ORGANIC LETTERS

2007
Vol. 9, No. 25
5327−5329

A Highly Stereoselective TMSOTf-Mediated Catalytic Carbocupration of Alkynoates

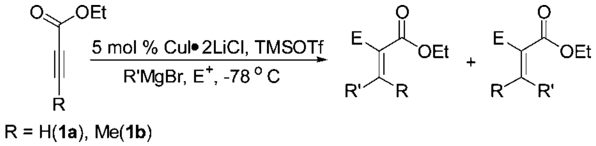
Amanda J. Mueller and Michael P. Jennings*

Department of Chemistry, The University of Alabama, Tuscaloosa, Alabama 35487-0336

jenningm@bama.ua.edu

Received October 30, 2007

ABSTRACT



The TMSOTf-mediated catalytic carbocupration of ynoates has been investigated. It has been shown that catalyst loadings as low as 5 mol % readily allow for high yields and diastereoselectivities for a series of aromatic Grignard reagents. In addition, we have been successful in vicinally functionalizing 1a via initial TMSOTf-mediated catalytic carbocupration followed by a secondary electrophilic capture of the TMS allenoate intermediate.

The first stoichiometric carbocupration of alkynoates was reported by Corey and afforded stereodefined α,β-unsaturated esters with high levels of diastereoselectivities and yields.[1] Subsequent to this paper, considerable attention has been given to understanding organocuprate additions to such substrates.[2] Most notably, it has been shown that Lewis acid additives such as TMSCl not only accelerate the carbocupration of alkynoates, but also isomerize the intermediate vinyl cuprate to the TMS allenoate thus releasing the bound organocuprate.[3] With this in mind, we have been interested in developing a diastereoselective carbocupration of α,β-acetylenic esters that utilizes only a catalytic amount of Cu(I) catalyst. As described in Figure 1, *syn*-carbocupration of ethyl propiolate (**1a**) with the diphenyl magnesiocuprate should furnish the vinyl cuprate that would then be isomerized, by addition of TMSOTf, to the TMS allenoate via release of the organocuprate.[4] Presumably, the byproduct phenyl cuprate would then be transformed into diphenyl cuprate by means of PhMgBr addition and, in turn, complete the catalytic cycle. Final protonation of the TMS allenoate

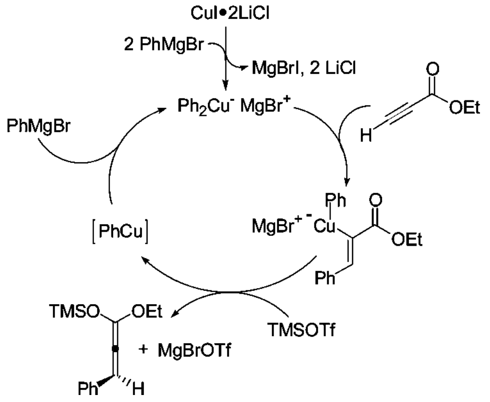


Figure 1. Catalytic carbocupration via a TMS allenoate.

---

[1] Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851.

[2] (a) Nakamura, E.; Mori, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3750. (b) Woodward, S. *Chem. Soc. Rev.* **2000**, *29*, 393. (c) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.

[3] (a) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 3368. (b) Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056. (c) Frantz, D. E.; Singleton, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 3288. (d) Nilsson, K.; Andersson, T.; Ullenius, C. *J. Organomet. Chem.* **1997**, *545−546*, 591. (e) Nilsson, K.; Andersson, T.; Ullenius, C.; Gerold, A.; Krause, N. *Chem. Eur. J.* **1998**, *4*, 2051. (f) Klein, J.; Levene, R. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1971. (g) Marino, J. P.; Linderman, R. J. *J. Org. Chem.* **1981**, *46*, 3696.

[4] Jennings, M. P.; Sawant, K. B. *Eur. J. Org. Chem.* **2004**, 3201.

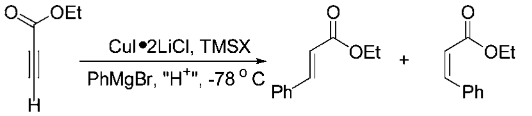
10.1021/ol702546w CCC: $37.00

(after organocuprate consumption) should provide the desired ester product.

Our initial concern with selective protonation of the TMS allenoate has since been resolved as described in our previous work.[4] Although we had modest success (≥20:1 (*E*)-selectivity at 50 mol % loading) with the TMSCl-promoted carbocupration of ynoates, we elected to further investigate the catalytic carbocupration of propiolate esters with TMSOTf as the Lewis acid additive. Our initial reasoning behind using TMSOTf was its increased Lewis acidity compared to TMSCl. We surmised that TMSOTf would lead to amplified catalytic efficiency and allow for a much lower catalyst loading. Herein we report that not only does TMSOTf allow for catalytic carbocupration of propiolate esters with 5 mol % of Cu(I), but also the incorporation of TFA as the proton source provides selectively (*Z*)-substituted α,β-unsaturated esters. This new catalytic protocol provided products that are complementary to our previous catalytic system and the Corey stoichiometric procedure.[1,4] In addition to a proton quench, we have also established that the intermediate TMS allenoate can undergo highly diastereoselective carbon−carbon, deuterium, and silyl bond forming processes in a single flask.

As shown in Table 1, we initially observed that TMSCl readily promoted the catalytic carbocupration of ethyl propiolate (**1a**) at high catalyst loadings with PhMgBr. The reaction afforded good yields and diastereoselectivities of (*E*)-ethyl cinnamate after quenching with NH_4Cl. However, proton addition to the TMS allenoate intermediate with TFA as the quenching source led to a decrease in *E* selectivity as shown in entry 4.

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



(1)

1a **2a**

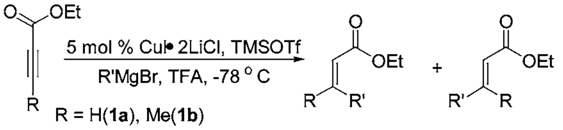
no.	mol %	TMS-X	quench	yield, %	E^a	Z
1	**50**	**Cl**	**NH_4Cl**	**91**	**20**	**1**
2	**40**	**Cl**	**NH_4Cl**	**90**	**12**	**1**
3	**30**	**Cl**	**NH_4Cl**	**87**	**9**	**1**
4	30	Cl	TFA	76	3	1
5	30	OTf	TFA	81	2	1
6	20	OTf	TFA	85	1	5
7	10	OTf	TFA	84	1	6
8	**5**	**OTf**	**TFA**	**91**	**1**	**13**
9	**3**	**OTf**	**TFA**	**81**	**1**	**12**
10	5	OTf	NH_4Cl	85	1	7
11	5	OTf	PPTS	55	1	4
12	5	OTf	TfOH	71	1	5
13	5	OTf	CSA	57	1	6
14	5	OTf	HCl	63	1	6
15^b	5	OTf	TFA	<5		
16^c	5	OTf	TFA	<5		

[a] *E*/*Z* ratio determined by ^1H NMR (360 or 500 Mhz) from the crude reaction mixture. [b] Reaction run in Et_2O. [c] Reaction run in *t*BuOMe.

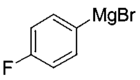
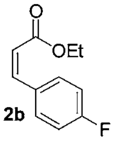
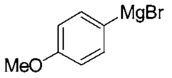
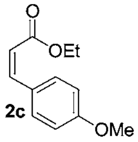
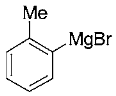
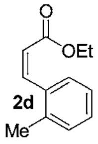
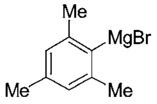
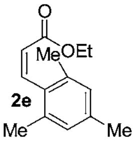
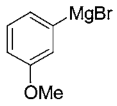
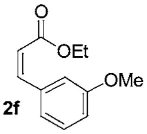
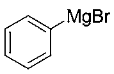
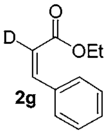
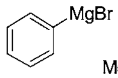
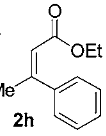
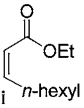
Switching the Lewis acid from TMSCl to TMSOTf and maintaining TFA as the proton source revealed additional degradation of the *E* selectivity but provided a comparable yield. Further lowering the catalyst loading to 20 mol % slightly improved the overall yield, but dramatically altered the selectivity providing the *Z* product in a 5:1 ratio. Much to our delight, dropping the catalyst loading down even further to 5 mol % led to a 91% yield and an exceptional 13:1 ratio for the (*Z*)-ethyl cinnamate product (entry 8). It is worth noting in entry 9, that even at 3 mol % high levels of diastereoselection were observed, but the yield did decrease from 91% to 81%. A series of other proton sources were examined (entries 10−14), but led to inferior results with respect to both yield and diastereoselectivity. It is worth noting that the TMSOTf-promoted catalytic carbocupration of **1a** proceeded with high yields in THF, but not significantly in other ethereal solvents such as Et_2O and MTBE. With this information in hand, we subsequently examined the scope and limitations of the TMSOTf-promoted catalytic carbocupration of **1a**.

As shown in Table 2, the reactions readily proceeded with

Table 2. TMSOTf−CuI·2LiCl-Catalyzed Carbocupration (5 mol %) of **1a** and **1b** with Various Grignard Reagents[a]



(2)

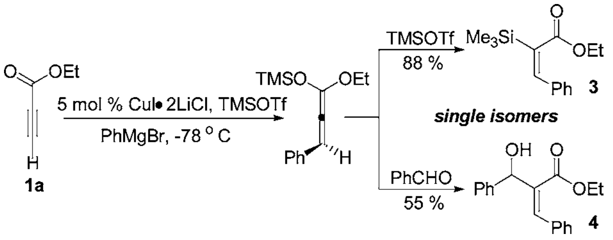
Grignard Reagent	Product Yield, (Z/E)	Grignard Reagent	Product Yield, (Z/E)
	 **2b** **91 %, 13/1:*Z/E***		 **2c** **79 %, 12/1:*Z/E***
	 **2d** **83 %, 11/1:*Z/E***		 **2e** **75 %, 10/1:*Z/E***
	 **2f** **73 %, 11/1:*Z/E***		 **2g** **84 %, 12/1:*Z/E***[b]
	 **2h** **88 %, 5/1:*Z/E***	*n*-hexylMgBr	 **2i** **84 %, 2/1:*Z/E***

[a] *E*/*Z* ratio determined by ^1H NMR (360 or 500 Mhz) from the crude reaction mixture. [b] Reaction quenched with CF_3COOD (≥95% deuterium incorporation).

ortho-, meta-, and para-substituted aryl Grignard reagents to provide the α,β-unsaturated esters in good to excellent yields (73−91%). In addition, high levels of diastereoselectivities were observed (10:1 → 13:1 for the *Z* product) for all of the reactions irrespective of steric or electronic differences resident in the arene. For example, both 4-fluoro- and 4-methoxyphenyl magnesium bromide readily underwent catalytic carbocupration of **1a** and afforded the ester products in good yields and high levels of *Z* diastereoselectivity (12−13:1). A few other table entries are notable. The first is that the sterically hindered mesityl Grignard reagent underwent *Z*-selective catalytic carbocupration in 75% yield with TMSOTf, whereas when TMSCl was used as the Lewis acid promoter no reaction with **1a** was observed. Second, quenching the TMS allenoate with TFA-D readily allowed for the chemo- and diastereoselective introduction of a deuterium atom α to the carbonyl moiety as predicted. Under the standard reaction conditions for **1a**, the β-methyl ynoate (**1b**) showed equal reactivity toward PhMgBr with a comparable 88% yield but with a slightly diminished 1/5 *E*/*Z* ratio. Nonetheless, the TMSOTf-mediated catalytic carbocupration of substituted ynoates was shown to be quite feasible, and also provided products that are complementary to our previous catalytic system and the Corey stoichiometric procedure.[1,4] Last, we were pleased to observe that aliphatic Grignard reagents underwent catalytic carbocupration and provided a yield (84%) comparable to that of the aromatic counterparts. However, the diastereoselectivity was significantly lower (2:1) in favor of the *Z* product.

In addition to a proton quench, we have also established that the intermediate TMS allenoate can undergo highly diastereoselective carbon−carbon and silyl bond forming processes in a single flask. As shown in Scheme 1, we have been successful in vicinally functionalizing **1a** via initial TMSOTf-mediated catalytic carbocupration followed by a secondary electrophilic capture of the TMS allenoate intermediate. Thus, trapping of the TMS allenoate with PhCHO and the external addition of $BF_3{\cdot}OEt_2$ afforded the aldol adduct **4** in 55% overall yield as a single stereoisomer. To the best of our knowledge, a Mukaiyama aldol reaction between a TMS allenoate of this type and an aldehyde has yet to be reported.[5] In addition to the carbon−carbon bond-forming process, capturing the allenoate with a second equivalent of TMSOTf furnished the (*E*)-stereodefined vinyl silane **3** in an outstanding yield of 88%.[6]

Scheme 1



In conclusion, we have shown that not only does TMSOTf allow for catalytic carbocupration of propiolate esters with 5 mol % of Cu(I), but also the incorporation of TFA as the proton source provides selectively (*Z*)-substituted α,β-unsaturated esters. Future directions of investigation will include increasing the *Z* selectivity for aliphatic Grignard reagents and further developments into the catalytic vicinal functionalization of ynoates with other electrophiles. Results from these studies will be reported in due course.

Acknowledgment. The authors would like to thank The University of Alabama for financial support of this work.

Supporting Information Available: General reaction procedures and tabulated ^{1}H NMR data for all of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL702546W

---

[5] (a) Crimmins, M. T.; Nantermet, P. G. *J. Org. Chem.* **1990**, *55*, 4235. (b) Reynolds, T. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 15382.

[6] (a) Boeckman, R. K., Jr.; Chinn, R. L. *Tetrahedron Lett.* **1985**, *41*, 5005. (b) Hartzell, S. L.; Rathke, M. W. *Tetrahedron Lett.* **1976**, *31*, 2737. (c) Hartzell, S. L.; Sullivan, D. F.; Rathke, M. W. *Tetrahedron Lett.* **1974**, *29*, 1403.