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EDGE ARTICLE

Palladium-catalyzed selective oxidative olefination and arylation of 2-pyridones†

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Substrate-controlled selective oxidative olefination of N-protected 2-pyridones has been achieved under palladium catalysis. The 5-position selectivity was followed for N-protected simple pyridones. Introduction of substituents into the 4- or the 6-position switched the site selectivity to the 3-position. Diolefination can also be achieved with high efficiency. Oxidative arylation with polyfluorobenzenes followed a similar selectivity except that the system is more sterically and electronically demanding.

Metal-catalyzed C–H bond activation has been increasingly explored in recent years for the construction of new chemical bonds, and this strategy has allowed the development of various synthetic methods in the construction of complex molecules.[1] In particular, selective cross-coupling of two C–H bonds under oxidative conditions (cross-dehydrogenative coupling) has been a powerful method to construct new C–C bonds.[1a–c] This process is advantageous in that C–H bonds are ubiquitous in organic molecules, and direct coupling of two C–H bonds under simple and controllable conditions constitutes an atom-efficient and step-economic strategy, where no prefunctionalization of any C–H bond is necessary. Research in this area has allowed efficient delivery of molecular complexity using simple organic substrates, thus achieving synthetic diversity. Oxidative arene–olefin and arene–arene cross-coupling are two systems that have been increasingly studied. The former system (the Fujiwara reaction)[2] is particularly attractive for the olefination of arenes since no haloarene is needed and thus is advantageous over the traditional Heck-type coupling. Two general strategies with respect to the arene substrate have been widely employed to achieve efficient C–H activation. With the introduction of a neighboring directing group into the arene, the C–H activation is facilitated by chelation-assistance.[3] Alternatively, when no directing group is present, metalation can occur for active (hetero)arenes *via* the electrophilic C–H activation mechanism (S_EAr) or the concerted metalation–deprotonation mechanism (CMD).[4] These features have allowed the extensive functionalization of a broad spectrum of arenes into useful organics in the pharmaceutical industry and in material synthesis.

Substrates of types **A–I** fall into the categories of heterocycles or alkenes that bear no directing group but donating heteroatoms, and they have been shown to undergo palladium-catalyzed oxidative C–H olefination or arylation reactions (Fig. 1).[5–13] The olefinations of related arene substrates have also been extensively reviewed.[14] The site selectivity of the C–H olefination of these substrates can often be controlled. In particular, previous reports indicated that C–H activation of substrates **C–G** and **I** seems to occur at the site with the highest electron density.[15] However, of note, either the S_EAr or the CMD mechanisms of the C–H activation can be operable and the site selectivity is not an indication of the mechanism.[15]

The pyridone ring is a core of various important biologically active compounds[16] and rapid access to pyridones bearing substituents at specific positions is of great interest to synthetic and medicinal chemistry. 2-Pyridones are particularly interesting substrates for olefination studies. Recently, Hiyama and coworkers reported their seminal work on the nickel-catalyzed redox-neutral olefination of 2-pyridones at the 6-position using alkynes.[17] Facile olefination of generic pyridones with complementary selectivity should provide important protocols for accessing diversely substituted pyridones under readily

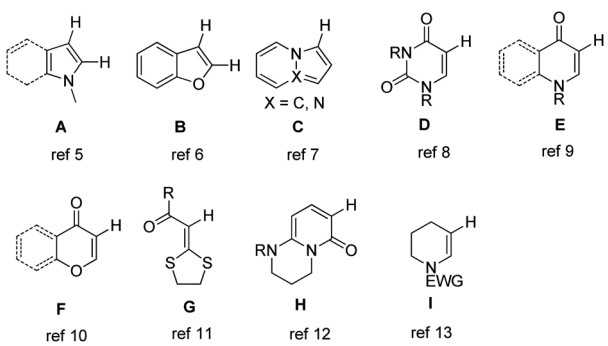

Fig. 1 Arenes and olefins bearing no directing groups in oxidative olefination reactions.

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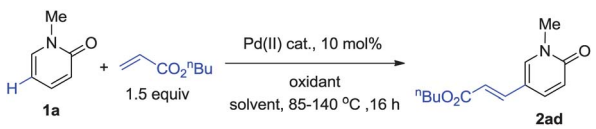
controlled conditions, which helps broaden the utility of the oxidative C–H activation strategy of this simple, readily available substrate.

We noted that the electrophilic bromination of *N*-methyl-2-pyridone using NBS afforded a mixture of the 3- and 5-bromo products, indicating that these two sites are of comparable reactivity.[18] By extending this result to palladium(II)-catalyzed C–H activation, we reason that in principle both the 3- and the 5-C–H bonds are prone to oxidative olefination if C–H selectivity parallels that in the bromination reaction. Notably, stoichiometric C–H olefination of 2-pyridones has been achieved, and in 1984 Itahara and Ouseto reported that a stoichiometric amount of $Pd(OAc)_2$ can mediate the oxidative olefination of *N*-methyl-2-pyridone with an acrylate and the products were isolated in moderate yield.[19] However, this reaction suffers from several drawbacks. In addition to the stoichiometric amount of palladium, the reaction failed for other olefins such as styrenes. In 2009 Gallagher and Cheng reported the olefination of a related substrate **H** (Fig. 1), a specific derivative of 2-pyridone, at the 3-position of the pyridone ring.[12] Despite this success, the substrate scope is quite narrow since only this very specific, highly functionalized pyridone substrate was demonstrated. Furthermore, the potential C–H activation at the alternative 5-position was not observed. Given these limitations and the well-recognized significance of pyridone building blocks in the synthesis of natural products and synthetic pharmaceuticals, we initiated studies of oxidative olefination and arylation of generic 2-pyridones. As a continuation of our interest in rhodium- and palladium-catalyzed oxidative olefination reactions,[20] we now report our studies on the selective oxidative olefination and arylation of 2-pyridones.

We set out to explore the oxidative olefination of N-substituted 2-pyridones. Using the conditions of choice ($Pd(OAc)_2$ catalyst, $Cu(OAc)_2 \cdot H_2O$ oxidant, DMF–DMSO, 85 °C) in the olefination of tetrahydropyrido[1,2-*a*]pyrimidine (substrate **H**),[11] the coupling between *N*-methyl-2-pyridone (**1a**) and *n*-butyl acrylate proceeded in poor conversion and the product **2ad** was obtained in only 29% GC yield (Table 1, entry 1), indicating that this substrate is less reactive. ^1H NMR analysis of the isolated product revealed that olefination occurred at the 5-position, consistent with the reported selectivity using a stoichiometric amount of $Pd(OAc)_2$.[19] Moving to other aprotic solvents such as DMF, dioxane, acetone and toluene and using $Cu(OAc)_2$ as an oxidant failed to improve the conversion and the yield to a synthetically useful level. When acetic acid was selected as a solvent at 120 °C, the reaction proceeded in improved yield, and the coupled product was isolated in 51% yield (entry 11). Further optimization revealed that a higher isolated yield (76%) was reached when PivOH was used as a solvent at 120 °C. Lowering the reaction temperature to 100 °C constitutes the optimal conditions (Conditions A), under which product **2ad** was isolated in 81% yield (entry 13). In all cases, only the 5-selectivity was observed (GC-MS), and under the optimal conditions, a small amount of the diolefination product has also been isolated. Thus increasing the reaction temperature to 120 °C or 130 °C resulted in a lower isolated yield due to the increased diolefination selectivity (entries 12, 14 and15).

With the optimized mono-olefination conditions in hand, we further studied the scope and limitations of this reaction (Table 2). Different acrylates readily coupled with *N*-methyl-2-pyridone in isolated yields ranging from 64 to 83%. In addition, the olefin substrate can be extended to styrenes bearing different *para* substituents (**2af–ah**). The generality of the pyridone substrate was next demonstrated. Under the standard or slightly modified conditions, different *N*-alkyl, -benzyl, and -aryl substituents in the pyridone substrate can be tolerated in the

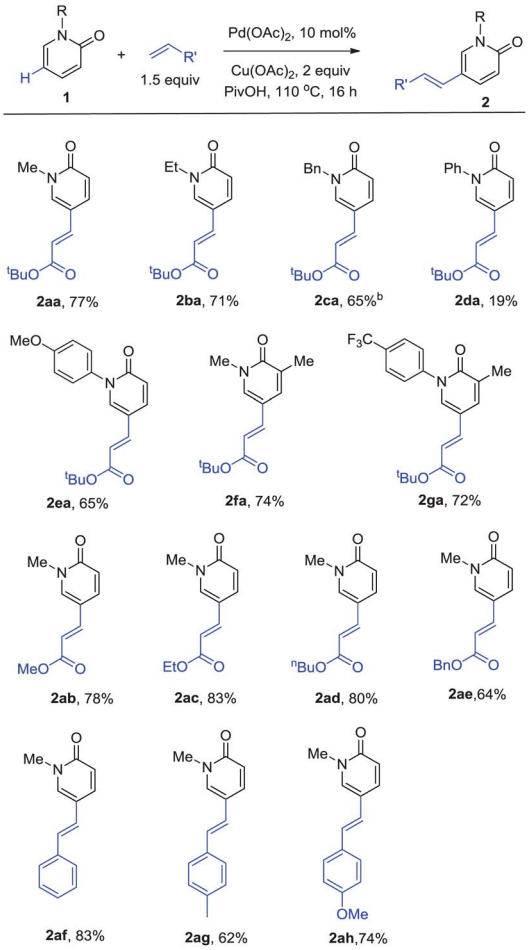
Table 1 Screening of the mono-olefination conditions[a]



Entry	Catalyst	Oxidant	Solvent	Temp./°C	Yield (%)
1	$Pd(OAc)_2$	$Cu(OAc)_2 \cdot H_2O$	DMF–DMSO(10 : 1)	85	29[b]
2	$PdCl_2$	$Cu(OAc)_2 \cdot H_2O$	DMF–DMSO(10 : 1)	85	31[b]
3	$Pd(OAc)_2$	AgOAc	DMF–DMSO(10 : 1)	120	54[b]
4	$Pd(OAc)_2$	Ag_2CO_3	DMF–DMSO(10 : 1)	120	47[b]
5	$Pd(OAc)_2$	BQ/O_2 (1 atm)	DMF–DMSO(10 : 1)	120	Trace
6	$Pd(OAc)_2$	AgF	DMF–DMSO(10 : 1)	120	Trace
7	$Pd(OAc)_2$	$Cu(OAc)_2$	Acetone	120	40[b]
8	$Pd(OAc)_2$	$Cu(OAc)_2$	Toluene	120	22[b]
9	$Pd(OAc)_2$	$Cu(OAc)_2$	PhMe	120	16[b]
10	$Pd(OAc)_2$	$Cu(OAc)_2$	Dioxane–DMSO	120	29[b]
11	$Pd(OAc)_2$	$Cu(OAc)_2$	AcOH	120	51[c]
12	$Pd(OAc)_2$	$Cu(OAc)_2$	PivOH	120	76[c]
13	$Pd(OAc)_2$	$Cu(OAc)_2$	PivOH	110	81[c]
14	$Pd(OAc)_2$	$Cu(OAc)_2$	PivOH	130	74[b]
15	$Pd(OAc)_2$	$Cu(OAc)_2$	PivOH	140	42[b]
16	None	$Cu(OAc)_2$	PivOH	110	Trace

[a] *Reaction conditions*: *N*-methyl-2-pyridone (0.3 mmol), $Pd(OAc)_2$ (0.03 mmol), *n*-butyl acrylate (0.45 mmol), oxidant (0.6 mmol), solvent (2 mL), 16 h. [b] GC yield. [c] Isolated yield after column chromatography.

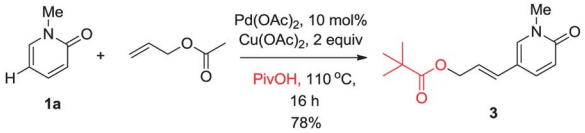
Table 2 Mono-olefination of pyridones at the C(5) position[a]



[a] *Reaction conditions* (Conditions A): pyridone (0.3 mmol), $Pd(OAc)_2$ (0.03 mmol), olefin (0.45 mmol), $Cu(OAc)_2$ (0.60 mmol), PivOH (2 g), 110 °C, 16 h, isolated yield. [b] *Reaction conditions*: pyridone (0.3 mmol), $Pd(OAc)_2$ (0.03 mmol), olefin (0.45 mmol), AgOAc (0.6 mmol), PivOH (2 g), 120 °C, 16 h, isolated yield.

reaction with *tert*-butyl acrylate. Two side-by-side independent reactions of the olefination of pyridones bearing *para*-OMe (**1e**) and *para*-CF_3 (**1g**) groups in the *N*-aryl ring were conducted using *tert*-butyl arylate, and HPLC analysis of the products **2ea** and **2ga** at low conversion (<8%) for both substrates revealed a relative rate of $k_{1e}/k_{1g} = 1.5$. These results revealed that a donating *N*-aryl group kinetically favors this coupling reaction. However, the eventually lower isolated yields of **2da** and **2ea** were caused by side reactions at high conversions. In all cases, the coupling reaction proceeds selectively at the 5-position when both C(3)–H and C(5)–H bonds in simple N-protected pyridones are accessible.

To better define the scope of the olefin, allyl acetate was allowed to couple with **1a** under the Conditions A. Interestingly, although the olefination proceeded at the expected 5-position, the product (**3**) is a pivalate instead of the expected acetate (eqn (1)). Palladium-catalyzed oxidative functionalization of allylic C–H bonds has been well studied, and Pd(η^3-allyl) species have been suggested in this transformation.[21,22] Of note, differences between Pd(II)- and Rh(III)-catalyzed olefination reactions using allyl acetate have been reported, where in Rh(III)-catalyzed systems deactivative olefination was observed to yield a simple allyl arene, which represents a redox-neutral coupling process that involves a β-acetoxyl elimination step.[20d,23]



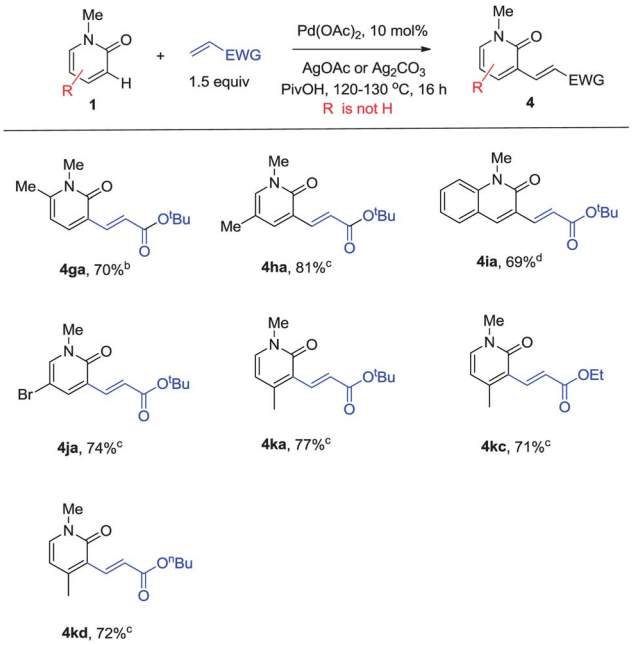
(1)

Moreover, when the 5-position of the substrate was blocked with a bromo, alkyl, or aryl group, olefination at the alternative 3-position with *tert*-butyl acrylate did occur using the Conditions A, but with low conversion. Further optimization by replacing the $Cu(OAc)_2$ oxidant with AgOAc (3 equiv.) significantly improved the isolated yield. Thus olefination products **4ha–ja** were all isolated in high yield (69–81%) under the new conditions (Conditions B, Table 3). It is noteworthy that essentially no Heck coupling product was detected in the coupling of *N*-methyl-5-bromo-2-pyridone with *tert*-butyl arylate; the C–Br bond in product **4ja** provides a straightforward handle for further functionalization such as C–C and C–N coupling under palladium or copper catalysis.

In addition, when a 6-methyl group was introduced to the pyridone ring, the coupling also occurred selectively at the C(3) position (**4ga**). This observed selectivity is at least partially due to steric effects because the C(5)–H bond is less accessible, although the electronic effect might also operate toward the same direction. Significantly, when a methyl group was introduced to the C(4) position, only the C(3) olefination product was consistently achieved, and products **4ka–kd** were isolated in 71–77% yield when several different acrylates were applied. These products were fully characterized, including by NOESY spectroscopy. The selectivity was affected by a combination of electronic and steric effects with the introduction of a methyl group (*vide infra*).

The ready switch of the chemoselectivity to the 3-olefination with the introduction of a 5-position blocking group, a 4-methyl, or a 6-methyl group indicates that C–H activation at both 3- and 5-positions is achievable. While the 3-position C–H functionalization took place with a somewhat higher kinetic barrier in N-substituted simple 2-pyridones, the site selectivity of C–H activation is subtly tuned by a combination of electronic and steric effects. To further probe the 3- *versus* 5-C–H activation, H/D exchange was carried out. Heating a sample of *N*-methyl-2-pyridone in CD_3COOD (75 °C, 24 h) in the presence of 10 mol% of $Pd(OAc)_2$ resulted in extensive H/D exchange at the 5-position (95% D) but slight exchange at the 3-position (Scheme 1a). These results suggest that both C–H bonds undergo reversible activation, and the higher level of deuteration at the 5-position is consistent with the observed 5-selectivity in the olefination of **1a**. In addition, the barriers of the C–H activation at these two positions should not be significantly different and thus can be comparable or even switchable. Interestingly, when H/D exchange studies were applied to **1k**, the H/D exchange consistently and predominantly occurred at the C(5) position although olefination took

Table 3 Olefination of pyridones at the C(3) position[a]



[a] Isolated yield. [b] *Reaction conditions*: pyridone (0.3 mmol), $Pd(OAc)_2$ (0.03 mmol), olefin (0.45 mmol), AgOAc (0.9 mmol), PivOH (2 g), 120 °C, 16 h. [c] Pyridone (0.3 mmol), $Pd(OAc)_2$ (0.03 mmol), olefin (0.45 mmol), AgOAc (0.9 mmol), PivOH (2 g), 130 °C, 16 h. [d] Pyridone (0.3 mmol), $Pd(OAc)_2$ (0.03 mmol), olefin (0.45 mmol), Ag_2CO_3 (0.6 mmol), PivOH (2 g), 130 °C, 16 h.

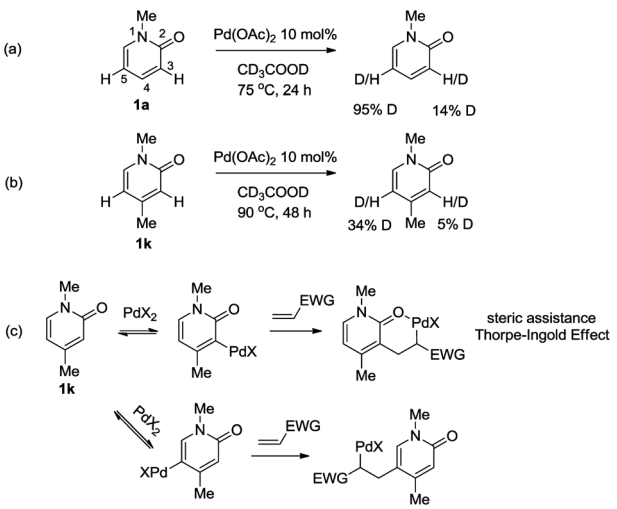
place exclusively at the C(3) position (Scheme 1b). This discrepancy can be reconciled by the inversion of relative rate of subsequent reactions when an olefin is present. We reason that when a C(3)-metalated species of **1k** undergoes olefin insertion, the steric repulsion between the methyl and the alkyl unit would entropically assist the formation of a six-membered metalacycle, resulting in a lower kinetic barrier than for a C(5)-metalated species (Scheme 1c). Steric-assisted switch of reaction selectivity in rhodium-catalyzed C–H activation has been recently reported by us.[24] However, at this stage we cannot rule out the inductive effect of a 4-methyl group, which may also function toward the same direction by favoring migratory insertion of the 3-aryl group into an olefin. In contrast, no such cyclometalated intermediate will be generated when metalation occurs at the C(5) position. Furthermore, when no 4-methyl group is present as in **1a**, the C(5)–H is kinetically more labile and this effect dominates the overall reactivity and the role of the cyclometalated insertion intermediate is likely no longer significant because olefin insertion into a C(3) metalated species of **1a**, if any, only gives a floppy six-membered metalacycle where no steric assistance is operating.

We reasoned that one-pot diolefination of **1a** using an excess of acrylates should be achievable under Conditions B since olefination at the 5-position is known to proceed under these conditions. Indeed, when an excess of various acrylates was coupled with **1a** under Conditions B (Table 4), the desired diolefination products (**5aaa–aee**) were isolated in 52–87% yield. The N-substituent can be further extended to ethyl, benzyl, and aryls, without much loss of the reaction efficiency (51–77% yield). In contrast, when a 4-methyl group is introduced into the pyridone ring (**1k**), the diolefination reaction is sluggish and no analytically pure product was isolated although the diolefination product was generated (LC-MS).

Sequential diolefination using two different olefins has been achievable by following a combination of Conditions A and B. When the mono-olefinated product **2aa** was subjected to the Conditions B, the coupling with an acrylate or a styrene readily occurred in good yield, leading to the overall formal unsymmetrical diolefination of **1a** (Scheme 2).

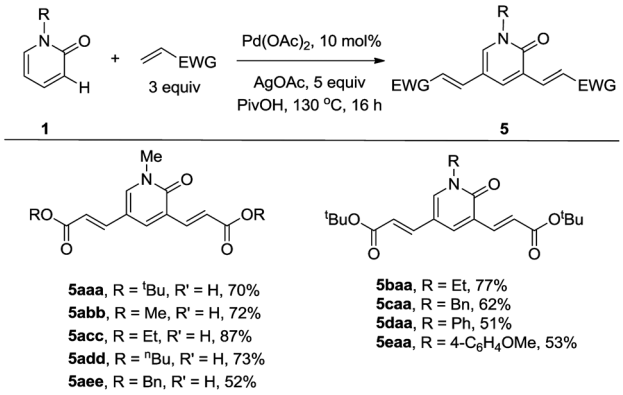
Electron-rich arenes have been recently reported to undergo palladium-catalyzed oxidative arene–arene cross-coupling.[25] Extensive screening has been performed for the coupling of **1a** and benzene. Unfortunately, no efficient coupling could be achieved. We then focused on activated arenes with acidic C–H bonds such as polyfluorinated arenes. By following the closely analogous conditions of arene–arene oxidative coupling reported by Zhang[25b] and following the related conditions reported by Shi,[25a] using $Pd(OAc)_2$ (10 mol%), the coupling between **1a** and pentafluorobenzene proceeded smoothly in the presence of $^{i}Pr_2S$ (5 equiv.) as an additive using Ag_2CO_3 as a stoichiometric oxidant (130 °C), and the desired product **6aa** was isolated in 72% yield. When DMSO (10 equiv.) was applied as an alternative stabilizing additive, **6aa** was obtained in slightly lower yield. In line with the observed 5-selectivity in olefination reactions, the same selectivity was followed in the coupling of simple *N*-alkyl, -benzyl, and -aryl substituted simple 2-pyridones (Table 5). Moreover, the same switch of site-selectivity was also followed in the cross-coupling of some substituted pyridones. Thus when the 5-position was blocked or when a methyl group was introduced to the 6-position, the cross-coupling took place selectively at the 3-position (**6ga**, **6ha**, **6hb** and **6ia**). Other polyfluoroarenes such as tri- and tetrafluorinated benzenes and pyridines are also highly efficient coupling partners, and in most cases high isolated yields of the coupled products were achieved (48–86%).

Despite the similarities between the olefin–arene and the arene–arene cross coupling reactions in terms of site selectivity, differences between these two types of reactions have been established. In contrast to the high-yielding olefination of

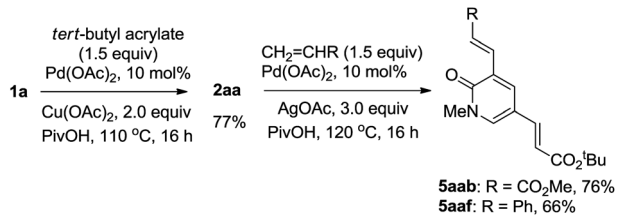


Scheme 1 Rationale of the C(3) selectivity.

Table 4 One-pot diolefination of pyridones[a]

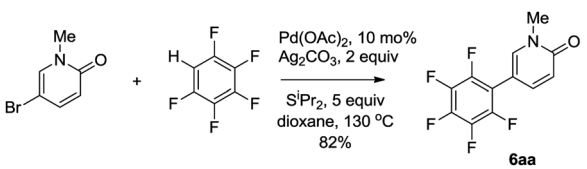


[a] *Reaction conditions* (Conditions B): pyridone (0.3 mmol), $Pd(OAc)_2$ (0.03 mmol), olefin (0.9 mmol), AgOAc (1.5 mmol), PivOH (2 g), 130 °C, 16 h.



Scheme 2 Sequential diolefination of a pyridone.

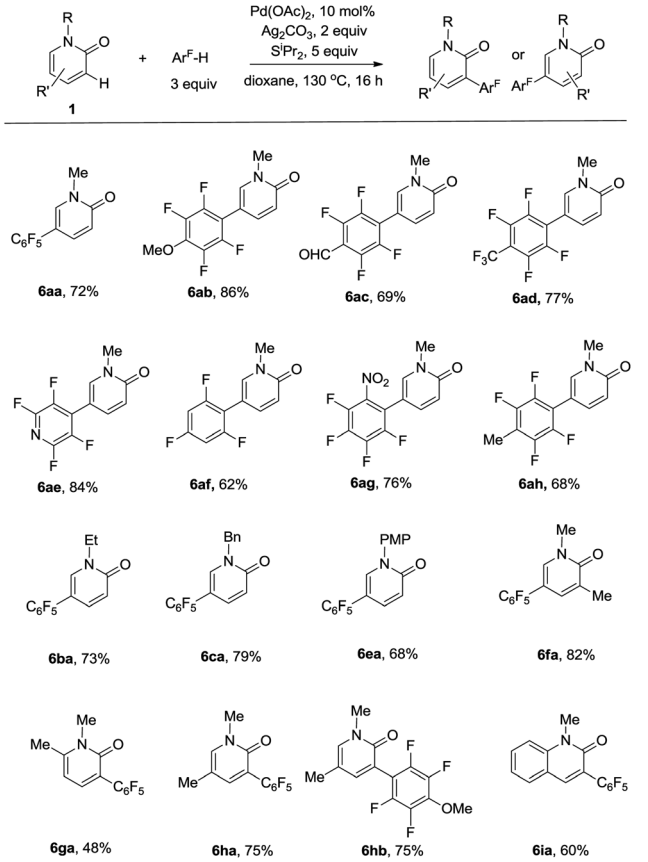
4-methyl-2-pyridone, essentially no desired arylation could be achieved under the standard conditions, indicating that the current reaction is more susceptible to steric hindrance. In addition, no diarylation could be achieved under the standard conditions; the initial arylation should significantly deactivate the pyridone ring such that no further electrophilic C–H activation can be achieved. When 5-bromo-*N*-methyl-2-pyridone was allowed to react with pentafluorobenzene under the standard conditions, **6aa** was isolated in 82% yield as a result of a direct C–H arylation process (eqn (2)), in contrast to the observed halogen-retentive olefination reaction of the same substrate. Here Ag_2CO_3 acts as a base to sponge the HBr co-product. In fact, a more general haloarene substrate such as bromobenzene can be smoothly coupled to C_6F_5H to give C_6H_5–C_6F_5 in 79% isolated yield, indicating the generality of these conditions for haloarene–polyfluoroarene cross-coupling reactions.[26]



(2)

In summary, we have achieved the selective olefination and arylation of N-substituted pyridones *via* palladium-catalyzed C–H activation. Mono-olefination of N-substituted simple 2-pyridones occurred selectively at the 5-position using $Cu(OAc)_2$ as an oxidant, where acrylates and styrenes are viable olefin substrates. The observed 5-selectivity agrees with the palladium catalyzed H/D exchange of *N*-menthyl-2-pyridone. However, the kinetic barriers of 3- and 5-C–H functionalization are not drastically different. Blocking the more reactive 5-position or the introduction of a methyl or a halogen group into the 4- or the 6-position switched the site selectivity to the 3-position when an Ag(I) oxidant was employed, as a result of substrate control. A broad scope of the pyridone substrate has been defined, including a brominated one. Selective diolefination has also been readily realized and the coupled products were isolated in high yields. The palladium-catalyzed oxidative arene–arene cross-coupling between N-substituted pyridones and polyfluorinated arenes has been achieved using Ag_2CO_3 as an oxidant, and similar reaction selectivity has been observed except that no diarylation can be obtained. In contrast to the olefination reactions, the arene–arene cross-coupling reaction is more sterically and electronically demanding. The oxidative C–H activation and C–C coupling strategies described for simple heteroarenes in this work will likely find applications in the synthesis of useful complex structures. Future work will be carried out to explore details of the reaction mechanisms and to extend the heterocycles to other useful ones.

Table 5 Oxidative arene–arene cross-coupling of pyridones[a]



[a] *Reaction conditions*: pyridone (0.3 mmol), fluorinated arene (0.9 mmol), Ag_2CO_3 (0.6 mmol), S^iPr_2 (1.5 mmol), $Pd(OAc)_2$ (0.03 mmol), dioxane (2 mL), 130 °C, 16 h, isolated yield.

Acknowledgements

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