TMSCl-Mediated Catalytic Carbocupration of Alkynoates: An Unprecedented and Remarkable Effect of Catalyst Loading on Highly Selective Stereochemical Induction via a TMS-Allenoate Intermediate

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Keywords: Carbocupration / Cuprates / Grignard reaction / Propiolates / TMS-allenoate

The TMSCl-mediated catalytic carbocupration of alkynoates has been investigated. It has been shown that catalyst loadings as low as 30 mol% readily allow for high yields and diastereoselectivities for a series of Grignard reagents. In addition, an unprecedented and remarkable effect of catalyst loading on stereochemical induction has been observed.

Introduction

Over the past 35 years, considerable attention has been given to the stoichiometric carbocupration of α,β-acetylenic esters with organocopper reagents resulting from lithium-derived organometallics for the synthesis of substituted olefins.[1] The stereoselectivity of these net 1,4-additions are dependent on a variety of conditions such as temperature, copper reagent, solvent effects, and external chelating ligands.[1] Interestingly, very little is reported on the utilization of Grignard reagents for these types of reactions.[2] Based on the report on modified Kharash reaction conditions utilizing CuI·2LiCl by Reetz and Kindler,[3] we decided to investigate the possibility of using catalytic amounts of a combination copper(I)-lithium halide salt in conjunction with Grignard reagents for the carbocupration of α,β-acetylenic esters. Herein we wish to report, to the best of our knowledge, the first highly diastereoselective carbocupration of any propiolate ester that uses only catalytic amounts of a copper(I) salt. Additionally, an unprecedented and remarkable effect of catalyst loading on stereochemical induction has been observed.

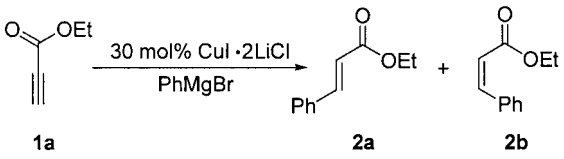
Results and Discussion

As shown in Equation (1), reaction of **1a** at 0 °C in THF with 30 mol% of CuI·2LiCl and 1.2 equivalents of PhMgBr furnished, after quenching with NH_4Cl and a standard workup, a crude product mixture of **2a** and **2b** as a diastereomeric ratio of 91:9 in favor of the *E*-isomer. In spite of the high level of selectivity, the ^1H NMR spectrum of the crude products reveals only 30% of the desired products in addition to decomposition of the starting material. After column chromatography, a combined yield of 28% was isolated. Performing the carbocupration at −35, −50, and −78 °C in THF had little or no effect on the cuprate turnover, diastereoselectivity, and yield of **2a** and **2b**. The yields remained under 30% and the selectivity for the *E*-isomer remained at 9:1 and slightly better in some instances. An interesting trend was observed when these conditions were examined in DME as the solvent. The *Z*-isomer selectivity gradually increased as the reaction temperature was decreased, as shown in Table 1.

Table 1. CuI·2LiCl Promoted carbocupration of **1a** with PhMgBr

Entry[a]	Temperature [°C]	Solvent	Yield [%]	*E*[b]	*Z*
1	0	THF	28	91	9
2	−35	THF	29	92	8
3	−50	THF	27	93	7
4[c]	−50	THF	85	78	22
5	−78	THF	26	91	9
6	0	DME	27	80	20
7	−35	DME	29	53	47
8	−78	DME	24	46	54

[a] All reactions ran with 60% LiCl, 30% CuI, and 1.2 equiv. of PhMgBr added in reverse, unless otherwise noted. [b] *E*/*Z* ratio determined by ^1H NMR spectroscopy (360 MHz) of the crude reaction mixture. [c] 1.3 equiv. TMSCl added.



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 DOI: 10.1002/ejoc.200400314

Based on the catalytic activities of Cu^I salts toward propiolate esters reported by Munch-Petersen, Klein, and Jalander, these preliminary results were discouraging.[2b,2d,2e] It appeared that the catalyst turnover was not proceeding due to the stability of the intermediate vinylcuprate **3** even at 0 °C.[2b] Thus, no isomerization to the magnesium allenoate **4** had occurred, therefore not allowing for the release of the cuprate reagent into a catalytic cycle (Figure 1). The stability of **3** helped to explain the high levels of stereoselectivity even at 0 °C, and contrasts that of lithium-based organocuprates.[1]

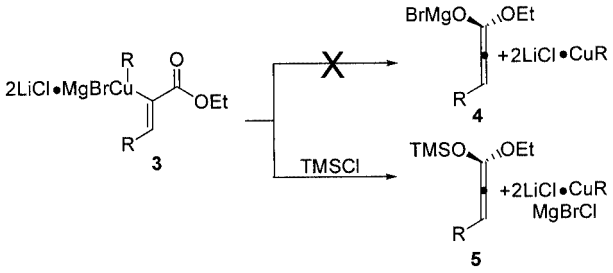


Figure 1. TMS-mediated isomerization of **3**−**5**

Based on previous observations that Lewis acid additives such as TMSCl and BF_3·Et_2O accelerate conjugate addition of cuprates to Michael acceptors,[4] it was reasoned that TMSCl might induce an isomerization of the vinylcuprate **3** to form the TMS-allenoate (**5**) and subsequently permit the release of the bound cuprate.[5] Thus, the addition of TMSCl might allow for a carbocupration that utilizes only a catalytic amount of Cu^I catalyst, as shown in Figure 1.

With this accelerated effect in mind, addition of 1.3 equivalents of TMSCl to **1a** (30 mol% CuI·2LiCl and 1.2 equivalents of PhMgBr in THF) at −50 °C led to a 90% consumption of the starting material, as shown by ^1H NMR spectroscopy of the crude mixture. A diastereomeric ratio of 78:22 was observed in favor of the *E*-isomer. Isolation of **2a** and **2b** by column chromatography provided an 85% combined yield. As anticipated, addition of TMSCl to the reaction mixture presumably leads to **5**,which allows for the turnover of the copper(I) salt, thus rendering the sequence catalytic. However, the degree of diastereoselective induction decreased from 9:1 to slightly more than 3:1. Nonetheless, it was gratifying to note that: a) the reaction was catalytic upon addition of TMSCl, thus providing proof-beyond-principle of the initial hypothesis, and b) protic quench furnished selectivity for **2a** over **2b** (3:1).

To further probe the nature of this TMSCl-mediated carbocupration, the reaction conditions were altered with respect to temperature and catalyst loading. The results are summarized in Table 2 and led to the following two conclusions. Firstly, it was observed that diastereoselectivity was influenced by reaction temperature at 30 mol% catalyst loading. Warming the temperature from −50 °C to −35 °C produced a lower *E*/*Z* isomeric ratio with a slightly lower yield, and moreover no catalysis was observed at 0 °C. However, by performing the reaction at −78 °C (Entry 7, Table 2), a slightly higher yield and a dramatic increase in diastereoselectivity from 3:1 to 9:1 for the *E*-isomer **2a** was observed. It is also worth noting that if the reaction was carried out at −78 °C and then quenched at 0 °C, the isomeric ratio decreased to 3:1, indicating that both the reaction and protic quench must be executed at a low temperature for maximum diastereoselectivity.

Table 2. TMSCl-CuI·2LiCl catalyzed carbocupration of **1a** with PhMgBr in THF

Entry	Temperature [°C]	Catalyst	mol%	Yield [%]	*E*[a]	*Z*
1	0	CuI·2LiCl	30	28	91	9
2	−35	CuI·2LiCl	30	72	64	36
3	−50	CuI·2LiCl	30	85	78	22
4[b]	−78	CuI·2LiCl	30	75	76	24
5	−78	CuI·2LiCl	10	44	43	57
6	−78	CuI·2LiCl	20	85	70	30
7	−78	CuI·2LiCl	30	87	90	10
8	−78	CuI·2LiCl	40	90	92	8
9	−78	CuI·2LiCl	50	91	95	5

[a] *E*/*Z* ratio determined by ^1H NMR spectroscopy (360 MHz) of the crude reaction mixture. [b] Reaction warmed to 0 °C, then quenched with NH_4Cl.

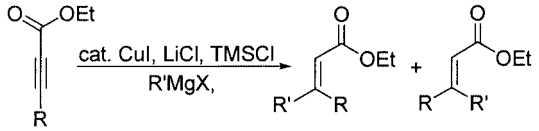
Secondly, the activity of the CuI·2LiCl catalyst was examined and the results are shown in Table 2, Entries 5−9. From the data, it can be seen that the catalytic system turned over approximately four times. Thus, when the reaction sequence was performed with only 10 mol% of catalyst, a 44% combined yield was isolated, and similarly with 20 mol%, a yield of 85% was observed. Interestingly, isomeric ratios rapidly decreased from 9:1 for **2a** at 30 mol% loading to 1.5:1 for **2b** (the opposite isomer) at 10 mol%. Even the difference in the *E*/*Z* ratio between 20 and 30 mol% CuI·2LiCl was unexpected (Entries 6 and 7). At higher catalyst loadings (40 and 50 mol%), better yields and excellent diastereoselectivities were observed (12:1 and 20:1, respectively) than those for 30 mol%.

Expansion of the scope of the reaction with **1a** to include other Grignard reagents and a substituted alkynoate (**1b**) is shown in Equation (2) and summarized in Table 3. All of the reactions, including that with MeMgBr, readily proceeded with **1a**, except for the reaction with the sterically hindered 2-mesityl organocuprate, and furnished selectivities ranging from 8:1 to 40:1 for the *E*-isomer. Interestingly, Et_2O does not allow for carbocupration under these conditions, while coordinating solvents such as THF or DME provide excellent yields and nearly stereochemically pure products. Much to our delight, the substituted alkynoate **1b** showed a propensity for a catalytic and selective carbocupration. Selectivities of about 9:1 for the *E*-isomer (with both PhMgBr and $PhCH_2MgCl$) have been observed for a 50 mol% catalyst loading with 72 and 74% isolated yields. A lower catalyst loading of 30 mol% provided a 7:1 selectivity; however the isolated yield was only 55%. These results greatly expand the scope of the TMS-promoted catalytic carbocupration to include substituted alkynoates.

Table 3. TMSCl-CuI·2LiCl catalyzed carbocupration (50 mol%) of **1a** and **1b** with various Grignard reagents

Entry	Ester	Solvent	Grignard reagent	Yield [%]	E[a]	Z
1	**1a**	THF	PhMgBr[b]	91	95	5
2	**1a**	Et_2O	PhMgBr	< 5	–	–
3	**1a**	DME	PhMgBr	92	93	7
4	**1a**	THF	MeMgBr[b]	87	87	13
5	**1a**	THF	hexylMgBr[b]	91	88	12
6	**1a**	THF	*tert*-butylMgCl[c]	77	88	12
7	**1a**	THF	*sec*-butylMgCl[d]	88	95	5
8	**1a**	THF	*o*-tolylMgCl[e]	71	97	3
9	**1a**	THF	MesitylMgBr[f]	23	98	2
10	**1a**	THF	$PhCH_2MgCl$[b]	92	97	3
11[g]	**1a**	THF	$PhCH_2MgCl$	89	93	7
12[g]	**1b**	THF	PhMgBr[b]	55	87	13
13	**1b**	THF	PhMgBr	72	89	11
14	**1b**	THF	$PhCH_2MgCl$[h]	74	91	9

[a] E/Z ratio determined by ^1H NMR spectroscopy (360 MHz) of the crude reaction mixture. [b] Resulting products are commercially available. [c] Ref. 8. [d] Ref. 9. [e] Ref. 10. [f] Ref. 11. [g] Reactions ran with 30 mol% CuI·2LiCl. [h] Ref. 12.



(2)

R = H, **1a**
R = Me, **1b**

R' = hexyl, Ph, *o*-tolyl, Bn, *t*Bu, *s*Bu
R = Me, H

Attempts to rationalize the observed selectivities are speculative at this point due to the complex nature of organocuprate chemistry.[1] However, a couple of key points merit discussion. First, the structure of the soluble intermediate magnesio-cuprate is unclear; however, the presence of LiCl is required to catalyze the carbocupration of **1a**. Secondly, it is believed that the organocuprate facilitates carbocupration of **1a**, thus producing an intermediate vinylcuprate species **3**, which undergoes TMSCl-mediated isomerization to the TMS-allenoate **5** with the liberation of the cuprate catalyst (Figure 1).[5]

Unfortunately, all attempts to isolate **5** have been unsuccessful. However, we have detected intermediate **5** by ^{13}C NMR spectroscopy prior to protic quench;[6] this provides proof that the TMS-allenoate is a true intermediate. Therefore, it was surprising to observe a direct correlation between catalyst loading and stereoselective induction from the protic quench of **5**.[1c] *These results suggest that the amount of catalyst plays a significant and unprecedented role in determining the diastereoselectivity during the proton quench of the TMS-allenoate.* Towards this end, Corey has suggested the formation of copper-allenolate π complexes to account for the high stereoselectivity of S_N2' displacement reactions of chiral 1,3-disubstituted bromoallenes.[7] Based on this premise, we believe that in our case the alkylcuprate might (from Figure 1) undergo a π complexation of the allenoate **5** and primarily "direct" the protonation of the copper-allenoate complex or an aggregate thereof.

Conclusion

In summary, we have accomplished the first highly diastereoselective TMSCl-promoted catalytic carbocupration of α,β-acetylenic esters with the use of sub-stoichiometric amounts (as low as 30 mol%) of a copper(I) salt in conjunction with a series of Grignard reagents. In addition, an unprecedented and remarkable effect of catalyst loading on stereochemical induction was observed. Future work will be geared toward searching for more robust and selective catalysts, and deciphering the role of the copper catalyst during the selective protic quench.

Experimental Section

All of the reactions were performed under Ar in flame-dried glassware. Anhydrous tetrahydrofuran (THF) and dimethoxyethane (DME) was obtained from commercial sources and used without purification. Deuterated chloroform ($CDCl_3$) was stored over molecular sieves (4 Å). Copper(I) iodide (98% purity) and lithium chloride (LiCl, 99%+, ACS) were obtained from Aldrich and used without any further purification. The NMR spectra were recorded with a 360 MHz Bruker spectrometer. ^1H NMR spectra were obtained using $CDCl_3$ as the solvent with either tetramethylsilane (TMS: δ = 0 ppm) or chloroform ($CHCl_3$: δ = 7.24 ppm) as the internal standard. Column chromatography was performed using 60−200 μm silica gel. Analytical thin layer chromatography was performed on silica coated glass plates with F-254 indicator. Visualization was accomplished by UV light (254 nm) and $KMnO_4$.

General Experimental Procedure for the TMSCl-Promoted Catalytic Carbocupration of 1a and 1b: CuI (0.291 g, 1.50 mmol) and LiCl (0.130 g, 3.0 mmol) was placed in a 100 mL round bottom flask (flame dried under vacuum) under Ar. Dry THF (20 mL) was added to these salts, and the mixture was stirred at room temperature for a period of 0.5 h until complete dissolution had occurred. The clear, light yellow homogeneous solution was cooled to −78 °C, and **1a** (0.294 g, 3.0 mmol) was added, followed by TMSCl (1.3 eq., 0.51 mL, 3.9 mmol). After 5 minutes at −78 °C, benzylmagnesium chloride (1.2 equiv., 3.60 mL, 3.6 mmol) was added dropwise with a syringe, and the solution was stirred at −78 °C for 1 h. Saturated ammonium chloride solution was added to quench the reaction at −78 °C, and the mixture was allowed to warm to room temperature and stir for 30 min. The product was extracted with Et_2O (3 × 25 mL) and washed with deionized H_2O followed by brine. The organic layer was separated, dried with $MgSO_4$, and concentrated in vacuo to give the crude product, which was then analyzed by ^1H NMR spectroscopy to determine regioselectivity. Column chromatography of the crude material (10% ethyl acetate in hexane) afforded an 89% yield of the diastereoselective pure (*E*)-olefin.

Acknowledgments

This work was supported by The University of Alabama.

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Received May 5, 2004

