Asymmetric Catalysis

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Enantioselective Synthesis of Spiroindenes by Enol-Directed Rhodium(III)-Catalyzed C–H Functionalization and Spiroannulation

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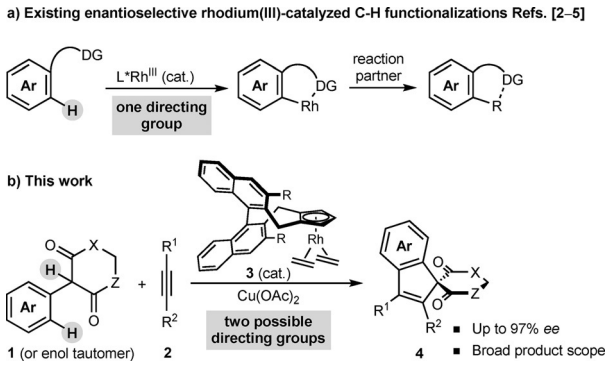
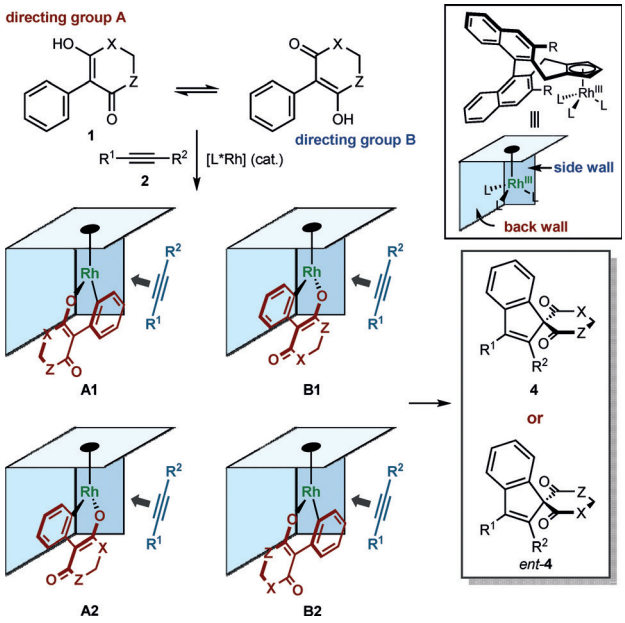
Abstract: *Chiral cyclopentadienyl rhodium complexes promote highly enantioselective enol-directed C(sp^2)-H functionalization and oxidative annulation with alkynes to give spiroindenes containing all-carbon quaternary stereocenters. High selectivity between two possible directing groups, as well as control of the direction of rotation in the isomerization of an O-bound rhodium enolate into the C-bound isomer, appear to be critical for high enantiomeric excesses.*

Cyclopentadienyl rhodium(III) complexes are well-established as highly active and versatile precatalysts in a diverse array of C–H functionalization reactions.[1] However, enantioselective variants of these reactions only became possible with the development of chiral C_2-symmetric cyclopentadienyl ligands by Ye and Cramer,[2] and an artificial Rh^{III}-containing metalloenzyme by Ward, Rovis, and co-workers.[3] To date, a handful of catalytic enantioselective Rh^{III}-catalyzed C–H functionalizations have been described,[2–5] but there is a compelling need to develop new processes to access novel classes of enantioenriched products.[6]

We recently reported Ru- and Pd-catalyzed oxidative annulations of α-aryl cyclic 1,3-dicarbonyl compounds (or their enol tautomers) with alkynes that provide achiral or racemic spiroindenes.[7] Given that indenes appear in several biologically active compounds,[8,9] the ability to prepare chiral spiro-fused indenes **4** by asymmetric C–H functionalization would be valuable.[4d,10] Because we also found that [{Cp*$RhCl_2$}$_2$] is an effective precatalyst,[7a,11] chiral cyclopentadienyl rhodium complexes **3** appeared to be highly promising for investigation. However, in contrast to existing enantioselective Rh^{III}-catalyzed C–H functionalizations, which all rely upon aryl C(sp^2)–H activation of substrates containing a single directing group (Scheme 1 a),[2–5] the substrates **1** required for our proposed study contain two potential directing groups (Scheme 1 b). Within the accepted model for enantioinduction using complexes **3**,[2b,5] cyclorhodation can generate up to four species, which differ in which directing group participates in cyclometallation, and/or the orientation of the rhodacycle within the chiral pocket (Scheme 2). This situation contrasts with existing processes,[2–5] including the dearomatizing oxidative spiroannulations of You and co-workers,[4d] in which only two conformations of one rhodacycle need to be considered. Given the possibility of other reaction pathways with potentially different stereochemical outcomes, the development of a highly enantioselective process was far from certain. Herein, we report the successful realization of asymmetric [3+2] spiroannulations to give a diverse range of spiroindenes in up to 97% *ee*.



Scheme 1. Enantioselective Rh^{III}-catalyzed C–H functionalizations.



Scheme 2. Possible species to consider upon cyclorhodation.

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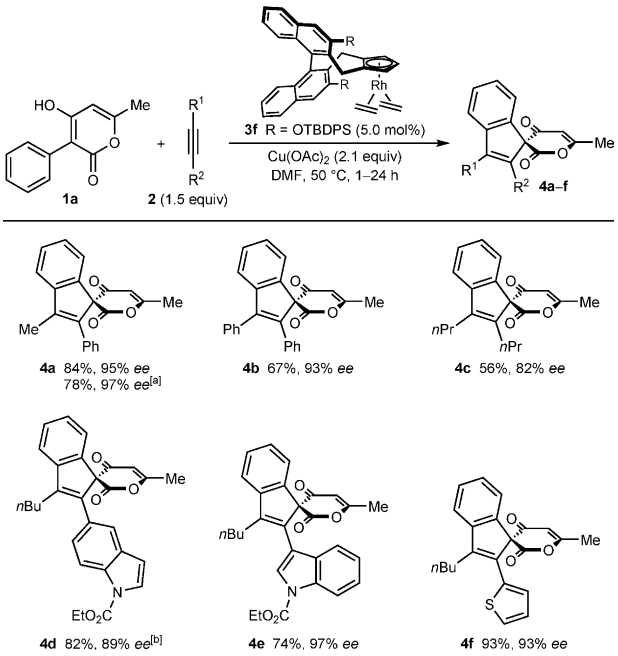
Our investigations began with an evaluation of chiral cyclopentadienyl rhodium complexes **3a**–**3f**[2b] in the reaction of 4-hydroxy-6-methyl-3-phenyl-2*H*-pyran-2-one (**1a**) with 1-phenylpropyne (**2a**, 1.5 equiv), using $Cu(OAc)_2$ (2.1 equiv) in DMF[12] at 50 °C for 24 h (Table 1). Benzoyl peroxide, which was employed as an additive in previous enantioselective Rh-catalyzed C–H functionalizations,[2,4] was unnecessary,[13] and in all cases, only one regioisomer of spiroindene **4a** was detected. The parent complex **3a** (R = H) gave **4a** in 93% NMR yield, but the enantioselectivity was moderate (entry 1).[14] Higher selectivities were obtained with complexes **3b–3f** containing larger groups at the 3,3′-positions (entries 2–6). The OTBDPS- containing complex **3f** was optimal, and provided **4a** in high NMR yield and 95% *ee* (entry 6).

With an effective chiral complex identified, the enantioselective spiroannulation of **1a** with various alkynes was explored (Scheme 3). With unsymmetrical alkynes, the regioselectivities of these reactions were excellent, and with the exception of spiroindene **4d**, which was formed as a 19:1 regioisomeric mixture, only single regioisomers were detected. With 1-phenylpropyne (**2a**), spiroindene **4a** was isolated in 84% yield and 95% *ee*. The same reaction run at room temperature provided **4a** in 78% yield and 97% *ee*. Diphenylacetylene reacted to give spiroindene **4b** in 67% yield and 93% *ee*, whereas a symmetrical dialkyl alkyne gave spiroindene **4c** in moderate yield and enantioselectivity. However, other alkyl/(hetero)aryl alkynes were excellent reaction partners. For example, alkynes containing 5-indolyl, 3-indolyl, or 2-thienyl substituents provided spiroindenes **4d**–**4f** in 74–93% yield and 89–97% *ee*.

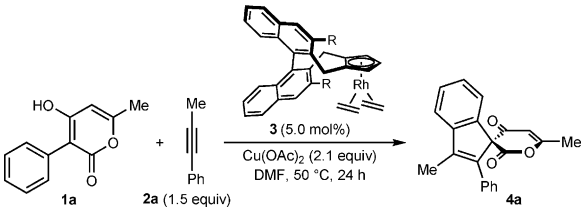
Various other substrates also underwent the spiroannulation with a range of alkynes to give spiroindenes containing ketoesters (**4g**–**4l**, **4q**, and **4r**), ketolactams (**4m**–**4p** and **4t**–**4v**), a diketone (**4s**), or a barbiturate (**4w**) with generally high enantioselectivities (Scheme 4). Although complex **3f** was generally effective, in some cases the less sterically hindered complex **3b** gave superior yields and enantioselectivities (**4t**–**4w**). The reason for the superiority of complex **3b** in these cases is not currently known. Substitution at the *meta*- or *para*-position of the α-phenyl group was tolerated (**4g**–**4i**). With a *meta*-CF_3 group, C–H functionalization occurred at the more sterically accessible site (**4g**).[14] In our previous oxidative annulation work,[7] only six-membered cyclic 1,3-dicarbonyl compounds were employed. Therefore, it is notable that, for the first time, five- and seven-membered substrates could be employed (**4l**, **4m**, and **4o**). The low yield of **4l** is attributed to its instability under the reaction conditions. Products containing the 1,3-dicarbonyl component within various polycyclic ring systems were also prepared (**4p**–**4r** and **4v**), although the enantioselectivities of **4p** and **4q** were more modest. A substrate in which the two possible directing groups are almost identical electronically, but sterically well-differentiated, gave spiroindene **4s** in 77% yield and a reasonable 78% *ee*. 1-Methyl-5-phenylbarbituric acid, in which the two carbonyl groups adjacent to the phenyl group are electronically and sterically similar, gave spiroindene **4w** with low enantioselectivity. Finally, several of the reactions could be carried out in dimethyl carbonate, a significantly more environmentally friendly solvent than DMF (**4i**, **4t**, and **4u**).[15]

To gain further insight into these annulations, deuteration reactions were conducted. Treatment of **1c** under the standard conditions in the absence of an alkyne but with the addition of D_2O for 4 h led to recovery of $[D]_n$-**1c** with 5% deuteration at the *ortho*-positions of the arene only (Scheme 5a). Furthermore, reaction of **1c** with alkyne **2f** under the



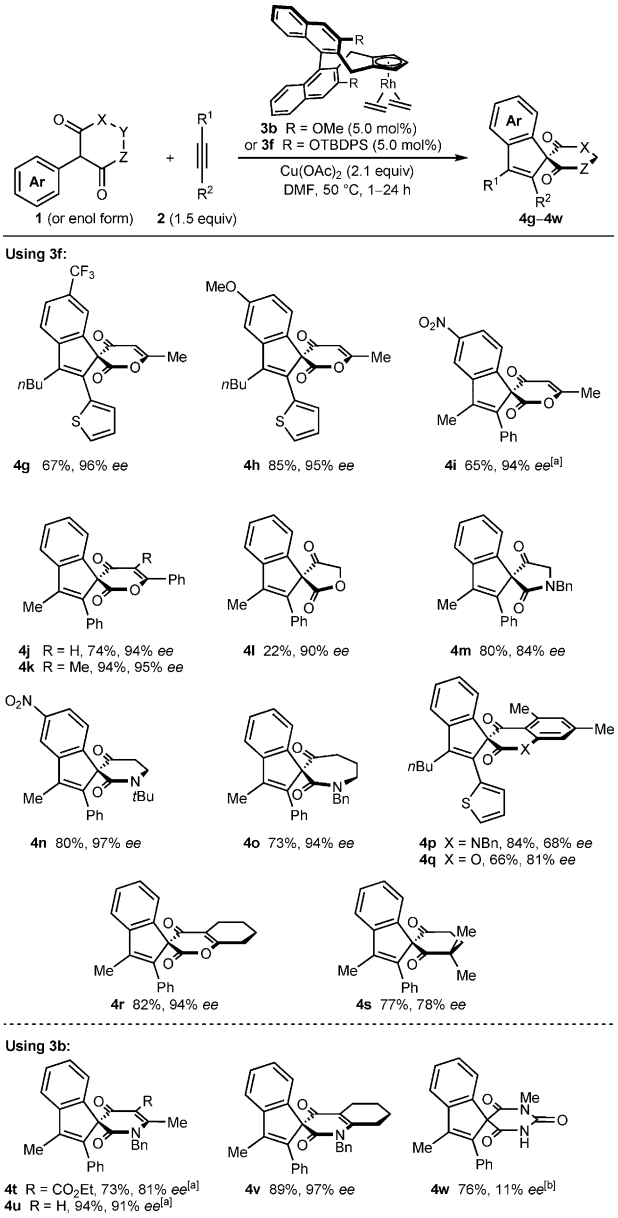
Scheme 3. Enantioselective oxidative annulations of **1a** with various alkynes. Reactions were conducted with 0.30 mmol of **1a**. Yields are of isolated products. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. [a] Conducted with 0.20 mmol of **1a** at room temperature for 24 h. [b] Formed as a 19:1 mixture of regioisomers as determined by ^{1}H NMR of the unpurified reaction mixture. The isolated product was also a 19:1 mixture of regioisomers.

Table 1: Catalyst evaluation in the reaction of **1a** with **2a**.[a]

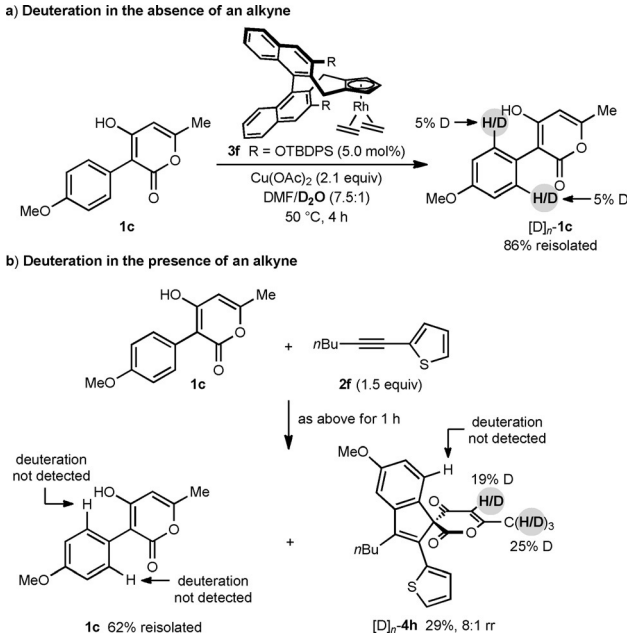


Entry	Rh complex **3**	NMR Yield [%][b]	*ee* [%][c]
1	**3a** R = H	93	58
2	**3b** R = OMe	97	90
3	**3c** R = O*i*Pr	33	78
4	**3d** R = Ph	41	88
5	**3e** R = OTIPS	84	92
6	**3f** R = OTBDPS	98	95

[a] Reactions were conducted with 0.05 mmol of **1a**. [b] Determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by HPLC analysis on a chiral stationary phase. TIPS = triisopropylsilyl, TBDPS = *tert*-butyldiphenylsilyl.



Scheme 4. Reactions were conducted with 0.20 or 0.30 mmol of **1** (see Supporting Information for details). Yields are of isolated products. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. [a] Dimethyl carbonate was used as the solvent. [b] The absolute stereochemistry of the major enantiomer of **4w** is not known.



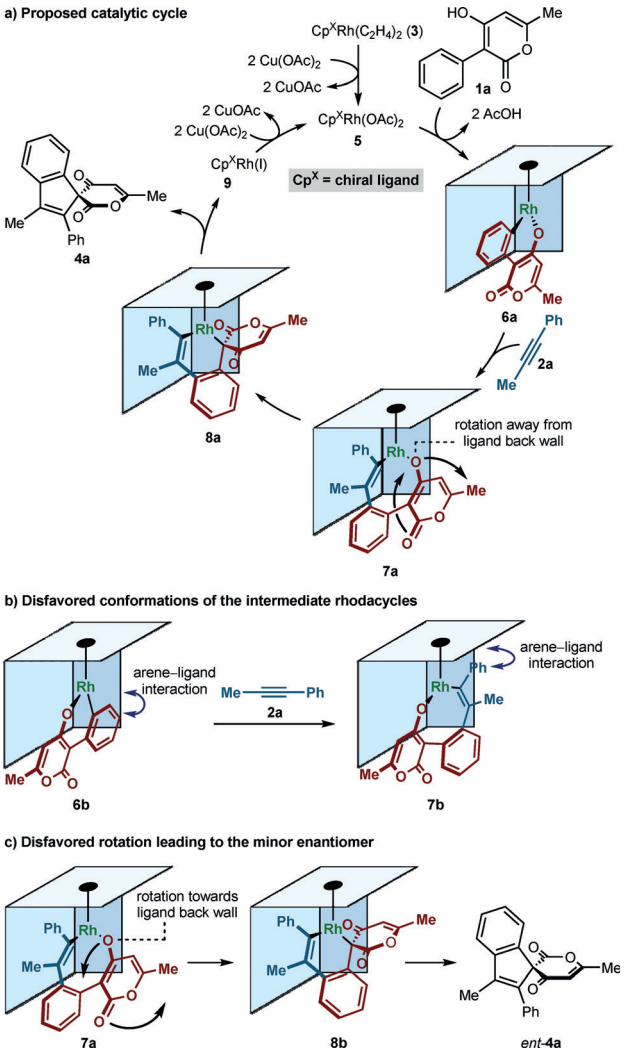
Scheme 5. Deuteration experiments.

same conditions led to recovered **1c** with no observable deuteration, and spiroindene $[D]_n$-**4h** that was partially deuterated at the pyran-2,4-dione ring[16] but not at the arene (Scheme 5b). Interestingly, the presence of D_2O decreased the regioselectivity of this reaction compared to the one conducted in DMF only (Scheme 4), and $[D]_n$-**4h** was isolated as an 8:1 mixture of inseparable regioisomers. The experiments shown in Scheme 5 suggest that cyclorhodation is largely irreversible under these conditions.

A proposed catalytic cycle and stereochemical model[14] for these reactions is shown in Scheme 6a, using **1a** and **2a** as representative substrates. After formation of rhodium diacetate complex **5**, we assume that cyclorhodation of **1a** is promoted by the most enolizable of the two possible directing groups, which is the enol derived from the ketone rather than the ester, to give rhodacycle **6a**. Coordination and migratory insertion of the alkyne would then give rhodacycle **7a**. The alternative conformations **6b** and **7b** appear to be disfavored because of steric interactions between the side wall of the cyclopentadienyl ligand with the metallated arene of **6b** or the phenyl substituent of **7b** (Scheme 6b). The next step is the isomerization of the *O*-bound rhodium enolate **7a** into the *C*-bound isomer **8a**, presumably through an oxa-π-allylrhodium species, which requires a rotation of the 4-alkoxypyran-2-one moiety. Because the rhodium alkoxide of this moiety is in closest proximity to the chiral ligand, it experiences the greatest steric interactions, and we propose there is a preference for this group to rotate away from the ligand to give **8a**. Reductive elimination of **8a** gives spiroindene **4a** and Rh^I species **9**, which is oxidized by $Cu(OAc)_2$ to regenerate **5**. The formation of the minor enantiomer from **7a** requires an unfavorable rotation of the rhodium alkoxide towards the back wall of the chiral ligand (Scheme 6c).

An alternative explanation that cannot be excluded is that migratory insertion of **6a** with the alkyne directly produces a rhodacycle with a conformation closely related to that of **7a**, but with the rhodium alkoxide already partially rotated away from the chiral ligand. Continued rotation of the 4-alkoxypyran-2-one moiety in the same direction, according to the principle of least motion,[17] would then give **8a**.

In conclusion, we have developed an enantioselective synthesis of spiroindenes from the oxidative annulation of α-aryl cyclic 1,3-dicarbonyl compounds (or their enol tautomers) with alkynes, using chiral cyclopentadienyl rhodium catalysts. The process tolerates a wide range of substrates to give diverse products containing all carbon-quaternary stereocenters with high enantioselectivities. Application of these



Scheme 6. Proposed catalytic cycle and stereochemical model.

chiral complexes in other classes of C–H functionalization/oxidative annulation is underway, and these results will be reported in due course.

Acknowledgements

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[13] We assume $Cu(OAc)_2$ oxidizes the precatalysts into the active Rh^{III} species.
[14] The absolute configurations of the spiroindenes prepared in this work were assigned by analogy to those of **4g**–**4j**, **4o**, and **4r**, which were determined by X-ray crystallography. CCDC 1415390, 1415391, 1415392, 1415393, 1415394, and 1415395 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
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