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Enantioselective Synthesis of 3-Substituted Cyclobutenes via Catalytic Conjugate Addition/Trapping Strategies

Changxu Zhong[+], Yingchao Huang[+], Haocheng Zhang, Qiang Zhou, Yu Liu, and Ping Lu*

Abstract: *The copper-catalyzed tandem process to access chiral cyclobutene derivatives has been developed, enabled by enantioselective conjugate addition or reduction of cyclobutenones, and sequential trapping with chlorophosphate in one pot. These phosphates are stable to mild acidic conditions and serve as good electrophiles for Negishi-coupling reactions.*

Cyclobutane motifs, due to high torsion strains and unique conformation properties, are important building blocks in organic synthesis and medicinal chemistry.[1] Some representative drugs or drug candidates with trisubstituted cyclobutane ring are depicted in Figure 1.[2] Although this area has received considerable attention, enantioselective synthesis of cyclobutanes is still an attractive yet challenging topic for synthetic community.[3,4] Functionalization of four-membered carbocycles continues to attract growing interests.[5]

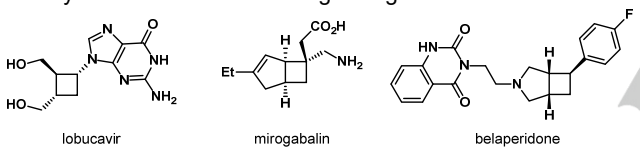
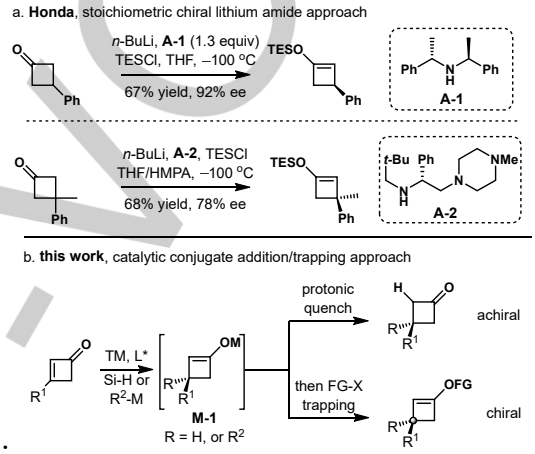


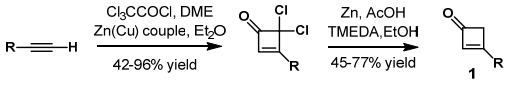
Figure 1. Selected drugs or drug candidates containing the trisubstituted cyclobutane subunit.

Enantioselective deprotonation of *meso* or prochiral cyclic ketones using chiral lithium amides as the base provided a straightforward approach to access enantiomerically enriched enol intermediates.[6] In 1993, Honda and co-workers developed an elegant enantioselective desymmetrization of 3-substituted cyclobutanone to access chiral silyl enol ether in the synthesis of lignin lactones (Scheme 1a).[7] Using stoichiometric lithium (*S*,*S'*)-α,α'-dimethyldibenzylamide (**Li-A-1)** as the base at −100 °C, the reaction of 3-phenyl cyclobutanone provided corresponding silyl enol ether in good yield and high enantioselectivity (67% yield, 92% ee). However, in the case of 3,3-disubstituted cyclobutanone, the selectivity is only moderate under optimal conditions (**A-2**, 78% ee). Recently, enantioselective synthesis of cyclobutene derivatives has been reported via [2+2]-cycloaddition approaches.[4a-c] To the best of our knowledge, functionalization of cyclobutenones is a far less studied strategy.[4d] In line with our continued interest in desymmetrization of cyclobutanones,[8] we planned to access these chiral cyclobutene derivatives with higher stability and efficiency in a catalytic process. We proposed that the transition-metal catalyzed conjugate reduction or addition to cyclobutenones would afford achiral cyclobutanone, when *in-situ* generated metal enol intermediate (**M-1**) was quenched with protonic solvent (Scheme 1b). However, if this enol intermediate **M-1** was trapped with electrophile, a chiral cyclobutene intermediate with a tri- or tetrasubstituted chiral center and a functionalized alkene could be produced, which is then amenable for further derivatization.



Scheme 1. Enantioselective synthesis of cyclobutene derivatives.

3-Substituted cyclobutenones were readily prepared using Danheiser's two-step procedure as depicted in Scheme 2.[9] [2+2]-Cycloaddition of alkyne and dichloroketene, followed by reductive dechlorination afforded desired cyclobutenone **1** smoothly.



Scheme 2. Preparation of 3-substituted cyclobutenone **1**.

With these thoughts in mind, we commenced our studies with copper-catalyzed 1,4-conjugate reduction of 3-substituted cyclobutenones. Pioneered by Brunner and Stryker,[10] the Cu-H catalyzed enantioselective hydrofunctionalization of carbonyl compounds and alkenes has evolved dramatically, and a wide array of enantiomerically enriched substrates could be synthesized via various processes.[11,12] We postulated that exposure of cyclobutenone **1a** to a copper catalyst and silane would afford the corresponding silyl enol ether **M-2**, then subsequent lithium-silicon exchange and diphenyl chlorophosphate trapping would provide cyclobutenyl phosphate **2a**. We reasoned that cyclobutenyl phosphate would be more stable than the corresponding silyl enol ether under mild acidic conditions. In addition, cyclobutenyl phosphate would serve as a good precursor for further cross-coupling reactions. Indeed, after screening several privileged ligands, we found that Josiphos ligands gave better results, as summarized in Table 1. The optimal conditions were achieved using (*R*, S_p)-Josiphos (**L-5**)

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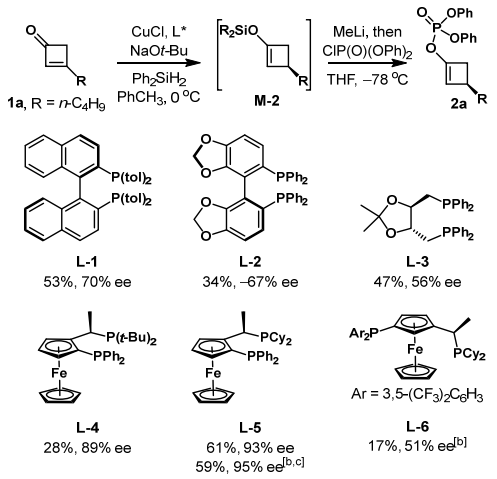
as ligand (59-61% yield, 93-95% ee). Lower temperature (–20 °C) gave slightly better selectivity, and THF was chosen as solvent for convenience.

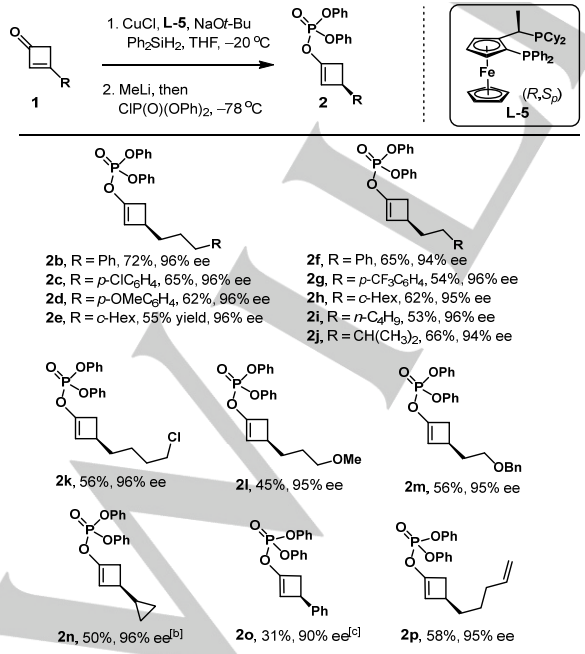
Table 1. Optimization of 1,4-reduction/trapping reaction of **1a**.[a]



[a] **1a** (0.5 mmol), CuCl (5 mol%), L* (5 mol%), Ph_2SiH_2 (0.54 equiv) in $PhCH_3$, then MeLi (1.25 equiv), THF, followed by $ClPO(OPh)_2$ (2 equiv), see SI for more details. [b] THF was used as solvent. [c] at –20 °C.

Guided by these optimized experiments, we investigated substrate scope of cyclobutenone **1** (Table 2). Under standard conditions, substrates with diverse 3-alkyl groups afforded the corresponding cyclobutene derivatives in high yields and in the range of 94-96% ee, including 3-aryl or cyclohexyl propyl (**2b-2e**), 3-aryl or cyclohexyl ethyl (**2f-2h**), and linear aliphatic substituents (**2i-2j**). Substrates with a variety of functional groups, for instance, chlorobutyl (**1k**), methoxypropyl (**1l**) and benzyloxyethyl (**1m**), were well tolerated, producing the expected products in good enantioselectivity uneventfully (**2k-2m**, 95-96% ee). 3-Cyclopropyl group (**2n**) was also compatible when diethoxymethylsilane was used in lieu of Ph_2SiH_2. And the

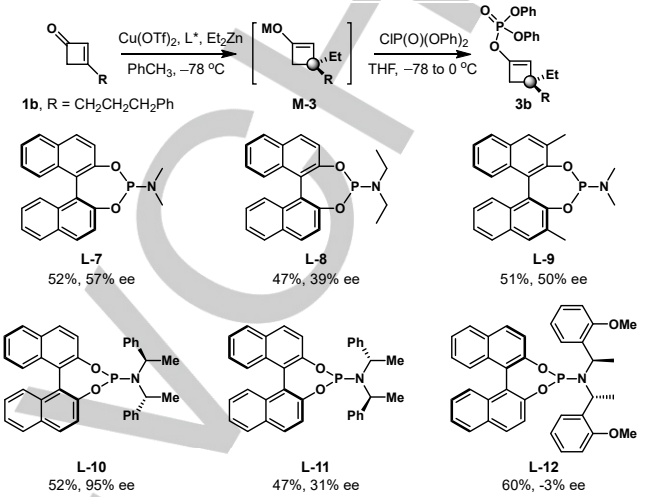
Table 2. Substrate scope of 1,4-reduction/trapping reaction **1**.[a]



[a] **1** (0.5 mmol) in THF. [b] Diethoxymethylsilane was used. [c] **L-4** was used.

reaction of 3-phenyl cyclobutenone (**2o**) performed as well when **L-4** was used (31% yield, 90% ee) albeit in a lower yield. In addition, product **2p** with alkene functional group could also be obtained in good yield and ee (58% yield, 95% ee). However, 1,4-reduction of 2,3-dibutyl cyclobutenone did not work under current conditions.

Table 3. Optimization of 1,4-addition/trapping reaction of **1b**.[a]



[a] **1b** (0.5 mmol), $Cu(OTf)_2$ (2.5 mol%), L* (2.5 mol%), $ZnEt_2$ (1.25 equiv) in $PhCH_3$, then $ClPO(OPh)_2$ (2 equiv) and THF, see SI for more details.

Next, we investigated 1,4-conjugate addition to cyclobutenone **1**. Asymmetric 1,4-conjugate addition is one of the most fundamental C−C or C−heteroatom construction processes in organic synthesis. Since the pioneering reports on copper-catalyzed enantioselective Michael addition by Alexakis and Feringa,[13] significant progress has been achieved with the development of chiral ligands and organometallic reagents.[14] However, installing chiral quaternary centers via 1,4-addition of zinc reagents is still underdeveloped.[15,16] Here we assumed that treatment of enol intermediate **M-3** in one-pot with electrophile would furnish 3,3-disubstitued cyclobutene derivative **3** containing a chiral quaternary center. We started our studies with the reaction of **1b**, choosing diethyl zinc as nucleophilic reagent and diphenyl chlorophsphate as electrophile. Gladly, due to high strain of cyclobutenone, conjugate addition took place at –78 °C smoothly. We screened several privileged ligands and the results are summarized in Table 3. Phosphoramidite ligands gave better results than Josiphos ligands (see supporting information for more details), and the optimal results were achieved when (*S*,*R*,*R*)-**L-10** was used as a chiral ligand and $Cu(OTf)_2$ as copper source (52% yield, 95% ee). Of note, (*S*,*S*,*S*)-**L-11** and **L-12** gave poor selectivity (3-31% ee).

We further examined the substrate scope of the above 1,4-addition/trapping reaction of cyclobutenones, as summarized in Table 4. Various 3-substituted cyclobutenones were compatible under optimal conditions. 3-Alkyl substituted cyclobutenones gave the corresponding products (**3a-3d**, **3f** and **3h-3j**) in 93-96% ee. A variety of functional groups, for example, methoxy and chloro, were also tolerated, and the resulting phosphates (**3k-l**) were obtained in excellent enantioselectivity (95-96% ee). 3-Cyclopropyl and 3-cyclohexyl cyclobutenones (**1n** and **1v**) provided the corresponding products (**3n** and **3v**) in 93-96% ee as well. In addition, aryl substituted cyclobutenones also provided desired products (**3o** and **3q-t**) in 90-97% ee and high

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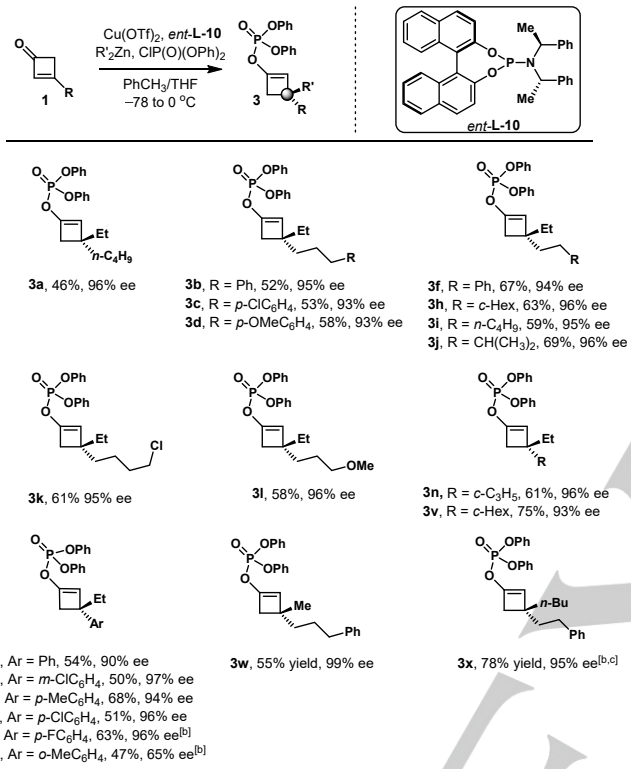
yields. Of note, **3u** with *o*-methylphenyl substituent were obtained in moderate enantioselectivity (65% ee).

Dialkyl znic reagents were also tested. Methyl and *n*-butyl addition products (**3w** and **3x**) were furnished in good enantioselectivity using commercially available dimethyl or dibutyl zinc. However, diphenyl zinc showed low reactivity under current conditions, and 1,4-addition of 2,3-disubstituted cyclobutenones with diethyl znic did not work either.

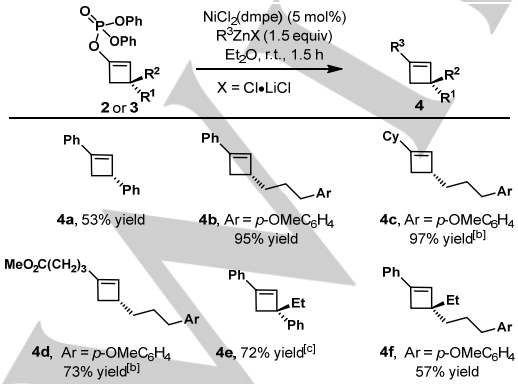
Table 4. Substrate scope of 1,4-addition/trapping reaction of **1**.[a]



[a] **1** (0.5 mmol), $Cu(OTf)_2$ (2.5 mol%), ***ent*-L-10** (2.5 mol%), ZnR'_2 (1.25 equiv) in $PhCH_3$, then $ClPO(OPh)_2$ (2 equiv) and THF was used, see SI for more details. [b] $Cu(OTf)_2$ (10 mol%), ***ent*-L-10** (10 mol%) were used. [c] Bu_2Zn (1.5 equiv) were used.

With chiral cyclobutenyl phosphates in hand, the nickel-catalyzed Negishi coupling reaction was examined. The optimal conditions were achieved using $NiCl_2$(dmpe) as a catalyst (Table 5).[17] Under these conditions, 3-substituted cyclobutenes (**4a**-**4d**) or 3,3-disubstituted cyclobutenes (**4e**-**4f**) were synthesized

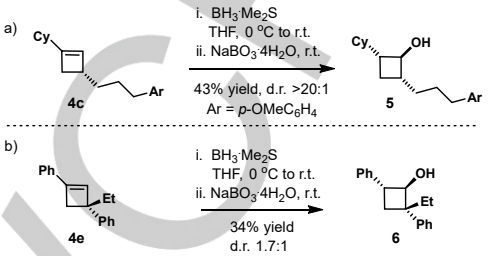
Table 5. Further transformations of cyclobutene phosphate.[a]



[a] Zinc reagents were prepared according to Knochel's procedure.[18] [b] $NiCl_2$(depe) was used. [c] At 0 °C.

smoothly at room temperature or 0 °C in the presence of aryl or alkyl zinc reagents without obvious erosion of enantiomeric purity (see SI for details). The absolute configuration could be determined by comparison of optical rotation values for products **4a** and **4e** with those reported in the literature.[3c]

At this point, hydroboration–oxidation of cyclobutene using $BH_3{\cdot}Me_2S$ and $NaBO_3$ was conducted (Scheme 3). The reaction of **4c** showed good diastereoselectivity (>20:1) to afford alcohol **5** in moderate yield, while the reaction of cyclobutene **4e** gave only poor (1.7:1) diastereoselectivity.[19]



Scheme 3. Functionalization of cyclobutene **4**.

In conclusion, we reported a highly enantioselective copper-catalyzed 1,4-addition/trapping of cyclobutenones to access cyclobutenyl phosphates. With the aid of enantioselective hydrosilylation and 1,4-conjugate addition, cyclobutenes with embedded chiral tertiary and quaternary carbon centers could be conveniently prepared. Subsequent cross-coupling reactions effectively afforded chiral cyclobutene derivatives. Development of further tandem processes to access chiral functionalized cyclobutane motifs from cyclobutenones is underway.

ACKNOWLEDGMENT

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Cyclobutenone • 1,4-addition• hydrosilylation • tandem reaction • cross-coupling

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[19] The configuration of major diastereomer (**6**) could not be unambiguously determined by 2D NMR yet.

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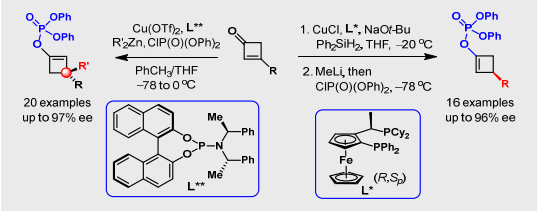

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