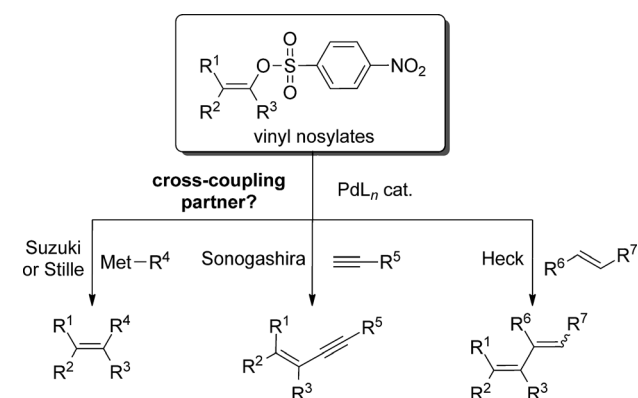


Vinyl Nosylates: An Ideal Partner for Palladium-Catalyzed Cross-Coupling Reactions

Nicolas P. Cheval, Anna Dikova, Aurélien Blanc, Jean-Marc Weibel,* and Patrick Pale*^[a]

Palladium-catalyzed cross-coupling reactions are nowadays essential to organic chemistry, allowing to conveniently build up complex molecules through C–C bond formation.^[1] These reactions usually involve two partners: a vinyl or aryl halide or triflate and different organometallic reagents, such as boronic acids or esters (Suzuki–Miyaura reaction),^[2] organotin (Stille reaction)^[3] and others,^[4] or alkenes (Mizoroki–Heck reaction)^[5] or alkynes (Sonogashira reaction).^[6] Numerous conditions are currently available with a large variety of palladium catalysts (Pd⁰ or Pd^{II}). However, limitations still exist regarding the conditions, but also regarding the nature of the starting material. Iodides and bromides are more reactive, but for industrial and cost reasons chlorides can now be used, although they require harsher conditions and/or specific catalysts.^[7] Usually triflates are as reactive as iodides, but their introduction through triflic anhydride requires specific conditions, owing to the sensitivity of this reagent, and is costly as such, because half of the reagent is lost. Thus, it is worth looking for convenient and cheaper alternatives to triflates.

The related mesylates,^[9,10] tosylates,^[10,11] and even phosphates^[12] have been explored, although with some drawbacks, mostly due to their introduction mode, but also with some success, especially with tosylates. We reasoned that the leaving-group ability of arylsulfonates in the first step (oxidative addition) of the catalytic cycle could easily be tuned with electron-withdrawing substituents. Herein, we show that the *para*-nitrophenylsulfonate (nosyl; Ns) group offers the required properties and that nosylates can act as excellent partners in various Pd-catalyzed cross-coupling reactions (Scheme 1). To the best of our knowledge, the reactivity of various vinyl nosylates with palladium catalysts in cross-coupling reactions has not been reported so far, the case of aryl nosylates being discussed only once in a Stille coupling reaction.^[13] Recently, the Skrydstrup group em-

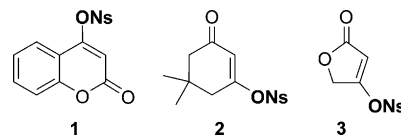


Scheme 1. Vinyl nosylates as partners in Pd-catalyzed cross-coupling reactions.

ployed an aryl nosylate in a Heck reaction catalyzed by a nickel complex;^[14] however, only one example was reported and the product was isolated in low yield (17%).

Compared to triflic anhydride, nosylating reagents—the chloride being the most common—are very cheap.^[15] Furthermore, the crystallinity of vinyl and aryl nosylates should facilitate their isolation and purification and favor stability.

Owing to its complex structure and applications,^[16] 4-hydroxycoumarin together with dimedone and 4-hydroxy-2-furanone were selected as model substrates for our study. These partners, especially coumarin, can be viewed as benchmarks for coupling methods.^[17] The corresponding nosylates **1**, **2**, and **3** (Scheme 2) were readily obtained upon



Scheme 2. Vinyl nosylate partners **1**, **2**, and **3**.

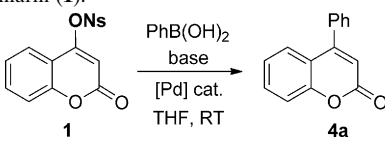
treatment with nosyl chloride and diisopropylethylamine in high yields (see the Supporting Information). As expected, these nosylates are solid crystalline materials and perfectly stable at room temperature for at least a year.

Due to its predominance in synthesis and industry, the Suzuki–Miyaura coupling reaction was first examined. Thus, nosylate **1** was employed in a screening of reaction condi-

[a] N. P. Cheval, A. Dikova, Dr. A. Blanc, Prof. J.-M. Weibel, Prof. P. Pale
Laboratoire de Synthèse, Réactivité Organiques & Catalyse
Institut de Chimie de Strasbourg, associé au CNRS
Université de Strasbourg
4 rue Blaise Pascal, 67070 Strasbourg (France)
Fax: (+33)368851517
E-mail: jmweibel@unistra.fr
ppale@unistra.fr

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/chem.201300127>.

Table 1. Screening of conditions for the Suzuki–Miyaura coupling of 4-nosyloxycoumarin (**1**).



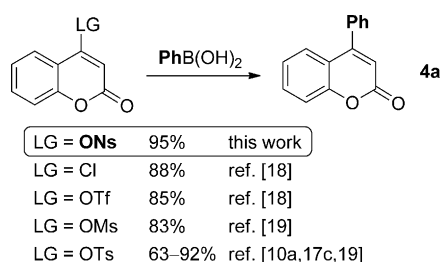
Entry	[Pd] ^[a]	Base ^[b]	Time [h]	Yield [%]
1	–	K ₂ CO ₃	24	<1
2	[Pd(PPh ₃) ₄]	K ₂ CO ₃	24	27 ^[c]
3	[Pd(OAc) ₂]	K ₂ CO ₃	24	85
4	[PdCl ₂ (RCN) ₂] ^[d]	K ₂ CO ₃	5	62–79
5	[PdCl ₂ (PPh ₃) ₂]	K ₂ CO ₃	14	79
6	[PdCl ₂ (dppf)]	K ₂ CO ₃	1	95
7	[PdCl ₂ (dppf)]	K ₃ PO ₄	1	93

[a] 2 mol%. [b] 2 equivalents of a 2 M aqueous solution. [c] Slow degradation to a black tar and hydrolysis occurred. [d] R = Me, Ph.

tions. A large number of palladium sources and bases were evaluated for their ability to promote the coupling of **1** with phenylboronic acid, and selected results are listed in Table 1.

Without palladium, no transformation could be detected (entry 1). In the presence of a zerovalent palladium catalyst, degradation and hydrolysis occurred, except when potassium carbonate was used as base (entry 2). In contrast, Pd^{II} catalysts proved very effective, even at room temperature, giving the expected 4-phenylcoumarin (**4a**) in good to excellent yields (entries 3–7). Catalysts based on bidentate phosphine gave better results than any other monodentate ligands (entries 6 and 7 vs. 4 and 5). 1,1'-Bis(diphenylphosphino)ferrocene (dppf) with palladium dichloride proved to be the best catalyst combination, especially in the presence of potassium carbonate as base (entry 6 vs. 7), giving the coupling product in almost quantitative yield within one hour (entry 6).

It is worth noting that the known Suzuki coupling of related 4-substituted coumarins required longer times and harsher conditions (Scheme 3). The corresponding chloride or tri-

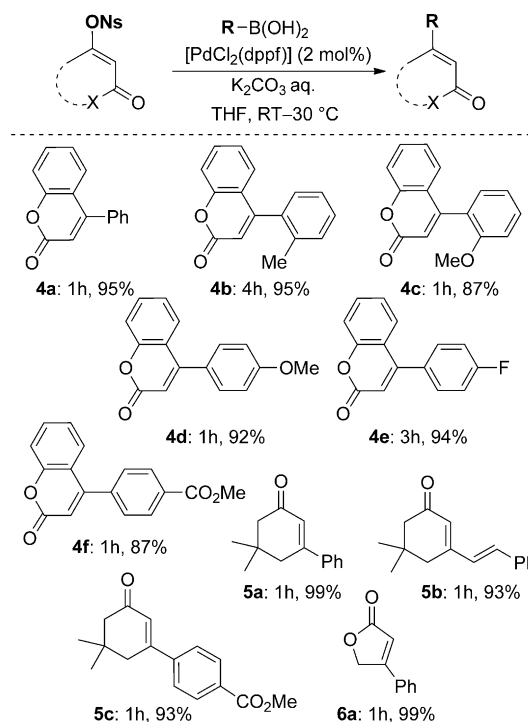


Scheme 3. Comparison of nosylates versus other leaving groups in Suzuki cross-coupling reactions.

flate required 4 mol% of [Pd(PPh₃)₄] and aqueous sodium carbonate (2 equiv) in refluxing benzene for 20 h, together with stoichiometric amounts of CuI for the triflate. Both substrates gave lower yields than when using the nosylate (83 and 88% vs. 95%).^[18] The mesylate partner provided

4-phenylcoumarin (**4a**) in 85% yield by using 2 mol% of [Pd(OAc)₂] in *tert*-butanol at 50 °C after 4 h along with CM-Phos ligand (CM-Phos = 2-[2-(dicyclohexylphosphino)phenyl]-1-methyl-1H-indole), while the tosylate gave **4a** in 92% yield under the same conditions.^[10a,17c,19] Furthermore, control experiments revealed that under our above-defined conditions, the analog 4-tosylate and 4-mesylate substrates were far less reactive than nosylate **1** and mostly decomposed.

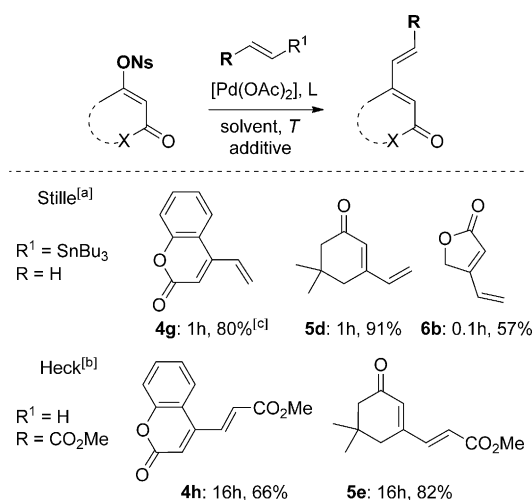
The scope of this novel version of the Suzuki–Miyaura reaction was briefly explored by coupling nosylates **1**, **2**, and **3** with various organoboron derivatives (Scheme 4). The



Scheme 4. Suzuki–Miyaura coupling of nosylates **1**, **2**, and **3** derived from 4-hydroxycoumarin, dimedone, and 4-hydroxy-2-furanone with various boronic acids. Conditions: Pd catalyst (2 mol%), nosylate (1 equiv), boronic acid (1.2 equiv), K₂CO₃ (2 M, 2 equiv), THF, RT.

above-defined conditions allowed for rapid and very efficient reactions, irrespective of the starting material and the substitution, providing the expected products **4a–f**, **5a–c**, and **6a** in excellent or even quantitative yields. *Ortho*-substituents as well as electron-withdrawing groups slightly slowed down the reaction without altering the efficiency (**4b** and **4e** vs. **4a**). Nosylate partners generally gave yields higher than 90% in such coupling reactions.

We then turned our attention to Stille and Heck coupling reactions (Scheme 5). After extensive experimentation, the Stille coupling was best achieved with 5 mol% of [Pd(OAc)₂]/bis(triphenylphosphine) and 3 equivalents of lithium bromide^[20] at 60 °C in THF. Under such conditions, the vinyl group of the corresponding tributylstannane could be transferred to either nosylate **1** or **2** within one hour, giving the coupling products **4g** and **5d** in excellent yields. Nosy-



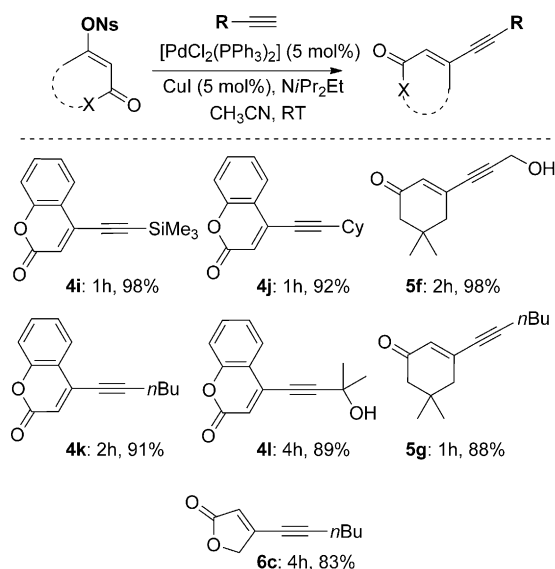
Scheme 5. Stille coupling and Heck reaction starting from nosylate derivatives **1–3**. [a] Stille conditions: $[\text{Pd}(\text{OAc})_2]$ (5 mol %), PPh_3 (10 mol %), nosylate (1 equiv), stannane (1.05 equiv), LiBr (3 equiv), THF, 60°C ; [b] Heck conditions: $[\text{Pd}(\text{OAc})_2]$ (2.5 mol %), 1,3-bis(diphenylphosphino)propane (dppp, 2.75 mol %), nosylate (1 equiv), alkene (4 equiv), NiPr_2Et (3 equiv), dioxane, $50\text{--}85^\circ\text{C}$. [c] Calculated yield from ^1H NMR integration relative to an internal standard (hexamethylbenzene); **4g** proved very sensitive and easily polymerized.

late **3** was much more reactive, since completion of the reaction was achieved in less than 10 min, but afforded compound **6b** in a modest yield owing to its low stability.

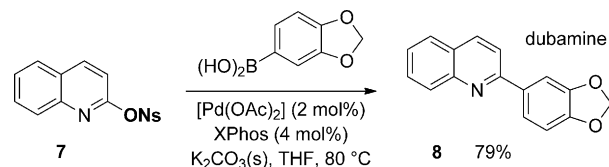
The Heck reaction could be performed by using $[\text{Pd}(\text{OAc})_2]$ under very similar conditions as well, except that a bidentate phosphine was beneficial for the reaction and, of course, a base was required, with diisopropylethylamine being the best in this case. Overnight reactions proved necessary for completion, leading to the isolation of the coupling products **4h** and **5e** as single isomers in good to high yields. The last was obtained in a yield similar to that reported starting from the corresponding tosylate.^[17a]

The other well-known Pd-catalyzed reaction we examined was the Sonogashira reaction. With so many applications,^[6] it was clearly worth developing a new version with an efficient, cheap and stable leaving group. After extensive experimentation, the best conditions were found to be $[\text{PdCl}_2(\text{PPh}_3)_2]$ as catalyst and copper iodide as co-catalyst in the presence of 1.25 equivalents of diisopropylethylamine in acetonitrile at room temperature (Scheme 6). Under such conditions, various alkynyl coumarins **4i–l**, dimedones **5f–g**, and furanone **6c** could be obtained in high yields, usually within one or two hours. It is worth mentioning that **4i** has already been prepared from the corresponding tosylate, with the triflate being instable, but in lower yield upon a prolonged reaction time (68% in 48 h vs. 98% in 1 h here) despite a higher catalyst loading.^[21]

To highlight this new type of partners for cross-coupling reactions and to further extend its application, the synthesis of the natural alkaloid dubamine (**8**), isolated from *Haplophylum dubium*, was attempted and efficiently achieved (Scheme 7).^[22] Starting from quinolyl nosylate (**7**), dubamine was readily obtained through a Suzuki coupling with 3,4-



Scheme 6. Sonogashira coupling of nosylates **1**, **2**, and **3** with various alkynes. Conditions: Pd catalyst (5 mol %), CuI (5 mol %), nosylate (1 equiv), alkyne (1.2 equiv), NiPr_2Et (1.25 equiv), CH_3CN , RT.



Scheme 7. Synthesis of dubamine by Suzuki cross-coupling reaction.

(methylenedioxy)phenylboronic acid. Under the conditions we developed (Scheme 4), the yield relative to conversion was very high, but the last was modest (50%).^[23] Replacing $[\text{PdCl}_2(\text{dppf})]$ by $[\text{Pd}(\text{OAc})_2]$ and XPhos phosphine (XPhos = 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl) allowed full conversion upon moderate heating overnight, and dubamine (**8**) was isolated in 79% yield. This result demonstrates the polyvalence of the nosylate leaving group, which is not limited to our model compounds.

In conclusion, we have developed an inexpensive and stable *p*-nitrophenylsulfonate (nosylate) leaving group for most types of cross-coupling reactions. Substantial effort has been devoted to the development of conditions capable of activating them under mild conditions and allowing for rapid and very efficient coupling reactions. Such nosylates would be of profound interest for C–C bond formation, leading to numerous applications in organic chemistry.

Further extensions are now in progress in our group, as well as mechanistic investigations to better understand these novel cross-coupling reaction conditions.

Experimental Section

Suzuki coupling of vinyl nosylates: An argon-degassed aqueous solution of K_2CO_3 (600 μL , 2 equiv, 2 M) was added to a solution of the boron de-

rivative (1.2 equiv, 0.6 mmol) in degassed THF (3 mL, 6 mL mmol⁻¹) under argon. After 5 min of stirring, the palladium catalyst (2 mol%) and the alkenyl nosylate (1 equiv, 0.5 mmol) were successively added to the reaction mixture. The mixture was kept at room temperature or warmed to 30°C and stirred until consumption of the starting material (TLC). The reaction mixture was partitioned between Et₂O (9 mL) and water (9 mL) and the layers separated. The aqueous layer was extracted with EtOAc (3×9 mL), and the combined organic layers were dried over Na₂SO₄ and evaporated in vacuo. The crude residue was purified by flash chromatography (cyclohexane/EtOAc gradient).

Acknowledgements

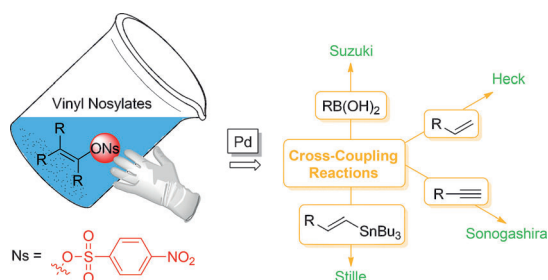
The authors thank the CNRS and the French Agency of Research (ANR 09-BLAN-0329 CADISCOM and ANR 11-JS07-001-01 SyntHetAu) for financial support. N.P.C. also thanks the ANR for a PhD fellowship. A.D. thanks the French Ministry of Research for a PhD fellowship.

Keywords: arenes • cross-coupling • palladium • vinyl compounds

- [1] a) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem.* **2012**, *124*, 5150–5174; *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5085; b) J. Tsuji, *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*, Wiley, Hoboken, **2005**; c) *Handbook of Organopalladium Chemistry for Organic Synthesis, Vol. 1* (Ed.: E.-I. Negishi), Wiley, Hoboken, **2002**, Part III; d) T. N. Mitchell in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**, Chapter 4.
- [2] a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483; b) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147–168; c) S. Kotha, K. Lahiri, D. Kashinath, *Tetrahedron* **2002**, *58*, 9633–9695.
- [3] a) M. V. N. De Souza, *Curr. Org. Synth.* **2006**, *3*, 313–326; b) T. N. Mitchell, *Synthesis* **1992**, 803–815.
- [4] a) For Negishi coupling, see: E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340–348; b) for Hiyama coupling, see: Y. Nakao, T. Hiyama, *Chem. Lett. Chem. Soc. Rev.* **2011**, *40*, 4893–4901; c) for Kumada coupling, see: S. I. Murahashi, *J. Organomet. Chem.* **2002**, *653*, 27–33.
- [5] a) A. B. Dounay, L. E. Overman in *The Mizoroki-Heck Reaction* (Ed.: M. Oestreich), Wiley, Chichester, **2009**, Chapter 16; b) I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009–3066.
- [6] a) R. Chinchilla, C. Najera, *Chem. Soc. Rev.* **2011**, *40*, 5084–5121; b) R. Chinchilla, C. Najera, *Chem. Rev.* **2007**, *107*, 874–922; c) H. Doucet, J.-C. Hierso, *Angew. Chem.* **2007**, *119*, 850–888; *Angew. Chem. Int. Ed.* **2007**, *46*, 834–871.
- [7] A. F. Littke, G. C. Fu, *Angew. Chem.* **1999**, *111*, 2568–2570; *Angew. Chem. Int. Ed.* **1999**, *38*, 2411–2413.
- [8] a) P. J. Stang, M. Hanack, L. R. Subramanian, *Synthesis* **1982**, 85–126; b) S. Chassaing, S. Specklin, J.-M. Weibel, P. Pale, *Curr. Org. Synth.* **2012**, *9*, 806–827; c) S. Chassaing, S. Specklin, J.-M. Weibel, P. Pale, *Tetrahedron* **2012**, *68*, 7245–7273.
- [9] C. M. So, F. Y. Kwong, *Chem. Soc. Rev.* **2011**, *40*, 4963–4972.
- [10] a) P. Y. Wong, W. K. Chow, K. H. Chung, C. M. So, C. P. Lau, F. Y. Kwong, *Chem. Commun.* **2011**, *47*, 8328–8330; b) W. K. Chow, C. M. So, C. P. Lau, F. Y. Kwong, *Chem. Eur. J.* **2011**, *17*, 6913–6917; c) P. Y. Choy, W. K. Chow, C. M. So, C. P. Lau, F. Y. Kwong, *Chem. Eur. J.* **2010**, *16*, 9982–9985.
- [11] For selected examples, see: a) M. Lüthy, R. J. K. Taylor, *Tetrahedron Lett.* **2012**, *53*, 3444–3447; b) C. M. So, C. P. Lau, A. S. C. Chan, F. Y. Kwong, *J. Org. Chem.* **2008**, *73*, 7731–7734; c) T. M. Goegsig, L. S. Soebjerg, A. T. Lindhardt, K. L. Jensen, T. Skrydstrup, *J. Org. Chem.* **2008**, *73*, 3404–3410; d) L. Zhang, T. Meng, J. Wu, *J. Org. Chem.* **2007**, *72*, 9346–9349; e) K. H. Chung, C. M. So, S. M. Wong, C. H. Luk, Z. Zhou, C. P. Lau, F. Y. Kwong, *Chem. Commun.* **2012**, *48*, 1967–1969; f) G. A. Molander, I. Shin, *Org. Lett.* **2012**, *14*, 3138–3141.
- [12] J. D. Sellars, P. G. Steel, *Chem. Soc. Rev.* **2011**, *40*, 5170–5180.
- [13] D. Badone, R. Cecchi, U. Guzzi, *J. Org. Chem.* **1992**, *57*, 6321–6323.
- [14] T. M. Goegsig, J. Kleimark, S. O. Nilsson Lill, S. Korsager, A. T. Lindhardt, P.-O. Norrby, T. Skrydstrup, *J. Am. Chem. Soc.* **2012**, *134*, 443–452.
- [15] Common current prices for 25 or 50 g batches (euro per mol, ABCR (Germany)/Sigma–Aldrich, 2012) of Ts₂O: 1540/2089; Tf₂O: 667/1594; MsCl: –/25, TsCl: –/70, NsCl: 264/448.
- [16] As bioactive motif, see: a) A. Lacy, R. O’Kennedy, *Curr. Pharm. Des.* **2004**, *10*, 3797–3811; b) I. Kostova, *Curr. Med. Chem. Anti-Cancer Agents* **2005**, *5*, 29–46; c) F. Borges, F. Roleira, N. Milhazes, L. Santana, E. Uriarte, *Curr. Med. Chem.* **2005**, *12*, 887–916; as fluorescent marker in biology, see: d) D. Wahler, F. Badalassi, P. Crotti, J. L. Reymond, *Angew. Chem.* **2001**, *113*, 4589–4592; *Angew. Chem. Int. Ed.* **2001**, *40*, 4457–4460; as dyes for solar cell and laser applications, see: e) X. Liu, J. M. Cole, P. G. Waddell, T.-C. Lin, J. Radia, A. Zeidler, *J. Phys. Chem. A* **2012**, *116*, 727–737; as polymer photo-cross-linker, see: f) S. R. Trenor, A. R. Shultz, B. J. Love, T. E. Long, *Chem. Rev.* **2004**, *104*, 3059–3077.
- [17] a) S. Valente, G. Kirsch, *Tetrahedron Lett.* **2011**, *52*, 3429–3432; b) A. L. Hansen, T. Skrydstrup, *Org. Lett.* **2005**, *7*, 5585–5587; c) J. Wu, L. Wang, R. Fahti, Z. Yang, *Tetrahedron Lett.* **2002**, *43*, 4395–4397.
- [18] G. M. Boland, D. M. X. Donnelly, J.-P. Finet, M. D. Rea, *J. Chem. Soc. Perkin Trans. 1* **1996**, 2591–2597.
- [19] M. D. Santana, R. Garcia-Bueno, G. Garcia, G. Sanchez, G. Garcia, A. R. Kapdi, M. Naik, S. Pednekar, J. Perez, L. Garcia, E. Perez, J. L. Serrano, *Dalton Trans.* **2012**, *41*, 3832–3842.
- [20] Halides or other additives are commonly added in Stille couplings. They enhance the stannane nucleophilicity and, in the case of cationic palladium intermediates, they coordinate to the stannane, rendering the complex neutral, more stable, and thereby facilitating transmetalation; see: P. Espinet, A. M. Echavarren, *Angew. Chem.* **2004**, *116*, 4808–4839; *Angew. Chem. Int. Ed.* **2004**, *43*, 4704–4734.
- [21] J. Wu, Y. Liao, Z. Yang, *J. Org. Chem.* **2001**, *66*, 3642–3645.
- [22] a) S. Y. Yunusov, G. P. Sidyakin, *Zh. Obshch. Khim.* **1955**, *25*, 2009–2016; b) J. Koyama, I. Toyokuni, K. Tagahara, *Chem. Pharm. Bull.* **1999**, *47*, 1038–1039.
- [23] Poisoning of the catalyst by quinoline might account for this result. Thus, we used a bulkier ligand and heating to minimize such phenomenon.

Received: January 14, 2013

Published online: ■ ■ ■, 0000



In a hurry to leave! Nosylates act as an excellent leaving group in various palladium-catalyzed cross-couplings, such as Suzuki, Stille, Heck, and Sonogashira reactions (see scheme). Crystalline, stable, and cheap vinyl and aryl nosylates proved better than classical

halides and triflates, consistently giving higher yields of coupling products. Their usefulness in C–C bond formation was also demonstrated by the rapid synthesis of the alkaloid dubamine.

Cross-Coupling

N. P. Cheval, A. Dikova, A. Blanc, J.-M. Weibel, P. Pale**

Vinyl Nosylates: An Ideal Partner for Palladium-Catalyzed Cross-Coupling Reactions

