Double Stereocontrol in α-Alkylation of Chiral Lithium Dienolates Generated from (*E*)-α,β-Olefinic Amides and Esters

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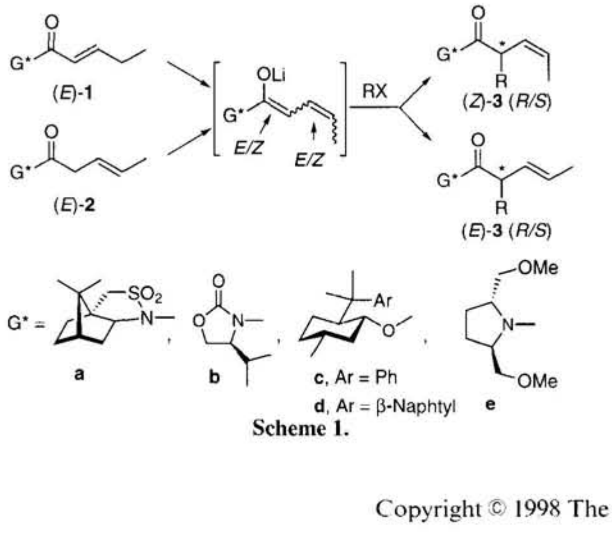
The methylation of the lithium dienolate generated from (*E*)-α,β-olefinic amide with Katsuki's chiral auxiliary affords the α-methylated β,γ-enamide in an exceptionally high Z-selectivity (99%) over the terminal olefinic bond along with 99% de at the α-chiral center. The origin of the high Z-selectivity is discussed.

In contrast to the eminent position of chiral enolate chemistry in asymmetric synthesis,[1] the chemistry of chiral dienolate derived from α,β- or β,γ-olefinic amides and esters remains unexplored. A key issue inherent in the chiral dienolate chemistry is how to control the geometry over the terminal olefin bond while gaining a high diastereofacial selectivity (% de) at the newly created α-chiral center (Scheme 1). The most crucial to solve this problem is the judicious choice of the chiral auxiliary (G*) and the position and geometry of the substrate olefin bond. Recently we have reported that the reaction of the lithium dienolates derived from (*E*)-**1a** and -**1b** with allyl bromide provides a moderate Z-selectivity (78 and 86%, respectively) to give the corresponding α-allylated product (*Z*)-**3** (R=allyl) with 99% and 49% de, respectively, while similar reactions of the (*E*)-β,γ-olefinic counterparts (*E*)-**2a**,**b** proceed with complete retention of the *E*-geometry to afford (*E*)-**3a**,**b** as the sole product with comparable % de's.[2] Since the selective formation of (*Z*)-**3** from (*E*)-**1** is of both synthetic value and mechanistic interest, we have now systematically studied the reactions of chiral lithium dienolates generated from (*E*)-**1** with different G* groups (**a**-**e**)[3] with methyl iodide. Disclosed herein is that among the chiral auxiliaries examined, the use of the amide-type auxiliary **e** provides the higher Z-selectivity together with an extremely high % de (99%).

The dienolate reactions were conducted at -78 ℃ in a mixture of THF and HMPA (3 equiv. to the base) by treatment of (*E*)-**1** with $MN(SiMe_3)_2$ (MHMDS, M=Li, Na, K) followed by addition of methyl iodide (3-5 equiv.) to give a diastereoisomeric mixture of (*Z*)- and (*E*)-**3** ($R=CH_3$).[4,5] Table 1 summarizes the stereochemical outcomes which reveal significant trends. (1) As expected, the use of the imide-type auxiliaries **a** and **b** provides a moderate Z-selectivity, while the former gives a much higher % de than the latter. (2) By contrast, the use of the 8-arylmenthol-derived ester-type auxiliaries **c** and **d** affords an extremely high Z-selectivity but with a relatively low % de. (3) In any cases, the effect of counter metals was small on the stereoselectivities concerned. (4) Most significantly, the amide-type auxiliary **e** (with C_2 symmetry) provided a remarkably high Z-selectivity together with an extremely high % de. Thus, a highly Z- and diastereoface-selective generation of chiral lithium dienolates from (*E*)-α,β-olefinic amides is now realized.[6]



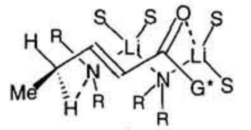
Scheme 1.

Table 1. Reaction of the chiral dienolates of (*E*)-**1** with methyl iodide[a]

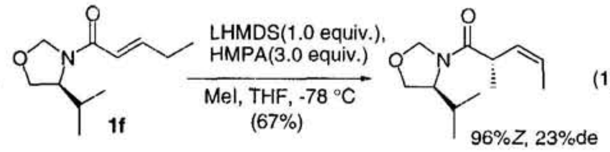
Subst.	Base	Yield (%)	(*E*)-**3** : (*Z*)-**3**	%*de*
1a	LHMDS	95	26 : 74	>99
	KHMDS	90	29 : 71	>99
	NHMDS	90	28 : 72	>99
1b	LHMDS	43	13 : 87	88
1c	LHMDS	71	6 : 94	44
	NHMDS	70	3 : 97	48
	KHMDS[b]	70	<1 : >99	72
1d	LHMDS	51	1 : 99	55
	KHMDS[b]	27	1 : 99	80
1e	LHMDS[c]	69	1 : 99	99
	KHMDS	71	<1 : >99	93

[a] Unless otherwise noted, the reactions were run at -78 °C in THF using a 1.0 equiv. of MHMDS and 3.0 equiv. of HMPA. [b]Carried out in toluene. [c]1.5eq. of LHMDS used.

These stereochemical trends raises the mechanistic question why the amide- and ester-type auxiliaries provides a significantly higher (*Z*)-selectivity than the imide-type one, aside from the observed variation in % de. This question is of particular interest because the mechanistic origin for the extremely high (*E*- to *Z*-)-selectivity widely observed in the lithium dienolate formation from *achiral* α,β-olefinic ester is the current subject of controversy.[7] While several explanations have been advanced, the cyclic transition state model recently proposed by Galatsis *et al.* is most informative,[7d] thereby permitting to visualize the high (*E*- to *Z*-)-selectivity observed with (*E*)-**1c**-**e** by the transition state **A** in which the lithium amide as the dimer form[8] interacts with both the amide- or ester-carbonyl and one of γ-hydrogens. Based on this rational, the relatively low Z-selectivity observed with **1a**, **b** might be explained as a result of the decrease in predominance of TS **A** through the partial coordination of the sulfone in **1a** or the carbonyl in **1b** toward the lithium amide. In other word, the removal of the carbonyl in the imide auxiliary **b** for instance, might leads to a higher Z selectivity. Indeed, the use of amide **1f**[3] as substrate was found to afford a significantly higher Z-selectivity (96%), albeit in a much lower % de (23%) (eq 1). Of course, more detailed studies are needed to verify this argument.



A



(1)

In summary, we have developed a highly stereoselective method for generating chiral lithium dienolates which employs the easily accessible (*E*)-α,β-olefinic amide with Katsuki's auxiliary as substrste to afford, after methylation, the α-methylated β,γ-olefinic amide in an exceptionally high Z-selectivity over the terminal olefin bond along with an extremely high % de. Synthetic application of the present method is in progress.

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References and Notes

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3 (*E*)-**1a-f** were prepared from (*E*)-2-pentenoyl chloride according to the reported procedures. **1a**: W. Oppolzer, J. Blagg, I. Rodriguez, and E. Walther, *J. Am. Chem. Soc.*, **112**, 2767 (1990). **1b**: J. R. Gage and D. A. Evans, *Org. Synth. Coll.*, **VIII**, 339 (1993). **1c**: E. J. Corey and H. E. Ensley, *J. Am. Chem. Soc.*, **97**, 6908 (1975). **1d**: J. d'Angelo and J. Maddaluno, *J. Am. Chem. Soc.*, **108**, 8112 (1986). **1e**: Y. Kawanami, Y. Ito, T. Kitagawa, Y. Taniguchi, T. Katsuki, and M. Yamaguchi, *Tetrahedron Lett.*, **25**, 857 (1984). **1f**: D. A. Evans and J. M. Takacs, *Tetrahedron Lett.*, **21**, 4233 (1980).

4 The geometric and diastereomeric purity of **3a-f** were determined by ^{1}H NMR analysis and capillary GC analysis. Data for selected products are as follows. **3a**: the δ value (ppm) of allylic methyl, 1.66 (d, *J*=5.1 Hz) for (Z, *S*)-isomer, 1.67 (d, *J*=4.8 Hz) for (Z, *R*)-isomer. **3b**: GC (PEG 20M, 50 m, 150 ℃) t_R=43.4 min for (Z, *S*)-isomer, t_R=41.4 min for (Z, *R*)-isomer, t_R=45.4 min for (*E*, *S*)-isomer, t_R=44.0 min for (*E*, *R*)-isomer. **3c**: GC (OV-1, 50 m, 200 ℃) t_R=23.7 min for (Z, *R*)-isomer, t_R=21.5 min for (Z, *S*)-isomer, t_R=22.6 min for (*E*, *R*)-isomer. **3e**: GC (CP-chiral-DEX CB, 25 m, 140 ℃) t_R=81.1 min for (Z, *S*)-isomer, t_R=64.9 min for (Z, *R*)-isomer, t_R=74.9 min for (*E*, *S*)-isomer, t_R=66.4 min for (*E*, *R*)-isomer. **3f**: GC (CP-chiral-DEX CB, 25 m, 155 ℃) t_R=21.3 min for (Z, *R*)-isomer, t_R=23.0 min for (*Z*, *S*)-isomer, t_R=22.3 min for (*E*, *R*)-isomer, t_R=20.6 min for (*E*, *S*)-isomer.

5 The stereochemistry at the α-position was assigned as (*S*) for **3a**, **b** and **3e**, (*R*) for **3c** and **3d**, based on the our allylation reaction (ref. 2) and reported results (ref. 3).

6 Note that, the allylation reaction also proceeds in a highly stereoselective manner: A reaction of the dienolate derived from (*E*)-**1e** with allyl bromide gave the (Z)-**3** (R=allyl) in 99% de, 98% Z.

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