

Effect of Additives on the Stereochemical Integrity and Reactivity of α -Alkoxy Carbonyl Alkenylcopper Intermediates. Optimal Conditions for the Synthesis of Isomerically Pure Tetrasubstituted Alkenes

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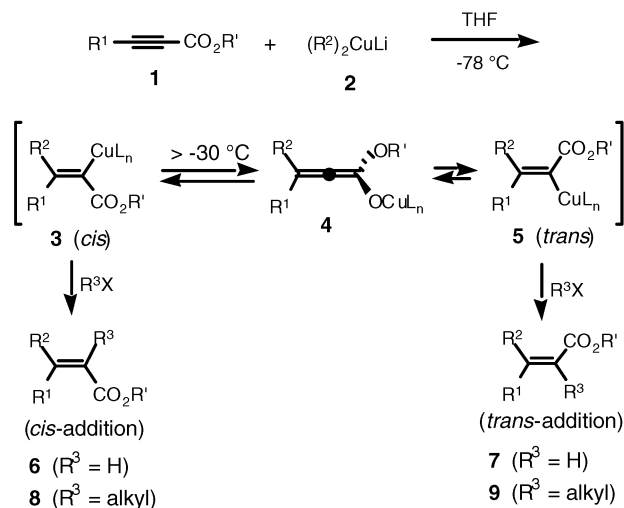
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Abstract: A systematic study on the effect of additives on the isomerizability of 1-alkoxycarbonyl alkenylcopper(I) intermediates revealed that the lithium chelator 12-crown-4 is significantly more efficient than HMPA at retarding isomerization. On the other hand, 12-crown-4 alone is unable to promote effective coupling with alkyl halides. The combination of 12-crown-4 and a reduced amount of HMPA, however, led to an improved procedure for the preparation of useful, isomerically pure tetrasubstituted alkenes such as allylation reagents and skipped dienes.

Stereocontrol in the formation of tri- and tetrasubstituted alkenes remains a challenging problem in organic synthesis.¹ In this respect, the conjugate addition of organocopper reagents to acetylenic esters followed by a cis-selective, low-temperature protic quench is one of the most efficient methods to access isomerically pure, trisubstituted α,β -unsaturated esters (**6** in Scheme 1).^{2,3} Unfortunately, unless very potent alkyl halides (R^3X) are employed as electrophiles,⁴ no efficient extensions of this chemistry are available for the construction of tetrasubstituted alkenes (**8**) in high overall cis-addition selectivity. The alkylation step is hampered by the low reactivity of the 1-alkoxycarbonyl alkenylcopper(I) intermediate **3**, and its tendency to isomerize via a copper allenolate (**4**) at higher temperatures (typically above $-30\text{ }^\circ\text{C}$) (Scheme 1).⁵

In the course of our studies on the preparation of tetrasubstituted allylboronates⁶ for use in Lewis acid-

SCHEME 1. Formation of Tri- and Tetrasubstituted Alkenes by Carbocupration/Electrophilic Trapping of Acetylenic Esters **1**



catalyzed allylboronations,⁷ we found that iodomethylboronates were sufficiently reactive, under optimal conditions with HMPA as a cosolvent, for trapping **3** with no loss of stereochemical integrity and afford tetrasubstituted allylboronates with overall cis double functionalization (**8** with $R^3 = CH_2B(OR)_2$ in Scheme 1). In contrast, poor yields and selectivities were observed when THF alone was used as solvent. These results suggest that the HMPA stabilizes alkenylcopper intermediate **3**, thereby allowing the electrophile to trap it prior to isomerization to **5**, hence avoiding erosion of selectivity and formation of trans-addition products **9**. We became interested in further examining the effect of additives and understanding the role of HMPA in the isomerization and alkylation of 1-alkoxycarbonyl alkenylcopper intermediates. Moreover, we were attracted by the possibility of replacing or minimizing the required amount of carcinogenic additive HMPA. Herein, we describe a systematic survey of additives that led to an optimized procedure for the formation of useful, isomerically pure tetrasubstituted alkenes, as well as providing new insight on the crucial effect of HMPA and other molecules on the stability and reactivity of 1-alkoxycarbonyl alkenylcopper intermediates.

Excess lithium was long known to have a deleterious effect on the stereochemical integrity of intermediate **3**, leading to the mechanistic hypothesis that the "free" lithium from $R_2CuLi \cdot LiX$ promotes the isomerization process through a lithium allenolate.⁸ As proposed by Krause and co-workers, the superior ability of polar solvents (e.g., THF over Et_2O) at retarding the isomerization of **3** is due to their more efficient coordination of the free lithium cation.⁵ This is supported by experiments where lithium was excluded through use of salt-free R_2CuLi .⁹ A priori, our previous observations⁶ on the

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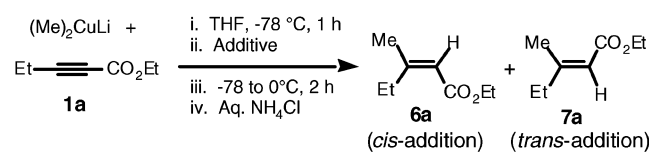
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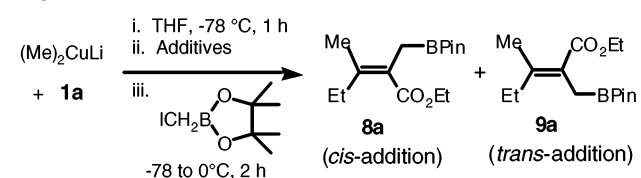
TABLE 1. Effect of Additives on the Stereochemical Integrity of α -Alkoxy carbonyl Alkenylcopper Intermediates (see Scheme 1)^a

entry	additive	equivalence ^b	ratio of 6a:7a ^c
1	none		1:1
2	HMPA	9	9:1
3	HMPA	6	4:1
4	HMPA	3	2.5:1
5	HMPA	2	2:1
6	DMPU	2	1:2
7	DMEU	2	1:2
8	DMSO	2	1:2
9	P(OEt) ₃	2	1:2
10	PPh ₃	2	1:2
11	P(<i>t</i> -Bu) ₃	2	2.5:1
12	tmeda	2	1:1
13	Dabco	2	1.5:1
14	sparteine	2	6:1
15	pyridine	2	1:2
16	bipyridine	2	1:2
17	Bu ₄ NCN	2	1:2
18	Bu ₄ NI	2	1:2
19	18-crown-6	2	2.5:1
20	15-crown-5	2	4:1
21	12-crown-4	2	9:1
22	12-crown-4	1	4:1

^a Reactions were conducted with Me₂CuBr–LiBr prepared from MeLi and CuBr–SMe₂ as described in the text and Supporting Information (typical scale: 1 mmol). ^b With respect to the starting alkyne **1a**. ^c Estimated by integration of representative ¹H NMR signals on crude reaction product isolated after a protic quench.

beneficial effect of HMPA at promoting stereoselective alkylation may thus be explained by its ability to sequester lithium and retard the isomerization process long enough to allow cis-addition intermediate **3** to react completely with the electrophile. Alternatively, HMPA may favor higher reaction yield and selectivity by accelerating the alkylation step without necessarily stabilizing intermediate **3**. We envisaged that a systematic study comparing different additives known to coordinate lithium cations may help clarify the putative role of HMPA in this reaction. By using pentynoic ester **1a** as a model substrate with Me₂CuLi·LiBr, the effect of a large number of additives on the isomerizability of **3** was investigated (Table 1).

For each entry, the additive (2 equiv) was added at –78 °C after the conjugate addition step. The temperature was then allowed to warm to 0 °C in the course of 2 h. At this point, an aqueous quench was carried out and the ratio of the respective *Z*- and *E*-trisubstituted isomers **6a** and **7a** was measured by ¹H NMR on a sample of the crude reaction product. Under these conditions, control runs in the absence of any additive provided a 1:1 ratio of isomers (entry 1). Similarly, a large number of additives were ineffective, and even led to the trans-addition

TABLE 2. Optimization of Additive Stoichiometry in the Selective Formation of Tetrasubstituted Allylboronate **8a^a**

entry	12-crown-4 (equiv)	HMPA (equiv)	yield ^b (%)	ratio of 8a:9a ^c
1	0	9	70	> 19:1
2	1	9	70	19:1
3	1	1	37	9:1
4	2	1	53	19:1
5	2	0	20	19:1
6	2	2	50	> 19:1
7	1	2	66	> 19:1

^a Reactions were conducted with Me₂CuBr–LiBr prepared from MeLi and CuBr–SMe₂ and 3 equiv of ICH₂BPin as described in the text and Supporting Information (typical scale: 1 mmol). ^b Yields based on the mass of isolated products after flash chromatography purification. Entries 3–5 are accompanied by variable amounts of trisubstituted alkene from the protic quench, indicative of incomplete alkylation. ^c Estimated by integration of representative ¹H NMR signals.

isomer **7a** as the major product.¹⁰ In comparison, while the use of 9 equiv of HMPA gave little isomerization, with a 9:1 ratio of isomers **6a** and **7a**, a rather modest 2:1 ratio was observed in the presence of only 2 equiv (entries 2–5). Yet, of over 15 additives surveyed, few fared as well as HMPA. The strong lithium chelator 12-crown-4 (entries 21 and 22), however, was significantly more efficient than HMPA at retarding alkenylcopper isomerization when both were compared under similar conditions (2 equiv).

Next we set out to seek optimal conditions, using different relative stoichiometries of 12-crown-4 and HMPA, to alkylate intermediates **3** and provide tetrasubstituted alkenes in high isomeric purity. Given our interest in the resulting allylboronates,^{6,7} we chose to use the electrophile iodomethylboron pinacolate as a model to fine-tune the use of additives in the reaction procedure (Table 2).

The ratio of cis- and trans-addition isomers **8a** and **9a** was measured by ¹H NMR on purified product obtained after 2 h of reaction. As previously demonstrated,⁶ as much as 9 equiv of HMPA are required to obtain **8a** in high cis-addition selectivity (entry 1). The data shown in Table 2 indicate that 12-crown-4, when used alone, is unable to provide high yields of alkylated product (entry 5). This observation is not surprising given the known retarding effect of crown ethers in S_N2 reactions with organocuprates.¹¹ Although the results of entries 2–4 show that the use of HMPA effectively leads to higher yields of allylboronate product, we ought to minimize the required amount of this carcinogenic additive. To obtain **8a** in acceptable yield and high isomeric purity, a satisfactory compromise was found in the combined use of 12-crown-4 (1 equiv) and HMPA (2 equiv) (entry 7).

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From the results of Table 1, it is clear that 12-crown-4 is highly efficient at stabilizing and retarding the isomerization of 1-alkoxycarbonyl alkenylcopper intermediates **3**. This behavior is in agreement with the hypothesis associating the stereochemical integrity of **3** with the lithium-coordination ability of the solvent or the additive. Of the three crown-ethers of Table 1, 12-crown-4 is indeed the most efficient lithium coordinator of this series.¹² On the other hand, the results of Table 2 suggest that 12-crown-4 does not provide any advantage in the coupling step with carbon-based electrophiles to make tetrasubstituted alkenes. Whereas HMPA is not as efficient for stabilizing intermediate **3** (as much as 9 equiv are required to match the efficiency of 2 equiv of 12-crown-4), it does appear to play a highly beneficial role in the alkylation step.¹³ The exact mechanism of carbon-carbon bond coupling involving intermediates of type **3** is not known.¹⁴ One of the more likely possibilities is that of halide displacement by copper to give a copper(III) intermediate, followed by reductive elimination with concomitant formation of the coupling product.¹⁵ Presumably, HMPA can facilitate the coupling of **3** to the electrophile by stabilizing the transient, high-energy copper(III) intermediate of type R³(alkenyl)CuR².¹⁶ Unlike 12-crown-4, the dual role of HMPA in this reaction may thus be assigned to its ability to coordinate with both lithium and copper. The combined use of these two additives (1 equiv of 12-crown-4 and 2 equiv of HMPA) makes efficient use of their respective abilities, and leads to a significant decrease in the amount of HMPA previously required in this reaction.

To test the generality of the optimized procedure, other alkyl halide electrophiles were evaluated toward accessing useful tetrasubstituted alkenes in high isomeric purity (Table 3). Other allylation reagents such as **8b** and **8c** were isolated respectively in good and modest yield with excellent *cis*-addition selectivity (entries 1 and 2). Furthermore, allylic bromides were found to react efficiently, providing skipped dienes such as **8e–g** (entries 4–6). The hindered di-*s*-butyl cuprate was equally effective (entry 7), and other useful alkynoate esters can be used, as shown by the formation of alkene **8i** containing a masked formyl group (entry 8). Among other alkyl halides, methyl iodide and butyl iodide gave a low yield of product. Other types of cuprates such as the cyanocuprates were not tested due to precedents documenting their inferior ability at preserving the stereochemical integrity of the resulting alkenylcopper intermediate.⁵

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TABLE 3. Evaluation of Different Electrophiles for the Synthesis of Tetrasubstituted Alkenes **8**^a

entry	alkynoate (R ¹)	cuprate (R ²)	electrophile (R ³ X)	product ^b	yield ^c (%)
1	Et	Me	ICH ₂ SnBu ₃	8b	80
2	Et	Me	ICH ₂ SiMe ₃	8c	30
3	Et	Me	BrCH ₂ Ph	8d	40
4	Et	Me	BrCH ₂ CH=CH ₂	8e	76
5	Et	Me	BrCH ₂ C(Br)=CH ₂	8f	57
6	Et	Me	BrCH ₂ CH=CMe ₂	8g	78
7 ^d	Et	<i>s</i> -Bu	BrCH ₂ CH=CH ₂	8h	72
8 ^e	TBDPSOCH ₂	Me	BrCH ₂ CH=CH ₂	8i	85

^a For entries 1–6 and 8, reactions were conducted with Me₂CuBr–LiBr prepared from MeLi and CuBr–SMe₂ and 3 equiv of electrophile (4 equiv for entries 3–5) as described in the text and the Supporting Information (typical scale: 1 mmol). ^b *Cis*-addition isomer with over 19:1 selectivity estimated by integration of representative ¹H NMR signals. Entries 2 and 3 were accompanied by variable amounts of trisubstituted alkene from the protic quench, indicative of incomplete alkylation. ^c Yields based on the mass of isolated products after flash chromatography purification. ^d The di-*s*-butyl cuprate was formed from *s*-BuLi as described in the Supporting Information. ^e The methyl ester was employed.

In summary, a systematic study of additives revealed that 12-crown-4 is most effective at protecting the stereochemical integrity of 1-alkoxycarbonyl alkenylcopper(I) intermediates (**3**) originating from the conjugate addition of R²CuLi·LiX onto acetylenic esters. Yet, as 12-crown-4 was found inept at increasing the reactivity of intermediates **3**, a small amount of HMPA is required to promote the alkylation step. With a judicious combination of these two additives (12-crown-4 and HMPA), however, it is possible to overcome the inherent isomerization tendency and low reactivity of 1-alkoxycarbonyl alkenylcopper(I) intermediates. By using an optimized procedure that successfully reduces the amount of HMPA previously required in this reaction, isomerically pure tetrasubstituted alkenes were synthesized in high isomeric purity from different alkynoate esters, cuprates, and electrophiles. These compounds are difficult to access by other means, and applications of the allylating reagents and skipped dienes thus formed will be reported in due course.

Experimental Section

General Procedure for Compounds **8b–i (Table 3).** A slurry of CuBr·Me₂S (0.208 g, 1.010 mmol) in dry THF (12 mL) at 0 °C under N₂ was treated with MeLi (1.40 M in Et₂O, 1.40 mL, 2.00 mmol). When a clear and colorless solution formed, the flask was placed in an acetone/CO₂ bath (–78 °C) and ethyl 2-pentynoate (140 μL, 1.00 mmol) was added dropwise. The resulting light yellow mixture was stirred at –78 °C for 1 h and then treated sequentially with 12-crown-4 (161 μL, 1.00 mmol), HMPA (346 μL, 2.00 mmol), and the electrophile (3 or 4 mmol, see Table 3). The mixture was allowed to warm at 0 °C for 2 to 3 h. The reaction was quenched with NH₄Cl_(aq) (5 mL) and the layers were separated. The aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were washed

with water (5 × 10 mL) and brine (10 mL), dried (anhydrous Na₂SO₄), and evaporated to give the crude product as an oil. The crude product was purified by flash chromatography on silica gel (Et₂O/hexanes) to give a colorless oil. The ratio of cis- and trans-addition isomers **8** and **9** was measured on the crude reaction mixture according to the height and integration of signals from the allylic protons.

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Supporting Information Available: General experimental details, representative model procedures for the preparation of **8a** and other tetrasubstituted alkenes, characterization data (MS and NMR) and copies of ¹H and ¹³C NMR spectra for all compounds of Table 3 (**8b–i**). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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