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Epoxidation of Chiral Camphor *N*-Enoylpyrazolidinones with Methyl(trifluoromethyl)dioxirane and Urea Hydrogen Peroxide/Acid Anhydride: Reversal of Stereoselectivity

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Abstract: Both diastereomeric isomers of epoxides with high optical purity are obtained when camphor *N*-methacryloylpyrazolidinone (**1a**) and *N*-tigloylpyrazolidinone (**1b**) are treated with a urea hydrogen peroxide/TFAA and methyl(trifluoromethyl)dioxirane, respectively.

The development of efficient methods for the stereochemical control of the epoxidation of olefins is of considerable interest since nonracemic chiral epoxides are important building blocks in organic synthesis.[1] The epoxidation of allylic substituents has been well documented,[2] but the reaction of less reactive electron deficient alkenes remains a synthetic challenge.[3] The two most popular epoxidants for use in alkene oxidations are dioxiranes[4] and peracids,[5] and both have received considerable attention. Recently, Adam et al. reported that the treatment of (*S*)-4-benzyl-2,2-dimethyloxazolidine-derived tiglic amide with oxidants resulted in a high stereoselectivity.[6] More interestingly, the opposite sense of π-face selectivity was obtained when different peroxidic oxidants were used. This reversal of stereoselectivity can be attributed to the steric interactions and hydrogen-bonding effects, respectively, for the DMD and *m*-CPBA epoxidations. The synthesis of both enantiomerically enriched stereoisomers without resorting to the use of a enantiomeric auxiliary is attractive in asymmetric synthesis.[7] We recently reported on the diastereoselective epoxidation of *N*-enoyl camphorpyrazolidinones using a urea hydrogen peroxide complex (UHP) in the presence of trifluoroacetic anhydride (TFAA).[8] A wide range of selectivities were obtained for a variety of chiral alkene substituents. Herein we report on an extension of this work to the synthesis of both diastereomers of epoxides in high optical purity by treatment of *N*-methacryloylpyrazolidinone (**1a**) and *N*-tigloylpyrazolidinone (**1b**) with UHP/TFAA and methyl(trifluoromethyl)dioxirane, respectively.

Treatment of *N*-methacryloylpyrazolidinone (**1a**) with UHP in the presence of TFAA gave the desired epoxide with good stereoselectivity (Table 1, entry 1).[8] The absolute stereochemistry of the newly generated stereogenic center of the major product was determined to be the *R* configuration as evidenced by single-crystal X-ray analysis. In the case of *N*-tigloylpyrazolidinone (**1b**), the use of trifluoromethanesulfonic anhydride (TFSA) or trichloroacetic anhydride gave the desired epoxide with excellent stereoselectivity (entries 2 and 3). The selectivity decreased in the presence of a Lewis acid (entry 4). It is noteworthy that no diastereoselectivity was observed when THF was used as solvent (entry 5). The observed significant solvent effects suggest that the preference of substrate conformations dependent on the reaction conditions employed. Although high material yields were obtained, the selectivity decreased substantially when these two substrates were treated with *m*-CPBA (entries 6 and 7). The epoxidation of alkenes with dioxiranes has been studied extensively in the past, with the goal of achieving high stereoselectivity.[4] Treatment of **1a** with methyl(trifluoromethyl)dioxirane, generated in situ, provides the desired epoxide in an 86% chemical yield (entry 8). The diastereoselectivity was determined to be greater than 90% de based on ^{1}H NMR analysis of the relevant peak. Even more interesting, the absolute stereochemistry in the epoxy group of the major isomer was found

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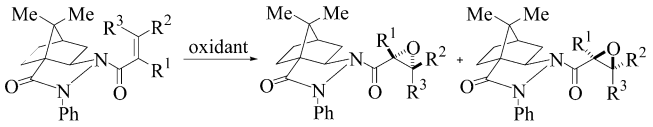
TABLE 1. Asymmetric Epoxidation of Camphor *N*-enoylpyrazolidinones 1a−d with Oxidants[a]



a: R^1 = Me R^2 = R^3 = H
b: R^1 = R^2 = Me R^3 = H
c: R^1 = H R^2 = i-Pr R^3 = H
d: R^1 = H R^2 = R^3 = Me

entry	substrate	conditions	*t*/h	% yield[b]	**2**:**3**[c]
1[d]	**1a**	UHP/TFAA	6	53	81:19
2[d]	**1b**	UHP/TFSA	1/4	75	>95:05
3	**1b**	UHP/$(CCl_3CO)_2O$	1/4	60	>95:05
4	**1b**	UHP/TFSA, $Sn(OTf)_2$	1/4	60	72:18
5[e]	**1b**	UHP/TFAA	1/4	30	50:50
6	**1a**	*m*-CPBA	72	95	39:61
7	**1b**	*m*-CPBA	24	95	76:24
8	**1a**	dioxirane, 0 °C	8	86	<05:95
9	**1b**	dioxirane, 0 °C	8	80	26:74
10	**1b**	dioxirane, −20 °C	8	50	15:85
11[d]	**1c**	UHP/TFAA	1/4	83	85:15
12[d]	**1d**	UHP/TFAA	1/4	95	83:17
13	**1c**	dioxirane, 0 °C	12	75	36:64
14	**1d**	dioxirane, 0 °C	4	95	45:55

[a] Unless specifically noted, all reactions were carried out with substrate **1a**−**d** (1.0 equiv) at ambient temperature with UHP/acid anhydride (20.0/6.0 equiv), *m*-CPBA (6.0 equiv) using CH_2Cl_2 as solvent while in aqueous CH_3CN when dioxirane is used [1,1,1-trifluoroacetone (37.3 equiv), Oxone (11.0 equiv), Na_2EDTA (aq), $NaHCO_3$]. [b] Isolated yield. [c] Determined by ^1H NMR analysis of relevant peaks. [d] From ref 8. [e] In THF.

to be the *S* configuration which is opposite that of the diastereomer obtained when UHP was used. *This is, to the best of our knowledge, the first example of the use of methyl(trifluoromethyl)dioxirane and UHP/TFAA to achieve high and opposite sense of diastereoselectivity in a chiral auxiliary derived enone.* The reversed facial selectivity was also observed to a lesser extent when **1b** was used under the same reaction conditions (entries 9 and 10). A slight increase in diastereoselectivity was found when the reaction was carried out at −20 °C. Various camphor *N*-enoylpyrazolidinones were investigated under the same reaction conditions to give either poor selectivities or no reaction (entries 11−14). The proper disposition of substituent(s) in the olefin functionality in the substrate is crucial in achieving high stereoselectivity.

For camphor *N*-enoylpyrazolidinone derivatives the *s-cis* conformations (**A1** and **A3**) are in equilibrium with their *s-trans* (**A2** and **A4**) conformers and are reaction conditions and substituent dependent (Figure 1).[6,9] In general, the *s-cis* conformers favor unsubstituted and *β*-substituted olefins, while the *s-trans* conformations dominate for α- and α,*β*-disubstituents.[9a] Furthermore, the N−C(O) amide bond oriented toward the phenyl group (**A1** and **A2**) is energetically significant based on the X-ray crystal structures of **1a**,**b** and related *N*-

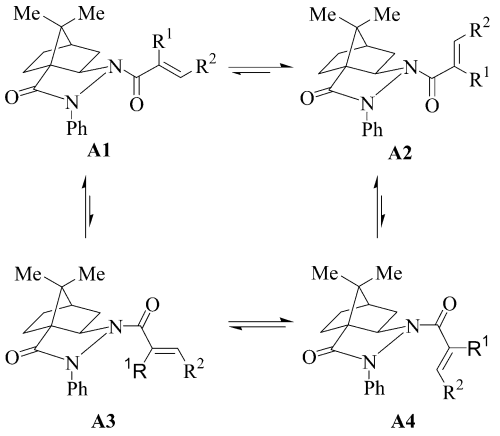


FIGURE 1. Possible conformations of camphor *N*-enoylpyrazolidinones **1**.

enoylpyrazolidinones in the solid state. This conformational preference may serve to minimize the unfavorable dipole−dipole interactions between the N−C(O) and the heterocyclic pyrazolidinone moiety.[9d] The alkene functionality is twisted from the planar orientation with respect to the carbonyl functionality in the cases of **1a**−**d**, thus preventing steric interactions between the substituent(s) with the camphor nucleus.[9c] Quantum chemistry calculations confirm the nonplanar conformations (see supplementary data for details). The dihedral angles of the double bond and the carbonyl group of the calculated optimized structures (HF/6-31G*) in the two lowest energy conformations of **1b** are −155° (**A2**) and 22° (**A1**), respectively. The free energy difference obtained using Gaussian[10] is 2.1 kcal/mol in favor the **A2** *s-trans* arrangement.

The high degree of reversal of diastereoselectivity may be rationalized in terms of energy differences between the transition structures in the epoxidation processes (Figure 2).[6,11] It has been well documented that hydrogen bonding plays an important role in peracids epoxidation.[12] This is applicable to the oxygen-transfer processes when a hydrogen peroxide derivative is used as an oxidant.[13] In the *s-cis* transition conformation (**T11**‡) the enone system is oriented in the optimal conformational alignment for UHP/TFAA epoxidation which is stabilized by hydrogen bonding. The lack of selectivity and the decreased reactivity when THF was used can be ex-

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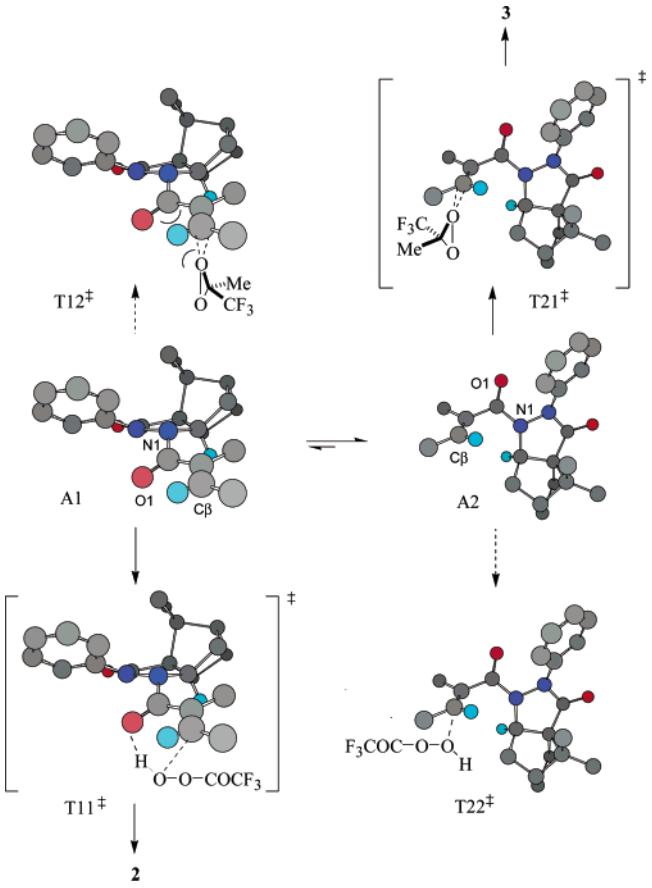

FIGURE 2. Proposed transition-state structures of **1b** with oxidants. The stereoview of the Chem3D structures of **1b** (**A1** *s-cis* and **A2** *s-trans*) was regenerated from the X-ray crystal coordinates. All hydrogen atoms, except for C2 and Cβ, are omitted for the sake of clarity.

plained by the disruption of hydrogen bonding between the enone moiety and UHP/TFAA (entry 5). An attack by the epoxidant from the less hindered Cα *re* face would afford the desired major diastereomer **2**. The use of *m*-CPBA gives poor selectivity (entries 6 and 7). This may be due to intramolecular hydrogen bonding in the mCPBA molecule.[12c] Intermolecular hydrogen bonding between the enone carbonyl group and oxidant became less effective.

A concerted spiro transition state for the dioxirane epoxidation of alkenes has been proposed from both the experimental and theoretical studies.[14] In this study, the dioxirane molecule approachs the olefin from the opposite side of the C8 and C9-dimethyl groups with the methyl(trifluoromethyl) groups positioned away from the camphor nucleus. The transition structure **T21**‡ is favored over **T12**‡ may be due to repulsion interaction between the dioxirane oxygen atom with the carbonyl carbon atom in **T12**‡.[3c] The close dipole−dipole interaction in **1b** is demonstrated by the relatively short distance between the oxygen atom and the Cβ atom in the enone functionality in **A1** (O1−Cβ: 2.77 Å) compared to that of **A2** (O1−Cβ: 3.51 Å). Undesired repulsion between the oxidant and the nitrogen atom (N1) in the pyrazolidinone ring appeared to exert a small effect and this effect on the diastereoselectivity is negligible (N1−Cβ: 3.61 Å in **A1** versus N1−Cβ: 2.81 Å in **A2**). In addition, the *s-cis* conformer is disfavored by steric interactions in the transition structure (**T12**$^{\neq}$) between the C2 hydrogen atom and the Cβ methyl group of the tiglate moiety.

In summary, epoxidation of camphor pyrazolidinone derived *N*-methacrylate (**1a**) and *N*-tiglate (**1b**) gives high but opposite sense in the diastereoselectivity, when UHP/TFAA and methyl(trifluoromethyl)dioxirane are used in the reaction. For UHP/TFAA epoxidation the *s-cis* conformation is favored due to beneficial intermolecular hydrogen bonding interactions and epoxide **2** is the major product. On the other hand, the electronic repulsion and/or steric interactions favor *s-trans* conformation and provide epoxide **3** as the major product when methyl(trifluoromethyl)dioxirane was used.

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Supporting Information Available: Experimental procedures and copies of ^{1}H (**2a**−**d** and **3a**−**d**) and ^{13}C (**2a**−**d** and **3a**,**b**,**d**) NMR spectra for epoxides. X-ray crystallographic data (thermal ellipsoid plot, experimental details, atomic coordinates, bond lengths, bond angles, and ORTEP diagrams) for compounds **2a**−**d** and **3b**. Quantum chemistry calculations for determining the preferred conformations of *N*-methacryloylpyrazolidinone (**1a**) and *N*-tigloylpyrazolidinone (**1b**). This material is available free of charge via the Internet at http://pubs.acs.org.

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