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# β-Aryl Nitrile Construction *via* Palladium-Catalyzed Decarboxylative Benzylation of α-Cyano Aliphatic Carboxylate Salts

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**Abstract:** The palladium-catalyzed decarboxylative benzylation of α-cyano aliphatic carboxylate salts with benzyl electrophiles was discovered. This reaction exhibits good functional group compatibility and proceeds under relatively mild conditions. A diverse range of quaternary, tertiary and secondary β-aryl nitriles can be conveniently prepared by this method.

**Keywords:** benzyl chlorides; carboxylates; decarboxylative benzylation; nitriles; palladium

## Introduction

Transition metal-catalyzed decarboxylative cross-coupling represents a useful strategy for carbon-carbon bond construction in modern synthetic organic chemistry.[1] Inspired by the seminal work of Myers[2] and Gooßen,[3] catalytic decarboxylative coupling reactions of aromatic[4], alkenyl[5] and alkynyl[6] carboxylic acids have been intensively studied. More recently we developed a palladium-catalyzed decarboxylative arylation of some aliphatic carboxylate salts with aryl halides. Related studies were also reported by Studer and Kwong et al.[7] Tunge et al. reported excellent studies on intramolecular decarboxylative allylations of some activated carboxylate allylic esters.[8] Recently, Tunge et al. reported an intramolecular decarboxylative benzylation of β-keto esters, but the benzyl groups participating in this chemistry were limited to benzyls with extend conjugations.[9] To the best of our knowledge, intermolecular decarboxylative benzylation of aliphatic carboxylates has not been explored. Because catalytic reactions involving π-benzyl-Pd intermediates are important and have drawn broad attention,[10] we were interested in the intermolecular decarboxylative benzylation of α-cyano aliphatic carboxylates. Note that palladium-catalyzed intramolecular decarboxylative benzylations of α,α-disubstituted benzyl cyanoacetic esters have been recently reported by Tunge et al.[14b]

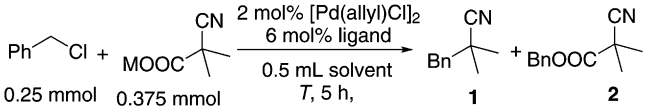
Traditionally, the β-aryl nitrile structures were constructed by strong base-mediated nucleophilic substitution of nitrile's α-C–H with benzyl halides.[11] The use of strong bases largely limits the substrate scope and ruins base-sensitive functional groups. In addition, for acetonitrile and primary nitriles, monobenzylation is often complicated due to the formation of multiply benzylated by-products. An alterative procedure is benzylation of cyanoacetate followed by hydrolysis and decarboxylation.[12] This procedure can be used for the synthesis of some secondary and tertiary β-aryl nitriles efficiently, but is unable to give the quaternary ones. Due to the importance of functionalized nitriles in both synthetic and medicinal chemistry,[13] we now report an intermolecular Pd-catalyzed decarboxylative benzylation reaction of α-cyano aliphatic carboxylate salts with benzyl electrophiles [Cl, OTFA, $OPO(OEt)_2$]. This reaction provides an efficient approach to construct a diverse range of functionalized quaternary, tertiary and secondary β-aryl nitriles. The reaction also represents the first example of intermolecular decarboxylative benzylation of aliphatic carboxylates, and expands the synthetic utility of the decarboxylative coupling methodology.

## Results and Disscussion

We initially chose benzyl chloride and potassium 2-cyano-2-methylpropanoate as the model substrates for screening the decarboxylative benzylation conditions (Table 1). First, we tested the catalyst consisting of $[Pd(allyl)Cl]_2$ and Xant-Phos which have been shown to be the best choice for our previously reported decarboxylative arylation process,[7b] but the for-

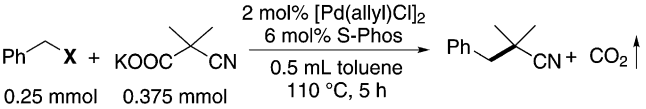
**Table 1.** Decarboxylative benzylation under various conditions.




| Entry | M | *T* | Ligand | Solvent | Yield [%][a] 1 | 2 |
|---|---|---|---|---|---|---|
| 1 | K | 140 °C | Xant-Phos | mesitylene | 8 | 53 |
| 2 | K | 140 °C | BINAP | mesitylene | 54 | 9 |
| 3 | K | 140 °C | DPPF | mesitylene | 80 | trace |
| 4 | K | 140 °C | DPE-Phos | mesitylene | 56 | trace |
| 5 | K | 140 °C | DPPPent | mesitylene | 71 | – |
| 6 | K | 140 °C | CataCXium A | mesitylene | 18 | – |
| 7 | K | 140 °C | Ph-Dave-Phos | mesitylene | 78 | – |
| 8 | K | 140 °C | *t*-BuX-Phos | mesitylene | 32 | – |
| 9 | K | 140 °C | Ru-Phos | mesitylene | 95 | – |
| 10 | K | 140 °C | X-Phos | mesitylene | 94 | – |
| **11** | **K** | **140 °C** | **S-Phos** | **mesitylene** | **98** | – |
| 12 | K | 140 °C | IPr•HCl | mesitylene | 74 | – |
| 13 | Na | 140 °C | S-Phos | mesitylene | 94 | – |
| 14[b] | Li | 140 °C | S-Phos | mesitylene | trace | – |
| 15 | K | 140 °C | S-Phos | DMA | 51 | – |
| 16 | K | 140 °C | S-Phos | diglyme | 95 | – |
| 17 | K | 140 °C | S-Phos | NMP | 57 | – |
| 18 | K | 140 °C | S-Phos | DMSO | 20 | 6 |
| 19 | K | 110 °C | S-Phos | mesitylene | 95 | – |
| **20** | **K** | **100 °C** | **S-Phos** | **mesitylene** | **95** | – |
| **21** | **K** | **110 °C** | **S-Phos** | **toluene** | **95** | – |

[a] GC yields using biphenyl as internal standard (average of two runs).
[b] Recovery of benzyl chloride in 90% yield.

**Table 2.** Survey of the benzyl electrophiles.




| Entry | X | Yield (GC) | Entry | X | Yield (GC) |
|---|---|---|---|---|---|
| 1 | Cl | 95% | 5 | OTFA | 86% |
| 2 | Br | 73% | 6 | $OPO(OEt)_2$ | 93% |
| 3 | OAc | 0% | 7 | OBoc | 12% |
| 4 | OTs | 64% | 8 | OCO(OEt) | 3% |

mation of benzyl ester (**2**) was observed (entry 1). Further experiments showed that the ratio of the decarboxylative benzylation product and benzyl ester was largely affected by the choice of the ligand. When dppf was used as the ligand, the decarboxylative benzylation product was obtained in 80% yield, accompanied with only a trace amount of the benzyl ester by-product (entry 3). Extensive screening of the ligands showed that Buchwald phosphines, such as S-Phos, X-Phos, Ru-Phos, were the best choice (entries 9, 10, and 11). When the combination of $[Pd(allyl)Cl]_2$ and S-Phos was employed, the desired transformation took place efficiently (98% yield) with no detection of the benzyl ester. We found that sodium salts can also serve as good substrates (entry 13), but the lithium salts failed to give any desired product (entry 14). Screening of the solvents revealed that non-polar arene solvents were good choices, whereas polar solvents were less effective (entries 15, 17, and 18). To our delight, the reaction can take place under relatively mild conditions (entry 20) and can proceed well in refluxing toluene (entry 21). Finally, we tested the intramolecular decarboxylative benzylation of benzyl 2-cyano-2-methylpropanoate under the optimized conditions but failed to obtain the benzylated product (see Supporting Information).[14]

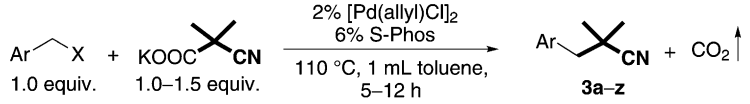
After finding the optimal conditions, we tested the scope of the leaving groups on the benzyl electrophiles. Data of the screening experiments are summarized in Table 2. Benzyl bromide, chloride, tosylate, trifluoroacetate and diethyl phosphate could serve as suitable electrophiles in this reaction. Benzyl carbonates such as OBoc and $OCO(OEt)_2$ gave low yields, while benzyl acetate could not be activated under the optimized conditions with total recovery of the starting material.

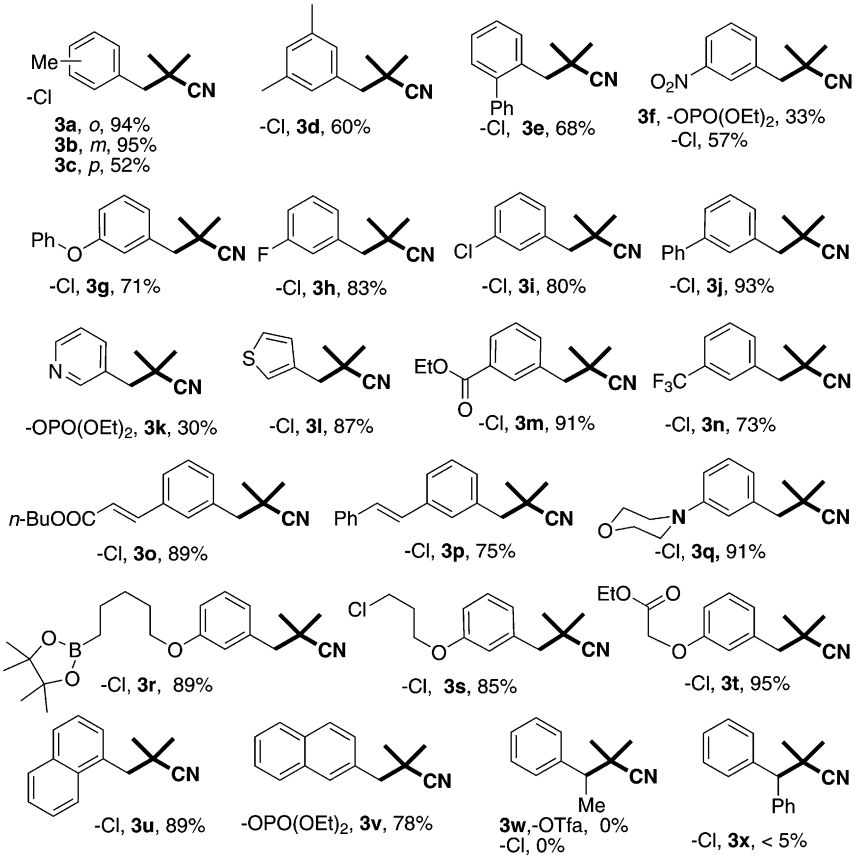
Table 3 illustrates the scope of the substituted benzyl electrophiles. From a convenience perspective, the inexpensive, stable benzyl chlorides can be easily prepared from the corresponding benzyl alcohol. For this reason, we decided to evaluate the scope of substituted benzyls mainly with this class of electrophiles.

To our delight, a variety of functionalized benzyl electrophiles could be well used for the benzylation of potassium 2-cyano-2-methylpropanoate under the optimized conditions with good to excellent yields. The electrophiles carrying substituents on *ortho* (**3a**, **3e**), *meta* (**3b**, **3d**), and *para* (**3c**) positions of the benzyl ring are all amenable substrates. The *para*-methyl substitution on the benzyl ring results in a relatively low yield (**3c**).[15] Benzyl electrophiles carrying either electron-withdrawing or electron-donating functional groups including alkyl (**3a**–**3d**), aryl (**3e**, **3j**), alkoxy (**3r**, **3s**, **3t**), aryloxy (**3g**), fluoro (**3h**), chloro (**3i**), trifluoromethyl (**3n**), ester (**3m**), C=C double bond (**3o**, **3p**), amine (**3q**), and nitro (**3f**) can all react with good yields of 52–95%. 3-Chloromethylthiophene can react and the product (**3l**) was obtained in 87% yield. Pyridine-3-methanol-derived phosphate can also react, albeit in relatively low yield (**3k**, 30%). It is important to note that alkyl pinacol boronate and alkyl chloride functionality can be well tolerated in the present transformation. In this way, products bearing useful β-aryl nitrile structures can be further transformed *via* other alkyl cross-coupling reactions.[16]

**Table 3.** Decarboxylative benzylation of 2-cyano-2-methylpropanoate salts.[a]



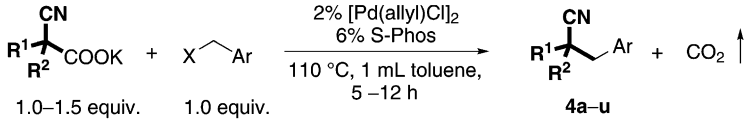

[a] Reactions were carried out on a 0.5 mmol scale. Yields are isolated yields based on the quantity of benzyl electrophiles. For more details see the Supporting Information.

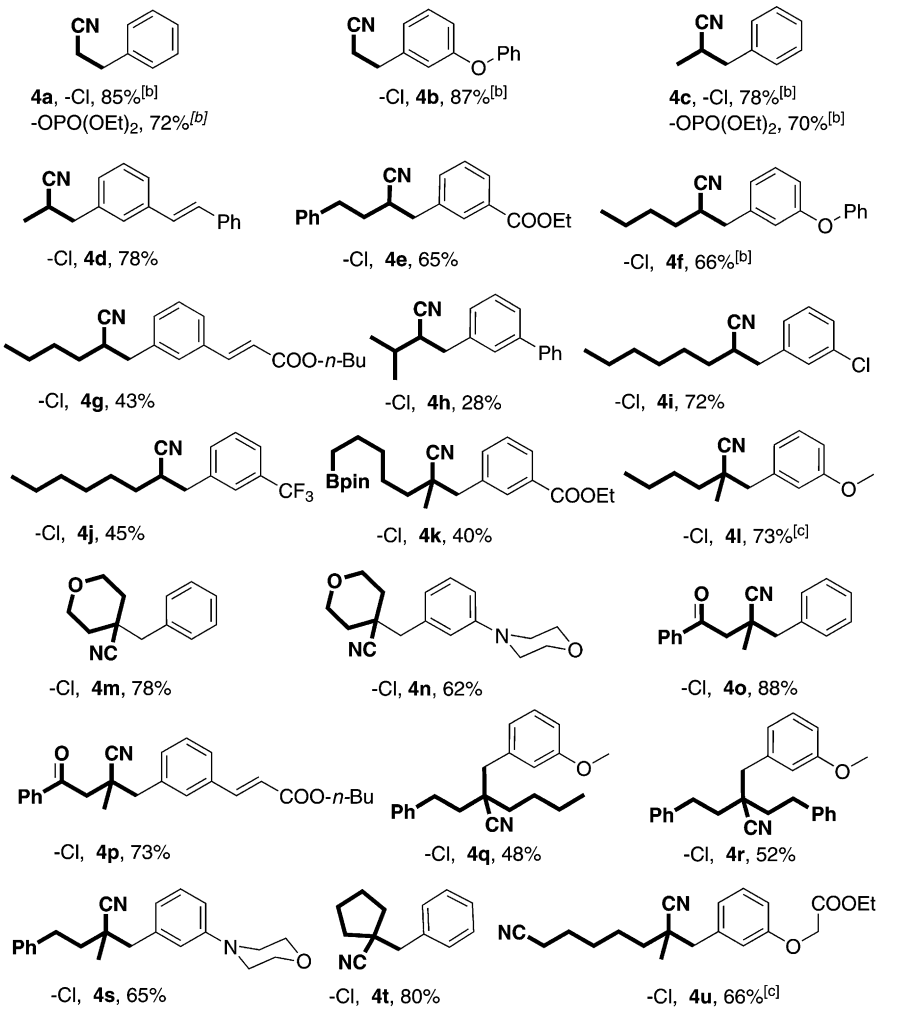
The presence of base sensitive, enolizable acidic C–H bond on the benzyl electrophiles can be well tolerated (**3t**) and the yield is 95%. The product can be further modified *via* reactions on enolizable C–H bond.[17] Note that this product (**3t**) is difficult to synthesize *via* strong base-mediated deprotonation/nucleophilic substitution pathways due to the presence of the acidic C–H moiety. Benzyl electrophiles with extended conjugations can also react, such as 1-chloromethyl naphthalene (**3u**) and 2-naphthyl methanol derived phosphate (**3v**). Unfortunately, α-substituted benzyl electrophiles failed to react under the present catalytic conditions (**3w**, **3x**).

We next explored the scope of the α-cyano aliphatic carboxylate salts (Table 4). Potassium cyanoacetate can react well with benzyl electrophiles to form 3-arylpropanenitriles cleanly without forming any dibenzylated by-product (**4a**, **4b**).[18] Tertiary α-cyano aliphatic carboxylate such as potassium 2-cyanopropanoate (**4c**, **4d**), potassium 2-cyano-4-phenylbutanoate (**4e**), potassium 2-cyanohexanoate (**4f**, **4g**), and potassium 2-cyanooctanoate (**4i**, **4j**) were all amenable to the decarboxylative benzylation reaction. The tertiary β-aryl nitrile products were obtained in moderate to good yields ranging from 43–78%. Potassium 2-cyano-3-methylbutanoate gave a low yield (**4h**, 28%). This is possibly due to the steric hindrance of the adjacent methyl group. Next, we examined the quaternary salt substrates particularly. Sodium 2-cyano-2-methylhexanoate can react well with 3-methoxybenzyl chlorides to afford the corresponding product (**4l**) in 73% yield. Quaternary α-cyano aliphatic carboxylate salts carrying aryl substitution on the aliphatic chain also serve as suitable substrates (**4q**, **4r**, **4s**). The aryl substituents on aliphatic chain expand the scope of salt substrates. Some other substituents on the aliphatic chain of the α-cyano aliphatic carboxylates were also investigated. The results show that a pinacol boronate functionality

**Table 4.** Decarboxylative benzylation of various α-cyano aliphatic carboxylate salts.[a]



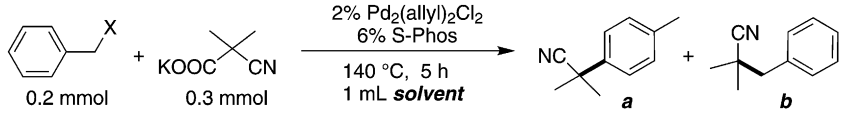




[a] Reactions were carried out on a 0.5 mmol scale. Isolated yields based on the quantity of benzyl electrophiles.
[b] Using X-Phos as the ligand.
[c] Sodium salt was used because the corresponding potassium salt is difficult to crystallize.

on the aliphatic chain can be well tolerated. This example illustrates that the alkyl decarboxylative benzylation shows selectivity toward traditional alkyl Suzuki coupling thus giving the further possibility of modification *via* alkyl boronate transformations.[16] α-Cyclic and oxygen containing cyclic carboxylate salts also serve as good substrates (**4m**, **4n**, **4t**). Finally, it is important to note that cyano and keto substitution on the aliphatic chain were well tolerated (**4o**, **4p**, **4u**). The decarboxylative benzylation took place regiospecifically on the carboxylate moiety to form a quaternary carbon center without any benzylation on enolizable C–H bond. These examples highlight the synthetic utility of the Pd-catalyzed decarboxylative benzylation processes.

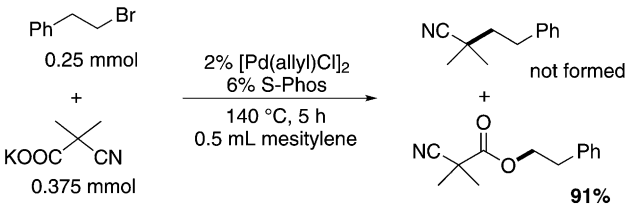
During our optimization study for the coupling of benzyl chloride with potassium 2-cyano-2-methylpropanoate, we observed a by-product which showed equal molecular weight with the desired product through GC-MS analysis. NMR analysis indicated that the by-product is 2-methyl-2-(*p*-tolyl)propanenitrile. Further investigation showed the ratio of the by-




| Solvent | X = Cl | | X = OTFA | |
|---|---|---|---|---|
| | ***a*** [%] | ***b*** [%] | ***a*** [%] | ***b*** [%] |
| mesitylene | 3 | 95 | 2 | 95 |
| NMP | 50 | 45 | 34 | 53 |

**Scheme 1.** Solvent effect on reaction selectivity.




**Scheme 2.** Tentative decarboxylative alkylation.

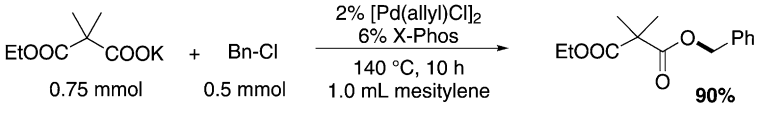
product is largely affected by the choice of the solvent (Scheme 1). Although the detailed mechanism and the solvent induced selectivity for the formation of the arylated product are not clear, the by-product formation process may involve a dearomatization of the Pd-benzyl intermediate.[19].

Next, we tried the decarboxylative alkylation of α-cyano carboxylate salts. Under the optimal conditions for benzylation, the attempted coupling of (2-bromoethyl)benzene with potassium 2-cyano-2-methylpropanoate led to the formation of alkyl ester (Scheme 2). Interestingly, when the above reaction was carried out in the absence of Pd catalyst, no alkyl ester was formed. This observation indicates that the alkyl ester formation is not a simple $S_N2$ type reaction, but is catalyzed by Pd under these conditions. We also tried the decarboxylative benzylation of benzyl chloride with potassium 3-ethoxy-2,2-dimethyl-3-oxopropanoate, but obtained the benzyl ester without decarboxylation in high yield (Scheme 3). The benzyl ester formation from the α-ester salt is possibly due to the different decarboxylative nature under Pd catalysis compared with the α-cyano substrate and merits further consideration.

Although the detailed mechanism of the decarboxylative benzylation is not clear at present, based on the observations above and our previous studies,[20] we consider that the outlined mechanism may contain the following steps (Figure 1). (i) The oxidative addition of benzyl electrophiles forms a phosphine ligated benzyl-Pd complex **II**. (ii) The carboxylate replaces the halide through anion exchange to form **III**, and intermediate **III** transforms to **IV** in which the palladium coordinates with the cyano nitrogen. (iii) The carboxylate decarboxylates on **IV** to form a nitrile nitrogen coordinated intermediate **V**. (iv) **V** isomerizes to C-coordinated style **VI** followed by reductive elimination to give the desired product. Notably, in intermediate **V**, the α-carbon of the nitrile could attack the *para* site of the benzyl group to produce a dearomatized product **VIII** which is followed by rearomatization to form the observed by-product.[21] The formation of the arylation by-product may give evidence that Pd interacts with the nitrile nitrogen in the catalytic process.

## Conclusions

In conclusion, an efficient and practical palladium-catalyzed decarboxylative benzylation of α-cyano aliphatic carboxylate salts with benzyl electrophiles has been established. This is the first example of intermolecular decarboxylative benzylation of activated aliphatic carboxylate salts. This reaction proceeds under relatively mild conditions, avoids the use of sensitive reagents, and possesses good functional group compatibility. A diverse range of quaternary, tertiary and secondary β-aryl nitriles can be conveniently prepared *via* this methodology. Many of these nitriles are difficult to synthesize *via* traditional base-mediated nucleophilic substitution reactions. Further efforts to eluci-




**Scheme 3.** Tentative decarboxylative benzylation of tertiary malonate ester salt.

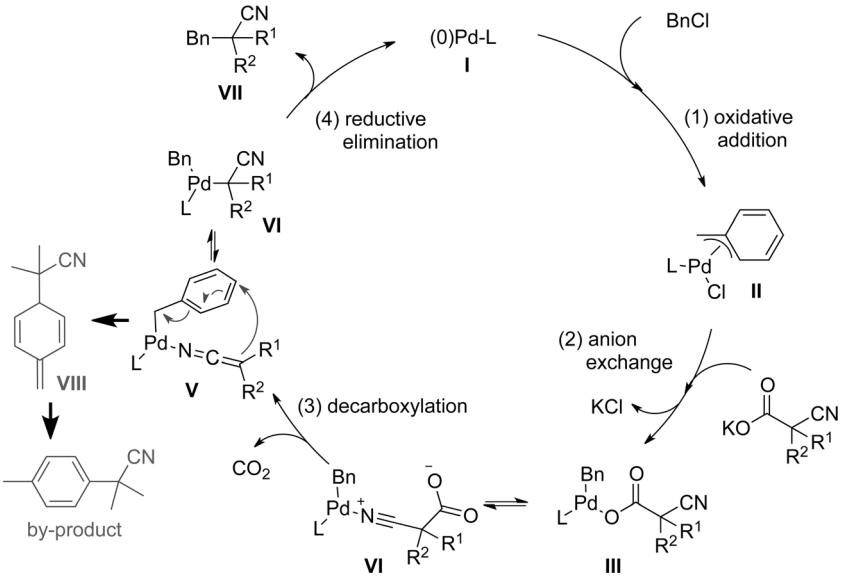



**Figure 1.** Proposed mechanism.

date the detailed mechanism and achieve an asymmetric decarboxylative benzylation of quaternary substrates will be the next goal of our research.

## Experimental Section

### General Information

All the reactions were carried out in oven-dried Schlenk tubes under argon atmosphere (purity $\geq$ **99.999%).** The toluene and mesitylene solvents were bought from TCI and used without further purification. Benzyl electrophiles were bought from Alfa Aesar and TCI or synthesized according to literature procedures. Allyl palladium chloride dimer was purchased from Sigma Aldrich and Sinocompound. All phosphine ligands were bought from Sinocompound, Sigma–Aldrich, Strem or Alfa Aesar and used as such. All the other reagents and solvents mentioned in this text were bought from Sinopharm Chemical Reagent Co. Ltd or Alfa Aesar and purified when necessary. $^1$H NMR, $^{13}$C NMR spectra were recorded on a Bruker Avance 400 spectrometer at ambient temperature in $CDCl_3$ unless otherwise noted. Data for $^1$H NMR are reported as follows: chemical shift ($\delta$ ppm), multiplicity, integration, and coupling constant (Hz). Data for $^{13}$C NMR are reported in terms of chemical shift ($\delta$ ppm), multiplicity, and coupling constant (Hz). Gas chromatographic (GC) analysis was acquired on a Shimadzu GC-2014 Series GC System equipped with a flame-ionization detector. GC-MS analysis was performed on Thermo Scientific AS 3000 Series GC-MS System. HR-MS analysis was performed on Finnigan LCQ advantage Max Series MS System. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Flash column chromatographic purification of products was accomplished using forced-flow chromatography on silica gel (200–300 mesh).

### General Procedure for the Decarboxylative Benzylation

A typical procedure for the decarboxylative benzylation of potassium 2-cyano-2-methylpropanoate (**3j** in Table 3) is as follows: A 10-mL oven-dried Schlenk tube was charged with $[PdCl(allyl)]_2$ (2 mol%), S-Phos (6 mol%), potassium 2-cyano-2-methylpropanoate (0.6 mmol) and 3-(chloromethyl)-1,1′-biphenyl (0.5 mmol). The tube was evacuated and filled with argon for three times. Then toluene (1.0 mL) was added *via* a syringe under a counter flow of argon. The tube was sealed with a screw cap, stirred at room temperature for 1 min, and stirred at 110 °C (oil bath) for 12 h. Upon completion, the mixture was cooled to room temperature. Purification of the residue by column chromatography (silica gel) afforded **3j**; yield: 93%.

**3-([1,1′-Biphenyl]-3-yl)-2,2-dimethylpropanenitrile(3j):** This compound is new. $^1$H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.61–7.57 (m, 2H), 7.54–7.48 (m, 2H), 7.46–7.38 (m, 3H), 7.37–7.31 (m, 1H), 7.24 (s, 1H), 2.87 (s, 2H), 1.38 (s, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta = 141.37$, 140.91, 136.17, 129.07, 128.79, 127.39, 127.21, 126.20, 124.72, 46.76, 33.57, 26.56; HR-MS: $m/z = 235.1350$, calcd. for $C_{17}H_{17}N$ ($M^+$): 235.1356.

### Supporting Information

General experimental methods, spectroscopic characterization and copies of $^1$H NMR and $^{13}$C NMR spectra for all compounds are available in the Supporting Information.

## Acknowledgements

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[21] Tunge et al. recently observed decarboxylative arylation on the furanyl ring in Pd-catalyzed decarboxylative benzylation of α,α-disubstituted furan-2-ylmethyl cyanoacetic esters. See ref.[14b]