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ARTICLE TYPE

Ruthenium-Catalyzed Direct C-3 Oxidative Olefination of Imidazo[1,2-a]pyridines

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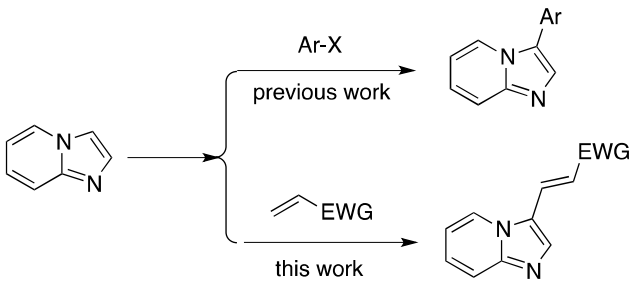
A highly regioselective oxidative olefination of imidazo[1,2-a]pyridines with acrylates has been accomplished in the presence of ruthenium catalysts to form only the C-3 coupling products. The oxidative olefination has provided step economical access to diversely substituted imidazo[1,2-a]pyridine derivatives with excellent C-3 regioselectivity and *E*-stereoselectivity.

Transition-metal-catalyzed direct oxidative olefination[1] of (hetero)arenes via two fold C-H bond cleavages has emerged as a powerful tools for the introduction of functional diversity and structural complexity into (hetero)arenes. As the pioneering work done by Fujiwara and coworkers,[2] elegant progress has been developed in this field. The direct oxidation olefination has already attracted much attention because of its chemical versatility and its environmental advantages. Recently, many organic chemists have sought to expand the synthetic utility of (hetero)arenes C-H olefination by improving the reactivity and controlling the positional selectivity. Consequently, successful processes have been achieved by using a variety of palladium[3], ruthenium,[4] rhodium,[5] iridium.[6] In spite of the tremendous progress made in this field, the development of efficient ruthenium-catalyzed transformation to form C-C bonds via direct oxidative olefination of (hetero)arenes is still highly favorable.

We are particularly interested in the development of new catalytic transformation that exploit selective C-H functionalization to elaborate simple imidazo[1,2-a]pyridines to useful products. Imidazo[1,2-a]pyridine rings are among the most important heterocyclic structural motifs.[7] It has been found to be key structural units in many pharmaceuticals and exhibited a wide range of biological activities,[8] such as zolpidem, zolimidine, and alpidem, necopidem, olprinone, and divalpon.[9] Thus, the development of short and facile routes for the construction of imidazo[1,2-a]pyridine compounds through transition-metal-catalyzed functionalizations has received intensive attention. Among these metal, Pd, Au, Ag, and Cu is the favorable catalysts for the preparation of imidazo[1,2-a]pyridine derivatives.[10] transition-metal-catalyzed transformation has been developed for the synthesis of imidazo[1,2-a]pyridine derivatives during the last few years, there has only been a rare example for the direct olefination of imidazo[1,2-a]pyridine.

We have recently developed metal-catalyzed C-H functionalization of imidazo[1,2-a]pyridine[11] and efficient transformation to construct functionalized heterocyclic compounds.[12] In this context, our attention is focused on the development of Ru-catalyzed olefinations of imidazo[1,2-a]pyridines to prepare useful and bioactive imidazo[1,2-a]pyridine derivatives.

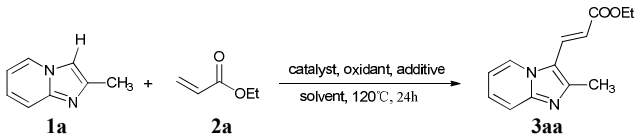


Scheme 1. Synthesis of Imidazo[1,2-a]pyridines

In light of recent advances in this area, our investigation has begun with the direct olefination of 2-methylimidazo[1,2-a]pyridine **1a** with ethyl acrylate **2a** in the presence of Ru catalyst and the results are summarized in Table 1. The reaction has provided a Heck-type product **3aa** in 45% GC yield with excellent *E*-stereoselectivity in the presence of 3 mol% of $[RuCl_2(p\text{-cymene})]_2$ as a catalyst, 1 equiv of $Cu(OAc)_2 \cdot H_2O$ as oxidant, and 40 mol% of KPF_6 as a additive in 1,2-dichloroethane (DCE) at 120℃ for 24 h (Table 1, entry 1). Other Ru sources, such as $Ru(acac)_2$ and $RuCl_2(PPh_3)_3$, have been also examined and given poor GC yields (Table 1, entries 2-3). Screening of additional Cu oxidants ($CuCl_2$, $CuBr_2$, $Cu(OTf)_2$) has led to significantly reduced yields (Table 1, entries 4-6). Several silver oxidants such as AgOTf, Ag_2CO_3 or AgOAc have been tested to improve the yield of the desired product. Unfortunately, only formation of trace amount of **3aa** has been detected (Table 1, entries 7-9). Subsequently, we have carried out evaluations of other additives (e.g., $AgBF_4$, $AgSbF_6$, AcOH, NaOAc, $CsCO_3$) with encouraging results: the additives of $AgSbF_6$ have been revealed as the best choice, and the yield of **3aa** has been improved to 76% (Table1, entries 10-14). Further screening of solvents with 1,4-dioxane, DMF, CH_3CN, DMSO or H_2O

hasn't improve the yield of our desired product (Table 1, entries 15-19). Furthermore, the control experiment showed that the ruthenium as catalyst is necessary to the success of the transformation (Table 1, entries 20).

Table 1. Optimization of Reaction Conditions[a]



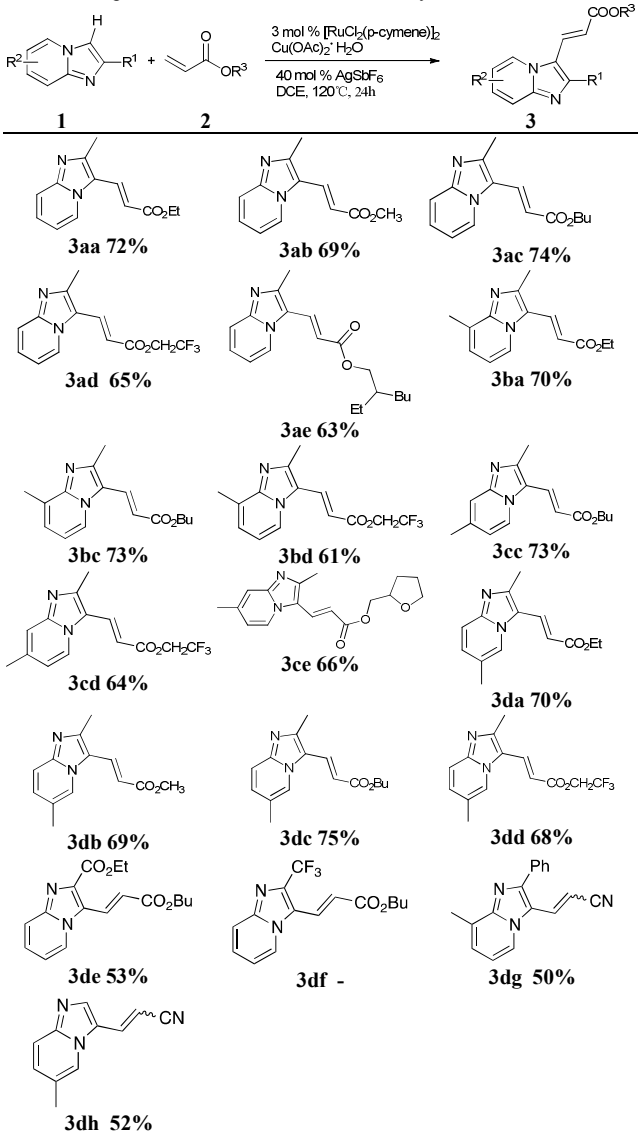
1a **2a** **3aa**

Entry	Catalyst	Oxidant	Additive	Solvent	Yield (%)[b]
1	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	KPF_6	DCE	45
2	$Ru(acac)_2$	$Cu(OAc)_2 \cdot H_2O$	KPF_6	DCE	trace
3	$RuCl_2(PPh_3)_3$	$Cu(OAc)_2 \cdot H_2O$	KPF_6	DCE	-
4	$[RuCl_2(p\text{-cymene})]_2$	$CuCl_2$	KPF_6	DCE	28
5	$[RuCl_2(p\text{-cymene})]_2$	$CuBr_2$	KPF_6	DCE	26
6	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OTf)_2$	KPF_6	DCE	10
7	$[RuCl_2(p\text{-cymene})]_2$	AgOTf	KPF_6	DCE	trace
8	$[RuCl_2(p\text{-cymene})]_2$	Ag_2CO_3	KPF_6	DCE	trace
9	$[RuCl_2(p\text{-cymene})]_2$	AgOAc	KPF_6	DCE	trace
10	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	$AgBF_4$	DCE	21
11	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	$AgSbF_6$	DCE	76
12	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	AcOH	DCE	5<
13	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	NaOAc	DCE	-
14	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	$CsCO_3$	DCE	-
15	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	$AgSbF_6$	dioxane	72
16	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	$AgSbF_6$	DMF	21
17	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	$AgSbF_6$	CH_3CN	54
18	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	$AgSbF_6$	DMSO	16
19	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	$AgSbF_6$	H_2O	-
20	-	$Cu(OAc)_2 \cdot H_2O$	$AgSbF_6$	DCE	-

[a] Reactions condition:**1** (0.5 mmol), **2a** (2.5 mmol), Ru-catalyst (5 mol%), oxidant (1.0 mmol), additives (40 mol%), solvent (3.0 mL), 120℃, 24 h. [b] GC yields.

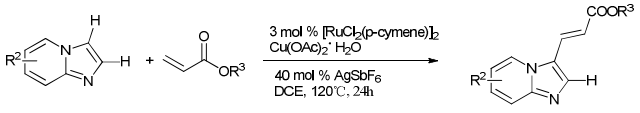
Under optimized reaction conditions, we evaluated different imidazo[1,2-a]pyridines derivatives **1** and various acrylates **2**. The results are summarized in Table 2. First, by using **1a** as a fixed substrate, we carried out the olefination of **1a** with various acrylates. We are delighted to find that acrylates such as ethyl acrylate **2a**, methyl acrylate **2b**, butyl acrylate **2c**, 2,2,2-trifluoroethyl acrylate **2d**, and 2-ethylhexyl acrylate **2e**, are compatible with the transformation. The desired products have been afforded in moderate to good yields. Subsequently, the scope of the reaction with respect to the substituted imidazo[1,2-a]pyridines reactant were also employed. The effect of substituents in different positions of imidazo[1,2-a]pyridines were tested. Electrondonating methyl groups at the 2-, 6-, 7-, and 8-positions of imidazo[1,2-a]pyridine ring participated well in the transformation, affording the desired 3-substituted imidazo[1,2-a]pyridine with moderate to good yield. To further evaluate the electronic effect of different substituents on the imidazo[1,2- a]pyridines, other substituted groups (C-2) such as CO_2Et, CF_3 were examined. The desired product **3de** was obtained in moderate yield. But the olefination product **3df** was not formed using 3-(trifluoromethyl)imidazo[1,2-a]pyridine as a substrate. Furthermore, a mixture of E/Z-isomers (**3dg**, **3dh**) has obtained, when the reaction of acrylonitrile with 8-methyl-2-phenylimidazo[1,2-a]pyridine was carried out under optimized condition. All the results indicated that these new conditions were also successfully applied to substituted imidazo[1,2-a]pyridines and acrylates.

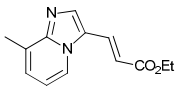
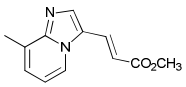
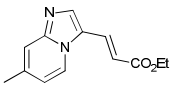
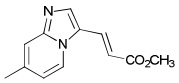
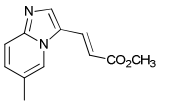
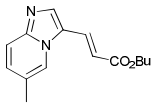
Table 2. Scope of Oxidative olefination with acrylates.



[a] Reaction conditions: **1a** (0.5 mmol), **2a** (2.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (3.0 mol %), $Cu(OAc)_2 \cdot H_2O$ (1.0 mmol), $AgSbF_6$ (40 mol%), DCE (3.0 mL), 120℃ for 24 h; [b] Isolated yields.

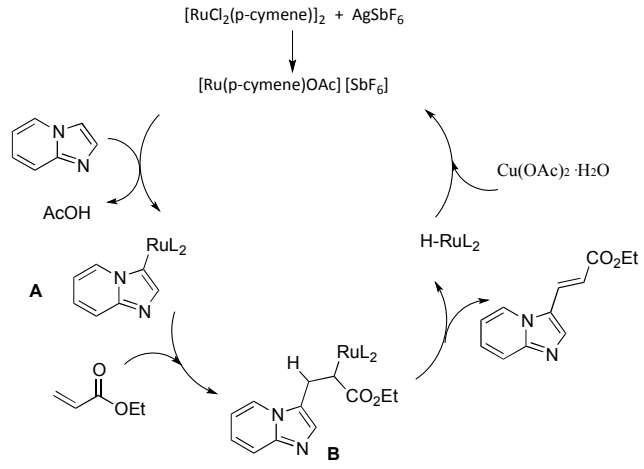
Table 3. Regioselective synthesis of imidazo[1,2-a]pyridines



1	2	3
		
3ea 72%	**3eb 74%**	**3fa 70%**
		
3fb 72%	**3gb 70%**	**3gc 75%**

[a] Isolated yields

The scope of this highly regioselective coupling reaction has been further explored by reacting 2,3-unsustituted imidazo[1,2-a]pyridines with acrylates. The results described in Table 3. As expected, acrylates have coupled with 2,3-unsustituted imidazo[1,2-a]pyridines to furnish the corresponding C-3 olefination products in moderate to good yields. These results indicated that this coupling reaction turned out to be a versatile reaction.



Scheme 2. Proposed mechanism.

On the basis of previous metal-catalyzed direct oxidative olefination via C-H bond activation, a plausible mechanism of the dierect olefination reaction could be described in Scheme 2. Migratory insertion of ethyl acrylate into the Ru-C bond of intermediate **A** forms intermediate **B**. Subsequently, intermediate **B** underwent reductive elimination to give the product and ruthenium hydride that was reoxidation with $Cu(OAc)_2$ to regenerate the active ruthenium species for the next catalytic.

In conclusion, an efficient ruthenium (II)-catalyzed regioselective C-3 alkenylation of substituted imidazo[1,2-a]pyridines with diverse acrylates is developed.This discovery could have important consequences for the selective elaboration of imidazo[1,2-a]pyridine core structures which is broadly applicable for the synthesis of biologically active molecules. We are currently investigating the application of this transformation as well as exploring the utility of imidazo[1,2-a]pyridine C-H bond transformation as a versatile platform for complex molecule synthesis.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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