Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2025, **16**, 19397

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 24th May 2025
Accepted 16th September 2025

DOI: 10.1039/d5sc03779d

rsc.li/chemical-science

Chiral benzo[2.2.1] α-hydroxyketones from a dirhodium(II)/bisphosphine-catalyzed desymmetrization addition reaction

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The [2.2.1]-bridged bicyclic framework represents a privileged structural motif prevalent in numerous bioactive molecules and functional materials. The development of efficient synthetic methods for constructing these valuable architectures remains highly desirable. In this study, we report a dirhodium(II)/bisphosphine-catalyzed desymmetrization reaction of benzobicyclo[2.2.1]heptane-2,3-diones with arylboronic acids. This transformation delivers enantioenriched benzo[2.2.1] α-hydroxy ketones with excellent enantioselectivity (up to 94% ee) across a diverse substrate scope. The synthetic utility of these chiral products is demonstrated through several transformations, including the preparation of a chiral phosphine.

Introduction

The [2.2.1]-bridged bicyclic scaffold represents a privileged structural motif that appears extensively in natural products,[1] bioactive molecules,[2] and functional materials,[3] exhibiting remarkable versatility in both biological applications and organic synthesis. This structural framework underpins numerous pharmaceutically significant compounds, exemplified by biperiden, which effectively alleviates extrapyramidal disorders secondary to neuroleptic drug administration with an IC_{50} value of 9 μM (Fig. 1a).[4] Cyclothiazide, a potent and orally effective therapeutic agent, is widely employed in the management of hypertension and heart failure.[5] Natural products containing this scaffold also demonstrate promising bioactivity, as illustrated by guaianodilactone C, a sesquiterpene lactone dimer isolated from *Carpesium faberi* that exhibits cytotoxicity against human leukemia (CCRF-CEM) cells with an IC_{50} value of 4.74 μM.[6]

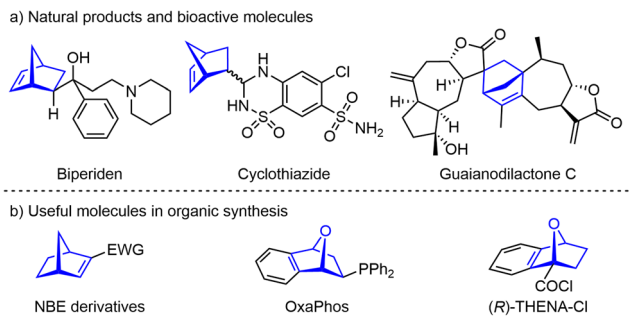
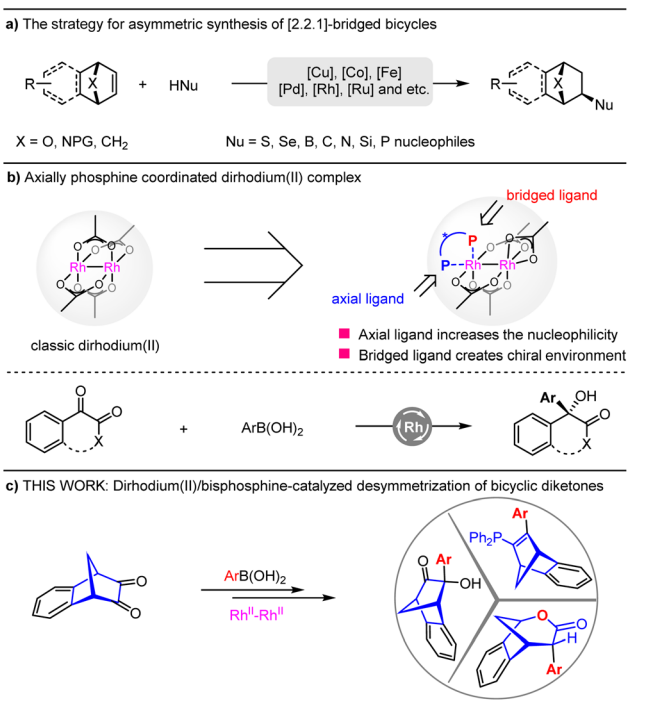


Fig. 1 [2.2.1]Bicycles in (a) bioactive molecules and (b) functional materials.



Scheme 1 Enantioselective strategies for the synthesis of [2.2.1]-bridged bicycles.

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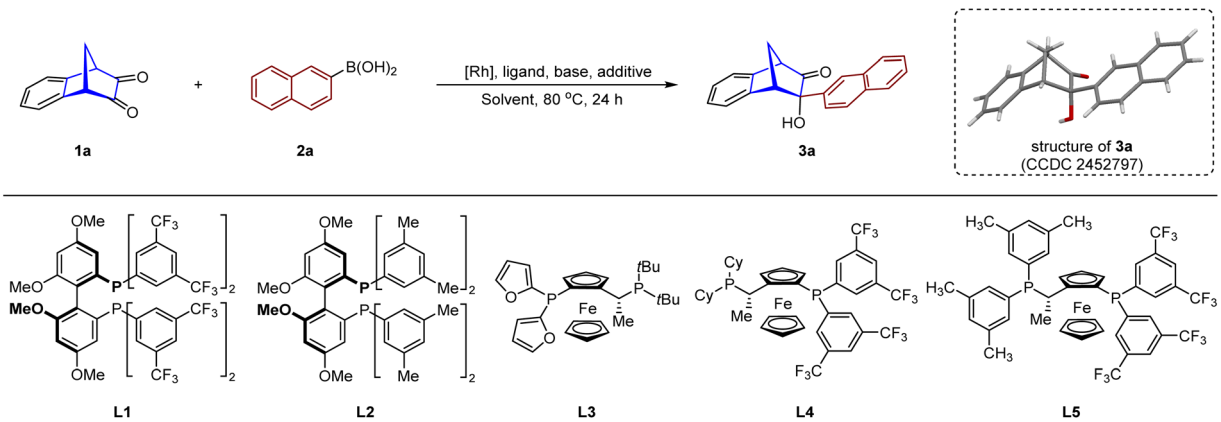
Beyond pharmaceutical applications, the [2.2.1]bridged bicyclic framework serves as a fundamental component in numerous synthetically valuable molecules (Fig. 1b). Norbornene (NBE) and its derivatives function as crucial shuttles for "palladium migration" in the Catellani reaction,[7] while Oxa-Phos represents an important chiral phosphine ligand employed in ruthenium-catalyzed arylation of aldehydes.[8] Additionally, (*R*)-THENA-Cl has established itself as an effective chiral resolving agent for the enantiomeric resolution of 7,7′-disubstituted 1,1′-bi-2-naphthols.[9] These diverse applications underscore the significant synthetic utility and structural importance of the [2.2.1]-bridged bicyclic architecture in contemporary chemical research.

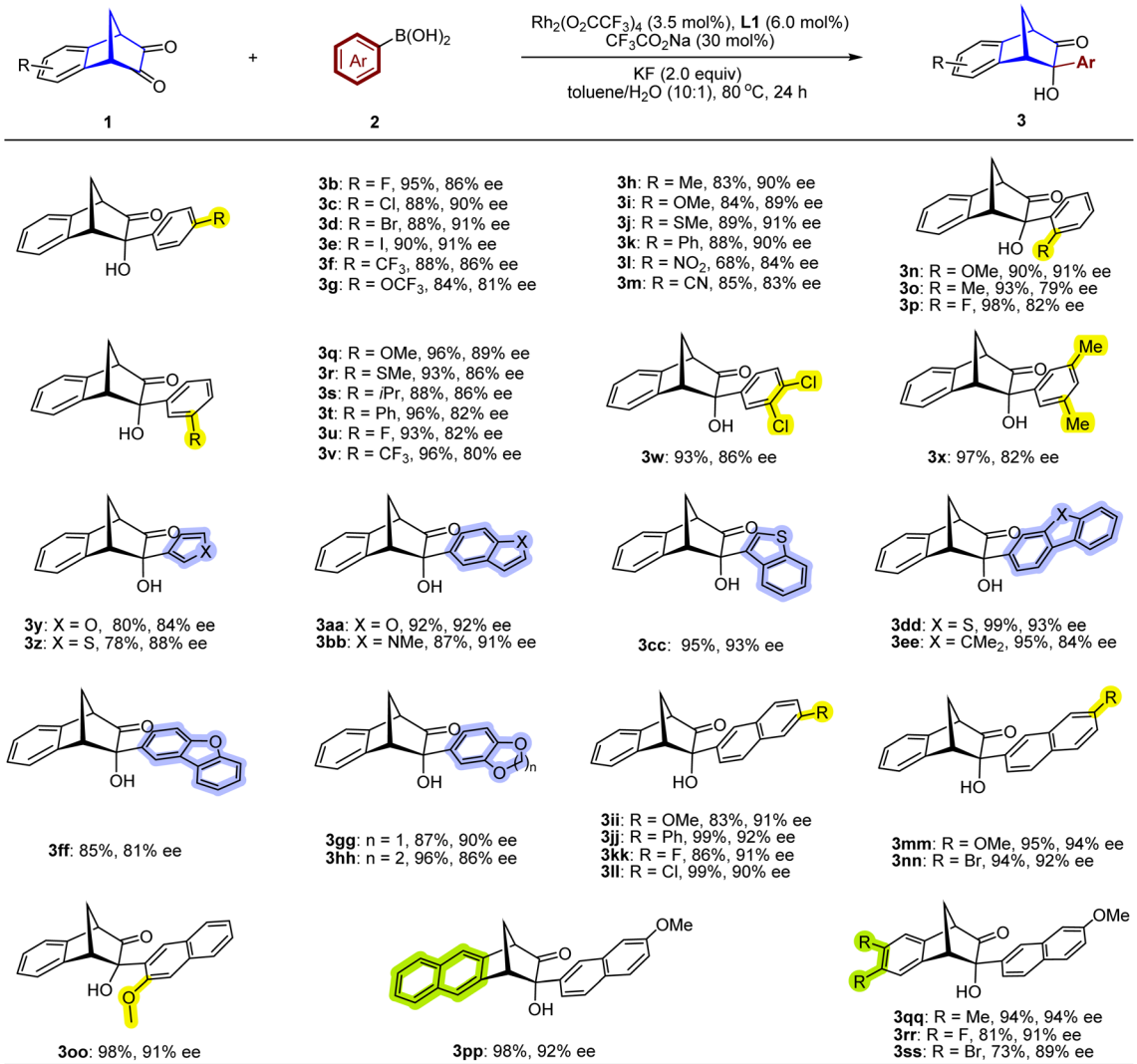
The [2.2.1]-bridged bicyclic framework has attracted significant attention due to its diverse bioactivities and important applications, prompting extensive research into efficient synthetic approaches for constructing these valuable molecular architectures. Current methodologies for accessing enantioenriched [2.2.1]-bridged bicycles primarily include cyclopenta-1,3-diene involved enantioselective cycloaddition reactions[10] and metal-catalyzed addition processes. The latter strategy typically employs metals such as Cu, Co, Fe, Rh, Pd, and Ru with [2.2.1]bicyclic alkenes as substrates, incorporating various nucleophilic reagents including boron, carbon, and nitrogen-based nucleophiles.[11] Dirhodium(II) complexes have been extensively utilized as catalysts for carbene and nitrene-mediated X–H insertion reactions, cyclopropanation, *etc.* These transformations can be rendered asymmetric through the incorporation of chiral carboxylic acids or chiral phosphoric acids. Modification of dirhodium(II) complexes with an additional ligand at the axial site of the paddlewheel Rh(II)–Rh(II) structure induces novel catalytic activities. However, stereochemical control by these complexes is hindered by the significant distance between the reactive site and the chiral ligand, which resides at the opposite axial position, thus limiting applications in asymmetric catalysis. Recently, our laboratory developed a novel dirhodium(II)-bisphosphine catalytic system that exhibits unique reactivity patterns and superior stereochemical control. In this system, one of the phosphine moieties sitting at the bridging site of the dirhodium(II) structure establishes a well-defined chiral environment that enables highly enantioselective addition reactions, demonstrating

Table 1 Optimization of reaction conditions[a]



Entry[a]	[Rh]	Ligand	Base/equiv.	Solvent	Additive per mol%	Yield[b]/%	ee[c]/%
1	$Rh_2(O_2CCF_3)_4$	**L1**	$LiOH\cdot H_2O$ (5.0)	Toluene	—	62	87
2	$Rh_2(O_2CCF_3)_4$	**L2**	$LiOH\cdot H_2O$ (5.0)	Toluene	—	ND	—
3	$Rh_2(O_2CCF_3)_4$	**L3**	$LiOH\cdot H_2O$ (5.0)	Toluene	—	Trace	36
4	$Rh_2(O_2CCF_3)_4$	**L4**	$LiOH\cdot H_2O$ (5.0)	Toluene	—	Trace	35
5	$Rh_2(O_2CCF_3)_4$	**L5**	$LiOH\cdot H_2O$ (5.0)	Toluene	—	Trace	15
6	$Rh_2(O_2CCF_3)_4$	**L1**	K_2CO_3 (1.0)	Toluene/H_2O (10 : 1)	—	Trace	90
7	$Rh_2(O_2CCF_3)_4$	**L1**	DABCO (1.0)	Toluene/H_2O (10 : 1)	—	ND	—
8	$Rh_2(O_2CCF_3)_4$	**L1**	KF (2.0)	Toluene/H_2O (10 : 1)	—	76	90
9	$Rh_2(O_2CCF_3)_4$	**L1**	CsF (2.0)	Toluene/H_2O (10 : 1)	—	65	90
10	$Rh_2(OAc)_4$	**L1**	KF (2.0)	Toluene/H_2O (10 : 1)	—	73	90
11	$Rh_2(O_2CC_7H_{15})_4$	**L1**	KF (2.0)	Toluene/H_2O (10 : 1)	—	70	90
12	$Rh_2(O_2CCF_3)_4$	**L1**	CsF (2.0)	Toluene/H_2O (10 : 1)	CF_3CO_2Na (15)	80	91
13[d]	$Rh_2(O_2CCF_3)_4$	**L1**	KF (2.0)	Toluene/H_2O (10 : 1)	CF_3CO_2Na (20)	91	91
14[d]	$Rh_2(O_2CCF_3)_4$	**L1**	KF (2.0)	Toluene/H_2O (10 : 1)	CF_3CO_2Na (30)	98	91
15[d,e]	$Rh_2(O_2CCF_3)_4$	**L1**	KF (2.0)	Toluene/H_2O (10 : 1)	CF_3CO_2Na (30)	95	91

[a] Conditions: **1a** (0.10 mmol), **2a** (0.20 mmol, 2.0 equiv.), $[Rh_2X_4]$ (2.5 mol%), ligand (5.0 mol%), and base (2.0 equiv.) in toluene/H_2O = 2.0/0.2 mL at 80 °C for 24 h. [b] Isolated yields are given. [c] ee values were determined by HPLC on a chiral column. [d] $[Rh_2(O_2CCF_3)_4]$ (3.5 mol%) and **L1** (6.0 mol%). [e] The reaction scale of **1a** was 1.0 mmol.



Scheme 2 Substrate scope. Conditions: **1** (0.20 mmol), **2** (0.40 mmol, 2.0 equiv.), $Rh_2(O_2CCF_3)_4$ (3.5 mol%), **L1** (6.0 mol%), CF_3CO_2Na (30 mol%), and KF (2.0 equiv.) in toluene/H_2O = 4.0/0.4 mL at 80 °C for 24 h.

particular efficiency for cyclic 1,2-dicarbonyl compounds.[12] However, the substrate scope was limited to aryl ketone derivatives. An attempt using 1,2-cyclohexanedione as the substrate was unsuccessful, likely due to its facile enolization. By contrast, the carbonyl groups in the bridged structure of bicyclo [2.2.1]heptane-2,3-diones are known to have a low enolization tendency, making them suitable candidates for 1,2-addition reactions. Building upon these findings, herein we report a $Rh_2(O_2CCF_3)_4$/GarPhos-catalyzed desymmetrization reaction of benzobicyclo[2.2.1]heptane-2,3-diones, accessing enantioenriched [2.2.1]-bridged bicyclic structures (Scheme 1c).

Results and discussion

Optimization

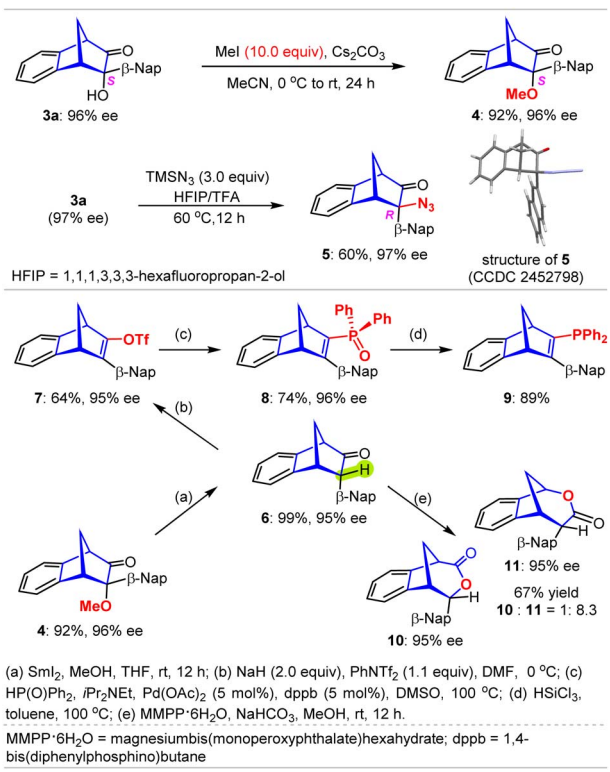
To test our hypothesis, we initiated our investigation using 1,4-dihydro-1,4-methanonaphthalene-2,3-dione (**1a**)[13] and naphthalen-2-ylboronic acid as model substrates. Our initial screening revealed that electron-deficient biphosphine ligands were essential for this reaction. Specifically, the catalyst system comprising $Rh_2(O_2CCF_3)_4$ and (*R*)-BTFM-GarPhos (**L1**) afforded the desired product **3a** in 62% yield with 87% enantiomeric excess (Table 1, entry 1). In contrast, replacing the trifluoromethyl groups with methyl groups, as in (*R*)-xyl-GarPhos (**L2**), completely suppressed product formation (entry 2). The Josiphos ligand family (**L3–L5**) proved similarly ineffective, generating only trace amounts of **3a** with poor enantioselectivity (entries 3–5). We then explored different base additives to improve the reaction's performance. Potassium fluoride (KF) enhanced both yield and stereoselectivity, which was even more effective than CsF (entries 8 and 9), whereas K_2CO_3 and organic bases such as DABCO showed little to no activity (entries 6 and 7). Subsequently, we re-examined the effectiveness of other rhodium catalysts, $Rh_2(OAc)_4$ and $Rh_2(O_2CC_7H_{15}\text{-}n)_4$, which resulted in slightly lower yields (entries 10 and 11). The addition of 15 mol% CF_3CO_2Na, thought to suppress decomposition of

$Rh_2(O_2CCF_3)_4$, further improved the yield (entry 12). Moreover, with 3.5 mol% $Rh_2(O_2CCF_3)_4$, optimizing the loading of CF_3CO_2Na led to an optimal yield of 98% (with 30 mol% CF_3CO_2Na) without compromising enantioselectivity (entries 13 and 14). The reaction also proceeded smoothly on a 1.0 mmol scale, demonstrating the robustness of this protocol (entry 15).

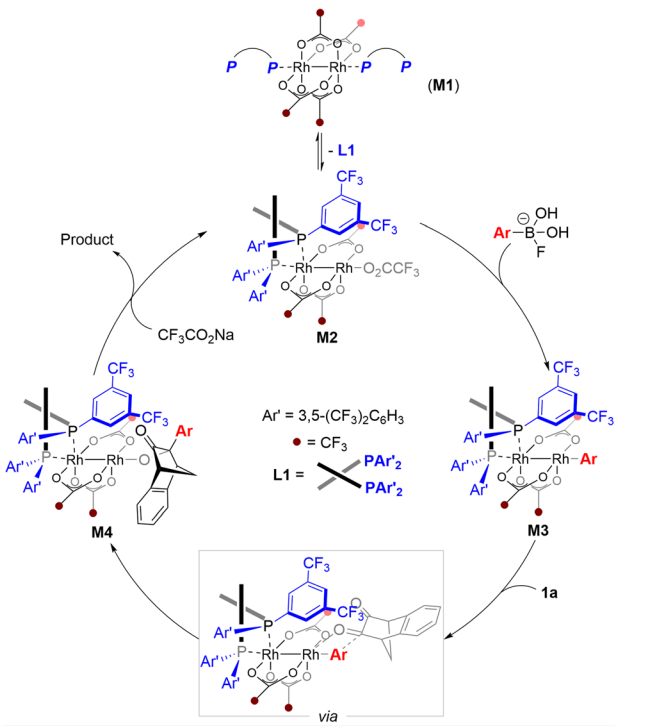
Substrate scope

With the optimized conditions established, we investigated the substrate scope of this reaction as detailed in Scheme 2. First, we examined a diverse array of arylboronic acids as arylation reagents, including substituted phenylboronic acids, heteroarylboronic acids, and naphthylboronic acids. Phenylboronic acids bearing various *para*-substituents demonstrated good reactivity (**3b–3m**). The weakly electron-withdrawing, electron-donating, and neutral groups maintained high stereoselectivity (**3b–3e**, **3h**, and **3i–3k**), while strongly electron-withdrawing substituents would slightly diminish the enantioselectivity (**3f**, **3g**, **3l** and **3m**). Substituents at the *meta* and *ortho* positions of phenylboronic acids exhibited similar electronic effects on stereoselectivity (**3n–3v**); however, 3,5-dimethylphenylboronic acid unexpectedly resulted in low enantioselectivity (82% ee) (**3x**). Furthermore, heterocyclic boronic acids, *e.g.* 3-furyl and 3-thiophenyl boronic acids, proved to be compatible substrates, providing corresponding α-hydroxy ketones **3y** and **3z** with moderate yields and enantiomeric excesses. Benzo-heterocyclic and 9*H*-fluorenyl-derived boronic acids were also well-tolerated, affording the desired products (**3aa–3hh**) in excellent yields with good enantiopurity. However, 2-pyridinylboronic acid failed to give the desired product. When substituted naphthyl-2-boronic acids containing various functional groups were subjected to the optimal conditions, the corresponding products (**3ii–3oo**) maintained both good stereoselectivity and high yields. We further evaluated the scope of bridged [2.2.1]diketones. All tested naphtho- and substituted benzo-derivatives were smoothly converted to their corresponding alcohols (**3pp–3ss**) with good yields and high enantiomeric excesses. In contrast to **1a**, bicyclo[2.2.1]hept-5-ene-2,3-dione, which lacks the fused benzene ring, afforded only a trace mixture, likely comprising the *exo* and *endo* isomers.

To demonstrate the synthetic utility of these compounds, we performed a series of transformations, as shown in Scheme 3. The hydroxyl group in compound **3a** could be methylated with methyl iodide to afford methyl ether in moderate yield. Notably, treatment of **3a** with $TMSN_3$ in $HFIP/CF_3CO_2H$ produced compound **5** with inversion of the corresponding chiral center from *S* to *R* configuration, suggesting the involvement of a carbocation intermediate. Subsequently, compound **4** was subjected to reduction with SmI_2 in a THF/MeOH mixed solvent, furnishing the corresponding ketone **6** in 99% yield. Deprotonation of **6** with NaH, followed by a reaction with $PhNTf_2$, yielded trifluoromethanesulfonate **7** in a moderate yield. This intermediate was further utilized in a palladium-catalyzed coupling reaction with diphenylphosphine oxide, followed by reduction, to deliver a chiral phosphine **9**. Additionally, compound **6** smoothly underwent Baeyer–Villiger oxidation: treatment with $MMPP{\cdot}6H_2O$ in methanol provided good



Scheme 3 Synthetic applications.



Scheme 4 Plausible catalytic cycle.

chemoselectivity, with compound **11** as the major product (**10** : **11** = 1 : 8.3), while the reaction involving *m*-CPBA as the oxidant delivered a mixture of **10** and **11** with low regioselectivity (see the SI for details). Notably, Baeyer–Villiger oxidation of **4** with either MMPP·6H_2O or *m*CPBA was unsuccessful, resulting in a complicated mixture.

Based on the above results, previous work, and relevant literature,[14,15] we propose a plausible mechanism for this arylation process (Scheme 4). The catalytic cycle begins with the formation of the active catalyst complex **M2**, which is generated from precatalyst **M1** through dissociation of one molecule of the biphosphine ligand **L1**. This is followed by intramolecular coordination of the remaining phosphine at the bridging site of the dirhodium core. Subsequent transmetalation of **M2** with arylboronic acid, activated by a fluoride anion, produces the arylrhodium species **M3**. This intermediate then undergoes stereoselective 1,2-addition to a diketone substrate, forming the alkoxide complex **M4**. Finally, hydrolysis of **M4** releases an enantioenriched product while regenerating the active catalyst **M2**, thus completing the catalytic cycle.

Conclusions

In summary, we have developed a $Rh_2(CF_3CO_2)_4$/(*R*)-BTFM-GarPhos-catalyzed enantioselective arylation of benzobicyclo[2.2.1]heptane-2,3-diones. The incorporation of CF_3CO_2Na as an additive significantly enhanced reaction efficiency without compromising stereoselectivity. This protocol provides expedient access to enantioenriched [2.2.1]-bridged bicyclic compounds with good yields and enantioselectivity across a diverse array of arylboronic acids and diketone substrates. The synthetic versatility of these enantioenriched products was demonstrated through various transformations, including the synthesis of a chiral phosphine ligand.

Author contributions

S. Zhan: methodology, investigation, data curation, and writing – original draft. C. Wang: methodology and investigation. L. Duan: supervision and funding acquisition. Z. Gu: conceptualization, funding acquisition, writing – original draft, and writing– review & editing. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

CCDC 2452797 and 2452798 contain the supplementary crystallographic data for this paper.[16a,b]

The data that support the findings of this study are available in the SI or on request from the corresponding authors. Supplementary information contains experimental procedures, new compounds characterization data, and copies of NMR spectra and HPLC traces. See DOI: https://doi.org/10.1039/d5sc03779d.

Acknowledgements

The authors are grateful for financial support from the National Natural Science Foundation of China (22301291 and 22471254) and the Open Research Fund of the State Key Laboratory of Coordination Chemistry, School of Chemistry and Chemical Engineering, Nanjing University. This work was partially carried out at the Instruments Center for Physical Science, University of Science and Technology of China.

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