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Friedel–Crafts-type Allylation of Phenol Derivatives Catalyzed by Silyl Cyanometallates Generated *In Situ*

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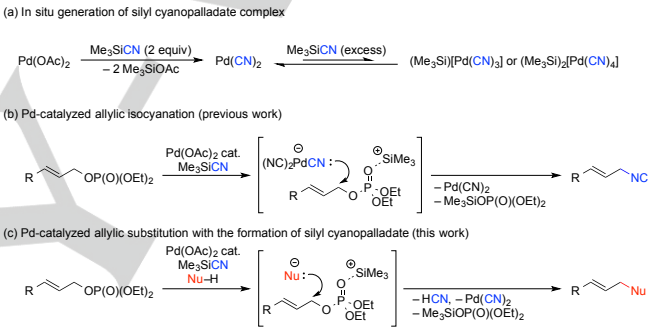
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Abstract: We successfully demonstrated that Friedel–Crafts-type allylation of phenol derivatives and allylic phosphates is catalyzed by the AgTFA/trimethylsilyl cyanide (Me_3SiCN) and $Pd(OAc)_2/Me_3SiCN$ combined systems to afford the *C*-allylated product in a highly regioselective manner. The corresponding silyl cyanometallates generated *in situ* are proposed to be the active catalytic species. Lewis acidity of the reversibly formed ion pairs is appropriately regulated for this reaction. The *para*-allylated anisole and phenol derivatives are selectively obtained. The *para*-substituted ones are converted to the *ortho*-allylated products. The reactivity of the catalytic systems is strongly dependent on the electronic nature of both electrophile and nucleophile. Substitution of an aromatic ring on the allylic phosphate is essential for the reaction. Thus, the competitive reaction of a 1:1 mixture of cinnamyl and simple allyl phosphates affords only the cinnamyl-substituted product.

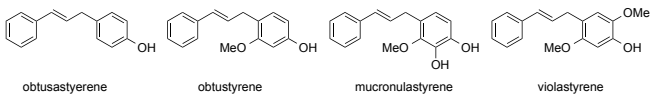
It is well known that the *C*-terminus of cyanide (CN^-) strongly interacts with several transition metal species to form chemically stable metal cyanide salts. In some cases, in the presence of excess amounts of cyanide sources, the corresponding cyanometallate complexes are also obtained.[1,2] Recently, we demonstrated an isocyanation of allylic phosphates using Me_3SiCN as a stoichiometric cyanide source with a catalytic amount of $Pd(OAc)_2$. Mechanistic studies suggested that cyanopalladates, $(Me_3Si)[Pd(CN)_3]$ and/or $(Me_3Si)_2[Pd(CN)_4]$, generated *in situ* acted as reactive species (Scheme 1a, 1b).[3] The cationic silyl group acts as a Lewis acid to activate the phosphate leaving group, and the *C*-blocked cyanides, such as $[Pd(CN)_3]^-$, $[Pd(CN)_4]^{2-}$, and Me_3SiCN, function as *N*-nucleophiles. The Lewis acidity of the reversibly formed catalyst system was appropriately controlled for activation of the allylic phosphates: the acidity was stronger than that of Me_3SiCN, but weaker than that of Me_3SiOTf in the isocyanation of allylic phosphates. We envisioned that other nucleophiles could be introduced by using the cyanometallate system with the addition of a nucleophile more reactive than the cyanide species (Scheme 1c). Based on this hypothesis, we focused on the Friedel–Crafts-type allylation using phenol and its derivatives.[4]



Scheme 1. Catalytic allylic substitution using *in situ*-generated silyl cyanopalladate complexes derived from $Pd(OAc)_2$ and Me_3SiCN.

Many *C*-cinnamyl phenol derivatives are known as common phytochemicals, and some show several unique bioactivities. For example, obtusastyrene and obtustyrene, which have been isolated from *Dalbergia retusa*, show antimicrobial properties (Figure 1).[5,6] Development of an effective approach for synthesizing these molecules is required from the perspective of both synthetic organic chemistry and biomolecular chemistry. One of the most reliable strategies for the synthesis of these 1,3-diarylpropenes is the Pd-catalyzed allylic arylation using suitable allylation reagents and aryl boronic acids or boronates.[7] With this protocol, the targeted C–C bond is constructed only at the boron-substituted carbon of the aryl ring. However, the corresponding hydroxy- or alkoxy-substituted arylboronic acid derivatives should be prepared in high regioselectivity beforehand. In addition, it is usually necessary to perform the allylic arylation carefully under an inert atmosphere, because most of the catalytically active Pd(0) species are air-sensitive. Friedel–Crafts-type allylation is another potent methodology to afford the *C*-cinnamyl phenol derivatives, with making good use of the electron-rich aromatic rings of phenolic nucleophiles. Both Lewis and Brønsted acids have been widely used as catalysts for activation of the cinnamyl electrophiles.[8,9] The straightforward and air-tolerant features make this method convenient and useful. However, the difficulty of precisely controlling the regioselectivity through nucleophilic substitutions

with the phenol derivatives showing the *ortho*-*para* orientations has been an intrinsic and general problem with this approach. Herein we described in detail the Friedel–Crafts-type allylation of phenol derivatives using the silyl cyanometallate catalysts derived from Pd(II) or Ag(I) salts with stoichiometric amounts of Me_3SiCN. The *C*-cinnamyl phenol products were obtained with high regioselectivity.

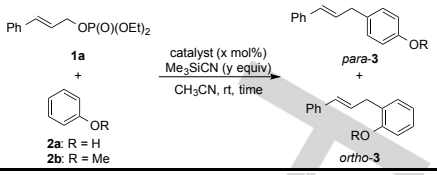


obtusastyerene obtustyrene mucronulastyrene violastyrene

Figure 1. Examples of phytochemical *C*-cinnamyl phenols.

We selected the reaction of cinnamyl phosphate **1a** with phenol **2a** and anisole **2b** for screening of catalysts and conditions (Table 1). The combination of $Pd(OAc)_2$ (2 mol%) and Me_3SiCN (2 equiv) promoted the allylation of **2a** to afford the *para*-cinnamyl phenol exclusively in 72% yield (entry 1). In this case, *O*-allylation product; that is, cinnamyl phenyl ether, the typical product of the Tsuji–Trost-type Pd-catalyzed allylations of phenol, was not observed.[10] Both $Pd(OAc)_2$ and Me_3SiCN were necessary to advance the transformation, suggesting that the allylation was catalyzed by $(Me_3Si)[Pd(CN)_3]$ and/or $(Me_3Si)_2[Pd(CN)_4]$ generated *in situ* (entries 2 and 3). AgTFA with Me_3SiCN showed even higher activity, although a mixture of *para*- and *ortho*-adducts was obtained when using this combination (entry 4). No reaction was observed in the absence of Me_3SiCN, suggesting that the Ag ate complex $(Me_3Si)[Ag(CN)_2]$ acted as the catalytic active species (entry 5).[11] The AgTFA/Me_3SiCN catalyst was suitable for the allylation of **2b** in terms of the activity and regioselectivity, affording the *para*-substituted product within 7 h quantitatively (entry 6). When $Pd(OAc)_2$ was employed instead of AgTFA, the *para*-product contaminated with the *ortho*-isomer was formed at a slower rate compared to the reaction of **2a** (entry 7 vs. 6). These results indicated that the cyanometallate counterpart in the catalytic species clearly affected both the efficiency and regioselectivity. Notably, some existing silyl Lewis acids unsuccessfully catalyzed the allylation. Me_3SiOAc did not furnish any product at all (entry 8). When Me_3SiCl was used instead of the combined catalyst, the allylation product was obtained in only 8% yield, with formation of undesired cinnamyl chloride in 2% yield (entry 9). A stronger Lewis acid, Me_3SiOTf, promoted the reaction along with the decomposition of the phosphate to give the *para*-product in 75% yield (entry 10). Formation of the *ortho*-isomer in 5% yield was also observed. Although the reaction should be carried out at 60 ºC, the amount of Ag salt could be reduced to 1 mol% (entry 11). Addition of 2 equiv of Me_3SiCN was necessary to complete the reaction regardless of the catalyst amount (entry 12). A catalytic amount of trifluoroacetic acid (1 mol%) without Me_3SiCN did not promote the reaction at all.

Table 1. Screening of catalysts and conditions for Friedel–Crafts-type allylation.[a,b]

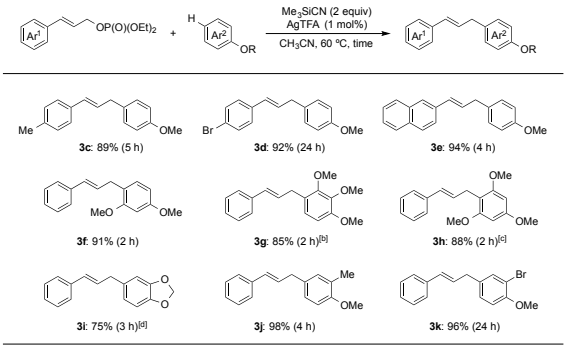


Entry	Nucleophile	Catalyst (x mol%)	y equiv	Time (h)	*para*-**3** (%)	*ortho*-**3** (%)
1	**2a**	$Pd(OAc)_2$ (2)	2	24	72 (72)	trace
2	**2a**	no	2	24	0	0
3	**2a**	$Pd(OAc)_2$ (2)	0	24	0	0
4	**2a**	AgTFA (2)	2	24	74	19
5	**2a**	AgTFA (2)	0	24	0	0
6	**2b**	AgTFA (2)	2	7	>99 (98)	0
7	**2b**	$Pd(OAc)_2$ (2)	2	24	69	4
8	**2b**	Me_3SiOAc (2)	0	24	0	0
9	**2b**	Me_3SiCl (2)	0	24	8	0
10	**2b**	Me_3SiOTf (2)	0	24	75	5
11[c]	**2b**	AgTFA (1)	2	5	>99	0
12[c]	**2b**	AgTFA (1)	1	5	28	0

[a] ^{1}H NMR yields of the product are shown. The isolated yield is given in parenthesis. [b] The product assignments are as follows: *para*-**3a**, 4-cinnamyl phenol; *ortho*-**3a**, 2-cinnamyl phenol; *para*-**3b**, 4-cinnamyl anisole; *ortho*-**3b**, 2-cinnamyl anisole. [c] The reaction was carried out at 60 ºC.

With the optimized reaction conditions in hand, we then investigated the scope of the Friedel–Crafts-type allylation of phenol derivatives (Table 2). The electron-rich anisole derivatives were smoothly converted into the corresponding *para*-allylated products, **3c**–**3k**, in high yield. Substituents on the cinnamyl phenyl ring affected the reaction rate. The *para*-methyl-substitution (**3c**) shortened the reaction time. Electron-withdrawing bromide suppressed the rate, although a high yield of **3d** was achieved after the longer reaction time. These results suggested that the allylation proceeded through an S_N1-type mechanism. An allylic phosphate with a 2-naphthyl group was also a suitable substrate to give the desired product **3e** in 94% yield within 4 h. As we expected, the more electron-rich aromatic nucleophiles rapidly reacted with the allylic phosphate to afford the monocinnamyl products **3f** and **3j** exclusively. The reaction of 1,2,3- and 1,3,5-trimethoxybenzenes as well as the less hindered 1,3-benzodioxole afforded the monoallylated products, **3g**, **3h** and **3i**, in 85%, 88% and 75% yield accompanied with the dicinnamyl compound in 12%, 4% and 18% yield, respectively. The reaction with 2-bromoanisole proceeded slowly, but the desired 4-cinnamyl product **3k** was obtained in 96% yield. The poor reactivity with electron-deficient aromatic nucleophiles is an obvious drawback of this method: no allylation product was observed in the reactions with *t*-butylbenzene, chlorobenzene, or phenylacetate.

Table 2. Allylation using anisole derivatives as nucleophiles with the AgTFA/Me_3SiCN combined catalyst.[a]

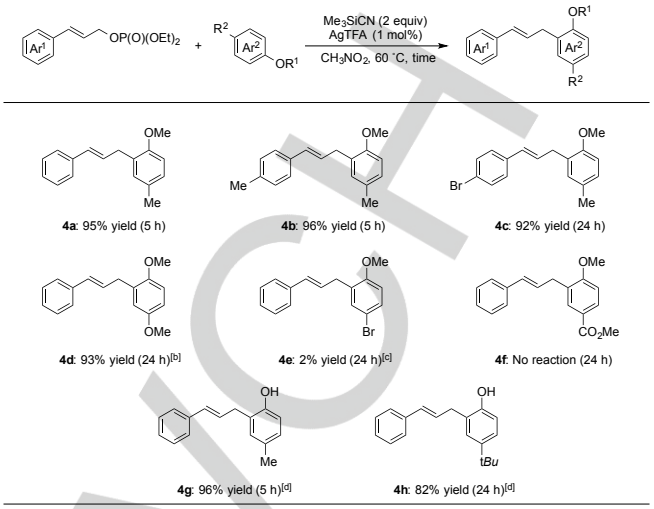


[a] Isolated yield is given. [b] The diallylated product was formed in 12% yield. [c] The diallylated product was formed in 4% yield. [d] The diallylated product was formed in 18% yield.

Some *para*-substituted phenols and anisoles reacted with the allylic phosphates catalyzed by the AgTFA/Me_3SiCN and $Pd(OAc)_2$/Me_3SiCN systems to afford the sterically hindered *ortho*-substituted products in high yield (Table 3). CH_3NO_2 was found to be the more suitable solvent in these cases. The effects of substituents on the cinnamyl electrophiles were similar to those observed in the allylation at the *para*-position of the anisole derivatives (**4a**–**4c**). The reaction of 4-bromocinnamyl phosphate was slower than the reactions of unsubstituted and 4-methylcinnamyl electrophiles. The influence of the substituents at the *para*-positions of the anisole nucleophiles on the reactivity was more obvious than that of the *ortho*-substituents (**4d**–**4f**). Highly reactive 1,4-dimethoxybenzene was converted to a mixture of 2-mono- and 2,5-disubstituted products in a 1.8:1 ratio under the original conditions. The yield of the desired monoallylated product **4d** increased to 93% under the milder reaction conditions: AgTFA (1 mol%), Me_3SiCN (2 equiv), CH_3CN, 30 ºC. On the other hand, the reaction of 4-bromoanisole gave the allylation product **4e** in only 2% yield. Methyl 4-methoxybenzoate was inert under these conditions. *para*-Substituted phenols were also suitable substrates for the Friedel‑Crafts-type allylation. With 1 mol% of $Pd(OAc)_2$ as a catalyst, *para*-cresol and 4-*tert*-butylphenol were converted into the *ortho*-cinnamyl products, **4g** and **4h,** in high yield.

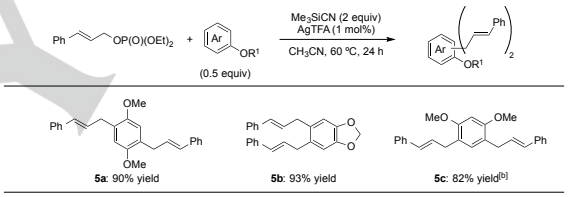
When the electron-rich aromatic nucleophiles were reacted with 2 equiv of cinnamyl phosphate, the diallylation products were obtained preferentially (Table 4). The reaction with 1,4-dimethoxybenzene afforded the 2,5-diallylated product **5a** in 90% yield as a sole product. Formation of the 2,3-disubstituted product was not observed. The diallylation on 1,3-benzodioxole proceeded predominantly at the 4,5-carbons (**5b**). In the same manner, *m*-dimethoxybenzene was converted to the 2,4-diallylated product (**5c**) accompanied by the branch-type monoallylation product, 2,4-dimethoxy-2-(1-phenylallyl)benzene, in 6% yield. This was only the case to give the branch-type compound in >2% yield as a byproduct, although the reason was not clear.

Table 3. Allylation using *para*-substituted anisole and phenol derivatives as nucleophiles with the AgTFA/Me_3SiCN or $Pd(OAc)_2$/Me_3SiCN combined catalyst.[a]



[a] Isolated yield is given. [b] CH_3CN was used instead of CH_3NO_2. The reaction was carried out at 30 ºC. [c] ^1H NMR yield. [d] $Pd(OAc)_2$ (1 mol%) was used instead of AgTFA as a catalyst.

Table 4. Diallyation on the electron-rich aromatics with the AgTFA/Me_3SiCN combined catalyst.[a]

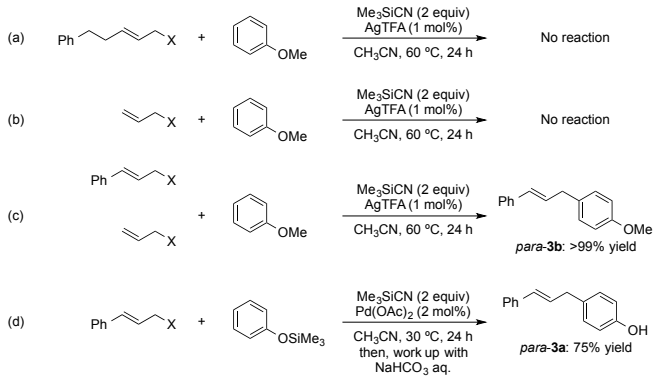


[a] Isolated yield is given. [b] 2,4-Dimethoxy-2-(1-phenylallyl)benzene was included as a side product (6% ^1H NMR yield).

Reactivity of the Friedel–Crafts-type allylation was significantly dependent on the electronic properties of substrates (Scheme 2). An aliphatic allylic phosphate did not react with anisole under the optimal conditions using the AgTFA/Me_3SiCN system (Scheme 2a). No conversion was observed at all, even with the simple allyl phosphate (Scheme 2b). Notably, the competitive reaction using a 1:1 mixture of cinnamyl and allyl phosphates resulted in the perfect chemoselectivity for producing the *para*-cinnamyl compound **3b** in quantitative yield (Scheme 2c). $(Me_3Si)[Ag(CN)_2]$ formed in the AgTFA/Me_3SiCN system seemed to activate arylated allylic phosphates specifically as a Lewis acid in CH_3CN.

As shown in Table 1, entry 1, the *para*-selective allylic substitution of phenol was catalyzed by the $Pd(OAc)_2$/Me_3SiCN system. A separate experiment using isolated Me_3SiOPh as the nucleophile under the regular conditions afforded the *para*-cinnamylphenol **3a** exclusively in 75% yield after desilylation (Scheme 3d). This observation suggested that the highly chemo- and regioselective allylation of phenol actually occurred on the Me_3SiOPh formed *in situ*.

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Scheme 2. Chemical properties observed in the Friedel–Crafts-type allylation (X = $OP(O)(OEt)_2$). Two equivalents of the aromatic nucleophiles to the allylic phosphates were used.

A plausible reaction mechanism is described in Figure 2. AgTFA reacts with Me_3SiCN to afford a stable cyanide salt, AgCN, quantitatively. In the presence of excess amounts of Me_3SiCN, $(Me_3Si)[Ag(CN)_2]$ is generated reversibly. The ate complex acts as a silyl Lewis-acid catalyst to activate the allylic phosphate. The reversible feature of the ion pair appropriately controlled the Lewis acidity for this transformation. Anisole, an electron-rich aromatic compound, has stronger nucleophilicity than $[Ag(CN)_2]^-$, and the substitution at the *para*-position proceeds to give the ion-pairing intermediate along with the release of a silyl phosphate, $(Me_3Si)OP(O)(OEt)_2$. The stability of the ionic intermediate may determine the regioselectivity. Volatile HCN is removed from the intermediate to generate the target allylation product and AgCN. Me_3SiCN reacted again with the resulting AgCN to form the reactive $(Me_3Si)[Ag(CN)_2]$. The system of $Pd(OAc)_2/Me_3SiCN$ also follows a similar pathway with formation of $(Me_3Si)[Pd(CN)_3]$ and/or $(Me_3Si)_2[Pd(CN)_4]$ as possible catalytic active species.[3] In this case, Me_3SiOPh formed *in situ* acts as a regioselective nucleophile.

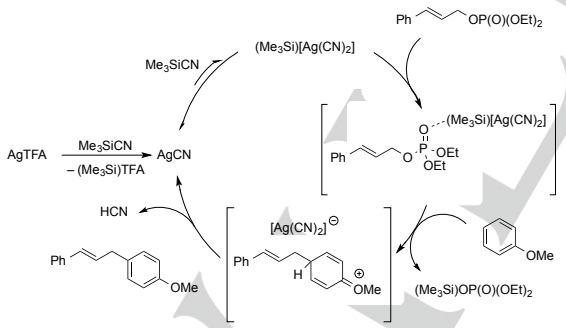


Figure 2. A plausible reaction mechanism of the AgTFA/Me_3SiCN-catalyzed Friedel–Crafts-type allylation.

In conclusion, we successfully employed the combined catalytic systems of transition metal species and Me_3SiCN for regioselective Friedel–Crafts-type allylation of phenol derivatives. The key active catalytic species are proposed to be the silyl cyanometallates generated *in situ*. The silyl moiety of the complex works as an appropriately regulated Lewis acid, and it efficiently promotes the *C*-allylation. The cyanometallate counterpart affects the regioselectivity at the substitution, in addition to contributing to the control of the Lewis acidity of the catalyst system. The obvious chemoselectivity on the allylic phosphates is also a characteristic of this catalytic system. Further studies and applications of the allylation with Ag/Si and Pd/Si combined catalysts are currently underway in our laboratory.

Acknowledgements

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Keywords: Silyl Lewis acid • Friedel–Crafts reaction • Allylic substitution • Ag catalyst • Pd catalyst

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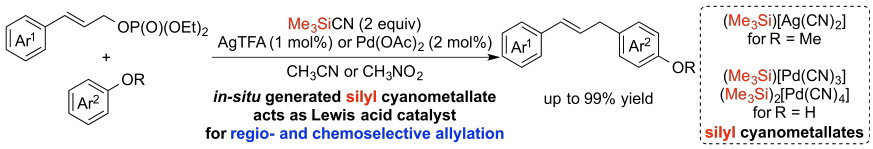
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Regioselective Friedel–Crafts-type allylation was achieved by combined catalytic systems derived from transition metal species, AgTFA or $Pd(OAc)_2$, and trimethylsilyl cyanide. The *para*-allylated anisole and phenol derivatives were selectively obtained. Silyl cyanometallates formed *in situ* activated allylic phosphates as Lewis acids. The cyanometallate counterparts appeared to control the acidity of silyl species and to affect the regioselectivity.

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