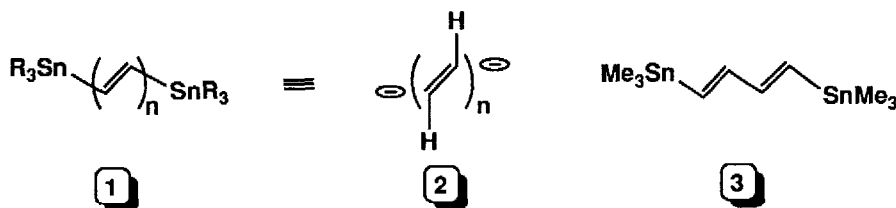


# A ONE-POT, LYNCHPIN APPROACH TO 1,4-DISUBSTITUTED E,E-BUTADIENES VIA MULTIPLE CYANOCUPRATE-MEDIATED TRANSMETALATIONS

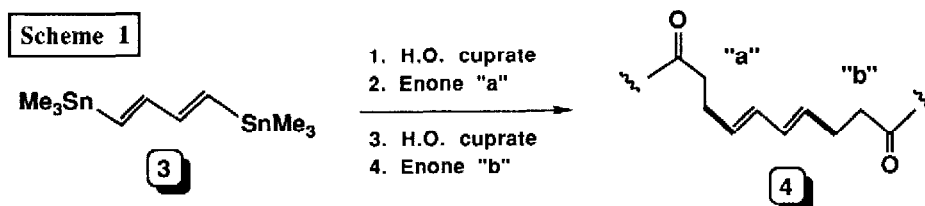
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**Summary.** Sequential transmetalation / Michael addition of *E,E*-1,4-bis-trimethylstannylbutadiene to enones using higher order cyanocuprates leads to products of double delivery in a 1-pot operation.

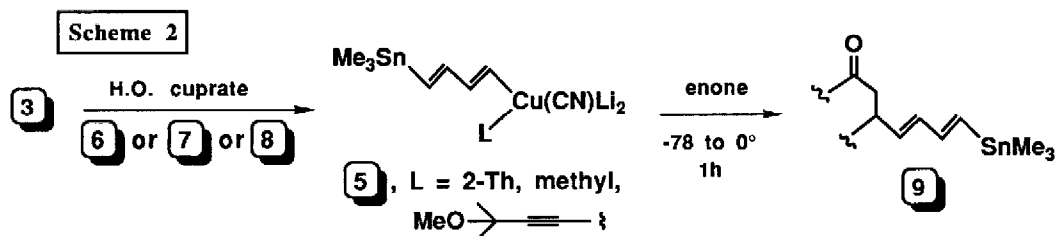
The facility with which higher order (H.O.) cyanocuprates effect transmetalation reactions with vinylic stannanes<sup>1</sup> suggests that the presence of two trialkylstannyl residues associated with an olefin or homolog (as in 1) might function as a soft, masked dianion (*cf.* 2). We now report that known *bis*-tri-methylstannylbutadiene 3,<sup>2</sup> upon sequential ligand exchange with a H.O. cuprate followed by conjugate



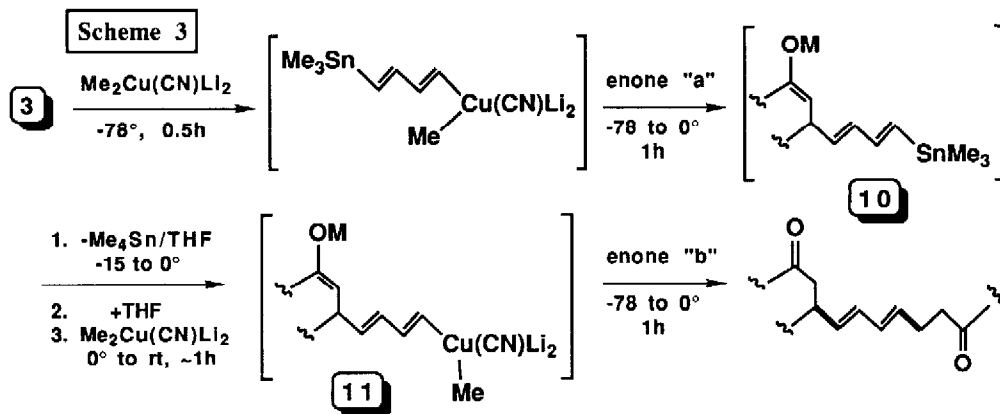
addition to an  $\alpha,\beta$ -unsaturated ketone, can be converted directly to products of double derivatization (4) in a single flask (Scheme 1).



Initially, it was necessary to establish that the first transmetalation would cleanly afford the mono-transmetalated cuprate **5** (2-Th = 2-thienyl), and that this reagent adds to enones in a 1,4-manner (Scheme 2). As illustrated in Table I, three different cuprates (**6-8**) are acceptable choices for arriving at 1,4-adducts *via* **5** in good isolated yields. Each reagent (**6-8**) requires only 1 equiv of **3** to form **5**, which ultimately transfers the desired diene moiety selectively to the enone. Vinylstannanes of type **9** are themselves of value given their potential as coupling agents *via* other (*i.e.*, non-copper based) organometallic intermediates (*e.g.*, using Pd(0) for Stille couplings).<sup>3</sup>




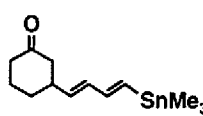


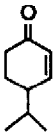
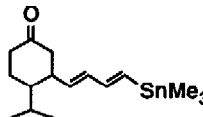

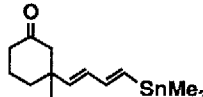
From these data, the H.O. species  $\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2$  was selected for the multiple transmetalation/conjugate addition process since it requires handling of only one organolithium (*i.e.*, MeLi). As shown in Scheme 3, the presumed intermediate **10** from the first series could be reconverted to the enolate-containing butadienyl cuprate **11** and subsequently delivered to a second Michael acceptor, again without significant competition from methyl transfer. Results from this preliminary study are summarized in Table II.



The success of this lynchpin approach is intimately tied to the removal of the  $\text{Me}_4\text{Sn}$  produced from the initial transmetalation. This could be readily accomplished under vacuum (*ca.*  $<0.1\text{mm Hg}$ ) between  $-15$  and  $0^\circ$ , given the volatility of the stannane. Visually, this simple manipulation (*vide infra*)<sup>4</sup> led to no apparent reagent decomposition, an observation fully supported by the data in Table II.



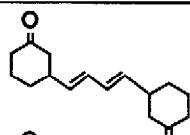

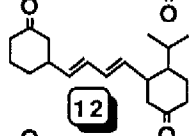

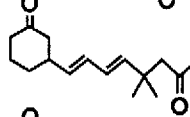
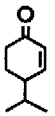

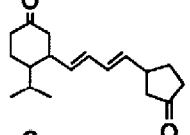


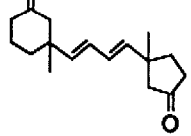
Once the first 1,4-addition has occurred, the by-product lower order cuprate  $\text{MeCu}(\text{CN})\text{Li}^5$  (perhaps associated with the enolate),<sup>6</sup> is susceptible to reversion back to  $\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2$  upon addition of 1 equiv MeLi. The remaining  $\text{Me}_3\text{Sn}$  group in **10** should then transmetalate, in essence, decreasing the amount of Cu(I) required for the overall sequence by 50%. As seen in Scheme 4 below, this is indeed a viable option.

Table I. Conjugate addition reactions of cuprates **5** in THF

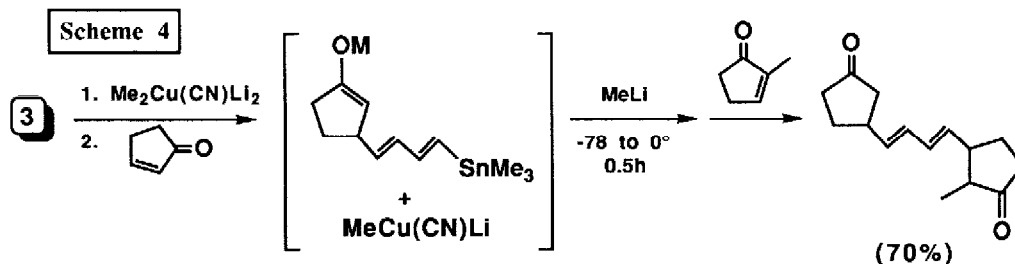
Enone	H.O. cuprate	Conditions of Transmetalation	Product <sup>a</sup>	Yield (%) <sup>b</sup>
	<b>6</b> = $\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2$	-78°, 0.5h		85
	<b>7</b> = $\text{Me}(2\text{-Th})\text{Cu}(\text{CN})\text{Li}_2$	0° to rt, 1h		81
	<b>8</b> = $(\text{Me})\text{MeO}-\text{C}(\text{Me})_2\text{C}\equiv\text{Cu}(\text{CN})\text{Li}_2$	-78° to rt, 2h		84
	<b>7</b> = $\text{Me}(2\text{-Th})\text{Cu}(\text{CN})\text{Li}_2$	-20° to rt, 1h		80
	<b>8</b> = $(\text{Me})\text{MeO}-\text{C}(\text{Me})_2\text{C}\equiv\text{Cu}(\text{CN})\text{Li}_2$	-78° to rt, 2h		70 <sup>c</sup>

<sup>a</sup> Fully characterized by spectral means. <sup>b</sup> Isolated. <sup>c</sup>  $\text{BF}_3\cdot\text{Et}_2\text{O}$  (1 equiv) used.

Table II. Double transmetalation / 1,4-addition reactions of **3** using  $\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2$ 

Enone "a"	Enone "b"	Product	Yield % <sup>a</sup> (%) <sup>b</sup>
			82 (91)
			71 (90)
			74 (97)
			64 <sup>c</sup> (93)
			60 (95)

<sup>a</sup> Isolated, chromatographically pure. <sup>b</sup> % E,E-isomer of product shown. <sup>c</sup> A single diastereomer was formed.



In summary, a readily available *bis*-stannylbutadiene (**3**) can be utilized as a 1,4-dianionic lynchpin by invoking a double ligand exchange/Michael addition induced by cyanocuprates. Further developments of one-pot polyene constructions involving the corresponding alkylations are presently under study.

**Acknowledgements.** Financial support provided by the NIH (GM 40287) and the KOSEF is gratefully acknowledged. Information on the preparation of **3** provided by Prof. A.J. Ashe is much appreciated.

#### References and Notes

- # On leave from Duksung Women's University, Seoul, Korea.
1. Behling, J.R., Babiak, K.A., Ng, J.S., Campbell, A.L., Moretti, R., Koerner, M., Lipshutz, B.H., *J. Am. Chem. Soc.*, **1988**, *110*, 2641.
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4. A typical procedure for the preparation of **12** is as follows. To CuCN (44mg, 0.49mmol) in THF (5mL) was added MeLi (0.81mL, 0.98mmol, 1.22M in Et<sub>2</sub>O) at -15°, and the mixture warmed to 0° for 20 min. The resulting Me<sub>2</sub>Cu(CN)Li<sub>2</sub> was cooled to -20° and added to a -78° THF (2mL) solution of **3** (215.5mg, 0.56mmol, 88% E,E-isomer) over a period of 25 min followed by stirring for another 5 min. To the resulting light tan solution was then added 2-cyclohexen-1-one (48μL, 0.49 mmol) to afford a nearly colorless solution. After 15 min at -78°, the mixture was warmed to -15° for 30 min, and the volume reduced by ca. half under vacuum (<0.1mm Hg). Fresh, dry THF (3mL) was added and the volume reduced again. To the resulting solution was introduced Me<sub>2</sub>Cu(CN)Li<sub>2</sub> (0.49mmol), prepared as above, and the mixture stirred between 0° and rt over 45 min during which a blue color developed. After cooling to -78°, 4-isopropyl-2-cyclohexen-1-one (65μL, 0.44mmol) was added neat to give a light yellow mixture. The reaction was allowed to warm to 0° and then quenched with 25mL of 10% NH<sub>4</sub>OH/sat NH<sub>4</sub>Cl solution and extracted 3x with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried (MgSO<sub>4</sub>), filtered, concentrated *in vacuo*, and chromatographed (SiO<sub>2</sub>, 30% EtOAc / hexane) to afford **12** (90.4mg, 71%, 90% E,E-isomer); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.01-5.88 (m, 2H), 5.61-5.49 (m, 1H), 5.43 (dd, 1H, J=8.4, 13.8Hz), 2.59-2.12 (m, 9H), 2.12-1.36 (m, 9H), 0.95 (d, 3H, J=6.9Hz), 0.74 (d, 3H, J=6.9Hz); IR (neat) cm<sup>-1</sup> 3025, 2960 1715, 1450, 1390, 1370, 1225, 990; EIMS 289(4, M+1), 288(30, M+), 245(5), 191(8), 163(6), 150(36), 138(87), 123(27), 110(36), 55(100); HREIMS calcd for C<sub>19</sub>H<sub>28</sub>O<sub>2</sub> 288.2096; found 288.2096.
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