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The Use of Phosphine Ligands to Control the Regiochemistry of Pd-Catalyzed Hydrostannations of 1-Alkynes: Synthesis of (*E*)-1-Tributylstannyl-1-alkenes

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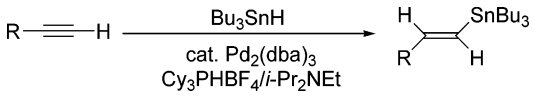
ABSTRACT

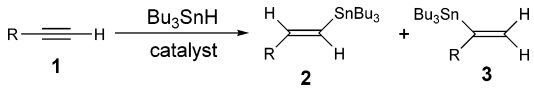


The regiochemistry of palladium-catalyzed hydrostannations of terminal alkynes is dramatically influenced by ligand effects. Use of phosphines such as Cy_3P, *t*-Bu_2PCH_2*t*-Bu, and *t*-Bu_3P provides (*E*)-1-tributylstannyl-1-alkenes with regioselectivities up to >99:<1 for substrates where the commonly used Ph_3P shows much lower regioselectivities.

The radical-induced hydrostannation of alkynes is a well-established method for the preparation of vinylstannanes, compounds of synthetic interest as precursors to vinyllithiums and as substrates for palladium-catalyzed cross-coupling (Stille) reactions.[1] Unfortunately, such hydrostannations often result in mixtures of regio- and stereoisomers. The development of transition metal-catalyzed hydrostannations, particularly with Pd- and Mo-based systems, in the 1980s solved some of the problems associated with the radical process.[2] In particular, only products of syn-hydrostannation were observed. However, regiochemistries with terminal alkynes were often low (Scheme 1). With molybdenum catalysts, regioselectivities were often close to 1:1[3] while with palladium catalysts, regioselectivities were variable with poor selectivities observed in some cases and excellent selectivities in others—high selectivities for (*E*)-1-tributylstannyl-1-alkenes were only observed with sterically biased systems.

Although (*E*)-1-tributylstannyl-1-alkenes are useful synthetic intermediates,[4] it appears that no determined efforts have been made to improve the regioselectivity of Pd-

Scheme 1. Syn Hydrostannation of 1-Alkynes



R	catalyst[a]	2:3
n-C_6H_{13}	Pd	43:57
	Mo	50:50
CH(OH)*n*-C_5H_{11}	Pd	75:25
	Mo	44:56
$C(CH_3)_2OH$	Pd	100:0
	Mo	47:53

[a] Data from ref 2. Catalysts used were $(Ph_3P)_2PdCl_2$ and (allyl)$Mo(CO)_2(CH_3CN)_2Br$.

(1) Reviews: (a) Smith, N. D.; Mancuso, J.; Lautens, M. *Chem. Rev.* **2000**, *100*, 3257−3282. (b) Trost, B. M.; Ball, Z. T. *Synthesis* **2005**, 853−887.

(2) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857−1867.

(3) More recent work with Mo catalysts has led to the development of methods to selectively prepare 2-tributylstannyl-1-alkenes with good regioselectivities and is thus complementary to the method described herein: (a) Kazmaier, U.; Schauss, D.; Pohlman, M. *Org. Lett.* **1999**, *1*, 1017−1019. (b) Dörrenbächer, S.; Kazmaier, U.; Ruf, S. *Synlett* **2006**, 547−550. (c) Lin, H.; Kazmaier, U. *Eur. J. Org. Chem.* **2007**, 2839−2843.

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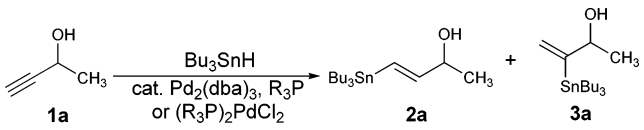
catalyzed hydrostannation of nonhindered 1-alkynes by modifying the Pd catalyst.[5] The lack of activity in this area may be attributable to an observation made during some of the early work on metal-catalyzed hydrostannations that "attempts to modify the regiochemistry by changing the catalyst and, in particular, the steric bulk of the ligands, met with no success."[2] Thus, more circuitous routes such as the use of 1-halo-1-alkynes were developed.[2,6] More recently, strategies involving modified stannanes such as trineophyltin hydride[7] and Bu_2SnClH have been reported.[8] For select substrates such as α,β-acetylenic carbonyl compounds, copper-catalyzed hydrostannations proceed with high regioselectivities.[9] We now report that substitution of other phosphine ligands in place of Ph_3P in Pd-catalyzed hydrostannations gives considerably improved regioselectivities.

We chose to begin our studies with a propargylic alcohol, 3-butyn-2-ol, partly since we expected that the regioisomeric products would be readily separable from each other and from nonpolar stannane byproducts by flash chromatography. We were delighted to find that the phosphine ligand does, in fact, dramatically influence the regiochemistry (Table 1).

Table 1. Hydrostannation of **1a** with Various Catalysts



1a **2a** **3a**

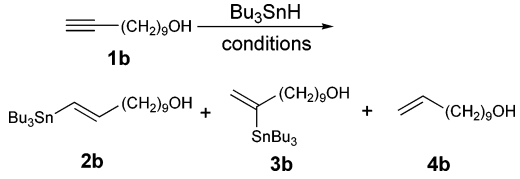
entry	catalyst[a,b]	**2a**:**3a** ratio[c]	yield of **2a**[d] (%)
1	$(Ph_3P)_2PdCl_2$	68:32	57
2	$(o\text{-}tol_3P)_2PdCl_2$	80:20	60
3	$(Cy_3P)_2PdCl_2$	95:5	84
4	$t\text{-}Bu_2PCH_2t\text{-}Bu$	96:4	70
5	$t\text{-}Bu_3P$	100:0	72
6	$(2\text{-furyl})_3P$	40:60	22
7	TTMPP[e]	47:53	45
8	$ArPCy_2$[f]	77:23	63

[a] 1% Pd, 2% phosphine, toluene, rt, 2 h. [b] Catalyst precursor or ligand used with $Pd_2(dba)_3$. [c] Determined by ^1H NMR analysis of crude reaction mixtures. [d] Isolated yield after flash chromatography. [e] Tris(2,4,6-trimethoxyphenyl)phosphine. [f] Ar = 2-(2′,6′-dimethoxybiphenyl).

The observed regioselectivity with $(Ph_3P)_2PdCl_2$ as catalyst precursor (entry 1, **2a**:**3a** = 68:32) was in line with selectivities reported previously for similar 2° propargylic alcohols (trans:gem = 76:24 to 80:20). Bulky trialkylphosphines all gave substantially higher regioselectivities in favor of the desired trans-isomer (entries 3−5). Somewhat perplexingly, while $t\text{-}Bu_3P$ gave none of the gem isomer **3a** (entry 5), the isolated yield of **2a** with this ligand was significantly lower than when $(Cy_3P)_2PdCl_2$ was used, suggesting the possibility of an undetected side reaction.

To probe for possible side reactions, alkyne **1b** was chosen to be sterically representative of a straight-chain alkyne but contained an alcohol group to facilitate the chromatographic separation of products. This compound was treated with Bu_3SnH under a variety of conditions with very enlightening results (Table 2). By using the "usual" $(Ph_3P)_2PdCl_2$ catalyst,

Table 2. Hydrostannation of **1b** under Various Conditions



1b **2b** **3b** **4b**

entry	conditions[a]	**2b**:**3b**:**4b** ratio[b]
1	1% $(Ph_3P)_2PdCl_2$	66:33:1
2	1% $(Cy_3P)_2PdCl_2$	69:4:27
3	0.5% $Pd_2(dba)_3$, 2% $t\text{-}Bu_3PHBF_4$, 4% $i\text{-}Pr_2NEt$	46:1:53
4	0.5% $Pd_2(dba)_3$, 2% Cy_3PHBF_4, 2% $i\text{-}Pr_2NEt$	84:4:12
5	0.5% $Pd_2(dba)_3$, 2% Cy_3PHBF_4, 4% $i\text{-}Pr_2NEt$	92:4:4
6	0.5% $Pd_2(dba)_3$, 2% Cy_3PHBF_4, 20% $i\text{-}Pr_2NEt$	93:4:3
7	0.5% $Pd_2(dba)_3$, 2% $(2\text{-}PhC_6H_4)PCy_2$	78:8:14
8[c]	0.5% $Pd_2(dba)_3$, 2% $ArPCy_2$	92:5:3
9	0.5% $Pd_2(dba)_3$, 2% $n\text{-}Bu_3P$, 2% $i\text{-}Pr_2NEt$	86:10:4
10	0.5% $Pd_2(dba)_3$, 2% $(2\text{-furyl})_3P$, 2% $i\text{-}Pr_2NEt$	57:42:1

[a] Mol % of catalyst and additives, toluene, rt, 2 h. [b] Determined by ^1H NMR analysis of crude reaction mixtures. [c] Ar = 2-(2′,6′-dimethoxybiphenyl).

hydrostannation of either **1a** or **1b** gave virtually identical results, i.e., a 2:1 mixture of regioisomers (entry 1). However, while hydrostannation of **1b** with $(Cy_3P)_2PdCl_2$ proceeded with the same regioselectivity as that observed for **1a** (entry 2, trans:gem = 95:5), a substantial amount of reduction product **4b** was also formed. Moreover, with $t\text{-}Bu_3P$, while only a trace of gem-product **3b** was detected, the major product formed was **4b**.[10] With other propargylic alcohols examined, up to 40% reduction was observed when $t\text{-}Bu_3P$ was used. Thus it seems likely that reduction (producing relatively volatile and thus undetected 3-buten-2-ol) may have been a significant side reaction with use of $t\text{-}Bu_3P$ with alkyne **1a.**

For hydrostannations of **1b** involving Cy_3P, the amount of reduction product could be dramatically decreased by

(4) Recent examples: (a) Volgraf, M.; Gorostiza, P.; Szobota, S.; Helix, M. R.; Isacoff, E. Y.; Trauner, D. *J. Am. Chem. Soc.* **2007**, *129*, 260−261. (b) Hosoya, T.; Sumi, K.; Doi, H.; Wakao, M.; Suzuki, M. *Org. Biomol. Chem.* **2006**, *4*, 410−415. (c) Gómez, A. M.; Barrio, A.; Amurrio, I.; Valverde, S.; Jarosz, S.; López, J. C. *Tetrahedron Lett.* **2006**, *47*, 6243−6246.

(5) The effect of different catalysts on the hydrostannation of a propargylglycine derivative has been reported: Crisp, G. T.; Gebauer, M. G. *J. Organomet. Chem.* **1997**, *532*, 83−88.

(6) Boden, C. D. J.; Pattenden, G.; Ye, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2417−2419.

(7) Dodero, V. I.; Koll, L. C.; Mandolesi, S. D.; Podestá, J. C. *J. Organomet. Chem.* **2002**, *650*, 173−180.

(8) Miura, K.; Wang, D.; Hosomi, A. *Synlett* **2005**, 406−410.

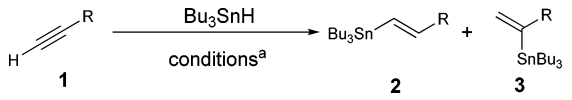
(9) (a) Leung, L. T.; Leung, S. K.; Chiu, P. *Org. Lett.* **2005**, *7*, 5249−5252. (b) Leung, L. T.; Chiu, P. *Pure Appl. Chem.* **2006**, *78*, 281−285. (c) Miao, R.; Li, S.; Chiu, P. *Tetrahedron* **2007**, *63*, 6737−6740.

(10) To test if **4b** might arise from protiodestannylation of **2b**, **2b** was isolated and re-subjected to the reaction conditions (Table 2, entry 3). No **4b** was detected.

varying the reaction conditions. With commercial (Aldrich) $(Cy_3P)_2PdCl_2$, up to 30% of the crude reaction mixture was the undesired alkene **4b**. Freshly prepared and purified $(Cy_3P)_2PdCl_2$[11] gave less **4b** (typically 5−10%) but gave unacceptably low conversions. After considerable experimentation it was found that the best results were obtained when the catalyst was prepared in situ from $Pd_2(dba)_3$, Cy_3PHBF_4, and *i*-Pr_2NEt.[12] It proved to be important to have an excess of amine compared to Cy_3PHBF_4 in order to minimize the formation of **4b** (compare Table 2, entries 4−6). The role of excess amine is not obvious but we speculate that it may serve a coordinative role to inhibit the pathway leading to reduction. The importance of coordination can also be inferred by comparing the reactions shown in Table 2, entries 7 and 8; considerably less reduction was observed when using the ligand bearing methoxy groups.

A relatively small, electron-rich phosphine, *n*-Bu_3P, increased the ratio of **2b**:**3b** (entry 9) while $(2\text{-furyl})_3P$ slightly decreased the ratio (entry 10, compared to Ph_3P, entry 1), suggesting that both electronic and steric effects are important in determining the regioselectivity of these reactions. In general, bulky electron-rich phosphines favored formation of **2b** but there was no overall clear correlation between steric bulk and regioselectivity.[13]

Table 3. Hydrostannation of Alkynes with $(Ph_3P)_2PdCl_2$ (condition A) and $Pd_2(dba)_3/Cy_3PHBF_4/i\text{-}Pr_2NEt$ (condition B)[a]



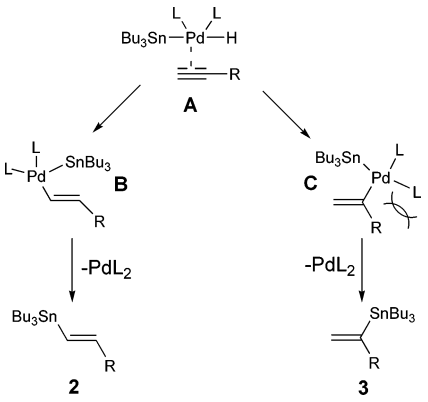
entry (alkyne)	R	**2**:**3**[b] ratio, yield of **2**[c] cond. A	cond. B
1 (**1b**)	$(CH_2)_9OH$	67:33, 50%	96:4, 87%
2 (**1c**)	$(CH_2)_9OTBS$	75:25, 53%	96:4, 86%
3 (**1d**)	CH_2OH	40:60, 31%	67:33, 61%
4 (**1e**)	CH_2OTBS	29:71, 37%	77:23, 64%
5 (**1f**)	$(CH_2)_2OH$	56:44, 42%	83:17, 70%
6 (**1g**)	$(CH_2)_3OH$	67:33, 45%	94:6, 84%
7 (**1h**)	$(CH_2)_4OH$	68:32, 52%	95:5, 85%
8 (**1i**)	CH(OH)*n*-C_5H_{11}	77:23, 57%	95:5, 82%
9 (**1j**)	CH(OTBS)*n*-C_5H_{11}	77:23, 50%	96:4, 77%
10 (**1k**)	CH(OH)*i*-Bu	76:24, 55%	96:4, 83%
11 (**1***l*)	CH(OH)*i*-Pr	76:24, 56%	97:3, 86%
12 (**1m**)	CH(OH)Ph	61:39, 50%	82:18, 76%
13 (**1n**)	$CH_2CH(N{=}CPh_2)CO_2Me$	50:50, 43%	84:16, 79%
14 (**1o**)	$(CH_2)_2OAc$	48:52, 82%	85:15, 80%
15 (**1p**)	$(CH_2)_2OTBS$	62:38, 79%	91:9, 83%
16 (**1q**)	Ph	56:44, 73%	81:19, 74%
17 (**1r**)	CO_2Me	0:100, 76%	0:100, 23%

[a] Condition A: 1% $(Ph_3P)_2PdCl_2$, toluene, rt, 2 h. Condition B: 0.5% $Pd_2(dba)_3$, 2% Cy_3PHBF_4, 4% *i*-Pr_2NEt, toluene, rt, 2 h. [b] Determined by ^1H NMR analysis of crude reaction mixtures. [c] Isolated yield of **2** after flash chromatography. For entries 1, 2, 7, and 14−16, the yield is of a mixture of **2** and **3** which were inseparable; for entry 17, the yield is of **3**.

We applied the conditions which gave optimal results for the hydrostannation of alkyne **1b** with $Pd_2(dba)_3/Cy_3PHBF_4/i\text{-}Pr_2NEt$ to other alkynes and compared the results with hydrostannations using $(Ph_3P)_2PdCl_2$ (Table 3).[14] In almost all cases, the catalyst system with Cy_3P gave much higher selectivity for the 1-stannylalkene, with regioselectivities of trans:gem = 95:5 commonly observed. With a series of alkynyl alcohols $HCC(CH_2)_nOH$ ($n = 1-4$), regioselectivities depended on chain length, with shorter chain lengths giving more gem isomer but the ratio was ~95:5 with $n = 3$ and above. Compared to 2-propyn-1-ol and 3-butyn-1-ol, the corresponding TBS ethers gave higher regioselectivities.[15] With substituted (2°) propargyl alcohols and a TBS ether, regioselectivities were uniformly high. Methyl propiolate afforded only the geminal isomer with either catalyst system but the reaction with Cy_3P was not clean and only a low yield of **3r** was isolated.

The shift in regioselectivity with bulkier ligands may be explained by invoking a mechanistic model involving hydropalladation rather than stannylpalladation (Scheme 2).[1b]

Scheme 2. Mechanistic Rationale



If the reaction proceeds via hydropalladation, one would expect that alkynes bearing larger R groups would give more of the 1-stannylalkene **2** since intermediate **C** would be disfavored for steric reasons. This is consistent with previous observations with alkynes such as *tert*-butylacetylene. One would also expect that larger ligands would also lead to increased steric interactions in **C** and therefore higher regioselectivities in favor of alkene **2**.

From a synthetic viewpoint, hydrostannation products **2** can be easily separated from geminal isomers **3** (which are

(11) Alper, H.; Grushin, V. V.; Bensimon, C. *Inorg. Chem.* **1994**, *33*, 4804−4806.

(12) Use of HBF_4 salts of trialkylphosphines is preferred to use of the free phosphine: Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295−4298.

(13) Tolman cone angles for some of the phosphines are the following: *n*-Bu_3P, 132°; Ph_3P, 145°; Cy_3P, 170°; and *t*-Bu_3P, 182°. Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313−348. The effective cone angle for $(2\text{-furyl})_3P$ (149°) is very similar to that for Ph_3P (148°): Meijboom, R.; Muller, A. *Acta Crystallogr.* **2006**, *E62*, m2642−m2644.

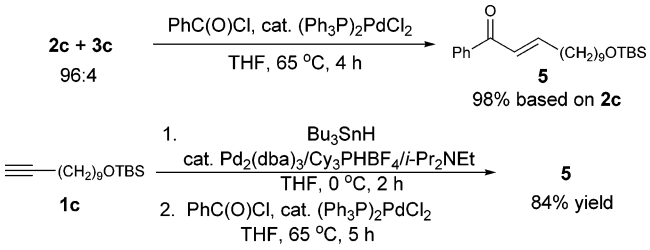
(14) Results reported are for reactions run in toluene but reactions of **1b** with $Pd_2(dba)_3/Cy_3PHBF_4/i\text{-}Pr_2NEt$ in a variety of other solvents (THF, ether, hexanes, CH_2Cl_2) gave very similar results. We now routinely use CH_2Cl_2 at 0 °C for these hydrostannations.

(15) The effect of different oxygen substituents on the regioselectivity of Pd-catalyzed hydrostannations has been documented: Rice, M. B.; Whitehead, S. L.; Horvath, C. M.; Muchnij, J. A.; Maleczka, R. E., Jr. *Synthesis* **2001**, 1495−1504.

less polar) by flash chromatography on silica gel when the substrates are propargyl alcohols. However, separations become increasingly difficult as the functional group becomes more remote and compounds such as **2b** and **3b** are inseparable. This may be problematic in some cases but it is known that 2-stannylalkenes (such as **3**) are notoriously slow to undergo Stille couplings,[16] one of the major applications of vinylstannanes, so may not interfere with many intended applications of 1-stannylalkenes **2**.

To test this supposition, we treated a mixture of **2c** and **3c** (96:4, respectively) with benzoyl chloride with a catalytic amount of $(Ph_3P)_2PdCl_2$ in THF; only enone **5** was isolated (Scheme 3, 98% yield based on **2c**) and stannane **3c** was

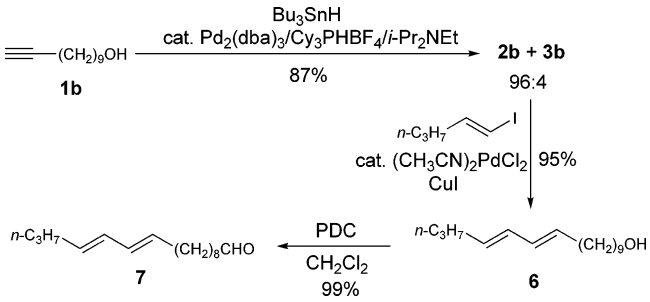
Scheme 3. Stille Coupling of Hydrostannation Products



recovered unchanged. In fact, hydrostannation/Stille coupling could be carried out in one pot to produce the desired enone **5** in good yield.[17]

To further illustrate the utility of this hydrostannation chemistry, we applied it to the synthesis of (*E*,*E*)-10,12-hexadecadienal, a sex pheromone component of the spotted bollworm (*Earias vittella*) and spiny bollworm (*E. insulana*) (Scheme 4).[18] Thus hydrostannation of alkyne **1b** under our new conditions provided a 96:4 mixture of vinylstannanes **2b** and **3b**. Treatment of this mixture with (*E*)-1-iodo-1-pentene[19] under Stille conditions [cat. $(CH_3CN)_2PdCl_2$, CuI, DMF][20] furnished the desired dienyl alcohol **6** in excellent

Scheme 4. Synthesis of (*E*,*E*)-10,12-Hexadecadienal



yield and stereochemical purity. Subsequent oxidation with PDC completes a short, efficient (3 steps, 82% overall yield from **1b**) synthesis of pheromone **7**.[21] While other alkyne hydrometalation/cross-coupling strategies could also be employed, one advantage of hydrostannation is that protection of hydroxyl groups is not necessary.

In summary, we have shown that, contrary to popular belief, ligands can profoundly affect the regioselectivity of palladium-catalyzed hydrostannations of 1-alkynes. High selectivities to produce synthetically useful (*E*)-1-stannyl-1-alkenes may be achieved by using $Pd_2(dba)_3/Cy_3PHBF_4/i\text{-}Pr_2NEt$ for a wide range of alkynes. This system gives much better regioselectivities than the traditional Ph_3P-based catalysts currently in use. Additional work is underway to expand the scope of these hydrostannations and to better understand the different possible mechanistic pathways.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support and Undergraduate Student Research Awards (to A.L. and T.K.) and FMCLithium for a generous gift of $t\text{-}Bu_2PCH_2t\text{-}Bu$.

Supporting Information Available: Experimental procedures and spectral data for stannanes **2a**−**q** and **3a**−**r** and compounds **5**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL702982X

(16) Corey, E. J.; Han, X.; Stoltz, B. M. *J. Am. Chem. Soc.* **1999**, *121*, 7600−7605.

(17) One-pot hydrostannation/Stille couplings have been reported: (a) Maleczka, R. E., Jr.; Terstiege, I. *J. Org. Chem.* **1998**, *63*, 9622−9623. (b) Maleczka, R. E., Jr.; Lavis, J. M.; Clark, D. H.; Gallagher, W. P. *Org. Lett.* **2000**, *2*, 3655−3658.

(18) (a) Cork, A.; Chamberlain, D. J.; Beevor, P. S.; Hall, D. R.; Nesbitt, B. F.; Campion, D. G.; Attique, M. R. *J. Chem. Ecol.* **1988**, *14*, 929−945. (b) Adati, T.; Tatsuki, S. *J. Chem. Ecol.* **1999**, *25*, 105−115.

(19) Zweifel, G.; Whitney, C. C. *J. Am. Chem. Soc.* **1967**, *89*, 2754−2755.

(20) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813−817.

(21) Other syntheses: (a) Yadav, J. S.; Deshpande, P. K.; Reddy, E. R. *Synth. Commun.* **1989**, *19*, 125−134. (b) Klug, J. T.; Skorka, J.; Shani, A. *Chem. Ind.* **1982**, 372−373.