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COMMUNICATION

N-Heterocyclic carbene-catalyzed [4 + 1] annulation of phthalaldehyde and imines†

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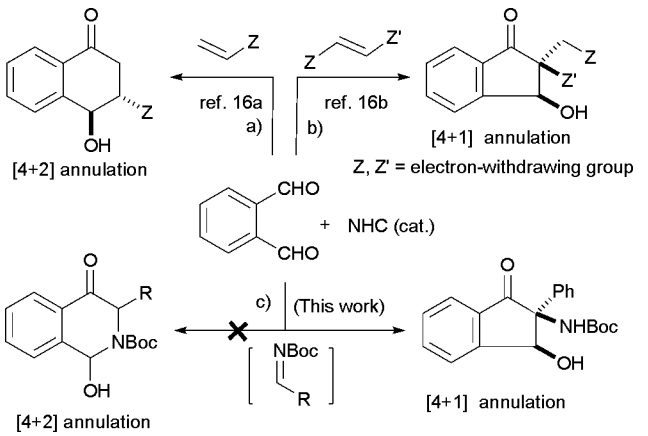
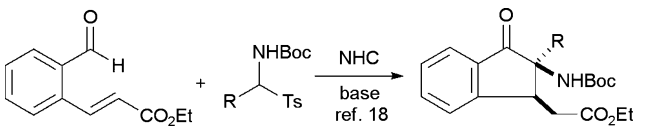
The diastereoselective synthesis of *cis*-2-amino-3-hydroxyindanones was realized by the N-heterocyclic carbene-catalyzed [4 + 1] annulation of phthalaldehyde and imines, which may involve a tandem aza-benzoin reaction and aldol reaction.

During recent decades, N-heterocyclic carbenes (NHCs) have been found to be efficient catalysts for a wide variety of reactions.[1] Following the pioneering NHC-catalyzed benzoin condensation of aldehydes,[2] the aza-benzoin reaction of aldehydes with imines and the Stetter reaction of aldehydes with Michael acceptors have also been developed.[3] In the past few years, NHCs were further demonstrated very successfully as catalysts for the extended umpolung of functionalized aldehydes, such as α,β-unsaturated-, α-halo-, α, β-epoxy-, α, β-aziridinyl-, and β-lactam aldehydes.[4] Furthermore, NHC catalysts were also effective for transesterification,[5] polymerization of lactides,[6] acylation,[7] umpolung of Michael acceptors,[8] aza-Morita–Baylis–Hillman reaction,[9] activation of silylated nucleophiles,[10] reactions of ketenes[11,12] and other reactions.[13]

Tandem reactions, which allow rapid construction of complex molecules from simple starting materials in one pot, have proved useful in modern synthesis.[14] Very recently, Gravel *et al.* reported an efficient synthesis of indanes by NHC-catalyzed tandem reaction of aldehydes with Michael acceptors.[15] We reported a tandem Stetter–aldol reaction of phthalaldehyde to give hydroxytetralones as the [4 + 2] annulation product or hydroxyindanones as the [4 + 1] annulation product by employing monoactivated or 1,2-diactivated Michael acceptors (Scheme 1, reactions a and b).[16] In this paper, we wish to report an NHC-catalyzed tandem reaction of phthalaldehydes with imines, which give 2-amino-3-hydroxyindanone [17] as the [4 + 1] annulation product instead of the expected [4 + 2] annulation product (Scheme 1, reaction c). During the preparation of this manuscript, You *et al.* reported a novel NHC-catalyzed tandem aza-benzoin–Michael reaction of aldehydes and imines (Scheme 2).[18]



Scheme 1 NHC-catalyzed annulation reaction of phthalaldehyde.



Scheme 2 NHC-catalyzed tandem aza-bezoin–Michael reaction with imines by You *et al.*

The optimization of the reaction conditions for the model reaction of phthalaldehyde and *tert*-butyl phenyl(phenylsulfonyl)methylcarbamate (**2a**) was summarized in Table 1. Initially, potassium phosphate was used as the base both for the generation of NHC from a thiazolium salt and for generation of imine from its precursor. The reaction catalyzed by thiazolium salt **4a** in THF gave the corresponding [4 + 1] annulation product in 55% yield with exclusive *cis*-diastereoselectivity (entry 1). No improvement was observed for the reaction in toluene, dichloromethane or acetonitrile (entries 2–4). The yield was improved to 70% when Cs_2CO_3 (0.2 equiv.) was used to generate the carbene, and K_2CO_3 (2.0 equiv.) to facilitate the formation of the imine (entry 5). Further improvement was achieved when diisopropylethylamine (2.0 equiv.) was used (entry 6). Thiazolium iodide **4b** with an *N*-ethyl substituent worked albeit with a decreased yield (entry 7). Thiazolium chloride **4c**, without the free hydroxy group, also worked well for the reaction (entry 8).

The structure of indanone **3a** was unambiguous established by X-ray analysis of its crystal (Fig. 1).†[19]

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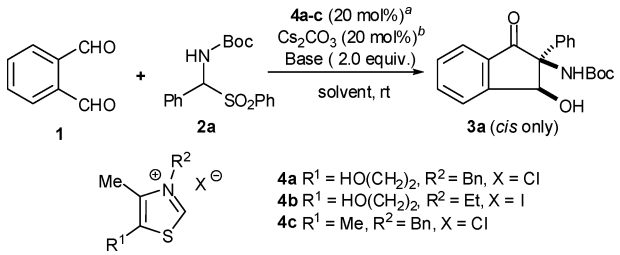
Table 1 Optimization of reaction conditions



Entry	4a–c	Base (2.0 equiv.)	Solvent	Yield (%)[c]
1[b]	**4a**	K_3PO_4	THF	55
2[b]	**4a**	K_3PO_4	toluene	37
3[b]	**4a**	K_3PO_4	CH_2Cl_2	34
4[b]	**4a**	K_3PO_4	CH_3CN	28
5	**4a**	K_2CO_3	THF	70
6	**4a**	DIPEA	THF	76
7	**4b**	DIPEA	THF	59
8	**4c**	DIPEA	THF	68

[a] NHCs **4a′–4c′** were generated from their precursors **4a–4c** (20 mol%) and Cs_2CO_3 (20 mol%) at room temperature for 20 min, and used immediately for the entries 5–8. [b] No Cs_2CO_3 was added for entries 1 to 4. [c] Isolated yield of pure *cis*-isomer, and no *trans*-isomer was observed for all the entries.

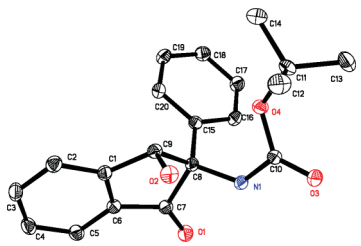
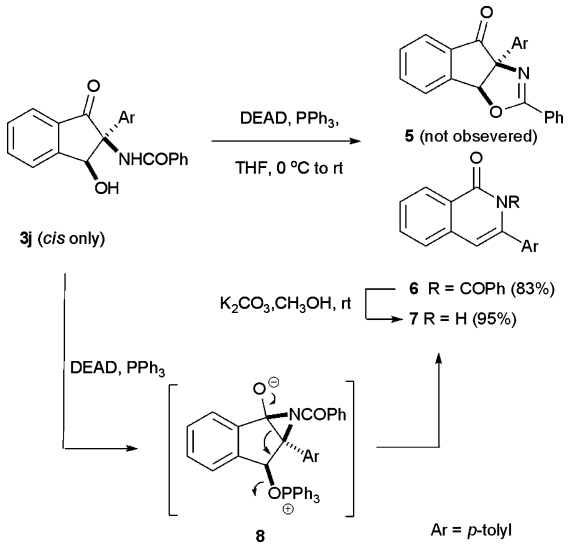


Fig. 1 X-Ray structure of indanone **3a**.

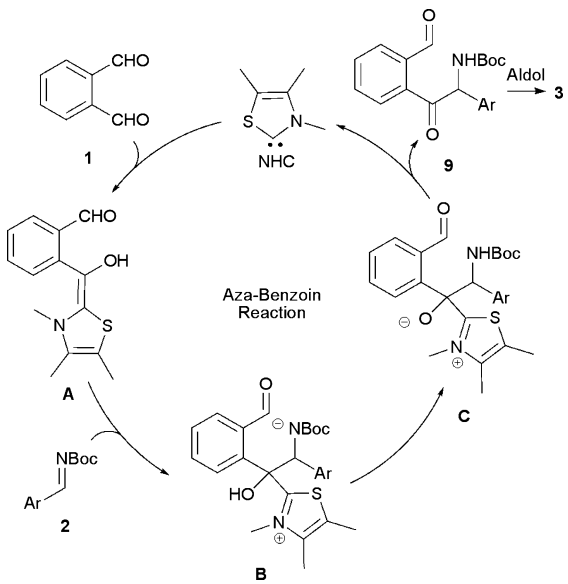
With the optimized reaction conditions in hand, the scope of the arylimines was then briefly investigated (Table 2). An imine with a *p*-chlorophenyl group gave the corresponding indanone in 83% yield (entry 2). Imines with electron-donating groups (4-Me, 4-MeO) on the phenyl ring worked but resulted in decreased yields (entries 3 and 4). The imine **2e** with a *m*-chlorophenyl group showed similar reactivity compared with *p*-chlorophenylimine, affording the corresponding indanone **3e** in 87% yield (entry 5). *m*-Nitrophenylimine worked very well for the [4 + 1] annulation reaction (entry 6). Heteroarylimines, such as 2-pyridylimine and 2-thienylimine, also worked well, giving the annulation product in very good yields (entries 7 and 8). *N*-Benzyl carbamate or *N*-benzoylimine is also compatible with the reaction (entries 9 and 10). It should be noted that only *cis*-isomers are observed for all reactions in Table 2.

The resulting highly functionalized indanones afford opportunity for chemical transformations. Interestingly, when the indanone **3j** was subject to the condition of DEAD and PPh_3, the generation of the expected dihydrooxazole **5** was not observed.[20] However, the isoquinolinone **6** was isolated in good yield, which may involve the aziridine **8** as the key intermediate (Scheme 3).[21] The structure of isoquinolinone **6** was proved by the synthesis of debenzoyl product **7** by a known procedure.[22]

A possible catalytic cycle of the NHC-catalyzed reaction is depicted in Scheme 4. The addition of the NHC to phthalaldehyde



Scheme 3 Synthesis of isoquinolinone **6**.

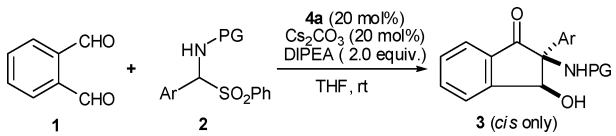


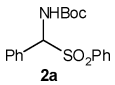
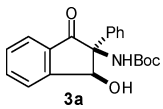
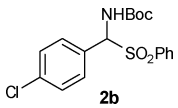
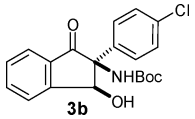
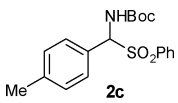
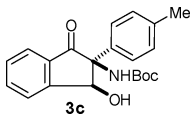
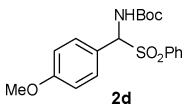
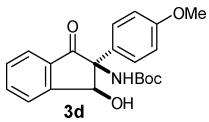
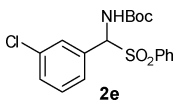
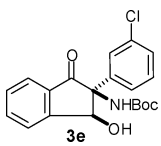
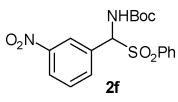
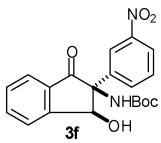
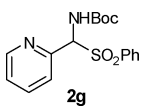
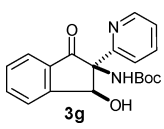
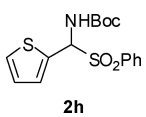
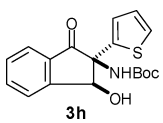
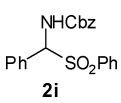
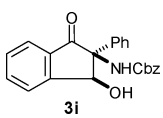
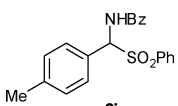
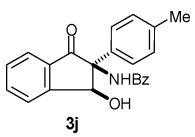
Scheme 4 Possible catalytic cycle.

gives Breslow intermediate **A**, which reacts with imine affording aza-benzoin reaction intermediate **B**. Proton shift(s) gives intermediate **C**, which is fragmented to regenerate the catalyst and α-aminoketone **9**.[23] The intramolecular aldol reaction of **9** affords the final 2-amino-3-hydroxyindanone **3**. An alternative reaction pathway without involving α-aminoketone **9** is also possible (Scheme 5). Proton shift of intermediate **B** gives a carbanion **D**, which attacks the aldehyde intramolecularly to give the cycloadduct **E**. Fragmentation of cycloadduct **E** releases the NHC catalyst and affords the final 2-amino-3-hydroxyindanone **3**.

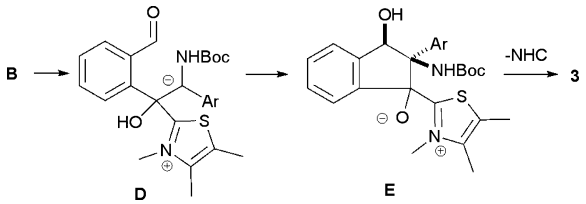
In conclusion, an N-heterocyclic carbene-catalyzed tandem aza-benzoin and aldol reaction of phthalaldehyde and imines was developed, which affords the corresponding *cis*-2-amino-3-hydroxyindanone as the formal [4 + 1] annulation product with exclusive *cis*-diastereoselectivity. The interesting reaction

Table 2 NHC-catalyzed [4 + 1] annulation of phthalaldehyde and imines



Entry	2	3	Yield[a] (%)
1			76
2			83
3			56
4			40
5			87
6			91
7			87
8			93
9			66
10			53

[a] Isolated yield of pure *cis*-isomer.



Scheme 5 Alternative reaction pathway.

mode of the imine and the potential application of the resulting aminohydroxyindanone may find application in organic synthesis.

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