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# Xantphos as an Efficient Ligand for Palladium-Catalyzed Cross-Coupling Reactions of Aryl Bromides and Triflates with Allyl Acetates and Indium

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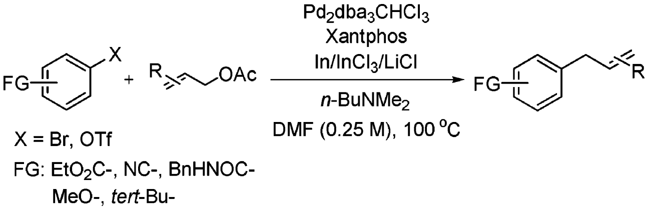
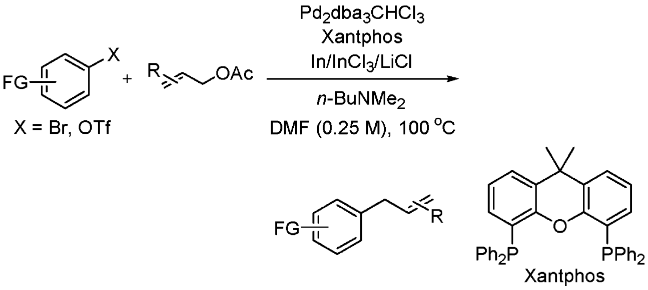


Xantphos was found to be an efficient ligand for palladium-catalyzed allyl cross-coupling reactions of aryl bromides and triflates with allylindium reagents generated in situ from allyl acetates and indium. These reactions occur in high yield with good functional group tolerance.

Palladium-catalyzed cross-coupling reactions are among the most useful synthetic methods for carbon−carbon bond formation.[1] Among them, allyl cross-coupling reactions with allylindium reagents have received much attention due not only to further applicability of the double bond in allyl groups but also their reactivity and selectivity, ease of preparation and handling, and operational simplicity.[2] Allylindium reagents are easily prepared from allyl halides and indium metal in polar solvents, including water.[3] Recently, new methods for the preparation of allylindiums via a reductive transmetalation of $\pi$-allylpalladium(II) complexes from allyl alcohols and its derivatives have been reported, and many successful examples of palladium and indium-mediated allylation have been described.[4] With regard to our ongoing research interest in transition metal-catalyzed cross-coupling reactions using a variety of organoindium reagents,[2,5] we demonstrated inter- and intramolecular Pd-catalyzed allyl cross-coupling reactions using aryl iodides and vinyl bromides and triflates via $\pi$-allylpalladium(II) complexes and their transmetalation with indium and indium trichloride in the presence of catalytic $Pd(PPh_3)_4$.[6] However, we failed unexpectedly to get the allyl cross-coupling products in the case of aryl bromides and triflates. Therefore, there is still a strong need for efficient catalytic systems for the cross-coupling reactions of aryl bromides and triflates with allylindiums derived from allyl acetates. Herein, we report Xantphos as an efficient ligand for palladium-catalyzed allyl cross-coupling reactions of aryl bromides and triflates with allylindium obtained from allyl acetates (Scheme 1).

**SCHEME 1. Allyl Cross-Coupling Reactions with Xantphos**



In a test reaction of trifluoromethanesulfonate (**1**) derived from 2-naphthol with allyl acetate (**2**), we found that cross-coupling reactions could be largely affected by ligands in the presence of Pd catalyst (Table 1). A variety of ligands with varied structural and electronic properties was scrutinized. Among the ligands tested, Xantphos gave the best results (entry 9). Generally, diphosphines have a marked influence on the reactivity and selectivity of a catalyst. Due to the effects of wide

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(1) (a) Trost, B. M.; Verhoeven, T. R. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G., Abel, E. W., Eds.; Pergamon: Oxford, UK, 1982; Vol. 8, pp 799−938. (b) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985. (c) Farina, V. In *Comprehensive Organometallic Chemistry II*; Wilkinson, G., Stone, F. G., Abel, E. W., Eds.; Pergamon: Oxford, UK, 1995; Vol. 12, pp 161−240. (d) Tsuji, J. *Palladium Reagents and Catalyst*; Wiley: Chichester, UK, 1995; Chapter 4. (e) *Metal-Catalyzed Cross-Couplings Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998. (f) Malleron, J.; Fiaud, J.; Legros, J. *Handbook of Palladium-Catalyzed Organic Reactions*; Academic Press: San Diego, CA, 1997. (g) Negishi, E. *Organopalladium Chemistry*; Wiley-Interscience: New York, 2002; Vols. I and II.

(2) (a) Lee, P. H.; Sung, S.-Y.; Lee, K. *Org. Lett.* **2001**, *3*, 3201−3204. (b) Lee, K.; Lee, J.; Lee, P. H. *J. Org. Chem.* **2002**, *67*, 8265−8268.

(3) (a) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023−2035. (b) Cintas, P. *Synlett* **1995**, 1087−1096. (c) Li, C.-J. *Tetrahedron* **1996**, *52*, 5643−5668. (d) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997. (e) Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149−11176. (f) Babu, G.; Perumal, P. T. *Aldrichim. Acta* **2000**, *33*, 16−22. (g) Chauhan, K. K.; Frost, C. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3015−3020. (h) Pae, A. N.; Cho, Y. S. *Curr. Org. Chem.* **2002**, *6*, 715−737. (i) Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633−655. (j) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095.

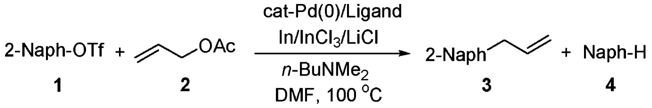
(4) (a) Araki, S.; Kamei, T.; Hirashita, T.; Yamamura, H.; Kawai, M. *Org. Lett.* **2000**, *2*, 847−849. (b) Jang, T.-S.; Keum, G.; Kang, S. B.; Chung, B. Y.; Kim, Y. *Synthesis* **2003**, 775−779. (c) Miyabe, H.; Yamaoka, Y.; Naito, T.; Takemoto, Y. *J. Org. Chem.* **2003**, *68*, 6745−6751. (d) Miyabe, H.; Yamaoka, Y.; Naito, T.; Takemoto, Y. *J. Org. Chem.* **2004**, *69*, 1415−1418. (e) Hirashita, T.; Kambe, S.; Tsuji, H.; Omori, H.; Araki, S. *J. Org. Chem.* **2004**, *69*, 5054−5059. (f) Nguyen, V. C.; Kim, Y.-T.; Yu, Y.-K.; Kang, H.-Y. *Bull. Korean Chem. Soc.* **2005**, *26*, 711−712.

(5) (a) Lee, K.; Seomoon, D.; Lee, P. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3901−3903. (b) Lee, P. H.; Sung, S.-Y.; Lee, K.; Chang, S. *Synlett* **2002**, 146−148. (c) Lee, P. H.; Lee, S. W.; Lee, K. *Org. Lett.* **2003**, *5*, 1103−1106. (d) Lee, P. H.; Lee, S. W.; Seomoon, D, *Org. Lett.* **2003**, *5*, 4963−4966. (e) Lee, S. W.; Lee, K.; Seomoon, D.; Kim, S.; Kim, H.; Kim, H.; Shim, E.; Lee, M.; Lee, S.; Kim, M.; Lee, P. H. *J. Org. Chem.* **2004**, *69*, 4852−4855. (f) Lee, P. H.; Lee, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3253−3256. (g) Lee, P. H.; Seomoon, D.; Lee, K. *Org. Lett.* **2005**, *7*, 343−345. (h) Lee, P. H.; Shim, E.; Lee, K.; Seomoon, D.; Kim, S. *Bull. Korean Chem. Soc.* **2005**, *26*, 157−160. (i) Lee, P. H.; Lee, K.; Kang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1139−1146.

(6) (a) Lee, P. H.; Seomoon, D.; Lee, K.; Kim, S.; Kim. H.; Kim, H.; Shim, E.; Lee, M.; Lee, S.; Kim, M.; Sridhar, M. *Adv. Synth. Catal.* **2004**, *346*, 1641−1645. (b) Seomoon, D.; Lee, K.; Kim, H.; Lee, P. H. *Chem. Eur. J.* **2007**, *13*, 5197−5206.

10.1021/jo702279t CCC: $40.75

**TABLE 1. Ligand Optimization in Pd-Catalyzed Allyl Cross-Coupling Reactions of 2-Naph-OTf with Allyl Acetates**[a]



| entry | catalyst | ligand | time (h) | yield (%) | | |
|---|---|---|---|---|---|---|
| | | | | $\mathbf{3}^{b}$ | $\mathbf{4}^{c}$ | $\mathbf{1}^{c}$ |
| 1 | 10% $Pd(PPh_3)_4$ | | 5 | 35 | 0 | 41 |
| 2 | 5% $Pd_2dba_3CHCl_3$ | 40% $PPh_3$ | 5 | 35 | 0 | 43 |
| 3 | 5% $Pd_2dba_3CHCl_3$ | 40% P(2-furyl)$_3$ | 5 | 30 | 0 | 55 |
| 4 | 5% $Pd_2dba_3CHCl_3$ | 40% $PCy_3$ | 5 | $5^{c}$ | 0 | 81 |
| 5 | 5% $Pd_2dba_3CHCl_3$ | 20% dppe | 20 | 0 | 79 | 20 |
| 6 | 5% $Pd_2dba_3CHCl_3$ | 20% dppf | 3 | 64 $(74)^{c}$ | 26 | 0 |
| 7 | 5% $Pd_2dba_3CHCl_3$ | 40% P(DMOP)$_3$ | 20 | 0 | 0 | 96 |
| 8 | 5% $Pd_2dba_3CHCl_3$ | 40% P(*o*-Tolyl)$_3$ | 20 | 0 | 0 | 97 |
| **9** | **5% $\mathbf{Pd_2dba_3CHCl_3}$** | **20% Xantphos** | **2** | **84 $\mathbf{(97)}^{c}$** | **3** | **0** |
| 10 | 2.5% $Pd_2dba_3CHCl_3$ | 10% Xantphos | 20 | 43 | 0 | 39 |
| 11 | 5% $Pd_2dba_3CHCl_3$ | 20% [1,2-($Ph_2P$)-Benzene] | 20 | 0 | 0 | 97 |
| 12 | 5% $Pd_2dba_3CHCl_3$ | 20% dppp | 20 | $10^{c}$ | 68 | 20 |
| 13 | 5% $Pd_2dba_3CHCl_3$ | 40% P(*t*-Bu)$_3$ | 20 | $2^{c}$ | 4 | 94 |
| 14 | 5% $Pd_2dba_3CHCl_3$ | 20% DPEphos | 20 | 32 | 0 | 67 |
| 15 | 10% $PdBr_2$ | 20% Xantphos | 2 | 17 | 3 | 73 |
| 16 | 5% $(\pi\text{-allyl})_2Pd_2Cl_2$ | 20% Xantphos | 2 | 15 | 3 | 77 |

[a] Naph: naphthyl. Reactions performed with **1** (0.5 mmol) in the presence of cat-Pd(0), In (1.0 mmol), $InCl_3$ (0.25 mmol), LiCl (1.5 mmol), and *n*-$BuNMe_2$ (1.0 mmol) unless otherwise noted. [b] Isolated yield. [c] GC yields based on 2-methoxynaphthalene as an internal standard.

bite angle, several groups have reported that palladium-catalyzed reactions with Xantphos, a ligand developed by van Leeuwen, could be effective.[7] However, P(2-Furyl)$_3$, $PCy_3$, dppe, dppp, dppf, P(DMOP)$_3$, P(*o*-Tolyl)$_3$, P(*t*-Bu)$_3$, DPEphos, and [1,2-($Ph_2P$)Benzene] produced the desired product in low yields. $Pd_2dba_3CHCl_3$ was the Pd source of choice for reactions. Of the catalytic systems examined, the best results were obtained with 5 mol % of $Pd_2dba_3CHCl_3$, 20 mol % of Xantphos, In (2 equiv), $InCl_3$ (0.5 equiv), LiCl (3 equiv), and *N*,*N*-dimethyl-*n*-butylamine (2 equiv) in DMF at 100 °C under a nitrogen atmosphere, producing product **3** in quantitative GC yield (97%) (entry 9). The use of 2.5 mol % of $Pd_2dba_3CHCl_3$ and 10 mol % of Xantphos gave a lower yield (43%) as well as longer reaction times (20 h, entry 10).

To demonstrate the efficiency and scope of the present method, we applied the optimum condition to a variety of allyl acetate and aryl triflates and bromides. The results are summarized in Table 2. For allyl acetates as coupling partners, the presence of methyl group at the α, $\beta$, and $\gamma$ positions had an effect on both reaction rates and product yields. Allyl acetate (**2**), 2-methylallyl acetate (**21**), but-1-en-3-yl acetate (**22**), and crotyl acetate (**23**) produced the corresponding allyl cross-coupling products in good yields. Reactions of triflate (**1**) and 2-bromonaphthalene (**5**) with allyl acetate (**2**) gave 2-allylnaphthalene (**3**) in 84% and 81% yields, respectively, under the optimized conditions with Xantphos (entries 1 and 3). However, use of $Pd(PPh_3)_4$ afforded **3** in 35% and 33% yields (entries 2 and 4). Treatment of **1** and **5** with **21** gave rise to the allyl cross-coupling product in 74% and 67% yields (entries 5 and 6). Exposure of **1** to the allylindium derived from **22** provided the desired products **25** and **26** in 52% yield, but the product **26** resulting from $\gamma$-attack predominated ($\alpha:\gamma = 1:3.5$) (entry 7). Also, reaction of **1** with **23** furnished the allyl cross-coupling product in 53% yield and the regioselectivity (1:4) of this reaction was similar to that of **22** (entry 8). Treatment of triflate (**6**) derived from 1-naphthol with **2** gave 1-allylnaphthalene (**27**) in 81% yield under the optimized conditions with Xantphos (entry 9), while use of $Pd(PPh_3)_4$ produced **27** in 26% yield and starting material was recovered in 57% yield (entry 10). Aryl triflates and bromides bearing ethoxycarbonyl (entries 11−15), cyano (entries 16 and 17), and *N*-benzylaminocarbonyl (entry 18) substituents as electron-withdrawing groups and methoxy (entries 19−21) and *tert*-butyl (entry 22) substituents as electron-donating groups smoothly reacted with allyl acetate under the optimum conditions to give the corresponding allyl-substituted aromatic compounds in good yields. In the case of aryl triflates and bromides bearing an ethoxycarbonyl group, both the yield and the selectivity are almost independent of the electronic and steric effect (entries 11−15). Heteroatoms turned out to be compatible with the employed reaction conditions. Reaction of 3-bromoquinoline (**19**) and 4-bromoisoquinoline (**20**) with allylindium in the presence of $Pd_2dba_3CHCl_3$/Xantphos produced the correspondding allyl cross-coupling products in 76% and 84% yields, respectively (entries 24 and 25). In contrast, use of $Pd(PPh_3)_4$ gave low yields of the allyl cross-coupling products for aryl triflates and bromides (entries 2, 4, 10, 23, and 26), indicating the Pd-Xantphos catalytic system is more efficient than $Pd(PPh_3)_4$.

In conclusion, we have demonstrated that Xantphos was an efficient ligand for palladium-catalyzed allyl cross-coupling reactions of aryl bromides and triflates with allylindium reagents generated in situ from allyl acetates and indium. These reactions occur in high yield with good functional group tolerance. The present method complements the existing synthetic methods because the previous methods were only successful for aryl iodides and vinyl bromides and triflates.

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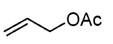
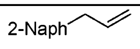
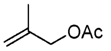
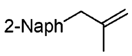
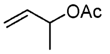
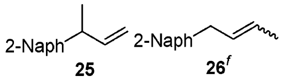
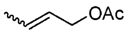
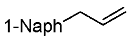
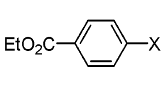
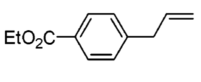
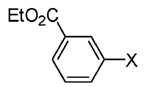
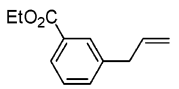
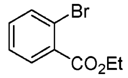
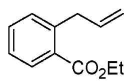
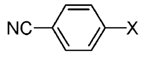
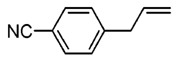
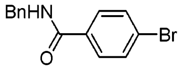
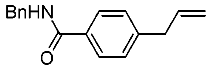
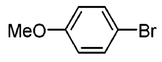
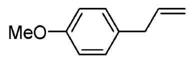
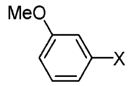
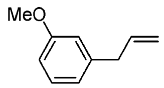
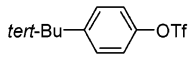
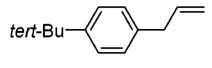
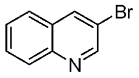
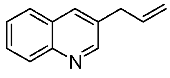
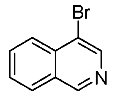
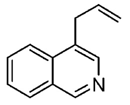
(7) (a) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995,** *14*, 3081−3089. (b) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741−2769. (c) Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Acc. Chem. Res.* **2001**, *34*, 895−904.

**TABLE 2. Palladium-Catalyzed Allyl Cross-Coupling Reactions of Aryl Bromides and Triflates with Allyl Acetates Using Xantphos**[a]

| entry | starting material | allyl acetate | product | isolated yield (%) |
|---|---|---|---|---|
| 1 | 2-Naph-OTf **1** |  **2** |  **3** | 84 |
| 2 | **1** | **2** | **3** | 35[b](43) |
| 3 | 2-Naph-Br **5** | **2** | **3** | 81 |
| 4 | **5** | **2** | **3** | 33[b](50) |
| 5 | **1** |  **21** |  **24** | 74(11)[c] |
| 6 | **5** | | | 67(16)[c] |
| 7 | **1** |  **22** |  **25** **26**[f] | 52(1:3.5)[d], 15[c], 20[e] |
| 8 | **1** |  **23**[g] | | 53(1:4)[d], 16[c], 17[e] |
| 9 | 1-Naph-OTf **6** | **2** |  **27** | 81 |
| 10 | **6** | **2** | | 26[b](57) |
| 11 |  **7** (X=OTf) | **2** |  **28** | 80 |
| 12 | **8** (X=Br) | **2** | | 88 |
| 13 |  **9** (X=OTf) | **2** |  **29** | 76 |
| 14 | **10** (X=Br) | **2** | | 76 |
| 15 |  **11** | **2** |  **30** | 70(19)[e] |
| 16 |  **12** (X=OTf) | **2** |  **31** | 78 |
| 17 | **13** (X=Br) | **2** | | 82 |
| 18 |  **14** | **2** |  **32** | 74 |
| 19 |  **15** | **2** |  **33** | 67 |
| 20 |  **16** (X=OTf) | **2** |  **34** | 74 |
| 21 | **17** (X=Br) | **2** | | 78 |
| 22 |  **18** | **2** |  **35** | 61(21)[e] |
| 23 | **18** | **2** | | trace[b](83) |
| 24 |  **19** | **2** |  **36** | 76 |
| 25 |  **20** | **2** |  **37** | 84 |
| 26 | **20** | **2** | | 35[b](47)[e] |

[a] Naph: naphthyl. Reactions performed with electrophiles (0.5 mmol) in the presence of $Pd_2dba_3CHCl_3$ (0.025 mmol), Xantphos (0.10 mmol), In (1.0 mmol), $InCl_3$ (0.25 mmol), LiCl (1.5 mmol), and *n*-$BuNMe_2$ (1.0 mmol) in DMF (2 mL) at 100 °C for 2 h in substrates bearing electron-withdrawing groups and for 6 h in substrates bearing electron-donating groups unless otherwise noted. Numbers in parentheses are recovered yields of starting material. [b] Reactions performed in the presence of $Pd(PPh_3)_4$ (0.05 mmol) for 5−16 h. [c] Yield of homocoupling product. [d] Ratio of **25** to **26**. [e] GC yields of reduction product of halide based on 2-methoxynaphthalene as an internal standard. [f] Diastereomeric ratio of **26**: cis:trans = 1:1. [g] Diastereomeric ratio of **23**: cis:trans = 1:15.

## Experimental Section

**Typical Experimental Procedure.** To a suspension of indium (114.8 mg, 1.0 mmol), indium trichloride (55.3 mg, 0.25 mmol), lithium chloride (63.5 mg, 1.5 mmol), $Pd_2dba_3CHCl_3$ (5 mol%, 10.3 mg), and Xantphos (20 mol%, 57.9 mg) in DMF (1 mL) was added *N*,*N*-dimethylbutylamine (101.2 mg, 2.0 mmol) and allyl acetate (250.3 mg, 2.5 mmol) at 35 °C under a nitrogen atmosphere. After 30 min, trifluoromethanesulfonic acid naphthalen-2-yl ester (138.1 mg, 0.5 mmol) in DMF (1 mL) was added and the mixture was stirred at 100 °C for 2 h. The reaction mixture was quenched with $NaHCO_3$ (saturated aqueous). The aqueous layer was extracted with ether (3 × 20 mL) and the combined organic layers were washed with water and brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, using *n*-hexane to give 2-allylnaphthalene (**3**) (70.7 mg, 84%). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.86−7.77 (m, 3H), 7.63 (s, 1H), 7.49−7.40 (m, 2H), 7.33 (dd, $J$ = 8.46, 1.42 Hz, 1H), 6.05 (ddt, $J$ = 16.98, 10.09, 6.77 Hz, 1H), 5.16−5.11 (m, 2H), 3.55 (d, $J = 6.66$ Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 137.55, 137.32, 133.65, 132.12, 128.04, 127.62, 127.48, 127.39, 126.66, 125.93, 125.27, 40.36; IR (film) 3003, 2916, 1684, 1606, 1414, 1358 cm$^{-1}$; HRMS (EI) calcd for $C_{13}H_{12}$ $M^+$ 168.0939, found 168.0934.

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**Supporting Information Available:** Spectral data of all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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