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Enantioselective Rh(II)-Catalyzed Desymmetric Cycloisomerization of Diynes: Constructing Furan-Fused Dihydropiperidines with an Alkyne-Substituted Aza-Quaternary Stereocenter

Rui Wu, Jiajun Lu, Tongxiang Cao, Jun Ma, Kai Chen,* and Shifa Zhu*

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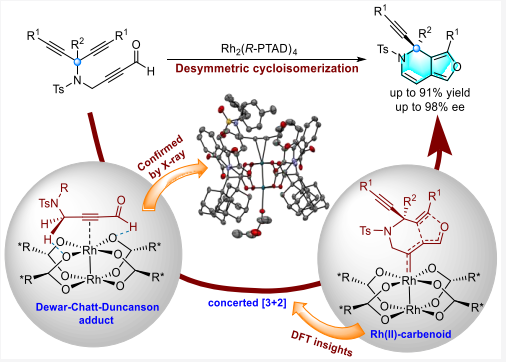
ABSTRACT: Described herein is an enantioselective dirhodium(II)-catalyzed cycloisomerization of diynes achieved by the strategy of desymmetrization, which not only represents a new cycloisomerization reaction of diynes but also constitutes the first Rh(II)-catalyzed asymmetric intramolecular cycloisomerization of 1,6-diynes. This protocol provides a range of valuable furan-fused dihydropiperidine derivatives with an enantiomerically enriched alkynyl-substituted aza-quaternary stereocenter in high efficiency, complete atom economy, and excellent enantioselectivity (up to 98% ee). Besides, the highly functionalized products could be easily transformed into various synthetically useful building blocks and conjugated with a series of pharmaceutical molecules. The mechanism involving a concerted [3+2] cycloaddition/[1,2]-H shift of the Rh(II) carbenoid intermediate was elucidated by DFT calculations and mechanistic studies. More importantly, the first single crystal of alkyne-dirhodium(II) was obtained to show that a η^2-coordinating activation of alkynal by dirhodium(II) was involved. Weak hydrogen bondings between the carboxylate ligands and alkynal were found, which probably made the well-defined paddlewheel-like dirhodium(II) distinctive from other metal complexes in catalyzing this transformation. Furthermore, the origin of the enantioselectivity was elucidated by a Rh_2(*R*-PTAD)$_4$-alkyne complex and additional calculational studies.



1. INTRODUCTION

Optically active molecules containing an alkynyl segment attached to a carbon stereocenter are often found in bioactive molecules and natural products, such as ethynylestradiol and efavirenz.[1] The alkyne functionality could also impact on specific properties of drugs, such as lipophilicity and rigidity.[2] In addition, they have been identified as crucial and useful synthons in synthetic chemistry.[3] Tremendous efforts therefore have been devoted to developing efficient methods for their synthesis.[4−6] The synthetic methods to access it could mainly be subdivided into three classes: (1) direct asymmetric alkynylation with terminal or leaving group capped alkynes as starting materials;[4] (2) the asymmetric nucleophilic addition of nucleophiles on alkynyl ketones or ketimines;[5] (3) desymmetric cyclization of diynes.[6] Among these, the desymmetric cyclization strategy has been recognized as one of the most efficient routes to create a fully substituted carbon stereocenter along with a rapid increase in structural complexity, as the reaction occurs at the tethered functionality rather than at the tetrasubstituted prochiral carbon and the adverse steric hindrance is relieved to some extent.[7] Moreover, the tetrasubstituted stereogenic carbon center could be generally formed in complete atom economy by this strategy, and there is no need to worry about the activation of low-active starting materials, such as ketones and ketimines, and the discrimination of two similar prochiral faces of carbonyl and imine, which are usually obstacles in other strategies.[8] However, to date, successful asymmetric examples of establishing alkynyl-containing tetrasubstituted carbon stereocenters by means of the desymmetric cyclization strategy are still quite scarce, partially because the reaction site is too far away from prochiral carbon to achieve high enantioselectivity control. Czekelius et al. reported the enantioselective desymmetrization of terminal 1,4-dynamides by employing gold complexes with highly sterically encumbered carbene ligands to build an alkynyl-capped oxa-quaternary carbon stereocenter (Scheme 1a).[9] On the basis of this work, alkynyl-substituted quaternary carbon stereocenters with higher enantioselectivity were achieved by the same group using cationic gold catalysts with optically active binol phosphates as counteranions (Scheme 1a).[10] Furthermore, the application of the methodology was demonstrated in the total synthesis of (+)-mesembrine.[11] In addition, Tanaka et al. reported rhodium(I)-

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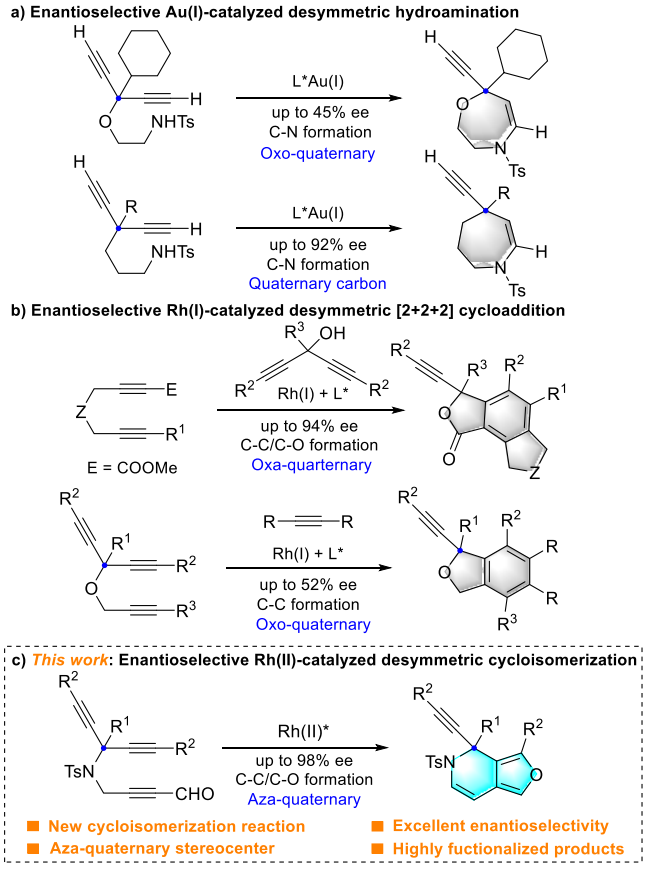
Scheme 1. Construction of Alkynyl-Substituted Quaternary Stereocenter via a Desymmetric Strategy



catalyzed desymmetric one-pot transesterification and [2+2+2] cycloaddition of diyne-ester and diynol with good enantioselectivities.[12a] Later, rhodium(I)-catalyzed asymmetric [2+2+2] cycloaddition with desymmetrization of prochiral triynes was realized by Michelet, Ratovelomanana-Vidal, and co-workers, although in moderate selectivities (Scheme 1b).[12b] Despite remarkable advances, catalytic enantioselective desymmetrization to create alkynyl-containing tetrasubstituted carbon stereocenters with wide substrate scope and high enantioselectivity is still a long-term challenge.

Over the past decades, the transition metal-catalyzed cycloisomerization of 1,*n*-diynes has become a powerful strategy for the rapid assembly of carbocyclic and heterocyclic compounds from relatively simple acyclic substrates in an economical route.[13] Among these, the cycloisomerization of 1,6-diynes has attracted much attention in recent years.[14] However, as far as we know, no direct catalytic asymmetric intramolecular cycloisomerization, excluding cycloaddition reaction,[15] of 1,6-diynes has been reported. It is therefore highly desirable to develop new methods to achieve enantioselective cycloisomerization of 1.6-diynes, which represent attractive and effective ways to construct chiral cyclic molecules. With our continuous interest in alkyne chemistry,[16] we herein report the realization of enantioselective dirhodium(II)-catalyzed desymmetric cycloisomerization of 1,6-diynal to rapidly assemble highly functionalized furan-fused dihydropiperidine derivatives with concomitant formation of an alkynyl incorporated aza-quaternary carbon stereocenter (Scheme 1c). In this process, both the carbon−carbon triple bond and formyl group of the enynal moiety were involved in the molecular reorganization. To the best of our knowledge, this represents a new type of cycloisomerization of diynes. This Rh(II)-catalyzed protocol features high efficiency, excellent enantioselectivity, and atom economy. DFT calculations and control experiments demonstrated that a dirhodium(II) carbenoid intermediate was involved in this process. More importantly, the first single crystal of alkyne-Rh(II) was obtained to show that a new η^2-coordinating activation of alkynal by Rh(II) was involved. Furthermore, the origin of the enantioselectivity was elucidated by a Rh_2(*R*-PTAD)$_4$-alkyne complex and additional calculational studies. Herein, we report the results of our detailed investigations of these.

2. RESULTS AND DISCUSSION

2.1. Optimization of Reaction Conditions. Initially, trynal **1a** was selected as the model substrate for the exploration and optimization of the reaction conditions (Table 1). We started our study with Au(I), Pt(II), etc., complexes as catalysts, which were typically regarded as good catalysts for the activation of alkynes.[17] However, all these complexes were found ineffective in catalyzing this transformation (entries 1−4, see SI for details). But when $Rh_2(OPiv)_4$ was employed instead, to our excitement, an unprecedented cycloisomerization occurred,[14] affording the furan-fused dihydropiperidine **2a** in 71% yield (entry 5). Then, a systematic examination of various chiral dirhodium(II) catalysts was then conducted (entries 6−12). Rh_2(*S*-BTPCP)$_4$ was first chosen to catalyze the reaction, but only giving the desired product in 23% yield and 8% ee (entry 6). Better results, 31% yield and 50% ee, could be observed with Rh_2(*R*-DOSP)$_4$ as catalyst (entry 7). Pleasingly, the phthalimide-based dirhodium(II) complexes, such as Rh_2(*S*-TFPTTL)$_4$, Rh_2(*S*-TCPTTL)$_4$, Rh_2(*S*-PTTL)$_4$, and Rh_2(*S*-PTAD)$_4$, performed excellently in stereocontrol with more than 90% ee (entries 8−11). Among these, Rh_2(*S*-PTAD)$_4$ was found to be the best, generating **2a** in 90% yield and 95% ee (entry 11).[18] Besides, similar results could also be obtained by using Rh_2(*S*-NTTL)$_4$ as the catalyst (entry 12). The catalyst loading could be reduced to 1 mol % with acceptable yield and almost no erosion of ee value (entry 13). Lowering the reaction temperature and concentration had no obvious effect on the results (entries 14, 15). In consideration of the effect of solvent, several frequently used solvents were screened and DCE gave the best results, 85% yield and 96% ee (entries 16−18). The absolute configuration of **2a** was unambiguously determined as *R* by an X-ray crystallographic analysis (entry 16). Switching to the opposite configurational catalyst Rh_2(*R*-PTAD)$_4$, the desired product **2a** was delivered in similar results (entry 19). Therefore, the optimal conditions were established as 1 mol % Rh_2(*R*-PTAD)$_4$, in DCE, for 48 h, at 25 °C.

2.2. Evaluation of Substrate Scope. Under the established optimal reaction conditions, we then examined the generality of this Rh(II)-catalyzed enantioselective desymmetric cycloisomerization of triynals (Scheme 2). The triynal with terminal alkynyl **1b** could proceed smoothly, but delivering the corresponding product **2b** with low ee value (83%, 32% ee). Much effort on further optimization was made, but was fruitless (see SI for details). Silicon groups usually serve as masking groups, which are easily deprotected and play vital roles in stereocontrol because of their sterically congested character. Considering these facts, substrates **1c−e**, with different sizes of silicon groups, were then tested. The triynal

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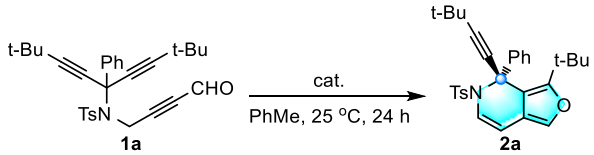
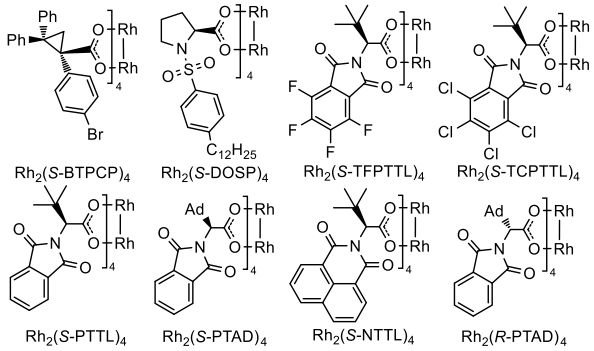
Table 1. Condition Screening of the Asymmetric Cycloisomerization of Triynal[a]



entry	cat. (mol%)	yield[b]	ee[c]	config.
1	$IPrAuBF_4$ (5)	nd	-	-
2	$PtCl_2$ (5)	nd	-	-
3	$Cu(OTf)_2$	nd	-	-
4	$Pd(PhCN)_2Cl_2$	nd	-	-
5	$Rh_2(OPiv)_4$ (2)	71%	-	-
6	Rh_2(*S*-BTPCP)$_4$ (2)	23%	8%	*R*
7	Rh_2(*R*-DOSP)$_4$ (2)	31%	50%	*R*
8	Rh_2(*S*-TFPTTL)$_4$ (2)	53%	91%	*R*
9	Rh_2(*S*-TCPTTL)$_4$ (2)	53%	91%	*R*
10	Rh_2(*S*-PTTL)$_4$ (2)	65%	90%	*R*
11	Rh_2(*S*-PTAD)$_4$ (2)	90%	95%	*R*
12	Rh_2(*S*-NTTL)$_4$ (2)	92%	94%	*R*
13[d]	Rh_2(*S*-PTAD)$_4$ (1)	77%	94%	*R*
14[e,f]	Rh_2(*S*-PTAD)$_4$ (1)	75%	96%	*R*
15[f,g]	Rh_2(*S*-PTAD)$_4$ (1)	80%	95%	*R*
16[d,h]	**Rh_2(*S*-PTAD)$_4$ (1)**	**85%**	**96%**	***R* (X-Ray)**
17[d,i]	Rh_2(*S*-PTAD)$_4$ (1)	77%	95%	*R*
18[d,j]	Rh_2(*S*-PTAD)$_4$ (1)	70%	96%	*R*
19[d,h]	**Rh_2(*R*-PTAD)$_4$ (1)**	**87%**	**96%**	***S***



[a]**3a** (0.1 mmol), [**3a**] = 0.1 M, 25 °C, 24 h, nd = not detected. [b]Isolated yield. [c]Determined by chiral HPLC. [d]48 h. [e]0 °C. [f]72 h. [g]0.05 M. [h]DCE as solvent. [i]DCM as solvent [j]$CHCl_3$ as solvent.

bearing a TMS group at the alkyne terminal position R^2 reacted well to furnish **2c** in good yield and enantioselectivity (87%, 86% ee). With the aid of a bulkier silicon group of TBS, the ee value of **2d** could be improved greatly to 98%, and the yield was diminished slightly (80%). Further increasing the steric hindrance with the TIPS group gave the corresponding product **2e** in 99% ee, but only in 6% yield. In addition to the silicon-protected triynals, the internal alkyne with a phenyl group could be tolerated as well, providing **2f** in a decent yield (74%) and excellent enantioselectivity (94% ee). The phenyls bearing electron-withdrawing groups at the para position on R^2 of triynals all worked nicely to afford enantiomerically enriched products **2g−j** (66−84%, 93−96% ee). However, inferior yields (37%, 45%) of products **2k,l** were acquired when the phenyls bearing electron-donating groups at the para and meta position were set up on R^2 of triynals, but the enantioselectivities were not affected, 94% ee for both. It is necessary to note that [4+2] cycloaddition could be the main cause of the diminished yield, especially for the electron-donating phenyl groups on R^2 (see SI for details).[14a] Besides, the catalytic system could be successfully applied to a variety of triynals bearing various alkyl groups (**1m−o**), and a slight loss of enantioselectivities was observed (76−88%, 80−91% ee).

A broad array of phenyls on R^1 could also be employed in this reaction. For example, different electron-donating groups (−Me, −^{t}Bu) **2p−r** at the para or ortho positions of phenyl were suitable for this conversion, giving similar results (80−88%, 96−98% ee). Various electron-withdrawing group (−F, $-CF_3$, $-NO_2$, −Cl, −Br)-substituted analogues **2s−w** were applicable as well (80−90%, 95−97% ee). Changing the position of $-NO_2$ from para to meta of phenyl led to a drop in ee value (84% ee). In addition, the transformations of substrates with alkyl groups on R^2, such as ethyl, cyclopropyl, and isopropyl, could furnish the desired products **2y−aa** in good yields (81−91%) and superb enantioselectivity (94−98% ee). While R^1 was installed with an allyl group, the product **2ab** was acquired in 82% yield with a lower enantioselectivity. Besides, we found that the reaction worked successfully when replacing the N-Ts linker with an oxygen linker, albeit with diminished ee (**2ac**, 78%, 66% ee). Unfortunately, this protocol could not be extended to the 1,7-triynal, and no conversion of the starting material was observed.

Additionally, when the diynals (R^1, R^3 = H) were employed, the reaction occurred efficiently with broad substrate scope as well, providing a variety of achiral furan-fused dihydropiperidine derivatives (**2ae−aj**). In addition to the terminal alkyne **2ae** (81%), the internal alkynes capped with aryl, benzoyl, and bromine were applicable to the catalytic system as well, leading to the desired products **2af−ai** in moderate yield (45−76%). Moreover, the diynal with a carbon linkage can also be subjected to the transformation, giving the desired product **2aj** in 16% yield at elevated temperature.

2.3. Synthetic Applications. To demonstrate the synthetic utility of this method, further transformations of the TBS-substituted product **2d** were surveyed. As shown in Scheme 3, a gram-scale reaction was initially performed, giving **2d** in 74% yield without erosion of the ee value. Notably, selective desilylation of **2d** proceeded smoothly at 0 °C by TBAF, giving **3a** in 89% yield. By increasing the equivalents of TBAF, both TBS groups could be removed, producing **2b** in quantitative yield. Besides, the alkyne group in **2b** could be reduced to a vinyl group in **3b**. Compound **2b** could also be converted to **3c** and **3d** through the A^3 coupling reaction and homocoupling. Sonogashira coupling with aryl halide provided **3e** in 63% yield. Additionally, a bromine atom could be selectively introduced into the α-position of furan **2b** with NBS as the brominating reagent, furnishing **3f** in 91% yield. Moreover, **2b** could be transformed to **3g** under click reaction conditions. It is notable that all the transformations above-mentioned could be carried out with full chiral retention. In addition, the obtained **2b** could undergo Sonogashira coupling with the anti-herpesvirus antiviral drug idoxuridine to afford **3h**. Besides, under the click reaction conditions, compound **2b** can also be readily conjugated with complex azides derived from a bioactive such as febuxostat, indomethacin, celecoxib, testosterone, and ibuprofen, giving the corresponding triazoles **3i−m** in 57−99% yield.

2.4. Mechanistic Discussion. To gain insights into the reaction mechanism of this novel cycloisomerization, a combined theoretical and experimental investigation was

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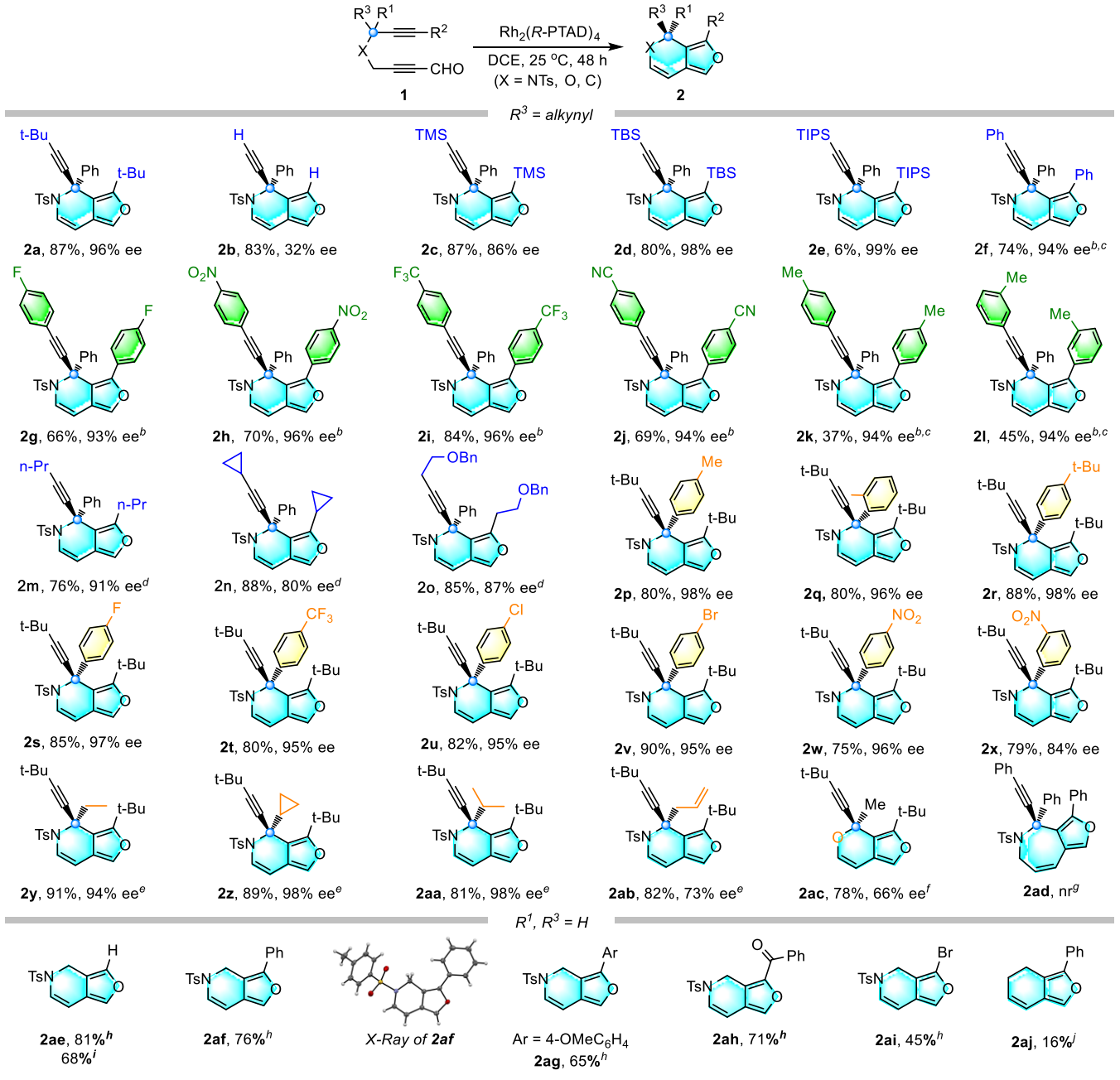
Scheme 2. Substrate Scope of Enantioselective Desymmetric Cycloisomerization of Trynals[a]



[a]Reaction conditions: Alkynal (0.2 mmol), Rh_2(*R*-PTAD)$_4$ (1 mol %), DCE (2 mL), 25 °C, 48 h. [b]i: propargyl alcohol (0.2 mmol), DMP (1.2 equiv), $NaHCO_3$ (10 equiv), DCM (2 mL), 0 °C, 1 h. ii: Rh_2(*S*-NTTL)$_4$ (1 mol %), PhMe (2 mL), 25 °C. [c]0 °C. [d]Rh_2(*S*-NTTL)$_4$ (1 mol %), PhMe (2 mL), 25 °C. [e]Rh_2(*S*-TCPTTL)$_4$ (1 mol %), PhMe (2 mL), 0 °C. [f]Rh_2(*1S,6S*-4-(3,5-diMe-C_6H_4)-PTsPCP)$_4$ (1 mol %), PhMe (2 mL), 22 °C. [g]Rh_2(OPiv)$_4$ (2 mol %), 25 °C. [h]1 mol % Rh_2(*S*-BTPCP)$_4$, PhMe (2 mL), 0 °C, 12 h. [i]1 mol % Rh_2(OPiv)$_4$, 36 h. [j]2.5 mol % Rh_2(*S*-BTPCP)$_4$, 80 °C, 12 h.

then carried out. To simplify the computations without sacrificing the understanding of the reaction mechanism, dirhodium(II) acetate and nitrogen-tethered 1,6-diynal **1ae** were chosen as the model catalyst and substrate, respectively. As depicted in Scheme 4a, the reaction commenced with the coordination of the dirhodium catalyst to the alkyne substrate, generating rhodium-alkyne complex **Iae**. Such a process is exergonic by 2.5 kcal/mol. Then, the [3+2] cycloaddition of **Iae** occurs via transition state **TS1ae**, leading to rhodium carbene intermediate **IIae**. This step is very exergonic and releases about 37.9 kcal/mol of energy, most of which may be contributed from the formation of the aromatic furan ring. The [3+2] step was concerted but asynchronous, and the forming C−C and C−O bonds in **TS1ae** are about 2.19 and 2.57 Å, respectively. The distances between the formyl hydrogen and two nearby carbonyl oxygen atoms are about 2.27 and 2.61 Å, below the sum of their van der Waals radii of 2.72 Å, which suggests nonclassical weak hydrogen-bonding interactions between them (Scheme 5).[19] The following intramolecular [1,2]-H shift is also exergonic and irreversible, with a ΔΔG about −26.6 kcal/mol. With the release of the rhodium catalyst, the furan-fused dihydropyridine product will be

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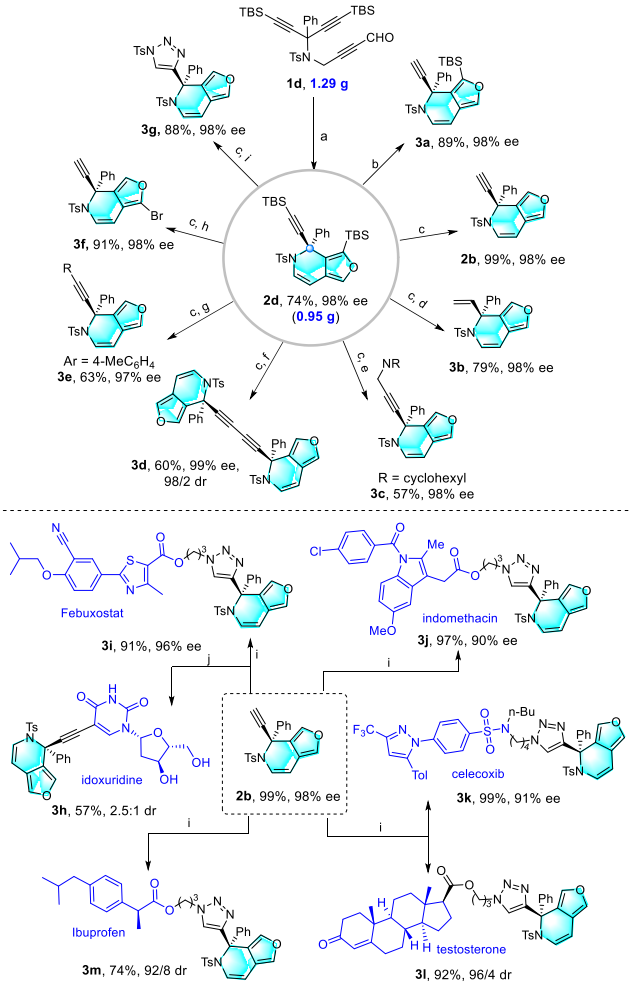
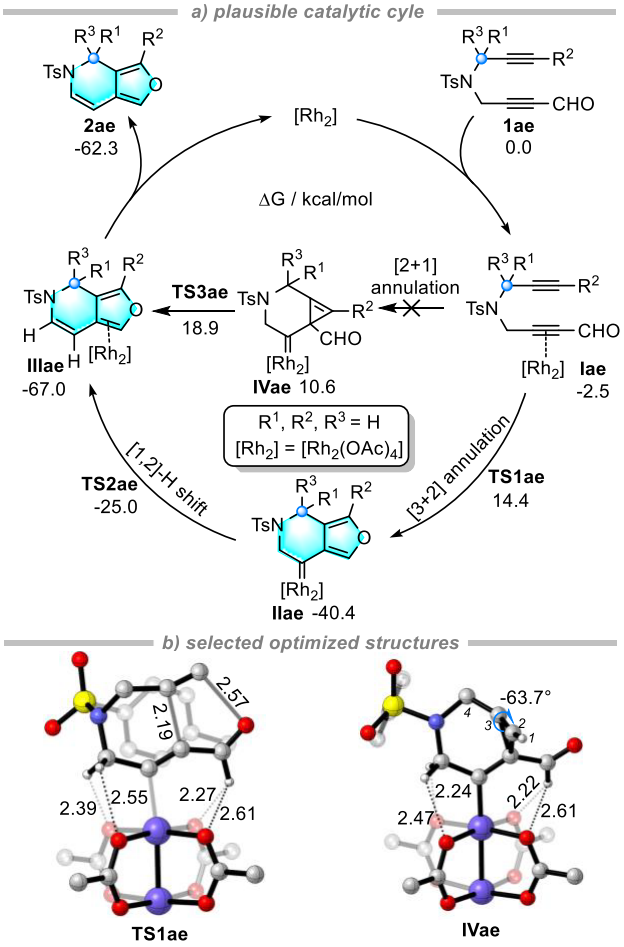
Scheme 3. Gram-Scale Reaction and Synthetic Applications[a]



[a]Reaction conditions: (a) Rh_2(*R*-PTAD)$_4$, DCE. (b) TBAF (1.2 equiv), 0 °C, THF, 1 h. (c) TBAF (3.0 equiv), THF, rt. (d) Lindlar catalyst, EtOH/EtOAc, 1 atm H_2, 0 °C, 30 min. (e) Dicyclohexylamine, $(HCHO)_n$, CuI, 1,4-dioxane, 110 °C. (f) CuI, $BnNH_2$, 1 atm O_2. THF. (g) 4-MeC_6H_4I, $PdCl_2(PPh_3)_2$, CuI, *i*-Pr_2NH, THF, 60 °C. (h) NBS (1.0 equiv), THF, 0 °C, 20 min. (i) RN_3, CuTC, toluene, rt. (j) idoxuridine, $PdCl_2(PPh_3)_2$, CuI, Et_3N, 1,4-dioxane, 70 °C.

Scheme 4. Plausible Reaction Mechanism[a]



[a]Bond lengths are shown in Å and energy in kcal/mol, and the calculations were performed at the M06 level of theory in toluene solvent.

obtained eventually. The whole reaction was highly exergonic, by about −62.3 kcal/mol. Taken together, the [3+2] annulation from **Iae** to **IIae** was found to be the rate-limiting step with a relatively low energy barrier of 16.9 kcal/mol, which could be easily surmounted at room temperature.

Besides the tandem [3+2] annulation/[1,2]-H shift pathway, other possible reaction pathways were also considered (see the SI for details). The possible 5-*exo*-*dig* or 6-*endo*-*dig* cyclopropenation pathway could be ruled out, as the expected cyclopropene intermediates are unstable, possibly due to the strain of cyclopropenes. In cyclopropene intermediate **IVae**, the fused six-membered ring decreases the stability of cyclopropene, as suggested by the strain dihedral angle (−63.7°) of H1−C2−C3−C4 in **IVae**, which should be near 0° if without strain (Scheme 4b). In addition, a two-step process, in which the aldehyde of intermediate **Iae** attacks on a free alkyne forming a vinyl anion that counterattacks at the Rh-alkynal part, was also considered. However, the expected vinyl anion intermediate could not be located. Moreover, an intramolecular [4+2] cycloaddition of alkynal with alkyne was also calculated, which is not as favorable as the [3+2] pathway.

Although [3+2] cycloaddition reactions of alkynes with 1,3-dipolars are common, the use of neutral three-atom components (TACs) remains comparatively sparse.[20] In our work, the alkynal was unprecedentedly used as a neutral three-atom component to engage [3+2] cycloaddition with a π-system, affording the fused furans. Theoretical calculations suggested that the reaction proceeded through a thermodynamically and kinetically favorable [3+2] annulation/[1,2]-H shift process. To further shed light on the reaction mechanism, experimental investigations have also been carried out (Scheme 5). First, the deuteration experiment was conducted. When the substrate **1ae-D** was subjected to the standard reaction conditions, 100%-D transfer was detected in the product **2ae-D**, which supports the intramolecular [1,2]-H shift process (Scheme 5, eq 1). Surprisingly, this intramolecular [1,2]-H shift process could be completely suppressed by the intermolecular cyclopropanation, giving the spiro-cyclopropane derivative **5a** in good yield (Scheme 5, eq 2). Inspired by the above results, in combination with the thermodynamically and kinetically favorable [3+2] cycloaddition process, we further envisioned that the relatively rigid benzo-1,*n*-diynal, which represents a new carbon-linked substrate, might also be

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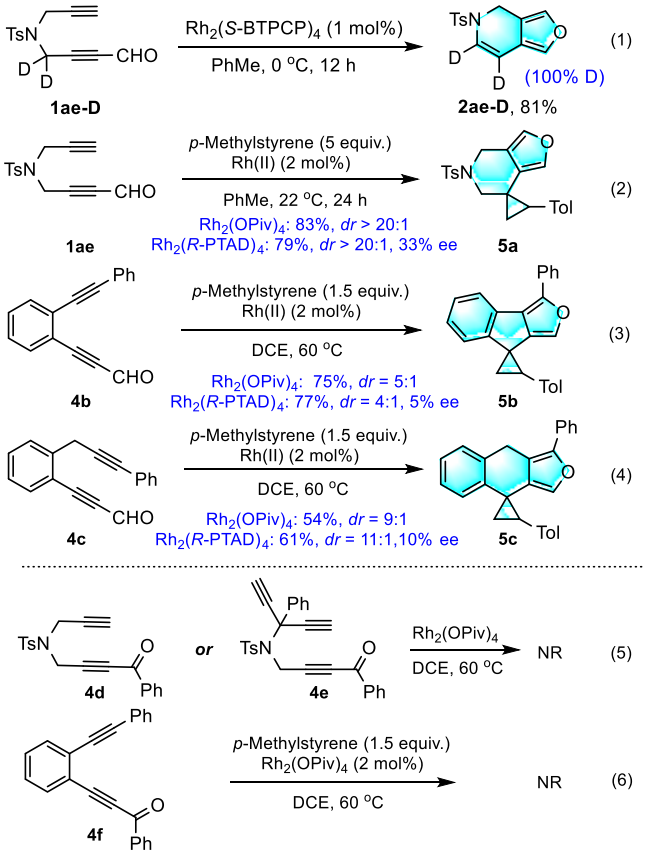
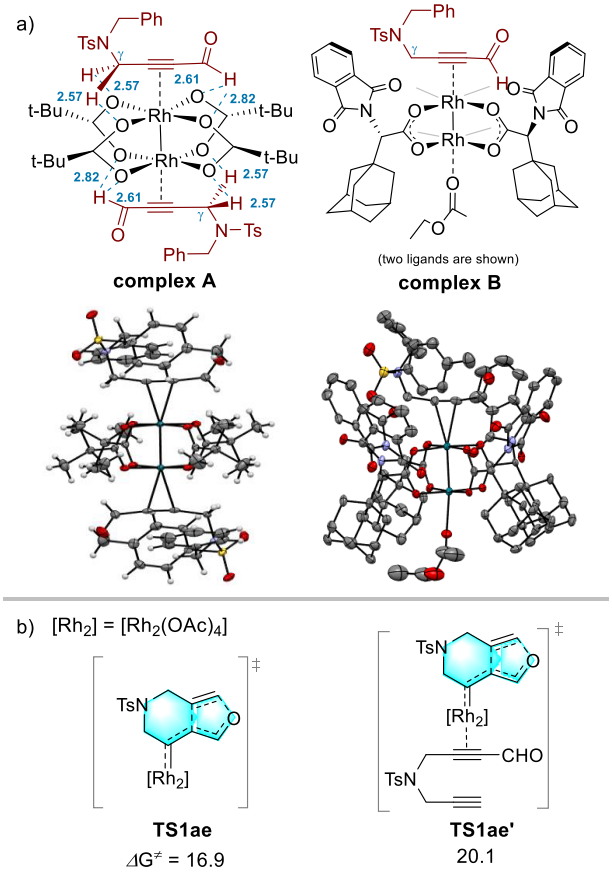
Scheme 5. Mechanistic Investigations



used as a suitable substrate to generate the Rh(II) carbene intermediate through the energetically feasible [3+2] process. For this purpose, benzo-1,5-diynal (**4b**) and benzo-1,6-diynal (**4c**) were then synthesized and subjected to the Rh(II)-catalyzed reaction conditions. As expected, in the presence of *p*-methylstyrene, the desired spiro-cyclopropane derivatives **5b** and **5c** could be obtained in good yields through the [3+2] annulation/cyclopropanation process (Scheme 5, eqs 3 and 4). These control experiments clearly support that this is a carbene-involved process. The preliminary explorations on the asymmetric cyclopropanation were also conducted by using Rh_2(*R*-PTAD)$_4$ as the catalyst, giving the products in good yield and diastereoselectivity, but low ee value (Scheme 5, eqs 2−4). To confirm the importance of the aldehyde group (CHO) in substrates, the reactions of diynones (**4d**, **4f**) and triynone (**4e**) were tested. As shown in eqs 5 and 6 of Scheme 5, no desired product was detected in the reaction system even at an elevated temperature (60 °C), which agrees well with our DFT calculations (Figure S9-3 in the SI). These results indicate that the weak hydrogen-bonding interactions between the formyl group and the carboxylate of Rh(II) might play an important role in promoting the reaction.

Considering the weak hydrogen bonding between the formyl group and carboxylate oxygen, we wondered whether a single crystal of the Rh(II) complex could be obtained to gain more information on the unique activation mechanism. Because **1ae** is prone to undergo further conversion when mixed with the dirhodium catalyst, we replaced the nucleophilic part of the alkyne with another inert benzyl. Delightedly, a stable Rh_2(OPiv)$_4$ π-complex (complex **A**) suitable for X-ray diffraction analysis was obtained successfully. As depicted in

Scheme 6. (a) X-ray Crystal Structure of Dirhodium Complexes with Alkyne Substrates; H-Atoms of Complex B Are Omitted for Clarity; (b) Comparison of Single- and Double-Site Reaction Models[a]



[a]Bond lengths are shown in Å; energy is in kcal/mol.

Scheme 6a, in contrast to the previously postulated coordination mode of the Rh(II) complex with the alkynal reported by Hashimoto and Doyle, in our findings, it is the C≡C of the alkynal that is coordinated to dirhodium rather than the formyl (CHO).[21] To the best of our knowledge, complex **A** represents the first alkyne-dirhodium(II) π-complex in which a molecule of Rh(II) is coordinated axially with two molecular alkynals in the opposite directions.[22] Moreover, the stable Rh_2(*R*-PTAD)$_4$ π-complex (complex **B**) could also be obtained in a similar method, but only one alkynal is coordinated to Rh(II) and the other axial position is occupied by the solvent EtOAc, which could be attributed to the sterically encumbered environment of four pendant adamantyl groups.[23] After close scrutiny of the crystal data, we found that the C≡C triple bond in complex **A** (1.202 Å) is only slightly elongated compared to that in the free alkynal (1.196 Å) (see the SI for detailed crystal data). The coordination-induced back bendings of the alkyne substituents NCH_2/CHO are found to be 9.3° and 2.6°. These data suggest that complex **A** is a weak π-complex and the Dewar−Chatt−Duncanson bonding model could be the most appropriate description of the Rh(II)-alkyne complex.[24] The results are also well consistent with the NMR data, in which no obvious coordination-induced shifts were observed. Further analysis of the complex show that there are close contacts between the carboxylate oxygen of catalyst and the formyl or the γ-

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hydrogen atoms. The formyl hydrogen of complex **A** is 2.61 and 2.82 Å away from the carboxylate oxygen atoms, whereas the distances between both hydrogen atoms at the γ position and carboxylate oxygen atoms were 2.57 Å. To sum up, there are three weak hydrogen bondings (C−H···O < 2.72 Å) between the substrate and the Rh(II) catalyst in complex **A**, which are also found in complex **B** (two weak hydrogen bondings; see the SI for details). This coordination mode is very similar to the optimized structure of **Iae** in our calculations (see the SI for details). It is worth mentioning that the weak hydrogen bondings between the carboxylate ligands, residing between the well-defined paddlewheel-like dirhodium(II) complexes and the alkynal, could partially explain why the dirhodium(II) stood out from other metal complexes in catalyzing the transformation of the alkynal effectively.[25] These unique weak hydrogen bondings might also be the reason for the successful isolation of the weak alkyne-metal complex, as typically only those strong π-complexes were stable enough to allow for isolation and characterization.[26] The bis-coordinating crystal structure of complex **A** indicated that both axial sites of the dirhodium catalyst may be involved in catalysis. However, it seems that the catalytic reaction will not benefit from the coordination of both rhodium atoms, since the free energy barrier via **TS1ae′** is larger than that via **TS1ae** by 3.2 kcal/mol (Scheme 6b). These results agree well with the previous study.[27]

To elucidate the origin of enantioselectivity, transition states of the rate-determining [3+2] cycloaddition of triynal substrate **1a** under the catalysis of chiral catalyst Rh_2(*R*-PTAD)$_4$ were then calculated. A comprehensive conformational search was conducted, and the most favorable *R*/*S* couples are shown in Figure 1. The free energy of [Rh_2(*R*-PTAD)$_4$]-(*R*)-TS**1a** is 5.0

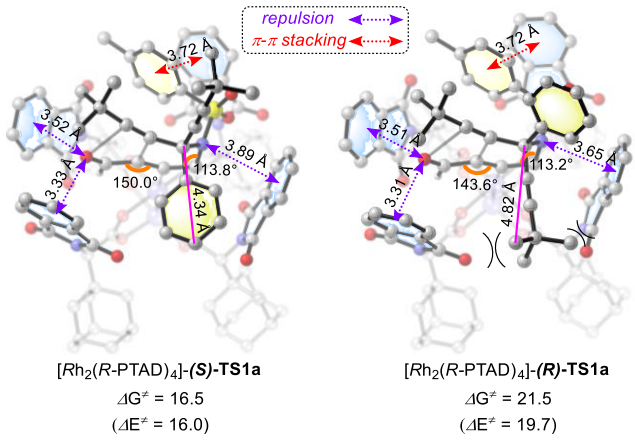

Figure 1. DFT calculations on the origin of enantioselectivity. The phenyl rings of the triynal substrates are colored in light yellow, while the phthalimido rings of the pockets are in light blue.

kcal/mol higher than that of [Rh_2(*R*-PTAD)$_4$]-(*S*)-TS**1a**, which is consistent with our experimental observations (96% ee). [Rh_2(*R*-PTAD)$_4$] was reported to adopt an all-up C_4 conformation in which the substrate binds in the pocket created by the four phthalimido groups. This is also consistent with complex **B** in Scheme 6a, and the radius of the chiral pocket is about 5.1 Å (see the SI for details). A $\pi-\pi$ stacking forms between the Ts group in substrate and the propeller ligand environment for both the *R*/*S*-TS**1a** (3.72 Å). The repulsion between the ligands and the pendant groups, including two −C≡C−^{t}Bu and phenyl, could be the main factor that results in the different energy between (*R*)- and (*S*)-TS**1a**. The repulsion caused by the two upward groups (two −C≡C−^{t}Bu in (*S*)-TS**1a**, one −C≡C−^{t}Bu and one phenyl in (*R*)-TS**1a**) could be negligible. However, the phenyl in (*S*)-TS**1a** and the other −C≡C−^{t}Bu in (*R*)-TS**1a**, which stretch toward the phthalimido groups, could result in repulsion. The −C≡C−^{t}Bu in (*R*)-TS**1a**, which is about 4.82 Å in length, is closer to the radius of the chiral pocket (5.1 Å) than the phenyl (4.34 Å) in (*S*)-TS**1a**. Considering the aza-quaternary center sits near the pocket center, the −C≡C−^{t}Bu in (*R*)-TS**1a** leads to an obvious distortion of the chiral pocket shape. This distortion might arise from the steric repulsion between the coordinated alkynal and nearby phthalimido groups, as suggested by shorter distances between the sulfonamide nitrogen and phenyl rings of the phthalimido groups (3.65 Å in (*R*)-TS**1a** and 3.89 Å in (*S*)-TS**1a**), resulting in a larger energy penalty in (*R*)-TS**1a**. In addition, the bending angles C1−C2−C3 and C3−C4−N in (*S*)-TS**1a** are 150.0° and 113.8°, respectively, closer to the equilibrium values (174.9° and 115.2°) in free substrates than those in (*R*)-TS**1a** (143.6° and 113.2°), which indicated more steric congestion in (*R*)-TS**1a**. This structural analysis suggested a bulky group at the terminus of the alkyne is requisite to achieve high enantioselectivity. In fact, the ee value increased from 32% to 99% when the H atom was replaced with another bulky group (substrate **1b** to **1e** in Scheme 2), which was in line with the calculation results.

3. CONCLUSION

In conclusion, we have developed an enantioselective Rh(II)-catalyzed desymmetric cycloisomerization of diynes, which provides an efficient access to the highly functionalized and enantiomerically enriched alkynyl-substituted furan-fused dihydropiperidine derivatives with wide substrate scope. Two heterocycles and an optically active alkynyl-substituted aza-quaternary carbon stereocenter are constructed in one step. To the best of our knowledge, this method not only represents a new cycloisomerization of diynes but also constitutes the first Rh(II)-catalyzed asymmetric intramolecular cycloisomerization of 1,6-diynes. In addition, the highly functionalized products can be readily converted into valuable building blocks and conjugated with various pharmaceutical molecules. Further calculational studies and control experiments indicate that the reaction undergoes a concerted [3+2] cycloaddition/[1,2]-H shift of the rhodium carbenoid intermediate. More importantly, the weak π-complex of alkyne-dirhodium(II) was successfully isolated and unambiguously characterized by the X-ray diffraction analysis. This represents the first single crystal of alkyne-dirhodium(II). Moreover, weak hydrogen bondings were observed between the carboxylate ligands and alkynal, which probably made the well-defined paddlewheel-like dirhodium(II) distinctive from other metal complexes in catalyzing this transformation. Lastly, the origin of the enantioselectivity was elucidated by the Rh_2(*R*-PTAD)$_4$-alkyne complex and additional calculational studies. These findings may shed new light on future studies on the enantioselective transformations of alkynes catalyzed by dirhodium(II) complexes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c07556.

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Detailed experimental procedures and DFT calculations (PDF)

Accession Codes

CCDC 2042780, 2053705, 2057705, and 2061558−2061559 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Authors

Shifa Zhu − *Key Laboratory of Functional Molecular Engineering of Guangdong Province, School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, People's Republic of China;* orcid.org/0000-0001-5172-7152; Email: zhusf@scut.edu.cn

Kai Chen − *College of Chemistry and Chemical Engineering, Central South University, Changsha 410083, People's Republic of China; Key Laboratory of Chemical Oncogenomics, Peking University Shenzhen Graduate School, Shenzhen 518055, People's Republic of China;* orcid.org/0000-0003-1012-0383; Email: kaichen@csu.edu.cn

Authors

Rui Wu − *Key Laboratory of Functional Molecular Engineering of Guangdong Province, School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, People's Republic of China*

Jiajun Lu − *Key Laboratory of Functional Molecular Engineering of Guangdong Province, School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, People's Republic of China*

Tongxiang Cao − *Key Laboratory of Functional Molecular Engineering of Guangdong Province, School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, People's Republic of China*

Jun Ma − *Key Laboratory of Functional Molecular Engineering of Guangdong Province, School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, People's Republic of China*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.1c07556

Notes

The authors declare no competing financial interest.

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