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Cross-Coupling of Aromatic Bromides with Allylic Silanolate Salts

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Abstract

The sodium salts of allyldimethylsilanol and 2-butenyldimethylsilanol undergo palladium-catalyzed cross-coupling with a wide variety of aryl bromides to afford allylated and crotylated arenes. The coupling of both silanolates required extensive optimization to deliver the expected products in high yields. The reaction of the allyldimethylsilanolate takes place at 85 °C in DME with allylpalladium chloride dimer (2.5 mol %) to afford 7–95% yields of the allylation products. Both electron-rich and sterically-hindered bromides reacted smoothly, whereas electron-poor bromides cross-coupled in poor yield because of a secondary isomerization to the 1-propenyl isomer (and subsequent polymerization). The 2-butenyldimethylsilanolate (*E/Z*, 80:20) required additional optimization to maximize the formation of the branched (γ-substitution product). A remarkable influence of added alkenes (dibenzylideneacetone and norbornadiene) led to good selectivities for electron-rich and electron-poor bromides in 4–83% yields. However, bromides containing coordinating groups (particularly in the ortho position) gave lower, and in one case even reversed, selectivity. Configurationally homogeneous *E*-silanolates gave slightly higher γ-selectivity than the pure *Z*-silanolates. A unified mechanistic picture involving initial γ-transmetalation followed by direct reductive elimination or σ–π isomerization can rationalize all of the observed trends.

Introduction

Allylated arenes represent an important class of substituted aromatic compounds since many natural products possess an allylic arene component.[1] Moreover, the allylic substituent is synthetically useful because of the multitude of asymmetric, oxidative, and reductive transformations that olefins undergo.[2] In addition, the olefin functional group of an allylated arene can serve in complex molecule synthesis in a number of ways, e.g. as a dienophile[3] or metathesis partner.[4] Therefore, methods for the direct installation of an allyl group are desirable.

The two fundamental disconnections for the polar construction of allylic arenes are shown in Figure 1.[5] The classical manifestation of the aryl nucleophile/allyl electrophile disconnection **A** is the Friedel-Crafts allylation of an aromatic ring using allylic halides or alcohols and an acid catalyst.[6] The Friedel-Crafts reaction often produces a complex mixture of products stemming from instability of the product in the reaction conditions. Additionally in electrophilic aromatic substitution the arene partner must be activated and substituted benzene substrates suffer from low site-selectivity of the coupling. Alternatively, allylic arenes are prepared by the reaction of arylcoppers[7a] or arylmagnesium halides[7b,c] with allylic halides. The use of reactive Grignard reagents is restricted to substrates without sensitive functional

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groups. A palladium-catalyzed variant of this disconnection is also well-known in which aryl metal nucleophiles react with π-allylpalladium(II) electrophiles.[1b,8]

The disconnection **B** in Figure 1 represents the combination of an aryl electrophile and an allyl nucleophile. Examples of this approach include palladium and copper-catalyzed reaction of aryl halides with allylic Grignard reagents.[9] Milder versions of this process can be accomplished through the use of allylic organometallic donors based on tin, boron, and silicon. These reagents react with aromatic halides (and their equivalent) in the presence of palladium (0) to afford allylated arenes (Scheme 1). Because the reactive site of the electrophile is predetermined by placement of the halide, a high degree of site-selectivity on the arene is achieved.[10] With unsubstituted or symmetrically substituted allylic donors, allylic site-selectivity is not an issue. However, with unsymmetrically substituted allylic donors, for example 2-butenyl (Scheme 1, R = Me), the coupling can afford a mixture of products: a branched, γ-coupled product along with linear, α-coupled products as *E* and *Z* isomers.

Allylic tin, boron, and silicon organometallic donors undergo palladium-catalyzed allylation.[11] Cross-coupling technology[10] was first extended to the use of allylmetal donors by Migita in 1977 wherein allyltributyltin successfully transferred an allyl group to an aryl halide in the presence of a palladium(0) catalyst.[12] Since then, the cross-coupling of allyltributyltin donors has been exhaustively studied.[13] A variety of electron-rich and electron-poor aryl iodides, bromides, and triflates undergo this reaction in good yield. However, when substituted allylic tin reagents are used a mixture of γ-coupled and α-coupled products is observed.[14] Tsuji was able to obtain modest yields of the (*E*)-α-coupled product for a narrow substrate scope using triphenylarsine and LiCl. However, when triphenylphosphine was employed the γ-coupled product was isolated albeit in low yield.[15]

A variety of allylboronic acid derivatives participate in cross-coupling reactions with electron-rich and electron-poor aryl bromides and triflates.[16,17] The use of linear, substituted allylic boranes is not described and *ortho*-substituted organic electrophiles are not reported. Unsubstituted allylic boronic esters couple with a variety of aryl iodides and bromides[18] and a few vinyl triflates.[19] Recently, Szabo showed that allylboronic acids formed *in situ* couple with aromatic iodides to afford high yields and site-selectivities.[20] *Ortho*-substituted organic electrophiles are incompatible and aromatic bromides are not reported. A γ-selective allylation of aryl bromides using trifluoroborate donors has been reported by Miyaura.[21] Ligands with large bite angles are required to achieve high γ-selectivity, e.g. 1,1'b-is(di-*t*-butylphosphino) ferrocene. An enantioselective variant of this reaction has been described using a Mandyphos ligand (er = >88.5:11.5).[22]

Although not formally an organometallic donor, homoallylic alcohols do transfer an allyl group through a β-carbon elimination reaction.[23] Yorimitsu and Oshima recently described the palladium-catalyzed allylation of aromatic halides and triflates in good yields with high γ-selectivity.[24] Although an intriguing process, the coupling reactions produce a seven or nine-carbon ketone by-product while transferring only a 4-carbon unit to the electrophile.

The first use of allylic silanes in palladium-catalyzed cross-coupling was reported by Hiyama in 1991.[25] The cross-coupling reaction of substituted allylic trifluorosilanes with organic halides or triflates catalyzed by $(Ph_3P)_4Pd$ and promoted by tetrabutylammonium fluoride (TBAF) provide constitutionally pure γ-coupled products. Studies on the mechanism of transmetalation using enantiomerically enriched allylic silanes revealed that electrophilic attack of palladium took place exclusively at the γ-carbon.[26] In addition, either the α- or γ-coupled product can be formed in high yield from allylic trifluorosilanes with an appropriate choice of ligand.[27] In the palladium-catalyzed, cross-coupling reaction of (*E*)-2-butenyltrifluorosilane with 4-bromoacetophenone those ligands with large bite angles such as

1,3-bis(diphenylphosphino)butane (dppb), or alternatively Ph_3P give rise to the γ-coupled product. In contrast, the use of ligands with smaller bite angles, 1,3-bis(diphenylphosphino) ethane (dppe) or 1,3-bis(diphenylphosphino)propane (dppp), yield the α-coupled product. These reactions demonstrate the power of ligand control on the site-selectivity of cross-coupling of substituted allylic organometallic donors. However, the dependence of the method on the use of trifluorosilanes and activation with TBAF limits its application.

Background

The use of organosilicon donors has many advantages. Primary among these are the low toxicity[28] and ease of synthesis of these reagents from inexpensive materials. However, the requirement for activation of organosilicon donors by fluoride represents a drawback as organic soluble fluoride sources are expensive, corrosive, and incompatible with silicon protecting groups. The development of "fluoride-free" cross-coupling reactions of organosilanes has been actively investigated in these laboratories.[29] We have discovered that organosilanols undergo palladium-catalyzed cross-coupling in the presence of a variety of Brønsted bases including NaO*t*-Bu, Cs_2CO_3, and potassium trimethylsilanolate.[30] Under these conditions, alkenyl-,[30] aryl-,[31] and heteroarylsilanols[32] cross-couple with aryl halides (and their equivalent) in high yields. Moreover, isolated alkali metal silanolates have been prepared and are stable, storable solids that can be used directly in cross-coupling reactions.[33,34]

Initial studies in these laboratories of the fluoride-free coupling of allylic silanols began with the reaction of allyldimethylsilanol **1** in the presence of potassium *tert*-butoxide and 1-iodonaphthalene under catalysis by allylpalladium chloride dimer (APC).[35] Unfortunately this reaction afforded an inseparable mixture of products in low yield (Scheme 2). However, these experiments predated the introduction of pre-formed alkali metal silanolates where strongly basic activators are not needed. We believed that the mild conditions provided by the use of these pre-formed reagents would allow for clean cross-coupling reactions of allylic silanolate salts with organic electrophiles.

The goals of this work were to synthesize alkali metal allylic dimethylsilanolate salts and study their stability and reactivity in palladium-catalyzed cross-coupling reactions. Initial cross-coupling experiments focused on sequential evaluation of reaction conditions (stoichiometry, catalyst, solvent). After optimal conditions were found, compatibility with aryl bromides bearing a variety of functional groups was explored. Unsubstituted allylic silanolates were evaluated first to avoid complications arising from the site-selectivity of the coupling, after which the use of substituted silanolates was examined.

Results

1 2-Propenyl(Allyl)silanol. 1.1. Synthesis of Sodium Allyldimethylsilanolate (Na^+1^-)

Alkali metal allylic silanolates were prepared to evaluate their stability and reactivity in palladium-catalyzed cross-coupling reactions. Allyldimethylsilanol (**1**) was prepared from commercially available allyldimethylchlorosilane using a modified procedure for the hydrolysis of silyl ethers (Scheme 3).[36,37] Deprotonation of silanol **1** using sodium hydride in THF provided $Na^+\mathbf{1}^-$ as a white, free-flowing powder upon concentration.[38] The silanolate $Na^+\mathbf{1}^-$ could be stored at room temperature in an anhydrous environment for months with no discernable change in purity or reactivity.

1.2 Optimization of Cross-Coupling of Na^+1^- with 4-Bromoanisole

Orienting experiments on the reactivity of $Na^+\mathbf{1}^-$ in palladium-catalyzed cross-coupling reactions were carried out under reaction conditions (allylpalladium chloride dimer, toluene, 70 °C) used successfully for the cross-coupling of other isolated silanolates.[29a] The

stoichiometric loading of $Na^+\mathbf{1}^-$, with respect to 4-bromoanisole **7a** was then examined (1.3 to 3.0 equiv). A mixture of $Na^+\mathbf{1}^-$, 4-bromoanisole, allylpalladium chloride dimer (APC), biphenyl (internal standard), and toluene was prepared in a dry-box, removed and heated under argon at 70 °C in a preheated oil bath (Table 1). Gratifyingly, 4-allylanisole (**8a**) was the major product in all these experiments. The ratio of $Na^+\mathbf{1}^-$ to **7a** was observed to have a dramatic effect on the yield of **8a**. Incomplete conversion and low yield of the desired product were observed when 1.3 equiv of silanolate was used (entry 1). A significant increase in yield of **8a** was observed when the amount of $Na^+\mathbf{1}^-$ was increased from 1.3 to 2.0 equiv (entry 2). Increasing the silanolate loading further resulted in only moderate increase in the yield of **8a** (entry 4). The remainder of the optimization reactions used 2.5 equiv of silanolate because it provided an acceptable yield without overloading.

The next set of experiments evaluated a number of different variables in reactions executed under an inert atmosphere outside the dry-box (Table 2). As seen from the results in entry 1, the reaction performed under otherwise identical conditions failed. The outcome is not surprising as no stabilizing ligands for palladium were present. More robust conditions could be found by using palladium(0) sources bearing stabilizing ligands. The use of $Pd(dba)_2$ containing the weakly coordinating olefin ligand dibenzylideneacetone (dba) afforded a modest increase in conversion of **7a** (entry 2) whereas $(Ph_3P)_4Pd$ (containing a more strongly coordinating phosphine ligand) improved the conversion markedly (entry 3). Coordinating solvents were next examined. Although no reaction occurred in acetonitrile at 70 °C (entry 4), and reactions in THF led to incomplete conversion after 6 h (entry 5), reactions in 1,2-dimethoxyethane (DME) and dioxane both provided complete consumption of **7a** (entries 6 and 7). The lower boiling DME was chosen for preparative reactions to expand substrate scope.

1.3 Preparative Allylations with $Na^+\mathbf{1}^-$ and Substituted Aromatic Bromides

The scope of the allylation reaction was next evaluated with a wide range of substrates (Table 3). Aryl bromides bearing electron-donating groups such as NMe_2 and OMe underwent allylation readily under the optimized conditions to provide good yields of the isolated, purified products (entries – and 10). Electronically neutral aryl bromides cross-coupled well using these conditions (entries 6, 8, and 9) and silicon protecting groups were left intact (entry 7). The sterically demanding 2-bromomesitylene **7j** could be allylated in good yield, although 5.0 equiv of silanolate, Ph_3PO (1.0 equiv/Pd), and elevated temperature (100 °C) were required to effect complete conversion (entry 11).

The substrate survey showed that electron-rich and electron-neutral, *ortho*-, *meta*-, and *para*-substituted aryl bromides reacted well under optimized conditions, whereas electron deficient aryl bromides were less useful. Activated aryl bromides bearing cyano, trifluoromethyl, carboxylate, and ketone functional groups were consumed under the reaction conditions yet did not provide any discernable products (GC/MS). After evaluating many activated aryl bromides, we found that 4-bromobenzophenone **7k** afforded one major product under the optimized conditions. However, that product was 1-(*E*)-propenyl ketone **9** which arose from isomerization of the allyl unit (Scheme 4).

The isomerization to **9** was likely a post facto Brønsted base mediated process. To test this hypothesis, 4-allylbenzophenone[39] and sodium allyldimethylsilanolate (1.0 equiv) were combined in deuterated THF and the progress of the reaction was monitored by ^1H NMR spectroscopy. After 3 h at 25 °C isomerization was not observed, however after an additional 13 h at 50 °C a 50:50 mixture of **8k** and the conjugated double bond isomer **9** were observed (Scheme 5).

Thus, allylated arenes bearing electron-withdrawing groups are incompatible with the basic conditions of the reaction. This incompatibility represents a limitation of the allylation process

and a number of options to avoid this isomerization were considered. The most appealing of these was the use of substituted silanolates to reduce the kinetic acidity of the product and increase the structural generality.

2 2-Butenyl(Crotyl)silanols. 2.1. Preparation of Sodium 2-Butenyldimethylsilanolate (Na^+13^-)

Sodium 2-butenyldimethylsilanolate Na^+**13**$^-$ was prepared to test the hypothesis that substituted allylic silanolates could suppress olefin isomerization while simultaneously introducing the issue of site-selectivity in the coupling. The synthesis of Na^+**13**$^-$began by reaction of commercially available 1-chloro-2-butene (*E*/*Z*, 80:20) with trichlorosilane using copper(I) chloride as the catalyst to produce 2-butenyltrichlorosilane **11** in 88% yield (Scheme 6).[40] Trichlorosilane **11** could then be converted to the 2-butenyldimethylchlorosilane **12** by addition of 2.0 equiv of methyllithium. Buffered hydrolysis of **12** then provided 2-butenyldimethylsilanol **13**.[36] The purified silanol **13** rapidly dimerized to the corresponding disiloxane upon concentration. Therefore, an ethereal solution of the silanol obtained after silica gel chromatography was treated directly with sodium hydride to afford the sodium 2-butenyldimethylsilanolate Na^+**13**$^-$ in 81% yield over two steps.[41] Olefin isomerization was not observed over the synthetic sequence as the white, free-flowing powder Na^+**13**$^-$ consisted of an 80:20, *E*/*Z* mixture of isomers.

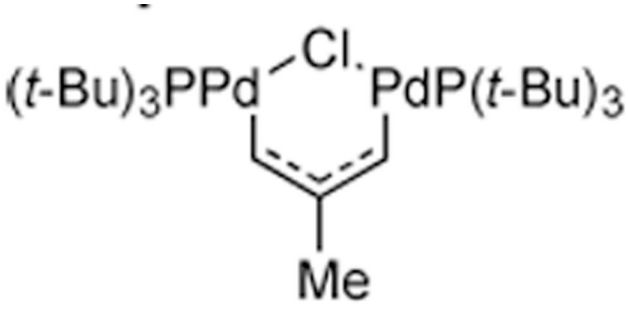
2. Cross-Coupling of Na^+13^- with 1-Bromonaphthalene

Initial attempts at cross-coupling Na^+**13**$^-$ were performed under the optimized conditions for allylation with 1-bromonaphthalene.[42] Both α- and γ-products of this cross-coupling reaction have been well characterized.[24a,43] The combination of Na^+**13**$^-$ (2.5 equiv) with **7h** using APC as the catalyst in DME at 85 °C produced an inseparable 50:50 mixture of the γ- and α-coupled products in 58% yield (Scheme 7). Although Na^+**13**$^-$ cross-coupled in good yield, the lack of site-selectivity stimulated a systematic optimization to obtain one of the isomers in high constitutional purity.

In view of the known effects of ligands on the site-selectivity of palladium-catalyzed allylation reaction,[15,21,25] an initial survey of ligands was undertaken (Table 4). In a coupling performed in the absence of a ligand, a slight preference for the γ-coupled product was observed (entry 1). Next, a variety of mono- (entries 2 and 3) and bidentate (entries 5–8) phosphine ligands was evaluated, as well as the more weakly-coordinating triphenylarsine (entry 4). Unlike the large differences in site-selectivity observed between triphenylphosphine and 1,3-*bis* (diphenylphosphino)propane in other palladium-catalyzed crotylation reactions,[21,25] these ligands had little effect on the site-selectivity of the coupling (entries 2 and 5). Only small variations in site-selectivity were seen with other bidentate phosphine ligands (entries 6–8). Of the phosphines evaluated under these conditions, Ph_3P provided the highest, albeit modest, selectivity (entry 2) and was chosen for further optimization.

The modest effects of ligands on the site selectivity of the coupling prompted a broader evaluation of palladium catalysts. A broad range of palladium sources of varying oxidation states with halide, acetate, phosphine, carbene, and olefinic ligands was then tested (Table 5). Although no reaction was observed with $PdCl_2$ (entry 1), $PdBr_2$ and $Pd(OAc)_2$ provided low site-selectivity (entries 2 and 3). Catalysts containing the electron-rich, sterically bulky tri-*t*-butylphosphine ligand (palladacycle[44] **15** and $(t\text{-}Bu_3P)_2Pd$) were examined, and the former resulted in improved γ-selectivity compared to the latter (entries 4 and 5). Poor site-selectivity was seen with the carbene-ligated PEPPSI catalyst[45] (entry 5). Most notable were the selectivities observed with the olefin ligated palladium(0) catalysts $Pd_2(dba)_3$ and $Pd(dba)_2$, wherein, increasing the ratio of the olefin ligand to palladium increased the γ-selectivity (entries

7 and 8). Moreover, removing the phosphine ligand from the reaction considerably increased the site-selectivity to 10:1 (entry 9).



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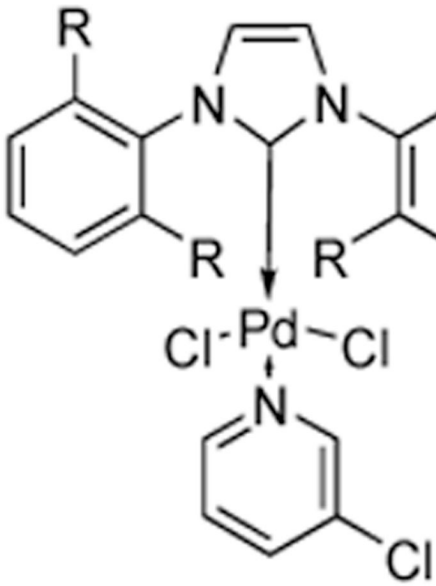

PEPPSI
(R= *i*-Pr)

The increased site-selectivity provided by $Pd(dba)_2$ demanded further investigation. A variety of ligands was examined to understand and improve the γ-selectivity provided by $Pd(dba)_2$ (Table 6). The weakly coordinating ligand Ph_3As provided a good yield of coupling products, albeit with low site-selectivity (entry 1). Increased γ-selectivity was observed using the electron-rich alkyl phosphine Cy_3P (Table 6, entry 2). Very slow conversion of **7h** was observed when 2.0 equiv/Pd of the sterically demanding *o*-tol_3P was used (entry 3). The reaction using the P-, O-chelating bidentate bis(diphenylphosphino)propane mono-oxide (dpppO) ligand provided good conversion of **7h** but a low yield and selectivity for formation of γ-**14h** (entry 4). Reactions carried out with Buchwald-type ligands provided low yields and selectivities of γ-**14h** (entries 5–7). Interestingly, 1-naphthol **17** was observed as the major product when the sterically demanding ligand 2-(di-*t*-butylphosphino)biphenyl was used. When this reaction was scaled to 1.0 mmol and 2.0 equiv $Na^+\mathbf{13}^-$ was used, 56% of **17** was isolated (Scheme 8).

However, the most striking result in this study was the effect of added olefinic ligands. Whereas the addition of 1,5-cyclooctadiene (cod) maintained a similar selectivity to that observed previously without added ligand (compare Table 6, entry 8 and Table 5, entry 9), an additional 2.0 equiv of dba (per Pd) further increased the site-selectivity to highly favor the γ-coupled product by 16:1 (Table 6, entry 9).

Olefinic ligands are known to have a variety effects on transition metal-catalyzed reactions.[46] The most important in the context of this reaction is an increased rate of reductive elimination attributed to the π-acidity of the ligand.[47] To this end, a variety of olefinic ligands with a range of electronic and steric attributes were examined (Table 7). The use of π-acidic 1,4-benzoquinone provided good selectivity albeit in low yields of γ-**14h** (entries 2–4). 1,4-

Benzoquinone is known[48] to oxidize palladium(0) to palladium(II) which under these conditions cannot re-enter the catalytic cycle. Norbornadiene (nbd) provided good site-selectivity (at low yield), but was seen to inhibit the reaction at loadings greater than 2.0 equiv/Pd (entries 5–7). The electron-rich, tetramethylethylene and the electron-poor maleic anhydride gave similar conversions and yields, yet the electron-deficient olefin provided higher γ-selectivity (entries 9 and 11). Decreased selectivity was observed when diallylcarbonate was added to the reaction (entry 12). However when diallyl ether was used, good γ-selectivity was observed at increased loadings, 4.0 equiv/Pd, but at the cost of decreased reactivity (entries 13 and 14).

To separate the site-selectivity contribution of the dba ligand of $Pd(dba)_2$ from the affects of added ligands, the palladium source was changed to APC, which can generate ligandless palladium(0) after reduction by a silanolate nucleophile.[49] A variety of olefinic ligands along with π-acidic phosphine ligands were surveyed in combination with APC in the same solvent and temperature. Slightly lower γ-selectivity was observed for APC with 20 mol % of dba (i.e. 4.0 equiv dba/Pd) and $Pd(dba)_2$ alone (compare Table 8, entry 1 and table 7, entry 1). Derivatives of dba[50] with appended electron-withdrawing groups provided higher site-selectivity than those with electron-donating groups (Table 8, entries 5 and 6). Low selectivity and decreased conversion was seen with cod when the loading was increased to 8.0 equiv/Pd (Table 8, entries 7 and 8). The use of 4,4-dimethylcyclohexadienone (**20**)[51] resulted in low site-selectivity (entry 15). The π-acidic ligands[52] $(MeO)_3P$, $(PhO)_3P$, and (*N*-pyrrolyl)$_3$P gave varying selectivity; $(PhO)_3P$ gave the highest selectivity of any phosphorus-containing ligand used (entry 13). With APC, only the electron-poor olefins diallyl ether, dba (and its derivatives), and the π-acidic triphenylphosphite provided site-selectivities greater than 5:1 (entries 1–6, 11, 13). Moreover, in general, increasing the dba loading increased the rate, yield, and site-selectivity of the reaction (entries 1–4).

2.3 Final Optimization of Silanolate Stoichiometry

The final stage of optimization involved adjustment of silanolate stoichiometry. This parameter was evaluated using $Pd(dba)_2$ (5 mol %) and additional dba ligand (4.0 equiv/Pd, see previous section) in toluene at 70 °C (Table 9). With 1.0 equiv of silanolate the reaction was only 49% complete at 3 h, whereas by increasing the equiv of silanolate to 1.5, the conversion increased to 85% (entries 1 and 2). Increasing the equiv of silanolate to 2.0 did not change the amount of **7h** consumed but did increase the yield of the desired product from 44% to 54% (entries 2 and 3). Since using more than 2.0 equiv of silanolate did not affect the reaction significantly (entries 5 and 6), 2.0 equiv of silanolate was chosen to evaluate substrate scope.

2.4 Preparative Cross-Coupling with Na^+**13**$^-$

The optimized conditions developed above ($Pd(dba)_2$ (5 mol %), Na^+**13**$^-$ (2.0 equiv) in toluene at 70 °C) were used to evaluate substrate scope. Norbornadiene was used in these studies because it provided good site-selectivity in the product and conversion of the electrophile at low loadings (1.0 equiv/Pd) when used in conjunction with $Pd(dba)_2$ (Table 7, entry 5). The results of these cross-coupling reactions with electron-neutral, electron-rich, and electron-poor aryl bromides bearing a variety of *ortho*-, *meta*-, and *para*-functional groups are compiled in Table 10. Good yields and excellent γ-selectivities were observed with unhindered, electron-neutral aryl bromides **7l** and **7g** (entries 1 and 2). The reaction with electronically neutral 1-bromonathphalene (**7h**) afforded the corresponding product **14h** in 50% yield, which could be increased to 63% by using an extra 0.5 equiv of Na^+**13**$^-$ (entry 4). Silicon protecting groups including triethylsilyl (TES) and *tert*-butyldimethylsilyl (TBS) are unaffected by the reaction conditions and the desired products were isolated in high yields (entries 5 and 10). Electron-rich aryl bromides, 4-bromo-*N*,*N*-dimethylaniline **7c** and 4-bromoanisole **7a**, provided the desired products in modest yield at 85 °C after 20 h (entries 8 and 10). The yields of these

couplings could be increased by raising the temperature to 110 °C (entries 9 and 11). A protected indole is compatible under these conditions and gives the desired γ-coupled product in good yield and site-selectivity (entry 11).

Although esters and unprotected aldehydes are compatible with these reaction conditions (entries 18 and 19) and give satisfactory results, substrates bearing strongly electron-withdrawing groups (compare entries 14, 15 and 16) yielded products of lower constitutional purity. Importantly, the product of the cross-coupling of Na^+**13**$^-$ and ketone **7k** was produced without isomerization to afford **14k** in 81% yield with high γ-selectivity (entry 17). Moreover, the allyl unit of linear, α-coupled products did not isomerize into conjugation with the aromatic ring confirming the hypothesis that these products would be less prone to isomerization (e.g. entry 20).

2.5 Effect of Silanolate Geometry on Site-Selectivity of Preparative Couplings

Because all of the foregoing coupling reactions of Na^+**13**$^-$ employed an 80:20, *E*/*Z* mixture of olefin isomers, configurationally homogeneous (*E*)- and (*Z*)-2-butenyltrichlorosilanes were needed to examine the reactivity and selectivity of these individual reagents. Synthesis of the (*E*)-2-butenyltrichlorosilane (*E*)-**11** began with $LiAlH_4$ reduction of 2-butynol to yield (*E*)-2-butenol (*E*)-**21** in high configurational purity (Scheme 9).[53] The alcohol (*E*)-**21** was then transformed to chloride (*E*)-**10** using hexachloroacetone and Ph_3P.[54] The (*E*)-1-chloro-2-butene (*E*)-**10** thus obtained was then combined with trichlorosilane in the presence of copper (I) chloride to provide (*E*)-**11**.

(*Z*)-2-Butenyltrichlorosilane (*Z*)-**11** was obtained by reaction of 1,3-butadiene and trichlorosilane catalyzed by $(Ph_3P)_4Pd$ (Scheme 10).[40] The configurationally pure trichlorosilanes (*E*)- and (*Z*)-**11** were then separately treated with methyllithium in diethyl ether and the resulting monochlorosilanes were hydrolyzed, and the silanols deprotonated in a sequence similar to that described above. Accordingly, sodium (*E*)- and (*Z*)-2-butenyldimethylsilanolates were produced in good yield without erosion of the configurational purity as determined by comparison of the allylic signals in their ^1H NMR spectra.

To evaluate the reactivity and selectivity of the geometrically pure 2-butenylsilanolates, aryl halides were chosen that displayed a wide range of reactivity (i.e. electron-rich and electron-poor aryl bromides). Also included in this survey were **7h**, the substrate used to optimize the reaction, and *tert*-butyl 2-bromobenzoate **7u**, the only substrate to yield the product arising from α-coupling as the major isomer. The results of these studies are compiled in Table 11. In all of the cases studied the geometrically pure Na^+(*E*)-**13**$^-$ produced a greater proportion of the branched, γ-coupled product than did the (*Z*)-isomer. The selectivity difference with **7a** at elevated temperature was observed to be the most pronounced for the geometrically pure (*E*)- and (*Z*)-silanolates (entry 2). Interestingly, the geometry of the silanolate had very little impact on the site-selectivity of coupling with **7u** which remained γ/α, 1:2.5 regardless of the silanolate geometry (entry 5).

Discussion

The primary aim of this work was to develop a palladium-catalyzed cross-coupling reaction using isolated allylic alkali metal silanolates. To this end, allylic silanolates were prepared and studied as organometallic donors. These reagents were found to be readily prepared, stable, easily handled, and more importantly, competent in palladium-catalyzed cross-coupling reactions.

1 Preparative Allylation with Substituted Aromatic Bromides

The optimized reaction conditions (Na^+**1**− (2.5 equiv), APC (2.5 mol %), DME (0.5 M) at 85 °C) were successfully applied to electron-rich and electron-neutral aryl bromides. These optimized conditions could be successfully modified to accommodate highly sterically demanding substrates such as the *ortho*-di-substituted 2-bromomesitylene **7j**, which using the standard optimized conditions provided very long reaction times (>40 h) and low yields of the desired product. Nucleophile degradation over the long reaction time was believed to be the main problem with this reaction. This issue was readily overcome by increasing the silanolate stoichiometry, temperature (100 °C in dioxane), and the addition of a stabilizing ligand (Ph_3PO).

However, electron-deficient aryl bromides were problematic. In these reactions, the aryl bromide was consumed but no major products were observed. The products of these reactions contain doubly activated protons that are both allylic and benzylic. Moreover, when the aromatic ring is substituted with an electron-withdrawing group the acidity of these protons is increased and Brønsted base mediated allylic isomerization was observed. While a preformed silanolate eliminated the necessity of a strongly basic Brønsted base activator and allowed for successful coupling of electronically neutral aryl bromides, Na^+**1**$^-$ is still a basic reagent. The kinetic basicity of Na^+**1**$^-$ could potentially be attenuated by the use of other more covalently bound alkali metal silanolate salts (Li), but this would also diminish the nucleophilicity of the silanolate and hinder the necessary displacement step of the catalytic cycle.[55]

2 Cross-Coupling Site-Selectivity Using 2-Butenylsilanolate Na^+**13**$^-$

Experiments using substituted allylic silanolate Na^+**13**$^-$ were conducted to address the issue of site-selectivity and test the hypothesis that these reagents would provide less base-sensitive products. A brief digression to a general discussion of the proposed mechanism of the palladium-catalyzed cross-coupling allylic organometallic donors is necessary to put the remainder of this discussion in context. Allylic organometallic donors are believed to undergo transmetalation through two discrete processes: (1) S_E2', forging a bond between the γ-carbon to the allylic unit and palladium, and (2) S_E2, forming a bond between the α-carbon and palladium (Scheme 11).[21,25] Direct S_E2 transmetalation is only favorable with allylic stannanes, presumably because of the long (2.14 Å[56] and weak (65 kcal/mol)[57] tin-carbon bond. When silicon or boron donors are used, transmetalation to the γ-carbon through an S_E2' process is proposed. After transmetalation, the σ-bound palladium species can either reductively eliminate to yield the *γ*- or α;-coupled products, or interconvert through an η^3, π-allyl palladium species.[58] Highly site-selective couplings are proposed to arise from a fast reductive elimination of the initially formed σ-bound intermediate.[21,25] However, if σ-π interconversion occurs the geometry of the olefin can become isomerized and lead to a mixture of geometrical as well as constitutional isomers. As previously mentioned, ligands can have marked effect on the outcome of this process, and ligands that provide a facile reductive elimination of the initially formed σ-bound palladium species can allow for one constitutional isomer of the product to be formed exclusively.

The substituted allylic silanolate Na^+**13**$^-$ underwent cross-coupling with 1-bromonaphthalene to produce the γ- and α-coupled products in nearly equal amounts under the optimized allylation conditions (APC, Ph_3PO, DME). Many perturbations of these initial conditions did not significantly change this site-selectivity including the use of ligands reported to impact site-selectivity with other allylic metal donors. For example, dppp which gave good results in both the cross-couplings of substituted allylic trifluorosilanes and trifluoroborates gave a mere 1.4:1, *γ:a* ratio with Na^+**13**$^-$.

3 Bulky Phosphine Ligands

Different phosphine ligands were investigated to improve the site-selectivity of the coupling. The palladacycle catalyst **15**, containing 1.0 equiv *t*-Bu_3P to palladium, increased the γ-selectivity substantially, but this selectivity was still only moderate. In addition, when the catalyst (*t*-$Bu_3P)_2Pd$ was used lower site-selectivity was observed. Interestingly, the use of *t*-Bu_2(2-biphenyl)P caused a dramatic change in product distribution (Scheme 12). The major product of the reaction was 1-naphthol **17**, resulting from C—O bond formation, and only a trace of the C—C bond coupled products was observed. In addition, 1-naphthol was consumed over time when only 1.0 equiv of silanolate was used. The formation of 1-naphthol is believed to result from a facile reductive elimination of the palladium bound silanolate **23**.[59] After cleavage of the silyl ether by Na^+**13**$^-$, 1-naphthoxide **26** and disiloxane **25** are produced, of which the former can reenter the catalytic cycle. It seems that *t*-Bu_2(2-biphenyl)P was too effective in facilitating a facile reductive elimination and that a balance of transmetalation and reductive elimination would be necessary to provide C—C bond formation and avoid out interconversion.

4 Effect of Dibenzylideneacetone on Site-Selectivity

A more preparatively useful balance of transmetalation and reductive elimination was found with the $Pd(dba)_2$ catalyst. Initial experiments with $Pd(dba)_2$ included added phosphine ligands and somewhat masked the beneficial effect of the dba ligand. When Ph_3P (2.0 equiv/Pd) was used only moderate γ-selectivity was observed. Substituting Ph_3P for a more bulky alkyl phosphine ligand, Cy_3P (2.0 equiv/Pd), slightly increased the γ-selectivity of the reaction, but in general all added phosphine ligands diminished the γ-selectivity that was observed when $Pd(dba)_2$ was used alone. However, without added ligand these reactions stalled before complete consumption of **7h**. Therefore, a ligand to stabilize the catalyst was required. This ligand would need to be less “palladaphilic” than a phosphine as to not interfere with the γ-selectivity provided by the dba ligand.

The use of olefinic ligands cod, nbd, as well as additional dba provided complete consumption of the electrophile. In addition, similar and often superior γ-selectivity was observed when these ligands were used. The electron-deficient olefin ligands 1,4-benzoquinone and diallyl ether were particularly beneficial to the γ-selectivity of the reaction. However, during studies using APC as catalyst only dba and its electron-deficient derivative **19** were observed to provide reactions with site-selectivity greater than 10:1, γ:α. Also, increasing the stoichiometry of dba lead to reactions with increased conversion of the electrophile and better γ-selectivity. Since the use of added dba can complicate purification, a stabilizing ligand that could be used at low loadings was sought.

5 Effect of Norbornadiene

At low loadings (1.0 equiv/Pd) when used in conjunction with $Pd(dba)_2$, norbornadiene increased the consumption of the aryl halide while marginally increasing the site-selectivity of the coupling. The increased turnover of the palladium catalyst provided by the use of norbornadiene is not completely understood, however two scenarios in which this effect would manifest are proposed. Electron deficient olefins can effectively slow oxidative addition through π-back bonding to palladium(0).[60] As norbornadiene is a somewhat electron-rich olefin, when ligated to palladium(0) it could aid in the oxidative addition step of the catalytic cycle. Secondly, norbornadiene may stabilize the resting state of the catalyst allowing for increased catalyst turnover. Importantly, experiments using norbornadiene with APC produced very low site-selectivity. This suggests that norbornadiene does not provide enhanced γ-selectivity but does allow for increased reactivity of the palladium catalyst.

6 Substituent Effect of the Aryl Bromide on the Site-Selectivity of Cross-Coupling of $Na^{+}13^{-}$

The electronic nature of aryl groups bound to palladium is known to affect the rate of reductive elimination.[61] In the allylation reaction, this effect contributes to the site-selectivity of the coupling. Excellent γ-selectivities were observed in reactions with electron-rich aryl bromides, for example 4-bromoanisole **7a** or 6-bromo-*N*-Boc-indole **7n**. However, some of the lowest γ-selectivities were seen when electron-poor aryl bromides (1-bromo-3,5-bis-(trifluoromethyl) benzene **7r**) were used. This electronic effect can be rationalized by either a more facile σ-π isomerization of an electron-deficient palladium(II) complex, or a slower reductive elimination of the electron-deficient aryl groups. The latter hypothesis contradicts the trends observed in other aryl — alkyl reductive eliminations in which aryl groups bearing electron-withdrawing substituents reductively eliminate to form alkyl arenes more quickly than those with electron-donating substituents.[62] It should not be overlooked that a weaker, more labile Pd–dba bond resulting from less π-back bonding of palladium(II) bearing an electron-deficient aryl group would also effectively slow reductive elimination and decrease the site-selectivity of the coupling.

Substituent effects not related to electronic contributions were also apparent. Aryl bromides bearing Lewis basic substituents affected the site-selectivity of the coupling. Lower than expected γ-selectivity was observed for the coupling of electron-rich 4-bromo-*N*,*N*-dimethylaniline **7c**. Also, very low selectivity was observed for 4-bromobenzonitrile **7p**. These results suggest that competitive ligation of palladium by Lewis basic substituents can lower the site-selectivity of the reaction. The carboxyl group of *t*-butyl 2-bromobenzoate **7u** plays a significant role in the site selectivity of the coupling. As this is the only substrate in which an α-coupled product was predominant it may provide insight into the composition of the species by which reductive elimination occurs. The coordination of the olefin of an allylic silanolate to palladium after halide displacement would effectively occupy two coordination sites (Scheme 13). When *t*-butyl 2-bromobenzoate is used, if the remaining two sites are occupied by the aryl group and ester function,[63] this would produce the coordinatively saturated palladium species **27**.[64] Thus, the dba ligand would be excluded from this complex and the γ-selectivity imparted by the dba ligand would be bypassed.

7 Effect of Silanolate Geometry

Geometrically pure (*E*)- and (*Z*)-2-butenyldimethylsilanolates were studied under the optimized reaction conditions to evaluate the effects of olefin geometry on the site- and stereoselectivity of the coupling. These studies established that the configuration of the double bond did in fact affect the site-selectivity of the reaction. Higher γ-selectivity was observed in all cases in which the pure *E*-silanolate was used. To explain this outcome, the immediate products of transmetalation must be considered (Scheme 14). For the purposes of this analysis we will assume an intramolecular transmetalation as we have described for alkenylsilanolates.[65] The two species (**32** and **35**) formed upon initial γ-selective transmetalation (via transition structures **31** and **34**, respectively) are different conformers of the enantiomeric products. It is proposed that a more facile reductive elimination pathway is available for conformer **32** to afford the γ-substitution product **33** compared to that for conformer **35**. Conformer **35** experiences greater $A^{1,3}$ strain which may facilitate σ→π isomerization and thus leads to formation of both ent-**33** and α-substituted product α-**14** resulting in attenuated overall selectivity. In addition, the geometry of the double bond of the silanolate is not preserved in the geometry of the double bond of the α-coupled product suggesting that the a-coupled product is generated after formation of a π-allyl palladium intermediate.

8 Mechanistic Hypothesis

All the results described herein can be accommodated by the mechanistic hypothesis presented in Figure 2. Three important features of this proposal are: (1) after oxidative addition, displacement of the bromide by Na^+**13**− forms a Si—O—Pd linkage,[29b,65] (2) an S_E2' transmetalation occurs from the palladium bound silanolate and (3) facile reductive elimination of the γ-bound palladium intermediate (**37**, L=dba) affords the product γ-**14** with high site-selectivity. The first conclusion is supported by the observation of 1-naphthol in reactions using the *t*-Bu_2(2-biphenyl)P which must arise from C—O bond formation. The second conclusion is corroborated by the fact that the configuration of a geometrically pure silanolate is not conserved in the α-coupled product. Therefore, the α-coupled product must be produced after generation of a π-allylpalladium intermediate from σ-π isomerization, and not from facile reductive elimination of an S_E2 transmetalation. The third conclusion finds support in the low site-selectivity observed in the absence of dba.

Conclusion

Allyl- and (2-butenyl)silanolate salts are stable, isolable solids that undergo facile cross-coupling with aryl bromides under palladium catalysis. Electron-neutral and electron-rich aryl bromides undergo cross-coupling in high yield with sodium 2-propenyldimethylsilanolate Na^+**1**$^-$, although with this nucleophile electron-poor substrates were problematic. Increased substrate scope, good yields and high γ-selectivities were obtained with sodium 2-butenyldimethylsilanolate Na^+**13**$^-$. The use of dba-derived palladium catalysts was crucial to the high γ-selectivities observed. In addition, increased γ-selectivity was observed using geometrically pure (*E*)-Na^+**13**$^-$. Configurational isomerization of the α-coupled products leads to the conclusion that these reagents suffer transmetalation through an S_E2' process. Evidence supporting the Si—O—Pd linkage prior to transmetalation was discovered in the formation C—O bonds when bulky phosphine ligands were used. Further studies on the mechanism of transmetalation and asymmetric variants of this reaction are currently underway.

Experimental Section

General Experimental (See Supporting Information)

Preparation of 4-(2-Propenyl)anisole (8a) from 4-Bromoanisole Using Na^+1$^-$— To a 5-mL, single-necked, round-bottomed flask containing a magnetic stir bar, equipped with a reflux condenser and an argon inlet capped with a septum was added $[allylPdCl]_2$ (9.2 mg, 0.025 mmol, 0.025 equiv). The flask was then sequentially evacuated and filled with argon three times. 4-Bromoanisole (187 mg, 1.0 mmol) was then added by syringe. Sodium 2-propenyldimethylsilanolate (346 mg, 2.5 mmol, 2.5 equiv), pre-weighed into a 10-mL, two-necked, round-bottomed flask in a dry-box, was then dissolved in DME (2.0 mL) then added by syringe. The reaction mixture was heated in a preheated oil bath to 85 °C under argon. After 3 h, the mixture was cooled to rt, filtered through silica gel (2 cm x 2 cm) in a glass-fritted filter (coarse, 2 cm x 5 cm) and the filter cake washed with ether (3 × 10 mL). The filtrate was concentrated *in vacuo* and the residue was purified by silica gel chromatography (20 cm x 20 mm, hexane/EtOAc, gradient 100:0 to 20:1) followed by Kugelrohr distillation (90 °C, 10 mmHg, ABT) to afford 119 mg (80%) of **8a** as a clear, colorless oil. Data for **8a**:[66] ^{1}H NMR (500 MHz, $CDCl_3$) 7.14 (d, *J* = 8.5, 2 H), 6.87 (d, *J* = 8.5, 2 H), 5.99 (ddt, *J* = 16.8, 10.3, 6.6, 1H), 5.09 (m, 2 H), 3.81 (s, 3 H), 3.36 (d, *J* = 6.6, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) 158.2, 138.2, 132.4, 129.8, 115.7, 114.1, 55.5, 39.6; IR 3077, 3032, 3003, 2978, 2954, 2934, 2906, 2835, 1639, 1611, 1584, 1511, 1464, 1441, 1321, 1301, 1247, 1177, 1111, 1038, 1012, 995, 914, 842, 830, 815, 761, 708, 639, 624; MS (EI, 70 eV) 148, 133, 121, 105, 91, 77; R_f 0.35 (hexanes/EtOAc, 20:1).

Preparation of 1-(1-Methyl-2-propenyl)naphthalene (14h) from 1-Bromonaphthalene Using Na^+13^-—To an oven dried, 5-mL, single-neck, round-bottomed flask, containing a magnetic stir bar, equipped with a reflux condenser and an argon inlet capped with a septum was added $Pd(dba)_2$ (28.8 mg, 0.05 mmol, 0.05 equiv). The flask was then sequentially evacuated and filled with argon three times. 1-Bromonaphthalene (207 mg, 1.0 mmol) was then added by syringe. Sodium 2-butenyldimethylsilanolate (386 mg, 2.5 mmol, 2.5 equiv), pre-weighed into a 10-mL, two-necked, round-bottomed flask in a dry-box, was then dissolved in toluene (2.0 mL) and then norbornadiene (5.2 μL, 0.05 mmol, 0.050 equiv) was added by syringe. The solution of Na^+**13**$^-$ and norbornadiene in toluene was then added by syringe. The reaction mixture was heated under argon to 70 °C in a preheated oil bath. After 6 h, the mixture was cooled to rt, filtered through silica gel (2 cm x 2 cm) in a glass-fritted filter (coarse, 2 cm x 5 cm) and the filter cake washed with ether (3 × 10 mL). The filtrate was concentrated *in vacuo* and the residue was purified by silica gel chromatography (20 cm x 20 mm, pentane) followed by Kugelrohr distillation (120 °C, 1 mmHg, ABT) to afford 116 mg (63%, 13:1, γ:α) of **14h** as a clear, colorless oil. Data for **14h**:[43] ^{1}H NMR (500 MHz, $CDCl_3$) 8.15 (d, *J* = 8.4, 1 H), 7.88 (d, *J* = 7.9, 1 H), 7.74 (d, *J* = 8.1, 1 H), 7.49 (m, 4 H), 6.18 (ddd, *J* = 17.7, 10.0, 5.8 1 H), 5.15 (m, 2 H), 4.32 (ap, *J* = 7.0, 1 H), 1.53 (d, *J* = 7.0, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) 143.1, 141.7, 134.2, 131.7, 129.1, 127.0, 126.0, 125.8, 125.6, 123.9, 123.7, 113.9, 38.1, 20.5; IR 3048, 2967, 2931, 2874, 1923, 1830, 1700, 1684, 1653, 1636, 1596, 1509, 1452, 1410, 1395, 1369, 1250, 1235, 1167, 1016, 997, 912, 859, 797, 777; MS (EI, 70 eV) 182, 167, 152, 128; R_f 0.42 (pentane).

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63. Nagayama K, Kawataka F, Sakamoto M, Shimizu I, Yamamoto A. Bull. Chem. Soc. Jpn 1999;72:573–580.A palladium(II) lactone [Pd(C_6H_4COO)(P(CH_3)$_3$)$_2$] that would require similar geometry about palladium has been isolated
64. A referee suggested that the high α-selectivity observed **7u** could be a simple consequence of the steric influence of the carboxyl group. This reasonable explanation could be eliminated as 2-bromotoluene provided the γ-coupled product in high selectivity (γ/α, 13:1) under the same conditions. We thank the referee for this suggestion.
65. Denmark SE, Sweis RF. J. Am. Chem. Soc 2004;126:4876–4882. [PubMed: 15080692]
66. Gomes P, Gosmini C, Perichon J. Org. Lett 2003;5:1043–1045. [PubMed: 12659569]

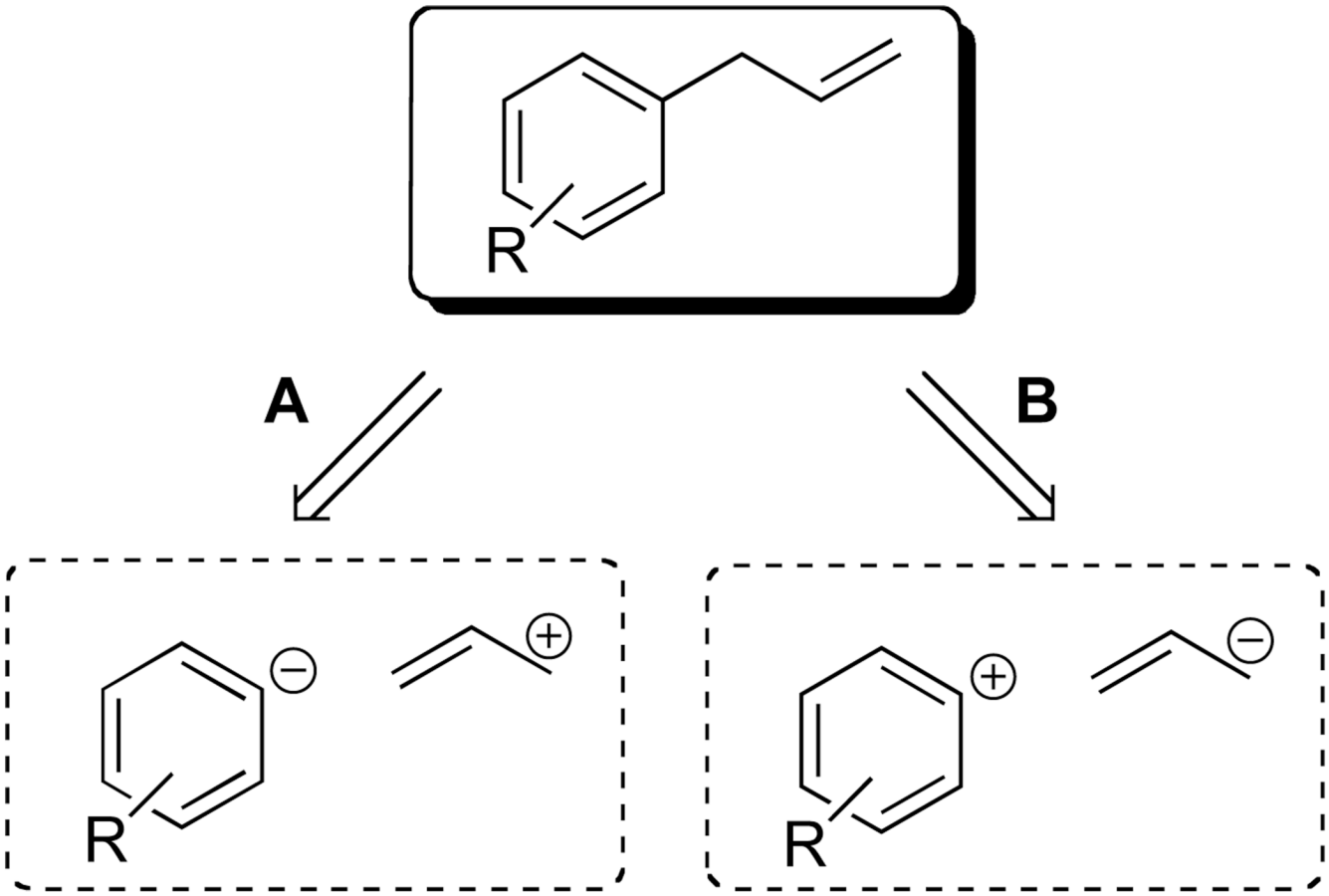


Figure 1.
Polar allylation disconnections.

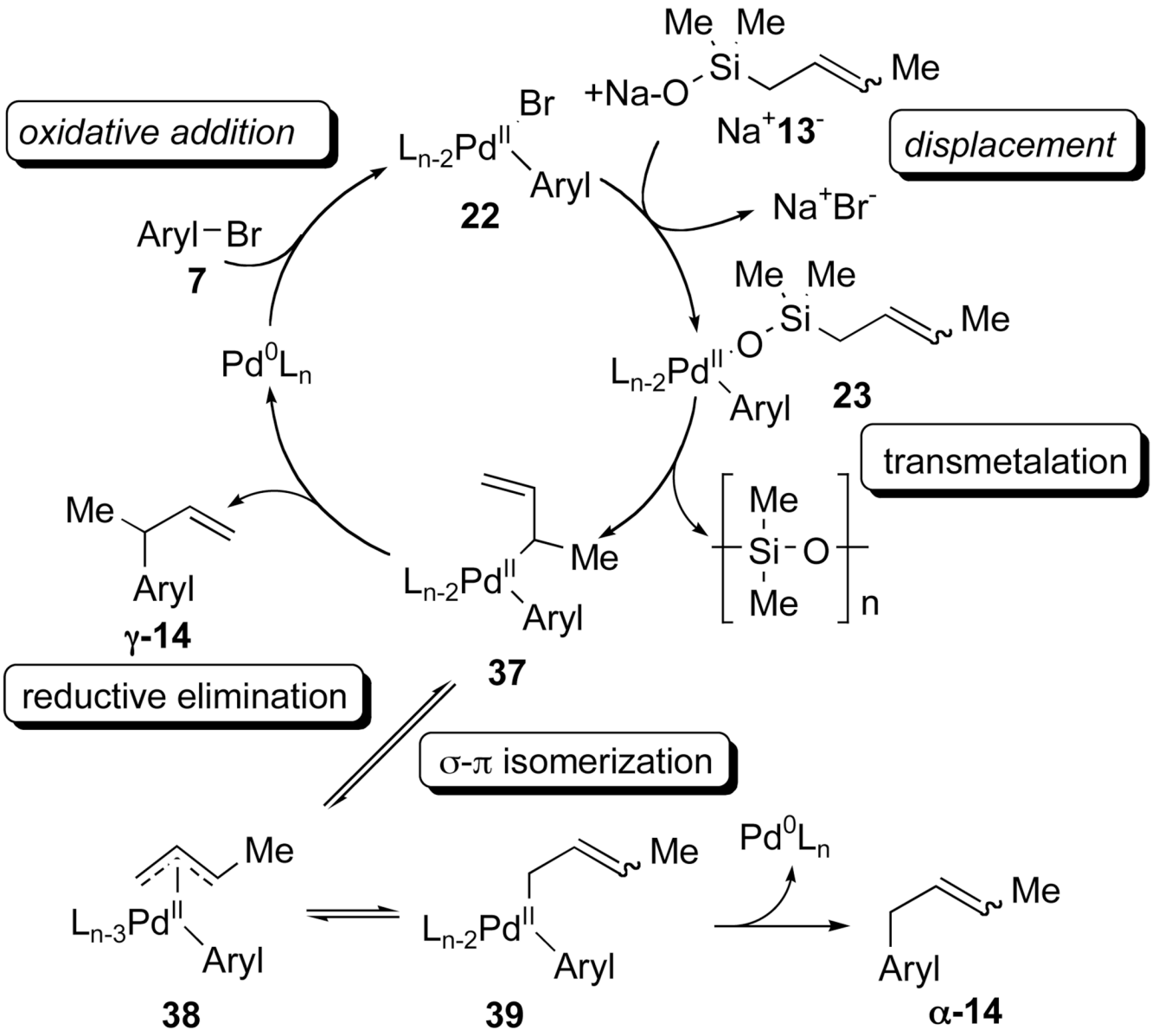
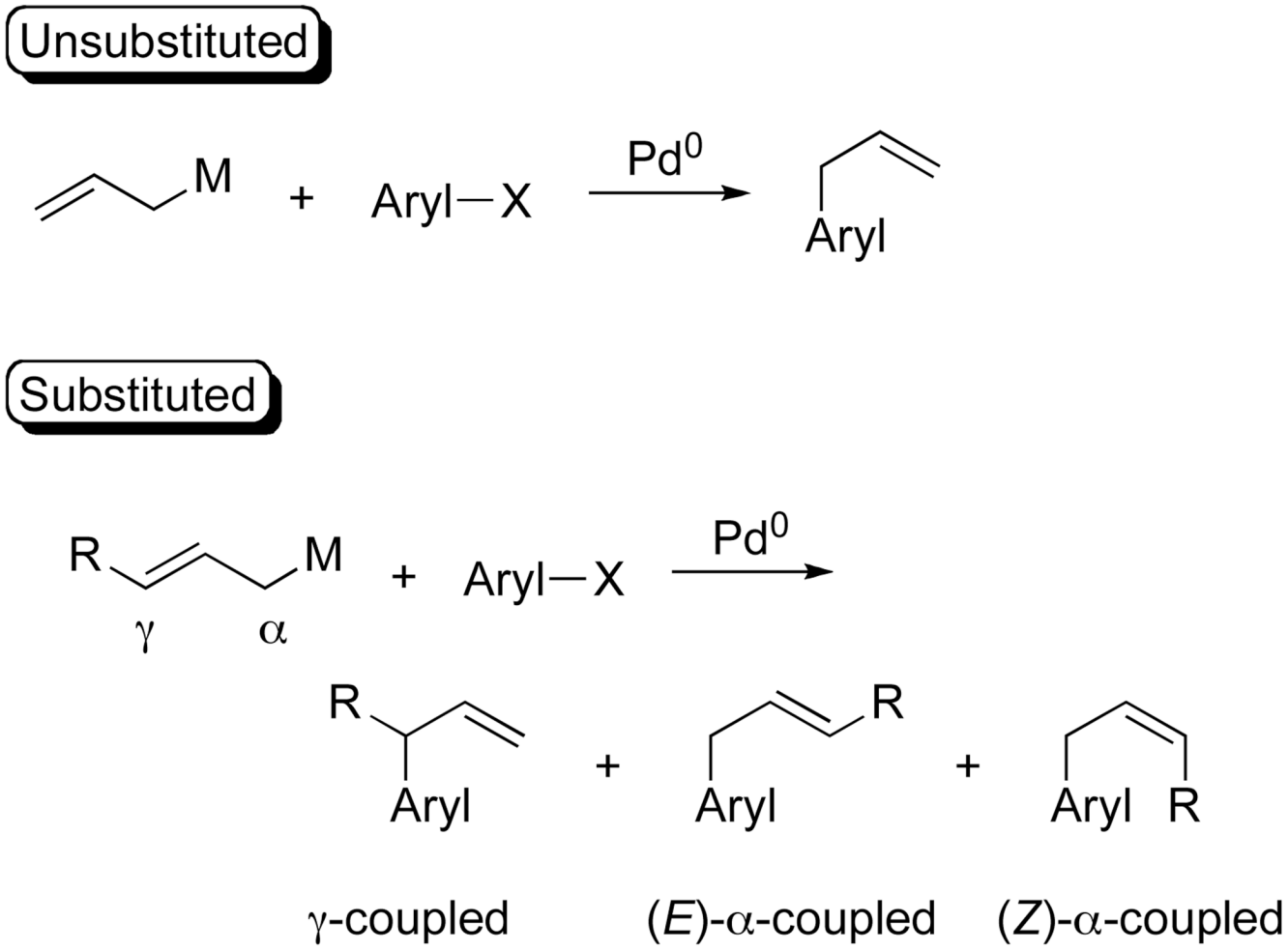
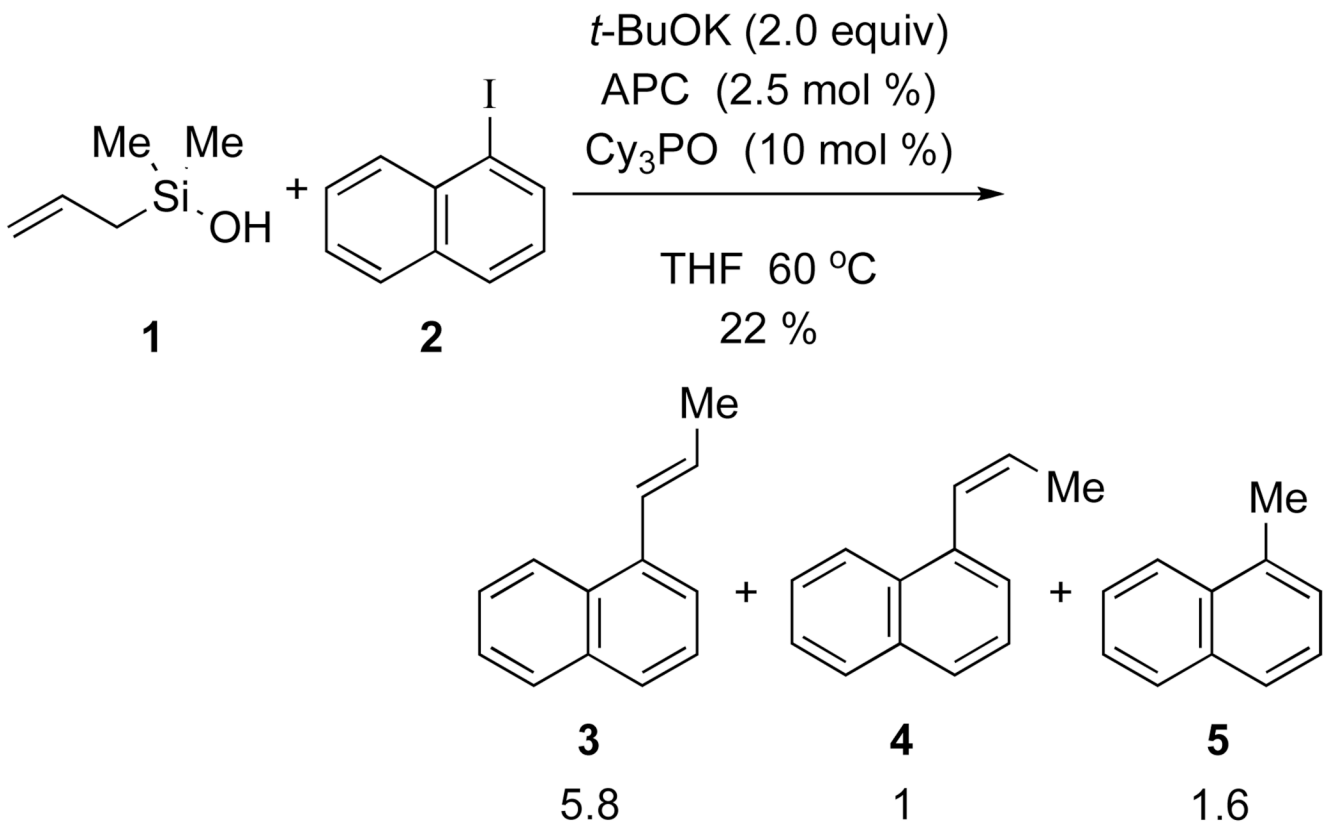


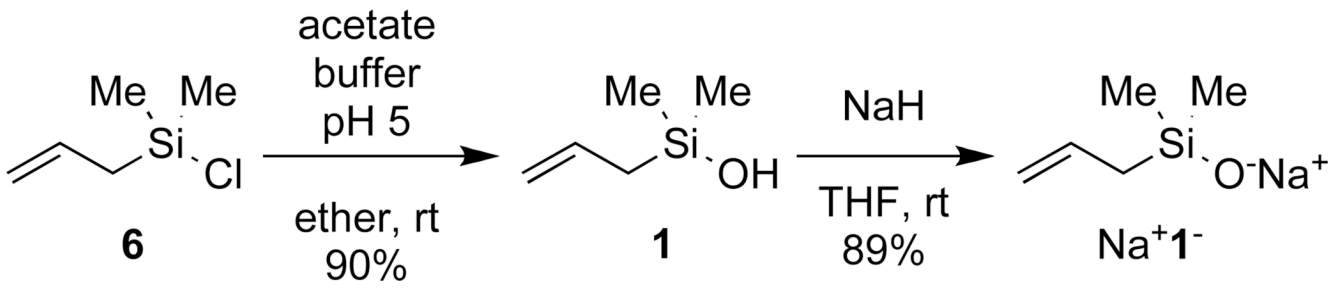
Figure 2.
Proposed catalytic cycle.



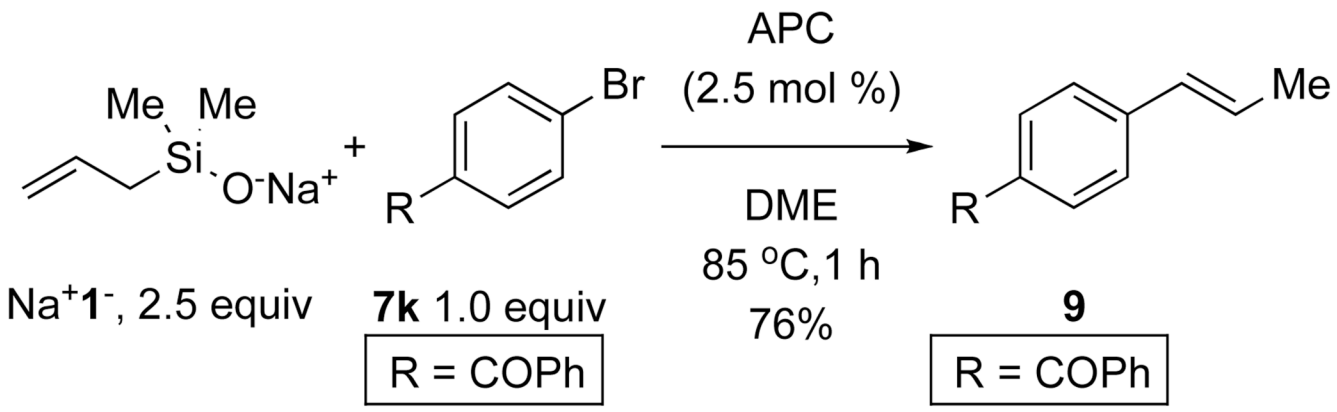
Scheme 1.



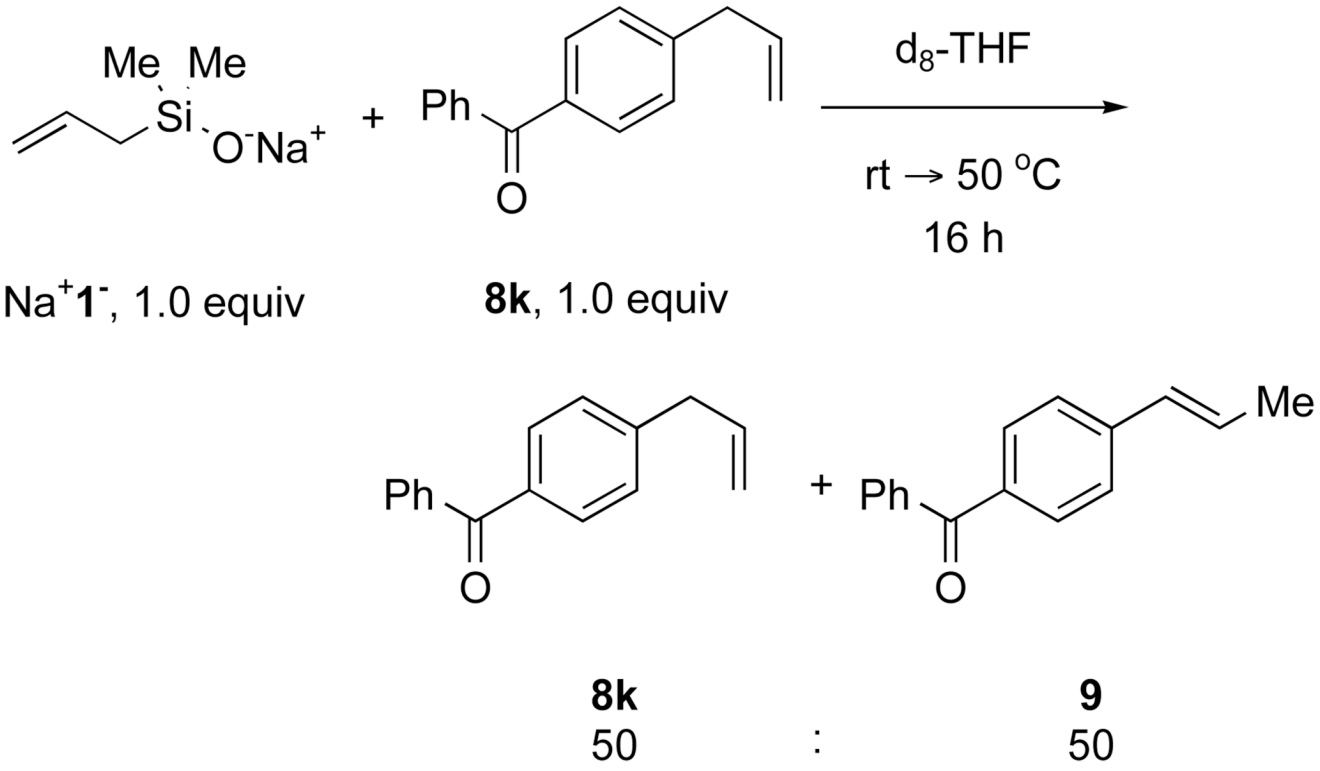
Scheme 2.



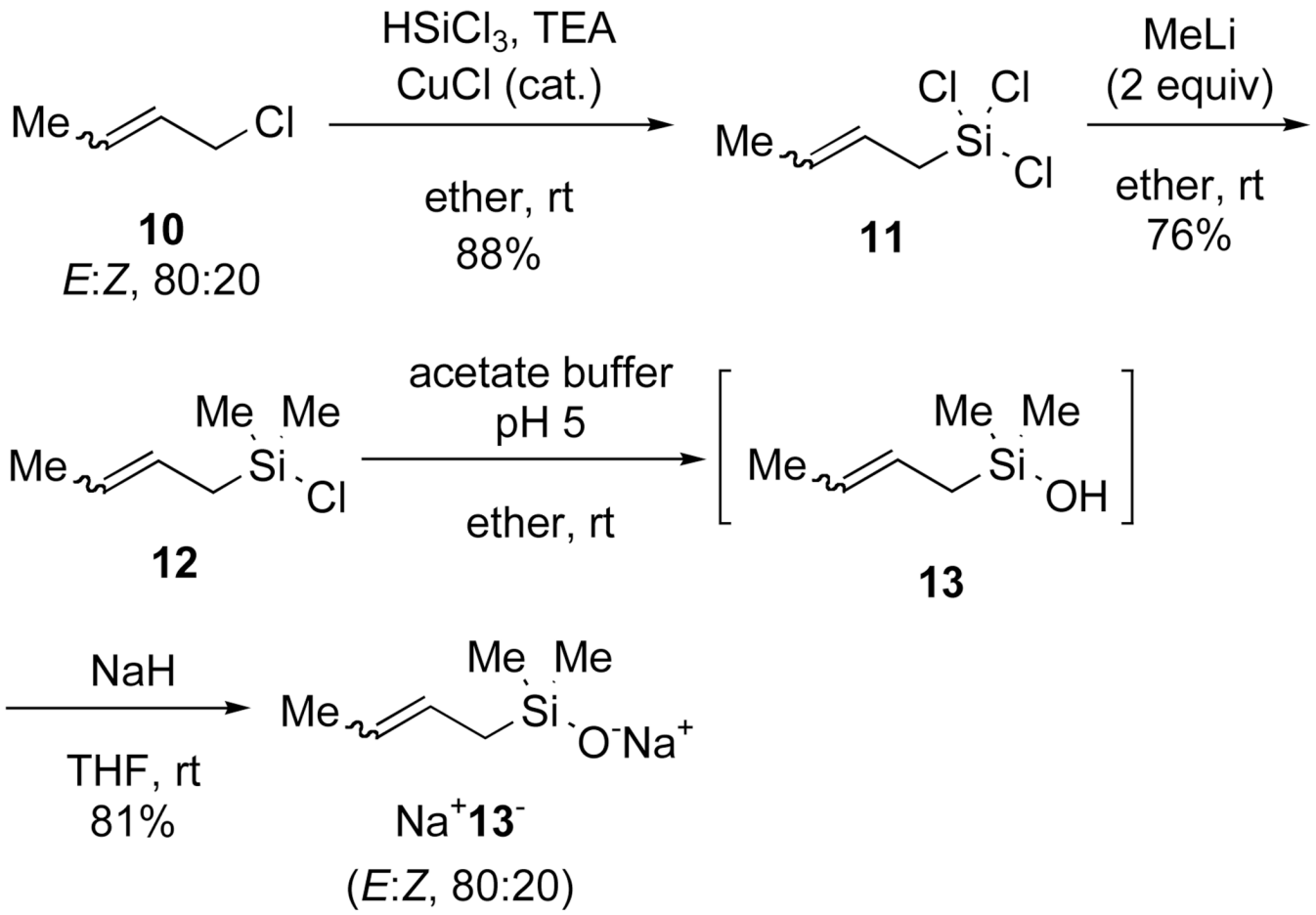
Scheme 3.



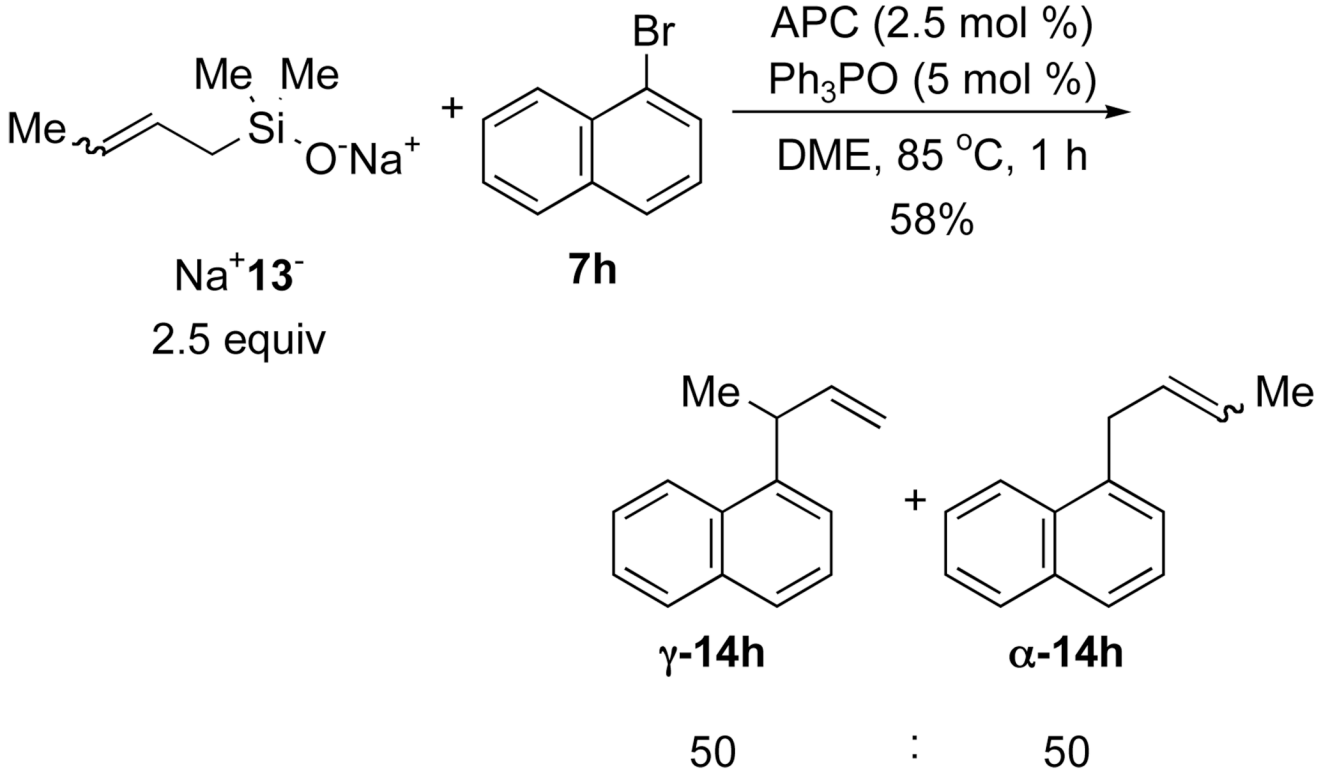
Scheme 4.



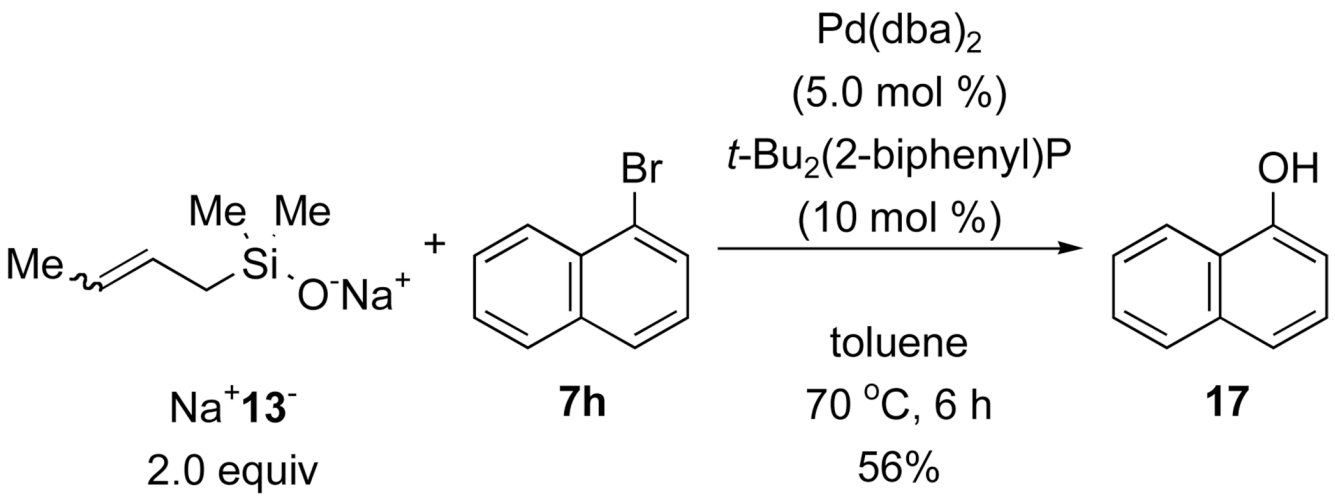
Scheme 5.



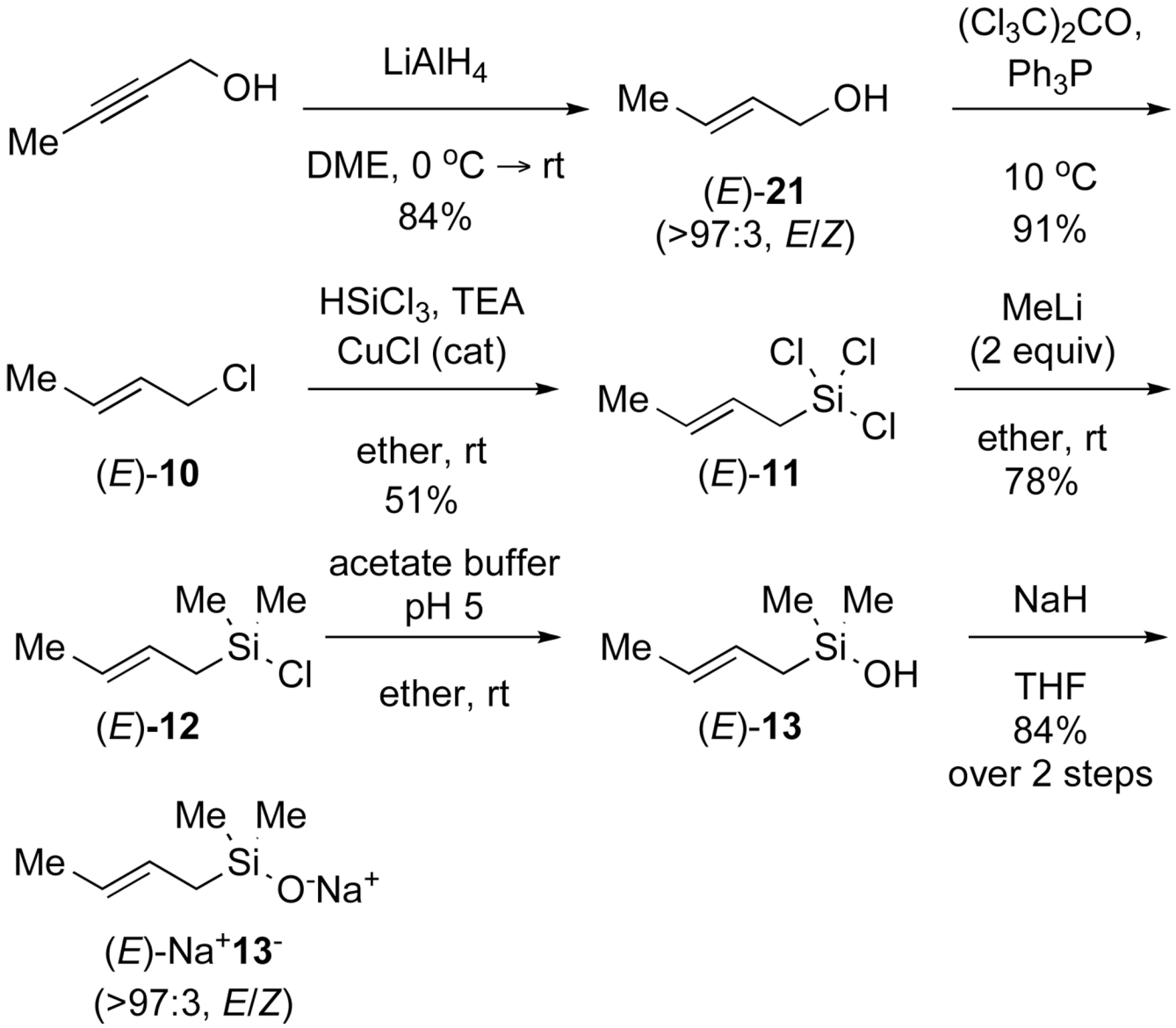
Scheme 6.



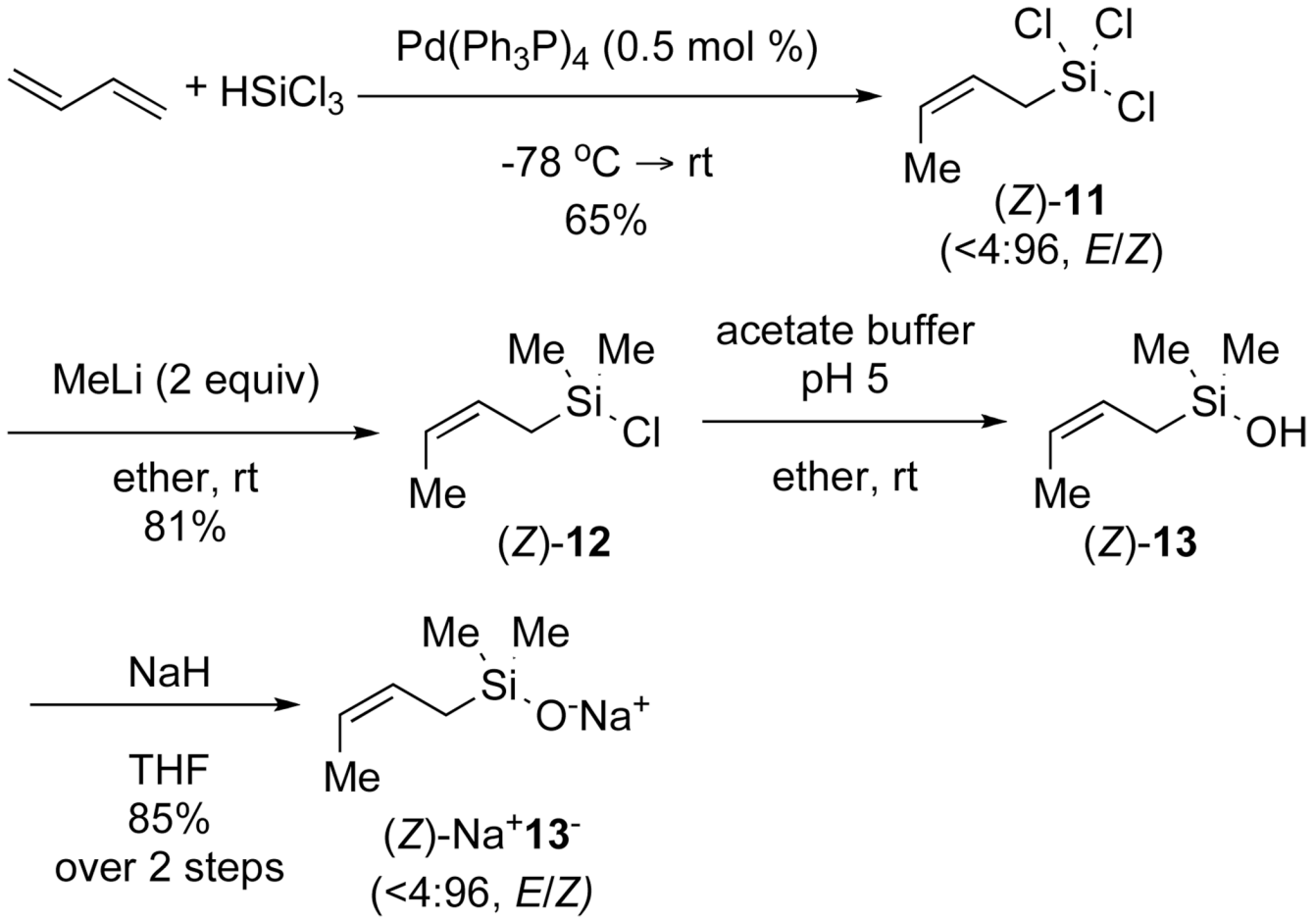
Scheme 7.



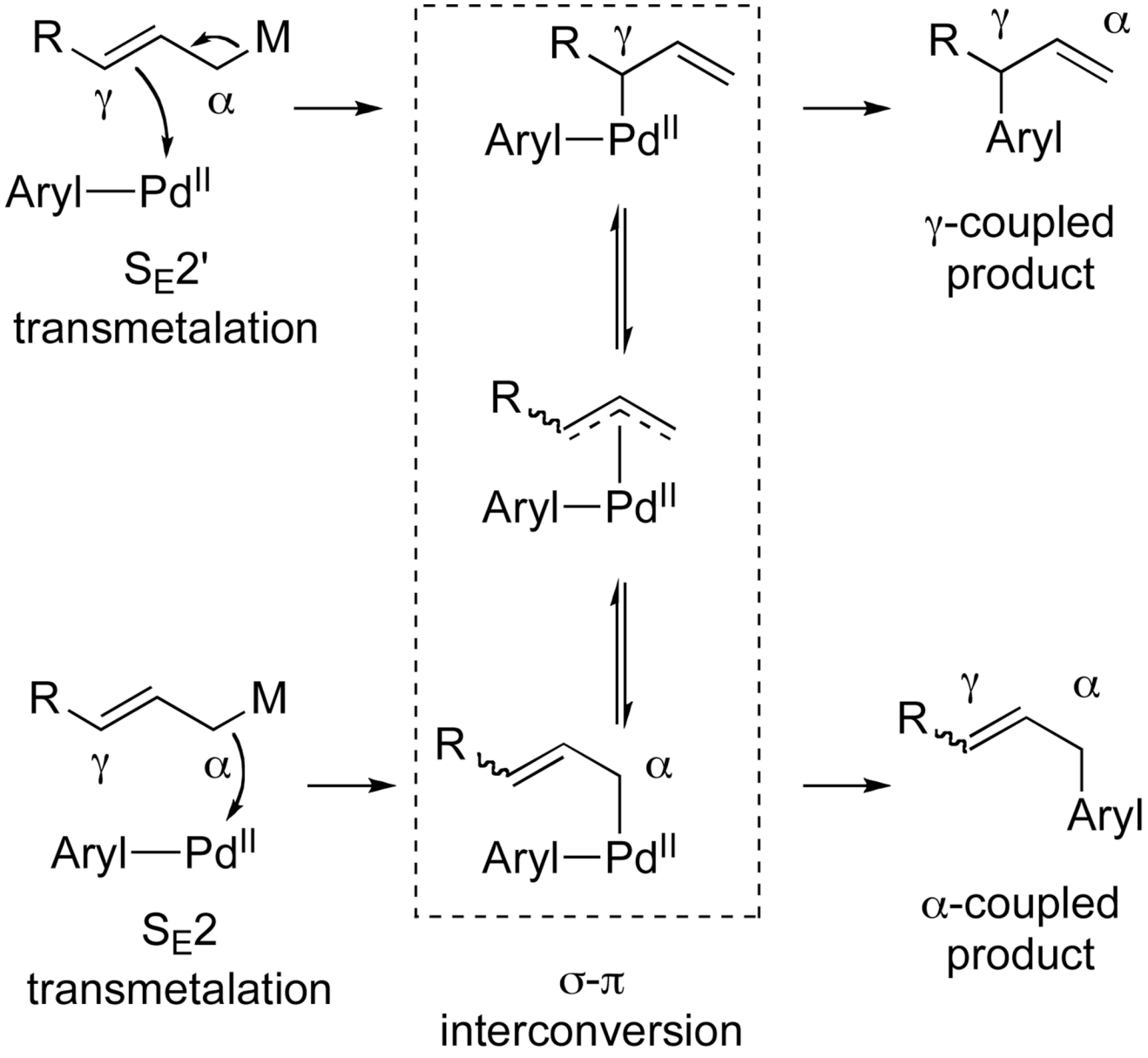
Scheme 8.



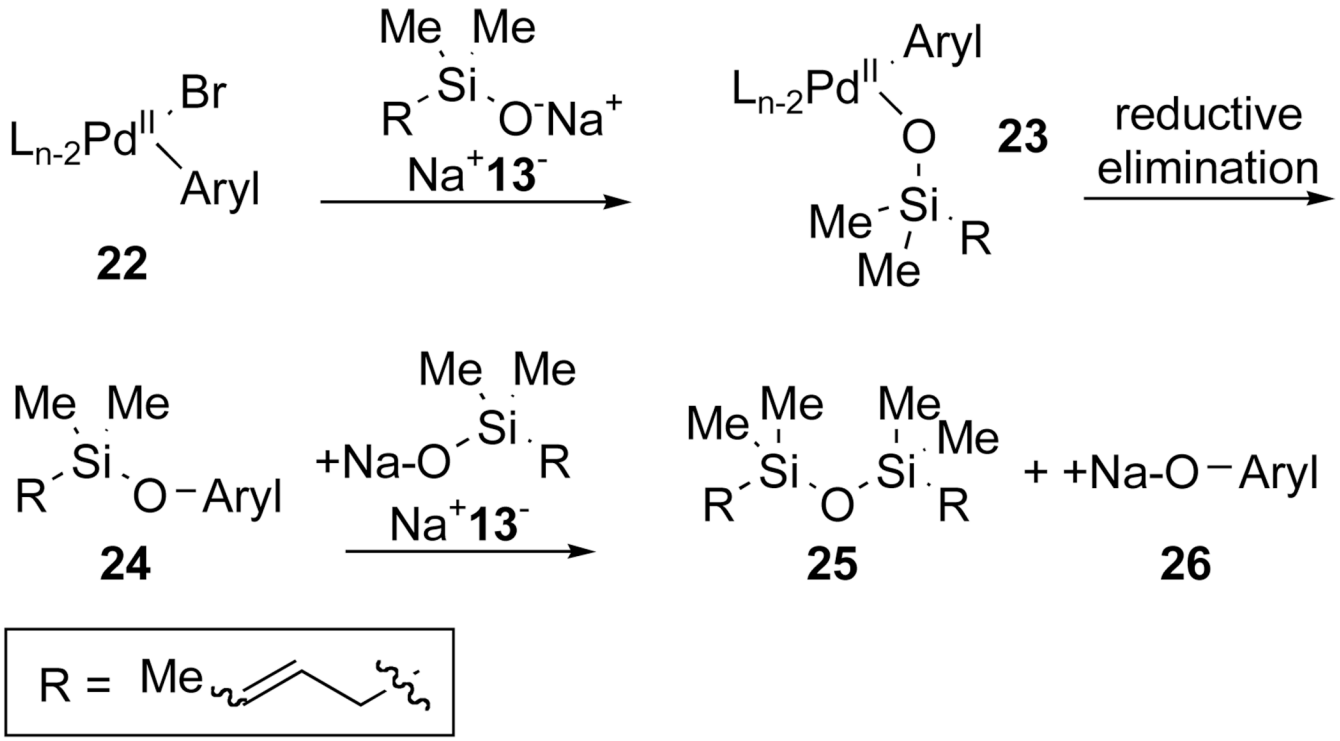
Scheme 9.



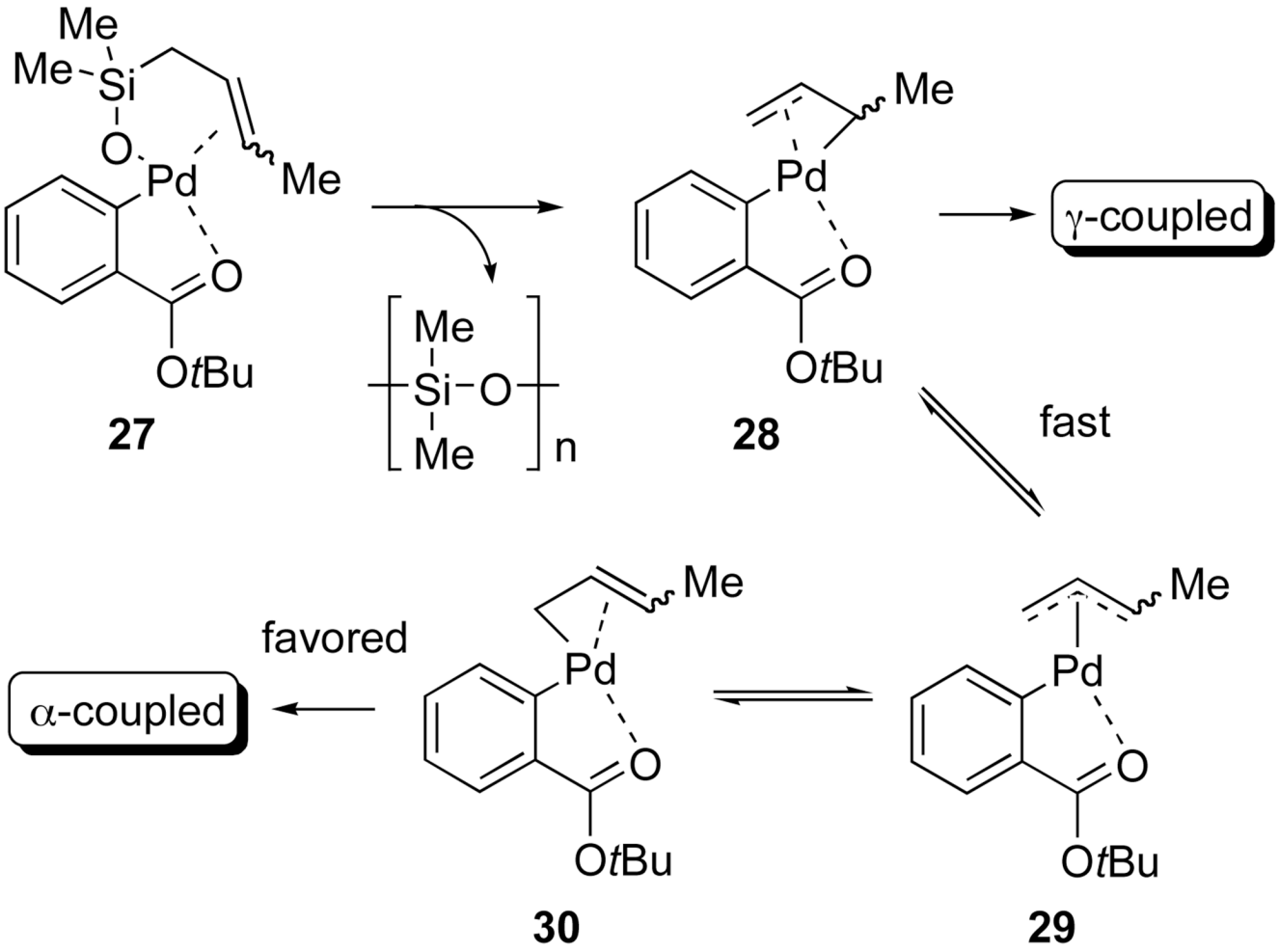
Scheme 10.



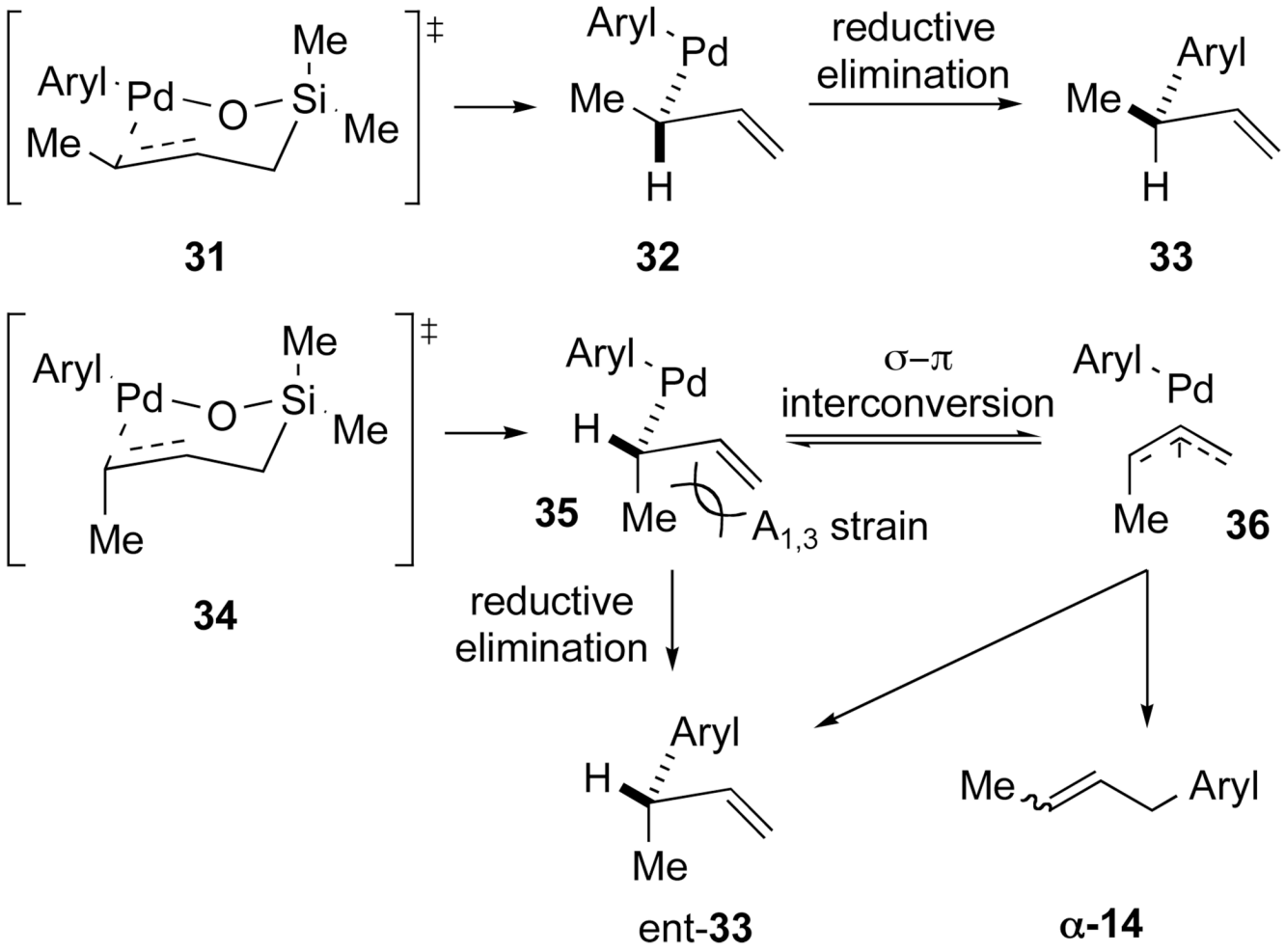
Scheme 11.



Scheme 12.



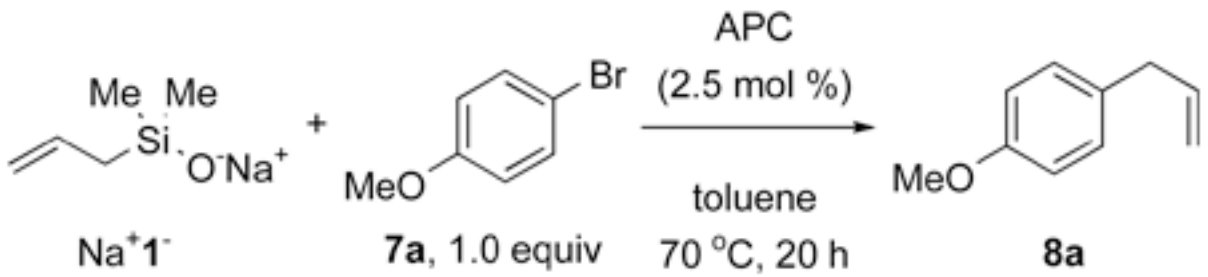
Scheme 13.



Scheme 14.

Table 1

Effect of Silanolate Loading on Allylation of 4-Bromoanisole[a]



entry	Na^+1^-, equiv	conversion[b], %	yield[c], %
1	1.3	87	51
2	2.0	100	80
3	2.6	100	84
4	3.0	100	93

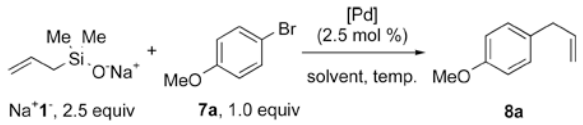
[a] Reactions performed on 0.4 mmol scale.

[b] Based on consumption of **7a**.

[c] Yield of **8a** by GC with respect to an internal standard (biphenyl).

Table 2

Bench-top Allylation of 4-Bromoanisole[a,b]



$Na^+\mathbf{1}^-$, 2.5 equiv **7a**, 1.0 equiv **8a**

entry	[Pd]	solvent	temp., °C	time, h	conversion[c], %	yield[d], %
1[e]	APC	toluene	70	20	10	5
2[f]	$Pd(dba)_2$	toluene	70	20	31	28
3[f]	$(Ph_3P)_4Pd$	toluene	70	20	72	59
4	APC	CH_3CN	70	20	trace	0
5	APC	THF	65	6	79	77
6	APC	DME	85	6	100	93
7	APC	dioxane	100	6	100	96

[a] Reactions performed on 0.5 mmol scale.

[b] The same batch of each reagent was used and all solvents were purified (see Supporting Information).

[c] Based on consumption of **7a**.

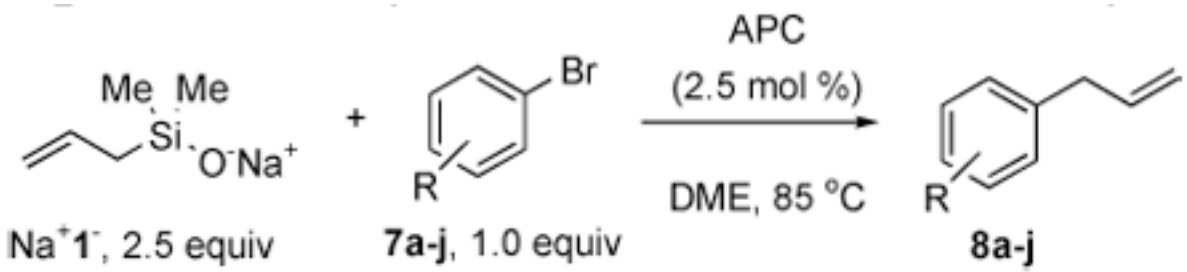
[d] Yield of **8a** by GC with respect to an internal standard (biphenyl).

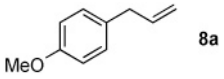
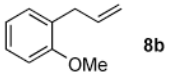
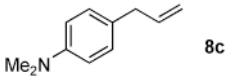
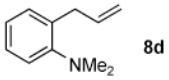
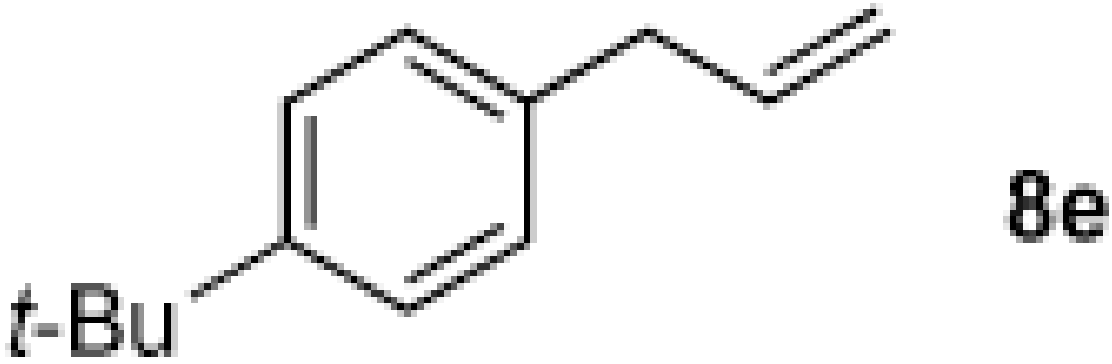
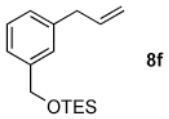
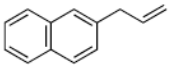
[e] Average of 3 experiments.

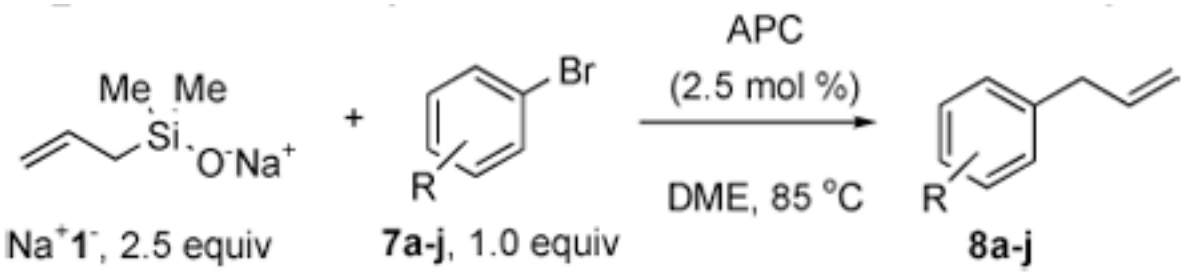
[f] 5.0 mol % catalyst used.

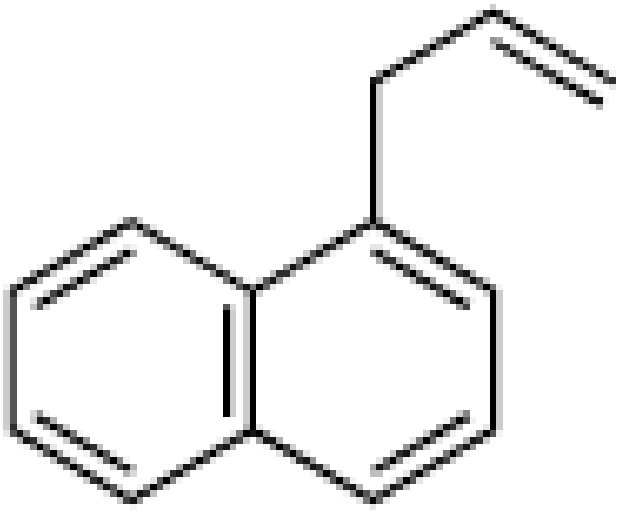
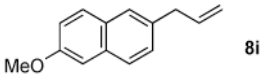
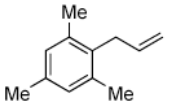
Table 3

Preparative Allylations of Substituted Aryl Bromides[a]



entry	product	time, h
1	 **8a**	3
2[c]		3
3	 **8b**	12
4	 **8c**	7
5	 **8d**	12
6	 **8e**	9
7	 **8f**	4
8	 **8g**	9



entry	product	time, h
9	 8h	2
10	 8i	6
11[d]	 8j	7

[a] Reactions performed on 1.0 mmol scale.

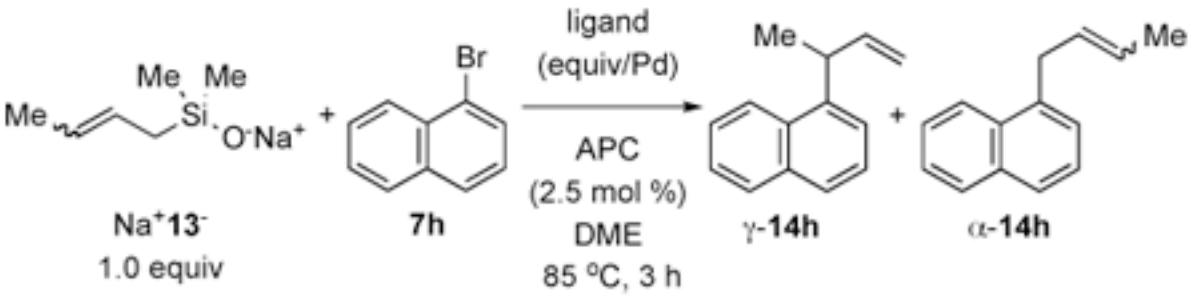
[b] Yields of isolated, purified products.

[c] 3.0 equiv of $Na^{+}\mathbf{1}^{-}$ were used.

[d] Dioxane at 100 °C, 1.0 equiv/Pd of Ph3PO and 5.0 equiv of $Na^{+}\mathbf{1}^{-}$ were used.

Table 4

Effect of Ligand on Crotylation of 1-Bromonaphthalene[a]



entry	ligand	ligand, equiv/Pd	conversion[b], %	(γ:α)[b]
1[c]	none	N/A	82	1.3:1
2	Ph_3P	2.0	58	1.7:1
3	Cy_3P	1.0	62	1.1:1
4[c]	Ph_3As	2.0	100	1.5:1
5	dppp	1.0	53	1.4:1
6	Dppf	1.0	73	1.4:1
7	BINAP	0.5	85	1:1.1
8	Josiphos	0.5	82	1:1.1

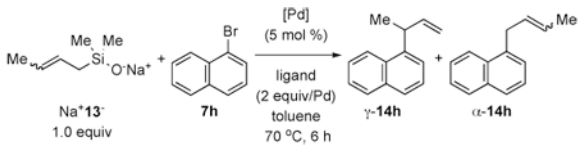
[a] Reactions performed on 0.25 mmol scale.

[b] Ratio of GC peak areas of the crude reaction mixture.

[c] Average of 2 experiments.

Table 5

Effect of Palladium Source on Crotylation of 1-Bromonaphthalene[a]



entry	[Pd]	ligand	conversion [b], %	(γ:α)[b]
1[c]	$PdCl_2$	Ph_3P	0	N/A
2[c]	$PdBr_2$	Ph_3P	12	2.1:1
3	$Pd(OAc)_2$	Ph_3P	58	2.5:1
4	$(t\text{-}Bu_3P)_2Pd$	none	59	2.3:1
5	**15**	none	100	4.7:1
6	PEPPSI	none	40	1.5:1
7[d]	$Pd_2(dba)_3$	Ph_3P	57	3.9:1
8	$Pd(dba)_2$	Ph_3P	59	5.0:1
9	$Pd(dba)_2$	none	47	10:1

[a] Reactions performed on 0.25 mmol scale.

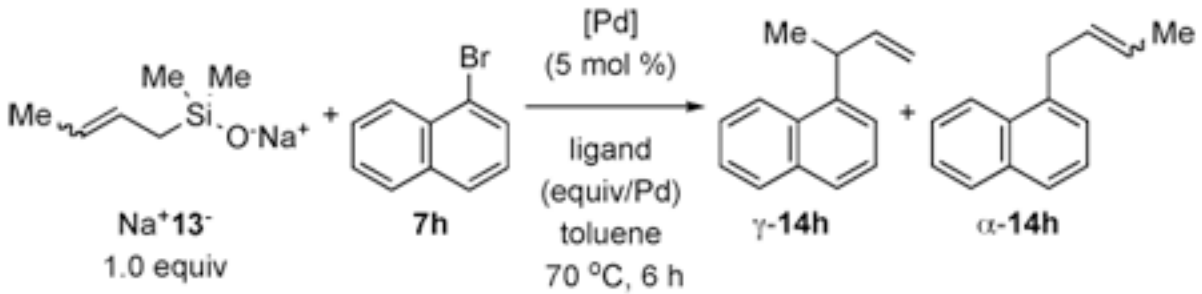
[b] Ratio of GC peak areas of the crude reaction mixture.

[c] At 20 h.

[d] 2.5 mol % catalyst used.

Table 6

Effect of Ligand on Crotylation Using $Pd(dba)_2$[a]



entry	ligand	ligand, equiv/Pd	conversion[b], %	yield γ[c], %	(γ:α)[d]
1	Ph_3As	4.0	75	40	2.0:1
2[e,f]	Cy_3P	1.0	47	16	6.3:1
3[e]	*o*-tol_3P	2.0	21	trace	N/A
4	dpppO	1.0	81	25	1.7:1
5[g,h]	*t*-Bu_2(2-biphenyl)P	2.0	55	trace	N/A
6[e]	**15**[i]	2.0	70	20	3.3:1
7	**16**[j]	1.0	29	14	2.2:1
8	cod	2.0	90	30	9.5:1
9	dba	2.0	77	40	16:1

[a] Reactions performed on 0.25 mmol scale.

[b] Conversion of **7h** by GC with respect to an internal standard (biphenyl).

[c] Yield of γ−**14h** by GC with respect to an internal standard (biphenyl).

[d] Ratio of GC peak areas of the crude reaction mixture.

[e] At 20 h.

[f] Reaction inhibition was observed when 2.0 equiv/Pd was used.

[g] At 3 h.

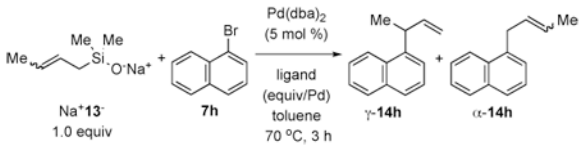
[h] Major product was 1-naphthol (15% at 3 h, 3% at 6 h).

[i] (2',6'-dimethoxy[1,1'biphenyl]-2-yldiphenthylphosphine (**15**)

[j] Diphenyl[2',4',6-tris(1-methylethyl)[1,1'-biphenyl]-2-yl]phosphine (**16**).

Table 7

Effect of Olefin Ligand on Crotylation Using $Pd(dba)_2$[a]



entry	ligand	ligand, equiv/Pd	conversion[b], %	yield γ[c], %	(γ:α)[d]
1	none	N/A	45	21	11:1
2	1,4-benzoquinone	2.0	72	32	9.1:1
3	1,4-benzoquinone	4.0	28	18	19:1
4	1,4-benzoquinone	8.0	13	11	61:1
5	norbornadiene	1.0	74	31	13:1
6	norbornadiene	2.0	28	8	15:1
7	norbornadiene	4.0	7	trace	N/A
8	norbornylene	6.0	50	25	9.6:1
9	tetramethylethylene	4.0	41	18	6.5:1
10	dicyclopentadiene	2.0	18	6	8.9:1
11	maleic anhydride	6.0	41	18	10:1
12	diallylcarbonate	2.0	69	35	7.0:1
13[e]	diallyl ether	2.0	29	8	6.6:1
14[e]	diallyl ether	4.0	28	12	19:1

[a] Reactions performed on 0.25 mmol scale

[b] Conversion of **7h** by GC with respect to an internal standard (biphenyl)

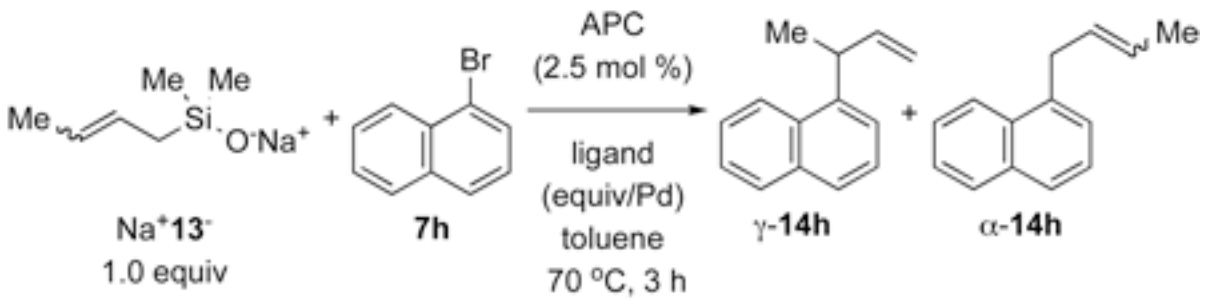
[c] Yield of γ-**14h** by GC with respect to an internal standard (biphenyl)

[d] Ratio of GC peak areas of the crude reaction mixture

[e] 2.0 equiv of silanolate was used.

Table 8

Effect of π-Acidic Ligands on Crotylation Using APC[a]



entry	Ligand	ligand, equiv/Pd	conversion[b], %	yield γ[c], %	(γ:α)[d]
1	dba	4.0	64	31	7.9:1
2	dba	6.0	71	28	9.4:1
3	dba	8.0	80	32	12:1
4	dba	10	85	45	18:1
5	**18**[f]	4.0	72	30	5.1:1
6	**19**[g]	4.0	61	26	12:1
7	cod	4.0	80	14	1.3:1
8	cod	8.0	54	20	3.8:1
9	norbornadiene	1.0	92	28	2.0:1
10	norbornadiene	2.0	20	trace	N/A
11	diallyl ether	4.0	59	18	6.2:1
12[e]	$(MeO)_3P$	4.0	100	51	3.6:1
13[e]	$(PhO)_3P$	4.0	100	25	6.0:1
14[e]	(*N*-pyrrolyl)$_3$P	2.0	100	39	3.4:1
15[e]	**20**[h]	4.0	45	16	1.2:1

[a] Reactions performed on 0.25 mmol scale.

[b] Conversion of **7h** by GC with respect to an internal standard (biphenyl).

[c] Yield of γ-**14h** by GC with respect to an internal standard (biphenyl).

[d] Ratio of GC peak areas of the crude reaction mixture.

[e] 2.0 equiv silanolate used.

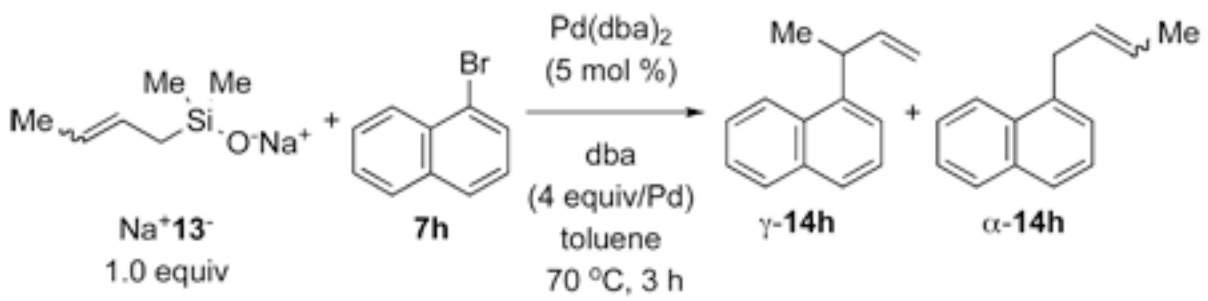
[f] *Bis*(4-methoxybenzylidene)acetone (**18**).

[g] *Bis*(4-trifluoromethylbenzylidene)acetone (**19**).

[h] 4,4-Dimethylcyclohexadienone (**20**).

Table 9

Effect of Silanolate Loading on Crotylation of 1-Bromonaphthalene



entry	$Na^{+}13^{-}$, equiv	conversion[b], %	yield γ[c], %	(γ:α)[d]
1	1.0	49	20	9.1:1
2	1.5	85	44	14:1
3	2.0	86	54	14:1
4	2.5	90	53	11:1
5	3.0	90	54	11:1

[a] Reactions performed on 0.25 mmol scale.

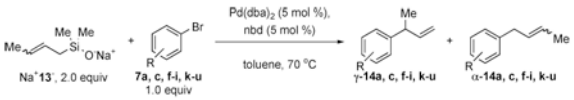
[b] Conversion of **7h** by GC with respect to an internal standard (biphenyl).

[c] Yield of γ−**14h** by GC with respect to an internal standard (biphenyl).

[d] Ratio of GC peak areas of the crude reaction mixture.

Table 10

Preparative Crotylation of Substituted Aryl Bromides[a]



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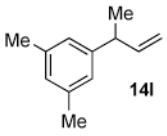
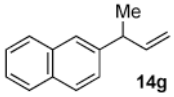
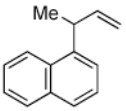
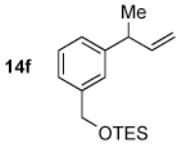
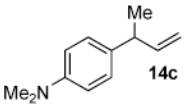
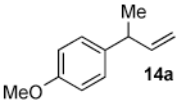
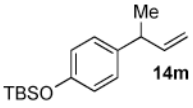
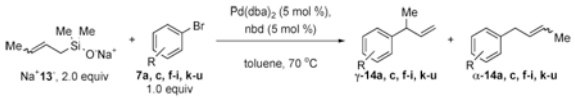
1	 **14l**	
2	 **14g**	
3	 **14h**	
4[d]		
5	 **14f** OTES	
6[e]	 **14c** Me_2N	
7[f]		
8[e]	 **14a** MeO	
9[f]		
10	 **14m** TBSO	



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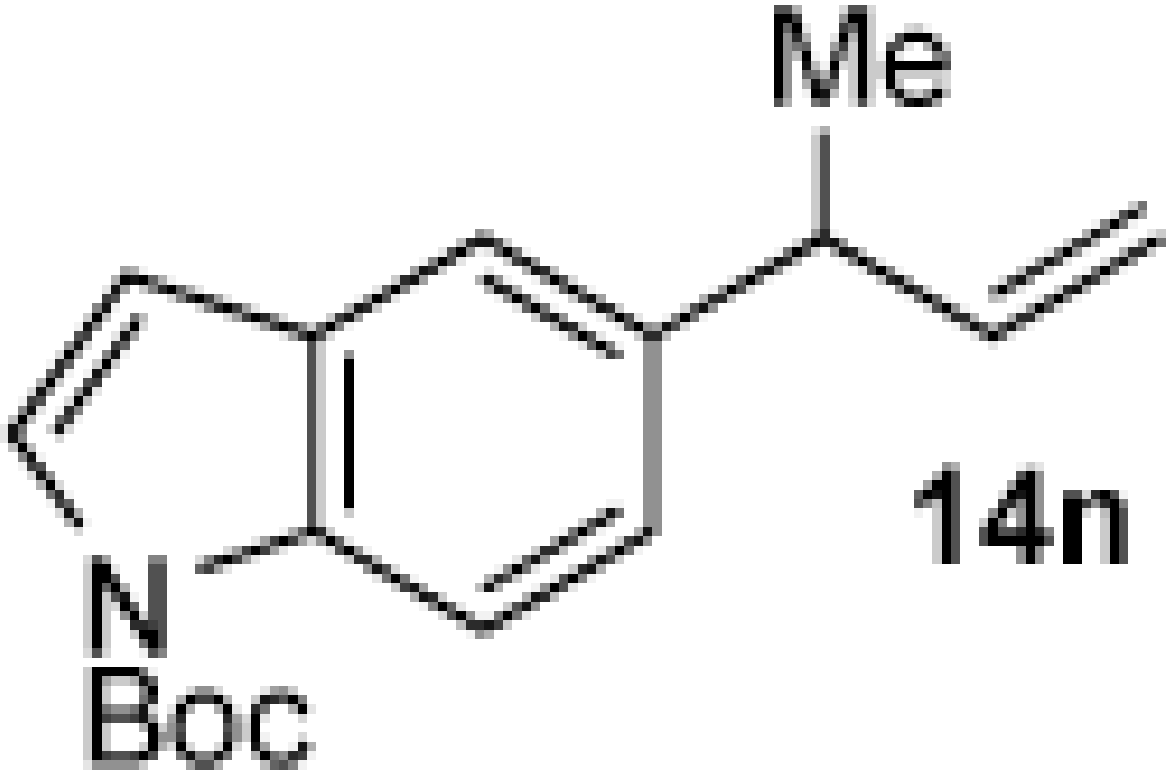
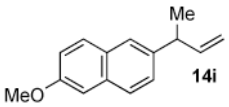
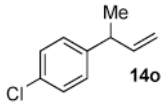
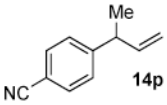
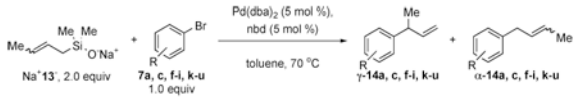
11		
12		
13		
14		



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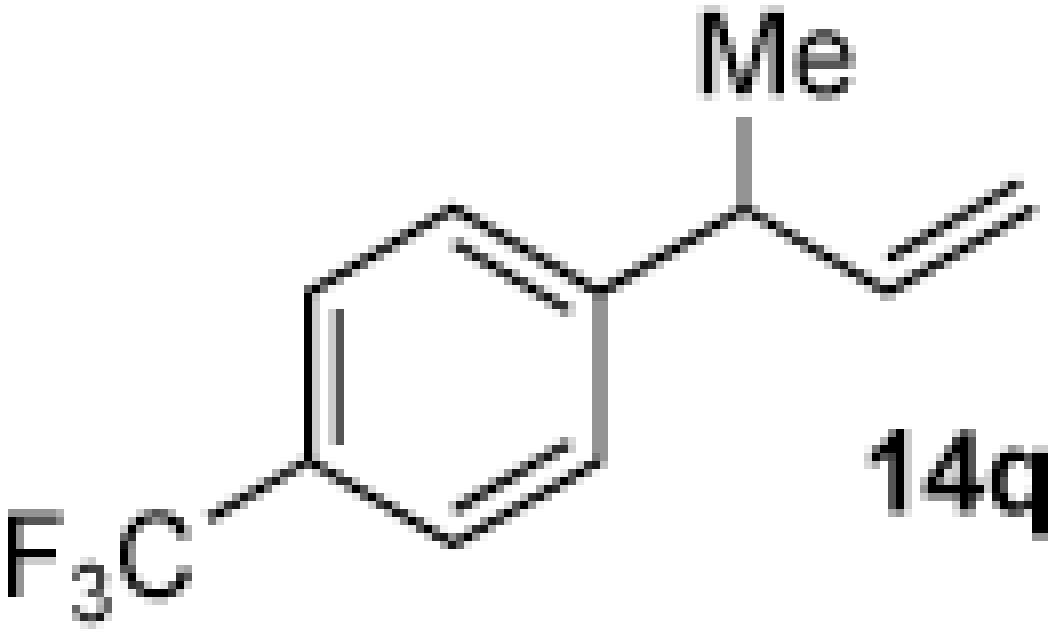
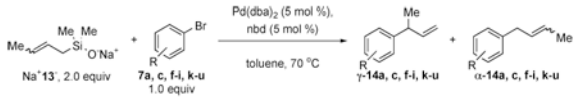
15		



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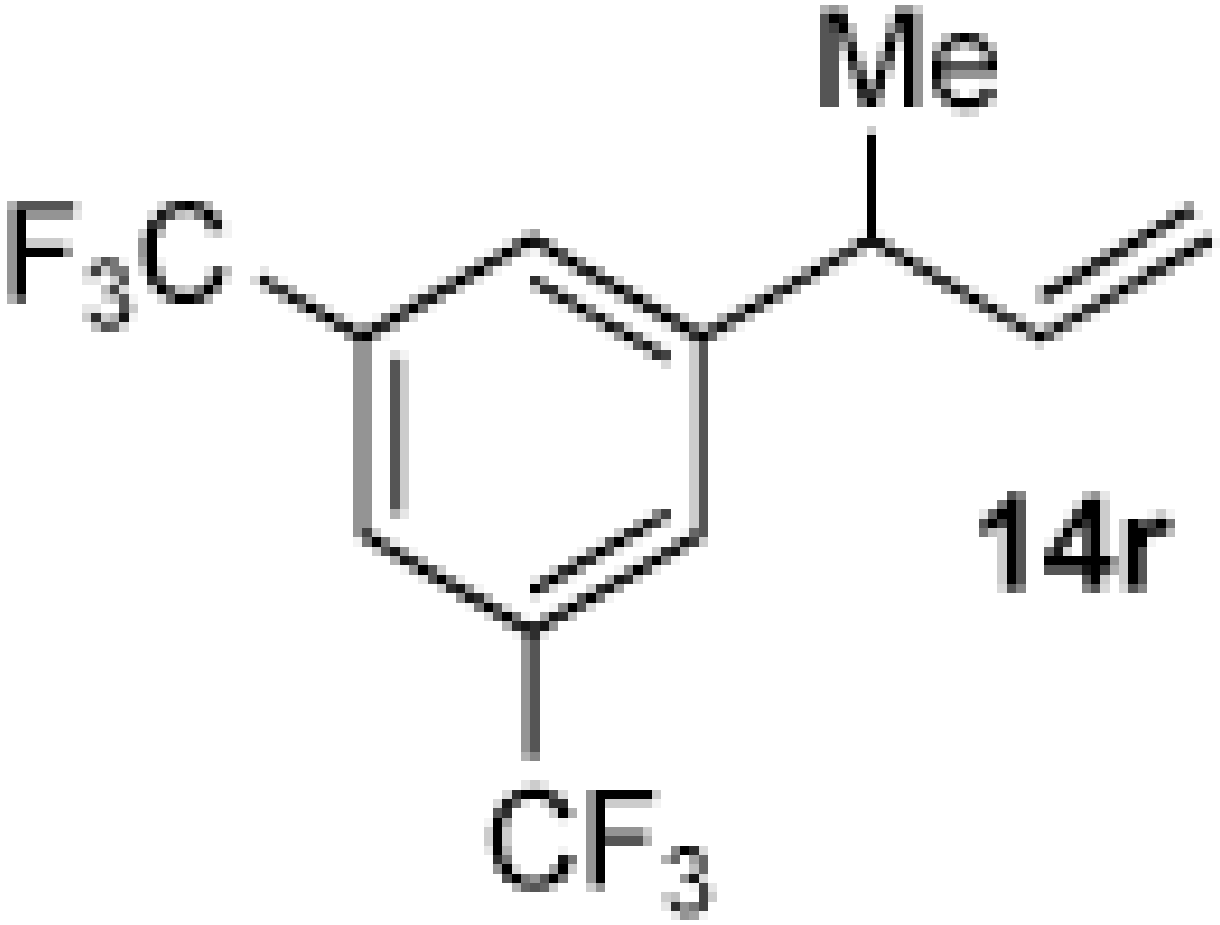
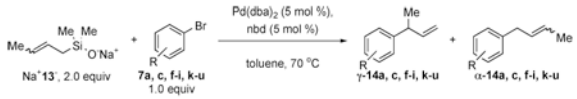
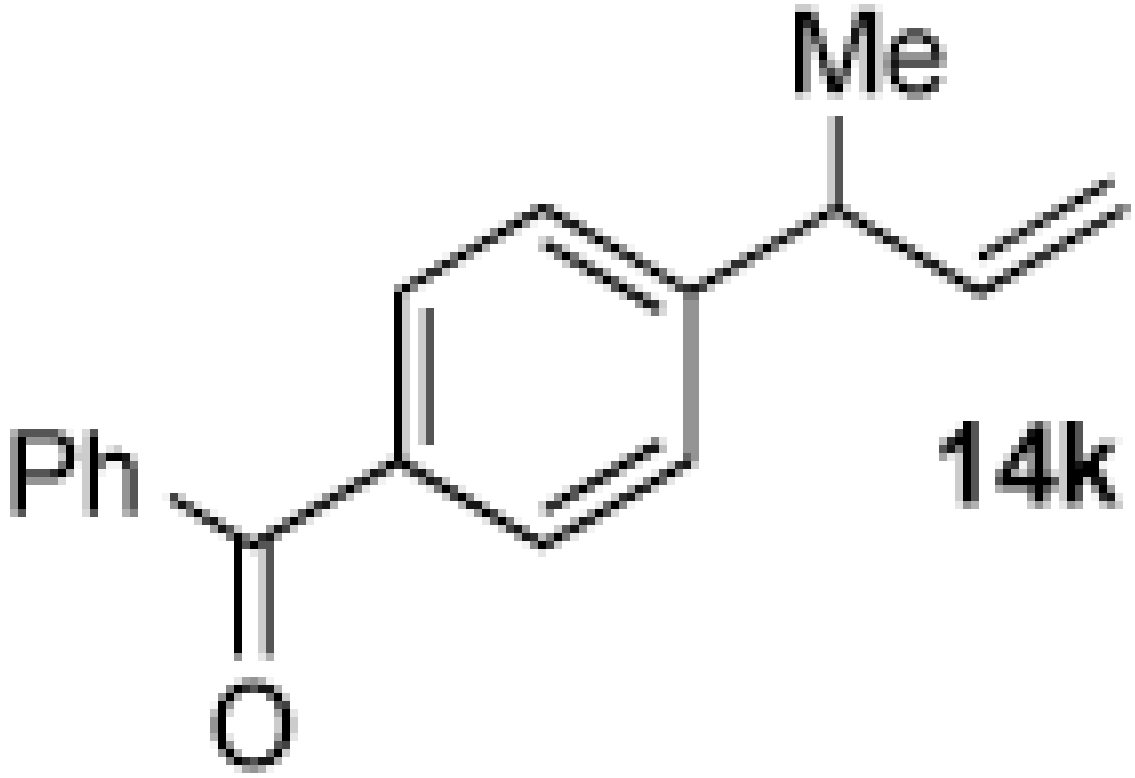
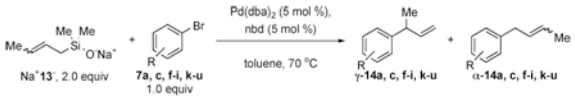
16		



entry	product	ti
17		



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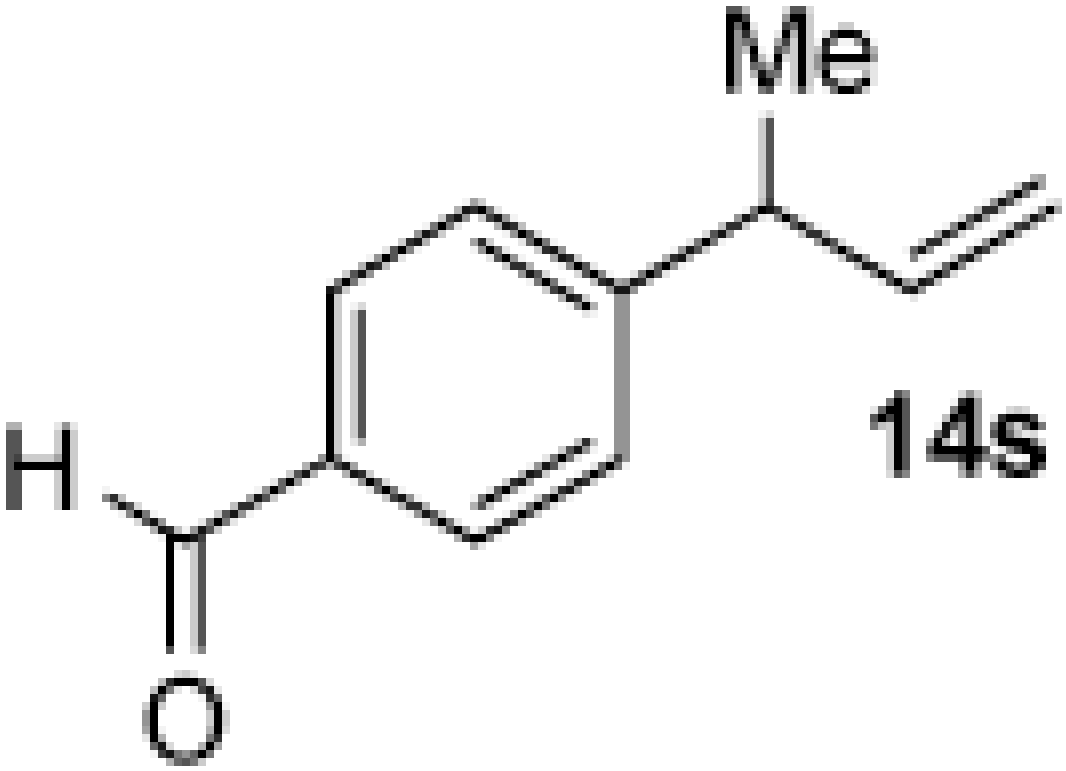
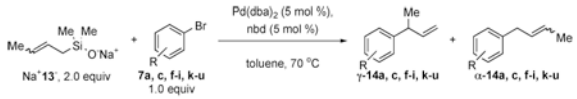
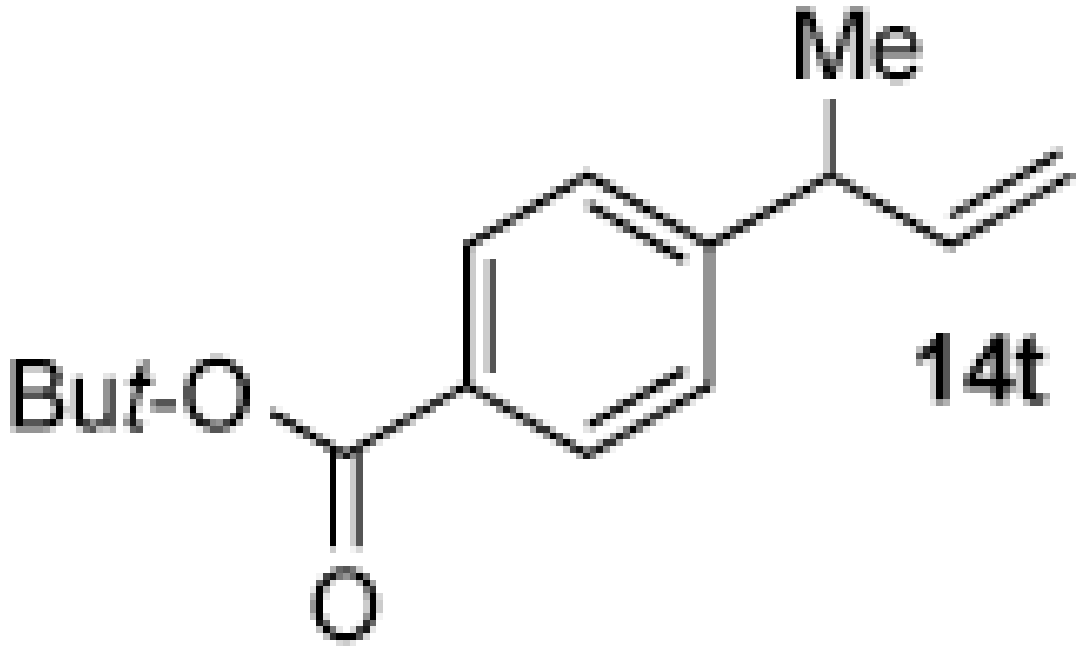
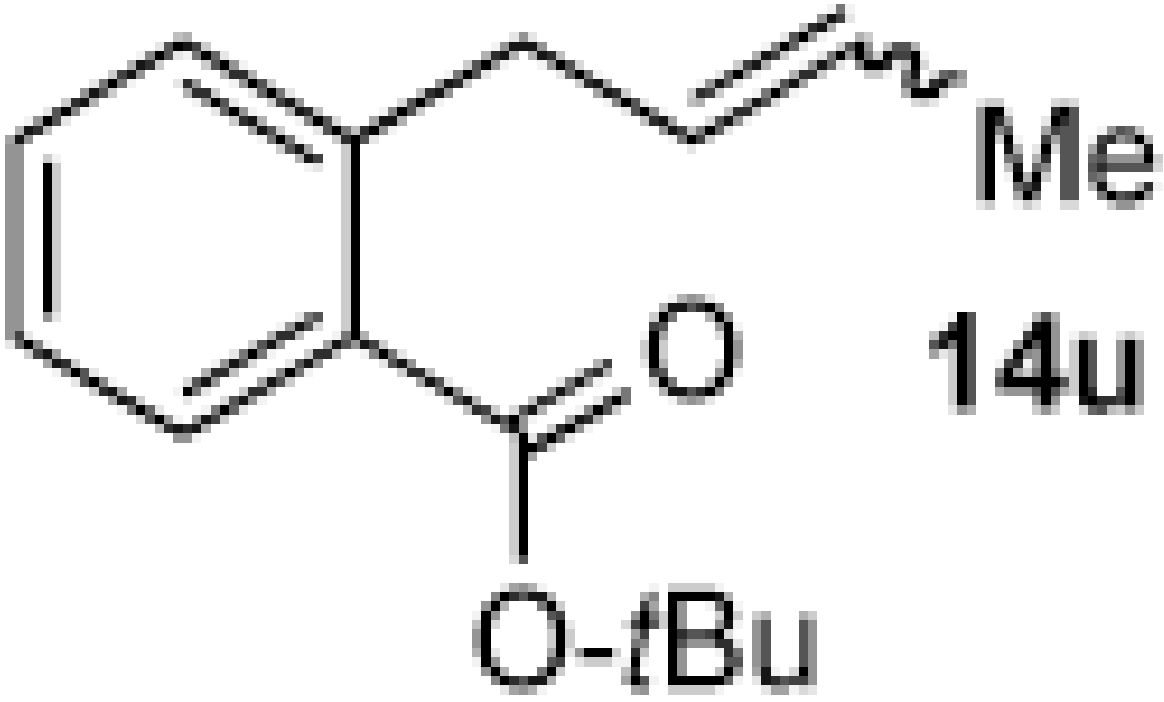
18		



entry	product	ti
19		
20		

[a] Reactions performed on 1.0 mmol scale.

[b] Yields of isolated, purified products.

[c] Ratio, γ:α, determined by GC analysis of purified products.

[d] 2.0 equiv Na^{+}**13**$^{-}$ used.

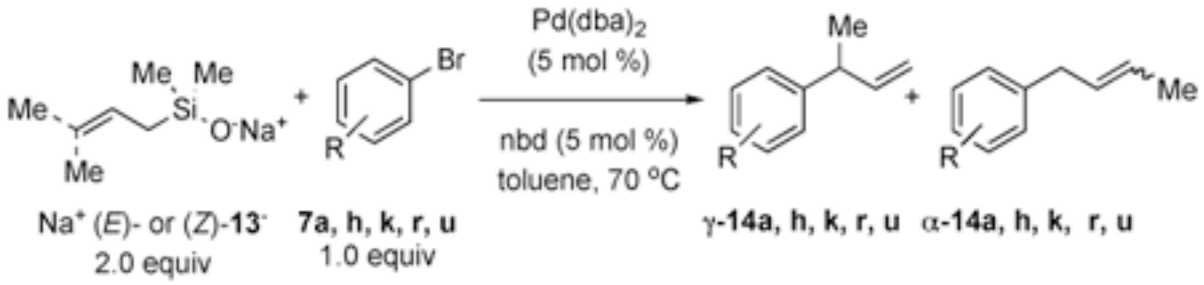
[e] Reaction run at 85 °C.

[f] Reaction run at 110 °C.

[g] Ratio, γ:α, determined by ^{1}H NMR analysis of purified product.

Table 11

Preparative Couplings with Geometrically Pure *E* and *Z* Silanolates



		olefin geometry of $Na^{+}13^{-}$, *E*/*Z*		
		80:20	**>97:3**	**<4:96**
entry	**product**	**yield[b], %(γ:α)[c]**	**yield[b], %(γ:α)[c]**	**yield[b], %(γ:α)[c]**
1	**14h**	50 (14:1)	51 (25:1)	51 (13:1)
2[d]	**14a**	46 (7.0:1)	46 (18:1)	59 (4.0:1)
3	**14k**	81 (14:1)	79 (24:1)	82 (11:1)
4	**14r**	62 (3.4:1)	74 (3.6:1)	68 (2.6:1)
5	**14u**	82 (1:2.5[e])	82 (1:2.5[f])	79 (1:2.5[g])

[a] Reactions performed on 1.0 mmol scale.

[b] Yields of isolated, purified products.

[c] Ratio determined by GC analysis of purified products.

[d] Reaction run at 110 °C.

[e] 8.3:1, *E*/*Z*.

[f] 8.4:1, *E*/*Z*.

[g] 8.4:1, *E*/*Z*.