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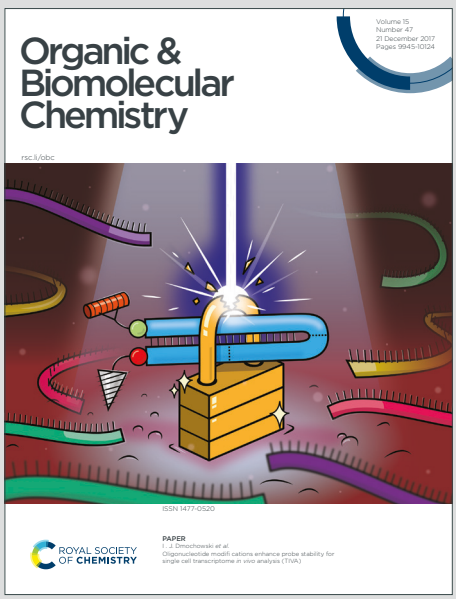




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# Stereoselective Construction of Deoxy-Cruciferane Alkaloids by NHC-Catalyzed Intramolecular Annulation of Homoenolate with Quinazolinone

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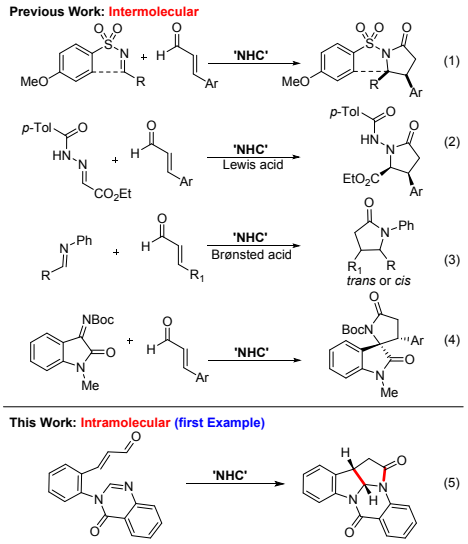
Milind M. Ahire[ab], Mahesh D. Pol[a], Dattatry S. Kavale[a], Rajesh G. Gonnade,[bc] and Santosh B. Mhaske*[ab]

**Chiral N-heterocyclic carbene (NHC)-catalyzed intramolecular [3 + 2] annulation of enals with unactivated imine moiety of quinazolinone via formal homoenolate cycloaddition has been demonstrated. It is an excellent approach for stereoselective syntheses of deoxy-cruciferane alkaloids comprising biologically important pyrroloindoline scaffold. Notably, this is the first report on the NHC-catalyzed asymmetric intramolecular homoenolate annulation with cyclic *N*-acyl amidine.**

Over the past decade, astonishing developments in the area of N-heterocyclic carbene (NHC)-catalyzed transformations revealed its important synthetic utilities in organic chemistry.[1] NHCs are being employed as organocatalysts and ligands for *p*-block elements and transition-metal catalysts.[1,2] Furthermore, organocatalysis by N-heterocyclic carbene provides a platform for the synthesis of pharmaceutically important compounds and natural products.[3] NHCs have the ability to alter the polarity of aldehyde or enal functionality to access numerous valuable synthetic processes via NHC-linked intermediates, such as Breslow intermediates, enolates, acylazoliums, homoenolates, and *α,β*-unsaturated acylazoliums, etc. Particularly, NHC-catalyzed reactions of homoenolate anion intermediates and its intervention with different electrophilic partners such as imines, ketones, and aldehydes through cycloaddition reaction provide access to an array of novel carbo- and heterocyclic compounds via carbon−carbon or carbon−heteroatom bond formation.[1,2]

NHC-catalyzed annulation of enals with imines via homoenolate equivalent is a unique strategy for the synthesis of substituted *γ*-lactams. Bode group reported NHC-catalyzed addition of enals to *N*-4-methoxybenzenesulfonyl imines as well as saccharin-derived ketimines (Scheme 1, eq 1).[4a,b] In 2010, Scheidt and co-worker developed highly diastereo- and enantioselective [3+2] cycloaddition reaction of *α,β*-unsaturated aldehydes with hydrazones using co-operative




**Scheme 1** NHC-Catalyzed Annulation of Enal with Various Imines and This Work.

catalysis of NHC and Lewis acid (Scheme 1, eq 2).[4c] Rovis and co-workers reported NHC and Brønsted acid co-operative catalysis for enantioselective synthesis of trans-*γ*-lactams (Scheme 1, eq 3).[4d] Furthermore, Chi group demonstrated the enantioselective construction of spirocyclic oxindole-*γ*-lactams via NHC-catalyzed annulation of isatin *N*-Boc ketimines and unsaturated aldehydes (Scheme 1, eq 4).[4e] Overall, our survey revealed that the NHC-catalyzed intermolecular annulation of enals with imines is well documented in the literature (Scheme 1, eq 1-4).[4] Interestingly, until now NHC-catalyzed intramolecular annulation of homoenolate with alkenes/aldehydes/ketones is known,[5] however such intramolecular cycloaddition is not reported with imine, probably because of a difficulty in the preparation of substrates containing imine and aldehyde functionality in the same molecule. NHC−homoenolate pathway for the synthesis of heterocycles is always a challenging but much desired synthetic transformation. We envisioned that intramolecular homoenolate cycloaddition with imine (IHCI) would be a good strategy to access the privileged *γ*-lactam containing scaffolds such as pyrroloindolines.

[a] Division of Organic Chemistry, CSIR-National Chemical Laboratory, Pune 411008, India. Email: sb.mhaske@ncl.res.in
[b] Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India.
[c] Physical and Materials Chemistry Division, CSIR-National Chemical Laboratory, Pune 411008, India.

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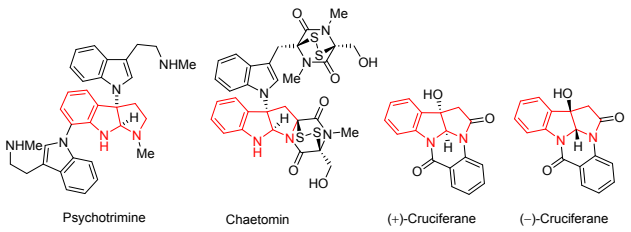
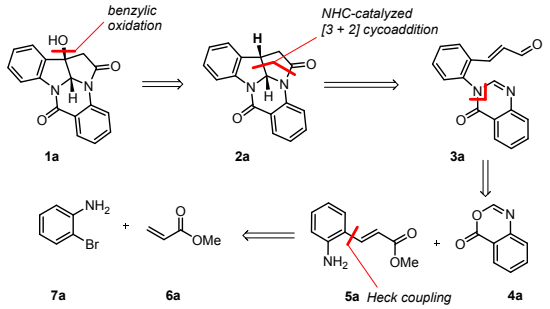



**Fig. 1** Natural Products Containing Pyrroloindoline Skeleton.

Pyrroloindolines are an important class of compounds and a common structural motif for a large number of natural products and pharmacologically important compounds.[6] This family of natural products is an attractive synthetic target for the scientific community due to excellent bioactivities, such as antifungal, antibacterial, antiviral, and analgesic (Figure 1).[7] The alkaloid (±)-cruciferane containing pyrroloindoline scaffold fused with quinazolinone was isolated in the racemic form from the herbaceous plant *Isatis indigotica* (Cruciferae family).[8] The dried roots and leaves of this plant are commonly used in traditional Chinese medicine for the treatment of influenza, cold, fever, and infections. The alkaloid (±)-cruciferane featuring a novel pyrroloindoloquinazolinone core and possessing potential hepatoprotective activity particularly caught our attention. The formation of the racemic pyrroloindoloquinazoline skeleton in low yield was observed by Bremner et al., much before the isolation of (±)-cruciferane, during photoinduced cyclization of *N*-(2-(1-indolylmethyl)-phenyl)chloroacetamide.[9] Until now, five total syntheses of cruciferane are reported in the literature.[10] Most of the synthetic routes to cruciferane involve the use of tryptanthrin as the key intermediate.

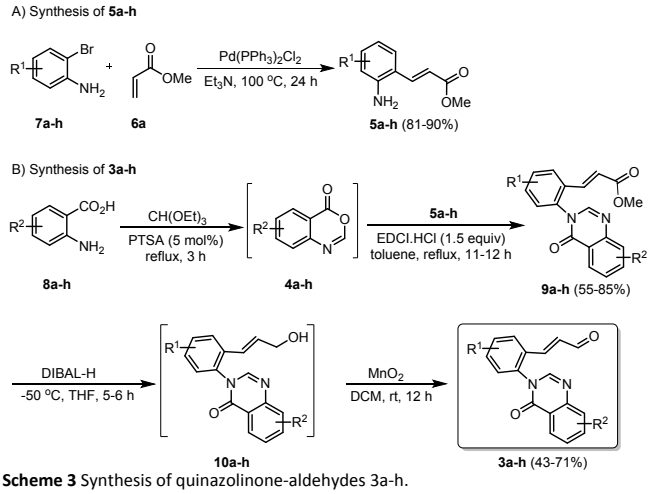
The challenging structural architecture and potential biological activity of (±)-cruciferane prompted us to investigate the application of our envisioned IHCI strategy for the stereoselective construction of the pyrroloindoloquinazolinone scaffold of cruciferane. The development of such novel synthetic methodologies and their successful application in the synthesis of bioactive scaffolds and natural products starting from simple precursors is always an interesting task for synthetic organic chemists. In this context, we report herein, an intramolecular NHC-catalyzed [3 + 2] annulation of enal with the internal imine of quinazolinone (Scheme 1, eq 5), which stereoselectively furnish the core structure of the cruciferane natural product.

Scheme 2 illustrates our retrosynthetic analysis, wherein, we envisioned a convergent construction of cruciferane alkaloid **1a** through benzylic oxidation of pyrroloindoloquinazolinone **2a**. The chirality in compound **2a** was imagined via N-heterocyclic carbene-catalyzed asymmetric intramolecular [3 + 2] cycloaddition of NHC-linked homoenolate intermediate of unsaturated aldehyde and internal imine present in the quinazolinone **3a**. The construction of quinazolinone **3a** was planned from benzoxazinone **4a** and the amine **5a**. The benzoxazinone **4a** could be easily accessed from anthranilic acid. The amine **5a** could be accessible from the commercially available *o*-bromoaniline (**7a**) and methyl acrylate (**6a**) using reported palladium-catalyzed Heck coupling reaction.




**Scheme 2** Retrosynthetic Analysis of Cruciferane.

Our investigation for the NHC-catalyzed intramolecular annulation reaction began with the synthesis of the key component quinazolinone-aldehyde **3a** (Scheme 3). The methyl cinnamate derivative **5a** was synthesized using the Heck coupling reaction of *o*-bromoaniline (**7a**) and methyl acrylate (**6a**) in high yield.[11] The treatment of anthranilic acid (**8a**) with triethyl orthoformate in the presence of a catalytic amount of PTSA provided unstable benzoxazinone **4a**,[12] which was reacted further without purification with amine **5a** in the presence of EDCI in toluene to deliver quinazolinone-ester **9a**




**Scheme 3** Synthesis of quinazolinone-aldehydes 3a-h.

in very good yield. Notably, the yield was very poor in the absence of EDCI. The quinazolinone-ester **9a** was reduced to alcohol **10a** using DIBAL-H in THF at -50 °C. The alcohol **10a** could not be isolated or purified; hence, the crude product was subjected to the oxidative condition using activated $MnO_2$ to furnish the desired aldehyde **3a** in good yield. The other quinazolinone-aldehydes **3b-h** were synthesized in moderate to good yields following the same route as used for **3a** (Scheme 3). The quinazolinone-aldehydes **3a-h** have strategically positioned two reacting centres, $\alpha,\beta$-unsaturated aldehyde and imine of quinazolinone, embedded in a single molecule as desired for our envisioned intramolecular cycloaddition process.

With the key intermediate **3a** in hand, we initiated optimization of the desired intramolecular cycloaddition protocol. Table 1 shows selected representative reaction

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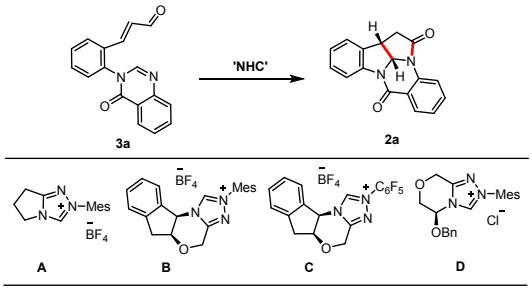
conditions that were used for the optimization. Our effort towards the [3 + 2] annulation reaction began by treating the

**Table 1** Optimization of Reaction Conditions[a]

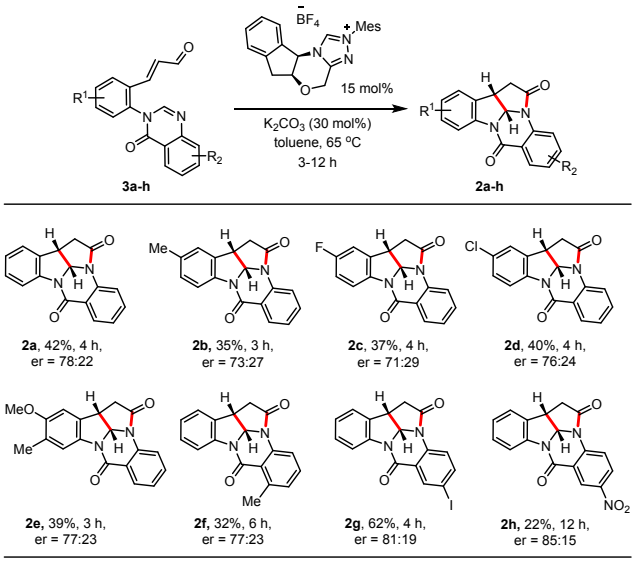



| entry | NHC | base | solvent | temp (°C) | yield (%)[b] | er |
|---|---|---|---|---|---|---|
| 01 | **A** | $K_2CO_3$ | toluene | 65 | <2 | ND |
| 02 | **B** | $K_2CO_3$ | DCE | rt | 6 | 70:30 |
| 03 | **B** | $K_2CO_3$ | DCM | rt | <2 | ND |
| 04 | **B** | $K_2CO_3$ | DMSO | rt/65 | NR | ND |
| 05 | **B** | $K_2CO_3$ | DMF | rt/65 | NR | ND |
| 06 | **B** | $K_2CO_3$ | toluene | rt | NR | ND |
| **07** | **B** | **$K_2CO_3$** | **toluene** | **65** | **42** | **78:22** |
| 08 | **B** | $K_2CO_3$ | benzene | 65 | 35 | 75:25 |
| 09 | **C** | $K_2CO_3$ | toluene | 65 | <2 | ND |
| 10 | **D** | $K_2CO_3$ | toluene | 65 | 13 | 71:29 |
| 11 | **B** | $Cs_2CO_3$ | toluene | 65 | NR | ND |
| 12 | **B** | $Na_2CO_3$ | toluene | 65 | NR | ND |
| 13 | **B** | $K_3PO_4$ | toluene | rt | NR | ND |
| 14 | **B** | DBU | toluene | rt | NR | ND |
| 15 | **B** | $PhCO_2Na$ | toluene | 65 | 12 | 78:22 |
| 16 | **B** | $PhCO_2Na$ | ACN, MS | rt/60 | trace | ND |

[a]Reaction conditions: **3a** (1.0 equiv, 0.18 mmol), pre-NHC catalyst **B** (15 mol %), $K_2CO_3$ (30 mol%), solvent (2 mL), 4 h, under argon atmosphere. [b]Isolated yields. rt = room temperature, NR = no reaction, ND = not determined, MS = 4 Å molecular sieves

aldehyde **3a** in the presence of achiral triazolium-derived pre-NHC catalyst **A** and various bases in different solvents at varying temperatures. The expected product pyrroloindoloquinazolinone **2a** was observed only when **3a** was treated with 15 mol% of pre-NHC catalyst **A** and 30 mol% of $K_2CO_3$ in toluene at 65 °C (Table 1, entry 1). Encouraged by this result, we began the screening of chiral NHC-catalysts in combination with various solvents. Interestingly, the expected cyclized product **2a** was obtained in 6% yield in the presence of chiral triazolium-derived pre-NHC catalyst **B** and 30 mol% of $K_2CO_3$ in 1,2-dichloroethane (DCE) at room temperature (Table 1, entry 2). The yield did not improve even after heating the reaction mixture at higher temperatures. Herein, we observed only a single diastereoisomer formation as confirmed by the crude $^1$H-NMR spectral analysis. The racemic version of the pre-NHC catalyst **B** was prepared to determine the enantiomeric ratio (er) of the product by direct comparison using chiral HPLC. Interestingly, the product **2a** was obtained in 70:30 er (Table 1, entry 2). Further variations in solvents did not show much improvement in the yield (Table 1, entries 3-6). However, when the reaction in toluene was heated at various temperatures, we observed improvement in the yield, and we could achieve the best yield 42% and 78:22 er at 65 °C (Table 1, entry 7). Recrystallization of this compound did not show any improvement in the er. The reaction in benzene furnished the product with little lower yield and er (Table 1, entry 8). The NHC-precatalysts **C** showed a drastic reduction in the yield though it has a similar backbone as the precatalyst **B**, except the absence of the bulkier mesitylene aromatic ring (Table 1, entry 9). The precatalyst **D** however furnished the product **2a** in 13% yield and comparable er (Table 1, entry 10). Screening of various bases did not show improvement in the yield (Table 1, entry 11 to 16). Further optimization of the reaction condition using different additives such as Lewis[4c] and Brønsted acid[4d] did not improve the reaction yield or er to much extent.

Deoxy-cruciferane **2a** was prepared in sufficient quantities using the optimized reaction condition (Table 1, entry 7) and its benzylic oxidation to achieve the total synthesis of (–)-cruciferane was attempted. However, when the compound **2a** was subjected to several oxidative conditions (see SI) using organic and inorganic oxidizing reagents, it always ended up in either decomposition or recovery of the starting material. The development of novel selective oxidizing reagent or reaction conditions would be necessary for this transformation.




[a]Reaction conditions: 3a-h (1.0 equiv, 0.18 mmol), pre-NHC catalyst B (15 mol %), $K_2CO_3$ (30 mol%), toluene (2 mL), 3-12 h, under argon atmosphere. [b]Isolated yields. er = enantiomeric ratio.

**Scheme 4** Synthesis of Various Deoxy-Cruciferanes[a,b]

We planned to synthesize various deoxy-cruciferane analogues using the optimized cycloaddition condition to demonstrate the scope and generality of the protocol by varying different substituents. Gratifyingly, a range of substituents were tolerated on both the aromatic rings of the molecule and the desired annulated products deoxy-cruciferanes **2a-h** were obtained in good to moderate yields and optimal er (Scheme 4). The yield and er observed for the unsubstituted aldehyde **3a** to obtain **2a** (42%, 78:22 er) was maintained in the methyl, methoxy, and halo-substituted

aldehydes **3b-f** to deliver the products **2b-f**, though with slightly less yield and er. Interestingly, the reaction worked very smoothly with iodo substituted quinazolinone-aldehyde **3g** and delivered the expected product **2g** in good yield (62%) and er (81:19). Additionally, the developed protocol worked well on the substrate **3h** having electron-withdrawing nitro substituent although in diminished yield but with a slight improvement in the enantiomeric ratio. The absolute configuration of deoxy-cruciferane **2a** was unambiguously assigned on the basis of X-ray crystallographic analysis (Figure 2, see SI) and extrapolated to the deoxy-cruciferane analogues **2b-h**.

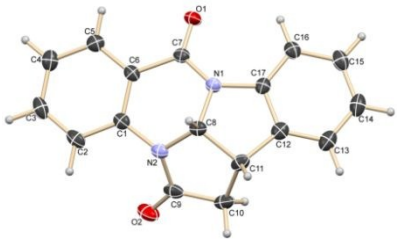


**Fig. 2** X-ray crystallographic structure of **2a**

A plausible mechanism of the developed IHCI protocol is depicted in figure 3. The homoenolate intermediate [**I**] is formed by the reaction of an in situ generated NHC catalyst with the aldehyde **3**. The homoenolate anion attacks the imine moiety of the quinazolinone scaffold. Probably, the hydrogen bonding between the imine nitrogen and enol facilitates this reaction. Further cyclization proceeds via intermediates [**II**] and [**III**] to construct the second pentacyclic ring, thus furnishing the desired deoxy-cruciferanes **2** and regenerating the NHC catalyst for the next catalytic cycle. The intermediate [**I**] displaying the hydrogen bonding interaction reasonably explains the observed enantio- and diastereoselctivity. Additionally, the formation of the cis-5-5 ring system is favourable, which justifies the complete diastereoselection. Further studies on the mechanism are essential.

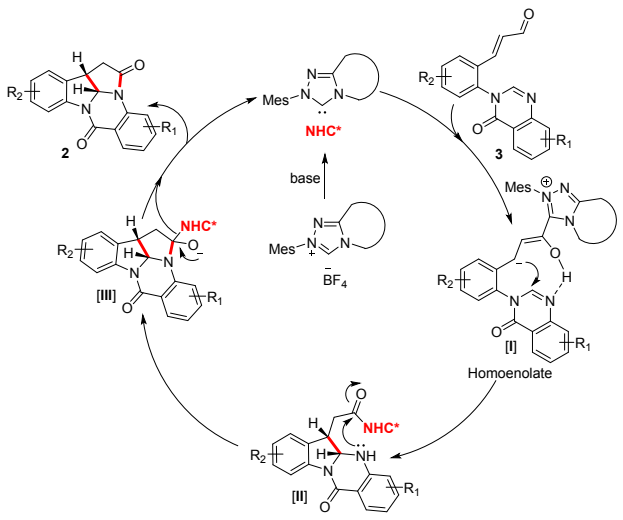



**Fig. 3** A plausible mechanism of the IHCI protocol

## Conclusions

In summary, a straightforward access to pyrrolomidolo-quinazolinone scaffold has been developed using NHC catalysis and applied in the synthesis of deoxy-cruciferane alkaloids. Novel NHC-catalyzed intramolecular stereoselective [3 + 2] cycloaddition of enal with quinazolinone was utilized as the key-step. The developed protocol provides a single diastereomer of cyclized products with a good enantiomeric ratio. The scope of the protocol was demonstrated by synthesizing varyingly substituted deoxy-cruciferane analogues. Currently, we are working on the improvement and application of the NHC-catalyzed intramolecular annulation strategy developed herein to access other bioactive molecules and natural products.

### Conflicts of interest

There are no conflicts to declare.

### Acknowledgments

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