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Highly Stereoselective Allylation to Chiral α-Keto Amides Derived from (*S*)-Indoline-2-carboxylic Acid. Asymmetric Synthesis of Functionalized Tertiary Homoallyl Alcohols.

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Abstract: The diastereoselective addition of allylsilane and - stannane in the presence of Lewis acids to new chiral α-keto amides derived from (*S*)-indoline-2-carboxylic acid resulted in optically active tertiary homoallyl alcohols with extremely high diastereoselectivities (up to dr ≥ 99 : 1).

The asymmetric addition of allylmetal reagents to carbonyl groups has developed into a useful and powerful method in organic synthesis.[1] Lewis acid promoted allylation of carbonyl compounds with allyltrimethylsilane has served as a versatile tool for the preparation of homoallyl alcohols,[2] and the several leading works on the diastereoselective addition of allylmetallics to chiral α-keto carboxylic acid derivatives have been intensively investigated.[3-6] Fixing to one of the possible conformers at the transition state may be essential to cause the high diastereoselectivity.[7] With regard to the diastereoselectivity in the nucleophilic addition of organometallics to α-keto amides of pyrrolidine derivatives, the chiral *trans*-2,5-disubstituted pyrrolidines[5] afforded higher diastereofacial selectivity than 2-monosubstituted pyrrolidines.[4,8] On the basis of these facts, we expected that the chiral pyrrolidine containing a benzene ring at its opposite side to the 2-position might play an important role and affect the diastereofacial selectivity in transition state; the steric effect of the benzene ring of (*S*)-indoline derivatives was expected to affect a high stereocontrolled selectivity. We have reported that (*S*)-indoline derivatives are the excellent chiral catalysts in asymmetric alkylation of aldehydes[9] and in asymmetric reduction of ketones[10], and that they also accomodate the chiral auxiliaries in asymmetric 1,3-dipolar cycloadditions.[11] Recently, we discovered the fact that the stereocontrolled addition of organometallics to new chiral α-keto amides which were synthesized from (*S*)-2-methoxymethylindoline resulted in α-hydroxy amides with extremely high diastereoselectivities.[12] In this paper, we wish to describe Lewis acid promoted asymmetric allylation to new chiral α-keto amides **1-2** and **5-6** derived from (*S*)-indoline-2-carboxylic acid.

The results obtained are summarized in Table 1 and 2.[13] Treatment of **1** or **2** with allyltrimethylsilane and allyltributylstannane respectively in the presence of Lewis acids such as $TiCl_4$ and $SnCl_4$ gave the corresponding cyclized lactones **1a** and **2a** in high diastereoselectivity.[14] Diastereoselective addition of allylsilane and -stannane to chiral α-keto amides forms optically active tertiary homoallyl alcohols and then sequential intramolecular lactonization may occur. In the similar reactions the spontaneous cyclolactonization was reported by Soai and his coworker.[4a] The results obtained are summarized in Table 1. As Table 1 shows, **2** resulted in higher diastereoselectivities (96-98% de) than **1** (80-94% de). When **2a** was treated with MeLi to obtain homoallyl alcohol by cleaving the lactone ring and by removing the chiral

auxiliary, interestingly the adduct **4a**[15] was obtained instead of **3a**, however.

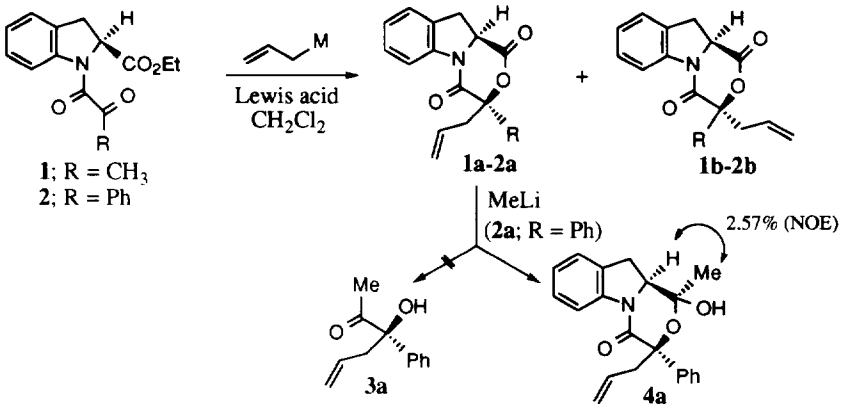


Table 1. Asymmetric Allylation of Chiral α-Keto Amides **1-2**

R	M	Lewis acid (2 eq.)	Time (h)	Temp (°C)	Yield[a] (%)	dr[b] (**a** : **b**)
CH_3	$SiMe_3$	$TiCl_4$	3	-78	78 (52)[c]	94 : 6 (78 : 22)[c]
		$SnCl_4$	3	-78	82	90 : 10
	$SnBu_3$	$TiCl_4$	1.5	-78	75	90 : 10
		$SnCl_4$	2.5	-78	80	97 : 3
Ph	$SiMe_3$	$TiCl_4$	14	-78	60	98 : 2
		$SnCl_4$	14	-78	65	99 : 1
	$SnBu_3$	$TiCl_4$	14	-78	62	98 : 2
		$SnCl_4$	14	-78	60	99 : 1

[a] Isolated Yield [b] Determined by HPLC (Hibar Pre-packed Column RT 250-4, LiChrosorb Si 60 (10 μm), n-Hexane/ EtOAc. (1 : 4. v/v)) and ^1H NMR (300 MHz) [c] 1 eq. of $TiCl_4$ was used.

In order to avoid the cyclolactonization, **5** and **6** containing *t*-butyl dimethylsilyloxy moiety instead of the ethyl carboxyl group in **1** and **2** were prepared and reacted with allylsilane or - stannane in the presence of Lewis acids (1 eq.) to give the corresponding **5a** or **6a** with extremely high diastereoselectivity (up to ≥ 98 de).[16] The TBDMS and phenyl group might influence effectively as the stereocontrolling elements.

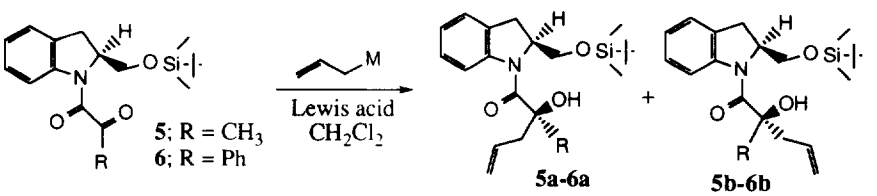
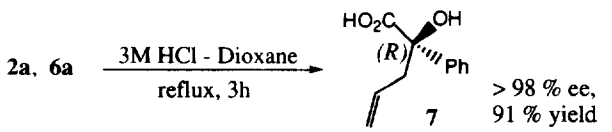


Table 2. Asymmetric Allylation of Chiral α-Keto Amides **5-6**

R	M	Lewis acid (1 eq.)	Time (h)	Temp (° C)	Yield[a] (%)	dr[b] (**a** : **b**)
CH_3	$SiMe_3$	$TiCl_4$	3	-78	82	99 : 1
		$SnCl_4$	4	-78	79	99 : 1
	$SnBu_3$	$TiCl_4$	2	-78	84	99 : 1
		$SnCl_4$	2.5	-78	81	99 : 1
Ph	$SiMe_3$	$TiCl_4$	16	-78 → r.t.	68	≥ 99 : 1
		$SnCl_4$	18	-78 → r.t.	67	≥ 99 : 1
	$SnBu_3$	$TiCl_4$	14	-78 → r.t.	72	≥ 99 : 1
		$SnCl_4$	15	-78 → r.t.	70	≥ 99 : 1

[a] Isolated Yield [b] Determined by HPLC (Chiralcel OD column, 25 cm x 0.46 cm, n-hexane / 2-propanol, (9 : 1, v/v)) and ^{1}H NMR (300 MHz)

The chiral products **2a** and **6a** were hydrolyzed to obtain (*R*)-2-hydroxy-2-phenyl-4-pentenoic acid **7**[17,18] which was used for determining their absolute configurations. The optical purity of **7** was determined by HPLC and ^{1}H NMR.



From the results described above, it may be concluded that the benzene ring of **1-2** and **5-6** plays an important role to affect the diastereofacial selectivity in the allylation. Although various possible conformers can be considered in the transition state, conformer **A** is more favorable than **B** due to the steric hindrance by the repulsion between the phenyl ring and R group (Fig. 1). Consequently, the allyl group may attack less hindered bottom side (*si*-face) to give the product[18]

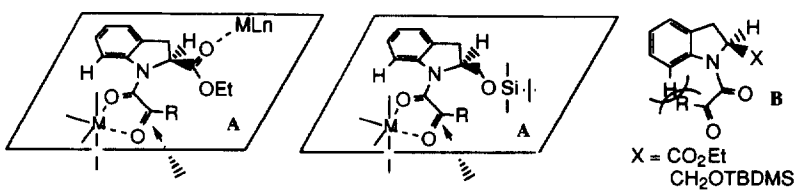


Figure 1.

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13. A typical experimental procedure: To a dichloromethane solution (3 ml) of **2** (0.5 mmol) under N_2 was added a Lewis acid (2 eq.) at -78 °C. After the mixture was stirred for 10 min, allylating reagent (1.2 eq.) was added to the mixture with stirring at -78 °C and stirred for 14h. The reaction was quenched by adding pH 7 buffer solution (5 ml). After the organic layer was separated, and then extracted with dichloromethane (10 ml x 3). The combined extracts were dried over anhydrous sodium sulfate and concentrated to give the crude diastereomeric mixture of **2a** and **2b** which was submitted to HPLC and ^{1}H NMR (300 MHz) analysis. Diastereomers were separated and purified by a silica gel column chromatography (230-400 mesh ASTM, eluent: n-hexane / EtOAc). Spectral data of **1b** and **2a** are listed in Note (14).
14. **2a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.80 (dd, 1H), 3.06 (dd, 1H), 3.24 (dd, 1H), 3.51 (dd, 1H), 4.25 (dd, 1H), 5.07 (m, 2H), 5.74 (m, 1H), 7.01-7.42 (m, 8H), 8.10 (d, 1H); ^{13}C NMR δ 31.52, 43.95, 58.09, 88.56, 116.11, 120.24, 124.70, 124.85, 125.38, 128.14, 128.55, 129.05, 129.21, 131.04, 136.67, 140.44, 163.59, 168.70; IR (NaCl) 1767 (ester), 1683 (amide) cm^{-1}; MS m/z 319 (M^+, 7.7), 158 (5.2), 117 (39.6). 105 (100.0), 89 (15.7), 77 (22.8); $[\alpha]_D^{20}$ + 84.8° (c 2.88, $CHCl_3$).

    1b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (s, 3H), 2.60 (dd, 1H), 2.72 (dd, 1H), 3.41 (m, 2H), 4.96 (t, 1H), 5.22 (m, 2H), 5.77 (m, 1H), 7.05-7.24 (m, 3H), 8.02 (d, 1H); IR (NaCl) 1752 (ester), 1678 (amide) cm^{-1}; MS m/z 257 (M^+, 20.1), 117 (100.0), 90 (18.4); $[\alpha]_D^{20}$ - 25.0° (c 0.4, $CHCl_3$).
15. The pure **2a** was used in this reaction. HPLC analysis of the crude product shows two diastereomer's peaks (dr 9 : 1, 80 %). The major product was separated and purified by a silica gel column and identified as **4a** by nuclear overhauser effect of ^{1}H NMR.
    4a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59 (s, 3H), 2.51 (m, 2H), 3.02 (m, 2H), 3.17 (dd, 1H), 3.95 (m, 1H), 5.03 (m, 2H), 5.83 (m, 1H), 6.92-7.54 (m, 8H), 8.05 (d, 1H); ^{13}C NMR δ 25.54, 31.36, 45.81, 62.69, 82.41, 96.54, 116.48, 118.69, 124.39, 124.51, 125.23, 127.61, 127.74, 128.42, 129.45, 134.71, 141.03, 142.12, 166.65; IR (NaCl) 3424 (br), 1625 (amide) cm^{-1}; MS m/z 335 (M^+, 2.6), 294 (7.9), 129 (10.1), 118 (31.0), 105 (100.0), 77 (24.1); $[\alpha]_D^{20}$ + 159.8° (c 1.53, $CHCl_3$).
16. **6a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (d, 6H), 0.82 (s, 9H), 2.45 (d, 1H), 2.69 (m, 2H), 3.12 (dd, 1H), 3.39 (m, 2H), 4.76 (m, 2H), 5.15 (m, 2H), 5.87 (m, 1H), 6.98-7.53 (m, 8H), 8.05 (d, 1H); ^{13}C NMR δ - 5.59, - 5.43, 18.28, 25.79, 31.45, 47.43, 59.93, 64.09, 79.51, 119.36, 119.58, 124.35, 124.58, 124.77, 127.05, 127.38, 128.30, 131.22, 133.91, 142.69, 142.71, 171.36; IR (NaCl) 3391 (alcohol), 1645 (amide) cm^{-1}; MS m/z 437 (M^+), 234 (43.3), 206 (17.3), 118 (100.0), 105 (93.4), 77 (14.2); $[\alpha]_D^{20}$ + 74.7° (c 1.7, $CHCl_3$).
17. **7**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.83 (m, 1H), 2.96 (m, 1H), 5.18 (m, 2H), 5.75 (m, 1H), 7.28-7.61 (m, 5H); IR (NaCl) 3463, 2939, 1719, 1642 cm^{-1}; $[\alpha]_D^{20}$ - 28° (c 2.1, $CHCl_3$), (lit. (*S*); $[\alpha]_D^{22}$ + 29° (c 1, $CHCl_3$))[6].
18. It is the first example to obtain the *R* configuration of optically almost pure **7** (> 98 % ee).

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