Cite this paper: Hu, J.; Zhou, L.; Wang, L.; Xie, Z.; Tang, Y. *Chin. J. Chem.* **2018**, *36*, 47—50.

Concise Report

DOI: 10.1002/cjoc.201700584

Copper Catalyzed Asymmetric [4 + 2] Annulations of D-A Cyclobutanes with Aldehydes

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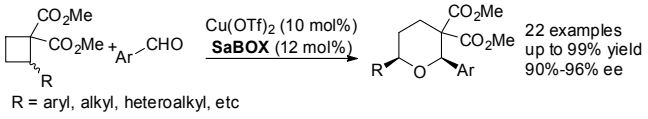
ABSTRACT Copper catalyzed enantioselective [4+2] annulations of D-A cyclobutanes and aldehydes have been developed. In the presence of a side arm modified chiral bisoxazoline (SaBOX) ligand, the [4+2] annulations proceeded smoothly with a broad substrate scope. 22 examples were studied, leading to the corresponding products with various functional groups in 41%—99% yields with >99/1 dr and 90%—96% ee. The resulting product with two ester groups was mono-reduced, giving the corresponding product in excellent diastereoselectivity without loss of the enantiopurity.

KEYWORDS [4+2] annulation, cyclobutane, enantioselective, copper, bisoxazoline

Introduction

The chemistry of strained ring compounds, activated by an electron donor-acceptor (D-A) system, attracted extensive attention.[1-2] Lots of elegant methods were developed and successfully applied in the total synthesis of natural products and drug molecules, based on the reactions of D-A cyclopropanes or D-A cyclobutanes with many different reactants.[3-5] Of those methods the D-A cyclobutanes participated, the [4+*n*] annulations provided effective accesses to the synthesis of abundant and various heterocyclic compounds.[6] For example, in 2009, Johnson *et al*. reported the [4+2] annulation of D-A cyclobutanes with aldehydes, leading to the stereoselective synthesis of substituted tetrahydropyrans in high yields with excellent levels of diastereoselectivity.[6b] The resulting substituted tetrahydropyrans bearing several stereogenic centers are found as a core structure in many biologically active natural products.[7] However, to the best of our knowledge, the enantioselective version of this reaction has not been reported yet. In fact, the asymmetric catalytic examples of D-A cyclobutane involved reactions are still rare,[5a,8] owing to the challenges of the enantioselective control of cyclobutanes. In this work, SaBOX/Cu(II) catalyzed enantioselective [4+2] annulations of D-A cyclobutanes with aldehydes were realized, furnishing a variety of optically active substituted tetrahydropyrans in up to 99% yield with >95/5 dr and 90%—96% ee. Herein, we report the preliminary results.

Scheme 1 [4+2] Annulations of D-A cyclobutanes with aldehydes

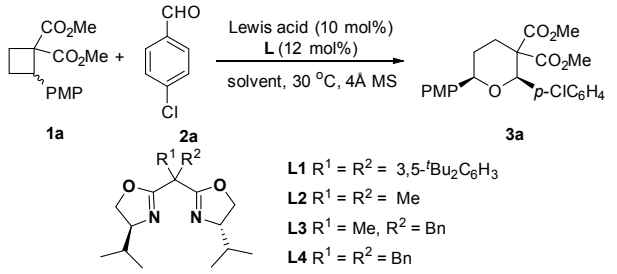


R = aryl, alkyl, heteroalkyl, etc

Results and Discussion

Our previous works on the asymmetric formal [4+3] cycloaddition of D-A cyclobutanes with nitrones[8b] exhibited that chiral bisoxazoline ligands modified with highly steric demand sidearms[9-10] always lead to excellent enantioselectivity. Based on this result, initially, we conducted the reaction of D-A cyclobutane **1a** with 4-chlorobenzaldehyde **2a** in the presence of 12 mol% of chiral ligand **L1** coordinated with some strong Lewis acids such as $Yb(OTf)_3$ and $Sc(OTf)_3$. As shown in Table 1, when $Yb(OTf)_3$ was employed, the desired multisubstituted tetrahydropyran **3a** was afforded in moderate yield without enantioselectivity (Entry 1). By using $Sc(OTf)_3$ as Lewis acid, the reactivity of the formal [4+3] cycloaddition was obviously increased, but still only a racemic product was obtained (Entry 2). Then different copper salts were screened including $Cu(NTf_2)_2$, $Cu(ClO_4)_2{\cdot}6H_2O$ and $Cu(OTf)_2$. $Cu(NTf_2)_2$ gave the optically active tetrahydropyran in 74% yield with moderate enantioselectivity, and $Cu(ClO_4)_2{\cdot}6H_2O$ could result in a 88% yield with 71% ee (Entries 3—4). Notably, when $Cu(OTf)_2$

Table 1 Reaction optimization



Entry[a]	Lewis acid	Solvent	L	Yield[b]/%	ee[c]/%
1	$Yb(OTf)_3$	DCM	**L1**	51	0
2	$Sc(OTf)_3$	DCM	**L1**	94	0
3	$Cu(NTf_2)_2$	DCM	**L1**	74	58
4	$Cu(ClO_4)_2{\cdot}6H_2O$	DCM	**L1**	88	71
5	$Cu(OTf)_2$	DCM	**L1**	85	83
6	$Cu(OTf)_2$	DCE	**L1**	85	88
7	$Cu(OTf)_2$	TTCE	**L1**	91	92
8	$Cu(OTf)_2$	TTCE	**L2**	84	83
9	$Cu(OTf)_2$	TTCE	**L3**	85	92
10	$Cu(OTf)_2$	TTCE	**L4**	88	94

[a] Reaction conditions: Lewis acid (0.02 mmol), **L** (0.024 mmol), **1a** (0.20 mmol) and **2a** (0.60 mmol) in 2.0 mL of solvent at 30 °C with 4 Å MS under Ar atmosphere for 10 h, dr was determined as *cis*/*trans*: >99/1 by crude ^{1}H NMR unless otherwise noted. [b] Isolated yield of the *cis* product. [c] Determined by chiral HPLC using a chiral stationary. DME=dichloromethane; DCE=1,2-dichloroethane; TTCE=1,1,2,2-tetrachloroethane.

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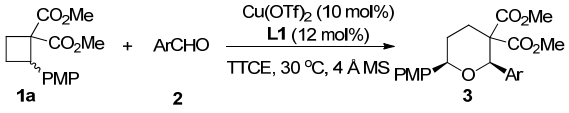
was employed as Lewis acid, the current reaction proceeded smoothly, furnishing the desired product in 85% yield with 83% ee (Entry 5). Further study on the effect of solvent showed that halogenated hydrocarbon behaved much better than other typical solvents.[11] When DCE was used, the enantioselectivity was slightly increased compared to the reaction with DCM as solvent (Entry 6). To our delight, employing TTCE as solvent, both the yield and the ee value of the reaction could be promoted to excellent level (91% yield and 92% ee, Entry 7). In order to further improve the enantioselectivity, various chiral ligands bearing different sidearms were systematically studied.[11] When **L2** was used, the ee value was dramatically dropped to 83% (Entry 8). Interestingly, it was found that the steric demand of the sidearms of the chiral ligands was not as much as those in the asymmetric formal [4+3] cycloaddition of D-A cyclobutanes with nitrones. When **L3** was employed, the reaction could also give 85% yield and 92% ee was obtained (Entry 9). Finally, **L4** containing two benzyl groups as sidearms led to the best result (88% yield and 94% ee, Entry 10).

Under the optimized reaction conditions, the substrate scope of the current reaction was studied. A variety of aldehydes were firstly used, and the results were shown in Table 2. Aromatic aldehydes **2a**—**2c** containing chloro-, bromo- and floro- substituents at the *para* position could result in the tetrahydropyrans **3a**—**3c** in high yields with excellent levels of enantioselecticity (Entries 1—3). When 4-methoxybenzaldehyde **2d** was employed, the yield of the formal [4+2] cycloaddition decreased, and 90% ee of **3d** was obtained (Entry 4). With 4-biphenylcarboxaldehyde **2e** as substrate, 99% yield and 92% ee could be achieved (Entry 5). Benzaldehyde **2f** could also led to 86% yield with 92% ee (Entry 6). Substituted benzaldehydes bearing electron-donating substituents such as methyl and methoxy groups at the *meta* position reacted smoothly, giving the corresponding products **3g**—**3h** in 96%—97% with 93%—94% ee (Entries 7—8). 1-Naphthyl and 2-naphthyl aldehydes were also good substrates, furnishing **3i** and **3j** in high yields with 92% ee and 93% ee, respectively (Entries 9—10). The absolute configuration of **3a** was established by X-ray crystallography.[11]

The scope of cyclobutanes was also investigated. As shown in Table 3, the current reaction system was compatible with the PhS-substituted cyclobutane, affording the product **3k** in 74% yield with 95% ee (Entry 2). With EtO- and BnO- substituted cyclobutanes, the yields of the corresponding products **3l** and **3m** dramatically decreased compared to **3j** and **3k**, but excellent levels of enantioselectivity were still obtained (95%—96% ee, Entries 3—4). Further study showed that a variety of cyclobutanes bearing *para-*, *meta-* and *ortho-* methylbenzyloxy groups were also tolerated, leading to the corresponding products **3n**—**3q** in good to high yields with 94%—96% ee (Entries 5—8). In addition, cyclobutane containing 2-chlorobenzyloxy groups resulted in 76% yield with 94% ee (Entry 9). 1-Naphthyl and 2-furyl substituted substrates could also react smoothly, giving the corresponding products **3s** and **3t** in 84% and 63% yields with 95% ee and 90% ee, respectively (Entries 10 and 11). Interestingly, chiral bicyclic acetals **3u** and **3v**, which exist as key motif in many biologically active natural products, could be furnished in high yields with excellent levels of enantioselectivity (94%—96% yields and 92%—94% ee, Entries 12 and 13).

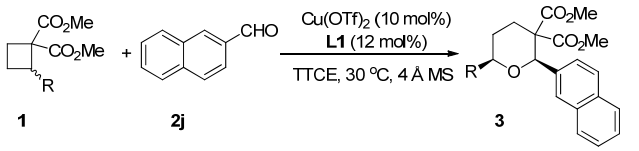
Table 2 Substrate scope of aldehyde

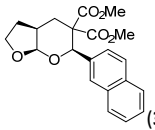
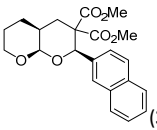


Entry[a]	Ar	Yield[b]/%	ee[c]/%
1	4-ClC_6H_4 (**3a**)	80	93
2	4-BrC_6H_4 (**3b**)	96	94
3	4-FC_6H_4 (**3c**)	99	92
4	4-$MeOC_6H_4$ (**3d**)	67	90
5	4-PhC_6H_4 (**3e**)	99	92
6	Ph (**3f**)	86	92
7	3-MeC_6H_4 (**3g**)	97	94
8	3-$MeOC_6H_4$ (**3h**)	96	93
9	1-naphthyl (**3i**)	87	92
10	2-naphthyl (**3j**)	92	93

[a] Reaction conditions: $Cu(OTf)_2$ (0.03 mmol), **L1** (0.036 mmol), **1a** (0.30 mmol), and **2** (0.90 mmol) in 2.0 mL of TTCE at 30 °C with 4 Å MS under Ar atmosphere, dr was determined as *cis*/*trans*: >99/1 by crude ^1H NMR unless otherwise noted. [b] Isolated yield of the *cis* product. [c] Determined by chiral HPLC using a chiral stationary.

Table 3 Substrate scope of cyclobutane



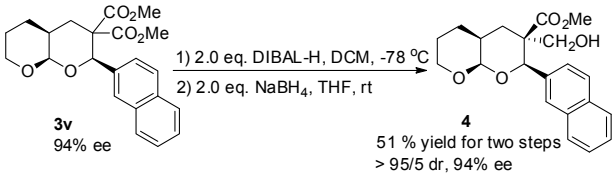
Entry[a]	R	Yield[b]/%	ee[c]/%
1	PMP (**3j**)	92	93
2	PhS (**3k**)	74	95
3	EtO (**3l**)	41	95
4	BnO (**3m**)	61	96
5	4-$MeC_6H_4CH_2O$ (**3n**)	63	96
6	3-$MeC_6H_4CH_2O$ (**3o**)	85	95
7	2-$MeC_6H_4CH_2O$ (**3p**)	82	96
8	2,6-$Me_2C_6H_3CH_2O$ (**3q**)	93	94
9	2-$ClC_6H_4CH_2O$ (**3r**)	76	94
10	1-naphthylCH_2O (**3s**)	84	95
11	2-furylCH_2O (**3t**)	63	90
12[d]	 (**3u**)	94	92
13[d]	 (**3v**)	96	94

[a] Reaction conditions: $Cu(OTf)_2$ (0.03 mmol), **L1** (0.036 mmol), **1** (0.30 mmol), and **2j** (0.90 mmol) in 2.0 mL of TTCE at 30 °C with 4 Å MS under Ar atmosphere, dr was determined as *cis*/*trans*: >99/1 by crude ^1H NMR unless otherwise noted. [b] Isolated yield of the *cis* product. [c] Determined by chiral HPLC using a chiral stationary. [d] **1** (0.90 mmol) and **2j** (0.30 mmol) were used.

As shown in Scheme 2, the product **3v** with 94% ee was reduced by 2.0 equiv. of DIBAL-H and then 2.0 equiv. of $NaBH_4$, giving the monoreduction product **4** in 51% yield with excellent diastereoselectivity without loss of the ee value. The relative configuration of the major diastereoisomer was confirmed by X-ray

analysis of the derivatives of **4**.[11]

Scheme 2 Chemical transformation



Conclusions

In conclusion, the copper catalyzed enantioselective [4＋2] annulations of D-A cyclobutanes and aldehydes have been developed. In the presence of a side arm modified chiral bisoxazoline (SaBOX) ligand **L1**, the [4＋2] annulations proceeded smoothly with a broad substrate scope. 22 examples were studied, leading to the corresponding products with various functional groups in 41%—99% yields with ＞99/1 dr and 90%—96% ee. The resulting product with two ester groups was mono-reduced, giving the corresponding product in excellent diastereoselectivity without loss of the enantiopurity. Further investigation of the application of this asymmetric catalysis is still on going in our laboratory.

Experimental

Typical procedure for the synthesis of 3a: A mixture of $Cu(OTf)_2$ (0.03 mmol) and ligand (**L1**, 0.036 mmol) in TTCE (1.5 mL) with activated 4 Å MS was stirred at 30 °C for 2 h under atmosphere of argon. Then, cyclobutane **1a** (0.3 mmol) and aldehyde **2a** (0.9 mmol) were added, and the tube wall was flushed with 0.5 mL TTCE. The resulting solution was stirred until the cyclobutane was completely consumed (monitoring by TLC, hexane/ethyl acetate＝5/1). Then the mixture was passed through a short silica gel column and eluted with DCM (50 mL). The combined elution was concentrated under reduced pressure to give the crude product **3a** for dr determination, which was further purified by flash chromatography on silica gel (hexane/ethyl acetate＝20/1) to afford the product **3a** (108 mg) as a white paste in 80% yield with ＞99/1 dr and 93% ee (Daicel Chiralcel IA-3 column (25 cm), hexanes/^{i}PrOH＝90/10, 0.7 mL/min, 260 nm; t_r(major)＝9.8 min, t_r(minor)＝14.5 min; $[\alpha]_D^{30.8}$＝＋51.3° (c＝0.73, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 (d, J＝8.4 Hz, 2H), 7.31 (d, J＝8.8 Hz, 2H), 7.24 (d, J＝8.4 Hz, 2H), 6.88 (d, J＝8.8 Hz, 2H), 5.10 (s, 1H), 4.62—4.59 (m, 1H), 3.79 (s, 3H), 3.68 (s, 3H), 3.56 (s, 3H), 2.70—2.65 (m, 1H), 2.32—2.25 (m, 1H), 2.15—2.04 (m, 1H), 1.92—1.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.2, 168.9, 159.1, 138.0, 134.2, 133.2, 128.8, 127.4, 127.1, 113.7, 81.7, 80.4, 58.4, 55.2, 52.5, 51.7, 32.6, 29.8; IR (neat) v: 2949, 2855, 1722, 1515, 1435, 1244, 1183, 1114, 1080, 1032, 1010, 937, 821 cm^{-1}; HRMS-ESI: $[M+NH_4]^+$ calculated for $C_{22}H_{27}ClNO_6^+$, 436.1521; Found: 436.1528.

Supporting Information

Experimental procedures and characterization data for all products and crystallographic data are included. The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.201700584.

Acknowledgement

We thank for the financial support from the National Natural Science Foundation of China (Nos. 21421091 and 21432011), the National Basic Research Program of China (973 Program) (2015CB856600), the Natural Science Foundation of Shanghai (17ZR1436900), the Strategic Priority Research Program of the Chinese Academy of Sciences (Grant No. XDB20000000) and the Youth Innovation Promotion Association CAS (2017301). We thank Dr. Xue-Bing Leng for X-ray crystal analysis

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[11] For details, see Supporting Information.

Manuscript received: September 19, 2017
Manuscript revised: October 12, 2017
Manuscript accepted: October 16, 2017
Accepted manuscript online: October 20, 2017
Version of record online: XXXX, 2017

