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$GaCl_3$-Catalyzed Ortho-Ethynylation of Phenols

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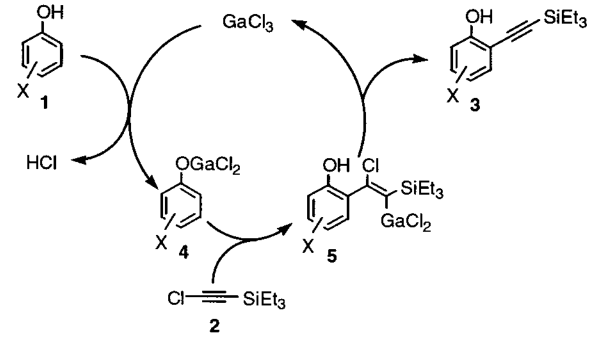
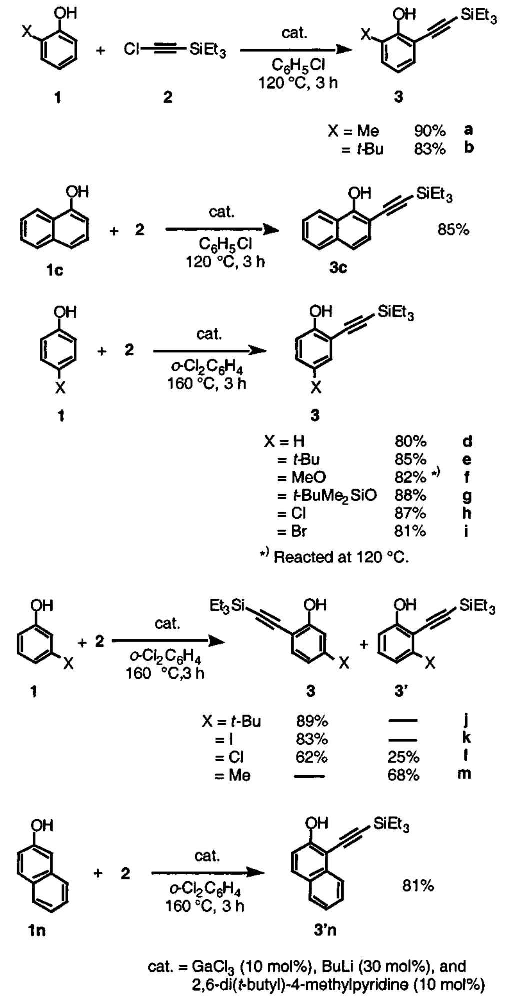
The introduction of the ethynyl group to organic molecules is an important transformation reaction in organic synthesis. The most common method is the nucleophilic reactions of ethynylmetals at carbonyl, halogen, or oxiranes.[1] Stepwise transformations as exemplified by the Corey−Fuchs method or Julia coupling are also often employed.[2] Electrophilic ethynylation of carbon nucleophiles is another attractive methodology, since organometallic species with C−M bonds in some cases can be generated directly from organic C−H bonds in the catalytic mode. Such catalytic ethynylation, however, has not been examined with the exception of the copper- or palladium-catalyzed coupling of terminal alkynes and haloacetylenes.[3] Described here is the ortho-ethynylation of phenol with chloroethyne using a catalytic amount of $GaCl_3$, which replaces the phenol ortho-hydrogen atom with an ethynyl group. We previously found that phenoxygallium **4** can be added to silylated ethyne.[4,5] The basic idea behind the present reaction is that the addition of **4** to silylated chloroethyne **2** will provide vinylgallium **5**, and that the β-elimination of **5** leads to the ortho-ethynylated phenol **3** and regenerates $GaCl_3$. Then, $GaCl_3$ reacts with phenol **1** to form the active species **4**, liberating hydrogen chloride (Scheme 1). Synthesis of *o*-ethynylphenols has been conducted by the Sonogashira coupling of *o*-iodophenols and terminal alkynes.[6] Rearrangement of polyhaloethyl aryl ethers using excess butyllithium was also reported.[7] The present synthesis provides *o*-ethynylphenols directly from phenols using a catalytic amount of $GaCl_3$.

Scheme 1



Scheme 2



A mixture of *o*-cresol (**1a**) and its lithium salt in chlorobenzene was prepared by the addition of butyllithium (30 mol %) to **1a**, to which were added $GaCl_3$ (10 mol %), 2,6-di(*tert*-butyl)-4-methylpyridine (10 mol %), and triethylsilylchloroethyne (**2**).[8] The solution was heated at 120 °C for 3 h, and 2-(triethylsilylethynyl)-6-methylphenol (**3a**) was obtained in 90% yield (turnover numbers based on $GaCl_3$: 9.0) (Scheme 2).[9] Lithium phenoxide prepared from LiOH and **1a** in methanol can also be used to give **3a** in 90% yield, provided that methanol is completely removed and the salt is dried at 80 °C (3 Torr) for 3 h. Use of the sodium phenoxide lowers the yield, and potassium or cesium phenoxides are not effective at all. The amount of butyllithium (30 mol %) is critical for the catalysis; use of 40 mol % butyllithium inhibits the reaction, and use of 20 mol % lowers the yield of **3a** to 28%; the catalytic ethynylation does not proceed in the absence of butyllithium. However, it is of interest that **3a** is obtained in 85% yield in the absence of the lithium salt, when stoichiometric amounts of $GaCl_3$ (100 mol %) and 2,6-di(*tert*-butyl)-4-methylpyridine (100 mol %) are employed. The lithium salt therefore is not involved in the C−C bond formation but rather in the regeneration of **4** in the catalytic cycle. When 2,6-di(*tert*-butyl)-4-methylpyridine was removed from the catalyst system, 2-acetyl-6-methylphenol (**6a**) was obtained in 59% yield.

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Since **6a** should be formed from **3a**, the role of the pyridine base is to inhibit desilylation of **3a** during the reaction. The catalytic reaction does not proceed at temperatures lower than 120 °C, although the stoichiometric reaction takes place at 80 °C in 98% yield. The higher temperature is therefore required for the regeneration of **4a** and not for the C−C bond formation or elimination of $GaCl_3$ from **5a**. The yield of **3a** decreases to 49% at 135 °C, and an adduct of **3a** and **1a**, 2-(1-(2-methylphenoxy)ethenyl)-6-methylphenol triethylsilyl ether, was obtained in 11% yield.

Several other ethynylating reagents were also investigated. The reaction of iodotrimethylsilylethyne under the catalytic conditions gave less than 10% yield of 2-(trimethylsilylethynyl)-6-methylphenol (**7a**), while the yield increased to 71% using stoichiometric amounts of $GaCl_3$, butyllithium, and 2,6-di(*tert*-butyl)-4-methylpyridine. Bromotrimethylsilylethyne behaves similarly. Phenyl(trimethylsilylethynyl)iodonium *p*-toluenesulfonate does not react. The use of trimethylsilylated chloroethyne in place of **2** decreases the yield of **7a** to 82% with the concomitant formation of **6a** in 10% yield. A reagent system of $SnCl_4$ (100 mol %),[10] butyllithium (100 mol %), and 2,6-di(*tert*-butyl)-4-methylpyridine (100 mol %) also promotes the ethynylation giving **3a** in 91% yield, but not the catalytic reaction. No reaction takes place with $GaBr_3$, GaI_3, $AlCl_3$, or $InCl_3$ under the catalytic conditions.

The $GaCl_3$-catalyzed ethynylation can be applied to various substituted phenols **1** giving the products **3** in high yields (Scheme 2), and the turnover numbers based on $GaCl_3$ are between 8 and 10. The optimum reaction temperature differs, depending on the substrate; ortho-substituted phenols **1a**−**c** react effectively at 120 °C in chlorobenzene; phenol (**1d**), para-substituted and meta-substituted phenols **1e**−**n** except for *p*-methoxyphenol (**1f**) require a higher temperature of 160 °C in *o*-dichlorobenzene. Reactions of meta-substituted phenols with *tert*-butyl-, iodo-, and chloro- groups take place at the less hindered site exclusively to predominantly. It is interesting that *m*-cresol (**1m**) reacts selectively at the more hindered site, giving **3′m**.

The mechanism of this catalytic ethynylation most likely involves carbogallation of **2** and **4** as initially designed (Scheme 1), although protonated **5** is not detected in the reaction mixture. β-Elimination of **5** appears to be more rapid than the carbometalation of **2** and **4**. The lithium salt may be involved in the formation of **4** from $GaCl_3$ and **1**, liberating hydrogen chloride.

In summary, phenols are ethynylated at the ortho position with chlorotriethylsilylethyne in the presence of a novel catalyst system, $GaCl_3$ (10 mol %), 2,6-di(*tert*-butyl)-4-methylpyridine (10 mol %), and butyllithium (30 mol %). The addition−elimination process of organogallium species to chloroethyne and catalytic phenol activation with $GaCl_3$ are successfully employed in the catalytic conversion of the organic C−H group to the C−C≡C−H group.

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Supporting Information Available: Spectroscopic details of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Brandsma, L. In *Preparative Acetylenic Chemistry Second Edition*; Elsevier: Amsterdam, 1988; p 79. (b) Garratt, P. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, p 271. (c) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, p 521.

(2) (a) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769. (b) Julia, M.; Righini, A.; D. Uguen, D. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1646. (c) Krebs, A.; Swienty-Busch, J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, p 949.

(3) For example, see: (a) Amatore, C.; Blart, E.; Genêt, J. P.; Jutand, A.; Lemaire-Audoire, S.; Savignac, M. *J. Org. Chem.* **1995**, *60*, 6829. (b) Cai, C.; Vasella, A. *Helv. Chim. Acta* **1995**, *78*, 2053. (c) Alami, M.; Ferri, F. *Tetrahedron Lett.* **1996**, *37*, 2763.

(4) Kobayashi, K.; Yamaguchi, M.; Arisawa, M. *Inorg. Chim. Acta* **1999**, *296*, 67. Also see the following for the carbometalation reaction of gallium enolates. (b) Yamaguchi, M.; Tsukagoshi, T.; Arisawa, M. *J. Am. Chem. Soc.* **1999**, *121*, 4074. (c) Arisawa, M.; Akamatsu, K.; Yamaguchi, M. *Org. Lett.* **2001**, *3*, 789. (d) Arisawa, M.; Miyagawa, C.; Yamaguchi, M. *Synthesis* **2002**, 138.

(5) Substitution reactions of aromatic hydrocarbons using $GaCl_3$. (a) Yamaguchi, M.; Kido, Y.; Hayashi, A.; Hirama, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1313. (b) Yonehara, F.; Kido, Y.; Yamaguchi, M. *Chem. Commun.* **2000**, 1189. (c) Yonehara, F.; Kido, Y.; Morita, S.; Yamaguchi, M. *J. Am. Chem. Soc.* **2001**, *123*, 11310. (d) Inoue, H.; Chatani, N.; Murai, S. *J. Org. Chem.* **2002**, *67*, 1414.

(6) Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280.

(7) Subramanian, R.; Johnson, F. *J. Org. Chem.* **1985**, *50*, 5430.

(8) Wolfgang, S.; Werner, Z. *J. Organomet. Chem.* **1966**, *6*, 109.

(9) Under an argon atmosphere, to a solution of *o*-cresol (**1a**) (1.08 g, 10.0 mmol) in chlorobenzene (50 mL) were added 1.6 M butyllithium in hexane (1.90 mL, 3.0 mmol) and 1 M $GaCl_3$ in methylcyclohexane (1.0 mL, 1.0 mmol) at 0 °C successively. The mixture was stirred for 10 min at room temperature, and then 2,6-di(*tert*-butyl)-4-methylpyridine (205 mg, 1.0 mmol) and chlorotriethylsilylethyne (**2**) (1.74 g, 10.0 mmol) were added. The mixture was heated at 120 °C for 3 h. Water (25 mL) and THF (25 mL) were added, and the organic materials were extracted with ethyl acetate, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. 6-Methyl-2-(triethylsilylethynyl)phenol (**3a**) (2.22 g, 90%) was obtained by flash chromatography (hexane:ethyl acetate = 50:1) over silica gel.

(10) (a) Yamaguchi, M.; Hayashi, A.; Hirama, M. *J. Am. Chem. Soc.* **1995**, *117*, 1151. (b) Yamaguchi, M.; Arisawa, M.; Omata, K.; Kabuto, K.; Hirama, M.; Uchimaru, T. *J. Org. Chem.* **1998**, *63*, 7298.

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