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Rhodium(III)-Catalyzed Selective Direct Olefination of Imidazoles

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Abstract: Rhodium(III)-catalyzed chelation-assisted highly regio- and stereoselective direct olefination of imidazoles with olefins has been developed. A broad range of C2-substituted N-(2-pyrimidyl)imidazoles underwent smooth C5-olefination with both activated and unactivated olefins to furnish the corresponding products in good to excellent yields with high tolerance of functional groups on both coupling partners in the presence of a cationic rhodium(III) catalyst. The combination of a catalytic amount of $Cu(OAc)_2$ (copper(II) acetate) and O_2 (oxygen) serves as the terminal oxidant. This protocol strongly relies on the use of 2-substituted imidazoles as the substrates, and the presence of readily installable and removable pyrimidyl directing group was found to be critical for catalysis. Mechanistic studies suggest the involvement of a five-membered rhodacycle as the key intermediate in the catalytic cycle. The method can also be extended to the coupling reaction of benzimidazoles with olefins.

Keywords: Rhodium; olefination; imidazole; C-H activation; pyrimidyl

Introduction

Substituted imidazoles constitute key structure units in a broad range of biologically active natural products and pharmaceutical compounds.[1] For example, midazolam (**A**)[1i] serves as a sedative before and during surgeries and medical procedures; Losartan (**B**)[1i] and olmesartan (**C**)[1i] are widely used drugs targeting hypertension; the imidazole-linked tripeptide **D**[1l] is a promising inhibitor of farnesyltransferase (Figure 1). Furthermore, imidazoles are known as versatile precursors to N-heterocyclic carbene ligands for important catalytic transformations, and serve as starting materials for the preparation of useful imidazolium-based ionic liquids.[2,3] Consequently, the efficient construction of imidazoles has been a topic of sustained interest during the past several decades,[4] and still attracts much research attention today.[5] With an aim to avoid the disadvantages associated with traditional cyclocondensation routes to imidazole compounds such as multistep syntheses, low reaction efficiency, limited substrate scope and the use of sensitive reagents, a great deal of effort has been dedicated to the use of transition-metal catalyzed cross-coupling reactions for the preparation of functionalized imidazole derivatives.[6] Although much progress has been made in this area, the necessity for prior preparation of halogenated or metalated imidazole starting materials greatly limited the versatility and applicability of these approaches.

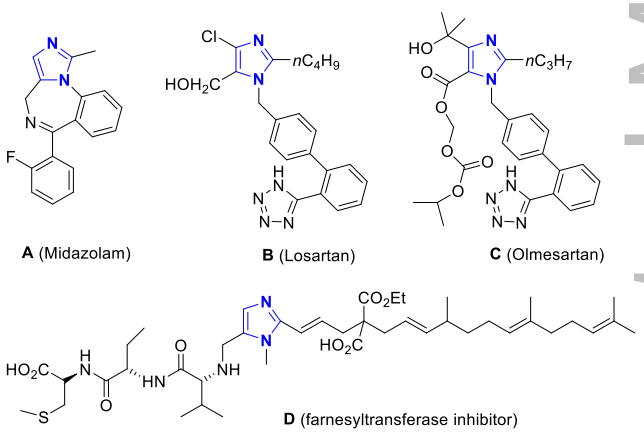

Figure 1. Some examples of imidazole-containing pharmaceuticals and bioactive molecules.

In past decades, transition-metal catalyzed C–H activation has undergone extensive investigation as an efficient, atom- and step-economical strategy for direct functionalization of various useful heterocycles.[7] Accordingly, it is not surprising that the development of short routes for the preparation of functionalized imidazoles through imidazyl C-H bonds activation/functionalization under transition-metal catalysis has received considerable interest,[8] and promising results in direct C-H arylation,[9] carbonylation,[10] alkylation[11] and annulation[12] of imidazoles have been achieved. However, studies

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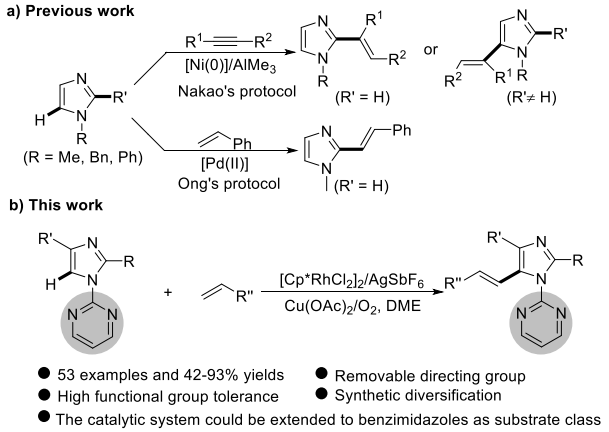
regarding direct olefination of imidazole C-H bonds has been less investigated despite the potential utility of such products.[13] The Nakao and Hiyama group first reported the selective direct olefination of N-substituted imidazoles with alkynes using a Ni(0)/lewis acid catalytic system, but the use of an excess amount of imidazoles, limited substrate scope and employing alkynes with little functionality decreased the attractiveness of this chemistry (Scheme 1a).[13a] Thereafter, Ong and co-workers demonstrated the Pd-catalyzed direct C2-olefination of *N*-methyl imidazole with styrene, but only one example was reported (Scheme 1a), and the general utility of this chemistry has never been explored.[13b]



Scheme 1. Regioselective direct olefination of imidazoles.

Recently Rh(III)-catalyzed direct C-H functionalization has emerged as a straightforward and powerful tool for the regioselective formation of carbon–carbon and carbon–heteroatom bonds due to their high selectivity, broad substrate scope and excellent functional group tolerance.[14] In this context, direct olefination of inert aryl and alkenyl C-H bonds with olefins under Rh(III) catalysis has attracted much attention among the synthetic community, and the contributions from the groups of Miura,[15] Glorius,[16] Li[17], Loh[18] and others[19] are noteworthy. In these reports, Cp*(pentamethylcyclopentadienyl) ligated rhodium complexes proved to be effective catalysts for this kind of transformation, and a variety of directing groups containing oxygen, nitrogen and sulfur atoms have exhibited their remarkable ability to promote the reactivity and selectivity. In particular, the 2-pyrimidyl and 2-pyridyl groups performed well as readily installable and removable directing groups in direct olefination of N-heterocycles such as indoles,[16i,18c,18e,19i,19p] pyrroles[18c,18e,19i,19p] and indolines[18d]. Inspired by these elegant studies, we envisioned that the installation of a pyrimidyl or pyridyl directing groups on the *N* atom of the imidazole ring may facilitate direct C-H olefination of imidazoles in the presence of a Rh(III) catalyst. In connection with our continuing interest in the selective olefination of (hetero)arenes,[20] herein we demonstrate the first example of Rh(III)-catalyzed selective olefination of various imidazoles and benzoimidazoles with activated olefins and unactivat ed olefins using a readily installable and removable pyrimidyl group as the directing group (Scheme 1b). This method features broad substrate scope, excellent regio- and stereo-selectivity and high functional group tolerance.

Results and Discussion

At the outset of our investigations, we first attempted the coupling reaction of 2-(1*H*-imidazol-1-yl)pyrimidine with *n*butyl acrylate under Rh(III) catalysis (Scheme 2a). It was expected that the reaction should take place at the most acidic C2-position to give butyl (*E*)-3-(1-(pyrimidin-2-yl)-1*H*-imidazol-2-yl)acrylate as the product. However, a variety of Rh(III) catalytic systems including those that have proved to be effective in catalysing direct olefination of structurally similar 2-phenylpyrimidines,[16i] 1-(pyrimidin-2-yl)-1*H*-indoles[18c,18e,19i,19p] and 2-(1*H*-pyrrol-1-yl)pyrimidines,[18c,18e,19i,19p] turned out to be totally ineffective, and only the starting materials were recovered (For details, see supporting information). Then the reaction of 2-(1*H*-imidazol-1-yl)pyrimidine with $[Cp^*RhCl_2]_2$ with NaOAc as the base in DCE at room temperature was carried out, and only the complex **C2** was isolated, and the formation of the expected five-membered rhodacycle **C1** was not detected (Scheme 2b). The structure of **C2** was determined by single-crystal X-ray diffraction analysis, in which the imidazole N(3) atom coordinates with the Rh(III) centre and both C(2)-H and C(5)-H bonds remain intact.[21] Clearly, this strong coordination of the imidazole N(3) atom with the Rh(III) centre prevented the catalyst from interacting with the imidazole C-H bonds via coordinating with the pyrimidine, thereby resulting in the failure of direct C-H olefination under Rh(III) catalysis. With an aim to overcome this problem, we reasoned that the introduction of a C2-substitutent on 2-(1*H*-imidazol-1-yl)pyrimidine would disfavor the coordination of the imidazole N atom with Rh(III) centre and facilitate the chelation-assisted direct C5-H activation. Bearing this in mind, we then initiated our studies by investigating the coupling reaction of 2-(2-methyl-1*H*-imidazol-1-yl)pyrimidine (**1a**) and *n*butyl acrylate (**2a**) in the presence of $[Cp^*RhCl_2]_2$ (2.5 mol%) catalyst, and $AgSbF_6$ (10.0 mol%) additive at 130 °C. With $Cu(OAc)_2$ as the oxidant, the reaction in 1,2-dichloroethane (DCE) indeed delivered the target product **3aa** in 73% isolated yield in 2 h (Table 1, entry 1), thereby validating the feasibility of our strategy. However, the reaction failed to proceed when replacing **1a** with either 2-(4-methyl-1*H*-imidazol-1-yl)pyrimidine or 1-methyl-3-(pyrimidine-2-yl) imidazolium hexafluorophosphate[22] in spite of their advantageous structures. The promising result achieved with **1a** prompted us to examine the performance of other N-

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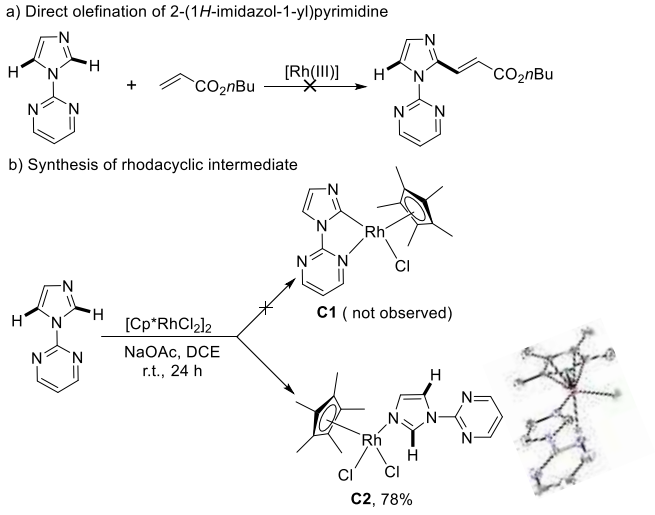
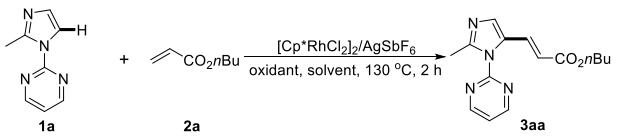
protected 2-methyl-imidazoles (Table S1, supporting information). However, no reaction occurred when Me, Bn, Ac, Tos, Boc, Piv and Me_2NCO was employed. Only 2-(2-methyl-1*H*-imidazol-1-yl)pyridine (**1a'**) was reactive, affording the expected product butyl (*E*)-3-(2-methyl-1-(pyridin-2-yl)-1*H*-imidazol-5-yl) acrylate (**3a'a**) in 53% yield. Obviously, N-(2-pyrimidyl) directing group proved to be the best choice. Using the optimal N-(2-pyrimidyl) directing group, the effect of solvent was then explored. The reaction efficiency was maintained when replacing DCE with PhCl, acetone and THF (Table1, entries 2, 3 and 5), but switching to MeCN, 1,4-dioxane and alcoholic solvents led to lower yields (Table 1, entries 4,6,8-10). Delightfully, the best solvent was identified as dimethoxyethane (DME), affording **3aa** in 92% yield (Table 1, entry 7). Subsequent optimization revealed that $Cu(OAc)_2$ outperformed other commonly employed oxidants (Table 1, entries 11-16). However the generation of copious inorganic waste made this process less ecofriendly and economical. Then we investigated the combination of catalytic amount of $Cu(OAc)_2$ with O_2 as the oxidant. It was found that the reaction provided essentially the same yield of **3aa** in the presence of 60 mol% of $Cu(OAc)_2$ under an atmosphere of O_2 (Table 1, entry 17). The yield of **3aa** dropped to 81% when conducting the reaction at a lower temperature (120 °C) (Table 1, entry 18). When the loading of $[Cp^*RhCl_2]_2$ was reduced, the yield decreased as well (Table 1, entry 19). The control experiments showed that the reaction did not take place in the absence of either $[Cp^*RhCl_2]_2$, $AgSbF_6$ or oxidant (Table 1, entries 20-22). Thus the optimal reaction conditions were finally determined as follows: $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10.0 mol%) and $Cu(OAc)_2$ (60 mol%)/O_2 (1 atm) in DME at 130 °C for 2 h.



Scheme 2. Direct olefination of 2-(1*H*-imidazol-1-yl)pyrimidine.

Table 1. Optimization of reaction conditions.[a]



Entry	Solvent	Oxidant	Yield(%)[b]
1	DCE	$Cu(OAc)_2$	73
2	PhCl	$Cu(OAc)_2$	71
3	acetone	$Cu(OAc)_2$	72
4	MeCN	$Cu(OAc)_2$	37
5	THF	$Cu(OAc)_2$	69
6	1,4-dioxane	$Cu(OAc)_2$	63
7	DME	$Cu(OAc)_2$	92
8	MeOH	$Cu(OAc)_2$	61
9	EtOH	$Cu(OAc)_2$	59
10	*i*PrOH	$Cu(OAc)_2$	42
11	DME	$Cu(OAc)_2•H_2O$	72
12	DME	Ag_2CO_3	52
13	DME	AgOAc	31
14	DME	Ag_2O	27
15	DME	O_2 (1.0 atm)	12
16	DME	Tempo	11
17[c]	DME	$Cu(OAc)_2/O_2$	91
18[c,d]	DME	$Cu(OAc)_2/O_2$	81
19[c,e]	DME	$Cu(OAc)_2/O_2$	71
20[c,f]	DME	$Cu(OAc)_2/O_2$	NR
21[c,g]	DME	$Cu(OAc)_2/O_2$	NR
22	DME	none	NR

[a]Reaction Conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10.0 mol%), oxidant (0.4 mmol), solvent (2.0 mL), 130 °C, 2 h, under air or O_2 (1 atm). [b] Isolated yield. [c] $Cu(OAc)_2$ (60 mol%) and O_2 (1 atm). [d] Reaction temperature 120 °C. [e] $[Cp^*RhCl_2]_2$ (1.0 mol%) was used. [f] No $[Cp^*RhCl_2]_2$. [g] No $AgSbF_6$.

With the optimized conditions in hand, we then investigated the scope of imidazoles with olefin **2a** as the coupling partner (Table 2). It was found that a series of 2-alkyl substituted imidazoles (**1b**-**1h**) worked well to give the target products (**3ba**-**3ha**) in good to excellent yields, and this reaction does not appear to be sensitive to steric hindrance of the alkyl groups. When the electron-deficient 1-(pyrimidin-2-yl)-1*H*-imidazole-2-carbaldehyde (**1i**) was employed, the product **3ia** was isolated only in 42% yield. Converting the aldehyde group into the corresponding acetal resulted in the formation of product **3ja** in 88% yield. These results suggest that the reaction efficiency is sensitive to the electronic nature of the substituent on C2-position, and the electron-rich moiety is favored. The imidazole substrate **1k** bearing a C2 olefinic substituent proved to be a viable coupling partner, giving rise to the target product **3ka** in 88% yield. The 2,4-disubstituted imidazoles (**1l**-**1p**) also performed readily under the current conditions to afford the corresponding olefinated products (**3la**-**3pa**) in good to excellent yields. The electronic nature of a substituent at the 4-position of the ring affected the outcome of the reaction, and better yields were observed in the cases of electron-rich substituents. It is noted that the functional groups including Br

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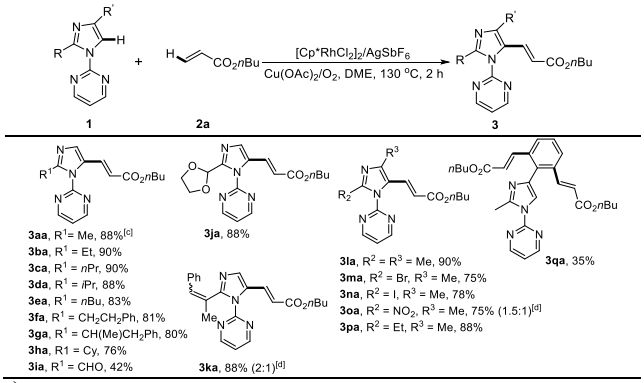
(**3ma**), I (**3na**) and NO_2 (**3oa**) were well tolerated, thereby providing the opportunity for further elaboration. When 2-(2-methyl-4-phenyl-1*H*-imidazol-1-yl)pyrimidine (**1q**) was employed, it was found that the olefination only took place on the aryl ring via the imidazoyl N2 chelation assistance to give the di-olefinated product **3qa** in 35% yield. It seems that the imidazoyl group is a more powerful directing group in this case. Finally, the reaction of **1a** and **2a** could be carried out on a gram scale to give the desired product **3aa** in 88% yield under the standard reaction conditions, clearly demonstrating the scalability of the current transformation (For details, see supporting information).

Table 2. Direct olefination of various imidazoles with **2a**.[a,b]

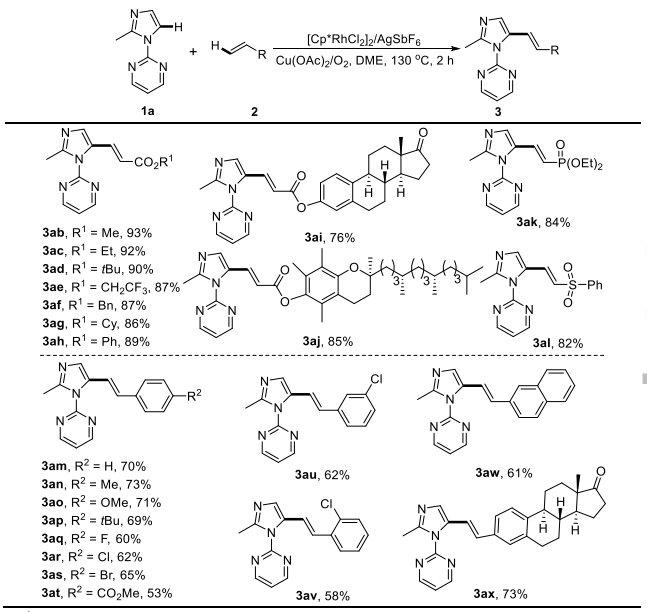


[a]Reaction Conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10.0 mol%), $Cu(OAc)_2$ (60 mol%) and O_2 (1 atm), solvent (2.0 mL), 130 °C, 2 h. [b] Isolated yield. [c] **1a** was olefinated in a gram scale. [d] Ratio of isomers (E/Z).

Subsequently the reactivity of various activated olefins was evaluated in the coupling reaction with **1a**. As shown in Table 3, a wide range of commercially available acrylates (**2b**-**2h**) underwent smooth reaction with **1a** to exclusively provide the corresponding C5-olefinated imidazole products (**3ab**-**3ah**) in good to excellent yields regardless of the nature of the substituents on the oxygen atom. Notably, under the current conditions, the acrylic esters of tocopherol and estrone (**2i**,**2j**) exhibited good reactivity, affording the target products (**3ai**,**3aj**) in good yields. Similarly, the electron-deficient diethyl vinylphosphonate (**2k**) and (vinylsulfonyl)benzene (**2l**) successfully engaged in the coupling reaction to give the expected products (**3ak**,**3al**) in good yields. The synthetic protocol could also be extended for the transformation of various styrenes. Differently substituted styrenes (**2m**-**2v**) proved to be suitable coupling partners to give rise to the products (**3am**-**3av**) in moderate to good yields, and a range of functional groups were compatible with the reaction conditions. 2-vinylnaphthalene (**2w**) was reactive, and gave the product **3aw** in 61% yield. The estrone-derived styrene **2x** also proceeded readily to deliver the product **3ax** in 73% yield, further indicating the robustness of the current catalytic system.

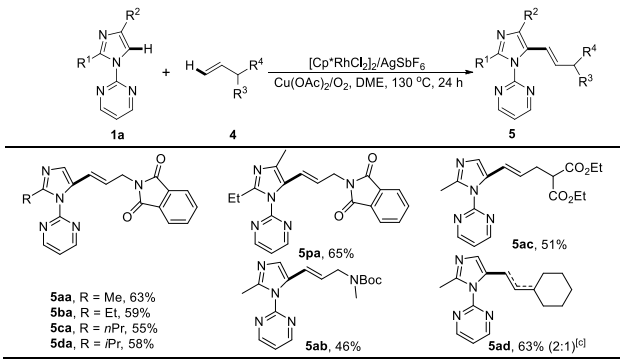
To further demonstrate the potential of our catalytic system, the reaction was extended to the unactivated olefins, and the results are listed in Table 4. It should be noted that in these reactions the reaction time should be extended to 24 h. It was found that differently substituted imidazoles (**1a**-**1d**,**1p**) reacted readily with the allylamide **4a** to give the desired products (**5aa**-**5da**,**5pa**) in moderate to good yields. Application of *tert*-butyl allyl(methyl)carbamate (**4b**) and diethyl 2-allylmalonate (**4c**) in this transformation led to the formation of **5ab** and **5ac** in 46% and 51% yields, respectively. However, vinylcyclohexane (**4d**) were demonstrated to generate a mixture of the thermodynamically favourable conjugated product together with the nonoconjugated positional isomer (**5ad**), and the formation of nonoconjugated products may result from to the migration of the C=C double bond along the aliphatic chain.

Table 3. Direct olefination of **1a** with activated olefins.[a,b]



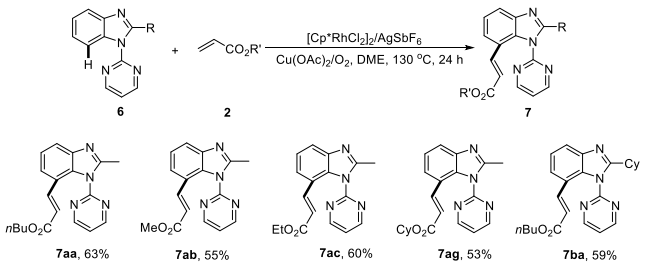
[a]Reaction Conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10.0 mol%), $Cu(OAc)_2$ (60 mol%) and O_2 (1 atm), solvent (2.0 mL), 130 °C, 2 h. [b] Isolated yield.

Table 4. Direct olefination of **1a** with unactivated olefins.[a,b]



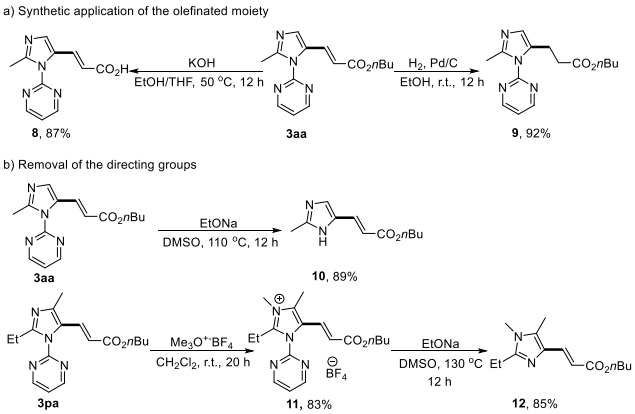
[a]Reaction Conditions: **1a** (0.2 mmol), **4** (0.3 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10.0 mol%), $Cu(OAc)_2$ (60 mol%) and O_2 (1 atm), solvent (2.0 mL), 130 °C, 24 h. [b] Isolated yield. [c] Ratio of isomers (styrenyl/allylic).

In order to further explore the utility of this transformation, we next examined the direct olefination of benzimidazoles under similar reaction conditions. Due to the steric hindrance, a longer reaction time of 24 h was required. As depicted in Scheme 3, moderate to good yields were achieved in the olefination of benzimidazole **6a** with various acrylate esters (**7aa**-**7ac**,**7ag**). 2-Cyclohexyl-1-(pyrimidin-2-yl)-1*H*-benzo[*d*]imidazole (**6b**) was also reactive, affording the corresponding product **7ba** in 59% yield.



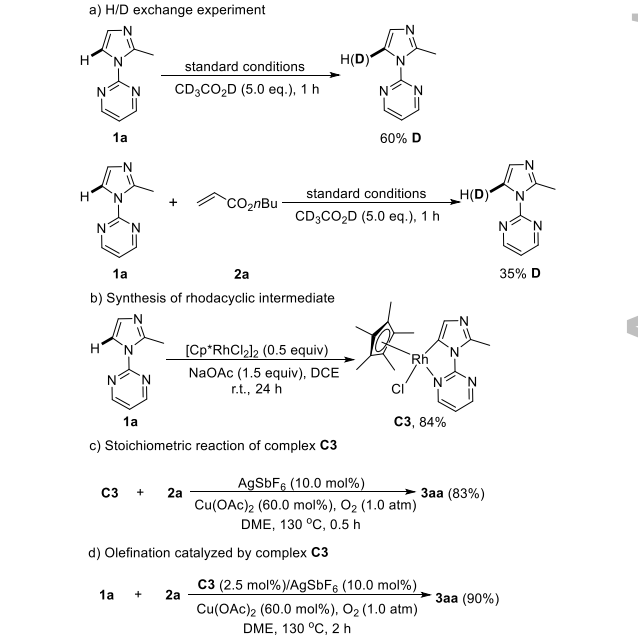
Scheme 3. Direct olefination of benzimidazoles with acrylic esters.

These olefinated imidazole products could be further transformed into synthetically useful derivatives. For example, product **3aa** could be subjected to hydrolysis and hydrogenation to give the corresponding products **8** and **9** in yields, respectively. Furthermore, the pyrimidyl group in the coupling products could be readily removed by treatment with EtONa in DMSO. For example, **3aa** could be converted into the free imidazole **10** in 89% isolated yield. Notably, alkylation of the N-3 position of the imidazole ring with alkylating agents followed by deprotection of the pyrimidyl group provides a useful approach for regioselective N-alkylation of complex imidazoles. Thus subjection of **3pa** to Meerwein reagent resulted in the formation of imidazolium product **11**, and the following cleavage of the pyrimidyl group gave rise to the N-methylated imidazole **12**. Similar strategy has been reported by using N-sulfamoyl protected imidazoles as the starting materials.[5e,9i]



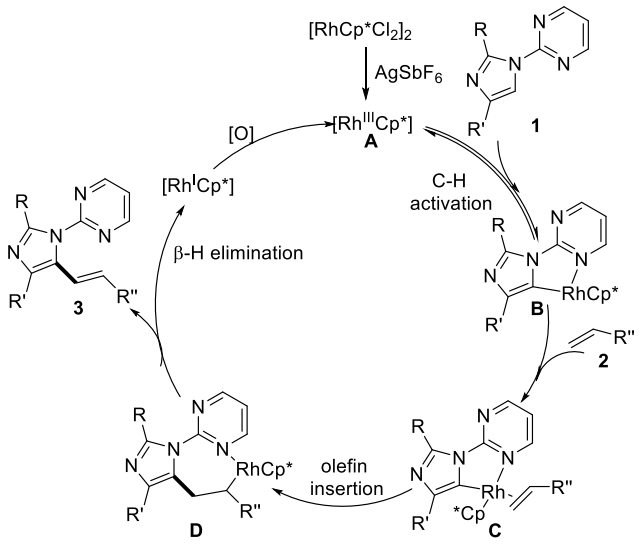
Scheme 4. Synthetic utility of the olefinated imidazoles.

Preliminary experiments were carried out to gain mechanistic insight (Scheme 5). First, we investigated the reversibility of the C-H activation step by treating **1a** with CD_3CO_2D under the standard conditions in the absence or presence of olefin. As shown in Scheme 5a, the observed H/D scrambling at the C5-position indicated that the C(5)-H bond undergoes reversible activation in the present Rh(I)-based catalytic system. Further studies showed that the thermodynamically stable five-membered rhodacycle intermediate **C3** could be easily synthesized from the reaction of **1a** with $[Cp^*RhCl_2]_2$ by employing NaOAc as the base in DCE at room temperature (Scheme 5b). Notably, complex **C3** reacted stoichiometrically with **2a** to give the product **3aa** in a good yield in shorter time (Scheme 5c), suggesting that C–H functionalization might be the rate-determining step. Moreover, complex **C3** exhibited almost the same catalytic activity in reaction of **1a** and **2a** as $[RhCp^*Cl_2]_2$ did (Scheme 5d), indicating that this five-membered complex was indeed an active species in the catalytic cycle.



Scheme 5. Mechanistic studies.

Although the exact mechanism of this coupling reaction is still not clear, a plausible mechanism (Scheme 6) is suggested based on previous reports[14-19] and our results. First, coordination of the imidazole **1** to the cationic Rh(III) complex species **A** generated from $[RhCp^*Cl_2]_2$ and $AgSbF_6$ would trigger ortho C-H bond activation to give the cyclorhodium intermediate **B**. The subsequent coordination of intermediate **B** with the incoming olefin **2** yields intermediate **C**, which is transformed into the less hindered intermediate **D** by regioselective migratory insertion of the olefin. The following β-H elimination furnishes the desired product **3** and Rh(I) species, which is reoxidized to Rh(III) complex **A** by the oxidant to complete the catalytic cycle.



Scheme 6. Plausible reaction mechanism.

Conclusion

In conclusion, we have developed a new, general and efficient method for highly regio- and stereoselective direct C5-olefination of imidazoles with both activated and unactivated olefins in the presence of a cationic Rh(III) catalyst. This method is characterized by its high efficiency, broad range and high functional group tolerance with regard to both coupling partners. The key to the successful catalysis is the appropriate choice of an imidazole substrate and a readily installable and removable N-directing group. Mechanistic studies were carried out and a reaction mechanism was proposed accordingly. Further investigation focusing on the mechanism of the reaction and synthetic applications is underway in our laboratory, and will be reported in due course.

Experimental Section

Unless otherwise noted, all commercially available chemicals were used as received without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Model Advance DMX 400 Spectrometer (^{1}H 400 MHz and ^{13}C 100.6 MHz, respectively). Chemical shifts (δ) are given in ppm and are referenced to residual solvent peaks, and coupling constants (*J*) were reported in Hertz.

General procedure for direct olefination of imidazoles

To an oven-dried pressure tube were sequentially added imidazole **1** (0.2 mmol), olefin **2** (0.3 mmol), $[RhCp^*Cl_2]_2$ (3.10 mg, 2.5 mol%), $AgSbF_6$ (6.87 mg, 10 mol%), $Cu(OAc)_2$ (21.8 mg, 0.12 mmol) and DME (2.0 mL). Then the tube was heated and stirred vigorously at 130 °C for 2 h in an oil bath under O_2 (1 atm). The tube was removed from the oil bath and cooled to room temperature. The solvent was removed by vacuum evaporation, and the residue was purified by column chromatography on silica gel using a mixture of ethyl acetate and hexane to give the pure product.

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[21] CCDC 1587247 (**C2**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[22] Choudhury and coworkers described the Rh(III)-catalyzed direct annulation of 1-methyl-3-(pyrimidine-2-yl)imidazolium hexafluorophosphate with alkynes, see: D. Ghorai, C. Dutta, J. Choudhury, *ACS Catal.* **2016**, *6*, 709.

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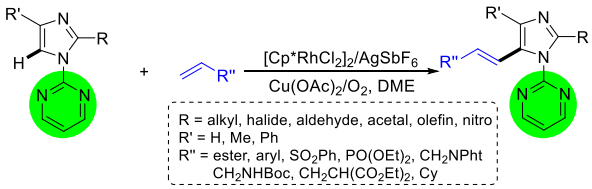
FULL PAPER

Rhodium(III)-Catalyzed Selective Direct Olefination of Imidazoles

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Haoqiang Zhao, Jianbin Xu, Changjun Chen, Xin Xu, Yixiao Pan, Zongyao Zhang, Huanrong Li and Lijin Xu*



- 53 examples and 42-93% yields
- High functional group tolerance
- The catalytic system could be extended to benzimidazoles as substrate class
- Removable directing group
- Synthetic diversification