Asymmetric Catalysis

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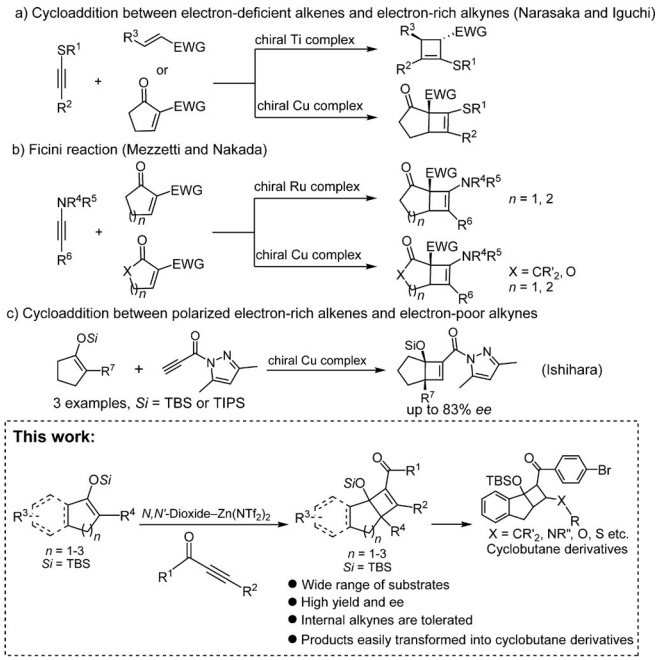
A Chiral *N,N′*-Dioxide–Zn^{II} Complex Catalyzes the Enantioselective [2+2] Cycloaddition of Alkynones with Cyclic Enol Silyl Ethers

Tengfei Kang, Shulin Ge, Lili Lin, Yan Lu, Xiaohua Liu, and Xiaoming Feng**

Abstract: *A highly efficient enantioselective [2+2] cycloaddition between alkynones and cyclic enol silyl ethers was developed by using a chiral N,N′-dioxide-zinc(II) complex as a catalyst. This method functions well for a variety of terminal alkynes as well as cyclic enol silyl ethers, with good to excellent enantioselectivity (up to 97% ee). This is also the first successful example for the catalytic enantioselective [2+2] cycloaddition of internal alkynes with cyclic enol silyl ethers to give fully substituted cyclobutenes. Meanwhile, the desired cyclobutene product can easily be transformed into fused cyclobutane derivatives.*

Cyclobutenes have proven to be important structural motifs and are found in numerous natural products and bioactive compounds.[1] They are also important synthetic intermediates for other useful scaffolds owing to their high reactivity, which originates from ring strain.[2] The [2+2] cycloaddition of an alkyne with an alkene is one of the most straightforward routes for preparing cyclobutenes. Consequently, numerous methods have been developed for cycloaddition.[3–9] However, regarding catalytic asymmetric version, only a few examples have been reported during the past decades.[10,11] Chiral transition-metal catalysts were found to be efficient for the [2+2] cycloaddition of alkynes with strained bicyclic alkenes.[12,13] In 2014, Bach[14] and co-workers documented an enantioselective [2+2] photo-cycloaddition of 2-pyridones with acetylenedicarboxylates. For chiral Lewis acid promoted [2+2] cycloaddition, there are three types of reaction models according to the electronic nature of the substrates (see Scheme 1): Cycloaddition with electron-deficient alkenes and electron-rich alkynes (type I),[15,16] Ficini reaction (type II),[17] and formal cycloaddition between polarized electron-rich alkenes and electron-poor alkynes (type III).[18] For type I and type II cycloadditions (Scheme 1 a,b), electron-rich alkynes are required, so S and N atoms are commonly introduced. For type III cycloaddition (Scheme 1 c), electron-deficient alkynes are needed, thus an electron-withdrawing group is often tethered to the alkyne. However, for formal cycloaddition between polarized electron-rich alkenes and electron-poor alkynes, the alkynes have until now been limited to terminal C≡C bonds. This might be due to the lower reactivity of internal alkynes and difficulty in controlling the stereoselectivity of the reaction. Therefore, a new catalyst system that could be applied not only to terminal alkynes but also to internal alkynes is greatly needed. Herein, we described our efforts in developing a chiral *N,N′*-dioxide-$Zn(NTf_2)_2$ catalyst for the catalytic enantioselective [2+2] cycloaddition of alkynones with cyclic enol silyl ethers.[19]



Scheme 1. Lewis acid catalyzed asymmetric [2+2] cycloaddition.

We initiated our study by optimizing the reaction conditions for the cycloaddition of alkynone **1a** with 1-indanone derived cyclic enol silyl ether **2a** as a model reaction. In the presence of 2 mol% of chiral *N,N′*-dioxide[20] L_3-$PiPr_2$–Zn-$(NTf_2)_2$ complex and 4 Å MS in CH_2Cl_2 at −10 °C, cyclobutene **3a** was obtained in 67% yield with 60% *ee* (Table 1, entry 1). Encouraged by this result, the structure of the chiral ligands was then evaluated. It was found that both the chiral backbone and the linker of the ligands greatly affect the selectivity and reactivity of the process. Ligand L_2-$PiPr_2$, which has a two-carbonic linkage, was superior to that of the three-carbonic L_3-$PiPr_2$ (entry 2 vs. entry 1). Variation of the chiral backbone revealed that the L-ramipril derived L_2-$RaPr_2$

[*] T. F. Kang, S. L. Ge, Dr. L. L. Lin, Y. Lu, Prof. Dr. X. H. Liu, Prof. Dr. X. M. Feng
Key Laboratory of Green Chemistry & Technology
Ministry of Education
College of Chemistry, Sichuan University
Chengdu 610064 (China)
E-mail: liuxh@scu.edu.cn
xmfeng@scu.edu.cn
Prof. Dr. X. M. Feng
Collaborative Innovation Center of Chemical Science and Engineering, Tianjin 300072 (China)

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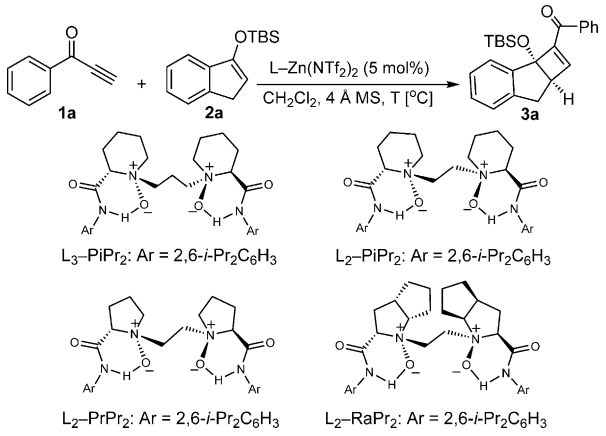
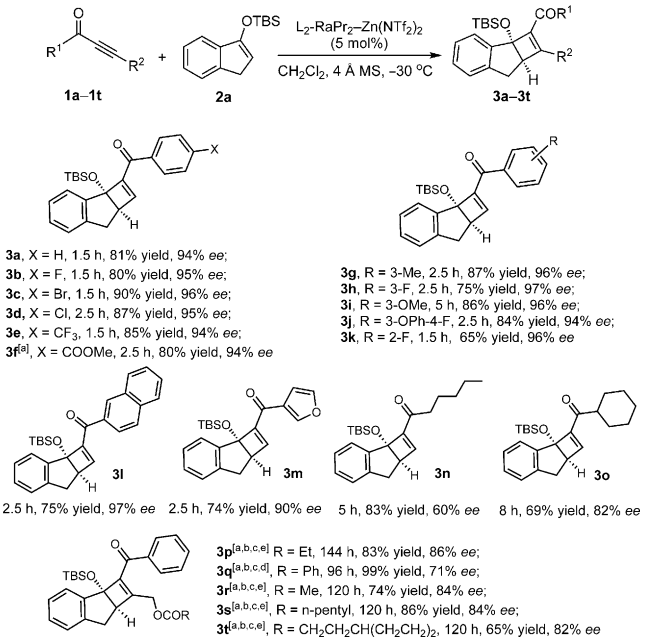
Table 1: Optimization of reaction conditions.



Entry[a]	Ligand	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	L_3-$PiPr_2$	−10	67	60
2	L_2-$PiPr_2$	−10	93	76
3	L_2-$PrPr_2$	−10	82	81
4	L_2-$RaPr_2$	−10	81	90
5	L_2-$RaPr_2$	−30	81	92
6	L_2-$RaPr_2$	−45	72	89
7[d]	L_2-$RaPr_2$	−30	81	94
8[e]	L_2-$RaPr_2$	−30	83	94

[a] Unless otherwise noted, all reactions were performed with L–$Zn(NTf_2)_2$ (2 mol%, 1:1), **1a** (0.20 mmol), **2a** (0.20 mmol), and 4 Å MS (100 mg) in CH_2Cl_2 (0.6 mL) under nitrogen for 1.5 h. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] 5 mol% of catalyst was used. [e] 10 mol% of catalyst was used.



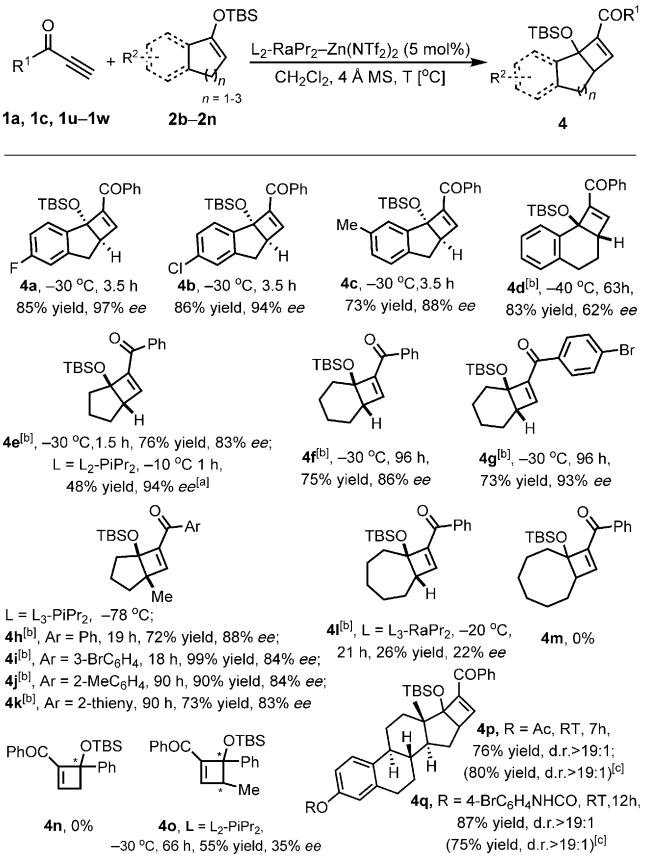
Scheme 2. Substrate scope for alkynones. Unless otherwise noted, all reactions were performed with L_2-$RaPr_2$–$Zn(NTf_2)_2$ (5 mol%, 1:1), **1** (0.20 mmol), **2a** (0.20 mmol), and 4 Å MS (100 mg) in CH_2Cl_2 (0.6 mL) at −30 °C under nitrogen. Yields of isolated product are given, *ee* values were determined by HPLC analysis. [a] The reaction was carried out on a 0.1 mmol scale. [b] L_2-$PiPr_2$ was used as the ligand. [c] 10 mol% of catalyst was used. [d] Run at −40 °C. [e] Run at −60 °C.

gives better enantioselectivity (90% *ee*) than the *S*-pipecolic acid derived L_2-$PiPr_2$ (76% *ee*) and L-proline derived L_2-$PrPr_2$ (81% *ee*; entry 4 vs. entries 2 and 3). With the aim of further improving the enantioselectivity, the reaction temperature and catalyst loading were tested. A slightly higher *ee* value (92%) was obtained by lowering the temperature to −30 °C, and the yield was maintained (entry 5). However, further reduction of the temperature to −45 °C gave no positive effect on the reactivity and enantioselectivity (entry 6). When the catalyst loading was increased from 2 mol% to 5 mol%, the *ee* value improved to 94% (entry 7). Upon further increase of the catalyst loading to 10 mol%, no increase in enantioselectivity was achieved. (entry 8). Therefore, the optimized conditions entail the use of 5 mol% L_2-$RaPr_2$–$Zn(NTf_2)_2$ as catalyst and 4 Å MS as an additive in CH_2Cl_2 at −30 °C for 1.5 h (entry 7).

With the optimized conditions in hand, we turned to explore the substrate scope of the catalytic system (Scheme 2). A wide range of terminal alkynones with different substituted phenyl R^1 groups (both electron-withdrawing and electron-donating groups at the *para*-, *meta*-, or *ortho*-positions) all reacted quite well with **2a** to form the corresponding cyclobutene products **3** in moderate to high yield (65–90%) with excellent *ee* values (94–97%). Functional groups such as halogens, alkyl groups, and esters were well tolerated. Furthermore, alkynones bearing 2-naphthyl or 3-furyl R^1 moieties also proved to be suitable substrates, affording **3l** in 75% yield with 97% *ee* and **3m** in 74% yield with 90% *ee*. Moreover, aliphatic alkynones **1n** and **1o** also produced results when prolonging the reaction time to 5 and 8 h, giving the corresponding cyclobutene **3n** and **3o** in 83% yield (60% *ee*) and 69% yield (82% *ee*), respectively.

Next, we focused on the [2+2] cycloaddition of **2a** with more difficult internal alkynes (Scheme 2).[21] Internal alkyne **1p**, which contains a propionate moiety, resulted in a moderate *ee* (63%)[22] under the standard conditions. To our delight, upon changing the ligand to L_2-$PiPr_2$, the cycloaddition product **3p** was obtained in 83% yield with 86% *ee*. Benzoate substrate **1q** reacted in 96 h to afford the corresponding **3q** in 71% *ee*. Moreover, the acetate, hexanoate and 3-cyclopentylpropanoate substrates **1r–1t** were transformed into the corresponding cyclobutenes **3r–3t** in moderate to good yield (65–86%) with good *ee* values (82–84%).

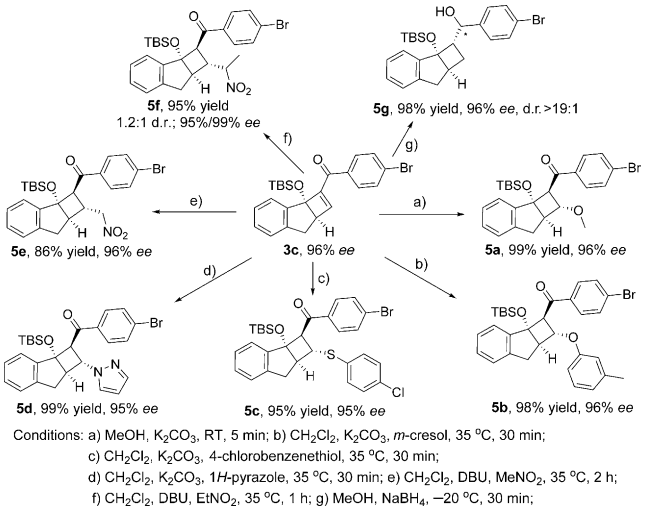
Subsequently, the substrate scope with respect to the benzocyclic enol silyl ethers was examined. As shown in Scheme 3, benzene-fused substrates with 5-fluoro, 5-chloro, or 6-methyl substituents (**2b–2d**) were tolerated well under the standard reaction conditions, giving cycloaddition product **4a–4c** in 73–86% yields with 88–97% *ee*. When the 3,4-dihydronaphthalen-1-one derived enol silyl ether **2e** was used, the product was obtained with 62% *ee*. Monocyclic enol silyl ethers were also tested. To our delight, both five- and six-membered-ring substrates (**2f** and **2g**) reacted well under the standard conditions (73–76% yields, 83–93% *ee*). In addition, the β-methyl substituted enol silyl ether **2h** was also a suitable substrate, affording the desired cyclobutenes **4h–4k** with two



Scheme 3. Substrate scope for silyl enol ethers. Unless otherwise noted, all reactions were performed with L_2-$RaPr_2$–$Zn(NTf_2)_2$ (5 mol%, 1:1), **1** (0.20 mmol), **2** (0.20 mmol), and 4 Å MS (100 mg) in CH_2Cl_2 (0.6 mL) under nitrogen. [a] 2 equiv of **2f** was used. [b] The bonds shown in bold indicate the *syn* relative configuration. [c] Run with *ent*-L_2-$RaPr_2$.

contiguous stereocenters in good to excellent yields (72–99%) and with good *ee* (83–88%). We also tried to expand the present catalytic system to cyclic enol silyl ethers with larger rings and acyclic enol silyl ethers. Unfortunately, **4l** was obtained in only 26% yield (22% *ee*). **4m** and **4n** not formed, however, **4o** was obtained in 55% yield with 35% *ee*. Finally, **4p** and **4q** were obtained in 76% and 87% yield with d.r. > 19:1.[23] The enantiomer of L_2-$RaPr_2$ was also tested and gave **4p** and **4q** in 80% and 75% yield, respectively, with d.r. > 19:1, which revealed that the diastereoselectivity of the reactions to give **4p** and **4q** might be controlled by the chiral backbones of **2m** and **2n** rather than the chiral ligand.

To evaluate the synthetic potential of this reaction, transformation of the [2+2] cycloaddition product **3c** was carried out (Scheme 4). Product **3c** reacted quite well with different nucleophiles, including methanol, *m*-cresol, 4-chlorobenzethiol, 1*H*-pyrazole, and nitromethane, to afford fused cyclobutane derivatives (**5a**–**5e**) with four contiguous stereocenters in excellent yield with excellent *ee* values under mild reaction conditions. The absolute configuration of cyclobutene **3c** was determined to be (2*aR*,7*aR*) by X-ray crystallography analysis of **5d**.[22] When nitroethane was utilized, the cyclobutane **5f** was obtained in 95% yield as



Scheme 4. Representative product transformations.

a 1.2:1 mixture of diastereomers.[24] Furthermore, both the C=C bond and the carbonyl group of **3c** could be easily reduced by $NaBH_4$ to afford the desired cyclobutane **5g**, which contains a secondary alcohol moiety, in 98% yield with 96% *ee* and d.r. > 19:1.

In summary, we have successfully realized a highly efficient [2+2] cycloaddition of alkynones with cyclic enol silyl ethers by using a chiral *N*,*N*′-dioxide L_2-$RaPr_2$–$Zn(NTf_2)_2$ as catalyst. A number of fused cyclobutenes were obtained in moderate to excellent yields (up to 99%) with high *ee* values (up to 97%). The method is notable because it can be applied not only to terminal alkynes but also to internal alkynes. Furthermore, the products can easily be transformed into fused cyclobutane derivatives that show great potential in organic synthesis. Further studies focusing on related reactions are underway.

Experimental Section

A dry reaction tube was charged with L_2-$RaPr_2$ (0.01 mmol), $Zn(NTf_2)_2$ (0.01 mmol), 4 Å MS (100 mg), and alkynone **1a** (0.20 mmol) under N_2 atmosphere. CH_2Cl_2 (0.6 mL) was added and the mixture was stirred at 35 °C for 0.5 h. Then, the mixture was cooled to −30 °C and cyclic enol silyl ether **2a** (0.20 mmol) was added under stirring. The reaction mixture was stirred at the same temperature for 1.5 h. Finally, the residue was directly purified by flash chromatography on silica gel (eluent: petroleum ether/CH_2Cl_2 2:1) to afford the desired product **3a**.

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[21] Aliphatic internal alkynones were not suitable as reactants; see the supporting information for details.

[22] See the supporting information for details.

[23] Only decomposition of chiral enol silyl ethers **2m** and **2n** was observed in the absence of L_2-$RaPr_2$.

[24] The diastereomers could be separated by flash chromatography on silica gel.

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