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# Control of enantioselectivity in rhodium(I)-catalysis by planar chiral dibenzo[*a*,*e*]cyclooctatetraenes

Michaela-Christina Melcher,[a] Trpimir Ivšić,[a] Charlotte Olagnon, [a] Christina Tenten,[b] Arne Lützen,[b] and Daniel Strand[a],*

**Abstract:** Planar chiral 5,11-disubstiuted dibenzo[*a*,*e*]cyclooctatetraenes (dbCOTs) have been developed as the first useful chiral homologs to dbCOT-ligands for asymmetric applications. Methods enabling preparation of such compounds on a gram-scale in enantiomerically pure form are described. Evaluated as ligands in rhodium(I) catalyzed 1,4- and 1,2-arylation reactions, tertiary and quarternary stereogenic centers were formed with excellent yields and selectivities of up to >99% ee. A catalytic asymmetric synthesis of a key cyclization precursor to (-)-penifulvin A highlights the system in an applied context.

The planar chirality of substituted dibenzo[*a*,*e*]cyclooctatetraenes (dbCOTs), where interconversion of enantiomers can occur dynamically via a tub-to-tub ring-inversion, has inspired synthetic and mechanistic interest for over half a century.[1] More recently, dbCOT has found prominence as a bis-$\eta^2$-ligand that confers exceptional catalytic activity and stability to late transition metals. Notable examples where dbCOT-metal complexes are known to exhibit superior performance in catalysis spans iridium(I) catalyzed allylic substitutions,[2] rhodium(I) catalyzed polymerizations,[3] ruthenium(0) catalyzed coupling reactions,[4] and rhodium(I)[5a,b] and iridium(I)[6] catalyzed cycloaddition reactions. Examples of chiral dbCOTs as ligands to transition metals are, on the other hand, scarce. Grützmacher[7] reported a conceptually intriguing enantiomerically pure planar chiral rhodium(I) salt of **1**, and Hayashi a planar chiral rhodium(I) complex of cycloocta-1,5-diene derivative **2** (Figure 1).[8] Unfortunately, these complexes gave only limited efficiency in asymmetric catalysis.[9] The utility of [8]annulene ligands like dbCOT would thus benefit significantly from development of derivatives also capable of efficient asymmetric induction. Structures of this type would moreover fill a particular niche in such catalyst systems where chirality cannot be readily introduced by other components of the ligand sphere.

We reasoned that substitution at both the 5 and 11 positions of dbCOT could offer a ligand that retains the unique π-acidity and resistance to metallation associated with dbCOT,[10] and provide improved performance with respect to chiral induction compared to prior systems. A two-fold axis of symmetry allows fewer reaction pathways leading to undesired stereoisomers and the dual substitution would contribute configurational integrity to the structure. Despite current interest in dbCOT derivatives, not only in catalysis and catalyst design, but also in areas like molecular recognition,[11] responsive materials,[12] and light emitting materials,[13] there is a lack of general methods for formation of dbCOTs with this 5,11-pattern of substitution.[14]

Herein, we report the development of a practical approach to the synthesis and chiral resolution of 5,11-dbCOT derivatives illustrated by $^{Me2}$dbCOT **3a**[15] and $^{Ph2}$dbCOT **3b**. Both compounds proved to be readily resolved by both chromatographic and crystallization techniques which grants access to gram-quantities of these compounds. Importantly, the structures were found to be stereochemically rigid at ambient temperature and coordinate readily to form stable complexes with rhodium(I). As catalysts, these perform excellently in asymmetric catalysis, to readily provide enantioselectivities of up to >99% ee. Furthermore, application of **3b** as a ligand in an asymmetric synthesis of a key cyclization precursor in Mulzer's synthesis of (-)-penifulvin A exemplifies the utility of this approach also in multistep enantioselective syntheses of natural products.[16,17]

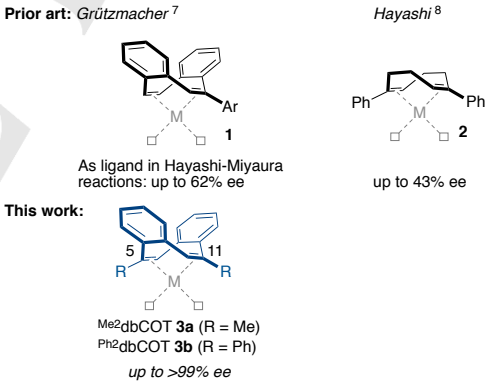


**Figure 1.** Planar chiral bis-$\eta^2$ C=C ligands in catalysis

At the outset, we envisioned ditriflate **6** as an attractive building block from which cross-coupling reactions would enable divergent access to 5,11-disubstituted dbCOTs (Scheme 1). In practice, a multigram synthesis of this compound was achieved from abundantly available (>100 g scale) dibromide **4**.[18] Addition of AgOTs in the previously reported Kornblum oxidation of **4** to diketone **5**[19] doubled the yield of this reaction and proved essential to the overall scalability of the synthesis. $^{Me2}$dbCOT **3a** and $^{Ph2}$dbCOT **3b** were then targeted for the present study to cover stereoelectronic diversity in catalysis.

Access to **3a** and **3b** in enantiomerically pure form is desirable not only for use in catalysis, but also for investigation of their respective physical properties. Pleasingly, the compounds were shown readily separable by chiral HPLC, also on a semi-preparative scale.

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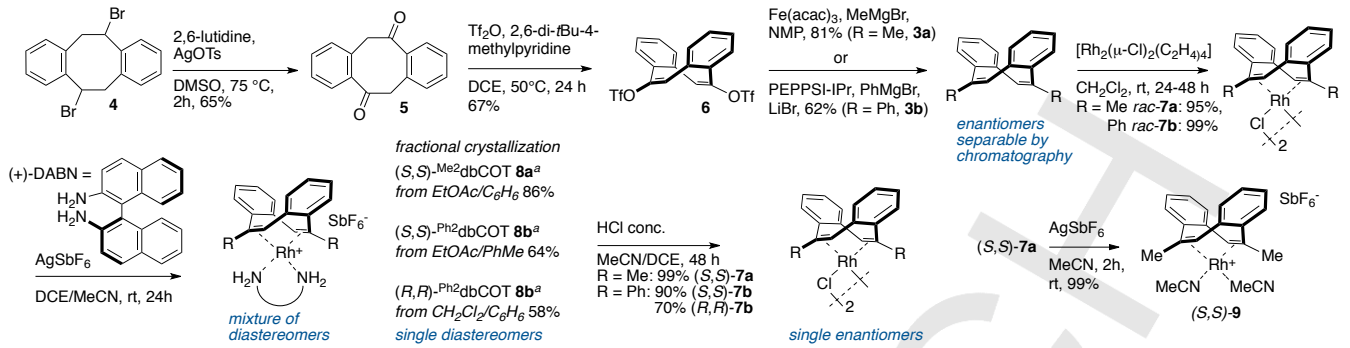



**Scheme 1.** Synthesis and resolution of $^{Me2}$dbCOT **3a** and $^{Ph2}$dbCOT **3b** and their rhodium(I) complexes **7**-**9** (for clarity, only the (*S*,*S*)-stereoisomers of **3a**/**b**, **7a**/**b**, and **8a**/**b** are shown; a) Stereochemical designation refers to the dbCOT ligand. Yields are given based on the stated diastereomer.

Non-chromatographic preparative resolution of unfunctionalized hydrocarbons of this type is more challenging, but Grützmacher's method for resolution of **1** via diastereomeric rhodium(I) complexes turned out to be surprisingly general and provides a convenient alternative to chromatography.[7a] Racemic rhodium dimers **7a** and **7b** were thus synthesized by reaction of the appropriate dbCOT ligand with $[(C_2H_4)_2RhCl]_2$. Diastereomeric mixtures of complexes **8a** and **8b** were then prepared by reaction of **7a** or **7b**, respectively, with $AgSbF_6$ and enantiomerically pure 1,1'-diamino-2,2'-binaphtyl (DABN). Prudent solvent selection allowed for fractional crystallization and isolation of either diastereomer of **8b** in pure form.[20] The (*S*,*S*)-$^{Me2}$dbCOT diastereomer of **8a** could also be readily and selectively crystallized but we were not able to identify conditions for selective crystallization of its diastereomer. Each of the resolved complexes could be reverted back to the corresponding dimers (*S*,*S*)-**7a**, (*S*,*S*)-**7b** or (*R*,*R*)-**7b**, which are directly suitable as catalysts or for use as catalyst precursors. Both **7a** and **7b** were found to be stable for months at ambient conditions without signs of decomposition or loss of stereochemical integrity. The absolute configurations of (*R*,*R*)-**7a** (obtained via resolution with (–)-DABN) and (*S*,*S*)-**7b** were determined by scXRD analysis using anomalous dispersion (Figure 2). To add to the number of catalyst candidates, the cationic complex (*S*,*S*)-**9** was also synthesized by treatment of (*S*,*S*)-**7a** with $AgSbF_6$ in MeCN.

Treatment of (*R*,*R*)-**7a** or (*R*,*R*)-**7b** with an excess of cycloocta-1,5-diene gave a clean decomplexation of the dbCOT ligands without detectible racemization (Scheme 2).

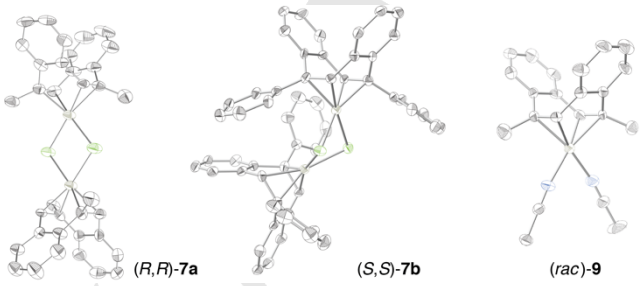
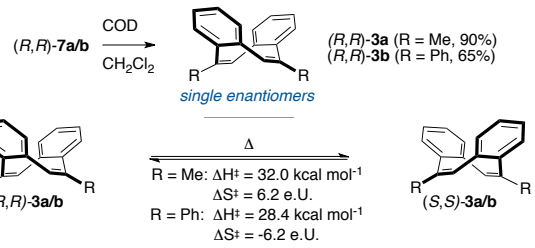



**Figure 2.** scXRD structures of rhodium complexes (*R*,*R*)-**7a**, (*S*,*S*)-**7b** and *rac*-**9** (thermal ellipsoids are shown at 30% probability; hydrogen atoms, counter ions, and solvate molecules are omitted for clarity).

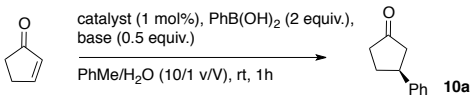
The free energy barriers for tub-to-tub inversion (racemization) of **3a** and **3b** were investigated using a stop-and-go heating experiment. Propylene carbonate solutions of either ligand were heated at three different temperatures and the deterioration of enantiomeric excess monitored over time by chiral HPLC. Both complexes exhibited a free energy barrier for racemization of ~30 kcal mol$^{-1}$ with small entropic contributions. Thus, both structures were shown to sustain prolonged moderate heating without extensive racemization, a prerequisite for more general use in coordination chemistry and catalysis. In practice, complexation of enantiomerically pure $^{Ph2}$dbCOT **3b** with $[Rh_2(\mu\text{-}Cl)_2(C_2H_2)_4]$ was shown to give **7b** without detectible racemization.




**Scheme 2.** Decomplexation (top) and investigation of the tub-to-tub inversion barrier of **3a** and **3b** (bottom).

The ability of **3a** and **3b** to induce chiral discrimination in catalysis was first evaluated in rhodium(I)-catalyzed carbon-carbon-bond forming conjugate additions[21] under Hayashi-Miyaura conditions.[22] In a model reaction between 2-cyclopentenone and phenyl boronic acid, catalysts **7a**, **7b,** and **9** produced cyclopentanone **10a** in excellent yields and with selectivities of 95-99% ee (Table 1).

**Table 1.** Evaluation of **7a**, **7b**, and **9** as catalysts in Hayashi-Miyaura reactions.



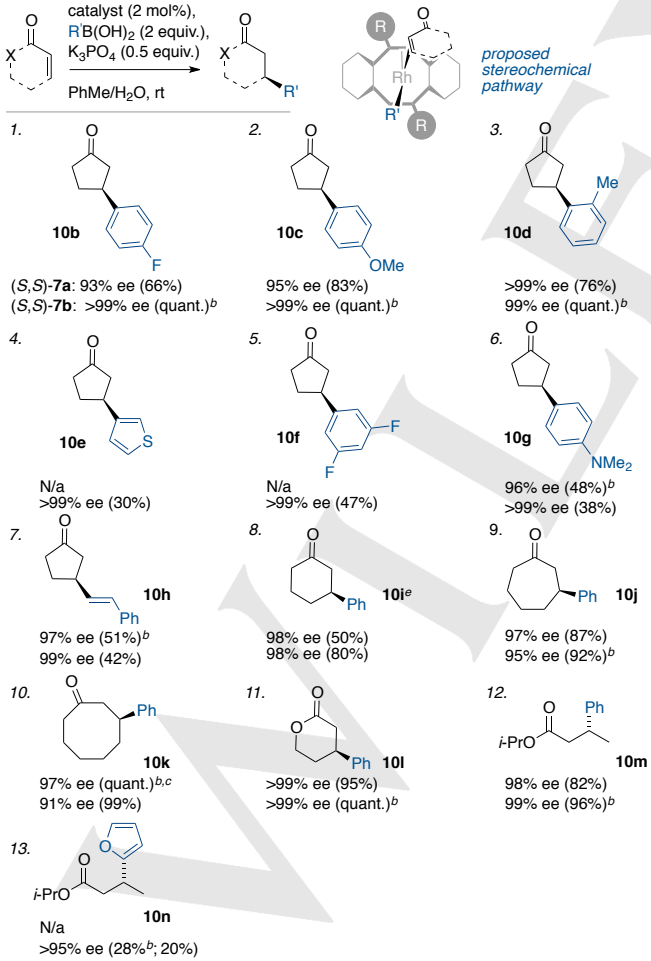

| entry | base | catalyst | Yield [%][a] | ee [%][b] |
|---|---|---|---|---|
| 1 | $K_3PO_4$ | (*S*,*S*)-**7a** | 94 | 97 |

| | | | | |
|---|---|---|---|---|
| 2 | $K_3PO_4$ | (*S*,*S*)-**7b** | 99 | >99 |
| 3 | $K_3PO_4$ | (*S*,*S*)-**9** | 95 | 95 |
| 4 | *t*BuOK | (*S*,*S*)-**7a** | 99 | 97 |
| 5 | KOH | (*S*,*S*)-**7a** | 92 | 97 |
| 6 | $(iPr)_2NH$ | (*S*,*S*)-**7a** | 94 | 96 |

[a] Determined by $^1$H NMR spectroscopy using an internal standard. [b] Determined by HPLC on a chiral stationary phase. See SI for details.

The choice of base and solvent had only minor impact on reaction performance. Catalysts **7a** and **7b** were then evaluated with various combinations of structurally diverse 1,4-acceptors and boronic acid derivatives (Table 2). Cyclic and linear ene-ones as well as a range of boronic acids including aryl, heteroaryl, and cinnamyl derivatives were screened and high enantioselectivities were maintained across the substrate scope. In the reaction between phenylboronic acid and cyclohexenone, 1,2-addition to the product ketone was observed as a competing side reaction (Entry 8). This was particularly pronounced with **7a** (50%), and with this catalyst, traces of the corresponding double addition product were also seen in entry 1. The observation is interesting as double addition of this type is rarely found under ambient conditions with traditional diene ligands.[22]

**Table 2.** Scope of **7a** and **7b** catalyzed asymmetric Hayashi-Miyaura reactions[a].

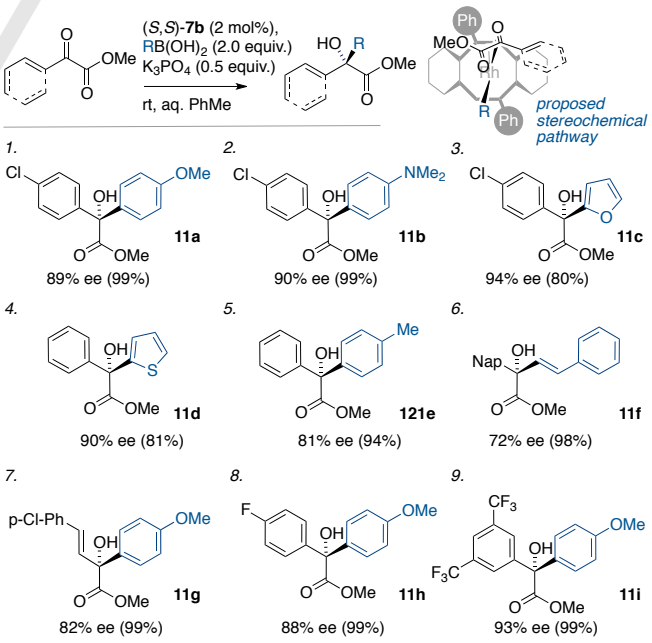



[a] See SI for experimental details and assignment of absolute configurations. Substructures from boronic acids are highlighted in blue. [b] Yield determined by $^1$H NMR spectroscopy using an internal standard. [c] (*R*,*R*)-**7a** was used as the catalyst. The major enantiomer is opposite to that shown. [d] A 1,4/1,2 double addition product was formed in 50% with **7a** and in 19% with **7b**.

In general, the diphenyl substituted **7b** was found both more efficient and selective than the methyl substituted **7a**. Even so, **7a** gave over 99% ee with certain substrates, which is noteworthy given the limited steric demands of the methyl steering groups. The moderate to fair yields obtained for certain substrate combinations were attributed to the lability of the boronic acids under the basic reaction conditions used (entries 5-9,15). The facial selectivity of addition for both ligands follows models for sterically related ligands where the ene-one is oriented to minimize steric interactions with the ligand substituents.[23b,d]

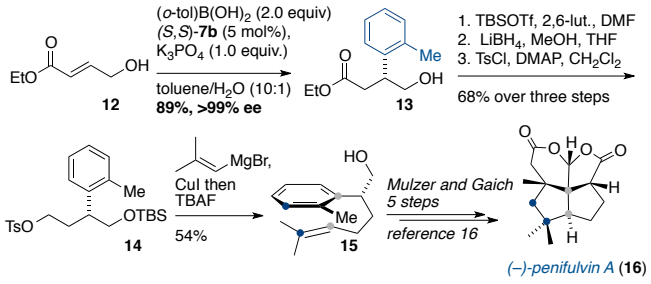
The successful application in 1,4-additions prompted us to also evaluate **7b** also in a more challenging transformation: The formation of tertiary glycolates by 1,2-addition of arylboronic acids to α-ketomethylesters (Table 3).[24] Diene ligated catalysts have previously met with very limited success for such substrates carrying $sp^2$-hybridized substituents on the keto-group (<10% ee).[25] Following a brief optimization, rhodium dimer **7b** was shown to give 1,2-addition product **11a** in a quantitative yield and with a useful enanantioselectivity of 91% ee.[26] Variation of the boronic acid component, utilizing both aryl and heteroaryl substituents, gave the desired 1,2-addition products in excellent yields and with selectivities of up to 94% ee. Minimization of steric clashes between the substrate aryl group and the phenyl substituents of the ligand likely accounts for the facial selectivity in this reaction. Accordingly, increased steric bulk of the ester moiety, which is in proximity to the ligand phenyl group, resulted in a significantly reduced selectivity (see SI for details).

**Table 3.** Scope of **7b** catalyzed asymmetric 1,2-arylation reactions[a]




[a] See SI for experimental details and assignment of absolute configurations. Substructures from boronic acids are highlighted in blue. Isolated yields.

Finally, **7b** was evaluated by a short catalytic asymmetric synthesis of the key cyclization precursor **15** in Mulzer's synthesis of the dioxafenestrene natural product (–)-penifulvin A (**16**) (Scheme 3). The prior asymmetric approach to this compound has relied on auxiliary control.[16] A 1,4-addition of *o*-tolyl boronic acid to ester **12** afforded **13** in high yield and as a single detected enantiomer. The reaction proceeded without competing lactonization or interference from the free hydroxyl group of the substrate. When conducting this reaction on a gram scale, the catalyst could be recovered in 76% yield by chromatography.[27]




**Scheme 3.** Formal catalytic asymmetric synthesis of (–)-penifulvin A.

No loss in catalytic activity or selectivity was seen over the course of three recovery cycles, emphasizing the robust nature of this complex. The synthesis of **15**, and hence, the formal synthesis of (–)-penifulvin A, was then completed in four additional steps concluding with a Cu-mediated $sp^2$-$sp^3$ coupling reaction. With small variations, this strategy should be applicable to also to related natural products and their structural analogs.

In summary, this work introduces 5,11-disubstituted dbCOTs as configurationally stable and readily accessible planar chiral homologs to the parent dbCOT ligand. In particular, 5,11-di-methyl and di-phenyl substituted dbCOTs were shown to form stable complexes with rhodium(I). When applied in 1,4- and 1,2-arylation reactions, high yields and ee's up to >99% were achieved over a wide range of substrates, and in a synthesis of a key intermediate in Mulzer's synthesis of (–)-penifulvin A. More broadly, we envision that 5,11-disubstituted dbCOTs in enantiopure form will find utility across many catalyst systems and types of catalytic reactions given the unique inertness and ligand-properties of these structures. The building blocks developed during the ligand syntheses should be of value also in other contexts. Such efforts are in progress and will be reported in due course.

## Acknowledgements

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**Keywords:** cyclooctatetraenes • planar chirality • asymmetric catalysis • rhodium(I) complexes • fenestrenes

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[26] Catalyst **7a** gave **12a** in 42% ee with an opposite facial selectivity to **7b**. See SI for details.

[27] It is unclear whether dimeric **7b** is reformed from a catalytically active monomeric species or recovered unreacted.

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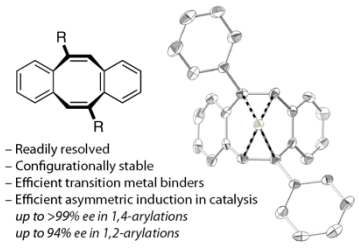
# COMMUNICATION

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**Control of enantioselectivity in rhodium(I)-catalysis by planar chiral dibenzo[*a*,*e*]cyclooctatetraenes**