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Rhodium(III)-catalyzed asymmetric [4+1] spiroannulations of *O*-pivaloyl oximes with α-diazo compounds†

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Chiral Rh^{III} catalysts can catalyze the asymmetric [4+1] spiroannulation of *O*-pivaloyl oximes with α-diazo homophthalimides under redox-neutral and acid/base-neutral conditions, leading to formation of chiral spirocyclic imines as a result of C–H activation and N–O cleavage. The reaction proceeded with high efficiency and features broad substrate scope, mild reaction conditions, and high to excellent enantioselectivities.

Spirocycles are commonly encountered structural motifs that have found wild applications in synthetic chemistry. Their unique 3D structures may impart diversified biological, chemical, and photochemical properties in various natural and synthetic compounds. Thus, they have also been used as key intermediates during synthesis and development of drug molecules.[1] Chiral spirocycles have also attracted much attention as prevalent scaffolds of chiral ligands.[2] A number of synthetic strategies have been documented to access spirocycles.[3] They can be prepared through alkylation, metal-catalyzed reactions, and cycloaddition reactions. Despite these synthetic routes, many of them suffer from employment of highly functionalized reagents and lengthy procedures with generation of waste. Therefore, atom- and step-economic catalytic synthesis of spirocycles with a quaternary carbon center in a regio- and stereocontrolled fashion remains an ongoing theme.

In the past decade, metal-catalyzed and chelation-assisted C–H bond functionalization has been developed as an increasingly important strategy for the construction of complex (hetero)cyclic molecules, including spirocyclic scaffolds.[4] Of note, rhodium(III) cyclopentadienyl complexes have been established as one of most efficient catalysts for synthesis of spirocyclic compounds *via* a C–H activation pathway.[5] By following this strategy, arenes bearing a heteroatom directing group have been successfully employed for the synthesis of various spirocyclic skeletons *via* coupling with unsaturated reagents such as alkynes, alkenes, and α-diazocarbonyl compounds.[6] Meanwhile, the discovery of chiral rhodium catalysts has opened a new avenue to access chiral polycyclic scaffolds.[7–11] In 2015, You and coworkers developed the first enantioselective dearomatization reaction of 2-naphthols for the synthesis of spirocyclic enones in excellent enantioselectivities (Scheme 1a).[6b] By using enol as a coordinating group, the Lam group realized Rh(III)-catalyzed enantioselective synthesis of spirocyclic indenes (Scheme 1a).[12] In 2019, the Waldmann group disclosed a related enantioselective [3+2] spiroannulation *via* formal C(sp^3)–H bond activation (Scheme 1a).[6c] Very recently, we realized oxidative [4+1] spiroannulation of nitrone and quinone diazides, which occurred *via* initial C–H arylation followed by axial-to-central chirality transfer (Scheme 1b).[13] Thus, these spirocyclic products were mostly constructed under oxidative conditions. On the other hand, in 2014 Cramer reported the [4+1] annulation of *N*-*O*Piv benzamides and diazo compounds for enantioselective synthesis of lactams.[14] Later, the arene substrate was extended to indoles by Song and coworkers.[11a] Our objective was to construct aza-spirocycles on different platforms *via* C–H activation assisted by other readily available oxidizing directing groups. As integration of eco-friendly synthesis of spirocycles and asymmetric C–H bond activation, we now report Rh(III)-catalyzed enantioselective [4+1] spirocyclization between *O*-pivaloyl oximes and α-diazo homophthalimides (Scheme 1c).

We initiated our studies using *O*-pivaloyl oxime **1a** as a model substrate, and its [4+1] spiroannulation with α-diazo homophthalimides was explored using the Cramer-type $Cp^XRh(III)$ catalysts (Table 1).[7c,d] The desired product (*R*)-**3** was obtained with generally good enantioselectivity and efficiency when (*R*)-**Rh2** was used in various solvents (entries 1–5), and

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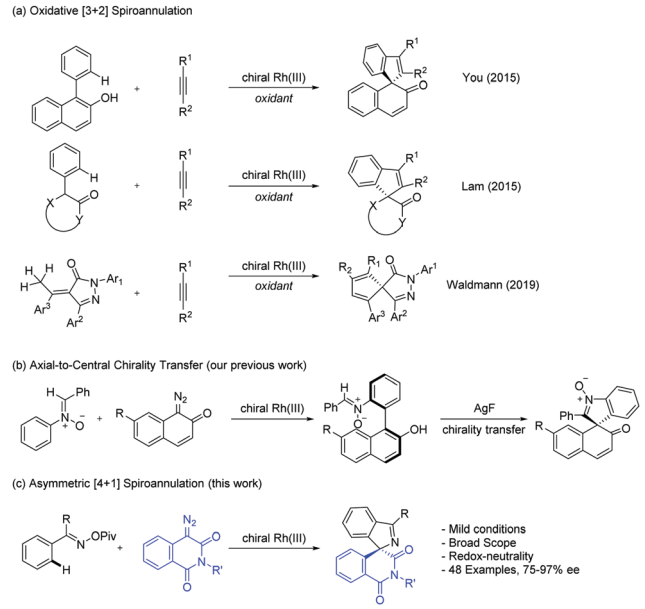


Scheme 1 Rhodium(III)-catalyzed C–H bond functionalization–spiroannulation.

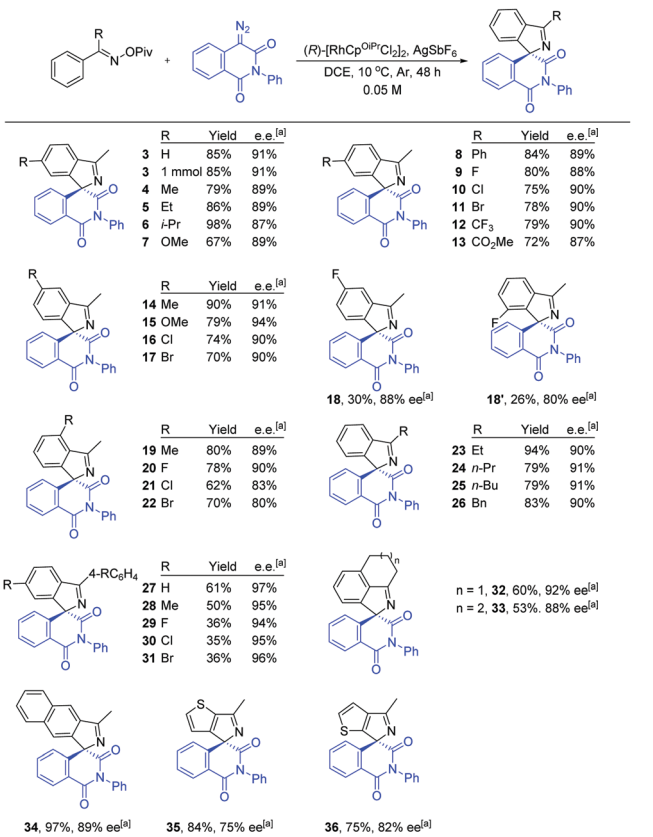
DCE seemed to outperform other solvents. The reaction temperature and additives were also screened (entries 5–8 and 9–14), and the enantioselectivity only slightly varied. To our delight, both high enantioselectivity and yield were maintained when the catalyst loading was lowered to 4 mol% even in the absence of any acid/base additive (entry 15). In contrast, replacing the catalyst with (*R*)-**Rh1** and (*R*)-**Rh3** gave lower enantioselectivities (see the ESI†).

Table 1 Optimization studies[a]

Entry	Additive	Solvent	*T* (°C)	Yield[b] (%)	ee[c] (%)
1	Li_2CO_3	PhCl	40	72	89
2	Li_2CO_3	TFE	40	65	75
3	Li_2CO_3	Et_2O	40	81	87
4	Li_2CO_3	EtOAc	40	80	80
5	Li_2CO_3	DCE	40	83	90
6[c]	Li_2CO_3	DCE	25	83	90
7[c]	Li_2CO_3	DCE	10	84	91
8[c]	Li_2CO_3	DCE	0	75	92
9[c]	LiOAc	DCE	10	72	88
10[c]	K_2CO_3	DCE	10	50	90
11[c]	Cs_2CO_3	DCE	10	NR	—
12[c]	HOAc	DCE	10	80	84
13[c]	PivOH	DCE	10	81	89
14[c]	—	DCE	10	83	91
15[cd]	—	DCE	10	85	91

[a] Reaction Conditions: **1a** (0.06 mmol), **2a** (0.05 mmol), (*R*)-**Rh2** (5 mol%), $AgSbF_6$ (20 mol%), additive (1.0 equiv.), solvent (1 mL), under Ar for 24 h. [b] Isolated yield. [c] Under Ar for 48 h. [d] (*R*)-**Rh2** (4 mol%) and $AgSbF_6$ (16 mol%) were used.

With the establishment of the optimal reaction conditions, we next investigated the scope of the *O*-pivaloyl oximes (Scheme 2). It was observed that introduction of various electron-donating, -withdrawing, and halogen groups at the *para* position of the phenyl ring gave consistently good yields and excellent enantioselectivities (**3–13**, 87–91% ee). Of note, a 1.0 mmol scale synthesis of product **3** also proved to be successful, with no deterioration of the yield or enantioselectivity. We also found that oxime esters bearing a *meta* methyl, methoxy, and halogen group also reacted efficiently (**14–17**) in comparably excellent enantioselectivity (70–90% yields, 90–94% ee). In contrast, *ortho*-fluorine substituted *O*-pivaloyl oxime (**1s**) underwent the C–H annulation with low regioselectivity and slightly lower enantioselectivity (**18** and **18′**). The presence of methyl and halogen group at the *ortho* position was also tolerated (**19–22**). No deterioration of the enantioselectivity was observed with different alkyl substitutions (**23–26**). Our studies further revealed that symmetrical benzophenone-derived *O*-pivaloyl oximes were tolerated giving moderate to good yields and excellent enantioselectivities (**27–31**, 94–97% ee). In addition, cyclic *O*-pivaloyl oximes also reacted smoothly with **2a**, affording products **32** and **33** with 88% and 92% ee, respectively. When 2-naphthyl-substituted *O*-pivaloyl oxime was employed, the corresponding spirocyclic product **34** was also obtained (97% yield, 89% ee). Furthermore, heteroatomic



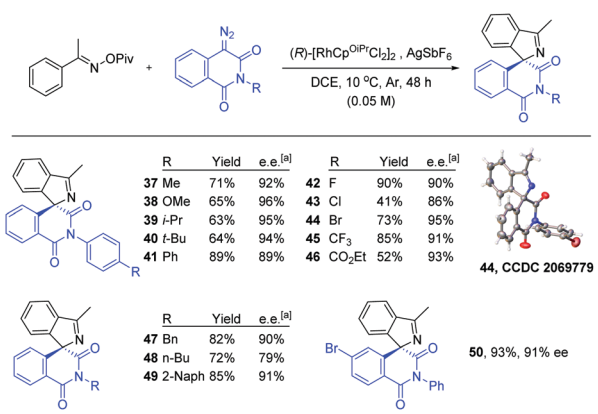
Scheme 2 Scope of *O*-pivaloyl oximes in spiro compounds synthesis. Reaction conditions: **1** (0.12 mmol), **2** (0.10 mmol), (*R*)-**Rh2** (4 mol%), and $AgSbF_6$ (16 mol%) in DCE (2 mL) under Ar for 48 h, isolated yield.

substrate such as thienyl ring, afforded the corresponding products with lower enantioselectivity (**35** and **36**).

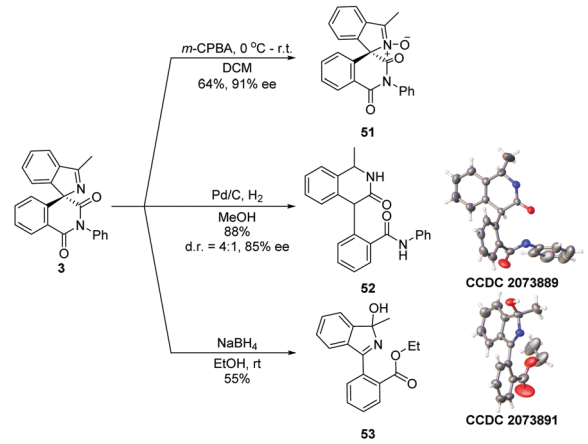
Next, we investigated the scope of the diazo compounds. As shown in Scheme 3, introduction of various electron-donating, -withdrawing, and halogen groups to the *N*-phenyl ring allowed the coupling to gave the desired products in good to excellent yields and high enantioselectivities (**37**–**46**, 86–96% ee), which revealed that the reaction efficiency was slightly affected by the electronic effect. Meanwhile, the absolute configuration of the product **44** was assigned as (***R***) by X-ray crystallography (CCDC† 2069779). Moreover, variation of the N-substituent to –Bn (**47**) and 2-Naph (**49**) group all led to high yields (82% and 85%, respectively) and enantioselectivities (90% ee and 91% ee, respectively). However, lower enantioselectivity (79% ee) was obtained for the *N*-^{n}Bu (**48**) diazo compound, indicative of the electronic effect. Examination of the 6-substituent in the diazo compound revealed compatibility of bromo group (**50**, 91% ee).

To demonstrate the synthetic utility of the reaction system, the synthetic transformations of **3** was conducted (Scheme 4). Treatment of **3** with *m*-CPBA afforded the oxidation product *N*-oxide **51** in 64% yield without loss of the enantiopurity. Pd/C-catalyzed reduction of **3**, surprisingly, afforded a ring-opening and ring-expansion product **52** (CCDC† 2073889) in 88% yield (4 : 1 dr), which may occur *via* C=N reduction and C–N reductive cleavage. Treatment of **3** with $NaBH_4$ in EtOH led to ring-opening of the imide group with incorporation of the solvent, affording hemiaminal **53** in 55% yield, and the structure of **53** (CCDC† 2073891) was determined by X-ray crystallography.

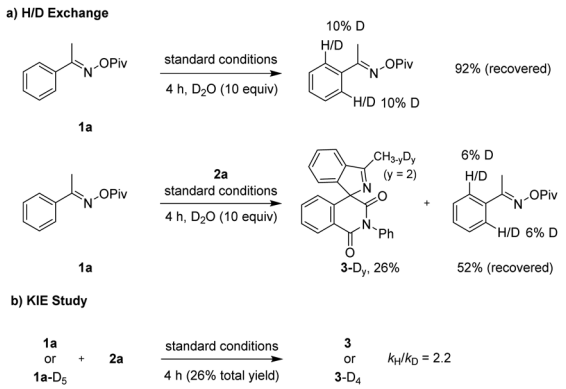
To shed light on the mechanism of this spirocyclization reaction, we carried out several experimental studies (Scheme 5). First, H/D exchange of **1a** was carried out in the presence of D_2O, the reactant was recovered in 92% yield and the ^{1}H NMR analysis revealed slight deuteration at the *ortho* positions of the phenyl ring, suggesting reversibility of the C–H cleavage. Second, another H/D exchange in the presence of **2a** was conducted under the standard conditions, affording compound **3**-D_y (D_y is a statistical average value of compound **3**-D_y), and the deuterium incorporation was observed at



Scheme 3 Scope of diazo compounds in spiro compounds synthesis (see Scheme 2 for reaction conditions).



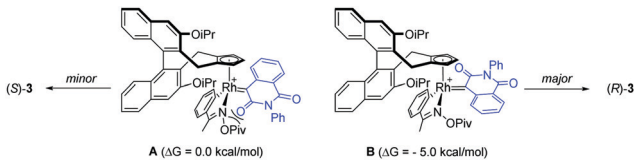
Scheme 4 Synthetic transformations of compounds **3**.



Scheme 5 Preliminary mechanistic studies.

the methyl group probably due to acidity of the α-methyl group.[15] Two parallel reactions of **1a** and **1a**-D_5 with **2a** were performed for kinetic isotope effect, and the k_H/k_D = 2.2 was obtained at a low conversion under the standard conditions, suggesting that the *ortho* C–H activation event might be involved in the turnover-limiting step.

On the basis of the previous reports,[11a,14] the enantioselectivity for the (*R*)-**3** formation may be explained by the following stereochemical model (Scheme 6). Following the C–H bond activation and formation of the carbene species, both intermediates **A** and **B** can be possible. Regarding the subsequent migratory insertion, the intermediate **B** is preferred likely because of the reduced steric interaction between the OPiv group and the carbene ligand as we have previously proposed in the [4+1] annulation of quinone diazides,[13] eventually leading



Scheme 6 Plausible stereochemical model of the chiral induction.

to the major product (*R*)-**3**. Indeed, our DFT studies revealed that the intermediate **B** is 5.0 kcal mol^{-1} more stable, and this may also suggest a lower kinetic barrier during the migratory insertion of the intermediate **B**.

In summary, we have developed an efficient and mild protocol for the enantioselective synthesis of spirocyclic imines through a procedure of rhodium-catalyzed enantioselective C–H functionalization and N–O cleavage. This asymmetric [4+1] spiroannulation occurred under redox-neutral and acid/base additive-free conditions *via* C–H bond activation of the oxime ester with cyclic α-diazo compounds as a coupling reagent. The reaction proceeded in high efficiency and features broad substrate scope, mild and redox-neutral reaction conditions, and high to excellent enantioselectivities. Further development of new reaction modes of rhodium-catalyzed enantioselective C–H activation reactions is underway in our laboratory.

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Conflicts of interest

The authors declare no competing financial interest.

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