Palladium-catalyzed hydrostannylations of highly hindered acetylenes in hexane

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Abstract—Hexane is particularly favorable as a solvent for hydrostannylation of hindered internal alkynes by minimizing the competing formation of H_2 and $Bu_3SnSnBu_3$. The optimum conditions involve $Pd(OAc)_2$ and a donor monophosphine (PCy_3) in hexane at 23°C.
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In the course of a synthesis effort, we required a conversion of the type shown in Scheme 1, the *cis* addition of a tin-hydride across a hindered internal triple bond. From the many examples of Pd-catalyzed addition of trialkyl-stannanes to triple bonds,[1] it is clear that *cis* addition is reliable, and that the propargylic oxygen functionality would favor the desired regioselectivity, presumably via internal coordination in a transient Pd intermediate.[2] The process is generally best for terminal alkynes, and yields and selectivity suffer with sterically hindered internal alkynes; few examples with a one tertiary substituent are known.[3] A general problem is that the activated Pd–H intermediate **2** can proceed down an alternate path by irreversible generation of H_2, dimerization of the stannane, and precipitation of the Pd as palladium black.[4]

The hydrostannylation is slowed with more hindered substrates, and the proportion of tin dimerization is concomitantly increased resulting in low conversions. Here we describe methods to optimize the regioselective addition for hindered internal alkynes, with attention to the solvent effects,[5] Pd(II) source,[6] and added ligands. Hindered internal alkyne **1a** was mixed with $Pd(PPh_3)_2Cl_2$ in THF. Upon addition of Bu_3SnH (Table 1, entry 1), vigorous hydrogen evolution began. Only product **3a**[7] was formed, but the conversion was low (35%). Higher temperature gave a similar conversion (entry 2), while slow addition of the Bu_3SnH over 3 h gave 59% completion, but a new stereoisomeric product (**4**) appeared (entry 3). Highly polar solvents such as MeOH and DMF, along with CH_2Cl_2, gave vigorous gas evolution and no hydrostannylation products. When hexane or Bu_3SnH were used as solvent, no H_2 evolution was observed and the product **3a** was isolated in moderate to excellent yields (entries 8 and 9) after somewhat longer reaction time.
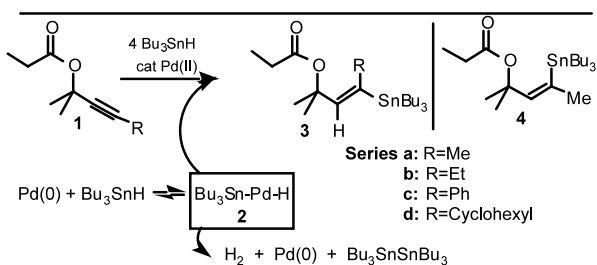

Scheme 1.

Table 1.

Entry[a]	Solvent	Time (h)/temp. (°C)	Ratio **3a:4**	**3a** yield (%)
1	THF	18/23	100:0	35
2	THF	18/70	100:0	28
3[b]	THF	18/70	66:34	59
4[c]	Et$_2$O	18/23	70:30	54
5	CH$_2$Cl$_2$	18/23	N/A	0
6	DMF	18/23	N/A	0
7	Methanol	18/23	N/A	0
8	Hexane	24/23	100:0	91
9	Neat	24/23	100:0	64

[a] 4 mol equiv. Bu_3SnH; 5 mol% $PdCl_2(PPh_3)_2$ unless otherwise noted.
[b] Bu_3SnH added over 3 h via syringe pump.
[c] 10 mol equiv. Bu_3SnH.

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Table 2.

Entry	R	Solvent	Time (h)	Temp. (°C)	Catalyst	Yield (%)
1	Me	Hexane	24	23	Pd(PPh$_3$)$_2$Cl$_2$	91
2[a]	Me	Neat	24	23	Pd(PPh$_3$)$_2$Cl$_2$	64
3	Et	Hexane	72	65	Pd(PPh$_3$)$_2$Cl$_2$	71
4	Et	Neat	72	60	Pd(PPh$_3$)$_2$Cl$_2$	49
5	Ph	Hexane	108	60	Pd(PPh$_3$)$_2$Cl$_2$	65
6	Ph	Neat	108	60	Pd(PPh$_3$)$_2$Cl$_2$	51
7	Cy	Hexane	168	60	Pd(PPh$_3$)$_2$Cl$_2$	0
8	Cy	Neat	168	60	Pd(PPh$_3$)$_2$Cl$_2$	0
9	**Me**	**Hexane**	**2**	**23**	**Pd(OAc)$_2$+PCy$_3$**	**92**
10	Me	Hexane	6	23	Pd(OAc)$_2$+P(*o*-tol)$_3$	54
11	Me	Hexane	6	23	Pd(OAc)$_2$+P(pyrrole)$_3$	67
12	Me	Hexane	24	23	Pd(OAc)$_2$+dppe	0
13	Et	Hexane	12	23	Pd(OAc)$_2$+PCy$_3$	50
14	**Et[a]**	**Hexane**	**3**	**23**	**Pd(OAc)$_2$+PCy$_3$**	**86**
15	Et[a]	Hexane	3	23	Pd(TFA)$_2$+PCy$_3$	78
16	**Ph**	**Hexane**	**2**	**23**	**Pd(OAc)$_2$+PCy$_3$**	**89**
17	Ph	Hexane	6	23	Pd(TFA)$_2$+PCy$_3$	71
18	Cy	Hexane	48	23	Pd(TFA)$_2$+PCy$_3$	5
19	Cy[b]	Hexane	24	23	Pd(TFA)$_2$+PCy$_3$	35

Representative procedure: To an oven-dried, argon-filled flask was added Pd(OAc)$_2$ (0.016 mmol, 3.6 mg, 5 mol%) and tricyclohexylphosphine (9.0 mg, 0.033 mmol, 10 mol%). The flask was evacuated and filled with argon three times. Freshly distilled hexane (2 mL) was added and the solution was stirred for 10 min until the solids had dissolved. Alkyne **1a** (50.0 mg, 0.325 mmol) in hexane (1 mL) was added dropwise, followed by slow addition of neat Bu$_3$SnH (378 mg, 349 μL, 1.30 mmol) over 5 min. Gas evolution began immediately and the reaction was monitored by TLC until the starting alkyne was gone. The mixture was transferred to a silica gel column and rapidly eluted with hexane until the excess Bu$_3$SnH (Bu$_3$Sn)$_2$ was removed, followed by elution with hexane/ether (10:1) to obtain **3a** (133 mg, 92%) as a colorless oil. R_f 0.65 (19:1 hexane/ether).

[a] 10% catalyst.
[b] 30% catalyst.

As the hindrance increases with other internal alkynes (Table 2), the hydrostannylation reaction is slowed, and H$_2$ evolution is observed in reactions performed both neat and in hexane. Reasonable conversions of **3b** and **3c** were observed (entries 3–6), but the cyclohexyl derivative **3d** did not react (entries 7, 8).

As both pathways have the same initial steps, it was not clear how ligand electronics would affect the process, and a small set of donating and withdrawing phosphine ligands were tested. PCy$_3$ was an excellent ligand, giving **3a** in 92% yield in only 2 h. P(*o*-tol)$_3$, which has previously been used for hydrostannylation of less hindered alkynes,[8] was more active than PPh$_3$, but significant H$_2$ evolution was observed and the yield of **3a** was only 54%. Similar results were obtained for P(pyrrole)$_3$, which is electronically comparable to CO.[9] The one bidentate ligand tested gave no reaction (entry 12).[10]

The optimized conditions were then applied to the more sterically demanding alkynes. Phenyl alkyne **3c** proved to be an excellent substrate (entries 16 and 17); however, more bulky alkyl groups (Et, Cy) were less efficiently converted. With 5% catalyst, **3b** was hydrostannylated in only 50% conversion and **3d** showed no reaction. Use of Pd(TFA)$_2$ in place of Pd(OAc)$_2$ was particularly effective with **3d**; however, conversion was only 35% even with the use of 30% catalyst (entry 19).

Acknowledgements

References

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2. Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768.
3. Hydrostannylation of an analog of **1** with a free hydroxyl and R = *o*-bromophenyl in THF was successful: Liron, F.; Le Garrec, P.; Alami, M. *Synlett* **1999**, *2*, 246.
4. For a discussion of the pathways and detection of intermediates, see: Trebbe, R.; Schager, F.; Goddard, R.; Pörschke, K.-R. *Organometallics* **2000**, *19*, 521.
5. As noted in a review (Ref. 1c), little exploration of the solvent effects have been reported; for an example with internal aryl alkynes, see Ref. 3. Hexane was not employed in this study; the emphasis was on regioselectivity.
6. In principle, the counter ion on the Pd(II) should not affect the reaction, since the Pd(II) is reduced to Pd(0) as the initiation step. Again, the issue has been little studied.

7. Products **3a–d** were fully characterized. The exact structure of **3a** was established by NOE difference studies. Irradiation of the vinyl proton (δ 5.59 ppm) gave a 4.8% enhancement of the propargylic methyl groups (δ 1.52 ppm) and a 3.8% enhancement of the terminal methyl groups (δ 0.84 ppm) in the Bu_3Sn moiety. The vinyl methyl group was not enhanced.

8. The effect of P(o-tol)$_3$ was studied in a limited way: (a) Greeves, N.; Torode, J. S. *Synlett* **1994**, 537; (b) See also Ref. 3.

9. For discussion and leading references, see: Moloy, K. G.; Petersen, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 7696.

10. Chelating diphosphines have been used with modest success in hydrostannylation of internal aryl alkynes: see Ref. 3.