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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†

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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 cisdiastereoselectivity 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. EDGE ARTICLE

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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.

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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 orthovinylanilines 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 $Rh_2(OAc)_4$ in toluene at room temperature (\sim 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 $^{\circ} \mathrm{C}$ as a single diastereoisomer, based on $^{1} \mathrm{H}$ 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 $Rh_2(OAc)_4$ to a bulkier catalyst such as $Rh_2(Oct)_4$ or $Rh_2(Piv)_4$ showed a significant improvement in the yield (Table 1, entries 3-4). Next, screening of $Rh_2(TBSP)_4$ 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,

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

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

further increasing the temperature to 120 °C with $Rh_2(Piv)_4$ 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. Flags Article

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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

Scheme 2 Rhodium catalyzed carbenylative amination: scope of the triazoles 1. $R^1 = p$ -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 K_2CO_3 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

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

Scheme 6 Synthesis of imidazoindolines 6. \dagger1 H NMR yield.

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 hypervalent iodine mediated oxidative cyclization.

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