

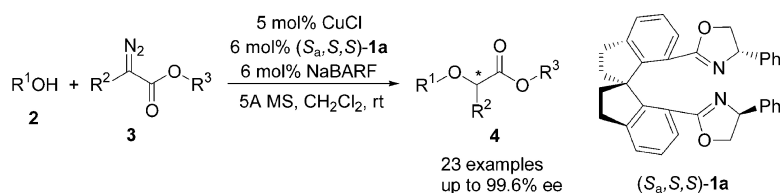
Communication

Highly Enantioselective Insertion of Carbenoids into O–H Bonds of Phenols: An Efficient Approach to Chiral α -Aryloxycarboxylic Esters

Chao Chen, Shou-Fei Zhu, Bin Liu, Li-Xin Wang, and Qi-Lin Zhou

J. Am. Chem. Soc., **2007**, 129 (42), 12616-12617 • DOI: 10.1021/ja074729k • Publication Date (Web): 29 September 2007

Downloaded from <http://pubs.acs.org> on February 14, 2009



More About This Article

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

- Supporting Information
- Links to the 11 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](#)



ACS Publications
 High quality. High impact.

Highly Enantioselective Insertion of Carbenoids into O–H Bonds of Phenols: An Efficient Approach to Chiral α -Aryloxy-carboxylic Esters

Chao Chen,[‡] Shou-Fei Zhu,[†] Bin Liu,[†] Li-Xin Wang,[†] and Qi-Lin Zhou^{*†}

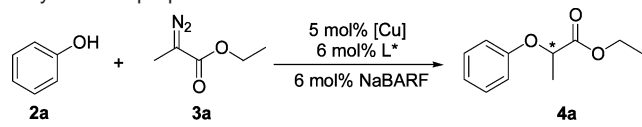
State Key Laboratory and Institute of Elemento-organic Chemistry, Nankai University, Tianjin 300071, China, and Institute of Fine Chemicals, East China University of Science and Technology, Shanghai 200237, China

Received June 28, 2007; E-mail: qlzhou@nankai.edu.cn

As a proven efficient means of constructing complex chemical structures from simple, readily available precursors, the catalytic insertion of α -diazocarbonyl compounds into X–H (X = C, N, O, S, etc.) bonds has been widely used in organic synthesis.¹ Remarkable advances have been made in the methodology for catalytic asymmetric diazo insertion into C–H bonds,² but only limited success has been achieved for asymmetric insertions into heteroatom–hydrogen bonds.³ The O–H insertion was an efficient method for preparing α -alkoxy or α -aryloxy ketones and esters, and oxygen-containing heterocyclic compounds.⁴ However, only recently Fu et al.⁵ have made a breakthrough in asymmetric O–H insertion. With a Cu complex of chiral biazaferrrocene as a catalyst, they realized the first highly enantioselective insertion of α -diazocarbonyl compounds into O–H bonds of alcohols. Under the optimal reaction conditions, various alcohols reacted with methyl α -diazo- α -phenylacetate, producing the corresponding α -alkoxy esters in high enantioselectivities. Unfortunately, when the Cu/biazaferrrocene catalyst was applied to phenol substrates, the enantioselectivity markedly decreased (11% ee). Thus, the catalytic asymmetric insertion reaction of α -diazocarbonyl compounds with phenols remains a challenge. In a previous paper, we accomplished the highly enantioselective insertion of α -diazoesters into N–H bonds by using the copper complexes of chiral spiro bisoxazolines.⁶ In this communication, we report the first efficient chiral catalyst for enantioselective insertion of carbenoids into O–H bond of phenols, yielding α -aryloxy-carboxylic esters in high yields with enantioselectivities of up to 99.6% ee.

The insertion reaction of ethyl α -diazopropionate (**3a**) and phenol (**2a**) was first carried out in the presence of copper catalyst generated in situ from 5 mol % CuCl, 6 mol % bisoxazoline ligands, and 6 mol % NaBARF⁷ additive in dichloromethane at 25 °C. As shown in Table 1, bisoxazoline ligands (*S,S*)-Ph-Box, (*S,S*)-*i*-Pr-Pybox, (*S_a,S_a,S_a*)-Ph-Binabox, and (*R_a,S_a,S_a*)-Ph-Binabox (Scheme 1) afforded O–H insertion products in moderate yields with very low enantioselectivities (Table 1, entries 1–4). In sharp contrast, the ligand Spirobox (*S_a,S_a,S_a*)-**1a**, containing a chiral spirobiindane backbone, has an excellent enantioselectivity (99% ee) (entry 5). The fact that the ligand (*R_a,S_a,S_a*)-**1a** gave a racemic product (entry 6) showed that the matched combination of the chiralities of backbone and oxazoline rings in the ligands **1a** played a crucial role in the enantiocontrol. The NaBARF additive is also essential for the reaction. Without NaBARF, no O–H insertion took place under the same reaction conditions. To improve the yield of the reaction, molecular sieves (MS) were added, with the addition of 600 mg of 5 Å MS giving the highest yield (entry 8). Uses of 5 equiv of phenol and 5 mol % catalyst are necessary for obtaining high yields. Reducing both the amount of phenol to 2 equiv and the catalyst loading to 2 mol % resulted in lower yields (entries 10 and 11). In

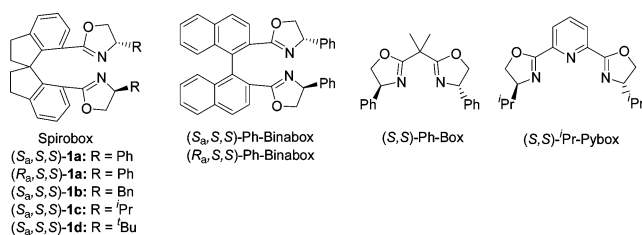
Table 1. Cu-Catalyzed Asymmetric O–H Insertion of Phenol by Ethyl α -Diazopropionate^a



| entry | ligand | [Cu]/additive ^b | solvent | yield (%) ^c | ee (%) ^d |
|-----------------|-----------------------------------------------------------------|-------------------------------------------|---------------------------------|------------------------|---------------------|
| 1 | (<i>S,S</i>)-Ph-Box | CuCl | CH ₂ Cl ₂ | 51 | 32 |
| 2 | (<i>S,S</i>)- <i>i</i> -Pr-Pybox | CuCl | CH ₂ Cl ₂ | 65 | 12 |
| 3 | (<i>S_a,S_a,S_a</i>)-Ph-Binabox | CuCl | CH ₂ Cl ₂ | 67 | 0 |
| 4 | (<i>R_a,S_a,S_a</i>)-Ph-Binabox | CuCl | CH ₂ Cl ₂ | 31 | 11 |
| 5 | (<i>S_a,S_a,S_a</i>)- 1a | CuCl | CH ₂ Cl ₂ | 52 | 99 |
| 6 | (<i>R_a,S_a,S_a</i>)- 1a | CuCl | CH ₂ Cl ₂ | 59 | 3 |
| 7 | (<i>S_a,S_a,S_a</i>)- 1a | CuCl/4 Å MS | CH ₂ Cl ₂ | 79 | 99 |
| 8 | (<i>S_a,S_a,S_a</i>)- 1a | CuCl/5 Å MS | CH ₂ Cl ₂ | 87 | 99 |
| 9 ^e | (<i>S_a,S_a,S_a</i>)- 1a | CuCl/5 Å MS | CH ₂ Cl ₂ | 70 | 99 |
| 10 ^f | (<i>S_a,S_a,S_a</i>)- 1a | CuCl/5 Å MS | CH ₂ Cl ₂ | 79 | 99 |
| 11 ^g | (<i>S_a,S_a,S_a</i>)- 1a | CuCl/5 Å MS | CH ₂ Cl ₂ | 60 | 96 |
| 12 | (<i>S_a,S_a,S_a</i>)- 1a | CuCl/5 Å MS | CHCl ₃ | 78 | 97 |
| 13 | (<i>S_a,S_a,S_a</i>)- 1a | CuCl/5 Å MS | DCE | 65 | 94 |
| 14 | (<i>S_a,S_a,S_a</i>)- 1a | CuCl/5 Å MS | toluene | 70 | 96 |
| 15 | (<i>S_a,S_a,S_a</i>)- 1a | CuCl/5 Å MS | hexane | 65 | 82 |
| 16 | (<i>S_a,S_a,S_a</i>)- 1a | Cu(OTf) ₂ /5 Å MS | CH ₂ Cl ₂ | 67 | 98 |
| 17 | (<i>S_a,S_a,S_a</i>)- 1a | Cu(PF ₆) ₂ /5 Å MS | CH ₂ Cl ₂ | 63 | 99 |
| 18 | (<i>S_a,S_a,S_a</i>)- 1b | CuCl/5 Å MS | CH ₂ Cl ₂ | 81 | 92 |
| 19 | (<i>S_a,S_a,S_a</i>)- 1c | CuCl/5 Å MS | CH ₂ Cl ₂ | 86 | 99 |
| 20 | (<i>S_a,S_a,S_a</i>)- 1d | CuCl/5 Å MS | CH ₂ Cl ₂ | 79 | 88 |

^a Reaction conditions: [Cu] (0.02 mmol), ligand (0.024 mmol), NaBARF (0.024 mmol), and solvent (4 mL) were stirred under argon at 25 °C for 2 h; then phenol (2.0 mmol) and ethyl α -diazopropionate (0.4 mmol) were introduced, and the reaction mixture was stirred for another 3 h. ^b 600 mg of MS was added unless otherwise noted. ^c Isolated yield. ^d Determined by chiral HPLC using a Chiralcel OD-H column. ^e 300 mg of 5 Å MS was added. ^f With 2 equiv of phenol. ^g With 2 mol % catalyst.

Scheme 1



addition to dichloromethane, chloroform, 1,2-dichloroethane, toluene, and hexane can serve as solvents in the insertion of ethyl α -diazopropionate into the O–H bond of phenol; however, the enantioselectivities were slightly lower, especially for the reaction in hexane (entries 12–15). In addition to CuCl, Cu(OTf)₂ and Cu(PF₆)₂ were also good catalyst precursors, affording excellent enantioselectivities in the reaction (entries 16 and 17). We examined the effect of the substituents of the oxazoline rings of spiro ligands **1** on the enantioselectivity of the O–H insertion reaction. The ligand

[†] Nankai University.

[‡] East China University of Science and Technology.

Table 2. Asymmetric Catalytic Carbenoid Insertion into O–H Bonds of Phenols^a

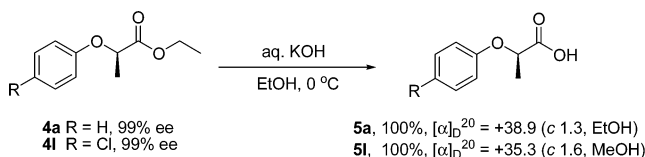
| entry | R ¹ | R ² | R ³ | product | yield (%) | ee (%) |
|-------|-----------------------------------|----------------|-----------------|-----------|-----------|-------------------|
| 1 | Ph | Me | Et | 4a | 87 | 99 (<i>R</i>) |
| 2 | <i>o</i> -MePh | Me | Et | 4b | 71 | 98 |
| 3 | <i>o</i> -MeOPh | Me | Et | 4c | 68 | 95 |
| 4 | <i>o</i> -PhPh | Me | Et | 4d | 83 | 99.2 |
| 5 | <i>m</i> -MePh | Me | Et | 4e | 79 | 99.3 |
| 6 | <i>m</i> -MeOPh | Me | Et | 4f | 71 | 99 |
| 7 | <i>m</i> -BrPh | Me | Et | 4g | 78 | 99 |
| 8 | <i>m</i> -PhPh | Me | Et | 4h | 82 | 99 |
| 9 | <i>p</i> -MePh | Me | Et | 4i | 88 | 99 |
| 10 | <i>p</i> -MeOPh | Me | Et | 4j | 78 | 99 |
| 11 | <i>p</i> - ^t BuPh | Me | Et | 4k | 70 | 98 |
| 12 | <i>p</i> -ClPh | Me | Et | 4l | 83 | 99.1 (<i>R</i>) |
| 13 | <i>p</i> -BrPh | Me | Et | 4m | 85 | 99.6 |
| 14 | <i>p</i> -MeO ₂ CPh | Me | Et | 4n | 62 | 99 |
| 15 | 2,4-diMePh | Me | Et | 4o | 80 | 99 |
| 16 | 3,5-diPhPh | Me | Et | 4p | 84 | 99 |
| 17 | 1-naphthyl | Me | Et | 4q | 77 | 99.1 (<i>R</i>) |
| 18 | 2-naphthyl | Me | Et | 4r | 83 | 98 (<i>R</i>) |
| 19 | Ph(CH ₂) ₃ | Me | Et | 4s | 63 | 59 |
| 20 | PhCH=CHCH ₂ | Me | Et | 4t | 85 | 61 (<i>R</i>) |
| 21 | Ph | Ph | Me | 4u | 71 | 10 (<i>R</i>) |
| 22 | Ph | Me | Me | 4v | 70 | 98 (<i>R</i>) |
| 23 | Ph | Me | ^t Bu | 4w | 80 | 99 |

^a Reaction conditions were the same as those in Table 1, entry 8. All reactions were completed within 3 h. For the characterization and analysis of ee values of insertion products, see Supporting Information.

(*S,S,S,S*)-**1c**, having an ⁱPr unit, gave the insertion product in 99% ee (entry 19), identical to that obtained with ligand (*S,S,S,S*)-**1a**. The ligands (*S,S,S,S*)-**1b** and (*S,S,S,S*)-**1d**, containing benzyl and *tert*-butyl groups, respectively, showed lower enantioselectivities (entries 18 and 20).

Under the optimized reaction conditions, a variety of substituted phenols were examined in the copper/Spirobox-catalyzed asymmetric O–H insertion of ethyl α -diazoacetates (Table 2). All substituted phenols including naphthols completed the insertion reaction in 3 h to produce the corresponding α -aryloxypropionates in good yields and extremely high enantioselectivities ($\geq 95\%$ ee) regardless of the nature and the position of the substituents (entries 1–18). In addition to phenols, aliphatic alcohols such as 3-phenylpropanol and cinnamic alcohol also underwent O–H insertion reaction under the same reaction conditions, although the enantioselectivities were not as high as those in the reactions with phenols (entries 19 and 20). The methyl of the R¹ group in the α -diazoester is vital for the reaction. When the methyl was changed to phenyl, the O–H insertion product was obtained in a negligible ee value (entry 21). In the reaction of benzyl α -diazoacetate (R² = Et), only the β -elimination product of carbenoid, benzyl 2-butenic ester (81%) was isolated. The reactions with methyl and *tert*-butyl α -diazoacetates gave O–H insertion products in good yields and with excellent enantiomeric excess (entries 22 and 23), showing that the size of R³ group in the α -diazoester has almost no influence on the enantioselectivity and reactivity in the O–H insertion reaction.

The α -aryloxypropionic acids are biologically important compounds and have been widely utilized as crop protection reagents and as key intermediates in the preparation of chiral drugs.⁸ They can be easily prepared from our O–H insertion products. For

Scheme 2

example, the hydrolysis of α -aryloxypropionates **4a** and **4l** with aqueous KOH at 0 °C afforded the acids (*R*)-**5a** and (*R*)-**5l** in quantitative yields (Scheme 2). Thus, the copper/(*S,S,S,S*)-**1a**-catalyzed asymmetric insertion of the O–H bond of phenols by α -diazoesters provided a new efficient access to the synthesis of optically pure α -aryloxypropionic acids from simple substrates in two steps.

In summary, the first highly enantioselective insertion of carbenoids into O–H bonds of phenols has been realized. By using copper complexes of chiral spiro bisoxazolines as catalysts, the optically active α -aryloxypropionates and the related acids were synthesized conveniently. The successful use of spiro bisoxazolines in the asymmetric insertion of O–H bonds of phenols indicates the potential of these novel nitrogen ligands in asymmetric insertion reactions of heteroatom–hydrogen bond (X–H) of a wide range of substrates.

Acknowledgment. We thank the National Natural Science Foundation of China, the Major Basic Research Development Program (Grant No. 2006CB806106), the “111” project (B06005) of the Ministry of Education of China, and Merck Research Laboratories for financial support.

Supporting Information Available: Experimental procedures, the characterizations of products, and the analysis of ee values of products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- For reviews, see: (a) Doyle, M. P.; McKevey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998; Chapters 3 and 8. (b) Ye, T.; McKevey, M. A. *Chem. Rev.* **1994**, *94*, 1091.
- For recent review, see: Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861.
- For enantioselective Si–H insertion, see: (a) Buck, R. T.; Doyle, M. P.; Drysdale, M. J.; Ferris, L.; Forbes, D. C.; Haigh, D.; Moody, C. J.; Pearson, N. D.; Zhou, Q.-L. *Tetrahedron Lett.* **1996**, *37*, 7631. (b) Davies, H. M. L.; Hansen, T.; Rutberg, J.; Bruzinski, P. R. *Tetrahedron Lett.* **1997**, *38*, 1741. (c) Dakin, L. A.; Schaus, S. E.; Jacobsen, E. N.; Panek, J. S. *Tetrahedron Lett.* **1998**, *39*, 8947.
- For recent examples, see: (a) Liao, M.; Dong, S.; Deng, G.; Wang, J. *Tetrahedron Lett.* **2006**, *47*, 4537. (b) Ronan, B.; Bacqué, E.; Barrière, J.-C. *Tetrahedron* **2004**, *60*, 3819. (c) Nagai, K.; Sunazuka, T.; Omura, S. *Tetrahedron Lett.* **2004**, *45*, 2507. (d) Xu, C.; Zhang, Y.; Yuan, C. *Eur. J. Org. Chem.* **2004**, 2253. (e) Morilla, M. E.; Molina, M. J.; Díaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. *Organometallics* **2003**, *22*, 2914. (f) Doyle, M. P.; Yan, M. *Tetrahedron Lett.* **2002**, *43*, 5929. (g) Moody, C. J.; Morfitt, C. N.; Slawin, A. M. Z. *Tetrahedron: Asymmetry* **2001**, *12*, 1657. (h) Jones, K.; Toutounji, T. *Tetrahedron* **2001**, *57*, 2427. (i) Jiang, N.; Wang, J.; Chan, A. S. C. *Tetrahedron Lett.* **2001**, *42*, 8511. (j) Kettle, J. G.; Faull, A. W.; Fillery, S. M.; Flynn, A. P.; Hoyle, M. A.; Hudson, J. A. *Tetrahedron Lett.* **2000**, *41*, 6905. (k) Nelson, T. D.; Song, Z. J.; Thompson, A. S.; Zhao, M.; DeMarco, A.; Reamer, R. A.; Huntington, M. F.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **2000**, *41*, 1877.
- Maier, T. C.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 4594 and refs therein.
- Liu, B.; Zhu, S.-F.; Zhang, W.; Chen, C.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 5834.
- BARF[−] = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.
- (a) Perron, Y. G.; Minor, W. F.; Holdrege, C. T.; Gottstein, W. J.; Godfrey, J. C.; Crast, L. B.; Babel, R. B.; Cheney, L. C. *J. Am. Chem. Soc.* **1960**, *82*, 3934. (b) Kawashima, Y.; Hanioka, N.; Kozuka, H. *J. Pharmacobiodyn.* **1984**, *7*, 286. (c) Bettoni, G.; Loiodice, F.; Tortorella, V.; Conte-Camerino, D.; Mambri, M.; Ferrannini, E.; Bryant, S.-H. *J. Med. Chem.* **1987**, *30*, 1267. (d) Chimichi, S.; Boccalini, M. *Tetrahedron Lett.* **2006**, *47*, 2405.

JA074729K