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Asymmetric synthesis of tricyclic-cyclobutane by means of enantioselective deprotonation and intramolecular Michael–aldol reaction

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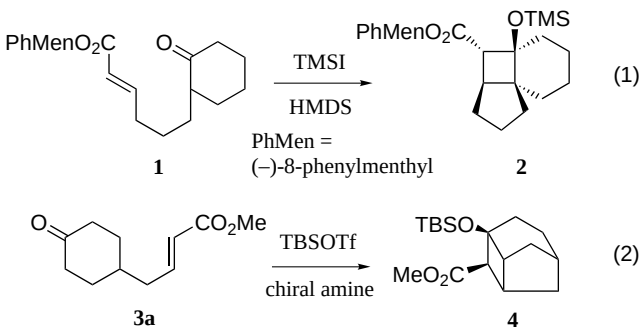
Abstract—We have demonstrated the syntheses of enantiomerically enriched tricyclo[4.2.1.$0^{3,8}$]nonanes from C_s symmetric cyclohexanones by means of enantioselective deprotonation, followed by an intramolecular Michael–aldol reaction. The asymmetric deprotonation was achieved in up to 79% ee and the following Michael–aldol reaction gave the corresponding tricyclononanes with almost the same optical purity.

We have developed a sequential intramolecular Michael–aldol reaction as a powerful methodology for the formation of fused cyclobutyric skeletons.[1,2] Cyclobutane derivatives have been known to be an important and attractive class of compounds. The ring systems are often found in natural substances,[3] and also play important roles in organic transformation as useful synthetic intermediates due to their unique reactivity originated from their high ring strain.[4] However, in spite of the usefulness, the methodology of the asymmetric formation of cyclobutyric ring is limited in preparative organic chemistry.[5,6] Recently, we have reported two types of asymmetric intramolecular Michael–aldol reaction, which could easily access to enantiomerically enriched cyclobutanes (Scheme 1). One example was chiral auxiliary induced diastereoselective Michael–aldol reaction of α-substituted cyclohexanones **1** (Eq. (1)).[2a,2c] Another was the enantioselective reaction of **3a** mediated by a chiral amine–silyltriflate complex, whose asymmetric induction was based on enantioselective enol silylation process of the C_s symmetric 4-substituted cyclohexanone **3a** (Eq. (2)).[2b] However, the resulted optical yields of **4** were not satisfactory for the synthetic needs. For further elaboration of the asymmetric Michael–aldol reaction, the more effective desymmetrization process of C_s symmetric substrates should be crucial. In this communication, we describe the asymmetric syntheses of tricyclic cyclobutane derivatives from 4-substituted cyclohexanones by means of an intramolecular Michael–aldol reaction adopted enantioselective deprotonation reaction[7] as an effectual asymmetric induction method.

Koga and Simpkins have elaborated asymmetric deprotonation reactions of C_s symmetric ketones by the use of chiral lithium amides to give optically active enolates in excellent enantioselectivities.[7] Recently, on the basis of the above reaction Weinreb succeeded in enantioselective intramolecular alkylation of 4-substituted cyclohexanone in 80% ee.[8] First, we tested direct intramolecular Michael–aldol reaction of **3a** using lithium amides, but no cyclobutane compounds were observed under any conditions. We modified the plan into stepwise synthesis as follows: the chiral enolate was trapped as the corresponded silyl enol ether, and then the enolate equivalent was subjected to Michael–aldol reaction conditions.



Scheme 1.

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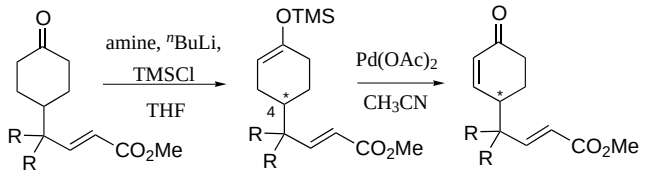
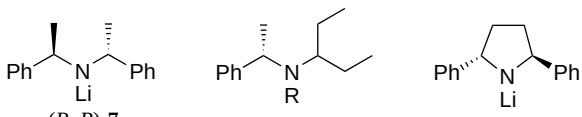
Asymmetric deprotonation reaction of **3a** and **3b** was explored using chiral lithium amide bases in the presence of trimethylsilyl chloride (TMSCl), which was called the ISQ (in situ quench) protocol.[9] The optical purity of **5** was determined by HPLC analysis using a chiral column after the transformation into enone **6** (Scheme 2). The treatment of **3a** with 1.3 equiv. of the lithium amide (*R*,*R*)-**7** resulted in no formation of silyl enol ether **5a** (Table 1, run 1). The use of more than 2 equiv. of base afforded the desired **5a** in good yields (runs 2–4). On the other hand, **3b**[10] having no acidic proton on γ-position of α,β-unsaturated ester was transformed into silyl enol ether **5b** by using only 1.3 equiv. of base (runs 5–7). Interestingly, these results indicated that the γ-proton of enoate moiety of **3a** would be preferentially abstracted rather than the α-proton of keto-carbonyl group under the above conditions, although it is generally accepted that the kinetic abstraction of enoate's γ-proton is slower than one of the α-proton of ketone. The reaction of **3a** along with 2.4 equiv. of (*R*,*R*)-**7** at −100°C gave (−)-**5a** in 65% ee (run 2). The use of (*S*)-**8a**[11] furnished (+)-**5a** in 66% ee (run 3), whereas cyclic amide (*S*,*S*)-**9**[12] resulted in low asymmetric induction (run 4). As was the case for the reaction of **3a**, (*S*)-**8a** gave the best result in asymmetric deprotonation of **3b** to furnish (+)-**5b** with 79% ee (run 6).



Scheme 2.

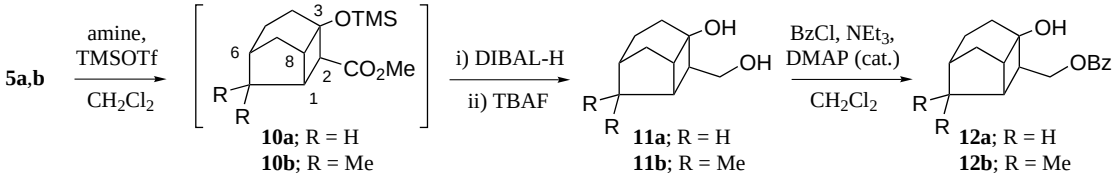
Next, intramolecular Michael–aldol reaction of optically active **5** was performed under amine–trimethylsilyl trifluoromethanesulfonete (TMSOTf) conditions.[2b] The reaction of (+)-**5a** and (+)-**5b** afforded tricyclo[4.2.1.0^{3,8}]nonanes (+)-**10a** and (+)-**10b**, respectively. However, on account of the difficulty to isolate pure **10**, full characterization was established after their transformation into the corresponding diol **11**. Their optical yields were concluded by chiral HPLC analyses after the conversion into benzoate **12** (Scheme 3). No racemization was observed in the Michael–aldol reaction of (+)-**5a** (66% ee) with $^{i}Pr_2NEt$–TMSOTf at −30°C and **11a** was obtained in 79% yield (Table 2, run 1). The reaction of (+)-**5b** (79% ee) resulted in the formation of **11b** with 77–78% ee,[13] but the chemical yield depended on the reaction temperature and the reagent (runs 2–4).

Table 1. Asymmetric deprotonation reaction of **3**



Run	Ketone	Base (equiv.)	5		6[e]	
			% Yield	$[\alpha]_D^{22}$	% ee[f]	Config.
1	**3a**	(*R*,*R*)-**7** (1.3)	0[a]	–	–	–
2	**3a**	(*R*,*R*)-**7** (2.4)	80[b]	nd[d]	65	*R*
3	**3a**	(*S*)-**8a** (2.4)	84[b]	+29.5	66	*S*
4	**3a**	(*S*,*S*)-**9** (2.4)	79[b]	+19.7	29	*S*
5	**3b**	(*R*,*R*)-**7** (1.3)	88[c]	−40.3	61	*S*
6	**3b**	(*S*)-**8a** (1.3)	85[c]	+49.2	79	*R*

[a] Reaction was carried out with **3a** (1 equiv.), amine (1.3 equiv.), BuLi (1.3 equiv.) and TMSCl (5.0 equiv.) in THF at −78°C.
[b] **3a** (1 equiv.), amine (2.4 equiv.), BuLi (2.4 equiv.) and TMSCl (5.0 equiv.) in THF at −100°C.
[c] **3b** (1 equiv.), amine (1.3 equiv.), BuLi (1.3 equiv.) and TMSCl (5.0 equiv.) in THF at −100°C.
[d] Nd means not determined.
[e] The chemical yields of **9** ranged from 65 to 99% yield.
[f] All enantiomeric excesses were determined through chiral HPLC analysis using a Chiralcel AD column.



Scheme 3.

Table 2. Intramolecular Michael–aldol reaction of nonracemic **5**

Run	Substrate (% ee)	Michael–aldol conditions		**11**	
		Reagents[a]	Temperature	% Yield[b]	% ee[c]
1	(+)-**5a** (66)	$^{i}Pr_2NEt$, TMSOTf	−30°C	79	66
2	(+)-**5b** (79)	NEt_3, TMSOTf	−30°C	29	78
3	(+)-**5b** (79)	NEt_3, TMSOTf	rt	54	78
4	(+)-**5b** (79)	(*S*)-**8b**, TMSOTf	rt	89	77

[a] Reaction was carried out with **5** (1 equiv.), amine (3.2 equiv.), TMSOTf (3 equiv.) in CH_2Cl_2.
[b] Overall yields from **5** in three steps.
[c] All enantiomeric excesses were determined through chiral HPLC analysis using a Chiralcel OJ column after transformation into **12**.

The best result was accomplished by the use of amine (*S*)-**8b** along with TMSOTf at room temperature (run 4).

The absolute configurations of **5a** and **10a** were determined by correlation with one of the known compound **12a** after the derivatization.[2b] In consequence, the chiralities of (+)-**5a** and (+)-**10a** were assigned as (4*S*) and (1*S*,2*S*,3*R*,6*S*,8*S*), respectively. The predominance of the introduced chirality during enantioselective deprotonation reaction of **3a** was consistent with the established rules by Simpkins.[7a] According to this, the absolute configurations of (+)-**5b** and (+)-**10b** might be (4*R*) and (1*S*,2*S*,3*R*,6*R*,8*S*), respectively.[14]

In summary, we have demonstrated the asymmetric syntheses of tricyclo[4.2.1.$0^{3,8}$]nonanes from C_s symmetric cyclohexanones by means of enantioselective deprotonation, followed by intramolecular Michael–aldol reaction. It is worth mentioning that five stereogenic centers of **10** could be constructed with up to 78% ee in the above operations.

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13. Spectral data for **11b**; colorless prisms: mp 56.5–57.5°C (as the racemate); ^{1}H NMR ($CDCl_3$) δ: 0.91 (3H, s), 1.01 (3H, s), 1.54–1.77 (8H, m), 2.16–2.24 (1H, m), 2.40–2.75 (1H, br s), 2.64 (2H, dd, J=12.1, 4.9 Hz), 3.75 (1H, dd, J=11.0, 4.4 Hz), 3.90 (1H, dd, J=11.0, 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ: 19.5, 20.3, 27.7, 30.5, 30.8, 40.0, 41.7, 43.7, 45.3, 47.5, 64.4, 74.2; HRMS calcd for $C_{12}H_{20}O_2$ 196.1462 (M^+), found 196.1443.
14. Although the absolute configurations of (+)-**5a** and (+)-**5b** would be the same stereochemical sense, the (*R*) and (*S*) symbols are defined as opposite to each other according to the IUPAC rule. Similarly, the *RS* designations of **10a** and **10b** are not identical.