Catalytic Atroposelective C7 Functionalisation of Indolines and Indoles

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Abstract: Axially chiral atropisomeric compounds are widely applied in asymmetric catalysis and medicinal chemistry. In particular, axially chiral indole- and indoline-based frameworks have been recognised as important heterobiaryl classes because they are the core units of bioactive natural alkaloids, chiral ligands and bioactive compounds. Among them, the synthesis of C7-substituted indole biaryls and the analogous indoline derivatives is particularly challenging, and methods for their efficient synthesis are in high demand. Transition-metal catalysis is considered one of the most efficient methods to construct atropisomers. Here, we report the enantioselective synthesis of C7-indolino- and C7-indolo biaryl atropisomers by means of C–H functionalisation catalysed by chiral RhJasCp complexes.

Axially chiral biaryls, have emerged as highly valuable chiral skeletons, with broad applications in drug discovery and chiral catalysis.[1] This has led to the development of novel catalytic methods for the asymmetric synthesis of axially chiral biaryl scaffolds.[2] In particular, axially chiral indole- and indoline-based frameworks have been recognised as important classes of heterobiaryls because they are the core units of natural alkaloids, chiral ligands and bioactive compounds.[3–5] Direct transition-metal mediated functionalisation of the C7-position of indolines and indoles through directing group-assisted C–H activation has become an efficient strategy for the synthesis of unique indoline derivatives (Scheme 1a).[6–8] Direct enantioselective C–H functionalisation of the indole at the C7-position has been described in a few cases,[9] but the enantioselective syntheses of C7-substituted indole and indoline atropisomers through C–H activation has not yet been reported. Chiral transition-metal Cp* complexes have proven to be effective tools for enantioselective C–H functionalisation reactions,[10] and different types of chiral Cp* complexes have been successfully applied in asymmetric reactions.[11] Enantioselective C–H functionalisation using chiral Cp* ligands has been employed as an alternative strategy to access atropisomers. Since the early report by Heller et al. on the Co-catalysed enantioselective synthesis of axial biaryls by means of [2 + 2 + 2] cycloadition reactions,[12] a variety of other MCP* complexes have successfully been developed by You et al.,[13] Cramer et al.,[14] Li et al.[15] and us[16] for the asymmetric synthesis of different atropisomers.

Diazonaphthoquinones (2) have proven to be advantageous coupling partners in several C–H functionalisation reactions,
including the synthesis of atropisomeric biaryls by means of MCP+C–H functionalisation. Thus, Cramer et al. reported their use in the Ir-catalysed enantioselective synthesis of biaryl phosphate oxides (Scheme 1b upper reaction). We demonstrated their use with our chiral Rh/JasCp complexes and aryl hydroxamates[11d] and more recently used them in the synthesis of more challenging five-membered ring atropoisomers (Scheme 1b lower reaction).[17]

Given the versatile reactivity of diazonaphthoquinones in C–H functionalisation reactions, we reasoned that they might serve as efficient coupling partners in transformations with indolines and indoles bearing a directing group on the nitrogen. Such transformations could yield heteroaryl atropoisomers at the 7-position of indolines and indoles. Herein, we report the development of a chiral Rh/JasCp-catalysed coupling of diazonaphthoquinones with indolines and indoles by C–H bond activation to construct atropoisomers (Scheme 1c), at the C7-position. To the best of our knowledge this is the first enantioselective C7 indoline functionalisation.

In initial experiments the directing group effect of different nitrogen substituents was investigated (Table 1). In contrast to previous reports, 2-pyrimidine (entry 1), amide (entry 2) and urea (entry 3) directing groups did not lead to the formation of the desired coupling products. However, with a hydroxamate directing group (entry 4), the desired product 3a was obtained in excellent yield and with appreciable enantiomer ratio (er). This finding indicates the importance of increased electronegativity on the nitrogen atom of the directing group to facilitate the coordination with the Rh catalyst.[16] Investigation of different JasCp catalysts which we had successfully employed in C–H activation reactions before (entries 5–7) did not lead to a significant increase in yield, and catalyst Rh1 differentiated best between the possible atropoisomers. To our surprise, cat Rh2 and Rh3 which gave the best results in similar transformations[11d,17] led to low enantiomer ratios in this transformation. Solvent screening revealed that 1,4-dioxane is most advantageous with respect to both yield and stereoselectivity (entries 8–10). Finally, varied substrate concentrations (entries 11–13) and external oxidants (entries 14–15) were tested and conditions were identified under which the desired product was obtained in excellent yield and with high er value (entry 11).

With these reaction conditions determined, we explored the substrate scope for this transformation. As shown in Scheme 2, a variety of diazonaphthoquinones (2) yielded the desired products in very good yields and with high er values (3a–d), and different functional groups on the indoline are also tolerated under the reaction conditions (3e–j). Particularly appealing is the finding that bromine is well tolerated (3c, 3e, 3f) which allows for further modification using a variety of cross coupling reactions. We hypothesised that in the presence of a substituent in the 6-position of the indoline, the enantiomer ratio might be improved, as the presence of such a substituent

![Table 1](image)

| Reaction optimisation for the enantioselective synthesis of six-membered-ring atropoisomeric indoline 3a.[a] |
|-----------------------------------|
| **DG** | **Cat.** | **Solvent** | **Conc [M]** | **Yield [%]** | **er** |
| Pym | Rh1 | THF | 0.25 | 0 n.d. |
| COMe | Rh1 | THF | 0.25 | 0 n.d. |
| CONHPr | Rh1 | THF | 0.25 | 0 n.d. |
| CONHOME | Rh1 | THF | 0.25 | 90 84:16 |
| CONHOME | Rh2 | THF | 0.25 | 88 56:44 |
| CONHOME | Rh3 | THF | 0.25 | 87 60:40 |
| CONHOME | Rh4 | THF | 0.25 | 83 80:20 |
| CONHOME | Rh1 | benzene | 0.25 | 66 78:22 |
| CONHOME | Rh1 | CH2Cl2 | 0.25 | 58 81:19 |
| CONHOME | Rh1 | 1,4-dioxane | 0.25 | 90 89:11 |
| CONHOME | Rh1 | 1,4-dioxane | 0.4 | 91 92:8 |
| CONHOME | Rh1 | 1,4-dioxane | 0.5 | 89 90:10 |
| CONHOME | Rh1 | 1,4-dioxane | 1.0 | n.d. |
| CONHOME | Rh1 | 1,4-dioxane | 0.0 | 20 n.d. |
| CONHOME | Rh1 | 1,4-dioxane | 0.4 | n.d. |

[a] Reactions were run for 16 h at RT. Yields were determined for isolated products. DG: Directing group. er: enantiomer ratio, determined using chiral HPLC. Pym: 2-pyrimidine. n.d.: not detected. [b] Cu(OAc)2 (10 mol%) was used as an oxidant. [c] Cu(OTf)2 (10 mol%) was used as an oxidant.

![Scheme 2](image)
should increase the rotation barrier. 6-Cl- and 6-Me-indolines did not give the desired product, which is in accordance with previous reports stressing steric hindrance as reason for this lack of reactivity.\textsuperscript{[19]} However, in the presence of a smaller atom (6-F) the desired product was formed, albeit in slightly lower yield, and with moderate ee value (3k). Investigation of different nitrogen heterocycles revealed that a piperidine moiety was not tolerated under the reaction conditions (3l). In contrast, in the presence of a morpholine derivative the transformation proceeded smoothly and products 3m and 3n were obtained in excellent yields and with appreciable enantioselectivity. In addition, C2- and C3-substituted indolines afforded the desired products 3o and 3p with excellent yield and good ee values.

C7 indoline functionalisation is a reliable method for the synthesis of C7-substituted indoles through an additional oxidation step. Based on our previous findings, we expected that indole hydroxamates would react exclusively at the C-2 position.\textsuperscript{[17]} In fact, for indole hydroxamate the exclusive functionalisation of the heterocycle at C-2 (4a) was observed (Scheme 3). This product however racemises quickly. When the C-2 position of the indole was blocked by introduction of a substituent, the reaction yielded the C7-functionalised indoles with good yield and ee (4b). This reaction is of high importance as efficient methodology for the regio- and enantioselective functionalisation of indoles at C-7 is only available for isolated cases.\textsuperscript{[9]}

Exploration of reaction scope revealed that, gratifyingly, different 2-substituted indoles bearing electron-donating and -withdrawing groups yielded the desired atropisomers in very good yields and with high ee values (4b–j; Scheme 4).

The absolute configuration of compound 3a was determined to be (aR) by means of vibrational circular dichroism (VCD) spectroscopy.\textsuperscript{[20]} A comparison of the obtained final spectra with the experimental IR and VCD spectra is shown in Figure 1. The visual comparison of the predicted VCD pattern of R isomer reveals an exceptionally good agreement with the experimental spectrum of 3a as all characteristic bands are found well reproduced. Hence, based on the VCD spectra, the configuration of 3a is confirmed as aR (see the Supporting Information for more details).

As a plausible mechanism for this transformation we propose that the reaction begins with an oxidative addition of the active Rh\textsuperscript{III} complex I to give the six-membered-ring rhodacycle II. Insertion of the diazophenoxathione 2a affords intermediate III, which upon loss of nitrogen (N\textsubscript{2}) yields the Rh-
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Conflict of Interest

The authors declare no conflict of interest.

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