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A New Copper-Catalyzed [3 + 2] Cycloaddition: Enantioselective Coupling of Terminal Alkynes with Azomethine Imines To Generate Five-Membered Nitrogen Heterocycles

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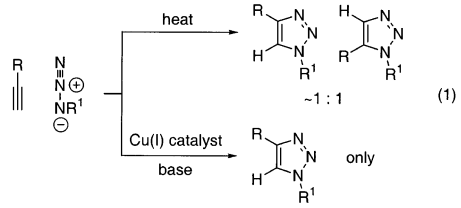
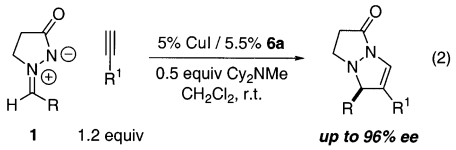
1,3-Dipolar cycloadditions are powerful methods for constructing a variety of five-membered heterocycles in a convergent manner from relatively simple precursors.[1,2] Recently, several examples of Cu(I)-catalyzed 1,3-dipolar cycloadditions to terminal alkynes—presumably proceeding via a copper acetylide—have been described (Figure 1).[3,4] In addition to achieving heterocycle formation under milder conditions, copper-catalyzed processes can overcome the poor regioselectivity observed in some of the corresponding thermal cycloadditions (e.g., eq 1),[3] as well as provide interesting new opportunities for asymmetric catalysis.[4b,5]



(1)

To date, such copper-catalyzed cycloadditions have been reported for just two families of dipoles, azides and nitrones, furnishing 1,2,3-triazoles[3] and β-lactams,[4] respectively (Figure 1). In this Communication, we considerably expand the scope of this useful mode of reactivity, demonstrating that 1,3-dipolar cycloadditions of azomethine imines to alkynes can be catalyzed by Cu(I); at the same time, we achieve effective asymmetric catalysis of this new process (eq 2).



(2)

In 1968, Dorn and Otto established that 3-oxopyrazolidin-1-ium-2-ides such as **1**, which are derived from the reaction of pyrazolidin-3-one with an aldehyde, are stable, easily handled compounds.[6] Cycloadditions of these dipoles even with highly electron-deficient alkynes (e.g., dimethyl acetylenedicarboxylate) are often conducted at elevated temperatures and, in the case of unsymmetrical alkynes, generally furnish mixtures of regioisomeric heterocycles.[6,7] The products of such cycloadditions have a variety of applications, including as antibacterial agents (e.g., LY186826).[8,9]

In an initial investigation, we examined the reaction of azomethine imine **2** with ethyl propiolate (**3**) (Table 1). At room temperature in the absence of a copper catalyst, essentially none of the target heterocycle (**4**) is generated (entry 1). In contrast, in the presence of 5% CuI, the desired 1,3-dipolar cycloaddition proceeds cleanly, affording the product as a single regioisomer (88% yield; entry 2).

Having established the viability of copper-catalyzed [3 + 2] cycloadditions of azomethine imines to alkynes, we turned our attention to asymmetric catalysis. Unfortunately, the addition of (*S*)-BINAP shuts down the reaction (<2% yield; entry 3). Although bidentate phosphines appear to generally inhibit catalysis by copper,[10] bidentate nitrogen-based ligands do not. Thus, cycloaddition proceeds smoothly in the presence of bisoxazoline **5**, although the desired heterocycle (**4**) is produced with very modest enantioselectivity (19% ee; entry 4).[11,12] Fortunately, copper catalysis is also effective in the presence of a P,N ligand, phosphaferrocene—oxazoline **6a**,[13] leading to cycloaddition in excellent yield and with high stereoselection (98% yield, 90% ee; entry 5). Increasing the steric demand of the substituent on the oxazoline (*i*-Pr → *t*-Bu) results in a decrease in ee (90% ee → 58% ee; entry 5 vs entry 6), as does a change in the planar chirality of the phosphaferrocene subunit (90% ee → 80% ee; entry 5 vs entry 7). Thus, the investigation outlined in Table 1 describes two critical discover-

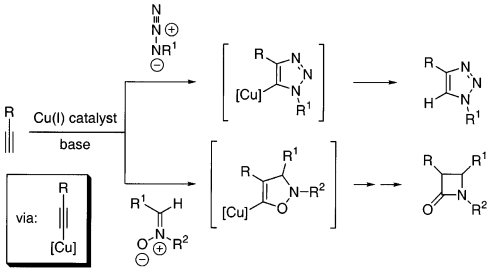
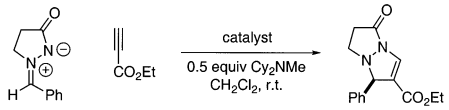


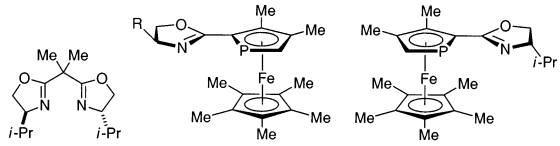
Figure 1. Examples of copper-catalyzed [3 + 2] cycloadditions.

Table 1. 1,3-Dipolar Cycloaddition of an Azomethine Imine to an Alkyne: Effect of Copper and Ligands on Yield and Enantioselectivity[a]



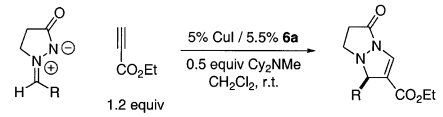
entry	catalyst	yield (%)[b]	ee (%)
1	none	<2	
2	5% CuI	88	
3	5% CuI/5.5% (*S*)-BINAP	<2	
4	5% CuI/5.5% **5**	98	19
5	5% CuI/5.5% **6a**	98	90
6	5% CuI/5.5% **6b**	100	58
7	5% CuI/5.5% **7**	100	80

[a] All data are the average of two runs. [b] Isolated yield.



10.1021/ja036922u CCC: $25.00

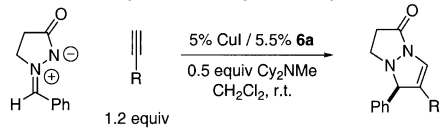
Table 2. Reaction Scope: The Azomethine Imine Component[a]



entry	R	yield (%)[b]	ee (%)
1	Ph	98	90
2	*o*-FC_6H_4	99	81
3	*m*-BrC_6H_4	99	86
4	*p*-$CF_3C_6H_4$	99	95
5	1-cyclohexenyl	98	94
6	*n*-pentyl	92	82
7	Cy	94	96

[a] All data are the average of two runs. [b] Isolated yield.

Table 3. Reaction Scope: The Alkyne Component[a]

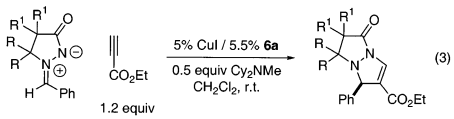


entry	R	yield (%)[b]	ee (%)
1	CO_2Et	98	90
2	COMe	98	90
3	CONMePh	100	94
4	*p*-$EtO_2CC_6H_4$	77	88
5	*p*-$CF_3C_6H_4$	90	86
6	2-pyridyl	100	84
7[c,d]	Ph	73	88
8[c,e]	*n*-pentyl	63	74

[a] All data are the average of two runs. [b] Isolated yield. [c] The reaction was conducted at 45 °C. The yield and the ee are those of the major regioisomer. [d] Regioselectivity: 5.6/1. [e] Regioselectivity: 6.6/1.

ies: Cu(I) can efficiently catalyze regioselective[14] 1,3-dipolar cycloadditions of azomethine imines to alkynes, and, in the presence of an appropriate chiral ligand, a highly enantioselective reaction can be achieved.

We have determined that the scope of the Cu(I)/phosphaferrocene−oxazoline-catalyzed asymmetric cycloaddition is fairly broad. With respect to the imine portion of the dipole, the process tolerates aromatic (Table 2, entries 1−4), alkenyl (entry 5), and alkyl (entries 6 and 7) groups on carbon, furnishing the products in excellent yields and with very good enantioselectivities.[15] With respect to variations in the pyrazolidinone ring of the dipole, the cycloaddition proceeds cleanly and with high ee for a range of substitution patterns (eq 3).



R = Me, R^1 = H: 99% yield, 98% ee
R = H, R^1 = Me: 100% yield, 96% ee

With regard to the alkyne, the best yields and enantioselectivities are obtained when this coupling partner is electron-poor (Table 3). Thus, if the alkyne bears a carbonyl (entries 1−3), an electron-deficient aromatic (entries 4 and 5), or a heteroaromatic group (entry 6), the ee of the cycloaddition is high. Simple aryl- or alkyl-substituted alkynes are also suitable substrates for Cu(I)/phosphaferrocene−oxazoline-catalyzed asymmetric cycloaddition, although gentle heating is necessary for a reasonable reaction rate, and an erosion in regioselectivity is observed (∼6:1; entries 7 and 8).[16] To the best of our knowledge, these are, however, the first examples of an unactivated alkyne undergoing cycloaddition with this family of dipoles.

In summary, we have developed a new copper-catalyzed 1,3-dipolar cycloaddition of terminal alkynes, presumably relying upon the transient formation of a copper acetylide to enhance the reactivity of the dipolarophile. By employing a phosphaferrocene−oxazoline as a chiral bidentate ligand, we have efficiently coupled a wide range of azomethine imines and alkynes to generate useful heterocycles in very good enantiomeric excess. Future studies will explore further expansion of the scope of copper-catalyzed cycloaddition reactions.

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Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) For a review of the chemistry of pyrazolidinones, see: Claramunt, R. M.; Elguero, J. *Org. Prep. Proced. Int.* **1991**, *23*, 273−320.

(9) The pyrazolidinone ring serves as a surrogate for the β-lactam unit that is a common feature of many antibiotics. For an overview of the chemistry and biology of LY186826, see: (a) Ternansky, R. J.; Holmes, R. A. *Drugs Future* **1990**, *15*, 149−157. (b) Ternansky, R. J.; Draheim, S. E. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Bentley, P. H., Southgate, R. H., Eds.; Royal Society of Chemistry: London, 1989; pp 139−156. (c) Jungheim, L. N.; Sigmund, S. K. *J. Org. Chem.* **1987**, *52*, 4007−4013. In contrast to LY186826, which is a [3.3.0]-fused (⟹ carbapenem analogue) pyrazolidinone, monocyclic (⟹ monobactam analogue) or [4.3.0]-fused (⟹ carbacephem analogue) pyrazolidinones do not show biological activity.

(10) For example, the addition of CHIRAPHOS, DUPHOS, or JOSIPHOS leads to a low yield of heterocycle **4**.

(11) (a) For a review of applications of C_2-symmetric bisoxazolines in asymmetric catalysis, see: Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1−45. (b) For some leading references to enantioselective copper-catalyzed reactions, see: Rovis, T.; Evans, D. A. *Prog. Inorg. Chem.* **2001**, *50*, 1−150.

(12) The 1,3-dipolar cycloaddition also proceeds cleanly in the presence of (−)-sparteine and a pybox ligand, albeit in lower ee.

(13) For previous reports, see: (a) Shintani, R.; Lo, M. M.-C.; Fu, G. C. *Org. Lett.* **2000**, *2*, 3695−3697. (b) Shintani, R.; Fu, G. C. *Org. Lett.* **2002**, *4*, 3699−3702. (c) Reference 5b.

(14) Unless otherwise noted, we detect none of the other regioisomer in these copper-catalyzed dipolar cycloadditions.

(15) Notes (Table 2, entry 1): (1) Use of other solvents leads to somewhat lower ee (THF, toluene, and anisole), slow reaction (MeCN), or many side products (EtOH). (2) The ee shows little dependence on reaction temperature. (3) Replacement of Cy_2NMe with *i*-Pr_2NEt has minimal impact (93% yield, 88% ee with *i*-Pr_2NEt). (4) CuBr, CuCl, and Cu(OTf) furnish comparable yield, but lower ee. (5) When the cycloaddition is conducted on a 4.0 mmol scale, the desired product is isolated in 97% yield (1.06 g) and with 84% ee. Ligand **6a** is recovered in 78% yield.

(16) Higher regioselectivity—at the expense of reaction rate—can be obtained by conducting the cycloadditions at room temperature.

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