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Efficient π-Facial Control in the Ene Reaction of Nitrosoarene, Triazolinedione, and Singlet Oxygen with Tiglic Amides of the Bornane-Derived Sultam as Chiral Auxiliary: An Economical Synthesis of Enantiomerically Pure Nitrogen- and Oxygen-Functionalized Acrylic Acid Derivatives

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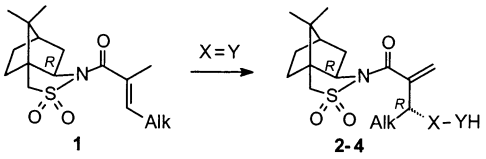
The ene reaction of singlet oxygen ($^1O_2$) and *N*-phenyl-1,2,4-triazoline-3,5-dione (PTAD) has been extensively used for the allylic functionalization of double bonds in a variety of olefins.[1] Recently, also the nitrosoarene (ArNO) enophile has been successfully utilized for the regioselective[2] and stereoselective[3] synthesis of nitrogen-functionalized compounds.[1b,4] Generally, for stereoselective control, chiral auxiliaries may be employed, a powerful tool in asymmetric synthesis.[5] Unquestionably, the economical preparation of optically active heteroatom-functionalized acids derivatives, in particular β-amino acids, has become an attractive goal, since these substances, and especially the therefrom derived peptides, are of biological and pharmaceutical interest.[6] For example, whereas a variety of methods is available to prepare optically active β-amino acids,[6,7] the synthesis of highly functionalized α-methylene β-amino acids is still demanding. Herein we demonstrate that the chiral-auxiliary-mediated regioselective and stereoselective ene reaction of ArNO, PTAD, and $^1O_2$ with tigloyl sultams affords enantiomerically pure acrylic-acid derivatives.

After extensive screening for a suitable chiral auxiliary, we found that the optically active tiglic-acid derivatives of the bornane-derived sultam[8] afforded the desired ene products in high yield and excellent regioselectivity and diastereoselectivity (Table 1). Only one diastereomer was obtained for the ene reaction of ArNO and PTAD with the tiglic amide **1a**, while $^1O_2$ afforded a 83:17 mixture of the *like* and *unlike* diastereomers. To raise the diastereoselectivity for $^1O_2$, the steric demand of the *lone* substituent[2a] in the substrate was increased by employing the amide **1b** (Alk = ^{i}Pr). Indeed, even for $^1O_2$, the smallest possible enophile, absolute diastereoselectivity was achieved with this isopropyl derivative. As expected, the ene reaction of ArNO with **1b** also yielded the diastereomerically pure ene product **2b** in good yield.

The configurational assignment of all four ene products **2**−**4** was achieved by chemical correlation. The sultam auxiliary was removed in the ene products by hydrolysis (PTAD), methanolysis ($^1O_2$), and silica gel treatment (ArNO) for all three enophiles in one step. The PTAD adduct **3a** was converted with LiOH to the corresponding amino acid derivative **6a** (Scheme 1), its absolute configuration was determined by comparison of the $[\alpha]_D$ value (−57.2°) with that of the known enantiomer (*S*)-**6a** (+61.7°),[9] which establishes the *like* configuration for urazole **3a**. The $^1O_2$ ene products **4a**,**b** were converted with sodium methoxide to the corresponding methyl esters **7a**,**b**. Comparison of the HPLC retention times and signs of their optical rotations with those reported in the literature,[10] revealed also the *R* configuration of the newly formed stereocenter in the $^1O_2$ ene products **4a**,**b**. The authentic racemic samples *rac*-**7a**,**b**, which were required for HPLC analysis as references, were prepared according to the literature procedures[11] (cf. Supporting Information).

Remarkable is the case of the nitroso enophile: The primary ene products **2a**,**b** were converted by silica gel treatment quantitatively to the highly functionalized α−methylene isoxazolidinones **5a**,**b** (Scheme 2). Reduction of their N−O bond with $Na_2S_2O_4$ provided the β-amino acids **8a** (**8b**) in 75% (84%) yield. An independent synthesis of (*R*)-**8a** was carried out to assign the configuration of the newly formed stereogenic center in the ene product **2a**. As described in the literature,[12] the free ammonium salt (*R*)-**9a** was prepared in seven steps starting from the racemic

Table 1. Product Studies for the Ene Reaction of ArNO, PTAD and $^1O_2$ with the Optically Active Tiglic Amides **1a**,**b**

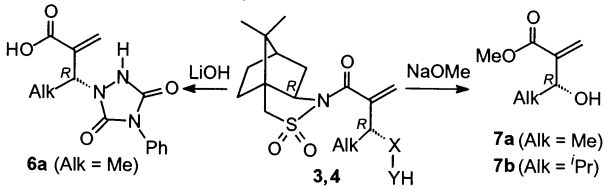


1 **2-4**

		Alk	enophile X = Y	time [d]	convn [%][a,c]	mb [%][a,c]	ene product	yield [%][d]	dr[a,b] *lk:ul*
1	**1a**	Me	ArNO[e]	2	85	80	**2a**	61[f]	>95:5
2	**1b**	^{i}Pr	ArNO	1	77	79	**2b**	55[f]	>95:5
3	**1a**	Me	PTAD	1	>95	>95	**3a**	80[f]	>95: 5
4	**1a**	Me	$^1O_2$	1	>95	>95	**4a**	90[g]	83:17
5	**1b**	^{i}Pr	$^1O_2$	3	90	87	**4b**	78[g]	>95: 5

[a] The reactions were run in $CDCl_3$ and analyzed by ^1H NMR spectroscopy; error ±5% of the stated values. [b] The configurations were assigned by chemical correlation. [c] Based on olefin, versus tetrachlorethane or pentafluorobenzene as internal standards. [d] Isolated material. [e] Ar = *p*-NO_2-C_6H_4, 2.5 equiv. [f] From preparative runs in CH_2Cl_2. [g] From semipreparative runs in $CDCl_3$; yield of alcohol obtained by Ph_3P reduction of the hydroperoxide.

Scheme 1. Configurational Assignment for the Ene Products **3a** of PTAD and **4a**,**b** of $^1O_2$ by Chemical Correlation[a]



6a (Alk = Me) **3,4** **7a** (Alk = Me) **7b** (Alk = ^{i}Pr)

[a] For $^1O_2$, the ene products **4a**,**b** are the corresponding alcohols after Ph_3P reduction (see Table 1, footnote g).

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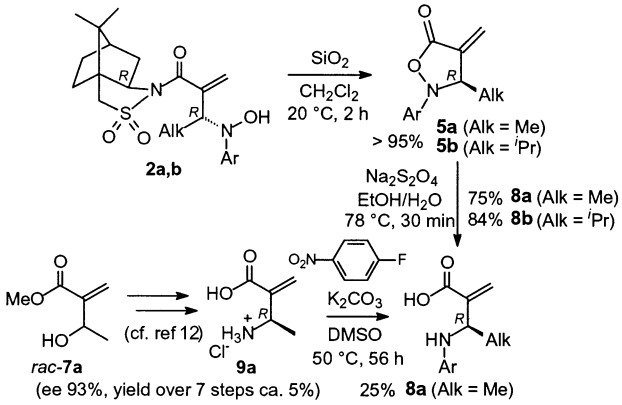
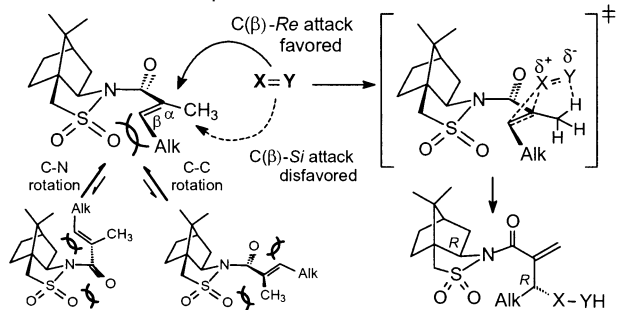
Scheme 2. Silica-Gel-Mediated Cyclization of the Nitroso Ene Products **2** to the Isoxazolidinones **5**, Reduction to the Corresponding β-Amino Acids **8**, and Determination of the Configurations by Chemical Correlation



Scheme 3. Preferred Conformation of the Olefin in the π-Facially Diastereoselective Enophilic Attack of ArNO, PTAD, and $^1O_2$



β-hydroxy ester *rac*-**7a**, which included lipase-catalyzed kinetic resolution of the hydroxy ester in an enantiomeric excess of 93%. Arylation of the ammonium salt (*R*)-**9a** afforded the β-amino acid (*R*)-**8a**.[13] The optical rotations ($[\alpha]_D = +2.4°$) of the β-amino acid **8a**, derived from the ene product **2a**, and the authentic material (*R*)-**8a** matched perfectly in sign and extent. To confirm the authenticity and the enantiomeric purity of the isoxazolidinone **5a**, obtained from the ene product **2a**, the racemic sample *rac*-**5a** was required for chiral HPLC analysis. The latter was prepared by cyclization of the racemic ene product of ArNO with methyl tiglate (cf. Supporting Information). The isopropyl derivatives **5b** and **8b** are also *R*-configured, since their optical rotations (**5b** −381.7°; **8b** +4.9°) match those of the methyl derivatives **5a** (−421.7°) and **8a** (+2.4°). Thus, in the ene reaction of ArNO with the tiglic amides **1a**,**b**, the *like* diastereomers *lk*-**2a**,**b** were exclusively formed.

The mechanistic rationalization of the very high diastereoselectivity in the ene reaction for all three enophiles ArNO, PTAD, and $^1O_2$ requires knowledge of the preferred conformation of the bornane-derived tiglic-acid sultamides. Informative in this regard is the known X-ray structure of tigloyl sultam **1a**,[14] and we assume that the preferred ground-state conformation in the crystalline state also applies in solution, to account for the observed selectivity in the π-facial attack (Scheme 3). The carbonyl group points away from the sulfonyl functionality, due to mutual electrostatic repulsion and the steric interaction between the CC double bond substituents and the bornane skeleton (C−N rotation). Furthermore, the carbonyl group and the double-bond possess the *s-trans* conformation (C−C rotation) about the clockwise-twisted C(α)−CO bond (the dihedral angle is 46° in the X-ray structure). This conformation results from the balance between the steric interactions of the carbonyl and of the sulfonyl groups with the double bond substituents. For this well-locked conformation, the C(β)-*re* attack[15] of the enophile is favored, whereas the C(β)-*si* attack is efficiently shielded by the sulfonyl oxygen atoms.[16] By employing the sterically more demanding isopropyl derivative **1b**, the diastereoselectivity is increased, and even for $^1O_2$ exclusively one diastereomer was obtained. This is the first example of absolute diastereoselectivity in $^1O_2$ ene reaction controlled by steric effects. Moreover, the high ene reactivity of the "electron-poor" double bond in the tiglic sulfonamides toward the enophiles, particularly ArNO, may be reconciled by the twisted conformation of the double bond and the carbonyl functionality, which reduces conjugation between the carbonyl group and the CC double bond[17] sufficiently such that the ene reactions proceed in high yield.

In conclusion, this asymmetric allylic heteroatom functionalization of the readily available tiglic sultams **1a**,**b** provides an efficient and economical route to valuable optically active building blocks. Moreover, since both enantiomers of the bornane auxiliary are easily accessible from (+)- and (−)-camphor, both stereoisomers of the ene product are available.[8] The cumbersome conventional synthesis of the β-amino acid **9a** in seven steps in only 5% overall yield and 93% enantiomeric purity (Scheme 2) emphasizes the convenience and advantage of the present synthetic concept.

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Supporting Information Available: Structure matrix and experimental section (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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