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Expedient, High-Yielding Synthesis of Silyl-Substituted Salen Ligands

Avinash N. Thadani, Yong Huang, and Viresh H. Rawal*

Department of Chemistry, The University of Chicago, 5735 South Ellis Avenue, Chicago, Illinois 60637

vrawal@uchicago.edu

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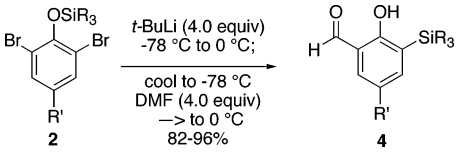
ABSTRACT



Described is an efficient synthesis of silyl-substituted salen ligands, used for the preparation of enantioselective catalysts. The salicylaldehyde precursors are synthesized from the silyl ethers of 2,6-dibromophenols via a one-pot double lithium halogen exchanges, to induce an intramolecular retro-Brook rearrangement and allow introduction of the aldehyde group. Condensation of the salicylaldehyde products with a chiral diamine affords the silyl-substituted salen ligands in high yields. The use of other electrophiles allows easy access to silyl-substituted phenolic esters, ketones, and boronic acids.

Asymmetric catalysis has grown explosively over the past two decades. It is no exaggeration to say that all important classes of reactions can now be rendered enantioselective. Fueling the rapid growth of this field has been the continual development of numerous and varied chiral ligands, the molds that impart asymmetry to the reactants.[1] Among the many broadly effective ligand types are the salen-derived metal complexes, which have been found to promote a range of asymmetric processes and, for this reason, have earned the designation "privileged ligands".[2] Salen ligands are easily prepared by condensation of a salicylaldehyde and a chiral 1,2-diamine. The salicylaldehyde precursors are typically 3,5-dialkyl substituted, with the 3,5-di-*t*-butyl variant being the most common.

Among the other substituted salens, those prepared from salicylaldehydes having a silyl group at the 3-position have been found to have useful properties. Burrows and co-workers developed such salen molybdenum catalysts for the epoxidation and aziridination of olefins.[3] Related chromium complexes were used by Jacobsen et al. for the asymmetric kinetic resolutions of *meso*-aziridines.[4] Silyl−salen ruthenium complexes were used by the Katsuki group for catalytic aerobic oxidation of diols.[5] In connection with our studies on the enantioselective cycloaddition chemistry of amino-substituted dienes,[6] we sought to enhance the subtle asymmetric topology of the standard 3,5-di-*t*-butyl−salen framework and found the corresponding silyl-substituted salen cobalt complexes to be superb catalysts for Diels−Alder reactions.[6d] The higher effectiveness of silyl−salen complexes, which allowed the catalysts to be used at loadings as low as 0.05 mol %, was rationalized to be a result of sterics-based distortion of the otherwise almost flat salen framework. Through similar reasoning, we recently identified triisobutylsilyl (TIBS) substituted Co−salen complexes as excellent catalysts for the carbonyl ene reaction of various 1,1-disubstituted and trisubstituted alkenes with ethyl glyoxylate.[7]

(1) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vols. 1−3.

(2) (a) Ito, Y. N.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 603−619. (b) Larrow, J. F.; Jacobsen, E. N. *Top. Organomet. Chem.* **2004**, *6*, 123−152.

(3) O'Conner, K. J.; Wey, S. J.; Burrows, C. J. *Tetrahedron Lett.* **1992**, *33*, 1001−1004.

(4) Li, Z.; Fernandez, M.; Jacobsen, E. N. *Org. Lett.* **1999**, *1*, 1611−1613.

(5) Miyata, A.; Furukawa, M.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **2002**, *43*, 3481−3484.

(6) (a) Huang, Y.; Iwama, T.; Rawal, V. H. *J. Am. Chem. Soc.* **2000**, *122*, 7843−7844. (b) Huang, Y.; Iwama, T.; Rawal, V. H. *Org. Lett.* **2002**, *4*, 1163−1166. (c) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628−4641. (d) Huang, Y.; Iwama, T.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 5950−5951. (e) Takenaka, N.; Huang, Y.; Rawal, V. H. *Tetrahedron* **2002**, *58*, 8299−8305. (f) McGilvra, J.; Rawal, V. H. *Synlett* **2004**, *13*, 2440−2442.

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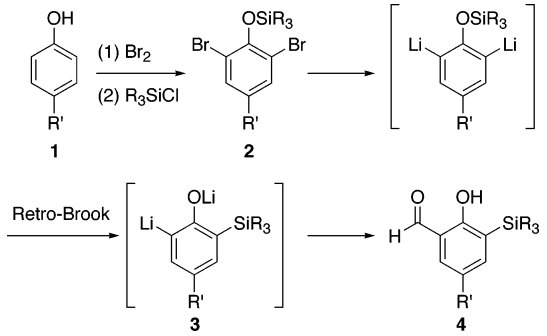
Despite their unique capabilities, silyl−salen complexes have not been widely adopted as catalysts, due in part to the challenges associated with their preparation. The reported syntheses of 3-silyl-substituted salicylaldehydes require several steps, some of which are low yielding.[3,4] Our standing interest in silyl−salens led us to devise a more efficient route to them. We report here a general, high-yielding synthesis of various 3-silyl-substituted salicylaldehydes as well as the corresponding salen ligands.[8] We also show the trapping of the intermediate lithiated phenoxide with other electrophiles to produce silyl-substituted phenolic esters, ketones, biaryls, and boronic acids.

Our route to 3-silyl-substituted salicylaldehydes capitalized on known metal−halogen exchange chemistry as well as on the intramolecular transfer of silyl groups from phenolic oxygens to the ortho-carbon, a type of retro-Brook rearrangement (Scheme 1).[3,9,10] On the basis of literature

Scheme 1



precedents, the silyl ether of a 2,6-dibromophenol (**2**) was expected to be converted to the corresponding dilithio intermediate upon treatment with excess butyl lithium. Intramolecular silyl transfer followed by trapping of the resultant aryllithium intermediate **3** with dimethylformamide would then give the desired 3-silyl-substituted salicylaldehyde (**4**). Subsequent condensation with an appropriate chiral diamine would then afford the salen ligand.

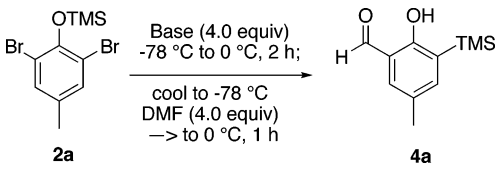
Initial exploratory studies were carried out on the trimethylsilyl (TMS) ether of 2,6-dibromo-4-methylphenol (**2a**).[11] The transformation was optimized by examining the effect of various reaction parameters, including the base, solvent, and additives (Table 1). Both *n*-butyllithium and *tert*-butyllithium were found to be effective for the one-pot silyl−salicylaldehyde synthesis. In the case of *n*-butyllithium, somewhat higher yields were obtained when TMEDA,

(7) See accompanying publication: (a) Hutson, G. E.; Dave, A. H.; Rawal, V. H. *Org. Lett.* **2007**, *9*, 3869−3872. (b) Hutson, G.; Rawal, V. H. *Abstracts of Papers*, 233rd ACS National Meeting, Chicago, IL, United States, March 25−29, 2007; American Chemical Society: Washington, DC, 2007; ORGN-557 (*Chemical Abstracts*: 2007:296584).

(8) Taken in part from: Huang, Y., Ph.D. Dissertation, University of Chicago, 2002.

(9) (a) Simchen, G.; Pfletschinger, J. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 428−429. (b) Habich, D.; Effenberger, F. *Synthesis* **1979**, 841−876. (c) Billedeau, R. J.; Sibi, M. P.; Snieckus, V. *Tetrahedron Lett.* **1983**, *24*, 4515−4518. Maruoka, K.; Itoh, T.; Araki, Y.; Shirasaka, T.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2975−2976.

Table 1. Protocol Optimization: Synthesis of 2-Trimethylsilyl-Substituted Salicylaldehyde **4a**



2a **4a**

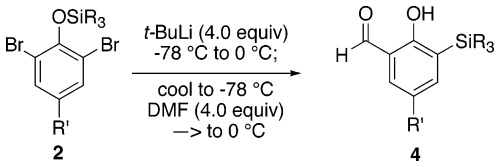
entry	base	solvent	yield [%][a]
1	*n*-BuLi	Et_2O	51
2	*n*-BuLi, 4 equiv of TMEDA	Et_2O	66
3	*n*-BuLi, 4 equiv of HMPA	Et_2O	71
4	*n*-BuLi, 4 equiv of DMPU	Et_2O	70
5	*t*-BuLi	Et_2O	96
6	*t*-BuLi	THF	92
7	*t*-BuLi	DME	92

[a] Isolated yield.

HMPA, or DMPU were used as additives. The salicylaldehyde product was obtained in considerably higher yield when the metal−halogen exchange was accomplished using *tert*-butyllithium, irrespective of the solvent used (Table 1, entries 5−7). Four equivalents of *tert*-butyllithium was ultimately used to ensure that the second lithium−halogen exchange proceeded to full conversion.

The optimized conditions were then utilized for the synthesis of assorted 3-silyl-substituted salicylaldehydes (Table 2). The requisite silyl ethers (**2**) were prepared via standard procedures and in most cases subjected directly, without purification, to the one-pot procedure. A variety of silyl phenol ethers successfully underwent the intramolecular silyl transfer and subsequent trapping with DMF. In the case of the more sterically demanding silyl groups (^{t}BuPh$_2$Si,

Table 2. One-Pot Synthesis of 3-Silyl-Substituted Salicylaldehydes



2 **4**

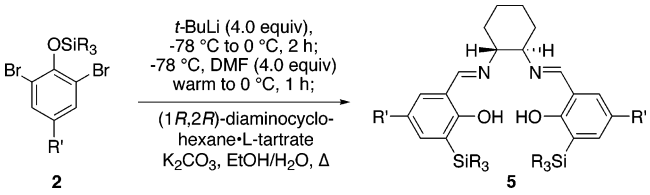
entry	R′	SiR_3	yield [%][a]
1	Me	$SiMe_3$	96 (**4a**)
2	Me	$SiMe_2{}^t$Bu	91 (**4b**)
3	Me	$Si^i Pr_3$	93 (**4c**)
4	Me	$Si^t BuPh_2$	82 (**4d**)[b,c]
5	Me	$SiPh_3$	91 (**4e**)
6	H	$SiPh_2Me$	87 (**4f**)[b,d]
7	^{t}Bu	$SiMe_3$	96 (**4g**)
8	^{t}Bu	$SiMe_2{}^t$Bu	92 (**4h**)
9	^{t}Bu	$Si^i Pr_3$	94 (**4i**)
10	F	$SiMe_3$	92 (**4j**)

[a] Isolated yield. [b] Reaction conducted in THF and warmed to rt during the lithium−halogen exchange. [c] Monobromide **4dBr** was isolated (7% yield). [d] Monobromide **4fBr** was isolated (6% yield).

Ph_2MeSi, and Ph_3Si), the reaction mixture was allowed to warm to room temperature to promote the silyl transfer step. The 3-silyl salicylaldehyde products were obtained in uniformly high yields. In a few instances, we isolated a small amount of a byproduct (2-bromo-6-silylphenol) that resulted from incomplete lithium−halogen exchange. Phenolic precursors (**2**) having a substituent other than methyl at the 4-position were also examined as substrates (entries 6−10). Precursors having a hydrogen, *t*-Bu, or fluorine at the 4-position were tolerated well, whereas nitro and trifluoromethyl substituents on the aromatic ring proved incompatible with the reaction conditions.

The purpose of developing a high-yielding synthesis of silyl-substituted salicylaldehydes (**4**) was to eventually transform these compounds into the corresponding silyl-substituted salen ligands (**5**). Having achieved the initial objective, we next explored the feasibility of a direct, purification-free synthesis of the silyl salens. A protocol was developed for the transformation of various dibromophenol ethers (**2**) into the corresponding salen ligands (**5**), and the results are summarized in Table 3. The crude salicylaldehydes, obtained as described in Table 2, were directly subjected to condensation with the representative chiral diamine, (1*R*,2*R*)-diaminocyclohexane. It is noteworthy that this diamine was generated in situ from its cost-effective l-tartrate salt precursor. The combined procedure allowed for the synthesis of several silyl-substituted salen ligands in high overall yields, without the necessity for any purification beyond simple filtration.

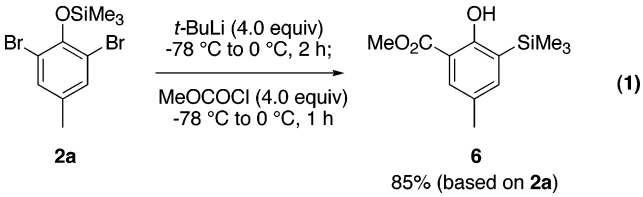
Table 3. Direct Synthesis of Silyl-Substituted Salen Ligands



entry	R′	SiR_3	yield [%][a]
1	Me	$SiMe_3$	84 (**5a**)
2	^{t}Bu	$SiMe_3$	83 (**5b**)
3	^{t}Bu	$SiMe_2{}^t$Bu	88 (**5c**)
4	^{t}Bu	Si^iPr_3	81 (**5d**)
5	F	$SiMe_3$	80 (**5e**)

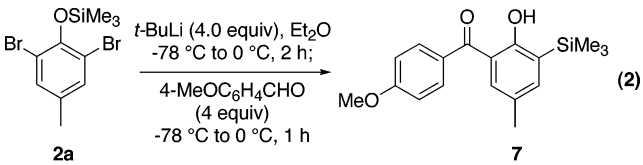
[a] Isolated yield.

Finally, given that the intermediate after the intramolecular silyl transfer reaction is an aryllithium species (**3**), we briefly examined the possibility of incorporating electrophiles other than DMF in the reaction protocol. Thus, after addition of *t*-BuLi to **2a** and allowing time for the silyl transfer step, the reaction mixture was treated with methylchloroformate rather than DMF. The product of the reaction was methyl salicylate **6**, obtained in 85% isolated yield (eq 1).



85% (based on **2a**)

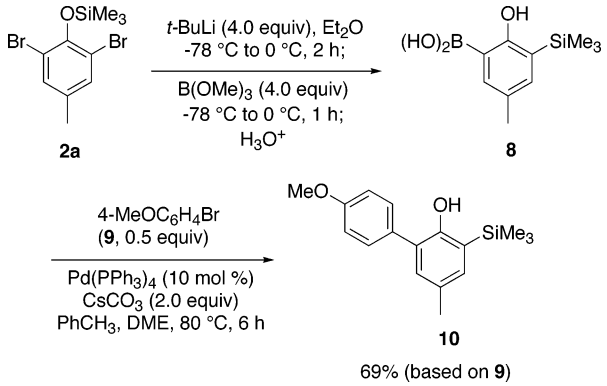
In a related reaction, treatment of the intermediate aryllithium species (**3**) with aldehydes led to an unexpected outcome. Specifically, quenching of the aryllithium intermediate from **2a** with excess *para*-anisaldehyde led to the isolation of ketone **7** rather than the expected diaryl carbinol. Ketone **7** is believed to arise through an Oppenauer oxidation of the expected carbinol anion by anisaldehyde. Attempts to avoid the oxidation product by reducing the number of equivalents of *para*-anisaldehyde proved unsuccessful, giving only lower yields of **7**, with none of the expected secondary benzylic alcohol product.



80% (based on **2a**)

To expand the scope of this versatile one-pot protocol, we explored the possibility of converting the monolithio intermediate to the corresponding boronic acid. The desired transformation was achieved by treating the putative aryllithium intermediate (**3**) with trimethyl borate, followed by an acid quench. Although the expected aryl boronic acid **8** was formed, it proved difficult to isolate. For this reason, the crude aryl boronic acid was utilized directly in a Suzuki−Miyaura cross-coupling reaction, as illustrated in Scheme 2. The desired cross-coupled product **10** was obtained in 69% isolated yield based on 4-bromoanisole.

Scheme 2

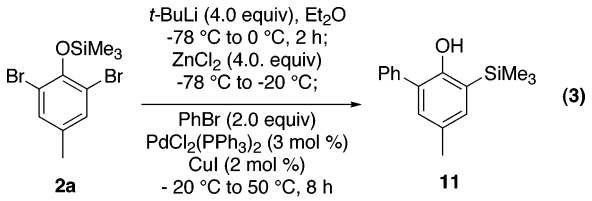


69% (based on **9**)

(10) Intramolecular silyl transfer on 2,6-dibromophenols has been previously described. See: (a) Razuvaev, G. A.; Vasileiskaya, N. S.; Khrzhanovskaya, I. L. *J. Gen. Chem. USSR, Engl. Trans.* **1975**, *45*, 2392−2395. (b) Razuvaev, G. A.; Vasileiskaya, N. S.; Oleinik, E. P.; Vavilina, N. N.; Muslin, D. V. *J. Gen. Chem. USSR, Engl. Trans.* **1976**, *46*, 2595−2598. (c) Muslin, D. V.; Lyapina, N. Sh. *Bull. Acad. Sci. USSR Div. Chem. Sci., Engl. Trans.* **1984**, *33*, 2141−2143. Review: (d) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065−2084.

(11) For a general procedure for the preparation of **2**, please see the Supporting Information.

An alternate synthetic route to biaryl compounds such as **10** could involve the direct cross-coupling of aryllithium species **3** under the Negishi cross-coupling conditions. In the event, the aryllithium intermediate **3** was converted to the aryl-zinc. The reaction mixture was then treated with bromobenzene, the palladium catalyst, and copper(I) iodide and heated. The nature of a palladium catalyst and the amount of copper iodide proved critical to the success of this cross-coupling reaction. Functionalized biaryl **11** was obtained in 70% isolated yield based on starting silyl ether **2a**.



2a **11** (3)

71% (based on **2a**)

In conclusion, we have developed an expedient, high-yielding synthesis of silyl-substituted salen ligands. Double lithiation of a 2,6-dibromosilylphenol ether followed by intramolecular silyl transfer and trapping with DMF affords the silyl-substituted salicylaldehydes in good to excellent yields. Subsequent condensation with an appropriate chiral diamine affords the silyl salen ligands without the necessity of any further purification. This one-pot silyl salen synthesis is convenient to carry out, even on a multigram scale. The ease of this protocol should encourage others to further explore the unique steric and electronic properties of silyl salen complexes. The above studies also illustrated the usefulness of the lithiation/intramolecular silyl transfer protocol. Reaction of the aryllithium intermediate with other electrophiles allowed for the synthesis of various functionalized, silyl-substituted phenols in good overall yields.

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Supporting Information Available: Preparation procedures and characterization data for **2**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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