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Ru(II)-Catalyzed Mild [3+2] Carbocyclization with Aromatic N-H Ketimines and Internal Alkynes Using N-Heterocyclic Carbene (NHC) Ligands

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Abstract

A convenient and highly efficient synthesis of indenamines has been developed via ruthenium-catalyzed [3+2] carbocyclization under very mild conditions. A catalyst system of Ru(II) π -allyl precursor and N-heterocyclic carbene (NHC) ligand promotes facile coupling between aromatic N–H ketimines with internal alkynes at mild temperatures, without added oxidants or other metal salts, and in non-polar solvents. A proposed mechanism involves imine-directed activation of aromatic C–H bond, alkyne insertion, and carbocyclization by intramolecular imine insertion into Ru–alkenyl linkages.

Keywords

N-H ketimine; indenamine; C-H bond activation; ruthenium; N-heterocyclic carbene

Transition metal-catalyzed direct functionalization of C–H bonds has become a powerful tool 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 and co-workers, who in 1993 reported ruthenium-catalyzed C–H alkylation of aromatic ketones with olefins.^[3] Since this

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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,i]

One of the major goals for catalytic C–H bond activation is to develop synthetically useful protocols *under mild reaction conditions*.^[4] Among reported catalyst systems for functionalization of C–H bonds with directing groups, most procedures 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] For practical synthetic applications with useful functional group compatibility, it is highly desirable to develop mild catalytic methods for directed C–H bond activation that proceed at ambient temperatures, without added oxidants, and under neutral conditions.^[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 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 analogs (e.g. 2-phenylpyridines) have been extensively studied for directed C–H activation catalysis that leads to the convenient formation of new carbon–carbon and carbon–heteroatom bonds.^[1,2,6] Imine-directed C–H activation was also involved in a number of tandem catalytic processes with multiple bond formations and *cyclizations towards N-heterocycles*.^[9,10] By contrast, 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] which undergoes carbocyclization via intramolecular imine insertion into the Rh–C linkage to form an amido intermediate **C**,^[10,12] and releases 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,15b,16a] and Ru(II)^[15c,16b] catalysts. These [3+2] processes generally require high reaction temperatures (120° or above), and Cu(OAc)₂ additive was used for Rh(III) and Ru(II) catalysts.^[9,15, 16b, 17]

To develop a mild catalyst system for [3+2] imine/alkyne carbocyclization, we have turned our attention to Ru(II)-based catalysts.^[15c,16b,18,19] Our study was inspired by a 2010 report by Kakiuchi, Murai and coworkers 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 step of C–H activation of N–H ketimines, we first studied stoichiometric reactions between benzophenone imine (**1a**) and selected Rh(I) and Ru(II) catalyst precursors (Scheme 2). [(cod)Rh(OH)]₂ and DPPP ligand failed to react with **1a** at 80 °C, which was consistent with the high reaction temperatures for corresponding Rh(I) catalysis.^[11,14] By contrast, a Ru(II) π -allyl complex [(cod)Ru(η^3 -methallyl)₂]^[21] (**5a**) reacted with **1a** *at room*

temperature quantitatively to form a doubly cyclometalated Ru(II) bis(imine) complex {Ru(cod)[η^2 -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 two N atoms from imine ligands *trans* to each other, as well as two Ru–C bonds at *cis* positions.^[22]

The Ru(II)-mediated room-temperature imine C–H bond activation encouraged us to evaluate Ru(II) catalyst precursors for ligand-assisted [3+2] ketimine/alkyne carbocyclization at room temperature (Table 1). In toluene solvent, ruthenacycle **6** alone failed to catalyze coupling between **1a** and diphenylacetylene (**2a**) (entry 1). However, room-temperature coupling was promoted by 3 mol% **6** and 3.3 mol% IPr ligand (**7a**) to selectively form [3+2] annulation product **3a** in 45% yield after 24 hours (entry 2). Replacing **6** with commercially available π -allyl complex **5a** as catalyst gave similar results (entry 3), suggesting that **6** is generated *in situ* from **5a** by eliminating isobutene. Thus, **5a** was further evaluated as catalyst precursor with other NHC ligands.^[23] Reactivity with IMes ligand (**7b**) was comparable to **7a** (entry 4), while saturated analogs SIPr (**8a**) and SIMes (**8b**) showed poor reactivity (entries 5, 6). In terms of solvent effect, much higher reactivity was observed in non-polar solvents than polar solvents (entries 7–11). Thus, room-temperature coupling between **1a** (1.1 equiv) and **2a** (1.0 equiv) proceeded smoothly in hexane solvent with 3.0 mol% **5a** and 3.3 mol% **7a**, giving **3a** as the only product in 95% yield (entry 7). Only a trace amount of **3a** was detected from reactions without ligand **7a** (entry 12). Lastly, reduced catalyst loading led to lower 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] annulation (Table 2). High reactivity and regioselectivity was observed for reactions between **1a** and non-symmetrical phenylacetylene derivatives with an alkyl, alkenyl, or 2-thiophenyl substituent (products **3b–f**).^[26] Reactions between **1a** and aliphatic internal alkynes required the use of IMes ligand (**7b**) and toluene solvent (**3g**, **3h**). A 60 °C reaction temperature 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, whose reactions were carried out at 60 °C to achieve high yields (**3o**, **3p**). A 60 °C reaction temperature was also necessary for 3,3'-(bis)CF₃-substituted benzophenone imine to form product **3k** in 91% yield. Non-symmetrical diaryl ketimines coupled with **2a** in moderate regioselectivities (~2:1 to 4:1) that favored C–H activation at the more electron-deficient aryl (**3l–3o**). Such electronic effect on regioselective C–H bond activation was most pronounced with product **3p**, which was formed with exclusive reactivity at the phenyl ring with *meta*-CF₃ substituent over the one with *meta*-methoxy substituent.^[11]

Current results on the substrate scope and substituent effects provide significant insights into the reaction mechanism. Firstly, high regioselectivity with non-symmetric alkyne substrates supported the proposed alkyne insertion into a Ru–aryl rather than Ru–H linkage.^[21] Secondly, the relatively low reactivity with 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 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 analogs **8a** and **8b**.^[23,30,31] Thirdly, regioselective functionalization at the more electron-deficient arenes (products **3l–3p**) suggested a C–H activation pathway via 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 mild [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 ligand (**7b**) at 60 °C (Eq. 1). Formation of product **3r** represents a very rare example of mild C–H functionalization with *unactivated and unprotected aryl-alkyl N-H ketimines*.^[11,14] In another preliminary study (Eq. 2), a mild [3+2] ketone/alkyne annulation was achieved using [(*p*-cymene)RuCl₂]₂ catalyst, IPr ligand, and catalytic amount of NaOAc at 60 °C.^[32,33]

(1)

(2)

In summary, we have developed a mild, Ru(II)-catalyzed [3+2] annulation between N–H ketimines and alkynes to form indenamines. Room-temperature C–H activation and subsequent carbocyclization was achieved using a Ru(II) π -allyl precursor, NHC ligands, and without strong oxidant or acid/base additives. Current efforts are focused on better understanding of the reaction mechanism and exploration of NHC ligands for mild and selective functionalization of C–H bonds for broader synthetic applications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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27. Ketimine substrates with *ortho*-CH₃ or –OCH₃ groups showed no reactivity under current catalytic conditions, presumably due to steric inhibition on cyclometalation. Such reduced reactivity by steric crowding at *ortho* positions was also observed for analogous [3+2] carbocyclization processes as discussed in refs 11–16.
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Scheme 1.

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

Scheme 2.

Attempted cyclometalation of benzophenone imine (**1a**) with Rh(I) and Ru(II) complexes.

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	IPr (7a)	toluene	45
3	[Ru(cod)(η ³ -C ₄ H ₇) ₂] (5a)	7a	toluene	44
4	5a	IMes (7b)	toluene	57
5	5a	SIPr (8a)	toluene	< 2
6	5a	SIMes (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

IPr (**7a**)

SIPr (**8a**)

IMes (**7b**)

SIMes (**8b**)

^[a] 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] GC yields with *n*-dodecane as internal standard.

^[c] Using 1.0 mol% **5a** and 1.1 mol% **7a**.

Table 2

Scope of the decarboxylative conjugate addition.^[a]

^[a] 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, 24h; averaged isolated yields of two runs.

^[b] Cpr = cyclopropyl.

^[c] Using IMes ligand (**7b**) in place of **7a**.

^[d] In toluene solvent and at 60 °C.

^[e] In toluene solvent.

^[f] *para* and *meta* positions are based on ketimine reactant **1** (relative to aminomethylene carbon).

^[g] At 60 °C.

^[h] Combined yield of two regioisomers; the ratio is determined by NMR analysis; structure of major isomer is shown.