Substrate controlled, regioselective carbopalladation for the one-pot synthesis of C4-substituted tetrahydroisoquinoline analogues†

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6-Exo-trig cyclization reaction through regioselective carbopalladation was demonstrated with N-(2-halobenzyl)-N-allylamines to furnish the corresponding C4-substituted tetrahydroisoquinoline derivatives. The scope of the reaction was extended to the synthesis of C4-quaternary tetrahydroisoquinoline derivatives also. The nature of the substituent on the olefin moiety dictates the course of the carbopalladation sequence. Regioselective carbopalladation is substantiated by performing the reaction with unsymmetrical diallylated amine substrates.

Introduction

Tetrahydroisoquinolines are one of the key nitrogen heterocycles with innumerable biological activities.1–4 Noscapine, salsolinol, giganjine are representative examples of tetrahydroisoquinolines with anticancer, antihistaminic and hallucinogenic activities.2 A representative list of bioactive tetrahydroisoquinoline derivatives is given in Fig. 1.

Among tetrahydroisoquinolines, C4-substituted analogues are well-acclaimed subset due to their highly desirable pharmacologically relevant properties. Nomifensine is a C4-substituted isoquinoline analogue used as antidepressant agent without any sedative side effect.3 C4-substituted analogues are also used as serotonin reuptake inhibitors with histamine H3 antagonist activity4 and function as 4-hydroxytamoxifen analogues.5 Cherylline is a C4-substituted tetrahydroisoquinoline isolated from the natural sources.6

Fig. 1 Selected bioactive tetrahydroisoquinoline analogues.

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Chart 1 Methods for the synthesis of C4-substituted tetrahydroisoquinolines and our methodology.
Despite several significances, only a limited number of examples are available for the one-pot synthesis of C4-substituted tetrahydroisoquinoline derivatives. These were prepared by the palladium catalysed [4+2] annulation reaction or superacid-catalyzed Pictet–Spengler cyclization reactions (Chart 1).\textsuperscript{7a} Hu et al., reported palladium mediated amino-alkenylation of alkynes for the synthesis of C4-substituted tetrahydroisoquinoline derivatives.\textsuperscript{7b} Nandakumar et al., reported the synthesis of similar tetrahydroquinoline by the intramolecular cyclization of more reactive alkynes.\textsuperscript{7b} Broggeni and co-workers reported palladium catalysed synthesis of C4-spiroannulated tetrahydroisoquinoline derivatives.\textsuperscript{8} However, the scope of the reaction was largely confined to N-allyl derivative.

Unlike N-allyl derivatives, 6-exo-trig cyclization of N-cinnamyl/N-crotyl derivatives is challenging due to the plausible formation of a mixture of isomers due to the regio- and stereochemical scrambling (vide infra). Since the generation of a convenient method to access these valuable pharmacophores is highly appreciated, it was decided to perform 6-exo-trig cyclization of terminal carbon substituted acyclic N-allylic amine derivatives with palladium catalysis (Chart 1).

**Results and discussion**

To obtain the highest level of stereocontrol in palladium catalysis, directing functional groups needs to be anchored on the alkene or the use of Ag or Ti salts is required.\textsuperscript{9a,b} In the absence of any directing group or metal salt additive, it is difficult to secure a single isomeric product from the mixture of stereo-regio-isomers (Scheme 1).

Apart from the formation of a mixture of isomers as shown in Scheme 1, the competitive deallylation reaction of the substrate 1a–1l is yet another challenge.\textsuperscript{10} To suppress deallylation, allyl moiety needs to be tethered to a heterocyclic ring or reaction must be performed with N-allyl amides.\textsuperscript{12a,b} These constraints limit the synthetic utility of the 6-exo-trig cyclization for accessing C4-substituted tetrahydroisoquinoline analogues.

It was previously reported in the literature that the nature of the substituent on the double bond plays a pronounced role in determining the type of the product formed in the reaction.\textsuperscript{13} Likewise, the use of alkyl amine would also facilitate the cyclization reaction by suppressing the undesired deallylation reaction. Hence, tertiary amine derivative 1a was designed to have a cinnamyl group anchored on the aliphatic amine. Reaction conditions were optimized with substrate 1a (Table 1).

Reaction performed with commercially available, pre-functionalized palladium phosphine complexes such as Pd(dppf)Cl\textsubscript{2} gave the corresponding tetrahydroisoquinoline product 3a in 60% yield (Table 1, entry 1). It is of interest to mention here that the exclusive formation of the isomer 3a with an exocyclic double bond was observed in the reaction medium. The migration of exocyclic double bond to the corresponding stable endocyclic double bond through the reinsertion of the palladium followed by second elimination was not observed. Encouraged by this result, we decided to investigate further the role of palladium on the 6-exo-trig cyclization reaction.

Gratifyingly, changing of palladium complex from Pd(dppf)Cl\textsubscript{2} to Pd\textsubscript{2}(dba)\textsubscript{3} (Pd\textsuperscript{3+} to Pd\textsuperscript{2+}) improved the product yield to 90% (Table 1, entry 2). Replacing the non-polar solvent toluene with polar aprotic solvents such as DMF or DMSO reduced the yield of the product 3a (Table 1, entries 3 and 4). Changing of base to K\textsubscript{2}CO\textsubscript{3} or reducing the reaction temperature drastically affected the yield of the product 3a (Table 1, entries 6 and 7). Interestingly, replacing pre-functionalized palladium complexes with in situ generated palladium phosphine complexes using Pd(OAc)\textsubscript{2}/PPh\textsubscript{3} gave the desired product 3a with 95% yield (Table 1, entry 8). Hence, it was decided to perform the reaction with Pd(OAc)\textsubscript{2}/PPh\textsubscript{3}. After optimizing the reaction conditions, the scope of the reaction was screened with diverse allyl/arylamine derivatives. The carbopalladation/cyclization reaction was found to be general for both N-(n-butyl) and N-ethyl amine derivatives (Fig. 2). The products 3a and 3b were obtained in appreciable yields. The replacement of N-ethyl substituent on the nitrogen atom with sterically more demanding tert-butyl substituent didn’t show much effect on the yield of the product 3b (87%) vs. 3e (78%). These results show that the nature of the aliphatic substituent on the nitrogen atom doesn’t influence much on the yield of the isoquinoline products 3.

Replacing the phenyl group on the terminal olefin with a relatively electron richer 4-methoxyphenyl group also did not affect the carbopalladation/cyclization sequence. The products 3d–f were obtained in high yields. In the case of benzylic amine derivatives, the presence of methoxy substituent on the olefin aromatic moiety or amine did not alter the yield of the products 3g–h. The structure of the product 3g was confirmed unequivocally by single crystal XRD and it revealed that the product 3g adopts (Z)-configuration (Fig. 2). As speculated, the replacement of aliphatic substituent on the nitrogen atom with an aromatic moiety resulted in more amounts of unreacted substrate 1l in the reaction medium. An increase in the reaction time or reaction temperature did not improve the yield of the product 3i.

Interestingly, the reaction carried out with N-aryl-N-allyl derivative gave the product 3j in 80% yield. Reaction performed with N,N-diallylated substrate gave the product 3k in 75% yield.

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Likewise, lipophilic N-octyl-N-allyl derivative also yielded the product 3l in good yields. In the synthesis of both 3k and 3l, cyclization proceeded with substituent-free allyl moiety itself. The formation of deallylated product was not observed even in the absence of any substituent at the terminal double bond. To demonstrate the practical utility of this method as a synthetic tool, we have performed a larger scale synthesis of 3c with 10 mmol of substrate 1c. It is imperative to mention that the desired product 3c was formed in 76% yield in this scale-up reaction. In addition, 3c synthesis performed with Pd(PPh3)4 also gave the product in 70% yields. This shows that Pd(0) plays a crucial role in this cyclization sequence.

Mechanistic investigations and quantum chemical calculations

It was previously reported in the literature that the facial selectivity of the olefin and the subsequent carbopalladation plays a crucial role in determining the product selectivity.14 Oxidative addition of palladium onto the aryl bromide could result in the formation of aryl palladium complex (Fig. 3). For the 6-exo-trig cyclization, intramolecular coordination of palladium with olefin moiety is necessary. We presume, during the carbopalladation, the phenyl substituent on the olefin tends to move away from the sterically more hindered triphenylphosphine ligand tethered palladium. This could have been resulted in the preferential formation of (Z)-isomer over (E)-isomer (Fig. 3). A detailed plausible mechanism is given in Scheme 3.

If steric factor plays a crucial role in the carbopalladation, then the use of unsymmetrical diallylated substrate 1m-p or 1s would lead to regioselective carbopalladation at sterically less

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Table 1  Optimization of reaction conditions

| Entry | Catalyst       | Base      | Temp. (°C) | Solvent | Time (h) | Yield (%) 3a<sup>a</sup> |
|-------|----------------|-----------|------------|---------|----------|--------------------------|
| 1     | Pd(dpdpf)Cl<sub>2</sub> | Cs₂CO₃    | 100        | NMP     | 26       | 60                       |
| 2<sup>A</sup> | Pd₂(db₃)₃ | Cs₂CO₃    | 110        | Toluene | 24       | 90                       |
| 3     | Pd₂(db₃)₃   | Cs₂CO₃    | 120        | DMF     | 26       | 74                       |
| 4     | Pd₂(db₃)₃   | Cs₂CO₃    | 120        | DMSO    | 24       | 65                       |
| 5     | Pd₂(db₃)₃   | Cs₂CO₃    | 130        | Xylene  | 24       | 75                       |
| 6     | Pd₂(db₃)₃   | K₂CO₃     | 110        | Toluene | 24       | 60                       |
| 7     | Pd₂(db₃)₃   | Cs₂CO₃    | 80         | Toluene | 30       | 60                       |
| 8<sup>d</sup> | Pd(OAc)<sub>2</sub> | Cs₂CO₃    | 110        | Toluene | 24       | 95                       |

<sup>a</sup> Unless otherwise mentioned, all the reactions were performed with aryl halide 1a (0.1 mmol), Pd catalyst (0.01 mmol) and base (0.2 mmol) in 3 mL of solvent. <sup>a</sup> Isolated Yield. <sup>A</sup> Presence of unreacted 1a was observed if the reaction mixture was quenched before 24 h. <sup>d</sup> PPh₃ (0.02 mmol) was used as ligand.

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Fig. 2  Substrate scope for 6-exo-trig cyclization reaction.

Fig. 3  Plausible cyclization pathway.
hindered olefin moiety. To check this hypothesis, acyclic amine substrates 1m-p were designed to have both substituted allyl and cinnamyl moieties tethered on to the nitrogen atom (Scheme 2(i) and (ii)). In the case of substrates 1m/1n, cyclization prefers sterically less hindered allyl moiety rather than relatively more steric cinnamyl moiety and the products 3m/3n are formed in good yields. Likewise, for the substrates 1o/1p, cyclization proceeds through sterically less hindered cinnamyl/allyl moiety than sterically more crowded 2,3-dimethylallyl moiety. Hence, products 3o/3p are formed in good yields. In scheme (i) and (ii), the formation of products 3m’/3n’ and 3o’/3p’ are not observed. The carbopalladation at 2,3-dimethyl allyl derivative 1q is challenging due to (i) the presence of sterically more demanding methyl groups, (ii) lack of β-hydrogen on the ring (Scheme 2(iii)). Interestingly, reaction performed with 1q gave the corresponding C4-quaternary isoquinoline derivative 3q. Thus the proposed method offers a facile method for the synthesis of C4-quaternary derivatives. However, the reaction performed with 1r failed to yield the desired product 3r. Lack of product selectivity was observed if the substrate (1s) possesses two cinnamyl groups with similar steric influence but varies in electronic effect (Scheme 2(iv)).

The carbopalladation/cyclization reaction performed under open-air reaction conditions also gave the product 3a in 74% yield (Scheme 2(v)). To further confirm the absence of radical pathway, the reaction was performed in the presence of radical quencher TEMPO (Scheme 2(v)). As predicted, TEMPO did not interfere with the course of the reaction and product 3a was obtained in 46% yield.

Quantum chemical calculations were performed using Gaussian09 program\textsuperscript{15} with B3LYP/6-311++G(d,p) level of theory for 1m and 1o. The result revealed that the electron density of the highest occupied molecular orbitals (HOMO) is localized over allyl and cinnamyl moieties and they are comparable (Fig. 4). Hence, the products 3o and 3m formed from 1o and 1m are largely driven by the steric factor. Studies performed on both (E) and (Z)-isomers of 3g revealed that the (Z)-isomer is 2.6 kcal mol\textsuperscript{-1} more stable form than the corresponding (E)-isomer (Fig. S1, ESI\textsuperscript{†}). Based on the results obtained from mechanistic studies and quantum chemical calculations, we propose a plausible mechanism for the formation of the product.

The addition of both Pd(OAc)\textsubscript{2} and PPh\textsubscript{3} could result in the formation of anionic palladium complex A (Scheme 3).\textsuperscript{16} Oxidative addition of anionic palladium on to the aryl halide followed by the coordination with olefin would result in the formation of palladium complex B\textsubscript{1} or B\textsubscript{2}.

The nature of the substituent on the olefin dictates this crucial carbopalladation step.\textsuperscript{13} If R = Me, the carbopalladation might proceed through sterically less hindered cinnamyl derivative via cycle I to form B\textsubscript{1}. In cycle I, the migratory insertion of the olefin on to the aryl palladium would result in the formation of complex C\textsubscript{1}. Likewise, if R = H, the reaction could proceed through cycle II and C\textsubscript{2} is formed. The syn coplanar arrangement of the metal center and the β-hydrogen atom is required for the β-hydride elimination to take place in C\textsubscript{2}.\textsuperscript{12} The β-hydride elimination of the complex C\textsubscript{1} and C\textsubscript{2} could

![Scheme 2](image-url)  
Scheme 2 Regioselective carbopalladation and mechanistic studies.

![Scheme 3](image-url)  
Scheme 3 Plausible mechanism for Pd-catalysed regioselective 6-exo-trig cyclization.

![Fig. 4](image-url)  
(I) HOMO of 1o; (II) HOMO of 1m.
result in the formation of the product 3m and 3o respectively. Interestingly, the re-insertion of the palladium on to the product was not observed under the reaction conditions. Hence the formation of the product with endocyclic double bond was not found.

Conclusion

In conclusion, we have developed an intramolecular sequential carbopalladation and cyclization methodology for the synthesis of highly biologically relevant C4-substituted tetrahydroisoquinoline analogues. The prime advantages of this transformation are being the exclusive formation of (Z)-exo olefin group containing tetrahydroisoquinoline derivatives. The possibility for the generation tetrahydroisoquinolines with all carbon quaternary stereogenic centers at C4 carbon atom is also demonstrated.

Conflicts of interest

There are no conflicts to declare.

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