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# Co(II)-Catalyzed Regioselective Pyridine C−H Coupling with Diazoacetates

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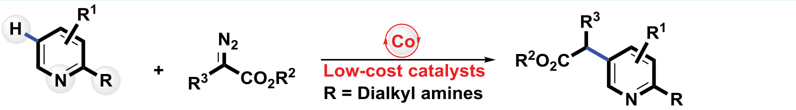
Supporting Information



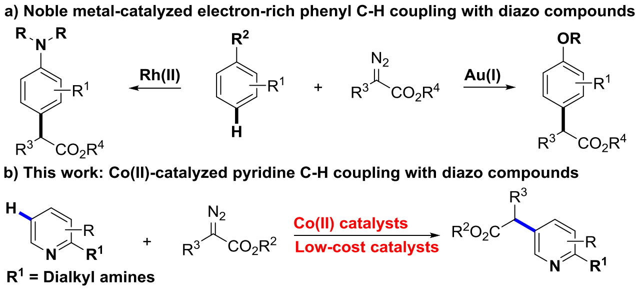
- The first pyridyl C-H carbenoid functionalization
- DFT study and mechanistic insights
- Highly regioselective carbene transfer at C3-position of pyridines

**ABSTRACT:** A Co(II)-catalyzed pyridyl C−H bond carbenoid insertion with α-diazoacetates has been realized. This transformation features a highly regioselective C−C bond formation at the C3-position of pyridines, providing an efficient access to diverse α-aryl-α-pyridylacetates.

Pyridine nuclei are ubiquitous structural motifs found in many bioactive molecules and pharmaceuticals.[1] Therefore, the site-selective C−H functionalization at different position of pyridines is of great importance in synthetic chemistry.[2] To access diversified pyridine skeletons, many methods have been developed to enable the formation of C2- and C4-selective C−X bonds (X = C, N, and O, etc.) by taking advantage of the coordination of active catalyst to pyridine "N" and directing groups.[3] However, the regioselectively introducing chemical bonds into the C3-position of pyridines without additional chelation assistance is very difficult to achieve.[4] In this regard, only Yu,[5] Shi,[6] and Oestreich[7] reported the C3-selective cross-coupling of pyridines with olefins, aryl halides, aldehydes, and hydrosilanes employing metal catalysts. As a consequence, developing diverse strategies to allow the C3-coupling of pyridines with different coupling partners is highly desirable.

Carbene transfer reaction provides a powerful tool to construct C−C bonds.[8] Recently, ligand-directed C−H carbenoid functionalizations have received intensive interest; this methodology could regioselectively install C−C bonds into the particular positions on the target molecules.[9] Among them, ammonium salts,[10] indoles,[11] ketoimines,[12] omines,[13] hydroxamic acids,[14] sulfoximines,[15] and others[16] have been widely utilized as a chelation platform to enable the phenyl *ortho*-C−H carbenoid insertion. In comparison, the site-selective coupling between diazo compounds and arenes without additional directing groups remains rather challenging. Yet, significant breakthroughs have been made recently by Zhou,[17] Zhang,[18] and Shi,[19] to realize noble-metal-catalyzed direct phenyl Csp$^2$−H carbenoid insertion of electron-rich benzenes through electrophilic aromatic substitution (SEAr) (Scheme 1a). However, the direct pyridyl Csp$^2$−H carbenoid insertion has not been achieved, because of its electron-deficient conjugated system. Nevertheless, our recent work about C−H metallene insertions[20] stimulates us to envision that efficiently leveraging electronic properties of pyridine ring would possibly allow for the direct pyridine C−H carbenoid insertion. To verify our hypothesis, herein we explored a Co-catalyzed cross-coupling reaction between pyridines and diazoesters, in which C−H carbenoid insertion high-regioselectively occurred at the C3-position of pyridines (Scheme 1b).

**Scheme 1. Versatile Csp$^2$−H Carbenoid Insertion**



We were intrigued to investigate whether modifying the substituent type and substituent position on the pyridines could lead to direct pyridyl C−H carbenoid insertion. To test the feasibility of this strategy, we initially conducted density functional theory (DFT) calculations on the electron density of different positions in the pyridine ring of pyridine **1a**, **1b**, **1c**, **1d**, and **1e** [see Scheme 2 and the Supporting Information (SI)

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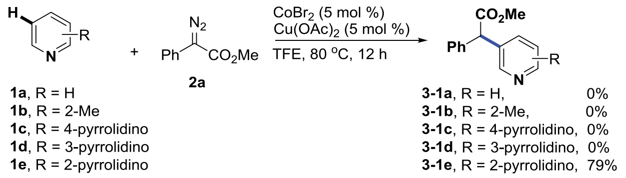
*Org. Lett.* XXXX, XXX, XXX−XXX

### Scheme 2. Optimization of the Reaction Parameters[a,b]

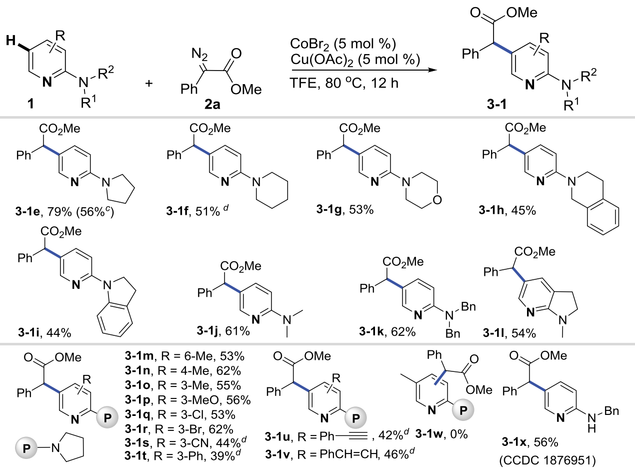


[a] All the reactions were performed using pyridines **1a**−**1e** (0.10 mmol) and $\alpha$-diazoester **2a** (0.30 mmol) with $CoBr_2$ (5 mol %) in the presence of $Cu(OAc)_2$ (5 mol %) in TFE (0.5 mL) at 80 °C for 12 h under an argon atmosphere in a sealed tube, followed by flash chromatography on $SiO_2$. [b] Isolated yield.

for more computational details]. The DFT results indicated that **1c** and **1e** possess stronger nucleophilic reactivity (see Figure S-9 in the SI), and could possibly couple with metal carbenes regioselectively at the C-3/C-5 position. Encouraged by these computational results, we proceeded to perform experimental studies with these substrates to explore the feasibility of the desired pyridyl C−H carbenoid functionalization. As expected, when these pyridines were employed as templates to couple with $\alpha$-phenyl-$\alpha$-diazoester (**2a**) in the presence of $Co(acac)_2$ catalysts, we soon found that the Co(II)-catalyzed C3-selective C−H carbenoid functionalization of pyridine occurred regioselectively by using **1e** as a substrate in 2,2,2-trifluoro ethanol (TFE) under an argon atmosphere at 80 °C for 12 h, and provided 75% yield of $\alpha$-phenyl-$\alpha$-(5-pyridyl) ester **3-1e** (see the SI for screening conditions).

With the optimized reaction conditions in hand, we then evaluated the regioselectivity and the substrate scope of this transformation with a variety of 2-aminopyridines. As summarized in Scheme 3, the carbene transfer reaction of **2a** with 2-cyclic and 2-acyclic secondary amine-substituted pyridines could proceed smoothly at the 5-position of the pyridine ring to deliver products **3-1e**−**3-1k** in yields of 44%−79%. In particular, 2,3-dihydro-1H-pyrrolo[2,3-*b*]pyridine is also tolerable to assemble **3-1l** (54%). Subsequently, we evaluated the substitution effects of the pyridine rings on this reaction. It was found that electron-donating group (Me, MeO) and weak electron-withdrawing halides (Cl and Br) could produce moderate to good yields of the desired products **3-1m**−**3-1r** (53%−62%), regardless of the substitution position of different substituent. In comparison, the more electron-deficient 3-cyanopyridine gave an inferior reaction conversion (**3-1s**, 44%). Of note, introducing a phenyl, alkynyl, and even alkenyl group to the 3-position of the pyridyl ring could still lead to acceptable yields of **3-1t**−**3-1v** (39%−46%). Unfortunately, 5-methyl-2-(*N*-pyrrolidino)pyridine in which the 5-position on the pyridine ring was blocked, could not deliver the corresponding product **3-1w**. The single-crystal data of **3-1x**, which was derived from **3-1k** through monodebenzylation (see the SI), directly indicated that the cross-coupling did occur at the 5-position of pyridines.

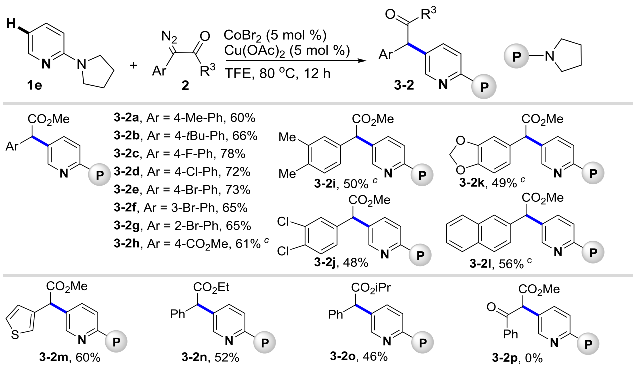
### Scheme 3. Pyridine Scope[a,b]



[a] Unless otherwise noted, all the reactions were performed using pyridines (**1**) (0.10 mmol) and $\alpha$-diazoester (**2a**) (0.3 mmol) with $CoBr_2$ (5.0 mol %) in the presence of $Cu(OAc)_2$ (5 mol %) in TFE (0.5 mL) at 80 °C for 12 h under an argon atmosphere in a sealed reaction tube, followed by flash chromatography on $SiO_2$. [b] Isolated yield. [c] 1.0 mmol of pyridine **1e** was employed. [d] 0.5 mmol of diazo compound was used.

The scope of the present procedure, with regard to different diazoesters, has also been established systematically (Scheme 4). 4-Alkylphenyl- and halophenyl-substituted donor/acceptor diazoesters could be transferred to $\alpha$-phenyl-$\alpha$-(5-pyridyl)-esters (**3-2a**−**3-2g**) with good efficiency (60%−78%). Among them, *ortho*-, *meta*-, and *para*-bromophenyl-substitution effect did not significantly affect the reaction conversions (**3-2e**, **3-2f**, and **3-2g**). Meanwhile, electron-deficient diazoester also gave good yield of the product **3-2h** (61%). In contrast, $\alpha$-(3,4-dimethylphenyl)-$\alpha$-diazoester, $\alpha$-(3,4-dichlorophenyl)-$\alpha$-diazoester, and $\alpha$-(3,4-alkoxyphenyl)-$\alpha$-diazoester produced lower yields of **3-2i**, **3-2j**, and **3-2k** (48%−50%). It is gratifying that the carbene transfer reaction could be further extended to $\alpha$-(2-naphthyl)-$\alpha$-diazoester and $\alpha$-(3-thienyl)-$\alpha$-diazoeste, affording good yields of the desired products **3-2l** (56%) and **3-2m** (60%), respectively. Compared with the $\alpha$-methoxycarbonyldiazo compound **2a**, $\alpha$-ethoxycarbonyl and $\alpha$-isoproxycarbonyl diazo compounds made the reaction somewhat sluggish, possibly because of the steric hindrance (**3-1e** vs **3-2n** and **3-2o**). Note that acceptor/acceptor diazoesters such as $\alpha$-diazo-

### Scheme 4. Diazo Compound Scope[a,b]

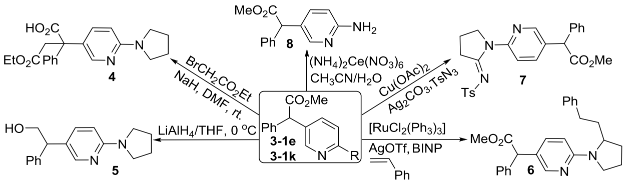


[a] Unless otherwise noted, all the reactions were performed using pyridines (**1e**) (0.10 mmol) and $\alpha$-diazoester (**2**) (0.3 mmol) with $CoBr_2$ (5.0 mol %) in the presence of $Cu(OAc)_2$ (5 mol %) in TFE (0.5 mL) at 80 °C for 12 h under an argon atmosphere in a sealed reaction tube, followed by flash chromatography on $SiO_2$. [b] Isolated yield. [c] 0.5 mmol of diazo compound was used.

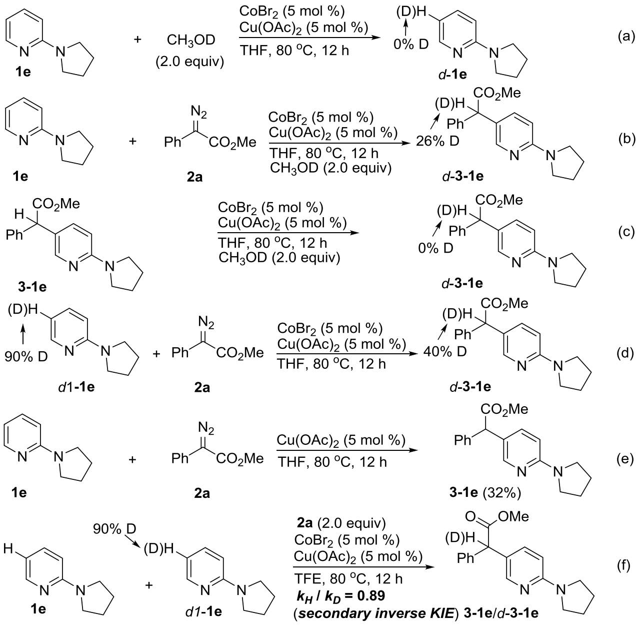
$\beta$-ketoesters did not allow this reaction to give the desired products (**3-2p**).

Methoxycarbonylmethylene could be introduced into **3-1e**, assembling quaternary carbon-containing 1,4-dicarbonate **4** (50% yield); and **3-1e** could be also reduced by $LiAlH_4$ to furnish $\beta$-phenyl-$\beta$-pyridyl-alcohol **5** in 71% yield. More importantly, the pyrrole moiety of **3-1e** could undergo cross-coupling with styrene and $TsN_3$ to assemble complex 2-alkylpyrrole **6** (75%) and *N*-sulfonyl amidine **7** (46%) under Ru(II)- and Cu(II)-catalytic systems, respectively. Finally, when $\alpha$-phenyl-$\alpha$-pyridylester **3-1k** was subjected to the $(NH_4)_2Ce(NO_3)_6$ reduction system, the free (N−H) $\alpha$-(2-aminopyridyl)ester **8** could be produced in 44% yield (see Scheme 5).

### Scheme 5. Synthetic Applications

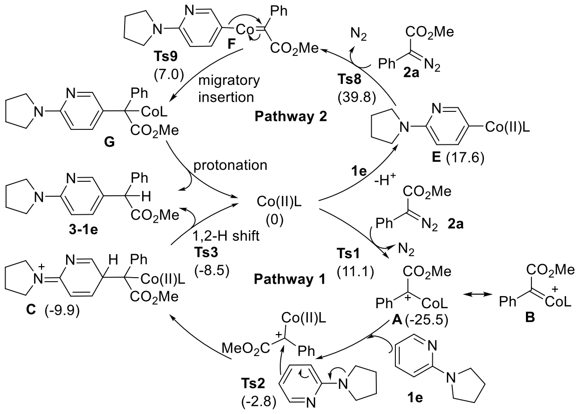


### Scheme 6. Preliminary Mechanism Studies



Designed control experiments (Scheme 6) were performed to elucidate the plausible reaction mechanism. The H/D exchange of **1e** with $CH_3OD$ (2.0 equiv) was first conducted in the absence of diazo compound **2a** under the standard conditions, no deuterium incorporation at the 5-position of pyridine **1e** implied that either electrophilic addition of cobalt-carbenoid or irreversible C−H activation process was possibly involved in this reaction (Scheme 6a). Subsequently, when the cross-coupling between **1e** and **2a** was performed under $CoBr_2/Cu(OAc)_2$/MeOD system, 26% deuterium was found to be incorporated at the $\alpha$-position of *d*-**3-1e** (Scheme 6b). Meanwhile, the treatment of **3-1e** with MeOD under the same conditions did not lead to the formation of *d*-**3-1e** (Scheme 6c). These two control experiments demonstrated that metal protonation instead of enol isomerization led to the H/D exchange at the $\alpha$-position of acetate ester **3-1e**. Moreover, cobalt-catalyzed cross-coupling between *d1*-**1e** (90% D) with **2a** resulted in the loss of 50% deuterium atoms in the product *d*-**3-1e**, indicating that a stepwise 1,2-H shift[17] was possibly involved in the carbene transfer process (Scheme 6d). Meanwhile, the cross-coupling of **1e** and **2a** could still happened in the absence of $CoBr_2$ salts (32% yield), indicating that $Cu(OAc)_2$ played the similar catalytical role as $CoBr_2$ (Scheme 6e). Finally, the secondary inverse KIE ($k_H/k_D$ = 0.89) further confirmed that a C−H (C−D) bond experiences $sp^2 \rightarrow sp^3$ rehybridization[21] in the electrophilic addition of cobalt carbenoids to pyridines, which possibly occurred in the rate-determining step (RDS) of this transformation (Scheme 6f) (see the SI for more details).

### Scheme 7. Proposed Mechanism



Plausible mechanisms were proposed based on the above control experiments and DFT studies (see the SI for more details). As shown in Pathway 1 of Scheme 7 (Figure S-10 in the SI), the Co(II)-catalyzed denitrogenation of **2a** first occurs to form the Co-carbenoid intermediate via **Ts1**. This Co-carbenoid could react as an electrophilic carbocation **A** to attack pyridine **1e** (**Ts2**, $\Delta G^{\ddagger}$ = 22.6 kcal/mol) to produce pyridinium cation **C**, which subsequently undergoes aromatization via a 1,2-H shift to assemble **3-1e** with the regeneration of Co(II) catalyst. DFT results suggest a stepwise 1,2-H shift (**Ts3**, $\Delta G^{\ddagger}$ = 17.0 kcal/mol) with the assistance of the carboxylate ligand is preferred over the concerted 1,2-H shift mechanism (**Ts4**, $\Delta G^{\ddagger}$ = 34.6 kcal/mol). This is in good agreement with the deuterium-labeled results (Scheme 6d). Along the overall reaction of Pathway 1, the RDS is found to be the electrophilic addition of cobalt-carbenoid to pyridine (**Ts2**), which is in good accordance with the experimental observed secondary KIE effect.

Meanwhile, Co(II)-catalyzed C−H functionalization generally involves irreversible C−H activation process, in which H/D exchange did not occur.[22] A concerted metalation/deprotonation could also form the $Csp^2$-metal bond at the C3-position of pyridine.[23] Therefore, another mechanistic Pathway 2 was also evaluated (Scheme 7), in which the irreversible electrophilic C3−H activation of pyridine **1e** gave the pyridinyl-Co(II) species **E**. The $\sigma$-complex **E** initiates the denitrogenation of **2a** to form Co-carbenoid **F**. The subsequent migratory insertion, followed by the protonation of intermediate **G**, furnishes the desired product **3-1e**.

However, DFT studies suggested that Pathway 2 is less feasible, because of the high free energy of the RDS transition state (**Ts8**, $\Delta G^{\ddagger} = 39.8$ kcal/mol; see Figure S-11 in the SI).

In summary, an unprecedented Co(II)-catalyzed carbenoid transfer between pyridines and diazo compounds has been developed. This transformation proceeds regioselectively at the C3-position of pyridines encompassing alkyl-, alkoxyl-, aryl-, halo-, cyano-, alkynyl- and alkenyl-substituted pyridines, allowing for the rapid assembly of $\alpha$-aryl-$\alpha$-pyridyl-acetates. The broad compatibility of diverse functional groups could render this strategy highly valuable for further constructing complex pyridine molecules. Our future efforts will focus on achieving an asymmetric version of this new reaction.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01196.

> Detailed experimental procedures, characterization data, single-crystal data of **3-1x**, copies of $^{1}$H NMR and $^{13}$C NMR spectra for all isolated compounds (PDF)

### Accession Codes

CCDC 1876951 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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[§]H.X, Y.S, and J.G. contributed equally to this work.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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