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1,3-Rearrangement of ketene-*N*,*O*-acetals

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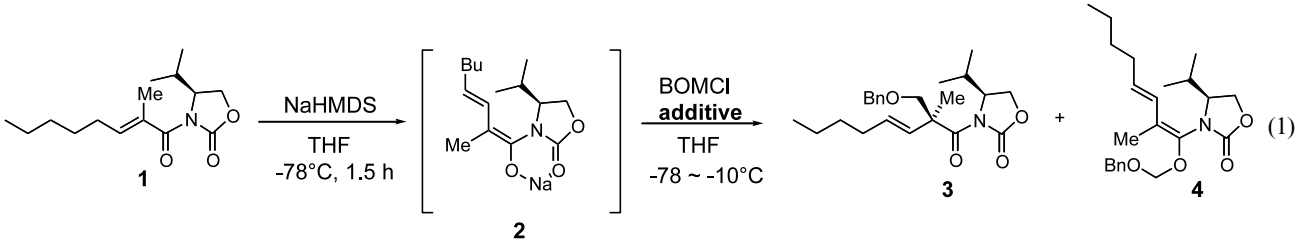
Abstract—Ketene *N*,*O*-acetals were prepared stereoselectively and submitted to a Lewis acid-mediated 1,3-rearrangement to afford *C*-alkylated products. The reactions proceeded in a stereoselective manner to construct a chiral quaternary carbon in high selectivity. The stereochemistry of the quaternary center was found to be opposite to that obtained by an anionic direct dienolate alkylation.

Evans alkylation is an excellent method to construct a chiral tertiary carbon and has been widely utilized in the synthesis of a number of natural products.[1,2] However, there had been no example of stereochemical control of a chiral quaternary carbon by Evans alkylation using Li- or NaHMDS and alkyl halide. During the course of our total synthesis of madindoline A, we developed a novel method for the stereoselective construction of a chiral quaternary carbon via a chiral dienolate **2** (Eq. (1)).[3] Thus, the γ-proton of α,β-unsaturated imide **1** was deprotonated with NaHMDS, and the resulting dienolate anion **2** was reacted with benzyloxymethyl chloride at the α-position with high regio- and stereoselectivities.

In this reaction, one of the by-products proved to be a ketene-*N*,*O*-acetal **4** which was isolated in 30% yield as a single isomer by *O*-alkylation of the dienolate anion **2**. The same ketene-*N*,*O*-acetal **4** was exclusively obtained in 92% yield by addition of HMPA (Table 1). The competing *O*-alkylation in Evans' chiral auxiliary methodology had seldom been observed,[4] and there has been no report concerning such a highly stereoselective and high-yielding *O*-alkylation.

With ketene *N*,*O*-acetal **4** in quantity, we became interested in the possibility of a rearrangement of ketene-*N*,*O*-acetal **4** to α-alkylated imide **3** (Scheme 1). We expected that a Lewis acid might coordinate to the

Table 1. Construction of ketene-*N*,*O*-acetal



Entry	Additive	Yield of **3** (dr)[a]	Yield of **4** (%)
1	–	65% (11:1)	30
2	HMPA	Trace	92

[a] dr = diastereomeric ratio. The ratio was determined by NMR.

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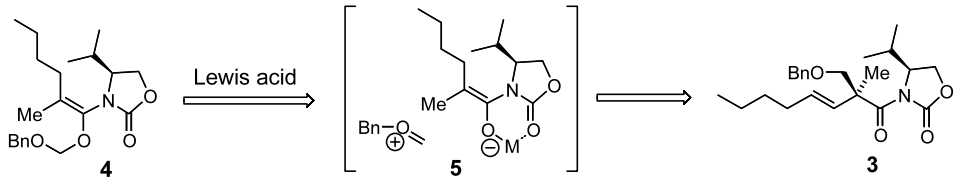


Scheme 1. Expected 1,3-rearrangement of ketene *N*,*O*-acetal.

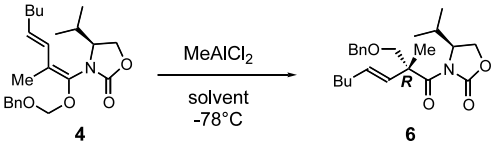
acetal oxygen close to the oxazolidone because the carbonyl oxygen would initially coordinate to the Lewis acid, and that cleavage of the C–O bond might occur to generate a metal enolate and an oxonium cation species. The resulting ion pair **5** might undergo a recombination at the α-position to afford the alkylated imide **3**. Since such a metal enolate would form a tight six-membered chelation structure, diastereoselectivity of a rearrangement was expected to be higher than that of a direct alkylation of Na dienolate **2**. To our knowledge, such a Lewis acid-promoted 1,3-rearrangement of ketene *N*,*O*-acetal is not yet known.[5]

When **4** was treated with methylaluminum dichloride[6] in CH_2Cl_2 at −78°C, rearrangement product **6** was isolated in 28% with diastereoselectivity of 14:1 (Table 2). Surprisingly, the ^{1}H NMR spectrum of the major isomer was found to be identical to that of the minor isomer obtained by the anionic dienolate reaction (Table 3).[7] Table 2 summarizes a solvent effect of the $MeAlCl_2$-mediated rearrangement, and toluene was found to be the most effective in terms of yield and selectivity. Relatively low to moderate yields were due to the formation of γ-alkylated products (18 ~ 37%).[8]

On the basis of these results, various ketene *N*,*O*-acetals were prepared and were treated with methylaluminum dichloride in toluene at −78°C. As shown in Table 4, yields of rearranged products were higher with alkyl substituted dienolate **4** and **7** than that of *exo*-dienolate **8**. The oxazolidine-2-ones derived from L-isoleucine gave comparable to better results than L-valine derivatives.

It is quite interesting to find that the opposite stereochemical course was observed by carrying out the reaction under acidic or basic conditions. Although we do not have any supporting evidence at present, we would like to propose the following mechanism (Scheme 2). Stereoselective formation of **6** might be explained by considering the intermediate ion pair **12** where the oxazolidone carbonyl oxygen coordinates to the other molecule of methylaluminum dichloride as depicted in Figure 1. The oxonium cation might recombine from

Table 2. 1,3-Arrangement of ketene *N*,*O*-acetal



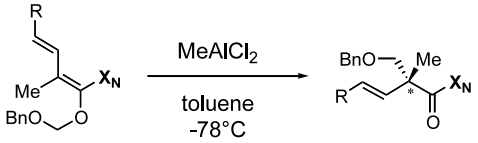
Entry	Solvent	Yield (dr)[a]
1	Hexane	27% (3:1)
2	CH_2Cl_2	28% (14:1)
3	$ClCH_2CH_2Cl$	37% (13:1)
4	Toluene	54% (>99:1)

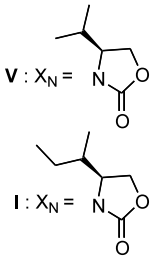
[a] dr = diastereomeric ratio. The diastereo ratio was determined by ^{1}H NMR.[6]

Table 3. Comparison of **3** and **6**

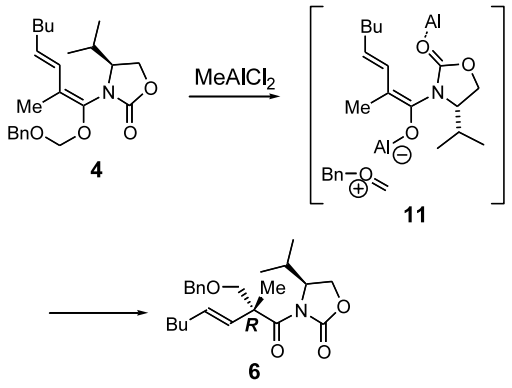
	3	**6**
Optical rotation	$[\alpha]_D^{26}$ +43.7 (*c* 1.03, $CHCl_3$)	$[\alpha]_D^{23}$ +72.9 (*c* 1.03, $CHCl_3$)
^{1}H NMR (δ)	*Me* 1.49 (s, 3H) BnO*CH*$_2$ 3.46 (d, 1H, *J* = 8.8 Hz) 4.29 (d, 1H, *J* = 8.8 Hz)	*Me* 1.54 (s, 3H) BnO*CH*$_2$ 3.44 (d, 1H, *J* = 8.8 Hz) 4.07 (d, 1H, *J* = 8.8 Hz)

Table 4. 1,3-Rearrangement of ketene *N*,*O*-acetal





Entry	Substrate	Product	Yield (dr)
1	**8V**	**10**	32% (20:1)
2	**8I**		36% (20:1)
3	**7V**	**9**	67% (33:1)
4	**7I**		57% (42:1)
5	**4V**	**6**	54% (>99:1)
6	**4I**		55% (>99:1)



Scheme 2. Proposed mechanism.

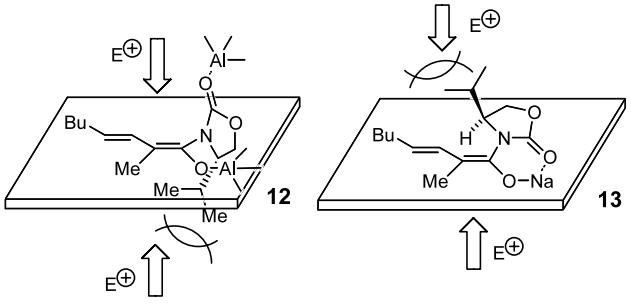


Figure 1.

the upper face (opposite to the isopropyl group) affording **6**. The transition state **13** of the direct alkylation of sodium dienolate **2** is also shown in Figure 1. These transition states, **12** and **13**, would explain the opposite stereochemical course of the reactions.

Although the present methodology is limited to the rearrangement of an alkoxymethyl group, we were able to control the stereochemistry of a chiral quaternary center by the choice of direct α-alkylation or stepwise alkylation via ketene *N*,*O*-acetal.

In a similar manner, the alkylation of α,α-disubstituted imide **14** was also examined. Under Evans alkylation conditions, the *C*-alkylation product **15** was obtained in very low yield (Table 5, entry 1). Addition of HMPA afforded *O*-alkylation product **16** exclusively (entry 2), and the resulting ketene *N*,*O*-acetal was submitted to 1,3-rearrangement to provide *C*-alkylation product **15** in good yield (Eq. (2)). Although the quaternary center of **15** is not chiral, Eq. (2) suggests the utility of the two-step transformation for construction of a quaternary carbon.

The reaction conditions presented here were not yet fully optimized, and studies on the scope and limitation of the rearrangement are now in progress.

The general experimental procedure (Table 4, entry 5) is as follows: To a solution of ketene-*N*,*O*-acetal **4V** (114 mg, 0.29 mmol) in toluene was dropwise added a solution of $MeAlCl_2$ in hexane (1.0 M, 0.59 ml, 0.59 mmol) at −78°C under an Ar atmosphere. After stirring for 1 day at the same temperature, the reaction mixture was quenched by addition of pyridine and then saturated $NaHCO_3$ aq. The resulting mixture was extracted with chloroform, and the organic layer was washed with brine and dried over Na_2SO_4. Evaporation and concentration gave a crude oil which was purified by silica gel column chromatography (hexane–AcOEt = 10:1) to afford colorless oil **6** (61.6 mg, 54%).

Acknowledgements

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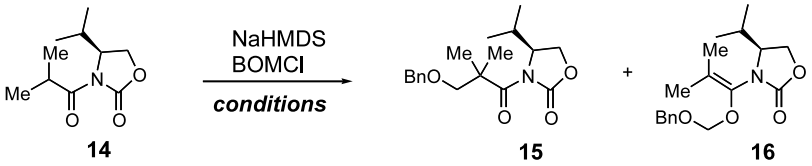
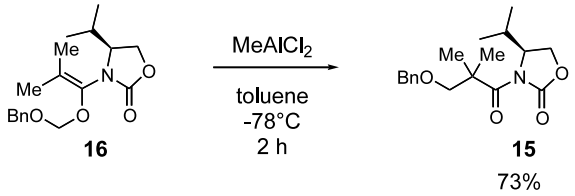
Table 5. Alkylation of α,α-disubstituted imide



Entry	Additive	Temperature (°C)	**15** (%)	**16** (%)
1	–	−78 ~ 0	9	43
2	HMPA	−78	Trace	70



(2)

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5. For [3,3]-sigmatropic rearrangement of *N*-allyl-ketene-*N*,*O*-acetal: (a) Huche, M. *Tetrahedron Lett*. **1976**, *17*, 2607–2610; (b) Corbier, J.; Cresson, P.; Jelenc, P. *C. R. Acad. Sci., Ser. C* **1970**, *270*, 1890–1893.
6. Other Lewis acids such as $BF_3{\cdot}OEt_2$, Et_2AlCl, $TiCl_4$, or $AlCl_3$ were not successful.
7. **3**: $[\alpha]_D^{26}$ +43.7° (*c* 1.03, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (d, 3H, $J=7.1$ Hz), 0.86 (t, 3H, $J=7.1$ Hz), 0.87 (d, 3H, $J=7.1$ Hz), 1.24–1.34 (m, 4H), 1.49 (s, 3H), 1.99 (q, 2H, $J=6.8$ Hz), 2.32 (m, 1H), 3.46 (d, 1H, $J=8.8$ Hz), 4.15 (dd, 1H, $J=2.9$, 9.0 Hz), 4.21 (t, 1H, $J=9.0$ Hz), 4.29 (d, 1H, $J=8.8$ Hz), 4.47 (d, 1H, $J=12.2$ Hz), 4.50 (dd, 1H, $J=2.9$, 3.7 Hz), 4.58 (d, 1H, $J=12.2$ Hz), 5.37 (td, 1H, $J=6.8$, 16.1 Hz), 5.75 (td, 1H, $J=1.5$, 16.1 Hz), 7.28–7.34 (m, 5H). **6**: $[\alpha]_D^{23}$ +72.9° (*c* 1.03, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, 3H, $J=7.0$ Hz), 0.86 (t, 3H, $J=7.0$ Hz), 0.88 (d, 3H, $J=7.0$ Hz), 1.22–1.32 (m, 4H), 1.54 (s, 3H), 2.00 (q, 2H, $J=6.7$ Hz), 2.28–2.38 (m, 1H), 3.44 (d, 1H, $J=8.8$ Hz), 4.07 (d, 1H, $J=8.8$ Hz), 4.13 (dd, 1H, $J=3.4$, 8.9 Hz), 4.16 (t, 1H, $J=8.9$ Hz), 4.45–4.49 (m, 1H), 4.52 (s, 2H), 5.38 (td, 1H, $J=6.7$, 15.9 Hz), 5.75 (d, 1H, $J=15.9$ Hz), 7.26–7.32 (m, 5H).
8. Results concerning a γ-alkylation will be reported in due course.