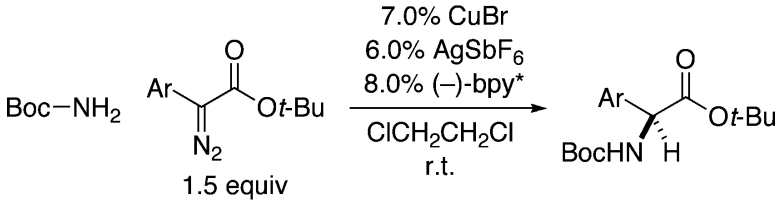
Communication

Copper-Catalyzed Asymmetric N–H Insertion Reactions: Couplings of Diazo Compounds with Carbamates to Generate α-Amino Acids

Elaine C. Lee, and Gregory C. Fu

J. Am. Chem. Soc., **2007**, 129 (40), 12066-12067• DOI: 10.1021/ja074483j • Publication Date (Web): 18 September 2007



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 14 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 09/18/2007

Copper-Catalyzed Asymmetric N−H Insertion Reactions: Couplings of Diazo Compounds with Carbamates to Generate α-Amino Acids

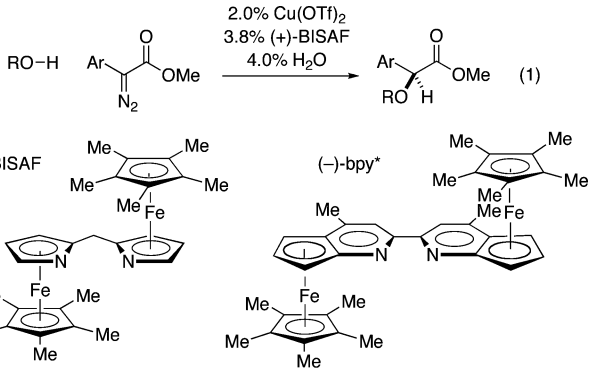
Elaine C. Lee and Gregory C. Fu*

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

Received June 19, 2007; E-mail: gcf@mit.edu

The development of efficient methods for the preparation of enantioenriched α-amino acids is of considerable importance in a variety of fields, including chemistry and biology.[1] For example, phenylglycine or other arylglycines are subunits of bioactive molecules such as amoxicillin and vancomycin.[2,3] As a consequence, a great deal of effort has been dedicated to the discovery of new approaches to the asymmetric synthesis of α-amino acids.[4]

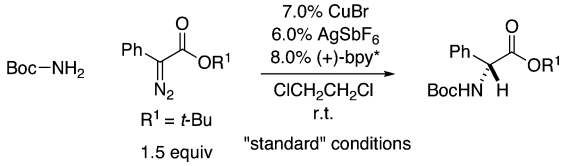
The enantioselective insertion of an α-diazocarbonyl compound into an N−H bond represents a potentially attractive route to α-amino acid derivatives.[5−7] However, whereas catalytic asymmetric insertions into C−H bonds have evolved into an extremely powerful tool in organic synthesis,[8] the development of corresponding reactions of X−H bonds (X = a heteroatom such as O or N) is still in its infancy. Thus, the first efficient method for catalytic enantioselective insertions into O−H bonds was just described in 2006 (eq 1).[9]



In view of the significance of nonracemic α-amino acids, we decided to examine enantioselective N−H insertion reactions of α-diazo esters. At the time that we initiated this program, the state-of-the-art for catalytic asymmetric intermolecular N−H insertions was defined by a pioneering study by Jørgensen, who demonstrated that a chiral copper/bis(oxazoline) catalyst can furnish 28% ee (54% yield) for the reaction of aniline with $MeC(N_2)CO_2Et$.[10,11] Very recently, Zhou has reported an impressive advance in this field, specifically, that a different copper/bis(oxazoline) catalyst achieves the insertion of $MeC(N_2)CO_2R$ into an array of anilines ($ArNH_2$) with excellent enantioselectivity (up to 98% ee).[12] The use of other N−H sources led either to no reaction (e.g., a primary alkyl amine) or to a racemic product (e.g., a carbamate). The Zhou study focused almost exclusively on $MeC(N_2)CO_2R$, although it was noted that the insertion of $EtC(N_2)CO_2R$ proceeds in good ee (94%) and modest yield (51%), whereas $PhC(N_2)CO_2R$ affords very low enantiomeric excess (8%).

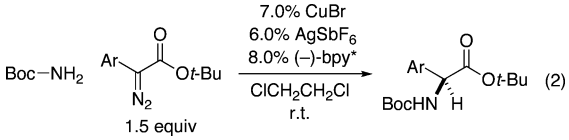
In this report, we describe further progress in achieving asymmetric N−H insertion reactions, in particular, the use of a chiral copper/bipyridine catalyst to couple α-aryl-α-diazo esters with readily deprotected carbamates, thereby furnishing access to aryl-glycine derivatives (eq 2). With regard to ligand structure and to reaction partners, this method complements the studies of Jørgensen and Zhou.

Table 1. Catalytic Asymmetric N−H Insertions: Effect of Reaction Parameters



entry	variation from the "standard" conditions	yield (%)[a,b]	ee (%)[a]
1	none	74	94
2	R^1 = *i*-Pr instead of *t*-Bu	69	84
3	R^1 = Bn instead of *t*-Bu	81	77
4	R^1 = Me instead of *t*-Bu	70	70
5	no $AgSbF_6$	<2	–
6	6.0% AgOTf instead of $AgSbF_6$	86	87
7	no bpy*	80	0
8	12% bpy* instead of 8% bpy*	77	92
9	8.0% of a bis(oxazoline)[c] instead of bpy*	80	<10
10	8.0% of BISAF instead of bpy*	70	<10
11	CH_2Cl_2 instead of $ClCH_2CH_2Cl$	71	88
12	THF instead of $ClCH_2CH_2Cl$	66	69
13	toluene instead of $ClCH_2CH_2Cl$	42	74

[a] Average of two experiments. [b] Isolated yield. [c] Isopropylidenebis[(4*R*)-4-*tert*-butyl-2-oxazoline].

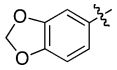


The procedure that we had developed for catalytic asymmetric insertions of α-diazo esters into the O−H bond of alcohols (eq 1) provides modest enantioselectivity for the reaction of $BocNH_2$ with $PhC(N_2)CO_2t$-Bu (<50% ee). In contrast, a copper/planar-chiral bipyridine[13,14] catalyst accomplishes the desired N−H insertion in good yield and ee (Table 1, entry 1).

The stereoselectivity diminishes as the steric demand of the ester decreases (Table 1, entries 2−4).[15] In the absence of $AgSbF_6$, N−H insertion does not occur (entry 5), which suggests that it is advantageous to generate a halide-free copper complex. Silver salts that bear poorly coordinating counteranions other than SbF_6 can be employed, although a slightly lower ee is obtained (entry 6). Because N−H insertion proceeds in the absence of bpy* (entry 7), we examined the possibility that a larger excess of bpy* might improve the ee by decreasing the amount of bpy*-free copper. However, additional bpy* does not lead to enhanced enantioselectivity (entry 8), which indicates that the equilibrium constant for complexation of bpy* to copper is high. A variety of other ligands, including a bis(oxazoline) and a bis(azaferrocene), are not effective

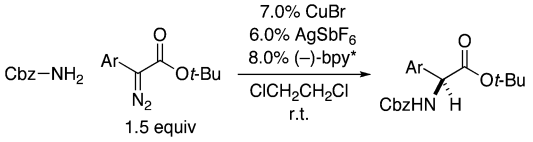
10.1021/ja074483j CCC: $37.00

Table 2. Catalytic Asymmetric N−H Insertions: Synthesis of Boc-Protected Arylglycines (for Reaction Conditions, See eq 2)

entry	Ar	yield (%)[a,b]	ee (%)[a]
1	Ph	75	94
2	(2-Me)C_6H_4	71	81
3	(3-Me)C_6H_4	75	88
4	(4-OMe)C_6H_4	61	95
5	(4-NHBoc)C_6H_4	77	91
6	(4-Br)C_6H_4	86	85 (95)[c]
7	(4-CF_3)C_6H_4	89	85
8	2-naphthyl	73	91
9		74	90
10	3-thienyl	48	80

[a] Average of two experiments. [b] Isolated yield. [c] After one crystallization from hexanes.

Table 3. Catalytic Asymmetric N−H Insertions: Synthesis of Cbz-Protected Arylglycines



entry	Ar	yield (%)[a,b]	ee (%)[a]
1	Ph	77	95
2	(4-OMe)C_6H_4	49	90
3	(4-CF_3)C_6H_4	78	82 (98)[c]

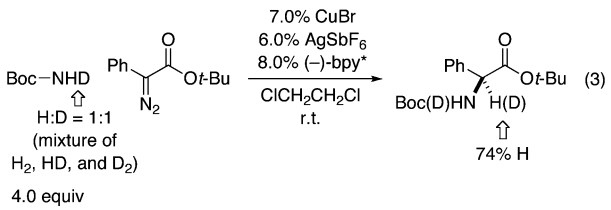
[a] Average of two experiments. [b] Isolated yield. [c] After one crystallization from hexanes.

under these conditions (entries 9 and 10). Finally, the use of solvents such as CH_2Cl_2, THF, or toluene, rather than $ClCH_2CH_2Cl$, results in a small to moderate loss in ee (entries 11−13).

This new method for catalytic asymmetric N−H insertions can be applied to a range of α-aryl-α-diazo esters (Table 2).[16] Thus, the aromatic ring can be substituted in the 2, 3, or 4 position, and the group can be electron-donating or electron-withdrawing (entries 2−7). A fused aromatic ring or a heterocycle can be present (entries 8−10), although the reaction proceeds in modest yield if Ar = 3-thienyl (entry 10). Finally, for an N−H insertion that occurs with relatively low stereoselectivity, the ee of the product can be enhanced through crystallization (entry 6).

The scope of this copper/bpy*-catalyzed asymmetric N−H insertion is not limited to the synthesis of Boc-protected arylglycines. As illustrated in Table 3, reactions of $CbzNH_2$ generally proceed with comparable ee as for $BocNH_2$ (but in somewhat lower yield), thereby providing access to Cbz-protected arylglycines.

In a competition experiment, we have determined that Cu/bpy* has a considerable bias for N−H rather than N−D insertion (eq 3). In an earlier study of O−H insertion reactions catalyzed by Cu/BISAF, we observed a similar preference.[9,17]



In summary, we have developed a Cu/bpy*-catalyzed method for the asymmetric insertion of α-diazocarbonyl compounds into the N−H bonds of carbamates to generate an array of easily deprotected arylglycines in good enantiomeric excess. This process complements the two earlier reports of catalytic asymmetric intermolecular N−H insertion reactions, both of which focused on the use of a chiral bis(oxazoline) as a ligand for copper-catalyzed couplings of anilines with α-methyl-α-diazo esters.

Acknowledgment. Support has been provided by the National Institutes of Health (National Institute of General Medical Sciences, R01-GM66960), Merck Research Laboratories, Novartis, and Boehringer Ingelheim.

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

References

(1) For example, see: Wang, L.; Schultz, P. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 34−66.
(2) (a) For leading references to the chemistry and biology of vancomycin, see: *Medical Chemistry of Bioactive Natural Products*; Liang, X.-T., Fang, W.-S., Eds.; Wiley: Hoboken, NJ, 2006; pp 35−72. (b) For an example of studies of vancomycin analogues, see: Christensen, B. G.; Judice, J. K.; Mu, Y. Preparation of Glycopeptide Derivatives as Antibacterial Agents. U.S. Patent Appl. 2003008812, 2003.
(3) For leading references to the asymmetric synthesis of arylglycines, see: (a) Shang, G.; Yang, Q.; Zhang, X. *Angew. Chem., Int. Ed.* **2006**, *45*, 6360−6362. (b) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889−917.
(4) For leading references on the asymmetric synthesis of amino acids, see: (a) Ma, J.-A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4290−4299 (catalytic processes). (b) Natchus, M. G.; Tian, X. *Org. Synth.: Theory Appl.* **2001**, *5*, 89−196. (c) Calmes, M.; Daunis, J. *Amino Acids* **1999**, *16*, 215−250. (d) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: Oxford, England, 1989.
(5) (a) For an early study of metal-catalyzed N−H insertions, see: Yates, P. *J. Am. Chem. Soc.* **1952**, *74*, 5376−5381. (b) For an overview of catalyzed insertions of diazo compounds into N−H bonds, see: Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998; Chapter 8.2.
(6) For a classic industrial application (thienamycin) of a metal-catalyzed insertion of a diazo compound into an N−H bond, see: Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6163−6165.
(7) For a pioneering investigation of diastereoselective N−H insertion to generate α-amino acids, see: Nicoud, J.-F.; Kagan, H. B. *Tetrahedron Lett.* **1971**, 2065−2068.
(8) For reviews and leading references, see: (a) Davies, H. M. L.; Long, M. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6422−6425. (b) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; pp 513−603. (c) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861−2903. (d) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905−2919.
(9) Maier, T. C.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 4594−4595.
(10) Bachmann, S.; Fielenbach, D.; Jørgensen, K. A. *Org. Biomol. Chem.* **2004**, *2*, 3044−3049.
(11) For a seminal study of catalytic asymmetric *intra*molecular N−H insertions, see: Garcia, C. F.; McKervey, M. A.; Ye, T. *Chem. Commun.* **1996**, 1465−1466.
(12) Liu, B.; Zhu, S.-F.; Zhang, W.; Chen, C.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 5834−5835.
(13) (a) For a recent application of bpy* as a ligand in asymmetric catalysis, see: Son, S.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 1046−1047. (b) For the initial report of bpy*, see: Rios, R.; Liang, J.; Lo, M. M.-C.; Fu, G. C. *Chem. Commun.* **2000**, 377−378.
(14) For reviews of chiral 2,2′-bipyridine ligands, see: (a) Malkov, A. V.; Kocovsky, P. *Curr. Org. Chem.* **2003**, *7*, 1737−1757. (b) Fletcher, N. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1831−1842.
(15) Interestingly, for catalytic asymmetric O−H insertion reactions, the opposite trend is observed: stereoselectivity *increases* as the steric demand of the ester decreases (ref 9).
(16) Notes: (1) An attempt to extend this catalytic asymmetric N−H insertion process to an α-alkyl-α-diazo ester led to a 1,2-H shift, thereby generating an α,β-unsaturated ester. (2) An α-pyridyl-α-diazo ester was unreactive. (3) The reaction of an α-alkenyl-α-diazo ester (2-phenylethenyl) proceeded in good ee (87%), but modest yield (25%). (4) An insertion into the N−H bond of an amine occurred with low enantioselectivity. All of these couplings were conducted under our standard conditions (eq 2) without any optimization.
(17) We observe a small negative nonlinear effect. For a review of nonlinear effects, see: Kagan, H. B.; Luukas, T. O. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Chapter 4.1.

JA074483J