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Planar-chiral rhodium(III) catalyst with sterically demanding cyclopentadienyl ligand and its application for enantioselective synthesis of dihydroisoquinolones

Evgeniya A. Trifonova, Nikita M. Ankudinov, Andrey A. Mikhaylov, Denis A. Chusov, Yulia V. Nelyubina, Dmitry S. Perekalin*

Abstract: Rapid development of enantioselective CH-activation reactions created a demand for new types of catalysts. Herein we report the synthesis of a novel planar-chiral rhodium catalyst $[(C_5H_2{}^tBu_2CH_2{}^tBu)RhI_2]_2$ in two steps from commercially available $[(cod)RhCl]_2$ and *tert*-butyl acetylene. Pure enantiomers of the catalyst were obtained through separation of its diastereomeric adducts with natural proline. The catalyst promoted the enantioselective reaction of arylhydroxamic acids with strained alkenes giving dihydroisoquinolones in high yields (up to 97%) and with good stereoselectivity (up to 95% ee).

In recent years cyclopentadienyl rhodium complexes have been extensively used for CH-activation of aromatic compounds with various directing groups.[1–3] They have opened a new way to synthesize and explore a number of valuable molecules, such as drugs[4] and fluorophores.[5,6] While most of the research has been done with the commercially available catalyst $[Cp^*RhCl_2]_2$, considerable attention has also been paid to complexes with other cyclopentadienyl ligands, which provide the control over selectivity of transformations.[7–11] In this field, the development of chiral catalysts is the most challenging.[12] Major progress has been achieved by Cramer et al. and You et al., who developed a series of cyclopentadienyl ligands with C_2-symmetry and used their rhodium complexes for asymmetric catalysis (Figure 1).[13–18] Ward and Rovis et al. have proposed an alternative approach, in which an achiral rhodium complex with the biotin tag is used in combination with biochemically engineered streptavidin proteins.[19] Very recently, Antonchik and Waldmann et al. have synthesized a large series of rhodium complexes with chiral cyclopentadienyl ligands, which were obtained by catalytic enantioselective cycloaddition of imino esters to fulvenes.[20] Although these approaches are elegant and efficient, they involve multi-step syntheses of chiral cyclopentadienyl ligands (or preparation of mutant streptavidin peptides) that require expensive reagents. This motivated us to propose an alternative approach to chiral rhodium catalysts based on separation of racemic mixtures of complexes through crystallization of their diastereomeric adducts with naturally available amino acids.[21] Apart from the simple synthesis this approach has two strategic advantages: 1) it gives access to complexes with planar chirality, which cannot be obtained from free chiral cyclopentadienyl ligands, 2) it simultaneously gives both enantiomers of the catalyst. Noteworthy, despite the success of planar-chiral complexes in other catalytic reactions,[22] apparently, they have not been previously used for enantioselective CH-activation.[12]

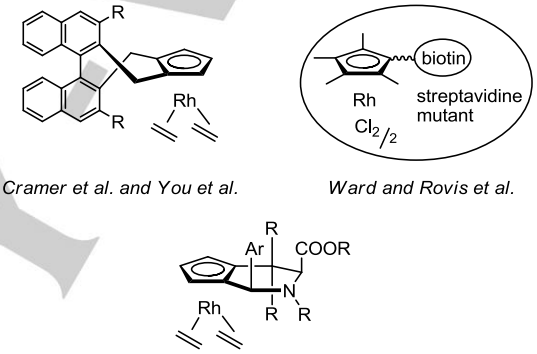

Figure 1. Previously reported types of the chiral cyclopentadienyl rhodium catalysts.

Driven by our interest in rhodium-catalysed transformation of alkynes,[23] we chose a non-classical route for the synthesis of our catalyst, namely [2+2+1]-cyclotrimerization of the terminal alkynes in the coordination sphere of a metal.[24] The reaction of the commercially available rhodium precursor $[(cod)RhCl]_2$ with *tert*-butylacetylene in the presence of $AgPF_6$ gave the cationic fulvene complex (±)-**1** in 64% yield (Scheme 1).[25,26] Interestingly, similar reactions with less hindered 1-hexyne, phenylacetylene, or cyclopropylacetylene led to mixtures of oligomerization products. Nucleophilic addition of a hydride from $NaBH_3CN$ to the coordinated fulvene of (±)-**1** produced the cyclopentadienyl complex (±)-**2a** and its subsequent oxidation with I_2 gave the desired new catalyst $[(C_5H_2{}^tBu_2CH_2{}^tBu)RhI_2]_2$ ((±)-**3a**). Two latter stages can be carried out *in one pot* to give (±)-**3a** in 63% total yield.

Modification of the catalyst structure is possible via addition of other nucleophiles to the fulvene complex (±)-**1**. For example, its reaction with MeOH/tBuOK gave the methoxy-substituted cyclopentadienyl complex (±)-**2b** which can be then transformed into the iodide (±)-**3b** in 80% total yield. Noteworthy, the addition of MeO-group proceeded with high diastereoselectivity. Such approach can be used for introduction of chelating pendant groups or attachment of the catalyst to a polymer support.

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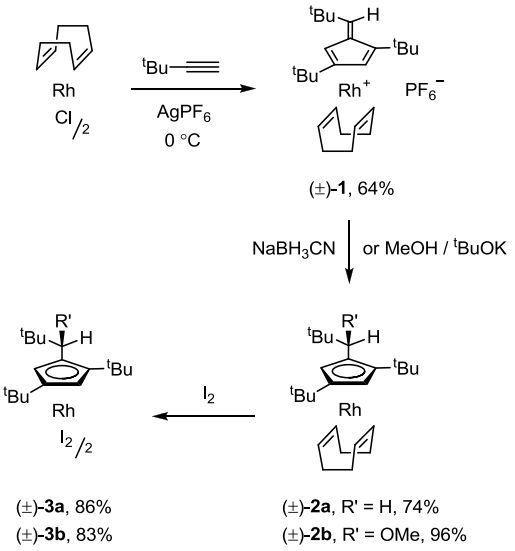
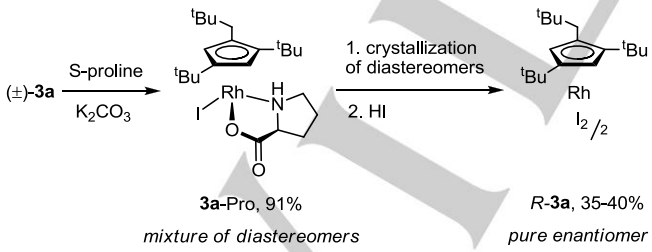


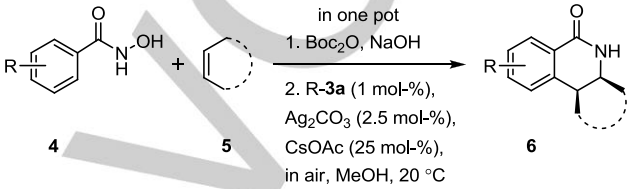
Scheme 1. Synthesis of the racemic rhodium catalysts.

Racemic complex (±)-**3a** reacts with the natural S-proline to give the mixture of diastereomeric adducts **3a**-Pro in high yield 91% (Scheme 2). Interestingly, the rigid cyclic structure of proline uniquely determines the configuration of the stereocenter at the metal atom.[27] Fortunately, it was possible to separate the diastereomers of **3a**-Pro without chromatography just by crystallization. Single crystallization from 1,2-dichloroethane gives the isomer R_{Cp}-**3a**-Pro in 35-40% yield (50% is theoretically possible) and >98:2 diastereomeric purity. Double crystallization of the residue from $CHCl_3$ affords the second isomer S_{Cp}-**3a**-Pro. The chirality of the diastereomers was assigned by the X-ray diffraction analysis of the crystals of R_{Cp}-**3a**-Pro. Noteworthy, these crystals contain 1,2-dichloroethane as solvate, which might explain the predominant crystallization of this diastereomer from this solvent. Treatment of the adduct R_{Cp}-**3a**-Pro with aqueous HI regenerates the iodide complex *R*-**3a** in the form of a pure enantiomer in almost quantitative yield.



Scheme 2. Separation of enantiomers of the catalyst **3a**.

The performance of the catalyst *R*-**3a** was tested in a benchmark enantioselective CH-activation reaction, namely the reaction of arylhydroxamic acids **4** with alkenes **5**, which gives dihydroisoquinolinones **6** (Figure 2).[28,29] Under optimized conditions phenylhydroxamic acid **4** was first activated by Boc-group and then reacted with norbornene in MeOH in the presence of the catalyst *R*-**3a** (1 mol-%), Ag_2CO_3 (2.5 mol-%), and CsOAc (25 mol-%) to give product **6a** in 81% total yield and 93% ee. Ag_2CO_3 acts as iodide-abstracting agent, while CsOAc is the source of acetate anion, which facilitates the abstraction of the *ortho*-hydrogen atom of the O-Boc-phenylhydroxamic acid.[30] The use of the Boc group is crucial, as O-pivaloyl and O-methyl derivatives of phenylhydroxamic acid reacted much slower. Variation of solvents and temperature did not significantly change the enantioselectivity (see Supporting information). It is possible to decrease the amount of the rhodium catalyst to 0.5 mol-%, which is notably lower than 5 mol-% typically reported in the literature.[13]



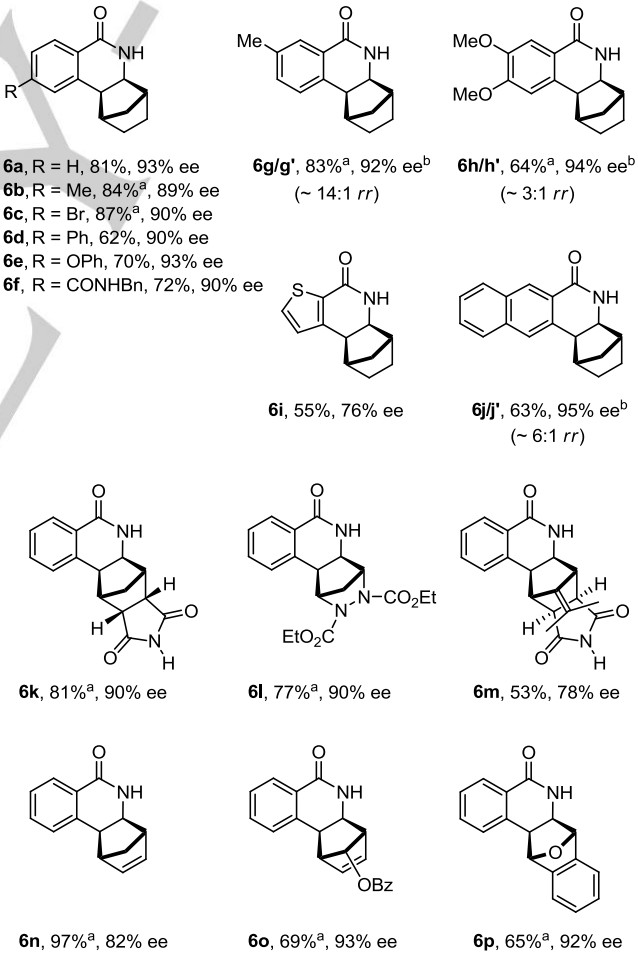


Figure 2. Synthesis of dihydroisoquinolinones **6** using the catalyst *R*-**3a**. [a] Prepared from isolated Boc-derivative of acid; yield given for the second (catalytic) step. [b] Total yield of both regioisomers is given, while *ee* corresponds to the major regioisomer.

Under these optimized conditions a wide range of substituted arylhydroxamic acids **4a**-**k** react with cyclic alkenes to give products **6a**-**6p** in 53−97% yields and with good stereoselectivity 76−95% *ee*. The *R*-isomer of the catalyst provides (3*S*,4*S*)-dihydroisoquinolinone scaffold as confirmed by the X-ray diffraction analysis of the bromine-substituted compound **6c** (Figure 3). The selectivity may be explained by the less hindered approach of an alkene to one of the sides of the proposed metallacycle intermediate (Figure 4).[10,28]

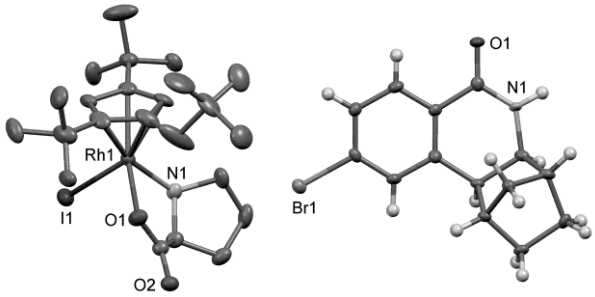


Figure 3. The crystal structures of the catalyst adduct R_{Cp}-**3a**-Pro and the reaction product **6c**, which confirm their stereochemistry.

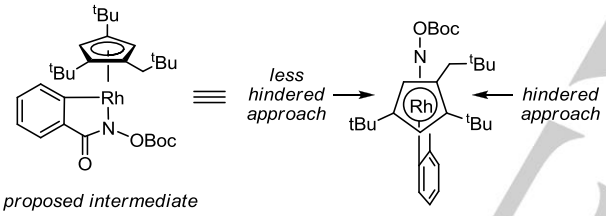
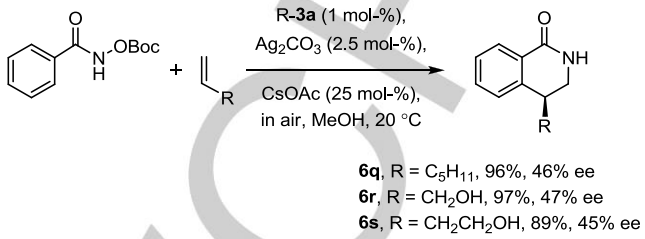


Figure 4. The proposed model for the origin of enantioselectivity.

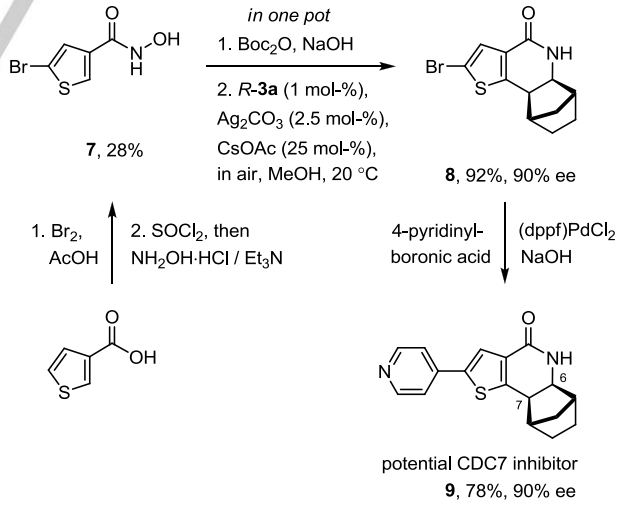
The reaction tolerates the presence of various functional groups in arene, except strong electron acceptors (*p*-CN, *p*-NO_2). In the case of *meta*-substituted aryl and 2-naphtyl hydroxamic acids the mixtures of regioisomers are formed with 3:1-14:1 selectivity, which is similar or better to that provided by the related achiral $[(C_5H_3{}^tBu_2)RhCl_2]_2$ catalyst.[7] The synthesized products **6h/6h'** are of interest, since both of them have structures similar to narciclasine alkaloids.[31] Compounds **6n** and **6o** can be also used for synthesis of alkaloids via ring-rearrangement metathesis.[32]

The best alkene components are norbornene-type derivatives, which are readily available via Diels-Alder addition to cyclopentadiene and provide a variety of options for further functionalization. Unstrained cyclic alkenes, such as cyclohexene, react slowly with phenylhydroxamic acid **4** under our catalytic conditions, while upon heating Lossen rearrangement becomes the dominant process (this typical problem has been observed previously for other rhodium catalysts).[33] On the other hand, acyclic terminal alkenes, such as 1-heptene, allyl alcohol or homoallyl alcohol, react smoothly with Boc-derivative of **4** to give 4-substituted dihydroisoquinolones **6q**-**s** in excellent yields 89-97% and with high regioselectivity (>15:1) (Scheme 3). However, the enantioselectivity is moderate in this case (45-47% ee), apparently because of insufficient steric interactions between the incoming alkene and the cyclopentadienyl ligand. Presumably, it can be improved by modification of the catalyst structure.



Scheme 3. Synthesis of dihydroisoquinolinones **6** from the terminal alkenes.

In order to illustrate the practical application of our catalyst for drug design we carried out a short synthesis of the compound **9** as a potential nanomolar inhibitor of CDC7 kinase[34] (Scheme 4). The key step of the synthesis is the reaction of hydroxamic acid **7** with norbornene in the presence of the catalyst *R*-**3a**, which gives the heterocycle **8** in 92% yield and 90% *ee*. Noteworthy, neither sulfur nor bromine substituent interferes with the catalyst and only one regioisomer of the product is formed. It is also important to note that this approach provides rigid non-planar structures and allows for variation of substituents in 6 and 7 positions of the thienopyridinone system, which is difficult to achieve by traditional methods. The pharmacophore model suggests that hydrophobic residues in these positions should increase the selectivity of inhibition.[34]



Scheme 4. Synthesis of potential CDC7 inhibitor **9** via catalytic annulation.

To conclude, we have developed a new planar-chiral rhodium catalyst $[(C_5H_2{}^tBu_2CH_2{}^tBu)RhI_2]_2$ (*R*-**3a**) with the sterically demanding cyclopentadienyl ligand and demonstrated its application for the enantioselective synthesis of dihydroiso-

quinolones from arylhydroxamic acids and alkenes. We think that the approach to chiral catalysts through separation of proline adducts can also be used for preparation of the planar-chiral ruthenium complexes[35] $[(arene)RuCl_2]_2$, which are difficult to obtain from the enantiomerically pure ligands.

Acknowledgements

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Keywords: Asymmetric catalysis • C-H-activation • Cyclopentadienyl ligands • Rhodium

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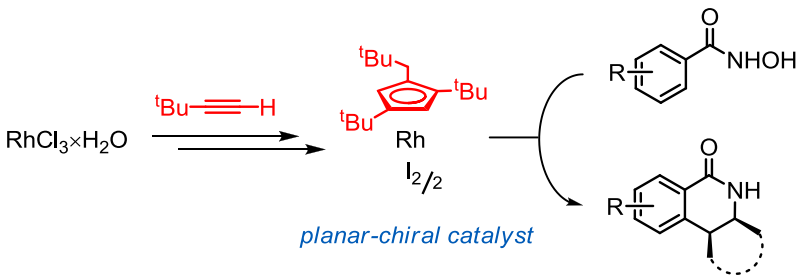

A surprising assembly of three alkynes into a cyclopentadienyl ligand gives a new planar-chiral rhodium catalyst for CH-activation reactions.

E. A. Trifonova, N. M. Ankudinov, A. A. Mikhaylov, D. A. Chusov, Y. V. Nelyubina, D. S. Perekalin

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Planar-chiral rhodium(III) catalyst with sterically demanding cyclopentadienyl ligand and its application for enantioselective synthesis of dihydroisoquinolones