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Synthesis of 2-Indolylphosphines by Palladium-Catalyzed Annulation of 1-Alkynylphosphine Sulfides with 2-Iodoanilines

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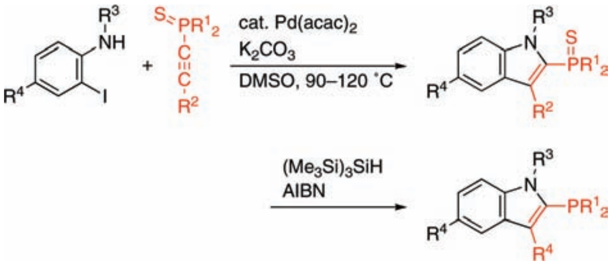
ABSTRACT



Palladium-catalyzed annulation of 1-alkynylphosphine sulfides with 2-iodoanilines followed by desulfidation affords 3-substituted 2-indolylphosphines. This annulation/desulfidation sequential protocol offers a conceptually new approach to bulky heteroarylphosphines.

In modern organic synthesis, organophosphines play indispensable roles as ligands applicable to a broad range of transition metal-catalyzed reactions. Creation of new phosphines and development of novel approaches to phosphines are thus quite important. Recently, bulky phosphines have attracted increasing attention as useful ligands for preparation of biologically intriguing compounds as well as functional organic materials.[1] We have been focusing on 1-alkynylphosphines and their derivatives as precursors of new phosphines.[2] Previously, we reported a method for the synthesis of bulky arylphosphines via rhodium-catalyzed formal [2+2+2] cycloaddition reactions[3] of tethered diynes with 1-alkynylphosphine sulfides (Scheme 1).[2a,f,4,5] In this reaction, the carbon−carbon triple bonds of 1-alkynylphos-

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(1) (a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004. (b) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley-VCH: Weinheim, Germany, 2004. (c) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002. (d) Miura, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2201–2203. (e) Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366–374. (f) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.* **2006**, *348*, 23–39. (g) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599–1626. (h) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338–6361.

(2) (a) Kondoh, A.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2007**, *129*, 6996–6997. (b) Kondoh, A.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2007**, *129*, 4099–4104. (c) Kondoh, A.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 1383–1385. (d) Kanemura, S.; Kondoh, A.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 2031–2033. (e) Kondoh, A.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, *10*, 3093–3095. (f) Kobatake, T.; Kondoh, A.; Yoshida, S.; Yorimitsu, H.; Oshima, K. *Chem. Asian J.* **2008**, *3*, 1613–1619. (g) Kondoh, A.; Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 506–514. (h) Kondoh, A.; Yorimitsu, H.; Oshima, K. *Chem. Asian J.* **2010**, *5*, 398–409.

(3) Tanaka, K. *Chem. Asian J.* **2009**, *4*, 508–518.

(4) (a) Nishida, G.; Noguchi, K.; Hirano, M.; Tanaka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 3951–3954. (b) Doherty, S.; Knight, J. G.; Smyth, C. H.; Harrington, R. W.; Clegg, W. *Org. Lett.* **2007**, *9*, 4925–4928. (c) Doherty, S.; Smyth, C. H.; Harrington, R. W.; Clegg, W. *Organometallics* **2008**, *28*, 4837–4840. (d) Nishida, G.; Noguchi, K.; Hirano, M.; Tanaka, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3410–3413.

(5) Cobalt-catalyzed [2+2+2] cycloaddition reactions of 1-alkynylphosphine oxides were reported: Heller, B.; Gutnov, A.; Fischer, C.; Drexler, H.-J.; Spannenberg, A.; Redkin, D.; Sundermann, C.; Sundermann, B. *Chem.*−*Eur. J.* **2007**, *13*, 1117–1128.

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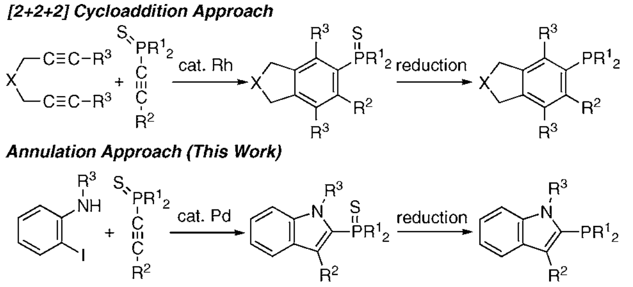
Scheme 1



phine sulfides participated in the construction of benzene rings.[6]

By using 1-alkynylphosphine derivatives as key starting materials, we have developed a new strategy aiming at the synthesis of bulky heteroarylphosphines (Scheme 1). We report herein palladium-catalyzed annulation[7] of 1-alkynylphosphine sulfides with 2-iodoanilines to afford 2-indolylphosphine sulfides. The newly formed indole rings naturally have a substituent derived from 1-alkynylphosphine sulfides adjacent to the thiophosphinyl group, which creates a sterically congested environment around the phosphorus in cooperation with a substituent on the nitrogen atom. The product, phosphine sulfides, can be easily reduced to the corresponding trivalent phosphines.

Although a variety of heteroarylphosphines,[8] including indole-based phosphines,[9,10] have been designed and synthesized so far, most of the syntheses involve metalation of heteroaromatic compounds followed by treating with chlorophosphines. This conventional approach requires preparation of proper heteroaromatic compounds prior to introduction of a phosphorus moiety, which sometimes necessitates a multistep synthesis. In the present reaction, incorporation of a phosphorus moiety and a substituent at the proper positions occurs at the same time as construction of a heteroaromatic ring. Hence, this protocol does not only provide new phosphines that are difficult to synthesize by other methods but also offers a conceptually new approach to heteroarylphosphines.

Treatment of diphenyl(phenylethynyl)phosphine sulfide (**1a**) with 2 equiv of *N*-methyl-2-iodoaniline (**2a**) in the presence of a catalytic amount of bis(acetylacetonato)palladium and 2 equiv of potassium carbonate in DMSO at 90 °C for 11 h afforded 2-diphenylthiophosphinyl-1-methyl-3-phenylindole (**3aa**) in 76% NMR yield and in 74% isolated yield as a major product (Table 1, entry 1).[11,12] Regioisomer **4aa** was also observed as a minor product (6% NMR yield), which was easily separable from **3aa** by column chromatographic purification. The choice of palladium source was important.[13] Other palladium(II) complexes such as $Pd(OAc)_2$ and $PdCl_2$, as well as palladium(0) complexes such as $Pd_2(dba)_3$, led to lower yields.[14] Aprotic polar solvents were suitable solvents and DMSO gave the best result. Choice of base also affected the yield. Cesium carbonate and sodium carbonate were less effective, while potassium phosphate gave a similar result to potassium carbonate. Addition of phosphine ligands such as triphenylphosphine led to lower yield. Under the reaction conditions, sulfur transfer from 1-alkynylphosphine sulfide to phosphine ligands occurred, which would deactivate the palladium catalyst.[15]

With the optimized reaction conditions in hand, the scope of 1-alkynylphosphine sulfides was investigated (Table 1, entries 1−9). Not only phenylacetylene derivative **1a** but also alkyl-substituted substrates **1b**−**d** underwent the annulation reactions (entries 1−4). The reactions of primary and secondary alkyl-substituted **1b** and **1c** proceeded smoothly, while *tert*-butyl-substituted **1d** provided product **3da** in low yield probably due to its bulkiness. It is worth noting that none of the regioisomers **4** were detected in the reactions of **1b**−**d**. A variety of functional groups, such as keto, ester, methoxy, and 2-thienyl groups, were compatible under the reaction conditions (entries 5−9).

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(6) Syntheses of arylphosphines by Diels−Alder reactions of 1-alkynylphosphine oxides were reported: (a) Ashburn, B. O.; Carter, R. G.; Zakharov, L. N. *J. Am. Chem. Soc.* **2007**, *129*, 9109–9116. (b) Ashburn, B. O.; Carter, R. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 6737–6741. (c) Doherty, S.; Smyth, C. H.; Harrington, R. W.; Clegg, W. *Organometallics* **2009**, *28*, 5273–5276.

(7) The palladium-catalyzed annulation of alkynes with 2-iodoanilines was reported by Larock and others: (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689–6690. (b) Larock, R. C.; Yum, E. K.; Refvic, M. D. *J. Org. Chem.* **1998**, *63*, 7652–7662. (c) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270–3271. (d) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644–4680. (e) Larock, R. C. *Pure Appl. Chem.* **1999**, *71*, 1435–1442. (f) Barluenga, J.; Rodríguez, F.; Fañanás, F. J. *Chem. Asian J.* **2009**, *4*, 1036–1048.

(8) For selected references, see: (a) Sergev, A. G.; Schulz, T.; Torborg, C.; Spannenberg, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7595–7599. (b) Schulz, T.; Torborg, C.; Schäffner, B.; Huang, J.; Zapf, A.; Kadyrov, R.; Börner, A.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 918–921. (c) Wu, J.; Chan, A. S. C. *Acc. Chem. Res.* **2006**, *39*, 711–720. (d) Fitzpatrich, M. O.; Coyne, A. G.; Guiry, P. J. *Synlett* **2006**, 3150–3154. (e) Shimizu, H.; Nagasaki, I.; Saito, T. *Tetrahedron* **2005**, *61*, 5405–5432. (f) End, N.; Stoessel, C.; Berens, U.; di Pietro, P.; Cozzi, P. G. *Tetrahedron: Asymmetry* **2004**, *15*, 2235–2239. (g) Au-Yeung, T. T.-L.; Chen, A. S. C. *Coord. Chem. Rev.* **2004**, *248*, 2151–2164. (h) Andersen, N. G.; Keay, B. A. *Chem. Rev.* **2001**, *101*, 997–1030. (i) Benincori, T.; Brenna, E.; Sannicolò, F.; Trimarco, L.; Antognazza, P.; Cesarotti, E.; Demartin, F.; Pilati, T. *J. Org. Chem.* **1996**, *61*, 6244–6251.

(9) (a) Lee, H. W.; Lam, F. L.; So, C. M.; Lau, S. P.; Chan, A. S. C.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 7436–7439. (b) Wassenaar, J.; van Zutphen, S.; Mora, G.; Le Floch, P.; Siegler, M. A.; Spek, A. L.; Reek, J. N. H. *Organometallics* **2009**, *28*, 2724–2734. (c) So, C. M.; Yeung, C. C.; Lau, C. P.; Kwong, F. Y. *J. Org. Chem.* **2008**, *73*, 7803–7806. (d) Wassenaar, J.; Kuil, M.; Reek, J. N. H. *Adv. Synth. Catal.* **2008**, *350*, 1610–1614. (e) Wassenaar, J.; Reek, J. N. H. *Dalton Trans.* **2007**, 3750–3753. (f) Yu, J. O.; Lam, E.; Sereda, J. L.; Rampersad, N. C.; Lough, A. J.; Browning, C. S.; Farrar, D. H. *Organometallics* **2005**, *24*, 37–47. (g) Artemova, N. V.; Chevykolava, M. N.; Luzikov, Y. N.; Nifant'ev, I. E.; Nifant'ev, E. E. *Tetrahedron* **2004**, *60*, 10365–10370. (h) Rataboul, F.; Zapf, A.; Jackstell, R.; Harkal, S.; Riermeier, T.; Monsees, A.; Dingerdissen, U.; Beller, M. *Chem.*−*Eur. J.* **2004**, *10*, 2983–2990. (i) Brnincori, T.; Piccolo, O.; Rizzo, S.; Sannicolò, F. *J. Org. Chem.* **2000**, *65*, 8340–8347. (j) Claridge, T. D. W.; Long, J. M.; Brown, J. M.; Hibbs, D.; Hursthouse, M. B. *Tetrahedron* **1997**, *53*, 4035–4050. (k) Berens, U.; Brown, J. M.; Long, J.; Selke, R. *Tetrahedron: Asymmetry* **1996**, *7*, 285–292.

(10) Synthesis of 2-indolylphosphine oxides was reported: Couture, A.; Deniau, E.; Gimbert, Y.; Grandclaudon, P. *Tetrahedron* **1993**, *49*, 1431–1444.

(11) The structure of **3aa** was confirmed by X-ray crystallographic analysis. See the Supporting Information.

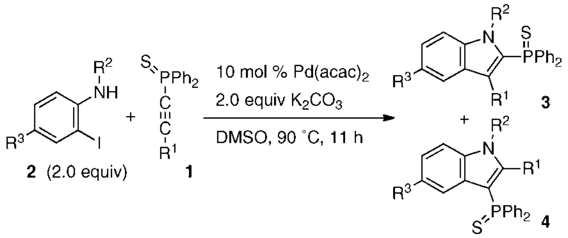
(12) The reaction of 1.2 equiv of **2a** gave **3aa** in 61% NMR yield. The concentration of **2a** would affect the efficiency of the reaction.

(13) See the Supporting Information.

(14) The reason why $Pd(acac)_2$ gave the best result is not clear at this stage. The ligand on palladium precursors would affect the catalytic activity. Pd(II) precursors would be reduced to Pd(0) complexes under the reaction conditions, which would participate in the catalytic cycle.

(15) A significant amount of phosphine sulfide derived from an additional phosphine ligand was observed after the reaction.

Table 1. Palladium-Catalyzed Annulation of (1-Alkynyl)diphenylphosphine Sulfides with 2-Iodoanilines[a]

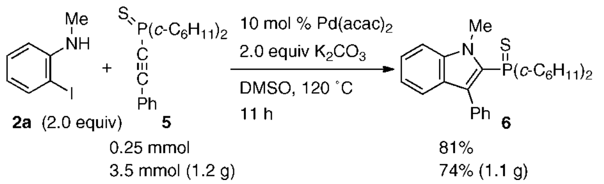


entry	1	R^1	2	R^2	R^3	3	yield,[b] %
1	**1a**	Ph	**2a**	Me	H	**3aa**	74 (6)
2	**1b**	n-C_6H_{13}	**2a**	Me	H	**3ba**	67 (0)
3	**1c**	c-C_6H_{11}	**2a**	Me	H	**3ca**	91 (0)
4	**1d**	t-Bu	**2a**	Me	H	**3da**	35 (0)
5	**1e**	p-Ac-C_6H_4	**2a**	Me	H	**3ea**	59 (6)
6	**1f**	p-MeO_2C-C_6H_4	**2a**	Me	H	**3fa**	58 (6)
7	**1g**	p-MeO-C_6H_4	**2a**	Me	H	**3ga**	75 (8)
8	**1h**	o-MeO-C_6H_4	**2a**	Me	H	**3ha**	54 (17)
9	**1i**	2-thienyl	**2a**	Me	H	**3ia**	57 (10)
10	**1a**	Ph	**2b**	Et	H	**3ab**	78 (6)
11	**1a**	Ph	**2c**	i-Pr	H	**3ac**	73 (0)
12[c]	**1a**	Ph	**2d**	Bn	H	**3ad**	59 (5)
13	**1a**	Ph	**2e**	Me	Me	**3ae**	71 (13)
14	**1a**	Ph	**2f**	Me	Cl	**3af**	56 (18)
15	**1a**	Ph	**2g**	Me	Br	**3ag**	57 (11)

[a] Reaction conditions: **1** (0.25 mmol), **2** (0.50 mmol), Pd(acac)$_2$ (0.025 mmol), K_2CO_3 (0.50 mmol), DMSO (2.0 mL), 90 °C, 11 h. [b] Isolated yields of **3**. NMR yields of **4** are in parentheses. [c] Performed at 120 °C. Bn = $C_6H_5CH_2$.

The scope of 2-iodoaniline derivatives was examined (entries 10−15). In this reaction, an alkyl substituent on nitrogen was crucial. Primary and secondary alkyl-substituted **2b**−**d** underwent the reaction smoothly to yield the corresponding indoles in good yields. However, the reactions of *N*-acetyl-, *N*-*tert*-butoxycarbonyl-, *N*-tosyl-2-iodoanilines and 2-iodoaniline did not proceed at all. Chloro and bromo groups on the benzene ring of **2** were intact under the reaction conditions. The halo moieties would allow further transformations of **3af** and **3ag**.

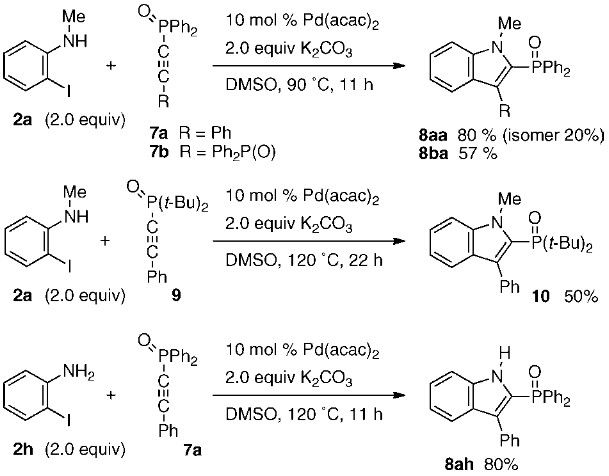
(1-Alkynyl)dicyclohexylphosphine sulfide also underwent the annulation reaction although a higher temperature was required (eq 1). This reaction was reliable enough to permit a gram-scale synthesis. The reaction of 1.2 g of **5** provided 1.1 g of **6** in 74% isolated yield after purification on silica gel followed by recrystallization.



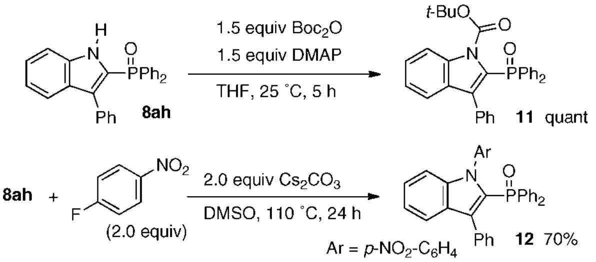
(1)

Next, we tested 1-alkynylphosphine oxides instead of 1-alkynylphosphine sulfides (Scheme 2). Interestingly, the use of 1-alkynylphosphine oxides as substrates expanded the scope of accessible 2-indolylphosphines. For instance, annulation of 1,2-bis(diphenylphosphinyl)ethyne (**7b**) occurred smoothly to yield diphosphine dioxide **8ba** in good yield, while the reaction of 1,2-bis(diphenylthiophosphinyl)ethyne did not proceed. The corresponding trivalent diphosphine would serve as a bidentate ligand. (1-Alkynyl)di-*tert*-butylphosphine oxide **9** also underwent the annulation reaction in moderate yield although the longer reaction time was required. Furthermore, 2-iodoaniline (**2h**) could react with **7a** to provide *N*-unprotected indolylphosphine oxide, which allowed further transformations on the nitrogen atom, i.e., *tert*-butoxycarbonylation and arylation^{16} (Scheme 3). The corresponding trivalent phosphine of **11** would serve as a potential bidentate ligand.^{9c} The product **12**, which has aryl groups at the 1,3-positions, would be a potential precursor of a very bulky phosphine.

Scheme 2. The Reactions of 1-Alkynylphosphine Oxides



Scheme 3. Transformation of **8ah**



Some of the phosphine sulfides thus synthesized were subjected to radical desulfidation conditions (Scheme 4).^{17} Treatment of 2-indolylphosphine sulfides with tris(trimethylsilyl)silane in the presence of a catalytic amount of AIBN

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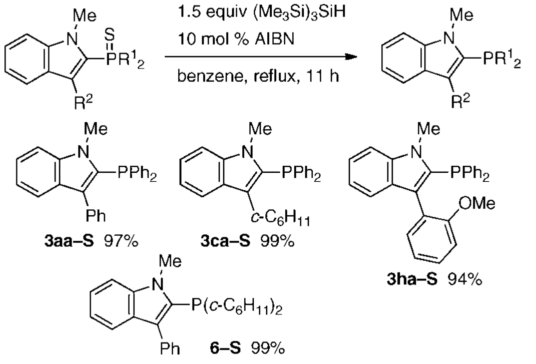
(16) Xu, H.; Liu, W.-Q.; Fan, L.-L.; Chen, Y.; Yang, L.-M.; Lv, L.; Zheng, Y.-T. *Chem. Pharm. Bull.* **2008**, *56*, 720–722.

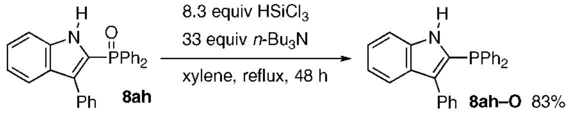
(17) Romeo, R.; Wozniak, L. A.; Chatgilialoglu, C. *Tetrahedron Lett.* **2000**, *41*, 9899–9902.

(18) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419–2440. (c) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461–1473.

Scheme 4. Radical Desulfidation of 2-Indolylphosphine Sulfides

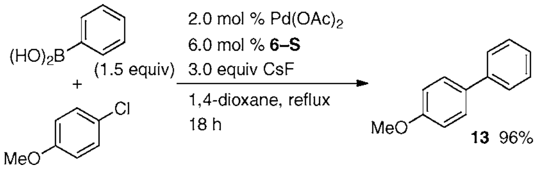


in benzene at reflux afforded the corresponding trivalent phosphines in good yields. The desulfidation reactions of these indolylphosphine sulfides were clean and high-yielding. The phosphine oxide **8ah** could also be reduced to the trivalent phosphine by treating with trichlorosilane and tributylamine (eq 2).[6c] The phosphines synthesized through this sequential annulation/reduction protocol were so stable under air that column purification on silica gel was applicable without any special care.



(2)

Finally, an application of the newly synthesized phosphine was examined. The ligand **6−S** proved to serve as an efficient ligand for the Suzuki−Miyaura cross-coupling reaction of electron-rich aryl chloride (eq 3).[18]



(3)

In conclusion, we have developed a conceptually new method for the synthesis of bulky indole-based heteroarylphosphines by using 1-alkynylphosphine derivatives as key starting materials. This method, the sequential annulation/desulfidation, offers an efficient alternative to the conventional approach to heteroarylphosphines. The phosphines synthesized by this method will find many applications in organic synthesis.

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Supporting Information Available: Experimental procedure, optimization of reaction conditions, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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