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The Application of the Shapiro Reaction to the Stereoselective Synthesis of *E*-Trisubstituted Olefins For Cation-Olefin Cyclization by Three Component Coupling

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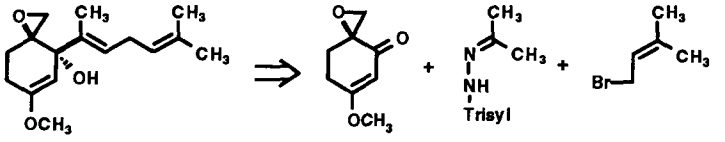
Abstract: *A method is described for the rapid and stereoselective assembly of E-trisubstituted olefins by a convergent process from three components* © 1997 Elsevier Science Ltd.

We have recently developed catalytic enantioselective routes to chiral substrates for cation-olefin cyclization, such as 2,3-oxidosqualene[1,2] and terminal epoxides of farnesol[2,3] or geranylgeraniol.[3] The availability of these chiral epoxides (and the corresponding 1,2-diols or derivatives) has had a dramatic impact on the enantioselective synthesis of polycyclic natural products by cation-olefin polycyclization, since the combination of the catalytic route to the chiral starting material and the polycyclization allows the rapid generation of structures having several stereocenters with absolute stereochemical control. The effectiveness of this approach has been demonstrated by recent enantioselective syntheses of oleanolic acid and β-amyrin,[4] lanosterol,[5] dammarenediol II,[6] neotripterifordin,[7] and sclarenedial.[8] These advances have increased the need for new short, convergent routes for the stereocontrolled assembly of the polyolefinic chiral substrates for polycyclization reactions. One such new method has recently been developed in these laboratories.[6,9] The present paper describes a different approach in which a modification of the Shapiro reaction[10] is used for the rapid assembly of trisubstituted polyolefinic substrates. In previous research on the total synthesis of (±)-ovalicin[11] the synthetic intermediate **A** was generated in a single step from the components shown in the first clear experimental demonstration of stereospecific and efficient *E*-trisubstituted olefin synthesis via the Shapiro reaction.[12]



A **Trisyl = 2,4,6-triisopropylbenzenesulfonyl**

The sequence of steps involved in the present route to trisubstituted olefins is shown in Scheme 1. Double deprotonation of acetone 2,4,6-triisopropylbenzenesulfonylhydrazone (**1**), first at nitrogen and then at the α-methyl that is *syn* to the *N*-trisyl group,[13] followed by coupling with an alkyl halide (R_1X) at -65 °C over 10-18 h produces the unsymmetrical hydrazone intermediate **2**. At low temperature **2** is configurationally stable, and the *N*-trisyl group remains *syn* to the alkylated carbon. Subsequent deprotonation with TMEDA and *n*-BuLi[14] occurs at the α-carbon *syn* to the *N*-trisyl group. Warming of the resulting dianion to 0 °C for several minutes effects extrusion of N_2 and formation of *Z*-vinyllithium reagent **3**. Conversion of the vinyllithium reagent **3** to the mixed cuprate with lithium 2-thienylcyanocuprate and coupling at 0 °C over 10-15 h with a second electrophile produces trisubstituted olefin **4**.[11,12,15]

Scheme 1. Reaction summary

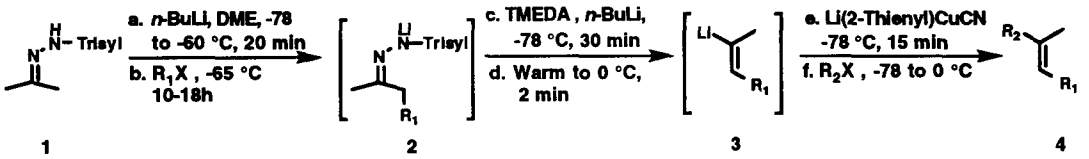
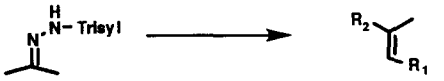
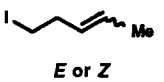
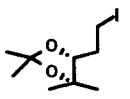
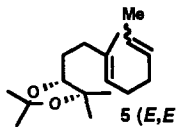
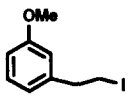
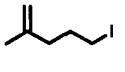
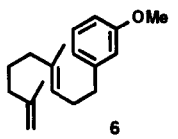
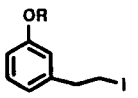
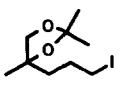
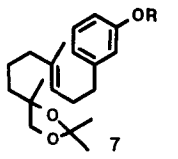
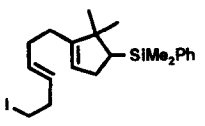
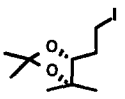
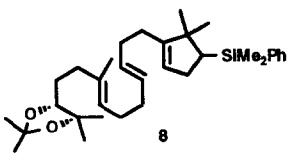
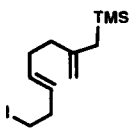
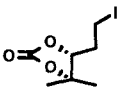
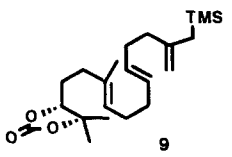


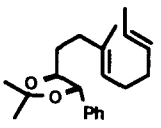
Table 1 details the copper-mediated coupling of various alkyl iodides with acetone trisylhydrazone (**1**) to provide a variety of polyolefins (**5** - **9**) stereospecifically in good yield. The results illustrate several advantages of this method of trisubstituted olefin synthesis. First, the coupling leads exclusively to an (*E*)-olefin. Second, the convergency of the transformation provides an efficient, concise and modular approach to the assembly of substrates for cation olefin cyclization. For example, the triene **8** in Entry F (65% yield) is the result of 15 total, but only 7 linear, synthetic steps from commercially available starting materials. Third, the functional group tolerance of the reaction affords access to a wide variety of coupled products.[16]

Table 1. Trisubstituted olefins from acetone trisylhydrazone by alkylation and copper-mediated coupling

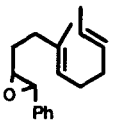


Entry	R_1X	R_2X	Product	Yield
A (*E* olefin) B (*Z* olefin)	 *E* or *Z*		 5 (*E,E* or *E,Z*)	72% (*E* olefin) 67% (*Z* olefin)
C			 6	64%
D (R = OMe) E (R = OTIPS)			 7	65% (R = OMe) 55% (R = OTIPS)
F			 8	65%
G			 9	54%

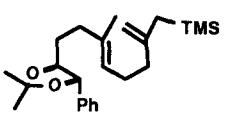
In addition to the polyolefins **5** - **9**, the coupling process outlined in Table 1 has also been applied to the facile synthesis of the dienes **10** - **12** in the indicated yields.



10
65% yield



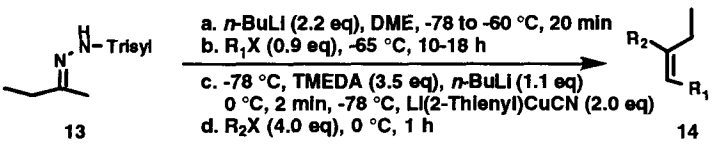
11
55% yield



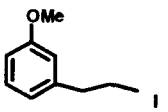
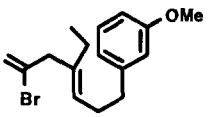
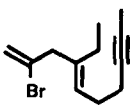
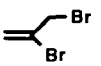
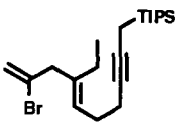
12
69% yield

The use of the trisylhydrazone of 2-butanone (**13**) in the coupling process provides access to products containing an ethyl-substituted olefin (**14**, Table 2). The starting unsymmetrical hydrazone in this case undergoes deprotonation and alkylation at the terminal alpha carbon leading to a single olefinic product. The electrophillic component 2,3-dibromopropene[17] leads to products (66 to 77% yield) which can be further elaborated via Stille or Suzuki coupling methodology. Entry J of Table 2 also illustrates that propargyl silanes are stable under the coupling conditions, although it is necessary to use the triisopropylsilyl derivative and to maintain temperature below -30 °C (for N_2 extrusion) in order to avoid silyl group cleavage.[18,19]

Table 2. Trisubstituted olefin synthesis from 2-butanone trisylhydrazone



13 **14**

Entry	R_1X	R_2X	Product	Yield
H				72%
I				77%
J				66%

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6. Corey, E. J.; Lin, S. *J. Am. Chem. Soc.* **1996**, *118*, 8765.
7. Corey, E. J.; Liu, K. *J. Am. Chem. Soc.* submitted.
8. Corey, E. J.; Luo, G.; Lin, L. S. *J. Am. Chem. Soc.* in press.
9. Corey, E. J.; Lin, S.; Luo, G. *Tetrahedron Lett.* **1997**, *38*, 5771.
10. See: Shapiro, R. H. *Org. React.* **1976**, *23*, 405.
11. Corey, E. J.; Dittami, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 256.
12. For a summary of the basic work in this area see: (a) Adlington, R. M.; Barrett, A. G. M. *Acc. Chem. Res.* **1983**, *16*, 55. (b) *J. Chem. Soc. Perkin Trans. I*, **1981**, 2848.
13. Deprotonation of a trisyl hydrazone nitrogen monoanion generally occurs at the α-carbon *syn* to the *N*-trisyl group. For information on the *syn* dianion effect, see: (a) Shapiro, R. H.; Heath, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 5734. (b) Shapiro, R. H. ref. 10.
14. Although *n*-BuLi is sufficient to effect deprotonation at a primary α-carbon, as in **1**, a stronger base (TMEDA-*n*-BuLi or *sec*-BuLi) is required to satisfactorily deprotonate at a secondary α-carbon such as in **2**. See: Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147.
15. The cuprate is necessary for successful coupling of the vinyl anion with an alkyl iodide. In the absence of a copper source, lithium-halogen exchange followed by homocoupling predominates. For information regarding lithium 2-thienylcyanocuprate, see: Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945.
16. **Representative experimental procedure for *E,E*-5.** *n*-Butyllithium (2.18 mL, 1.80 *M* in hexanes, 3.93 mmol, 2.2 equiv) was added dropwise to a solution of acetone 2,4,6-triisopropylbenzenesulfonylhydrazone (**1**) (605 mg, 1.78 mmol, 1.0 equiv) in dimethoxyethane (6 mL) at -78 °C. The golden yellow solution was warmed to -60 °C for 20 min and recooled to -78 °C. A solution of *trans* 1-iodo-3-pentene (1 : 2 w/w in C_7H_8, 946 μL, 1.60 mmol, 0.90 equiv, azeotropically dried with C_7H_8) was added, and the bright yellow suspension was stirred at -65 °C for 18 h. TMEDA (944 μL, 6.26 mmol, 3.5 equiv) was added to the pale yellow suspension at -78 °C, and, after 10 min, *n*-butyllithium (1.09 mL, 1.80 *M* in hexanes, 1.97 mmol, 1.1 equiv) was slowly added to form a bright orange-red suspension. After 15 min, the suspension was warmed to 0 °C until N_2 evolution had ceased (2 min). Lithium 2-thienylcyanocuprate (14.3 mL, 0.25 *M* in THF, 3.57 mmol, 2.0 equiv) was added to the yellow solution at -78 °C, and the resulting brown solution was stirred for 15 min. The iodoacetonide (365 μL, 1.78 mmol, 1.0 equiv) was added, and the solution was warmed to 0 °C over 1 h. After 18 h at 0 °C, 1 : 1 10% aqueous NH_4OH and saturated aqueous NH_4Cl solution (10 mL) were added, the mixture was stirred for 10 min at 23 °C, diluted with H_2O (50 mL) and extracted with Et_2O. The extract was dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (30 g of SiO_2; eluent: 3% Et_2O - pentanes) afforded *E,E*-**5** (312 mg, 1.17 mmol, 72% yield) as a clear oil: R_f product: 0.41 (10 : 1 hexanes - Et_2O, *p*-anisaldehyde); $[\alpha]_D^{23}$ +2.5 (*c* 1.2, $CHCl_3$); FTIR (film): 2982, 2936, 2857, 1453, 1370, 1217, 1115, 1001, 965 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.42-5.44 (m, 2H), 5.18 (dd, 1H, *J* = 6.2), 3.66 (dd, 1H, *J* = 3.5, 9.3), 2.16-2.23 (m, 1H), 1.98-2.06 (m, 6H), 1.64 (d, 3H, *J* = 3.9), 1.61 (s, 3H), 1.44-1.51 (m, 1H), 1.42 (s, 3H), 1.33 (s, 3H), 1.23 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.4, 131.1, 124.9, 124.6, 106.4, 82.7, 80.1, 36.6, 32.8, 28.6, 28.1, 27.7, 26.8, 26.0, 22.9, 17.9, 16.0; HRMS (CI, NH_3) *m/z* calc'd for $[C_{17}H_{30}O_2]^+H$: 267.2324 found 267.2335.
17. Four equivalents of 2,3-dibromopropene were used. Due to the greater reactivity of the allyl bromide, significant coupling of 2,3-dibromopropene with thienylcopper occurred.
18. Use of the *tert*-butyldimethylsilyl derivative leads to facile decomposition.

19. This research was supported by the National Science Foundation and the National Institutes of Health.

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