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Authors: Wei Huang and Fanke Meng

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COMMUNICATION

Cobalt-Catalyzed Diastereo- and Enantioselective Hydroalkylation of Cyclopropenes with Cobalt-Homoenolates

Wei Huang,[a] and Fanke Meng*[a]

Dedicated to the 70th anniversary of Shanghai Institute of Organic Chemistry ((optional))

[a] W. Huang, Prof. Dr. F. Meng
State Key Laboratory of Organometallic Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences
Chinese Academy of Sciences
345 Lingling Road, Shanghai, 200032 (China)
E-mail: mengf@sioc.ac.cn

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Abstract: Catalylic diastereo- and enantioselective hydroalkylation of 3,3-disubstituted cyclopropenes with Co-homoenolate in situ generated from ring-opening of easily accessible cyclopropanols promoted by a chiral phosphine–Co complex is presented. Such a process represents the unprecedented and direct introduction of a wide range of functionalized alkyl groups without the need of pre-formation of stoichiometric amounts of organometallic reagents onto the cyclopropane motif, affording multi-substituted cyclopropanes in up to 99% yield with >95:5 dr and 98:2 er. Functionalization of the products delivered enantioenriched cyclopropanes that are otherwise difficult to access.

Enantioenriched functionalized cyclopropanes are important building blocks that can be transformed to a variety of useful molecules in organic synthesis, as well as key structures in biologically active molecules.[1] Therefore, it is of great importance to establish a versatile approach for diastereo- and enantioselective preparation of a wide range of functionalized alkylcyclopropanes in complex molecule synthesis and drug development (Figure 1).[2] Numerous strategies have been developed for enantioselective access to cyclopropyl motifs, including the metal-catalyzed carbene insertion of terminal alkenes,[3] the Simmons-Smith cyclopropanation of allylic and homoallylic alcohols,[4] and conjugate addition followed by cyclization of activated alkenes[5]. Although high selectivity is achieved through these methods, some limitations are present (the requirement of an electron-withdrawing group for the carbene insertion and conjugate addition followed by cyclization and the presence of a coordinating group for the Simmons-Smith cyclopropanation). A more general approach to prepare enantioenriched alkylcyclopropanes is catalytic enantioselective hydroalkylation of cyclopropenes.[6] The advantage is that a broad range of multisubstituted cyclopropanes can be rapidly accessed through a single set of transformations without the requisite of pre-installation of a specific functional group, starting from readily available materials and catalyst.

In the context of catalytic enantioselective functionalization of cyclopropenes, Rh-catalyzed hydrostannation,[7] hydroboration,[8] hydroformylation,[9] and hydroacylation,[10] Cu-catalyzed hydroboration,[11] hydronitronylation,[12] carbocupration,[13] carbozincation,[14] carbomagnesiation[15] and hydroallylation,[16] Fe-[17] and Pd-catalyzed carbozincation,[18] hydroalkynylation[19] and lanthanide-catalyzed hydroamination,[20] hydroalkynylation,[21] and addition of 2-methyl azaarenes,[22] Co-catalyzed hydroalkenylation[23] and hydrosilylation,[24] and NHC-catalyzed hydroacylation[25] have been reported for enantioselective synthesis of various functionalized cyclopropanes. However, few protocols have been developed for enantioselective introduction of diversified alkyl groups to cyclopropenes. Pioneering works by Marek and co-workers revealed that simple alkyl groups can be incorporated in high diastereo- and enantioselectivity with Grignard or organozinc reagents promoted by Cu complexes.[14b,15b-c] However, only alkyl groups without functional groups can be introduced. In addition, preparation of sensitive reagents is necessary and stoichiometric amounts of by-products are generated.

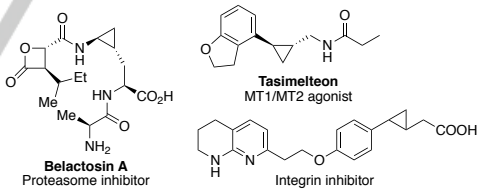

Figure 1. Biologically active molecules bearing functionalizaed alkylcyclopropane structures.

Coupling of metal homoenolates represents a direct and important method to access β-functionalized ketones.[26] Although significant progress has been made in the formation of homoenolates from catalytic ring-opening of cyclopropanols followed by cross-coupling and addition to unsaturated hydrocarbons,[27] enantioselective transformations remained scarce.[27e] Yoshikai and co-workers reported an enantioselective process for addition of the Co homoenolates to oxabicyclic alkenes in high stereoselectivity albeit with limited scope of the oxabicyclic alkenes.[27e] We are interested in the development of a more general and atom-economical solution to incorporation of Co homoenolates into cyclopropenes, affording enantioenriched multisubstituted cyclopropanes with functionalized alkyl groups. The challenges for such a process are the possible low reactivity

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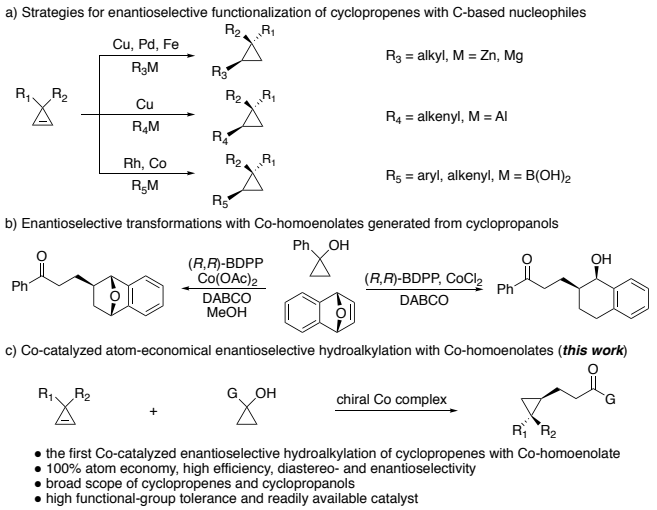
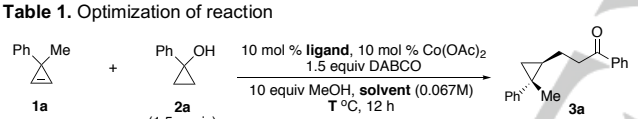
and elevated temperature is normally required. It is nontrivial to control the enantioselectivity. In addition, possible β-H elimination of the homoenolate might retard the desired pathway. Herein, we disclosed the first Co-catalyzed atom-economical addition of homoenolates generated from a wide range of cyclopropanols to cyclopropenes in high diastereo- and enantioselectivity.

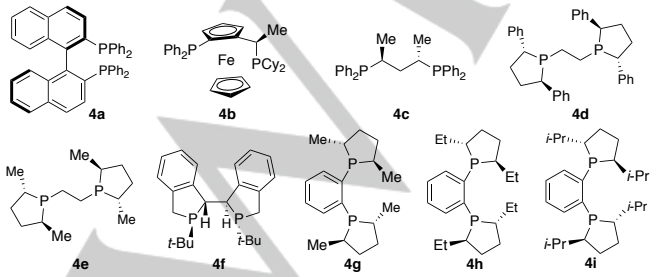


Scheme 1. Catalytic enantioselective transformations of cyclopropenes and cyclopropanols.

Table 1. Optimization of reaction

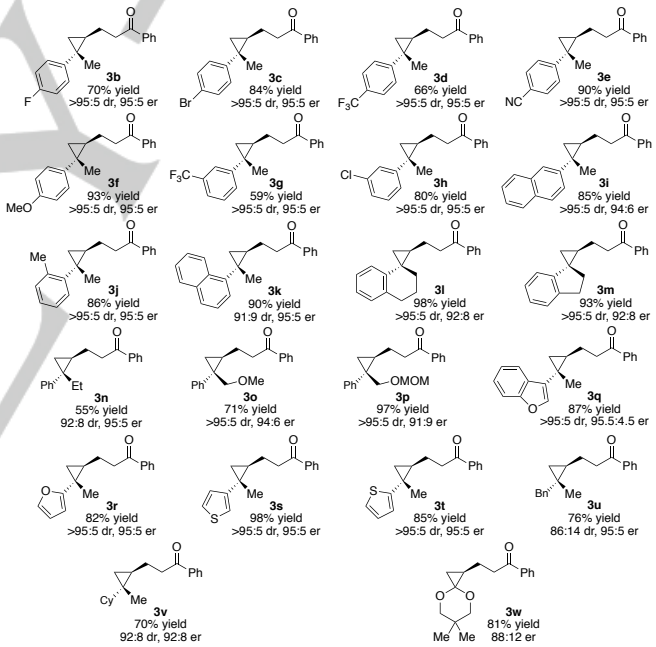


Entry	Ligand	Solvent	T [°C]	Yield [%][a]	dr [b]	er [c]
1	**4a**	DMSO	70	<5	na [d]	na [d]
2	**4b**	DMSO	70	47	92:8	72.5:27.5
3	**4c**	DMSO	70	66	79:21	15:85
4	**4d**	DMSO	70	52	91:9	7:93
5	**4e**	DMSO	70	87	>95:5	84:16
6	**4f**	DMSO	70	90	93:7	45.5:54.5
7	**4g**	DMSO	70	80	>95:5	89.5:10.5
8	**4h**	DMSO	70	87	>95:5	91:9
9	**4i**	DMSO	70	83	>95:5	26:74
10	**4h**	MeCN	70	88	>95:5	92:8
11	**4h**	MeCN	23	91	>95:5	95:5
12	**4h**	MeCN	10	83	>95:5	96:4
13 [e]	**4h**	MeCN	10	86	>95:5	94:6
14 [f]	**4h**	MeCN	10	86	>95:5	94:6
15 [g]	**4h**	MeCN	10	85	>95:5	95:5



[a] Yield of isolated product. [b] Determined by analysis of ^{1}H NMR spectra of unpurified mixtures. [c] Determined by analysis of HPLC spectra. [d] Not available. [e] Performed in the absence of MeOH. [f] Performed in the absence of MeOH and DABCO. [g] The reaction was conducted at a concentration of 0.2 M in the presence of 7.5 mol % $Co(OAc)_2$ and 7.5 mol % **4h** without the addition of MeOH and DABCO.

We commenced our studies with the treatment of the 3,3-disubstituted cyclopropane **1a** with cyclopropanol **2a** at 70 °C in the presence of Co complexes derived from a variety of phosphine ligands (Table 1, entries 1–9). We found that Co complex generated from **4h** provided the highest efficiency, diastereo- and enantioselectivity, affording the desired product **3a** in 87% yield and 91:9 er as a single diastereomer. Switching the solvent from DMSO to MeCN delivered similar yield and stereoselectivity (entry 10). Lowering the reaction temperature resulted in an improvement of enantioselectivity without the diminishment of efficiency (entries 11–12). In contrast to previous systems,[27c–e] the addition of MeOH and DABCO were unnecessary for the reaction, whereas the counterion of the Co salt is crucial for the efficiency and stereoselectivity in the absence of DABCO (see Supporting Information for more details). Cobalt halides provided much lower enantioselectivity and $Co(acac)_2$ promoted the reaction inefficiently. Reduction of the catalyst loading to 7.5 mol % afforded **3a** in 85% yield, >95:5 dr and 95:5 er. A highly atom-economical, efficient and stereoselective transformation can be achieved through simple treatment of cyclopropenes and cyclopropanols with a readily available Co complex without any additive.



Scheme 2. Scope of cyclopropenes.

With the optimal conditions in hand, we investigated the substrate scope. As shown in Scheme 2, cyclopropenes bearing aryl rings substituted with electron-withdrawing (**3b**–**e**, **3g**–**h**), electron-donating (**3f**), sterically congested groups (**3i**–**k**), heterocycles (**3q**–**t**), and halogens (**3b**–**c**, **3h**) are suitable substrates. Transformations of cyclopropenes that contain alkyl groups other than methyl afforded the desired products in 55–98% yield with greater than 95:5 dr and 91:9–95:5 er (**3l**–**p**). Reaction of the cyclopropene substituted with a benzyl and methyl groups delivered lower diastereoselectivity but high enantioselectivity due to the diminished size difference of the two alkyl groups (**3u**), whereas the cyclopropene bearing a cyclohexyl

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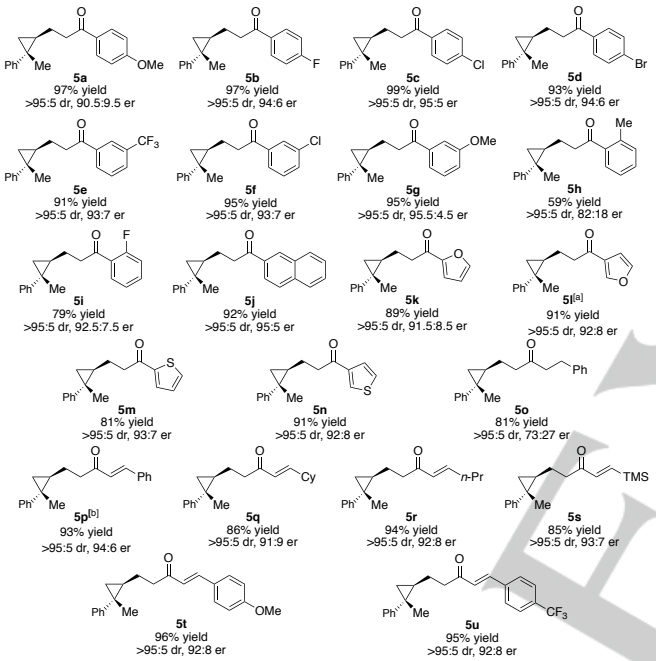
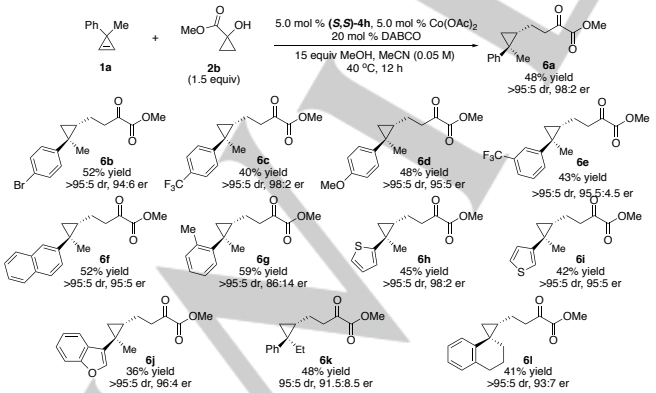
and methyl group can be transformed to the desired product in 70% yield with 92:8 dr and 92:8 er.

Reactions of a wide range of easily accessible cyclopropanols bearing electron-deficient (**5b**–**f**, **5i**), electron-rich aryls (**5a**, **5g**, **5j**) and heteroaryls (**5k**–**n**) proceeded in high efficiency and stereoselectivity. Transformations of cyclopropanols that contain sterically demanding aryl groups (**5h**) and alkyl groups (**5o**–**p**) furnished the desired products with lower enantioselectivity. Cyclopropanols substituted with alkenyl groups, a class of substrates that have never been investigated in previous catalytic enantioselective protocols, reacted in 85–96% with 91:9–94:6 er as a single diastereomer, affording the multisubstituted cyclopropanes containing a α,β-unsaturated ketone moiety that can be further functionalized to construct remote stereogenic centers.[28]

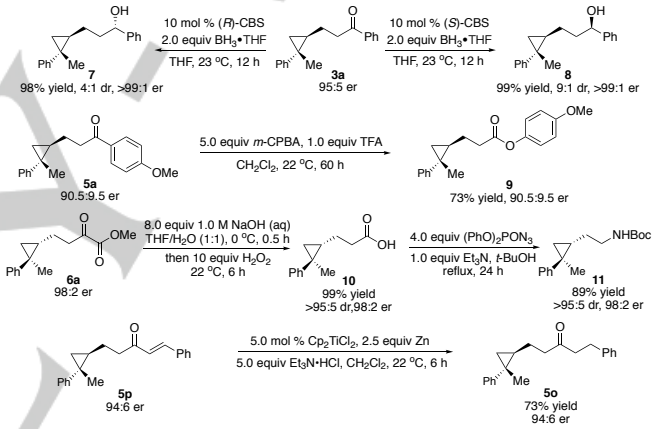


Scheme 3. Scope of cyclopropanols. [a] The reaction was performed at 25 °C. [b] The reaction time was 20 h.



Scheme 4. Scope of reactions with the ester-containing cyclopropanol.

The commercially available ester-containing cyclopropanol is a challenging substrate, as the strong electron-withdrawing ester group of the resulting Co homoenolate weakened the coordination of the ketone carbonyl to the Co center, leading to lower reactivity of the Co homoenolate. As shown in Scheme 4, further modification of the reaction conditions indicated that the addition of 20 mol % DABCO and 15 equivalents of MeOH is necessary to achieve optimal efficiency and enantioselectivity (see Supporting Information for more details). Increasing the catalyst loading didn't provide any improvement, as the catalyst decomposed faster when the reaction concentration was over 0.05 M. We next explored the scope of the Co homoenolate derived from cyclopropanol **2b**. A variety of cyclopropenes are suitable substrates (**6b**–**l**). The efficiencies are generally lower than those of reactions with aryl- and alkenyl-substituted cyclopropanols (36–59% yield) without erosion of the enantioselectivity (86:14–98:2 er). The resulting enantioenriched cyclopropane-containing α-ketoesters could be important precursors for chiral α-hydroxy- and α-aminoesters that are widely used in the synthesis of biologically active molecules.[29]



Scheme 5. Functionalization.

The assortment of enantioenriched multisubstituted cyclopropanes can be functionalized in a number of ways to deliver valuable and otherwise difficult-to-access building blocks (Scheme 5). Treatment of **3a** with (*R*)-CBS or (*S*)-CBS in the presence of 2.0 equivalents of BH_3•THF furnished the diastereomer **7** in 98% yield with 4:1 dr or the other diastereomer **8** in 99% yield with 9:1 dr as a single enantiomer.[30] Baeyer-Villiger oxidation of **5a** selectively cleaved the carbonyl–aryl bond, affording the ester **9** in 73% yield without erosion of enantioselectivity.[31] The α-ketoester **6a** can be decarboxylated to generate carboxylic acid **10** in 99% yield,[32] which underwent subsequent Curtius rearrangement to deliver **11** in 89% yield with 98:2 er.[33] The enantioenriched cyclopropane 5p bearing α,β-unsaturated ketone moiety can be reduced efficiently, addressing the low enantioselectivity of reactions with alkyl-substituted cyclopropanols.[34]

To gain some preliminary insight into the reaction mechanism, a series of experiments were performed. Similar with our hydroalkenylation system, a single diastereomer **3x** was obtained with the deuterium-labeled substrate **1a-D**, suggesting that the addition of the Co homoenolate to the cyclopropane proceeded in a *syn*-fashion, and no racemerization of the resulting Co–C bond

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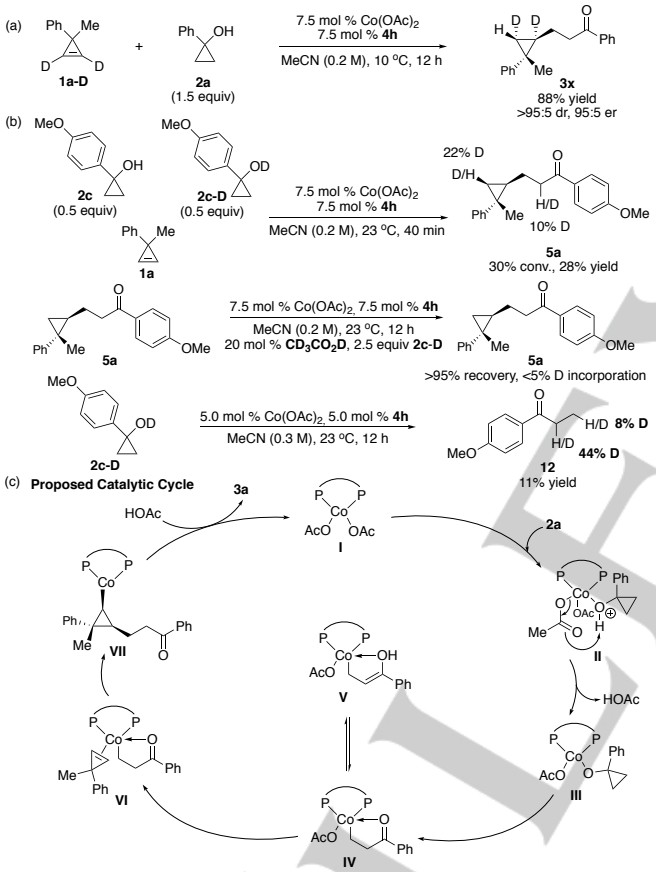
was observed during the protonation process (Scheme 6a). Treatment of **1a** with 1:1 mixture of deuterium-labelled (**2c-D**) and non-isotope-labelled (**2c**) cyclopropanols delivered the addition products with 22% D incorporation at the cyclopropane ring (Scheme 6b), indicating that the proton transfer process might be the rate-determining step (**II**→**III** or **VII**→**3a**, Scheme 6c). Unexpectedly, we found that 10% deuterium was also incorporated at ketone α-position. Control experiments revealed that the addition product **5a** cannot undergo enolization followed by protonation to introduce deuterium, whereas enolization of the Co homoenolate intermediate **IV** might occur under the reaction conditions. Based on all the observations, the proposed catalytic cycle is shown in Scheme 6c. The acetate that coordinated at Co center underwent intramolecular deprotonation followed by β-C–C bond cleavage to generate the Co homoenolate **IV**, which added to the cyclopropene and protonated with HOAc to furnish **3a** and regenerated the catalyst **I**.



Scheme 6. Preliminary mechanistic studies.

In conclusion, we have developed the first example of a Co-catalyzed diastereo- and enantioselective hydroalkylation of cyclopropenes via Co homoenolate intermediates generated from ring-opening of a wide range of easily accessible cyclopropanols. A high diversity of enantioenriched cyclopropanes can be prepared through this highly efficient, stereoselective, and atom-economical approach, promoted by an earth-abundant metal salt and a commercially available chiral ligand. Further mechanistic studies and stereoselective hydrofunctionalization of cyclopropenes are underway.

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Keywords: cobalt • cyclopropanes • enantioselective catalysis• hydroalkylation • small ring

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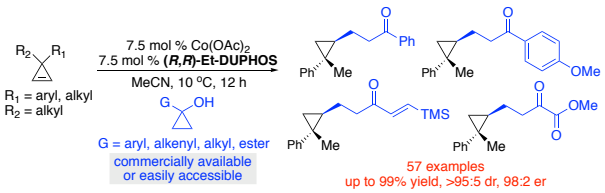

A new approach for highly atom-economical, efficient, diastereo- and enantioselective hydroalkylation of cyclopropenes promoted by an easily accessible Co complex was developed. This protocol represents the first example of introduction of a wide range of Co homoenolates generated from ring-opening of cyclopropanols to the cyclopropanes.

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