

A new synthesis of pyrrolidines via imino-aldol reaction of (2-trimethylsilylmethyl)cyclopropyl ketones with imines

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Abstract

A new synthesis of 2,3,5-trisubstituted pyrrolidines from the imino-aldols formed from Lewis acid-mediated reactions of (2-trimethylsilylmethyl)cyclopropyl ketones with benzylimines is described. The ring closure of the imino-aldols formed from the benzylimines of 2-chloro-, 2-fluoro-, and 2-trifluoromethylbenzaldehydes proceeds with predominantly 2,5-*anti* selectivity to generate the corresponding pyrrolidines in moderate yields.

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The [3+2] addition of aldehydes, ketones, acetylenes, and allenes to 1,3-dipoles generated from silylmethyl-substituted cyclopropanes constitutes a reliable method for the stereoselective synthesis of carbocycles and heterocycles containing an oxygen atom.¹ The enolate generated from the ring-cleavage of a trimethylsilylmethyl-substituted cyclopropyl ketone has previously been reported by us to react with carbonyls to deliver aldol products that were subsequently transformed into tetrahydrofuran² derivatives under oxidative conditions. As an extension, we considered the reaction of the above enolate with imines to deliver imino-aldols. Reactions allowing the formation of σ_{C-C} bonds from imines have been widely studied due to their important synthetic applications.³ The above imino-aldol products were transformed further into substituted pyrrolidine derivatives, an important five-membered ring heterocycle due to its frequent occurrence in many biologically active molecules,⁴ applications as valuable synthetic intermediates⁵ and as organocatalysts.⁶ Often the type and degree of substitution about the pyrrolidine ring can have

a pronounced effect on the biological activity of a given substrate.

We searched for a protocol for the reaction of cyclopropyl phenyl ketone **1a** with benzylimine of benzaldehyde **2a** mediated by a Lewis acid in dichloromethane. Among the several common Lewis acids, which were examined under different conditions, $TiCl_4$ (1.2 equiv, CH_2Cl_2 , 0 °C → rt, 6 h) was found to work reasonably well and the desired products, **3a** and **4a**, were isolated as an 80:20 diastereomeric mixture in 41% combined yield. The **2a:1a** stoichiometry was 1.5:1. The remainder of the cyclopropyl substrate was transformed into 3-butenyl phenyl ketone in 46% yield and the imine was hydrolyzed to benzaldehyde and benzylamine. Increasing the **2a:1a** stoichiometry to 3:1 did not improve the yield.

The above experiment using suspended K_2CO_3 (2 equiv) furnished the product in a slightly improved 50% yield with an identical diastereomeric ratio (Eq. 1). The remainder of the cyclopropyl substrate was transformed into 3-butenyl phenyl ketone (35% yield). With a view to effectively neutralizing any HCl that may be formed from the hydrolysis of $TiCl_4$ by the adventitious moisture and, thus, prevent quenching of the enolate, an experiment with a combination of $TiCl_4$ and Et_2AlCl (1.2 equiv each, 0 °C → 25 °C,

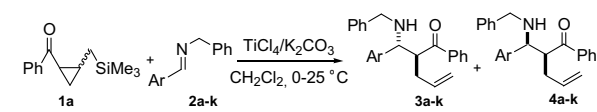
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1 h) was carried out.^{1e} However, the reaction was complicated and several products were formed. With $\text{BF}_3 \cdot \text{OEt}_2 \cdot \text{K}_2\text{CO}_3$ (1.2 equiv $\text{BF}_3 \cdot \text{OEt}_2$, 2.0 equiv K_2CO_3 , $0^\circ\text{C} \rightarrow 25^\circ\text{C}$, 6 h), the diastereomeric ratio was raised to 87:13. However, the yield was poor (24%). The cyclopropane substrate was transformed largely into 3-butenyl phenyl ketone (67% yield). The relative stereochemistry of the imino-aldol products was determined from the relative stereochemistry of the derived pyrrolidine products that, in turn, was determined from NOE experiments (vide infra). We, therefore, used the $\text{TiCl}_4 \cdot \text{K}_2\text{CO}_3$ combination and explored other reactions.

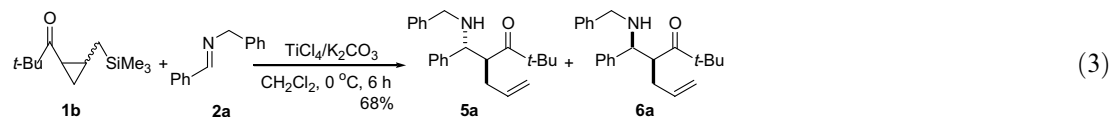
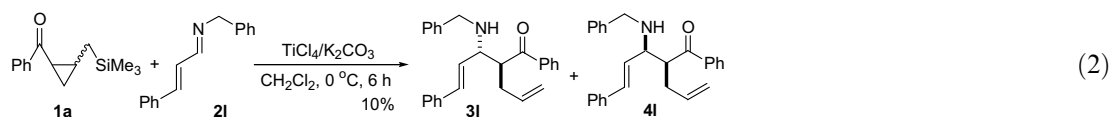
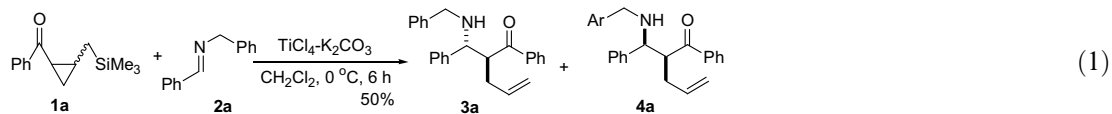
The substituents on the nitrogen of the imine influenced the reaction strongly. *N*-Sulfonylimine was a poor substrate, the reaction was complicated and the desired imino-aldol product was not formed. *N*-*p*-Methoxy-benzylimine afforded the desired imino-aldol products in 41% combined yield as a 77:23 diastereomeric mixture. *N*-Benzylimine, therefore, offered the optimal results in terms of both the yield and the diastereoselectivity.

Having established the feasibility and optimal conditions for the imino-aldol reaction, we studied the reactions of the benzylimines of different aromatic aldehydes with cyclopropane **1a**. The imines were synthesized by condensation of benzylamine and the corresponding aldehydes in 1:1 ratio in dichloromethane in the presence of 4 Å molecular sieves, followed by filtration and concentration. The residue, thus obtained, was used directly for the reactions. As shown in Table 1, the reaction of **1a** with several benzylimines **2a–k** furnished the expected imino-aldol products in moderate yields and high diastereoselectivity. The ratio of the two diastereomers ranged from 80:20 to 98:2. Aromatic benzylimines with electron-donating substituents were less reactive than aromatic benzylimines with electron-attracting substituents (cf. entries 2–4 vs 5–11).

Table 1
Reactions of **1a** with imines **2a–k**



Entry	Ar	Yield of 3 + 4 (%)	dr (<i>anti:syn</i>)
1		50	80:20
2		30	93:7
3		28	74:26
4		38	88:12
5		43	87:13
6		44	85:15
7		41	80:20
8		47	80:20
9		48	98:2
10		41	80:20
11		43	93:7



The benzylimines of vinylogous aromatic aldehydes reacted poorly. The reaction of **1a** with the benzylimine of *trans*-cinnamaldehyde **2l** provided the products **3l** and **4l** as an 85:15 diastereomeric mixture in only 10% yield (Eq. 2). The benzylimines of pyridine-3-carboxaldehyde and furfural were hydrolyzed into the corres-

ponding aldehydes and amines and all the cyclopropane had transformed into 3-butenyl phenyl ketone. Likewise, the benzylimine of 3-methyl-2-butenal also did not react; it too was hydrolyzed into its constituents and the cyclopropane substrate had transformed into 3-butenyl phenyl ketone. Aliphatic aldehydes

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