Asymmetric Catalysis

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Highly Enantioselective [3+2] Annulation of Cyclic Enol Silyl Ethers with Donor–Acceptor Cyclopropanes: Accessing *3a*-Hydroxy [*n*.3.0]Carbobicycles**

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[*n*.3.0]Carbobicycles containing a tertiary alcohol moiety located at the ring junction are found as a key structure in a large number of biologically active and naturally occurring molecules such as botrydials, africanols, palustrols, lucinones, furoscrobiculins, etc. (Figure 1).[1] In the past decades, considerable effort[2–7] has been focused on the synthesis of these [*n*.3.0]bicycles, and many methods have been documented,

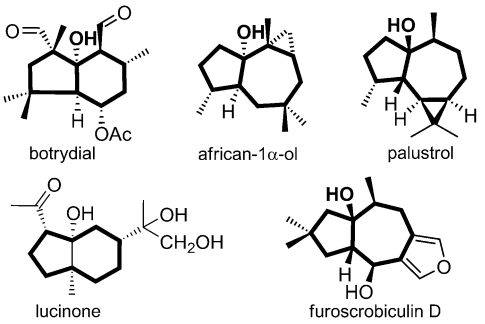
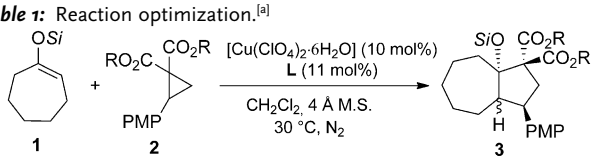


Figure 1. *3a*-Hydroxy [*n*.3.0]carbobicycles in natural products.

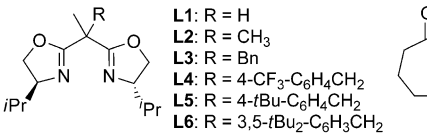
such as nBu$_3$Sn$^{\bullet}$- or SmI$_2$-initiated radical cyclization,[2] ring-closing metathesis,[3] and [$n+2$] annulations[4–6] based on cyclic enol ethers. So far, however, very few direct and catalytic asymmetric versions have been developed.[3a,4h,i] As the [3+2] annulation[5] of cyclic enol ethers with cyclopropanes can efficiently establish the bicyclic skeleton, the tertiary alcohol unit, and at least two contiguous chiral centers in one step, it provides an appealing and concise approach to synthesize the *3a*-hydroxy [*n*.3.0]carbobicyclic structure. Unfortunately, this efficient cycloaddition method often results in low diastereoselectivity and the formation of the ring-opened side products.[5] Recently, we showed a highly efficient and diastereoselective annulation reaction of enol silyl ethers with donor–acceptor (D–A) cyclopropanes using copper(II)/bisoxazoline (BOX) catalysts.[6] However, initial attempts to employ chiral Ph-PYBOX and Ph-DBFOX for the asymmetric version gave very poor results.[8,9] To our delight, the annulation reaction can finally be accomplished with high diastereo- and enantioselectivity by using modified BOX ligands, thus providing a new and facile access to a series of optically active *3a*-hydroxy [*n*.3.0]carbobicycles. Herein we report the preliminary results.

In view of the prevalence of [5.3.0]bicyclic skeletons in natural products,[1b,c,e–h] we first commenced our study with the screening of BOX ligands using the cycloheptanone-derived enol silyl ether **1** and PMP-substituted cyclopropane **2** (Table 1). Cu(ClO$_4$)$_2$ was employed as the copper(II) source and dichloromethane as the solvent.[6] A screening of several

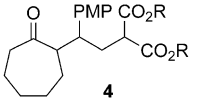
Table 1: Reaction optimization.[a]



Si = TBDPS (**1a**), TIPS (**1b**), TBS (**1c**)
R = 2-Adamantyl (**2a**), CH$_2$*t*Bu (**2b**)



L1: R = H
L2: R = CH$_3$
L3: R = Bn
L4: R = 4-CF$_3$-C$_6$H$_4$CH$_2$
L5: R = 4-*t*Bu-C$_6$H$_4$CH$_2$
L6: R = 3,5-*t*Bu$_2$-C$_6$H$_3$CH$_2$
L7: R = 3,4,5-(MeO)$_3$-C$_6$H$_2$CH$_2$



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Entry	1	2	L	*t* [h]	Conv. [%][b]	d.r.[b]	*ee* [%][c]
1	**1a**	**2a**	**L1**	24	88	80:20	76
2	**1a**	**2a**	**L2**	24	92	85:15	93
3	**1a**	**2a**	**L3**	24	>99	86:14	95
4	**1a**	**2a**	**L4**	24	>99	84:16	90
5	**1a**	**2a**	**L5**	24	>99	85:15	96
6	**1a**	**2a**	**L6**	24	>99	82:18	97
7	**1a**	**2a**	**L7**	11	>99(85)	87:13	97
8	**1a**	**2b**	**L7**	42	>99	80:20	88
9	**1b**	**2a**	**L7**	19	88(0)	–	(94)[d]
10	**1c**	**2a**	**L7**	10	>99(27)	68:32	90(96)[d]

[a] Reaction conditions: [Cu(ClO$_4$)$_2$·6H$_2$O] (0.02 mmol), **L** (0.022 mmol), **1** (0.30 mmol), and **2** (0.20 mmol) in 2.0 mL of CH$_2$Cl$_2$. [b] Conversion and d.r. values (*cis/trans*) were determined by ^{1}H NMR spectroscopy. Value within the parentheses is the yield of the isolated product. [c] Measured by HPLC using a chiral stationary phase. The *ee* values are those of the *cis* products. [d] The *ee* values within the parentheses are of the major isomer (d.r. > 20:1) of product **4**. PMP = *para*-methoxyphenyl, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

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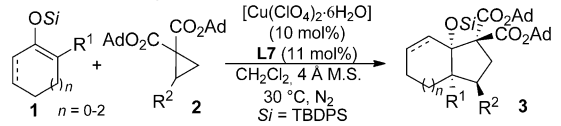
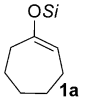
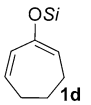
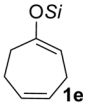
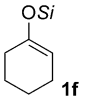
bisoxazoline ligands unveiled that *i*Pr-BOX gave the best enantioselectivity (entry 2),[8] and encouraged us to further elaborate this framework. To our delight, the sidearm strategy[10,11] of introducing a pendant group at the bridging carbon atom of the bisoxazoline ligand proved to be quite effective in this reaction, and the enantioselectivity of the reaction was gradually improved to 97% *ee* by increasing the steric hindrance at the *para* position of the aryl sidearm groups (entries 3–7). It is worth noting that the racemic D–A cyclopropanes **2a** and **2b** were used in this reaction, thus suggesting that the current reaction proceeds with a dynamic kinetic resolution[9b–d] of the cyclopropanes. Reaction acceleration was consistently observed with the sidearm-modified ligands (entries 3–7 versus entries 1 and 2). In contrast, alteration of the ester group of **2** indicated that a large ester group is also important to the enantioselectivity with 2-adamantyl (Ad) being the best (entry 7 versus 8).[12] It is noteworthy that the TBDPS protecting group proved to be crucial to suppress the formation of the ring-opened product **4** and ensure a high yield of the desired [3+2] product (entries 9 and 10). For example, in the reactions of the TBDPS enol ether **1a**, only a trace or a small (< 10%) amount of the ring-opened product can be detected by proton NMR spectroscopy, which is in contrast to reaction of the TIPS-protected enol ether **1b** which exclusively produced the ring-opened product (entry 9). The formation of **4** may result from the hydrolysis of the carboxonium intermediate before the ring closure or the abstraction of its α proton followed by desilylation.[5,6] In addition, other metal salts such as $Cu(SbF_6)_2$, $Cu(OTf)_2$, $CuBr_2$, $Ni(ClO_4)_2$, and $Co(ClO_4)_2$ were also examined. Only $Cu(SbF_6)_2$ and $Cu(OTf)_2$ showed a good activity, but resulted in slightly lower enantioselectivities.[8]

Having the optimized reaction conditions, we moved to the investigation of the reaction scope. As shown in Table 2, apart from a PMP-substituted D–A cyclopropane, 2-thiophenyl- (**2c**), 3,4,5-trimethoxyphenyl- (TMP, **2d**), and alkenyl-substituted (**2e**) cyclopropanes also reacted well with **1a**, thus giving the desired fused cyclic products in good to excellent enantiomeric excesses (entries 1–4). The reaction of the TMP-substituted cyclopropane was slower, and could probably be ascribed to the steric hindrance of the TMP group or the competing bidentate coordination of the methoxy groups to the copper (entry 3). Notably, both conjugate and isolated dienol-ether-type substrates (**1d** and **1e**) also react smoothly under the standard reaction conditions, thus affording carbon–carbon double-bond-containing [5.3.0]bicyclic products, with the potential for additional transformation of this functionality (entries 5 and 6). To our great pleasure, the current reaction works quite well with six- and five-membered substrates (entries 7–13). Thus, a range of [*n*.3.0] (*n* = 3–5) 3*a*-hydroxy bicycles in high enantiomeric purity are accessible by this reaction. Remarkably, in the reactions with five- and six-membered enol silyl ethers, perfect diastereoselectivities (> 99:1) were consistently observed (entries 7–12). In fact, in these cases only one diastereoisomer was detected by ^{1}H NMR analysis of the crude reaction mixture. In addition, the ß-disubstituted enol silyl ether **1h** is also a suitable substrate with high enantioselectivity, and notably the corresponding product (**3ha**) contains three contiguous quaternary centers, two of which are at the ring juncture (entry 13). The configurations of the products **3aa**, **3da**, and **3gc** were determined by X-ray crystal structure analysis,[13] and the configurations of other products were assigned by analogy.

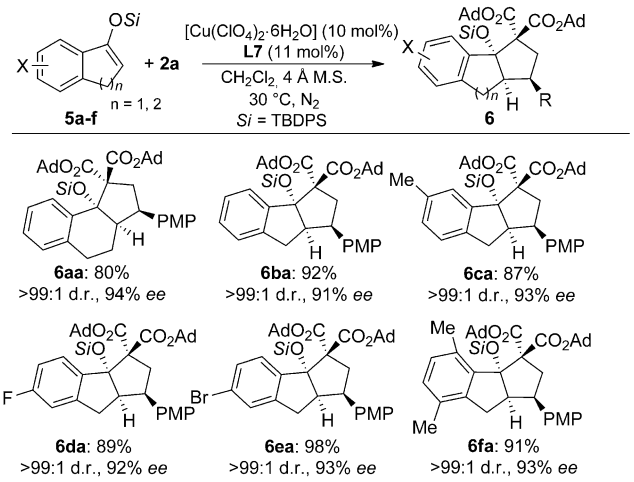
Table 2: Reaction scope.[a]



Entry	1	R^2	P	Yield [%] (d.r.)[b]	*ee* [%][c]
1		4-$MeOC_6H_4$ (**2a**)	**3aa**	85 (87:13)	97
2		2-thiophenyl (**2c**)	**3ac**	62 (87:13)	93
3[d]		(3,4,5-$MeO)_3C_6H_2$ (**2d**)	**3ad**	78 (91:9)	99
4		CH=CHPh (**2e**)	**3ae**	74 (80:20)	92
5		4-$MeOC_6H_4$ (**2a**)	**3da**	94 (81:19)	91
6[e]		4-$MeOC_6H_4$ (**2a**)	**3ea**	70 (85:15)	92
7		4-$MeOC_6H_4$ (**2a**)	**3fa**	61 (> 99:1)	95
8		4-$MeOC_6H_4$(**2a**)	**3ga**	87 (> 99:1)	93
9		2-thiophenyl (**2c**)	**3gc**	83 (> 99:1)	93
10		(3,4,5-$MeO)_3C_6H_2$ (**2d**)	**3gd**	81 (> 99:1)	97
11[f,14]		CH=CHPh (**2e**)	**3ge**	45 (> 99:1)	95
12[g]		2-furyl (**2f**)	**3gf**	68 (> 99:1)	92
13[e,14]		4-$MeOC_6H_4$ (**2a**)	**3ha**	45 (> 95:5)	98[h]

[a] Reaction conditions: $[Cu(ClO_4)_2{\cdot}6H_2O]$ (0.02 mmol), **L7** (0.022 mmol), **1** (0.30 mmol), and **2** (0.20 mmol) in 2.0 mL of CH_2Cl_2 at 30°C with 4 Å M.S. and N_2. [b] Yield of the isolated product. A trace amount of ring-opened product **4** was observed. The d.r. values (*cis*/*trans*) were determined by ^{1}H NMR spectroscopy. [c] Values for the *cis* products as determined by HPLC using a chiral stationary phase. [d] Using 3 equiv of **1a**. [e] $Cu(SbF_6)_2$. [f] $Cu(OTf)_2$, Ref. [14]. [g] $Cu(OTf)_2$, 0°C, in 1,1,2,2-tertrachloroethane. [h] When $Cu(SbF_6)_2$ was used, the yield was 70% with 91% *ee*. Ad = 2-adamantyl, M.S. = molecular sieves, Tf = trifluoromethanesulfonyl.

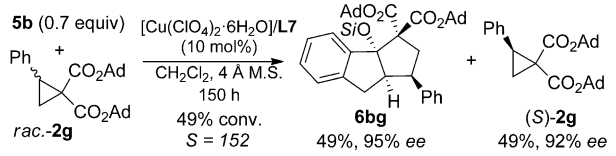
The success with monocyclic enol silyl ethers encouraged us to extend the current method to benzocyclic enol silyl ethers, which can deliver the benzene-fused cyclic products. As shown in Scheme 1, the reaction works extraordinarily well with these benzene-fused substrates, such as 3,4-dihydronaphthalen-1-one- and 1-indanone-derived silyl enol ethers (**5a–f**), and different substitution patterns such as 6-bromo, 6-fluoro, 7-methyl, and 5-methyl substituents are tolerated under the standard reaction conditions. In all cases high yield (80–98%) and complete diastereoselectivity



Scheme 1. Extension to the syntheses of benzocycles.

(>99:1) were obtained. The sterically demanding 4,7-dimethyl-substituted enol silyl ether **5f** also reacted well under the current reaction conditions, thus giving the desired cycloaddition product **6fa** in 91% yield and 93% *ee*.

For less reactive cyclopropanes, it is worth mentioning that the present reaction proceeds in a kinetic resolution fashion, though normally the reaction is slower. As exemplified in Scheme 2, a high selectivity factor ($S = 152$) was

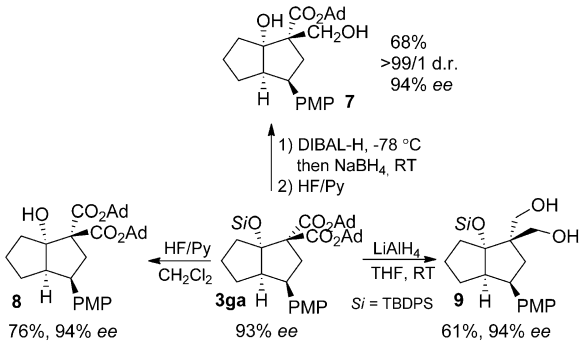


Scheme 2. Concurrent kinetic resolution of the cyclopropane **2g**.

obtained with the phenyl-substituted cyclopropane **2g**. Both the [3+2] cycloaddition product **6bg** and the remaining cyclopropane (*S*)-**2g** were isolated in nearly quantitative yields and high optical purities (95% and 92% *ee*, respectively, Scheme 2).

With respect to the transformation of the [3+2] annulation products, manipulations on the silyl and ester groups in the product **3ga** can be preformed without erosion of enantiomeric purity (Scheme 3). The silyl protecting group can be readily removed with HF/pyridine. In contrast, the two ester groups can be selectively reduced. One ester can be reduced with DIBAL-H/$NaBH_4$ to give **7**, which accommodates four contiguous stereocenters. And both esters can be reduced with $LiAlH_4$ to give the diol **9**. These transformations showed that the current reaction is potentially useful in organic synthesis.

In summary, a highly diastereo- and enantioselective formal [3+2] cycloaddition reaction of cyclic enol silyl ethers with D–A cyclopropanes was realized using modified copper(II)/BOX catalysts, thus providing an efficient, new, and facile access to a range of *3a*-hydroxy [*n*.3.0]carbobicycles of high optical purity. This reaction works well with five- to



Scheme 3. Transformations of the annulation products. DIBAL-H = diisobutylaluminum hydride.

seven-membered cyclic-ketone-derived enol silyl ethers, and can be further extended to α,β-unsaturated- and benzocyclic-ketone-derived substrates. To our knowledge, these reactions represent the first examples of catalytic enantioselective [3+2] annulation reactions of enol silyl ethers with cyclopropanes. Further exploration and application of the current reaction to natural product synthesis is ongoing in our laboratory.

Experimental Section

Typical procedure (**3aa** as an example): A mixture of [Cu(ClO_4)$_2$·6H_2O] (0.02 mmol) and the ligand (**L7**, 0.022 mmol) in dichloromeethane (1.0 mL), with activated 4 Å M.S., was stirred at room temperature for 2 h under N_2. Then the mixture was then warmed to 30 °C for 10 min, and the cyclopropane **2a** (0.20 mmol) was added. The enol silyl ether **1a** (0.30 mmol) in dichloromethane (1.0 mL) was then added. The resulting solution was stirred until the cyclopropane was completely consumed. The reaction mixture was then passed through a short silica gel column and eluted with dichloromethane. The combined elution was concentrated under reduced pressure to give the crude reaction mixture for the d.r. value determination (87:13), and was additionally purified by silica gel column (*n*-hexane/ethyl acetate, v/v, 150:1) to give the desired product as a white solid: 126 mg (*cis*), 19 mg (*trans*), 85% yield, 97% *ee* (*cis*).

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[13] CCDC 917548 (**3aa**-*cis*), 917502 (**3da**-*trans*), and 917503 (**3gc**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] The corresponding ring-opened products were isolated in approximately 30% yield in the enol silyl ether form.

