd for $C_{14}H_{16}BrFO_3$ $[M]^+$ 330.0267, found 330.0261.

2.6.4 Procedure for Synthesis of 2.30



In a N_2-filled glovebox $[Ir(COD)Cl]_2$ (0.5 equiv.), P-N ligand O,O'-(S)-(1,1'-dinaphthyl-2,2'-diyl)-N,N-di-(S,S)-[2-phenylethylphosphoramidite] or O,O'-(R)-(1,1'-dinaphthyl-2,2'-diyl)-N,N-di-(R,R)-[2-phenylethylphosphoramidite] (1 equiv.) (prepared according to literature

procedure)[154] and THF (12 mL/mmol) were added to a 4 dram (20 mL) vial. Cinnamyl *tert*-butyl carbonate was added as a solution in THF and the mixture was stirred for 2 minutes. $AgClO_4$ was added as a solution in THF and the reaction mixture was stirred at room temperature until complete conversion of the ligand was observed by ^{31}P NMR spectroscopy. The reaction mixture was removed from the glovebox, filtered through Celite and concentrated to a viscous brown oil. The material was triturated by adding 7 mL Et_2O, followed by 7 mL pentane and the resulting yellow solid crushed against the walls of the vial. The supernatant was removed, 7 mL additional Et_2O added and the solid crushed again. The solid was re-dissolved in a minimum of CH_2Cl_2 and the above trituration steps repeated twice more. After decanting the supernatant for the final time no CH_2Cl_2 was added and the solid dried under high vacuum. Isolated in 96% yield as a >95% pure, pale yellow powder. Spectroscopic data agreed with that reported for analogous compounds.[155]

^{1}H NMR ($CDCl_3$, 500MHz) δ 8.30 (d, *J* = 8.8 Hz, 1H), 8.22 (d, *J* = 9.0 Hz, 1H), 8.05 – 8.12 (m, 2H), 7.82 (d, *J* = 9.0Hz, 1H), 7.72 (d, *J* = 9.0 Hz, 1H), 7.55 – 7.66 (m, 4H), 7.28 – 7.55 (m, 15H), 7.11 – 7.20 (m, 2H), 5.65 (m, 1H), 5.19 (m, 1H), 4.85 (m, 1H), 4.18 (m, 1H), 3.87 – 4.00 (m, 2H), 3.55 (m, 1H), 2.89 – 3.01 (m, 2H), 2.71 – 2.89 (m, 2H), 2.36 – 2.53 (m, 2H), 2.20 (m, 1H), 2.06 – 2.14 (m, 2H), 1.81 – 1.95 (m, 1H), 1.55 – 1.70 (m, 2H), 1.23 (m, 1H), 0.61 (d, *J* = 7.5 Hz, 3H);

^{31}P NMR ($CDCl_3$, 162MHz) δ 119.6.

2.6.5 General Procedure for α-Aryl Ester Synthesis

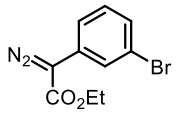
To a flask equipped with a stir bar was added $MgSO_4$ (5.5 equiv.), carboxylic acid (1.0 equiv.) and alcohol (14 equiv). Dichloromethane (4 mL/mmol) was added and the mixture stirred vigorously. Concentrated sulfuric acid (0.22 mL/mmol) was added slowly and the reaction progress was monitored by ^{1}H NMR spectroscopy. When maximum yield of the product was

observed the mixture was filtered through Celite, washed with water and neutralized with concentrated $NaHCO_3$. The organic layers were washed with brine, dried over Na_2SO_4 and the solvent removed by rotary evaporation. The residue was purified by flash chromatography to give the α-aryl ester.[156]

2.6.6 General Procedure for α-Diazo Ester Synthesis

To a flask equipped with a stir bar was added p-ABSA (4-acetamidobenzenesulfonyl azide) (1.2 equiv.) and ester. The flask was placed under N_2 by evacuating/backfilling three times, anhydrous MeCN (5 mL/mmol) was added and the mixture was cooled to 0 °C in an ice water bath. DBU (1.4 equiv.) was added dropwise and the mixture was stirred at room temperature overnight. Upon complete conversion of the starting material by TLC the mixture was diluted with 20 mL water and extracted with hexanes (5 x 10 mL) or until the organic layer was no longer yellow in colour. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent removed by rotary evaporation. The residue was purified by flash chromatography (Hex/EtOAc gradient) as a 95% pure clear, colorless oil.

Substrates **2.25**,[157] **2.59**,[156] **2.66**,[158] **2.67**,[87] **2.68**,[159] **2.69**,[160] **2.71**[161]were prepared according to General Procedure 1 and spectroscopic data agreed with that reported.



Substrate 2.64 Prepared according to the General Procedure from the corresponding α-aryl ester (288 mg, 1.1 mmol). Isolated in 43% yield after purification by flash chromatography (Hex/EtOAc gradient) as a red solid.

^{1}H NMR ($CDCl_3$, 700MHz) δ 7.69 (m, 1H), 7.39 (m, 1H), 7.29 (m, 1H), 7.23 (m, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 179.9, 164.6, 130.2, 128.6, 128.1, 126.5, 123.1, 122.1, 61.2, 14.5;

HRMS (EI): calcd for $C_{10}H_9BrN_2O_2$ $[M]^+$ 267.9845, found 267.9845.

2.7 Ir-Catalyzed Cross Coupling of α-diazo esters and Allylic Carbonates

2.7.1 General Procedure 1 (Room Temperature)

To a 2 dram (10 mL) vial containing a stirbar was added *tert*-butyl carbonate electrophile (0.75 mmol, 1.5 equiv.) and the catalyst (0.05 mmol, 0.1 equiv.) as a 1.25 mL DMA solution. After stirring 5 minutes, the diazo (0.50 mmol, 1.0 equiv.) was added. The resulting mixture was stirred for 2 minutes and triethylamine (1.5 mmol, 3 equiv.) was added by volume. The reaction mixture was stirred 18 hours, over which time the solution turned form orange to dark brown and significant pressure developed within the vial (Note: a headspace approximately 3 times the solution volume is necessary to prevent pressure buildup). Conversion and yield were judged by ^{1}H NMR of a 5 μL aliquot. The DMA was removed by diluting with 20 mL EtOAc, washing with 2 x 10 mL H_2O and 10 mL of brine, followed by drying over Na_2SO_4. The resulting mixtures was concentrated and purified by column chromatography (generally Hex/EtOAc). Products isomers were sometimes isolated as inseparable mixtures (as indicated).

2.7.2 General Procedure 2 (Elevated Temperature)

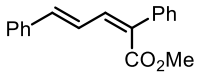
To a 2 dram (10 mL) vial containing a stirbar was added *tert*-butyl carbonate electrophile (0.75 mmol, 1.5 equiv.) and the catalyst (0.05 mmol, 0.1 equiv.) as a 1.25 mL DMA solution. After

stirring 5 minutes, the diazo (0.50 mmol, 1.0 equiv.) was added. The resulting mixture was stirred for 2 minutes and triethylamine (1.5 mmol, 3 equiv.) was added by volume. The reaction mixture was stirred 20 hours at 35 °C, over which time the solution turned form orange to dark brown and significant pressure developed within the vial (Note: a headspace approximately 3 times the solution volume is necessary to prevent pressure buildup). Conversion and yield were judged by ^{1}H NMR of a 5 μL aliquot. The DMA was removed by diluting with 20 mL EtOAc, washing with 2 x 10 mL of H_2O and 10 mL of brine, followed by drying over Na_2SO_4. The resulting mixtures was concentrated and purified by column chromatography (generally hexane/EtOAc). Products were isolated as pure or inseparable mixtures of isomers as indicated.

2.7.3 General Procedure 3 (Residual Electrophile Removal by Amination)

To a 2 dram (10 mL) vial containing a stirbar was added *tert*-butyl carbonate electrophile (0.75 mmol, 1.5 equiv.) and the catalyst (0.05 mmol, 0.1 equiv.) as a 1.25 mL DMA solution. After stirring 5 minutes, the diazo (0.50 mmol, 1.0 equiv.) was added. The resulting mixture was stirred for 2 minutes and triethylamine (1.5 mmol, 3 equiv.) was added by volume. The reaction mixture was stirred 18 - 48 hours, over which time the solution turned form orange to dark brown and significant pressure developed within the vial (Note: a headspace approximately 3 times the solution volume is necessary to prevent pressure buildup). Conversion and yield were judged by ^{1}H NMR of a 5 μL aliquot. The DMA was removed by diluting with 20 mL of EtOAc, washing with 2 x 10 mL of H_2O and 10 mL of brine, followed by drying over Na_2SO_4. The crude material was placed under N_2 in a stir bar-equipped 4 dram (20 mL) vial and **2.30** (0.01 equiv.) was added as a solution in dry THF (6 mL/mmol). Neat $HNEt_2$ (2 equiv.) was added by syringe and the mixture was stirred until full conversion of the carbonate was observed by TLC. The solvent was removed under vacuum and the resulting mixture was purified by column chromatography

(generally hexane/EtOAc). Products were isolated as pure or inseparable mixtures of isomers as indicated.

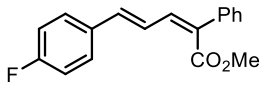


Product 2.27 Prepared according to the General Procedure 1 from the corresponding diazo (115 mg, 0.44 mmol). Isolated in 87% yield, *Z,E*/*E,E* = 66:34, after purification by flash chromatography (20:1 Hex/EtOAc) as a clear, pale yellow oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.64 (dd, *J* = 15.6, 11.3 Hz, 1H), 7.48 – 7.53 (m, 2H), 7.34 – 7.41 (m, 6H), 7.27 – 7.34 (m, 2H), 6.84 – 6.89 (m, 2H), 3.88 (s, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 168.1, 139.7, 138.8, 138.2, 136.7, 132.6, 128.8, 128.7, 128.4, 127.9, 127.8, 127.3, 125.6, 52.0;

HRMS (EI): calcd for $C_{18}H_{16}O_2$ $[M]^+$ 264.1150, found 264.1148.



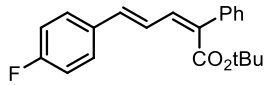
Product 2.37 Prepared according to the General Procedure 1 from the corresponding diazo (96 mg, 0.34 mmol). Isolated in 68% yield, *Z,E*/*E,E* = 62:38, after purification by flash chromatography (Hex/EtOAc gradient) as a pale yellow solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.57 (dd, *J* = 15.6, 11.3 Hz, 1H), 7.44 – 7.51 (m, 2H), 7.34 – 7.40 (m, 4H), 7.28 – 7.34 (m, 1H), 7.01 – 7.07 (m, 2H), 6.77 – 6.88 (m, 2H), 3.85 – 3.90 (m, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 168.0, 163.6 (J_{CF} = 249 Hz), 138.5 (J_{CF} = 67.1 Hz), 138.2, 132.9 (J_{CF} = 3.3 Hz), 132.5 (J_{CF} = 1.6 Hz), 128.8 (J_{CF} = 8.4 HZ), 128.3, 127.8, 127.8 (2), 125.3 (J_{CF} = 2.7 Hz), 115.8 (J_{CF} = 21.6 Hz), 51.9;

^{19}F NMR ($CDCl_3$, 176 MHz) δ –112.2;

HRMS (EI): calcd for $C_{18}H_{15}O_2F$ $[M]^+$ 282.1056, found 282,1058.



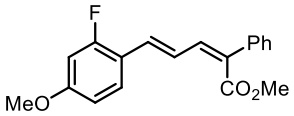
Product 2.58 Prepared according to the General Procedure 1 from the corresponding diazo (82 mg, 0.25 mmol). Isolated in 72% yield, *Z,E*/*E,E* = 81:19, after purification by flash chromatography (Hex/EtOAc gradient) as 92% pure pale yellow solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.39 – 7.47 (m, 4H), 7.35 (m, 2H), 7.27 – 7.32 (m, 2H), 7.04 (m, 2H), 6.73 – 6.80 (m, 2H), 1.60 (s, 9H);

^{13}C NMR ($CDCl_3$, 176 MHz) (Mixture of *EZ* and *EE* Isomers) δ 167.2, 163.8, 161.8, 138.0, 136.8 (2), 135.1 (2), 134.9 (2), 133.1 (2), 130.4, 128.7, 128.6, 128.5, 128.3, 127.8, 127.7, 127.3, 127.0, 125.4 (2), 115.9, 115.7, 81.9, 28.3, 28.2;

^{19}F NMR ($CDCl_3$, 376 MHz) δ − 112.7;

HRMS (EI): calcd for $C_{21}H_{21}O_2F$ $[M]^+$ 324.1526, found 324.1526.



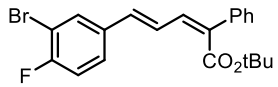
Product 2.59 Prepared according to the General Procedure 1 from the corresponding diazo (95 mg, 0.31 mmol). Isolated in 61% yield, *Z,E*/*E,E* = 59:41, after purification by flash chromatography (Hex/EtOAc gradient) as a yellow oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.59 (dd, *J* = 15.7, 11.3 Hz, 1H), 7.53 (m, 1H), 7.25 – 7.43 (m, 5H), 6.95 (d, *J* = 15.6 Hz, 1H), 6.87 (m, 1H), 6.70 (m, 1H), 6.61 (m, 1H), 3.86 (s, 3H), 3.82 (s, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) (Mixture of *Z,E* and *E,E* Isomers) δ 167.2, 163.8, 161.8, 139.0, 138.4, 138.0, 136.8, 135.1, 134.9, 133.1, 130.4, 128.8, 128.6, 128.5, 128.3, 127.8, 127.7, 127.3, 127.0, 125.4 (2), 115.9, 115.8, 115.7, 115.6, 81.9, 28.3, 28.2;

^{19}F NMR ($CDCl_3$, 377 MHz) δ – 114.2;

HRMS (EI): calcd for $C_{19}H_{17}O_3F$ $[M]^+$ 312.1162, found 312.1162.



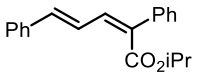
Product 2.60 Prepared according to the General Procedure 3 from the corresponding diazo (97 mg, 0.24 mmol). Isolated in 69% yield, *Z,E*/*E,E* =72:28, after purification by flash chromatography (30:1 pentane/Et_2O) as a colorless oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.63 (dd, *J* = 6.6, 2.2 Hz, 1H), 7.27 – 7.49 (m, 7H), 7.10 (m, 1H), 6.64 – 6.78 (m, 2H), 1.60 (s, 9H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 167.1, 158.9 (J_{CF} = 249.6 Hz), 137.8, 135.8, 135.1, 134.7 (J_{CF} = 4.1 Hz), 134.5, 131.8, 128.3, 127.9, 127.3, 127.2 (J_{CF} = 7.2 Hz), 126.6 (J_{CF} = 2.5 Hz), 116.8 (J_{CF} = 22.9 Hz), 109.5 (J_{CF} = 21.5 Hz), 82.0, 28.3;

^{19}F NMR ($CDCl_3$, 176 MHz) δ − 107.4;

HRMS (EI): calcd for $C_{24}H_{20}O_2FBr$ $[M]^+$ 404.0599, found 404.0603.

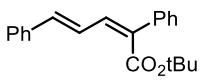


Product 2.66 Prepared according to the General Procedure 1 from the corresponding diazo (123 mg, 0.42 mmol). Isolated in 84% yield, *Z,E*/*E,E* = 79:21, after purification by flash chromatography (Hex/EtOAc gradient) as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.56 (dd, *J* = 15.6, 11.3 Hz, 1H), 7.47 (m, 2H), 7.39 – 7.43 (m, 2H), 7.35 (m, 4H), 7.27 – 7.32 (m, 2H), 6.78 – 6.89 (m, 2H), 5.25 – 5.35 (m, 1H), 1.37 (d, *J* = 6.3 Hz, 6H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 167.5, 138.7, 136.8, 136.6, 133.6, 128.8, 128.6, 128.3, 127.8, 127.5, 127.1, 125.7, 68.7, 22.0;

HRMS (EI): calcd for $C_{20}H_{20}O_2$ $[M]^+$ 292.1463, found 292.1464.

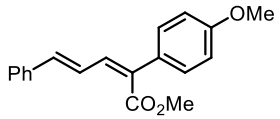


Product 2.67 Prepared according to the General Procedure 3 from the corresponding diazo (138 mg, 0.45 mmol). Isolated in 91% yield, *Z,E*/*E,E* = 86:14, after purification by flash chromatography (Hex/EtOAc gradient) as a brown oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.53 (dd, *J* = 11.0, 15.8 Hz, 1H), 7.46 – 7.50 (m, 2H), 7.41 – 7.45 (m, 2H), 7.32 – 7.38 (m, 4H), 7.27 – 7.32 (m, 2H), 6.78 – 6.85 (m, 2H), 1.57 – 1.69 (m, 9H).

^{13}C NMR ($CDCl_3$, 176 MHz) δ 167.4, 138.1, 138.0, 137.0, 135.1, 134.9, 128.8, 128.5, 138.3, 127.7, 127.3, 127.0, 125.7, 81.9, 28.4;

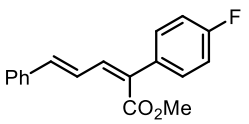
HRMS (EI): calcd for $C_{21}H_{22}O_2$ $[M]^+$ 306.1620, found 306.1623.



Product 2.68 Prepared according to the General Procedure 1 from the corresponding diazo (94 mg, 0.32 mmol). Isolated in 64% yield, *Z,E*/*E,E* = 72:28, after purification by flash chromatography (Hex/EtOAc gradient) as pale yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.57 (dd, *J* = 15.4, 11.6 Hz, 1H), 7.46 – 7.51 (m, 2H), 7.27 – 7.39 (m, 5H), 6.87 – 6.92 (m, 2H), 6.79 – 6.85 (m, 2H), 3.88 (s, 3H), 3.83 (s, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) (Mixture of *Z,E* and *E,E* Isomers) δ 168.4, 168.2, 159.4, 159.2, 140.3, 140.2, 138.7, 136.9, 136.8, 136.4, 132.2, 132.0, 131.6, 130.6, 128.9, 128.8, 128.7, 128.5, 127.4, 127.2, 127.1, 125.7, 125.0, 113.8, 113.5, 55.3 (2), 52.2, 51.9.



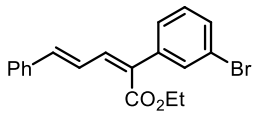
Product 2.69 Prepared according to the General Procedure 1 from the corresponding diazo (101 mg, 0.36 mmol). Isolated in 72% yield, *Z,E*/*E,E* = 58:42, after purification by flash chromatography (20:1 Hex/EtOAc) as a yellow solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.67 (dd, *J* = 15.6, 11.3 Hz, 1H), 7.48 – 7.53 (m, 2H), 7.34 – 7.40 (m, 4H), 7.30 (m, 1H), 7.03 – 7.08 (m, 2H), 6.81 – 6.88 (m, 2H), 3.88 (s, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 167.8, 162.4 (d, J_{CF} = 247.6 Hz), 140.0, 139.2 (d, J_{CF} = 1.2 Hz), 136.5, 134.4 (d, J_{CF} = 3.4 Hz), 131.2, 129.6 (d, J_{CF} = 8.1 Hz), 128.8, 128.7, 127.2, 125.5, 115.2 (d, J_{CF} = 21.6 Hz), 52.0;

^{19}F NMR ($CDCl_3$, 377MHz) δ − 114.1;

HRMS (EI): calcd for $C_{18}H_{15}O_2F$ $[M]^+$ 282.1056, found 282.1057.

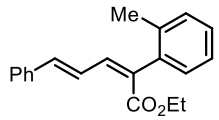


Product 2.70 Prepared according to the General Procedure 2 from the corresponding diazo (104 mg, 0.29 mmol). Isolated in 58% yield, *Z,E*/*E,E* = 42:58, after purification by flash chromatography (20:1 Hex/EtOAc) as pale yellow oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.67 (dd, *J* =15.5, 11.4 Hz, 1H), 7.56 (m, 1H), 7.48 – 7.51 (m, 2H), 7.44 (m, 1H), 7.35 – 7.40 (m, 2H), 7.29 – 7.34 (m, 2H), 7.22 (m, 1H), 6.84 – 6.90 (m, 2H), 4.37 (q, *J* =7.1 Hz, 2H), 1.38 (t, *J* =7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 167.2, 140.5, 139.5, 136.6, 131.3, 130.8, 130.7, 129.7, 128.9, 128.8, 127.3, 126.6, 125.4, 122.3, 61.1, 27.8, 14.4;

HRMS (EI): calcd for $C_{19}H_{17}O_2Br$ $[M]^+$ 358.0392, found 358.0397.



Product 2.71 Prepared according to the General Procedure 1 from the corresponding diazo (138 mg, 0.47 mmol). Isolated in 94% yield, *Z,E*/*E,E* = 45:55, after purification by flash chromatography (Hex/EtOAc gradient) as pale yellow oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.03 (dd, *J* = 15.6, 11.4 Hz, 1H), 7.55 (d, *J* = 7.3 Hz, 2H), 7.36 – 7.43 (m, 2H), 7.16 – 7.36 (m, 5H), 6.84 (d, *J* = 15.6 Hz, 1H), 6.72 (d, *J* = 11.4 Hz, 1H), 4.30 (q, *J* = 6.97 Hz, 2H), 2.28 (s, 3H), 1.27 – 1.34 (m, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 167.0, 142.6, 140.2, 139.4, 136.7, 136.5, 132.0, 129.9, 129.7, 128.7 (2), 127.8, 127.3, 125.8, 125.7, 60.7, 20.0, 14.3;

HRMS (EI): calcd for $C_{20}H_{20}O_2$ $[M]^+$ 292.1463, found 292.1466.

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