Diastereoselective Synthesis of 3-Hydroxyindanones via N-Heterocyclic Carbene Catalyzed [4+1] Annulation of Phthalaldehyde and 1,2-Diactivated Michael Acceptors

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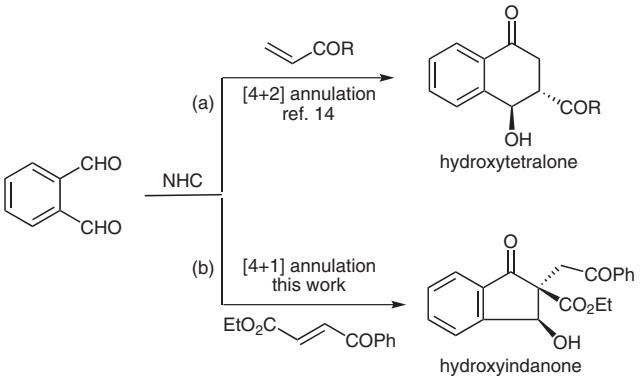
Abstract: The diastereoselective synthesis of 2,2-disubstituted-3-hydroxy-indanones was realized by the N-heterocyclic carbene catalyzed [4+1] annulation of phthalaldehyde and 1,2-diactivated Michael acceptors, which involves a tandem process of Stetter reaction, proton shift, and aldol reaction.

Key words: [4+1] annulation, tandem reaction, N-heterocyclic carbenes, indanone, Stetter reaction

Indanones are presented widely in many natural and unnatural bioactive compounds, various drugs and pharmaceutical candidates.[1] Thus, many methods have been developed for their construction,[2] including the classic intramolecular Friedel–Crafts acylation[3] and Nazarov cyclization.[4] In addition, many interesting approaches have been reported in recent years, such as the Pd-catalyzed cyclization of 3-(2-iodoaryl)propanenitriles,[5] Rh-catalyzed [5+1+2+1] cycloaddition of vinylcyclopropane, alkynes, and CO,[6] Rh-catalyzed hydroacylation of 2-vinyl benzaldehyde,[7] and other reactions.[8]

As a subunit of indanones, 3-hydroxyindanones show interesting bioactivity and are useful intermediates for organic synthesis.[9] However, the efficient methods for rapid construction of 3-hydroxyindanones are far less developed. There are only a few examples which synthesize 3-hydroxyindanones from simple starting materials.[10] Representative examples include Hallberg et al.'s Heck–aldol reaction of salicylic aldehydes with vinyl ether[11] and Grée et al.'s intramolecular isomerisation–aldolization of allylic alcohols.[12]

Tandem reactions, which allow two or more reactions occur consecutively in one pot, are of great interest in modern synthesis.[13] Recently, Gravel et al. reported a NHC-catalyzed tandem Stetter–Michael reaction,[14] and You et al. reported a tandem aza-benzoin–Michael reaction with interesting on-site reversal of the reactivity of *N*-Boc imines.[15,16] We reported a N-heterocyclic carbene (NHC)-catalyzed tandem Stetter–aldol reaction of phthalaldehyde and Michael acceptors to give hydroxytetralones as the [4+2]-annulation products (Scheme 1, a).[17] Interestingly, when we try to expand the substrate to 1,2-diactivated Michael acceptors, the corresponding hydroxyindanone was formed exclusively instead of hydroxytetralones (Scheme 1, b). Here we wish to report the primitive results of this tandem [4+1]-annulation reaction.



Scheme 1 NHC-catalyzed tandem reactions of phthalaldehyde and Michael acceptors

It was found that thiazolium NHC **4a′**, generated in situ from thiazolium salt **4a** in the presence of Cs_2CO_3, could catalyze the reaction of phthalaldehyde (**1**) and 1,2-diactivated Michael acceptor **2a** to give the [4+1]-annulation product of 3-hydroxyindanone **3a** in 96% yield with exclusive *cis* selectivity (Table 1, entry 1). It is interesting that thiazolium salt **4b** with *N*-ethyl substituent showed similar catalytic activity with **4a**, but salt **4c** without a free hydroxy group resulted in very low yield (entries 2 and 3). Solvent screening revealed that reaction worked well in THF, toluene, or dichloromethane but did not in diethyl ether (Table 1, entries 1, 4–6). Base screening showed K_2CO_3 and DBU worked as well as Cs_2CO_3 (Table 1, entries 7–9).

With the optimized reaction conditions in hand, the scope of the 1,2-diactivated Michael acceptors was briefly investigated (Table 2). Michael acceptors **2b**,**c** with electron-withdrawing group (4-$O_2NC_6H_4$, 4-ClC_6H_4) worked much better than **2d**,**e** with electron-donating group (4-MeC_6H_4, 4-$MeOC_6H_4$) (Table 2, entries 1–5). Michael acceptors **2f**,**g** with bulky substituent (2-ClC_6H_4, 2-naphthyl) also worked well (Table 2, entries 6 and 7). Considering the low yield of reaction of Michael acceptors **2d**,**e**

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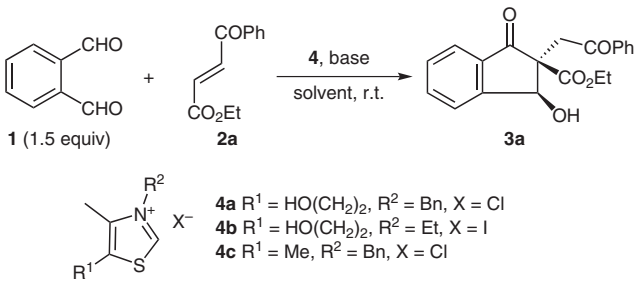
Table 1 Optimization of Reaction Conditions



4a $R^1 = HO(CH_2)_2$, R^2 = Bn, X = Cl
4b $R^1 = HO(CH_2)_2$, R^2 = Et, X = I
4c R^1 = Me, R^2 = Bn, X = Cl

Entry	4	Base (mol%)[a]	Solvent	Yield (%)[b]
1	**4a**	Cs_2CO_3 (20)	THF	96
2	**4b**	Cs_2CO_3 (20)	THF	95
3	**4c**	Cs_2CO_3 (20)	THF	20
4	**4a**	Cs_2CO_3 (20)	toluene	89
5	**4a**	Cs_2CO_3 (20)	CH_2Cl_2	94
6	**4a**	Cs_2CO_3 (20)	Et_2O	24
7	**4a**	Cs_2CO_3 (10)	THF	95
8	**4a**	K_2CO_3 (10)	THF	94
9	**4a**	DBU (10)	THF	95

[a] The NHC **4′** was generated from the corresponding thiazolium salt **4** in situ in the presence of the noted base.
[b] Isolated yields of pure *cis* isomer of **3a**. No *trans*-**3a** was detected.

with an electron-rich aryl group, it is better than expected that Michael acceptors with 2-furyl and 2-thienyl gave the corresponding hydroxyindanone in very good yields (entries 8 and 9). Michael acceptor **2j** with diketo group also showed good reactivity (entry 10). The spirocyclic hydroxyindanone **3k** could be obtained in reasonable yield (46%) when *N*-phenylmaleimide was used as the substrate (Table 2, entry 11).

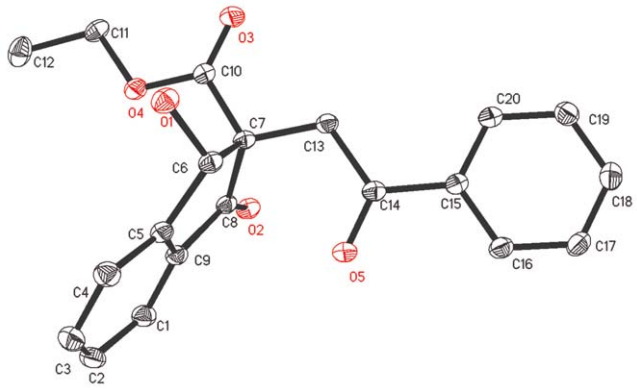
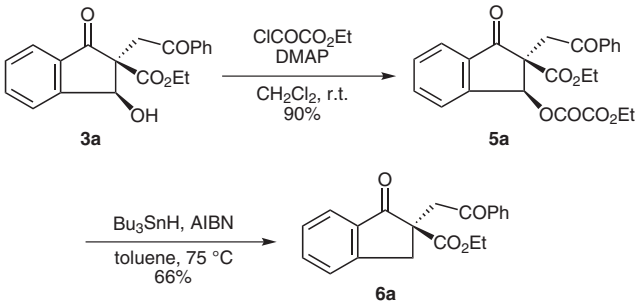


Figure 1 X-ray crystal structure of hydroxyindanone **3a**

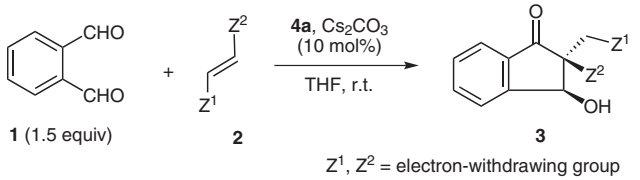
The *cis* stereochemistry of hydroxyindanone **3a** was unambiguously assigned by the X-ray analysis of its crystal (Figure 1). It is worthwhile to note that only *cis* isomer of the hydroxyindanone was detected for all the reactions examined in Table 2.

The resulted highly functionalized indanones offer opportunities for further chemical transformations. For example, indanone **6a** could be prepared smoothly from hydroxyindanone **3a** via a two-step dehydroxy process (Scheme 2).



Scheme 2 Synthesis of indanone **6a** from hydroxyindanone **3a**

Table 2 Synthesis of 3-Hydroxyindanones via NHC-Catalyzed Tandem Reaction of Phthalaldehyde and Michael Acceptors **2**



Z^1, Z^2 = electron-withdrawing group

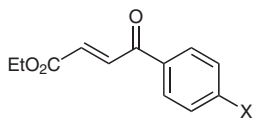
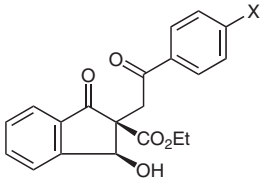
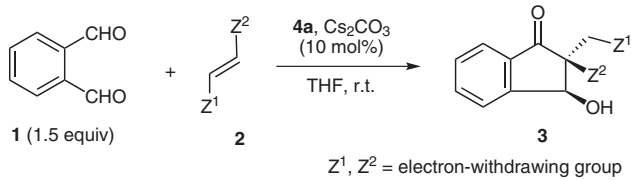
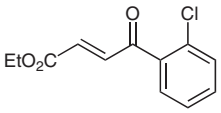
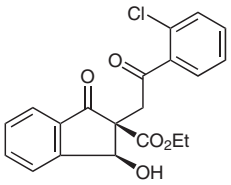
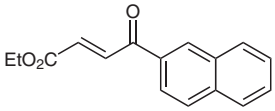
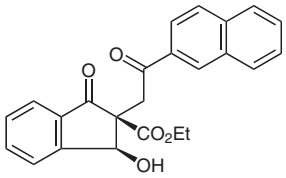
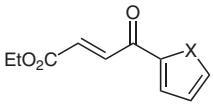
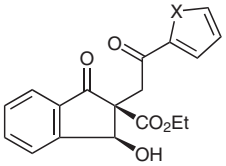
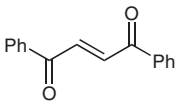
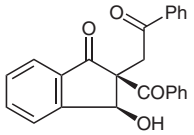
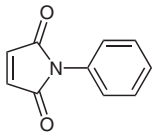
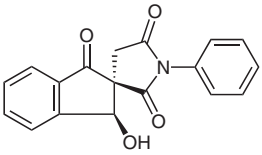
Entry	2	3	Yield (%)[a]
1	 **2a** X = H	 **3a** X = H	95
2	**2b** X = NO_2	**3b** X = NO_2	97
3	**2c** X = Cl	**3c** X = Cl	95

Table 2 Synthesis of 3-Hydroxyindanones via NHC-Catalyzed Tandem Reaction of Phthalaldehyde and Michael Acceptors **2** (continued)



1 (1.5 equiv) **2** **3**

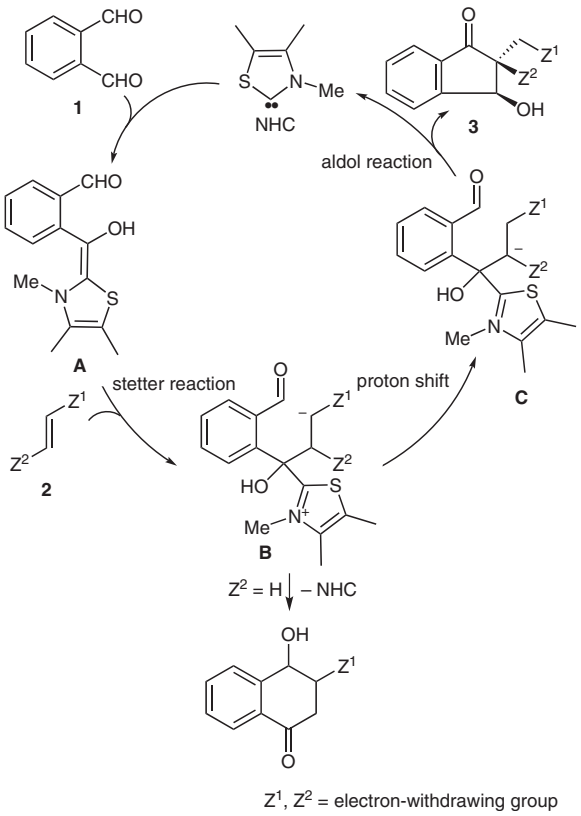
Z^1, Z^2 = electron-withdrawing group

Entry	2	3	Yield (%)[a]
4	**2d** X = Me	**3d** X = Me	58
5	**2e** X = OMe	**3e** X = OMe	50
6	 **2f**	 **3f**	92
7	 **2g**	 **3g**	93
8	 **2h** X = O	 **3h** X = O	98
9	**2i** X = S	**3i** X = S	95
10	 **2j**	 **3j**	65
11	 **2k**	 **3k**	46

[a] Isolated yields of pure *cis* isomer of **3** and no *trans*-**3** was detected for all entries.

A possible catalytic cycle of this NHC-catalyzed [4+1]-annulation reaction is depicted in Scheme 3. The addition of NHC to phthalaldehyde gives the Breslow intermediate **A**, which reacts with Michael acceptor **2** affording zwitterion B. As we reported previously, zwitterion **B** reacts via an intramolecular aldol reaction to give [4+2]-annulation product if no additional withdrawing group is installed in the Michael acceptor (Z^2 = H). However, when the additional withdrawing group is present in the β-position of the Michael acceptor (Z^2 = electron-withdrawing group), proton shift occurs to provide another zwitterionic **C** which is stabilized by the additional electron-withdrawing group (Z^2), hydroxy and thiazolium group. The intramolecular aldol reaction and fragmentation of intermediate **C** affords final [4+1]-annulation product of hydroxyindanone and regenerates the N-heterocyclic carbene.[18]

In conclusion, the synthesis of 2,2-disubstituted 3-hydroxyindanones was realized by a NHC-catalyzed tandem reaction of phthalaldehyde and 1,2-diactivated Michael acceptors. The additional electron-withdrawing group in



Scheme 3 Proposed catalytic cycle

the Michael acceptor facilitates the proton shift of the intermediate of the Stetter reaction and thus results in a [4+1]-annulation product. This tandem reaction features several advantages, including exclusive *cis* diastereoselectivity, readily available starting materials, and catalyst, and construction of two C–C bonds in one pot, which makes it potentially useful for the synthesis of the 3-hydroxyindanones.

Typical Procedure of the NHC-Catalyzed [4+1] Annulation

To an oven-dried 50 mL Schlenk tube equipped with a stir bar was charged with thiazolium salt **4a** (12.7 mg, 0.047 mmol) and phthalaldehyde (94.9 mg, 0.71 mmol). The tube was closed with a septum, evacuated, and back-filled with argon. To this mixture was added solvent THF (4.7 mL) and Michael acceptor **2a** (96.3 mg, 0.47 mmol). Then, Cs_2CO_3 (15.4 mg, 0.047 mmol) was added to the tube. The mixture was further stirred overnight, then diluted with EtOAc and passed through a short silica pad. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (EtOAc–PE, 1:3) to give 151.6 mg (95%) of hydroxyindanone **3a** as a white solid; R_f = 0.22 (PE–EtOAc, 3:1); mp 125–126 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 7.2 Hz, 2 H), 7.87–7.83 (m, 2 H), 7.79–7.74 (m, 1 H), 7.63 (t, *J* = 7.2 Hz, 1 H), 7.57–7.48 (m, 3 H), 5.46 (s, 1 H), 4.33 (d, *J* = 18.3 Hz, 1 H), 4.15–4.08 (m, 3 H), 3.53 (d, *J* = 18.3 Hz, 1 H), 1.11 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.4, 198.3, 168.4, 153.5, 136.3, 135.8, 135.5, 133.7, 129.2, 128.7, 128.3, 125.2, 123.8, 76.4, 65.5, 62.1, 40.8, 13.8. IR (KBr): ν = 1738, 1717, 1684, 1210. MS (EI): *m/z* (%) = 338 (3.0), 105 (100). HRMS (EI): *m/z* [M$^+$] calcd for $C_{20}H_{18}O_5$: 338.1154; found: 338.1150.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(18) At this stage, we don't know whether the NHC leaves before or after the aldol reaction.