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Stereoselective cyclopropanation with a sultam carbenoid

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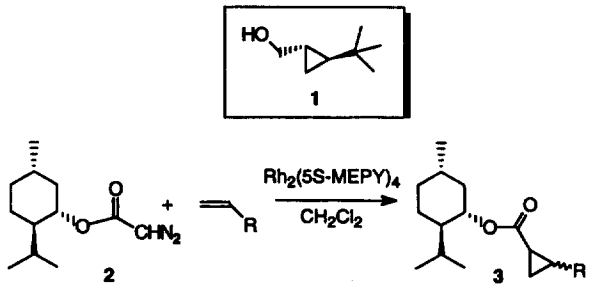
Abstract: Stereoselective cyclopropanation of alkenes with the Oppolzer's sultam carbenoid was examined for the first time. The addition reaction proceeds in high yields on substituted alkenes and provides an easy access for stereoselective preparation of *di-* and *tri*-substituted cyclopropanes. The synthetic utility of the title reaction was demonstrated in the stereoselective preparation of **1**. © 1997 Elsevier Science Ltd

Cyclopropanation of olefins with carbenoids is a well documented reaction and provides the method of choice for stereoselective synthesis of substituted cyclopropanes.[1] Chiral catalysis, using Rh, Co, Ru and mainly Cu chiral complexes was demonstrated to provide good to high stereoselectivity in the cyclopropanation of diazocarbonyl compounds to olefins. However, in a large number of examples, double chiral induction was necessary to improve the stereoselectivity of this reaction by introducing a chiral auxiliary at either the diazocarbonyl[2] or the olefin.[3] We present herein a new chiral carbenoid that was found to overcome a general problem of highly stereoselective synthesis of *tri*-substituted or sterically hindered *di*-substituted cyclopropanes.

As a part of our interest in applying substituted cyclopropanes as trapping probes for radical intermediates[4] we became interested in a practical stereoselective synthesis of **1**, possessing a *tert*-butyl substituent in the *trans* configuration. Doyle's asymmetric cyclopropanation,[5] using D-α-menthyldiazoacetate (**2**) or l-α-menthyldiazoacetate (MDA) with chiral Rh^{II} catalysis (Scheme 1), could provide the desired product, however, in low yield and moderate diastereomeric excess.



R	MDA	% yield	*trans*:*cis*	%de *trans*	%de *cis*
Ph	l	47	67:33	56 (1*S*,2*S*)	79 (1*S*,2*R*)
Ph	d	69	67:33	48 (1*S*,2*S*)	86 (1*S*,2*R*)
t-Bu	d	42	71:29	65	91

Scheme 1.

Following Hacksell's approach which provides very high stereoselective cyclopropanation of chiral alkene **4a** with diazomethane,[6] we have examined the addition of diazomethane to **4b** (Scheme 2). No cyclopropanation was detected in this reaction, presumably due to steric hindrance, since low

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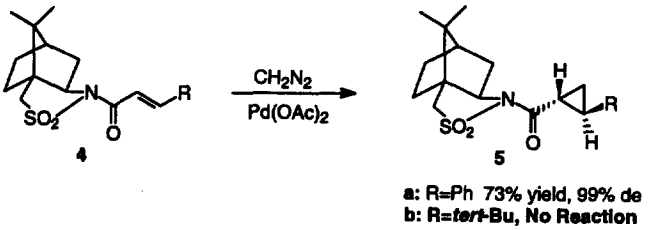
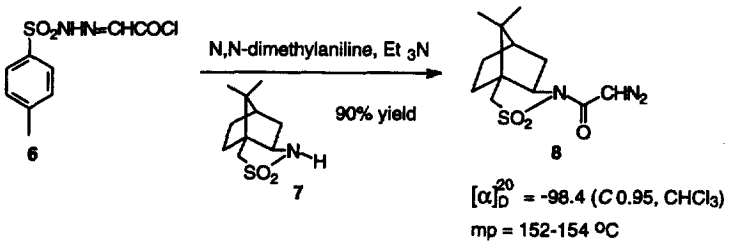
yields (15–30%) and tedious separations were reported in applying this approach for the synthesis of *tri*-substituted alkenes.[6b]



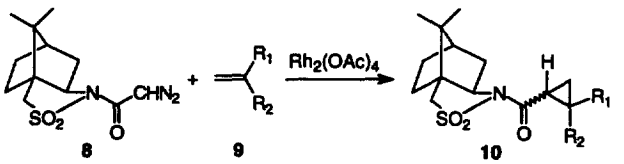
Scheme 2.

Based on this information, we became interested in developing a new and practical stereoselective cyclopropanation for the formation of sterically hindered cyclopropanes. The approach is based on the addition of the α-diazoamide derivative of Oppolzer's sultam **8** to olefins. Diazoacetamide **8** was prepared from glyoxylchloride-p-tosylhydrazone[7] **6** and bornane-10,2-sultam **7** (Oppolzer's sultam) following a known procedure (Scheme 3).[8]



Scheme 3.

Cyclopropanation of the sultam carbenoid was examined on 3,3-dimethylbutene **9a**, isopropylene **9b** and styrene **9c**, in the presence of the *achiral* catalyst[9] $Rh_2(OAc)_4$, following a reported procedure.[9,10] The following results present considerable improvement in the chemical yield and the stereoselectivity in the case of **9a** (Scheme 1), even though the sultam derivative provides the only source for chiral induction in the cyclopropanation (Scheme 4).

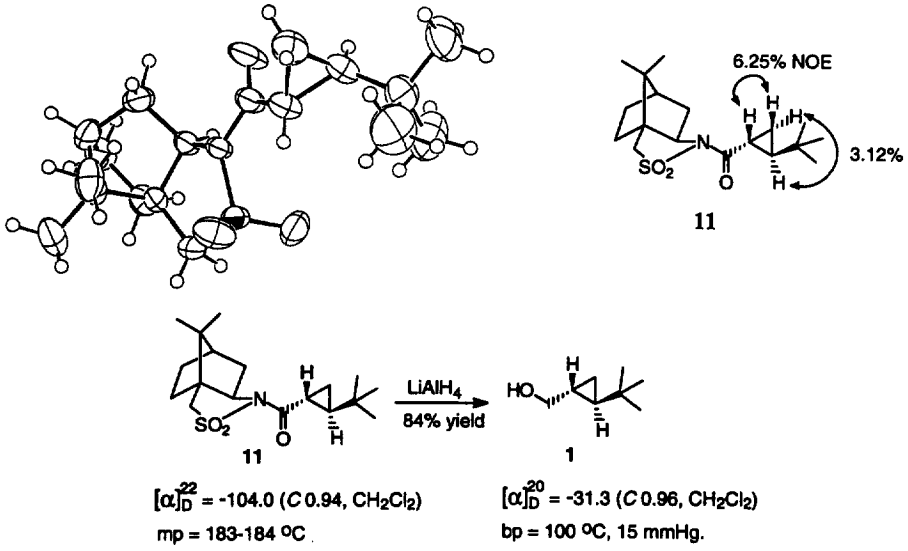


9	R_1	R_2	% yield	*trans*:*cis*	% de *trans*	% de *cis*
a	*tert*-Bu	H	85	76:24	81	>98
b	Me	Me	83	-	90	
c	Ph	H	67	68:32	67	70

Scheme 4.

Cyclopropanation of **9a** with **8** afforded two *trans*-diastereomers **10a** in 81% diastereomeric excess (de) and 65% yield in a mixture with a single *cis*-product (20% yield, >98% de, GC). All isomers were separated by column chromatography, and the relative configuration at the cyclopropyl rings was determined by NOE experiments.

Crystallization of the product mixture from EtOAc, afforded the major isomer of *trans*-**10a** (**11**) in 55% yield and 95.5% de (GC). However, further crystallizations were required to obtain purity of over 99% de and ca 30% yield. Reduction of pure **11** with $LiAlH_4$ afforded the desired cyclopropane **1** in 84% yield (Scheme 5).[11] The absolute configuration of **11** was determined by X-ray structure analysis.



Scheme 5.

The utility of the sultam carbenoid in stereoselective preparation of *tri*-substituted cyclopropanes was examined by its addition to isobutylene (**9b**), affording **10b** in 90% de and 83% yield. The diastereomers were separated by column chromatography (Silica, Hex.:CH_2Cl_2, 4:1) and their structures were confirmed by spectroscopic methods (^{1}H-NMR, ^{13}C-NMR, MS, IR). Moderate stereoselectivity was obtained in the cyclopropanation of styrene (**9c**). Isomers **10c** were determined by comparison (GC-MS) with authentic samples of *trans*-**10c**[4b] and the corresponding *cis*/*trans* isomers of **1**, obtained by reduction of **10c** in the presence of tetradecane as an internal standard. It should be noted that improved selectivity could be expected via addition of the sultam carbenoid to alkenes, using a chiral catalyst of a matched double chiral induction.

Acknowledgements

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10. *Typical procedure*: diazoacetamide **8** (2.5 g, 8.8 mmol) in dichloromethane solution (53 mL) was added dropwise, over a period of 6 h, to a precooled solution (0°C) of the alkene (88.0 mmol) in dichloromethane (53 mL). The reaction mixture was stirred for an additional 15 min. at room temperature [no more diazoacetamide **8** could be detected on TLC (Hex.:EtOAc 3:1, R_f=0.36)], filtered through a short column of basic alumina then concentrated under reduced pressure.
11. Characterization data: **8**: ^{1}H-NMR ($CDCl_3$) δ 5.69 (s, 1H), 3.86 (q, *J*=7.6 Hz, 1H), 3.39 (dd, J_1=14.1 Hz, J_2=2.7 Hz, 2H), 2.13 (dd, J_1=13.7 Hz, J_2=2.2 Hz, 1H), 2.04 (dd, J_1=13.6 Hz, J_2=7.7 Hz, 1H), 1.86 (bs, 3H), 1.42 (m, 1H), 1.33 (m, 1H), 1.09 (s, 3H), 0.92 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 163.0, 65.0, 52.5, 49.7, 48.7, 47.9, 44.5, 38.1, 32.4, 26.6, 20.4, 19.8; IR ($CHCl_3$) 2150, 1700, 1340 cm^{-1}. **11**: ^{1}H-NMR ($CDCl_3$) δ 3.85 (q, *J*=7.2 Hz, 1H), 3.44 (q, *J*=17.1 Hz, 2H), 2.18 (m, 1H), 2.05 (m, 2H), 1.85 (m, 3H), 1.36 (m, 4H), 1.22 (t, 1H), 1.20 (s, 3H), 0.95 (s, 3H), 0.87 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ 173.2, 65.4, 53.1, 48.5, 47.7, 44.7, 38.6, 36.9, 32.9, 30.1, 28.0, 26.5, 20.8, 19.9, 18.1, 13.2; IR ($CHCl_3$) 1690, 1340 cm^{-1} ; HRMS (EI): Calcd for $C_{18}H_{29}NO_3S$ m/z 339.1868, Found m/z 339.1886. **1**: ^{1}H-NMR ($CDCl_3$) δ 3.39 (d, *J*=6.8 Hz, 2H), 0.94 (m, 1H), 0.81 (s, 9H), 0.51 (m, 1H), 0.42 (m, 1H), 0.21 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ 67.5, 30.7, 29.1, 28.4, 17.0, 6.0; IR ($CHCl_3$) 3420, 1360 cm^{-1}.

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