

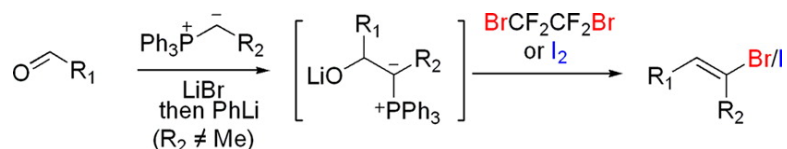
Communication

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

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

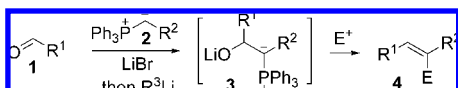
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The Wittig reaction is a widely used regioselective and often highly stereoselective way of making alkenes using readily available carbonyl compounds and phosphonium ylides.¹ With aldehydes **1**, nonstabilized triphenylphosphonium ylides **2** ($R^2 = \text{alkyl}$) are well-known to give *cis*-alkenes preferentially, whereas the Wittig–Schlosser variant² provides a synthetically important entry to *trans*- (“without exception”^{2b}) 1,2-disubstituted alkenes **4** ($E = \text{H}$) 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

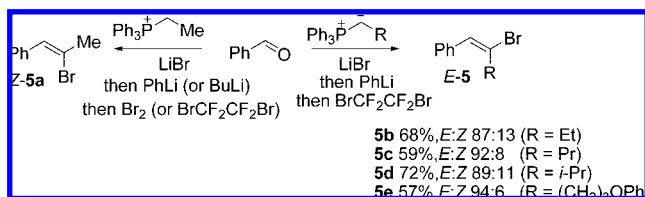
Scheme 1. Wittig–Schlosser Reaction



than a proton [SCOOPY (α -Substitution plus Carbonyl Olefination via β -Oxido Phosphorus Ylides) process]³ has the potential to generate trisubstituted olefins **4** ($E \neq \text{H}$), which would be of significant value provided the process occurred with high stereocontrol. The latter 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**, $E = \text{CH}_2\text{OH}$).²

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

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

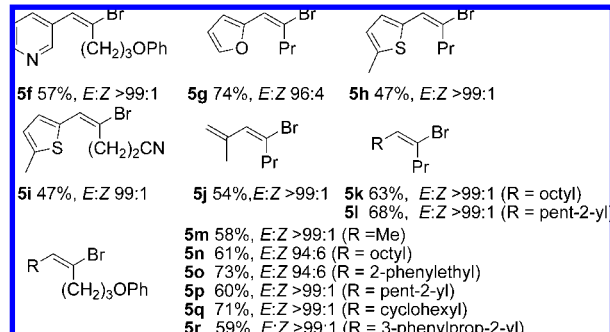


Br_2 and the β -oxido ylide derived from benzaldehyde and ethylidene(triphenyl)phosphorane.⁴ In 2001 Fu and co-workers in Shanghai improved the yield using $\text{BrCF}_2\text{CF}_2\text{Br}$ as the electrophile, although reactions using hexylidene(triphenyl)phosphorane and benzaldehyde or hexanal were found to be nonstereoselective (E/Z 68:32 and 59:41, respectively).⁵ (*Z*)-Iodoalkenes **4** ($E = \text{I}$, $R^1 = \text{alkyl/aryl}$, $R^2 = \text{Me}$, 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 ethylidene phosphorane and also that the limited studies with a higher alkylidene phosphorane⁵ 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.

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 $\text{BrCF}_2\text{CF}_2\text{Br}$, 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

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

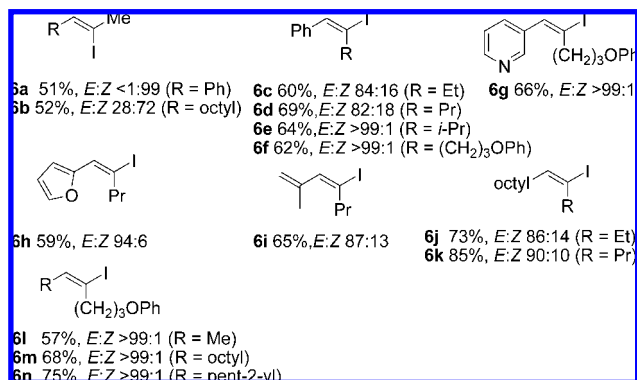


new method for accessing such systems.^{12,13} In most of these examples, the β -oxido ylide was added to $\text{BrCF}_2\text{CF}_2\text{Br}$ as this was found to maximize yields¹⁴ (stereoselectivity was not affected by the order of addition), and addition of *t*-BuOK at the end of the reaction was not required to induce elimination of Ph_3PO .²

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 iodoalkenes derived from aromatic aldehydes.

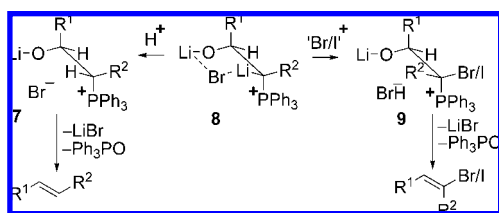
A representative intermediate β -oxido ylide **3** ($R^1 = \text{octyl}$, $R^2 = \text{Pr}$), which on bromination led to *E*-alkenyl bromide **5k** (octyl and Pr groups exclusively *cis*), gave on standard protonation *trans*-1,2-dialkylsubstituted alkene **4** [octyl (R^1) and Pr (R^2) groups exclusively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

Chart 2. Iodoalkenes 6a–n Obtained by SCOOPY Reaction



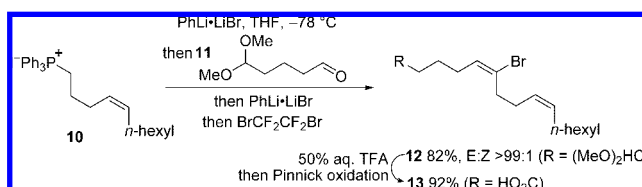
is also crucially dependent on the electrophile added.^{2,15} Our results necessarily prompt a reappraisal of the origins of stereoselectivity on trapping β -oxido phosphonium ylides with electrophiles, which needs to account for protonation (or reaction with formaldehyde) generating alkenes **4** with 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 $R^2 = \text{Me}$). Although a β -oxido ylide in solution is likely comprised of complex species,¹⁶ a model resembling **8** (Scheme 3)

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



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**.

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**

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 $\text{BrCF}_2\text{CF}_2\text{Br}$;²¹ subsequent acetal deprotection²² and Pinnick oxidation²³ 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 convergence of the process, combining $\text{C}=\text{C}$ and $\text{C}-\text{Hal}$ bond-forming steps in a single operation, together with the regioselectivity of the halide introduction and ready availability of the starting materials suggests this methodology will provide a significant alternative to alkyne hydro-metalation 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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- (12) In contrast, alkenyl halide syntheses starting with halogenated ylides [$\text{Ph}_3\text{P}=\text{CRBr}$ (or I)] are known to be nonstereoselective (unless $R = \text{Me}$, 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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