Chiral amine–silyl triflate complex mediated asymmetric intramolecular Michael–aldol reaction *via* a novel enantioselective enol silylation process

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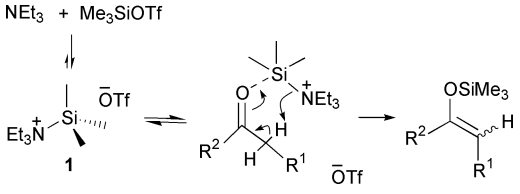
An asymmetric intramolecular Michael–aldol reaction of a C_s symmetric ketone using chiral amine and silyl triflate is described as a new methodology of chiral induction; nonracemic tricyclic cyclobutanes were obtained from a 4-substituted cyclohexanone in high yields with moderate enantioselectivities in one step.

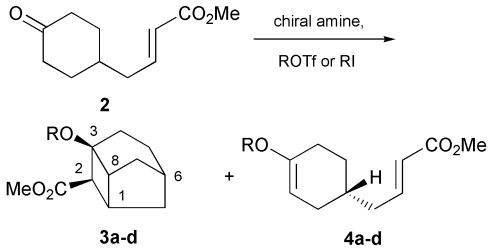
Carbon–carbon bond-forming reactions are among the most fundamental and important methodologies in organic transformations, and many of them have been focused and elaborated to give asymmetric products. Recently, the asymmetric C–C bond formations induced by the desymmetrization of C_s symmetric compounds have emerged as a powerful strategy for asymmetric synthesis.[1] For example, an asymmetric deprotonation of the prochiral ketones, followed by C–C bond formation (alkylation, aldol reaction, Michael reaction, *etc.*), can afford useful chiral intermediates.[2,3] Simpkins and Koga have elaborated the excellent desymmetrization process of C_s symmetric ketones by the use of chiral lithium amide bases to give enantiomerically enriched enolate equivalents with excellent enantioselectivities.[2–4]

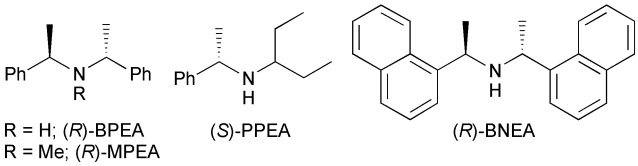
We have established the intramolecular Michael–aldol reaction as a new and efficient methodology to build polycyclic cyclobutanes.[5] The reaction of a C_s symmetric substrate, such as **2**, could form two bonds and five stereogenic centers with high stereoselectivity in a single operation. However, the use of lithium amides resulted in the termination of the reaction at the mono-Michael addition stage.[5b] The cascade reaction proceeded only under silyl triflate–amine, silyl iodide–hexamethyldisilazane (HMDS), or boron triflate–HMDS conditions. Simchen has shown that enol silylation using triethylamine in the presence of TMSOTf proceeds through the coordination of silyl ammonium complex **1** to carbonyl oxygen followed by deprotonation and silylation (Scheme 1).[6] Based on this mechanism, a chiral amine reagent in the presence of silyl triflate could be envisaged to effect an asymmetric induction in the Michael–aldol reaction. We herein report an enantioselective intramolecular Michael–aldol reaction of a prochiral substrate *via* asymmetric enol silylation as a new method of chiral induction.

We first examined suitable conditions for the intramolecular Michael–aldol reaction of **2** (Scheme 2). It was observed that more than 3 equiv. of amine and silyl triflate at temperatures higher than −30 °C were required for the production of **3** in high yield, whereas the use of 1.2 equiv. of the reagents gave the enol ether **4** quantitatively at −78 °C. The Michael–aldol reaction was typically performed as follows. To a solution of **2**



Scheme 1





Scheme 2

(0.26 mmol) in CH_2Cl_2 was added chiral amine (0.83 mmol) at room temperature. This solution was then cooled to −78 °C and silyl triflate (0.78 mol, −78 °C) was added dropwise. The whole was stirred for several hours at −78 °C, and further stirring was continued at −30 °C or at rt.[7] After the usual work up, the product **3** was purified by column chromatography (silica gel). The enantiomeric excess of **3** was determined, after its transformation into **5**, by HPLC analysis using a chiral column.[8] The asymmetric reaction using a variety of silyl Lewis acids with bis[(*R*)-1-phenylethyl]amine (BPEA) was investigated (Table 1). The reaction with TMSOTf afforded (−)-**3a** with 23% ee (run 1). Although no significant improvement was observed in the reaction with TMSI instead of triflate (run 2), the enantioselectivities were increased by the use of bulky silyl triflates such as TESOTf and TBDMSOTf (runs 3 and 4). However, the reaction with the bulkier triflate, TIPSOTf, furnished no Michael–aldol adduct **3d** but only the silyl enol ether **4d** (run 5). On the basis of the above observation, the following studies were carried out using TBDMSOTf as the silyl Lewis acid.

Results using various chiral amines under standard conditions are shown in Table 2. With bis[(*R*)-1-(1-naphthyl)ethyl]-

Table 1 Effect of silyl Lewis acids to the Michael–aldol reaction of **2** in the presence of (*R*)-BPEA[a]

Run	Reagent	Product	Yield (%)	ee (%)[b]	Yield of **4** (%)
1	TMSOTf	(−)-**3a**	58	23	6
2	TMSI	(−)-**3a**	39	24	Not isolated
3	TESOTf	(−)-**3b**	31	28	46
4	TBDMSOTf	(−)-**3c**	89	31	Trace
5	TIPSOTf	**3d**	0	—	73

[a] Reactions were carried out at −78 to −30 °C. [b] All enantiomeric excesses were determined, after transformation into **5**, through chiral HPLC analysis using a Chiracel OJ column.

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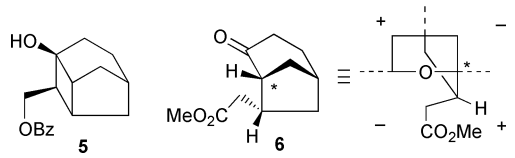
Table 2 Asymmetric Michael–aldol reactions using chiral amine and TBDMSOTf

			Yield (%)		ee (%)	
	Chiral amine	Temp./°C	**3c**	**4c**	**3c**[a]	**4c**[b,c]
1	(*R*)-BPEA	−78 to rt	85	14	32	nd
2	(*R*)-MPEA	−78 to rt	82	11	7	nd
3	(*S*)-PPEA	−78 to rt	87	8	8[d]	nd
4	(*R*)-BNEA	−78 to rt	88	12	36	35
5	(−)-sparteine	−78 to rt	77	9	8	nd
6	(*R*)-BPEA	rt	75	8	12	nd
7	(*R*)-BPEA	−78	0	88	—	31
8	(*R*)-BPEA	−90 to rt	85	13	42	nd

[a] All enantiomeric excesses were determined, after transformation into **5**, through chiral HPLC analysis using a Chiralcel OJ column. [b] Ees were determined in the same manner as **3c**, after conversion into (−)-**3c** by the treatment of (−)-**4c** with TBDMSOTf in the presence of NEt_3 at rt. [c] 'nd' means 'not determined'. [d] (+)-**3c** was obtained.

amine (BNEA) as chiral amine, (−)-**3c** and (−)-**4c** were obtained in 88 and 12% yield with 36 and 35% ee, respectively (run 4). Reactions in the presence of other amines, such as *N*-methylbis[(*R*)-1-phenylethyl]amine (MPEA), 3-pentyl-(*S*)-1-phenylethylamine (PPEA)[3a] and (−)-sparteine, afforded less than 10% ee of **3c** (runs 2, 3 and 5). The effect of temperature was as expected; higher enantioselectivities were observed at lower temperature (see runs 1, 6 and 8). The reaction, carried out at −90 °C to rt, resulted in 42% ee of **3c** (run 8). Note, quenching the reaction at −78 °C produced only the silyl enol ether **4c** having 31% ee (run 7).

The absolute configuration of (−)-**3c** was determined by circular dichroism of bicyclo[3.2.1]octanone **6** (24% ee; $[\theta]$ = +708, λ = 296 nm), which was obtained by treatment of (−)-**3c** (24% ee) with hydrogen fluoride–pyridine complex. The application of the octant rule[9] suggested (*R*)-configuration at the asterisked carbon of **6**. Accordingly, (−)-**3c** has a (1*S*,2*R*,3*S*,6*R*,8*R*)-tricyclo[4.2.1.0^{3,8}]nonane structure.



Some possibilities can be considered for the asymmetric induction of the above reaction. One is the desymmetrization of C_s symmetric substrate **1** by means of enantioselective enol silylation. Another possibility is that kinetic resolution is involved in the Michael–aldol reaction of silyl enol ether **4**. However the latter induction process could be ruled out by the observation that the treatment of isolated racemic **4c** with TBDMSOTf in the presence of (*R*)-BPEA at −78 °C to rt furnished only the racemate of **3c**. Hence, the asymmetric induction of the reaction occurs in the enol silylation step. To our knowledge this is the first demonstration of asymmetric enol silylation without the use of amide base.[10] The asymmetric intramolecular Michael–aldol reaction subsequently proceeds under the same conditions. It is worth noting that we have demonstrated the direct asymmetric C–C bond-forming reaction of a C_s ketone in a single operation, omitting the isolation of an enolate equivalent, to give a nonracemic tricyclo-[4.2.1.0^{3,8}]nonane compound. Further studies on the development and the application of this asymmetric process are in progress.

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7 We found that **4a** was racemized at temperatures higher than −30 °C under the Michael–aldol conditions, but **4b**–**c** were not racemized even at room temperature. Consequently, the asymmetric Michael–aldol reaction with TMSX had to be carried out at −78 to −30 °C.

8 **5** was obtained from **3** in 3 steps. That is, the reduction of **3** by DIBAL-H, followed by desilylation and acylation with benzoyl chloride, gave the benzoate **5**.

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