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Dual-Ligand Catalyst for the non-Directed C–H Olefination of Heteroarenes

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Abstract

Pd(II)-catalyzed non-directed C–H functionalization of heteroarenes is a significant challenge for the following reasons: poor reactivity of electron-deficient heterocycles and the un-productive coordination of the Lewis basic nitrogen atoms. Existing methodologies using palladium catalysis often employ a large excess of heterocycle substrates to overcome these hurdles. Despite recent advances in non-directed functionalization of arenes that allow them to be used as limiting reagent, the reaction conditions are incompatible with electron-deficient heteroarenes. Herein we report a dual-ligand catalyst that enables Pd(II)-catalyzed non-directed C–H olefination of heteroarenes without using a large excess of substrate. In general, the use of 1–2 equivalents of substrates was sufficient to obtain synthetically useful yields. The reactivity was rationalized by the synergy between two types of ligands: a bidentate pyridine-pyridone ligand promotes C–H cleavage; the monodentate heterocycle substrate acts as a second ligand to form a cationic Pd(II) complex that has high affinity for arenes. The proposed dual ligand cooperation is supported by a combination of X-ray, kinetics, and control experiments.

Graphical Abstract

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ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge *via* the Internet at http://pubs.acs.org.

Accession Code

CCDC 2172693 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.

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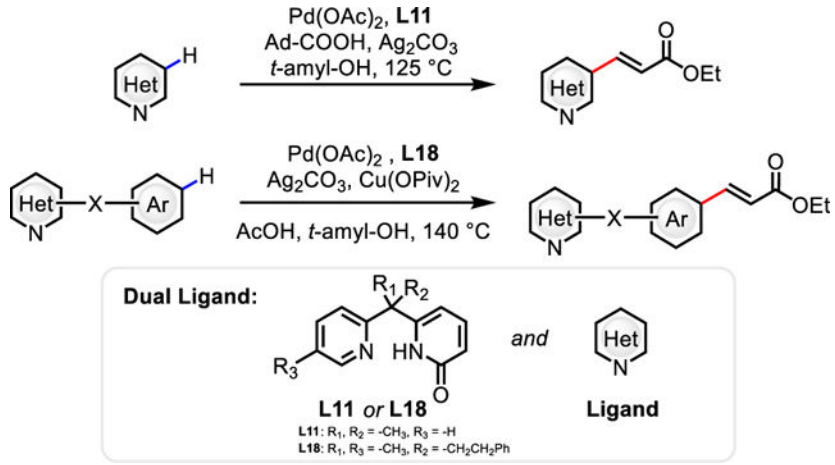

1. Introduction

The development of selective C–H functionalization of heteroarenes is of great significance to the synthesis of pharmaceuticals, agrochemicals and natural products (Figure 1).[1] However, using heteroarenes as the substrate renders reaction development considerably more challenging than the analogous arenes, as heteroarenes are generally less reactive. Additionally, the Lewis basic nitrogen atoms often engage in unproductive coordination with the metal catalysts which results in suppression of catalytic activity (Figure 2A). This is exemplified by the stark contrast between the progress of C–H functionalization of arenes and heteroarenes, in which the former could be achieved through multiple directed and non-directed strategies with a broad scope of transformations,[2–5] whereas the latter is still limited, requiring directing groups,[6] and reversible bifunctional templates.[7,8] Non-directed C–H functionalization of heteroarenes, complementary to the directed strategies, remains a significant challenge.[9] In particular, the design of active catalysts to enable the use of the heteroarene substrate as a limiting reagent akin to arenes has been a major hurdle.

Two rational approaches *via* ligand design can be envisaged to arrive at a potential solution to this problem: attenuation of catalyst poisoning through enforcement of strong *trans*-effect; employment of an appropriate internal base to accelerate the C–H cleavage step. Both approaches have been individually demonstrated in previous studies: non-directed C–H activation of pyridines *via* the *trans*-effect of bipyridine ligands and the pyridone ligands as internal base at cleaving aryl C–H bonds.[5a,9a,9b] To combine these two design principles, we therefore examined a wide range of bidentate pyridine-pyridone ligands.[6b,10] Through extensive experimentation, we propose that the heteroarene substrate itself may cooperate with the bidentate pyridine-pyridone ligand as a secondary monodentate ligand,[11] for the assembly of a dual-ligand catalyst. This dual-ligand catalyst, in conjunction with our proposed σ to π coordination switch of the heteroarene substrate through the *trans*-effect,[9a,9b] would allow the generation of a more reactive cationic palladium catalyst, and thus potentially enable the use of significantly lower equivalents of the heteroarene substrate (Figure 2B). Herein, we report a dual ligand catalytic system involving a bidentate pyridine-pyridone ligand and a monodentate heteroarene ligand that enables a Pd(II)-catalyzed non-

directed C–H olefination of heteroarenes using only 1–2 equivalents of heteroarene substrate with broad substrate scope, and wide functional group tolerance (Figure 2C).

2. Results and Discussion

We began our campaign with an investigation of ligand effects using simple pyridine **1a** as the model substrate and ethyl acrylate as the olefination coupling partner. (Table 1). It was found that no desired olefination product was detected in the absence of ligand. Ligands **L1**-**L4**, previously reported monodentate pyridines and pyridones which accelerated C–H activation of simple arenes,[11,12] were not effective for this reaction. The use of bidentate MPAA (monoprotected amino acid) ligand (**L5**),[13] and several representative L,L-type bidentate ligands (**L6–L7**) only gave high efficiency with a large excess of substrate. The bidentate APAQ (acetyl-protected aminoethyl quinoline) ligand (**L8**), previously found to promote C(sp^3)–H activation, gave trace product for this transformation.[14]

To our delight, we observed that ligand **L9** and **L10** provided the desired olefination product in 25% and 32% yields, respectively. However, further optimization of the reaction conditions with these two ligands was not fruitful. In our recent report, we discovered a tautomeric bidentate ligand which enabled C–H hydroxylation with broad substrate scope.[6b] Notably, by tuning the chelation ring size, these L, X-type ligands can precisely adapt the desired coordination modes in different catalytic steps. We therefore wondered whether this new type of ligand would also enable the desired C–H activation of heteroarenes. A series of six-membered chelating pyridine-pyridone bidentate ligands (**L11–L18**) were tested. Excitingly, the yield of the reaction was improved to 67% using ligand **L11**. Further ligand optimization by modulating their electronic (**L12–L14**) and steric (**L15–L18**) properties did not further enhance reaction efficiency. While the optimized temperature is 125 °C, 47% and 14% yield could be obtained at 115 °C and 105 °C, respectively. Notably, good yield (52%) was achieved when pyridine was reduced from 2.0 equiv. to 1.0 equiv., thus providing a promising method for late-stage functionalization of bio-active molecules (Table 2, 2a). The addition of 1-adamantanecarboxylic acid was found to slightly improve the reaction efficiency.[15]

With the optimized ligand and reaction conditions in hand, we evaluated a wide range of pyridine derivatives (Table 2). Using ethyl acrylate as the coupling partner, the corresponding olefination products of pyridines were obtained in moderate to good yields with good regioselectivity (**2a**-**2o**). Simple pyridine gave the desired product in 67% yield with high C-3 selectivity (13.5/1.0/0.4). Both electron-donating (**2b–2d**) and electron-withdrawing (**2e, 2f**) substituents were tolerated, giving corresponding olefination products in good yields with high C-3 selectivity. A synthetically valuable halide substituent was also tolerated (**2i**), outcompeting the Heck reaction pathway. However, a substrate with C-4 substitution (**2j**) gave lower yield most likely due to the increased steric hindrance. To our delight, other heterocycles including pyrimidine (**2k**), quinolines (**2l–2n**) and quinoxaline (**2o**) all provided moderate to good yields.

Considering the broad utility of biaryls in drug discovery, the potential application of this catalytic system in heterocyclic biaryls is appealing. Interestingly, when 4-phenylpyridine

(**1p**) was employed as the substrate in this reaction, we found that the olefination mainly occurred on the phenyl ring (Scheme 1), with only trace olefination (< 2%) on pyridine ring. The observed regioselectivity could be mainly due to electronic effect with the highly electrophilic cationic catalyst as the arenes are generally more electron-rich compared to the heteroarenes. This catalytic system could offer a promising solution to active the remote C–H bonds of heterocycle-containing arenes. With extensive investigation of ligands and reaction conditions (see SI for detailed information), the yield of this reaction was successfully improved to 74% with ligand **L18**. Furthermore, $Cu(OPiv)_2$ (0.5 equiv.) was added as co-oxidant in addition to Ag_2CO_3 (0.5 equiv.).

With the optimized conditions in hand, a wide range of heterocyclic biaryls were examined (Table 3). Firstly, we evaluated 4-phenylpyridines and found that a range of derivatives were compatible (**2p–2ad**), affording moderate to good yields. Substrates **2r–2s** showed lower reactivity due to the presence of steric hindrance next to the coordinative *N*-atom. In such cases, 3,5-lutidine (1.0 equiv.) was found to be a necessary additive for achieving moderate yields. It is worth noting that this reaction system is very sensitive to steric effect, which could help increase the regioselectivity for certain substrates (**2t, 2w, 2y, 2z, 2ab**), but it will also weaken the reactivity in other substrate (**2ac**). Interestingly, the preferential *ortho*-olefination of fluoro-containing substrates was observed and dominated the selectivity for substrates **2u, 2x** and **2aa**. As expected, we did not observe any non-directed C–H activation product of 2-phenylpyridine due to the favored *ortho*-directed palladation. Next, different types of heterocycle-containing arenes were investigated (**2ae–2ao**). Olefination of isoquinoline-, quinoxaline-, benzo[*c*][*1,2,5*]thiadiazole- and functionalized quinoline-containing substrates gave the desired products with moderate to good yields (**2ae–2ai**). A substrate containing two pyridine rings (**2aj**) also gave good yield. Many pharmaceutically important heterocycles such as pyrimidines and pyrazoles were functionalized with good yields (**2ak–2ao**). To further extend this methodology beyond heterocyclic biaryls, we tested pyridine-containing arenes without biaryl bond (**2ap–2av**). The linkage between pyridine and arene can be an ether (**2ap, 2at, 2av**), ester (**2as, 2au**), amine (**2aq**) or alkyl chain (**2ar**). Overall, this method provides a rather general tool to functionalize previously inaccessible C–H bonds of heterocycle-containing substrates.

We next tested the scope of the olefin coupling partners using 4-phenyl pyridine as the model substrate (Table 4). A variety of acrylates (**2p, 2aw–2az**), were all installed in good yields. Acrylamide and vinyl phosphate were also well tolerated (**2ba, 2bc**). Unfortunately, less reactive styrenes and aliphatic alkenes only afforded trace products under our conditions, however, pentafluorostyrene successfully delivered the olefination product in 50% yield (**2bb**).

Although palladium-catalyzed C–H bond activation has gained considerable attention as an efficient tool to construct molecules, expensive silver salts are generally used as oxidants. To further showcase the potential of our methodology, we successfully developed silver-free conditions for this transformation. We were pleased to find that by using 1.0 equivalent of $Cu(OAc)_2$ as the sole oxidant, this reaction gave good yield (64%) for substrate **1p** (Scheme 2).

3. Experimental Evidence for Dual Ligand Participation

The observation of the enhanced reactivity in the presence of a second equivalent of 3,5-lutidine in substrate scope survey led to the proposal of dual ligand catalyst. Accordingly, we conducted several control experiments to probe whether the heterocycle substrate was acting as the second ligand in the catalytic system. First, we found that non-heterocyclic substrate benzene was not reactive under the standard conditions. Sterically hindered pyridyl-containing biaryl **1s** did not give any olefination product either (Scheme 3a). Reactivity was restored in both cases by adding coordinative 3,5-lutidine as a second ligand, affording the olefination products in 30% and 44% yields respectively (Scheme 3b). These results indicate that the presence of a sterically accessible heterocyclic nitrogen is required for enabling the C–H olefination reaction. Second, we have obtained and characterized the proposed intermediate **Int-II** with the dual ligand bound to Pd(II) by X-ray. Finally, stoichiometric reaction of pyridine-catalyst complex **Int-II** (Scheme 4) was investigated. In the absence of 3,5-lutidine, **Int-II** did not undergo C–H olefination. However, when one equivalent of 3,5-lutidine was added, this intermediate was converted to olefination product in 56% yield. Ag_2CO_3 was found necessary to this stoichiometric reaction indicating its additional roles in addition to being the oxidant for Pd(0).[16] 3,5-Lutidine could displace the acetate to form cationic intermediate (**Int III**) which can then isomerize to the reactive **Int IV** (Scheme 5). A kinetic isotope effect of $k_H/k_D = 2.35$ was observed using **Int-II** and **Int-II-*D*$_5$**, which supports C–H cleavage being turnover-limiting (See SI for more information). The reaction order in monodentate 3,5-lutidine ligand was determined (Scheme 5), and visualizing these data using the Burés method with an x-axis that was normalized by ligand concentration showed that the reaction was first order in the 3,5-lutidine,[17] which indicated the involvement of one molecule of 3,5-lutidine in the turnover-limiting step, in line with our hypothesis of a cationic mechanism where acetate is displaced by lutidine prior to the C–H cleavage step (See SI for more information).

Based on these mechanistic investigations, a possible catalytic cycle that is outlined in Scheme 6. First, the reactive **Int-I** is generated through coordination of $Pd(OAc)_2$ with the bidentate ligand. In our previous report, we successfully prepared and characterized **Int-I** by NMR and X-ray, which exists as a dimer.[6b] Subsequent ligand exchange of **Int-I** with one molecule of pyridine is proposed to generate **Int-II**, which was prepared, isolated, and characterized by NMR spectroscopy and X-ray (See SI for detailed information). Further ligand exchange of **Int-II** with the second molecule of pyridine is proposed to generate cationic palladium species (**Int-III)**. The strong *trans*-effect[18] promotes the formation of the reactive precursor **Int-IV**, in which the pyridyl ring coordinates with Pd(II) via π interaction to trigger the C–H activation step.[9a-9b]

4. Conclusion

In summary, we have developed a dual ligand catalyst for Pd(II)-catalyzed non-directed C–H activation of heteroarenes, including heterocyclic biaryls. This reaction features broad substrate scope and good functional group tolerance. The cooperation of the L-X pyridine-pyridone ligand and pyridine ligand provides an insight for further design of new ligands to achieve more efficient non-directed C–H activation reactions of heterocycles.

5. Experimental Section

General procedure for non-directed C–H olefination of pyridine:

Pyridine (0.2 mmol), ethyl acrylate (0.1 mmol), $Pd(OAc)_2$ (15 mol%), **L11** (15 mol%), Ag_2CO_3 (1.0 equiv.), 1-adamantanecarboxylic acid (1.0 equiv.) and *t*-amyl-OH (0.25 ml) were added to a reaction vial (10 ml). The vial was capped and closed tightly. Then the reaction mixture was stirred at 125 °C for 20 hours. After cooling to room temperature, the mixture was filtered through a pad of celite with ethyl acetate as the eluent to remove the insoluble precipitate. The resulting solution was concentrated and purified by preparative thin-layer chromatography to afford the desired product.

General procedure for non-directed C–H olefination of heterocyclic biaryls:

4-phenylpyridine (0.1 mmol), ethyl acrylate (2.0 equiv.), $Pd(OAc)_2$ (15 mol%), **L18** (15 mol%), Ag_2CO_3 (0.5 equiv.), $Cu(OPiv)_2$ (0.5 equiv.), acetic acid (0.2 equiv.) and *t*-amyl-OH (0.4 ml) were added to a reaction vial (10 ml). The vial was capped and closed tightly. Then the reaction mixture was stirred at 140 °C for 20 hours. Upon completion, the reaction mixture was cooled to room temperature and saturated aqueous solution of sodium sulfide (0.5 ml) was added. The mixture was stirred at ambient temperature for 20 minutes and then extracted with ethyl acetate (5 ml x 3). The organic layers were combined and filtered through a pad of celite with ethyl acetate as the eluent. The resulting solution was dried with Na_2SO_4, concentrated, and purified by preparative thin-layer chromatography to afford the desired product.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(18). *Trans* effect refers to the destabilization of transition metal-ligand coordination by the ligand with strong σ-donation ability in the opposite position (*trans* position). The *trans* effect strength

correlates with the σ-donation ability of the ligand in *trans* position. In our case, palladium coordinates with N-atom of pyridine-type ligands forming square planar complex. These two ligands with strong σ-donation ability in *trans* position share the same *d*-orbital of Pd and the formal competition results in the elongation of Pd-ligand bond which further labilizes the ligand coordination. For comprehensive discussion on *trans* effect, see:Coe BJ; Glenwright SJ Trans-effects in octahedral transition metal complexes. Coord. Chem. Rev 2000, 203, 5–80.

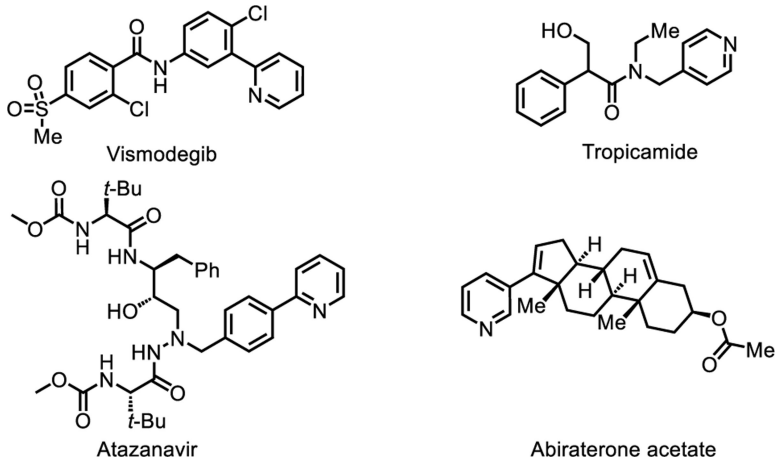


Figure 1. Heterocycle-Containing Bioactive Compounds

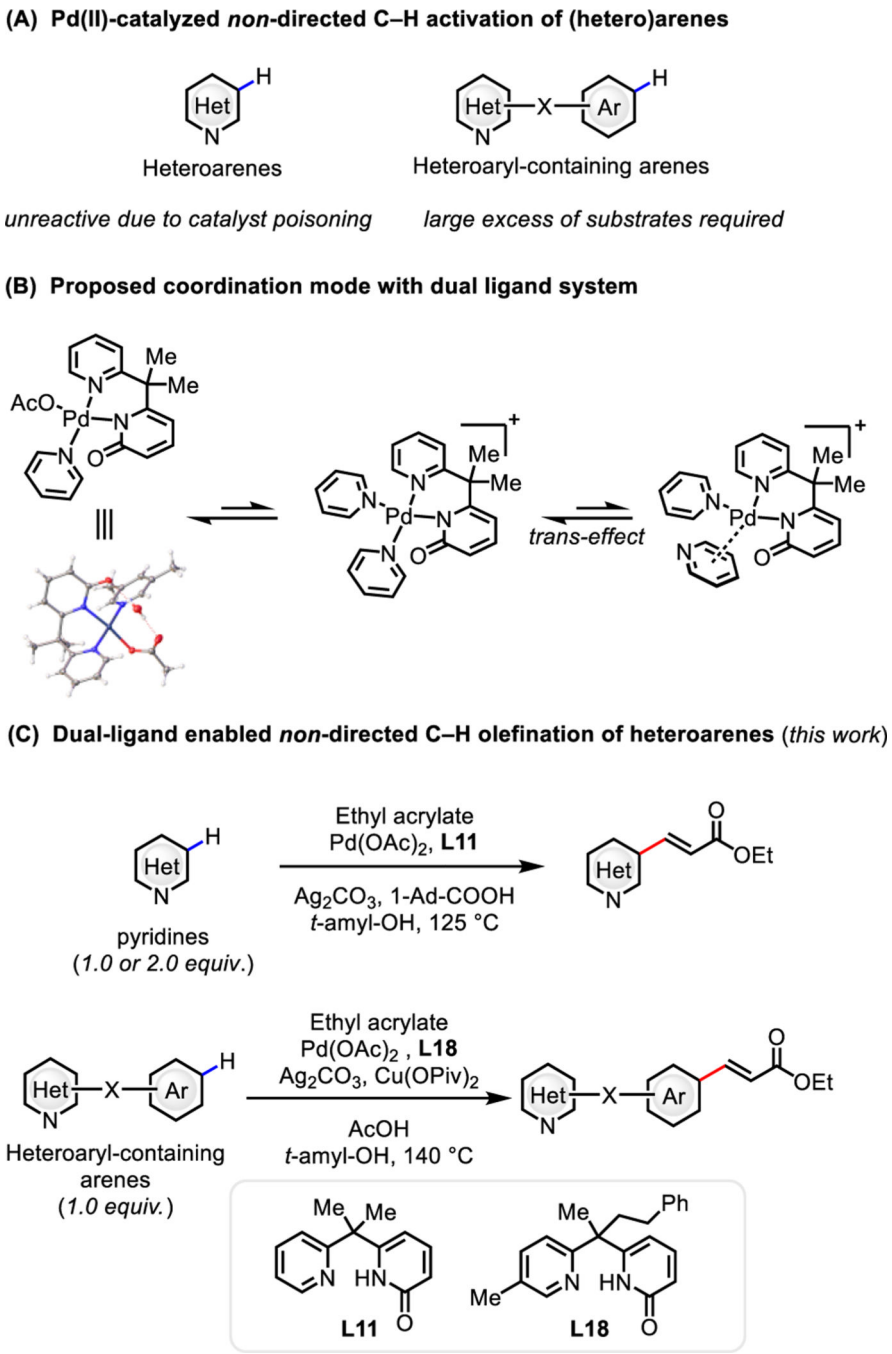
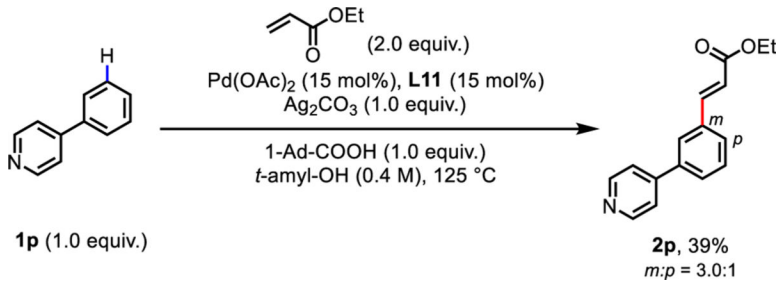
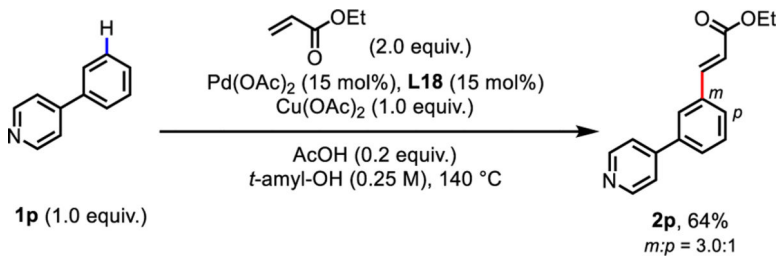


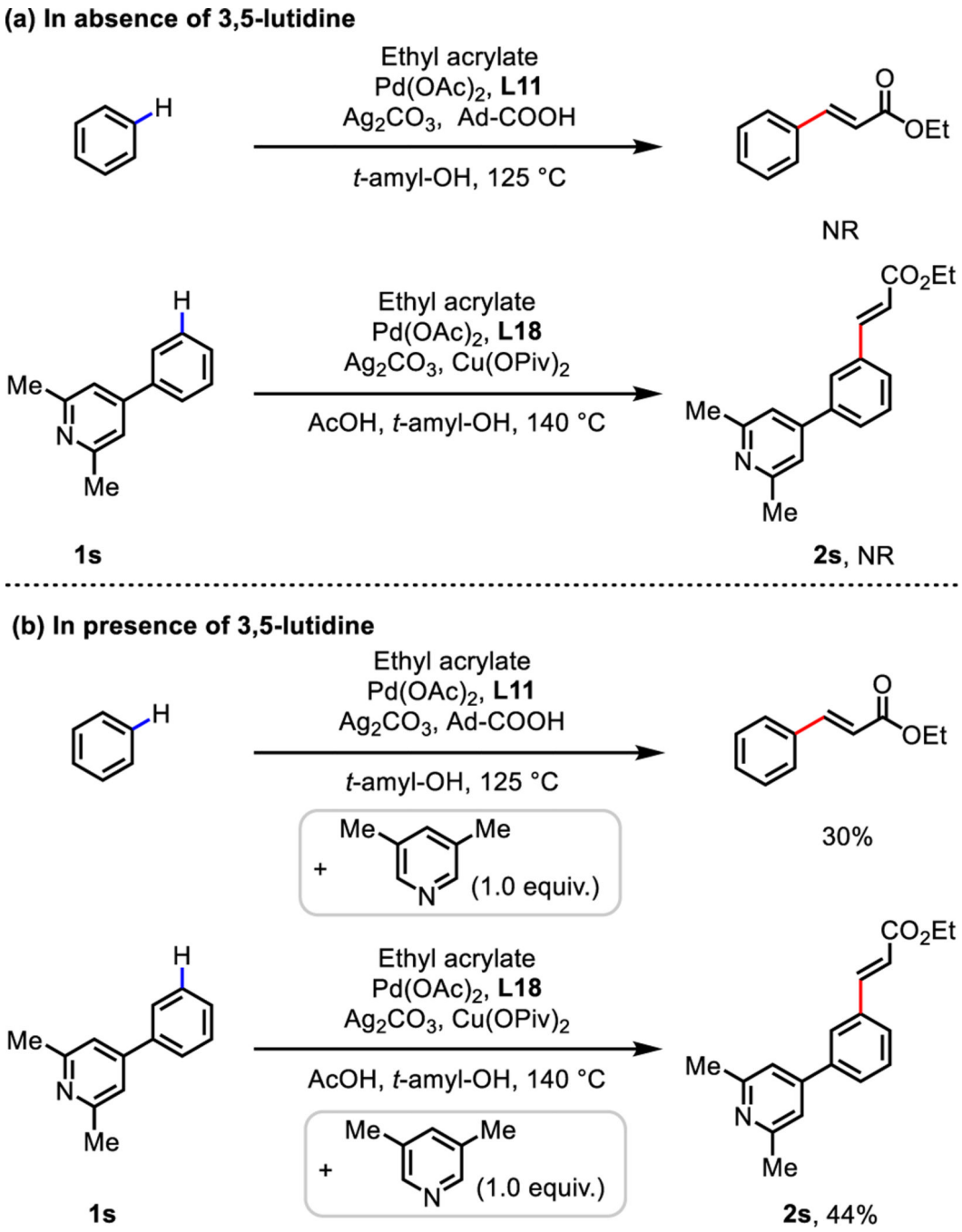
Figure 2. Strategies for non-Directed C–H Functionalization of (Hetero)Arenes.



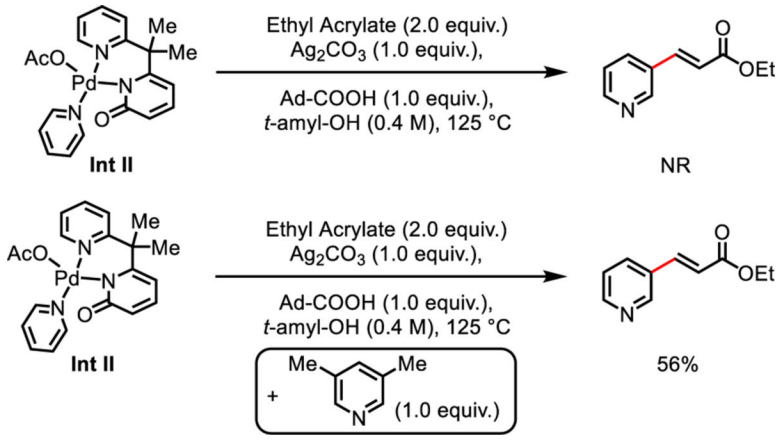
Scheme 1. C–H Activation of 4-Phenylpyridine



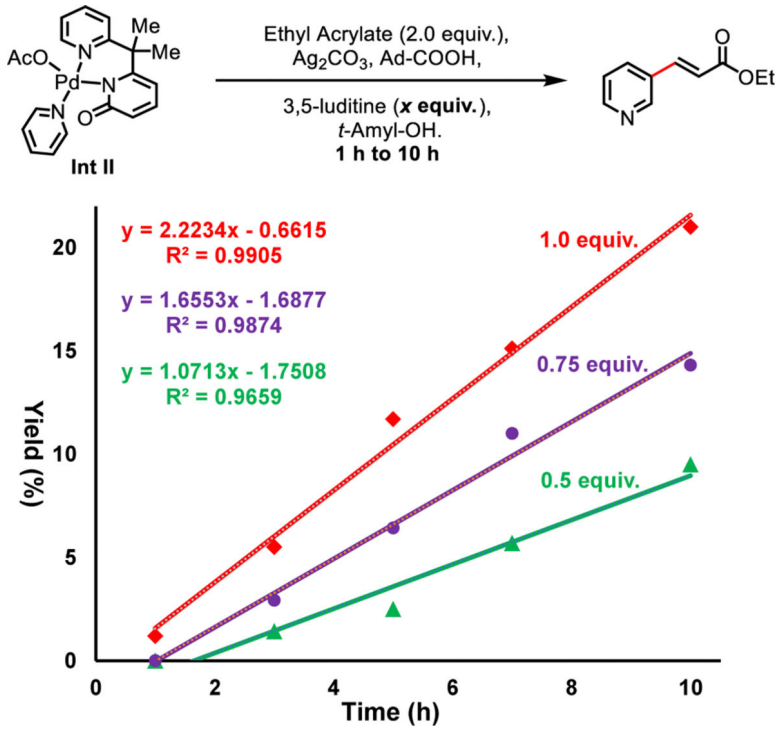
Scheme 2. Silver-Free Condition



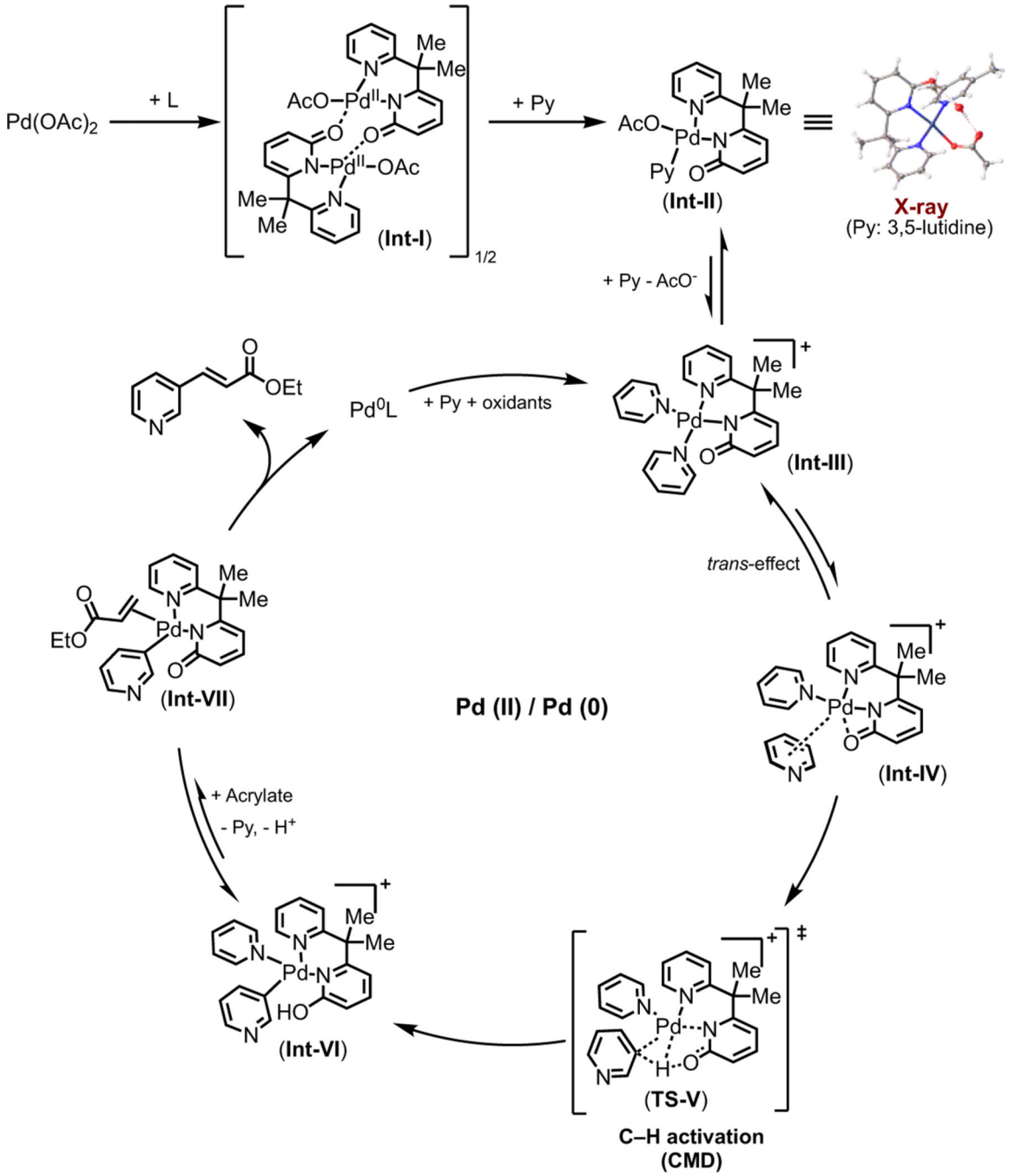
Scheme 3. Control Experiments



Scheme 4. Ligand Effect on Int-II



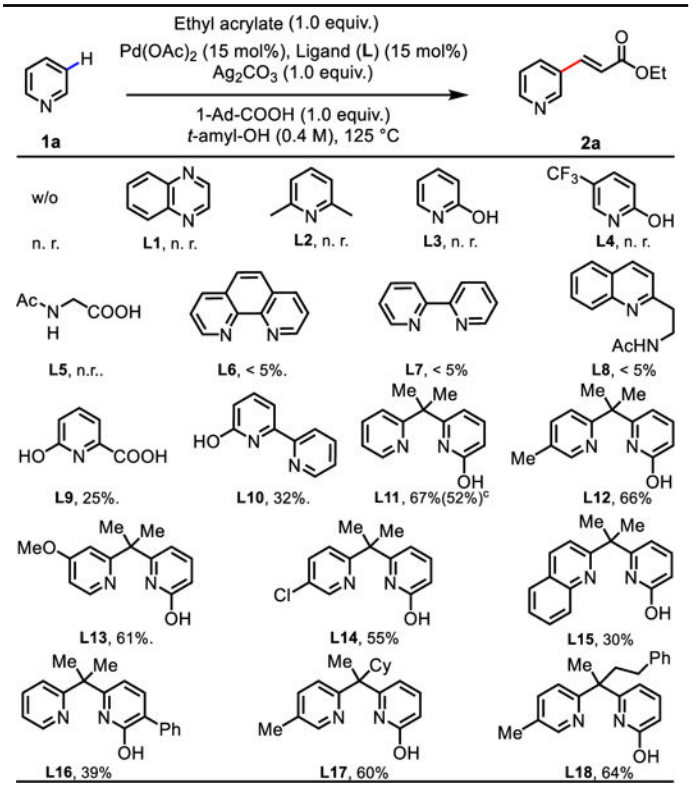
Scheme 5. Reaction Order in 3,5-Lutidine



Scheme 6. Proposed Mechanism

Table 1.

Evaluation of Ligands[a,b,c]



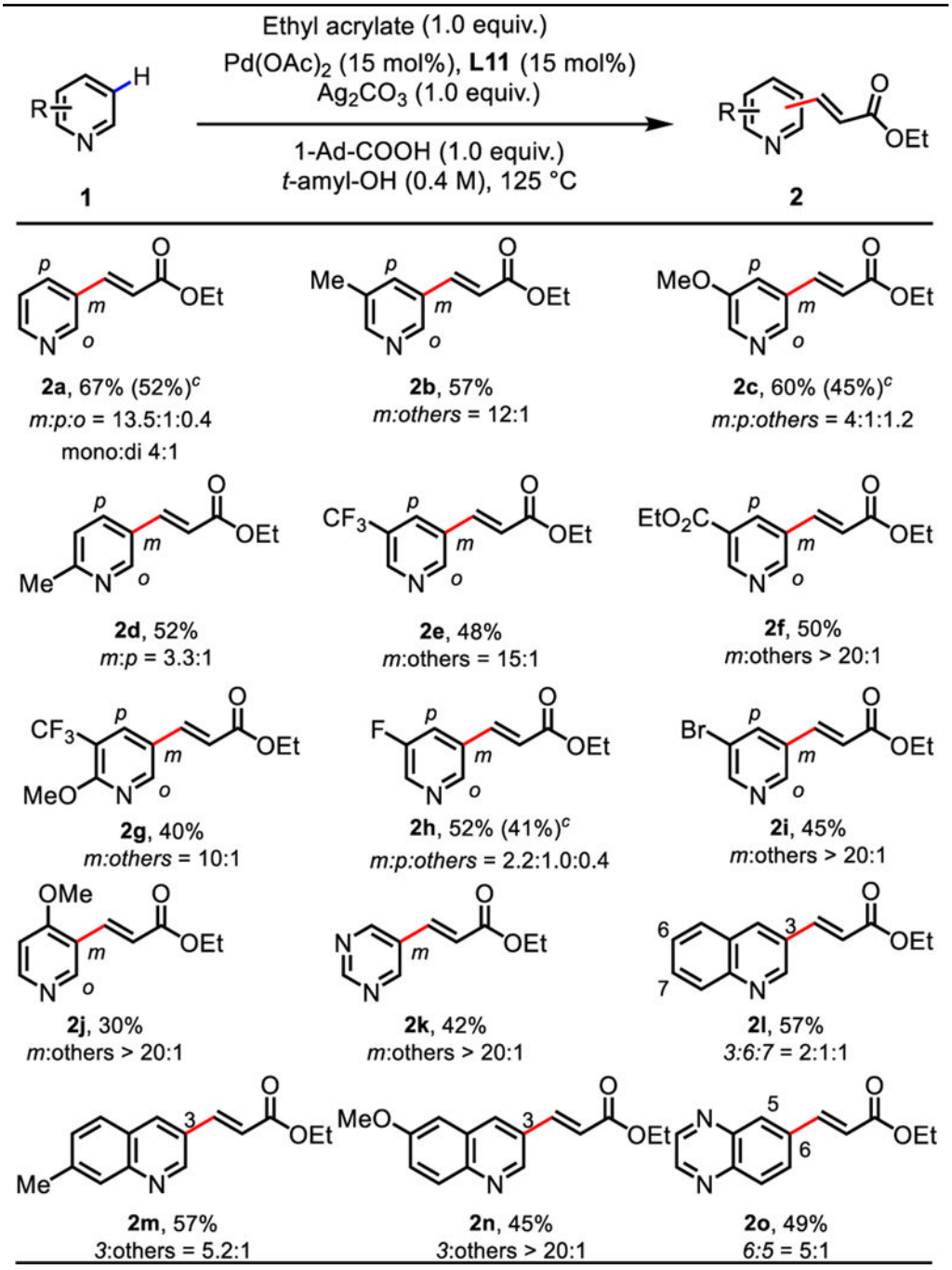
[a] conditions: **1a** (0.2 mmol, 2.0 equiv.), ethyl acrylate (1.0 equiv.), $Pd(OAc)_2$ (15 mol%), **L** (15 mol%), Ag_2CO_3 (1.0 equiv.), 1-admantanecarboxylic acid (1.0 equiv.), *t*-amyl-OH (0.25 mL), 125 °C, under air, 20 h.

[b] ^1H NMR yields, using CH_2Br_2 as an internal standard.

[c] **1a** as limiting reagent.

Table 2.

C–H Activation of Pyridine Derivatives[a,b,c]



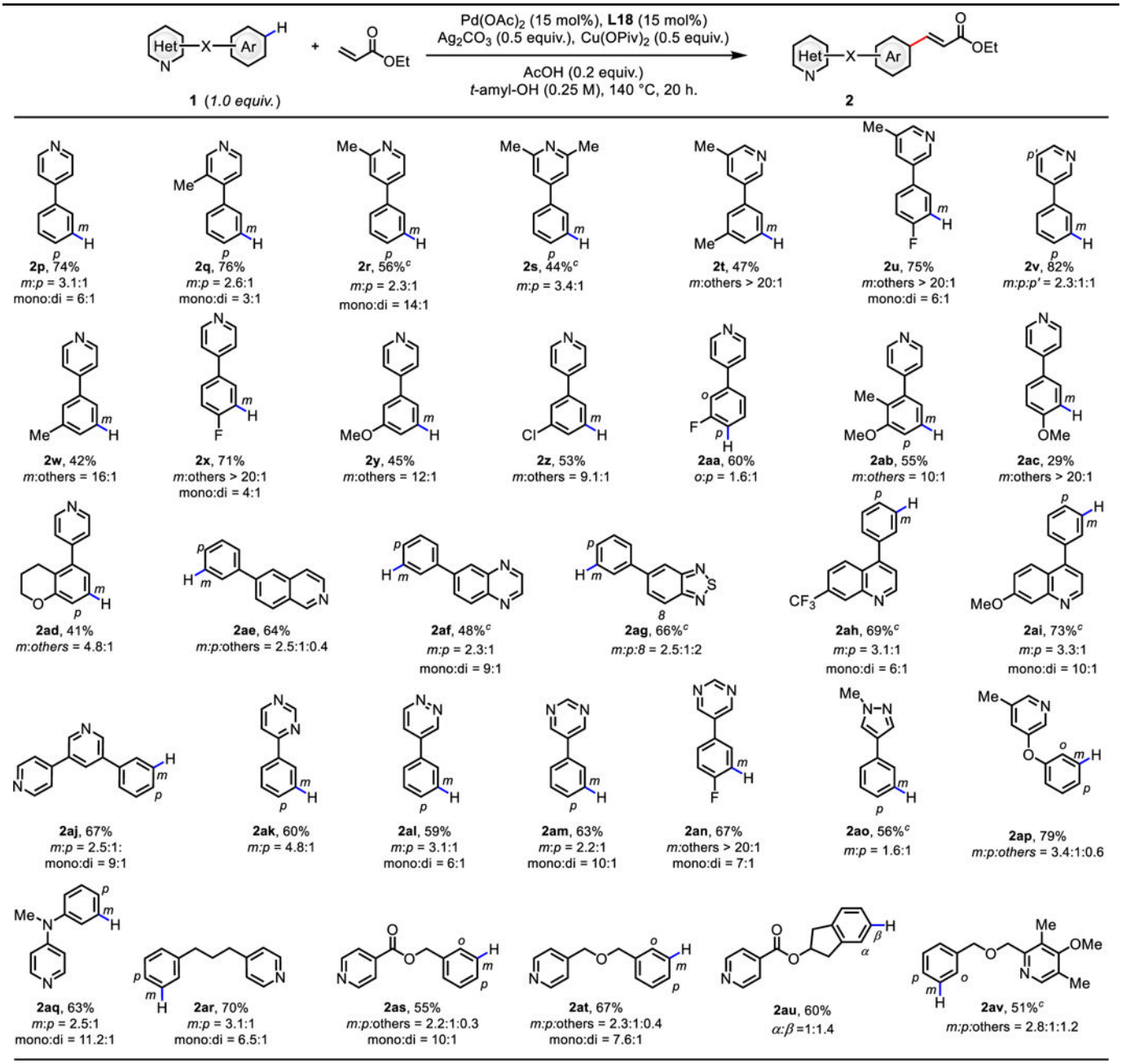
[a] conditions: **1** (0.2 mmol, 2.0 equiv.), ethyl acrylate (1.0 equiv.), $Pd(OAc)_2$ (15 mol%), **L11** (15 mol%), Ag_2CO_3 (1.0 equiv.), 1-admantanecarboxylic acid (1.0 equiv.), *t*-amyl-OH (0.25 mL), 125 °C, under air, 20 h.

[b] isolated yield,

[c] **1a** as limiting reagent.

Table 3.

Scope of Heterocyclic Biaryls[a,b,c]



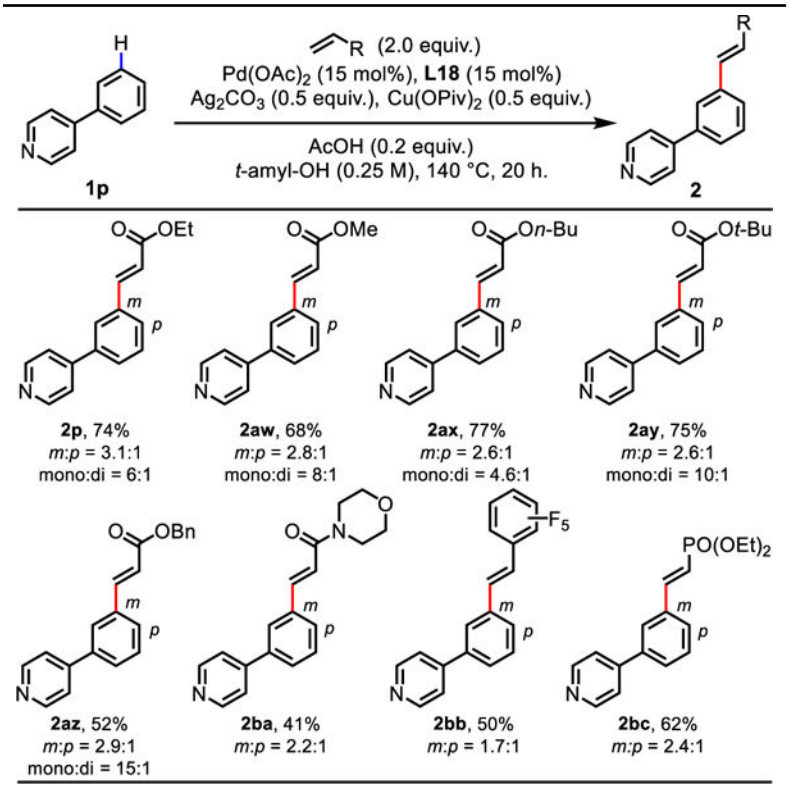
[a] conditions: **1** (0.1 mmol, 1.0 equiv.), ethyl acrylate (2.0 equiv.), $Pd(OAc)_2$ (15 mol%), **L18** (15 mol%), Ag_2CO_3 (0.5 equiv.), $Cu(OPiv)_2$ (0.5 equiv.), acetic acid (0.2 equiv.), *t*-amyl-OH (0.4 mL), 140 °C, under air, 20 h.

[b] isolated yield.

[c] 3,5-lutidine (1.0 equiv.) was added.

Table 4.

Scope of Olefin Partners[a,b]



[a] conditions: **1p** (0.1 mmol, 1.0 equiv.), olefin (2.0 equiv.), $Pd(OAc)_2$ (15 mol%), **L18** (15 mol%), Ag_2CO_3 (0.5 equiv.), $Cu(OPiv)_2$ (0.5 equiv.), acetic acid (0.2 equiv.), *t*-amyl-OH (0.4 mL), 140 °C, under air, 20 h.

[b] isolated yield.