C–H Activation

DOI: 10.1002/anie.201404895

Asymmetric Synthesis of Isoindolones by Chiral Cyclopentadienyl-Rhodium(III)-Catalyzed C–H Functionalizations**

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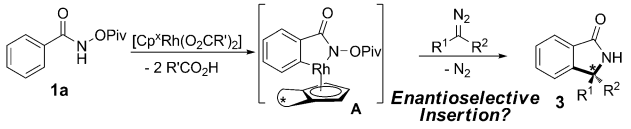
Abstract: *Directed Cp*Rh^{III}-catalyzed carbon–hydrogen (C–H) bond functionalizations have evolved as a powerful strategy for the construction of heterocycles. Despite their high value, the development of related asymmetric reactions is largely lagging behind due to a limited availability of robust and tunable chiral cyclopentadienyl ligands. Rhodium complexes comprising a chiral Cp ligand with an atropchiral biaryl backbone enables an asymmetric synthesis of isoindolones from arylhydroxamates and weakly alkyl donor/acceptor diazo derivatives as one-carbon component under mild conditions. The complex guides the substrates with a high double facial selectivity yielding the chiral isoindolones in good yields and excellent enantioselectivities.*

Transition-metal-catalyzed C–H functionalization evolved to an important synthetic tool for the rapid construction of molecular complexity from simple starting materials.[1] For instance, a wide range of transformations catalyzed by the Cp*Rh^{III} fragment has been developed over the past years giving access to various heterocycles.[2] Despite its large synthetic potential, the corresponding asymmetric C–H functionalization reactions remain underdeveloped due to the lack of suitable ligands.[3,4] In this respect, chiral versions of the very important cyclopentadienyl (Cp) and pentamethylcyclopentadienyl (Cp*) ligands hold a particular high promise. Two complementary strategies for chiral Cp-type ligands were reported by us[5,6] and Rovis and Ward[7] and have been applied in Rh^{III}-catalyzed asymmetric C–H functionalization reactions. The complex from the Rovis/Ward approach derives its chirality from a supramolecular assembly of a Cp* fragment and a protein, whereas our strategy is based on C_2-symmetric disubstituted Cp rings with a chiral backbone. Despite good reactivity and selectivity, the amenable reaction types are so far limited to cyclization reactions with olefin or allene acceptors. An extension beyond these boundaries is highly desirable. For instance, diazo derivatives are versatile reagents for metal-catalyzed C–C and C–Het bond constructions with Rh^{II} catalysts.[8] Very recently they found applications as one-carbon components in Rh^{III}-catalyzed C–H functionalization reactions.[9–11] Rovis reported the use of donor–acceptor-substituted diazo derivatives[12] as couplings partners for the synthesis of isoindolones from aryl hydroxamates.[11] However, no asymmetric version of this valuable transformation has been reported, making it a suitable candidate to showcase the application potential of our chiral Cp^x complexes (Scheme 1). Herein we report the enantioselective construction of isoindolones **3** through asymmetric C–H functionalization reactions with a chiral Cp^{x}Rh^{III} catalyst.



Scheme 1. Selective insertion of a diazo reagent into metallocyclic intermediate **A** provides chiral isoindolones **1**.

We have previously established two classes of chiral Cp ligands that can efficiently control the orientation of the five-membered rhodacyclic intermediate **A** obtained from C–H activation of aryl hydroxamates **1**.[5,6] This control exposes a single face of the metallacycle leading subsequently to the formation of the tetrahedral chiral-at-metal intermediates with high precision. The additional selectivity challenge for the envisioned diazo incorporation stems from the required facial recognition of the diazo component by the rhodium center (Scheme 2). A coordination of the diazo-bearing carbon atom to the rhodium(III) center[13] should lead to the four most probable conformers **B**–**E**.

Depending on the size and nature of the substituents R^1 and R^2, a specific conformation should be preferred. Upon the loss of dinitrogen, rhodium carbenoids[14,15] are formed with possible alignments of R^1 and R^2 as shown for **F** and **G**. Potential rotation of the Rh–carbenoid bond[14] could result in an equilibration between **F** and **G**, but the existing chiral environment should favor one orientation. Subsequent migratory insertion[15] sets the stereogenic center, and reductive elimination of the arising intermediates **H** and **I** delivers the enantiomeric isoindolone products.

The envisioned enantioselective process was investigated with a range of different chiral Cp–rhodium complexes using phenyl hydroxamate **1a** and two different diazo ester classes as model substrate combinations (Table 1). Both Cp ligand families promoted the desired reaction and gave the corresponding isoindolone **3aa** in promising enantioselectivity (entries 1–3). Although somewhat less reactive, the biaryl

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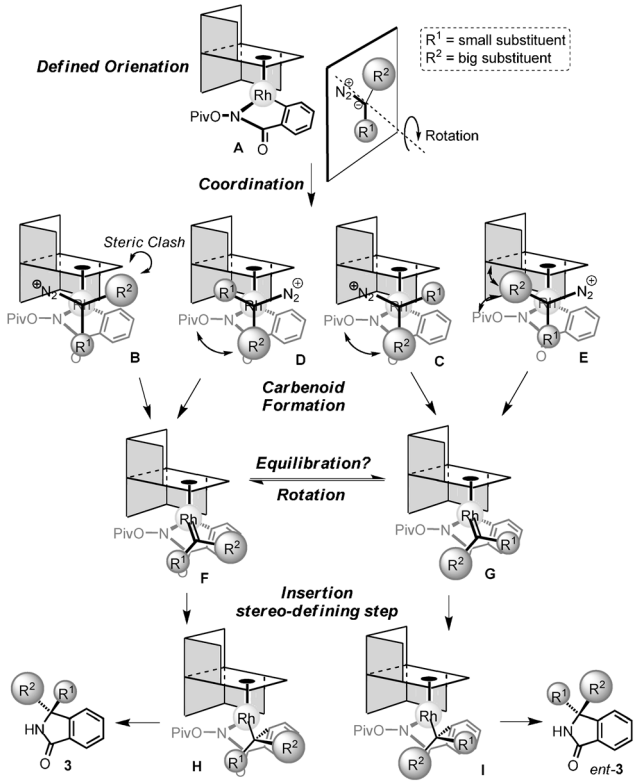
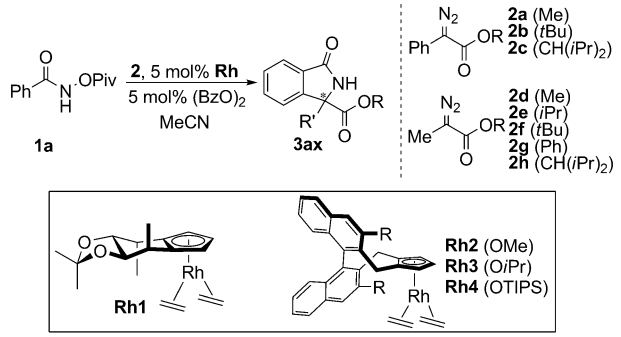
[**] This work is supported by the European Research Council under the European Community's Seventh Framework Program (FP7 2007–2013)/ERC Grant agreement no. 257891. We thank Dr. R. Scopelliti for X-ray crystallographic analysis of **3ja** and **3jh**.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201404895.



Scheme 2. Representation of the induced facial selectivity of the diazo component with chiral Cp ligands.

Table 1: Optimization of the chiral Cp^{x}Rh-catalyzed asymmetric isoindolone synthesis.[a]



Entry	Rh	Diazo ester 2	T [°C]	Yield [%][b]	e.r.[c]
1	**Rh1**	**2a**	23	80	78:22
2[d]	**Rh2**	**2a**	23	32	86:14
3	**Rh2**	**2a**	50	83	81.5:18.5
4	**Rh2**	**2b**	50	83	52:48
5	**Rh2**	**2c**	50	83	55.5:44.5
6	**Rh2**	**2d**	35	17	81:19
7	**Rh2**	**2e**	35	50	87:13
8	**Rh2**	**2f**	35	48	89:11
9	**Rh2**	**2g**	35	60	88:12
10	**Rh2**	**2h**	35	91	93:7
11	**Rh1**	**2h**	35	75	85.5:14.5
12	**Rh3**	**2h**	35	83	90:10
13	**Rh4**	**2h**	35	75	96:4
14	**Rh4**	**2h**	**23**	**84 (83)**	**96.5:3.5**
15[e]	**Rh4**	**2h**	23	60	95.5:4.5
16[f]	**Rh4**	**2h**	23	35	95.5:4.5

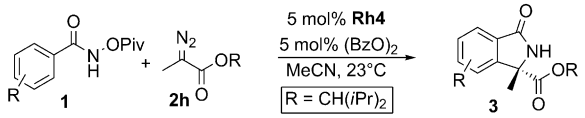
[a] Reaction conditions: 0.05 mmol **1a**, 0.05 mmol of **2**, 2.50 μmol **Rh**, 2.50 μmol $(BzO)_2$, 0.10 M in MeCN. TIPS = triisopropylsilyl. [b] Yields determined by ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard, yield of the isolated compound in parentheses. [c] Determined by HPLC with a chiral stationary phase. [d] 42% Conversion. [e] **1a** with *N*-OAc instead of *N*-OPiv. [f] **1a** with *N*-OBz instead of *N*-OPiv.

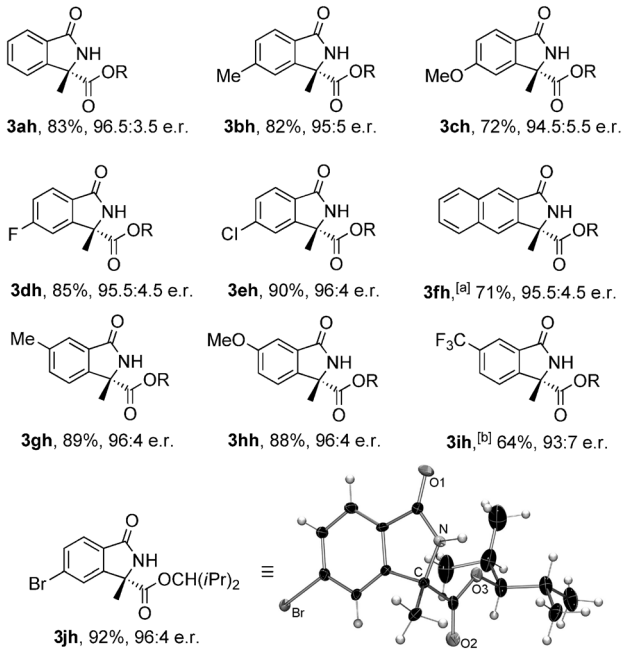
ligand scaffold of complex **Rh2** showed a better potential for the asymmetric induction. Variations in the size of the ester moiety led to an important observation. A larger ester (**2b** and **2c**) almost completely abolishes the selectivity of the reaction (entries 4 and 5). Most presumably the two diazo substituents become too similar in size, making it virtually impossible for the catalyst to discriminate between the two enantiotopic faces. In conclusion, the smallest possible ester group (Me) would lead to highest enantioselectivity with the phenyl substituent. The opposite trend was observed for methyl-substituted diazo esters **2d**–**2h**. The methyl group represents the small substituent in this class. Consequently, we anticipated to increase the enantioselectivity by choosing a larger ester. A steady increase in size from Me→*i*Pr→*t*Bu/Ph translated into steadily improved selectivities (entries 6–9). Along the same lines, the yield of **3** improved due to a reduced Bamford–Stevens decomposition pathway of the diazo ester. The optimal ester group was found to be 3-(2,4-dimethyl)-pentyl[16] (**2h**) providing a superior selectivity (entry 10). Fine-tuning of the biaryl ligand scaffold revealed that **Rh4** with its bulky OTIPS groups provided isoindolone **3ah** in excellent enantiomeric ratio of 96:4 e.r. (entry 13). Furthermore, **Rh4** displays a high reactivity even at ambient temperature (entry 14). Other internal oxidants on **1a** did not influence the selectivity but were detrimental to the yield (entries 15 and 16).

With the optimized conditions, we next explored the reaction scope with a variety of aryl hydroxamates **1** with diazo ester **2h** (Table 2). The reaction performance is largely independent from the arene substitution pattern. For instance, electron-rich substituents as well as halogen atoms at the *para*-position to the hydroxamate group are well tolerated delivering isoindolones **3** in good yields and excellent enantioselectivities. Notably, *meta*-substituted arenes (**1d**–**1i**) having two unequal *ortho* C_{sp^2}–H bonds which could result in the formation of two regioisomeric products gave excellent regioselectivities (> 20:1) and similar levels of stereoselectivity. Due to some unknown catalyst deactivation, a higher catalyst loading was required for the full conversion of substrate **1f**. The absolute configuration of isoindolone **3jh** was established by X-ray crystallographic analysis to be (*S*).[17] By analogy, the same configuration is attributed to all 2,4-dimethylpentyl ester products.

We next evaluated the suitability of a range of diazo esters **2** as one-carbon component in the reaction (Table 3). Simple alkyl- or aryl-containing substituents (**2i**–**2k**) as well as ether (**2o**) or ketal (**2p**) moieties did not interfere with the reactivity nor the enantioselectivity. However, no isoindolone product **3** was formed with allyl diazo ester **2l**, presumably

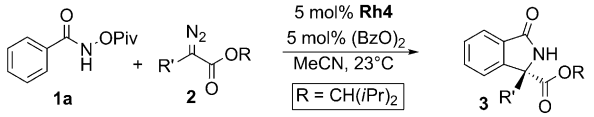
Table 2: Enantioselective isoindolone synthesis using different aryl hydroxamates **1**.

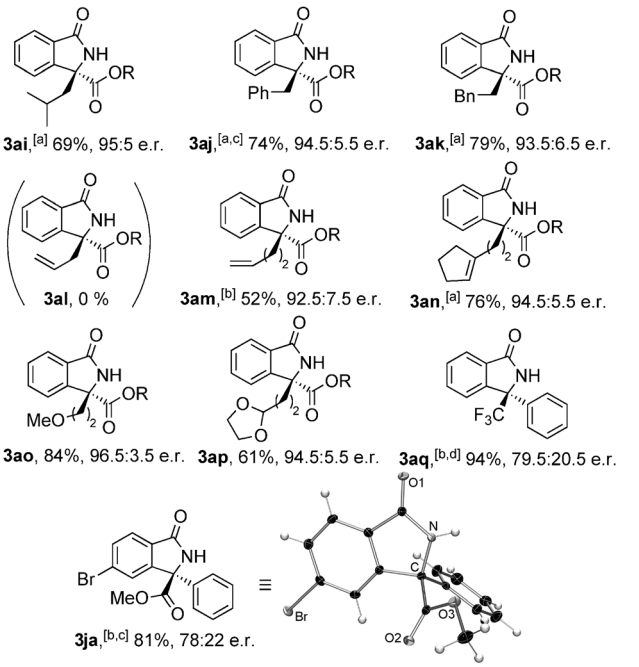




Reaction conditions: 0.10 mmol **1**, 0.10 mmol **2a**, 5.00 μmol **Rh4**, 5.00 μmol $(BzO)_2$, 0.10 M in MeCN at 23 °C for 16 h. Yields are those of the isolated product; enantiomeric ratios were determined by HPLC with a chiral stationary phase. [a] 10 mol% **Rh4**; [b] at 50 °C.

Table 3: Enantioselective isoindolone synthesis with different diazo esters.

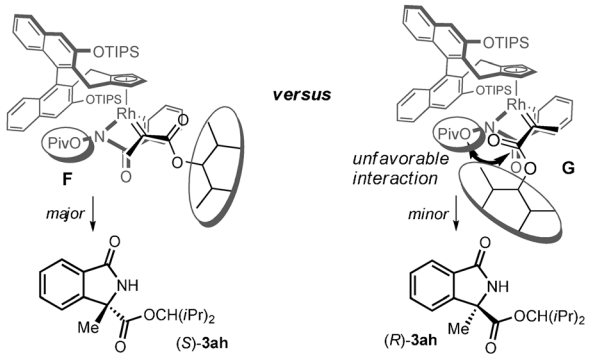




Reaction conditions: 0.10 mmol **1a**, 0.10 mmol **2**, 5.00 μmol **Rh4**, 5.00 μmol $(BzO)_2$, 0.10 M in MeCN at 23 °C for 16 h. Yields are those of the isolated product; enantiomeric ratios were determined by HPLC with a chiral stationary phase. [a] At 35 °C. [b] At 50 °C. [c] 10 mol% **Rh4**; [d] **Rh2** instead of **Rh4**.

due to the dominant Bamford–Stevens pathway. In contrast, homoallyl diazo ester **2m** proved to be compatible affording the corresponding product **3am** in slightly reduced enantioselectivity. Improved reactivity and selectivity was observed for its congener **2n** with a three-substituted double bond. Besides the ester-stabilized diazo donors, CF_3-substituted diazo donor **2j** provided the product **3aj** in excellent yield albeit in moderate selectivity. This observation is attributed to the reduced size difference of the two substituents on the diazo group. A similar observation was made for the phenyl diazo methyl ester **2a**. Importantly, as demonstrated by the X-ray crystallographic analysis of its major enantiomer, product **3ja** displays the opposite absolute configuration compared to product **3jh** with the bulky ester.[17] This outcome in both cases derives from a switch of the facial selectivity of the diazo components.

The origin of enantioselectivity for the isoindolone formation might be rationalized by the stereochemical model (Scheme 3). With the favored orientation of the hydroxamate group away from the bulky OTIPS moiety,[6b] the carbene unit should prefer the orientation **F**. This mode avoids unfavorable interaction of the large ester substituent with the bulk of the hydroxamate and leads to the observed product (*S*)-**3ah**. The minor isomer (*R*)-**3ah** might be formed



Scheme 3. Plausible model for the formation of (*S*)-**3ah**.

through either the opposite orientation of the cyclometalated species or the carbene part.

In summary, we reported a mild and highly enantioselective rhodium(III)-catalyzed C–H functionalization to access functionalized isoindolones. Moreover, a salient feature is the high double-facial differentiation of the catalyst allowing for high levels of enantioselectivity with weak alkyl donor–acceptor diazoderivatives. Further mechanistic and computa-

tional studies aim for a refined understanding of the selectivity determining factor of this class of chiral cyclopentadienyl ligands.

Received: May 2, 2014
Published online: ■■ ■■, ■■■■

Keywords: asymmetric catalysis · C–H activation · cyclopentadienyl ligand · diazo ester · rhodium

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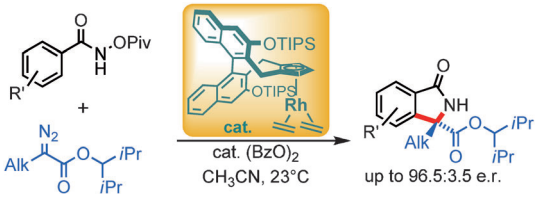
Communications

C–H Activation

B. Ye, N. Cramer* _____ ■■■■–■■■■

Asymmetric Synthesis of Isoindolones by Chiral Cyclopentadienyl-Rhodium(III)-Catalyzed C–H Functionalizations



Heterocycle synthesis: Chiral isoindolones are obtained by rhodium(III)-catalyzed enantioselective reactions of aryl hydroxamates with alkyl-substituted diazo esters through C–H functionalization under mild conditions. Chiral cyclopentadienyl ligands with a biaryl backbone lead to excellent enantioselectivities.