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Rh(III)-Catalyzed Oxidative Coupling of *N*-Aryl-2-aminopyridine with Alkynes and Alkenes

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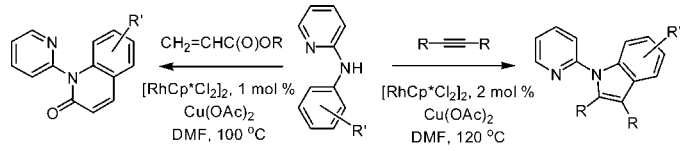
ABSTRACT



[RhCp*Cl$_2$]$_2$ (1−2 mol %) can catalyze the oxidative coupling of *N*-aryl-2-aminopyridines with alkynes and arylates to give *N*-(2-pyridyl)indoles and *N*-(2-pyridyl)quinolones, respectively, using Cu(OAc)$_2$ as an oxidant. Coupling with styrenes gave mono- and/or disubstituted olefination products.

Transition-metal-catalyzed activation of aromatic C−H bonds has attracted considerable attention because it enables efficient synthesis of organic building blocks.[1] Oxidative coupling of arenes and unsaturated molecules represents an atom-economic method to construct complex molecules, and this process is highly attractive in that no prior functionalization of the arene is necessary.[2] Rhodium catalysts are well-known for C−C coupling reactions that proceed via a C−H activation pathway owing to broad synthetic utility.[1p] However, rhodium-catalyzed oxidative C−H activation has been less studied. Over the past several years, rhodium(III) complexes, particularly [RhCp*Cl$_2$]$_2$, have stood out as a highly efficient catalyst to mediate oxidative C−C, C−N, and C−O coupling involving alkynes or alkenes.[3] This protocol constitutes an increasingly important strategy to construct various heterocycles, which has been recently reviewed.[3]

Recent studies on the Rh(III)-catalyzed oxidative coupling reaction by Satoh and Miura, Fagnou, Jones, Glorius, and Zhang reveal that in most cases C−H activation of arenes requires chelation assistance by a proximal amide,[4]

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(1) For reviews on C−H bond functionalization, see: (a) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (b) Kakiuchi, F.; Murai, S. *Top. Organomet. Chem.* **1999**, *3*, 47. (c) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (d) Jun, C.-H.; C. Moon, W.; Lee, H.; Lee, D.-Y. *J. Mol. Catal. A* **2002**, *189*, 145. (e) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (f) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 212. (g) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (h) Park, Y. J.; Jun, C.-H. *Bull. Korean Chem. Soc.* **2005**, *26*, 871. (i) Kakiuchi, F. *Top. Organomet. Chem.* **2007**, *24*, 1. (j) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (k) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (l) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (m) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (n) Sun, C. L.; Li, B. J.; Shi, Z. J. *Chem. Commun.* **2010**, *46*, 677. (o) Satoh, T.; Miura, M. *Top. Organomet. Chem.* **2007**, *24*, 61. (p) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (q) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677.

(2) For reviews on oxidative C−H functionalization, see: (a) Zhang, M. *Adv. Syn. Catal* **2009**, *351*, 2243. (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (c) Xu, L.-M.; Li, B.-J.; Yang, Z.; Shi, Z.-J. *Chem. Soc. Rev.* **2010**, *39*, 712. (d) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (e) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318.

(3) (a) Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *37*, 11212. (b) Satoh., T.; Ueura, K.; Miura, M. *Pure Appl. Chem.* **2008**, *80*, 1127.

(4) (a) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474. (b) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908. (c) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585. (d) Hyster, T. K.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565. (e) Mochida, S.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2010**, *39*, 744. (f) Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9982.

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pyridyl,[5] imine,[6] hydroxyl,[7] and carboxyl[8] group to direct the C−H functionalization to the *ortho* position. The coupling of these substrates with alkynes constitutes an important method to access heterocycles such as pyrroles,[4c] indoles,[4a] isoquinolines,[6a,b] isoquinolones,[4d,e] and isocoumarins[8] (Figure 1). Despite the wide scope of

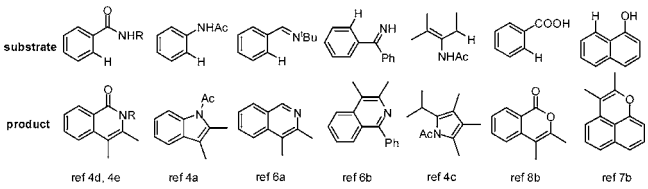


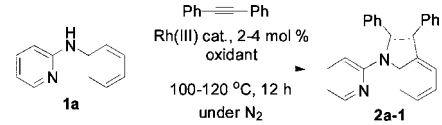
Figure 1. Previously reported oxidative coupling with alkynes.

substrates that have been studied, it is still necessary to explore arenes bearing other easily installed directing groups. We now report the oxidative coupling of *N*-aryl-2-aminopyridines with alkynes and alkenes. Importantly, quinolones were readily obtained when acrylates were used as the coupling partner.

We reasoned that *N*-aryl-2-aminopyridines are suitable substrates for C−H activation in the *N*-aryl ring with the pyridyl being a directing group. Furthermore, the proximal NH functional group may act as a nucleophile to undergo further transformations. Indeed, cyclopalladation of *N*-phenyl-2-aminopyridine has been reported,[9] and the six-membered palladacycle can undergo alkyne insertion. However, no catalytic coupling between *N*-phenyl-2-aminopyridine and alkyne or alkene has been reported. In fact, the first example of intramolecular oxidative C−N coupling of *N*-phenyl-2-aminopyridine has not been reported until very recently.[10]

We initiated our investigation using *N*-phenyl-2-aminopyridine (**1a**) and diphenylacetylene as substrates. It has been shown that $[RhCp^*(MeCN)_3](PF_6)_2$ and $[RhCp^*Cl_2]_2$ are the most commonly used Rh(III) catalysts for the oxidative functionalization of arenes, and Cu(II) and Ag(I) are often used as oxidants. Our initial screening indicated that the use of $[RhCp^*(MeCN)_3](PF_6)_2$ (4 mol %) as a catalyst and anhydrous $Cu(OAc)_2$ (2.2 equiv) as an oxidant in toluene at 100 °C produced the anticipated indole **2a-1** in 56% isolated yield (entry 2, Table 1). Switching the solvent to 1,4-dioxane or 1,2-dichloroethane led to an increase of the yield to 70%.

Table 1. Screening of Reaction Conditions[a]



entry	cat. (mol %)[b]	oxidant	solvent	temp (°C)	yield (%)[c]
1	A (4)	Ag_2CO_3	PhMe	100	<2
2	A (4)	$Cu(OAc)_2$	PhMe	100	56
3	A (4)	$Cu(OAc)_2$	dioxane	100	70
4	B (4)	$Cu(OAc)_2$	dioxane	100	63
5	B (2)	$Cu(OAc)_2$	dioxane	120	69
6	B (2)	$Cu(OAc)_2$	DMF	120	96
7	A (2)	$Cu(OAc)_2$	DMF	120	80

[a] Reaction conditions: **1a**, diphenylacetylene (1.3 equiv), oxidant (1.5 equiv of Ag_2CO_3 or 2.2 equiv of $Cu(OAc)_2$), catalyst, solvent (3 mL), sealed tube under nitrogen, 12 h. [b] A: $[RhCp^*(MeCN)_3](PF_6)_2$. B: $[RhCp^*Cl_2]_2$. [c] Isolated yield.

A comparable yield (63%) was also obtained when the catalyst was replaced by $[RhCp^*Cl_2]_2$ (4 mol %) in 1,4-dioxane at 100 °C. However, no significant improvement of the yield could be achieved when the reaction was conducted at a higher temperature (120 °C) if the catalyst loading was reduced to 2 mol % (entry 5). We were delighted to find that the combination of $[RhCp^*Cl_2]_2$ (2 mol %) and $Cu(OAc)_2$ (2.2 equiv) in DMF at 120 °C afforded product **2a-1** in 96% isolated yield (entry 6), and $[RhCp^*Cl_2]_2$ showed higher activity than $[RhCp^*(MeCN)_3](PF_6)_2$ (entry 7). For both catalyst systems, essentially no product was detected when Ag_2CO_3 was used (entry 1). No coupling proceeded when Ph_2NH was attempted as a substrate under the optimized reaction conditions, indicating the significance of the pyridyl directing group.

The scope of this transformation was expanded under these optimized conditions (Scheme 1). 4-Octyne could be applied, and the indole product **2a-2** was isolated in 87% yield (Scheme 1). The scope of the 2-aminopyridines was studied in detail, and substrates bearing both electron-rich (**2d**−**f**, **2j**) and electron-poor *N*-aryl groups (**2h**, **2i**, **2l**) can couple with PhC≡CPh in high isolated yield. Furthermore, *ortho* substituents (such as Me, Ph, and OMe groups) in both the *N*-aryl and the pyridyl groups can be tolerated (**2c**, **2d**, **2i**, **2k**), indicating the tolerance of the steric bulk of the two aryl groups in the substrate. However, the *N*-1-naphthyl substituent retarded the coupling, and product **2g** was obtained in only 47% yield. To examine the regioselectivity of this coupling reaction, substrate **1e** was applied, and **2e** was obtained in 95% yield as the single isomer, where C−C coupling occurred at the less hindered position *para* to the OMe substituent. This observed selectivity agrees with those previously reported in Rh-catalyzed oxidative coupling.[3a] In contrast, moderate regioselectivity of **2j′**:**2j** (2.3:1) was observed for substrate **1j**, and the major coupling product

(5) (a) Umeda, N.; Tsurugi, H.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4019. (b) Li, L.; Brennessel, W. W.; Jones, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 12414. (c) Guan, Z.-H.; Spinella, S. M.; Yu., S.; Liang, Y.-M.; Zhang, X. *J. Am. Chem. Soc.* **2009**, *131*, 729. (d) Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 2068. (e) Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 7094.

(6) (a) Guimond, N.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 12050. (b) Fukutani, T.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Commun.* **2009**, 5141.

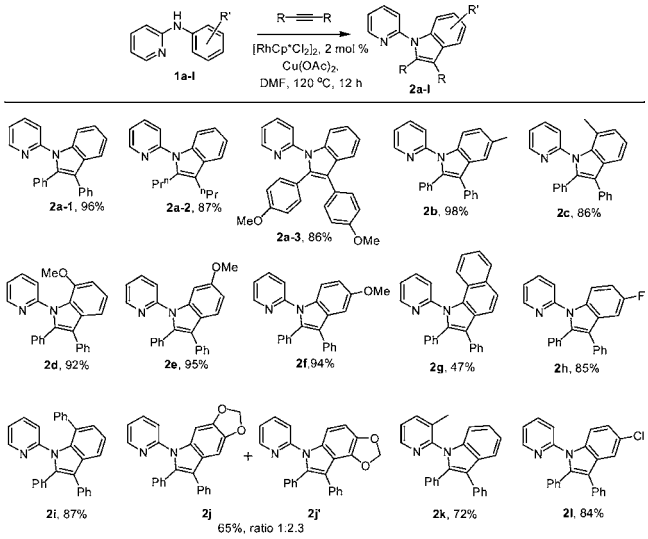
(7) (a) Uto, T.; Shimizu, M.; Ueura, K.; Tsurugi, H.; Satoh, T.; Miura, M. *J. Org. Chem.* **2008**, *73*, 298. (b) Mochida, S.; Shimizu, M.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Asian J.* **2010**, *5*, 847.

(8) (a) Shimizu, M.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 3478. (b) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407.

(9) Maassarani, F.; Pfeffer, M.; Spencer, J.; Wehman, E. *J. Organomet. Chem.* **1994**, *466*, 265.

(10) Wang, H.; Wang, Y.; Peng, C.; Zhang, J.; Zhu, Q. *J. Am. Chem. Soc.* **2010**, *132*, 13217.

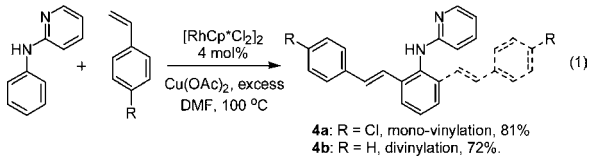
Scheme 1. Coupling of *N*-Aryl-2-aminopyridines and Alkynes[a]



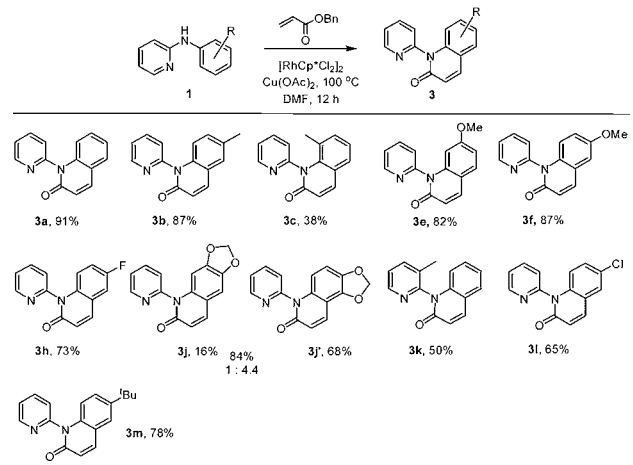
[a] Reaction conditions: substrate **1**, alkyne (1.3 equiv), 2.2 equiv of $Cu(OAc)_2$, 2 mol % of $[RhCp^*Cl_2]_2$, DMF (3 mL), under nitrogen, 12 h, isolated yield.

(**2j′**) corresponds to C−C coupling at a more hindered position. This observation is most plausibly ascribed to the directing effect of the O-atom and/or the electronic effect of the aryl ring. In addition, halogen substituents in the substrate can also be tolerated, and indole **2l** was obtained in 84% yield.

To better define the scope of *N*-aryl-2-aminopyridine in oxidative coupling, we further applied acylates as the coupling partners for oxidative Heck reactions. Methyl, ethyl, and benzyl arylates all readily coupled with *N*-phenyl-2-aminopyridines in high yields (80−91%) using 1 mol % of $[RhCp^*Cl_2]_2$ and $Cu(OAc)_2$ in DMF (100 °C). The coupled product was identified as an interesting quinolone on the basis of IR and NMR spectroscopy. The scope of this reaction was outlined in Scheme 2. Substrates with both electron-rich and electron-poor *N*-aryl groups reacted in high isolated yield, although relatively lower yields were obtained for those bearing electron-withdrawing groups (**3h**, **3l**). Analogous to its coupling with alkynes, the same regioselectivity was observed for **3e** and **3j**/**3j′**. Unlike the tolerance of *ortho* substituents in the coupling with alkynes, the introduction of a methyl group into the *ortho* position of either the pyridyl or the *N*-phenyl ring retarded this reaction (**3c**, **3k**). We noted that acetanilides can also undergo Rh(III)-[4f] and Pd(II)[11]-catalyzed oxidative coupling with acrylates. However, no further nucleophilic attack of the amide NH group on the ester was involved, and the product is a *trans*-olefin.

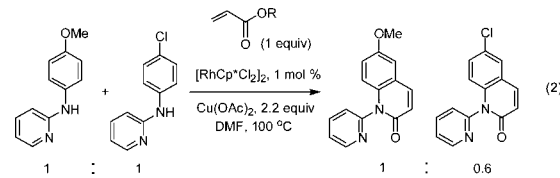


Scheme 2. Oxidative Cyclization of *N*-Aryl-2-aminopyridines with Benzyl Acrylate[a]



[a] Reaction conditions: substrate **1**, benzyl acylate (2 equiv), 2.2 equiv of $Cu(OAc)_2$, 1 mol % of $[RhCp^*Cl_2]_2$, DMF (3 mL), 100 °C, under nitrogen, 12 h, isolated yield.

The formation of the quinolone products most likely involves the olefination of *N*-phenyl-2-aminopyridine, followed by cyclization. The olefination intermediate is unusual in that it must be a rare *cis*-olefin to allow subsequent cyclization. However, we failed to observe this plausible *cis*-olefin intermediate when carrying out this reaction at a lower temperature. We reasoned that when using electron-neutral olefins the reaction should stop after the olefination stage. Indeed, the coupling between *N*-phenyl-2-aminopyridine and *p*-$Cl(C_6H_4)CH{=}CH_2$ (1.1 equiv) under the same conditions gave the monovinylation product **4a** (81% yield) with *trans* geometry (eq 1). Shifting this olefin to simple styrene caused differences in product distribution. Both mono- and divinylation products were observed even though only 1 equiv of styrene was provided. Thus, this divinylation product **4b** can be optimized and was isolated in 72% yield when 10 equiv of styrene and an excess (4.1 equiv) of $Cu(OAc)_2$ were used, and it was further characterized by X-ray crystallography.



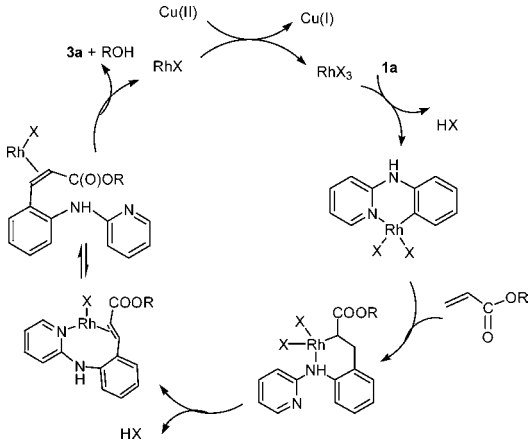
To gain insight into the mechanism of this coupling reaction, an equimolar mixture of **1a** and **1a-*d*$_5$** was heated (DMF, 100 °C) in the presence of $[RhCp^*Cl_2]_2$ (2 mol %) and $Cu(OAc)_2$. H−D exchange occurred at the *ortho* position of the *N*-phenyl ring in these two isotopologues. This result indicated that the C−H activation is reversible under these

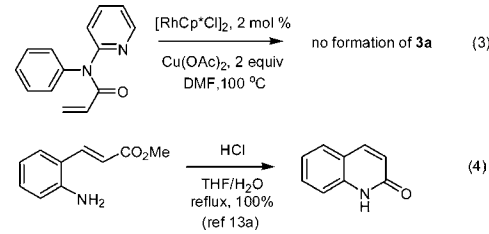
(11) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P.W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586.

conditions, which precludes any KIE measurement on the basis of inter- or intramolecular C−H and C−D competition. A competition reaction to examine the electronic effect of the *N*-aryl ring was carried out using an equimolar mixture of **1f**, **1l**, and benzyl acrylate under the standard conditions (eq 2). NMR analysis of the product mixtures showed that quinolones **3f** and **3l** were obtained in 1:0.6 ratio, where an electron-rich *N*-aryl group favors this coupling reaction. The same trend was also observed in the oxidative coupling with PhC≡CPh, and these observation are in sharp contrast to those in $[RhCp^*Cl_2]_2$-catalyzed oxidative coupling of *N*-aryl benzamides, where the coupling is favored for an electron-poor *N*-aryl or benzoyl group.[4f] In the case of benzamides, it has been suggested on the basis of electronic perturbation that metalation at the (deprotonated) NH nitrogen instead of at the amide oxygen plays a vital role in facilitating the C−H *ortho*-metalation.[4f] The observed electronic effect here seems inconsistent with the coordination of the (deprotonated) NH nitrogen. Instead, chelation assistance offered by the pyridine nitrogen is more likely.

Two distinct pathways for the coupling between *N*-aryl-2-aminopyridines and acrylates can be envisioned. In one pathway, amidation between the coupling partners might take place to give the corresponding acylamide, which subsequently undergoes catalyzed oxidative C(vinyl)−C(aryl) coupling to furnish the final product. To test this possibility, we have synthesized acylamide **5**. Subjection of **5** to the standard conditions gave essentially no coupling product, and only a small amount of decomposition products was observed (eq 3). These results suggest that this amidation−oxidation pathway is unlikely. A more plausible pathway for the oxidative coupling is thus proposed in Scheme 3. Cyclometalation gives a six-membered Rh(III) intermediate with a loss of an acid,[9,12] which can undergo insertion of an incoming acylate. Interestingly, no C_α−N coupling occurs for this Rh(III) alkyl species. Instead, subsequent β-hydride elimination occurs to afford a (metal-bound) *trans*-olefin, which can isomerize to the *cis* isomer. Attack of the NH group on the carbonyl group of this *cis* intermediate generates the final product. The catalytic cycle is completed when the Rh(III) species is regenerated when the Rh(I) intermediate is oxidated by Cu(II). We have noted that related acid-catalyzed cyclization of *ortho*-amino-substituted *trans*-cinnamates by the nucleophilic attack of the nitrogen at the ester carbonyl has been reported to give quinolones (eq 4).[13] This indicates that the isomerization of the *trans* C=C bond geometry to the *cis* one is at least feasible, where annulation is an apparent driving force.

Scheme 3. Plausible Mechanism for the Formation of Quinolones





In summary, we have successfully applied *N*-aryl-2-aminopyridine to the oxidative coupling with alkynes and alkenes using $[RhCp^*Cl_2]_2$ as a catalyst and $Cu(OAc)_2$ as an oxidant. The coupling with internal alkynes furnished *N*-pyridyl-substituted indoles, and coupling with acrylates gave *N*-(2-pyridyl)quinolones as a result of oxidative cyclization. Substrates bearing electron-rich *N*-aryl groups react preferentially. The reaction between *N*-aryl-2-aminopyridine and styrenes under similar conditions afforded mono- and/or disubstituted *trans*-olefins, depending on the electronic effect of the styrene, where an electron-poor styrene favors the monosubstituted olefin. This methodology proves that 2-aminopyridyl can act as an efficient directing group, and this method should find important applications in the synthesis of complex molecules.

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Supporting Information Available: Synthetic procedures, characterization data, NMR spectra of all new compounds, and X-ray crystallographic data of comounds **2a-1**, **2g**, and **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) (a) Li, L.; Brennessel, W. W.; Jones, W. D. *Organometallics* **2009**, *28*, 3492. (b) Davies, D. L.; Al-Duaij, O.; Fawcett, J.; Giardiello, M.; Hilton, S. T.; Russell, D. R. *Dalton Trans.* **2003**, 4132.

(13) (a) Knight, R. L.; Allen, D. R.; Birch, H. L.; Chapman, G. A.; Galvin, F. C.; Jopling, L. A.; Lock, C. J.; Meissner, J. W. G.; Owen, D. A.; Raphy, G.; Watson, R. J.; Williams, S. C. *Biol. Med. Chem. Lett.* **2008**, *18*, 629. (b) Alabaster, C. T.; Bell, A. S.; Campbell, S. F.; Ellis, P.; Henderson, C. G.; Morris, D. S.; Roberts, D. A.; Ruddock, K. S.; Samuels, G. M. R.; Stefaniak, M. H. *J. Med. Chem.* **1989**, *32*, 575. (c) Horino, H.; Inoue, N. *Tetrahedron Lett.* **1979**, *20*, 2403.