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Stereoselective Synthesis of All-Carbon Tetrasubstituted Alkenes from In Situ Generated Ketenes and Organometallic Reagents

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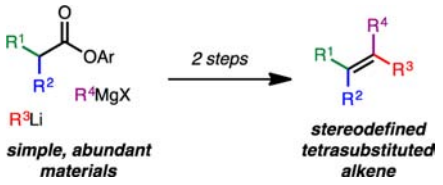
ABSTRACT



Stereoselective synthesis of tetrasubstituted alkenes is a challenging problem in chemical synthesis. New protocols to access this important, yet simple, structural motif are of fundamental significance because they are found in many valuable molecules and can be utilized in a variety of important complexity building chemical transformations. The two-step strategy presented herein involves stereoselective generation of an alkenyl pseudohalide followed by a stereospecific metal-catalyzed cross-coupling.

The alkene moiety is one of the most versatile and widespread functional groups among small molecules. Oftentimes, it is necessary to prepare substituted alkenes with high degrees of stereoselectivity, either because it is present in an important molecule[1] or because subsequent chemical reactions require an established geometry.[2] While many methods have been developed for the stereoselective synthesis of di- and trisubstituted alkenes,[3] stereoselective synthesis of all-carbon tetrasubstituted alkenes remains a challenge.[4]

Herein, we present a two-step strategy to prepare a wide-range of stereodefined all-carbon tetrasubstituted alkenes from simple carboxylic esters and organometallic reagents (Scheme 1B). This method is notable not only for the ease in which tetrasubstituted alkenes can be prepared but also the substrate scope.

Traditional methods for the stereoselective synthesis of all-carbon tetrasubstituted alkenes are based on metal-catalyzed vicinal-dicarbofunctionalization of alkynes.[4] While significant progress has been achieved in this area, many of these methods rely on the use of directing groups to control stereoselectivity. This strategy results in inherently less practical processes, as these groups must be first introduced and later removed.[4] An alternative approach toward stereodefined tetrasubstituted alkenes is outlined in Scheme 1A. Alkenyl pseudohalides are competent partners for metal-catalyzed cross-coupling.[5,6] Therefore, if these species (**II** or **III**) could be generated with control

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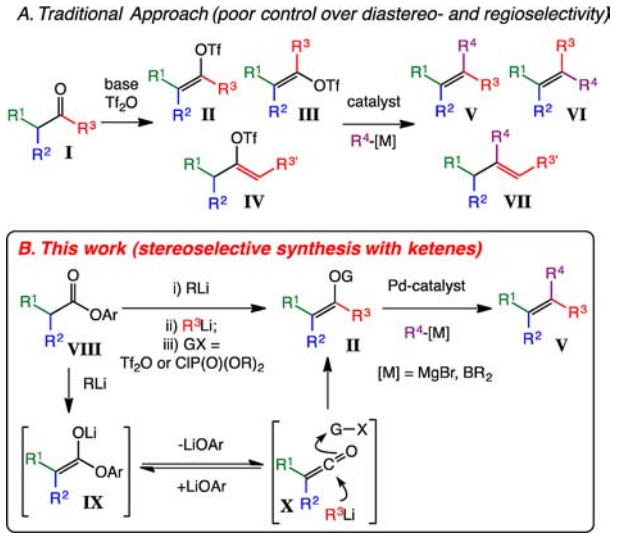
of stereochemistry, this would constitute a straightforward synthesis of stereodefined tetrasubstituted alkenes (**V** or **VI**).

Scheme 1. General Strategy for the Stereoselective Synthesis of All-Carbon Tetrasubstituted Alkenes

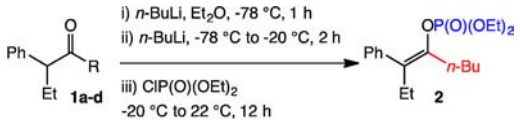


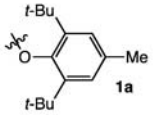
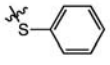
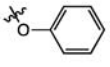
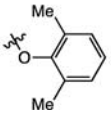
Common strategies for the synthesis of trisubstituted alkenyl pseudohalides (**II**–**III**) generally rely on enolization of a ketone (**I**) and subsequent trap with an appropriate electrophile. However, unless specialized substrates/conditions are utilized that favor formation of one alkene isomer (e.g., **II** and not **III** or **IV**), low selectivity is observed.[7,8,9d] To render this straightforward strategy feasible for the synthesis of stereodefined tetrasubstituted alkenes, we sought to develop a general method for the stereoselective synthesis of alkenyl pseudohalides from enolates.

We were inspired by seminal studies by Tidwell[9] and Seebach[10,11] on the stereoselective synthesis of stereodefined lithium enolates. Each method relies on the stereoselective addition of an organolithium reagent to a differentially substituted ketene. In general, as established by Tidwell, good selectivities are observed when the size difference between the ketene substituents is large (e.g., Ph/Et ketene, >20:1 dr whereas Ph/*i*-Pr ketene, 1:4 dr).[9] Tidwell's method, however, remains limited to ketenes that are relatively easy to handle and isolate (e.g., Ph/Et ketene). When less stable ketenes are used (e.g., Et/Et ketene), low yields of the desired products are observed and significant quantities of ketene dimerization adducts are formed.[9f]

To avoid complications arising from the use of isolated ketenes, Seebach and co-workers reported that ketenes could be generated in situ by fragmentation of 2,6-di-*tert*-butyl hydroxytoluene (BHT) ester lithium enolates (**VIII** → **IX** → **X**) (Scheme 1B).[10] When the ketenes (**X**) are generated in the presence of an alkyllithium reagent (R^3Li), stereoselective addition occurs to provide the corresponding enol silanes (**II,** G = $SiMe_3$) after quench of the lithium enolates with Me_3SiCl. These reactions are limited to only dialkylketenes but do provide the products with moderate to excellent levels of stereoselectivity (e.g., *i*-Pr/Me ketene, 7:1 dr, and *t*-Bu/Me ketene, >99:1 dr).

Table 1. Optimization Studies[a]



entry	R	yield (%)[b]	Z:E[c]
1	 **1a**	<2	--
2	 **1b**	<2	--
3	 **1c**	<2	--
4	 **1d**	88	>20:1

[a] See the Supporting Information for experimental details. [b] Yield of isolated product after silica gel column chromatography. [c] Determined by ^{31}P NMR (170 MHz) analysis of the unpurified reaction mixture.

To initiate our studies, we attempted the synthesis of **2** starting from phenolic esters (**1a**–**d**) under the conditions illustrated in Table 1. In line with reports by Seebach,[10] aryl/alkyl-substituted ester enolates derived from **1a** do not undergo fragmentation to generate ketenes (Table 1, entry 1). We reasoned that perhaps the low reactivity of these ester enolates was due to the poor leaving group ability of BHT. Therefore, we guided the selection of esters to evaluate based on two characteristics: (1) sufficient steric hindrance so as to protect the carbonyl from nucleophilic addition by the first equivalent of *n*-BuLi and (2) good

(7) This strategy has been shown to be effective in one example. Wallace, D. J.; Campos, K. R.; Shultz, C. S.; Klapars, A.; Zewge, D.; Crump, B. R.; Phenix, B. D.; McWilliams, J. C.; Krska, S.; Sun, Y.; Chen, C.; Spindler, F. *Org. Process Res. Dev.* **2009**, *13*, 84–90.

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(11) For use of BHT ester enolates, see (a) Barbero, A.; Pulido, F. J. *Synlett* **2001**, 827–829. (b) Fehr, C.; Galindo, J. *J. Org. Chem.* **1988**, *53*, 1828–1830. (c) Fehr, C.; Galindo, J. *J. Am. Chem. Soc.* **1988**, *110*, 6909–6911.

leaving group ability (R in Table 1) such that the potentially unstable ketene is generated readily at low temperatures (−20 °C) and short reaction time (< 2 h). Furthermore, we initially investigated the formation of enol phosphates (vs enol triflates) as these compounds are stable. Reactions with phenylthio ester **1b** or a phenyl ester **1c** result in competitive addition of the first equivalent of *n*-BuLi to the carbonyl as opposed to deprotonation (Table 1, entries 2 and 3). We ultimately identified the ester derived from 2,6-dimethylphenol (**1d**) (Table 1, entry 4) as having an ideal balance between sufficient steric hindrance to block nucleophilic addition of the first equivalent of *n*-BuLi and reasonable rate of ketene generation at low temperatures (−20 °C, 2 h).

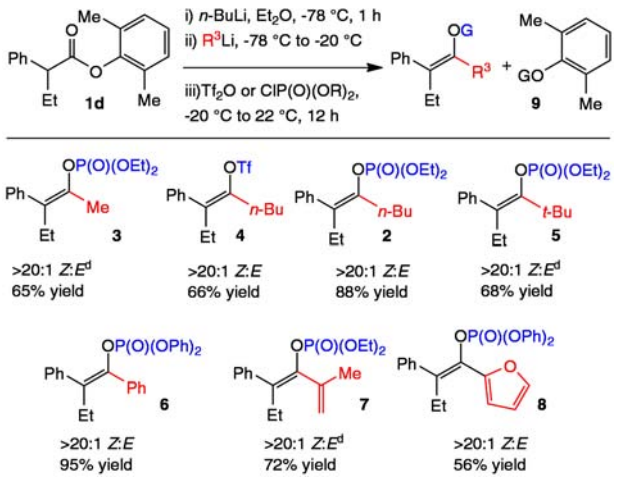

Figure 1. Diastereoselective synthesis of enol triflates and phosphates from ester **1d**. Key: (a) See the Supporting Information for experimental details. (b) Yield of isolated product after silica gel column chromatography. (c) Determined by either ^{1}H NMR (400 MHz), ^{31}P NMR (170 MHz), or ^{19}F NMR (376 MHz) analysis of the unpurified reaction mixture. Relative configuration determined by analysis of 2D NMR spectra. (d) After addition of R^3Li, the reaction mixture was allowed to warm to 0 °C.

With an optimized set of conditions in hand, we explored the substrate scope of the organolithium reagent.[12,13] As illustrated in Figure 1, a variety of organolithium reagents (alkyl-, aryl-, vinyl-, heteroaryl-based) can be utilized in this process with uniform success (generally, > 65% yield and > 20:1 *Z*/*E*). The generated lithium enolate can either be trapped with Tf_2O or $ClP(O)(OR)_2$ (R = Et or Ph) to provide the alkenyl pseudohalide in good yield and selectivity. In general, formation of the enol phosphate results in higher yield than the enol triflate primarily due to the lower stability associated with the enol triflates (compare Figure 1, compounds **4** and **2**).

The method has also been extended to reactions of esters with various substituents (Figure 2). Several points are noteworthy: (1) good to excellent selectivities are observed

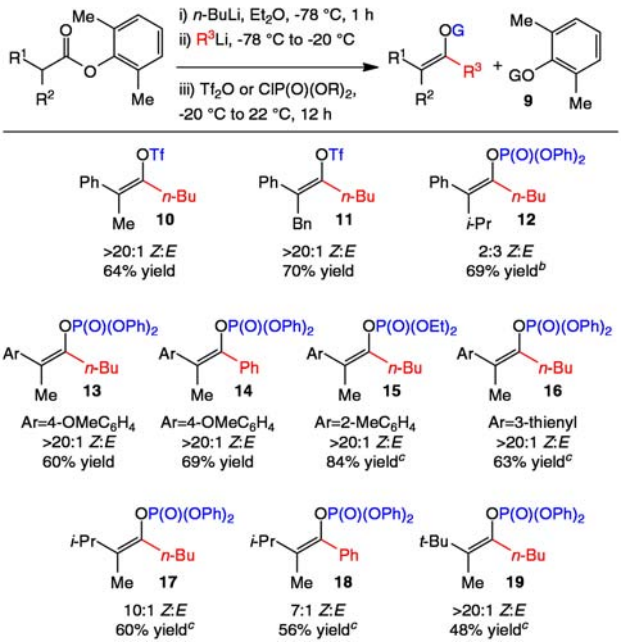

Figure 2. Stereoselective synthesis of various enol triflates and phosphates. Key: (a) See the Supporting Information for experimental details. Yield refers to yield of isolated product after silica gel column chromatography. *Z*/*E* ratios determined by either ^{1}H NMR (400 MHz), ^{31}P NMR (170 MHz), or ^{19}F NMR (376 MHz) analysis of the unpurified reaction mixture. Relative configuration determined by analysis of 2D NMR spectra. (b) After the addition of R^3Li the reaction was warmed to 0 °C. (c) *t*-BuLi was used instead of *n*-BuLi for generation of the enolate.

for most cases, the exception being **12** (2:3, *Z*/*E*) where both the substituents are similar in size.[9] (2) Reactions with esters bearing heteroaryl (**16**), electron-rich aryl (**13** and **14**), and sterically hindered aryl groups (**15**) work well in this process. Esters that bear an electron-deficient aryl group undergo competitive arene deprotonation with *n*-BuLi and thus lead to a complex mixture of products. (3) Dialkyl esters undergo reaction with good selectivities (**17**−**19**).

With an efficient procedure for the stereoselective synthesis of enol phosphates and enol triflates in hand (Figures 1 and 2) we then focused on establishing conditions for stereospecific Pd-catalyzed cross-coupling. As illustrated in Figure 3, we have identified that Pd-catalyzed cross-coupling of enol phosphates with Grignard reagents proceeds in good yield with < 5% loss in stereochemical purity.[5,6,14,15] Through application of this reaction, a variety of structurally diverse tetrasubstituted alkenes (**20**-**27**) can be prepared readily (Figure 3).

Use of alkyl Grignard reagents that bear *β*-hydrogens (e.g., *n*-BuMgX), however, led to the formation of the

(12) Use of Grignard reagents in place of lithium reagents leads to a complex mixture of products

(13) See the Supporting Information for complete experimental details.

(14) For select cases, purification of the enol phosphate was complicated due to difficult separation of **9** (G = $P(O)(OEt)_2$ or $P(O)(OPh)_2$) from the desired product. The cross-coupling reactions presented in Figure 3, however, are largely unaffected by the presence of **9** (G = $P(O)(OEt)_2$ or $P(O)(OPh)_2$); thus, its separation from the enol phosphates is not crucial. See the Supporting Information for details.

(15) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461–1473.

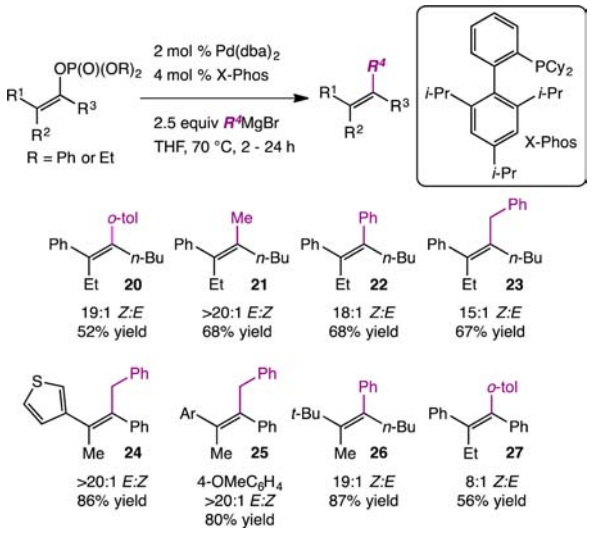

Figure 3. Cross-coupling with enol phosphates. Key: see the Supporting Information for experimental details. Yield refers to yield of isolated product after silica gel column chromatography. *Z*/*E* ratios determined by GC/MS analysis of the unpurified reaction mixtures.

corresponding trisubstituted alkenes through incorporation of hydrogen. This product presumably arises from β-hydride elimination of the generated Pd−alkyl intermediate prior to reductive elimination. Therefore, we directed our efforts toward cross-coupling with alkyl boron reagents as success has been documented in related transformations.[16] As illustrated in eq 1 (Scheme 2), Pd-catalyzed cross-coupling with *n*-Hex-9-BBN and enol triflate **4** generates **28** in good yield (89%) with excellent retention of stereochemistry ($<2\%$ of the corresponding trisubstituted alkene is observed) (eq 1, Scheme 2).[17] It should be noted that multialkyl tetrasubstituted alkenes are difficult to prepare with existing reaction methodology.[4] The present method allows for their synthesis via two distinct routes (e.g., synthesis of **26** and **28**).

The enol triflates prepared herein are also amenable to various other cross-coupling reactions including aryl-Suzuki and Sonogashira (eqs 2 and 3, respectively, Scheme 2).[18] We have by no means explored all possible

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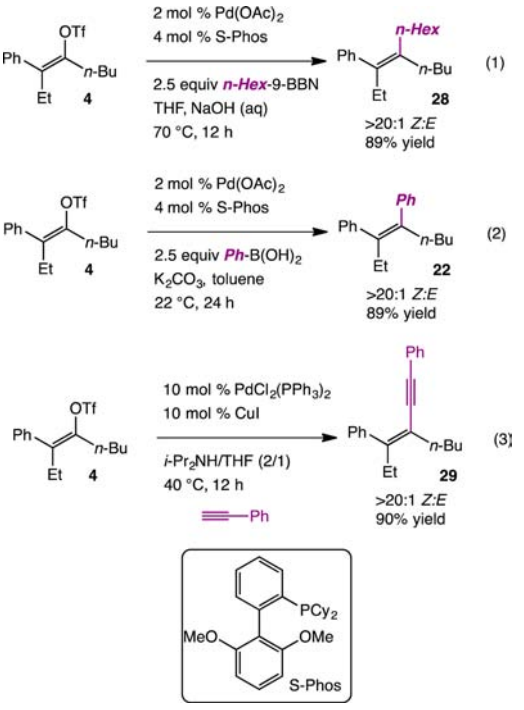
Scheme 2. Cross-Coupling with Enol Triflates



metal-catalyzed cross-coupling reactions, and there are undoubtedly other applications of the enol phosphates and enol triflates prepared in this study.[5]

In summary, a simple two-step synthesis of a wide range of stereodefined tetrasubstituted alkenes from readily available esters and organometallic reagents has been developed. Furthermore, the synthesis and use of in situ generated ketenes described herein should be of utility for the preparation of a variety of other alkenyl systems. Studies along these lines are currently under investigation.

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Supporting Information Available. Experimental procedures, analytical data for all compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.