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Enantioselective Cobalt-Catalyzed $[4\pi + 2\pi + 2\pi]$ Cycloadditions

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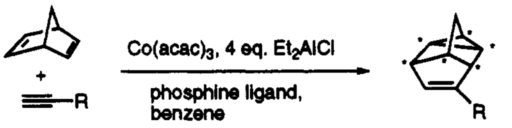
Summary: Cobalt-catalyzed $[4\pi + 2\pi + 2\pi]$ cycloaddition reactions are reported. Various 2-substituted butadienes have been shown to undergo cycloaddition with enantioselectivities of up to 79% ee.

Metal-catalyzed cycloaddition processes are of current interest due to the mild reaction conditions and unique reactivity and selectivity which can be imparted by the metal. Four-, six-, and eight-electron processes have been studied with encouraging results.[2–5] We have focused on determining the scope and limitations of the metal-catalyzed $[2\pi + 2\pi + 2\pi]$ homo Diels–Alder (HDA) reaction as a method for the synthesis of strained polycyclic compounds.[6–10] A cobalt complex in the presence of catalytic quantities of a chiral phosphine leads to substituted deltacyclenes with high enantioselectivity where six stereocenters were created in a single operation, eq 1. Enantiomeric excesses up to 91% were obtained.[6,10]



(1)

As part of a synthetic program aimed at the synthesis of terpenoids such as longicyclene and the pseudoguianolides,[17–20] we investigated a related $[4\pi + 2\pi + 2\pi]$ cycloaddition process between a 1,3-diene and norbornadiene (NBD).[9] In contrast to the excellent methods which exist for achieving good asymmetric induction in $[2\pi + 2\pi]$ and $[4\pi + 2\pi]$ cycloadditions, reports of successful enantioselective higher order cycloadditions are sparse.[11,12] We now describe an enantioselective higher order cycloaddition reaction with enantiomeric excesses >70%. The diene–norbornadiene coupling reaction generates a seven-membered ring and a cyclopropane in one operation, eq 2.

Our initial studies focused on the cycloaddition between norbornadiene and isoprene (eq. 2, R = Me), Table I.[13] Typical reaction conditions consisted of the use of 2 mol% of the cobalt salt, 2 mol% of the chiral phosphine, and 4 equiv of Et$_2$AlCl (based on Co).[6] An excess of diene (1.5–3 equiv) vs norbornadiene was necessary to minimize the competitive homodimerization of norbornadiene[16] and the

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(13) A typical procedure is as follows: Azeotropically dried Co(acac)$_2$ (2 mol%) and the phosphine ligand (2 mol%) were added to a flask followed by the solvent, diene, and norbornadiene. After 5 min, a pink suspension was formed. Diethylaluminum chloride (4–5 equiv based on Co(acac)$_2$) was added dropwise producing a brownish-green solution. The reaction was stirred for 24–48 h and then the solution was passed through a short plug of silica gel to remove the catalyst. The resulting colorless solution was purified by bulb-to-bulb distillation or flash column chromatography.

(14) Mosher's model was found to be reliable in the HDA studies, see ref 6 and (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. (b) Dale, J. E.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. For the use of *O*-methylmandelate esters, see: (c) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M. *J. Org. Chem.* **1986**, *51*, 2370. (d) Roy, B.; Deslongchamps, P. *Can. J. Chem.* **1985**, *63*, 651.

(15) (a) Deprotonation is isoprene (KO^{t}Bu, LiTMP, THF) and trapping with octyl bromide or ethylene oxide provided efficient synthesis of **1b**, **1d**, and **1e**. For the direct metalation of isoprene, see: Brandsma, L.; Klusener, P. A. A.; Hommes, H. H.; Verkruijsse, H. D. *J. Chem. Soc., Chem. Commun.* **1985**, 1677. (b) **1f** was prepared by a coupling reaction between 2-chlorobutadiene and (chloromethyl)trimethylsilane using Ni(dppp)Cl$_2$ as catalyst. For experimental details, see: Sakurai, H.; Hosomi, A.; Saito, M. *Tetrahedron Lett.* **1979**, *21*, 429.

(16) When norbornadiene was subjected to the same experimental conditions in the absence of any other diene, 52% of NBD dimer was formed, see ref 21 and (a) Schrauzer, G. N.; Ho, R. K. Y.; Schlesinger, G. *Tetrahedron Lett.* **1970**, 543. (b) Schrauzer, G. N.; Bastian, B. N.; Fosselius, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 4890.

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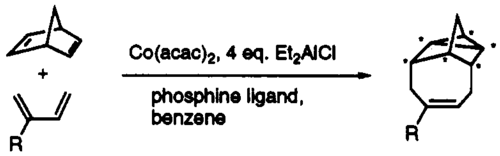


(2)

loss due to polymerization of the diene. Enantioselectivity was measured for a series of phosphines. In contrast to our results in the HDA study where (*S*,*S*)-chiraphos gave the highest ee's, (*R*)-prophos was found to be superior in the eight-electron cycloaddition. The other phosphines led to reduced yields of the desired cycloadduct and an increase in the presence of the norbornadiene dimer and a cycloadduct from [4π + 2π] cycloaddition of the unsubstituted olefin with norbornadiene, Table I.[21]

Co(acac)$_2$ or Co(acac)$_3$ in the presence of the reducing agent were both effective as precatalysts and gave similar levels of asymmetric induction but catalysts formed from the *in situ* reduction of Co^{+2} gave higher yields and so this system was used for the remainder of the studies. The [4π + 2π + 2π] reaction was substantially slower than the acetylene–NBD cycloadditions[6] and required >24 h for all substrates. Benzene or benzene/toluene mixtures were the only solvents studied which led to cycloadduct. We had previously noted that addition of THF minimized the NBD-dimerization by deactivating the catalyst; however, the complexing ability to THF to the metal catalysts totally inhibited the [4π + 2π + 2π] cycloaddition.

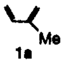
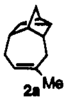
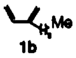
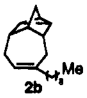
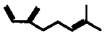
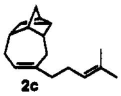
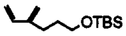
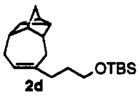
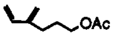
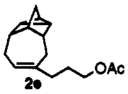
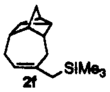
In order to study the generality of the reaction, other dienes were prepared and subjected to the standard conditions, Table II.[15] In contrast to the reaction of NBD and acetylenes where significant effects were noted as R was varied, very little change in the ee was observed for the 2-substituted dienes. However, the yields were generally in the 40–65% range probably due to the competing polymerization of the dienes under the reaction conditions. Remote oxygens in the form of silyl ethers or esters had little or no effect on the ee nor did an allylic silicon (Table II, entries 4–6).

The ee of the cycloadducts was determined using the same strategy as previously described for the HDA reaction.[6] Hydroboration–oxidation (BH$_3$, NaOH, H$_2$O$_2$) gave a single regio- and stereoisomeric alcohol which was esterified with the Mosher acid chloride. The diastereomeric ratio was measured by ^{1}H and/or ^{19}F NMR. This approach was not suitable for **2c** since selective hydroboration of the endocyclic olefin was not possible in the presence of the remote olefin. Instead the ee was determined by conversion of **2d** into **2c** and comparison of the optical rotations. This process involved cleavage of the acetate protecting group, Swern oxidation of the alcohol to the aldehyde, and Wittig olefination (Me$_2$C=PPh$_3$, THF, rt).

Table I. Asymmetric [4π + 2π + 2π] Cycloaddition between NBD and Isoprene with Different Chiral Phosphine Ligands

ligand	catalyst	yield, %	[α]$_D$, deg	ee, %
(*R*)-PROPHOS	Co(acac)$_2$	66	−20.6	72
	Co(acac)$_3$	57	−21.5	74
(*S*,*S*)-CHIRAPHOS	Co(acac)$_2$	25	+11.5	40
(*S*,*S*)-Me-BPE	Co(acac)$_2$	40	+10.1	35
(*R*,*R*)-iPr-BPE	Co(acac)$_2$	12	+11.5	40
(*S*,*S*)-Me-DuPHOS	Co(acac)$_2$	18	−2.4	9

Table II. Asymmetric [4π + 2π + 2π] Cycloaddition between NBD and Various 2-Substituted Buta-1,3-dienes

diene	[4 + 2 + 2] cycloadduct	yield,[a] %	[α]$_D$,[b] deg	ee, %
 **1a**	 **2a**	66	−20.6	72
 **1b**	 **2b**	40	−5.1	74
 **1c**	 **2c**	49	−10.5	79
 **1d**	 **2d**	40	−5.4	73
 **1e**	 **2e**	52	−6.3	73
 **1f**	 **2f**	49	−13.5	71

[a] In case of **2a**, **3c**, and **2f**, 5–10% of NBD dimer was inseparable from the [4 + 2 + 2] cycloadducts. The yields indicated above were corrected from the unseparated NBD dimers. [b] The [α]$_D$s of **2a**, **2c**, and **2f** were also corrected from the unseparated NBD dimer by correcting the concentration.

The absolute stereochemistry of the cycloadducts can be assigned by using Mosher's model.[14] (*R*)-prophos gives the cycloadducts with the absolute stereochemistry as depicted in eq 2. The same sense of asymmetric induction was observed in the [2π + 2π + 2π] homo Diels–Alder reaction.[6] The assignment was supported by X-ray crystallography.[22]

In summary, we have found the first catalysts for promoting a catalytic asymmetric [4π + 2π + 2π] cycloaddition. Application of this reaction in the synthesis of natural and unnatural products is underway.

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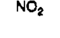
(21) Structure of (i) NBD dimers. (ii) [4π + 2π] cycloadducts.

(22) Cycloadduct **2f** was hydroborated, oxidized (BH$_3$, NaOH, H$_2$O$_2$), and esterified with *O*-methylmandelic acid/DCC.[14c,d] After separation of the major diastereomer, treatment with NaOMe and MeOH gave the alcohol as a single enantiomer. Esterification with 3,5-dinitrobenzoyl chloride and recrystallization from metanol/pentane (1:1) gave suitable quality crystals. The absolute configuration proposed from the Mosher model was supported by X-ray crystallography of the 3,5-dinitrobenzoate ester.



Research, Eli Lilly and Co., and the Alfred P. Sloan Foundation for their generous support of our programs, and Dr. Mark Burk (Dupont Central Research) for providing samples of chiral Duphos ligands. Dr. Alan Lough, University of Toronto, is thanked for the X-ray structure determination.

Supplementary Material Available: Experimental procedures and compound characterization data (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.