Synthetic Methods

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Stereoselective Simmons–Smith Cyclopropanation of Chiral Enamides**

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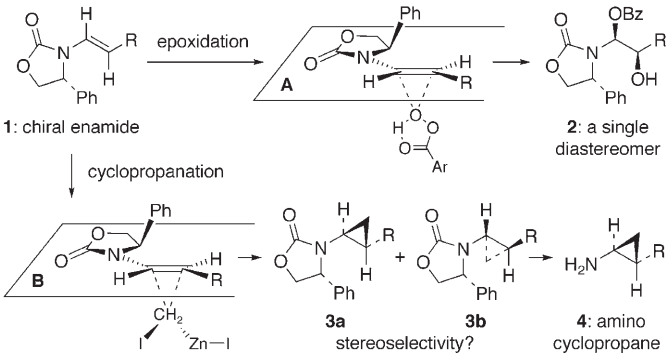
Enamides, unlike enamines, have remained relatively obscure in synthesis.[1,2] The limited use of enamides could be due in part to synthetic inaccessibility; however, recent developments in copper- and palladium-catalyzed N alkenylation[3,4] should provoke a strong interest in the development of synthetic methods based on the use of enamides as versatile building blocks. Among notable studies,[5] there have been reports of both normal-electron-demand Diels–Alder cycloadditions[6] and inverse-electron-demand hetero-Diels–Alder cycloadditions[7] of enamides. We reported the epoxidation of chiral enamides in the synthesis of chiral α-hydroxyhemiaminals (**1**→**2** in Scheme 1).[8,9] The high level of diastereoselectivity in this epoxidation was surprising and led us to speculate that enamides **1** could favor the conformation shown in **A**,[8,9] which provides an excellent π-facial bias for the observed stereochemical outcome.

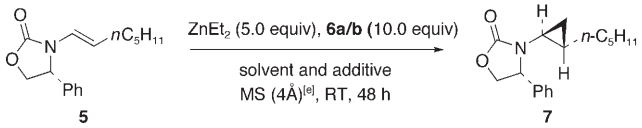
This conformation analysis prompted us to examine the possibility of using chiral enamides **1** as unique templates for the development of stereoselective methods. Specifically, given the significance of cyclopropanation reactions[10] and the lack of systematic studies undertaken in this area with chiral enamides,[1,11] we explored a possible stereoselective Simmons–Smith cyclopropanation[12] of chiral enamides on the basis of a related conformation analysis (see **B**, Scheme 1). We report herein a highly stereoselective Simmons–Smith cyclopropanation of chiral enamides for the synthesis of chiral aminocyclopropanes.



Scheme 1. A π-facially differentiated chiral enamide template. Bz = benzoyl.

The feasibility of this approach was quickly established (Table 1). The use of the chiral enamide **5** led to the amidocyclopropane **7**[13] in excellent yield (80%) with a diastereomeric ratio of 95:5 (see later discussion on the assignment of configuration) after optimization of the reaction conditions. Key features of the reaction are the use of the more reactive dihaloalkane ICH_2Cl (Table 1, entry 5) as the methylidene source (although ICH_2I, which is cheaper, can also be used; Table 1, entry 1) and the presence of molecular sieves. The scope of this cycloaddition is summarized in Table 2.

Table 1: Feasibility and optimization of the Simmons–Smith cyclopropanation.



Entry	6	Solvent	Additive[d]	Yield [%][a,c]	d.r.[b,c]
1	**6a**: ICH_2I	CH_2Cl_2	none	40	95:5
2	**6a**	CH_2Cl_2	DME	10	95:5
3	**6a**	CH_2Cl_2	$ZnCl_2$	n.d.	n.d.
4	**6a**	CH_2Cl_2	$SnBr_4$	n.d.	n.d.
5	**6b**: ICH_2Cl	$(CH_2Cl)_2$	none	80	95:5

[a] Yield of the isolated product. [b] The diastereomeric ratio was determined by ^{1}H NMR spectroscopy. [c] n.d.: not determined. [d] DME = 1,2-dimethoxyethane. [e] MS = molecular sieves.

In general, the nature of the chiral amide, which serves as an auxiliary, does not appear to be critical for high stereoselectivity (Table 2, entries 1–3). However, the Close auxiliary[14] is less effective in terms of selectivity (Table 2, entries 4 and 5), although reactions with this chiral amide were faster. This result is in accord with the electrophilic nature of Simmons–Smith cyclopropanation and the fact that enamides substituted with the Close auxiliary are more electron rich[15] than those substituted with Evans-type auxiliaries.[16] Furthermore, chiral enamides with 1,1-disubstituted (Table 2,

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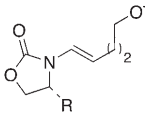
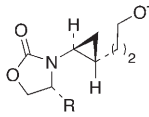
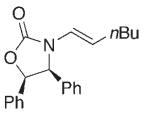
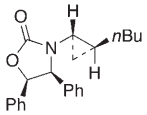
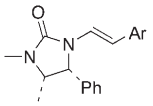
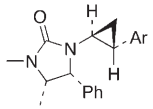
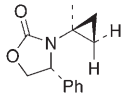
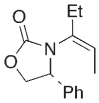
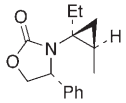
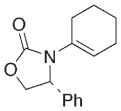
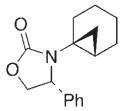
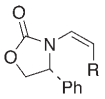
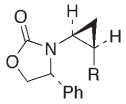
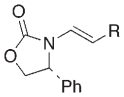
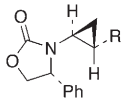
Table 2: Stereoselective cyclopropanation of chiral enamides.[h]

Entry	Chiral enamide		Cyclopropane product		*t* [h]	Yield [%][a]	d.r.[b]
1		**8**: R = Ph		**16**: R = Ph	48	50[c]	94:6
2		**9**: R = Bn		**17**: R = Bn	72	60[c]	> 95:5
3		**10**		**18**	48	61	> 95:5
4		**11**: Ar = PMB		**19**: Ar = PMB	1	92	72:28
5		**12**: Ar = Ph		**20**: Ar = Ph	5	70	80:20
6		**13**		**21**	1	72	> 95:5
7		**14**		**22**	72[d]	40	88:12
8		**15**		**23**	24[e]	80	> 95:5
9		**24**: R = *n*-C_6H_{13}		**27**: R = *n*-C_6H_{13}	48	57	> 95:5
10		**25**: R = Ph		**28**: R = Ph	48	64	> 95:5
11		**5**: R = *n*-C_5H_{11}		**7**: R = *n*-C_5H_{11}	48	80	95:5[f]
12		**26**: R = Ph		**29**: R = Ph	48[g]	50	83:17

[a] Yield of the isolated product. [b] The diastereomeric ratio was determined by $^1H/^{13}C$ NMR spectroscopy. [c] Desilylation was observed, and the yield was reduced as a result. [d] The reaction was carried out at 50 °C. [e] The reaction was carried out at room temperature for 12 h, and then at 50 °C for 12 h. [f] See Table 1. [g] The reaction was carried out at room temperature for 12 h, and then at 50–80 °C for 36 h. [h] Bn = benzyl, PMB = *p*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl.

entry 6) and with trisubstituted double bonds(entries 7 and 8) were suitable substrates for the cyclopropanation.

The *Z* enamides **24** and **25** were also suitable substrates for the Simmons–Smith cyclopropanation (Table 2, entries 9 and 10). The stereoselectivity of the cyclopropanation appeared to be higher with *Z* enamides than with *E* enamides, especially when a phenyl substituent was present on the alkene (Table 2, entries 9 and 10 versus 11 and 12). We determined the configuration of the products on the basis of the X-ray crystal structures of **19** and **28** (Figure 1) and were intrigued to find that both *E* and *Z* enamides appear to favor cyclopropanation at the same π face.

To rationalize these observations, we carried out PM3 calculations with Spartan Model and found that *E* enamides (R = alkyl or aryl) indeed assume the minimized conformation ***E₁*** (drawn with ChemDraw for clarity),[13] as we had speculated earlier during our epoxidation studies (Scheme 2).[8,9] The other locally minimized conformation found was ***E₂***. Conformation ***E₁*** is favored over ***E₂*** by 1.24 kcal mol^{-1}, although in both conformations the alkene is almost coplanar with the oxazolidinone ring, which allows delocalization of the nitrogen lone pair into the alkene. ***E₁*** is probably favored as a result of the dipole–dipole interaction

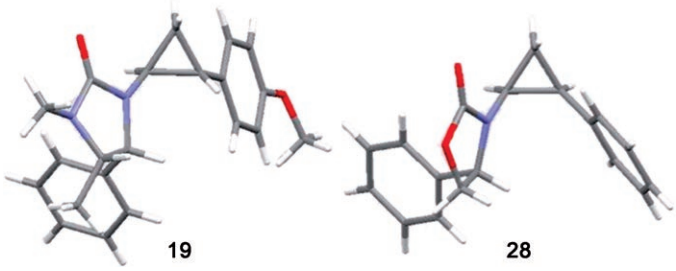
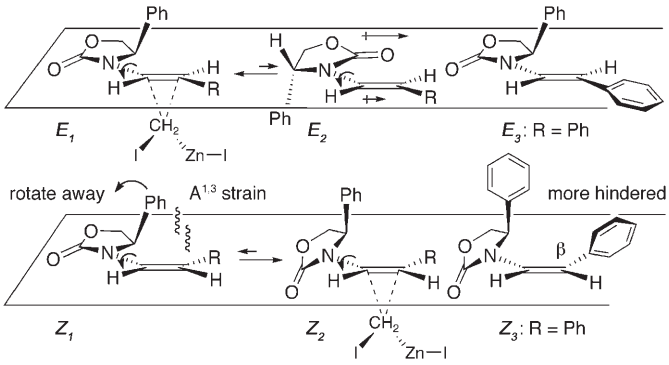


Figure 1. X-ray crystal structures of cyclopropanes **19** and **28**.

present in ***E₂***.[17] Consequently, conformation ***E₁*** provides the necessary π-facial differentiation for the observed stereochemical outcome; ***E₂*** is a possible source of the other diastereomer.

On the other hand, for *Z* enamides, the conformation shifts distinctly from the coplanar motif in ***Z₁*** to favor ***Z₂*** ($\Delta E \approx 1.0$–1.3 kcal mol^{-1}), in which the oxazolidinone ring has been rotated about the C–N bond to alleviate allylic strain: The direction of rotation is such that the phenyl substituent is moved away from the R group on the alkene. Despite the conformational change relative to the *E* enamide, the bottom



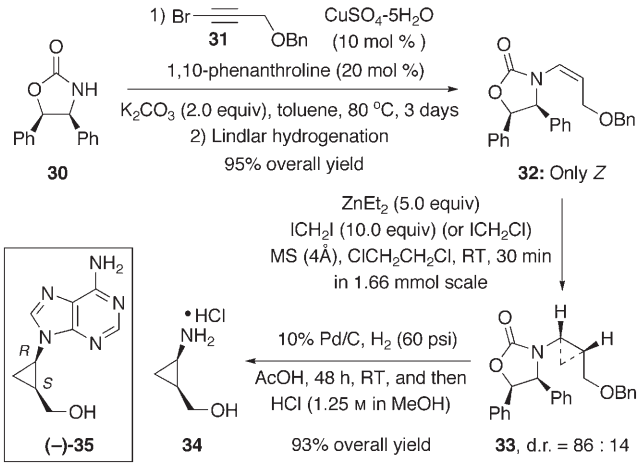
Scheme 2. Analysis of π-facial bias in chiral *E* and *Z* enamides.

face in ***Z₂*** remains accessible sterically. Thus, the same π-facial selectivity is observed in the cyclopropanation as for the *E* enamide. Furthermore, when R = Ph (see ***Z₃***), the dihedral angle between the alkene and the oxazolidinone ring is 47.4°, and the phenyl ring attached to the β carbon atom is also almost orthogonal to the alkene. These groups could shield the top face further (relative to that of ***E₃***) in a synergistic manner, which could thus lead to higher diastereoselectivity.

Finally, not least because of the biological significance of chiral aminocyclopropanes, especially in the design of antiviral agents,[18] there remains a genuine need to develop efficient approaches to their synthesis.[19,20] We therefore pursued this unique opportunity to establish a useful synthetic application of the Simmons–Smith cyclopropanation of chiral amides.

Toward this goal, the chiral *Z* enamide **32** was prepared by a two-step protocol that we reported recently for the synthesis of *Z* enamides in a stereoselective manner:[21] Cu-catalyzed amidation[22] of the alkynyl bromide **31**, followed by Lindlar hydrogenation of the ynamide[23] intermediate (Scheme 3). The Simmons–Smith cyclopropanation of **32** (1.66 mmol) proceeded in high yield in the presence of either ICH_2Cl or ICH_2I, although the diastereomeric ratio of the product was lower with the former. Reduction of the major isomer gave the chiral aminocyclopropane **34**, which was used in the synthesis of the de novo cyclopropyl nucleoside (−)-**35**.[18a]

We have described herein a highly stereoselective Simmons–Smith cyclopropanation of chiral enamides and the application of this methodology to the preparation of a chiral aminocyclopropane. These studies not only illustrate the potential of enamides as viable chiral templates in organic synthesis, but also provide a solution to the design of efficient syntheses of chiral aminocyclopropanes.



Scheme 3. An approach to chiral aminocyclopropanes.

Experimental Section

Typical procedure (Table 2, entry 10): Molecular sieves (4 Å, 50.0 mg) and ICH_2Cl (140.0 μL, 1.89 mmol, 10.0 equiv) were added to a solution of the chiral enamide **25** (50.0 mg, 0.189 mmol) in anhydrous $ClCH_2CH_2Cl$ (1.9 mL), and the resulting mixture was stirred at room temperature for 30 min. A solution of $ZnEt_2$ (0.94 mL, 1.0 M in hexane, 0.94 mmol, 4.9 equiv) was then added carefully dropwise. After further stirring at room temperature for 48 h, TLC analysis showed that **25** had been consumed entirely. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and then extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with saturated aqueous NaCl (2 × 5 mL), dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude product. Purification of the crude residue by flash column chromatography on silica gel (eluent gradient: 15–33% EtOAc/hexanes) afforded the major isomer **28** (30.0 mg, 64%) as a white solid. R_f = 0.14 (20% EtOAc/hexanes); m.p. 113–113.5 °C; $[\alpha]_D^{23} = -87.5$ ($c = 0.8$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.43$ (ddd, $J = 7.5$, 7.5, 9.0 Hz, 1H), 1.92 (ddd, $J = 4.5$, 7.5, 7.5 Hz, 1H), 2.11 (ddd, $J = 7.5$, 7.5, 9.0 Hz, 1H), 2.44 (ddd, $J = 4.5$, 7.5, 7.5 Hz, 1H), 3.61 (dd, $J = 4.5$, 9.0 Hz, 1H), 3.95 (dd, $J = 4.5$, 9.0 Hz, 1H), 4.05 (dd, $J = 9.0$, 9.0 Hz, 1H), 7.10–7.40 ppm (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 11.7$, 22.7, 31.5, 60.0, 69.6, 126.9, 127.2, 127.8, 128.6, 129.2, 129.5, 136.9, 138.5, 158.8 ppm; IR (film): $\tilde{\nu} = 1740$ (s), 1407 (m), 1126 (s), 1051 (m), 1031 (m), 1011 cm^{-1} (m); MS (ESI): *m/z* (%): 302 (100) $[M+Na]^+$, 280 (40) $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{18}H_{17}NO_2Na$: 302.1157; found: 302.1163.

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