Ph.D. thesis

Lewis Acidic Catalysis of Silyl Cyanometallates in Transformations of Phenol and Aniline Derivatives

(フェノールおよびアニリン誘導体変換反応における

シリルシアノメタラートの **Lewis** 酸触媒作用**)**

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General Introduction

Silicon is a group 14 element exhibiting tetravalency, which is similar to carbon. Silicon is able to construct a stable sp^3 orbital hybridized with two 3s and two3p orbitals. The structures of most organosilicon compounds are tetrahedral because of the hybridization. However, chemical property of an organosilicon compound is different from the corresponding organic analog with carbon chain. The length of Si–C bond is typically 1.84 Å, which is a little longer than C–C single bond (1.54 Å). Silicon atom is relatively positive than carbon center from the viewpoint of Pauling's electronegativity. In addition, Si atom shows strong interaction with several hetero atoms such as oxygen, nitrogen and fluorine, rather than carbon.

Organosilicon compounds are generally low toxic, air and moisture stable reagents and part of them are commercially available. Their usage has received extensive interests in various research areas, such as pharmaceuticals, agrochemicals, and functionalized material for decades.[1] In synthetic organic chemistry, the extraordinal controllable reactivity and availability is remarkable feature of organosilicon reagent. They have been employed for several organic transformations such as oxidation, amination, halogenation and cross-coupling reaction.[1]

The study of organosilicon chemistry as Lewis acid species originally started from 1970s. To date, silyl Lewis acids (SLAs) occupies the major research area in the Lewis acid-catalyzed transformations. SLAs have shown some advantages for their use in synthetic organic chemistry. For example, they are compatible with wide varieties of reactive and well-

used *C*-nucleophiles, such as silyl enol ether, allyl organometallic reactants, and cuprates. SLAs do not form their aggregation easily, unlikely to many organometallic compounds.[1c] ^{29}Si center is NMR active. These features efficiently help to analyze the reaction mechanism of the catalytic reactions. In addition, the preparation methods of organosilicon compounds have been well-studied, and thus the researchers can easily design with appropriate steric volume and electronic properties by themselves.

1. Lewis Acidity of Silicon Center

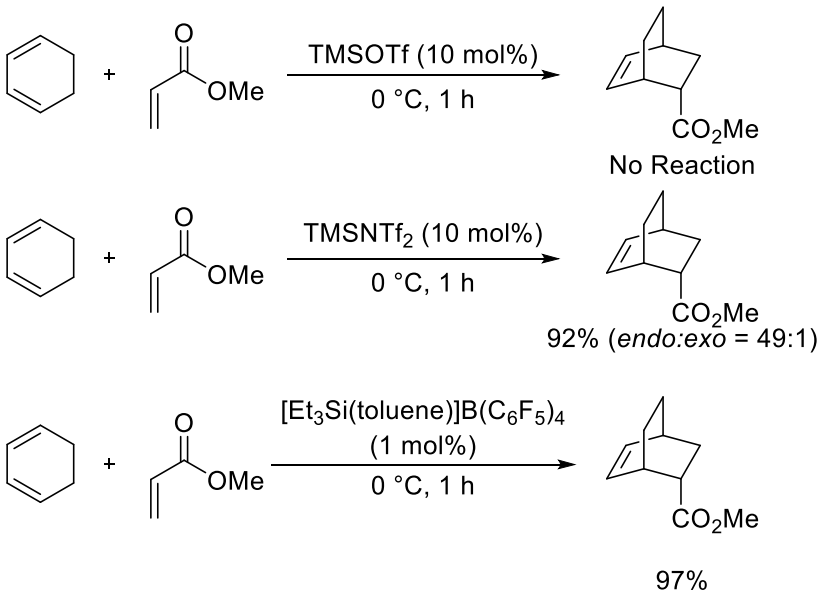
Most of the organosilicon compounds easily form the hyper-coordinated (penta and hexa coordinated) species with a strong Lewis base. This means, the organosilicon potentially plays as a Lewis acid. The acidity and catalytic performance of tetracoordinate organosilicon Lewis acids (R_3SiX) is largely depending on the counter anion (X group) and the R group. The influence of the counter anion is more pronounced. Graddon and Rana reported a method to estimate Lewis acidity of silyl acetates ($R_nSi(OAc)_{4-n}$) by measuring the coordination with amines.[2] They revealed that the silicon compound bound with the more acetate groups formed the thermodynamically more stable amine adduct. In general, the Lewis acidic property of neutral alkyl- and alkoxysilanes is too weak to activate the organic reagents as catalysts. However, when one of the four substituents on silicon is changed to a soft Lewis base, such as triflate (TfO^-) or iodide (I^-) ion, they become strong Lewis acids bearing one coordination site.[3] The ^{29}Si NMR measurement can estimate how strongly electronegative groups effecting on Lewis acidity of the silicon center (Table 1). The signal of $TMSNTf_2$ (**1**) is observed at 55.9 ppm, which is in downer field than those of $TMSN(SO_2F)_2$ (**2**: 44.9 ppm), TMSOTf (**3**: 43.5 ppm) and TMSCl (**4**: 31.1 ppm).[4a] When triethylsilyl cation is coupled with almost non-coordinating $[B(C_6F_5)_4]^-$ as the counter anion (**5**), the signal is found at 81.8 ppm.[4b] When

these organosilicon compounds are employed as catalysts for the Diels–Alder reaction between 1,3-cyclohexadiene and methyl acrylate, the obvious differences are found (Scheme 1). TMSOTf (10 mol%) is not able to promote the reaction at all at 0 ºC. In contrast, $TMSNTf_2$ (10 mol%) gave the product in 92% yield with a 49:1 *endo*/*exo* selectivity through the one-hour reaction.[4c] $[Et_3Si(toluene)][B(C_6F_5)_4]$ is the more highly efficient catalyst affording the Diels–Alder adduct in 97% yield with 1 mol% catalyst loading.[5]

Table 1. ^{29}Si Chemical shifts (in ppm) of TMS-X compounds

$TMSNTf_2$	$TMSN(SO_2F)_2$	TMSOTf	TMSCl	$[Et_3Si(toluene)][B(C_6F_5)_4]$
1	**2**	**3**	**4**	**5**
55.9	44.9	43.5	31.1	81.8

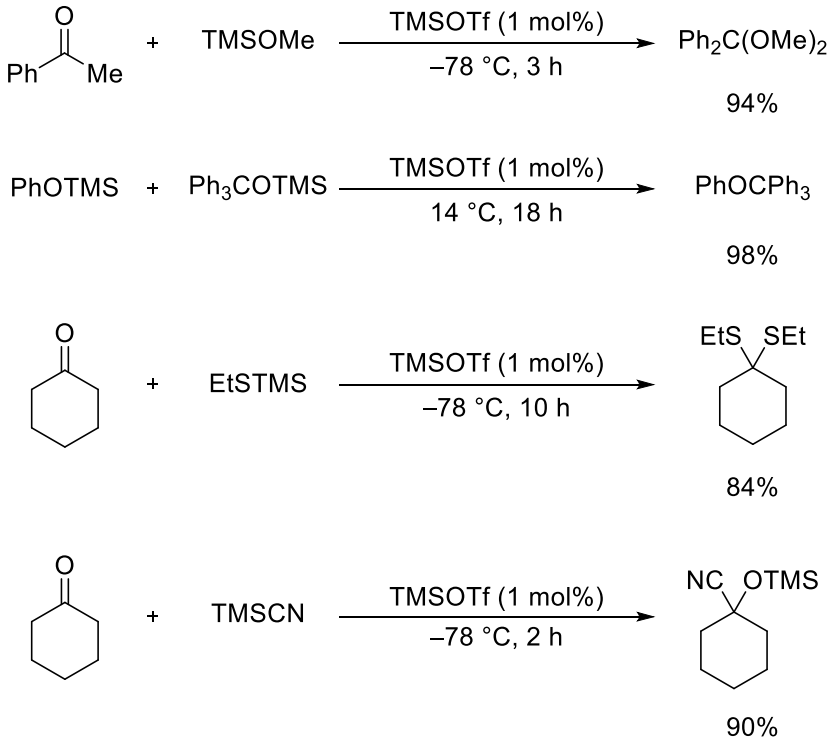
Scheme 1. Organosilicon Lewis acid-catalyzed Diels–Alder reactions for estimating the catalytic activities



2. Formation of Silyl Lewis Acids and Their Synthetic Use

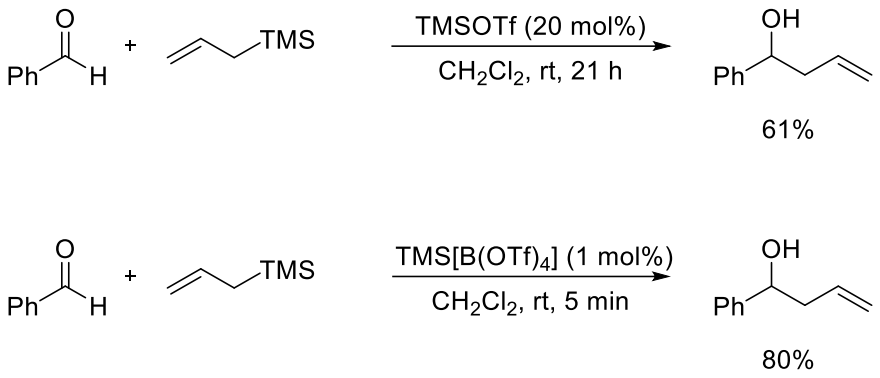
The family of R_3SiOTf is originally regarded as a silylation reagent.[6] Noyori and coworkers reported the pioneering study for catalytic utility of TMSOTf, which is one of the most typical SLAs now. The *O*-tritylation of trimethylsilyl ether was promoted by 1 mol% of TMSOTf, and then wide varieties of transformations were demonstrated including ring-opening of epoxides, formation of acetals and thioacetals, cyanosilylation of ketones, and Mukaiyama aldol reaction (Scheme 2).[7,8] To date, TMSOTf is commercially available reagent, and is often applied to the numerous transformations.

Scheme 2. Selected example of TMSOTf–catalyzed transformations



The Lewis acidity of organosilicon compounds are strongly depending on their counter anions. For achieving more reactive species than TMSOTf, exchange of the counter anion by less basic one is potent strategy for designing the catalytic species. Davis and coworkers reported the TMS[B(OTf)$_4$] generated *in situ* from TMSOTf and B(OTf)$_3$.[9] The species effectively catalyzed Hosomi–Sakurai allylation (Scheme 3): The reaction between allyl trimethylsilane and benzaldehyde afforded the allylated product in 61% yield in the presence of TMSOTf (20 mol%). On the other hands, 1 mol% of TMS[B(OTf)$_4$] was enough to complete the same reaction within 5 min resulting in 80% yield of the product.

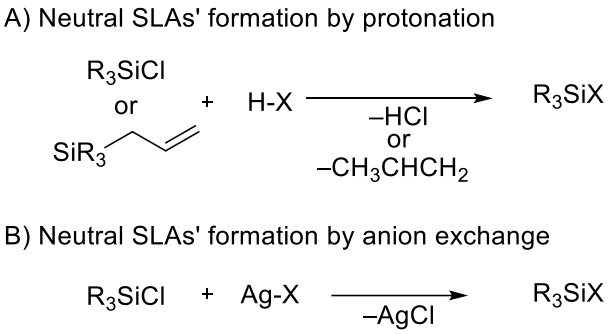
Scheme 3. Counter anion's effect on Hosomi-Sakurai Allylation



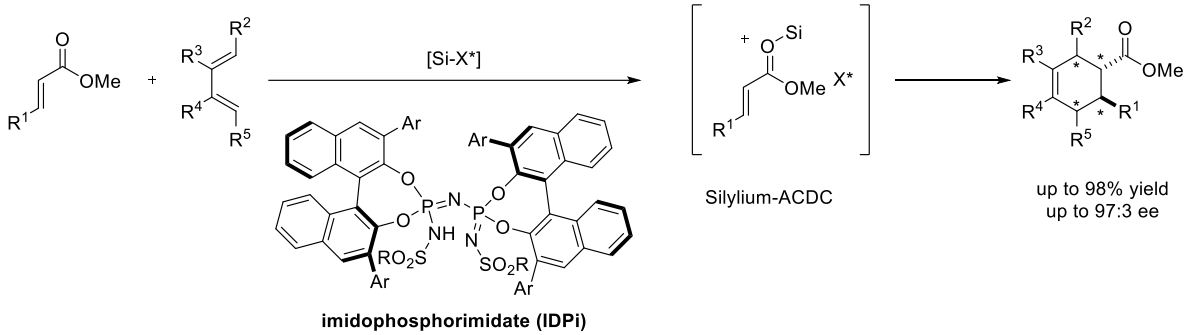
The procedures for exchanging the counter anion of SLAs are shown as follows. The typical tetrahedral SLAs possessing a less-coordinative counter anion, such as R$_3$SiOTf and R$_3$SiNTf$_2$, are formed through the protonation of the silyl chloride or allyl silanes with the corresponding Brønsted acid (Scheme 4A).[10] In the same manner, silyl Lewis acid possessing chiral counter anions for enantioselective transformations is also prepared (Scheme 5).[11] These SLAs are extremely hydrophilic, and thus on-demand preparation is necessary for avoiding deactivation. In some cases, the anion exchange reaction of silyl chloride (R$_3$SiCl)

with the help of a silver salt, AgX, is efficient for obtaining the R_3SiX compound, along with the formation of chemically stable AgCl.[12–14]

Scheme 4. Typical procedures for formation of neutral SLAs by protonation (A) and anion exchange (B)

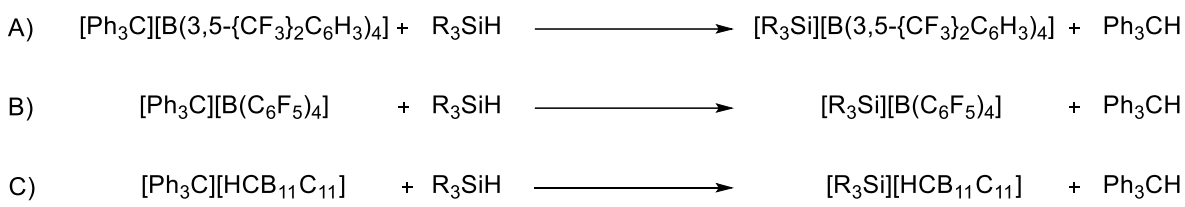


Scheme 5. Enantioselective transformation catalyzed by a chiral SLA *in situ* generated



SLAs with non-coordinative counter anion serves like silylium ion (R_3Si^+). These cationic SLAs have recently been focused because of their extremely high reactivity. The typical method for preparation of these species is hydride abstraction from the trialkylsilanes, R_3SiH (Scheme 6). This strategy is performed with the help of the trityl salt ($Ph_3C^+X^-$) through Bartlett–Condon–Schneider reaction.[15] The initial attempt for formation of silylium (silicenium) species was demonstrated by Corey in 1975.[16] A blue-green colored solution was obtained through the reaction with trialkylsilane and trityl perchlorate (Ph_3CClO_4), but the detection of the silylium species was not achieved. Kira, Sakurai research group and Lambert research group independently revealed that the less-coordinative tetraarylborate was an effective anion for the stabilization of silylium compound.[17,18] The former employed tetrakis[3,5-bis(trifluoromethyl)phenylborate, and the other used tetrakis(pentafluorophenyl)borate, respectively (Scheme 6A, 6B). Another effective counter anion is "weakly-coordinating anion," WCA; $[HCB_{11}H_{11}]^-$ or $[HCB_{11}Cl_{11}]^-$ (Scheme 6C).[19]

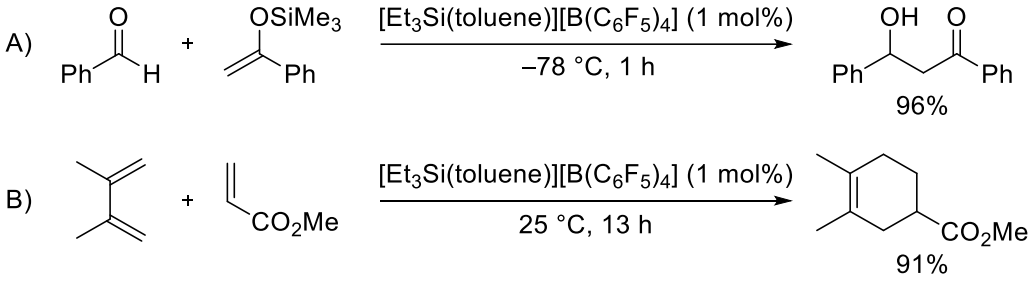
Scheme 6. Selected examples of successfully synthesized cationic SLAs by trityl cation



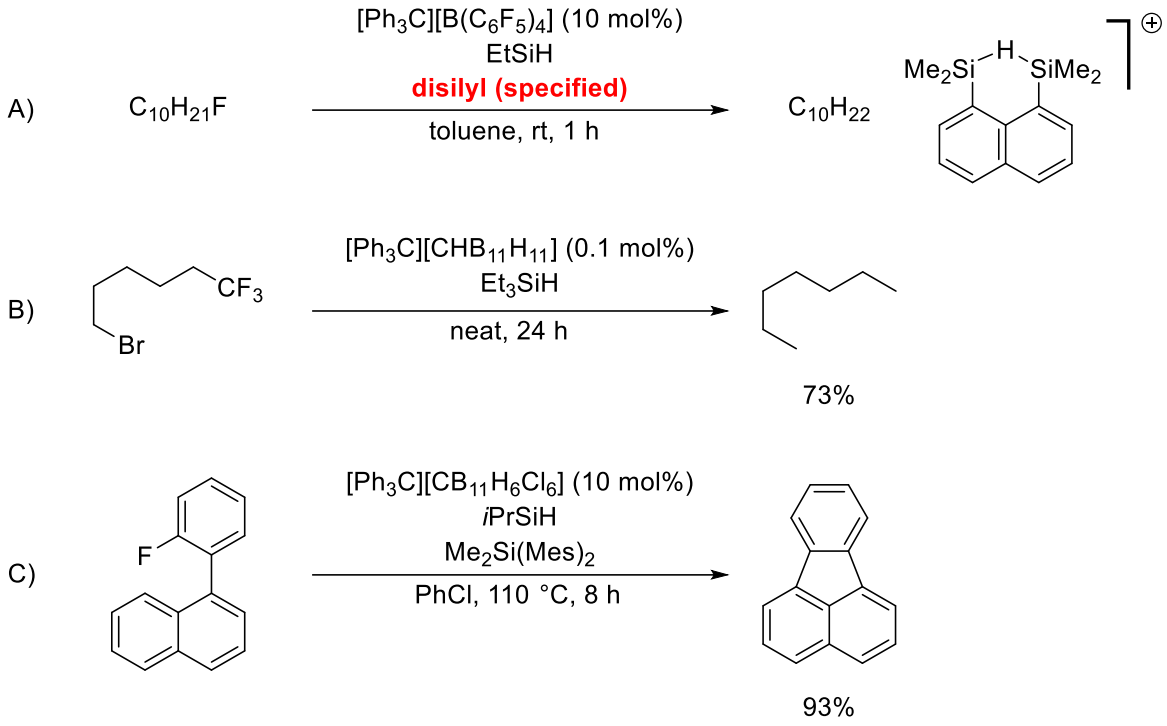
Similar to traditional SLAs, these silylium cations can be used successfully in Mukaiyama aldol reactions and Diels–Alder reactions (Scheme 7).[20] The high reactivity of these SLAs causes notable decrease of the catalyst loading. The obvious breakthrough with the cationic SLAs was their utility as catalysts for C–F bond functionalization. C–F linkage is one of the most chemically stable covalent bonds and is hard to cleave in organic transformations. Since

the Si atom has strong affinity to fluoride, silylium species can affect for the cleavage of C–F bond. Müller and coworkers demonstrated hydrogenative C–F cleavage of alkyl fluoride with specially designed disilyl compound (Scheme 8A).[21a] The largest TON of catalysis is 45 in this case. Ozerov and co-workers showed more effective catalytic system with $[R_3Si][WCA]$ system; in this case, alkyl fluoride can be transformed into the corresponding alkanes with low catalyst loading under mild conditions (Scheme 8B).[21b] The TON reaches up to 2,700. Another demonstration was carried out by Siegel and coworkers. Intramolecular Friedel–Crafts-type reaction affording fused-aromatic ring from *ortho*-arylated fluoroarene substrate (Scheme 8C).[22] Triisopropylsilylium carborane, $(i\text{Pr}_3\text{Si})[CB_{11}H_6Cl_6]$ catalyzed the defluorination, and neighboring aromatic substructure played as nucleophile to form C–C bond. The addition of $Me_2Si(Mes)_2$ is important for the reaction. The proton released from the intermediate react with the additive $Me_2Si(Mes)_2$ affording the $[Me_2Si(Mes)]^+$ species, and that worked as next silylium cation.

Scheme 7. Selected example of cationic SLAs catalyzed reactions



Scheme 8. Selected examples of silyl cation catalyzed C–F bond functionalization

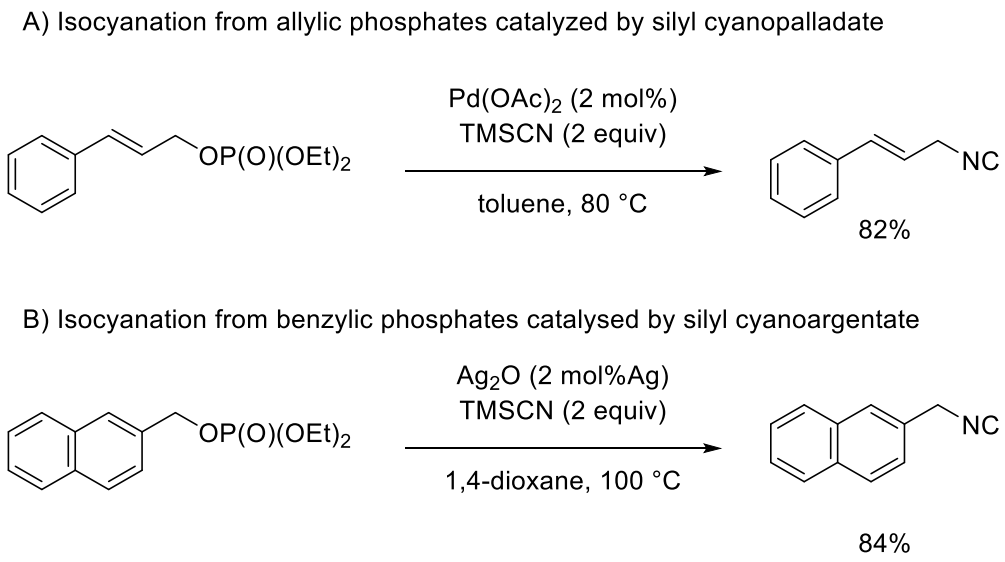


3. Silyl Cyanometallates as the New Class of Silyl Lewis Acid

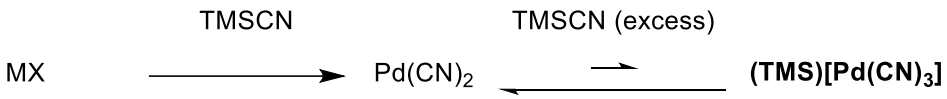
Recently, Ohkuma, Yurino, and co-workers proposed a new hypothesis for *in situ* formation of SLA catalysts in the specific transformations (Scheme 9).[23] The reaction between trimethylsilyl cyanide (TMSCN) and $Pd(OAc)_2$ resulted in the formation of $Pd(CN)_2$. When the excess amount of TMSCN exists in the reaction mixture, the silyl cyanometallate complex, $(TMS)[Pd(CN)_3]$ is formed in equilibrium. The complex can be regarded as a silylium cation with a counter anion $[Pd(CN)_3]^-$. The most part of the mixture is $Pd(CN)_2$, which is extremely chemically stable species. The population of $(TMS)[Pd(CN)_3]$ is significantly low, but it obviously shows Lewis acidic property. A similar tendency is also observed when Ag_2O is used instead of $Pd(OAc)_2$, affording $(TMS)[Ag(CN)_2]$. They successfully employed this method for the catalytic nucleophilic isocyanation affording

allylic and benzylic isonitriles.[23] The silyl group of cyanometallate complex effectively activates allylic and benzylic phosphates, and the counter anion, $[Pd(CN)_3]^-$ or $[Ag(CN)_2]^-$ react as an *N*-nucleophile. In both cases, the *C*-terminus of the cyanide is no longer reactive because of the strong coordination onto the transition metal center (Scheme 10).

Scheme 9. Isocyanation from allylic and benzylic phosphates catalyzed by silyl cyanometallates



Scheme 10. General strategy for formation of silyl cyanometallates

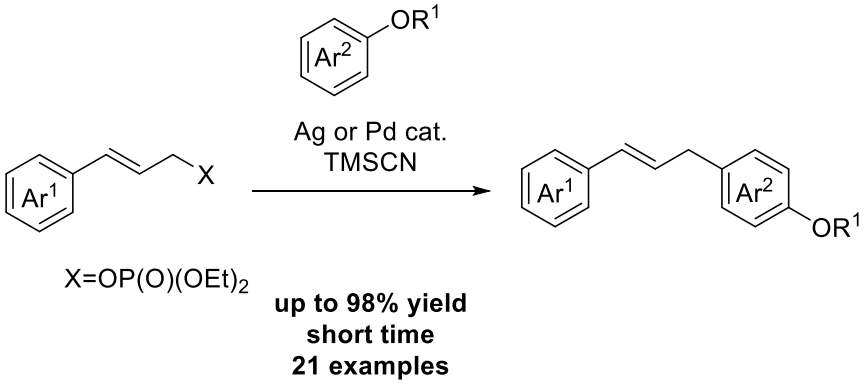


The author investigated the applicability of the silyl cyanometallate complexes for other transformations other than nucleophilic isocyanation. The author successfully developed the following three new catalytic reactions; (i) intermolecular Friedel–Crafts-type allylation of

phenols and anisoles, (ii) intramolecular Friedel–Crafts-type benzylation affording 3-aryloxindole derivatives, and (iii) oxidative cyanomethylation of secondary arylamines.

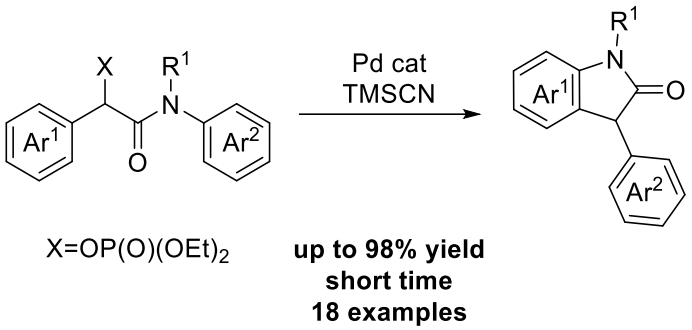
Chapter 1 describes the intermolecular Friedel–Crafts-type substitution of allylic phosphates and phenol derivatives catalyzed by *in situ* generated trimethylsilyl cyanometallate (Scheme 11).[24] This work provides highly regioselective synthesis of *para*-allylated phenol and anisole derivatives. The selection of the transition metal species is the key of the reaction; the Pd complex is effective for the transformation of phenol, in contrast, the Ag complex is suitable for the anisoles.

Scheme 11. Intermolecular Friedel—Crafts-type substitution of allylic phosphates and phenol derivatives



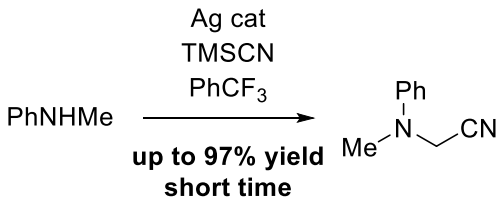
Chapter 2 describes the first catalytic example of intramolecular Friedel–Crafts-type substitution of amido phosphates affording the corresponding oxindoles (Scheme 12).[25] In this case, *in situ* generated silyl cyanopalladate is the only suitable catalyst. Not only 5-membered, but also 6-membered rings could be constructed through this methodology.

Scheme 12. Intramolecular Friedel–Crafts-type substitution of amido phosphates



Chapter 3 describes the first example of oxidative cyanomethylation catalyzed by *in situ* generated silyl cyanoargentate (Scheme 13). The addition of benzotrifluoride ($CF_3C_6H_5$) drastically improves the catalytic performance and α-amino nitriles are obtained in high yield.

Scheme 13. Oxidative cyanomethylation mediated by benzotrifluoride



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Chapter 1.

In Situ Generated Silyl Cyanometallate Friedel–Crafts-type Allylation of Phenol Derivatives

Abstract

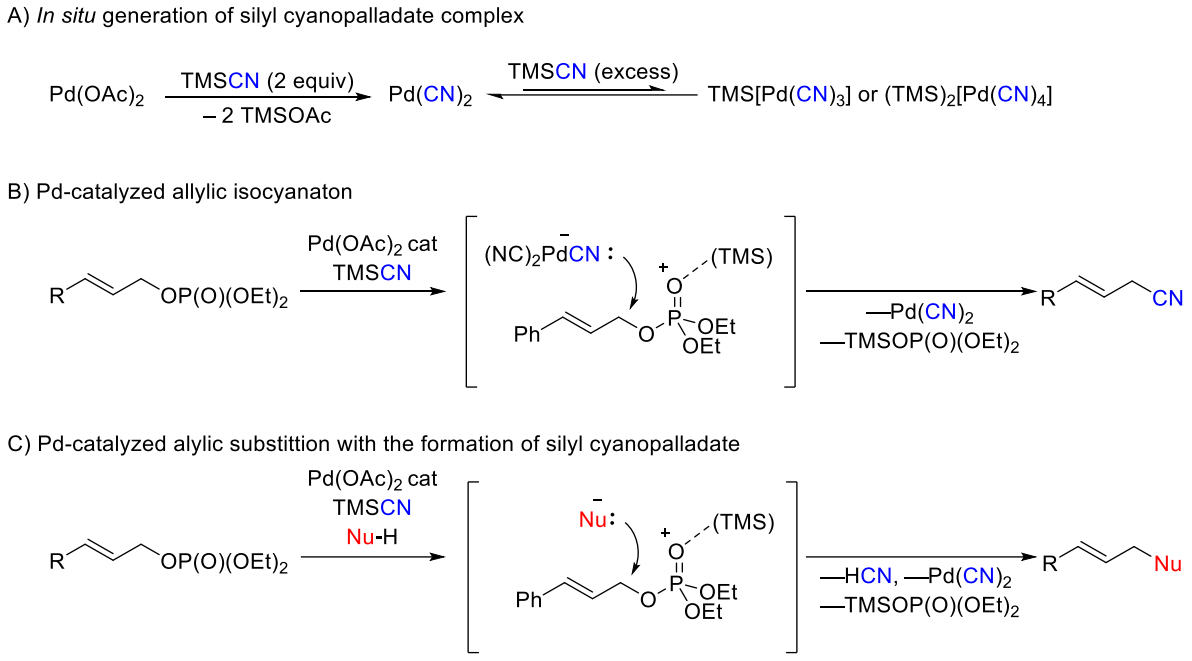
The first Friedel–Crafts-type allylation of phenol derivatives and allylic phosphates has been accomplished catalyzed by silyl cyanometallates to afford the *C*-allylated product in a highly regioselective manner. *In situ* formed ate complexes from AgTFA/trimethylsilyl cyanide (TMSCN) and $Pd(OAc)_2$/TMSCN combined systems are proposed to be the active catalytic species. The reaction requires appropriate ion pairs for Lewis acidity. The *para*-allylated anisole and phenol derivatives are selectively obtained. The *para*-substituted ones are converted to the *ortho*-allylated products. Substitution of an aromatic ring on the allylic phosphate is essential for the reaction.

1.1 Introduction

It is well known that *C*-terminus of cyanide strongly interacts with several transition metal species affording the stable metal cyanide salts. Some studies have been reported that the cyanometallate complexes are also obtained in the presence of excess amount of cyanide sources.[1,2] Currently, our group successfully examined nucleophilic isocyanation of allylic and benzylic phosphates catalyzed by *in situ* formed silyl cyanopalladate in the presence of stoichiometric amount of trimethylsilyl cyanide (TMSCN) as cyanide source with catalytic amount of $Pd(OAc)_2$. Mechanistic experiments revealed that cyanopalladates, $TMS[Pd(CN)_3]$ and/or $(TMS)_2[Pd(CN)_4]$, acted as catalytic species (Scheme 1A, 1B).[3]

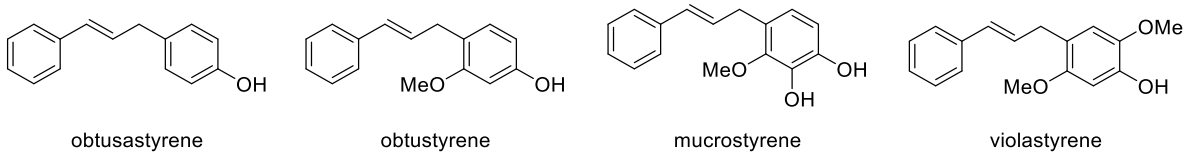
The ate complexes behave as Lewis acid to activate the phosphate and the *C*-blocked cyanide, such as $[Pd(CN)_3]^-$, $[Pd(CN)_4]_2^-$, Me_3SiCN, function as *N*-nucleophiles. The allylic phosphates were activated by controlling the Lewis acidity of the reversibly generated catalyst system. The Lewis acidity of active catalytic species in the isocyanation of allylic phosphates found that stronger than that of TMSCN, but weaker than that of TMSOTf.[3] Our group predicted that in the presence of more reactive nucleophile the cyanometallate could be worked with other nucleophiles (Scheme 1C). Based on this hypothesis, the author focused on the Friedel–Crafts-type substitution allylation using phenol and its derivatives.[4] *C*-cinnamyl phenol derivatives are generally known for their photochemical properties and have extraordinary bioactivities. For instance, obtusastyrene and obtustyrene, which have been isolated form *Dalbergia retusa*, show antimicrobial properties (Figure 1).[5,6] An effective method is needed for highly selective formation of these compounds in the field of synthetic organic chemistry and biochemistry.

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



C-cinnamyl phenol derivatives are generally known for their photochemical properties and have extraordinary bioactivities. For instance, obtusastyrene and obtustyrene, which have been isolated form *Dalbergia retusa*, show antimicrobial properties (Figure 1).[5,6] An effective method is needed for highly selective formation of these compounds in the field of synthetic organic chemistry and biochemistry.

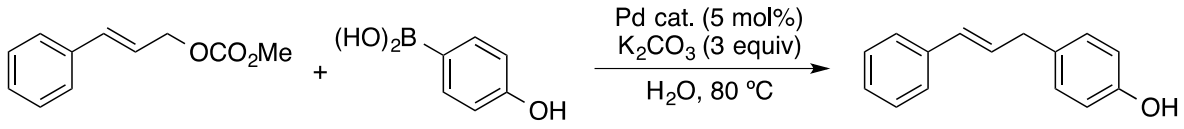
Figure 1. Examples of phytochemical *C*-cinnamyl phenols



obtusastyrene obtustyrene mucrostyrene violastyrene

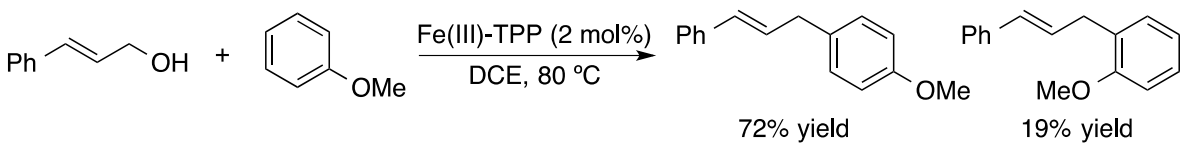
Pd-catalyzed allylic arylation with proper allylic reagents and aryl boronic acids or boronates is one of the powerful strategies for formation of obtusastyrene derivatives.[7] However, this method has some drawbacks. For example, the corresponding hydroxy- or alkoxy-substituted aryl boronic species is needed to be pre-prepared for high regioselectivity (Scheme 2). The protocol usually requires inert atmosphere for effective results, because most of the catalytically active Pd(0) species are air sensitive.

Scheme 2. Selected example for Pd-catalyzed allylic arylation



The second potential powerful strategy for synthesizing *C*-cinnamyl phenol derivatives is Friedel–Crafts-type allylation with use of electron-rich aromatic rings of phenolic nucleophiles as simple and air-tolerant method. Both Lewis and Brønsted acids have been widely used as catalysts for activation of the cinnamyl electrophiles.[8,9] However, controlling the regioselectivity through nucleophilic substitution with phenol derivatives remain as the most important drawback of this method due to *ortho-para* orientation of targeted products (Scheme 3).

Scheme 3. Selected example of Friedel–Crafts-type allylation



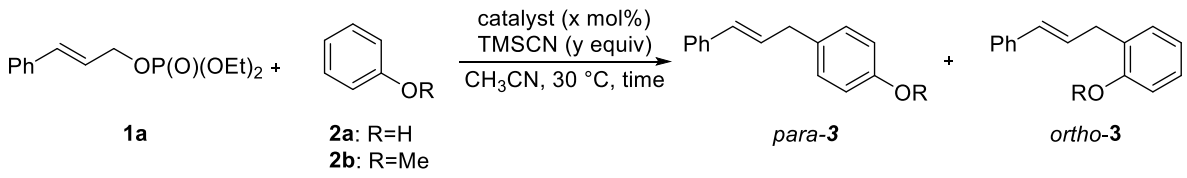
Herein, the author reported the first example of silyl cyanometallates formed from Pd(II) and Ag(I) salts with stoichiometric amount of TMSCN catalyzed Friedel–Crafts-type allylation of phenol derivatives. The *C*-cinnamyl phenol derivatives were obtained with high regioselectivity.[12]

1.2 Results and Discussion

The author selected the cinnamyl phosphate **1a** with phenol **2a** and anisole **2b** for screening of optimization (Table 1).[12] The allylation of **2a** was completed in the presence of $Pd(OAc)_2$ (2 mol%) and TMSCN (2 equiv) in CH_3CN at 60 °C within 24 h to afford *para*-cinnamyl phenol in 72% yield (entry 1). The Tsuji–Trust-type Pd-catalyzed allylations of phenol product, *O*-allylated product that is cinnamyl phenyl ether, is not observed.[10] Both $Pd(OAc)_2$ and TMSCN were necessary for formation of desired *para*-product **3a**, suggesting that *in situ* formed $TMS[Pd(CN)_3]$ and/or $(TMS)_2[Pd(CN)_4]$ is the catalytic species for this transformation (entries 2 and 3). The combination of AgTFA with TMSCN was more effective for formation of **3a**, however a mixture of *para*- and *ortho*-allylated products was obtained with this catalytic system (entry 4). Formation of targeted compound was not observed in the absence of TMSCN, proposing that the Ag ate complex $TMS[Ag(CN)_2]$ acted as the catalytic active species (entry 5).11 The combination of AgTFA and TMSCN was appropriate for formation of *para*-allylated product **3b** within 7 h quantitatively (entry 6) that showed this combination is more suitable for anisole derivatives as nucleophile. When $Pd(OAC)_2$ was used instead of AgTFA, the *ortho*-substituted product was formed with the *para*-product with slower rate compared to the reaction of **2a** (entry 7 vs 6). These results showed that the cyanometallate counterpart in the catalytic species clearly affected both the

efficiency and regioselectivity. It is noteworthy that some existing silyl Lewis acids did not work for allylation. No product obtained with TMSOAc as a silyl Lewis acid catalyst (entry 8). The allylated product was obtained only in 8% with formation of side product cinnamyl chloride in 2% yield catalyzed by TMSCl instead of the silyl cyanometallare. TMSOTf, a stronger Lewis acid, supported the reaction to give the *para*-product in 75% yield with *ortho*-isomer in 5% yield. However, electrophile was partially decomposed. When the reaction was carried out at 60 °C, it completed within 5 h (entry 11). However, the catalytic amount decreasing into 1 mol%, the yield of the product was obviously dropped down (entry 12). A catalytic amount of trifluoroacetic acid (1 mol%) without TMSCN did not promote the reaction at all (entry 13).

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



1a **2a**: R=H **2b**: R=Me *para*-***3*** *ortho*-**3**

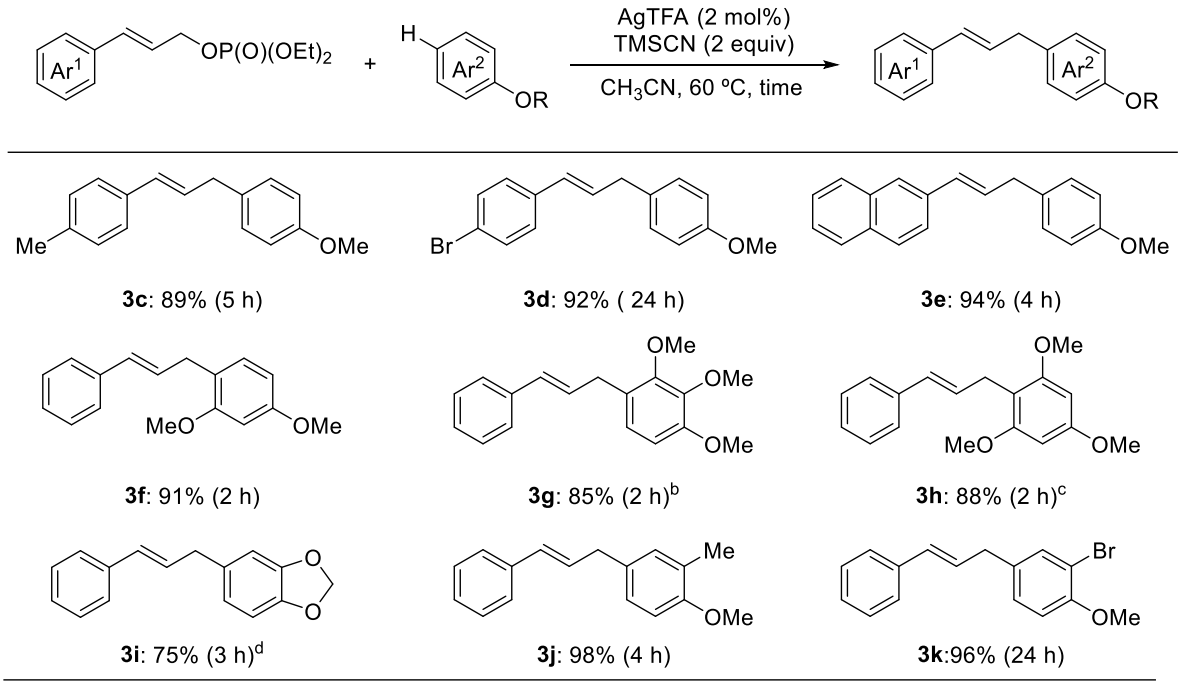
Entry	Nucleophile	Catalyst (x mol%)	y equiv	Time (h)	*para*-**3** (%)	*ortho*-**3** (%)
1	**2a**	$Pd(OAc)_2$ (2)	2	24	72 (72)	trace
2	**2a**	no	2	24	0	0
3	**2a**	$Pd(OAc)_2$ (2)	0	24	0	0
4	**2a**	AgTFA (2)	2	24	74	19
5	**2a**	AgTFA (2)	0	24	0	0
6	**2b**	AgTFA (2)	2	7	>99 (98)	0
7	**2b**	$Pd(OAc)_2$	2	24	69	4
8	**2b**	TMSOAc (2)	0	24	0	0
9	**2b**	TMSCl (2)	0	24	8	0
10	**2b**	TMSOTf (2)	0	24	75	5
11[c]	**2b**	AgTFA (2)	2	5	>99	0
12[c]	**2b**	AgTFA (1)	2	5	28	0
13	**2b**	TFA (1)	0	24	0	0

[a] 1H NMR yield 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*-**3b**, 2-cinnamyl anisole. [c] The reaction was carried out at 60 °C.

With the optimized reaction conditions in hand, the author then investigated the scope of the Friedel–Crafts-type allylation of phenol derivatives (Scheme 4).[12] The optimized conditions successfully applied to electron-rich anisole derivatives for formation of *para*-allylated products **3c–3k** in high yield. The *para*-methyl-substitution (**2c**) accelerated the

reaction rate and electron withdrawing group substituted starting compound (**2d**) slowed the reaction even providing a high yield in long time. These results suggested that the reaction is affected by substitutents on the cinnamyl phenyl ring. The reaction mechanism is likely to S_N1-type substitituon. 2-Naphthyl group was also suitably employed under the optimized conditions for formation of the corresponding allylation product **3e** in 94% yield within 4h. The allylated products **3f** and **3j** were formed in short time, and that suggested the electron-rich aromatic nucleophiles reacted with cinnamyl phosphates rapidly. The undesired diallylation compounds formed with 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 with 12%, 4% and 18% yield, respectively. The desired compound 4-cinnamyl product **3k** obtained in 94% yield from 2-bromoanisole with slower rate. The reaction with the electron deficient nucleophiles; *t*-butylbenzene, chlorobenzene, or phenylacetate; did not afford the corresponding allylated products. These results supported that the poor reactivity of the electron deficient nucleophiles is the significant limitation of this method.

Scheme 4. Allylation using anisole derivatives as with the AgTFA/TMSCN combined catalyst[a]

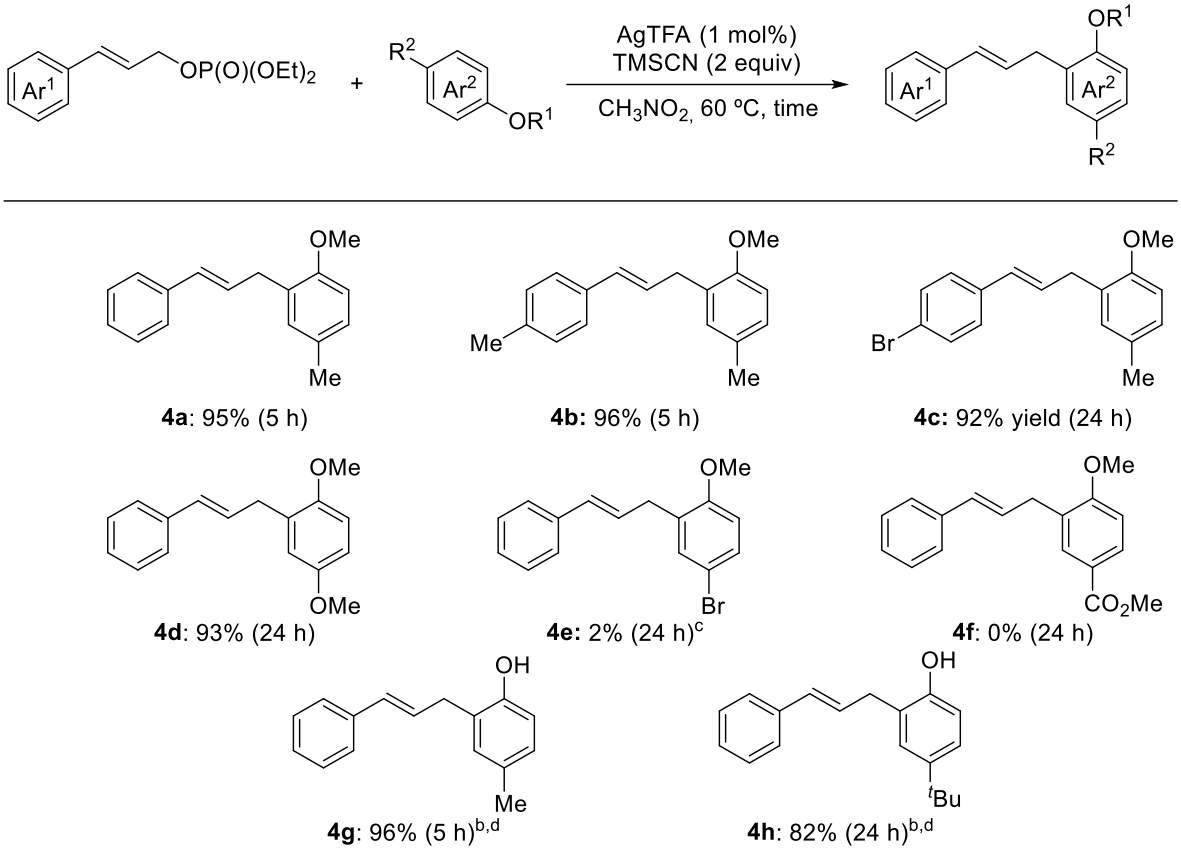


[a] Isolated yield, is given. [b] The diallylated product was formed in 12% yield. [c] The diallylated product was formed in 4% yield. [d] The diallylated product was formed in 18% yield.

Some *para*-substituted phenols and anisoles reacted with the allylic phosphates catalyzed by the AgTFA/TMSCN and $Pd(OAc)_2$/TMSCN systems to afford sterically hindered *ortho*-substituted products in high yield (Scheme 5).[12] The allylation was carried out in CH_3NO_2 as the suitable solvent in these cases. The substituents on the cinnamyl phosphates had similar effects of the mono substituted nucleophiles (**4a**–**4c)**. The reaction rate 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**). The reaction of 1,4-dimethoxybenzene formed a mixture of 2-mono- and 2,5-disubstituted products in a 1.8:1

ration with optimized conditions because of its high reactivity. The allylation of **3d** were carried out under milder conditions as with AgTFA (1 mol%), TMSCN (2 equiv) in CH_3CN at 30 °C to afford corresponding allylated compound **4d** 93% yield that the yield of it increased. On the other hand, the product **4e** formed in only 2% yield from the reaction of 4-bromoanisole. No product formation was observed under the optimized conditions. *para*-Cresol and 4-*tert*-butylphenol were found to be suitable substrates for the Friedel–Crafts-type allylation. With 1 mol% $Pd(OAc)_2$ as catalyst were converted into the *ortho*-cinnamyl product, **4d** and **4h**, in high yield.

Scheme 5. Allylation using *para*-substituted anisole and phenol derivatives as nucleophiles with the AgTFA/TMSCN or $Pd(OAc)_2$/TMSCN combined catalyst[a]

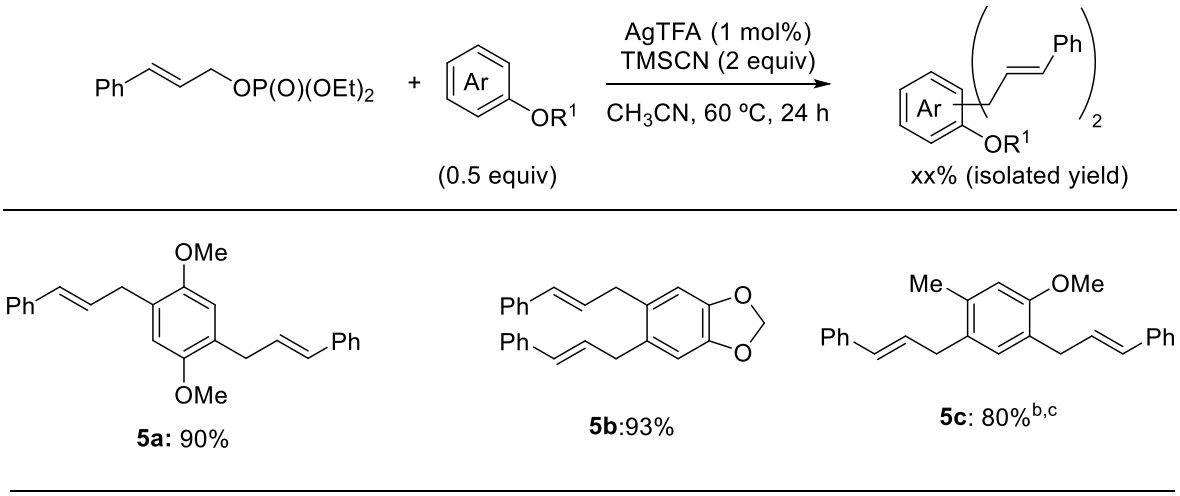


[a] Isolated yield is given. [b] CH_3CN was used instead of CH_3NO_2. The reaction was carried out at 30 °C. [c] ^1H NMR yield. [d] $Pd(OAc)_2$ (1 mol%) was used instead of AgTFA as a catalyst.

Diallylated products were obtained with 2 equiv. of cinnamyl phosphate suggested that the electron-rich nucleophiles were appropriate substrates for this reaction (Scheme 6).[12] 2,5-diallylated product **5a** formed from the reaction with 1,4-dimethoxybenzene in 90% yield as a sole product without formation of the 2,3-disubstituted product. The diallylation on 1,3-benzodioxole took place at the 4,5-carbons (**5b**). *m*-Dimethoxybenzene was converted to the 2,4-diallylated product (**5c**). In this case, branch-type monoallylation product, 2,4-dimethoxy-

2-1(1-phenyallyl)-benzene formed in 6% yield as the only case to give the branch-type compound in >2% yield as a byproduct, although the reason was not clear.

Scheme 6. Diallylation on the electron-rich aromatics with the AgTFA/TMSCN combined catalyst

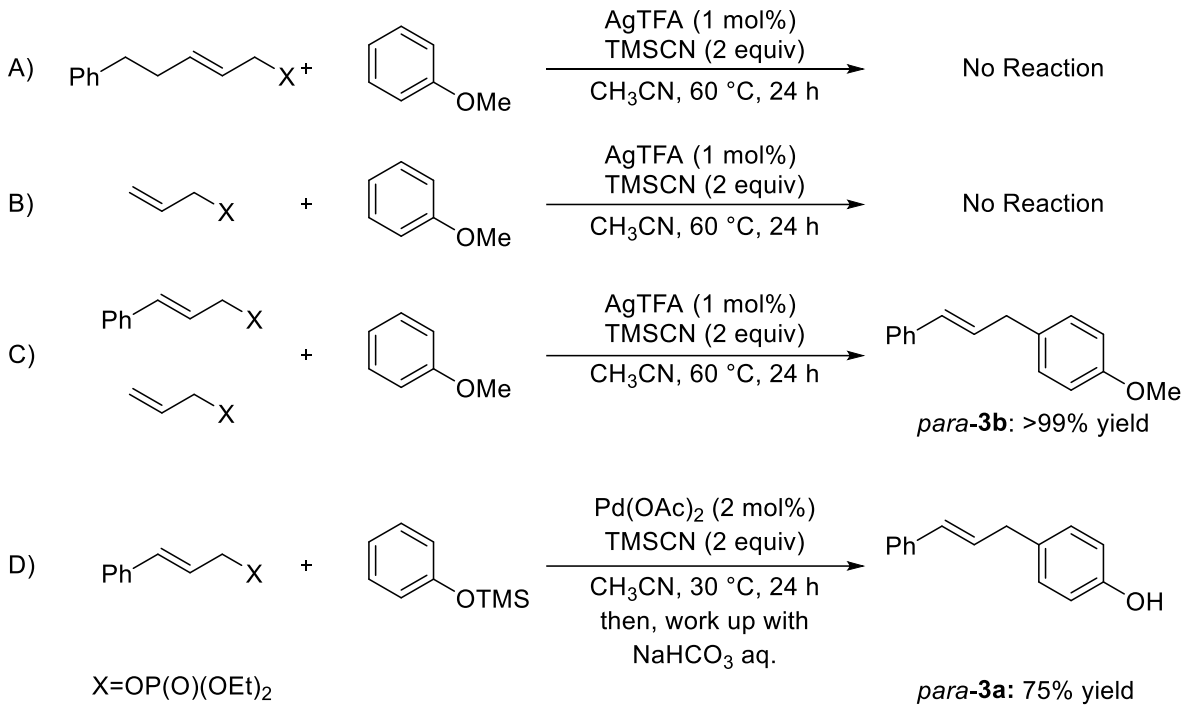


[a] Isolated yield is given. [b] 2,4-Dimethoxy-2-(1-phenylallyl)benzene was included as a side product (6% ^{1}H NMR yield). [c] Nucleophile was used as 0.25 equiv.

Reactivity of the Friedel–Crafts-type allylation was significantly dependent on the electronic properties of substrates (Scheme 7).[12] No product formation was observed from the reaction of an aliphatic allylic phosphate anisole under the optimal conditions using the AgTFA/TMSCN system (Scheme 7A). The simple allyl phosphate was inactive to give the allylated product (Scheme 7B). The perfect chemoselectivity was observed with the competitive reaction using 1:1 mixture of cinnamyl and allyl phosphates for affording the *para*-cinnamyl compound **3b** in quantitative yield (Scheme 7C). The allylic phosphates activated by TMS[$Ag(CN)_2$] generated in the combination of AgTFA/TMSCN system as Lewis acid in CH_3CN.

As shown in Table1, entry 1, the *para*-selective allylic substitution of phenol was catalyzed by the $Pd(OAc)_2$/TMSCN system. A separate experiment using isolated TMSOPh as the nucleophile under the regular conditions afforded the *para*-cinnamyl phenol **3a** exclusively in 75% yield after desilylation (Scheme 5D). This observation suggested that the highly chemo-regioselective allylation of phenol occurred on the TMSOPh formed *in situ*.

Scheme 7. Chemical properties observed in the Friedel–Crafts-type allylation ($X=OP(O)(OEt)_2$).[a]

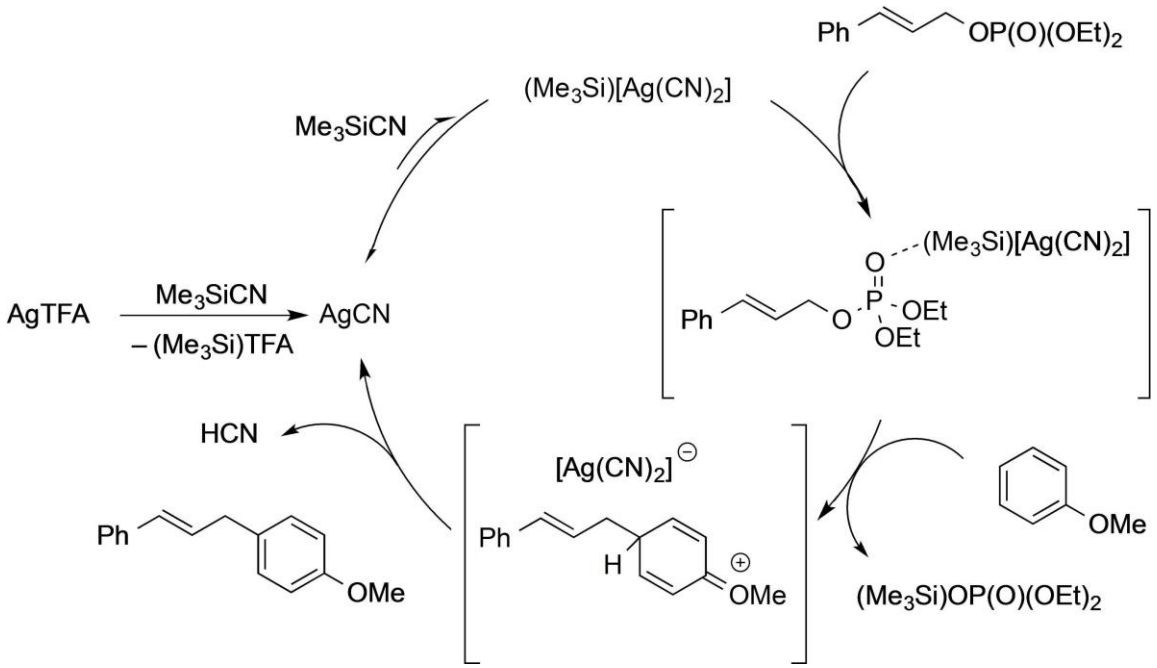


[a]Two equivalents of the aromatic nucleophiles to the allylic phosphates were used.

A plausible reaction mechanism is described in Scheme 8. The stable cyanide salt , AgCN, formed from AgTFA and TMSCN. In the presence of excess amounts of TMSCN, reversible silyl cyanoargentate complex ($TMS[Ag(CN)_2]$) is generated. The ate complex activated the allylic phosphate as a silyl Lewis-acid. The reversibility of the ion pair could be controlled

the Lewis acidity for this transformation. Anisole, an electron-rich aromatic compound, has stronger nucleophilicity than $[Ag(CN)]^-$, and the substitution at the *para*-position proceeds to give the ion-pairing intermediate along with the release of a silyl phosphate, $TMSOP(O)(OEt)_2$. The regioselectivity could be determined by the stability of the ionic intermediate. Volatile HCN is removed from the intermediate to generate the target allylation product and AgCN and followed with generation of $TMS[Ag(CN)_2]$ and/or $TMS[Pd(CN)_3]$ from TMSCN reacted again with the resulting AgCN. In the same manner, the plausible mechanism could be proposed for the combination of $Pd(OAc)_2$/TMSCN with formation of $TMS[Pd(CN)_3]$ and/or $(TMS)_2$ $[Pd(CN)_4]$ as possible catalytic active species.[3] In this, case TMSOPh formed *in situ* acts as a regioselective nucleophile.

Scheme 8. A plausible reaction mechanism of the AgTFA/TMSCN-catalyzed Friedel–Craft-type allylation



1.3 Conclusion

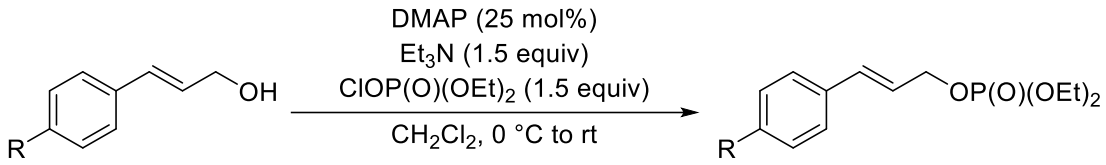
In conclusion, the author successfully developed an efficient method for regioselective Friedel–Crafts-type allylation of phenol derivatives with cinnamyl phosphates catalyzed by combination of $Pd(OAc)_2$/TMSCN and AgTFA/TMSCN. The *in situ* formed silyl cyanometallate complexes were envisioned as active catalytic species. The silyl moiety of the ate complexes works as an suitable Lewis acids that activates cinnamyl phosphates to afford *C*-allylated products. Regioselectivity of substitution is affected by counterpart of the cyanometallate as well as Lewis acidity of catalyst system. The chemoselectivity of the allylic phosphates is a significant character of the catalytic system.

1.4 Experimental Section

General Information: ^{1}H NMR spectra were measured on a JEOL JNM-ECX400P (400 Mhz) spectrometer and JNM-ECS400 (400 MHz) spectrometer. Data were reported as follows: chemical shifts in ppm from tetramethysilane or the residual solvent as an internal standard, integration multiplicity (s = singlet, d = doublet, t = triplet, dd = double-doublet, td = triple-doublet, q = quartet, m = multiplet, br = broad, and app = apparent), coupling constants (Hz), and assignment. ^{13}C NMR were measured on a JEOL JNM-ECX400P (100 MHz) spectrometer will complete proton decoupling. Chemical shifts were reported in ppm, from the residual solvent as an internal standard. Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 and FT/IT-4600. Gel permeation chromatography (GPC) was performed using an LC-918 recycling preparative HPLC system equipped with JAIGEL-1H and -2H columns in series (Japan Analytical Industry Co., Ltd.). Mass spectrometry was carried out at the Instrumental Analysis Division, Global Facility Center, Creative Research Institution, Hokkaido University. The products were purified by preparative thin layer (PTLC) using Wakogel® B-5F (FUJIFILM Wako Pure Chemical Co.). Trimethylsilyl cyanide (TMSCN) was purchased from Kanto Chemical Co. Inc. and was used after distillation. Dehydrated acetonitrile was purchased from Kanto Chemical Co. Inc. and was used as received. Nitromethane was purchased from Kanto Chemical Co. Inc. and was used after distillation. Palladium diacetate ($Pd(OAc)_2$) was purchased from Sigma-Aldrich Co. LLC., and was used as received. Silver trifluoroacetate (AgTFA) was purchased from Kanto Chemical Co. Inc. and was used as received.

Preparation of Allylic Phosphates

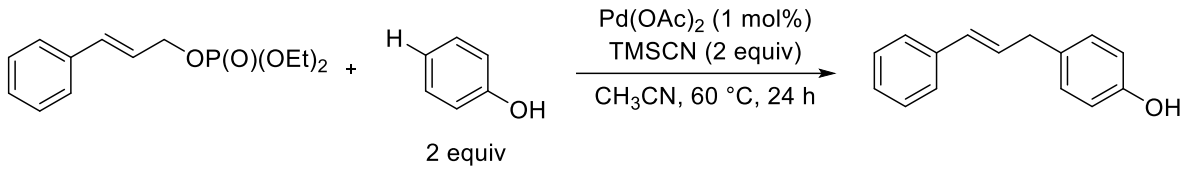
The substrates affording **1a**[13], **1c**[14], **1d**[13] and **1e**[14] were prepared through the reported procedure. A round bottomed flask was charged with allylic alcohol (1.0 equiv) and CH_2Cl_2 to prepare the solution (0.1 M). Et_3N (1.50 equiv) and *N*,*N*-dimethyl-4-aminopyridine (DMAP; 25 mol%) were then added to the solution. The mixture was cooled to 0 °C and diethyl chlorophosphate (1.50 equiv) was added dropwise.



A round bottomed flask was charged with allylic alcohol (1.0 equiv) and CH_2Cl_2 to prepare the solution (0.1 M). Et_3N (1.50 equiv) and *N*,*N*-dimethyl-4-aminopyridine (DMAP; 25 mol%) were then added to the solution. The mixture was cooled to 0 °C and diethyl chlorophosphate (1.50 equiv) was added dropwise. The reaction mixture allowed warm up to room temperature and stirred until the reaction was judged complete by TLC analysis. The reaction was quenched by the addition of saturated $NaHCO_3$ aq. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 3 times. The combined organic layers were washed with water, then brine, and dried over Na_2SO4. After Na_2SO4 was filtered off, the collected filtrate was concentrated *in vacuo*. The crude residue was purified by silica-gel column chromatography. The isolated allylic phosphates were repurified by Kugelrohr distillation.

AgTFA- and $Pd(OAc)_2$-Catalyzed Friedel–Crafts-type Allylic Substitution of Phenol Derivatives

General Procedure for *ortho* or *meta* substituted phenol derivatives

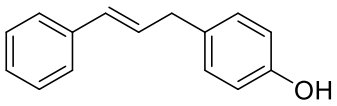


Caution: Trimethylsilyl cyanide (TMSCN) must be used in a well-ventilated hood fue tı its high toxicity.

The typical procedure for $Pd(OAc)_2$-catalyzed allylic substitution is described as follows.

To a solution of (*E*)-cinnamyldiethylphosphate (136 mg, 0.50 mmol) in CH_3CN (2.5 mL) was added $Pd(OAC)_2$ (1.1 mg, 0.050 mmol). The resulting mixture was stirred for 15 min at 30 °C, followed by the addition of phenol (95 mg, 1.01 mmol) and TMSCN (100 mg, 1.00 mmol). The reaction mixture was then continuously stirred at 30 ºC for 24 h. Completion of the reaction was judged by TLC (AcOEt: hexane = 1:4). A saturated $NaHCO_3$ aq was added to quench the reaction, and the aqueous layer was extracted by CH_2Cl_2 (10 mL × 3). The collected organic layer was washed with brine and dried over Na_2SO4. After Na^2SO4 was filtered off, the resulting mixture was concentrated *in vacuo*. The yield of the product was calculated from ^1H NMR spectra of the crude 4- cinnamyl phenol with pyrazine as an internal standard (72% yield). The product was isolated by PTLC (AcOEt:hexane = 1:4), as a pale-yellow oil (76 mg, 0.36 mmol, 72% yield).

4-Cinnamylphenol (Obtusastyrene) (3a)

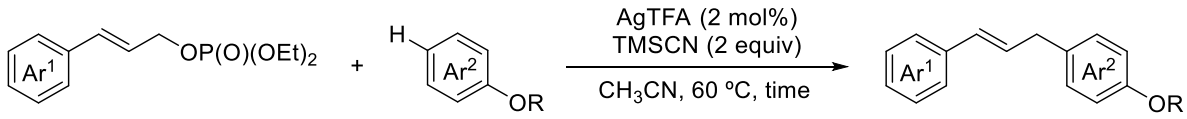


Was obtained as pale-yellow solid (72%).

Spectra data are in accordance with the literature.[15]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (app. . d, *J* = 8.4 Hz, 2H, Ar–H), 7.32–7.28 (m, 2H, Ar–H), 7.21 (app. t, *J* = 6.8 Hz, 1H, Ar–H), 7.12 (d, *J* = 7.6 Hz, 2H, Ar–H), 6.45 (d, *J* = 16.0 Hz, 1H, PhC*H*=CH), 6.34 (dt, *J* = 15.6, 6.8 Hz, 1 H, PhCH=C*H*), 4.68 (s, 1H, OH), 3.49 (d, *J* = 6.8 Hz, 2H, CH=CHCH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 137.4, 132.3, 130.7, 129.8, 129.6, 128.5, 127.1, 126.1, 115.2, 38.4 ppm.

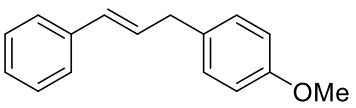
AgTFA-catalyzed Friedel–Crafts-type allylic substitution of anisole is described as a typical procedure.



Method A: To a solution of (*E*)-cinnamyldiethylphosphate (138 mg, 0.51 mmol) in CH_3CN (2.5 mL) was added AgTFA (1.2 mg, 0.050 mmol). The resulting mixture was stirred for 15 min at 60 ºC, followed by the addition of anisole (112 mg, 1.03 mmol) and TMSCN (109 mg, 1.10 mmol). The reaction mixture was then continuously stirred at 60 ºC for 5 h. Completion of the reaction was judged by TLC (AcOEt:hexane = 1:4). A saturated $NaHCO_3$ aq. was added to quench the reaction, and the aqueous layer was extracted by AcOEt (10 mL × 3). The collected organic layer was washed with brine and dried over Na_2SO_4. After Na_2SO_4 was

filtered off, the resulting mixture was concentrated *in vacuo*. The yield of the product was calculated from ^{1}H NMR spectra of the crude 1-cinnamyl-4-methoxybenzene with pyrazine as an internal standard (99% yield). The product was isolated by PTLC (AcOEt:hexane = 1:50), as a yellow oil (113 mg, 0.50 mmol, 99% yield).

Method B: To a solution of (*E*)-cinnamyldiethylphosphate (137 mg, 0.51 mmol) in CH_3NO_2 (2.5 mL) was added AgTFA (1.1 mg, 0.050 mmol). The resulting mixture was stirred for 15 min at 60 ºC, followed by the addition of anisole (112 mg, 1.03 mmol) and TMSCN (101 mg, 1.02 mmol). The reaction mixture was then continuously stirred at 60 ºC for 5 h. Completion of the reaction was judged by TLC (AcOEt:hexane = 1:4). A saturated $NaHCO_3$ aq. was added to quench the reaction, and the aqueous layer was extracted by AcOEt (10 mL × 3). The collected organic layer was washed with brine and dried over Na_2SO_4. After Na_2SO_4 was filtered off, the resulting mixture was concentrated *in vacuo*. The yield of the product was calculated from ^{1}H NMR spectra of the crude 1-cinnamyl-4-methoxybenzene with pyrazine as an internal standard (99% yield). The product was isolated by PTLC (AcOEt:hexane = 1:50), as a yellow oil (112 mg, 0.50 mmol, 98% yield). **1-Cinnamyl-4-methoxybenzene (3b)**



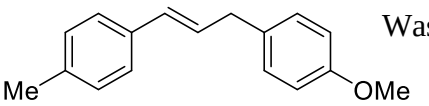
Was obtained as colorless oil (99%).

Spectra data are in accordance with the literature.[16]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (app. d, *J* = 7.6 Hz, 2H, Ar–H), 7.29 (app. t, *J* = 8.0 Hz, 2H, Ar–H), 7.22–7.15 (m, 1H, Ar–H), 7.16 (app. d, *J* = 8.8 Hz, 2H, Ar–H), 6.86 (app. d, *J* = 8.8 Hz, 2H, Ar–H), 6.44 (d, *J* = 16.4 Hz, 1H, PhC*H*=CH), 6.36 (dt, *J*=16.0, 6.8 Hz, 1H, PhCH=*CH*), 3.80 (s, 3H, OCH_3), 3.50 50 (d, *J* = 6.8 Hz, 2H, CH=CH*CH_2*) ppm; **^{13}C NMR**

(100 MHz, $CDCl_3$): δ 157.9, 137.2, 132.1, 130.7, 129.7, 129.6, 128.5, 127.0, 126.1, 113.9, 55.3, 38.4 ppm.

(*E*)-1-Methoxy-4-(3-(*p*-tolyl)allyl)benzene (3c)

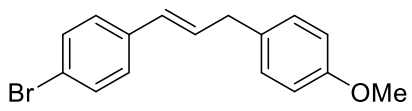


Was isolated as yellow oil, following the method A for 5 h.

Spetra data are in accordance with the literature.[17]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (app. d, *J* = 8.4 Hz, 2H, Ar–H), 7.16 (app. d, *J*= 8.8 Hz, 2H, Ar–H), 7.10 (d, *J* = 7.6 Hz, 2H, Ar–H), 6.86 (app. d, *J*= 8.4 Hz, 2H, Ar–H), 6.41 (d, *J* = 16.0 Hz, 1H, Ar*CH*=CH), 6.30 (dt, *J* = 16.0, 6.8 Hz, 1H, ArCH=*CH*), 3.80 (s, 3H, OCH_3), 3.48 (d, *J* = 6.8 Hz, 2H, CH=CH*CH_2*), 2.33 (s, 3H, $ArCH_3$) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 158.0, 136.8, 134.7, 132.3, 130.6, 129.6, 129.2, 128.6, 126.0, 113.8, 55.3, 38.4, 21.1 ppm.

(*E*)-1-Bromo-4-(3-4(4-methoxyphenyl)prop-1-en-1-yl)benzene (3d)

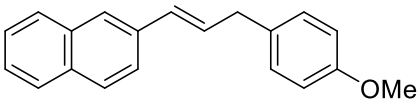


Was isolated as yellow oil (92%), followed the method B for 24 h.

Spectra data are in accordance with the literature. [17]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (app. d, *J* = 8.4 Hz, 2H, Ar–H), 7.21 (app. d, *J* = 8.8 Hz, 2H, Ar–H), 7.15 (app. d, *J* = 8.4 Hz, 2H, Ar–H), 6.86 (app. d, *J* = 8.4 Hz, 2H, Ar–H), 6.36–6.32 (m, 2H, Ar*CH*=*C*H and ArCH=C*H*), 3.80 (s, 3H, OCH_3), 3.48 (d, *J* = 5.2 Hz, 2H, CH=CH*CH_2*) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 158.1, 136.4, 131.8, 131.5, 130.6, 129.6,

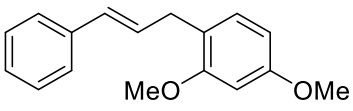
129.5, 127.6, 120.7, 113.9, 55.3, 38.4 ppm. **(*E*)-2-(3-(4-Methoxyphenyl) prop-1-en-1yl) naphthalene (3e)**



Was isolated as white solid (94%), followed the method A for 4 h.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79–7.75 (m, 3H, Ar–H), 7.70 (br s, 1H, Ar–H), 7.59 (dd, *J* = 8.4, 1.5 Hz,1H, Ar–H), 6.88 (d, *J* = 8.8 Hz, 2H, Ar–H), 6.59 (d, *J* = 15.6 Hz, Ar*CH*=CH), 6.49 (dt, *J* = 15.6, 7.2 Hz, 1H, ArCH=*CH*), 3.81 (s, 3H, OCH_3), 3.55 (d, *J* = 6.8 Hz, 2H, CH=CH*CH_2*) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 158.0, 134.9, 133.6, 132.7, 132.1, 130.8, 130.2, 129.6, 128.0, 127.8, 127.6, 126.1, 125.7, 125.5, 123.5, 113.9, 55.3, 38.6 ppm ; **IR (neat):** 2957, 1740, 1506, 1362, 1249, 1034, 961, 823, 736 cm^{-1}; **HRMS (EI):** *m/z* calcd for $C_{20}H_{18}O$: 274.1358 $[M]^+$; found: 274.1356.

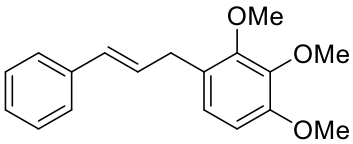
1-Cinnamyl-2,4-dimethoxynenzene (3f)



Was isolated by PTLC (AcOEt:hexane = 1:50) and then (AcOEt:hexane = 1:15) as colorless oil (91%), followed the method A for 2 h.

Spectra data is in accordance with the literature.[18]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (app. d, *J* = 7.2 Hz, 2H, Ar–H), 7.29 (t, *J* = 8.0 Hz, 2H, Ar–H), 7.19 (app. t, *J* = 7.2 Hz, 1H, Ar–H), 7.10 (d, *J* = 8.0 Hz, 2H, Ar–H), 6.49–6.44 (m, 2H, Ar–H and PhC*H*=CH), 6.41–6.37 (m, 2H, Ar–H and PhC*H*=*CH*), 3.84 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.48 (d, *J* = 5.6 Hz, 2H, CH=CH*CH_2*) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 159.4, 158.1, 137.8, 130.3, 130.0, 129.3, 128.4, 126.8, 126.0, 121.0, 103.9, 98.5, 55.4 (two peaks overlapped), 32.7 ppm. **1-Cinnamyl-2,3,4-trimethoxybenzene (3g)**

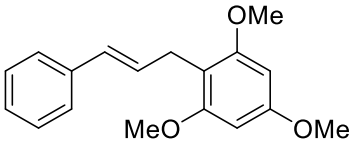


Was isolated as yellow oil (85%), followed the method A for 2 h.

Spectra data are in accordance with the literature. [19]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (app. d, *J* = 6.8 Hz, 2H, Ar–H), 7.28 (app. t, *J* = 6.8 Hz, 2H, Ar–H), 7.18 (app. t, *J* = 7.2 Hz, 1H, Ar–H) 6.89 (d, *J*= 8.8 Hz, 2H, Ar–H), 6.63 (d, *J* = 8.4 Hz, 1H, Ar–H), 6.42 (d, *J* = 16.0 Hz, 1H, PhC*H*=CH), 6.34 (dt, *J* = 15.6, 6.4 Hz, 1H, PhCH=C*H*), 3.89 (s, 6H, OCH_3), 3.85 (s, 3H, OCH_3), 3.49 (d, *J* = 6.4 Hz, 2H, CH=CH*CH_2*), ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 152.2, 151.8, 142.3, 137.6, 130.6, 129.4, 128.4, 126.9, 126.1, 126.0, 124.0, 107.2, 61.0, 60.8, 56.0, 33.0 ppm.

2-Cinnamyl-1,3,5-trimethoxybenzene (3h)

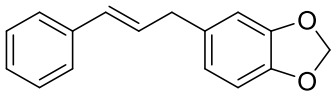


Was isolated by PTLC (Et_2O:toluene = 1:40) as colorless oil, followed the method A for 2 h.

Spectra data are in accordance with the literature.[19]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, *J*=8.4 Hz, 2H, Ar-H), 7.24 (app. t, *J* = 8.0 Hz, 2H, Ar–H), 7.14 (app. t, *J* = 8.0 Hz, 1H, Ar–H), 6.37–6.23 (m, 2H, PhC*H*=C*H*), 6.16 (s, 2H, Ar–H), 3.81 (s, 9H, OCH_3), 3.47 (d, *J* = 4.4 Hz, 2H, CH=CH*CH_2*), ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 159.5, 158.8, 138.1, 129.4, 129.1, 128.3, 126.5, 126.0, 108.8, 90.6, 55.8, 55.3, 26.1 ppm.

5-Cinnamylbenzo[*d*][1,3]dioxole (3i)

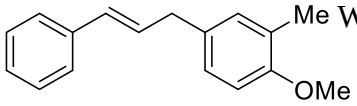


Was isolated by PTLC (Et_2O:toluene = 1:20) as colorless oil, followed the method A for 2 h.

Spectra data are in accordance with the literature.[20]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (app. d, *J* = 8.0 Hz, 2H, Ar–H), 7.31 (t, *J* = 7.6 Hz, 2H, Ar–H), 7.22 (t, *J* = 7.2 Hz, 1H, Ar–H), 6.78–6.69 (m, 3H, Ar–H), 6.45 (d, *J* = 16.0 Hz, 1H, PhC*H*=CH), 6.31 (dt, *J* = 15.6, 6.8 Hz, 1H, PhCH=C*H*), 5.94 (s, 2H, OCH_2O), 3.47 (d, *J* = 6.8 Hz, 2H, CH=CHCH_2), ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 147.6, 145.9, 137.4, 133.9, 130.9, 129.3, 128.5, 127.1, 126.1, 121.4, 109.1, 108.2, 100.8, 39.0 ppm.

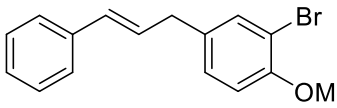
4-Cinnamyl-1methoxy-2-methylbenzene (3j)



Was isolated colorless oil, followed the method A for 4 h.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 7.6 Hz, 2H, Ar–H), 7.29 (t, *J* = 7.6 Hz, 2H, Ar–H), 7.20 (t, *J* = 7.2 Hz, 1H, Ar–H), 7.03 (app. d, *J* = 8.0 Hz, 1H, Ar–H), 7.02 (s, 1H, Ar–H), 6.77 (d, *J* = 8.0 Hz, 2H, Ar–H), 6.44 (d, *J* = 15.6 Hz, 1H, PhC*H*=CH), 6.32 (dt, *J* = 16.0, 6.8 Hz, 1 H, PhCH=C*H*), 3.82 (s, 3H, OCH_3), 3.47 (d, *J* = 6.4 Hz, 2H, CH=CHCH_2), 2.21 (s, 3H, $ArCH_3$) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 156.2, 137.8, 131.7, 131.0, 130.5, 129.8, 128.5, 127.0, 126.6, 126.1, 109.9, 55.4, 38.5, 16.2 ppm; **IR (neat):** 2917, 1606, 1496, 1254, 1131, 1029, 970, 808, 747, 693 cm^{-1} ; **HRMS (EI):** *m/z* calcd for $C_{17}H_{18}O$: 238.1358 $[M]^+$; found: 238.1351.

2-Bromo-4-cinnamyl-1-methoxybenzene (3k)

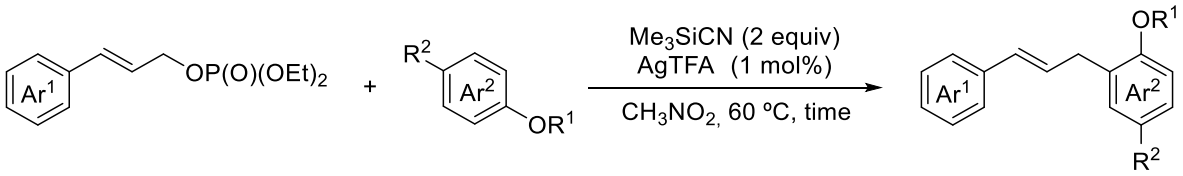


Was isolated as yellow oil (96%), followed the method B for 24 h.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J*= 1.6 Hz, 1H, Ar–H), 7.37 (app. d, *J* = 6.8 Hz, 2H, Ar–H), 7.31 (app. t, *J* = 7.6 Hz, 2H, Ar–H), 7.22 (app. t, *J* = 7.2 Hz, 1H, Ar–H), 7.14 (dd, *J* = 8.4, 2.0 Hz, 1H, Ar–H), 6.85 (d, *J* = 8.4 Hz, 1H, Ar–H), 6.44 (d, *J* = 16.0 Hz, 1H, PhC*H*=CH), 6.30 (dt, *J* = 16.0, 6.8 Hz, 1H, PhCH=C*H*), 3.88 (s, 3H, OCH_3), 3.47 (d, *J* = 6.8 Hz, 2H, CH=CHCH_2), 2.21 (s, 3H, CH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 154.3, 137.2, 133.7, 133.4, 131.3, 128.7, 128.5 (two peaks overlapped), 127.2, 126.1, 111.9, 111.5, 56.3, 38.0 ppm; **IR (neat):** 2894, 1598, 1490, 1436, 1280, 1251, 1051, 965, 803, 728, 690 cm^{-1}; **HRMS (EI):** *m/z* calcd for $C_{16}H15BrO$: 302.0306 $[M]^+$; found: 302.0292.

General Procedure for *para*-Substituted Phenol Derivatives

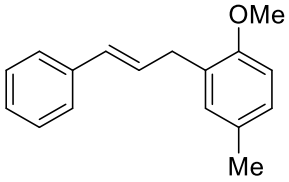
AgTFA-catalyzed Friedel–Crafts-type allylic substitution of *p*-methyl anisole is described as a typical procedure.



To a a solution of (*E*)-cinnamyldiethylphosphate (135 mg, 0.50 mmol) in CH_3NO_2 (2.5 mL) was added AgTFA (1.1 mg, 0.050 mmol). The resulting mixture was stirred for 15 min at 60ºC, followed by the addition of *p*-methyl anisole (122 mg, 1.0 mmol) and TMSCN (99 mg, 1.0 mmol). The reaction mixture was then continuously stirred at 60 ºC for 5 h.

Completion of the reaction was judged by TLC (AcOEt:hexane = 1:4). A saturated $NaHCO_3$ aq was added to quench the reaction, and the aqueous layer was extracted by CH_2Cl_2 (10 mL × 3). The collected organic layer was washed with brine and dried over Na_2SO_4. After Na_2SO_4 was filtered off, the resulting mixture was concentrated in vacuo. The yield of the product was calculated from ^{1}H NMR spectra of the 2-cinnamyl-1-methoxy-4-methylbenzene with pyrazine as an internal standard (99% yield). The product was isolated by PTLC (AcOEt:hexane = 1:50), as colorless oil (113 mg, 0.5 mmol, 95% yield).

2-Cinnamyl-1-methoxy-4-methylbenzene (4a)

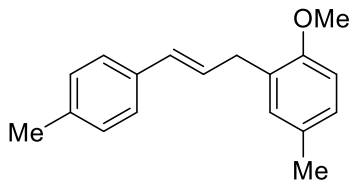


Was isolated as colorless oil (95%), followed the general procedure for 5 h.

Spectra data are in accordance with the literature.[21]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (app. d, *J* = 7.2 Hz, 2H, Ar–H), 7,30 (t, *J* = 7.2 Hz, 2H, Ar–H), 7.20 (app. t, *J* = 7.2 Hz, 1H, Ar–H), 7.02–7.01 (m, 2H, Ar–H), 6.79 (app. d, *J* = 9.2 Hz, 1H, Ar–H), 6.46 (d, *J* = 16.0 Hz, 1H, PhC*H*=CH), 6.39 (dt, *J* = 16.0, 6.0 Hz, 1H, PhCH=C*H*), 3.84 (s, 3H, OCH_3), 3.53 (d, *J* = 5.6 Hz, 2H, CH=CHCH_2), 2.29 (s, 3H, $ArCH_3$) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 155.2, 137.7, 130.6, 130.5, 129.7, 129.0, 128.4, 128.3, 127.6, 126.8, 126.1, 110.3, 55.5, 33.4, 20.5 ppm.

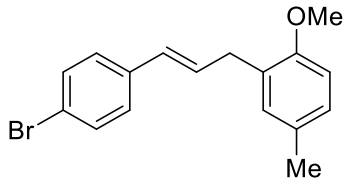
(*E*)-1-Methoxy-4-methyl-2-(3-(*p*-tolyl)allyl)benzene (4b)



Was isolated as colorless oil (96%), followed the general method for 5 h.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (app. d, *J* = 8.4 Hz, 2H, Ar–H), 7.09 (d, *J* = 7.6 Hz, 2H, Ar–H), 6.99 (app. d, *J* = 5.2 Hz, 2H, Ar–H), 6.77 (d, *J* = 8.8 Hz, 1H, Ar–H), 6.40 (d, *J* = 15.6 Hz, 1H, PhC*H*=CH), 6.31 (dt, *J* = 15.6, 6.4 Hz, 1H, PhCH=C*H*), 3.82 (s, 3H, OCH_3), 3.49 (d, *J* = 6.4 Hz, 2H, CH=CHCH_2), 2.32 (s, 3H, CH_3), 2.26 (s, 3H, Me) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 155.1, 136.6, 135.0, 130.5, 130.4, 129.7, 129.1, 128.5, 127.9, 127.5, 125.9, 110.3, 55.6, 33.3, 21.1, 20.5 ppm; **IR (neat):** 2930, 1599, 1490, 1461, 1416, 1274, 1092, 1011, 963, 791, 726, 690 cm^{-1}; **HRMS (EI):** *m/z* calcd for $C_{18}H_{20}O$: 252.1514 $[M]^+$; found: 252.1514.

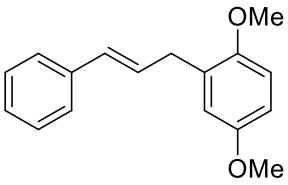
(*E*)-2-(3-(4-Bromophenyl)allyl)-1methoxy-4-methylbenzene (4c)



Was isolated as pale-yellow solid (92%), followed the general method for 24 h.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (app. d, *J* = 8.4 Hz, 2H, Ar–H), 7.22 (app. d, *J* = 8.0 Hz, 2H, Ar–H), 7.03–6.98 (m, 2H, Ar–H), 6.79 (d, *J* = 8.0 Hz, 1H, Ar–H), 6.39–6.37 (m, 2H, ArC*H*=C*H*), 3.83 (s, 3H, OCH_3), 3.50 (d, *J* = 5.2 Hz, 2H, CH=CHCH_2), 2.28 (s, 3H, CH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 155.1, 136.7, 131.4, 130.6, 130.0, 129.7, 129.3, 128.0, 127.7, 127.6, 120.4, 110.4, 55.5, 33.5, 20.5 ppm; **IR (KBr):** 2928, 1499, 1485, 1248, 1107, 1031, 819, cm^{-1} ; **HRMS (EI):** *m/z* calcd for $C_{17}H_{17}BrO$: 316.0463 $[M]^+$; found: 316.0457.

2-Cinnamyl-1,4-dimethoxybenzene (4d)

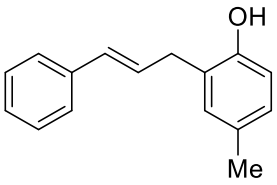


Was isolated by PTLC (AcOEt/hexane = 1/7) as yellow oil (93%), followed the general method for 24 h.

Spectra data are in accordance with the literature.[22]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (app. d, *J* = 6.8 Hz, 2H, Ar–H), 7.28 (app. t, *J* = 7.6 Hz, 2H, Ar–H), 7.18 (app. t, *J* = 7.2 Hz, 1H, Ar–H), 6.82–6.71 (m, 3H, Ar–H), 6.44 (d, *J* = 16.0 Hz, 1H, PhC*H*=CH), 6.36 (dt, *J* = 15.6, 6.4 Hz, 1H, PhCH=C*H*), 3.81 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.51 (d, *J* = 6.0 Hz, 2H, CH=CHCH_2) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 153.6, 151.6, 137.7, 130.8, 129.9, 128.6, 128.4, 126.9, 126.1, 116.3, 111.4, 111.3, 56.0, 55.6, 33.5 ppm.

2-Cinnamyl-4-methylphenol (4g)

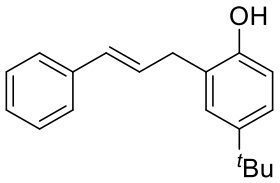


Was isolated as colorless oil (96%), followed the general procedure with $Pd(OAc)_2$ (1 mol%) as a catalyst for 24 h.

Spectra data are in accordance with the literature.[23]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (app. d, *J* = 7.2 Hz, 2H, Ar–H), 7.30 (app. t, *J* = 7.2 Hz, 2H, Ar–H), 7.21 (m, *J* = 7.6 Hz, 1H, Ar–H), 6.97–6.93 (m, 2H, Ar–H), 6.72 (d, *J* = 8.4 Hz, 1H, Ar–H), 6.50 (d, *J* = 15.6 Hz, 1H, PhC*H*=CH), 6.38 (dt, *J* = 16.0, 6.4 Hz, 1H, PhCH=C*H*), 4.73 (s, 1H, OH), 3.53 (d, *J* = 6.4 Hz, 2H, CH=CHCH_2), 2.27 (s, 3H, CH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 151.7, 137.1, 131.3, 131.0, 130.2, 128.5, 128.2, 128.0, 127.3, 126.2, 125.4, 115.6, 34.1, 20.5 ppm.

4-(*tert*-Butyl)-2-cinnamylphenol (4h)

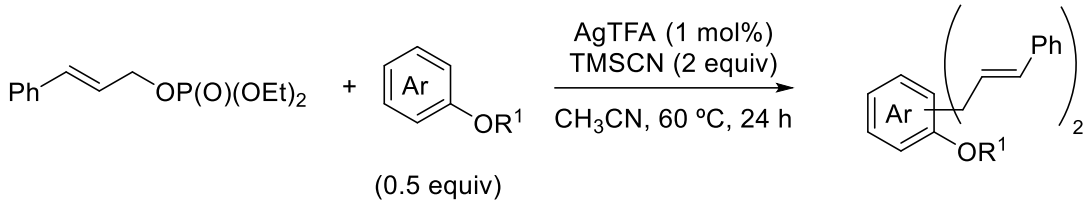


Was isolated as white solid (82%), followed the general method with $Pd(OAc)_2$ (1 mol%) as a catalyst for 24 h.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 7.6 Hz, 2H, Ar–H), 7.29 (app. t, *J* = 7.6 Hz, 2H, Ar–H), 7.21 (app. t, *J* = 7.6 Hz, 1H, Ar–H), 7.17–7.15 (m, 3H, Ar-H), 6.76 (d, *J* = 8.8 Hz, 1H, Ar–H), 6.53 (d, *J*=16.0 Hz, 1H, PhC*H*=CH), 6.40 (dt, *J* = 16.0, 6.4 Hz, 1H, PhCH=C*H*), 4.81 (br s, 1H, OH), 3.57 (d, *J* = 6.4 Hz, 2H, CH=CHCH_2), 1.30 (s, 9H, $C(CH_3)_3$) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 151.8, 143.7, 137.1, 131.3, 128.5 (two peaks overlapped), 128.2, 127.4, 127.3, 126.2, 124.7, 115.3, 35.0, 34.1, 31.6 ppm; **IR (neat):** 3384, 2951, 1739, 1501, 1274, 1212, 1123, 966, 822, 738, 692 cm^{-1} **HRMS (EI):** *m/z* calcd for $C_{19}H_{22}O$: 266.1671 $[M]^+$; found: 266.1667.

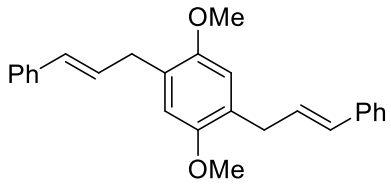
General Procedure for Diallylation of Phenol Derivatives

AgTFA-catalyzed Friedel–Crafts-type allylic substitution of 1,3-benzodioxole is described as a typical procedure.



To a solution of (*E*)-cinnamyldiethylphosphate (220 mg, 0.81 mmol) in CH_3CN (2.5 mL) was added AgTFA (1.8 mg, 0.081 mmol). The resulting mixture was stirred for 15 min at 60 ºC, followed by the addition of 1,3-benzodioxole (50 mg, 0.41 mmol) and TMSCN (167 mg, 1.68 mmol). The reaction mixture was then continuously stirred at 60 ºC for 5 h. Completion of the reaction was judged by TLC (AcOEt/hexane = 1/4). A saturated $NaHCO_3$ aq. was added to quench the reaction, and the aqueous layer was extracted by AcOEt (10 mL × 3). The collected organic layer was washed with brine and dried over Na_2SO_4. After Na_2SO_4 was filtered off, the resulting mixture was concentrated *in vacuo*. The yield of the product was calculated from ^{1}H NMR spectra of the crude 1-cinnamyl-4-methoxybenzene with pyrazine as an internal standard (97% yield). The product was isolated by PTLC (AcOEt:hexane = 1:50), as a yellow oil (136 mg, 0.38 mmol, 93% yield).

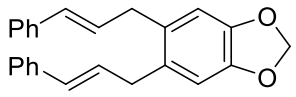
((1*E*,1'*E*)-(2,5-Dimethoxy-1,4-phenylene)bis(prop-1-ene-3.1-diyl))dibenzene (5a)



Was isolated as colorless oil (90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (app d, *J* = 7.2 Hz, 4H, Ar–H), 7.28 (app. t, *J* = 7.56 Hz, 4H, Ar–H), 7.18 (app. t, *J* = 7.6 Hz, 2H, Ar–H), 6.74 (s, 2H, Ar–H), 6.44 (d, *J* = 16.0 Hz, 2H, PhC*H*=CH), 6.36 (dt, *J* = 16.0, 6.4 Hz, 2H, PhCH=C*H*), 3.79 (s, 6H, OCH_3), 3.52 (d, *J* = 6.0 Hz, 4H, CH=CHCH_2) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 151.3, 137.7, 130.5, 129.0, 128.4, 127.1, 126.9, 126.1, 113.1, 56.4, 33.5 ppm; **IR (neat):** 2935, 1491, 1464, 1414, 1274, 1255, 1086, 1020, 964, 796, 749, 730, 678 cm^{-1} **HRMS (EI):** *m/z* calcd for $C_{26}H_{26}O_2$: 370.1933 $[M]^+$; found: 370.1932.

5,6-Dicinnamylbenzo[*d*][1,3]dioxole (5b)

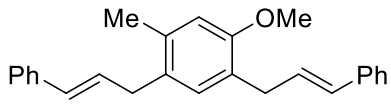


Was isolated as yellow oil (93%).

Spectra data are in accordance with the literature.[23]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (app. d, *J* = 7.2 Hz, 4H, Ar–H), 7.27 (app. t, *J* = 7.6 Hz, 4H, Ar–H), 7.19 (app. t, *J* = 7.2 Hz, 2H, Ar–H), 6.74 (s, 2H, Ar–H), 6.37 (d, *J* = 16.0 Hz, 2H, PhC*H*=CH), 6.31 (dt, *J* = 16.0, 5.2 Hz, 2H, PhCH=C*H*), 5.92 (s, 2H, OCH_2O), 3.50 (d, *J* = 4.8 Hz, 4H, CH=CHCH_2) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 146.3, 137.4, 131.2, 130.9, 129.0, 128.5, 127.1, 126.1, 109.9, 100.8, 36.2 ppm.

((11*E*,1'*E*)-(4-methoxy-6-methyl-1,3-phenylene)bis(prop-1-ene-3,1-diyl))dibenzen (5c)



Was isolated by PTLC (AcOEt:hexane = 1:15) as yellow oil (82%) with monoallylated branched isomer[18] (6%), followed the general procedure with 4.0 equiv of cinnamyl phosphate as electrophile.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (app d, *J* = 7.2 Hz, 4H, Ar–H), 7.29–7.25 (m, 4H, Ar–H), 7.19 (s, 1H, Ar–H), 7.17 (app. t, *J* = 6.8 Hz, 2H, Ar–H), 6.97 (s, 1H, Ar–H), 6.41(d, *J* = 16.0 Hz, 2H, PhC*H*=CH),6.35 (dt, *J* = 15.6, 6.0 Hz, 2H, PhCH=C*H*), 3.86 (s, 6H, OCH_3), 3.46 (d, *J* = 6.0 Hz, 4H, CH=CHCH_2) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 156.6, 137.8, 131.0, 130.2, 129.5, 128.4, 126.7, 126.0, 120.2, 95.5, 55.8, 32.8 ppm; **IR (neat):** 2943, 1607, 1586, 1498, 1451, 1283, 1200, 1154, 1113, 1035, 827, 740, 686 cm^{-1}; **HRMS (EI):** *m/z* calcd for $C_{26}H_{26}O_2$: 370.1933 $[M]^+$; found: 370.1924.

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Chapter 2

Silyl Cyanopalladate Catalyzed Friedel–Crafts-type Cyclization Affording 3-Arlyoxindole Derivatives

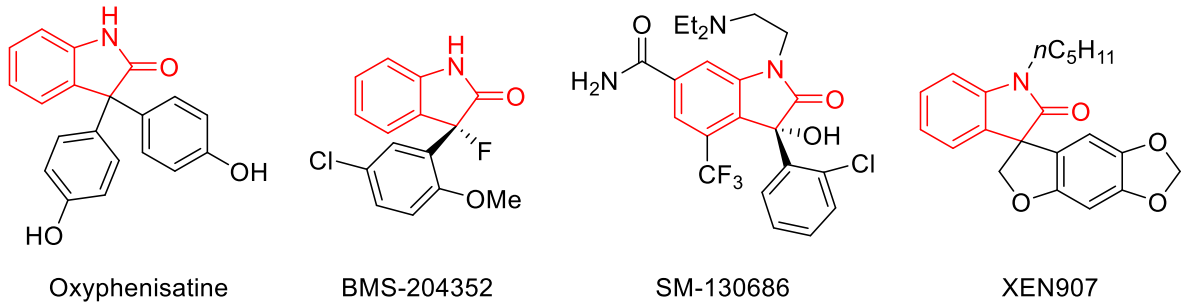
Abstract

3-Aryloxindole derivatives were synthesized through the Friedel–Crafts-type cyclization from the appropriate mandelamide derivative as substrates. The reaction was catalyzed by a trimethylsilyl tricyanopalladate complex, (TMS)[Pd(CN)$_3$], generated *in situ* from trimethylsilyl cyanide (TMSCN) and Pd(OAc)$_2$. Wide varieties of diethylphosphate derived from *N*-arylmandelamides were almost quantitatively converted to the corresponding 3-aryloxindols. When *N*,*N*-dibenzyl amide was used instead of the anilide substrates, the benzo-fuzed δ-lactam was obtained. The oxindole product was applied to the substitution reactions to afford the 3,3-diaryloxindoles with two different aryl groups.

2.1 Introduction

Oxindole derivatives, a class of benzo-fused 5-membered lactams, are well known for their bioactive properties and found in naturally formed alkaloids. In particular, 3-aryloxindole derivates are worked as pharmaceutical agents (Figure 1).[1-4]

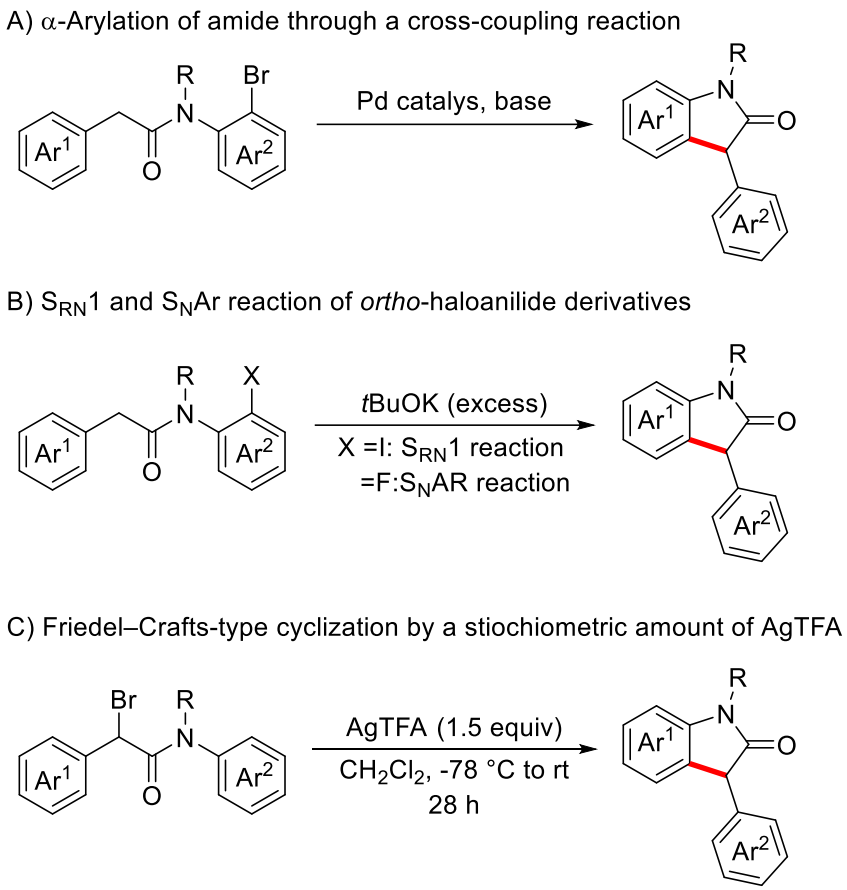
Figure 1. Bioactive compounds including the 3-aryloxindole moiety



Several studies have performed synthetic methods for formation of these therapeutic structures.[5] The intramolecular C–C bond formation between the α-position of amide and *ortho*-carbon of *N*-aryl ring is a typical strategy for the reaction. Three synthetic approaches have been focused for several years for forming the 3-aryloxindoles moiety (Scheme 1).[6-10] The first strategy requires Pd complex and base for an intramolecular C(sp^2)-C(sp^3) cross coupling reaction of *N*-acyl-*ortho*-haloanilides (Scheme 1A).[6] Coordination by the amide group helps oxidative cleavage of the *C*-halogen bond catalyzed by Pd(0) species. The reversibly formed amide-enolate binds on the Pd(II) instead of the halide. Pd(0) is released by reduction that helped to form the lactam. The second strategy, is a helpful method using the *N*-acyl-*ortho*-iodoanilides, is *a*-arylation through a radical-nucleophilic aromatic

substitution ($S_{RN}1$) (Scheme 1B).[7,8] Enolate transfers an electron to the aryl iodide (SET) in the presence of a stoichiometric or excess amount of alkali base. This helps the construction the C–C linkage with homolysis of the C–I bond. Using the *ortho*-fluoroanilides as substrate is one of the disadvantages. These substrates limit the nucleophilic substitution by the amide-enolate for electron-deficient aromatic ring under similar basic conditions (S_NAr reaction).[9] The third strategy is generation the C–C bond through Friedel–Crafts-type cyclization of α-halo-*N*-arylamide with the help of releasing the halide (S_N1-type reaction) (Scheme 1C).[10] This method needed more than an equimolar amount of the silver Lewis acid for obtaining the desired compound in high yield. The main advantage of this method is that substrates without *ortho*-haloanilide moiety can be introduced. Thus, an efficient catalytic model of this reaction is highly needed to develop with more preferable substrates such as alcoholic derivatives instead of halide compounds.

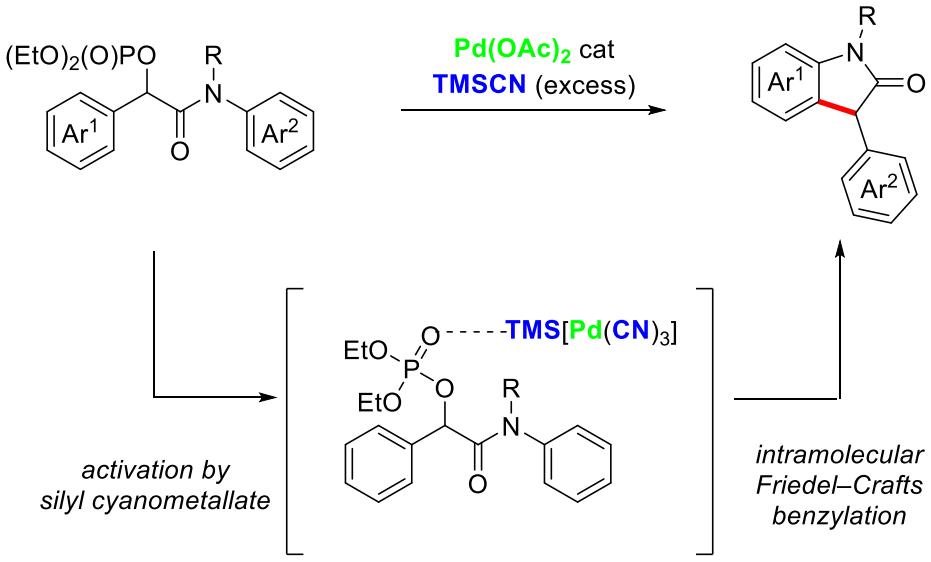
Scheme 1. Previous strategy for formation of 3-aryloxindole derivatives



Recently, our group has focused on Lewis-acid catalysis of *in situ* formed silyl cyanometallate complexes. It is well-known that transition metal compounds strongly interact with the *C*-terminus of cyanide (CN^-). Thermodynamically stable metal cyanide ($M(CN)_n$), generates from transition metal salt (MX_n) reacts with an excess amount of trimethylsilyl cyanide (TMSCN). Some studies have revealed that a small part of the $M(CN)_n$ is possibly converted to the silyl cyanometallate $(TMS)[M(CN)_{n+1}]$ that in equilibrium with $M(CN)_n$. The silyl part of the ate complex behaves as a Lewis acid and paved the way for several organic transformation as a suitable catalyst. In fact, our group has successfully proposed new protocols for nucleophilic isocyanations of allylic and benzylic cinnamyl alcohol derivatives and Friedel–Crafts-type allylations catalyzed by silyl cyanometallate complexes (M = Pd,

Ag).[11,13] Notably, the transition metal species has effect on the Lewis acidity of these catalysts. The intensity of the acidity could be controlled by the reversibility of the catalysts. Here, the author reports the first example of catalytic method that catalyzed by a trimethylsilyl cyanopalladate (M = Pd, n = 2) intramolecular Friedel–Crafts type substitution affording 3-aryloxindole derivatives from more suitable substrates, the benzylic diethyl phosphates, than the corresponding halides for this catalytic system (Scheme 2).

Scheme 2. Silyl cyanopalladate-catalyzed Friedel–Crafts cyclization affording 3-aryloxindole derivatives

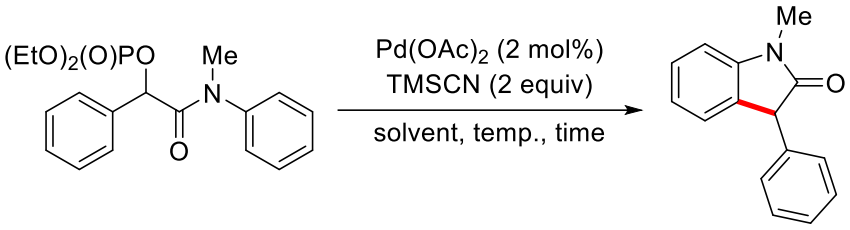


2.2 Results and Discussion

The author started the investigation of optimization conditions with *N*-methyl-*N*-phenylmandelamide derivative **1a** as the model substrate with diethylphosphate as a leaving group of choice according to our group previous studies on nucleophilic isocyanation and Friedel–Crafts-type allylation (Table 1).[11–13] The cyclization of **1a** was

completed in the presence of $Pd(OAc)_2$ (2 mol%) and TMSCN (2 equiv) in CH_3NO_2 at 80 °C within 20 h to afford the 3-phenyloxindole **2a** in almost quantitative yield (entry 1). In the same manner, the targeted compound **2a** formed in high yield in CH_3CN and 1,2-dimethoxyethane (1,2-DME) (entries 2,3). On the other hand, the yield of cyclization product **2a** decreased significantly in 1,4-dioxane, a cyclic ether, and less polar toluene that suggested the reaction rate slowed with those solvents (entries 4,5). No formation of the compound **2a** was observed in DMF due to high polar and easy coordination (entry 6). The reaction without catalyst prevented the formation of the product. These results showed that addition of $Pd(OAc)_2$ is crucial for carrying out this reaction (entry 7). Consequently, the reaction is completed in 10 h at 60 °C in CH_3NO_2, and therefore the author adopted these as the optimized conditions (entry 8). The reaction is suppressed with using TMSCN as 1.2 equiv that yielded the desired compound **2a** in 47% yield (entry 9). These results showed that a large amount of TMSCN relative to the Pd catalyst was required for generation of sufficient amount of the active catalytic species, $TMS[Pd(CN)_3]$, in the reaction system.

Table 1. Optimization of reaction conditions



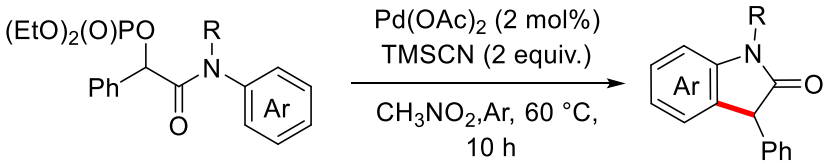
entry	solvent	temp (°C)	time (h)	yield (%)[a]
1	CH_3NO_2	80	20	>99
2	CH_3CN	80	20	85
3	1,2-DME	80	20	96
4	1,4-dioxane	80	20	32
5	Toluene	80	20	48
6	DMF	80	20	0
7[b]	CH_3NO_2	80	20	0
8	CH_3NO_2	60	10	>99 (98)
9[c]	CH_3NO_2	60	10	47

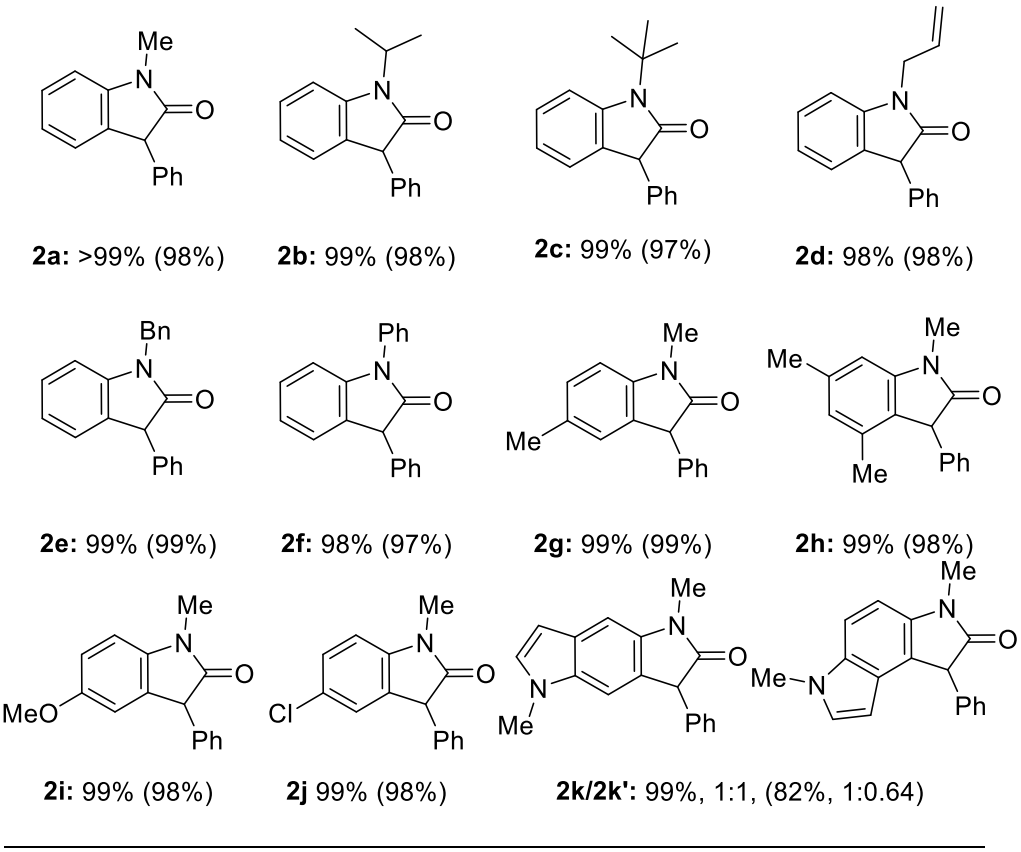
[a] ^{1}H NMR yield. The isolated yield is given in parenthesis. [b] No $Pd(OAc)_2$ was employed as a catalyst. [c] TMSCN (1.2 equiv) was added in the reaction mixture

With the optimized reaction conditions in hand, the author investigated the scope and limitations of the intramolecular Friedel–Crafts-type reaction (Scheme 3). Methyl and more sterically hindered 2-propyl and *tert*-butyl groups were easily introduced on the *N*-atom without retardation of the oxindole formation (**2b, 2c**). The cyclization products **2d** and **2e** were obtained without any decomposition of the *N*-allyl and *N*-benzyl substituents in the presence of the palladate complex. The cyclization product triaryl **2f** was easily

generated from *N,N*-diphenylamide **1f** as pre-prepared aniline phenyl rings. 4-Methyl- as well as 3,5-dimethyl-substituted substrates were converted to corresponding cyclization products **2g** and **2h** in 99% yield. The yield of the electron-donating methoxy group and electron-withdrawing chloro group at *para*-position of the aniline phenyl ring slightly differed from **2g**. A 1:1 mixture of the regioisomers of **2k** was obtained from the reaction of the mandelamide **1k** in 99% yield. However relatively unstable **2k'** was partially decomposed during the purification.

Scheme 3. Scope and limitations on *N*-alkylaniline substructures



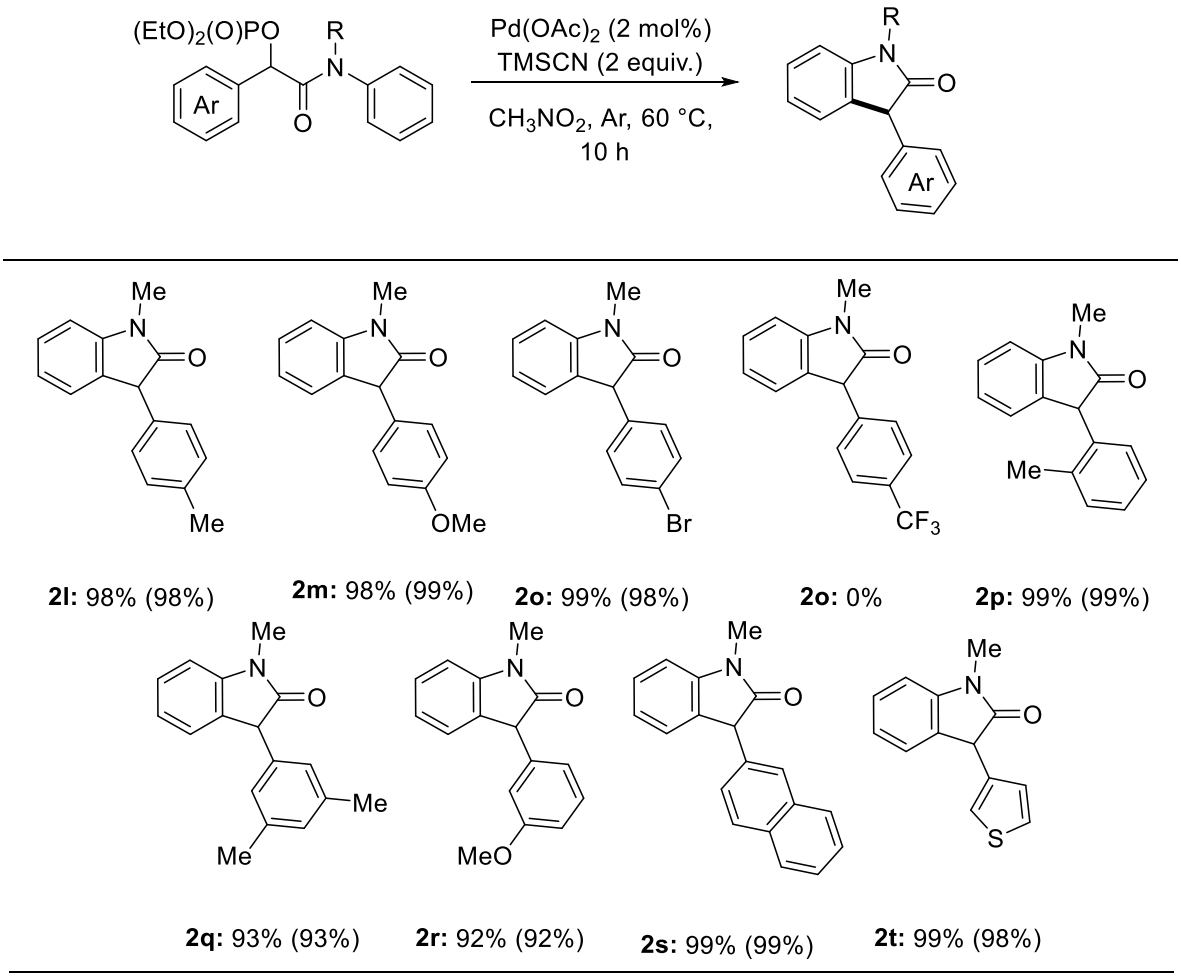


[a] ^{1}H NMR yield. The isolated yield is given in parenthesis. [b] A 1:1 mixture of the regioisomers was obtained.

3-Aryl moieties were screened under the same conditions (Scheme 4). The reactivity of the substrate was suspected to affect by substituents at C4 position of the aryl group. The reaction of the desired compounds methyl, methoxy, and also bromo substituted **2l**, **2m** and **2n** resulted in 98%, 99% and 98% yield. On the other hand, strongly electron deficient substrate, *para*-trifluoromethyl substituted **1o**, did not form the cyclization product **2o** at all.

These results suggested that the reaction possibly occurred through S_N1-type mechanism like Friedel–Crafts-type allylation catalyzed by the silyl cyanometallate.[13] Catalytic system worked efficiently even with steric hindered substrate to afford corresponding cyclized product **2p** in high yield with optimal conditions. Substitution on the C3 of the mandelic acid substructure's phenyl rings has little effect on the yield of the **2q** and **2r**. 2-Naphthyl and hetero atom included 3-thienyl substituted oxindoles were formed quantitatively.

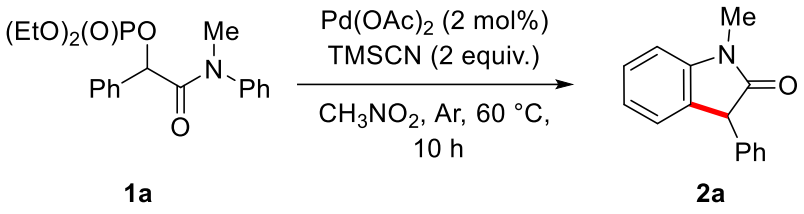
Scheme 4. Scope and limitations on mandelic acid substructures[a]



[a] ^{1}H NMR yield. The isolated yield is given in parenthesis.

Gram-scale synthesis of substrate **1a** was successfully carried out with the optimized conditions. Oxindole **2a** was formed 1.78 g from 3.02 g of **1a** (Scheme 5)**.**

Scheme 5. Gram-scale synthesis of oxindole **2a** under the optimized conditions

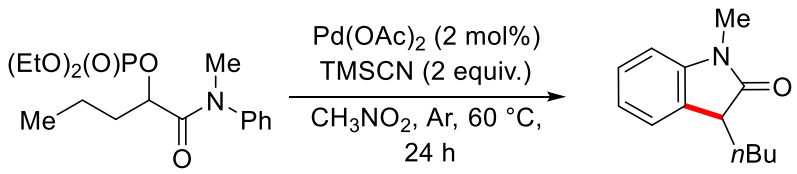


1a **2a**

3.02 g (7.99 mmol) 1.78 g (7.97 mmol)

The cyclized product **4** from the aliphatic diethylphosphate 2-hydroxypentamide **3** were not obtained under optimized conditions as limitation of this method supported that benzylic α-cationic intermediate is stabilized by α-aryl structure of substrates (Scheme 6).

Scheme 6. Applied reaction of the aliphatic diethylphosphate 2-hydroxypentamide **3** through intramolecular Friedel–Crafts-type cyclization

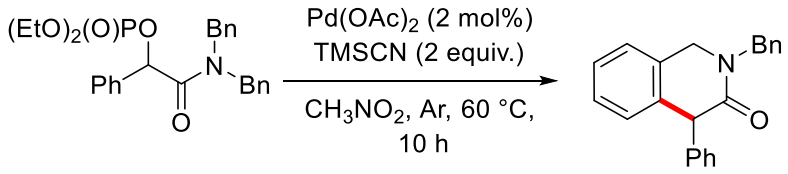


3 **4**: 0% yield

Formation of the δ-lactam **6** was carried out with this method successfully (Scheme 7). The cyclized product **6** was obtained from dibenzylamide substrate **5** in 99% yield with 2 mol% $Pd(OAc)_2$ in 10 h. The strong nucleophilicity of the aniline moiety has effects on product formation. For example, when the benzylanilide **1e** introduced as a substrate, γ-

lactam product **2e** was obtained in 99% yield that supported predomination of product formation over δ-lactam (Scheme 3, **2e**).

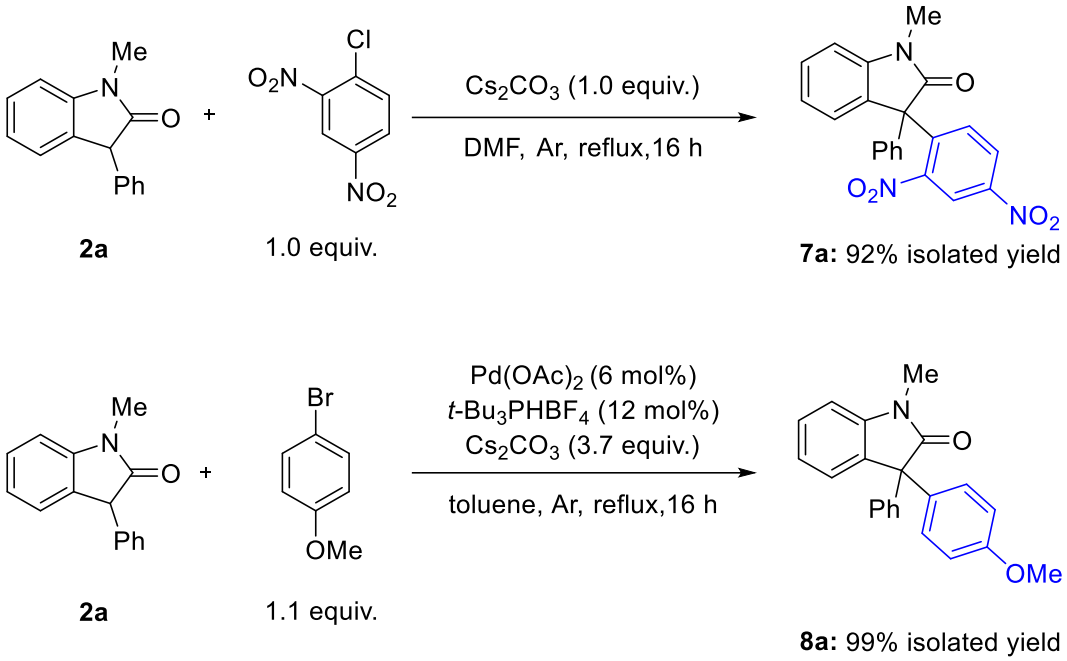
Scheme 7. Formation of a δ-lactam derivative through intramolecular Friedel–Crafts-type cyclization



5 **6:** 99% (98%)

The synthetic utility of 3-aryloxindoles **2** was investigated by the transformation into the 3,3-diaryloxindoles bearing two different aromatic substructures (Scheme 8). An electron-deficient aromatic ring was introduced by nucleophilic aromatic substitution. The diaryloxindole **7a** was transformed with Cs_2CO_3 (1 equiv) by the reaction between Friedel–Crafts-type cyclization product **2a** and 2,4-dinitrochlorobenzene in 92% isolated yield.[14] An electron-rich aromatic reagent was successfully employed by Pd-catalyzed cross coupling reaction. The reaction of **2a** was occurred with a catalytic amount of $Pd(OAc)_2$ and *t*BuPHBF$_4$ with the addition of Cs_2CO_3 (3.7 equiv) to affording the diaryl product **8a** in 99% isolated yield.[14]

Scheme 8. Transformations of 3-aryloxindole **2a**



2.3 Conclusion

The author reported the first example of a Friedel–Crafts-type cyclization of diethylphosphates derived from *N*-arylmandelamides to afford 3-aryloxindoles. This method successfully catalyzed by silyl cyanopalladate generated from $Pd(OAc)_2$ (2 mol%) as a catalyst and excess amount of TMSCN *in situ*. The ate complex $TMS[Pd(CN)_3]$ activated the phosphates substrates as a Lewis acid. The acidity of the active catalytic species could be controlled with the reversibility of $Pd(CN)_2$ and TMSCN. Transformation wide range of substrate scope was carried out with this method in high yield and it applied to a gram-scale synthesis. The aromaticity of the substrates was the main limitation of this procedure. Cyclized product formation was not obtained under the optimized condition from an aliphatic α-hydroxyamide derivative that because of the stability of the cationic species by α-aryl

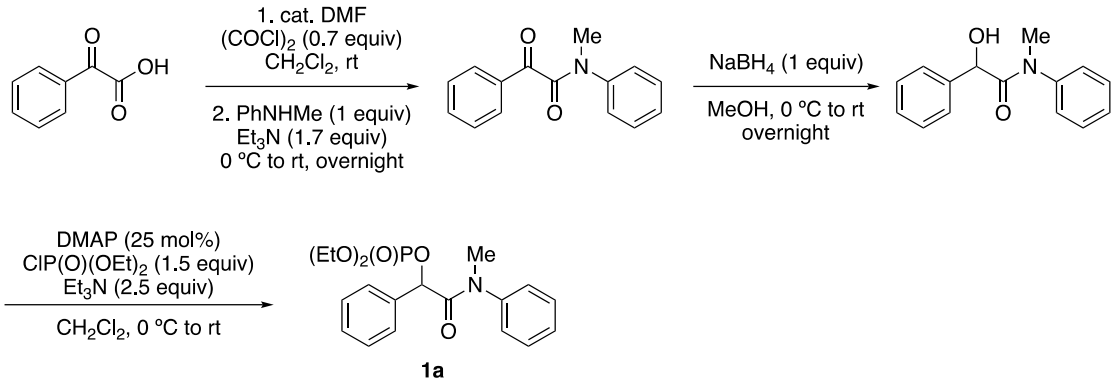
structure. When *N*,*N*-dibenzylmandelamide was introduced as suitable substrate for this method, product formation was dominated by γ-lactam over δ-lactam. Substitution was took place at C3 position with the 3-phenyloxindole. Transformations of two different aromatic substructures were occurred in high yield.

2.4 Experimental Section

General Information: ^{1}H NMR spectra were measured on a JEOL JNM-ECX400P (400 MHz) spectrometer and JNM-ECS400 (400 MHz) spectrometer. Data were reported as follows: chemical shifts in ppm from tetramethysilane or the residual solvent as an internal standard, integration, multiplicity (s = singlet, d = doublet, t = triplet, dd = double-doublet, td = triple-doublet, q = quartet, m = multiplet, br = broad, and app = apparent), coupling constants (Hz), and assignment. ^{13}C NMR spectra were measured on a JEOL JNM-ECX400P (100 MHz) spectrometer and a JNM-ECS400 (100 MHz) spectrometer with complete proton decoupling. ^{31}P NMR spectra were measured on a JEOL JNM-ECX400 (400 MHz) spectrometer. ^{19}F NMR spectra were measured on a JEOL JNM-ECX400 (400 MHz) spectrometer. Chemical shifts were reported in ppm, from the residual solvent as an internal standard. Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 and FT/IR-4600. Mass spectrometry was carried out at the Instrumental Analysis Division, Global Facility Center, Creative Research Institution, Hokkaido University. The products were purified by silica-gel column chromatography prepared from silica gel 60N (Kanto Chemical Co. Inc) or preparative thin-layer chromatography (PTLC) prepared from Wako Gel B-5F (Wako Pure Chemical Industries). Trimethylsilyl cyanide (TMSCN) and Nitromethane (CH_3NO_2) were purchased from Kanto Chemical Co. Inc. and were used after distillation. Palladium diacetate ($Pd(OAc)_2$) was purchased from Sigma-Aldrich Co. LLC., and was used as received.

Preparation of Amido Phosphates

General procedure for the preparation of amido phosphates 1 from benzoylformic acid derivatives (Method A)



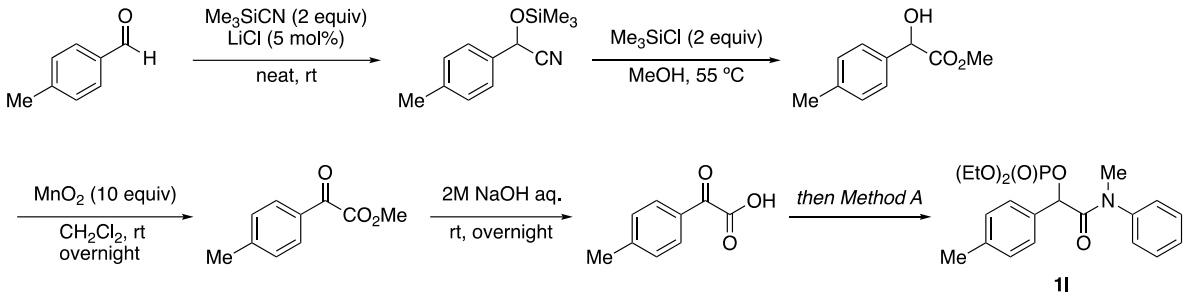
Synthesis of amido phosphate **1a** is selected as the typical procedure for method A. Two drops of DMF were added to a round-bottomed flask (100 mL) charged with benzoylformic acid (1.08 g, 7.2 mmol) in CH_2Cl_2 (25 mL). Oxalyl chloride (686 mg, 5.4 mmol) was then added to the solution. A base trap stuffed with solid NaOH was put on the reaction flask to abstract the released HCl gas. The reaction mixture was stirred for several hours until the bubble formation was stopped, and then it was cooled to 0 °C. PhNHMe (816 mg, 7.6 mmol) in Et_3N (1.28 g, 12.7 mmol) was added dropwise to the solution. The mixture was allowed to warm to room temperature and was continuously stirred overnight. The reaction was judged complete by TLC analysis (AcOEt:hexane = 1:4). The reaction was quenched by H_2O and the layers were separated, and then the aqueous layer was extracted with AcOEt (15 mL) 3 times. The combined organic layers were washed with brine and dried over Na_2SO_4. After Na_2SO_4 was filtered off, the collected filtrate was concentrated in vacuo. The crude residue was

purified by silica-gel column chromatography to afford the α-ketoamide (AcOEt:hexane = 2:1).

The α-ketoamide (1.04 g, 4.4 mmol) was dissolved in MeOH and cooled to 0 °C. $NaBH_4$ (173 mg, 4.6 mmol) was added to the solution and the reaction mixture was allowed to warm to room temperature and was continuously stirred overnight. The reaction was quenched by the addition of saturated NH_4Cl (aq.). The layers were separated, and the aqueous layer was extracted with AcOEt (15 mL) 3 times. The combined organic layers were washed with brine and dried over Na_2SO_4. After Na_2SO_4 was filtered off, the collected filtrate was concentrated in vacuo. The crude residue was used for further synthesis without purification.

The obtained α-hydroxyamide was dissolved in CH_2Cl_2 (25 mL). Et_3N (653 mg, 6.6 mmol) and *N*,*N*-dimethyl-4-aminopyridine (DMAP; 129 mg, 1.1 mmol) were then added to the solution. The mixture was cooled to 0 °C and diethyl chlorophosphate (1.07 g, 6.2 mmol) was added dropwise. The reaction mixture was allowed to warm up to room temperature and was continuously stirred until the reaction was judged complete by TLC analysis. The reaction was quenched by the addition of saturated $NaHCO_3$ (aq.). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (10 mL) 3 times. The combined organic layers were washed with water, then brine, and dried over Na_2SO_4. After Na_2SO_4 was filtered off, the collected filtrate was concentrated in vacuo. The crude residue was purified by silica-gel column chromatography (AcOEt:hexane = 1:2) to afford the *N*-methyl-*N*-phenylmandelamide derivative **1a** (784 mg, 2.1 mmol).

General procedure for the preparation of amido phosphates 1 from benzaldehyde derivatives (Method B)

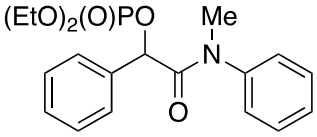


Caution: Trimethylsilyl cyanide (TMSCN) must be used in a well-ventilated hood due to its high toxicity.

Synthesis of amido phosphate **1l** is selected as the typical procedure for method B. Trimethylsilyl cyanide (TMSCN; 8.63 g, 86.3 mmol) was added to a round-bottomed flask (50 mL) charged with *p*-tolualdehyde (5.20 g, 43.2 mmol). LiCl (94 mg, 2.2 mmol) was added to the reaction mixture and was continuously stirred at room temperature until the reaction was judged complete by TLC analysis. The reaction was quenched by the addition of saturated $NaHCO_3$ (aq.). The layers were separated, and the aqueous layer was extracted with Et_2O (20 mL) 3 times. The combined organic layers were washed with water, then brine, and dried over Na_2SO_4. After Na_2SO_4 was filtered off, the collected filtrate was concentrated in vacuo. The resulting residue was dissolved in MeOH (25 mL). Trimethylsilyl chloride (TMSCl; 10.2 g, 93.9 mmol) was then added to this solution. The reaction mixture was heated to 55 °C and continuously stirred until the reaction was judged complete by TLC analysis. The reaction was quenched by the addition of saturated $NaHCO_3$ (aq.). The layers were separated, and the aqueous layer was extracted with AcOEt (20 mL) 3 times. The combined organic layers were washed with water, then brine, and dried over Na_2SO_4. After Na_2SO_4 was

filtered off, the collected filtrate was concentrated in vacuo. The resulting residue was dissolved in CH_2Cl_2 (75 mL). MnO_2 (63.0 g, 337 mmol) was added to the solution and was continuously stirred overnight. The reaction mixture was filtered through a cake of Celite and the filtrate was concentrated in vacuo. 2 M NaOH (aq.) was directly added to the residue and the resulting mixture was stirred overnight. The reaction was acidified with conc. H_2SO_4 until the pH of the solution became 1. The layers were separated, and the aqueous layer was extracted with Et_2O (20 mL) 3 times. The combined organic layers were washed with water, then brine, and dried over Na_2SO_4. After Na_2SO_4 was filtered off, the collected filtrate was concentrated in vacuo. The obtained benzoylformic acid derivative was applied without further purification to **Method A**, affording the amido phosphate **1l** (1.59 g, 4.05 mmol).

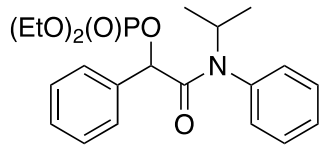
Diethyl-(2-(methyl(phenyl)amino-2-oxo-1-phenylethyl) phosphate (1a)



Was isolated as pale-yellow viscous oil (51%, 784 mg), followed the general method A.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.34 (br m, 3H, Ar-H), 7.31–7.21 (m, 4H, Ar-H), 7.08 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.04 (br s, 2H, Ar-H), 5.73 (d, *J* = 7.6 Hz, 1H, PhCH), 4.31–4.17 (m, 2H, OC*H*$_2$CH$_3$), 3.88–3.81 (m, 2H, OC*H*$_2$CH$_3$), 3.26 (s, 3H, NCH$_3$), 1.36 (app. t, *J* = 7.6 Hz, 3H, OCH$_2$C*H*$_3$), 1.10 (t, *J* = 7.6 Hz, 3H, OCH$_2$C*H*$_3$) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 168.0 (d, *J* = 4.8 Hz), 142.1, 135.2 (d, *J* = 6.7 Hz), 135.2 129.7, 129.0, 128.4, 128.3, 128.1 (two peaks overlapped), 75.2 (d, *J* = 4.8 Hz), 64.2 (d, *J* = 5.8 Hz), 63.7 (d, *J* = 6.7 Hz), 38.0, 16.0 (d, *J* = 6.7 Hz), 15.8 (d, *J* = 7.7 Hz) ppm; **^{31}P NMR (162 MHz, $CDCl_3$):** δ –1.5 ppm; **IR (neat):** 2988, 1669, 1596, 1496, 1382, 1010, 997, 964, 891, 740, 700 cm^{-1}; **HRMS (EI):** *m/z* calcd for $C_{19}H_{24}NO_5P$: 377.1391 $[M]^+$; found: 377.1404.

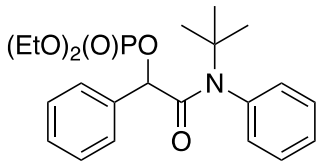
Diethyl-(2-(isopropyl(phenyl)amino)2-oxo-1-phenylethyl) phosphate (1 b)



Was isolated as a colorless viscous oil (66%, 1.75 g), followed the general method A.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.38–7.34 (m, 2H, Ar-H), 7.31–7.27 (m, 1H, Ar-H), 7.25–7.21 (m, 2H, Ar-H), 7.13 (app. t, *J* = 7.6 Hz, 1H, Ar-H), 7.09–7.07 (m, 2H, Ar-H), 6.41 (d, *J* = 8.0 Hz, 1H, Ar-H), 5.47 (d, *J* = 7.2 Hz, 1H, PhCH), 5.04–4.94 (m, 1H, NC*H*$(CH_3)_2$), 4.30–4.15 (m, 2H, OC*H*$_2$$CH_3$), 3.86–3.79 (m, 2H, OC*H*$_2$$CH_3$), 1.35 (tt, *J* = 7.2, 1.2 Hz, 3H, OCH_2C*H*$_3$), 1.09 (tt, *J* = 7.2, 1.2 Hz, 3H, OCH_2*CH*$_3$), 1.02 (dd, *J* = 6.8, 0.8 Hz, 3H, NCHC*H*$_3$$CH_3$), 0.98 (dd, *J* = 6.8, 0.8 Hz, 3H, NCHC*H*$_3$$CH_3$) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 167.2 (d, *J* = 3.9 Hz), 136.4, 135.3 (d, *J* = 6.7 Hz), 131.3, 130.9, 129.5, 129.0, 128.7, 128.5, 128.4, 128.3, 75.9 (d, *J* = 3.8 Hz), 64.2 (d, *J* = 5.8 Hz), 63.6 (d, *J* = 5.7 Hz), 46.9, 20.9, 20.3, 16.0 (d, *J* = 6.7 Hz), 15.8 (d, *J* = 6.7 Hz) ppm; **^{31}P NMR (162 MHz, $CDCl_3$):** δ –1.5 ppm; **IR (neat):** 2982, 1670, 1491, 1393, 1267, 1242, 1018, 961, 894, 699 cm^{-1}; **HRMS (EI):** *m/z* calcd for $C_{21}H_{28}NO_5P$: 407.1705 $[M]^+$; found: 405.1698.

2-(*tert*-Butyl(phenyl)amino-2-oxo-1-phenylethyl diethyl phosphate (1c)

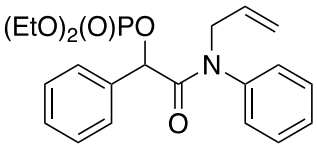


Was isolated as a yellow viscous oil (70%, 1.15 g), followed the general method A.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (td, *J* = 7.6, 1.2 Hz, 1H, Ar-H), 7.37–7.27 (m, 3H, Ar-H), 7.25–7.21 (m, 2H, Ar-H), 7.09–7.03 (m, 3H, Ar-H), 6.34 (d, *J* = 6.8 Hz, 1H, Ar-H), 5.37 (d, *J* = 7.2 Hz, 1H, PhCH), 4.28–4.15 (m, 2H, OC*H*$_2$$CH_3$), 3.86–3.78 (m, 2H, OC*H*$_2$$CH_3$),

1.36–1.33 (m, 3H, OCH_2CH_3), 1.35 (s, 9H, $NC(CH_3)_3$), 1.09 (td, J = 7.2 Hz, 1.2 Hz, 3H, OCH_2CH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 167.5 (d, J = 3.8 Hz), 139.3, 135.5 (d, J = 6.7 Hz), 131.4, 130.3, 129.4, 128.9, 128.5, 128.4, 128.3, 128.2, 76.5 (d, J = 3.8 Hz), 64.1 (d, J = 5.8 Hz), 63.5 (d, J = 6.7 Hz), 59.0, 28.8, 16.0 (d, J = 7.7 Hz), 15.7 (d, J =6.7 Hz) ppm; **^{31}P NMR (162 MHz, $CDCl_3$):** δ –1.5 ppm; **IR (neat):** 2980, 1674, 1367, 1270, 1191, 1015, 955, 885, 728, 697 cm^{-1}; **HRMS (ESI):** *m/z* calcd for $C_{22}H_{30}NO_5NaP$: 442.1754 $[M+Na]^+$; found: 442.1755.

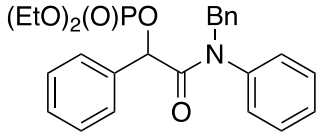
2-(Allyl(phenyl)amino)-2-oxo-1-phenylethyl diethyl phosphate (4d)



Was isolated as a yellow viscous oil (62%, 4.02 g), followed the general method A.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.21 (m, 6H, Ar-H), 7.08 (d, J = 6.8 Hz, 2H, Ar-H), 6.99 (br s, 2H, Ar-H), 5.85–5.75 (m, 1H, NCH_2CH), 5.69 (d, J = 7.2 Hz, 1H, PhCH), 5.07–4.98 (m, 2H, NCH_2CHCH_2), 4.33–4.16 (m, 4H, OCH_2CH_3 + NCH_2), 3.88–3.81 (m, 2H, OCH_2CH_3), 1.35 (td, J = 6.8, 0.8 Hz, 3H, OCH_2CH_3), 1.10 (td, J = 7.2, 0.8 Hz, 3H, OCH_2CH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 167.6 (d, J = 3.1 Hz), 140.5, 135.2 (d, J = 6.8 Hz), 132.3, 129.5, 129.04, 129.01, 128.4 (two peaks overlapped), 128.1, 118.1, 75.4 (d, J = 4.6 Hz), 64.2 (d, J = 6.1 Hz), 63.7 (d, J = 6.1 Hz), 52.8, 16.0 (d, J = 6.8 Hz), 15.8 (d, J = 6.9 Hz) ppm; **^{31}P NMR (162 MHz, $CDCl_3$):** δ –1.5 ppm; **IR (neat):** 2982, 1676, 1593, 1494, 1394, 1265, 1021, 983, 895, 741, 696 cm^{-1}; **HRMS (ESI):** *m/z* calcd for $C_{21}H_{26}NO_5NaP$: 426.1441 $[M+Na]^+$; found: 426.1436.

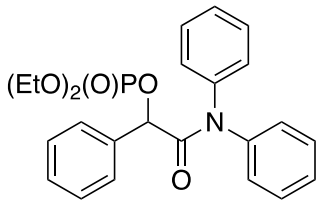
2-(Benzyl(phenyl)amino)-2-oxo-1-phenylethyl dethyl phosphate (1e)



Was isolated as a pale-yellow viscous oil (53%, 1.60 g), followed the general method A.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.28 (m, 3H, Ar-H), 7.25–7.20 (m, 7H, Ar-H), 7.14–6.85 (m + br s, 5H, Ar-H), 5.71 (d, *J* = 7.6 Hz, 1H, PhCH), 4.92 (d, *J* = 14.4 Hz, 2H, NC*H*HPh), 4.80 (d, *J* = 14.4 Hz, 2H, NCH*H*Ph), 4.32–4.17 (m, 2H, OC*H*$_2$CH$_3$), 3.90–3.82 (m, 2H, OC*H*$_2$CH$_3$), 1.35 (td, *J* = 7.2, 1.2 Hz, 3H, OCH$_2$C*H*$_3$), 1.11 (td, *J* = 7.2 Hz, 1.2 Hz, 3H, OCH$_2$C*H*$_3$) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 168.0 (d, *J* = 8.8 Hz), 140.3, 136.7, 135.1 (d, *J* = 7.7 Hz), 129.4, 129.1 (two peaks overlapped), 128.6, 128.4 (two peaks overlapped), 128.3, 128.1, 127.4, 75.5 (d, *J* = 4.8 Hz), 64.2 (d, *J* = 5.7 Hz), 63.7 (d, *J* = 5.7 Hz), 53.7, 16.0 (d, *J* = 6.7 Hz), 15.8 (d, *J* = 7.7 Hz) ppm; **^{31}P NMR (162 MHz, $CDCl_3$):** δ –1.4 ppm; **IR (neat):** 2979, 1736, 1677, 1495, 1397, 1271, 1021,993, 888, 737, 695 cm^{-1}; **HRMS (ESI):** *m/z* calcd for $C_{25}H_{28}NO_5NaP$: 476.1597 $[M+Na]^+$; found: 476.1589.

2-(Diphenylamino)-2-oxo-1-phenylethyl diethyl phosphate (1f)

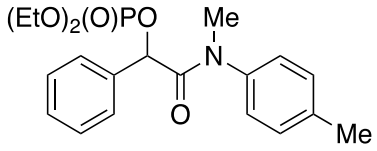


Was isolated as a colorless viscous oil (62%, 289 mg), followed the general method A.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.27 (m, 8H, Ar-H), 7.18–7.16 (m + br s, 7H, Ar-H), 5.93 (d, *J* = 7.2 Hz, 1H, PhCH), 4.32–4.23 (m, 2H, OC*H*$_2$CH$_3$), 3.92–3.84 (m, 2H, OC*H*$_2$CH$_3$), 1.36 (td, *J* = 7.2, 1.2 Hz, 3H, OCH$_2$C*H*$_3$), 1.12 (td, *J* = 7.2 Hz, 0.8 Hz, 3H, OCH$_2$C*H*$_3$), ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 168.3 (d, *J* = 2.9 Hz), 142.4, 140.9, 134.9 (d, *J* = 7.6 Hz), 129.6, 129.2, 129. 0, 128.6, 128.2, 126.3, 126.0, 75.9 (d, *J* = 3.8 Hz), 64.4 (d, *J* = 5.7 Hz), 63.8 (d, *J* = 5.8 Hz), 16.0 (d, *J* = 7.6 Hz), 15.8 (d, *J* = 6.7 Hz) ppm; **^{31}P NMR (162 MHz,**

$CDCl_3$): δ –1.3 ppm; **IR (neat):** 2977, 1685, 1492, 1262, 1013, 974, 756, 739, 699 cm^{-1}; **HRMS (EI):** *m/z* calcd for $C_{24}H_{26}NO_5P$: 439.1549 $[M]^+$; found: 439.1561.

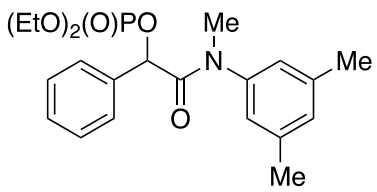
Diethyl (2-(methyl(*p*-tolyl)amino)-2-oxo-1-phenylethyl) phosphate (1g)



Was isolated as a pale-yellow viscous oil (56%, 2.09 g), followed the general method A.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.28 (m, 1H, Ar-H), 7.26–7.22 (m, 2H, Ar-H), 7.15–7.12 (m, 4H, Ar-H), 6.93 (br s, 2H, Ar-H), 5.74 (d, *J* = 7.2 Hz, 1H, PhCH), 4.31–4.17 (m, 2H, OC*H*$_2$CH$_3$), 3.88–3.80 (m, 2H, OC*H*$_2$CH$_3$), 3.23 (s, 3H, NCH_3), 2.37 (s, 3H, $PhCH_3$), 1.35 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.10 (t, *J* = 6.8 Hz, 3H, OCH_2CH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 168.1 (d, *J* = 3.9 Hz), 139.5, 138.3, 135.4 (d, *J* = 6.7 Hz), 130.3, 129.0, 128.4, 128.1, 127.8, 75.1 (d, *J* = 3.8 Hz), 64.2 (d, *J* = 5.8 Hz), 63.7 (d, *J* = 6.7 Hz), 38.0, 21.1, 16.0 (d, *J* = 7.7 Hz), 15.8 (d, *J* = 6.7 Hz) ppm; **^{31}P NMR (162 MHz, $CDCl_3$):** δ –1.5 ppm; **IR (neat):** 2981, 1738, 1673, 1514, 1385, 1266, 1009, 968, 893, 822, 734, 697 cm^{-1}; **HRMS (EI):** *m/z* calcd for $C_{20}H_{26}NO_5P$: 391.1549 $[M]^+$; found: 391.1561.

2-((3,5-Dimethylphenyl)(methyl)amino)-2-oxo-1-phenylethyl diethyl phosphate (1h)

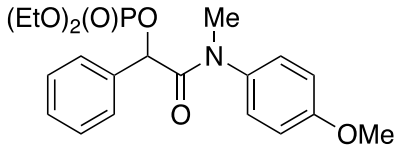


Was isolated as a ale-yellow viscous oil (71%, 695 mg), followed the general method A.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.21 (m, 3H, Ar-H), 7.10 (d, *J* = 6.8 Hz, 2H, Ar-H), 6.94 (s, 1H, Ar-H), 6.56 (br s, 2H, Ar-H), 5.67 (d, *J* = 7.6 Hz, 1H, PhCH), 4.28–4.13 (m, 2H,

OC*H*$_2$CH$_3$), 3.85–3.78 (m, 2H, OC*H*$_2$CH$_3$), 3.20 (s, 3H, NCH$_3$), 2.22 (s, 6H, CH$_3$), 1.33 (td, *J* = 7.2 Hz, 0.8 Hz, 3H, OCH$_2$C*H*$_3$), 1.07 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$), ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** 167.8 (d, *J* = 4.8 Hz), 141.6, 139.4, 135.5 (d, *J* = 5.7 Hz), 129.9, 128.9, 128.2 (two peaks overlapped), 125.6, 75.3 (d, *J* = 3.8 Hz), 64.1 (d, *J* = 5.7 Hz), 63.6 (d, *J* = 5.8 Hz), 37.8, 21.0, 16.0 (d, *J* = 6.7 Hz), 15.7 (d, *J* = 6.7 Hz) ppm; **^{31}P NMR (162 MHz, CDCl$_3$):** δ –1.6 ppm; **IR (neat):** 2993, 1741, 1676, 1596, 1376, 1265, 1214, 1017, 958, 727, 707, 697 cm^{-1}; **HRMS (EI):** *m/z* calcd for $C_{21}H_{28}NO_5P$: 405.1705 $[M]^+$; found: 405.1711.

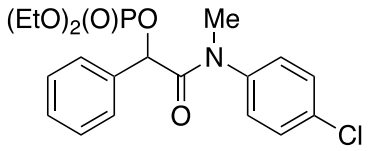
Diethyl (2-((4-methoxyphenyl)(methyl)amino)-2-oxo-1-phenylethyl) phosphate (1i)



Was isolated as a pale-yellow viscous oil (77%, 799 mg), followed the general method A.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.32–7.22 (m, 3H, Ar-H), 7.14–7.12 (m, 2H, Ar-H), 6.84 (br s + br s, 4H, Ar-H), 5.73 (d, *J* = 7.2 Hz, 1H, PhCH), 4.31–4.17 (m, 2H, OC*H*$_2$CH$_3$), 3.88–3.78 (m, 2H, OC*H*$_2$CH$_3$), 3.82 (s, 3H, OCH$_3$), 3.22 (s, 3H, NCH$_3$), 1.36 (td, *J* = 7.2, 0.8 Hz, 3H, OCH$_2$C*H*$_3$), 1.10 (td, *J* = 7.2, 0.8 Hz, 3H, OCH$_2$*CH*$_3$) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** 168.2 (d, *J* = 3.9 Hz), 159.2, 135.3 (d, *J* = 6.7 Hz), 134.7, 129.2, 129.0, 128.4, 128.1, 114.7, 75.1 (d, *J* = 3.8 Hz), 64.2 (d, *J* = 5.8 Hz), 63.7 (d, *J* = 6.7 Hz), 55.5, 38.1, 16.0 (d, *J* = 7.7 Hz), 15.7 (d, *J* = 7.7 Hz) ppm; **^{31}P NMR (162 MHz, CDCl$_3$):** δ –1.5 ppm; **IR (neat):** 2969, 1742, 1676, 1590, 1367, 1263, 1230, 1219, 1010, 957, 789, 696 cm^{-1}; **HRMS (EI):** *m/z* calcd for $C_{20}H_{26}NO_6P$: 407.1498 $[M]^+$; found: 407.1512.

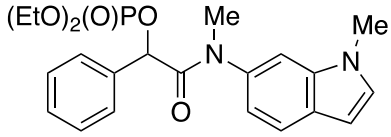
2-((4-Chlorophenyl)(methyl)amino)-2-oxo-1- phenylethyl diethyl phosphate (1j)



Was isolated by alumina column chromatography (AcOEt:hexane = 1:2) as a colorless viscous oil (43%, 1.65 g), followed the general method A.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.25 (m, 5H, Ar-H), 7.12 (br d, *J* = 7.2 Hz, 2H, Ar-H), 7.00 (br s, 2H, Ar-H), 5.69 (d, *J* = 7.2 Hz, 1H, PhCH), 4.33–4.19 (m, 2H, OC*H*$_2$CH$_3$), 3.89–3.82 (m, 2H, OC*H*$_2$CH$_3$), 3.23 (s, 3H, NCH$_3$), 2.22 (s, 6H, CH$_3$), 1.37 (td, *J* = 6.8, 0.8 Hz, 3H, OCH$_2$C*H*$_3$), 1.11 (t, *J* = 6.8 Hz, 3H, OCH$_2$*CH*$_3$) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 168.0 (d, *J* = 3.9 Hz), 140.6, 134.9 (d, *J* = 5.8 Hz), 134.2, 129.9, 129.5, 129.2, 128.6, 128.0, 75.2 (d, *J* = 3.8 Hz), 64.4 (d, *J* = 5.8 Hz), 63.8 (d, *J* = 5.8 Hz), 38.0, 16.0 (d, *J* = 6.7 Hz), 15.8 (d, *J* = 6.8 Hz) ppm; **^{31}P NMR (162 MHz, $CDCl_3$):** δ –1.4 ppm; **IR (neat):** 2984, 1678, 1491, 1385, 1267, 1005, 964, 722 cm^{-1}; **HRMS (ESI):** *m/z* calcd for $C_{19}H_{23}NO_5NaPCl$: 434.0895 $[M+Na]^+$; found: 434.0891.

Diethyl (2-(methyl(1-methyl-1*H*-indol-6-yl)amino)-2-oxo-1-phenylethyl) phosphate (1k)

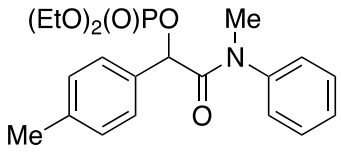


Was isolated by alumina column chromatography (AcOEt:hexane = 1:2) as a pale-pink solid (31%, 340 mg), followed the general method A.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.27 (m, 1H, Ar-H), 7.23–7.19 (m, 3H, Ar-H), 7.12–7.09 (m, 4H, Ar-H), 6.43 (br s, 2H, Ar-H), 5.75 (br s, 1H, PhCH), 4.30–4.15 (m, 2H, OC*H*$_2$CH$_3$), 3.86–3.79 (m, 2H, OC*H*$_2$CH$_3$), 3.83 (s, 3H, indole-NCH$_3$), 3.30 (s, 3H, CONCH$_3$), 2.22 (s, 6H, CH$_3$), 1.35 (td, *J* = 7.2, 0.8 Hz, 3H, OCH$_2$C*H*$_3$), 1.08 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 168.4 (d, *J* = 4.8 Hz), 135.9, 135.6 (d, *J* = 6.7 Hz), 133.9, 130.3, 128.8, 128.7, 128.2 (two peaks overlapped), 121.2, 120.6, 110.3,

101.4, 75.0 (d, J = 2.9 Hz), 64.1 (d, J = 5.7 Hz), 63.6 (d, J = 5.8 Hz), 38.6, 33.1, 16.1 (d, J = 6.7 Hz), 15.8 (d, J = 6.7 Hz) ppm; **^{31}P NMR (162 MHz, $CDCl_3$):** δ –1.6 ppm; **IR (neat):** 2985, 1747, 1668, 1370, 1274, 1216, 1205, 964, 889, 726 cm^{-1}; **HRMS (ESI):** *m/z* calcd for $C_{22}H_{27}N_2O_5NaP$: 453.1550 $[M+Na]^+$; found: 453.1547.

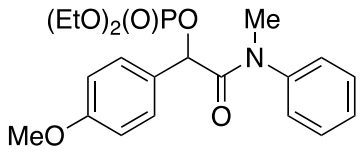
Diethyl (2-(methyl(phenyl)amino)-2-oxo-1-(*p*-tolyl)ethyl) phosphate (1l)



Was isolated as a pale-yellow viscous oil (40%, 1.59 g), followed the general method B.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.33 (m, 3H, Ar-H), 7.04 (br s, 2H, Ar-H), 7.03 (d, J = 8.0 Hz, 2H, Ar-H), 6.97 (d, J = 8.0 Hz, 2H, Ar-H), 5.68 (d, J = 7.2 Hz, 1H, ArCH), 4.30–4.16 (m, 2H, OCH_2CH$_3$), 3.87–3.80 (m, 2H, OCH_2CH$_3$), 3.24 (s, 3H, NCH$_3$), 2.30 (s, 3H, ArCH$_3$), 1.34 (td, J = 7.2 Hz, 0.8 Hz, 3H, OCH$_2$CH_3), 1.10 (td, J = 7.2, 0.8 Hz, 3H, OCH$_2$CH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 168.1 (d, J = 3.9 Hz), 142.1, 139.0, 132.2 (d, J = 6.7 Hz), 129.7, 129.1, 128.3, 128.1, 128.0, 75.0 (d, J = 3.9 Hz), 64.2 (d, J = 5.7 Hz), 63.7 (d, J = 5.7 Hz), 38.0, 21.2, 16.0 (d, J = 7.6 Hz), 15.8 (d, J = 7.7 Hz) ppm; **^{31}P NMR (162 MHz, $CDCl_3$):** δ –1.5 ppm; **IR (neat):** 2975, 1682, 1391, 1279, 1013, 960, 903, 775, 697 cm^{-1}; **HRMS (ESI):** *m/z* calcd for $C_{20}H_{26}NO_5NaP$: 414.1441 $[M+Na]^+$; found:414.1440.

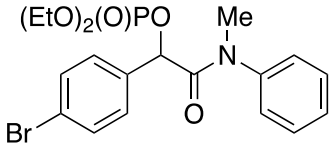
Diethyl (1-(4-methoxyphenyl)-2-(methyl(phenyl)amino)-2-oxoethyl) phosphate (1m)



Was isolated by alumina column chromatography (AcOEt:hexane = 1:2) as a pale-yellow viscous oil (22%, 533 mg), followed the general method B.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.33 (m, 3H, Ar-H), 7.02 (br s, 2H, Ar-H), 7.01 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.74 (d, *J* = 8.8 Hz, 2H, Ar-H), 5.66 (d, *J* = 7.6 Hz, 1H, ArCH), 4.29–4.15 (m, 2H, OCH_2CH_3), 3.87–3.79 (m, 2H, OCH_2CH_3), 3.77 (s, OCH_3), 3.24 (s, 3H, NCH_3), 1.34 (td, *J* = 7.2, 0.8 Hz, 3H, OCH_2CH_3), 1.10 (td, *J* = 7.2, 0.8 Hz, 3H, OCH_2CH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 168.2 (d, *J* = 3.8 Hz), 160.1, 142.1, 129.7, 129.6, 128.3, 128.1, 127.3 (d, *J* = 6.7 Hz), 113.7, 74.9 (d, *J* = 3.8 Hz), 64.2 (d, *J* = 6.7 Hz), 63.6 (d, *J* = 6.7 Hz), 55.2, 37.9, 16.0 (d, *J* = 6.7 Hz), 15.8 (d, *J* = 6.7 Hz) ppm; **^{31}P NMR (162 MHz, $CDCl_3$):** δ –1.4 ppm; **IR (neat):** 2971, 1740, 1673, 1596, 1513, 1387, 1369, 1251, 1011, 998, 898, 802, 771, 700 cm^{-1}; **HRMS (EI):** *m/z* calcd for $C_{20}H_{26}NO_6NaP$: 430.1390 $[M+Na]^+$; found: 430.1385.

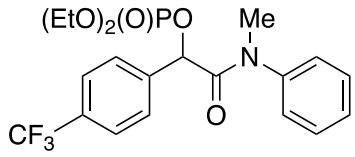
1-(4-(Bromophenyl)-2-(methyl(phenyl)amino-2-oxoethyl diethyl phosphate (1n)



Was isolated as a pale-orange viscous oil (32%, 869 mg), followed the general method B.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.35 (m, 5H, Ar-H), 7.06 (br s, 2H, Ar-H), 6.95 (d, *J* = 8.0 Hz, 2H, Ar-H), 5.68 (d, *J* = 7.6 Hz, 1H, ArCH), 4.29–4.15 (m, 2H, OCH_2CH_3), 3.89–3.82 (m, 3H, OCH_2CH_3), 3.24 (s, 3H, NCH_3), 1.35 (td, *J* = 7.2, 0.8 Hz, 3H, OCH_2CH_3), 1.12 (td, *J* = 7.2, 0.8 Hz, 3H, OCH_2CH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 167.6 (d, *J* = 3.8 Hz), 141.9, 134.3 (d, *J* = 6.7 Hz), 131.6, 129.9, 129.7, 128.5, 128.0, 123.4, 74.3 (d, *J* = 3.8 Hz), 64.4 (d, *J* = 5.8 Hz), 63.8 (d, *J* = 6.7 Hz), 38.0, 16.0 (d, *J* = 6.7 Hz), 15.8 (d, *J* = 6.7 Hz) ppm; **^{31}P NMR (162 MHz, $CDCl_3$):** δ –1.5 ppm; **IR (neat):** 2989, 1685, 1596, 1487, 1388, 1260, 1010, 900, 797, 772, 705, 670 cm^{-1}; **HRMS (EI):** *m/z* calcd for $C_{19}H_{23}BrNO_5P$: 455.0497 $[M]^+$; found: 455.0511.

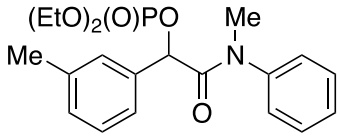
Diethyl (2-(methyl(phenyl)amino)-2-oxo-1(4-trifluoromethyl) phenyl) ethyl phosphate (1o)



Was isolated as a green viscous oil (64%, 260 mg), followed the general method B.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.39 (app. br s, 3H, Ar-H), 7.22 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.09 (br s, 2H, Ar-H), 5.80 (d, *J* = 7.2 Hz, 1H, ArCH), 4.32-4.18 (m, 2H, OCH_2CH_3), 3.92–3.85 (m, 3H, OCH_2CH_3), 3.27 (s, 3H, NCH_3), 1.37 (td, *J* = 7.2, 1.2 Hz, 3H, OCH_2CH_3), 1.13 (td, *J* = 7.2, 0.8 Hz, 3H, OCH_2CH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 167.4 (d, *J* = 3.9 Hz), 141.8, 139.1 (d, *J* = 6.7 Hz), 131.1 (q, 2.5 Hz), 130.0, 128.6, 128.3, 128.0, 125.4 (q, *J* = 3.8 Hz), 123.8 (app. d, *J* = 271.3 Hz), 74.2 (d, *J* = 3.8 Hz), 64.5 (d, *J* = 5.7 Hz), 63.9 (d, *J* = 5.7 Hz), 38.1, 16.1 (d, *J* = 7.7 Hz), 15.8 (d, *J* = 7.7 Hz) ppm; **^{31}P NMR (162 MHz, $CDCl_3$):** δ –1.5 ppm; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –62.7 ppm; **IR (neat):** 2989, 1739, 1672, 1367, 1320, 1121, 1010, 962, 900, 773, 698 cm^{-1}; **HRMS (EI):** *m/z* calcd for $C_{20}H_{23}F_3NO_5P$: 445.1266 $[M]^+$; found: 445.1287.

Diethyl (2-(methyl(phenyl)amino)-2-oxo-1-(*m*-tolyl)ethyl) phosphate (1p)

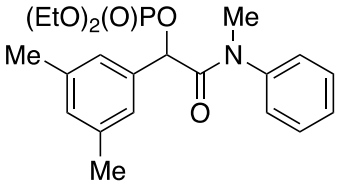


Was isolated as a pale-yellow viscous oil (41%, 382 mg), followed the general method B.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.34 (m, 3H, Ar-H), 7.13–7.09 (m, 2H, Ar-H), 7.05 (br s, 2H, Ar-H), 6.90 (br s, 1H, Ar-H), 6.83 (br d, *J* = 6.4 Hz, 1H, Ar-H), 5.70 (d, *J* = 7.6 Hz, 1H, ArCH), 4.32–4.18 (m, 2H, OCH_2CH_3), 3.89–3.82 (m, 3H, OCH_2CH_3), 3.26 (s, 3H, NCH_3), 2.26 (s, 3H, $ArCH_3$), 1.36 (td, *J* = 7.2, 0.8 Hz, 3H, OCH_2CH_3), 1.11 (td, *J* = 6.8 Hz,

0.8 Hz, 3H, OCH_2CH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 168.1 (d, *J* = 3.8 Hz), 142.1, 138.1, 135.0 (d, *J* = 6.8 Hz), 129.8, 129.6, 128.6, 128.3, 128.22, 128.16, 125.1, 75.3 (d, *J* = 3.9 Hz), 64.2 (d, *J* = 5.7 Hz), 63.7 (d, *J* = 5.7 Hz), 38.0, 21.2, 16.0 (d, *J* = 6.7 Hz), 15.8 (d, *J* = 6.7 Hz) ppm; **^{31}P NMR (162 MHz, $CDCl_3$):** δ –1.4 ppm; **IR (neat):** 2978, 1739, 1676, 1496, 1373, 1259, 1218, 1011, 968, 891, 770, 697 cm^{-1}; **HRMS (EI):** *m/z* calcd for $C_{20}H_{26}NO_5P$: 391.1549 $[M]^+$; found: 391.1566.

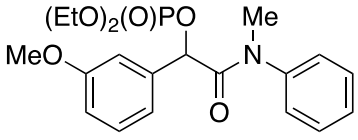
1-(3,5-Dimethylphenyl)-2-(methyl(phenyl)amino-2-oxoethyl diethyl phosphate (1q)



Was isolated as a pale-yellow viscous oil (54%, 2.22 g), followed the general method B.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.34 (m, 3H, Ar-H), 7.03 (br s, 2H, Ar-H), 6.90 (s, 1H, Ar-H), 6.63 (s, 2H, Ar-H), 5.65 (d, *J* = 7.6 Hz, 1H, ArCH), 4.31–4.17 (m, 2H, OCH_2CH_3), 3.89–3.82 (m, 3H, OCH_2CH_3), 3.25 (s, 3H, NCH_3), 2.20 (s, 6H, $ArCH_3$), 1.35 (td, *J* = 7.2, 0.8 Hz, 3H, OCH_2CH_3), 1.11 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 168.1 (d, *J* = 3.8 Hz), 142.1, 137.9, 134.8 (d, *J* = 6.7 Hz), 130.6, 129.6, 128.2 (two peaks overlapped), 125.7, 74.5 (d, *J* = 2.2 Hz), 64.2 (d, *J* = 5.7 Hz), 63.7 (d, *J* = 5.7 Hz), 38.0, 21.1, 16.0 (d, *J* = 6.7 Hz), 15.8 (d, *J* = 7.7 Hz) ppm; **^{31}P NMR (162 MHz, $CDCl_3$):** δ –1.4 ppm; **IR (neat):** 2971, 1682, 1594, 1494, 1256, 1023, 1012, 963, 924.7, 890, 775, 699 cm^{-1}; **HRMS (EI):** *m/z* calcd for $C_{21}H_{28}NO_5P$: 405.1705 $[M]^+$; found: 405.1694.

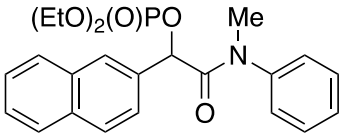
Diethyl (1-(3-methoxyphenyl)-2-(methyl(phenyl)amino)-2-oxoethyl) phosphate (1r)



Was isolated as a pale-yellow viscous oil (83%, 1.22 g), followed the general method B.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.35 (m, 3H, Ar-H), 7.13 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.08 (br s, 2H, Ar-H), 6.82 (dd, *J* = 8.4, 1.8 Hz, 1H, Ar-H), 6.65–6.62 (m, 2H, Ar-H), 5.70 (d, *J* = 8.0 Hz, 1H, ArCH), 4.31–4.17 (m, 2H, OCH_2CH_3), 3.90–3.83 (m, 2H, OCH_2CH_3), 3.72 (s, 3H, OCH_3), 3.26 (s, 3H, NCH_3), 2.20 (s, 6H, CH_3), 1.36 (td, *J* = 7.2, 0.8 Hz, 3H, OCH_2CH_3), 1.21 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 167.9 (d, *J* = 3.8 Hz), 159.5, 142.1, 136.5, 129.7, 129.4, 128.3, 128.1, 120.4, 115.3, 112.9, 75.1, 64.3 (d, *J* = 6.7 Hz), 63.8 (d, *J* = 6.7 Hz), 55.2, 38.0, 16.0 (d, *J* = 6.7 Hz), 15.8 (d, *J* = 7.7 Hz) ppm; **^{31}P NMR (162 MHz, $CDCl_3$):** δ –1.5 ppm; **IR (neat):** 2985, 1663, 1589, 1476, 1451.2, 1391, 1260, 1014, 769, 696 cm^{-1}; **HRMS (EI):** *m/z* calcd for $C_{20}H_{26}NO_5P$: 407.1498 $[M]^+$; found: 407.1501.

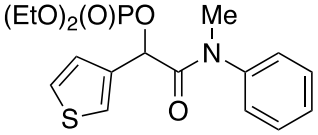
Diethyl (2-(methyl(phenyl)amino)-1-(naphtalen-2-yl)-2-oxoethyl) phosphate (1s)



Was isolated as a yellow viscous oil (72%, 1.30 g), followed the general method B.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (app. d, *J* = 7.2 Hz, 1H, Ar-H), 7.74 (d, *J* = 8.4 Hz, 1H, Ar-H) 7.68 (app. d, *J* = 8.4 Hz, 1H, Ar-H), 7.49–7.30 (m, 7H, Ar-H), 7.03 (br s, 2H, Ar-H), 5.91 (d, *J* = 7.6 Hz, 1H, ArCH), 4.34–4.20 (m, 2H, OCH_2CH_3), 3.86–3.79 (m, 3H, OCH_2CH_3), 3.26 (s, 3H, NCH_3), 1.37 (td, *J* = 7.2, 0.8 Hz, 3H, OCH_2CH_3), 1.05 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 167.9 (d, *J* = 3.9 Hz), 142.0, 133.4, 132.7, 132.4 (d, *J* = 6.7 Hz), 129.7, 128.4, 128.3, 128.2, 128.1, 127.8, 127.6, 126.6, 126.2, 125.0, 75.4 (d, *J* = 3.9 Hz), 64.3 (d, *J* = 5.8 Hz), 63.7 (d, *J* = 6.7 Hz), 38.0, 16.0 (d, *J* = 6.7 Hz), 15.7 (d, *J* = 6.7 Hz) ppm; **^{31}P NMR (162 MHz, $CDCl_3$):** δ –1.4 ppm; **IR (neat):** 2974, 1738, 1672, 1598, 1494, 1373, 1260, 1014, 954, 804, 771, 698 cm^{-1}; **HRMS (EI):** *m/z* calcd for $C_{23}H_{26}NO_5P$: 427.1549 $[M]^+$; found: 427.1565.

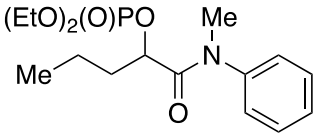
Diethyl (2-(methyl(phenyl)amino)-2-oxo-1(thiophen-3-yl)ethyl) phosphate (1t)



Was isolated as a yellow viscous oil (73%, 1.17 g), followed the general method B.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.35 (m, 3H, Ar-H), 7.23–7.21 (m, 1H, Ar-H) 7.06 (br s, 2H, Ar-H), 7.01 (br s, 1H, Ar-H), 6.98 (d, *J* = 4.4 Hz, 1H, Ar-H), 5.81 (d, *J* = 6.8 Hz, 1H, ArCH), 4.28–4.14 (m, 2H, OCH_2CH_3), 3.90–3.82 (m, 2H, OCH_2CH_3), 3.27 (s, 3H, NCH_3), 1.35 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.13 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 167.7 (d, *J* = 4.8 Hz), 142.1, 135.8 (d, *J* = 6.8 Hz), 129.8, 128.4, 127.8, 126.9, 126.1, 125.5, 70.6 (d, *J* = 2.9 Hz), 64.2 (d, *J* = 5.8 Hz), 63.8 (d, *J* = 6.7 Hz), 38.0, 16.0 (d, *J* = 7.7 Hz), 15.8 (d, *J* = 6.7 Hz) ppm; **^{31}P NMR (162 MHz, $CDCl_3$):** δ –1.5 ppm; **IR (neat):** 2979, 1681, 1594, 1496, 1384, 1254, 1010, 998, 970, 900, 770, 701 cm^{-1}; **HRMS (EI):** *m/z* calcd for $C_{17}H_{22}NO_5PS$: 383.0956 $[M]^+$; found: 383.0955.

Diethyl (1-(methyl(phenyl)amino-1-oxopentan-2-yl) phosphate (3)

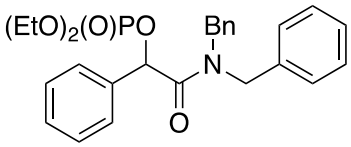


Was isolated as a colorless viscous oil (45%, 1.46 g), followed the general method B.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (app. t, *J* = 7.6 Hz, 2H, Ar-H), 7.36 (app. t, *J* = 7.6 Hz, 1H, Ar-H), 7.31 (d, *J* = 7.6 Hz, 2H, Ar-H), 4.79–4.74 (m, 1H, CH_2CH), 4.22–4.14 (m, 2H, OCH_2CH_3), 4.09–4.02 (m, 3H, OCH_2CH_3), 3.29 (s, 3H, NCH_3), 1.79–1.71 (m, 1H, CHH), 1.56–1.49 (m, 1H, CHH), 1.36–1.32 (m, 1H, CHH), 1.34 (td, *J* = 7.2, 1.2 Hz, 4H, OCH_2CH_3), 1.27 (t, *J* = 7.6 Hz, 3H, OCH_2CH_3), 1.22–1.15 (m, 1H, CH_3), 0.68 (t, *J* = 7.2 Hz, 3H, $CH_2CH_2CH_3$) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 169.9, 142.5, 129.9, 128.3, 127.7, 72.8 (d, *J* = 4.8 Hz), 64.0 (d, *J* = 6.7 Hz), 63.8 (d, *J* = 5.8 Hz), 37.8, 35.0 (d, *J* = 8.7 Hz), 18.0,

16.0 (d, J = 6.7 Hz), 13.1 ppm; **^{31}P NMR (162MHz, $CDCl_3$):** δ –1.1 ppm; **IR (neat):** 2962, 1737, 1673, 1596, 1496, 1365, 1267, 1019, 982, 819, 806, 775, 702 cm^{-1}; **HRMS (EI):** *m/z* calcd for $C_{16}H_{26}NO_5P$: 343.1549 $[M]^+$; found: 343.1561.

2-(Dibenzylamino)-2-oxo-1-phenylethyl diethyl phosphate (5)



Was isolated as a colorless viscous oil (67%, 1,42 g), followed the general method B.

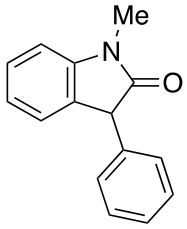
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.46 (m, 2H, Ar-H), 7.37–7.34 (m, 3H, Ar-H), 7.31–7.24 (m, 6H, Ar-H), 7.15–7.13 (m, 2H, Ar-H), 7.03–7.01 (m, 2H, Ar-H), 6.13 (d, J = 8.0 Hz, 1H, PhCH), 4.75 (br d, J = 14.8 Hz, 1H, PhCH*H*), 4.41 (br d, J = 17.2 Hz, 1H, PhCH*H*), 4.37 (br d, J = 15.6 Hz, 1H, PhC*H*H), 4.31 (br d, J = 16.8 Hz, 1H, PhC*H*H), 4.27–4.14 (m, 2H, OC*H*$_2$CH$_3$), 3.96–3.89 (m, 3H, OC*H*$_2$CH$_3$), 1.34 (td, J = 7.2, 1.2 Hz, 3H, OCH$_2$C*H*$_3$), 1.16 (td, J = 6.8 Hz, 1.2 Hz, 3H, OCH$_2$C*H*$_3$) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 168.4 (d, J = 4.8 Hz), 136.6, 135.4, 135.1 (d, J = 5.7 Hz), 129.4, 129.0, 128.8, 128.5, 128.2, 128.0, 127.8, 127.4, 127.0, 76.1 (d, J = 4.8 Hz), 64.4 (d, J = 5.7 Hz), 63.9 (d, J = 5.7 Hz), 49.3, 48.1, 16.0 (d, J = 6.7 Hz), 15.8 (d, J = 6.7 Hz) ppm; **^{31}P NMR (162 MHz, $CDCl_3$):** δ –1.3 ppm; **IR (neat):** 2990, 1671, 1499, 1264, 998, 957, 897, 704 cm^{-1} ; **HRMS (ESI):** *m/z* calcd for $C_{26}H_{30}NO_5NaP$: 490.1754 $[M+Na]^+$; found: 490.1750.

$Pd(OAc)_2$-catalyzed Friedel–Crafts-type Cyclization of Oxindole and 1,4-Dihydro-3-(2*H*)-isoquinolinone Derivatives

All the manipulations were performed under an argon atmosphere using standard Sclenk techniques.

$Pd(OAc)_2$ (1.6 mg, 7.0 μmol) was added to a 20 mL Schlenk flask charged with diethyl (2-(methyl(phenyl)amino)-2-oxo-1-phenylethyl) phosphate (**1a**: 130 mg, 0.35 mmol) followed by 3 repetitions of a vacuum–argon replacement procedure. CH_3NO_2 (2.0 ml) was added and the solution was stirred for 15 min at 60 ºC. TMSCN (71 mg, 0.72 mmol) was added and the reaction mixture was then continuously stirred at 60 ºC for 10 h. Completion of the reaction was judged by TLC (AcOEt:hexane = 4:1). Saturated $NaHCO_3$ (aq.) was added to quench the reaction, and the aqueous layer was extracted by AcOEt (10 mL × 3). The collected organic layers were washed with brine and dried over Na_2SO_4. After Na_2SO_4 was filtered off, the resulting mixture was concentrated in vacuo. The yield of the product was calculated from ^1H NMR spectra of the crude 1-methyl-3-phenylindolin-2-one (**2a**) with pyrazine as an internal standard (>99% yield). The product was isolated by PTLC (AcOEt:hexane = 1:4) as a white solid (76 mg, 0.34 mmol, 98% yield).

1-methyl-3-phenylindolin-2-one (2a)

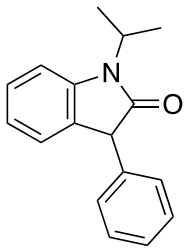


Was isolated by silica-gel column chromatography (AcOEt:hexane = 1:4) as a white solid (98%, 76 mg)

Spectra data are in accordance with the literature.[15]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.28 (m, 4H, Ar-H), 7.22–7.16 (m, 3H, Ar-H), 7.07 (t, *J* = 7.6 Hz, 1H, Ar-H), 6.91 (d, *J* = 7.6 Hz, 1H, Ar-H), 4.62 (s, 1H, CH), 3.26 (s, 3H, NCH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 176.0, 144.4, 136.6, 128.83, 128.79, 128.4 (two peaks overlapped), 127.5, 125.0, 122.7, 108.1, 52.0, 26.4 ppm.

1-Isopropyl-3-phenylindolin-2-one (2b)

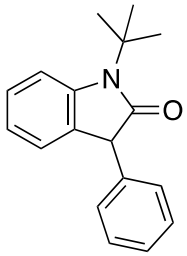


Was isolated by silica-gel column chromatography (AcOEt:hexane = 1:4) as a white solid (98%, 125 mg)

Spectra data are in accordance with the literature. [16]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.27 (m, 4H, Ar-H), 7.18–7.14 (m, 3H, Ar-H), 7.08 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.03 (t, *J* = 7.6 Hz, 1H, Ar-H), 4.68 (sep, *J* = 7.2 Hz, 1H, $NCH(CH_3)_2$), 4.55 (s, 1H, CH), 1.515 (d, *J* = 7.6 Hz, 3H, $NCH(CH_3)(CH_3)$), 1.510 (d, *J* = 7.6 Hz, 3H, $NCH(CH_3)(CH_3)$) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 175.7, 143.1, 137.1, 129.5, 128.9, 128.3, 128.0, 127.5, 125.3, 122.1, 109.9, 52.1, 43.9, 19.5, 19.3 ppm.

1-*tert*-Butyl-3-phenylindolin-2-one (2c)

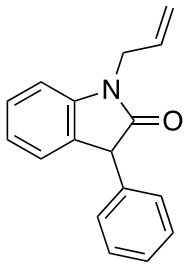


Was isolated by PTLC (AcOEt:hexane = 1:4) as a yellow viscous oil (98%, 72 mg).

Spectra data are in accordance with the literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.32 (m, 3H, Ar-H), 7.30–7.24 (m, 2H, Ar-H), 7.19–7.16 (m, 2H, Ar-H), 7.12 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.01 (td, *J* = 7.2, 0.8 Hz, 1H, Ar-H), 4.50 (s, 1H, CH), 1.76 (s, 9H, CH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 176.7, 144.8, 137.6, 129.9, 128.8, 128.3, 127.6, 127.3, 125.1, 121.8, 113.1, 57.7, 53.0, 29.1 ppm; **IR (neat):** 2966, 1741, 1673, 1366, 1266, 1228, 1198, 1016, 957, 886, 727, 694 cm^{-1} ; **HRMS (EI):** *m/z* calcd for $C_{18}H_{19}NO$: 265.1467 $[M]^+$; found: 265.1466.

1-Allyl-3-phenylindolin-2-one (2d)

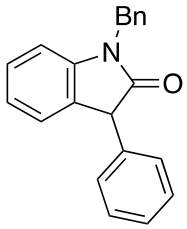


Was isolated by silica-gel column chromatography (AcOEt:hexane = 1:4) as a white solid (98%, 130 mg).

Spectra data are in accordance with the literature. [17]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.27 (m, 4H, Ar-H), 7.23–7.20 (m, 2H, Ar-H), 7.18 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.06 (td, *J* = 7.6, 0.8 Hz, 1H, Ar-H), 6.90 (d, *J* = 8.0 Hz, 1H, Ar-H), 5.87 (ddt, *J* = 16.8, 10.4, 5.2 Hz, 1H, NCH_2CHCH_2), 5.29–5.25 (m, 1H, NCH_2CHCHH), 5.24–5.22 (m, 1H, NCH_2CHCHH), 4.65 (s, 1H, PhCH), 4.45–4.33 (m, 2H, NCH_2) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 175.7, 143.6, 136.7, 131.4, 128.9, 128.8, 128.4, 128.3, 127.5, 125.1, 122.7, 117.6, 109.0, 52.0, 42.4 ppm.

1-Benzyl-3-phenylindolin-2-one (2e)

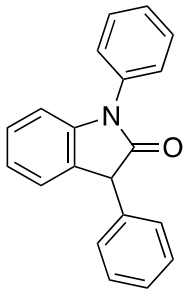


Was isolated by silica-gel column chromatography (AcOEt:hexane = 1:4) as pale-yellow solid (99%, 144 mg).

Spectra data are in accordance with the literature. [15]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.27 (m, 9H, Ar-H), 7.26–7.17 (m, 3H, Ar-H), 7.04 (td, *J* = 7.6, 0.8 Hz, 1H, Ar-H), 6.81 (d, *J* = 8.0 Hz, 1H, Ar-H), 5.02 (d, *J* = 15.6 Hz, 1H, NC*H*H), 4.92 (d, *J* = 15.2 Hz, 1H, NCH*H*), 4.73 (s, 1H, CH) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 176.0, 143.5, 136.7, 135.8, 128.9, 128.8, 128.7, 128.4, 128.2, 127.58, 127.55, 127.3, 125.1, 122.7, 109.1 52.0, 43.9 ppm.

1,3-Diphenylindolin-2-one (2f)[1]

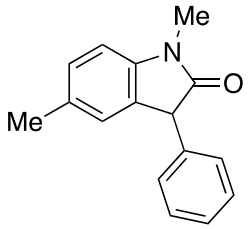


Was isolated by silica-gel column chromatography (AcOEt:hexane = 1:4) as a green viscous oil (97%, 133 mg).

Spectra data are in accordance with the literature.[15]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55–7.51 (m, 2H, Ar-H), 7.46–7.22 (m, 10H, Ar-H), 7.10 (td, *J* = 7.6, 0.8 Hz, 1H, Ar-H), 6.89 (d, *J* = 7.6 Hz, 1H, Ar-H), 4.80 (s, 1H, CH) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 175.3, 144.4, 136.7, 134.5, 129.6, 128.9, 128.7, 128.5, 128.3, 128.1, 127.7, 126.6, 125.4, 123.2, 109.5, 52.2 ppm.

1,5-Dimethyl-3-pphenylindolin-2-one (2g)

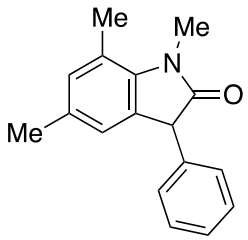


Was isolated by silica-gel column chromatography (AcOEt:hexane = 1:4) as a white solid (99%, 129 mg).

Spectra data are in accordance with the literature.[18]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.27 (m, 3H, Ar-H), 7.24–7.21 (m, 2H, Ar-H), 7.14 (app. d, *J* = 8.0 Hz, 1H, Ar-H), 7.00 (s, 1H, Ar-H), 6.81 (d, *J* = 8.0 Hz, 1H, Ar-H), 4.58 (s, 1H, CH), 3.25 (s, 3H, NCH_3), 2.33 (s, 3H, $ArCH_3$) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 175.8, 141.9, 136.7, 132.1, 128.8, 128.7, 128.5, 128.3, 127.3, 125.7, 107.7, 52.0, 26.3, 20.9 ppm.

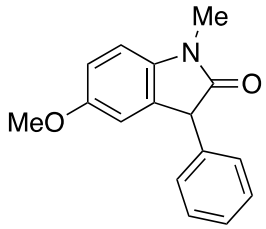
1,4,6-Trimethyl-3-phenylindolin-2-one (2h)



Was isolated by PTLC (AcOEt:hexane = 1:4) as a white solid (98%, 49 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.23 (m, 3H, Ar-H), 7.15–7.12 (m, 2H, Ar-H), 6.70 (s, 1H, Ar-H), 6.58 (s, 1H, Ar-H), 4.48 (s, 1H, CH), 3.20 (s, 3H, NCH_3), 2.39 (s, 3H, $ArCH_3$), 1.94 (s, 3H, $ArCH_3$) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 176.3, 144.8, 138.5, 136.1, 134.8, 128.8, 128.2, 127.4, 125.0, 123.9, 106.6, 51.5, 26.5, 21.7, 18.4 ppm; **IR (neat):** 2920, 1713, 1619, 1604, 1454, 1362, 1293, 1077, 831, 727, 695 cm^{-1} ; **HRMS (EI):** *m/z* calcd for $C_{17}H_{17}NO$: 251.1310 $[M]^+$; found: 251.1301.

5-Methoxy-1-methyl-3-phenylindolin-2-one (2i)

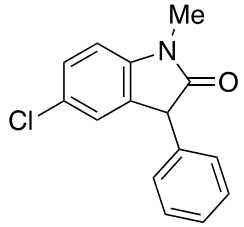


Was isolated by silica-gel column chromatography (AcOEt:hexane = 1:4) as a pale-yellow solid (98%, 105 mg).

Spectra data are in accordance with the literature.[18]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.28 (m, 3H, Ar-H), 7.22–7.19 (m, 2H, Ar-H), 6.88–6.85 (m, 1H, Ar-H), 6.81–6.79 (m, *J* = 8.0 Hz, 2H, Ar-H), 4.59 (s, 1H, CH), 3.76 (s, 3H, OCH_3), 3.23 (s, 3H, NCH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 175.6, 156.0, 137.9, 136.6, 130.0, 128.8, 128.4, 127.5, 112.8, 112.2, 108.4, 55.7, 52.4, 26.5 ppm.

5-Chloro-1-methyl-3-phenylindolin-2-one (2j)

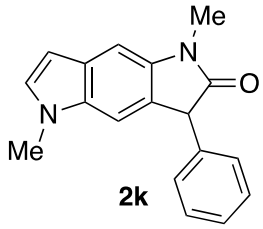


Was isolated by PTLC (AcOEt:hexane = 1:4) as a white solid (98%, 67 mg).

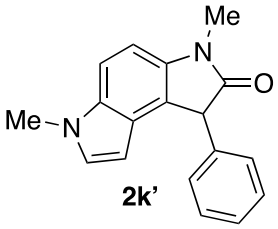
Spectra data are in accordance with the literature.[19]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.28 (m, 4H, Ar-H), 7.19–7.16 (m, 2H, Ar-H), 7.15–7.14 (m, 1H, Ar-H), 6.82 (d, *J* = 8.4 Hz, 1H, Ar-H), 4.60 (s, 1H, CH), 3.24 (s, 3H, NCH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 175.4, 142.9, 135.8, 130.4, 129.0, 128.3 (two peaks overlapped), 128.0, 127.8, 125.4, 109.0, 51.9, 26.5 ppm.

1,5-Dimethyl-3-phenyl-3,5-dihydropyrrolo[2,3-f]indol-2(1*H*)-one (2k) and 3,6-dimethyl-1-phenyl-3,6-dihydropyrrolo[3,2-*e*]indol-2(1*H*)-one (2k') (1:0.64 mixture)



2k

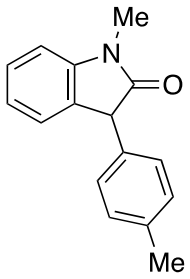


2k'

Was isolated by pale-yellow solid (82%, 380 mg).

^{1}H NMR (400 MHz, $CDCl_3$): for **2k** δ 7.36–7.23 (m, 5H, Ar-H), 7.12 (s, 1H, Ar-H), 7.07 (s, 1H, Ar-H), 7.04 (d, *J* = 3.2 Hz, NC*H*=CH), 6.49 (d, *J* = 3.2 Hz, 1H, NCH=C*H*), 4.70 (s, 1H, CH), 3.31 (s, 3H, $CONCH_3$) ppm; for **2k'** δ 7.36–7.23 (m, 6H, Ar-H), 7.02 (d, *J* = 3.2 Hz, 1H, NC*H*=CH), 6.89 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.02 (d, *J* = 3.2 Hz, 1H, NCH=C*H*), 4.81 (s, 1H, CH), 3.79 (s, 3H, indole-CH_3), 3.31 (s, 3H, $CONCH_3$); **^{13}C NMR (100 MHz, $CDCl_3$):** 176.3, 175.7, 138.0, 137.2, 136.5, 134.7, 133.5, 131.1, 128.9, 128.8, 128.7, 128.54, 128.51, 127.7, 127.4, 127.2, 125.4, 124.4, 118.0, 108.7, 106.9, 103.4, 100.8, 99.1, 97.8, 52.3, 52.2, 33.11, 33.08, 26.8, 26.6 ppm; **IR (neat):** 3102, 3029, 2935, 1704, 1636, 1594, 1498, 1328, 1270, 1110, 1077, 752, 718, 695 cm^{-1} ; **HRMS (EI):** *m/z* calcd for $C_{18}H_{16}ON_2Na$: 299.1155 $[M]^+$; found: 299.1152.

1-Methyl-3-(*p*-toly)indolin-2-one

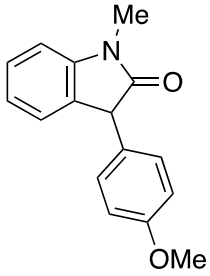


Was isolated by silica-gel column chromatography (AcOEt:hexane = 4:1) as a white solid (98%, 94 mg).

Spectra data are in accordance with the literature.[15]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.18–7.13 (m, 3H, Ar-H), 7.10–7.04 (m, 3H, Ar-H), 6.90 (d, *J* = 7.6 Hz, 1H, Ar-H), 4.58 (s, 1H, CH), 3.25 (s, 3H, NCH_3), 2.33 (s, 3H, $ArCH_3$) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 176.1, 144.4, 137.2, 133.5, 129.5, 129.0, 128.3, 128.2, 124.9, 122.6, 108.0, 51.6, 26.4, 21.0 ppm.

3-(4-Methoxyphenyl)-1-methylindolin-2-one (2m)

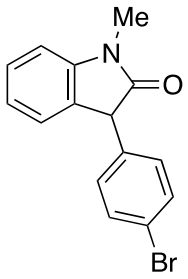


Was isolated by PTLC (AcOEt:hexane = 1:4) as a yellow solid (99%, 64 mg).

Spectra data are in accordance with the literature.[15]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.16 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.12 (app. d, *J* = 8.8 Hz, 2H, Ar-H), 7.06 (td, *J* = 7.6, 0.8 Hz, 1H, Ar-H), 6.89 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.86 (app. d, *J* = 9.2 Hz, 2H, Ar-H), 4.56 (s, 1H, CH), 3.78(s, 3H, OCH_3), 3.25 (s, 3H, NCH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 176.3, 159.0, 144.4, 129.4, 129.0, 128.6, 128.3, 125.0, 122.7, 114.3, 108.1, 55.3, 51.2, 26.4 ppm.

3-(4-Bromophenyl)-1-methylindolin-2-one (2n)

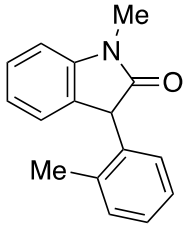


Was isolated by silica-gel column chromatography (AcOEt:hexane = 1:4) as a white solid (98%, 125 mg).

Spectra data are in accordance with the literature.[20]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (app. d, *J* = 8.0 Hz, 2H, Ar-H), 7.35 (app. t, *J* = 7.6 Hz, 1H, Ar-H), 7.15 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.11–7.06 (m, 3H, Ar-H), 6.91 (d, *J* = 8.0 Hz, 1H, Ar-H), 4.56 (s, 1H, CH), 3.25 (s, 3H, NCH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 175.7, 144.7, 135.9, 132.2, 130.4, 129.0, 128.4, 125.3, 123.1, 121.9, 108.6, 51.6, 26.8 ppm.

1-Methyl-3-(*o*-tolyl)indolin-2-one (2p)

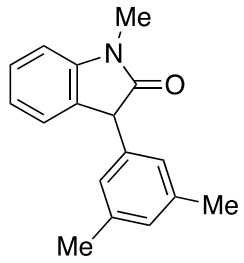


Was isolated by PTLC (AcOEt:hexane = 1:4) as a white solid (99%, 54 mg).

Spectra data are in accordance with the literature.[15]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (app. t, *J* = 7.6 Hz, 1H, Ar-H), 7.22 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.17 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.11–7.05 (m, 2H, Ar-H), 7.01–6.99 (m, 2H, Ar-H), 6.91 (d, *J* = 8.0 Hz, 1H, Ar-H), 4.58 (s, 1H, Ar-H), 3.27 (s, 3H, NCH_3), 2.32 (s, 3H, $ArCH_3$) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 176.1, 144.4, 138.5, 136.5, 129.01, 128.99, 128.7, 128.31, 128.28, 125.4, 124.9, 122.7, 108.1, 52.0, 26.4, 21.4 ppm.

3-(3,5-Dimethylphenyl)-1-methylimdolin-2-one (2q)

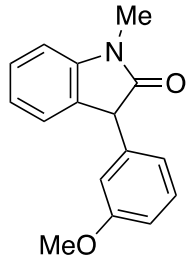


Was isolated by silica-gel column chromatography (AcOEt:hexane = 1:4) as a white solid (93%, 114 mg).

Spectra data are in accordance with the literature.[21]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.16 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.06 (td, *J* = 7.6, 0.8 Hz, 1H, Ar-H), 6.92–6.90 (m, 2H, Ar-H), 6.80 (s, 2H, Ar-H), 4.53 (s, 1H, CH), 3.27 (s, 3H, NCH_3), 2.28 (s, 6H, $ArCH_3$) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 176.2, 144.3, 138.3, 136.4, 129.3, 129.2, 128.2, 126.1, 124.9, 122.6, 108.0, 52.0, 26.4, 21.2 ppm.

3-(3-Methoxyphenyl)-1-methylindolin-2-one (2r)

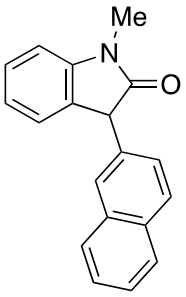


Was isolated by silica-gel column chromatography (AcOEt:hexane = 1:4) as a pale-yellow viscous oil (92%, 115 mg).

Spectra data are in accordance with the literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.25 (t, *J* = 8.0 Hz, 1H, Ar-H),7.18 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.06 (t, *J* = 7.6 Hz, 1H, Ar-H), 6.90 (d, *J* = 7.6 Hz, 1H, Ar-H), 6.83–6.78 (m, 2H, Ar-H), 6.76–6.75 (m, 1H, Ar-H), 4.58 (s, 1H, CH), 3.77 (s, 3H, OCH_3), 3.25 (s, 3H, NCH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 175.8, 159.8, 144.4, 138.0, 129.8, 128.7, 128.4, 125.0, 122.7, 120.7, 114.3, 112.8, 108.1, 55.2, 51.9, 26.4 ppm.

1-Ethyl-3-(naphthalen-2-yl)indolin-2-one (2s)

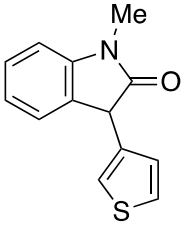


Was isolated by PTLC (AcOEt:hexane = 1:4) as a pale-yellow solid (98%, 71 mg).

Spectra data are in accordance with the literature.[15]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82–7.80 (m, 3H, Ar-H), 7.71 (s, 1H, Ar-H), 7.48–7.45(m, 2H, Ar-H), 7.37 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.28–7.25 (m, 1H, Ar-H), 7.20 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.09 (t, *J* = 7.2 Hz, 1H, Ar-H), 6.95 (d, *J* = 7.6 Hz, 1H, Ar-H), 4.79 (s, 1H, CH), 3.30 (s, 3H, NCH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 176.0, 144.5, 134.0, 133.4, 132.7, 128.8, 128.7, 128.5, 127.8, 127.6, 127.5, 126.2, 126.1, 125.9, 125.1, 122.8, 108.2, 52.2, 26.5 ppm.

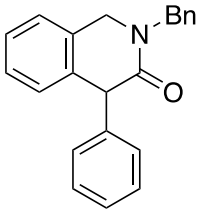
1-Methyl-3-(thiophen-3-yl)indolin-2-one (2t)



Was isolated by PTLC (AcOEt:hexane = 1:4) as a yellow solid (98%, 67 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.30 (m, 2H, Ar-H), 7.28 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.15–7.14 (m, 1H, Ar-H), 7.11–7.06 (m, 2H, Ar-H), 6.89 (d, *J* = 7.6 Hz, 1H, Ar-H), 4.72 (s, 1H, CH), 3.24 (s, 3H, NCH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 175.2, 144.2, 135.7, 128.4, 128.1, 127.2, 126.2, 124.8, 122.6, 122.5, 108.2, 47.3, 26.4 ppm; **IR (KBr):** 2965, 1711, 1495, 1462, 1182, 1083, 1021, 963, 875, 842, 777, 691 cm^{-1}; **HRMS (EI):** *m/z* calcd for $C_{13}H_{11}NOS$: 229.0561 $[M]^+$; found: 229.0557.

2-Benzyl-4-phenyl-1,4-dihydroisoquinolin-3(2*H*)-one (6)

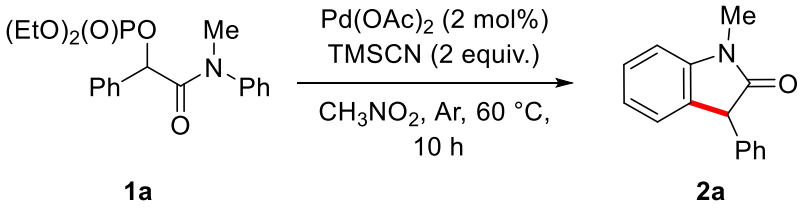


Was isolated by silica-gel column chromatography (AcOEt:hexane = 1:4) as a green viscous oil (98%, 108 mg).

Spectra data are in accordance with the literature.[16]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.22 (m, 8H, Ar-H), 7.18–7.13 (m, 6H, Ar-H), 4.98 (s, 1H, CH), 4.74 (s, 2H, CH_2Ph), 4.45 (d, *J* = 15.6 Hz, 1H, ArC*H*H), 4.22 (d, *J* = 15.6 Hz, 1H, ArCH*H*) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 170.1, 138.6, 136.6, 135.4, 131.7, 128.6 (two peaks overlapped), 128.4, 127.93, 127.86, 127.8, 127.5, 127.2, 127.1, 125.3, 53.0, 50.2, 49.8 ppm.

Gram-Scale Synthesis of 2a



1a **2a**

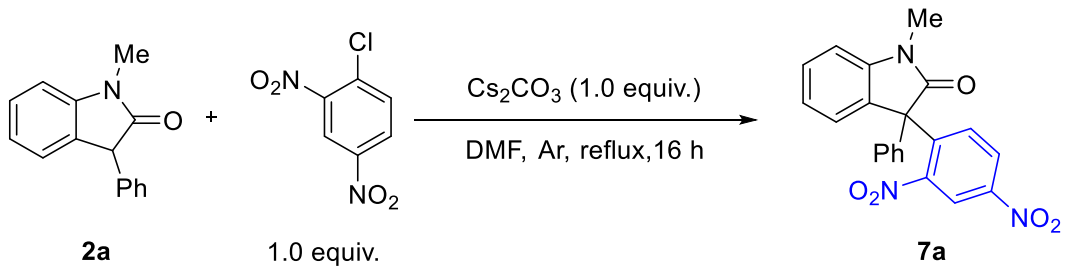
3.02 g (7.99 mmol) 1.78 g (7.97 mmol)

$Pd(OAc)_2$ (36 mg, 0.16 mmol) was added to a 20 mL Schlenk flask charged with diethyl (2-(methyl(phenyl)amino)-2-oxo-1-phenylethyl) phosphate (**1a**: 3.02 g, 7.99 mmol) followed by 3 repetitions of a vacuum–argon replacement procedure. CH_3NO_2 (25 mL) was added and the solution was stirred for 15 min at 60 ºC. TMSCN (1.66 g, 16.8 mmol) was added and the reaction mixture was continuously stirred at 60 ºC for 10 h. Completion of the reaction was

judged by TLC (AcOEt:hexane = 4:1). Saturated $NaHCO_3$ (aq.) was added to quench the reaction, and the aqueous layer was extracted by AcOEt (30 mL × 3). The collected organic layers were washed with brine and dried over Na_2SO_4. After Na_2SO_4 was filtered off, the resulting mixture was concentrated in vacuo. The product **2a** was isolated by silica-gel column chromatography (AcOEt:hexane = 1:4) as a white solid (1.78 g, 7.97 mmol, >99% yield).

Derivatizations: 3-Arylation of 2a

S_NAr-type Substitution with 2,4-Dinitrochlorobenzene

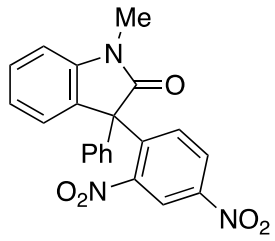


2a 1.0 equiv. **7a**

The reaction was carried out according to the reported procedure with the appropriate modification.[8] Oxindole derivative **2a** (144 mg, 0.62 mmol), 2,4-dinitrochlorobenzene (135 mg, 0.67 mmol, 1.1 equiv), and Cs_2CO_3 (214 mg, 0.66 mmol, 1.1 equiv) were charged in a 20 mL Schlenk flask, which was purged with Ar. Dry DMF (5 mL, degassed by Ar sparging) was added to the Schlenk flask. The mixture was stirred under reflux conditions for 24 h. After cooling to ambient temperature, the reaction was quenched by 10 mL of saturated NH_4Cl (aq.). The separated water layer was extracted with a 1:1 mixture of AcOEt and hexane (10 mL × 3). The combined organic layers were washed by water and brine, then dried over Na_2SO_4. After Na_2SO_4 was filtered off, the filtrate was concentrated in vacuo. The residue

was purified by alumina column chromatography (AcOEt:hexane = 4:1), and the resulting compound was recrystallized from a mixture of hexane and AcOEt (1:1) to provide 3-(2,4-dinitrophenyl)-1-methyl-3-phenylindolin-2-one (**7a**) as a pale-yellow solid. (92%, 220 mg).

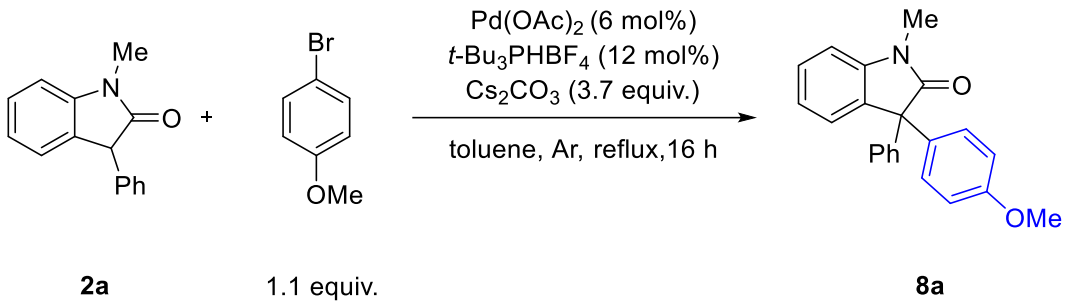
3-(2,4-dinitrophenyl)-1-methyl-3-phenylindolin-2-one



Spectra data are in accordance with the literature.[14]

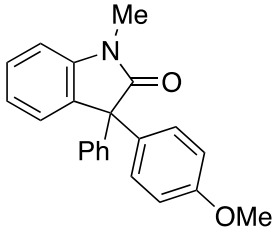
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (d, *J* = 2.8 Hz, 1H, Ar-H), 8.32 (dd, *J* = 2.4 Hz, 8.8 Hz, 1H, Ar-H), 7.46–7.41 (m, 1H, Ar-H), 7.42 (d, *J* = 8.8 Hz, 1H, Ar-H), 7.34–7.26 (m + br s, 5H, Ar-H), 7.18–7.12 (m, 2H, Ar-H), 7.00 (d, *J* = 8.0 Hz, 1H, Ar-H), 3.25 (s, 3H, NCH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 175.4, 149.4, 146.7, 144.0, 142.8, 139.1, 135.1, 129.5, 129.0, 128.9, 128.7, 128.6, 126.1, 124.8, 122.7, 120.5, 109.2, 60.6, 26.8 ppm; **IR (neat):** 1711, 1609, 1536, 1523, 1489, 1465, 1347, 899, 761 cm^{-1}; **HRMS (EI):** *m/z* calcd for $C_{21}H_{15}N_3O_5$: 389.1012 $[M]^+$; found: 389.1007.

Pd-catalyzed 3-Arylation of 2a with Aryl Bromide



2a 1.1 equiv. **8a**

The reaction was carried out according to the reported procedure with the appropriate modification.[14] Oxindole derivative **2a** (102 mg, 0.37 mmol), $Pd(OAc)_2$ (5.2 mg, 0.023 mmol), *t*-Bu_3PHBF_4 (13 mg, 0.046 mg), and Cs_2CO_3 (446 mg, 1.37 mmol) were charged in a 20 mL Schlenk flask, which was purged with Ar. *p*-Bromoanisole (94 mg, 0.50 mmol) was dissolved in dry toluene (5 mL), and the solution was degassed by Ar sparging before cannulating into the Schlenk flask. The reaction mixture was stirred under reflux conditions overnight. After cooling to ambient temperature, the reaction was quenched by the addition of 1 M HCl (10 mL) and the separated water layer was extracted with AcOEt (25 mL × 3). The combined organic layers were washed with brine, then dried over Na_2SO_4. After Na_2SO_4 was filtered off, the filtrate was concentrated in vacuo. The residue was purified by silica-gel column chromatography (AcOEt:hexane = 4:1), providing 3-(4-methoxyphenyl)-1-methyl-3-phenylindolin-2-one (**8a**) as a pale-yellow solid (99%, 149 mg).



Spectra data are in accordance with the literature.[14]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.24 (m, 7H, Ar-H), 7.19 (app. d, *J* = 8.8 Hz, 2H, Ar-H), 7.09 (td, *J* = 7.6, 0.8 Hz, 1H, Ar-H), 6.93 (d, *J* = 7.6 Hz, 1H, Ar-H), 6.82 (app. d, *J* = 8.8 Hz, 2H, Ar-H), 3.77 (s, 3H, OCH_3), 3.30 (s, 3H, NCH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 177.8, 158.7, 143.0, 142.2, 133.7, 133.1, 129.6, 128.4, 128.3, 128.2, 127.2, 125.9, 122.8, 113.7, 108.5, 61.8, 55.2, 26.6 ppm.

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Chapter 3

Silyl Cyanoargentate Catalyzed Oxidative Cyanomethylation Mediated by Benzotriflouride

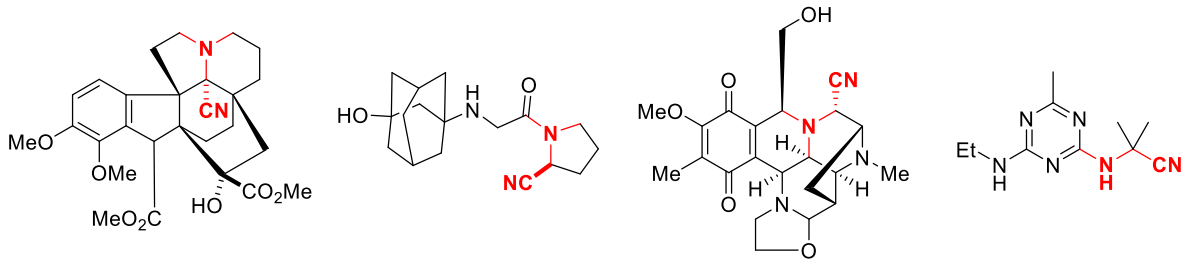
Abstract

Oxidative cyanomethylation of secondary arylamine has successfully been performed by *in situ* formed silyl cyanoargentate. The methyl group of CH_3NO_2 served as a methylene source connecting between *N*-atom and cyanide. Benzotrifluoride ($CF_3C_6H_5$) effectively accelerates the reaction, and the yield of the product achieved to 97% under the optimized reaction conditions. Amount of both CH_3NO_2 and $CF_3C_6H_5$ crucially affected the efficiency of the reaction.

3.1 Introduction

α-Amino nitriles are the analogs of amino acid and are found in many bioactive molecules (Figure 1).[1] They are also regarded as building blocks for bifunctional molecules like 1,2-diamines, α-amino acids, α-amino aldehydes, α-amino alcohols, α-amino ketones, and alkaloids that are widely used in pharmaceuticals, agrochemicals, and catalyst structures.[1b,2]

Figure 1. α-Amino nitrile moiety contained bioactive compounds

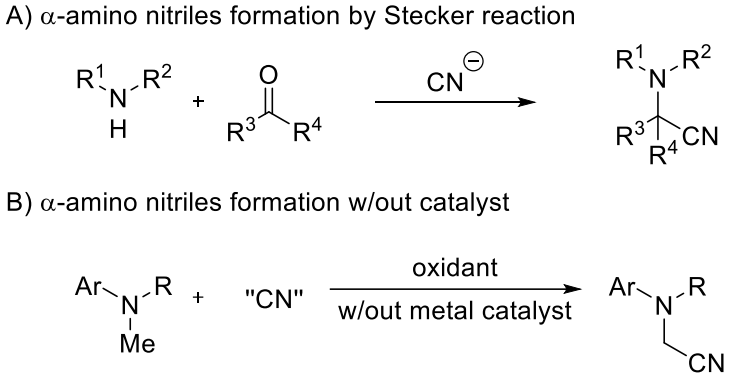


lahadinine B vildagliptin cyanocycline A halimedin

One of the most common and traditional approaches affording α-amino nitriles is the Strecker reaction that a three-component condensation between aldehydes or ketones, amines, and cyanide sources (Scheme 1A).[3] *In situ* generated imine or iminium intermediate plays as electrophile accepting cyanide. This method is well-suited to obtain the *N*-free or *N*-monosubstituted aminonitriles. On the other hands, the oxidative Strecker-type cyanation is powerful strategy to afford *N*,*N*-disubstituted α-aminonitriles. The iminium ions are formed through the oxidation of the corresponding *N*-alkyl tertiary amines, and those contributes as intermediates for the cyanation (Scheme 1B). Several metal salts including Ru,[4] V,[5] Au,[6] Mo,[7] Fe,[8] Cu,[9] Ir,[10] Ti,[11] Co[12] and Re[13] catalyzes the oxidative formation of the intermediate for the

Strecker-type reaction. Metal-free oxidation of tertiary amine is accelerated by tropylium ions,[14] hypervalent iodine compound (PIFA),[15] eosin Y (with blue LED)[16] or AIBN[17] as an oxidant (Scheme 1B).

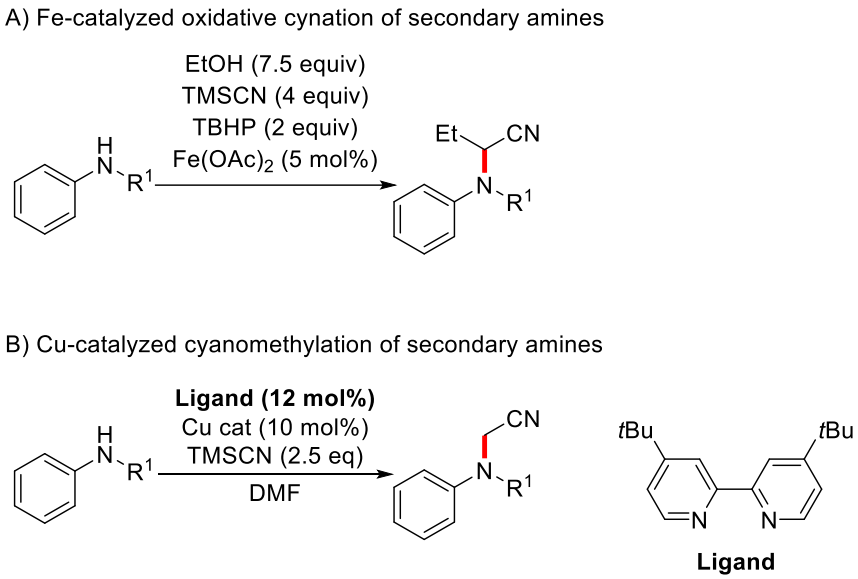
Scheme 1. Synthetic approaches of formation of α-amino nitriles



Cyanomethylation of secondary arylamines is relatively rare. Because of the low-nucleophilicity, those amines are not efficiently applicable to the simple Strecker-type cyanation. Oxidative condensation among those amines, primary alcohol and TMSCN was the first possible demonstration giving the target compound (Scheme 2A).[18] The combination of TBHP (*t*BuOOH) and a catalytic amount of $Fe(OAc)_2$ forms the corresponding aldehyde, and that is the key step of the reaction. EtOH is the effective alcohol reagent for this reaction forming 2-amino propionitrile derivatives. However, the cyanomethylation using MeOH is still problematic, and the yield of the product is up to 51% even with the most suitable amine. Cu-catalyzed cyanomethylation in DMF is the first successful report (Scheme 2B).[19] The methylene source connecting between *N*-atom and cyanide is methyl group of DMF. Although the yield of the product is high, 10 mol% of CuOAc with 12 mol% of bipyridyl ligand is necessary. In both cases, the addition of the excess amount of oxidant is inevitable.

In this chapter, the author describes about successful example of Ag-catalyzed cyanomethylation of secondary arylamines. In the presence of AgCN (2 mol%) with 2 equiv of TMSCN, *N*-methylaniline are cyanomethylated in $MeNO_2$. An obvious oxidant was not added in the reaction mixture. The addition of $CF_3C_6H_5$ is effective to improve the yield, and the target compound was obtained almost quantitatively under the optimized conditions.

Scheme 2. Several approaches to obtain α-amino nitriles through secondary amines

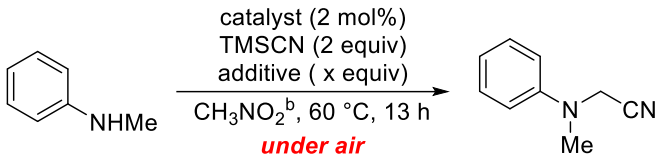


3.2 Results and Discussion

N-methyl aniline was selected as the model substrate for the optimization of reaction conditions (Table 1). The desired cyanomethylated product **2a** was obtained with AgTFA (2 mol%) as a catalyst in CH_3NO_2 (2.5 mL) within 13 h in 32% yield under air (entry 1). When the reaction was carried out under argon atmosphere, the yield of the desired product **2a** was decreased (entry 2). Surprisingly, the addition of bezotrfluoride ($CF_3C_6H_5$) obviously affected on the yield of the product. More amount of the additive gave more product and **2a** was

afforded in 94% yield with 6 equiv of $CF_3C_6H_5$ (entries 3,4). When the reaction was carried out under inert conditions, the yield of the product little decreased even with the additive (entry 5). No product formation was observed in the absence of AgTFA (entry 6). When 1 mol% AgTFA was employed, the reaction yielded in 40% within 24 h (entry 8). TMSCN (1.2 equiv) was not enough to promote the reaction (entry 9). These results showed that 2 mol% AgTFA and 2 equiv TMSCN were crucial for the protocol that was in consistent with our previous observation on formation of active catalytic species.[20-22] Changing the reaction temperature from 60 °C to 80 °C was resulted in 4% yield (entry 10). The author then moved the focus onto the counter anion of silver salts. Both AgCN and AgCl instead of AgTFA worked well (entries 11, 12). Notably, the reaction with AgCN (2 mol%) were increased the formation of the **2a** from 93% to 96% yield in CH_3NO_2. In the previous studies, silyl cyanopalladate complex was generated from Pd salt with an excess amount of TMSCN in equilibrium. In some cases, the species more effectively accelerate the reaction than Ag salt. However, the attempts of using Pd salts with TMSCN (2 equiv) were not sufficient for the oxidative cyanomethylation (entries 13, 14). The author concluded the reaction is specifically promoted by silyl cyanoargentate.

Table 1. Screening of conditions



1a **2a**

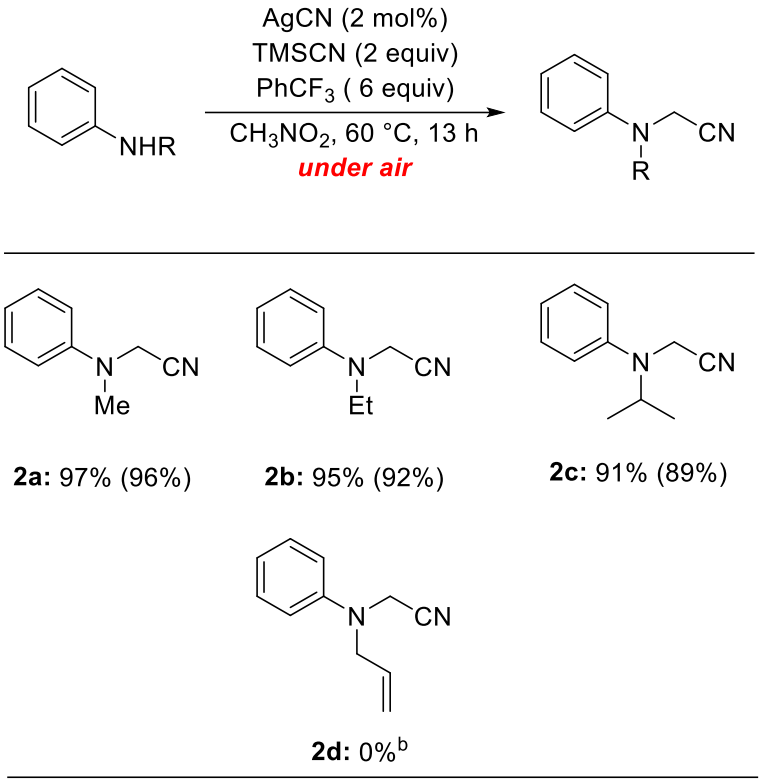
entry	catalyst	additive (x equiv)	**2a** (%)[a]	entry	catalyst	additive (x equiv)	**2a** (%)[a]
1	AgTFA		32	8[e]	AgTFA	$PhCF_3$ (6)	16
2[c]	AgTFA		25	9[d,g]	AgTFA	$PhCF_3$ (6)	22
3	AgTFA	$PhCF_3$ (3)	69 (67)	10	AgCN	$PhCF_3$ (6)	97 (96)
4	AgTFA	$PhCF_3$ (6)	94 (93)	11	AgCl	$PhCF_3$ (6)	94
5[c]	AgTFA	$PhCF_3$ (6)	90	12	$Pd(OAc)_2$	$PhCF_3$ (6)	35
6[d]		$PhCF_3$ (6)	4	13	$Pd(CN)_2$	$PhCF_3$ (6)	37
7[d,f]	AgTFA	$PhCF_3$ (6)	40				

[a] ^{1}H NMR yield is given. The isolated yield is shown in parenthesis. [b] CH_3NO_2 (2.5 mL) [c] The reaction was carried out under argon atmosphere. [d] The reaction was carried out for 24 h. [e] 1 mol% catalyst was employed. [f] 1.2 equiv of TMSCN was employed. [g] The reaction was carried out at 80 °C.

With optimized reaction conditions in hand, the author investigated the limitations of oxidative cyanomethylation with aromatic amines (Scheme 3). The products containing ethyl and isopropyl groups, **2b** and **2c,** were obtained in 92% and 90% under optimal conditions. No CN introduction was obtained in ethyl and isopropyl groups. These results suggested that the methylene part bridging *N*-atom and cyano group came from $MeNO_2$. When *N*-allyl aniline **1d** was introduced as the substrate, no formation of 2-(allyl(phenyl)amino) acetonitrile **2d** was observed. This result is possibly because of substrate disturbed the reaction; both the

alkene moiety and *N*-atom of *N*-allylaniline has coordinative ability, and the amine may form the relatively stable silver complex, which is inactive species in the reaction.

Scheme 3. Substrate scope of aromatic amines



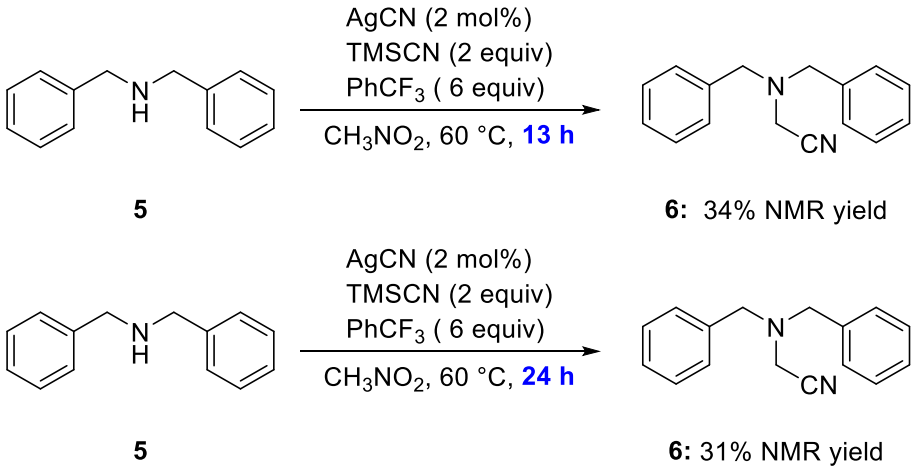
[a] ^{1}H NMR is given. Isolated yield is shown in parenthesis. [b] The reaction was carried out for 24 h.

We then investigated the application of dialkyl amines to cyanomethylation. When a cyclic amine, piperidine **3**, was used in the presence of AgTFA (2 mol%), TMSCN (2 equiv), $CF_3C_6H_5$ (6 equiv) in CH_3NO_2 for 24 h under air, no target product **4** was obtained (Scheme 4). That is the obvious limitation of this catalytic protocol. 2-(Dibenzylamino) acetonitrile **6** was formed in 34% NMR yield under optimized conditions. However, when the reaction time was lengthened to 24 h, the yield of the

product was not changed (Scheme 5). The result suggested that the lifetime of the silyl cyanoargentate is not so long.

Scheme 4. Attempted oxidative cyanomethylation of piperidine **3**

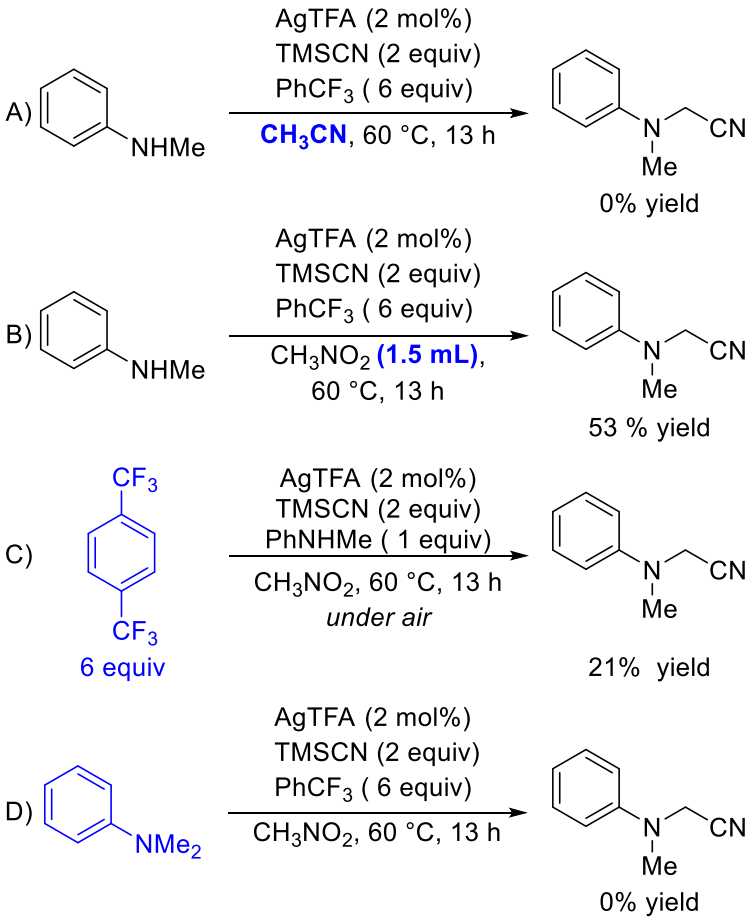
Scheme 5. Silyl cyanoargentate-catalyzed formation of 2-(dibenzylamino)acetonitrile **6**



Some control experiments were carried out for understanding the reaction mechanism (Scheme 6). When CH_3CN was used instead of CH_3NO_2, no product was formed. This result clarified that CH_3NO_2 was not the only the solvent, but also possible methylene source in this reaction (Scheme 6A). The yield of the **2a** was affected by amount of the CH_3NO_2. Less amount of CH_3NO_2 decreased the yield (Scheme 6B). When 1,4-bis(trifluoromethyl)benzene was emloyed instead of benzotriflouride with *N*-methyl aniline (1 equiv), AgTFA (2 equiv),

TMSCN (2 equiv) in CH_3NO_2 for 13 h (Scheme 6C). The desired cyanomethylated compound was formed in 21% yield. Electronically more deficient fluoroalkylated aryl additive does not help the reaction. When *N*,*N*-dimethylaniline was applied to the reaction, no target product was obtained (Scheme 6D). The result indicated that the oxidative cyanomethylation did not proceed from *in situ* generated from *N*,*N*-dimethylaniline from *N*-methylaniline and CH_3NO_2. Further investigation on the reaction mechanisms is still underway.

Scheme 6. Control experiments for investigation of mechanism



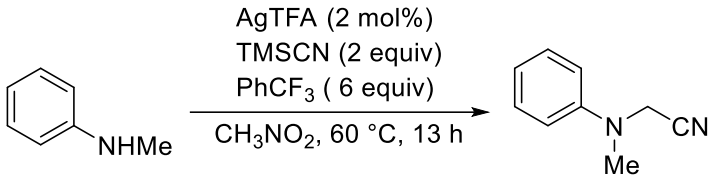
3.3 Conclusion

In conclusion, a novel method for transformation of secondary amines was successfully demonstrated to afford corresponding α-amino nitriles through silyl cyanoargentate catalyzed oxidative cyanomethylation in high yield. $CF_3C_6H_5$ is an effective additive to promote the reaction. This protocol was less applicable to aliphatic amines and *N*-alyl aniline, and thatwas main limitation of the reaction. Subsrate scope and mechanistic investigation are still under way.

3.4 Experimental Section

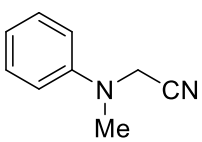
General Information: ^{1}H NMR spectra were measured on a JEOL JNM-ECX400P (400 MHz) spectrometer and JNM-ECS400 (400 MHz) spectrometer. Data were reported as follows: chemical shifts in ppm from tetramethysilane or the residual solvent as an internal standard, integration, multiplicity (s = singlet, d = doublet, t = triplet, dd = double-doublet, td = triple-doublet, q = quartet, m = multiplet, br = broad, and app = apparent), coupling constants (Hz), and assignment. ^{13}C NMR spectra were measured on a JEOL JNM-ECX400P (100 MHz) spectrometer and a JNM-ECS400 (100 MHz) spectrometer with complete proton decoupling. ^{31}P NMR spectra were measured on a JEOL JNM-ECX400 (400 MHz) spectrometer. ^{19}F NMR spectra were measured on a JEOL JNM-ECX400 (400 MHz) spectrometer. Chemical shifts were reported in ppm, from the residual solvent as an internal standard. Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 and FT/IR-4600. Mass spectrometry was carried out at the Instrumental Analysis Division, Global Facility Center, Creative Research Institution, Hokkaido University. The products were purified by silica-gel column chromatography prepared from silica gel 60N (Kanto Chemical Co. Inc) or preparative thin-layer chromatography (PTLC) prepared from Wako Gel B-5F (Wako Pure Chemical Industries). Trimethylsilyl cyanide (TMSCN) and Nitromethane (CH_3NO_2) were purchased from Kanto Chemical Co. Inc. and were used after distillation. Silver cyanide (AgCN) was purchased from Fujifilm Wako Pure Chemical Industries, Ltd and was used as received.

AgTFA-catalyzed Oxidative Cyanomethylation of Secondary Amine Derivatives



To a solution of benzotriflouride (485.9 mg, 3.33 mmol) in CH_3NO_2 (2.5 mL) was added AgCN (1.4 mg, 0.010 mmol). The resulting mixture was stirred for 15 min at 30 °C, followed by the addition of *N*-methyl aniline (55.1 mg, 0.51 mmol) and TMSCN (111.0 mg, 1.11 mmol). The reaction mixture was then continuously stirred at 60 ºC for 13 h. Completion of the reaction was judged by TLC (AcOEt:hexane = 1:4). A saturated $NaHCO_3$ aq was added to quench the reaction, and the aqueous layer was extracted by AcOEt (10 mL × 3). The collected organic layer was washed with brine and dried over Na_2SO_4. After Na_2SO_4 was filtered off, the resulting mixture was concentrated *in vacuo*. The yield of the product was calculated from ^{1}H NMR spectra of the crude 2-(methyl(phenyl)amino) acetonitrile with pyrazine as an internal standard (97% yield). The product was isolated by PTLC (AcOEt:hexane = 1:4), as a pale-yellow oil (72.1 mg, 0.49 mmol, 76% yield).

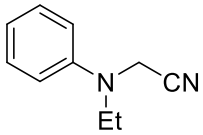
2-(methyl(phenyl)amino) acetonitrile (2a)



Spectra data are in accordance with the literature.[23]

^{1} H NMR (400 MHz, $CDCl_3$): δ 7.35–7.30 (m, 2H, Ar-H), 6.93 (app. t, *J* = 7.8 Hz, 1H, Ar-H), 6.88 (app. d, *J* = 7.6 Hz, 2H, Ar-H), 4.18 (s, 2H, NCH_2), 3.02 (s, 3H, NCH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 147.7, 129.4, 120.2, 115.6, 114.8, 42.2, 39.2 ppm.

2-(ethyl(phenyl)amino) acetonitrile (2b)

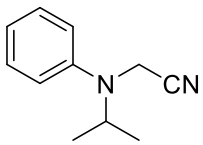


Was isolated as a pale-yellow oil (92%, 73.7 mg).

Spectra are in accordance with the literature.[23]

^{1} H NMR (400 MHz, $CDCl_3$): δ 7.34–7.29 (m, 2H, Ar-H), 6.93-6.87 (m, 3H, Ar-H), 4.16 (s, 2H, NCH_2), 3.45 (q, 2H, NCH_2CH_3), 2.26 (t, *J* = 7.2 Hz, 3H, NCH_2CH_3) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 146.7, 129.5, 120.0, 116.3, 115.0, 46.3, 39.6, 12.3 ppm.

2-(isopropyl(phenyl)amino)acetonitrile (2c)



Was isolated as a pale-yellow oil (89%, 90.4 mg).

Spectra data are in accordance with the literature. [24]

^{1} H NMR (400 MHz, $CDCl_3$): δ 7.34–7.29 (m, 2H, Ar-H), 6.93-6.88 (m, 3H, Ar-H), 4.14-4.10 (m, 1H, NCH), 4.08 (s, 2H, NCH_2), 1.29 (s, 3H, $NCHCH_3$), 1.27 (s, 3H, $NCHCH_3$) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** 147.2, 129.5, 119.7, 117.7, 115.2, 49.4, 33.8, 19.9 ppm.

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List of Publications

Chapter 1

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

Yurino, T.; Ece, H.; Ohkuma, T. *Asian J: Org. Chem.* **2020**, *9*, 557.

Chapter 2

Silyl Cyanopalladate-Catalyzed Friedel–Crafts-type Cyclization Affording 3-Aryloxindole Derivatives

Ece, H.; Tange, Y.; Yurino, T.; Ohkuma, T. ***manuscript is submitted.***

Other Publications

Amberlyst-15 Catalyzed Michael Addition of β-Dicarnonyl Compounds to the Enones and Unexpected Ring Closure Products

Gunduz, H.; Ece,H.; Atsay, Armagan, Kumbaraci, V.; Talinli, N. *Tetrahedron* **2017**, *73*, 4335.

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