

Synthetic Methods

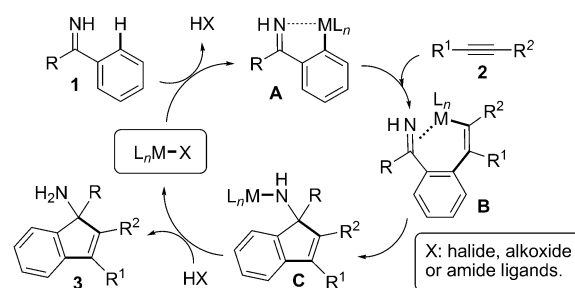
Ruthenium(II)/N-Heterocyclic Carbene Catalyzed [3+2] Carbocyclization with Aromatic N–H Ketimines and Internal Alkynes**

Jing Zhang, Angel Ugrinov, and Pinjing Zhao*

Transition-metal-catalyzed direct functionalization of C–H bonds has become a powerful method for chemical synthesis over the past two decades.^[1] A major strategy for catalytic C–H activation is to utilize heteroatom-based neighboring functional groups by formation of cyclometalated reactive intermediates.^[2] One of the most influential advancements for this directed C–H activation strategy was achieved by Murai et al., who, in 1993, reported ruthenium-catalyzed C–H alkylation of aromatic ketones with olefins.^[3] Since this seminal discovery, a variety of transition metal catalysts have been developed to exploit various directing groups for selective functionalization of C–H bonds.^[1c,d,f,h,j]

One of the major goals for catalytic C–H bond activation is to develop synthetically useful protocols involving mild reaction conditions.^[4] Most reported procedures for the catalytic functionalization of C–H bonds by the directing group strategy require relatively harsh conditions such as high reaction temperatures (commonly 100 °C or higher), stoichiometric amounts of strong oxidants such as Ag^I and Cu^{II} salts, as well as strong-acid or -base additives.^[4] It is highly desirable to develop catalytic methods for directed C–H bond activation that proceed at ambient temperatures, in the absence of oxidants, and under neutral conditions, and therefore should have broad functional-group compatibility and wide applications.^[5–8] We herein describe the development of a ruthenium(II) catalyst that promotes mild C–H functionalization by imine-directed tandem C–H bond activation and carbocyclization with alkynes to form indenamines. The combination of a Ru^{II}/π-allyl catalyst precursor and N-heterocyclic carbene (NHC) ligands allows this formal [3+2] annulation to occur at mild temperatures of 20 to 60 °C, in simple hydrocarbon solvents, and without the need for other additives.

Aromatic imines and their structural analogues (e.g. 2-phenylpyridines) have been extensively studied as substrates for catalytic imine-directed C–H activation for the convenient formation of new carbon–carbon and carbon–heteroatom bonds.^[1,2,6] Imine-directed C–H activation has also been used in a number of tandem catalytic reactions involving multiple bond formations and cyclizations to give N-heterocycles.^[9,10] Our recent report on Rh^I-catalyzed C–H coupling of aromatic N–H ketimines (**1**) with alkynes (**2**) involves a selective [3+2] carbocyclization to form indenamines (**3**).^[11–13] We proposed a catalytic cycle initiated by imine-directed aromatic C–H bond activation to form rhodacycle **A** (Scheme 1, M = Rh^I).^[2] Subsequent alkyne insertion gives a cyclometalated Rh^I/alkenyl intermediate **B**.^[10] Intermediate **B** undergoes carbocyclization through intramolecular imine insertion into the



Scheme 1. Proposed mechanism for catalytic imine/alkyne [3+2] carbocyclization.

Rh–C linkage to form an amido intermediate **C**,^[10,12] which forms indenamine **3** upon protonation. This general mechanism has also been proposed by other groups for analogous catalytic [3+2] carbocyclizations to form indenamines and indenols with Re^I,^[13] Rh^I,^[14] Rh^{III},^[9,15a,b,16a] and Ru^{II}.^[15c,16b] These [3+2] processes generally require high reaction temperatures (120 °C or above), and Cu(OAc)₂ is needed when Rh^{III} and Ru^{II} catalysts are used.^[9,15,16b,17]

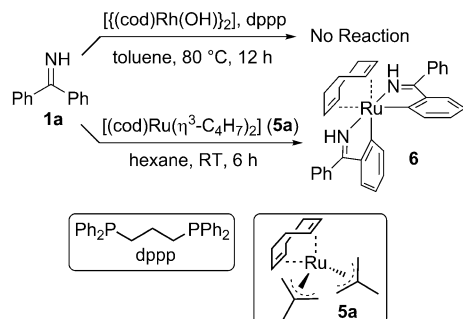
To develop a catalyst system for [3+2] imine/alkyne carbocyclization under mild reaction conditions, we turned our attention to Ru^{II}-based catalysts.^[15c,16b,18,19] Our study was inspired by a 2010 report by Kakiuchi, Murai, and co-workers on a cyclometalated Ru^{II} hydride catalyst for C–H alkylation of aromatic ketones at room temperature.^[7d] In addition, several recent studies have described Ru^{II}-mediated stoichiometric cyclometalation of aromatic imine derivatives and subsequent alkyne insertions under mild conditions.^[10b,20] To explore the key C–H activation of N–H ketimines, we first

[*] J. Zhang, Dr. A. Ugrinov, Prof. Dr. P. Zhao
Department of Chemistry and Biochemistry
North Dakota State University, Dept 275
P.O. Box 6050, Fargo, ND 58108-6050 (USA)
E-mail: pinjing.zhao@ndsu.edu
Homepage: <http://www.chem.ndsu.nodak.edu/people/faculty/zhao.html>

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studied stoichiometric reactions between benzophenone imine (**1a**) and selected Rh^I and Ru^{II} catalyst precursors (Scheme 2). [(cod)Rh(OH)]₂ and 1,3-bis(diphenylphosphino)propane (dppp) ligand did not react with **1a** at 80 °C, which is comparable to the high reaction temperatures required for similar Rh^I catalyzed reactions.^[11,14] In contrast,



Scheme 2. Attempted cyclometalation of benzophenone imine (**1a**) with Rh^I and Ru^{II} complexes. cod = cyclooctadiene.

the Ru^{II}/π-allyl complex [(cod)Ru(η³-methallyl)]₂ (**5a**) reacted with **1a** at room temperature quantitatively to form the doubly cyclometalated Ru^{II} bis(imine) complex [Ru(cod)-{η²-HNC(C₆H₅)C₆H₄}]₂ (**6**). The solid-state structure of complex **6** was determined by single crystal X-ray diffraction, which shows a near-octahedral Ru^{II} center with the two N atoms of the imine ligands *trans* to each other, and two Ru–C bonds at *cis* to each other.^[22]

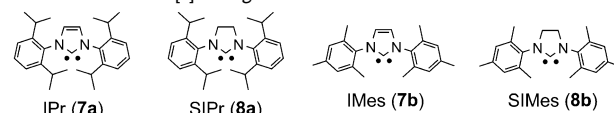
The Ru^{II}-mediated activation of an imine C–H bond at room temperature encouraged us to evaluate Ru^{II} catalyst precursors for a ligand-assisted [3+2] ketimine/alkyne carbocyclization at room temperature (Table 1). In toluene, ruthenacycle **6** did not catalyze the coupling between **1a** and diphenylacetylene (**2a**; entry 1). However, coupling was promoted at room temperature by 3 mol % of **6** in combination with 3.3 mol % of IPr ligand (**7a**), to selectively form the [3+2] annulation product **3a** in 45 % yield after 24 h (entry 2). Replacing **6** with commercially available π-allyl complex **5a** as catalyst gave similar results (entry 3), thus suggesting that **6** is generated in situ from **5a** by the elimination of isobutene. Thus, **5a** was further evaluated as a catalyst precursor in combination with other NHC ligands.^[23] The use of IMes ligand (**7b**) gave comparable yield to **7a** (entry 4), whereas when saturated analogues SIPr (**8a**) and SIMes (**8b**) were used poor results were obtained (entries 5 and 6). In terms of solvent effect, better results were observed with nonpolar solvents rather than polar solvents (entries 7–11). Thus, coupling between **1a** (1.1 equiv) and **2a** (1.0 equiv) proceeded smoothly at room temperature in hexane with 3.0 mol % of **5a** and 3.3 mol % of **7a**, to give **3a** as the only product in 95 % yield (entry 7). Only a trace amount of **3a** was detected from reactions in the absence of ligand **7a** (entry 12). Lastly, lower catalyst loading led to diminished catalytic reactivity (entry 13).^[24]

With the standard reaction conditions established, various internal alkyne^[25] and diaryl N–H ketimine substrates were studied for Ru^{II}-catalyzed room-temperature [3+2] annula-

Table 1: Development of the catalytic reactions.^[a]

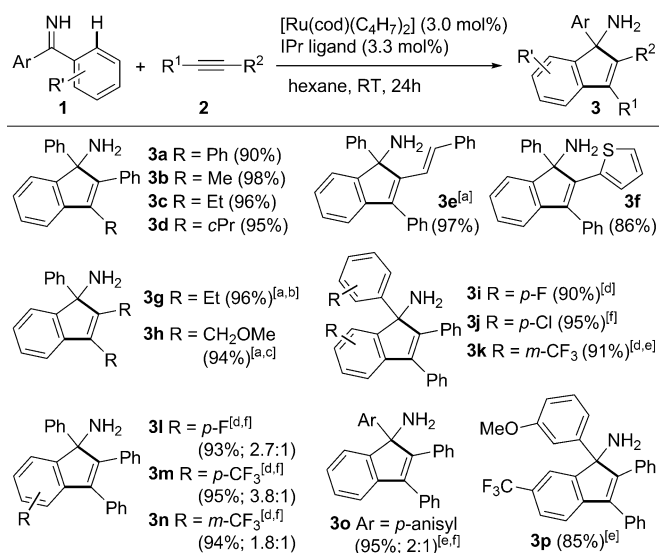
Entry	Ru Catalyst	Ligand	Solvent	Yield [%] ^[b]
1	[(cod)Ru(C,N-ketimine)] ₂ (6)	none	toluene	< 2
2	6	7a	toluene	45
3	[Ru(cod)(η ³ -C ₄ H ₇) ₂] (5a)	7a	toluene	44
4	5a	7b	toluene	57
5	5a	8a	toluene	< 2
6	5a	8b	toluene	5
7	5a	7a	hexane	95
8	5a	7b	hexane	68
9	5a	7a	Et ₂ O	64
10	5a	7a	THF	9
11	5a	7a	DMF	< 2
12	5a	none	hexane	< 2
13 ^[c]	5a	7a	hexane	23

[a] Reaction conditions: **2a** (0.10 mmol, 1 equiv), **1a** (1.1 equiv), Ru catalyst (0.030 equiv), ligand (0.033 equiv), solvent (0.5 mL), room temperature (20–22 °C), 24 h. [b] Determined by GC with *n*-dodecane as internal standard. [c] Using 1.0 mol % **5a** and 1.1 mol % **7a**.



tion (Scheme 3). High yields and regioselectivity were achieved for reactions between **1a** and nonsymmetrical phenylacetylene derivatives having an alkyl, alkenyl, or 2-thiophenyl substituent (products **3b–f**).^[26] Reactions between **1a** and aliphatic internal alkynes required the use of IMes (**7b**) as ligand and toluene as solvent (**3g, 3h**). Heating to 60 °C was necessary to form the diethyl-substituted **3g** in high yield. Among ketimine substrates, diaryl ketimines with electron-withdrawing F, Cl, and CF₃ groups at *para* and *meta* positions readily reacted with **2a** to give [3+2] adducts in high yields (**3i, 3j, 3l–n**).^[27] In comparison, lower reactivity was observed for imines with a *para*- or *meta*-methoxy group, the reactions of which were carried out at 60 °C to achieve high yields (**3o** and **3p**). A temperature of 60 °C was also necessary for 3,3'-(bis)CF₃-substituted benzophenone imine to form product **3k** in 91 % yield. Nonsymmetrical diaryl ketimines coupled to **2a** with moderate regioselectivity (ca. 2:1 to 4:1); C–H activation at the more electron-deficient aryl (**3l–3o**) was favored. This electronic influence on regioselective C–H bond activation was most pronounced with product **3p**, which was formed by exclusive reaction at the *meta*-CF₃ substituted phenyl ring over the *meta*-methoxy substituted one.^[11]

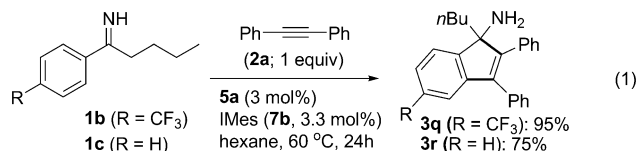
The substrate scope and substituent effects provide significant insights into the reaction mechanism. Firstly, high regioselectivity with nonsymmetric alkyne substrates supported the proposed alkyne insertion into a Ru–aryl rather than a Ru–H linkage.^[21] Secondly, the relatively low reactivity of 3-hexyne (product **3g**) compared to aromatic alkynes was consistent with a rate-limiting alkyne insertion.^[28] Thus, the remarkable reactivity enhancement by NHC ligands is likely



Scheme 3. Scope of the decarboxylative conjugate addition. Reaction conditions: **2** (0.10 mmol, 1.0 equiv), **1** (1.1 equiv), [Ru(cod)(η^3 -C₄H₇)₂] (**5a**; 0.030 equiv), IPr ligand (**7a**; 0.033 equiv), hexane (0.5 mL), room temperature, 24 h. Average yields of the isolated product from two runs are reported. [a] Using IMes (**7b**) in place of **7a**. [b] In toluene solvent and at 60 °C. [c] In toluene solvent. [d] *para* and *meta* positions are based on ketimine reactant **1** (relative to aminomethylene carbon atom). [e] At 60 °C. [f] Combined yield of two regioisomers; the ratio is determined by NMR analysis; structure of major isomer is shown.

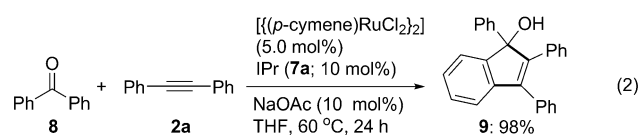
due to their electron richness and ability to promote insertions of organic π systems into metal–carbon linkages.^[29] However, it remains unclear why unsaturated NHC ligands **7a** and **7b** are much more effective than their saturated analogues **8a** and **8b**.^[23,30,31] Thirdly, regioselective functionalization at the more electron-deficient arenes (products **3l**–**3p**) suggested a C–H activation pathway through σ -bond metathesis or nucleophilic deprotonation rather than electrophilic aromatic substitution.^[10]

With high catalyst efficiency and tunable ancillary ligands, the Ru^{II}/NHC catalyst system is expected to facilitate [3+2] annulations for more challenging substrates. For example, effective coupling of **2a** with valerophenone imines **1b** and **1c** was promoted by 3 mol % of **5a** and IMes (**7b**) at 60 °C [Eq. (1)]. Formation of product **3r** represents a very rare



example of C–H functionalization with unactivated and unprotected aryl,alkyl ketimines under mild reaction conditions.^[11,14] In another preliminary study, a [3+2] ketone/alkyne annulation was achieved by using [(*p*-cymene)-RuCl₂]₂ as catalyst, IPr as ligand, and a catalytic amount of NaOAc at 60 °C [Eq. (2)].^[32,33]

In summary, we have developed a Ru^{II}-catalyzed [3+2] annulation between N–H ketimines and alkynes to form



indenamines under mild reaction conditions. Room-temperature C–H activation and subsequent carbocyclization was achieved by using a Ru^{II}/ π -allyl catalyst precursor, NHC ligands, and without strong oxidant or acid/base additives. Current efforts are focused on gaining a better understanding of the reaction mechanism and exploration of NHC ligands for selective functionalization of C–H bonds for broader synthetic applications.

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