Synthetic Methods

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Cobalt(II)-Catalyzed Asymmetric Olefin Cyclopropanation with α-Ketodiazoacetates**

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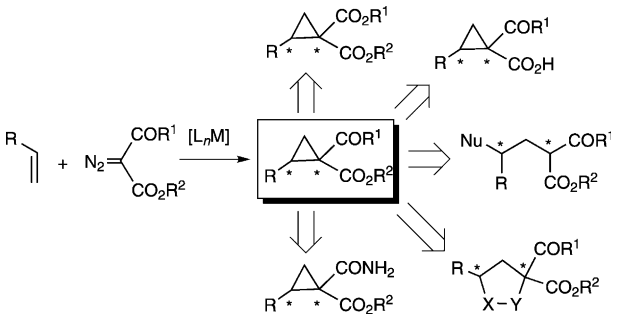
Cyclopropanes are a unique class of structural elements found in a number of biologically important compounds and have been demonstrated for a wide range of fundamental and practical applications.[1] One particularly attractive strategy for enantioselective synthesis of chiral cyclopropanes is based on transition-metal-catalyzed asymmetric olefin cyclopropanation with diazo reagents.[2] In principle, chiral cyclopropane derivatives having all substitution patterns may be accessible in enantioenriched form by asymmetric cyclopropanation because of the availability of a diverse array of both alkenes and diazo reagents. Among different classes of diazo reagents with various combinations of α-substituents, many acceptor- and donor/acceptor-substituted diazo reagents have been successfully employed as effective carbene sources for metal-catalyzed asymmetric cyclopropanation.[2] In contrast, the capacity of catalytic asymmetric cyclopropanation has not been fully explored with acceptor/acceptor-substituted diazo reagents, which would afford synthetically useful cyclopropane compounds bearing geminal electron-withdrawing functionalities.[3,4] Although there have been some recent successes in this area,[5–9] several important types of acceptor/acceptor-substituted diazo reagents remain challenging for asymmetric olefin cyclopropanation.

The dicarbonyl diazo reagents α-ketodiazoacetates (KDA) represent one type of acceptor/acceptor-substituted diazo reagent which has not been effectively utilized for asymmetric cyclopropanation (Scheme 1). This catalytic process would be highly attractive as the resulting chiral 1,1-cyclopropaneketoesters, which bear both ketone and ester functionalities, can serve as versatile synthons for a wide range of useful asymmetric transformations. In addition to their ready conversion into chiral cyclopropane derivatives having different geminal functionalities,[5a,10] 1,1-cyclopropaneketoesters can be transformed into other valuable chiral molecules through various ring-opening and ring-expanding reactions, which are greatly facilitated by the presence of two electron-withdrawing groups at the geminal position (Scheme 1).[1c,d,3b] While the nonasymmetric protocols have already been fruitfully applied to natural product synthesis,[11] there have been only a few previous reports on catalytic systems for asymmetric cyclopropanation with KDA.[5a,12,13] Among them, the most notable example is the [Rh_2]-based system developed recently by Charette and co-workers.[5a] It was shown that the PMP-substituted (PMP = *para*-methoxyphenyl) KDA could be successfully used for asymmetric cyclopropanation, thus producing the corresponding *Z*-1,1-cyclopropaneketoesters in high diastereo- and enantioselectivity when conducted at low temperature (−40 °C). Aside from the fact that PMP was required as a stereoselectivity controlling group,[4b,5d] this [Rh_2]-catalyzed system, however, was limited to aromatic olefins and generally gave low yields (10–70 %), even when using excess olefins (5.0 equiv). It would be synthetically desirable if effective catalytic systems could be developed for asymmetric cyclopropanation with simple KDA for substrates beyond styrene derivatives. Furthermore, would it be possible to access both *E*- and *Z*-1,1-cyclopropaneketoesters in highly asymmetric manner?



Scheme 1. Synthesis of 1,1-cyclopropaneketoesters by metal-catalyzed asymmetric cyclopropanation with α-ketodiazoacetates and further transformations.

Cobalt(II) complexes of D_2-symmetric chiral amidoporphyrins [Co(D_2-Por*)] have emerged as a new class of effective catalysts for asymmetric cyclopropanation.[6a,b,d,14] Increasing evidence supports that the Co^{II}-based metalloradical cyclopropanation proceeds by a stepwise radical mechanism and possesses a reactivity and selectivity profile that is distinct from electrophilic cyclopropanation using the widely studied [Rh_2]- and Cu-based closed-shell systems.[15] To date, Co^{II}-based metalloradical catalysis (MRC) has been shown to be effective for asymmetric cyclopropanation reactions of different types of olefins with several classes of diazo reagents, including acceptor/acceptor-substituted diazo reagents such as α-cyanodiazoacetates (CDA)[6b] and α-nitrodiazoacetates (NDA).[6d] To further exploit the unique potential of Co^{II} MRC, we began to investigate the possibility of [Co(D_2-Por*)]-based catalysts for asymmetric cyclopropanation using acceptor/acceptor-substituted diazo reagents

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beyond CDA and NDA. Considering the aforesaid challenges in the area, we embarked on a specific project to investigate the use of dicarbonyl diazo reagents such as KDA for asymmetric intermolecular cyclopropanation by Co^{II} MRC. In view of the radical nature of Co^{II}-based metalloradical cyclopropanation,[15] it was unclear at the onset of this project if [Co(D_2-Por*)] could allow achievement of high control of enantio- and diastereoselectivity by discriminating between two similar carbonyl groups of a common KDA. As the result of this investigation, we herein report the first catalytic system for asymmetric cyclopropanation with simple α-acetodiazoacetates (ADA) and it is effective for different kinds of olefins, thus leading to high-yielding synthesis of 1,1-cyclopropaneketoesters as *E* diastereoisomers in high enantiomeric purity. In addition to using olefins as limiting substrates, this highly asymmetric catalytic system can be run at room temperature without the need for slow addition of the diazo reagents. Furthermore, we describe an unprecedented epimerization process promoted by NaI and it allows conversion of the resulting *E*-1,1-cyclopropaneketoesters into their *Z* isomers with complete retention of the enantiopurity.

The cobalt(II) complex of the D_2-symmetric chiral porphyrin 3,5-Di^{t}Bu-ChenPhyrin, [Co(**P1**)] (Figure 1a), was shown to be an effective catalyst for asymmetric cyclopropanation with NDA[6d] and CDA.[6b] Its catalytic effectiveness

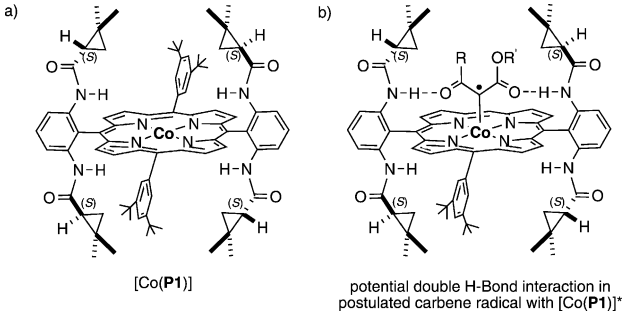
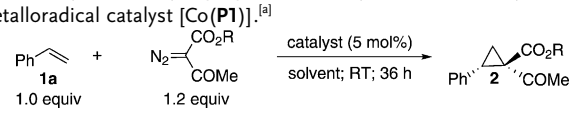


Figure 1. Structures of D_2-symmetric chiral Co^{II} porphyrins. * For clarity, 3,5-di-*tert*-butylphenyl unit in the back of the ligand is omitted.

toward these two acceptor/acceptor-substituted diazo reagents was attributed to the double hydrogen-bonding interactions between the amide NH donors on the **P1** ligand and two acceptors on the carbene moiety in the postulated metallocarbene radical intermediate.[6b,d] Since the C=O unit of ketone groups is also known as a suitable hydrogen-bond acceptor, we hypothesized the potential existence of similar double hydrogen-bonding interactions in the resulting cobalt–carbene radical intermediate from the reaction with KDA (Figure 1b). This hypothesis prompted us to systematically examine the asymmetric cyclopropanation with the common α-acetodiazoacetates using styrene (**1a**) as a model substrate (Table 1). We were pleased to observe that the simple methyl acetodiazoacetate (MADA) could be effectively activated by [Co(**P1**)] to cyclopropanate styrene under mild reaction conditions using a practical protocol (at room temperature with the alkene as the limiting reagent without slow addition of the diazo reagent), thus affording the desired cyclopropane

Table 1: Asymmetric cyclopropanation of styrene with ADA by the metalloradical catalyst [Co(**P1**)].[a]



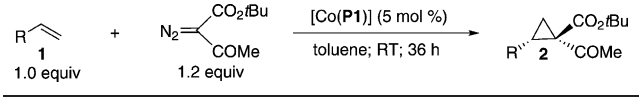
Entry	CO_2R	Catalyst	Solvent	Yield [%][b]	*E*/*Z*	*ee* [%][c]
1	CO_2Me	$[Rh_2(Oct)_4]$	CH_2Cl_2	62	22:78	–
2	CO_2Me	[Co(**P1**)]	CH_2Cl_2	99	79:21	63
3	CO_2tBu	[Co(**P1**)]	CH_2Cl_2	86	>99:1	90
4	CO_2tBu	[Co(**P1**)]	PhCl	81	>99:1	92
5	CO_2tBu	[Co(**P1**)]	hexanes	71	96:4	82
6	CO_2tBu	[Co(**P1**)]	toluene	88	96:4	94[d]

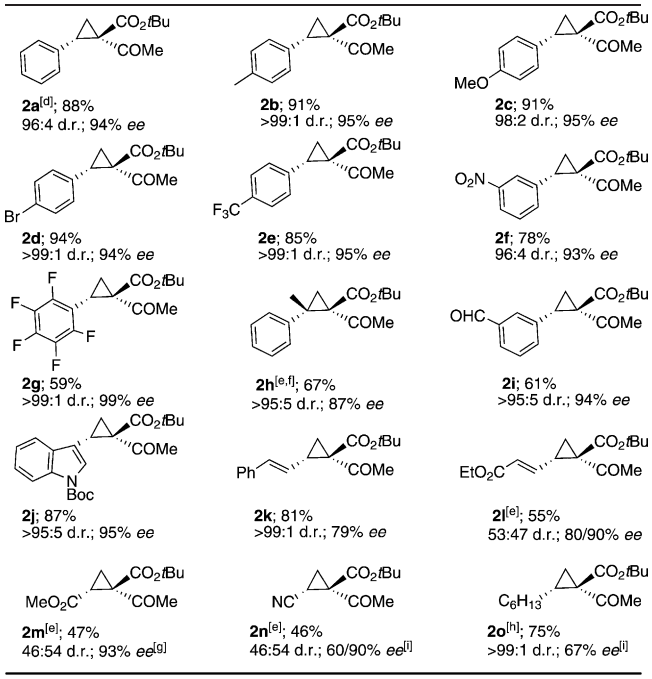
[a] Reactions were carried out in a one-time protocol using 5 mol% [Co(**P1**)] under N_2 at RT for 36 h with [olefin] = 0.20 M. [b] Yields of isolated products. [c] Enantiomeric excess of the major *E* diastereoisomer was determined by HPLC analysis using a chiral stationary phase. [d] [1*R*,2*S*] Absolute configuration determined by X-ray diffraction measurement on single crystal.

in near quantitative yield (entry 2). In addition to the excellent yield, it is important to note that the *E* diastereoselectivity exhibited by the Co^{II}-based system is the opposite of that previously reported for [Rh_2]-based catalytic systems (entry 1).[4b,5d,16] Furthermore, the *E* selectivity allowed us to improve the diastereoselectivity of the catalytic system significantly by employing the bulkier *tert*-butyl acetodiazoacetate (*t*-BADA) while increasing its enantioselectivity at the same time (entry 3). Among the solvents screened, toluene was found to be the solvent of choice, thus producing the 1,1-cyclopropaneketoester **2a** in 88% yield with 92% *de* and 94% *ee* (entries 3–6). The relative and absolute configurations of **2a** were established as *E* and (1*R*,2*S*), respectively, by anomalous-dispersion effects in X-ray diffraction measurement of its single crystal (see Figure S1 in the Supporting Information).

The [Co(**P1**)]-catalyzed asymmetric cyclopropanation could be successfully applied to a wide range of olefins under similar reaction conditions (Table 2). For example, styrene derivatives, regardless of the position and electronic property of the substituent (including electron-donating Me and MeO as well as electron-withdrawing Br, CF_3, and NO_2 groups), could be reliably cyclopropanated with *t*-BADA, thus generating the corresponding cyclopropaneketoesters **2a**–**f** in high yields with both high diastereoselectivity and enantioselectivity. As a further highlight of the unique catalytic property of the Co^{II} MRC, cyclopropanation of even the extremely electron-deficient pentafluorostyrene could be positively performed to form the desired cyclopropane **2g** with complete control of stereoselectivity, albeit in a lower yield. The use of α-methylstyrene allowed the stereoselective construction of the cyclopropane **2h** having two contiguous all-carbon quaternary stereogenic centers. Furthermore, the Co^{II}-based asymmetric cyclopropanation could be effectively applied to styrenes containing sensitive functionalities such as an aldehyde group (**2i**) and olefins derived from heteroarenes such as indole (**2j**) without complications arising from potential ylide-mediated reactions. When conjugated alkenes were used as substrates, regioselective cyclopropanation of the terminal double bonds

Table 2: [Co(**P1**)]-catalyzed diastereo- and enantioselective cyclopropanation of various alkenes with *t*-BADA.[a–c]

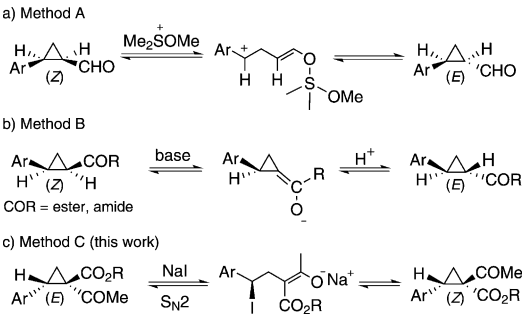




[a–c] See Table 1. [d] [1*R*,2*S*] Absolute configuration determined by X-ray diffraction measurements on a single crystal. [e] Used 5.0 equiv of olefin. [f] At 40 °C. [g] Enantiomeric excess of minor. [h] Neat reaction. [i] Determined by GC analysis using a chiral stationary phase. Boc = *tert*-butoxycarbonyl.

was observed, thus affording the corresponding vinyl cyclopropanes in moderate to good yields with varied stereoselectivities (**2k** and **2l**). Electron-deficient olefins such as α,β-unsaturated esters and nitriles, which have been known to be challenging substrates for cyclopropanation, could be also asymmetrically cyclopropanated by [Co(**P1**)] with *t*-BADA, but with diminished diastereoselectivity (**2m** and **2n**). Under neat reaction conditions, aliphatic alkenes, which represent another type of problematic substrate for metal-catalyzed asymmetric cyclopropanation, were also successfully converted into the desired cyclopropanes as exemplified with 1-octene for the highly diastereoselective formation of the cyclopropane **2o**, despite the moderate enantioselectivity.

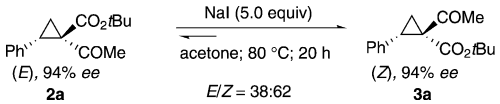
The Co^{II}-based metalloradical cyclopropanation displayed a different sense of diastereoselectivity from the reported [Rh_2]-based catalytic systems,[4b,5d,16] thus allowing high-yielding production of *E*-1,1-cyclopropaneketoesters in high enantiopurity. In an effort to gain accesses of enantiopure 1,1-cyclopropaneketoesters in both *E*- and *Z*-diastereoisomeric forms, we explored the possibility of obtaining the corresponding *Z* diastereoisomers through stereospecific epimerization of the resulting *E* diastereoisomers **2**. Two major methods have been previously developed for the epimerization of cyclopropane carbonyl derivatives. The first method involved a pathway of ring cleavage and reformation mediated by in situ generated methoxy dimethyl sulfonium iodide (Scheme 2a).[17] The sulfonium ion was proposed to function



Scheme 2. Epimerization of cyclopropane carbonyls. a) Lewis acid catalyzed ring-cleavage and reformation pathway (Ref. [17]). b) Base-catalyzed deprotonation/protonation sequence (Ref. [4b,17b,18]). c) S_N2 nucleophilic ring-opening and ring-closing pathway.

as a Lewis acid to facilitate the cleavage of a cyclopropane ring by coordinating with the carbonyl group of the formylcyclopropanes. Because of the destruction of both chiral centers in the acyclic intermediate, racemization was observed for this type of epimerization.[17b] The second method proceeded via a cyclopropane enol intermediate by employing a sequence of deprotonation and protonation under basic reaction conditions (Scheme 2b).[4b,17b,18] Although racemization could be avoided through the use of suitable bases, this pathway was not compatible for the epimerization of 1,1-cyclopropaneketoesters because of the lack of the required acidic C–H bonds on the cyclopropane ring at the position adjacent to the carbonyl group. In search for a suitable epimerization method, we postulated a stereocontrolled epimerization pathway through ring-opening and ring-closing steps by a succession of double S_N2 reactions (Scheme 2c). This proposal is in part based on the increased electrophilicity of 1,1-cyclopropaneketoesters as a result of the two geminal electron-withdrawing groups.[3b,19]

The key to the realization of the proposed S_N2-type epimerization pathway is the identification of a suitable reagent that could function as both nucleophile and leaving group. Given that I^- ion is known as a good leaving group as well as a nucleophile, ionic iodide reagents were targeted for such a dual role (Scheme 2c). While cyclopropane ring-closing by an intramolecular S_N2 reaction with I^- as a leaving group is unknown, iodides have been previously employed as nucleophiles for ring-opening of cyclopropanes.[20] Among various iodides having different counter cations that were evaluated, NaI was shown to be the best reagent for promoting epimerization of 1,1-cyclopropaneketoester (see Table S1). As demonstrated with (*E*)-**2a**, treatment of its acetone solution with 5 equivalents of NaI at 80 °C resulted in the formation of the (*Z*)-**3a** with preservation of the high enantiomeric excess [Eq. (1)]. The epimerization was found to be reversible and could reach equilibrium within 20 hours, with a diastereoisomeric ratio of 38:62 for (*E*)-**2a**/(*Z*)-**3a**. When isolated (*Z*)-**3a** was treated with NaI under the

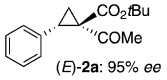
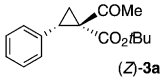
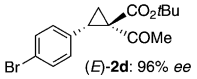
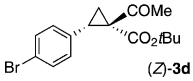
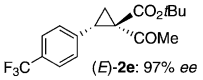
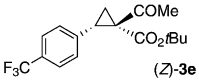
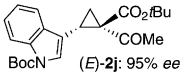
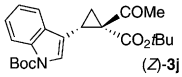


(1)

identical conditions, the same distribution of (*E*)-**2a** and (*Z*)-**3a** was obtained. Although counterintuitive, these results indicate that the *Z* isomer is relatively more stable than the *E* isomer [Eq. (1)]. To the best of our knowledge, this represents the first example of cyclopropane epimerization allowing conversion of the *E* diastereoisomer into the sterically encumbered *Z* diastereoisomer without loss of optical purity.

The NaI-promoted epimerization process appeared to be general and could be applied to different *E*-1,1-cyclopropaneketoesters for the synthesis of corresponding *Z*-1,1-cyclopropaneketoesters with retention of their original enantiopurity (Table 3). By taking advantage of the reversibility of the epimerization process, the overall yield for conversion into *Z*-1,1-cyclopropaneketoesters could be improved by subjecting the remaining *E* isomers into a second round of epimerization after their isolation from the first round. For example, the isolated yield of (*Z*)-**3a** from (*E*)-**2a** was increased to 70% without racemization by using this double epimerization procedure (entry 1). Similarly, the *Z*-1,1-cyclopropaneketoesters (*Z*)-**3d** and (*Z*)-**3e** could be obtained in 65% and 70% yields, respectively, with maintenance of high enantiopurity from the corresponding *E* isomers (entries 2 and 3). The epimerization procedure was also successfully applied to the indole-based 1,1-cyclopropaneketoester (*E*)-**2j**, thus affording (*Z*)-**3j** in 68% yield and 95% *ee* (entry 4).

Table 3: Stereospecific epimerization of 1,1-cyclopropaneketoesters promoted by sodium iodide.

Entry	*E* cyclopropane	*Z* cyclopropane	Yield [%][a]	*ee* [%][b]
1	 (*E*)-**2a**: 95% *ee*	 (*Z*)-**3a**	70	95
2	 (*E*)-**2d**: 96% *ee*	 (*Z*)-**3d**	65	96
3	 (*E*)-**2e**: 97% *ee*	 (*Z*)-**3e**	70	97
4	 (*E*)-**2j**: 95% *ee*	 (*Z*)-**3j**	68	93[c]

[a] Combined yield of products isolated after two successive epimerization processes. [b] Enantiomeric excess determined by GC analysis using a chiral stationary phase. [c] Enantiomeric excess determined by HPLC analysis using a chiral stationary phase.

In summary, we have demonstrated that the metalloradical catalyst [Co(**P1**)] is highly effective for asymmetric olefin cyclopropanation with α-ketodiazoacetates (KDA). This represents the first successful application of Co^{II}-based metalloradical catalysis (MRC) for asymmetric cyclopropanation with acceptor/acceptor-substituted diazo reagents bearing two α-carbonyl groups. In addition to high enantioselectivity, the [Co(**P1**)]-catalyzed cyclopropanation displays a distinct sense of diastereoselectivity, thus permitting for the first time the direct synthesis of chiral *E*-1,1-cyclopropaneketoesters from a broad range of alkenes with simple KDA. Furthermore, we have uncovered an iodide-promoted stereospecific epimerization process which allows the conversion of enantioenriched *E*-1,1-cyclopropaneketoesters into their *Z* diastereoisomers with retention of optical purity. Together, these two processes provide practical access to both *E*- and *Z*-1,1-cyclopropaneketoesters in a highly asymmetric manner.

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