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NHC-Mediated Stetter-Aldol and Imino-Stetter-Aldol Domino Cyclization to Naphthalen-1(2*H*)-ones and Isoquinolines

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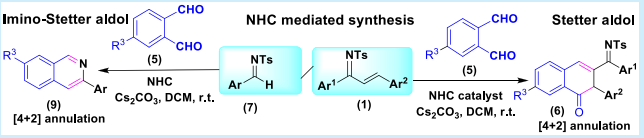
ABSTRACT: N-Heterocyclic carbene-catalyzed tandem Stetter-aldol reaction of phthalaldehyde and α,β-unsaturated ketimines has been developed to afford functionalized naphthalen-1(2*H*)-one derivatives as the formal [4+2] annulation product. Interestingly, the reaction of aldimines led to the formation of isoquinoline derivatives instead of the expected indanone derivatives as a [4+1] annulation product.



N-Heterocyclic carbene (NHC)-catalyzed carbon−carbon bond-forming reactions have become a very powerful tool in organic synthesis.[1] One such important reaction is the Stetter reaction, in which NHC catalyzes the addition of aldehyde to the electron deficient olefin. NHC typically changes the mode of action of aldehydes in the form of an acyl anion equivalent to generate an enolate intermediate through coupling with olefins. This enolate intermediate could perform as a nucleophile and is susceptible to reaction with electron deficient olefins.[2] A significant advancement is observed involving the enolate intermediate.[3] Seminal discoveries have emerged from the work of Gravel,[4] Ye,[5] Glorius,[6] Rovis,[7] and others.[3a] However, the application of this domino strategy via an enolate activation mode with α,β-unsaturated ketimines or aldimines has been limited so far.[3c] In 2008, Bode et al. reported an umpolung/Michael/Mannich/lactamization domino sequence to synthesize corresponding cyclopentane-fused β-lactams [**3** (Scheme 1)].[8] Chi and co-workers synthesized spirocyclic oxindoles (**4**) employing α,β-unsaturated enals (**2**) and α,β-unsaturated imines.[9] It is noteworthy that in most cases monocarbonyl substrates unlike phthalaldehyde (**5a**) were chosen in our case to furnish naphthalen-1(2*H*)-one derivatives (**6**) as [4+2] annulation products.

Ye and co-workers revealed NHC-catalyzed domino Stetter-aldol reaction for synthesizing hydroxyindanone, i.e., [4+1] annulation product (**8**), by using phthalaldehyde (**5a**) and *N*-*tert*-butoxycarbonyl(Boc) imine (**7a**).[5d] As a part of our ongoing research program on NHC-catalyzed domino reaction,[10] we were curious to know about the effect of NHC on the *N*-tosyl-α,β-unsaturated ketimine while reacting with phthalaldehydes (**5a**). We anticipated that the enolate transformation intermediate generated from initial Stetter reaction may undergo intramolecular aldol reaction to afford the [4+2] annulation product (**6**), keeping the imine residue intact. We also extended this idea for the unprecedented synthesis of isoquinoline derivatives (**9**) by using aldimines (**7b**). Unlike Ye et al., we did not detect the formation of any hydroxyindanone (**10**) in our strategy.

In general, derivatives of naphthalen-1(2*H*)-ones are synthesized by an intra/intermolecular Friedel−Crafts cyclization[11] whereas isoquinolines and their derivatives are generally prepared by modified traditional methods such as Pictet−Spengler cyclization,[12] Bischler−Napieralski cyclization/reduction,[13] and Pomeranz−Fritsch−Bobbitt cyclization.[14] However, in spite of significant advances,[15] these methods suffer from limitations such as the use of expensive metal catalysts, special ligands, and/or harsh reaction conditions. Hence, the development of a suitable non-metal-catalyzed mild method for accessing substituted isoquinolines is highly desirable.

To explore the scope of our concept, we first investigated the viability of the Stetter-aldol reaction by using phthalaldehyde (**5a**) and ketimine (**1a**) as a model Michael acceptor (Table 1).

This reaction was first attempted in the presence of the NHC precursor using different bases and solvents at ambient temperature. The use of NHC precursors (**11a** and **11b**) in solvents like DMF, CH_3CN, and THF in the presence of organic and inorganic bases furnished disappointing outcomes with either poor conversion or no reaction at all (entries 1−9). Finally, the use of NHC precursor thiazolium bromide (**11c**) and Cs_2CO_3 in CH_3CN furnished 2,3-disubstituted naphthalen-1(2*H*)-one (**6a**) in moderate yield (entry 10). To improve the yield, we utilized several solvents of different polarities; however, no significant improvement was observed

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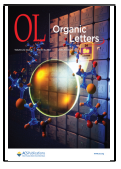

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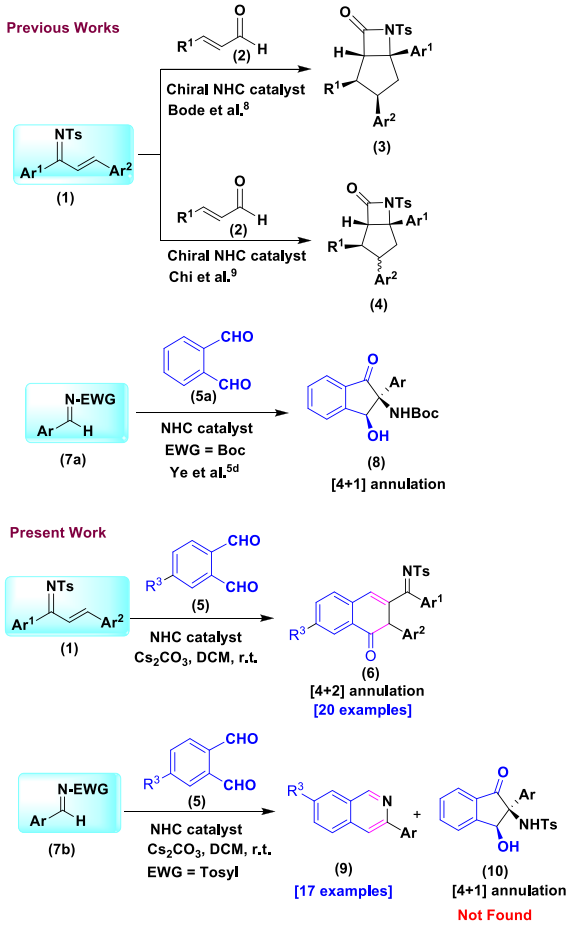
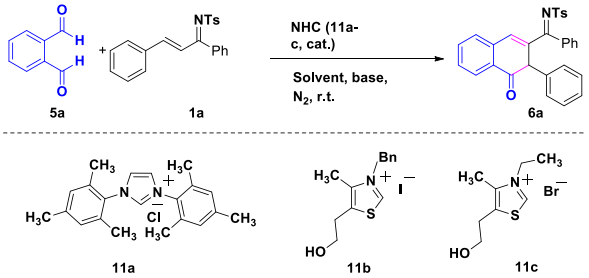
Scheme 1. NHC-Mediated Reaction of Aldehydes with Imines



(entries 11−13). To our delight, the yield and reaction rate were improved significantly by switching the reaction medium to DCM (entry 14). Additionally, screening some other bases, such as DBU, DABCO, Et_3N, and K_2CO_3, was performed; however, Cs_2CO_3 proved to be superior in activity and was the best choice for our protocol (entries 15−18). A slightly lower yield was observed when the reaction was conducted under open air (entry 19). Increasing the reaction time and reducing the catalyst loading to 10% did not help much in terms of the yield of the naphthalen-1(2*H*)-one derivative (entries 20 and 21). A further reduction in catalyst loading to 5 mol % resulted in a mere low conversion of the substrates (entry 22). The reaction did not occur in the absence of the catalyst (entry 23).

Having established the optimal reaction conditions (Table 1, entry 14), we investigated the scope of substrates (Scheme 2). Various ketimines bearing an electron-donating group (-Me and -OMe) produced the corresponding naphthalen-1(2*H*)-one derivatives (**6b−d**, **6k**, and **6n**) in good yields. An aromatic residue possessing electron-withdrawing substituents (-F, -Cl, -Br, and -CN) also furnished respective naphthalen-1(2*H*)-one analogues (**6e−j**, **6l**, **6m**, and **6p**) in high yields (74−91%). Moreover, the simultaneous presence of both electron-withdrawing and electron-donating groups in the phenyl rings of ketimine led to high yields of the desired products (**6o** and **6q**). Notably, heterocyclic furan and thiophene substrates as well as substituted phthalaldehyde (**5b**) were also found to be suitable for the reaction, and the desired products (**6r−t**) were obtained in 62%, 68%, and 75%

Table 1. Screening Optimal Conditions for the Dual Stetter-Aldol Reaction[a]



entry	NHC precursor	base	solvent	time (h)	yield of **6** (%)[b]
1	**11a**	DBU	DCM	24	nd[c]
2	**11a**	DABCO	DCM	24	nd[c]
3	**11a**	Cs_2CO_3	DCM	24	nd[c]
4	**11a**	Cs_2CO_3	CH_3CN	24	nd[c]
5	**11b**	Cs_2CO_3	THF	12	12
6	**11b**	Cs_2CO_3	CH_3CN	12	22
7	**11b**	DBU	DMF	12	<10
8	**11b**	DABCO	DCM	12	15
9	**11b**	Cs_2CO_3	DCM	12	20
10	**11c**	Cs_2CO_3	CH_3CN	12	48
11	**11c**	Cs_2CO_3	DMF	12	46
12	**11c**	Cs_2CO_3	THF	12	52
13	**11c**	Cs_2CO_3	toluene	12	38
14	**11c**	Cs_2CO_3	DCM	6	74
15	**11c**	DBU	DCM	6	45
16	**11c**	DABCO	DCM	6	55
17	**11c**	Et_3N	DCM	6	51
18	**11c**	K_2CO_3	DCM	6	56
19[d]	**11c**	Cs_2CO_3	DCM	6	59
20	**11c**	Cs_2CO_3	DCM	48	62
21[e]	**11c**	Cs_2CO_3	DCM	6	61
22[f]	**11c**	Cs_2CO_3	DCM	6	51
23[g]	–	Cs_2CO_3	DCM	6	nd[c]

[a]Reaction conditions: phthalaldehyde (**5a**, 1.0 mmol), *N*-tosyl-*α*,*β*-unsaturated ketimine (**1a**, 1.0 mmol), solvent (5 mL), NHC precursor **11a−c** (15 mol %), base (20 mol %), 4 Å molecular sieves, stirred at ambient temperature. [b]Yield of the product obtained after purification by silica gel column chromatography. [c]**6a** not detected. [d]**11c**, without a N_2 atmosphere. [e]**11c**, at 10 mol %. [f]**11c**, at 5 mol %. [g]Without NHC.

yields, respectively. The structure of all of the unknown 2,3-disubstituted naphthalen-1(2*H*)-one derivatives (**6a−t**) was unambiguously established by NMR, FTIR, and ESI-MS spectroscopy and also X-ray crystallographic analyses of compound **6e** (Supporting Information).[16]

Observing this phenomenon and a recent report by Ye group to obtain 2-substituted 3-hydroxyindanone [**10** (Scheme 1)],[5d] we were curious to know whether an *N*-tosylaldimine (**7b**) may follow the initial formation of an uncommon aza-"Breslow intermediate", which on reaction with phthalaldehyde to furnish isoquinoline through successive expulsion of thiazolidinone and TsOH. To examine this hypothesis, *N*-benzylidenebenzenesulfonamide (**7b**) was reacted with NHC (in excess) and phthalaldehyde [**5a** (Scheme 3)] under the optimized reaction conditions (Table 1, entry 14). Surprisingly, instead of expected 2-substituted 3-hydroxyindanone [**10** (Scheme 1)], 3-phenyl isoquinoline (**9a**) was formed (Supporting Information) in 80% yield (Scheme 3).

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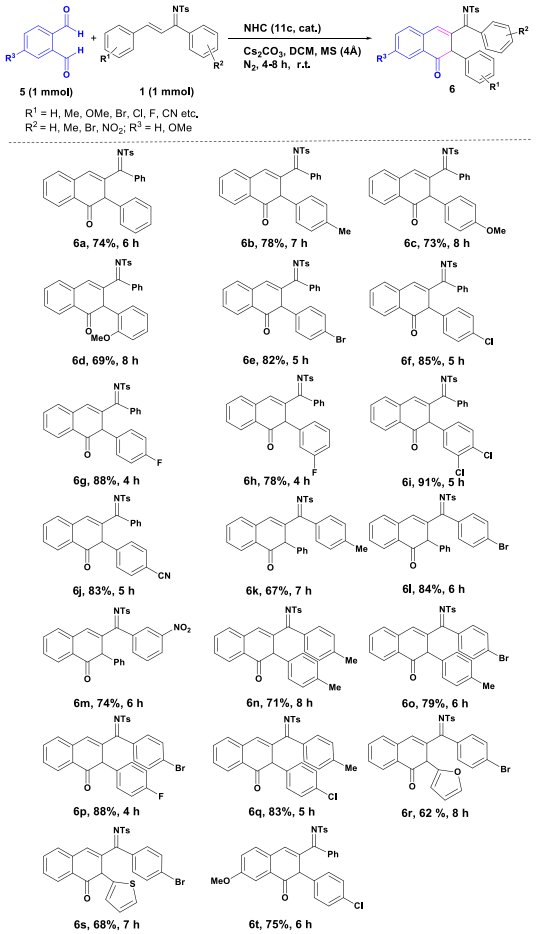
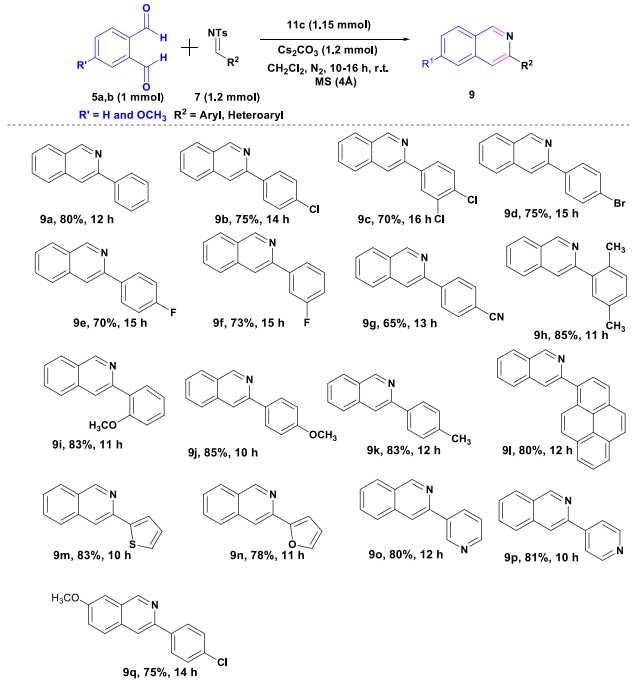
Scheme 2. NHC-Catalyzed [4+2] Annulation to Naphthalen-1(2*H*)-ones



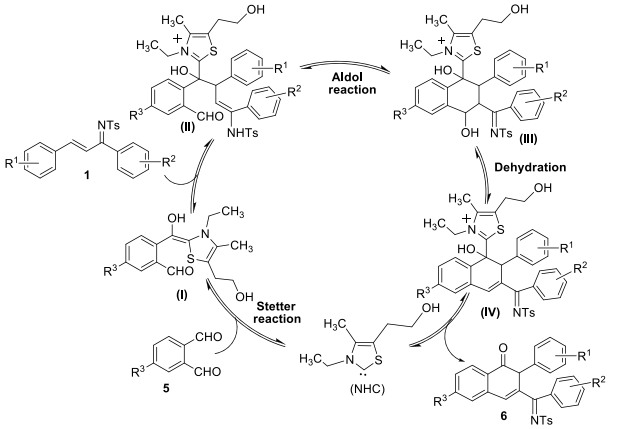
Scheme 3. NHC-Mediated Synthesis of Isoquinolines



The scope of the *N*-tosylimines was extensively investigated (Scheme 3). Interestingly, tosylimines with electron-withdrawing groups (-Br, -F, and -CN) in the phenyl ring were tolerated under the mild reaction conditions to produce respective isoquinolines (**9c**−**g**) in moderate to good yields (65−75%) and slower reaction rates. The tosylimines bearing electron-donating groups (-Me and -OMe) furnished isoquinolines (**9h**−**k**) in excellent yields (80−85%). The tosylimine-containing α-pyrene group was found to be compatible with the reaction, as well (**9l**). The heteroarylimines, such as tosylimine of thiophene-2-carboxaldehyde, furan-2-carboxaldehyde, nicotinaldehyde, and isonicotinaldehyde, also worked well under the reaction conditions to form the corresponding isoquinolines (**9m**−**p**) in high yields (78−83%). Notably, substituted phthalaldehyde (**5b**) was also found to be suitable for the reaction, and the desired product was obtained in 75% yield (**9q**). The structure of isoquinolines was unambiguously established by NMR, FTIR, and ESI-MS spectroscopy and also X-ray crystallographic analyses of **9b** (Supporting Information).[17]

The exact mechanism for the new organocatalytic reactions is unknown to us. However, a plausible mechanism is proposed on the basis of the literature reports and our ESI-MS study of the ongoing reactions (Scheme 4). We postulate that the

Scheme 4. Mechanistic Pathway to Naphthalen-1(2*H*)-one



catalytic cycle for the formation of naphthalen-1(2*H*)-one proceeded through the internal formation of a "Breslow intermediate" (**I**) via the nucleophilic addition of the NHC to phthalaldehyde (**5**), which on reaction with *N*-tosyl-α,β-unsaturated ketimine (**1**) generates enol intermediate **II**. This may further undergo intramolecular aldol reaction to transform into intermediate **III**, followed by dehydration to generate intermediate **IV**. In addition, fragmentation leads to desired product **6** along with the regeneration of free NHC for the next catalytic cycle. From our ESI-MS reaction kinetics of an ongoing reaction among **5a**, **1f**, and **11c** to give **6f**, symbolic ESI-MS peaks were detected for "Breslow intermediate" **I** (**11c**−**5a** adduct) at e/m 306.1034, intermediate **II** at e/m 701.2092, intermediate **III** at e/m 701.2039, and product **6f** at e/m 534.0912. These findings support the proposed catalytic cycles.

Herein, the formation of isoquinoline is expected via initial selective nucleophilic addition of the NHC (**11c**) to *N*-tosylaldimines (**7**), instead of phthalaldehyde, to generate an aza-"Breslow intermediate" **V**, which on reaction with phthalaldehyde (**5a**) to form putative intermediate **VI** (Scheme 5). The nucleophilic addition of this enolate species (**VII**) to the cationic thiazolium moiety followed by NHC

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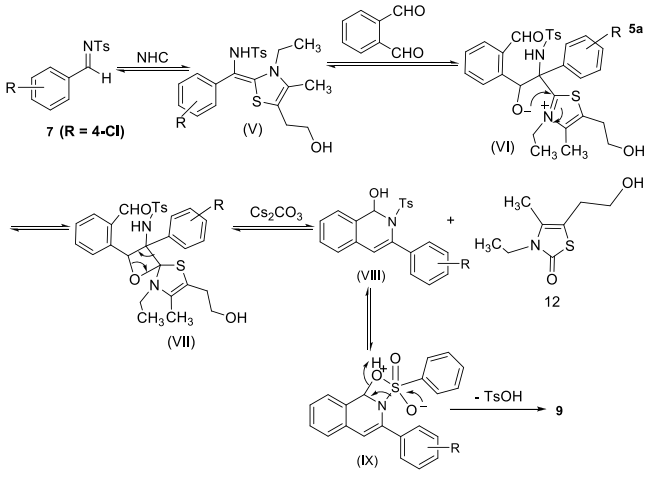
Scheme 5. Mechanistic Pathway to Isoquinolines



elimination as a thiazolidinone derivative (**12**) leads to the generation of intermediate **VIII**, which on probable *N*- to *O*-sulfonyl migration (**IX**) followed by removal of 4-methyl benzenesulfonate triggers final compound **9**. From our ESI-MS reaction kinetics of the ongoing reaction among compound **5a**, **7b**, and NHC **11c**, characteristic ESI-MS peaks were detected for intermediate **V** at e/m 465.1149, intermediate **VI**/**VII** at e/m 599.1497, **VIII**/**IX** at e/m 433.0803, **12** at e/m 188.0561 and product **9b** at e/m 240.0384. These findings support our proposed mechanistic pathway.

In conclusion, we have developed an N-heterocyclic carbene-catalyzed domino Stetter-aldol reaction of phthalaldehyde and α,β-unsaturated ketimines, which afforded the corresponding 2,3-disubstituted naphthalen-1(2*H*)-one derivatives as the formal [4+2] annulation product. Interestingly, an extension of this strategy to aldimines led to the formation of unprecedented isoquinolines as a sole product through the formation of the unusual aza-"Breslow intermediate". Our protocol opens up a new avenue for the synthesis of the isoquinoline scaffold under this set of mild reaction conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00337.

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all compounds (PDF)

Accession Codes

CCDC 1923004 and 2062484 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

§D. Barman and Tanmoy Ghosh contributed equally to this work.

Notes

The authors declare no competing financial interest.

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(17) CCDC number of compound **9b**: 1923004.

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