



III.2.13 Palladium-Catalyzed Cross-Coupling Involving α -Hetero-Substituted Organometals

III.2.13.1 Palladium-Catalyzed Cross-Coupling Involving Metal Cyanides

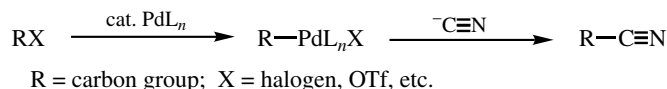
KENTARO TAKAGI

A. INTRODUCTION

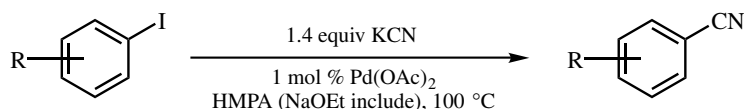
Pd-catalyzed cross-coupling using CN^- as a carbon nucleophile was first reported for the reaction between aryl halides and KCN in 1973.^[1] The cross-coupling is equivalent to the nucleophilic displacement of aryl halides with CN^- ; hence, it is also called cyanation. Up to that time the Rosenmund–von Braun reaction using a stoichiometric amount of CuCN as the cyanide source had been the sole method for carrying out this synthetically important transformation.^[2] Thereafter, many studies investigated effective Pd catalysts, metal cyanides, solvents, or additives, intending to provide the efficient catalytic reactions of a variety of carbon electrophiles including aryl halides under mild conditions (**Scheme 1**). This Pd-catalyzed method has occasionally been called modestly reliable in terms of reproducibility. This largely stems from the fact that CN^- plays the role of an inhibitor in the catalytic reaction due to its coordination to the Pd^{2+} or Pd^0 species, besides the role of an indispensable reaction component. In general, metal cyanides dissolve only partially in the solvent. However, free CN^- can deactivate Pd complexes to a significant extent. Therefore, in order to provide an efficient catalytic reaction, it is critical to select the proper combination of metal cyanides and solvents or to use the appropriate additives like a crown-ether to keep the concentration of free CN^- moderately low. The choice of phosphorus ligands is also a determinate, especially for the reaction using relatively unreactive substrates.

B. CYANATION OF ARYL, ALKENYL, AND SOME OTHER HALIDES AND TRIFLATES

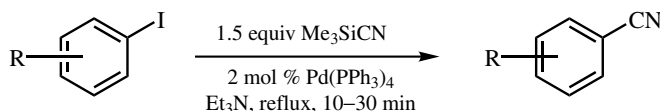
The order of reactivity of the aryl electrophiles in Pd-catalyzed cyanation is as follows: aryl iodides > aryl triflates > aryl bromides > aryl chlorides. The lower the reactivity of the

**Scheme 1**

substrate, the more strict the control of reaction conditions required as noted above (**Table 1**). For the reaction of the aryl iodides, not only $\text{Pd(PPh}_3)_4$ ^[3] but also phosphine-free Pd^0 , that is, the one generated *in situ* from Pd(OAc)_2 and a reducing reagent like NaOEt (**Scheme 2**)^{[4],[5]} or $\text{Pd}_2(\text{dba})_3$ ^[6], is available as a catalyst. In the reaction, KCN is often used as the metal cyanide and polar solvents such as NMP, HMPA, DMF, or THF are used as the reaction media. A reaction temperature of around 60–100 °C is usually necessary. Due to the problem of solubility, NaCN is not the first choice for the metal cyanide. However, NaCN sometimes shortens the reaction time compared with the reaction using KCN as the metal cyanide, if NaCN does not disturb the catalytic reaction. A modified metal cyanide like Me_3SiCN (**Scheme 3**)^[7] Me_3SnCN ,^[8] or Bu_3SnCN ^{[9],[10]} can be used in place of KCN but the special advantage over KCN is not observed for the reactions using aryl halides as the substrates. Impregnation onto Al_2O_3 or the addition of Al_2O_3 is also a useful method for modifying NaCN . Such a modified NaCN is available for the catalytic reaction of aryl halides including bromobenzene in toluene using $\text{Pd(PPh}_3)_4$ as the catalyst.^[11] For the synthesis of the cyano-derivatives of adenocine (**Scheme 4**)^{[9],[10]} or the precursor of (+)-estradiol (**Scheme 5**)^[12] from the corresponding aryl halides, modified metal cyanides were used as the cyanide sources.



R, Reaction time (h), GLC yield (%), Remark^[4] = H, 4.5, 98, -; *p*-CH₃, 2, 93, -; *o*-CH₃, 2, 96, -; *m*-Cl, 5.5, 70, *m*-CN (21%); *p*-NO₂, 10, 70, -.

Scheme 2

R, Isolated yield (%), Remark^[7] = H, 88, -; *o*-CH₃, 76, -; *p*-CH₃O, 89, -; *p*-Cl, 70, -; *p*-Br, 56, *p*-CN (15%); *p*-I, 53, *p*-CN; *p*-CH₃O₂C, 68, -.

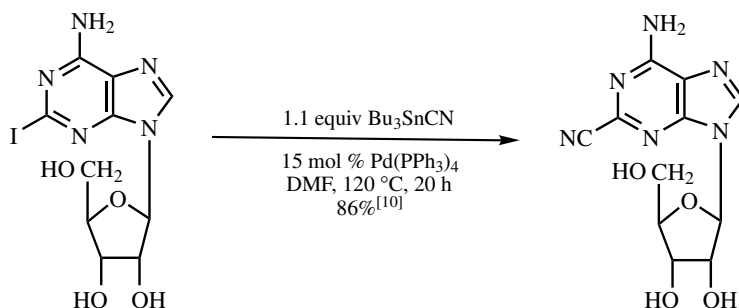
Scheme 3**Scheme 4**

TABLE 1. Pd-catalyzed Cyanation of Halobenzenes and Phenyl Triflate

| Aryl Compound | Metal Cyanide | Catalyst ^a | Solvent | Reaction Temperature (°C) | Yield ^b (%) | Reference |
|--------------------------|-------------------------------------|-----------------------|---------------------------------|---------------------------|------------------------|-----------|
| PhI | KCN | Ia | HMPA | 100 | 98 | 4 |
| PhI | KCN | Ib | HMPA | 60 | 99 | 4 |
| PhI | KCN | IIa | THF | Reflux | 98 | 3 |
| PhI | KCN | IIIa | NMP | 60 | 40 | 6 |
| PhI | Me ₃ SiCN | IIf | Et ₃ N | Reflux | 98 | 7 |
| PhI | Me ₃ SnCN | IIc | CH ₂ Cl ₂ | 40 | 36 | 8 |
| PhI | NaCN-Al ₂ O ₃ | IId | Toluene | 80 | 98 | 11 |
| PhI | Zn(CN) ₂ | IIb | DMF | 80 | (92) | 13 |
| PhI | KCN | IIIb | NMP | 60 | 98 | 20 |
| PhI | H ¹¹ CN, KOH | Ile | THF | 90 | 95 ± 5 ^c | 28 |
| PhI | NaCN | IV | Dioxane | Reflux | 91 | 33 |
| PhI | NaCN, ZnCl ₂ | V | Heptane, H ₂ O | Reflux | 99 | 31 |
| PhI | KCN | IIf | THF | Reflux | 100 ^d | 32 |
| PhBr | KCN | Ib | HMPA | 90 | 94 | 4 |
| PhBr | NaCN | IIg | Toluene | 80 | 98 | 11 |
| PhBr | Zn(CN) ₂ | IIh | DMF | 80 | (94) | 13 |
| PhBr | KCN | IIIi | Benzene | 100 | 93 ^e | 26 |
| PhBr | H ¹¹ CN, KOH | Ile | THF | 90 | 90 ^c | 28 |
| PhBr | Zn(CN) ₂ | IIIc | Wet DMF | 120 | (95) | 22 |
| PhBr | NaCN | IV | Dioxane | Reflux | 85 | 33 |
| PhCl | H ¹¹ CN, KOH | Ile | THF | 90 | 45 ^c | 28 |
| PhCl·Cr(CO) ₃ | H ¹¹ CN, KOH | IIj | DMSO | 135 | 95 ^c | 28 |
| PhCl | Et ₄ NCN | IIk | DMF ^f | 130 | 96 ^g | 39 |
| PhOTf | KCN | IIId | NMP | 60 | 94 | 19 |
| PhOTf | H ¹¹ CN, KOH | Ile | THF | 90 | 62 ^c | 28 |

^aIa = 1 mol % Pd(OAc)₂, NaOEt. Ib = 1.5 mol % Pd(OAc)₂, KOH, KI. IIa = 1 mol % Pd(PPh₃)₄. IIf = 2 mol % Pd(PPh₃)₄. IIc = 18 mol % Pd(PPh₃)₄. IId = 10 mol % Pd(PPh₃)₄. Ile = 2–4 mol % Pd(PPh₃)₄, kryptofix[®] 2.2.2. IIg = 5 mol % Pd(PPh₃)₄, CuI. IIh = 10 mol % Pd(PPh₃)₄, Al₂O₃. IIi = 6 mol % Pd(PPh₃)₄. IIIi = 20 mol % Pd(PPh₃)₄, 18-crown-6. IIj = 2–13 mol % Pd(PPh₃)₄. IIk = 0.125 mol % Pd(PPh₃)₄, -0.3 to -0.8 V (reducing potential). IIIa = 0.5 mol % Pd₂(dba)₃·CHCl₃. IIIb = 0.5 mol % of Pd₂(dba)₃·CHCl₃, dppf. IIIc = 0.05 mol % Pd₂(dba)₃, dppf. IIId = 2 mol % Pd₂(dba)₃·CHCl₃, dppf. IV = 0.3 mol % PhPdBr{PPh₂(bc-5)}₂. V = 2 mol % PdCl₂{PPh₂(ms)}₂, NaBH₄.

^bGLC yield. Yields in parentheses are isolated ones.

^cRadiochemical yield.

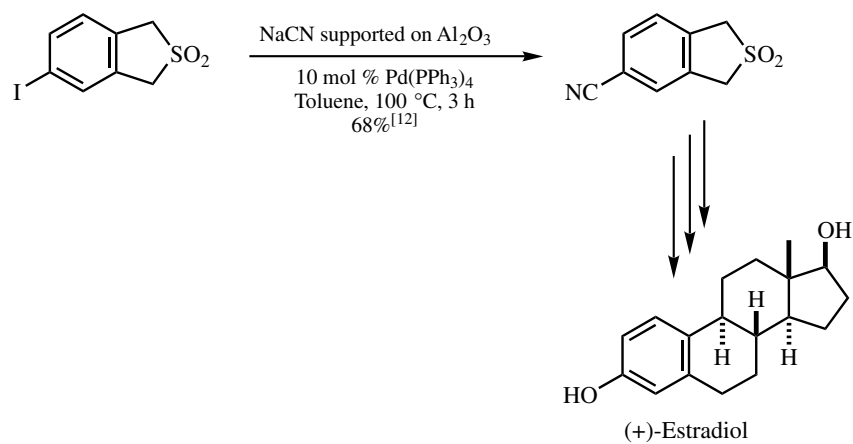
^dConversion.

^eThe yield is not specified as GLC or isolated.

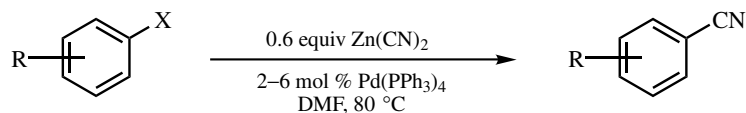
^f0.1 M solution of Et₄NCl.

^gNumber of catalyst turnovers.

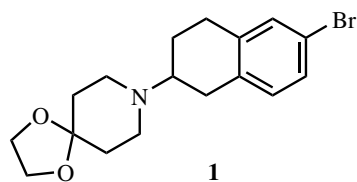
Although the Pd(PPh₃)₄-catalyzed cyanation of aryl bromides with KCN or NaCN does not take place under ordinary conditions, Zn(CN)₂ as the cyanide source enables the reaction in DMF at 80 °C. The solubility of Zn(CN)₂ is lower than that of KCN or NaCN and the covalency of the Zn–CN bond is higher than that of K–CN or Na–CN. Therefore, the concentration of free CN[−] must be a minimum in the reaction solution using Zn(CN)₂ as the metal cyanide. Thus, Zn(CN)₂ is probably able to maintain the active form of the Pd⁰ catalyst over a longer period of time than KCN or NaCN (Scheme 6).^{[13],[14]} Zn(CN)₂ is also an effective cyanide source for the Pd⁰-catalyzed reaction of aryl triflates (Schemes 7–10).^{[15]–[18]}



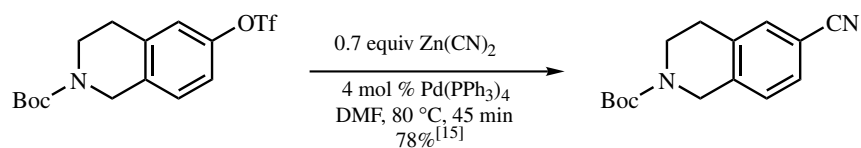
Scheme 5



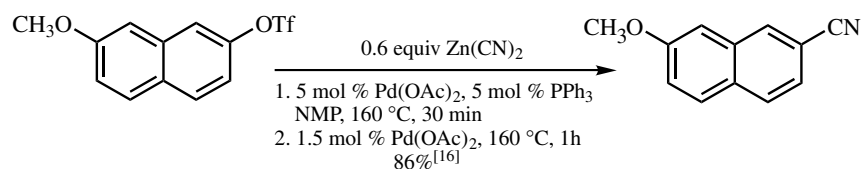
R (or **1**), X, Reaction time (h), Isolated yield (%)^[13] = H, I, 0.5, 92; *p*-CH₃O, I, 0.5, 92; 2-NH₂-5-CH₃CO, I, 0.5, 90; H, Br, 6, 94; *p*-CH₃CO, Br, 5.5, 91; *p*-CH₃O, Br, 7, 95; *p*-CH₃, Br, 6, 84; *p*-NO₂, Br, 6, 92; (**1**), Br, 5–6, 92.



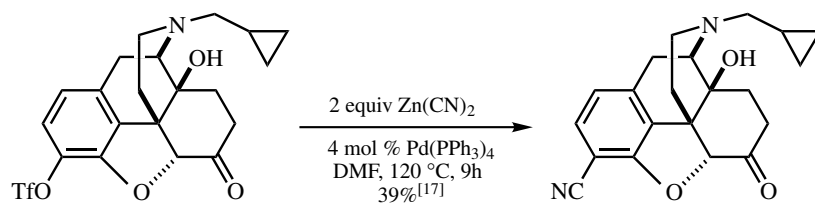
Scheme 6



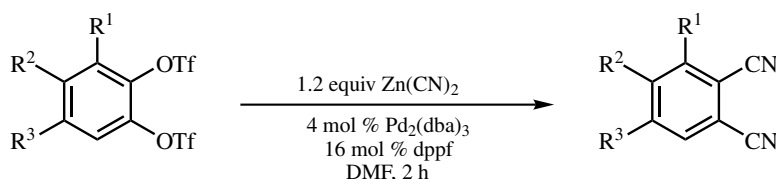
Scheme 7



Scheme 8



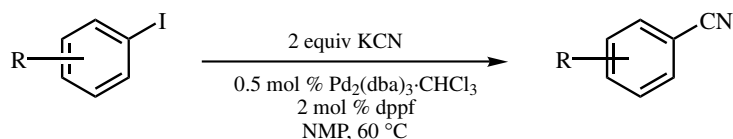
Scheme 9



R^1 , R^2 , R^3 (or R^1 , R^2 - R^3), Reaction temperature (°C), Isolated yield (%)^[18] = H, CH_3 , H, 70, 92; CH_3 , H, H, 90, 88; H, $\text{CO}_2\text{C}_2\text{H}_5$, H, 60, 98; $(\text{CH}_2)_4\text{CO}_2\text{CH}_3$, H, H, 90, 81; H, $\text{CH}_2\text{CH}(\text{NHBoc})\text{CO}_2\text{CH}_3$, H, 60, 95; H, $\text{C}_2\text{H}_4\text{CO}_2\text{C}_2\text{H}_5$, $\text{C}_2\text{H}_4\text{CO}_2\text{C}_2\text{H}_5$, 60, 75; (H,—CH=CH—CH=CH—), 70, 85.

Scheme 10

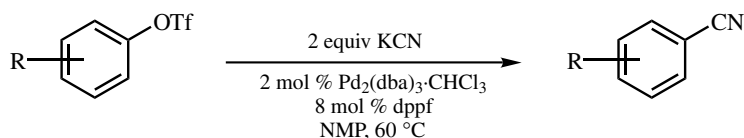
Pd^0 containing the dppf ligand exhibits a higher catalytic efficiency than $\text{Pd}(\text{PPh}_3)_4$ for the cross-coupling, partly because of the robust binding of dppf to Pd^0 compared with PPh_3 . The complex is usually prepared *in situ* from $\text{Pd}_2(\text{dba})_3$ or $\text{Pd}(\text{dba})_2$ and dppf and enables the reaction of aryl iodides or aryl triflates with KCN in NMP or DMF (**Schemes 11 and 12**).^{[6,18]–[20]} This catalyst is utilized in the synthesis of benzodiazepine derivatives (**Scheme 13**).^[21] When $\text{Zn}(\text{CN})_2$ is used as the cyanide source, the catalytic cyanation of aryl bromides and even one of aryl chlorides are achieved by the catalyst system in wet DMF and *N,N*-dimethylacetamide, respectively. Reactions of aryl bromides or electron-deficient aryl chlorides take place at 120 °C and ones of electron-rich aryl chlorides take place at 150 °C (**Schemes 14 and 15**).^{[22],[23]} $\text{Pd}(\text{dppf})_2$ or Pd^0 , generated *in situ* from Pd^{2+} , dppf, and Zn, enables the catalytic reaction of aryl bromides with KCN (**Scheme 16**).^[24]



R, Reaction time (h), Isolated yield (%), Remark^[20] = *p*- COCH_3 , 2, 94, -; *p*-Cl, 2, 93, -; *p*- CH_3 , 4, 94, -; *p*- CH_3O , 1, 92, 80 °C; *m*- CO_2CH_3 , 2, 96, -; *o*- CO_2CH_3 , 8, 93, -; *o*- CH_3 , 4, 87, -.

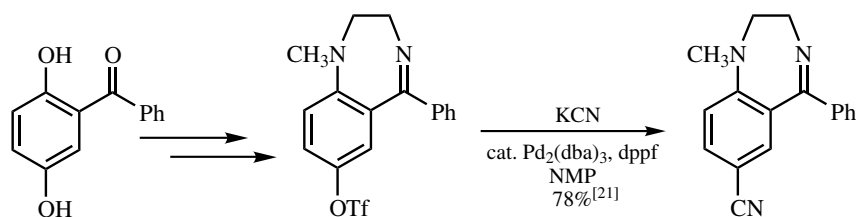
Scheme 11

The utility of additives often provides a beneficial effect on the cross-coupling reaction using CN^- as the carbon nucleophile by adjusting both the concentration and the reactivity of CN^- in the reaction media. First, the addition of a phase-transfer catalyst (PTC) like 18-crown-6 (**Schemes 17 and 18**),^{[25]–[27]} kriptofix® 2.2.2,^[28] or 12-crown-4 (**Scheme 19**)^{[29],[30]} to the reaction mixture allows the $\text{Pd}(\text{PPh}_3)_4$ -catalyzed

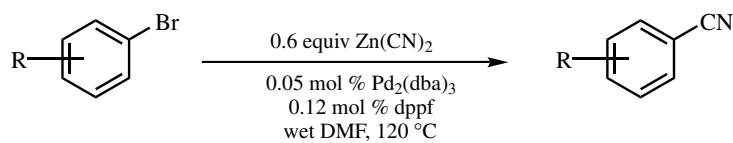


R (or Ar), Reaction time (h), Isolated (or GLC) yield (%)^[20] = H, 8, (94); *p*-COCH₃, 3, 92; *p*-Cl, 3, (94); *p*-CH₃, 25, 87; *p*-CN, 2, 95; *p*-CO₂CH₃, 3, 94; *p*-NO₂, 2, 90; *p*-C₆H₅, 8, 92; *p*-CH₃O, 25, (45); *p*-NHCOCH₃, 25, (35); (2-Naphthyl), 4, 91; (2-Oxo-2*H*-benzopyran-7-yl), 2, 98; (8-Quinolyl), 2, 95.

Scheme 12

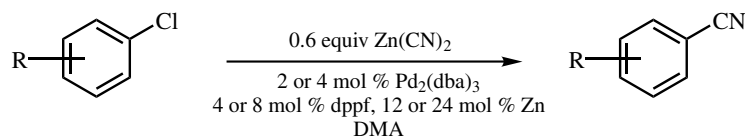


Scheme 13

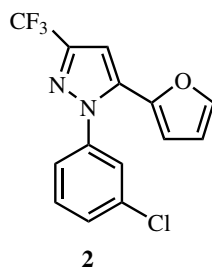


R (or Ar), Reaction time (h), Isolated yield (%)^[22] = H, 72, 95; *o*-CH₃O, 72, 87; (1-Naphthyl), 72, 91; (2-Methyl-6-amino-3-pyridyl), 20, 94.

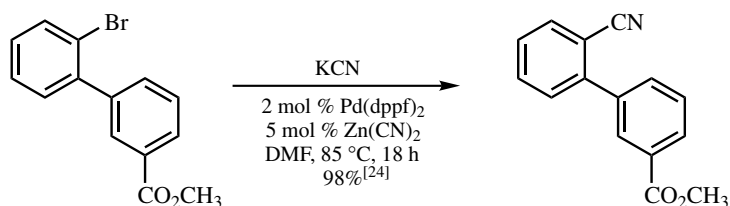
Scheme 14



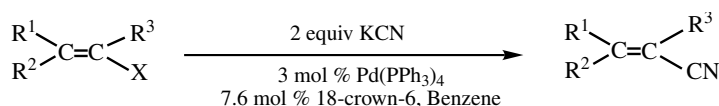
R (or Ar or 2), Reaction time (h), Reaction temperature (°C), Isolated yield (%)^[23] = *o*-F, 12, 150, 85; *o*-CO₂CH₃, 2, 120, 93; *p*-CH₃O, 4, 150, 88; *m*-CO₂CH₃, 10, 120, 91; *p*-CO₂CH₃, 2, 120, 97; *p*-CHO, 0.75, 120, 92; (1-Naphthyl), 2, 150, 96; (2), 10, 150, 91.



Scheme 15

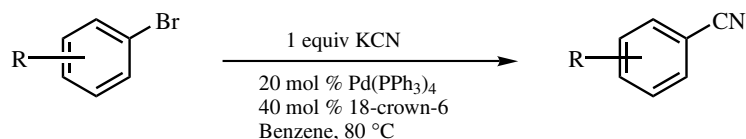


Scheme 16



R¹, R², R³, X, Reaction temperature (°C), Reaction time (h), Isolated (or GLC) yield (%), Isomeric purity (%), Remark^[25] = Ph, H, H, Br, 70–75, 2, 94, 97, -; Ph, H, H, Br, 70–75, 2, 95, 97, NaCN and 15-crown-5; Ph, H, H, Cl, 95–100, 15, 84, 97, -; H, Ph, H, Br, 55–60, 6, 94, 97, -; C₄H₉, H, H, Br, 100, 12, (96), 99, -; H, C₄H₉, H, Br, 100, 12, (98), 99, -; Ph, CH₃, H, Br, 90–95, 10, 93, 92, -; Ph, Ph, H, Br, 90–95, 5, 98, -, -; Ph, Ph, Ph, Br, 90–95, 15, 85, -, -.

Scheme 17

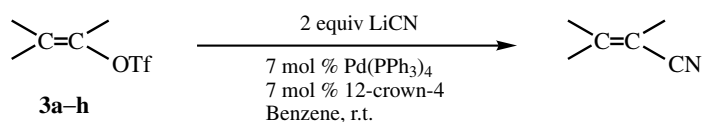


R, Yield (%), Remark^[26] = H, 93, 100 °C for 65 h; *p*-CO₂CH₃, 95, -; *p*-CH₃S, 97, -; *p*-CH₃O, 85, 70 °C; *p*-CH₃, 85, -; *m*-CO₂CH₃, 87, -; *m*-CH₃S, 92, -; *m*-CH₃O, 81, 70 °C; *m*-CH₃, 87, -.

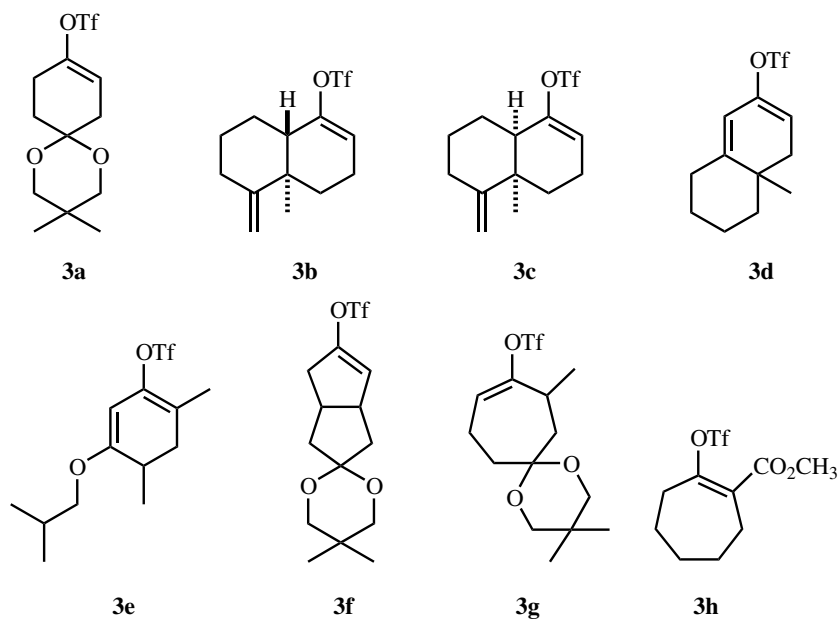
Scheme 18

reaction of not only the aryl or alkenyl iodides or triflates but also the aryl or alkenyl bromides with KCN or LiCN to smoothly occur in benzene, THF, or DMF. Here, the configurations of the alkenyl carbons are mainly retained throughout the reaction.^{[25],[26],[31],[32]} When crown-ethers are bound to a phosphorus ligand, the Pd complex containing such ligands shows a good catalytic effect for the reaction of aryl bromides with NaCN (**Scheme 20**).^[33] The high reactivity of the crowned complexes is attributed to a proximity effect as in enzyme chemistry. A sulfonated phosphorus ligand allows the Pd⁰-catalyzed reaction to occur under heptane–water two-phase conditions by the mechanism of counter phase-transfer catalysis using the *in situ* generated Zn(CN)₄²⁻ as the cyanide source (**Scheme 21**).^[31]

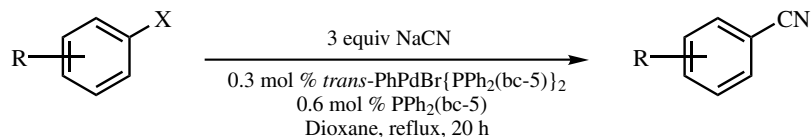
Second, the addition of a catalytic amount of second metal salts, especially CuI, to the reaction mixture accelerates the Pd⁰-catalyzed cyanation.^{[32],[34],[35]} Nitrile solvents are the best reaction media for the Cu⁺ cocatalyzed processes (**Scheme 22**). The activating effect of Cu⁺ is attributed to the role of vehicle transferring the CN⁻ between the poorly soluble cyanide source and the Pd²⁺ intermediate.^[32] The same role exerted by the Pd²⁺ species is also proposed for the Pd⁰-catalyzed reaction.^[5] CuCN itself is an effective source of cyanide (**Scheme 23**).^{[36]–[38]}



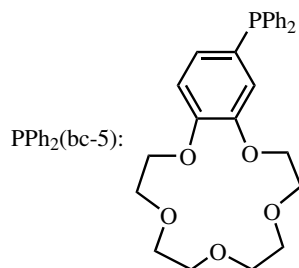
3, Reaction time (h), Isolated yield (%), Remark^[30] = **3a**, 2, 80, -; **3b**, 2, 89, -; **3c**, 2.5, 87, -; **3d**, 3, 78, -; **3e**, 2, 85, -; **3f**, 20, 76, Additional 7 mol % Pd(PPh₃)₄; **3g**, 2, 78, -; **3h**, 4, 59, Additional 21 mol % of Pd(PPh₃)₄.



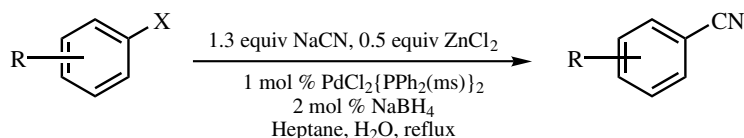
Scheme 19



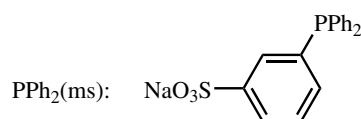
R, X, GLC yield (%)^[33] = H, Br, 85; *p*-CH₃, Br, 92; *p*-Cl, Br, 93; *p*-CH₃O, Br, 86; H, I, 91; *m*-Cl, I, 87.



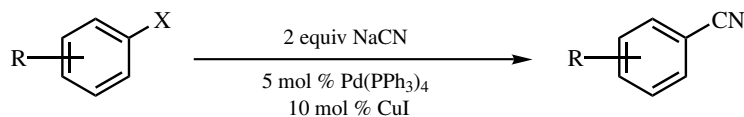
Scheme 20



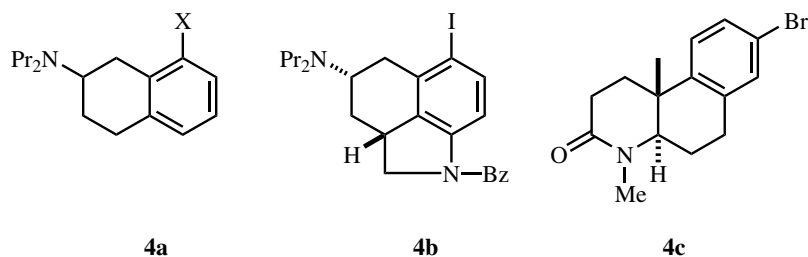
R (or Aryl), X, Reaction time (h), GLC yield (%), Remark^[31] = *p*-CH₃O, I, 7, 98, -; *p*-Cl, I, 5, 90, -; *p*-Br, I, 3, 82, *p*-CN (13%); *p*-CH₃CO, I, 1, 97, -; *p*-CO₂C₂H₅, I, 3, 94, -; *m*-Cl, I, 3, 98, -; *m*-CF₃, I, 3, 98, -; *o*-CH₃O, I, 24, 78, -; (1-Naphthyl), I, 7, 97, -; *p*-CN, Br, 7, 88, -; *p*-CH₃CO, Br, 10, 95, -.



Scheme 21



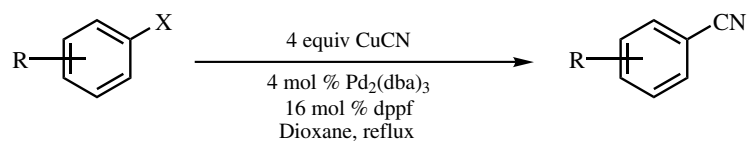
R (or Aryl or **4**), X, Solvent, Reaction temperature (°C), Reaction time (h), Conversion (or Isolated yield) (%), Remark^[32] = *p*-CH₃O, I, THF, -, 4, 97, KCN; H, I, THF, 1, 100, KCN; *p*-COCH₃, I, THF, -, 1, 100, KCN; *p*-NO₂, THF, -, 5, 48, KCN; *p*-(1-pyrrolyl), CH₃CN, reflux, 1, (90), -; (1-Naphthyl), I, THF, -, 1, 100, KCN; (1-Naphthyl), Br, CH₃CN, reflux, 7, 97, -; (1-Naphthyl), OTf, CH₃CN, reflux, 1, (90), -; (8-Quinolyl), OTf, CH₃CN, reflux, 1, (87), -; (3-pyridyl), Br, C₂H₅CN, reflux, 4, (71), -; (5-Indolyl), Br, Valeronitrile, 115, 2, (76), -; (**4a**), I, CH₃CN, reflux, 1, (92), -; (**4a**), Br, C₂H₅CN, reflux, 6, (91), -; (**4b**), I, THF, reflux, 3, (89), 1.1 equiv KCN; (**4c**), Br, C₂H₅CN, reflux, 2, (83), -.



Scheme 22

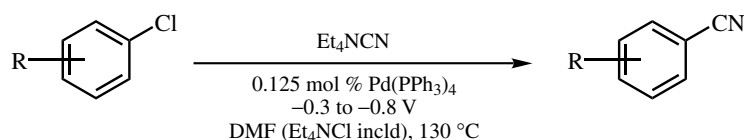
Electrochemical reduction provides a powerful method for maintaining the activity of the Pd⁰ catalyst. Following this method, catalytically inactive Pd species formed in deleterious side reactions with CN⁻ are electrochemically intercepted and restored to a catalytically active state. Under these conditions, aryl chlorides undergo cross-coupling with CN⁻ at 130 °C in DMF (Scheme 24)^[39] Binding to a Cr(CO)₃ fragment to form the π -complex is another way of activating aryl chlorides for the attack of CN⁻ in the presence of Pd⁰ catalyst.^[28]

The Pd⁰-catalyzed cross-coupling with CN⁻ is applicable to heteroaryl electrophiles. In general, the reactivity of the heteroaryl electrophile is so high that substrates containing not only I⁻, Br⁻, or OTf⁻ but also Cl⁻ as a nucleofuge are subject to the



R (or Heteroaryl), X, Et₄NCN (equiv), Reaction time (h), Isolated yield (%)^[38] = *p*-CH₃O, I, 1, 2, 82; *p*-CO₂CH₃, I, 1, 1, 88; *p*-NO₂, I, 1, 2, 65; *o*-CH₃O, I, 1, 1, 94; *o*-CO₂CH₃, I, 1, 1, 88; *o*-NO₂, I, 1, 1, 67; *p*-CH₃O, Br, 1, 3, 91; *p*-CO₂CH₃, Br, 1, 1, 89; *p*-NO₂, Br, 1, 3, 56; *o*-CH₃O, Br, 1, 1, 76; *o*-CO₂CH₃, Br, 1, 1, 83; *o*-NO₂, Br, 1, 1, 23; (1-Phenylsulfonyl-2-indolyl), I, -, 3, 94; (1-Phenylsulfonyl-3-indolyl), I, -, 4, 99; (1-Phenylsulfonyl-2-pyrrolyl), I, -, 1, 97; (1-Phenylsulfonyl-3-pyrrolyl), I, -, 1, 69; (3,5-Dimethyl-1-phenylsulfonyl-4-pyrazolyl), I, -, 1, 90; (2-Quinolyl), Br, 1, 1, 77; (2-Quinolyl), I, -, 1, 90; (3-Quinolyl), I, -, 91; (2-Methyl-4-quinolyl), I, -, 1, 96.

Scheme 23

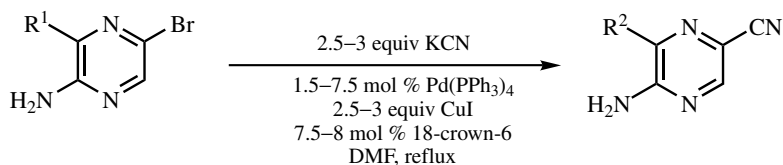


R, Catalyst turnover^[39] = H, 96; *p*-CF₃, 162; *p*-CH₃, 2; *m*-CF₃, 130.

Scheme 24

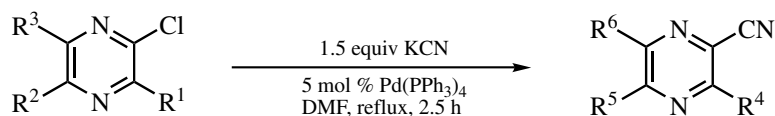
reaction with CN⁻. Pyrazinecarbonitriles,^{[34],[40]} 9*H*-purinecarbonitriles,^{[41],[42]} 7*H*-purinecarbonitriles,^[41] and 4(3*H*)-pyrimidinonecarbonitrile^[43] are synthesized using the Pd⁰-catalyzed methodology (Schemes 25–28).

Cross-coupling of allyl acetates or carbonates with CN⁻ requires the catalysis of the Pd⁰ complex. As a cyanide source, the utility of Me₃SiCN is essential for the reaction (Scheme 29).^[44]



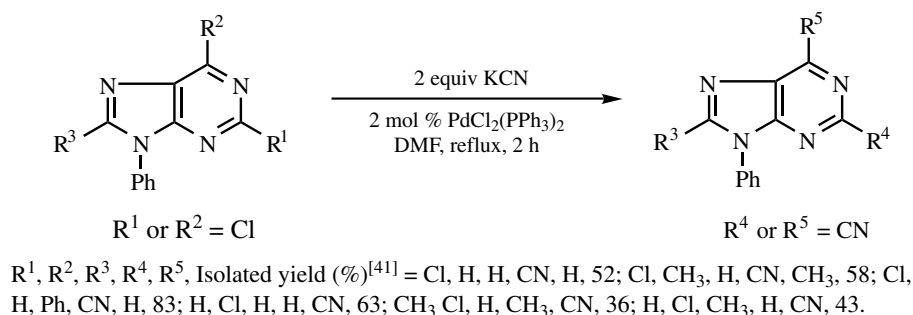
R¹, R², Reaction time (h), Isolated yield (%)^[34] = H, H, 2, 88; Br, CN, 1, 50.

Scheme 25

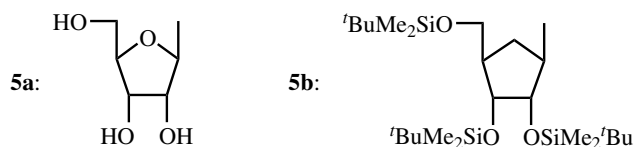
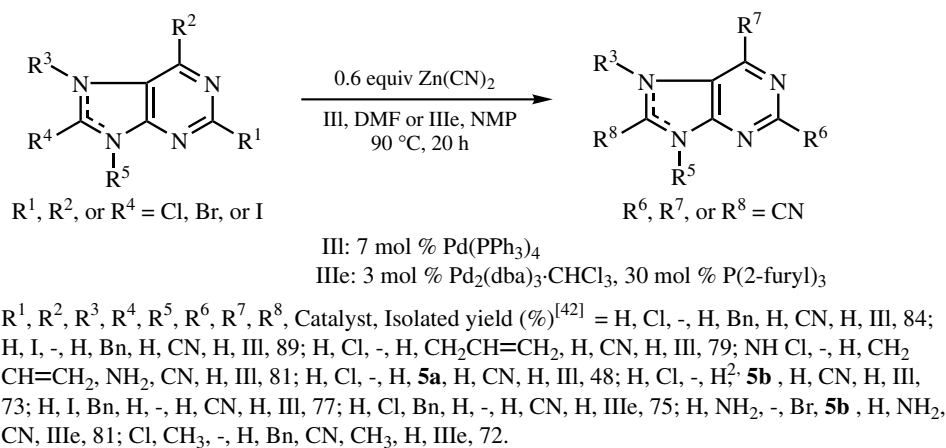


R¹, R², R³, R⁴, R⁵, R⁶, Isolated yield (%)^[40] = H, Ph, Ph, H, Ph, Ph, 81; Ph, H, Ph, Ph, H, Ph, 31; Ph, Ph, H, Ph, Ph, H, 98; CH₃, H, CH₃, CH₃, H, CH₃, 80; *i*-C₃H₇, H, *i*-C₃H₇, *i*-C₃H₇, H, *i*-C₃H₇, 47; *i*-C₄H₉, H, *i*-C₄H₉, *i*-C₄H₉, H, *i*-C₄H₉, 77; H, Ph, CH₃, H, Ph, CH₃, 66; CH₃, Ph, H, CH₃, Ph, H, 58; *i*-C₄H₉, Cl, *i*-C₄H₉, *i*-C₄H₉, CN, *i*-C₄H₉, 76; Ph, Ph, Cl, Ph, CN, 68; Cl, Ph, Ph, CN, Ph, Ph, 16.

Scheme 26



Scheme 27

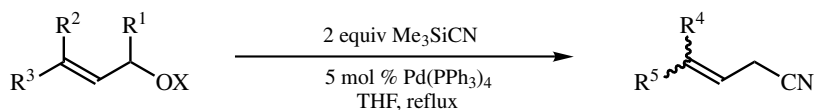


Scheme 28

The kinetic studies of catalytic cyanation of iodobenzene with KCN^[5] and reductive elimination from the complexes (diphosphine)Pd(R)(CN)^[45] have been investigated.

C. MULTICOMPONENT COUPLING INVOLVING CAPPING WITH CN⁻

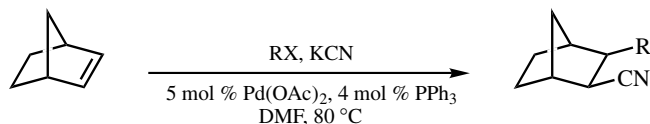
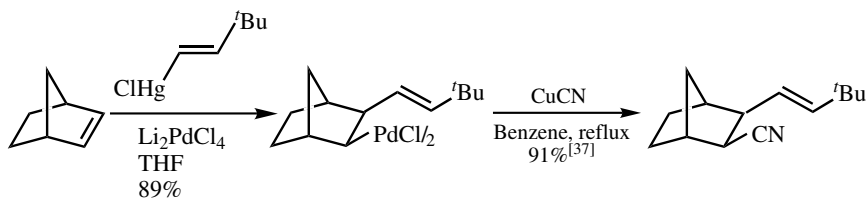
Besides its use as the carbon nucleophile in cross-coupling reactions with carbon electrophiles containing appropriate nucleofuges, CN⁻ is also an available capping agent in Pd⁰-catalyzed multicomponent-coupling reactions. The inceptive stepwise process was employed in the synthesis of the prostaglandin analog, where organopalladium intermediates, generated through the Pd²⁺ mediated addition of alkenylmercurials to norbornene, are captured by CuCN (**Scheme 30**).^{[36],[37]} In spite of the inherent malicious property of CN⁻ to Pd species, tandem assembly ending on the capping with CN⁻ is attained for the three components of alkenyl or aryl halides, norbornene, and KCN (**Schemes 31**



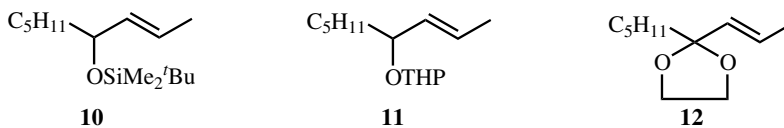
6 ($\text{R}^1, \text{R}^2, \text{R}^3, \text{X}$), (or **8** (Y) or **9** (Z)), **7** (R^4, R^5) (or **8** (Y) or **9** (Z)), Reaction time (h), Isolated (or GLC) yield (%), *E/Z*, Remark^[44] = **6** (H, H, Ph, COCH₃), **7** (H, Ph), 16, (98), >99, -; **6** (Ph, H, H, COCH₃), **7** (H, Ph), 23, 82, >99, -; **6** (H, H, Ph, CO₂CH₃), **7** (H, Ph), 16, 92, >99, -; **6** (H, H, C₃H₇, CO₂CH₃), **7** (H, C₃H₇), 5, 78, 80/20, -; **6** (H, CH₃, (CH₃)₂C=CHCH₂CH₂, CO₂CH₃), **7** (CH₃, (CH₃)₂C=CHCH₂CH₂), 5, 89, 71/29, -; **6** (H, (CH₃)₂C=CHCH₂CH₂, CH₃, CO₂CH₃), **7** (CH₃, (CH₃)₂C=CHCH₂CH₂), 5, 80, 71/29, -; (**8** (OCO₂CH₃)), **8** (CN)), 15, 92, -, Pd(CO)(PPh₃)₃ in toluene under reflux; (**9** (OCO₂CH₃)), (**9** (CN)), 18, 88, -, -.



Scheme 29

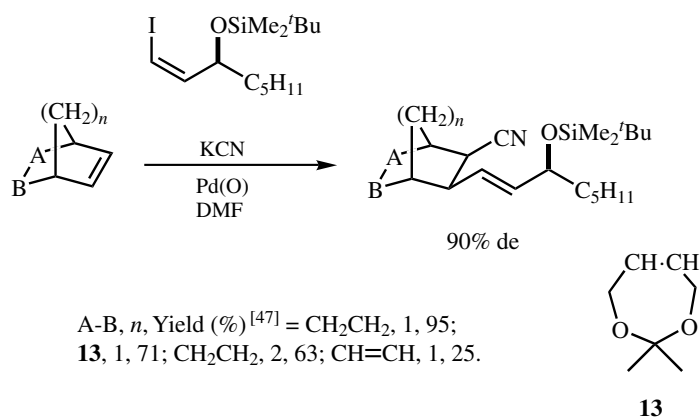


R, X, Reaction time (h), Isolated yield (%)^[46] = (*E*)-Styryl, Br, 12.5, 81; **10**, I, 18, 65; **11**, I, 12.5, 60; **12**, I, 12, 70; (*E*)-1-Hexenyl, I, 12, 74; Ph, I, 12, 68; *p*-Anisyl, 12, 72; *p*-*t*-Butylphenyl, I, 12, 73; 1-Naphthyl, Br, 12.5, 52.

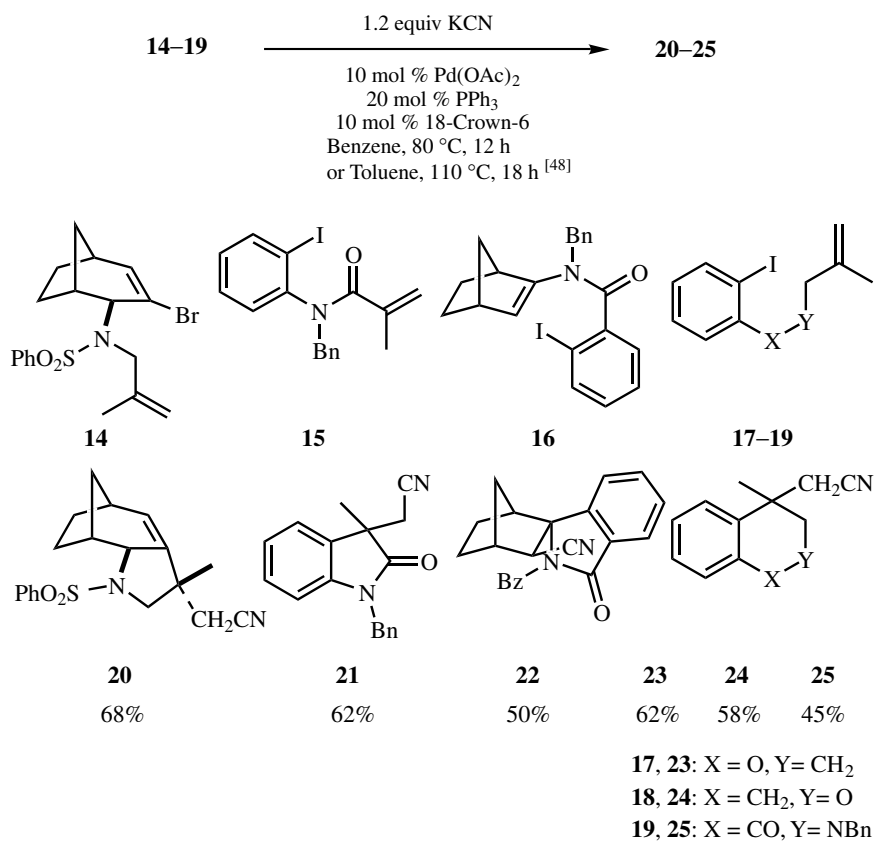


Scheme 31

and **32**),^{[46],[47]} or alkenyl or aryl halides, tethered alkenes, and KCN (**Scheme 33**)^[48] by the catalysis of Pd⁰. The three-component coupling of activated olefins, allylic chlorides, and Me₃SiCN also proceeds very well (**Scheme 34**).^[49] In the presence of CO, the insertion of CO into C—Pd bonds precedes the capture of the organopalladium intermediates with CN[−], resulting in the production of acylpalladium intermediates, which finally react with CN[−] to yield acyl cyanides. In this way, aroyl cyanides are obtained by the

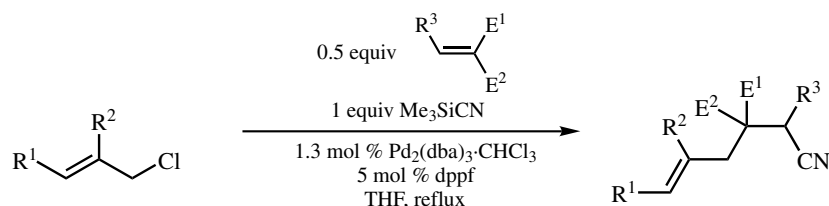


Scheme 32



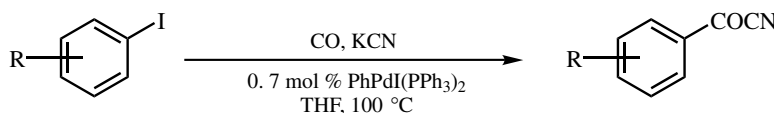
Scheme 33

Pd⁰-catalyzed reaction between aryl halides, CO, and KCN (**Scheme 35**).^[50] The tandem four-component assembly is possible for the combination of aryl halides, alkynes, CO, and KCN, which yields β -aryl substituted alkenoyl cyanides by the catalysis of Pd⁰ (**Scheme 36**).^[51]



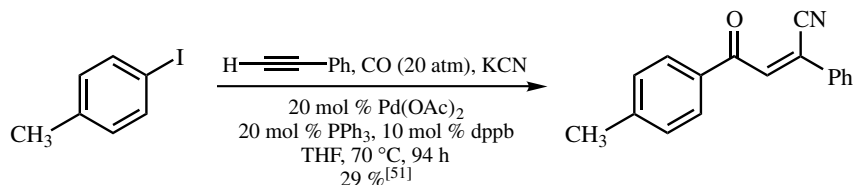
R¹, R², R³, E¹, E², Isolated yield (%), Diastereomer ratio^[49] = H, H, Ph, CN, CN, 89, -; H, H, *p*-CH₃OC₆H₄, CN, CN, 80, -; H, H, *p*-CH₃C₆H₄, CN, CN, 84, -; H, H, *p*-CH₃O₂CC₆H₄, CN, CN, 82, -; H, H, *n*-C₅H₁₁, CN, CN, 77, -; H, H, *t*-C₄H₉, CN, CN, >99, -; H, H, *i*-C₃H₇, CN, CN, 86, -; H, H, Ph, CN, CO₂C₂H₅, 34, 67:33; H, H, *n*-C₅H₁₁, CN, CO₂C₂H₅, 48, 46:36; H, CH₃, *t*-C₄H₉, CN, >99, -; CH₃, H, *t*-C₄H₉, CN, CN, 74, -; Ph, H, *t*-C₄H₉, CN, CN, 74, -; H, Cl, *t*-C₄H₉, CN, CN, 40, -.

Scheme 34



R (or Aryl), *P*_{CO} (atm), Reaction time (h), GLC yield (%)^[50] = H, 20, 20, 91; *p*-CH₃O, 20, 15, 92; *p*-CH₃, 8, 18, 69; (2-Thienyl), 8, 24, 45.

Scheme 35



Scheme 36

D. SUMMARY

1. Pd-catalyzed nucleophilic displacement of carbon electrophiles with CN⁻ provides an efficient synthetic method of aryl or alkenyl cyanides from the corresponding aryl or alkenyl halides or triflates. Compared to the Rosenmund–von Braun reaction, the advantages of the present method are the necessarily mild reaction conditions, compatibility with a variety of functional groups, and simple work-up procedures.

2. In the most Pd-catalyzed reactions, Zn(CN)₂ and dppf give the best results as the metal cyanide and commercially available ligand, respectively.

3. The reaction using aryl or alkenyl chlorides as carbon electrophiles is still not easy. The development of an efficient Pd catalyst, which maintains the active form of Pd at such high temperatures that the less reactive chlorides can react with Pd⁰, is highly desired.

4. For the same conversion, a Ni-based catalyst is also available.^[52] The Pd catalyst is commonly used for the cyanation but this tendency does not necessarily stem from the fact that Pd is more reactive in this reaction than Ni but stems from the fact that the Pd-based one is usually simpler to prepare, purify, handle, and store than Ni. One should try the reaction using a Ni catalyst together with one using Pd, if the reactivity of the substrate is low.

5. The utility of CN^- as a capping agent in a multicomponent-coupling reaction has only been studied using limited combinations. Judging from the synthetic versatility of the nitrile functional group in products, further study is desired to find new combinations of available components.

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