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Carbocupration−Functionalization of Arynes: Rapid Access to Variably Ortho-Substituted ((*E*)-3-Phenylprop-1-enyl)silanes

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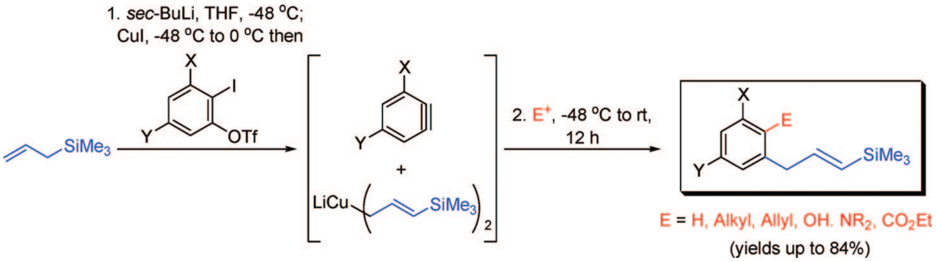
ABSTRACT



A consecutive three-component coupling reaction involving a lithium di[3-(prop-1-enyltrimethylsilyl)]cuprate, variably substituted *ortho*-arynes, and a selection of common electrophiles is described. The method affords readily functionalized homobenzylic vinylsilanes with exceptional *E*-diastereoselectivity and allows for *in situ* incorporation of carbon- or heteroatom-based electrophiles into the arene.

Homobenzylic alkenes are components of biologically active natural products including the salicylihalamides,[1] lobotamides,[2] and radulanin A[3] to name a few. The most common approaches for installing homobenzylic alkenes include olefin metathesis and transition metal-catalyzed coupling approaches. Although such routes have led to elegant syntheses of targets bearing the moiety, these efforts have also revealed limitations including unexpectedly poor diastereoselectivities during olefin metathesis[4] or lengthy routes, from commercially available materials, to the requisite vinyl halides for cross-coupling reactions.[5] As such, we were compelled to explore an alternative approach to homobenzylic olefin preparation that would compliment existing routes. We also wished to devise a method by which the substituted arenes could serve as precursors for diversity-oriented or target-directed synthetic endeavors where the alkene functions as an appealing synthetic handle.

We considered an approach involving aryne allylmetalation followed by trapping of the intermediate metalated arene with one of many possible heteroatom- or carbon-based electrophiles (Figure 1).[6] Ideally, the allyl group would feature a synthetic handle, aside from an unfunctionalized alkene, that could lead to multiple derivatives, thereby broadening the utility of the envisioned products. Also, the allylmetalation

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[1] (a) Erickson, K. L.; Beutler, J. A.; Cardellina, J. H., II; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8188–8192. (b) Yet, L. *Chem. Rev.* **2003**, *103*, 4283–4306. (c) Beutler, J. A.; McKee, T. C. *Curr. Med. Chem.* **2003**, *10*, 787–796.

[2] Galinis, D. L.; McKee, T. C.; Pannell, L. K.; Cardellina, J. H., II; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8968–8969, and references 1a,c.

[3] Macías, F. A.; Molinillo, J. M. G.; Varela, R. M.; Torres, A. *J. Org. Chem.* **1994**, *59*, 8261–8266.

[4] For an interesting example, see: (a) Yang, K. L.; Blackman, B.; Diederich, W.; Flaherty, P. T.; Mossman, C. J.; Roy, S.; Ahn, Y. M.; Georg, G. I. *J. Org. Chem.* **2003**, *68*, 10030–10039. (b) Lebreton, S.; Xie, X. S.; Ferguson, D.; De Brabander, J. K. *Tetrahedron* **2004**, *60*, 9635–9647. For a related discussion see: (c) Gradillas, A.; Pérez-Castells, J. *Angew. Chem., Int. Ed. Engl.* **2006**, *45*, 6086–6101.

[5] (a) Herb, C.; Maier, M. *J. Org. Chem.* **2003**, *68*, 8129–8135. (b) Yadav, J. S.; Srihari, P. *Tetrahedron: Asymmetry* **2004**, *15*, 81–89. (c) Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425–2430.

10.1021/ol8021885 CCC: $40.75

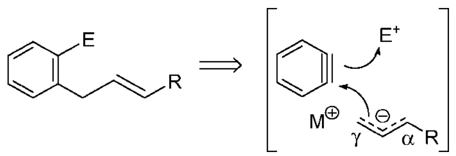
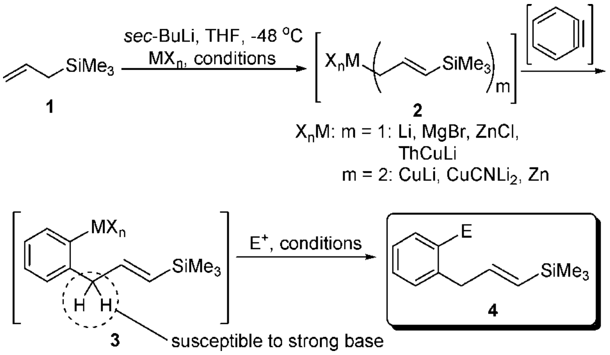


Figure 1. Conceptualized one-pot synthesis of substituted homobenzylic alkenes.

would need to feature high diastereoselectivity and predictable regioselectivity (i.e., γ- versus α-substitution) from a substituted allyl anion intermediate (Figure 1).

Research by the Corriu and Magnus groups highlighted an intriguing possibility for satisfying our outlined criteria. Corriu treated a lower-order cyanocuprate, prepared from lithiated allyltrimethylsilane and CuCN, with a variety of electrophiles. Products were formed in 15−80% yields but proved regioselective for the γ-substitution product.[7] Magnus established that lithiated allyltrimethylsilane, or the corresponding zinc chloride species, efficiently added to carbonyl compounds with high γ-regioselectivity and complete (*E*)-alkene diastereoselectivity.[8]

Scheme 1. Generalized Method for One-Pot Preparation of Ortho-Substituted ((*E*)-3-Phenylprop-1-enyl)silanes



Prompted by the precedented high levels of γ-regio- and (*E*)-alkene diastereoselectivity furnished by metalated allyltrimethylsilane (Scheme 1), we next considered the stability of **3** and **4** and the synthetic versatility of the products. The vinylsilane in putative intermediate **3** was expected to be resistant to common electrophiles employed for installation into the arene, although avoiding alkene migration into conjugation with the arene, following possible deprotonation at the benzylic position, was a concern throughout. Despite their inherent stability under a variety of reaction conditions, vinylsilanes are remarkably versatile synthetic handles. A variety of functionalities are directly attainable from vinylsilanes or α,β-epoxysilanes.[9] Hence, our planned route to compounds of type **4** seemed amenable to functionalizing the arene *in situ* and the propenylsilane postpreparation with minimal synthetic operations.

We needed to consider two other variables before exploring the planned allylmetalation-arene functionalization protocol. The aryne would play the key role in the tandem reaction, as the yield of the overall process could be no greater than that of the aryne formed. It was necessary to generate the aryne efficiently under conditions compatible with the carbometalation step. Given the conditions outlined to prepare and employ the metalated allyltrimethysilane, the aryne would need to be generated in ethereal solvent at or below ambient temperature for use with **2**. We recently reported a comparative study of common aryne precursors formed under such conditions and found 2-iodophenyl triflates as the superior candidates.[10]

We also needed to establish which metalated allyltrimethylsilane would furnish both efficient aryne allylmetalation and subsequent functionalization of **3**. Due to the potential for the newly installed homobenzylic alkene to migrate to the thermodynamically preferred benzylic position under highly basic reaction conditions, we immediately disregarded lithium and magnesium halide as possible counterions for **2**. Organocuprates and diorganozinc species seemed to offer the best potential, although the latter would necessitate an added step, such as inclusion of a nickel or palladium source, to effect functionalization of **3** in many cases.[11]

Attempts at generating an aryne from **5** (Table 1) with 3.0 equiv of lithium di[3-(prop-1-enyltrimethylsilyl)]cuprate at 0 °C in THF in the presence of 10 equiv of furan resulted in a 44% isolated yield of the Diels−Alder cycloadduct. However, three other byproducts were generated under these conditions, as well as during analogous aryne trapping experiments at lower temperatures. As a result, we attempted to preform the aryne by adding a commercial alkyl lithium reagent (i.e., *t*-BuLi, *s*-BuLi, or *n*-BuLi) to **5** at low temperatures (ranging from −110 to −63 °C), then rapidly transferring a 0 °C THF solution of 3.0 equiv of lithium di[3-(prop-1-enyltrimethylsilyl)]cuprate. This afforded a complex mixture of products and marginal yields of **8**.

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[6] For an inspiring example, see: (a) Pansegrau, P. D.; Riecker, W. F.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7178–7184. For a recent catalytic alkynylcupration−alkynylation of symmetrical arynes, see: (b) Xie, C.; Liu, L.; Zhang, Y.; Xu, P. *Org. Lett.* **2008**, *12*, 2393–2396.

[7] Corriu, R. J. P.; Guerin, C.; M'Boula, J. *Tetrahedron Lett.* **1981**, *22*, 2985–2986.

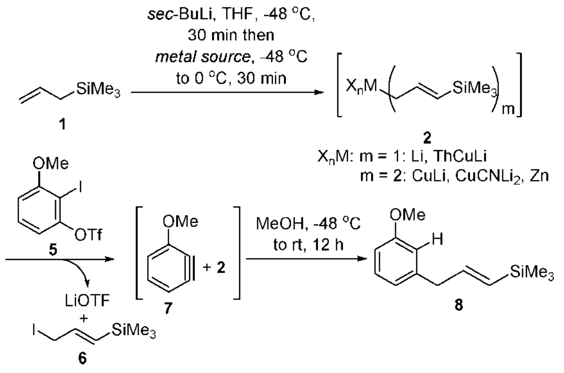
[8] (a) Ayalon-Chass, D.; Ehlinger, E.; Magnus, P. *J. Chem. Soc., Chem. Commun.* **1977**, 772–773. (b) Ehlinger, E.; Magnus, P. *J. Am. Chem. Soc.* **1980**, *102*, 5004–5011. For theoretical consideration of the high diastereoselectivity, see: (c) Fraenkel, G.; Chow, A.; Winchester, W. R. *J. Am. Chem. Soc.* **1990**, *112*, 2582–2585.

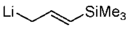
[9] For reviews see: (a) Oshima, K. *Sci. Synth.* **2002**, *4*, 713–756. (b) Whitham, G. H. *Sci. Synth.* **2002**, *4*, 633–646, and references therein.

[10] Ganta, A.; Snowden, T. S. *Synlett* **2007**, *222*, 7–2231.

[11] (a) Negishi, E.-I. Palladium-catalysed carbon-carbon cross-coupling. Overview of the Negishi protocol with Zn, Al, Zr, and related metals. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed; John Wiley & Sons: New York, 2002; Vol. 1, pp 229−247. (b) Negishi, E.-I., Dumond, Y. Palladium-catalyzed cross-coupling substitution. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; John Wiley & Sons: New York, 2002; Vol. 1, pp 767−789, and references therein.

Table 1. Metal Sources for Carbometalation of **7**

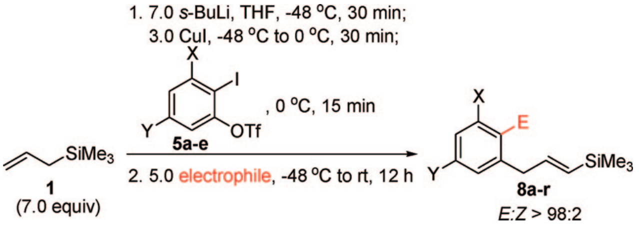


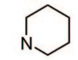
entry	metal source[a]	 equiv[b]	**8**, yield (%)[d]
1	CuCN	7.0	50
2	CuI	7.0	84
3	$CuBr{\cdot}Me_2S$	7.0	69
4	CuI, ThLi	4.0	65
5	$ZnCl_2$	7.0	73
6	CuI[c]	5.0	78

[a] 3.0 equiv was added, and the solution was warmed from −48 to 0 °C over 30 min. [b] Prepared by treating **1** with an equimolar portion of titrated *s*-BuLi at −48 °C for 30 min. [c] 2.0 equiv of CuI was added. [d] Yield of purified product; average of two runs.

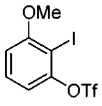
Recognizing that lithiated allyltrimethylsilane could effect rapid lithium−halogen exchange with **5**[12] and that the metalated species serves as the direct precursor to the requisite lithium diorganocuprate, we elected to include 1.0 equiv of lithiated allyltrimethylsilane beyond that needed to prepare **2** in order to promote aryne formation. Employment of lithiated allyltrimethylsilane circumvented possible formation of mixed diorganocuprates that could arise by introduction of 1 equiv of a commercial alkyllithium followed by ligand exchange with lithium di[3-(prop-1-enyltrimethylsilyl)]cuprate. In the described milieu, the lithiated allyl trimethylsilane and Gilman-type cuprate may be in equilibrium with a homoleptic “higher order” R_3CuLi_2 species. However, it is unclear what species actually promotes metal−halogen exchange, and therewith, subsequent aryne formation. What is clear is that the inclusion of 1.0 equiv of lithiated allytrimethylsilane with the lithium diorganocuprate envisioned for aryne carbometalation is required to form **8** in satisfactory yields.

Table 2. Trimethysilylpropenylation−Functionalization of Arynes

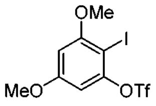


entry	compd	electrophile	E	product	yield (%)[a]
1	**5a**	MeOH	H	**8a**	84
2		$C_8H_{17}I$	C_8H_{17}	**8b**	80
3		AllylBr	$CH_2CH{=}CH_2$	**8c**	71
4		$ClCO_2Et$	CO_2Et	**8d**	60
5		O_2	OH	**8e**	70
6		*O*-Benzoyl Hydroxyl-piperidine (**9**)	 **10**	**8f**	73
7		MVK	$C_2H_4C(O)CH_3$	-	-
8	**5b**	MeOH	H	**8g**	81
9		AllylBr	$CH_2CH{=}CH_2$	**8h**	72
10		$ClCO_2Et$	CO_2Et	**8i**	61
11		**9**	**10**	**8j**	70
12	**5c**	MeOH	H	**8k**	81
13		AllylBr	$CH_2CH{=}CH_2$	**8l**	74
14		$ClCO_2Et$	CO_2Et	**8m**	60
15		**9**	**10**	**8n**	74
16	**5d**	AllylBr	$CH_2CH{=}CH_2$	**8o**	80
17		$ClCO_2Et$	CO_2Et	**8p**	57
18		**9**	**10**	**8q**	67
19	**5e**	**9**	**10**	**8r**	39[b]

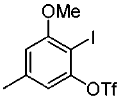
[a] Yield of purified material. [b] The 2-fluorophenyl regioisomer was also obtained in 9% yield.



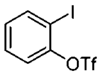
5a



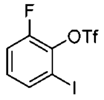
5b



5c



5d



5e

Given our results concerning efficient aryne formation, reactions were conducted by preparing 7.0 equiv of lithiated allyltrimethylsilane at −48 °C and then treating this solution with 3.0 equiv of a metal source at 0 °C for 30 min. This provided 3.0 equiv of the corresponding lithium diorganocuprate, or di(trimethylsilylpropenyl)zinc in entry 5, and the mandatory 1.0 equiv of lithiated **2** to promote efficient metal−halogen exchange upon addition of **5** (Table 1).[13] After being stirred for 15 min at 0 °C to effect aryne carbometalation,[14] the reaction mixture was cooled to −48 °C, and degassed MeOH was added to afford **8**.[15] Investigation of several metal sources revealed that CuI offered a significantly higher yield than any other. As noted in entry 6, employment of 2.0 equiv of CuI (creating 2.0 equiv of diorganocopper lithium species and 1.0 equiv of lithiated allyltrimethylsilane) was also effective, albeit slightly less than with 3.0 equiv. A minimum of 2.0 equiv is required, as

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(12) 2-Iodophenyl triflate **5** is converted to the corresponding aryne in the presence of 1.0 equiv of lithiated allyltrimethylsilane and 10 equiv of furan at −78 °C, affording 88% of the Diels−Alder cycloadduct.

(13) When the reaction is conducted with 3.0 equiv of lithium di[3-(prop-1-enyltrimethylsilyl)]cuprate, in the absence of the extra equivalent of lithiated allyltrimethylsilane under otherwise identical conditions, **8** is generated in 39% yield.

(14) Longer reaction times or lower temperatures have insignificant impact on yield.

(15) Acetic acid could be added with comparable results.

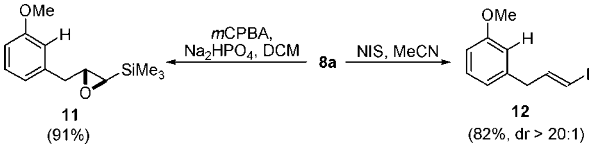
at least 1.0 equiv must be available to react with the aryne and another to consume the 1.0 equiv of **6** generated by the metal−halogen exchange so that it does not compete with the intended electrophile in the terminal step.

With optimal conditions established, we explored the preparation of several ortho-substituted ((*E*)-3-phenylprop-1-enyl)silanes (Table 2). Electron-rich and unsubstituted 2-iodophenyl triflates (**8a−d**) behaved as planned during the carbocupration−functionalization sequence when treated with a variety of electrophiles. Protonation and alkylations offered uniformly high yields. Phenols were created by replacing the argon blanket with an O_2 balloon after carbocupration,[16] and anilines were produced in good yields after addition of *O*-benzoyl hydroxylamines.[17] Meanwhile, treatment of the arylcuprate with excess ethyl chloroformate afforded substituted salicylates in moderate yields. Numerous attempts were made to enhance this outcome through varied reaction modifications, without melioration. Unfortunately, treatment of the carbometalated intermediate derived from **5a** with methyl vinyl ketone (MVK, entry 7) offered disappointing results, in part, due to competitive 1,2- and 1,4-addition.

We found that deactivated 2-iodophenyl triflates, including 6-fluoro-derivative **5e** and 2-iodo-3-trifluoromethylphenyl triflate (not shown) are not suitable substrates for the method. This is presumably due to the extreme instability of the destabilized aryne intermediates that rapidly suffer side reactions upon formation.[18]

As expected, the installed vinylsilanes are readily transformed to useful functionalities. For instance, epoxidation of **8a** using *m*-CPBA in buffered dichloromethane furnished **11**,[19] while halodesilylation garnered **12** with outstanding diastereoselectivity (Scheme 2).[20]

Scheme 2. Example Derivatization of Vinylsilane **8a**



We have established a consecutive three-component coupling reaction involving carbocupration of substituted *o*-arynes with the possibility of incorporating diverse substituents into the arene. The products feature an *E*-homobenzylic vinylsilane as a versatile synthetic handle. The approach has potential for diversity-oriented synthesis applications and for syntheses featuring the preparation or functionalization of homobenzylic alkenes.

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Supporting Information Available: Full experimental procedures, characterization data, and NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Möller, M.; Husemann, M.; Boche, G. *J. Organomet. Chem.* **2001**, *624*, 47–52.

(17) (a) Oguri, T.; Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.* **1975**, *23*, 167–172. (b) Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680–5681. (c) Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2007**, *9*, 1521–1524.

(18) For a theoretical evaluation of relative energies of monosubstituted arynes, see: Maurin, P.; Ibrahim-Ouali, M.; Parrain, J.-L.; Santelli, M. *THEOCHEM* **2003**, *637*, 91–100.

(19) Alexakis, A.; Jachiet, D. *Tetrahedron* **1989**, *45*, 381–389.

(20) Staamos, D. P.; Taylor, A. G.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 8647–8650.