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Enantioselective Copper-Catalyzed Intramolecular O−H Insertion: An Efficient Approach to Chiral 2-Carboxy Cyclic Ethers

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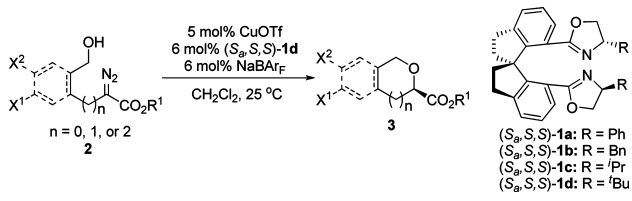
Abstract: A copper-catalyzed asymmetric intramolecular O−H insertion of ω-hydroxy-α-diazoesters has been accomplished by using chiral spiro bisoxazoline ligands. This highly enantioselective intramolecular O−H insertion reaction provides an efficient approach to a variety of synthetically important chiral 2-carboxy cyclic ethers with different ring sizes as well as substitution patterns.

Because carbon−heteroatom (C−X) bonds are prevalent in organic compounds, the development of reliable and efficient methods for construction of such bonds is of high practical value. Transition-metal-catalyzed insertion of carbenes into heteroatom−hydrogen bonds (X−H, X = O, N, S, etc.) provides one of the most efficient approaches to the formation of C−X bonds.[1] In particular, the O−H insertion reaction has attracted increasing attention over the past decades, and various O−H donors have been used in this reaction.[2] Recently, transition-metal-catalyzed asymmetric intermolecular O−H insertions of alcohols, phenols, and water have been accomplished with excellent enantioselectivities by Fu's group[3] and our group.[4] Although the catalytic intramolecular O−H insertion is a very useful reaction for the construction of cyclic ethers and esters, which are ubiquitous building blocks for chiral drugs and natural products,[5] the asymmetric version of intramolecular O−H insertion has not been documented to date.[6] Here we report a copper-catalyzed asymmetric intramolecular O−H insertion reaction of ω-hydroxy-α-diazoesters (Scheme 1). By using copper complexes of chiral spiro bisoxazoline ligands **1** as catalysts, we obtained a variety of chiral 2-carboxy cyclic ethers **3** in high yields (up to 98%) with excellent enantioselectivities (up to 97% ee). To the best of our knowledge, this is the first highly enantioselective intramolecular carbene insertion into X−H bonds.[7]

Scheme 1



Optically pure 2-carboxy cyclic ethers are important intermediates in the preparation of biologically active compounds such as those shown in Figure 1.[8] Although great effort has been expended, efficient methods for the preparation of optically pure 2-carboxy cyclic ethers are still limited. For instance, (*R*)-tetrahydrofuran-2-carboxylic acid is the key intermediate in the synthesis of the clinically efficacious non-natural β-lactam antibiotic faropenem.[8b] Although the structure looks simple, there is no enantioselective process for the preparation of the optically pure tetrahydrofuran-2-carboxylic acid.[9] This intermediate is generally obtained by means of tedious and time-consuming chemical resolution via diastereomeric salts or by means of enzyme-catalyzed kinetic resolutions.[10] We found that copper-catalyzed asymmetric intramolecular O−H insertion of ω-hydroxy-α-diazoesters **2** provides a direct synthetic route to chiral 2-carboxy cyclic ethers. Because ω-hydroxy-α-diazoesters **2** can be prepared in good yields from a readily available starting material (see the Supporting Information for details) and are easily modified, the catalytic asymmetric intramolecular O−H insertion reactions of **2** have high potential usefulness for the synthesis of various chiral 2-carboxy cyclic ethers **3** with different ring sizes and substitution patterns.

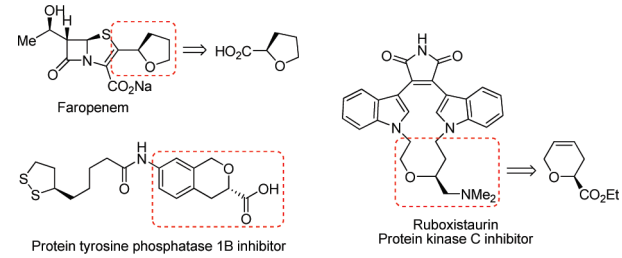


Figure 1. Representative biologically active compounds derived from 2-carboxy cyclic ethers.

In the initial study, we performed the intramolecular insertion reaction of **2a** using chiral copper catalysts prepared in situ from copper chloride, ligand (*S*$_a$,*S*,*S*)-**1a**, and sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBAr$_F$) in dichloromethane at 25 °C. The reaction was complete within 1 h, and the desired product, benzyl tetrahydro-2*H*-pyran-2-carboxylate (**3a**), was obtained in 93% yield with 53% ee (Table 1, entry 1). Under identical reaction conditions, ligand (*R*$_a$,*S*,*S*)-**1a** afforded only the racemic product (entry 2), and this result clearly indicates that ligand (*S*$_a$,*S*,*S*)-**1a** had matched chiralities in this reaction. Systematic evaluation of the 4-substituents on the spiro bisoxazoline ligand revealed that ligands with bulkier 4-substituents on the oxazoline rings provided higher enantioselectivity; the ligand (*S*$_a$,*S*,*S*)-**1d**, which has 4-*tert*-butyl groups, showed the highest enantioselectivity (87% ee; entries 3−5). Varying the copper precursors also strongly affected both the reactivity and the enantioselectivity. Cu(I) salts were suitable precursors for the transformation, with CuOTf giving the best result (93% ee; entry 6). Cu(II) salts such as Cu(OTf)$_2$ and CuCl$_2$ could also be used but showed lower yields (entries 8 and 9). However, CuSO$_4$ was completely inert under the standard reaction conditions (entry 10). The chlorinated solvents CH$_2$Cl$_2$, CHCl$_3$, and dichloroethane (DCE) were suitable for this transformation, whereas THF and toluene afforded poor yields (entries 11−14). In contrast, the highly coordinating solvent MeCN completely inhibited the insertion reaction (entry 15). As we observed in the

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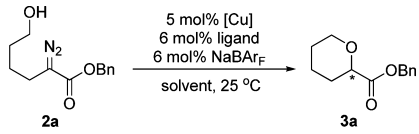
copper-catalyzed asymmetric intermolecular insertions into O−H,[4] N−H,[11] and S−H[12] bonds, the additive $NaBAr_F$ was necessary to achieve high yield and high enantioselectivity in the asymmetric intramolecular insertion of **2a** (compare entries 6 and 16). The activity of the present catalyst was sufficiently high to catalyze the intramolecular O−H insertion of **2a** with a catalyst loading of 2 mol % (entry 17).

Table 1. Copper-Catalyzed Asymmetric Intramolecular O−H Insertion of **2a**: Optimization of Reaction Conditions[a]

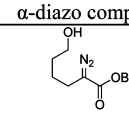
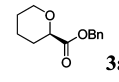
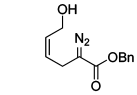
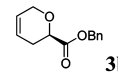
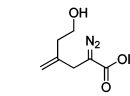
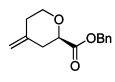
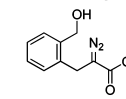
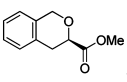
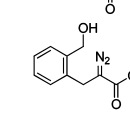
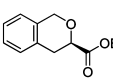
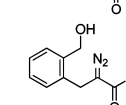
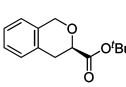
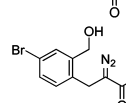
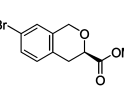
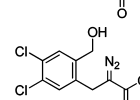
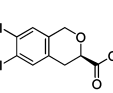
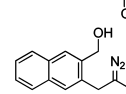
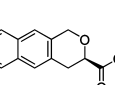
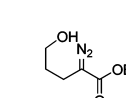
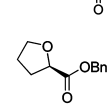
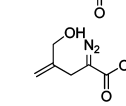
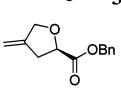
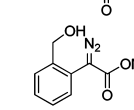
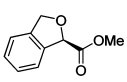
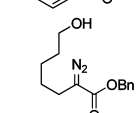
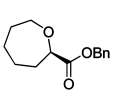


entry	[Cu]	ligand	solvent	time (h)	yield (%)[b]	ee (%)[c]
1	CuCl	(S_a,*S*,*S*)-**1a**	CH_2Cl_2	1	93	53
2	CuCl	(R_a,*S*,*S*)-**1a**	CH_2Cl_2	0.5	91	*rac*
3	CuCl	(S_a,*S*,*S*)-**1b**	CH_2Cl_2	0.5	86	51
4	CuCl	(S_a,*S*,*S*)-**1c**	CH_2Cl_2	1.5	88	59
5	CuCl	(S_a,*S*,*S*)-**1d**	CH_2Cl_2	1.5	74	87
6	CuOTf·$^1/_2$toluene	(S_a,*S*,*S*)-**1d**	CH_2Cl_2	0.1	80	93
7	$CuPF_6(MeCN)_4$	(S_a,*S*,*S*)-**1d**	CH_2Cl_2	16	92	83
8	$Cu(OTf)_2$	(S_a,*S*,*S*)-**1d**	CH_2Cl_2	0.5	52	83
9	$CuCl_2$	(S_a,*S*,*S*)-**1d**	CH_2Cl_2	4	55	87
10	$CuSO_4$	(S_a,*S*,*S*)-**1d**	CH_2Cl_2	NR[d]	−	−
11	CuOTf·$^1/_2$toluene	(S_a,*S*,*S*)-**1d**	$CHCl_3$	3	68	90
12	CuOTf·$^1/_2$toluene	(S_a,*S*,*S*)-**1d**	DCE	0.5	72	89
13	CuOTf·$^1/_2$toluene	(S_a,*S*,*S*)-**1d**	THF	2	36	91
14	CuOTf·$^1/_2$toluene	(S_a,*S*,*S*)-**1d**	toluene	36	27	85
15	CuOTf·$^1/_2$toluene	(S_a,*S*,*S*)-**1d**	MeCN	NR[d]	−	−
16[e]	CuOTf·$^1/_2$toluene	(S_a,*S*,*S*)-**1d**	CH_2Cl_2	6	48	87
17[f]	CuOTf·$^1/_2$toluene	(S_a,*S*,*S*)-**1d**	CH_2Cl_2	1.5	78	91

[a] Reaction conditions: [Cu]/ligand/$NaBAr_F$/**2a** = 0.02/0.024/0.024/0.4 (mmol) in 4 mL of CH_2Cl_2 at 25 °C. $NaBAr_F$ = sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate. [b] Isolated yield. [c] Determined by HPLC using a Chiralcel OD-H column. [d] No reaction. [e] Without the $NaBAr_F$ additive. [f] Using 2 mol % catalyst.

Under the optimal reaction conditions, various ω-hydroxy-α-diazoesters **2** were subjected to the intramolecular O−H insertion reaction (Table 2). For the substrates with 6-hydroxy chains (**2a**−**i**), which afforded the corresponding six-membered cyclic ethers (**3a**−**i**), the catalyst Cu-(S_a,*S*,*S*)-**1d** exhibited excellent activities and enantioselectivities. The double bonds in the chains of **2b** and **2c** were compatible with the standard reaction conditions, and no competitive cyclopropanation reactions were observed (Table 2, entries 2 and 3). A benzo group in the chain of the substrate was helpful for increasing the yield of the reaction (entries 4−8). Substrates with a less sterically hindered methyl (**2d**) or ethyl (**2e**) ester gave 92% ee, which was close to that for benzyl ester **2a**. However, substrate **2f** with a *tert*-butyl ester group afforded a lower enantioselectivity (82% ee). Introducing an electron-withdrawing substituent on the benzo ring increased the enantioselectivity, and substrate **2g,** with a 4-bromobenzo group, afforded the highest enantioselectivity (97% ee; entry 7). The absolute configuration of **3g** was determined to be *R* by X-ray diffraction analysis of a single crystal (see the Supporting Information for detailed crystallographic data). Diazo compound **2i** with a naphthyl ring in the chain also gave good enantioselectivity (93% ee; entry 9). The catalyst Cu-(S_a,*S*,*S*)-**1d** was also suitable for the asymmetric intramolecular O−H insertion reactions of 5-hydroxy-2-diazoesters **2j**−**l**, which yielded the corresponding cyclic ethers with five-membered rings (**3j**−**l**). A carbon−carbon double bond (**2k**) or a benzo ring (**2l**) in the chain of the substrate had a positive effect on the enantioselectivity (entries 11 and 12). When 7-hydroxy-2-diazoester **2m** was used as the substrate, the desired O−H insertion product with a seven-membered ring (**3m**) was isolated in only 14% yield with 95% ee (entry 13). The competitive β-H elimination of the carbene intermediate became the main reaction, giving benzyl 7-hydroxyhept-2-enoate (*Z*/*E* = 2.2:1) in 81% yield. Interestingly, β-H elimination of the carbene intermediate was markedly suppressed when the ligand (S_a,*S*,*S*)-**1c**, which has less bulky isopropyl groups on the oxazoline rings, was employed, and the desired O−H insertion product (**3m**) was obtained in acceptable yield (70%) with good enantioselectivity (83% ee).

Table 2. Copper-Catalyzed Asymmetric Intramolecular O−H Insertion: Substrate Scope[a]

entry	α-diazo compound **2**	product **3**	yield (%)	ee (%)
1	 **2a**	 **3a**	80	93
2	 **2b**	 **3b**	89	90
3	 **2c**	 **3c**	77	88
4	 **2d**	 **3d**	95	92
5	 **2e**	 **3e**	96	92
6	 **2f**	 **3f**	97	82
7	 **2g**	 **3g**	98	97 (*R*)
8	 **2h**	 **3h**	94	95
9	 **2i**	 **3i**	63	93
10	 **2j**	 **3j**	81	88
11	 **2k**	 **3k**	80	95
12	 **2l**	 **3l**	79	97
13	 **2m**	 **3m**	14 (70)[b]	95 (83)[b]

[a] The reaction conditions were the same as those in Table 1, entry 6. All of the reactions reached completion within 15 min. For analyses of products, see the Supporting Information. [b] The results were obtained by using ligand (S_a,*S*,*S*)-**1c**.

In summary, we have developed a highly enantioselective catalytic intramolecular O−H insertion reaction. When copper complexes of chiral spiro bisoxazoline ligands were used as the

catalyst, the ω-hydroxy-α-diazoesters smoothly underwent intramolecular insertion reactions to afford chiral cyclic ethers in good yields with high enantioselectivities. This O−H insertion reaction provides an efficient protocol for the preparation of chiral 2-carboxy cyclic ethers and their derivatives.

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Supporting Information Available: Detailed experimental procedures, characterizations and analytical data of ee values of products, and crystallographic data for **3g** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For a comprehensive review, see: (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998. For recent reviews, see: (b) Moody, C. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 9148. (c) Zhang, Z.-H.; Wang, J.-B. *Tetrahedron* **2008**, *64*, 6577.

(2) For an elegant review, see: Miller, D. J.; Moody, C. J. *Tetrahedron* **1995**, *51*, 10811.

(3) Maier, T. C.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 4594.

(4) (a) Chen, C.; Zhu, S.-F.; Liu, B.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 12616. (b) Zhu, S.-F.; Chen, C.; Cai, Y.; Zhou, O.-L. *Angew. Chem., Int. Ed.* **2008**, *47*, 932. (c) Zhu, S.-F.; Cai, Y.; Mao, H.-X.; Xie, J.-H.; Zhou, Q.-L. *Nat. Chem.* **2010**, *2*, 546.

(5) For examples of intramolecular O−H insertion reactions, see: (a) Moyer, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 5223. (b) Heslin, J. C.; Moody, C. J.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron Lett.* **1986**, *27*, 1403. (c) Heslin, J. C.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1417. (d) Davies, M. J.; Moody, C. J.; Taylor, R. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1. (e) Sarabia-García, F.; López-Herrera, F. J.; Pino-González, M. S. *Tetrahedron Lett.* **1994**, *35*, 6709. (f) Karady, S.; Amato, J. S.; Reamer, R. A.; Weinstock, L. M. *Tetrahedron Lett.* **1996**, *37*, 8277. (g) Padwa, A.; Sá, M. M. *Tetrahedron Lett.* **1997**, *38*, 5087. (h) Calter, M. A.; Zhu, C. *J. Org. Chem.* **1999**, *64*, 1415. (i) Jones, K.; Toutounji, T. *Tetrahedron* **2001**, *57*, 2427. (j) Xu, C.-F.; Zhang, Y.-H.; Yuan, C.-Y. *Eur. J. Org. Chem.* **2004**, 2253. (k) Zhang, W.; Romo, D. *J. Org. Chem.* **2007**, *72*, 8939.

(6) For a diastereoselective intramolecular O−H insertion reaction using chiral tethers in the substrates, see: Im, C. Y.; Okuyama, T.; Sugimura, T. *Chem. Lett.* **2005**, *34*, 1328.

(7) McKevery and co-workers reported a rhodium-catalyzed asymmetric intramolecular N−H insertion reaction with modest enantioselectivity (45% ee). See: García, C. F.; McKervey, M. A.; Ye, T. *Chem. Commun.* **1996**, 1465.

(8) (a) Nagatomo, T.; Tajiri, A.; Nakamura, T.; Hokibara, R.; Tanaka, Y.; Aono, J.; Tsuchihashi, H. *Chem. Pharm. Bull.* **1987**, *35*, 1629. (b) Ishiguro, M.; Iwata, H.; Nakatsuka, T.; Tanaka, R.; Maeda, Y.; Nishihara, T.; Noguchi, T. *J. Antibiot.* **1988**, *41*, 1685. (c) Alajarin, R.; Vaquero, J. J.; Alvarez-Builla, J.; Pastor, M.; Sunkel, C.; de Casa-Juana, M. F.; Priego, J.; Statkow, P. R.; Sanz-Aparicio, J.; Fonseca, I. *J. Med. Chem.* **1995**, *38*, 2830. (d) Jirousek, M. R.; Gillig, J. R.; Gonzalez, C. M.; Heath, W. F.; McDonald, J. H., III; Neel, D. A.; Rito, C. J.; Singh, U.; Stramm, L. E.; Melikian-Badalian, A.; Baevsky, M.; Ballas, L. M.; Hall, S. E.; Winneroski, L. L.; Faul, M. M. *J. Med. Chem.* **1996**, *39*, 2664. (e) Lakshminarayana, N.; Prasad, Y. R.; Gharat, L.; Thomas, A.; Ravikumar, P.; Narayanan, S.; Srinivasan, C. V.; Gopalan, B. *Eur. J. Med. Chem.* **2009**, *44*, 3147. (f) Hagmann, W. K.; Delaszlo, S. E.; Doherty, G.; Chang, L. L.; Yang, G. X. WO 01/12183, 2001. (g) Frank, C. I.; Navarro, H. A.; Brieaddy, L. E.; Runyon, S. P. U.S. Patent Appl. Pub. No. US 2006/0183743 A1, 2006.

(9) For a diastereoselective hydrogenation of chiral furan-2-carboxylic acid derivatives on heterogeneous catalysts, see: Sebek, M.; Holz, J.; Börner, A.; Jähnisch, K. *Synlett* **2009**, 461.

(10) (a) Bélanger, P. C.; Williams, H. W. R. *Can. J. Chem.* **1983**, *61*, 1383. (b) van Eikeren, P.; McConville, F. X.; Lopez, J. WO 96/36584, 1996. (c) Fujima, Y.; Hirayama, Y.; Ikunaka, M.; Nishimoto, Y. *Tetrahedron: Aymmetry* **2003**, *14*, 1385, and references therein.

(11) Liu, B.; Zhu, S.-F.; Zhang, W.; Chen, C.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 5834.

(12) Zhang, Y.-Z.; Zhu, S.-F.; Cai, Y.; Mao, H.-X.; Zhou, Q.-L. *Chem. Commun.* **2009**, 5362.

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