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

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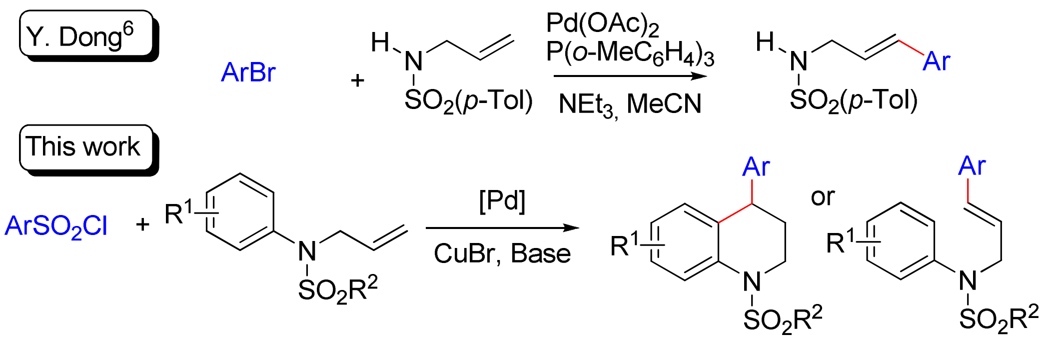
KEYWORDS Palladium • C-H activation • catalysis • desulfitative coupling • cascade

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(sp^2)-C(sp^3) bonds were formed *via* activation of C(sp^2)-H bonds. The reaction proceeds using easily accessible $PdCl_2$ catalyst, with Li_2CO_3 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* arylations, alkylations or alkenylations;[1] whereas, the formation of two C-C bonds *via* consecutive Heck type reaction followed by an 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 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 sp^2 C-H bond activation.[3g] On the other hand, the Heck reaction[4,5] using *N*-allylbenzenesulfonamides and aryl halides as coupling partners has been described by Y. Dong (Scheme 1 top).[6]

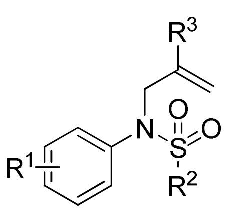
In this article, we report on the unexpected one pot synthesis of 4-aryl-1,2,3,4-tetrahydroquinolines, from *N*-allyl-*N*-benzenesulfonamides and $ArSO_2Cl$ through a palladium-catalyzed cascade desulfitative addition–cyclization reaction (Scheme 1, bottom).[7-9] It should be mentioned that 1,2,3,4-tetrahydroquinoline 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.[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.



Scheme 1.

Results and discussion

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



1-22

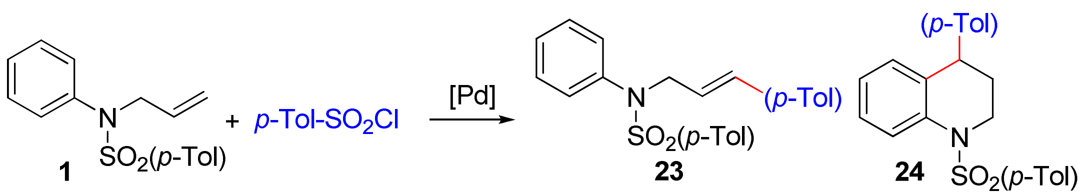
R^1	R^2	R^3		R^1	R^2	R^3	
H	$4\text{-}MeC_6H_4$	H	**1**	4-F	Me	Me	**13**
H	$4\text{-}BrC_6H_4$	H	**2**	3,5-diF	Me	H	**14**
H	Me	H	**3**	2,4-diF	Me	H	**15**
4-Br	Me	H	**4**	2-Me	Me	H	**16**
4-I	Me	H	**5**	$4\text{-}CO_2Et$	Me	H	**17**
4-Me	Me	H	**6**	4-(5-Cyano-thiophen-2-yl)	Me	Me	**18**
4-OMe	Me	H	**7**				
H	Me	Me	**8**	Cy*	Me	H	**19**
H	$4\text{-}MeC_6H_4$	Me	**9**	H	Me	Ph**	**20**
3-Br	Me	H	**10**	2,4,6-triMe	Me	H	**21**
3-OMe	Me	H	**11**	C_6D_5***	Me	H	**22**
3,4-diMe	Me	H	**12**				

*: *N*-Cy instead of *N*-Aryl
**: cinnamyl derivative
***: from aniline-2,3,4,5,6-d_5

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 $PdCl_2$ catalyst and Li_2CO_3 as base in dioxane as reaction conditions, which had been previously found operative for direct arylations of heterocycles,[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 $Pd(OAc)_2$, $PdCl_2(MeCN)_2$, $PdCl(C_3H_5)$(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_2CO_3 and Na_2CO_3; whereas, Cs_2CO_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_2CO_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).

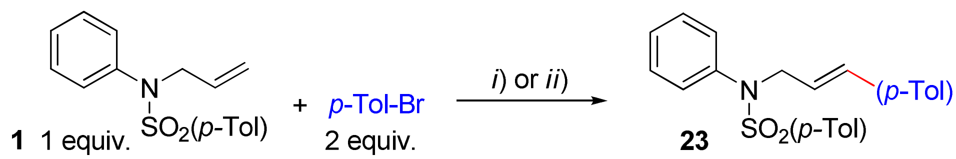
Table 1. Influence of the Reaction Conditions for the Po-Catalyzed Functionalization of **1**.



Entry	Catalyst (mol%)	Base	CuBr (equiv.)	Temp (°C)	Conv. of **1** (%)	Yield in **24** (%)
1	$PdCl_2$	Li_2CO_3	-	140	<10	0
2	$PdCl_2$	Li_2CO_3	1.1	140	89	75
3	$Pd(OAc)_2$	Li_2CO_3	1.1	140	81	75
4	$PdCl_2(CH_3CN)_2$	Li_2CO_3	1.1	140	83	74
5	$PdCl(C_3H_5)(dppb)$	Li_2CO_3	1.1	140	76	68
6	$Pd(TFA)_2$	Li_2CO_3	1.1	140	70	67
7	$Pd_2(dba)_3$	Li_2CO_3	1.1	140	74	53
8	$Pd_2(dba)_3$	Li_2CO_3	-	140	100	trace
9	$PdCl_2$	Li_2CO_3	0.5	140	88	83
10	$PdCl_2$	Li_2CO_3	0.1	140	80	73
11	$PdCl_2$	Li_2CO_3	0.01	140	23	20
12	$PdCl_2$	K_2CO_3	0.5	140	73	31
13	$PdCl_2$	Na_2CO_3	0.5	140	85	42
14	$PdCl_2$	Cs_2CO_3	0.5	140	0	0
15	$PdCl_2$	-	0.5	140	40	0
16	$PdCl_2$	Li_2CO_3	0.5	100	83	74
17	$PdCl_2$	Li_2CO_3	0.5	120	0	0[a]
18	$PdCl_2$	Li_2CO_3	0.5	120	0	0[b]
19	$PdCl_2$	Li_2CO_3	0.5	120	72	65[c]
20	$PdCl_2$	Li_2CO_3	0.5	140	<10	<5[d]
21	$PdCl_2$	Li_2CO_3	0.5	140	0	0[e]
22	$PdCl_2$	Li_2CO_3	0.5[f]	140	30	<10
23	$PdCl_2$	Li_2CO_3	0.5	140	<20[g]	-

Conditions: **1** (1 equiv.), *p*-TolSO_2Cl (2 equiv.), base (3 equiv), 1,4-dioxane. [a] in xylene, [b] in DMF, [c] in diethyl carbonate, [d] *p*-TolSO_2Cl (1 equiv.) and TEMPO as additive (1.2 equiv.), [e] without *p*-TolSO_2Cl. [f] $CuBr_2$ instead of CuBr, [g] Using *tert*-butyl allyl(phenyl)carbamate instead of **1**.

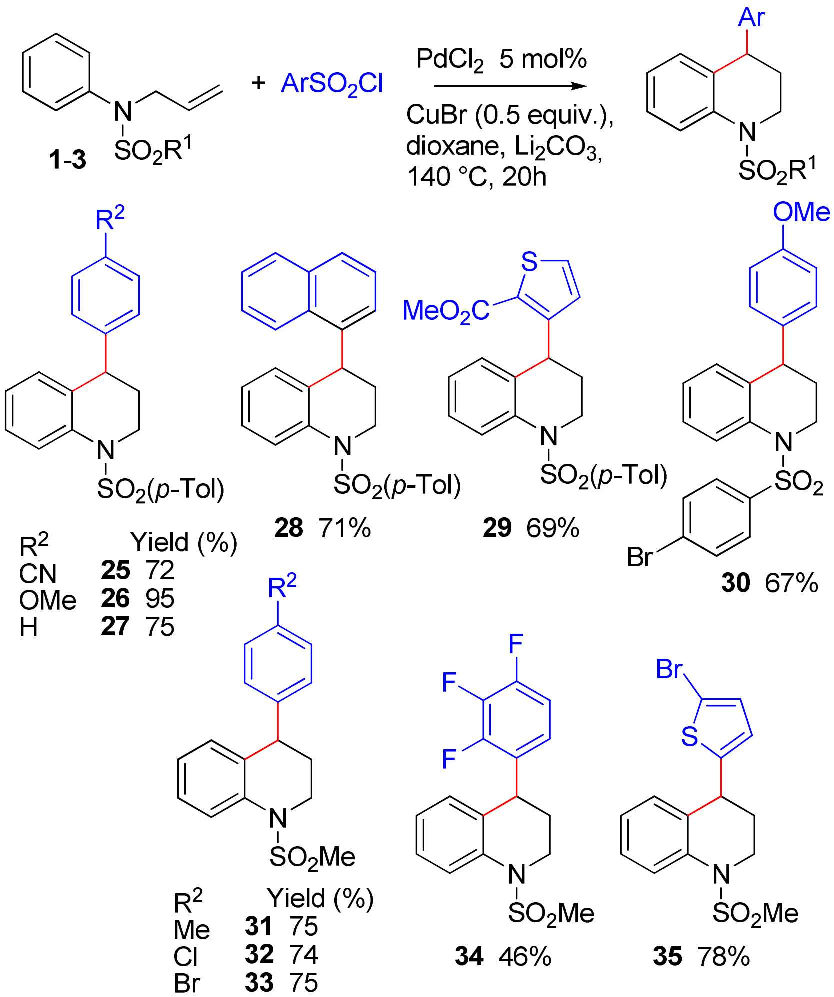
The use of benzenesulfonyl chlorides as coupling partner is crucial for this reaction, as 4-bromotoluene under conditions *i* led to starting material **1**; whereas the use of $PdCl(C_3H_5)$(dppb) catalyst and K_2CO_3 as base in DMF (conditions *ii*) selectively afforded the Heck type product **23** in 77% yield (Scheme 3).



i) $PdCl_2$ 5 mol%, CuBr (0.5 equiv.), Li_2CO_3 (3 equiv.), 1,4-dioxane, 140 °C, 20h: **1** recovered
ii) $PdCl(C_3H_5)$(dppb) 2.5 mol%, K_2CO_3 (3 equiv.), DMF, 140 °C, 20h: **23** 77%

Scheme 3. Control Reaction with an Aryl Bromide

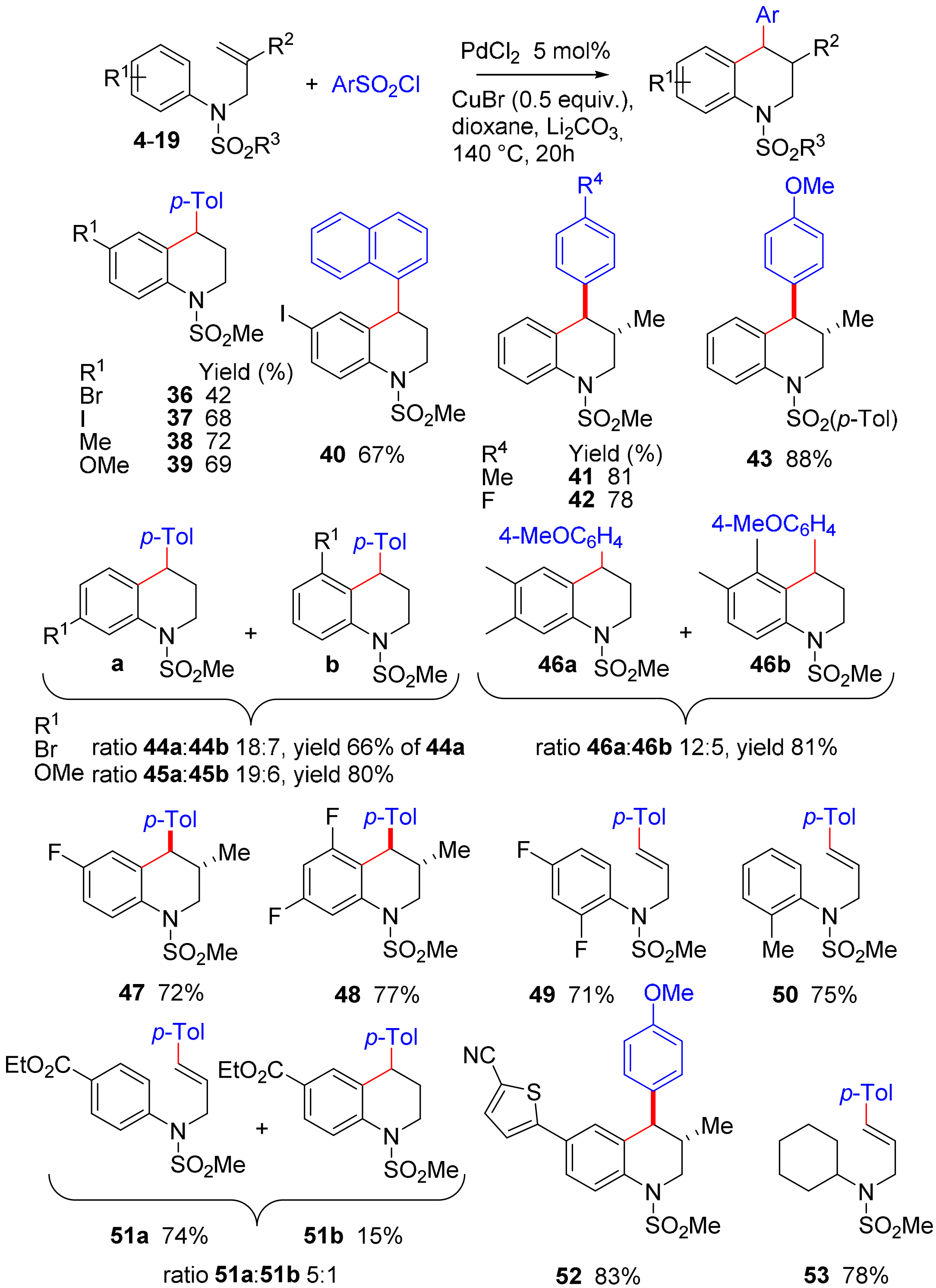
Then, the scope of the $ArSO_2Cl$ substituent for the synthesis of 4-aryl-1,2,3,4-tetrahydroquinoline derivatives from **1** was examined using 5 mol% $PdCl_2$ catalyst in the presence of 0.5 equiv. of CuBr and Li_2CO_3 at 140 °C as reaction conditions (Scheme 4). Both 4-cyano- and 4-methoxybenzenesulfonyl chlorides afforded the target products **25** and **26** in 72% and 95% yields, respectively. The reaction also proceeded nicely in the presence of $PhSO_2Cl$ or 1-naphthyl-SO_2Cl to give **27** and **28** in 75% and 71% yields, respectively. A thiophene-2-carboxylate bearing a SO_2Cl substituent at C3 was also employed. Again the expected product **29** was obtained in good yield. The influence of the SO_2R moiety on the *N*-allyl-*N*-arylsulfonamide was also investigated. A 4-bromobenzenesulfonamide 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-bromo-benzenesulfonyl 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. Scope of the $ArSO_2Cl$ and SO_2R^1 Substituents.

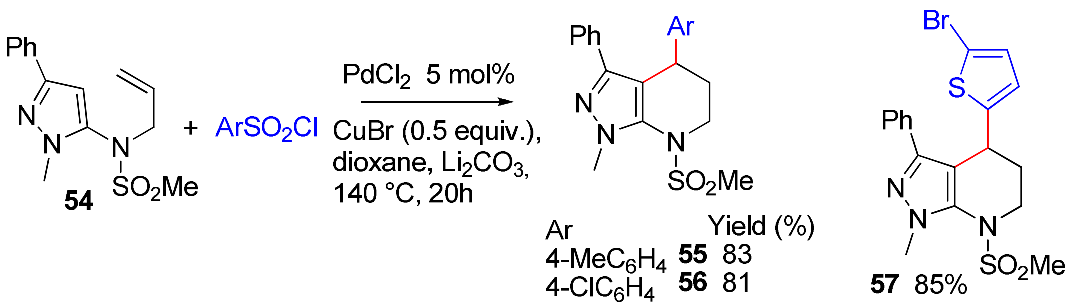
The influence of the substituents on the aniline moiety was also examined (Scheme 5). From *N*-allyl-*N*-(4-bromophenyl)methanesulfonamide **4** and *p*-$TolSO_2Cl$ as reaction partner, **36** was obtained in 42% yield. A 4-iodo substituent on the aniline was also tolerated to afford **37** and **40** 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_2Cl, **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 *trans*-stereochemistry was unambiguously assigned by X-ray analysis of **43** (see SI). The regioselectivity of the reaction with aniline derivatives bearing *meta*-bromo or *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 *ortho*-fluoro or methyl substituents was observed. From both *N*-(2,4-difluorophenyl)methanesulfonamide **15** and *N*-(2-methylphenyl)methanesulfonamide **16** using *p*-TolSO_2Cl 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.



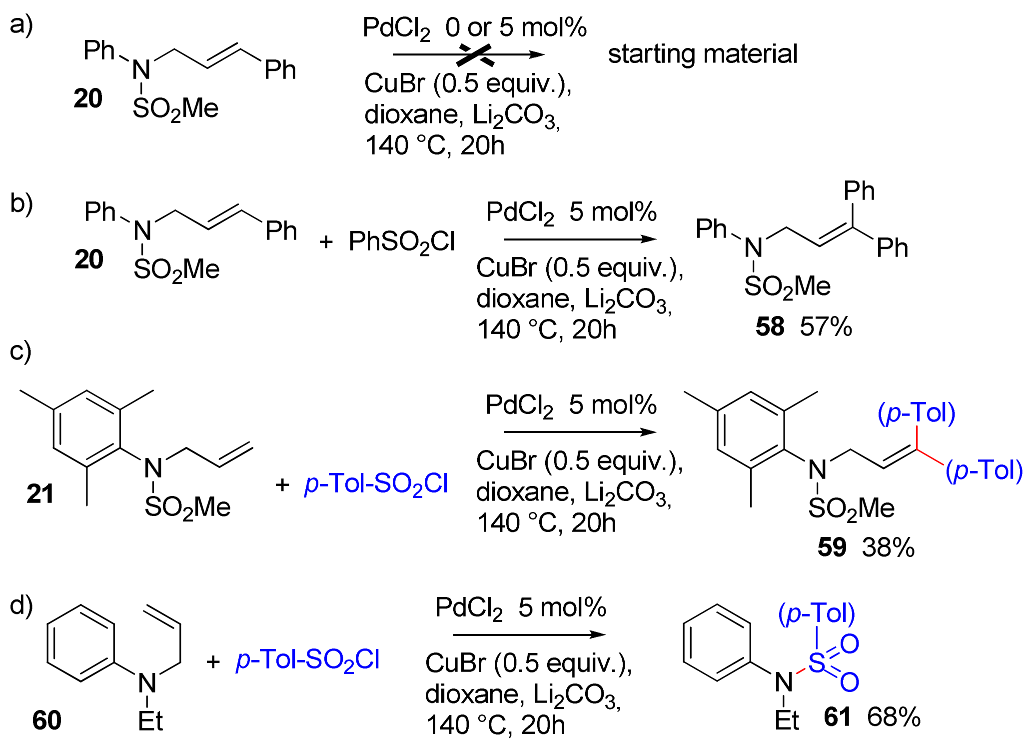
Scheme 5. Scope of the Substituents on the Aniline and Allyl moieties.

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.



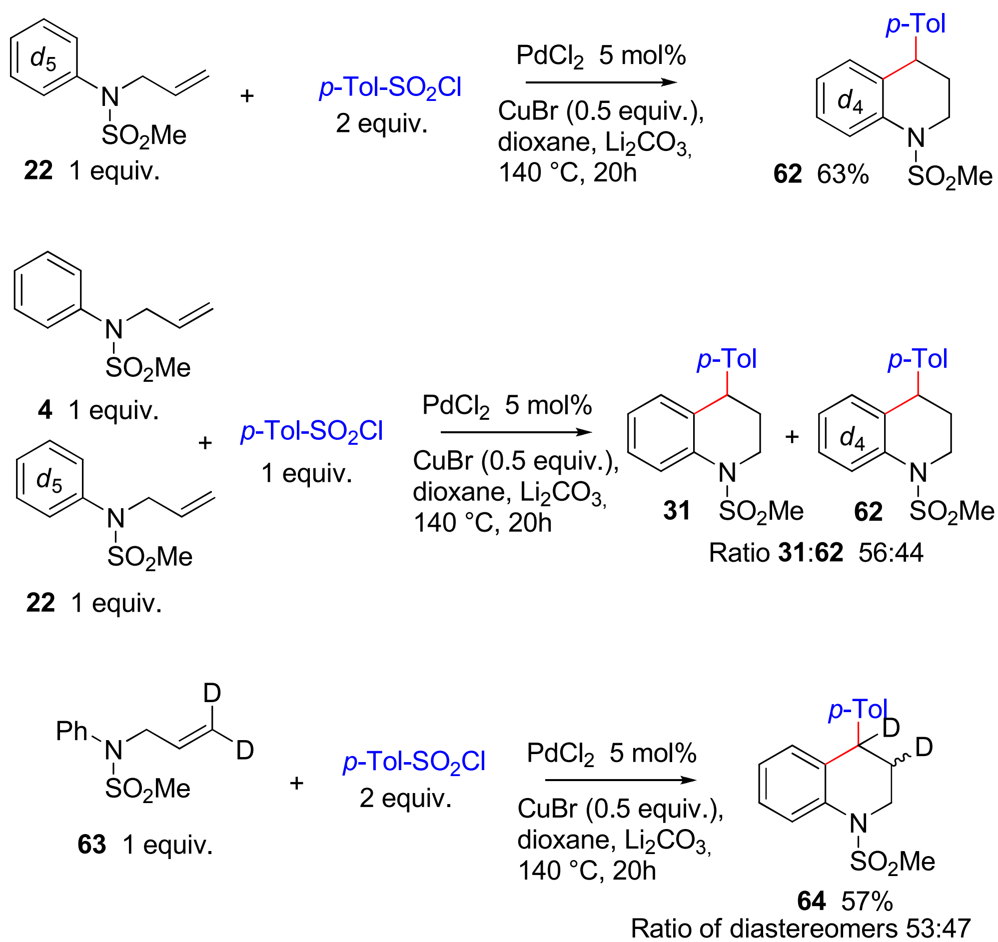
Scheme 6. Reactivity of 5-Aminopyrazole Derivative **54**.

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_2CO_3 at 140 °C, with or without Pd-catalyst was recovered unreacted (Scheme 7, a). On the other hand, from **20** and $PhSO_2Cl$, 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_2R substituent on the aniline derivative is also crucial as *N*-allyl-*N*-ethylaniline **60** led to **61** in 68% yield (Scheme 7, d).



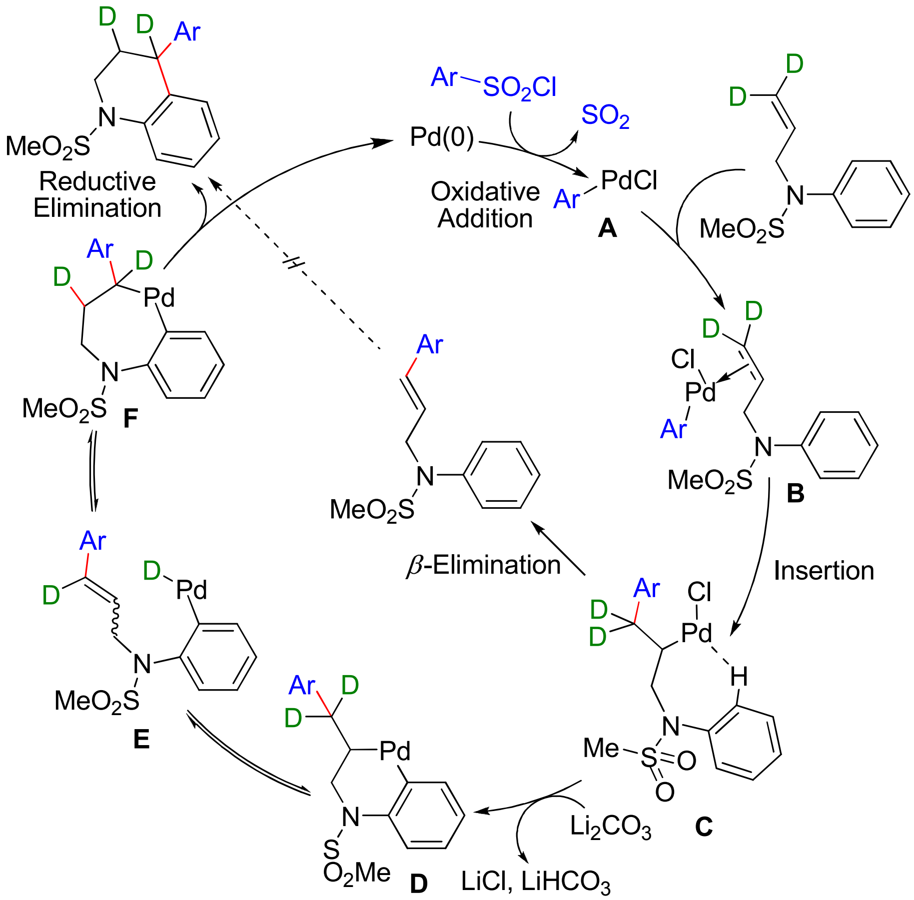
Scheme 7. Mechanistic Investigations

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 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 $ArSO_2Cl$ to a Pd(0) species and release of SO_2 to afford the Pd(II) intermediate **A**, although a Pd(II)/Pd(IV) mechanism is also possible.[13] 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/$LiHCO_3$. 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,[14] 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 sp^2 C-H functionalization. The reaction is chemo- and diastereo-selective and proceeds with an easily accessible phosphine-free air stable palladium catalyst, and Li_2CO_3 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 CH_2Cl_2 (15 mL) at 22 °C, then, R^2SO_2Cl (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 K_2CO_3 (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), $PdCl_2$ (4.4 mg, 0.0025 mmol), CuBr (0.035 g, 0.25 mmol), Li_2CO_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 ^{o}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, $CDCl_3$): δ 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, $CDCl_3$): δ 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 $C_{23}H_{23}NO_2S$ (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."

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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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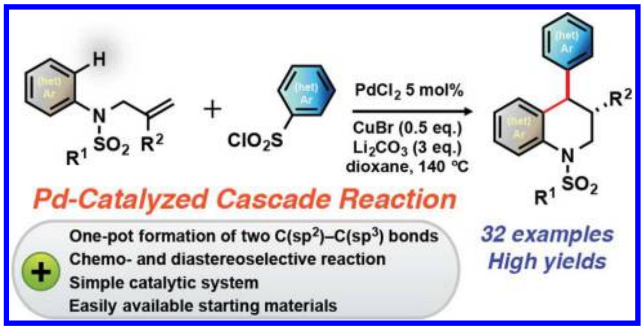
PdCl2 5 mol%
CuBr (0.5 eq.)
Li2CO3 (3 eq.)
dioxane, 140 °C
Pd-Catalyzed Cascade Reaction
One-pot formation of two C(sp2)–C(sp3) bonds
Chemo- and diastereoselective reaction
Simple catalytic system
Easily available starting materials
32 examples
High yields