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# Pd-Catalyzed Direct C−H Alkenylation and Allylation of Azine *N*-Oxides

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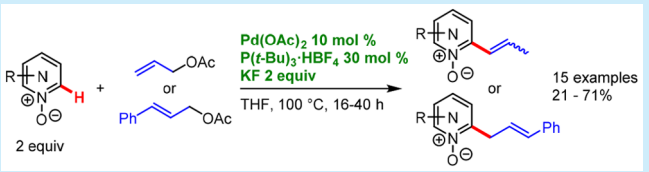
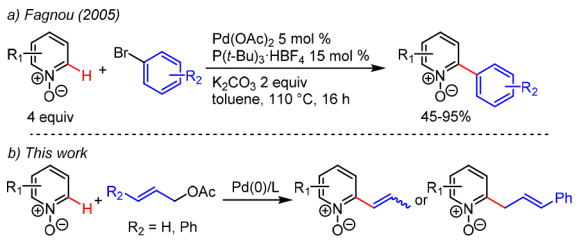
Supporting Information

**ABSTRACT:** A Pd-catalyzed direct $C_2$-alkenylation of azine *N*-oxides with allyl acetate is disclosed. The products are formed through an allylation/isomerization cascade process. The use of a tri-*tert*-butylphosphonium salt as the ligand precursor and KF is mandatory for optimal yields. When cinnamyl acetate is used, the same catalytic system promotes $C_2$-cinnamylation of the azine *N*-oxide without subsequent isomerization. A mechanism is proposed on the basis of experimental studies and DFT calculations.




Azines constitute a prominent family of six-membered nitrogen-containing heteroaromatics,[1] and pyridine, the simplest member of this class of compounds, is found in a great number of natural products, pharmaceutical agents, supramolecular assemblies, and molecular materials.[2] Given the ubiquity of this substructure, it is of no surprise that the functionalization of this motif has garnered much interest within the synthetic community, and significant efforts have been devoted to this objective.[2] However, despite remarkable progress in the field of catalytic C−H activation,[3] the direct functionalization of azines remains a difficult task.[2c] To overcome the intrinsic low reactivity of the pyridine nucleus and the undesirable Lewis basicity of the pyridine nitrogen atom, several research groups have implemented direct functionalization strategies through the corresponding *N*-oxides[4] or *N*-iminopyridinium ylide[5] derivatives. In particular, Fagnou reported the first example of Pd-catalyzed direct $C_2$-arylation of pyridine *N*-oxides (PNOs) using aryl bromides as arylating agents (Scheme 1a),[6] which revealed the potential of the PNO unit to undergo a C−H activation process. The following studies were devoted mainly to arylation of azine *N*-oxides.[7] The focus on other PNO C−H functionalizations such as alkylations[8] and alkenylations has only been sporadic.[7c,9] In particular, the direct PNO allylation and vinylation[10] are, to the best of our knowledge, thus far unknown transformations. Such reactions could represent an important asset, as these unsaturated substituents, once installed onto the heteroaromatic nucleus, can serve as a handle for a variety of synthetically relevant manipulations. Following from our ongoing interest in $\eta^3$-allylpalladium chemistry,[11] as well as C−H activation reactions,[12] we describe here the Pd-catalyzed $C_2$-alkenylation and allylation of azine *N*-oxides in the presence of allyl and cinnamyl acetates, respectively (Scheme 1b). In particular, we anticipated that the allylpalladium(II) intermediates initially generated through the oxidative addition of an allylic ester to a Pd(0) complex[13,14] could activate the $C_2$−H bond of a PNO, thereby allowing its functionalization. This expectation proved to be correct.

**Scheme 1. C−H Functionalizations of Pyridine *N*-Oxides**




We started our investigation using PNO **1a** and allyl acetate.[15] In line with the typical conditions used by Fagnou in the PNO $C_2$-arylations,[6] we carried out our first reaction using $Pd(OAc)_2$ (10 mol %), $P(t\text{-}Bu)_3{\cdot}HBF_4$ (30 mol %), and $K_2CO_3$ (2.0 equiv) in toluene at 100 °C (Table 1, entry 1) but using 2.0 equiv of PNO instead of 4.0 equiv. These conditions generated $C_2$-propenylated PNO **2a** as the major compound (56% NMR yield), along with small amounts of the $C_2$-allylated product **2a′** and the diallylated product **2a″**. Scrutiny of the base needed to release free $P(t\text{-}Bu)_3$[16] was undertaken next. A switch to $Na_2CO_3$ or *i*-$Pr_2NH$ (entries 2 and 3) led to a yield drop, while the use of CsF and KF gave 66% and 70% NMR yields, respectively, with a quasi-total selectivity for **2a** (entries 4 and 5). Variation of the solvent was next addressed. While xylene led to an NMR yield similar to that of toluene, $CH_3CN$ was inefficient (entries 6 and 7) and THF increased the yield and eased the workup (entry 8). The use of phosphines other than $P(t\text{-}Bu_3)$ (mono- or bidentated, see the Supporting

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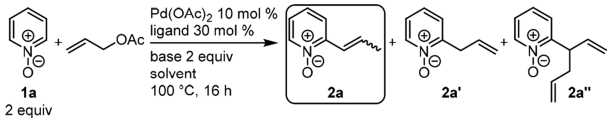
**Table 1. Optimization of the Pd-Catalyzed PNO Alkenylation**[a]




| entry | ligand[b] | base | solvent | ratio (2a/2a′/2a″)[c] | 2a, NMR yield (%) (E/Z)[c] |
|---|---|---|---|---|---|
| 1 | P(*t*-Bu$_3$) | $K_2CO_3$ | Tol | 78:4:13 | 56 (75/25) |
| 2 | P(*t*-Bu$_3$) | $Na_2CO_3$ | Tol | 74:16:10 | 36 (47/53) |
| 3 | P(*t*-Bu$_3$) | *i*-$Pr_2NH$ | Tol | 100:0:0 | 11 (91/9) |
| 4 | P(*t*-Bu$_3$) | CsF | Tol | 100:0:traces | 66 (95/5) |
| 5 | P(*t*-Bu$_3$) | KF | Tol | 100:traces:0 | 70 (86/14) |
| 6 | P(*t*-Bu$_3$) | KF | xylene | 100:0:traces | 74 (92/8) |
| 7 | P(*t*-Bu$_3$) | KF | MeCN | 100:0:traces | 3 |
| **8** | **P(*t*-Bu$_3$)** | **KF** | **THF** | **100:0:0** | **80 (84/16)** |
| 9 | PMe(*t*-Bu$_2$) | KF | THF | 0:0:0 | |
| 10 | $PCy_3$ | KF | THF | 0:0:0 | |
| 11 | $PMe_3$ | KF | THF | 0:0:0 | |
| 12 | P(*t*-Bu$_3$) | KF | THF | 100:0:0 | 31 (50:50) |

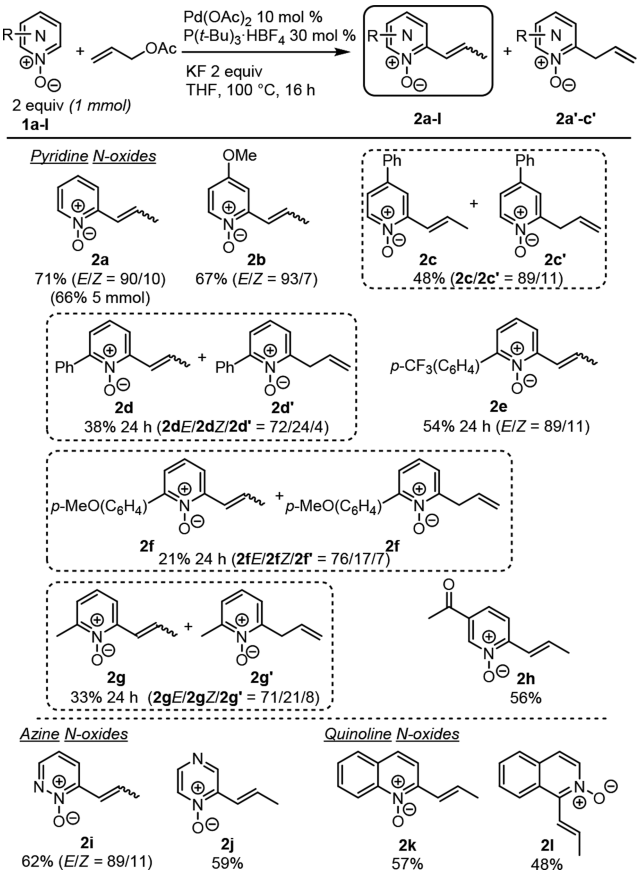
[a]Reaction conditions: **1a** (2 equiv), allyl acetate (1 equiv), solvent (0.25 M). [b]Except for entry 12, the phosphines used were as the $HBF_4$ salts. [c]Determined by $^1H$ NMR analysis of the crude mixture using dimethyl sulfone as internal standard.

Information, SI) as well as other trialkylphosphonium salts did not allow further improvements (entries 9−11). These results confirmed that this transformation needs a bulky, monodentate, electron-rich phosphine, and the tetrafluoroborate salt of the phosphine is preferred to the corresponding air-sensitive free phosphine (compare entries 7 and 12). Finally, separated control experiments carried out by omitting the Pd source, the ligand, or the base resulted in exclusive recovery of the starting materials, which confirmed that each of the above three components were necessary for the catalytic process (see the SI).

With the optimal conditions in hand, several azine *N*-oxides were coupled with allyl acetate to give 2-propenylazine *N*-oxides (**2a−l**) in moderate to good isolated yields, with a selectivity in favor of the *E* olefin (Scheme 2). The presence of the electron-donating methoxy group at $C_4$ (**1b**) gave a similar yield as obtained for **1a** (**1a**: 71% or 66% yield, from 0.5 or 5 mmol of allyl acetate, respectively; **1b**: 67%). An aryl moiety at $C_4$ (**1c**) or $C_2$ (**1d**, **1f**) as well as a methyl group at $C_2$ (**1g**) led to the corresponding internal *E* olefins as major products, along with minor amounts of the allylated compounds (**2c′**, **2d′**, **2f′**). In contrast, a 4-(trifluoromethyl)phenyl substituent at $C_2$ gave solely the corresponding propenylated adduct **2e** without any detectable amount of the allylated precursor. In general, the presence of a substituent at the $C_2$ position renders the transformation more sluggish, and 24 h is necessary to obtain an optimal result. 3-Acetylpyridine *N*-oxide (**1h**) gave 56% yield of the expected propenylated pyridine *N*-oxide **2h**, confirming that this C−H functionalization is directed by the *N*-oxide and not by the acetyl moiety and that keto functions are tolerated. Finally, pyridazine (**1i**), pyrazine (**1j**), quinoline (**1k**), and isoquinoline (**1l**) *N*-oxides also reacted satisfactorily. It is worth noting that, in the case of isoquinoline, the propenylation reaction took place exclusively at position 2.

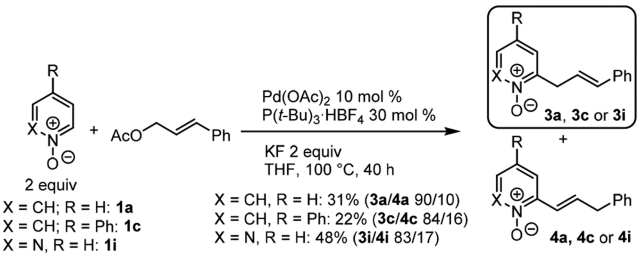
Then the scope of the reaction was studied with other allyl acetates. Unfortunately, the introduction of substituents at

**Scheme 2. Scope with Allyl Acetate**




positions 1, 2, or 3 completely inhibited the reaction (see the SI). However, the use of cinnamyl acetate as a coupling partner proved to be effective, giving PNOs **1a** and **1c** and pyridazine *N*-oxide **1i** and leading to the corresponding cinnamylated adducts **3a** (31% yield), **3c** (22% yield), and **3i** (48% yield) as major products, together with minor amounts of the corresponding isomerized adducts **4a**, **4c**, and **4i** (Scheme 3).

**Scheme 3. Scope with Cinnamyl Acetate**




The synthetic applications of alkenylated PNOs were then evaluated (Scheme 4). First, compounds **2a** and **2b** could be deoxygenated by treatment with $PCl_3$ in toluene to give pyridines **5a** and **5b**.[7b] Furthermore, treatment of **2a** with $OsCl_3$ cat./NMO smoothly gave the diol **6a**, while ozonolysis led to 2-formylpyridine *N*-oxide **7a**.[17]

Then, to gain insight into the mechanism, and particularly the C−H bond activation step, deuterium labeling experiments were carried out (Scheme 5). The intermolecular competition reaction between PNO and PNO-$d_5$ gave a primary kinetic isotopic effect (KIE) value of 4, while the parallel reactions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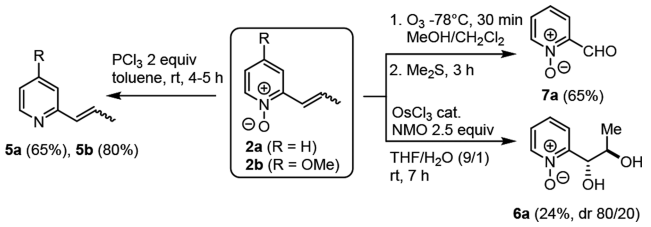
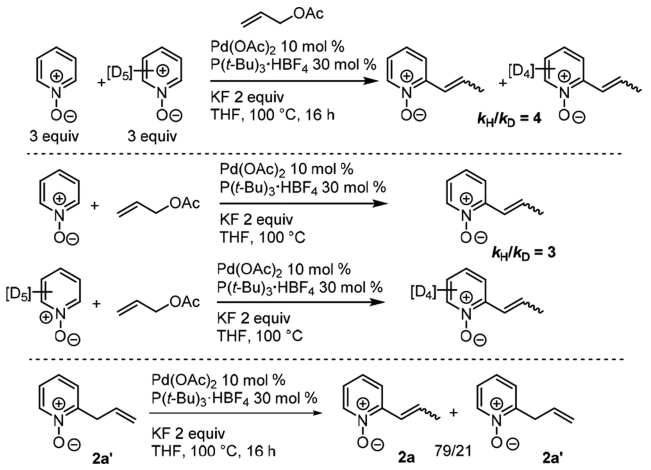
**Scheme 4. Synthetic Applications**



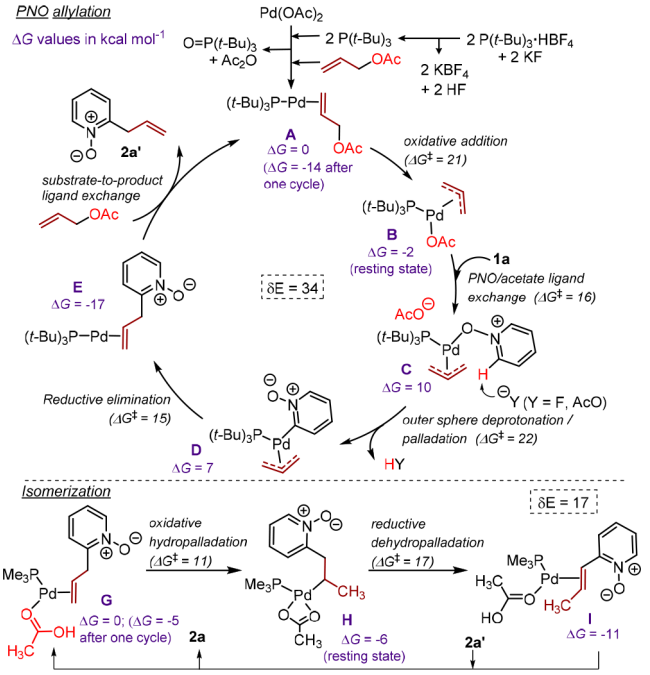

**Scheme 5. Mechanistic Studies**




experiment resulted in a KIE value of 3 (see the SI). These results suggest that C−H bond breaking is involved in the turnover-limiting step of the catalytic cycle. The isomerization step was studied next. Accordingly, 2-allyl PNO **2a′** was prepared via an independent synthesis[18] and tested for isomerization. While heating of **2a′** in a sealed tube at 100 °C for 16 h in THF gave only 10% of isomerization, its treatment under the classical reaction conditions for 16 h brought about 79% of isomerized product **2a**.

Finally, a DFT study of the full transformation[19] was accomplished, which led to the following mechanistic proposal (Scheme 6). First, the allyl acetate coordinates complex Pd(0)P(*t*-$Bu_3$) was generated from the in situ reduction of $Pd(OAc)_2$ by the phosphine, affording intermediate **A**. Then, oxidative addition led to the $\eta^3$-allylpalladium(II) complex **B** with an energy barrier of 21 kcal/mol.[20] In keeping with the observation of the cyclic intermediate $\kappa^2$(AcO)Pd$\kappa^2$((*t*-$Bu_3$)-$PCMe_2CH_2$) by the Hartwig group[21] in the $Pd(OAc)_2$/P(*t*-$Bu)_3$-catalyzed arylation of PNOs, we checked at this stage the viability of a mechanism involving cyclometalation of **B**. However, generation of such a 4-membered palladacycle via propene expulsion was energetically much too costly (see Figure S7). Formation of the related palladacycle $\eta^3$(allyl)-Pd$\kappa^2$((*t*-$Bu_3$)$PCMe_2CH_2$) via AcOH expulsion was instead found to be energetically accessible, with a barrier of 33 kcal/mol, but again, its subsequent evolution was energetically implausible, as C−H activation of the PNO by the palladacycle has a prohibitive barrier of over 60 kcal/mol (see Figure S8). On the other hand, PNO/acetate ligand exchange to afford intermediate [$\eta^3$(allyl)Pd(P(*t*-$Bu_3$))(PNO)]$^+$/$AcO^-$ **C** is only moderately exergonic ($\Delta G$ = 10 kcal/mol)[22] and sets the stage for the turnover-limiting outer-sphere deprotonation/palladation at $C_2$ of the coordinated PNO ligand to provide complex **D** ($\Delta G$ = 7 kcal/mol). This crucial C−H activation step

**Scheme 6. Proposed Mechanism of the Catalytic Cycle**




requires a high energy barrier (22 kcal/mol) and is in full accordance with the experimental reaction conditions (16 h, 100 °C).[20] The subsequent reductive elimination affords the allylated PNO **E** ($\Delta G$ = −17 kcal/mol) coordinated to Pd(0)P(*t*-$Bu_3$). Finally, substrate-to-product ligand exchange releases **2a′** and regenerates complex **A**. As for the diallylated product **2a″**, sometimes observed (in particular in the presence of carbonate as the base), it is expected to derive from a subsequent C−H activation of the allylic position of **2a**.[23]

The isomerization step was next studied (Scheme 6, bottom).[24] Starting from the $C_2$-allylated PNO ($Me_3P$)-(AcOH)Pd(0) complex **G**, a regioselective oxidative hydropalladation[25] leads to intermediate **H** ($\Delta G$ = −6 kcal/mol) with an energy barrier of 11 kcal/mol. The subsequent reductive dehydropalladation involving an internal H atom generates the more stable $C_2$-coordinated alkene isomer **I** ($\Delta G$ = −11 kcal/mol), which finally undergoes ligand exchange with a new molecule of **2a′** ($\Delta G$ = 6 kcal/mol), providing **2a**.

In summary, we have developed a method for the direct Pd-catalyzed $C_2$ alkenylation and cinnamylation of azine *N*-oxides with allyl acetate and cinnamyl acetate, respectively. This straightforward C−H functionalization method requires the use of a P(*t*-$Bu)_3$·$HBF_4$/KF system as the ligand precursor. On the basis of our experimental results in combination with DFT calculations a mechanism involving a turnover limiting outer sphere deprotonation/palladation as the key C−H activation step is proposed.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00689.

Further optimizations, DFT study details, atomic coordinates of all optimized species, experimental procedures, compound characterization (PDF)



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### Notes

The authors declare no competing financial interest.

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## REFERENCES


(1) (a) Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, W. W., Ed.; Elsevier: New York, 1999; Vol. *13*, p 92. (b) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 5th ed.; John Wiley & Sons: Chichester, U.K., 2010. (c) Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society: An Introduction to Heterocyclic Chemistry, Biochemistry and Applications*, 2nd ed.; John Wiley & Sons: Chichester, 2011.

(2) (a) Nakao, Y. *Synthesis* **2011**, *2011*, 3209. (b) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012**, *112*, 2642. (c) Allais, C.; Grassot, J.-M.; Rodriguez, J.; Constantieux, T. *Chem. Rev.* **2014**, *114*, 10829. (d) Murakami, K.; Yamada, S.; Kaneda, T.; Itami, K. *Chem. Rev.* **2017**, *117*, 9302.

(3) For recent books and reviews on C−H bond functionalizations, see: (a) Yu, J.-Q. *Catalytic Transformations via C−H Activation*; Science of Synthesis; Thieme: Stuttgart, 2016; Vols. *1 and 2*. (b) Dixneuf, P. H.; Doucet, H. *C−H Bond Activation and Catalytic Functionalization I and II*; Topics in Organometallic Chemistry 55 and 56; Springer: Switzerland, 2016. (c) Dastbaravardeh, N.; Christakakou, M.; Haider, M.; Schnürch, M. *Synthesis* **2014**, *46*, 1421. (d) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900. (e) Hartwig, J. F. *J. Am. Chem. Soc.* **2016**, *138*, 2. (f) Davies, H. M. L.; Morton, D. *J. Org. Chem.* **2016**, *81*, 343. (g) Roudesly, F.; Oble, J.; Poli, G. *J. Mol. Catal. A: Chem.* **2017**, *426*, 275.

(4) (a) Liu, C.; Luo, J.; Xu, L.; Huo, Z. *ARKIVOC* **2013**, 15. (b) Wang, Y.; Zhang, L. *Synthesis* **2015**, *47*, 289.

(5) (a) Larivée, A.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 52. (b) Mousseau, J. J.; Bull, J. A.; Charette, A. B. *Angew. Chem., Int. Ed.* **2010**, *49*, 1115. (c) Ding, S.; Yan, Y.; Jiao, N. *Chem. Commun.* **2013**, *49*, 4250. (d) Chau, S. T.; Lutz, J. P.; Wu, K.; Doyle, A. G. *Angew. Chem., Int. Ed.* **2013**, *52*, 9153.

(6) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020.

(7) For C−H arylation, see: (a) Leclerc, J.-P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7781. (b) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (c) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291. (d) Schipper, D. J.; El-Salfiti, M.; Whipp, C. J.; Fagnou, K. *Tetrahedron* **2009**, *65*, 4977. (e) Duric, S.; Tzschucke, C. C. *Org. Lett.* **2011**, *13*, 2310. (f) Gong, X.; Song, G.; Zhang, H.; Li, X. *Org. Lett.* **2011**, *13*, 1766. (g) Wang, Z.; Li, K.; Zhao, D.; Lan, J.; You, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5365. (h) Ackermann, L.; Fenner, S. *Chem. Commun.* **2011**, *47*, 430. (i) Tan, Y.; Barrios-Landeros, F.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 3683. (j) Mai, P.; Yuan, J.; Li, Z.; Sun, G.; Qu, L. *Synlett* **2012**, *2012*, 145. (k) Duric, S.; Sypaseuth, F. D.; Hoof, S.; Svensson, E.; Tzschucke, C. C. *Chem. - Eur. J.* **2013**, *19*, 17456. (l) Liu, W.; Li, Y.; Wang, Y.; Kuang, C. *Org. Lett.* **2013**, *15*, 4682. (m) Shen, Y.; Chen, J.; Liu, M.; Ding, J.; Gao, W.; Huang, X.; Wu, H. *Chem. Commun.* **2014**, *50*, 4292. (n) Odani, R.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2015**, *80*, 2384. (o) Bering, L.; Antonchick, A. P. *Org. Lett.* **2015**, *17*, 3134. (p) Kianmehr, E.; Faghih, N.; Khan, K. M. *Org. Lett.* **2015**, *17*, 414. (q) Liu, S.; Tzschucke, C. C. *Eur. J. Org. Chem.* **2016**, *2016*, 3509. (r) Théveau, L.; Schneider, C.; Fruit, C.; Hoarau, C. *ChemCatChem* **2016**, *8*, 3183.

(8) For C−H alkylation, see: (a) Andersson, H.; Almqvist, F.; Olsson, R. *Org. Lett.* **2007**, *9*, 1335. (b) Deng, G.; Ueda, K.; Yanagisawa, S.; Itami, K.; Li, C.-J. *Chem. - Eur. J.* **2009**, *15*, 333. (c) Zhang, F.; Duan, X. F. *Org. Lett.* **2011**, *13*, 6102. (d) Ryu, J.; Cho, S. H.; Chang, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3677. (e) Zhang, S.; Liao, L. Y.; Zhang, F.; Duan, X. F. *J. Org. Chem.* **2013**, *78*, 2720. (f) Xiao, B.; Liu, Z.-J.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 616. (g) Larionov, O. V.; Stephens, D.; Mfuh, A.; Chavez, G. *Org. Lett.* **2014**, *16*, 864. (h) Jha, A. K.; Jain, N. *Chem. Commun.* **2016**, *52*, 1831. (i) Kianmehr, E.; Faghih, N.; Karaji, S.; Lomedasht, Y. A.; Khan, K. M. *J. Organomet. Chem.* **2016**, *801*, 10. (j) Zhang, W.-M.; Dai, J.-J.; Xu, J.; Xu, H.-J. *J. Org. Chem.* **2017**, *82*, 2059.

(9) For C−H alkenylation, see: (a) Kanyiva, K. S.; Nakao, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 8872. (b) Wu, J.; Cui, X.; Chen, L.; Jiang, G.; Wu, Y. *J. Am. Chem. Soc.* **2009**, *131*, 13888. (c) Huckins, J. R.; Bercot, E. A.; Thiel, O. R.; Hwang, T.-L.; Bio, M. M. *J. Am. Chem. Soc.* **2013**, *135*, 14492. (d) Crisenza, G. E. M.; Dauncey, E. M.; Bower, J. F. *Org. Biomol. Chem.* **2016**, *14*, 5820. (e) Xia, H.; Liu, Y.; Zhao, P.; Gou, S.; Wang, J. *Org. Lett.* **2016**, *18*, 1796.

(10) For a recent review, see: (a) Mishra, N. K.; Sharma, S.; Park, J.; Han, S.; Kim, I. S. *ACS Catal.* **2017**, *7*, 2821. (b) For an example of propenylation of pyridine at C-6, see: Goriya, Y.; Ramana, C. V. *Chem. - Eur. J.* **2012**, *18*, 13288.

(11) For some examples, see: (a) Giboulot, S.; Liron, F.; Prestat, G.; Wahl, B.; Sauthier, M.; Castanet, Y.; Mortreux, A.; Poli, G. *Chem. Commun.* **2012**, *48*, 5889. (b) Lorion, M. M.; Gasperini, D.; Oble, J.; Poli, L. *Org. Lett.* **2013**, *15*, 3050. (c) Erray, I.; Rezgui, F.; Oble, J.; Poli, G. *Synlett* **2014**, *25*, 2196. (d) Kammerer, C.; Prestat, G.; Madec, D.; Poli, G. *Acc. Chem. Res.* **2014**, *47*, 3439.

(12) For some examples, see: (a) Nahra, F.; Liron, F.; Prestat, G.; Mealli, C.; Messaoudi, A.; Poli, G. *Chem. - Eur. J.* **2009**, *15*, 11078. (b) Liron, F.; Oble, J.; Lorion, M. M.; Poli, G. *Eur. J. Org. Chem.* **2014**, *2014*, 5863. (c) Rajabi, J.; Lorion, M. M.; Ly, V. L.; Liron, F.; Oble, J.; Prestat, G.; Poli, G. *Chem. - Eur. J.* **2014**, *20*, 1539. (d) Lorion, M. M.; Oble, J.; Poli, G. *Pure Appl. Chem.* **2016**, *88*, 381. (e) Diamante, D.; Gabrieli, S.; Benincori, T.; Broggini, G.; Oble, J.; Poli, G. *Synthesis* **2016**, *48*, 3400. (f) Pezzetta, C.; Veiros, L. F.; Oble, J.; Poli, G. *Chem. - Eur. J.* **2017**, *23*, 8385.

(13) (a) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: New York, 2004. (b) Poli, G.; Prestat, G.; Liron, F.; Kammerer-Pentier, C.; Kazmaier, U. *Top. Organomet. Chem.* **2011**, *38*, 1−63.

(14) For Pd-catalyzed direct allylations on aromatic rings, see: (a) Fan, S.; Chen, F.; Zhang, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 5918. (b) Yu, Y.-B.; Fan, S.; Zhang, X. *Chem. - Eur. J.* **2012**, *18*, 14643. (c) Bae, S.; Jang, H.-L.; Jung, H.; Joo, J. M. *J. Org. Chem.* **2015**, *80*, 690. (d) Lee, J. Y.; Ha, H.; Bae, S.; Han, I.; Joo, J. M. *Adv. Synth. Catal.* **2016**, *358*, 3458. (e) Lee, S. Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2016**, *138*, 15278.

(15) Preliminary optimization of the reaction conditions were done by varying parameters such as the nature of the allylic partner, the PNO/allylic derivative ratio, the molarity of the reaction partners, the temperature, as well as the reaction time (see the SI for more details).

(16) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295.

(17) Cross-metathesis and Wacker-type oxidation tests did not afford the expected coupling products.

(18) Duan, X.-F.; Ma, Z.-Q.; Zhang, F.; Zhang, Z.-B. *J. Org. Chem.* **2009**, *74*, 939.

(19) (a) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989. (b) DFT




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calculations at the M06/[SDD* (Pd), 6-311++G(d,p)]//PBE0/[SDD* (Pd), 6-31G(d,p)] level were performed using the Gaussian 09 package. Solvent effects (THF) were considered by means of the PCM model with SMD radii. A complete account of the computational details and the corresponding list of references are provided as SI..

(20) This is a rather high barrier but not so for a reaction that occurs at high temperature (100 °C) over a long period (16 h) and achieves moderate yields. See, for example: Mastalir, M.; Glatz, M.; Gorgas, N.; Stöger, B.; Pittenauer, E.; Allmaier, G.; Veiros, L. F.; Kirchner, K. *Chem. - Eur. J.* **2016**, *22*, 12316.

(21) Tan, Y.; Barrios-Landeros, B.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 3683.

(22) (a) Free energy values relative to **A**.. (b) From complex **B**, an $\eta^3$-$\eta^1$-allyl equilibrium, followed by PNO coordination is feasible but leads to a mechanistic dead end (see SI, Figure S4)..

(23) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266.

(24) As the computations showed identical mechanisms using $PMe_3$ or P(*t*-Bu)$_3$, the isomerization study was carried out with the former phosphine for computational expediency.

(25) Mekareeya, A.; Walker, P. R.; Couce-Rios, A.; Campbell, C. D.; Steven, A.; Paton, R. S.; Anderson, E. A. *J. Am. Chem. Soc.* **2017**, *139*, 10104.



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