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Catalytic, Three-Component Assembly Reaction for the Synthesis of Pyrrolidines

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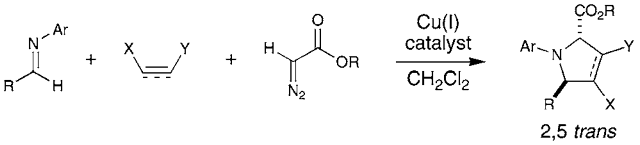
ABSTRACT

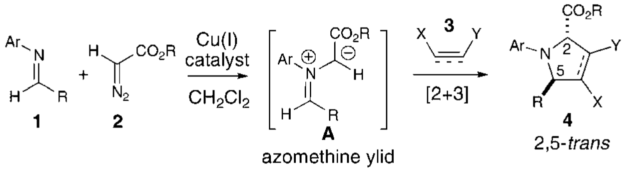


Copper(I) salts catalyze the three-component assembly reaction between an α-diazo ester, an imine, and various alkenes and alkynes to form substituted pyrrolidines with excellent to good diastereoselectivities in high yields. The transition metal-catalyzed decomposition of the α-diazo compound in the presence of the imine likely generates a transient azomethine ylid that undergoes addition with various dipolarophiles in a highly convergent manner.

Pyrrolidines are an important class of heterocycles found in numerous natural products and medicinal structures. Consequently, the efficient construction of these molecules has received significant attention.[1] A powerful method for the synthesis of these compounds involves the 1,3-dipolar cycloaddition of an azomethine ylid to an unsaturated partner. Although many cycloaddition strategies for the construction of substituted pyrrolidines have been explored, a convergent, one-pot approach to generate a reactive azomethine ylid in the presence of a suitable dipolarophile has not fully emerged. Herein, we report a catalytic, three-component assembly of pyrrolidines that utilizes a convenient copper(I) catalyst to generate an azomethine ylid in situ that undergoes subsequent addition to alkenes and alkynes (Scheme 1).

Dipolar cycloadditions utilizing azomethine ylids and related species are important and concise methods for the stereoselective synthesis of nitrogen-containing five-membered rings.[2] Past approaches to generate 1,3-dipolar species have focused predominantly on thermal ring-opening of aziridines,[3] deprotonation of α-imino esters,[4] and exposure of α-silylammonium salts to fluoride.[5] A very attractive and mild method for accessing azomethine ylids is the combination of a metallocarbenoid species with an imine (**1**, Scheme 1). The 1,3-dipole intermediate **A** generated in situ can then be employed in a cycloaddition process when an appropriate dipolarophile (**3**) is present.[6] Related strategies have been successful involving rhodium(II)-catalyzed intramolecular cycloadditions of α-diazo carbonyl compounds.[7] However, the intermolecular, three-component strategy has not received the same attention. Our current investigations of new catalytic reactions led us to explore this process, thereby differentiating

Scheme 1. Catalytic, Three-Component Assembly of Pyrrolidines



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(1) (a) Pichon, M.; Figadere, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927−964. (b) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435−446 and references therein. (c) Broggini, G.; Zecchi, G. *Synthesis* **1999**, 905−917. (d) Pearson, W. H. *Pure Appl. Chem.* **2002**, *74*, 1339−1347. (e) Pearson, W. H.; Stoy, P. *Synlett* **2003**, 903−921.

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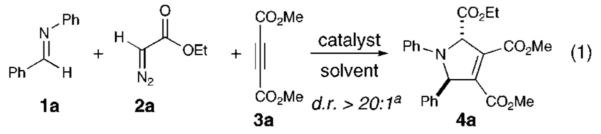
the positions of the pyrrolidine ring simultaneously in a convergent, one-pot reaction.[8]

We began the exploration of this cycloaddition process by surveying different potential catalysts and solvents in the presence of *N*-benzylidene imine (**1a**), dimethyl acetylenedicarboxylate (DMAD, **3a**), and ethyl diazoacetate (EDA, **2a**) (Table 1, eq 1). Gratifyingly, both copper(I) trifluoromethanesulfonate, $(C_6H_6)\cdot[Cu(OTf)]_2$, and rhodium(II) acetate dimer are catalysts for the reaction, with copper(I) being superior in terms of yield and reliability. The cycloaddition is highest yielding in chlorinated solvents such as dichoromethane (entry 2, 91%), 1,2-dichloroethane (entry 3, 40%), and chloroform (entry 4, 71%). The reaction performed in diethyl ether proceeds in 75% yield (entry 5) but does not afford the desired product in more coordinating ethereal solvents such as THF and DME (entries 6 and 7), possibly due to interactions with the copper(I) catalyst. When hydrocarbon solvents such as hexanes (entry 8) or toluene (entry 9) are employed, the yield of **4a** is moderate (58 and 54%, respectively). In all solvents we examined, the diastereoselectivity of the reaction (eq 1) was determined to be exclusively the 2,5-*trans*-pyrrolidine stereoisomer by ^{1}H NMR (500 MHz, >20:1) analysis of the unpurified reaction mixtures.[9]

Table 1. Catalytic, Three-Component Coupling of *N*-Benzylidine Imine (**1a**), EDA (**2a**) and DMAD (**3a**) (Eq 1)

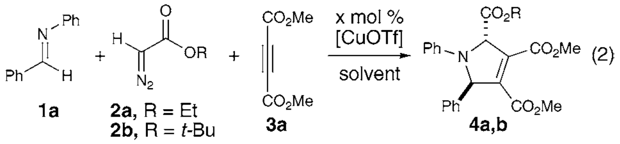


entry	catalyst	solvent	time (h), temp (°C)	yield (%)
1	Rh_2OAc_4[b]	CH_2Cl_2	13.5, 40	62
2	$[Cu(SO_3CF_3)]$[c]	CH_2Cl_2	4, 40	**91**
3	$[Cu(SO_3CF_3)]$	$CHCl_3$[d]	4, 60	40
4	$[Cu(SO_3CF_3)]$	$ClCH_2CH_2Cl$	4, 60	71
5	$[Cu(SO_3CF_3)]$	Et_2O	6, 38	75
6	$[Cu(SO_3CF_3)]$	THF	14, 60	nr[e]
7	$[Cu(SO_3CF_3)]$	DME	13.5, 60	nr
8	$[Cu(SO_3CF_3)]$	hexanes	6, 65	58
9	$[Cu(SO_3CF_3)]$	toluene	6, 65	54

[a] Diastereomeric ratios determined by ^{1}H NMR (500 MHz) spectra of unpurified reaction mixtures. Relative stereochemistry of **4a** was assigned by analogy to **10** (X-ray structure, see Figure 1). [b] EDA (**2a**, 1 equiv) in CH_2Cl_2 (2.5 mL) was added over 2 h to a solution of imine (**1a,** 3 equiv), DMAD (**3a**, 3 equiv), and Rh_2OAc_4 (1 mol %) in CH_2Cl_2 (5 mL) then heated at reflux for 12 h. [c] Reaction conditions: a solution of EDA (**2a**, 3 equiv) in CH_2Cl_2 (2.5 mL) was added via syringe pump over 3 h to a solution of imine (**1a,** 3 equiv), DMAD (**3a**, 1 equiv), and $[Cu(OTf)]_2\cdot C_6H_6$ (10 mol %) in CH_2Cl_2 (5 mL) with heating at the indicated temperature. The reaction was stirred for an additional hour; the solvent was removed, and the residue was purified on SiO_2. [d] Passed through Al_2O_3 immediately prior to use. [e] No reaction.

The effect of catalyst loading was then determined using the same reaction conditions (Table 2, eq 2). Although copper(I) triflate is commercially available as the dimer· benzene complex, we observe higher yields with catalyst prepared in our laboratory.[10] The reaction proceeds well with 10 mol % (entry 1, 91% yield) and 5 mol % (entry 2, 60% yield) [Cu(OTf)]. However, the yield decreases to less than 20% after the catalyst loading is reduced to 2.5 and 1 mol % (entries 3 and 4).

Table 2. Effect of Catalyst Loading and α-Diazo Ester Substitution on Catalytic Pyrrolidine Synthesis (Eq 2)[a]



entry	mol % [CuOTf]	diazo ester	yield (%)	dr[b]	compd
1	10	**2a**	91	20:1	**4a**
2	5	**2a**	60	20:1	**4a**
3	2.5	**2a**	18	20:1	**4a**
4	1	**2a**	12	20:1	**4a**
5	10	**2b**	83	20:1	**4b**

[a] Reaction conditions: a solution of diazo ester (**2a**,**b**, 3 equiv) in CH_2Cl_2 (2.5 mL) was added via syringe pump over 3 h to a solution of imine (**1a**, 3 equiv), DMAD (**3a**, 1 equiv), and $[Cu(OTf)]_2\cdot C_6H_6$ in the indicated amounts in CH_2Cl_2 (5 mL) with heating at reflux. [b] Diastereomeric ratios determined by ^{1}H NMR (500 MHz) spectra of unpurified reaction mixtures.

To differentiate the resulting esters from the reaction for future synthetic endeavors, various α-diazo esters were utilized in the reaction (Table 2). As indicated earlier, commercial ethyl diazoacetate affords high yields of the desired pyrrolidine **4a** (Table 1). Additionally, use of *tert*-butyl diazoacetate (entry 5) produces the substituted pyrrolidine (**4b**) in 83% yield.

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(2) (a) Harwood, L. M.; Vickers, R. J. In *The Chemistry of Heterocyclic Compounds: Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products.*; Padwa, A., Pearson, W. H., Eds.; Wiley: New York, 2002; Vol. 59, pp 169−252. (b) Doyle, M. P.; Yan, M.; Hu, W. H.; Gronenberg, L. S. *J. Am. Chem. Soc.* **2003**, *125*, 4692−4693 and references therein.

(3) (a) Heine, H. W.; Peavy, R. *Tetrahedron Lett.* **1965**, 3123−3126. (b) Padwa, A.; Hamilton, L. *Tetrahedron Lett.* **1965**, 4363−4367. (c) Huisgen, R.; Scheer, W.; Szeimies, G.; Huber, H. *Tetrahedron Lett.* **1966**, 397−404. (d) Bartnik, R.; Mloston, G. *Tetrahedron* **1984**, *40*, 2569−2576. (e) DeShong, P.; Kell, D. A.; Sidler, D. R. *J. Org. Chem.* **1985**, *50*, 2309−2315. (f) Wenkert, D.; Ferguson, S. B.; Porter, B.; Qvarnstrom, A.; McPhail, A. T. *J. Org. Chem.* **1985**, *50*, 4114−4119.

(4) (a) Grigg, R.; Kemp, J.; Sheldrick, G.; Trotter, J. *Chem. Commun.* **1978**, 109−111. (b) Grigg, R.; Kemp, J. *Tetrahedron Lett.* **1980**, *21*, 2461−2464.

(5) Vedejs, E.; West, F. G. *Chem. Rev.* **1986**, *86*, 941−955 and references therein.

(6) This process has been observed previously in the catalytic synthesis of aziridines from imines: (a) Bartnik, R.; Mloston, G. *Tetrahedron* **1984**, *40*, 2569−2576. (b) Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 676−678.

(7) (a) Padwa, A. *Top. Curr. Chem.* **1997**, *189*, 121−158 and references therein. (b) Kitagaki, S.; Anada, M.; Kataoka, O.; Matsuno, K.; Umeda, C.; Watanabe, N.; Hashimoto, S.-i. *J. Am. Chem. Soc.* **1999**, *121*, 1417−1418.

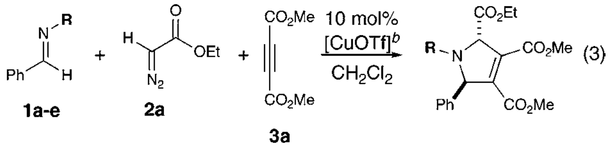
(8) During the last stage of preparation of our manuscript, a related approach to pyrrolidines using Ru(CO)porphyrin catalysts appeared in the literature: Li, G.-Y.; Chen, J.; Yu, W.-Y.; Hong, W.; Che, C.-M. *Org. Lett.* **2003**, *5*, 2153−2156.

(9) See Supporting Information for details.

(10) Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 1889−1897. Yield (eq 1) with 10 mol % commercial [CuOTf]: 10−25%

Encouraged by the results from optimizing this initial reaction, we examined the scope of this process regarding substitution on the nitrogen atom (Table 3). As with our earlier optimization studies, dimethyl acetylene−dicarboxylate (DMAD, **3a**) was employed as the dipolarophile, ethyl diazoacetate (EDA, **2a**) as the carbenoid source, and 10 mol % [CuOTf] as the catalyst. As the data from Table 3 indicate, the reaction proceeds with halogen or alkoxy substitution on the *N*-phenyl ring (entries 2 and 3), but not with an electron-withdrawing nitro group (entry 4). Surprisingly, the reaction with the more basic *N*-benzyl imine of benzaldehyde (**1e**, entry 5) generated the *N*-benzyl pyrrolidine (**7**), although only in 43% yield.

Table 3. Effect of Nitrogen Substitution of Imine on Catalytic Pyrrolidine Synthesis (Eq 3)[a]



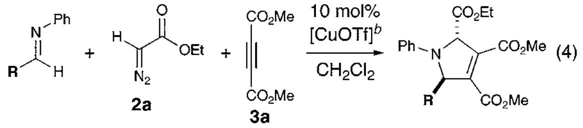
entry	R	yield (%)	dr[c]	compd
1	Ph (**1a**)	91	>20:1	**4a**
2	4-ClPh (**1b**)	75	>20:1	**5**
3	4-OMePh (**1c**)	43	>20:1	**6**
4	4-NO_2Ph (**1d**)	nr[d]		
5	$PhCH_2$ (**1e**)	43	>10:1[e]	**7**

[a] Reaction conditions: a solution of EDA (**2a**, 3 equiv) in CH_2Cl_2 (2.5 mL) was added via syringe pump over 3 h to a solution of imine (**1a**−**e**, 3 equiv), DMAD (**3a**, 1 equiv), and CuOTf (10 mol %) in CH_2Cl_2 (5 mL) with heating at the indicated temperature. [b] $[Cu(OTf)]_2 \cdot C_6H_6$. [c] Diastereomeric ratios determined by ^{1}H NMR (500 MHz) spectra of unpurified reaction mixtures. Relative stereochemistry of **5**−**7** were assigned by analogy to **10** (X-ray structure, see Figure 1). [d] No reaction. [e] As determined by gas chromatography.

The impact of substitution on the benzylidene portion of *N*-phenyl imines on the cycloaddition process was also explored. We again employed dimethyl acetylene−dicarboxylate (DMAD, **3a**) as the dipolarophile and ethyl diazoacetate (EDA, **2a**) as the carbenoid source with 10 mol % [CuOTf] as the catalyst. As Table 4 indicates, the reaction tolerates electron-withdrawing substituents (entries 4−6). Interestingly, inclusion of a nitro group in the substrate produces no reaction (entry 3). This deleterious effect of a nitro group on pyrrolidine formation was previously observed (Table 3, entry 4), and we postulate that the nitro group is deactivating the copper catalyst in both cases.[11] Electron-donating groups decrease the yield of the reaction (entries 8 and 9), but substantial quantities of product are still isolated. Cyclohexyl-*N*-phenyl imine was also utilized in the reaction (entry 10, 35% yield).[12]

Crystallization of **10** (Table 4, entry 4) from ether yielded single crystals that were analyzed by X-ray crystallography (Figure 1). The relative stereochemistry of **10** was determined to be trans with respect to the 2 and 5 positions of the pyrrolidine ring.[13]

Table 4. Catalytic, Three-Component Coupling of EDA (**2a**), DMAD (**3a**), and Various *N*-Phenyl Imines (Eq 4)[a]



entry	R	yield (%)	dr[c]	compd
1	Ph	91	20:1	**4a**
2	4-CH_3Ph	86	20:1	**8**
3	4-NO_2Ph	nr[d]		**9**
4	4-BrPh	79	20:1	**10**
5	4-ClPh	77	20:1	**11**
6	2-ClPh	74	20:1	**12**
7	2-Furyl	94	20:1	**13**
8	4-OMePh	54	20:1	**14**
9	3-OMePh	51	20:1	**15**
10	cyclohexyl	35	20:1	**16**

[a] Reaction conditions: a solution of EDA (**2a**, 3 equiv) in CH_2Cl_2 (2.5 mL) was added via syringe pump over 3 h to a solution of imine (3 equiv), DMAD (**3a**, 1 equiv) and [CuOTf] (10 mol %) in CH_2Cl_2 (5 mL) heating at the indicated temperature. The reaction was stirred for an additional hour, the solvent was removed and the residue was purified on SiO_2. [b] $[Cu(OTf)]_2 \bullet C_6H_6$. [c] Diastereomeric ratios determined by ^{1}H NMR (500 MHz) spectra of unpurified reaction mixtures. [d] No reaction.

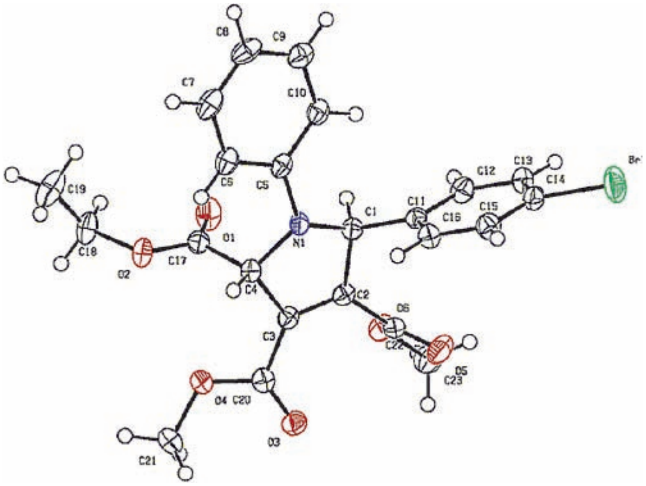


Figure 1. ORTEP representation of the crystal structure of substituted pyrrolidine **10**. Thermal ellipsoids are drawn at 50% probability.

We have also examined the scope of our three-component coupling with regard to the dipolarophile structure (Table 5). Electron-deficient alkenes undergo cyclization readily to

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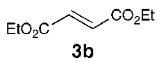
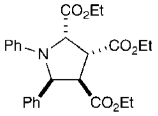
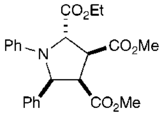
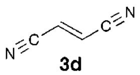
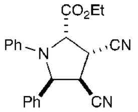
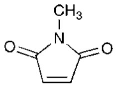
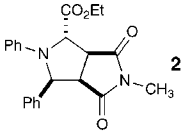
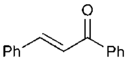
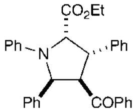
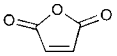
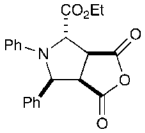
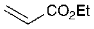
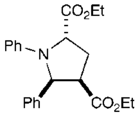
(11) For an example of a nitro group binding to copper(I), see: Yokota, S.; Tachi, Y.; Nishiwaki, N.; Ariga, M.; Itoh, S. *Inorg. Chem.* **2001**, *40*, 5316−5317.

(12) Yield suffers presumably due to the instability of the starting material imine under the reaction conditions.

(13) Crystallographic data for **10** have been deposited with the Cambridge Crystallographic Data Centre. See Supporting Information for details.

Table 5. Three-Component Assembly Reaction of *N*-Benzylidene Imine (**1a**), EDA (**2a**), and Dipolarophiles Catalyzed by [CuOTf][a]

entry	dipolarophile	major product	yield (%)	d.r.[b]
1	 **3b**	 **17**	77	2:1
2	 **3c**	 **18**	51	3:1
3	 **3d**	 **19**	83	3:2
4	 **3e**	 **20**	70	2:1
5[c]	 **3f**	 **21**	43	5:1
6[c]	 **3g**	 **22**	55	5:1
7[c]	 **3h**	 **23**	47	2:1

[a] Reaction conditions: a solution of EDA (**2a**, 3 equiv) in CH_2Cl_2 (2.5 mL) was added via syringe pump over 3 h to a solution of imine (**1a,** 3 equiv), dipolarophile (**3b**−**e**, 1 equiv) and 10 mol % $[Cu(OTf)]_2{\cdot}C_6H_6$ in CH_2Cl_2 (5 mL). The reaction was stirred for an additional hour; the solvent was removed, and the residue was purified on SiO_2. [b] Diastereomeric ratios determined by ^{1}H NMR (500 MHz) spectra of unpurified reaction mixtures. Minor products (not shown) possess inverted stereocenters at C3 and C4. Relative stereochemistry of products were assigned by analogy to the X-ray crystal structure of **10** (Figure 1) and known compound **23**; see Supporting Information for details. [c] EDA (**2a**, 1 equiv), imine (**1a,** 1 equiv), dipolarophile (**3f**−**h**, 6 equiv).

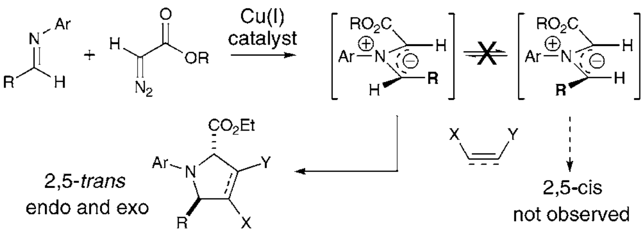


Figure 2. Proposed model for the three-component assembly of 2,5-*trans*-pyrrolidines.

afford the desired substituted pyrrolidines (entries 1−7). In some cases, an excess of the less-reactive dipolarophile was required (entries 5−7) to minimize competitive cycloaddition with fumarate (**3b**), which results from Cu(I)-catalyzed EDA dimerization. In the reactions employing unsymmetrical dipolarophiles (entries 5 and 7), no regioisomers were observed.

Our current working model of this reaction is shown in Figure 2). The combination of copper(I) and diazo compounds produces the corresponding metallocarbenoid. The presence of an imine during this process generates an azomethine ylid intermediate with the carbenoid carbon cis to the benzylidene substituent. We are currently engaged in determining whether this transient species is interacting with the metal center. The rate of (*E*)−(*Z*) isomerization of the azomethine ylid is apparently slower than the rate of the cycloaddition since only 2,5-trans stereochemistry of the resulting substituted pyrrolidine is observed. In addition, the dipolarophile alkene geometry is directly translated to the cycloaddition products: *trans*-alkenes (Table 4, entries 1, 3, and 5) give 3,4-trans products, and *cis*-alkenes (entries 2) afford 3,4-cis products. The factors that govern the *endo* and *exo* facial selectivity (with respect to the benzylidene substituent) of the azomethine ylid are currently under investigation.

In summary, the combination of an α-diazo ester and an imine in the presence of a copper(I) catalyst generates a transient azomethine ylid. This 1,3-dipole, generated in situ, undergoes diastereoselective cycloadditions with activated dipolarophiles to afford highly substituted pyrrolidines in a convergent, three-component assembly reaction. Notably, this process is capable of generating four contiguous stereogenic centers in one operation by employing a readily available catalyst. Our current efforts are focused on the development of the analogous asymmetric three-component coupling reaction and the utilization of these processes toward the synthesis of bioactive natural products.

Acknowledgment. Support for this research has been provided by Northwestern University. M.A.B. thanks Northwestern University for a Summer Undergraduate Research Grant. We thank Dr. B. Ramirez and Dr. C. Stern of the Analytical Services Laboratory (NU) for assistance with NMR experiments and single-crystal X-ray diffraction, respectively.

Supporting Information Available: Experimental procedures and characterization data for new compounds, as well as X-ray crystallographic data for **10** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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