VIP C–H activation

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Pd^{II}-Catalyzed C–H Olefination of *N*-(2-Pyridyl)sulfonyl Anilines and Arylalkylamines**

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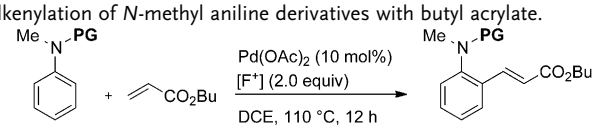
The metal-catalyzed direct C–H olefination (Fujiwara–Moritani reaction) has emerged as a powerful method for the introduction of functional diversity and structural complexity into arene compounds because of its chemical versatility and its environmental advantages.[1,2] In spite of the tremendous progress made in this field,[3–7] some important challenges still remain. Very often the directing groups[1,8] used for promoting the carbometallation of a proximal C–H bond are difficult to remove, thus compromising the synthetic usefulness of the procedures. In addition, the tether length of the directing group is typically found to be crucial for reactivity. A tether that is one or two atoms longer frequently leads to insufficient or no reactivity.

Nitrogen-containing products are especially attractive since they are found in a myriad of natural products and biologically active molecules. In this regard, NH-acetanilides and their derivatives have proven to be very effective in directing Rh-[3] and Pd-catalyzed[4] oxidative olefination. In the latter case, the reaction is usually restricted to the use of acrylates as alkene partners and the carbopalladation step exhibits marked electronic and steric sensitivity, which limit its applicability. For instance, low yields are usually obtained from NH-anilides substituted with electron-withdrawing groups as well from *ortho*-substituted anilides.[4] Also disfavored for steric reasons are the *ortho* alkenylation of N-substituted anilides (instead of NH-anilides), for which a general protocol is still required, and the double *ortho* C–H alkenylation to produce bisolefinated anilines.[3a] Examples of direct C–H alkenylation of benzylamine derivatives[5] are even scarcer, in spite of their great synthetic value.

Herein, we report a general procedure for the Pd-catalyzed C–H olefination of aniline derivatives with electron-poor alkenes that relies on the use of the 2-pyridylsulfonyl group as a protecting and directing group,[9] thus expanding the scope of this reaction to difficult-to-activate substrates, most notably to N-alkylated and *ortho*-substituted anilines, and also enabling a double *ortho*-alkenylation process. The flexibility with regard to the tether length of the directing group allows the extension of this method to the C–H olefination of benzylamines and β-arylethylamines.

At the outset we focused on finding a catalyst system for the olefination of protected *N*-methyl aniline, as a model substrate (Table 1). A set of potentially coordinating protecting groups (PG)[10] were examined in the reaction of

Table 1: Screening of a suitable directing group for the direct C–H alkenylation of *N*-methyl aniline derivatives with butyl acrylate.



$[F^+]$ = *N*-fluoro-2,4,6-trimethylpyridinium triflate

Entry	PG	Aniline	Product	Yield [%][a]
1	Boc	**1**	–	–[b]
2	Ts	**2**	–	–[c]
3	*p*-Ns	**3**	–	–[c]
4	(8-quinolyl)SO_2	**4**	–	–[c]
5	(2-pyridyl)SO_2	**5**	**7**	87
6	(3-pyridyl)SO_2	**6**	–	–[c]

[a] Yield of the isolated product after chromatography on silica gel. [b] A complex mixture was observed (^{1}H NMR spectroscopy). [c] Only starting material was detected (^{1}H NMR spectroscopy). Boc = *tert*-butyloxycarbonyl ,DCE = dichloroethane, Ns = p-nitrobenzenesulfonyl, Ts = *p*-toluenesulfonyl.

substrates **1**–**6** with butyl acrylate under $Pd(OAc)_2$ catalysis (10 mol%)[11] using *N*-fluoro-2,4,6-trimethylpyridinium triflate (2.0 equiv) as an oxidant[12] in DCE[13] at 110 °C. The *N*-Boc derivative **1** led to a complex mixture of products (entry 1). Switching to an *N*-Ts group (**2**) or an *N*-Ns group (**3**) led to the recovery of the starting material, even after 24 hours (entries 2 and 3), and an identical disappointing result was obtained with the *N*-(8-quinolyl)sulfonyl aniline **4** (entry 4). Pleasingly, the *N*-(2-pyridyl)sulfonyl[9] group (**5**) provided complete conversion and *ortho* regiocontrol, thus affording **7** in 87% yield upon isolation (entry 5). The absence of any reaction in the case of the *N*-(3-pyridyl)sulfonyl derivative **6**, an isomer of **5**, highlights the key role of the 2-pyridylsulfonyl group likely involved in the formation of the presumed palladated intermediate.[14]

The structural versatility of the *N*-alkyl group (R) and of the alkene component was next explored (Scheme 1). Other *N*-alkyl groups such as *n*-butyl (substrate **8**) or the functionalized *N*-CH_2CO_2Me group (substrate **9**) are equally well

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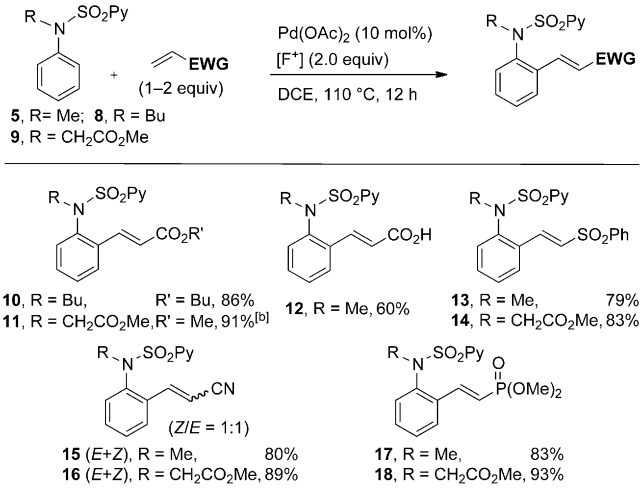
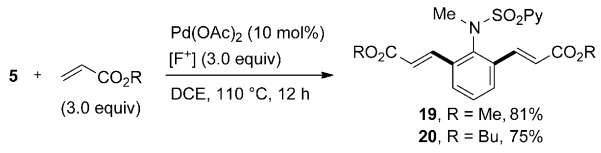


Scheme 1. Versatility of the *N*-alkyl group and olefin scope in the *ortho* alkenylation of *N*-(2-pyridyl)sulfonyl anilines. Reaction conditions: substrate (0.15 mmol), $Pd(OAc)_2$ (10 mol%), *N*-fluoro-2,4,6-trimethylpyridinium triflate (2 equiv), alkene (1-2 equiv), DCE, 110°C, 12 h. [b] 5 equiv of methyl acrylate were used. EWG = electron-withdrawing group, [F⁺] = *N*-fluoro-2,4,6-trimethylpyridinium triflate.

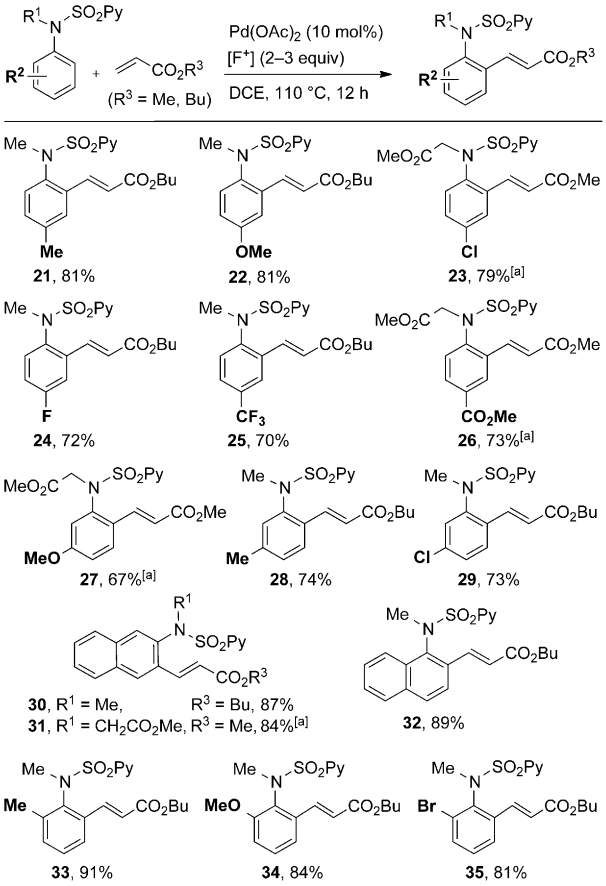
tolerated, leading to the corresponding olefinated products in high yields (**10** and **11** in 86% and 91% yield, respectively).[15] Regarding the olefin scope, not only acrylates but also a variety of monosubstituted electrophilic alkenes including acrylic acid, vinyl sulfones, vinyl phosphonates, and vinyl nitriles (1–2 equiv) reacted efficiently with *N*-(2-pyridyl)sulfonyl anilines **5** (*N*-Me) and **9** (N-CH_2CO_2Me), leading to the corresponding monoalkenylated products in high yields upon isolation (typically $\geq$ 80%). Unfortunately, nonactivated alkenes such as styrene failed to provide high conversions.

Under the reaction conditions shown in Scheme 1, in some cases the formation of a minor amount of the diolefinated product was detected by ^1H NMR spectroscopy. Interestingly, increasing the amount of both the alkene and the oxidant to 3 equivalents resulted in a clean diolefination reaction (products **19** and **20** in 81% and 75% yield, respectively; Scheme 2).[16]



Scheme 2. *ortho*-Dialkenylation of aniline derivative **5**.

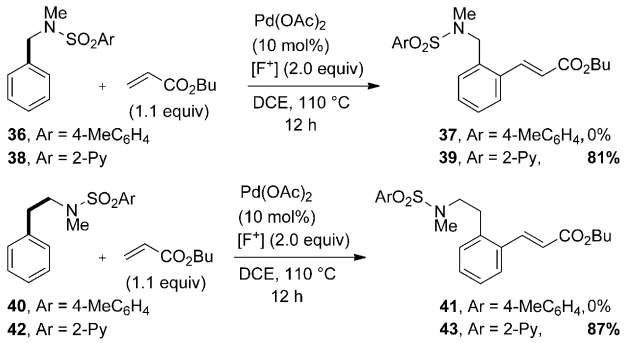
This C–H olefination protocol was then tested on a variety of *N*-(2-pyridyl)sulfonyl aniline derivatives, having either a *N*-Me or a *N*-CH_2CO_2Me group, with butyl or methyl acrylate (Scheme 3). A broad range of *para*-, *meta*-, and *ortho*-substituted aryl rings with diverse steric and electronic properties (ether, alkyl, halide, and ester groups) can be readily exploited in this procedure, thus affording the corresponding olefinated products in yields typically above 70%.[17] Halides, such as chloride and bromide, survived under the reaction conditions; this is a synthetically interesting result as such substituents are versatile handles for further transformations by cross-coupling. In some cases, under the optimal reaction conditions the monoolefination product was accompanied by roughly 5% of the *ortho*-diolefinated product, which could be readily separated by flash chromatography. High regiocontrol was observed in *meta*-substituted anilines, in favor of the C–H functionalization at the sterically less-hindered *ortho*-position (products **27**–**29**, 67–73% yield). Notably, 1- and 2-naphthalenamine derivatives were also amenable to the olefination reaction, which proceeded with high selectivity at the more-accessible position (products **30**–**32**, 84–89% yield). Excellent catalyst performance was noted with especially challenging aniline substrates, including those bearing a strong electron-withdrawing substituent[18] (e.g. CF_3 and CO_2Me; products **25** and **26** in 70% and 73% yield, respectively) and *ortho*-substituted products (**33**–**35**, 81–91% yield), although for products **34** and **35** 3 equivalents of oxidant were required for complete conversion.



Scheme 3. Structural variations to the aniline counterpart. Reaction conditions: substrate (0.15 mmol), $Pd(OAc)_2$ (10 mol%), *N*-fluoro-2,4,6-trimethylpyridinium triflate (2-3 equiv), alkene (1-2 equiv), DCE, 110°C, 12 h. [a] 5 equiv of methyl acrylate were used.

The high reactivity of this method prompted us to test its applicability to the C–H alkenylation of arylalkylamine derivatives. The reaction of *N*-methyl-*N*-(2-pyridyl)sulfonyl benzylamine (**38**) and *N*-methyl-*N*-(2-pyridyl)sulfonyl phenethylamine (**42**) with butyl acrylate under the optimized reaction conditions occurred cleanly to give the corresponding alkenylated products **39** and **43** in good yield (81% and

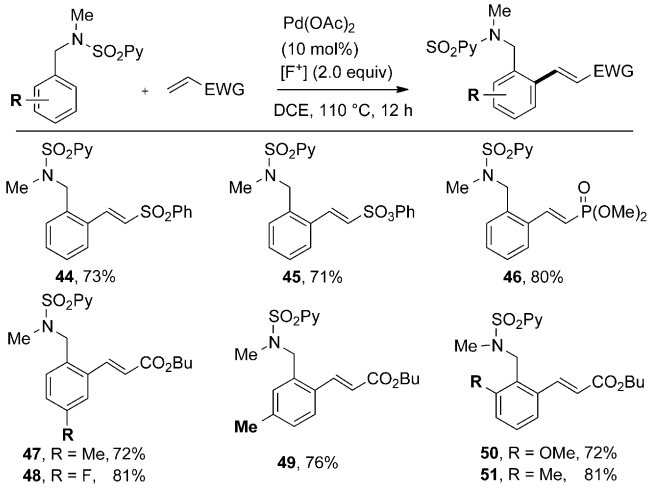
87%, respectively; Scheme 4). The higher reactivity displayed by substrates **38** and **42** compared to that of the aniline derivatives made it necessary to adjust the amount of butyl



Scheme 4. Extension to arylalkylamine derivatives.

acrylate to 1.1 equivalents to minimize the formation of the diolefinated product. At this point we confirmed again the key directing role of the 2-pyridylsulfonyl unit, as demonstrated by the lack of reactivity of the related *N*-tosyl protected substrates **36** and **40**.

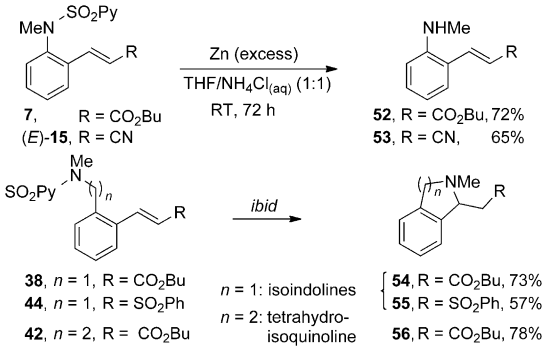
As shown in Scheme 5, the range of electrophilic alkenes amenable to the reaction with substrate **38** (R = H) includes not only acrylates but also vinyl sulfones, vinyl sulfonates, and vinyl phosphonates, and the corresponding monoolefinated products are furnished with consistently good yields (products **44**–**46**, 71–80% yield). Steric and electronic modifications to the aryl substrate were also explored for the benzylamine series, with butyl acrylate as the alkene counterpart (Scheme 5; products **47**–**51**). The olefination reaction proved to be rather general (yields typically above 70%) regardless of the electron-donating (Me, OMe) or electron-



Scheme 5. Olefin scope and structural variations to the benzylamine counterpart. Reaction conditions: substrate (0.15 mmol), $Pd(OAc)_2$ (10 mol%), *N*-fluoro-2,4,6-trimethylpyridinium triflate (2.0 equiv), alkene (1-2 equiv), DCE, 110°C, 12 h. [b] 3.0 equiv of oxidant were required for complete conversion. [F+] = *N*-fluoro-2,4,6-trimethylpyridinium triflate.

withdrawing (F) nature of the attached groups and the substitution pattern, including *ortho*-substituted arenes.

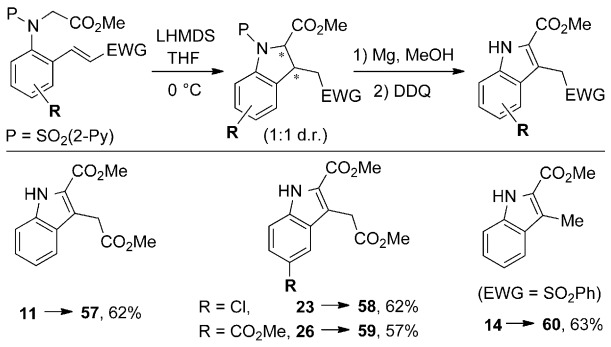
The easy reductive removal of the *N*-(2-pyridyl)sulfonyl directing group under acidic conditions (Zn powder, 1:1 THF/sat. aq NH_4Cl) enables access to different nitrogen-containing skeletons (Scheme 6).[19] The treatment of sulfonyl aniline olefinated adducts **7** and **15** with Zn powder led to the



Scheme 6. *N*-(2-pyridyl)sulfonyl removal.

corresponding free amino derivatives **52** and **53** in good yield (72% and 65%, respectively). The deprotection of sulfonamide products possessing one or two carbons between the nitrogen atom and the aryl moiety simultaneously triggers the cyclization of the free amines under the reaction conditions, thus allowing the rapid construction of isoindoline (**54** and **55**) and tetrahydroisoquinoline (**56**) bicyclic frameworks in synthetically useful yields (57–78%; Scheme 6).

Scheme 7 shows the three-step transformation of the olefinated aniline products with an *N*-CH_2CO_2Me group into functionalized indoles, thus exploiting the reactivity of a functionalized *N*-alkyl substituent. The indoline skeleton was assembled by an intramolecular Michael addition of the ester enolate (LHMDS, THF, 0°C) and subsequent reductive desulfonylation (Mg turnings, MeOH, sonification). Aromatization of the resulting NH-indoline with DDQ afforded the corresponding indole in acceptable overall yields (**57**–**60**, 58–63% yield). This Mg-promoted N deprotection is compatible with sensitive functional groups (Cl and CO_2Me, products **58** and **59**, respectively). In the case of aniline **14**, bearing an α,β-unsaturated phenylsulfone moiety, the application of this



Scheme 7. Application to indole synthesis.

sequence led to 3-methyl-substituted indole **60** as a result of both N and C desulfonylation with Mg/MeOH (63% overall yield for the three steps).

In summary, a general and reliable method for the Pd^{II}-catalyzed *ortho* C–H olefination of *N*-alkyl aniline, benzylamine, and phenethylamine derivatives enabling the generation of relevant nitrogen-containing architectures, such as indoles, isoindolines or tetrahydroisoquinolines, is described. This protocol relies on the *N*-(2-pyridyl)sulfonyl group as a directing and removable protecting group and features remarkable tolerance with regard to the tether length, alkene partner, and steric and electronic substitution on the arene, including electron deficient and *ortho*-substituted arenes. In addition, the double *ortho*-alkenylated products can be also obtained in good yields. Mechanistic studies, as well as further exploration of the synthetic potential of this novel C–H bond functionalization platform are underway in our laboratory.

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[10] The use of the unprotected *N*-methyl aniline in the C–H olefination with butyl acrylate under various reaction conditions failed to provide the desired product. Only decomposition products were observed.

[11] Investigation of catalyst loading in the reaction of **5**→**7** under the optimized reaction conditions shown in Table 1 revealed no conversion in the absence of a Pd catalyst, while 57% and 90% conversion was observed in the presence of 2 mol% and 5 mol% of $Pd(OAc)_2$, respectively.

[12] *N*-fluoro-2,4,6-trimethylpyridinium triflate has been used as an oxidant in Pd-catalyzed C–H fluorination, trifluoromethylation, and aminations, presumably through Pd^{II}/Pd^{IV} mechanisms, see: a) N. D. Ball, J. W. Kampf, M. S. Sanford, *J. Am. Chem. Soc.* **2010**, *132*, 2878; b) N. D. Ball, J. B. Gary, Y. Ye, M. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 7577; c) K. S. L. Chan, M. Wasa, X. Wang, J.-Q. Yu, *Angew. Chem.* **2011**, *123*, 9247; *Angew. Chem. Int. Ed.* **2011**, *50*, 9081; and reference [5b]. Other strong oxidants, such as $PhI(OAc)_2$ and $Ce(SO_4)_2$, used in Pd-catalyzed C–H activation processes provided unpractical conversions, whereas very low reactivity was observed with weaker oxidants such as $Cu(OAc)_2$, $Cu(OTf)_2$, and benzoquinone.

[13] Acetic acid was also a suitable solvent (100% conversion after 18 h). In contrast, a very low reactivity was observed in other polar solvents such as CH_3CN, *N*,*N*′-dimethylformamide, and dimethylacetamide.

[14] For a recent example, in which the participation of seven-membered-palladacycle intermediates in Pd-catalyzed C–H functionalization is implicated, see: G.-W. Wang, T.-T. Yuan, D.-D. Li, *Angew. Chem.* **2011**, *123*, 1416; *Angew. Chem. Int. Ed.* **2011**, *50*, 1380.

[15] The unsubstituted NH-*N*-(2-pyridyl)sulfonyl aniline proved to be unreactive under the optimized Pd-catalyzed reaction conditions.

[16] For the Pd-catalyzed diolefination reaction of benzylsulfonamides, see reference [6e]. For aryl C–H diolefination of carboxylic acid derivatives, see references [7a and b].

[17] This C–H olefination protocol can be scaled up by 10 times (from 0.15 mmol to 1.5 mmol scale) with similar efficiency. For example, the reaction of **9** (459 mg, 1.5 mmol) with phenyl vinyl sulfone afforded **16** (576 mg) in 81% yield (83% yield on 0.15 mmol scale).

[18] As noted in previous Pd-catalyzed C–H alkenylations of NH-acetanilides (reference [4]), competition experiments showed that substrates having electron-donating substituents are more reactive than those substituted with electron-withdrawing groups (see the scheme below, product ratio **21**/**25**, $k_{p-Me}/k_{p-CF_3}=12$).

[19] For the hydrolysis of ureas used as directing groups, see: C. E. Houlden, M. Hutchby, C. D. Bailey, J. G. Ford, S. N. G. Tyler, M. R. Gagné, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Angew. Chem.* **2009**, *121*, 1862; *Angew. Chem. Int. Ed.* **2009**, *48*, 1830. To the best of our knowledge, in previous reports on the C–H alkenylation of NH-acetanilides (references [3a and 4]), the final N deprotection of the amide products, having a potentially sensitive α,β-unsaturated ester, has not been described.