1,3-DIPOLAR CYCLOADDITION OF ELECTRON-RICH ALKYNES AND OPTICALLY ACTIVE ALLENES IN ASYMMETRIC CATALYSIS

APPROVED BY SUPERVISORY COMMITTEE

Joseph M. Ready, Ph.D, Supervisor

Chuo Chen, Ph.D

Jef K. DeBrabander, Ph.D

John B. MacMillan, Ph.D

Dedication

This dissertation is dedicated to my dear wife, Fang Wang, whose encouragement and supports have assisted me tremendously in all of my life struggles. I would also dedicate this to my adorable son, Maximillian Wang Qi, his born during my hard life and the happiness he brought to me inspirited me to work harder and make very well progress in my research. I appreciate his pressure. I would also dedicate this to my parents, grandparents, my brother, and friends who have given me so much love and supports.

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Finally, thanks to all of my friends that I have met here at UT southwestern over the last four years. I have met so many fantastic people here and I will always look back on my time at UT southwestern with fondness.

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Xiangbing Qi

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Xiangbing Qi, Ph.D.

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Joseph M. Ready, Ph.D.

This dissertation includes two parts. The first part focuses on two 1,3-dipolar cycloadditions of electron-rich alkynes. Chapter one describes a copper-promoted cycloaddition reaction of acetylides with diazocarbonyl compounds. This novel cycloaddition offers a direct and efficient approach to the synthesis of pyrazoles. The method is a rare example of an inverse-electron-demand cycloaddition, it represents a conceptually novel approach to this important class of heterocycles. Chapter two investigates a cycloaddition reaction between donor-acceptor cyclopropanes and silyl ynol ethers. Lewis acid promoted ring-opening of donor-acceptor cyclopropanes generates a 1,3-zwitterion; cycloaddition with a silyl ynol ether leads to a general

synthesis of cyclopentenones. Substitution is tolerated on the ynol and on all positions of the cyclopropane to give tri-, tetra-, and penta-substituted cyclopentenones in high yield. (MeO)AlMeCl, which is generated from Me_2AlCl by oxidation, appears strong reactivity towards ring-opening of donor-acceptor cyclopropanes and cycloaddition with silyl ynol ethers. This infrequently used species might be extended to other classes of cycloadditions or Lewis acid promoted reactions.

The second part describes a new asymmetric catalysis design using optically active allenes as backbone and the application in an asymmetric *meso*-epoxides opening reaction. Allenes are inherently chiral and can be prepared in optically pure form. They have not been incorporated into ligands or catalysts for asymmetric reactions. Since allenes project functionality differently than either tetrahedral carbon or chiral biaryls, they may create complementary chiral environments. Chapter three demonstrates that optically active, C_2-symmetric allene-containing bisphosphine oxides can catalyze the addition of $SiCl_4$ to *meso*-epoxides with high enantioselectivity. The fact that high asymmetric induction is observed suggests that allenes may represent a new platform for the development other classes of organic catalysts or ligands for asymmetris reactions.

Table of Contents

Prior publications

1. Pu, X.; **Qi, X**.; Ready, J. M. "Allenes in Asymmetric Catalysis: Asymmetric Ring Opening of *meso*-Epoxides Catalyzed by Allene-Containing Phosphine Oxides" *J. Am. Chem. Soc.* http://pubs.acs.org | doi: 10.1021/ja9041127.
2. **Qi, X**.; Ready, J. M. "Synthesis of Cyclopentenones from Cyclopropanes and Silyl Ynol Ethers" *Angew. Chem. Int. Ed.* **2008**, *47*, 7068-7070.
3. **Qi, X**.; Ready, J. M. "Copper-Promoted Cycloaddition of Diazocarbonyl Compounds with Copper Acetylides'" *Angew. Chem. Int. Ed.* **2007**, *46*, 3242-3244.

List of Schemes

List of Tables

List of Figures

List of Abbreviations

Ac	acetyl
acac	acetylacetonyl
anhyd	anhydrous
APCI	atmospheric pressure chemical ionization
aq	aqueous
Ar	aryl (substituted aromatic ring)
BBN (9-BBN)	9-borabicyclo[3.3.1]nonane (9-BBN)
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2,2'-naphthol
Bn	benzyl
Boc	^{t}-butoxycarbonyl
BOP-Cl	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
bp	boiling point
BQ	benzoquinone
BSA	*N*,*O*-bis(trimethylsilyl)acetamide
Bz	benzoyl
br	broad (NMR signal)
^{n}Bu	*n*-butyl
^{t}Bu	tertiary butyl
ca	circa(approximately)
CAN	cerium(IV) ammonium nitrate (cericammonium nitrate)

°C	degrees Celcius
cat.	catalytic
Cbz (Z)	benzyloxycarbonyl
conc.	concentrated
COD	1,5-cyclooctadiene
Cp	cyclopentadienyl
Cp*	pentamethyl cyclopentadienyl
CSA	camphorsufonic acid
Cy	cyclohexyl
d	doublet (NMR signal)
DABCO	1,4-diazabicyclo[2.2.2]octane
DBA (dba)	dibenzylideneacetone
dd	doublet of doublets (NMR signal)
dt	doublet of triplets (NMR signal)
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
1,3-DC	1,3-dipolar cycloaddition
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
dr	diastereomeric ratio
DIBAL (DIBAH) DIBAL-H	diisobutylaluminum hydride
DIPEA(Hünig's base)	diisopropylethylamine
DMAD	dimethyl acetylene dicarboxylate

DMAP	*N*,*N*-4-dimethylaminopyridine
DMDO	dimethyl dioxirane
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DPA (DIPA)	diisopropylamine
dppe	1,2-bis(diphenylphosphino)ethane
dppf	diphosphinoferrocene
E^+	electrophile (denotes any electrophile in general)
EDA	ethyl diazoacetate
EDC (EDAC)	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimidehydrochloride
EDG	electron-donating group
ee	enantiomeric excess
e.g.	exempli gratia (for example)
EI	electron ionization
E1	unimolecular elimination
E2	bimolecular elmination
ESI	electronspray ionization
Et	ethyl
Equiv	equivalent
FT-IR	Fourier transform infra-red

EWG	electron-withdrawing group
FMO	frontier molecular orbital (theory)
δ	chemical shift
g	gram
GC	gas chromatography
GC/MS	gas chromatography/mass spectroscopy
h	hour
hν	irradiation with light
hpt	heptet (NMR signal)
HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium Hexafluorophosphate
Hgmm	millimeter of mercury (760 Hgmm = 1 atm = 760 Torr)
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoric acid triamide
HMPT	hexamethylphosphorous triamide
HOBt (HOBT)	1-hydroxybenzotriazole
HOMO	highest occupied molecular orbital
HPLC	high-pressure (performance) liquid chromatography
HWE	Horner-Wadsworth-Emmons
Hz	hertz
IBA	2-iodosobenzoic acid
IBX	o-iodoxybenzoic acid
Imid (Im)	imidazole

IPA	isopropyl alcohol
iPr	isopropyl
J	coupling constant (NMR signal)
L	ligand
LA	Lewis acid
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
liq.	liquid
LUMO	lowest unoccupied molecular orbital
m	multiplet (NMR signal)
MAO	methyl aluminum oxide
m-CPBA	*meta*-chloroperbenzoic acid
mg	milligram
MHz	megahertz
min	minutes
mL	milliliter
mmol	millimole
m/z	mass/charge
Me	methyl
Mes	mesityl
MOM	methoxymethyl
MPa	megapascal = 106 Pa = 10 atm
Ms	mesyl (methanesulfonyl)

MS	mass spectrometry
MS	molecular sieves
MTO	methyltrioxorhenium
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine oxide
NMR	nuclear magnetic resonance
Nuc	nucleophile (general)
o	ortho
Ph	phenyl
p	para
PCC	pyridinium chlorochromate
PMB (MPM)	*p*-methoxybenzyl
ppm	parts per million (NMR signal)
PPTS	pyridinium p-toluenesulfonate
Pr	propyl
Py	pyridine
q	quartet (NMR signal)
rac	racemic
Rds (or RDS)	rate-determining step
Red-Al	sodium bis(2-methoxyethoxy) aluminum hydride
R_f	retention factor in chromatography

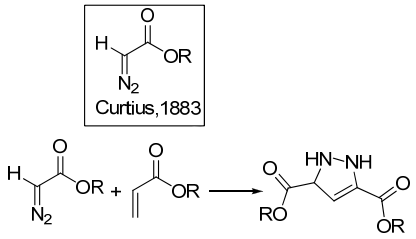
RT	room temperature
s	singlet (NMR signal)
Salen	*N*,*N'*-ethylenebis(salicylideneiminato)bis (salicylidene) ethylenediamine
sec	secondary
t	triplet (NMR signal)
TBAF	tetra-n-butylammonium fluoride
TBDMS(TBS)	*t*-butyldimethylsilyl
TBDPS(BPS)	*t*-butyldiphenylsilyl
TBHP	*t*-butyl hydroperoxide
TEA	triethylamine
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMS	trimethylsilyl
tol	toluene
T_R	Retention time
Ts	tosyl

Chapter 1. Copper-Promoted Cyloaddition of Diazocarbonyl Compounds and Acetylides

1.1. Introduction of 1,3-dipolar cycloaddition reaction

1,3-Dipolar cycloadditions (1,3-DC) are one type of cycloaddition reactions in which multiple unsaturated molecules combine to form cyclic addition products. They combine 1,3-dipoles and dipolarophiles to generate five-membered rings.[1] The first dipole and 1,3-DC were discovered by Curtius[2] and Buchner[3] in the 1880's (**Scheme 1.1**).

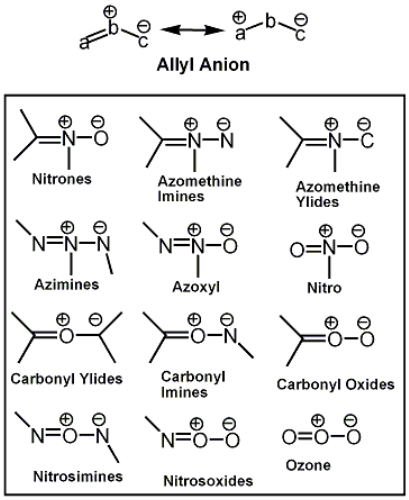
Scheme 1.1. General scheme of 1,3-DC



The concept of the1,3-DC was first introduced by Rolf Huisgen and co-workers in the early 1960's.[4] These reactions have been developed into very general and useful methods for the synthesis of five-membered hetereocycles or carbocycles.

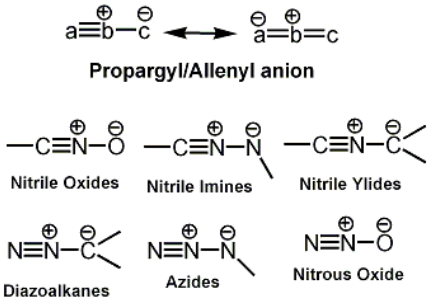
Basically, 1,3-dipoles can be divided into two different types:[5] the allyl anion type and the propargyl/allenyl anion type. The allyl anion type is bent and has four electrons in three parallel p orbitals perpendicular to the plane of the dipole (**Scheme 1.2**).

Scheme 1.2. Allyl anion 1,3-dipoles



The propargyl/allenyl anion type dipole is normally linear. The central atom is occasionally presented as hypervalent and is limited to nitrogen (**Scheme 1.3**). The other dipole atoms can be carbon, oxygen and nitrogen. Other main group IV, V, VI elements like phosphorus and sulfur can also be involved in dipoles.

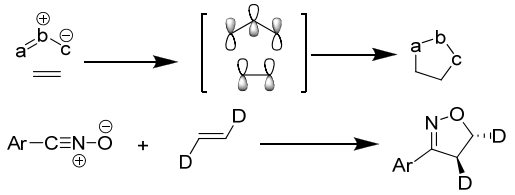
Scheme 1.3. Propargyl/allenyl anion dipoles



Dipolarophiles display less diversity than dipoles. The most commonly used dipolarophiles are substituted alkenes and alkynes. Double or triple bonds with heteroatoms like carbonyl, iminium and cyano groups can also be dipolarophiles.

Two types of mechanisms for 1,3-DC reactions have been recognized: step-wise and concerted. In the concerted pathway, the 1,3-DC reaction involves 4 π electrons from the dipole and 2 π electrons from the dipolarophile. According to the Woodward-Hoffmann rules,[6] if the 1,3-DC reaction proceeds via a concerted mechanism, three p_z orbitals of the 1,3-dipole and two p_z orbitals of the dipolarophile will combine suprafacially, symbolized as [π 4_s+ π 2_s]. The stereochemistry of the reactants could be transferred to the product. For example, the 1,3-DC of benzonitrile oxide with trans-dideuterated ethylene gave exclusively the *trans*-isoxazoline (**Scheme 1.4**).[7]

Scheme 1.4 Concerted pathway of 1,3-DC

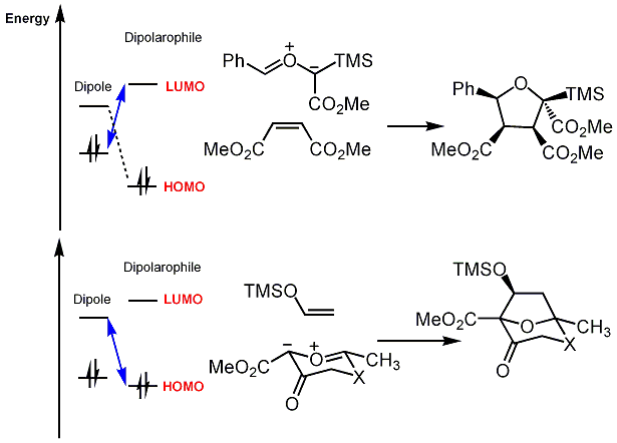


For those step-wise 1,3-DC involving some intermediates, the stereochemical information will be destroyed during these transformations.

Concerted 1,3-DC can be interpreted by frontier molecular orbital theory (FMO).[8] Based on FMO, two types of concerted 1,3-DC can occur. One is the FMO interaction between the highest occupied molecular orbital (HOMO) of the dipole and the lowest unoccupied molecular orbital (LUMO) of the dipolarophile. A second type is dominated by the reaction between the HOMO of the dipolarophile and the LUMO of the dipole (**Scheme 1.5**). Without any activation of either component, the reaction between an electron-rich dipole (*e.g.,*TMS substituted carbonyl ylides) and an electron-deficient

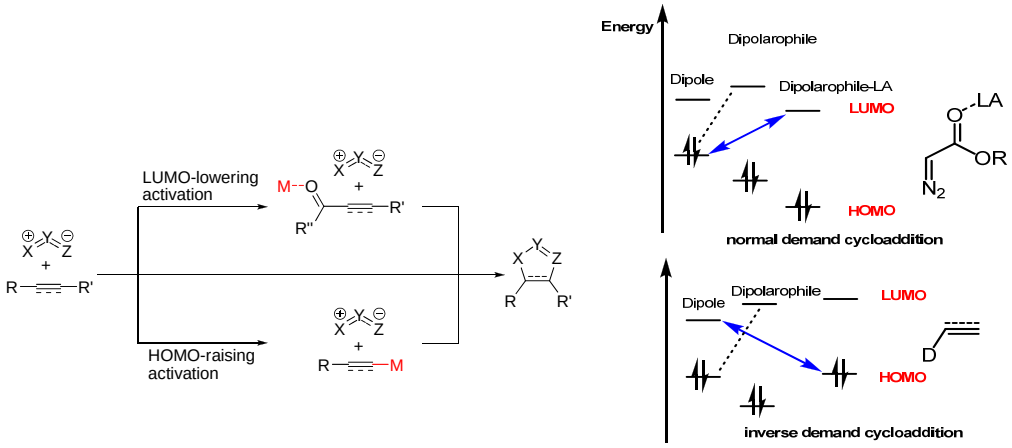
dipolarophile (*e.g.*,dimethyl maleate)[9] is dominated by the interaction between the dipole HOMO and the dipolarophile LUMO.

Scheme 1.5. FMO interaction of 1,3-DC



Even though some cases, like ozonolysis of olefins and addition of nitrile oxides to alkynes,[10] proceed without additional promoters, many more substrate combinations result in no cycloadduct formation when dipole and dipoarophile are simply mixed. To accelerate these types of reactions, two complementary strategies focus on modulating the reactivity of the dipolarophile (**Scheme 1.6**).

Scheme 1.6. General promotion to accelerate 1,3-DC



In the first strategy, Lewis acids are included to lower the LUMO of the dipolarophile.[6] Under such conditions the dipole reacts through its HOMO to generate the cycloaddition product.[11] Alternatively, additives that increase the electron density of the dipolarophile can accelerate cycloaddition via an $HOMO_{(dipolarophile)}$-$LUMO_{(dipole)}$ interaction. This approach is less common than the Lewis acid-based methods[12] but is most notably operative in the copper-catalyzed synthesis of triazoles from alkynes and azides.[13]

The presence of additives like metals or Lewis acids in 1,3-DC reactions can modify both the orbital coefficients and the energy of the frontier orbitals of the 1,3-dipole or the dipolarophiles depending on the electronic properties of the promotion reagents or the Lewis acid. The coordination of a Lewis acid or metal to the 1,3-DC reactants provides a promising strategy to accelerate 1,3-DC reactions. The fundamental importance can be attributed to the ability to control the regio-, diastereo-, and enantioselectivity in asymmetric 1,3-DC reactions since the metal-ligand can catalyze the reaction by polarizing one of the reactants. This transformation provides an efficient and convergent approach to generate multi-functionalized five-membered hetereocycles or carbocycles containing several contiguous stereocenters in a single operation.

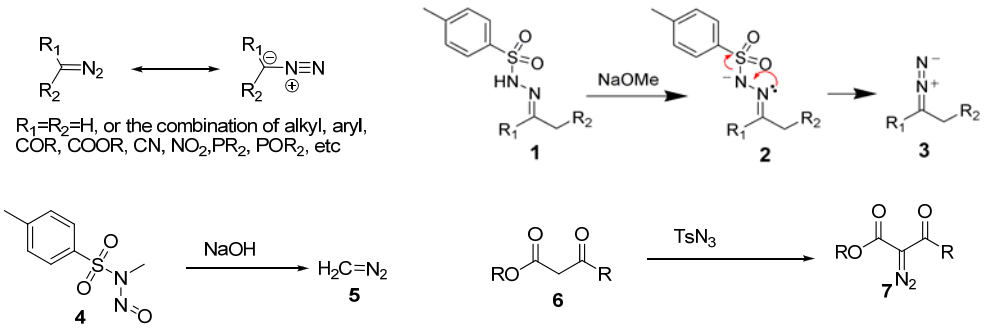
1.2 Introduction and background of diazo dipoles and pyrazole synthesis

Diazo compounds are one of the earliest 1,3-dipoles used in history. In 1890s', Buchner[3] and Pechmann[14] discovered the first [3+2] cycloaddition reactions using diazoacetate and diazomethane as dipole components respectively. After that, diazo compounds as well as azide have been developed to be some of the most useful dipoles in

organic synthesis over the past century. Often, diazo compounds have been used as carbene precursors under thermolysis, photolysis or in the presence of transition metals. This type of chemistry is well known in reactions with various multiple-bond systems.[15] However, the focus here will be on the use of the diazo functional group as a dipole rather than a carbene precursor.

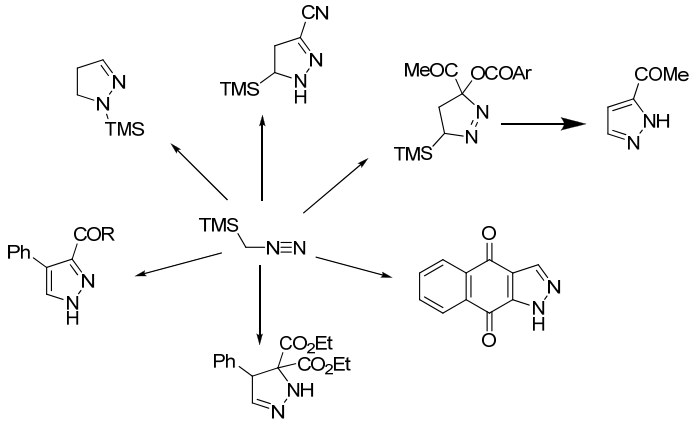
Versatile diazo compounds can be used as cycloaddition partners, such as alkyl, aryl and carbonyl substituted diazo species. To generate diazo compounds, the major methods include dehydrogenation of hydrazones,[16] alkaline cleavage of *N*-alkyl-*N*-nitroso sulfonamides[17] and diazo group transfer from azides (**Scheme 1.7**).[18]

Scheme 1.7. Diazo compound synthesis.



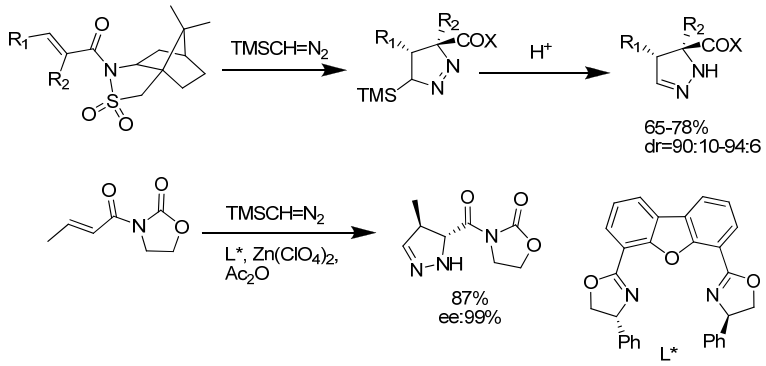
The utility of 1,3-DC of diazo compounds has been expanded based on the investigations of novel dipolarophiles, such as functionalized carbon-carbon double and triple bonds, carbon-hetereoatom double and triple bonds, and hetereoatom-hetereoatom double and triple bonds.[1] Among these dipolarophiles, alkenes have been extensively studied as cycloaddition partners for different types of diazo dipoles. Depending on the substitution of these two cycloaddition partners, the cycloaddition can yield dihydropyrazoles (pyrazolines) or, after 1,2-elimination reaction, pyrazoles (**Scheme 1.8**).

Scheme 1.8. 1,3-DC of diazo compounds.



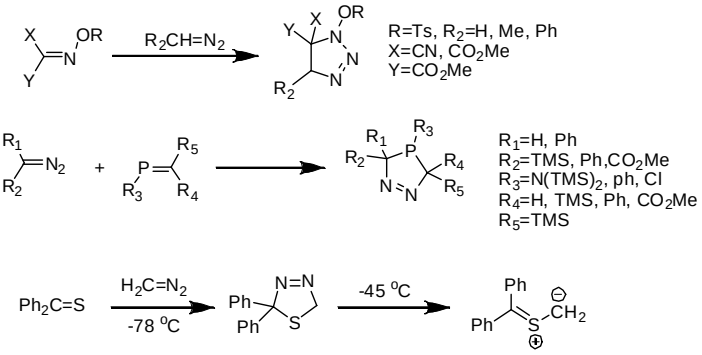
In most cases, the alkene dipolarophiles are electron-deficient and the diazo compounds are electron-rich dipoles. Also in this type of 1,3-DC, the diastereoselectivity and enantioselectivity can be controlled by either a chiral auxiliary[19] or a chiral ligand (**Scheme 1.9**).[20]

Scheme 1.9. 1,3-DC of diazo compounds with olefins



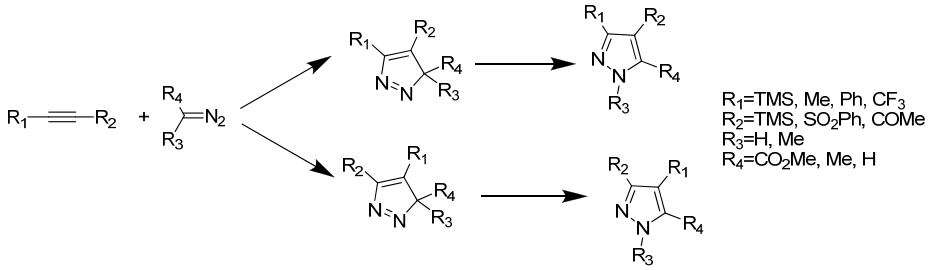
Besides alkenes, other double bonds like C=N,[21] C=P[22] and C=S[23] can also be dipolarophiles (**Scheme 1.10**).

Scheme 1.10. 1,3-DC of diazo compounds with heteroatom double bonds



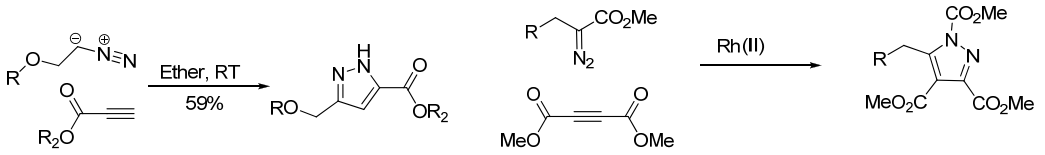
The reaction between diazo compounds and alkyne triple bonds will generate pyrazole products indirectly through tautomerization of the initially formed cycloadduct (**Scheme 1.11**).

Scheme 1.11. 1,3-DC of diazo compounds with alkynes.



In general, the regio-selectivity is mainly dependant on the functional groups on the alkyne, and the reactivity of the 1,3-DC reaction is dominantly controlled by $HOMO_{(dipole)}$-$LUMO_{(alkyne)}$ interactions. So, an electron-withdrawing substitutent on the alkyne will accelerate the reaction with diazo compounds usually under very mild conditions (**Scheme 1.12**).[24]

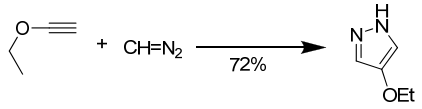
Scheme 1.12. 1,3-DC of diazo compounds with electron-deficient alkynes**.**



The most common type of alkyne dipolarophiles are propiolate derivatives or DMAD (**Scheme 1.12**).[25] Their high reactivities towards various diazo compounds may be attributed to their electron-deficient nature which leads to lower LUMO energy levels. There are hundreds of reported 1,3-DC using these types of alkynes as dipolarophiles.

On the contrary, the reaction of an electron-rich alkyne (e.g. ethoxylacetylene) with diazomethane is very slow (2 weeks at rt) (**Scheme 1.13**).[26] This type of reaction is very rare, and most of these reaction conditions are very harsh or need promoters.

Scheme 1.13. 1,3-DC of diazomethane with ethoxyethyne

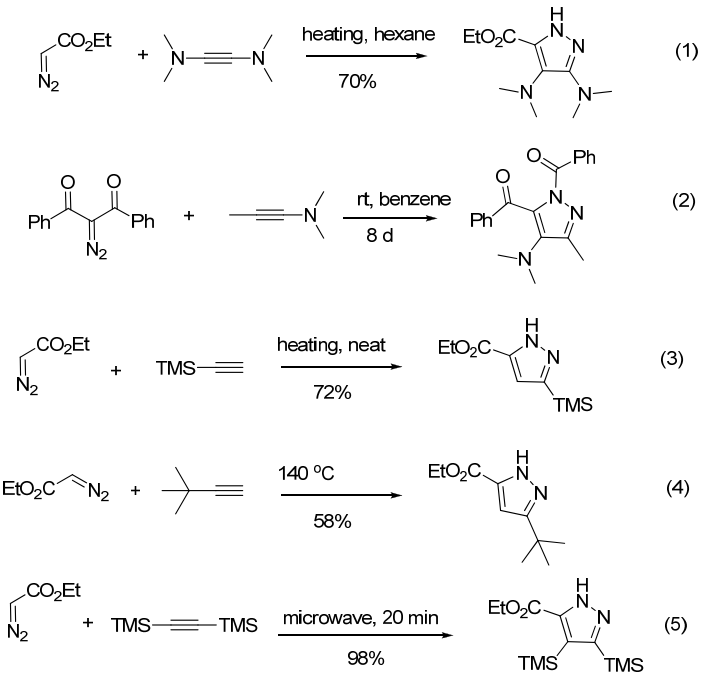


Without any promoters, only a limited number of electron-rich alkynes have been found to undergo 1,3-DC with diazo compounds to generate pyrazoles (**Scheme 1.14)** The electron rich alkyne *N, N, N', N'*-tetramethylethyne -1,2-diamine can react with diazoacetate under thermal condition to generate trisubstituted pyrazoles in good yield (**Scheme 1.14**, eq. 1).[27] The two electron-rich dimethylamino groups increase the HOMO of the alkyne and the carbonyl group decreases the LUMO of the diazo dipole so that the energy gap between $HOMO_{(dipolarophile)}$-$LUMO_{(dipole)}$ is smaller than $HOMO_{(dipole)}$-$LUMO_{(dipolarophile)}$. Similarly, two carbonyl groups on the diazocompound decrease the

LUMO of the dipole further and the reaction between less electron-rich alkyne *N, N*-dimethylprop-1-yn-1-amine is possible (**Scheme 1.14,** eq. 2).[28]

Trimethylsilyl[29] or alkyl[30] groups can also be electron- donating substituents to make alkynes more reactive towards 1,3-DC with electron-deficient diazo dipoles to form pyrazoles. In most of these cases, the reaction conditions are harsh (high temperature or long reaction time), and the regioselectivities are poor. In addition, the substrate scopes are normally not very broad.

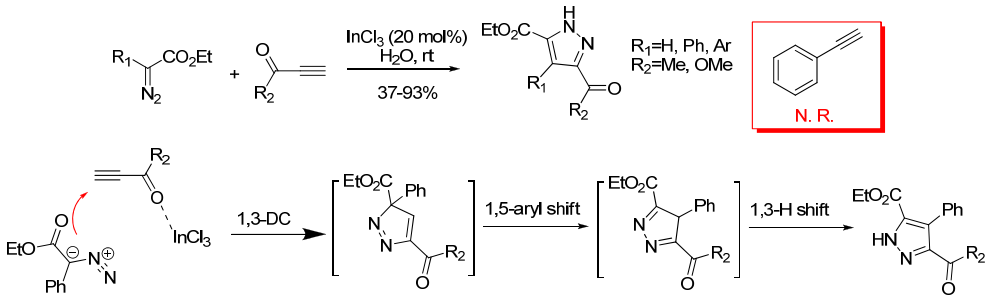
Scheme 1.14. 1,3-DC of diazo compounds with electron-rich alkynes



In the presence of Lewis acids or transition metals, the orbital coefficients and the energy of the frontier orbitals of either the 1,3-dipole or the dipolarophiles can be modified depending on the electronic properties of these promoters. These additives can provide high reactivities, regioselectivities and diastereoselectivities.

For example, the Lewis acid $InCl_3$ has been shown to catalyze the 1,3-DC of diazocarbonyl compounds with different alkynes in water (**Scheme 1.15**).[31] Indium was proposed to activate the alkyne by coordinating to the adjacent carbonyl group, and thus lowering the LUMO of the alkyne dipolarophile. Consistent with this hypothesis, no reaction occurred when phenylacetylene was exposed to this reaction condition. In this reaction system, the use of water as solvent is crucial. Reactions in non-polar solvents like benzene gave only trace amount of the desired pyrazole. This phenomenon provided more evidence for the coordination. Diazocarbonyl compounds are electron-deficient dipoles, so the energy gap between $HOMO_{(dipole)}$-$LUMO_{(dipolarophile)}$ was supposed to be big. Lewis acids were used as coordinating group to lower the LUMO of the alkyne dipolarophile, thus decreasing the FMO energy gap, and very high reactivities and regioselectivities were observed. However, the carbonyl acetylene prerequisite limited the scope of this reaction.

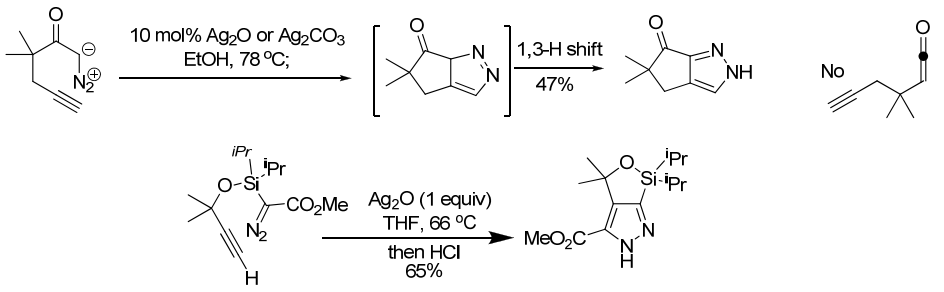
Scheme 1.15. $InCl_3$-catalyzed 1,3-DC of diazocarbonyl compounds with alkynes



Besides Lewis acids, transition metals are also known to promote the 1,3-DC of diazo compounds even though these are much less developed. This may be attributed to the fact that transition metals can decompose diazo compounds to generate carbenoid species and then result in various side reactions, such as dimerization, X-H insertion or

cyclopropanation. The first transition metal catalyzed 1,3-DC of diazo compound with alkynes was published in 1995 by Kende *et al*. using Ag(I) as catalyst (**Scheme 1.16**).[32] This method was later extended to more substrates by Maas et al.[33] Even in the presence of Ag(I) intramolecular [3+2] cycloaddition was observed instead of a Wolff rearrangement. Kende proposed that the Ag(I) played a crucial role in activation of the acetylenic bond by side-on coordination. Maas assumed the activation by Ag is end-on coordination since no reaction was observed by using an internal alkyne. In both cases, the gem-dialkyl substitution is a prerequisite for this specific intramolecular cycloaddition.

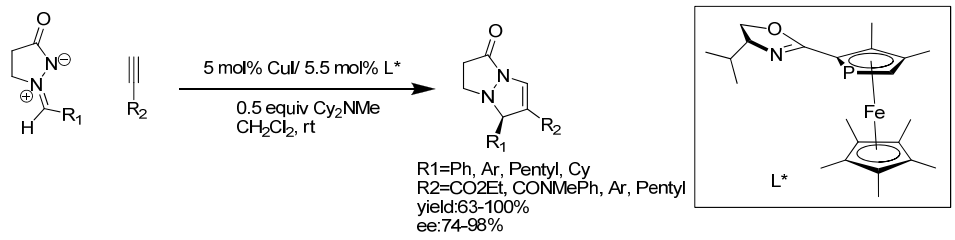
Scheme 1.16. Ag(I) catalyzed intramolecular 1,3-DC of diazocarbonyl compounds



Gregory Fu *et al* in 2003[34] showed that Cu(I) can catalyze 1,3-DC of alkynes. In the presence of Cu(I), azomethine imine underwent cycloaddition with various terminal alkynes to generate five-membered nitrogen hetereocycles in very high yields and exclusive regioselectivities (**Scheme 1.17**). The Cu(I) catalyzed 1,3-DC to terminal alkynes has been well known in two type of dipoles-azides and nitrones-presumably through a copper acetylide intermediate to activate the dipolarophile. This is the first example applying Cu catalysis to diazo equivalents. Even though this type of cycloaddition is general for various terminal alkynes, the specificity of this azomethine

imine limited the application scope. Interestingly, the enantioselectivity can be excellently controlled by using a chiral ligand.

Scheme 1.17. Cu(I) catalyzed 1,3-DC of diazocarbonyl compounds with alkynes

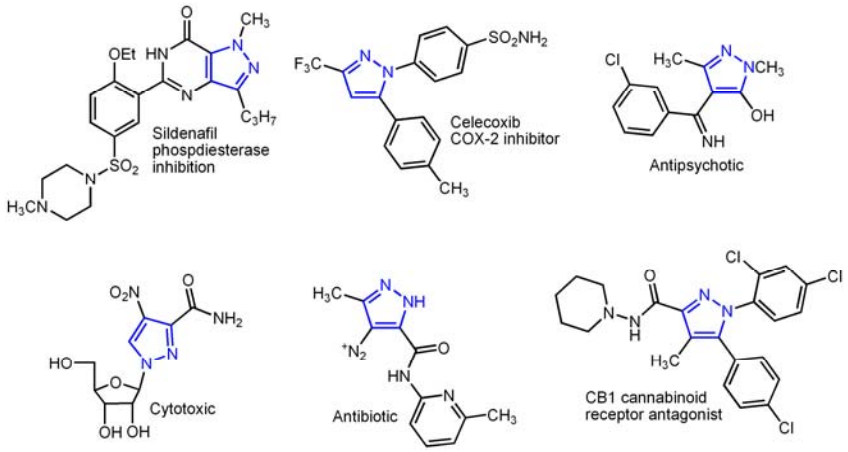


In conclusion, more than century after their discovery, diazo compounds are still widely applied in 1,3-DC. These types of unique dipoles have been extremely useful in the regioselective and stereoselective syntheses of novel nitrogen heterocyclic ring systems.

1.3 Brief overview of the synthesis of pyrazoles.

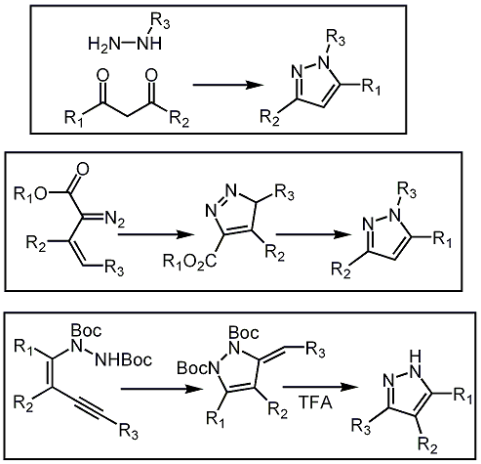
The pyrazole substructure appears in small molecules possessing a wide range of biological activities and, accordingly, represents a valuable target for organic synthesis (**Scheme 1.18**).[35]

Scheme 1.18. Pyrazole-containing pharmaceutical compounds



A common tactic for the preparation of pyrazoles relies on the condensation of β-diketones with hydrazines.[36] Alternatively, cyclization of diazo-alkenes[37] or unsaturated hydrazines[38] provides improved control of regiochemistry relative to the dicarbonyl-hydrazine condensation, although the precursors are more challenging to prepare (**Scheme 1.19**).

Scheme 1.19. Preparation of pyrazoles



The cycloaddition of diazo compounds with alkynes would provide a direct approach to pyrazoles. In this regard, electron-rich diazo compounds (e.g. diazomethane) react under mild conditions with electron-deficient alkynes.[39] In contrast, Lewis acids are required to promote the cycloaddition between electron deficient alkynes and diazocarbonyl compounds.[31] (See the discussion in section 1.2 for more details.)

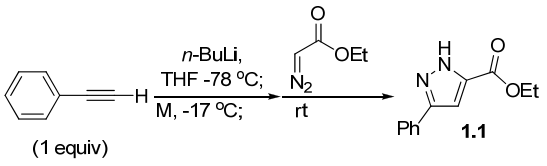
However, simple alkyl- or arylacetylenes generally fail to react with diazocarbonyl compounds under normal conditions or in the presence of Lewis acids. An alternative mode of activation is necessary for a general 1,3-DC approach to synthesize pyrazoles.

1.4 Results and discussion

1.4.1 Optimizing conditions

A general inverse electron-demand ($HOMO_{(dipolarophile)}$-$LUMO_{(dipole)}$) 1,3-DC has still not been developed. The inaccessibility may be attributed to the large energy gap between the FMO of the two partners under thermal conditions. To overcome this restriction, ethyl diazoacetate was examined as a typical electron-deficient diazo compound; presumably the electron-withdrawing carbonyl group can decrease the LUMO of this type of dipole. With respect to the dipolarophile, terminal alkynes were converted to metal acetylides to test the hypothesis that transition metals could render the alkyne more electron-rich via backbonding.

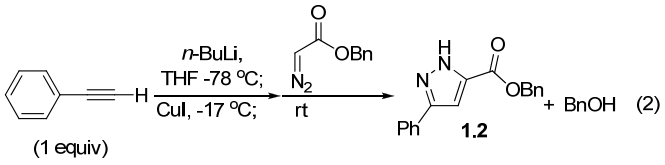
Specifically, phenylacetylene was deprotonated with BuLi at -78 ^{o}C. The resultant lithium acetylide was transferred to reaction mixtures containing different transition metals such as $ZnCl_2$, $CoCl_2$, $NiCl_2$, $PdCl_2$, $FeCl_2$, AgBr, AuCl and CuI. When the transmetalation was complete (1h at -17 ^{o}C), a solution of ethyl diazoacetate was added and then the reaction mixture was warmed to rt (**eq 1**).



(1)

High reactivity was observed only when CuI was used as promoter. The product was isolated, and the structure was identified to be pyrazole **1.1** by NMR spectrum and X-ray analysis of a single crystal. The reaction was relatively clean, but the isolated yield was very low (around 20%). The low mass balance and the absence of observable side

products suggested that material was being lost during the reaction or purification. Reasoning that the byproduct could be either very volatile and lost after work-up or very polar and soluble in aqueous solution, benzyl diazoacetate was used as the diazo starting material. After careful analysis, benzyl alcohol was confirmed to be the major byproduct (**eq 2**).



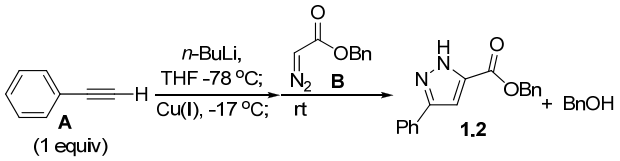
(2)

When lithium phenylacetylide was treated with CuI and benzyl diazoacetate, pyrazole **1.2** was formed along with benzyl alcohol. The conversion of diazoester was complete, and over 90% of the mass balance was accounted for by **1.2**, BnOH and recovered alkyne. Since base is crucial for the first step, different type of bases, such as BuLi, LDA, BuMgCl, LiHMDS, NaHMDS, KHMDS, Et_3N, pyridine, EDTA, TMEDA, $(PhO)_3P$ and HMPT were investigated in the beginning using a catalytic amount of CuI (20 mol%). Desired pyrazole product was observed only when the alkali metal acetylide was generated from strong bases (BuLi, LDA, BuMgCl, LiHMDS, NaHMDS, KHMDS). Even starting with copper phenylacetylene, weak base like Et_3N did not promote pyrazole formation. Among the strong bases screened, the reaction with BuLi provided the best ratio of pyrazole to BnOH.

Different copper sources, stoichiometry of Cu(I) and additives were then carefully tested. When a stiochiometric amount of CuCN was used, (**Table 1.1**, entry 6 and 7) much higher ratio of pyrazole to BnOH was observed based on NMR analysis (based on

benzyl protons). Other Cu(I) sources can also promote this reaction, although they gave even lower ratios. Based on the results, equimolar quantities of Cu(I) are better than catalytic amount of Cu(I) (**Table 1.1,** entry 5 vs. 6; 8 vs.9).

Table 1.1 Investigation of the Cu source.



Entry	Cu(I)	Equiv Cu(I)	**1.2**:BnOH[a]
1	CuI	0.2	1.0:1
2	CuI	0.5	1.5:1
3	CuI	1.0	[b]
4	CuI·2LiCl	0.5	0.9:1
5	CuI·2LiCl	1.0	[b]
6	CuCN	0.5	2.0:1
7	CuCN	1.0	4.0:1
8	CuBr·SMe_2	0.2	[b]
9	CuCN·2LiCl	0.5	1.9:1
10	**CuCN·2LiCl**	**1.0**	**5.4:1**
11	CuSCN·2LiCl	0.5	1.8:1
12	CuBr·2LiCl	0.5	1.2:1
13	CuCl·2LiCl	0.5	1.7:1

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Complex mixture.

In stoichiometric amounts, LiCl was found to increase the ratio of pyrazole to BnOH when CuCN was used (**Table 1.1,** entry 10 vs. 7). Systematic variation of stoichiometry of CuCN and the ratio of LiCl led to the discovery that CuCN·6LiCl[40] minimized BnOH formation and maximized the yield of pyrazole (**Table 1.2**).

Table 1.2. Copper stoichiometry screen

Entry	Cu(I)	Equiv Cu(I)	**1.2**:BnOH
1	CuI	0.5	1.5:1
2	CuI	1.0	[a]
3	CuI·2LiCl	0.2	1.0:1
4	CuI·2LiCl	0.5	0.9:1

5	CuI·2LiCl	1.0	[a]
6	CuI·6LiCl	1.0	1.0:1
7	CuCN	0.5	2.0:1
8	CuCN·2LiCl	0.5	2.0:1
9	CuCN·4LiCl	0.5	2.4:1
10	CuCN·6LiCl	0.5	3.1:1
11	CuCN·8LiCl	0.5	1.6:1
12	CuCN	1.0	4.0:1
13	CuCN·2LiCl	1.0	5.4:1
14	CuCN·4LiCl	1.0	5.9:1
15	**CuCN·6LiCl**	**1.0**	**6.0:1**
16	CuCN·8LiCl	1.0	5.4:1
17	CuCN·10LiCl	1.0	4.4:1
18	CuCN·6LiCl	1.5	4.0:1

[a]Complex mixture.

The relationship between the components of the reaction mixture and the product distribution is complex. For example, while the inclusion of LiCl does not improve reactions involving CuI (entry 1 vs. 2-6), small but reproducible enhancements in the **1.2**:BnOH ratio were observed when up to 6 equiv of LiCl were added to reaction mixtures containing CuCN (entries 7-17). Similarly, whereas 1:1 molar ratios of CuI and alkyne produced complex mixtures, optimal results were obtained using the lower order cuprate derived from CuCN·6LiCl. Other lithium sources and salts of alkaline earth metals were also screened, but none showed better result (**Table 1.3**).

Table 1.3 Lithium source and alkaline earth metals effects

Entry	Cu(I)	Equiv Cu(I)	**1.2**:BnOH
1	CuCN·2LiCl	0.5	2.0:1
2	CuCN·2LiBr	0.5	1.3:1
3	CuCN·2LiI	0.5	1.2:1
4	CuCN·2NaI	0.5	1.1:1
5	CuCN·2KI	0.5	1.2:1
6	CuCN·6LiCl	1.0	6.0:1
7	CuCN·6$LiNO_3$	1.0	2.2:1
8	CuCN·6LiOAc	1.0	2.9:1
9	CuCN·6LiOTf	1.0	2.3:1
10	CuCN·6$LiClO_4$	1.0	1.9:1
11	CuCN·6Li_3PO_4	1.0	3.1:1

The stoichiometry of starting material **B** was studied and a 1:1 ratio of **B** to **A** showed the best result (**Table 1.4**).

Table 1.4 Stoichiometry of starting material **B**

Entry	Cu(I)	**(B : A)**	**1.2**:BnOH
1	CuCN·6LiCl	1.0	6.0:1
2	CuCN·6LiCl	1.2	5.2:1
3	CuCN·6LiCl	1.5	4.6:1
4	CuCN·6LiCl	2.0	3.5:1

Several types of solvents were screened. Since the deprotonation is heavily solvent-dependent (only diethyl ether and THF are proper solvents), the solvent effect of the whole reaction was investigated via changing only the solution of the diazoester (**Table 1.5**).

Table 1.5 Solvent effect

Entry	Cu(I)	Solvent	**1a**:BnOH
1	CuI(20 mol%)	CH_2Cl_2	1.5:1
2	CuI(20 mol%)	Ether	1.0:1
3	CuI(20 mol%)	Benzene	1.4:1
4	CuCN·6LiCl	MeCN	4.0:1
5	CuCN·6LiCl	CH_2Cl_2	1.3:1
6	CuCN·6LiCl	Toluene	1:1.5
7	CuCN·6LiCl	Ether	1:3.0
8	CuCN·6LiCl	THF	6.0:1

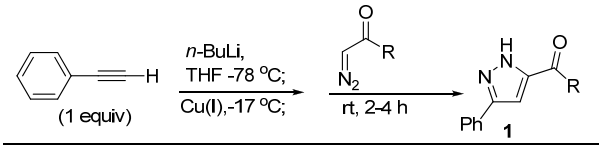
Based on the ratios of pyrazole to BnOH, THF was proved to be the best solvent with CuCN as the copper source. No big solvent effect was observed when CuI was used as catalyst.

1.4.2 Reaction generality

This cycloaddition displays substantial generality with respect to both the alkyne and diazocarbonyl component, and in all cases the products were formed as single

regioisomers. Different diazo compounds like esters, ketones and amides have been investigated (**Scheme 1.20**). Diazoesters showed better reactivities than amides and ketones. Different diazoesters showed similar reactivities.

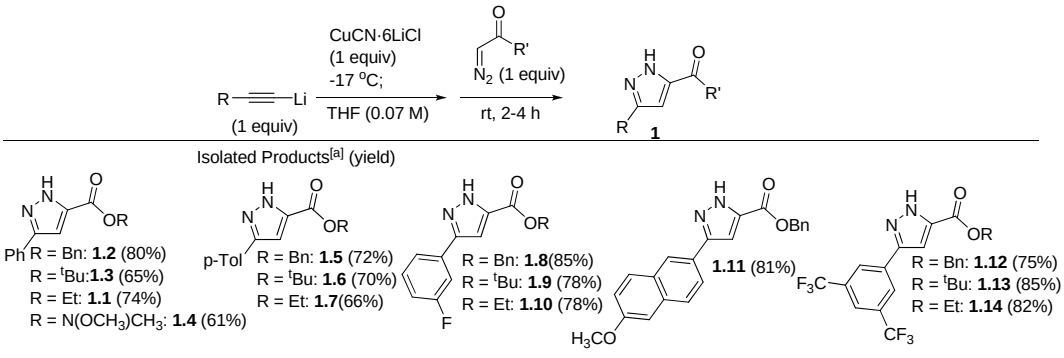
Scheme 1.20. Investigation of different diazo compounds



Entry	Cu(I)	R	yield[a]
1	CuCN·6LiCl	OEt	74%
2	CuCN·6LiCl	OBn	80%
3	CuCN·6LiCl	O^{t}Bu	65%
4	CuCN·6LiCl	N(OMe)Me	60[b]
5	CuCN·6LiCl		44[b]
6	CuCN·6LiCl	Ph	32%

a. Isolated yield; b. Average isolated yield of two experiments.

Scheme 1.21. Aryl alkynes as reaction substrates

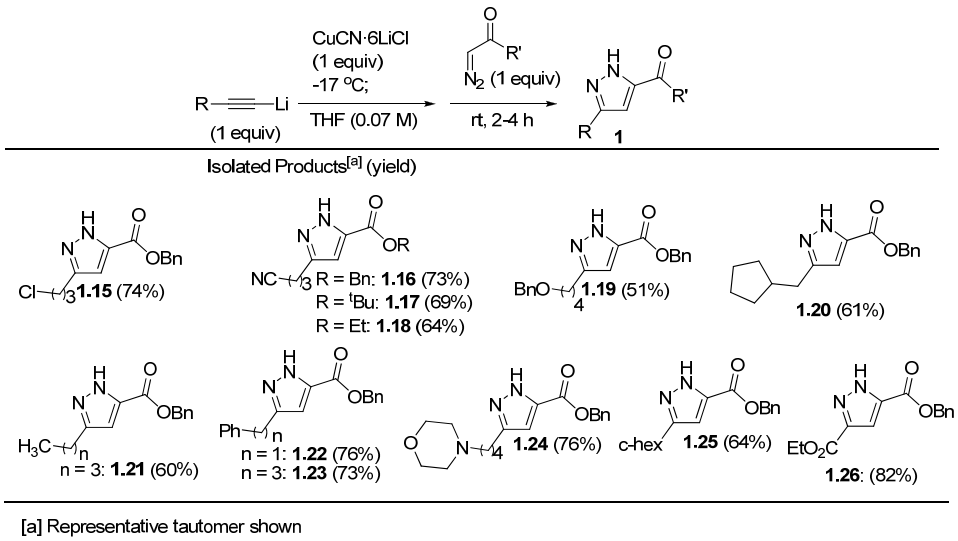


[a] Representative tautomer shown

Electron-poor and electron-rich aryl acetylenes perform well in the cycloaddition (**Scheme 1.21**). Alkyl-substituted terminal alkynes react cleanly, and halides, tertiary

amino groups, esters and nitriles are well tolerated (**Scheme 1.22**). In many cases, the pyrazoles can be isolated in >90% purity by trituration with hexanes; in all cases analytically pure product can be isolated by column chromatography on silica gel.

Scheme 1.22. Alkyl-substituted terminal alkynes



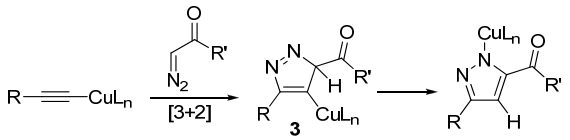
[a] Representative tautomer shown

1.5 Mechanism discussion

1.5.1 Mechanism study

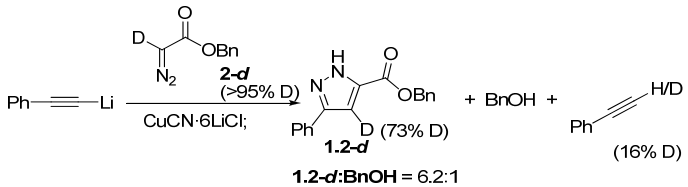
The copper-mediated cycloaddition of alkynyl anions with diazoesters is reminiscent of the copper-catalyzed cycloaddition of terminal alkynes with azides.[41] Accordingly, we suspect a similar reaction mechanism is operative in both cases. Copper may serve as an electron-donating group and raise the energy of the alkyne HOMO. Cycloaddition involving the LUMO of the diazocarbonyl compound generates a (pyrazolyl)Cu intermediate which can tautomerize under the reaction conditions (**Scheme 1.23**).

Scheme 1.23 Mechanism proposal



This proposal accounts for several important observations. First, the fact that the reaction rate is similar in THF, ether and benzene is consistent with a concerted cycloaddition but not with stepwise formation of charged intermediates. Second, the observed regioselectivity is consistent with theoretical predictions regarding cycloaddition featuring $HOMO_{(dipolarophile)}$-$LUMO_{(dipole)}$ interactions.[42] Third, electron withdrawing groups on the alkyne slow the reaction (reaction times were longer than electron-rich alkynes); these groups should lower the HOMO of the alkyne and therefore increase the HOMO-LUMO gap. Fourth, diazomethane does not react with lithiumacetylides under the reaction conditions, presumably a reflection of its high-energy LUMO relative to diazoesters. Finally, deuterium labeling experiments support the proposed tautomerization: copper-mediated cycloaddition with α-D-benzyl diazoacetate (**2**-*d*) yields **1.2**-*d* with substantial deuterium incorporation on the pyrazole ring (**Scheme 1.24**). Additionally, recovered phenyl acetylene was partially deuterated, likely reflecting deprotonation of the initial cycloadduct **3** by alkynyl anion.[43]

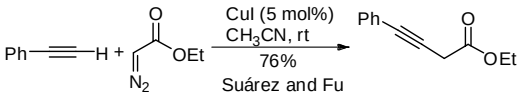
Scheme 1.24 Deuterium labeling experiments



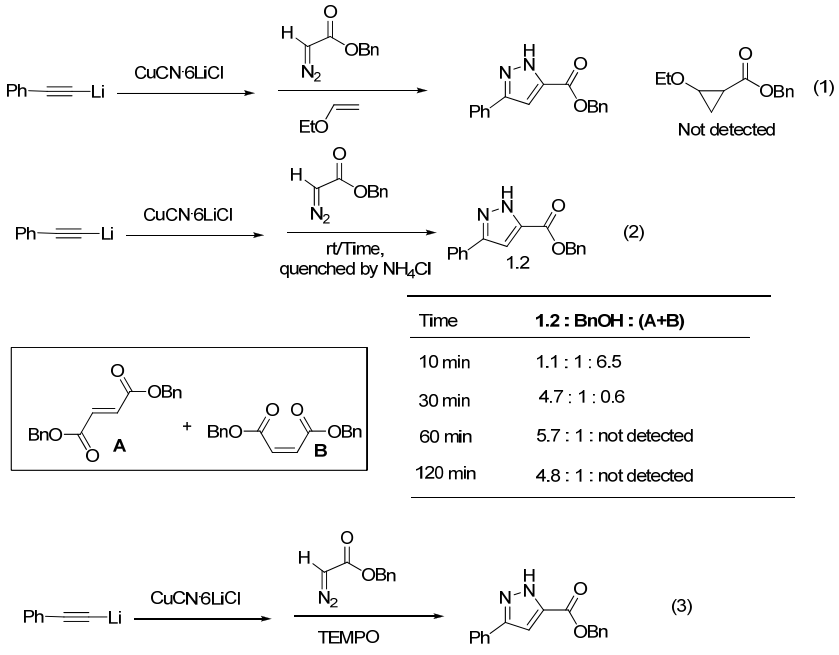
1.5.2 Side reaction analysis

Comparison of the present cycloaddition and Fu's Cu(I)-catalyzed alkynylation of diazoesters (**Scheme 1.25**) is striking.[44] They developed a metal-catalyzed intermolecular coupling of terminal alkynes with diazo compounds to provide ready access to 3-alkynoates. This carbon–carbon bond-forming reaction proceeds efficiently under nonbasic conditions at room temperature. Under their neutral conditions, no pyrazole is formed. Likewise, reaction of ethyl dizaoacetate with PhCCLi/CuCN·6LiCl generates no observable alkynyl ester. (**Scheme 1.25**)

Scheme 1.25 Cu(I)-catalyzed alkynylation of diazoesters



Scheme 1.26. Analysis of the possibilities of byproduct generation

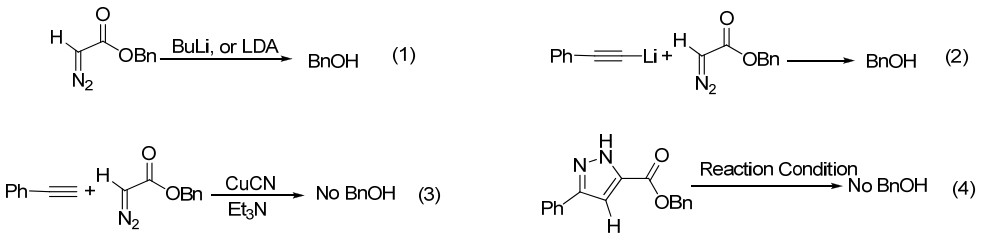


The critical difference between the two systems is likely the use of the alkynyl anion in the cycloaddition versus the neutral alkyne in the Fu reaction. The amount of copper used in the reaction does not appear significant as even catalytic CuI promotes the cycloaddition of lithium phenylacetylene and benzyl diazoacetate. To understand more about how copper can promote cycloaddition instead of carbene coupling under basic conditions, experiment were conducted to intercept potential carbene intermediates (**Scheme 1.26**).

Presumably, carbenes can be trapped by olefins; however, when the reaction mixture included ethyl vinyl ether, no cyclopropane product was identified (**Scheme 1.26**, eq 1). Furthermore, after benzyl diazoacetate was added and the mixture was warmed to rt, the reaction was quenched at different times by sat. aq. NH_4Cl solution (reaction was then under neutral or slightly acidic conditions). Within a short amount of time (10 min), substantial amounts of carbene dimerization products, fumarate and maleate, were observed in the crude NMR spectrum (**Scheme 1.26**, eq 2 and table). This might be generated from the decomposition of unreacted diazo starting material after quenching. In contrast, almost no dimerization products were detected when the reaction was quenched after 60 min, when all the diazo starting material was consumed and the cycloaddition product was generated to the maximium extent. Although only negative data, these results suggest that no carbene intermediate is generated under the current reaction system. In addition, when an equimolar quantity of a radical scavenger reagent such as TEMPO was added into reaction system, high yield of the cycloaddition product was still observed (**Scheme 1.26**, eq 3).

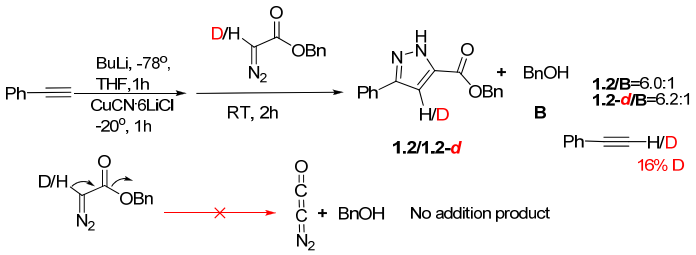
The origin of the benzyl alcohol side product is not clear at present, although several obvious mechanisms for its formation can be ruled out. Generation of BnOH requires a general base and not acetylides or copper salts specifically; benzyl diazoacetate reacts completely with butyllithium, $Li_2Cu(n\text{-}C_4H_9)_2CN$, lithium phenylacetylide or LDA to yield BnOH as the major product under mild conditions. This data, and the fact that the pyrazole is stable to the reaction conditions, implicates benzyl diazoacetate as the source of BnOH rather than the pyrazole product (**Scheme 1.27**).

Scheme 1.27 Benzyl diazoacetate is the source of BnOH



In principle, direct E_2 elimination of alkoxide from benzyl diazoacetate could account for BnOH formation. If so, reducing the kinetic acidity of **2** might increase the ratio of **1.2**:BnOH.[45] However, reactions with **2** or **2**-*d* yielded nearly identical **1.2**:BnOH ratios (**Scheme 1.28**).

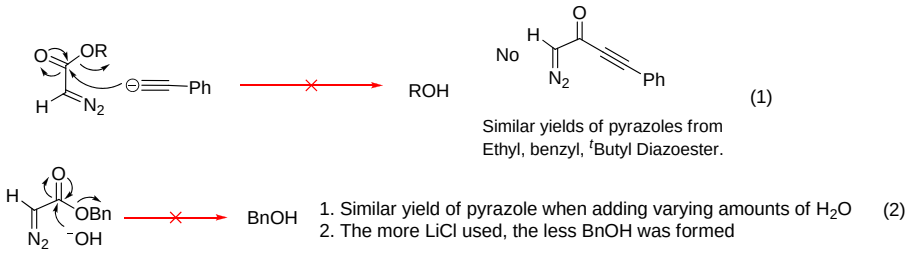
Scheme 1.28. Isotope effect



Additionally, after reaction with 2-*d*, recovered phenylacetylene was only partially deuterated. Thus deprotonation does not account for all of the BnOH formation.

Direct addition to the carbonyl could release BnOH, yet such a pathway is not supported by the data. In particular, unreacted phenylacetylene is recovered after the reaction, and no addition products are observed in the crude reaction mixtures. Furthermore, the similar yields of pyrazole obtained with small (ethyl) and large (*tert*-butyl) diazoesters argue against a competing mechanism involving addition to the carbonyl. (**Scheme 1.29,** eq 1)

Scheme 1.29. Impossible pathways to generate BnOH



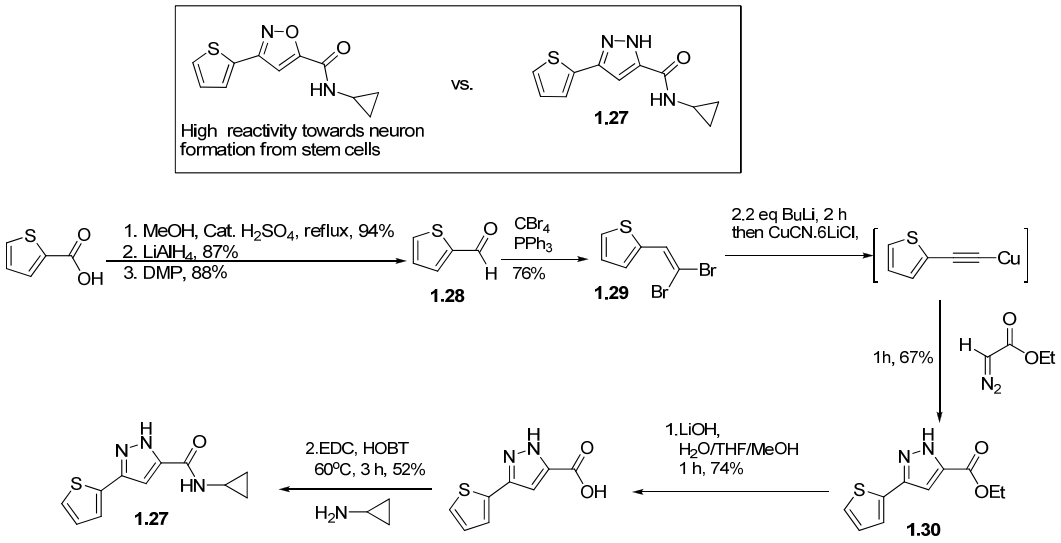
Finally, simple ester hydrolysis appears unlikely. Specifically, reactions performed with varying sub-stoichiometric amounts of water yielded similar amounts of BnOH while excess water inhibits the reaction. Further, the production of BnOH is inversely related to the amount of LiCl (a possible source of water) included in the reaction mixture (**Scheme 1.29,** eq 2).

1.6 Application in the synthesis of a small molecule.

Several 3,5-disubstituted isoxazole compounds have been demonstrated to selectively convert neural stem cells into neurons.[46] Presumably, substituted pyrazoles as a structural analog might have similar bioactivities. Based on this hypothesis, a novel *N*-

cyclopropyl-5-(thiophen-2-yl)-1*H*-pyrazole-3-carboxamide compound was synthesized (**Scheme 1.30**).

Scheme 1.30. Application in synthesis of *N*-cyclopropyl-5-(thiophen-2-yl)-1*H*-pyrazole-3-carboxamide



Starting from thiophene-2-carboxylic acid, the corresponding aldehye was synthesized via a high-yielding, three-step sequence: methylation, reduction and Dess-Martin oxidation. Aldehyde **1.28** was reacted with CBr_4 and PPh_3 in CH_2Cl_2, and dibromoalkene **1.29** was formed in good yield. This dibomoalkene was treated with two equivalent of BuLi to provide the lithium acetylene. Transmetalation to copper acetylene and cycloaddition with ethyl diazoacetate generated ethyl 3-(thiophen-2-yl)-1H-pyrazole-5-carboxylate **1.30** in one pot and high yield. After hydrolysis to the acid and condensation with cyclopropanamine, the final N-cyclopropyl-3-(thiophen-2-yl)-1H-

pyrazole-5-carboxamide **1.27** was synthesized in an efficient and straightforward pathway.

1.7 Conclusion

The copper-promoted cycloaddition of acetylides with diazocarbonyl compounds offers a direct and efficient approach to the synthesis of pyrazoles. The method is operationally simple and tolerates substantial variation in the two reacting partners. Furthermore, as a rare example of an inverse-electron-demand cycloaddition, it represents a conceptually novel approach to this important class of heterocycles.

1.8. Experimental section

1.8.1. Methods and materials

General methods.

Unless otherwise stated, reactions were performed using freshly purified solvents. Solvents were purified using solvent purification columns purchased from Glass Contour, Laguna Beach, CA. All reactions were monitored by thin-layer chromatography with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). Gas chromatography (GC) was performed on an HP 6890N autosampling GC with an HP-5 capillary column and equipped with a FID detector. Flash chromatography was performed with indicated solvents using silica gel (particle size 0.032-0.063 m) purchased from Sorbent Technologies.^{1}H and ^{13}C NMR spectra were recorded on Varian Inova-400, 500 or Mercury-300 spectrometer. Chemical shift are reported relative to internal chloroform ($CDCl_3$: ^{1}H, δ = 7.27, ^{13}C, δ = 77.26). Coupling constants are in Hz and are reported as d (doublet), t (triplet), q (quartet). For signals having multiple coupling patterns, the coupling constant are listed in the same order as the pattern (e.g. dt, J = 2.0, 4.0; 2.0 is the

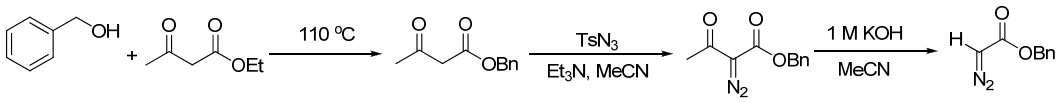
coupling constant for the doublet and 4.0 is for the coupling constant for the triplet). HPLC analyses were carried out on a Shimadzu LC-2010A system. Infrared spectra were recorded on a Perkin- Elmer 1000 series FTIR. Mass spectra were acquired on a Shimadzu QP5000 GC/MS or Agilent technologies 1200 series LC/MS using indicated ionization methods.

Materials:

All transition metal reagents, alkynes and ethyl diazoacetate were used as received from Sigma-Aldrich, Acros chemical, Strem and Alfa Aesar. Other diazo compounds and intermediates were prepared as indicated. Spectra data are available on the WWW under http://www.wiley-vch.de/contents/jc_2002/2008/z801957_s.pdf.

CuCN·6LiCl: CuCN (1eq) and LiCl (6eq) were mixed and heated (180 ^{o}C) under vacuum (0.1 mm Hg) for 10 h.

1.8.2. General procedure for synthesis of diazo compounds.[47]



Benzyl diazoacetate: Benzyl alcohol (0.54 g, 5 mmol) and ethyl acetoacetate (6.5 g, 50 mmol) were combined, sparged with N_2 for 10 min, and then heated at reflux for 5h. Unreacted ethyl acetoacetate was removed under reduced pressure, and benzyl acetoacetate was purified by flash chromatography (5% ethyl estate in hexanes). To a solution of benzyl acetoacetate (192 mg, 1 mmol) in acetonitrile (1.2 ml) was added Et_3N (131.5 mg, 1.3 mmol). The reaction mixture was cooled in an ice bath and a solution of tosyl azide (217 mg, 1.1 mmol) in acetonitrile (1.2 ml) was added slowly. The reaction

mixture was allowed to warm to rt. After stirring for 10h, solvent was removed under reduced pressure. The residue was dissolved in ether and washed with 5% aqueous KOH. To a solution of the crude benzyl 2-diazo-acetoacetate (1.87 g, 9 mmol) in acetonitrile (30 ml) was added 5% KOH (30 ml), and the reaction mixture was stirred for 1h. The reaction mixture was extracted with ether, and the organic phase was separated, dried over Mg_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (5% ethyl acetate in hexanes) provided the desired benzyl diazoacetate (yield: 68% from benzyl 2-diazo-3-acetoacetate) as a yellow liquid.

***Tert*-butyl diazoacetate**: same procedure as benzyl diazoacetate but starting from *tert*-butyl acetoacetate (two step yield: 64%).

Diazo-N-methoxy-N-methylacetamide: same procedure as for benzyl diazoacetate but starting from *N,O*-dimethylhydroxylamine (three step yield: 22%).

2-Diazo-1-morpholinoethanone: same procedure as for benzyl diazoacetate but starting from 1-morpholinobutane-1,3-dione (yield: 20%).

Characterization data for diazo compounds:

Benzyl diazoacetate:[48] Yellow liquid, ^{1}H NMR ($CDCl_3$) δ= 4.79 (s, *1*H), 5.20 (s, 2H), 7.35 (m, 5H). EI-MS (m/z): 176 $[M]^+$.

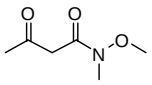
***Tert*-butyl diazoacetate**:[49] Yellow liquid, ^{1}H NMR ($CDCl_3$) δ= 1.49 (s, *9*H), 4.61 (s, 1H). EI-MS (m/z): 142 $[M]^+$.

Diazo-N-methoxy-N-methylacetamide: Yellow liquid, ^{1}H NMR ($CDCl_3$) δ= 3.17 (s, *3*H), 3.68 (s, 3H), 5.32 (s, *1*H). EI-MS (m/z): 129 $[M]^+$.

N-methoxy-N-methyl-3-oxobutanamide (synthesized from refluxing the

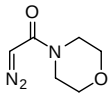
mixture of Weinreb's amine and ethyl acetoacetate in toluene in the presence of DMAP, Et_3N, and DMF)

***N*-methoxy-N-methyl-3-oxobutanamide**:[50]



^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 3H), 3.52 (s, 2H), 3.16 (s, 3H), 2.20 (s, 3H).

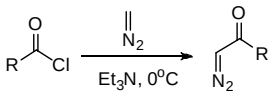
Diazo-1-morpholinoethanone:[51]



Yellow liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 (s, 1H), 3.71 - 3.62 (m, 4H), 3.40 (m, 4H).

1-Morpholinobutane-1,3-dione: (which is generated from refluxing the mixture of morpholine and ethyl acetoacetate in toluene in the presence of DMAP): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 - 3.58 (m, 6H), 3.54 (s, 2H), 3.41 - 3.38 (t, J = 4.7 Hz, 2H), 2.26 (s, 3H).

Synthesis of diazoketone:

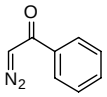


A solution of diazomethane in ether was added directly into a solution of acetyl chloride in ether at 0^{o}C. After reaction (1-2 h), the product was purified by distillation or flash chromatography without any work-up.

Diazopropan-2-one:[52]

Yellow liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25 (s, 1H), 2.07 (s, 4H).

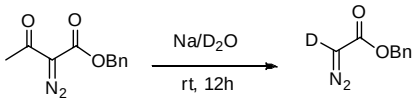
Diazo-1-phenylethanone:[53]



Yellow liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 - 7.71 (m, 2H), 7.57 - 7.50

(m, 1H), 7.48 – 7.41 (m, 2H), 5.89 (s, 1H).

Deuterium benzyl diazoacetate synthesis:



1 M NaOD solution: Sodium metal (69 mg, 3 mmol) was cut in pentane and added into 3 ml of D_2O slowly. To a solution of benzyl 2-diazo-3-oxobutanoate (0.5 mmol, 104 mg) in MeCN, 1M NaOD solution was added and stirred at rt for 12h. After reaction, ether was added. The ether layer was separated and dried by Mg_2SO_4. The product was purified by flash chromatography.

Synthesis of N-cyclopropyl-3-(thiophen-2-yl)-1H-pyrazole-5-carboxamide (**Scheme 1.30, 1.27**)

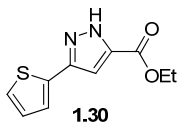
An oven-dried round bottom flask (100 mL in volume) with a Teflon-coated stir bar was charged with thiophene-2-carboxylic acid (1 equiv, 20 mmol, 2.576 g) under a N_2 atmosphere. MeOH (50 ml) and con. H_2SO_4 (0.2 ml) were added and then the flask was heated to 64 ^oC. After refluxed for 12 h, the reaction was cooled to rt and diluted with ethyl acetate (30 ml). The resulting solution was then separated. The aqueous layer was extracted with ethyl acetate (3 X 30 ml). The organic phases were combined, washed with brine, and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the resulting liquid was purified by flash chromatography on silica gel (100% hexane to 5% ethyl acetate in hexane) to give pure methyl thiophene-2-carboxylate.(2.66 g, 94%) ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 - 7.78 (m, 1H), 7.55 (d, J = 4.2 Hz, 1H), 7.11 - 7.08 (m, 1H), 3.88 (s, 3H).

An oven-dried flask (100 mL in volume) with a Teflon-coated stir bar was charged with the methyl thiophene-2-carboxylate (1 equiv, 18.7 mmol, 2.66 g), and THF (60 ml) was added. The flask was cooled to -5^{o}C. $LiAlH_4$ (1.1 equiv, 20.6 mmol, 782 mg) was added to the flask slowly (Caution: substantial gas evolution). The resulting solution was stirred at the same temperature for 1 h. The reaction was quenched by adding H_2O (2.66 ml) very carefully at 0 ^{o}C, followed by addition of NaOH aqueous solution (15%, 2.66 ml) and more H_2O (8 ml). The resulting mixture was stirred at rt for 20 min and then filtered. After removal of the solvent under reduced pressure, the resulting yellow oil was purified by flash chromatography on silica gel (100% hexane to 10% ethyl acetate in hexane) to give pure thiophen-2-ylmethanol. (1.86g, 87%) This compound (1 equiv, 16.3 mmol, 1.86 g) was dissolved in CH_2Cl_2 (30 ml) and a solution of Dess-Martin periodinane (DMP) (1.1 equiv, 18 mmol, 7.6 g) in CH_2Cl_2 (30 ml) was added slowly at 0 ^{o}C. The resulting solution was warmed to rt and stirred at the same temperature for 1h. The reaction was quenched by adding sat. aq. $Na_2S_2O_3$ solution (15 ml) and separated. The CH_2Cl_2 solution was washed by brine and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the resulting liquid was purified by flash chromatography on silica gel (100% hexane to 5% ethyl acetate in hexane) to give pure thiophene-2-carbaldehyde **1.28**. (1.6 g, 88%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.95 (d, J = 1.2 Hz, 1H), 7.87 - 7.68 (m, 2H), 7.25 - 7.19 (m, 1H).

Dibromoolefin was synthesized by following the known procedure.[54] PPh_3 (4 equiv, 4 mmol, 1.05 g) was added to a solution of CBr_4 (2 equiv, 2 mmol, 663 mg) in CH_2Cl_2 (2 ml) at 0 ^{o}C. After stirring at the same temperature for 20 min, a solution of thiophene-2-carbaldehyde **1.28** (1 equiv, 1 mmol, 112 mg) in CH_2Cl_2 (3 ml) was transferred to the

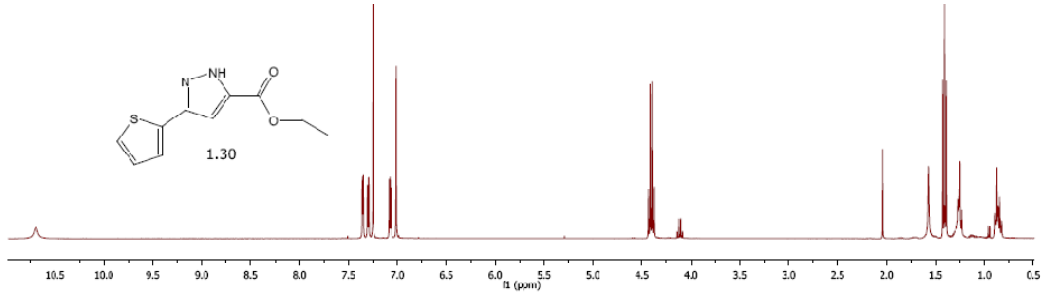
reaction solution. The resulting solution was warmed to rt and stirred at the same temperature for 30 min. The desired 2-(2,2-dibromovinyl)thiophene **1.29** was purified by filtering through a thin pad of silica gel. (185 mg, 70%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.39 - 7.35 (m, 1H), 7.26 - 7.23 (m, 1H), 7.03 (dd, *J* = 5.1, 3.7 Hz, 1H).

Synthesis of ethyl 3-(thiophen-2-yl)-1*H*-pyrazole-5-carboxylate **1.30**. An oven-dried flask (100 mL in volume) with a Teflon-coated stir bar was added to a solution of 2-(2,2-dibromovinyl)thiophene (1 equiv, 3 mmol, 804 mg) in THF (18 ml). BuLi (2.2 equiv, 6.6 mmol, 2.64 ml, 2.5 M solution in hexane) was added to reaction at -78 ^{o}C. After 1 hour this solution was transferred to solution of CuCN·6LiCl (345 mg, 1.0 mmol) in THF (6 mL) and then the general procedure for the formation of pyrazole was followed to provide ethyl 3-(thiophen-2-yl)-1*H*-pyrazole-5-carboxylate **1.30** (251 mg).



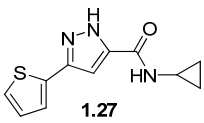
1.30

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.70 (s, 1H), 7.35 (dd, *J* = 3.6, 1.0 Hz, 1H), 7.30 (dd, *J* = 5.1, 0.9 Hz, 1H), 7.07 (dd, *J* = 5.0, 3.6 Hz, 1H), 7.01 (s, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H). EI-MS (m/z): 222 $[M]^+$. (see ^{1}HNMR spectrum below)



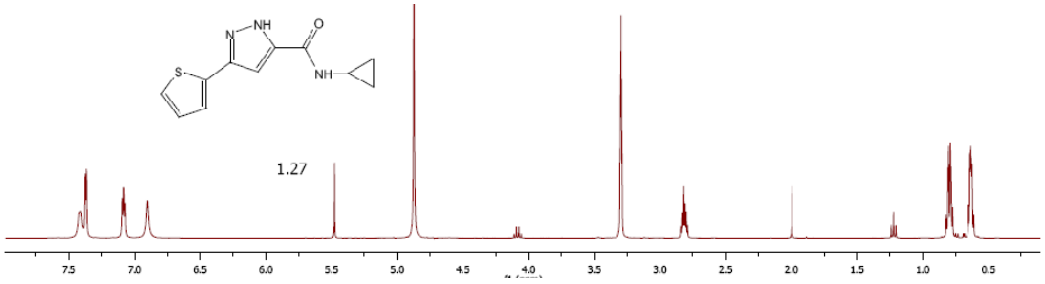
To a solution of **1.30** (1 equiv, 0.6 mmol, 147 mg) in THF (4 ml) was added $LiOH.H_2O$ (10 equiv, 6 mmol, 277 mg), H_2O (4 ml) and MeOH (1 ml). The resulting solution was heated to 60 ^{o}C for 2 h and then was cooled to rt. The solution was extracted

with ethyl acetate (5 ml X 2). The aqueous solution was neutralized to pH 7 with 1 M HCl solution and then extracted with ethyl acetate (5 ml X 2). To the aqueous solution was added NaCl (2 g) and then it was extracted with ethyl acetate (5 ml X 2). The combined organic fractions were dried over magnesium sulfate. Rremoval of the solvent under reduced pressure provided the crude product. To a solution of this crude compound in THF (10 ml), another solution of EDC (1equiv, 0.43 mmol, 82.2 mg) and HOBT (0.2 equiv, 0.086 mmol, 12 mg) in CH_2Cl_2 (10 ml) was added at rt. Cyclopropylamine (5 equiv, 2.15 mmol, 123 mg) was added via syringe. The resulting solution was heated to 60 ^oC for 3 h. The reaction was cooled to rt, diluted with ethyl acetate (20 ml) and then separated. The aqueous layer was extracted with ethyl acetate (3 X 20 ml). The organic phases were combined, washed with brine, and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the resulting liquid was purified by flash chromatography on silica gel (5% to 50% ethyl acetate in hexane) to give pure N-cyclopropyl-3-(thiophen-2-yl)-1*H*-pyrazole-5-carboxamide **1.27**. (51.6 mg), ^1H NMR



1.27

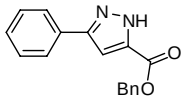
(400 MHz, CD_3OD) δ 7.41 (s, 1H), 7.39 - 7.35 (m, 1H), 7.08 (dd, *J* = 4.7, 3.9 Hz, 1H), 6.90 (s, 1H), 2.98 - 2.65 (m, 1H), 0.86 - 0.67 (m, 2H), 0.67 - 0.57 (m, 2H). EI-MS (m/z): 233 $[M]^+$. (see spectrum below)



1.8.3. General procedure for the formation of pyrazole.

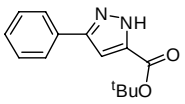
BuLi (0.625 mL of 1.6M in hexane, 1.0 mmol, 1.0 equiv) was added to a solution of alkyne (1.0 mmol) in THF (4 mL) at -78 ^{o}C. After 1 hour this solution was transferred to solution of CuCN·6LiCl (345 mg, 1.0 mmol) in THF (6 mL). The reaction mixture was warmed to -17 ^{o}C (dry ice/brine) and stirred for 1 h. A solution of diazo compound (1.0 mmol) in THF (4 mL) was added and the cold bath was removed. The resulting solution was stirred for 2-4 h at room temperature. After TLC analysis indicated complete consumption of the diazo carbonyl compound, aqueous ammonium chloride and ether were added. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic phases were washed with brine and dried over $MgSO_4$, concentrated and purified by flash chromatography on silica gel. Characterization data are provided below for all substrates.

Benzyl 3-phenyl-1H-pyrazole-5-carboxylate (1.2): White solid, ^{1}H NMR ($CDCl_3$) δ=



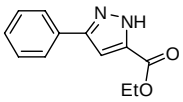
5.29 (s, *2*H), 7.11 (s, 1H), 7.38 (m, 8H), 7.70 (d, *J* = 7.6, 2H), 11.92 (bs, NH). ^{13}C NMR ($CDCl_3$) δ= 67.0, 105.7, 125.9, 128.6, 128.8, 129.1, 130.4, 135.5, 140.0, 148.5, 160.9. FTIR (thin film) 3101, 3013, 1727, 1415, 1236, 1136, 1009, 760.8, 693.7cm^{-1}. EI-MS (m/z): 278 $[M]^{+}$.

***tert*-butyl 3-phenyl-1*H*-pyrazole-5-carboxylate (1.3)**: White solid, ^{1}H NMR ($CDCl_3$) δ=



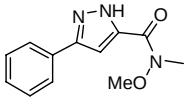
1.52 (s, 9H), 7.01 (s, 1H), 7.32 (t, *J* = 7.2 1H), 7.38 (t, *J* = 7.2, 2H), 7.76 (d, *J* =7.6, 2H), 12.89 (NH).^{13}C NMR ($CDCl_3$) δ= 28.4, 82.5, 105.6, 125.9, 128.6, 129.1, 131.2, 140.5, 149.5, 160.3. FTIR (thin film):2978, 1720, 1459, 1413, 1368, 1253, 1139, 841, 763, 691cm^{-1}. EI-MS (*m/z*): 244 $[M]^{+}$

Ethyl 3-phenyl-1*H*-pyrazole-5-carboxylate (1.1):[55] Brown solid, ^{1}H NMR ($CDCl_3$) δ= 1.44 (t, *J* = 7.2, 3H), 4.44 (q, J = 7.2, 2H), 7.14 (s 1H), 7.38 (t, J = 7.6, 1H), 7.46 (t, J= 7.6,



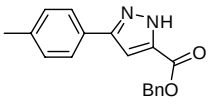
2H), 7.77 (d, *J* = 7.6, 2H), 10.68 (NH). ^{13}C NMR ($CDCl_3$) δ= 14.2, 61.1, 105.1, 125.8, 128.7, 129.1, 130.0, 140.9, 147.9, 161.5. FTIR (thin film):3140, 2980, 1726, 1466, 1415, 1276, 1244, 1140, 1025, 762, 691cm^{-1}. EI-MS (*m/z*): 216 $[M]^+$

***N*-methoxy-*N*-methyl-3-phenyl-1*H*-pyrazole-5-carboxamide (1.4)**: Brown solid, ^{1}H



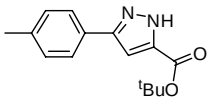
NMR ($CDCl_3$) δ= 3.41 (s, 3H), 3.78 (s, 3H), 7.14(s 1H), 7.32 (t, *J* = 7.6 1H), 7. 41 (t, J = 7.6, 2H), 7.91 (d, *J* = 7.6, 2H), 11.99 (bs, NH). ^{13}C NMR ($CDCl_3$) δ= 33.2, 61.9, 106.0, 126.0, 128.3, 129.0, 132.9, 136.3, 152.3, 159.8. FTIR (thin film): 3102, 2978, 1720, 1482, 1414, 1368, 1279, 1252, 1171, 1138, 1007, 840, 762, 691cm^{-1}. EI-MS (*m/z*): 231 $[M]^+$

Benzyl 3-p-tolyl-1*H*-pyrazole-5-carboxylate (1.5) (Table 2, entry 2): White solid, ^{1}H



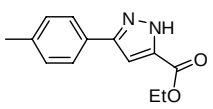
NMR ($CDCl_3$) δ= 2.35 (s, 3H), 5.22 (s, 2H), 6.98 (br. s, 1H), 7.15 (t, *J* = 7.5, 2H), 7.28-7.32 (m, 5H), 7.55 (d, J = 7.8, 2H), 12.33 (bs, NH). ^{13}C NMR ($CDCl_3$) δ= 21.5, 66.9, 105.4, 125.8, 128.5, 128.8, 129.8, 135.6, 138.7, 140.2, 148.3, 161.0. FTIR (thin film) 2923, 1727, 1417,1236, 1134, 1009cm^{-1}.EI-MS (m/z): 292 $[M]^+$.

***tert*-butyl 3-p-tolyl-1*H*-pyrazole-5-carboxylate (1.6)**: White solid, ^{1}H NMR ($CDCl_3$) δ=



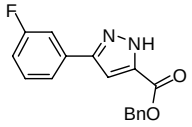
1.60 (s, 9H), 2.37 (s, 3H), 7.00 (s, 1H), 7.22 (d, *J* = 7.2, 2H), 7.66 (d, *J* = 7.2, 2H), 10.69 (bs, NH). ^{13}C NMR ($CDCl_3$) δ= 21.5, 28.4, 82.8, 105.5, 125.8, 128.9, 129.8, 138.6, 139.5, 150.8, 159.8. FTIR (thin film): 2924, 2870, 1718, 1415, 1368, 1277, 1137, 1008cm^{-1}. EI-MS (*m/z*): 258 $[M]^+$.

Ethyl 3-p-tolyl-1*H*-pyrazole-5-carboxylate (1.7): Brown solid, ^{1}H NMR ($CDCl_3$) δ=



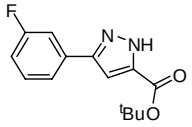
1.28 (t, *J* = 6.8, 3H), 2.35(s, 3H), 4.27 (q, *J* = 6.8, 2H), 6.99 (s 1H), 7.18 (d, *J* =7.2, 2H), 7.6 (d, *J* = 7.2, 2H), 12.9 (bs, NH). ^{13}C NMR ($CDCl_3$) δ= 14.2, 21.5, 61.1, 104.9, 125.8, 127.0, 129.7, 138.6, 141.3, 147.2, 161.75. FTIR (thin film):3416, 2982, 1725, 1419, 1273, 1242, 1138, 1025, 817, 775cm^{-1}. EI-MS (*m/z*): 230 $[M]^+$.

Benzyl 3-(3-fluorophenyl)-1*H*-pyrazole-5-carboxylate (1.8): White solid, ^{1}H NMR



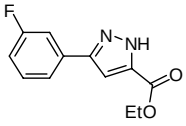
($CDCl_3$) δ= 5.40 (s, 2H), 7.06 (dt, *J* = 1.6, 8.4, 1H), 7.15 (s, 1H), 7.37-7.52 (m, 7H), 7.56 (d, *J* = 7.6, 1H), 10.48 (bs, NH). ^{13}C NMR ($CDCl_3$) δ= 66.6, 106.9, 112.8 (d, J = 23), 115.7 (d, J = 21), 122.1, 128.8, 128.9, 129.2, 131.7 (d, J = 9), 133.4, 136.6, 140.2, 146.8, 161.0, 163.2 (d, J = 241). FTIR (thin film): 3136, 1726, 1591, 1458, 1248, 1213, 1180, 1132, 1012, 857, 776, 696cm^{-1}. EI-MS (*m/z*): 296 $[M]^+$.

***tert*-butyl 3-(3-fluorophenyl)-1*H*-pyrazole-5-carboxylate (1.9)**: White solid, ^{1}H NMR



($CDCl_3$) δ= 1.61 (s, 9H), 7.00-7.09 (m, 2H), 7.38 (dt, J = 7.6, 10.8, 1H), 7.56 (d, *J* = 7.6, 1H), 7.60 (d, *J* = 10, 1H), 10.94 (bs, NH). ^{13}C NMR ($CDCl_3$) δ= 28.4, 83.1, 106.0, 112.9 (d, J = 20), 115.3 (d, J =20), 121.6, 130.6 (d, J = 9), 134.4, 138.3, 150.2, 159.6, 164.7 (d, J = 250). FTIR (thin film): 3138, 2980, 1720, 1591, 1478, 1369, 1255, 1217, 1162, 1134, 1010, 864, 779cm^{-1}. EI-MS (*m/z*): 262 $[M]^+$.

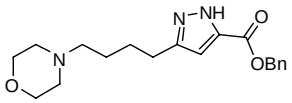
Ethyl 3-(3-fluorophenyl)-1*H*-pyrazole-5-carboxylate (1.10): Brown solid, ^{1}H NMR



($CDCl_3$) δ= 1.29 (t, *J* = 9.6, 3H), 4.30 (q, *J* = 9.6, 2H), 6.97-7.18 (m, 2H), 7.35 (dd, *J* =8.0, 10, 1H), 7.47 (d, *J* =14.2, 1H), 7.53 (d, *J* = 10, 1H). 12.70 (bs, NH). ^{13}C NMR ($CDCl_3$) δ= 14.3, 61.6, 105.9, 112.9 (d, J = 30), 115.6 (d,

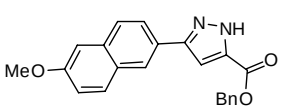
J = 29), 121.6, 130.7 (d, J = 10), 133.1, 138.9, 148.8, 160.7, 165.0 (d, J = 330). FTIR (thin film): 2983, 1726, 1419, 1273, 1242, 1138, 1025, 817, 775cm^{-1}. EI-MS (*m/z*): 234 $[M]^+$.

Benzyl 3-(4-morpholinobutyl)-1*H*-pyrazole-5-carboxylate (1.11): Brown oil, ^{1}H NMR



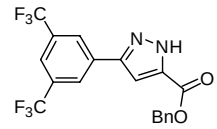
($CDCl_3$) δ= 1.46-1.56 (m, 2H), 1.57-1.66 (m, 2H), 2.37 (dt, *J* = 4.8, 7.2, 2H), 2.37-2.48(m, 4H), 2.71 (dt, *J* = 3.9, 7.5, 2H), 3.73 (q, *J* = 4.5, 4H), 5.34 (s, 2H), 6.60 (d, J = 4.5, 1H), 7.30-7.45 (m, 5H), 9.25 (bs, NH). ^{13}C NMR ($CDCl_3$) = 25.9, 26.0, 27.0, 53.8, 58.6, 66.7, 67.0, 106.8, 128.5, 128.8, 136.0, 141.8, 147.5, 162.3. FTIR (thin film): 3202, 2948, 2862, 1724, 1451, 1233, 1115, 865, 780, 699cm^{-1}. EI-MS (*m/z*): 343 $[M]^+$.

Benzyl 3-(6-methoxynaphthalen-2-yl)-1*H*-pyrazole-5-carboxylate (1.12):



White solid ^{1}H NMR (CDCl3) δ= 3.85 (s, 3H), 5.34 (s, 2H), 7.16 (dd, J = 2.0, 8.8, 1H), 7.33 (dt, J =1.4, 8.3, 3H), 7.38 (t, J = 7.0, 2H), 7.46 (d, J = 7.3, 2H), 7.81 (d, J = 9.0, 1H), 7.84, (d, J = 8.8, 1H), 7.93 (d, J = 7.8, 1H), 8.33 (s, 1H), 13.4, (bs, 2H). ^{13}C NMR (DMSO) δ= 55.9, 66.5, 106.0, 106.7, 120.0, 124.6, 124.7, 125.9, 128.0, 128.8, 128.8, 129.1, 129.2, 130.3, 134.7, 136.7, 141.0, 147.4, 158.4, 161.5. FTIR (thin film): 3237, 1691, 1488, 1275, 1254, 1146, 856, 770, 695cm^{-1}. ESI-MS (*m/z*): 359 $[M+H]^+$.

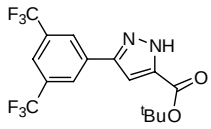
Benzyl 3-(3,5-bis(trifluoromethyl)phenyl)-1*H*-pyrazole-5-carboxylate (1.13):



White solid, ^{1}H NMR ($CDCl_3$) δ = 5.40 (s, 2H), 7.26 (bs, 1H), 7.25-7.47 (m, 5H), 7.84 (s, 1H), 8.30 (bs, 2H), 12.0 (bs, 1H). ^{13}C NMR

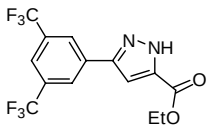
($CDCl_3$) δ = 67.9, 106.7, 122.0, 124.9 (q, J = 270), 125.9, 128.8, 129.0, 129.1, 132.4, (q, J = 33), 134.3, 135.0, 135.9, 150.0, 159.78. FTIR (thin film): 3294, 3099, 3070, 1733, 1709, 1345, 1279, 1174, 1136, 1016, 897, 698, 682cm^{-1}. EI-MS (*m/z*): 414 $[M]^+$.

***tert*-butyl 3-(3,5-bis(trifluoromethyl)phenyl)-1*H*-pyrazole-5-carboxylate (1.14)**:



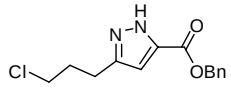
White solid, ^1H NMR ($CDCl_3$) δ= 1.68 (s, 9H), 7.20 (s, 1H), 7.86 (s, 1H), 8.38 (s, 2H), 12.88 (s, 1H). ^{13}C NMR ($CDCl_3$) δ = 28.40, 83.83, 106.2, 121.77, 123.6 (q, J = 270), 125.9, 132.4 (q, J = 45), 134.80, 137.46, 149.84, 159.10. FTIR (thin film): 2984, 1726, 1348, 1279, 1139, 1012, 895, 773, 707, 682cm^{-1}. EI-MS (*m/z*): 380 $[M]^+$.

Ethyl 3-(3,5-bis(trifluoromethyl)phenyl)-1*H*-pyrazole-5-carboxylate (1.15):



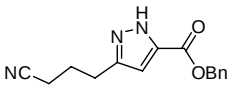
White solid, ^1H NMR ($CDCl_3$) δ = 1.44 (t, *J* = 7.2, 3H), 4.45 (q, *J* = 7.2, 2H), 7.26 (s 1H), 7.85 (s, 1H), 8.29 (s, 2H), 11.2 (br, s, 1H). ^{13}C NMR ($CDCl_3$) δ= 14.4, 62.2, 106.5, 122.0, 123.5 (q, J = 270), 125.9, 132.5 (q, J = 34), 134.6, 136.0, 150.0, 159.8. FTIR (thin film): 3273, 1745, 1703, 1461, 1348, 1282, 1130, 1026, 897, 682cm^{-1}. EI-MS (*m/z*): 352 $[M]^+$.

Benzyl 3-(3-chloropropyl)-1*H*-pyrazole-5-carboxylate (1.16): Brown solid, ^1H NMR



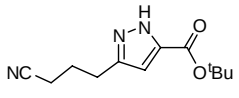
($CDCl_3$) δ = 1.99 (quintet, J = 6.5, 2H), 2.77 (t, *J* = 6.4, 2H), 3.43 (t, *J* = 6.4, 2H), 5.31 (s, 2H), 6.59 (s, 1H), 7.31-7.43 (m, 5H), 12.6 (bs, NH). ^{13}C NMR ($CDCl_3$) δ= 23.3, 31.9, 44.1, 66.8, 107.0, 128.57, 128.62, 128.8, 135.8, 141.6, 146.4, 161.9. FTIR (thin film): 3187, 3093, 2870, 1726, 1453, 1420, 1226, 1162, 1108, 1004, 779, 750 cm^{-1}. EI-MS (*m/z*): 278 $[M]^+$.

Benzyl 3-(3-cyanopropyl)-1*H*-pyrazole-5-carboxylate (1.17): Brown solid, ^{1}H NMR



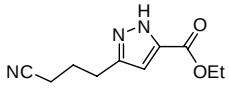
($CDCl_3$) δ= 1.91 (quintet, J = 7.4, 2H), 2.26 (t, *J* = 7.2, 2H), 2.78 (t, *J* = 7.6, 2H), 5.32 (s, 2H), 6.61 (s, 1H), 7.30-7.39 (m, 5H), 11.8 (bs, NH). ^{13}C NMR ($CDCl_3$) δ= 16.6, 25.1, 25.1, 66.9, 107.2, 119.5, 128.5, 128.7, 128.9, 135.8, 141.4, 146.0, 161.8. FTIR (thin film): 3191, 2963, 1725, 1454, 1421, 1226, 1161, 1003, 779, 751 cm^{-1}. EI-MS (*m/z*): 269 $[M]^+$.

***tert*-butyl 3-(3-cyanopropyl)-1*H*-pyrazole-5-carboxylate (1.18)**: Brown solid, ^{1}H NMR



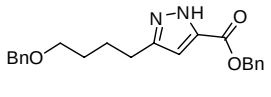
($CDCl_3$) δ = 1.51 (s, 9H), 1.91-2.04 (m, 2H), 2.34 (t, *J* = 7.2 2H), 2.83 (t, *J* = 7.2, 2H), 6.51(s, 1H), 10.7 (bs, NH). ^{13}C NMR ($CDCl_3$) δ= 16.6, 25.3, 25.6, 28.4, 82.2, 107.0, 119.6, 141.5, 147.2, 160.7. FTIR (thin film): 2978, 1714, 1415, 1368, 1248, 1152, 999, 841, 782cm^{-1}. EI-MS (*m/z*): 179 $[M-{}^{t}Bu]^+$.

Ethyl 3-(3-cyanopropyl)-1*H*-pyrazole-5-carboxylate (1.19): Brown solid, ^{1}H NMR



($CDCl_3$) δ = 1.31 (t, *J* = 7.2, 3H), 1.94-2.03 (m, 2H), 2.35 (t, *J* = 7.2, 2H) 2.86 (t, *J* = 7.2, 2H), 4.31 (q, *J* = 7.2, 2H), 6.58 (s 1H), 10.45 (bs, NH). ^{13}C NMR ($CDCl_3$) δ= 14.5, 16.6, 25.2, 25.2, 61.3, 107.0, 119.5, 141.5, 146.4, 161.9. FTIR (thin film): 3134, 2980, 1717, 1422, 1241, 1174, 1110, 784cm^{-1}. EI-MS (*m/z*): 207 $[M]^+$.

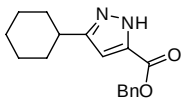
Benzyl 3-(4-(benzyloxy)butyl)-1*H*-pyrazole-5-carboxylate (1.20): Brown solid, ^{1}H



NMR ($CDCl_3$) δ = 1.59-1.64 (m, 2H), 1.66-1.71(m, 2H), 2.64 (t, *J* = 7.2, 2H), 3.46 (t, *J* = 6.4, 2H), 4.48 (s, 2H), 5.32 (s, 2H), 6.59 (s, 1H), 7.25-7.40 (m, 10H), 10.91, (bs, NH). ^{13}C NMR ($CDCl_3$) δ = 25.8, 26.2, 29.2, 66.7, 70.2, 73.2, 106.7, 127.86, 127.92, 128.49, 128.55, 128.6, 128.8, 136.0, 138.6, 142.2,

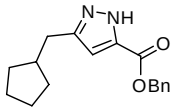
147.8, 162.2. FTIR (thin film): 3190, 2942, 1725, 1453, 1420, 1231, 1162, 737, 697cm^{-1}. EI-MS (*m/z*): 364 $[M]^+$.

Benzyl 3-cyclohexyl-1*H*-pyrazole-5-carboxylate (1.21): Brown solid, ^{1}H NMR ($CDCl_3$)



δ= 1.04-1.26 (m, 5H), 1.58-1.73 (m, 3H), 1.82-1.88 (m, 2H), 2.41-2.52 (m, 1H), 5.29 (s, 2H), 6.55 (s, 1H), 7.29 (m, 5H), 10.68 (bs, NH). ^{13}C NMR ($CDCl_3$) δ = 26.0, 26.1, 32.5, 35.4, 66.6, 104.9, 128.4, 128.4, 128.7, 135.9, 141.9, 152.2, 162.4. FTIR (thin film): 3089, 2929, 1725, 1450, 1231, 1162, 1008, 778, 749, 697 cm^{-1}. EI-MS(*m/z*): 284 $[M]^+$.

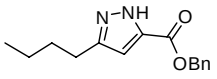
Benzyl 3-(cyclopentylmethyl)-1*H*-pyrazole-5-carboxylate (1.22): Brown solid, ^{1}H



NMR ($CDCl_3$) δ = 1.06-1.18 (m, 2H), 1.49- 1.59 (m, 4H), 1.62-1.71 (m, 2H), 2.10 (sep, *J* = 7.6, 1H), 2.66 (d, *J* = 7.6, 2H), 5.33 (s, 2H), 6.63 (s, 1H), 7.25-7.41 (m, 5H), 12.63 (bs, NH). ^{13}C NMR ($CDCl_3$) = 25.2, 32.0, 32.6, 40.0, 66.6, 106.9, 128.46, 128.52, 128.8, 136.0, 142.0, 147.1, 162.3.

FTIR (thin film):3092, 1726, 1453, 1417, 1224, 1161, 1104, 778, 749, 697 cm^{-1}. EI-MS (*m/z*): 284 $[M]^+$.

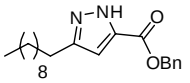
Benzyl 3-butyl-1*H*-pyrazole-5-carboxylate (1.23): Brown solid, ^{1}H NMR ($CDCl_3$) δ =



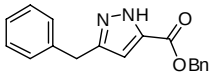
0.86 (t, *J* = 7.2, 3H), 1.26 (sextuplet, *J* = 7.2, 2H), 1.51 (quintet, *J* = 7.2, 2H), 2.58 (t, *J* = 7.2, 2H), 5.31 (s, 2H), 6.56 (s, 1H), 7.3-7.37 (m, 5H), 11.5, (bs, NH). ^{13}C NMR ($CDCl_3$) δ = 14.0, 22.4, 22.6, 31.3, 66.6, 106.5, 128.5, 128.5, 128.8, 136.1, 142.0, 147.5, 162.3.

FTIR (thin film): 3185, 2959, 1726, 1455, 1224, 1160, 1005, 750, 778, 697 cm^{-1}. EI-MS (*m/z*): 258 $[M]^+$.

Benzyl 3-decyl-1*H*-pyrazole-5-carboxylate: Brown solid, ^{1}H NMR ($CDCl_3$) δ = 0.89 (t, *J* = 6.8, 3H), 1.20-1.35 (m, 14H), 1.51-1.60 (br, 2H), 2.59 (t, *J* = 7.6, 2H), 5.33 (s, 2H), 6.58 (s, 1H), 7.3-7.4 (m, 5H), 11.04 (bs, NH). ^{13}C NMR ($CDCl_3$) δ= 14.4, 22.9, 26.0, 29.3, 29.4, 29.6, 29.8, 29.8, 32.2, 66.6, 106.6, 128.45, 128.49, 128.8, 136.0, 141.9, 147.5, 162.3. FTIR (thin film): 2925, 1727, 1452, 1159, 1005, 778, 749, 696 cm^{-1}. EI-MS (*m/z*): 342 $[M]^+$.

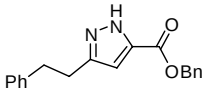


Benzyl 3-benzyl-1*H*-pyrazole-5-carboxylate (1.24):



Brown solid, ^{1}H NMR ($CDCl_3$) δ= 4.00 (s, 2H), 5.30 (s, 2H), 6.57 (s, 1H), 7.16-7.38 (m, 10 H), 12.67 (bs, NH). ^{13}C NMR ($CDCl_3$) δ = 32.6, 66.8, 107.7, 128.6, 128.7, 128.8, 128.9, 129.0, 135.8, 138.4, 141.4, 147.1, 162.0. FTIR (thin film) 3185, 3066, 2962, 1725, 1455, 1416, 1495, 1224, 1160, 1108, 697 cm^{-1}. EI-MS (*m/z*): 292 $[M]^+$.

Benzyl 3-phenethyl-1*H*-pyrazole-5-carboxylate (1.25):

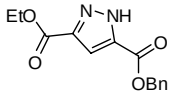


Brown solid, ^{1}H NMR ($CDCl_3$) δ = 2.85-3.03 (m, 4H), 5.30 (s, 2H), 6.63 (s, 1H), 7.18 (t, *J* = 6.4, 2H), 7.22 (d, *J* = 7.2, 2H), 7.28 (t, *J* = 7.2, 2H), 7.33 (m, 4H), 11.10 (bs, NH). ^{13}C NMR ($CDCl_3$) δ = 27.9, 35.6, 66.7, 106.9, 126.5, 127.4, 128.5, 128.6, 128.7, 128.8, 136.0, 141.0, 142.2, 146.7, 162.3.

FTIR (thin film): 3089, 2960, 1725, 1454, 1226, 1161, 1108, 1004, 750, 698 cm^{-1}.

EI-MS (*m/z*): 306 $[M]^+$.

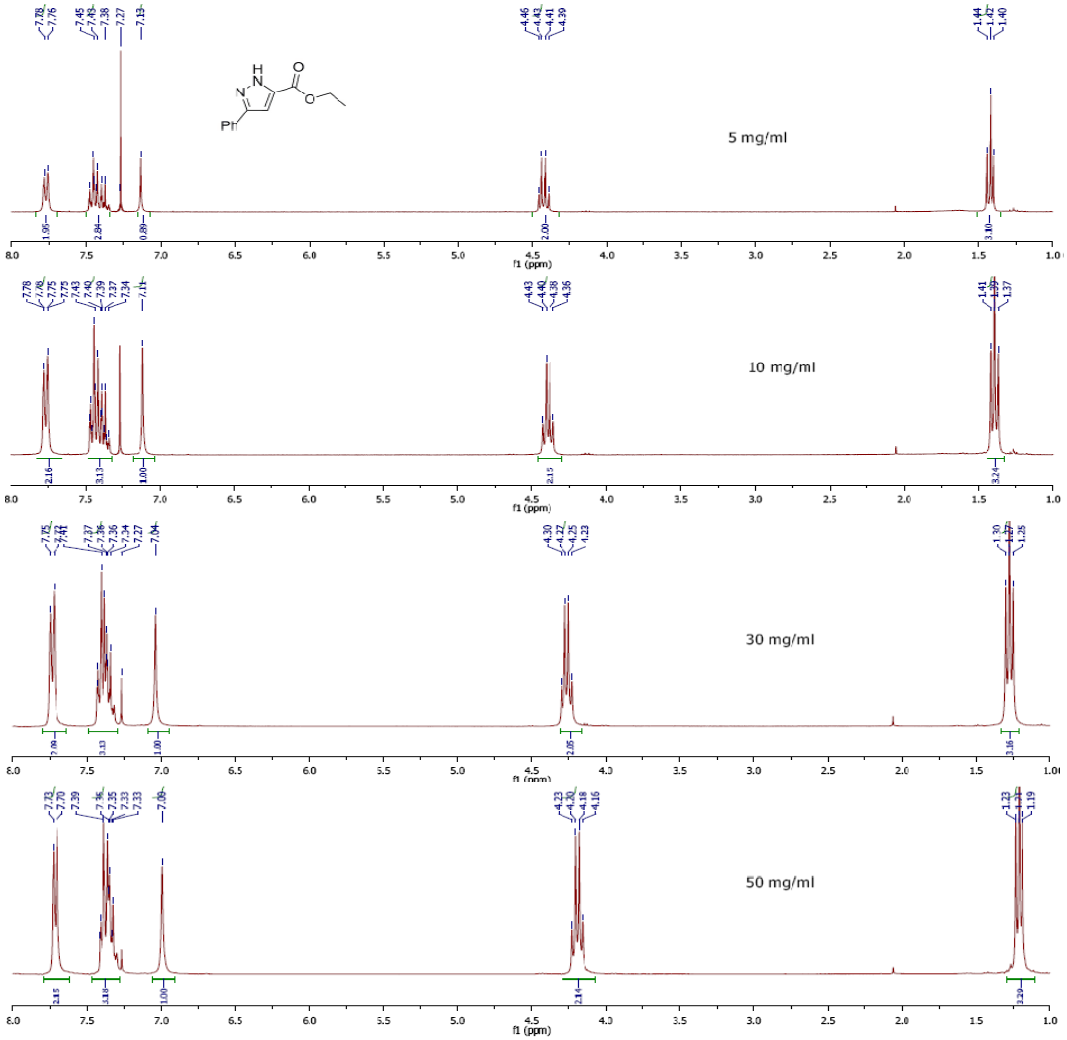
5-benzyl 3-ethyl 1*H*-pyrazole-3,5-dicarboxylate (1.26):

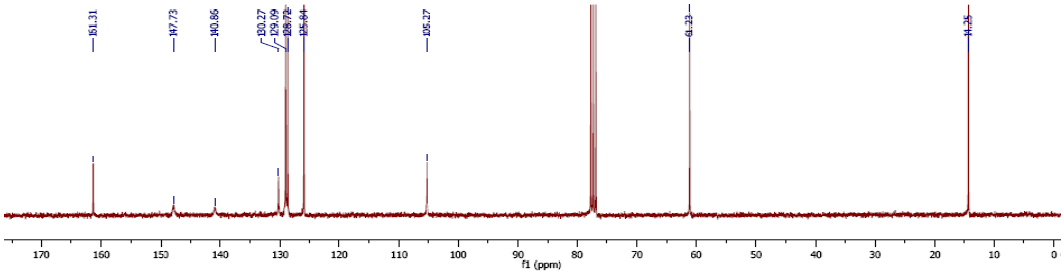


Brown solid, ^{1}H NMR ($CDCl_3$) δ = 1.29 (t, *J* = 7.2, 3H), 4.31 (q, *J* = 7.2, 2H), 5.3 (s, 2H), 7.28-7.37 (m, 6H), 11.41 (bs, NH). ^{13}CNMR ($CDCl_3$) δ = 14.33, 61.81, 67.34, 111.69, 128.68, 128.78, 135.35, 140 (bs), 160.43, 160.52. FTIR

(thin film): 3145, 2983, 1729, 1455, 1315, 129, 1169, 1086, 1019, 767, 698cm^{-1}. EI-MS (*m/z*): 274 $[M]^+$.

Pyrazoles display concentration-dependent NMR spectra (See next page). The largest changes are observed for the pyrazole methine proton and the methylene of the ester. ^{1}H NMR data was collected at approximately 5 mg/mL; ^{13}C NMR data was collected at approximately 20 mg/mL. The broad peaks at 141 and 148 ppm are the quaternary pyrazole carbons.




161.31
147.73
140.86
130.27
129.09
128.72
125.84
105.27
61.23
14.25
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

1.9. References

[1] *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, (Eds: A. Padwa, W. H. Pearson), John Wiley & Sons, Inc., Hoboken, **2003**.

[2] Curtius, T. *Ber. Dtsch. Chem. Ges*. **1883**, 2230.

[3] Buchner, E. *Ber. Dtsch. Chem. Ges*. **1888**, 2637.

[4] Huisgen, Rolf , *Angew. Chem. Intel. Ed.*, **1963**, *2*, 565.

[5] Gothelf, K. V. and Jørgensen, K. A. *Chem. Rev*. **1998**, Vol. *98*, No. 2 865.

[6] Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, 1970.

[7] Houk, K. N.; Gonzales, J.; Li, Y. *Acc. Chem. Res.*, **1995,** *28*, 81.

[8] Ian Fleming, *Frontier Orbitals and Organic Chemical Reactions*, John Wiley & Sons, **1976**.

[9] Alt, M.; Mass, G. *Tetrahedron*, **1994**, *50*, 7435.

[10] Pinho e Melo, T. M. V. D. *Curr. Org. Chem.* **2005**, *9*, 925.

[11] a) Sustmann, R. *Tetrahedron Lett.* **1971**, *29*, 2717.b) Bastide, J.; Henri-Rousseau, N. C. O. *Tetrahedron Lett*. **1972**, *41*, 4225. c) Houk, K. N. *Accts. Chem. Res.* **1975**, *8*, 361.

[12] a) Barluenga, J.; Valdes, C.; Beltran, G.; Escribano, M.; Aznar, F. *Angew. Chem. Int. Ed.* **2006**, *45*, 6893. b) Barluenga, J.; Valdes, C.; Beltran, G.; Escribano, M.; Aznar, F. *Angew. Chem. Int. Ed.* **2006**, *118*, 7047.

[13] a) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B. Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210. b) Bock, V. D.; Hiemstra, H.; van

Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51.

[14] Pechmann, H. V. *Ber. Dtsch. Chem.Ges.* **1895**, *28*, 855.

[15] Ye, T. and Mckervey, M. A. *Chem. Rev*. **1994**, *94*, 1091.

[16] Bamford, W. R., Stevens, T. S. *J. Chem. Soc.* **1952,** 4735.

[17] De Boer, Th. J.; Backer, H. J. *Organic Syntheses* Coll. **1963**, 4, 250; **1956**, 36, 16.

[18] Regitz, M. *Angew. Chem. Int. Ed. Engl*. **1967,** *6,* 733.

[19] Okada, K., Samizo, F.; Oda, M. *Chem. Lett*. **1987**, 93.

[20] Kanemasa, S.; Kanai, T. *J. Am. Chem. Soc*. **2000**, *122*, 10710.

[21] Perrocheau, J.; Carrie, R. *Bull. Soc. Chim. Belges*. **1993**, *102*, 749.

[22] Niecke, E.; Schoeller, W. W.; Wildbredt, D. A. *Angew. Chem. Int. Ed. Engl*. **1981**, *20*, 131.

[23] Kalwinsch, I.; Xingya, L.; Gottstein, J.; Huisgen, R. *J. Am. Chem. Soc*., **1981**, *23*, 7032.

[24] Schneller, S. W. *J. Org. Chem*, **1990**, *55*, 5535.

[25] Padwa, A.; Zhang, Z.; Zhi, L. *J. Org. Chem.* **2000**, *65*, 5223.

[26] Sustman, R.; Sicking, W.; Felderhoff, M. *Tetrahedron* **1990,** *46*, 783.

[27] Tinant, B.; Declercq, J.; Meerssche, M. V.; Bouvy, A. *J. Chem. Soc., Perkin. 2* **1985**, 1419.

[28] Huisgen, R.; Verderol, M. P. B.; Gieren, A.; Lamm, V. *Angewandte Chemie;* **1981**, *93*, 710.

[29] Barnes, M. J.; Conroy, R.; Miller, D. J.; Mills, J. S.; Montana, J. G.; Pooni, P. K.; Showell, G. A.; Walsh, L. M.; Warneck, J. B. H. *Bioorg. Med. Chem. Lett*. **2007**,

354.

[30] Zrinski, I.; Juribasic, M.; Eckert-Maksic, M. *Heterocycles* **2006,** 1961.

[31] Jiang, N.; Li, C.-J. *Chem. Commun.* **2004**, 394.

[32] Kende, A. S.; Journet, M. *Tetrahedron Lett*. **1995**, *36*, 3087.

[33] Maas, G.; Gettwert, V. *Tetrahedron* **2000**, *56*, 4139.

[34] Shintani, R.; Fu, G. C. *J. Am. Chem. Soc*. **2003**, *125*, 10778.

[35] Representative examples of biologically active pyrazoles: a) β-Adrenergic blocking activity: Large, M. S.; Smith, L. H. *J. Med. Chem*. **1982**, *25*, 1417-1422. b) antipsychotic activity: Wise, L. D.; Butler, D. E.; DeWald, H. A.; Lustgarten, D. M.; Pattison, I. C.; Schweiss, D. N.; Coughenour, L. L.; Downs, D. A.; Heffner, T. G.; Pugsley, T. A. *J. Med. Chem*. **1987**, *30*, 1807-1812. c) Antibacterial activity: Baraldi, P. G.; Cacciari, B.; Leoni, A.; Recanatini, M.; Marinella, R.; Manfredini, S.; Periotto, V.; Simoni, D. *Farmaco*, **1991**, *46*, 1337-1350. d) antitumor activity: Manfredini, S.; Bazzanini, R.; Baraldi, P. G.; Guarneri, M.; Simoni, D.; Marongiu, M. E.; Pani, A.; Tramontano, E. P.; Colla, L. *J. Med. Chem*. **1992**, *35*, 917-924. e) Phosphodiesterase inhibition (Viagra): Terrett, N. K.; Bell, A. S.; Brown, D.; Ellis, P. *Bioorg. Med. Chem. Lett.* **1996**, *6,* 1819-1824. f) Cyclooxygenase inhibition (Celebrex): Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, J. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K A.; Veenhuizen, W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347-1365. g) Insecticidal activity: Finkelstein, B. L.; Strock, C. J.

Pestic. Sci. **1997**, *50*, 324-328. h) herbicidal activity: Parlow, J. J. *J. Heterocycl. Chem*. **1998**, *35*, 1493-1499. i) PPARγ Agonists: Collins, J. L.; Glanchard, S. G.; Boswell, G. E.; Charifson, P. S.; Cobb, J. E.; Henke, B. R.; Hull-Ryde, E. A.; Kazmierski, W. M.; Lake, D. H.; Leesnitzer, L. M.; Lehmann, J.; Lenhard, J. M.; Orband-Miller, L. A.; Gray-Nunez, Y.; Parks, D. J.; Plunkett, K. D.; Tong, W.-Q. *J. Med. Chem.* **1998**, *41*, 5037-5054. j) Cannabinoid receptor agonists and antagonists: Lan, R.; Liu, Q.; Fan, P.; Lin, S.; Fernando, S. R.; McCallion, D.; Pertwee, R.; Makriyannis, A. *J. Med. Chem*. **1999**, *42*, 769-776. k) Review: Elguero, J. in *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W. E.; Scriven, F. V. Eds.: Pergamon Oxford, **1996**; Vol 5.

[36] For lead references: Heller, S. T.; Natarajan, S. R. *Org. Lett*. **2006**, *8*, 2675.

[37] Padwa, A.; Kulkarni, Y. S.; Zhang, Z. *J. Org. Chem*. **1990**, *55*, 4144.

[38] Martin, R. Rivero, M. R.; Buchwald, S. L. *Angew. Chem. Int. Ed*. **2006**, *45*, 7079;

[39] (a) Sauer, D. R.; Schneller, S. W. *J. Org. Chem.* **1990**, *55*, 5535. (b) Aggarwal, V. K.; de Vicente, J.; Bonnert, R. B. *J. Org. Chem.* **2003**, *68*, 5381.

[40] CuCN·2LiCl: Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2392.

[41] a) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210. b) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem*. **2006**, 51.

[42] a) Sustmann, R. *Tetrahedron Lett.* **1971**, *29*, 2717. b) Bastide, J.; Henri-Rousseau, N. C. O. *Tetrahedron Lett*. **1972**, *41*, 4225. c) Houk, K. N. *Accts. Chem. Res.* **1975**, *8*, 361.

[43] Quenching with DCl yielded >90% deuterated recovered alkyne and 79% deuterated

1.2-*d*.

[44] Suarez, A.; Fu, G. *Angew. Chem. Int. Ed.* **2004**, *43*, 3580.

[45] a) Bestmann, H. J.; Soliman, F. M. *Angew. Chem. Int. Ed.* **1979**, *18*, 947.

[46] Schneider, J. W.; Gao, Zh. L.; Li, Sh.; Farooqi, M.; Tang, T.; Bezprozvanny, I.; Frantz, D.; Hsieh, J. *Nature Chemical Biology*, **2008**, *4*, 408.

[47] Qu, Z.; Wang, J. *Chinese J. Org. Chem.* **2003**, *23*, 988.

[48] Schroen, M.; Braese, S. *Tetrahedron* **2005,** *61*,12186.

[49] Dominh, T.; Strausz, O. P.; Gunning, H. E. *Tetrahedron Lett.* **1968,** *9*, 5237.

[50] Inokuchi, T.; Kawafuchi, H. *J. Org. Chem*. **2006**, *71*, 947

[51] Saghatelian, A.; Buriak, J.; Lin, V. S. Y.; Ghadiri, M. R. *Tetrahedron* **2001**, *57*, 5131.

[52] Seburg, R. A.; McMahon, R. J. *J. Am. Chem. Soc*. **1992**, *114*, 7183.

[53] Haiss, P.; Zeller, K.-P. *Zeitschrift fuer Naturforschung, B: Chemical Sciences*; **2003**, 58, 595.

[54] Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett*. **1972**, 3769.

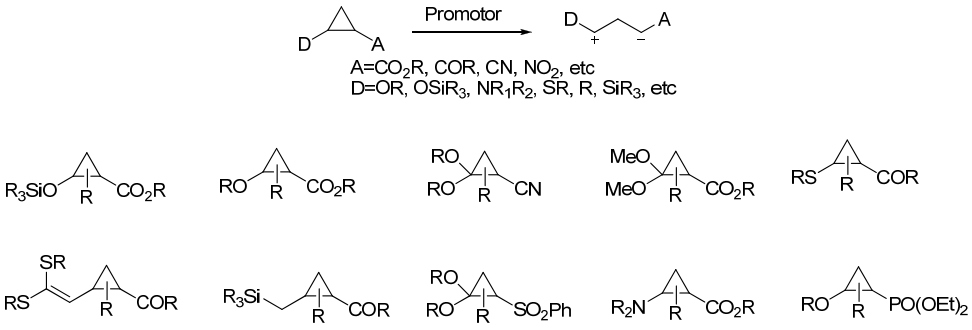
[55] Martins, M. A. P.; Freitag, R.; Zanatta, N. *Synthesis* **1995**, 1491.

Chapter 2. Synthesis of Cyclopentenones from Cyclopropanes and Silyl Ynol Ethers

2.1 Background and introduction of Donor-Acceptor cyclopropanes (DAC).

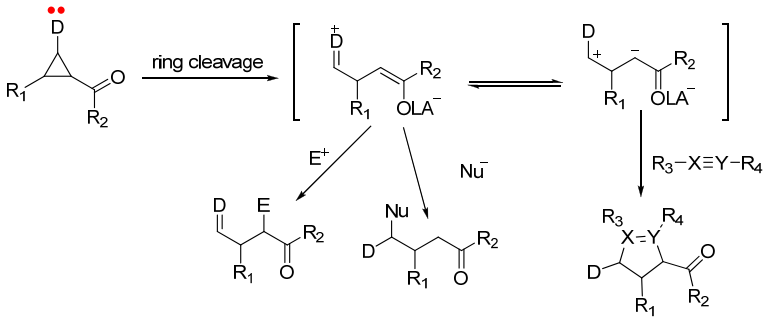
Cyclopropanes with electron-donating (donor) and electron-withdrawing (acceptor) substituents on vicinal positions are very useful building blocks in synthetic chemistry.[1] (**Scheme 2.1**). In the presence of Lewis acids, D-A cyclopropanes undergo ring-opening to yield 1,3-zwitterions intermediates. To pursue a general interest in the reactivity of electron-rich alkynes, we envisioned a cycloaddition between electron-rich alkynes and such intermediates.

Scheme 2.1 Donor-Acceptor cyclopropanes



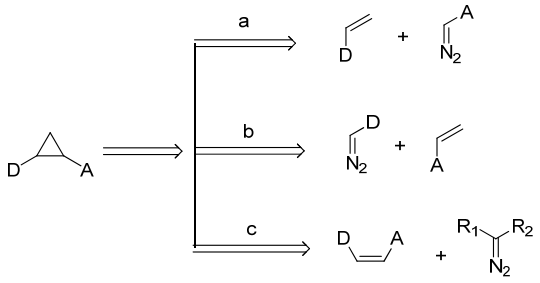
Depending on the stability and reactivity of the cyclopropane, the donor and acceptor can be modified with various functional groups (**Scheme 2.1**). These multi-functionalized cyclopropanes can be transferred to various synthetically useful intermediates through 1,3-zwitterions when activated by a Lewis acid (**Scheme 2.2**). After ring-opening, the carbanion can be trapped by an electrophile to generate an α-substituted carbonyl product. The carbocation can then be trapped by nucleophile to form γ-substituted carbonyl product, or trapping both charges with unsaturated systems will result in formal [3+2] cycloadditions to furnish highly functionalized five-membered rings.

Scheme 2.2 1,3-zwitterions generated by Lewis acid activation



The most general way to synthesize cyclopropanes is from addition of carbenes to olefins.[2] Based on this methodology, there are three distinct methods to synthesize DAC. The first is the most common and involves the addition of an acceptor-substituted carbene from a diazocarbonyl compound to electron-rich olefins (**Scheme 2.3,** path a). Other methods include additions of donor-substituted carbenes (Fischer carbene) to electron-deficient alkenes (path b) and methylenation of donor-acceptor olefins (path c).

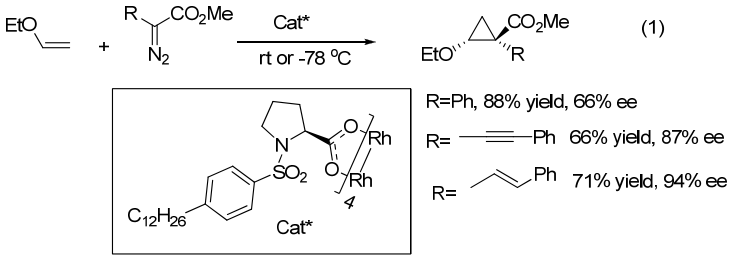
Scheme 2.3 Synthesis of D-A cyclopropanes

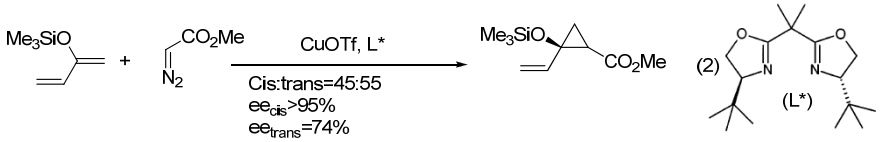


In the presence of transition metals, diazocompounds will be decomposed to metal carbenes. A series of rhodium (II) prolinate derivatives (**Scheme 2.4**, Cat*)[3] have been shown to be very good catalysts for enantioselective cyclopropanation of enol ethers with diazoacetates in excellent yield and trans/cis selectivity (ee up to 94%). Copper catalysts with various bisoxazoline ligands catalyzed cyclopropanation of vinyl acetate with

diazoacetates, and can achieve moderate cis/trans-selectivity with high enantiomeric excess[4] (**Scheme 2.4**, reaction 2).

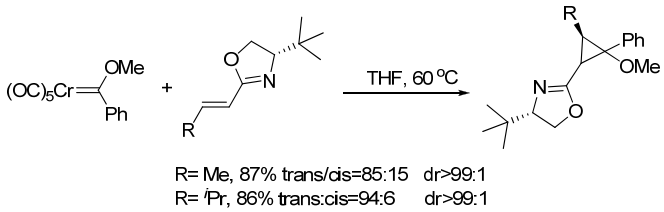
Scheme 2.4 Transition metal catalyzed asymmetric cyclopropanation





Transfer of Fischer carbene complexes to electron-deficient alkenes will also result in the formation of D-A cyclopropanes (pathway b, **Scheme 2.3**). Chromium carbene complexes react with a variety of acceptor-substituted olefins to provide the corresponding D-A cyclopropanes in moderate to excellent yields[5] (**Scheme 2.5**). Under the assistance of chiral auxiliaries, high enantioselectivity can be achieved.

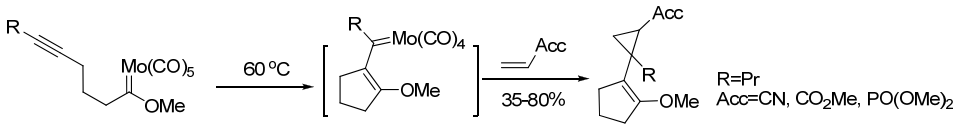
Scheme 2.5 D-A cyclopropanes from chromium carbene



An intriguing approach to D-A cyclopropanes via Fischer carbene complexes was introduced by Harvey[6], who combined the well-known insertion reactions of these complexes and alkynes with cyclopropanation reactions. Intramolecular reaction of a

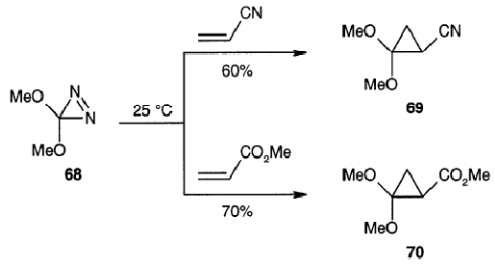
molybdenum carbene first generated the alkenylsubstituted carbene complex, which was trapped with electron-deficient olefins to furnish cyclopropanes in moderate to good yield but with poor diastereoselectivity (**Scheme 2.6**).

Scheme 2.6 Cyclopropanation of molybdenum carbene



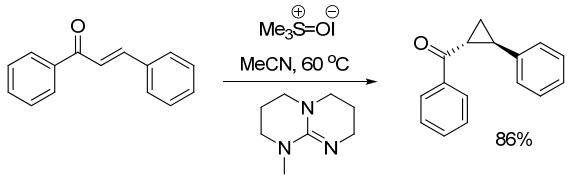
Besides diazocompounds, the isomeric diazirines may also be used as a carbene source for cyclopropanation reactions. Alkoxy-substituted diazirines produce nucleophilic carbenes that react with electron-deficient olefins to generate D-A cyclopropanes[7] (**Scheme 2.7**).

Scheme 2.7 D-A cyclopropanes from diazirines



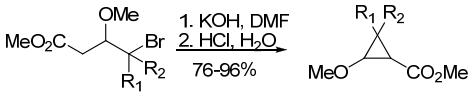
Methylene-transfer reagents like CH_2I_2/(Cu)Zn (Simmons-Smith reaction) and dimethylsulfoxonium methylide (Corey-Chaykovsky reaction) are well known to generate cyclopropanes. These methods are also suitable for D-A cyclopropanes. For example, dimethylsulfoxonium methylide can react with α,β-unsaturated carbonyl compounds to synthesize cyclopropanes efficiently[8] (**Scheme 2.8**).

Scheme 2.8 D-A cyclopropanes from dimethylsulfoxonium methylide



DAC can be synthesized indirectly through intramolecular S_N2 displacement of γ-bromo carbonyl compounds in good yields and stereoselectivities.[9] (**Scheme 2.9**).

Scheme 2.9 S_N2 reaction of γ-bromo carbonyl compounds to generate D-A cyclopropanes



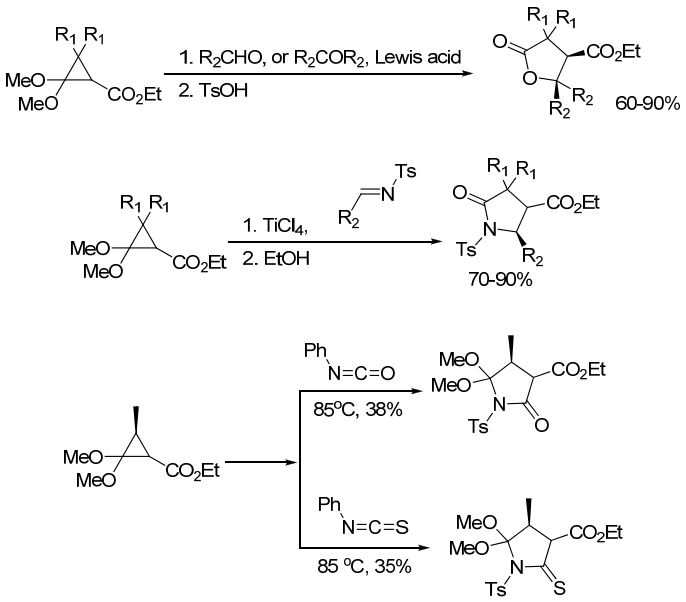
2.2 Cycloaddition of DAC with multiple bonds

Most synthetic applications involving DAC are based on ring cleavage. This includes rearrangement of vinylcyclopropanes to provide cyclopropenes,[10] decomposition of alkoxyl DAC to generate carbonyl compounds,[11] and Michael-type addition to carbonyl substituted DAC.[12] Modifications at the DAC core without ring opening are also known. For example, alkylation or nucleophilic addition to a EWG substituted DAC to produce functionalized DAC.[13] In this chapter, only [3+2] cycloaddition of multiple bonds with DAC after ring cleavage will be discussed.

The most important synthetic application of DAC is [3+2] cycloaddition with multiple bonds to generate five-membered carbocyclic and hetereocyclic ring systems. Five-membered carbocyclic and hetereocyclic rings appear in all classes of organic materials including pharmaceutical agents, polymers, natural products, and catalysts. Accordingly, their preparation has challenged synthetic chemists since the inception of

the field.[14] In this regard, [3+2] cycloadditions (both concerted and stepwise) represent convergent strategies for the formation of the five member nucleus.[15] Dipolar cycloadditions, in particular, have proven especially successful for this construction. Of the various all-carbon dipolar synthons available, donor–acceptor cyclopropanes have proven especially versatile.

Scheme 2.10 [3+2] cycloadditions of dialkoxyl and carbonyl substituted cyclopropane

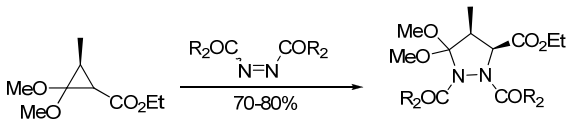


The reaction of dialkoxy and carbonyl substituted cyclopropanes with aldehydes or ketones followed by acidic work-up will form γ-lactone products. Excellent stereocontrol was observed during these transformations[16,17] (**Scheme 2.10**).Similar reactions with carbon nitrogen double bonds like imines,[18] isocyanates[19] and isothiocyanates[20] were also reported.

Nitrogen-nitrogen double bonds can also go through cycloaddition with D-A cyclopropanes under thermal conditions to generate pyrazolidine derivatives[21] (**Scheme**

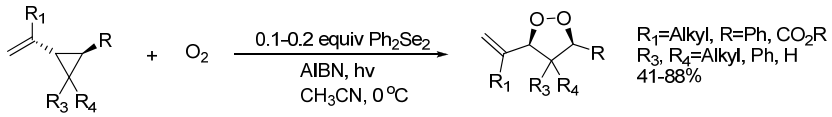
2.11). The diastereoselectivities of these reactions depend on the conformations of the cyclopropane and the polarity of the solvent.

Scheme 2.11 [3+2] cycloadditions of DAC with nitrogen-nitrogen double bonds



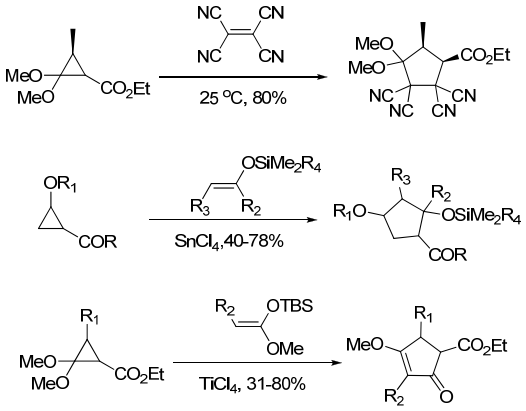
Another interesting aspect of cycloadditions with D-A cyclopropanes is the reaction with molecular oxygen[22] (**Scheme 2.12**). Initiated by a radical, vinyl substituted DAC can be cyclized with molecular oxygen to generate various substituted dioxolanes in moderate to excellent yields.

Scheme 2.12 [3+2] cycloadditions of DAC with oxygen-oxygen double bonds



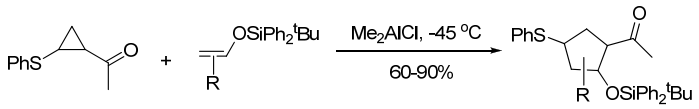
Electron-deficient olefins can react with this type of cyclopropane to form cyclopentanes under mild conditions.[23] But Lewis acids are required for cycloaddition with electron-rich olefins[24,25] (**Scheme 2.13**).

Scheme 2.13 [3+2] cycloadditions of DAC with carbon-carbon double bonds



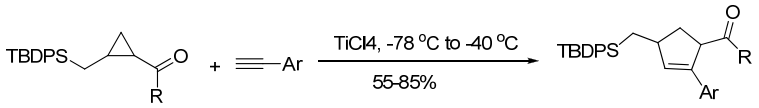
In the presence of a Lewis acid, D-A cyclopropanes with sulfur as the donor group also react with olefins to form cyclopentanes in good yields[26] (**Scheme 2.14).**

Scheme 2.14 [3+2] cycloadditions of D-A cyclopropane with sulfur as donor



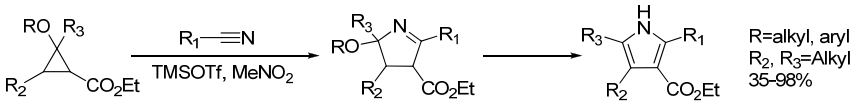
Many D-A cyclopropanes are known to react with triple bonds in the formation of unsaturated five-member rings. For example, D-A cyclopropane with silyl methylene as the donor group can react with terminal arylalkynes in the presence of $TiCl_4$ to form cyclopentenes with good regio- and stereoselectivities (**Scheme 2.15**).[27]

Scheme 2.15 [3+2] cycloadditions of DAC with carbon-carbon triple bonds



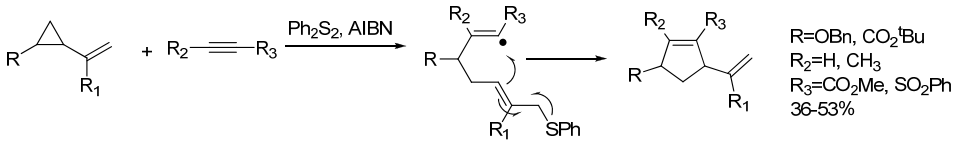
Pyrrole products can also be formed when the cycloaddition occurs between D-A cyclopropanes and carbon-nitrogen triple bonds.[28] Based on this novel cycloaddition, highly functionalized pyrrole derivatives can be easily synthesized in high yields and regioselectivities (**Scheme 2.16**).

Scheme 2.16 [3+2] cycloadditions of DAC with carbon-nitrogen triple bonds



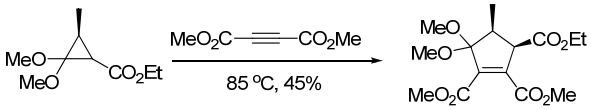
Another type of cycloaddition between D-A cyclopropane and a triple bond is the radical mediated [3+2] strategy for the synthesis of substituted cyclopentenes (**Scheme 2.17**). In this transformation, ether and ester substituted vinylcyclopentenes can be prepared in moderate yields.

Scheme 2.17 Radical mediated [3+2] cycloaddition of DAC



Electron deficient alkynes like DMAD can react with D-A cyclopropane under thermal conditions to generate multi-functionalized cyclopentenes in good yield and stereoselectivity (**Scheme 2.18**).[29]

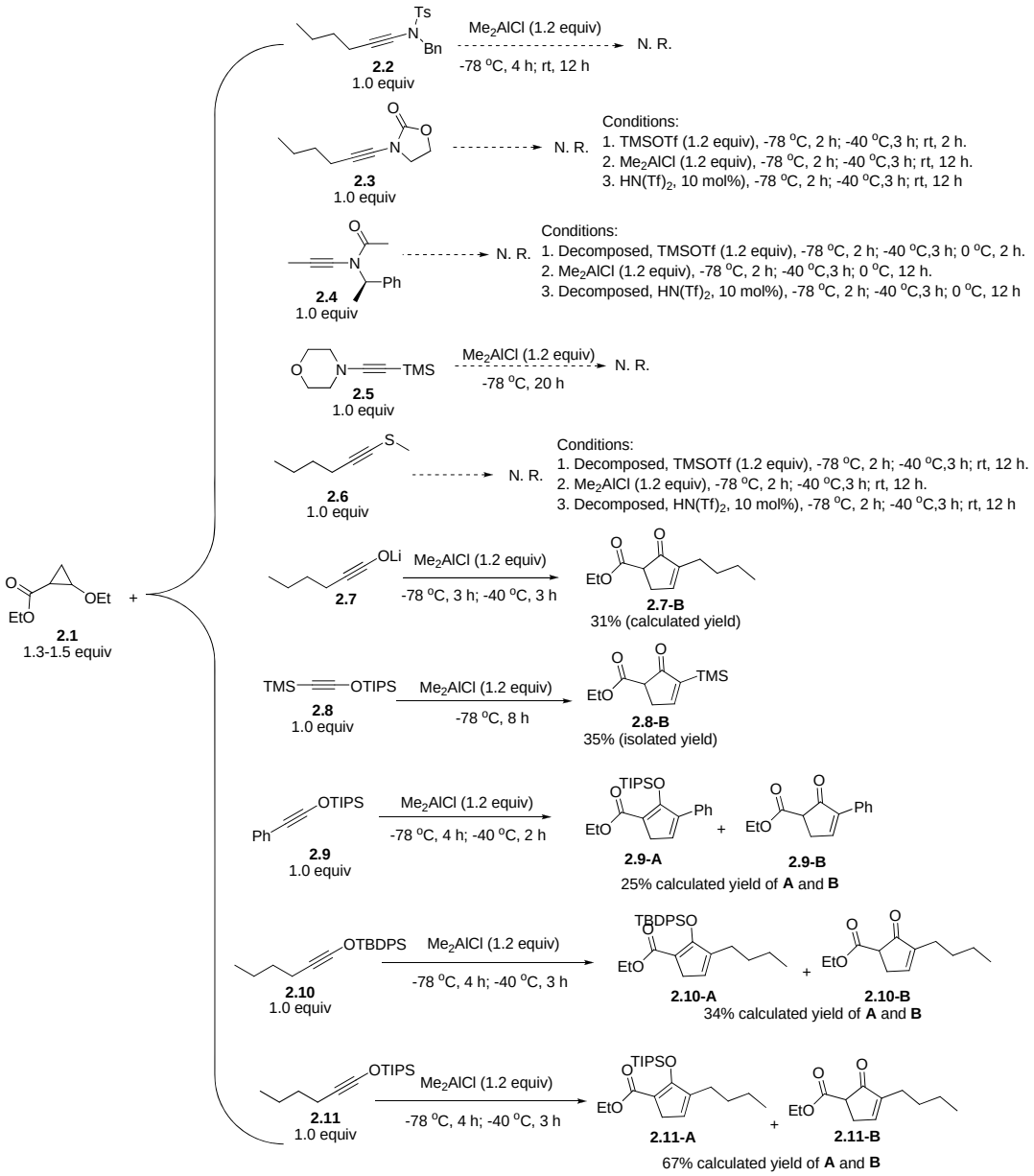
Scheme 2.18 [3+2] cycloadditions of DAC with electron deficient alkyne



2.3 Results and Optimization

While donor-acceptor cyclopropanes have been shown to combine with indoles,[30] enol ethers,[31] and aryl acetylenes,[27] a condensation with electron-rich alkynes has not been documented. Indeed, these alkynes have hardly been explored in the context of [3+2] cycloadditions.[32] To improve the scope of alkyne trapping reagents and also to pursue a general interest in the reactivity of electron-rich alkynes, we envisioned cycloadditions between such intermediate and various electron-rich alkynes (**Scheme 2.19**). To evaluate this hypothesis, we examined the reactivity of a varity of electron-rich alkynes with a D-A cyclopropane in the presence of both Lewis and Bronsted acids. No cycloaddition was observed with ynamines, ynamides or thioethers. However, we did observe reactivity between donor-acceptor cyclopropanes and ynol ethers in the presence of Me_2AlCl.

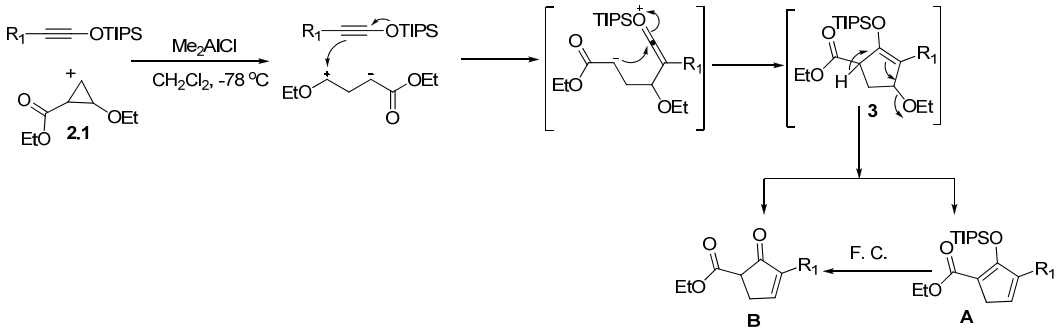
Scheme 2.19 [3+2] cycloadditions of DAC with electron-rich alkynes



A possible pathway to generate both products (**Scheme 2.19, 2.11-A** amd **2.11-B**) is shown in **Scheme 2.20**. First, [3+2] cycloaddition could generate cyclopentenol silyl ether. Elimination of ethoxyl group from the original cycloaddition product could provide

cyclopentadiene (**A**); after acidic work-up and flash column chromatography, cyclopentenone **B** was formed due to proto-desilylation. Under neutral or basic condition, silyloxycyclopentadiene **A** was stable enough to be isolated.

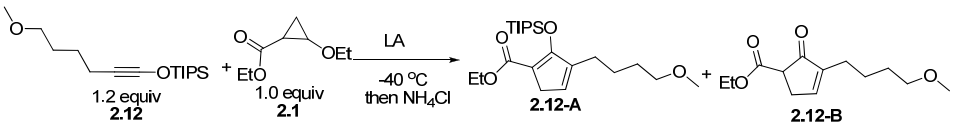
Scheme 2.20 [3+2] cycloadditions of DAC with ynol ethers



Encouraged by this preliminary result, we investigated the reaction of cyclopropane **2.1** with ynol ether **2.12**, (**Table 2.1**) which was prepared in a single step from the terminal alkyne.[33] First, different Lewis acids were investigated. No reactions occurred with $SnCl_4$, $Sc(OTf)_3$, SmI_2, $InCl_3$, $Bi(OTf)_3$, $BiCl_3$, Cp_2TiCl_2, $TiCl(O^iPr)_3$, AgOTf, CuI or $Au(PPh_3)Cl$. Only trace amount of product was observed with $TiCl_4$, BCl_3, BF_3-OEt_2 and BBr_3. High reactivity was detected with Me_2AlCl and the major cyclopentenone product **2.12-B** was isolated if the reaction was quenched with aqueous solution of NH_4Cl (52% yield). If the reaction was quenched with H_2O or sat. aq. solution of $NaHCO_3$, the major product was cyclopentadiene **2.12-A**.

The success of Me_2AlCl encouraged us to screen other Al Lewis acids in this reaction (**Table 2.1**). Similar reactivity was observed with Me_2AlCl, $MeAlCl_2$, $EtAlCl_2$, Et_2AlCl; among those LA, Me_2AlCl was the best reagent. Me_3Al, $Al(OEt)_3$, MAO and $AlCl_3$ were less reactive (Yields lower than 10%).

Table 2.1 Investigation of Al-based Lewis acids.



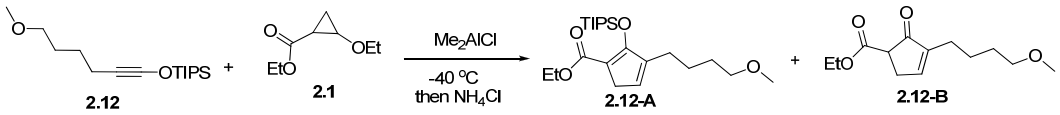
Entry	LA(1.2 equiv)	**A+B** (yield)[a]
1	Me_2AlCl	40
2	Me_2AlCl (-78 °C)	78
3	$MeAlCl_2$	34
4	Et_2AlCl	37
5	$EtAlCl_2$ (-78 °C)	53
6	$EtAlCl_2$	39
7	Me_3Al	Trace
8	$AlCl_3$	Trace
9	$Al(OEt)_3$	trace
10	MeAlO	10

[a] Determined by ^1H NMR analysis of the crude reaction mixture with mesitylene as standard

Different solvents were also investigated. There was no reaction in Et_2O, MeCN, toluene, DMF and $CHCl_3$. Only CH_2Cl_2 gave good reactivity. Different stoichiometries of Me_2AlCl were also investigated (0.2, 0.5, 1.2, 2 equiv). Catalytic amounts of Lewis acids gave poor results. The reaction with 2 equivalents of LA was slow and resulted in multiple products.

The stoichiometries of these three reactants were carefully adjusted, and an optimal temperature profile was established: initially -78 °C for 4 h and then -30 °C for 3 h. All reactions were quenched by $NaHCO_3$ and extracted with ether (**Table 2.2**). The aqueous solution was then neutralized with 5% HCl solution and extracted with ether. The crude mixture was checked by NMR, and in all cases, the major product was cyclopentadiene.

Table 2.2 Stoichiometries of reactants



Entry	**2.12**	**2.1**	Me_2AlCl	**A + B** (yield)[a]
1	1.0	1.0	1.0	50+12(62)
2	1.0	1.2	1.0	54+14(68)
3	1.0	1.2	1.2	56+14(70)
4	1.0	1.3	1.2	64+13(77)
5	1.0	1.5	1.0	55+18(73)
6	1.0	1.5	1.5	50+12(62)
7	1.2	1.0	1.0	52+3(55)
8	1.2	1.0	1.2	56+9(65)
9	1.5	1.0	1.0	59+10(69)
10	1.5	1.0	1.5	47+5(52)

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture with mesitylene as standard

Addition of a desilylation reagent, such as KF, ZnF_2 or CsF to the reaction system slows the reaction. Other additives like transition metals (Cu, Au, Ag), strong bases (K_3PO_4, K_2CO_3) and salts (LiCl) were not helpful. Further attempts to optimize the reaction, such as temperature, times and concentrations were also performed. The best result at that time was **entry 4** in **Table 2.2**. Slow addition of reactant showed no improvement.

Since Me_2AlCl could not be further optimized, other Lewis acids such as $AgN(Tf)_2$ and Bronsted acid such as TfOH and $HN(Tf)_2$were investigated. Catalytic amounts of these catalysts were also shown to catalyze this cycloaddition (**Table 2.3** and **2.4**). These results were not an improvement over Me_2AlCl.

Table 2.3 $AgN(Tf)_2$ catalyzed pathway.

Entry	$AgN(Tf)_2$	**A + B** (yield)
1	1 mol%	-- (Slow)
2	5 mol%	48%
3	5 mol% (with BINAP)	45%

4	10 mol%	34%
5	20 mol%	55%
6	50 mol%	28%
7	1.0 equiv	10%

Table 2.4 Bronsted acid catalyzed conditions.

Entry	$HN(Tf)_2$ (-78 ^oC)	**A + B** (yield)[a]
1	1 mol%	-- (Slow)
2	2 mol%	37%
3	5 mol%	32%
4	10 mol%	40%
5	1.2 equiv	31%
6	$LiN(Tf)_2$	N.R.
7	TfOH(rt)	42%

[a] Determined by ^1H NMR analysis of the crude reaction mixture with mesitylene as standard

Alkyl silyl trifluoromethanesulfonate were effective Lewis acids for this transformation. Different silyl trifluoromethanesulfonate were screened at -78 ^oC for 15 h and then -40 ^oC for 17 h. In all cases, these reactions were slow but very clean.

Table 2.5 Alkyl silyl trifluoromethanesulfonate type Lewis acids screen

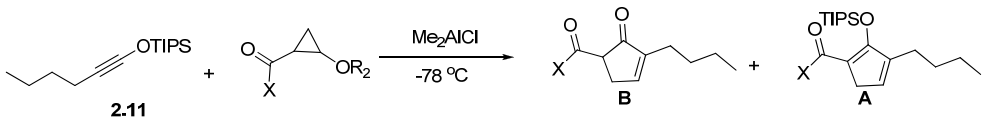
Entry	LA (1.2 equiv)	**A + B** (yield)
1	TMSOTf	35%
2	TIPSOTf	51%
3	TIPSOTf (-78 ^oC, 50 h)	45%
4	TIPSOTf (rt)	53%
5	TIPSOTf (2 equiv)	41%
6	TIPSOTf (3 equiv)	43%
7	TIPSOTf (4 equiv)	43%
8	TIPSOTf (5 equiv)	42%
9	TBDMSOTf	38%
10	TESOTf	39%
11	$SiCl_4$	N. R.

Yield was determined by ^1H NMR analysis of the crude reaction mixture with mesitylene as standard

The electronic properties of the substrate were modified in an attempt to improve the low reactivity. Different types of D-A cyclopropanes and electron-rich alkynes were

synthesized and investigated in this regard. First, various substitutions on the cyclopropane were tested (**Scheme 2.21**). Benzyl substituted ester provided similar reactivity as ethyl ester, but remarkably the methyl ester was unreactive. Electron-deficient functional groups (Ac) on the donor side inhibited the reaction. A Weinreb amide (**2.16, Scheme 2.21)** also proved unreactive.

Scheme 2.21 Different type of D-A cyclopropanes



2.1 X=OEt, R_2=Et, 67% (total calculated yield)
2.13 X=OBn, R_2=Et, 70% (total calculated yield)
2.14 X=OMe, R_2=Et, N.R.
2.15 X=O^{t}Bu, R_2=Et, 13%
2.16 X=NMe(OMe), R_2=Et, N.R.
2.17 X=OEt, R_2=Ac, N.R.

After investigating these different conditions, a control reaction (TIPS ynol ether **2.11**) was set up in parallel with TBDPS ynol ether **2.10**. Curiously, different reactivity was observed compared to the same reaction studied four months earlier (Isolated yield: 80% vs. 67%; Reaction time: 6h vs. 12h). Our early experiments suggested mediocre performance with Me_2AlCl; therefore, when we reinvestigated the use of this Lewis acid several months after our initial experiments, we were surprised to find that it promoted the cycloaddition cleanly and rapidly!

To figure out why this had occurred, several hypotheses needed to be investigated. First, the Lewis acid (1.0 M solution in hexanes) concentration might have changed due to solvent evaporation. The stoichiometry of Me_2AlCl was re-checked carefully. There was not a large difference when the amount of fresh Me_2AlCl was varied with the best result still not comparing to the aged bottle.

Another possibility might be H_2O in the aged bottle. Different amount of H_2O were added to the reaction system. All the reactions were faster compared to the reaction without H_2O, but the calculated yields were lower and the NMRs of the crude mixtures were relatively messy. More than 50 mol% of H_2O inhibited the reaction.

Me_2AlCl was known [34] to react with MeOH to generate a new Lewis acid, Me(MeO)AlCl, which has already been characterized. The ^{1}HNMR of the aged bottle of Me_2AlCl, was similar to Me(MeO)AlCl. We interpret that the Me(MeO)AlCl might be generated from oxygenation of Me_2AlCl by adventitious air. To investigate this possibility, various amounts of dried air were bubbled through a solution of fresh Me_2AlCl before used in the reaction (**Table 2.6**).

Table 2.6 Investigation of air effect

Entry	Air (dried by MS)	**2.11-A +2.11-B** (yield)[a]
1	0 ml	77%
2	10 ml	83%
3	20 ml	91%
4	40 ml	84%

[a].Calculated yield

Interestingly, each reaction gave a yield comparable to that with the aged bottle of reagent. Higher reactivity, higher yield and shorter reaction times were achieved. To support this explanation that a more reactive Lewis acid might be generated from oxygenation, we exposed a solution of fresh Me_2AlCl to different amounts of CD_3OD and generated $Me(CD_3O)AlCl$ in situ. The reactivities of these new Lewis acids were investigated (**Table 2.7**). Similar reactivities were observed as the reactions with air. Unfortunately, the reaction resulting from the addition of methanol was noticeably messier: an unidentified precipitate was formed during formation of the active catalyst.

Thus, aerobic oxidation of dialkyl alanes constituted a clean and efficient method to generate a strong but selective Lewis acid.

Table 2.7 Investigation of MeOH involved reactions.

Entry	CD_3OD (equiv)	**2.11-A +2.11-B** (yield)[a]
1	0	69%
2	0.2	74%
3	0.4	72%
4	0.5	63%
5	0.8	74%
6	1.0	77%
7	1.5	45%

[a] Calculated yield

In order to ease the isolation, different quenching and desilylating reagents were studied (**Table 2.8**). Both basic ($NaHCO_3$) and acidic (NH_4Cl and 5 % HCl) quenching resulted in a mixture of two products. PPTS promoted the desilylation very slowly. TBAF converted cyclopentadiene to cyclopentenone, but this reagent gave messier product mixture and lower yield. HF-Pyridine turned out to generate the cyclopentenone cleanly and efficiently.

Table 2.8 Investigation of different quenching reagents

Quenching Reagent	A	B	Total
Sat. $NaHCO_3$	62%	19%	81%
Sat. NH_4Cl	62%	14%	76%
5%HCl	69%	16.2%	85.2%
HF-Py.	0	86.5%	
TBAF	Messy NMR Spectrum		lower yield
PPTS	Slower Conversion of A to B		lower yield

After careful investigation of various crucial factors, final optimized reaction conditions were obtained: air was bubbled through a solution of Me_2AlCl (1 mmol) at room temperature. Then at -78 ^oC, cyclopropane (1.3 mmol) and ynol ether (1 mmol)

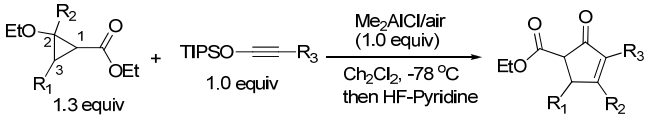
were added, and the mixture was stirred until the reaction was complete (2–24 h). Subsequently, HF-pyridine was added, and after aqueous workup, the residue was purified by column chromatography to give cyclopentenone.

2.4 Reaction scope

Under optimized reaction conditions, a series of substituted donor-acceptor cyclopropanes were combined with a range of ynol ethers to yield cyclopentenones in generally good yields. Silyl ynol ethers bearing olefins, alkynes, ethers, halides, and aromatic rings all performed well with cyclopropane *cis*-**2.1** in this transformation (**Table 2.9**, entries 1-8). Five- and six-membered rings on the silyl ynol ethers were also good cycloaddition partners with high reactivities (**Table 2.9**, entries 9, 10). All the products were generated with exclusive regioselectivity.

The ynol ethers derived from phenyl acetylene or trimethylsilylacetylene were poor substrates (**Table 2.10**, entries 1 and 2). The reason for this is not clear; the possible hypothesis might be that the phenyl ring conjugates to the triple bond and makes the alkyne less polarized. The poor performance of trimethylsilyl ynol ether might be due to unfavorable steric interaction. Lower yields were obtained with *tert*-butyl-diphenylsilyl ynol ethers, while *tert*-butyl-dimethylsilyl ynol ethers could not be prepared in satisfactory yields.

Table 2.9 Reaction scope with different silyl ynol ethers



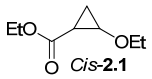
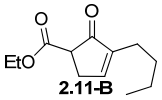
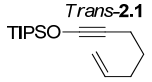
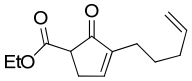
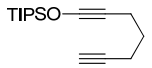
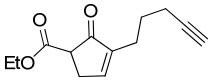
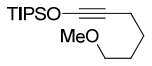
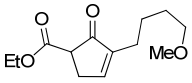
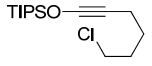
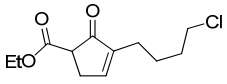
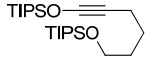
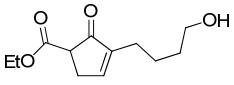
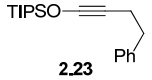
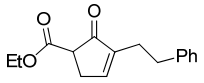
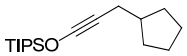
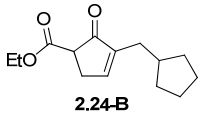
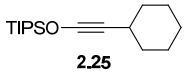
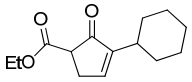
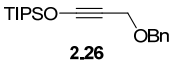
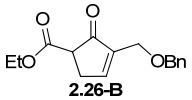
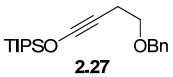
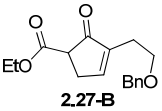
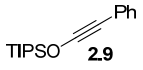
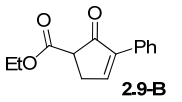
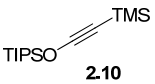
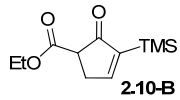
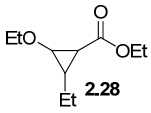
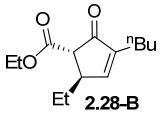
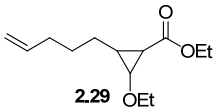
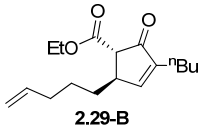
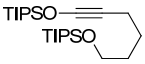
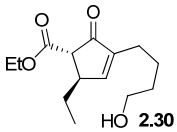
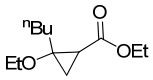
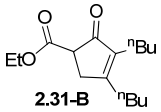
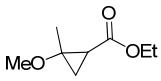
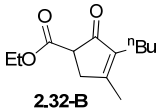
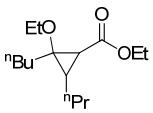
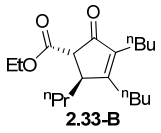
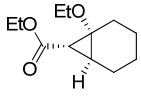
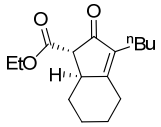
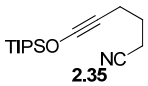
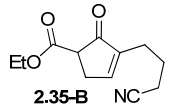
Entry	SM	Product	Time	Yield(%)
1	 *Cis*-**2.1**	 **2.11-B**	7 h	77
2	*Trans*-**2.1**		8 h	75
3	 **2.18**	 **2.18-B**	6 h	67
4	 **2.19**	 **2.19-B**	6 h	71
5	 **2.20**	 **2.20-B**	8 h	72
6	 **2.21**	 **2.21-B**	8 h	72
7	 **2.22**	 **2.22-B**	9 h	79
8	 **2.23**	 **2.23-B**	3 h	52
9	 **2.24**	 **2.24-B**	4 h	82
10	 **2.25**	 **2.25-B**	4 h	76
11	 **2.26**	 **2.26-B**	24 h	75
12	 **2.27**	 **2.27-B**	3 h	54

Table 2.10 Reaction scope with different cyclopropanes

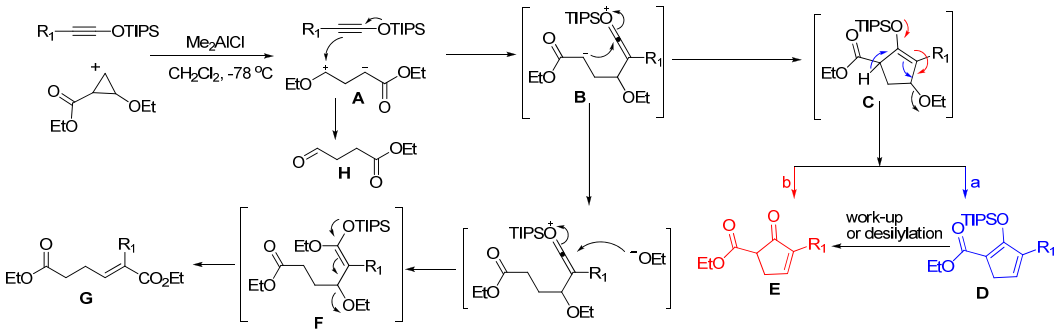
Entry	SM	Product	Time	Yield(%)
1	 **2.9**	 **2.9-B**	-78°C/10h; rt/12 h	24
2	 **2.10**	 **2.10-B**	24 h	35
3	 **2.28**	 **2.28-B**	24 h	76
4	 **2.29**	 **2.29-B**	24h	69
5	 **2.22** + **2.29**	 **2.30**	24 h	81
6	 *trans*-**2.31**	 **2.31-B**	24 h	63
7	 **2.32**	 **2.32-B**	7 h	53
8	 *trans*-**2.33**	 **2.33-B**	72 h/-78 °C 8 h/-40 °C 12 h/rt	46
9	 *trans*-**2.34**	 **2.34-B**	4 h	79
10	 **2.35**	 **2.35-B**	1 h/-78 °C 4 h/rt 12 h/40 °C	42%

Both cis- and trans-disubstituted cyclopropanes appear to behave identically (**Table 2.9**, entries 1 and 2). Likewise, substitution at C3 (**Table 2.10**, entries 3, 4 and 5), C2 (**Table 2.10**, entries 6 and 7), or both (**Table 2.10**, entries 8 and 9) are accommodated in the cycloaddition. Thus, tri-, tetra-, and even penta-substituted cyclopentenones can be formed in good yields and in a convergent manner. When two stereocenters were generated in the reaction (**Table 2.10**, entries 3, 4, 5, 8 and 9), we observed greater than 10:1 diastereoselectivity favoring the more stable trans- isomer. Furthermore, both partners in the cycloaddition can be accessed in a single operation from readily available materials.

2.5. Discussion

1,3-zwitterion **A** is formed from decomposition of D-A cyclopropane. Its intermediacy is supported by the observation of an aldehyde product when the cyclopropane was treated with strong Lewis acid such as $TiCl_4$. Silyl ether is an electron-rich substituent of the alkyne and makes the triple bond more polarized for cycloaddition with the 1,3-zwitterions to generate the original five-member ring **C**. Two major products, silyl cyclopentadiene ether **D** and cyclopentenone **E,** were observed during the reaction and isolated after the reaction. To generate **D**, the most likely pathway involves EtOH elimination from intermediate **C**, which is the cycloadduct of 1,3-zwitterion and silyl ynol ether (**Scheme 2.22**). The formation of product **E** can result from desilylation of **D** or simultaneous desilylation and EtOH elimination from **C**.

Scheme 2.22 Proposed mechanism



A minor quantity of G was also isolated from the reaction mixture. This byproduct might be generated from ketene cation, which is trapped by ethoxy anion, followed by desilylation and ethanol elimination. This phenomenon indicates that the cycloaddition might be stepwise.

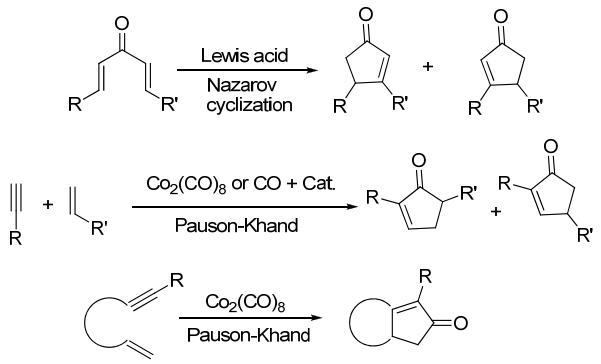
Methyl alkynyl thio-ether **2.6** (**Scheme 2.19**) was found to be unreactive in this transformation. This is reasonable due to the poor sulfur-carbon orbital overlap in this electron-rich alkyne. Since nitrogen is also an electron donating group, several ynamines or ynamides (**Scheme 2.19**) were synthesized and examined. Unfortunately, under the present reaction system, no reactivity was observed.

Based on several comparisons, for example, TIPS vs. TBDPS ynol ether, ynamine or ynamide vs. ynol ether, phenylacetylene vs. alkyl alkyne, trimethylsilylacetylene vs. alkyl alkyne, a reasonable conclusion can be drawn: that is, both the electronic and steric effects on the alkyne play crucial roles during this novel cycloaddition. Since nitrile is known to react with D-A cyclopropanes to generate pyrroles, it is interesting to observe that the desired product was still formed even in the presence of the nitrile group with no

pyrrole products observed (**Table 2.10**, entry 10 vs. **Scheme 2.16**). So, under the present cycloadditon system, ynol ether is more reactive than nitrile.

With respect to the utility of the methodology described in this chapter, comparisons to two standard syntheses of cyclopentenones are appropriate. The present cycloaddition is more direct than the Nazarov cyclization[35] (**Scheme 2.23**), and in contrast to that cyclization, yields a single olefin positional isomer. Additionally, the precursor of the Nazarov cyclization is normally difficult to prepare. The substituents α to the keto group are prone to racemization under the strong Lewis or Bronsted acids used in this cyclization, and therefore the diastereoselectivity is usually low.

Scheme 2.23 Compare of reactions



The Pauson-Khand[36] reaction, another method to prepare cyclopentenone, is generally limited to intramolecular cyclizations. Harsh condition such as high temperature is normally employed to effect this transformation, and such high temperatures often lead to decomposition of substrates or products. Regioselectivity during this transformation is also a problem. While the reaction is usually selective with respect to substituents on the alkyne, the alkene substituents are not selectively incorporated. Internal alkynes are less effective than terminal alkynes, and trisubstituted

alkenes are often unreactive. The cyclopenenone from cycloaddition of D-A cyclopropane with silyl ynol ether functions efficiently in an intermolecular context.

While (MeO)AlMeCl has been characterized previously,[34] it has found infrequent use as a Lewis acid. In the present transformation, this species appears to be strong enough to activate the cyclopropane towards ring-opening and to mediate the decomposition of the vinylogous acetal (**Scheme 2.22, C**); it is mild enough to coexist with the ynol ether and the cyclopentenone. This favorable reactivity profile might be extended to other classes of cycloadditions and, more broadly, to other Lewis acid promoted reactions.

In conclusion, in this chapter, a novel transformation between D-A cyclopropane and ynol silyl ether was discovered. High reactivity was observed in the presence of a modified Me_2AlCl Lewis acid. Promoted by this efficient Lewis acid, tri-, tetra-, and even penta-substituted cyclopentenones can be formed in good yields and in a convergent manner. We observed greater than 10:1 diastereoselectivity favoring the more stable trans- isomer. Furthermore, both partners in the cycloaddition can be conveniently accessed from readily available materials.

2.6 Experimental details

2.6.1 Methods and materials

General. Unless otherwise stated, reactions were performed using freshly purified solvents. Solvents were purified using solvent purification columns purchased from Glass Contour, Laguna Beach, CA. All reactions were monitored by thin-layer chromatography with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). Gas chromatography (GC) was performed on an HP 6890N autosampling GC with an HP-5 capillary column and

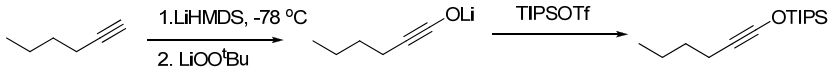
equipped with a FID detector. Flash chromatography was performed with indicated solvents using silica gel (particle size 0.032-0.063 μm) purchased from Sorbent Technologies.^{1}H and ^{13}C NMR spectra were recorded on Varian Inova-400, 500 or Mercury-300 spectrometer. Chemical shift are reported relative to internal chloroform ($CDCl_3$: ^{1}H, δ = 7.27, ^{13}C, δ= 77.26). Coupling constants are in Hz and are reported as d (doublet), t (triplet), q (quartet). For signals having multiple coupling patterns, the coupling constant are listed in the same order as the pattern (e.g. dt, *J* = 2.0, 4.0; 2.0 is the coupling constant for the doublet and 4.0 is for the coupling constant for the triplet). Infrared spectra were recorded on a Perkin- Elmer 1000 series FTIR. Low-resolution mass spectra were acquired on a Shimadzu QP5000 GC/MS using the indicated ionization method.

Materials. Most alkynes and ethyl diazoester were used as received from Sigma-Aldrich. Multi-substituted cyclopropanes and silyl ynol ethers were prepared as indicated. Spectra data are available on the WWW under http://www.wiley-ch.de/contents/jc_2002/2007/z700069_s.pdf.

2.6.2 Procedure for syntheses of alkyne derivatives.

Silyl ynol ethers were synthesized according to the literature procedures[37] without optimizing.

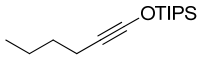
Scheme 2.24 syntheses of alkyne derivatives



An oven-dried round bottom flask (250 mL in volume) with a Teflon-coated stir bar was cooled under vacuum and refilled with nitrogen. The flask was capped with a rubber

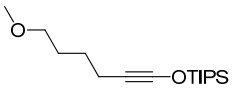
septum, evacuated and backfilled with nitrogen (This evacuation/backfill procedure was performed three times.) A solution of alkyne (10 mmol, 820 mg, 1 equiv) in 50 ml THF was added through septum by syringe. The flask was cooled to -78 ^{o}C. Lithium bis(trimethylsilyl)amide (12 mmol, 12 ml 1 M solution in THF, 1.2 equiv) was added into the flask drop-wise. The resulting solution was stirred at the same temperature for 1 h. Another oven-dried round bottom flask (100 mL in volume) with a Teflon-coated stir bar was cooled under vacuum and refilled with nitrogen. THF (50 ml) was added to this flask and the a solution of ^{t}BuOOH (12 mmol, 3.24 ml 3.7 M solution in toluene, 1.2 equiv) was added through septum by syringe. The flask was cooled to -78 ^{o}C. Lithium bis(trimethylsilyl)amide (13 mmol, 13 ml 1 M solution in THF, 1.3 equiv) was added into the flask drop-wise. The resulting solution was stirred at the same temperature for 30 min, and then this LiOO^{t}Bu solution was transferred to the lithium acetylide solution via cannula. The resulting solution was warmed to 0 ^{o}C and stirred at the same temperature for 2 h. After the flask was cooled to -78 ^{o}C, TIPSOTf (13 mol, 3.5 ml, 1.3 equiv) was added drop-wise to the reaction mixture. The resulting yellow solution was allowed to warm to 0 ^{o}C and stirred for 30 minutes. The reaction was diluted with hexane (50 ml) and then quenched by adding sat. $NaHCO_3$ (100 ml) at a low temperature. The aqueous solution was extracted with hexanes (3 X 50 ml). The organic phases were combined, washed with H_2O and brine, and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the resulting liquid was purified by low pressure distillation.

(hex-1-ynyloxy)triisopropylsilane (**2.11**):[38]



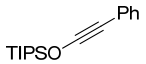
Colorless liquid, bp 75-81 ^{o}C/ ca. 0.5 mmHg, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (t, *J* = 6.8 Hz, 2H), 1.44 – 1.33 (m, 4H), 1.30 – 1.18 (m, 3H), 1.12 – 1.09 (m, 18H), 0.87 (t, *J* = 7.1 Hz, 3H).

Triisopropyl(6-methoxyhex-1-ynyloxy)silane (**2.12**):



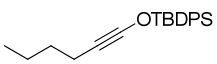
Colorless liquid, bp 112 ^{o}C/ 0.5 mmHg, ^{1}H NMR ($CDCl_3$) δ 1.10 (d, *J* = 6.8, 18H), 1.18-1.27 (m, 3H), 1.43-1.51 (m, 2H), 1.60-1.67 (m, 2H), 2.08 (t, *J* = 6.8, 2H), 3.31 (s, 3H), 3.36 (t, *J* = 6.8, 2H). ^{13}C NMR ($CDCl_3$) δ 12.5, 17.8, 17.9, 24.8, 25.8, 29.3, 34.1, 58.6, 72.7.

triisopropyl(phenylethynyloxy)silane (**2.9**)[39]

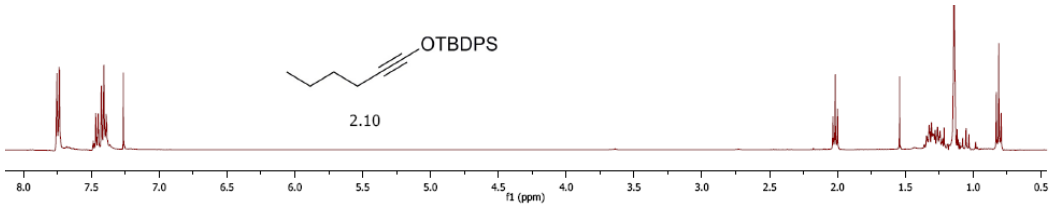


Yellow liquid, bp 125 ^{o}C/ 0.5 mmHg, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.10 (m, 5H), 1.40 – 1.26 (m, 3H), 1.18 (d, *J* = 7.2 Hz, 18H).

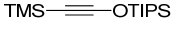
tert-butyl(hex-1-ynyloxy)diphenylsilane (**2.10**)



Colorless liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.71 (m, 4H), 7.48 – 7.37 (m, 6H), 2.02 (t, *J* = 6.8 Hz, 2H), 1.39 – 1.18 (m, 4H), 1.14 (s, 9H), 0.81 (t, *J* = 7.2 Hz, 3H).

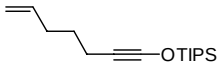


triisopropyl((trimethylsilyl)ethynyloxy)silane (**2.8**) [40]



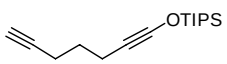
Colorless liquid, ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.34 – 1.21 (m, 1H), 1.14 (d, *J* = 7.2 Hz, 6H), 0.11 (s, 2H).

(hept-6-en-1-ynyloxy)triisopropylsilane (**2.18**):



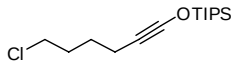
Colorless liquid, bp 85 °C/ 0.5 mmHg, ^{1}H NMR ($CDCl_3$) δ 1.14 (d, *J* = 7.2, 18H), 1.19-1.28 (m, 3H), 1.50 (quintet, *J* = 7.2, 2H), 2.04-2.14 (m, 4H), 4.90-5.01 (m, 2H), 5.72-5.82 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 12.0, 16.9, 17.5, 18.3, 29.5, 33.1, 87.1, 114.8, 138.6. EI-MS (*m/z*): 266 $[M+H]^+$.

(hepta-1,6-diynyloxy)triisopropylsilane(**2.19**):



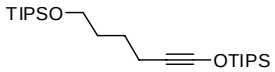
Colorless liquid, bp 90 °C/ 0.5 mmHg, ^{1}H NMR ($CDCl_3$) δ 1.11 (d, *J* = 7.2, 18H), 1.19-1.28 (m, 3H), 1.64 (quintet, *J* = 7.2, 2H), 1.92 (t, *J* = 2.4, 1H), 2.19 (t, *J* = 7.2, 2H), 2.27 (dt, *J* = 2.4, 7.2, 2H). ^{13}C NMR ($CDCl_3$) δ 12.0, 16.6, 17.5, 17.7, 29.0, 29.4, 68.5, 84.1, 87.4. EI-MS (*m/z*): 264 $[M]^+$.

(6-chlorohex-1-ynyloxy)triisopropylsilane (**2.21**):



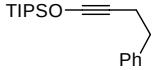
Colorless liquid, bp 105 °C/0.5mmHg, ^{1}H NMR ($CDCl_3$) δ 1.10 (d, *J* = 6.8, 18H), 1.19-1.28 (m, 3H), 1.56 (quintet, *J* = 6.8, 2H), 1.86 (quintet, *J* = 6.8, 2H), 2.11 (t, *J* = 6.8, 2H), 3.53 (t, *J* = 6.8, 2H). ^{13}C NMR ($CDCl_3$) δ 12.0, 16.8, 17.6, 18.3, 27.2, 31.8, 45.0, 87.4. EI-MS (*m/z*): 288 $[M]^+$.

3,3,12,12-tetraisopropyl-2,13-dimethyl-4,11-dioxa-3,12-disilatetradec-5-yne (**2.22**):



Colorless liquid, bp 165 °C/ 0.5 mmHg, ^{1}H NMR ($CDCl_3$) δ 1.01 (m, 21H), 1.11 (d, *J* = 7.2, 18H), 1.19-1.28 (m, 3H), 1.43-1.53 (m, 2H), 1.57-1.64 (m, 2H), 2.08 (t, *J* = 7.2, 2H), 3.67 (t, *J* = 6.4, 2H). ^{13}C NMR ($CDCl_3$) δ 12.0, 12.2, 17.3, 17.5, 18.2, 26.6, 30.6, 32.4, 63.3, 87.0.

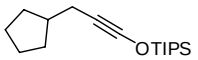
triisopropyl(4-phenylbut-1-ynyloxy)silane (**2.23**):[41]



Colorless liquid, bp 125 °C/ 0.5 mmHg, ^{1}H NMR (400 MHz, $CDCl_3$) δ

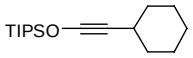
7.30 - 7.15 (m, 5H), 2.77 (t, *J* = 7.2, 2H), 2.40 (t, *J* = 7.2, 2H), 2.22 - 1.18 (m, 3H), 1.10 (d, *J* = 7.2 Hz, 18H).

(3-cyclopentylprop-1-ynyloxy)triisopropylsilane(**2.24**):



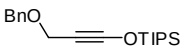
Colorless liquid, bp 105 ^{o}C/ 0.5mmHg, ^{1}H NMR ($CDCl_3$) δ 1.11 (d, *J* = 6.8, 18H), 1.17-1.28 (m, 5H), 1.47-1.61 (m, 3H), 1.67-1.75 (m, 2H), 1.90-1.97 (m, 1H), 2.05 (d, *J* = 6.8, 2H). ^{13}C NMR ($CDCl_3$) δ 12.0, 17.6, 18.3, 23.4, 25.6, 30.1, 32.1, 40.3, 86.8.

(cyclohexylethynyloxy)triisopropylsilane (**2.25**):[39]



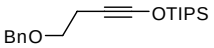
Colorless liquid, bp 100 ^{o}C/ 0.5mmHg, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 - 2.22 (m, 1H), 1.75 - 1.62 (m, 4 H), 1.52 - 1.31 (m, 2H), 1.35 - 1.18 (m, 7H), 1.13 - 1.04 (m,18H).

(3-(benzyloxy)prop-1-ynyloxy)triisopropylsilane (**2.29**):



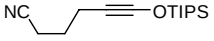
Colorless liquid, bp 140 ^{o}C / 0.5 mmHg, ^{1}H NMR ($CDCl_3$) δ 1.15 (d, *J* = 7.2, 18H), 1.27-1.35 (m, 3H), 4.20 (s, 2H), 4.58 (s, 2H), 7.27-7.36 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 12.1, 17.6, 57.8, 70.9, 73.4, 92.7, 127.8, 127.9, 128.3, 128.6, 138.4.

(4-(benzyloxy)but-1-ynyloxy)triisopropylsilane (**2.27**):



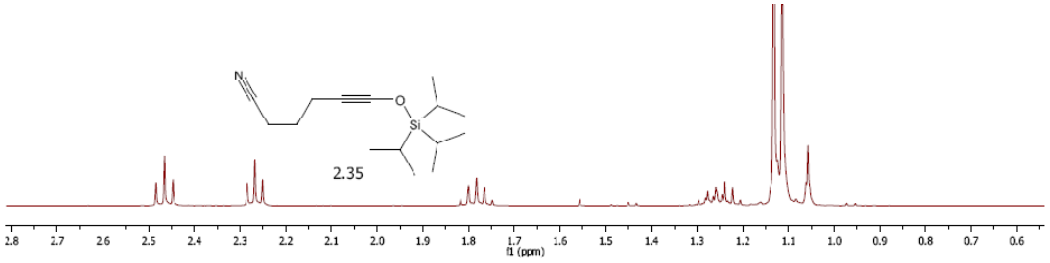
Colorless liquid, bp 150 ^{o}C/ 0.5 mmHg, ^{1}H NMR ($CDCl_3$) δ 1.15 (d, *J* = 7.2, 18H), 1.24-1.33 (m, 3H), 2.43 (t, *J* = 7.2, 2H), 3.55 (t, *J* = 7.2, 2H), 7.25-7.38 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 12.1, 17.6, 18.9, 27.4, 70.3, 73.1, 87.7, 127.7, 127.8, 128.6, 138.7.

6-(triisopropylsilyloxy)hex-5-ynenitrile (**2.35**)



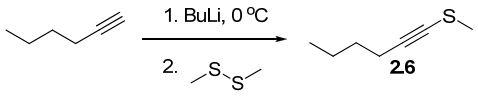
Colorless liquid, bp 120 ^{o}C / 0.5 mmHg, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (t, *J* = 7.3 Hz, 1H), 2.27 (t, *J* = 6.6 Hz, 1H), 1.78 (p, *J* = 7.0 Hz, 1H), 1.31 - 1.19

(m, 1H), 1.12 (d, J = 7.1 Hz, 10H).



Synthesis of hex-1-ynyl(methyl)thioether [42] (**2.6**).

Scheme 2.25 Synthesis of hex-1-ynyl(methyl)thioether

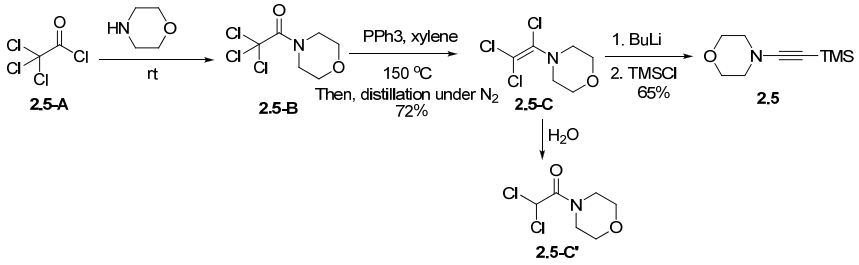


An oven-dried round bottom flask (50 mL in volume) with a Teflon-coated stir bar was charged with 1-hexyne (1 equiv, 32.4 mmol, 2.66 g) under a N_2 atmosphere. THF (24 ml) was added and then the flask was cooled to 0 ^oC. ^{n}BuLi (1 equiv, 32.4 mmol, 20.2 ml 1.6 M solution in hexanes) was added into the flask drop-wise. The resulting solution was stirred at 0 ^oC for 2 h before a solution of 1,2-dimethyldisulfide (1.1 equiv, 35.6 mmol, 3.2 ml) in THF (5 ml) was added to reaction via syringe. After addition, the resulting mixture was allowed to warm to room temperature and was stirred at the same temperature for 2 h. The reaction was quenched by adding H_2O (15 ml) very slowly. The resulting solution was diluted with ethyl acetate (10 ml) and then separated. The aqueous solution was extracted with ethyl acetate (3 X 10 ml). The organic phases were combined, washed with brine, and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the resulting solid was purified by low pressure distillation to give pure

product. Colorless liquid, bp: 140 °C / 0.5mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.29 (t, *J* = 6.9 Hz, 2H), 1.54 - 1.34 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 3H).

Synthesis of 4-((trimethylsilyl)ethynyl)morpholine (**2.5**)[32]

Scheme 2.26 Synthesis of 4-((trimethylsilyl)ethynyl)morpholine



To an oven-dried round bottom flask (100 mL in volume) with a Teflon-coated stir bar was added THF (30 ml) and morpholine (2.08 equiv, 114.4 mmol, 9.97 g, 10 ml) under a N_2 atmosphere. At 0 °C, a solution of 2,2,2-trichloroacetyl chloride **2.20-A** (1 equiv, 55 mmol, 10 g, 6.17 ml) in THF (5 ml) was added at a controlled rate (8 ml/h). After addition, the resulting solution was warmed to rt and stirred for 12 h before 1 M HCl solution was added to quench the reaction. After quenching, the resulting mixture was diluted with ether and then separated. The aqueous solution was extracted with ether (3 X 50 ml). The organic phases were combined, washed with $NaHCO_3$, H_2O and brine, and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the resulting white solid was confirmed to be the desired **2.5-B** by NMR and GC/MS. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81-3.71 (m, 4H), 2.85-2.73 (m, 4H).

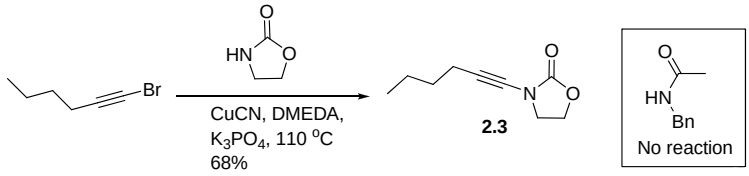
An oven-dried round bottom flask (100 mL in volume) with a Teflon-coated stir bar was charged with the above crude product **2.5-B** (1 equiv, 32.2 mmol, 7.5 g) and PPh_3 (1.1 equiv, 35.4 mmol, 9.3 g). The flask was capped with a rubber septum, evacuated and

backfilled with nitrogen (This evacuation/backfill procedure was performed three times.) Xylene (5 ml) was then added through syringe. The resulting solution was heated to 150 ^{o}C and stirred at the same temperature for 1.5 h. After reaction, xylene was removed under reduced pressure (140 ^{o}C/140 mbar). The resulting liquid was then purified by low pressure distillation (48 ^{o}C/ 0.5 mmHg) to give pure 4-(1,2,2-trichlorovinyl)morpholine (5.07 g, 72%). N_2 protection was applied before and after distillation. (Without N_2 protection, the product will be hydrolyzed easily to 2,2-dichloro-1-morpholinoethanone **2.5-C'**.) ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77-3.75 (m, 4H), 2.84-2.77 (m, 4H).

To prepare the final 4-((trimethylsilyl)ethynyl)morpholine (**2.5**), two steps were combined. Firstly, an oven-dried round bottom flask (250 mL in volume) with a Teflon-coated stir bar was cooled under vacuum and refilled with nitrogen. The flask was capped with a rubber septum, evacuated and backfilled with nitrogen (This evacuation/backfill procedure was performed three times.) A solution of trichloroalkene (23.4 mmol, 5.07 g, 1 equiv) in 60 ml ether was added through septum by syringe. The flask was cooled to -78 ^{o}C. BuLi (51.4 mmol, 20.6 ml 2.5 M solution in THF, 2.2 equiv) was added into the flask drop-wise. The resulting suspension was allowed to warm to rt and stirred at the same temperature for 30 min before being cooled to -20 ^{o}C. TMSCl (1.2 equiv, 28 mmol, 3.03 g) was added by syringe at -20 ^{o}C. The flask was warmed to rt and stirred overnight. The reaction was diluted with hexane (50 ml) and then the precipitate was removed by centrifuge. The resulting solution was concentrated and the residue was purified by Kugelrohr distillation to provide pure 4-((trimethylsilyl)ethynyl)morpholine **2.5** (2.44 g, 65%). H NMR (400 MHz, $CDCl_3$) δ 3.71 - 3.56 (m, 4H), 3.08 - 2.98 (m, 4H), 0.10 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 108.80, 66.16, 62.52, 51.79, 0.95.

Synthesis of 3-(hex-1-ynyl)oxazolidin-2-one **2.3**[43].

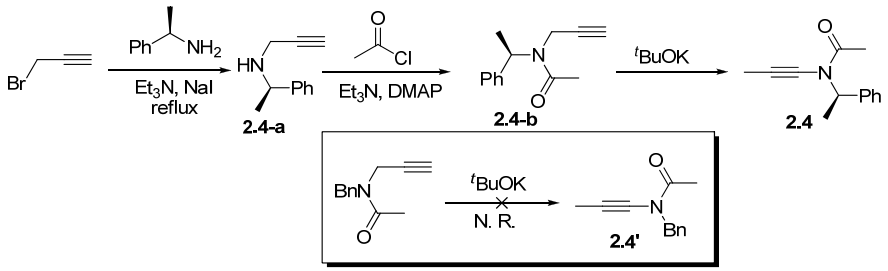
Scheme 2.27 Synthesis of 3-(hex-1-ynyl)oxazolidin-2-one **2.3**



An oven-dried round bottom flask (15 mL in volume) with a Teflon-coated stir bar was charged with CuCN (0.05 mmol, 4.5 mg, 5 mol%), oxazolidin-2-one (1 mmol, 87.1 mg, 1 equiv) and K_3PO_4 (2mmol, 424 mg, 2 equiv). The flask was capped with a rubber septum, evacuated and backfilled with nitrogen (This evacuation/backfill procedure was performed three times.) Toluene (10 ml) and DMEDA (0.1 mmol, 8.8 mg, 10 mol%) were added through syringe. The resulting solution was heated to 110 ^oC and stirred at the same temperature for 18 h. After reaction, the suspension was filtered. The resulting filtrate was then concentrated and purified by flash chromatography on silica gel (5% to 50% ethyl acetate in hexane) to give pure 3-(hex-1-ynyl)oxazolidin-2-one **2.3** (114 mg, 68%).^{1}H NMR (400 MHz, $CDCl_3$) δ 4.41 (t, *J* = 7.2 Hz, 2H), 3,88 (t, *J* = 6.9 Hz, 2H), 2.31 (t, *J* = 7.2 Hz, 2H), 1.54 - 1.46 (m, 2H), 1.45 - 1.36 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H). There was no reaction if using N-benzylacetamide as starting material.

To synthesize (R)-N-(1-phenylethyl)-N-(prop-1-ynyl)acetamide **2.4**, a different procedure was applied.[44]

Scheme 2.28 Synthesize (R)-N-(1-phenylethyl)-N-(prop-1-ynyl)acetamide



An oven-dried round bottom flask (500 mL in volume) with a Teflon-coated stir bar was charged with NaI (3 mmol, 450 mg, 10 mol%). The flask was capped with a rubber septum, evacuated and backfilled with nitrogen (This evacuation/backfill procedure was performed three times.) THF (300 ml), 3-bromoprop-1-yne (24 mmol, 2.86 g, 0.8 equiv), (R)-1-phenylethanamine (30 mmol, 3.63 g, 1 equiv) and Et_3N (90 mmol, 12.5 ml, 3 equiv) were added through syringe. The resulting solution was heated to 70 ^oC and refluxed for 12 h. After reaction, the mixture was diluted with ether. The resulting suspension was filtered. The filtrate was then concentrated and purified by flash chromatography on silica gel (5% to 20% ethyl acetate in hexane) to give pure (R)-N-(1-phenylethyl)prop-2-yn-1-amine **2.4-A**. ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.11 (m, 5H), 4.03 (q, J = 6.6 Hz, 1H), 3.37 (dd, J = 17.1, 2.5 Hz, 1H), 3.18 (dd, J = 17.1, 2.4 Hz, 1H), 2.23 - 2.21 (m, 1H), 1.38 (d, J = 6.6 Hz, 3H).

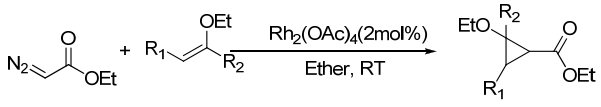
An oven-dried round bottom flask (100 mL in volume) with a Teflon-coated stir bar was charged with **2.4-a** (1 equiv, 5.4 mmol, 858 mg) and DMAP (53mg, 0.08 equiv) under a N_2 atmosphere. THF (50 ml), Et_3N (2.26 ml) acetyl chloride (1 equiv, 5.4 mmol, 0.383 ml) were added into the flask at 0 ^oC. The resulting solution was stirred at room temperature for 3 h until the starting material had been completely consumed as indicated

by TLC analysis. The reaction was quenched by adding saturated aqueous NH_4Cl solution (10 ml) very slowly at 0 ^oC. The resulting solution was diluted with Et_2O (30 ml). The aqueous layer was separated and extracted with Et_2O (3 X 20 ml). The organic phases were combined, washed with brine, and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the resulting solid was purified by flash chromatography on silica gel (5% to 50% ethyl acetate in hexane) to give pure (R)-N-(1-phenylethyl)-N-(prop-2-ynyl)acetamide **2.4-b**. NMR analysis showed a mixture of two rotamers).

An oven-dried round bottom flask (10 mL in volume) with a Teflon-coated stir bar was charged with acetamide **2.4-B** (1 equiv, 2 mmol, 402 mg) and KO^tBu (0.2 equiv, 0.4 mmol, 45 mg). The flask was capped with a rubber septum, evacuated and backfilled with nitrogen (This evacuation/backfill procedure was performed three times.) THF (2 ml) was added through syringe. The resulting solution was stirred at rt for 12 h. After reaction, the mixture was diluted with ether. The resulting suspension was filtered. The filtrate was then concentrated and purified by flash chromatography on silica gel (5% to 30% ethyl acetate in hexane) to give pure (R)-N-(1-phenylethyl)-N-(prop-1-ynyl)acetamide **2.4.** ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 - 7.19 (m, 5H), 5.65 (q, J = 7.1 Hz, 1H), 2.29 (s, 3H), 1.93 (s, 3H), 1.57 (d, J = 7.1 Hz, 3H).

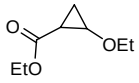
2.6.3 General procedure for the formation of cyclopropanes.[45] (This procedure has not been optimized) (Scheme 2.29)

Scheme 2.29 General procedure for the formation of cyclopropanes



$Rh_2(OAc)_4$ (0.02 equiv) was added to a solution of enol ether (3 equiv) in anhydrous ethyl ether (0.5 M) Under an atmosphere of N_2, a solution of diazoester (1 equiv) in ethyl ether (0.5 M) was added at a controlled rate(1ml/h). After addition, the reaction solution was stirred at room temperature for one hour, then filtered and concentrated. Purified products were isolated by flash chromatography on silica gel (100% hexane to 10% ethyl acetate in hexane). (Stereochemistry is assigned based on coupling constant or comparation the NMR data of known compound)

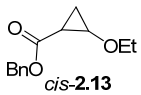
Ethyl 2-ethoxycyclopropanecarboxylate[45] (*cis*-**2.1**) purified by flash chromatography (100% hexane to 10% ethyl acetate in hexane):



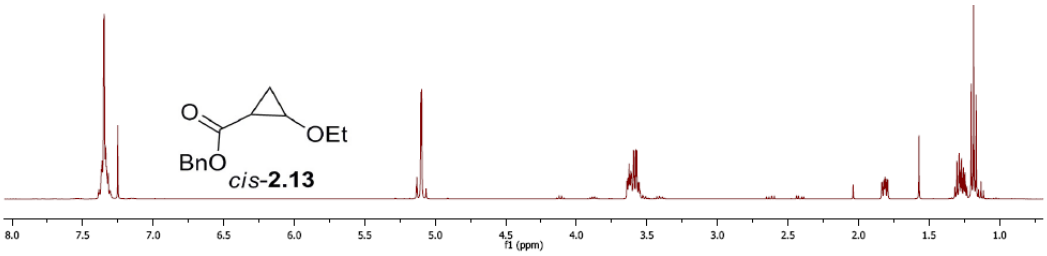
Colorless liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (q, *J* = 7.1 Hz, 1H), 3.66 - 3.54 (m, 1H), 1.75 (ddd, *J* = 9.4, 6.1, 2.0 Hz, 0H), 1.28 - 1.22 (m, 2H), 1.19 (t, *J* = 7.1 Hz, 2H).

Ethyl 2-ethoxycyclopropanecarboxylate[46] (*trans*-**2.1**) was purified by reduced pressure distillation. bp: 95 ^{o}C/38 mbar, density: 0.982 g/ml, colorless liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (q, *J* = 7.1 Hz, 2H), 3.56 (ddt, *J* = 11.8, 6.6, 5.9 Hz, 2H), 3.43 (dq, *J* = 9.4, 7.1 Hz, 1H), 1.68 (dt, *J* = 8.6, 6.6 Hz, 1H), 1.55 (td, *J* = 6.4, 4.8 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.0 Hz, 3H), 1.05 (dt, *J* = 8.6, 6.4 Hz, 1H).

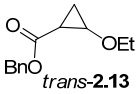
Benzyl 2-ethoxycyclopropanecarboxylate (**2.13**) was synthesized from benzyl diazoacetate and vinyl ethyl ether according to the general procedure. Pure compound was isolated by flash chromatography on silica gel (100% hexane to 10% ethyl acetate in hexane). Colorless liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 - 7.32 (m, 5H), 5.12 (dd, *J* = 12.4, 14.8 Hz, 2H), 3.70 - 3.52 (m, 3H), 1.83 (ddd, *J* = 9.5, 6.0, 2.0 Hz, 1H), 1.35 - 1.24 (m, 2H), 1.20 (t, *J* = 7.1 Hz, 3H).

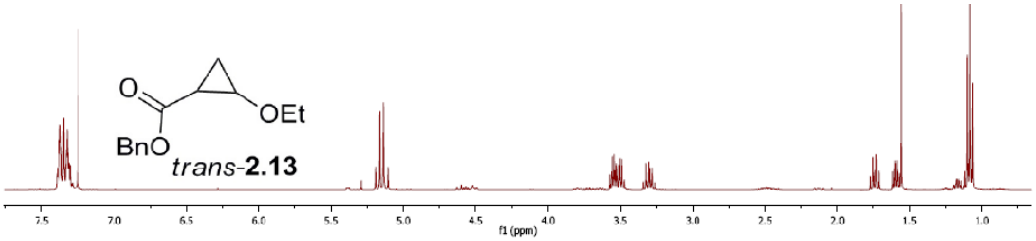


cis-**2.13**

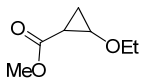


Colorless liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 - 7.30 (m, 5H), 5.17 (q, *J* = 12.3 Hz, 2H), 3.60 - 3.48 (m, 2H), 3.32 (dq, *J* = 9.4, 7.0 Hz, 1H), 1.76 (dt, *J* = 8.5, 6.6 Hz, 1H), 1.62 (td, *J* = 6.4, 4.9 Hz, 1H), 1.24 - 1.14 (m, 1H), 1.10 (t, *J* = 7.0 Hz, 3H).



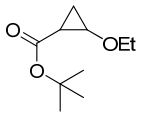


Methyl 2-ethoxycyclopropanecarboxylate (cis-**2.14**) was synthesized from methyl diazoacetate and ethyl vinyl ether. Methyl diazoacetate is generated from ethyl diazoacetate and sodium methoxide.



Colorless liquid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.63 – 3.54 (m, 3H), 1.76 (ddd, *J* = 9.1, 6.3, 2.0 Hz, 1H), 1.37 - 1.12 (m, 5H).

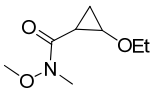
tert-butyl 2-ethoxycyclopropanecarboxylate (*cis*-**2.15**).



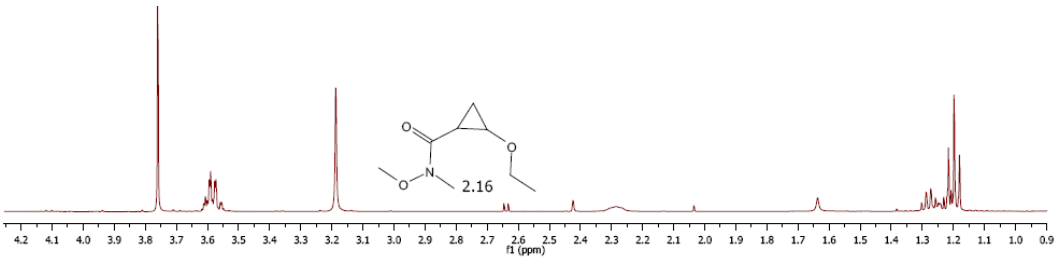
Colorless liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 - 3.52 (m, 3H), 1.68 (ddd, *J* = 9.1, 6.3, 2.0 Hz, 1H), 1.45 (s, 9H), 1.21 - 1.12 (m, 5H).

tert-butyl 2-ethoxycyclopropanecarboxylate (*trans*-**2.15**). Colorless liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 - 3.42 (m, 3H), 1.62-1.54 (m, 1H), 1.50-1.42 (m, 1 H), 1.45 (s, 9H), 1.18 (t, *J* = 7.2 Hz 3 H), 1.21 - 0.95 (m, 1 H).

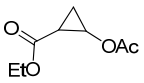
2-Ethoxy-N-methoxy-N-methylcyclopropanecarboxamide (**2.16**) is synthesized from ethyl vinyl ether and 2-diazo-N-methoxy-N-methylacetamide, which is the product from known procedure as described in chapter **1**. Pure *cis*-**2.16** was isolated by flash chromatography:



Colorless liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.62 – 3.53 (m, 3H), 3.19 (s, 3H), 2.35 - 2.21 (m, 1H), 1.31 - 1.18 (m, 5H).

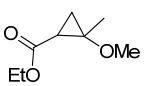


Ethyl 2-acetoxycyclopropanecarboxylate [47] (*trans*-**2.17**) is synthesized from ethyl diazoester and vinyl acetate. Pure *trans*-**2.17** was isolated by flash chromatography:



Colorless liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19-4.11 (m, 3H), 2.05 (s, 3H), 1.94 (q, *J* = 7.1 Hz, 1H), 1.54 (q, *J* = 7.1 Hz, 2H), 1.25-1.17 (m, 4H).

Ethyl 2-methoxy-2-methylcyclopropanecarboxylate 2.12' [48] was synthesized from 2-methoxyprop-1-ene and ethyl diazoacetate according to the general procedure. Pure 2.12 was isolated by flash chromatography.



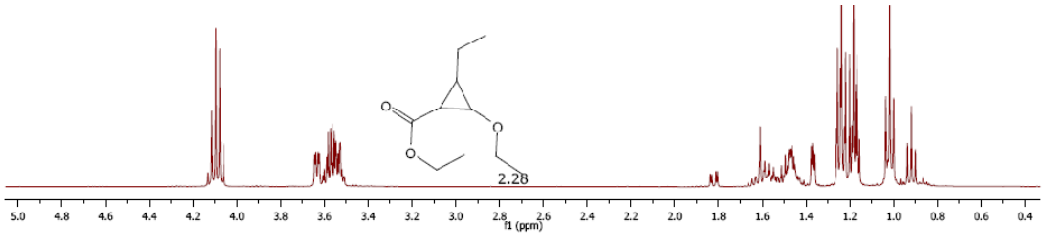
Cis-**2.12'**, colorless liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 - 4.03 (m, 2H), 3.29 (s, 3H), 1.85 (dd, *J* = 9.6, 6.8 Hz, 1H), 1.48 (s, 3H), 1.32 - 1.28

(m, 1H), 1.25 (t, J = 7.1 Hz, 3H), 1.21 - 1.15 (m, 1H).

Trans-**2.12'**, colorless liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (qd, J = 7.1, 2.0 Hz, 2H), 3.26 (s, 3H), 1.70 - 1.56 (m, 2H), 1.43 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H), 0.96 (td, J = 9.2, 6.6 Hz, 1H).

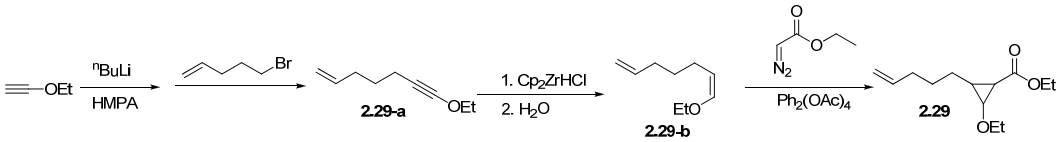
Even though *cis*- and *trans*-**2.12'** were stored under the protection of N_2, *cis/trans* isomerization happened after several days at rt.

Ethyl 2-ethoxy-3-ethylcyclopropanecarboxylate **2.28** was synthesized from 1-ethoxybut-1-ene and ethyl diazoacetate. The product was a mixture of two diastereoisomers.



Ethyl 2-ethoxy-3-(pent-4-enyl)cyclopropanecarboxylate **2.29** was prepared through a series transformations.[49]

Scheme 2.30 Synthesis of ethyl 2-ethoxy-3-(pent-4-enyl)cyclopropanecarboxylate



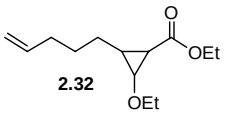
An oven-dried round bottom flask (10 mL in volume) with a Teflon-coated stir bar was cooled under vacuum and refilled with nitrogen. The flask was capped with a rubber septum, evacuated and backfilled with nitrogen (This evacuation/backfill procedure was performed three times.) A solution of ethoxyethyne (3.75 mmol, 262 mg, 1.25 equiv) in 4

ml THF was added through septum by syringe. At 0 ^{o}C n-butylithium (4.2 mmol, 1.68 ml 2.5 M solution in Hexane, 1.4 equiv) was added into the flask drop-wise. The resulting solution was stirred at the same temperature for 30 min. HMPA (8.25 mmol, 1.5 ml, 2.75 equiv) was added and then the resulting solution was stirred at the same temperature for 15 min. 5-bromopent-1-ene (1 equiv, 3 mmol, 447 mg) was added into the flask drop-wise. The resulting solution was then warm to rt and stirred at rt for 12 h. The reaction was quenched by adding H_2O (3 ml) at 0 ^{o}C. The reaction mixture was diluted with ether (10 ml) and then separated. The aqueous solution was extracted with ether (3 X 10 ml). The organic phases were combined, washed with brine, and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the resulting solid was purified by flash chromatography on silica gel (100% hexane to 10% ethyl acetate in hexane) to give pure 7-ethoxyhept-1-en-6-yne (**2.29-a**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 - 5.67 (m, 1H), 5.06 - 4.90 (m, 2H), 4.01 (qd, J = 7.1, 0.5 Hz, 2H), 2.20 - 2.08 (m, 4H), 1.61 - 1.49 (m, 2H), 1.36 - 1.31 (m, 3H).

An oven-dried round bottom flask (15 mL in volume) with a Teflon-coated stir bar was charged with Cp_2ZrHCl (1 equiv, 1.05 mmol, 258 mg) under a N_2 atmosphere. THF (2 ml) and **2.29-a** (1 equiv, 1.05 mmol, 145 mg) were added into the flask drop-wise. The resulting solution was stirred at rt for 1 h before quenched by H_2O (2 ml). The resulting solution was diluted with ether (5 ml) and then separated. The aqueous solution was extracted with ether (3 X 10 ml). The organic phases were combined, washed with brine, and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the resulting solid was purified by flash chromatography on silica gel (100% ethyl acetate to 5% methanol in ethyl acetate) to give pure (E)-1-ethoxyhepta-1,6-diene **2.29-b**.

Colorless liquid, ^{1}H NMR ($CDCl_3$) δ 1.25 (t, *J* = 7.2, 3H), 1.42 (quintet, *J* = 7.2, 2H), 1.91 (dq, *J* = 1.2, 7.2, 2H), 2.01-2.07 (m, 2H), 3.69 (q, *J* = 6.8, 2H), 4.72-4.78 (m, 1H), 4.91-5.02 (m, 2H), 5.74-5.84 (m, 1H), 6.20 (d, *J* = 12.4, 1H). ^{13}C NMR ($CDCl_3$) δ 15.0, 27.4, 30.1, 33.3, 64.8, 104.1, 114.6, 139.1, 146.4.

Ethyl 2-ethoxy-3-(pent-4-enyl)cyclopropanecarboxylate 2.29 was then synthesized according to the general cyclopropanation procedure.

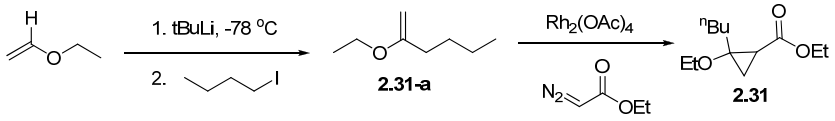


2.32

Colorless liquid, single unassigned diastereoisomer was used in the cycloaddition reaction. R_f = 0.46 (ethyl acetate / hexane = 1: 4). ^{1}H NMR ($CDCl_3$) δ 1.17 (t, *J* = 7.2, 3H), 1.24-1.32 (m, 5H), 1.45-1.59 (m, 3H), 1.85-1.91 (m, 1H), 2.06 (q, *J* = 7.2, 2H), 3.32 (dd, *J* = 7.2, 4.4, 1H), 3.37-3.43 (m, 1H), 3.50-3.58, (m, 1H), 4.14 (q, *J* = 7.2, 2H), 4.92-5.02 (m, 2H), 5.71-5.82 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 14.5, 15.1, 27.1, 27.7, 27.8, 30.2, 33.4, 60.6, 65.6, 66.9, 115.0, 138.7, 184.8. FTIR, 2978, 2928, 2857, 1732, 1160 cm^{-1}.

Ethyl 2-butyl-2-ethoxycyclopropanecarboxylate (**2.31**) was synthesized from ethyl diazoacetate and 2-ethoxyhex-1-ene, which was prepared from ethyl vinyl ether and 1-iodobutane.

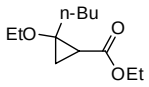
Scheme 2.31 Synthesis of ethyl 2-butyl-2-ethoxycyclopropanecarboxylate



Synthesis of 2-ethoxyhex-1-ene **2.31-a**[50]: An oven-dried round bottom flask (25 mL in volume) with a Teflon-coated stir bar was cooled under vacuum and refilled with nitrogen. The flask was capped with a rubber septum, evacuated and backfilled with nitrogen (This evacuation/backfill procedure was performed three times.) A solution of

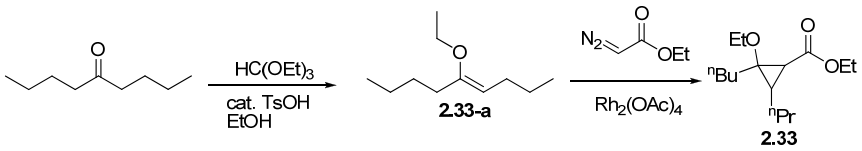
ethyl vinyl ether (10 mmol, 721 mg, 1 equiv) in 8 ml THF was added by syringe. The flask was cooled to -78 ^{o}C. t-butylithium (4.2 mmol, 4.7 ml 1.7 M solution in Hexane, 0.8 equiv) was added into the flask drop-wise. The resulting yellow solution was allowed to warm to rt over 1.5 h. The reaction mixture was then cooled to -78 ^{o}C before a solution of 1-iodobutane (0.5 equiv, 5 mmol, 920 mg) in THF (2 ml) was added. The resulting solution was allowed to warm to 0 ^{o}C and stirred at the same temperature for 4 h. The reaction was quenched by adding sat. NH_4Cl solution (10 ml) at 0 ^{o}C. The resulting solution was diluted with ether (20 ml) and then separated. The aqueous solution was extracted with ether (3 X 20 ml). The organic phases were combined, washed with brine, and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the resulting solid was purified by flash chromatography on silica gel (100% hexane to 10% ethyl acetate in hexane) to give pure ethyl diazoacetate and 2-ethoxyhex-1-ene (**2.31-a**).

Ethyl 2-butyl-2-ethoxycyclopropanecarboxylate (**2.31**), Colorless liquid, single unassigned diastereoisomer was used in the cycloaddition reaction. R_f = 0.60 (Ethyl acetate / Hexane = 1: 4). ^{1}H NMR ($CDCl_3$) δ 0.90 (t, *J* = 7.2, 3H), 0.95 (dd, *J* = 10, 6.4, 1H), 1.12 (t, *J* = 7.2, 3H), 1.25 (t, *J* = 7.2, 3H), 1.29-1.38 (m, 3H), 1.40-1.57 (m, 2H), 1.58-1.67 (m, 2H), 1.80-1.89 (m, 1H), 3.22-3.32 (m, 1H), 3.52-3.62 (m, 1H), 4.14 (q, *J* = 7.2, 2H). ^{13}C NMR ($CDCl_3$) δ 14.2, 14.4, 15.5, 19.7, 22.7, 27.4, 27.8, 34.8, 60.5, 63.0, 67.6, 170.3. FTIR (neat) 2961, 2932, 2874, 1726, 1379, 1161, 1070 cm^{-1}. EI-MS (*m/z*): 215 $[M+H]^+$.



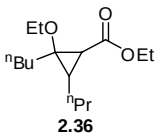
Ethyl 2-butyl-2-ethoxy-3-propylcyclopropanecarboxylate (**2.33**) was synthesized in two straight-forward steps. Other tetra-substituted cyclopropanes can also be synthesized from this transformation.[51]

Scheme 2.32 Synthesis of ethyl 2-butyl-2-ethoxy-3-propylcyclopropanecarboxylate



Synthesis of 5-ethoxynon-4-ene (**2.33-a**): An oven-dried round bottom flask (50 mL in volume) with a Teflon-coated stir bar was charged with TsOH (4 mol%, 0.4 mmol, 75 mg) under a N_2 atmosphere. EtOH (25 ml) and ketone (1 equiv, 0.1 mol, 14.2 g) were added into the flask. Triethyl orthoformate (1.1 equiv, 0.11 mol, 16.3 g) was added slowly to the reaction. The resulting solution was then heated to reflux for 15 min before another portion of TsOH (0.53 mmol, 100 mg) was added. After addition, the resulting mixture was then distillated. Pure 5-ethoxynon-4-ene (**2.33-a**) was collected by reduced pressure distillation. Colorless liquid, bp: 91 °C /36 mbar, ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.32 (t, *J* = 7.3 Hz, 1H), 3.64 (q, *J* = 7.0 Hz, 2H), 2.16 - 1.89 (m, 4H), 1.49 - 1.19 (m, 9H), 0.93-0.87 (m, 6H).

Ethyl 2-butyl-2-ethoxy-3-propylcyclopropanecarboxylate (**2.33**), colorless liquid, single unassigned diastereoisomer was used in the cycloaddition reaction. R_f = 0.57 (Ethyl acetate / Hexane = 1: 4). ^{1}H NMR ($CDCl_3$) δ 0.85-0.91 (m, 6H), 1.08-1.18 (m, 5H), 1.20-1.53 (m, 13H), 1.68-1.74 (m, 1H), 1.86-1.91 (m, 1H), 3.23 (m, 1H), 3.51 (m, 1H), 4.10 (q, *J* = 7.2, 2H). ^{13}C NMR ($CDCl_3$) δ 14.1, 14.3, 14.5,15.6, 22.5, 23.0, 27.9, 30.4, 30.5, 32.4, 33.7, 60.5, 62.6, 71.6, 170.7. FTIR (neat) 2959, 2932, 2874, 1733, 1466, 1159, 1079 cm^{-1}. EI-MS (*m/z*): 257 $[M+H]^+$.

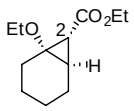


(1R,6S,7S)-ethyl 1-ethoxybicyclo[4.1.0]heptane-7-carboxylate (*trans*-**2.34**) was synthesized according to the same procedure.

Ethoxycyclohex-1-ene (**2.34-a**)[51] was purified by distillation (150 °C/760 mmHg). ^{1}H

NMR (300 MHz, $CDCl_3$) δ 4.60 (dd, *J* = 4.7, 1.9 Hz, 1H), 3.69 (q, *J* = 7.0 Hz, 2H), 2.14 - 1.97 (m, 4H), 1.76 - 1.61 (m, 2H), 1.59 - 1.48 (m, 2H), 1.28 (t, *J* = 7.0 Hz, 3H).

(1S,6R,7R)-Ethyl 1-ethoxybicyclo[4.1.0]heptane-7-carboxylate (**2.34**):

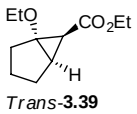


Colorless liquid, single cis-diastereoisomer was used in the cycloaddition reaction; stereochemistry is assigned by comparing coupling constants for the C2 proton (J_{cis} = 10.8; J_{trans} = 6.4). R_f = 0.43 (Ethyl acetate / Hexane = 1: 4). ^{1}H NMR ($CDCl_3$) δ 1.12 (t, *J* = 7.2, 3H), 1.25 (t, *J* = 7.2, 3H), 1.10-1.32 (m, 3H), 1.45-1.52 (m, 2H), 1.54 (d, *J* = 6.4, 1H), 1.95-2.04 (m, 2H), 2.08-2.19 (m. 2H), 3.23 (dq, *J* = 8.8, 7.2, 1H), 3.63 (dq, *J* = 8.8, 7.2, 1H), 4.13 (q, *J* = 7.2, 2H). ^{13}C NMR ($CDCl_3$) δ 14.5, 15.6, 21.1, 21.6, 23.5, 27.3, 28.9, 32.1, 60.6, 62.6, 67.8, 170.9. FTIR (neat) 3433, 2932, 2361, 1732, 1309, 1183, 1151, 1048 cm^{-1}. bp: 72 °C /0.5 mmHg, EI-MS (*m/z*): 257 $[M+H]^+$.

1-ethoxycyclopent-1-ene (**3.36-a**),[51] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.47 – 4.40 (m, 1H),

3.79 (q, *J* = 7.0 Hz, 2H), 2.38 - 2.25 (m, 4H), 1.96 - 1.79 (m, 2H), 1.31 (td, *J* = 7.0, 0.5 Hz, 3H).

(1S,5R,6S)-ethyl 1-ethoxybicyclo[3.1.0]hexane-6-carboxylate (**3.36**), Colorless liquid,



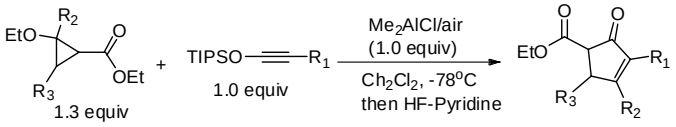
Trans-**3.39**

single *trans*-diastereoisomer was used in the cycloaddition reaction; stereochemistry is assigned by comparing coupling constants for the C2 proton (J_{cis} = 10.8; J_{trans} = 6.4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (q, *J* = 7.1 Hz, 2H), 3.67 - 3.50 (m, 2H), 2.29 (ddd, *J* = 12.5, 8.9, 2.1 Hz, 1H), 2.08 - 1.97 (m, 2H), 1.97 (d, *J*

= 10.4, 1H), 1.90 - 1.74 (m, 3H), 1.42 - 1.29 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).

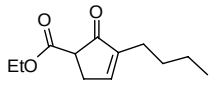
2.6.4 General procedure for the formation of cyclopentenones. (All the reactions were set up in 16 X 100 mm test tubes)

Scheme 2.33 General procedure for the formation of cyclopentenones



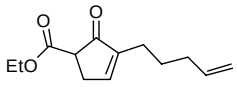
A dried test tube with septum was sparged with dried air (air was dried by actived molecular sieves). Anhydrous dichloromethane (1 mL) and Me_2AlCl (0.5 mL of 1M solution in hexanes, 1 equiv) were added into the tube. Dried air (20 mL) was bubbled through the solution at room temperature. The resulting solution was cooled to -78 °C. Cyclopropane (0.65 mmol, 1.3 equiv) and silyl ynol ether (0.5 mmol, 1 equiv) were added into the reaction. The resulting reaction mixture was stirred at -78 °C and monitored by TLC. After the reaction was judged complete, it was quenched by adding 0.5 mL of 30% HF-pyridine solution. After stirring at –78 °C for 5 minutes, the reaction mixture was diluted with 8 ml ethyl ether. The ether solution was transferred into separation funnel. The tube was washed with water and ether. The aqueous layer was washed with 30 mL ether. The combined organic fractions were washed with 50 ml of brine and dried with anhydrous $MgSO_4$, concentrated and purified by flash chromatography on silica gel (100% hexane to 10% ethyl acetate in hexane).

Ethyl 3-butyl-2-oxocyclopent-3-enecarboxylate (**table 2.9**, **2.11-B**):



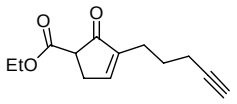
Reaction time: *cis*-cyclopropane, 7 h; *trans*-cyclopropane, 8 h; colorless liquid, ^{1}H NMR ($CDCl_3$) δ 0.87 (t, *J* = 7.2, 3H), 1.26-1.38 (m, 5H), 1.47 (quintet, *J* = 7.6, 2H), 2.18 (dt, *J* = 1.6, 7.6, 2H), 2.76-2.83 (m, 1H), 2.91-3.98 (m, 1H), 3.41 (dd, *J* = 2.4, 8.8, 1H), 4.18 (q, *J* = 7.2, 2H), 7.33 (t, *J* = 2.4, 1H). ^{13}C NMR ($CDCl_3$) δ 14.0, 14.4, 22.6, 24.8, 29.2, 31.0, 51.7, 61.7, 145.1, 157.1, 169.4, 202.8. FTIR (neat) 2959, 2932, 1737, 1708, 1156 cm^{-1}. EI-MS (*m/z*): 210 $[M]^+$.

Ethyl 2-oxo-3-(pent-4-enyl)cyclopent-3-enecarboxylate (**table 2.9, 2.18-B**):



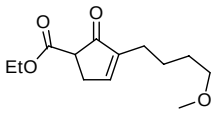
Reaction time: 6 h, colorless liquid, ^{1}H NMR ($CDCl_3$) δ 1.25 (t, *J* = 7.2, 3H), 1.55 (quintet, *J* = 7.2, 2H), 2.03 (q, *J* = 7.2, 2H), 2.16 (dt, *J* = 1.6, 7.2, 2H), 2.72-2.80 (m, 1H), 2.87-2.94 (m, 1H), 3.37 (dd, *J* = 2.8, 6.8, 1H), 4.17 (dq, *J* = 0.8, 7.2, 2H), 4.91-5.00 (m, 2H), 5.70-5.80 (m, 1H), 7.33 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 14.4, 24.6, 26.9, 31.0, 33.5, 51.6, 61.7, 115.2, 138.3, 144.7, 157.3, 169.3, 202.7. FTIR (neat) 2931, 1737, 1706, 1155 cm^{-1}. EI-MS (*m/z*): 222 $[M]^+$.

Ethyl 2-oxo-3-(pent-4-ynyl)cyclopent-3-enecarboxylate (**table 2.9**, **2.19-B**):



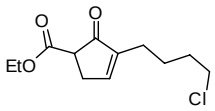
Reaction time: 6 h, colorless liquid, ^{1}H NMR ($CDCl_3$) δ 1.23 (t, *J* = 7.2, 3H), 1.66 (quintet, *J* = 7.2, 2H), 1.92 (t, *J* = 2.8, 1H), 2.14 (dt, *J* = 2.8, 7.2, 2H), 2.26 (dt, *J* = 1.6, 7.2, 2H), 2.71-2.79 (m, 1H), 2.86-2.94 (m, 1H), 3.36 (dd, *J* = 2.8, 7.2, 1H), 4.15 (q, *J* = 7.2, 2H), 7.36 (quintet, *J* = 1.6, 1H). ^{13}C NMR ($CDCl_3$) δ 14.4, 18.2, 24.2, 26.4, 31.1, 51.6, 61.8, 69.1, 83.8, 143.9, 157.8, 169.3, 202.5. FTIR (neat) 3279, 2932, 1735, 1703, 1154 cm^{-1}. EI-MS (*m/z*): 220 $[M]^+$.

Ethyl 3-(4-methoxybutyl)-2-oxocyclopent-3-enecarboxylate (**table 2.9, 2.20-B**):



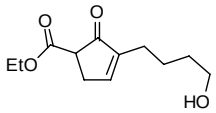
Reaction time: 8 h, colorless liquid, ^{1}H NMR ($CDCl_3$) δ 1.26 (t, *J* = 7.2, 3H), 1.52-1.55 (m, 4H), 2.17 (t, *J* = 6.8, 2H), 2.72-2.79 (m, 1H), 2.91 (dt, *J* = 18.8, 2.0, 1H), 3.28 (s, 3H), 3.33-3.39 (m, 3H), 4.17 (q, *J* = 7.2, 2H), 7.34-7.36 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 14.4, 24.3, 24.9, 29.5, 31.1, 51.6, 58.8, 61.7, 72.5, 144.7, 157.3, 169.3, 202.7. FTIR (neat) 2935, 2868, 1737, 1706, 1202, 1156, 1118 cm^{-1}. EI-MS (*m/z*): 240 $[M]^+$.

Ethyl 3-(4-chlorobutyl)-2-oxocyclopent-3-enecarboxylate (**table 2.9**, **2.21-B**):



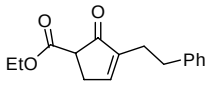
Reaction time: 8 h, colorless liquid, ^{1}H NMR ($CDCl_3$) δ 1.30 (t, *J* = 7.2, 3H), 1.60-1.68 (m, 2H), 1.74-1.81 (m, 2H), 2.21 (dt, *J* = 1.2, 7.6, 2H), 2.75-2.83 (m, 1H), 2.91-2.98 (m, 1H), 3.41 (dd, *J* = 2.8, 6.8, 1H), 3.53 (t, *J* = 6.8, 2H), 4.20 (dq, *J* = 0.8, 7.2, 2H), 7.38-7.40 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 14.4, 24.4, 25.0, 31.1, 32.3, 44.9, 51.6, 61.8, 144.4, 157.6, 169.3, 202.7. FTIR (neat) 3428, 1736, 1703, 1633, 1155 cm^{-1}. EI-MS (*m/z*): 244 $[M]^+$.

Ethyl 3-(4-hydroxybutyl)-2-oxocyclopent-3-enecarboxylate (**table 2.9**, **2.22-B**):



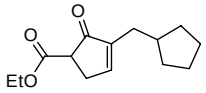
Reaction time: 9 h, colorless liquid, ^{1}H NMR ($CDCl_3$) δ 1.28 (t, *J* = 7.2, 3H), 1.57 (quintet, *J* = 3.2, 4H), 2.19-2.24 (m, 2H), 2.74-2.82 (m, 1H), 2.90-2.97 (m, 1H), 3.40 (dd, *J* = 2.4, 6.8, 1H), 3.63-3.66 (m, 2H), 4.20 (q, *J* = 7.2, 2H), 7.37 (t, *J* = 1.2, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 24.0, 24.8, 31.1, 32.3, 51.6, 61.8, 62.4, 144.7, 157.7, 169.4, 203.0. FTIR (neat) 2937, 1733, 1703, 1203, 1156, 1046 cm^{-1}. EI-MS (*m/z*): 227 $[M+H]^+$.

Ethyl 2-oxo-3-phenethylcyclopent-3-enecarboxylate (**table 2.9**, **2.23-B**): Reaction time:



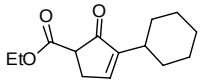
3 h, colorless liquid, ^{1}H NMR ($CDCl_3$) δ 1.29 (t, *J* = 7.2, 3H), 2.49-2.53 (m, 2H), 2.71-2.81 (m, 3H), 2.88-2.95(m, 1H), 3.40 (dd, *J* = 2.8, 6.8, 1H), 4.21 (dq, *J* = 1.2, 7.2, 2H), 7.20-7.24 (m, 3H), 7.25-7.28(m, 3H). ^{13}C NMR ($CDCl_3$) δ 14.4, 26.9, 31.1, 33.8, 51.6, 61.8, 126.3, 128.5, 128.6, 141.3, 143.9, 158.0, 169.3, 202.6. FTIR (neat) 3416, 1705, 1632, 1155 cm^{-1}. EI-MS (*m/z*): 258 $[M]^+$.

Ethyl 3-(cyclopentylmethyl)-2-oxocyclopent-3-enecarboxylate (**table 2.9**, **2.24-B**):



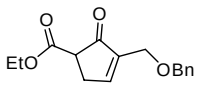
Reaction time: 4 h, colorless liquid, ^{1}H NMR ($CDCl_3$) δ 1.08-1.16 (m, 2H), 1.30 (t, *J* = 7.2, 3H), 1.49-1.65 (m, 4H), 1.69-1.77 (m, 2H), 1.95-2.10 (m, 1H), 2.20 (dt, *J* = 7.2, 1.6, 2H), 2.76-2.84 (m, 1H), 2.92-2.99 (m, 1H), 3.41 (dd, *J* = 2.4, 6.8, 1H), 4.22 (dq, *J* = 0.8, 7.2, 2H), 7.36-7.39(m, 1H). ^{13}C NMR ($CDCl_3$) δ 14.4, 24.9, 25.2, 31.1, 31.2, 32.7, 38.4, 51.6, 61.7, 144.6, 157.6, 169.4, 202.9. FTIR (neat) 2950, 1737, 1707, 1200, 1156, 1017 cm^{-1}. EI-MS (*m/z*): 236 $[M]^+$.

Ethyl 3-cyclohexyl-2-oxocyclopent-3-enecarboxylate (**table 2.9**, **2.25-B**):



Reaction time: 4 h, colorless liquid, ^{1}H NMR ($CDCl_3$) δ 1.09-1.23 (m, 3H), 1.27-1.38 (m, 5H), 1.68-1.84 (m, 5H), 2.27-2.32 (m, 1H), 2.73-2.79 (m, 1H), 2.92 (dq, *J* = 18.8, 2.5, 1H), 3.40 (dd, *J* = 2.5, 7.0, 1H), 4.16-4.26 (m, 2H), 7.29 (dt, *J* = 1.0, 3.0, 1H). ^{13}C NMR ($CDCl_3$) δ 14.4, 26.4, 30.9, 31.8, 32.0, 34.7, 52.0, 61.6, 149.9, 155.5, 169.4, 202.3. FTIR (neat) 2926, 1738, 1705, 1200, 1155 cm^{-1}. EI-MS (*m/z*): 236 $[M]^+$.

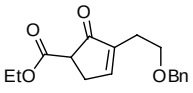
Ethyl 3-(benzyloxymethyl)-2-oxocyclopent-3-enecarboxylate (**table 2.9**, **2.26-B**):



Reaction time: 24 h, colorless liquid, ^{1}H NMR ($CDCl_3$) δ 1.29 (t, *J* =

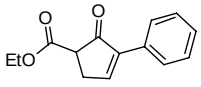
7.2, 3H), 2.82-2.89 (m, 1H), 2.95-3.60 (m, 1H), 3.47 (dd, *J* = 2.4, 6.8, 1H), 4.19-4.24 (m, 4H), 4.57 (s, 2H), 7.27-7.36 (m, 5H), 7.67-7.70 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 14.4, 31.5, 52.1, 61.9, 64.2, 73.4, 127.9, 128.0, 128.7, 138.0, 142.1, 159.6, 169.0, 201.3. FTIR (neat) 2860, 1736, 1705, 1368, 1201, 1155, 1025 cm^{-1}. ESI-MS (*m/z*): 275 $[M]^+$, 297 $[M+Na]^+$.

Ethyl 3-(2-(benzyloxy)ethyl)-2-oxocyclopent-3-enecarboxylate (**table 2.9**, **2.27-B**):



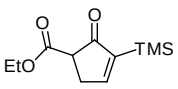
Reaction time: 3 h, colorless liquid, ^{1}H NMR ($CDCl_3$) δ 1.31 (t, *J* = 7.2, 3H), 2.50-2.55 (m, 2H), 2.76-2.87 (m, 1H), 2.94-3.03 (m, 1H), 3.42 (dd, *J* = 2.7, 6.9, 1H), 3.63 (t, *J* = 6.4, 2H), 4.22 (q, *J* = 7.2, 2H), 4.52 (s, 2H), 7.28-7.39 (m, 5H), 7.51-7.53 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 14.4, 25.7, 31.3, 51.5, 61.9, 67.9, 73.1, 127.9, 128.0, 128.7, 138.4, 141.8, 159.1, 169.3, 202.7. FTIR (neat) 2863, 1736, 1705, 1201, 1155, 1102 cm^{-1}. ESI-MS (*m/z*): 289 $[M+H]^+$.

Ethyl 2-oxo-3-phenylcyclopent-3-enecarboxylate (**table 2.10, entry 1, 2.9-B**):



Reaction time: -78℃,10 h, then rt, 12 h, colorless liquid, ^{1}H NMR ($CDCl_3$) δ 1.30 (t, *J* = 7.2, 3H), 2.91 (ddd, *J* = 3.2, 7.2, 19.6, 1H), 3.09 (dt, *J* = 19.6, 2.8, 1H), 3.59 (dd, *J* = 2.8, 6.8, 1H), 4.20 - 4.26 (m, 2H), 7.32 - 7.39 (m, 3H), 7.50 - 7.68 (m, 2H), 7.86 (t, *J* = 2.8, 1H). ^{13}C NMR ($CDCl_3$) δ 14.4, 30.7, 52.8, 61.9, 127.3, 128.7, 128.9, 131.1, 142.0, 158.6, 169.1, 200.6. FTIR (neat) 2983, 1736, 1707, 1304, 1204, 1114, 1158 cm^{-1}. EI-MS (*m/z*): 230 $[M]^+$.

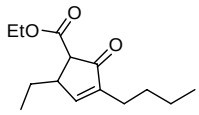
Ethyl 2-oxo-3-(trimethylsilyl)cyclopent-3-enecarboxylate (**table 2.10**, **entry 2, 2.10-B):**



Reaction time: 8 h, colorless liquid , ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (t, *J* = 2.6 Hz, 0H), 4.20 (q, *J* = 7.1 Hz, 0H), 3.37 (dd, *J* = 7.2, 3.1 Hz,

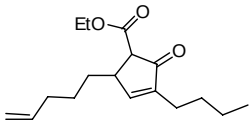
0H), 3.07 (dt, *J* = 19.2, 2.8 Hz, 0H), 2.86 (ddd, *J* = 19.2, 7.2, 2.7 Hz, 0H), 1.28 (t, *J* = 7.1 Hz, 0H), 0.16 (s, 1H). ^{13}C NMR ($CDCl_3$) δ -1.8, 14.4, 34.8, 52.3, 61.7, 145.7, 169.5, 171.9, 206.2.

Ethyl 3-butyl-5-ethyl-2-oxocyclopent-3-enecarboxylate (**table 2.10**, **entry 3, 2.28-B**): Reaction time: 24 h, colorless liquid with about 2% of unidentified inpurity, ^{1}H NMR



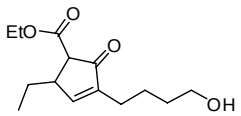
($CDCl_3$) δ 0.88 (t, *J* = 7.6, 3H), 0.96 (t, *J* = 7.6, 3H), 1.19 - 1.34 (m, 5H), 1.40 - 1.51 (m, 3H), 1.56 - 1.68 (m, 1H), 2.12 - 2.17 (m, 2H), 2.99 (d, *J* = 2.8, 1H), 3.04 - 3.08 (m, 1H), 4.18 (q, *J* = 7.2, 2H), 7.22 - 7.24 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 11.9, 14.0, 14.4, 22.6, 24.7, 27.5, 29.9, 45.3, 58.4, 61.6, 144.6, 160.6, 169.7, 202.7. FTIR (neat) 2928, 1737, 1708, 1155, 1023 cm^{-1}. EI-MS (*m/z*): 238 $[M]^+$.

Ethyl 3-butyl-2-oxo-5-(pent-4-enyl)cyclopent-3-enecarboxylate (**table 2.10, entry 4,**



2.29-B):Reaction time: 24 h, colorless liquid with about 5% of unidentified inpurity, purified sample for spectra can be obtained by Preparative TLC. ^{1}H NMR ($CDCl_3$) δ 0.89 (t, *J* = 7.2, 3H), 1.20-1,36 (m, 6H), 1.41-1.51 (m, 4H), 1.56 - 1.62 (m, 1H), 2.08 (q, *J* = 6.4, 2H), 2.15 (t, *J* = 7.6, 2H), 3.00 (d, *J* = 2.4, 1H), 3.13 - 3.16 (m, 1H), 4.20 (q, *J* = 7.2, 2H), 4.92 - 5.03 (m, 2H), 5.19 - 5.82 (m, 1H), 7.22 - 7.25 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 14.1, 14.4, 22.6, 24.7, 26.9, 29.9, 33.7, 34.0, 43.7, 58.8, 61.7, 115.3, 138.3, 144.5, 160.6, 169.6, 202.6. FTIR (neat) 2930, 1737, 1709, 1155 cm^{-1}. EI-MS (*m/z*): 279 $[M+H]^+$.

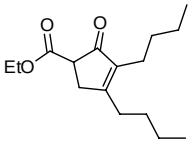
Ethyl 5-ethyl-3-(4-hydroxybutyl)-2-oxocyclopent-3-enecarboxylate (**table2.10, entry**



5, 2.30):Reaction time: 24 h, colorless liquid, ^{1}H NMR ($CDCl_3$) δ 1.00 (t, *J* = 7.2, 3H), 1.30 (t, *J* = 6.8, 3H), 1.47 - 1.69 (m, 6H), 2.21-2.23 (m, 2H), 3.03 (d, *J* = 2.8, 1H), 3.08 - 3.12 (m, 1H), 3.67 (t, *J* = 6.0, 2H), 4.22 (q,

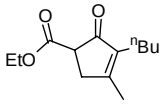
J = 6.8, 2H), 7.30 (t, *J* = 1.2, 1H). ^{13}C NMR ($CDCl_3$) δ 11.9, 14.3, 24.0, 24.7, 27.4, 32.4, 45.4, 58.3, 61.6, 62.4, 144.2, 161.1, 169.6, 202.8. FTIR (neat) 3401, 2932, 1736, 1703, 1248, 1156, 1042 cm^{-1}. ESI-MS (*m/z*): 255 $[M+H]^+$, 277 $[M+Na]^+$.

Ethyl 3,4-dibutyl-2-oxocyclopent-3-enecarboxylate (**table2.10, entry 6, 2.31-B**):



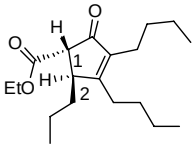
Reaction time: 24 h, colorless liquid, ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.2, 3H), 0.94 (t, *J* = 7.2, 3H), 1.28-1.42 (m, 9H), 1.49-1.57 (m, 2H), 2.16 (t, *J* = 7.2, 2H), 2.38-2.51 (m, 2H), 2.68 (dd, *J* = 7.2, 18.4, 1H), 2.86 (d, *J* = 18.4, 1H), 3.36 (dd, *J* = 2.6, 7.2, 1H), 4.19 (dq, *J* = 1.8, 7.2, 2H). ^{13}C NMR ($CDCl_3$) δ 14.1, 14.4, 22.8, 23.0, 23.3, 29.7, 30.8, 31.0, 33.5, 51.4, 61.6, 139.1, 169.8, 174.1, 202.7. (one carbon on *n*-Butyl overlapped). FTIR (neat) 2958, 2931, 1737, 1703, 1641, 1157, 1021 cm^{-1}. ESI-MS (*m/z*): 267 $[M+H]^+$.

Ethyl 3-butyl-4-methyl-2-oxocyclopent-3-enecarboxylate (**table2.10, entry 7, 2.32-B**):



Reaction time: 7 h, colorless liquid, ^{1}H NMR (400 MHz, $cdcl_3$) δ 4.20 (qd, *J* = 7.1, 0.8 Hz, 2H), 3.38 (dd, *J* = 7.1, 2.8 Hz, 1H), 2.87 (ddd, *J* = 18.2, 2.6, 1.1 Hz, 1H), 2.68 (ddd, *J* = 18.2, 7.1, 0.9 Hz, 1H), 2.17 (t, *J* = 7.4 Hz, 2H), 2.08 (s, 3H), 1.42 – 1.19 (m, 7H), 0.88 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $cdcl_3$) δ 202.32, 170.19, 169.78, 139.31, 61.66, 51.49, 35.84, 30.50, 23.16, 22.77, 17.36, 14.40, 14.09.

Ethyl 2,3,4-tributyl-5-oxocyclopent-3-enecarboxylate (**table2.10, entry 8, 2.33-B**):

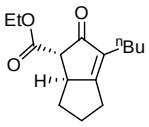


Reaction time: 72 h/-78℃., 8 h/-40℃, 12h/rt, colorless liquid, stereochemistry is assigned based on coupling constant for C1 and C2 protons (*J* = 2.8). ^{1}H NMR ($CDCl_3$) δ 0.85-0.96 (m, 9H), 1.12-1.49 (m, 13H), 1.51-1.61 (m, 1H), 1.71-1.79 (m, 1H), 2.08-2.20 (m, 2H), 2.24-2.32 (m, 1H), 2.48-2.55 (m, 1H), 3.03 (d, *J* = 2.8, 1H), 3.09-3.12 (m, 1H), 4.18 (dq, *J* = 2.0, 7.2, 2H). ^{13}C

NMR ($CDCl_3$) δ 14.2, 14.3, 14.4, 20.6, 22.8, 23.0, 23.3, 28.6, 29.8, 30.9, 34.8, 44.9, 57.9, 61.6, 139.2, 170.1, 177.1, 202.2..FTIR (neat) 2958, 2933, 1738, 1703, 1637, 1155 cm^{-1}. EI-MS (*m/z*): 308 $[M]^+$.

Ethyl 3-butyl-2-oxo-2,4,5,6,7,7a-hexahydro-1H-indene-1-carboxylate (table2.10, entry 9, 2.34-B):Reaction time: 4 h, colorless liquid with about 5% of unidentified impurity; stereochemistry is assigned based on coupling constant for C1 and C2 protons ($J < 3$). ^1H NMR ($CDCl_3$) δ 0.87 (t, $J = 7.2$, 3H), 1.06-1.16 (m, 1H), 1.21-1.39 (m, 8H), 1.47-1.58 (m, 1H), 1.82-1.89 (m, 1H), 1.98-2.04 (m, 1H), 2.13-2.25 (m, 4H), 2.84-2.91 (m, 2H), 2.93 (bs, 1H), 4.14-4.23 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 14.1, 14.4, 22.6, 22.7, 25.5, 26.6, 28.8, 30.9, 34.4, 44.8, 58.6, 61.5, 136.1, 169.9, 175.6, 201.5. FTIR (neat) 3402, 2932, 1736, 1703, 1647, 1155, 1024 cm^{-1}. EI-MS (*m/z*): 264 $[M]^+$.

Ethyl 3-butyl-2-oxo-1,2,4,5,6,6a-hexahydropentalene-1-carboxylate (2.36-B):

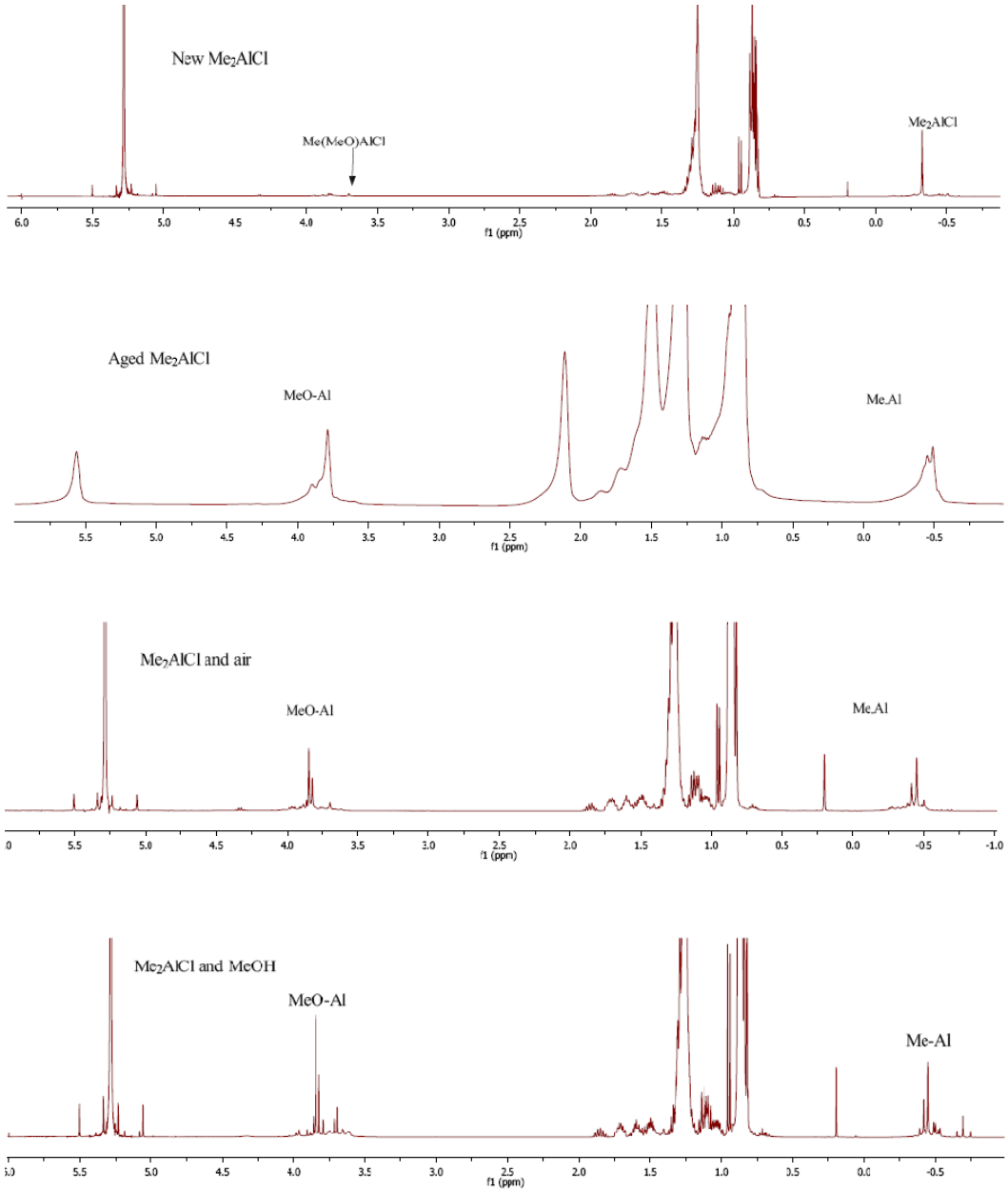


Reaction time: 48 h, reaction was set up under the condition without bubbling air. Colorless liquid, ^1H NMR (400 MHz, cdcl$_3$) δ 4.28 - 4.13 (m, 2H), 3.19 - 3.07 (m, 1H), 2.99 (d, $J = 3.7$ Hz, 1H), 2.60 - 2.42 (m, 2H), 2.25 - 2.12 (m, 2H), 2.13 - 1.90 (m, 4H), 1.48 - 1.34 (m, 2H), 1.30-1.19 (m, 5H), 0.86 (t, $J = 7.3$ Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 203.7, 182.7, 170.0, 134.6, 61.5, 59.1, 48.5, 30.7, 30.1, 25.8, 25.3, 24.0, 22.8, 14.4, 14.0.

2.6.5 Catalyst or Lewis acid synthesis.

$AgN(Tf)_2$ was synthesized from Ag_2CO_3 and $HN(Tf)_2$ according to the literature.[52] The white powder was stored in the glove box.

Me(MeO)AlCl was generated in situ by bubbling dried air through the Me_2AlCl solution at room temperature (40 ml/mol Me_2AlCl). Air was dried by 4 Å molecular sieves in a round bottom flask. See detailed NMR spectra below (all the peaks in the 0.8-1.3ppm range are from hexanes):



2.7 Reference

[1] Reissig, H.-U.; Zimmer, R. *Chem.Rev*. **2003**, *103*, 1151.

[2] Harvey, D. F.; Sigano, D. M. *Chem. Rev.* **1996**, *96*, 271.

[3] (a) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897. (b) Davies, H. M. L.; Boebel, T. A. *Tetrahedron Lett.* **2000**, *41*, 8189.

[4] Bedekar, A. V.; Koroleva, E. B.; Andersson, P. G. *J. Org. Chem.* **1997**, *62*, 2518.

[5] Barluenga, J.; Suarez-Sobrino, A. L.; Tomas, M.; Garcia-Granda, S.; Santiago-Garcia, R. *J. Am. Chem. Soc.* **2001**, *123*, 10494.

[6] Harvey, D. F.; Brown, M. F. *J. Am. Chem. Soc.* **1990**, *112*, 7806.

[7] Moss, R. A.; Wlostowski, M.; Shen, S.; Krogh-Jespersen, K.; Matro, A. *J. Am. Chem. Soc.* **1988**, *110*, 4443.

[8] Paxton, R. J., Taylor, Richard J. K. *Synlet.* **2007**, *4*, 633.

[9] Rasmussen, P. B.; Bøwadt, S. *Synthesis* **1989**, 114-117.

[10] Davies, H. M. L.; Hu, B. *J. Org. Chem.* **1992**, *57*, 3186-3190.

[11] Kunkel, E.; Reichelt, I.; Reissig, H.-U. *Liebigs Ann. Chem.* **1984**, 802-819.

[12] Grimm, E. L.; Zschiesche, R.; Reissig, H.-U. *J. Org. Chem.* **1985**, *50*, 5543-5545.

[13] (a) Leblanc, Y.; Fitzsimmons, B. J.; Springer, J. P.; Rokach, J. *J. Am. Chem. Soc.* **1989**, *111*, 2995-3000. (b) Bo¨hm, C.; Schinnerl, M.; Bubert, C.; Zabel, M.; Labahn, T.; Parisini, E.; Reiser, O. *Eur. J. Org. Chem.* **2000**, 2955-2965. (c) Reichelt, I.; Reissig, H.-U. *Liebigs Ann. Chem.* **1984**, 531-551.

[14] G. Mehta, A. Srikrishna, *Chem. Rev*. **1997**, *97*, 671.

[15] Danheiser, R. L.; Carini, D. J.; Basak, A. *J. Am. Chem. Soc*. **1981**, *103*, 1604.

[16] Shimada, S.; Hashimoto, Y.; Sudo, A.; Hasegawa, M.; Saigo, K. *J. Org. Chem*. **1992**, *57*, 7126.

[17] Shimada, S.; Hashimoto, Y.; Saigo, K. *J. Org. Chem*. **1993**, *58*, 5226.

[18] Saigo, K.; Shimada, S.; Hasegawa, M. *Chem. Lett*. **1990**, 905.

[19] Graziano, M. L.; Iesce, M. R. *J. Chem. Res*. (S) **1987**, 362.

[20] Graziano, M. L.; Cimminiello, G. *J. Chem. Res.* (S) **1989**, 42.

[21] Graziano, M. L.; Cimminiello, G. *J. Chem. Res.* (M) **1989**, 446.

[22] Feldman, K. S.; Simpson, R. E. *J. Am. Chem. Soc.* **1989**, *111*, 4878.

[23] Graziano, M. L.; Chiosi, S. *J. Chem. Res*. (S) **1989**, 44.

[24] Saigo, K.; Shimada, S.; Shibasaki, T.; Hasegawa, M. *Chem. Lett*. **1990**, 1093.

[25] Komatsu, M.; Suehiro, I.; Horiguchi, Y.; Kuwajima, I. *Synlett* **1991**, 771.

[26] Horiguchi, Y.; Suehiro, I.; Sasaki, A.; Kuwajima, I. *Tetrahedron Lett.* **1993**, *34*, 6077.

[27] Yadav, V. K.; Sriramurthy, V. *Angew. Chem., Int. Ed*. **2004**, 43, 2669.

[28] Yu, M.; Pagenkopf, B. L. *Org. Lett*. **2003**, *5*, 5099.

[29] Graziano, M. L.; Iesce, M. R.; Cermola, F.; Cimminiello, G. *J. Chem. Res*. (S) **1992**, 157.

[30] Bajtos, B.; Yu, M.; Zhao,H. Pagenkopf, B. L. *J. Am. Chem. Soc*. **2007**, *129*, 9631.

[31] Saigo, K.; Shimada, S.; Shibasaki, T.; Hasegawa, M. *Chem. Lett*.**1990**, 1093.

[32] a) For cycloaddition of ynolates with nitrones, see: Shindo, M.; Itoh, K.; Tsuchiya, C.; Shishido, K. *Org. Lett*. **2002**, *4*, 3119. b) Shindo, M.; Ohtsuki, K.; Shishido, K.

Tetrahedron: Asymmetry **2005**, *16*, 2821. c) with epoxides, see: Kai, H.; Iwamoto, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc*. **1996**, *118*, 7634. d) with aziridines, see: Iwamoto, K.; Kojima, M.; Chatani, N.; Murai, S. *J. Org. Chem*. **2001**, *66*, 169. e) cycloaddition of ynamines with epoxides, see: Movassaghi, M.; Jacobsen, E. J. *J. Am. Chem. Soc.* **2002**, *124,* 2456.

[33] Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc*. **2004**, *126*, 11806.

[34] a) Fried, J.; Sih, J. C. *Tetrahedron Lett*. **1973**, *14*, 3899.

b) Daniewski, A. R.; Wovkulich, P. M.; Uskokivic, M. R. *J. Org. Chem***. 1992**, 7133.

[35] a) Pellissier, H. Tetrahedron **2005**, *61*, 6479. b) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7557.

[36] Schore N. E. in *Comprehensive Organometallic Chemistry II, Vol. 12* (Eds: E.W. Abel, F. G. Stone, G. Wilkinson), Elsevier, New York, **1995**, pp. 703 – 739.

[37] Zhang L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 11806.

[38] Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron* **1998**, *54*, 2411.

[39] Sun, J.; Kozmin, S. A. *Angew. Chem., Int. Ed*. **2006**, *45*, 4991.

[40] Ponomarev, S. V.; Zolotareva, A. S.; Ezhov, R. N.; Kuznetsov, Yu. V.; Petrosyan, V. S. *Russian Chemical Bulletin* **2001**, *50*, 1093.

[41] Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc*. **2004**, *126*, 10204.

[42] Narasaka, K.; Hayashi, Y.; Shimadzu, H., Niihata, S. *J. Am. Chem. Soc*. **1992**, *114*, 8869.

[43] Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J. *J. Am. Chem. Soc.* **2003**, *125*, 2368.

[44] Huang, J.; Xiong, H.; Hsung, R. P. *Org. Lett*. **2002**, *4*, 2417.

[45] Doyle, M. P.; Leusen, D. V. *J. Org. Chem*. **1982,** *47*, 5326.

[46] Kusuyama, I.; *Bull. Chem. Soc. Jpn*. 1977, 50, 1784.

[47] Bendeddouche, K. C.; Rechsteiner, B.; Texier-Boullet, Fr.; Hamelin, J.; Benhaoua, H. *J. Chem. Res., Synopses* **2002**, *3*,114.

[48] Doyle, M. P.; Leusen, D.; Tamblyn, W. H. *Synthesis* **1981,** 10 787.

[49] Wiskur, S. L.; Korte, A.; Fu, G. C. *J. Am. Chem. Soc*. **2004**, *126*, 82.

[50] Owen, D. R.; Whitby, R. J. *Synthesis* **2005**, 2061.

[51] Tian, S.; Deng, L. *J. Am. Chem. Soc*. **2001**, *123,* 6195.

[52] Vij, A.; Zheng, Y. Y.; Kirchmeier, R. L., Shreeve, J.M. *Inorg. Chem.* **1994**, *33*, 3281.

Chapter 3. Optically Active Allenes as Organocatalysts in Asymmetric Reactions

3.1 Introduction and background

3.1.1 Introduction and background of asymmetric catalysis.

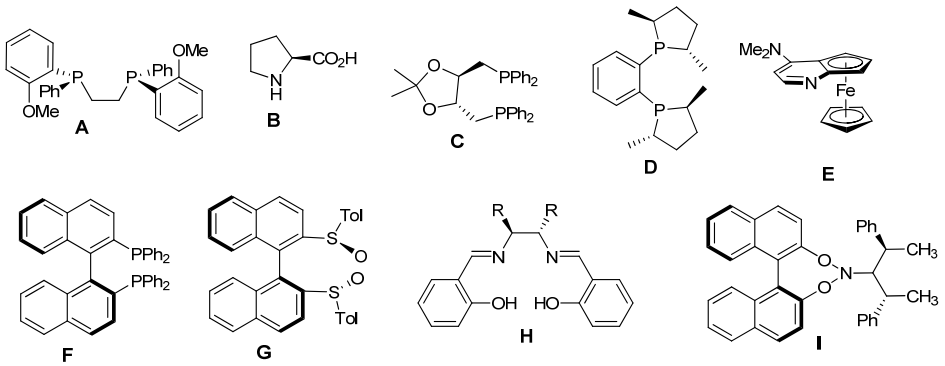
This chapter describes a new project about asymmetric catalysis: A family of organocatalysts and ligands characterized by optically active allenes. These catalysts and ligands incorporate optically active allenes as the source of chirality.

The synthesis of both natural and unnatural organic compounds in optically active form, especially in the study of biologically active compounds, is one of key challenges in organic chemistry. Most biological natural products and pharmaceutical drugs[1] are chiral compounds, which are composed of only one of the two mirror-image isomers. The demand for chiral compounds, often as single enantiomers, has escalated in recent years,[2] driven particularly by the demands of the pharmaceutical industry and other applications such as agricultural chemicals, flavors, fragrances, and materials.[3] There are several ways to generate enantiomerically enriched compounds in a selective manner. Chiral pool synthesis is the easiest approach: a chiral starting material is manipulated through successive reactions. This is especially attractive for target molecules having the similar chirality to a relatively inexpensive naturally occurring building block such as a sugar or amino acid.[4] This approach requires a stoichiometric amount of the enantiopure starting material, which may be rather expensive if not occurring in nature. An alternative is asymmetric induction; the aim is to make enantiomers into diastereomers, since diastereomers have different reactivity. The selectivity may arise either from the properties inherent to the substrate (substrate control) or from an external agent (reagent or catalyst control). A third strategy involves resolution an equimolar (racemic) mixture

of the two enantiomers. The limitation of this approach is yielding only up to 50% of the desired enantiomer. Compared to these approaches to control absolute stereochemistry, asymmetric catalysis offers significant advantages.

Asymmetric catalysis is used to synthesize enantiomerically pure or enriched products out of achiral substrates.[5] Nearly all nonenzymatic catalysts for asymmetric organic synthesis can be assigned to one of two categories:[6] organometallic catalyst involving transition metals and their associated ligands and organocatalyst involving "purely" organic structures. Most existing ligands and organic catalysts are characterized by either of two types of chirality: some species owe their chirality to stereogenic atoms (for example, proline), usually tetrahedral carbon or phosphorus. Many others are chiral by virtue of hindered rotation around a carbon-carbon single bond, the exemplar of which is the binaphthyl backbone found in BINOL,[7] BINAP[8] and their various derivatives. These types of ligands have been successfully applied in asymmetric catalysis. Some of the most successful catalysts combine the elements of both central and axial chirality.[9,10] (**Scheme 3.1**)

Scheme 3.1 Significant ligands and catalysts used in asymmetric synthesis.



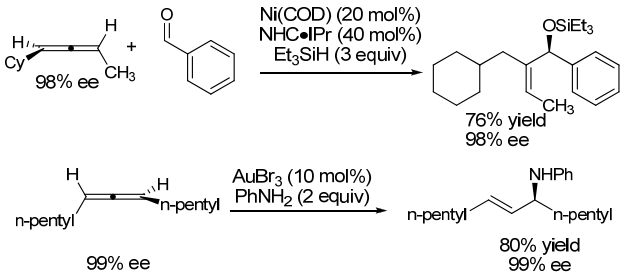
The last several decades have witnessed continued introduction and development of chiral organic catalysts and ligands for transition and main-group metals.[11] A major breakthrough occurred in the early 1970s, when William Knowles and co-workers[12] demonstrated that rhodium complexes containing chiral phosphine ligands (**Scheme 3.1, A**) were able to catalyze the enantioselective addition of H_2 to one of the faces of a prochiral olefinic substrate generating a chiral C-H center with high enantioselectivity. Likewise, numerous research groups struggled to construct chiral phosphine that would serve as ligands in asymmetric hydrogenation.[13] The significant progress, especially in the industrial application in this area was achieved by Noyori and colleagues in 1980[14] with a Rh complex of BINAP (**Scheme 3.1**, structure **F**). The early example in organocatalysis is the utilization of cinchona alkaloids as catalysts for cyanohydrin formation in 1912.[15] The key discovery reported in 1971 by Eder *et al*[16] and in 1974 by Hajos and Parrish[17] demonstrated that amino acids, notably proline (**Scheme 3.1**, structure **B**), effected an intramolecular aldol reaction in high yields and enantioselectivity. More than 20 years later, the implications of this finding began to be realized by the demonstration that such a simple amino acid can promote enormous remarkable chemo-, diastereo-, and enantioselective reactions.[18]

3.1.2 Introduction and background of optically active allene.

Allenes, which have the propa-1,2-diene motif with two π-orbitals perpendicular to each other, have gained increasing attention as useful building blocks in modern organic chemistry.[19] Their synthetic utility is demonstrated both by a variety of regio- and stereoselective carbon-carbon or carbon-heteroatom bond formations and by the fact that they can transfer their axial chirality efficiently to one or several new stereogenic

centers.[20] These characteristics, as well as the interesting allenic structures in an abundance of natural products and pharmacologically active compounds,[21] gave rise to plentiful interest in the stereoselective synthesis and application of allenes. Over the past century, a large number of reactions involving allenes have been developed, such as cycloaddition,[22] cyclization,[23] rearrangement,[24] electrophilic addition,[25] nucleophilic addition,[26] radical reactions[27] and transition metal catalyzed transformations.[28] The facile generation of allenes and the subsequent use of the generated allenic moiety for a chirality transfer also make these methods highly applicable in the synthesis of natural products.[21](**Scheme 3.2**)

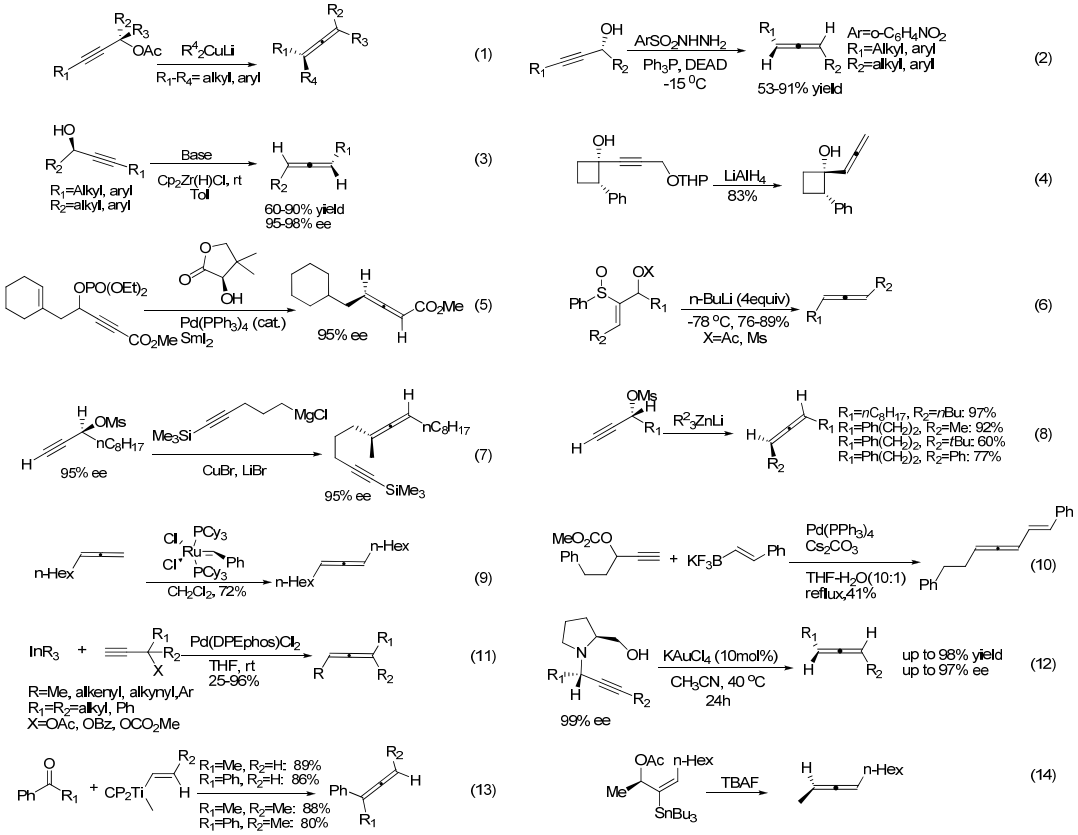
Scheme 3.2 Axial-to-central transfer of chirality with allenes



Compared to their broad utility as reagents or substrates in synthetic chemistry, chiral allenes are rarely used as asymmetric catalysts or ligands in asymmetric reactions. We hypothesized that chiral allenes might represent an attractive framework for developing ligands for asymmetric catalysis; the chirality of an allene might be communicated effectively to a transition state in the context of an enantioselective transformation. Allenes can be formed and retain chemical and stereochemical integrity under a broad range of reaction conditions. (**Scheme 3.3**) They can be formed from, and are thus stable towards, cuprate reagents,[29] phosphines,[30] strong reductants

($Cp_2Zr(Cl)H$,[31] $LiAlH_4$ and AlH_3,[32] SmI_2[33]) and nucleophiles (RLi,[34] RMgX,[35] RZnX,[36] $RZrCp_2Cl$,[37], RBF_3K[38]) as well as Pd,[39] Au,[40] Fe,[41] Zn,[42] Cr[43], Sn[44] and Ti[45] salts. Therefore existing literature suggested that we would have substantial latitude to develop catalysts with allene backbones.

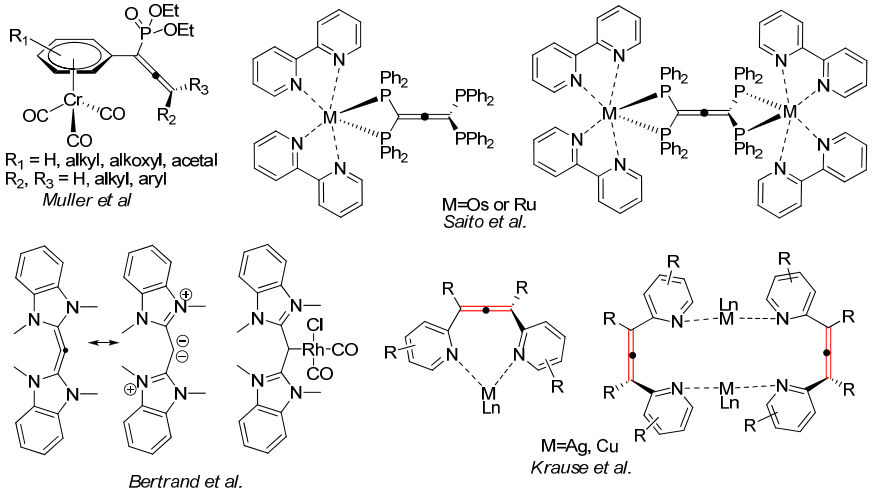
Scheme 3.3 Synthesis of allene



Several groups have synthesized complex allenes and either demonstrated or suggested their ability to bind transition metals. (**Scheme 3.4**) For example, Muller and coworkers prepared optically active chromiumcarbonyl complexed arene,[46] which have broad applications in the synthesis of complex structures. This aryl allene compound

could be a suitable acceptor for Michael addition and olefination substrate. However, this type of structure has never been induced into asymmetric catalyst or ligands. The second two Os and Ru complexes [47] have allene-briged polyphosphine structure. Their luminescent and redox-active properties were investigated, but the potential application in asymmetric catalysis has not been recognized. Bertrand's group [48] prepared an extremely electron-rich, achiral allene and showed that it could ligate Rh through the central carbon. Norbert Krause *et al*[49] is the first group to propose that the axial chirality can be introduced into a ligand for stereoselective transition metal catalysis, and his group designed a series of allenic bipyridines as chiral ligands for transition metals such as Ag and Cu. However, no asymmetric reaction was demonstrated using these complexes as asymmetric catalysis.

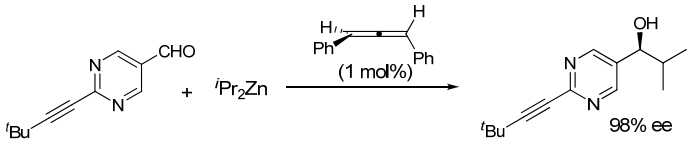
Scheme 3.4 Transition metal-allene complexes



A report from Soai and coworkers demonstrated that optically active disubstituted allenes could induce asymmetry in the addition of diisopropyl zinc to pyrimidine caroboxaldehyde (**Scheme 3.5**).[50] The actual effectiveness of the allene as a chiral

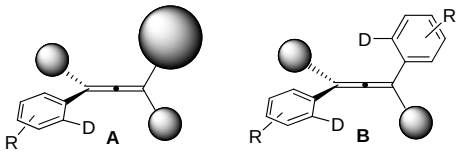
modulator was difficult to gauge because other experiments with the same system indicate that a strong non-linear effect coupled with auto-catalysis conspire to amplify even unmeasurable enantiomeric excesses.[51] So far, the optically active allenes have never been shown to function as asymmetric catalysts themselves or ligands for metals involved in asymmetric catalysis.

Scheme 3.5. Auto-catalytic addition of diisopropyl zinc to pyrimidine aldehyes induced by optically active allenes.

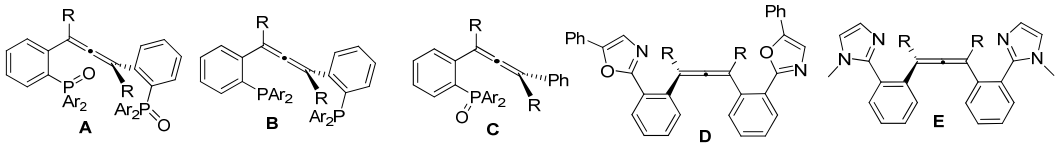


We hypothesized that allenes of the general structure **A** or **B** might represent attractive frameworks for developing ligands for asymmetric catalysis. The relationship between the donor group and the allene may facilitate asymmetric induction by orienting metals or sites of reactivity towards the source of chirality (**Scheme 3.6**). This basic platform could be amenable to introduction of a variety of donor groups and could find utility in main group and transition-metal catalysis or organocatalysis. Specifically, we initially started with diaryl substituted allene-based ligands or organocatalysts. Representations of potential allene-based ligands and catalysts are shown in **Scheme 3.6.**

Scheme 3.6 Diaryl substituted allene based ligands or organocatalysts



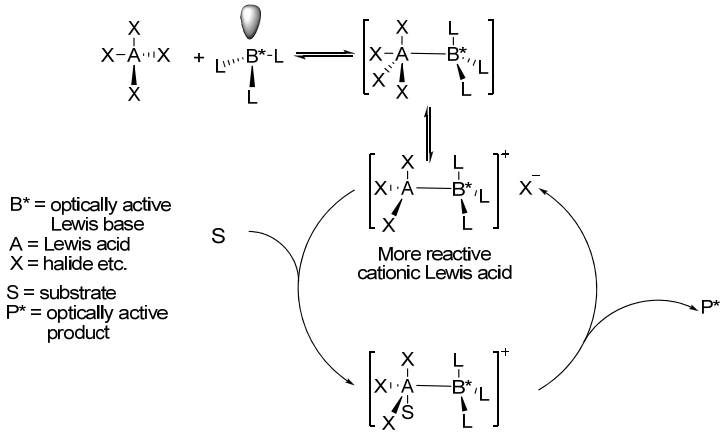
D = donor group



Among these examples, we firstly focused on phosphine oxide type of catalysts. Phosphine oxides are easily accessible and air-stable; they have strong electron-donor properties and can form complexes with various acceptors and then in turn activate the acceptors. This phenomenon which was termed 'Lewis base activation of Lewis acids' by Scott E. Denmark,[52] has been observed in numerous examples where stable, acid-base adducts show enhanced reactivity.

3.1.3 Introduction and background of Lewis base catalyzed reactions.

Scheme 3.7 Electronic redistribution resulting from Lewis acid-base complexation and mechanism in asymmetric catalysis.

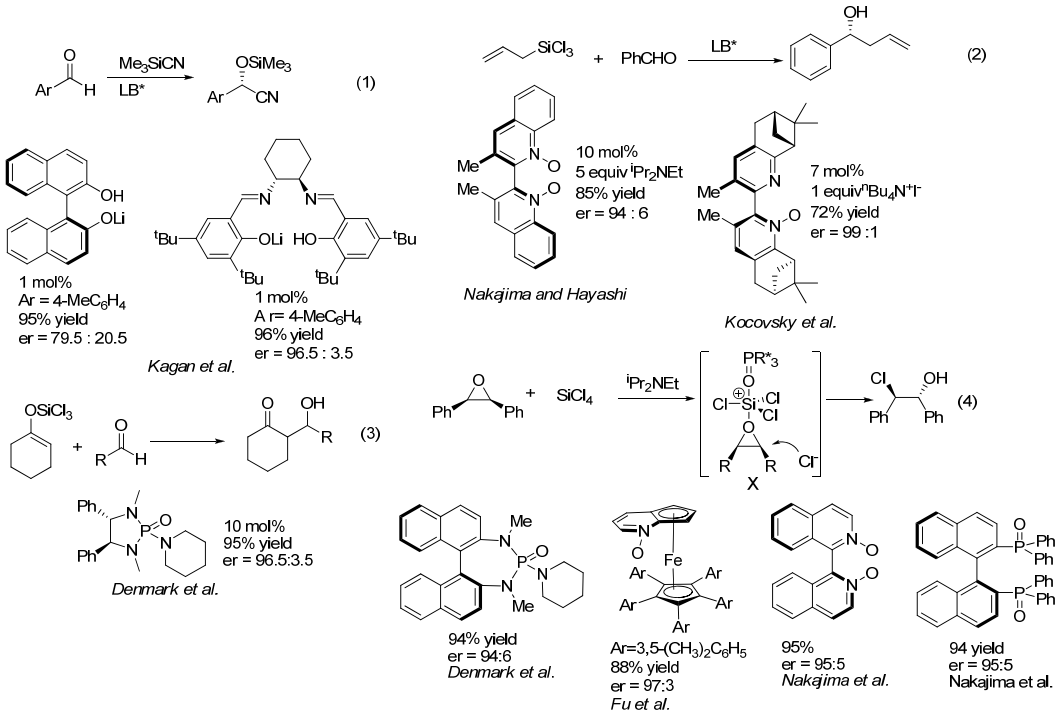


A Lewis base catalyzed reaction is the reaction that is accelerated by the activation of an electron-pair donor (Lewis base catalyst) on an electron-pair acceptor (Lewis acid substrate).[53] This activation will lead to a polarization and transfer of electron density to

the acceptor and a hypervalent species is then created with unique patterns of reactivity, [54] where both the electrophilicity and nucleophilicity of the adduct are enhanced. (**Scheme 3.7**) Other cases exist where the binding of the Lewis base(s) generates such a strong polarization and ionization occurs, thereby yielding an ion pair. In this ion pair, both the electrophilicity of the **A** center, and the nucleophilicity of the X unit are highly improved.

A variety of Lewis bases, especially chiral Lewis bases can be used as asymmetric catalysts to active Lewis acids in enantioselective reactions. Kagan and co-workers[55] have extended the use of chiral anionic nucleophiles for the enantioselective catalysis of silylcyanation. (**Scheme 3.8** rection **1**) Monolithiated (S)-binolate catalyzes the formation of silyl cyanohydrins of aromatic aldehydes with only modest selectivity (e.r.=79.5:20.5), whereas the monolithiated (*R*,*R*)-salen generally affords higher selectivities with aromatic aldehydes. The Nakajima[56] and Hayashi[57] research groups have both investigated the use of chiral 2,2'-bipyridyl bis-*N*-oxides in allylation of aldehydes. (**Scheme 3.8** reaction **2**) The strong basicity of the *N*-oxide oxygen atom along with their rigid structures makes them extremely effective activators. Kocovsky and co-workers have examined the use of chiral bis-*N*-oxides and mixed quinoline/isoquinoline *N*-oxides. [58] The yields and selectivities are comparable to those obtained in other catalyst systems. Asymmetric aldol reactions of trichlorosilyl enol ethers with aldehyde can be catalyzed by phosphoramide type catalysts in good yield and enantioselectivity.[59] (**Scheme 3.8** reaction **3**)

Scheme 3.8 Enantioselective Lewis-base promoted reactions

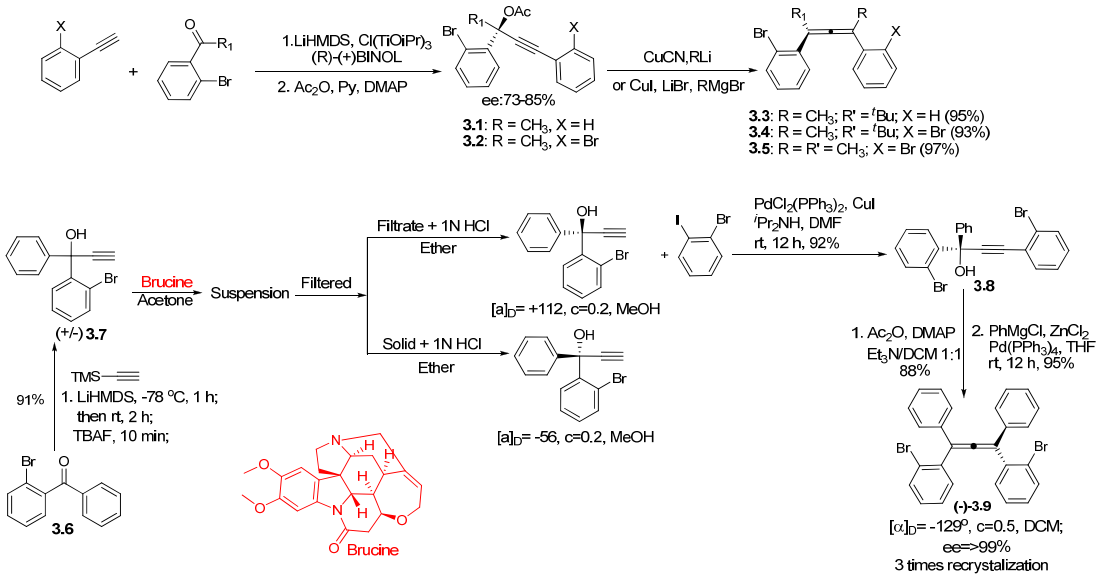


The Denmark group has shown that meso-epoxides are rapidly opened to the enantiomerically enriched vicinal chlorohydrins in good yields and selectivities in the presence of weak Lewis acid $SiCl_4$ and a substoichiometric amount of a chiral phosphoramide.[60] Other structurally distinct Lewis bases are also useful in this reaction. The research groups of both Nakajima and Fu have employed chiral *N*-oxides or phosphine oxide to promote the opening of meso-epoxides in good yields and selectivities (**Scheme 3.8** reaction **4**).[61] In the case of the planar-chiral *N*-oxide, initial kinetic studies demonstrate that the reaction is second order in the catalyst and zeroth order in $SiCl_4$ and therefore suggests a stoichiometric complexation of the catalyst and formation of the active intermediate.

3.2 Chiral allene based organocatalyst design and synthesis.

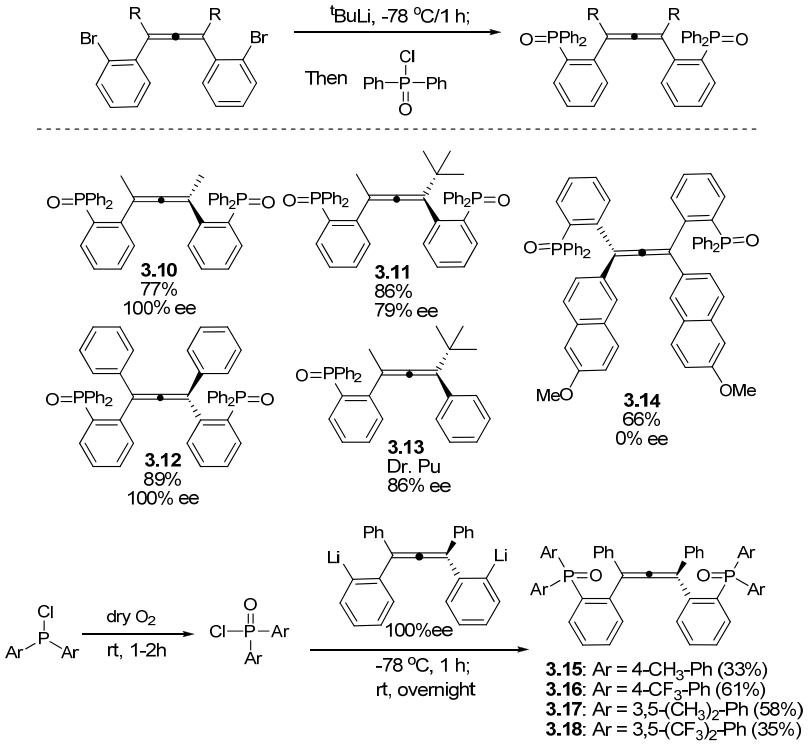
To generate optically active mono- and bis-phosphine oxides that contain an allene backbone, we chose chiral aryl bromides as key intermediates (**Scheme 3.9, 3.3-3.5**). which can be prepared from optically active proparygylic acetates (**3.1, 3.2**). Thus, proparygylic acetates were prepared from the corresponding alcohols which, in turn, were generated in optically active form through either asymmetric addition of terminal alkynes to the corresponding ketone or resolution of the racemic tertiary alcohol (**3.7**) by brucine.[62] Brucine resolution is appropriate for terminal propargylic alcohol with aryl and bulky substitutions such as t-butyl and bromophenyl. Moderate to good enantioselectivity was only achieved even after two resolutions. Sonogashira coupling was applied to generate internal aryl substituted propargylic alcohols (**3.8**). Propargylic substitution with diorganocuprate reagents or aryl zinc halides then generated the tetrasubstituted allenes.

Scheme 3.9 Synthesis of allene-containing aryl bromides.



The aryl bromides were treated with *tert*-butyl lithium, and the corresponding aryl lithium intermediates were trapped with diaryl chloro-phosphine oxides. In this way, we synthesized several mono- and bisphosphine oxides (**Scheme 3.10**).

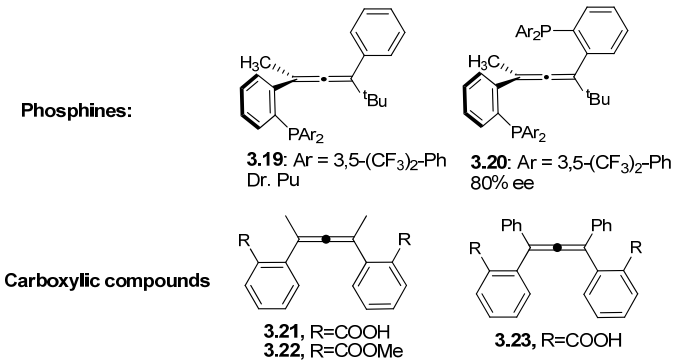
Scheme 3.10 Synthesis of bisphosphine oxides



Other diarylphosphinic chlorides can be generated in situ from oxidation of diarylchlorophosphine by dried oxygen at rt. Both the substitution and lithiation/trapping reactions occurred without substantial loss of optical activity, except in the case of catalyst **3.14**, which was racemized during the trapping step. In this way, we synthesized several mono- and bisphosphine oxides displaying diverse substitution patterns on both the allene backbone and the phosphorus**.** In a similar manner trapping with chloro-diarylphosphines yielded mono- or bisphosphines. It is noteworthy that this synthetic

scheme provides the flexibility to introduce substituents on allene and various functional groups in a modular fashion such as carboxylic compounds. (**Scheme 3.11**)

Scheme 3.11 Functionalization of allene-containing aryl bromides



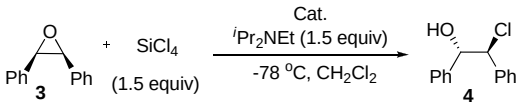
3.3 Bisphosphine oxides catalyzed meso epoxides opening reaction.

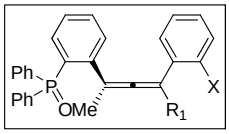
The asymmetric ring opening of meso epoxides is an efficient process for preparing optically active chlorohydrins. We initially investigated the epoxide opening of *cis*-stilbene oxide with $SiCl_4$ and $^{i}Pr_2NEt$ in the presence of catalytic allene-containing mono- or bisphosphine oxides (**Table 1**) at -78 ^{o}C.

These experiments revealed that allene-containing catalysts can promote the reaction and induce enantioselectivity in catalytic reactions. In general, the bisphosphine oxides displayed higher reactivity and enantioselectivity than the monphosphine oxide (entry **3.13** vs. **3.11**). Substantial variation was tolerated on the allene itself, as both the phenyl- and methyl substituted catalysts (**3.10** vs **3.12**) showed similar reactivity and enantioselectivity. The ring-opening is very sensitive to the aryl substitution on the phosphine oxide. Both electron-donating groups (**3.15** and **3.17**) and, more profoundly, electron-withdrawing groups (**3.16** and **3.18**) decreased reactivity and, where measurable, selectivity. The diphenyl substituted catalyst **3.12** is the most reactive and

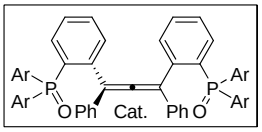
enantioselective catalyst for this transformation, displaying nearly 1000 turnovers under optimized conditions (entry 10).

Table 3.1. Evaluation of phosphine oxides as catalysts for the addition of $SiCl_4$ to cis-stilbene oxide.[a]





Entry	R_1	X	Cat. (mol%)	Yield (%)	ee (%)[b]
1[c]	**3.13**: ^{t}Bu	H	10	39	<10
2[c]	**3.13**: ^{t}Bu	H	2	<10	--
3[d]	**3.11**: ^{t}Bu	PPh_2	2	47	54 (-)
4	**3.10**: CH_3	PPh_2	2	76	84 (-)



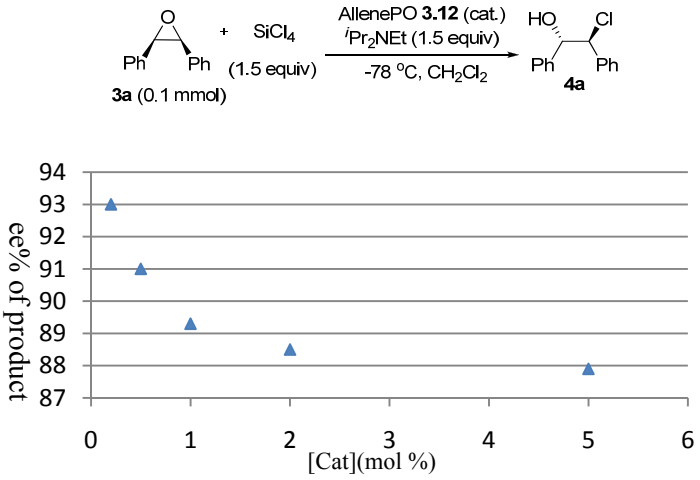
Entry	Ar	Cat. (mol%)	Yield (%)	ee (%)[b]
5	**3.12**: Ph	2	93	89 (+)
6	**3.15**: 4-CH_3-Ph	2	86	84 (+)
7	**3.16**: 4-CF_3-Ph	2	<5	--
8	**3.17**: 3,5-$(CH_3)_2$-Ph	2	58	78 (+)
9	**3.18**: 3,5-$(CF_3)_2$-Ph	2	<5	--
10[e]	**3.12: Ph**	**0.1**	**97**	**94 (+)**

[a]Reactions carried out with [**3**] = 0.02M unless otherwise noted. [b]Determined by HPLC. [c]**3.13** was 70% ee. [d]**3.11** was 79% ee. [e][**3**] = 0.2M

Targeting the catalyst **3.12**, we investigated the reactions and attempted to optimize the conditions. Slow addition of either the $SiCl_4$ or the substrate resulted in lower conversion. The use of 1.5 equiv of $^i Pr_2NEt$ is crucial for obtaining optimal reactivity and enantioselectivity. The reasonable explanation is that the $^i Pr_2NEt$ can trap the hydrogen chloride, which may be generated from the accidental hydrolysis of tetrachlorosilane and avoid the direct reaction between HCl and the epoxide in a non-stereoseletive process.

Dr. Xiaotao Pu has tried different solvents such as CH_2Cl_2, ether, toluene and THF, and realized that the catalyst showed high reactivity only in CH_2Cl_2. He also examined different bases and adducts, with $^{i}Pr_2NEt$ being the best choice. The influence of catalyst loading and the concentration of both catalyst and substrate were carefully investigated. Figure 3.1 showed different catalyst **3.12** loading while the substrate concentrations were consistent.

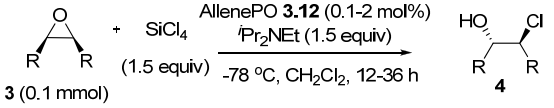
Figure 3.1 The ee of chlorohydrins as a function of catalyst loading with catalyst **3.12**.



An inverse relationship between enantioselectivity and catalyst concentration was observed when the catalyst concentration is higher than 0.1 mM (0.2 mol%). Thus, at constant concentration of the other components of the reaction mixture, the ee decreased from 93% at 0.1 mM (0.2 mol%) to 88% at 2.5 mM (5.0 mol%). While the effect is small, we observed a smooth and reproducible trend. Control experiments ruled out temperature fluctuations as the source of the effect.

Under the optimized conditions, a variety of meso epoxides were treated with $SiCl_4$ in the presence of catalyst **3.12** (Table 2).

Table 3.2. Asymmetric ring-opening of *meso*-epoxides.[a]



Entry	R	**3.12** (mol %)	Yield (%)[b]	ee (%)[c]
1	Ph (**3a**)	0.1	97	94
2	4-F-Ph (**3b**)	0.1	96	93
3	4-CH_3-Ph (**3c**)	0.1	92	89
4	4-CF_3-Ph (**3d**)	2	97	87
5	4-Cl-Ph (**3e**)	0.1	89	82
6	3-CH_3-Ph (**3f**)	0.2	89	91
7	3-Cl-Ph (**3g**)	2	96	90
8	3-CF_3-Ph (**3h**)	2	91	88
9	3-CH_3O-Ph (**3i**)	0.2	95	88
10	2-Br-Ph (**3j**)	2	<5	--
11	$BnOCH_2$ (**3k**)	2	90	60
12	$(CH_2)_4$ (**3l**)	0.1	95	29
13	*exo*-2,3-norbornyl (**3m**)	0.1	76	45

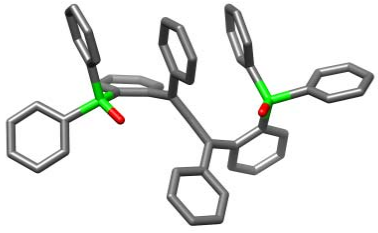
[a]All reactions quenched with propylene oxide and KF/KH_2PO_4 buffer. [b]Isolated yields. [c]Entries 1-12: ee determined by HPLC; Entry 13: ee determined by GC.

For most entries, the products were generated exclusively in high yields; however, the enantioselectivity was highly substrate-dependent. In general, the reaction is effective for substituted stilbene oxides. Both electron-releasing and electron-withdrawing substituents are tolerated in the meta- or para- position, although the latter tend to decrease reactivity such that higher catalyst loadings are required (Entries 4, 7, 8). In contrast, ortho substituted stilbene oxides were not reactive (Entry 10). Finally, both cyclic and acyclic aliphatic epoxides with various substitutions can form the corresponding chlorohydrins cleanly in excellent yield but with rather unimpressive enantiomeric excesses (Entries 11-13). For cyclic substrates, there was no obvious enantioselective dependence on ring size: chlorocyclohexanol, Table 2, entry 12, 29% ee; chlorocycloheptanol (Dr. Pu), 25% ee; 8-chlorocyclooct-4-enol, (Dr. Pu), 27% ee. For

acyclic aliphatic epoxides, linear chains longer than four carbons were shown to exhibit no enantioselectivity (1,6-bis(benzyloxy)-4-chlorohexan-3-ol, ee%=0).

The crystal structure of catalyst **3.12** shows a conformation characterized by π-stacking interactions involving two phenyl rings of the phosphine oxides and one of the backbone phenyl rings (Fig 3.2). A consequence of this arrangement is that the two oxygen atoms project in roughly the same direction. The significance of this conformation is not clear, however, as the bisphosphine oxide appears C_2 symmetric in $CDCl_3$ on the NMR time scale. In addition, the catalyst showed high stability under the present reaction system. Allenes have attracted attention from the synthetic community because of their high reactivities, as they can react with both nucleophiles and electrophiles, often under mild reaction conditions. In the present circumstance, however, this reactivity profile represented a potential liability inasmuch as catalyst stability would be critical for a practical synthetic method. With regard to a practical aspect, we were encouraged by the observation that we could recover catalyst **3.12** in 94% yield from a reaction involving the ring-opening of epoxide **3a**. The recovered catalyst was rechecked in the same reaction and excellent enantioselective induction was still observed (90% ee).

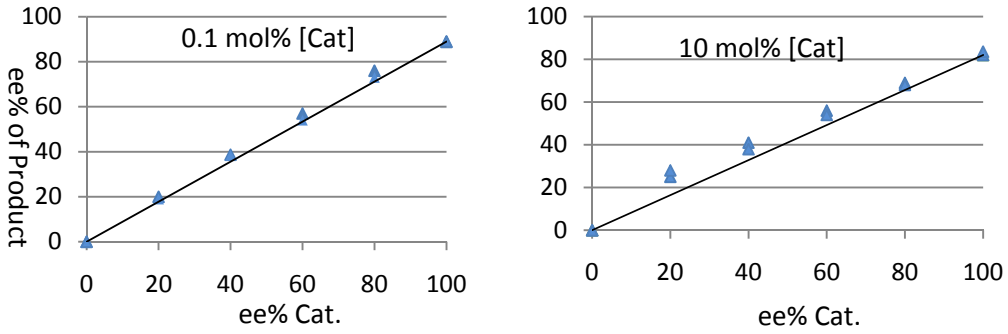
Figure 3.2. X-ray crystal structure of **3.12**.



As described above, in the course of our optimization studies we noticed a trend that is unusual in asymmetric catalysis: an inverse relationship between ee and catalyst

concentration. To investigate the mechanism and also to obtain a clearer understanding of the role of the catalyst and its potential to induce enantioselectivity, the correlation between the ee of the catalyst and the ee of the product was examined. Epoxide-openings were performed at both high (10 mol%) and low (0.1 mol%) catalyst loadings using catalyst **3.12** of varying optical purity. At low catalyst concentration, we observed a completely linear relationship between catalyst ee and product ee (Fig 3.3, left). In contrast, at higher concentration we detected a small but reproducible positive nonlinear effect, consistent with the intervention of a pathway involving multiple catalyst molecules at or before the transition state (Fig 3.3, right).

Figure 3.3 ee% of chlorohydrin **3a** as a function of catalyst ee with **3.12** at low and high catalyst loading.



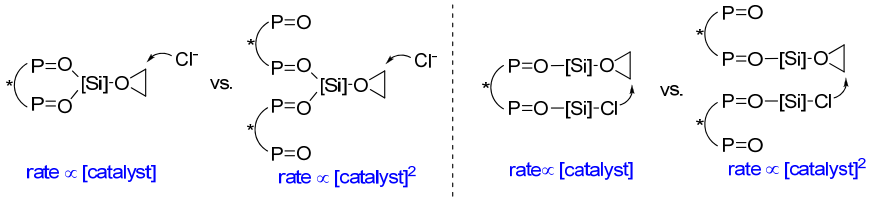
Combining the reaction phenomenon with the non-linear effect analysis, the data could suggest the existence of two different mechanistic pathways involved in the rate- and stereo-chemistry-determing steps: a more selective pathway dominant at low catalyst concentration and a less selective pathway that intervenes as the catalyst concentration increases. The fact that the relative contribution of the pathways changes as a function of

concentration indicates that they display different kinetic dependence on catalyst concentration. Such a scenario could be described by a two-term rate law such as eq 1.[63]

$$\textbf{Rate} = \mathbf{k_{obs}[catalyst] + k'_{obs}[catalyst]^2} \qquad \textbf{(1)}$$

In the less selective pathway, multiple bisphosphine oxides would participate in the stereodetermining transition structure. It can be expected that two or more diastereomeric complexes (homochiral complexes having (*S*,*S*) or (*R*,*R*) catalyst combinations and hetereochiral complexs having (*R*,*S*) or (*S*,*R*) combinations) would be involved in the transition structure. Each diastereomeric complex might contribute different reaction rates during the rate- and stereo-chemistry-determining step. A slight positive non-linear effect indicates that in this pathway, the homochiral complex played a dominant role and was faster during the enantioselective transformation. A reservoir model, which features inactive multimeric homo- and heterochiral complexes with the hetereochiral complexes as predominantly existent (thermodynamically stable but catalytically inactive), despite being consistent with a positive non-linear effect, would not account for the inverse relationship between catalyst concentration and product ee.[64] Two scenarios that could account for the available data are shown in **Scheme 3.12**.

Scheme 3.12 Two possible scenarios could account for the available data



In one possibility, the active Lewis acid includes two phosphine oxide moieties, and they can come from either a single bisphosphine oxide or from two different catalyst

molecules. Alternatively, like many other epoxide-opening reactions,[65] the present transformation may require activation of both the nucleophile and electrophile. In particular, a phosphine oxide-coordinated silicate might deliver chloride to an epoxide activated by a phosphine oxide coordinated Lewis acid. Thus, delivery could be either intra- or intermolecular. Of note, the Denmark group demonstrated that the racemic reaction catalyzed by $P(O)(NMe_2)_3$ displays a second order kinetic dependence on catalyst.

The small magnitude of the effects - both the dependence of product ee on catalyst concentration and the nonlinear effect - may simply reflect the similarity of the pathways and minimal stereochemical communication between the various molecules of catalyst. Alternatively, the data may indicate that the pathway displaying second order (or higher) kinetic dependence on catalyst is substantially slower than the dominant pathway (i.e. $\mathbf{k}_{obs} > \mathbf{k'}_{obs}$ in eq 1). In this connection, it is perhaps noteworthy that the monophosphine oxide (**3.13**) displays substantially lower reactivity than its bisphosphine oxide counterparts. Further mechanism studies, including kinetic analysis of the reaction and precise interpretation of the relative contributions of the two pathways awaits a detailed investigation.

In conclusion, for the first time we have demonstrated that allene-containing ligands have induced enantioselectivity in catalytic reactions. In the present example we have prepared allene containing bisphosphine oxides as Lewis bases and have shown that they can activate $SiCl_4$. The diphenyl substituted catalyst **3.12** is a highly reactive and enantioselective catalyst for this transformation, displaying nearly 1000 turnovers under

optimized conditions. However, this design principle may extend equally well to other classes of organocatalysts or ligands for transition metals.

3.4 experimental sections

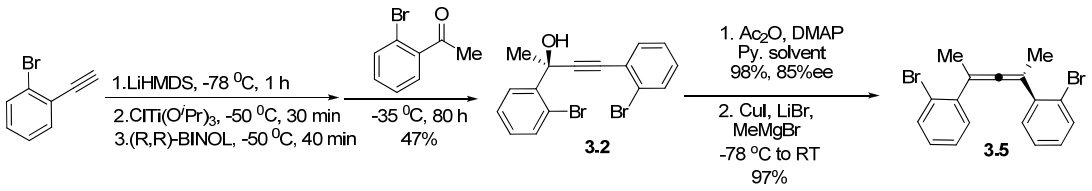
3.4.1 Method and Materials

General. Unless otherwise stated, reactions were performed using freshly purified solvents which were purified using solvent purification columns purchased from Glass Contour, Laguna Beach, CA. All reactions were monitored by thin-layer chromatography with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). Gas chromatography (GC) was performed on an HP 6890N autosampling GC with an HP-5 capillary column and equipped with a FID detector. Flash chromatography was performed with indicated solvents using silica gel (particle size 0.032-0.063m) purchased from Sorbent Technologies.^{1}H and ^{13}C NMR spectra were recorded on Varian Inova-400, 500 or Mercury-300 spectrometer. Chemical shift are reported relative to internal chloroform ($CDCl_3$: ^{1}H, δ = 7.27, ^{13}C, δ = 77.26). Coupling constants are in Hz and are reported as d (doublet), t (triplet), q (quartet). For signals having multiple coupling patterns, the coupling constant are listed in the same order as the pattern (e.g. dt, J = 2.0, 4.0; 2.0 is the coupling constant for the doublet and 4.0 is for the coupling constant for the triplet). ^{31}PNMR is using triphenylphosphine as external standard (CDCl3, δ = -6 ppm). HPLC analyses were carried out on a Shimadzu LC-2010A system. Optical rotations were measured on a Rudolph Research Analytical Autopol® IV Polarimeter (50/60 Hz). Infrared spectra were recorded on a Perkin- Elmer 1000 series FTIR. Mass spectra were acquired on a Shimadzu QP5000 GC/MS or Agilent technologies 1200 series LC/MS using indicated ionization methods.

Materials: Starting materials were purchased from Sigma-Aldrich, Strem Chemical or Alfa Aesar. Spectra data are available via the internet at http://pubs.acs.org/doi/suppl/10.1021/ja9041127.

3.4.2 Preparation of bis(bromophenyl)allenes.

3.4.2.1 Procedure for the enantioselective synthesis of bis(bromophenyl)dimethyl-allene (Scheme 3.13).



(*S*)-2,4-bis(2-bromophenyl)but-3-yn-2-ol.The first step (propargylic alcohol formation) is modified from a known procedure.[66] An oven-dried Schlenk flask (15 ml) with a Teflon-coated stir bar was cooled under vacuum and refilled with nitrogen. The flask was capped with a rubber septum, evacuated and backfilled with nitrogen (This evacuation/backfill procedure was performed three times.) A solution of 2-bromophenylacetylene (11 mmol, 2 g, 2.2 equiv) in 10 ml toluene was added by syringe. The flask was cooled to -78 °C. LiHMDS (10 mmol, 10 ml 1 M solution in THF, 2 equiv) was added into the flask drop-wise. The resulting solution was stirred at the same temperature for 1 h. After the flask was warmed to -50 °C by transferring it to an acetonitrile-dry ice bath, a 1 M solution of $Cl(TiO^{i}Pr)_3$ in toluene (10 mol, 10 ml, 2 equiv) was added drop-wise to the reaction mixture. The resulting yellow solution containing un-dissolved LiCl was stirred for 30 minutes maintaining the temperature around -50 °C. (*R*)-BINOL (1.5 mmol, 420.5 mg, 30 mol%) was directly

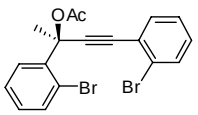
added to the mixture under the protection of nitrogen. The flask was re-sealed and the reaction mixture was stirred for 40 min maintaining the temperature around -50 ^{o}C. Gradually the color of the reaction mixture turned orange. Bromophenylacetone (5 mmol, 1g, 1 equiv) was added slowly. The resulting mixture was warmed to -35^{o}C and stirred at the same temperature for 80 hours. The reaction was quenched by adding H_2O (2 ml) at a low temperature and diluted with Et_2O (10 ml). The reaction mixture was stirred at room temperature for 15 minutes, and then it was filtered through Celite. The collected phases were separated and the aqueous solution was extracted with Et_2O (3 X 20 ml). The organic phases were combined, washed with brine, and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the resulting yellow oil was purified by flash chromatography on silica gel (100% hexane to 5% ethyl acetate in hexane) to give pure desired propargylic alcohol (825 mg, 47% yield). The enantioselectivity was checked after acetylation step.

Data for propargylic alcohol **3.2:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.64 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.57 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.50 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.36 (td, *J* = 7.6, 1.3 Hz, 1H), 7.26 (td, *J* = 7.6, 1.3 Hz, 1H), 7.14-7.21 (m, 2H), 3.28 (s, 1H), 2.08 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 142.5, 135.2, 133.7, 132.6, 129.9, 129.6, 127.8, 127.4, 127.2, 125.9, 125.0, 121.3, 96.2, 83.9, 70.5, 29.9; MS: ESI-MS (*m/z*): 362.9 $[M-H_2O]^+$, 402.9 $[M+Na]^+$; FTIR (neat) 2349, 1469, 1432, 1022, 753 cm^{-1}

(*S*)-2,4-bis(2-bromophenyl)but-3-yn-2-yl acetate 3.2-a: An oven-dried test tube with a Teflon-coated stir bar was charged with propargylic alcohol (1.0 equiv, 2.17 mmol, 825 mg) and DMAP (20 mg, 0.07 equiv). Under nitrogen, pyridine (10 ml) and then acetic

anhydride (4 equiv, 8.68 mmol, 891.7 mg, 0.825 ml) were added to the reaction solution. After stirring at room temperature for 12 hours the reaction was quenched by adding saturated NH_4Cl (5 ml) slowly at 0 ^oC and diluted with Et_2O (30 ml). The reaction mixture was partitioned between Et_2O and water. The organic layer was separated and the aqueous solution was extracted with Et_2O (3 X 20 ml). The organic phases were combined and washed with brine, dried over $MgSO_4$. After removal of the solvent under reduced pressure, the resulting crude product was purified by flash chromatography on silica gel (100% hexane to 5% ethyl acetate in hexane) to give pure propargylic acetate (900 mg, 98%). The enantiomer excess (ee) was determined to be 85% by chiral HPLC analysis (Chiracel OD-H column, 1% isopropanol in hexane, 0.5 mL/min, T_R=14.22 (major), 19.48 min).

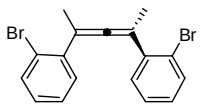
Data for propargylic acetate **3.2-a**:



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.60 (ddd, *J* = 7.9, 3.6, 1.2 Hz, 2H), 7.56 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.36 (td, *J* = 7.9, 1.2 Hz, 1H), 7.29 (td, *J* = 7.7, 1.2 Hz, 1H), 7.21 (td, *J* = 7.9, 1.7 Hz, 1H), 7.16 (td, *J* = 7.6, 1.7 Hz, 1H), 2.17 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 139.5, 135.6, 133.9, 132.6, 130.1, 130.0, 129.6, 127.6, 127.2, 126.0, 124.8, 119.3, 93.1, 86.2, 29.0, 21.5; FTIR (neat) 1748, 1469, 1426, 1366, 1231, 1023, 754 cm^{-1}; HPLC: Chiracel OD-H column, 1% isopropanol in hexane, 0.5 mL/min, T_R=14.22 (major), 19.48 min; MS: ESI-MS (*m/z*): 362.9 $[M\text{-}OAc]^+$.

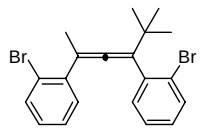
2,2'-(penta-2,3-diene-2,4-diyl)bis(bromobenzene) (3.5): An oven-dried Schlenk flask (50 mL in volume) with a Teflon-coated stir bar was charged with CuI (10 equiv, 30 mmol, 5.7 g) and LiBr (10 equiv, 30 mmol, 2.6 g). The flask was capped with a rubber

septum, evacuated and refilled with nitrogen (evacuation/backfill procedure was performed three times). The flask was cooled to -78^{o}C. A solution of 3.0 M MeMgBr in THF (10 equiv, 30 mmol, 3 ml) was added to the flask drop-wise. The resulting solution was warmed up to 0 ^{o}C and stirred at the same temperature for 20 min. The flask was cooled to -78 ^{o}C, a solution of propargylic acetate in 5 ml THF (1 equiv, 3 mmol, 1.24 g) was added drop-wise to the reaction. The resulting mixture was allowed to warm to room temperature over 1 h and stirred at the same temperature for 2 h. The reaction was quenched by adding saturated aqueous NH_4Cl solution (10 ml) very carefully and slowly at 0 ^{o}C. (Caution: substantial gas evolution). The resulting mixture was diluted with Et_2O (30 ml) and stirred at room temperature for 5 minutes. The aqueous layer was separated and extracted with Et_2O (3 X 20 ml). The organic phases were combined, washed with brine, and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the resulting yellow oil was purified by flash chromatography on silica gel (100% hexane to 2% ethyl acetate in hexane) to give pure 2,2'-(penta-2,3-diene-2,4-diyl)bis(bromobenzene) **3.3** (1.1 g, 97% yield).



^{1}HNMR: (400, $CDCl_3$) δ 7.31 (d, *J* = 6.4, 2H), 7.00 (m, 4H), 6.82, (t, *J* = 1.6), 1.88 (s, 6H); ^{13}CNMR:(100 $CDCl_3$) δ 203.5, 140.0, 133.5, 130.0, 128.4, 127.4, 123.0, 100.9, 20.3; MS: EI-MS (*m/z*): 378 $[M]^+$, 299, 218, 203.

Similarly, **2,2'-(5,5-dimethylhexa-2,3-diene-2,4-diyl)bis(bromobenzene)** (**3.2**) was

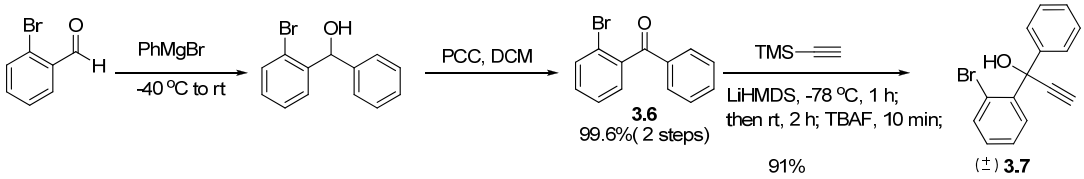


synthesized according to this procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.1 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.19-7.26 (m, 4H), 7.16 – 7.04 (m, 2H), 2.14 (s, 3H), 1.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.80, 140.53, 138.54, 133.15, 133.02, 131.52, 130.68, 128.41, 128.37, 127.36, 126.60, 125.37,

122.88, 113.70, 102.79, 36.34, 30.04, 19.69; MS: EI-MS (*m/z*): 363 $[M\text{-}^{t}Bu]^{+}$; FTIR (neat) 2964, 1466, 1429, 1360, 1024, 745cm^{-1}

3.4.2.2 Procedure for the enantioselective preparation of bis(2-bromophenyl) diphenyllallene.

Scheme 3.14. Synthesis of **1-(2-bromophenyl)-1-phenylprop-2-yn-1-ol** (**3.7**)



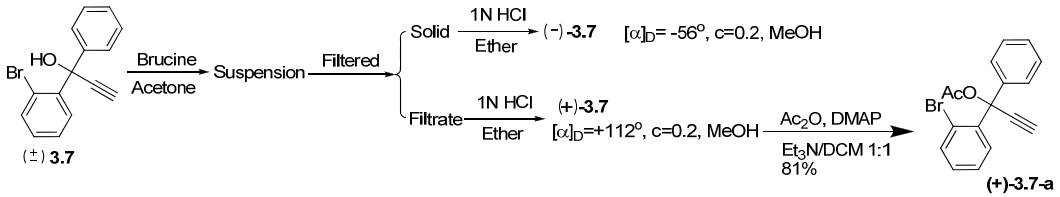
A solution of 2-bromobenzaldehyde (1 equiv, 15 mmol, 2.78 g,) in 50 ml THF under a N_2 atmosphere was cooled to -40 ^{o}C. PhMgBr (2 equiv, 30 mmol, 10 ml 3 M solution in THF) was added drop-wise. The resulting solution was then allowed to warm to room temperature and stirred at the same temperature for 1 h. The reaction was quenched by adding saturated aqueous NH_4Cl solution (10 ml) very slowly at 0 ^{o}C. The resulting solution was diluted with Et_2O (30 ml). The reaction mixture was stirred at room temperature for 5 minutes, and then separated. The aqueous solution was extracted with Et_2O (3 X 20 ml). The organic phases were combined, washed with brine, and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the resulting yellow oil was dissolved in 50 ml of CH_2Cl_2 and transferred into a round bottom flask. Celite (5 g) and pyridinium chlorochromate (16 g, 5 equiv) were added and the resulting slurry was stirred at room temperature for 2 hours until the alcohol had been completely consumed as judged by TLC analysis. The reaction was diluted with 50 ml of diethyl ether causing substantial precipitation. The suspension was filtered through Celite, and the filtrate was concentrated under reduced pressure. The resulting yellow oil was

purified by flash chromatography on silica gel (100% hexane to 2% ethyl acetate in hexane) to give pure (2-bromophenyl)(phenyl)ketone **3.6**[67] (4g, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 - 7.77 (m, 2H), 7.67 - 7.62 (m, 1H), 7.63 - 7.56 (m, 1H), 7.43-7.48 (m, 2H), 7.41 (dd, *J* = 6.9, 1.5 Hz, 1H), 7.38 - 7.31 (m, 2H).

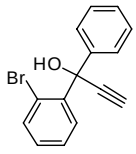
A solution of trimethylsilyl acetylene (1.5 equiv, 15 mmol, 1.47 g) in 50 ml THF under a N_2 atmosphere was cooled to -78 ^{o}C. Lithium bis(trimethylsilyl)amide (15 mmol, 15 ml 1 M solution in THF, 1.5 equiv) was added drop-wise. The resulting solution was stirred at -78 ^{o}C for 1 h after which a solution of (2-bromophenyl)(phenyl)ketone **3.6** (1 equiv, 10 mmol, 2.61g) in THF (5 ml) was added into reaction solution. After addition, the resulting mixture was allowed to warm to room temperature and was stirred at the same temperature for 2 h. Tetra-*n*-butylammonium fluoride (TBAF, 2 equiv, 20 mmol, 20 ml of 1 M solution in THF) was added at room temperature and stirred at the same temperature for 10 minutes. The reaction was quenched by adding saturated aqueous NH_4Cl solution (10 ml) very slowly at 0 ^{o}C. The resulting solution was diluted with Et_2O (30 ml) and then separated. The aqueous solution was extracted with Et_2O (3 X 20 ml). The organic phases were combined, washed with brine and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the resulting yellow oil was purified by flash chromatography on silica gel (100% hexane to 5% ethyl acetate in hexane) to give pure 1-(2-bromophenyl)-1-phenylprop-2-yn-1-ol **3.7** (2.62 g, 91% yield; characterization data below).

Scheme 3.15 Resolution of propargylic alcohol **3.7**



An oven-dried round bottom flask (10 mL in volume) with a Teflon-coated stir bar was charged with racemic1-(2-bromophenyl)-1-phenylprop-2-yn-1-ol **3.7** (1 equiv, 1 mmol, 281 mg). Acetone (6 ml) was added into the flask followed by addition of brucine (1 equiv, 1 mmol, 395 mg). The resulting mixture was stirred at room temperature for 12 hours. During stirring the mixture first became nearly homogeneous and then a white precipitant formed. After 12 h, the mixture was filtered. The filtrate was treated with 1N HCl (10 ml) and diethyl ether (15 ml). The resulting mixture was stirred for 5 minutes and then separated. The aqueous solution was extracted with Et_2O (3 X 10 ml). The organic phases were combined, washed with brine, and dried over magnesium sulfate. Removal of the solvent under reduced pressure provided the dextrorotatory enantiomer of **3.7** as a yellow oil (103 mg, 37% yield, $[\alpha]_D$= + 112°, c=0.2 in MeOH). The solid was treated in an identical manner to provide the levorotatory enantiomer of **3.7** as a yellow oil (180 mg, 63% yield,).

Data for **3.7**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.57 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.54 - 7.49 (m, 2H), 7.41 (td, *J* = 7.7, 1.3 Hz, 1H), 7.38 - 7.31 (m, 3H), 7.22 (td, *J* = 7.6, 1.7 Hz, 1H), 3.24 (s, 1H), 2.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0, 141.7, 135.1, 129.9, 128.8, 128.6,

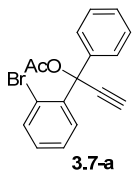


3.7

128.4, 127.5, 127.0, 122.1, 84.4, 76.6, 75.0; FTIR (neat) 3536, 3290, 1463, 1449, 1431, 1334, 1181, 1025, 980, 897, 756, 697, 662, 635 cm^{-1}; MS: ESI-MS (*m/z*): 270.9 $[M-H_2O]^+$, 556.9 $[2M-H_2O]^+$.

Optical Rotation: (+)-**3.7**: $[\alpha]_D$= + 112°, c=0.2 in MeOH; (-)-**3.7**: $[\alpha]_D$= -56°, c=0.2 in MeOH; Lit: 100% optically active **3.7** $[\alpha]_D$= -114°, c=0.2 in MeOH). See analysis of **3.7-a** for analysis of ee by chiral shift reagent.

(+)-1-(2-bromophenyl)-1-phenylprop-2-ynyl acetate 3.7-a: ^{1}H NMR (400 MHz, $CDCl_3$)

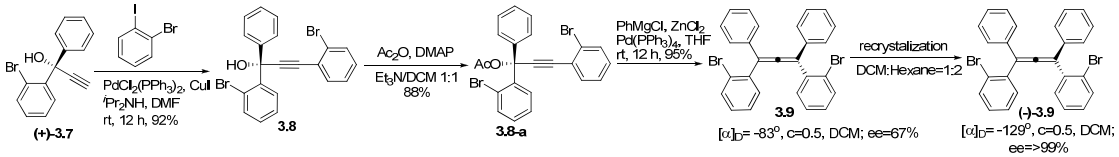


3.7-a

δ 8.10 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.54 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.46 - 7.36 (m, 3H), 7.36 - 7.29 (m, 3H), 7.19 (td, *J* = 7.6, 1.6 Hz, 1H), 3.01 (s, 1H), 2.19 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ =168.4, 140.7, 138.9, 135.6, 131.1, 130.1, 128.4, 128.3, 127.2, 127.0, 121.3, 81.7, 79.3, 29.5, 21.7; MS: ESI-MS (*m/z*): 270.9 $[M-OAc]^+$, 352.9 $[M+Na]^+$; FTIR (neat) 3286, 1755, 1466, 1366, 1228, 1027, 982, 757, 697 cm^{-1}

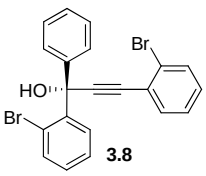
Enantiomeric excess (ee) of **3.7-a** was determined to be ca. 75% by NMR analysis of its acetate in $CDCl_3$ with the chiral shift reagent, tris[3-(heptafluoropropylhydroxy-methylene)-d-camphorato]europium(III), $Eu(hfc)_3$ (Aldrich, 99+%).

Scheme 3.16 Synthesis of **1,3-bis(2-bromophenyl)-1,3-diphenylpropa-1,2-diene**



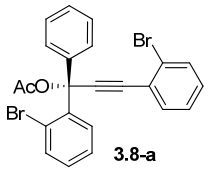
(*R*)-1,3-bis(2-bromophenyl)-1-phenylprop-2-yn-1-ol 3.8: An oven-dried test tube (16 X 100 mm, 10 mL in volume) with a Teflon-coated stir bar was charged with

enantiomerically enriched (+)-**3.7** (1 equiv, 0.58 mmol, 162 mg), CuI (6 mol%, 0.036 mmol, 7 mg) and $PdCl_2(PPh_3)_2$ (3 mol%, 0.018 mmol, 13 mg). The test tube was capped with a rubber septum and sealed, evacuated and refilled with nitrogen (This evacuation/backfill procedure was performed three times). DMF (1 ml) was added into the tube and then $^{i}Pr_2NEt$ (5 equiv, 2.9 mmol, 0.41 ml) and 1-bromo-2-iodobenzene (1.5 equiv, 0.807 mmol, 248 mg) were added sequentially. The resulting solution was stirred at the room temperature for 20 h until the starting terminal alkyne had been completely consumed as judged by NMR analysis (TLC showed exactly the same R_fs of starting material and the product). The reaction was quenched by adding saturated aqueous NH_4Cl solution (2ml) and diluted with Et_2O (5 ml). The resulting mixture was stirred at room temperature for 5 min and then separated. The aqueous solution was extracted with Et_2O (3 X 20 ml). The organic phases were combined, washed with brine, and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the resulting yellow oil was purified by flash chromatography on silica gel (100% hexane to 5% ethyl acetate in hexane) to give pure 1,3-bis(2-bromophenyl)-1-phenylprop-2-yn-1-ol **3.8** (236 mg, 92% yield).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.64 (dd, *J* = 7.8, 1.4 Hz, 2H), 7.58 (d, *J* = 7.8 Hz, 2H), 7.52 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.44 - 7.30 (m, 5H), 7.28 - 7.12 (m, 2H), 3.28 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.2, 142.1, 135.1, 133.9, 132.7, 130.0, 129.8, 128.8, 128.5, 128.4, 127.42, 127.38, 127.2, 125.9, 124.9, 122.3, 94.4, 86.5, 75.6; MS: ESI-MS (*m/z*): 424.9 $[M-H_2O]^+$, 464.9 $[M+Na]^+$; FTIR (neat) 3533, 3061, 2361, 1469, 1449, 1434, 1336, 1162, 1123, 1056, 1026, 980, 896, 753, 697 cm^{-1}



3.8

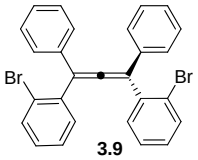
(*R*)-1,3-bis(2-bromophenyl)-1-phenylprop-2-ynyl acetate 3.9: An oven-dried round bottom flask (10 mL in volume) with a Teflon-coated stir bar was charged with 1,3-bis(2-bromophenyl)-1-phenylprop-2-yn-1-ol **3.8** (1 equiv, 0.36 mmol, 158 mg) and DMAP (5mg, 0.1 equiv) under a N_2 atmosphere. CH_2Cl_2 (2 ml) was added into the flask and followed by addition of Et_3N (2 ml). Acetic anhydride (20 equiv, 7.15 mmol, 0.68 ml) was added to the reaction solution slowly. The resulting solution was stirred at room temperature for 3 h until the starting material had been completely consumed as indicated by TLC analysis. The reaction was quenched by adding saturated aqueous NH_4Cl solution (3 ml) very slowly at 0 ^oC. The resulting solution was diluted with Et_2O (30 ml). The aqueous layer was separated and extracted with Et_2O (3 X 20 ml). The organic phases were combined, washed with brine, and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the resulting solid was purified by flash chromatography on silica gel (100% hexane to 5% ethyl acetate in hexane) to give pure 1,3-bis(2-bromophenyl)-1-phenylprop-2-ynyl acetate **3.8-a** (153 mg, 88% yield).



3.8-a

^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.60 – 7.54 (m, 4H), 7.50 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.44 - 7.38 (m, 1H), 7.38 - 7.27 (m, 3H), 7.27 - 7.18 (m, 2H), 7.13-7.18 (m, 1H), 2.23 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 140.8, 139.5, 135.6, 133.9, 132.6, 131.2, 130.1, 130.0, 128.3, 128.2, 127.4, 127.2, 127.1, 126.0, 124.8, 121.5, 91.8, 89.2, 80.1, 21.8; MS: ESI-MS (*m/z*): 424.9[M-OAc]$^+$; FTIR (neat) 2361, 2343, 1752, 1468, 1364, 1224, 1178, 1026, 978, 754, 696, 668 cm^{-1}

1,3-bis(2-bromophenyl)-1,3-diphenylpropa-1,2-diene 3.9[68]



3.9

An oven-dried Schlenk flask (25 mL in volume) with a Teflon-coated stir bar was charged with freshly fused $ZnCl_2$ (2 equiv, 1.1 mmol, 150 mg) under a N_2 atmosphere. THF (4 ml) was added and then a solution of PhMgCl (2 equiv, 1.1 mmol, 0.55 ml of 2.0 M in ether) was added drop-wise. The resulting solution was stirred at room temperature for 15 min. The reaction mixture was cooled to -40 ^oC and a solution of $Pd(PPh_3)_4$ (5 mol%, 0.0275 mmol, 32 mg) in THF (1 ml) was added via cannula. A solution of 1,3-bis(2-bromophenyl)-1-phenylprop-2-ynyl acetate **3.8-a** (1 equiv, 0.55 mmol, 266 mg) in THF (1 ml) was added to the reaction via syringe. The resulting mixture was allowed to warm to room temperature slowly and stirred at the same temperature for 12 h. The reaction was quenched by adding saturated aqueous NH_4Cl solution (5 ml) very slowly. The resulting solution was diluted with Et_2O (10 ml). The reaction mixture was stirred at room temperature for 5 min and then separated. The aqueous solution was extracted with Et_2O (3 X 10 ml). The organic phases were combined, washed with brine, and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the resulting solid was purified by flash chromatography on silica gel (100% hexane to 2% ethyl acetate in hexane) to give pure 1,3-bis(2-bromophenyl)-1,3-diphenylpropa-1,2-diene **3.9** (262 mg, 95% yield, $[\alpha]_D$= -83^o, c=0.5 in CH_2Cl_2). The ee was determined to be 67% by chiral HPLC analysis (Chiracel OD-H column, 0.1% isopropanol in hexane, 1 mL/min, T_R: 11.7 min, 12.2 min (major)).

After recrystalized from CH_2Cl_2/Hexane (1:2) for 3 times, 100% optically pure enantiomer **(-)-3.9** was obtained ($[\alpha]_D$= -129^o, c=0.5 in CH_2Cl_2).

Spectra data of **3.9**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 - 7.64 (m, 2H), 7.46 - 7.32 (m, 12H), 7.23-7.31 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.0, 137.0, 135.3, 133.4, 132.3,

129.6, 128.9, 127.8, 127.8, 127.3, 124.6, 112.5; MS: EI-MS (*m/z*): 502 $[M]^+$; HPLC: Chiracel OD-H column, 0.1% isopropanol in hexane, 1 mL/min, T_R: 12.2 min. FTIR (neat) 3057, 2361, 2343, 1595, 1492, 1470, 1446, 1432, 1046, 1027, 908, 764, 746, 692, 596 cm^{-1}

The absolute stereochemistry of **3.9** was confirmed by X-ray crystallography (**Fig 3.4**). Crystals grew as long, colorless laths by slow evaporation from Hexane and CH_2Cl_2. The data crystal was cut from a long lath and had approximate dimensions; 0.34 x 0.08 x 0.05 mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with MoKα radiation (λ = 0.71073Å). A total of 259 frames of data were collected using ω-scans with a scan range of 2° and a counting time of 170 seconds per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Data reduction was performed using DENZO-SMN.[70] The structure was solved by direct methods using SIR97[71] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[72] The hydrogen atoms were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The absolute configuration was determined by the method of Flack.[73] The Flack x parameter refined to 0.01(1). The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.0402*P)^2 + (0.8712*P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.0790, with R(F) equal to 0.0322 and a goodness of fit, S, = 1.06. Definitions used for calculating R(F), $R_w(F^2)$ and the goodness of fit, S, are given below.[74] The data were corrected for secondary extinction effects. The correction takes the form: $F_{corr} = kF_c/[1$

+ $(3.6(7)x10^{-6})* F_c^2 \lambda^3/(\sin 2\theta)]^{0.25}$ where k is the overall scale factor. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992). [75] All figures were generated using SHELXTL/PC.[76]

Figure 3.4. Crystal structure of **3.4**. Three molecules in the unit cell.

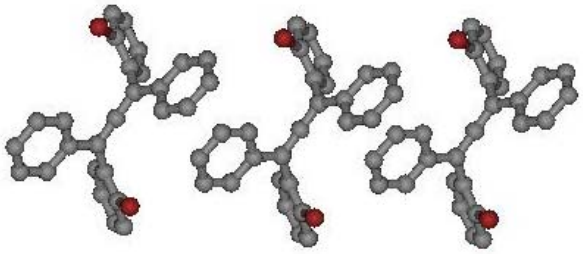


Table 3.3. Crystal data and structure refinement for **3.4**. (cif file has been published[69])

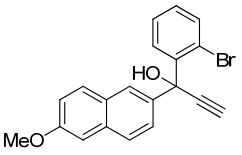
Empirical formula		C27 H18 Br2
Formula weight		502.23
Temperature		153(2) K
Wavelength		0.7107 Å
Crystal system		Monoclinic
Space group		C2
Unit cell dimensions	a = 14.7945(8) Å	α= 90°.
	b = 7.6873(5) Å	β= 107.147(3)°.
	c = 10.2968(8) Å	γ = 90°.
Volume		1119.00(13) $Å^3$

Z	2
Density (calculated)	1.491 Mg/m^3
Absorption coefficient	3.632 mm^{-1}
F(000)	500
Crystal size	0.34 x 0.08 x 0.05 mm
Theta range for data collection	2.07 to 27.46°.
Index ranges	-19<=h<=19, -9<=k<=9, -13<=l<=13
Reflections collected	2399
Independent reflections	2399
Completeness to theta = 27.46°	99.6 %
Absorption correction	Analytical
Max. and min. transmission	0.844 and 0.420
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2399 / 1 / 133
Goodness-of-fit on F^2	1.062
Final R indices [I>2sigma(I)]	R1 = 0.0322, wR2 = 0.0757
R indices (all data)	R1 = 0.0378, wR2 = 0.0790
Absolute structure parameter	0.003(13)
Extinction coefficient	$3.6(7)x10^{-6}$
Largest diff. peak and hole	0.514 and -0.461 $e.Å^{-3}$

3.4.2.3 Procedure for the enantioselective preparation of 1,3-bis(2-bromophenyl)-1,3-bis(6-methoxynaphthalen-2-yl)propa-1,2-diene 3.7-a

According to the same synthesis procedure as 1,3-bis(2-bromophenyl)-1,3-diphenylpropa-1,2-diene **3.4,** 100% optically pure enantiomer 1,3-bis(2-bromophenyl)-1,3-bis(6-methoxynaphthalen-2-yl)propa-1,2-diene (-)**3.7-a** was prepared.

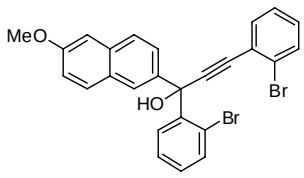
Spectra data of **1-(2-bromophenyl)-1-(6-methoxynaphthalen-2-yl)prop-2-yn-1-ol**



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 - 7.96 (m, 2H), 7.70 (dd, *J* = 13.7, 8.8 Hz, 2H), 7.57 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.39-7.46 (m, 2H), 7.22 (ddd, *J* = 9.2, 5.0, 1.3 Hz, 1H), 7.17 - 7.08 (m, 2H), 3.91 (s, 3H), 2.94 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.36, 141.70, 138.00, 135.17, 134.44, 130.19, 129.92, 128.88, 128.56, 127.52, 127.32, 126.29, 125.20, 122.18, 119.36, 105.85, 84.62, 76.64, 75.02, 55.58; MS: ESI-MS (*m/z*): 350.0 $[M-H_2O]^+$, 351.0 $[M-H_2O]^+$, 390.9$[M+Na]^+$; FTIR (neat) 3287, 1606, 1464, 1264, 1223, 1167, 1028, 853, 757 cm^{-1}.

Resolution by brucine provided the dextrorotatory enantiomer of **(+)-3.7-a** as a white solid ($[\alpha]_D$= + 70^o, c=0.5 in $CDCl_3$; 81% ee (Chiral OD-H column, 2.5% isopropanol in hexane, 1 mL/min. 35 min, 39 min(major)) and the levorotatory enantiomer of **(-)-3.7-a** ($[\alpha]_D$= - 7^o, c=0.5 in $CDCl_3$ 12% ee).

After recrystalized from CH_2Cl_2/Hexane (1:2) for once, 100% optically pure enantiomer **(+)-3.7** was obtained (T_R= 39 min). After recrystalized from CH_2Cl_2/Hexane (1:2) for twice, 100% optically pure enantiomer **(-)-3.7-a** was obtained (T_R= 35 min).

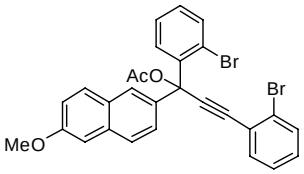


Data for **1,3-bis(2-bromophenyl)-1-(6-ethoxynaphthalen-2-yl)prop-2-yn-1-ol**, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (s,

1H), 8.11 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.75 (dd, *J* = 17.9, 8.8 Hz, 2H), 7.65 - 7.54 (m, 4H), 7.43 (dd, *J* = 10.9, 4.4 Hz, 1H), 7.35 - 7.10 (m, 5H), 3.93 (s, 3H), 3.49 (s, 1H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 158.36, 142.13, 138.20, 135.13, 134.45, 134.01, 132.69, 130.25, 130.03, 129.80, 128.93, 128.61, 127.46, 127.24, 126.74, 125.98, 125.57, 125.00, 122.43, 119.28, 105.88, 94.58, 86.61, 75.65, 55.58.

MS: ESI-MS (*m/z*): 504.9[M-H_2O]$^+$; FTIR (neat) 3434, 1606, 1468, 1432, 1390, 1265, 1221, 1166, 1027, 885, 853, 754 cm^{-1}

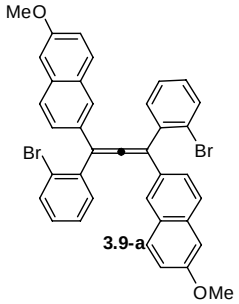
Data of **1,3-bis(2-bromophenyl)-1-(6-methoxynaphthalen-2-yl)prop-2-ynyl acetate**,



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.97 (d, *J* = 1.8 Hz, 1H), 7.71 (dd, *J* = 8.6, 6.1 Hz, 2H), 7.61 - 7.51 (m, 3H), 7.49 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.44 - 7.38 (td, *J* = 7.7, 1.8 Hz, 1H), 7.26 - 7.07 (m, 5H), 3.90 (s, 3H), 2.24 (s, 3H).

Data of **1,3-bis(2-bromophenyl)-1,3-bis(6-methoxynaphthalen-2-yl)propa-1, 2-diene 3.9-a**

^{1}H NMR (500 MHz, cdcl$_3$) δ 7.78 – 7.70 (m, 6H), 7.62 (d, *J* = 8.9 Hz, 2H), 7.52 - 7. 45 (m, 4H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.33 - 7.26 (m, 2H), 7.15 - 7.09 (m, 4H), 3.92 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.61, 158.11, 137.29, 134.22, 133.44, 132.37, 130.63, 129.97, 129.61, 129.25, 127.83, 127.42, 126.09, 126.00, 124.70, 119.1, 112.86, 106.1, 55.6; MS: ESI-MS (*m/z*): 662 [M]$^+$, 663 [M+H]$^+$; HPLC: ee was determined by chiral HPLC analysis,100% ee (Chiral OD-H column, 5% isopropanol in hexane, 1 mL/min. 7.5 min, 8.9 min(major)); Optical Rotation: $[\alpha]_D$= -25^o, c=0.25 in

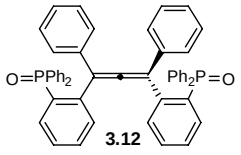


CH_2Cl_2, 50 mm cell; FTIR (neat) 2933, 2362, 1627, 1603, 1502, 1481, 1390, 1269, 1211, 1164, 1029, 889, 852, 746 cm^{-1}.

3.4.3 General procedure for syntheses of 1,3-bis(2-(diphenylphosphoryl)phenyl)-1,3-dialkyl/diaryl propa-1,2-diene.

General procedure: An oven-dried round bottom flask (10 mL in volume) with a Teflon-coated stir bar was charged with **3.1** (1 equiv, 0.13 mmol, 66 mg) under a N_2 atmosphere. Diethyl ether (3 ml) was added and then the flask was cooled to -78 ^oC. ^{t}BuLi (5 equiv, 0.66 mmol, 0.39 ml 1.7 M solution in pentane) was added into the flask drop-wise. The resulting solution was stirred at -78 ^oC for 1 h before a solution of diphenylphosphinic chloride (4 equiv, 0.53 mmol, 124 mg) in ether (1 ml) was added to reaction via syringe. After addition, the resulting mixture was allowed to warm to room temperature and was stirred at the same temperature for 12 h. The reaction was quenched by adding saturated aqueous NH_4Cl solution (3 ml) very slowly at 0 ^oC. The resulting solution was diluted with ethyl acetate (10 ml) and then separated. The aqueous solution was extracted with ethyl acetate (3 X 10 ml). The organic phases were combined, washed with brine, and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the resulting solid was purified by flash chromatography on silica gel (100% ethyl acetate to 5% methanol in ethyl acetate) to give pure bisphosphine oxide.

Data for **1,3-bis(2-(diphenylphosphoryl)phenyl)-1,3-diphenylpropa-1,2-diene (-)-3.12**:



3.12

yield: 89%, $[\alpha]_D$= -83^o, c=0.5 in CH_2Cl_2; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 – 7.11 (m, 24H), 7.07 – 6.85 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.6 (center C of allene), 112.5 (terminal C of allene).Other peaks cannot be interpreted because of the overlap; C-P coupling signals

are overlapped with aryl-carbons; ^{31}P NMR (121 MHz, $CDCl_3$) δ 29.0; MS: ESI-MS (*m/z*): 745.1 $[M+H]^+$, 767.1 $[M+Na]^+$; HPLC: enantiomeric excess (ee) was determined by chiral HPLC analysis,>99% ee (Chiral OD-H column, 3% ethanol in hexane, 1 mL/min.T_R=25.8 min); FTIR (neat) 2924, 1438, 1130, 1035, 730, 694, 561, 540 cm^{-1}

A single crystal suitable for X-ray diffraction was grown slow evaporation of a CH_2Cl_2/Tol (ca. 1:2) solution of **3.12.** The examined crystal was cut from a larger crystal and had approximate dimensions; 0.3 x 0.1 x 0.1 mm. The data were collected on a Rigaku R-Axis Spider diffractometer with an image plate detector using a graphite monochromator with CuKα radiation (λ = 1.5418Å). A total of 108 images of data were collected using ω-scans with a scan range of 5° and a counting time of 450 seconds per image. The data were collected at 100 K using a Rigaku XStream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data reduction was performed using the Rigaku Americas Corporation's Crystal Clear version 1.40.[70] The structure was solved by direct methods using SIR97[71] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[72] The absolute configuration was assigned the method of Flack.[73] The Flack x parameter refined to 0.03(3). The hydrogen atoms were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.0001*P)^2 + (2.339*P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_W(F^2)$ refined to 0.122, with R(F) equal to 0.0583 and a goodness of fit, S, = 1.14. Definitions used for calculating R(F), $R_W(F^2)$ and the goodness of fit, S, are given

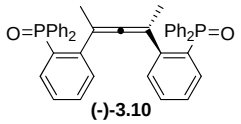
below.[74] The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[75] All figures were generated using SHELXTL/PC.[76]

Table 3.4 Crystal data for 3.12. (cif file has been published[69])

Empirical formula		C51 H40 O3 P2
Formula weight		762.77
Temperature		173(2) K
Wavelength		1.54180 Å
Crystal system		Monoclinic
Space group		P21
Unit cell dimensions	a = 10.8456(4) Å	α = 90°.
	b = 16.0031(5) Å	β = 96.834(2)°.
	c = 11.1904(5) Å	γ = 90°.
Volume		1928.44(13) $Å^3$
Z		2
Density (calculated)		1.314 Mg/m^3
Absorption coefficient		1.378 mm^{-1}
F(000)		800
Crystal size		0.30 x 0.10 x 0.10 mm
Theta range for data collection		6.66 to 72.40°.
Index ranges		-12<=h<=13, -19<=k<=18, -11<=l<=11

Reflections collected	13679
Independent reflections	4920 [R(int) = 0.0583]
Completeness to theta = 72.40°	83.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.87 and 0.64
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4920 / 1 / 514
Goodness-of-fit on F^2	1.145
Final R indices [I>2sigma(I)]	R1 = 0.0583, wR2 = 0.1005
R indices (all data)	R1 = 0.0829, wR2 = 0.1219
Absolute structure parameter	0.03(3)
Largest diff. peak and hole	0.293 and -0.338 e.Å^{-3}

(2,2'-(penta-2,3-diene-2,4-diyl)bis(2,1-phenylene))bis(diphenylphosphine oxide) 3.10:



(-)-3.10

yield:77%; $[\alpha]_D$= -162^o, c=0.1 in CH_2Cl_2, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 - 7.51 (m, 8H), 7.50 - 7.36 (m, 10H), 7.32 (td, *J* = 7.5, 2.9 Hz, 4H), 7.23 - 7.17 (m, 4H), 7.10 (dd, *J* = 7.3, 4.1 Hz, 2H), 1.39 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8 (center C of allene), 101.7 (terminal C of allene), 21.5 (Me). Other peaks cannot be interpreted because of the overlap; C-P coupling signals are overlapped with aryl-carbons; ^{31}P NMR (121 MHz, $CDCl_3$) δ 30.9; MS:LC-APCI-MS (*m/z*): 621.3 $[M+H]^+$; FTIR (neat) 3055, 2362, 2343, 1587, 1560, 1466, 1437, 1196, 1129, 1116, 1105, 730, 720, 695, 544, 526 cm^{-1}; HPLC: enantiomer excess (ee) was determined by chiral HPLC analysis, >99% ee after recrystalization from 70% ee product

in CH_2Cl_2 and hexane (Chiral OD-H column, 4% ethanol in hexane, 1 mL/min, T_R=31.4 min).

(2,2'-(5,5-dimethylhexa-2,3-diene-2,4-diyl)bis(2,1-phenylene))bis(diphenylphosphine oxide) 3.11: yield:86%, A mixture of two sets of NMR spectra, presumably reflecting the existence of atropisomers. (HPLC showed one peak) $[\alpha]_D$= -44°, c=0.1 in CH_2Cl_2; ^{1}H NMR (400 MHz, cdcl$_3$) shows two sets of protons (around 2:1). δ 7.91 (dd, *J* = 7.6, 4.3 Hz), 7.64 – 6.94 (m), 6.88 (t, *J* = 7.1 Hz), 6.78 (dd, *J* = 11.6, 7.4 Hz), 6.33 (dd, *J* = 7.3, 4.8 Hz), 1.94 (s), 1.62 (s), 1.31 (s), 1.05 (s); ^{13}C NMR (75 MHz, $CDCl_3$) there are two sets of ^{13}C signals. δ 201.56, 201.31 (center C of allene), 114.55, 113.84, 105.52, 104.98 (terminal C of allene), 37.37, 36.32, 30.76, 30.45(t-Butyl carbons), 22.33, 20.50 (Methyl carbon). Other peaks cannot be interpreted because of the overlap; C-P coupling signals are overlapped with aryl-carbons); ^{31}P NMR (121 MHz, $CDCl_3$) δ 31.10, 30.97, 30.88, 27.50. (Four ^{31}P signals); MS: LC-APCI-MS (*m/z*): 663.3$[M+H]^+$; FTIR (neat) 2950, 1560, 1437, 1201, 1116, 743, 719, 696, 544 cm^{-1}

Data for **1,3-bis(2-(diphenylphosphoryl)phenyl)-1,3-bis(6-methoxynaphthalen-2-yl)propa-1,2-diene 3.14**: yield:66%, ^{1}H NMR (500 MHz, cdcl$_3$) δ 7.68 (dd, *J* = 12.6, 7.6 Hz, 2H), 7.60 (t, *J* = 7.2 Hz, 4H), 7.51 - 7.43 (m, 8H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.25-7.31 (m, 6H), 7.16 (d, *J* = 6.4 Hz, 2H), 7.09 (s, 4H), 7.03 – 6.85 (m, 8H), 6.80 (s, 4H), 3.92 (s, 6H);^{13}C NMR (126 MHz, cdcl$_3$) δ 207.26(center C of allene), 105.72 (terminal C of allene), 55.52 (Methoxyl carbon). Other peaks cannot be interpreted because of the

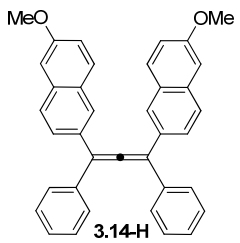
3.14

overlap; C-P coupling signals are overlapped with aryl-carbons);MS: LC-APCI-MS (*m/z*): 905.2 $[M+H]^+$.

HPLC: enantiomer excess (ee) was determined by chiral HPLC analysis, 0% ee (Chiral AD-H column, 8% ethanol in hexane, 1 mL/min, T_R=27.2, 35.9); Optical Rotation: $[\alpha]_D$= 0°, c=0.35 in CH_2Cl_2, 50 mm cell;

FTIR (neat) 2925, 2361, 1603, 1437, 1264, 1207, 1117, 720, 546 cm^{-1}

Note: Lithium-halogen exchange step was confirmed to be stereospecific, there was no enantioselectivity lost after quenching by H_2O. Data for protonated **3.14-H**: ^1H NMR



3.14-H

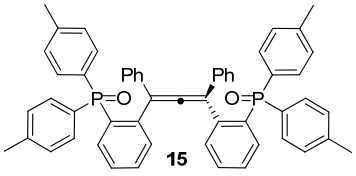
(400 MHz, $CDCl_3$) δ 7.73-7.70 (m, 4H), 7.65 (d, *J* = 8.7 Hz, 2H), 7.58 (dd, *J* = 8.5, 1.8 Hz, 2H), 7.51 - 7.46 (m, 4H), 7.41 - 7.30 (m, 6H), 7.15 - 7.07 (m, 4H), 3.92 (s, 6H). HPLC: ee was determined by chiral HPLC analysis, 0% ee (Chiral OD-H column, 0.3% isopropanol in hexane, 1 mL/min, T_R=21.6, 24.1 (major))

3.4.4 General procedure for syntheses of 1,3-bis(2-(diarylphosphoryl)phenyl)-1,3-diphenylpropa-1,2-diene.

This procedure was modified from literature.[77] An oven-dried test tube with a Teflon-coated stir bar was charged with diarylchlorophosphine (4 equiv, 0.4 mmol) under a N_2 atmosphere. Dried benzene (1 ml) was added via syringe and oxygen was bubbled through the reaction solution at RT with the following apparatus: An oxygen tank was connected to an empty flask; the outlet of that flask was connected to a bubbler containing H_2SO_4 (the empty flask was a safety precaution in case back pressure forced H_2SO_4 out of the bubbler). The outlet of the bubbler was split with a T-joint, one arm of which was connected to the reaction flask via a needle submerged in the reaction mixture.

The second branch was equipped with a clamp to adjust flow. The outlet from the reaction flask was connected to a small trap with silicon oil for monitoring the pressure of the system. The oxygen cylinder was opened and the delivery pressure was adjusted to a slow rate through the reaction mixture (1-2 bubbles/second through the silicon oil-filled bubbler). Gas was introduced for 1-2 hours before transfer. Another oven-dried test tube with a Teflon-coated stir bar was charged with (-)-1,3-bis(2-bromophenyl)-1,3-diphenylpropa-1,2-diene **3.9** (1 equiv, 0.1 mmol) under a N_2 atmosphere. Diethyl ether (1 ml) was added and then the tube was cooled to -78^{o}C. ^{t}BuLi (3 equiv, 0.3 mmol, 1.7 M solution in pentane) was added into the tube drop-wise via syringe. The resulting solution was stirred at -78 ^{o}C for 1 hour. And then the solution of freshly-made diarylphosphinic chloride (4 equiv, 0.4 mmol) in benzene (1 ml) was transferred into reaction via cannula. After addition, the resulting mixture was allowed to warm to room temperature and was stirred at the same temperature for 12 h. The reaction was quenched by adding saturated aqueous NH_4Cl solution (2 ml) very slowly at 0 ^{o}C. The resulting solution was diluted with ethyl acetate (10 ml) and then separated. The aqueous solution was extracted with ethyl acetate (3 X 10 ml). The organic phases were combined, washed with brine, and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the resulting solid was purified by flash chromatography on silica gel (100% ethyl acetate to 5% methanol in ethyl acetate) to give pure bisphosphine oxides (**15-18**).

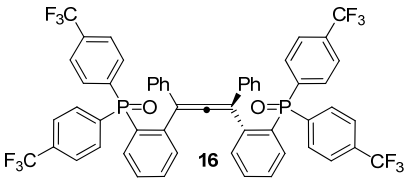
(*S*)-1,3-bis(2-(dip-tolylphosphoryl)phenyl)-1,3-diphenylpropa-1,2-diene 15: yield: 33%, $[\alpha]_D$= -58^{o}, c=0.1 in CH_2Cl_2; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.7 Hz, 1H), 7.66 (d, *J* = 7.6 Hz,



15

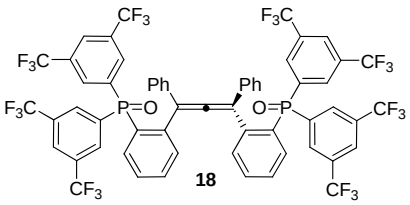
1H), 7.55 (dd, *J* = 7.7, 6.6 Hz, 2H), 7.42 (dd, *J* = 7.4, 7.5 Hz, 2H), 7.36 - 7.19 (m, 11H), 6.89-6.95 (m, 14H), 6.82 (d, *J* = 7.1 Hz, 3H), 2.23 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ =206.5 (center C of allene), 112.5 (terminal carbon of allene), 21.7, 21.4 (two methyl carbons). Other peaks cannot be interpreted because of the overlap; C-P coupling signals are overlapped with aryl-carbons; ^{31}P NMR (121 MHz, $CDCl_3$) δ 30.7; MS: ESI-MS (*m/z*): 801.4 $[M+H]^+$, 823.4 $[M+Na]^+$; FTIR (neat) 3054, 2922, 2364, 1602, 1492, 1446, 1187, 1115, 807, 764, 729, 694, 659, 537 cm^{-1}.

(*S*)-1,3-bis(2-(bis(4-(trifluoromethyl)phenyl)phosphoryl)phenyl)-1,3-diphenylpropa-



1,2-diene 16: yield: 61%, $[\alpha]_D$= –60°, c=0.5 in CH_2Cl_2; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 - 7.52 (m, 14H), 7.52 - 7.35 (m, 6H), 7.16 (d, *J* = 6.4 Hz, 4H), 6.96-7.07 (m, 6H), 6.82 (d, *J* = 7.1 Hz, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.9 (center C of allene), 112.2 (terminal C of allene), Other peaks cannot be interpreted because of the overlap; C-P and C-F coupling signals are overlapped with aryl-carbons; ^{31}P NMR (121 MHz, $CDCl_3$) δ 25.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.54, -63.60; MS: EI-MS (*m/z*): 1017.15 $[M+H]^+$, 1039.05 $[M+Na]^+$; FTIR (neat) 2361, 2343, 1399, 1322, 1169, 1130, 1062, 1018, 836, 711, 668, 543 cm^{-1}.

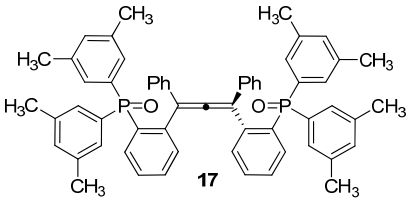
Data for **1,3-bis(2-(bis(3,5-bis(trifluoromethyl)phenyl)phosphoryl)phenyl)-1,3-**



diphenylpropa-1,2-diene 18: yield:35%; $[\alpha]_D$= -32°, c=0.5 in CH_2Cl_2; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 - 7.69 (m, 14H), 7.50-7.61 (m, 6H), 6.98 - 6.76 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.1 (center C of allene), 112.0 (terminal C of allene). Other peaks cannot be interpreted because of the

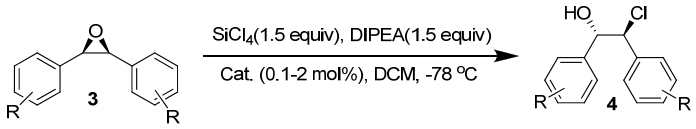
overlap; C-P and C-F coupling signals are overlapped with aryl-carbons); ^{31}P NMR (121 MHz, $CDCl_3$) δ 25.48; ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.35, -63.37; MS: ESI-MS (*m/z*): 1289.00 $[M+H]^+$, 1311.00 $[M+Na]^+$; FTIR (neat) 2365, 1280, 1132 cm^{-1}.

Data for **1,3-bis(2-(bis(3,5-dimethylphenyl)phosphoryl)phenyl)-1,3-diphenylpropa-1,2-diene 17**: yield:58%; $[\alpha]_D$= -360°, c=0.1 in $CHCl_3$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 - 7.65 (m, *J* = 13.0, 7.7 Hz, 2H), 7.46 (dt, *J* = 25.6, 7.3 Hz, 2H), 7.31 - 7.21 (m, 4H), 7.11 (d, *J* = 12.5 Hz, 4H), 7.00 - 6.72 (m, *J* = 27.3, 14.2 Hz, 18H), 2.14 (s, 12H), 2.08 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 206.8 (center C of allene), 112.6 (terminal C of allene), 21.50, 21.47 (two methyl carbons). Other peaks cannot be interpreted because of the overlap; C-P coupling signals are overlapped with aryl-carbons; ^{31}P NMR (121 MHz, $CDCl_3$) δ 29.94; MS: ESI-MS (*m/z*): 857.30 $[M+H]^+$, 879.35 $[M+Na]^+$; FTIR (neat) 3410, 2921, 2361, 2343, 1638, 1274, 1131, 850, 727, 691, 576 cm^{-1}



3.4.5 Representative procedure for epoxide opening with chiral bisphosphine oxides

Scheme 3.17 Epoxide opening with chiral bisphosphine oxides

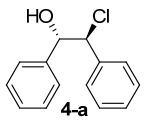


Procedure I (0.1 mol% catalyst)**:** An oven-dried test tube (16 X 100 mm, 10 mL in volume) with a Teflon-coated stir bar was charged with *cis*-stilbene oxide (1 equiv, 0.1 mmol) under an atmosphere of N_2. A solution of bisphosphine oxide in CH_2Cl_2 (0.1 mol%, 0.5 ml, 0.002 M solution) was added by syringe. ^{i}Pr$_2$NEt (1.5 equiv, 0.15 mmol,

26 μl) was added and then the tube was cooled to -78 ^{o}C. A solution of $SiCl_4$ (1.5 equiv, 0.15 mmol, 1.0 M solution in CH_2Cl_2) was added into the flask drop-wise by syringe. The resulting solution was stirred at -78 ^{o}C for the indicated time. The reaction was quenched by adding propylene oxide (0.1 ml) followed by adding saturated aqueous $NaHCO_3$ solution (0.7 ml) and saturated aqueous KF/KH_2PO_4 solution (0.7 ml) at -78 ^{o}C.[78] The resulting solution was warmed to room temperature and diluted with ether (3 ml). The aqueous solution was separated and extracted with ether (3 X 10 ml). The organic phases were combined and washed with brine, dried over magnesium sulfate and filtered. After removal of the solvent under reduced pressure, the resulting oil was purified by flash chromatography on silica gel (100% hexane to 2% ethyl acetate in hexane) to give pure chlorohydin product.

Procedure II (2 mol% catalyst)**:** An oven-dried test tube (16 X 100 mm, 10 mL in volume) with a Teflon-coated stir bar was charged with bisphosphine oxide catalyst (2 mol%, 0.002 mmol) and *cis*-stilbene oxide (1 equiv, 0.1 mmol) under an atmosphere of N_2. CH_2Cl_2 (5 mL) and dried $^{i}Pr_2NEt$ (1.5 equiv, 0.15 mmol, 26 μl) were added and the tube was cooled to –78 ^{o}C. A solution of $SiCl_4$ (1.5 equiv, 0.15 mmol, 1.0 M solution in CH_2Cl_2) was added into the flask drop-wise via syringe. The resulting solution was stirred at -78 ^{o}C for the indicated time. The product was isolated as in procedure 1.

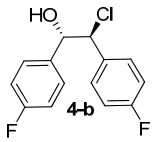
(1*S*,2*S*)-2-chloro-1,2-diphenylethanol 4-a:[61] this compound was prepared by following procedure **I** using catalyst **3.12**. Reaction time was 12-16 h at -78 ^{o}C. Colorless liquid, yield: 97%, ee: 94%; $[\alpha]_D$= +21.2^{o}, c=1.0 in EtOH; ^{1}HNMR: ($CDCl_3$) δ 7.08-7.25 (m, 10H), 5.00 (d, J = 8.4),



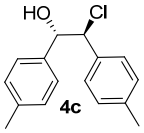
4-a

4.94 (d, J = 8.4); HPLC: ee:94% , Chiral OD-H column, 3% isopropanol in hexane, 1 mL/min.T_R: 23.8 min (major) and 26.4 min (minor); MS: ESI-MS (*m/z*): 216[M-OH]$^+$.

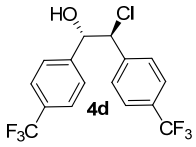
(*1S,2S*)-2-chloro-1,2-bis(4-fluorophenyl)ethanol 4-b: this compound was prepared by following procedure **I** using catalyst **3.12**. Catalyst loading was 0.1 mol% (0.5 ml of 0.002 M solution in CH_2Cl_2). Reaction time was 36 h at -78 ^oC. Colorless liquid, yield: 96%, ee: 93%; $[\alpha]_D$= –4.0^o, c=0.85 in $CHCl_3$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.11-7.14 (m, 2H), 7.05-7.07 (m, 2H), 6.90-6.95 (m, 4H), 4.53 (d, *J* = 8.4 Hz, 1H), 4.90 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ =161.87 (d, *J* = 247), 161.76 (d, *J* = 247), 134.5 (d, *J* = 3.3), 133.6 (d, *J* = 3.8), 130.0 (d, *J* = 8.1), 128.9 (d, *J* = 8.2), 115.6 (d, *J* = 21), 115.3 (d, *J* = 21), 78.6, 70.0; MS: ESI-MS (*m/z*): 251.0 [M-HO]$^+$, 233.0 [M-Cl]$^+$; HPLC condition: Chiracel AD-H column, 3% isopropanol in hexane, 0.5 mL/min. T_R=:26.1 min (major), and 28.2 min (minor).



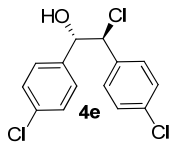
(*1S,2S*)-2-chloro-1,2-dip-tolylethanol 4c: this compound was prepared by following procedure **I** using catalyst **3.12**. Catalyst loading was 0.1 mol% (0.5 ml of 0.002 M solution in CH_2Cl_2). Reaction time was 12 h at -78 ^oC. Colorless liquid, yield: 92%, ee: 89%; $[\alpha]_D$= -37^o, c=0.8 in $CHCl_3$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.01 (m, 4H), 4.98 (d, *J* = 8.0 Hz, 1H), 4.91 (d, *J* = 7.9 Hz, 1H), 2.29 (s, 3H), 2.27 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ = 138.5, 138.0, 136.3, 135.3, 129.2, 129.0, 128.1, 127.1, 78.5, 70.9, 21.2; MS: ESI-MS (*m/z*): 243.0 [M-HO]$^+$, 225.1 [M-Cl]$^+$; HPLC: condition: Chiracel AD-H column, 10% isopropanol in hexane, 0.5 mL/min. T_R = 9.7 min (major), and 10.7 min (minor).



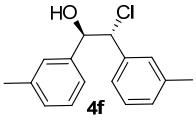
(*1S,2S*)-2-chloro-1,2-bis(4-(trifluoromethyl)phenyl)ethanol 4d: this compound was prepared by following procedure **II** using catalyst **3.12**. Catalyst loading was 2 mol% (2 ml CH_2Cl_2). Reaction time was 36 h at -78 ^oC. Colorless liquid, yield: 89%, ee: 87%; $[\alpha]_D$= -11.9^o, c=0.65 in $CHCl_3$; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 5.04 (s, 2H); ^{13}C NMR (125MHz, $CDCl_3$) δ 142.5, 141.3, 131.2 (m), 130.8 (m), 128.7, 127.6, 125.8 (m), 125.1 (m), 125.1, 125.0, 78.1, 69.0; MS: ESI-MS (*m/z*): 392.0 $[M+Na]^+$, 374 $[M-OH+ Na]^+$; HPLC condition: Chiracel AD-H column, 10% isopropanol in hexane, 0.5 mL/min. T_R = 6.4 min (minor) and 8.5 min (major).



(1*S*,2*S*)-2-chloro-1,2-bis(4-chlorophenyl)ethanol 4e: this compound was prepared by following procedure **I** using catalyst **3.12**. Catalyst loading was 0.1 mol% (0.5 ml of 0.002 M solution in CH_2Cl_2). Reaction time was 36 h at -78 ^oC. Colorless liquid, yield: 89%, ee: 82%; $[\alpha]_D$= -50.2^o, c=0.85 in $CHCl_3$; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, *J* = 9.0 Hz, 2H), 7.10 (d, *J* = 9.0 Hz, 2H), 7.09 (d, *J* = 8.7 Hz, 2H), 7.00 (d, *J* = 8.7 Hz, 2H), 4.89 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.1, 136.1, 134.8, 134.4, 129.6, 128.9, 128.7, 128.6, 78.3, 69.6; MS: ESI-MS (*m/z*): 284.9 $[M-H_2O]^+$, 306.0 $[M-H_2O+Na]^+$; HPLC condition, Chiracel AD-H column, 3% isopropanol in hexane, 0.5 mL/min. T_R=10.5 min (minor) and 12.7 min (major).

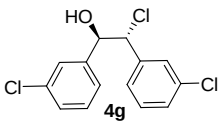


(1*S*,2*S*)-2-chloro-1,2-dim-tolylethanol 4f: this compound was prepared by following procedure **I** using catalyst **3.12**. Catalyst loading was 0.2 mol% (1

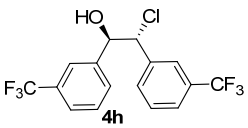


ml of 0.002 M solution in CH_2Cl_2). Reaction time was 36 h at -78 ^oC. Colorless liquid, yield: 89%, ee: 91%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 - 6.94 (m, 7H), 6.88 (d, *J* = 7.4 Hz, 1H), 4.99 (d, *J* = 7.9 Hz, 1H), 4.93 (d, *J* = 7.9, 2.8 Hz, 1H), 2.99 (d, *J* = 2.9 Hz, 1H), 2.28 (d, *J* = 9.2 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ = 139.0, 138.2, 137.96, 137.92, 129.5, 129.1, 128.8, 128.4, 128.2, 127.7, 125.3, 124.3, 78.7, 71.0, 21.6, 21.5; MS: ESI-MS (*m/z*): 243.0 $[M-H_2O]^+$, 225.0 $[M-Cl]^+$; HPLC: ee: 91% , Chiral OD-H column, 2% isopropanol in hexane, 0.5 mL/min. T_R: 20 min (major) and 23 min (minor); FTIR (neat) 3426, 3025, 2921, 2361, 1608, 1489, 1456, 1260, 1155, 1057, 775, 724, 702, 639 cm^{-1}

(1*S*,2*S*)-2-chloro-1,2-bis(3-chlorophenyl)ethanol 4g: this compound was prepared by following procedure **II** using catalyst **3.12** (2 mol%), CH_2Cl_2 (2 ml) was used. Reaction time was 12 h at -78 ^oC. Colorless liquid, yield: 96%; ^1H NMR (400 MHz, $cdcl_3$) δ 7.32 – 7.07 (m, 6H), 7.02 – 6.98 (td, *J* = 1.4, 7.8 Hz , 1H), 6.92 – 6.88 (td, *J* = 1.4, 7.8 Hz, 1H), 4.99 – 4.79 (m, 2H), 3.01 (d, *J* = 2.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.6, 139.5, 134.6, 134.5, 129.9, 129.7, 129.2, 128.8, 128.3, 127.2, 126.4, 125.4, 78.1, 69.3; MS: ESI-MS (*m/z*): 284.9 $[M-H_2O]^+$, 306.0 $[M-H_2O+Na]^+$; HPLC: ee: 90 %, Chiral OD-H column, 3% isopropanol in hexane, 0.5 mL/min. T_R: 30 min (minor) and 40.6 min (major); FTIR (neat) 3420, 2923, 2852, 2360, 1575, 1477, 1432, 1190, 1080, 884, 764, 694 cm^{-1}.

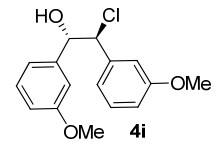


(1*S*,2*S*)-2-chloro-1,2-bis(3-(trifluoromethyl)phenyl)ethanol 4h: this compound was prepared by following procedure **II** using catalyst **3.12**. CH_2Cl_2 (2 ml) was used. Reaction time was 48 h at -78 ^oC. Colorless solid, yield: 91%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 15.8, 7.5 Hz, 2H), 7.36 (m, 4H), 7.29 - 7.24 (m, 2H), 4.99 (s, 2H), 3.07 (s, br, 1H); ^{13}C NMR (101



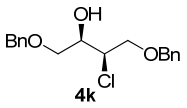
MHz, cdcl$_3$) δ 139.4, 138.3, 131.5(q, *J* = 1.2 Hz), 131.1 (q, *J* = 32 Hz), 130.9 (q, *J* = 32 Hz), 130.4 (q, *J* = 1.2 Hz), 129.2, 129.0, 125.8 (q, *J* = 3.7 Hz), 125.5 (q, *J* = 3.7 Hz), 125.1 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 3.8 Hz),123.9 (q, *J* = 272 Hz), 123.8 (q, *J* = 272 Hz), 78.4, 69.1; MS: ESI-MS (*m/z*): 351.0 $[M\text{-}H_2O]^+$, 374.0 $[M\text{-}H_2O\text{+}Na]^+$; HPLC: ee: 88 %, Chiral AD-H column, 8% isopropanol in hexane, 0.5 mL/min. T_R: 6.5 min (minor) and 7.2 min (major); FTIR (neat) 3417, 2923, 1451, 1331, 1167, 1127, 1074, 906, 812, 701 cm^{-1}

(*1S,2S*)-2-chloro-1,2-bis(3-methoxyphenyl)ethanol 4i: this compound was prepared by following procedure **I** using catalyst **3.12**. Catalyst loading was 0.2 mol% (1 ml of 0.002 M solution in CH_2Cl_2). Reaction time was 16 h at -78 ^oC. Colorless liquid, yield: 95%. $[\alpha]_D$= -17.5^o, c=0.8 in $CHCl_3$; ^1H NMR (500 MHz, $CDCl_3$) δ 7.12 - 7.27 (m, 2H), 6.70 - 6.80 (m, 6H), 4.97 (d, *J* = 5.4 Hz, 1H), 4.92 (d, *J* = 5.6 Hz, 1H), 3.73 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.65, 159.62, 140.6, 139.4, 129.6, 129.4, 120.6, 119.6, 114.4, 114.3, 113.8, 112.5, 78.8, 70.6, 55.5, 55.4; MS: ESI-MS (m/z): 275.0 $[M\text{-}HO]^+$, 257.1 $[M\text{-}Cl]^+$; HPLC: ee:88%, HPLC condition, Chiracel AD-H column, 15% isopropanol in hexane, 0.5 mL/min. T_R = 13.2 min (major), 14.3 min (minor).



4i

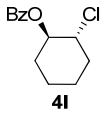
(2S,3S)-1,4-bis(benzyloxy)-3-chlorobutan-2-ol 4k: this compound was prepared by following procedure **II** using 2 mol% catalyst **3.12**. CH_2Cl_2 (2 ml) was used. Reaction time was 36 h at -78 ^oC. Colorless liquid, yield: 90%; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 - 7.28 (m, 10H), 4.64 - 4.49 (m, 4H), 4.31 - 4.23 (td, *J* = 6.1, 2.5 Hz, 1H), 4.18 (td, *J* = 6.1, 2.5 Hz, 1H), 3.85 (ddd, *J* = 10.2, 6.2, 1.6 Hz, 1H), 3.76 (ddd, *J* = 10.2, 5.5, 1.6 Hz, 1H), 3.66 - 3.53 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0,



4k

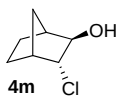
137.7, 128.74, 128.70, 128.16, 128.09, 128.02, 127.99, 73.8, 73.74, 7.8, 71.3, 70.3, 61.0; HPLC condition, ee: 60%, Chiral OD-H column, 4% ethanol in hexane, 1mL/min. T_R:21.8 min (major) and 25.2 min (minor); FTIR (neat) 3443, 3064, 3031, 2919, 2865, 1722, 1496, 1454, 1364, 1207, 1102, 1028, 737, 698 cm^{-1}

(1R,2R)-2-chlorocyclohexyl benzoate 4l: this compound was prepared from alcohol, which was generated by following procedure **I** using catalyst **3.12**. Reaction time was 1 h at -78 ^oC. Colorless liquid, yield: 95%; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.3 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 5.03-5.08 (m, 1H), 4.00-4.06 (m, 1H), 2.41 - 2.11 (m, 2H), 1.90 - 1.68 (m, 3H), 1.58 - 1.29 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ =165.9, 133.2, 130.5, 129.9, 128.6, 76.6, 60.8, 34.9, 30.9, 24.6, 23.4; HPLC: ee was determined from benzoate **3l**: 29% , Chiral OD-H column, 0.2% isopropanol in hexane, 1mL/min. T_R: 12.4 min(major) and 13.8 min(minor); FTIR (neat) 2920, 2361, 2343, 1720, 1450, 1267, 1108, 710 cm^{-1}.



4l

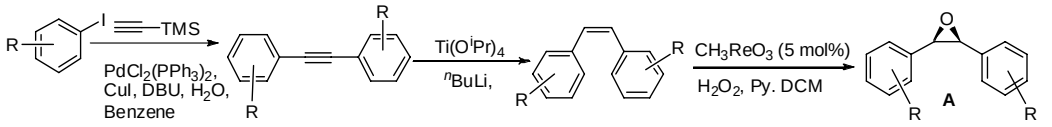
(1*S,2*R**,3*R**,4*R**)-3-chlorobicyclo[2.2.1]heptan-2-ol 4m**: this compound was prepared by following procedure **I** using catalyst **3.12**. Catalyst loading was 0.1 mol% (0.5 ml of 0.002 M solution in CH_2Cl_2). Reaction time was 36 h at -78 ^oC. Colorless liquid, yield: 76%; $[\alpha]_D$= -18.6^o, c=0.19 in $CHCl_3$; ^1H NMR (400 MHz, $CDCl_3$) δ 4.02-4.06 (m, 2H), 2.36 (m, 1H), 2.32 (m, 1H), 2.24 (t, *J* = 4.4 Hz, 1H), 2.16 (dd, *J* = 8.8, 10.4 Hz, 1H), 1.68 (m, 1H), 1.53(m, 1H), 1.10 (d quintet, *J* = 4.4, 10.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 80.8, 61.4, 48.4, 42.0, 41.3, 25.3, 24.7; ee: 50%, GC condition: Astec Chiraldex G-TA, 100 ^oC, 1.60 mL/min carrier gas flow. T_R= 29.5 min (major), 31.9 min (minor).



4m

3.4.6 Representative procedure for synthesis of diaryepoxide. (Scheme 3.18)

Scheme 3.18 Synthesis of diaryepoxide



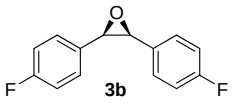
The first intermediate alkyne was synthesized according to the known procedure.[79] Thus, an oven-dried test tube (16 X 100 mm, 10 mL in volume) with a Teflon-coated stir bar was charged with CuI (10 mol%, 0.1 mmol, 19 mg) and $PdCl_2(PPh_3)_2$ (63 mol%, 0.06 mmol, 42 mg) under a N_2 atmosphere. Benzene (5 ml) was added into the tube and then iodobenzene (1 equiv, 1 mmol), H_2O (0.4 equiv, 0.4 mmol, 7.2 mg) and DBU (6 equiv, 6 mmol, 0.897 ml) were added sequentially by syringe. Trimethylsilylacetylene (0.5 equiv, 0.5 mmol, 49 mg) was added last. The test tube was covered by aluminum foil to protect from light. The resulting solution was heated to 60 ^oC and stirred at the same temperature for 12-24 hours until the reaction appeared to have ceased as judged by TLC analysis. The reaction was quenched by adding saturated aqueous NH_4Cl (2ml) and diluted with Et_2O (3 ml). The resulting mixture was stirred at room temperature for 5 minutes, and then separated. The aqueous solution was extracted with Et_2O (3 X 10 ml). The organic phases were combined, washed with brine, and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the resulting crude product was purified by flash chromatography on silica gel (100% hexane to 1% ethyl acetate in hexane) to give pure coupling products alkyne.

A know procedure[80] was followed for the second step. An oven-dried test tube (16 X 100 mm, 10 mL in volume) with a Teflon-coated stir bar was charged with the diarylalkyne (1 equiv, 0.45 mmol) under a N_2 atmosphere. THF (2 ml) was added and the

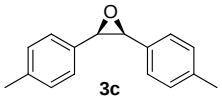
tube was cooled to -78 ^{o}C. $Ti(O^{i}Pr)_4$ (2 equiv, 0.9 mmol, 0.263 ml) was added and then ^{n}BuLi (4 equiv, 1.8 mmol, 2.9 M in hexane, 0.62 ml) was added drop-wise. The resulting solution was warmed up to -50 ^{o}C and stirred at the same temperature for 2-4 h.[81] The reaction was quenched by adding saturated aqueous NH_4Cl solution (2 ml) and diluted with Et_2O (3 ml). The resulting mixture was stirred at room temperature for 5 minutes, and then separated. The aqueous solution was extracted with Et_2O (3 X 10 ml). The organic phases were combined, washed with brine, and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the resulting crude product was purified by flash chromatography on silica gel (100% hexane to 1% ethyl acetate in hexane) to give pure cis olefins.

The last epoxidation step was using CH_3ReO_3 as catalyst.[82] An oven-dried test tube (16 X 100 mm, 10 mL in volume) with a Teflon-coated stir bar was charged with the diarylalkene **I** (1 equiv, 0.8 mmol) and then CH_2Cl_2 (2 ml) was added. The test tube was cooled to 0 ^{o}C, CH_3ReO_3 (5 mmol%, 0.04 mmol, 10 mg) was added into this solution, and then pyridine (13 mol%, 9 µl) and H_2O_2 (3 equiv, 2.4 mmol, 100µl) were added. The test tube was capped with a rubber septum and sealed. The resulting solution was warmed up to room temperature and stirred at the same temperature for 40-48 h. The reaction was quenched by adding 15 mg of MnO_2 slowly and carefully. The resulting mixture was filtered through celite and rinsed by 5 ml of CH_2Cl_2. The organic phases were combined, washed with brine, and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the resulting crude product was purified by flash chromatography on silica gel (100% hexane to 5% ethyl acetate in hexane) to give pure epoxide products **A**.

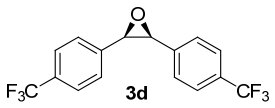
***cis*-2,3-bis(4-fluorophenyl)oxirane 3b**.[82] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08-7.12 (m, 4H), 6.85- 6.89 (m, 4H), 4.31 (s, 2H); MS: ESI-MS (*m/z*): 233.1 $[M+H]^+$, 255.1 $[M+Na]^+$.



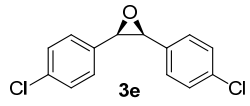
***cis*-2,3-dip-tolyloxirane 3c**.[82] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (d, *J* = 8.0 Hz, 4H), 6.98 (d, *J* = 8.0 Hz, 4H), 4.29 (s, 2H), 2.24 (s, 6H); MS: ESI-MS (*m/z*): 225.1 $[M+H]^+$.



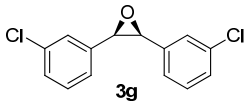
***cis*-2,3-bis(4-(trifluoromethyl)phenyl)oxirane 3d**,[82] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.2 Hz, 4H), 7.25 (d, *J* = 8.2 Hz, 4H), 4.43 (s, 2H); MS: ESI-MS (*m/z*): 333.0 $[M+H]^+$, 374.0 $[M+H_2O+Na]^+$.



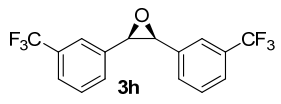
***cis*-2,3-bis(4-chlorophenyl)oxirane 3e**,[83] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (d, *J* = 8.5 Hz, 4H), 7.10 (d, *J* = 8.5 Hz, 4H), 4.33 (s, 2H); MS: ESI-MS (*m/z*): 265.0 $[M+H]^+$.

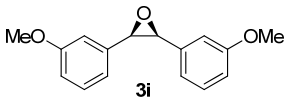


***cis*-2,3-bis(3-chlorophenyl)oxirane 3g**, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (d, *J* = 2.0 Hz, 2H), 7.10-7.16 (m, 4H), 7.05- 7.00 (m, 2H), 4.32 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.2, 134.2, 129.5, 128.2, 127.2, 125.1, 59.3; FTIR (neat) 2981, 2361, 1600, 1574, 1480, 1426, 1357, 1182, 1076, 907, 781, 724, 692, 682, 599 cm^{-1}



***cis*-2,3-bis(3-(trifluoromethyl)phenyl)oxirane 3h,** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 - 7.37 (m, 4H), 7.28-7.35 (m, 4H), 4.44 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 135.0 (s), 130.7 (q, *J* = 32.6 Hz), 130.2 (s), 128.7 (s), 124.8 (q, *J* = 4.0 Hz), 124.0 (q, *J* = 275.0 Hz), 123.8 (q, *J* = 4.0), 59.31 (s); MS: ESI-MS (*m/z*): 333.0 $[M+H]^+$, 374.0 $[M+H_2O+Na]^+$; FTIR (neat) 2363, 1448, 1332, 1282, 1156, 1120, 1095, 1071, 812, 704 cm^{-1}



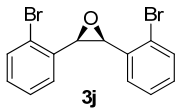


3i

***cis*-2,3-bis(3-methoxylphenyl)oxirane 3i,** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (t, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 8.0 Hz, 2H), 6.71- 6.73 (m, 4H), 4.32 (s, 2H), 3.68 (s, 6H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.6, 136.3, 129.1, 119.7, 113.9, 112.5, 59.9, 55.3; MS: ESI-MS (*m/z*): 257.1 $[M+H]^+$.

***cis*-2,3-bis(2-bromophenyl)oxirane 3j**, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.12 (t, *J* = 7.6 Hz, 2H), 7.02 (t, *J* = 7.6 Hz, 2H), 4.58 (s, 2H).



3j

^{13}C NMR (125 MHz, $CDCl_3$): δ 133.5, 132.4, 129.4, 128.9, 126.6, 123.0, 60.9.

MS: ESI-MS (*m/z*): 354.9, 352.9 $[M+H]^+$.

3.4.7 Catalyst recovery experiment.

Catalyst **3.12** was recovered from reaction, purified by PTLC. (Yield: 94%)

According to procedure **II**, (1R,2R)-2-chloro-1,2-diphenylethanol was synthesized by using this recovered catalyst **3.12**. Ee was determined by chiral HPLC analysis, 90% ee (Chiral OD-H column, 2% isopropanol in hexane, 1 mL/min.). $[\alpha]_D$= -83^o, c=0.5 in CH_2Cl_2.

3.5 Reference

[1] Stinson, S. C. Chiral Drugs. *Chem. Eng. News* **1998**, *76*, 83-104.

[2] Stinson, S. C. *Chem. Eng. News* **2001**, 79, 79.

[3] a) Sheldon, R. A. *Chirotechnology*; Marcel Dekker Inc.: New York, NY, 1993. b) Collins, A. N., Sheldrake, G. N., Crosby, J., Eds. *Chirality in Industry*; John Wiley & Sons: New York, NY, 1992.

[4] Taylor, M. S.; Jacobsen, E. N. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5368.

[5] Halpern, J.; Trost, B. M. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5347.

[6] Denmark S. E.; Stavenger, R. A. *Acc. Chem. Res*. **2000,** *33*, 432-440.

[7] Brunel, J. M. *Chem. Rev.* **2005,** *105*, 857.

[8] Berthod, M.; Mignani, G.; Woodward, G.; Lemaire, M. *Chem. Rev***. 2005**, *105*, 1801.

[9] Feringa, B. L. *Acc. Chem. Res*. **2000**, *33,* 346.

[10] Fu, Y.; Xie, J.-H.; Hu, A.-G.; Zhao, H.; Wang, L.-X.; Zhou, Q.-L. *Chem. Commun.* **2002**, *5,* 480.

[11] *Comprehensive Asymmetric Catalysis*. Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer-Verlag: Berlin, **1999**.

[12] a) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946. b) Knowles, W. S., Sabacky, M. J., Vineyard, B. D.; Weinkauff, D. J. *J. Am. Chem. Soc*. **1975,** *97***,** 2567.

[13] a) Kagan, H. B.; Dang, T. P. *J. Am. Chem.Soc.* **1972***, 94***,** 6429. b) Burk, M. J., Feaster, J. E., Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993,** 115**,** 10125. c) Nugent, W. A., Rajan Babu, T. V.; Burk, M. J. *Science* **1993,** *259***,** 479.

[14] a) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980,** 102**,** 7932. b) Noyori, R. *Adv. Synth. Catal.* **2003,** 345**,** 15.

[15] Bredig, G.; Fiske, P. S. *Biochem. Z.* **1913**, 46**,** 7.

[16] Eder, U.; Sauer, G.; Wiechert, R. *Angew.Chem. Int. Ed.* **1971**, *10***,** 496.

[17] Hajos, Z. G.; Parrish, D. R. *J. Org.Chem.* **1974**, *39***,** 1615.

[18] a) List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122***,** 2395. b) List, B. *Tetrahedron* **2002,** 58**,** 5573.

[19]Taylor, D. R. *Chem. Rev.* **1967**, *67*, 317.

[20] a) *The Chemistry of Ketenes, Allenes and Related Compounds* (Ed.: S. Patai), Wiley, New York, **1980**; b) *The Chemistry of the Allenes* (Ed.: S. R. Landor), Academic Press, London, **1982**; c) Schuster, H. F.; Coppola, G. M. *Allenes in OrganicSynthesis*, Wiley, New York, **1984**.

[21] a) Crimmins, M. T.; Emmitte, K. A. *J. Am. Chem. Soc*. **2001**, *123*, 1533. b) Furuichi, N.; Hara, H.; Osaki, T.; Mori, H.; Katsumura, S. *Angew. Chem. Int. Ed*. **2002**, *41*, 1023.

[22] Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535.

[23] Schmittel, M.; Strittmatter, M.; Vollmann, K.; Kiau, S. *Tetrahedron Lett.* **1996**, *37*, 999.

[24] Tsuboi, S.; Masuda, T.; Takcda, A. *Tetrahedron* **1982**, *47*, 4478.

[25] Radom, L., Harikaran, R. C., Pople, J. A.; Schleyer, P. R. *J. Am. Chem. Soc*. **1973**, *95,* 6531.

[26] a) van Henegouwen, W. G. B.; Hiemstra, H. *J. Org. Chem.* **1997**, *62*, 8862. b) van Henegouwen, W. G. B.; Fieseler, R. M.; Rutjes, F. P. J. T.; Hiemstra, H. *J. Org. Chem.* **2000**, *65*, 8317. c) Nishina, N.; Yamamoto, Y. *Angew. Chem. Int. Ed*. **2006**, *45*, 3314.

[27] a) Holemann, A.; Reissig, H.-U. *Org. Lett.* **2003**, *5*, 1463. b) Kang, S.-K.; Ko, B.-S.; Ha, Y.-H. *J. Org. Chem.* **2001**, *66*, 3630. c) Kang, S.-K.; Ha, Y.-H.; Kim, D.-H.; Lim, Y.; Jung, J. *Chem. Commun.* **2001**, 1306.

[28] a) Zimmer, R.; Dinesh,C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev*. **2000**, *100*, 3067. b) Ng, S.-S.; Jamison, T. F. *Tetrahedron* **2005**, *61*, 11405.

[29] Lipshutz, B. H.; Sengupta, S. *Org. React*. **1992**, *41*, 135.

[30] Myers, A. G.; Zheng, B. *J. Am. Chem. Soc*. **1996**, *118*, 4492.

[31] Pu, X.; Ready, J. M. *J. Am. Chem. Soc*. **2008**, *130*, 10874.

[32] a) Claesson, A.; Olsson, L.-I. *J. Am. Chem. Soc*. **1979**, *101*, 7302. b) Keck, G.; Webb, R. R., II *Tetrahedron Lett.* **1982**, *23*, 3051.

[33] Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett*. **1986**, *27*, 5237.

[34] Satoh, T.; Hanaki, N.; Kuramochi, Y.; Inoue, Y.; Hosoya, K.; Sakai, K. *Tetrahedron* **2002**, *58*, 2533.

[35] Satoh, T.; Kuramochi, Y.; Inoue, Y. *Tetrahedron Lett*. **1999**, *40*, 8815.

[36] Elsevier, C. J.; Stehouwer, P. M.; Westmijze, H.; Vermeer, P. *J. Org. Chem*. **1983**, *48*, 1103.

[37] Tucker, C. E.; Greve, B.; Klein, W.; Knochel, P. *Organometallics* **1994**, *13*, 94.

[38] Molander, G. A.; Sommers, E. M.; Baker, S. R. *J. Org. Chem*. **2006**, *71*, 1563.

[39] a) Yoshida, M.; Gotou, T.; Ihara, M. *Tetrahedron Lett*. **2004**, *45*, 5573. b) Hayashi, S.; Hirano, K.; Yorinitsu, H.; Oshima, K. *J. Am. Chem. Soc*. **2008**, *130*, 5048.

[40] Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc*. **2004**, *126*, 15978.

[41] Li, C.-Y.; Wang, X.-B.; Sun, X.-L.; Tang, Y.; Zheng, J.-C.; Xu, Z.-H.; Zhou, Y.-G.; Dai, L.-X. *J. Am. Chem. Soc*. **2007**, *129*, 1494.

[42] Varghese, J. P.; Zouev, I.; Aufauvre, L.; Knochel, P.; Marek, I. *Eur. J. Org. Chem*. **2002**, *24*, 4151.

[43] Molander, G. A.; Sommers, E. M. *Tetrahedron Lett.* **2005**, *46*, 2345.

[44] Konoike, T.; Araki, Y. *Tetrahedron Lett.* **1992**, *33*, 5093.

[45] Buchwald, S. L; Grubbs, R. H. *J. Am. Chem. Soc*. **1983**, *105*, 5490.

[46] Muller, T.; Ansorge, M. *Tetrahedron* **1998**, 1457.

[47] Hong, B.; Woodcock, S. R.; Saito, S. K.; Ortega, J. V. *J. Chem. Soc., Dalton trans*., **1998**, 2615.

[48] Dyker, C. A.; Lavallo, V.; Donnadieu, B.; Bertrand, G. *Angew. Chem. Int. Ed*. **2008**, *47*, 3206.

[49] Lohr, S.; Averbeck, J.; Schurmann, M.; Krause, N. *Eur. J. Inorg. Chem*. **2008**, 552.

[50] Sato, I.; Matsueda, Y.; Kadowaki, K.; Yonekubo, S.; Shibata, T.; Soai, K. Helv. Chim. Acta **2002**, *85*, 3383.

[51] Kawasaki, T.; Sato, M.; Ishiguro, S.; Takahiro, S.; Yosuke, M.; Sato, I.; Nishino, H.; Inoue, Y.; Soai, K. *J. Am. Chem. Soc.* **2005**, *127*, 3274.

[52] Denmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed*. **2008**, *47*, 1560.

[53] Denmark, S. E. *Chimia* **2008**, *62*, 37.

[54] Gutmann, V. *The Donor-Acceptor Approach to Molecular Interactions*, Plenum, New York, **1978**, chap. 1.

[55] a) Holmes, I. P.; Kagan, H. B. *Tetrahedron Lett*. **2000**, *41*, 7453. b) Holmes, I. P.; Kagan, H. B. *Tetrahedron Lett*. **2000**, *41*, 7457.

[56] a) Nakajima, M.; Saito, M.; Hashimoto, S. *Chem. Pharm. Bull*. **2000**, *48*, 306; b) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc*. **1998**, *120*, 6419.

[57] a) Shimada, T.; Kina, A.; Hayashi, T. *J. Org. Chem*. **2003**, *68*, 6329; b) Shimada, T.; Kina, A.; Ikeda, S.; Hayashi, T. *Org. Lett.* **2002**, *4*, 2799.

[58] a) Malkov, A. V.; DufkovV, L.; Farrugia, L.; Kocovsky, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 3674; b) Malkov, A. V.; Bell, M.; Vassieu, M.; Bugatti, V.; Kocovsky, P. J. *Mol. Catal. A* **2003**, *196*, 179.

[59] a) Denmark, S. E.; Pham, S. M. *J. Org. Chem*. **2003**, *68*, 5045; b) Denmark, S. E.; Stavenger, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 8837; c) Denmark, S. E.; Stavenger, R. A.; Wong, K.-T.; Su, X. *J. Am. Chem. Soc.* **1999**, *121*, 4982; d) Denmark, S. E.; Stavenger, R. A.; Wong, K.-T. *Tetrahedron* **1998**, *54*, 10389; e) Denmark, S. E.; Stavenger, R. A.; Wong, K.-T. *J. Org. Chem.* **1998**, *63*, 918; f) Denmark, S. E.; Wong, K.-T.; Stavenger, R. A. *J. Am. Chem. Soc*. **1997**, *119*, 2333. g) Denmark, S. E.; Fujimori, S.; Pham, S. M. *J. Org. Chem.* **2005**, *70*, 10823.

[60] Denmark, S. E.; Barsanti, P. A.; Beutner, G. L.; Wilson, T. W. *Adv. Syn. Catal*. **2007**, *348*, 567.

[61] a) Tao, B.; Lo, M.-C.; Fu, G. *J. Am. Chem. Soc*. **2001**, *123*, 353. b) Nakajima, M.; Saito, M.; Uemura, M.; Hashimoto, S. *Tetrahedron Lett.* **2002**, *43*, 8827.

[62] Toda, F.; Tanaka, K. *Tetrahedron. Lett*. **1981**, *22*, 4669.

[63] The two terms need only be different with respect to catalyst dependence. Eq 1 represents only the simplest scenario. However, the fact that we observe no non-linear effect at low [catalyst] is consistent with a first order pathway under these conditions.

[64] Additionally, the low reactivity of the mono-phosphine oxide (**3.13**) would be more difficult to reconcile with the reservoir model. See Girard, C.; Kagan, H. B. *Angew.*

Chem. Int. Ed. **1998**, *37*, 2922.

[65] Selected examples: a) McCleland, B. W.; Nugent, W. A.; Finn, M. G.*J. Org. Chem*. **1998**, *63*, 6656. b) Jacobsen, E. N. *Acc. Chem. Res*. **2000**, *33*, 421.

[66] Cozzi, P. G.; Alesi, S., *Chem. Commun.* **2004**, 2448.

[67] Wagner, P. J.; Sedon, J. H.; Gudmundsdottir, A. *J. Am. Chem. Soc*. **1996**, *118*, 746

[68] Elsvier, C. J.; Stehouwer, P. M.; Westmijze, H.; Vermeer, P. *J. Org. Chem*. **1983**, *48*, 1103.

[69] http://pubs.acs.org | doi: 10.1021/ja9041127

[70] Otwinowski, Z.; Minor, W. *Methods in Enzymology*, **276**: *Macromolecular Crystallography, part A*, 307- 326, Carter, Jr. C. W.; Sweets, R. M. Editors, Academic Press.

[71] SIR97. (1999). A program for crystal structure solution. Altomare, A.; Burla, M.C.; Camalli, M.; Cascarano, G.L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A.G.G.; Polidori, G.; Spagna, R. *J. Appl. Cryst*. **1999**, *32,* 115-119.

[72] Sheldrick, G. M. (1994). SHELXL97. *Program for the Refinement of Crystal Structures.* University of Gottingen, Germany.

[73] Flack, H. D. *Acta Cryst.* **1983**, *A39*, 876-881.

[74] $R_W(F^2) = \{\Sigma w(|F_o|^2 - |F_c|^2)^2/\Sigma w(|F_o|)^4\}^{1/2}$ where w is the weight given each reflection. $R(F) = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|\}$ for reflections with $F_o > 4(\sigma(F_o))$. $S = [\Sigma w(|F_o|^2 - |F_c|^2)^2/(n - p)]^{1/2}$, where n is the number of eflections and p is the number of refined parameters.

[75] *International Tables for X-ray Crystallography* (**1992**). Vol. C, Tables 4.2.6.8 and

6.1.1.4, A. Wilson, J. C. editor, Boston: Kluwer Academic Press.

[76] Sheldrick, G. M. (**1994**). SHELXTL/PC (Version 5.03). *Siemens Analytical X-ray Instruments,* Inc., Madison, Wisconsin, USA.

[77] Wu, H.; Yu, J.; Spencer, J. B. *Org. Lett*. **2004**, *6*, 4675.

[78] Denmark, S. E.; Barsanti, P. A.; Beutner, G. L. Wilson, T. W. *Adv. Synth. Catal.* **2007**, *349*, 567. For two substrates [cis-bis-(benzyloxymethy)-oxirane and cis-bis-(1-naphthyl)-oxirane], propylene oxide appears to promote the reversal of the reaction. Thus, TLC analysis of the crude reaction mixture showed complete conversion, after addition of propylene oxide, only starting epoxide was recovered. We presume that in these cases $SiCl_4$ is transferred from the desired product to propylene oxide. Accordingly, in these cases the crude reaction product was added directly to silica gel

[79] Mio, M. J.; Kopel, L. C.; Braun, J. B.; Gadzikwa, T. L.; Hull, K. L.; Brisbois, R. G.; Markworth, C. J.; Grieco, P. A., *Org. Lett*, **2002**, *4*, 3199.

[80] Lara-Ochoa, F.; Espinosa-Perez, G. *Tetrahedron Lett*. **2007**, *48*, 7007.

[81] For electron-deficient arylalkynes, some over-reduced products (alkanes) were observed.

[82] Tao, B.; Lo, M.-C.; Fu, G. *J. Am. Chem. Soc*. **2001**, *123*, 353.

[83] Takenaka, N.; Sarangthem, R. S.; Captain, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 9708.