ORGANIC LETTERS

2011
Vol. 13, No. 17
4636–4639

Synthesis of 1-Aminoisoquinolines via Rh(III)-Catalyzed Oxidative Coupling

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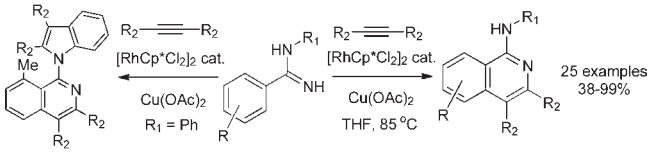
Received July 10, 2011

ABSTRACT



[RhCp*Cl$_2$]$_2$ can catalyze the oxidative coupling of N-aryl and N-alkyl benzamidines with alkynes to give N-substituted 1-aminoisoquinolines in high selectivity.

Transition-metal catalyzed organic reactions via activation of C−H bonds have attracted increasing attention.[1] This process is attractive in that C−H bonds are ubiquitous and prefunctionalization of C−H bonds is no longer necessary. Therefore, selective and efficient functionalization of C−H bonds under mild conditions has been long sought, and this should allow the construction of complex molecules in an energy-efficient and step-economic fashion. Significant progresses have been made, and this topic has been extensively reviewed.[2] Among the various promising activation strategies is the utilization of a proximal directing group, which facilitates the activation of substrate *ortho* C−H bonds. By utilizing this strategy with oxygen and nitrogen directing groups, rhodium complexes have stood out as efficient catalysts in the functionalization of C−H bonds using unsaturated coupling partners.[3]

Recently, Rh(III)-catalyzed oxidative C−H functionalization of arenes with alkynes has been increasingly explored, which allowed for the synthesis of a broad spectrum of heterocycles.[4] A number of research groups, including ours,[5] have successfully applied this method to the synthesis of isoquinolines,[6] isoquinolones,[5c,7] indoles,[8] isocoumarins,[9] indenols,[4b,d] pyrroles,[10] and pyridones.[5d,11]

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10.1021/ol2018505
Published on Web 08/03/2011

Despite the success, it is still necessary to explore substrates with readily installed directing groups that lead to otherwise less accessible structures.

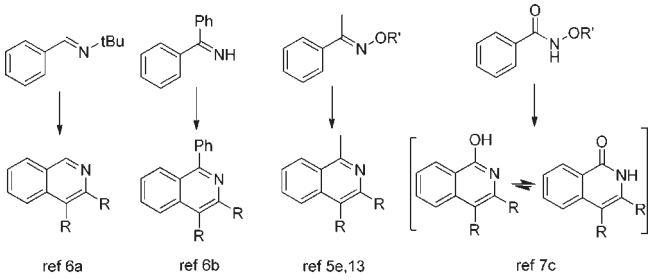


Figure 1. Rh(III)-catalyzed synthesis of isoquinolines.

Isoquinolines are key structural motifs in compounds with important biological activity, and they are also important organic building blocks.[12] Recently, Fagnou,[6a] Miura and Satoh,[6b] Chiba,[13] and We[5e] have successfully applied Rh(III) catalysts to the synthesis of isoquinolines via a C−H activation pathway (Figure 1). However, these products are generally less functionalized at the 1-position. To expend the synthetic utility of Rh(III) catalysis, we aim to prepare less accessible 1-aminoisoquinolines.[14] We noted that the nitrogen in benzamide can act as an efficient directing group for C−H activation in metal-catalyzed oxidative cyclization.[15] However, no oxidative cross-coupling has been reported. We now report Rh(III)-catalyzed oxidative C−C and C−N coupling between *N*-substituted benzamidines and alkynes, leading to 1-(alkylamino)- and 1-(arylamino) isoquinolines.

Recent studies by Miura and Satoh,[7b] Rovis,[7a] and us[5c] indicated that Rh(III) can catalyze the oxidative C−H activation of *N*-aryl benzamides (PhC(O)NHAr) in the *C*-ring. We feel that *N*-aryl benzamidines are structurally related and should undergo analogous reactions with alkynes. However, these two classes of substrates are intrinsically different in that *N*-aryl benzamidines are essentially bifunctional with two N−H bonds. In addition, the low thermostability of benzamidines might cause complications. Thus, at least three oxidation products (**A**−**C**) can be expected when **1a** reacts with PhC≡CPh (eq 1). Moreover, further coupling of these products with a second equivalent of PhC≡CPh is also possible. We herein report the successful isolation of type **A** products.

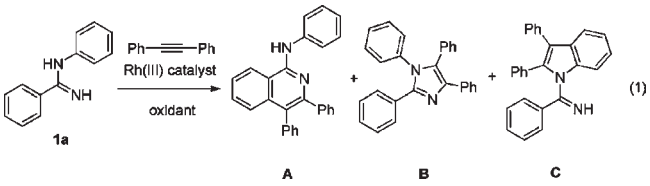
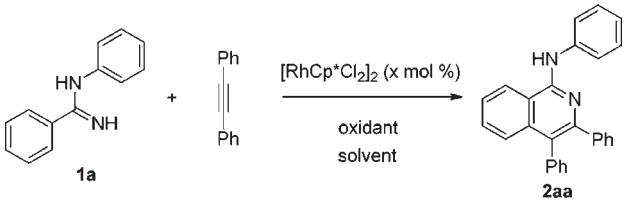


Table 1. Screening of Conditions[a,b]



entry	oxidant	x	solvent	temp (°C)	yield (%)[c]
1	Ag_2CO_3	4	acetone	120	13
2	Ag_2CO_3	4	acetone	90	25
3	$Cu(OAc)_2$	2.5	acetone	90	38
4	$Cu(OAc)_2$	2.5	*o*-xylene	100	58
5	$Cu(OAc)_2$	2.5	DMF	100	14
6	$Cu(OAc)_2$	2.5	^{t}AmOH	110	37
7	$Cu(OAc)_2$	2.5	MeCN	120	28
8	$Cu(OAc)_2$	2.5	DME	90	45
9	$Cu(OAc)_2$	4	THF	85	74
10[d]	$Cu(OAc)_2$	4	THF	85	47

[a] Reaction conditions: **1a** (0.3 mmol), diphenyl acetylene (1.05 equiv), oxidant (2.1 equiv for $Cu(OAc)_2$ or 1.3 equiv for Ag_2CO_3), solvent (3 mL), 13 h, sealed tube under N_2. [b] No evidence for the formation of products of types **B** and **C**. [c] Isolated yield. [d] **1a** (0.3 mmol), PhC≡CPh (1.05 equiv), $Cu(OAc)_2$ (2.1 equiv), $[RhCp^*Cl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %), THF (3 mL), 13 h, sealed tube under N_2.

We commenced our studies with the oxidative coupling of *N*-phenylbenzamidine (**1a**) and PhC≡CPh. The conditions that are optimal for the coupling of *N*-phenylbenzamide and alkynes were applied first (Ag_2CO_3, $[RhCp^*Cl_2]_2$ (4 mol %), acetone, 120 °C).[5c] Although a full conversion was reached (Table 1, entry 1), product **2aa** was isolated in only 13% yield together with an unindentifiable yellow mixture, indicative of a low selectivity. By lowering the

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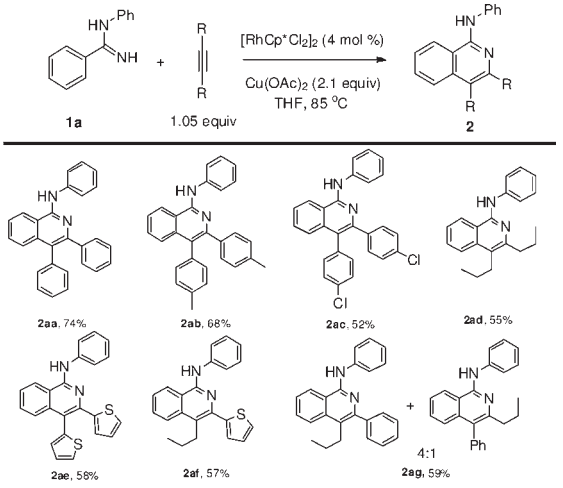
temperature to 90 °C, the yield of **2aa** is slightly increased (entry 2). When $Cu(OAc)_2$ was used as an oxidant, a comparable isolated yield was achieved with 2.5 mol % loading of the catalyst (entry 3). Further optimization using solvents such as MeCN, DME, *o*-xylene, DMF, and *tert*-AmOH all failed to give synthetically viable yields. The well-studied cationic catalyst system $[RhCp^*Cl_2]_2$ (4 mol %)/$AgSbF_6$ (16 mol %) also failed to give synthetically acceptable yield. Fortunately, using THF as a solvent (85 °C) and $Cu(OAc)_2$ as an oxidant, product **2aa** was isolated in 74% yield with 4 mol % catalyst loading (entry 9). The structure of compound **2aa** was determined as an isoquinoline (type **A**) on the basis of NMR spectroscopy.[16] Under these optimized conditions, **2aa** is the only major product that can be isolated, although the unidentifiable yellow mixture still exists. In all cases, no evidence for the formation of products of types **B** and **C** could be obtained, and no such products were isolated.

With the optimized conditions in hand, we explored the coupling of benzamidine **1a** with other alkynes (Scheme 1). Coupling with symmetrically substituted diarylacetylenes, including di(2-thiophenyl)acetylene, afforded the desired products in moderate to good yield (52−74%). The coupling of **1a** with 4-octyne proceeded smoothly, and product

Scheme 1. Coupling of **1a** with Alkyne[a,b,c]



[a] Reaction conditions: **1a** (0.3 mmol), diphenyl acetylene (1.05 equiv), $Cu(OAc)_2$ (2.1 equiv), solvent (3 mL), 13 h, sealed tube under nitrogen.

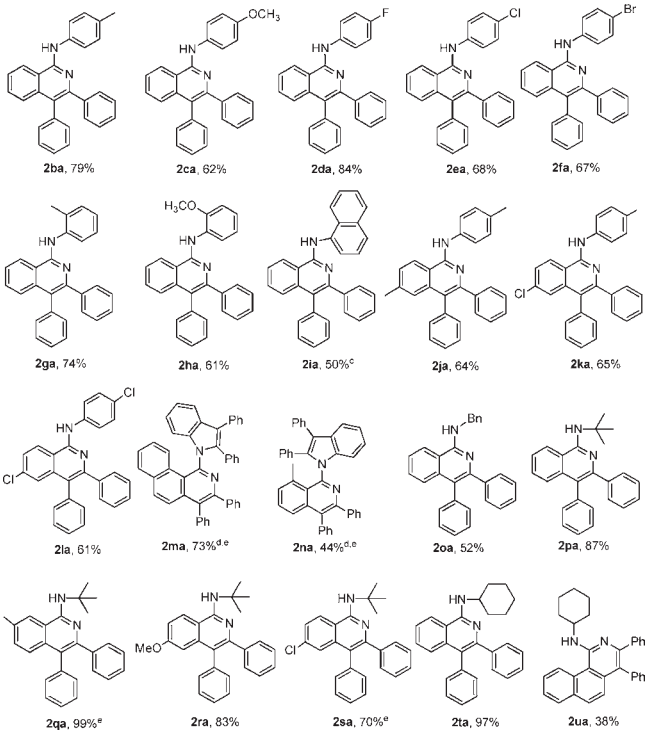
[b] Isolated yield.

[c] No product of type **B** or **C** could be isolated.

2ad was obtained in 55% yield. Unsymmetrically substituted alkyne PhC≡C^{n}Pr reacted to afford a mixture of two regioisomers (**2ag**) in 59% yield and in 4:1 ratio. In contrast, **2af** was isolated (57%) as a single isomer using an unsymmetrical thiophenyl-substituted alkyne.

The scope and limitations of this reaction were further defined using diphenylacetylene as a coupling partner (Scheme 2). A series of *N*-aryl benzamidines was examined first. Benzamidines with *para*-substituted (including halogens) *N*-phenyl groups coupled smoothly with PhC≡CPh to give the correponding product in yield ranging from 62 to 84% (**2ba**, **2ca**, **2da**, **2ea**, and **2fa)**, where the highest yield was obtained for *N*-(*para*-fluorophenyl)benzamidine. However, there seems to be no direct correlation between the electronic parameter of the *para*-substitutent and the reaction yield, which might be ascribed to the presence of the unidentifiable coupling product in each reaction. Further examinations indicated that the reaction yield is not significantly affected by the steric bulk of the *N*-aryl

Scheme 2. Coupling of Benzamidines with PhC≡CPh[a,b]



[a] Reaction conditions: **1a** (0.3 mmol), diphenyl acetylene (1.05 equiv), $Cu(OAc)_2$ (2.1 equiv), THF (3 mL), sealed tube under N_2, 13 h.

[b] No product of type **B** or **C** could be isolated.

[c] **1a** (0.3 mmol), diphenyl acetylene (1.05 equiv), $Cu(OAc)_2$ (2.1 equiv), acetone (3 mL), 110 °C, sealed tube under nitrogen.

[d] **1a** (0.3 mmol), diphenyl acetylene (2.1 equiv), $Cu(OAc)_2$ (4.2 equiv), acetone (3 mL), sealed tube under nitrogen.

[e] 24 h.

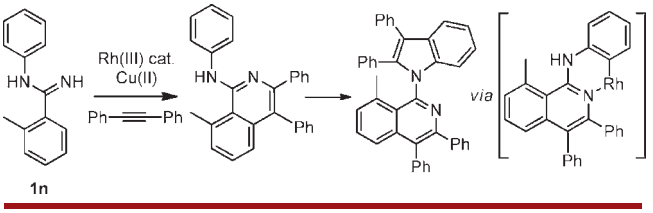
group in the benzamidine when *o*-Me (**2ga**) and *o*-OMe (**2ha**) are introduced, and these products were isolated in good yield. However, essentially no reaction occurred when *N*-(1-naphthyl)benzamidine was subjected to the standard conditions. Only by moving to harsh conditions (acetone, 110 °C) was the desired product obtained in 50% yield (**2ia**).

To better define the scope of this coupling reaction, two benzamidines with a sterically less accessible *C*-ring were examined. Fusing an extra phenyl ring to the *C*-phenyl (**1m**) caused significant differences in reactivity and selectivity.

(16) On the basis of the ^{13}C NMR spectrum of compound **2da**, the structure was further confirmed, where the presence of $^{13}C-^{19}F$ coupling can help rule out structures **B** and **C**.

Essentially no reaction between **1m** and PhC≡CPh occurred under the standard conditions (THF, 85 °C), However, a clean reaction did proceed in acetone at 110 °C (24 h), and ^{1}H NMR analysis of the isolated product revealed the incorporation of two alkynes units, even though only 1.05 equiv was provided. Simple optimization by providing an excess of PhC≡CPh and $Cu(OAc)_2$ afforded this product in 73% yield. The structure of this indole-functionalized isoquinoline **2ma** was unambiguously confirmed by X-ray crystallography (see the Supporting Information). Analogously, substrate **1n** reacted to afford **2na** in 44% isolated yield. In both cases, we falied to isolate the 1:1 oxidative coupling product (Type **A**). We reasoned that the isolation of the 2-fold oxidative coupling product is due to steric assistance. After the formation of the 1-(phenylamino)isoquinoline intermediate (Scheme 3), the steric repulsion between the *o*-Me and the *N*-phenyl group renders these two groups distal to each other, leading to a conformation that is exactly favored for C−H activation. With this conformational assistance, the isoquonoline ring nitrogen coordinated to the Rh(III) to give an intermediate in which the *ortho* C−H bond in the *N*-phenyl ring is pointed favorable to the metal center, leading to cyclomatalation and eventually C−C and C−N formation. Oxidative coupling between the closely related *N*-aryl-2-aminopyridines and alkynes has been reported by us using $[RhCp^*Cl_2]_2$ as a catalyst.[5a] In contrast, we attempted but failed to further oxidatively couple **2aa** with PhC≡CPh using $[RhCp^*Cl_2]_2$ as a catalyst even under harsh conditions. Clearly, the entropic effect and the favored steric assistance are of great importance for further C−H activation.

Scheme 3. Formation of Two-fold Oxidative Coupling Products



Although *N*-benzylbenzamidine coupled with PhC≡CPh to give **2oa** in moderate yield, even higher reactivity and selectivity of the coupling were observed when we moved to other *N*-alkyl benzamidines. Compound **2pa** is the exclusive product in the coupling between *N*-*tert*-butylbenzamidine and PhC≡CPh (87% isolated yield), and essentially no side product could be detected (GC-MS). The differences for benzamidines with *N*-Ph and *N*-^{t}Bu groups indicate that the selectivity of this reaction is significantly affected by the *N*-substituent. In the case of *N*-aryl group, the substrate is bifunctional, so that side reaction products such as types **B** and **C** can be possible, while those are suppressed for *N*-alkyl substrates. In addition, since the ^{t}Bu group is distal to the reaction site, its steric bulk is well-tolerated. Thus *N*-*tert*-Bu and *N*-Cy benzamidines coupled with PhC≡CPh in high yield for substrates bearing different *para* substituents in the *C*-ring (**2pa**−**2ta**). Significantly, **2qa** was even isolated in nearly quantitative yield when a *m*-Me group was introduced to the *C*-phenyl ring, and the product corresponds to C−H activation at a less hindered position (**2qa**). Further studies indicated that this coupling reaction is significantly affected by the steric bulk of the *C*-ring. For example, no reaction occurred when a Me group was introduced to the *ortho* position of *N*-*tert*-Bu benzamidine. In line with this observation, by fusing an extra phenyl ring to the *C*-pehyl ring of the benzamidine, this coupling is also less efficient since product **2ua** was isolated in 38% yield.

Competition reactions have been carried out to explore some details of this reaction. The competition between substrates **1s** and **1p** in the reaction with an equimolar amount of PhC≡CPh afforded **2sa** and **1pa** in 1:2.1 ratio, indicating that this coupling is favored for benzamidines with electron-rich *C*-aryl rings. This observation seems to suggest that the benzamidine nitrogen is metalated as a neutral donor and this parallels that in the oxidative coupling of *N*-aryl-2-aminopyridines with alkynes,[5a] where chelation assistance is believed to be offered by the neutral pyridine ring nitrogen. This observation is in contrast to that in the oxidative coupling of *N*-aryl benzamides and alkynes,[7a] where the nitrogen metalated as an anionic group.

In summary, we have achieved the synthesis of *N*-substituted 1-aminoisoquinolines via Rh(III)-catalyzed oxidative coupling of *N*-aryl and *N*-alkyl benzamidines with alkynes. This reaction occurred via *ortho* C−H activation of the *C*-aryl ring. The coupling of *N*-aryl benzamidines gave functionalized isoquonilines in moderate to good yield, and *N*-^{t}Bu and *N*-Cy benzamidines showed even higher efficiency and selectivity. A broad scope of substrates has been defined. In both cases steric bulk of the *C*-aryl ring has a significant influence on the reaction selectivity and efficiency. Given the wide presence of isoquinolines in natural products and in organic synthesis, the current reactions are likely to find synthetic utility.

Acknowledgment. We thank the Dalian Institute of Chemical Physics, Chinese Academy of Sciences for financial support.

Supporting Information Available. General experimental procedure and characterization data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.