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Raising the pK_a Limit of "Soft" Nucleophiles in Palladium-Catalyzed Allylic Substitutions. Application of Diarylmethane Pronucleophiles

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ABSTRACT: The Tsuji–Trost allylic substitution reaction provides a useful and efficient approach to construct C–C bonds between sp^3-hybridized carbons. The widely accepted paradigm for classifying the mode of attack of nucleophiles on palladium π-allyl intermediates in the Tsuji–Trost reaction is based on the pK_a of the pronucleophile: (1) stabilized or "soft" carbon nucleophiles and heteroatom nucleophiles (e.g., pronucleophiles with pK_a's < 25), and (2) unstabilized or "hard" nucleophiles (those from pronucleophiles with pK_a's > 25). One of the keys to the continuing development of allylic substitution processes remains broadening the scope of "soft" nucleophiles. Herein we report a general method for the room temperature Pd-catalyzed allylic substitution with diarylmethane derivatives (pK_a's up to 32). The synthetic significance of the method is that it provides a rapid access to products containing allylated diarylmethyl motifs. The method is general for a wide range of nucleophiles derived from diarylmethanes and heterocyclic derivatives. A procedure for the Pd-catalyzed allylic substitutions to afford diallylation products with quaternary centers is also described. With triarylmethanes and, alkylated diarylmethanes the corresponding allylated products are isolated. We anticipate that the described method will be a valuable complement to the existing arsenal of nucleophiles in Pd-catalyzed allylic substitutions. Mechanistic studies show that the nucleophile derived from diphenylmethane undergoes external attack on π-allyl palladium species under our reaction conditions. This unexpected observation indicates that diarylmethane derivatives behave as "soft" or stabilized nucleophiles. The results of this study indicate that the cutoff between "soft" and "hard" nucleophiles should be raised from a pronucleophile pK_a of 25 to at least 32.

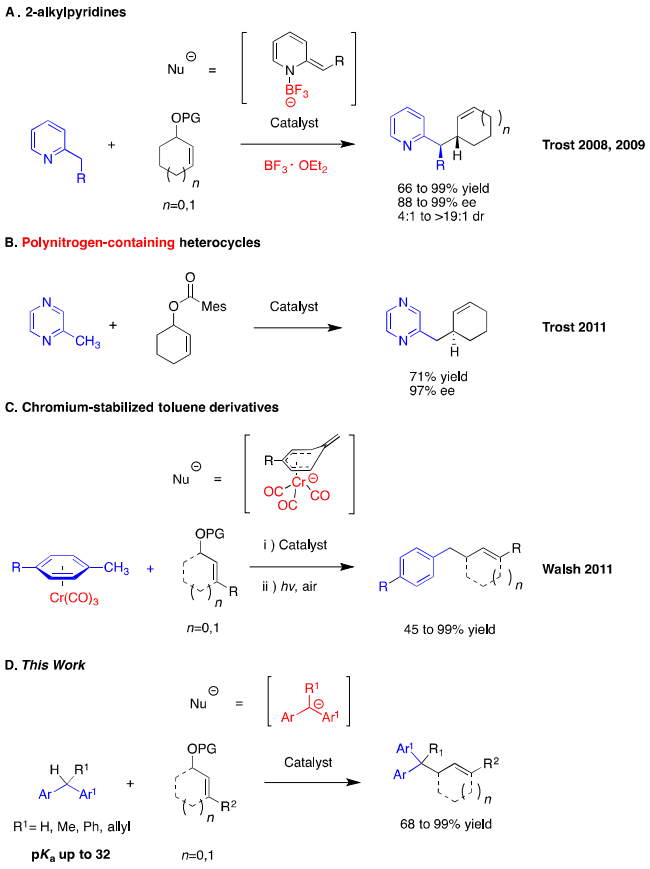
1. INTRODUCTION

Palladium-catalyzed C–C bond-forming reactions are among the most important and well-developed processes in modern organic chemistry.[1-10] Of these, the Tsuji–Trost allylic substitution reaction provides a useful and efficient approach to construct C–C bonds between sp^3-hybridized carbons. As a result, it has been widely used to synthesize natural products and bioactive molecules. [11-17] The widely accepted paradigm for classifying the mode of attack of nucleophiles on transition metal η^3-π-allyl intermediates in the Tsuji–Trost reaction is based on the pK_a of the pronucleophile.[18] Nucleophiles are divided into two classes: 1) stabilized or "soft" carbon nucleophiles and heteroatom nucleophiles (e.g., enolates and those from pronucleophiles with pK_a's < 25), and (2) unstabilized or "hard" nucleophiles (those from pronucleophiles with pK_a's > 25). The distinction between these two classes is "soft" nucleophiles directly attack the π-allyl moiety while "hard" nucleophiles first attack the metal center (*via* transmetallation) before bond formation with the allyl group. Importantly, these two pathways lead to distinct stereochemical outcomes (soft nucleophiles result in net retention in the Tsuji–Trost allylic substitution whereas hard nucleophiles react by single inversion). The scope of "soft" nucleophiles has received significant attention in asymmetric catalysis,[11,13,14,19] although non-enantioselective Pd-catalyzed allylic substitution with "hard" nucleophiles are also known.[20-22]

One of the keys to the continuing development of allylic substitution processes remains broadening the scope of "soft" nucleophiles. With this in mind, Trost and co-workers increased the reach of "soft" nucleophiles in the allylic substitution with use of 2-picoline-derived nucleophiles (pK_a = 34)[23]. Essential to their success was to increase the acidity of the 2-picoline CH_3. This was accomplished by BF_3 coordination to the pyridine nitrogen to facilitate deprotonation. The resulting "softened" nucleophile was successfully employed in Pd-catalyzed asymmetric allylic alkylation (AAA, Scheme 1A).[18,24] The same group later reported no such activation was necessary with more acidic heterocycles, including pyrazine, pyrimidine, pyridazine, quinoxaline, and benzimidazole derivatives. (Scheme 1B).[25]

Our group recently introduced a strategy to employ toluene derivatives (RC_6H_4–CH_2R', pK_a ~ 44)[26] as "soft" pronucleophiles in Pd-catalyzed allylic substitution reactions using $Cr(CO)_3$ to increase the acidity of the benzylic C–H's (Scheme 1C).[27] The drawback of this approach is the stoichiometric use of chromium. We, therefore, set out to develop benzylic nucleophiles in the absence of chromium activating groups.

Scheme 1. Palladium-Catalyzed Benzylic Allylations



Application of unactivated diarylmethane derivatives as pronucleophiles in Pd-catalyzed allylic substitution reactions are unknown, but would have significant potential in medicinal chemistry. Hundreds of bioactive drug-like molecules contain allylated diarylmethyl motifs (Figure 1), with applications in treatment of breast cancer[28], inhibitor of HIV protease[29], blocker of human T-cells[30] and antagonist of the thyroid hormone receptor,[31] among others. Given these important applications, we set out to introduce diarylmethane-derived nucleophiles for the Pd-catalyzed allylic substitution. To achieve this objective, it is essential to find conditions to deprotonate diarylmethane derivatives that are compatible with the catalyst and substrates. Based on our previous studies on deprotonative cross-coupling processes (DCCP) using diarylmethane derivatives,[32-35] we hypothesized that diarylmethane derivatives could be reversibly deprotonated *in situ* by $MN(SiMe_3)_2$ (M = Li, Na, K) under mild conditions. These conditions would be more amenable to catalysis than deprotonation under traditional conditions with *n*-BuLi at low temperature.[36] Herein we report an approach to the room temperature Pd-catalyzed allylic substitution with diarylmethane derivatives (Scheme 1D). This method enables rapid access to a variety of allylated products, including heteroaryl-containing derivatives as well as molecules bearing quaternary centers. The mild reaction conditions that have been identified employ $MN(SiMe_3)_2$ at room temperature and a Pd catalyst based on van Leeuwen's Xantphos ligand.[37] Surprisingly, stereochemical studies indicate that nucleophiles derived from diarylmethane derivatives (pK_a = 25–33)[26,38] *behave as "soft" nucleophiles*, significantly extending the range of nucleophiles undergoing the double inversion mechanism in the Tsuji–Trost allylic substitution.

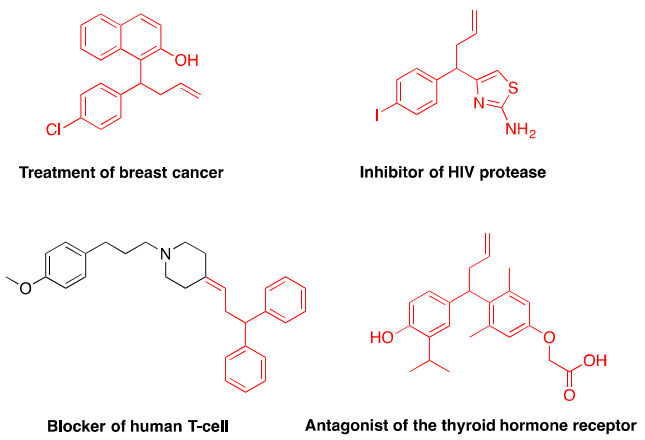
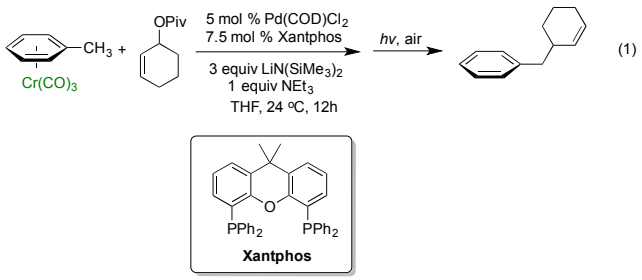


Figure 1. Selected bioactive compounds containing the allylated diarylmethyl motif.

2. RESULTS AND DISCUSSION

As mentioned above, we recently disclosed a Pd–Xantphos catalyst system to promote the allylic substitution with $Cr(CO)_3$-stabilized toluene-derived nucleophiles (eq 1).[27] We hypothesized the reaction conditions in eq 1 would be a good starting point for allylic substitution with diarylmethanes and related pronucleophiles.



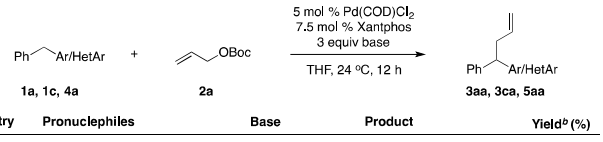
2.1. Development and Optimization of Palladium-Catalyzed Allylic Substitution with Diarylmethanes.

Given the perceived challenge to the application of diphenylmethane (pK_a = 32.2)[39] in allylic substitutions, we initiated our studies with the more acidic 2-benzylpyridine (**1a**, pK_a = 28.2)[38] under the reaction conditions in eq 1. The desired product **3aa** was formed in 80% assay yield (Table 1, entry 1). Switching the base to $NaN(SiMe_3)_2$ led to **3aa** in 99% assay yield (entry 2). The additive NEt_3, which proved very useful in eq 1, was not necessary for the Pd-catalyzed allylic substitution with 2-benzylpyridine (entry 3 vs 2). The allylic substitution product formed with 2-benzylpyridine was isolated in 99% yield.

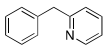
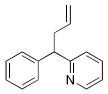
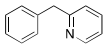
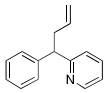
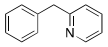
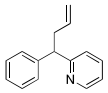
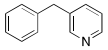
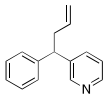
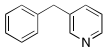
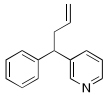
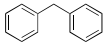
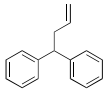
We next sought to increase the pK_a of the pronucleophile. The less acidic 3-benzylpyridine (**1c**) (pK_a = 30.1),[38] however, led to only 27% assay yield (entry 4). We increased the assay

yield of **3ca** to 70% by using the more reactive base, $KN(SiMe_3)_2$ (entry 5). Unfortunately, further decreasing the acidity of the pronucleophile was challenging: using diphenylmethane (**4aa**, pK_a = 32.3)[39] gave desired product **5aa** in only 10% assay yield (entry 6). We next set out to optimize the reaction conditions for Pd-catalyzed allylic substitution with pronucleophiles with pK_a's >30, such as diphenylmethane.

Table 1. Preliminary Results of Allylic Substitution Reactions[a]



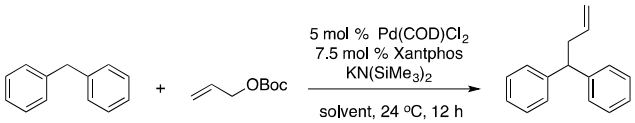
1a, 1c, 4a — 2a — 3aa, 3ca, 5aa

Entry	Pronuclephiles		Base	Product		Yield[b] (%)
1[d]		1a	$LiN(SiMe_3)_2$		3aa	80
2[d]		1a	$NaN(SiMe_3)_2$		3aa	(99[c])
3		1a	$NaN(SiMe_3)_2$		3aa	(99[c])
4		1c	$NaN(SiMe_3)_2$		3ca	27
5		1c	$KN(SiMe_3)_2$		3ca	70
6		4a	$KN(SiMe_3)_2$		5aa	10

[a] Reaction conducted on a 0.1 mmol scale with 1 equiv of pronucleophile and 2 equiv of **2a** at 0.1 M. [b] Yield determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Isolated yield after chromatographic purification. [d] 1 equiv of NEt_3.

From the results in Table 1, we hypothesized that the generation of the deprotonated diphenylmethane was problematic, and that choice of base would significantly impact the conversion. Since the traditional protocols preparing allylated diarylmethanes require strong bases (such as *n*-BuLi) at low temperature[36] or under other harsh reaction conditions[40], we limited ourselves to use of $KN(SiMe_3)_2$ as the strongest base in this study. We then screened different ethereal solvents (THF, 2-methyl THF, 1,4-dioxane, DME and CPME) and found that DME was the leading solvent of those examined (Table 2, entry 2, see the Supporting Information for details). Another important variable in optimizing Pd-catalyzed allylic substitution with diphenylmethane is the ratio of reagents. We observed decomposition of allyl *tert*-butyl carbonate **2a** during the reaction. Increasing **2a** to 3 equiv led to significant improvement in yield (entry 3). In addition, increasing the concentration of base led to higher concentrations of the nucleophile and improved yields (entries 4–5). Under these conditions, the allylic substitution product **5aa** was obtained in 95% isolated yield in DME with diphenylmethane **4a** as the limiting reagent, 5 equiv of $KN(SiMe_3)_2$ and 3 equiv of the allyl electrophile **2a**. The yield dropped if the equivalence of **2a** (entry 6) or the catalyst loading (entry 7) were decreased. With the optimized conditions in Tables 1 and 2, we examined various benzylic heterocycles and diarylmethanes as pronucleophiles in the allylic substitution.

Table 2. Optimization of Allylic Substitution with Diphenylmethane **4a**[a]



4a — 2a — 5aa

Entry	Ratio (4a:base:2a)	Solvent	yield[b] (%)
1	1:3:2	THF	10
2	1:3:2	DME	55
3	1:3:3	DME	79
4	1:4:3	DME	88
5	1:5:3	DME	(95[c])
6	1:5:2	DME	62
7[d]	1:5:3	DME	68

[a] Reaction conducted on a 0.1 mmol scale at 0.1 M. [b] Yield determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Isolated yield after chromatographic purification. [d] 2.5 mol % $Pd(COD)Cl_2$/3.75 mol % Xantphos.

2.2. Scope of Heterocyclic Diarylmethanes in Palladium-Catalyzed Allylic Substitution.

Based on the optimization process above, we anticipated that the choice of base would be critical to expand the scope of pronucleophiles and that each substrate class might require reexamination of bases. We first evaluated the scope of heterocyclic diarylmethanes as pronucleophiles in Pd-catalyzed allylic substitution (Table 3). The diarylmethane derivatives containing heterocycles are interesting targets in medicinal chemistry.[41-43] Our method provides a rapid access to the heteroaryl-containing allylated products in good to excellent yields using 1–5 mol % catalyst loading (80–99% yield). Silylamide bases, $MN(SiMe_3)_2$ (M = Li, Na, K), were used to accommodate the wide range of pronucleophile pK_a's. In general, $LiN(SiMe_3)_2$ was used for the most acidic pronucleophiles (pK_a < 28), $NaN(SiMe_3)_2$ for moderately acidic (pK_a = 28–31) and $KN(SiMe_3)_2$ for the least acidic (pK_a > 31). The 2-, 4- and 3-benzylpyridines underwent allylation in 91–99% yield (Table 3, entries 1–3). Xanthene (**1d**) derivatives are important components of dyes.[44] Xanthene underwent monoallylation in 82% yield (entry 4). Furan[45] and thiophene[46] derivatives are valuable building blocks in agrochemicals and pharmaceuticals. Under the reaction conditions with $KN(SiMe_3)_2$ as the base, we observed decomposition of 2-benzylfuran (**1e**). Under the same reaction conditions with $NaN(SiMe_3)_2$ as the base, the desired product **3ea** was obtained in only 32% yield. Using $NaN(SiMe_3)_2$, in combination with 15-crown-5 (2.5 equiv), the allylic substitution reaction afforded the desired

product **3ea** in 80% yield (entry 5). This result demonstrates that the use of additives, such as crown ethers, are useful in transition metal catalyzed processes other than deprotonative cross-coupling processes.[32] With 2-benzylthiophene (**1f**) the desired substitution product **3fa** was isolated in 93% with $NaN(SiMe_3)_2$ (entry 6). Di(3-pyridyl)methane (**1g**) was applied to give **3ga** in 85% yield (entry 7). To establish the scalability of this method, the allylation of 3-benzylpyridine (**1c**) was examined on a 10 mmol scale, affording the allylated product **3ca** in 89% yield (eq 2).

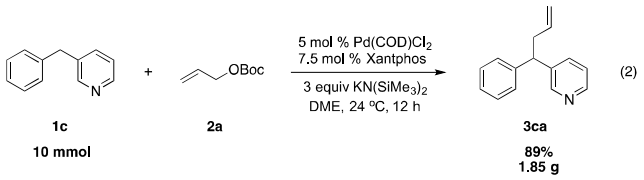
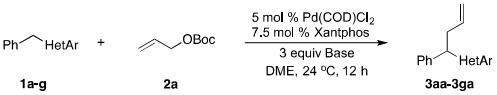
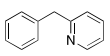
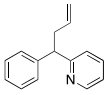
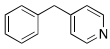
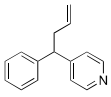
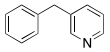
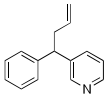
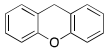
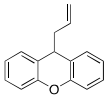
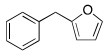
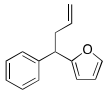
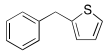
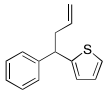
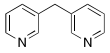
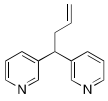


Table 3. Scope of Heterocyclic Diarylmethanes in the Allylic Substitution[a]



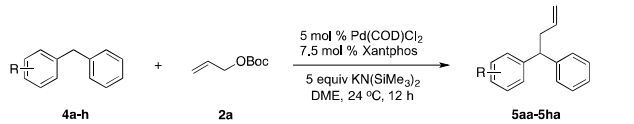
Entry	Pronucleophiles		Base	Products		Yield[b] (%)
1[c]		1a	$NaN(SiMe_3)_2$		3aa	99
2[c]		1b	$LiN(SiMe_3)_2$		3ba	99
3		1c	$KN(SiMe_3)_2$		3ca	91
4		1d	$NaN(SiMe_3)_2$		3da	82
5[d]		1e	$NaN(SiMe_3)_2$		3ea	80
6		1f	$NaN(SiMe_3)_2$		3fa	93
7		1g	$LiN(SiMe_3)_2$		3ga	85

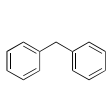
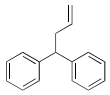
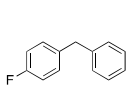
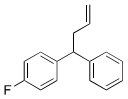
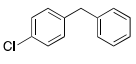
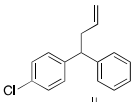
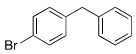
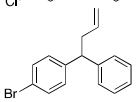
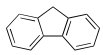
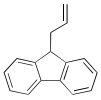
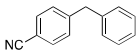
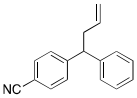
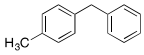
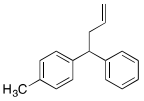
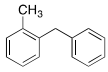
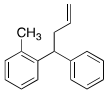
[a] Reaction conducted on a 0.1 mmol scale with 1 equiv of **1** and 2 equiv of **2a** at 0.1 M . [b] Isolated yield after chromatographic purification. [c] 1 mol % $Pd(COD)Cl_2$, 1.5 mol % Xantphos. [d] 2.5 equiv of $NaN(SiMe_3)_2$ and 2.5 equiv of 15-crown-5.

2.3. Scope of Diphenylmethane Derivatives in the Allylic Substitution

Diphenylmethane derivatives are more challenging pronucleophiles due to their higher pK_a's.[39] To compensate for the less favorable equilibrium for deprotonation of these pronucleophiles, the amount of base was increased to 5 equiv. With the optimized reaction conditions for **4a** (Table 4, entry 1), we investigated 4-halogenated diphenylmethanes (entries 2–4). Compounds containing fluorine are important because of their bioactivities and uses in material science.[47] The reaction with 4-fluoro diphenylmethane (**4b**) as pronucleophile afforded the desired product **5ba** in 84% yield (entry 2). We then applied our reaction conditions to 4-bromo and 4-chloro diphenylmethanes (**4c** and **4d**). A potential problem with these substrates lies in the competing oxidative addition of C–X (X = Cl, Br) bonds to the active Pd(0) species. We were pleased to find that Pd-catalyzed allylic substitution afforded the allylated products **5ca** and **5da** in 95% and 73% yield, respectively (entries 3 and 4). These results suggest that generation of the π-allyl palladium intermediate is significantly faster than the oxidative addition of C–X bonds to the Pd(0) species under our reaction conditions. Fluorene (**4e**) derivatives have interesting characteristics and can be used in organic light-emitting diodes.[44] By using 1.5 equiv $LiN(SiMe_3)_2$ and 1.1 equiv of **2a**, **5ea** was generated in 87% yield (entry 5). 4-Cyano diphenylmethane (**4fa**) is potentially problematic because benzonitriles are known to undergo additions with strong bases and organometallic reagents.[48] Nonetheless, this substrate provided the product **5fa** in 90% yield (entry 6). As might be anticipated, pronucleophiles with electron donating groups are less acidic and, therefore, more difficult to deprotonate. We found that 4-methyl diphenylmethane **4g** underwent substitution to give **5ga** in 68% yield at 50 °C (entry 7). Notably, 2-methyl diphenylmethane (**4h**) reacted to provide **5ha** in 70% yield at 50 °C (entry 8). Unfortunately, 4-methoxy diphenylmethane did not react under these, or a variety of other conditions.

Table 4. Scope of Diphenylmethane Derivatives in Allylic Substitution Reactions[a]



Entry	Pronucleophiles		Products		Yield[b] (%)
1		4a		5aa	95
2		4b		5ba	84
3		4c		5ca	95
4		4d		5da	73
5[c]		4e		5ea	87
6[d]		4f		5fa	90
7[e, g]		4g		5ga	68
8[f, g]		4h		5ha	70

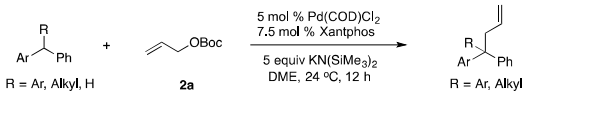
[a] Reaction conducted on a 0.1 mmol scale with 1 equiv of **4** and 3 equiv of **2a** at 0.1 M. [b] Isolated yield after chromatographic purification. [c] 1.5 equiv of $LiN(SiMe_3)_2$ and 1.1 equiv of **2a**. [d] 1.5 equiv of $KN(SiMe_3)_2$ and 2 equiv of **2a**. [e] 8 equiv of $KN(SiMe_3)_2$. [f] 10 equiv of $KN(SiMe_3)_2$. [g] Reaction conducted at 50 °C.

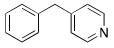
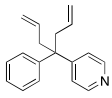
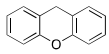
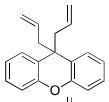
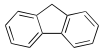
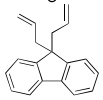
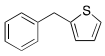
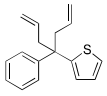
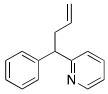
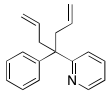
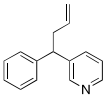
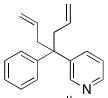
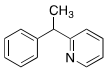
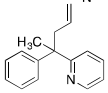
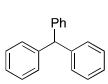
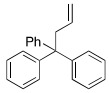
2.4. Diallylation with Heteroaryl Diarylmethanes

Having demonstrated the monoallylation of diarylmethanes and heteroaryl-containing derivatives, we next explored the possibility of adding a second allyl group to the allylated products prepared above. We were encouraged by the formation of small amounts of diallylation products with more acidic pronucleophiles (pK_a < 30) in the monoallylation optimization process. We, therefore, reoptimized the conditions to enable allylation of the purified monoallylated products. By employing 5 equiv of $KN(SiMe_3)_2$ and 3 equiv of **2a** with the monoallylated substrates (**3aa**–**3ga**, Table 3), we obtained the corresponding diallylation products (**6aa**–**6ga**, 70–95% yield). These results indicate that the allylation chemistry outlined here can be used to establish quaternary centers.

A more efficient method to prepare the diallylated products would be from the diarylmethane derivatives. We, therefore, set out to develop a one-pot diallylation protocol. We rationalized that the conditions mentioned above for the allylation of the mono-allylated diarylmethanes would be suitable for the one-pot diallylation. This approach proved fruitful: the yields for the double allylation ranged from 65 to 85% (Table 5, entries 1–5). The one-pot syntheses were not efficient for 2-benzylpyridine (**1a**) and 3-benzylpyridine (**1c**) as pronucleophiles, because the deprotonation events are more difficult for these substrates. Nonetheless, starting from monoallylation products **3aa** and **3ca** we obtained the bis-allylated products **6aa** and **6ca** in 84 and 80% yield (entries 6–7). We were also able to use 1,1-diarylethane (e.g., **8a**) as pronucleophile to install an allyl group to afford a quaternary stereocenter (entry 8). Notably, triphenylmethane (**9a**) was used as pronucleophile to give the sterically congested **9aa** in 90% yield (entry 9). To summarize, our method afforded diaryl- or triarylmethane products containing at least one allyl group on the quaternary carbon. Some of the products in Table 5 could presumably be employed in ring-closing metathesis reactions[49] to prepare 1,1-diarylcyclopent-3-ene or Pauson–Khand type [2+2+1] reactions[50] to afford bicyclic scaffolds.

Table 5. Diallylation with Diarylmethanes[a]



Entry	Pronucleophiles		Products		Yield[b] (%)
1[c, d]		1b		6ba	85
2		1d		6da	65
3[e]		4e		7ea	85
4[f]		1f		6fa	70
5[e]		3aa		6aa	84
6		3ca		6ca	80
7		8a		8aa	90
8		9a		9aa	90

[a] Reaction conducted on a 0.1 mmol scale with 1 equiv of pronucleophile and 3 equiv of **2a** at 0.1 M. [b] Isolated yield after

chromatographic purification. [c] Reaction conducted at 0.066 M. [d] Reaction conducted at 50 °C. [e] 3 equiv of $KN(SiMe_3)_2$ and 2 equiv of **2a**. [f] 8 equiv of $KN(SiMe_3)_2$.

2.5. Scope of Electrophiles in Palladium-Catalyzed Allylic Substitutions

Having demonstrated that the simplest allyl electrophile can be used with a variety of pronucleophiles, we turned our attention to the nature of the electrophilic partner. We chose the more acidic pronucleophile di(3-pyridyl)methane (**1g**, Table 3, entry 7) and examined the influence of different leaving groups on Pd-catalyzed allylic substitution with cyclohexenyl electrophiles (**2b**, **2c**). Both the Boc (**2b**) and benzoate ester (**2c**) derivatives gave similar yields of **10a** (89 and 90% yield, entries 1–2). Changing the ring size of the electrophile from six to five (**2d**) resulted in 90% yield (entry 3) when the Boc analogue was used. The classic 1,3-diphenyl allyl precursor **2e** afforded the allylic substitution product **10c** in 87% yield with a 10:1 *trans*:*cis* ratio (entry 4).

Next, the less acidic diphenylmethane (**4a**) was employed as pronucleophile (entries 5–7). The Boc derived cyclohexenyl substrate **2b** underwent reaction leading to the product in 85% yield (entry 5). In contrast, the benzoate derivative **2c** resulted in only 20% yield (entry 6). The low yield is likely due to attack of nucleophile on the ester carbonyl. Changing the benzoate ester **2c** to the pivalate ester **2f** resulted in an increase in the yield to 70% (entry 7). Cyclopentenyl OBoc electrophile **2d** underwent substitution in the presence of diphenylmethane in 94% yield (entry 8).

Many electrophilic partners used in allylic substitution reactions lead to unsymmetrical η^3-allyl groups. We, therefore, examined the regioselectivity with unsymmetrical linear Boc-protected electrophiles such as cinnamyl alcohol (**2g**), geranyl alcohol (**2h**) and prenyl alcohol (**2i**) (Table 6, entries 9–11). It is well known that π-allyl palladium complexes are prone to react with carbon nucleophiles at the less substituted terminus of the π-allyl.[51] For the Pd-catalyzed allylic substitution with Boc-protected cinnamyl alcohol (**2g**), the linear product **10f** was the major product, albeit with moderate regioselectivity (2.6:1, entry 9). The reduced regioselectivity in this case, relative to cases with less basic nucleophiles, is likely a manifestation of the high reactivity of the 4-benzylpyridine-derived nucleophile.[27] Interestingly, the prenylation and geranylation exhibited opposite regioselectivities (entries 10–11). The Boc activated geranyl underwent reaction with 4-benzylpyridine slightly favoring the terminal substitution product (1.9:1.0, linear:branched). In contrast, the prenylation afforded the branched product **10h'** with a linear:branched ratio of 1.0:4.5 (entry 11). We hypothesize that the origin of the regioselectivity in the prenylation is a result of the non-bonded interaction between the bulky, wide-bite angle Xantphos ligand and the more substituted carbon of the η^3-allyl. This interaction places a larger δ+ partial charge on the more substituted terminus and, therefore, nucleophilic attack at this position prevails. The additional substituent (=R) on the η^3-allyl in the geranylation causes this group to adopt a conformation positioning it anti to the bulky (Xantphos)Pd center (Figure 2). The substituent partially obstructs the nucleophilic attack at the more substituted terminus, resulting in a shift of the regioselectivity toward the less substituted carbon of the allyl.

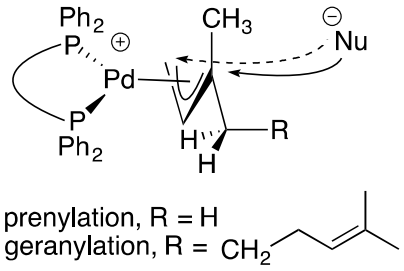
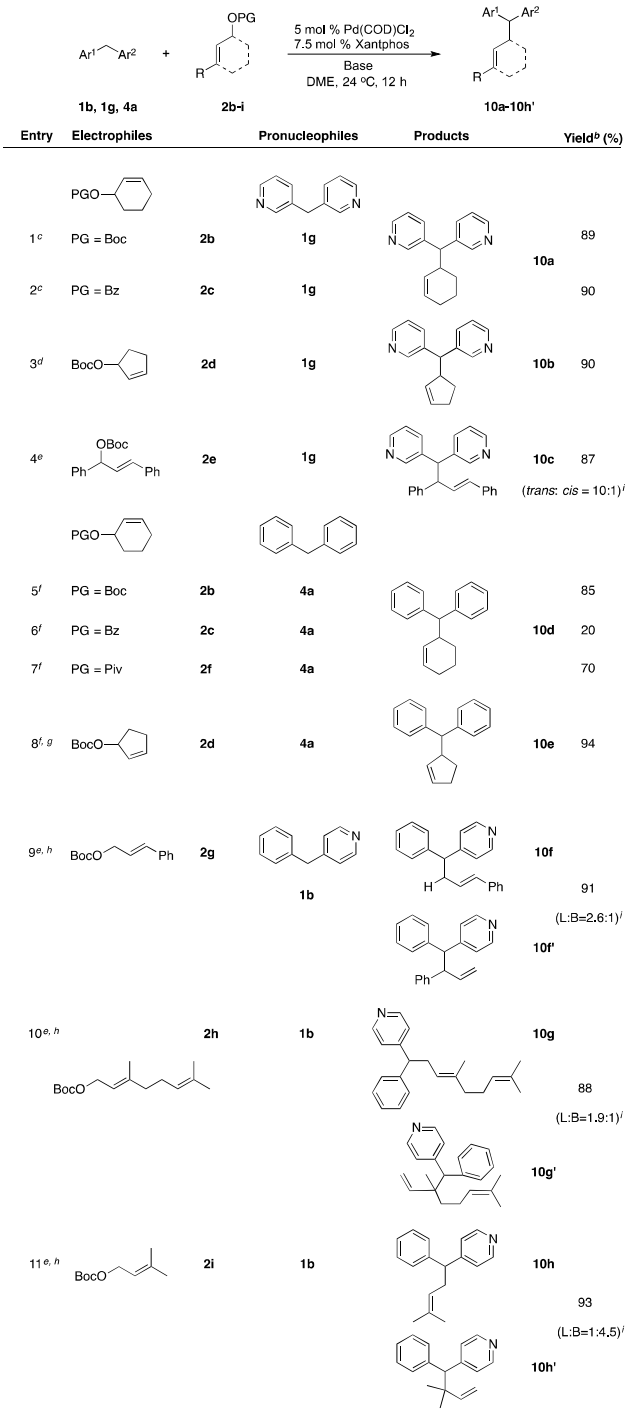


Figure 2. Proposed conformational model to explain the reversal in regioselectivity between the prenylation and geranylation (Table 6, entries 10–11). When R=H nucleophilic attack is favored at the more substituted terminus (solid arrow). When R=alkyl, attack follows the dashed arrow leading to the linear product.

Table 6. Scope of Electrophiles in Allylic Substitution Reactions[a]



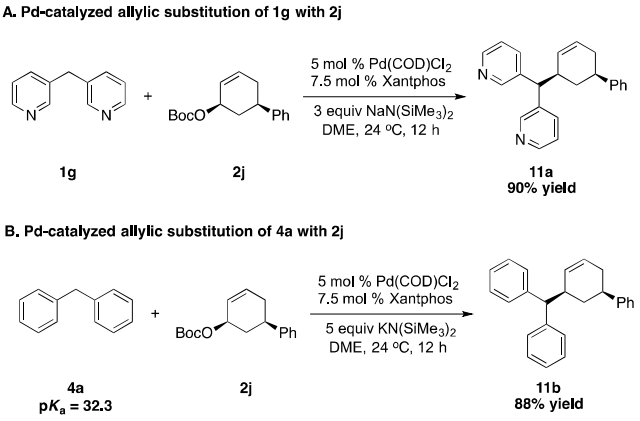
[a] Reaction conducted on a 0.1 mmol scale at 0.1 M. [b] Isolated yield after chromatographic purification. [c] 3 equiv of $NaN(SiMe_3)_2$ and 2 equiv of **2**. [d] 3 equiv of $KN(SiMe_3)_2$ and 2 equiv of **2**. [e] 3 equiv of $LiN(SiMe_3)_2$ and 2 equiv of **2**. [f] 5 equiv of $KN(SiMe_3)_2$ and 3 equiv of **2**. [g] Reaction conducted at 50 °C. [h] Reaction conducted at 0 °C. [i] Ratio of *trans*:*cis* or linear:branched (L:B) determined by ^{1}H NMR.

2.6. Internal vs. External Attack of Diarylmethane on π-Allyl Palladium Intermediate

As outlined in the Introduction, nucleophiles in allylic substitutions can directly add to the π-allyl or to the metal in their reactions with $[(\eta^3\text{-allyl})ML_n]^+$ intermediates. It is generally accepted that nucleophiles with conjugate acids of $pK_a < 25$, classified as "soft" nucleophiles, undergo external attack on π-allyl palladium complexes. Soft nucleophiles, therefore, result in stereoretentive allylic substitutions reactions (*via* double inversion).[52] On the other hand, "hard" nucleophiles, those with $pK_a > 25$ are proposed undergo attack on the metal center of the π-allyl palladium complexes (i.e., transmetallation) followed by reductive elimination to afford net inversion for the allylic substitution.[53]

To examine the mechanistic pathway of the reaction, di(3-pyridyl)methane (**1g**) was reacted with *cis*-disubstituted stereoprobe **2j** (Scheme 2A) and afforded *cis*-product **11a** in 90% isolated yield as a single diastereomer (determined by ^{1}H NMR spectroscopy). Reaction of the less acidic pronucleophile diphenylmethane (**4a**) ($pK_a = 32.3$) with **2j** (Scheme 2B) similarly furnished the *cis*-product **11b** as a single diastereomer (determined by ^{1}H NMR spectroscopy and single crystal X-ray diffraction) in 88% yield. The results indicated both nucleophiles derived from di(3-pyridyl)methane (**1g**) and diphenylmethane (**4a**) behave as "soft" nucleophiles and that the pK_a limit for "soft" nucleophiles should be raised from 25 to 32, a change of 7 orders of magnitude.

Scheme 2. Allylic Substitution with Retention of Configuration



3. SUMMARY AND OUTLOOK

Herein we have developed a general method for Pd-catalyzed allylic substitution with diarylmethane derivatives at room temperature. The synthetic significance of the method is that it provides a rapid access to products containing allylated diarylmethanyl motifs. The method is general for a wide range of nucleophiles derived diarylmethanes and heteroaryl derivatives. A tandem procedure for the Pd-catalyzed allylic substitutions to afford diallylation products with quaternary centers is also described. With alkylated diarylmethanes and triarylmethanes, the method is also efficient to afford the corresponding allylated products. We anticipate that the described method will be a valuable complement to the existing arsenal

of nucleophiles in Pd-catalyzed allylic substitutions. Mechanistic studies show that diarylmethane derivatives behave as "soft" or stabilized nucleophiles. The nucleophile derived from diphenylmethane undergoes external attack on π-allyl palladium species under our reaction conditions. The results of this study indicate that the cutoff between "soft" and "hard" nucleophiles should be raised from a pK_a of 25 to at least 32.

4. EXPERIMENTAL SECTION

Representative procedures are described herein. Full experimental details and characterization of all compounds are provided in the Supporting Information.

4.1. General Methods. All reactions were performed under nitrogen using oven-dried glassware and standard Schlenk or vacuum line techniques. Air- and moisture-sensitive solutions were handled under nitrogen and transferred *via* syringe. The solvents (DME and THF) were sparged for 20 min with dry N_2 and dried using a commercial two-column solvent purification system comprising columns packed with neutral alumina. Unless otherwise stated, reagents were commercially available and used as purchased without further purification. Chemicals were obtained from Sigma-Aldrich, Acros, TCI America, Strem Chemicals or Matrix Scientific, and solvents were purchased from Fisher Scientific. The progress of the reactions was monitored by thin-layer chromatography using Whatman Partisil K6F 250 μm precoated 60 Å silica gel plates and visualized by short-wavelength ultraviolet light as well as by treatment potassium permanganate ($KMnO_4$) stain or iodine. Silica gel (230–400 mesh, Silicycle) was used for flash chromatography. The ^{1}H NMR and ^{13}C{^{1}H} NMR spectra were obtained using a Brüker AM-500 Fourier transform NMR spectrometer at 500 and 126 MHz, respectively. Chemical shifts are reported in units of parts per million (ppm) downfield from tetramethylsilane (TMS), and all coupling constants are reported in hertz. The infrared spectra were obtained with KBr plates using a Perkin-Elmer Spectrum 100 Series FTIR spectrometer. High-resolution mass spectrometry (HRMS) data were obtained on a Waters LC–TOF mass spectrometer (model LCT-XE Premier) using chemical ionization (CI) or electrospray ionization (ESI) in positive or negative mode, depending on the analyte. Melting points were determined on a Unimelt Thomas-Hoover melting point apparatus and are uncorrected.

4.2. General Procedure A: Palladium-Catalyzed Allylic Substitution with Heterocyclic Diarylmethanes Under Room Temperature. An oven-dried 10 mL reaction vial equipped with a stir bar was charged with NaN($SiMe_3$)$_2$ (55 mg, 0.30 mmol, 3 equiv) under a nitrogen atmosphere. A solution (from a stock solution) of Pd(COD)Cl_2 (1.43 mg, 0.0050 mmol) and Xantphos (4.34 mg, 0.0075 mmol) in 1 mL of dry DME was taken up by syringe and added to the reaction vial. After stirring for 5 min at 24 °C, 2-benzylpyridine **1a** (16 μL, 0.1 mmol, 1 equiv) was added to the reaction mixture followed by **2a** (34 μL, 0.2 mmol, 2 equiv). Note that the diarylmethanes or allyl-OBoc in a solid form was added to the reaction vial prior to NaN($SiMe_3$)$_2$. The reaction mixture was stirred for 12 h at 24 °C, quenched with two drops of H_2O, diluted with 3 mL of ethyl acetate and filtered over a pad of $MgSO_4$ and silica. The pad was rinsed with additional ethyl acetate, and the solution was concentrated *in vacuo*. The crude material was loaded onto a silica gel column and purified by flash chromatography eluting with EtOAc/hexanes.

4.3. General Procedure B: **Palladium-Catalyzed Allylic Substitution with Heterocyclic Diarylmethanes Under 50 °C**. An oven-dried 10 mL reaction vial equipped with a stir bar was charged with KN($SiMe_3$)$_2$ (160 mg, 0.80 mmol, 8 equiv) under a nitrogen atmosphere. A solution (from a stock solution) of Pd(COD)Cl_2 (1.43 mg, 0.0050 mmol) and Xantphos (4.34 mg, 0.0075 mmol) in 1 mL of dry DME was taken up by syringe and added to the reaction vial. After stirring for 5 min at 24 °C, 4-methyl diphenylmethane **4g** (18.5 μL, 0.1 mmol, 1 equiv) was added to the reaction mixture followed by **2a** (51 μL, 0.3 mmol, 3 equiv). The reaction mixture was stirred for 12 h at 50 °C, quenched with two drops of H_2O, diluted with 3 mL of ethyl acetate, and filtered over a pad of $MgSO_4$ and silica. The pad was rinsed with additional ethyl acetate and the solution was concentrated *in vacuo*. The crude material was loaded onto a silica gel column and purified by flash chromatography eluting with EtOAc/hexanes.

4.4 General Procedure C: **Palladium-Catalyzed Allylic Substitution with Heterocyclic Diarylmethanes Under 0 °C**. An oven-dried 10 mL reaction vial equipped with a stir bar was charged with LiN($SiMe_3$)$_2$ (51 mg, 0.30 mmol, 3 equiv) under a nitrogen atmosphere. A solution (from a stock solution) of Pd(COD)Cl_2 (1.43 mg, 0.0050 mmol) and Xantphos (4.34 mg, 0.0075 mmol) in 1 mL of dry DME was taken up by syringe and added to the reaction vial. After stirring for 5 min at 0 °C, 4-benzylpyridine **1b** (16 μL, 0.1 mmol, 1 equiv) was added to the reaction mixture followed by Boc-protected cinnamyl alcohol **2g** (46 μL, 0.2 mmol, 2 equiv). The reaction mixture was stirred for 12 h at 0 °C, quenched with two drops of H_2O, diluted with 3 mL of ethyl acetate, and filtered over a pad of $MgSO_4$ and silica. The pad was rinsed with additional ethyl acetate and the solution was concentrated *in vacuo*. The crude material was loaded onto a silica gel column and purified by flash chromatography eluting with EtOAc/hexanes

ASSOCIATED CONTENT

Supporting Information

Procedures and full characterization of new compounds. This material is available free of charge *via* the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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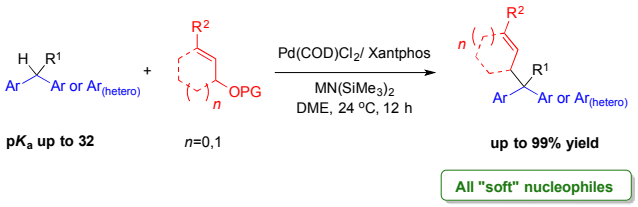

pK_a up to 32 *n*=0,1 **up to 99% yield**

All "soft" nucleophiles