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Palladium-Catalyzed Cascade sp² C-H Bond Functionalizations Allowing the One Pot Access to 4-Aryl-1,2,3,4-tetrahydroquinolines from N-Allyl-N-arylsulfonamides

Kedong Yuan,[a,b] Jean-François Soulé,*[b] Vincent Dorcet,[b] Henri Doucet*[b]

[a] Tianjin Key Laboratory of Advanced Functional Porous Material, Institute for New Energy Materials & Low-Carbon Technologies, School of Materials Science and Engineering, Tianjin University of Technology, Tianjin 300384, China.

[b] UMR 6226 CNRS-Université de Rennes 1, 35042 Rennes, France.

KEYWORDS Palladium • C-H activation • catalysis • desulfitative coupling • cascade

ABSTRACT We have developed a palladium-catalyzed cascade reaction allowing an efficient synthesis of 4-aryl-1,2,3,4-tetrahydroquinolines from N-allyl-N-arylsulfonamides and benzenesulfonyl chlorides. In this transformation, two C(sp²)-C(sp³) bonds were formed via activation of C(sp²)-H bonds. The reaction proceeds using easily accessible PdCl₂ catalyst, with Li₂CO₃ as inexpensive base and CuBr as additive and tolerates a wide variety of substituents on both reaction partners.
Introduction

One current important area of modern synthetic chemistry is the development of methods minimizing both the requisite number of steps and formation of wastes. Among these methods, the metal-catalyzed functionalization of C-H bonds has emerged as a simpler and “greener” way for the access to useful molecules for biological or material applications, as such processes are capable of forming similar products while avoiding the use of stoichiometric organometallic reagents. Most of the examples of such C-H bond functionalizations concern the formation of C-C bonds via arylation, alkylation, or alkenylation;\(^1\) whereas, the formation of two C-C bonds via consecutive Heck type reaction followed by an \(\text{sp}^2\) C-H bond activation has attracted less attention.\(^2,3\) Among rare examples, Fagnou et al. described the formation of indolines from 2-bromoaniline derivatives and heteroarenes via a domino palladium-catalyzed Heck-intermolecular direct arylation.\(^3d\) In 2012, Wu et al. described the synthesis of 4-polyfluoroaryl pyrrolo[1,2-a]quinolines via intermolecular followed by intramolecular palladium-catalyzed \(\text{sp}^2\) C-H bond activations.\(^3e\) Recently, Zhu and co-workers reported the synthesis of [3,4]-fused oxindoles via a double palladium-catalyzed \(\text{sp}^3\) C-H bond activation.\(^3g\) On the other hand, the Heck reaction\(^4,5\) using \(\text{N-allylbenzenesulfonamides}\) and aryl halides as coupling partners has been described by Y. Dong (Scheme 1 top).\(^6\)

In this article, we report on the unexpected one pot synthesis of 4-aryl-1,2,3,4-tetrahydroquinolines, from \(\text{N-allyl-N-benzenesulfonamides}\) and \(\text{ArSO}_2\text{Cl}\) through a palladium-catalyzed cascade desulfurative addition–cyclization reaction (Scheme 1, bottom).\(^7,9\) It should be mentioned that 1,2,3,4-tetrahydroquinoline is an important motif found in numerous compounds with important antitumoral, antibacterial or antioxidant activities.\(^10\) Several methods are leading to the synthesis of 1,2,3,4-tetrahydroquinolines, including partial reduction of quinolines,
condensation of anilines with two molecules of an aldehyde, or from a Schiff base and an alkene.\textsuperscript{10,11} However, most of these methods involve a multi-steps synthesis and in several cases does not allow the introduction of specific functional groups at the desired positions.

\[ \text{Y. Dong}^{6} \]

\[ \text{This work} \]

\[ \text{ArSO}_2\text{Cl} + \text{R}^1\text{N} = \text{SO}_2\text{R}^2 \xrightarrow{[\text{Pd}]} \text{Ar} \]

\[ \text{H}^+ \text{N} \rightarrow \text{SO}_2(\rho-\text{tol}) \xrightarrow{\text{Pd(OAc)}_2 \text{P(o-MeC}_6\text{H}_4)_3} \text{H}^+ \text{N} \rightarrow \text{Ar} \]

\[ \text{N} \rightarrow \text{ArSO}_2(\rho-\text{tol}) \]

\[ \text{Scheme 1.} \]

Results and discussion

The \( N \)-allyl-\( N \)-aryl sulfonamides \( 1-22 \) were first prepared in high yields from anilines, methyl- or benzene-sulfonyl chlorides and allyl bromides (Scheme 2).

\[ \text{Scheme 2. Structures of 1-22} \]

We then examined the influence of the conditions on the products formation using \( N \)-allyl-\( N \)-\( p \)-tolylbenzenesulfonamide \( 1 \) and 4-methylbenzenesulfonyl chloride as the coupling partners (Table 1). Using \( \text{PdCl}_2 \) catalyst and \( \text{Li}_2\text{CO}_3 \) as base in dioxane as reaction conditions, which had been previously found operative for direct arylations of heterocycles,\textsuperscript{12} no reaction occurred. On
the other hand, under the same conditions, but in the presence of 1.1 equiv. of CuBr as additive, the unexpected 4-tolyl-1,2,3,4-tetrahydroquinoline 24 –resulting from a formal 6-endo-trig cyclization after desulfitative addition– was obtained in 75% yield with 89% conversions of 1 (Table 1, entry 2). It should be noted that no formation of the expected Heck type product 23 was observed under these conditions. The use of Pd(OAc)$_2$, PdCl$_2$(MeCN)$_2$, PdCl(C$_3$H$_5$)(dppb), Pd(TFA)$_2$ or Pd$_2$(dba)$_3$ catalysts did not increase the yield in the desired product 24 (Table 1, entries 3-7). With Pd$_2$(dba)$_3$ catalyst in the absence of CuBr, deallylated 1 was the major product. With PdCl$_2$ catalyst, a decrease of the CuBr loading to 0.1 equiv. had almost no influence on the yield in 24; whereas using 1 mol% CuBr gave 24 in low yield (Table 1, entries 9-11). Then, the influence of several bases was examined using 5 mol% of PdCl$_2$ associated to 0.5 equiv. of CuBr. Lower yields in 24 were obtained with K$_2$CO$_3$ and Na$_2$CO$_3$; whereas, Cs$_2$CO$_3$ or a reaction without base were completely ineffective (Table 1, entries 12-15). The decrease of the reaction temperature to 100 °C also affords 24 in good yield (Table 1, entry 16). The influence of a few solvents was also investigated. No reaction occurred in xylene or DMF; whereas 1 was obtained in 65% yield in diethyl carbonate (Table 1, entries 17-19). The addition of 1.2 equiv. of TEMPO was found to quench almost completely the reaction without its incorporation in 1 or 2. This result suggests that no radical species is involved in this 6-endo-trig cyclization (Table 1, entry 20). From 1 using 5 mol% PdCl$_2$ catalyst in the presence of CuBr and Li$_2$CO$_3$ at 140 °C, but without benzenesulfonyl chloride, no cyclization to afford a 1,2,3,4-tetrahydroquinoline occurred and 1 was recovered (Table 1, entry 21). When CuBr$_2$ was used as additive instead of CuBr, a low conversion of 1 was observed, and 24 was formed in very low yield together with unidentified side-products (Table 1, entry 22). Finally, the replacement of 1 by tert-butyl allyl(phenyl)carbamate led to several unidentified side-products; whereas, the
desired cyclized product was not detected by GC/MS analysis of the crude mixture (Table 1, entry 23).

**Table 1.** Influence of the Reaction Conditions for the Po-Catalyzed Functionalization of 1.

![Chemical Structure](image)

<table>
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<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Base</th>
<th>CuBr (equiv.)</th>
<th>Temp (°C)</th>
<th>Conv. of 1 (%)</th>
<th>Yield in 24 (%)</th>
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<td>74</td>
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<tr>
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<tr>
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<tr>
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<tr>
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<td>100</td>
<td>83</td>
<td>74</td>
</tr>
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<td>120</td>
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<td>120</td>
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<td>0</td>
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<tr>
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<td>72</td>
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<tr>
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<td>Li$_2$CO$_3$</td>
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<td>&lt;5$^d$</td>
</tr>
<tr>
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<td>140</td>
<td>0</td>
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<tr>
<td>22</td>
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<td>0.5$^f$</td>
<td>140</td>
<td>30</td>
<td>&lt;10</td>
</tr>
<tr>
<td>23</td>
<td>PdCl$_2$</td>
<td>Li$_2$CO$_3$</td>
<td>0.5</td>
<td>140</td>
<td>&lt;20$^g$</td>
<td>-</td>
</tr>
</tbody>
</table>
Conditions: 1 (1 equiv.), p-TolSO₂Cl (2 equiv.), base (3 equiv), 1,4-dioxane. a in xylene, b in DMF, c in diethyl carbonate, d p-TolSO₂Cl (1 equiv.) and TEMPO as additive (1.2 equiv.), e without p-TolSO₂Cl. f CuBr₂ instead of CuBr, g Using tert-butyl allyl(phenyl)carbamate instead of 1.

The use of benzenesulfonyl chlorides as coupling partner is crucial for this reaction, as 4-bromotoluene under conditions i led to starting material 1; whereas the use of PdCl(C₃H₅)(dppb) catalyst and K₂CO₃ as base in DMF (conditions ii) selectively afforded the Heck type product 23 in 77% yield (Scheme 3).

Scheme 3. Control Reaction with an Aryl Bromide

Then, the scope of the ArSO₂Cl substituent for the synthesis of 4-aryl-1,2,3,4-tetrahydroquinoline derivatives from 1 was examined using 5 mol% PdCl₂ catalyst in the presence of 0.5 equiv. of CuBr and Li₂CO₃ at 140 °C as reaction conditions (Scheme 4). Both 4-cyano- and 4-methoxybenzenesulfonyl chlorides afforded the target products 25 and 26 in 72% and 95% yields, respectively. The reaction also proceeded nicely in the presence of PhSO₂Cl or 1-naphthyl-SO₂Cl to give 27 and 28 in 75% and 71% yields, respectively. A thiophene-2-carboxylate bearing a SO₂Cl substituent at C3 was also employed. Again the expected product 29 was obtained in good yield. The influence of the SO₂R moiety on the N-allyl-N-arylsulfonamide was also investigated. A 4-bromobenzenesulfonyl chloride was tolerated to afford 30 in 67% yield, without cleavage of the C-Br bond. The reaction also proceeds nicely with N-allyl-N-phenylmethanesulfonamide 3, as the coupling with 4-methyl-, 4-chloro-, and 4-bromobenzenesulfonyl chlorides affords the target products 31-33 in 74-75% yields. A lower yield in 34 was obtained from 2,3,4-trifluorobenzenesulfonyl chloride and 3. It is worth mentioning that
even 5-bromothiophene-2-sulfonyl chloride afforded the desired product 35 in 78% yield, without cleavage of the thienyl C-Br bond.

![Scheme 4](image)

**Scheme 4.** Scope of the ArSO₂Cl and SO₂R¹ Substituents.

The influence of the substituents on the aniline moiety was also examined (Scheme 5). From N-allyl-N-(4-bromophenyl)methanesulfonamide 4 and p-TolSO₂Cl as reaction partner, 36 was obtained in 42% yield. A 4-iodo substituent on the aniline was also tolerated to afford 37 and 40 in 68% and 67% yields. In both cases, the reaction was highly chemoselective, as the C–X bonds were not involved in the cascade process. Electron-donating substituents on the aniline part were tolerated as both N-allyl-N-(4-methylphenyl)methanesulfonamide 6 and N-allyl-N-(4-methoxyphenyl)methanesulfonamide 7 led to 38 and 39 in good yields.
The influence of substituent on the N-allyl moiety was also investigated. From \((E)\)-N-(but-2-enyl)-N-phenylmethanesulfonamide 8 and p-TolSO\(_2\)Cl, 41 was obtained in 81% as a single diastereomer. Similar results were obtained for the coupling of 8 and 9 with 4-fluoro- and 4-methoxybenzenesulfonyl chlorides affording 42 and 43 in 78% and 88% yields, respectively. The \textit{trans}-stereochemistry was unambiguously assigned by X-ray analysis of 43 (see SI). The regioselectivity of the reaction with aniline derivatives bearing \textit{meta}-bromo or \textit{meta}-methoxy substituents was then studied. In both cases, the formation of mixture of 1,2,3,4-tetrahydroquinolines was obtained. The major products 44a and 45a arises from coupling at less hindered position. Similar regioselectivity was observed using 3,4-dimethylaniline, as 46a and 46b were obtained in 12:5 ratio. The reactivity of several fluoro-containing N-allyl-N-(aryl)methanesulfonamides was also examined. 4-Fluoroaniline and 3,5-difluoroaniline derivatives 13 and 14 gave the 1,2,3,4-tetrahydroquinolines 47 and 48 in 72% and 77% yields, respectively with formation of only trace amount of Heck type products. On the other hand, a very significant effect of aniline \textit{ortho}-fluoro or methyl substituents was observed. From both N-(2,4-difluorophenyl)methanesulfonamide 15 and N-(2-methylphenyl)methanesulfonamide 16 using p-TolSO\(_2\)Cl as the reaction partner, only the Heck type products 49 and 50 were obtained. This result might be explained by lower degree of freedom of C–N bond, which prevents the suitable conformation for the formal 6-endo-trig cyclization. An aniline substituted at C4 by an electron-withdrawing group such as ethyl ester led to a mixture of Heck type product 51a and tetrahydroquinoline 51b in 5:1 ratio; whereas, an aniline bearing a para-thienyl at C4 only gave tetrahydroquinoline 52 in 83% yield. Finally the reactivity of N-allyl-N-cyclohexylmethanesulfonamide 19 was examined. No sp\(^3\) C-H bond functionalization of the
cyclohexyl moiety was observed and the Heck type product 53 was selectively obtained in 78% yield.

Scheme 5. Scope of the Substituents on the Aniline and Allyl moieties.
Interestingly, the reaction is not limited to the use of aniline derivatives. From 5-aminopyrazole derivative 54 and 4-methyl- or 4-chloro-benzenesulfonyl chlorides, the expected products 55 and 56 were obtained in 83% and 81% yields, respectively (Scheme 6). Even 5-bromothiophene-2-sulfonyl chloride reacts with 54 to afford 57 in 85% yield, without cleavage of the thienyl C-Br bond.

![Scheme 6. Reactivity of 5-Aminopyrazole Derivative 54.](image-url)

Then, a set of reactions was performed in order to get a better insight into the reaction mechanism. N-cinnamyl-N-phenylsulfonamide derivative 20 in the presence of CuBr and Li$_2$CO$_3$ at 140 °C, with or without Pd-catalyst was recovered unreacted (Scheme 7, a). On the other hand, from 20 and PhSO$_2$Cl, the Heck type product 58 was selectively obtained in 57% yield (Scheme 7, b). This is probably due to the higher acidity of the C-H bond of the CHPh$_2$ motif obtained after insertion of the C=C bond into the Ar-Pd bond, which favors the β-H elimination. From N-allyl-N-(2,4,6-trimethylphenyl)methanesulfonamide 21, again only the Heck type product 59 was obtained in 38% yield (Scheme 7, c). No sp$^3$ C-H bond activation of the aniline methyl substituents was observed. The presence of a SO$_2$R substituent on the aniline derivative is also crucial as N-allyl-N-ethylaniline 60 led to 61 in 68% yield (Scheme 7, d).
Finally, labelling experiments were carried out. From deuterated aniline derivative 22, 62 was obtained in 63% yield, without any incorporation of deuterium (Scheme 8, top). An equimolar mixture of 4 and 22 led to the formation of 31 and 62 in 56:44 ratio showing no significant effect of the use of a deuterated aniline derivative on the reaction rate (Scheme 8, middle). This result suggests that the C-H bond activation step is probably not rate limiting for the catalytic cycle.

From the N-allyl-N-phenylmethanesulfonamide 63 containing two deuterium atoms on the allyl moiety (Scheme 8, bottom), the formation of 64 as a mixture of two diastereomers was observed. The deuterium migration seems to confirm a mechanism involving a β-D elimination followed by a reinsertion in the Pd-D species (See scheme 9).

Scheme 7. Mechanistic Investigations
Scheme 8. Experiments using Deuterated Derivatives

Although the mechanism is not yet elucidated, on the basis of the preliminary mechanistic study and on the previous reports, a catalytic cycle can be proposed (Scheme 9). The first step of is probably the oxidative addition of ArSO₂Cl to a Pd(0) species and release of SO₂ to afford the Pd(II) intermediate A, although a Pd(II)/Pd(IV) mechanism is also possible. Then, A affords B by coordination of the N-allyl-N-phenylmethanesulfonamide. Insertion of the allyl C=C bond into the Ar-Pd bond affords C. Then, C-H bond activation affords the 6-membered palladacycle D and releases LiCl/LiHCO₃. As benzylic C-H are quite acidic, D might give E via β-H elimination. Finally, reinsertion in the Pd-D bond affords the 7-membered palladacycle F which
releases, via reductive elimination, the 1,2,3,4-tetrahydroquinoline derivative and regenerates Pd(0).

Scheme 9. Proposed Catalytic Cycle

Formation of 1,2,3,4-tetrahydroquinoline does not result from a Pd-catalyzed cyclisation of the β-elimination product (See, scheme 7, a). Currently available data do not allow to explain the remarkable effect of copper in this reaction. It might work in synergy with palladium for the desulfitative process, or activate palladium.
Conclusions

In summary, we report here the first palladium-catalyzed synthesis of 4-aryl-1,2,3,4-tetrahydroquinoline derivatives via successive insertion of an alkene into a Pd-Ar bond followed by an intramolecular sp² C-H functionalization. The reaction is chemo- and diastereo-selective and proceeds with an easily accessible phosphine-free air stable palladium catalyst, and Li₂CO₃ as inexpensive base associated to CuBr. The reaction can be successful for a variety of substituents both on aniline, allyl and on the benzenesulfonyl moieties. Due to the described usefulness of 1,2,3,4-tetrahydroquinoline derivatives, such simple reaction conditions offer a new attractive method for access to such structures.

Experimental Section

General procedure for the synthesis of N-allyl-N-phenylmethanesulfonamides 1-22, 54, 63:

A mixture of the aniline derivative (5 mmol) and triethylamine (0.505 g, 5 mmol) was stirred in CH₂Cl₂ (15 mL) at 22 °C, then, R₂SO₂Cl (5 mmol) was slowly added to the mixture and the reaction was monitored by TLC. When a complete conversion of the starting material was observed, the mixture was concentrated then filtrated through a short silica column and evaporated to afford the desired aryl sulfamide. A mixture of this aryl sulfamide, allyl bromide derivative (7.5 mmol) and K₂CO₃ (1.725 g, 12.5 mmol) in acetone (30 mL) was refluxed overnight. After reaction cooling down, the mixture was concentrated and purified by silica gel chromatography (ethyl acetate/pentane) to afford the desired products 1-22, 54 and 63.

General procedure for the synthesis of 24-53, 55-62 and 64:
To an oven dried 25 mL Schlenk tube under argon, \( N \)-allyl-\( N \)-phenylsulfonamides (0.5 mmol), arenesulfonyl chlorides (1.0 mmol), \( \text{PdCl}_2 \) (4.4 mg, 0.0025 mmol), \( \text{CuBr} \) (0.035 g, 0.25 mmol), \( \text{Li}_2\text{CO}_3 \) (0.110 g, 1.5 mmol) and 1,4-dioxane (1.5 mL) were successively added. Then, the reaction mixture was settled in a preheated (140 °C) oil bath for 20 h under stirring. Upon the reaction finished, the crude mixture was purified on silica chromatography (ethyl ether/ pentane, ethyl acetate/ pentane).

**4-p-Tolyl-1-tosyl-1,2,3,4-tetrahydroquinoline  (24):** From \( N \)-allyl-\( N \)-p-tolylbenzenesulfonamide 1 (0.144 g, 0.5 mmol) and 4-methylbenzenesulfonyl chloride (0.191 g, 1 mmol), 24 was obtained in 83% (0.156 g) yield as a white solid: mp 107-109 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.97 (d, \( J = 8.2 \) Hz, 1H), 7.56 (d, \( J = 8.3 \) Hz, 2H), 7.29-7.20 (m, 3H), 7.02 (t, \( J = 7.6 \) Hz, 1H), 6.98 (d, \( J = 7.9 \) Hz, 2H), 6.78 (d, \( J = 7.7 \) Hz, 1H), 6.55 (d, \( J = 8.3 \) Hz, 2H), 4.15-4.07 (m, 1H), 3.83 (dd, \( J = 8.5, 7.0 \) Hz, 1H), 3.80-3.70 (m, 1H), 2.45 (s, 3H), 2.31 (s, 3H), 2.00-1.88 (m, 1H), 1.77-1.65 (m, 1H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 143.6, 142.0, 137.0, 136.8, 136.0, 132.9, 130.3, 129.7, 129.1, 128.1, 127.4, 126.8, 125.0, 124.6, 45.5, 43.0, 30.3, 21.6, 21.0. Elemental analysis: calcd (%) for C\(_{23}\)H\(_{23}\)NO\(_2\)S (377.50): C 73.18, H 6.14; found: C 73.30, H 6.00.

**ASSOCIATED CONTENT**

Supporting Information.

Reaction procedures and \(^1\)H and \(^{13}\)C NMR of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.”

**AUTHOR INFORMATION**

**Corresponding Author**

E-mail:  jean-francois-soule@univ-rennes1.fr; henri.doucet@univ-rennes1.fr
Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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REFERENCES


Pd-Catalyzed Cascade Reaction

One-pot formation of two C(sp²)-C(sp²) bonds
Chemo- and diastereoselective reaction
Simple catalytic system
Easily available starting materials

32 examples
High yields