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

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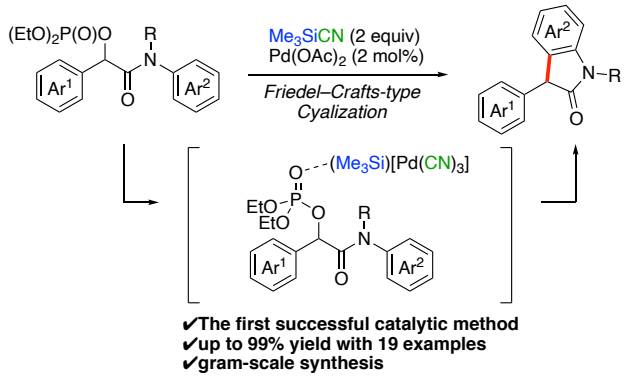

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Abstract 3-Aryloxindole derivatives were synthesized through the Friedel–Crafts-type cyclization. The reaction was catalyzed by a trimethylsilyl tricyanopalladate complex generated *in situ* from trimethylsilyl cyanide and $Pd(OAc)_2$. Wide varieties of diethylphosphates derived from *N*-arylmandelamides were almost quantitatively converted to the oxindols. When *N,N*-dibenzylamide 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.

Key words silyl cyanopalladate, Lewis acid catalyst, $Pd(OAc)_2$, TMSCN, Friedel–Crafts-type cyclization, 3-aryloxindole, S_N1-type reaction, α-hydroxyacetamide

Oxindoles are a class of benzo-fused 5-membered lactams, which are found in several biologically active compounds, including naturally occurring alkaloids. Among them, 3-aryloxindole derivatives are frequently utilized as pharmaceutical agents (Figure 1).[1–4] To meet the demand for these therapeutic agents, numerous studies have investigated efficient synthetic methods.[5] Scheme 1 illustrates three typical cyclization strategies for constructing the 3-aryloxindole structures.[6–10] All three consist of C–C bond formations between the α-position of amide and *ortho*-carbon of the *N*-aryl ring. (a) The first strategy is an intramolecular $C(sp^2)$–$C(sp^3)$ cross coupling reaction of the *N*-acyl-*ortho*-haloanilides catalyzed by the Pd complex with a base.[6] Pd(0) species oxidatively cleaves the C–halogen bond with the help of coordination by the amide group. The reversibly formed amide-enolate binds on the Pd(II) instead of the halide. The lactam is obtained by reductive release of the Pd(0) species. (b) The second strategy, α-arylation through a radical-nucleophilic aromatic substitution ($S_{RN}1$ reaction), is also a useful approach using the *N*-acyl-*ortho*-iodoanilides.[7,8] In the presence of a stoichiometric or excess amount of alkali metal base, the resulting enolate transfers an electron to the aryl iodide (SET), forming the C–C linkage with homolysis of the C–I bond. When the *ortho*-fluoroanilides are employed as substrates, the electron-deficient aromatic ring suffers nucleophilic substitution by the amide-enolate under similar basic conditions (S_NAr reaction).[9] (c) Friedel–Crafts-type cyclization of α-halo-*N*-arylamide is the third method; in this approach, the aromatic part reacts as a nucleophile to form the C–C bond with release of the halide (S_N1-type reaction).[10] More than an equimolar amount of silver Lewis acid is required to obtain the product in high yield. This cyclization method has the benefit that the *ortho*-haloanilide moiety is not necessary in the substrate. Therefore, the development of a catalytic version of this reaction is highly desired. Use of the alcoholic derivatives instead of the halide compounds as substrates is even more preferable.

Recently, we focused on the Lewis-acid catalysis of silyl cyanometallate complexes generated *in situ*. It is well-known that transition metal compounds strongly interact with the *C*-terminus of cyanide (CN^-). Transition metal salt (MX_n) reacts with an excess amount of trimethylsilyl cyanide (TMSCN), spontaneously affording thermodynamically stable metal cyanide ($M(CN)_n$), and a small part of the $M(CN)_n$ is further reversibly converted to the silyl cyanometallate ($(Me_3Si)[M(CN)_{n+1}]$). The silyl part of the ate complex has a Lewis acid character and is possibly applicable as a catalyst to several organic transformations. Indeed, we have successfully demonstrated nucleophilic isocyanations and Friedel–Crafts-type allylations catalyzed by silyl cyanometallate complexes (M = Pd, Ag).[11–13] Notably, the Lewis acid character of these catalysts is varied by changing the transition metal species. The reversible feature of the catalysts may appropriately control the intensity of acidity. Herein we report a trimethylsilyl cyanopalladate (M = Pd, n = 2)-catalyzed intramolecular Friedel–Crafts-type substitution affording 3-aryloxindole derivatives (Scheme 2). The benzylic diethyl phosphates facilely

derived from the alcohols are well suited for the catalytic system in place of the corresponding halides.

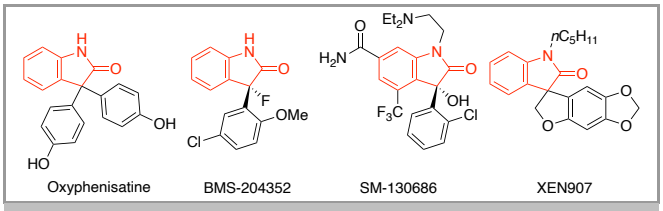
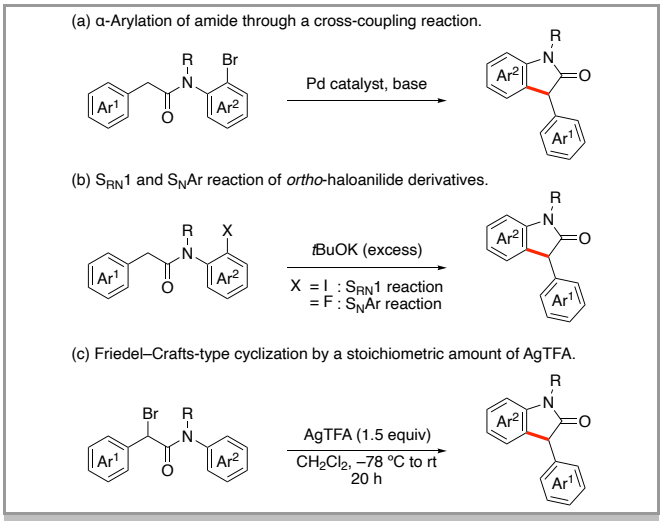
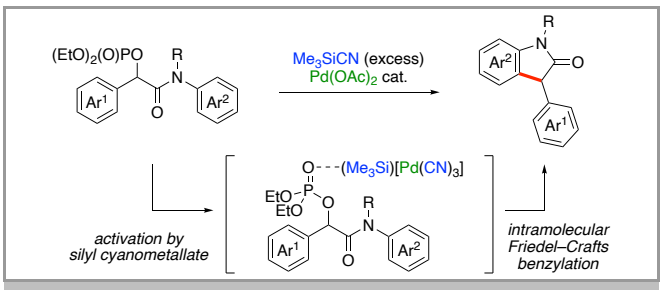


Figure 1 Bioactive compounds including the 3-aryloxindole moiety



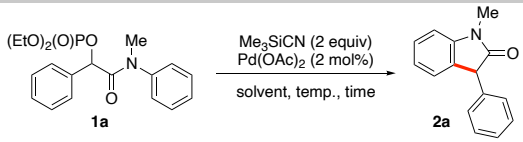
Scheme 1 Previous strategies to afford 3-aryloxinndole derivatives



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

Our investigation commenced with the optimization of reaction conditions (Table 1). We selected *N*-methyl-*N*-phenylmandelamide derivative **1a** as the model substrate. Diethylphosphate was a leaving group of choice according to our previous studies on nucleophilic isocyanation and Friedel–Crafts-type allylation.[11–13] The cyclization of **1a** was completed in the presence of $Pd(OAc)_2$ (2 mol%) and Me_3SiCN (2 equiv) in CH_3NO_2 at 80 ºC within 20 h to afford the 3-phenyloxindole **2a** in almost quantitative yield (entry 1). CH_3CN and 1,2-dimethoxyethane (1,2-DME) were also suitable solvents for this reaction (entries 2, 3). The reaction rate significantly slowed in 1,4-dioxane, a cyclic ether, and less polar toluene (entries 4, 5). The highly polar and coordinative DMF completely prevented the reaction (entry 6). Addition of $Pd(OAc)_2$ was indispensable for the reaction (entry 7). No desired product was observed without the catalyst under otherwise identical conditions. Consequently, the reaction in CH_3NO_2 was completed at 60 °C in 10 h, and we therefore adopted these as the optimized conditions (entry 8).[14] When the reaction was conducted with 1.2 equiv of Me_3SiCN, the yield of **2a** obviously decreased (entry 9). These results suggested that maintaining a large excess amount of Me_3SiCN relative to the Pd catalyst throughout the reaction was required to form a sufficient amount of the active species, $(Me_3Si)[Pd(CN)_3]$, in the reaction system. Me_3SiOAc did not work as an alternative of $Pd(OAc)_2$ at all (entry 10). The yield of the product was obviously low, although Me_3SiCl played as a catalyst for the transformation (entry 11). These experiments indicated that the silyl Lewis acid potentially promotes the cyclization as an active species, and the silyl cyanopalladate generated *in situ* is more suitable catalyst.

Table 1 Optimization of reaction conditions



Entry	Solvent	Temp (ºC)	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
10[d]	CH_3NO_2	60	24	0
11[e]	CH_3NO_2	60	24	11

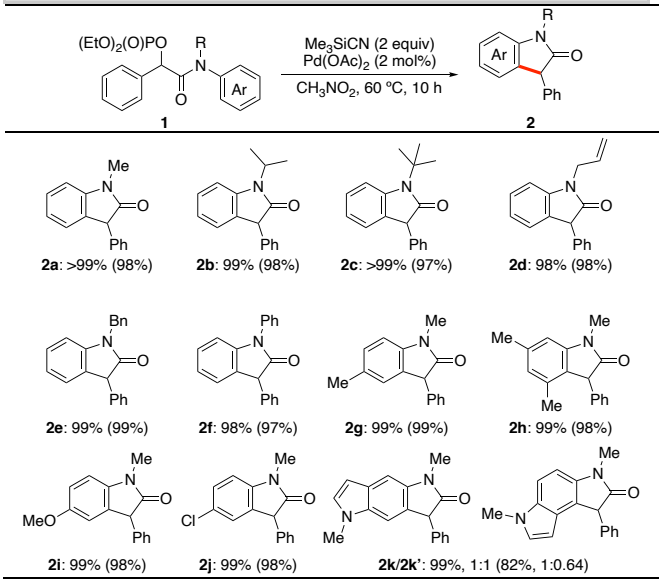
[a] ^{1}H NMR yield. The isolated yield is given in parenthesis. [b] No $Pd(OAc)_2$ was employed as a catalyst. [c] Me_3SiCN (1.2 equiv) was added in the reaction mixture. [d] Me_3SiOAc was used instead of $Pd(OAc)_2$ without Me_3SiCN. [e] Me_3SiCl was used instead of $Pd(OAc)_2$ without Me_3SiCN.

With the optimized reaction conditions in hand, we investigated the scope and limitations of the intramolecular Friedel–Crafts-type reaction (Table 2). Not only the methyl group but also the sterically hindered 2-propyl and *tert*-butyl groups were allowed to be introduced on the *N*-atom without retardation of the oxindole formation (**2b**, **2c**). *N*-Allyl and *N*-benzyl moieties were left intact in the presence of the Pd compound, and the cyclized products, **2d** and **2e**, were obtained almost quantitatively. *N*,*N*-Diphenylamide **1f** was also successfully converted to the triaryl product **2f**. In contrast to the cyclization methods using *ortho*-haloanilide derivatives (Scheme 1: (a) and (b)), substituents are readily introduced on the aniline phenyl rings in this approach. Both the 4-methyl- and 3,5-dimethyl-substituted products, **2g** and **2h**, were obtained in 99% yield. Introduction of an electron-donating methoxy group and electron-withdrawing chloro group at the C4 position little affected the yield of the products (**2i**, **2j**). The transformation of mandelamide **1k** derived from 5-aminoindole afforded the indole-fused oxindoles **2k/2k'** as a 1:1 mixture of the regioisomers in 99% yield. Through the purification, relatively unstable **2k'** was partially decomposed. We then screened a series of 3-aryl moieties of oxindoles (Table 3). The *para*-substituents were expected to influence the reactivity at the benzylic positions. The cyclization occurred quantitatively with the substrates connecting electron-donating methyl and

methoxy, and electron-withdrawing bromo groups (**2l**–**2n**). The substitution of strongly electron-withdrawing CF_3 completely hampered the reaction (**2o**). This is probably because the reaction proceeds through S_N1-type substitution, similar to the Friedel–Crafts-type allylation catalyzed by the silyl cyanometallate.[13] The *ortho*-methyl group which caused steric hindrance around the reactive site was uninfluential on the catalysis (**2p**). The yield of oxindoles with *meta*-substituted phenyl rings, **2q** and **2r**, slightly decreased. 2-Naphthyl and 3-thienyl products, **2s** and **2t,** were both obtained in 99% yield under the typical conditions. This catalytic strategy was well suited to the gram-scale synthesis (Scheme 3). The transformation of 3.02 g of **1a** with 2 mol% of $Pd(OAc)_2$ was completed in 10 h affording **2a** quantitatively (1.78 g).

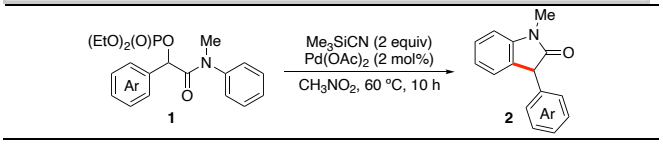
When a diethylphosphate derived from 2-hydroxypentanamide **3**, an aliphatic analogue, was exposed to the optimized reaction conditions, no cyclized product **4** was observed (Scheme 4). This indicated that the α-aryl structure of the substrate is required for the cyclization to stabilize the benzylic α-cationic intermediate.

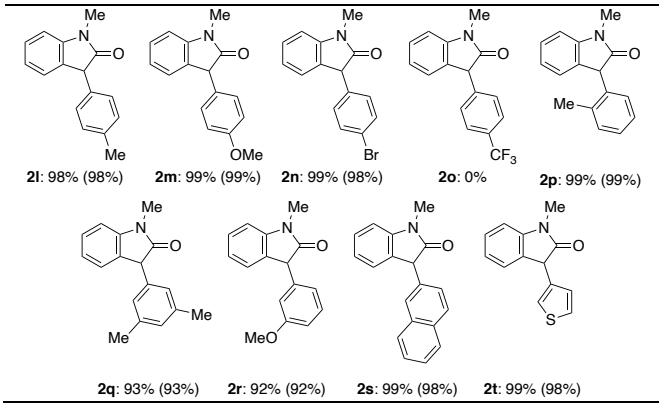
Table 2 Scope and limitations on *N*-alkylaniline subsructures[a]



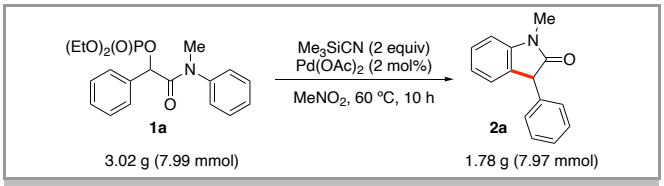
[a] ^{1}H NMR yield. The isolated yield is given in parenthesis.

Table 3 Scope and limitations on mandelic acid substructures

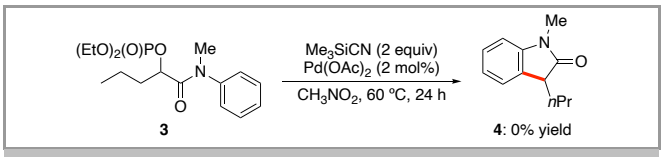




[a] ^{1}H NMR yield. The isolated yield is given in parenthesis.

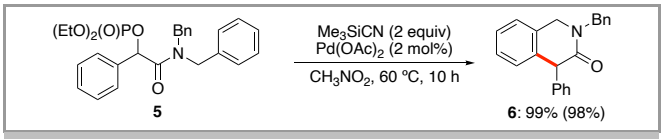


Scheme 3 Gram-scake synthesis of oxindole **2a** under the optimized conditions



Scheme 4 Attempted intramolecular Friedel–Crafts-type reaction of an aliphatic α–hydroxyamide derivatives

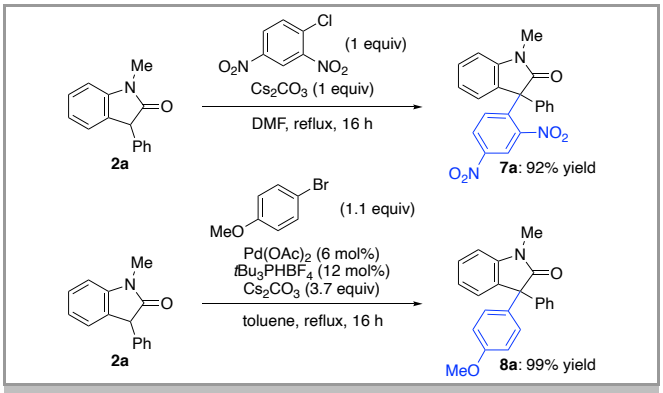
This reaction was successfully applied to the formation of a δ-lactam structure (Scheme 5). The dibenzylamide substrate **5** was smoothly transformed into 1,4-dihydroisoquinoline-3(*2H*)-one **6** in 99% yield under the regular conditions. It should be noted that the formation of γ-lactam predominantly occurred over the δ-lactam construction when the benzylanilide **1e** was employed as a substrate (see, Table 2). It may be caused by the strong nucleophilicity of the anilide moiety.



Scheme 5 Intramolecular Friedel–Crafts-type reaction affording a benzo-fused 6-membered lactam

We demonstrated the synthetic utility of 3-aryloxindoles **2** by the transformation into the 3,3-diaryloxindoles bearing two different aromatic substructures (Scheme 6). Nucleophilic aromatic substitution was employed for introduction of an electron-deficient aromatic ring. The reaction of 3-phenyloxindole **2a** and 2,4-dinitrochlorobenzene was promoted by Cs_2CO_3 (1 equiv) to afford the diaryloxindole **7a** in 92% isolated yield.[15] The Pd-catalyzed coupling reaction was effective for the substitution with an electron-rich aromatic moiety. In the presence of a catalytic amount of $Pd(OAc)_2$ and tBu_3PHBF_4 with the addition of Cs_2CO_3 (3.7 equiv), **2a** coupled

with 4-methoxybromobenzene to give the diaryl product **8a** in 99% isolated yield.[15]



Scheme 6 Transformations of 3-aryloxindole **2a**

In conclusion, we successfully demonstrated a Friedel–Crafts-type cyclization affording synthetically useful 3-aryloxindole derivatives. The reaction of diethylphosphates derived from *N*-arylmandelamides was promoted with a catalytic amount of $Pd(OAc)_2$ (2 mol%) in the presence of 2 equiv of Me_3SiCN. Trimethylsilyl cyanopalladate $(Me_3Si)[Pd(CN)_3]$ generated *in situ* was suggested to act as a Lewis-acid catalyst. The reversible character with $Pd(CN)_2$ and Me_3SiCN could appropriately control the acidity. This procedure was applicable to a gram-scale reaction. Wide varieties of *N*-arylmandelamide derivatives were transformed into the corresponding 3-aryloxindoles nearly quantitatively (19 examples). No cyclization product was observed in the reaction of an aliphatic α-hydroxyamide derivative, probably because benzylic stabilization of the cationic intermediate was necessary. The benzo-fuzed δ-lactam was also quantitatively obtained when *N*,*N*-dibenzylmandelamide was employed as a substrate. The 3-phenyloxindole was applicable to the substitution reactions at the C3 position. Two different 3,3-diaryloxindoles were obtained in high yield. Investigations of the properties of silyl cyanometallate catalysts are underway in our laboratory.

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Supporting Information

YES

Primary Data

NO

References and Notes

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(14) **Oxindole 2a: Typical Procedure**
$Pd(OAc)_2$ (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 (hexane:AcOEt = 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 (hexane:AcOEt = 4:1) as a white solid (76 mg, 0.34 mmol, 98% yield).
1-Methyl-3-phenylindolin-2-one (2a)
^1H 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, 1H, 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.

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