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Palladium(II)-Catalyzed Conjugate Phosphination of Electron-Deficient Acceptors

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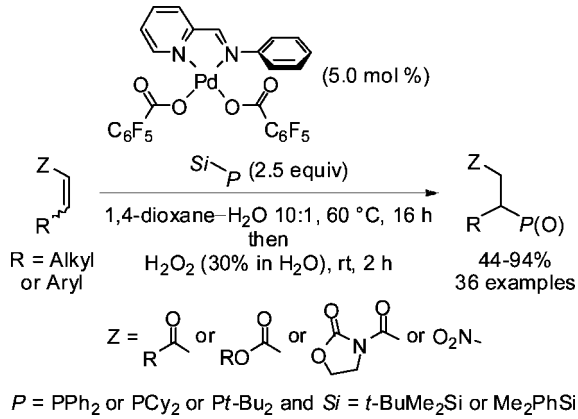
ABSTRACT



A general protocol for the conjugate transfer of diphenyl-, dicyclohexyl-, and di-*tert*-butylphosphinyl groups from silylphosphines to cyclic and acyclic electron-deficient acceptors employing a bench-stable palladium(II) catalyst is reported. Several *E* and *Z* configured α,β-unsaturated carbonyl and carboxyl acceptors (including imides) as well as nitroalkenes participate in this palladium(II)-catalyzed process in high chemical yields.

The area of transition-metal-catalyzed conjugate element transfer onto α,β-unsaturated carbonyl and carboxyl acceptors is currently witnessing tremendous growth.[1] Prior to the C-element bond forming event, an interelement linkage is usually activated by a ligand-stabilized transition metal either through oxidative addition of the element−element bond to the low-valent metal center[2,3] or through element-to-metal transmetalation.[3] Indicators for the recent substantial progress are several novel (asymmetric) C−B (B−B bond activation[4]), C−Si (B−Si[5] or Si−Si bond activation[6]), as well as C−P bond forming

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(1) Suginome, M.; Matsuda, T.; Ohmura, T.; Seki, A.; Murakami, M. In *Comprehensive Organometallic Chemistry III*; Mingos, D. M. P., Crabtree, R. H., Ojima, I., Eds.; Elsevier: Oxford, 2007, Vol. 10, pp 725−787.

(2) Han, L.-B.; Tanaka, M. *Chem. Commun.* **1999**, 395–402.

(3) Burks, H. E.; Morken, J. P. *Chem. Commun.* **2007**, 4717–4725.

(4) Rhodium(I) catalysis: (a) Kabalka, G. W.; Das, B. C.; Das, S. *Tetrahedron Lett.* **2002**, *43*, 2323–2325. Copper(I) catalysis: (b) Ito, H.; Yamanaka, H.; Tateiwa, J.-i.; Hosomi, A. *Tetrahedron Lett.* **2000**, *41*, 6821–6825. (c) Mun, J.; Lee, J.-E.; Yun, J. *Org. Lett.* **2006**, *8*, 4887–4889. (d) Lee, J.-E.; Yun, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 145–147. Nickel(0) catalysis: (e) Hirano, K.; Yorimitsu, H.; Ohshima, K. *Org. Lett.* **2007**, *9*, 5031–5033. Platinum(0) catalysis: (f) Lawson, Y. G.; Lesley, M. J. G.; Marder, T. B.; Norman, N. C.; Rice, C. R. *Chem. Commun.* **1997**, 2051–2052. (g) Bell, N. J.; Cox, A. J.; Cameron, N. R.; Evans, J. S. O.; Marder, T. B.; Duin, M. A.; Elsevier, C. J.; Baucherel, X.; Tulloch, A. A. D.; Tooze, R. P. *Chem. Commun.* **2004**, 1854–1855.

(5) Rhodium(I) catalysis: (a) Walter, C.; Auer, G.; Oestreich, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5675–5677. (b) Walter, C.; Oestreich, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3818–3820.

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reactions (Si−P bond activation[7]). Our contribution is the disclosure of a rhodium(I)-catalyzed activation of interelement compounds in basic aqueous media,[5,7] a process believed to hinge upon a hydroxyrhodium(I) complex as the active catalyst. Its Lewis basic oxygen will interact chemoselectively with the more electronegative element of the interelement reagent, thereby weakening the element−element bond eventually resulting in transmetalation of the less electronegative element. This general strategy for the conjugate element transfer was inspired and guided by the related 1,4-addition of arylboronic acids[8] and its mechanism of action.[9]

As the logical next step, we reasoned that palladium(II)-catalyzed protocols for conjugate arylation,[10] which are tantamount to the aforementioned rhodium(I) catalysis,[8,9] might also qualify for our purposes.[5,7] Accordingly, a transmetalation mechanism involving a hydroxypalladium(II) complex was verified.[11] As we had elaborated an efficient rhodium(I)-catalyzed 1,4-addition of phosphinyl groups yet limited in substrate scope,[7] we decided to investigate its unprecedented palladium(II)-catalyzed counterpart. In this Letter, we report a robust method for the conjugate phosphination of electron-deficient acceptors[12] using silylphosphines[7,13] as a source of nucleophilic trivalent phosphorus.[14]

Catalyst identification commenced with bench-stable palladium(II) catalyst **1** developed by Itami et al. for the hydroarylation of fullerene with arylboronic acids.[15] This work also included examples of conjugate arylation of cyclic and acyclic α,β-unsaturated carbonyls. We were then delighted to see that **1** also facilitated the phosphinyl transfer from *t*-$BuMe_2Si-PPh_2$ (**2a**)[7,16] to cyclic acceptor **4** (Scheme 1). Variation of reaction conditions (only a selection is shown) led to a straightforward procedure, affording the adduct in high chemical yield.

Scheme 1. Conjugate Phosphination Using Bench-Stable Palladium(II) Complex **1**

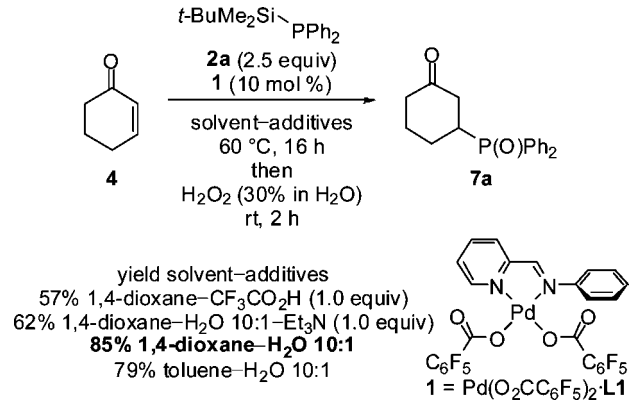
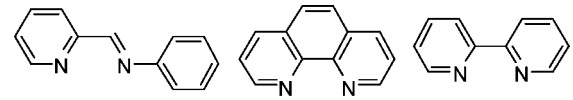


Table 1. Ligand [$Pd(OAc)_2$·**L**] and Additive Screening[a]



entry	ligand **L**	mol %	$C_6F_5CO_2H$ (mol %)	yield (%)
1	Ph_3P	20	–	45
2	**L1**	20	–	76
3	**L2**	20	–	64
4	**L3**	20	–	55
5	Ph_3P	5.0	–	36
6	**L1**	5.0	–	74
7	**L2**	5.0	–	66
8	**L3**	5.0	–	58
9	Ph_3P	5.0	10	41
10	**L1**	5.0	10	80
11	**L2**	5.0	10	71
12	**L3**	5.0	10	63

[a] Conjugate phosphinations of **4** were conducted using $Pd(OAc)_2$ and an equimolar amount of the indicated ligand **L1**−**L3** (twice the amount in the case of Ph_3P) as well as **2a** (2.5 equiv) in 1,4-dioxane:H_2O = 10:1 (0.20 M) at 60 °C. Yields after oxidation and flash chromatography.

To ascertain whether **1** (= $Pd(O_2CC_6F_5)_2$·**L1**) is the ideal counteranion−ligand combination, we surveyed four different ligands—Ph_3P and **L1**−**L3**—with $Pd(OAc)_2$ as the palladium(II) source with or without $C_6F_5CO_2H$ as additive[15a] (Table 1). Independent of the catalyst loading and the presence of added acid, a clear trend was observed: Ph_3P[10a] performed poorly, while all nitrogen-based ligands[10b] were superior in the order **L1** > **L2** > **L3**. Any further decrease in the amount of $Pd(OAc)_2$ gave lower yields.

(6) Palladium(0) catalysis: (a) Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 5579–5581. Copper(I) catalysis: (b) Ito, H.; Ishizuka, T.; Tateiwa, J.-i.; Sonoda, M.; Hosomi, A. *J. Am. Chem. Soc.* **1998**, *120*, 11196–11197. Rhodium(I) catalysis: (c) Nakao, Y.; Chen, J.; Imanaka, H.; Hiyama, T.; Ichikawa, Y.; Duan, W.-L.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 9137–9143.

(7) Rhodium(I) catalysis: (a) Trepohl, V. T.; Oestreich, M. *Chem. Commun.* **2007**, 3300–3302. (b) For a related example, see: Hayashi, M.; Matsuura, Y.; Watanabe, Y. *J. Org. Chem.* **2006**, *71*, 9248–9251.

(8) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229–4231.

(9) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052–5058.

(10) (a) Phosphine ligand:Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 2768–2770. (b) Bipyridine ligand:Lu, X.; Lin, S. *J. Org. Chem.* **2005**, *70*, 9651–9653. (c) Carbene ligand:Zhang, T.; Shi, M. *Chem.−Eur. J.* **2008**, *14*, 3759–3764.

(11) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Organometallics* **2004**, *23*, 4317–4324.

(12) For an authoritative summary of conjugate phosphorus(III) and phosphorus(V) transfer, see: Enders, D.; Saint-Dizier, A.; Lannou, M.-I.; Lenzen, A. *Eur. J. Org. Chem.* **2006**, 29–49.

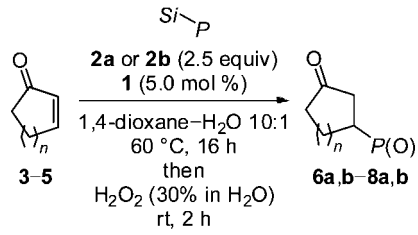
(13) For thermal as well as fluoride-mediated conjugate addition of R_3Si-PR_2, see: (a) Couret, C.; Escudie, J.; Satge, J.; Anh, N. T.; Soussan, G. *J. Organomet. Chem.* **1975**, *91*, 11–30. (b) Hayashi, M.; Matsuura, Y.; Watanabe, Y. *Tetrahedron Lett.* **2004**, *45*, 9167–9169.

(14) Selected examples of 1,4-addition of R_2P groups: (a) Thermal addition of R_2PH: Zabotina, E. Y.; de Kanter, F. J. J.; Bickelhaupt, F.; Wife, R. L. *Tetrahedron* **2001**, *57*, 10177–10180. (b) Thermal addition of R_2PH·BH_3: Join, B.; Delacroix, O.; Gaumont, A.-C. *Synlett* **2005**, 1881–1884. (c) Addition of metalated, borane-protected R_2PH: Imamoto, T.; Oshiki, T.; Onozawa, T.; Kusumoto, T.; Sato, K. *J. Am. Chem. Soc.* **1990**, *112*, 5244–5252. (d) For the Conant reaction (transfer of P(V) nucleophile generated from R_2PCl/glacial acetic acid), see: Conant, J. B.; Braverman, J. B. S.; Hussey, R. E. *J. Am. Chem. Soc.* **1923**, *45*, 165–171.

(15) (a) Mori, S.; Nambo, M.; Chi, L.-C.; Bouffard, J.; Itami, K. *Org. Lett.* **2008**, *10*, 4609–4612. (b) For a complementary Rh(I) catalysis, see: Nambo, M.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2007**, *129*, 8080–8081.

(16) Hayashi, M.; Matsuura, Y.; Watanabe, Y. *Tetrahedron Lett.* **2004**, *45*, 1409–1411.

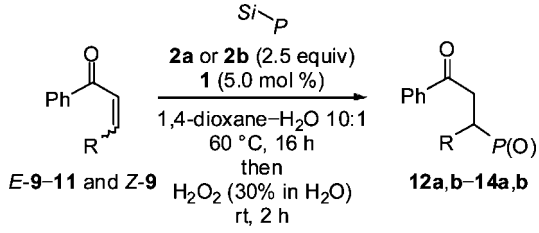
Table 2. Conjugate Phosphination of Cyclic α,β-Unsaturated Carbonyl Compounds



entry	silylphosphine Si–P	acceptor	n	adduct	yield (%)
1	t-BuMe$_2$Si–PPh$_2$ (**2a**)	**3**	1	**6a**	94
2	t-BuMe$_2$Si–PPh$_2$ (**2a**)	**4**	2	**7a**	84
3	t-BuMe$_2$Si–PPh$_2$ (**2a**)	**5**	3	**8a**	90
4	Me$_2$PhSi–PCy$_2$ (**2b**)	**3**	1	**6b**	72
5	Me$_2$PhSi–PCy$_2$ (**2b**)	**4**	2	**7b**	80
6	Me$_2$PhSi–PCy$_2$ (**2b**)	**5**	3	**8b**	88

We then continued to apply this procedure to conventional cyclic α,β-unsaturated carbonyl compounds **3**−**5** using both t-BuMe$_2$Si−PPh$_2$ (**2a**) and Me$_2$PhSi−PCy$_2$ (**2b**) representative for diaryl- and dialkylphosphinyl groups (Table 2). As in all preceding and subsequent examples, phosphinyl→phosphinoyl oxidation with H_2O_2 or sulfurization with S_8 allowed facile purification by flash chromatography on silica gel. The yields obtained with substrates **3**−**5** compare well with those of the rhodium(I)-catalyzed variant.[7a]

Table 3. Conjugate Phosphination of Acyclic α,β-Unsaturated Carbonyl Compounds

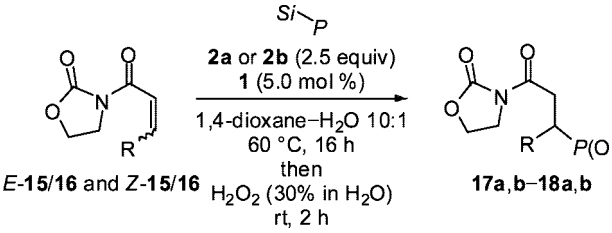


entry	silylphosphine Si–P	acceptor	R	adduct	yield (%)
1	t-BuMe$_2$Si–PPh$_2$ (**2a**)	E-**9**	Ph	**12a**	78
2	t-BuMe$_2$Si–PPh$_2$ (**2a**)	Z-**9**	Ph	**12a**	91
3	t-BuMe$_2$Si–PPh$_2$ (**2a**)	E-**10**	Me	**13a**	84
4	t-BuMe$_2$Si–PPh$_2$ (**2a**)	E-**11**	n-Bu	**14a**	71
5	Me$_2$PhSi–PCy$_2$ (**2b**)	E-**9**	Ph	**12b**	74
6	Me$_2$PhSi–PCy$_2$ (**2b**)	Z-**9**	Ph	**12b**	80
7	Me$_2$PhSi–PCy$_2$ (**2b**)	E-**10**	Me	**13b**	85
8	Me$_2$PhSi–PCy$_2$ (**2b**)	E-**11**	n-Bu	**14b**	65

Acyclic α,β-unsaturated carbonyl compounds, e.g., acceptors **9**−**11**, had emerged as unreactive with the rhodium(I) catalytic system but reacted cleanly under the palladium(II) catalysis (Table 3). We note that isolated yields were invariably higher for Z than for E configured precursors (vide infra).

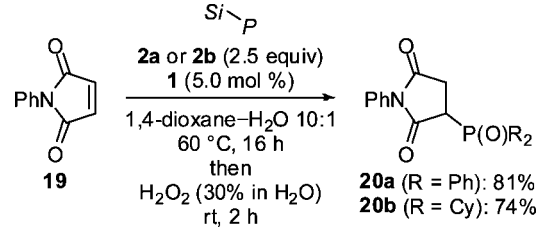
Gratifyingly, α,β-unsaturated imides **15** and **16** with E and Z double bond geometry extended the scope (Table 4), opening the door for auxiliary-based, diastereoselective 1,4-additions.[17] Again, Z alkenes performed better than E alkenes. Maleimide **19** afforded even higher yields (Scheme 2).

Table 4. Conjugate Phosphination of α,β-Unsaturated Imides



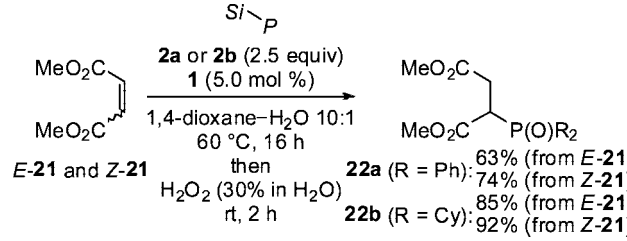
entry	silylphosphine Si–P	acceptor	R	adduct	yield (%)
1	t-BuMe$_2$Si–PPh$_2$ (**2a**)	E-**15**	Ph	**17a**	62
2	t-BuMe$_2$Si–PPh$_2$ (**2a**)	Z-**15**	Ph	**17a**	73
3	t-BuMe$_2$Si–PPh$_2$ (**2a**)	E-**16**	n-Bu	**18a**	58
4	t-BuMe$_2$Si–PPh$_2$ (**2a**)	Z-**16**	n-Bu	**18a**	64
5	Me$_2$PhSi–PCy$_2$ (**2b**)	E-**15**	Ph	**17b**	51
4	Me$_2$PhSi–PCy$_2$ (**2b**)	Z-**15**	Ph	**17b**	55
5	Me$_2$PhSi–PCy$_2$ (**2b**)	E-**16**	n-Bu	**18b**	63
6	Me$_2$PhSi–PCy$_2$ (**2b**)	Z-**16**	n-Bu	**18b**	82

Scheme 2. Conjugate Phosphination of a Maleimide



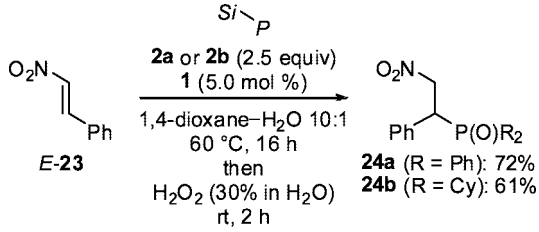
Being aware of the fact that α,β-unsaturated carboxyls are intrinsically less reactive than carbonyl compounds, we were nevertheless surprised to learn these were reluctant to participate in this reaction.[18] Conversely, both fumaric (*E*-**21**) and maleic ester (*Z*-**21**) gave the desired products in chemical yields expected for the respective double bond isomer (Scheme 3).

Scheme 3. Conjugate Phosphination of Fumaric and Maleic Esters



The range of conceivable substrates for this reaction was completed with nitroalkene *E*-**23**, furnishing the 1,4-adduct in good isolated yield (Scheme 4).

Scheme 4. Conjugate Phosphination of a Nitroalkene



After identification of all these acceptors, we tested $Me_2PhSi-Pt\text{-}Bu_2$ (**2c**) to realize the transfer of the electron-rich di-*tert*-butylphosphinyl group (Figure 1). Although chemical yields were somewhat lower, conjugate phosphination worked except for α,β-unsaturated imides, thereby rounding off the scope of this palladium(II) catalysis.

In summary, we elaborated a general method for the conjugate phosphinyl transfer employing easy-to-handle silylated diaryl- and dialkylphosphines **2a**−**c**[7] (Figure 2). This novel palladium(II) catalysis for interelement bond activation is superior to the rhodium(I)-catalyzed process previously reported by us.[7] Future work will be devoted to mechanistic investigations and the development of enantioselective[19] and substrate-controlled[17,20] variants.

(17) (a) Conjugate addition of lithiated $R_2PH{\cdot}BH_3$: Léautey, M.; Castelot-Deliencourt, G.; Jubault, P.; Pannecoucke, X.; Quirion, J.-C. *Tetrahedron Lett.* **2002**, *43*, 9237–9240. (b) Conjugate addition of lithiated or sodiated $(EtO)_2P(O)H$: Castelot-Deliencourt, G.; Pannecoucke, X.; Quirion, J.-C. *Tetrahedron Lett.* **2001**, *42*, 1025–1028.

(18) There is precedence for the conjugate phosphination of α,β-unsaturated esters using alkali metal or "naked" phosphinides. See for example refs 13b and 14c.

(19) For organocatalytic conjugate phosphination of α,β-unsaturated aldehydes, see: (a) Carlone, A.; Bartoli, G.; Bosco, M.; Sambri, L.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 4504–4506. (b) Ibrahem, I.; Rios, R.; Vesely, J.; Hammar, P.; Eriksson, L.; Himo, F.; Cordova, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 4507–4510.

(20) A remarkable reagent-contolled 1,4-addition of a metalated *P*-stereogenic phosphine oxide is known: Haynes, R. K.; Lam, W. W.-L.; Yeung, L.-L. *Tetrahedron Lett.* **1996**, *37*, 4729–4732.

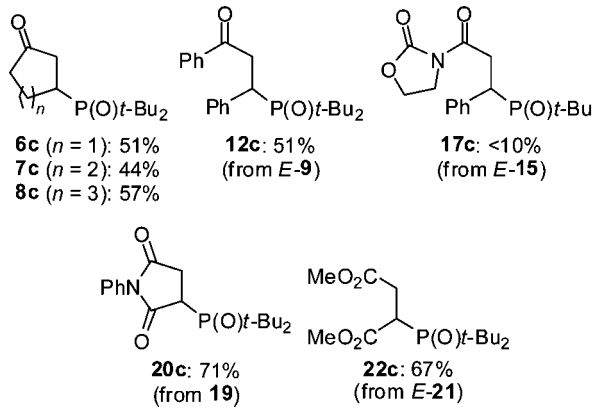


Figure 1. Selected examples of conjugate $Pt\text{-}Bu_2$ transfer using $Me_2PhSi-Pt\text{-}Bu_2$ (**2c**).

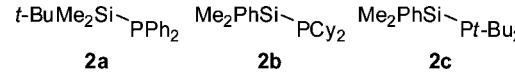


Figure 2. Silylphosphines surveyed in this work.[7,16]

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Supporting Information Available: General procedure, characterization data, as well as ^1H, ^{13}C, and ^{31}P NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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