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Rh(I)-catalyzed stereoselective desymmetrization of prochiral cyclohexadienones *via* highly *exo*-selective Huisgen-type [3 + 2] cycloaddition†‡

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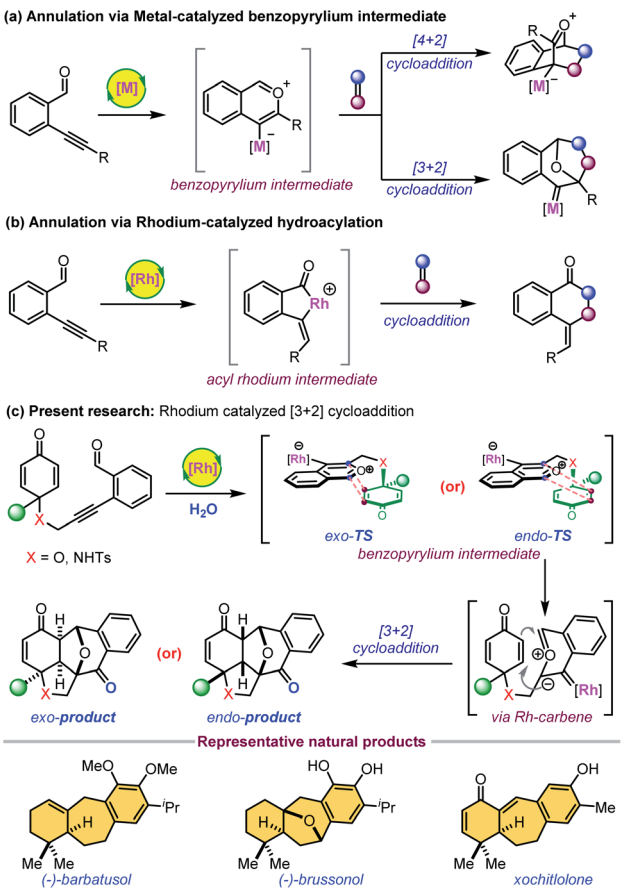
A Rh(I)-catalyzed highly stereoselective desymmetrization of 2-alkynylbenzaldehyde-tethered cyclohexadienones triggered by intramolecular Huisgen-type [3 + 2] cycloaddition has been developed. This method enables convergent construction of complex epoxy-bridged polycyclic ring systems with five contiguous stereocenters with excellent *exo*-selectivity and broad substrate scope. The highly atom-economical process involves 6-*endo*-dig cyclization of carbonyl oxygen onto an activated alkyne resulting in a highly reactive metal–benzopyrylium intermediate, which readily undergoes intramolecular [3 + 2] annulation/hydration. Asymmetric induction is also achieved for the first time in Rh(I)-catalyzed 1,3-dipolar cycloaddition using an easily accessible chiral diene as the ligand.

Introduction

Highly diastereoselective and enantioselective synthesis of polycyclic scaffolds fused with six- or seven-membered carbocycles is of significant interest as a large number of biologically active molecules have this core structure.[1,2] Transition-metal-catalyzed electrophilic activation of 2-enynylbenzaldehydes is a powerful and effective strategy for the formation of such complex frameworks *via* highly reactive metal–benzopyrylium intermediates (Scheme 1a).[3,4] This transient species undergoes various [4 + 2] and [3 + 2] cycloadditions with alkenes to form the corresponding products with high skeletal diversity. A very limited number of [3 + 2] cycloaddition reactions are reported and commonly involve electron-rich olefins and platinum-bonded pyrylium ylides.[4b–f] Interestingly, there is only one report on the Rh(I)-catalyzed intramolecular [3 + 2] cycloaddition of 2-enynebezaldehydes with electron-rich olefins.[4g] However, an asymmetric version of Huisgen-type [3 + 2] cyclization has not been studied to date. Previously, Padwa *et al.* reported the formation of highly reactive six-membered carbonyl ylides from the decomposition of relatively stable *o*-alkyl-2-enoxycarbonyl-α-diazoacetophenones with rhodium(II) catalysts.[5] These transient species subsequently undergo facile



Scheme 1 Previous and present reports on Rh(I)-catalysed annulations of *ortho*-alkynylbenzaldehydes.

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† Dedicated to Padma Bhushan Dr A. V. Rama Rao on the occasion of his 85th birthday.

‡ Electronic supplementary information (ESI) available. CCDC 2008483. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0sc05543c

intramolecular dipolar cycloadditions to afford a similar type of polyoxacyclic skeleton. However, diazo compounds are often prepared from energetic reagents in multiple steps. Another possible mode of cationic Rh(I)-catalysis with 2-alkynylbenzaldehydes is the formation of a five-membered acylmetallacycle which subsequently undergoes various cycloaddition reactions to give six-membered carbocycles (Scheme 1b).[6]

In continuation of our efforts in exploring new desymmetrization methods[7,8] and the unique reactivity of *ortho*-alkynylbenzaldehydes,[9] we envisaged that the rhodium-catalyzed Huisgen-type [3 + 2] cyclization[10] of 2-alkynylbenzaldehyde-tethered cyclohexadienones would provide highly strained complex epoxy bridged polycycles with multiple stereocenters (Scheme 1c). This highly atom-economical reaction would generate seven-membered carbocycles fused with a phenyl ring, which is present in several natural products including barbatusol, pisiferin, brussonoll, and xochitlolone (Scheme 1).[11] The starting substrates were easily accessible from dearomatization/Sonogashira coupling of the corresponding phenols in two steps (see the ESI‡). The electrophilic activation of an alkyne with Rh(I) gives a kinetically unstable metal–benzopyrilium intermediate that could undergo intramolecular [3 + 2] cycloaddition with an enone to form the desired product by adopting *exo*- or *endo*-configuration *via* a rhodium–carbene intermediate. The major challenges for this cascade reaction are: (1) the *exo*- or *endo*-selectivity of [3 + 2] cycloaddition; (2) competitive intramolecular [4 + 2] cycloaddition through the Rh-benzopyrilium intermediate or acylrhodium intermediate; (3) imparting enantioselectivity to the [3 + 2] cycloaddition.

Results and discussion

Our investigation towards intramolecular cycloaddition began using 2-alkynylbenzaldehyde **1a** as the model substrate (Table 1). After extensive optimization of reaction conditions (see the ESI‡), we were delighted to afford the [3 + 2] annulation product *exo*-**2a** in 75% yield with complete diastereoselectivity in the presence of 5 mol% $[Rh(COD)Cl]_2$ as the catalyst in H_2O solvent at 100 °C for 1 h (Table 1, entry1). The *exo*-selectivity of [3 + 2]-cycloaddition and the molecular structure of product **2a** were confirmed by X-ray crystallographic analysis (Fig. 1).[12] The product formation through *exo*-TS would significantly reduce the steric repulsion between the metal–benzopyrilium intermediate and cyclohexadienone ring.[13] Fortunately, we did not observe any [4 + 2] cycloaddition products from either rhodium–benzopyrilium intermediates or acylrhodium intermediates. Overall, this rigid and short tethered intramolecular annulation reaction ruled out the potential competitive *endo*-selective [3 + 2] and [4 + 2] cycloaddition probably due to such processes producing high ring-strain in the transition states. Using 5% aqueous xylene as a solvent at 120 °C, only 56% yield of **2a** was obtained (Table 1, entry 2). The reaction performed in other solvents such as CH_3CN, THF, dioxane and *t*-BuOH returned inferior yields, indicating that H_2O is the best solvent for this reaction (entries 3–6). Moreover, reducing the reaction temperature to 80 °C led to a diminished yield of the polycyclic product even with a prolonged reaction time (entry 7).

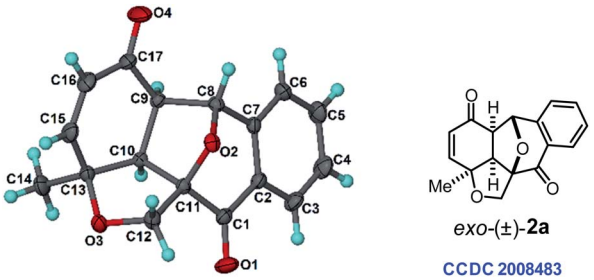
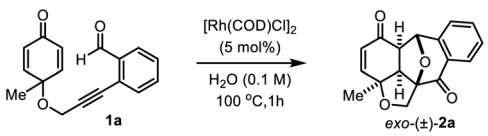


Fig. 1 ORTEP diagram of compound *exo*-(±)-**2a**.

Table 1 Optimization of reaction conditions[a,b]



Entry	Deviation from the standard conditions	Yield[c,d] [%]
1	None	75
2	5% aq. xylene/120 °C instead of H_2O/100 °C	56[e]
3	CH_3CN/80 °C instead of H_2O/100 °C	21
4	THF/70 °C instead of H_2O/100 °C	32
5	1,4-Dioxane/100 °C instead of H_2O/100 °C	25
6	*t*-BuOH/85 °C instead of H_2O/100 °C	31
7	80 °C instead of 100 °C	48
8	$Rh(COD)_2OTf$/xylene instead of $[Rh(COD)Cl]_2$ catalyst/H_2O	16
9	$Rh(COD)_2SbF_6$/xylene instead of $[Rh(COD)Cl]_2$ catalyst/H_2O	25
10	$[Ir(COD)Cl]_2$/xylene instead of $[Rh(COD)Cl]_2$ catalyst/H_2O	21
11	$[Ru(p\text{-cymene})Cl_2]_2$/xylene instead of $[Rh(COD)Cl]_2$ catalyst/H_2O	12

[a] Reaction conditions: **1a** (0.3 mmol) and catalyst (5 mol%) in 3 mL of solvent under an inert atmosphere. [b] All commercial solvents used in the reaction. [c] Isolated yields of *exo*-**2a**. [d] Observed exclusive *exo*-selectivity. [e] 46% yield observed in the presence of commercial xylene.

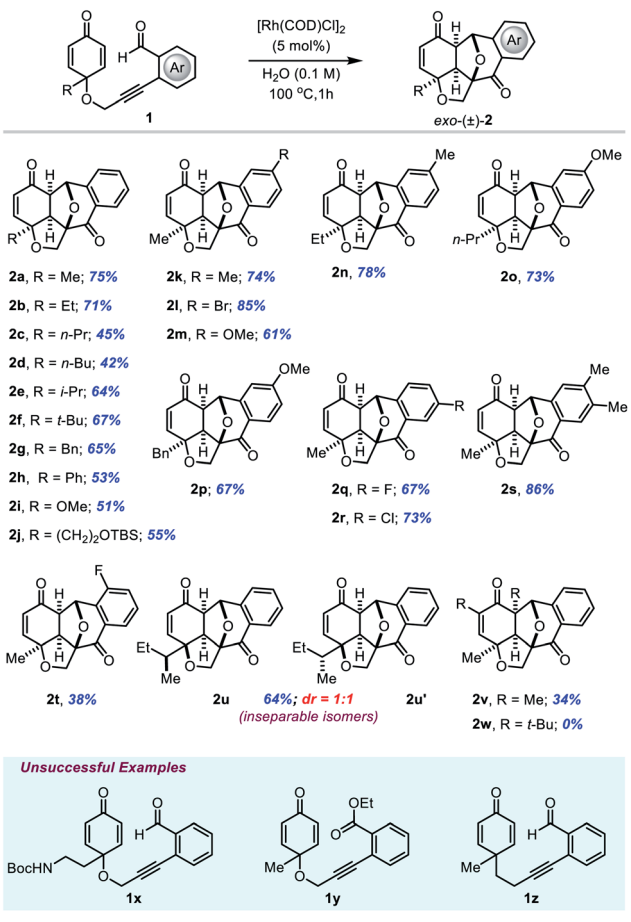
Additional optimization revealed that the reaction with other transition-metal (Rh, Ir and Ru) catalysts also gave desired product **2a** in lower yields (entries 8–11).

Initially, we explored the scope and limitations of *O*-tethered-cyclohexadienones under the optimal reaction conditions (Table 2). With substituents such as alkyl, benzyl, phenyl and methoxy groups at the substrate's quaternary carbon center, the reaction proceeded well with moderate to high yields and complete diastereoselectivity (entries **2a–2j**). All *meta*-substituted and *para*-substituted 2-enynylbenzaldehydes regardless of the electronic effect of substituents at the phenyl ring afforded polycyclic products in very good yields (entries **2k–2s**). The reaction of the *ortho*-fluoro substituted substrate gave the corresponding product **2t** in lower yield. The annulation of a substrate containing a *sec*-butyl group at the cyclohexadienone prochiral center proceeded smoothly to give cycloadduct **2u**/**2u′** in 64% yield with a 1 : 1 ratio of diastereomers with respect to the stereocenter on the *sec*-butyl group. It is worth mentioning that the reaction with the methyl substituent at the α-position of the dienone also afforded annulation product **2v** in 34% yield, but with a sterically more hindered *tert*-butyl group on the substrate's dienone ring it was unable to participate in the reaction (entry **2w**). In addition, substrates **1x** with the NHBoc group and *o*-alkynyl benzoate-tethered cyclohexadienone **1y** were found to be inert in the [3 + 2] annulation reaction. Also, the C-tethered substrate **1z** under the standard reaction conditions failed to give the desired product probably due to the absence of the Thorpe–Ingold effect.

With these promising results in hand, next we sought to examine the reactivity of *N*-tethered cyclohexadienones (Table 3). The reactions still proceeded equally well with a wide range of NTs-linked 2-alkynylbenzaldehydes substituted with various groups on the phenyl ring (entries **4a–4g**). However, substrates with electron-withdrawing substituents on the phenyl ring gave slightly lower yields compared to those with electron-donating substituents. A Boc-protected N-tethered substrate was unable to provide the required product, probably due to intervention from the carbonyl functionality of the Boc group in 6-*endo*-dig cyclization (entry **4a′**). Notably, the phenyl group at the substrate's prochiral centre was also well tolerated in this electrophilic cyclization reaction to give the corresponding product **4h** in 67% yield.

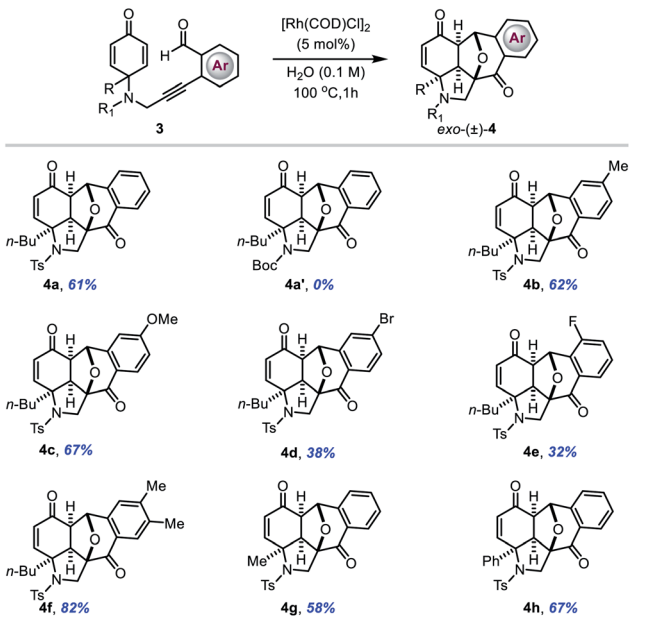
The process is not only limited to aryl aldehydes; 2-alkynylphenyl ketones **5** are also well tolerated in the annulation reaction (Table 4). Both alkyl and aryl substituted phenyl ketones smoothly underwent the [3 + 2] cycloaddition reaction irrespective of the electronic nature of substituents on the aryl ring to afford the corresponding products in higher yield with excellent diastereoselectivity (entries **6a–6e**). It is important to mention that ketones **5** gave slightly higher yields than aldehyde substrates **1** in the annulation reaction. Significantly, *N*-

Table 2 Substrate scope for *O*-tethered cyclohexadienones[a,b,c,d]



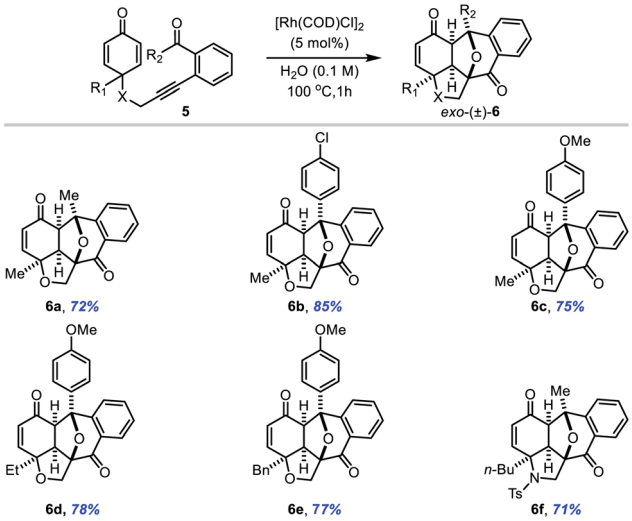
[a] Reaction conditions: **1** (0.3 mmol) and $[Rh(COD)Cl]_2$ (5 mol%) in H_2O (3 mL) under an inert atmosphere at 100 °C for 1 h. [b] Isolated yields of *exo*-**2**. [c] Observed exclusive *exo*-selectivity. [d] Both **1x** and **1y** were decomposed and **1z** was recovered.

Table 3 Substrate scope for *N*-tethered-cyclohexadienones[a,b,c]



[a] Reaction conditions: the same as in Table 2. [b] Isolated yields of *exo*-**4**. [c] Observed exclusive *exo*-selectivity chromatography.

Table 4 Substrate scope of 2-alkynylphenyl ketones[a,b,c]

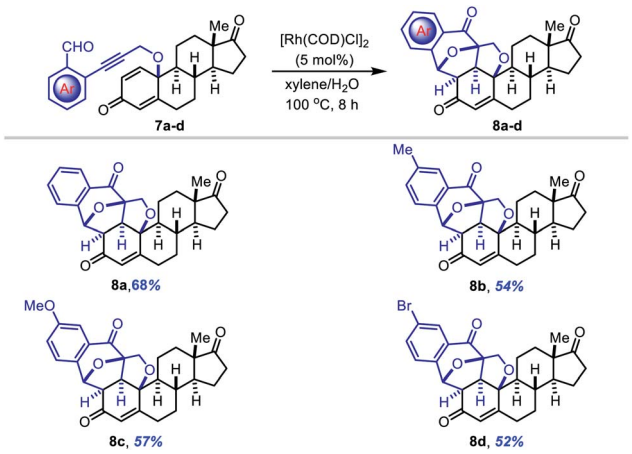


[a] Reaction conditions: the same as in Table 2. [b] Isolated yields of *exo*-**6**. [c] Observed >20 : 1 ratio of *exo*-selectivity assigned by ^{1}H NMR analysis.

tethered alkynylphenyl ketone was also converted to polycyclic enone **6f** in 71% yield.

Late-stage functionalization (LSF) is a prevalent concept for the rapid generation of analogues from lead molecules and bioactive natural products. Herein, we successfully demonstrated the synthetic utility of the Rh(I)-catalyzed cascade annulation reaction for the late-stage functionalization of estrone (Table 5). Initially, estrone derivatives **7** (converted from estrone in two steps using a known procedure)[14] were subjected to the standard reaction conditions. However, we observed poor

Table 5 Late-stage functionalization of estrone[a,b,c,d]

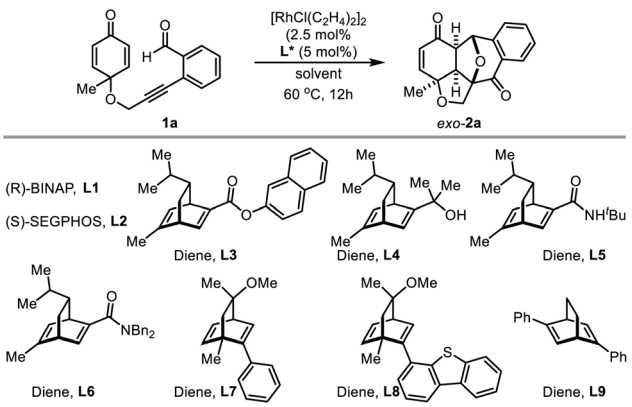


[a] Reaction conditions: **7** (0.2 mmol) in 5% aqueous xylene (2 mL, 0.1 M) under an inert atmosphere at 100 °C for 8 h. [b] The diastereomeric ratio of **7a** (12 : 1), **7b** (15 : 1), **7c** (9 : 1) and **7d** (15 : 1) assigned by ^{1}H NMR after column purification. [c] Isolated yields of **8**. [d] The diastereomeric ratio of **8** (dr = >30 : 1) assigned by ^{1}H NMR analysis of the crude aliquot.

reaction yields due to substrate insolubility in the water solvent, related to the highly hydrophobic nature of steroidal compounds. To our delight, the [3 + 2] cyclization of **7** in 5% aqueous xylenes as the solvent underwent smoothly to produce the corresponding polycyclic products **8a–d** with five new stereogenic centers in 52–68% yield and excellent diastereoselectivity.

Surprisingly, transition-metal catalyzed enantioselective transformations of benzopyryliums are limited and most of them are based on the use of bulky chiral Brønsted acids as a counter anion, presumably due to the planar structure and lack of appropriate coordination sites.[15] To the best of our knowledge, so far there is no report on Rh(I)-catalyzed asymmetric [3 + 2] cycloaddition of 2-enynylbenzaldehydes. Encouraged by the results from the diastereoselective annulation reaction, we sought to investigate enantioselective Rh(I)-catalyzed Huisgen-type [3 + 2] cyclization using various chiral ligands (Table 6). Initially, chiral bisphosphine ligands (**L1** and **L2**) were examined for the annulation of model substrate **1a** in 5% aqueous xylene at 60 °C (entries 1 and 2). Unfortunately,

Table 6 Optimization of enantioselective cyclization[a,b]



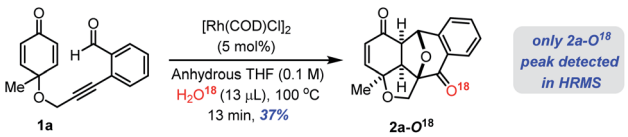
Entry	Ligand (**L***)	Solvent	Yield[c] [%]	er[d]
1	(R)-BINAP, **L1**	5% aq. xylene	34	56 : 44
2	(S)-SEGPHOS, **L2**	5% aq. xylene	21	55 : 45
3	Diene, **L3**	5% aq. xylene	59	55 : 45
4	Diene, **L4**	5% aq. xylene	54	81 : 19
5	Diene, **L5**	5% aq. xylene	51	61 : 39
6	Diene, **L6**	5% aq. xylene	53	65 : 35
7	Diene, **L7**	5% aq. xylene	47	61 : 39
8	Diene, **L8**	5% aq. xylene	71	57 : 43
9	Diene, **L9**	5% aq. xylene	58	59 : 41
10	Diene, **L4**	*t*-BuOH	70	88 : 12
11	Diene, **L4**	THF	75	89 : 11
12	Diene, **L4**	CH_3CN	55	81 : 19
13	Diene, **L4**	DMF	32	78 : 22
14	Diene, **L4**	DCE	47	76 : 24
15	Diene, **L4**	THF at 45 °C	74	91 : 09

[a] Reaction conditions: **1a** (0.3 mmol), $[RhCl(C_2H_4)_2]_2$ (2.9 mg, 2.5 mol%) and ligand **L*** (5 mol%) in solvent (3 mL, 0.1 M) under an inert atmosphere. [b] All commercial solvents used in the reaction. [c] Isolated yields of *exo*-**2a**. [d] er determined by HPLC analysis using a chiral stationary phase.

these bidentate ligands were not effective to promote the asymmetric induction. Next, several varieties of chiral diene ligands (**L4–L9**)[16] were evaluated and promising enantioselectivity was obtained with diene **L4** (entry 4, 54% yield, 81 : 19 er). Additional optimization (entries 10–14) revealed that the reaction in THF as the solvent improved the reaction yield and enantiomeric ratio (entry 11). When the reaction was conducted in THF at 45 °C, the best result was obtained forming the product in 74% yield with a 91 : 9 er (entry 15).

With the optimized reaction conditions for the enantioselective reaction in hand, the scope of representative alkyne-tethered cyclohexadienones was explored with various substituents on **1** or **5** (Table 7). With R_1 substituents such as methyl, isopropyl, *tert*-butyl and phenyl groups, the reactions proceeded smoothly with good yields and good enantiomeric ratios (entries **2a**, **2e**, **2f** and **2h**). Both electron donating and withdrawing groups on aryl aldehyde were compatible with the enantioselective reaction and afforded the corresponding products **2m** and **2r** with high enantioselectivity. Notably, a methyl substituent at the α-position of the dienone was also well tolerated to give bridged polycycle **2v** in good 62% yield with an 82 : 18 er. In addition, alkyl and aryl ketones were also amenable to furnish the annulation products (**6a** and **6b**) in good yield, albeit with a moderate enantiomeric ratio.

To get further insight into the reaction mechanism, we subsequently conducted a ^{18}O labelling study on the Rh(I)-catalyzed cyclization of **1a** under the standard reaction conditions in anhydrous THF/$H_2{}^{18}O$ solvent which furnished **2a**–^{18}**O** confirmed by ESI-HRMS analysis (see the ESI‡). This reaction clearly suggests that the oxygen atom is from H_2O molecules in the solvent system (Scheme 2).

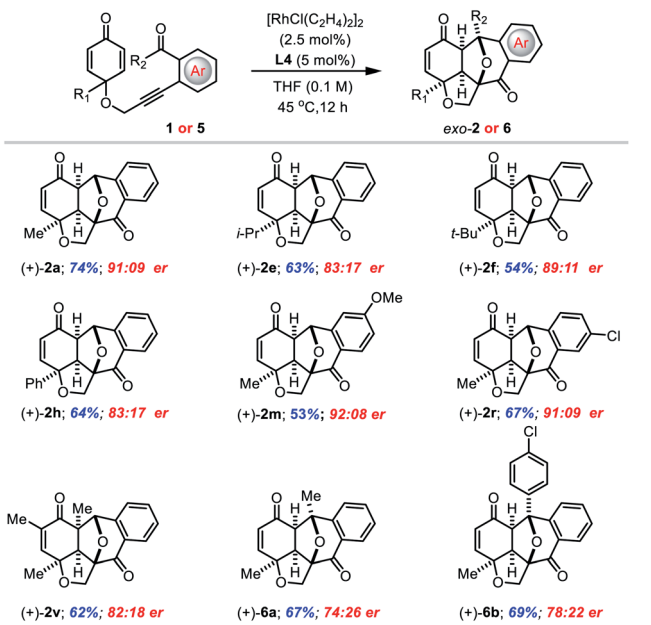


Scheme 2 O^{18}-Labelling study.

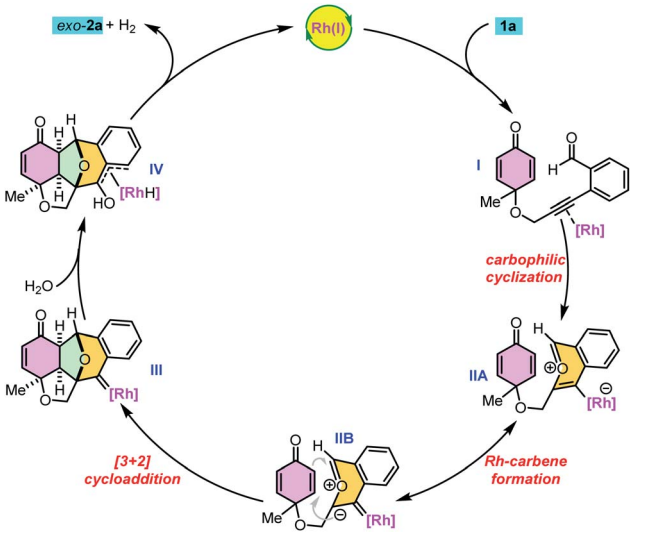
On the basis of the above experimental results, a possible reaction mechanism was proposed as shown in Scheme 3. First, the alkyne moiety of **1a** is activated through π-complex formation (**I**) to initiate 6-*endo*-dig cyclization. The intramolecular nucleophilic attack of the carbonyl oxygen on the activated triple bond results in intermediates **IIA** and **IIB**.[4] The intramolecular [3 + 2] cycloaddition of transient carbonyl ylide **II** with the electron deficient dienone ring generates highly reactive rhodium–carbene complex **III**, which readily undergoes hydration to give the desired product **2a** *via* intermediate **IV** with the regeneration of Rh(I) and liberation of molecular hydrogen.[4g] Here, the benzopyrylium intermediate has a planar 10π-electron aromatic structure and the chiral catalyst would be located on the favourable face and subsequently undergo cycloaddition from the opposite side.

To demonstrate the synthetic utility of Huisgen-type [3 + 2] cycloaddition, a gram-scale reaction of **1a** was carried out with 2.5 mol% catalyst loading under standard reaction conditions. The reaction still proceeded well to afford (±)-**2a** with 72% yield (Scheme 4a). The complex polycyclic products have enone functionality, which can further undergo various transformations (Scheme 4b). Catalytic hydrogenation of **2a** afforded **7** in 96% yield without affecting the highly strained epoxy-bridged polycyclic rings. The intermolecular 1,4-addition of **2a** with indole and intramolecular 1,4-addition of **2j** by desilylation gave corresponding products **8** and **9**, respectively with exclusive

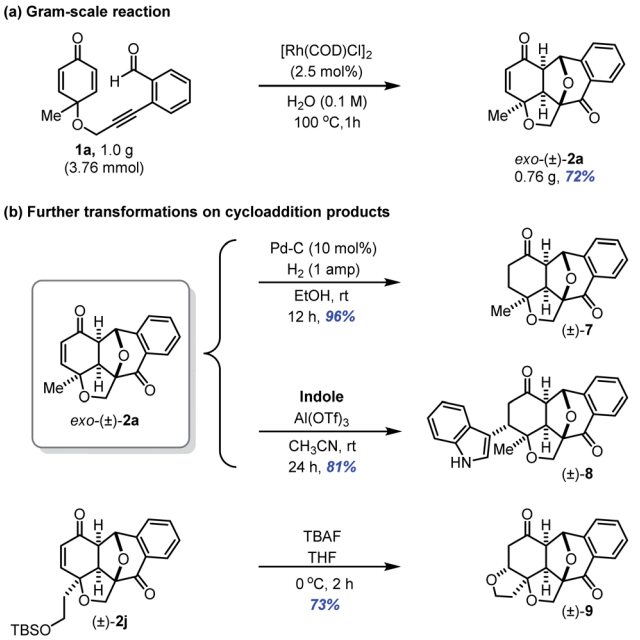
Table 7 Rh(I)-catalyzed enantioselective cyclization[a,b,c]



[a] Reaction conditions: **1** or **5** (0.3 mmol), $[RhCl(C_2H_4)_2]_2$ (2.9 mg) and diene, **L4** (3.3 mg) in THF (3 mL) under an inert atmosphere. [b] Isolated yields of *exo*-**2** or **6**. [c] er determined by chiral HPLC analysis.



Scheme 3 Plausible mechanism for the cascade cyclization reaction.



Scheme 4 Gram scale reaction and subsequent transformations on cycloaddition products.

diastereoselectivity due to the concave nature of starting substrates.

Conclusions

In summary, we have developed a highly diastereoselective desymmetrization of prochiral *ortho*-alkynylbenzaldehyde-tethered cyclohexadienones by Rh(I)-catalyzed intramolecular Huisgen-type [3 + 2] cycloaddition. This atom economical reaction involves a highly reactive Rh–benzopyrylium intermediate that emanates from 6-*endo*-dig cyclization of 2-enynylbenzaldehyde, which readily undergoes *exo*-selective 1,3-dipolar cycloaddition. The reaction has broad substrate scope including 2-alkynylbenzaldehyes, 2-alkynylphenylketones and complex estrone derivatives giving highly strained epoxy-bridged polycyclic products bearing five contiguous stereocenters in high yields. The first enantioselective Rh(I)-catalyzed Huisgen-type [3 + 2] cycloaddition was achieved by using easily accessible chiral diene ligands. Further investigations on the design of new chiral ligands and applications are underway in our laboratory and will be reported in due course.

Experimental

General procedure

A dried screw-cap vial was charged with 2-alkynylbenaldehyes **1** or **3** or 2-alkynylphenyl ketones **5** (0.3 mmol, 1.0 equiv.), and $[Rh(COD)Cl]_2$ (7.4 mg, 5.0 mol%) in distilled H_2O (1.5 mL, 0.1 M) under an inert atmosphere, and the reaction mixture was stirred at 100 °C for 1 hour (monitored by TLC). Then, it was cooled to room temperature and diluted with EtOAc (8 mL). The mixture was extracted with EtOAc (3 × 8 mL) and combined organic solvent was concentrated under reduced pressure. The residue was purified by silica gel column chromatography on silica gel with a gradient eluent of petroleum ether and EtOAc to afford the desired [3 + 2] cyclization product **2** or **4** or **6**, respectively.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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