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A Brønsted Acid Catalyzed Cascade Reaction for the Conversion of Indoles into α-(3-Indolyl) Ketones Using 2-Benzyloxy Aldehydes

Ankush Banerjee[a] and Modhu Sudan Maji*[a]

Abstract: *A Brønsted acid catalyzed, operationally simple, scalable route to several functionalized α-(3-indolyl) ketones is developed. The long standing regio-isomeric issue has been eliminated by choosing appropriate carbonyls. Readily available and cheap bottle reagent was used as catalyst. This protocol was also applicable to synthesize densely functionalized α-(3-pyrrolyl) ketones. A detailed mechanistic studies confirmed the involvement of enolether as a reaction intermediate. Several post synthetic modifications along with easy access to β-carboline, tryptamines, tryptophols and spiro-indolenine proclaims the synthetic utility of this powerful building block. Based on this concept, functionalized carbazoles were constructed by cascade annulation strategy.*

Introduction

Synthesis of several indole based scaffolds has gained prime importance in recent years because of the widespread existence

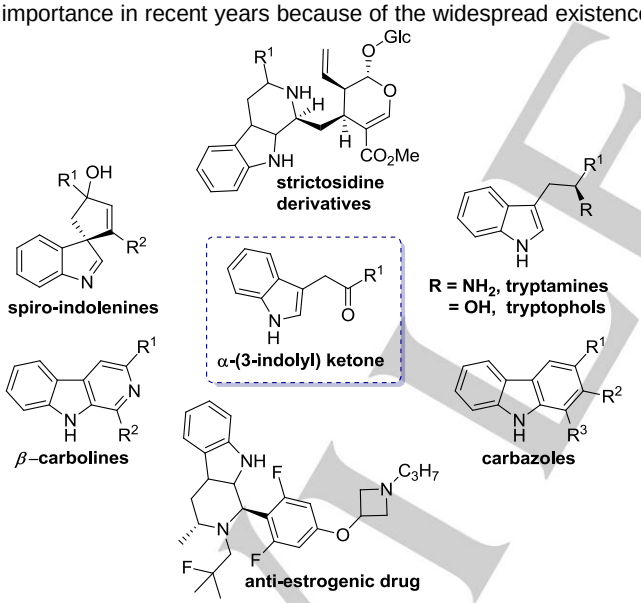
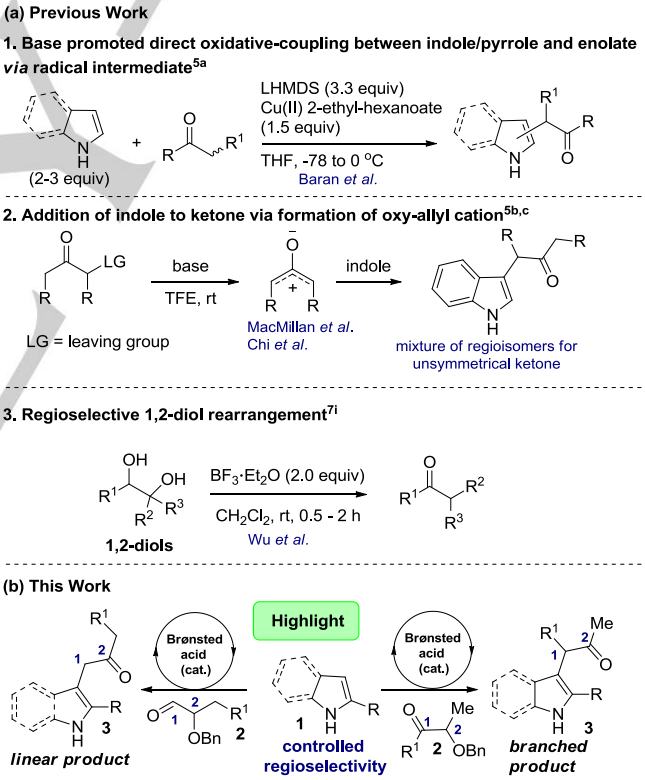


Figure 1: Important scaffolds synthesized from α-(3-indolyl) ketones.

of indole moiety in alkaloid superfamily as well as drug molecules.[1] In particular, *α*-(3-indolyl) ketone has gained considerable attention for concise synthesis of several biologically active compounds and medicines.[1a,c,e] For examples, it plays a pivotal role for the construction of several classes of heterocycles like carbazoles, *β*-carbolines, spiro-indolenines, etc. (Figure 1).[2-3] More important, due to the presence of important carbonyl functionality, it provides an elegant route to several tryptamines, tryptophols and other related natural alkaloids *via* simple functional group interconversion (**FGI**).[4]



Scheme 1. Previous reports and our strategy.

Intrigued by the notable importance of this structural motif, tremendous efforts have been devoted till date to streamline their synthesis,[5-7] however, besides their own advantages, most if not all reports, confront certain major limitations like, low regio-selectivity for unsymmetrical ketones, harsh reaction conditions, multi-step synthesis, low yields, use of expensive catalyst, stoichiometric or super-stoichiometric amount of reagents to eliminate side reactions, limited substrate scopes, etc. For examples, classical transition metal catalyzed cross-coupling

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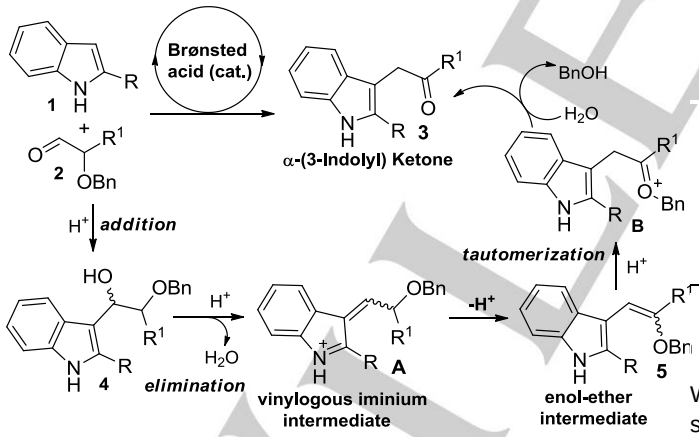
reactions suffer from requiring expensive catalyst as well as ligand, pre-functionalized halides or pseudo halides, and use of excessive strong bases which suppress the economic viability.[7a,b,e] Similarly, traditional Friedel-Crafts arylation reactions mainly rely on elaborated tertiary alcohols with electron donating aryl substituents, harsh conditions, and strong acids with high catalyst loading.[6c,d] An elegant Cu(II) mediated base promoted enolate coupling of indole with ketone was reported by Baran *et al*., however, excess of indole was needed to overcome the homo-coupling of enolates and the yields were generally low.[5a] MacMillan *et al.* and Chi *et al.* independently developed the addition of indole to ketone *via* formation of oxo-allyl cation intermediate, however it is mostly effective for symmetrical ketones, and for unsymmetrical ketones regio-isomeric mixture of products were isolated.[5b,c] You *et al.* documented a unique *N*-heterocyclic carbene catalyzed cross-coupling between aldehyde and aryl-sulfonyl indole which is mostly effective for aromatic aldehyde.[7d] Antilla *et al.* reported a chiral Brønsted acid catalyzed pinacol rearrangement to deliver several enantiomerically pure *α*-(3-indolyl) ketones with 1,2-shift of aryl group.[7f] Recently, Wu *et al.* described a $BF_3{\cdot}Et_2O$ promoted 1,2-diol rearrangement to obtain *α*-substituted ketones.[7i] However, besides the advantages of this 1,2-diol rearrangement, the major concerns are limited scope and the generation of the pre-functionalized indole derivatives which needs considerable synthetic efforts. The literature survey clearly reveals that regioselective, operationally simple, scalable protocol to access this important *α*-(3-indolyl) ketone scaffolds directly starting from readily available indole derivatives and unsymmetrical ketones having aliphatic substitutions at *α*-centers is still elusive and a daunting task.

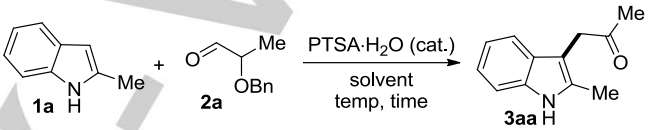


Scheme 2. Working hypothesis.

In continuation of our interest on new reaction development based on indoles,[8] herein, we disclosed an operationally simple route to obtain *α*-(3-indolyl) ketones (**3**) using unprotected indole and *α*-(benzyloxy)-aldehydes or ketones as coupling partners.[9] Under Brønsted acid catalysis, we envisioned that first indolyl alcohol **A** would generate by reaction of indole **1** and aldehyde **2** which subsequently would undergo water elimination to form vinylogous iminium intermediate **4** which will rapidly convert to the enol-ether intermediate **5** (Scheme 2). Finally, under acidic conditions the hydrolysis of **5** would give our desire products **3** *via* intermediate **B**. So the overall reaction proceeded *via* three fundamental steps i.e., first addition, followed by elimination and then tautomerization to generate the desired product **3**. One of the key highlight of this strategy is the elimination of the regioselectivity issue, as by choosing appropriate electrophiles (Scheme 1), exclusively either linear or branched regioisomer can be achieved. In contrast to the previous reports, here emphasize was given to the synthesis of **3** bearing various aliphatic substitution at the *α*-carbon of ketone.

Results and Discussion

Table 1: Optimization of Reaction Conditions [a]



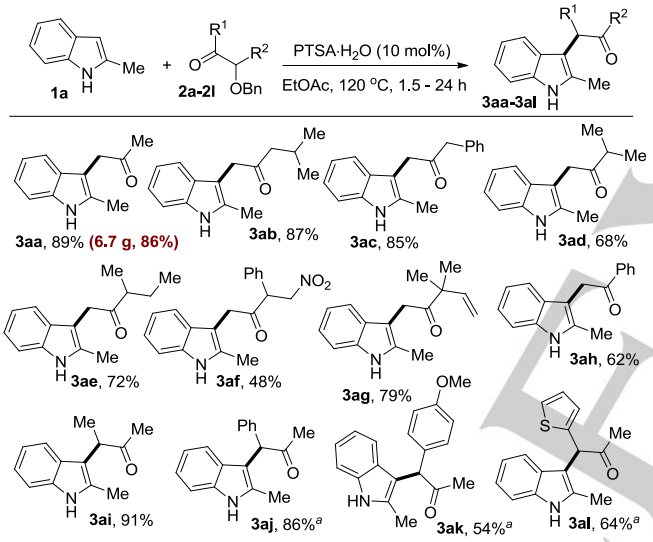
Entry	Cat. (mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	10	EtOAc	rt	24	33
2	10	EtOAc	80	4	63
3	10	EtOAc	100	2.5	80
4	**10**	**EtOAc**	**120**	**1.5**	**89**
5[c]	10	EtOAc	120	3.5	73
6	10	THF	120	2.0	83
7	10	CH_3CN	120	1.5	76
8	7.5	EtOAc	120	2.5	83
9	2.5	EtOAc	120	5	77
10	-	EtOAc	120	-	-

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol). [b] Isolated yield. [c] 0.24 mmol **2a** was used.

With this strategy in hand, we commenced the optimization studies by choosing 2-methyl indole (**1a**) and 2-benzyloxy propanal (**2a**) as prototypes. Pleasingly, commercially available and cheap *p*-toluenesulfonic acid ($PTSA{\cdot}H_2O$) was found to be the most suitable catalyst for this strategy. After extensive screening, we found that temperature has a pivotal role for the outcome of this reaction as on increasing temperature yields improved significantly (Table 1, entries 1-4). EtOAc was found to be the most suitable solvent (entries 4-7). Decreasing the catalyst loading diminished the yields (entries 8 and 9). The reaction did not proceed in the absence of catalyst (entry 10). The conditions described under entry 4 is the optimized condition for this protocol (89%). To our delight, the formation of

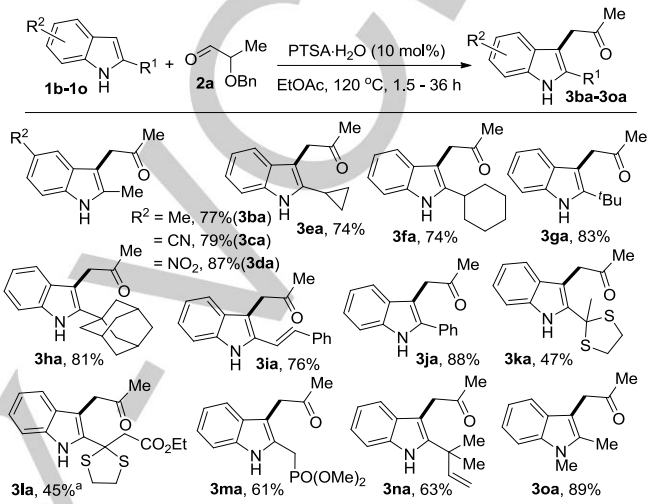
bis-indolylmethane was not detected during the course of our study.

With the optimized conditions in hand, we first explored the scope of various electrophiles. Aldehydes bearing different linear as well as branched alkyl chain provided desired products **3aa**-**3ae** in good to excellent yields (68-89%, Scheme 3). Similarly, aldehyde containing a nitro functional group in the alkyl chain, a challenging substrate for enolate coupling, was also suitable substrate (**3af**, 48%). To our delight, even a terminal alkene functional group also survived the reaction conditions (**3ag**, 79%). Acetophenone derivative **3ah** can also be synthesized using this method in 62% yield. To explore the scope of electrophiles further, we chose several *α*-benzyloxy ketones as coupling partners and pleasingly in all cases the products **3ai**-**3al** were isolated in good to excellent yields (54-91%). Next, to demonstrate the practicality of this present protocol, we performed a gram-scale reaction using 5.5 g of **1a** and 10.3 g of **2a** as prototypes. To our delight, this reaction worked smoothly and 6.7 g of product **3aa** was isolated in 86% yield.

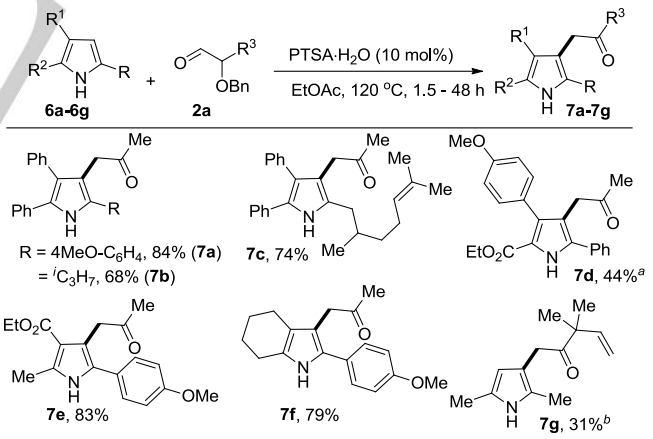


Scheme 3. Scope of elctrophiles. Reaction conditions: **1a** (0.2 mmol), **2a-2l** (0.3 mmol), PTSA·H_2O (10 mol%), EtOAc, 120 °C; isolated yield. [a]20 mol% PTSA·H_2O was used.

The scope of indole was next investigated using **2a** as coupling partner. Indole bearing both electron donating and withdrawing groups at the C5-position did not affect the outcome of the reaction (**3ba**-**3da**, 77-87%, Scheme 4). 2-Cyclopropyl and 2-cyclohexyl indoles successfully took part in the reaction to furnish the desire products **3ea** and **3fa** in 74% yields in both cases. To our joy, even sterically hindered *tert*-butyl and adamantyl group at C2-position of indole did not deter the reactivity and the corresponding ketones were isolated in excellent yields (**3ga**-**3ha**, 81-83% yields). The reactions proceeded efficiently for both styryl and phenyl substituted indoles. Though, indoles bearing keto functional group at the C2 position failed to react, gratifyingly the corresponding thioketals were well-tolerated to deliver the desired products **3ka-3la** in 45-47% yields; and this opens up a route to the downstream chemical modifications. Even indole, bearing phosphonate functional group at C2-position was also a suitable substrate (**3ma**, 61%). 2-(2-Methylbut-3-en-2-yl)-1*H*-indole is an important scaffold present in hapalindole based alkaloids like, ambiguine A, ambiguine B, ambiguine C, ambiguine H which prompted us to synthesized **3na**. Although main focus was to use unprotected indoles, however *N*-methyl protected indole was also a suitable substrate (**3oa**, 89%).



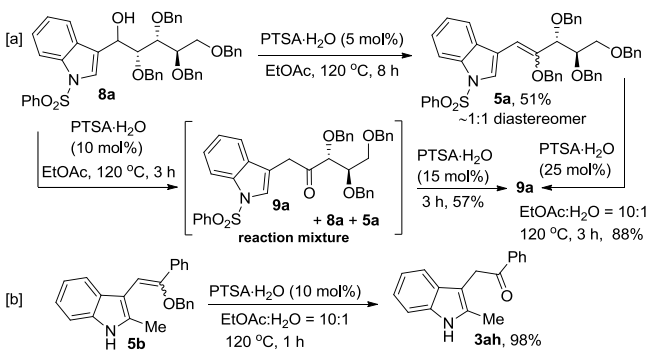
Scheme 4. Scope of indoles. Reaction conditions: **1b-1o** (0.2 mmol), **2a** (0.3 mmol), PTSA·H_2O (10 mol%), EtOAc, 120 °C; isolated yield. [a]DCE was used as solvent.



Scheme 5. Scope of pyrroles. Reaction conditions: **6a-6g** (0.2 mmol), **2a** (0.3 mmol), PTSA·H_2O (10 mol%), EtOAc, 120 °C; isolated yield. [a]DCE was used as solvent. [b]30 mol% of PTSA was used.

To further demonstrate the versatility of this strategy, next several pyrroles were reacted to achieve densely functionalized pyrroles. High propensity of pyrrole toward polymerization under Brønsted acid conditions, renders pyrrole a challenging substrate. Pleasingly, the tri-aryl substituted pyrrole **6a** reacted efficiently with aldehyde **2a** to deliver the desired product **7a** in

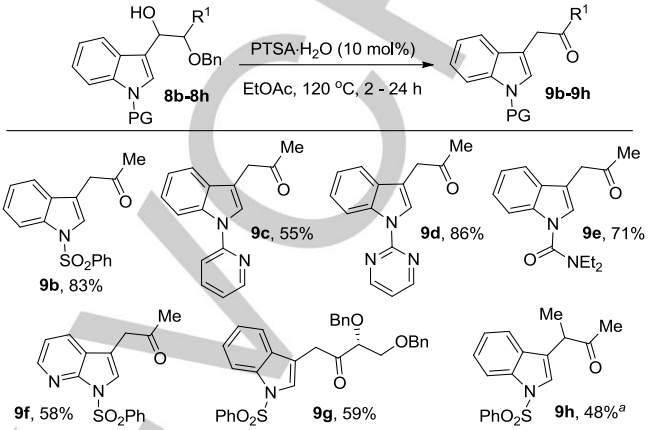
84% yield (Scheme 5). Pyrroles bearing isopropyl and branched alkyl chain at C2-position were also suitable substrates (**7b**-**7c**, 68-74%). Pyrroles containing an electron withdrawing ester functionality either at C2 or C3 positions were also tolerated and delivered the desired products **7d** and **7e** in 44% and 83% yields, respectively. Tetrahydroindole derivative **6f** was also found to be an excellent coupling partner (**7f**, 79%). The 2,3-dimethyl pyrrole furnished **7g** in only 31% yield.



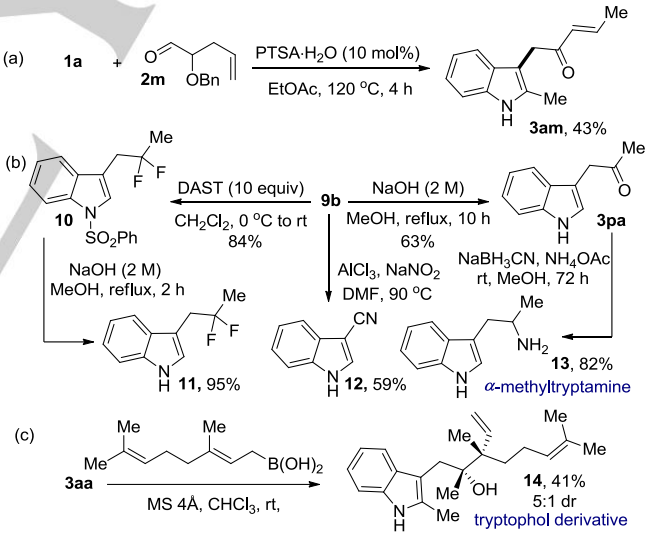
Scheme 6. Mechanistic studies.

Next we focused to investigate the mechanistic pathway of this strategy (Scheme 6). During the course of our reaction, several attempts to isolate any of the intermediates as shown in scheme 2 were unsuccessful due to the high reactivity. This directed us to adopt an alternative pathway where first *N*-protected indolyl alcohol **8a** was prepared by addition of 3-indolyl Grignard reagent to the corresponding aldehyde. Here, electron withdrawing benzenesulfonyl group was selected to slowdown the reaction rate and to stabilize the intermediates. Interestingly, when **8a** was treated with 5 mol% PTSA·H_2O over 8 h, the intermediate enolether **5a** was isolated in 51% yield in a 1:1 mixture of E/Z isomers. Furthermore, when **8a** was subjected to the standard conditions, after 3 h the reaction mixture mostly contained enolether **5a** along with starting material **8a** and desired product **9a**. Upon further addition of 15 mol% PTSA·H_2O, this mixture of products was eventually converted to optically pure ketone **9a** exclusively which confirmed that the reaction proceeds via enolether intermediate. This observation was further supported by the fact that, when **5a** was independently treated with 25 mol% of PTSA·H_2O in the presence of 10:1 mixture of ethylacetate and water at 120 °C, desired product **9a** was isolated in 88% yield. In addition, the *N*-unprotected 3-alkenyl indole **5b** also provided desired product **3ah** in 98% yield which also strongly support our aforementioned hypothesis.

During the exploration of this method without 2-substituted indole, unfortunately, a complex reaction mixture was observed. Encouraged by the above mentioned mechanistic studies, we next explored the scope of *α*-(3-indolyl) alcohols in order to deliver *α*-(3-indolyl) ketones without 2-substitution (Scheme 7). 2-Pyridyl, 2-pyrimidyl, and $CONEt_2$ protected indolyl alcohols successfully took part in reaction and the desired products were isolated in good to excellent yields (**9c**-**9e**, 55-86%). Even electron deficient *α*-(3-azaindolyl) alcohol was also a suitable substrate (**9f**, 58%). Like **9a** as discussed during the mechanistic studies, indolyl ketone **9g** was also isolated in 59% yield. Hence, the present strategy enables the synthesis of *α*-(3-indolyl) ketone stitched with a long alcohol chain which is extremely challenging and scarce. The ketone derived indolyl alcohol was reacted to deliver the desired product **9h** in 48% yield.



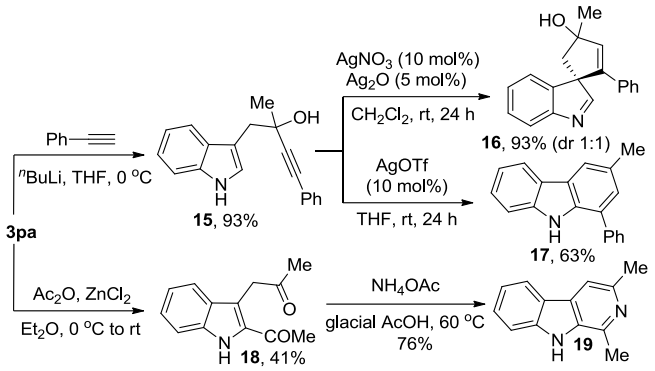
Scheme 7. Scope of *α*-(3-Indolyl) Alcohol. Reaction conditions: **8b-8h** (0.2 mmol), PTSA·H_2O (10 mol%), EtOAc, 120 °C; isolated yield. [a]DCE was used as solvent.



Scheme 8. Functional group transformations.

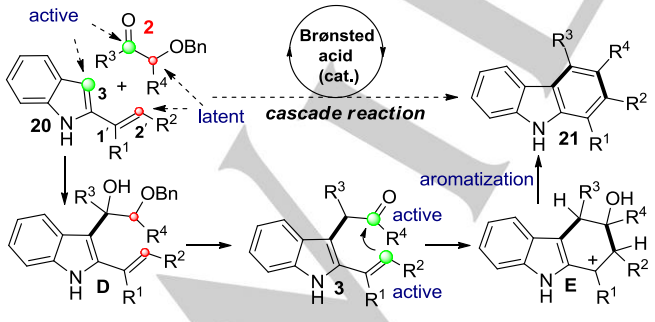
Interestingly, reaction of **1a** with aldehyde **2m** under standard conditions provided the product **3am** in 43% yield with exclusive *E*-selectivity. Here during the course of the reaction double bond underwent isomerization to furnish more stable *α,β*-unsaturated ketone (Scheme 8a). The existence of ketone functionality in the final product along with reactive indole moiety provided ample opportunities for various functional group transformations. In this line, on desulfonylation of **9b** using 2 M NaOH, the product **3pa** was isolated in 63% yield. The entactogen drug *α*-methyltryptamine was isolated in 82% yield on treatment of **3pa**

with $NaBH_3CN$ in the presence of NH_4OAc (Scheme 8b).[4a] Next, fluorination of **9b** with diethylaminosulfur trifluoride (DAST) exclusively delivered the difluorinated product **10** (84%) which was fully converted to the corresponding desulfonylated product (**11**, 95%).[10] When **9b** was subjected with $AlCl_3$ in the presence of $NaNO_2$ in DMF, desulfonylated 3-cyanoindole **12** was obtained in 59% yield.[11] The reaction of **3aa** with geranylboronic acid generated the densely substituted 5:1 diastereomeric mixture of tryptophol derivative **14**.[12]



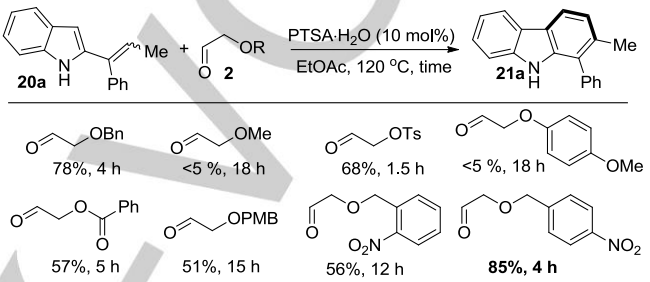
Scheme 9. Synthesis of carbazole, *β*-carboline, spiro-indolenine.

The importance of this *α*-(3-indolyl) ketone was further illustrated by transforming it to various essential heterocycles. To do so, the indolyl ketone **3pa** was picked as model substrate and first treated with lithium phenylacetylide to obtain the corresponding alcohol **15** in 93% yield (Scheme 9). The spiro-indolenine **16** was isolated in 93% yield when the alcohol **15** was treated with catalytic amount of $AgNO_3$ and Ag_2O.[3a] In a similar fashion, the synthesis of carbazole **17** was accomplished using AgOTf as catalyst.[3a] Next, **3pa** was subjected under Friedel-Craft acylation reaction conditions to furnish the di-keto product **18** in moderate yield. The compound **18** was completely transformed to *β*-carboline **19** using excess of NH_4OAc in the presence of glacial acetic acid.[2a]

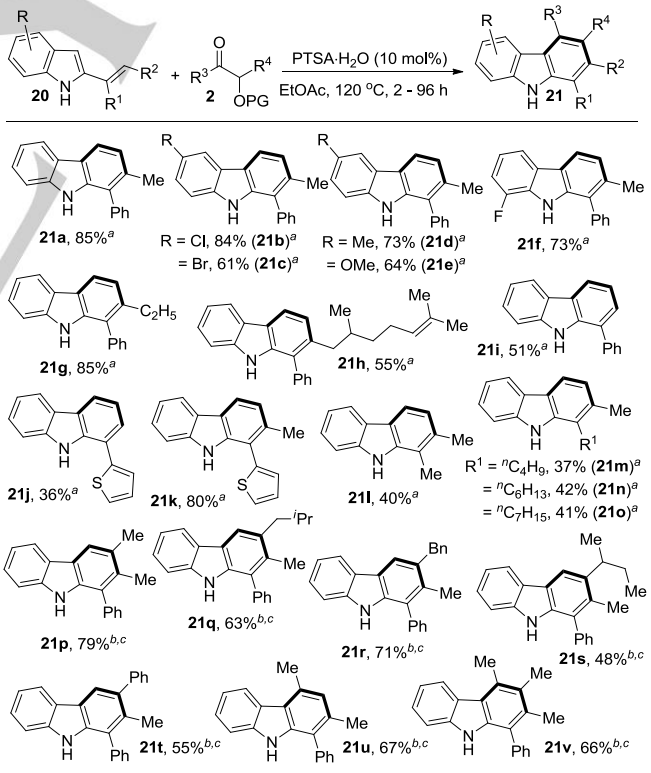


Scheme 10. Proposed hypothesis for cascade synthesis of carbazole.

Inspired by the versatile applicability and importance of *α*-(3-indolyl) ketone, we intended to utilize the carbonyl functionality *in situ* for Brønsted acid catalyzed cascade synthesis of functionalized carbazoles through benzannulation. To execute our hypothesis, alkenyl functionality was planned to install at the C2 position of indole. Here, the indole **20** plays a role of bis-nucleophile as it can undergo nucleophilic attack through C3 position of indole ring and terminal position of the alkene carbon. Due to much higher nucleophilicity, the first attack is expected to occurs through C3-position of indole (Scheme 10). We envisioned that, in the presence of Brønsted acid catalyst, at first *α*-(3-indolyl) carbonyl compound **3** will be generated from indolyl alcohol **D** which will undergo a second intramolecular nucleophilic attack to furnish the desired carbazole **21**.



Scheme 11. Screening for suitable aldehydes.



Scheme 12. Scope of carbazoles. Reaction conditions: **20** (0.2 mmol), **2** (0.4 mmol), PTSA·H_2O (10 mol%), EtOAc, 120 °C; isolated yield. [a]PG = 4-nitro benzyl group. [b]PG = benzyl group. [c]20 mol% PTSA·H_2O was used.

To test our hypothesis, 2-alkenyl indole **20a** and 2-benzyloxy acetaldehyde were chosen as model substrates and treated under standard reaction conditions used for the synthesis of *α*-(3-indolyl) ketones. Pleasingly, the desired carbazole **21a** was isolated in 78% yield (Scheme 11). To improve the yield, we screened various aldehydes bearing different protecting groups and found that *p*-nitrobenzyl protected aldehyde provided the best result (85%).

Keeping the synthetic utility of carbazoles in mind, the generality of this annulation strategy was studied in details by reacting different 2-alkenylindoles with various aldehydes and ketones. 2-Alkenyl indoles bearing various functional groups such as chloro, bromo, methoxy, methyl at the C5 positon and fluoro at the C7 position of indole underwent smooth conversion and the corresponding carbazoles were isolated in good to excellent yields (**21b**-**21f**, 61-84%, Scheme 12). Then the alkenyl part of indole was varied and found that ethyl or even long alkyl chain substitutions did not retard the second nucleophilic attack (**21g**-**21h**, 55-85%). 1-Phenyl and 1-thiophenyl substituted carbazoles were also synthesized using this protocol (**21i**-**21k**, 36-80%). 2-Alkenyl indoles bearing two alkyl substitutions were also compatible to provide the desired carbazoles (**21l**-**21o**, 37-42%). Although the yields are in the lower side, stitching of two different aliphatic functional groups at C1 and C2 positions of carbazole is extremely elusive and a challenging task. Next, we checked the scope of various aldehydes for this benzannulation reaction. Aldehydes bearing methyl, isobutyl, benzyl, and *sec*-butyl groups at R^4 position were suitable coupling partners and corresponding trisubstituted carbazoles bearing three different functional groups at 1,2,3-positions were accomplished in good yields (**21p**-**21s**, 48-79%). Hence the present protocol opens up a facile route to install different aliphatic chains at C1, C2, C3 position of carbazoles. Aldehydes bearing phenyl group at R^4 was also suitable for this reaction (**21t**, 55%). To our delight, using the standard conditions, synthesis of 1,2,4-trisubstituted carbazole **21u** and even a tetrasubstituted carbazole **21v** were successfully obtained as ketone was also a suitable electrophile for this reaction.

Conclusion

In conclusion, we have developed an operationally simple and scalable strategy to obtain diversely functionalized *α*-(3-indolyl) ketones using easily available Brønsted acid as catalyst. A wide range of indoles and even challenging pyrroles took part in this reaction. Selectively linear and branched ketones were obtained by choosing appropriate carbonyl precursors. Pleasingly different key functional groups such as ester, nitro, phosphonate, alkene, thioketals, protected alcohols, halides, etc. were tolerated the reaction conditions rendering this method attractive for further functional group manipulation. A detailed mechanistic investigation and isolation of the key intermediate suggested that the reaction proceeded *via in situ* generated enol ether intermediate. The application of the product ketones was demonstrated by transforming it to 3-cyano indole, tryptophol, *α*-methyltryptamine, indolenine, etc. Synthesis of diversely functionalized carbazoles and *β*-carboline is another highlight of this work. We believe this method will be highly effective for the synthesis of *α*-(3-indolyl) and *α*-(3-pyrrolyl) ketones.

Experimental Section

General Procedure I (GP I): Synthesis of α-Indolyl Ketones

To a 10 mL sealed pressure tube equipped with a magnetic stirring bar, indole **1** (0.2 mmol, 1.0 equiv.), *p*-toluenesulfonic acid monohydrate (0.02 mmol, 0.1 equiv.) were taken (in some cases, 0.2 equiv. of PTSA·H_2O was needed, check individual examples). To the mixture, aldehyde **2** (0.3 mmol, 1.5 equiv.) dissolved in ethyl acetate (1.5 mL) was added at the room temperature. Finally, the resulting reaction mixture was heated to 120 °C under constant stirring. After complete consumption of starting material **1** (generally takes 1.5 to 24 h, check individual examples) as indicated by TLC (the products are $KMnO_4$ and DNP active), the crude reaction mixture was diluted with ethylacetate, transferred to a round bottom flask, and the solvent was evaporated under vacuo. The crude residue was purified by column chromatography on silica gel to obtain the pure desired products **3**.

General Procedure II (GP II): Synthesis of α-(3-Pyrrolyl) Ketone

To a 10 mL sealed pressure tube equipped with a magnetic stirring bar, pyrrole **6** (0.2 mmol, 1.0 equiv.) and *p*-toluenesulfonic acid monohydrate (0.02 mmol, 0.1 equiv.) were taken. To the mixture, aldehyde **2** (0.3 mmol, 1.5 equiv.) dissolved in ethyl acetate (1.5 mL) was added at room temperature. Finally, the resulting reaction mixture was heated to 120 °C under constant stirring. After complete consumption of starting material **6** as indicated by TLC (the product is $KMnO_4$ and DNP active), the crude reaction mixture was diluted with ethylacetate, transferred to a round bottom flask and the solvent was evaporated under *vacuo.* The crude product was purified by column chromatography on silica gel to obtain the pure products **7**.

General Procedure IV (GP IV): Synthesis of Carbazoles

In a 10 mL sealed pressure tube equipped with a magnetic stirring bar, 2-alkenylindole **20** (0.2 mmol, 1.0 equiv.) and *p*-toluenesulfonic acid monohydrate (0.02 mmol, 0.1 equiv.) were taken (in few cases, 0.2 equiv. of PTSA·H_2O was needed, check individual examples). To the mixture, the aldehyde **2** (0.4 mmol, 2.0 equiv.) dissolved in ethyl acetate (1.5 mL) was added at room temperature. Finally, the resulting reaction mixture was heated to 120 °C under constant stirring condition. After complete consumption of starting material **20** (generally takes 2 to 96 h, check individual examples) as indicated by TLC, the crude reaction mixture was diluted with ethylacetate and carefully transferred to a round bottom flask. Then the solvent was evaporated under *vacuo* and the crude product was purified by column chromatography on silica gel to obtain the pure desired product **21**.

Acknowledgements

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Keywords: *α*-Indolyl Ketones • Indole • Pyrrole • Carbazole • Brønsted acid • Annulation

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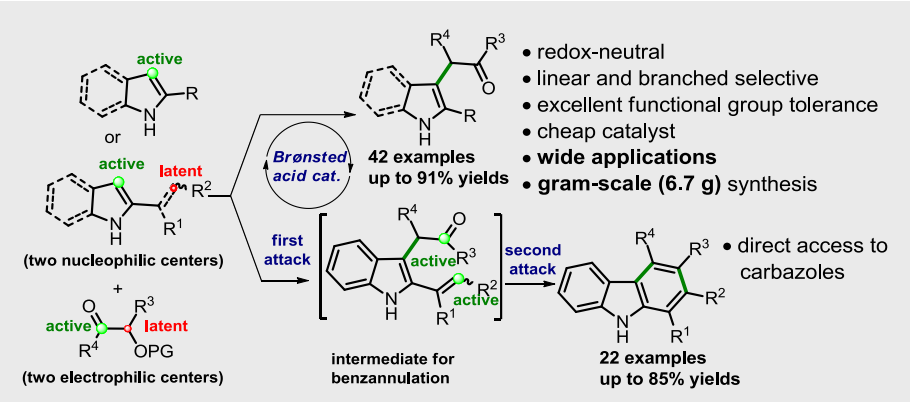

*Ankush Banerjee and Modhu Sudan Maji**

A Brønsted Acid Catalyzed Cascade Reaction for the Conversion of Indoles into α-(3-Indolyl) Ketones Using 2-Benzyloxy Aldehydes

Carbonyl does not get consumed! The synthesis of functionalized α-(3-indolyl) and α-(3-pyrrolyl) ketones are realized by direct reaction of α-benzyloxy carbonyls with indoles or pyrroles employing readily available Brønsted acid catalyst. This method is operationally simple, scalable and eliminates the long standing regio-isomeric issue. A detailed mechanistic studies confirmed the involvement of enolether as a reaction intermediate. Several post synthetic modifications along with easy access to β-carboline, tryptamines, tryptophols and spiro-indolenine proclaims the synthetic utility of this powerful scaffold. Based on this concept, functionalized carbazoles were constructed by cascade annulation strategy.