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Diastereoselective Addition of Organometallic Reagents to Imines or Hydrazones Containing 1,3-Oxathiane As a Chiral Template

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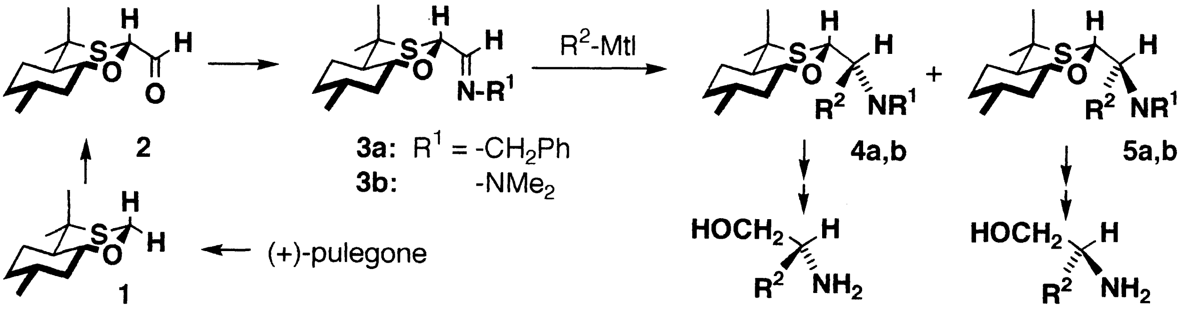
The addition of organometallic reagents to imines or hydrazones containing 1,3-oxathiane as a chiral auxiliary proceeded with high diastereoselectivity and can be used as a key reaction for the preparation of chiral β-amino alcohols.

The diastereoselective additions of organometallic reagents to imines or hydrazones bearing a chiral auxiliary have been applied to the preparation of chiral amines those are important substrates for the syntheses of bioactive compounds.[1,2] Various combinations of metals and chiral auxiliaries have been examined to pursue higher diastereoselectivity. We have reported that the coordination of lanthanoid metal to the three heteroatoms in 2-acyl-1,3-oxathiane derivatives plays an important role for the diastereoselectivity of the reaction.[3] Application to imines derived from 2-acyl-1,3-oxathianes was conceivable to provide an efficient synthesis of chiral amines. Here we wish to report highly diastereoselective addition of organolithium reagents to imine **3a** or hydrazone **3b** containing 1,3-oxathiane moiety as a chiral auxiliary and the reversal of the diastereoselectivity by the use of lanthanoid salt-mediated organolithiums[4a,c] to **3b**. The substrates **3a** and **3b** were derived from a chiral oxathiane **1** via aldehyde **2**.[5-7]



Scheme 1.

Additions of organolithium reagents to **3a** or **3b** were performed according to the following procedure. To a solution of organolithium reagent (1.5 mmol) in a solvent (5 ml) was added a solution of **3a** or **3b** (1.0 mmol) in THF (1 ml) at -78 °C. The mixture was stirred for 0.5 h at -78 °C and then for 2 h at room temperature. The mixture was poured into water (10 ml) and extracted with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The ratio of diastereomers was determined by ^{1}H-NMR analysis of the crude product,[8] and the yield of the product was determined after purification by a silica gel column chromatography. Lanthanoid–mediated organolithium reagents were prepared according to the reported procedure,[3,4] and the reactions with **3a** or **3b** were carried out according

Table 1. Diastereoselective Addition of Organometallic Reagents to Imine **3a** and Hydrazone **3b**[a)]

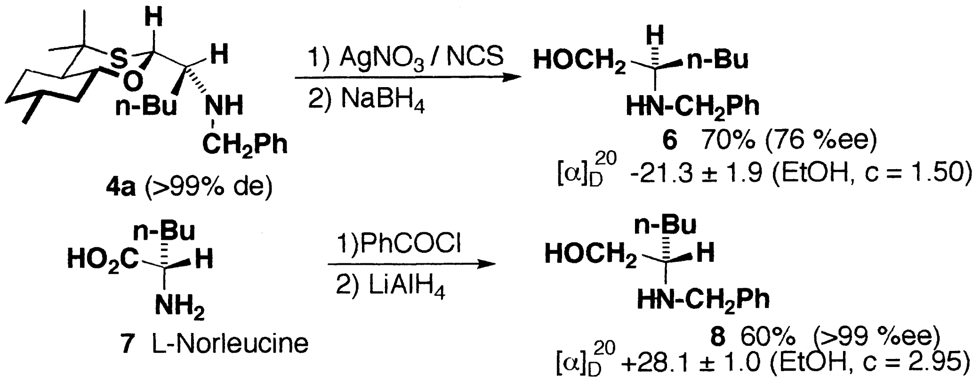
entry	Substrate (**3a**,**b**)	R^2–Mtl	solvent	Yield (%)[b)]	**4** / **5** [c)]
1	**3a** (imine)	n-BuLi	hexane / THF [d)]	85	>99 / <1
2	"	n-BuMgBr	ether	56	>99 / <1
3	"	n-BuLi / $CeCl_3$	hexane / THF [d)]	72	>99 / <1
4	"	n-BuLi / $Yb(OTf)_3$	"	65	>99 / <1
5	**3b** (hydrazone)	n-BuLi	"	90	>99 / <1
6	"	n-BuLi / $CeCl_3$	"	>99	17 / 83
7	"	n-BuLi / $Yb(OTf)_3$	"	18	34 / 66
8	"	MeLi	ether / THF [e)]	>99	>99 / <1
9	"	MeLi / $Yb(OTf)_3$	"	68	14 / 86
10	**3a** (imine)	PhLi	"	81	>99 / <1
11	"	$CH_2=C(CH_3)$-Li [f)]	hexane / THF [d)]	91	>99 / <1
12	"	$CH_3(CH_2)_4C\equiv C$-Li [g)]	"	45	>99 / <1
13	**3b** (hydrazone)	PhLi	ether / THF [e)]	65	>99 / <1
14	"	PhLi / $Yb(OTf)_3$	"	80	14 / 86
15	"	$CH_2=C(CH_3)$-Li [f)]	hexane / THF [d)]	88	>99 / <1

a) Substrate (**3a**, **b**, 1.0 mmol), R^2-Mtl (1.5 mmol), and solvent (6 ml) were used. b) Isolated yield. c) The ratio of diastereomers was determined by ^{1}H-NMR. d) hexane: 1 ml; THF: 5 ml. e) ether: 1.5 ml; THF: 4.5 ml. f) Prepared from $CH_2=C(CH_3)$-Sn(n-Bu)$_3$ and n-BuLi. g) Prepared from 1-heptyne and n-BuLi.

to the above described procedure. The results were summarized in Table 1.

The reaction of imine **3a** with n-butyllithium or n-butylmagnesium bromide yields single diastereomer **4a** exclusively. Judging from the stereochemistry of the product, the reaction can be explained by Cram's chelation model (entry 1, 2); namely chelate formation of lithium or magnesium metal with N of imine moiety and O of oxathiane ring.[5, 9)] In the reactions with imine **3a**, an addition of lanthanoid(III) salt did not affect the diastereoselectivity (entry 3,4). Bulky benzyl group on N prevents from the highly congested multi-coordination of lanthanoid to O, S, and N. Reaction with lanthanoid-mediated reagent proceeds in similar mechanism to that with lithium reagent. Phenyl-, alkenyl-, alkynyllithium as well as alkyllithium reacted with imine **3a** to give **4a** selectively (entry 10-12). In the case of reactions with hydrazone **3b**, a reversal of diastereoselectivity was observed by using lanthanoid-mediated organolithium reagents;[3)] reaction of **3b** with RLi gave **4b** selectively, whereas lanthanoid-mediated reagent gave diastereomer **5b** predominantly (entry 5–9, 13–15). The reversal of diastereoselectivity caused by the lanthanoid-mediated organolithium reagents might be explained by multi-site coordination model as we suggested in the reaction of 2-acyl-1,3-oxathiane with lanthanoid-mediated reagents.[3,10)]

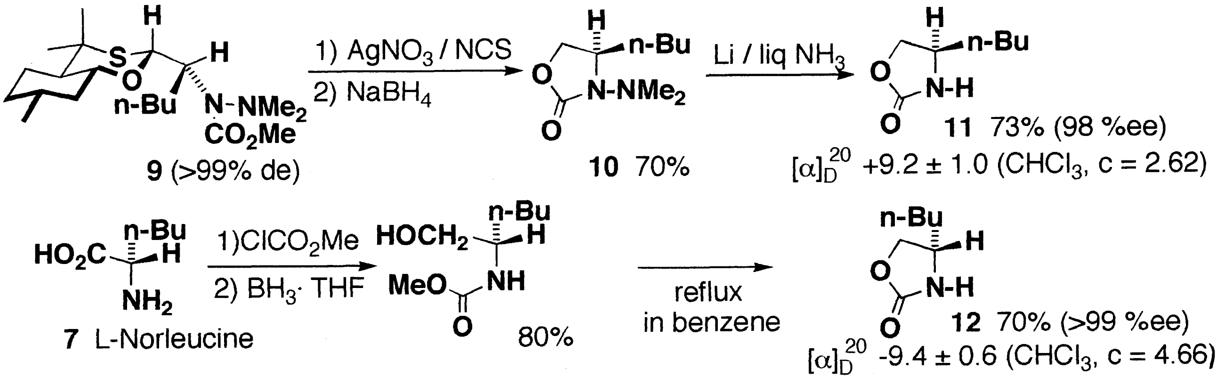
Transformation of the adducts into β-amino alcohols was illustrated in Scheme 2 and 3. Successive treatments of diastereomerically pure amine **4a** (R^2= n-Bu) with N-chlorosuccinimide (NCS) / $AgNO_3$ and $NaBH_4$[5,11)] gave β-amino alcohol **6** [78%ee, $[\alpha]_D^{20}$-21.3±1.9 (EtOH, c=1.50)] in 70% yield. Partial racemization was observed by HPLC analysis. Authentic β-amino alcohol **8** [$[\alpha]_D^{20}$+28.1±1.0 (EtOH, c=2.95)] was derived from L-Norleucine **7**. The comparison of optical rotation of **6** with that of **8** confirmed



Scheme 2.

the absolute configuration of **6**, that was consonant with the absolute configuration of **4a** (R^2= n-Bu).

Treatment of hydrazine **4b** or **5b** with NCS / $AgNO_3$ gave a complex mixture, because hydrazines are sensitive to oxidizing reagents. The corresponding carbamate **9** was obtained by trapping the initial adduct between **3b** and n-BuLi with methyl chloroformate.12) Successive treatment of **9** with NCS / $AgNO_3$ and $NaBH_4$ afforded N-aminooxazolidinone **10**. A reductive cleavage12) of N-N bond by Li / liqNH_3 gave **11** [98%ee, $[\alpha]_D^{20}$+9.2±1.0 ($CHCl_3$, c=2.62)];13) a partial racemization was observed in the transformation. The absolute configuration of **11** was confirmed by the comparison of spectral data with that of authentic **12** [$[\alpha]_D^{20}$-9.4±0.6 ($CHCl_3$, c=4.66)] derived from L-Norleucine (Scheme 3).



Scheme 3.

As mentioned above, addition of organometallic reagents to **3a** and **3b** proceeded diastereoselectively. Although the procedure for cleavage of oxathiane has not been well optimized, these reactions provide a selective preparation of both enantiomers of β-amino alcohols.15)

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6) A hexane solution of n-BuLi (1.6 M, 6.5 ml, 10.4 mmol) was added dropwise at -78 °C to a solution of **1** (2.0 g, 10 mmol) in THF (15 ml). The mixture was stirred for 0.5 h at -78 °C and for 15 min at 0 °C. The equatorial lithiated **1** was added dropwise to a THF (10 ml) solution of N,N-dimethyl formamide (0.88 g, 12 mmol) at -78 °C and the mixture was stirred at 0 °C for 2 h. An aqueous work up and a purification by a silica gel column chromatography gave aldehyde **2** in 77% yield (1.8 g).
7) Stereochemistry and purity of the imine **2a** and hydrazone **2b** were determined by ^1H NMR analysis: See also, M. M. Midland and R. W. Koops, *J. Org. Chem.*, **57**, 1158 (1992); E. J. Corey and D. Enders, *Chem. Ber.*, **111**, 1337 (1978).
8) **4a** (R^2= n-Bu): ^1H NMR ($CDCl_3$): δ 7.1-7.4 (m, 5H), 4.90 (d, J=6.5 Hz, 1H), 3.79 (bs, 2H), 3.30 (ddd, J=10.4, 10.4, 4.0, 1H), 2.71 (dt, J=6.7, 5.0 Hz, 1H), 1.33 (s, 3H), 1.20 (s, 3H), 0.84 (d, J=6.4 Hz, 3H),0.82 (t, J=7.2 Hz, 3H), 0.75-2.2 (m, 15H).;^{13}C NMR ($CDCl_3$): δ 140.5, 128.6, 128.5, 127.1, 81.7,60.4, 51.5, 51.0, 43.2, 41.8, 34.9, 31.6, 30.0, 29.9, 28.1, 27.7, 24.5, 23.0, 22.2, 14.2.

   5a (R^2= n-Bu): ^1H NMR ($CDCl_3$): δ 7.1-7.4 (m, 5H), 4.94 (d, J=4.2 Hz, 1H), 3.81 (bs, 2H), 3.30 (ddd, J=10.4, 10.4, 4.0, 1H), 2.65- 2.75 (m, 1H), 1.32 (s, 3H), 1.20 (s, 3H), 0.83 (d, J=6.4 Hz, 3H), 0.81 (t, J=7.2 Hz, 3H), 0.75-2.3 (m, 15H).;^{13}C NMR ($CDCl_3$): δ 141.0, 128.5, 128.4, 127.0, 81.9, 60.4, 51.7, 51.1, 42.9, 41.9, 34.9, 31.6, 30.7, 29.9, 28.4, 27.5, 24.5, 22.9, 22.2, 14.2.
9) The reactions of alkyllithium with α-heteroketone often proceed via non chelation intermediate, while Grignard reagent favors the chelate intermediate.[14)] In the case of α–alkoxyhydrazone, organolithium reagent possesses a strong tendency to form a chelate intermediates.[2f)]
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