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1. Introduction

The addition of a 1,3-dipole to an alkene or alkyne is a prominent transformation in organic synthesis.[1] Over the past two decades the intense study of enantioselective 1,3-dipolar cycloaddition methodologies has provided organic chemists with the tools necessary to synthesize a variety of chiral heterocycles in highly enantioenriched forms.[2] The majority of advances in this area are a direct result of studies focusing on chiral Lewis acid-catalyzed or chiral metal-mediated 1,3-dipolar cycloaddition methodologies. It is important to note that even though the many dipoles possess very strong donor atoms it is still possible to carry out enantioselective Lewis acid-catalyzed dipolar cycloadditions. However, a large number of dipoles require highly basic conditions for their preparation and these conditions could potentially be deleterious for reactions mediated by Lewis acids. Strategies to address these potential drawbacks have been put forth in the literature. One of the more successful strategies among these is dipolar cycloadditions using organocatalysts. Several highly efficient and enantioselective dipolar cycloadditions using different types of organocatalysts have been recently reported in the literature.[3]

Dipoles can be classified as either allyl anion type or propargyl/allenyl anion type according to their structure (for classification of common 1,3 dipoles, see Table 1). Highly enantioselective 1,3-dipolar cycloadditions of both allyl anion and propargyl/allenyl anion type 1,3-dipoles are well-known at this point. Of the allyl anion type 1,3-dipoles, enantioselective methodologies have been developed for the cycloadditions of nitrones,[4] azomethine imines,[3c,f,5] azomethine ylides,[6] and carbonyl ylides.[7] Furthermore, chiral Lewis acid catalysis has made possible highly enantioselective cycloadditions of nitrilium and diazonium betaines (propargyl/allenyl type 1,3-dipoles), such as nitrile oxides,[8] nitrile imines,[9] diazoalkanes and diazoacetates.[10]

Over the years a variety of chiral Lewis acids have been evaluated for dipolar cycloadditions. The most successful of these have employed copper, silver, nickel, aluminum, zinc, and lanthanide Lewis acids, generally in combination with one of the privileged classes of chiral ligands such as the bisoxazolines, BINAPs, and Pyboxs. This chapter focuses on the use of copper Lewis acids in dipolar cycloadditions. Reactions with silver and nickel Lewis acids will be discussed in other chapters of this special issue.

Chiral copper(I) and (II) salts figure prominently in the development of enantioselective 1,3-dipolar cycloaddition reactions. In particular, chiral copper salts have been fundamental to the development of enantioselective 1,3-dipolar cycloadditions involving allyl anion type 1,3-dipoles that contain a nitrogen atom in the middle of the dipole (aza-allyl type 1,3-dipoles, Figure 1). Since the majority of enantioselective copper-catalyzed 1,3-dipolar cycloadditions involve aza-allyl type 1,3-dipoles, they will necessarily serve as the focus of this review.

The activation of the dipole or the dipolarophile in copper-catalyzed enantioselective cycloadditions of aza-allyl type 1,3-dipoles generally occurs via one of four primary pathways. Two modes of activation involve metal-dipole interactions (Figure 2), while the other two modes of activation involve metal-dipolarophile interactions (Figure 3). For stable aza-allyl type 1,3-dipoles, such as electron-deficient nitrones, coordination of the chiral copper salt to the dipole leads to lowering of the energy levels of the frontier molecular orbitals (FMOs) of the dipole (Figure 2, eq 1). This type of activation has been used to facilitate $LUMO_{dipole}-HOMO_{dipolarophile}$ interactions and is common when electron-rich alkenes are used as dipolarophiles. A second type of activation is common when glycine imines are used as precursors to *N*-metalated azomethine ylides. In this situation coordination of the glycine imine by the chiral copper salt facilitates deprotonation of the glycine imine to form a well-organized chiral *N*-metalated azomethine ylide complex, which can react with a variety of electron-deficient alkenes (Figure 2, eq 2). The third common mode of activation involves coordination of the chiral copper catalyst to a conjugated carbonyl of an electron-deficient alkene (Figure 3,eq 1). In this scenario the FMOs of the dipolarophile are lowered, facilitating $HOMO_{dipole}-LUMO_{dipolarophile}$ interactions. The final mode of activation with relevance to this review is the activation of alkynes. This type of activation involves coordination of the chiral copper catalyst to an alkyne (Figure 3, eq 2). Subsequent deprotonation of the copper−alkyne complex leads to the formation of a chiral copper acetylide that is activated toward cycloaddition with aza−allyl type 1,3-dipoles.

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Mukund Sibi hails from Bangalore, India. After undergraduate studies in Bangalore, he joined Hunter College, CUNY, and received his Ph.D. degree under the guidance of Prof. Robert Lichter. After postdoctoral studies he joined North Dakota State University in 1987, where he is currently James A. Meier Professor and a University Distinguished Professor. Prof. Sibi currently serves as the project director for the Center for Protease Research at North Dakota State University. Prof. Sibi has received several awards including the Arthur C. Cope Scholar award in 2008 from the American Chemical Society. His research interests include development of new asymmetric processes, free radical chemistry, and total synthesis of natural products.

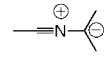
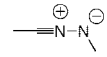
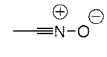
This review aims to summarize achievements of the many scientists who have been integral to the development of enantioselective copper-catalyzed 1,3-dipolar cycloaddition reactions.

2. Nitrone Cycloadditions

2.1. Reactions with Electron-Deficient Alkenes

1,3-Dipolar cycloaddition reactions of nitrones with electron-deficient alkenes allow for efficient syntheses of isoxazolidines with high degrees of regio- and stereocontrol.[11] In recent years many groups have reported chiral Lewis acid-catalyzed nitrone cycloadditions that give enantiomerically enriched isoxazolidine derivatives.[4a,d–m] At this point in the development of enantioselective nitrone cycloadditions, a variety of Lewis acid and chiral ligand combinations have been used with great success to access the *endo* isoxazolidine

Table 1. Classification of Common 1,3-Dipoles

Allyl Anion Type			
Nitrogen-centered		Oxygen-centered	
	Nitrones		Carbonyl Ylides
	Azomethine Imines		Carbonyl Imines
	Azomethine Ylides		Carbonyl Oxides
	Azimines		Nitrosimines
	Azoxy Compounds		Nitrosoxides
	Nitro Compounds		Ozone
Propargyl/Allenyl Anion Type			
Nitrilium Betaines		Diazonium Betaines	
	Nitrile Ylides		Diazoalkanes
	Nitrile Imines		Azides
	Nitrile Oxides		Nitrous Oxide

cycloadduct in high regio-, diastereo-, and enantioselectivity. Examples of chiral Cu(II) complexes that catalyze *endo* and enantioselective nitrone cycloadditions are included in this body of literature.

Saito and co-workers reported that the combination of $Cu(OTf)_2$ with aminoindanol-derived bis(oxazoline) ligand **4** efficiently promotes the cycloaddition of nitrones derived from aromatic aldehydes with 3-alkenoyl-oxazolidin-2-ones.[12] When *N*-crotonoyloxazolidinone **2** was used as the dipolarophile, cycloadditions of nitrones **1a-f** led to the formation of isoxazolidine cycloadducts *endo*-**5** and *exo*-**6** with moderate *endo* selectivity and high enantioselectivity for both *endo* and *exo* cycloadducts (Table 2, entries 1−6). Interestingly, the use of *N*-acryloyloxazolidinone **3** as the dipolarophile also gave a mixture of cycloadducts, but the *exo* cycloadduct **6** was the major product and no rationale for the reversal in diastereoselectivity is proposed (Table 2, entry 7). This methodology showed chiral Cu(II) salts to be competent catalysts for enantioselective nitrone cycloadditions, but left room for improvement due to the modest *endo*/*exo* selectivities that were observed.

Saito and co-workers also studied chiral bis(imine) ligand **7a**−**d**/$Cu(OTf)_2$ complexes as a potential solution to the moderate diastereoselectivities that were observed when bis(oxazoline) **4** was used as the chiral ligand in Cu(II)-catalyzed nitrone cycloadditions.[13] The aromatic imine subunit of the bis(imine) ligands was found to have a dramatic effect on the chemical yields and levels of enantioselectivity (Table 3, entries 1−4). Bis(imine) ligand **7c** was determined to be optimal on the basis of a model cycloaddition of α,*N*-diphenyl nitrone **1a** with *N*-crotonoyloxazolidinone **2**. The combination of $Cu(OTf)_2$ and **7c** gave the desired cycloadduct as a 91:9 (*endo*/*exo*) mixture in 94% yield and 90% *endo* ee (Table 3, entry 3). Surprisingly, the pentafluorophenyl bis(imine) derivative **7d** led to poor enantioselectivity (−13%) for the *endo* cycloadduct, but the diastereoselectivity was the highest for all the ligands surveyed (Table 3, entry 4). The scope of the $Cu(OTf)_2$/**7c**

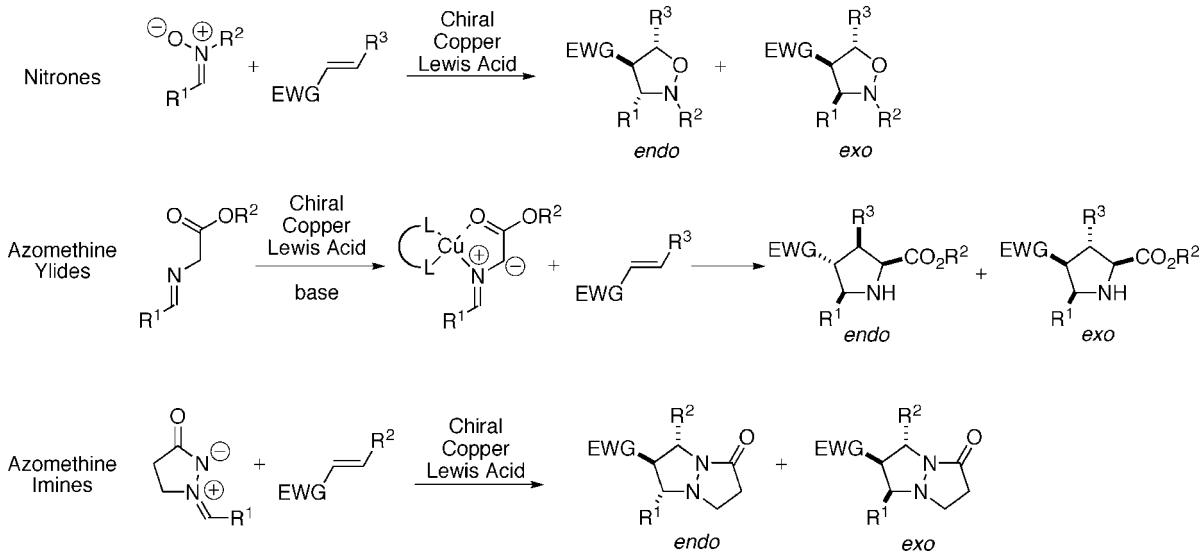


Figure 1. Common allyl anion type dipoles used in enantioselective copper-catalyzed 1,3-dipolar cycloadditions.

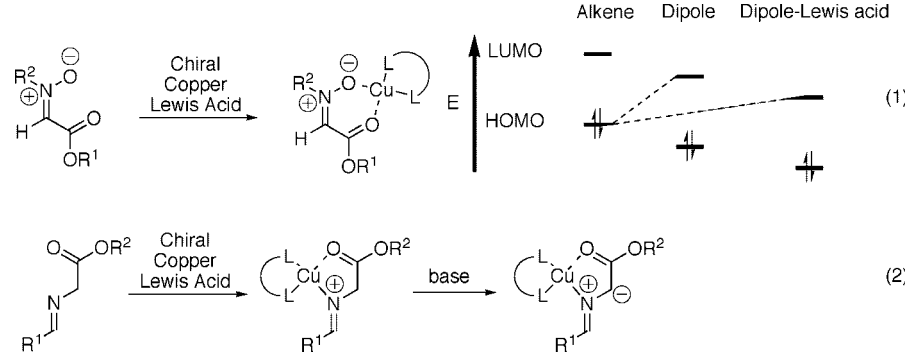


Figure 2. Common modes of dipole activation in copper-catalyzed 1,3-dipolar cycloadditions and the effect of activation on the relative energy of the dipole frontier molecular orbitals.

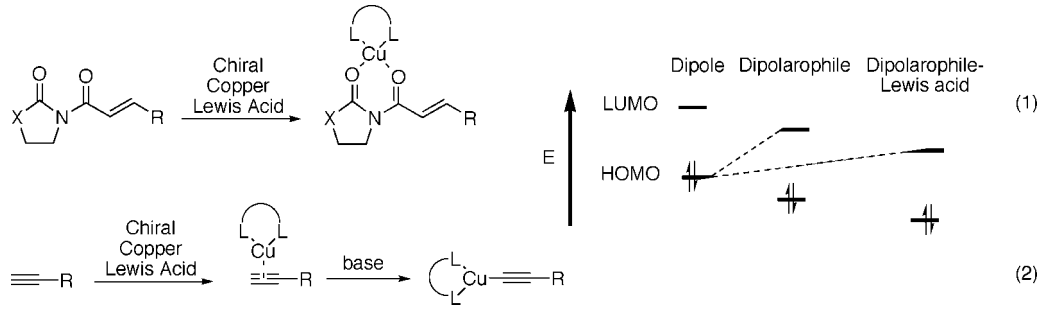


Figure 3. Common modes of dipolarophile activation in copper-catalyzed 1,3-dipolar cycloadditions and the effect of activation on the relative energy of the dipolarophile frontier molecular orbitals.

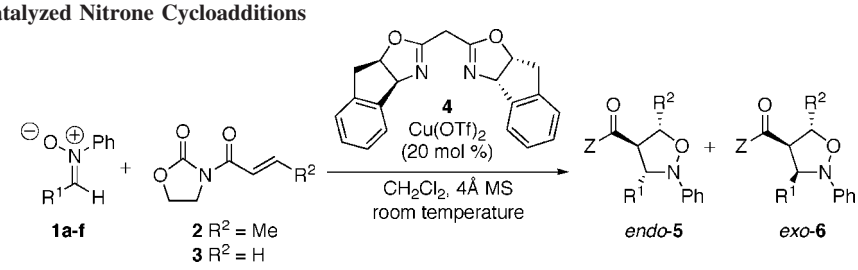
catalyst was demonstrated in cycloadditions of a variety of nitrones derived from aromatic aldehydes (Table 3, entries 5−8). In general the yields, *endo*/*exo* ratios, and enantioselectivities are excellent. However, the scope of the dipolarophile is limited to crotonate **2** as the cycloaddition of α,*N*-diphenyl nitrone with acrylate **3** led to poor *endo*/*exo* selectivity (56:44, entry 9) and reactions with additional substituted 3-alkenoyl-oxazolidin-2-ones were not reported.

Palomo and co-workers have since reported an additional copper catalyst−substrate combination for *endo*- and enantioselective nitrone cycloadditions.[14] The $Cu(OTf)_2$/*t*-Bu BOX **10**-catalyzed cycloadditions of nitrones with β-unsubstituted dipolarophile **8** are highly *endo* and enantioselective (Scheme 1, eq 1). In addition, cycloadditions of nitrones with β-substituted dipolarophile **13** are also efficient. The $Cu(OTf)_2$/*t*-Bu BOX **10**-catalyzed cycloaddition of **13** with nitrone **1a** is reported to give isoxazolidine **14** with 98:2 diastereoselectivity and 99% ee (Scheme 1, eq 2).

Iwasa et al. reported one example of a $Cu(OTf)_2$/4,5-bis(2-oxazolinyl)-(2,7-di-*tert*-butyl-9,9-dimethyl)-9*H*-xanthene(xabox)-catalyzed cycloaddition of α,*N*-diphenyl nitrone with 3-crotonoyl-2-oxazolidinone.[15] The corresponding isoxazolidine was isolated in 55% yield as an 86:14 *endo*/*exo* mixture of diastereomers. The enantiomeric excess for the *endo* cycloadduct was 77%. However, Mg(II) and Mn(II) Lewis acids were found to give improved yields and selectivities, and further investigation of the Cu(II)-catalyzed process has not been reported with the xabox ligands.

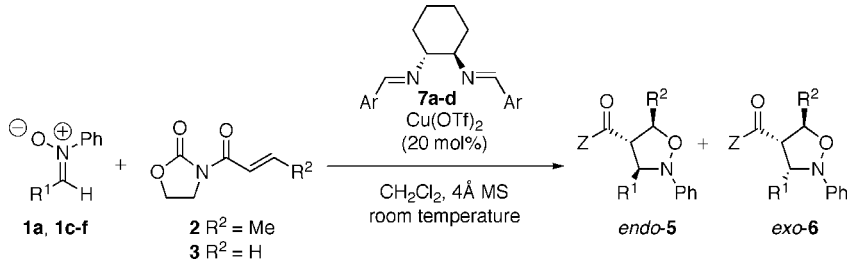
Saito and Palomo's chiral Cu(II)-catalyzed nitrone cycloadditions represent nice additions to the existing body of literature detailing *endo* and enantioselective nitrone cycloadditions, but the ability to perform highly *exo* and

Table 2. Cu(OTf)$_2$/4-Catalyzed Nitrone Cycloadditions



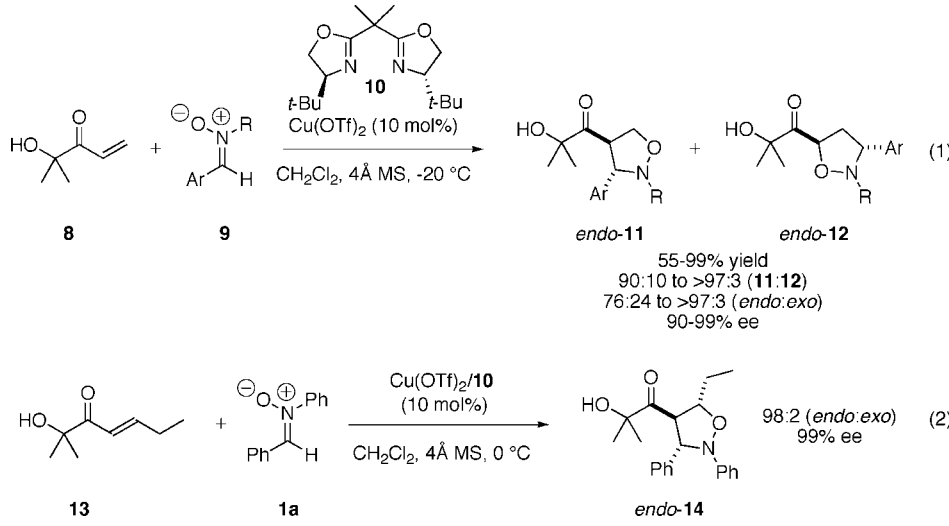
entry	R^1	R^2	yield (%)	*endo*/*exo*	*endo* ee (%)	*exo* ee (%)
1	Ph (**1a**)	Me	99	70:30	99	99
2	4-$CH_3OC_6H_4$ (**1b**)	Me	71	50:50	99	99
3	4- $CH_3C_6H_4$ (**1c**)	Me	97	70:30	99	99
4	4- $CF_3C_6H_4$ (**1d**)	Me	99	86:14	95	94
5	2-Naphthyl (**1e**)	Me	94	60:40	95	98
6	2-Furyl (**1f**)	Me	90	91:09	96	99
7	Ph (**1a**)	H	93	22:78	52	96

Table 3. Cu(OTf)$_2$/bis(imine) 7a−d-Catalyzed Nitrone Cycloadditions



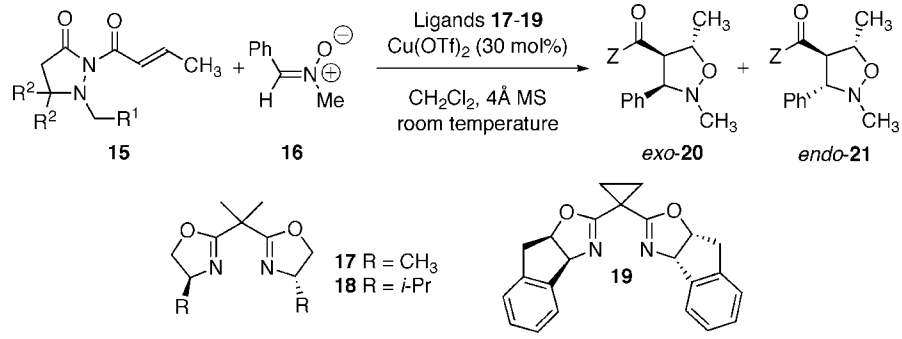
entry	R^1	R^2	Ar (Ligand)	yield (%)	*endo*: *exo*	*endo* ee (%)
1	Ph (**1a**)	Me	Ph (**7a**)	37	88:12	7
2	Ph (**1a**)	Me	2,6-$(MeO)_2C_6H_4$ (**7b**)	32	90:10	78
3	Ph (**1a**)	Me	2,6-$Cl_2C_6H_4$ (**7c**)	94	91:9	90
4	Ph (**1a**)	Me	C_6F_5 (**7d**)	84	95:5	−13
5	4- $CH_3C_6H_4$ (**1c**)	Me	2,6-$Cl_2C_6H_4$ (**7c**)	26	80:20	76
6	4- $CF_3C_6H_4$ (**1d**)	Me	2,6-$Cl_2C_6H_4$ (**7c**)	99	99:1	92
7	2-Naphthyl (**1e**)	Me	2,6-$Cl_2C_6H_4$ (**7c**)	90	92:08	97
8	2-Furyl (**1f**)	Me	2,6-$Cl_2C_6H_4$ (**7c**)	99	99:1	98
9	Ph (**1a**)	H	2,6-$Cl_2C_6H_4$ (**7c**)	90	56:44	90

Scheme 1



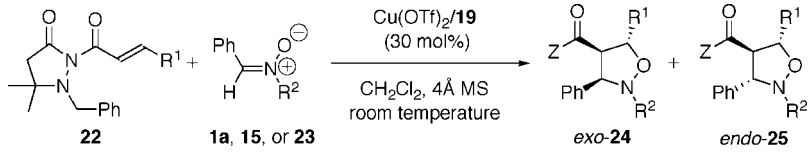
enantioselective nitrone cycloadditions remained a significant challenge. The Sibi group has since addressed this issue by using Cu(OTf)$_2$/chiral bis(oxazoline) complexes as catalysts for cycloadditions of nitrones with α,β-unsaturated pyrazolidinone imides.[16] A survey of common bis(oxazoline) ligands in a model cycloaddition of nitrone **16** with pyrazolidinone crotonate dipolarophiles **15** led to the identification of Cu(OTf)$_2$ and aminoindanol-derived bis(oxazoline) **19** as a combination that could provide highly *exo* and enantioselectivity cycloadditions (Table 4, entries 1−3). Originally it was believed that the pyrazolidinone template was responsible, in part, for the high level of *exo* selectivity, but an evaluation of N(1) and C(5) pyrazolidinone substitution showed that pyrazolidinone templates could be used to

Table 4. *exo* Selective Nitrone Cycloadditions: Effect of Bisoxazoline Ligands and Pyrazolidinone Substitution



entry	ligand	R^1	R^2	yield (%)	*exo*/*endo*	*exo* ee (%)
1	**17**	Ph	CH_3	96	90:10	75
2	**18**	Ph	CH_3	91	79:21	71
3	**19**	Ph	CH_3	94	96:04	98
4	**17**	CH_3	CH_3	96	92:08	78
5	**17**	1-Naphthyl	CH_3	93	89:11	86
6	**17**	Ph	$-(CH_2)_5-$	93	95:05	79
7	**17**	Ph	Bn	94	91:09	92

Table 5. $Cu(OTf)_2$/19-Catalyzed *exo* Selective Nitrone Cycloadditions



entry	R^1	R^2	yield (%)	*exo*/*endo*	*exo* ee (%)
1	CH_3	CH_3 (**15**)	94	96:04	98
2	CH_3	Bn (**23**)	92	93:07	99
3	CH_3	Ph (**1a**)	85	52:48	99
4	Et	CH_3 (**15**)	88	94:06	99
5	H	CH_3 (**15**)	85	66:34	99
6	CO_2Et	CH_3 (**15**)	44	67:33	85

amplify the level of enantioselectivity, but had minimal impact on the *exo*/*endo* selectivity (Table 4, entries 1, 4−7). Furthermore, a $Cu(OTf)_2$/**17**-catalyzed cycloaddition of nitrone **16** with oxazolidinone crotonate **2** was also highly *exo* selective, suggesting that the pyrazolidinone template was not the source of *exo* selectivity.

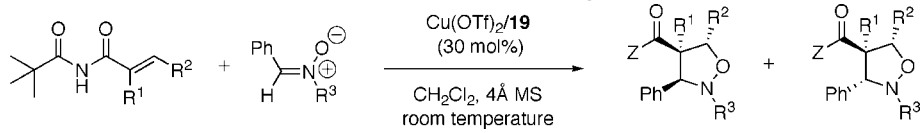
The scope of α,β-unsaturated pyrazolidinone imides and nitrones that can be used as dipolarophiles and dipoles in this methodology is modest, and some notable problems remain to be addressed. Diastereo- and enantioselectivities are high when nitrones derived from *N*-alkyl hydroxylamines are utilized (Table 5, entries 1 and 2), but the *exo*/*endo* selectivity was 1:1 when nitrone **1a**, which is derived from benzaldehyde and *N*-phenyl hydroxylamine, was used as the dipole (entry 3). β-Alkyl substituted α,β-unsaturated pyrazolidinone imides are excellent dipolarophiles, but pyrazolidinone acrylate and pyrazolidinone fumarate substrates lead to lower diastereoselectivity (compare entries 1 and 4 with entries 5 and 6). Although additional improvements in terms of substrate scope remain to be made, this methodology represents the first highly *exo* and enantioselective nitrone cycloadditions and clearly demonstrates the potential of chiral copper Lewis acids to advance the utility of enantioselective nitrone cycloadditions.

Highly *exo* and enantioselective nitrone cycloadditions are also possible when α,β-disubstituted α,β-unsaturated substrates are used as dipolarophiles. These reactions are particularly challenging for one primary reason. That is because common achiral auxiliaries, such as oxazolidinone, lead to poor reactivity and enantioselectivity due to poor control of rotamer geometry. The poor control of rotamer geometry is thought to be a result of undesirable $A^{1,3}$ interactions. The Sibi group reported a solution to this problem that utilizes the optimal catalyst from their previous study, $Cu(OTf)_2$/**19**, in combination with α,β-disubstituted acrylimides **26** as the dipolarophiles.[17] The $Cu(OTf)_2$/**19**-catalyzed cycloadditions of nitrones with a number of these templates give the corresponding cycloadducts *exo*-**27** and *endo*-**28** in moderate to good chemical yields with high enantioselectivity and good to excellent *exo*/*endo* ratios (Table 6). Two factors proved critical to the development of these cycloadditions reactions. First the $Cu(OTf)_2$/**19** catalyst provides for high *exo* and facial selectivity. Second, the N−H imide templates **26** effectively relieve $A^{1,3}$ interactions between the achiral auxiliary and the alkene moiety, thus providing the enhanced reactivity necessary for cycloadditions between nitrones and α,β-disubstituted α,β-unsaturated dipolarophiles. However, it should be noted that reactivity is still problematic. To achieve yields of >60% reaction times of up to 10 days are required in specific cases.

2.2. Reactions with Electron-Rich Alkenes

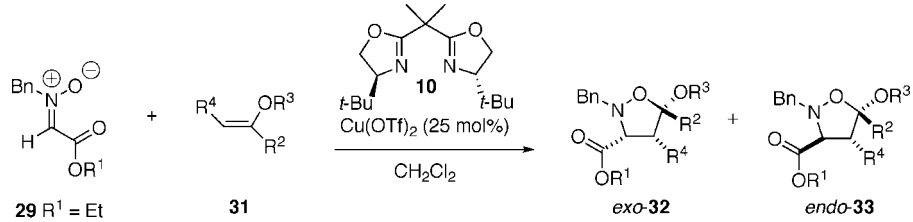
In contrast to the well-developed enantioselective cycloadditions between electron-deficient alkenes and electron-neutral or electron-rich nitrones, inverse electron-demand nitrone cycloadditions are much less prominent. Inverse electron-demand nitrone cycloadditions rely on interaction between the HOMO of the alkene and the LUMO of the nitrone. Thus, lowering the energy of the nitrone frontier

Table 6. Cu(OTf)$_2$/19-Catalyzed *exo* Selective Cycloadditions of Nitrones with α,β-Disubstituted Acrylamides



entry	R^1	R^2	R^3	yield (%)	*exo*/*endo*	*exo* ee (%)
1	Me	Me	Me (**15**)	60	99:01	94
2	Me	H	Me (**15**)	57	81:19	89
3	Me	Et	Me (**15**)	63	99:01	91
4	-$(CH_2)_3$-		Me (**15**)	82	99:01	92
5	-$(CH_2)_3$-		Bn (**23**)	89	99:01	94
6	-$(CH_2)_3$-		Ph (**1a**)	77	94:06	89

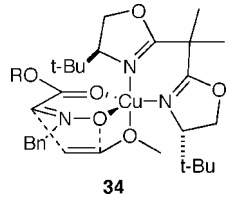
Table 7. Cu(OTf)$_2$/10-Catalyzed Inverse Electron-Demand Nitrone Cycloadditions



entry	R^1	R^2	R^3	R^4	yield (%)	*exo*/ *endo*	ee (*exo*/*endo* %)
1	Et	H	Et	H	83	77:23	89/16
2	Et	Me	Me	H	83	31:69	90/94
3	Et	H	-$(CH_2)_2$-		43	50:50	12/0
4	*t*-Bu	H	Et	H	52	50:50	0/0

molecular orbitals accelerates this type of 1,3-dipolar cycloaddition. Jørgensen and co-workers reported the first enantioselective copper-catalyzed inverse electron-demand 1,3-dipolar cycloaddition between nitrones and electron-rich alkenes.[18] A key feature of their work was the use of nitrone substrates that contain an ester that allows a well-organized complex to be formed upon bidentate coordination of the nitrone to a chiral copper(II) Lewis acid.

Cu(OTf)$_2$/*t*-Bu-BOX **10**-catalyzed cycloadditions between ethyl glyoxylate-derived nitrone **29** and vinyl ethers, such as ethyl vinyl ether and 2-methoxy propene, proceed in moderate to good yields and stereoselectivities (Table 7, entries 1 and 2). A pentacoordinated complex **34** of the Lewis acid, nitrone, and vinyl ether is proposed to account for the observed stereoselectivity in the cycloaddition of **29** with ethyl vinyl ether (Figure 4). In this complex, effective organization of the dipole and substrate is thought to occur by bidentate coordination of the nitrone and monodentate coordination of the vinyl ether. However, this methodology is limited by the lack of nitrones and vinyl ethers that lead to high yields and selectivities. The cycloadditions of nitrone **29** with 2,3-dihydrofuran and *t*-butyl glyoxylate-derived nitrone **30** with ethyl vinyl ether gave 1:1 ratios of the *exo* and *endo* cycloadducts with low enantioselectivities (Table 7, entries 3 and 4).



34

Figure 4. A pentacoordinated intermediate (**34**) proposed to account for the stereoselectivity observed for cycloaddition of nitrone **29** with ethyl vinyl ether.

It should be noted that Jørgensen and co-workers have also utilized a complementary chiral aluminum Lewis acid in inverse electron-demand nitrone cycloadditions.[19] The optimal (*R*)-3,3′-diphenyl-BINOL-AlMe complex allows nitrones that are not capable of bidentate coordination to be used in highly *exo* and enantioselective inverse electron-demand nitrone cycloadditions. Cycloadditions of a variety of α-aryl-*N*-phenyl nitrones and cyclic nitrones (3,4-dihydroisoquinoline *N*-oxides) with vinyl ethers proceed to give the corresponding cycloadducts with good to excellent *exo* and enantioselectivity.

2.3. Reactions with Alkynes

β-Lactams are synthetic targets of great biological importance owing to their presence in antibiotics, such as the penicillins and the cephalosporins.[20] β-Lactams are also useful as building blocks in synthetic organic chemistry.[21] The most famous use of a β-lactam as a synthetic intermediate is the semisynthesis of paclitaxel (Taxol), which employs a β-lactam to install the β-amino acid-derived side chain.[22] The importance of β-lactams in synthetic and medicinal chemistry has made methods to synthesize them a high priority. The Kinugasa reaction, which involves the reaction of a copper acetylide with a nitrone to form a β-lactam, is one approach that has received increased attention during the past decade.

At first glance one may question the fit of the Kinugasa reaction in a review of 1,3-dipolar cycloadditions, but an examination of the proposed reaction mechanism reveals a [3 + 2] cycloaddition to be fundamental for the transformation (Figure 5). The requisite copper acetylide **37** is initially formed by deprotonation of a copper-complexed alkyne. A subsequent 1,3-dipolar cycloaddition between a nitrone and the copper acetylide provides the five-membered intermediate

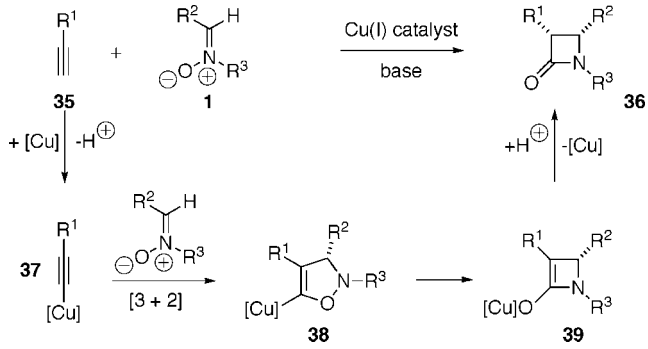
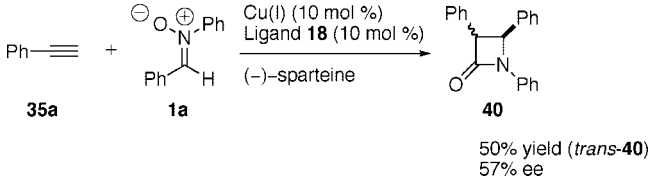


Figure 5. Proposed mechanism of the Kinugasa reaction.

Scheme 2



38. Rearrangement of **38** to the copper enolate intermediate **39** and subsequent protonation leads to the formation of the β-lactam **36**.

Despite the attractive features of the Kinugasa reaction as a method to synthesize β-lactams, direct catalytic and highly enantioselective variants of this transformation have remained rare since its discovery in 1972.[23] Miura reported the first catalytic enantioselective example of the Kinugasa reaction in 1995.[24] The reaction of phenylacetylene with α,*N*-diphenylnitrone **1a** in the presence of CuI (10 mol %), *i*-Pr BOX **18** (20 mol %), and (−)-sparteine as the base led to the formation of β-lactam *trans*-**40** in 50% yield with 57% ee (Scheme 2). The ratio of *trans*/*cis* isomers is not reported. Although Miura's work is limited in terms of yields, selectivities, and substrate scope, it serves as the groundwork for the highly selective variants of the Kinugasa reaction that are possible today.

Lo and Fu reported the first enantioselective Kinugasa reaction with broad substrate scope in 2002.[25] They identified the combination of a C_2-symmetric planar-chiral bis(azaferrocene) ligand **45** and CuCl to be a highly stereoselective catalyst for the Kinugasa reaction. One particularly interesting observation that came out of this work is that the yield and enantioselectivity of CuCl/**45**-catalyzed Kinugasa reactions is highly dependent on the electronic nature of the nitrone. The cycloaddition of a nitrone bearing an electron-rich *N*-aryl substituent led to the formation of β-lactam *cis*-**46** in high enantioselectivity and moderate yield (Table 8, entry 1). Conversely, the cycloaddition of a nitrone bearing an electron-deficient *N*-aryl substituent led to the formation of the corresponding β-lactam with lower enantioselectivity and improved yield (Table 8, entry 3). The scope of the process is sufficiently broad with respect to both the alkyne and nitrone components. Cycloadditions of a variety of nitrones with monosubstituted alkynes form the corresponding β-lactams in generally high *cis*/*trans* ratios and enantioselectivities (Table 8, entries 4−7). The majority of the nitrones employed in the survey of the reaction scope have an electron-rich *N*-aryl substituent, thus the isolated yields of the β-lactams are moderate.

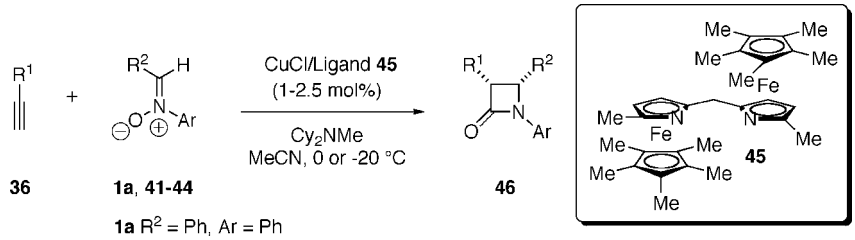
After the development of the enantioselective intermolecular Kinugasa reaction methodology, Shintani and Fu reported an enantioselective intramolecular variant of the Kinugasa reaction.[26] Interestingly, the optimal ligand from the previous study of the intermolecular Kinugasa reactions led to low yield and enantioselectivity in the reaction of alkyne−nitrone **47a**. The yield and enantioselectivity for the reaction of **47a** could be dramatically improved by employing phosphaferrocene-oxazoline **48** as the chiral ligand. The optimal catalyst combinations of CuBr with ligands **48** or **49** allowed for cycloadditions of a variety of alkyne−nitrone substrates **47a**−**c** to form tricyclic β-lactam derivatives **50a**−**c** in moderate to good yields and high enantioselectivities (Table 9).

The intramolecular Kinugasa reaction methodology was further extended by the development of conditions that allow α-allylated β-lactams to be prepared with the same catalyst (Scheme 3). Shintani and Fu showed that a highly diastereoselective allylation of the intermediate copper enolate (see intermediate **39**, Figure 5) was possible when the reaction was run in the presence of allyl iodide and a mixture of silyl enol ether **52** and KOAc as the base. When alkyne−nitrone **47a** was exposed to these reaction conditions, the corresponding α-allylated tricyclic β-lactam **53** was formed in 76% yield with 85% ee. This reaction sequence is quite impressive because of the formation of two carbon−carbon bonds, a carbon−nitrogen bond, a carbocyclic ring, a β-lactam, a carbonyl group, a tertiary stereocenter, and an all-carbon quaternary stereocenter.

A common problem associated with Cu(I)-catalyzed Kinugasa reactions is low chemical yield of the desired β-lactam presumably due to the Glaser oxidative coupling side-reaction.[27] Thus, the majority of Cu(I)-catalyzed Kinugasa reactions require inert reaction conditions. Tang and coworkers have reported a potential solution to the requirement for inert conditions. They reported the combination of $Cu(ClO_4)_2$ and pseudo-C_3-symmetric trisoxazoline **54** to be an efficient, air-stable, and water-tolerant catalyst for intermolecular Kinugasa reactions.[28] The use of $Cu(ClO_4)_2$/**54** as the catalyst for the reaction of nitrone **1a** with phenylacetylene led to the formation of β-lactam **40** as a 27:1 ratio of *cis*/*trans* isomers, in 64% yield with 83% ee for the *cis* isomer (Scheme 4). It should be noted that the authors propose a Cu(I) species to be the active catalyst in the reaction via an in situ reduction of the Cu(II) species by phenylacetylene.

Basak and Ghosh have developed a variant of the Kinugasa reaction that allows for straightforward synthesis of 3-exomethylene β-lactams.[29] The reaction of propargylic alcohol **55** with nitrones in the presence of CuI/L-proline resulted in good yields of the desired 3-exomethylene β-lactams **56** (Table 10). Unfortunately, the enantioselectivity for reaction of **55** with α,*N*-diphenylnitrone **1a** was poor, and enantioselectivities for reactions of additional substrates were not reported (Table 10, entry 1). It should be noted that the use of DMSO as the solvent is critical to the formation of the 3-exomethylene β-lactam **56** in favor of the corresponding *cis*-β-lactam **57**. Furthermore, the authors explain that the use of common amines as bases in this reaction leads only to formation of the *cis*-β-lactam, and that the amphoteric nature of the amino acid is necessary to promote elimination and formation of the 3-exomethylene β-lactam. The authors suggest an intermediate complex **58** with the carboxylic acid of proline oriented to provide the driving force for elimination as a reasonable explanation for the experimental observations (Figure 6).

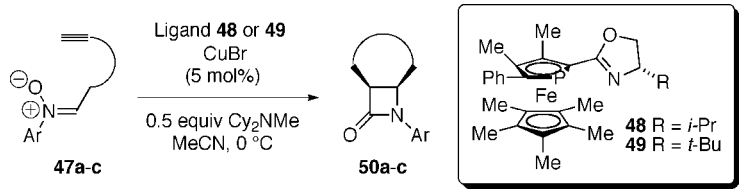
Table 8. Intermolecular Cu(I)/Bis(azaferrocene)-Catalyzed Kinugasa Reactions

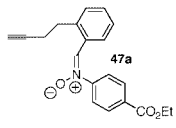
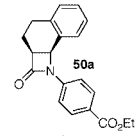
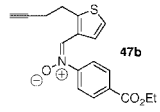
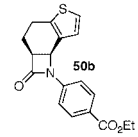
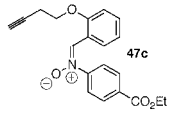
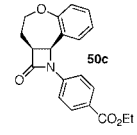


1a R^2 = Ph, Ar = Ph
41 R^2 = Ph, Ar = 4-(MeO)C_6H_4
42 R^2 = Ph, Ar = (EtO_2C)C_6H_4
43 R^2 = 4-(F_3C)C_6H_4, Ar = 4-(MeO)C_6H_4
44 R^2 = Cyclohexyl, Ar = 4-(MeO)C_6H_4

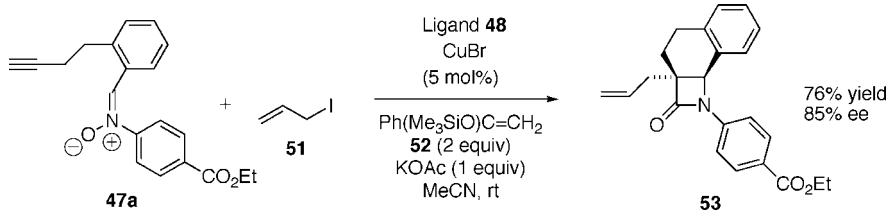
entry	R^1	nitrone	yield (cis, %)	*cis*/*trans*	ee *cis* (%)
1	Ph	**41**	53	95:05	85
2	Ph	**1a**	69	95:05	77
3	Ph	**42**	79	94:06	67
4	Ph	**43**	50	93:07	90
5	Ph	**44**	57	93:07	89
6	4-(F_3C)C_6H_4	**44**	57	>95:05	93
7	$PhCH_2$	**44**	43	71:29	73

Table 9. Intramolecular Cu(I)/Phosphaferrocene-Oxazoline-Catalyzed Kinugasa Reactions



Entry	Substrate	Ligand	Product	Yield (%)	ee (%)
1		**48**		74	88
2		**49**		64	90
3		**49**		68	91

Scheme 3



3. Azomethine Ylide Cycloadditions

The drive to synthesize pyrrolidine and proline derivatives in enantiomerically enriched form owes greatly to the incorporation of these heterocyclic cores into a variety of pharmaceuticals and alkaloids.[30] In addition, the use of numerous proline derivatives as chiral organocatalysts has increased the demand for these heterocycles in recent years.[31] Though a number of methods exist for the synthesis of chiral pyrrolidine and proline derivatives, few can match the synthetic potential of 1,3-dipolar cycloadditions of azome-

Scheme 4

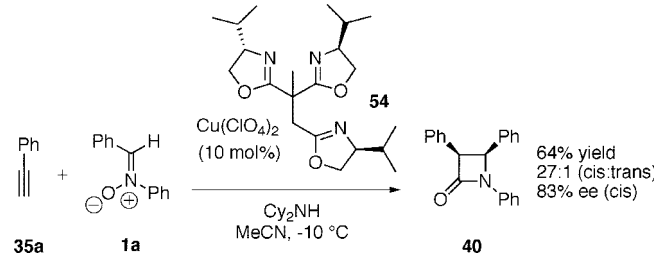
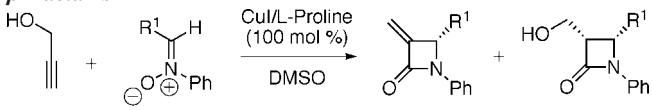


Table 10. CuI/L-Proline-Mediated Synthesis of 3-*exo*-methylene *β*-Lactams



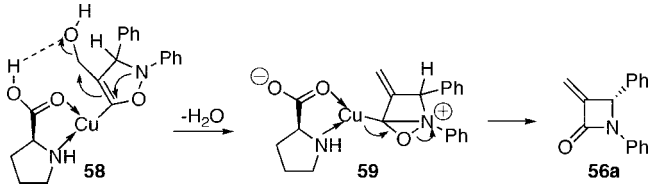
55 1a-b, 1f-g 56 57

entry	R^1	yield **57** (%)	ee **57** (%)	yield **58** (%)
1	Ph	71	15	10
2	2-Furyl	70	NA	10
3	2-Thienyl	71	NA	8
4	4-Methoxyphenyl	75	NA	10

thine ylides with alkenes. The power of azomethine ylide cycloadditions lies in the fact that pyrrolidine derivatives with up to four stereocenters can be generated in a single operation from readily available starting materials.

Many methods are available to generate azomethine ylides, but the in situ metalation of imino esters to form metalloazomethine dipoles has become the most widely used approach. The attractiveness of this method for azomethine ylide generation is due in large part to the ease with which catalytic enantioselective cycloadditions can be accomplished. Metalation of an α-imino ester with a chiral metal complex results in the formation of a well-organized ligand/metal/azomethine ylide complex that, in many cases, will add to electron-deficient alkenes with high degrees of regio-, diastereo-, and enantioselectivity. The first reports of metal-mediated enantioselective azomethine ylide cycloadditions came from Grigg and co-workers in the early to mid-1990s. Their work showed that combinations of $CoCl_2$ with a chiral aminoalcohol and AgOTf with a chiral bisphosphine effectively promote enantioselective azomethine ylide cycloadditions.[32] However, stoichiometric amounts of the chiral metal complexes were used in Grigg's studies, and it was not until 2002 that the stage was set for efficient catalytic, enantioselective azomethine ylide cycloadditions to emerge.

Zhang and co-workers reported the first catalytic enantioselective cycloadditions of azomethine ylides using a combination of AgOAc and the chiral bisphosphine **62** as the catalyst precursors (Figure 7, eq 1).[33] They demonstrated that chiral Ag(I)-catalyzed azomethine ylide cycloadditions could be used to prepare enantioenriched pyrrolidines from a variety α-imino ester and electron-deficient alkene substrates. Subsequent studies have led to the development of additional chiral ligands that improve the substrate scope, reaction conditions, and/or selectivity of chiral Ag(I)-catalyzed azomethine ylide cycloadditions. Of particular interest are Schreiber's application of (*S*)-QUINAP ligand **65** that allows synthesis of pyrrolidines bearing a *tert*-alkyl amino stereocenter (Figure 7, eq 2)[34] and the use of a chiral ferrocene-derived N,P ligand **67** by Zeng and Zhou that allows the AgOAc-catalyzed cycloadditions to proceed in the absence of added amine base (Figure 7, eq 3).[35] In a more recent work Zhou and co-workers reported a new class



58 59 56a

Figure 6. Proposed role of L-proline in the formation of 3-*exo*-methylene *β*-lactams.

of N,P ligands (**69** and **70**) that lead to nearly complete reversal of enantioselectivity based on the hydrogen-bonding ability of the ligand amino functionality (Figure 7, eq 4).[36]

Each of the Ag(I)-catalyzed azomethine ylide cycloadditions described above result in the selective formation of the *endo* pyrrolidine cycloadduct in high enantioselectivity, however access to corresponding *exo* isomer is currently not possible when chiral Ag(I) catalysts are employed. In addition, the use of α,α-diphenylprolinol[37] and Zn(II)/chiral bis(oxazoline)[38] complexes as catalysts for azomethine ylide cycloadditions with α,*β*-unsaturated aldehydes or acrylates and fumarates, respectively, also results in the formation of *endo* cycloadducts. A complementary catalyst is, therefore, necessary to access the corresponding *exo* cycloadducts in high yields and stereoselectivities. Chiral Cu(I) and Cu(II) complexes serve to effectively address this limitation of Ag(I)-catalyzed azomethine ylide cycloadditions.

Komatsu reported that $Cu(OTf)_2$-BINAP **74** and $Cu(OTf)_2$-SEGPHOS **75** catalyze the *exo* and enantioselective cycloadditions of azomethine ylide **72** with *N*-methylmaleimide and *N*-phenylmaleimide (Table 11).[39] The authors propose transition states **78** and **79** to account for the observed *exo* selectivity (Figure 8). Steric repulsion between the maleimide nitrogen substituent and the phenyl groups on the phosphorus atom of the chiral phosphine ligand in transition state **79** is thought to favor transition state **78** and lead to formation of the *exo* cycloadduct. These transition state models are further supported by the observation that reactions with *N*-phenylmaleimide gave higher *exo* selectivity than reactions with *N*-methylmaleimide, presumably due to the larger steric volume of the *N*-phenyl substituent (Table 11, compare entries 1 and 3 with entries 2 and 4). Although this work is noteworthy as the initial example of catalytic *exo* and enantioselective azomethine ylide cycloadditions, drawbacks to the Cu(II)-BINAP and Cu(II)-SEGPHOS catalysts exist. Foremost among the drawbacks is that the *exo*:*endo* ratios decrease when acyclic dipolarophiles are utilized. In the most selective example the $Cu(OTf)_2$-SEGPHOS-catalyzed cycloaddition of **72** with fumaronitrile **80** gave a 63:37 mixture of *exo*/*endo* cycloadducts in 54% yield (92% ee *exo*, 83% ee *endo*, Scheme 5). $Cu(OTf)_2$-BINAP-catalyzed cycloadditions of **72** with diethyl fumarate and fumaronitrile were *endo* selective.

Zhang addressed the need for a chiral copper catalyst that could generate *exo* pyrrolidine cycloadducts from acyclic dipolarophiles and azomethine ylides by using a combination of $CuClO_4$ and the ferrocene-derived phosphino-oxazoline ligand **85** (Table 12).[40] $CuClO_4$/**85**-catalyzed cycloadditions of a variety of azomethine ylides **83** with acrylate and maleate dipolarophiles proceed to afford the cycloadducts *exo*-**86** in good yields with excellent diastereo- and enantioselectivities.

The *exo* and enantioselective copper-catalyzed azomethine ylide cycloadditions have been described in the previous paragraphs, but the *endo* and enantioselective complements have also been reported. Carretero and co-workers reported the combination of $Cu(CH_3CN)_4ClO_4$ and Fesulphos ligand **90** to be a remarkable catalyst for *endo* and enantioselective cycloadditions of azomethine ylides with a variety of electron-deficient alkenes.[41] In the presence of $Cu(CH_3CN)_4ClO_4$/**90** aryl imines of glycine methyl ester react with *N*-phenylmaleimide to give the corresponding *endo* pyrrolidinones in nearly complete diastereo- and enantioselectivity (Figure 9, eq 1). In addition, azomethine ylides bearing an

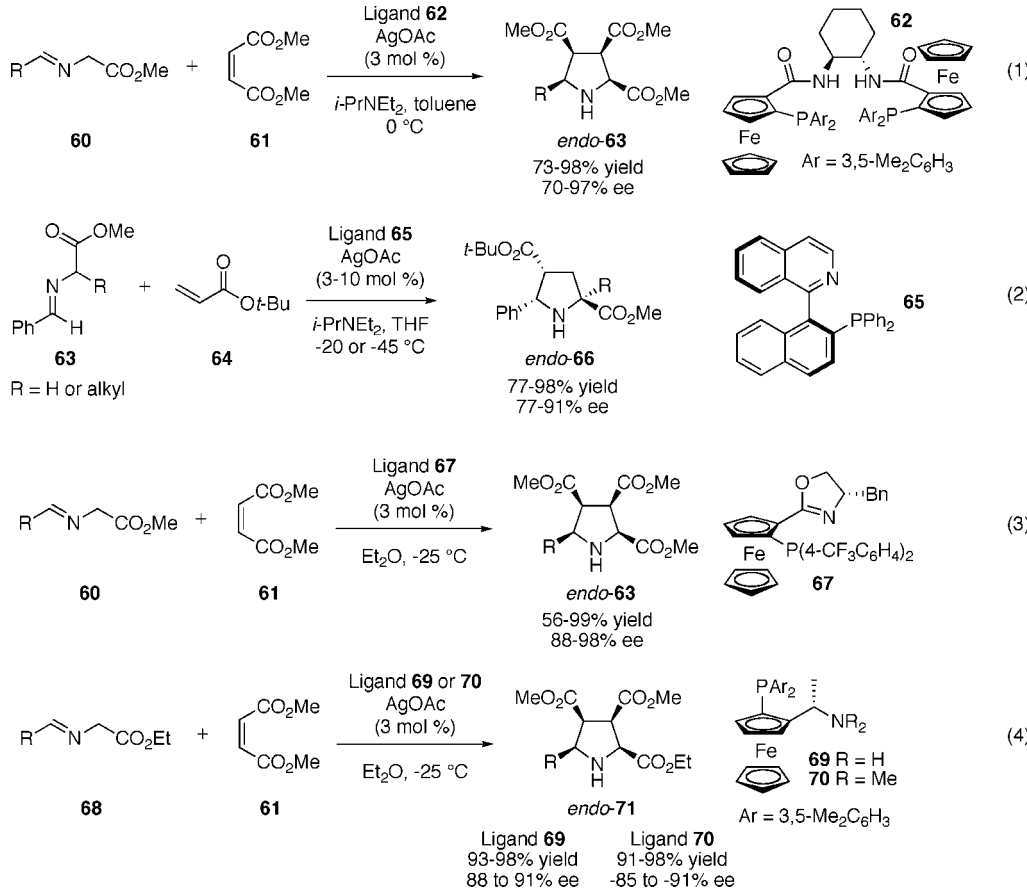
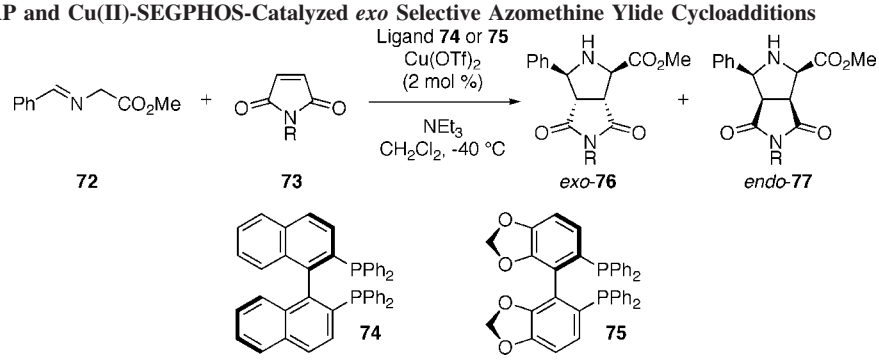


Figure 7. Summary of enantioselective Ag(I)-catalyzed azomethine ylide cycloadditions.

Table 11. Cu(II)-BINAP and Cu(II)-SEGPHOS-Catalyzed *exo* Selective Azomethine Ylide Cycloadditions



entry	ligand	R	yield (%)	*exo*:*endo*	*exo* ee (%)
1	**74**	Ph	71	>95:05	64
2	**75**	Ph	78	89:11	72
3	**74**	Me	64	72:28	55
4	**75**	Me	64	86:14	62

additional α-substituent and ketimine-derived azomethine ylides are also effective dipoles, leading to the formation of pyrrolidinones containing a *tert*-alkylamino stereocenter at the C-2 or C-5 position respectively (Figure 9, eq 2 and 3). The $Cu(CH_3CN)_4ClO_4$/**90** catalyst is also selective in azomethine ylide cycloadditions that employ acyclic dipolarophiles. For example, the cycloaddition of the azomethine ylide derived from **72** with dimethyl fumarate gives the pyrrolidine cycloadducts as a 90:10 *endo*/*exo* mixture in 89% yield with 99% ee for the *endo* isomer (Figure 9, eq 4). The Cu(I)−Fesulphos catalyst system also allows azomethine ylide cycloadditions to monoactivated alkenes. The most striking example is the cycloaddition of **72**-derived azomethine imine with methacrolein to form a pyrrolidine bearing an all-carbon quaternary stereocenter at C-4 in 48% yield with nearly complete *endo* selectivity (Figure 9, eq 5). Additional dipolarophiles, such as dimethyl maleate, fuma-

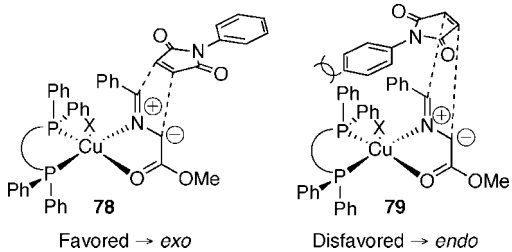


Figure 8. Transition states proposed to account for *exo* selectivity in the cycloaddition of **72** with *N*-phenylmaleimide.

Scheme 5

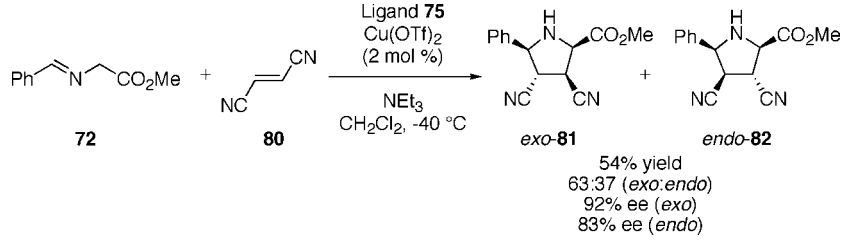
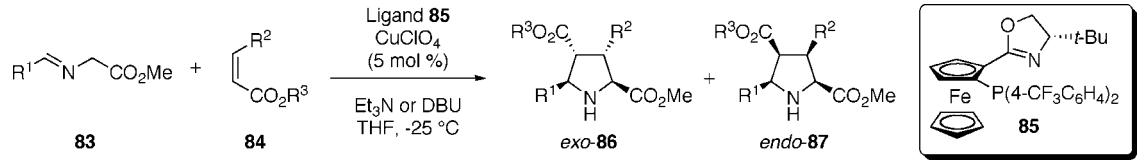


Table 12. $CuClO_4$/85-Catalyzed *exo* Selective Azomethine Ylide Cycloadditions



entry	R^1	R^2	R^3	*exo*:*endo*	yield of *exo*-**86** (%)	ee of *exo*-**86** (%)
1	Ph	H	*t*-Bu	95:05	65	84
2	*p*-Cl-C_6H_4	H	*t*-Bu	96:04	85	91
3	*p*-MeO-C_6H_4	H	*t*-Bu	97:03	82	91
4	*p*-NC-C_6H_4	H	*t*-Bu	95:05	84	91
5	2-naphthyl	H	*t*-Bu	98:02	84	90
6	*p*-Cl-C_6H_4	CO_2Me	Me	98:02	87	93

ronitrile, methyl acrylate, and β-nitrostyrene, are also competent in this methodology. However, the diastereoselectivities are highly substrate dependent.

Carretero and co-workers have also developed polymer-supported derivatives of the Fesulphos ligands.[42] The performance of the optimal polystyrene-supported Fesulphos derivative in Cu(I)-catalyzed enantioselective cycloadditions of azomethine ylides with electron-deficient alkenes was comparable in terms of yields and selectivities to the nonsupported Fesulphos ligand. The authors also showed that

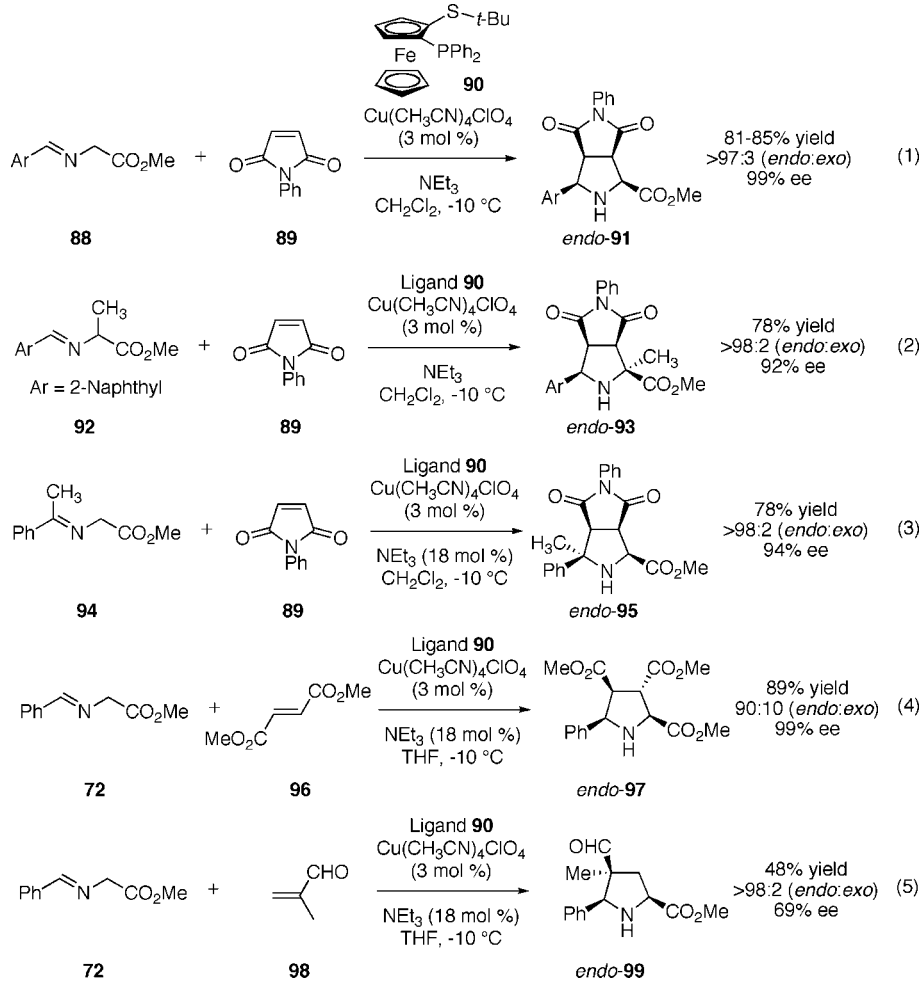


Figure 9. Overview of Cu(I)−Fesulphos **90**-catalyzed azomethine ylide cycloadditions.

Scheme 6

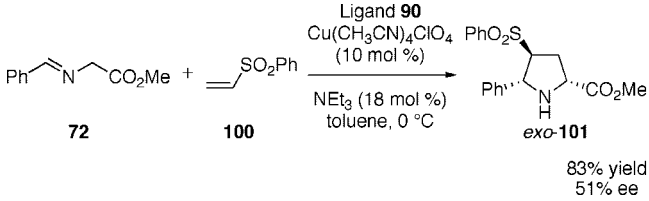
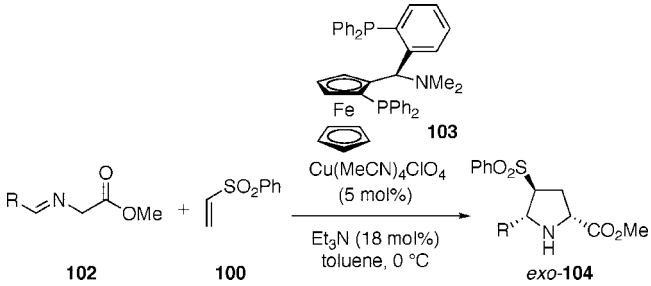


Table 13. Cu(I)/Taniaphos-Catalyzed Cycloadditions of Azomethine Ylides with Phenyl Vinyl Sulfone

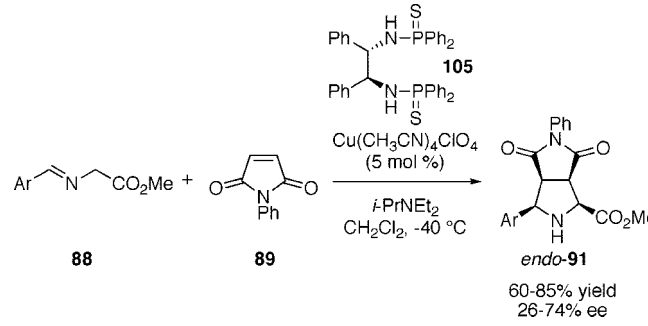


entry	R	yield (%)	ee (%)
1	4-FC_6H_4	91	82
2	3-$FC_{>6}H_4$	83	85
3	4-$MeOC_6H_4$	71	84
4	2-naphthyl	71	65
5	cyclohexyl	50	69

the polystyrene-supported Fesulphos/Cu(I) catalyst could be recovered and reused with no detrimental effects to reactivity or selectivity.

Despite the broad utility of the Cu(I)−Fesulphos catalyst system in enantioselective azomethine ylide cycloadditions, there are some substrates for which it is not ideal. For example, the $Cu(CH_3CN)_4ClO_4$/**90**-catalyzed cycloaddition of *N*-benzylideneglycine methyl ester **72** with phenyl vinyl sulfone **100** proceeds to give the corresponding *exo*-pyrrolidine **101** in high yield, but with moderate enantioselectivity (Scheme 6). However, Carretero and co-workers discovered that a combination of $Cu(CH_3CN)_4ClO_4$ and Taniaphos ligand **103** led to a more active and selective catalyst for cycloadditions of azomethine ylides with vinyl sulfones.[43] A variety of azomethine ylides react with phenyl vinyl sulfone in the presence of 5 mol % $Cu(CH_3CN)_4ClO_4$/**103** to give the corresponding pyrrolidines in moderate to high yields with moderate to good enantioselectivities (Table 13).

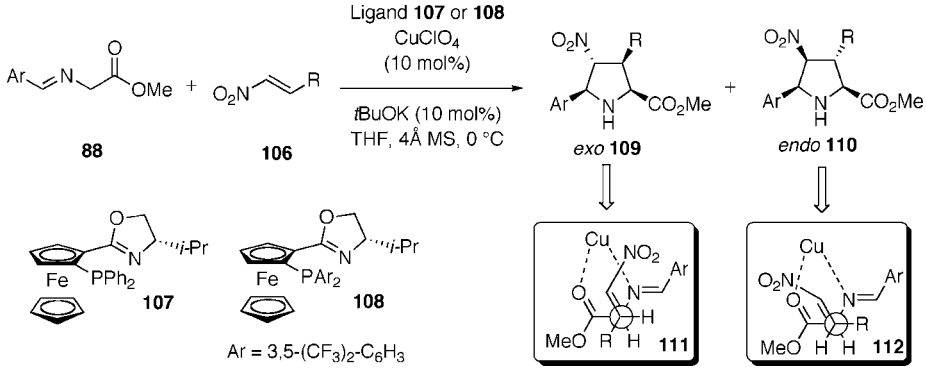
Scheme 7



An additional example of Cu(I)-catalyzed 1,3-dipolar cycloadditions of azomethine ylides bears mention at this point. Shi used the chiral thiophosphoramide ligand **105** as the source of chirality in $Cu(CH_3CN)_4ClO_4$-catalyzed cycloadditions of azomethine ylides with *N*-aryl and *N*-alkylmaleimides.[44] The $Cu(CH_3CN)_4ClO_4$/**105** catalyst system is reported to be completely *endo* selective, but the observed enantioselection is generally moderate (Scheme 7).

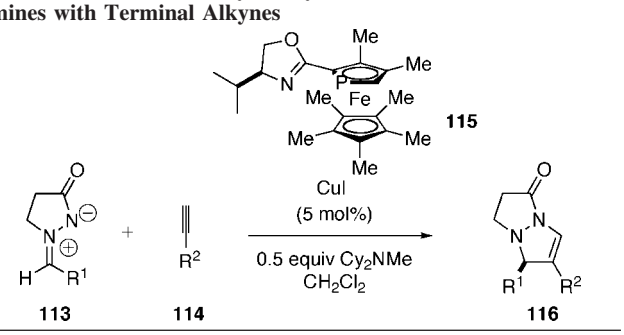
To this point a variety of chiral Cu(I) and Cu(II) catalyst systems have been discussed that are effective for either *exo* or *endo* selective azomethine ylide cycloadditions. However, a catalyst system that could be used to access both *exo* and *endo* cycloadducts remained elusive until recently. Hou and co-workers have utilized an interesting approach that allows access to either diastereomer on the basis of the electronic nature of the phosphorus substituents in a ferrocene-derived P,N ligand scaffold to address this issue.[45] $CuClO_4$/**107**-catalyzed cycloadditions between azomethine ylides and nitroalkenes **106** are highly *exo* and enantioselective (Table 14, entries 1−6). Alternatively, $CuClO_4$/**108**-catalyzed cy-

Table 14. Cu(I)-P,N-Ferrocene-Catalyzed Cycloadditions of Azomethine Ylides with Nitroalkenes



entry	Ar	R	ligand	*exo*/*endo*	yield (%)	*exo* ee (%)	*endo* ee (%)
1	Ph	Ph	**107**	only *exo*	87	95	
2	Ph	4-NO_2−C_6H_4	**107**	only *exo*	70	96	
3	Ph	4-MeO-C_6H_4	**107**	only *exo*	77	96	
4	Ph	*i*-Pr	**107**	only *exo*	74	98	
5	4-MeO-C_6H_4	Ph	**107**	89:11	96	97	
6	2-naphthyl	Ph	>**107**	92:08	92	92	
7	Ph	Ph	**108**	14:86	85		98
8	Ph	4-MeO-C_6H_4	**108**	30:70	79		95
9	Ph	*i*-Pr	**108**	06:94	88		97
10	4-MeO-C_6H_4	Ph	**108**	18:82	79		96
11	2-naphthyl	Ph	**108**	19:81	98		97

Table 15. Cu(I)/115-Catalyzed Cycloadditions of Azomethine Imines with Terminal Alkynes



entry	R^1	R^2	temp (°C)	yield (%)	ee (%)
1	Ph	CO_2Et	room temp	98	90
2	4-FC_6H_4	CO_2Et	room temp	99	95
3	*n*-pentyl	CO_2Et	room temp	92	82
4	cyclohexyl	CO_2Et	room temp	94	96
5	Ph	CONMePh	room temp	100	94
6	Ph	4-$EtO_2CC_6H_4$	room temp	77	88
7[a]	Ph	Ph	45	73	88
8[b]	Ph	*n*-pentyl	45	63	74

[a] Regioselectivity = 5.6:1. [b] Regioselectivity = 6.6:1.

cloadditions of identical substrates result in selective formation of the *endo* cycloadducts **110** with excellent enantioselectivities (Table 14, entries 7−11). It should be noted that the only difference between ligands **107** and **108** are the aryl substituents on the phosphorus atom of each ligand. An electron-neutral aryl substituent (Ar = Ph) is proposed to lead the *exo* approach of the dipole via transition state **111**, while an electron-deficient aryl substituent (Ar = 3,5-$(CF_3)_2$-C_6H_3) leads to *endo* approach of the dipole through transition state **112**. Hou's work places chiral copper catalysis at the forefront of enantioselective azomethine ylide cycloadditions. However, the ability to extend the reversal of diastereoselectivity to additional dipolarophiles remains a significant goal that has yet to be addressed.

4. Azomethine Imine Cycloadditions

4.1. Reactions with Alkynes

The final aza-allyl type dipole to be utilized in a catalytic enantioselective process is the azomethine imine. Azomethine imines react with copper acetylides in a manner similar to the reactions of azides and nitrones with copper acetylides. In 2003 Shintani and Fu demonstrated that not only were reactions of azomethine imines with alkynes efficiently catalyzed by Cu(I) salts, but the reactions could also be rendered highly enantioselective.[46] The combination of CuI and phosphaferrocene−oxazoline ligand **115** proved optimal in [3 + 2] cycloadditions of 3-oxopyrazolinin-1-ium-2-ides **113**, derived from pyrazolidin-3-ones and aldehydes, with terminal alkynes (Table 15). High yields and enantioselectivities of the resulting bicyclic heterocycles **116** are observed when a variety of azomethine imines and terminal alkynes are employed as substrates. Azomethine imines derived from both aromatic and aliphatic aldehydes are tolerated, while alkynes bearing electron-withdrawing substituents provide optimal reactivity and enantioselectivity. Selected alkynes without an electron-withdrawing substituent require more forcing reaction conditions that lead to lower enantioselectivity in one case and 6:1 to 7:1 regioisomeric ratios (Table 15, entries 7 and 8).

Fu's azomethine imine/alkyne cycloaddition strategy has been extended to the kinetic resolution of azomethine imines **117** that contain a stereocenter at the 5-position of the pyrazolidinone core (Table 16).[47] The authors determined that phosphaferrocene−oxazoline **119** was superior to **115** in terms of selectivity and allowed the catalyst loading to be decreased to 1 mol %. CuI/**119** proved to be a remarkable catalyst for the kinetic resolution of azomethine imines derived from a variety of aldehydes. Selectivity factors ranged from 15 for an azomethine imine derived from

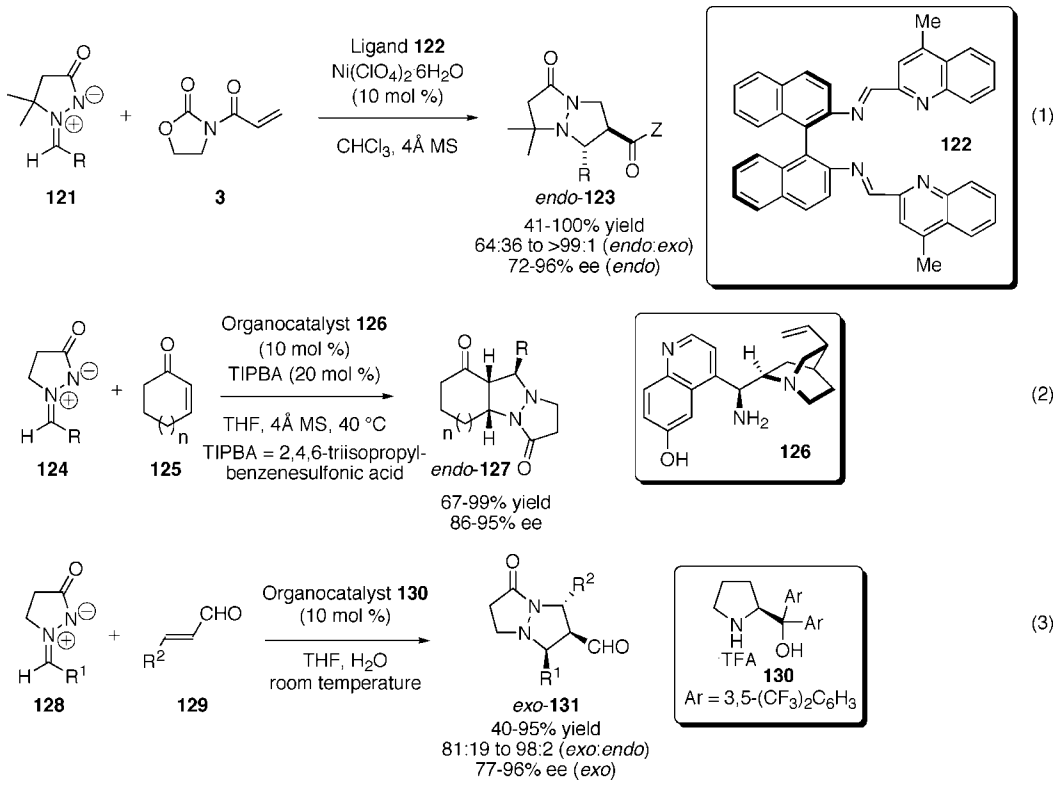
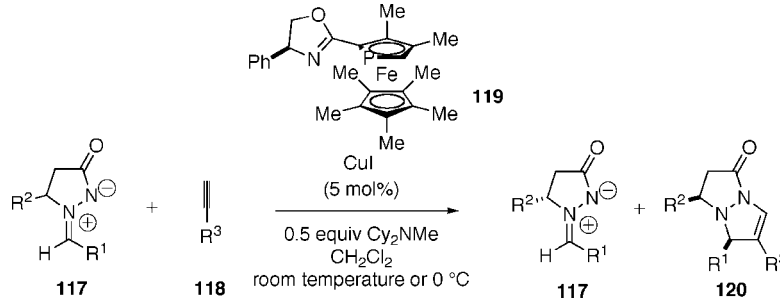


Figure 10. Summary of catalytic, enantioselective cycloadditions of azomethine imines with electron-deficient alkenes.

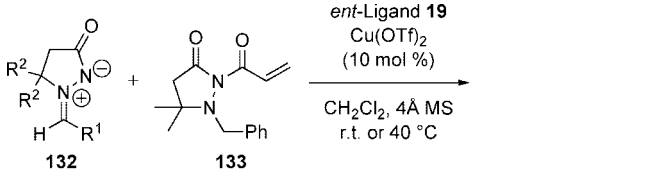
Table 16. Cu(I)/119-Catalyzed Kinetic Resolution of Azomethine Imines



entry	R^1	R^2	R^3	s^a	ee **117** (%)	yield **117** (%)
1	Ph	Ph	CO_2Et	53	99	42
2	5-Me-2-Furyl	Ph	CO_2Et	96	95	48
3	cyclohexyl	Ph	CO_2Et	15	91	36
4	Ph	2-thienyl	CO_2Et	15	98	31
5	Ph	*i*-Pr	CONMePh	51	98	40

[a] s = selectivity factor = [rate of fast-reacting enantiomer/rate of slow-reacting enantiomer].

Table 17. $Cu(OTf)_2$/19-Catalyzed *exo* Selective Azomethine Imine Cycloadditions



entry	R^1	R^2	yield (%)	*exo*:*endo*	*exo* ee (%)
1	Ph	H	79	>96:04	95
2	Ph	Me	90	88:12	94
3[a]	Ph	$-(CH_2)_5-$	65	86:14	95
4	4-$MeOC_6H_4$	Me	81	96:04	98
5	4-ClC_6H_4	Me	82	92:08	98
6	2-ClC_6H_4	Me	89	94:06	98
7[b]	*i*-Pr	Me	72	88:12	87

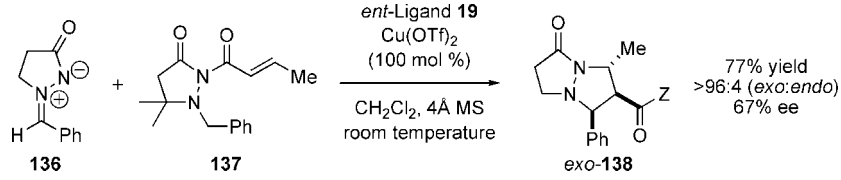
[a] No 4 Å MS. [b] Run with 20 mol % loading of $Cu(OTf)_2$/**19**.

cyclohexane carboxaldehyde to 96 for an azomethine imine derived from 5-methylfurfural when ethyl propiolate was used as the dipolarophile (Table 16, entries 1−3). In addition, kinetic resolutions of azomethine imines bearing aryl, heteroaryl, and branched aliphatic substituents are also highly selective (s = 15−76) (Table 16, entries 1−5). The only apparent limitations to this methodology are low selectivities (s < 5) for kinetic resolutions of C4-substituted azomethine imines as well as linear aliphatic C5-substituted azomethine imines.

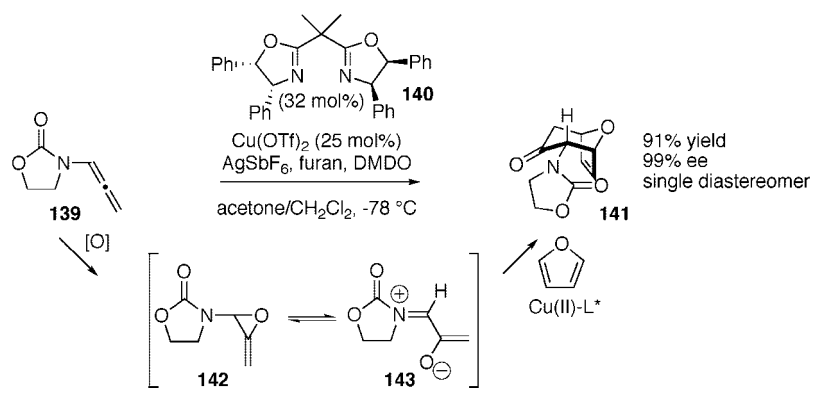
4.2. Reactions with Electron-Deficient Alkenes

Over the past two years, reports of enantioselective cycloadditions of azomethine imines with electron-deficient olefins have begun to emerge.[3c,f,5] The synthesis of the resulting heterocycles in enantioenriched forms is challenging because of the multiple contiguous stereocenters that must be controlled in the 1,3-dipolar cycloaddition reactions. Suga reported a chiral Ni(II)-catalyzed cycloaddition of azomethine imines to oxazolidinone acrylate that provides access to the corresponding *endo* cycloadducts (Figure 10, eq 1).[5] Chen

Scheme 8



Scheme 9



and co-workers have used an organocatalyst to prepare *endo* cycloadducts from azomethine imines and cycloalkenes (Figure 10, eq 2).[3f] In addition Chen's group has also reported the cycloaddition of azomethine imines with α,β-unsaturated aldehydes to form the corresponding *exo* cycloadducts (Figure 10, eq 3).[3c]

The Sibi group has since examined Cu(II)-catalyzed *exo* and enantioselective cycloadditions of azomethine imines.[48] The combination of $Cu(OTf)_2$ and aminoindanol-derived bis(oxazoline) *ent*-**19** efficiently catalyzes the addition of a variety of azomethine imines **132** to pyrazolidinone acrylate **133** (Table 17, entries 1−6). The major limitation of this methodology is that β-substituted α,β-unsaturated pyrazolidinone imides lead to decreased reactivity and enantioselectivity. For example, the cycloaddition of azomethine imine **136** with pyrazolidinone crotonate requires extended reaction times to form the corresponding cycloadduct in 74% yield as a >96:4 mixture of *exo*/*endo* isomers (Scheme 8). The ee of cycloadduct *exo*-**134** was 67%, a marked decrease from reactions that employ acrylate **132** as the dipolarophile. Nevertheless, this extension of the previously discussed *exo* selective nitrone cycloaddition methodology[16,17] serves as the Lewis acid-catalyzed complement to Suga's *endo* selective cycloaddition of azomethine imines with *N*-acryloyl oxazolidinone. Considering the recent interest in enantioselective azomethine imine cycloadditions, it is likely that the substrate scope for these cycloadditions will be greatly expanded and solutions to the unsolved stereochemical issues will be detailed in the near future.

5. Miscellaneous Cycloadditions

As illustrated in the previous sections of this review, the vast majority of enantioselective copper-catalyzed dipolar cycloadditions involve a [3 + 2] cycloaddition. However, Hsung has developed an efficient chiral Cu(II)-catalyzed [4 + 3] cycloaddition of nitrogen-stabilized oxyallyl cations with dienes (Scheme 9).[49] The nitrogen-stabilized oxyallyl cations are generated in situ via epoxidation of allenamides **139**. $Cu(OTf)_2$/BOX complexes were found to provide useful levels of activation and enantioselectivity. Although useful levels of enantioselectivity were observed when $Cu(OTf)_2$/**140** was employed as the chiral Lewis acid, significant improvements in both reactivity and selectivity were realized upon the addition of 4 Å molecular sieves and $AgSbF_6$. The latter presumably serves to generate $Cu(SbF_6)_2$ in situ, thus providing additional activation of the nitrogen-stabilized oxyallyl cation **143**. Furan and a variety of substituted furans serve as competent dienes in the desired cycloaddition. When cyclopentadiene is employed as the diene the desired cycloadduct is isolated in excellent yield, but the enantioselectivity is reduced because of a significant rate of uncatalyzed background reaction.

6. Concluding Remarks

1,3-Dipolar cycloaddition reactions represent the premier method to access enantioenriched five-membered heterocycles. The growth in the number and quality, in terms of efficiency and stereoselectivity, of catalytic, enantioselective 1,3-dipolar cycloadditions has been remarkable from the mid-1990s onward. Chiral copper catalysts have played a central role in the rapid development of enantioselective 1,3-dipolar cycloaddition reactions. The applications of chiral copper catalysts in catalytic, enantioselective cycloadditions of azaallyl type 1,3-dipoles, such as nitrones, azomethine imines, and azomethine ylides, are particularly noteworthy. However, there remains a need for additional research in this area to develop new copper catalysts that will expand the scope of dipoles and dipolarophiles that can be employed in dipolar cycloadditions. Given the outstanding achievements made over the past decade, the potential for new developments, and the increased demand for methods to access enantiopure heterocycles, it is likely that enantioselective copper-catalyzed 1,3-dipolar cycloadditions will remain a powerful tool for synthetic chemists for the foreseeable future.

7. Acknowledgments

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8. References

(1) (a) For a comprehensive review of 1,3-dipolar cycloadditions, see: *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products;* Padwa, A., Pearson, W. H., Eds.; John Wiley and Sons: Hoboken, NJ, 2003. For additional reviews of 1,3-dipolar cycloadditions, see: (b) Nájera, C.; Sansano, J. M. *Curr. Org. Chem.* **2003**, *7*, 1105. (c) Kanemasa, S. *Synlett* **2002**, 1371. (d) Gothelf, K. V. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, Germany, 2002; pp 211−245.

(2) For reviews of asymmetric 1,3-dipolar cycloadditions, see:(a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (b) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235.

(3) For examples, see:(a) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874. (b) Karlsson, S.; Högberg, H.-E. *Eur. J. Org. Chem.* **2003**, 2782. (c) Chen, W.; Yuan, X.-H.; Li, R.; Du, W.; Wu, Y.; Ding, L.-S.; Chen, Y, C. *Adv. Synth. Catal.* **2006**, *348*, 1818. (d) Chow, S. S.; Nevalainen, M.; Evans, C. A.; Johannes, C. W. *Tetrahedron: Asymmetry* **2007**, *18*, 277. (e) Vicario, J. L.; Reboredo, S.; Badia, D.; Carrillo, L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5168. (f) Chen, W.; Du, W.; Duan, Y.-Z.; Wu, Y.; Yang, S.-Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 7667.

(4) For recent examples of enantioselective nitrone cycloadditions, see: (a) Hashimoto, T.; Omote, M.; Kano, T.; Maruoka, K. *Org. Lett.* **2007**, *9*, 4805. (b) Shintani, R.; Murakami, M.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12356. (c) Shintani, R.; Park, S.; Duan, W.-L.; Hayashi, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5901. (d) Carmona, D.; Lamata, M. P.; Viguri, F.; Rodríguez, R.; Fischer, T.; Lahoz, F. J.; Dobrinovitch, I. T.; Oro, L. A. *Adv. Synth. Catal.* **2007**, *349*, 1751. (e) Kang, Y.-B.; Sun, X.-L.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3918. (f) Sibi, M. P.; Manyem, S.; Palencia, H. *J. Am. Chem. Soc.* **2006**, *128*, 13660. (g) Evans, D. A.; Song, H.-J.; Fandrick, K. R. *Org. Lett.* **2006**, *8*, 3351. (h) Carmona, D.; Lamata, M. P.; Viguri, F.; Rodríguez, R.; Oro, L. A.; Lahoz, F. J.; Balana, A. I.; Tejero, T.; Merino, P. J. *Am. Chem. Soc.* **2005**, *127*, 13386. (i) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 11926. (j) Desimoni, G.; Faita, G.; Guala, M.; Laurenti, A.; Mella, M. *Chem. Eur. J.* **2005**, *11*, 3816. (k) Desimoni, G.; Faita, G.; Mella, M.; Boicchi, M. *Eur. J. Org. Chem.* **2005**, 1020. (l) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 5764. (m) Suga, H.; Nakajima, T.; Itoh, K.; Kakehi, A. *Org. Lett.* **2005**, *7*, 1431.

(5) Suga, H.; Funyu, A.; Kakehi, A. *Org. Lett.* **2007**, *9*, 97.

(6) For reviews discussing cycloadditions of azomethine ylides, see:(a) Nájera, C.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6272. (b) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484. (c) Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2006**, 2873. (d) Bonin, M.; Chauveau, A.; Micouin, L. *Synlett* **2006**, 2349. (e) Husinec, S.; Savic, V. *Tetrahedron: Asymmetry* **2005**, *16*, 2047. (f) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765.

(7) For examples of enantioselective carbonyl ylides cycloadditions, see: (a) Tsutsui, H.; Shimada, N.; Abe, T.; Anada, M.; Nakajima, M.; Nakamura, S.; Nambu, H.; Hashimoto, S. *Adv. Synth. Catal.* **2007**, *349*, 521. (b) Suga, H.; Ishimoto, D.; Higuchi, S.; Ohtsuka, M.; Arikawa, T.; Tsuchida, T.; Kakehi, A.; Baba, T. *Org. Lett.* **2007**, *9*, 4359. (c) Torssell, S.; Somfai, P. *Adv. Synth. Catal.* **2006**, *348*, 2421. (d) Suga, H.; Suzuki, T.; Inoue, K.; Kakehi, A. *Tetrahedron* **2006**, *62*, 9218. (e) Hodgson, D. M.; Brückl, T.; Glen, R.; Labande, A. H.; Selden, D. A.; Dossetter, A. G.; Redgrave, A. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5450. (f) Hodgson, D. M.; Labande, A. H.;

Pierard, F. Y. T. M.; Exposito Castro, M. A. *J. Org. Chem.* **2003**, *68*, 6153. (g) Suga, H.; Inoue, K.; Inoue, S.; Kakehi, A. *J. Am. Chem. Soc.* **2002**, *124*, 14836. (h) Hodgson, D. M.; Stupple, P. A.; Johnstone, C. *Chem. Commun.* **1999**, 2185. (i) Kitagaki, S.; Anada, M.; Kataoka, O.; Matsuno, K.; Umeda, C.; Watanabe, N.; Hashimoto, S. *J. Am. Chem. Soc.* **1999**, *121*, 1417.

(8) (a) Toker, J. D.; Tremblay, M. R.; Yli-Kauhaluoma, J.; Wentworth, A. D.; Zhou, B.; Wentworth, P., Jr.; Janda, K. D. *J. Org. Chem.* **2005**, *70*, 7810. (b) Sibi, M. P.; Itoh, K.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 5366. (c) Tsuji, M.; Ukaji, Y.; Inomata, K. *Chem. Lett.* **2002**, 1112. (d) Toker, J. D.; Wentworth, P.; Hu, Y.; Houk, K. N.; Janda, K. D. *J. Am. Chem. Soc.* **2000**, *122*, 3244. (e) Shimizu, M.; Ukaji, Y.; Inomata, K. *Chem. Lett.* **1996**, 455. (f) Ukaji, Y.; Sada, K.; Inomata, K. *Chem. Lett.* **1993**, 1847.

(9) (a) Sibi, M. P.; Stanley, L. M.; Soeta, T. *Adv. Synth. Catal.* **2006**, *348*, 2371. (b) Sibi, M. P.; Stanley, L. M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 8276.

(10) (a) Kanemasa, S.; Kanai, T. *J. Am. Chem. Soc.* **2000**, *122*, 10710. (b) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2174. (c) Sibi, M. P.; Stanley, L. M.; Soeta, T. *Org. Lett.* **2007**, *9*, 1553.

(11) Gothelf, K. V.; Jørgensen, K. A. *Chem. Commun.* **2000**, 1449.

(12) Saito, T.; Yamada, T.; Miyazaki, S.; Otani, T. *Tetrahedron Lett.* **2004**, *45*, 9581.

(13) Saito, T.; Yamada, T.; Miyazaki, S.; Otani, T. *Tetrahedron Lett.* **2004**, *45*, 9585.

(14) Palomo, C.; Oiarbide, M.; Arceo, E.; García, J. M.; López, R.; González, A.; Linden, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6187.

(15) Iwasa, S.; Ishima, Y.; Widagdo, H. S.; Aoki, K.; Nishiyama, H. *Tetrahedron Lett.* **2004**, *45*, 2121.

(16) Sibi, M. P.; Ma, Z.; Jasperse, C. P. J. *Am. Chem. Soc.* **2004**, *126*, 718.

(17) Sibi, M. P.; Ma, Z.; Itoh, K.; Prabagaran, N.; Jasperse, C. P *Org. Lett.* **2005**, *7*, 2349.

(18) Jensen, K. B.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 2353.

(19) (a) Simonsen, K. B.; Bayón, P.; Hazell, R. G.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 3845. (b) Jensen, K. B.; Roberson, M.; Jørgensen, K. A. *J. Org. Chem.* **2000**, *65*, 9080.

(20) (a) *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic: New York, 1982; *Vol. 1*−*3*. (b) *Synthesis of β-Lactam Antibiotics*; Bruggink, A., Ed.; Kluwer: Dordrecht, Netherlands, 2001.

(21) (a) *The Chemistry of β-Lactams*, Page, M. I., Ed.; Blackie Academic & Professional: New York, 1992. (b) *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1993. (c) Ojima, I.; Delaoge, F. *Chem. Soc. Rev.* **1997**, *26*, 377. (d) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997.

(22) Kingston, D. G. I. *Chem. Commun.* **2001**, 867.

(23) Kinugasa, M.; Hashimoto, S. *J. Chem. Soc., Chem. Commun.* **1972**, 466.

(24) Miura, M.; Enna, M.; Okuro, K.; Nomura, M. *J. Org. Chem.* **1995**, *60*, 4999.

(25) Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 4572.

(26) Shintani, R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 4082.

(27) (a) Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422. (b) Glaser, C. *Justus Liebigs Ann. Chem.* **1870**, *154*, 159. (c) Kabalka, G. W.; Wang, L.; Pagni, R. M. *Synlett* **2001**, 108.

(28) Ye, M.-C.; Zhou, J.; Tang, Y. *J. Org. Chem.* **2006**, *71*, 3576.

(29) Basak, A.; Ghosh, S. C. *Synlett* **2004**, 1637.

(30) (a) Pyne, S. G.; Davis, A. S.; Gates, N. J.; Nicole, J.; Hartley, J. P.; Kindsay, K. B.; Machan, T.; Tang, M. *Synlett* **2004**, 2670. (b) Cheng, Y.; Huang, Z.-T.; Wang, M.-X. *Curr. Org. Chem.* **2004**, *8*, 325. (c) Notz, W.; Tanaka, R.; Barbas, C. F., III *Acc. Chem. Res.* **2004**, *37*, 580. (d) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693. (e) Pearson, W. H.; Soy, P. *Synlett* **2003**, 903.

(31) (a) *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, Germany, 2007. (b) *Asymmetric Organocatalysis*; Berkessel, A., Gröger, H, Eds.; Wiley-VCH: Weinheim, Germany, 2005.

(32) (a) Allway, P.; Grigg, R. *Tetrahedron Lett.* **1991**, *41*, 5817. (b) Grigg, R. *Tetrahedron: Asymmetry* **1995**, *6*, 2475.

(33) Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400.

(34) Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174.

(35) Zeng, W.; Zhou, Y.-G. *Org. Lett.* **2005**, *7*, 5055.

(36) Zeng, W.; Chen, G.-Y.; Zhou, Y.-G.; Li, Y.-X. *J. Am. Chem. Soc.* **2007**, *129*, 750.

(37) Vicario, J. L.; Reboredo, S.; Badía, D.; Carrillo, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5168.

(38) Gothelf, A. S.; Gothelf, K. V.; Hazel, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4236.

(39) Oderaotoshi, Y.; Cheng, W.; Fujitomi, S.; Kasano, Y.; Minakata, S.; Komatsu, M. *Org. Lett.* **2003**, *5*, 5043.

(40) Gao, W.; Zhang, X.; Raghunath, M. *Org. Lett.* **2005**, *7*, 4241.

(41) (a) Cabrera, S.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394. (b) Cabrera, S.; Arrayás, R. G.; Martín-Matute, B.; Cossío, F. P.; Carretero, J. C. *Tetrahedron* **2007**, *63*, 6587.

(42) Martín-Matute, B.; Pereira, S. I.; Peña-Cabrera, E.; Adrio, J.; Silva, A. M. S.; Carretero, J. C. *Adv. Synth. Catal.* **2007**, *349*, 1714.

(43) (a) Llamas, T.; Arrayás, R. G.; Carretero, J. C. *Org. Lett.* **2006**, *8*, 1795. (b) Llamas, T.; Arrayás, R. G.; Carretero, J. C. *Synthesis* **2007**, 950.

(44) Shi, M.; Shi, J.-W. *Tetrahedron: Asymmetry* **2007**, *18*, 645.

(45) Yan, X.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.-L.; Wu, Y.-D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1979.

(46) Shintani, R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 10778.

(47) Suárez, A.; Downey, C. W.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11244.

(48) Sibi, M. P.; Rane, D.; Stanley, L. M.; Soeta, T. *Org. Lett.* **2008**, published online June 13, 2008, http://dx.doi.org/10.1021/ol800904t.

(49) Huang, J.; Hsung, R. P. *J. Am. Chem. Soc.* **2005**, *127*, 50.

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