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Palladium-Catalyzed Allylic Substitution with (η^6-Arene−CH_2Z)$Cr(CO)_3$-Based Nucleophiles

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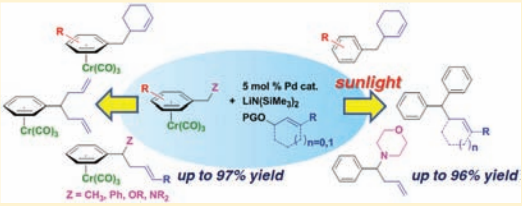
S Supporting Information

ABSTRACT: Although the palladium-catalyzed Tsuji−Trost allylic substitution reaction has been intensively studied, there is a lack of general methods to employ simple benzylic nucleophiles. Such a method would facilitate access to "α-2-propenyl benzyl" motifs, which are common structural motifs in bioactive compounds and natural products. We report herein the palladium-catalyzed allylation reaction of toluene-derived pronucleophiles activated by tricarbonylchromium. A variety of cyclic and acyclic allylic electrophiles can be employed with in situ generated (η^6-C_6H_5CHLiR)$Cr(CO)_3$ nucleophiles. Catalyst identification was performed by high throughput experimentation (HTE) and led to the Xantphos/palladium hit, which proved to be a general catalyst for this class of reactions. In addition to η^6-toluene complexes, benzyl amine and ether derivatives (η^6-$C_6H_5CH_2Z$)$Cr(CO)_3$ (Z = NR_2, OR) are also viable pronucleophiles, allowing C−C bond-formation α to heteroatoms with excellent yields. Finally, a tandem allylic substitution/demetalation procedure is described that affords the corresponding metal-free allylic substitution products. This method will be a valuable complement to the existing arsenal of nucleophiles with applications in allylic substitution reactions.



1. INTRODUCTION

The formation of carbon−carbon bonds represents one of the most fundamental and well-studied processes in organic synthesis. Nonetheless, the efficient catalytic generation of C−C bonds between sp^3-hybridized carbons remains challenging.[1] Although palladium-catalyzed cross-coupling reactions have received significant recent attention, an alternative approach to such C−C bond-formations is the palladium-catalyzed Tsuji−Trost allylic substitution reaction. This reaction has been intensively studied, because it provides a variety of efficient and atom-economical methods for synthesis of natural products and bioactive targets.[2]

Although a broad array of stabilized or "soft" nucleophiles (those derived from conjugate acids with $pK_a < 25$) has been explored, palladium-catalyzed allylic alkylations with "hard" nucleophiles (derived from conjugate acids with $pK_a > 25$) have received considerably less attention. "Hard" nucleophiles used in palladium-catalyzed allylic alkylations are largely organometallic compounds such as alkyllithium and Grignard reagents.[3] Their high reactivity and limited functional group tolerance, however, render the use of these hard nucleophiles in allylic substitution less attractive. One strategy to develop allylic substitution reactions with nucleophiles that are traditionally considered hard is to "soften" them by addition of an activating agent to acidify the conjugate acid. Recent advances based on this strategy were reported by Trost and co-workers with nucleophiles derived from 2-methylpyridines (Scheme 1A).[4] The sp^3-hybridized C−H's of 2-methylpyridine have a pK_a of 34,[5] and therefore its conjugate base is classified as hard. To moderate the reactivity of the conjugate base, the pyridine nitrogen was coordinated to BF_3. The resulting BF_3-bound complex was deprotonated and employed in palladium-catalyzed asymmetric allylic substitution with excellent enantio- and diastereoselectivity. Interestingly, no such activation was necessary with more activated benzylic C−H's, such as those of methylated pyrazine (Scheme 1B), pyrimidine, pyridazine, quinoxaline, and benzoimidazole pronucleophiles.[4c]

Despite the elegance and medicinal relevance of Trost's synthesis of enantioenriched pyridine derivatives, an approach to activation of weakly acidic benzylic C−H's for use in allylic substitution reactions is needed. Toluene, for example, with a pK_a of 44 ± 1,[6] is very weakly acidic, and the conjugate base of toluene has not been used in palladium-catalyzed allylic substitution reactions (Scheme 1C).[7−9] Yet hundreds of bioactive compounds and natural products contain the "α-2-propenyl benzyl" motif (Figure 1), with applications ranging from medicinal agents for hyperkalemia,[10] Alzheimer's,[11] and urinary tract diseases,[12] to cosmetics,[13] antibiotics,[14] and phytoncides.[15]

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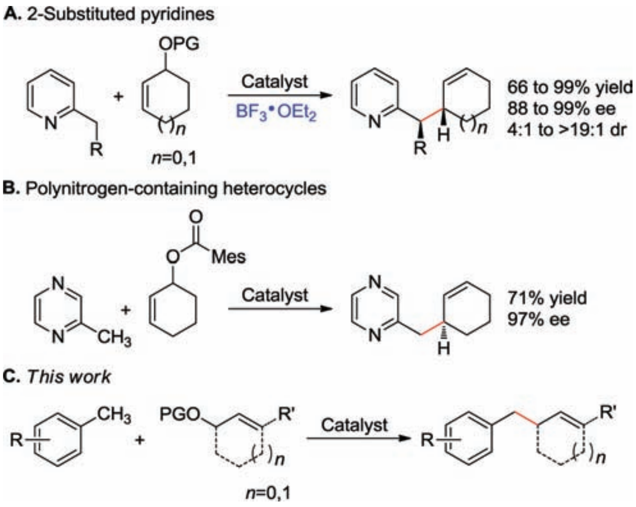
Scheme 1. Palladium-Catalyzed Benzylic Allylations



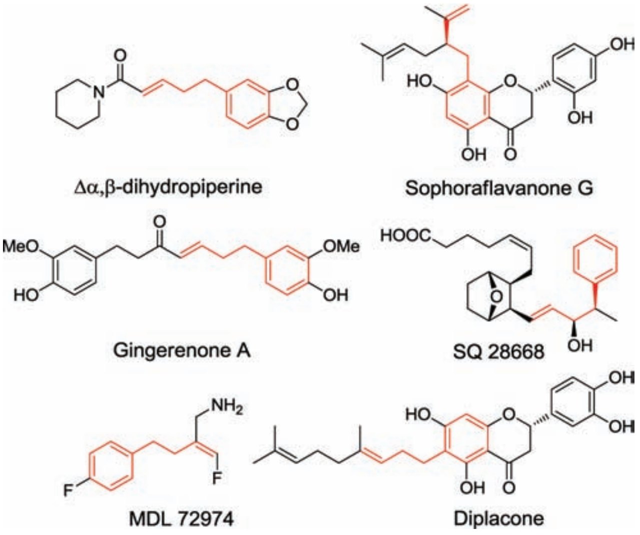
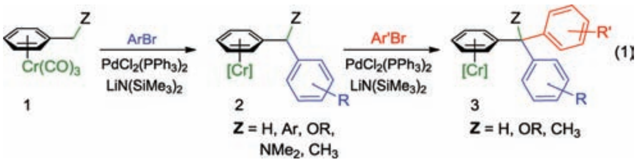


Figure 1. Selected bioactive compounds and natural products containing the "α-2-propenyl benzyl" motif.

To broaden the scope of useful nucleophiles for the palladium-catalyzed Tsuji–Trost reaction, we set out to develop the application of toluene derivatives as precursors to benzylic nucleophiles. To achieve this goal, conditions to deprotonate toluene derivatives that are compatible with the catalyst, reagents, and products in the allylic substitution reaction would be necessary. It is known that η^6-coordination of arenes to metals activates the benzylic C–H's toward deprotonation.[16,17] We hypothesized that η^6-arene complexes could be reversibly deprotonated[18] under palladium-catalyzed allylic substitution reaction conditions and would serve as surrogates for hard benzylic organometallic reagents. Herein we report the successful application of $(\eta^6\text{-}C_6H_5CH_2R)Cr(CO)_3$ complexes as nucleophile precursors in allylic substitution reactions (Scheme 1C). This method enables the synthesis of a variety of valuable aryl-containing compounds that would be otherwise difficult to access.

2. RESULTS AND DISCUSSION

We recently disclosed the palladium–triphenylphosphine-catalyzed cross-coupling of aryl bromides and $(\eta^6\text{-}C_6H_5CH_2R)Cr(CO)_3$ complexes in the presence of $LiN(SiMe_3)_2$ to afford a broad range of di- and triarylmethanes (eq 1).[18] The $Cr(CO)_3$ fragment is easily installed simply by refluxing the arene with $Cr(CO)_6$. After the coupling reaction, decomplexation of the chromium moiety is performed by exposure of the solution of the chromium arene complex to room light and air. On the basis of this study, we hypothesized that $(\eta^6\text{-}C_6H_5CH_2R)Cr(CO)_3$ complexes might be suitable substrates in palladium-catalyzed allylic substitution reactions.



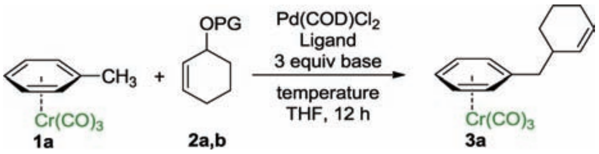
(1)

2.1. Development and Optimization of Palladium-Catalyzed Allylic Substitution with $(\eta^6\text{-}C_6H_5CH_3)Cr(CO)_3$. Given that the cross-coupling of $(\eta^6\text{-}C_6H_5CH_3)Cr(CO)_3$ with aryl bromides was successfully catalyzed by palladium–triphenylphosphine complexes, which also catalyze allylic substitutions,[19] we initially examined the allylic substitution reaction with the same catalyst and base. Combination of the toluene complex $(\eta^6\text{-}C_6H_5CH_3)Cr(CO)_3$ (**1a**) with *tert*-butyl cyclohex-2-enyl carbonate (**2a**) as the electrophilic partner, $LiN(SiMe_3)_2$ to reversibly deprotonate the toluene complex, and THF solvent was performed. Heating the reaction mixture to 60 °C in THF resulted in only trace amounts of product after 12 h (Table 1, entry 1). We then turned to microscale high-throughput experimentation (HTE) techniques[20] to identify an initial catalyst lead. Using 12 diverse phosphine ligands, 4 palladium precursors, and 4 bases (see Supporting Information for details) revealed that the combination of 10 mol % $Cl_2Pd(COD)$ and Xantphos with 3 equiv of $LiN(SiMe_3)_2$ in THF at 60 °C was the most promising combination of those examined for conversion of **1a** to the corresponding allylation product **3a**. Translation of this lead to laboratory scale under the same conditions afforded **3a** in 39% yield (Table 1, entry 2). Decreasing the reaction temperature from 60 °C to ambient temperature and further to 0 °C indicated that conducting the reaction above or below ambient temperature proved deleterious to the yield (Table 1, entries 2–4). Combination of 1 equiv of the stronger bases LDA or *n*-BuLi with 3 equiv of $LiN(SiMe_3)_2$ to favor deprotonation of **1a** resulted in poor yields (Table 1, entries 5 and 6).

A key variable in optimizing organolithium reactions is the degree of aggregation.[21] To reduce the degree of aggregation, a single equiv of NEt_3 was added in combination with 3 equiv of $LiN(SiMe_3)_2$. With this mixture, **3a** was formed in >95% yield (Table 1, entry 7). Under these conditions, catalyst loading could be reduced to 5 mol % (Table 1, entry 8). Switching the allylic partner from the carbonate **2a** to the pivalate **2b** also resulted in excellent isolated yield (96%, Table 1, entry 9). The structure of **3a** was determined by X-ray diffraction (see Supporting Information) and is consistent with allylic substitution outlined in Table 1. Using these optimized conditions, we then examined various $(\eta^6\text{-}C_6H_5CH_2R)Cr(CO)_3$ complexes as nucleophile precursors.

2.2. Scope of Nucleophiles in Palladium-Catalyzed Allylic Substitution Reactions. Employing the optimized conditions with the pivalate ester **2b** (Table 1, entry 9), we evaluated the scope of the $(\eta^6\text{-}Ar\text{–}CH_2R)Cr(CO)_3$ pronucleophiles in the

Table 1. Optimization of Allylic Substitution with **1a**[a]



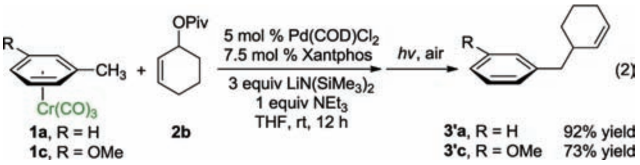
entry	PG	mol %	ligand	base	temp (°C)	yield[b] (%)
1	Boc (**2a**)	10	PPh_3	$LiN(SiMe_3)_2$	60	trace
2	Boc	10	Xantphos	$LiN(SiMe_3)_2$	60	39
3	Boc	10	Xantphos	$LiN(SiMe_3)_2$	rt	72
4	Boc	10	Xantphos	$LiN(SiMe_3)_2$	0	39
5	Boc	10	Xantphos	$LiN(SiMe_3)_2$/LDA[d]	rt	29
6	Boc	10	Xantphos	$LiN(SiMe_3)_2/^{n}BuLi$[d]	rt	<10
7	Boc	10	Xantphos	$LiN(SiMe_3)_2/NEt_3$[e]	rt	>95
8	Boc	5	Xantphos	$LiN(SiMe_3)_2/NEt_3$[e]	rt	88[c]
9	Piv (**2b**)	5	Xantphos	$LiN(SiMe_3)_2/NEt_3$[e]	rt	96[c]

[a] Reactions conducted on a 0.1 mmol scale using 1 equiv of **1a** and 2 equiv of **2** at 0.1 M. [b] Yield determined by ^1H NMR spectroscopy of the crude reaction mixture. [c] Isolated yield after chromatographic purification. [d] Mixed bases of 3 equiv of $LiN(SiMe_3)_2$ and 1 equiv of LDA (or $^{n}BuLi$). [e] Amine additive (1 equiv) treated with 3 equiv of $LiN(SiMe_3)_2$.

allylic substitution reaction (Table 2). In addition to the toluene complex (entry 1), use of (η^6-$ArCH_2R$)$Cr(CO)_3$ complexes bearing various substituents on the η^6-arene were well tolerated. Although the *p*-isopropyl-substituted arene was a good substrate (entry 2, 89% yield), *p*-methylanisole gave only trace product. In contrast, the *meta* isomer underwent allylation in 80% yield (entry 3). The difference between these isomeric substrates is likely due to the decreased acidity of the benzylic C−H bonds *para* to the methoxy. Aryl substituents on the η^6-arene were good substrates. To highlight the increase in reactivity of (η^6-tolyl)$Cr(CO)_3$ compared with an unactivated tolyl group, the 4,4′-dimethylbiphenyl complex was employed. This substrate underwent allylation exclusively at the chromium-activated position (entry 4, 90% yield). Although the $Cr(CO)_3$ moiety is known to "walk" between neighboring arenes at high temperature,[22] only the monoallylation product was observed under our conditions, indicating that walking did not occur. Heteroaryl substrates containing 2-pyridyl, 2-thiophenyl, and *N*-pyrrolyl groups attached to the η^6-tolyl group proved to be good substrates (entries 5−7, 74−80% yield). Heteroaromatic compounds are well-known for their utility in medicinal chemistry.

Notably, (η^6-*p*-chlorotoluene)$Cr(CO)_3$ complex participated in the allylic substitution to furnish the product in 45% yield (entry 8). Surprisingly, no products derived from Ar−Cl oxidative addition of (η^6-*p*-chlorotoluene)$Cr(CO)_3$ by palladium were observed, although η^6-coordination is known to facilitate oxidative addition of chloroarene complexes.[23] The chloro-substituted biphenyl derivative underwent allylic substitution to give the chloro-containing product in 71% yield (entry 9).

The (η^6-arene)$Cr(CO)_3$ allylic substitution product in Table 2 could be used in a variety of subsequent transformations facilitated by the chromium.[17] However, the chromium-free complexes are often the desired products. Arene complexes of the type (η^6-arene)$Cr(CO)_3$ can be decomplexed simply by exposure to light and air to afford the corresponding arenes. To demonstrate the synthetic utility of this chemistry, a tandem allylic substitution/demetalation procedure was examined. With the (η^6-toluene)$Cr(CO)_3$ and 3-methoxy analogue, the allylic substitution was performed to generate the new arene complex, as outlined in eq 2. The reaction mixture was then exposed to light and air by removing the septum and placing the reaction vessel on a stir plate on the windowsill (eq 2). After the mixture was stirred for 3−6 h under light and air, the demetalated products were isolated in 92% (**3′a**) and 73% (**3′c**) yield.



2.3. Scope of Electrophiles in Palladium-Catalyzed Allylation Reactions with Arene Nucleophiles.

We next studied the impact of the leaving group on the allylic substitution. Varying the leaving group on 2-cyclohexen-1-ol from Boc (**2a**) to pivalate (**2b**) and benzoate esters (**2c**) resulted in 87−96% isolated yields of the allylation product **3a** (Table 3, entries 1−3). Although the pivalate ester resulted in the highest yield, these results indicate that the reaction with this substrate class is tolerant of the nature of the leaving group. The reaction of **1a** with **2c** *in the absence of* $Cl_2Pd(COD)$/Xantphos was performed as a control experiment. Instead of formation of the allylic substitution product **3a**, $PhCOCH_2$−(η^6-C_6H_5)$Cr(CO)_3$ was isolated in 98% yield as the exclusive product, which was formed from nucleophilic addition to the carbonyl group of **2c** (eq 3). This result indicates that palladium−Xantphos-based catalyst changes the chemoselectivity of the reaction from carbonyl addition to allylic substitution.

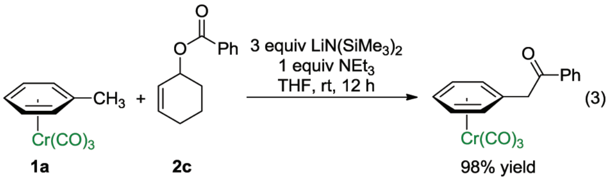
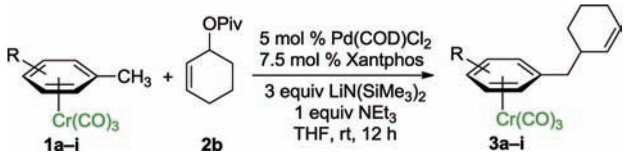
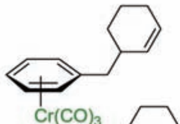
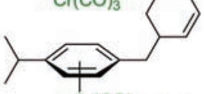
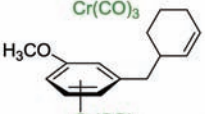
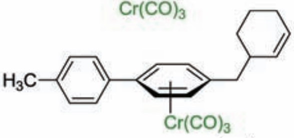
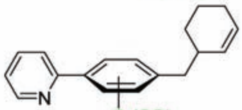
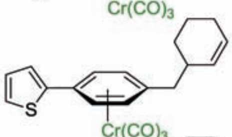
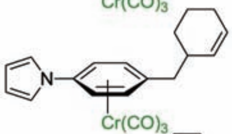
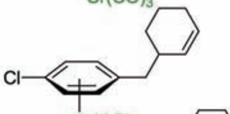
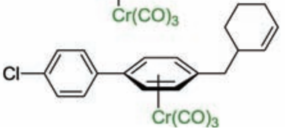


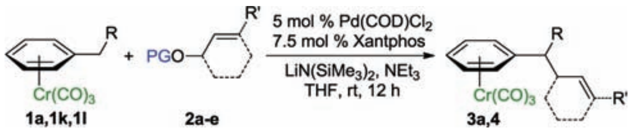
Table 2. Scope of Nucleophiles in Allylic Substitution Reactions[a]

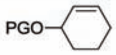
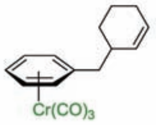
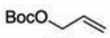
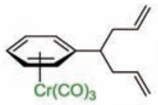
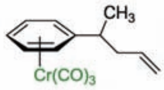
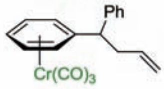
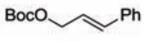
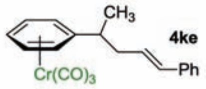


Entry	Product	Compound	Yield (%)
1		**3a**	96[b]
2		**3b**	89[b]
3		**3c**	80[b]
4		**3d**	90[b]
5		**3e**	77[b]
6		**3f**	80[b]
7		**3g**	74[b]
8		**3h**	45[b,c]
9		**3i**	71[b]

[a] Reactions conducted on a 0.1 mmol scale using 1 equiv of **1** and 2 equiv of **2b** at 0.1 M. [b] Isolated yield after chromatographic purification. [c] Reaction time was 1.5 h.

Table 3. Scope of Electrophiles in Allylic Substitution Reactions[a]

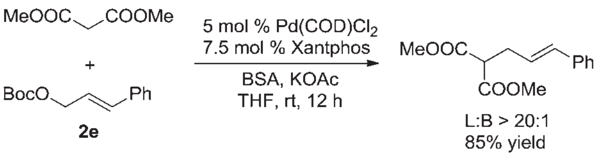


Entry	Electrophile	R	Product		Yield
					
1	PG = Boc (**2a**)	H		**3a**	88%[b]
2	PG = Piv (**2b**)	H			96%[b]
3	PG = Bz (**2c**)	H			87%[b]
4	 **2d**	H		**4ad**	81%[b,c]
5		Me		**4kd**	86%[b,c]
6		Ph		**4ld**	91%[b,c]
7	 **2e**	Me		**4ke**	L:B = 77:23[c,d] L: 71% yield[b,e]
8		Me			L:B = 85:15 [c,d] L: 75% yield[b,e]

[a] Reactions conducted on a 0.1 mmol scale using 1 equiv of **1**, an excess of LiN(SiMe$_3$)$_2$ and **2** at 0.1 M. (see Supporting Information for details). [b] Isolated yield after chromatographic purification. [c] PMDTA was added as an amine additive in place of NEt$_3$. [d] Ratio of linear:branched (L:B) was determined by ^{1}H NMR of the crude reaction mixture. [e] The regioisomers were separable by silica gel chromatography.

We next examined acyclic electrophiles as partners in the allylic substitution. The Boc derivative of allyl alcohol, **2d**, reacted with various (η^6-arene)Cr(CO)$_3$ complexes to yield substitution products (Table 3, entries 4–6). Reaction of the (η^6-toluene) Cr(CO)$_3$ complex with BocOCH$_2$CH═CH$_2$ (**2d**) resulted in formation of the diallylation product **4ad** (81% yield) when 1 equiv of **1a** was treated with 6 equiv of LiN(SiMe$_3$)$_2$, 4 equiv of the allylic substrate (**2d**), and 2 equiv of *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA) as additive in place of NEt$_3$. When (η^6-arene)Cr(CO)$_3$ complexes derived from ethylbenzene (**1k**) and diphenylmethane (**1l**) were reacted with **2d**, the monoallylation products were obtained in 86% (**4kd**) and 91% (**4ld**) yields (entries 5 and 6, respectively).

With unsymmetrical linear electrophiles derived from Boc-protected cinnamyl alcohol (**2e**), full consumption of (η^6-PhEt)-Cr(CO)$_3$ (**1k**) was observed. It is well-known that π-allyl-palladium complexes formed from cinnamyl alcohol derivatives tend to react with carbon-based nucleophiles at the unsubstituted terminus of the π-allyl group for both steric and electronic reasons.[16b] Surprisingly, however, the allylation product was obtained as a mixture of regioisomers at ambient temperature with a linear:branched ratio (L:B) of 77:23 (as determined by ^{1}H NMR of the crude reaction mixture, entry 7). Regioselectivity in palladium-catalyzed allylic substitution reactions can be influenced by the nature of the ligands,[24] solvent, and counterion.[25] For the purpose of comparison, we employed the stabilized nucleophile derived from dimethyl malonate under the same reaction conditions with the Xantphos-based palladium catalyst (eq 4). In this case, the linear product was obtained with excellent regioselectivity (linear:branched >20:1, 85% yield).[26] We hypothesize that the reduced regioselectivity with the nucleophile generated from (η^6-ethylbenzene)Cr(CO)$_3$ is a result of the high reactivity of the $Cr(CO)_3$-stabilized organolithium, which led to lower selectivity. We therefore conducted the reaction at 0 °C and observed an increase in the linear:branched ratio to 85:15 (Table 3, entry 8). The linear product was separated from the branched by column chromatography and isolated in 75% yield.



(4)

2.4. Tandem Allylation/Demetalation with Diphenylmethane Derivatives.

Diarylmethane derivatives are attracting considerable attention due to their growing importance in pharmaceutical development,[27] dye precursors,[28] and applications in materials science.[29] Given the utility of these compounds, we investigated palladium-catalyzed allylic substitutions with (η^6-$C_6H_5CH_2Ph$)$Cr(CO)_3$ (**1l**) with a variety of cyclic and acyclic allylic partners. The reaction mixtures were then exposed to light and air to afford metal-free diphenylmethane derivatives in a one-pot tandem fashion (Table 4).

We initiated our study employing the cyclohex-2-enyl pivalate **2b**. The allylic substitution was performed in THF with 1 equiv of (η^6-$C_6H_5CH_2Ph$)$Cr(CO)_3$ (**1l**), 2 equiv of pivalate **2b**, and 3 equiv of $LiN(SiMe_3)_2$ (entry 1). When the allylic substitution was complete, as judged by TLC, the flask was opened to air and placed on a stir plate on the windowsill to expose the reaction mixture to sunlight. A green precipitate formed during the demetalation as the chromium was oxidized. The reaction mixture was then filtered through a pad of $MgSO_4$ and silica, concentrated in vacuo, and loaded directly onto a silica gel column. The metal-free product **5lb** was isolated as clear oil in 96% yield after column chromatography. The reaction of *tert*-butyl cyclopent-2-enyl carbonate (**2g**) was performed under similar conditions and provided the substitution product in 89% yield (**5lg**, entry 2).

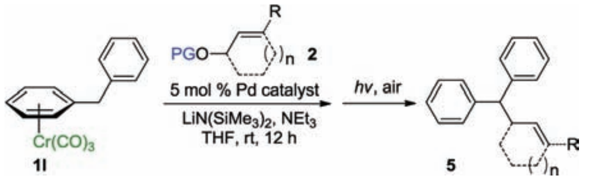
Acyclic allylic alcohol derivatives were also good substrates in the allylic substitution/demetalation tandem reaction. Use of the Boc derivative of the parent allyl alcohol (**2d**) resulted in isolation of the substitution product in 91% yield (**5ld**, entry 3). Note that the reaction of diphenylmethane [$Cr(CO)_3$-free] with allylic partners did not give substitution products, underscoring the necessity of the activating $Cr(CO)_3$ agent. *trans*-1,3-Diphenylallyl acetate (**2f**) underwent the allylic substitution/demetalation to give **5lf** in 96% isolated yield (entry 4). Reaction of **1l** with a bifunctional substrate, *cis*-1,4-diacetoxy-2-butene (**2h**), gave 77% isolated yield (88% per C−C bond formation) of the diallylation product **5lh** as an E/Z ratio of 1:2 (entry 5).[30]

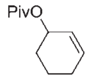
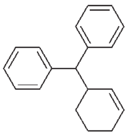
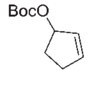
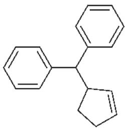
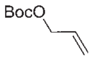
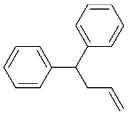
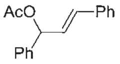
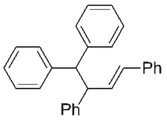
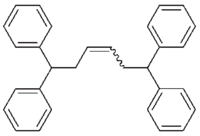
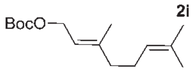
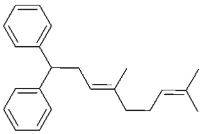
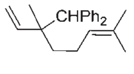
Evaluation of π-geranylpalladium complex was motivated by the recent isolation of several α-geranylated toluene derivatives.[31] Furthermore, α-geranylated toluene derivatives have shown interesting bioactive properties[32] and are key intermediates in total synthesis of antibiotics.[33] Addition of the organolithium derived from (η^6-$C_6H_5CH_2Ph$)$Cr(CO)_3$ (**1l**) to *tert*-butyl geranyl carbonate complex **2i** exhibited good regioselectivity (L:B = 78:22) and good isolated yield of the linear product **5li** (73% yield, entry 6). The carbon−carbon double bond of the products in Table 4 will facilitate subsequent functionalizations to afford a variety of diphenylmethane derivatives.

2.5. Allylation with Benzyl Amine and Ether Derivatives.

Stereogenic centers α to heteroatoms are important in the synthesis of bioactive compounds. We therefore examined reactions of benzyl ether and amine substrates (η^6-$C_6H_5CH_2Z$)Cr-$(CO)_3$ (Z = OR, NR_2). Benzylamines often direct metalation to the *ortho* position[34] as do activated (η^6-$C_6H_5CH_2Z$)$Cr(CO)_3$ complexes in the presence of strong organolithium bases (Z = NR_2). Interestingly, under the reversible deprotonation conditions employed herein, (η^6-C_6H_5−CH_2Z)$Cr(CO)_3$ complexes exhibit orthogonal chemoselectivity with metalation taking place at the benzylic C−H's. As illustrated in eq 5, the (η^6-$C_6H_5CH_2Z$)$Cr(CO)_3$ benzyl ether (**1o**) and amines (**1p**, **1q**) are excellent substrates for the allylic substitution reaction with allyl *tert*-butyl carbonate **2d**, giving products in high yields (90−97%).

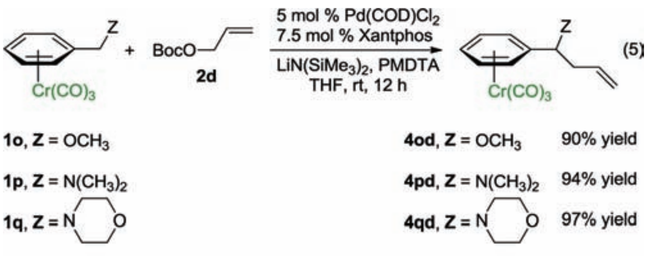
Table 4. Tandem Synthesis of Diphenylmethane Derivatives[a]

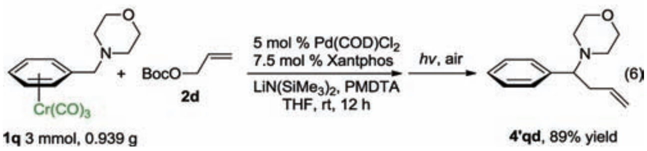


Entry	Electrophile		Product		Yield (%)
1		2b		5lb	96[b]
2		2g		5lg	89[b]
3		2d		5ld	91[b]
4		2f		5lf	96[b,d]
5		2h		5lh *cis*:*trans* = 2:1	77[b,d]
6		2i		5li *linear product*	73%[b]
				5li' *Crude product* 5li :5li' = 78:22[c]	

[a] Reactions conducted on a 0.1 mmol scale using 1 equiv of **1l**, an excess of $LiN(SiMe_3)_2$ and **2** at 0.1 M (see Supporting Information for details). [b] Isolated yield after chromatographic purification. [c] Ratio of linear: branched (L:B) was determined by ^1H NMR of the crude reaction mixture. The regioisomers were separable by silica gel chromatography. [d] $[Pd(allyl)Cl]_2$/1,3-bis(diphenylphosphino)propane (DPPP) was used as catalyst in place of $Pd(COD)Cl_2$/Xantphos.

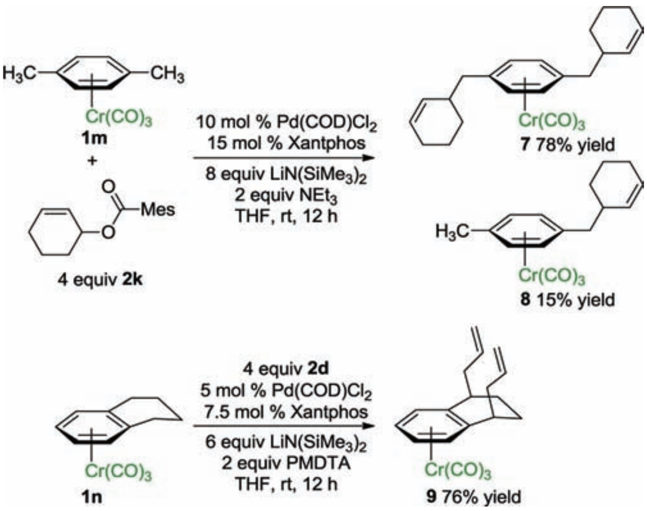
The scalability of this method was demonstrated by a tandem allylic substitution/demetalation reaction of benzyl morpholine (**1q**) on a 3 mmol scale, which afforded the metal-free organic product in 89% yield (eq 6).





2.6. Allylation at Multiple Benzylic Sites. Having demonstrated that diallylation could occur on a single benzylic methyl group (Table 3, entry 4), we explored the possibility of activation of multiple benzylic positions in (η^6-arene)Cr(CO)$_3$ complexes of *p*-xylene and tetralin (Scheme 2). Subjecting (η^6-*p*-xylene)Cr(CO)$_3$ (**1m**) to allylation conditions with a sterically hindered allylic partner, cyclohex-2-enyl mesitoate (**2k**), furnished the diallylation product **7** in 78% isolated yield.

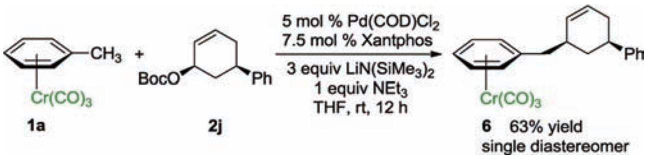
Scheme 2. Allylation at Multiple Benzylic Sites



In the case of (η^6-tetralin)Cr(CO)$_3$ (**1n**), we were somewhat concerned that after the first allylation, the newly formed 2-propenyl moiety would hinder deprotonation of the second benzylic center by the bulky base, LiN(SiMe$_3$)$_2$. As shown in Scheme 2, however, the double allylation proceeded smoothly at ambient temperature and the *cis*-diallylation product **9** was isolated in 76% yield.[17,18] Presumably this approach could be coupled with ring closing metathesis to afford bicyclic scaffolds.

2.7. Internal vs External Attack of (η^6-ArCH$_2$Li)Cr(CO)$_3$ on π-Allyl Palladium Intermediate. One significant difference between “hard” and “soft” nucleophiles in allylic substitution reactions is their distinct mechanistic pathways. Nucleophiles classified as “soft” undergo external attack on the π-allyl ligand[35] and the net process of the allylic substitution is stereoretentive (via double inversion). In contrast, “hard” nucleophiles undergo addition to the metal center of the π-allyl complex (i.e., transmetalation) followed by reductive elimination to form the new C−C bond.[36] This latter mechanism results in an overall inversion of configuration in the allylic substitution.

Scheme 3. Allylic Substitution with Retention of Configuration



To determine whether the conjugate bases of the (η^6-arene)-Cr(CO)$_3$ complexes behave as “soft” or “hard” nucleophiles in the palladium-catalyzed allylic substitution, (η^6-toluene)Cr(CO)$_3$ complex **1a** was reacted with the *cis*-disubstituted stereochemical probe **2j** (Scheme 3). In the allylic substitution with **2j** the product *cis*-**6** was obtained in 63% isolated yield as a single diastereomer, as determined by comparison of the splitting patterns and coupling constants with related products by ^{1}H NMR spectroscopy (see Supporting Information for details). Formation of *cis*-**6** indicates that the reaction occurs predominantly via external attack of the “soft” conjugate base derived from (η^6-toluene)Cr(CO)$_3$ on the palladium-bound π-allyl ligand. The observed double inversion is consistent with the ability of the Cr(CO)$_3$ moiety to stabilize benzyl anions by delocalization of the negative charge onto the chromium to “soften” the nucleophilicity of the organolithium.[16,17]

3. SUMMARY AND OUTLOOK

We have developed the first general method for palladium-catalyzed allylic substitution with the conjugate bases of toluene derivatives. Key to the success of our method is the activation of the arene's benzylic C−H's by η^6-coordination to tricarbonylchromium. Also very important was the HTE approach to identify the Xantphos/Pd(COD)Cl$_2$ combination as an excellent catalyst for this allylic substitution reaction. Mechanistic studies indicate that (η^6-toluene)Cr(CO)$_3$ derivatives behave as “soft” or stabilized nucleophiles. They attack the palladium π-allyl complex externally, leading to a net double inversion in the allylic substitution. The (η^6-arene)Cr(CO)$_3$ derivatives are reversibly deprotonated by LiN(SiMe$_3$)$_2$ under mild conditions, allowing for the in situ generation of the nucleophilic organolithium intermediates.

The synthetic significance of this method is that it enables the application of a variety of benzylic nucleophiles in palladium-catalyzed allylic substitution reactions and provides access to allylation products that are otherwise difficult to prepare. The method is general in that a range of nucleophiles, derived from (η^6-arene)Cr(CO)$_3$ complexes, can be readily employed with structurally diverse allylic alcohol derivatives bearing OAc, OBz, OBoc, or OPiv leaving groups. A tandem allylic substitution/demetalation procedure has been developed for the one-pot synthesis of diarylmethane derivatives, which are increasing in their importance. We believe this method will be a valuable complement to the existing arsenal of nucleophiles with applications in allylic substitution reactions. Identification of catalysts for asymmetric palladium-catalyzed allylic substitution reactions is underway.[37]

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. THF was freshly distilled from Na/benzophenone ketyl under nitrogen. Unless otherwise stated, reagents were commercially available and used as purchased without further purification. Chemicals were obtained from Sigma-Aldrich or Acros, and solvents were purchased from Fisher Scientific. The progress of reactions was monitored by thin-layer chromatography using Whatman Partisil K6F 250 μm precoated 60 Å silica gel plates and visualized by short-wave ultraviolet light as well as by treatment with ceric ammonium molybdate (CAM) stain. 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 125 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 on KBr plates using a Perkin-Elmer Spectrum 100 Series FTIR spectrometer. The masses of chromium-complexes were recorded with electrospray + (ES+) HRMS methods, and $[M]^+$ or $[M - (CO)_3]^+$ (unless otherwise stated) was confirmed by the presence of the characteristic chromium isotope pattern. Chromium-decomplexed masses were recorded with chemical ionization + (CI+) HRMS methods.

4.2. Cautionary Note. Care should be taken to avoid direct exposure of reaction mixtures to bright light, as arene tricarbonylchromium complexes can decompose in solution under bright light and air.

4.3. General Procedure A. Synthesis of (η^6-Toluene)Cr(CO)$_3$ Derivatives. A solution of $Cr(CO)_6$ (1.10 g, 5.0 mmol), arene (1.2−5 equiv), and THF (3 mL) in 1,4-dioxane (8 mL) was heated under reflux (oil bath temp = 120 °C) under a nitrogen atmosphere for 3−5 days. The yellow−orange solution was allowed to cool, and completion of the reaction was verified by the absence of solid $Cr(CO)_6$ on the sides of the flask (from sublimation) after refluxing subsided. After cooling to rt, the solution was filtered through Celite and then evaporated under reduced pressure. The yellow product was either recrystallized from diethyl ether and hexanes or purified by column chromatography eluting with EtOAc/hexanes.

4.4. General Procedure B. Pd-Catalyzed Allylic Substitution with (η^6-Arene-CH$_2$Z)Cr(CO)$_3$-Based Nucleophiles. An oven-dried reaction vial equipped with a stir bar was charged with (η^6-arene-CH$_2$Z)Cr(CO)$_3$ (0.10 mmol). To the reaction vial was added $LiN(SiMe_3)_2$ (50.2 mg, 0.30 mmol, 3 equiv) under a nitrogen atmosphere followed by 0.5 mL of dry THF, and the reaction mixture was stirred for 5 min. A solution of Pd(COD)Cl$_2$ (1.43 mg, 0.0050 mmol) and Xantphos (4.34 mg, 0.0075 mmol) in 0.5 mL of THF was taken up by syringe and added to the reaction vial. After stirring for 5 min, the allylic electrophile (0.2 mmol, 2 equiv) was added to the reaction followed by NEt$_3$ (14 μL, 0.1 mmol, 1 equiv). The reaction mixture was stirred for 12 h at rt. The reaction mixture was 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.

4.5. General Procedure C. Tandem Allylic Substitution/Demetalation. The reaction was conducted according to General Procedure B described above. After 12 h, the reaction was quenched with two drops of H_2O and diluted with 10−20 mL of diethyl ether, and the solution was exposed to sunlight by placing it on the windowsill and stirring for 3−6 h. The demetalation step was monitored until TLC showed complete consumption of the (η^6-arene)Cr(CO)$_3$ product. During this time, a green precipitate formed as the chromium was oxidized. The reaction mixture was then filtered through a pad of MgSO$_4$ and silica, concentrated in vacuo, and loaded directly onto a silica gel column. After demetallation, the crude material was purified by flash chromatography on silica gel (eluted with hexanes to EtOAc/hexanes = 5:95).

ASSOCIATED CONTENT

Ⓢ Supporting Information. Procedures, full characterization of new compounds, and crystallographic data for **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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