Readily Available [2.2.2]-Bicyclooctadienes as New Chiral Ligands for Ir(I): Catalytic, Kinetic Resolution of Allyl Carbonates

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The design, synthesis, and study of novel chiral ligands for metals offer new opportunities in the development of reaction processes leading to useful building blocks for chemical synthesis.[1] The advances in the application of late transition metals for asymmetric catalysis have primarily been fueled by phosphorus and nitrogen ligands. We have become interested in addressing the question of whether chiral dienes could be employed as ligands for enantioselective reaction processes involving late transition metals. In a recent report, Hayashi documented a chiral norbornadiene–Rh complex in the conjugate addition reaction of phenyl boronic acids to enones.[2] Independently and concurrently, we have been investigating chiral dienes as ligands for catalytic iridium-mediated processes. Herein we report chiral [2.2.2]-bicyclooctadienes as a new family of ligands. These are notable because of their convenient preparation in optically active form from (*R*)- or (*S*)-carvone. We demonstrate the potential utility of these ligands in Ir(I)-catalyzed kinetic resolution of allylic carbonates **2** (Scheme 1).[3,4]

Catalytic, enantioselective allylation reactions using transition-metal complexes have become one of the work-horses in asymmetric synthesis.[5,6] Such processes can be quite general; they have been shown to be amenable to variation in ligand and metal as well as the allyl donors and nucleophilic reactants.[7,8] These have been the subject of in-depth mechanistic studies that have themselves become classics.[9] Although the allylation reaction of malonate and related nucleophiles has been the subject of intense investigations, the use of phenols in enantioselective allylation chemistry has only recently been studied.[10a] The Pd-catalyzed reaction of allylic carbonates and phenols has been examined by Trost using *C*₂-symmetric chiral bisphosphine ligands.[10] In a similar fashion the use of the same phosphine ligands has permitted the resolution of Baylis–Hillman adducts with substituted phenols to give optically active β-phenoxy-α-methylene nitriles and esters.[10b] Most recently, Hartwig has documented the use of monophosphine complexes in the reaction of allylic carbonates and lithium phenoxides.[11]

Our recent interest in catalysis by late transition metals[12] led to a study of chiral dienes as ligands for Ir(I) in allylic displacement reactions. However, given the lack of precedence using chiral diene–Ir complexes as catalysts, we set out to examine the general reactivity of diene–Ir complexes which could subsequently be made chiral and nonracemic. In this respect, the reaction of **2** (R = Ph) with phenol and catalytic [IrCl(COD)]₂ served as a benchmark: the formation of the phenyl ether proceeds to completion at 23 °C in 24 h. Accompanying studies revealed that [IrCl(COE)₂]₂ (COE = cyclooctene) was inactive as a catalyst. Subsequent prospecting studies with two [2.2.1]-bicyclo-heptadienes **4** and **5** as ligands gave unsatisfactory results (Chart 1). Norbornadiene (**4**) only furnished adducts after 4 days, with concomitant byproduct formation. The 2,5-diphenyl-substituted counterpart **5** failed altogether to form a complex with Ir(I). In stark contrast, the simple [2.2.2]-bicyclooctadiene ligand **1a**, however, gave a complex whose reactivity
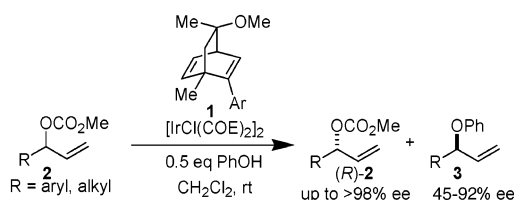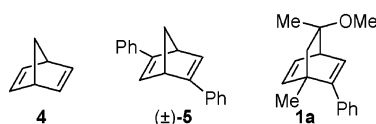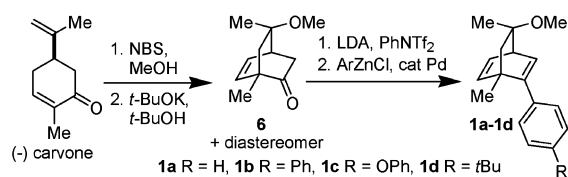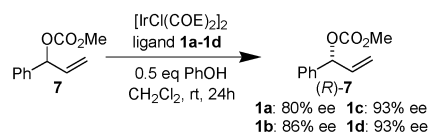
Scheme 1

Chart 1

Scheme 2

Scheme 3

equaled that of [IrCl(COD)]₂. Thus, we decided to focus on [2.2.2]-bicyclooctadiene ligands.[13]

A key factor that determines the utility of any ligand for asymmetric catalysis is the ease with which it can be accessed. We recognized that the core scaffold for a chiral [2.2.2]-bicyclooctadiene could be derived from (*R*)- or (*S*)-carvone. Because of their use in cosmetics and flavorings (e.g., spearmint chewing gum), both are available in bulk cheaply at <$100/kg.[14] Significantly, in two steps (NBS/MeOH then KO*t*Bu/*t*BuOH) this terpene is converted into alkenyl ketone **6** in 68% yield as a mixture of diastereomers, easily separated by chromatography on silica gel.[15,16] Ketone **6** can then be converted into the corresponding triflate which is a substrate for Pd-mediated coupling reactions (46% yield, two steps), permitting access to dienes **1a**–**d** (Scheme 2).[17] Thus, this family of [2.2.2]-diene ligands can be synthesized in large scale in four steps. This contrasts with the enantioselective synthesis of the [2.2.1]-norbornadiene ligand which prescribes nine steps, proceeds in 10% overall yield from the achiral norbornadiene, and consequently necessitates the use of an expensive chiral ligand (MOP) for Pd.[2]

At the outset (Scheme 3), we noted that treatment of allylic carbonate **7** with phenol and Ir(I) complexes prepared in situ from [IrCl(COE)₂]₂ with **1a**–**d** leads to formation of the phenyl ether

Table 1. Kinetic Resolution of Allylic Carbonates (Scheme 1)[a]

entry	R	yield/% (%)[b]	ee/% [c]
1	C_6H_5	32 (72)	93
2	2-naphthyl	33 (81)	94
3	1-naphthyl	28 (78)	90
4	$(3\text{-MeO})C_6H_4$	37 (87)	97
5	$(4\text{-Br})C_6H_4$	38 (88)	97
6	$(4\text{-Cl})C_6H_4$	39 (87)	91
7	$(4\text{-F})C_6H_4$	34 (82)	85
8	$(3\text{-Br})C_6H_4$	40 (90)	88
9	$(4\text{-CF}_3)C_6H_4$	37 (83)	96
10	$(4\text{-NO}_2)C_6H_4$	45 (94)	95
11	$(4\text{-CO}_2\text{Me})C_6H_4$	46 (91)	80
12	$(3\text{-Me})C_6H_4$	39 (89)	80
13	$(4\text{-Me})C_6H_4$	28 (78)	87
14	cC_6H_{11}	30 (68)	>98
15	$BnOCH_2$	32 (77)	84

[a] Reactions conducted with 1.5 mol % $[IrCl(COE)_2]_2$, 3.6 mol % **1d** and 0.5 mmol **2** in 3 mL of CH_2Cl_2. [b] The combined yield of recovered optically active carbonate and optically active phenyl ether in parentheses. [c] ee was determined by chiral HPLC; the absolute configuration has been established as (R) for entries 1, 3, and 6. For details see Supporting Information.

with enantiomeric excesses ranging from 51 to 71%. The recovered starting carbonate was isolated in good yield and 80−93% ee. While both are isolated in optically active form, the enantioselectivity of the recovered starting material is particularly noteworthy as a lead result, given that the optically active allyl carbonates reisolated are preparatively useful as chiral building blocks.[18,19] Because diene **1d** proved optimal (with respect to scope along with selectivity) and was crystalline, it was chosen for subsequent study.

As shown in Table 1,[20] the reaction is conveniently carried out at room temperature with 1.5 mol % $[IrCl(COE)_2]_2$ and 3.6 mol % **1d**.[21] A broad range of aryl- and alkyl (entries 14 and 15)-substituted allylic carbonates can be successfully employed, with respect to the former, both electron-rich and -deficient serve as substrates for the reaction.[22]

The reactivity differences of the Ir(I) complexes as a function of the structure of the bicyclic diene ([2.2.1] versus [2.2.2]) observed in the prospecting studies were intriguing. We proceeded to examine whether such differences would be manifest in other reactions, such as the conjugate addition reaction of $PhB(OH)_2$ to cyclohexenone reported by Hayashi.[2] In this regard, although chiral 2,5-dibenzyl-NBD·Rh(I) was reported to work well, the corresponding **1d**·Rh-(I) complex furnished product in only 52% yield and 71% ee. Thus, the [2.2.1] and [2.2.2] ligands complement each other, and display different preferences as a function of metal and reaction processes. These observations suggest that further investigations on the use of both are warranted and potentially fruitful.

In conclusion, we report a novel chiral diene ligand. A salient feature of the bicyclooctadiene ligand is its convenient synthesis in four steps from readily available, inexpensive (R)- or (S)-carvone. Another attractive aspect of the route to the ligand is the fact that the modulating group is introduced in the last step of the synthetic sequence and, more generally, that it provides access to a variety of [2.2.2]-dienes which are of potential interest for other transition-metal catalyzed processes. We have introduced their use in the context of the Ir(I)-catalyzed kinetic resolution of chiral allylic carbonates, which can be isolated in up to 98% ee and are useful in numerous asymmetric processes for complex molecule synthesis.[23] Further studies and applications are at present being conducted and will be reported in due time.

Supporting Information Available: Experimental procedures and spectral data for all products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The versatility of the ligand synthesis can be exemplified by a route to another [2.2.2]-bicyclooctadiene skeleton, under current investigation.
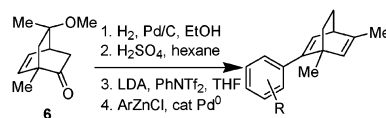
(18) The fact that the phenyl ethers vary in enantioselectivity much more than the isolated carbonates, for a given conversion, is an interesting mechanistic aspect which is currently being investigated.
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(20) The yields (%) and ees (%) of the phenyl ethers are: entry 1: 40, 66 ee; entry 2: 48, 80 ee; entry 3: 50, 73 ee; entry 4: 50, 77 ee; entry 5: 50, 87 ee; entry 6: 48, 87 ee; entry 7: 48, 53 ee; entry 8: 50, 80 ee; entry 9: 46, 82 ee; entry 10: 49, 86 ee; entry 11: 45, 92 ee; entry 12: 50, 45 ee; entry 13: 50, 75 ee, entry 14: 38, 72 ee; entry 15: 45, 61 ee; for details, see Supporting Information.
(21) The selectivity factors were roughly calculated to be in general range between 5 and 15 for most substrates (with single entries as high as 30).
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