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Planar-chiral arene ruthenium complexes: synthesis, separation of enantiomers, and application for catalytic C–H activation†

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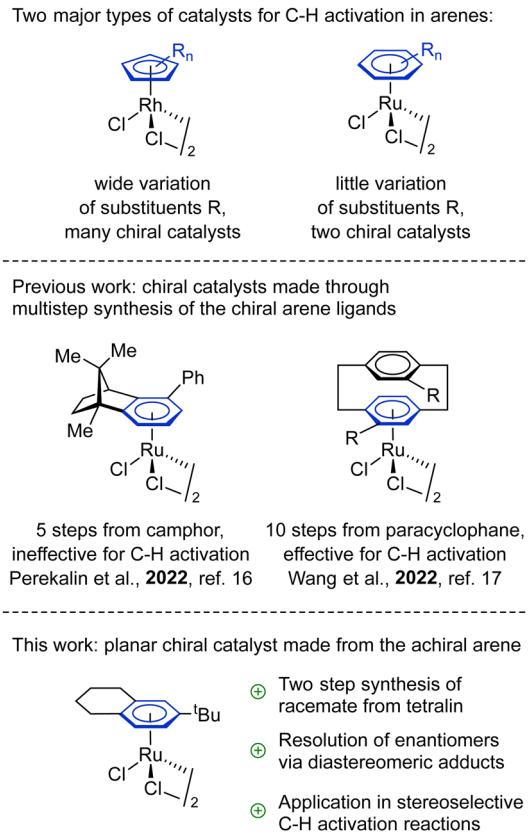
Heating *tert*-butyl-tetraline with $[(p\text{-cymene})RuCl_2]_2$ produces the racemic complex $[(arene)RuCl_2]_2$, which can be separated into enantiomers by chromatography of its diastereomeric adducts with chiral phosphine ligand. The resolved chiral complex catalyzes C–H activation of *N*-methoxy-benzamides and their annulation with *N*-vinyl-pivaloyl amide giving dihydroisoquinolones in 50–80% yields and with 40–80% enantiomeric excess.

Activation of C–H bonds in aromatic compounds containing directing groups is a very active field of research, which has revolutionized the synthesis of heterocycles. The most common catalysts for such reactions are the cyclopentadienyl rhodium complex[1] $[(C_5Me_5)RhCl_2]_2$ and its arene ruthenium congener[2,3] $[(p\text{-cymene})RuCl_2]_2$ (Scheme 1). Asymmetric transformations have been achieved using a number of rhodium complexes with chiral cyclopentadienyl ligands.[4–7] On the contrary, ruthenium complexes with chiral arene ligands are scarce and their first applications as catalysts for C–H activation reactions have been reported only two years ago,[8] although complementary approaches using chiral carboxylic acids[9–11] and chiral directing groups[12–15] have been developed. In particular, our group has synthesized a ruthenium complex with an arene ligand derived from chiral natural camphor, but unfortunately it turned out to be too hindered and susceptible to replacement of the arene in C–H activation reactions.[16] At the same time, Wang *et al.* reported the synthesis of a ruthenium complex with a chiral arene ligand derived from paracyclophane, which successfully catalyzed asymmetric C–H activation of *N*-methoxy-benzamides and their annulation with alkynes providing axially chiral isoquinolones (up to 99% yield and 96% ee).[17]

However, both of these works are based on the multistep syntheses of sophisticated arene ligands, which prompted us to develop an alternative approach to the chiral ruthenium catalysts (Scheme 1). We noticed that it is possible to synthesize racemic ruthenium complexes from trisubstituted arenes and then to separate them into enantiomers by using chiral



Scheme 1 Background research and the topic of this work.

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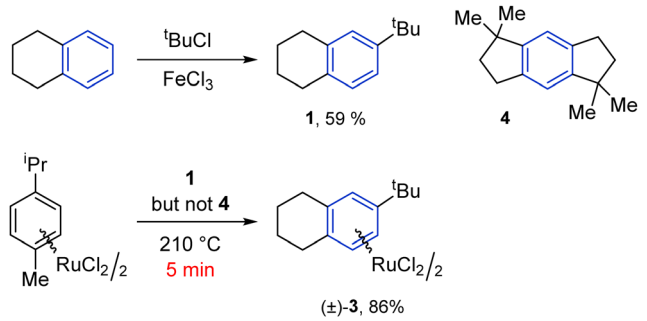
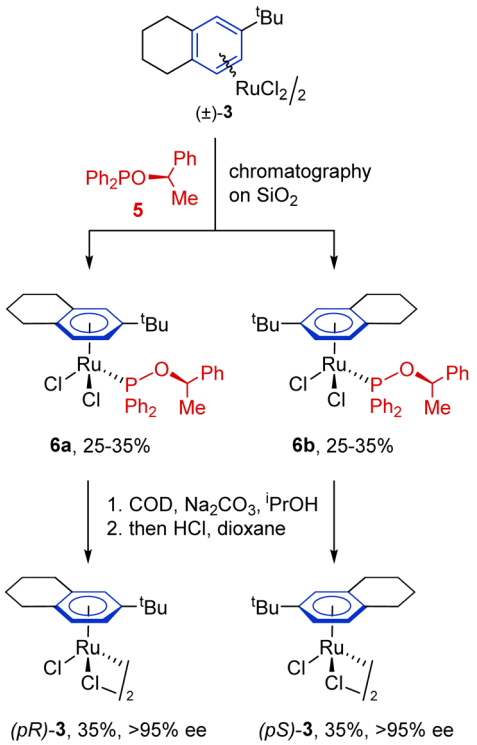


Scheme 2 Synthesis of the racemic ruthenium complex by arene exchange.

auxiliary ligands.[18–20] Recently, Wang *et al.*[21] as well as our group[22–26] have used a similar approach for the synthesis of planar chiral rhodium catalysts.

To make the approach simple we chose the arene ligand **1**, which was obtained in one step by Friedel–Crafts alkylation of tetralin with *tert*-butyl chloride (Scheme 2). This compound can be isolated in large quantities without chromatography by simple distillation. Further heating of the common catalyst $[(p\text{-cymene})RuCl_2]_2$ with an excess of the ligand **1** led to arene exchange and produced the corresponding racemic complex (±)-**3**. The reaction can be carried out in just 5 minutes by heating the mixture at *ca.* 210 °C. The structure of the complex (±)-**3** was confirmed by X-ray diffraction. Interestingly, the related C_2-symmetric arene **4** did not react under similar conditions (ruthenium metal was formed), indicating that steric hindrance can strongly inhibit the arene exchange.

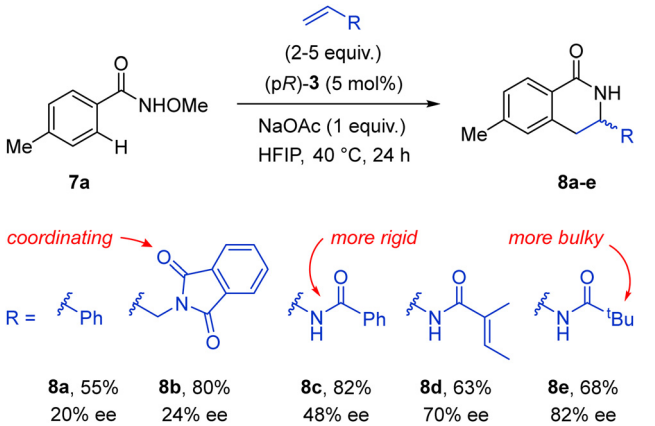
As the auxiliary ligand, we chose the chiral phosphine **5** (Scheme 3), which was obtained from the (*R*)-1-phenylethanol (with 96 : 4 er purity) and Ph_2PCl.[27] The reaction of **5** with the ruthenium complex (±)-**3** quantitatively provided an equimolar mixture of diastereomeric adducts **6a**,**b**. They were separated using column chromatography to give pure complexes **6a** and **6b** in 25–35% yields (50% is theoretically possible) with >95% diastereomeric purity (according to ^{31}P NMR). The absolute configuration of the isomers was established through the X-ray diffraction study of **6a**. The auxiliary phosphine was then removed by the literature procedure:[18] each diastereomer was heated in isopropanol with 1,5-cyclooctadiene and Na_2CO_3 to form the intermediate complex (η^6-arene)Ru(η^4-cod) and then treated with HCl to obtain the enantiomerically pure chlorides (*pR*)-**3** and (*pS*)-**3** in 30–40% yields. To ensure that these transformations did not affect the enantiomeric purity, we recorded ^1H NMR spectra of the complexes (*pR*)-**3** and (*pS*)-**3** in the presence of (*S*)-1-phenylethylamine, which formed weak diastereomeric adducts with characteristic chemical shifts (see ESI† for details).[20] Overall, the advantage of the auxiliary ligand **5** is its availability and the high stability of its ruthenium complexes, while the disadvantage is the sophisticated procedure of its decoordination. Our attempts to use other ligands such as chiral amines and amino acids for chromatographic separation of enantiomers of (±)-**3** have not been successful so far.



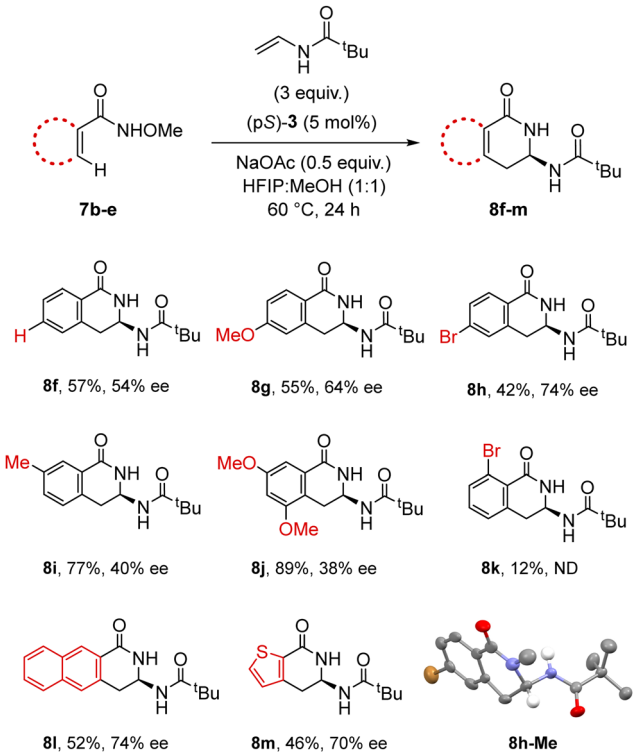
Scheme 3 Separation of the enantiomers of the ruthenium complex **3**.

With chiral complexes in hand, we tested their catalytic activity and selectivity in the reaction of *N*-methoxy-*p*-methyl-benzamide (**7a**) with various alkenes (Scheme 4).[28] It was found that **7a** does not react with aliphatic alkenes such as 1-hexene or norbornene in the presence of the classical catalyst $[(p\text{-cymene})RuCl_2]_2$ or the chiral complex (*pR*)-**3** (5 mol% loading) under typical conditions (HFIP, 20–60 °C, 24 h).

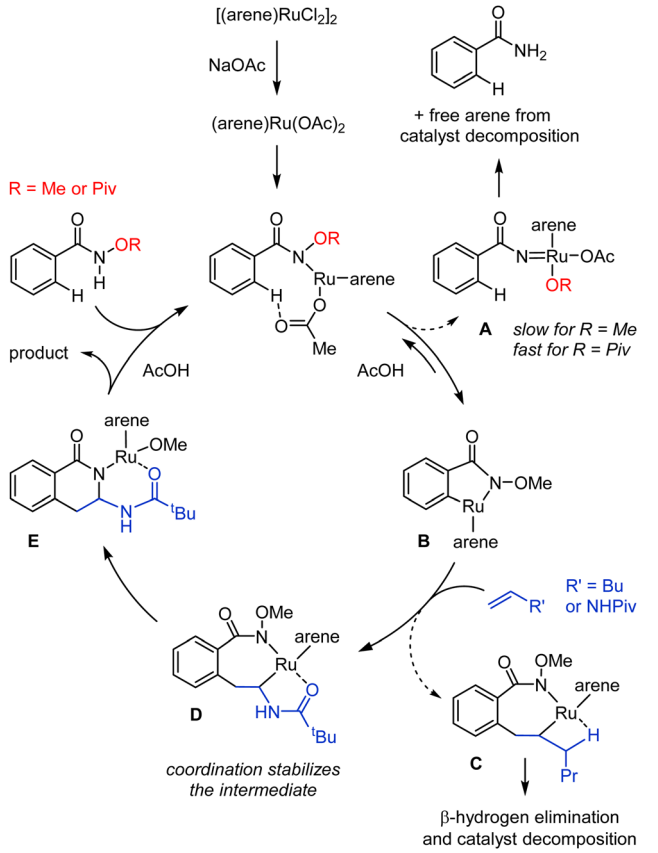
However, styrene reacted with **7a** and gave the target dihydroisoquinolone **8a** in a reasonable 55% yield, although with a low enantiomeric excess of 20%. In accordance with the previous reports of Baidya *et al.*[29–31] the reaction proceeded more efficiently with allyl phthalimide, which contains a coordinating amide



Scheme 4 Reactions of *N*-methoxy-*p*-methyl-benzamide **7a** with various alkenes.



Scheme 5 Scope of *N*-methoxy-benzamides suitable for the reaction.



Scheme 6 Proposed mechanism of the catalytic reaction.

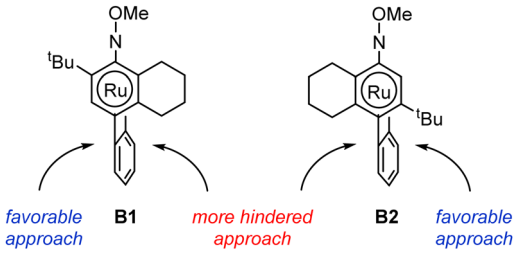
group, and gave the expected product **8b** in 80% yield, but still with 24% ee. Switching from allyl phthalimide to *N*-vinyl-benzamide increased the rigidity and steric bulk of the alkene substrate, and therefore the product **8c** was obtained with the increased stereoselectivity of 48% ee. Finally, the bulkier *N*-vinyl-pivaloyl amide gave **8e** with a satisfying selectivity of 82% ee. Unfortunately, even more promising *N*-vinyl-pyrrolidone reacted with HFIP solvent instead of the substrate **7a**.

Next, we explored the scope of *N*-methoxy-benzamides suitable for the reaction with *N*-vinyl-pivaloyl amide (Scheme 5). We found that catalyst (*pS*)-**3** (5 mol%) provided *p*-bromo- and *p*-methoxy-derivatives **8g,h** in *ca.* 50% yields and *ca.* 70% ee (the yields can be increased to *ca.* 90% by using 10 mol% catalyst loading). *meta*-Methyl- and methoxy-substituted products **8i,j** were obtained in good yields of *ca.* 80–90% albeit with a lower enantioselectivity of 40% ee. For unknown reasons, *o*-methyl- and *o*-bromo-substituted arenes reacted too slowly. Electron-acceptor substituents in the benzamide ring such as NO_2 also slowed down the reaction, presumably because they overstabilize the Ru–C bond in the intermediate metallacycle.[32] In this case the addition of HFIP to *N*-vinyl-pivaloyl amide and the catalyst decomposition became the major side processes. At the same time, the process was quite suitable for the synthesis of electron-rich naphthalene and thiophene derivatives **8l** and **8m**. The absolute configuration of the products was proposed on the basis of the X-ray diffraction study of the *N*-methylated derivative *S*-**8h-Me**, which was obtained using the (*pR*)-enantiomer of the catalyst **3**.

Next, we carried out several experiments and DFT calculations to clarify some important details of the classic mechanism[29] of this catalytic reaction (Scheme 6). In particular, we found that the use of the popular *N*-pivaloyloxy- or *N*-Boc-benzamide[33,34] instead of the *N*-methoxy derivatives **7** led to the formation of the unsubstituted benzamide and the decomposition of the catalyst with the quantitative release of the free arene ligand (confirmed by ^{1}H NMR). This presumably occurs *via* the nitrene intermediate **A**, which was experimentally trapped by sulphides under similar conditions.[35]

In the case of *N*-methoxy-benzamide, the main process is the reversible[31] C–H activation of arene to give metallacycle **B**.[32] Its further reaction with 1-hexene presumably leads to the unsaturated intermediate **C**, which can undergo β-hydrogen elimination and catalyst decomposition. The calculated barrier for the latter process is only 1.0 kcal mol^{-1} (see ESI† for details). On the opposite side, the reaction of **B** with an alkene containing weakly-coordinating groups (*e.g.* *N*-vinyl-pivaloyl amide) leads to the stabilized intermediate **D** with a saturated 18-electron ruthenium center. Reductive elimination in **D** with the formation of a C–N bond gives the intermediate **E**, and eventually the target product. It is noteworthy that coordination groups in alkenes are not required for the related rhodium-catalyzed annulation of *N*-pivaloyloxy-benzamides, presumably because the pivaloyl group itself provides such intramolecular coordination and stabilization of the intermediate.[33]

The stereo-determining step of the reaction is the addition of alkene to the metallacycle **B**, which occurs from the less



Scheme 7 Rationalization of stereoselectivity.

hindered side of the arene ligand, opposite to the annulated cyclohexane. However, the arene in **B** can adopt two almost equally stable conformations **B1** and **B2** (Scheme 7). According to DFT calculations, the approach of the alkene to the conformer **B1** formed by (*pR*)-**3** catalyst from the left side is the most favorable and it leads to the experimentally observed *R*-enantiomer of the product. However, the approach of the alkene from the right side of the conformer **B2** is only 0.9 kcal mol^{-1} less favorable and it leads to the opposite *S*-enantiomer, thus decreasing the overall enantioselectivity of the reaction. In theory, this problem can be avoided by using C_2-symmetric arene ligands, such as **4**.

To conclude, we proposed a concise approach to the planar-chiral arene ruthenium complex *via* separation of the diastereomeric adducts of the racemic complex with chiral phosphine. The obtained chiral complex (*pS*)-**3** catalyzed the annulation of *N*-methoxy-benzamides **7** with *N*-vinyl-amides giving various *S*-3-amino-dihydroisoquinolones **8** in 50–90% yields and 40–80% ee. Taking into account the challenging synthesis of ruthenium complexes from chiral arenes,[8,17] this approach may be useful for further development of chiral catalysts. Generally, it seems that cyclopentadienyl rhodium complexes are more promising catalysts for C–H activation reactions than the ruthenium congeners, because they are not susceptible to the pi-ligand replacement and promote a wider variety of reactions at lower temperatures with lower catalyst loading. However, ruthenium catalysts often have different selectivity. For example, as demonstrated here, they provide 3-alkyl-dihydroisoquinolones **8**, which cannot be obtained selectively using rhodium catalysts.[36]

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Conflicts of interest

There are no conflicts to declare.

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