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Regio- and Stereoselective Hydroamidation of 1-Alkynylphosphine Sulfides Catalyzed by Cesium Base

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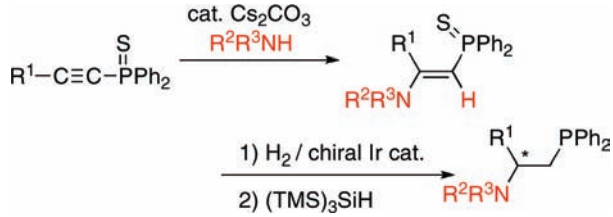
ABSTRACT



Regio- and stereoselective hydroamidation of 1-alkynylphosphine sulfides proceeds in the presence of cesium carbonate to provide (*E*)-2-amino-1-thiophosphinyl-1-alkenes. Asymmetric hydrogenation of the adducts catalyzed by an iridium complex followed by desulfidation yields 2-amino-1-phosphinoalkanes, which offers a new approach to chiral N,P-ligands that will potentially serve as ligands in asymmetric reactions.

Organophosphines play invaluable roles in organic synthesis, especially as ligands for transition-metal catalysts. Development of novel approaches to organophosphines is thus quite important. We have been focusing on 1-alkynylphosphine derivatives as precursors of new phosphines[1] and reported addition reactions of diphenylphosphine[1a] and thiols.[1b] Considering the importance of bidentate aminophosphine ligands in homogeneous transition-metal catalysis,[2] we report here cesium-catalyzed addition of amides or imides to 1-alkynylphosphine sulfides,[3–5] directed toward the construction of vicinal N,P-frameworks.

Treatment of diphenyl(phenylethynyl)phosphine sulfide (**1a**) with 2 equiv of *N*-benzyltosylamide (**2a**) in the presence of a catalytic amount of cesium carbonate (10 mol %) in DMSO for 11 h at 90 °C provided 1-(*N*-benzyl-*N*-tosylamino)-2-diphenylthiophosphinyl-1-phenylethene (**3a**) in 84% isolated yield with an *E*/*Z* ratio of 96/4 (Table 1, entry 1). Recrystallization of the product allowed for the isolation of the *E* isomer in 71% yield.[6] Aprotic polar solvents, such as DMSO, DMF, and NMP, are the solvents of choice. The reactions in 1,4-dioxane (bp 100 °C), THF (bp 67 °C), and toluene (bp 111 °C) at reflux afforded the product in moderate yields. In protic solvents such as 2-propanol at reflux, a trace amount of the product was obtained. Cesium

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(2) (a) Rönnholm, P.; Södergren, M.; Hilmersson, G. *Org. Lett.* **2007**, *9*, 3781–3783. (b) Krauss, I. J.; Leighton, J. L *Org. Lett.* **2003**, *5*, 3201–3203, and references cited therein. (c) Anderson, C.; Cubbon, R. J.; Harling, J. D. *Tetrahedron: Asymmetry* **2001**, *12*, 923–935. (d) Ito, M.; Ikariya, T. *Chem. Commun.* **2007**, 5134–5142.

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(4) For recent examples of intermolecular hydroamidation of alkynes, see: (a) Yudha, S. S.; Kuninobu, Y.; Takai, K. *Org. Lett.* **2007**, *9*, 5609–5611. (b) Goossen, L. J.; Rauhaus, J. E.; Deng, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4042–4045. (c) Kondo, T.; Tanaka, S.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 413–414.

(5) For base-mediated additions of tosylamides to propiolates, see: (a) Barbazanges, M.; Meyer, C.; Cossy, J. *Org. Lett.* **2007**, *9*, 3245–3248. (b) Lee, E.; Kang, T. S.; Joo, B. J.; Tae, J. S.; Li, K. S.; Chung, C. K. *Tetrahedron Lett.* **1995**, *36*, 417–420.

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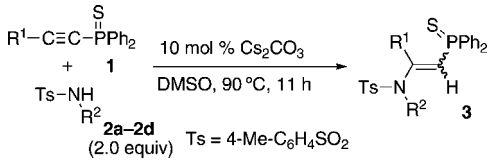
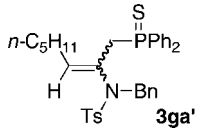
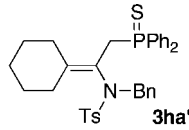
Table 1. Hydroamidation of 1-Alkynylphosphine Sulfides



entry	1	R^1	2	R^2	3	yield (%)	*E*/*Z*
1	**1a**	Ph	**2a**	Bn[a]	**3aa**	84	96/4
						71[b]	100/0
2	**1b**	4-Ac-C_6H_4	**2a**	Bn	**3ba**	74	97/3
3	**1c**	4-MeO_2C-C_6H_4	**2a**	Bn	**3ca**	83	95/5
4	**1d**	4-MeO-C_6H_4	**2a**	Bn	**3da**	82[c]	95/5
5	**1e**	2-pyridyl	**2a**	Bn	**3ea**	89	>99/1
6	**1f**	H	**2a**	Bn	**3fa**	88	>99/1
7	**1g**	*n*-C_6H_{13}	**2a**	Bn	**3ga′**	92	87/13
8	**1h**	*c*-C_6H_{11}	**2a**	Bn	**3ha′**	70	
9	**1a**	Ph	**2b**	*n*-C_4H_9	**3ab**	97	96/4
10	**1a**	Ph	**2c**	*c*-C_6H_{11}	**3ac**	15	92/8
11	**1a**	Ph	**2d**	H	**3ad**	23	>99/1

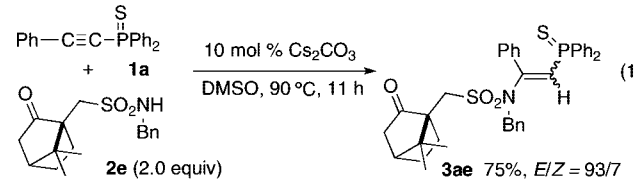
[a] Bn = $C_6H_5CH_2$. [b] After recrystallization. [c] Performed for 24 h.



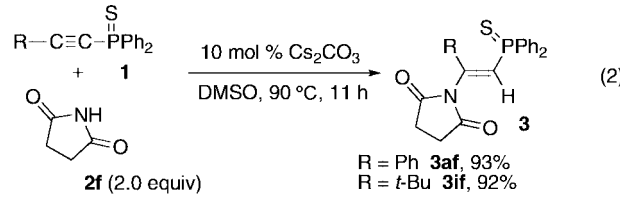


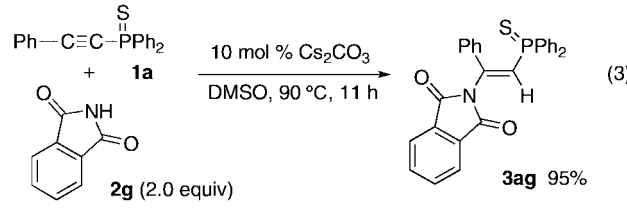
carbonate is the most effective base. The uses of potassium carbonate and sodium carbonate led to lower yields. When organic bases such as DBU and DABCO were used, no reaction occurred.

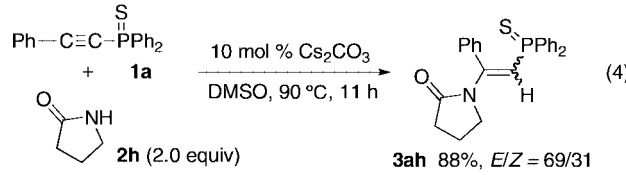
Various combinations of 1-alkynylphosphine sulfides and amides were examined under the optimized reaction conditions (Table 1). A variety of functional groups, such as keto, ester, methoxy, and pyridyl groups, were compatible under the reaction conditions (entries 2−5). The reaction of ethynyldiphenylphosphine sulfide (**1f**) also proceeded smoothly with perfect stereoselectivity (entry 6). However, the reactions of sterically demanding *o*-methoxyphenyl- and *tert*-butyl-substituted substrates did not take place. The additions to primary and secondary alkyl-substituted 1-alkynylphosphine sulfides also proceeded, although migration of the carbon−carbon double bond occurred to afford **3ga′** and **3ha′** exclusively (entries 7 and 8). The scope of sulfonamides was investigated (entries 9−11). The addition of primary alkyl-substituted tosylamides proceeded in high yields (entries 1 and 9). However, additions of secondary alkyl-substituted tosylamide **2c** and tosylamide (**2d**) provided the corresponding products in low yields (entries 10 and 11), and no reaction occurred when *N*-phenyltosylamide and *N*-*tert*-butyltosylamide were used. The reaction of *N*-benzyl-10-camphorsulfonylamide proceeded smoothly (eq 1).



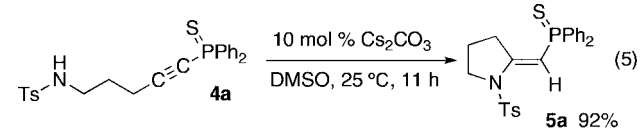
Other nitrogen nucleophiles were examined. Imides were suitable nucleophiles for this addition reaction (eqs 2 and 3). Interestingly, the stereoselectivity was completely controlled when imides were used. In addition, succinimide (**2f**) could react with sterically hindered *tert*-butyl-substituted substrate, with which *N*-benzyltosylamide (**2a**) could not react, and the corresponding adduct was obtained in good yield. The addition of 2-pyrrolidinone also proceeded, albeit with lower stereoselectivity (eq 4). Acyclic amides such as *N*-benzylacetamide did not react at all.

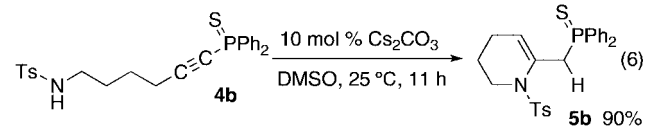






The amidation was applicable to intramolecular cyclizations. When 1-alkynylphosphine sulfide **4a** which has a tosylamido group was treated with cesium carbonate at ambient temperature, the cyclization proceeded smoothly (eq 5). In the case of eq 6, where tetramethylene-tethered **4b** was used as a substrate, the migration of the C−C double bond of the product occurred.





We envisioned that the enantioselective hydrogenation of the adducts would offer a new approach to chiral bidentate

(6) The X-ray crystallographic analysis of **3ca** verified the *E* stereochemistry of the major isomers. See the Supporting Information.

(7) For recent reviews, see: (a) Källström, K.; Munslow, I.; Andersson, P. G. *Chem. -Eur. J.* **2006**, *12*, 3194–3200. (b) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272–3296.

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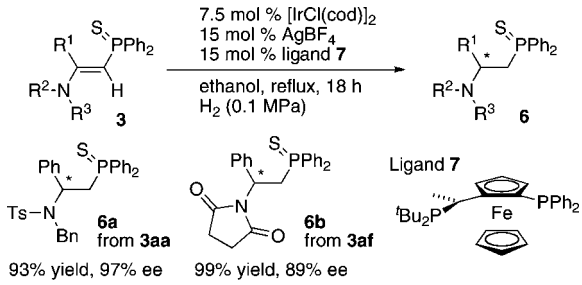
N,P-ligands. However, the enantioselective hydrogenation was not trivial because the adducts are regarded as the sterically demanding and doubly heteroatom-substituted unusual alkenes. After extensive screening of the reaction conditions, we finally found that a combination of a cationic iridium complex[7] and ligand **7**[8] catalyzed the desired reaction with high enantioselectivity (Scheme 1).[9] The hydrogenation

Scheme 1. Iridium-Catalyzed Enantioselective Hydrogenation



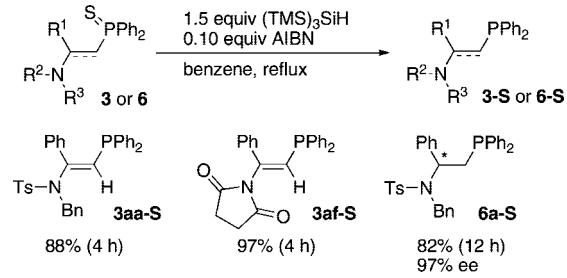
of **3aa** in the presence of catalytic amounts of $[IrCl(cod)]_2$, $AgBF_4$, and **7** under 0.1 MPa of hydrogen in boiling ethanol provided **6a** in excellent yield (93%) with 97% ee. The hydrogenation of **3af** was less enantioselective (89% ee), yet high enough to potentially allow for improving the optical purity by recrystallization.

Some of the phosphine sulfides thus synthesized were subjected to radical desulfidation conditions[10] to provide the corresponding trivalent phosphines in high yields (Scheme 2).

(9) When (*R*)-BINAP was used as a ligand instead of **7**, 91% ee of **6a** was obtained in 82% yield. However, (*R*)-BINAP was less effective for the enantioselective hydrogenation of **3af** to provide **6b** in 99% yield with 15% ee.

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

Scheme 2. Desulfidation with Tris(trimethylsilyl)silane



In particular, the optically active phosphine **6a-S** would be useful as a ligand after further modifications.

In conclusion, we have found that the cesium-catalyzed hydroamidation of 1-alkynylphosphine sulfides proceeds in good yields with high regio- and stereoselectivities. In light of the importance of organophosphorus compounds, the products and their derivatives can be useful in organic synthesis. In addition, we have demonstrated that the iridium-catalyzed enantioselective hydrogenation of the adducts afforded optically active phosphine sulfides. The protocol, the sequential hydroamidation/hydrogenation, offers an alternative to the conventional approach to chiral 2-amino-1-phosphinoalkanes.

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

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