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Rhodium catalyzed diastereoselective synthesis of 2,2,3,3-tetrasubstituted indolines from *N*-sulfonyl-1,2,3-triazoles and *ortho*-vinylanilines†

Dongari Yadagiri, Angula Chandra Shekar Reddy and Pazhamalai Anbarasan*

An efficient diastereoselective rhodium catalyzed synthesis of indolines possessing two contiguous tetrasubstituted carbon centers has been achieved with good to excellent yields using *ortho*-vinylanilines and iminocarbenes derived from *N*-sulfonyl-1,2,3-triazoles. The reaction affords excellent *cis*-diastereoselectivity through the initial formation of a *N*-ylide followed by intramolecular trapping with unactivated alkenes *via* an ene-type reaction with a well-organized transition state, namely intramolecular carbenylative amination of alkenes. The developed transformation was further extended to the successful synthesis of tricyclic compounds, imidazoindolines, through reduction and hypervalent iodine mediated oxidative cyclization.

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Introduction

2,3-Multisubstituted indolines are widely present in various alkaloid natural products and therapeutically important molecules possessing diverse biological activities.¹ Representative examples include minfiensine, vindoline and strychnine, which exhibit significant anticancer activities (Fig. 1).² Hence, over several decades 2,3-multisubstituted indolines have attracted great synthetic interest.³

Most of the known traditional methods involve different functionalizations of (ox)indole derivatives.⁴ Recently, these methods have been replaced with transition metal catalyzed⁵ or free radical⁶ construction of indoline either through C–C or C–N bond forming reactions.⁷ Hu and co-workers⁸ utilized the intramolecular trapping of ammonium ylides, generated from diazo carbonyl compounds and an amine, with either a polar

double bond-like ketone or an activated alkene for the synthesis of 2,2,3-trisubstituted indolines. Although the intramolecular trapping of ammonium ylides with activated double bonds has been studied, trapping with an unactivated alkene, such as styrene which would afford 2,3-multisubstituted indolines, is very rare and highly desirable.

Over the past few years, *N*-sulfonyl-1,2,3-triazoles have emerged as a valuable resource for the generation of imino carbenes, a new reactive intermediate in organic synthesis.⁹ Unlike the traditional α -oxocarbenes, imino carbenes possess unique reactivity due to the presence of both an electrophilic carbene and nucleophilic nitrogen. This has been utilized in the construction of pharmaceutically important nitrogen based building blocks and heterocycles, through various carbene induced transformations.¹⁰ For instance, Fokin *et al.*¹¹ and Yoo *et al.*¹² demonstrated a formal stereoselective 1,3-insertion of rhodium imino carbenes into the N–H bond of amine derivatives through the generation of a *N*-ylide (Scheme 1).

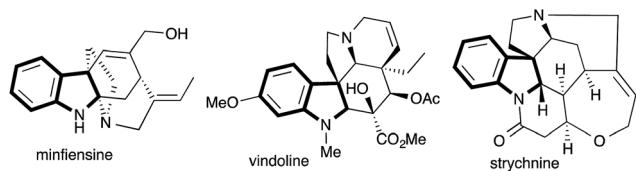
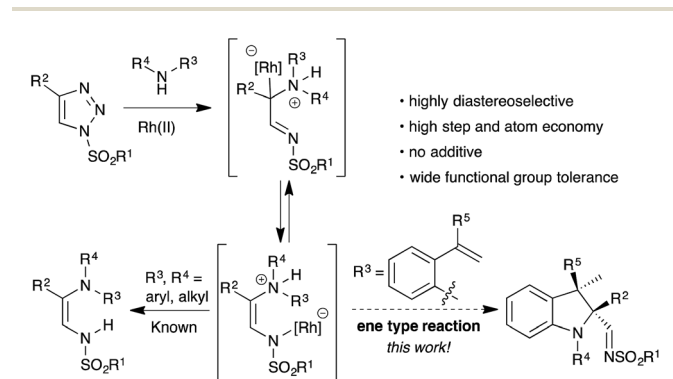


Fig. 1 Representative examples of indoline alkaloids.

Department of Chemistry, Indian Institute of Technology Madras, Chennai 600036, India. E-mail: anbarasansp@iitm.ac.in; Web: <http://chem.iitm.ac.in/faculty/anbarasan/profanbu/>

† Electronic supplementary information (ESI) available. CCDC 1438963 and 1438964. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6sc01075j



Scheme 1 Rhodium-catalyzed reactions of *N*-sulfonyl-1,2,3-triazoles.



Inspired by these studies and our continuous efforts for the functionalization of imino carbenes,¹³ we reasoned that ammonium ylides generated from suitably substituted *ortho*-vinylanilines and a rhodium imino carbene could undergo intramolecular trapping in a ene type fashion with an unactivated alkene (Scheme 1). This transformation would enable access to the stereoselective synthesis of 2,2,3,3-tetrasubstituted indoline motifs containing contiguous tetrasubstituted carbon centers *via* the formation of C–N and C–C bonds in a single operation, namely carbenylative amination of alkenes.

Results and discussion

Intramolecular carbenylative amination of *ortho*-vinylaniline **2a** with *N*-sulfonyl-1,2,3-triazole **1a** to provide 2,2,3,3-tetrasubstituted indoline **3aa** was chosen at the start of our investigation as a model reaction. The reaction of 1 equivalent of **1a** and 1.5 equivalents of **2a** in the presence of 2 mol% of Rh₂(OAc)₄ in toluene at room temperature (~35 °C) did not afford the expected product **3aa**. To our delight, increasing the temperature to 90 or 100 °C furnished the tetrasubstituted indoline **3aa**, wherein formation of **3aa** was observed with a 15% yield at 100 °C as a single diastereoisomer, based on ¹H NMR and HPLC analysis (Table 1, entries 1–2). NOE results suggested that the relative stereochemistry of the isolated diastereomer is *cis*, *i.e.* the methyl and imine substituents are *cis* in relation (see ESI†).

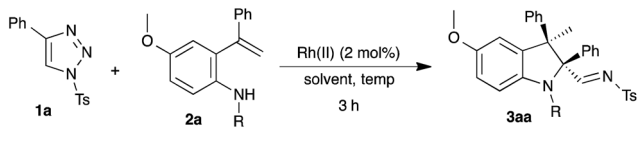
Encouraged by this result, next, the influence of the catalyst was examined. Changing Rh₂(OAc)₄ to a bulkier catalyst such as Rh₂(Oct)₄ or Rh₂(Piv)₄ showed a significant improvement in the yield (Table 1, entries 3–4). Next, screening of Rh₂(TBSP)₄ and Rh₂(*S*-NTTL)₄, chiral rhodium catalysts, under similar conditions afforded **3aa** in diminished yield (Table 1, entries 5–6). Unfortunately, no appreciable enantioselectivity was observed. Similarly, a low yield of **3aa** was observed with other solvents such as benzene and 1,2-DCE (Table 1, entries 7–8). Gratifyingly,

further increasing the temperature to 120 °C with Rh₂(Piv)₄ provided the product **3aa** in 85% yield, and the conditions used for this reaction were chosen as the optimized conditions for studying the reaction scope and limitations (Table 1, entry 9).

Having optimized the conditions, the generality of the present method was investigated with functionally different 1,2,3-triazoles **1**. As can be seen in Scheme 2, various substituted triazoles **1** underwent efficient rhodium catalyzed intramolecular carbenylative amination with **2a** to afford multisubstituted indolines **3**. Changing the sulfonyl moiety of the triazole afforded the corresponding indolines **3aa–3ea** in excellent yield. Interestingly, both electron donating and withdrawing groups as well as reactive functional groups like a nitro group and enolizable ketone were well tolerated under the optimized conditions to furnish the indolines (**3fa–3ha**, **3ja–3ma**) with good to excellent yields. Medicinally important fluorinated and trifluoromethylated indolines (**3ia**, **3na**, **3oa**) were successfully obtained from the corresponding triazoles in 92%, 77% and 80% yield, respectively. Furthermore, thiophene substituted and 4,5-disubstituted triazoles also underwent the reaction smoothly to provide indoline **3pa** and **3qa**, respectively. It is important to note that in all cases the *cis*-diastereomer was the only detectable isomer.

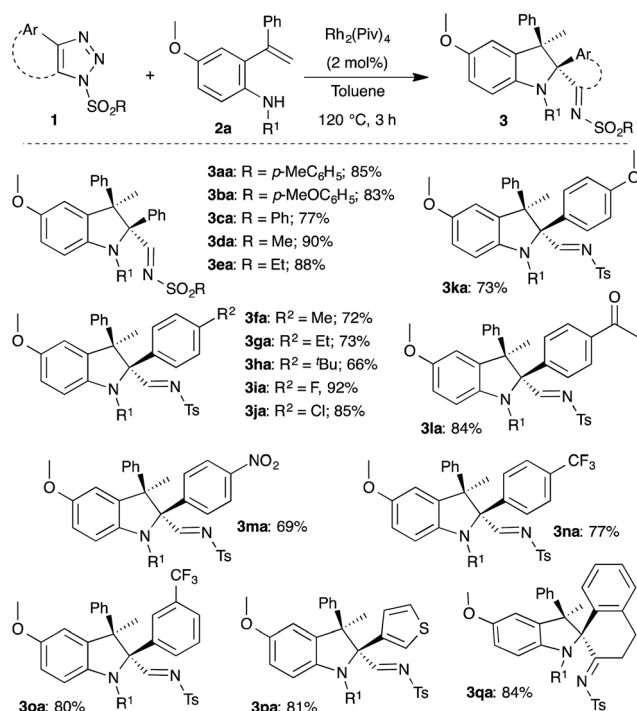
Next, the scope in relation to *ortho*-vinylanilines **2** was investigated using the optimized conditions. Initially, the effect of the substituent on the nitrogen was examined. *p*-Methoxybenzyl and methyl substituted aniline derivatives provided indolines **3ab** and **3ad** in good yield (Scheme 3). The structure and relative stereochemistry of indole **3ad** was unambiguously confirmed using single crystal X-ray analysis.¹⁴ A sterically

Table 1 Rhodium catalyzed carbonylative amination of *o*-vinylaniline **2a** and triazole **1a**: optimization



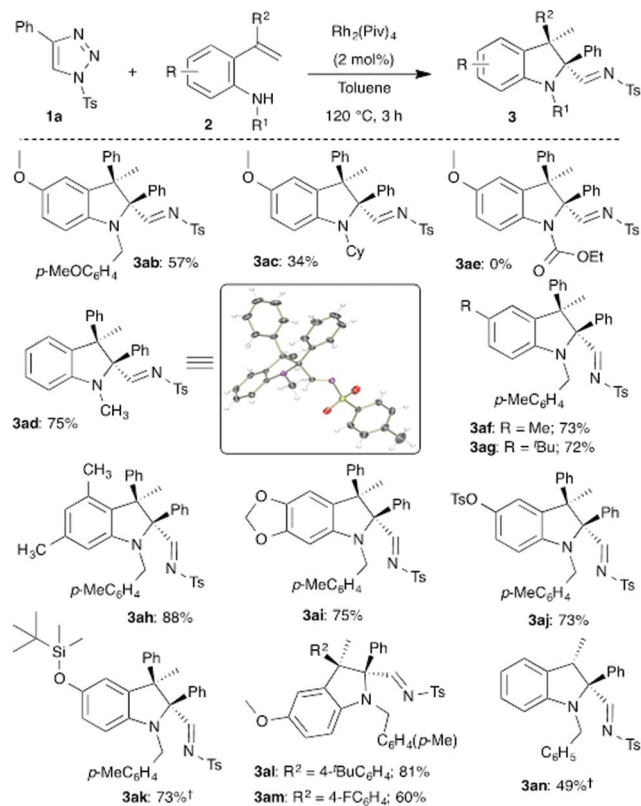
| Entry | Rh(II) | Solvent | Temp (°C) | Yield ^a (%) |
|-------|--|---------|-----------|------------------------|
| 1 | Rh ₂ (OAc) ₄ | Toluene | 90 | <5 |
| 2 | Rh ₂ (OAc) ₄ | Toluene | 100 | 15 |
| 3 | Rh ₂ (Oct) ₄ | Toluene | 100 | 30 |
| 4 | Rh ₂ (Piv) ₄ | Toluene | 100 | 45 |
| 5 | Rh ₂ (TBSP) ₄ | Toluene | 100 | 18 |
| 6 | Rh ₂ (<i>S</i> -NTTL) ₄ | Toluene | 100 | 8 |
| 7 | Rh ₂ (Piv) ₄ | Benzene | 100 | 35 |
| 8 | Rh ₂ (Piv) ₄ | 1,2-DCE | 100 | 29 |
| 9 | Rh ₂ (Piv) ₄ | Toluene | 120 | 85 |
| 10 | Rh ₂ (Piv) ₄ | Toluene | 120 | 75 ^b |

^a Isolated yields. ^b 1 mol% of Rh₂(Piv)₄. R = *p*-methylbenzyl.



Scheme 2 Rhodium catalyzed carbenylative amination: scope of the triazoles **1**. R¹ = *p*-methylbenzyl.

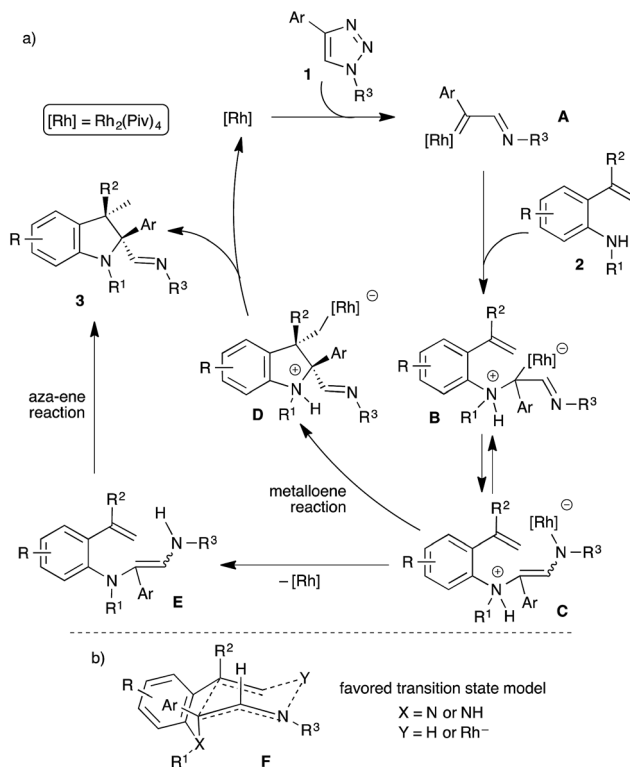




Scheme 3 Rhodium catalyzed carbenylative amination: scope of the *o*-vinylanilines **2**. [†]NMR yield.

hindered cyclohexyl substituted aniline provided **3ac** in relatively low yield. Unfortunately, having an electron-withdrawing substituent on the nitrogen did not afford the expected product **3ae**. Subsequently, screening of different substituents on the aromatic ring of the aniline was carried out. Electronically and sterically different substituents on the aromatic ring were well tolerated, especially, reactive functional groups such as acetal, sulfonate and silyl ether groups were untouched under the reaction conditions, and led to the formation of the corresponding indolines (**3af–3ak**) with good to excellent yields. Different C3-substituted indolines **3al** and **3am** were also obtained in 81% and 60% yield, respectively, from the corresponding alkene derivative. Furthermore, 2,2,3-trisubstituted indoline **3an** was also synthesized, employing the present method, in 49% yield with excellent diastereoselectivity from a simple vinyl substituted aniline.

Diastereoselective formation of the tetrasubstituted indolines can be explained with the following plausible mechanism (Scheme 4a). The reaction starts with the generation of rhodium carbenoid **A** from the *N*-sulfonyl-1,2,3-triazole using the rhodium catalyst,⁹ which on subsequent reaction with the *o*-vinylaniline **2** would afford the ammonium ylide **B**. A 1,3-rhodium shift in the ammonium ylide **B** would produce the zwitterion **C**. Formation of indoline **3** from **C** could be rationalized with two pathways: (1) a rhodium promoted intramolecular metalloene¹⁵ reaction of **C** would generate the cyclized intermediate **D** with high diastereoselectivity, and

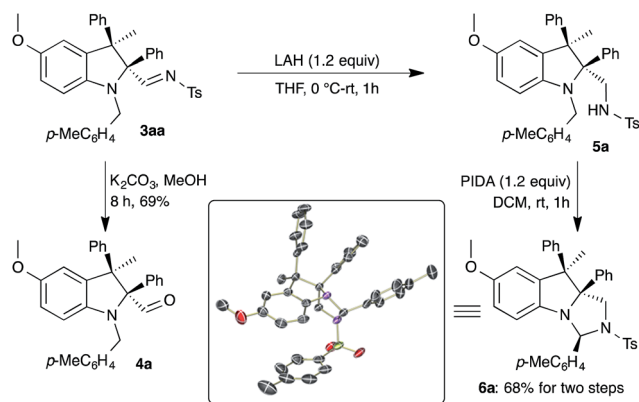


Scheme 4 (a) Plausible mechanism; (b) proposed transition state for the ene-type reaction.

a following protonation of rhodium species **D** would furnish the product **3** along with regeneration of the rhodium catalyst which continues the catalytic cycle. (2) Initial protonation of rhodium species **C** to provide enamine **E** followed by an intramolecular aza-ene reaction¹⁶ would afford the observed product **3**. To investigate the feasible pathways, various attempts were made to isolate the enamine **E**. Unfortunately, all our attempts either resulted in no reaction or the formation of product **3**, formation of enamine **E** was not observed. Hence, at this point both the pathways are equally possible. As can be seen in Scheme 4a, the *cis*-diastereoselectivity possibly arises from an intramolecular ene-type reaction. To explain the observed stereochemistry, a plausible transition state model is proposed (Scheme 4b). The 1,3-rhodium shift or the formation of an enamine through intramolecular protonation could afford preferentially the *Z*-alkene.¹¹ Subsequent cyclization through a six membered ene-type transition state **F** is highly favourable, where intramolecular interactions between [Rh] or H and the alkene would facilitate the cyclization and the *cis*-diastereoisomer could be obtained.

After successful demonstration of the generality of the carbenylative amination, synthetic applications of the substituted indolines **3** were revealed *via* the manifestation of readily available functional groups. Reaction of **3aa** with K₂CO₃ and methanol afforded the corresponding aldehyde **4a** in 69% yield (Scheme 5). On the other hand, conversion of the imine moiety in **3aa** to a sulfonamide (**5a**) was achieved through reduction with LAH. Next, a hypervalent iodine mediated cyclization¹⁷ of



Scheme 5 Synthesis of imidazoindoline **6a**.

5a was envisaged for the synthesis of a nitrogen based tricyclic compound. The reaction of sulfonamide **5a** with (diacetoxyiodo) benzene (PIDA) in DCM at room temperature afforded imidazoindoline **6a** in 68% yield over two steps, as a single diastereomer. The formation of **6a** can be explained as due to oxidation of the tertiary amine in **5a** with PIDA to provide an iminium ion followed by cyclization. The structure of **6a** was unambiguously confirmed using single crystal X-ray analysis¹⁸ (see ESI†).

The developed two-step protocol was subsequently applied to functionally different indolines **3**. In general, all of the indolines that were examined afforded the imidazoindolines **6b–k** in good yield under the two-step reduction and oxidative cyclization sequence (Scheme 6). It is important to note that the oxidative cyclization tolerates oxidation prone electron rich

arene and thiophene substituents as well as electron deficient arenes, and led to the synthesis of the corresponding imidazoindolines **6d–j** in good yield. Interestingly, replacement of *N*-Bn with *N*-Me also provided the imidazoindoline **6k** in 69% yield.

Conclusions

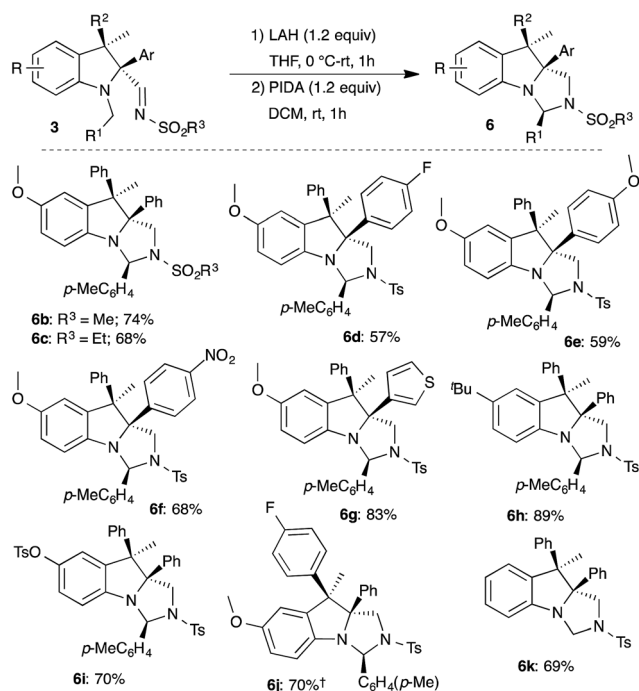
In conclusion, an efficient rhodium catalyzed formal carbenylative amination of *ortho*-vinylanilines with iminocarbenes derived from *N*-sulfonyl-1,2,3-triazoles has been accomplished for the diastereoselective synthesis of indolines possessing two contiguous tetrasubstituted carbon centers. The reaction affords excellent *cis*-diastereoselectivity through the initial formation of a *N*-ylide, followed by trapping with unactivated alkenes *via* an ene-type reaction with a well-organized transition state. The present method tolerates various reactive functional groups, which allows the synthesis of various indoline derivatives in good to excellent yield. The developed transformation was further extended to the successful synthesis of tricyclic compounds, imidazoindolines, through reduction and hyper-valent iodine mediated oxidative cyclization.

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Scheme 6 Synthesis of imidazoindolines **6**. ¹H NMR yield.

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