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Convergent and Stereoselective Synthesis of Trisubstituted *E*-Alkenyl Bromides and Iodides via *β*-Oxido Phosphonium Ylides

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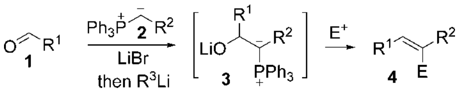
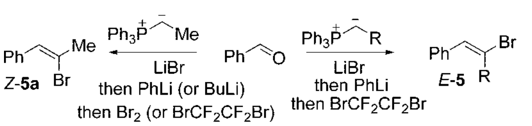
The Wittig reaction is a widely used regiospecific and often highly stereoselective way of making alkenes using readily available carbonyl compounds and phosphonium ylides.[1] With aldehydes **1**, nonstabilized triphenylphosphonium ylides **2** (R^2 = alkyl) are well-known to give *cis*-alkenes preferentially, whereas the Wittig−Schlosser variant[2] provides a synthetically important entry to *trans*- ("without exception"[2b]) 1,2-disubstituted alkenes **4** (E= H) by way of stereoselective *C*-protonation of an intermediate *β*-oxido ylide **3** (Scheme 1). Trapping the intermediate *β*-oxido ylide **3** with electrophiles other than a proton [SCOOPY (α-Substitution plus Carbonyl Olefination via *β*-Oxido Phosphorus Ylides) process][3] has the potential to generate trisubstituted olefins **4** (E ≠ H), which would be of significant value provided the process occurred with high stereocontrol. The later has been previously realized using several nonstabilized ylides and trapping the intermediate *β*-oxido ylides with aldehyde electrophiles (e.g., formaldehyde gives *Z*-allylic alcohols **4**, E = CH_2OH).[2]

Scheme 1. Wittig−Schlosser Reaction



The original study by Schlosser and Christmann in 1969 reported a single example of bromination: (*Z*)-2-bromo-1-phenylprop-1-ene (*Z*-**5a**, Scheme 2) was prepared (23% yield by GC, *E*/*Z* < 10:90) from Br_2 and the *β*-oxido ylide derived from benzaldehyde and ethylidene(triphenyl)phosphorane.[4] In 2001 Fu and co-workers in Shanghai improved the yield using $BrCF_2CF_2Br$ as the electrophile, although reactions using hexylidene(triphenyl)phosphorane and benzaldehyde or hexanal were found to be nonstereoselective (*E*/*Z* 68:32 and 59:41, respectively).[5] (*Z*)-Iodoalkenes **4** (E = I, R^1 = alkyl/aryl, R^2 = Me, 32−51% yield, *E*/*Z* < 10:90, Scheme 1) have been obtained using 1,2-diiodoethane with *β*-oxido ylides derived from aldehydes and ethylidene(triphenyl)phosphorane.[6] Analysis of all the prior halogenation studies indicated that they had been mainly carried out with ethylidenephosphorane and also that the limited studies with a higher alkylidenephosphorane[5] were likely carried out under conditions not conducive to high stereocontrol.[2b] Given the enduring challenge of developing general methods for the stereocontrolled synthesis of trisubstituted alkenes,[7] together with the importance of stereodefined alkenyl bromides and iodides as precursors to a host of organometallic intermediates (e.g., alkenyl lithiums, coppers, palladiums) for such processes,[8] we sought to investigate the SCOOPY reaction to such alkenyl halides and communicate here results which significantly expand its utility, remarkably providing *E*-isomers, with high geometrical integrity.

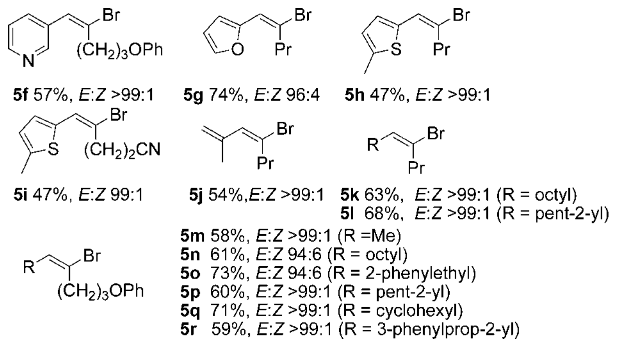
Scheme 2. Synthesis of 2-Bromo-1-phenylalkenes **5a**−**e**



5b 68%,*E*:*Z* 87:13 (R = Et)
5c 59%,*E*:*Z* 92:8 (R = Pr)
5d 72%,*E*:*Z* 89:11 (R = *i*-Pr)
5e 57%,*E*:*Z* 94:6 (R = $(CH_2)_3OPh$)

Under the conditions described by Schlosser as optimal for generating *trans*-1,2-disubstituted alkenes,[2b] we first synthesized 2-bromo-1-phenylprop-1-ene and uneventfully obtained *Z*-**5a** as expected (47%, *E*/*Z* < 1:99 using $BrCF_2CF_2Br$, Scheme 2).[4,5,9,10] Surprisingly however, we found the stereochemical outcome on bromination is acutely sensitive to the size of the alkylidene: increasing the latter beyond ethylidene led predominantly to *E*-2-bromo-1-phenylalkenes *E*-**5b**−**e** (*E*/*Z* 87:13−94:6, Scheme 2). Furthermore, stereocontrol is essentially complete for *E*-alkenyl bromides in the majority of the subsequent cases we have examined: from heteroaromatic aldehydes (**5f**−**i**), an α,*β*-unsaturated aldehyde (**5j**), and aliphatic aldehydes (**5k**−**r**)[11] (Chart 1), thus providing a preparatively useful new method for accessing such systems.[12,13] In most of these examples, the *β*-oxido ylide was added to $BrCF_2CF_2Br$ as this was found to maximize yields[14] (stereoselectivity was not affected by the order of addition), and addition of *t*-BuOK at the end of the reaction was not required to induce elimination of Ph_3PO.[2]

Chart 1. *E*-Bromoalkenes **5f**−**r** Obtained by SCOOPY Reaction



5f 57%, *E*:*Z* >99:1
5g 74%, *E*:*Z* 96:4
5h 47%, *E*:*Z* >99:1
5i 47%, *E*:*Z* 99:1
5j 54%,*E*:*Z* >99:1
5k 63%, *E*:*Z* >99:1 (R = octyl)
5l 68%, *E*:*Z* >99:1 (R = pent-2-yl)
5m 58%, *E*:*Z* >99:1 (R =Me)
5n 61%, *E*:*Z* 94:6 (R = octyl)
5o 73%, *E*:*Z* 94:6 (R = 2-phenylethyl)
5p 60%, *E*:*Z* >99:1 (R = pent-2-yl)
5q 71%, *E*:*Z* >99:1 (R = cyclohexyl)
5r 59%, *E*:*Z* >99:1 (R = 3-phenylprop-2-yl)

Compared with alkenyl bromides, alkenyl iodides often show beneficial levels of increased reactivity and/or selectivity in synthetic endeavors.[8] Iodination of *β*-oxido ylides to give iodoalkenes **6a**−**n** (Chart 2) was found to display a similar selectivity profile to that observed in the brominations. Moving from 1,2-diiodoethane to iodine as the electrophile to which the *β*-oxido ylides were added improved yields and, in particular, geometrical purities of iodooalkenes derived from aromatic aldehydes.

A representative intermediate *β*-oxido ylide **3** (R^1 = octyl, R^2 = Pr), which on bromination led to *E*-alkenyl bromide **5k** (octyl and Pr groups exculsively *cis*), gave on standard protonation *trans*-1,2-dialkylsubstituted alkene **4** [octyl (R^1) and Pr (R^2) groups exclusively *trans*, 77%] expected[2a,b] from Schlosser's studies; these results emphasize that alkene stereochemistry arising from a *β*-oxido ylide **3**

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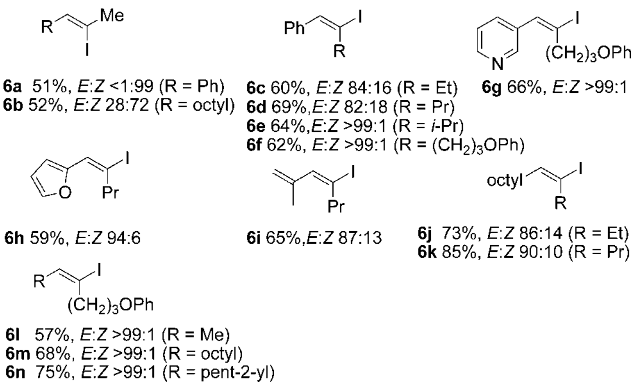
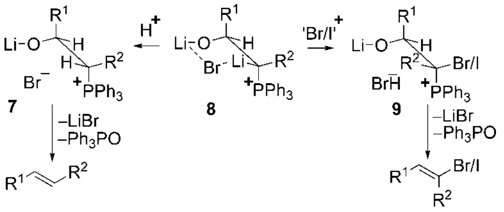
Chart 2. Iodoalkenes **6a**−**n** Obtained by SCOOPY Reaction



6a 51%, *E*:*Z* <1:99 (R = Ph)
6b 52%, *E*:*Z* 28:72 (R = octyl)
6c 60%, *E*:*Z* 84:16 (R = Et)
6d 69%,*E*:*Z* 82:18 (R = Pr)
6e 64%,*E*:*Z* >99:1 (R = *i*-Pr)
6f 62%, *E*:*Z* >99:1 (R = $(CH_2)_3OPh$)
6g 66%, *E*:*Z* >99:1
6h 59%, *E*:*Z* 94:6
6i 65%,*E*:*Z* 87:13
6j 73%, *E*:*Z* 86:14 (R = Et)
6k 85%, *E*:*Z* 90:10 (R = Pr)
6l 57%, *E*:*Z* >99:1 (R = Me)
6m 68%, *E*:*Z* >99:1 (R = octyl)
6n 75%, *E*:*Z* >99:1 (R = pent-2-yl)

is also crucially dependent on the electrophile added.[2,15] Our results necessarily prompt a reappraisal of the origins of stereoselectivity on trapping *β*-oxido phosphonium ylides with electrophiles, which needs to account for protonation (or reaction with formaldehyde) generating alkenes **4** with R^1 and R^2 *trans* (regardless of the size of R^2),[2] whereas bromination and iodination lead to alkenes in which R^1 and R^2 are *cis* (unless R^2 = Me). Although a *β*-oxido ylide in solution is likely comprised of complex species,[16] a model resembling **8** (Scheme 3) has previously been invoked to rationalize protonation (and trapping with carbonyl groups) which proceeds with retention of configuration (possibly aided by prior coordination of the electrophile to LiO) *via* betaine **7**.[2] We tentatively suggest that reaction of noncoordinating halogen electrophiles with the majority of *β*-oxido ylides examined in the present study may predominantly occur by inversion, *via* betaine **9**.

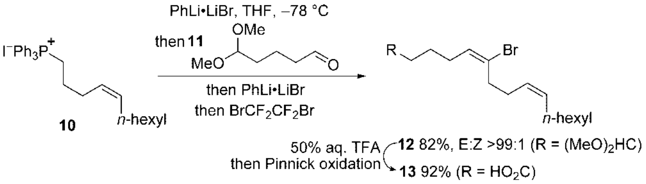
Scheme 3. Possible Origin of Dependence of Alkene Stereochemistry on Electrophile in SCOOPY Reaction



7 **8** **9**

So as to demonstrate utility of the above methodology, we focused on a synthesis of (5*E*,9*Z*)-6-bromohexadeca-5,9-dienoic acid (**13**) isolated from the Okinawan marine sponge *Xestospongia* sp. (Scheme 4).[17]

Scheme 4. Synthesis of Naturally Occurring Brominated Fatty Acid **13**



10

12 82%, E:Z >99:1 (R = $(MeO)_2HC$)
13 92% (R = HO_2C)

Acid **13** is part of a family of fatty acids containing (5*E*,9*Z*)-6-bromodiene functionality, some of which show cytotoxic activity.[18] In the key step, alkenyl bromide **12** was formed in 82% yield with >99% *E*-selectivity from known unsaturated phosphonium salt **10**,[19] acetal aldehyde **11** (1 step from cyclopentene),[20] and $BrCF_2CF_2Br$;[21] subsequent acetal deprotection[22] and Pinnick oxidation[23] gave acid **13** (92%).

In summary, alkylidene(triphenyl)phosphoranes [other than ethylidene(triphenyl)phosphorane] have been shown, on reaction with aldehydes followed by in situ lithiation and subsequent bromination or iodination of the intermediate *β*-oxido ylide, to provide a highly stereoselective route to *E*-alkenyl bromides and iodides. The convergency of the process, combining C═C and C−Hal bond-forming steps in a single operation, together with the regiospecificity of the halide introduction and ready availability of the starting materials suggests this methodology will provide a significant alternative to alkyne hydrometalation strategies, where regioselectivity can also be problematic in unbiased cases.[24] Studies to clarify the origins of the stereoselectivity and extension to other electrophiles are currently under investigation.

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

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(9) All yields reported are for chromatographically purified products. All *E*/*Z* ratios reported were determined on crude reaction mixtures by GC/MS; in some cases, slight variation was observed following chromatographic purification (ref 10). *E*/*Z* assignments were based on NOE studies; also usefully diagnostic is the fact that ═CH *cis* to Br (or I) is uniformly at larger chemical shift relative to ═CH *trans* to Br (or I). For an unambiguous example supporting this, see: Brown, H. C.; Bhat, N. G.; Rajagopalan, S. *Synthesis* **1986**, 480–482.
(10) See Supporting Information for details.
(11) Whilst α-branched aliphatic aldehydes were excellent substrates (giving alkenyl bromides **5l**−**m, q**−**r**), use of pivaldehyde led only to *trans*-1,2-disubstituted alkene **4** (R^1 = CMe_3, R^2 = $(CH_2)_3OPh$, 59%).
(12) In contrast, alkenyl halide syntheses starting with halogenated ylides [Ph_3P═CRBr (or I)] are known to be nonstereoselective (unless R = Me, which leads to *Z*-selectivity); see: (a) Smithers, R. H. *J. Org. Chem.* **1978**, *43*, 2833–2838. (b) Chen, J.; Wang, T.; Zhao, K. *Tetrahedron Lett.* **1994**, *35*, 2827–2828.
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