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Catalytic Solvent-Free Arsination: First Catalytic Application of Pd–Ar/As–Ph Exchange in the Syntheses of Functionalized Aryl Arsines

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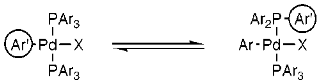
Environmental concerns have brought more awareness into the development of green chemistry.[1] The transformation of an undesirable side reaction into a synthetically versatile method and the continuous discovery of solventless reaction system without the use and disposal of organic solvents constitute two important areas in green chemistry.

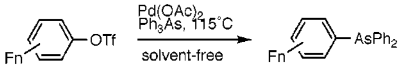


(1)

The undesirable aryl/aryl exchanges between the palladium-bound Ar′ with phosphorus bound Ar (eq 1) are frequently observed in the palladium-catalyzed cross-coupling reactions leading to the formation of scrambled side products.[2] The stoichiometric mechanistic studies of these Pd–Ar/P–Ph exchange reactions have been reported by Cheng,[3] Novak,[4] Grushin,[5] and Norton.[6] Recently, these undesirable Ar/Ar′ exchange reactions have been utilized in the synthesis of substituted tertiary phosphines in a catalytic manner.[7]

Arsines, the arsenic analogue of phosphines, have been reported to be ligands superior to phosphines in a number of transition metal-catalyzed organic reactions both in rate acceleration and product-yield enhancement. Examples include Stille,[8] Heck,[9] Negishi,[10] Suzuki–Miyaura coupling,[11] epoxidation,[12] cyclization of an allylic enyne,[13] hydroformylation,[14] and carbonylation.[15] The extended application of the transition metal-catalyzed aryl–aryl exchange reactions from phosphorus to arsenic would provide a facile synthesis of functionalized arisnes. Such a method would be a great improvement to the existing methods, which are difficult and limited in scope.[16]

The solvent-free reaction conditions for arsination would add a further attractive feature to the synthesis. The solventless/solid-state reactions bear many advantages such as reducing pollution, low cost, and simplicity in process and handling.[17] However, most of the reported reactions required stoichiometric amount of catalysts (nonsupported) for the organic transformation.[18,19] Herein, we report the first catalytic solvent-free arsination for the synthesis of functionalized aryl arsines using triphenylarsine as the reagent by the first catalytic[20] application of Pd–Ar/As–Ph exchange reactions (eq 2).



(2)

Fn = COOMe, COMe, CHO, CN, NO_2, OMe

Though no arsination occurred for aryl bromides, the more reactive aryl triflates were found to undergo catalytic arsinations in solventless conditions. The methyl ester phenyl triflate **1a** was transformed to the corresponding arsine **1b** in 51% isolated yield in the presence of 10 mol % of $Pd(OAc)_2$ and 2.3 equiv of triphenylarsine under the solvent-free conditions (Table 1, entry 1). Interestingly, the reaction exhibited a similar rate and yield of reaction when compared with that carried out in DMF (Table 1, entry 1). The redox-sensitive aryl triflates **2a** and **3a** which bear ketone and aldehyde groups, respectively, were transformed to arsines **2b** and **3b** directly without complementary protection and deprotection steps (Table 1, entries 2 and 3). The electron-withdrawing and reducible nitrophenyl triflate **4a** was found to be compatible in these arsination conditions to give the corresponding arsine **4b** (Table 1, entry 4).[21] No significant electronic effect was observed in this arsination since both the electron-withdrawing cyano group and the electron-donating methoxy group showed similar rates and yields of reaction (Table 1, entries 5 and 6). The meta-substituted formylphenyl triflate **7a** was transformed to the 3-(diphenylarsino)benzaldehyde **(7b)** in similar yield and reaction time when compared with that of para-analogue **3b** (Table 1, entries 3 and 7). Moreover, the sterically hindered ortho-substituted triflates **8a** and **9a** were converted to ortho-substituted arsines **8b** and **9b** in comparable rate of reaction as their para-substituted triflates (Table 1, entries 5,6 and 8,9).[22] The triflate alternative, nonaflate **10a**,[23] was converted to the corre-

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[1] (a) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 2000. (b) Janssen, F. J. J. G.; van Santen, R. A. *Environmental Catalysis*; Imperial College Press: London, 1999.

[2] For exchanged product formation in Stille coupling, see: (a) Segelstein, B. E.; Butler, T. W.; Chenard, B. L. *J. Org. Chem.* **1995**, *60*, 12–13. In Suzuki coupling, see: (b) O'Keefe, D. F.; Dannock, M. C.; Marcuccio, S. M. *Tetrahedron Lett.* **1992**, *33*, 6679–6680. In Heck coupling, see: (c) Hunt, A. R.; Stewart, S. K.; Whiting, A. *Tetrahedron Lett.* **1993**, *34*, 3599–3602. In C–S coupling, see: (d) Barañano, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 2937–2938.

[3] Kong, K.-C.; Cheng, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6313–6315.

[4] Goodson, F. E.; Wallow, T. I.; Novak, B. M. *J. Am. Chem. Soc.* **1997**, *119*, 12441–12453.

[5] Grushin, V. V. *Organometallics* **2000**, *19*, 1888–1900.

[6] For Me/Ar exchange, see: Morita, D. K.; Stille, J. K.; Norton, J. R. *J. Am. Chem. Soc.* **1995**, *117*, 8576–8581.

[7] (a) Kwong, F. Y.; Chan, K. S. *Organometallics* **2000**, *19*, 2058–2060. (b) Kwong, F. Y.; Chan, K. S. *Chem. Commun.* **2000**, 1069–1070.

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[9] (a) Kojima, A.; Boden, C. D. J.; Shibasaki, M. *Tetrahedron Lett.* **1997**, *38*, 3459–3460. For Heck reactions, see: (b) Namyslo, J. C.; Kaufmann, D. E. *Synlett* **1999**, 114–116.

[10] (a) Rossi, R.; Bellina, F.; Carpita, A.; Mazzarella, F. *Tetrahedron* **1996**, *52*, 4095–4110.

[11] (a) Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014–11015.

[12] van Vliet, M. C. A.; Arends, I. W. C. E.; Sheldon, R. A. *Tetrahedron Lett.* **1999**, *40*, 5239–5242.

[13] Trost, B. M.; Edstrom, E. D.; Carter-Petillo, M. B. *J. Org. Chem.* **1989**, *54*, 4489–4490.

[14] van der Veen, L. A.; Keeven, P. K.; Kamer, P. C.; van Leeuwen, P. W. N. M. *Chem. Commun.* **2000**, 333–334.

[15] Ceccarelli, S.; Piarulli, U.; Gennari, C. *J. Org. Chem.* **2000**, *65*, 6254–6256.

[16] There are no direct synthetic methodologies for functional group incorporation to arsine ligands. A synthesis of arsine sulfonic acid from aryl fluoride has been pointed out by a reviewer (Wallow, T. I.; Goodson, F. E.; Novak, B. M. *Organometallics* **1996**, *15*, 3708–3716). The traditional arsination involved the reaction of organolithium/magnesium reagents with Ph_2AsCl (pyrophoric and not commercially available) or the reaction of aryl halides with Ph_2AsLi/Na (prepared in situ from Ph_3As with Li or Na in liquid NH_3), see: (a) Aguiar, A. M.; Archibald, T. G. *J. Org. Chem.* **1967**, *32*, 2627–2628. (b) Ellermann, J.; Dorn, K. *Chem. Ber.* **1967**, *100*, 1230–1234. (c) Reference 9b. To our best knowledge, only the work by Shibasaki on the catalyzed arsination using Ni(0) and Ph_2AsH was reported (pyrophoric and not commercially available), see: ref 9a.

[17] (a) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025–1074. (b) Knochel, P., Ed. *Modern Solvents in Organic Synthesis*; Springer: New York, 1999; pp 153–207.

[18] Toda, F.; Tanaka, K.; Iwata, S. *J. Org. Chem.* **1989**, *54*, 3007–3009.

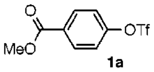
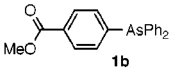
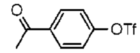
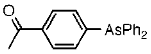
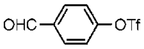
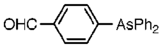
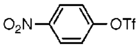
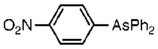
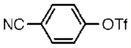
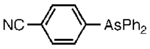
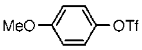
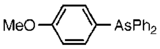
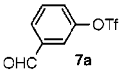
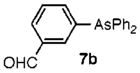
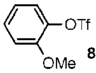
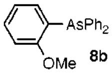
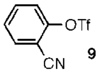
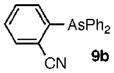
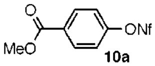
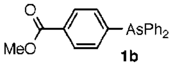
[19] For recent catalytic solventless reaction (but which required an Al_2O_3-supported catalyst), see: Kabalka, G. W.; Pagni, R. M.; Hair, C. M. *Org. Lett.* **1999**, *1*, 1423–1425.

[20] For stoichiometric aryl/aryl exchange reactions of Ph_3P, see: refs 3–6. For reported side reaction and stoichiometric mechanistic study of aryl–aryl exchange reactions of Ph_3As with Pd complexes: see refs 2a and 6, respectively.

[21] It should be noted that initial experiments showed the nitro group was reduced to an amino group in the presence of $Ph_3P/Pd(OAc)_2$ in the catalytic phosphination.

10.1021/ja005875s CCC: $20.00

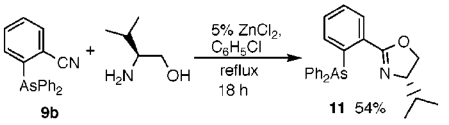
Table 1. Palladium-Catalyzed Solvent-Free Arsination of Functionalized Aryl Triflates Using Triphenylarsine[a]

Entry	Substrates	Products	Time/d	Yield/%[b]
1	 **1a**	 **1b**	5 (4.5)[c]	51 (50)[c]
2	 **2a**	 **2b**	4	47
3	 **3a**	 **3b**	5	50
4	 **4a**	 **4b**	5	40
5	 **5a**	 **5b**	5	51
6	 **6a**	 **6b**	4.5	50
7	 **7a**	 **7b**	5	48
8	 **8a**	 **8b**	5	49
9	 **9a**	 **9b**	5	41
10	 **10a**	 **1b**	4	50

[a] Reaction conditions: 10 mol % of $Pd(OAc)_2$, 2.3 equiv of Ph_3As and aryl triflate were heated to 115−120 °C under N_2. [b] Isolated yields. [c] Results of arsination in DMF in parentheses.

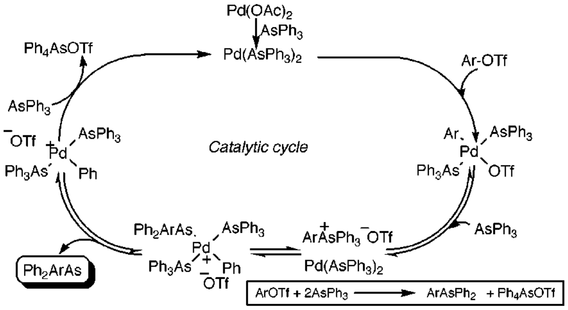
sponding arsine **1b** slightly faster than the triflate **1a**[24] (Table 1, entries 1 and 10).

The *o*-cyano arsine **9b** was found to be a versatile precursor for the synthesis of a new type of chiral *As,N* ligand **11** for asymmetric catalysis[25] (eq 3). Arsine **9b** was reacted with (*S*)-2-amino-3-methyl-1-butanol in the presence of $ZnCl_2$ catalyst in chlorobenzene to afford the new type of optically active *As,N* ligand **11** in 54% yield (eq 3).[26]

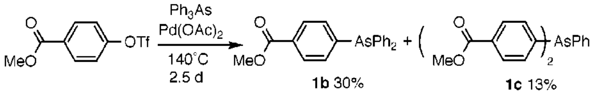


(3)

Scheme 1. Suggested Mechanism for Pd-Catalyzed Arsination



The double aryl/aryl exchange was observed when the reaction was heated at elevated temperature (eq 4). The diaryl arsine **1c** was isolated in 13% yield together with **1b** when the reaction mixture was heated at 140 °C for 2.5 days. However, only monosubstituted arsine **1b** was detected by GC−MS when the reaction was heated at 115 °C.



(4)

Scheme 1 illustrates a plausible mechanism. $Pd(OAc)_2$ is likely in situ reduced to Pd(0) by triphenylarsine,[27] which subsequently undergoes oxidative addition with an aryl triflate to yield the aryl−Pd(II) species (Scheme 1). The Pd-bound aryl ring then undergoes reductive elimination with $AsPh_3$ to afford the aryltriphenylarsonium salt and Pd(0) species, which was supported by the observed brown solid formation during the course of the reaction (Scheme 1).[28] This arsonium salt intermediate was also isolated by quenching the reaction and was confirmed by mass spectrometry (see Supporting Information). The substituted arsonium salt then undergoes As−C oxidative addition to yield the desired functionalized arsine (Scheme 1). The Pd(0) complex is regenerated by the reductive elimination of another equivalent of triphenylarsine with palladium-bound phenyl group to form the arsonium triflate coproduct in 70% isolated yield.

In summary, the first catalytic solvent-free Pd−Ar/As−Ph exchange was reported. The functional group compatible palladium-catalyzed solventless arsination uses commercially available, air-stable, and inexpensive triphenylarsine as the arsinating reagent.[29] It was found that the solvent-free reactions have a rate of reaction comparable to that in solution. Moreover, **9b** was found to be a versatile precursor for the synthesis of a new type of chiral *As,N* ligand. Further studies are in progress.

Acknowledgment. We thank the Research Grants Council of Hong Kong for financial support (ERB003).

Supporting Information Available: Experimental details, spectral data of all new compounds, **1b, 1c, 2b**−**9b**, and **11** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[22] (a) Novak et al. reported that ortho-substituted aryl halides retarded the rate of aryl−aryl exchange. see: ref 4. (b) Migita et al. reported similar results which concerned the ortho-substituted aryl halides retarding the rate of reaction and giving quite low yield of phosphonium salts. Migita, T.; Nagai, T.; Kiuchi, K.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2869−2870.

[23] Nonaflate = ^{n}Nonafluorobutanesulfonate. (a) Niederprüm, H.; Voss, P.; Beyl, V. *Liebigs. Ann. Chem.* **1973**, 20−32. (b) For a review, see: Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85−126.

[24] Knochel et al. reported nonaflate has a 1.4 times faster rate of reaction compared with that of triflate in zinc-mediated coupling. Rottländer, M.; Knochel, P. *J. Org. Chem.* **1998**, *63*, 203−208.

[25] For a recent review concerning similar chiral *P,N* derivatives, see: Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336−345.

[26] Bolm, C.; Weickhardt, K.; Zehnder, M.; Ranff, T. *Chem. Ber.* **1991**, *124*, 1173−1180.

[27] Jutand et al. reported the evidences concerning the reduction of Pd(II) to Pd(0) by triphenylphosphine, but no direct evidence for Pd(II)/Pd(0) reduction by triphenylarsine. Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992**, *11*, 3009−3013.

[28] Grushin, Novak, and Cheng proposed the Pd−Ar/P−Ph exchange through a phosphonium salt intermediate, see: refs 3−5.

[29] Traditional arsine synthesis involved the reaction of aryl Grignard reagents with Ph_2AsCl, see: ref 16. To our knowledge, no direct synthetic, functional group tolerable arsination of aryl triflates was reported.