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Tandem Asymmetric Conjugate Addition–Silylation of Enantiomerically Enriched Zinc Enolates. Synthetic Importance and Mechanistic Implications

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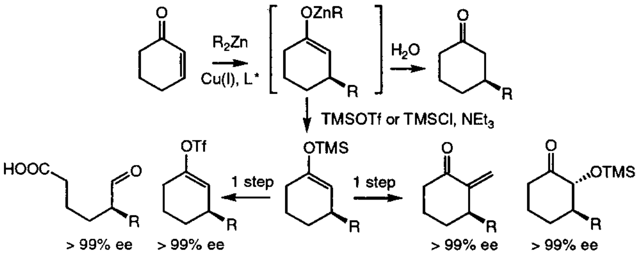
ABSTRACT



The zinc enolates, resulting from the copper-catalyzed enantioselective conjugate addition of dialkyl zinc reagents to cyclic and acyclic enones, could be trapped, quantitatively, as silyl enol ethers with TMSOTf in apolar solvents or with TMSCl and NEt$_3$. These enantiomerically enriched silyl enol ethers were submitted to four synthetic transformations to show their synthetic utility. The zinc enolates obtained from acyclic enones were found to be configurationally stable, as shown by the stereochemistry of the silyl enol ethers.

Asymmetric copper-catalyzed conjugate addition has stirred tremendous interest in the last few years.[1] Considerable progress has been made, using dialkyl zinc reagents as primary organometallics, with enantioselectivities reaching >99% on both cyclic and acyclic enones.[2] The common feature of these reactions is the generation of enantiomerically enriched zinc enolates.

Tandem conjugate addition and trapping of the zinc enolate with an electrophile could be an excellent way to quickly build more complex molecules.[3] Despite their low reactivity, zinc enolates could be made to react with aldehydes,[4] with acetals[5] (with BF$_3$·Et$_2$O as an additive), with allylic acetates[6] (with Pd catalysis), and with homopropargylic iodide.[7] In

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(2) (a) Alexakis, A.; Frutos, J.; Mangeney, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2427. (b) Alexakis, A.; Burton, J.; Vastra, J.; Benhaïm, C.; Fournioux, X.; van den Heuvel, A.; Levêque, J.-M.; Mazé, F.; Rosset, S. *Eur. J. Org. Chem.* **2000**, 4011. (c) Alexakis, A.; Benhaïm, C.; Fournioux, X.; van den Heuvel, A.; Levêque, J.-M.; March, S.; Rosset, S. *Synlett* **1999**, 1811. (d) Arnold, L. A.; Imbos, R.; Mandoli, A.; de Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron*, **2000**, *56*, 2865. (e) Escher, I. H.; Pfaltz, A. *Tetrahedron* **2000**, *56*, 2879. (f) Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 779.

(3) (a) Taylor, R. J. K. *Synthesis* **1985**, 364. (b) Chapdelaine, M. J.; Hulce, M. *Org. React.* **1990**, *38*, 225.

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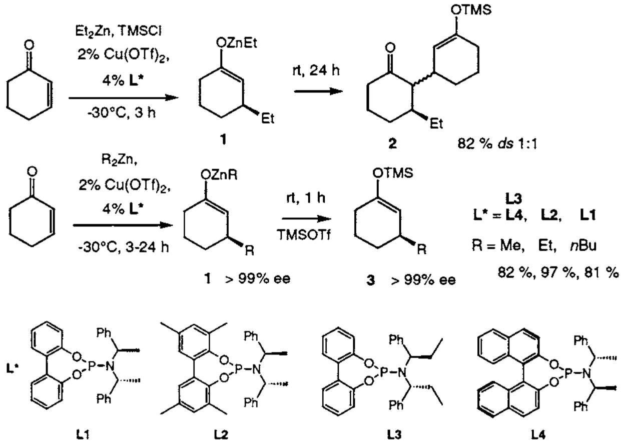
Scheme 1

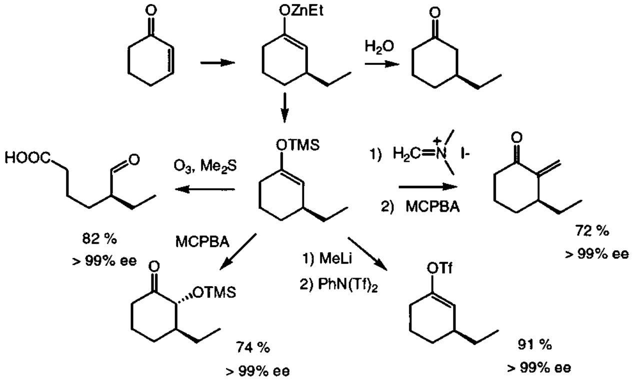


view of the versatility of silyl enol ethers,[8] it would be desirable to trap zinc enolates with a silylating agent. The resulting homochiral silyl enol ethers would then be excellent substrates for further synthetic elaboration.

Using the phosphoramidate ligands **L***,[9] one can generate enantiomerically enriched zinc enolate **1** (ee > 99%). We made an unexpected observation when we added trimethyl silyl chloride (TMSCl) as an additive for the copper-catalyzed addition of diethylzinc to cyclohexenone.

Surprisingly, the O-silylated product **2** was obtained in 82% yield (ds 1:1) if TMSCl was added before the addition of cyclohexenone to a mixture of diethylzinc, Cu(OTf)$_2$, and the ligand **L*** in CH$_2$Cl$_2$. We believe that TMSCl slowed the rate of the conjugate addition reaction of diethylzinc[10] so that the formed zinc enolate intermediate **1** could react with the starting material. This is in contrast to the known acceleration effect of TMSCl for the conjugate addition of cuprates.[11] If, however, TMSCl was added after quantitative formation of the enolate **1**, the O-silylated product **3** was obtained in 83% yield and 99% ee. With TMSOTf, or TMSCl and NEt$_3$, the corresponding silyl enol ether **3** was formed in nearly quantitative yield in 1 h at room temperature (97%). To our knowledge, this is the first O-silylation of zinc enolates in an apolar solvent (CH$_2$Cl$_2$) in high yield.[12]

Scheme 2



The use of racemic **3** (R = Me) as a synthon in total synthesis underlines the synthetic importance of this reaction sequence to enantiomerically enriched silyl enol ethers.[13]

This finding considerably widens the synthetic scope of the tandem conjugate addition−trapping of electrophile. Among the many possible reactions of these silyl enol ethers,[8] we have performed the reactions to form the following interesting enantiomerically enriched synthons (Scheme 2).[14−17] It should be pointed out, that these transformations could not be accomplished directly from the zinc enolate.

The easy silylation of zinc enolates may also shed some light on the mechanism of the conjugate addition on acyclic enones **4**. If the zinc enolate intermediates **5** would be configurationally stable at the reaction temperature, we could find out whether the copper-catalyzed conjugate addition occurs on either the *s*-trans **4** or the *s*-cis **4** conformer or at both.[18] On the other hand, it would be interesting to know if the (*E*)- and (*Z*)-zinc enolates **5** ((*E*)- and (*Z*)-silyl enol ethers **6**) were formed with the same enantiomeric excess. Some of the results are reported in Table 1.

For the conjugate addition at −30 °C, enones **4** showed an (*E*)-selectivity[19] in the formation of zinc enolates **5** (entries 1−6). In diethyl ether, higher amounts of the (*E*)-isomer (*E*)-**6** were obtained (enties 3 and 6). In all cases, the ee of the silyl enol ether was determined, after desilylation, and found to be similar to that of the simple conjugate addition−hydrolysis process.[2c]

The question of the configurational stability of zinc enolate intermediate **5** was addressed as follows. The solvent of the

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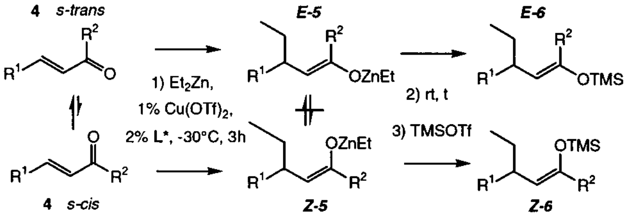
(19) This is in contrast to the (*Z*)-selectivity (96:4) observed when the ketone is reacted with TMSCl and triethylamine. See ref 20.

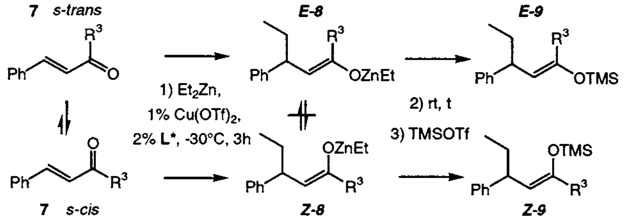
Table 1. Silylation of Acyclic Zinc Enolates



entry	R^1	R^2	solvent	t [h] at room temperature	(**E**)-**6**/(*Z*)-**6** (yield, ee^a)
1	Me	hex	CH_2Cl_2	1 or 24	57/43 (93%, **85% ee**)
2	Me	hex	toluene	1 or 24	76/24 (94%, **83% ee**)
3	Me	hex	Et_2O	1 or 24	95/5 (89%, **78% ee**)
4	pent	Me	CH_2Cl_2	1	84/16 (72%, **69% ee**)
5	pent	Me	toluene	1	92/8 (86%, **62% ee**)
6	pent	Me	Et_2O	1	94/6 (93%, **63% ee**)

^{a} ee after desilylation to the corresponding ketone.

Table 2. Silylation of Acyclic Zinc Enolates



entry	R^3	solvent	t [h]	(*E*)-**9**/(*Z*)-**9** (yield, ee^a)
1	Me	CH_2Cl_2	1	43/57 (54%, **76% ee**)
2	Me	toluene	1	30/70 (61%, **83% ee**)
3	Me	Et_2O	1	69/31 (64%, **84% ee**)
4	Ph	CH_2Cl_2	1	14/86 (92%, **69% ee**)
5	Ph	toluene	1	5/95 (93%, **61% ee**)
6	Ph	Et_2O	1	3/97 (82%, **59% ee**)

^{a} ee after desilylation to the corresponding ketone.

mixtures of zinc enolates (*E*)-**5**/(*Z*)-**5** = 57/43 (CH_2Cl_2, entry 1) and zinc enolates (*E*)-**5**/(*Z*)-**5** = 95/5 (Et_2O, entry 3) was changed to toluene with removal of CH_2Cl_2 or Et_2O. These mixtures, which were stirred for 2 h at room temperature in toluene, showed after silylation the same *E/Z* ratio. This suggests that the zinc enolate, once formed, is configurationally stable at room temperature.[20]

The (*E*)-selectivity in the formation of the zinc enolates could be explained by the preference of **4** for the *s*-trans conformer (75%).[21] Indeed, enones **7**, which are known to prefer the *s*-cis conformation (65%),[22] showed a (*Z*)-selectivity in the formation of zinc enolate **8** in apolar solvents (entries 1, 2, and 4−6, Table 2). Again, in diethyl ether, higher amounts of the (*E*)-isomer were formed (entry 3, Table 2).[23]

The results of entries 2 and 3 (Table 2) suggest that the enantiomeric excess of the silyl enol ethers **9** is not dependent on the *E/Z* ratio of zinc enolate intermediates **8**. This is a clear indication that the ratio of *s*-trans/*s*-cis conformers of enone **7** does not affect the enantiomeric excess of **9**. The silyl enol ethers were obtained in the same enantiomeric excess when they were formed from addition to both the *s*-trans and *s*-cis conformers. It was also possible to separate the enantiomers of (*Z*)-**9** (entry 4, Table 2, R^3 = Ph) on a chiral SFC column. (*Z*)-**9** had the same enantiomeric excess (69% ee) as the desilylated ketone of the mixture (*E*)-**9**/(*Z*)-**9** (69% ee). This proved again that the (*E*)- and (*Z*)-silyl enol ethers were obtained in the same enantiomeric excess.

In summary, we have shown that silyl enol ether could be obtained from enantiomerically enriched zinc enolates in apolar solvents in good to high yield, thus considerably enhancing the synthetic scope of the conjugate addition. We could also prove that zinc enolates are configurationally stable at room temperature. The *E/Z* ratio of the formed zinc enolate from acyclic α,*β*-unsaturated ketones is probably dependent on the ratio of conformers of the substrate in the reaction mixture. Further findings established that the obtained enantiomeric excess of silyl enol ethers is not dependent on the preferred conformation of the acyclic substrate (*s*-trans or *s*-cis).

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Supporting Information Available: Experimental details and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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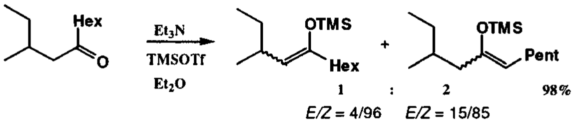
[20] When the ketone (3-methyl-5-undecanone) was treated with TMSCl and Et_3N, in Et_2O, a mixture of four enol ethers was obtained with a (*Z*)-selectivity for the minor regioisomers (*E*)-**5**/(*Z*)-**5** = 4/96.



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[23] This may be due to a change of the confomer ratio in the presence of ZnX_2 in Et_2O.