

Published on Web 12/15/2004

Palladium-Catalyzed Intramolecular Coupling between Aryl lodides and Allyl Moieties via Thermal and Microwave-Assisted Conditions

Mark Lautens,* Eiji Tayama, and Christelle Herse

Davenport Research Laboratories, Department of Chemistry, University of Toronto, Toronto, Ontario, Canada M5S 3H6

Received October 6, 2004; E-mail: mlautens@chem.utoronto.ca

5

6

 $Pd_2(dba)_3^b(5)$

 $Pd_2(dba)_3^b(5)$

Palladium-catalyzed cross-coupling reactions are valuable processes in organic synthesis. Many reactions have been developed and applied to natural products syntheses, including Heck, Stille, and Suzuki coupling processes and nucleophilic addition to π -allyl palladium intermediates.¹ Despite immense progress, coupling between an aryl halide and an allyl moiety has not been well developed. Until now, this coupling reaction has needed stoichiometric amounts or excess of metal reagents such as hexa-nbutylditin,² (tri-*n*-butylstannyl)diethylalane,³ zinc metal,⁴ or indium metal⁵ to generate an organometallic reagent *in situ* as a nucleophile, which reacts with a palladium(II) intermediate. More recently, cobalt-catalyzed cross-coupling reactions between an aryl halide and an allyl ester have been reported; however, these methods required a large excess of metal reagents^{6a} or use of electrochemical reactions.^{6b} Herein, we report on palladium-catalyzed intramolecular cross-coupling reactions between an aryl iodide and an allyl moiety, leading to 2,4-disubstituted 1,2,3,4-tetrahydroquinoline^{7,8} 2 under conventional thermal conditions as well as to various carbo- and heterocycles 6 under microwave irradiation. This is a rare example of a palladium-catalyzed direct cross-coupling reaction between an aryl halide and an allyl acetate or carbonate.9

Preparation of allyl acetates 1a-h was easily achieved in three steps by our recently reported method¹⁰ (direct vinylogous Mannichtype reaction) in excellent yields.

Following optimization studies, we determined that a mixture of **1a**, $Pd_2(dba)_3$ ·HCCl₃, tri-*o*-tolylphosphine, and *N*,*N*-dimethylbutylamine in CH₃CN-H₂O at reflux promotes coupling to yield the cyclization product **2a** in 76% yield as the *trans* isomer¹¹ (Table 1, entry 1).

Changing the palladium catalysts and phosphine ligands to Pd- $(OAc)_2$ - $(o-tolyl)_3P$ or PdCl₂[$(o-tolyl)_3P$]₂ gave similar results (entries 2 and 3). The use of Pd(PPh₃)₄ and Pd₂(dba)₃—PPh₃ resulted in almost no reaction (entries 4 and 5). Only $(o-tolyl)_3P$ gave good yields among the common phosphine ligands; for example, a bidentate ligand, 1,2-bis(diphenylphosphino)ethane (dppe), gave only 19% yield (entry 6). In the absence of H₂O, the reaction yield was ca. 30% with the formation of Pd-black and recovery of starting material. A tertiary alkylamine was used to regenerate the palladium(0) catalyst; *N*,*N*-dimethylbutylamine gave the best result among the common organic bases.¹² Inorganic bases resulted in very low yields. Cyclization of an aryl bromide or aryl triflate with allyl acetate did not give the product.

This palladium-catalyzed cyclization is general for a range of substrates (Table 2). At the R¹ position, 4-methylphenyl and 4-chlorophenyl (entries 2 and 3) gave the corresponding 2,4-disubstituted 1,2,3,4-tetrahydroquinolines in good yields, and 4-bro-mophenyl (entry 4) reacted selectively at the C–I bond. At the R² and R³ positions, dimethyl (entry 5), chloro (entry 6), and methoxy (entry 7) substituents can be introduced on the quinoline. Regardless of the electronic characteristic of the substrate, 2,4-disubstituted

 Table 1.
 Effects of Palladium Catalysts and Phosphine Ligands in Palladium-Catalyzed Intramolecular Cyclization



 a Isolated yields. b CHCl3 adduct was used. c 1a was recovered in 58% yield.

Ph₃P (22)

dppe (11)

2

19

Table 2. Intramolecular Palladium Catalyzed Cross-Coupling Reactions between an Aryl Iodide and Allyl Acetate



 $^a\,\rm CHCl_3$ adduct was used. b Isolated yields. $^c\,\rm Cis$ isomer was isolated in 2% yield.

1,2,3,4-tetrahydroquinolines 2e-g were obtained in approximately 80% yields. We further applied the intramolecular cross-coupling reaction to the construction of a 2-quinolinic acid ester. Indeed, **1h** cyclized to give the 1,2,3,4-tetrahydro-2-quinolinic acid ester **2h** in 84% yield (entry 8) with a trace of the *cis* isomer (2% yield).

We decided to study the effect of the ring size as well as the nature of the atom connecting the aryl and allyl moieties (X = O, N, and C, Table 3) on the reactivity of the cross-coupling process. Preparation of five-membered-ring precursors 3a-e was achieved in one step by the reaction of the corresponding iodinated derivatives¹³ with (Z)-BrCH₂CH=CHCH₂OCO₂Et.¹⁴ The six- and seven-membered ring precursors 4a-d were easily prepared in four

Table 3. Effects of Microwave Irradiation and Ring Size on the Formation of Various Carbo- and Heterocycles via Palladium-Catalyzed Intramolecular Cyclization



6 62 2 0 Η Naph f 46 7 3 0 Η Naph g 72 49 8 3 65 NTs Н Ph h 9 3 C(CO₂Et)₂ Η Ph i 73 10 1 CH_2O н Ph 45 j

^{*a*} CHCl₃ adduct was used. ^{*b*} Isolated yields. ^{*c*} Microwave-assisted conditions. ^{*d*} Conventional thermal conditions. Ph = phenyl, Naph = Naphthyl.

steps from the same iodinated aromatic derivatives.¹⁵ The benzylic oxygen-containing substrate **5** was prepared from the 2-iodobenzylic alcohol following a procedure similar to the one used for the preparation of five-membered-ring precursors.¹⁵

Oxygen-containing substrates 3a-c gave the cyclized products 6a-c in poor yields (Table 3, entries 1-3), probably due to the competitive formation of the π -allyl complex that generates the corresponding phenol. In an effort to improve these yields, we subjected the reaction to microwave irradiation, which is known to accelerate transition-metal-catalyzed homogeneous reactions.¹⁶ Carrying out the reaction in the microwave at 160 °C for 1 min was found to improve the yield in each case (entries 1-3) by as much as 41% for 6b (entry 2). According to this procedure, fivemembered rings 6a-e (entries 1-5) as well as six- and sevenmembered rings 6f-j (entries 6-10) were efficiently formed. Variation of the X group did not affect the cross-coupling process since nitrogen- and carbon-containing cycles, 6d,h and 6e,i, respectively (entries 4, 8 and 5, 9), were obtained in good yields. The cyclization also proceeded with a benzylic oxygen-containing substrate to form the six-membered heterocycle 6j (entry 10). We found that the yields increased as the ring size increased from five to seven (**6a**,**f**,**g**, entries 1, 6, and 7).

In conclusion, palladium-catalyzed intramolecular cross-coupling reactions between aryl iodides and allyl moieties were successfully demonstrated. We describe a new rapid synthetic approach to a variety of *trans*-2,4-disubstituted 1,2,3,4-tetrahydroquinolines **2** with excellent diastereoselectivities as well as to various five- to sevenmembered carbo- and heterocycles **6** *via* conventional thermal and microwave-assisted conditions. We are currently investigating the mechanism of the reaction but believe the role of the amine base is to reduce Pd(II) back to Pd(0) after each catalytic cycle. Acknowledgment. We thank Merck Frosst Canada, the NSERC IRC program, the Swiss National Fund, and the University of Toronto for support of this research program.

Supporting Information Available: Experimental procedures, spectroscopic characterization of substrates and products, and determination of configuration. This material is available free of charge via the Internet at http://pubs.acs.org.

References

- (1) (a) Heck, R. F. Palladium Reagents in Organic Synthesis; Academic Press: New York, 1985. (b) Trost, B. M.; Verhoeven, T. R. In Comprehensive Organometallic Chemistry; Wilkinson, G., Stone, F. G., Abel, E. W., Eds.; Pergamon: Oxford, 1982; Vol. 8, pp 799–938. (c) Farina, V. In Comprehensive Organometallic Chemistry II; Wilkinson, G., Stone, F. G., Abel, E. W., Eds.; Pergamon: Oxford, 1995; Vol. 12, pp 161–240. (d) Metal-Catalyzed Cross-coupling Reactions; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. (e) Hegedus, L. S. In Organometallics in Synthesis: A Manual; Schlosser, M., Ed.; Wiley: Chichester, U.K., 1994; Chapter 5. (f) Link, J. T. In Organic Reactions; Overman, L. E., Ed.; Wiley: New Jersey, 2002; Vol. 60, pp 157–534 and references therein.
- (2) Yokoyama, Y.; Ito, S.; Takahashi, Y.; Murakami, Y. Tetrahedron Lett. 1985, 26, 6457.
- (3) Trost, B. M.; Walchli, R. J. Am. Chem. Soc. 1987, 109, 3487.
- (4) Ikegami, R.; Koresawa, A.; Shibata, T.; Takagi, K. J. Org. Chem. 2003, 68, 2195.
- (5) Lee, P. H.; Sung, S.-Y.; Lee, K. Org. Lett. 2001, 3, 3201.
- (6) (a) Gomes, P.; Gosmini, C.; Périchon, J. Org. Lett. 2003, 5, 1043. (b) Gomes, P.; Gosmini, C.; Périchon, J. J. Org. Chem. 2003, 68, 1142 and references therein.
- (7) Review: Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* 1996, 52, 15031.
- (8) Recent examples of diastereoselective synthesis of substituted 1,2,3,4-tetrahydroquinolines: (a) Ori, M.; Toda, N.; Takumi, K.; Tago, K.; Kogen, H. Angew. Chem., Int. Ed. 2003, 42, 2540. (b) Fabio, R. D.; Alvaro, G.; Bertani, B.; Donati, D.; Giacobbe, S.; Marchioro, C.; Palma, C.; Lynn, S. M. J. Org. Chem. 2002, 67, 7319. (c) Stevenson, P. J.; Nieuwenhuyzen, M.; Osborne, D. Chem. Commun. 2002, 444. (d) Cheng, D.; Zhou, J.; Saiah, E.; Beaton, G. Org. Lett. 2002, 44411. (e) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. J. Am. Chem. Soc. 2001, 123, 6801. (f) Sundararajan, G.; Prabagaran, N.; Varghese, B. Org. Lett. 2001, 3, 1973. (g) Bunce, R. A.; Herron, D. M.; Johnson, L. B.; Kotturi, S. V. J. Org. Chem. 2001, 66, 2822.
- (9) Although this process is rare, several examples have been reported. For an intramolecular cross-coupling reaction between alkenyl bromide and allyl acetate, see: Steinig, A. G.; Meijere, A. *Eur. J. Org. Chem.* **1999**, 1333. For an intramolecular Heck cyclization, followed by a palladium*β*-alkoxy elimination see: Sinou, D.; Bedjeguelal, K. *Eur. J. Org. Chem.* **2000**, 4071 and references therein.
- (10) Lautens, M.; Tayama, E.; Nguyen, D. Org. Lett. 2004, 6, 345. Lautens, M.; Tayama, E.; Nguyen, D. Tetrahedron Lett. 2004, 45, 5131.
- (11) The configuration was determined by preparation of *trans-* and *cis-*4isopropyl-2-phenyl-1,2,3,4-tetrahydroquinoline, respectively. For details, see the Supporting Information.
- (12) By our experimental studies, we expect that the tertiary amine generates Pd(0) from Pd(II). Reaction of Pd(II) and tertiary amines: McCrindle, R.; Ferguson, G.; Arsenault, G. J.; McAlees, A. J. J. Chem. Soc., Chem. Commun. 1983, 571.
- (13) Prepared according to procedures described in the literature: (a) Adimurthy, S.; Ramachandraiah, G.; Ghosh, P. K.; Bedekar, A. V. *Tetrahedron Lett.* 2003, 44, 5099. (b) Cockerill, G. S.; Levett, P. C.; Whiting, D. A. J. Chem. Soc., Perkin Trans. 1 1995, 1103. (c) Zenner, J. M.; Larock, R. C. J. Org. Chem. 1999, 64, 7312.
- (14) (Z)-BrCH₂CH=CHCH₂OCO₂Et was prepared by monoprotecting the (Z)-1,4-butenediol with pyridine and ethylchloroformate, followed by OH/Br exchange according to the procedure described in the literature: Oppolzer, W.; Fürstner, A. *Helv. Chim. Acta* **1993**, *76*, 2329. See Supporting Information for details.
- (15) See Supporting Information for details.
- (16) (a) Larhed, M.; Moberg, C.; Hallberg, A. Acc. Chem. Res. 2002, 35, 717. (b) Walla, P.; Kappe, O. C. Chem. Commun. 2004, 564.

JA043898R