ORGANIC LETTERS

2002
Vol. 4, No. 18
3115−3118

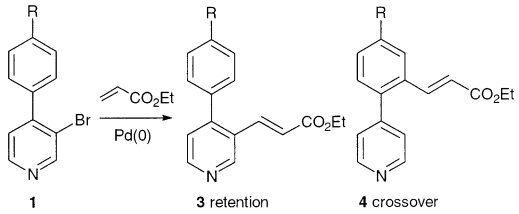
C–H Activation and Palladium Migration within Biaryls under Heck Reaction Conditions

Gunter Karig, Maria-Teresa Moon, Nopporn Thasana,[†] and Timothy Gallagher*

School of Chemistry, University of Bristol, Bristol BS8 1TS U.K.
t.gallagher@bristol.ac.uk

Received June 26, 2002

ABSTRACT

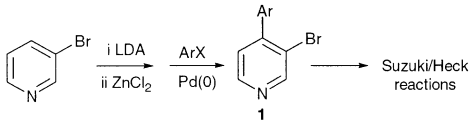


Biaryl bromides such as 1 (R═NO_2, H, OMe) undergo the Heck reaction to give both the expected products 3 ("retention") as well as "crossover" products 4 derived from a migration of Pd and net transfer of reactivity from one aryl ring to the other. Under the conditions used, crossover is increasingly favored when electron-deficient arenes are involved. Crossover products derived from transfer onto the pyridine ring have also been observed.

We recently described the synthesis of substituted pyridines based on the ability of, e.g., 3-bromopyridine to undergo lithiation/transmetalation (Li to Zn), and chemoselective Pd(0)-mediated Negishi coupling.[1]

The resulting adducts **1** then undergo useful synthetic reactions involving the bromo moiety (Scheme 1). While

Scheme 1. Functionalization of Bromopyridines



4-aryl-3-bromopyridines **1** function well in Suzuki couplings, their use in the Heck reaction led to unexpected results, which are the focus of this communication.

The Heck reaction[2,3] involving **1a** was carried out using ethyl acrylate as the alkene component and although the overall yield was reasonable, three products were isolated (Scheme 2).[4] 4-(4-Nitrophenyl)pyridine (**2a**), the product of C−Br reduction, was obtained in 10% yield as well as the expected ("retention") Heck adduct **3a** (in 53% yield). In addition, we observed another Heck product **4a** (17% yield), which results from a transfer of reactivity (migration of palladium) within the biaryl scaffold from the pyridine ring to the adjacent *ortho* position of the 4-nitrophenyl component.[5] The formation of "crossover" products, such as **4a**,

[†] On leave from Chulabhorn Research Institute, Bangkok 10210, and Department of Chemistry, Mahidol University, Bangkok 10400, Thailand.

(1) Karig, G.; Spencer, J. A.; Gallagher, T. *Org. Lett.* **2001**, *3*, 835−838. Karig, G.; Thasana, N.; Gallagher, T. *Synlett* **2002**, 808−810.

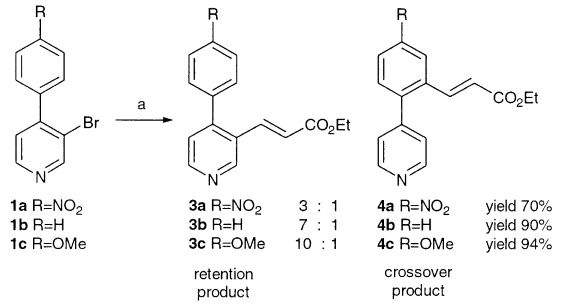
(2) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320−2322. Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.

(3) For overviews of the Heck reaction, see: de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379−2411. Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; pp 99−166. Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066. For recent mechanistic work, including a role for Pd(IV) intermediates, see: Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427−436. Shaw, B. L. *New J. Chem.* **1998**, *22*, 77−79. Shaw, B. L.; Perera, S. D.; Staley, E. A. *Chem. Commun.* **1998**, 1361−1362. Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254−278. Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314−321. Böhm, V. P. W.; Herrmann, W. A. *Chem. Eur. J.* **2001**, *7*, 4191−4197. Sundermann, A.; Uzan, O.; Martin, J. M. L. *Chem. Eur. J.* **2001**, *7*, 1703−1711.

(4) Preparation of **1**, **5**, and **10** used procedures described earlier.[1] The preparation of biaryls **12a**−**d** was carried out using an aryl boronic acid and an appropriately substituted 2-iodo-1-bromoarene. Experimental details are available in Supporting Information.

10.1021/ol026426v CCC: $22.00
Published on Web 08/14/2002

Scheme 2. Retention and Crossover Heck Adducts from 4-Aryl-3-bromopyridines[a]



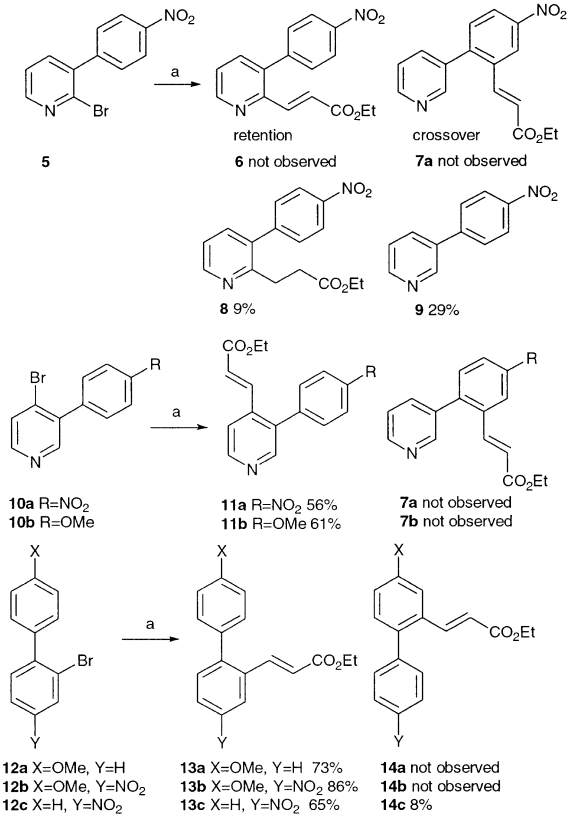
[a] Reagents and conditions: (a) $H_2C{=}CHCO_2Et$ (3 equiv), $Pd(OAc)_2$ (0.1 equiv), (*o*-Tol)$_3$P (0.2 equiv), NEt_3 (5 equiv), MeCN, 125 °C (sealed tube), 20 h.

associated with biaryl derivatives has not been described previously, although in a more general sense, processes involving C−H activation[6] are known to be associated with Heck reaction conditions.[7]

Heck adducts **3a** and **4a** were formed in a 3:1 ratio, and this raises a number of issues. First, what structural and/or electronic factors determine the proportion of crossover product generated? Second, can the migration pathway be controlled and either suppressed or promoted? Although a detailed mechanistic interpretation remains to be elucidated, some of these questions have been addressed.

To examine the scope of this process, we have synthesized a number of other biaryls, including the 4-aryl-3-bromopyridines **1b** and **1c** (analogous to **1a**). In addition, 2- and 4-bromopyridyl variants **5** and **10a/b** have been prepared, together with the series of simple substituted biaryl substrates **12a**−**c**. These latter substrates incorporate an *o*-bromo moiety but lack a heteroaryl component. The propensity of these biaryl substrates to undergo Pd migration and to generate crossover products in the Heck reaction has been examined (Schemes 2 and 3).

Scheme 3. Heck Reactions of 2- and 4-Bromopyridines and Other Biaryl Derivatives[a]



[a] Reagents and conditions: (a) $H_2C{=}CHCO_2Et$ (3 equiv), $Pd(OAc)_2$ (0.1 equiv), (*o*-Tol)$_3$P (0.2 equiv), NEt_3 (5 equiv), MeCN, 125 °C (sealed tube), 20 h.

It is clear that the crossover process, while the minor pathway, is nevertheless general for 4-aryl-3-bromopyridines (Scheme 2). Both **1b** and **1c** gave mixtures of retention and crossover Heck products **3b/c** and **4b/c**, respectively. However, the proportion of crossover product increases as the electron-withdrawing ability of the 4-aryl substitutent is enhanced: R = NO_2 > H > OMe. Accordingly, the 4-nitrophenyl derivative **1a** gave a 3:1 ratio (in favor of the retention Heck product **3a**), whereas **1b** and **1c** gave 7:1 and 10:1 ratios of **3b** and **4b**, and **3c** and **4c**, respectively.[8]

With 3-(4-nitrophenyl)-2-bromopyridine **5** (see Scheme 3), neither retention nor crossover products **6** or **7a** were observed, but the reduced 2-*alkyl* product **8** was obtained in 9% yield. Reduction to give 3-(4-nitrophenyl)pyridine (**9**) was the major pathway (29%), and a significant amount of **5** (59%) was recovered under the conditions used.[9] Importantly, the formation of both Heck adducts **6** and **7** has been achieved in a process that utilizes the crossover mechanism

(5) For a Heck reaction based on a simple biaryl, see: Díaz-Ortis, A.; Prieto, P.; Vazquez, E. *Synlett* **1997**, 269−270. By using **1a** as a substrate a variety of Heck conditions have been evaluated. Under Jeffrey conditions [**1a** (1 equiv), $Pd(OAc)_2$ (0.1 equiv), *n*-Bu_4NI (2 equiv), NaOAc (5.5 eqiv), ethyl acrylate (1.6 equiv), DMF, 100 °C, 4.5 days under N_2] we observed a small increase in crossover and obtained a 3:2 ratio of **3a** and **4a**. Under either aqueous or strictly anhydrous conditions, we observed slow reactions, and use of CsOAc or EtNi-Pr_2 under our conditions gave no crossover product.

(6) Ryabov, A. D. *Chem. Rev.* **1990**, *90*, 403−424. Dyker, G. *Chem. Ber*. **1997**, *130*, 1567−1578. Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1699−1712. Jia, C. G.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633−639. For insertion into aryl C−H via electrophilic substitution, see: Markies, B. A.; Wijkens, P.; Kooijman, H.; Spek, A. L.; Boersma, J.; van Koten G. *J. Chem. Soc., Chem. Commun*. **1992**, 1420−1423. For the effect of substituents on the rate of C−H, see: Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1992**, *425*, 151−154.

(7) de Meijere, A.; Bräse, S. *J. Organomet. Chem.* **1999**, *576*, 88−110. Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111−124. Cámpora, J.; López, J. A.; Palma, P.; Valerga, P.; Spillner, E.; Carmona, E. *Angew. Chem., Int. Ed.* **1999**, *38*, 147−151. Catellani, M.; Motti, E.; Paterlini, L.; Bocelli, G.; Righi, L. *J. Organomet. Chem.* **1999**, *580*, 191−196. Catellani, M.; Motti, E.; Paterlini, L. *J. Organomet. Chem.* **2000**, *594*, 240−244. Catellani, M.; Motti, E.; Baratta, S. *Org. Lett.* **2001**, *3*, 3611−3614. C−H Activation via *ortho*-palladation has been used to mediate the Heck reaction: Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586−1587.

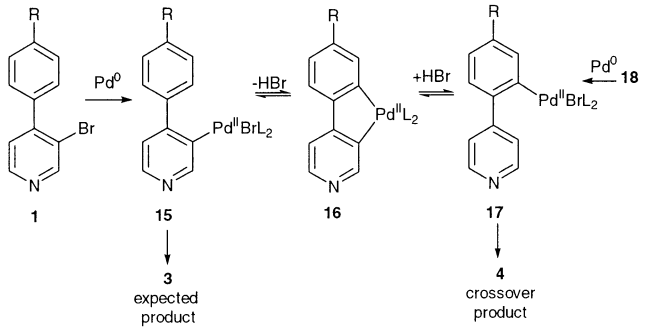
(8) Intervention of the crossover pathway is not simply a function of the alkene component, and reaction of **1a** with styrene led to the corresponding retention and crossover products in a 3:1 ratio.

(see below). The 4-bromopyridines **10a** and **10b** both gave the retention products **11a** and **11b**, but no crossover (to give **7a**/**7b**) was observed.

On the basis of the results shown in Schemes 2 and 3, the crossover pathway is favored for 3-bromopyridines rather than the 2- or 4-bromo isomers, although it should also be appreciated that Heck reactions of 2-bromopyridines do represent an unusual case.[10] A selection of simpler biaryls **12a**−**c** has also been examined under our standard Heck reaction conditions. No crossover was observed for Heck reactions involving **12a** and **12b**, and the retention products **13a** and **13b** were isolated in 73% and 86% yield, respectively. Starting with **12c**, we obtained an 8:1 mixture of retention and crossover products **13c** and **14c** in 65% and 8% yields, respectively.

In terms of the mechanism associated with the formation of crossover product, the initial oxidative addition of **1** to give **15** may be followed by C−H insertion leading (via a Pd(IV) species $R_2Pd(X)H$) to palladacycle **16** as a possible intermediate (Scheme 4). Both retention and crossover

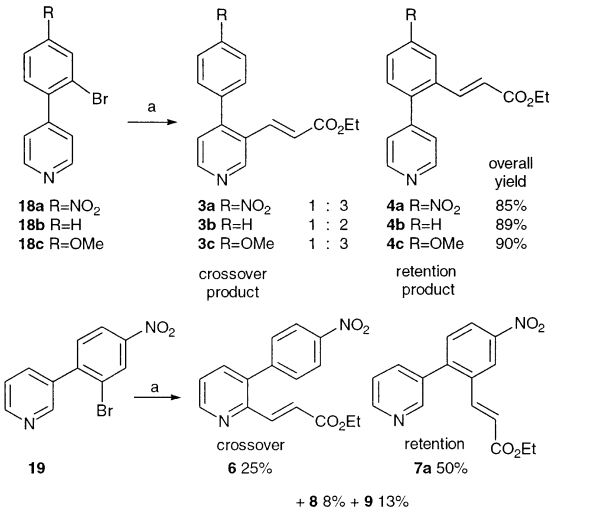
Scheme 4



products may arise from **16** serving as a vehicle for equilibration of **15** to the isomeric aryl Pd(II) intermediate **17**.[11]

Two further sets of experiments have been carried out to shed more light on the mechanism of palladium migration. First, we have examined the alternative crossover pathway *from* the 4-aryl residue *into* pyridyl moiety using the isomeric bromoarene **18**. This provides a complementary entry to, for example, palladacycle **16** (via **17**) and serves to probe the role of a common intermediate (Scheme 5).

Scheme 5. Heck Reactions Involving Crossover from the Phenyl Residue into the Pyridine Moiety[a]



[a] Reagents and conditions: (a) $H_2C{=}CHCO_2Et$ (3 equiv), $Pd(OAc)_2$ (0.1 equiv), $(o\text{-Tol})_3P$ (0.2 equiv), NEt_3 (5 equiv), MeCN, 125 °C (sealed tube), 20 h.

To this end, 3-bromo-4-(4-pyridyl)arenes **18a**−**c** (isomeric with **1a**−**c**) were subjected to the Heck reaction, and in each case **4a**−**c** (which here is the retention product) predominated. Nevertheless, the crossover process leading to **3a**−**c** was also observed, and in all three cases we obtained approximately the same proportions (2−3:1) of retention **4a**−**c** and crossover **3a**−**c** products *regardless* of the nature of the 4-substitutent on the phenyl ring. Again, it would appear that migration of Pd is favored when taking place into an electron-deficient pyridine ring, which is now a feature common to the three substrates **18a**−**c** shown in Scheme 5. We have carried out a similar experiment using **19**, the regioisomer of the 2-bromopyridine **5**. Here **7a**, which corresponds to the retention product, was the major adduct (50% yield), and we also isolated the crossover Heck product **6** in 25% yield. The 2-alkyl adduct **8** (8%) and reduced **9** (13%) were also characterized. It is worth noting that **6** was not observed starting from **5** (see Scheme 3), and the crossover mechanism provides access to a Heck product that is unavailable via the conventional process. This observation is also interesting from a mechanistic stance and will be studied further.

These results shown in Scheme 5 do not exclude participation of a palladacycle as a common intermediate arising from both **1** and **18**, and the possibility that palladacycle **16** provides a direct pathway to the Heck products should also be considered.[12] However, these data—the ratio of retention

(9) Heck reactions of 2-bromopyridines are reported to be problematic.[10] The formation of the 2-alkyl, as opposed to 2-alkenyl adducts, may results from direct protonation of the initial carbopalladation product (which is a Pd enolate) that may, in turn, be stabilized by the adjacent pyridyl nitrogen lone pair. We have also observed this pathway for Heck reactions of other 3-aryl-2-bromopyridines with ethyl acrylate (ref 1 and Moon, M.-T., unpublished results). These Heck processes are also inefficient with significant amounts of both starting material and the product of simple C−Br reduction being observed.

(10) Bozell, J. J.; Vogt, C. E.; Gozum, J. *J. Org. Chem.* **1991**, *56*, 2584−2587. Basu, B.; Frejd, T. *Acta Chem. Scand.* **1996**, *50*, 316−322.

(11) The formation of aryl halides via reductive elimination from Pd(II) has been reported recently: Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 1232−1233. The possibility of a Pd-mediated aryl halide exchange occurring between, e.g., **1** and **18**, though not detected, cannot be discounted at this time, and the lack of strongly donating ligands may argue against this.

(12) Jones has shown that palladacycles corresponding to **16**, which are generated by oxidative addition to biphenylene, do undergo Heck and other Pd-mediated reactions. These processes are best performed in the presence of a weak acid, such as *p*-cresol, to achieve protonolysis of the palladacycle to give species analogous to **15** and **17**. Satoh, T.; Jones, W. D. *Organometallics* **2001**, *20*, 2916−2919. Edelbach, B. L.; Lachicotte, R. J.; Jones, W. D. *J. Am. Chem. Soc.* **1998**, *120*, 2843−2853. See also: Catellani, M.; Cugini, F.; Bocelli, G. *J. Organomet. Chem.* **1999**, *584*, 63−67.

vs. crossover adducts as a function of the origin of the bromo moiety in one or other of the aryl rings—suggest that alternative and competing pathways are operating. These pathways may be direct Heck reaction of the initial oxidative addition product **15** (or **17** if starting from **18**) vs formation of palladacycle **16** and subsequent equilibration, with the rates of these competing processes being determined by the characteristics of the intermediates involved.

The results obtained with **18b** and **18c** (as compared to **1b** and **1c**) point toward the importance of an electrophilic C−H (pyridyl H(3)) favoring formation of a palladacycle intermediate via oxidative addition.[13,14] With **1a**/**18a**, both C−H bonds on each of the aryl units involved are electron-deficient and similarly activated. As a result, comparable ratios of retention to crossover products are obtained regardless of the original position of the halogen component. Substrate **19** provides H(2) and H(4) of the pyridyl unit as competing sites for crossover, and insertion into H(2) is favored.[15,16]

A corollary to an oxidative addition pathway for palladacycle formation would be the requirement for a nucleophilic palladium center in going from **15** (or **17**) to **16**. This may, in turn, explain why no crossover is observed for 4-bromopyridines **10a/b** where initial oxidative addition into the C−Br bond would lead to a 4-palladated pyridine intermediate. The nucleophilic characteristics of this intermediate would be expected to be lowered in comparison to the corresponding 3-palladated intermediates **15** (from **1**) or **17** (from **18**) thus disfavoring Pd migration.

We have also carried out Heck reactions of **1a**, limiting the amount of ethyl acrylate used. With 3 equiv of ethyl acrylate, a 3:1 ratio of retention **3a** to crossover **4a** is observed, but with 0.25 equiv of ethyl acrylate, equal amounts of **3a** and **4a** were obtained. This may be interpreted as favoring palladacycle formation (and equilibration) at the expense of the direct and intermolecular reaction of **15** with ethyl acrylate, thereby allowing the crossover pathway to compete more effectively.

In summary, the Heck reaction of *o*-bromo biaryls can lead to a transfer of reactivity from one aryl unit to the other, and an ability to control the extent of crossover would have important synthetic and mechanistic implications for this most famous of palladium-mediated reactions. The migration of Pd and formation of crossover products during Heck reactions of a range of other biaryl substrates has also been observed by Larock and co-workers.[17] Further work is, however, needed to define the synthetic potential of this migration process, and key to this will be gaining a more extensive understanding of the mechanisms involved.

Acknowledgment. We thank Dr. Guy C. Lloyd-Jones for his insight and advice, Professor Richard C. Larock for exchange of information prior to publication, and Merck Research Laboratories San Diego (studentship to M.-T.M.) and the Biomolecular Sciences Panel (BBSRC/EPSRC) for financial support. N.T. thanks the Thailand Research Fund for award of a Royal Golden Jubilee Scholarship through Professor Somsak Ruchirawat.

Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026426V

(13) González, J. J.; García, N.; Gómez-Lor, B.; Echavarren, A. M. *J. Org. Chem.* **1997**, *62*, 1286−1291. See also: Martín-Matute, B.; Mateo, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J* **2001**, *7*, 2341−2348

(14) Palladacycles have been implicated in Heck reactions, and a variety of mechanisms have been put forward to rationalize palladacycle formation, including electrophilic aromatic substitution and oxidative addition.[6] Given the correlation we have observed between the extent of crossover and more electron-deficient arenes, we feel that electrophilic substitution, while viable elsewhere, is less likely in these cases. Oxidative addition to a C−H bond is favored by electron-withdrawing substituents,[6,13] and this is more consistent with our observations.

(15) It is interesting to compare this result to recent annulation processes developed by Larock,[16] where Pd insertion into both H(2) and H(4) of a pyridine nucleus is observed, but in this case H(4) insertion is preferred.

(16) Larock, R. C.; Tian, Q. P. *J. Org. Chem.* **2001**, *66*, 7372−7379.

(17) Larock, R. C.; Campo, M. A. Submitted for publication. These authors observe different trends to those described here, and it is important to appreciate that other conditions for the Heck reaction have been used. The significance of these experimental factors will hopefully emerge in the future.