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Cobalt-Mediated, Enantioselective Synthesis of C_2 and C_1 Dienes

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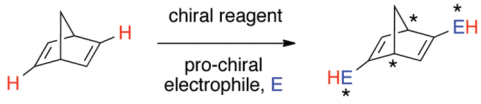
Abstract: The asymmetric C−H functionalization of norbornene and norbornadiene with five-, six-, and seven-membered cyclic enones mediated by the reactive intermediate [{η^5-(^{t}BuMe$_2$Si)C$_5$H$_4$}Co(NO)$_2$] is reported. A novel base mixture derived from enantiopure ammonium salts and NaHMDS was used as a source of chirality, and this enantioselective desymmetrization of C_s alkenes has been applied to the asymmetric synthesis of C_2- and C_1-symmetric diene ligands in high regioselectivity (3.7−20:1 *anti*/*syn*), near perfect diastereoselectivity (>99:1 *dr*), and high enantioselectivity (90−96% *ee*).

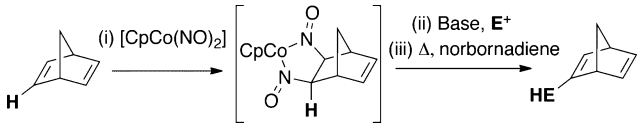
In recent years, enantiopure C_2- and C_1-symmetric dienes have been established as authoritative ligands for asymmetric reactions mediated by late transition metals.[1] Despite their utility, current synthetic routes to these ligands remain unsatisfying and often rely upon preparative chiral HPLC, chiral auxiliaries, chiral pool starting materials, or chemoenzymatic reactions to access enantiopure material.[2−6] Hayashi and co-workers reported an effective enantioselective synthesis of C_2-symmetric dienes based upon the desymmetrization of norbornadiene.[2a,b] In the first step in the synthesis of the chiral ligand, a double asymmetric hydrosilylation of norbornadiene with $HSiCl_3$ catalyzed by [PdCl(η^3-C$_3$H$_5$)]$_2$ and a chiral phosphine ligand was reported to yield an enantiopure di(silane). However, a multistep reaction sequence was required to re-establish the diene moiety and build steric bulk into the chiral scaffold.[2a,b,3]

If the synthesis of C_2-dienes could be achieved *via* a direct desymmetrization of the parent diene by an asymmetric C−H functionalization of the sp^2-carbons, it would represent a concise approach to this important class of chiral ligands (Scheme 1). In addition, the use of a prochiral electrophile in the reaction would allow for the preparation of enantiopure ligands that bear additional stereocenters, provided these reactions proceed with high stereoselectivities.

Scheme 1. Synthesis of C_2-Dienes by Desymmetrization of Norbornadiene



Scheme 2. C−H Functionalization Mediated by [CpCo(NO)$_2$]



Recently, we reported a stepwise C−H functionalization of the sp^2 carbon of simple alkenes mediated by the reactive intermediate [CpCo(NO)$_2$] (Scheme 2).[7−9] Herein we report that *N*-benzylated ammonium chloride salts (Chart 1, **1**−**4**) combined with sodium hexamethyldisilazide (NaHMDS) can promote this reaction, while serving as a source of chirality to desymmetrize norbornene and norbornadiene. This methodology has been applied to a modular asymmetric synthesis of C_1- and C_2-symmetric diene ligands.

Initial experiments demonstrated that addition of a mixture of NaHMDS and the quininium salt **1** to a mixture of 2-cyclohexen-1-one and cobalt complex **5** gave adduct **6** in 87% *de* and high yield. Subsequent cycloreversion of **6** in the presence of norbornene yielded **5** and the diastereomerically impure alkene **7** which was obtained in a low but significant 18% *ee* (Table 1, entry 1). The order of reagent addition proved to be critical to the enantioinduction; in fact, adding NaHMDS to a mixture containing the remaining reagents gave the product with only 2% *ee* (entry 2). As NaHMDS alone can promote a racemic background reaction, we suspect a chiral base formed upon mixing **1** with NaHMDS is responsible for the observed enantioinduction.

Chart 1. *N*-Benzylated Ammonium Chlorides

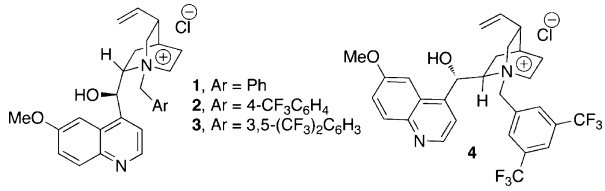
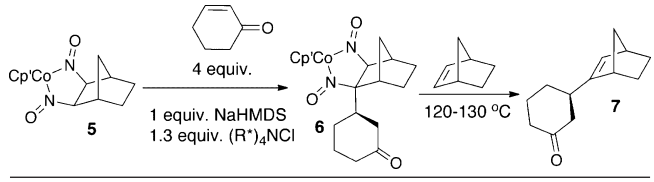


Table 1. Screening of Reaction Conditions for Addition of Norbornene to 2-Cyclohexen-1-one



Entry	Temp (°C)	Solvent	Cp′	(R*)$_4$NCl	time	Yield of **6**	*de* of **6**	*ee* of **7**[a]
1	25	THF/HMPA[c]	Me$_4$Cp	**1**	3 h	87%	87%	18%
2[b]	25	THF/HMPA[c]	Me$_4$Cp	**1**	4 h	81%	72%	2%
3	25	THF	Me$_4$Cp	**1**	17.5 h	75%	94%	36%
4	−60 to 0	THF	Me$_4$Cp	**1**	6 days (14 h at 0 °C)	74%	>99%	58%
5	0	THF	tBuCp	**1**	22 h	35%	>99%	72%
6	−45	THF	tBuCp	**2**	17 h	53%	>99%	74%
7	−58	THF	TBDMSCp	**3**	15 h	73%	>99%	83%

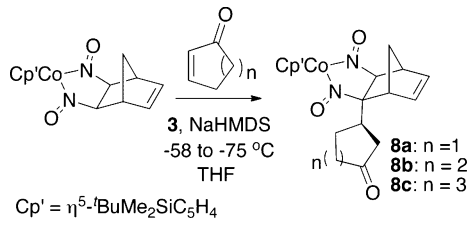
[a] NaHMDS and (R*)$_4$NCl premixed and filtered, *ee* of major diastereomer only. [b] NaHMDS added to mixture of substrates and (R*)$_4$NCl. [c] 5.3:1 THF to HMPA. Abbreviations: Me$_4$Cp = η^5-Me$_4$C$_5$H, ^{t}BuCp = η^5-^{t}BuC$_5$H$_4$, TBDMSCp = η^5-^{t}BuMe$_2$SiC$_5$H$_4$.

Several alternative solvents gave comparable or inferior results compared to those observed with THF/hexamethylphosphoramide

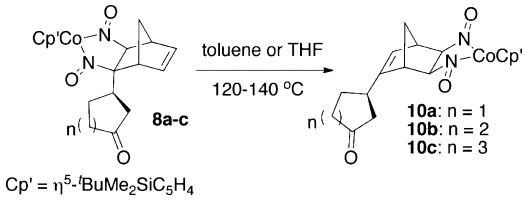
(HMPA). Performing reactions in THF, however, gave significantly higher *ee* at room temperature (entry 3), while lowering the reaction temperature to −60 °C increased the *ee* to 58% (entry 4). It is noteworthy that at lower temperatures, commensurate with the improvement of enantioselectivity, there was an improvement in the diastereoselectivity of the reaction. Employing the bulkier and more directional ligand [η^5-(^{t}Bu)C_5H_4] on cobalt allowed optimization to 72% *ee* (entry 5). Comparable results were obtained with [η^5-(^{t}BuMe$_2$Si)C_5H_4] in place of the [η^5-(^{t}Bu)C_5H_4] ligand, and using quininium salts bearing trifluoromethyl groups on their *N*-benzyl moieties allowed further optimization, with the bis(trifluoromethyl) substituted salt **3** yielding the Michael adduct **6** in 73% yield and >99% *de* and the corresponding alkene in 83% *ee* (entry 7).

Using these conditions, we examined the asymmetric C−H functionalization of both norbornene and norbornadiene with five-, six-, and seven-membered cyclic enones. The details of these experiments are provided in the Supporting Information (Table S3). Michael addition reactions proceeded in good yields (66−90%) to give enantioenriched cobalt complexes with high diastereoselectivity (>99% *de*) with subsequent retrocycloaddition yielding alkene products with moderate enantioselectivity (43−85% *ee*). The enantioselective functionalization of norbornadiene prompted the application of this methodology to asymmetric ligand synthesis (Scheme 3). If two sequential C−H activation/Michael addition steps could be carried out efficiently and benefit from double stereodifferentiation, it not only could result in overall higher enantioselectivities but also would obviate the requirement for enantiopure precursors in the synthesis of chiral diene ligands.

Scheme 3. Synthesis of C−H Functionalized Norbornadiene Complexes



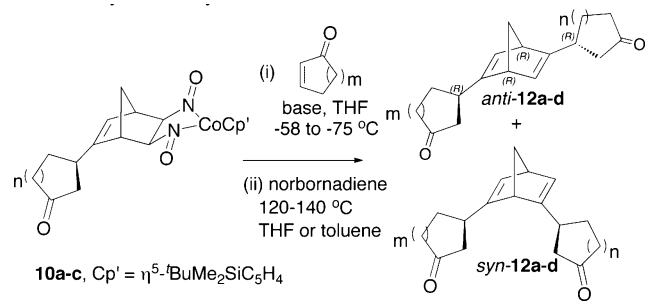
Scheme 4. Isomerization of **8a**−**c** to **10a**−**c**



The first step of this preparation was the isomerization of enantioenriched complexes **8a**−**c** to **10a**−**c** (Scheme 4). Despite the fact that the alkene that accepts the [Cp′Co(NO)$_2$] fragment is not present in excess, these reactions proceeded cleanly and in high yield (80−93%) by simply heating samples of **8a**−**c** in toluene or THF solution. A second asymmetric C−H functionalization of **10a**−**c** yielded a mixture of cobalt complexes *anti*-**11a**−**d** and *syn*-**11a**−**d** which could be converted, *via* alkene exchange with norbornadiene, to a mixture of the corresponding dienes *anti*-**12a**−**d** and *syn*-**12a**−**d** respectively (Table 2).

While poor *anti*/*syn* selectivity (1.3−2.7:1) was observed using achiral starting materials and a nonchiral base (see Supporting Information, Figure S6),[10] by using enantioenriched starting materials and the asymmetric base mixture (*vide supra*) *anti*/*syn* ratios were 3.7−20:1 across the series of substrates. Under these conditions only one diastereomer of each regioisomeric product was observed, and following retrocycloaddition, dienes *anti*-**12a**−**d** were isolated in good yield and 90−96% *ee*.

Table 2. Asymmetric Synthesis of C_2- and C_1-Dienes



n	*m*	complex	yield of **11**[a]	diene	*anti*/*syn*	*ee* of *anti*-**12**
1	1	**11a**	42%	**12a**	3.7:1	90% (*R,R,R,R*)
2	2	**11b**	67%	**12b**	20:1	96% (*R,R,R,R*)
2	2	**11b**	73%[b]	**12b**	10:1	94% (*S,S,S,S*)[c]
3	3	**11c**	87%	**12c**	11:1	91% (*R,R,R,R*)
2	3	**11d**	84%[b]	**12d**	11:1	96% (*R,R,R,R*)

[a] Chiral conditions; **3**/NaHMDS premixed, filtered, and then added to reaction mixture at −58 °C. [b] Reaction conducted at −75 °C. [c] Salt **4** used in place of **3**.

Recrystallization of a mixture of *anti*- and *syn*-**12b** from *n*-pentane removed the minor regioisomer and increased the *ee* to 99%. The absolute configuration of *anti*-**12b** was determined as (*R,R,R,R*)-**12b** by single crystal X-ray diffraction analysis (Figure 1). The enantiomer, (*S,S,S,S*)-**12b**, is available in 94% *ee via* use of chiral ammonium salt **4** in the synthetic sequence.

We propose that the high selectivity in this C−H functionalization reaction sequence occurs because desymmetrization of the nucleophile controls enantioselectivity while the approach of the electrophile controls diastereoselectivity (Figure 2). The two stereoselection events are orthogonal, and two pairs of noncontiguous stereocenters are set with near perfect control in the enantioselective synthesis of the *anti*-regioisomer of these diene ligands. The minor regioisomeric products, *syn*-**12a**−**c**, are *meso*-symmetric and arise from imperfect regiocontrol in the second carbon−carbon bond forming step.

In a further demonstration of utility, the ease of ligand derivatization by functional group manipulation of the ketone moieties of (*R,R,R,R*)-**12b** was demonstrated. Thus, reduction of the carbonyl groups with NaBH$_4$ followed by xanthate formation and Barton−

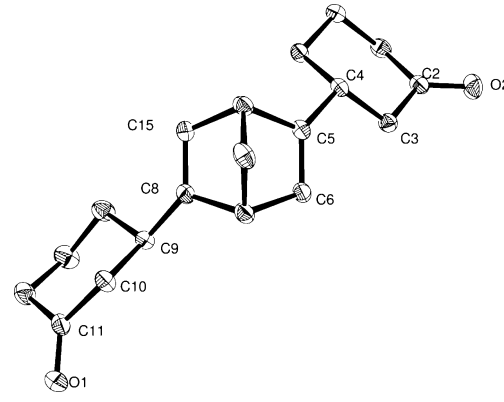


Figure 1. ORTEP representation of (*R,R,R,R*)-**12b**. H-atoms omitted for clarity. Selected bond lengths (Å): C(5)−C(6) 1.332(2), C(5)−C(4) 1.502(2), C(2)−O(2) 1.216(2). Flack parameter = 0.1451(0.1655).

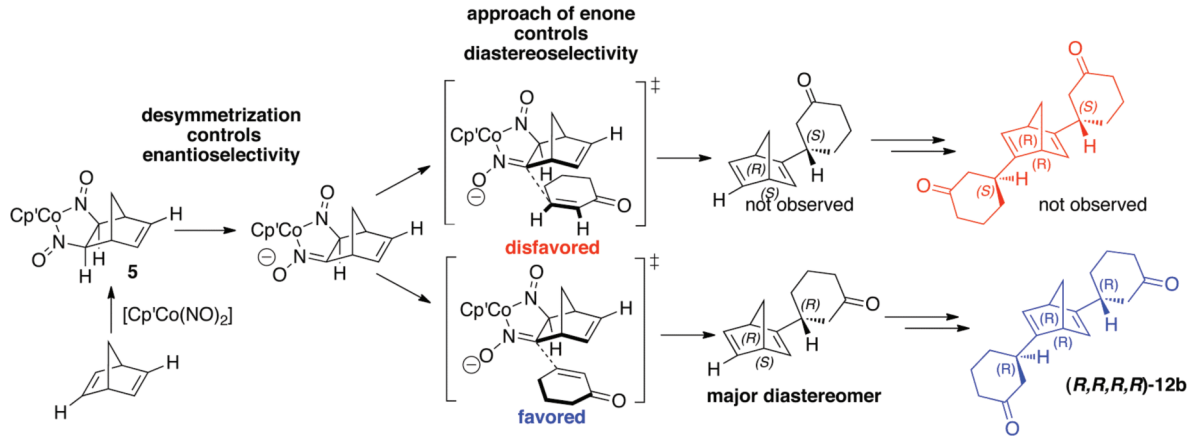


Figure 2. Proposed origin of stereoselectivity.

McCombie reduction yielded (1*R*,4*R*)-2,5-dicyclohexylbicyclo-[2.2.1]hepta-2,5-diene, an effective ligand for rhodium-catalyzed asymmetric conjugate addition (see Supporting Information for experimental details).[3]

In short, we have demonstrated an asymmetric synthesis of C_2- and C_1-symmetric dienes, based upon a C−H functionalization reaction mediated by cobalt di(nitrosyl) complexes that proceeds with excellent regio-, diastereo-, and enantiocontrol. We are continuing to study the nature of the active base derived from quininium salt/metal amide mixtures and the applications of the enantiopure products described herein as ligands in asymmetric catalysis.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds; conditions for chiral GC and HPLC methods; and CIF file for **12b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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