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Aldol Reactions of Ketone Donors with Aryl Trifluoromethyl Ketone Acceptors Catalyzed by 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) for Concise Access to Aryl- and Trifluoromethyl-Substituted Tertiary Alcohols

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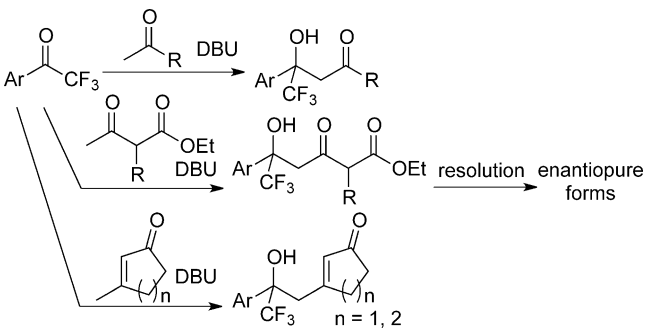
Abstract: Molecules bearing aryl- and trifluoromethyl-substituted tertiary alcohol moieties are important as bioactive molecules, enantiomer-discriminating reagents, and their synthons and building blocks. To concisely synthesize these molecules, we have developed aldol reactions of ketone donors with aryl trifluoromethyl ketone acceptors catalyzed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The reactions were relatively fast, and the products were obtained in good to high yields under mild conditions. The C–C bonds of the aldol reactions formed in perfect regioselectivities at the methyl group of the alkyl methyl ketones, at the γ-position of the β-keto esters, and at the methyl group of the β-methyl-substituted cyclic enones. For the aldol products from the reactions of β-keto esters, the enantiomerically pure forms were obtained by resolution of the enamines of the aldol products with a homochiral amine. Our methods provide a concise, fast access to molecules with tetrasubstituted carbon centers with trifluoromethyl-substituted alcohol moieties.

Keywords: aldol reaction; amines; chiral resolution; organocatalysis; regioselectivity

Molecules bearing aryl- and trifluoromethyl-substituted tertiary alcohol moieties are often found in pharmaceuticals, biological probes, enantiomer-discriminating reagents, and the synthons and building blocks of these molecules.[1] Accordingly, the development of the methods to efficiently synthesize these molecules is of interest.[1,2] Here we report the development of aldol and vinylogous aldol reactions of aryl trifluoromethyl ketones as acceptors catalyzed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) that concisely provide molecules bearing tertiary alcohols with aryl and trifluoromethyl groups (Scheme 1). We also report the development of a method to provide access to enantiomerically pure forms of the aldol products obtained from the reactions of the β-keto ester donors.

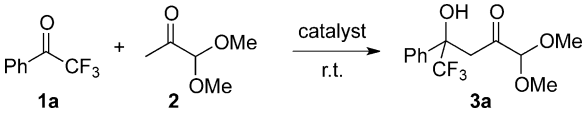
Recently we reported DBU-catalyzed aldol reactions of a pyruvic aldehyde derivative with isatins.[3] The reactions were fast and efficient to provide the aldol products with tetrasubstituted carbon centers under mild conditions; reactions for only 15 to 30 min gave the aldol products in reasonable yields. Based on these previous results, we reasoned that the DBU catalysis would be useful for aldol reactions of aryl trifluoromethyl ketone acceptors to construct molecules with tetrasubstituted carbon centers bearing aryl, trifluoromethyl, and hydroxy groups.

First, DBU catalysis conditions were evaluated to obtain the aldol product in the reaction of phenyl trifluoromethyl ketone (**1a**) with a pyruvic aldehyde de-



Scheme 1. Aldol and vinylogous aldol reactions performed using DBU as catalyst, and the following resolution of the enantiomers in this study.

Table 1. Reaction of **1a** with **2** to give **3a**.[a]

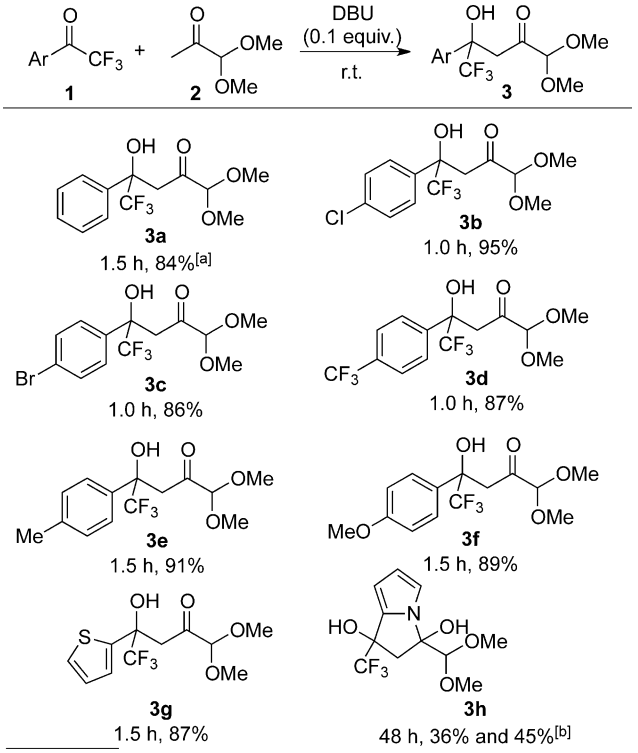


Entry	Catalyst (equiv.)	Time [h]	Conversion[b] [%]	Yield[c] [%]
1[d]	DBU (0.2)	6	ND	52
2	DBU (0.2)	1.5	>95	83
3[e]	DBU (0.2)	1.5	>95	ND
4[e]	DBU (0.1)	1.5	>95	84
5[e,f]	DBU (0.1)	1.5	>95	94
6	Et_3N (0.2)	6	0	–
7	DMAP (0.2)	6	0	–
8	DABCO (0.2)	6	0	–

[a] *Reaction conditions:* Ketone **1a** (0.5 mmol, 1 equiv.), **2** (10 equiv.), and catalyst (0.2 or 0.1 equiv. as indicated) were stirred at 25 °C except where noted otherwise. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DMAP = 4-(dimethylamino)pyridine; DABCO = 1,4-diazabicyclo[2.2.2]octane. ND = not determined.
[b] Conversion of **1a** was determined by ^1H NMR.
[c] Isolated yield.
[d] Toluene (1.0 mL) was used as solvent.
[e] Ketone **2** (5.0 equiv.).
[f] Ketone **1a** (5.0 mmol), ketone **2** (25.0 mmol), DBU (0.5 mmol).

rivative **2**, which was used for our previous DBU-catalyzed reactions with isatins.[3] The results are shown in Table 1. Similar to previous results,[3] the DBU catalysis in toluene afforded aldol product **3a** at room temperature (25 °C) (entry 1). But, the reaction rate was not fast; a 6 h-reaction yielded **3** in 52% (entry 1). When reactions were performed in neat conditions, the aldol product was obtained in high yields (83–94%) after 1.5 h (entries 2–5). Use of 0.1 equiv. of DBU was sufficient to give **3a** in high yields (entries 4 and 5). The conditions used for entries 4 and 5 (**1a**, 1 equiv.; **2**, 5 equiv.; DBU 0.1 equiv.; 25 °C) were the best among the conditions tested. Note that other amine bases such as Et_3N, DMAP, and DABCO did not act as catalyst for this aldol reaction (entries 6–8).

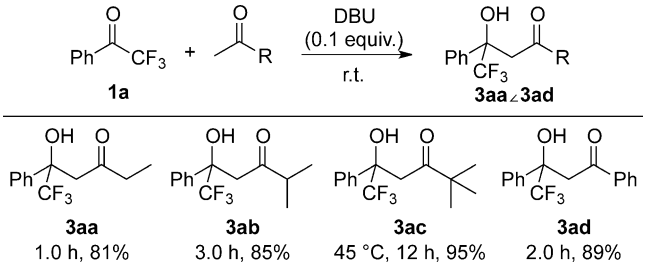
Next, the best conditions identified for the reaction between **1a** and **2** were used for aldol reactions of **2** with various aryl trifluoromethyl ketones (Scheme 2). A series of trifluoromethyl-substituted aldol products **3a**–**3g** were obtained in high yields within 1.0 h to 1.5 h regardless the electron-withdrawing or electron-donating substituent on the aryl group of the substrate. For the pyrrole-bearing substrate with an acidic proton, protection of the pyrrole NH was not necessary to lead to the aldol C–C bond formation, and the reaction gave **3h**, the cyclized form of the product.



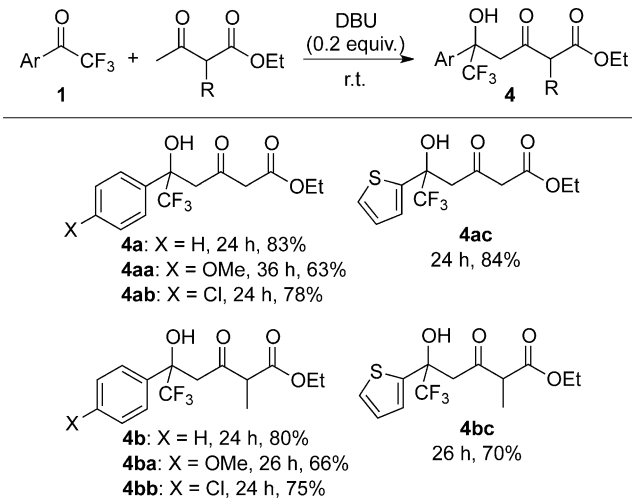
[a] Data from Table 1, entry 4.
[b] DBU (0.2 equiv.) was used. Two diastereomers of **3h** were separately obtained.

Scheme 2. Aldol reactions of **2** with various aryl trifluoromethyl ketones. *Reaction conditions:* ketone **1** (1.0 equiv.), ketone **2** (5.0 equiv.), and DBU (0.1 equiv.) at 25 °C.

The DBU catalysis was also tested in reactions of various ketone donors with phenyl trifluoromethyl ketone acceptor (Scheme 3). Ethyl methyl ketone, isopropyl methyl ketone, *tert*-butyl methyl ketone, and phenyl methyl ketone also acted as nucleophiles to give the corresponding aldol products **3aa**–**3ad** in high yields. The C–C bond formation occurred regioselectively at the methyl group, the less substituted α-carbon, when applicable. For the reaction of hindered *tert*-butyl methyl ketone, on heating at 45 °C product **3ac** was obtained in high yield.



Scheme 3. Aldol reactions of **1a** with alkyl methyl ketones and with methyl phenyl ketone. *Reaction conditions:* ketone **1a** (1.0 equiv.), donor ketone (5.0 equiv.), and DBU (0.1 equiv.) at 25 °C except as noted otherwise.

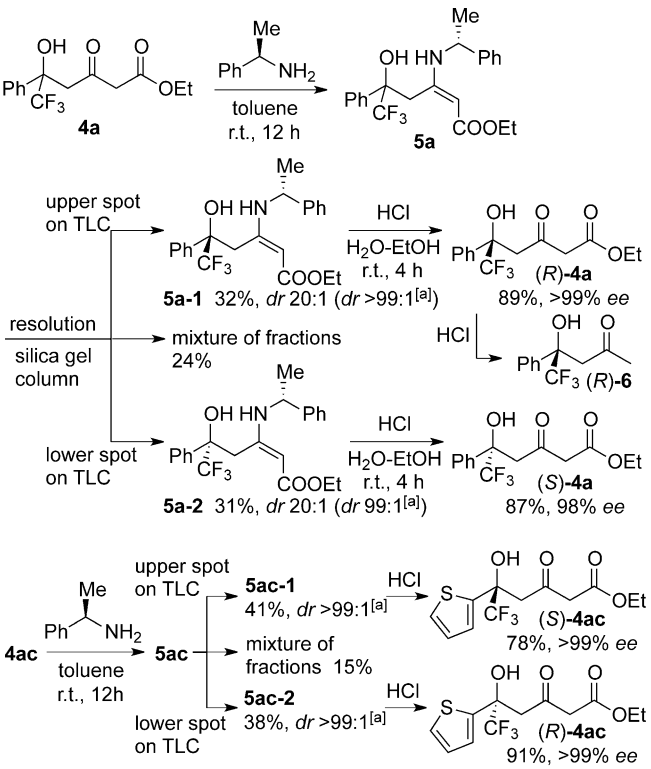


Scheme 4. Aldol reactions of β-keto esters with various aryl trifluoromethyl ketones. *Reaction conditions:* ketone **1** (1.0 equiv.), β-keto ester (10 equiv.), and DBU (0.2 equiv.) at 25 °C.

β-Keto esters also acted as nucleophiles to give the corresponding aldol products **4** under the DBU catalysis. For these reactions, the C–C bond formation occurred at the γ-position regioselectively (Scheme 4). During the reaction to form **4a**, formation of **4a** was observed by ^{1}H NMR analyses even at the initial stages of the reaction (such as at 5 min, 50 min, 130 min, and 220 min); however, no sign of the product with the bond formation at the α-position of the β-keto ester was detected.

In reported reactions of β-keto esters, the bond formation often occurs at the α-position.[4] In previously reported methods for bond-forming reactions at the γ-position of β-keto esters, severe conditions, such as the use of two equivalents of strong bases to form a dianion, are typically required.[5,6] Alternatively, aldol reactions of β-keto esters at the γ-position have been performed using preformed silyl dienol ethers or alkyl dienol ether derivatives.[7] In our reactions, β-keto esters were directly used as the substrates, and only catalytic amounts of DBU were necessary to give the aldol products of the bond formation at the γ-position of β-keto esters under mild conditions.

Whereas DBU-catalyzed aldol reactions give racemic products, enantiomerically pure forms of the aldol products were obtained through resolution *via* the formation of enamines with a homochiral amine (Scheme 5). When aldol products were mixed with (*R*)-1-phenylethylamine, stable enamines **5** were obtained. Purification of each of the diastereomers of the enamines, followed by hydrolysis of the enamines afforded essentially enantiomerically pure forms (such as >99% *ee*) of the aldol products. In addition, a 15 mmol scale (**1a**, 2.1 mL) aldol reaction to give **4a** was easily performed; with the resolution of enamine



[a] Data after crystallization.

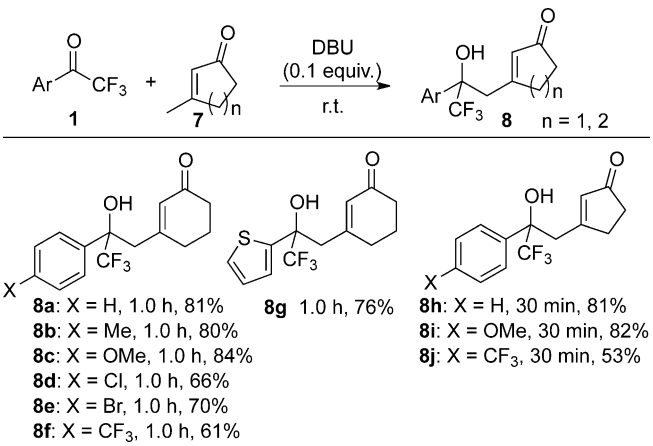
Scheme 5. Resolution of **4** to give the enantiomerically pure forms. Separations of **5a-1** and **5a-2**, and of **5ac-1** and **5ac-2**, were performed using single-time, typical silica gel flash column chromatography.[8] The *dr* values were determined by ^{1}H NMR. The *ee* values were determined by HPLC.

5a, 0.4 g of the enantiopure form of (*R*)-**4a** was concisely obtained. These results suggest that the DBU-catalyzed aldol reactions and the resolution method can easily be further scaled up.[8]

The absolute stereochemistry of enantiomer **4a** obtained from enamine **5a-1** (upper spot product on TLC) was determined to be *R* by conversion to the known ketone **6**[2c] and also by X-ray crystal structure analysis of enamine **5a-1**.[9]

The DBU catalysis was also useful for vinylogous aldol reactions of β-methyl-substituted cyclic enones **7** to give **8** (Scheme 6). For these substrates, the bond formation occurred selectively at the methyl group.[10,11]

In summary, we have developed concise, fast, practical DBU-catalyzed aldol and vinylogous aldol reactions of ketone donors with aryl trifluoromethyl ketones that can be performed under neat, mild conditions to give aldol products bearing tetrasubstituted carbon centers with trifluoromethyl-substituted alcohols. The C–C bond formation occurred regioselectively at the methyl group of alkyl methyl ketones, at the γ-position of β-keto esters, and at the methyl group of β-methyl-substituted cyclic enones to give



Scheme 6. Vinylogous aldol reactions of β-methyl-sustituted cyclic enones. *Reaction conditions:* ketone **1** (1.0 equiv.), enone (5.0 equiv.), and DBU (0.1 equiv.) at 25 °C.

the respective products. For the aldol products from the reactions of β-keto esters, enantiomerically pure forms of the products were concisely obtained by the resolution of the enamines of the aldol products with a homochiral amine. The reactions were easily performed on small scale to gram scale. The DBU catalysis methods reported here efficiently provided products including those that were previously difficult to synthesize, that were synthesized only in slow reactions, and/or that required preactivation/protection and deprotection steps. Our DBU catalysis methods are complementary to other methods including organocatalytic methods, such as amine-based organocatalysis methods involving formation of enamines *in situ*, and Mukaiyama aldol methods.[12] Further development of the DBU catalysis method is underway in our laboratory.

Experimental Section

General Procedure

To a mixture of donor ketone (2.5 mmol) and **1** (0.5 mmol) was added DBU (0.05 mmol), and the mixture was stirred at room temperature (25 °C) until **1** was consumed (monitored by TLC). The reaction mixture was diluted with hexane-EtOAc and purified by silica gel flash column chromatography (hexane/EtOAc = 8:1 to 4:1) to give **3**.

Acknowledgements

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