ACES Asian Chemical Editorial Society

DOI: 10.1002/asia.201500829

CHEMISTRY
AN ASIAN JOURNAL
Communication

C–H Activation

# Phosphinic Amide as Directing Group Enabling Palladium(II)-Catalyzed *ortho* C–H Alkenylation of Anilines without and with Alkylation at the Nitrogen Atom

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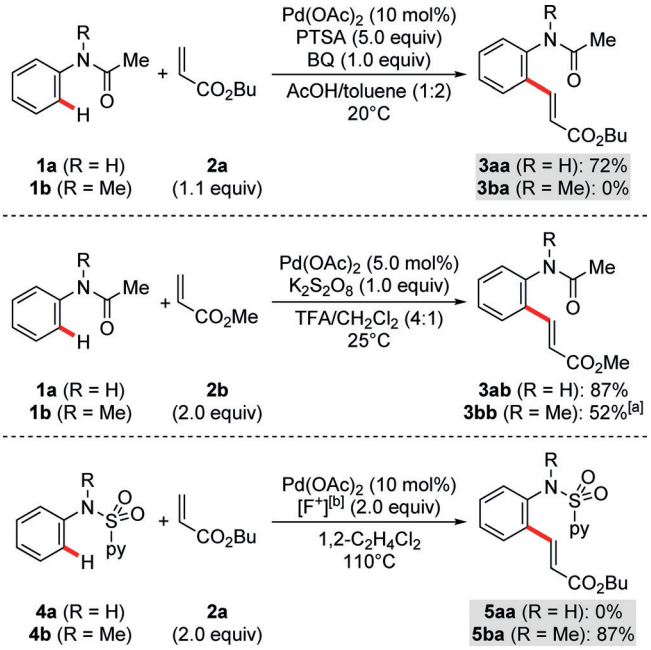
**Abstract:** A phosphinic amide is introduced as a directing group for the *ortho* C–H alkenylation of anilines. The new donor group distinguishes itself from existing ones by assisting the C–H bond activation of anilides without (NH group) and with alkylation (NMe group) at the amide nitrogen atom. The reactivity is even reversed with the methyl-substituted anilide being more reactive than its unsubstituted counterpart. Electron-donating substituents at the arene ring enhance their reactivity while halogenation is not tolerated. The phosphinic amide also enables the C-7-selective C–H alkenylation of indoline.

Anilines are often-used arenes in various C–H bond functionalization reactions,[1–3] also because of the ease of transforming the amino group into a directing group. For example, the straightforward acetylation of aniline yields an anilide that undergoes palladium(II)-catalyzed C–H bond alkenylation at room temperature (**1a**→**3aa**, Scheme 1, top).[2a] However, the same setup applied to cognate **1b** did not form any **3ba**.[2a] It turns out that substitution of the amide nitrogen atom leads to an entirely different behavior in C–H bond activation, and general procedures for the C–H bond functionalization of both are rare and have remained largely unexplored. A recent report demonstrates that it is possible to overcome the lower reactivity of the tertiary amide with higher catalyst loading (**1a**/**1b**→**3ab**/**3bb**, Scheme 1, middle).[2e] An interesting case is the C–H alkenylation of anilides directed by a sulfonyl-tethered pyridyl group where it is **4b** with an NMe group that participates in the catalysis while **4a** with an NH group is totally unreactive (Scheme 1, bottom).[2h]




**Scheme 1.** Reactivity difference between aniline with NH and NMe groups in directed palladium(II)-catalyzed C–H bond alkenylation. [a] $Pd(OAc)_2$ (10 mol%) in TFA. [b] *N*-Fluoro-2,4,6-trimethylpyridinium triflate. BQ = 1,4-benzoquinone, PTSA = 4-toluenesulfonic acid, py = pyridin-2-yl, TFA = trifluoroacetic acid.

Recently, a diverse range of phosphorus-based donors groups was applied to directed transition-metal-catalyzed C–H bond functionalization (Figure 1),[4–6] and these performed efficiently in, for example, palladium(II)-catalyzed C–H alkenylation[4a,c,d] and arylation[4b,f] of arenes. Amide derivatives had been included into these reports but not to enable C–H bond activation at the amide nitrogen substituent. We therefore embarked on an investigation of a chemically robust phosphinic amide as a directing group for the palladium(II)-catalyzed C–H

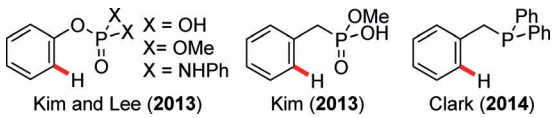



**Figure 1.** Literature-known phosphorus-based donors used as directing groups in palladium(II)-catalyzed C–H bond activation.

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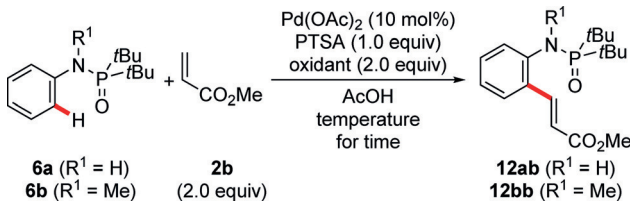
*Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/asia.201500829.*

*This manuscript is part of a special issue on catalysis and transformation of complex molecules. Click here to see the Table of Contents of the special issue.*

alkenylation of anilines without and with alkylation of the amide nitrogen atom.

Initial experiments were done with anilide **6a** containing a free NH group using acrylate **2b** as the alkene component (**6a**→**12ab**, Table 1, entries 1–9). We quickly found that, at

**Table 1.** Identification of the terminal oxidant.




**6a** ($R^1$ = H) **6b** ($R^1$ = Me) | **2b** (2.0 equiv) | **12ab** ($R^1$ = H) **12bb** ($R^1$ = Me)

| Entry | Anilide | Oxidant | *T* [°C] | *t* [h] | Conv. [%][a] | Yield [%][b] |
|---|---|---|---|---|---|---|
| 1 | **6a** | BQ | 60 | 18 | 51 | 34 |
| 2 | **6a** | $Cu(OAc)_2$ | 60 | 18 | 29 | 15 |
| 3 | **6a** | AgOAc | 60 | 18 | 24 | –[c] |
| 4 | **6a** | $Ag_2CO_3$ | 60 | 18 | 25 | –[c] |
| 5 | **6a** | $Na_2S_2O_8$ | 60 | 18 | 71 | 54 |
| 6[d] | **6a** | $K_2S_2O_8$ | 60 | 18 | 74 | 57 |
| 7 | **6a** | $K_2S_2O_8$ | 75 | 12 | 78 | 57 |
| **8**[e] | **6a** | **$K_2S_2O_8$** | **90** | **4** | **98** | **71** |
| 9 | **6a** | $K_2S_2O_8$ | 100 | 6 | 100 | 55 |
| 10 | **6b** | BQ | 60 | 15 | 98 | 53 |
| 11 | **6b** | $Na_2S_2O_8$ | 60 | 15 | 99 | 58 |
| 12 | **6b** | $K_2S_2O_8$ | 60 | 15 | 99 | 59 |
| 13 | **6b** | $K_2S_2O_8$ | 50 | 15 | 96 | 64 |
| **14** | **6b** | **$K_2S_2O_8$** | **40** | **21** | **96** | **81** |

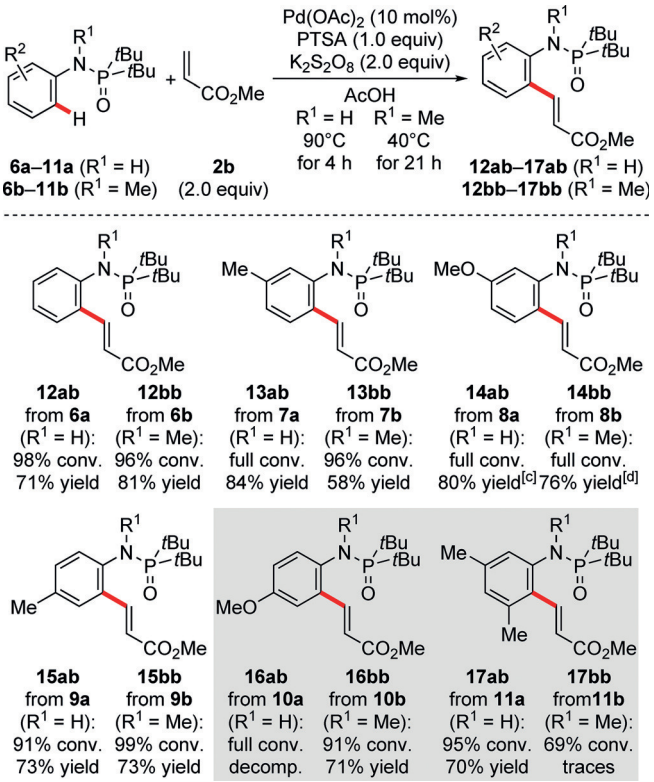
[a] Determined by GLC analysis with tetracosane as internal standard. [b] Isolated yield after purification by flash column chromatography on silica gel. [c] Not determined. [d] Other palladium sources such as $Pd(TFA)_2$ and $Pd_2dba_3$ worked equally well. [e] Yield did not deteriorate at longer reaction times, e.g., 6 h for comparison with entry 9.

60 °C in acetic acid, the *ortho*-selective C–C bond formation occurred in moderate yield with 1,4-benzoquinone (BQ) as the terminal oxidant and 4-toluenesulfonic acid (PTSA) as an additive (entry 1). Acetic acid was superior to other solvents that gave either lower or no conversion (see the Supporting Information for a solvent screen). Other mild oxidants such as $Cu(OAc)_2$, AgOAc, and $Ag_2CO_3$ were not effective (entries 2–4). In turn, the use of peroxydisulfates $Na_2S_2O_8$ and $K_2S_2O_8$ greatly improved conversion and isolated yield (entries 5 and 6).[7] Full conversion was achieved in shorter reaction times at higher temperatures, and 71% isolated yield was obtained at 90 °C (entries 7–9). The use of a mono-protected amino acid[8] (MPAA) such as Ac-L-*tert*-Leu-OH (20 mol%) as ligand had little effect on conversion and yield; results were better in AcOH than in 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP).

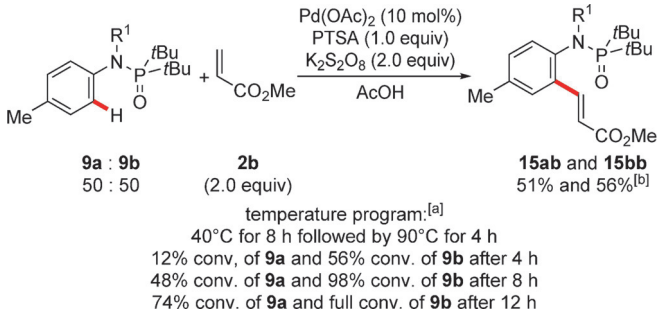
We then turned our attention to tertiary anilide **6b** with the same directing group (**6b**→**12bb**, Table 1, entries 10–14). Much to our surprise, we found **6b** to be more reactive than **6a** even with BQ as terminal oxidant (entry 10 vs. entry 1). Changing to the stronger oxidants $Na_2S_2O_8$ and $K_2S_2O_8$ showed no improvement at 60 °C but isolated yields increased significantly at lower temperature (entries 11–14). At 40 °C, 81% isolated yield at full conversion was obtained (entry 14). Again, running this C–H bond alkenylation in the presence of an MPAA in either AcOH or HFIP as solvent was without effect. Compared to anilides **1a** and **1b** (cf. Scheme 1),[2a,e] the reactivity is reversed for **6a** and **6b**.

With these optimized conditions at hand, we began investigating the scope of these transformations with differently substituted anilides **6a**–**11a** (90 °C for 4 h, Table 1, entry 8) and **6b**–**11b** (40 °C for 21 h, Table 1, entry 14). The results are summarized in Scheme 2. Electron-donating substituents such as methyl and methoxy groups were generally tolerated but halogenated anilides did not react at all (not shown, see the Supporting Information for details). A methoxy group at C-3 enhanced the reactivity dramatically, and **8a** was fully converted at room temperature (90 °C before) within 3 h and **8b** at 40 °C within 5 h (21 h before). Two more observations are particularly noteworthy (gray box): **10a** with a methoxy group at C-4 fully decomposed whereas **10b** afforded **16bb** in 71% isolated yield. This electronic effect is not understood. Conversely, the steric situation in 3,5-dimethyl-substituted **11a** and **11b** led to completely different reactivity. Compound **11a** with the NH group furnished **17ab** in 70% yield but **11b** yielded only trace amounts of the *ortho* alkenylated arene. We explain this by the NMe group that hampers optimal orientation of the directing group to allow for the C–H bond activation.

The faster reaction of NMe compared to NH anilides was also verified in an intermolecular competition experiment be-



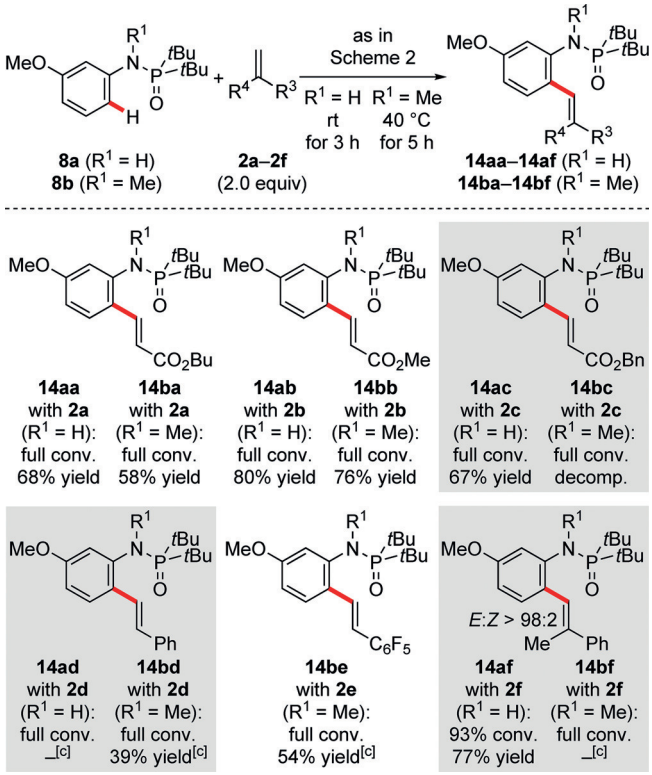

**Scheme 2.** Palladium(II)-catalyzed C–H bond alkenylation directed by phosphinic amide groups.[a,b] [a] Conversions determined by GLC analysis with tetracosane as internal standard. [b] Isolated yields after purification by flash column chromatography on silica gel. [c] Reaction performed at room temperature for 3 h. [d] Reaction performed at 40 °C for 5 h.




**Scheme 3.** Competition experiment. [a] Monitored by GLC analysis with tetracosane as internal standard. [b] Isolated yield after separation by flash column chromatography on silica gel.

tween **9a** and **9b** (Scheme 3). As expected, **9b** was consumed at higher rate than **9a**. What is interesting here though is that the reaction times were shorter than in the individual experiments (cf. Scheme 2, bottom left).

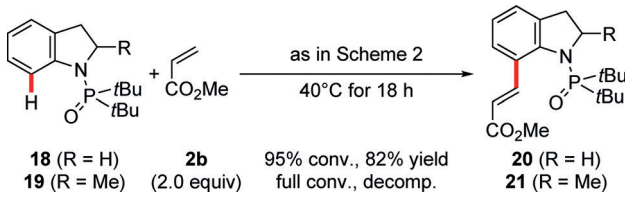
To examine the compatibility of this protocol with different alkenes, we tested various acrylates **2a**–**2c** and styrenes **2d**–**2f** with the very reactive substrates **8a** and **8b** under the previously established mild conditions (Scheme 4). Yields were consistently good with acrylates at full conversion, although tertiary anilide **9b** did not react with benzyl acrylate (**2c**, gray box, top). This was not the only peculiarity. The results with styrenes were in fact unforeseeable (gray boxes, bottom).




**Scheme 4.** Phosphinic amide-directed C–H bond alkenylation with various alkenes.[a,b] [a] Conversions determined by GLC analysis with tetracosane as internal standard. [b] Isolated yields after purification by flash column chromatography on silica gel. [c] Homocoupling.

Compound **9a** did not couple with styrene (**2d**) but reacted cleanly with the more electron-rich α-methylstyrene (**2f**). The situation with **9b** was the exact opposite. C–H alkenylation occurred with **2d** and the $C_6F_5$-substituted derivate **2e**, but no cross-coupling was seen with **2f**.

We also applied the new directing group to the C-7-selective C–H alkenylation of indolines that we and others had developed recently (Scheme 5).[9–11] Again, steric effects emerged as




**Scheme 5.** Application of the phosphinic amide directing group to the C-7 alkenylation of indolines.

crucial for the success of the coupling. The parent indoline **18** gave an excellent result (**18**→**20**) whereas **19** with a methyl group at C-2 decomposed rather than forming any desired **21**.

In summary, we reported here the palladium(II)-catalyzed C–H alkenylation of aniline-derived phosphinic amides. The new directing group enables couplings of both secondary (with NH group) and tertiary (with NMe group) anilides. This is a rare case of a directed C–H bond activation of anilines where alkylation of the amide nitrogen atom does not lead to completely different reactivity (cf. Scheme 1).[2a,e,h] The tertiary amide is even more reactive. While the methodology is not general at this stage and the removal of the directing group not established yet,[12] it revealed several interesting features. Depending on the electronic and steric situation of the arene, the NH and NMe anilides show (in an unpredictable way) opposite reactivity. Their reactivity toward styrenes is particularly remarkable. The anilide with an NH group reacts with α-methylstyrene but not styrene itself. For the NMe anilide, it is the other way round.

## Acknowledgements

L.-Y.J. thanks the China Scholarship Council (CSC) for a predoctoral fellowship (2011–2015), and A.V.F was supported by the Brazilian Council for Scientific and Technological Development (CNPq, Science without Borders Program, 2013–2015). M.O. is indebted to the Einstein Foundation (Berlin) for an endowed professorship. We are grateful to Jonas Scharfbier (TU Berlin) for his initial experimental contributions.

**Keywords:** alkenylation · C–H activation · cross-dehydrogenative coupling · homogeneous catalysis · palladium

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Manuscript received: August 9, 2015
Accepted Article published: September 15, 2015
Final Article published: September 24, 2015