ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2024, **60**, 1448

Received 4th December 2023,
Accepted 3rd January 2024

DOI: 10.1039/d3cc05923e

rsc.li/chemcomm

Enantioselective synthesis of spiro-*N*,*O*-ketals *via* iridium and Brønsted acid co-catalyzed asymmetric formal [4+2] cycloaddition†

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We present an iridium and Brønsted acid co-catalyzed enantioselective formal [4+2] cycloaddition reaction of cyclic enamides with 2-(1-hydroxyallyl)phenols. This method yields a wide range of *N*-unsubstituted spiro-*N*,*O*-ketals, with good efficiency (up to 94%) and excellent enantioselectivities (most >95% ee). The protocol features easy scale-up and facile product derivatization.

Spiro-*N*,*O*-ketals are key structural motifs found in a wide range of pharmaceutical drugs and bioactive natural products,[1] such as penictrinine A,[2] marineosins A,[3] spirocollequins A,[4] and azaspiracid-1 (Fig. 1).[5] Given the significance of spiro-*N*,*O*-ketals, substantial efforts have been devoted to their synthesis. Apart from the intramolecular cyclization of well-designed starting materials,[6] several efficient metal-catalyzed cascade systems to access spiro-*N*,*O*-ketals using easily available fragments have been reported.[7] Nonetheless, much less attention has been dedicated to exploiting the asymmetric synthesis of chiral spiro-*N*,*O*-ketals. Indeed, unlike the non-asymmetric synthesis of spiro-*N*,*O*-ketals, the construction of chiral spiro-*N*,*O*-ketals is challenging because of the instability of the structure and the consequent difficulties in enantioselective control for establishing *N*- and *O*-substituted quaternary stereocenters.

In 2016, the Feng and Liu group first reported an elegant Au^{I}/Ni^{II} bimetallic relay asymmetric catalysis to synthesize [6,5]-spiro-*N*,*O*-ketals based on a dihydropyran subunit *via* a [4+2] cycloaddition (Scheme 1a).[8] Recently, the Deng group developed a stereoselective cycloisomerization–allylation–spiroketalization cascade transformation for bisbenzannulated [6,6]-spiro-*N*,*O*-ketals *via* Ir–Ag–acid combined catalysis with high diastereoselectivities and enantioselectivities (Scheme 1b).[9] However, despite the flexibility and modularity, the two strategies still have some limitations, such as the use of a bimetallic catalytic system with relatively high catalyst loadings, and limited access to *N*-substituted chiral spiro-*N*,*O*-ketals. Therefore, the development of an efficient catalytic enantioselective synthesis of spiro-*N*,*O*-ketals, especially *N*-unsubstituted ketals is imperative.

In recent years, metal-catalyzed asymmetric allylic substitution was recognized as a powerful tool for the enantioselective construction of C–C and C–X (X = heteroatom) bonds in organic synthesis.[10] In the combined iridium-acid catalytic system, hydroxyallyl phenols or anilines can react to generate the active allylic carbon–oxygen dipoles, which are employed to synthesize chiral heterocycles, such as tetrahydroquinazolines, dihydroquinazolinones.[9,11] However, applying such a strategy to the synthesis of chiral spiro-heterocycles remains challenging, and reports of highly enantioselective synthesis of *N*-unsubstituted chiral spiro-*N*,*O*-ketals are scant.[12]

In addition, 3-methylene isoindolones are stable and readily available feedstocks and have been employed as potential two-carbon synthons in cycloaddition reactions due to the push–pull properties of their double bonds.[13] In this regard, we expected to harness the power of such reactive Ir-π-allyl-oxa-dipoles and the good reactivity of 3-methylene isoindolones to construct the unique chiral N–H spiro-*N*,*O*-ketals enantioselectively through formal [4+2] cycloaddition (Scheme 1c). Herein, we report an iridium and Brønsted acid co-catalyzed asymmetric formal [4+2] cycloaddition of enamides with 2-(1-hydroxyallyl)phenols to synthesize a wide range of chiral spiro-*N*,*O*-ketals in good yields and excellent enantioselectivities.

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† Electronic supplementary information (ESI) available: Experimental procedures, compound characterization and copies of NMR spectra. CCDC 2310615 and 2310616. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3cc05923e

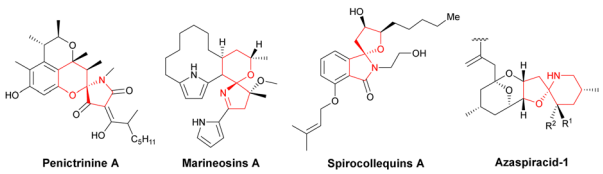
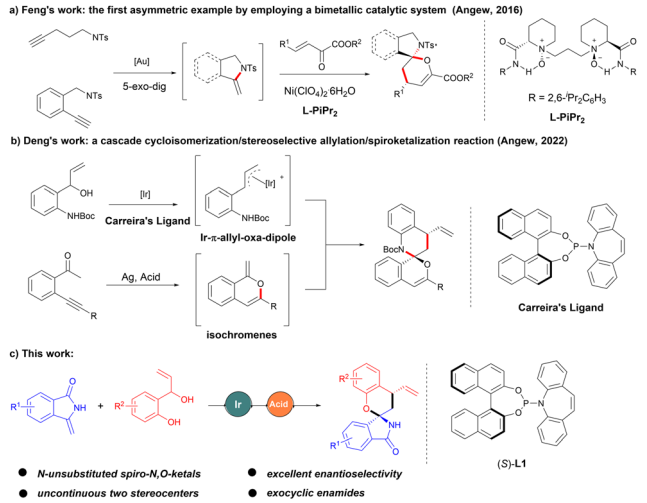


Fig. 1 Selected biologically active spiro-*N*,*O*-ketals.

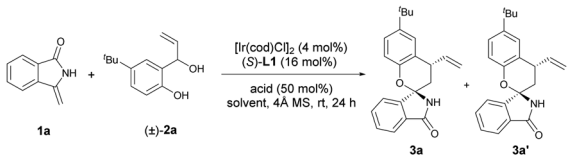


Scheme 1 Synthetic strategies for chiral spiro-*N*,*O*-ketals. (a) Feng's work; (b) Deng's work; (c) our strategy.

To test our reaction hypothesis, enamide **1a** and racemic alcohol **2a** were employed as the substrates (Table 1). When using $[Ir(cod)Cl]_2$, Carreira's P-olefin ligand (*S*)-**L1**, and the acid promoter $(PhO)_2POOH$ as the catalytic system, the expected asymmetric cycloaddition proceeded successfully, to afford the desired spiro-*N*,*O*-ketal product **3a** in 55% yield with 1.8 : 1 dr and 34%/39% ee (entry 1). Next, various solvents were examined (entries 2–6), and it was found solvent effects on the reactivity and enantioselectivity were significant. Compared to other solvents, dichloromethane (DCM) and dimethylsulfoxide (DMSO) resulted in significantly lower yields (entries 2 and 3). When toluene and MeOH were used, the ee values of **3a** increased, albeit with moderate yields (entries 4 and 5). Acetone was the optimal choice (entry 6, 77% yield, 96%/97% ee). Subsequently, various acid promoters were tested to improve reaction efficiency. Although $^{n}Bu_4NHSO_4$ proved ineffective in this reaction (entry 7), other strong (camphorsulfonic acid, TsOH) and weak acid ($PhCO_2H$) led to decreased yields and ee values (entries 8–10). However, none of them could afford results superior to $(PhO)_2POOH$ in terms of yield and stereoselectivity. Furthermore, lowering or elevating the reaction temperature decreased the enantioselectivity or yield (entries 11 and 12). Gratifyingly, the best enantioselective control (98%/99% ee) was achieved by further increasing the acid loading and reaction concentration without much loss in reaction efficiency (entries 13 and 14). Chiral phosphoric acids were also screened and some of them could improve the diastereoselectivity to some degree, yet with unsatisfactory yields or ee values (see Table S1, ESI†).

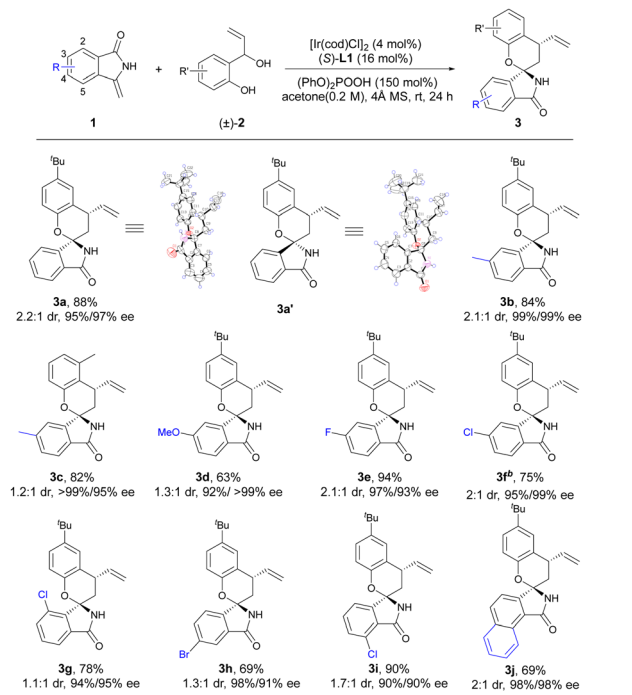
With the optimal reaction conditions in hand (Table 1, entry 14), we investigated the scope of enamides (Scheme 2). A range of enamides **1** bearing electron-donating groups (methyl or methoxy) on the phenyl ring showed good reactivity in this asymmetric spirocyclization reaction; specifically, **3b**–**3d** were delivered in moderate to good yields (63–84%) and excellent enantioselectivities (92% to >99% ee). The enamide bearing fluoro substituent reacted smoothly with **2a** to furnish **3e** with excellent yield (94%), indicating that the electronic properties

Table 1 Optimization of reaction conditions[a]



Entry	Acid	Solvent	Yield (%)	dr	ee (%)
1	$(PhO)_2POOH$	DCE	55	1.8 : 1	34/39
2	$(PhO)_2POOH$	DCM	21	1.9 : 1	71/77
3	$(PhO)_2POOH$	DMSO	14	1.8 : 1	85/99
4	$(PhO)_2POOH$	Toluene	60	1.3 : 1	66/91
5	$(PhO)_2POOH$	MeOH	47	1.6 : 1	92/99
6	$(PhO)_2POOH$	Acetone	77	1.5 : 1	96/97
7	$^{n}Bu_4NHSO_4$	Acetone	Trace	—	—
8	CSA	Acetone	60	1.5 : 1	93/96
9	TsOH	Acetone	30	2 : 1	70/96
10	PhCOOH	Acetone	13	1.6 : 1	93/99
11[b]	$(PhO)_2POOH$	Acetone	80	1.7 : 1	95/77
12[c]	$(PhO)_2POOH$	Acetone	57	2.6 : 1	91/97
13[d]	$(PhO)_2POOH$	Acetone	67	2.4 : 1	98/98
14[de]	$(PhO)_2POOH$	Acetone	78	2.3 : 1	98/99

[a] Reaction conditions: **1a** (0.05 mmol), (±)-**2a** (0.10 mmol), $[Ir(cod)Cl]_2$ (4 mol%), (*S*)-**L1** (16 mol%), acid (50 mol%) and 4 Å MS (15 mg) in solvent (0.5 mL) at room temperature (rt) for 24 h. The yields and dr values were determined by ^1H NMR analysis. The ee values were determined by HPLC analysis. [b] 0 °C. [c] 40 °C. [d] 150 mol% $(PhO)_2POOH$. [e] 0.25 mL.

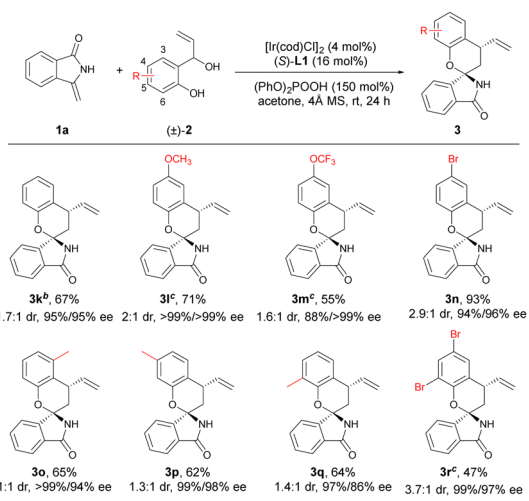


Scheme 2 Reaction scope of asymmetric spirocyclization reaction with enamides.[a] Reaction conditions: **1** (0.4 mmol), (±)-**2a** (0.8 mmol), $[Ir(cod)Cl]_2$ (4 mol%), (*S*)-**L1** (16 mol%) at rt for 24 h. Isolated yields. [b] $[Ir(cod)Cl]_2$ (10 mol%), (*S*)-**L1** (40 mol%).

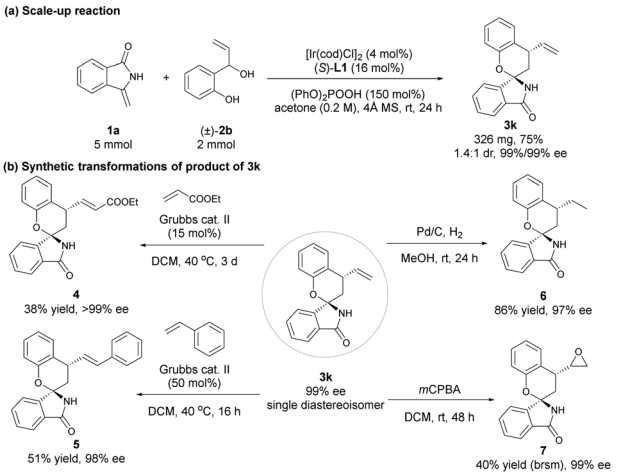
of enamide have a significant influence on the reaction. Furthermore, substituents at the C4, C5, C3 or C2 position of the phenyl ring were found to provide the corresponding chiral spiro-*N*,*O*-ketals **3f**–**3i** in moderate to good yields (69–90%) and excellent ee values, which suggests that steric hindrance does not affect the reaction. Moreover, naphthalene nucleus spiroketal **3j** could also be obtained with good efficiency using the current method. The absolute configuration of the spiro-*N*,*O*-ketal products were determined by the single crystal X-ray structure analysis of **3a** and **3a′** (see ESI†).

To broaden the scope of this asymmetric [4+2] cycloaddition, we examined the reactions of 2-(1-hydroxyallyl)phenols (Scheme 3). First, the electronic properties of the substituents at the 4-position of the aryl ring in **2** were investigated. Methoxy, trifluoromethoxyl, and bromo groups proceeded smoothly as well to give enantioenriched adducts **3l**–**3n** in 55–93% yield with 88–99% ee. In addition, substrates with different substituents at the C3, C5, and C6 positions maintained excellent enantioselectivity and moderate yields (**3o**–**3q**, 62–65% yield). It should be noted that dihalogen substitution was also compatible with this reaction, furnishing **3r** with excellent enantioselectivity (99%/97% ee), albeit in a slightly reduced yield.

The developed asymmetric [4+2] cycloaddition was further applied and elaborated with potential synthetic transformations in Scheme 4. Spiroketal **3k** was obtained in a good yield in a scaled-up (2 mmol) reaction with excellent enantioselectivity (Scheme 4a). In addition, a series of synthetic transformations of **3k** with a single diastereoisomer were explored (Scheme 4b). The olefin cross-metathesis reaction provided spiroketals **4** and **5**, respectively maintaining high ee values. In the presence of Pd/C, the hydrogenation of ethenyl moiety of **3k** proceeded smoothly, delivering spiroketal **6** in 86% yield with 97% ee. The



Scheme 3 Reaction scope of asymmetric spirocyclization reaction with 2-(1-hydroxyallyl)phenols.[a] Reaction conditions: **1** (0.4 mmol), (±)-**2a** (0.8 mmol), $[Ir(cod)Cl]_2$ (4 mol%), (*S*)-**L1** (16 mol%) at rt for 24 h. Isolated yields. [b]**1a** (1.0 mmol), (±)-**2b** (0.4 mmol). [c]$[Ir(cod)Cl]_2$ (10 mol%), (*S*)-**L1** (40 mol%).

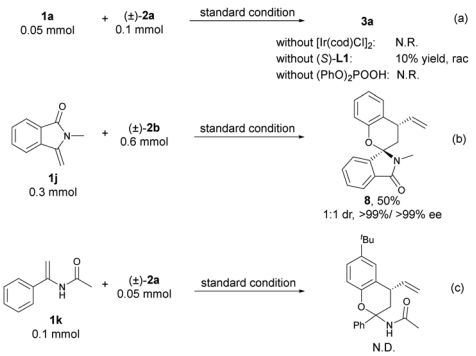


Scheme 4 Scale-up reaction and synthetic transformations of products. (a) Scale-up reaction; (b) synthetic transformations.

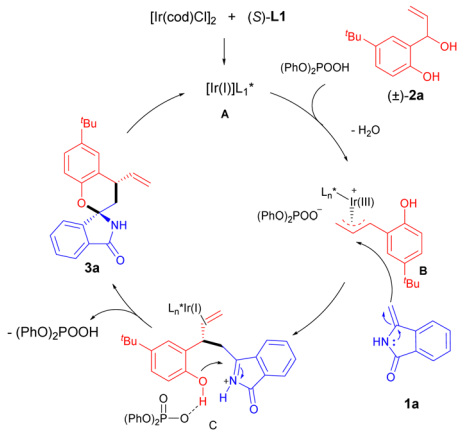
Prilezhaev epoxidation of alkene **3k** was carried out with excellent enantioselectivity (99% ee), albeit only in acceptable yield.

Control experiments were carried out to gain some insight into the mechanism. The reactions in Scheme 5a show that the no desired product could be detected without using $[Ir(cod)Cl]_2$ or $(PhO)_2POOH$. Moreover, in absence of the chiral ligand (*S*)-**L1**, **3a** racemates were obtained with sharp lower efficiency. Notably, *N*-methyl-protected enamide was also tolerated in the reaction to provide the expected spiro-*N*,*O*-ketals **8** with excellent ee values, suggesting that the N–H group of 3-methylene isoindolinone is not indispensable for this asymmetric [4+2] cycloaddition (Scheme 5b). However, when an acyclic enamide was used under the optimal conditions, the corresponding *N*,*O*-ketal was not detected (Scheme 5c).

Based on the observations described above and the literature precedent,[9,11c,13a,c] a putative mechanism was proposed (Scheme 6). First, with the aid of $(PhO)_2POOH$, the chiral Ir(I) species **A** activates **2a** to produce π-allyl-Ir species **B**, simultaneously generating of H_2O and the anion of the acid. Subsequently, the enantioselective nucleophilic attack from **1a** to the allylic iridium species **B** provides the iminium intermediate **C** with excellent enantioselectivity. Finally, spiroketalization delivered the



Scheme 5 Control experiments. (a) Control experiments; (b) reaction of **1j** and **2b**; (c) reaction of **1k** and **2a**.



Scheme 6 Proposed reaction mechanism.

final diastereomer **3a** with excellent enantioselectivity and regenerated the Ir catalyst and $(PhO)_2POOH$.

In summary, we established an asymmetric iridium/Brønsted acid co-catalyzed [4+2] cycloaddition of enamides with 2-(1-hydroxyallyl)phenols for the synthesis of chiral *N*-unsubstituted spiro-*N*,*O*-ketals. A series of structurally novel chromane-2,1′-isoindolins were smoothly obtained with good efficiency (up to 94%) and high enantioselectivities (most >95%). The utility of this protocol was demonstrated by the millimole experiment and a variety of useful transformations.

This work was supported by the National Natural Science Foundation of China (no. 22201073, 21925201 and 2216116 0319) and the Fundamental Research Funds for the Central Universities. We thank the Research Center of Analysis and Test of East China University of Science and Technology for help in the characterization.

Conflicts of interest

There are no conflicts of interest.

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