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Enantioselective Formal C(sp^3)-H Bond Activation in the Synthesis of Bioactive Spiropyrazolone Derivatives

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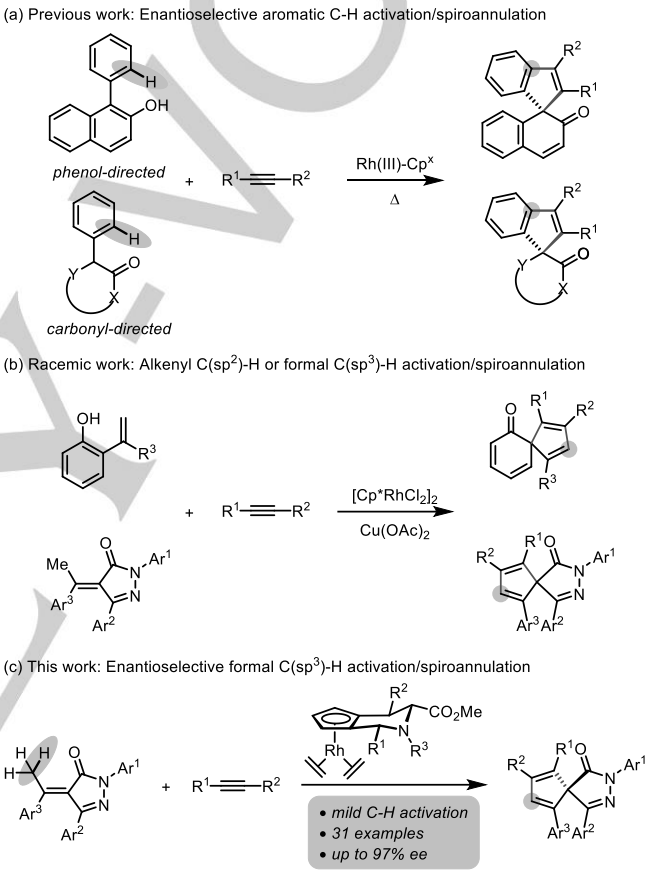
Abstract: Herein we report the first enantioselective annulation of α-arylidene pyrazolones through a formal C(sp^3)-H activation under mild conditions enabled by highly variable Rh(III)-Cp^x catalysts. The method has wide substrate scope proceeds with good to excellent yields and enantioselectivity. Its synthetic utility was demonstrated by late-stage functionalization of drugs and natural products as well as preparation of enantioenriched [3]-dendralenes. Preliminary biological investigation also identified the spiropyrazolones as a novel class of Hedgehog pathway inhibitors.

Rh(III)-catalyzed C-H bond activation followed by an annulation reaction with alkynes using cyclopentadienyl (Cp) rhodium(III) complexes as precatalysts has been explored as a rapid approach to construct various heterocycles and carbocycles.[1-4] Enantioselective variants have only become possible since the introduction of chiral *C*$_2$-symmetric Cp^x ligands by Cramer *et al.*, and of an artificial Rh(III)-containing metalloenzyme by Ward and Rovis *et al.*[5-10] Thereafter, You *et al.* reported the first asymmetric annulative dearomatization reaction of β-naphthols with alkynes using chiral Rh(III)-Cp^x catalysts (Scheme 1a).[7l] In addition, carbonyl-directed Rh(III)-catalyzed enantioselective C-H activation/spiroannulation reactions have been developed by Lam *et al.* followed by Yu *et al.*[7h,n] These spiroannulation reactions provide unique access to novel classes of enantioenriched spirocycles containing all-carbon quaternary centers. Current enantioselective variants all include direct activation of aromatic C(sp^2)-H bonds under relatively demanding reaction conditions (Scheme 1a).[7h,l,n] Rh(III)-catalyzed enantioselective spiroannulation reactions through activation of alkenyl C(sp^2)-H and alkyl C(sp^3)-H bonds still stand as a great challenge. Relevant racemic examples have already been demonstrated recently (Scheme 1b).[3a,b,d]



Scheme 1. Enantioselective C-H Activation/Spiroannulation Reactions Using Rh(III)-Cp^x Catalysts.

Recently we reported a novel class of piperidine-fused Cp^x ligands.[10a,11] We envisaged that the above-mentioned enantioselective spiroannulation reactions could be steered efficiently using our highly variable Rh(III)-Cp^x catalysts (Scheme 1c). Here we describe the first enantioselective annulation of α-arylidene pyrazolones through a formal C(sp^3)-H activation under mild conditions enabled by Rh(III)-Cp^x catalysts.[12]

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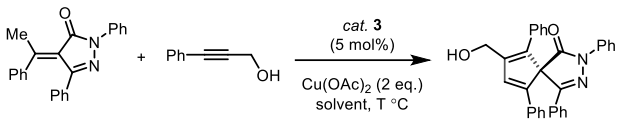
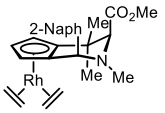
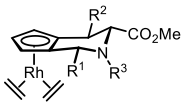
Table 1. Optimization of reaction conditions[a]







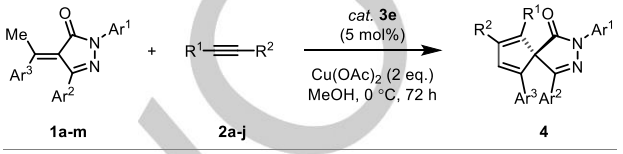
3b, R^1 = 4-Br-C_6H_4, R^2 = 4-F-C_6H_4, R_3 = Me
3c, R^1 = 4-Br-C_6H_4, R^2 = 4-F-C_6H_4, R_3 = H
3d, R^1 = 4-F-C_6H_4, R^2 = 4-Br-C_6H_4, R_3 = H
3e, R^1 = 2-Naph, R^2 = 4-Br-C_6H_4, R_3 = H

Entry	Cat.	Solvent	T (°C)	Yield (%)[b]	*ee* (%)[c]
1	**3a**	MeCN	80	56%	69
2	**3a**	MeCN	23	18%	75
3	**3a**	MeOH	23	86%	75
4	**3b**	MeOH	23	46%	81
5	**3c**	MeOH	23	57%	84
6	**3d**	MeOH	23	64%	84
7[d]	**3e**	MeOH	23	82%	86
8[d]	**3e**	MeOH	0	70%	91
9[e]	**3e**	MeOH	0	<10	n.d.[f]

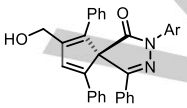
[a] Reaction conditions: **1a** (0.15 mmol), **2a** (0.10 mol), **3** (5 mol%), $Cu(OAc)_2$ (2 equiv) in the indicated solvent (4.0 mL), under inert atmosphere unless otherwise noted. [b] Isolated yields. [c] Determined by chiral HPLC. [d] Using 2 equiv of **1a**. [e] Under O_2 atmosphere. [f] n.d. = not determined.

Initially, α-arylidene pyrazolone (**1a**) was chosen as model substrate (Table 1).[3d,13] The oxidative annulation reaction with the nonsymmetrical alkyne (**2a**) proceeded smoothly at 80 °C using 5 mol% of **3a**, albeit with only 69% *ee* (entry 1). Drastically reduced reactivity was observed at ambient temperature (entry 2). Gratifyingly, upon solvent screening, methanol was found to greatly facilitate the annulation reaction at 23 °C with comparable enantioselectivity (entry 3). We next screened our highly modular and structurally variable Rh(I)-Cp^x catalyst library. Compared to catalyst **3a** and other structurally similar analogues, pseudo C_2-symmetric Cp^x ligands **3b**-**3e** proved to be superior in terms of induction of enantioselectivity, although slightly lower reactivity was observed (entries 4-7). Fine-tuning of catalysts through replacement of the 4-fluorophenyl group with a 2-naphthyl substituent afforded **3e** as most advantageous Rh(I)-Cp^x catalyst (entry 7). Of note, **3e** stands as a new Rh(I)-Cp^x catalyst which has not been reported before. Finally, the model reaction proceeded well at 0 °C and afforded the desired spiropyrazolone (**4a**) with 91% *ee* (entry 8). The reaction was drastically prohibited in the presence of O_2 under otherwise identical reaction conditions (entry 9).[7l]

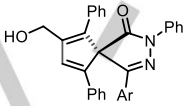
Based on previous reports,[3d] a putative mechanism was proposed.[14] A six-membered rhodacycle intermediate is initially formed through an enol-directed formal C(sp^3)-H activation. In the following alkyne insertion step, the C−C bond formation occurs preferentially at the alkyne carbon adjacent to the alkyl group, thus affords spiropyazolone **4a** as a single regioisomer (> 20:1 r.r.). The absolute configuration of product (**4a**) was determined to be (*S*) by means of vibrational circular dichroism (VCD) spectroscopy.[14]



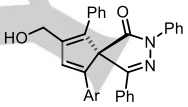
R^1 = Ph, R^2 = CH_2OH



4a (Ar = Ph), 70%, 91% *ee*, > 20:1 r.r.
4b (Ar = *p*-$MeOC_6H_4$), 84%, 87% *ee*, > 20:1 r.r.
4c (Ar = *m*-$MeOC_6H_4$), 65%, 90% *ee*, > 20:1 r.r.
4d (Ar = *p*-FC_6H_4), 63%, 87% *ee*, > 20:1 r.r.
4e (Ar = *o*-FC_6H_4), 65%, 88% *ee*, > 20:1 r.r.

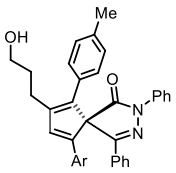


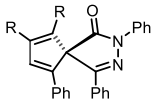
4f (Ar = *p*-$MeOC_6H_4$), 70%, 92% *ee*, > 20:1 r.r.
4g (Ar = *o*-$MeOC_6H_4$), 32%, 82% *ee*, > 20:1 r.r.[a]
4h (Ar = *p*-FC_6H_4), 62%, 87% *ee*, > 20:1 r.r.
4i (Ar = *o*-FC_6H_4), 66%, 89% *ee*, > 20:1 r.r.[a]



4j (Ar = *p*-$MeOC_6H_4$), 64%, 89% *ee*, > 20:1 r.r.
4k (Ar = *o*-$MeOC_6H_4$), 52%, 85% *ee*, > 20:1 r.r.[a]
4l (Ar = *p*-FC_6H_4), 73%, 91% *ee*, > 20:1 r.r.
4m (Ar = *o*-FC_6H_4), 73%, 91% *ee*, > 20:1 r.r.

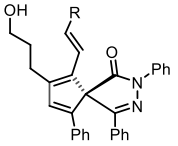
Ar^1 = Ar^2 = Ar^3 = Ph



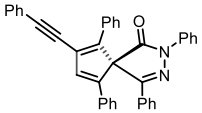


4r (R = Ph), 70%, 94% *ee*[a]
4s (R = *p*-FC_6H_4), 56%, 97% *ee*[a]
4t (R = *n*-Pr), 67%, 34% *ee*

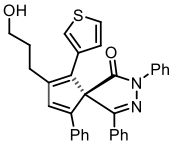
4n (Ar = Ph), 90%, 91% *ee*, > 20:1 r.r.
4o (Ar = *p*-$MeOC_6H_4$), 78%, 87% *ee*, > 20:1 r.r.
4p (Ar = *p*-FC_6H_4), 72%, 90% *ee*, > 20:1 r.r.
4q (Ar = *o*-FC_6H_4), 76%, 86% *ee*, > 20:1 r.r.



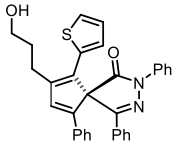
4u (R = H), 83%, 87% *ee*, > 20:1 r.r.
4v (R = Ph), 73%, 87% *ee*, > 20:1 r.r.



4w, 45%, 93% *ee*, > 20:1 r.r.



4x, 64%, 87% *ee*, > 20:1 r.r.



4y, 66%, 87% *ee*, > 20:1 r.r.

Scheme 2. Substrate scope of the reaction. Reaction conditions: **1** (0.20 mmol), **2** (0.10 mol), **3e** (5 mol%), $Cu(OAc)_2$ (2 equiv) in MeOH (4.0 mL) at 0 °C under inert atmosphere for 72 h. [a] Using 10 mol% of **3e**.

Investigation of the substrate scope using substituted α-arylidene pyrazolones (**1a**-**m**) under optimal reaction conditions

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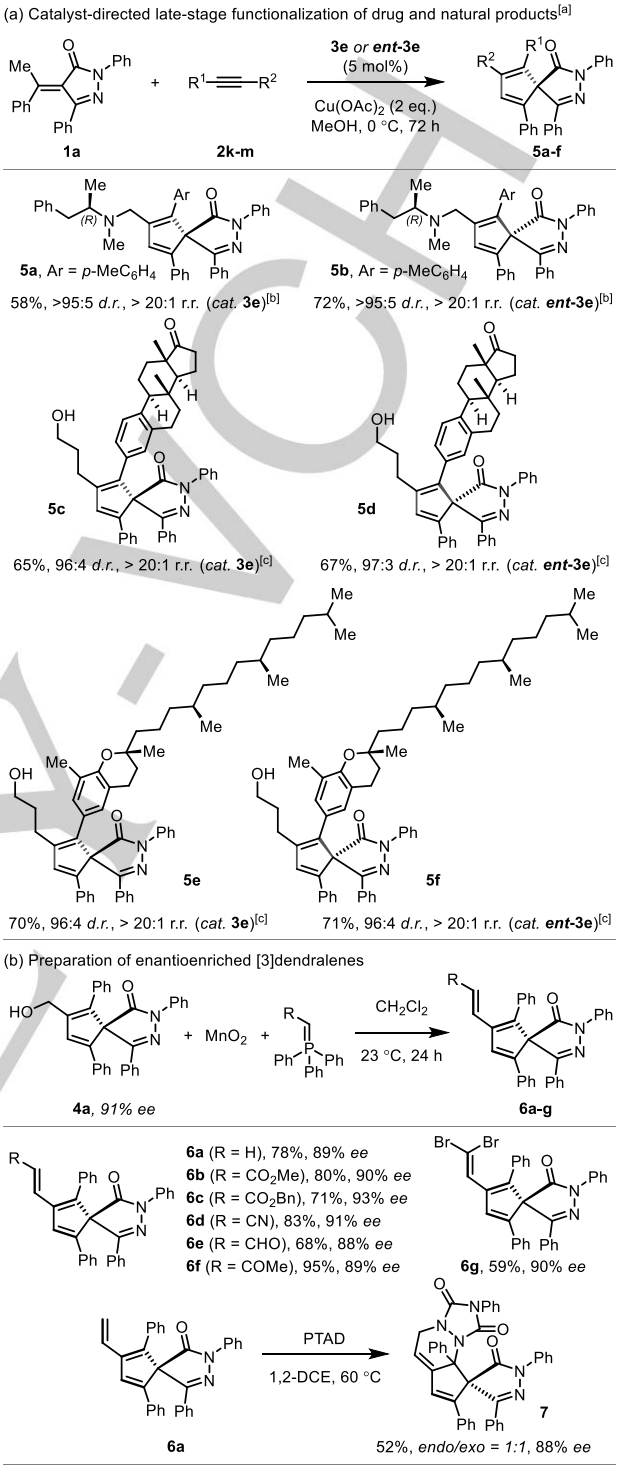
revealed that both electron-withdrawing and electron-donating groups on the *ortho*-, *para*-, and *meta*-position were well tolerated and delivered the desired products with good to excellent enantioselectivity (Scheme 2, **4a**-**m**). In some cases, the reaction outcome was found to be sensitive to the presence of *ortho*-substituents presumably due to steric hindrance, and in these cases 10 mol% of **3e** was required (**4g**, **4i**, **4k**).

Various alkynes (**2a**-**j**) were afforded the desired spiropyrazolones with enantioselectivities of up to 97% *ee* (Scheme 2, **4n**-**4y**). For the annulation of symmetrical aryl/aryl alkynes (**4r**, **4s**) 10 mol% of **3e** was specifically required. When a more challenging symmetric alkyl/alkyl alkyne was applied, the product **4t** was formed smoothly, albeit with low enantioselectivity (34% *ee*). Nonetheless, nonsymmetrical alkynes including aryl/alkyl (**4n**-**q**), vinyl/alkyl (**4u**, **4v**), and heteroaryl/alkyl alkynes (**4x**, **4y**) were all excellent reaction partners. Interestingly, when 1,4-diphenylbutadiyne was tested, mono annulation product (**4w**) was isolated exclusively in 93% *ee* and no double annulation product was detected. Again, for all annulation reactions with nonsymmetrical alkynes mentioned above, regioselectivity was excellent and only a single regioisomer was detected (> 20:1 r.r.).

Finally, we performed late-stage functionalization studies of drugs and natural product derivatives.[15] As shown in Scheme 3a, alkynes were prepared from (*R*)-(-)-deprenyl (a selective Monoamine Oxidase B inhibitor), estrone and (+)-δ-tocopherol and then carefully evaluated. To our delight, in all cases we obtained exclusively a single diastereoisomer (>95:5 *d.r.*) upon treatment with catalyst **3e**. Furthermore, catalyst-directed diastereoselective annulation reactions proceeded well, and the other diastereoisomers were formed predominantly (>95:5 *d.r.*) by switching the catalyst to ***ent*-3e**.[16]

[3]-Dendralenes have gained widespread attention,[17] as they are valuable building blocks for the rapid construction of polycyclic frameworks through multiple cycloaddition sequences.[18] To further demonstrate the synthetic utility of our annulation reaction, we conducted product diversifications through a one-pot allylic alcohol oxidation-Wittig reaction of **4a** (Scheme 3b).[19] Accordingly, a series of unprecedented enantioenriched [3]-dendralenes was obtained using various Wittig reagents with good to excellent yields and enantioselectivity. Of special note, the Corey-Fuchs reaction was also compatible with this protocol and gave dibromo [3]-dendralene (**6g**) in 59% isolated yield. Upon treatment with PTAD (4-phenyl-1,2,4-triazoline-3,5-dione), further diversification of [3]-dendralene (**6a**) could be realized to afford the cycloaddition adduct **7** through Diels-Alder reaction.

To investigate whether the compound collection modulates biological pathways, 72 spiropyrazolones were synthesized and subjected to different cell-based screens, including an osteoblast differentiation assay that indirectly monitors Hedgehog (Hh) signaling activity in pluripotent mouse mesenchymal C3H10T1/2 cells upon stimulation with purmorphamine.[20] Hh signaling is essential for embryonic development and highly important for stem cell homeostasis and tissue regeneration.[21,22] Constitutive activation of Hh signaling is associated with the development and progression of various types of cancer, including medulloblastoma and basal cell carcinoma.[22,23] Therefore, novel small-molecule modulators of the Hh pathway are in high demand.[22]



Scheme 3. Late-stage functionalization and product diversification. [a] Reaction conditions: **1** (0.20 mmol), **2** (0.10 mol), **3e** or ***ent*-3e** (5 mol%), $Cu(OAc)_2$ (2 equiv) in MeOH (4.0 mL) at 0 °C under inert atmosphere for 72 h. [b] Diastereomeric ratios (d.r.) were determined based on ^1H NMR analysis of crude reaction mixtures. [c] Diastereomeric ratios (d.r.) were determined by chiral HPLC. 1,2-DCE = 1,2-dichloroethene.

Gratifyingly, several spiropyrazolones inhibited osteogenesis with half-maximal inhibitory concentrations (IC_{50}) in the low

micromolar range, as detected by reduced activity of the osteogenic marker alkaline phosphatase.[24] The most potent compound **4f** inhibited Hh-dependent osteogenesis with a half maximal inhibitory concentration (IC_{50}) of 3.6 ± 0.8 µM. To confirm the Hh inhibition, compound **4f** was additionally characterized in an orthogonal, GLI-dependent reporter gene assay using Shh-LIGHT2 cells.[25] In this assay, compound **4f** inhibited the GLI-dependent expression of the reporter firefly luciferase with an IC_{50} of 8.8 ± 0.5 µM.[14] Therefore, the chemotype defined by spiropyrazolones defines a structurally novel class of Hedgehog pathway inhibitors.

In summary, we demonstrated the first enantioselective annulation of α-arylidene pyrazolones through a formal C(sp^3)-H activation under very mild conditions enabled by highly variable Rh(III)-Cp^x catalysts. The method gave access to a set of structurally diverse spiropyrazolones containing all-carbon quaternary centers in high yields and with high enantioselectivity. Preliminary biological investigation in different cellular assays led to the identification of the spiropyrazolones as a novel class of Hedgehog pathway inhibitors.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: C-H activation • Enantioselective catalysis • Rhodium • Spiropyrazolones • Hedgehog pathway inhibitors

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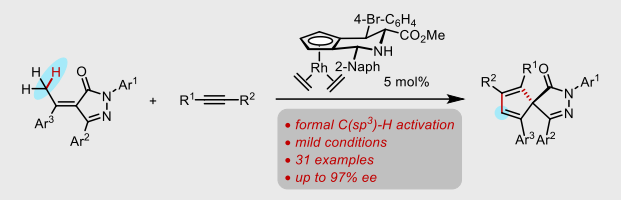

The first Rh(III)-catalyzed enantioselective annulation of α-arylidene pyrazolones through a formal C(sp^3)-H activation under very mild conditions was developed using a novel chiral Cp^x ligand, yielding a novel class of Hedgehog pathway inhibitors.

H. Li, R. Gontla, J. Flegel, C. Merten, S. Ziegler, A. P. Antonchick, and H. Waldmann**

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Enantioselective Formal C(sp^3)-H Bond Activation in the Synthesis of Bioactive Spiropyrazolone Derivatives