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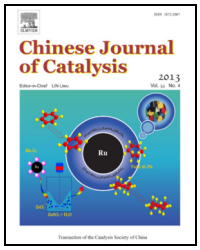

Communication

Rh(III)-catalyzed oxidative synthesis of pyrazoles from azomethines and acrylamides

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ABSTRACT

A cationic Rh(III) complex has been developed to catalyze the oxidative coupling of azomethine imines to acrylamides, to give trisubstituted pyrazoles in moderate yield. In this process, the olefinic C–H bond of the acrylamide undergoes C–H activation, and the reaction subsequently proceeds via a different selectivity to that reported for the coupling of acrylate esters.

Metal-catalyzed C–H bond activation reactions have been extensively explored in recent years, and research in this area has allowed the development of a large number of synthetic methodologies [1–14], which have been successfully applied to the synthesis of a variety of complex natural products [15,16]. Nitrogen-containing heterocycles are a key structural motif in a variety of biologically active compounds, and the chemoselective functionalization of organic molecules leading to the efficient construction of these heterocycles therefore represents an important task in synthetic chemistry. Rh (III) catalysts, with particular emphasis of Cp*Rh(III) complexes, have recently been reported as powerful catalysts in the catalytic activation of C–H bonds, leading to the construction of C–C, C–N, and C–O bonds [17,18]. Thus, Rh(III)-catalyzed C–H activation has provided a powerful platform for the efficient construction of a variety of different heterocycles, including indoles [19–21], pyridines [22,23], quinolones [24,26], dihydropyridines [27,29], isoquinolines [30–34], isoquinolones [35–37], and isocoumarins [38–41]. Pyrazoles are present in a large number of natural products, synthetic drugs, and mulfunctional materials [42]. They have also been employed as precursors to *N*-heterocyclic carbenes [43,44], which play an important role in organometallic chemistry and catalysis. Despite the significance of this particular heterocyclic system, no methods have been reported in the literature for the construction of pyrazole rings via a C–H activation pathway.

We recently reported a Rh(III)-catalyzed oxidative olefination-cyclization reaction between azomethine imines and activated olefins, leading to the selective synthesis of 1,2-dihydrophthalazines (Scheme 1) [45]. In this process, C–H

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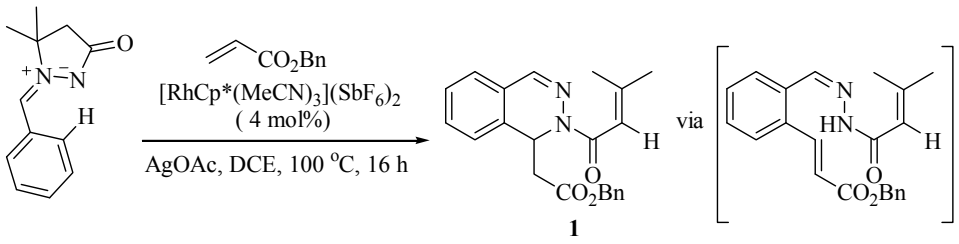
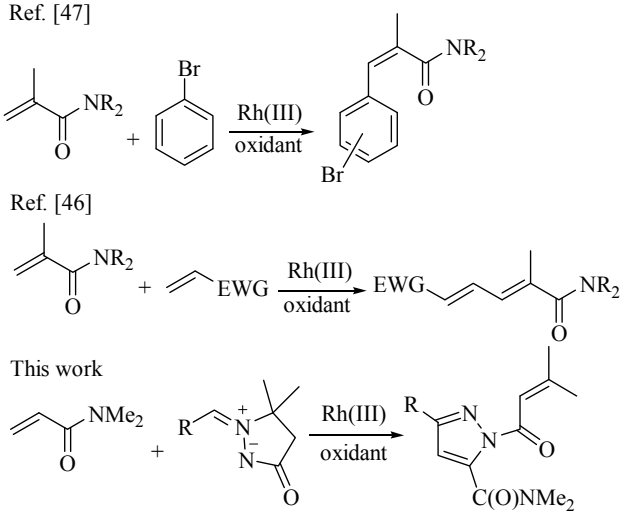


Scheme 1. Rh(III)-catalyzed oxidative olefination-cyclization.

activation occurred at the *ortho* position of the phenyl group of the azomethine substrate. Our mechanistic studies indicated that this process occurred via an initial oxidative C–H olefination followed by the scission of the pyrazolidinone ring through an E_1 mechanism, and that the 1,2-dihydrophthalazine ring was eventually constructed via an intramolecular Michael reaction [13]. Because an aza-Michael reaction was involved in the overall transformation, this reaction was limited to activated olefins such as acrylates and acrylonitriles. Although *N,N*-dimethylacrylamide (DMA) is also an active olefin commonly used in coupling reactions, we found in one example that the coupling of DMA with an azomethine followed a different selectivity pathway to yield a trisubstituted pyrazole. Although acrylamides have been applied as substrates in Rh(III) catalyzed C–H activation and C–C coupling reactions (Scheme 2) [46,47], to the best of our knowledge, no Rh(III) catalyzed C–N coupling reactions have ever been reported in the literature using acrylamide based substrates. Herein, we report the Rh(III)-catalyzed oxidative synthesis of trisubstituted pyrazoles from arylamides and azomethines.

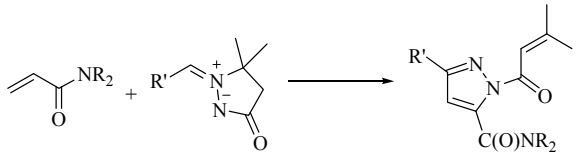
Our initial conditions for this pyrazole synthesis included $[RhCp^*(MeCN)_3](SbF_6)_2$ as a catalyst (4 mol%) and CH_3COOAg (AgOAc) as an oxidant, with 1,4-dioxane being the solvent. Consideration of the process revealed that 4 equiv of AgOAc would be necessary to remove the four hydrogen atoms from the reaction system, and the AgOAc was therefore used in slight excess (4.2 equiv). The amount of DMA in the reaction system had a significant impact on the isolated yield of this reaction, and a lower yield of the pyrazole product was isolated when 1.5 equiv of DMA was used. However, no difference was observed in the isolated yield when 2 or 3 equiv of DMA were used in the reaction. Although a longer reaction time was found to be beneficial, the extension of the reaction time beyond 16 h provided no further improvement of the yield. Thus, our established conditions included a $[RhCp^*(MeCN)_3](SbF_6)_2$ catalyst (4 mol%), AgOAc (4.2 equiv), and DMA (2 equiv) in 1,4-dioxane at 110 °C for 16 h. The isolated pyrazole product was fully characterized and the identity of the pyrazole ring was confirmed by ^1H and ^{13}C NMR spectroscopic analyses, including by nuclear Overhauser effect spectroscopy. The previously reported structure was mistakenly assigned, and the correct structure is the regioisomer of the previously reported one [45].

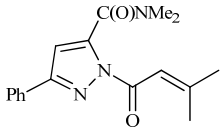
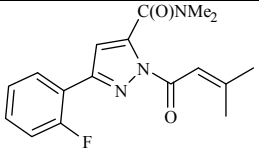
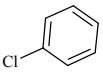
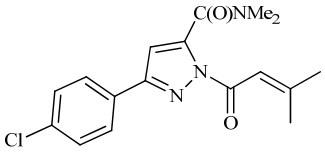
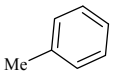
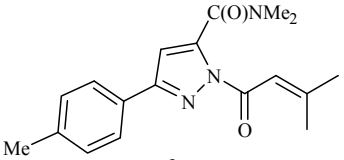
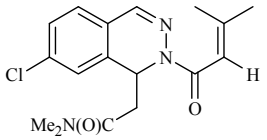
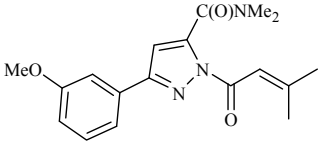
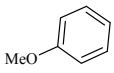
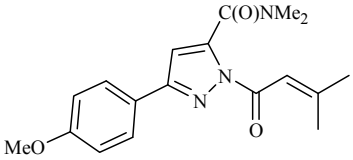
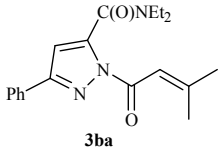
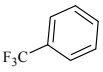
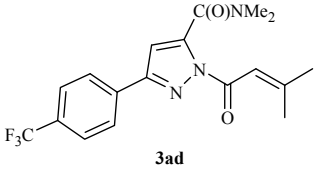
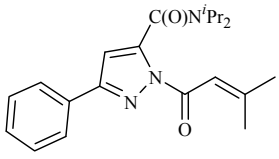
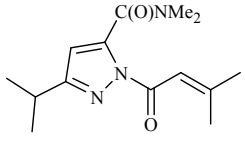


Scheme 2. C–H activation of acrylamides.

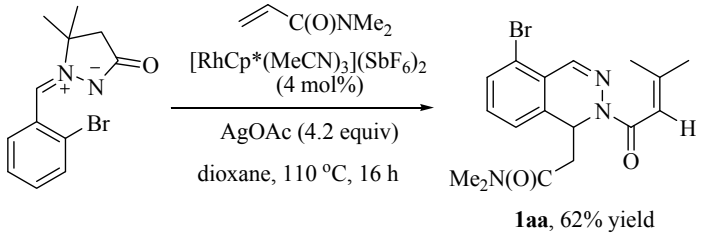
To evaluate the scope of our newly developed transformation, the optimized reaction conditions were extended to a variety of different azomethine imines with DMA (Table 1). Electron-donating and electron-withdrawing groups at the *ortho*, *meta*, and *para* positions of the phenyl ring of the azomethine were well tolerated under the optimized conditions, and the resulting products were isolated in moderate to good yield. Of note, when a *para*-Cl substituted azomethine was used, the selectivity of the coupling reaction was low, with the 1,2-dihydrophthalazine (**1ab**) and the pyrazole (**3ab**) products both being isolated. It was envisaged that these two products were generated via two independent and competitive pathways, with the 1,2-dihydrophthalazine formation being the favored of the two reactions. These preferences were found to be more pronounced for the *ortho*-Br substituted azomethine substrate, where only the 1,2-dihydrophthalazine product was isolated (**1aa**, Scheme 3). These observations stood in sharp contrast to the outcome of the reaction involving the *ortho*-F substituted azomethine (**3af**, 51% yield). Thus, the selectivity could be delicately tuned by changing the electronic and steric effects of the substituents in the phenyl ring. Despite the apparent substituent-dependent selectivity of this reaction, the electronic effects imposed by the *para* substituents were found to be insignificant, as evidenced by the isolation of **3ac**, **3ad**, and **3ag** in comparable yields. In addition to DMA, other acrylamides were also found to be viable coupling partners (Table 1, entries 9 and 10). Given that no C–H activation of the azomethine was involved in the transformation, it was envisaged that the presence of an alkyl R group in the azomethine should be also tolerated. Indeed, the use an *iso*-propyl substituted azomethine resulted in the isolation of product **3ae** in a good yield (Table 1, entry 5).

Table 1
Rh(III)-catalyzed synthesis of trisubstituted pyrazoles.



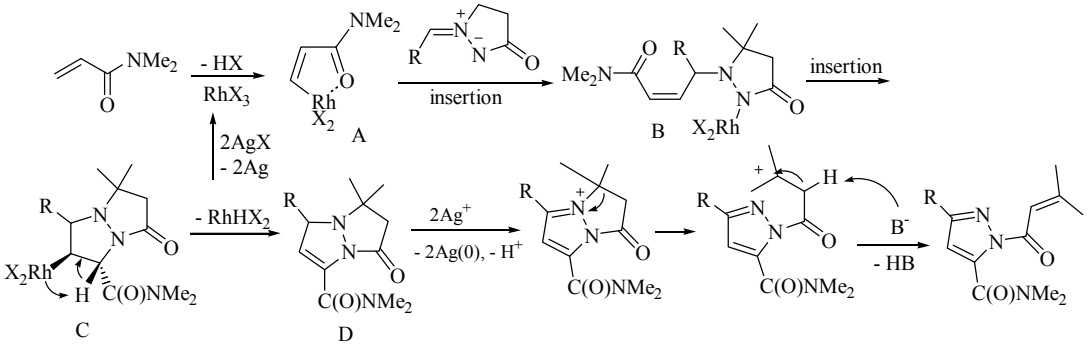
Entry	R	R'	Product	Yield* (%)	Entry	R	R'	Product	Yield* (%)
1	–CH_3 **1a**	Ph **2a**	 **3aa**	62%	6	–CH_3 **1a**	 **2f**	 **3af**	51%
2	–CH_3 **1a**	 **2b**	 **3ab**	34%	7	–CH_3 **1a**	 **2g**	 **3ag**	53%
			 **1ab**	52%	8	–CH_3 **1a**	 **2h**	 **3ah**	67%
3	–CH_3 **1a**	 **2c**	 **3ac**	64%	9	–C_2H_5 **1b**	Ph **2a**	 **3ba**	51%
4	–CH_3 **1a**	 **2d**	 **3ad**	64%	10	^{i}Pr **1c**	Ph **2a**	 **3ca**	34%
5	–CH_3 **1a**	isopropyl **2e**	 **3ae**	69%					

Reaction conditions: azomethine 0.54 mmol, DMA 1.08 mmol, $[RhCp^*(MeCN)_3](SbF_6)_2$ 4 mol%, AgOAc 2.27 mmol, 1,4-dioxane 4 ml, 110 °C, 16 h. *Isolated yield.



Scheme 3. Coupling of *ortho*-Br substituted azomethine with DMA.

Although no solid evidence was obtained during the course of the current study to allow for the elucidation of the reaction mechanism, a tentative mechanism has been proposed to account for the observations made during this transformation, as shown in Scheme 4. Using the initial RhX_3 catalyst, amide-assisted C–H activation of DMA would give rise to a



Scheme 4. Proposed mechanism for the formation of pyrazoles.

five-membered rhodacycle A. Insertion of the Rh–C bond into the azomethine would then generate a Rh(III) amidate intermediate B. It is noteworthy that insertions of this nature have been proposed in related Ru(II) catalyzed reactions [48]. Subsequent migratory insertion of the amidate group into the α position of the olefin would afford a five-membered Rh(III) alkyl intermediate C. This intermediate would then undergo β-H elimination to give a 1,2-dihydropyrazole derivative D together with a Rh(III) hydride intermediate. The active Rh(III) catalyst would then be regenerated when this intermediate undergoes elimination of HX followed by AgOAc oxidation. In addition, Ag(I) oxidation of the tertiary imine moiety of this 1,2-dihydropyrazole would lead to the formation of an iminium ion, and E_1 elimination from this species would furnish the final pyrazole product. Based on this mechanism, C–H activation of DMA would be the key step and this reactivity was not observed in acrylates because of the weaker directing effect of the ester group.

In summary, we have successfully developed a two-fold oxidative coupling reaction between azomethine imines and DMA that occurs via the C–H activation of the DMA. A series of trisubstituted pyrazoles have been prepared in moderate yields using this process. In some cases, competitive C–H activation of the DMA and the azomethine imines was observed, and the selectivity between these two competing processes was found to be substrate dependent. Efforts directed towards expanding upon the scope of this reaction, as well as mechanistic studies, are currently underway in our laboratories.

Acknowledgements

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Graphical Abstract

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Rhodium(III)-catalyzed oxidative synthesis of pyrazoles from azomethines and acrylamides

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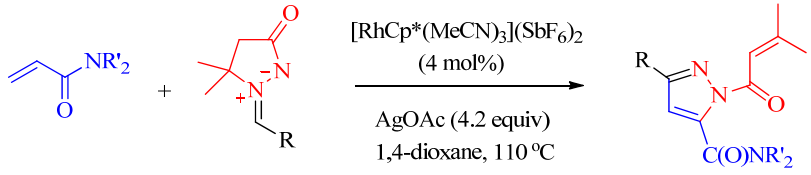

Rh(III)-catalyzed oxidative coupling of azomethine imines with acrylamides has been achieved to give trisubstituted pyrazoles. The reaction proceeds via C–H activation of the acrylamide substrate.

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