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Mixed La–Li heterobimetallic complexes for tertiary nitroaldol resolution

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ABSTRACT

Full details of the kinetic resolution of tertiary nitroaldols derived from simple ketones are described. Mixed BINOL/biphenol La–Li heterobimetallic complexes gave the best selectivity in retro-nitroaldol reactions of racemic tertiary nitroaldols. Using a 2:1 mixture of La–Li_3-(binaphthoxide **1a**)$_3$ complex (LLB) and La–Li_3-(biphenoxide **1e**)$_3$ complex, chiral tertiary nitroaldols were obtained in 80–97% ee and 30–47% recovery yield. Transformations of products were also investigated.

1. Introduction

Catalytic asymmetric nitroaldol (Henry) reactions[1] are synthetically useful carbon–carbon bond-forming reactions. Since our first report of the catalytic asymmetric nitroaldol reaction of aldehydes,[2] various chiral catalysts effective for the reaction of nitromethane with aldehydes have been developed.[3] Diastereo- and enantioselective nitroaldol reactions using nitroethane and other nitroalkanes as donors have also been intensively studied by us[4] and other groups.[5] In contrast, there is only a limited number of nitroaldol reactions of ketones that lead to synthetically versatile chiral tertiary nitroaldols. Enantioselective nitroaldol reactions of α-keto esters have been achieved using chiral Cu[6a–e] and Mg complexes,[6f] and cinchona alkaloids.[6g,h] A highly enantioselective nitroaldol reaction of trifluoromethyl ketone has also been realized using a chiral rare earth metal catalyst.[7] There are no reports, however, on the asymmetric synthesis of tertiary nitroaldols derived from simple non-activated ketones. Even for a racemic version, only a few methodologies with limited substrate scope are available.[8] The difficulty is due to the attenuated reactivity of ketones and the strong tendency toward a retro-nitroaldol reaction under basic conditions. Therefore, the synthesis of tertiary nitroaldols with chirality control is in high demand. Herein, we describe the full details of a kinetic resolution approach using BINOL **1a**-H_2/biphenol **1e**-H_2 mixed La–Li heterobimetallic complexes (Fig. 1).[9]

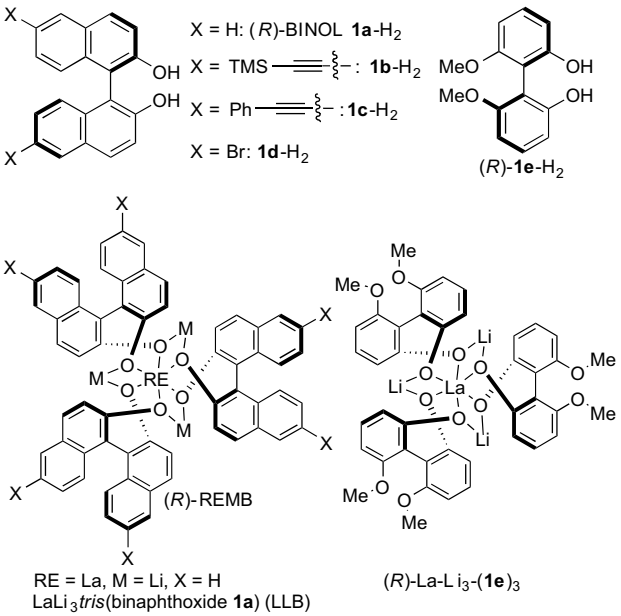

Figure 1. Structures of (*R*)-BINOL **1a**-H_2, BINOL derivatives **1b**–**1d**-H_2, biphenyldiol (*R*)-**1e**-H_2, and La–Li_3-(ligand)$_3$ heterobimetallic complexes (*R*)-REMB (RE=rare earth), (*R*)-LLB, and (*R*)-La–Li_3-(**1e**)$_3$.

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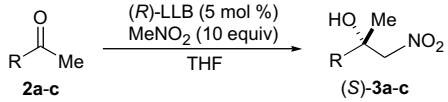
2. Initial trials of a catalytic asymmetric nitroaldol reaction of simple ketones

Initially, we investigated the catalytic asymmetric nitroaldol reaction of ketone **2** with nitromethane. Catalyst screening revealed that (*R*)-LLB (Fig. 1),[10] which is suitable for the nitroaldol reaction of aldehydes, had high enantioselectivity with ketones. (*R*)-LLB promoted the reaction of ketone **2a** with 10 equiv of nitromethane at −40 °C to afford (*S*)-**3a** in 95% ee, albeit in poor yield (2%), after very long reaction time (Table 1, entry 1, 120 h). Excess nitromethane was essential to obtain product **3a**. The yield of the nitroaldol adducts depended on the substituents of the methyl ketones,[11] and nitroaldol adduct **3c** was obtained in 18% yield and 90% ee at −40 °C (entry 3). Further trials to improve the yield, however, failed. When the reaction of **2c** was performed at −20 °C, **3c** was obtained in 15–20% yield (entries 4–6). The enantiomeric excess of **3c** gradually decreased at −20 °C over time, but the conversion yield did not change much. The results shown in entries 4–6 suggested that the nitroaldol reaction of simple ketone **2** is thermodynamically unfavorable, and that the retro-nitroaldol reaction catalyzed by (*R*)-LLB gradually decreased the enantiomeric excess.[11] Good conversion is difficult to achieve in the absence of stoichiometric amounts of trapping reagents, such as a silylating reagent to make the reaction irreversible or stoichiometric amounts of chelating metals to stabilize the product.

3. Kinetic resolution of tertiary nitroaldols via a retro-nitroaldol reaction

On the basis of the results shown in Table 1, we planned to use (*R*)-LLB for the kinetic resolution of racemic tertiary nitroaldols via a retro-nitroaldol reaction.[12,13] The high enantioselectivity achieved in the nitroaldol reaction shown in Table 1, entries 1–3, led us to hypothesize that (*R*)-LLB would preferentially convert the matched enantiomer (*S*)-**3a** into **2a** and nitromethane, and the mismatched enantiomer (*R*)-**3a** would remain unchanged and be recovered in an enantiomerically enriched form. Kinetic resolution of (±)-**3a** using 5 mol % of (*R*)-LLB proceeded at −40 °C. As expected, **3a** was recovered in 76% yield and 30% ee [(*R*)-**3a** major, selectivity factor: s=52.3][14] after 24 h, together with ketone **2a** and nitromethane. To enhance the reaction rate, the reaction was performed at −20 °C, giving good enantioselectivity (86% ee) in 48% recovery yield of (*R*)-**3a** (Table 2, entry 1, 24 h, s=23.8). To further improve selectivity, we investigated several REMB complexes (Fig. 1, RE=rare earth, M=alkali metal, B=biaryldiol). Rare earth metal screening and alkali metal screening results are summarized in entries 2–7. Rare earth metals with a smaller ionic radius, such as Pr, Sm, Gd, and Dy, had poor selectivity (entries 2–5).

Table 1
Initial trials on catalytic asymmetric nitroaldol reaction of simple ketones



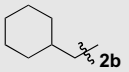
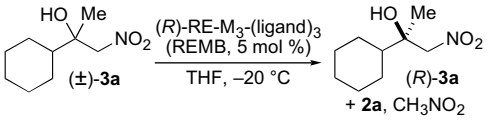
Entry	Ketone: R	Temp (°C)	Time (h)	Yield (%)	ee (%)
1	Cyclohexyl **2a**	−40	120	2	95
2	 **2b**	−40	120	5	90
3	$PhCH_2CH_2$– **2c**	−40	96	18	90
4	$PhCH_2CH_2$– **2c**	−20	24	15	66
5	$PhCH_2CH_2$– **2c**	−20	48	20	55
6	$PhCH_2CH_2$– **2c**	−20	72	20	43

Table 2
Optimization studies of kinetic resolution using various (*R*)-REMB complexes



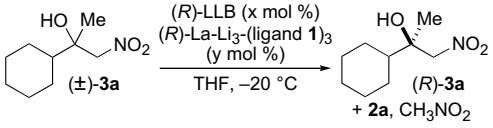
Entry	RE	M	Ligand	Time (h)	Yield[a] (%)	ee[b] (%)	s
1	La	Li	**1a**	24	48	86	23.8
2	Pr	Li	**1a**	24	57	39	4.5
3	Sm	Li	**1a**	24	83	3	1.4
4	Gd	Li	**1a**	42	67	5	1.3
5	Dy	Li	**1a**	42	46	1	1.0
6	La	Na	**1a**	36	68	3	1.2
7	La	K	**1a**	36	57	2	1.1
8	La	Li	**1b**	24	42	56	4.0
9	La	Li	**1c**	24	35	83	6.3
10	La	Li	**1d**	24	45	75	9.1
11	La	Li	**1e**	48	58	14	1.7

[a] Determined by ^{1}H NMR analysis using mesitylene as an internal standard.
[b] Determined by chiral HPLC analysis.

Alkali metals Na and K also resulted in poor selectivity (entries 6–7). The combination of La and Li produced the best results (entry 1). Several chiral ligands such as BINOL derivatives **1b–1d** and biphenol **1e**[15] were also investigated, but the results were not promising (entries 8–11).

For the REMB complexes, three same BINOL units and three same alkali metals were utilized to construct a symmetric chiral environment. REMB complexes have a D_3-symmetric structure under strictly anhydrous conditions and a C_3-symmetric crystal structure in the presence of H_2O.[16] We hypothesized that symmetry in the REMB complexes is not always required to induce high enantioselectivity in asymmetric reactions. To increase the diversity of the chiral environment in REMB complexes, mixed-ligand and/or mixed-alkali metal complexes would be potentially more suitable for some asymmetric reactions. Inspired by recent reports of a mixed-ligand chiral catalyst screening strategy,[17,18] we examined the mixture of two chiral ligands (Table 3). Because the ligands of REMB complexes are known to readily exchange in situ,[19] we performed the reactions by mixing two different (*R*)-La–Li_3-(ligand)$_3$ complexes. Although mixtures of BINOL **1a** with BINOL derivatives **1b–1d** did not afford positive results (entries 2–4) compared with the result with LLB alone (entry 1), a mixture of BINOL **1a** with biphenol **1e** gave a promising result (entry 5, 90% ee of **3a** with 50% conversion, s=58.4). The best selectivity was

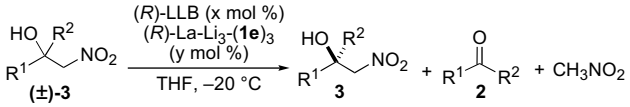
Table 3
Optimization studies of kinetic resolution using mixtures of (*R*)-LLB and (*R*)-REMB-type La–Li_3-(ligand **1**)$_3$ complexes

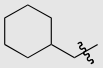


Entry	LLB (x mol %)	La–Li_3-(ligand)$_3$ (y mol %)	Time (h)	Recov. yield[a] (%)	ee[b] (%)	s
1	5	None (0)	24	48	86	23.8
2	3.33	Ligand **1b** (1.67)	24	49	57	5.9
3	3.33	ligand **1c** (1.67)	24	39	93	12.7
4	3.33	Ligand **1d** (1.67)	24	44	74	8.1
5	3.33	Ligand **1e** (1.67)	23	50	90	58.4
6	1.67	Ligand **1e** (3.33)	24	51	52	5.5
7	0	Ligand **1e** (5)	48	58	14	1.7

[a] Determined by ^{1}H NMR analysis using mesitylene as an internal standard.
[b] Determined by chiral HPLC analysis.

Table 4
Kinetic resolution of *tert*-nitroaldols **3a**–**3g** promoted by a 2:1 mixture of (*R*)-LLB and (*R*)-La–Li_3-(**1e**)$_3$[a]



Entry	3	R^1	R^2	LLB (*x* mol %)	La–Li_3-(**1e**)$_3$ (*y* mol %)	Time (h)	Conv.[b] (%)	Yield of 3[c] (%)	ee [d] (%)	*s*
1	**3a**	Cyclohexyl	Me	3.33	1.67	23	50	47	90	58.4
2	**3b**		Me	3.33	1.67	15	58	40	95	19.3
3	**3c**	$PhCH_2CH_2$	Me	6.67	3.33	19	60	40	80	7.7
4	**3d**		Me	3.33	1.67	15	58	40	97	23.1
5	**3d**		Me	1.67	0.83	48	57	40	90	15.7
6	**3e**		Me	3.33	1.67	24	58	41	85	11.0
7[e]	**3f**	Ph	Me	3.33	1.67	26	69	30	88	6.1
8	**3g**		Et	3.33	1.67	13	65	33	88	7.6

[a] Reaction was performed in THF (0.4 M) at −20 °C using a 2:1 mixture of (*R*)-LLB and (*R*)-La–Li_3-(**1e**)$_3$ unless otherwise noted.
[b] Determined by ^{1}H NMR analysis using mesitylene as an internal standard.
[c] Isolated yields after column chromatography. The theoretical maximum is 100−conv. (%).
[d] Determined by chiral HPLC analysis.
[e] Reaction was run at −40 °C.

obtained when using a 2:1 mixture of (*R*)-LLB and (*R*)-La–Li_3-(**1e**)$_3$ (Fig. 1). Neither LLB/La-Li_3-(**1e**)$_3$ at a 1:2 ratio nor La–Li_3-(**1e**)$_3$ alone produced satisfactory selectivity (entries 6 and 7).

The substrate scopes and limitations of the present kinetic resolution are summarized in Table 4. Retro-nitroaldol reactions of methylketone-derived substrates **3a**–**3e** with aliphatic substituents proceeded smoothly to afford chiral **3a**–**3e** with good enantioselectivity (entries 1–6). For each substrate, the reaction time was optimized to achieve both a good recovery yield of **3** and good to high enantiomeric excess (97–80% ee, 47–40% isolated yield). With **3d**, catalyst loading was successfully reduced to 2.5 mol % (LLB: 1.67 mol %, La–Li_3-(**1e**)$_3$: 0.83 mol %), still affording good selectivity (entry 5, 90% ee and 40% yield). In the case of acetophenone-derived substrate **3f** and ethylketone-derived substrate **3g**, higher conversion (entry 7: 69% conv., 30% recovery yield of **3f**; entry 8: 65% conv., 33% recovery yield of **3g**) was required to achieve good enantioselectivity (**3f**: 88% ee, **3g**: 88% ee).

In the present reaction, a 2:1 mixture of (*R*)-LLB and (*R*)-La–Li_3-(**1e**)$_3$ gave the best results. To gain insight into the structure of the active species in the reaction, we analyzed the mixture of LLB/La-Li_3-(**1e**)$_3$=2:1 by ESI-MS (Fig. 2). Peaks corresponding to [La–Li_3-(**1a**)$_2$/(**1e**)+Li]$^+$ and [La–Li_3-(**1a**)/(**1e**)$_2$+Li]$^+$ complexes were observed as major peaks in addition to minor peaks of LLB and La–Li_3-(**1e**)$_3$. In the retro-nitroaldol reaction of **3a**, the selectivity factor was 58.4 with LLB/La-Li_3-(**1e**)$_3$=2:1 mixture (Table 3, entry 5), while the selectivity factor was 5.5 with LLB/La-Li_3-(**1e**)$_3$=1:2 mixture (Table 3, entry 6). Furthermore, a 2:1 mixture of LLB/La-Li_3-(**1e**)$_3$ gave better results than LLB alone (*s*=23.8, Table 3, entry 1). On the basis of these experimental results and ESI-MS observations, we speculate that a ligand exchange between LLB and La–Li_3-(**1e**)$_3$ occurred to generate a mixed-ligand La–Li_3-(**1a**)$_2$/(**1e**) complex in equilibrium, which would be the most enantioselective and reactive catalyst. We assume that distorted, less symmetric, chiral environment of the mixed-ligand La–Li_3-(**1a**)$_2$/(**1e**) complex was suitable for the present kinetic resolution.

A postulated catalytic cycle of the reaction is shown in Figure 3. We assume that the reaction would proceed in the reverse fashion of the LLB-catalyzed nitroaldol reaction of aldehydes. The mixed-ligand (*R*)-La–Li_3-(**1a**)$_2$/(**1e**) complex selectively reacts with (*S*)-**3** over (*R*)-**3**. Because both La and Li metals were essential for good selectivity (Table 2), we believe that both La and Li in the La–Li_3-(**1a**)$_2$/(**1e**) complex might interact with *tert*-nitroaldol **3** in the

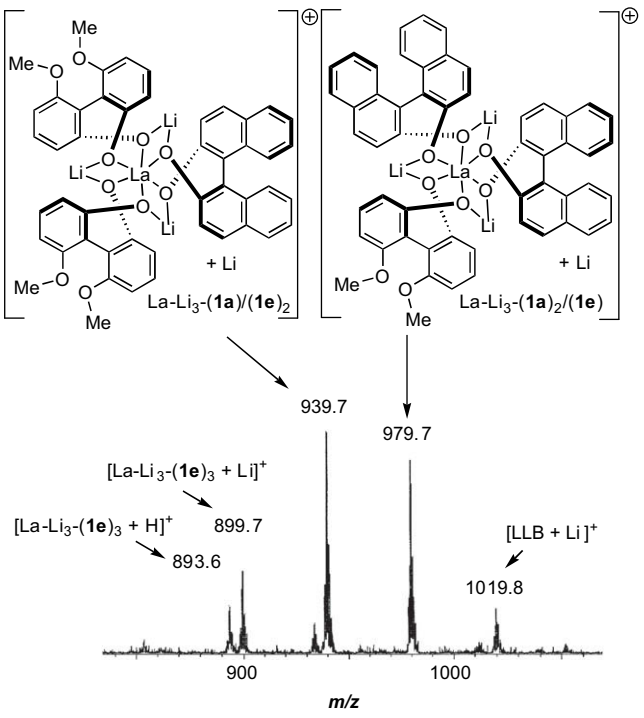


Figure 2. ESI-MS chart of a 2:1 mixture of LLB/La-Li_3-(**1e**)$_3$ [*m*/*z*: 840–1060].

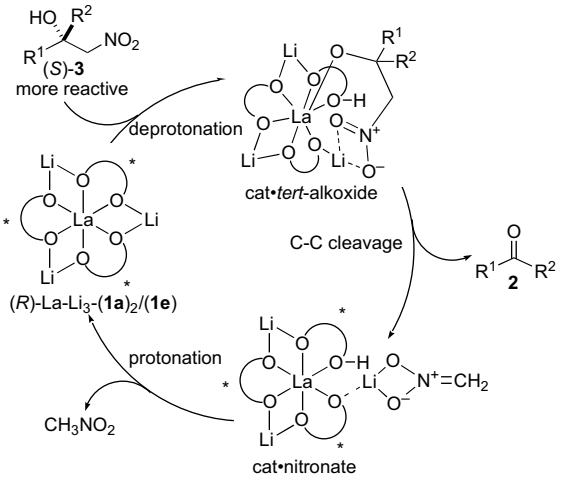
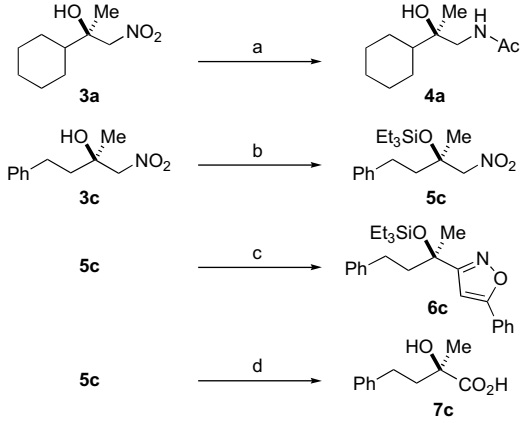


Figure 3. Postulated catalytic cycle of the retro-nitroaldol reaction.

enantio-discrimination step. La–Li_3-(**1a**)$_2$/(**1e**) would function as a Brønsted base to deprotonate the hydroxyl group of (*S*)-**3** to afford a cat·*tert*-alkoxide complex. The *tert*-nitroaldol **3** is thermodynamically unfavorable; thus, carbon–carbon bond-cleavage via the retro-nitroaldol reaction proceeds to give a cat·nitronate complex and ketone **2**. Protonation of the nitronate regenerates the (*R*)-La–Li_3-(**1a**)$_2$/(**1e**) complex. After appropriate reaction time, less reactive (*R*)-**3** can be recovered in an enantiomerically enriched form.

4. Transformation of *tert*-nitroaldol

To demonstrate the synthetic utility of tertiary nitroaldols as chiral building blocks, several transformations were investigated (Scheme 1). Hydrogenation of **3a** with Pd/C under H_2 atmosphere (1 atm), followed by acetylation, gave *N*-Ac amine **4a** in 86% yield. Protection of the hydroxyl group in **3c** was performed with Et_3SiH and 20 mol % of $B(C_6F_5)_3$ at room temperature to avoid retro-nitroaldol reaction,[20] giving silylated adduct **5c** in 90% yield. The reaction of **5c** with phenyl acetylene proceeded in the presence of PhNCO and catalytic amount of Et_3N to afford isoxazole **6c** in 84% yield.[21] Compound **5c** was also successfully converted into α-hydroxy carboxylic acid **7c** in 99%.[22]



Scheme 1. Transformations of *tert*-nitroaldols: reagents and conditions: (a) cat. Pd/C, H_2 (1 atm), MeOH, rt; Ac_2O, Et_3N, CH_2Cl_2, 86% (two steps) (b) cat. $B(C_6F_5)_3$, Et_3SiH, CH_2Cl_2, rt, 90%; (c) Ph-acetylene, PhNCO, cat. Et_3N, benzene, reflux, 84%; (d) $NaNO_2$, AcOH, DMSO, rt to 40 °C, 99%.

5. Conclusion

In summary, we achieved a kinetic resolution of tertiary nitroaldols (±)-**3** derived from simple ketones. A 2:1 mixture of La–Li_3-(binaphthoxide **1a**)$_3$ complex (LLB) and La–Li_3-(biphenoxide **1e**)$_3$ complex had the best selectivity, giving tertiary nitroaldols in 97–80% ee with 47–30% recovery yield. ESI-MS analysis supported the idea that a mixed-ligand La–Li_3-(**1a**)$_2$/(**1e**) complex was generated in equilibrium as the most enantioselective active species in the present system. It is interesting to note that the chiral environment of the mixed-ligand heterobimetallic complex with less symmetry was more suitable for the present kinetic resolution. Further application of the present mixed heterobimetallic catalyst system to other asymmetric reactions is ongoing.

6. Experimental section

6.1. General

Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. NMR spectra were recorded on JEOL JNM-LA500 and JNM-ECX500 spectrometers, operating at 500 MHz for ^{1}H NMR and 125.65 MHz for ^{13}C NMR. For ^{1}H NMR, chemical shifts in $CDCl_3$ were reported downfield from TMS (=0) or in the scale relative to $CHCl_3$ (7.24 ppm); chemical shifts in CD_3OD were reported in the scale relative to CH_3OH (3.31 ppm). For ^{13}C NMR, chemical shifts were reported in the scale relative to $CHCl_3$ (77.0 ppm for ^{13}C NMR) or to CH_3OH (49.0 ppm for ^{13}C NMR) as an internal reference. Optical rotations were measured on a JASCO P-1010 polarimeter. ESI mass spectra were measured on Waters-ZQ4000. FAB mass spectra were measured on a JEOL JMS-MS700V in positive ion mode. Column chromatography was performed with silica gel Merck 60 (230–400 mesh ASTM). The enantiomeric excess (ee) was determined by HPLC analysis. HPLC was performed on JASCO HPLC systems consisting of the following: pump, PU-2080; detector, UV-2075, measured at 230 nm or 254 nm; column, DAICEL CHIRALPAK AD-H, DAICEL CHIRALCEL OD-H; mobile phase, hexane/2-propanol. Reactions were carried out in dry solvents under an argon atmosphere, unless otherwise stated. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. La(O-*i*-Pr)$_3$ was purchased from Kojundo Chemical Laboratory Co., LTD., (sales@kojundo.co.jp). La(O-*i*-Pr)$_3$ is also available from Aldrich (Cat. No. 665193).

6.2. General procedure for catalyst preparation

To a stirred solution of (*R*)-BINOL **1a**-H_2 (859 mg, 3.00 mmol) in THF (8 mL) at 0 °C was added slowly a solution of La(O-*i*-Pr)$_3$ (5 mL, 1.00 mmol, 0.20 M in THF). The solution was allowed to stir for 30 min at room temperature, and then solvent and *i*-PrOH was removed slowly under reduced pressure and dried for 1 h under vacuum. The residue was cooled at 0 °C and THF (8 mL) was added. To the solution was added slowly *n*-BuLi (1.88 mL, 3.00 mmol, 1.60 M in hexane). After stirring for 1 h at room temperature, the solvent was removed slowly under reduced pressure and dried for 3 h under vacuum. The residue was cooled at 0 °C and THF (7.52 mL) was added. The mixture was stirred at room temperature for 1 h to afford (*R*)-LLB solution (0.133 M in THF). (*R*)-La–Li_3-(biphenoxide **1e**)$_3$ was prepared in a similar procedure using (*R*)-biphenol **1e**-H_2. (*R*)-La–Li_3-(**1e**)$_3$was stocked as 0.067 M solution in THF.

6.3. General procedure for kinetic resolution of racemic tertiary nitroaldols

To a test tube were added THF (0.2 mL), (*R*)-LLB (0.050 mL, 0.0067 mmol, 0.133 M in THF), and (*R*)-La–Li_3-(**1e**)$_3$ (0.0500 mL,

0.0033 mmol, 0.067 M in THF), and the mixture solution was stirred for 45 min at room temperature. The solution was cooled at −20 °C, and then (±)-**3a** (0.200 mL, 0.200 mmol, 1 M solution in THF) was added. After stirring for 23 h at −20 °C, the reaction was quenched by citric acid (0.5 mL, 0.25 M solution in THF). The resulting mixture was diluted with Et_2O and poured onto water. The aqueous layer was extracted with Et_2O (×3) and the combined organic layers were washed with brine, and then dried over Na_2SO_4. After removing solvent under reduced pressure, the residue was purified by flash column chromatography (neutral SiO_2, hexane/acetone=20/1) to give (*R*)-**3a** (47% recovery) as pale yellow oil.

*6.3.1. (R)-2-Cyclohexyl-1-nitro-2-propanol (**3a**)*

Pale yellow oil; IR (neat) ν 3543, 2926, 2855, 1384 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.52 (d, *J*=12.0 Hz, 1H), 4.41 (d, *J*=12.0 Hz, 1H), 2.81 (s, 1H), 1.87–1.79 (m, 4H), 1.70 (m, 1H), 1.44 (m, 1H), 1.25–0.97 (m, 5H), 1.23 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 83.3, 73.8, 46.4, 27.7, 26.7, 26.4, 26.2, 21.5; ESI-MS *m*/*z* 210 $[M+Na]^+$; HRMS [FAB(+)] calcd for $C_9H_{17}CsNO_3^+$ $[M+Cs]^+$: 320.0257; found 320.0265; $[\alpha]_D^{22}$ −2.7 (*c* 2.4, $CHCl_3$); HPLC (DAICEL CHIRALPAK AD-H, 2-propanol/hexane 1/9, flow 1.0 mL/min, detection at 230 nm) t_R 8.3 min (minor) and 11.5 min (major). The absolute configuration of **3a** was determined after conversion into known acetamide **4a**.

*6.3.2. (R)-3-Cyclohexyl-2-methyl-1-nitro-2-propanol (**3b**)*

Pale yellow oil; IR (neat) ν 3541, 2923, 2851, 1550, 1382 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.45 (d, *J*=12.0 Hz, 1H), 4.39 (d, *J*=12.0 Hz, 1H), 2.80 (s, 1H), 1.84–1.44 (m, 8H), 1.32 (s, 3H), 1.30–0.95 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 84.9, 72.2, 46.8, 35.1, 34.9, 33.3, 26.3, 26.2, 26.1, 24.8; ESI-MS *m*/*z* 224 $[M+Na]^+$; HRMS [FAB(+)] calcd for $C_{10}H_{19}CsNO_3^+$ $[M+Cs]^+$: 334.0414; found 334.0410; $[\alpha]_D^{20}$ −1.9 (*c* 1.3, $CHCl_3$); HPLC (DAICEL CHIRALPAK AD-H, 2-propanol/hexane 1/9, flow 1.0 mL/min, detection at 230 nm) t_R 8.3 min (minor) and 12.7 min (major).

*6.3.3. (R)-2-Methyl-1-nitro-4-phenyl-2-butanol (**3c**)*

Colorless oil; IR (neat) ν 3269, 2922, 2849, 1548, 1384 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31–7.18 (m, 5H), 4.50 (d, *J*=12.0 Hz, 1H), 4.45 (d, *J*=12.0 Hz, 1H), 2.92 (s, 1H), 2.77–2.74 (m, 2H), 1.90–1.86 (m, 2H), 1.39 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 141.0, 128.6, 128.3, 126.2, 84.1, 71.5, 41.5, 29.8, 24.4; ESI-MS *m*/*z* 232 $[M+Na]^+$; HRMS [FAB(+)] calcd for $C_{11}H_{15}CsNO_3^+$ $[M+Cs]^+$: 342.0101; found 342.0094; $[\alpha]_D^{20}$ −3.7 (*c* 2.40, $CHCl_3$); HPLC (DAICEL CHIRALCEL OD-H, 2-propanol/hexane 1/4, flow 1.0 mL/min, detection at 254 nm) t_R 12.0 min (major) and 15.3 min (minor). For the absolute configuration of **3c**, see section 6.4.4.

*6.3.4. (R)-2,4-Dimethyl-1-nitro-2-pentanol (**3d**)*

Pale yellow oil; IR (neat) ν 3541, 2958, 2872, 1551, 1382 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.45 (d, *J*=12.0 Hz, 1H), 4.39 (d, *J*=12.0 Hz, 1H), 2.81 (s, 1H), 1.88–1.81 (m, 1H), 1.52–1.43 (m, 2H), 1.32 (s, 3H), 1.00 (d, *J*=6.4 Hz, 3H), 0.98 (d, *J*=6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 84.9, 72.1, 47.9, 24.7, 24.6, 24.3, 24.0; ESI-MS *m*/*z* 184 $[M+Na]^+$; HRMS [FAB(+)] calcd for $C_7H_{15}CsNO_3^+$ $[M+Cs]^+$: 294.0101; found 294.0097; $[\alpha]_D^{22}$ −2.3 (*c* 1.4, $CHCl_3$); HPLC (DAICEL CHIRALPAK AD-H, 2-propanol/hexane 1/20, flow 1.0 mL/min, detection at 230 nm) t_R 10.7 min (minor) and 12.4 min (major).

*6.3.5. (R)-3-Ethyl-2-methyl-1-nitro-2-pentanol (**3e**)*

Pale yellow oil; IR (neat) ν 3544, 2967, 2878, 1553, 1382 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.54 (d, *J*=12.0 Hz, 1H), 4.43 (d, *J*=12.0 Hz, 1H), 2.84 (s, 1H), 1.67 (m, 1H), 1.54 (m, 1H), 1.27–1.20 (m, 3H), 1.24 (s, 3H), 1.00 (t, *J*=7.1 Hz, 3H), 0.97 (t, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 83.5, 75.0, 50.1, 23.2, 22.2, 21.8, 13.9, 13.4; ESI-MS *m*/*z* 198 $[M+Na]^+$; HRMS [FAB(+)] calcd for $C_8H_{17}CsNO_3^+$ $[M+Cs]^+$: 308.0263; found 308.0261; $[\alpha]_D^{22}$ +1.4 (*c* 1.4, $CHCl_3$); HPLC (DAICEL CHIRALPAK AD-H, 2-propanol/hexane 1/20, flow 1.0 mL/min, detection at 230 nm) t_R 8.9 min (minor) and 10.7 min (major).

*6.3.6. (R)-1-Nitro-2-phenyl-2-propanol (**3f**)*

(±)-**3f** is a known compound.[23] Colorless oil; $[\alpha]_D^{22}$ +6.7 (*c* 3.6, $CHCl_3$); HPLC (DAICEL CHIRALCEL OD-H, 2-propanol/hexane 1/6, flow 1.0 mL/min, detection at 230 nm) t_R 13.0 min (major) and 15.3 min (minor). The absolute configuration of **3f** was determined after conversion into a known acetamide by following the reaction conditions in Scheme 1, conditions (a).

*6.3.7. (R)-2-Ethyl-4-methyl-1-nitro-2-pentanol (**3g**)*

Colorless oil; IR (neat) ν 3550, 2958, 1555, 1381 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.44 (d, *J*=12.0 Hz, 1H), 4.41 (d, *J*=12.0 Hz, 1H), 2.73 (s, 1H), 1.82–1.74 (m, 1H), 1.67–1.56 (m, 2H), 1.47 (dd, *J*=15.0, 5.5 Hz, 1H), 1.38 (dd, *J*=15.0, 6.8 Hz, 1H), 0.97–0.90 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 82.9, 74.4, 44.7, 30.2, 24.6, 24.3, 23.6, 8.1; ESI-MS *m*/*z* 198 $[M+Na]^+$; HRMS [FAB(+)] calcd for $C_8H_{17}CsNO_3^+$ $[M+Cs]^+$: 308.0263; found 308.0262; $[\alpha]_D^{22}$ +1.0 (*c* 2.05, $CHCl_3$); HPLC (DAICEL CHIRALPAK AD-H, 2-propanol/hexane 1/20, flow 1.0 mL/min, detection at 230 nm) t_R 9.5 min (minor) and 13.6 min (major).

6.4. Transformation of *tert*-nitroaldols

*6.4.1. (R)-N-(2-Cyclohexyl-2-hydroxy-propyl)-acetamide (**4a**)*

A suspension of **3a** (21.4 mg, 0.114 mmol) and 10% Pd/C (6.1 mg) in MeOH (1 mL) was stirred under H_2 (1 atm) at room temperature for 12 h. Then, the reaction mixture was filtrated through Celite pad and washed with Et_2O. The filtrates were evaporated under reduced pressure to give a crude amine. To a solution of the crude amine and Et_3N (0.017 mL, 0.122 mmol) in CH_2Cl_2 was added acetic anhydride (0.013 mL, 0.138 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched satd aq NH_4Cl. The mixture was extracted with Et_2O (×3), and combined organic layers were washed with brine and dried over Na_2SO_4. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH=90:10) to give **4a** (19.5 mg, 86%) as a colorless solid. Analytical data matched well with reported data in the literature.[24] Colorless solid; ^1H NMR ($CDCl_3$) δ 5.85 (br s, 1H), 3.31 (dd, *J*=14, 6.4 Hz, 1H), 3.21 (dd, *J*=14.0, 5.2 Hz, 1H), 2.00 (s, 3H), 1.83–1.64 (m, 5H), 1.41–1.33 (m, 1H), 1.25–0.95 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 170.3, 74.7, 47.6, 46.5, 27.8, 26.7, 26.6, 26.6, 26.4, 23.2, 21.4; $[\alpha]_D^{26}$ +2.4 (*c* 1.2, $CHCl_3$).

*6.4.2. (R)-Triethyl-(1-methyl-1-nitromethyl-3-phenyl-propoxy)-silane (**5c**)*

To a stirred solution of **3c** (51.7 mg, 0.247 mmol), and Et_3SiH (0.047 mL, 0.296 mmol) in CH_2Cl_2 (0.5 mL) was added $B(C_6F_5)_3$ (12.6 mg, 0.0247 mmol) at room temperature. After being stirred for 1.5 h at the same temperature, $B(C_6F_5)_3$ (12.6 mg) was added again. After 2.5 h, the reaction was quenched with H_2O. The mixture was extracted with Et_2O (×3). The combined organic layers were washed with brine and dried over Na_2SO_4. After concentration under reduced pressure, the residue was purified by neutral silica gel column chromatography (neutral SiO_2, hexane/Et_2O=95:5) to give **5c** (71.9 mg, 90%) as a colorless oil. IR (neat) ν 2956, 1552, 1145, 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30–7.18 (m, 5H), 4.40 (d, *J*=10.0 Hz, 1H), 4.11 (d, *J*=10.0 Hz, 1H), 2.77–2.64 (m, 2H), 1.98–1.87 (m, 2H), 1.46 (s, 3H), 0.96 (t, *J*=8.0 Hz, 9H), 0.63 (q, *J*=8.0 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 141.4, 128.5, 128.3, 126.0, 83.9, 74.2, 43.1, 30.4, 26.2, 7.0, 6.6; ESI-MS *m*/*z* 346 $[M+Na]^+$; HRMS [FAB(+)] calcd for $C_{17}H_{29}CsNO_3Si^+$ $[M+Cs]^+$: 456.0971; found 456.0964; $[\alpha]_D^{29}$ −6.5 (*c* 2.4, $CHCl_3$).

*6.4.3. (R)-3-(1-Methyl-3-phenyl-1-triethylsilanyloxy-propyl)-5-phenyl-isoxazole (**6c**)*

To a solution of **5c** (6.51 mg, 20.1 μmol) in dry benzene (0.5 mL) with one drop of Et_3N was added phenyl acetylene (4.4 μL,

40.2 μmol) and phenyl isocyanate (10.9 μL, 0.10 mmol) successively at room temperature. After stirring for 30 min, the mixture was refluxed for 40 h. Water was added to the mixture at rt, then one drop of 1 M HCl was added. The product was extracted with Et_2O (×3), and combined organic layer was washed with brine, and then dried over Na_2SO_4. After filtration, Et_2O was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=12:1) to give **6c** (6.87 mg, 84% yield) as a colorless oil. IR (neat) ν 2954, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.81–7.79 (m, 2H), 7.49–7.43 (m, 3H), 7.26 (dd, *J*=7.6, 7.7 Hz, 2H), 7.17–7.14 (m, 3H), 6.57 (s, 1H), 2.71 (ddd, *J*=4.9, 12.5, 13.5 Hz, 1H), 2.61 (ddd, *J*=5.2, 12.5, 12.5 Hz, 1H), 2.20 (ddd, *J*=5.2, 12.5, 13.5 Hz, 1H), 2.09 (ddd, *J*=4.9, 12.5, 12.5 Hz, 1H), 1.77 (s, 3H), 1.00–0.97 (m, 9H), 0.67–0.62 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 171.1, 169.3, 142.2, 130.0, 128.9, 128.3, 127.7, 125.8, 125.7, 98.4, 73.7, 46.7, 30.5, 27.5, 7.1, 6.6; ESI-MS *m*/*z* 193 $[M+Na]^+$; HRMS [FAB(+)] calcd for $C_{25}H_{33}CsNO_2Si^+$ $[M+Cs]^+$: 540.1329; found 540.1334; $[\alpha]_D^{26}$ +1.1 (*c* 3.2, $CHCl_3$).

6.4.4. (*R*)-2-Hydroxy-2-methyl-4-phenyl-butyric acid (**7c**)

To a stirred solution of **5c** (28.4 mg, 87.8 μmol) in dimethyl sulfoxide (0.44 mL) and acetic acid (75.4 μL, 1.32 mmol) was added sodium nitrite (60.6 mg, 0.878 mmol) at room temperature. The resulting mixture was stirred at room temperature for 12 h and then at 40 °C for 8 h. The solution was cooled down to room temperature and quenched with 1 M HCl. The mixture was extracted with Et_2O (×3). The combined organic layers were washed with 2 M NaOH (3). Then, the combined water layers were acidified with 4 M HCl. The acidic water layer was again extracted with diethyl ether (×3), and combined organic layers were dried over Na_2SO_4. After filtration of Na_2SO_4, solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH=6:1) to give **7c** (16.8 mg, 99% yield) as a colorless solid. **7c** is known compound.[25] The absolute configuration of **7c** was determined after conversion into a known ethyl ester. ^1H NMR (CD_3OD) δ 7.21–7.18 (m, 2H), 7.13–7.09 (m, 3H), 2.82 (ddd, *J*=3.4, 13.2, 13.2 Hz, 1H), 2.53 (ddd, *J*=4.1, 12.6, 13.2 Hz, 1H), 2.10 (ddd, *J*=3.4, 12.6, 13.2 Hz, 1H), 1.85 (ddd, *J*=4.1, 13.2, 13.2 Hz, 1H), 1.45 (s, 3H); ^{13}C NMR (CD_3OD) δ 179.4, 143.3, 129.4, 129.3, 126.8, 75.4, 43.7, 31.3, 26.5; $[\alpha]_D^{31}$ +16.9 (*c* 0.13, MeOH).

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