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Vicinal Functionalization of Propiolate Esters via a Tandem Catalytic Carbocupration–Mukaiyama Aldol Reaction Sequence

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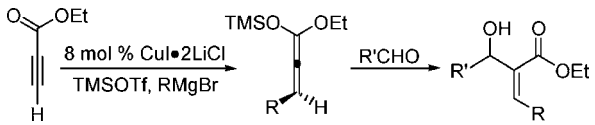
ABSTRACT



The vicinal functionalization of propiolate esters via a tandem catalytic carbocupration–Mukaiyama aldol reaction sequence has been investigated. It has been shown that catalyst loadings as low as 8 mol % readily allow for good yields and excellent diastereoselectivities (>20:1) for a series of Grignard reagents and aldehydes.

The advent of new catalytic reactions that allow for the construction of two carbon−carbon bonds with high levels of diastereoselectivity in a single flask are of great interest to the synthetic organic field. Some of the more popular approaches to multiple carbon−carbon bond-forming reactions are deeply rooted in transition-metal-catalyzed processes. For example, Negishi has reported on multiple intramolecular Heck type processes en route to "zipping" multiple rings together via Pd catalysis.[1] Another approach to multiple carbon−carbon bond-forming reaction processes is vicinal functionalization of olefinic or acetylenic compounds. One such thought along this line is a Michael addition to an α,β-unsaturated carbonyl via a classical Kharash or Gilman reagent followed by electrophilic quenching of the resultant enolate. While this reaction process is well-known, very few reports have been published regarding a vicinal functionalization of α,β-acetylenic esters.[2] As reported by Li and co-workers in 1999, they observed that a stoichiometric carbocupration under Corey's conditions with classical Gilman reagents followed by electrophilic quenching of the metal allenolate intermediate with an aldehyde led to product β-hydroxy-α-olefinic esters in good yields and excellent dr.[3] Based on our interest in developing a diastereoselective, catalytic carbocupration of α,β-acetylenic esters, we envisaged trapping an in situ generated silyl allenolate with an electrophilic coupling partner.[4] It has been shown that Lewis acid additives such as TMSOTf not only accelerate the carbocupration of alkynoates but also isomerize

(1) For a leading review in this area, see: Negishi, E.; Coperet, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365.

(2) For some leading references, see: (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. (d) Kennedy, J. W. J; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 898. (e) Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851. (f) Chen, D.; Guo, L.; Kotti, S. R. S. S.; Li, G. *Tetrahedron: Asymmetry* **2005**, *16*, 1757. (g) Wei, H.-X.; Hu, J.; Jasoni, R. L.; Li, G.; Pare, P. W. *Helv. Chim. Acta* **2004**, *87*, 2359. (h) Wei, H.-X.; Timmons, C.; Farag, M. A.; Pare, P. W.; Li, G. *Org. Biomol. Chem.* **2004**, *2*, 2893. (i) Wei, H.-X.; Jasoni, R. L.; Hu, J.; Li, G.; Pare, P. W. *Tetrahedron.* **2004**, *60*, 10233. (j) Wei, H.-X.; Chen, D.; Xu, X.n; Li, G.; Pare, P. W. *Tetrahedron: Asymmetry* **2003**, *14*, 971. (k) Wei, H.-X.; Kim, S. H.; Li, G. *Org. Lett.* **2002**, *4*, 3691. (l) Li, G.; Wei, H.-X.; Phelps, B. S.; Purkiss, D. W.; Kim, S. H. *Org. Lett.* **2001**, *3*, 823. (m) Wei, H.-X.; Willis, S.; Li, G. *Tetrahedron Lett.* **1998**, *39*, 8203.

(3) Wei, H.-X.; Willis, S.; Li, G. *Synth. Commun.* **1999**, *29*, 2959.

(4) The electrophilic capture of silyl allenes derived from carbonyl compounds have been reported, but not via a one-pot, intermolecular vicinal functionaliztion. For some leading references, see: (a) Reynolds, T. E.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7806. (b) Reynolds, T. E.; Stern, C. A.; Scheidt, K. A. *Org. Lett.* **2007**, *9*, 2581. (c) Reynolds, T. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 15382. (d) Crimmins, M. T.; Nantermet, P. G. *J. Org. Chem.* **1990**, *55*, 4235.

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the intermediate vinyl cuprate to the TMS allenolate thus releasing the bound organocuprate.[5,6] As described in Figure 1, *syn*-carbocupration of ethyl propiolate (**1a**) with the dialkyl

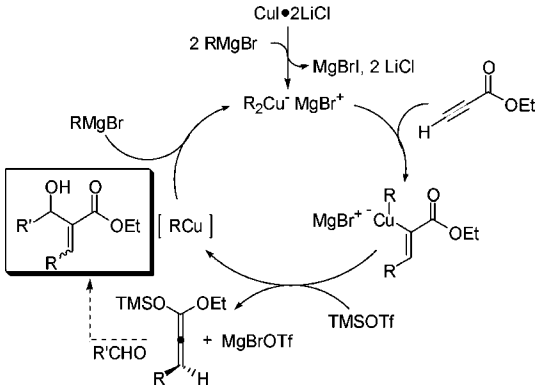
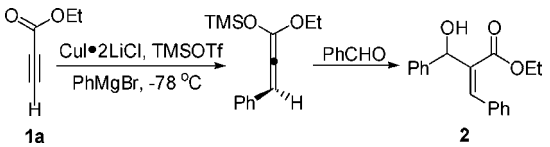


Figure 1. Catalytic cycle for carbocupration of **1a**.

or aryl magnesiocuprate should furnish the vinyl cuprate which would then be isomerized, by addition of TMSOTf, to the TMS allenolate via release of the organocuprate.[6] Presumably, the byproduct alkyl or aryl cuprate would then be transformed into the corresponding dialkyl or aryl cuprate by means of RMgBr addition and, in turn, complete the catalytic cycle. Final electrophilic capture of the TMS allenolate (after organocuprate consumption) by an aldehyde should provide the desired aldol ester product.[4] Herein, we wish to report on the successful vicinal functionalization of an α,*β*-acetylenic ester via a catalytic carbocupration/Mukaiyama aldol reaction sequence.

As shown in Table 1, we initially observed that utilizing 5 mol % of CuI·2LiCl for the initial carbocupration of **1a** with PhMgBr followed by the addition of PhCHO and warming of the reaction to rt did indeed afford **2** with an exceptional 20:1 dr for the (*Z*)-aldol product but with a low yield of 13−20% over the two-step process (entries 1 and 2). Initially, we speculated that the 30 mol % excess of TMSOTf was responsible (although we cannot rule out either the Mg or Cu salts) for the activation of the aldehyde toward nucleophilic addition of the intermediate TMS allenolate. In our efforts to increase the overall yield, we allowed the reaction to remain at −78 °C for 3 → 5 h and were provided with an improved yield of 30%. Unfortunately, a longer reaction time of 21 h (entry 5) did not improve the overall yield but furnished a slightly inferior yield of 21%. Based on these results, we surmised that the addition of a stoichiometric amount of Lewis acid would increase the electrophilicity of the aldehyde acceptor and ultimately improve the overall yield via an enhanced capture of the nucleophilic TMS allenolate. Much to our delight, the addition of $TiCl_4$ or BF_3·OEt_2 did advance the overall yield nearly 2-fold with yields of 40 and 59%, respectively. As shown in entry 8, increasing the catalyst loading to 30 mol % and alternatively using TMSCl in place of TMSOTf furnished an overall lower yield while maintaining a dr of 20:1 in favor of the *Z* product. In addition, we also observed that using a lower equivalence of TMSOTf (1.05 equiv) decreased the yield over the two-step process from 59 to 32%. It should be noted that in all cases the remaining material balance was a mixture of the (*Z*)-α,*β*-unsaturated ester (arising from an incomplete aldol reaction and proton quench of the allenolate) and starting material.

Table 1. Vicinal Functionalization of **1a** via a Catalytic Carbocupration/Mukaiyama Aldol Reaction Sequence



1a **2**

no.	mol %	*T* (°C)	time (h)	additive	yield (%)	*Z*/*E*[a]
1	5	rt	1	none	13	>20:1
2	5	rt	3	none	20	>20:1
3	5	−78	3	none	30	>20:1
4	5	−78	5	none	30	>20:1
5	5	−78	21	none	22	>20:1
6	5	−78	3	$TiCl_4$	40	>20:1
7	5	−78	3	BF_3·OEt_2	59	>20:1
8[b]	30	−78	3	BF_3·OEt_2	40	>20:1
9[c]	5	−78	3	BF_3·OEt_2	32	>20:1

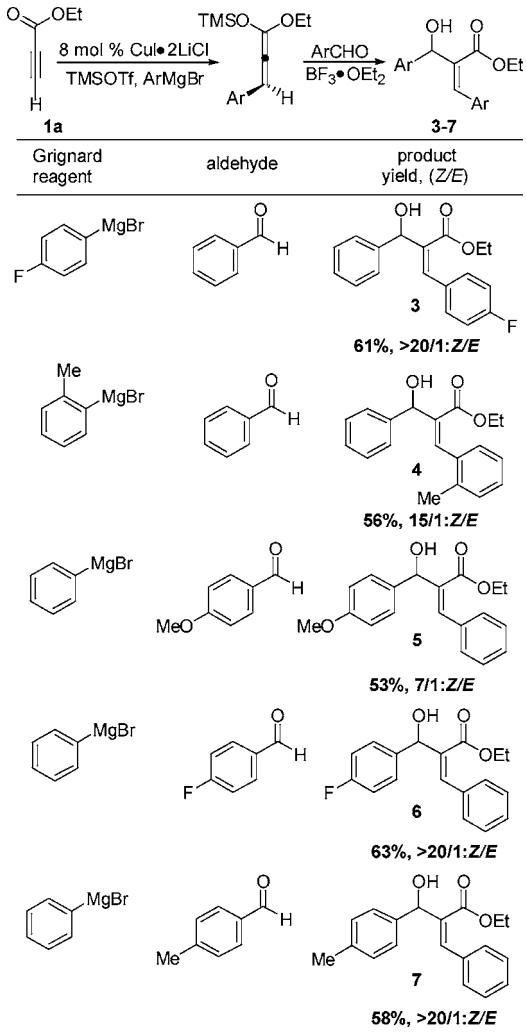
[a] *E*/*Z* ratio determined by ^{1}H NMR (360 or 500 MHz) from the crude reaction mixture. [b] Reaction ran with TMSCl in place of TMSOTf. [c] Reaction ran with 1.05 equiv of TMSOTf instead of 1.3 equiv as reported in entries 1−7.

Based on the optimized conditions in Table 1 (entry 7), we decided to investigate the scope of the vicinal functionalization of **1a** with a series of aromatic Grignard reagents and aldehydes. We initially observed that utilizing 4-fluorophenyl MgBr for the carbocupration and benzaldehyde as the electrophilic coupling partner provided product **3** with a 55% yield and an excellent dr of >20:1 for the *Z* product. While pleased with the overall process, we decided to raise the catalyst loading from 5 to 8 mol % and observed ∼10% amplification in yield from 55% to 61%. Further increases in the catalyst loading (>8%) unfortunately did not translate into higher overall yields. With the new optimized conditions in hand (8 mol % of CuI·2LiCl and 1.3 equiv of TMSOTf), we continued our investigation as previously indicated. As delineated in Table 2, the vicinal functionalization of **1a** with *o*-tolyl MgBr and benzaldehyde proceeded to afford the desired adduct **4** in good yield (58%) with an excellent dr of 15:1 for the *Z*-aldol stereoisomer. The slight degradation of dr from 20:1 *Z*/*E* for the aldol adduct **3** to 15:1 for *β*-hydroxy-α-methylene ester **4** was attributed to the more sterically hindered Grignard reagent. It is worth noting that

(5) (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.

(6) (a) Mueller, A. J.; Jennings, M. P. *Org. Lett*. **2007**, *9*, 5327. (b) Jennings, M. P.; Sawant, K. B. *Eur. J. Org. Chem*. **2004**, 3201.

Table 2. Vicinal Functionalization of **1a** via a Catalytic Carbocupration/Mukaiyama Aldol Reaction Sequence with Various Aromatic Grignard Reagents and Aldehydes[a,b]



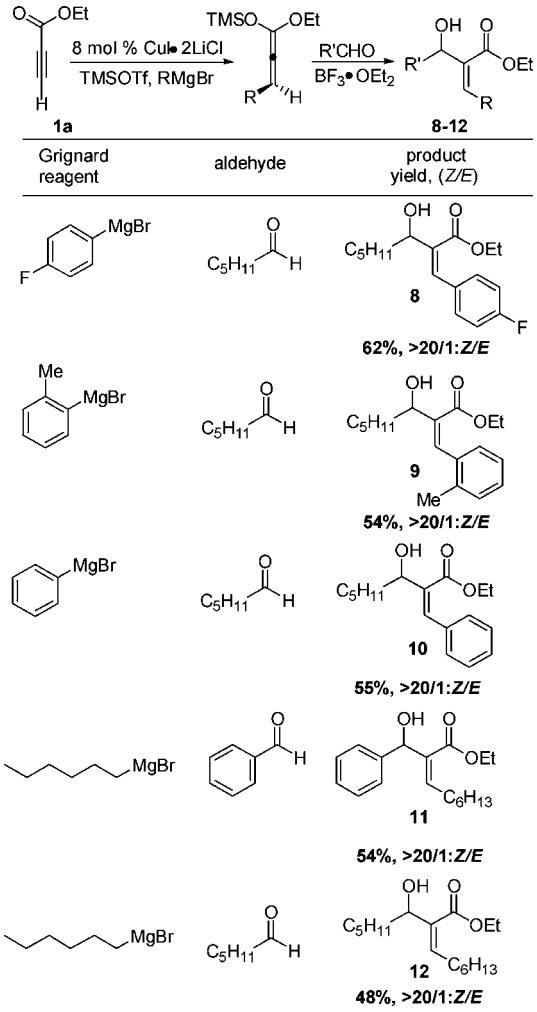
[a] *E*/*Z* ratio determined by ^{1}H NMR (360 or 500 MHz) from the crude reaction mixture. [b] Yields are of the isolated, pure compounds.

when the electrophilic quench of the silyl allenolate derived from the catalytic carbocupration of **1a** with the *o*-tolyl Grignard reagent was a proton, the dr was 11:1, which was slightly lower than that of the Ph derived silyl allenolate (dr of 13:1 for the *Z* product).[6a] We also observed a lower level of dr when anisaldehyde was utilized as the electrophilic quench of the TMS allenolate derived from the catalytic carbocupration of **1a** with PhMgBr. The aldol product **5** was isolated as a 7:1 *Z*/*E* mixture with a combined yield of 53%.

Gratifyingly, the vicinal functionalization of **1a** with PhMgBr and the electron-poor 4-fluorobenzaldehyde provided the β-hydroxy-α-olefinic ester **6** in one of the best yields in Table 2 of 63%, while re-establishing very high levels of dr (>20:1 for the *Z*-product). Similarly, the catalytic addition of the diphenyl cuprate to **1a** followed by nucleophilic addition of the TMS allenolate to *p*-tolylaldehyde afforded virtually an identical dr of >20:1 for the final product **7** (compared with that of **6**) in an acceptable yield of 58% over the one-pot, two-step process. With the results from Table 2 in hand, we sought to further investigate the scope of the tandem catalytic carbocupration−Mukaiyama aldol reaction of **1a** with a variety of both aromatic and aliphatic Grignard reagents and aldehydes.

As reported in Table 3, the vicinal functionalization of **1a**

Table 3. Vicinal Functionalization of **1a** via a Catalytic Carbocupration/Mukaiyama Aldol Reaction Sequence with Various Grignard Reagents and Aldehydes[a,b]



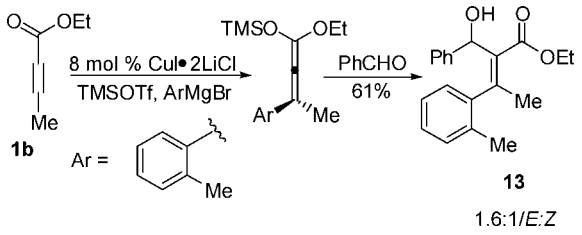
[a] *E*/*Z* ratio determined by ^{1}H NMR (360 or 500 MHz) from the crude reaction mixture. [b] Yields are of the isolated, pure compounds.

with the 4-fluorophenyl Grignard reagent readily provided the TMS allenolate, and subsequent treatment with hexanal and BF_3•OEt_2 afforded the aldol adduct **8** in 62% yield with an excellent dr of >20:1 for the *Z*-product. Similarly, initial catalytic carbocupration of **1a** with both *o*-tolylMgBr and PhMgBr followed by an ensuing treatment of the allenolates with hexanal afforded the β-hydroxy-α-olefinic esters **9** and **10** in practically identical yields of 54 and 55%, respectively, while maintaining very high levels of dr (>20:1 for **9** and **10**) for both of the *Z*-aldol adducts. Much to our delight, exchanging from an aromatic Grignard reagent to an aliphatic

one had little effect on yield or diastereoselectivity. Thus, catalytic carbocupration of **1a** with hexylMgBr followed by a subsequent quenching of the TMS allenolate with benzaldehyde led to the desired aldol adduct **11** in 54% yield with an exceptional dr of 20:1, once again favoring the *Z*-product. It is worth noting that when the electrophilic quench of the silyl allenolate derived from the catalytic carbocupration of **1a** with the hexyl Grignard reagent was a proton, the dr was a trivial 2:1, which was considerably lower than that of the aromatic-derived silyl allenolates (dr of 10 → 13:1 for the *Z* product).[6a] Based on our observation, it appeared that the nucleophilic addition of an aliphatic TMS allenolate is quite dependent on the steric environment of the approaching electrophile (aldehyde versus a proton). Last, vicinal functionalization of **1a** with hexylMgBr and hexanal selectively furnished the *β*-hydroxy-α-olefinic ester **12** in an acceptable yield of 48% coupled with an analogous dr of 20:1, as seen with compounds **8**−**11**.

With the results from Tables 2 and 3 in hand, we decided to investigate the vicinal functionalization of the *β*-substituted-α,*β*-acetylenic ester **1b** with the hope of affording the highly stereodefined *β*-hydroxy-α- tetrasubstituted ester **13**. Thus, catalytic carbocupration of **1b** with the *o*-tolyl Grignard reagent under the standardized conditions of Tables 2 and 3 presumably furnished the tetra-substituted TMS allenolate. Subsequent quenching of the nucleophilic allenolate with $BF_3{\cdot}OEt_2$ coordinated benzaldehyde provided the aldol adduct **13** in 61% overall yield, but with a disappointing dr of 1.6:1 in favor the *E*-*β*-hydroxy-α-olefinic ester as described in Scheme 1.

Scheme 1



As shown in Figure 2, the olefin geometry of **4** was determined by means of ^{1}H NMR. The strong 1D NOE for both the methine allylic and *β*-vinylic protons provided unquestionable proof for the assigned *Z*-olefin geometry. On the basis of the NOE experiment results for **4**, the stereochemistry of the remaining aldol adducts **2**−**3** and **5**−**12** were assigned by analogy.

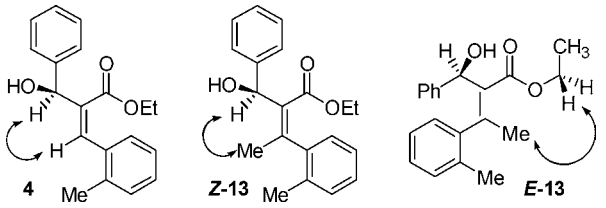


Figure 2. Key NOE enhancements for **4**, **13-*E*,** and **13-*Z***.

The relative stereochemical determination of **13** was more challenging than that of **4** due to the initial difficulty in assigning the vinyl methyl group versus that of the aromatic methyl moiety. Much to our delight, the ^{1}H−^{13}C NMR correlation spectroscopy (HMBC) furnished a four-bond cross-correlation peak between the allylic methyl protons and the carbonyl of the ester functional group. With the peak assignments in hand, a strong NOE for both the methine aldol and *β*-methyl protons provided unquestionable proof for the assigned *Z*-olefin geometry. Likewise, a strong NOE between the *β*-methyl and the methylene protons of the ethyl group resident in the ester moiety provided convincing evidence for the *E*-olefin isomer.

In conclusion, we have shown that vicinal functionalization of propiolate esters via a tandem catalytic carbocupration−Mukaiyama aldol reaction sequence with catalyst loadings as low as 8 mol % readily allows for good yields and excellent diastereoselectivities (>20:1) for a series of Grignard reagents and aldehydes. Future directions of investigation will include further developments into the catalytic vicinal functionalization of ynoates with other electrophiles and chiral Lewis acid catalysts. Results from these studies will be reported in due course.

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Supporting Information Available: The general reaction procedure and NMR data (^{1}H and ^{13}C) for all of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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