A Dearomative Synthesis of Chiral Dienes Enables Improved Late-Stage Ligand Diversification

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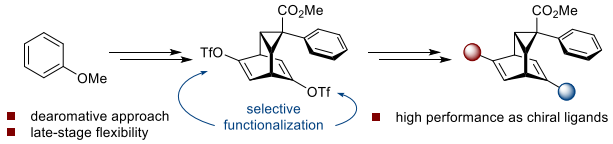
Supporting Information Placeholder



ABSTRACT: An efficient synthesis of chiral nonracemic diene ligands is facilitated by an enantioselective dearomative intermolecular arene cyclopropanation of anisole. The functionality of the resulting cycloheptatriene engenders distinct chemical environments in a downstream tricyclic bis(enol) triflate that permits selective late-stage functionalization. The synthesis of diverse C_1- and pseudo-C_2-symmetric dienes is therefore viable by iterative palladium catalyzed cross-coupling reactions. The ligands provide moderate to high selectivities in known Rh(I)-mediated asymmetric transformations.

Chiral dienes are a privileged ligand class in transition metal-catalyzed asymmetric carbon-carbon bond forming reactions.[1] Foundational reports by Hayashi[2] and Carreira[3] demonstrated efficient aryl transfer reactions of organoboron reagents to prototypical Michael acceptors, and subsequent work has expanded the diversity of effective electrophiles to yield synthetically useful 1,2-[4] and 1,4-aryl[5] transfer reactions. In addition, Rh(I)-chiral diene complexes have been employed as catalysts for asymmetric [4+2]-cycloadditions,[6] arylative carbocyclizations,[7] intermolecular carbene insertions,[8] and α,γ-difunctionalization of electron-poor dienes.[9] Chiral dienes have also been integrated into heterogenous catalysts, allowing for facile catalyst recovery and recycling.[10] Extant syntheses of chiral diene ligands have some remaining limitations and a practical modular, *de novo* synthesis would be of interest.

Chiral dienes based on the bicyclo[2.2.2]octadiene (bod) scaffold have attracted considerable attention and prior synthetic efforts can be organized into three categories: (1) resolution of racemic starting materials;[2,4b,11] (2) modification of chiral pool reagents;[3,12] and (3) asymmetric catalysis[13,14b] (Figure 1a). Despite successful application to other diene ligand scaffolds,[14] asymmetric catalysis has not been as widely demonstrated as a method of preparing bicyclo[2.2.2]octadienes. Possible attractive features include obviating classical chiral resolution and allowing access to both enantiomers of the chiral diene ligands through catalyst selection. We were interested in the novel C_1-symmetric bis(aryl) dienes demonstrated by Abele and coworkers and wondered if a late-stage divergent approach to the synthesis of both C_1-symmetric and *pseudo*-C_2-symmetric dienes was possible (Figure 1b). Our interest in [2+1]-annulations of readily available aromatic feedstocks[15] led to the hypothesis that cycloheptatriene **3**, reported by Fleming and Beeler,[16a] offers the possibility for direct access to chiral dienes. The dirhodium tetracarboxylate catalyst that facilitates that intermolecular Buchner reaction (*vide infra*) is commercially available in both enantiomeric forms, which could allow for straightforward access to both enantiomers of the proposed diene ligands. Herein, we describe a catalytic, asymmetric, dearomative approach to the synthesis of chiral dienes as ligands for Rh(I)-mediated asymmetric processes.

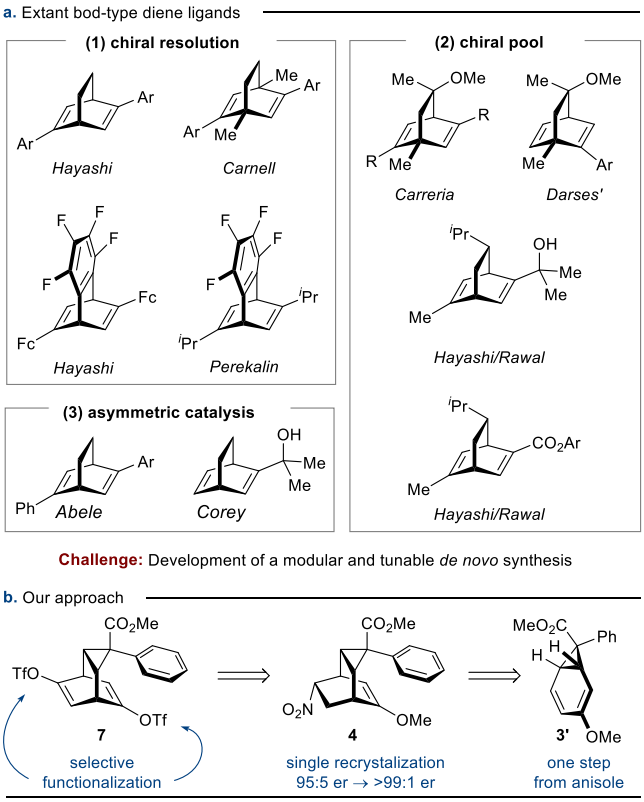
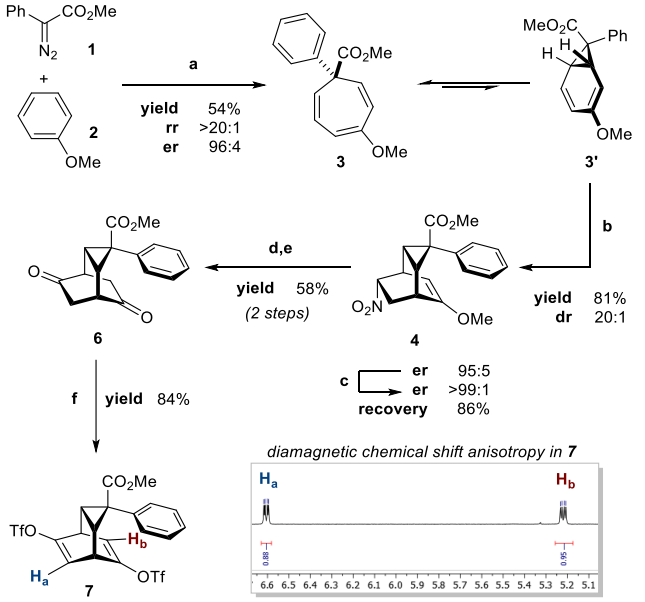


Figure 1. Bicyclo[2.2.2]octadiene (bod) ligands

Using a modified batch procedure based on the flow method developed by Fleming and Beeler,[16a] cycloheptatriene **3** was synthesized with high enantio- and regioselectivity in moderate yield (Scheme 1). With gentle warming, norcaradiene **3'** participated in a highly diastereoselective [4+2]-cycloaddition with the ketene equivalent nitroethylene[17] to give tricycle **4** in good yield (81% yield, dr 20:1). The exclusive formation/participation of the illustrated *exo*-ester norcaradiene **3'** versus its *endo* diastereomer in the cycloaddition is not fully understood at this stage, but is consistent with prior examples in the literature.[16b] A single recrystallization from EtOAc/hexanes gave enantiopure tricycle **4** with minimal loss of material (86% recovery, >99:1 er). Sequential treatment of tricycle **4** with *p*-toluenesulfonic acid and sodium nitrite[18] afforded nitro-ketone intermediate **5** (not shown) and dione **6**, respectively. Bis(enol) triflate **7** was obtained in 84% yield upon reaction of dione **6** with Comins's[19] reagent under basic conditions. Bis(enol) triflate **7** offers a particularly clear example of diamagnetic chemical shift anisotropy: the proton (H_b) lying within the magnetic field of the pendant arene is shifted upfield by 1.39 ppm (see SI page S22 for the full ^{1}H NMR spectrum).

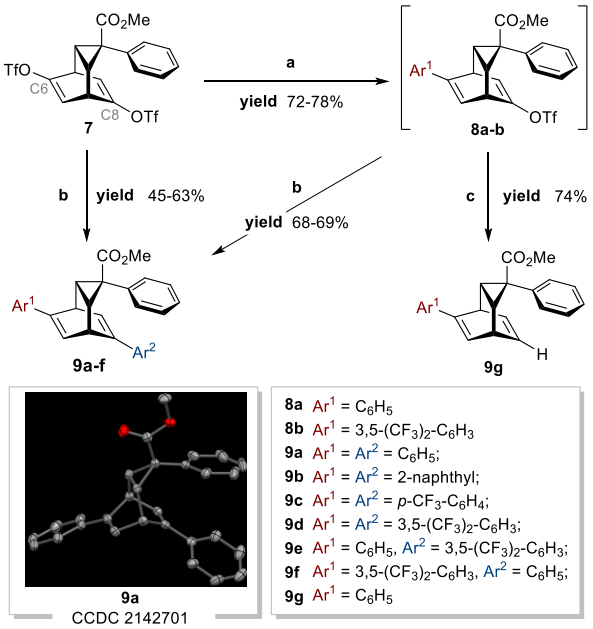
Scheme 1. Synthesis of bis(enol) triflate 7[a]



[a]Reagents and conditions: (a) Rh_2[(*R*)-PTAD]$_4$ (0.1 mol %), 23 °C, slow addition over 2 h; (b) nitroethylene (2.5 equiv), PhMe, 50 °C, 3 h; (c) Recrystallization (23% EtOAc in hexanes); (d) *p*TSA (5.0 equiv), THF/H_2O, 50 °C, 5 h; (e) $NaNO_2$ (6.0 equiv), DMSO/H_2O, 65 °C, 16 h; (f) Comins's reagent (3.2 equiv), LiHMDS (3.0 equiv), THF, -78 °C to 0 °C, 3 h.

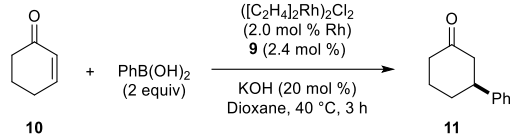
The different steric environments of the enol triflates at C6 and C8 was exploited to allow for selective functionalization of each position via palladium-catalyzed cross-coupling (Scheme 2), allowing us to synthesize a diverse set of electron-neutral and electron deficient bis(aryl) dienes, which have seen the widest application in the literature. The reaction of bis(enol) triflate **7** with $Pd(PPh_3)_4$ and an arylboronic acid at room temperature for 16 h installed the arene at the more sterically accessible C6-position with minimal over-reaction, giving mono(enol) triflates **8a-b**. The reaction of bis(enol) triflate **7** with Buchwald's 4th generation XantPhos palladacycle[20] and arylboronic acids at 85 °C allowed for incorporation of an arene at both the C6- and C8-positions to give *pseudo*-C_2-symmetric dienes **9a-d**. This methodology was also applied to the conversion of the mono(enol) triflates **8a-b** to C_1-symmetric dienes **9e-f**. Using the same catalyst, mono(enol) triflate **8a** can be selectively reduced to give diene **9g**. Single crystal X-ray diffraction analysis of diene **9a** unambiguously confirmed the absolute stereochemistry of the tricyclononadiene (tnd) ligands **9a-9g**.

Scheme 2. Selective functionalization of bis(enol) triflate 7[a,b]



[a]Reagents and conditions: (a) $Pd(PPh_3)_4$ (5 mol %), $ArB(OH)_2$ (3.0 equiv), 2 M aq. Na_2CO_3 (10 equiv), PhMe/MeOH, 23 °C, 16 h. (b) G4 XantPhos palladacycle (5 mol %), $ArB(OH)_2$ (5 equiv), CsF (10.0 equiv), 1,4-dioxane/H_2O, 85 °C, 16 h; (c) G4 XantPhos palladacycle (5 mol %), HCO_2H (3.0 equiv), Bu_3N (3.0 equiv), DMF, 60 °C, 16 h. [b]X-ray structure of **9a** is shown at 50% thermal ellipsoids and hydrogen atoms are omitted for clarity.

Table 1. Benchmark conjugate addition to cyclohexenone 10[a,b,c]

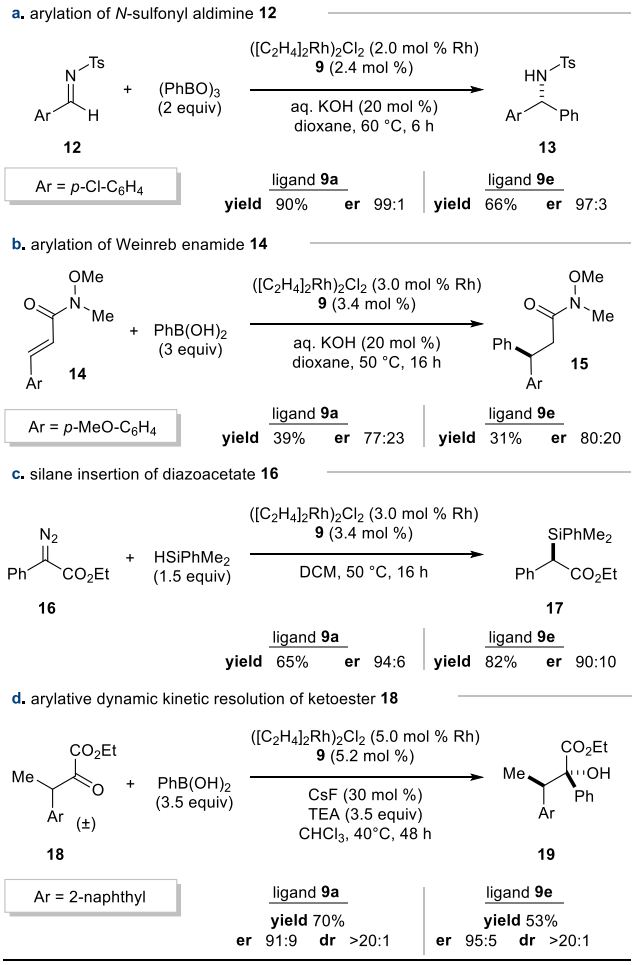


entry	diene	yield %	er[d]
1	**9a**	(92)[e]	98:2
2	**9a**	(98) 98	98:2
3	**9b**	85	98:2
4	**9c**	80	98:2
5	**9d**	75	96:4
6	**9e**	95	97:3
7	**9f**	76	88:12
8	**9g**	87	84:16

[a]All reactions were carried out on a 0.20 mmol scale; values shown represent an average of two individual experiments. [b]We use ( ) to denote ^{1}H NMR yield using phenanthrene as an internal standard. [c]The absolute stereochemistry was assigned by comparing the sign of the optical rotation to values reported in the literature. [d]Determined by HPLC using a chiral stationary phase. [e]Identical conditions but 1.0 mol % of Rh and 1.2 mol% of **9a**.

To assess the utility of the tnd-ligands in asymmetric transformations, the benchmark Rh-catalyzed 1,4-conjugate addition of $PhB(OH)_2$ to cyclohexenone was probed (Table 1). Initial results using ligand **9a** were promising, and slightly diminished yields (but identical enantioinduction) was observed using 1 mol % of rhodium. The tnd-ligands **9b-9g** were subjected to identical reaction conditions to assess the utility of the ligand class. The bis(naphth-2-yl) tnd-ligand **9b** and bis(4-trifluoromethylphenyl) tnd-ligand **9c** preformed comparably to diene **9a**, although with slightly reduced yields. The tnd-ligand **9e** performed significantly better in this transformation than the other C_1-symmetric dienes (97:3 er). The reaction delivered ketone **11** in high enantioselectivity, albeit in slightly lower yield, on a 1 mmol scale using 2 mol % of rhodium and diene **9a** (89% yield, 97:3 er, see SI S76.)

Scheme 3. Application to other synthetically useful systems using diene 9a and 9e[a,b,c,d]



[a]All reactions were carried out on a 0.20 mmol scale; values shown represent an average of two individual experiments. [b]Enantioselectivity was determined by HPLC using a chiral stationary phase. [c]The absolute stereochemistry was assigned by comparing the sign of the optical rotation to values reported in the literature. [d]The diastereoselectivity was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

To further evaluate the utility of the tnd ligands, we subjected both a high preforming C_1- and *pseudo*-C_2-symmetric ligand to a variety of synthetic transformations (Scheme 3). Ligands **9a** and **9e** both facilitated the 1,2-arylation of *N*-sulfonyl aldimine **12**. In particular, ligand **9a** gave sulfonamide **13** in 90% yield and 99:1 er. The use of phenylboroxine is

vital to high performance in these reactions, as phenylboronic acid facilitated the rapid hydrolysis of imine **12** to the aldehyde precursor. The tnd-ligands **9a** and **9e** also successfully arylated a significantly more challenging Michael acceptor, enamide **14** (31% yield, 80:20 er). While the isolated yields are modest, the level of enantioinduction is similar to Hayashi's Ph-bod* ligand in the original report (73% yield, 85:15 er).[5d,21] We also wanted to confirm the tnd-ligands were proficient facilitators of Rh(I)-mediated carbene insertions. The pseudo-C_2-symmetric tnd-ligand **9a** outperformed C_1-symmetric tnd-ligand **9e** (65% yield, 94:6 er), in contrast to the findings of the Xu group who obtained higher yield and enantioinduction using a similar C_1-symmetric diene[8c] (84% yield and 97:3 er). The differing results highlights the complementary reactivity of these ligands in comparison to existing scaffolds. Finally, both diene **9a** and **9e** performed effectively in the arylative dynamic kinetic resolution of an α-ketoester.[4d] Diene **9e** gave higher enantioselectivity, albeit in slightly lower yields than diene **9a** (53% yield, >20:1 dr, 95:5 er).

In summary, we have developed an efficient synthesis of chiral diene ligands originating from the dearomative, asymmetric, intermolecular arene cyclopropanation of anisole. The steric environment of the diene precursors proved to be advantageous, as this allowed for improved late-stage diversification. These ligands have been demonstrated to be proficient steering ligands for several asymmetric transformations. Further applications of these tnd-ligands are currently being explored in our research group.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, materials, methods, characterization data, NMR spectra for all compounds, chromatograms for chiral separations, and information on X-ray diffraction experiments (PDF).

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Notes

The authors declare no competing financial interest.

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(20) Hayashi's Ph-bod* ligand is not the optimized ligand in this report but is the best point of comparision to the ligands that are discussed in this manuscript.