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Synthesis of pyrroles via ruthenium-catalyzed nitrogen-transfer $[2 + 2 + 1]$ cycloaddition of α,ω -diynes using sulfoximines as nitrene surrogates

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Pyrrole is a privileged five-membered aromatic nitrogen heterocycle, which is ubiquitous in natural products, drug molecules, and functional materials. Therefore, numerous synthetic routes to substituted pyrroles have been extensively developed. Nevertheless, the efficient and short-step synthesis of highly substituted and/or fused pyrroles has remained a significant challenge in organic chemistry. Here we report a ruthenium-catalyzed nitrogen-transfer $[2 + 2 + 1]$ cycloaddition of α,ω -diynes involving cyclic biscarbenoid intermediates. To achieve the key nitrogen transfer to carbenoid carbons, sulfoximines are employed as nitrene surrogates. Consequently, diverse fused pyrroles are successfully synthesized in good yields with wide functional group compatibility. Moreover, this method allows the synthesis of *N*-alkyl, *N*-aryl, and even *N*-H pyrroles, which are difficult to obtain using previous $[2 + 2 + 1]$ -type reactions. Nitrogen transfer from sulfoximines to cyclic biscarbenoid intermediates is supported by density functional theory calculations and control experiments.

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Transition metal (TM)-catalyzed nitrene-transfer reactions (NTRs) have been extensively investigated as they provide efficient access to valuable nitrogen compounds via C–H amination, aziridination, sulfimination, etc.¹. Because nitrenes are extremely reactive, the combination of TM catalysts with nitrene surrogates is generally employed to control both the reactivity and selectivity of NTRs^{1–5}. Thus, the development of methods involving a novel nitrene surrogate would significantly expand the synthetic potential of NTRs. A recent study by Tonks and coworkers demonstrated that Ti(IV) imido species, which were derived from *N,N'*-diaryl diazenes, participated in a [2 + 2 + 1] cycloaddition with alkynes to afford *N*-aryl pyrroles (Fig. 1a)⁶. Our group has also been engaged in the development of atom-transfer [2 + 2 + 1] cycloadditions of α,ω -diynes^{7–9}. However, a similar nitrogen transfer has never been observed when conventional nitrene surrogates were employed.

Pyrroles are among the most important five-membered heteroaromatic compounds that are ubiquitously found in natural products, bioactive compounds, and functional molecules^{10–15}. Although diverse synthetic routes to substituted pyrroles have been continuously devised beyond the conventional Paal–Knorr and related methods, there is still an ample need for mild, efficient, selective, and short-step synthesis of highly substituted pyrroles^{16–21}. In this regard, [2 + 2 + 1]-type cyclocondensation reactions of alkynes with amines provide promising routes to fully substituted pyrroles in a single operation^{22–26}. However, activated alkyne substrates are essential for these reactions, and stoichiometric promoters are often required. In contrast, Wang, Lu, and coworkers developed Pd-catalyzed methods to synthesize fully substituted pyrroles from arylalkynes and primary amines (Fig. 1b)^{27,28}. Buchwald and coworkers also reported an indirect [2 + 2 + 1] synthesis of *N*-Boc pyrroles via a Cu-catalyzed coupling of BocNH₂ with 1,4-diiodo-1,3-dienes, which were prepared beforehand from two alkyne molecules²⁹. Recently, Tonks' group

reported a Ti-catalyzed [2 + 2 + 1] cycloaddition of alkynes using *N,N'*-diaryl diazenes as nitrene surrogates (Fig. 1a)⁶. Although these advances enable the catalytic synthesis of highly substituted pyrroles using simple amines or diazenes, most of the methods are limited to monocyclic and/or less functionalized pyrroles. Thus, an efficient protocol for the catalytic synthesis of functionalized polycyclic pyrroles remains undeveloped. Because fused pyrroles are found in bioactive molecules and functional materials (Fig. 1d), development of a catalytic nitrogen-transfer [2 + 2 + 1] synthesis of fused pyrroles would contribute significantly to pyrrole-based design of drugs and materials^{30,31}. Nevertheless, the straightforward application of the state-of-the-art catalytic nitrogen-transfer systems to the targeted [2 + 2 + 1] reaction poses a major challenge: late-transition-metal nitrenoids generally undergo C–H insertion and/or [2 + 1] aziridination with unsaturated compounds¹, and thus, the chemoselective transformation of functionalized α,ω -diynes into the target pyrroles requires a novel strategic approach: nitrogen transfer without involving metal nitrenoids.

Here we investigate the ruthenium-catalyzed nitrogen-transfer [2 + 2 + 1] cycloaddition of α,ω -diynes using sulfoximines as effective nitrene surrogates for ruthenacyclic intermediates bearing a cyclic biscarbenoid character (Fig. 1c). It should be noted that because sulfoximines are rather stable, their loss of nitrogen to give sulfoxides is very rare^{32,33}. Sulfoximines can be synthesized via sulfimination of the corresponding sulfoxides including ruthenium-catalyzed nitrene transfer^{34–36}, and a reverse reaction, i.e., nitrogen transfer from sulfoximines, has not been previously disclosed, to the best of our knowledge. The newly developed process is operationally simple and compatible with a wide variety of diyne substrates bearing reactive functional groups. Moreover, the use of sulfoximines enables the introduction of reactive *N*-substituents on the pyrrole products and even an *N*-unprotected pyrrole can be directly obtained without a

Fig. 1 [2 + 2 + 1] Approaches to substituted pyrroles. **a** Ti-catalyzed reaction of alkynes with diazenes. **b** Pd-catalyzed reaction of arylalkynes with amines. **c** Ru-catalyzed reaction of α,ω -diynes with sulfoximines. **d** Examples of highly substituted and fused pyrroles

Fig. 2 Reaction optimization using diynes **1a** and **1b**. **a** Screening of sulfoximines as nitrene surrogates. **b** Reactions of diynes **1a** and **1b** with sulfoximine **2f** under optimized conditions. **Ru1**: $[\text{CpRu}(\text{MeCN})_3]\text{BF}_4$

Fig. 3 Scope of [2 + 2 + 1] pyrrole synthesis in terms of diyne substrates **1**. ^a2f (1.5 equiv). ^b2d was used instead of 2f. ^c1,2-Dichloroethane reflux. ^dDesilylated with TBAF

Fig. 4 Reactions with other sulfoximines and transformations of *N*-propargyl pyrroles. **a** Reactions of diyne **1a** with sulfoximines **2g–m**. **b** Transformations of *N*-propargyl pyrrole **8**. **Ru1**: [CpRu(MeCN)₃]BF₄, **Ru2**: [Cp*Ru(MeCN)₃]BF₄, **Ru3**: Cp*RuCl(cod), cod = 1,5-cyclooctadiene

deprotection step. A plausible mechanism of nitrogen transfer from sulfoximines to cyclic biscarbenoid intermediates is proposed based on control experiments and density functional theory calculations.

Results

Reaction optimization. The key to the successful realization of the elusive catalytic nitrogen-transfer [2 + 2 + 1] synthesis of fused pyrroles is the identification of the optimal nitrene surrogates toward ruthenacycle intermediates as electrophilic biscarbenoids. Thus, we screened various alkyl-substituted and aryl-substituted *N*-methyl sulfoximines toward the reaction with ether-tethered diyne **1a** in the presence of ruthenium catalyst [CpRu(MeCN)₃]PF₆ (**Ru1**, Cp = η⁵-cyclopentadienyl), as shown in Fig. 2a. When diphenyl sulfoximine **2a** was used, the expected product **3a** was obtained, albeit in a low yield (25%). Although dialkyl sulfoximine **2b** was totally inefficient, methyl phenyl sulfoximine **2c** was found to be more competent than **2a**. Further electronic tuning was conducted based on **2c**. The weakly electron-withdrawing *p*-chlorophenyl substituent in **2d** had a negative impact on the product yield, while sulfoximine **2e** bearing an electron-donating *p*-methoxyphenyl substituent increased the yield of **3a**. Further improvement was observed when sulfoximine **2f** with a weakly electron-donating *p*-fluorophenyl substituent was used, and thus, **2f** was selected as the optimal nitrene surrogate. Other parameters were also examined. The more electron-rich catalyst [Cp*Ru(MeCN)₃]PF₆ (**Ru2**, Cp* = η⁵-pentamethylcyclopentadienyl) gave a much inferior result and common organic solvents such as AcOEt, THF, MeCN, and 1,2-dichloroethane (DCE) were less efficient than dimethylformamide (DMF). With increased loadings of **Ru1** (2 mol%) and **2f** (1.1 equiv), the reactions of **1a** and sulfonamide-tethered diyne **1b** proceeded to completion within 0.5 h in dry DMF at 80 °C, affording the desired pyrroles **3a** and **3b** in 92% and 98% yields, respectively (Fig. 2b).

Scope of [2 + 2 + 1] pyrrole synthesis. To further demonstrate the substrate scope, various diynes were subjected to the nitrogen-transfer [2 + 2 + 1] cycloaddition using **2f**; the results obtained

with optimal catalyst loadings and reaction times are shown in Fig. 3. Amide (**3c**), imide (**3d**), ketone (**3e**), nitrile (**3f**), ester (**3g**) and alcohol (**3h**) moieties on the tethers were well tolerated in the reaction protocol. Phenyl groups possessing electron-donating alkoxy (**3k–m**) or electron-withdrawing (**3n**, **3q**, and **3s**) groups, and thiophenes (**3r**) were compatible as alkyne terminal groups. Notably, reactive C–I and C–B bonds (**3o** and **3p**) were also tolerated. Acenaphthene-fused and benzopyran-fused pyrroles (**3i** and **3j**) as well as unsymmetrical pyrroles (**3s** and **3t**) could be obtained in high yields. One of the terminal groups could be an alkyl group, as **3t** was obtained in good yield. Although diyne **1u** bearing methyl terminals did not afford the corresponding product **3u** under similar conditions, the reaction of diyne **1v** bearing cyclopropyl groups on both terminals afforded the corresponding product **3v** in 68% yield with the cyclopropyl groups intact. Nevertheless, the use of **2d** instead of **2f** and a 10 mol% catalyst loading converted **1u** into **3u** in 52% yield. Silyl-substituted diynes also underwent nitrene-transfer [2 + 2 + 1] cycloaddition when DCE was used as the solvent instead of DMF under reflux. Unsymmetrical pyrrole **3w** bearing a bulky Si^tBuMe₂ group was obtained in 91% yield, albeit an increased catalyst loading (10 mol %) was required. The reaction of bis(trimethylsilyl)diyne **1x** was performed similarly to afford 2,5-unsubstituted pyrrole **3x** in 83% yield after exhaustive desilylation using ^tBu₄NF [tetra-*n*-butylammonium fluoride (TBAF)].

Because various sulfoximines are readily available^{34,35}, the scope of *N*-substituents was investigated for the reaction of diyne **1a** (Fig. 4a). Although increased loadings of sterically more demanding sulfoximines **2g–k** (2 equivs) were required, the corresponding pyrroles **4–6**, **8**, and **9** were obtained in 69–82% yields. Although the reason was unclear, the reaction with *N*-prenyl sulfoximine **2i** afforded *N*-H pyrrole **7** in 13% yield along with the expected product **6** (74%). *N*-aryl pyrrole **10** was also obtained in 67% yield. In this case, 1.5 equiv of sulfoximine **2l**, bearing a more electron-donating *p*-methoxyphenyl substituent on the sulfur center, was required. In the syntheses of complex molecules including reactive pyrrole scaffolds, *N*-protecting groups play a critical role³⁷. However, the removal of *N*-protecting groups often requires elaborate manipulations and/

Fig. 5 Control experiments and proposed mechanism. **a** Reaction of enantiopure sulfoximine **2c**. **b** Reaction of preformed ruthenacycle **14** with sulfoximine **2f** in the presence of AgPF_6 . **c** Plausible catalytic cycle. **Ru1**: $[\text{CpRu}(\text{MeCN})_3]\text{BF}_4$

or affords low yields. Thus, the direct synthesis of *N*-unprotected highly substituted pyrroles has a significant advantage. Notably, the use of *N*-triethylsilyl sulfoximine **2m** (1.5 equiv) as an *N*-H nitrene surrogate directly produced *N*-H pyrrole **7** in 70% yield, although a higher reaction temperature of 120 °C was required. The potency of sulfoximines as nitrogen donors is attributable to their sufficient nucleophilicity toward the electrophilic ruthenacycle intermediates as well as the leaving-group ability of the corresponding sulfoxides. In fact, much less nucleophilic *N*-Boc sulfoximine **2n** ($\text{R} = \text{Boc}$, $\text{Y} = \text{F}$) proved to be totally inefficient. It should be noted that alkyne moieties, which can be used for further derivatizations, could be introduced on the *N*-substituents, because α,ω -diynes are selectively transformed into pyrroles in our nitrogen-transfer $[2 + 2 + 1]$ cycloaddition. *N*-Propargyl pyrrole **8** underwent ruthenium-catalyzed Markovnikov hydrosilylation with triethylsilane and $[3 + 2]$ cycloaddition with benzyl azide to regioselectively afford vinylsilane **11** and triazole **12** in 78% and 91% yields, respectively (Fig. 4b)^{38,39}.

Mechanistic considerations. To gain insights into the mechanism, several control experiments were carried out. The reaction of diyne **1a** with enantiopure sulfoximine (*R*)-**2c** (99% ee, 1.1 equiv) was performed using acetone as the solvent to ensure the isolation of the resultant sulfoxide. After reaction for 6 h, methyl phenyl sulfoxide (*R*)-**13** was obtained in 68% yield with 98% ee along with pyrrole **3a** (Fig. 5a). Thus, it was confirmed that the nitrogen transfer from sulfoximines occurs with retention of configuration at the sulfur center. The influence of the sulfoxide side products on the reaction efficiency was also examined by comparing rates for the reactions of diyne **1a** and sulfoximine **2c** with or without adding sulfoxide **13** (Supplementary Methods). As a result, the

reaction rate was slightly decreased by initially adding 1 equiv of **13**, suggesting that sulfoxides slow the catalyst turnover by their coordination to the ruthenium center.

Moreover, the involvement of cationic ruthenacycle intermediates was experimentally corroborated by the formation of **3a** from the reaction of isolated ruthenacycle **14**⁴⁰ with sulfoximine **2f** (1.1 equiv) in the presence of AgPF_6 (1.1 equiv) in DMF at 80 °C (Fig. 5b). In this case, the cationic ruthenacycle derived from **14** was less electrophilic than that derived from **Ru1** because the Cp^* ligand in **14** was more electron-donating than the Cp ligand in **Ru1**. Nevertheless, **3a** was obtained in a moderate yield of 58%.

Based on these observations and the results obtained in our previous studies^{7–9}, a plausible mechanism for the nitrogen-transfer $[2 + 2 + 1]$ cycloaddition is proposed, as shown in Fig. 5c. The reaction of **Ru1** with a diyne substrate produces the ruthenacycle key intermediate **I**. Because **I** behaves as a cyclic biscarbenoid^{40–43}, nitrogen transfer from sulfoximines **2** to one of the carbenoid carbons in **I** occurs via **TS_{I-II}** to produce azadienylcarbene complex **II**. Subsequent cycloisomerization of **II** affords η^5 -pyrrole complex **III**. Finally, the pyrrole ligand of **III** is replaced by diyne substrate **1** to afford free pyrrole **3**, and subsequent oxidative cyclization regenerates **I**. This mechanism is quite distinct from that of Tonks' titanium-catalyzed reaction, which involves the formation of Ti(IV) imido species and its sequential reactions with alkynes⁶. Our reaction is the first example of a $[2 + 2 + 1]$ cycloaddition via a catalytic nitrogen transfer to a five-membered metallacycle intermediate. However, stoichiometric reactions of cobaltacyclopentadienes or titanacyclopentadienes with nitrene surrogates leading to pyrroles has been reported^{44–46}.

Fig. 6 Calculated energy surface for the model reaction of diyne **1a** with sulfoximine **2f**. Relative Gibbs free energies (298 K, 1 atm) are shown. Computed models: hydrogen, white; carbon, gray; nitrogen, blue; oxygen, red; fluorine, yellow green; sulfur, yellow; and Ru, green

To support the proposed mechanism, the reaction of diyne **1a** with sulfoximine **2f** was analyzed by density functional theory calculations at the PCM (DMF) rM06L/6-311 G++(d,p)-SDD//rB3LYP/6-31 G(d)-LanL2DZ level of theory (for details, see Supplementary Methods). This method has been reliably used for the computational analysis of TM-catalyzed reactions⁴⁷. The calculated energy surface is shown in Fig. 6. The initial oxidative cyclization of cationic diyne complex **A** with one DMF ligand proceeds via TS_{AB} with an activation energy of $\Delta G^\ddagger = +12.1$ kcal/mol. After passing through TS_{AB} , ruthenacyclopentadiene **B** is located at a slightly lower energy level than **A**. Subsequently, **B** undergoes facile isomerization to planar delocalized ruthenacycle **C** through a small activation barrier of $\Delta G^\ddagger = +5.1$ kcal/mol. The geometry of **C** is comparable to that of previously reported ruthenacyclopentatrienes³⁷: the Ca–C β bonds (1.413 and 1.415 Å) are only slightly longer than the C β –C β' bond (1.389 Å). In addition, the Ru–Ca bonds (1.994 and 1.995 Å) are shorter than a normal Ru–C single bond (ca. 2.0 Å), indicating that **C** has a biscarbenoid character. The formation of **C** from **A** is estimated to be 18.2 kcal/mol exergonic.

After oxidative cyclization, ligand exchange of DMF-bound ruthenacycle **C** with sulfoximine **2f** generates *N*-bound sulfoximine complex **D**, which undergoes the key nitrogen transfer with an activation energy of $\Delta G^\ddagger = +27.7$ kcal/mol to generate azadienyl carbene complex **E** with the concomitant extrusion of the sulfoxide residue. The shortened Ru–N/Ca–N and elongated

Ru–Ca/N–S distances in TS_{DE} suggest that the nitrogen transfer is a concerted process. The formation of **E** from **D** is thermodynamically favorable as it is exergonic (–50.4 kcal/mol). The subsequent cycloisomerization of azadienyl carbene complex **F** is very facile and thermodynamically favorable as it proceeds via TS_{FG} with a small activation energy of $\Delta G^\ddagger = +7.2$ kcal/mol, and the formation of η^5 -pyrrole complex **G** from **F** is exergonic (–21.9 kcal/mol). The rate-determining step is the nitrogen transfer, and the largest energetic span between **C** and TS_{DE} is estimated to be 28.4 kcal/mol, which is reasonably small under the experimental conditions. Moreover, the high exergonicity (–96.6 kcal/mol) of the formation of **G** from **A** suggests that the overall process is thermodynamically feasible.

Discussion

In conclusion, a catalytic [2 + 2 + 1] cycloaddition route to fused pyrroles, using sulfoximines as the nitrene surrogates, has been successfully developed. Screening of several sulfoximines led to the identification of methyl *p*-fluorophenyl sulfoximines as the optimal surrogates. The optimized protocol enabled the short-step synthesis of diverse fused pyrroles with good functional group compatibility. A plausible mechanism, involving the nitrogen transfer from sulfoximines to cationic ruthenacycle intermediates, was proposed based on several control experiments. The kinetic and thermodynamic feasibility of the proposed

mechanism was also inspected by DFT calculations on a model system.

Methods

Synthesis and characterization. Full synthetic procedures are available in the Supplementary Methods. HPLC charts for *rac*-2c and (*R*)-2c, and *rac*-13 and (*R*)-13 are available in Supplementary Figures 1 and 2. NMR spectra of purified compounds are available in Supplementary Figures 6–49.

Kinetic study. Full details are available in the Supplementary Methods, Supplementary Table 1, and Supplementary Figure 3.

Computational study. Full details are available in the Supplementary Methods, Supplementary Table 2, and Supplementary Figures 4 and 5. Cartesian coordinates of calculated molecules are available in Supplementary Table 3.

Data availability. The authors declare that the data supporting the findings of this study are available within the article and Supplementary Information file, or from the corresponding author upon reasonable request.

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References

- Dequierez, G., Pons, V. & Dauban, P. Nitrene chemistry in organic synthesis: still in its infancy? *Angew. Chem. Int. Ed.* **51**, 7384–7395 (2012).
- Müller, P. & Fruit, C. Enantioselective catalytic aziridinations and asymmetric nitrene insertions into CH bonds. *Chem. Rev.* **103**, 2905–2919 (2003).
- Katsuki, T. Azide compounds: nitrogen sources for atom-efficient and ecologically benign nitrogen-atom-transfer reactions. *Chem. Lett.* **34**, 1304–1309 (2005).
- Minakata, S. Utilization of N–X bonds in the synthesis of N-heterocycles. *Acc. Chem. Res.* **42**, 1172–1182 (2009).
- Darses, B., Rodrigues, R., Neuville, L., Mazurais, M. & Dauban, P. Transition metal-catalyzed iodine(III)-mediated nitrene transfer reactions: efficient tools for challenging syntheses. *Chem. Commun.* **53**, 493–508 (2017).
- Gilbert, Z. W., Hue, R. J. & Tonks, I. A. Catalytic formal [2+2+1] synthesis of pyrroles from alkynes and diazenes via Ti^{II}/Ti^{IV} redox catalysis. *Nat. Chem.* **8**, 63–68 (2016).
- Yamashita, K., Yamamoto, Y. & Nishiyama, H. Ruthenium-catalyzed transfer oxygenative cyclization of α,ω -diynes: Unprecedented [2+2+1] route to bicyclic furans via ruthenacyclopentatriene. *J. Am. Chem. Soc.* **134**, 7660–7663 (2012).
- Matsui, K., Shibuya, M. & Yamamoto, Y. Ruthenium-catalyzed transfer oxygenative [2+2+1] cycloaddition of silyldiynes using nitrones as adjustable oxygen atom donors. Synthesis of bicyclic 2-silylfurans. *ACS Catal.* **5**, 6468–6472 (2015).
- Matsui, K., Shibuya, M. & Yamamoto, Y. Catalytic [2+2+1] synthesis of fused thiophenes using thiocarbonyls as sulfur donors. *Angew. Chem. Int. Ed.* **55**, 15397–15400 (2016).
- Walsh, C. T., Garneau-Tsodikova, S. & Howard-Jones, A. R. Biological formation of pyrroles: nature's logic and enzymatic machinery. *Nat. Prod. Rep.* **23**, 517–531 (2006).
- Loudet, A. & Burgess, K. BODIPY dyes and their derivatives: syntheses and spectroscopic properties. *Chem. Rev.* **107**, 4891–4932 (2007).
- Maeda, H. Supramolecular chemistry of acyclic oligopyrroles. *Eur. J. Org. Chem.* **2007**, 5313–5325 (2007).
- Fan, H., Peng, J., Hamann, M. T. & Hu, J.-F. Lamellarins and related pyrrole-derived alkaloids from marine organisms. *Chem. Rev.* **108**, 264–287 (2008).
- Domagala, A., Jarosz, T. & Lapkowski, M. Living on pyrrolic foundations—advances in natural and artificial bioactive pyrrole derivatives. *Eur. J. Med. Chem.* **100**, 176–187 (2015).
- Saha, I., Lee, J. T. & Lee, C.-H. Recent advancements in calix[4]pyrrole-based anion-receptor chemistry. *Eur. J. Org. Chem.* **2015**, 3859–3885 (2015).
- Gulevich, A. V., Dudnik, A. S., Chernyak, N. & Gevorgyan, V. Transition metal-mediated synthesis of monocyclic aromatic heterocycles. *Chem. Rev.* **113**, 3084–3213 (2013).
- Estévez, V., Villacampa, M. & Monénde, J. C. Recent advances in the synthesis of pyrroles by multicomponent reactions. *Chem. Soc. Rev.* **43**, 4633–4657 (2014).
- Zhou, N.-N., Zhu, H.-T., Yang, D.-S. & Guan, Z.-H. Recent developments in the group-1B-metal-catalyzed synthesis of pyrroles. *Org. Biomol. Chem.* **14**, 7136–7149 (2016).
- Vessally, E. A new avenue to the synthesis of highly substituted pyrroles: synthesis from *N*-propargylamines. *RSC Adv.* **6**, 18619–18631 (2016).
- Chelucci, G. Metal-catalyzed dehydrogenative synthesis of pyrroles and indoles from alcohols. *Coord. Chem. Rev.* **331**, 37–53 (2017).
- Kornienko, A. & La Clair, J. J. Covalent modification of biological targets with natural products through Paal–Knorr pyrrole formation. *Nat. Prod. Rep.* **34**, 1051–1060 (2017).
- Liu, W., Jiang, H. & Huang, L. One-pot silver-catalyzed and PIDA-mediated sequential reactions: synthesis of polysubstituted pyrroles directly from alkynoates and amines. *Org. Lett.* **12**, 312–315 (2010).
- Sayyed-Alangi, S. Z., Hossaini, Z. & Rostami-Charati, F. Synthesis of highly functionalized pyrroles from primary amines and activated acetylenes in water. *Chin. Chem. Lett.* **23**, 1119–1121 (2012).
- Madabhushi, S. et al. Cerium(IV) ammonium nitrate (CAN) mediated synthesis of pyrrole-2,3,4,5-tetracarboxylates by reaction of dimethyl acetylenedicarboxylate with an amine. *Tetrahedron Lett.* **54**, 6737–6739 (2013).
- Zhang, L., Wang, X., Li, S. & Wu, J. Synthesis of pyrrole-2,3,4,5-tetracarboxylates via a copper-catalyzed reaction of amine with but-2-ynedioate. *Tetrahedron* **69**, 3805–3809 (2013).
- Chong, Q., Xin, X., Wang, C., Wu, F. & Wan, B. Synthesis of polysubstituted pyrroles via Ag(I)-mediated conjugate addition and cyclization reaction of terminal alkynes with amines. *Tetrahedron* **70**, 490–494 (2014).
- Chen, X., Jin, J., Wang, Y. & Lu, P. Palladium-catalyzed synthesis of 7,9-diaryl-8H-acenaphtho[1,2-*c*]pyrroles and their application in explosives detection. *Chem. Eur. J.* **17**, 9920–9923 (2011).
- Chen, X. et al. Palladium-catalyzed reaction of arylamine and diarylacetylene: solvent-controlled construction of 2,3-diarylindoles and pentaarylpyrroles. *Eur. J. Org. Chem.* **2012**, 4380–4386 (2012).
- Martin, R., Larsen, C. H., Cuenca, A. & Buchwald, S. L. Cu-catalyzed tandem C–N bond formation for the synthesis of pyrroles and heteroarylpyrroles. *Org. Lett.* **9**, 3379–3382 (2007).
- Bhardwaj, V., Gumber, D., Abbot, V., Dhiman, S. & Sharma, P. Pyrrole: a resourceful small molecule in key medicinal hetero-aromatics. *RSC Adv.* **5**, 15233–15266 (2015).
- Gholap, S. S. Pyrrole: an emerging scaffold for construction of valuable therapeutic agents. *Eur. J. Med. Chem.* **110**, 13–31 (2016).
- Cram, D. J. et al. Stereochemistry of sulfur compounds. I. Stereochemical reaction cycles involving an open chain sulfoxide, sulfimide, and sulfoximine. *J. Am. Chem. Soc.* **92**, 7369–7384 (1970).
- Li, Zhen, Yu, H. & Bolm, C. Dibenzothiophene sulfoximine as an NH_3 surrogate in the synthesis of primary amines by copper-catalyzed C–X and C–H bond amination. *Angew. Chem. Int. Ed.* **56**, 9532–9535 (2017).
- Okamura, H. & Bolm, C. Sulfoximines: Synthesis and catalytic applications. *Chem. Lett.* **33**, 482–487 (2004).
- Bizet, V., Hendriks, C. M. M. & Bolm, C. Sulfur imidations: access to sulfimides and sulfoximines. *Chem. Soc. Rev.* **44**, 3378–3390 (2015).
- Bizet, V., Buglioni, L. & Bolm, C. Light-induced ruthenium-catalyzed nitrene transfer reactions: a photochemical approach towards *N*-acyl sulfimides and sulfoximines. *Angew. Chem. Int. Ed.* **53**, 5639–5642 (2014).
- Jolicoeur, B., Chapman, E. E., Thompson, A. & Lubell, W. D. Pyrrole protection. *Tetrahedron* **62**, 11531–11563 (2006).
- Trost, B. M. & Ball, Z. T. Markovnikov alkyne hydrosilylation catalyzed by ruthenium complexes. *J. Am. Chem. Soc.* **123**, 12726–12727 (2001).
- Zhang, L. et al. Ruthenium-catalyzed cycloaddition of alkynes and organic azides. *J. Am. Chem. Soc.* **127**, 15998–15999 (2005).
- Yamamoto, Y., Arakawa, T., Ogawa, R. & Itoh, K. Ruthenium(II)-catalyzed selective intramolecular [2 + 2 + 2] alkyne cyclotrimerizations. *J. Am. Chem. Soc.* **125**, 12143–12160 (2003).
- Yamamoto, Y. et al. Ru(II)-catalyzed cycloadditions of 1,6-heptadiynes with alkenes: new synthetic potential of ruthenacyclopentatrienes as biscarbenoids in tandem cyclopropanation of bicycloalkenes and heteroatom-assisted cyclocotrimerization of 1,6-heptadiynes with heterocyclic alkenes. *J. Am. Chem. Soc.* **122**, 4310–4319 (2000).
- Le Pailh, J. et al. Biscarbene-ruthenium complexes in catalysis: novel stereoselective synthesis of (1*E*,3*E*)-1,4-disubstituted-1,3-dienes via head-to-head coupling of terminal alkynes and addition of carboxylic acids. *J. Am. Chem. Soc.* **125**, 11964–11975 (2003).
- Schmid, R. & Kirchner, K. Ruthenium-mediated C–C coupling reactions of alkynes—the key role of ruthenacyclopentatriene complexes. *Eur. J. Inorg. Chem.* **2004**, 2609–2626 (2004).
- Wakatsuki, Y., Kuramitsu, T. & Yamazaki, H. Cobaltacyclopentadiene complexes as starting materials in the synthesis of substituted benzenes, cyclohexadienes, thiophenes, selenophenes and pyrroles. *Tetrahedron Lett.* **1974**, 4549–4552 (1974).
- Hong, P. & Yamazaki, H. Reaction of cobaltacyclopentadiene complexes with organic azides directed toward synthesis of highly substituted pyrroles. *J. Organomet. Chem.* **373**, 133–142 (1989).

46. Hill, J. E., Fanwick, P. E. & Rothwell, I. P. Formation of a terminal aryl-imido compound of titanium by cleavage of the N=N double bond in benzo[c]cinnoline. *Inorg. Chem.* **30**, 1143–1144 (1991).
47. Sperger, T., Sanhueza, I. A., Kalvet, I. & Schoenebeck, F. Computational studies of synthetically relevant homogeneous organometallic catalysis involving Ni, Pd, Ir, and Rh: an overview of commonly employed DFT methods and mechanistic insights. *Chem. Rev.* **115**, 9532–9586 (2015).

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Author contributions

K.M. conceived the project, carried out the experimental works, and analyzed the experimental results. Y.Y. performed computational studies and wrote the manuscript. M.S. discussed the results.

Additional information

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