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

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Keywords

Cyclopropanes are a unique class of structure 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 with all substitution patterns may be accessible in enantioenriched form by asymmetric cyclopropanation due to the diverse availability 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 reagents that have 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 to chiral cyclopropane derivatives having different geminal functionalities,[5a,10] 1,1-cyclopropaneketoesters can be transformed to 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,1d,3b] While its non-asymmetric 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 Rh₂-based system developed recently by Charette and coworkers.[5a] It was shown that the PMP-substituted KDA could be successfully used for asymmetric cyclopropanation, 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 stereoselectivity controlling groups,[4b,5d] this Rh_2-catalyzed system, however, was limited to aromatic olefins and generally gave low yields (10–70%) even 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 achievable to access both (E)- and (Z)-1,1-cyclopropaneketoesters in highly asymmetric manner?

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,6b,6d,14] Increasing evidence supports that the Co(II)-based metalloradical cyclopropanation proceeds with stepwise radical mechanism and possesses a distinct reactivity and selectivity profile from electrophilic cyclopropanation by 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 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 via 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 for achieving high control of enantioselectivity and diastereoselectivity through discriminating two similar carbonyl groups of common KDA. As the result of this investigation, herein we wish to report the first catalytic system for asymmetric cyclopropanation with simple α-acetodiazoacetates (ADA) that is effective for different kinds of olefins, leading to high-yielding synthesis of 1,1-cyclopropaneketoesters as (E)-diastereomers in high enantiomeric purity. In addition to using olefins as limiting substrates, this highly asymmetric catalytic system can be operated at room temperature without the need of slow addition of the diazo reagents. Furthermore, we describe an unprecedented epimerization process promoted by NaI that allows for conversion of the resulting (E)-1,1-cyclopropaneketoesters to 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 toward these two acceptor/acceptor-substituted diazo reagents was attributed to the double hydrogen bonding interactions between the amide N–H donors on the **P1** ligand and two acceptors on the carbene moiety in the postulated metallocarbene radical intermediate.[6b,6d] 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 for a systematic effort to examine asymmetric cyclopropanation with 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 conditions with a practical protocol (at room temperature with the alkene as the limiting reagent without slow addition of the diazo reagent), affording the desired cyclopropane 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 bulkier *tert*-butyl acetodiazoacetate (*t*-BADA) while increasing its enantioselectivity at the same time (entry 3). Among solvents screened, toluene was found to be the solvent of choice, producing 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 (Figure S1).

The [Co(**P1**)]-catalyzed asymmetric cyclopropanation could be successfully applied for 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, generating the corresponding cyclopropaneketoesters **2a–f** in high yields with both high diastereoselectivity and enantioselectivity (entries 1–6). 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 stereoselectivities, albeit in a lower yield (entry 7). The use of α-methylstyrene allowed for the stereoselective construction of cyclopropane **2h** with two contiguous all-carbon quaternary stereogenic centers (entry 8). Furthermore, the Co(II)-based asymmetric cyclopropanation could be effectively applied for styrenes containing sensitive functionalities such as aldehyde group (entry 9) and olefins derived from heteroarenes such as indole (entry 10) without complications arising from potential ylide-mediated reactions. When conjugated alkenes were used as substrates, regioselective cyclopropanation of the terminal double bonds was observed, affording the corresponding vinyl cyclopropanes in moderate to good yields with varied stereoselectivities (entries 11 and 12). 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 (entries 13 and 14). Under a neat condition, aliphatic alkenes, which represent another type of problematic substrates for metal-catalyzed asymmetric cyclopropanation, were also successfully converted into the desired cyclopropanes as exemplified with 1-octene for highly diastereoselective formation of cyclopropane **2o**, despite with moderate enantioselectivity (entry 15).

The Co(II)-based metalloradical cyclopropanation displayed a different sense of diastereoselectivity from the reported Rh_2-based catalytic systems,[4b,5d,16] allowing for 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*)-diastereomeric forms, we explored the possibility of obtaining the corresponding (*Z*)-diastereomers through stereospecific epimerization of the resulting (E)-diastereomers **2**. Two major methods have been previously developed for the epimerization of cyclopropane carbonyl derivatives (Scheme 2). 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 as a Lewis acid to facilitate the cleavage of cyclopropane ring by coordinating with the carbonyl group of the formylcyclopropanes. Due to 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 condition (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 due to 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 -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 dual role (Scheme 2C). While cyclopropane ring-closing via intramolecular S_N2 reaction with I$^-$ as 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 (Table S1). As demonstrated with (E)-cyclopropane **2a**, treatment of its acetone solution with 5 equiv NaI at 80 °C resulted in the formation of (Z)-cyclopropane **3a** with preservation of the high enantiomeric excess (eq 1). The epimerization was found to be reversible and could reach equilibrium within 20 h, with a diastereomeric ratio of 38:62 for (E)-**2a**:(Z)-**3a**. When isolated (Z)-**3a** was treated with NaI under the 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 (E)- to sterically encumbered (Z)-diastereomer without loss of optical purity.
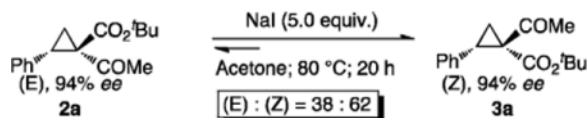
(1)

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). Taking advantage of the reversibility of the epimerization process, the overall yield for conversion to (Z)-1,1-cyclopropaneketoesters could be improved by subjecting the remaining (E)-isomers to 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, (Z)-1,1-cyclopropaneketoesters **3d** and **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 for the indole-based 1,1-cyclopropaneketoester **2j**, affording (Z)-**3j** in 68% yield and 95% ee (entry 4).

In summary, we have demonstrated that 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, 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 that allows for the conversion of enantioenriched

(*E*)-1,1-cyclopropaneketoesters to their (*Z*)-diastereomers 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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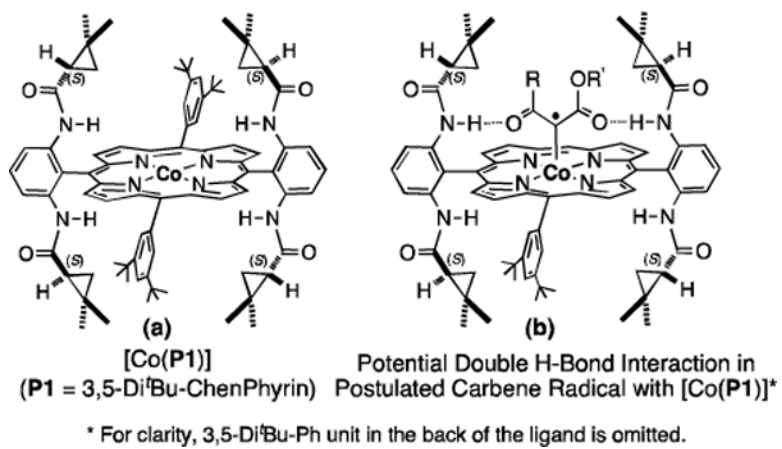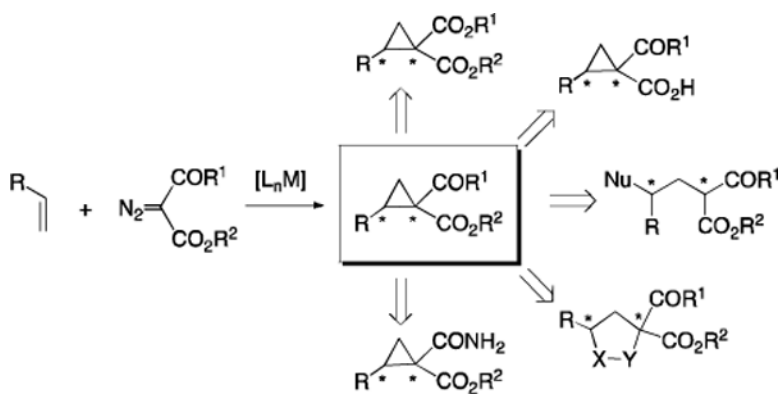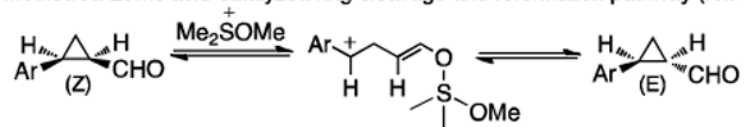
[Co(P1)]
(P1 = 3,5-Di^{t}Bu-ChenPhyrin)

Potential Double H-Bond Interaction in
Postulated Carbene Radical with [Co(P1)]*

* For clarity, 3,5-Di^{t}Bu-Ph unit in the back of the ligand is omitted.

Figure 1.
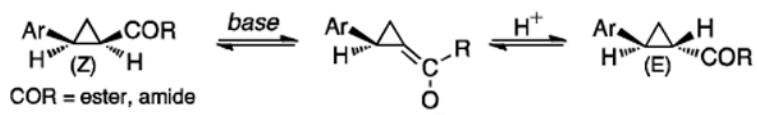Structures of D_2-symmetric Chiral Co(II) Porphyrins.

Scheme 1.
Synthesis of 1,1-Cyclopropaneketoesters by Metal-Catalyzed Asymmetric Cyclopropanation with α-Ketodiazoacetates and Further Transformations.
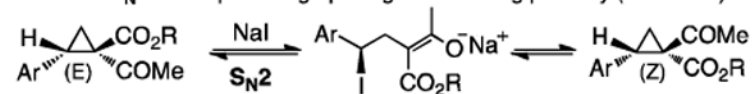
Scheme 2.
Epimerization of Cyclopropane Carbonyls.

Table 1

Asymmetric Cyclopropanation of Styrene with ADA by Metalloradical Catalyst [Co(**P1**)].[a]

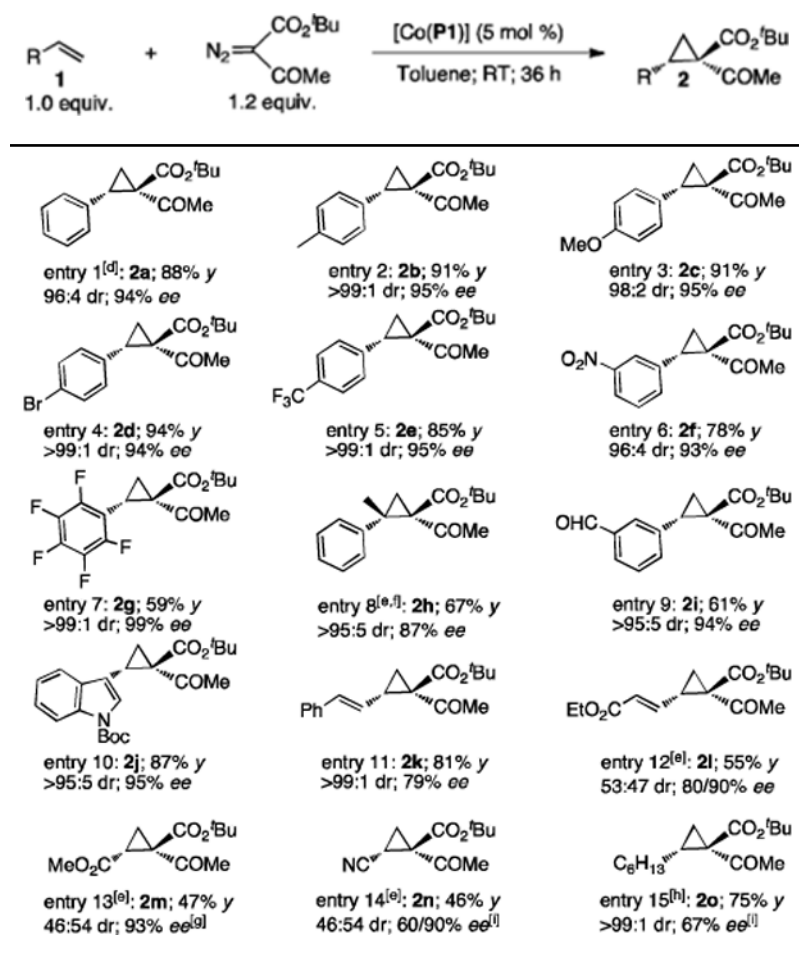| entry	CO₂R	catalyst	solvent	yield (%)[b]	(E):(Z)	ee(%)[c]
1	CO₂Me	Rh₂(Oct)₄	DCM	62	22:78	–
2	CO₂Me	Co(P1)	DCM	99	79:21	63
3	CO₂ᵗBu	Co(P1)	DCM	86	>99:1	90
4	CO₂ᵗBu	Co(P1)	PhCl	81	>99:1	92
5	CO₂ᵗBu	Co(P1)	Hexanes	71	96:4	82
6	CO₂ᵗBu	Co(P1)	Toluene	88	96:4	94[d]

[a]Reactions were carried out in a one-time protocol using 5 mol % [Co(**P1**)] under N₂ at RT for 36 h with [olefin] = 0.20 M.

[b]Isolated yields.

[c]Enantiomeric excess of major (E)-diastereomer determined by chiral HPLC.

[d][1R,2S] Absolute configuration determined by X-ray diffraction measurement on single crystal.

Table 2

[Co(**P1**)]-Catalyzed Diastereo- and Enantioselective Cyclopropanation of Various Alkenes with *t*-BADA.[a–c]

entry 1[d]: **2a**; 88% *y*
96:4 dr; 94% *ee*

entry 2: **2b**; 91% *y*
>99:1 dr; 95% *ee*

entry 3: **2c**; 91% *y*
98:2 dr; 95% *ee*

entry 4: **2d**; 94% *y*
>99:1 dr; 94% *ee*

entry 5: **2e**; 85% *y*
>99:1 dr; 95% *ee*

entry 6: **2f**; 78% *y*
96:4 dr; 93% *ee*

entry 7: **2g**; 59% *y*
>99:1 dr; 99% *ee*

entry 8[e,f]: **2h**; 67% *y*
>95:5 dr; 87% *ee*

entry 9: **2i**; 61% *y*
>95:5 dr; 94% *ee*

entry 10: **2j**; 87% *y*
>95:5 dr; 95% *ee*

entry 11: **2k**; 81% *y*
>99:1 dr; 79% *ee*

entry 12[e]: **2l**; 55% *y*
53:47 dr; 80/90% *ee*

entry 13[e]: **2m**; 47% *y*
46:54 dr; 93% *ee*[g]

entry 14[e]: **2n**; 46% *y*
46:54 dr; 60/90% *ee*[i]

entry 15[h]: **2o**; 75% *y*
>99:1 dr; 67% *ee*[i]

[a–c]See Table 1.

[d][1*R*,2*S*] Absolute configuration determined by X-ray diffraction measurements on single crystal.
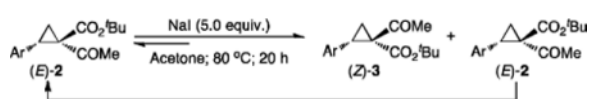
[e]5.0 equiv. of olefin.

[f]At 40 °C.

[g]Enantiomeric excess of minor.

[h]Neat reaction.

[i]Determined by chiral GC.

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 isolated yields from two succesive epimerization processes.

[b] Enantiomeric excess determined by chiral GC.

[c] Enantiomeric excess determined by chiral HPLC.