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Stereoselective synthesis of aminoindanols *via* an efficient cascade aza-Michael–aldol reaction†‡

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An efficient organocatalyzed strategy for the synthesis of 3-amino-1-indanols has been developed. This method is complementary to the conventional Friedel–Crafts strategy. It is also applicable to the synthesis of enantioenriched 3-amino-1-indanols.

Indane is an important structural unit in organic synthesis and medicinal chemistry.[1] Specifically, aminoindanols represent a particularly important family of indane-containing compounds, which are found in numerous natural products and biologically active compounds, such as HIV protease inhibitors (*e.g.* **I**, Fig. 1)[2] and rasagiline derivatives with anti-Parkinson activity (*e.g.* **II**).[3] Nevertheless, despite the significance, methods for the efficient and stereocontrolled assembly of the aminoindanol skeletons are underdeveloped. For example, currently most widely employed synthesis of 3-amino-1-indanols and their derivatives largely relies on the reduction of the corresponding aminoindanones obtained from an intramolecular Friedel–Crafts acylation reaction of 3-amino-3-phenylpropanoic acid derivatives, typically in the presence of a strong Lewis or Brønsted acid, such as $AlCl_3$, H_2SO_4, or PPA.[4,5] The use of strong acids may hamper its utility when labile functional groups are involved. Moreover, the inherent nature of Friedel–Crafts reaction, which typically favors electron-rich aromatic rings, may limit the scope of this synthetic strategy. Furthermore, enantioenriched aminoindanols were obtained with chiral HPLC separation or chiral resolving agents, such as tartaric acid derivatives and enzymes.[6] Herein, we report a new organocatalyzed strategy for the stereoselective synthesis of 3-amino-1-indanols *via* an efficient aza-Michael–aldol cascade reaction under basic conditions.

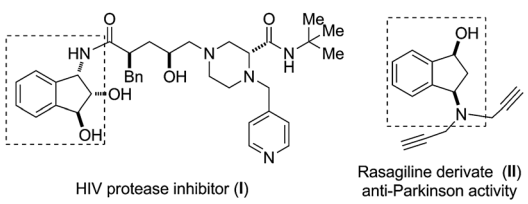
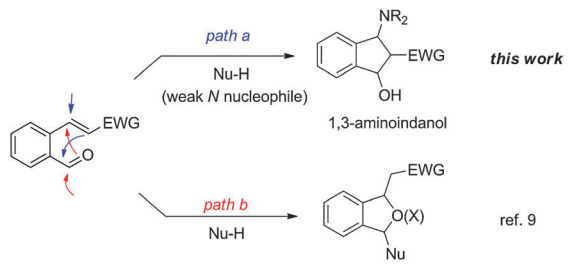


Fig. 1 Selected bioactive compounds with aminoindanol subunits.



Scheme 1 Design of the aza-Michael–aldol cascade reaction.

Recently, organocatalytic cascade reactions have been demonstrated as a powerful tool for rapid construction of various complex scaffolds.[7] Among them, aza-Michael and aldol reactions proved to be successful components. Inspired by these examples, we hypothesized that benzaldehyde substituted with a Michael acceptor at the *ortho*-position may provide a good setup for an aza-Michael–aldol cascade reaction with a nitrogen-nucleophile to synthesize 1,3-aminoindanols (path a, Scheme 1).[8] However, the expected aza-Michael-initiated cascade may be interfered by the initial nucleophilic attack on the more reactive aldehyde functionality to alter the reaction sequence (path b).[9] Therefore, in order to favor the desired path a, we reasoned that the proper choice of a weak nitrogen-nucleophile is important.

With the above reasoning in mind, we set out to evaluate our hypothesis with the weak nucleophile *p*-toluenesulfonamide **2a** (Table 1). We were pleased to find that the reaction between **1a** and **2a**, in the presence of 20 mol% of ^{t}BuOK, proceeds smoothly to afford the desired aminoindanol product **3a**, albeit in low yield and with moderate diastereoselectivity (entry 1). The structure and stereochemistry of the product were confirmed by single crystal X-ray diffraction.[10] In the absence of a base, no desired product **3a** was observed (entry 2). Next, we examined a range of inorganic and

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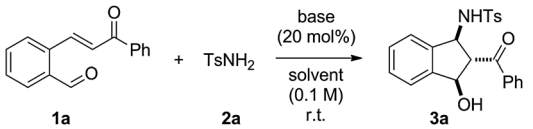
‡ Electronic supplementary information (ESI) available: Experimental procedure and compound characterization. CCDC 902390–902392 and 904189. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc37102b

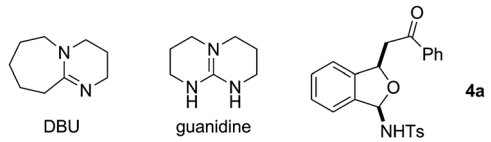
Table 1 Condition optimization



1a 2a 3a

Entry	Base	Solvent	Time (h)	Conv. (%)	Yield[a] (%)	dr[b]
1	^{t}BuOK	MeCN	6	100	63	5 : 1
2	—	MeCN	6	<5	0	—
3	DABCO	MeCN	6	<10	—	—
4	KHMDS	MeCN	6	90	—[g]	—
5	NaHMDS	MeCN	6	90	—[g]	—
6	Et_3N	MeCN	6	<30	0[h]	—
7	Na_2CO_3	MeCN	6	<60	<5[h]	—
8	K_2CO_3	MeCN	6	100	49	7 : 1
9	$CsCO_3$	MeCN	6	100	63	9 : 1
10	K_3PO_4	MeCN	6	90	48[h]	7 : 1
11	Guanidine	MeCN	6	100	57	5 : 1
12	DBU	MeCN	6	100	82	10 : 1
13	DBU	THF	6	100	78	4 : 1
14	DBU	EtOAc	6	100	76	8 : 1
15[c]	DBU	MeCN	6	100	80	8 : 1
16[d]	DBU	MeCN	6	100	72	11 : 1
17[e]	DBU	MeCN	12	90	71	7 : 1
18[f]	**DBU**	**MeCN**	**20**	**100**	**92**	**8 : 1**

[a] Isolated yield. [b] dr was determined by ^{1}H NMR and represents the ratio of the major diastereomer and the total of the minor isomers. [c] Run at 0.2 M concentration. [d] Run at 0.05 M concentration. [e] 10 mol% of DBU was used. [f] Run at 0 °C. [g] A mixture of many products was obtained. [h] Product **4a** was observed.



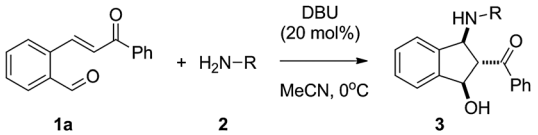
4a

organic bases (entries 3–12), such as DABCO, Et_3N, Na_2CO_3, DBU, *etc.* It is worth noting that the reaction with some of these bases, such as Na_2CO_3 and K_3PO_4 (entries 7 and 10), affords a mixture of **3a** and **4a**, suggesting that the proposed path b (Scheme 1) is a competitive reaction. Among these bases, DBU provides the best results with exclusive formation of the desired **3a** (entry 12). Further screening of reaction parameters, such as solvent, concentration, catalyst loading, and reaction temperature, identified the best reaction conditions (entry 18). We also employed aniline and benzylamine as nucleophiles, but both reactions afford a complex mixture of various products. These results corroborate our hypothesis that the choice of a weak nucleophile is important.

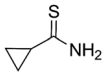
With the standard conditions established (entry 18, Table 1), we next examined the reaction scope. As shown in Table 2, a range of electron-rich and electron-deficient arenesulfonamides participate efficiently in the aza-Michael–aldol cascade reaction and the desired 3-amino-1-indanol products can be obtained in good yield and with good stereoselectivity (entries 1–5). This process can also be applied to other weak nitrogen-nucleophiles, such as alkyl sulfonamides and thioamides (entries 6–8).

During our scope study of the nucleophiles, we found that thiourea as the nucleophile results in the formation of a completely different set of products. As shown in eqn (1)–(3), regardless of the different electron-withdrawing groups (*e.g.* ketone **1a**, nitrile **1i**, and ester **1j**), the reactions with thiourea all gave the isoindolin-1-ol type products (**5a**–**5c**), presumably due to the relatively strong nucleophilicity of the

Table 2 Nucleophile scope

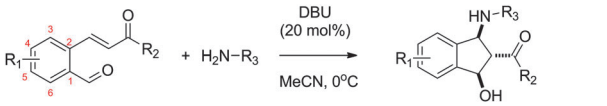


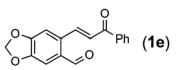
1a 2 3

Entry	R–NH_2	Product	Yield[a] (%)	dr
1	R_1 = *p*-Me	**3a**[b]	92	8 : 1
2	R_1 = H	**3b**	88	6 : 1
3	R_1 = *p*-MeO	**3c**	85	8 : 1
4	R_1 = *o*-NO_2	**3d**	72	>30 : 1
5	R_1 = *p*-NO_2	**3e**	89	15 : 1
6	$MeSO_2NH_2$	**3f**	82	5 : 1
7	^{t}BuSO_2NH_2	**3g**	84	8 : 1
8		**3h**[b]	86	5 : 1

[a] Isolated yield. [b] The structure was confirmed by X-ray diffraction.

Table 3 Aldehyde scope

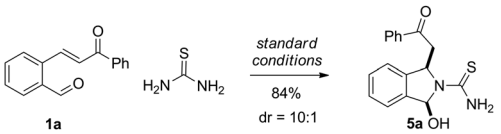


Entry	R_1	R_2	R_3–NH_2[b]	Product	Yield[a] (%)	dr
1	4-F	Ph (**1b**)	$TsNH_2$	**3i**	87	8 : 1
2	4-F	Ph (**1b**)	$NosNH_2$	**3j**	80	3 : 1
3	5-CF_3	Ph (**1c**)	$TsNH_2$	**3k**	93	8 : 1
4	5-CF_3	Ph (**1c**)	$NosNH_2$	**3l**	82	7 : 1
5	4,5-$(MeO)_2$	Ph (**1d**)	$NsNH_2$	**3m**	84	20 : 1
6		(**1e**)	$TsNH_2$	**3n**	86	10 : 1
7	H	*p*-MeOPh (**1f**)	$TsNH_2$	**3o**	89	9 : 1
8	H	*p*-MeOPh (**1f**)	$NosNH_2$	**3p**	80	3 : 1
9	H	*p*-NO_2Ph (**1g**)	$TsNH_2$	**3q**	90	4 : 1
10	H	*p*-NO_2Ph (**1g**)	$NsNH_2$	**3r**	76	20 : 1
11	H	Me (**1h**)	$NosNH_2$	**3s**	84	7 : 1

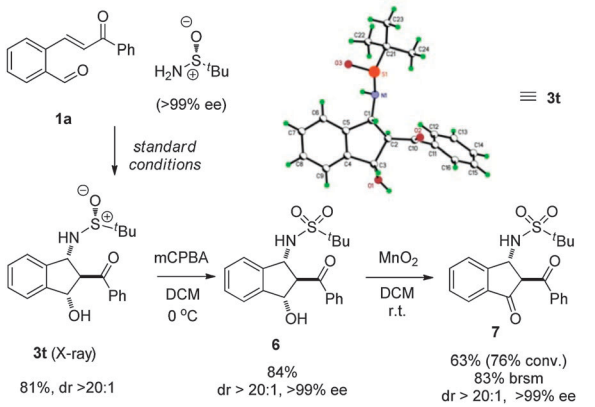
[a] Isolated yield. [b] Ns: 2-nitrobenzenesulfonyl; Nos: 4-nitrobenzenesulfonyl.

nitrogen atom in the cyclization step. In the case of ester **1j**, tricyclic product **5c** was obtained, which results from a further intramolecular transamidation step (eqn (3)). It is noteworthy that all these reactions are highly efficient and diastereoselective.

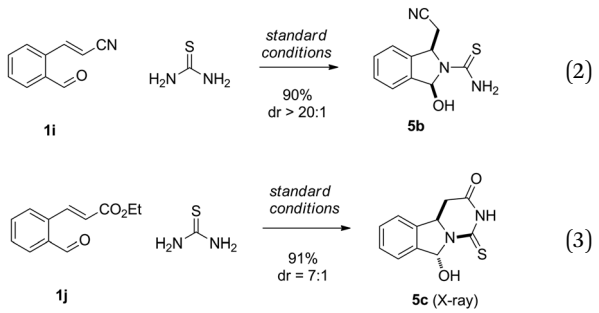
The aldehyde substrate scope is shown in Table 3. The reaction efficiency is not affected by the electronic nature of the aryl linker, which is a potential problem in the conventional synthesis employing Friedel–Crafts reaction. Thus, substrates with either electron-rich or electron-deficient aryl linkers all give good to excellent yield and diastereoselectivity. Similarly, we also evaluated the effect of the substituent (R_2) on the carbonyl group. Again, the desired aminoindanol products are efficiently formed with either an electron-rich or an electron-poor aryl group. Alkyl ketones are also effective substrates (entry 11).



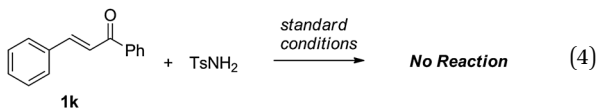
1a 5a (1)



Scheme 2 Synthesis of enantioenriched 3-amino-1-indanol derivatives.



We have also carried out a control experiment, hoping to get some insight into the kinetic and thermodynamic profile of the reaction. As shown in eqn (4), chalcone **1k** does not participate in the conjugate addition reaction with $TsNH_2$ under our standard conditions. This result is consistent with the mechanism in which the first aza-Michael reaction is reversible, favoring the starting material, and the subsequent intramolecular aldol reaction is thermodynamically favorable and rate-determining.



We were also interested in applying our method in the synthesis of enantioenriched aminoindanol products. Gratifyingly, without modification of the standard conditions, the desired aza-Michael–aldol cascade process with (*R*)-*tert*-butanesulfinamide[11] as the nucleophile proceeds smoothly to afford the desired product **3t** with excellent efficiency and stereocontrol (Scheme 2). The structure and absolute stereochemistry of the product were also confirmed by single crystal X-ray diffraction.[10] The product can also be transformed to other useful compounds. For example, after a simple oxidation step, sulfonamide **6** can be obtained with >99% ee; further oxidation by MnO_2 affords enantiopure aminoindanone **7** with high efficiency (83% yield based on recovered starting material, >99% ee).

In summary, we have developed an organocatalyzed strategy for the efficient and diastereoselective synthesis of 3-amino-1-indanols, a privileged skeleton of significant importance in organic synthesis and medicinal chemistry. Under mild and basic conditions, the current reaction is complementary to the conventional Friedel–Crafts strategy, where strong acidic conditions are employed and the cyclization step highly depends on the substrate electronic environment. Without modification, the standard conditions can be applied to the synthesis of enantioenriched 3-amino-1-indanols using a cleavable chiral sulfinamide nucleophile.

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10 CCDC 902390 (**3a**), 902391 (**3h**), 904189 (**5c**) and 902392 (**3t**). Compounds **3a**, **3h**, and **5c** are racemic, and compound **3t** is enantiopure‡.

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