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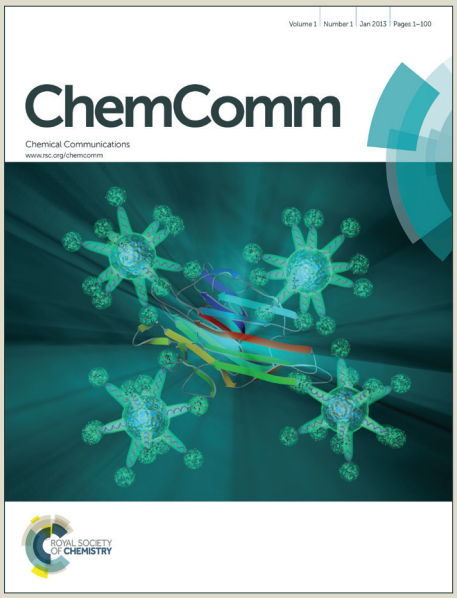

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ARTICLE TYPE

Rh(III)-Catalyzed Chelation-Assisted Intermolecular Carbenoid Functionalization of α-Imino Csp^3-H Bonds

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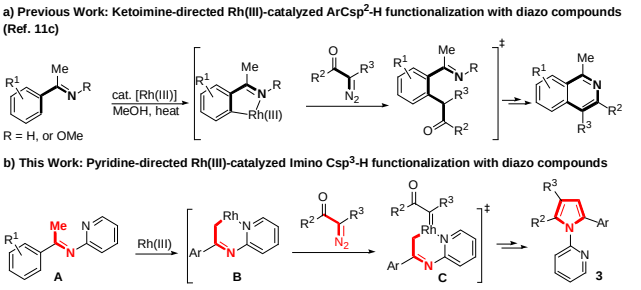
A Rh(III)-catalyzed cross-coupling/cyclization cascade of α-imino Csp^3-H bonds with donor/acceptor α-acyl diazocarbonyl compounds has been developed. This novel transformation involves ligand-directed Csp^3-H bond functionalization with carbenoids under the pyridine-chelation assistance, and offered an efficient access to synthetically versatile polysubstituted *N*-(2-pyridyl)pyrroles with broad range of functional group tolerance.

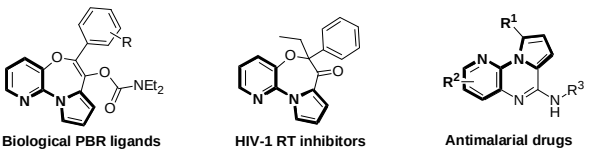
Introduction

Carbon-carbon bond-forming reactions are most important transformation in modern organic chemistry. [1] A single-step chemical process involving diverse C-C and C-X bond formations (X = C, N, and O *etc*.) provides a step-economic approach to assembling complex molecules. Over the past decades, transition metal-catalyzed C-H insertion of carbenoids represents a powerful tool for constructing C-C and C-X bonds. [2] In this regard, various carbene precursors have been extensively explored to allow for efficient cross-coupling with alkanes, [3] alkenes, [4] alkynes, [5] arenes [6] and carbonyl compounds.[7] However, despite enormous progress in this field, there are very rare examples about transition metal-catalyzed cross-coupling of carbenoids with imines,[8] albeit the method will provide a novel approach to versatile nitrogen-containing compounds. To date, the pioneering report by Doyle ever described Rh(II) or Cu(II)-catalyzed synthesis of dihydropyrroles through a [3 + 2] cycloaddition of vinyldiazoacetates with imines. [9] Recently, Hu also developed a novel Rh(II) and chiral phosphoric acid co-catalyzed C-H insertion/C-C coupling cascade of *N*-aryl diazoamides with imines, in which imines were acted as an electrophilic reagent to trap zwitterionic rhodium carbenes.[10] More recently, prompted by many achievements of C-H activation, several breakthroughs about chelation-assisted Csp^2-H insertions of carbenoids have been made for site-selectively forming C-C bonds. [11] Representative work by Glorious took advantage of the directing character of ketoimines to enable a Rh(III)-catalyzed tandem Csp^2-H activation/cyclization of *N*-substituted acetophenone imines with α-diazo ketones for rapidly assembling isoquinolines (Scheme 1a), [11c] in which insertion of carbenoids into α-imino alkyl Csp^3-H bonds could not be accessed through imine/enamine-isomerization and C-H activation process, [12] and such a useful cross-coupling is believed to be of great importance for organic synthetic chemistry.

We recently focus on developing transition metal-catalyzed C-C and C-N bond cross-coupling reaction involving imines to construct kinds of α-amino carboxylic acids and heterocycles. [13] Very recently, we further found a six-membered cyclopalladium species which derived from *N*-(2-pyridyl)-ketoimines **A** (Scheme 1b) through Csp^3-H activation process, could be trapped by unsaturated alkynes and CO to furnish heteroarenes, respectively. [14] These results inspired us to envision that Rh salts could possibly activate saturated α-imino alkyl Csp^3-H bonds to form rhodacycle intermediate (**B**) (Scheme 1b) with the assistance of Rh(III)/pyridine nitrogen-chelation, then followed by resulting in C-C coupling with diazo ketones via rhodium carbene complexes (**C**) (Scheme 1b). To identify this hypothesis, herein we report a novel Rh(III)-catalyzed pyridine-directed cross-coupling cascade of α-imino alkyl Csp^3-H bonds with α-acyldiazoacetates to rapidly assemble *N*-(2-pyridyl)pyrrole (N-PPR) library, these compounds are ubiquitous in synthetic building blocks and biological molecules (Scheme 2). [15]



Scheme 1. Rh(III)-Catalyzed C-C Coupling Cascade Involving Imines and Diazo compounds



Scheme 2. Selected Examples of Biological N-PPR-Containing Molecules

Results and Discussion

To begin, the cross-coupling of *N*-(2-pyridyl)-ketoimine (**1a**) and α-acyldiazoacetate (**2a**) was investigated for screening various transition-metal Pd(II), Ir(III) and Rh(III) salts etc. in

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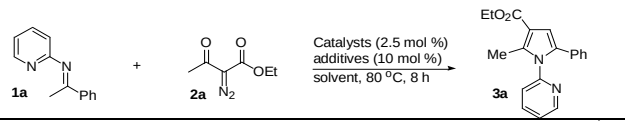
the presence of $AgClO_4$ (10 mol %) in THF at 80 °C under Ar atmosphere for 8 h (Table, entries 1-8). We were pleased to find that catalyst $(Cp^*IrCl_2)_2$ and $(Cp^*RhCl_2)_2$ could give us the desired polysubstituted N-PPR **3a** in 21% and 27% yield (entries 5 and 8), respectively. With a promising Rh(III) catalyst in hand, we then turned our attention to evaluating various silver additives such as $AgBF_4$, AgOAc and $AgNTf_2$ etc. For further increasing the reaction conversion (entries 8-12), and we found that a slightly improved yield (36%) was obtained by employing $AgSbF_6$ as additive (compare entries 8-11 with 12). To maximize the yield of the reaction, the additional optimization of the solvent system revealed that 1, 2-dichloroethane (DCE) and acetonitrile could result in excellent yields (entries 14 and 17), and acetonitrile proved to be the optimal solvent (90% yield of **3a**, entry 17). Moreover, directly employing $Cp^*Rh(SbF_6)_2$ (5 mol %) as catalyst could also afford 92% yield of **3a** (compare entry 17 with 19). It should be noted that the yield of **3a** would decrease to 59% in absence of $AgSbF_6$ (compare entry 17 with 18); Moreover, lowering or increasing the reaction temperature also led to poorer yield (compare entries 21 and 22 with 17) (see ESI for the more details about screening of reaction conditions).

Table 1. Reaction Optimization [a]



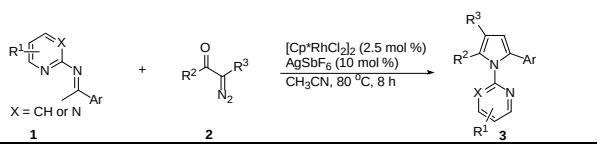
entry	catalysts	additives	solvent	yield (%) [b]
1	$Pd(OAc)_2$	$AgClO_4$	THF	0
2	$Cu(OAc)_2$	$AgClO_4$	THF	0
3	CuI	$AgClO_4$	THF	0
4	$[Ru(p\text{-cymene})Cl_2]$	$AgClO_4$	THF	0
5	$(Cp^*IrCl_2)_2$	$AgClO_4$	THF	21
6	$RhCl_3$	$AgClO_4$	THF	0
7	$Rh_2(COD)_2Cl_2$	$AgClO_4$	THF	0
8	$(Cp^*RhCl_2)_2$	$AgClO_4$	THF	27
9	$(Cp^*RhCl_2)_2$	$AgBF_4$	THF	31
10	$(Cp^*RhCl_2)_2$	$AgNTf_2$	THF	34
11	$(Cp^*RhCl_2)_2$	AgOAc	THF	29
12	$(Cp^*RhCl_2)_2$	$AgSbF_6$	THF	36
13	$(Cp^*RhCl_2)_2$	$AgSbF_6$	EtOH	23
14	$(Cp^*RhCl_2)_2$	$AgSbF_6$	DCE	85
15	$(Cp^*RhCl_2)_2$	$AgSbF_6$	toluene	trace
16	$(Cp^*RhCl_2)_2$	$AgSbF_6$	dioxane	52
17	$(Cp^*RhCl_2)_2$	$AgSbF_6$	MeCN	90
18	$(Cp^*RhCl_2)_2$	--	MeCN	59
19	$Cp^*Rh(SbF_6)_2$	--	MeCN	92
20	$(Cp^*RhCl_2)_2$	$AgSbF_6$	DMSO	26
21	$(Cp^*RhCl_2)_2$	$AgSbF_6$	MeCN	81 [c]
22	$(Cp^*RhCl_2)_2$	$AgSbF_6$	MeCN	87 [d]

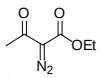
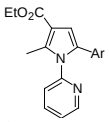
[a]Unless otherwise noted, all the reactions were carried out using ketoimine (**1a**) (0.10 mmol) and diazocompound (**2a**) (0.20 mmol) with catalysts (2.5 mol %) in the presence of silver salts additives (10 mol %) in solvent (2.0 mL) at 80 °C for 8 h under Ar in a sealed reaction tube, followed by flash chromatography on SiO_2. [b]Isolated yield. [c]The reaction temperature is 60 °C. [d]The reaction temperature is 100 °C.

The generality of the reaction was then explored (Table 2), and it was found that common functional groups on the imino phenyl rings were well tolerated in this transformation to provide the corresponding polysubstituted pyrroles in good to excellent yields (entries 1-8), including electron-donating methyl (**1b**), methoxyl (**1c**), and acetal group (**1i**), and electron-withdrawing halogen (**1d-1f**), ester (**1g**), and nitro group (**1h**). Notably, *meso* or *ortho*-substituted phenyl rings resulted in a decreased yield possibly because of the increased steric hindrance around the ketoimine (**1d-1f**). [16] Moreover, 2-furan and 2-thiophene substituted ketoimines also allowed for this transformation and furnished the desired 2-heteroaryl-substituted pyrroles (**3j** and **3k**) in 61% and 58% yields, respectively (entries 9 and 10). Subsequently, the substitution effects from pyridine ring on this transformation was evaluated, and we found electron–rich or electron-deficient pyridines could provide good to excellent yields of **3l-3o** regardless of the electronical properties of substituents (entries 11-14). In addition, *N*-(2-pyrimidyl)ketoimine (**1p**) was also a suitable substrate for this transformation and provided 78% yield of the desired pyrrole **3p** (entry 15).

Meanwhile, the present carbenoid functionalization of α-imino Csp^3-H bonds could also be successfully applied to a wide range of α-acyldiazo compounds with particular *N*-(2-pyridyl) ketoimine **1a**. Remarkably, α-alkylacyl, α-arylacyl, α-homoallylic acyl, and α-alkoxymethylacyl substituted diazoacetates could easily enable assembling the desired N-PPR **3q-3v** in 72-92% yields (Table 2, entries 16-21). Moreover, when α-acyl diazoketone **2h** was employed as the substrate in this reaction system, the desired 3-acetyl group-substituted pyrrole **3w** was obtained in 76% yield (entry 22). More importantly, α-acyl diazophosphonate **2i** and α-acyl diazosulfone **2j** could also be rapidly converted to 3-phosphonyl and 3-sulfonyl-containing N-PPR **3x** and **3y** in 55% and 63% yields (entries 23 and 24), respectively. Existing synthetic approaches to these pyrrole derivatives generally need tedious reaction steps and harsh reaction conditions.[17] By the way, the structures of pyrrole **3r** and **3y** were already unambiguously assigned by their single crystal X-ray analysis (see ESI for more details).

Table 2. Substrate Scope [a]



entry	ketoimine (**1**)	diazocompd. (**2**)	prod./yield (%) [b]
	 **1**	 **2a**	 **3**
1	**1b**, Ar = 4-Me-Ph	**2a**	**3b**, Ar = 4-Me-Ph 82

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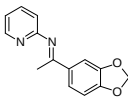
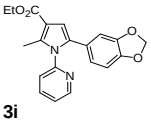
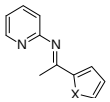
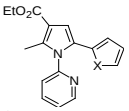
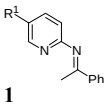
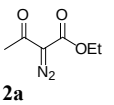
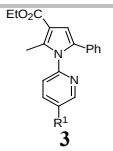
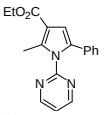
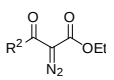
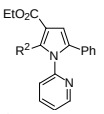
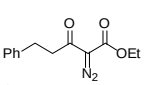
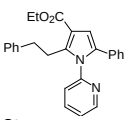
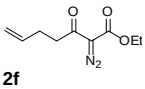
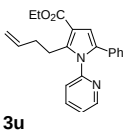
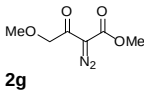
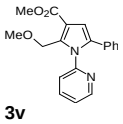
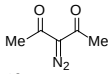
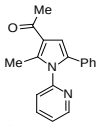
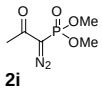
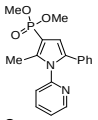
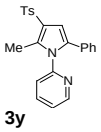
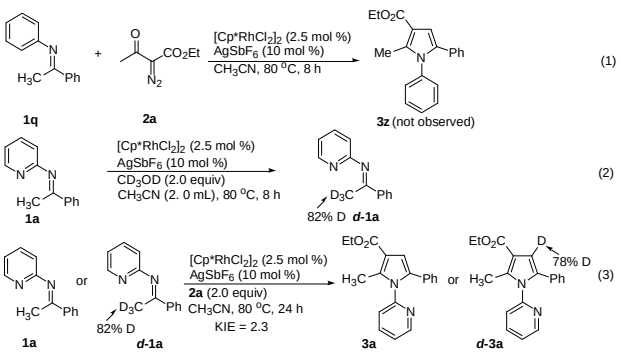
2	**1c**, Ar = 4-MeO-Ph	**2a**	**3c**, Ar = 4-MeO-Ph	72
3	**1d**, Ar = 4-Cl-Ph	**2a**	**3d**, Ar = 4-Cl-Ph	91
4	**1e**, Ar = 3-Cl-Ph	**2a**	**3e**, Ar = 3-Cl-Ph	85
5	**1f**, Ar = 2-Cl-Ph	**2a**	**3f**, Ar = 2-Cl-Ph	62
6	**1g**, Ar = 4-CO2Me-Ph	**2a**	**3g**, Ar = 4-CO2Me-Ph	86
7	**1h**, Ar = 4-NO2-Ph	**2a**	**3h**, Ar = 4-NO2-Ph	95
8	 **1i**	**2a**	 **3i**	61
	 **1**	**2a**		 **3**
9	**1j**, X = O	**2a**	**3j**, X = O	61
10	**1k**, X = S	**2a**	**3k**, X = S	58
	 **1**	**2a**		 **3**
11	**1l**, R^1 = Me	**2a**	**3l**, R^1 = Me	81
12	**1m**, R^1 = Cl	**2a**	**3m**, R^1 = Cl	78
13	**1n**, R^1 = Br	**2a**	**3n**, R^1 = Br	75
14	**1o**, R^1 = CN	**2a**	**3o**, R^1 = CN	79
15	 **1p**	**2a**	 **3p**	78
	 **1a**	 **2**	 **3**	
16	**1a**	**2b**, R^2 = Et	**3q**, R^2 = Et	87
17	**1a**	**2c**, R^2 = Ph	**3r**, R^2 = Ph	72
18	**1a**	**2d**, R^2 = Cy	**3s**, R^2 = Cy	74
19	**1a**	 **2e**	 **3t**	84
20	**1a**	 **2f**	 **3u**	71
21	**1a**	 **2g**	 **3v**	92
22	**1a**	 **2h**	 **3w**	76
23	**1a**	 **2i**	 **3x**	55
24	**1a**	 **2j**	 **3y**	63

[a] All the reactions were carried out using ketoimines (**1**) (0.10 mmol) and diazocompounds (**2**) (0.2 mmol) with $(Cp^*RhCl_2)_2$ (2.5 mol %) in the presence of $AgSbF_6$ (10 mol %) in CH_3CN (2.0 mL) at 80 °C for 8 h under Ar in a sealed reaction tube, followed by flash chromatography on SiO_2. [b] Isolated yield.

To better understand the α-imino Csp^3-H functionalization process, the cross-coupling/cyclization cascade of *N*-phenyl ketoimine (**1q**) with α-acyl diazoacetate (**2a**) was performed under our standard conditions, and no desired *N*-phenyl substituted pyrrole **3z** was observed by the ^1H NMR and GC-MS methods (Scheme 3-1). This result remarkably implied that pyridyl group played a key chelation in this transformation. Subsequently, when *N*-(2-pyridyl) ketoimine **1a** was subjected to Rh(III)/CD_3OD/Ar system for 24 h in the absence of diazoacetate **2a**, 82% deuterium incorporation was detected at the imino methyl group of **1a** (Scheme 3-2) (see SI for more details), [18] this experiment indicated that imine-enamine tautomerization could efficiently occur with the assistance of the Rh(III)/pyridine nitrogen-chelation. In addition, the KIE value (K_H/K_D = 2.3) from kinetic isotope effect experiments further indicated that α-imino C-H bond cleavage possibly dominate the reaction rate (see ESI for more details).



Scheme 3. Preliminary Mechanism Studies

Based on the above-mentioned results, a plausible reaction mechanism is shown in **Figure 1**. Firstly, enamine **A-1**

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derived from imine/enamine-isomerization [12] could be electrophilically attacked by Rh(III) to produce a rhodacycle intermediate **B-1**, and **B-1** could isomerize to form rhodacycle intermediate **C-1**. Subsequently, the coordination of the diazoestate **(2)** was followed by the denitrogenation to form Rh-carbene **D-1**, which would undergo migratory insertion to afford enamine intermediate **E-1**. Finally, protonolysis/intramocular cyclization cascade generated the desired pyrrole product **3** and the active Rh catalyst.

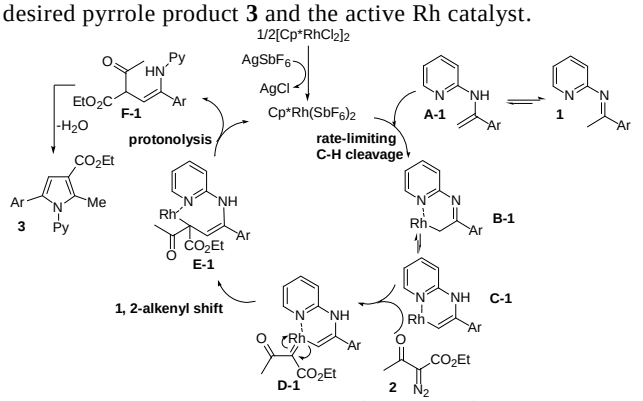

Figure 1. Possible Mechanism for the Transformation

Conclusions

In conclusion, we have disclosed for the first time that β-dicarbonyl α-Rh-carbene could cross-couple with α-imino Csp^3-H bonds through migratory insertion process. This transformation offered an efficient access to synthetically versatile polysubstituted *N*-(2-pyridyl)pyrroles from readily available ketoimines and α-acyl diazocompounds with tolerance of a broad range of functional groups. Further exploration about ligand-assisted remote unactive Csp^3-H functionzalization with carbenoids is underway in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details and compound data, including ^{1}H NMR spectrum and X-ray crystallographic data of **3r** and **3y**. See DOI: 10.1039/c000000x/ :

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