Organic LETTERS

Letter

pubs.acs.org/OrgLett

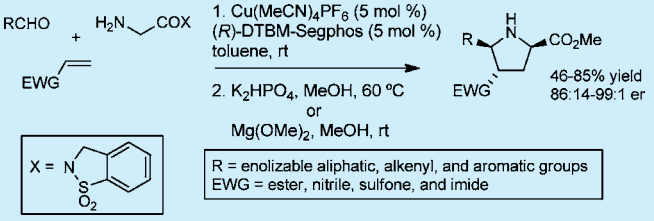
Catalytic Asymmetric *Exo*-Selective [C+NC+CC] Reaction

Ryan Joseph, Charles Murray, and Philip Garner*

Department of Chemistry, Washington State University, Pullman, Washington 99164-4630, United States

Supporting Information

ABSTRACT: A catalytic asymmetric version of the *exo*-selective [C+NC+CC] reaction is reported. This multicomponent reaction utilizes a readily prepared achiral glycyl sultam as the "NC" component and commercially available catalyst components. The method can be applied to a variety of aldehydes ("C" component) and activated alkenes ("CC" component) to provide substituted pyrrolidines in good yields and high enantioselectivities. Of particular note is the ability to employ labile enolizable aldehydes (e.g., acetaldehyde and propionaldehyde) in this reaction.

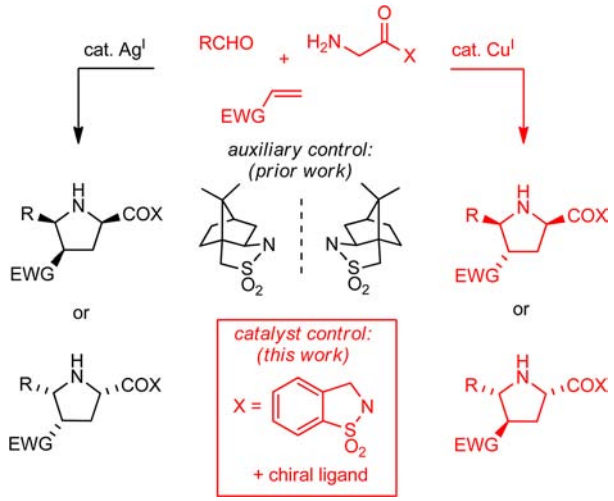


The pyrrolidine ring is found at the core of a diverse range of biologically active and structurally intriguing molecules. As a consequence, the synthesis of pyrrolidine-containing targets has been the focus of intense research. The foremost method for the synthesis of substituted pyrrolidines, namely the [3 + 2] cycloaddition of azomethine ylides and olefins, has undergone considerable development since its initial classification by Huisgen.[1,2] Grigg's seminal work in this area, utilizing stoichiometric Lewis acid metal salts together with chiral ligands and tertiary amine bases, first suggested the possibility of asymmetric catalysis in this reaction.[3] Since that time, a plethora of catalytic asymmetric versions of this reaction have been developed.[4] Despite these important advances, a critical limitation of current methods is that, except for a few isolated examples,[5] they are largely restricted to stable imine precursors derived from nonenolizable (usually aromatic) aldehydes. Most of the aliphatic examples have employed branched imines that may be conformationally protected from tautomerization. Very few groups have reported the use of more labile unbranched aliphatic imines in catalytic asymmetric azomethine ylide cycloadditions.[5b,i,k,l,n]

Our interest in this problem, necessitated by our desire to synthesize several target molecules possessing pyrrolidine cores with aliphatic substituents, led to the development of the asymmetric [C+NC+CC] reaction. In this multicomponent cycloaddition reaction, an aldehyde ("C" component), chiral glycyl sultam ("NC" component), and dipolarophile ("CC" component) combine to form functionalized pyrrolidines (Scheme 1).[6−9] Oppolzer's chiral glycyl sultam serves both to control the developing absolute stereochemistry and activate the α-proton for rapid dipole formation. The latter point is of particular significance because it enables the in situ generation of azomethine ylides derived from enolizable aliphatic aldehydes, thus differentiating this method from existing azomethine ylide cycloadditions that require one to preform an unstable imine.

We now report a catalytic asymmetric version of the *exo*-selective [C+NC+CC] reaction in which we demonstrate the enantioselective synthesis of a variety of substituted pyrrolidines using a catalytic Cu(I)/chiral ligand system. This atom-economical method utilizes a readily prepared achiral glycyl sultam "NC" component derived from the commodity chemical saccharine, allowing the in situ generation of azomethine ylides starting from enolizable unbranched aliphatic aldehydes. Although not the focus of this study, the reaction is also shown to proceed with aromatic and olefinic aldehydes. It is notable that no external base beyond the glycyl sultam amine component is required nor is the addition of any dehydrating agent.

Scheme 1. Asymmetric [C+NC+CC] Reaction Manifold



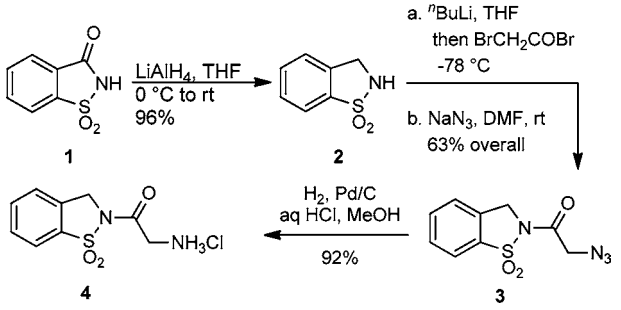
Our initial design for a catalytic asymmetric variant of the [C+NC+CC] reaction required the identification of an achiral auxiliary for the "NC" component. Based on our experience with Oppolzer's chiral glycyl sultam, we decided on a sultam-

Received: November 19, 2013
Published: March 6, 2014

   dx.doi.org/10.1021/ol500474a | *Org. Lett.* 2014, 16, 1550−1553

containing auxiliary that could be easily accessed from inexpensive, commercially available starting materials. The commodity chemical saccharine, which is readily reduced to the corresponding benzosultam, met our criteria and served as a starting point for our studies. The synthesis of the achiral glycyl benzosultam "NC" component is outlined below (Scheme 2).

Scheme 2. Synthesis of the Glycyl Benzosultam

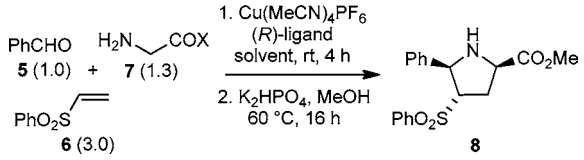


Reduction of saccharine gave benzosultam **2** in excellent yield.[10] Subsequent acylation with bromoacetyl bromide, followed by azide formation and reduction, was accomplished using adaptations of conditions developed for the camphor-derived auxiliary.[11] The resulting ammonium salt **4** was stable for storage and was conveniently converted to its more labile free amine form just before use.

Our next step involved evaluation of the achiral glycyl sultam employing our previously established *exo*-selective [C+NC+CC] reaction conditions.[7] An initial control experiment was performed in which the glycyl sultam was mixed with hydrocinnamaldehyde and methyl acrylate in DMSO in the presence of an achiral Cu(I) catalyst. We were pleased to find that the achiral saccharine-derived auxiliary participated in an *exo*-selective [C+NC+CC] reaction. Having demonstrated that the saccharine-derived achiral glycyl sultam was a viable "NC" component, we began our search for a chiral ligand and optimal reaction conditions for the catalytic asymmetric [C+NC+CC] reaction. This initial study was performed with benzaldehyde rather than enolizable aliphatic aldehydes such that we might more readily compare our results with the literature. A survey of known successful catalytic asymmetric azomethine ylide cycloadditions guided our selection of chiral ligands. The screening of commercially available ligands along with optimization of the reaction conditions is summarized in Table 1.

To evaluate ligand enantioselectivity, we converted the initially formed cycloadduct to the known methyl ester **8** by adapting Ohfune's conditions[12] for methanolysis. As entries 1−4 demonstrate, the Fesulphos, Taniaphos, Walphos, and DM-Segphos ligands showed little to no enantioselectivity in THF. However, an initial observation of enantioselectivity occurred when the more sterically demanding DTBM-Segphos was tested in THF (entry 5). With this promising result in hand, we wondered whether a simple change to a noncoordinating solvent might result in increased enantioselectivity. Indeed, changing the solvent to toluene resulted in a substantial improvement in enantioselectivity (entry 6) while DMSO did not (entry 7), lending support to our hypothesis. The use of CH_2Cl_2 as a solvent resulted in both poor yield and enantioselectivity (entry 8). Using DTBM-Segphos as ligand and toluene as the solvent, we found that high enantioselectivities could be achieved with catalyst levels as low as 5 mol %

Table 1. Ligand Screening and Reaction Optimization[a]



entry	ligand	solvent	yield of **8** (%)	er[d]
1	Fesulphos	THF	62[b]	52:48
2	Taniaphos	THF	58[b]	50:50
3	Walphos	THF	60[b]	50:50
4	DM-Segphos	THF	65[b]	52:48
5	DTBM-Segphos	THF	55[b]	67:33
6	DTBM-Segphos	toluene	70[b]	>99:1
7	DTBM-Segphos	DMSO	60[b]	58:42
8	DTBM-Segphos	CH_2Cl_2	25[b]	55:45
9	DTBM-Segphos	toluene	81[c]	>99:1
10	DM-Segphos	toluene	63[b]	55:45

[a]X = saccharine-derived sultam. [b]$Cu(MeCN)_4PF_6$ (10 mol %), (*R*)-ligand (10 mol %). [c]$Cu(MeCN)_4PF_6$ (5 mol %), (*R*)-ligand (5 mol %). [d](*R*/*S*) as determined from chiral HPLC analysis.

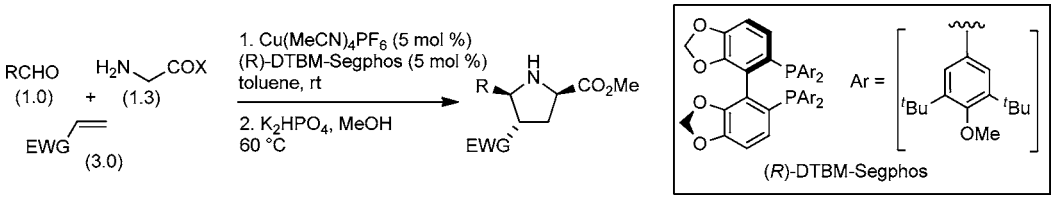
(entry 9). This combination defined our optimal reaction conditions. Somewhat surprisingly, switching to toluene did not improve the enantioselectivity associated with the DM-Segphos ligand (entry 10).

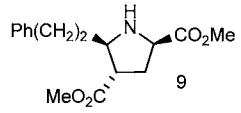
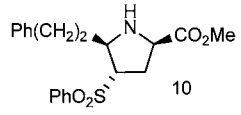
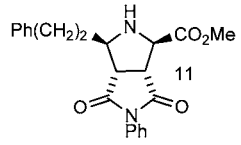
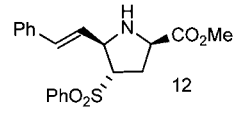
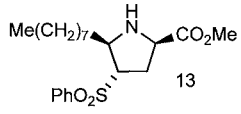
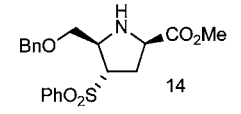
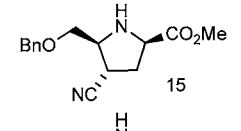
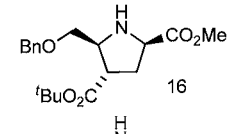
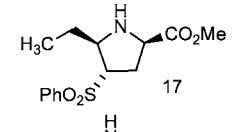
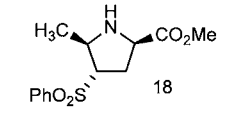
With optimized conditions in hand, we next sought to explore the scope of the catalytic asymmetric exoselective [C+NC+CC] reaction with various aldehydes and activated alkenes (Table 2). To aid in purification and analysis, the cycloadducts were converted to their corresponding methyl esters. As shown in this collection of examples, the optimal reaction conditions enable the enantioselective catalytic asymmetric [CC+NC+CC] synthesis of substituted pyrrolidines using a variety of aliphatic enolizable aldehydes. These reactions were all *exo*-selective with the relative configuration assignments being made through NOE experiments. The absolute configurations were based on a combination of chemical correlation and chiral HPLC relative retention times. Entries 1−3 demonstrate [C+NC+CC] cycloadditions of hydrocinnamaldehyde with standard dipolarophiles, giving excellent enantioselectivities and good overall yields with only trace levels of detectable diastereomers.[13] Cinnamaldehyde also gave excellent enantio- and diastereoselectivity (entry 4). The reaction with 1-nonanal exhibited very good enantioselectivity (entry 5). Entries 6−8 explored the catalytic-asymmetric [CC+NC+CC] reaction with the more synthetically useful benzyloxyacetaldehyde while also expanding the scope to several other dipolarophiles. These reactions proceeded with slightly lower but still very good enantioselectivities. Finally, we successfully demonstrated the catalytic asymmetric [C+NC+CC] cycloaddition protocol using the volatile enolizable aliphatic aldehydes propionaldehyde and acetaldehyde (entries 9 and 10, respectively). Both of these reactions gave very good enantioselectivities. To our knowledge, this is the first example of the use of acetaldehyde in this class of cycloadditions, clearly illustrating the utility of the catalytic asymmetric [C+NC+CC] reaction.

In conclusion, we have developed a unique catalytic asymmetric *exo*-selective [C+NC+CC] reaction for the stereocontrolled synthesis of substituted pyrrolidines. By utilizing a readily prepared achiral glycyl sultam and a commercially available metal salt + chiral ligand catalyst, [C+NC+CC]

dx.doi.org/10.1021/ol500474a | *Org. Lett.* 2014, 16, 1550−1553

Table 2. Catalytic−Asymmetric [C+NC+CC] Reaction[a]



entry	aldehyde	dipolarophile	reaction time [h]	isolated yield [%][b]	dr (exo:endo)	er	major product
1	$Ph(CH_2)_2CHO$	methyl acrylate	4	68	>99:1	>99:1	 9
2	$Ph(CH_2)_2CHO$	phenyl vinyl sulfone	4	72	>99:1	>99:1	 10
3	$Ph(CH_2)_2CHO$	*N*-phenylmaleimide	3	65	>99:1	>99:1	 11
4	(*E*)-$Ph(CH)_2CHO$	phenyl vinyl sulfone	2	85	>99:1	99:1	 12
5	$CH_3(CH_2)_7CHO$	phenyl vinyl sulfone	6	65	>99:1	94:6	 13
6	$BnOCH_2CHO$	phenyl vinyl sulfone	3	81	96:4	92:8	 14
7	$BnOCH_2CHO$	acrylonitrile	5	75	93:7	86:14	 15
8[c]	$BnOCH_2CHO$	*tert*-butyl acrylate	4	82	>99:1	95:5	 16
9[c,d]	CH_3CH_2CHO	phenyl vinyl sulfone	4	60	97:3	88:12	 17
10[c,d]	CH_3CHO	phenyl vinyl sulfone	4	46	>99:1	96:4	 18

[a]X = saccharine-derived sultam. [b]Isolated yield over two steps. [c]Methanolysis performed with $Mg(OMe)_2$. [d]An excess of aldehyde was used.

cyclizations can be performed with a variety of enolizable aliphatic aldehydes and electron-deficient alkenes producing functionalized pyrrolidines with very good to excellent enantioselectivity. The reaction augments existing methods and should prove useful in synthetic applications.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ppg@wsu.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by a grant from the National Science Foundation (CHE-1149327). We thank Dr. Frank Dyer (Washington State University) for helpful discussions.

REFERENCES

(1) Huisgen, R. *Angew. Chem., Int. Ed.* **1963**, *2*, 565.
(2) Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; Wiley: New York, 1984.
(3) Allway, P.; Grigg, R. *Tetrahedron Lett.* **1991**, *41*, 5817.
(4) Reviews of the area: (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (b) Husinec, S.; Savic, V. *Tetrahedron: Asymmetry* **2005**, *16*, 2047. (c) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484. (d) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235. (e) Najera, C.; Sansano, J. M. *Org. Biomol. Chem.* **2009**, *7*, 4567. (f) Kissane, M.; Maguire, A. R. *Chem. Soc. Rev.* **2010**, *39*, 845. (g) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2011**, *47*, 6784.
(5) (a) Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400. (b) Alemparte, C.; Blay, G.; Jørgensen, K. A. *Org. Lett.* **2005**, *7*, 4569. (c) Zeng, W.; Zhou, Y. G. *Org. Lett.* **2005**, *7*, 5055. (d) Llamas, T.; Arrayás, R. G.; Carretero, J. C. *Org. Lett.* **2006**, *8*, 1795. (e) Cabrera, S.; Arrayás, R. G.; Martín-Matute, B.; Cossió, F. P.; Carretero, J. C. *Tetrahedron* **2007**, *63*, 6587. (f) Llamas, T.; Arrayás, R. G.; Carretero, J. C. *Synthesis* **2007**, 950. (g) Fukuzawa, S. I.; Oki, H. *Org. Lett.* **2008**, *10*, 1747. (h) López-Pérez, A.; Adrio, J.; Carretero, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 10084. (i) Chen, X. H.; Wei, Q.; Luo, S. W.; Xiao, H.; Gong, L. Z. *J. Am. Chem. Soc.* **2009**, *131*, 13819. (j) Liu, T.-L.; Xue, Z.-Y.; Tao, H.-Y.; Wang, C.-J. *Org. Biomol. Chem.* **2011**, *9*, 1980. (k) Yamashita, Y.; Imaizumi, T.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 4893. (l) Yamashita, Y.; Imaizumi, T.; Guo, X.-X.; Kobayashi, S. *Chem.—Asian J.* **2011**, *6*, 2550. (m) Gu, X.; Xu, Z.-J.; Lo, V. K.-Y.; Che, C.-M. *Synthesis* **2012**, *44*, 3307. (n) Reboredo, S.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L.; de Cózar, A.; Cossío, F. P. *Chem.—Eur. J.* **2012**, *18*, 7179. (o) Liu, T.-L.; He, Z.-L.; Tao, H.-Y.; Wang, C.-J. *Chem.—Eur. J.* **2012**, *18*, 8042. (p) Awata, A.; Arai, T. *Chem.—Eur. J.* **2012**, *18*, 8278. (q) Yan, S.; Zhang, C.; Wang, Y.-H.; Cao, Z.; Zheng, Z.; Hu, X.-P. *Tetrahedron Lett.* **2013**, *54*, 3669.
(6) Garner, P.; Kaniskan, H. Ü.; Hu, J.; Youngs, W. J.; Panzner, M. *Org. Lett.* **2006**, *8*, 3647.
(7) Garner, P.; Hu, J.; Parker, C. G.; Youngs, W. J.; Medvetz, D. *Tetrahedron Lett.* **2007**, *48*, 3867.
(8) Garner, P.; Kaniskan, H. U.; Keyari, C. M.; Weerasinghe, L. *J. Org. Chem.* **2011**, *76*, 5283.
(9) Garner, P.; Weerasinghe, L.; Youngs, W.; Wright, B.; Wilson, D.; Jacobs, D. *Org. Lett.* **2012**, *14*, 1326.
(10) Chapman, J. M.; Cocolas, G. H.; Hall, I. H. *J. Med. Chem.* **1983**, *26*, 243.
(11) Kaniskan, H. Ü. Ph.D. Dissertation, Case Western Reserve University, Cleveland, OH, 2007.
(12) Shinada, T.; Hamada, M.; Ohfune, Y. *Synlett* **2007**, *14*, 2141.
(13) The cycloaddition with dimethyl maleate produced an inseparable mixture of four diastereomers in a 7:4:2:1 ratio, suggesting that a stepwise mechanism may be operative. The major product was tentatively assigned as the *exo*-isomer based on COSY and NOE analysis (see the Supporting Information). No enantiomeric ratio measurement was made due to the complicating presence of multiple diastereomers in similar relative ratios.

dx.doi.org/10.1021/ol500474a | *Org. Lett.* 2014, 16, 1550−1553