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Applications of Planar-Chiral Heterocycles as Ligands in Asymmetric Catalysis

Gregory C. Fu

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Applications of Planar-Chiral Heterocycles as Ligands in Asymmetric Catalysis

GREGORY C. FU*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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ABSTRACT

A new family of ligands for asymmetric transition metal-catalyzed reactions has been designed and synthesized. Thus, planar-chiral heterocycles furnish high enantioselectivity in a variety of processes, including isomerizations of allylic alcohols, O−H insertions, and 1,3-dipolar cycloadditions.

1. Introduction

Because of the "handedness" of the molecules of life (peptides, DNA, RNA, carbohydrates, etc.), enantiomeric compounds often display quite different biological activity.[1] The resulting need to efficiently generate compounds in enantiopure form (9 of the top 10 pharmaceutical drugs have chiral active ingredients, 7 of which are enantiopure[2]) has led to burgeoning interest in asymmetric synthesis, and important progress has been achieved during the past few decades.[3] Of course, stereoselective reactions that are based on chiral catalysts rather than on stoichiometric chiral reagents or substrate-bound chiral auxiliaries can be advantageous from the standpoints of efficiency and economy.[4]

Transition-metal complexes catalyze a remarkable array of powerful transformations, and a great deal of effort has therefore been dedicated to the design of chiral ligands for metal-catalyzed reactions.[5] With respect to the three types of chirality discussed by Cahn, Ingold, and Prelog,[6] ligands with central and axial chirality have been the most extensively explored (e.g., Figure 1). In addition, a number of ligands based on planar chirality had been described at the time that we initiated our program,[7] although no applications of planar-chiral *heterocycles* (e.g., right-hand side of Figure 1) had been reported.[8]

Figure 2 contrasts the chiral environment provided by a simple tertiary phosphine with that of a planar-chiral phosphorus heterocycle. On the basis of this analysis, we anticipated that planar-chiral heterocycles might serve as useful ligands for asymmetric catalysis. Indeed, in earlier studies, we had demonstrated that they can function as effective "organocatalysts".[9]

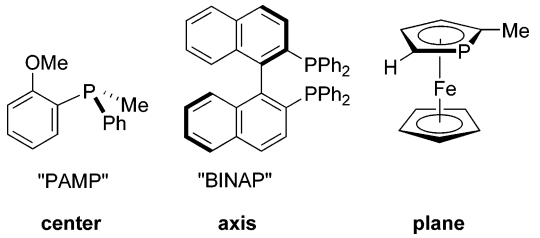
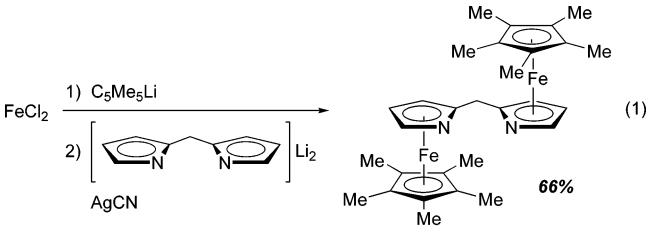


FIGURE 1. Examples of chiral phosphines with central, axial, and planar chirality.

For our initial investigations, we decided to focus on phosphole, pyrrole, and pyridine derivatives, because the organic chemistry of these heterocycles is well-developed and a number of π complexes had been described.[10] With regard to the choice of the metal fragment (e.g., ML_n in Figure 2), for our early work, we selected FeCp′ (Cp′ = a cyclopentadienyl-derived ligand), because of the well-established stability of ferrocenes[11] and the ready accessibility of a sterically and electronically diverse array of cyclopentadienes [e.g., C_5Me_5H and C_5Ph_5H are commercially available, and substituted pentaarylcyclopentadienes (C_5Ar_5H) can be synthesized from Ar−Br in a single step[12]]. Thus, the flexible route outlined in Figure 3 can furnish a wide range of planar-chiral ligands simply by combining two sets of building blocks, cyclopentadienes and heterocycles.

2. Cyclopropanation of Olefins

As part of an early study, we synthesized bis(azaferrocene) **BIS−AF**, a C_2-symmetric bidentate nitrogen ligand (eq 1).[13] As a test of our design, we examined the utility of **BIS−AF** in copper-catalyzed asymmetric cyclopropanations of olefins, a process that has been extensively explored with other ligands.[14]



We were pleased to determine that CuOTf/**BIS−AF** effectively catalyzes the diastereo- and enantioselective cyclopropanation of a variety of aryl-, alkyl-, and silyl-substituted alkenes, furnishing the trans product preferentially (Table 1). Doyle subsequently demonstrated that, for an intramolecular cyclopropanation, copper/**BIS−AF** can provide superior results to copper/bis(oxazoline) and $Rh_2(MEPY)_4$.[15]

Gregory C. Fu received a B.S. degree from MIT in 1985, where he worked in the laboratory of Prof. K. Barry Sharpless. After earning a Ph.D. from Harvard in 1991 under the guidance of Prof. David A. Evans, he spent 2 years as a postdoctoral fellow with Prof. Robert H. Grubbs at Caltech. In 1993, he returned to MIT, where he is currently Professor of Chemistry. His research program is focused on organic and organometallic chemistry.

* To whom correspondence should be addressed. E-mail: gcf@mit.edu.

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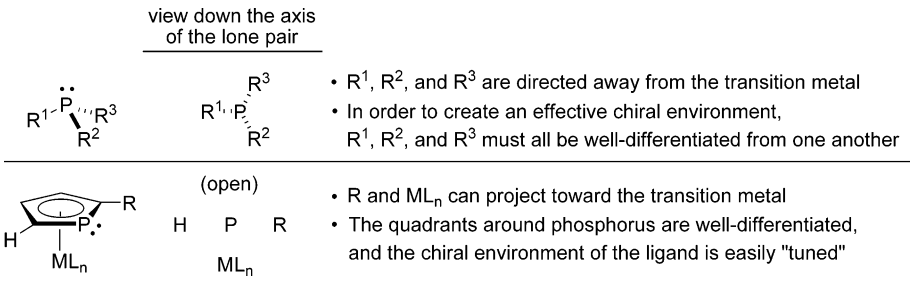


FIGURE 2. Design of chiral ligands. A simple tertiary phosphine versus a planar-chiral phosphorus heterocycle.

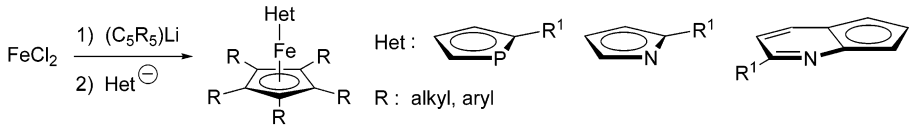
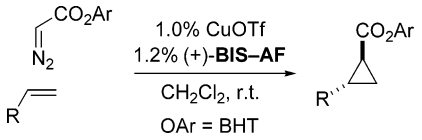


FIGURE 3. Synthesis of planar-chiral heterocycles.

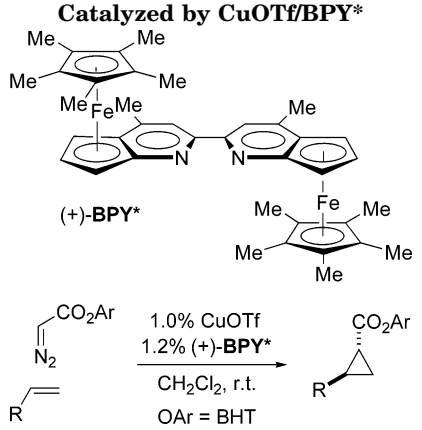
Table 1. Asymmetric Cyclopropanations of Olefins Catalyzed by CuOTf/BIS−AF



entry	R	trans/cis	% ee, trans	yield (%)
1	Ph	96:4	94	79
2	*p*-$(F_3C)C_6H_4$	94:6	96	81
3	*p*-$(MeO)C_6H_4$	94:6	87	90
4	$PhCH_2$	94:6	91	78
5	*n*-Hex	93:7	90	80
6[a]	Et_3Si	99:1	95	64

[a] A total of 2.0% CuOTf/2.4% (+)-**BIS**−**AF** was used.

Table 2. Asymmetric Cyclopropanations of Olefins Catalyzed by CuOTf/BPY*



entry	R	trans/cis	% ee, trans	yield (%)
1	Ph	97:3	87	78
2	*p*-$(MeO)C_6H_4$	95:5	75	71
3	*p*-$(F_3C)C_6H_4$	94:6	94	83
4	*n*-Hex	94:6	78	78
5	Et_3Si	96:4	80	60

We later extended our studies of C_2-symmetric bidentate nitrogen ligands to a planar-chiral bipyridine derivative (**BPY***), which also proved to be effective in copper-catalyzed cyclopropanations of olefins (Table 2).[16] A crystal structure revealed the well-defined binding pocket provided by the chiral ligand (Figure 4).

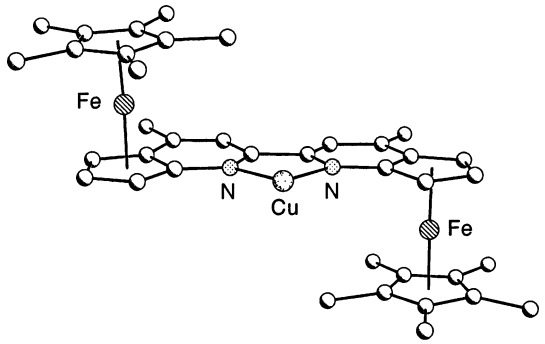
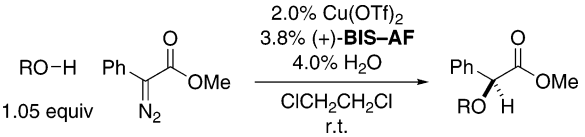


FIGURE 4. ORTEP of [Cu(BPY*)(styrene)]PF_6 (for clarity, the styrene and the noncoordinating PF_6 counterion have been omitted).

Table 3. Catalytic Enantioselective O−H Insertions: Variation of the Alcohol

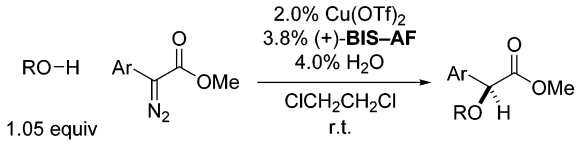


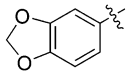
entry	R	yield (%)	ee (%)
1	Me	86	69
2	Et	85	87
3	*i*-Pr	76	68
4	*t*-Bu	<2	–
5	CH_2CH_2TMS	94	90
6	CH_2CF_3	<2	–
7	*p*-methoxybenzyl	87	82

3. Catalytic Enantioselective O−H Insertion

Although exciting progress has been described in the development of methods for catalytic asymmetric insertion into C−H bonds,[17] there had been almost no success in accomplishing corresponding reactions of O−H bonds [best enantiomeric excess (ee) = 8%].[18,19] Our attempts to achieve copper-catalyzed O−H insertions by diazo compounds, using a variety of chiral ligands [e.g., bis(oxazoline)s, semicorrins, Et-DUPHOS, and BINAP], led to generally disappointing results (≤40% ee), with a notable exception: a bis(azaferrocene) ligand furnished good enantioselectivity (Table 3).[20]

Table 4. Catalytic Enantioselective O−H Insertions: Variation of the Diazo Compound



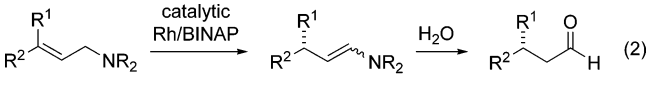
entry	Ar	yield (%)	ee (%)
1	Ph	94	90
2	(2-OMe)C_6H_4	90	96
3	(4-NHAc)C_6H_4	89	87 (99)[a]
4		88	89
5	3-thienyl	88	88

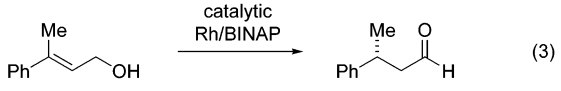
[a] Value in parentheses = ee after one recrystallization.

The copper/**BIS**−**AF**-catalyzed asymmetric O−H insertion process is ineffective for alcohols that are very hindered (entry 4 in Table 3) or electron-poor (entry 6). The reaction proceeds in fairly high ee with ethanol, 2-trimethylsilylethanol, and *p*-methoxybenzyl alcohol (entries 2, 5, and 7); of course, the latter two are readily deprotected to generate useful α-hydroxy esters.[21] With respect to the diazo compound, copper/**BIS**−**AF** is useful for enantioselective O−H insertions by an array of α-aryl-α-diazo esters (Table 4).

4. Isomerization of Allylic Alcohols to Aldehydes

The highly enantioselective Rh^+/BINAP-catalyzed isomerization of allylic amines to enamines (eq 2) represents a particularly noteworthy accomplishment in the field of asymmetric catalysis, because of both its early discovery and its application on a large scale in industry.[22] In contrast, comparable success had not been achieved for the corresponding isomerization of readily available allylic alcohols; 53% ee was the highest enantioselectivity that had been described (eq 3).[23]





In an initial study, we established that a planar-chiral phosphaferrocene (**PF**−**PPh$_2$**) serves as a promising ligand for rhodium-catalyzed asymmetric isomerizations of allylic alcohols, furnishing the desired aldehyde in improved ee and yield relative to the previous state-of-the-art (left-hand side of Figure 5 versus eq 3).[24] Nevertheless, there was clearly room for improvement. Fortunately, the structure of the tertiary phosphine portion of these planar-chiral phosphaferrocenes, which are synthesized via displacement reactions of **PF**−**X**, is very easily modified. We investigated a variety of ligands, and we were pleased to determine that more sterically demanding phosphaferrocene **PF**−**Ptol$_2$** is significantly more effective than our first-generation ligand, **PF**−**PPh$_2$** (Figure 5).

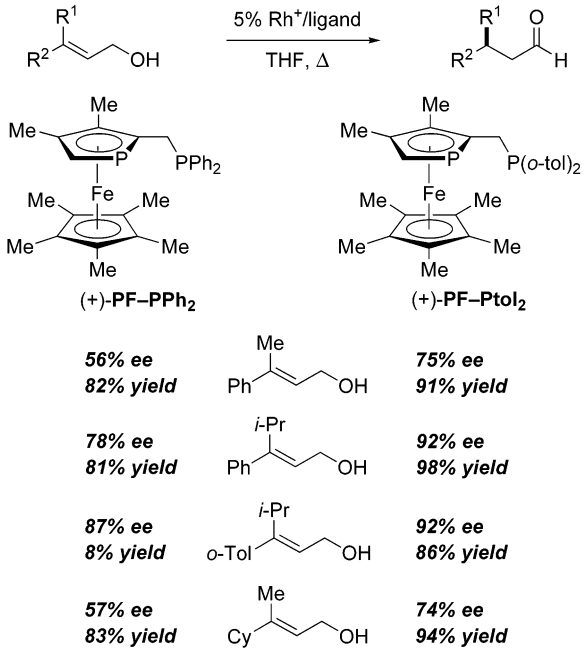


FIGURE 5. Asymmetric isomerization of allylic alcohols catalyzed by Rh^+/phosphaferrocenes.

Interestingly, in contrast to [Rh(cod)(**PF**−**PPh$_2$**)]BF_4, [Rh(cod)(**PF**−**Ptol$_2$**)]BF_4 is air- and moisture-stable. Indeed, the rhodium complex can typically be recovered at the end of an isomerization reaction in >80% yield and re-used without any erosion in enantioselectivity or yield.

With regard to the mechanism, it has been proposed that Rh^+/BINAP-catalyzed isomerizations of allylic amines proceed through the pathway depicted in eq 4.[25] Our data are consistent with an analogous mechanism for [Rh(cod)-(**PF**−**Ptol$_2$**)]BF_4-catalyzed isomerizations of allylic alcohols. For example, deuterium-labeling studies establish that the reaction occurs through an *intra*molecular 1,3-migration pathway (eq 5).

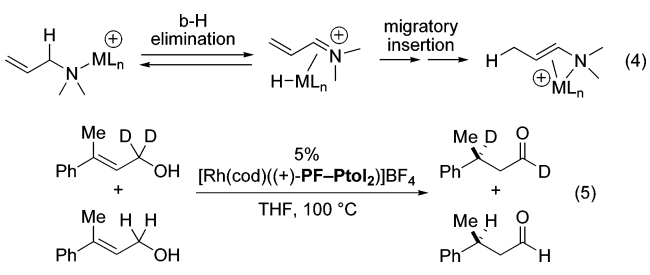
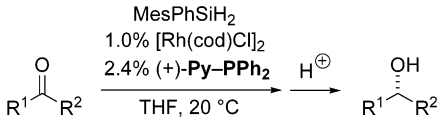
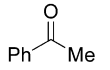
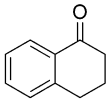
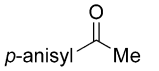
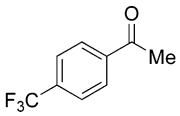
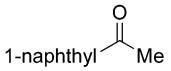
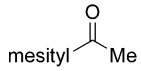
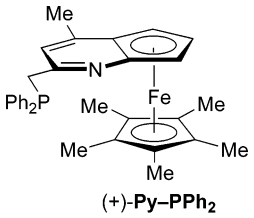


Table 5. Catalytic Asymmetric Hydrosilylation of Aryl Alkyl Ketones



entry	ketone	ee (%)	yield (%)
1		98	94
2		98	95
3		98	96
4		97	97
5		96	88
6		99	97
7		98	99



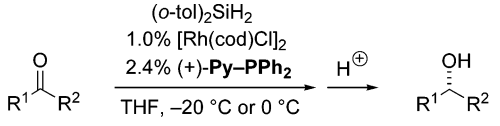
(+)-**Py–PPh$_2$**

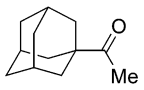
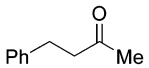
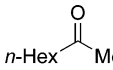
5. Hydrosilylation of Ketones

The utility of enantioenriched secondary alcohols (including silyl-protected derivatives) provides a strong impetus to develop effective catalysts for the asymmetric hydrosilylation of ketones.[26] We have determined that a planar-chiral P,N−ligand (**Py**−**PPh$_2$**) furnishes excellent enantioselectivities in rhodium-catalyzed hydrosilylations.[27] Thus, as illustrated in Table 5, a sterically and electronically diverse set of aryl alkyl ketones are reduced with high efficiency. If the alkyl group of the ketone is larger than methyl, the hydrosilylations proceed rather slowly but with excellent enantioselectivity (entries 2 and 3; 3 days at room temperature).

The rhodium/**Py**−**PPh$_2$** catalyst can also be applied to asymmetric hydrosilylations of dialkyl ketones (Table 6), which are generally more challenging substrates for enantioselective reduction than are aryl alkyl ketones. Thus, adamantyl methyl ketone and cyclohexyl methyl ketone are hydrosilylated with excellent enantioselectivity and yield (entries 1 and 2). The catalyst can even achieve reductions of (*n*-alkyl) methyl ketones in good ee (entries 3 and 4).

Table 6. Catalytic Asymmetric Hydrosilylation of Dialkyl Ketones



entry	ketone	ee (%)	yield (%)
1		96	92
2		94	91
3		82	98
4		72	81

6. Asymmetric Coupling of Nitrones and Acetylenes To Generate β-Lactams

Because of the biological activity of β-lactams,[28] as well as their utility as building blocks in synthetic organic chemistry, extensive effort has been devoted to the development of methods for their stereoselective synthesis.[29] Considerable progress has been achieved, but nearly all of the successful approaches rely on the use of chiral, nonracemic precursors.[30]

In 1972, Kinugasa reported a convergent route to β-lactams through the reaction of a copper acetylide with a nitrone,[31] and, in 1995, Miura described a variant that employs a catalytic amount of copper in combination with a base and a terminal alkyne (Figure 6).[32] Miura also provided the first example of asymmetric catalysis of this powerful transformation, generating a β-lactam in up to 57% ee, ~2:1 cis/trans diastereoselectivity, and 50% yield [10% CuI/20% bis(oxazoline)].

In our initial studies of the Kinugasa reaction, we examined the utility of **BIS**−**AF**, but, disappointingly, we observed only moderate stereoselection. Fortunately, however, our ligand design permits ready modification of the chiral environment of the bis(azaferrocene). Accordingly, we synthesized a substituted derivative (**BIS**−**AF-Me**), and we were pleased to determine that this ligand provides good stereoselectivity for a range of coupling partners (Table 7).[33,34] Because base-catalyzed cis → trans

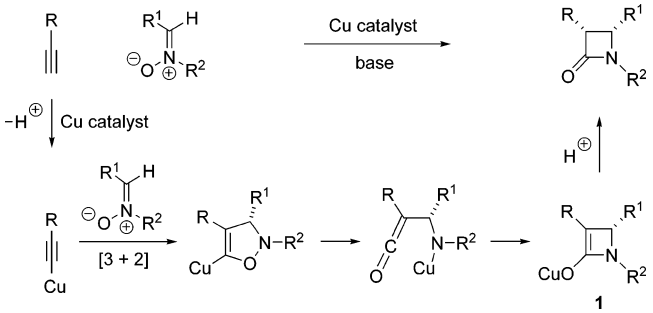
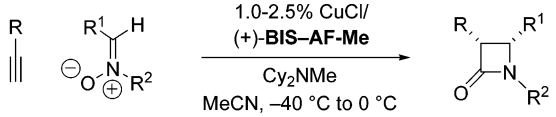
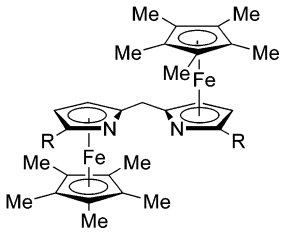


FIGURE 6. Possible mechanism for the Kinugasa reaction.

Table 7. Catalytic Asymmetric Synthesis of β-Lactams via the Kinugasa Reaction



entry	R	R^1	cis : trans	% ee, cis	isolated yield, cis isomer (%)
1	Ph	Ph	95 : 5	85	53
2	Ph	Cy	93 : 7	89	57
3	Ph	PhCO	91 : 9	72	42
4	1-cyclohexenyl	PhCO	90 : 10	91	45
5	CH_2Ph	Cy	71 : 29	73	43



R = H: (+)-**BIS–AF**
R = Me: (+)-**BIS–AF-Me**

isomerization of β-lactams is well-established, the enantioselective copper/(**BIS**−**AF-Me**)-catalyzed Kinugasa reaction effectively furnishes stereoselective access to all four possible isomers of the target compounds.

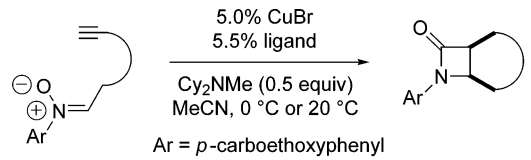
Because of the potent bioactivity of bi- and polycyclic β-lactams (e.g., penicillins and trinems/tribactams), the development of efficient methods for the asymmetric synthesis of these heterocycles is an important objective. Although an intramolecular Kinugasa reaction can, in principle, generate these structures, no examples of such a process had been described.

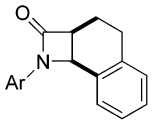
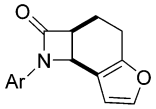
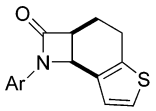
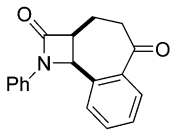
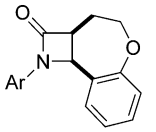
During a preliminary investigation, we were disappointed to find that **BIS**−**AF-Me** is relatively ineffective for copper-catalyzed intramolecular Kinugasa reactions. Upon exploring a range of other ligand architectures [including bis(oxazoline)s], we determined that the desired cyclizations proceed with good enantioselectivity in the presence of a planar-chiral phosphaferrocene−oxazoline (**PF**−**Oxaz-*i*-Pr** or **PF**−**Oxaz-*t*-Bu**),[35] thus providing an array of 6,4 and 7,4 bicyclic structures (Table 8).[36]

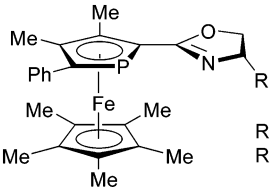
As illustrated in Figure 6, we believe that an enolate (**1**) is the final intermediate in the catalytic cycle for the Kinugasa reaction, protonation of which (e.g., by $[Cy_2NHMe]^+$) affords the β-lactam and regenerates the copper catalyst. On the basis of this mechanistic hypothesis, we decided to pursue the possibility that we could further enhance the utility of the Kinugasa reaction by intercepting enolate **1** with an electrophile, thereby producing a quaternary rather than a tertiary stereocenter. Of course, this objective requires that the enolate reacts with the added electrophile in preference to undergoing protonation.

Under our standard conditions (Table 8), we were unable to achieve the desired α functionalization with any of a variety of electrophiles. However, we were pleased to discover that, if we employ a mixture of a silyl enol ether

Table 8. Intramolecular Kinugasa Reactions

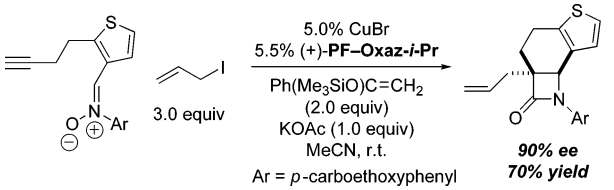


entry	product	ligand	ee (%)	yield (%)
1		(+)-**PF–Oxaz-*i*-Pr**	88	74
2		(+)-**PF–Oxaz-*i*-Pr**	90	46
3		(+)-**PF–Oxaz-*t*-Bu**	90	64
4		(+)-**PF–Oxaz-*t*-Bu**	85	53
5		(+)-**PF–Oxaz-*t*-Bu**	91	68



R = *i*-Pr: (+)-**PF–Oxaz-*i*-Pr**
R = *t*-Bu: (+)-**PF–Oxaz-*t*-Bu**

and KOAc, rather than Cy_2NMe, as the base, the anticipated formation of a quaternary stereocenter can indeed be accomplished with good stereoselection and yield (eq 6). This process generates two rings (including a β-lactam), a carbon−nitrogen bond, two carbon−carbon bonds, a carbonyl group, and adjacent tertiary and quaternary stereocenters.

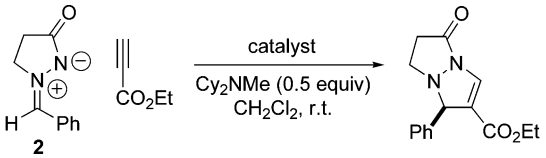


(6)

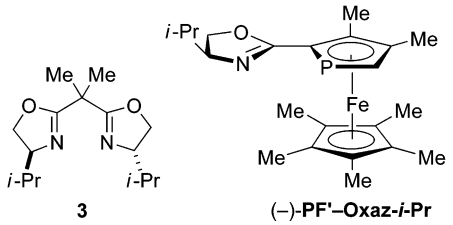
7. A New Copper-Catalyzed Dipolar Cycloaddition of Terminal Alkynes

1,3-Dipolar cycloadditions can provide ready access to a range of five-membered heterocycles in a convergent manner from simple precursors.[37,38] By 2002, two families of copper-catalyzed dipolar cycloadditions to terminal alkynes had been described: the Kinugasa reaction of

Table 9. A New Copper-Catalyzed Dipolar Cycloaddition of Terminal Alkynes: Reactions with Azomethine Imines



entry	catalyst	yield (%)	ee (%)
1	none	<2	–
2	5.0% CuI	88	–
3	5.0% CuI/5.5% (*S*)-BINAP	<2	–
4	5.0% CuI/5.5% **3**	98	19
5	5.0% CuI/5.5% (–)-**PF'–Oxaz-*i*-Pr**	98	90



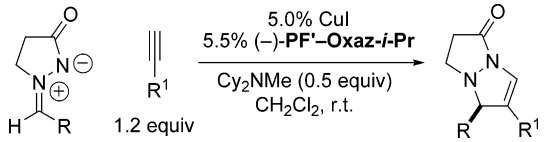
nitrones (Figure 6) and the remarkable Sharpless–Meldal cycloaddition of azides to produce triazoles.[39] Both processes presumably involve the reaction of the dipole with a transiently generated copper acetylide.

We decided to explore the possibility that such copper-catalyzed cycloadditions could be expanded to dipoles other than nitrones and azides. 3-Oxopyrazolidin-1-ium-2-ides (e.g., **2** in Table 9), which are derived from the reaction of pyrazolidin-3-ones with aldehydes,[40] had previously been employed as partners in 1,3-dipolar cycloadditions to alkynes; unfortunately, elevated temperatures are generally required, and reactions of unsymmetrical alkynes often furnish mixtures of regioisomeric heterocycles.[41] The products of such cycloadditions are of interest in a variety of contexts, including as antibacterial agents.[42]

As indicated in Table 9, in the absence of a catalyst, dipole **2** does not react with ethyl propiolate at room temperature (entry 1).[43] Fortunately, the simple addition of 5% CuI leads to the formation of the fused ring system in 88% yield (entry 2). Having established the viability of copper catalysis, we turned our attention to developing an enantioselective process. Unfortunately, the use of a chiral bidentate phosphine shuts down the reaction (entry 3). In contrast, the copper-catalyzed cycloaddition proceeds efficiently in the presence of a N,N or a P,N ligand (entries 4 and 5). Although bis(oxazoline) **3** furnishes only modest ee (19%; entry 4), planar-chiral ligand **PF'–Oxaz-*i*-Pr** provides excellent enantioselectivity (90% ee; entry 5).

The scope of this copper-catalyzed asymmetric cycloaddition is illustrated in Table 10. With regard to the dipole, the group attached to the imine carbon can be aromatic, alkenyl, or alkyl. A preference for an electron-poor substituent on the alkyne is the primary limitation of the method (entries 1–7 versus 8 and 9). On the other

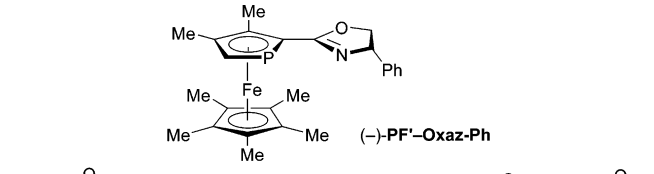
Table 10. Copper-Catalyzed Dipolar Cycloadditions of Terminal Alkynes with Azomethine Imines

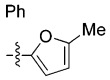


entry	R	R^1	yield (%)	ee (%)
1	Ph	CO_2Et	98	90
2	1-cyclohexenyl	CO_2Et	98	94
3	*n*-pentyl	CO_2Et	92	82
4	Cy	CO_2Et	94	96
5	Ph	COMe	98	90
6	Ph	*p*-$(CF_3)C_6H_4$	90	86
7	Ph	2-pyridyl	100	84
8[a]	Ph	Ph	73	88
9[a]	Ph	*n*-pentyl	63	74

[a] Reaction temperature = 45 °C and regioselectivity ~ 6:1. The yield value is for the illustrated regiosomer.

Table 11. Kinetic Resolutions of Azomethine Imines



entry	R^1	R^2	R	s	ee of the dipole (%) [isolated yield (%)]
1	Ph	Ph	CO_2Et	**53**	99 [42]
2	Ph		CO_2Et	**96**	95 [48]
3	Ph		CO_2Et	**35**	95 [36]
4	Ph	Cy	CO_2Et	**15**	91 [36]
5	Ph	Ph	CO_2Et	**53**	99 [42]
6	*i*-Pr	Ph	CONMePh	**76**	97 [40]
7	*t*-Bu	Ph	CONMePh	**51**	93 [48]

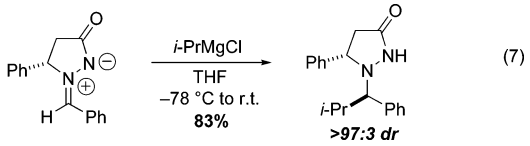
hand, to the best of our knowledge, the cycloaddition described in entry 9 represents the first example of a reaction of an azomethine imine with a simple alkyne.

We have also explored the possibility of conducting these copper-catalyzed cycloadditions in a kinetic-resolution manifold.[44] There are few examples of kinetic resolutions in which a 1,3-dipolar cycloaddition is the enantiomer-differentiating step,[45] and, to the best of our knowledge, there were no reports of catalytic asymmetric processes.

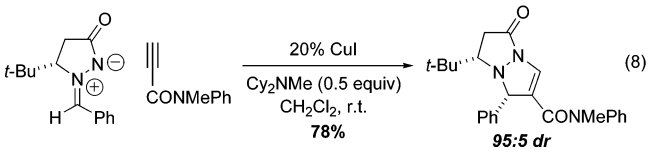
In our initial studies, we determined that, whereas **PF'–Oxaz-*i*-Pr** furnishes a very good selectivity factor, **PF'–Oxaz-Ph** is even more effective, affording higher selectivity with a lower catalyst loading [*s* = selectivity factor = (rate of fast-reacting enantiomer/rate of slow-reacting enantiomer); Table 11].[46] The scope of this kinetic resolution is fairly broad. For example, the group attached to the imine carbon (R^2) can be aromatic, heteroaromatic, alkenyl, or

alkyl. Although C4-substituted azomethine imines are not suitable substrates ($s < 2$), a variety of C5-substituted dipoles can be effectively resolved by CuI/**PF′−Oxaz-Ph**. Thus, the 5 position can bear not only an aryl (entries 1−5) but also a branched alkyl (entries 6 and 7) group.

The highly enantioenriched dipoles that are generated in these kinetic resolutions serve as precursors to useful classes of heterocycles, including mono- and bicyclic pyrazolidinones (eq 7 and 8).[47,48]



(7)



(8)

8. Conclusion

An array of C_1- and C_2-symmetric planar-chiral heterocycles have been synthesized (including N,N, P,N, and P,P ligands) and applied to a variety of copper- and rhodium-catalyzed processes. Gratifyingly, these ligands furnish state-of-the-art enantiomeric excesses for a range of reactions (e.g., isomerizations of allylic alcohols, O−H insertions, and 1,3-dipolar cycloadditions), presumably because of the well-defined chiral environment provided by their intriguing structures. We are optimistic that, during the coming years, this family of ligands will find application in an ever-widening spectrum of metal-catalyzed transformations.

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(4) For leading references, see (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 1−3. (b) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 2000. (c) *Asymmetric Catalysis on Industrial Scale*; Blaser, H. U., Schmidt, E., Eds.; Wiley−VCH: New York, 2004.

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