ORGANIC LETTERS

2013
Vol. 15, No. 13
3460–3463

Rhodium(III)-Catalyzed Oxidative Olefination of Pyridines and Quinolines: Multigram-Scale Synthesis of Naphthyridinones

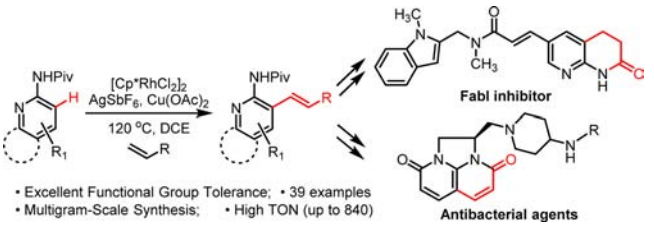
Jun Zhou,[†] Bo Li,[†] Fang Hu,[‡] and Bing-Feng Shi*[,†,‡]

Department of Chemistry, Zhejiang University, Hangzhou 310027, China, and State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

bfshi@zju.edu.cn

Received May 31, 2013

ABSTRACT



A Rh(III)-catalyzed oxidative olefination of pyridines and quinolines has been achieved. This method has a broad substrate scope and has been applied to the expeditious, multigram-scale synthesis of naphthyridinones.

The pyridine ring is a common motif in nature and has extensive application in pharmaceuticals and agrochemicals, as well as material science.[1] Consequently, tremendous efforts have been made to construct these scaffolds. Among them, the expeditious synthesis via direct C−H functionalization of pyridine is of broad interest in terms of atom and step economy.[2] A number of research groups have made considerable progress in the transition-metal-catalyzed direct alkylation and arylation of pyridines.[3,4] In contrast, although transition-metal-catalyzed direct olefination of C−H bonds (Fujiwara−Moritani reaction)[5] has emerged as a powerful method for the introduction of functional diversity and structural versatility,[6,10] relatively few examples of the direct olefination of pyridyl C−H bonds have been reported.[7−9] Nakao and Hiyama demonstrated C-2 selective alkenylation of pyridine-*N*-oxides catalyzed by nickel and the direct alkenylation of pyridines by nickel/Lewis acid catalyst.[7a,b] Shortly after that, the same group and the Yap group independently realized the

[†] Zhejiang University.
[‡] Shanghai Institute of Organic Chemistry.

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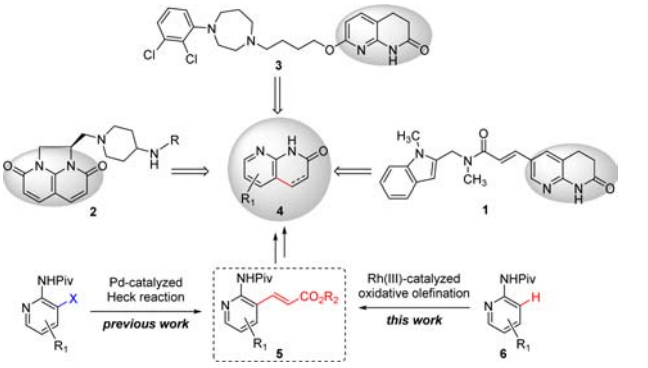
10.1021/ol401540k
Published on Web 06/24/2013

C-4 selective alkenylation of pyridines by the bimetallic nickel aluminum catalyst.[3f,7c] The Chang group reported the C-2 dehydrative olefination of pyridine *N*-oxides with external oxidants.[7d] Recently, the Yu group developed a novel C-3 selective olefination catalyzed by Pd/1,10-phenanthroline.[8] There are a few other important discoveries in this area;[9] however, many of these methods still suffer from a limited substrate scope, require a large excess of pyridines, and employ symmetrical alkynes with little functionality or prefunctionalized alkenyl iodides as the coupling partners.

Recently there has been great success in the Rh(III)-catalyzed oxidative C−H olefination of simple arenes owing to high efficiency and good functional group tolerance;[10,11] however, reported examples of Rh-catalyzed oxidative C−H/C−H cross-coupling reactions between pyridines and alkenes are still very limited. To the best of our knowledge, there are only a few isolated examples of Rh(III)-catalyzed C−H activation of pyridines, except that Li has reported systematic studies of Rh(III)-catalyzed olefination and oxidative annulation of isonicotinamides.[9c,12] Thus, it still remains a challenge to achieve selective direct functionalization of pyridines, especially in terms of substrate scope, synthetic versatility, and catalyst loading.

3-Alkenyl pyridines are valuable building blocks for pharmaceuticals owing to their functional diversity. For example, 3-alkenyl-2-aminopyridines (**5**) were precursors to 3,4-dihydro-1,8-naphthyridin-2(1*H*)-ones (**4**), which were common synthons to biologically important compounds, such as **1**−**3**.[13] It has been reported that compounds **1**−**3** were a FabI inhibitor,[13a] an antibacterial agent,[13b] and a selective ligand of dopamine D2 receptors,[13c] respectively (Scheme 1). We realized that the directed alkenylation of *N*-(pyridin-2-yl)pivalamide **6b** would allow the straightforward synthesis of a large family of such skeletons from abundant 2-aminopyridine derivatives.

Scheme 1. Strategy for the Synthesis of 3,4-Dihydro-1,8-naphthyridin-2(1*H*)-ones (**4**) Using Direct Oxidative Olefination of Pyridines as a Key Step



Our studies commenced with applying reaction conditions previously established by Glorius for the Rh(III)-catalyzed oxidative Heck reaction of acetanilide and styrene.[11c] However, no desired product was observed when **6a** was used as the substrate (Table 1, entry 1). We were delighted to find that the reaction of *N*-(pyridin-2-yl)-pivalamide **6b** with ethyl acrylate resulted in the formation of the desired product, albeit in low yield (entry 2). DCE was found to be the ideal solvent for the reaction providing **5c** in quantitative yield (entry 4). $Cu(OAc)_2$ is essential to the success of this tranformation, while other additives such as Ag_2CO_3 and $Zn(OAc)_2$ resulted in low yields (entries 5−6). Attempts to lower the $Cu(OAc)_2$ loading under the atmospheric pressure of O_2 led to reduced yields (entries 7−8). Notably, *N*-(pyridin-2-yl)acetamide **6a** decomposed to 2-aminopyridine under the optimized reaction conditions (entry 9).

With the optimized conditions in hand, we further studied the scope and limitations of this reaction (Scheme 2). Different acrylates all gave good to excellent yields (**5b**−**5d**), while unactivated alkenes such as styrene failed in this case (**5a**). A wide range of 2-aminopyridine derivatives are compatible with this protocol, furnishing the desired products in good yields. Importantly, halides, such as chloride, bromide, and iodide, survived under the standard or slightly modified conditions, affording the

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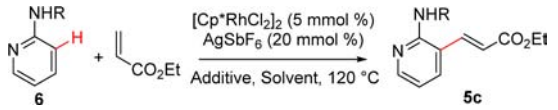
Table 1. Optimization of Reaction Conditions[a]



entry	R	additive	solvent	yield (%)
1	Ac (**6a**)	2.0 equiv of $Cu(OAc)_2$	*t*-AmylOH	0[b]
2	Piv (**6b**)	2.0 equiv of $Cu(OAc)_2$	*t*-AmylOH	6[b]
3	Piv (**6b**)	2.0 equiv of $Cu(OAc)_2$	DCE	42
4	Piv (**6b**)	2.0 equiv of $Cu(OAc)_2$	DCE	100
5	Piv (**6b**)	2.0 equiv of Ag_2CO_3	DCE	58
6	Piv (**6b**)	2.0 equiv of $Zn(OAc)_2$	DCE	31
7[c]	Piv (**6b**)	1.0 equiv of $Cu(OAc)_2$	DCE	91
8[c]	Piv (**6b**)	0.5 equiv of $Cu(OAc)_2$	DCE	49
9	Ac (**6a**)	2.0 equiv of $Cu(OAc)_2$	DCE	–

[a] Conditions: **6** (0.2 mmol), ethyl acrylate (0.3 mmol), $[Cp^*RhCl_2]_2$ (5 mmol %), $AgSbF_6$ (20 mmol %), additive in solvent (2 mL) for 24 h. Isolated yield. [b] Determined by ^1H NMR. [c] Under O_2.

corresponding olefinated products in moderate to good yields (**5f**–**5j**, 44%–76%); this was a synthetically interesting result as such substituents could serve as versatile handles for further elaboration using conventional Pd-mediated cross-coupling (see Scheme 4 for synthetic applications). 2-Aminopyridine derivatives containing electron-donating groups at the 6-position and/or 5-position were generally more reactive and afforded higher yields than those carrying electron-withdrawing groups (**5k**–**5t**). The strong electron-withdrawing cyanide group is also tolerated, albeit affording the product in a reduced yield (**5t**, 33%). The oxidative C–H olefination was very sensitive to steric hindrance, since only the 4-F derivative gave the desired product in lower yield (**5v**, 39%) while other substituents failed in this case (**5u**). Moreover, 5,6-disubstituted substrates were olefinated effectively to giving even higher yields (**5w**, 90%; **5x**, quantitative), which suggested this reaction protocol might be applied to synthetic useful intermediates with more complicated functional groups. Furthermore, diolefinated product **5y** was obtained in 98% yield by adding 3.0 equiv of ethyl acrylate under this protocol.

The nature of the heteroarenes can also be varied to electron-rich heterocycles such as indole and pyrazole (Scheme 3, **5z**–**5aa**).[14] Indeed, the olefination of 4-aminoindole proceeded selectively by *N*-pivalamide-directed *ortho* reactivity rather than either the C2 or C3 olefination. This protocol serves as a complementary method to the oxidative C2 and C3 olefination of indoles.[15] *N*-Methyl-3-aminopyrozole pivalamide **5aa** was very reactive, and a high yield (96%) was obtained.

We were delighted to find that oxidative C–H olefination also occurred smoothly with quinoline derivatives

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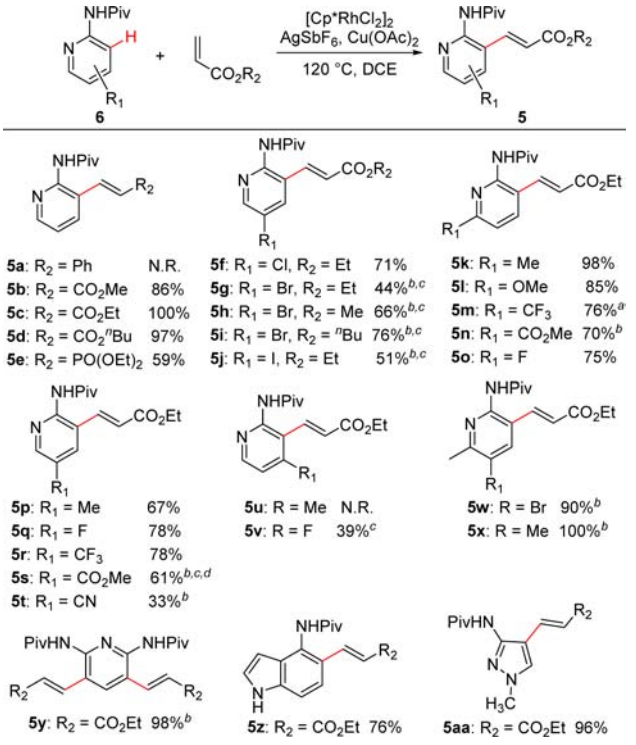
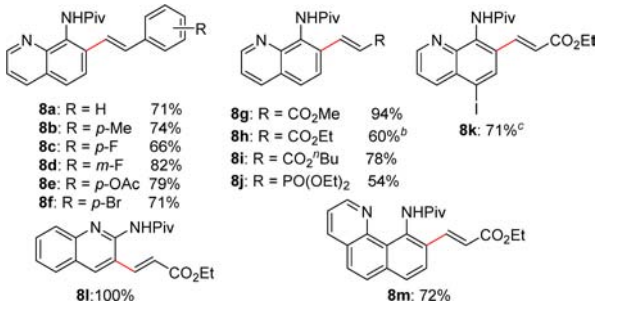
Scheme 2. Olefination of 2-Aminopyridine Pivalamides[e]



[a] 100 °C. [b] 3.0 equiv ethyl acrylate was added. [c] Run for 24 h and ethyl acrylate was added in three portions. [d] 0.1 equiv $[Cp^*RhCl_2]_2$ and 0.4 equiv $AgSbF_6$ was added. [e] Conditions: **6** (0.2 mmol), alkene (0.3 mmol), $[Cp^*RhCl_2]_2$ (5 mmol %) and $AgSbF_6$ (20 mmol %) in 2 mL of DCE for 24 h. Isolated yield.

Scheme 3. Olefination of Quinoline Pivalamides[a]



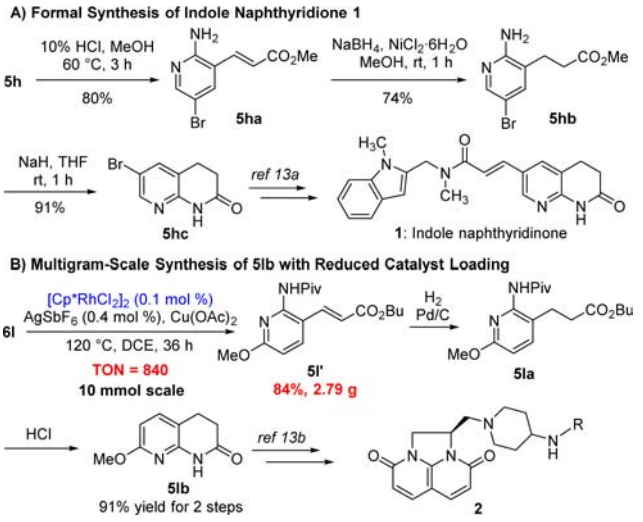
[a] Isolated yield. [b] 100 °C. [c] 3.0 equiv of ethyl acrylate were added.

(Scheme 3). In this case, styrenes bearing either electron-withdrawing or -donating groups all afforded olefinated products in good yields (**8a**–**8f**). Different acrylates readily coupled with **7** in isolated yields ranging from 60% to 94% (**8g**–**8i**). In addition, other electrophilic alkenes such as vinyl phosphonate also reacted under these conditions (**8j**). The generality of the quinoline pivalamide was next demonstrated. Under the standard conditions, iodo-substitution in the substrate can be tolerated, enabling additional modification reactions at the iodogenated position. Moreover, both *N*-(quinolin-2-yl)pivalamide (**7l**) and

N-(benzo[*h*]quinolin-10-yl)pivalamide (**7m**) reacted with ethyl acrylate in high yields (**8l**, quantitative; **8m**, 72%).

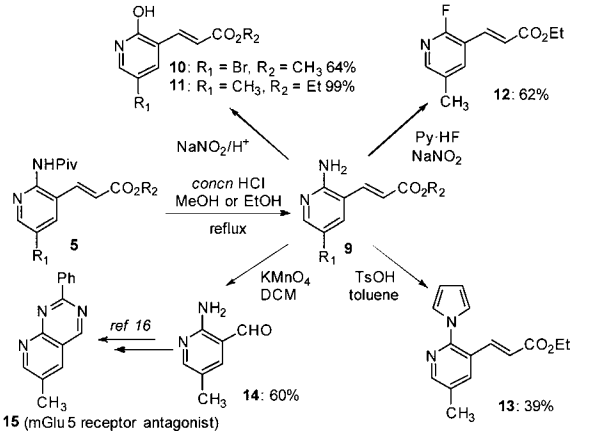
Our strategy was then applied to the formal synthesis of pharmaceutically important compounds **1**–**2** (Scheme 4). Hydrolysis of the olefinated product **5h** under acidic conditions afforded **5ha** in 80% yield. 6-Bromo-3,4-dihydro-1,8-naphthyridin-2(1*H*)-one (**5hc**) was achieved after selective reduction and cyclization. Amide **5hc** can be converted to indole naphthyridinone **1** according to a literature procedure (Scheme 4A).[13a] Moreover, under our optimized conditions, a multigram-scale synthesis of 7-methoxy-3,4-dihydro-1,8-naphthyridin-2(1*H*)-one **5lb** was achieved in three steps starting from **6l** in 76% overall yield. **5lb** was the key building block for the synthesis of antibacterial agent **2** (Scheme 4B).[13b] Notably, this reaction proceeded smoothly on a multigram scale with a low catalysis loading (0.1 mol %) and high turnover (TON = 840). In comparison with previous approaches, the current method is advantageous for rapid library synthesis in drug discovery because of its operational simplicity, tolerance of various functional groups, and broad availability of starting materials.

Scheme 4. Synthetic Applications



The significance of this rhodium-catalyzed oxidative olefination of pyridine derivatives is additionally demonstrated by its chemoselective transformations to various synthetic useful intermediates. The pivalamide can be deprotected under acidic conditions to afford free amine **9**. As outlined in Scheme 5, the amino group in compound **9** can be readily coverted into 2-OH compounds **10**–**11** and 2-fluoro compound **12** by means of the well-known Sandmeyer reaction. The biologically important 2-(1*H*-pyrrol-1-yl)pyridine (**13**) was constructed by treatment with 2,5-dimethoxytetrahydrofuran. In addition, the C=C double bond can be oxidatively cleaved by $KMnO_4$ to afford compound **14**, which is a precursor of pyrido[2,3-*d*]-pyrimidines (**15**), a potent mGlu5 receptor antagonist.[16]

Scheme 5. Synthetic Transformations of **5**



In summary, we have achieved the effective oxidative olefination of both pyridine and quinoline pivalamides at the *ortho*-position of the directing group, which involves a rhodium(III)-catalyzed C–H activation pathway using $Cu(OAc)_2$ as a convenient oxidant. This protocol is operationally simple and has been successfully applied to the expeditious, multigram-scale synthesis of naphthyridinones with a low catalyst loading (0.1 mol %). The high reactivity might result from the competitive coordination of $Cu(OAc)_2$ with the pyridine nitrogen, which may facilitate the Rh(III)-catalyzed C–H activation.[10a,12] Further investigations to study the mechanism of this reaction are underway.

Acknowledgment. Financial support from the National Science Foundation of China (21002087, 21272206), the Fundamental Research Funds for the Central Universities (2010QNA3033), Zhejiang Provincial NSFC (Z12B02000), and the Ministry of Education (SRFDP 20110101110005) is gratefully acknowledged. We also are thankful for the Scholarship Award for Excellent Doctoral Student granted by the Ministry of Education to J.Z. (2011).

Supporting Information Available. Experimental details, spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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