

New Synthetic Applications Involving Arynes and Wynberg Lactone

CH 586
Research Seminar, Ph. D

Presented by
Ashok Ganta

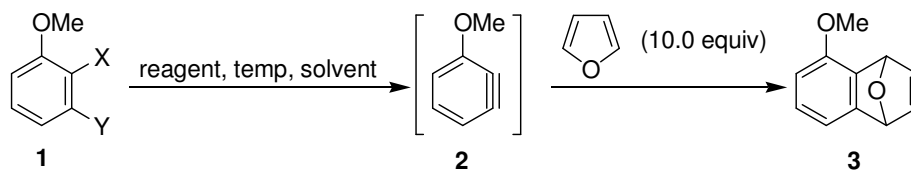
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151, Shelby Hall

The University of Alabama

Part A: Facile Preparation of 2-Iodophenyl Trifluoromethylsulfonates: Superior Aryne Precursors.

As a part of our exploration of the preparation of polysubstituted aromatic compounds *via* regioselective disubstitution of arynes,¹ we required aryne precursors that could afford arynes under low temperatures and in non-polar solvents for additions to carbon nucleophiles. Despite the many methods described in the literature to generate benzyne,² no comparative investigation of the efficiency with which different aryne precursors could afford substituted *ortho*-arynes under such conditions was reported. Hence, we conducted a comparative aryne-generation study, leading to 3-methoxybenzyne (**2**), using various common aryne precursors (**1**). Each 3-methoxybenzyne (**2**) formed from a unique aryne precursor was trapped *in situ* by a cycloaddition with furan (**3**), and then quantified based upon the isolated yield of the benzofuran cycloadduct (Scheme 1). Through our investigation,³ we found that **2** was generated from 2-iodo-3-methoxyphenyl triflate in excellent yield and with negligible by-product formation. The 2-iodophenyl triflates proved to be superior aryne precursors at reduced temperatures in non-polar media, compared to other common precursors, thereby meeting our criteria for a compatible and convenient pre-aryne substrate.



Scheme 1. Comparative study of aryne generation from precursors 1.

The efficiency with which 2-iodophenyl triflates afford arynes *via* metal-halogen exchange and their potential as partners in transition metal-catalyzed cross-coupling reactions motivated us to develop a general method for their synthesis. We envisioned that 2-iodophenyl triflates could be obtained from 2-iodophenols, which in turn, would be accessible from iodination of phenols. One direct way to access the desired iodophenols is by electrophilic aromatic substitution of phenols. However, the direct iodination of aromatic compounds by electrophilic aromatic substitution is limited to electron-rich aromatic compounds and often

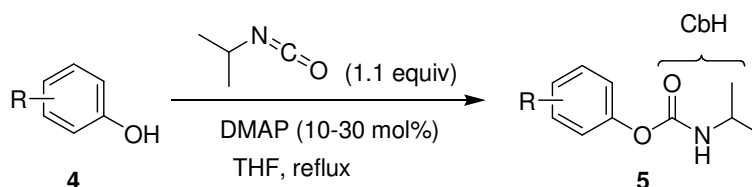
¹ Ganta, A.; Snowden, T. S. *Org. Lett.* **2008**, *10*, 5103.

² For a recent review on different ways to generate arynes, see: Dyke, A. M.; Hester, A. J.; Lloyd-Jones, G. C. *Synthesis* **2006**, 4093 and references therein.

³ Ganta, A.; Snowden, T. S. *Synlett*, **2007**, 2227.

suffers from poor regioselectivity and polyiodination.⁴ Alternatively, directed *ortho*-metallation-iodination has an attractive feature in terms of regiospecific introduction of the iodine.⁵ *N*-isopropylcarbamates are excellent *ortho*-directing groups that are easy to install and require mild basic conditions for removal.⁶ Moreover, anionic Fries-rearrangement is not observed with these carbamates.

N-isopropylcarbamates (**5**) of a variety of phenols (**4**) were prepared in excellent yields following the method of Hoppe.⁶ The preparation of the *O*-aryl-*N*-isopropylcarbamates (**5**) of electron rich phenols required inclusion of 10 mol% of DMAP with the isopropylisocyanate at 70 °C in THF. However, electron deficient phenols required treatment with 30 mol% of DMAP and heating for 72 h to afford **5** in high yields.



Scheme 2. General preparation of *O*-aryl-*N*-isopropylcarbamates.

Kauche and Hoppe reported the preparation of two 2-iodophenols (**9**) by directed *ortho*-metallation-iodination of *N*-isopropylcarbamates.⁷ We similarly treated numerous *O*-aryl carbamates with 1.0 equiv of TMEDA followed by addition of TMSOTf to effect the *N*-silylation of **5**. Such *N*-protected carbamates (**6**) direct the *ortho*-lithiation of aromatic compounds (**7**) with *n*-BuLi or *t*-BuLi in the presence of TMEDA in diethyl ether at -78 °C.

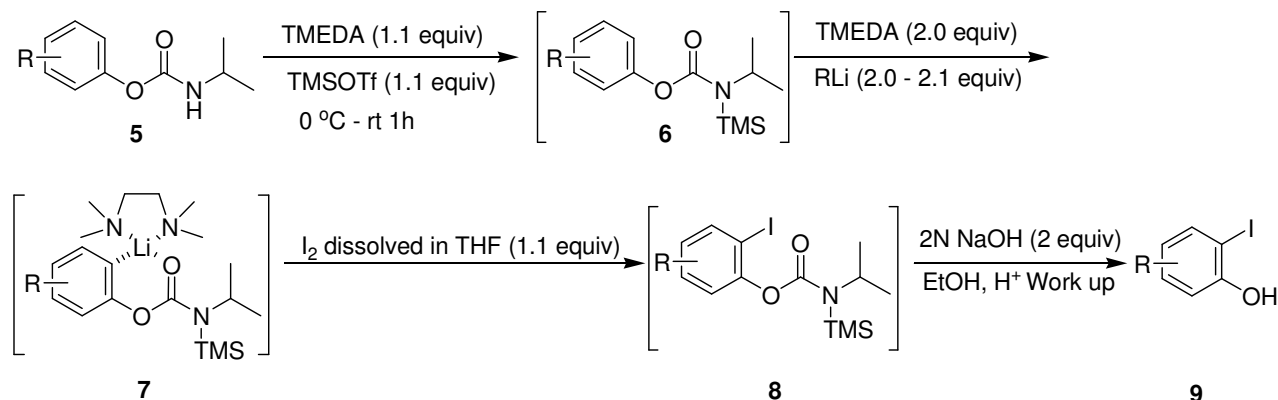
⁴ (a) Srebnik, M.; Mechoulam, R.; Yona, I. *J. Chem. Soc. Perkin Trans. 1* **1987**, 1423. (b) Doad, G. J. S.; Barltrop, J. A.; Petty, C. M.; Owen, T. C. *Tetrahedron Lett.* **1989**, *30*, 1597. (c) Thomsen, I.; Torssell, K. B. G. *Acta Chem. Scand.* **1991**, *45*, 539. (d) Barluenga, J.; González, J. M.; García-Martín, M. A.; Campos, P. J.; Asensio, G. *J. Org. Chem.* **1993**, *58*, 2058. (e) Yonezawa, S.; Komurasaki, T.; Kawda, K.; Tsuru, T.; Fuji, M.; Kugiyama, A.; Haga, N.; Mitsumori, S.; Inagaki, M.; Nakatani, T.; Tamura, Y.; Takechi, S.; Taishi, T.; Ohtani, M. *J. Org. Chem.* **1998**, *63*, 5831. (f) Yang, S. G.; Kim, Y. H. *Tetrahedron Lett.* **1999**, *40*, 6051. (g) Deniuel, M. R.; Laursen, B.; Hazell, R.; Skrydstup, T. *J. Org. Chem.* **2000**, *65*, 6052. (h) Mukiyama, T.; Kitagawa, H.; Matsuo, J. *Tetrahedron Lett.* **2000**, *41*, 9383. (i) Narender, N.; Srinivasu, P.; Kulkarni, S. J.; Raghavan, K. V. *Synth. Commun.* **2002**, *32*, 2319. (j) Jereb, M.; Zupan, M.; Stavber, S. *Chem. Commun.* **2004**, 2614. (k) Krishna Mohan, K. V. V.; Narender, N.; Kulkarni, S. J. *Tetrahedron Lett.* **2004**, *45*, 8015. (l) Patil, B. R.; Bhusare, S. R.; Pawar, R. P.; Vibhute, Y. B. *Tetrahedron Lett.* **2005**, *46*, 7179.

⁵ (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (b) Gray, M.; Tinkl, M.; Snieckus, V. In *Comprehensive Organometallic Chemistry II*, Vol. 11. Edited by Abel, E. W.; Stone, F. G. A.; Wilkinson, G. Pergamon Press: Elmsford, NY, 1995. pp 1-92. (c) Brandsma, L. In *Modern der Organischen Chemie*; Hanack, M. Ed.; Thieme: Stuttgart, 1993; Vol. E19d, pp 369-447. (d) Chauder, B.; Green, L.; Snieckus, V. *Pure Appl. Chem.* **1999**, *71*, 1521. (e) For a perspective on the mechanistic aspects see, Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 2206.

⁶ (a) Kauch, M.; Hoppe, D. *Can. J. Chem.* **2001**, *79*, 1736. (b) Kauch, M.; Snieckus, V.; Hoppe, D. *J. Org. Chem.* **2005**, *70*, 7149.

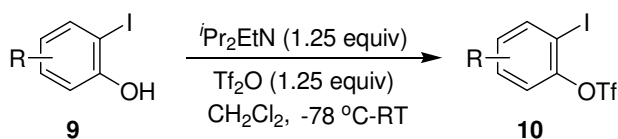
⁷ Kauch, M.; Hoppe, D. *Synthesis* **2006**, 1578.

Subsequently, the 2-iodophenyl carbamates (**8**) were obtained upon treatment of the *ortho*-lithiated species (**7**) with iodine dissolved in THF. Decarbamation of **8** under mild basic conditions followed by an acidic work-up afforded the desired 2-iodophenols (**9**) in high yields.



Scheme 3. General method for the preparation of 2-iodophenols using carbamates as *ortho*-directing groups

Activated aromatic compounds required special care during workup to avoid the generation of regioisomeric and polyiodinated products. At pH = 0-1, a 1:1:1 mixture of diiodinated product/desired product/non-iodinated product was obtained during the workup of iodophenol.⁸ However, these side reactions were successfully avoided by careful adjustment of the aqueous phase pH to 6-8 prior to work-up. With the various substituted 2-iodophenols in hand, the desired 2-iodophenyl triflates (**10**) were obtained in quantitative yields upon treatment of **9** with triflic anhydride under basic conditions, irrespective of the electronic nature of the phenols.⁹



Scheme 4. General method for preparation of 2-iodophenyl triflates

We identified 2-iodophenyltriflates (**10**) as privileged aryne precursors in nonpolar solvents. The regioselective preparation of both activated and select deactivated iodophenyl triflates was possible using a directed *ortho*-lithiation approach. Ten new 2-iodophenyltriflates that we prepared will likely to find utility in the preparation of disparate polysubstituted

⁸ Thomsen, I.; Torssell, K. B. G. *Acta Chem. Scand.* **1991**, *45*, 539.

⁹ Hamura, T.; Hosoya, T.; Yamaguchi, H.; Kuriyama, Y.; Tanabe, M.; Miyamoto, M.; Yasui, Y.; Matsumoto, T.; Suzuki, K. *Helv. Chim. Acta* **2002**, *85*, 3589.

aromatics via the popular use of benzyne in organic synthesis. These compounds should also prove useful in transition metal-catalyzed processes.

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

Polysubstituted aromatic compounds are important constituents of many biologically active natural products such as salicylhalamides,¹⁰ lobatamides,¹¹ psymberin,¹² radicicol,¹³ and more. A structural feature common to these natural products is either a salicylic acid or a resorcylic acid segment bearing a homobenzylic alkene or a functionality that can be derived from a homobenzylic alkene. Even though total syntheses of these natural products bearing the homobenzylic alkene moiety have been achieved, these efforts revealed limitations. These include poor diastereoselectivities during olefin metathesis or lengthy routes to the requisite vinylhalides for cross-coupling reactions. As such, we were compelled to explore an alternative approach to homobenzylic olefin preparation that would complement or improve upon existing routes. We also wished to devise a method by which the substituted arenes could also 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 allylmetalation of an aryne followed by trapping of the intermediate metalated arene with one of many possible heteroatom- or carbon-based electrophiles (Scheme 5).¹⁴ Ideally, the allyl group would feature a synthetic handle, aside from an unfunctionalised alkene, that would lead to multiple derivatives, thereby broadening the utility of the envisioned products. Also, the allylation would need to feature high alkene diastereoselectivity and predictable regioselectivity (i.e., γ - versus α -substitution) from a substituted allyl anion intermediate (**11**).

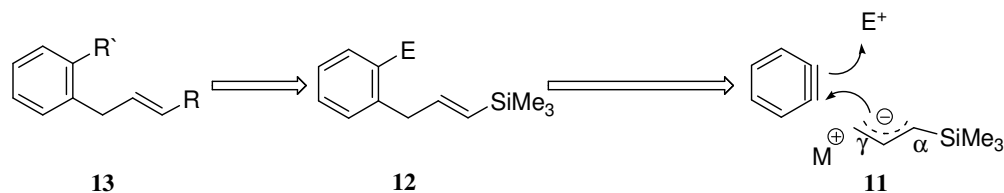
¹⁰ (a) Erikson, K. L.; Beutler, J. A.; Cardellina, J. H., II; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8188. (b) Yet, L. *Chem. Rev.* **2003**, *103*, 4283. (c) Beutler, J. A.; McKee, T. C. *Curr. Med. Chem.* **2003**, *10*, 787.

¹¹ Galinis, D. L.; McKee, T. C.; Pannell, L. K.; Cardellina, J. H., II; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8968 and references 10a, c.

¹² (a) Cichewicz, R. H.; Valeriote, F. A.; Crews, P. *Org. Lett.* **2004**, *6*, 1951. (b) Jiang, X.; Garcia-Fortanet, J.; De Brabander, J. K. *J. Am. Chem. Soc.* **2005**, *127*, 11254.

¹³ Delmotte, P.; delmotte-Plaquee, J. *Nature* **1953**, *171*, 344.

¹⁴ For a directed *ortho*-metallation aryne generation see: (a) Pansegrau, P. D.; Rieker, W. F.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7178. For a recent catalytic alkynylcupration-alkynylation of symmetrical arenes see (b) Xie, C.; Liu, L.; Zhang, Y.; Xu, P. *Org. Lett.* **2008**, *12*, 2393.



Scheme 5. Conceptualized allylmethallation of arynes

We envisioned that allyltrimethylsilane could serve as the source of a suitably functionalized alkene. Earlier work by Corriu and Magnus demonstrated that the metallo propenylsilanes derived from either CuCN or ZnCl₂ upon addition to electrophiles and ketones resulted exclusively in γ -substituted products possessing *E*-vinylsilanes.^{15,16} Prompted by the precedented high levels of γ -regio- and (*E*)-alkene diastereoselectivity furnished by metallated allyltrimethylsilane, we next considered the stability of vinylsilane and the synthetic versatility of the products. The vinylsilane in putative intermediate **12** 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. A variety of functionalities are directly attainable from vinylsilanes or α,β -epoxysilanes.¹⁷ Hence, our planned route to compounds of type **12** seemed amenable to functionalizing the arene *in situ* and the propenylsilane postpreparation with minimal synthetic operations.

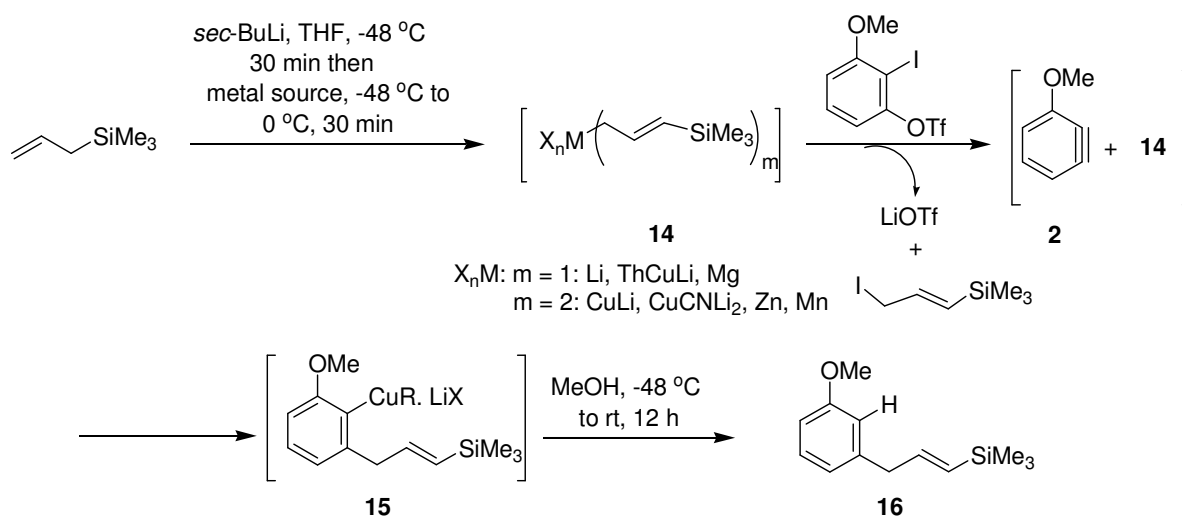
We needed to consider two other variables before exploring the planned allyl-methallation-arene functionalization protocol. The aryne would play a key role in the tandem reaction, as the yield of the overall process could be no greater than that of the aryne formed. It was necessary to generate the aryne efficiently under conditions compatible with the carbometallation step. Given the conditions outlined to prepare and employ the metallated allyltrimethylsilane, the aryne would need to be generated in ethereal solvent at or below room temperature. The substituted 2-iodophenyl triflates outlined in Part A were ideal for this purpose.

¹⁵ Corriu, R. J. P.; Guerin, C.; M'Boula, J. *Tetrahedron Lett.* **1981**, 22, 2985.

¹⁶ (a) Aylon-Chass, D.; Ehlinger, E.; Magnus, P. *J. Chem. Soc., Chem. Commun.* **1977**, 772. (b) Ehlinger, E.; Magnus, P. *J. Am. Chem. Soc.* **1980**, 102, 5004. For theoretical consideration of the diastereoselectivity, see: (c) Fraenkel, G.; Chow, A.; Winchester, W. R. *J. Am. Chem. Soc.* **1990**, 112, 2582. (d) Fraenkel, G.; Qiu, F. *J. Am. Chem. Soc.* **1997**, 119, 3571. (e) Fraenkel, G.; Cabral, J.; Lanter, C.; Wang, J. *J. Org. Chem.* **1999**, 64, 1302. (f) Fraenkel, G.; Duncan, J. H.; Wang, J. *J. Am. Chem. Soc.* **1999**, 121, 432. (g) Fraenkel, G.; Qiu, F. *J. Am. Chem. Soc.* **2000**, 122, 12806. (h) Fraenkel, G.; Chow, A.; Liu, H. *J. Am. Chem. Soc.* **2004**, 126, 3983. (i) Fraenkel, G.; Liu, H. *J. Am. Chem. Soc.* **2004**, 126, 5202.

¹⁷ For reviews see: (a) Oshima, K. *Sci. Synth.* **2002**, 4, 713-756. (b) Whitham, G. H. *Sci. Synth.* **2002**, 4, 633-646.

We also needed to establish which metallated allyltrimethylsilane would furnish both efficient aryne allylation and subsequent functionalization of **15** (Scheme 6). Due to the potential for the newly installed homobenzylic alkene to migrate to the thermodynamically preferred benzylic position under highly basic reaction conditions, we disregarded lithium and magnesium halide as possible counterions for **14**. On the other hand, employing manganese as the counterion resulted in the complex mixture of inseparable regioisomers. 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 the functionalization of **15** in many cases.¹⁸



Scheme 6. Proposed route for the carbometallation of arynes

Attempted aryne generation from 2-iodophenyl triflate 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 by-products 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., *tert*-BuLi, *sec*-BuLi or *n*-BuLi) to **14** at low temperatures 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 **16**. However, 2-iodophenyl

¹⁸ (a) Negishi, E.-I. Palladium-catalyzed 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.

triflate was converted to the corresponding aryne in the presence of 1.0 equiv of lithiated allyltrimethylsilane and 10.0 equiv of furan at $-78\text{ }^{\circ}\text{C}$, affording 88% of the Diels-Alder cycloadduct.

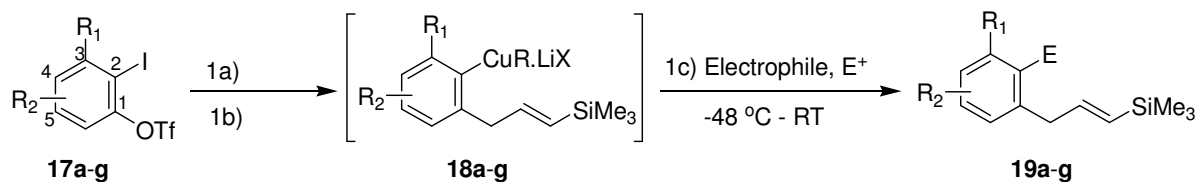
Recognizing that lithiated allyltrimethylsilane could initiate a rapid lithium-halogen exchange with 2-iodophenyltriflate and that the metallated species serves as the direct precursor to the lithium diorganocuprate, we elected to include 1.0 equiv of lithiated allyltrimethylsilane. In the described milieu, the lithiated allyltrimethylsilane 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 allyltrimethylsilane, along with the lithium diorganocuprate envisioned for aryne carbometallation, is required to form **16** in excellent yield.

Given our results concerning aryne formation, we next investigated a suitable metal source for the carbometallation step. These investigations were conducted by preparing 5.0 to 11.0 equiv of lithiated allyltrimethylsilane at $-48\text{ }^{\circ}\text{C}$ and then treating this solution with 2.0 to 5.0 equiv of a metal source at $0\text{ }^{\circ}\text{C}$ for 30 min. This provided 2.0 to 5.0 equiv of the respective di(trimethylsilylpropenyl)metallo species. The mandatory inclusion of 1.0 equiv of lithiated **14** promoted efficient metal-halogen exchange upon addition of a 2-iodophenyltriflate. After stirring for 15 min to effect aryne carbometallation, the reaction mixture was cooled to $-48\text{ }^{\circ}\text{C}$, and degassed MeOH was added to afford **16**. After extensive investigation, we found that 3.0 equiv of lithium di(trimethylsilylpropenyl)cuprate derived from CuI and lithiated allyltrimethylsilane offered the best results. Another study regarding optimal reaction temperature and time revealed that $0\text{ }^{\circ}\text{C}$ and 15 min reaction time were optimum for high-yielding carbometallation.

Once the optimum reaction conditions are established, we investigated the scope of the carbometallation-functionalization by varying both the electrophiles used and the substitution patterns on the aromatic ring (Scheme 7). As expected, electron rich compounds proved to be excellent substrates for the carbocupration reaction by furnishing excellent yields of the desired products. In contrast, electron deficient arenes provided poor yields of the desired products presumably due to rapid aryne decomposition.

As expected, the installed vinylsilane was readily transformed to useful functionalities. For instance, epoxidation of **16** using *m*-CPBA in buffered dichloromethane furnished the

corresponding epoxysilane,¹⁹ while halodesilylation garnered the respective vinylhalide with outstanding diastereoselectivity²⁰



1a) Li-allylTMS (7.0 equiv), -48 °C, 30 min,

1b) CuI (3.0 equiv), -48 °C - RT, 15 min.

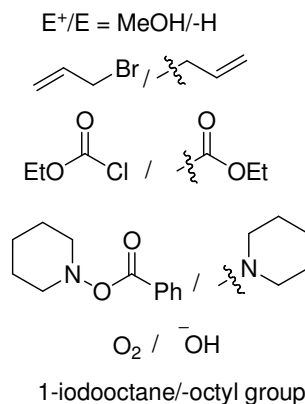
17a = R₁ = (OMe)/ R₂ = H

17b = R₁ = (OMe)/ R₂ = 5-OMe

17c = R₁ = (OMe)/ R₂ = 5-Me

17d = R₁/R₂ = H

17e = R₁ = F/ R₂ = H



Scheme 7. Representative examples of carbocupration-functionalization with various aromatic substrates

We established a consecutive three-component coupling reaction involving a 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 is particularly appealing for diversity-oriented synthesis applications given the easy incorporation of various substituents into the arene and for target-directed syntheses featuring the preparation or functionalization of homobenzylic alkenes.

Part C: Synthetic Applications of Wynberg Lactone: Asymmetric Synthesis of α,γ -Disubstituted Butyrolactones

Heteroatom-substituted butyrolactones serve as multipurpose intermediates in organic synthesis providing direct access to highly functionalized carbonyl compounds through standard transformations. Substituted butyrolactones also find applications in the preparation of liquid

¹⁹ Alexakis, A.; Jachiet, D. *Tetrahedron* **1989**, *45*, 381.

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

crystals,²¹ and several exhibit biological activities including cytotoxicity.²² It has been estimated that asymmetric butyrolactones exist as components of about 10% of all natural products.²³ Even though there are several approaches that are currently in use for preparing disubstituted butyrolactones,²⁴ there is no method available to access all four possible stereoisomers with varied heteroatom substitution at C₂.

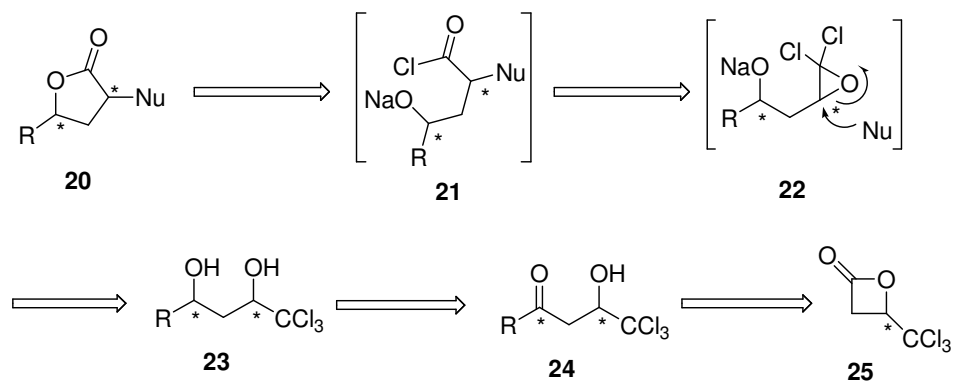
We envisioned that α,γ -disubstituted butyrolactones would be accessible in a single operation from a chiral 1-trichloromethyl-1,3-diol (**23**, Scheme 8). Treatment of **23** with base in protic media would initiate a reaction cascade where asymmetric *gem*-dichloroepoxide **22** would form after deprotonation of a trichloromethyl carbinol. Inclusion of the desired nucleophile for installation at C₂ would promote regioselective substitution with stereospecific inversion of configuration followed by acid chloride generation. The acyl chloride would be subject to intermolecular nucleophilic acyl substitution by the tethered alkoxide (**21**) to afford the decorated butyrolactone in a one-pot operation. We envisioned that the requisite *syn*- or *anti*-1,3-diols could arise from substrate-directed borohydride reductions, whereby a newly formed *R*- or *S*-stereocenter would be furnished based upon the absolute stereochemistry of the carbinol substrate. Hence, we required convenient and affordable access to asymmetric 3-ketotrichloromethyl carbinols bearing disparate 'R-groups' and a tethered alkoxide (**24**) to initiate the approach.

²¹ Ikemoto, T.; Sakashita, K.; Kageyama, Y.; Onuma, F.; Shibuya, Y.; Ichimura, K.; Mori, K. *Mol. Liq. Cryst.* **1994**, *250*, 31, 247.

²² For example see: Amagata, T.; Usami, Y.; Minoura, K.; Ito, T.; Numata, A. *J. Antibiot.* **1998**, *51*, 33.

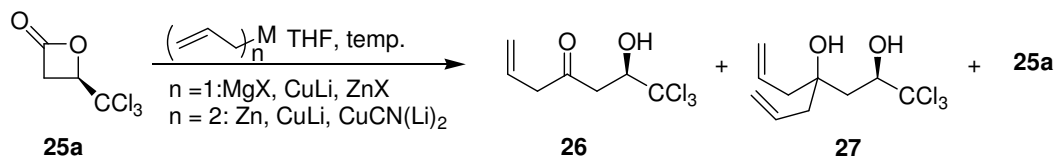
²³ Koch, S. S. C.; Chamberlin, A. R. Enantiomerically pure γ -butyrolactones in natural product synthesis. In *Studies in Natural Products Chemistry*; Atta-ur-Rehman, Ed.; Elsevier, 1995, pp 687-725.

²⁴ For details on several approaches in use please see: Shamshina, J. L. New Synthetic Application of Trichloromethylcarbinols. Synthesis of Small Molecule Natural Product. Ph. D. Dissertation, The University of Alabama, Tuscaloosa, AL, Aug 2008.



Scheme 8. Retrosynthetic analysis for the synthesis of α,γ -disubstituted butyrolactones.

We began by investigating formation of the requisite ketones by addition of common organometallic reagents to Wynberg lactone (**25a**) (Scheme 9). Although **25a** smoothly undergoes Friedel-Crafts acylation with aromatic substrates, we discovered that treatment with 1.0 equivalent of allylmagnesium, zinc, or copper reagent afforded roughly equal mixtures of monoaddition product (**26**), di-addition product (**27**), and recovery of **25a**.



Scheme 9. Attempted direct allylation of Wynberg lactone.

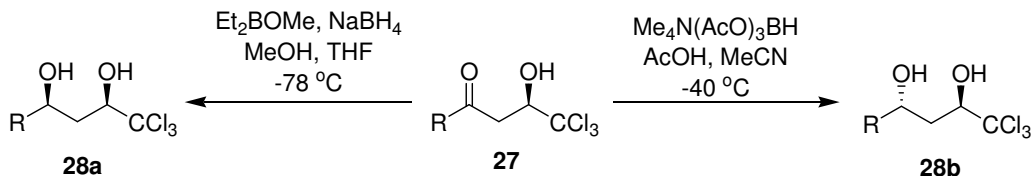
In order to minimize the formation of the diaddition products, we opted for addition of organometallic reagents on the corresponding Weinreb amide. Lewis acid-promoted amidation on **25** afforded the desired product quantitatively, even on multigram scales.²⁵ The Weinreb amide was reliably converted to the β -hydroxyketones by treatment with any freshly prepared organolithium or commercial Grignard reagent. We found that preliminary hydroxyl deprotonation by introduction of *i*-PrMgCl, followed by addition of desired nucleophile, offered superior yields.²⁶ Maintaining the temperature *below* -10 °C was critical, because higher temperatures permitted some double addition.

Next we explored directed *syn*- and *anti*-1,3-reductions of β -hydroxyketones (**27**) to establish the γ -stereocenter in the prospective substituted butyrolactones. Diethylmethoxyborane

²⁵ Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett.* **1997**, 38, 2685.

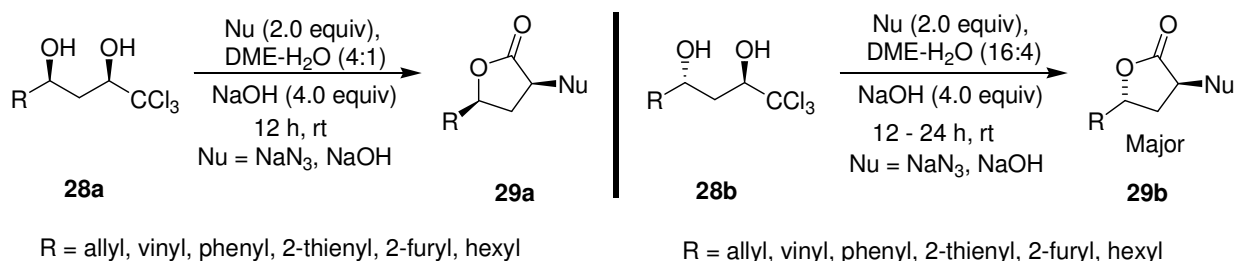
²⁶ Liu, J.; Ikemoto, N.; Petrillo, D.; Armstrong, J. D. III, *Tetrahedron Lett.* **2002**, 43, 8223.

and NaBH₄ in cold methanol-THF furnished *syn*-diols (**28a**) in 79-97% yields and with good to exceptional diastereoselectivities.²⁷ *Anti*-diols (**28b**) were rendered with comparable results using Evans' triacetoxyborohydride/anhydrous acetic acid protocol.²⁸



Scheme 10. *syn*- and *anti*-reduction of β -hydroxy ketones.

Treatment of the *syn*- and *anti*-diols in the presence of nucleophiles such as NaN₃ or NaOH in basic DME-water generates 2,4-disubstituted butyrolactones with azido or hydroxyl groups installed at the 2-position, respectively. Butyrolactones from *syn*-diols are prepared in high yields with little or no epimerization at the configurationally labile C₂-position. Conversely, partial epimerization takes place during the formation of butyrolactones derived from *anti*-diols.



Scheme 11. Synthesis of 2,4-disubstituted butyrolactones from *syn*- and *anti*-diols.

We devised a versatile route to any of the four possible stereoisomers of 2,4-disubstituted butyrolactones from (*R*)- or (*S*)-Wynberg lactone in just three or four steps. The approach is amenable to installation of varied carbon substituents at C₄ and heteroatom functionalities at C₂ and is particularly attractive for diversity-oriented synthesis applications.

²⁷ Chen, K. M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, 28, 155.

²⁸ Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, 110, 3560.