

***Cis*-2-Tri-*n*-Butylstannylvinyl Cuprates: A New Synthone for the *cis*-1,2-Ethene Dianion**

J.P. Marino^{†*}, Mark V.M. Emonds[†], Peter J. Stengel[†],
Alfredo R.M. Oliveira^{‡†}, Fabio Simonelli^{‡†} and J. Tercio B. Ferreira^{‡†}

[†]Departments of Chemistry and Medicinal Chemistry, The University of Michigan, Ann Arbor, Michigan 48109

and

[‡]Departamento de Química Universidade Federal de São Carlos-Caixa Postal 676, São Carlos, S.P.-13560- Brazil

Key Words: Higher-order Cuprate; *cis*-2-Tri-*n*-Butylstannylvinyl Cyano Cuprate

Abstract: Conjugate additions of lower order and higher order cyano cuprates containing the *cis*-2-tri-*n*-butylstannylvinyl group to cycloalkenones have been studied. The higher order cuprates were more reactive towards hindered enones such as 4,4-dimethylcyclohexenone and 2,4,4-trimethylcyclohexenone, and produced higher yields with the base-sensitive acetonide of *cis*-4,5-dihydroxycyclohexenone.

Recently, we have described a new annulation protocol that utilizes a Michael addition of lithium *cis*-2-tri-*n*-butylstannylvinyl cyano cuprate to a cyclic enone as its initial step.¹ In the course of applying this methodology towards the synthesis of several natural products, we discovered that the yields obtained using our original cuprate were often poor if the enone was hindered or particularly sensitive to basic conditions. In this paper, we report the development of new, higher order *cis*-2-tri-*n*-butylstannylvinyl cuprates which lead to much improved conjugate additions. The general utility of *cis*-2-tri-*n*-butylstannylvinyl cuprates I lies in the fact that their chemical reactivity is synthetically equivalent to a *cis*-1,2-ethene dianion II (Figure 1).

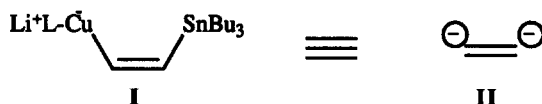


Figure 1

After conjugate additions or substitution reactions of I, the *cis*- β -stannyl group can be utilized in metallations or coupling reactions. In the latter context, palladium-catalyzed coupling reactions can lead to a *cis*-disubstituted ethene system.

While the *trans*-2-tri-*n*-butylstannylvinyl cuprate has been known for quite some time,² the *cis*-isomer had not been studied in conjugate addition reactions.³ Adaptation of methodology developed by Normant⁴ enabled us to generate the cyano cuprate (L=CN) of synthon I at low temperatures. Our original procedure¹ (Method I) involved the deprotonation of tri-*n*-butylstannane 1 at -78 °C with LDA in THF, and the transfer of this solution

to cuprous cyanide and lithium chloride in THF. After one hour at $-45\text{ }^{\circ}\text{C}$, excess acetylene⁵ was added to the solution to generate the *cis*-tri-*n*-butylstannylvinyl cuprate **2**. The reactivity of this cyano cuprate was assessed by its conjugate addition to a variety of cyclic enones. A solution of the enone was added to the cuprate **2** at $-78\text{ }^{\circ}\text{C}$, followed by the addition of triethylsilyl chloride. When cyclohexenone was used, a good yield of the triethylsilyl enol ether of the adduct **4** was obtained.

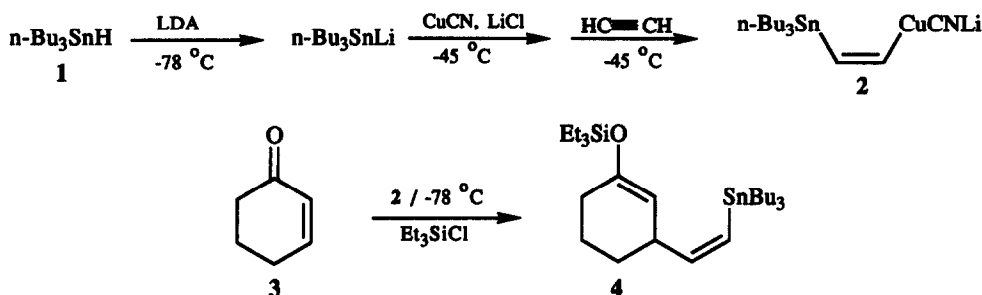


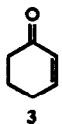
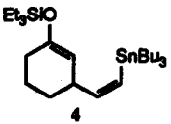

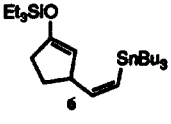
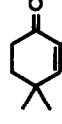
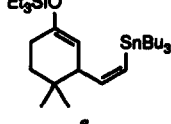
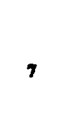
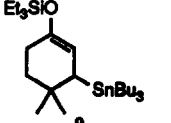

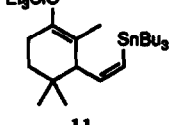

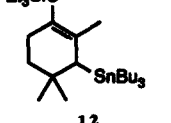
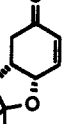
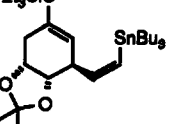
Figure 2

The efficacy of cyano cuprate **2** was diminished with cyclopentenone and more hindered cyclohexenones. While 4,4-dimethylcyclohexenone reacted with **2** to yield 66% of the expected adduct, the more hindered 2,4,4-trimethylcyclohexenone failed to yield a *cis*-tri-*n*-butylstannylvinyl adduct. In the latter case, the only product isolated was the conjugate adduct of tri-*n*-butylstannyl cuprate (see Table I for summary). If we assume that the more hindered enones react more slowly with **2**, there should be more opportunity for reagent **2** to revert to acetylene and the tri-*n*-butylstannyl cuprate.

In an effort to discover a more reactive version of cuprate **2**, we initiated a study of different ligands and stoichiometries with higher order cuprates⁶ in mind. Our choice of enones ranged from cyclohexenone to the hindered 2,4,4-trimethylcyclohexenone and the base-sensitive acetonide⁷ of 4,5-dihydroxycyclohexenone **13**. The first type of higher order cuprate investigated, incorporated the 2-thienyl ligand. Higher order cuprates containing the 2-thienyl and cyano ligands have been shown to add efficiently to enones.⁸ The procedure of Lipshutz was used to prepare the higher order cuprate from commercially available lithium 2-thienylcyanocuprate and acetylene at $-45\text{ }^{\circ}\text{C}$. As indicated in Table I under Method II, the yields of adducts from cyclohexenone, cyclopentenone and acetonide **13** improved; however, no conjugate addition to 2,4,4-trimethylcyclohexenone **10** occurred. Once again, the reaction with the more hindered enone **10** only yielded the adduct of the tri-*n*-butylstannyl group **12**.

We next examined the higher order cyanocuprates containing one equivalent of cuprous cyanide and two tri-*n*-butylstannylvinyl ligands (Method III). Reactions of this cuprate with cyclohexenone, cyclopentenone and 4,4-dimethylcyclohexenone gave the highest yields of adducts **4**, **6**, and **8** respectively. At the same time, no tri-*n*-butylstannyl adducts were detected. In fact, it was the higher order cyano cuprate that yielded the conjugate addition of the vinyl ligand to enone **10** for the first time. There was still a significant amount of the tri-*n*-butylstannyl adduct **12** produced with this cuprate. Another advantage of the higher order cyano cuprate was revealed in the very high yield of adduct **14** from the acetonide of 4,5-dihydroxycyclohexenone.

Table 1: Reactions of Enones with *Cis*-2-Tri-*n*-Butylstannylvinyl Cuprates

| Enone | Product(s) | Method ^a | | | |
|---|---|---------------------|-----|-------|-----|
| | | I | II | III | IV |
|  |  | 78% | 90% | 96% | 88% |
|  |  | 35% | 46% | 86% | 81% |
|  |  | (66%) | 55% | 85% | 82% |
|  |  | (16%) | 0% | 0% | 0% |
|  |  | 0% | 0% | (32%) | 92% |
|  |  | 80% | 26% | (48%) | 0% |
|  |  | 51% | 55% | 93% | 90% |

^a Isolated Yields, () indicate GC ratio; Method I: 1 eq. of *cis*-tri-*n*-butylstannylvinyl ligand and 1 eq. copper cyanide; three equivalents of the cuprate were used; Method II: 1 eq. of 2-thienyl ligand, 1 eq. of *cis*-tri-*n*-butylstannylvinyl ligand and 1 eq. copper cyanide; 1.5 equivalents of the cuprate were used; Method III: 2 eq. of *cis*-tri-*n*-butylstannylvinyl ligand and 1 eq. copper cyanide; one equivalent of the cuprate was used; Method IV: 2 eq. of *cis*-tri-*n*-butylstannylvinyl ligand, 1 eq. copper cyanide and 2 eq. of lithium chloride; one equivalent of the cuprate was used.

One final modification of the *cis*-tri-*n*-butylstannylnylvinyl cuprate was made by adding two equivalents of lithium chloride to the higher order cyanocuprate (Method IV)⁹. The addition of lithium chloride to a cuprate reagent usually enhances the solubility of cuprous cyanide and hence the mixed cyano cuprates.¹⁰ The major advantage of this Method IV was revealed in the reaction of the hindered 2,4,4-trimethylcyclohexenone. Dramatically, the yield of the conjugate adduct **11** was increased to 92% and none of the side-product **12** could be detected.

In conclusion, the availability of a bifunctional synthon for the *cis*-1,2-ethene dianion is enhanced with the generation of higher order cuprates. The conjugate additions of *cis*-2-tri-*n*-butylstannylnylvinyl cuprates **1** to a number of hindered enones and the *in situ* trapping of the intermediate enolate provide an efficient regioselective and stereoselective route to highly functionalized cycloalkenones. A final note of significance involves the nature of the ligands in the higher order cuprates. The highest yields of conjugate adducts were obtained with Methods III and IV which only required one equivalent of the cuprate reagent.

Acknowledgments

F.S., J.T.B.F., and A.R.M.O. are grateful for financial support from CNPq (Brazil) during their stay at the University of Michigan. M.V.M.E. gratefully acknowledges fellowship support from the American Foundation for Pharmaceutical Education.

References and Footnotes

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5. Approximately 30-35% excess of acetylene was added to the reaction flask. Acetylene was measured using the technique of displacement of mineral oil in a calibrated buret. The mineral oil was saturated with acetylene before measurements were taken.
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8. Lipshutz, B.H.; Koerner, M.; Parker, D.A. *Tetrahedron Lett.* **1987**, *28*, 945.
9. A typical Experimental Procedure (Method IV) is as follows: LDA (6.54 mmol) was prepared at -20°C according to the standard procedure, then cooled to -78°C. Tributylstannane (1.73g, 5.95 mmol, 1.60 mL) was added via syringe. This solution was stirred for 30 min, and then added via cannula to a solution of cuprous cyanide (0.266 g, 2.97 mmol) and lithium chloride (.252g, 5.95 mmol) in 30 mL of dry THF. The resulting (slightly greenish) amber solution was stirred for 1h at -45°C. The nitrogen supply was removed, and the acetylene apparatus was connected. Acetylene (8.03 mmol, 180 mL) was added via a Pasteur pipette whose tip was immersed beneath the surface of the solution. After completion of the acetylene addition, the reaction mixture was allowed to slowly warm to -20°C over 30 min. The nitrogen supply was then reattached, and the reaction mixture was cooled to -78°C. The cyclic enone (2.97 mmol) was added and after 30 min. triethylsilyl chloride (5.94 mmol) was added and the reaction mixture stirred for 15 min at -78°C. The reaction mixture was poured in to a rapidly stirring ice cold mixture of diethyl ether, and a 4:1 mixture of saturated aqueous ammonium chloride and ammonium hydroxide. After stirring for 5 min, the mixture was placed in a separatory funnel and the phases were allowed to separate, further work up and purification gave the desired addition product.
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(Received in USA 3 October 1991)