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Palladium-Catalyzed Ring-Closing Reaction via C−N Bond Metathesis for Rapid Construction of Saturated *N*-Heterocycles

Bangkui Yu, Suchen Zou, Hongchi Liu, and Hanmin Huang*

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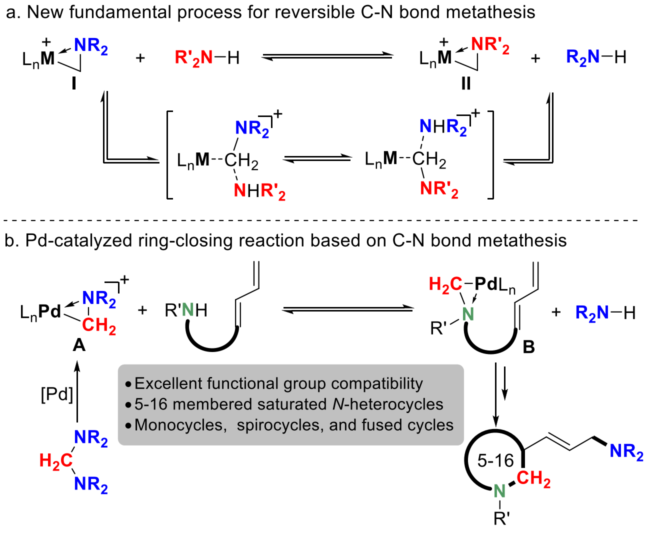
ABSTRACT: The ring-closing reactions based on chemical bond metathesis enable the efficient construction of a wide variety of cyclic systems which receive broad interest from medicinal and organic communities. However, the analogous reaction with C−N bond metathesis as a strategic fundamental step remains an unanswered challenge. Herein, we report the design of a new fundamental metallic C−N bond metathesis reaction that enables the palladium-catalyzed ring-closing reaction of aminodienes with aminals. The reactions proceed efficiently under mild conditions and exhibit broad substrate generality and functional group compatibility, leading to a wide variety of 5- to 16-membered *N*-heterocycles bearing diverse frameworks and functional groups.

The discovery of novel metal complexes and their new transformations plays a crucial role in the development of transition-metal-catalyzed new reactions. In this context, the discovery of metal-carbene and involving fundamental [2 + 2] cycloaddition as well as [2 + 2] cycloreversion reaction has established an alkene metathesis reaction, which has revolutionized the C═C bond formation paradigm and proved remarkably powerful for constructing previously inaccessible complex molecules for both industrial and academic settings.[1−3] Intramolecular application of alkene metathesis, i.e. the ring-closing alkene metathesis (RCM) reaction, has been widely employed for the construction of various cyclic molecular architectures.[4] Inspired by the power of RCM, the ring-closing reactions via the metathesis of other chemical bonds have also been developed and shown to be promising in the preparation of complex molecules.[5−8]

The recent clinical success achieved by increasing the proportion of sp^3 carbon atoms of potential drug candidates has inspired considerable interest in the development of new synthetic approaches to saturated *N*-heterocycles.[9−14] To date, modular and predictable synthetic methods for the preparation of these compounds, especially medium-sized and large-sized rings, are limited, and these in turn limit medicinal chemists' ability to explore potentially fertile regions of chemical space.[15,16] We envisioned that a methodology leveraging C−N bond metathesis for forming saturated *N*-heterocycles had a broadly beneficial impact on the molecular sciences and drug development. To our chagrin, catalytic reactions for the synthesis of *N*-heterocycles with C−N bond metathesis as a strategic fundamental reaction step remain largely elusive, while C═N bond metathesis[17,18] and amidic C−N bond metathesis[19] have been reported for a long time.

Carbon−nitrogen bond metathesis swaps the respective nitrogen moiety in a manner analogous to alkene metathesis. We envisaged that once the C−N bond metathesis occurred in a C−N bond-containing metal-complex, such a process could be viewed as an alternative elementary reaction to incorporate a nitrogen nucleophile into the metal center. In this context, the seminal work on the Pd-catalyzed amine exchange reaction[20] and the transition-metal-catalyzed σ-bond metathesis[21] prompted us to propose that the aminomethyl metal complex might be utilized to realize the desired metallic C−N bond metathesis with a secondary amine via reversible reductive elimination, 1,3-hydrogen transfer, and oxidative addition sequence (Scheme 1a). Given these considerations, we speculated that the palladium-catalyzed C−N bond

Scheme 1. Catalytic Ring-Closing Reaction via C−N Bond Metathesis



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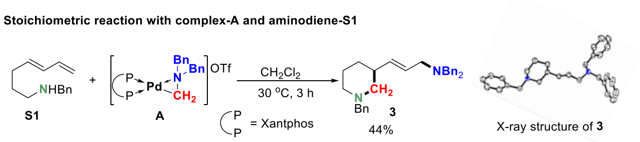
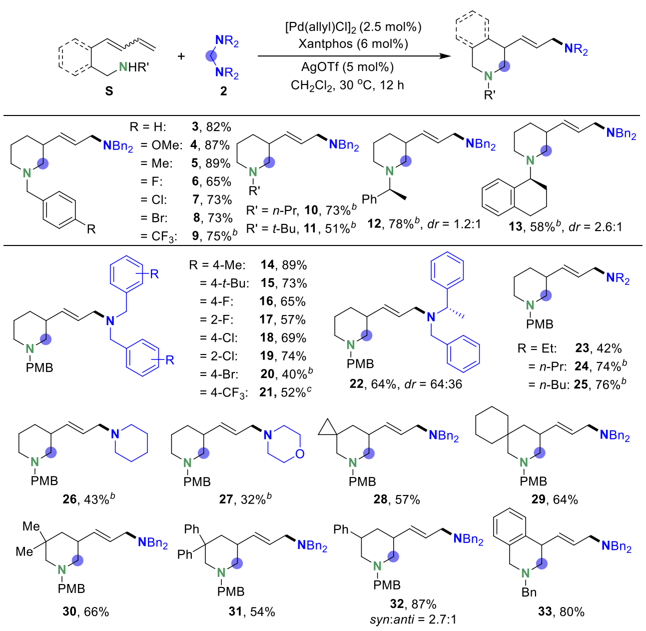
activation of aminals recently reported by our laboratory might be an ideal platform for the development of such a C−N bond metathesis reaction.[22−26] The unique palladacycle-complex **A** could be generated readily by the oxidative addition of aminal to Pd(0). The X-ray diffraction analysis[22] and DFT calculations[27] suggested that the Pd(0)-iminium cation complex was one limiting resonance form of the palladacycle-complex **A**. It indicates that the methylene of **A** is electrophilic and prone to be attacked by a secondary amine to furnish the desired C−N bond metathesis. Once an aminodiene was utilized as the secondary amine, the diene-tethered palladium-complex **B** would form via the C−N bond metathesis, which could undergo further transformations to afford functionalized *N*-heterocycles (Scheme 1b). Herein, we disclose an applicable and highly efficient C−N bond metathesis strategy, which enables a palladium-catalyzed ring-closing reaction between aminodienes and aminals. The reaction proceeds efficiently under mild conditions and exhibits broad substrate generality and functional group compatibility, leading to a wide variety of 5- to 16-membered *N*-heterocycles bearing diverse frameworks and functional groups.

For a proof-of-concept for the proposed ring-closing C−N bond metathesis reaction, we treated diene-tethered amine **S1** (*N*-benzylhepta-4,6-dien-1-amine) with a stoichiometric amount of Xantphos-ligated cyclopalladated complex **A** at 30 °C. To our delight, the reaction indeed took place and the desired piperidine **3** was isolated in 44% yield. The C−N bond of the aminomethyl group (−CH_2NR_2) contained in the cyclopalladated complex **A** was cleaved, and the methylene was incorporated into the backbone of the piperidine ring, implying the involvement of C−N bond metathesis in the reaction.



Based on the stoichiometric reaction described above, optimization of the reaction conditions (see Supporting Information (SI), Table S1) was achieved by conducting the reaction at 30 °C in CH_2Cl_2 with $[Pd(allyl)Cl]_2$/Xantphos/AgOTf combination as the catalyst system. Furthermore, typical Lewis acids and Brønsted acids were ineffective for this reaction (see SI), which indicated that the aza-Prins reaction is most likely not involved in the present protocol.[28,29] With the optimized reaction conditions in hand, we first targeted the synthesis of the piperidine-containing allylamines, a class of compounds bearing scaffolds of pharmaceutical interest.[30] A variety of hepta-4,6-dien-1-amines with several different large substituents on the nitrogen atom reacted with aminal **2a** smoothly, leading to the corresponding products in 51−89% yields (Table 1, **3**−**13**). In addition, a series of aminals derived from benzylamines were examined and the ring-closing products were obtained in good yields (Table 1, **4** and **14**−**22**). Fluorine, chlorine, and bromine were all tolerated under the reaction conditions. Besides, aminals prepared from the simple aliphatic amines were also applicable in this reaction system to give the corresponding products (**23**−**27**) in 32−76% yields. We further explored the generality of the present method by varying the substituents on the backbone of the diene-tethered amines. It was found that the transformation

Table 1. Substrate Scope for Six-Membered *N*-Heterocycles[a]

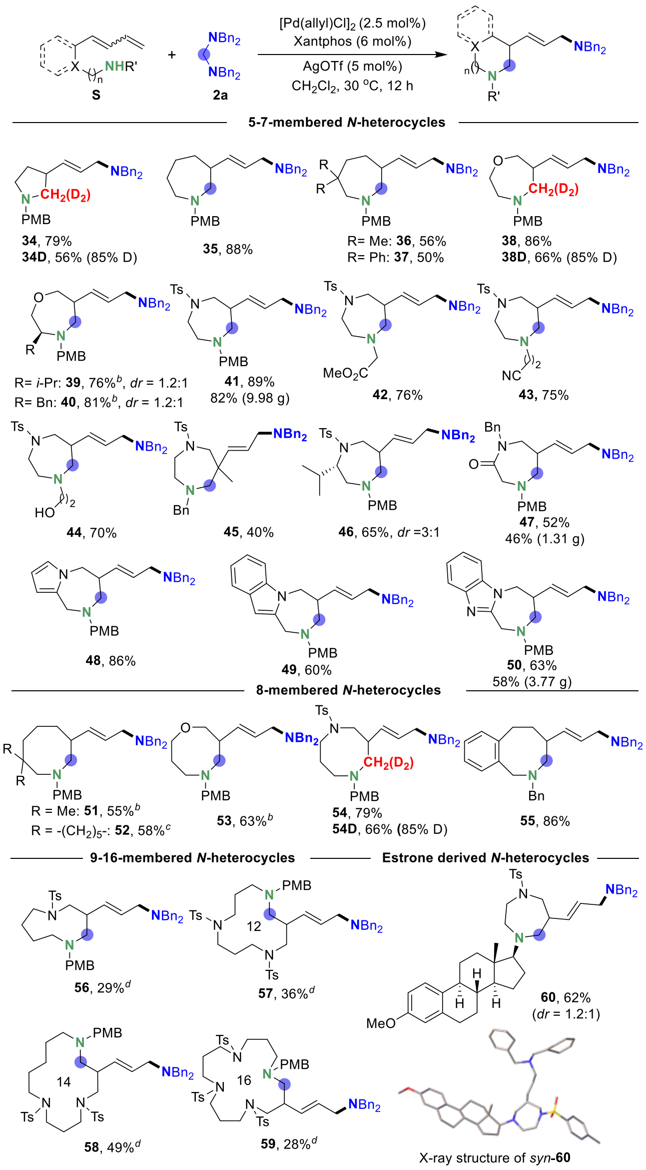


[a]Reaction conditions: **S** (0.36 mmol), **2** (0.30 mmol), $[Pd(allyl)Cl]_2$ (2.5 mol %), Xantphos (6 mol %), AgOTf (5 mol %), CH_2Cl_2 (1.0 mL), 30 °C, 12 h. Isolated yield. [b]80 °C. [c]100 °C.

was less efficient for substrates bearing *gem*-disubstituents at the tether backbones (**28**−**31**) due to the Thorpe−Ingold effect. In contrast, the efficiency was improved when only one substituent was present at the C2 position (**32**). The benzyl-tethered aminodiene also underwent the desired cyclization to afford the tetrahydroisoquinoline (**33**) with exocyclic allylamine at the C4-position in 80% yield.

Motivated by the successful construction of the piperidine products, we sought to extend the C−N bond metathesis reaction to more synthetically challenging saturated *N*-heterocycles with smaller or larger ring sizes (Table 2) by changing the tether length. As expected, with a two-methylene tether, the allylamine-containing pyrrolidine (**34**) was obtained in 79% yield. Besides, a series of allylamine-containing azepanes, oxazepanes, diazepanes, and their derivatives with seven-membered rings (**35**−**50**) were obtained in 50−89% yields by further prolonging the tether length of the aminodienes. The substituent on the diene moiety could be tolerated to give the corresponding product **45** with a quaternary carbon chiral center. The electron-withdrawing substituents, such as ester, nitrile, and hydroxyl, could be attached in the amine-protection groups (**42**−**44**), and the amide functionality (**47**) could be tolerated in the ring system as well. Moreover, the pharmaceutically relevant heterocycles, such as pyrrole, benzimidazole, and indole, could be introduced into the tether backbone to afford the corresponding products (**48**−**50**) in 60−86% yields. When a chiral tether was employed, the corresponding saturated azepanes were obtained with lower diastereoselectivities (**39**−**40** and **46**). Further prolonging the tether length, a series of eight-membered ring products (**51**−**55**) were produced in moderate to good yields (55−86%). Similar to the formation of seven-membered ring products, the incorporation of nitrogen or oxygen into the backbone of the azocanes was possible, and the unique spirocyclic azocanes (**52**) were also obtained in 58%

Table 2. Substrate Scope of Linear Aminodienes[a]

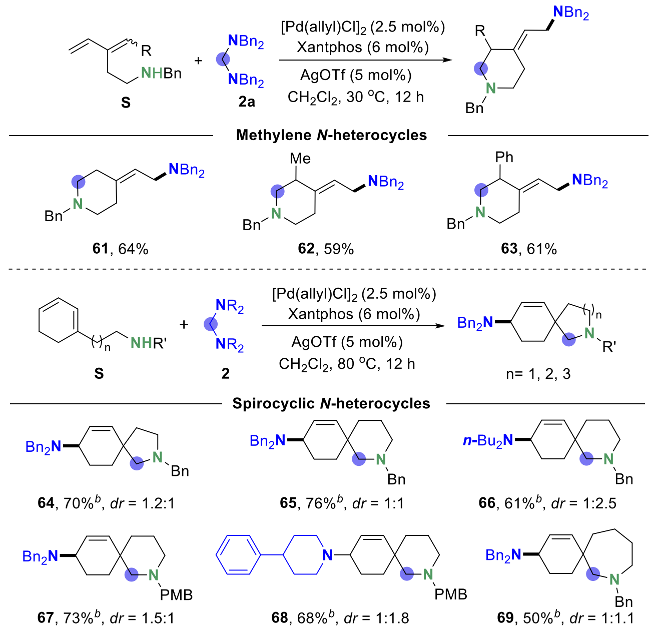


[a]Reaction conditions: **S** (0.36 mmol), **2a** (0.30 mmol), $[Pd(allyl)Cl]_2$ (2.5 mol %), Xantphos (6 mol %), AgOTf (5 mol %), CH_2Cl_2 (1.0 mL), 30 °C, 12 h. Isolated yield. [b]80 °C. [c]100 °C. [d]$[Pd(allyl)Cl]_2$ (5 mol %), Xantphos (12 mol %), AgOTf (10 mol %), CH_2Cl_2 (20 mL), 100 °C, 36 h.

yields. To our delight, the challenging 9-, 12-, 14-, and even 16-membered ring products (**56**−**59**) with multiple *N*-atoms were also successfully produced in low-to-moderate yields. The cyclization of estrone derived aminodiene bearing a steroid scaffold led to two separable diastereoisomers (**60**) in good yields.[31] In addition, several substrates were demonstrated on a 1−10 g scale with lower catalyst loading to demonstrate the practical laboratory-scale utility (**41**, **47**, and **50**).

Except for the linear aminodienes, the branched counterparts could also be smoothly converted to the desired products (**61**−**63**) in good yields under standard conditions (Table 3). The amine-tethered cyclohexa-1,3-dienes could also be employed in the present protocol to afford a series of spirocyclic *N*-heterocycles (**64**−**69**) in good yields at 80 °C (Table 3). The results demonstrated here represent one of the

Table 3. Substrate Scope of Branched Aminodienes[a]

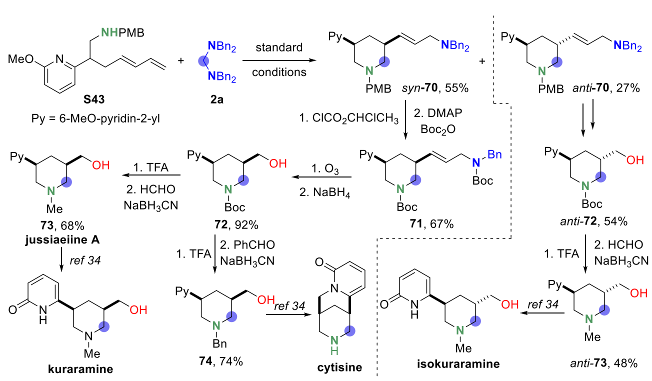


[a]Reaction conditions: **S** (0.36 mmol), **2** (0.30 mmol), $[Pd(allyl)Cl]_2$ (2.5 mol %), Xantphos (6 mol %), AgOTf (5 mol %), CH_2Cl_2 (1.0 mL), 30 °C, 12 h. Isolated yield. [b]80 °C.

most reliable methods to date for the preparation of a wide range of saturated *N*-heterocycles with allylic amine substitutions, which are attractive scaffolds for medicinal chemistry and difficult to prepare by traditional synthetic methods.[30−32] It is also worth pointing out that the deuterium-labeled products (**34D**, **38D**, and **54D**), which are potentially valuable for drug design,[33] could be facilely obtained in good yields by using D-labeled aminal **2a**-d_2 as the reactant.

The synthetic potential of this method can be demonstrated in the synthesis of natural products (Scheme 2). With pyridine-

Scheme 2. Synthetic Applications



containing aminodiene as starting material, the separable *syn*-**70** and *anti*-**70** were obtained on a gram scale (5.39 g) with good yields under standard reaction conditions. From *syn*-**70**, the alkaloids jussiaeiine **A**, kuraramine, and cytisine[34] could be synthesized by using conventional protocols. Moreover, the isokuraramine could also be obtained by using *anti*-**70** as a key starting material through similar methods (see SI).

We propose a tentative mechanism for the reaction, which begins with palladacycle-complex **A** (Scheme 3a). First, the

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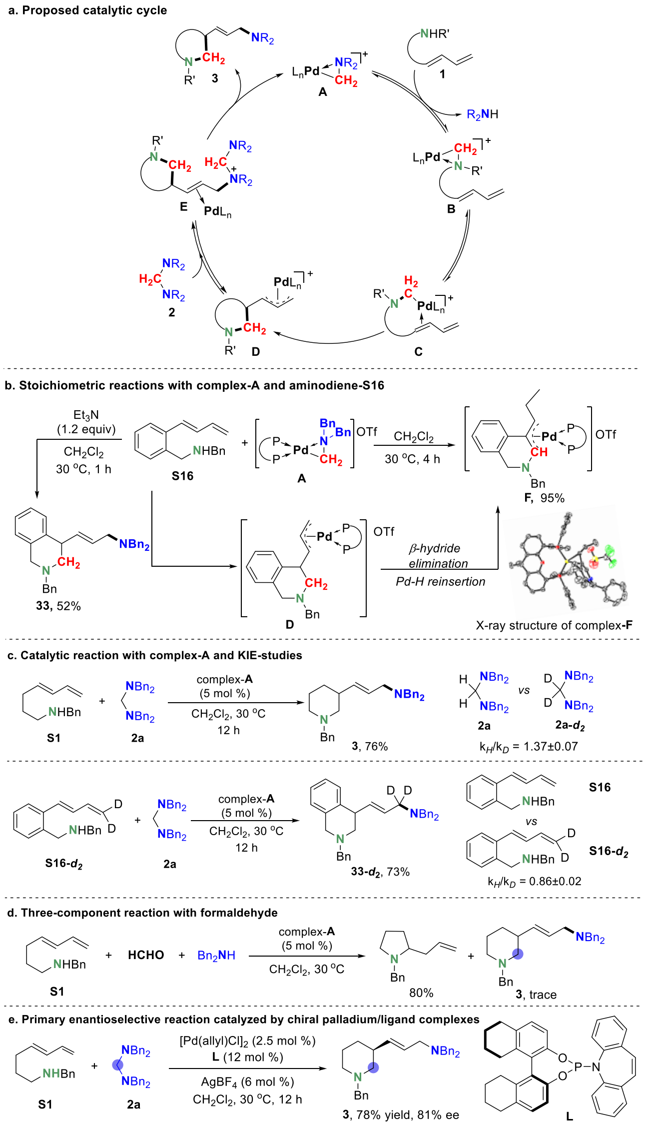
Scheme 3. Proposed Catalytic Cycle and Mechanistic Studies



palladium-complex **A** is generated *in situ* via the reaction of aminal **2** with $[Pd(allyl)Cl]_2$, AgOTf, and Xantphos (see SI), which is then converted to the active diene-tethered palladium-complex **B** through the putative C−N bond metathesis via reversible reductive elimination, 1,3-hydrogen transfer, and oxidative addition sequence. The intermediate **B** then isomerizes to **C**, in which the internal alkene coordinates with the Pd(II) center. Intramolecular alkene-migratory insertion generates the π-allylpalladium species **D**, which is then intercepted by an aminal **2** to form intermediate **E** via reductive elimination to forge an allylic C−N bond. Finally, the oxidative addition of intermediate **E** to Pd(0) delivers the saturated *N*-heterocycles together with regenerating the active palladium-complex **A** to complete the catalytic cycle.

Several experiments were conducted to gain insights into the mechanism. Treatment of the palladium-complex **A** with a stoichiometric amount of aminodiene **S16** at 30 °C resulted in the near-quantitative formation of Pd(II)-complex **F** (Scheme 3b). The complex **F** was fully characterized by NMR, X-ray diffraction analysis, HRMS, and XPS. *In situ* ^{31}P NMR and HRMS studies indicated that complex **F** was generated from Pd(II)-intermediate **D** through β-hydride elimination and Pd−H reinsertion (see SI). The desired cyclization adduct **33** formed in 52% yield when the reaction was performed in the presence of Et_3N. Moreover, complex **A** was found to be capable of catalyzing the desired ring-closing reaction with almost no H/D-scrambling when **S16**-d_2 was utilized as the starting material (Scheme 3c). These results indicate the plausible intermediacy of complex **A** and **D** before being intercepted by aminal in the catalytic cycle.[23] Kinetic analysis of the catalytic reaction discloses that the formation of product **3** proceeds with the first-order dependence on aminodiene **S1** concentration, aminal **2a** concentration, and palladium-catalyst concentration (see SI). These results are consistent with the formation of complex **A** from intermediate **D** as rate-determining in catalysis. To provide a support for the rate-limiting formation of complex **A**, we conducted competition experiments between aminal **2a** and deuterated **2a**-d_2 (Scheme 3c). Based on carbon-hybridization change from sp^3 to sp^2 as expected, we observed a normal secondary isotope effect (k_H/k_D) of 1.37 ± 0.07. Moreover, an inverse secondary k_H/k_D = 0.86 ± 0.02 was observed in the competition experiments between **S16** and deuterated **S16**-d_2 (Scheme 3c), indicating a significant Csp^2 to Csp^3 rehybridization in the transition state of the C−N formation process.[35] These results suggested that the formation and consumption of the transient intermediate **E** was involved in the rate-determining step. The three-component reaction with HCHO (Scheme 3d) and the primary enantioselective reaction established by chiral Pd/ligand complexes (Scheme 3e) further ruled out that the aza-Prins mechanism was involved in this reaction (see SI).[28,29]

In summary, we describe a novel cyclization strategy via the C−N bond metathesis of aminodienes as well as its successful applications to a wide variety of substrates and ring sizes. We anticipate that the palladium-catalyzed ring-closing reactions demonstrated herein will enhance chemists' access to a diverse array of saturated and functionalized *N*-heterocycles. From a broader perspective, we envision that this fundamental C−N bond metathesis strategy will not only be a versatile platform for medicinal chemists to explore the structure−activity relationship but also inspire more research into leveraging C−N bond metathesis for synthetic methodology development.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c10615.

Experimental details and full spectroscopic data for all new compounds (PDF)

Crystallographic data for complex **F** (CIF)

Crystallographic data for **3** (CIF)

Crystallographic data for **60** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

Hanmin Huang − *Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei 230026, P. R. China; Center for Excellence in Molecular Synthesis of CAS, Hefei 230026, P. R. China;* orcid.org/0000-0002-0108-6542; Email: hanmin@ustc.edu.cn

Authors

Bangkui Yu — *Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei 230026, P. R. China*

Suchen Zou — *Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei 230026, P. R. China*

Hongchi Liu — *Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei 230026, P. R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.0c10615

Notes

The authors declare no competing financial interest.

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(31) CCDC 1897577 (complex **F**), 1897578 (**3**), and 1914878 (**60**) contain the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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