Synlett S. Jung et al. Letter

Facile Synthesis of Stereodefined α-Iodovinyl Sulfoxides, Versatile Platform to Trisubstituted Olefins

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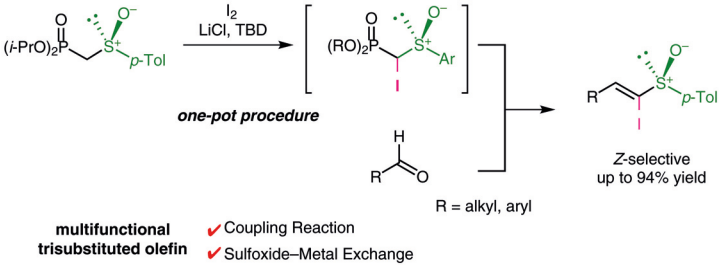


Received: 06.04.2016
Accepted after revision: 09.05.2016
Published online: 01.06.2016
DOI: 10.1055/s-0035-1561654; Art ID: st-2016-u0238-l

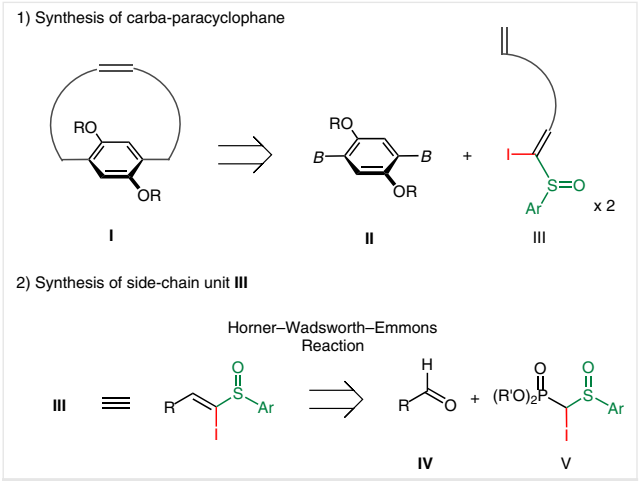
Abstract Stereodefined α-iodovinyl sulfoxides bearing a sulfinyl group and an iodo group were prepared by a one-pot iodination/Horner–Wadsworth–Emmons reaction protocol. This reaction can be applied to a wide range of aldehydes, and further application was demonstrated.

Key words sulfoxides, vinyl iodide, vinyl sulfoxides, sulfinyl phosphonates, trisubstituted olefins, olefination, Horner–Wadsworth–Emmons reaction, halovinyl sulfoxides

α-Halovinyl sulfoxides are useful building blocks in organic synthesis.[1] For example, they have been used as precursors of vinylidene carbene species for various synthetic transformations,[2] and also as a platform for the stereoselective synthesis of hetero- and carbocyclic compounds.[3] Although further potential utilities are expected, the existing synthetic approaches to their availability have been limited in terms of synthetic efficacy and stereoselectivity.

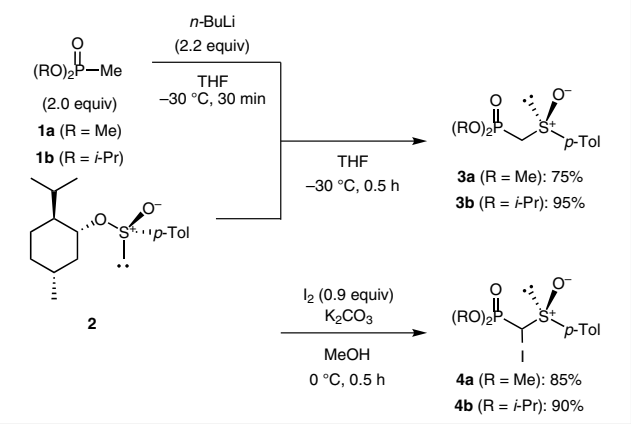
In our recent study on the modular synthesis of planar chiral carba-paracyclophanes (Scheme 1), we employed stereodefined α-iodovinyl sulfoxide **III** as a building block, which was prepared by exploiting iodo-sulfinylphosphonate **V** for the Horner–Wadsworth–Emmons (HWE) reaction with aldehydes.[4] Recognizing the potential utility of **III** in broader sense of organic synthesis, we became interested in addressing the scope and limitation of the above-stated preparative method.

In this communication, we report a synthetic protocol for the highly *Z*-selective synthesis of α-iodovinyl sulfoxides from various aldehydes. In particular, the protocol has been made convenient by the in situ generation of **V** by iodination of phosphonate followed by HWE reaction with aldehydes. The details of this optimization processes are now disclosed.



Scheme 1 Use of α-halovinyl sulfoxides in carba-paracyclophane synthesis

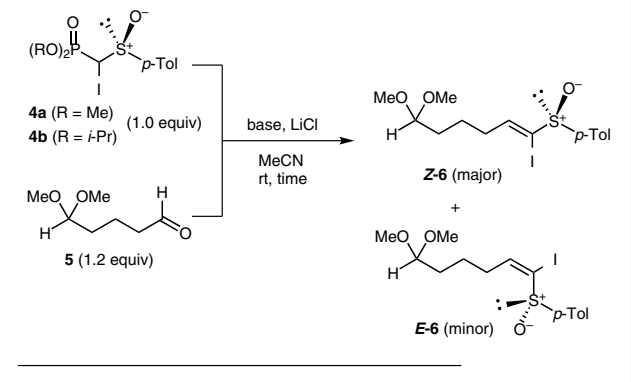
Scheme 2 illustrates the preparation of iodo-phosphonates **4a** (R = Me) and **4b** (R = *i*-Pr). Upon treatment of Andersen's sulfinate[5] (**2**) in THF with two mole equivalents of the anion, generated from dimethyl methylphosphonate (**1a**) or diisopropyl methylphosphonate (**1b**) by treatment with *n*-BuLi at –30 °C, the corresponding sulfinyl-phosphonates **3a** and **3b** were obtained in 75% and 95% yield, respectively.[6] Iodination of phosphonates **3a** and **3b** was carried out by using iodine in the presence of K_2CO_3 in methanol, giving iodo-phosphonate **4a** and **4b** in 85% and 90% yield, respectively. However, these compounds are unstable because the carbon–iodine bond is labile and easily cleaved during workup (10% $Na_2S_2O_3$) and purification.[7] In addition, **4a** and **4b** gradually decomposed even when stored in the refrigerator. Therefore, freshly prepared **4a** and **4b** were needed to be employed in the HWE reaction.



Scheme 2 Synthesis of iodophosphonates **4a** and **4b**

Having iodo-phosphonates **4a** and **4b** in hand, the HWE reaction with aldehyde **5**[8] was examined by the combined use of LiCl and organic bases (Scheme 3).[9] As an initial attempt, the reaction of methyl derivative **4a** was examined by using Hünig's base, giving the desired product **6** in 22% yield with poor stereoselectivity (Scheme 3, entry 1). By using 1,8-diazabicylo[5.4.0]undec-7-ene (DBU), the yield was improved to 68%, albeit poor stereoselectivity (Scheme 3, entry 2). In contrast, the reaction of isopropyl derivative **4b** with Hünig's base showed excellent stereoselectivity (Scheme 3, entry 3).[10] Furthermore, use of DBU gave **6** in better yield (60%) without any decrease in the stereoselectivity (Scheme 3, entry 4).

The *Z*/*E* stereochemistry of **6** was assigned by the ^{1}H NMR chemical shift of the vinyl proton according to the literature.[11] The signal of a vinyl proton with *cis* relationship to a sulfinyl group appears at a lower field compared to that of the *trans* counterpart (Figure 1, a). By considering this general tendency, the major isomer of **6** was assigned to be *Z*, while the minor isomer was assigned to be *E*.[12]



entry	R	base	time / min	yield / %	*Z*/*E*
1	Me	*i*-Pr$_2$NEt	60	22	62/38
2	Me	DBU	10	68	63/37
3	*i*-Pr	*i*-Pr$_2$NEt	60	31	93/7
4	*i*-Pr	DBU	10	60	94/6

Scheme 3 HWE reaction with iodo phosphonates **4a**,**b** and aldehyde **5**

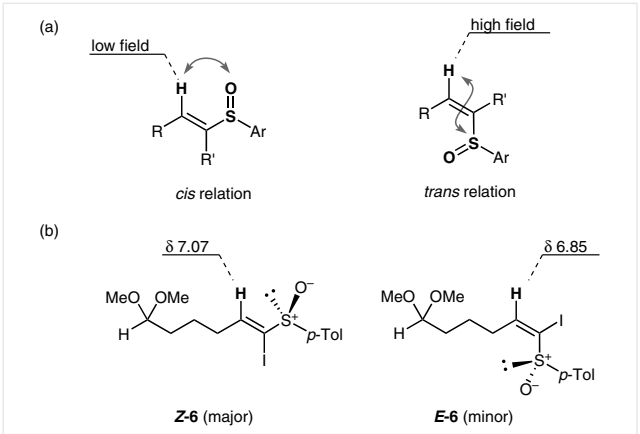
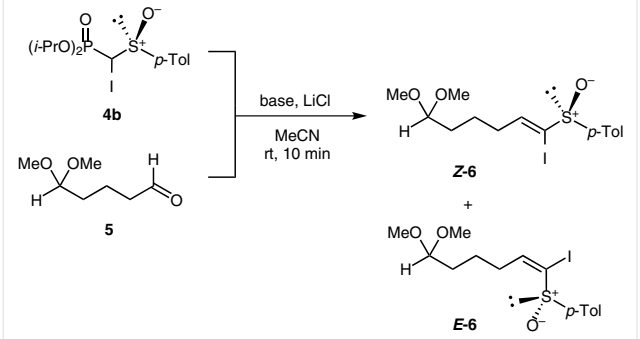


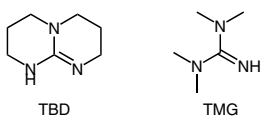
Figure 1 Stereoidentification of vinyl sulfoxides

We next screened bases to improve the yield in the reaction of isopropyl derivative **4b** (Scheme 4). The use of 1,1,3,3-tetramethylguanidine (TMG) as a base gave the desired product in 74% yield with an excellent *Z*/*E* selectivity (Scheme 4, entry 1). When 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) was used as the base, product **6** was obtained in comparable yield (Scheme 4, entry 2). Furthermore, use of excess **4b** (1.5 equiv) over aldehyde **5** resulted in the com-



entry	base	**4b**	**5**	yield / %	*Z*/*E*
1	TMG	1.0	1.2	74[a]	94/6
2	TBD	1.0	1.2	73[a]	93/7
3	TBD	1.5	1.0	81[b]	98/2
4	DBU[c]	1.0	1.2	60[a]	94/6

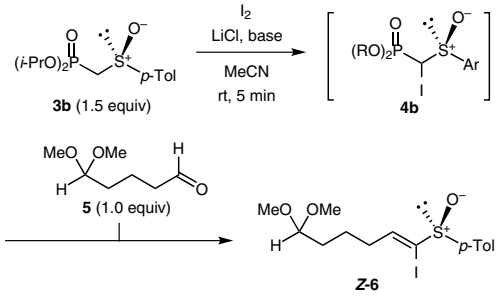
a) Based on **4b**, b) Based on **5**
c) See Scheme 3, entry 4



Scheme 4 Optimization of the reaction conditions

plete consumption of aldehyde **5**, giving **6** in high yield (Scheme 4, entry 3).

Although an optimal set of reaction conditions was thus secured, a difficulty that still remained was the instability of iodo-sulfinylphosphonate **4b**. To resolve this issue, a one-pot protocol was examined to generate **4b** in situ, followed by HWE reaction (Scheme 5).[13] Upon treatment of phosphonate **3b** with TBD and LiCl in MeCN, I_2 was added at room temperature.[14] After consumption of **3b** and generation of **4b** assured by TLC monitoring (**3b**: R_f = 0.40, **4b**: R_f = 0.58, EtOAc), aldehyde **5** was added. Further stirring for ten minutes at room temperature gave α-iodovinyl sulfoxide **6** in 94% yield with excellent stereoselectivity (*Z*/*E* =97:3, Scheme 5, entry 1). Comparably, when DBU was employed, a high yield (86%) and excellent *Z*-stereoselectivity (*Z*/*E* = 97:3, Scheme 5, entry 2) resulted, while the use of TMG gave poor yield (Scheme 5, entry 3).



entry	base	yield / %	*Z*/*E*
1	TBD	94	97/3
2	DBU	86	97/3
3	TMG	44	96/4

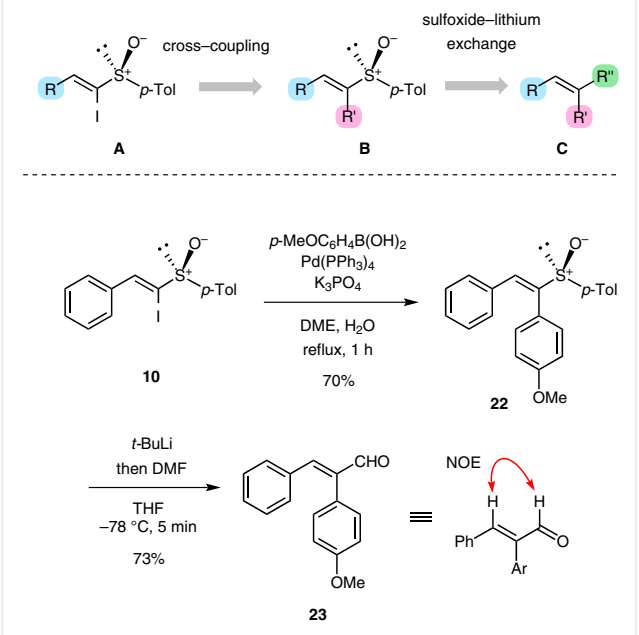
Scheme 5 Optimization of conditions by varying bases

This one-pot protocol would be useful for the preparation of various α-iodovinyl derivatives, and for the large-scale preparation, DBU (less expensive base) is more attractive. Indeed, when the same reaction was conducted with DBU on a 16 g scale, the desired product **6** was obtained in 82% yield without any loss of the stereoselectivity. Characteristics of this protocol are: 1) the one-pot procedure avoids tedious handling of iodo-phosphonate, 2) excellent *Z*/*E* selectivity, 3) use of inexpensive base (DBU), in particular for the large-scale synthesis.

We next focused on the scope of the reaction, employing several carbonyl compounds (Table 1). For comparison, DBU and TBD were employed as the base. With DBU, the stereoselectivity was poor in some cases, which can be compensated by the use of TBD.[15]

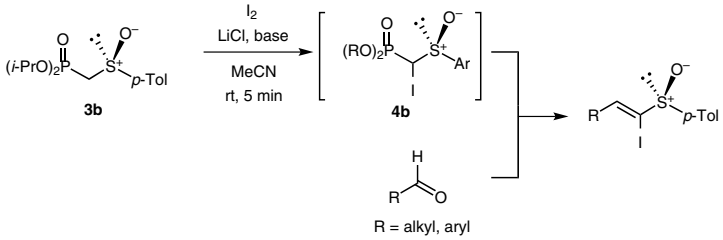
Hydrocinnamaldehyde (**7**) gave the corresponding product **8** in high yields with excellent *Z* selectivities (Table 1, entries 1, 2). Aromatic aldehydes, such as benzaldehyde (**9**, Table 1, entries 3, 4) and furfural (**11**, Table 1, entries 5, 6), worked well. When TBD was used as a base, the products **10** and **12** were obtained in 71% yield (Table 1, entry 3) and 85% yield (Table 1, entry 6), respectively, with excellent *Z* selectivities. In contrast, use of DBU decreased the *Z*/*E* selectivity to 77:23 (Table 1, entry 4) or 90:10 (Table 1, entry 5), though the yields were good. The reaction of conjugated aldehyde **13** gave the desired trisubstituted olefin **14** in excellent yield with perfect *Z* selectivity in both cases of DBU (Table 1, entry 7) and TBD (Table 1, entry 8). Unfortunately, α-methyl cinnamaldehyde (**15**) resulted in low yield (Table 1, entries 9, 10). Moreover, branched aliphatic aldehydes **17** and **19** gave only moderate yields with the significantly decreased stereoselectivities (Table 1, entries 11–14). In addition, this protocol turned out to be inapplicable for ketone such as **21**[16] (entries 15, 16), indicating a limitation of this procedure toward tetrasubstituted olefins.

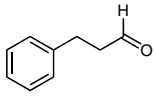
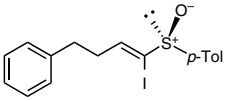
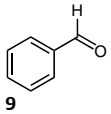
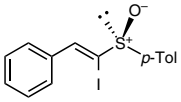
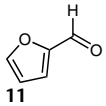
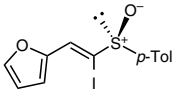
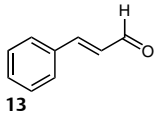
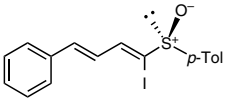
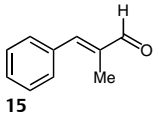
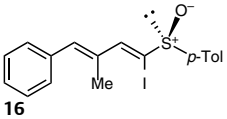
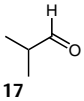
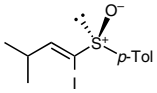
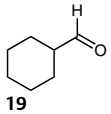
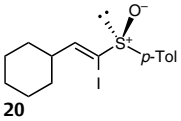
Some utility of α-halovinyl sulfoxide in the synthesis of trisubstituted olefin was demonstrated by successive cross-coupling and sulfoxide–lithium exchange followed by trapping with electrophile (Scheme 6). The cross-coupling reaction of **10** with *p*-methoxyphenylboronic acid by using $Pd(PPh_3)_4$ and K_3PO_4 gave **22** in stereospecific manner (70% yield). Sulfoxide–lithium exchange[17] of **22** with *t*-BuLi followed by the trapping with DMF gave trisubstituted olefin **23** in 73% yield. The diagnostic NOE correlation between the vinyl proton and the formyl group verified the *E* stereochemistry of **23**. This result shows potential utility of α-halovinyl sulfoxides for the preparation of various trisubstituted olefins with a high stereoselectivity.



Scheme 6 Further transformation

Table 1 Substrate Scope



Entry	Aldehyde	Product	Base	Yield (%)	*Z*/*E*
1	 **7**	 **8**	DBU	85	94:6
2			TBD	86	94:6
3	 **9**	 **10**	DBU	78	77:23
4			TBD	71	95:5
5	 **11**	 **12**	DBU	81	90:10
6			TBD	85	*Z* only
7	 **13**	 **14**	DBU	94	*Z* only
8			TBD	83	*Z* only
9[a]	 **15**	 **16**	DBU	30	83:17
10[a]			TBD	27	*Z* only
11	 **17**	 **18**	DBU	50	67:33
12			TBD	49	67:33
13	 **19**	 **20**	DBU	76	71:29
14			TBD	55	71:29
15	 **21**	–	DBU	n.r.	–
16			TBD	n.r.	–

[a] Recovery of **15**.

In conclusion, the stereoselective synthesis of α-iodovinyl sulfoxides became possible by a one-pot iodination–HWE protocol employing sulfinyl phosphonate, iodine, and aldehyde. The resulting α-iodovinyl sulfoxides serve as potential precursors for the preparation of trisubstituted olefins, by subsequent coupling and sulfoxide–lithium exchange. Further studies on applications are in progress in our group.

Acknowledgment

This work was supported by a Grant-in-Aid for Specially Promoted Research (No.23000006 and No.15K13690) from JSPS.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561654.

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(6) Mikolajczyk, M.; Midura, W.; Grzejszczak, S.; Zatorski, A.; Chefczynska, A. *J. Org. Chem.* **1978**, *43*, 473.

(7) The iodination was quenched by adding H_2O. Quenching by aq 10% $Na_2S_2O_3$ gave only the starting material **3a**,**b**, though the full conversion of the starting material and generation of desired product **4a**,**b** was confirmed by TLC analysis.

(8) Aldehyde **5** was used for the optimization study in the context of our study on modular synthesis of planar chiral carba-paracyclophanes. For the synthesis of **5**: Claus R. E., Schreiber S. L.; *Org. Synth.*; **1986**, *64*: 150; see also ref. 4.

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(10) Use of a bulky phosphonate tends to increase the *Z* selectivity. This fact suggests that formation of the oxaphosphetane intermediate and/or elimination of the phosphate become slow presumably due to the steric hindrance around the phosphorus atom. Therefore, a thermodynamically controlled product is preferably obtained. For related examples see: (a) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. (b) Boschelli, D.; Takemasa, T.; Nishitani, Y.; Masamune, S. *Tetrahedron Lett.* **1985**, *26*, 5239.

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(12) For related examples of the NMR analyses of tri- or tetrasubstituted α-iodovinyl sulfoxide, see: (a) Satoh, T.; Takano, K.; Ota, H.; Someya, H.; Matsuda, K.; Koyama, M. *Tetrahedron* **1998**, *54*, 5557. (b) Fernández de la Pradilla, R.; Viso, A.; Castro, S.; Fernández, J.; Manzano, P.; Tortosa, M. *Tetrahedron* **2004**, *60*, 8171; and references cited therein.

(13) One-pot iodination and HWE reaction was hinted by: (a) Kozawa, Y.; Mori, M. *J. Org. Chem.* **2003**, *68*, 3064. (b) Shibahara, S.; Fujino, M.; Tashiro, Y.; Okamoto, N.; Esumi, T.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Synthesis* **2009**, 2935.

(14) This reaction is exothermic, therefore, the reaction was conducted in water bath for the large-scale reaction.

(15) **Typical Procedure of One-Pot Iodination–HWE Reaction**
In a two-necked round-bottomed flask was placed LiCl (44.7 mg, 0.314 mmol), to which a solution of sulfinyl-phosphonate **3b** (100 mg, 0.314 mmol) in MeCN (1 mL) and TBD (87.4 mg, 0.628 mmol) or DBU (94.0 µL, 0.628 mmol) was added successively at room temperature. The mixture was stirred, and I_2 (solid, 79.7 mg, 0.314 mmol) was added in several portions. The mixture turned into an orange color solution. After stirring for 10 min, a solution of benzaldehyde (**9**, 22.2 mg, 0.209 mmol) in MeCN (1 mL) was added slowly, and the stirring was continued for 5 min at room temperature. The reaction was quenched by adding 10% $Na_2S_2O_3$ aqueous solution, the products were extracted with EtOAc (3×), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane–EtOAc = 2:1) to obtain **10** in 71% yield (*Z*/*E* = 95:5, TBD) or 78% yield (*Z*/*E* = 77:23, DBU). Recrystallization (EtOAc–hexane = 2:1) gave pure (***Z***)-**10** as colorless needles.
Analytical Data for (***Z***)-**10**: R_f = 0.74 (hexane–EtOAc = 2:3); mp 84–86 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.41 (s, 3 H), 7.31 (d, 2 H, *J* = 8.1 Hz), 7.41–7.42 (m, 3 H), 7.60 (d, 2 H, *J* = 8.1 Hz), 7.77 (dd, 2 H, *J* = 6.5, 2.8 Hz), 8.16 (s, 1 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.5, 110.3, 126.0, 128.4, 129.2, 129.9, 130.0, 134.1, 138.9, 139.8, 142.3. IR (neat): 3052, 3023, 2973, 2920, 2865, 2360, 2342, 1593, 1491, 1445, 1397, 1266, 1178, 1084, 1059, 925, 872, 808, 749, 692 cm^{-1}. $[\alpha]_D^{20}$ +22.3 (*c* 1.11, $CHCl_3$). HRMS (ESI-TOF): *m*/*z* calcd for $C_{15}H_{14}IOS$ $[M + H]^+$: 368.9805; found: 368.9807. Anal. Calcd for $C_{15}H_{13}IOS$: C, 48.93; H, 3.56; S, 8.71. Found: C, 48.96; H, 3.53; S, 8.52.

(16) Attempt for the reaction with acetophenone also failed, resulting in the formation of many unidentified byproducts.

(17) (a) Gilman, H.; Eidt, S. H. *J. Am. Chem. Soc.* **1956**, *78*, 3848. (b) Durst, T.; LeBelle, M. J.; Van den Elzen, R.; Tin, K. C. *Can. J. Chem.* **1974**, *52*, 761.