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Vicinal Functionalization of Propiolate Esters via Catalytic Carbocupration: Stereoselective Formation of Substituted Vinyl Silanes

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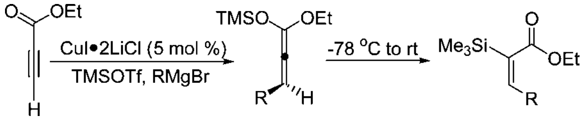
ABSTRACT



The vicinal functionalization of propiolate esters via a catalytic carbocupration−silicon group migration sequence has been investigated. We have observed that catalyst loadings as low as 5 mol % allow for good yields and excellent diastereoselectivities (>20:1) with a series of Grignard reagents for the synthesis of substituted *E*-vinyl silanes.

The stereoselective synthesis of multifunctional alkenes within a single reaction flask remains a challenging task to organic chemists. While many methods currently exist, high levels of diastereoselectivity still can be difficult to obtain. Some of the more successful reaction processes include olefination of complex aldehydes with Horner−Wadsworth−Emmons (HWE) stabilized phosphonate esters, the Still−Gennari modification of the HWE reaction, and the classical stabilized Wittig ylide reagents to name a few.[1] In addition, olefin synthesis by means of transition metal catalysis has carved a significant niche in the modern context of organic chemistry. For example, there are numerous examples of Heck, Negishi, Stille, and Suzuki couplings catalyzed by Pd, accompanied by Mo, W, and Ru promoted olefin metatheses.[2,3]

A less utilized method for the synthesis of stereodefined olefins centers on the partial reduction of propiolate esters with cuprate complexes (i.e., Gilman or Kharash reagents). Initially reported in 1969 by Corey and Katzenellenbogen, the stoichiometric carbocupration of ethyl propiolate with a variety of Gilman reagents and subsequent electrophiles provided α,*β*-unsaturated esters with high levels of diastereoselectivity.[4] It was observed that reaction conditions (i.e., solvent and temperature) played a vital role in determining the *E*/*Z* ratio of the final alkene products. Subsequent to this report, there have been a multitude of investigations into the stoichiometric carbocupration of propiolate esters.[5] However, one area that has garnered little attention is the *catalytic*

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(1) (a) Horner, L.; Hoffman, H.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61. (b) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733. (c) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405. (d) For a review on stabilized Wittig reagents, see: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(2) Negishi, E.-I.; de Meijere, A., Eds. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley: New York, 2002; *2* Vols.

(3) For a leading review on Mo and W metathesis, see: (a) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592. (b) For a recent review on Ru metathesis, see: Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746.

(4) Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851.

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

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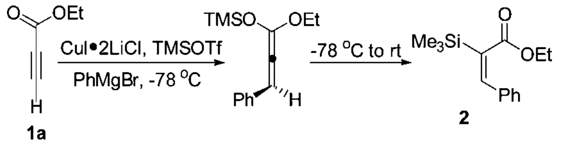
carbocupration of such substrates utilizing Kharash reagents. Recently, we have reported on the stereoselective synthesis of both *E* and *Z* α,*β*-unsaturated esters via catalytic carbocupration of propiolate esters. The diastereoselectivity diverges from a common TMS allenolate depending on reaction conditions such as temperature and the proton source used to quench the highly reactive intermediate.[6] We also recently expanded the scope of the TMS allenolate as a potent nucleophile by demonstrating a vicinal functionalization of propiolate esters via a tandem catalytic carbocupration−Mukaiyama aldol reaction sequence.[7] During this process, we observed that excess TMSOTf did not promote the second carbon−carbon bond formation as desired but instead facilitated a tautomerization of the TMS allenolate to a stereodefined α-TMS-α,*β*-unsaturated ester upon allowing the reaction to warm to rt. Armed with this curious silyl group migration and the synthetic potential of the formed products, we chose to further investigate this reaction, and our results are presented herein.[8]

As shown in Table 1, we initially examined the equivalency of TMSOTf needed to perform the tautomerization from the TMS allenolate to the α-TMS-α,*β*-unsaturated ester (**2**).

Table 1. Vicinal Functionalization of **1a** via a Catalytic Carbocupration−Silicon Group Migration Sequence

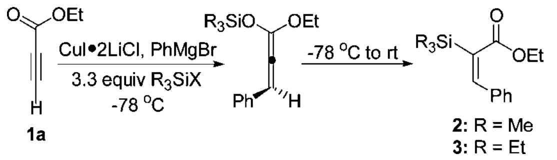


entry	CuI·2LiCl mol %	TMSOTf equiv	solvent	yield %^{a}	*E*/*Z*^{b}
1	5	1.3	THF	43^{c}	>20/1
2	5	2.3	THF	86	>20/1
3	5	3.3	THF	92	>20/1
4	10	3.3	THF	95	>20/1
5	20	3.3	THF	98	>20/1
6	5	3.3	Et_2O	0	---
7	5	3.3	MTBE	15^{c}	>20/1
8^{d}	5	3.3	THF	80	>20/1
9^{e}	5	3.3	THF	85	>20/1
10^{f}	5	1.3 then 1	THF	72^{c}	>20/1
11^{g}	5	1.3 then 2	THF	90	>20/1

[a] Purified, isolated yield of vinyl silane. [b] *E*/*Z* ratio determined by ^{1}H NMR (360 or 500 MHz) from the crude reaction mixture. [c] Remaining mass balance was the α,*β*-unsaturated ester from the proton quench of the TMS allenolate. [d] Reaction ran at −10 °C. [e] Reaction ran at −40 °C. [f] Reaction ran with 1.3 equiv of TMSOTf followed by addition of 1 equiv before warming to rt. [g] Reaction ran with 1.3 equiv of TMSOTf followed by addition of 2 equiv before warming to rt.

Thus, under our standard catalytic carbocupration reaction conditions as previously described for ethyl propiolate (**1a**) and PhMgBr, 1.3 equiv of TMSOTf provided only a 43% yield of the desired vinyl silane **2** with a d.r. of >20:1 for the *E* isomer upon warming the reaction to rt. The stereochemistry was initially established by 1D NOE experiments on the purified ester **2**. The remaining mass balance was a mixture of both *E* and *Z* α,*β*-unsaturated ester isomers (arising from the proton quench of the intermediate TMS allenolate). Increasing the amount of TMSOTf to 2.3 and even further to 3.3 equiv furnished much greater yields (86% and 92%) of vinyl silane **2**, while maintaining the high level of diastereoselectivity of >20:1 for the *E* isomer. Increasing the catalyst loading to 10 and 20 mol % had limited effects on the yield and stereoselectivity of **2** when using 3.3 equiv of TMSOTf. A significant solvent effect was observed by switching from THF to MTBE or Et_2O as the yields of **2** significantly dropped from 92% down to 15% and 0%, respectively. In addition, a slight change in yield for **2** was observed when the initial carbocupration was performed at a warmer temperature. Thus, initial carbocupration at −40 and −10 °C followed by warming to rt afforded yields of 85% and 80%, while maintaining comparable diastereoselectivities of **2** (>20:1 for the *E* isomer). Lastly, portionwise addition of TMSOTf did have a slight effect on the overall yield of **2** (see Table 1, examples 10 and 11) but did not diminish the *E*-olefin selectivity.

Table 2. Vicinal Functionalization of **1a** via a Catalytic Carbocupration−Silicon Group Migration Sequence with Various Silane Promoters



entry	CuI·2LiCl mol %	R_3SiX	yield %^{a}	*E*/*Z*^{b}
1	5	TMSCl	67^{c}	>20/1
2	5	TMSBr	80	>20/1
3	5	TMSI	89	>20/1
4	5	TESOTf	88	>20/1
5	5	TESCl	32^{c}	>20/1
6	5	TBSOTf	0	N/A
7	5	TBSCl	0	N/A

[a] Purified, isolated yield of vinyl silane. [b] *E*/*Z* ratio determined by ^{1}H NMR (360 or 500 MHz) from the crude reaction mixture. [c] Remaining mass balance was the α,*β*-unsaturated ester from the proton quench of the TMS allenolate or decomposed material.

With standardized reaction conditions in hand from Table 1, we next investigated a variety of silanes with respect to their catalytic activities and migratory aptitude. As delineated in Table 2, all of the TMS halide Lewis acids (i.e., TMSCl, Br, I) exhibited high levels of activity with yields ranging from 67 to 89% using 3.3 equiv for either the desired vinyl silane **2** and/or the side-product α,*β*-unsaturated ester. Interestingly, it appeared that TMS migration via tautomerization is dependent on Lewis acidity. For example, TMSCl-mediated carbocupration of **1a** provided only a 67% yield for vinyl silane **2**, whereas TMSBr and TMSI afforded greater yields of 80 and 89% for **2**, presumably via the identical TMS allenolate intermediate. Keeping in mind that

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(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.

(7) Mueller, A. J.; Jennings, M. P. *Org. Lett.* **2008**, *10*, 1649.

(8) Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 4799.

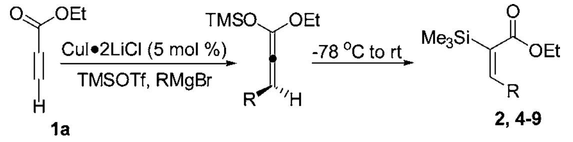
TMSOTf furnished compound **2** in 92% yield, there appears to be a direct correlation between the Lewis acidity of the silane promoter and tautomerization of the TMS allenolate. It should be noted that all three TMS halides (and TMSOTf) provided selectively the *E* isomer of vinyl silane **2** with a >20:1 ratio. Similarly, catalytic carbocupration utilizing either TESCl or TESOTf as the additive proceeded fairly smoothly to consume **1a** but provided mixed results with respect to the TES group migration from the allenolate to the vinyl silane. The yields of the α-TES-α,*β*-unsaturated ester **3** varied from 32% with TESCl to 88% with TESOTf with very high levels of diastereoselectivity (>20:1) for the *E* isomer. Once again, it appeared that Lewis acidity played an important and key role in tautomerizing the TES allenolate to vinyl silane **3**. Lastly, we examined TBSCl and OTf as carbocupration-isomerization additives but observed no formation of either the desired vinyl silane or even the α,*β*-unsaturated ester, although all of the starting material **1a** was consumed. It is our belief that both TBS additives do not promote even the initial catalytic carbocupration, and the excess Grignard reagent simply helped to decompose ester **1a**.

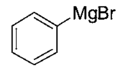
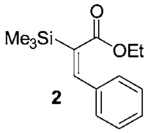
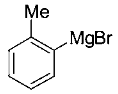
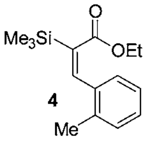
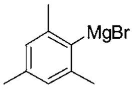
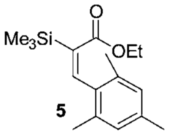
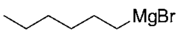
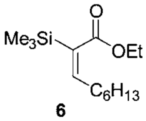
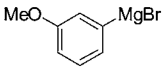
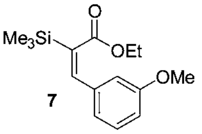
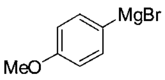
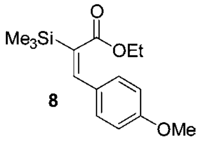
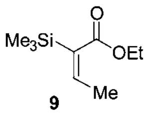
With the scope somewhat defined by the silane additives for the catalytic carbocupration−tautomerization sequence in Tables 1 and 2, we chose to further investigate the above-mentioned reaction with a series of Grignard reagents coupled with ester **1a**. Given the utility of the final product vinyl silanes, we were quite hopeful for a *general stereoselective* synthesis of such compounds, as they have eluded synthetic chemists.[9] Much to our delight, the carbocupration−TMS tautomerization readily proceeded with 5 mol % of the CuI•2LiCl catalyst and 3.3 equiv of TMSOTf with a variety of aromatic Grignard reagents (1.2 equiv) to afford compounds **4**−**5** and **7**−**8** in very good yields ranging from 88 to 93%. In addition, all of the *β*-aromatic-α-TMS-α,*β*-unsaturated esters were virtually a single isomer, >20:1 for the *E* diastereomer as determined by ^{1}H NMR. Likewise, two aliphatic Grignard reagents performed admirably as well. The addition of hexyl MgBr to **1a** under the standard reaction conditions led to the corresponding product **6** in a 93% yield with a diastereoselectivity of greater than 20:1 for the *E* isomer. Similarly, MeMgBr mirrored the reactivity and outcome of that of the hexyl derived Grignard reagent with **1a** and provided the very simple methyl synthon **9** in 85% yield as a single *E* isomer as well. Unfortunately, the attempted addition of alkenyl and alkynyl Grignard reagents did not proceed and led only to the decomposition of **1a**.

There are a couple of key points that merit further discussion. The first is that all of the tandem reaction processes occur in very high yield. The lowest yield is 85% for both aromatic as well as aliphatic Grignard reagents. Also, products **2**−**9** are formed and isolated as single diastereomers. Given the nature that two bond forming processes are taking place in a single flask in such high yields and diastereoselectivities, we feel this reaction is quite remarkable. Also, the final product α-TMS-α,*β*-unsaturated esters are incredibly useful synthons in organic chemistry. Thus, compounds **2**−**9** are simply an olefin reduction and deprotonation away from a series of stabilized Peterson reagents, and silanes **6** and **9** could serve as precursors for higher-order nucleophilic allyl silanes.[10,11]

With the information of Tables 1−3 in hand, we decided to examine two more substrates as shown in Scheme 1. As

Table 3. Vicinal Functionalization of **1a** via a Catalytic Carbocupration−Silicon Group Migration Sequence with Various Grignard Reagents and TMSOTf[a,b]



Grignard reagent	product yield, (*E*/*Z*)
	 **2** 92% (*E*/*Z* > 20/1)
	 **4** 88% (*E*/*Z* > 20/1)
	 **5** 92% (*E*/*Z* > 20/1)
	 **6** 93% (*E*/*Z* > 20/1)
	 **7** 88% (*E*/*Z* > 20/1)
	 **8** 90% (*E*/*Z* > 20/1)
CH_3MgBr	 **9** 85% (*E*/*Z* > 20/1)

[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.

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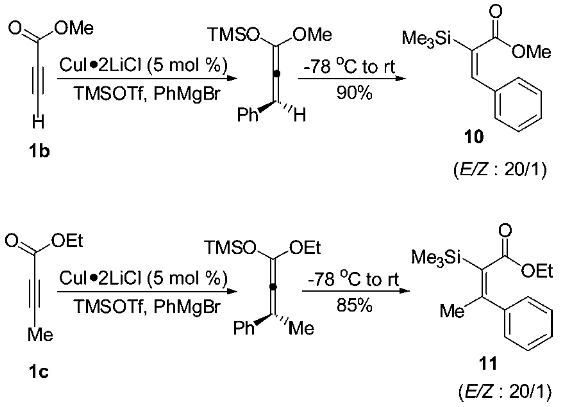
(9) (a) Hartzell, S. L.; Rathke, M. W. *Tetrahedron Lett.* **1976**, *17*, 2737. (b) Sato, Y.; Takeuchi, S. *Synthesis* **1983**, *9*, 734. (c) Boeckman, R. K., Jr.; Chinn, R. L. *Tetrahedron Lett.* **1985**, *26*, 5005.

Scheme 1



anticipated and analogous to **1a**, the catalytic carbocupration−TMS tautomerization of methyl propiolate (**1b**) readily proceeded under the standard reaction conditions and furnished the α-TMS-*β*-phenyl-α,*β*-unsaturated ester **10** in 90% yield as a single diastereomer. While all of the successful examples to this point have been propiolate esters that lack substitution at the *β*-carbon, we deemed it prudent to investigate ethyl 2-butynoate (**1c**) under the standardized reaction conditions. Much to our delight and surprise, the catalytic carbocupration of **1c** with 5 mol % of CuI•2LiCl catalyst, 1.2 equiv of PhMgBr, and 3.3 equiv of TMSOTf readily proceeded to the presumed TMS allenolate intermediate, and subsequent tautomerization furnished the tetrasubstituted alkene **11** in 85% yield and as a single diastereomer (>20:1 for the *E*-isomer). This result is quite remarkable given that Knochel reported that a similar *stoichiometric* reaction did not provide high levels of diastereoselectivity (the greatest dr was 88:12 for one example).[10] The result greatly expands this catalytic reaction process to include stereodefined tetrasubstituted α-TMS-*β*,*β*-disubstituted-α,*β*-unsaturated esters.

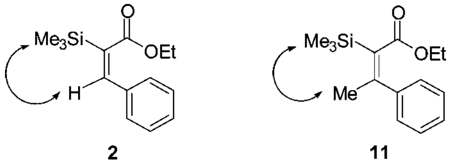


Figure 1. Key NOE enhancements for **2** and **11**.

As shown in Figure 1, the olefin geometry of **2** was determined by means of ^{1}H NMR. The strong 1D NOE for both the silane methyl groups and *β*-vinylic proton provided conclusive proof for the assigned *E*-olefin geometry. In addition, the ^{1}H NMR chemical shifts of **2**−**10** mirror that of similar vinyl silanes as synthesized by Zweifel.[11b] For example, the resonance of the vinyl proton in **6** is upfield (∼6.1 ppm), strongly suggesting the *E*-isomer in accordance to Zweifel's observations of *E*- and *Z*-isomeric vinyl silane compounds. The resonance of the *Z*-isomer was shown to be roughly 1 ppm downfield at ∼7.1 ppm.[11b] On the basis of the NOE experiment results for **2** and by analogy to Zweifel's observations, the stereochemistry of the remaining vinyl silanes **3**−**10** was assigned as the *E*-isomer. The relative stereochemical determination of **11** was also determined in a similar fashion. Much to our delight, a strong NOE for both the silane methyl groups and the *β*-methyl protons provided persuasive proof for the assigned *E*-olefin geometry.

In conclusion, we have shown that vicinal functionalization of propiolate esters via a catalytic carbocupration−silicon group migration sequence with catalyst loadings as low as 5 mol % allows for good yields and excellent diastereoselectivities (>20:1) with a series of Grignard reagents for the synthesis of substituted *E*-vinyl silanes. Future directions of investigation will include further developments into the catalytic vicinal functionalization of ynoates with other electrophiles. Also, we are currently examining the broad synthetic utility of the stereodefined vinyl silane products in the context of natural product synthesis. Results from these studies will be reported in due course.

Acknowledgment. Support for this project was provided by the University of Alabama and the National Science Foundation CAREER program under CHE-0845011.

Supporting Information Available: The general reaction procedure and full 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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[10] (a) Hartzell, S. L.; Sullivan, D. F.; Rathke, M. W. *Tetrahedron Lett.* **1974**, *15*, 1403. (b) Shimoji, K.; Taguchi, H.; Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 1620. (c) Yamamoto, K.; Tomo, Y.; Suzuki, S. *Tetrahedron Lett.* **1980**, *21*, 2861. (d) Larson, G. L.; Fernandez de Kaifer, C.; Seda, R.; Torres, L. E.; Ramirez, J. R. *J. Org. Chem.* **1984**, *49*, 3385. (e) Tsuge, O.; Kanemasa, S.; Ninomiya, Y. *Chem. Lett.* **1984**, 1993. (f) Cooke, M. P., Jr. *J. Org. Chem.* **1987**, *52*, 5729. (g) Gillies, M. B.; Tønder, J. E.; Tanner, D.; Norrby, P.-O. *J. Org. Chem.* **2002**, *67*, 7378.

[11] (a) Albaugh-Robertson, P.; Katzenellenbogen, J. A. *J. Org. Chem.* **1983**, *48*, 5288. (b) Najafi, M. R.; Wang, M.-L.; Zweifel, G. *J. Org. Chem.* **1991**, *56*, 2468.