Cycloaddition

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Cy-SaBOX/Copper(II)-Catalyzed Highly Diastereo- and Enantioselective Synthesis of Bicyclic N,O Acetals

Qiong-Jie Liu, Lijia Wang, Qi-Kai Kang, X. Peter Zhang, and Yong Tang**

Abstract: *Facile and effective access for the asymmetric construction of the useful and important skeleton of the bicyclic N,O-acetals is described. Cu^{II}/SaBOX could catalyze the reaction of β,γ-unsaturated α-ketoesters with cyclic enamines efficiently, thus affording the desired products in excellent yields with excellent stereoselectivities (21 examples; up to 99% yields; up to >95:5 d.r.; and 95–99% ee). This reaction can be well performed on gram scale, even with only 1 mol% catalyst loading. The single-crystal structures of the copper complexes lead to a good understanding of the stereosynergistic effects of the sidearm.*

Bicyclic N,O-acetals are important motifs in many biologically active natural products such as (+)-graciline, (−)-digracine, and ajaconine (Figure 1).[1] Developing effective methods aimed at these motifs is of great interest to chemists. Although several elegant methods have been developed for these target skeletons,[2] most of them still suffer from harsh reaction conditions, moderate yields, and poor stereoselectivities. Efficient protocols, especially enantioselective ones from simple starting materials, are rare. To the best of our knowledge, the only example was developed by Wang et al. and was based on the chiral BINOL/$Ti(OiPr)_4$-catalyzed cascade cyclization of enamides with salicylaldehydes, thus resulting in pyrrolidine-fused 4-chromanols in 27–99% yields with greater than 20:1 d.r. and 43–99% *ee*.[2e] To date, however, effective synthetic methods towards optically active bicyclic N,O-acetals bearing an all-carbon center at the 3-position, which is usually contained in the structure of natural products (Figure 1), are lacking. Since the asymmetric hetero-Diels–Alder (hetero-DA) reactions[3] of β,γ-unsaturated α-ketoesters with electron-rich alkenes[4–7] emerged as a powerful tool for the synthesis of enantioenriched 3,4-dihydropyrans, it was envisioned that the reaction of β,γ-unsaturated α-ketoesters with cyclic enamines potentially provides new and facile access to bicyclic N,O-acetals. These N,O-acetals, bearing three continuous chiral centers, could be readily converted into various highly functionalized useful heterocycles. Unfortunately, simple trials by employing several known hetero-DA catalysts in the reaction of β,γ-unsaturated α-ketoesters with cyclic enamines proved to be unsuccessful. Herein, we report our efforts in addressing this issue.

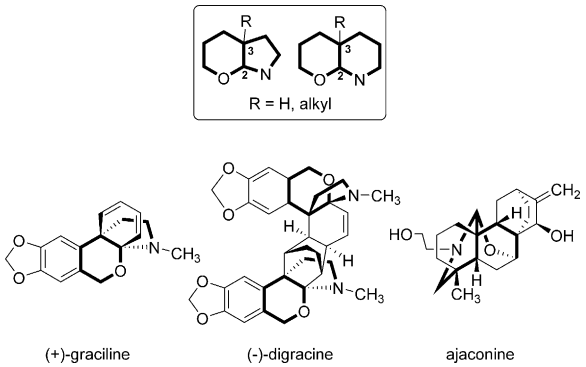

Figure 1. Bicyclic N,O-acetal skeletons in natural products.

Initially, we tried several catalysts which proved very efficient in the asymmetric hetero-DA reactions for the envisioned reaction, but they all failed. For example, it was demonstrated that the chiral *t*Bu-bisoxazoline (*t*Bu-BOX)/Cu^{II} catalyst system exhibited high efficiency in the enantioselective reaction of cyclic enol ethers and β,γ-unsaturated α-ketoesters, thus resulting in optically active bicyclic O,O-acetals.[4a,b] However, the cyclic enamine **1a** (see Table 1), instead of enol ethers, did not work, even when the reaction temperature was elevated to 30 °C. Further optimization of the reaction conditions, by replacing the *t*Bu-BOX ligand with **L1**, resulted in smooth reaction in dichloromethane (DCM), thus affording the desired product **3a** in 93% yield but only with 77:23 d.r. and 35% *ee* (Table 1, entry 1). And then, we investigated the reaction parameters such as additives, substituents on the ester group, and more than 20 ligands.[8] The combination of $Cu(OTf)_2$ and **L2** as the catalyst (entry 2) led to a dramatic increase in both diastereo- and enantioselectivity (85:15 d.r. and 84% *ee*) while maintaining an excellent yield (99%). Further study showed that the use of the sidearm-modified cyclohexyl SaBOX **L3** resulted in a smooth reaction with improved stereoselectivities, thus affording the desired product in 88% yield with 90:10 d.r. and 92% *ee* (entry 3).[9–11] Subsequently, a variety of Cy-SaBOX ligands were evaluated. As summarized in Table 1, introduction of two benzyl sidearm groups provided no enhancement of the diastereo- and enantioselective (entry 4). The Cy-TOX **L5** was very efficient in promoting the reaction but resulted in both a lower diastereo- and enantioselectivity (entry 5).

[*] Q.-J. Liu, Dr. L. Wang, Q.-K. Kang, Prof. Dr. Y. Tang
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
345 Lingling Lu, Shanghai 200032 (China)
E-mail: tangy@mail.sioc.ac.cn
Prof. Dr. Y. Tang
Collaborative Innovation Center of Chemical Science and Engineering, Tianjin 300072 (China)
Prof. Dr. X. P. Zhang
Department of Chemistry, Merkert Chemistry Center, Boston College
Chestnut Hill, MA 02467 (USA)
E-mail: peter.zhang@bc.edu

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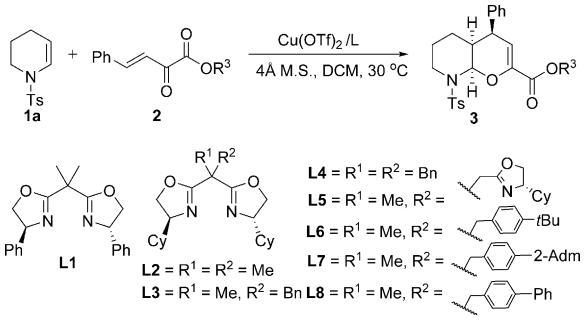
Table 1: Optimization of reaction conditions.[a]



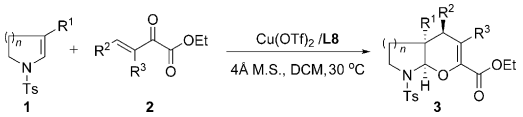
Entry	L	R^3	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**L1**	Me (**2a**)	13	93	77:23	35
2	**L2**	Me (**2a**)	18.5	99	85:15	84
3	**L3**	Me (**2a**)	12	88	90:10	92
4	**L4**	Me (**2a**)	11	98	90:10	85
5	**L5**	Me (**2a**)	12	89	84:16	81
6	**L6**	Me (**2a**)	48	99	92:8	94
7	**L7**	Me (**2a**)	11	98	92:8	94
8	**L8**	Me (**2a**)	13	99	92:8	95
9	**L8**	Et (**2b**)	13	99	94:6	98
10	**L8**	*i*Pr (**2c**)	13	99	95:5	97
11	**L8**	Bn (**2d**)	13	98	92:8	96

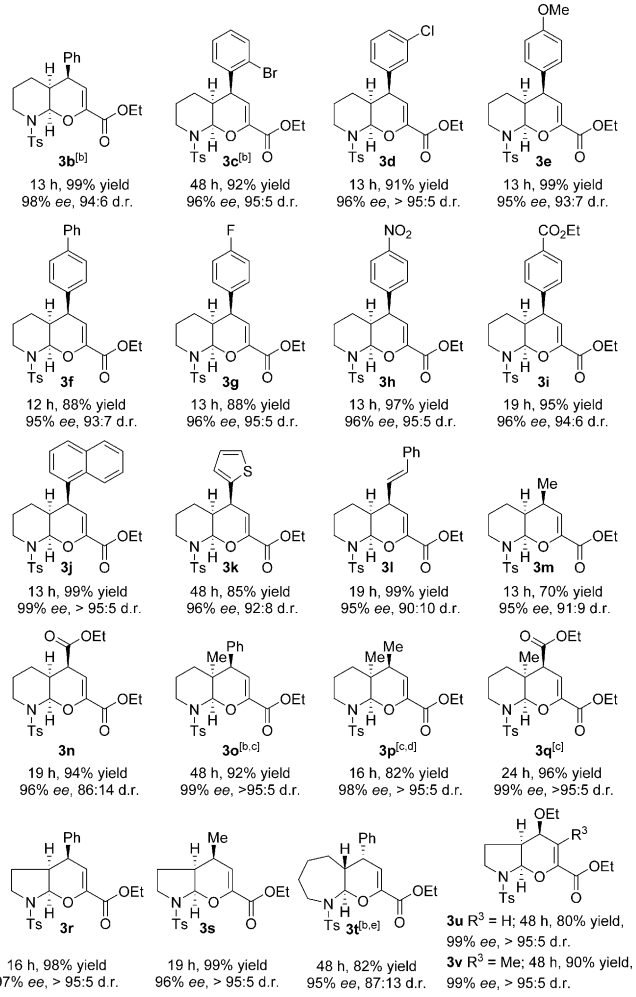
[a] Performed with 0.2 mmol **1a**, 0.3 mmol **2**, and 100 mg 4 Å M.S. in 4 mL DCM. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] Determined by chiral-phase HPLC. Adm = adamantyl, DCM = dichloromethane, M.S. = molecular sieves, Tf = trifluorromethanesulfonyl, Ts = 4-toluenesulfonyl.

Notably, it was found that introduction of a benzyl sidearm group achieved an impressive improvement in the diastereo- and enantioselectivity. Aiming at improving the diastereo- and enantioselectivity of the current reaction, a variety of substituted benzyl sidearm groups were investigated. The Cy-SaBOX **L6** and **L7**, bearing a steric sidearm could also promote the reaction efficiently, thus affording the cycloaddition product **3a** in 98% yield with 92:8 d.r. and 94% *ee* (entries 6 and 7). The best result was achieved by employing Cy-SaBOX **L8**, which gave 99% yield of **3a** with 95% *ee* and 92:8 d.r. (entry 8). As the steric interaction of the ester group of the β,γ-unsaturated α-ketoester with the catalyst could interfere with the stereochemical control, different ester groups were explored. When the methyl ester group of the β,γ-unsaturated α-ketoester was replaced by a bulkier aliphatic ethyl, isopropyl, or benzyl group, the yield and selectivity was further improved (entries 9–11). Finally, **1a** reacted with **2b** in the presence of $Cu(OTf)_2$/**L8** in DCM, thus providing **3b** in 99% yield with 98% *ee* and 94:6 d.r. as the best result (entry 9).

Under the optimized reaction conditions, the substrate scope was investigated and the results are shown in Table 2. The different electronic properties of *ortho*, *para*, and *meta* substituents on the phenyl group of the β,γ-unsaturated α-ketoesters had little effect on the yields (88–99%) and stereoselectivities (95–98% *ee* and 93:7→95:5 d.r., **3b–i**). 1-Naphthyl unsaturated α-ketoester was also a suitable substrate, thus affording the corresponding product **3j** with a perfect level of stereoselectivity (> 95:5 d.r., 99% *ee*) and

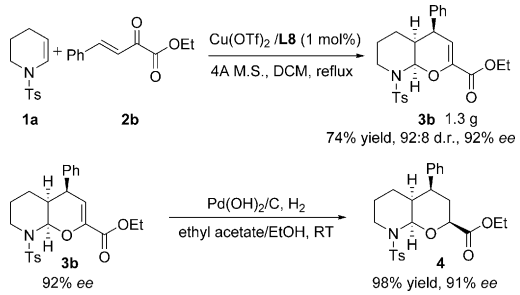
Table 2: Reaction scope of the copper-catalyzed asymmetric hetero-DA reaction.[a]





[a] Performed with 0.3 mmol **1**, 0.45 mmol **2**, and 150 mg 4 Å M.S. in 6 mL DCM. Yield is that of isolated product. The d.r. value was determined by ^{1}H NMR spectroscopy of the crude reaction mixture and the *ee* value was determined by chiral-phase HPLC. [b] The relative configurations of **3b**, **3o**, and **3t**, and the absolute configuration of **3c** were established by X-ray crystallography.[12] [c] Carried out at 40 °C. [d] Performed with 0.2 mmol **1**, 0.4 mmol **2**, nd mg 4 Å M.S. in 4 mL DCM. [e] Yield of the isolated major isomer.

99% yield. Notably, the reaction could be applied to ketoesters bearing styryl, heterocyclic, alkyl, and ester groups with good to excellent stereoselectivities and yields (up to 92:8 d.r. and 96% *ee*, **3k–n**). Significantly, the 3-methyl tetrahydropyridine also reacted smoothly with a variety of β,γ-unsaturated α-ketoesters at 40 °C, thus affording the desired products, bearing an all-carbon quaternary stereocenter, in high yields with excellent diastereo- and enantioselectivities (97–99% *ee* and > 95:5 d.r., **3o–q**). Furthermore, five- and seven-membered cyclic enamines also reacted well, thus furnishing the corresponding products **3r–t** in high yields



Scheme 1. Gram-scale reaction and hydrogenation of **3b**.

with excellent diastereoselectivities and up to 99% *ee*. In addition, the trisubstituted β,γ-unsaturated α-ketoesters **2u** and **2v** were also suitable substrates in the current reaction system, thus leading to the desired products **3u** and **3v** in 80 and 90% yields, respectively, with greater than 95:5 d.r. and very excellent enantioselectivities (99% *ee*).

Considering the high efficiency of the $Cu(OTf)_2$/**L8**-catalyzed hetero-DA reaction of β,γ-unsaturated α-ketoesters, the scale-up of the catalytic process was performed. The gram-scale reaction of **1a** with **2b** proceeded well, even with only 1 mol% catalyst loading, thus providing 1.3 grams of the desired product **3b** in 74% yield with 92% *ee* and 92:8 d.r. Furthermore, hydrogenation of **3b** provided **4** smoothly without any loss of enantiopurity (Scheme 1). The relative configuration of **4** was established by X-ray crystallography.[12]

To understand the synergistic effect of the sidearm, the single crystals of the complexes $CuBr_2$/**L2** and $CuBr_2$/**L8** were prepared and analyzed by X-ray crystallography.[12] As shown in Figure 2, in the cases of $CuBr_2$/**L8**, the pendant sidearm groups swing towards the copper center. Comparing $CuBr_2$/**L8** with $CuBr_2$/**L2,** the lengths of the N–Cu bond are similar but with a slight decrease [length (N1-Cu1) $_{CuBr2/L2}$ = 1.969 Å and length (N1-Cu1) $_{CuBr2/L8}$ = 1.959 Å]. Notably, the dihedral angles of the chiral skeletons have an obvious increase [torsion (C6-C5-N1-C3) $_{CuBr2/L2}$ = 119.17 °; torsion (C28-C6-N2-C4) $_{CuBr2/L8}$ = 128.34(25)°]. This observation suggests that by installing the sidearm groups, the chiral cavity of the $CuBr_2$/**L8** becomes more crowded compared with the one with the parent ligand **L2**.

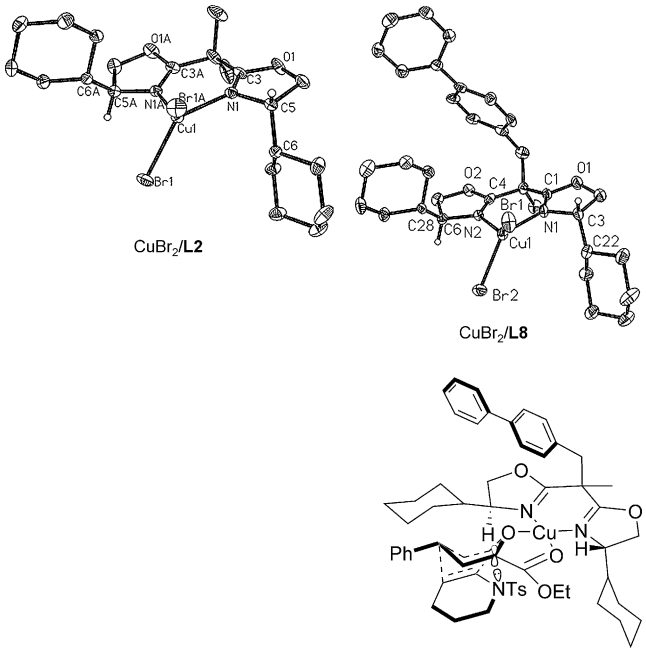


Figure 2. X-ray structures of $CuBr_2$/**L2** and $CuBr_2$/**L8**, and proposed enantioinduction model. Thermal ellipsoids shown as 30% probability.

To gain insight into the enantioselectivity, we investigated the effects of counterions, such as OTf^-, ClO_4^-, SbF_6^-, and PF_6^-, having different sizes and coordinating properties, on the enantioselectivity of the reactions. Notably, in all cases, both the diastereo- and enantioselectivities of the reactions were at the same level.[8] Combining these results with the stereoinduction model of hetero-DA reaction of β,γ-unsaturated α-ketoester **2b** with enol ethers, as reported by the groups of Evans,[4d] Jørgensen, and Houk independently,[4a–f,13] an enantioinduction model of the current reaction is proposed as shown in Figure 2. In this model, **2b** engages in bidentate coordination to the **L8**/Cu^{II} complex with a distorted square-planar geometrical structure. Compared with **L2**/Cu^{II}, the more rigid chiral environment of **L8**/Cu^{II} leads to a better enantioselectivity. Based on this model, the absolute configuration of the product delivered is completely in accordance with the experimental results.[12]

In conclusion, an efficient Cu^{II}/SaBOX-catalyzed hetero-DA reaction of β,γ-unsaturated α-ketoesters with cyclic enamines has been developed. By employing a newly designed chiral Cy-SaBOX, the asymmetric reaction proceeded well with a variety of β,γ-unsaturated α-ketoesters and cyclic enamines under mild reaction conditions, thus affording the desired bicyclic N,O-acetals bearing three continuous chiral centers with excellent diastereoselectivities (up to > 95:5 d.r.) and enantioselectivities (95–99% *ee*). Hydrogenation of **3b** was achieved to afford the octahydro-2*H*-pyrano-[2,3-*b*]pyridine **4** smoothly without any loss of enantioselectivity. This method provides a facile and practical access to the asymmetric construction of the useful and important bicyclic heterocycles under mild reaction conditions on gram scale with 1 mol% catalyst loading. The single-crystal structures of the copper complexes have been determined, thus leading to the better understanding of the stereo-synergistic effects of the sidearm of the ligand. Further application of this methodology for total synthesis of natural products is ongoing in our laboratory.

Experimental Section

A mixture of $Cu(OTf)_2$ (0.03 mmol), cyclohexyl bisoxazoline (**L8**, 0.036 mmol) and 150 mg 4 Å M.S. in DCM (3 mL) was stirred at 30 °C for 2 h under nitrogen. Then, a mixture of **1** (0.3 mmol) and **2** (0.45 mmol) in DCM (3 mL) was added to the catalyst solution by syringe. The resulting suspension was stirred at 30 °C and monitored by TLC until the complete consumption of **1**. Then, the mixture was filtered through a thin layer of celite and eluted with DCM. The filtrate was poured into saturated aqueous NH_4Cl (15 mL), and extracted with DCM (20 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography over silica gel (ethyl acetate/petroleum ether, 1:7) to afford **3**.

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