

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

Shou-Fei Zhu, Xiao-Guang Song, Yu Li, Yan Cai, and Qi-Lin Zhou*

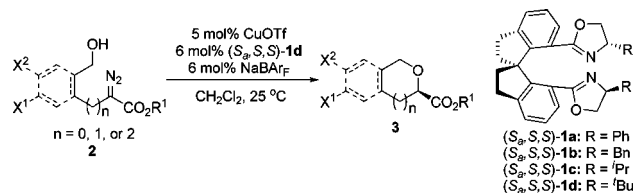
State Key Laboratory and Institute of Elemento-organic Chemistry, Nankai University, Tianjin 300071, China

Received September 10, 2010; E-mail: qlzhou@nankai.edu.cn

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 group³ 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.

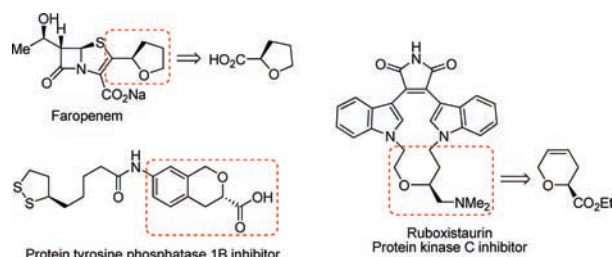


Figure 1. Representative biologically active compounds derived from 2-carboxy cyclic ethers.

In the initial study, we performed the intramolecular insertion reaction of **2a** using chiral copper catalysts prepared in situ from copper chloride, ligand (*S,S,S,S*)-**1a**, and sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) 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,S,S,S*)-**1a** afforded only the racemic product (entry 2), and this result clearly indicates that ligand (*S,S,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,S,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 CuCl₂ could also be used but showed lower yields (entries 8 and 9). However, CuSO₄ was completely inert under the standard reaction conditions (entry 10). The chlorinated solvents CH₂Cl₂, CHCl₃, 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

copper-catalyzed asymmetric intermolecular insertions into O–H,⁴ N–H,¹¹ and S–H¹² 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

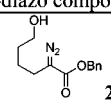
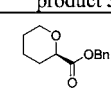
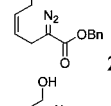
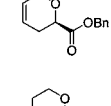
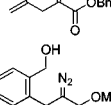
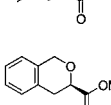
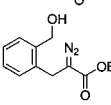
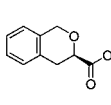
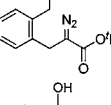
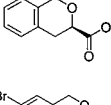
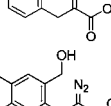
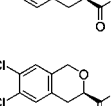
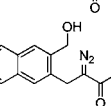
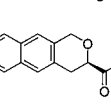
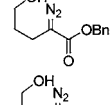
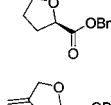
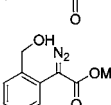
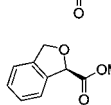
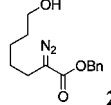
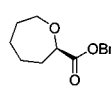
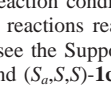
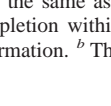
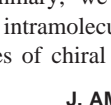
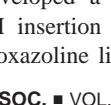


entry	[Cu]	ligand	solvent	time (h)	yield (%) ^b	ee (%) ^c
1	CuCl	(<i>S</i> , <i>a</i> , <i>S</i> , <i>S</i>)- 1a	CH ₂ Cl ₂	1	93	53
2	CuCl	(<i>R</i> , <i>a</i> , <i>S</i> , <i>S</i>)- 1a	CH ₂ Cl ₂	0.5	91	<i>rac</i>
3	CuCl	(<i>S</i> , <i>a</i> , <i>S</i> , <i>S</i>)- 1b	CH ₂ Cl ₂	0.5	86	51
4	CuCl	(<i>S</i> , <i>a</i> , <i>S</i> , <i>S</i>)- 1c	CH ₂ Cl ₂	1.5	88	59
5	CuCl	(<i>S</i> , <i>a</i> , <i>S</i> , <i>S</i>)- 1d	CH ₂ Cl ₂	1.5	74	87
6	CuOTf·½toluene	(<i>S</i> , <i>a</i> , <i>S</i> , <i>S</i>)- 1d	CH ₂ Cl ₂	0.1	80	93
7	CuPF ₆ (MeCN) ₄	(<i>S</i> , <i>a</i> , <i>S</i> , <i>S</i>)- 1d	CH ₂ Cl ₂	16	92	83
8	Cu(OTf) ₂	(<i>S</i> , <i>a</i> , <i>S</i> , <i>S</i>)- 1d	CH ₂ Cl ₂	0.5	52	83
9	CuCl ₂	(<i>S</i> , <i>a</i> , <i>S</i> , <i>S</i>)- 1d	CH ₂ Cl ₂	4	55	87
10	CuSO ₄	(<i>S</i> , <i>a</i> , <i>S</i> , <i>S</i>)- 1d	CH ₂ Cl ₂	NR ^d	–	–
11	CuOTf·½toluene	(<i>S</i> , <i>a</i> , <i>S</i> , <i>S</i>)- 1d	CHCl ₃	3	68	90
12	CuOTf·½toluene	(<i>S</i> , <i>a</i> , <i>S</i> , <i>S</i>)- 1d	DCE	0.5	72	89
13	CuOTf·½toluene	(<i>S</i> , <i>a</i> , <i>S</i> , <i>S</i>)- 1d	THF	2	36	91
14	CuOTf·½toluene	(<i>S</i> , <i>a</i> , <i>S</i> , <i>S</i>)- 1d	toluene	36	27	85
15	CuOTf·½toluene	(<i>S</i> , <i>a</i> , <i>S</i> , <i>S</i>)- 1d	MeCN	NR ^d	–	–
16 ^e	CuOTf·½toluene	(<i>S</i> , <i>a</i> , <i>S</i> , <i>S</i>)- 1d	CH ₂ Cl ₂	6	48	87
17 ^f	CuOTf·½toluene	(<i>S</i> , <i>a</i> , <i>S</i> , <i>S</i>)- 1d	CH ₂ Cl 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 CH₂Cl₂ 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			80	93
2			89	90
3			77	88
4			95	92
5			96	92
6			97	82
7			98	97 (<i>R</i>)
8			94	95
9			63	93
10			81	88
11			80	95
12			79	97
13			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>.

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