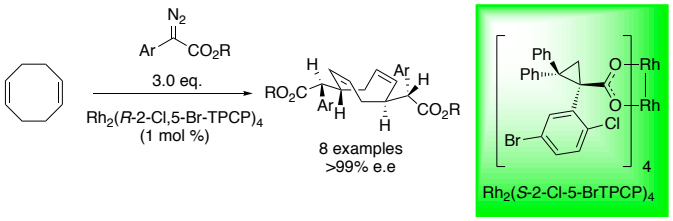
C–H Functionalization Approach for the Synthesis of Chiral C_2 Symmetric 1,5-Cyclooctadiene Ligands

Bowen Zhang, Michael R. Hollerbach, Simon Blakey* and Huw M. L. Davies*

Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, Georgia 30322

Supporting Information Placeholder

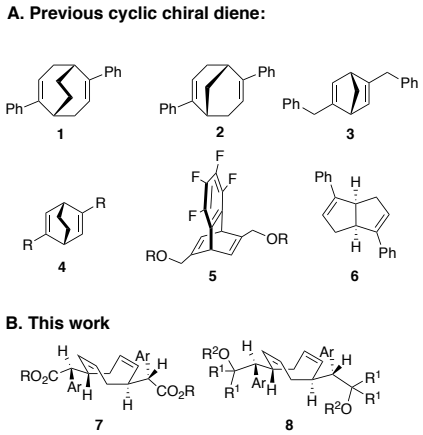


ABSTRACT: Chiral cyclooctadiene (COD) derivatives are readily prepared by rhodium-catalyzed allylic C—H functionalization of COD. Either mono or difunctionalization of COD is possible generating the products in high yield, diastereoselectivity and enantioselectivity. The double C—H functionalization generates C_2 symmetric COD derivatives with four new stereogenic centers in >99% ee, which can be readily converted to a series of chiral COD ligands. Preliminary evaluations revealed that the COD ligands can be used in rhodium-catalyzed asymmetric arylation of cyclohex-2-enone, leading to the conjugate addition products in up to 76% ee.

1,5-Cyclooctadiene (COD) is widely used as a ligand in transition metal complexes.[1] Metal-COD complexes are useful because many are sufficiently stable to be isolated and easily handled, often more robust than the related ethylene complexes because of chelation. Even though the metal-COD complexes were initially considered as stable precursors to active catalysts, it became clear in many instances that the COD ligand was not lost and was an integral part of the catalytic cycle.[2-4] Consequently, there became interest in designing chiral COD ligands for chiral catalysis. The Chiral COD ligands **1** and **2** have shown considerable promise but their synthesis requires a multistep synthesis and a resolution.[4b] This has led to the synthesis of other skipped cyclic dienes as chiral ligands,[4-6] including a number of C_2 symmetric ligands **3-6**. However, all require a multistep synthesis and most involve a racemic synthesis followed by resolution[4-6] (Scheme 1). In this paper we describe an enantioselective C—H functionalization method for the direct synthesis of C_2 symmetric COD derivatives **7**, with four stereogenic centers. Furthermore, we describe their derivatization to other C_2 symmetric COD derivatives **8** and their initial evaluation as chiral ligands for rhodium-catalyzed conjugate addition.

The motivation for this study was the realization that COD would be an intriguing substrate to challenge catalyst-controlled C—H functionalization by rhodium-stabilized donor/acceptor carbenes (Scheme 2).[7,8] We have recently shown that dirhodium catalysts of defined shapes are capable of selecting between primary, secondary and tertiary unactivated

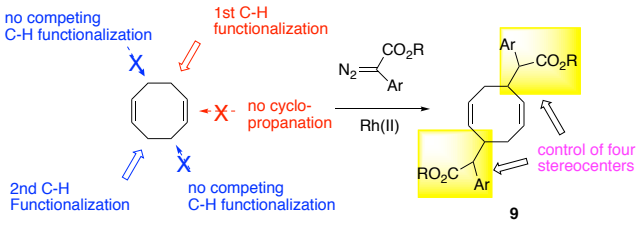
Scheme 1 Chiral cyclic diene ligands



C—H bonds.[8a-e] We have also shown that catalysts can be designed that would select between different secondary C—H bonds.[8c,f,g] COD was considered to be an interesting substrate because even though the methylene sites are allylic and relatively activated, the cis alkene would be expected to be a competing site for cyclopropanation. Therefore, we would need to identify a catalyst that would lead to selective C—H functionalization instead of cyclopropanation. Then, ideally once the mono C—H functionalization has occurred, the catalyst would select the C5 site for a second C—H functionalization, over the two other allylic methylene sites at C3 and C6 to generate the COD derivative **9**. For the overall

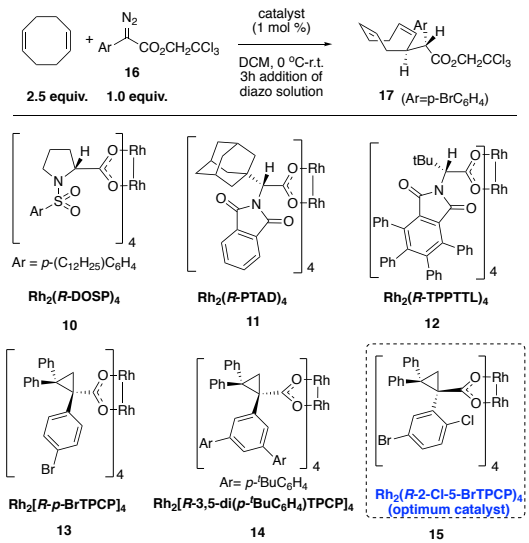
scheme to be useful we would need to be able to control the stereochemistry of the four newly formed stereogenic centers so that the C_2-symmetric form of **7** is generated.

Scheme 2. Synthetic Challenge



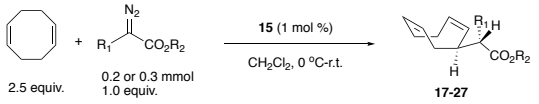
The first stage of the study focused on the mono-C—H functionalization reactions using the most promising catalysts in our tool box for selective reactions at methylene sites (Scheme 3). Rh_2(*S*-DOSP)$_4$ (**10**) is our original catalyst and has been shown to be broadly applicable for functionalization of activated methylene sites.[7b] Rh_2(*S*-PTAD)$_4$ (**11**) is an uncrowded catalyst that can give different stereochemical results to Rh_2(*S*-DOSP)$_4$ at methylene C—H functionalization.[7b] Rh_2(*R*-TPPTTL)$_4$ (**12**) has shown remarkable site selectivity for C3 over C4 C—H functionalization of alkylcyclohexanes.[8f] The triphenylcyclopropanecarboxylates (TPCP) derivatives generate the most sterically crowded dirhodium tetracarboxylate catalysts. Rh_2(*R*-*p*-BrTPCP)$_4$ (**13**) was the first member of this class and preferentially reacts at less crowded C—H bonds.[8a,b] Rh_2(*R*-3,5-(*p*-^{t}BuC$_6$H$_4$)TPCP)$_4$ (**14**) and Rh_2(*R*-2-Cl-5-BrTPCP)$_4$ (**15**) selectively react at the most accessible unactivated methylene site in linear alkanes.[8c,g] We have recently found that C—H functionalization with donor/acceptor carbenes tend to proceed in higher yields when the acceptor group is a trihaloethyl derivative.[8b] Therefore, the test reaction was initially conducted with the trichloroethyl aryldiazoacetate **16** and 2.5 equiv of COD. Most of the catalysts gave an undefined mixture of products, consisting of cyclopropanation, diastereomeric mono-insertion and likely diastereomeric and/or regioisomeric di-insertion products (see supplementary information for details). In contrast, the Rh_2(*R*-2-Cl-5-BrTPCP)$_4$-catalyzed reaction was relatively clean and the desired mono C—H functionalization product **17** could be isolated in 72% yield, >30:1 dr and 91% ee.

Scheme 3 Catalyst screening



The scope of the reaction was then examined with a range of aryldiazoacetates as summarized in Scheme 4. The first three systems examined the influence of the ester functionality. The methyl ester gave the C—H functionalization product **18** with lower diastereoselectivity and enantioselectivity compared to the trichloroethyl ester **17**, further underscoring the advantage of the trihaloethyl esters in C—H functionalization reactions. The trifluoroethyl derivative **19** was formed with the highest yield and enantioselectivity and retained the high diastereoselectivity. Therefore, the further studies focused on the trifluoroethyl derivatives. A series of *p*-substituted aryl (**20-24**) and a pyridyl derivative (**25**) were prepared and they were formed in high yield and dr, with the asymmetric induction in the range of 79-95% ee. The reaction with a *meta*-substituted aryldiazoacetate gave the mono-insertion product **26** but with decreased enantioselectivity (63% ee). We also examined the reaction with the styryldiazoacetate and it similarly gave an effective reaction to form **27** in 67% yield, >30:1 dr, 88% ee.

Scheme 4. Mono C—H functionalization of COD

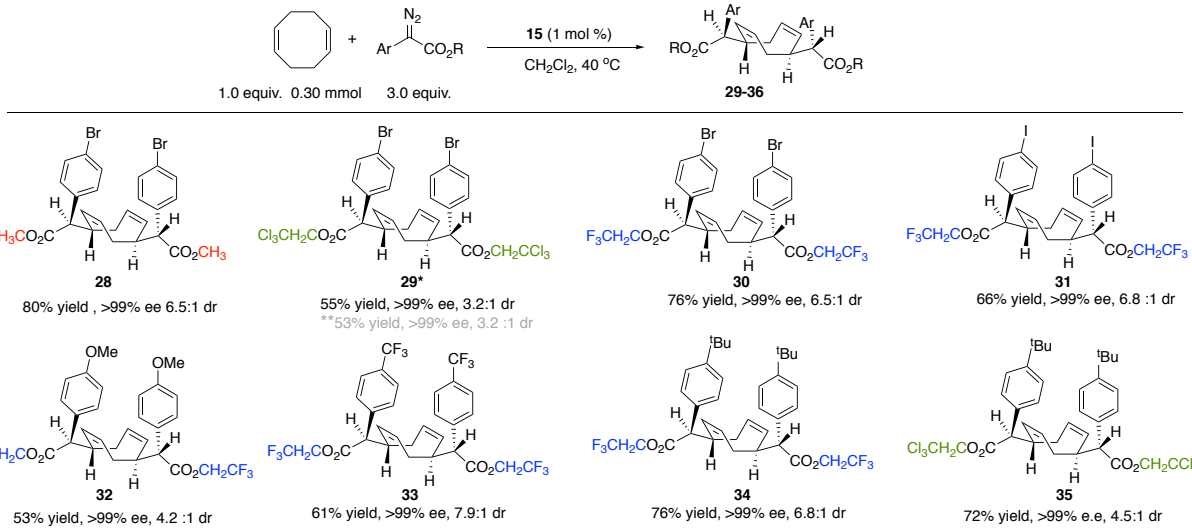


product	R_1	R_2	yield, %	dr	ee, %
17	*p*-BrC_6H_4	CH_2CCl_3	72/80*	>30:1	91/89*
18	*p*-BrC_6H_4	CH_3	73	11.6:1	72
19	*p*-BrC_6H_4	CH_2CF_3	83	>30:1	93
20	*p*-IC_6H_4	CH_2CF_3	78	>30:1	95
21	*p*-(MeO)C_6H_4	CH_2CF_3	72	>30:1	81
22	*p*-(CF_3)C_6H_4	CH_2CF_3	78	>30:1	94
23	*p*-t-BuC_6H_4	CH_2CF_3	85	>30:1	88
24	*p*-(AcO)C_6H_4	CH_2CF_3	70	>30:1	79
25	6-(2-Clpyridine)	CH_2CF_3	72	>30:1	87
26	*m*-BrC_6H_4	CH_2CF_3	64	>30:1	63
27	styryl	CH_2CF_3	67	>30:1	88

* larger scale reaction at 3.0 mmol of diazo compound

With the vision of designing chiral COD ligands, we decided to explore whether a double C—H functionalization could be achieved because this could be a direct way for the synthesis of C_2 symmetric ligands. At the onset of this work, it was considered to be a challenging C—H functionalization because a stereoselective reaction would be required at a specific allylic methylene site in the presence of two other allylic methylene sites and two cis-alkenes. Nevertheless, the double C—H functionalization turned out to be very effective (Scheme 5). The reaction was conducted using 3 equiv of the diazo compound at elevated temperature (40 °C), and under these conditions the bis C—H functionalization products **28-35** were formed in good yield. All the products are produced with very high levels of enantioselectivity (>99% ee) even though the enantiomeric purity of the mono C—H functionalization products was considerably lower (72-95% ee). This is because the minor enantiomer of the mono-insertion product is primarily transformed into the meso diastereomer of the final bis C—H insertion product during the second insertion. Also, imperfect asymmetric induction of the major enantiomer of the mono insertion product generates a diastereomer rather than an enantiomer of the final bis C—H insertion products. Consequently **28-35** are produced with very high enantioselectivity but with moderate diastereoselectivity. Fortunately, the desired major diastereomer is easily purified on silver-impregnated silica.

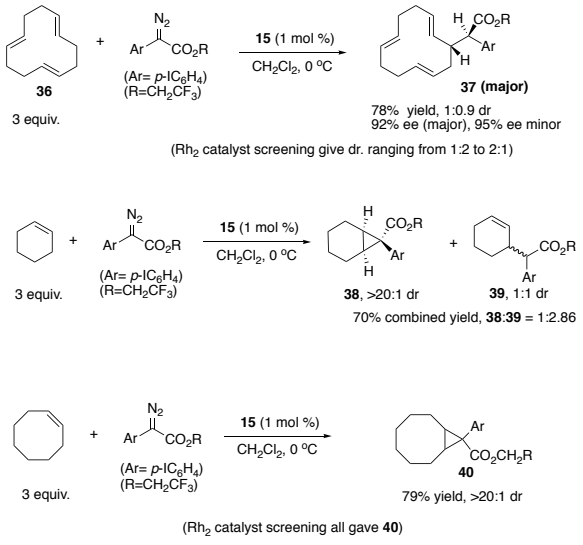
Scheme 5. Double C—H functionalization of COD



*minor dr. is meso compound, the minor dr. for **29** is isolated and characterized in supporting information.
** larger scale of reaction at 0.8 mmol scale of COD

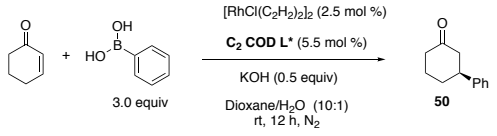
In order to understand the unprecedented site selectivity exhibited by COD, control experiments were conducted on related substrates using Rh_2(2-Cl,5-BrTPCP)$_4$ (**15**) as catalyst (Scheme 6). 1E,5E,9E-Cyclododecatriene (**36**) was found to be an effective substrate, forming the allylic C—H functionalization product **37** with poor diastereoselectivity but high enantioselectivity. The diastereomeric ratio could be altered slightly (2:1 – 1:2) with different dirhodium catalysts, but no catalyst rendered the reaction highly diastereoselective. The reaction with cyclohexene gave a mixture of cyclopropanation (**38**) and C—H functionalization products (**39**), ranging from 1.27:1 to 1:2.85, and the diastereoselectivity was also poor ranging from 3.11:1 to 1:3.12 dr (see supporting information for details). The reaction with cis-cyclooctene, however, was very clean but the only product formed was the cyclopropane (**40**) (scheme 3). These results indicate that the structural features of COD are ideally suited for stereoselective allylic C—H functionalization, and other cycloalkenes can have a very different reactivity profile.

Scheme 6. Evaluation of related cycloalkenes

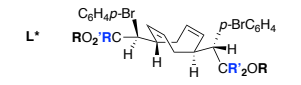


The bis C—H functionalization products can be further derivatized by either ester hydrolysis, ester reduction, or aryllithium addition, and the resulting alcohol products can be either methylated or silylated (See supporting information for details), leading to the formation of a variety of C_2-symmetric chiral COD ligands (**41**-**49**). A preliminary exploratory study was conducted to determine if these chiral COD ligands were compatible with rhodium-catalyzed conjugate addition of phenylboronic acid to cyclohexenone (Scheme 7). The reactions with all of the ligands, except for the aryl iodide derivative **31** resulted in the formation of conjugate addition product **50** in reasonable yield (32-84%) and variable levels of enantioselectivity (26-76% ee). Most of the direct double C—H insertion products gave about 30-40% ee but some of the ligands derived from the aryllithium addition gave higher levels of enantioselectivity. The most promising ligand to date has been **49**, which resulted in the formation of **50** in 63% yield and 76% ee.

Scheme 7. Enantioselective conjugate addition



L*	Ar	R	yield, %	ee, %
28	*p*-BrC_6H_4	CH_3	67	39
29	*p*-BrC_6H_4	CH_2CCl_3	84	34
30	*p*-BrC_6H_4	CH_2CF_3	81	36
31	*p*-IC_6H_4	CH_2CF_3	~2	45
32	*p*-OMeC_6H_4	CH_2CF_3	68	30
33	*p*-$CF_3C_6H_4$	CH_2CF_3	60	33
34	*p*-^{t}BuC_6H_4	CH_2CF_3	45	22
41	*p*-BrC_6H_4	H	43	27



L*	R	R'	yield, %	ee, %
42	H	H	61	26
43	TBS	H	78	53
44	H	Ph	58	47
45	CH_3	Ph	32	60
46	H	*p*-^{t}BuC_6H_4	69	69
47	CH_3	*p*-^{t}BuC_6H_4	81	59
48	H	*3,5*-di-Me-C_6H_4	63	41
49	H	*3,5*-di-^{t}Bu-C_6H_4	63	76

In conclusion, a one-step enantioselective synthesis of C_2-symmetric chiral COD ligands was achieved by means of a double allylic C—H functionalization of COD. This transformation illustrates the capacity of C—H functionalization to rapidly generate synthetic complexity from a simple starting material. Initial evaluation of these chiral COD ligands along with their derivatives revealed they were effective in the rhodium-catalyzed asymmetric arylation of cyclohex-2-enone.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website.
Complete experimental procedures and compound characterization are available in the Supporting Information. (PDF)
CIF file for **22** (CCDC 1960982), **35** (after reduction) (CCDC 1960983), **37** (major) (CCDC 1960993)

AUTHOR INFORMATION

Corresponding Author

* hmdavie@emory.edu
* sblakey@emory.edu

Notes

HMLD is a named inventor on a patent entitled, Dirhodium Catalyst Compositions and Synthetic Processes Related Thereto (US 8,974,428, issued March 10, 2015). The other authors have no competing financial interests.

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