

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 3632

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

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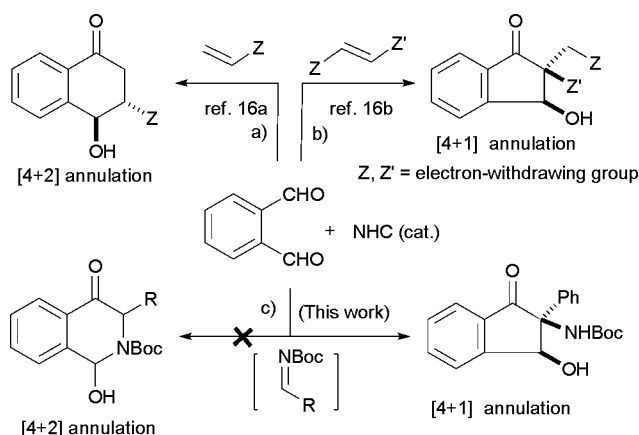
Received 18th January 2011, Accepted 23rd March 2011

DOI: 10.1039/c1ob05092c

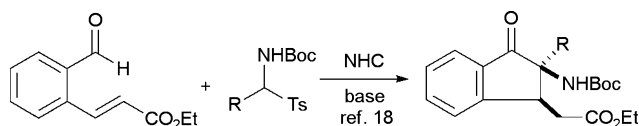
The diastereoselective synthesis of *cis*-2-amino-3-hydroxyindanonones was realized by the *N*-heterocyclic carbene-catalyzed [4 + 1] annulation of phthalaldehyde and imines, which may involve a tandem aza-benzoin reaction and aldol reaction.

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 hydroxyindanonones 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-hydroxyindanonone¹⁷ 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.

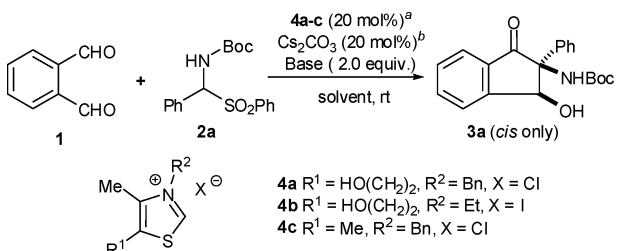
Scheme 2 NHC-catalyzed tandem aza-benzoin–Michael reaction with imines by You *et al.*

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 Cs₂CO₃ (0.2 equiv.) was used to generate the carbene, and K₂CO₃ (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 indanonone **3a** was unambiguously established by X-ray analysis of its crystal (Fig. 1).^{†19}

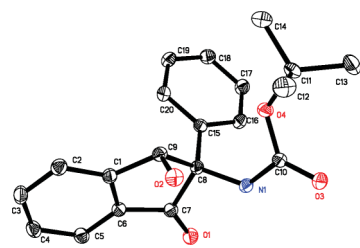
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† Electronic supplementary information (ESI) available: Copies of ¹H NMR, ¹³C NMR and CD spectra. CCDC reference number 807044. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05092c

Table 1 Optimization of reaction conditions


Entry	4a–c	Base (2.0 equiv.)	Solvent	Yield (%) ^c
1 ^b	4a	K ₃ PO ₄	THF	55
2 ^b	4a	K ₃ PO ₄	toluene	37
3 ^b	4a	K ₃ PO ₄	CH ₂ Cl ₂	34
4 ^b	4a	K ₃ PO ₄	CH ₃ CN	28
5	4a	K ₂ CO ₃	THF	70
6	4a	DIPEA	THF	76
7	4b	DIPEA	THF	59
8	4c	DIPEA	THF	68

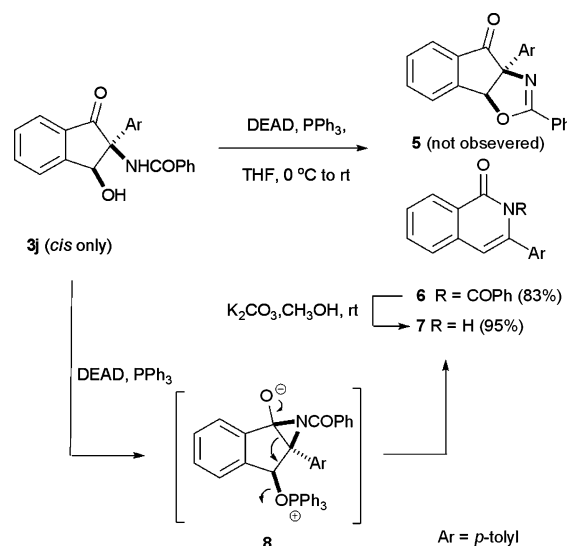
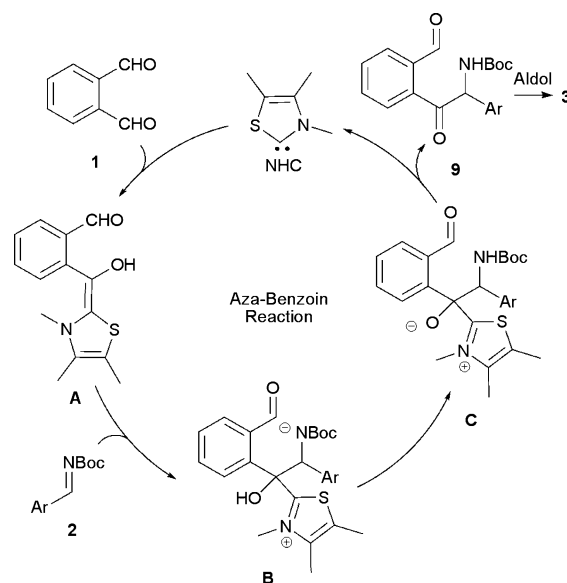
^a NHCs **4a'–4c'** were generated from their precursors **4a–4c** (20 mol%) and Cs₂CO₃ (20 mol%) at room temperature for 20 min, and used immediately for the entries 5–8. ^b No Cs₂CO₃ was added for entries 1 to 4. ^c Isolated yield of pure *cis*-isomer, and no *trans*-isomer was observed for all the 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 PPh₃, 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.

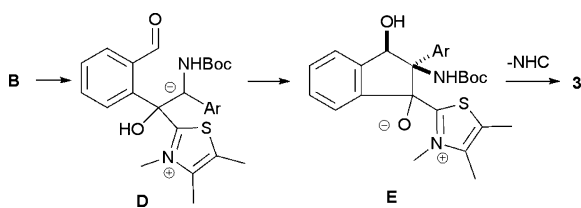
gives Breslow intermediate **A**, which reacts with imine affording aza-benzoin reaction intermediate **B**. Proton shift(s) gives intermediate **C**, which is fragmented to regenerate the catalyst and α -aminoketone **9**.²³ The intramolecular aldol reaction of **9** affords the final 2-amino-3-hydroxyindanone **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.

Financial support from National Science Foundation of China (20932008, 21072195), the Ministry of Science and Technology of China (2011CB808600) and the Chinese Academy of Sciences is gratefully acknowledged.

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