Promotion of Asymmetric Aza-Claisen Rearrangement of *N*-Allylic Carboxamides Using Excess Base

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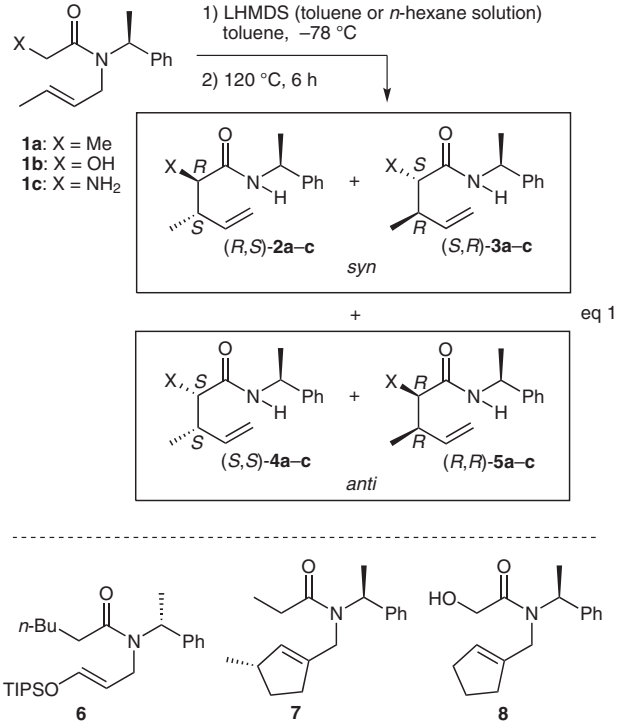
Abstract: The aza-Claisen rearrangement of the enolate of *N*-(*Z*)-crotyl-*N*-(*S*)-phenethylpropanamide did not proceed in the presence of 1.5 equivalents of LHMDS as a base. However, the use of a large excess of base (10 equiv) promoted the reaction to give *N*-(*S*)-phenethyl-*anti*-2,3-dimethylpent-4-enamide with good stereoselectivities (*anti*/*syn* = ca. 95:5). An excess of base stabilized the amide enolates and prevented the decomposition to the ketene to prompt the rearrangement of various carboxamides with good stereoselectivity. This reaction provided a new method for the construction of asymmetric quaternary carbon centers.

Key words: aza-Claisen rearrangement, amide enolate, asymmetric reaction

The aza-Claisen rearrangement is a powerful tool in synthetic organic chemistry and has attracted much attention.[1] Previously, we reported that the asymmetric aza-Claisen rearrangement of the enolates of carboxamides **1** provided 2,3-*syn* stereochemistry with excellent stereoselectivities (*syn*/*anti* 99:1, **2**/**3** = ca. 89:11, Scheme 1).

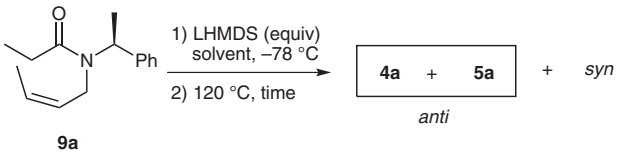
This rearrangement was adaptable to carboxamides with various substituents (X = Me, OH, or NH_2 in Scheme 1), and the major rearrangement products, 2,3-disubstituted pent-4-enamides **2**,[2] could be used efficiently as synthetic precursors for (–)-verrucarinolactone[2b] and D-allo-isoleucine.[2b] This methodology was applied to the reactions of carboxamides **6**–**8** to synthesize (–)-antimycin A_{3b},[2d,e] (–)-isoiridomyrmecin,[2f] (+)-a-skytanthine,[2g] and (+)-brefeldin C.[2h]

Thus, the aza-Claisen rearrangement has potential for broad use in the stereocontrolled construction of naturally occurring carbon skeletons with 2,3-*syn* stereochemistry. However, using the same conditions for the transformation of **1a**, *N*-(*Z*)-crotyl propanamide **9a** did not undergo this rearrangement to afford the expected product with 2,3-*anti* stereochemistry. To overcome this problem, we examined the reaction under various conditions (solvent, temperature, additives, and amount of base), and found that the use of excess base promoted the rearrangement quite satisfactorily. Herein, we describe the results.



Scheme 1 Aza-Claisen rearrangement of carboxamides

Table 1 Optimization of the Reaction Conditions for the Aza-Claisen Rearrangement of **9a**



Entry	LHMDS (equiv)	Solvent	Time (h)	Yield (%)	*anti*/*syn*[a] (**4a**/**5a**)[b]
1	1.5	toluene–*n*-hexane or toluene	6	–[c]	–
2	3.0	toluene	6	38	74:26 (10:90)
3	5.0	toluene	6	42	94:6 (11:89)
4	5.0	toluene	15	58	93:7 (11:89)
5	10	toluene	15	63	95:5 (11:89)

[a] The ratio of (**4a** + **5a**)/(**2a** + **3a**).
[b] The ratio of *anti* isomers (**4a**/**5a**) is shown.
[c] Complex mixture.

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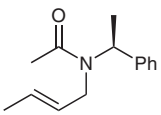
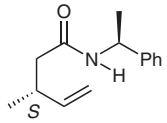
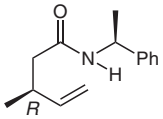
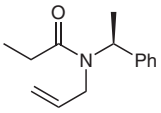
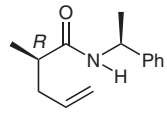
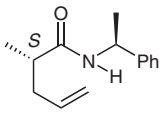
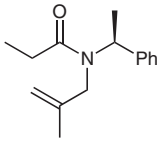
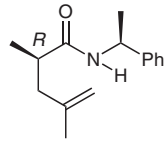
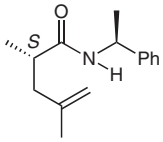
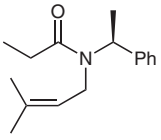
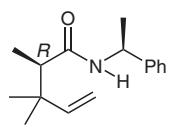
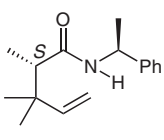
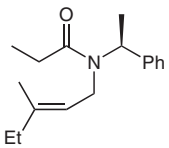
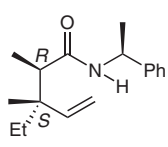
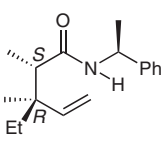
The rearrangement of the enolate of **1a** took place in the presence of 1.5 equivalents of LHMDS in toluene at 120 °C in 85% yield with excellent stereoselectivities (Scheme 1). In contrast, the reaction of **9a** afforded messy products with no desired rearrangement products and the starting material **9a** under the same conditions (Table 1, entry 1). However, the use of excess LHMDS led to some improvement in the yields and/or stereoselectivities. When three equivalents of LHMDS were used, 38% of rearranged products **2a**–**5a** were obtained with moderate stereoselectivities (*anti*/*syn* = ca. 74:26, **5a**/**4a** = 90:10,[3] Table 1, entry 2). The yield of the rearranged products increased to 63% by using a greater excess of base and by extending the reaction periods (Table 1, entries 3–5). Furthermore, the *anti* vs. *syn* selectivity was also increased, reaching a ratio of 95:5 in the presence of ten equivalents of LHMDS.[4] This good internal asymmetric induction (*anti* selectivity) was dependent on the olefin geometry of **9a**, and the high relative asymmetric induction (**5a** vs. **4a**) was due to a chiral auxiliary, the *S*-phenethyl group, on the nitrogen atom. Thus, this reaction was very useful to construct 2,3-*anti* stereochemistry.

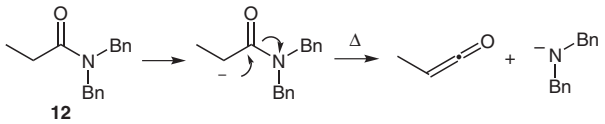
On the basis of this finding, we then examined the rearrangement of carboxamides **9b**–**f**,[5] because the reaction with 1.5 equivalents of LHMDS also gave messy products with a small amount of the desired rearrangement products and none of the starting materials **9b**–**f**. Actually, although the reaction of **9b** with 1.5 equivalents of LHMDS gave a poor yield again (Table 2, entry 1), increasing the amount of base (5 equiv) and prolonging the reaction periods (48 h) improved the yield (89%) and the stereoselectivity (3*S*/3*R* = 88:12,[8] Table 2, entry 2). In the cases of **9c**–**f**, excess base also provided good results with high yields and high stereoselectivities[10] (Table 2, entries 3, 5, 7, 9 vs. entries 4, 6, 8, 10). The level of the stereoselectivity (about 90:10) was quite similar to those of the reactions of **1** and **9a**. Furthermore, the *S*-phenethyl group controlled the absolute configurations at the C-2 and C-3 positions. The reaction of **9f** indicated that this rearrangement reaction could be applied to the construction of asymmetric quaternary carbon centers with good selectivity.

Table 2 Scope and Limitation of the Aza-Claisen Rearrangement of **9b**–**f**

Entry	Substrate	LHMDS (equiv)	Temp (°C)	Period (h)	Major product	Minor product	Yield (%)	Selectivity (**10**/**11**)
1		1.5	120	48			18	75:12
2		5.0	120	48			89	88:12
	9b				**10b**	**11b**		
3		1.5	120	24			<30[a]	91:9
4		5.0	120	24			94	91:9
	9c				**10c**	**11c**		
5		1.5	120	24			–[b]	–[c]
6		5.0	100[d]	24			84	87:13
	9d				**10d**	**11d**		
7		1.5	120	12			–[b]	–[c]
8		5.0	120	12			77	89:11
	9e				**10e**	**11e**		
9		1.5	120	12			–[b]	–[c]
10		5.0	120	12			98	88:12[e]
	9f				**10f**	**11f**		

[a] Difficult to purify.
[b] Complex mixture.
[c] Not determined.
[d] The reaction at 120 °C gave a lower yield (57%).
[e] 2*R*,3*R* and 2*S*,3*S* isomers were not detected.

When the reaction gave poor results, we suspected that the decomposition of the enolates of the carboxamides via the ketene[12] was one of the undesired reactions.[13] However, as the reaction of **9** with 1.5 equivalents of LHMDS gave a complex mixture of products, no direct evidence for this decomposition pathway could be found. So, *N*,*N*-dibenzyl propanamide (**12**) was employed as a model compound for studies of the decomposition pathways of the amide enolate. First, *N*,*N*-dibenzyl propanamide (**12**) was treated with 1.5 equivalents of LHMDS at 80 °C for one hour, giving 83% of recovered **12**. However, when the reaction was conducted at 120 °C for one hour with 1.5 equivalents of LHMDS, only 46% of **12** was recovered along with some dibenzylamine. In contrast, use of five equivalents of LHMDS (120 °C, 1 h) increased the recovery yield of **12** to 86%. These findings suggested the following: 1) decompositions occurred at around 120 °C, the temperature at which the aza-Claisen rearrangement took place, and 2) excess base stabilized the amide enolates and prevented the decomposition to ketene and other undesirable side reactions (Scheme 2), although the reason was unclear.



Scheme 2 Decomposition of the lithium enolate of **12**

Based on Ireland's investigation[14] of Claisen rearrangement of silyl enol ethers derived from esters, we propose an explanation for the results described in this paper. Ireland reported that the alkyl substituent on the 1,5-diene system affected the reaction rate, with the reaction rate of the less substituted 1,5-diene being considerably slower. In our investigation, the reaction of **9b**,**c** required a longer reaction period than that of **1a** did. In the case of **9a** and **9d**–**f**, it seems feasible that the rate of the reaction was slowed by steric repulsion caused by the pseudo-axial substituents on the allylic olefin in the six-membered chairlike transition state. In this situation, we presumed that the decomposition of the lithium enolates of **9a**–**f** to the respective ketenes and other byproducts became the predominant reaction. However, as mentioned above, the addition of excess base prevented the decomposition and promoted the desired rearrangement.

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References and Notes

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(2) (a) Tsunoda, T.; Sakai, M.; Sasaki, O.; Sako, Y.; Hondo, Y.; Itô, S. *Tetrahedron Lett.* **1992**, *33*, 1651. (b) Tsunoda, T.; Tatsuki, S.; Shiraishi, Y.; Akasaka, M.; Itô, S. *Tetrahedron Lett.* **1993**, *34*, 3297. (c) Itô, S.; Tsunoda, T. *Pure Appl. Chem.* **1994**, *66*, 2071. (d) Tsunoda, T.; Nishii, T.; Yoshizuka, M.; Yamasaki, C.; Suzuki, T.; Itô, S. *Tetrahedron Lett.* **2000**, *41*, 7667. (e) Nishii, T.; Suzuki, S.; Yoshida, K.; Arakaki, K.; Tsunoda, T. *Tetrahedron Lett.* **2003**, *44*, 7829. (f) Tsunoda, T.; Tatsuki, S.; Kataoka, K.; Itô, S. *Chem. Lett.* **1994**, 543. (g) Tsunoda, T.; Ozaki, F.; Shirakata, N.; Tamaoka, Y.; Yamamoto, H.; Itô, S. *Tetrahedron Lett.* **1996**, *37*, 2463. (h) Inai, M.; Nishii, T.; Mukoujima, S.; Esumi, T.; Kaku, H.; Tominaga, K.; Abe, H.; Horikawa, M.; Tsunoda, T. *Synlett* **2011**, 1459.

(3) The stereochemistry of the products was determined by the comparison with the samples, which had been obtained by the rearrangement of **1a**; see ref. 2a.

(4) It was suspected that the basicity of LHMDS was not sufficient to deprotonate the amides, and stronger bases must be required. However, the reaction with LDA gave lower yields and stereoselectivities; see ref. 2a. Furthermore, the reaction of **9a** utilizing *s*-BuLi (1.5 equiv) gave the same results as with LHMDS (1.5 equiv).

(5) **Typical Procedure for the Aza-Claisen Rearrangement**
To a solution of LHMDS (1.0 M in toluene, 5.0 mL) in toluene (3 mL) was added a toluene solution (3 mL) of carboxamide **9d** (231 mg, 1.0 mmol) at –78 °C under an argon atmosphere in a pressure tube.[6] After 30 min with stirring, the reaction mixture was allowed to warm to r.t. and was sealed. After heating of the sealed solution at 120 °C for 24 h, a sat. aq $NaHCO_3$ (24 mL) was added, and the mixture was extracted with CH_2Cl_2 (30 mL), dried (Na_2SO_4), and evaporated.[7] The residual mixture was purified by SiO_2 column chromatography (*n*-hexane–EtOAc = 3:1) to give 156 mg (68%) of **11d** and 39 mg (17%) of a mixture of **10d** and **11d** as colorless needles, respectively.
Compound **10d**: mp 84.5–85.5 °C (*n*-hexane–EtOAc). $[\alpha]_D^{21}$ –94.7 (*c* 0.65, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.20 (m, 5 H), 5.65 (br d, *J* = 7.2 Hz, 1 H), 5.13 (quin, *J* = 7.6 Hz, 1 H), 4.76 (m, 1 H), 4.73 (m, 1 H), 2.45–2.30 (m, 2 H), 2.09 (ddd, *J* = 12.5, 5.2, 0.8 Hz, 1 H), 1.72 (dd, *J* = 1.2, 0.8 Hz, 3 H), 1.47 (d, *J* = 6.8 Hz, 3 H), 1.11 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.9, 143.24, 143.21, 128.6, 127.3, 126.2, 112.4, 48.5, 42.2, 39.6, 22.4, 21.6, 17.6. IR (ATR): 3269, 2970, 1637, 1542, 1450 cm^{-1}. MS (CI): *m/z* = 232 $[M + H]^+$ (base peak), 231 $[M]^+$, 128, 105. HRMS (CI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{22}ON$: 232.1701; found: 232.1701.
Compound **11d**: mp 54.2–55.5 °C (*n*-hexane–EtOAc); $[\alpha]_D^{21}$ –84.6 (*c* 0.43, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.20 (m, 5 H), 5.66 (br d, *J* = 6.8 Hz, 1 H), 5.13 (quin, *J* = 7.2 Hz, 1 H), 4.74 (br s, 1 H), 4.68 (br s, 1 H), 2.45–2.30 (m, 2 H), 2.07 (dd, *J* = 17.2, 10.8 Hz, 1 H), 1.67 (s, 3 H), 1.48 (d, *J* = 6.8 Hz, 3 H), 1.14 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.0, 143.2, 143.1, 128.6, 127.3, 126.2, 112.4, 48.4, 42.1, 39.6, 22.3, 21.5, 17.6. IR (ATR): 3285, 2970, 1639, 1538, 1450 cm^{-1}. MS (CI): *m/z* = 232 $[M + H]^+$ (base peak), 231 $[M]^+$, 128, 105. HRMS (CI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{22}ON$: 232.1701; found: 232.1701.

(6) An air-tight cylinder for high-pressure experiments is available at Alltech Associates, Inc.

(7) At this point, the diastereomeric ratio was determined by GLC or LC.

(8) **Determination of the Stereochemistry of the Products** A 88:12 mixture of **10b** and **11b** was subjected to hydroboration(disiamylborane), oxidation (aq NaOH–H_2O_2), and heating with PTSA to give 3-methylvalerolactone whose specific rotation {$[\alpha]_D^{23}$ –19.8 (*c* 4.5, $CHCl_3$)} was compared with its 3*R*-isomer {$[\alpha]_D^{25}$ +27.6 (*c* 5.6, $CHCl_3$)}.[9] Thus, the major product **10b** was determined to have the *S* configuration at the C-3 position.

(9) Konoike, T.; Araki, Y. *J. Org. Chem.* **1994**, *59*, 7849.

(10) **Determination of the Stereochemistry of the Products** A: A 91:9 mixture of **10c** and **11c** was subjected to hydroboration(disiamylborane), oxidation (aq NaOH–H_2O_2), and heating with PTSA to give 2-methylvalerolactone whose specific rotation {$[\alpha]_D^{22}$ –56.3 (*c* 2.48, MeOH)} was compared with its 2*S*-isomer {$[\alpha]_D^{25}$ +67.3 (*c* 6.59, $CHCl_3$)}.[11] Thus, the major product **10c** was determined to have the *R* configuration at the C-2 position. B: The stereochemistry of the major product **10d** was confirmed by X-ray analysis as shown in Figure 1. Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 832610. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk]. C: The stereochemistries of the major products **10e** and **10f** were estimated empirically.

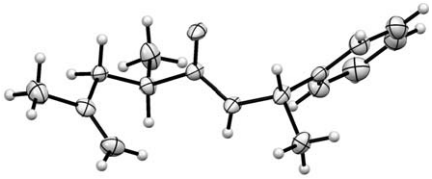

Figure 1 The crystallographic analysis of **10d**

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(12) It was reported that enolates of esters decomposed completely to ketene at 0 °C; see ref. 11.

(13) Although it was suspected that there were several decomposition pathways, we could not isolate any meaningful compounds, not even Claisen-type condensation products, from the reaction mixtures.

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