

# Asymmetric Co(II)-Catalyzed Cyclopropanation with Succinimidyl Diazoacetate: General Synthesis of Chiral Cyclopropyl Carboxamides

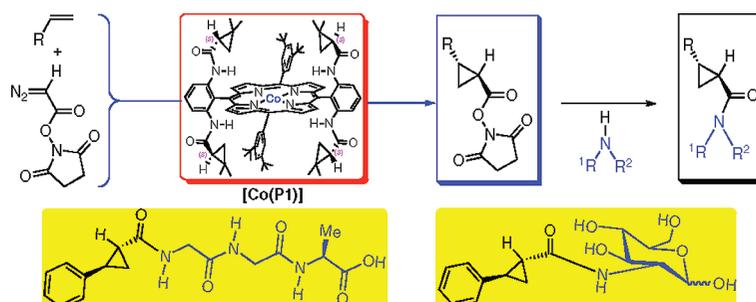
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## ABSTRACT



[Co(P1)] is an effective catalyst for asymmetric cyclopropanation with succinimidyl diazoacetate. The Co(II)-catalyzed reaction is suitable for various olefins, providing the desired cyclopropane succinimidyl esters in high yields and excellent diastereo- and enantioselectivity. The resulting enantioenriched cyclopropane succinimidyl esters can serve as convenient synthons for the general synthesis of optically active cyclopropyl carboxamides.

The well-documented importance of cyclopropanes in numerous fundamental and practical applications has stimulated vast efforts for the synthesis of these smallest carbocycles.<sup>1</sup> Metal-catalyzed asymmetric cyclopropanation of alkenes with diazo reagents constitutes the most direct and general approach for the stereoselective construction of these unique all-carbon triangular structures.<sup>2</sup> A number of outstanding

chiral catalysts have been reported to achieve high diastereo- and enantioselectivity for several classes of cyclopropanation reactions, most of which employed diazoacetates.<sup>1–3</sup> Ongoing endeavors in the field aim at further expanding the substrate scope to include a broader variety of alkenes as

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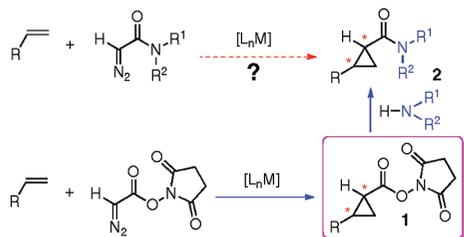
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well as to utilize more challenging classes of diazo reagents for use in asymmetric cyclopropanation.

In contrast to the large body of excellent results achieved with diazoacetates,<sup>1–3</sup> diazoacetamides have not been successfully employed for asymmetric intermolecular cyclopropanation (Scheme 1)<sup>4</sup> except for the Rh<sub>2</sub>-based

**Scheme 1.** Routes to Chiral Cyclopropyl Carboxamides



intramolecular reactions by Doyle and co-workers.<sup>5,6</sup> The absence of effective intermolecular asymmetric cyclopropanation with diazoacetamides may be attributed to two major factors: (i) inherent low reactivity of the resulting metal-carbene intermediate due to reduced electrophilicity and increased steric hindrance and (ii) complications resulting from competitive intramolecular C–H insertion.<sup>7</sup> Inspired by their important biomedical applications,<sup>8</sup> we envisioned a postderivatization approach to synthesize chiral cyclopropyl carboxamides **2** in enantioenriched form through reacting preformed cyclopropyl chiral building blocks **1** with various amines (Scheme 1).<sup>9</sup> Herein, we report a cobalt-catalyzed asymmetric cyclopropanation process with succinimidyl diazoacetate (N<sub>2</sub>CHCO<sub>2</sub>Su),<sup>10</sup> which forms cyclopropanes

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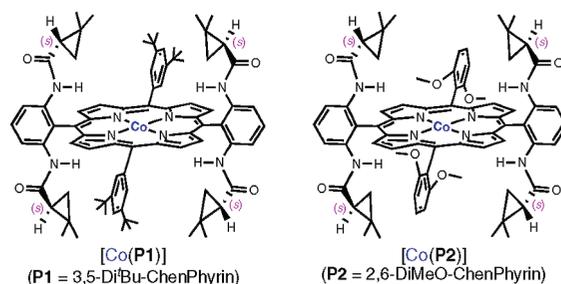
(6) For a recent example on asymmetric cyclopropanation of  $\alpha$ -amido-diazoacetates, see: Marcoux, D.; Charette, A. B. *Agnew. Chem. Int. Ed.* **2008**, *47*, 10155.

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(8) For select recent examples, see: (a) Garrido, D. M.; Corbett, D. F.; Dwornik, K. A.; Goetz, A. S.; Littleton, T. R.; McKeown, S. C.; Mills, W. Y.; Smalley, T. L.; Briscore, C. P.; Peat, A. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1840. (b) Jiang, T.; Kuhlen, K. L.; Wolff, K.; Yin, H.; Biezia, K.; Caldwell, J.; Bursulaya, B.; Wu, T. Y.-H.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2105. (c) Sandanayaka, V. P.; Prashad, A. S.; Yang, Y.; Williamson, T.; Lin, Y. I.; Mansour, T. S. *J. Med. Chem.* **2003**, *46*, 2569. (d) Morain, P.; Lestage, P.; De Nanteuil, G.; Jochemsen, R.; Robin, J.-L.; Guez, D.; Boyer, P.-A. *CNS Drug Rev.* **2002**, *8*, 31. (e) Graham, D. W.; Ashton, W. T.; Barash, L.; Brown, J. E.; Brown, R. D.; Canning, L. F.; Chen, A.; Springer, J. P.; Rogers, E. F. *J. Med. Chem.* **1987**, *30*, 1074.

**1** with excellent diastereo- and enantioselectivities. As a result of the highly reactive hydroxysuccinimide esters present, **1** could serve as convenient synthons for the general preparation of chiral amides **2** through reactions with a range of different amines and without loss of pre-established enantiomeric purity.

Structurally well-defined cobalt(II) complexes of *D*<sub>2</sub>-symmetric chiral porphyrins ([Co(Por\*)]) have emerged as a class of effective catalysts for asymmetric cyclopropanation reactions,<sup>11–13</sup> with both electron-sufficient<sup>12a,b</sup> and electron-deficient<sup>12c</sup> olefins using diazoacetates,<sup>12b,c</sup> diazosulfones,<sup>12d</sup> and  $\alpha$ -nitro diazoacetates.<sup>12e</sup> Among this family of [Co(Por\*)],<sup>12</sup> a group of six derivatives [Co(**P1**)]–[Co(**P6**)] (Figures 1 and S1 (Supporting Information)), possessing



**Figure 1.** *D*<sub>2</sub>-Symmetric chiral cobalt(II) porphyrins.

diverse electronic, steric, and chiral environments, were evaluated as potential catalysts for the asymmetric cyclopropanation of styrene with the sterically bulky N<sub>2</sub>CHCO<sub>2</sub>Su (Table 1). As a practical attribute of [Co(Por)]-catalyzed cyclopropanation,<sup>14a</sup> these reactions were carried out *in a one-pot fashion with alkene as limiting reagent and without the occurrence of the common dimerization side reaction*. Upon examination of the results (Table 1), it was evident that the steric bulkiness of the carbene source governed the reactivity difference of these catalysts. For example, no

(9) For an example of ineffective asymmetric cyclopropanation directly with diazoacetamides by current Co(II)-based catalysts, see Scheme S1, Supporting Information.

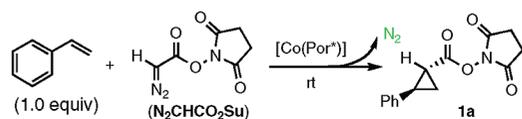
(10) The solid N<sub>2</sub>CHCO<sub>2</sub>Su, which is stable and can be handled safely, has not been previously employed for asymmetric cyclopropanation. For a single report on Ru-catalyzed nonasymmetric cyclopropanation with N<sub>2</sub>CHCO<sub>2</sub>Su, see: (a) Werle, T.; Maas, G. *Adv. Synth. Catal.* **2001**, *343*, 37. For the use of N<sub>2</sub>CHCO<sub>2</sub>Su to synthesize diazo derivatives, see: (b) Ouhia, A.; Rene, L.; Guilhem, J.; Pascard, C.; Badet, B. *J. Org. Chem.* **1993**, *58*, 1641. (c) Fuerst, D. E.; Stoltz, B. M.; Wood, J. L. *Org. Lett.* **2000**, *2*, 3521. (d) Clark, J. P.; Middleton, M. D. *Org. Lett.* **2002**, *4*, 765. (e) Grohmann, M.; Buck, S.; Schaffler, L.; Maas, G. *Adv. Synth. Catal.* **2006**, *348*, 2203. (f) Reference 5.

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**Table 1.** Asymmetric Cyclopropanation of Styrene with Succinimidyl Diazoacetate by  $D_2$ -Symmetric Chiral Cobalt(II) Porphyrins<sup>a</sup>



entry	[Co(Por*)] <sup>b</sup>	additive	solvent	yield <sup>c,i</sup> (%)	trans:cis <sup>d</sup>	ee <sup>e</sup> (%)
1	[Co( <b>P1</b> )]	DMAP	C <sub>6</sub> H <sub>5</sub> Me	86	>99:1	92
2	[Co( <b>P2</b> )]	DMAP	C <sub>6</sub> H <sub>5</sub> Me	70	>99:1	96
3	[Co( <b>P3</b> )]	DMAP	C <sub>6</sub> H <sub>5</sub> Me	10	>99:1	63
4	[Co( <b>P4</b> )]	DMAP	C <sub>6</sub> H <sub>5</sub> Me	0		
5	[Co( <b>P5</b> )]	DMAP	C <sub>6</sub> H <sub>5</sub> Me	0		
6	[Co( <b>P6</b> )]	DMAP	C <sub>6</sub> H <sub>5</sub> Me	0		
7 <sup>f</sup>	[Co( <b>P1</b> )]	DMAP	C <sub>6</sub> H <sub>5</sub> Me	74	>99:1	91
8 <sup>f</sup>	[Co( <b>P1</b> )]	NMI	C <sub>6</sub> H <sub>5</sub> Me	85	>99:1	88
9 <sup>f</sup>	[Co( <b>P1</b> )]		C <sub>6</sub> H <sub>5</sub> Me	86	>99:1	88
10 <sup>f,g</sup>	[Co( <b>P1</b> )]	DMAP	C <sub>6</sub> H <sub>5</sub> Me	66	>99:1	91
11 <sup>f,h</sup>	[Co( <b>P1</b> )]	DMAP	C <sub>6</sub> H <sub>5</sub> Me	64	>99:1	91
12 <sup>f</sup>	[Co( <b>P1</b> )]	DMAP	C <sub>6</sub> H <sub>5</sub> Cl	67	>99:1	87

<sup>a</sup> Performed at rt for 48 h using 5 mol % of [Co(Por\*)] under N<sub>2</sub> with 1.0 equiv of styrene and 1.5 equiv of N<sub>2</sub>CHCO<sub>2</sub>Su in the presence of 0.5 equiv of additive; [styrene] = 0.25 M. <sup>b</sup> See Figures 1 and S1 (Supporting Information) for structures. <sup>c</sup> Isolated yields. <sup>d</sup> Determined by HPLC. <sup>e</sup> Trans isomer ee determined by chiral HPLC. <sup>f</sup> 1.2 equiv of N<sub>2</sub>CHCO<sub>2</sub>Su. <sup>g</sup> 24 h. <sup>h</sup> 2 mol % of [Co(**P1**)]. <sup>i</sup> Similar olefin conversions with no side reactions.

reactions were observed with the more sterically demanding catalysts [Co(**P4**)], [Co(**P5**)], and [Co(**P6**)] (entries 4–6). Furthermore, the yields of the desired cyclopropane **1a** by the less steric catalysts [Co(**P1**)], [Co(**P2**)], and [Co(**P3**)] were correlated well with the relative hindrance of the ligand environment (entries 1–3). For these reactions, outstanding diastereoselectivities were achieved, with *trans*-**1a** produced as the sole diastereomer. While the best ee was attained by [Co(**P2**)], the use of [Co(**P1**)] afforded the best yield in addition to high enantioselectivity. Reduction of the N<sub>2</sub>CHCO<sub>2</sub>Su from 1.5 to 1.2 equiv gave similarly high diastereo- and enantioselectivity for the [Co(**P1**)]-catalyzed reaction but resulted in decreased yields (entries 1 and 7). As demonstrated previously,<sup>14b</sup> a more positive *trans* effect of DMAP on enantioselectivity was observed (entries 7–9). Although selectivity was not affected, by lowering catalyst loading or reducing reaction time, decrease in the overall product yield was observed (entries 10 and 11). Finally, toluene seemed to be the solvent of choice as the use of other solvents such as chlorobenzene led to lower yields and decreased enantioselectivities (entry 12).

Under the optimized reaction conditions, different olefin substrates were subject to catalytic cyclopropanation using N<sub>2</sub>CHCO<sub>2</sub>Su. As shown with select examples (Table 2), both electron-sufficient and electron-deficient olefins could be successfully cyclopropanated by [Co(**P1**)]. For example, asymmetric cyclopropanation of styrene derivatives bearing various substituents, including alkyl and halide groups as well as electron-donating and -withdrawing groups, could be catalyzed by [Co(**P1**)] to form the corresponding cyclopropanes **1a–f** in good to high yields with outstanding diastereoselectivities and excellent enantioselectivities (entries 1, 3, 5, 7, 9, and 11). Further

**Table 2.** [Co(**P1**)]-Catalyzed Diastereo- and Enantioselective Cyclopropanation of Different Alkenes with N<sub>2</sub>CHCO<sub>2</sub>Su<sup>a</sup>

entry	cyclopropane	yield (%) <sup>b,h</sup>	trans:cis <sup>c</sup>	ee (%) <sup>d</sup>	[α] <sup>e</sup>
1		86	>99:1	92	(–)
2 <sup>f</sup>	<b>1a</b>	70	>99:1	96	(–)
3		90	>99:1	95	(–) <sup>g</sup>
4 <sup>f</sup>	<b>1b</b>	71	98:2	96	(–) <sup>g</sup>
5		80	>99:1	97	(–)
6 <sup>f</sup>	<b>1c</b>	81	>99:1	98	(–)
7		71	>99:1	95	(–)
8 <sup>f</sup>	<b>1d</b>	75	99:1	97	(–)
9		66	>99:1	90	(–)
10 <sup>f</sup>	<b>1e</b>	48	>99:1	92	(–)
11		77	>99:1	90	(–)
12 <sup>f</sup>	<b>1f</b>	30	>99:1	94	(–)
13		71	>99:1	91	(–)
14		50	>99:1	92	(–)
15		33	99:1	91	(–)
16		57	>99:1	89	(–)
17		52	>99:1	96	(–)
18		55	>99:1	91	(–)

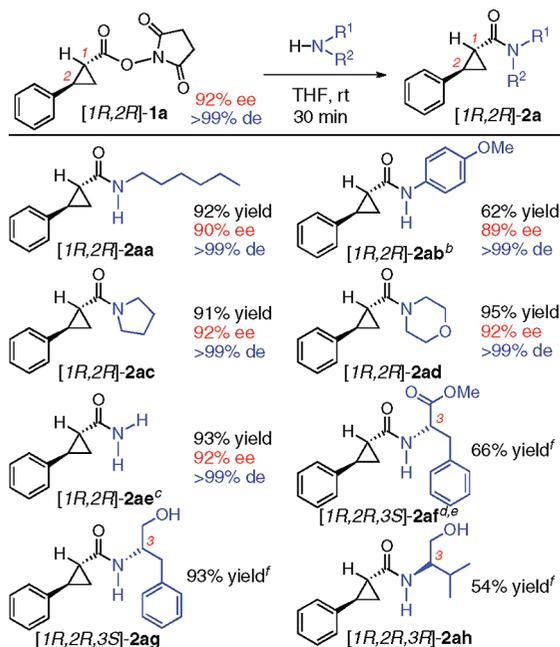
<sup>a</sup> Performed at rt for 48 h using 5 mol % of [Co(**P1**)] under N<sub>2</sub> with 1.0 equiv of styrene and 1.5 equiv of N<sub>2</sub>CHCO<sub>2</sub>Su in the presence of 0.5 equiv of DMAP; [styrene] = 0.25 M. <sup>b</sup> Isolated yields. <sup>c</sup> Trans:cis ratio determined by NMR or HPLC. <sup>d</sup> Trans isomer ee determined by chiral HPLC. <sup>e</sup> Sign of optical rotation. <sup>f</sup> [Co(**P2**)] as catalyst. <sup>g</sup> [1R,2R] absolute configuration by X-ray crystal structural analysis and optical rotation. <sup>h</sup> Similar olefin conversions with no side reactions.

improvement in enantioselectivity was achieved uniformly for all these substrates when the relatively bulkier [Co(**P2**)] was employed as the catalyst, albeit in lower yields for most of the cases (entries 2, 4, 6, 8, 10, and 12). In addition, the Co-based catalytic process exhibited functional group tolerance as demonstrated with the reactions of acetoxy- and nitro-substituted styrenes to form **1g,h** (entries 13 and 14). Due to the steric bulkiness of N<sub>2</sub>CHCO<sub>2</sub>Su, the catalytic system was shown to be less efficient for large aromatic olefins as exemplified by the [Co(**P1**)]-catalyzed cyclopropanation reaction of 2-vinylnaphthalene, offering **1i** in 33% yield with 98% de and 91% ee (entry 15). In addition to aromatic olefins, the [Co(**P1**)]/N<sub>2</sub>CHCO<sub>2</sub>Su-based system could also selectively cyclopropanate challenging electron-deficient olefins such as α,β-unsaturated esters, amides, and ketones (entries 16–18). It is worth noting that the cyclopropanes prepared from these olefins (**1j,l**) are highly electrophilic in nature

and have proven to be valuable synthetic intermediates for a variety of applications.<sup>15</sup>

With the established availability of enantioenriched succinimidyl cyclopropyl carboxylate derivatives **1** through the [Co(**PI**)]-catalyzed asymmetric cyclopropanation with N<sub>2</sub>CHCO<sub>2</sub>Su, their potential application as chiral building blocks for the synthesis of cyclopropyl carboxamides **2** (Scheme 1) was subsequently explored. Using (1*R*,2*R*)-**1a** as a representative synthon, a range of different amines were examined for the postderivatization synthetic approach (Scheme 2). Both aliphatic and aromatic amines

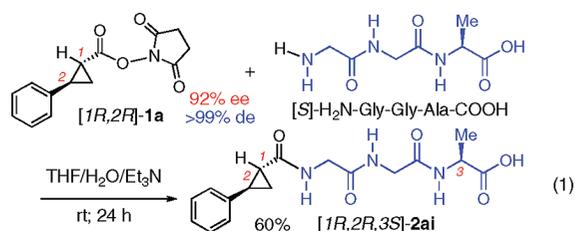
**Scheme 2.** Post-Derivatization Approach for Synthesis of Chiral Cyclopropyl Carboxamides via Reaction with Different Amines<sup>a</sup>



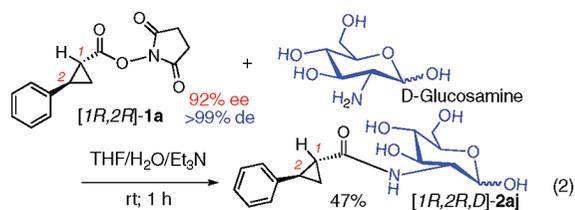
<sup>a</sup> Isolated yields; de determined by NMR or HPLC; ee determined by chiral HPLC <sup>b</sup> 24 h. <sup>c</sup> In dioxane. <sup>d</sup> 1 h. <sup>e</sup> In THF/H<sub>2</sub>O with Et<sub>3</sub>N. <sup>f</sup> Isolated as single diastereomer.

reacted with **1a** smoothly, affording the desired cyclopropyl carboxamides **2a** with retention of configuration (**2aa** and **2ab**). Cyclic amines, such as pyrrolidine and morpholine, could also be effectively converted to the corresponding amides in high yields with complete preservation of the stereochemistry (**2ac** and **2ad**). The *transformation of 1a* into the corresponding primary amide using ammonia also occurred in a high yield without loss of diastereo- and enantioselectivity (**2ae**). Owing to the mild and neutral reaction conditions, the postderivatization approach was able to tolerate a number of different functional groups as exemplified by the reactions with

chiral  $\alpha$ -amino acids such as methyl (*S*)-phenylalaninate as well as chiral  $\beta$ -amino alcohols such as (*S*)-phenylalaninol and (*R*)-valinol (**2af**, **2ag**, and **2ah**). The resulting multifunctional cyclopropyl amides **2af**, **2ag**, and **2ah**, bearing three stereogenic centers, could be isolated as single diastereomers in good to excellent yields.



To further demonstrate the utility of this synthetic approach, (1*R*,2*R*)-**1a** was allowed to react with the unprotected tripeptide (*S*)-H<sub>2</sub>N-Gly-Gly-Ala-COOH at room temperature in a mixture of water and THF in the presence of Et<sub>3</sub>N (eq 1). The corresponding cyclopropyl tripeptide (1*R*,2*R*,3*S*)-**2ai** was isolated as single diastereomer in 60% yield without affecting the carboxylic acid functionality.



The versatility and functional group tolerance of the synthetic approach was further highlighted with the reaction of (1*R*,2*R*)-**1a** with D-(+)-glucosamine without protecting the hydroxyl groups (eq 2). The reaction proceeded smoothly under mild conditions, forming the desired cyclopropyl carboxamide of the amino sugar (1*R*,2*R*,*D*)-**2aj** in 47% yield.

In summary, a highly diastereo- and enantioselective Co-catalyzed asymmetric cyclopropanation of alkenes with N<sub>2</sub>CHCO<sub>2</sub>Su has been established for the first time, and the resulting enantioenriched succinimidyl cyclopropylcarboxylates have proven to be valuable synthons for general synthesis of optically active cyclopropyl carboxamide derivatives. The key attributes of the post-derivatization approach include versatility and a high degree of functional group tolerance. Together with the suitability of various olefins for the asymmetric cyclopropanation process, this two-step synthetic scheme should permit straightforward access to a wide range of chiral cyclopropyl carboxamides.<sup>8</sup>

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**Supporting Information Available:** Experimental procedures and analytical data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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