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Ruthenium-catalyzed alkenylation of azoxybenzenes with alkenes through *ortho*-selective C–H activation†

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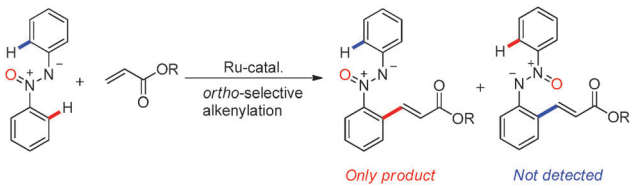
A highly selective alkenylation of azoxybenzenes catalyzed by the Ru^{III}-complex was developed. It provides a direct access to a series of olefinated azoxy compounds in good yields.

Recently, transition metal-catalyzed alkenylation of C–H bonds has been one of the most practical, atom- and step-economical method in synthetic organic chemistry.[1] Especially noteworthy is that Fujiwara's group has made the initial work on the catalytic alkenylation of electron-rich aromatic C–H bonds with alkenes by a palladium complex.[2] After that, the palladium catalyst was broadly employed in the catalytic alkenylation of functionalized substrates.[3] In addition, rhodium-catalyzed alkenylations of amides, esters and ketones were also developed in recent years.[4] Most recently, ruthenium complexes have been exploited as alternative catalysts for the direct C–H bond alkenylations.[5] For example, Ackerman,[5a,b] Wang,[5c,d] and others[5e–h] have done excellent work on the Ru-catalyzed alkenylations. However, more substrates with new directing groups and the regio-selective reactions at their *ortho*-positions were necessary to be explored. As far as we know, the useful azoxybenzenes with two kinds of C–H bonds at the *ortho*-position of the nitrogen atom have been rarely studied in group-directed C–H activation and functionalizations.[6]

Azoxy compounds are important materials and useful intermediates in electronic devices due to their liquid crystalline properties,[7] and they have also been used as dyes, polymer inhibitors and stabilizers.[8] In light of their importance, numerous methods for the preparation of azoxy compounds have been developed.[9] However, there is no report on the synthesis of *ortho*-alkenyl azoxybenzenes. Very recently, Ru^{II}-catalyzed C–H bond activation and functionalizations have been reported,[5,10] and which promoted us to explore the possibility of Ru^{III}-catalyzed alkenylation of azoxybenzenes with alkenes.



Scheme 1 Ru^{III}-catalyzed *ortho*-selective alkenylation.

As part of our ongoing interest in C–H activation,[11] herein we wish to report the first Ru^{III}-catalyzed *ortho*-selective alkenylation of azoxybenzenes, which provided a simple approach to a variety of olefinated azoxy compounds (Scheme 1).

The initial reaction of azoxybenzene (**1a**) with ethyl acrylate (**2a**) was carried out in the presence of 2.5 mol% of $[\{RuCl_2(p\text{-cymene})\}_2]$ and $Cu(OAc)_2{\cdot}H_2O$ (1.0 equiv.) in 1,2-dichloroethane (DCE) at 110 °C for 12 h, which only generated the mono-substituted alkenylation product **3a** in 17% yield (Table 1, entry 1). The structure of **3a** was indirectly confirmed by the hydrolysis of **3a** into its carboxylic acid **4a** in NaOH–CH_3OH,[12] and the structure of **4a** was further determined by X-ray single crystal analysis, as described in Scheme 2 (details in ESI†). After that, the use of anhydrous $Cu(OAc)_2$ was investigated in the model reaction under a nitrogen atmosphere, and 29% of **3a** was isolated (Table 1, entry 2). To our delight, an enhanced yield of **3a** was observed in the presence 5.0 mol% of $[Cp^*RuCl_2]_n$ as the catalyst (Table 1, entry 3). Some other common additives, such as KPF_6 and $AgSbF_6$, were also examined and results showed that the employment of $AgSbF_6$ (20 mol%) obviously accelerated this transformation (Table 1, entries 4–7).

Subsequently, the optimization of reaction time and temperature did not improve the yield of product **3a** (Table 1, entries 8–11). When the molar ratio of **1a**/**2a** (1 : 2) was controlled, a lower yield of **3a** was achieved (41%), and the formation of disubstituted product may account for this result (Table 1, entry 12).[13] It was found that the use of silver salt as an additive resulted in lower yields of **3a** (Table 1, entries 13 and 14). Additionally, it was found that the Ru-catalyzed alkenylation reaction could not proceed in the absence of $Cu(OAc)_2$ (Table 1, entries 15 and 16). Finally, some typical reaction media

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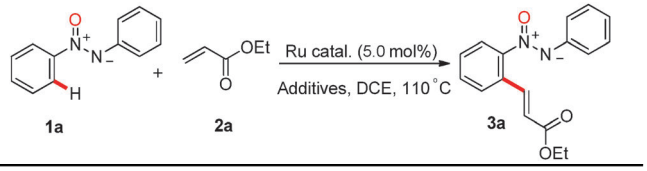
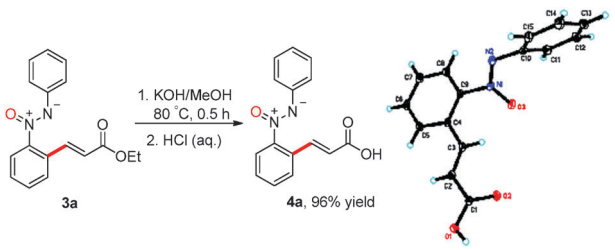
Table 1 Optimization of Ru source and additives[a]



Entry	Ru source	Additive **1** (1.0 equiv.)	Additive **2** (mol%)	Yield[b] (%)
1	$[RuCl_2L]_2$	$Cu(OAc)_2{\cdot}H_2O$	/	17
2	$[RuCl_2L]_2$	$Cu(OAc)_2$	/	29
3	$[Cp^*RuCl_2]_n$	$Cu(OAc)_2$	/	35
4	$[Cp^*RuCl_2]_n$	$Cu(OAc)_2$	KPF_6 (10)	33
5	$[Cp^*RuCl_2]_n$	$Cu(OAc)_2$	$AgSbF_6$ (10)	56
6	$[Cp^*RuCl_2]_n$	$Cu(OAc)_2$	$AgSbF_6$ (20)	68
7	$[Cp^*RuCl_2]_n$	$Cu(OAc)_2$	$AgSbF_6$ (30)	70[c]
8	$[Cp^*RuCl_2]_n$	$Cu(OAc)_2$	$AgSbF_6$ (20)	62[d]
9	$[Cp^*RuCl_2]_n$	$Cu(OAc)_2$	$AgSbF_6$ (20)	69[e]
10	$[Cp^*RuCl_2]_n$	$Cu(OAc)_2$	$AgSbF_6$ (20)	51[f]
11	$[Cp^*RuCl_2]_n$	$Cu(OAc)_2$	$AgSbF_6$ (20)	70[g]
12	$[Cp^*RuCl_2]_n$	$Cu(OAc)_2$	$AgSbF_6$ (20)	41[h]
13	$[Cp^*RuCl_2]_n$	AgOAc	$AgSbF_6$ (20)	24
14	$[Cp^*RuCl_2]_n$	Ag_2CO_3	$AgSbF_6$ (20)	11
15	$[Cp^*RuCl_2]_n$	/	$AgSbF_6$ (20)	0
16	$[Cp^*RuCl_2]_n$	/	$AgSbF_6$ (20)	0[i]

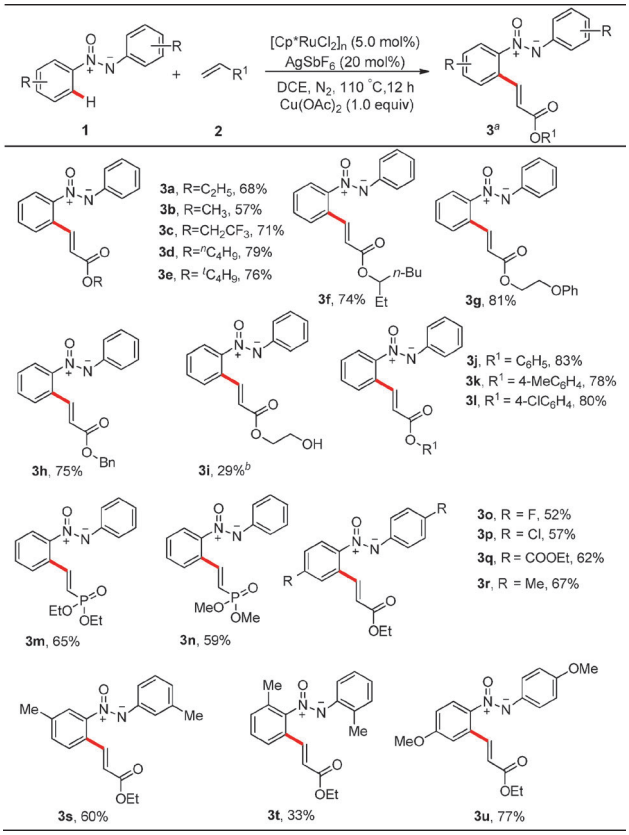
[a] Reaction conditions: azoxybenzene (**1a**, 0.20 mmol), ethyl acrylate (**2a**, 0.30 mmol), Ru complex (containing 5.0 mol% Ru), additive **1** (0.20 mmol), additive **2** amount indicated in this Table in DCE (1.0 mL) at 110 °C under N_2 for 12 h. [b] Isolated yields. [c] 30 mol% of $AgSbF_6$. [d] 90 °C. [e] 130 °C. [f] 8 h. [g] 15 h. [h] Molar ratio of **1a** with **2a** = 1 : 2. [i] **2a** (0.60 mmol) was used. Cp* = pentamethylcyclopentadienyl, L = *p*-cymene.



Scheme 2 Hydrolysis of **3a** into **4a**, and the structure of **4a** determined by X-ray single crystal analysis.

were investigated and experimental results indicated that DCE was the most suitable solvent for this reaction (Table S1 in ESI†).

With the optimized reaction conditions in hand, we next explored the substrate scope in Ru-catalyzed alkenylation of azoxybenzenes **1** with alkenes **2**, as shown in Scheme 3. Under a nitrogen atmosphere, a variety of alkyl acrylates reacted with azoxybenzene **1a** smoothly under present reaction conditions, and the corresponding products **3a–h** were isolated in 57–81% yields. Generally, alkyl acrylates with low boiling point would lead to much lower yields of the desired products (**3a–c** *vs.* **3d–h**). When 2-hydroxyethyl acrylate **2i** was used to couple with **1a**, the corresponding olefinated product **3i** was isolated only in 29% yield, even at elevated temperature. On the other hand, aryl acrylates (**2j–l**) were used as the coupling partners in the alkenylation of **1a**, providing the anticipated products (**3j–l**) in satisfactory yields. Interestingly, the reactions of diethyl and dimethyl vinylphosphonates with **1a** generated the coupling products **3m** in 65% yield, and **3n** in 59% yield, respectively. Next, the scope of

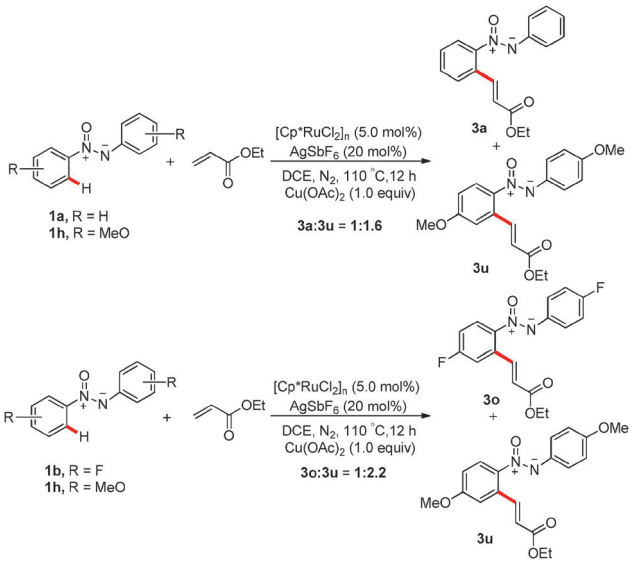


Scheme 3 The alkenylation of azoxybenzenes with alkenes. [a] Reaction conditions: azoxybenzene (**1**, 0.20 mmol), alkene (**2**, 0.30 mmol), $[Cp^*RuCl_2]_n$ (5.0 mol%), $AgSbF_6$ (0.04 mmol), $Cu(OAc)_2$ (0.20 mmol), DCE (1.0 mL), 110 °C, N_2, 12 h; isolated yields. [b] 130 °C.

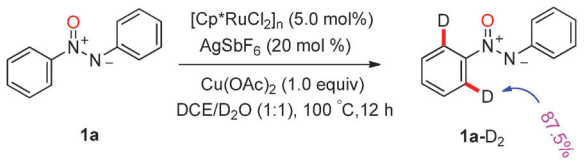
azoxybenzenes was also examined using ethyl acrylate as one of the coupling partner. Electron-withdrawing groups (F, Cl, and CO_2Et) and electron-donating groups (Me, and MeO) at the *para*-positions of the nitrogen on the benzene rings were all tolerated under the optimized reaction conditions. In the most cases, electron-rich azoxybenzenes seemed to be more active than that electron-deficient one, and the former gave slightly high yields of the corresponding products (**3q** *vs.* **3u**). Moreover, the steric effect was distinctively observed when methyl-substituted azoxybenzenes at their *para*-, *meta*- and *ortho*-positions were used to react with ethyl acrylate, giving products **3r–t** in 67%, 60% and 33% yields, respectively.

Next, we focused on the intermolecular competition experiments,[5a,14] which were performed using differently substituted azoxybenzenes and ethyl acrylate under standard reaction conditions, as shown in Scheme 4. The experimental results revealed that electron-rich azoxybenzene was preferentially functionalized in C–H activation, and high yields of the corresponding products were obtained (Scheme 4).

In addition, we continued our investigation into selective H–D exchange[15] at the *ortho*-positions of the azoxy group on the benzene ring, which was performed in the mixture of DCE–D_2O (1 : 1) at 110 °C under a nitrogen atmosphere for 12 h (Scheme 5). A significant D–H exchange (87.5%) provided the solid evidence for a reversible C–H bond ruthenation process.

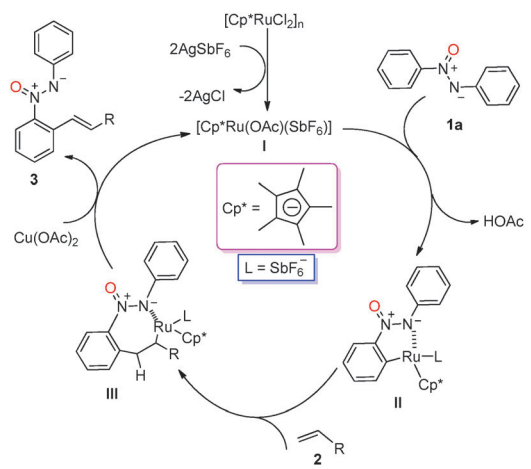


Scheme 4 Intermolecular competition experiments.



Scheme 5 Ru^{III}-catalyzed *ortho*-selective alkenylation.

Building on the above experimental results and known Ru-catalyzed C–H bond activation,[5,14,15] a possible reaction mechanism is described in Scheme 6. Firstly, the anion exchange of $AgSbF_6$ with $[Cp^*RuCl_2]_n$ generated Ru^{III} species **I**, which reacted with **1a** to form a five-membered metallacycle **II** by Ru-catalyzed *ortho*-selective C–H bond activation of **1a** and its coordination. Then, the coordinative insertion of alkene **2** into intermediate **II** afforded a seven-membered intermediate **III**. Finally, the β-hydrogen elimination from intermediate **III** gave the final product **3** and regenerated the active ruthenium species **I** for the next run. Although the exact role of the Cu^{II} salt was not clear, we proposed that the acetate anion may be coordinated to the ruthenium species and accelerate the *ortho*-metalation.[14b]



Scheme 6 The proposed reaction mechanism.

In conclusion, we have developed a highly selective Ru^{III}-complex-catalyzed *ortho*-alkenylation of azoxybenzenes with activated alkenes in the presence of $AgSbF_6$ and $Cu(OAc)_2$ to afford a variety of olefinated azoxy derivatives in good yields. Further application of these useful azoxy compounds and detailed mechanistic investigation are in progress.

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