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A Mutually π-Facial Selective Cyclopropanation of Chiral Enamides Using Dirhodium(II) Carbenoids

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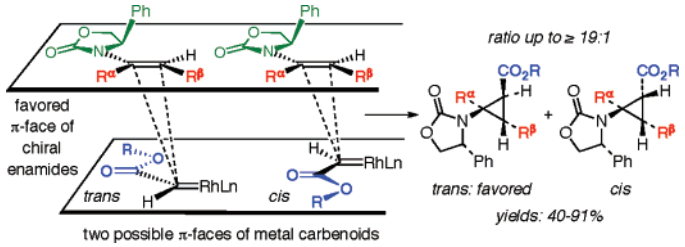
ABSTRACT



A mutually π-facial selective cyclopropanation of chiral enamides using dirhodium(II) carbenoids is described here. This work illustrates the influence of enamide substituents on stereoselectivity and reveals insights into this cyclopropanation.

Enamides are useful building blocks in organic synthesis.[1] Recent development in metal-catalyzed C−N bond formations[2−5] has elicited a strong interest in employing chiral enamides in a range of stereoselective synthetic transformations.[6−11] High levels of diastereoselectivity can be attained from these reactions because of the π-facial bias present in the preferred conformation[8a−c,10a] of chiral enamides **1** (Scheme 1). Given that cyclopropanation[12] via transition-

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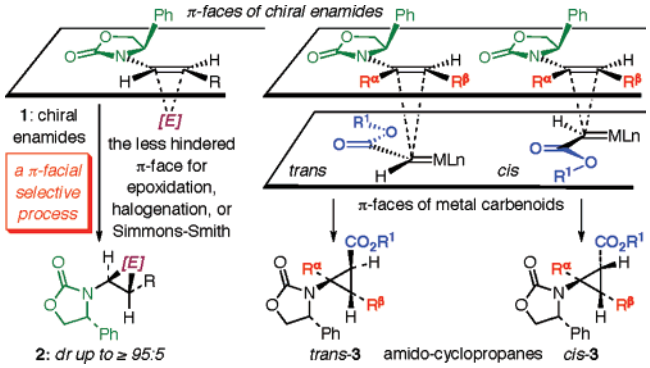
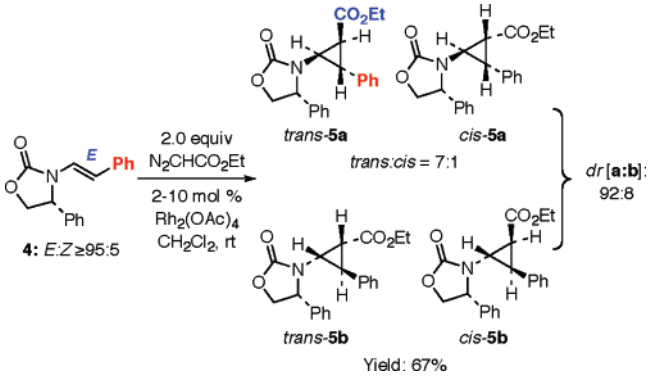
Scheme 1. π-Facial Selectivities for Reactions of Chiral Enamides



metal-catalyzed decomposition of α-diazo esters[13−17] represents a powerful method for constructing highly functionalized cyclopropanes and that such cyclopropanations employing chiral enamides are rare,[18] we investigated the reaction of **1** with metal carbenoids en route to amido cyclopropanes **3**.[19,20] While the π-facial preference in **1** may be high,[10a] the reactive electrophilic metal carbenoid derived from α-diazo esters poses its own π-facial differentiation, leading to *trans*- and *cis*-amidocyclopropanes **3** via two possible approaches. Although influence of metals, ligands, and ester substituents on the trans/cis selectivity has been reported,[13,14] this selectivity has not responded to structural variations on the olefin in a distinct or consistent manner.[13a,14] We examined the impact of enamide substituents on the π-facial preference of approaching metal carbenoids, and we report herein a mutually π-facial selective cyclopropanation of chiral enamides employing dirhodium(II) carbenoids.

The feasibility for the cyclopropanation of chiral enamides using transition-metal-catalyzed decompositions of α-diazo esters could be quickly established after screening several metal catalysts.[12−14] As shown in Scheme 2, dirhodium(II) tetraacetate appeared to be the most effective catalyst.[14,21] When using 2 mol % of dirhodium(II) tetraacetate at rt, cyclopropanation of chiral enamide **4** (*E*/*Z* ≥95:5 by ^{1}H NMR) proceeded smoothly to give amido cyclopropanes

Scheme 2. Choice of Metal Carbenoids for the Cyclopropanation[a]



[a] dr of **a:b** is designated for the enamide π-facial selectivity. Ratios were assigned using ^{1}H and/or ^{13}C NMR.

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(21) The only other metal catalysts used were $AgSbF_6$, CuOTf, and $Pd(OAc)_2$, and we did not examine other cyclopropanations conditions known in the literature (see ref 18). In addition, to elimate extra parameters in this mechanistic based study, we only examined enamides with the oxazolidinone or Evans' auxiliary.

5a/b[22] in 67% with a diastereomer ratio of 92:8 (the dr of **a**/**b** designates π-facial selectivity of enamides) and a trans/cis ratio of 7:1 in favor of *trans*-**5a**. The relative stereochemistry of *trans*-**5a** was confirmed by X-ray structure of its aldehyde derivative (Figure 1A), whereas the cis isomer

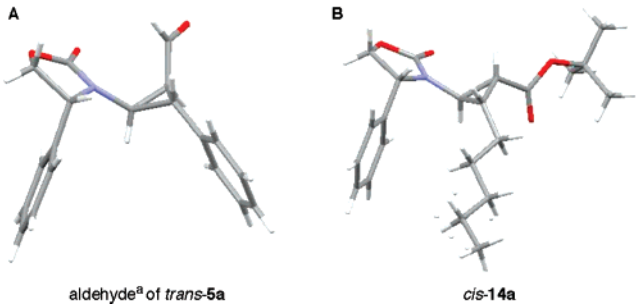
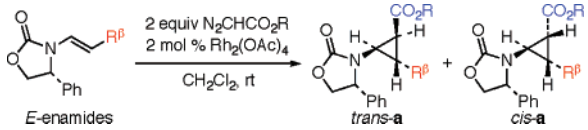


Figure 1. X-ray structures of *trans*- and *cis*-amidocyclopropanes. (a) Derived from *trans*-**5a** via Dibal-H [H] (see the Supporting Information).

was unambiguously assigned later using another cyclopropanation product (see *cis*-**14a** in Table 1).

Table 1. Cyclopropanations of *E*-Enamides



entry	enamides: R^β =	products: R =	yield[a] (%)	dr[b] (**a**/**b**)	**a:** trans/cis[b]
1	**6:** CH_2CH_2OTBS	**12a/b:** Et	74	≥95:5	2.5:1
2	**7:** *n*-pent	**13a/b:** Et	66	≥95:5	2.5:1
3	**7:** *n*-pent	**14a/b:** *t*-Bu	54[c]	≥95:5	2.5:1
4	**8:** Bn	**15a/b:** Et	66	≥95:5	4:1
5	**4:** Ph	**5a/b:** Et	67	92:8	7:1
6	**4:** Ph	**16a/b:** *t*-Bu	40[c]	≥95:5	7:1
7	**9:** *c*-hex	**17a/b:** Et	67	≥95:5	8:1
8	**9:** *c*-hex	**18a/b:** *t*-Bu	62[c]	≥95:5	≥19:1
9	**10:** *i*-Pr	**19a/b:** Et	91	≥95:5	9:1
10	**10:** *i*-Pr	**20a/b:** *t*-Bu	78[c]	≥95:5	≥19:1
11	**11:** *t*-Bu	**21a/b:** Et	n.d.[c,d]		

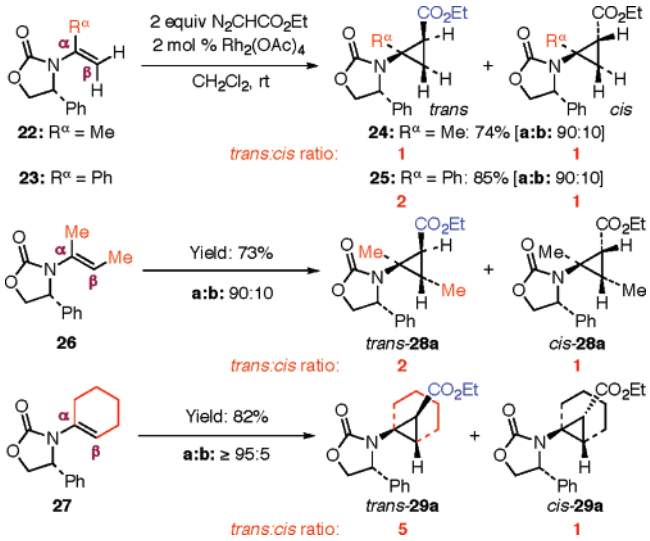
[a] Isolated yields. [b] Ratios were assigned using ^1H and/or ^{13}C NMR. [c] 4 equiv of N_2CHCO_2-*t*-Bu was used. [d] n.d.: not determined.

We proceeded to examine cyclopropanations of a range of β-substituted *E*-enamides as shown in Table 1. In all cases, the cycloaddition exhibits an excellent π-facial selectivity with respect to the enamide (**a**/**b** 92:8 to ≥ 95:5). The trans/cis selectivity, on the other hand, appeared to be directly correlated with the size of the β-substituent. Simple unbranched alkyl groups gave a lower trans/cis ratio (entries 1 and 2), whereas enamides with a bulky cyclohexyl (*c*-hex) or *i*-Pr group led to higher ratios (entries 7 and 9) with Bn and Ph groups providing a ratio in between (entries 4 and 5). When R^β = *t*-Bu, the reaction was actually shut down (entry 11).

Intriguingly, when using *tert*-butyl α-diazoacetate, while there was no change in ratio with R^β = *n*-pent (entry 3) and Ph (entry 6), the trans/cis ratio drastically improved relative to ethyl α-diazoacetate with R^β = *c*-hex and *i*-Pr (entry 7 versus 8 and entry 9 versus 10, respectively). We did have to use 4 equiv of *tert*-butyl α-diazoacetate, and reactions were relatively slower than those using ethyl α-diazoacetate. The minor cis isomer was assigned via the X-ray structure of *cis*-**14a** (Figure 1B).

In contrast, α-substituents of enamides appeared to have no significant impact on the trans/cis selectivity. As shown in Scheme 3, cyclopropanation of chiral enamide **22** with

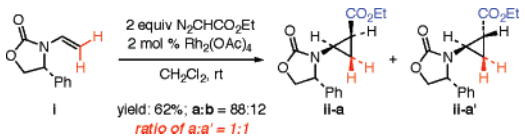
Scheme 3. Impact of the α-Substituent of Chiral Enamides



R^α = Me afforded **24** with no trans/cis selectivity, and even when R^α = Ph as in enamide **23**, the selectivity remained low in the cycloadduct **25**. The ratio from the cyclopropanation of **22** also implies that the Evans' chiral oxazolidinone ring does not play an important role in the trans/cis selectivity.[23] On the other hand, the selectivity was noticeably improved if a β-substituent was added. For instance, enamide **26** with just an additional methyl group at the β-position led to a ratio that is already better than enamide **22** and comparable to that of enamide **23**, while enamide **27** gave a much improved trans/cis ratio.

(22) See the Supporting Information.

(23) The ratio of 1:1 isomer **ii-a** and **ii-a′** (the designation of trans/cis used in the text is not suitable here) obtained from the cyclopropanation of chiral enamide **i** further confirms this point.



These collective observations imply that a mutually π-facial selective cyclopropanation has taken place and that the β-substituent appears to be solely responsible for the π-facial preference of the approaching dirhodium(II) carbenoid. These results can be rationalized using a mechanistic model based on the one proposed by Doyle.[24,25] As shown in Figure 2, the π-facial selectivity observed with respect to

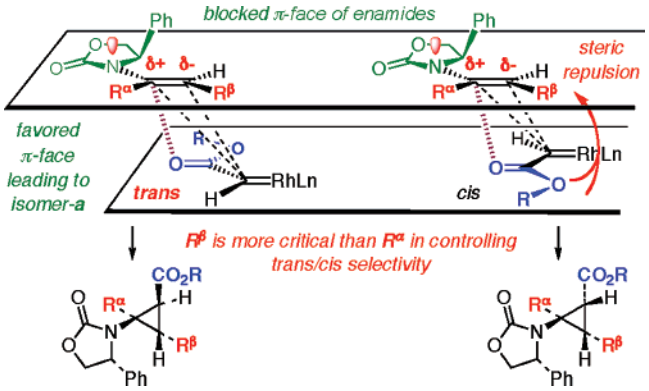


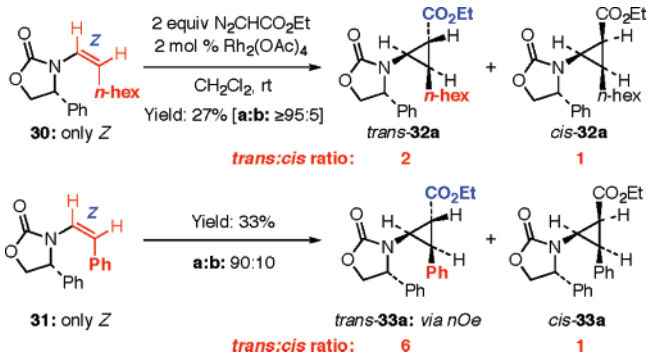
Figure 2. Doyle's model for the observed π-facial selectivity.

chiral enamides is in accordance with the preferred conformation chiral enamide in which the oxazolidinone ring is coplanar with the olefin,[8,10a] thereby allowing the metal carbene to approach favorably from the bottom face of enamides.

On the other hand, for the π-facial preference of the approaching the dirhodium(II) carbenoid, a Markovnikov addition should take place because of the electrophilicity of metal carbenoids and would likely occur in an unusually skewed manner in favoring of the β-carbon. This key assessment is based on the electronic bias posed by the nitrogen substitution that places a greater partial negative charge distribution at the β-carbon of enamides. Such a skewed approach of the carbenoid would still allow a potential "second-effect" in which the carbonyl oxygen of the ester group serves to stabilize the pending carbocation formation at the α-carbon of the enamide (see the maroon hash line in Figure 2).

Our model is consistent with the observation that R^{β} exerts a much greater influence on the trans/cis selectivity than R^{α}. Such a skewed approach would render the dirhodium(II) carbenoid more sensitive to the sterics or structural variations at the β-position of these chiral enamides. While previous reports[23] documented steric influences of olefinic substituents

Scheme 4. Cyclopropanations of *Z*-Enamides



on the trans/cis selectivity, there was no real predictable order, and cyclopropanations of these enamides have revealed a distinct influence of R^{β} substituents.

To further support this model, we examined *Z*-enamides **30** and **31** (*Z*/*E* ≥95:5 by ^{1}H NMR) as shown in Scheme 4. Although the yields are inferior to those from cyclopropanations of *E*-enamides, the trans/cis ratios again reflect the same preference for the π-face of the dirhodium(II) carbenoid that would allow the ethoxy carbonyl group to be trans to the R^{β} substituent.

Finally, the observed trans/cis selectivity is likely not a result of thermodynamic equilibration through an epimerization.[26] Based on PM3 calculations using Spartan Model, *trans*-**5a** and *cis*-**5a** products show virtually identical energies with $\Delta E = -0.2$ kcal mol^{-1}, whereas for **14a**, *cis*-**14a** is actually more stable than *trans*-**14a** by ∼0.7 kcal mol^{-1}.

We have described herein a dirhodium(II) tetracetate catalyzed stereoselective cyclopropanation of chiral enamides for constructing highly functionalized amido cyclopropanes. This work reveals a distinct influence of enamide β-substituents on the π-facial preference of the approaching dirhodium(II) carbenoids, thereby constituting a mutually π-facial selective cyclopropanation process. Studies involving synthetic applications as well as examining other enamide systems are currently underway.

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Supporting Information Available: Experimental details, characterization data, X-ray structural analysis, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) Epimerization of either *trans*-**14a** or *cis*-**14a** employing 0.20−5.0 equiv of *t*-BuOH/*t*BuOK at temperatures ranging from rt to 80 °C did not lead to any observable epimerization but recovered starting material and some decomposition.