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Enantioselective, Zirconium-Mediated Synthesis of Allylic Amines

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The development of simple and general methods for the preparation of enantiomerically pure organic compounds from readily available, achiral substrates is one of the major challenges of organic synthesis today.[1] A reagent-controlled approach[2] is particularly useful because it allows for the formation of either enantiomer of a particular compound from the same substrates. We recently reported a method for the synthesis of racemic allylic amines from simple amines and unfunctionalized alkynes via imine complexes of zirconocene,[3] and we now report the development of an *asymmetric* variant of this reaction that proceeds to give products with ee's up to 99% in moderate to good yields.[4]

We required a chiral equivalent of zirconocene dichloride, the achiral organometallic precursor to much of the chemistry we have previously described, for use as a starting material. Several such compounds have been synthesized,[7] and we chose to focus our attention on [1,2-ethylenebis(η^5-4,5,6,7-tetrahydro-1-indenyl)]-zirconium dichloride [(EBTHI)$ZrCl_2$, **1**],[7a-c,8] first synthesized by Brintzinger. Briefly, kinetic resolution of **1**[10] was accomplished by using lithium (*S*)-[1,1′-binaphthyl]-2,2′-diolate, in a method similar to that used to resolve the titanium analogue,[11] and unreacted **1** was removed by stirring with alumina. The enantiomerically pure dimethyl derivative, (*S,S*)-**2** ($[\alpha]^{21}_D = +170 \pm 3°$ (c = 0.05, CH_2Cl_2)), was obtained in 63% overall yield from (*S,S*)-**1**.[12]

Scheme I

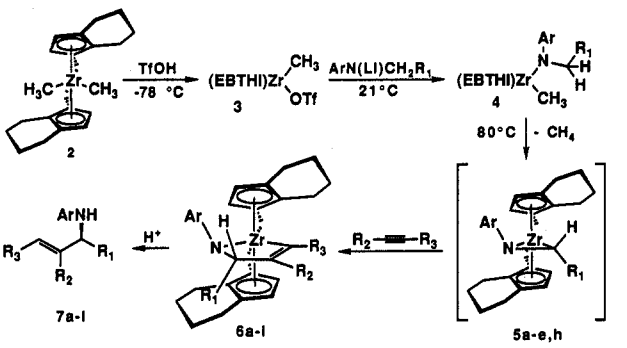
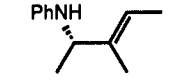
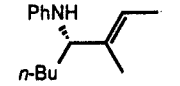
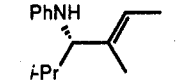
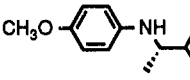
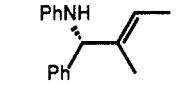
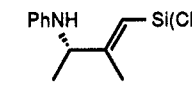
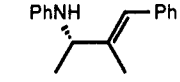
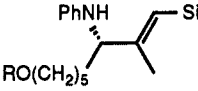
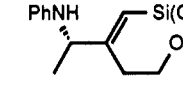
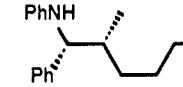
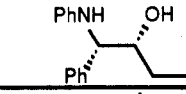


Table I

product	structure[a]	yield,[b] %	ee,[c] %	diastereo- or regioselectivity[d]
7a		72	>95	–
7b		72	>95	–
7c		60	>95[e]	–
7d		64	~99	–
7e		38	18	–
7f		68	>95	24:1
7g		50	>90	100:0[f]
7h		53	>95	22:1
7i		59	>95	17:1
8		54	high[g]	8:1
9		43	94[h]	7:1

[a] R = Si(*t*-Bu)$(CH_3)_2$. [b] Isolated yields, >95% pure by GC and ^1H NMR, of both diastereomers or regioisomers where applicable. [c] By Eu(hfc)$_3$ shift studies, except where noted. [d] The minor component was established to be an isomer by comparison of the GC-MS of the two species. [e] Determined by capillary GC on a CyclodexB chiral column (J&W Scientific). [f] The regioisomer was initially present (7:1 ratio), but it was removed during chromatography. [g] One diastereomer of the metallacycle precursor was clearly predominant by ^1H NMR. [h] Determined by ^{19}F NMR studies of the Mosher's ester of the major diastereomer.

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(4) Until now, the only methods (to our knowledge) for the preparation of enantiomerically pure allylic amines involved the modification of enantiomerically pure allylic alcohols, amino acids, or α-hydroxy esters[5] or the action of a chiral palladium catalyst on amines and racemic, symmetrically substituted allylic carbonates or phosphinates.[6]
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(8) Enantiomerically pure **1** has been used as a precatalyst for the catalytic asymmetric hydrogenation[9a] and oligomerization[9b] of olefins, and its titanium analogue has been used for the stoichiometric, asymmetric allylation of aldehydes.[9c]
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For the synthesis of allylic amines, compound **2** was treated with 1 equiv of triflic acid at −78 °C to afford **3** (see Scheme I). A solution of lithium anilide was then added at room temperature, followed by an alkyne, and the solution was heated to 80 °C for several hours. During this time **4** lost methane to give imine complex/zirconaaziridine **5**, which was trapped in situ by the alkyne to give metallapyrroline **6**. We expected that the steric constraints of the EBTHI ligand would force the imine complex **5** to exist only as the trans diastereomer, as shown in Scheme I. Insertion of an alkyne was then expected to proceed with retention of configuration at the imine carbon atom,[14] generating diastereomerically pure metallacycle **6**. Indeed, in most cases, the metallapyrroline **6** appeared to be diastereomerically and regioisomerically pure by ^{1}H NMR. Hydrolysis of **6** (aqueous HCl/ether), followed by chromatographic purification, afforded the allylic amine **7** in moderate to good yield. When (*S,S*)-**2** was used as the starting material, **7** was obtained with ee's >90% to ~99% (except for **7e**; see below).[15] Thus, for 100:1 diastereoselectivity at 80 °C, we compute either $\Delta\Delta G^{\ddagger}$ or $\Delta\Delta G^{\circ} \geq 3.2$ kcal/mol for formation of the two diastereomers of **5**.

The method tolerates a wide variety of structures in both the alkyne and the amine, as shown in Table I, including substrates with oxygen functionalities. Also, 1-(trimethylsilyl)alkynes and 1-phenylalkynes react in a highly regioselective manner. Unfortunately, terminal alkynes do not insert, giving instead the alkynyl(amido)zirconium species, in contrast to their reaction with imine complexes of unsubstituted zirconocene.[3,16] To our surprise, imine complex **5e** (Ar = R_1 = Ph) does not couple alkynes diastereoselectively, and allylic amine **7e** is obtained with a low ee.[17] However, **5e** does couple diastereoselectively to propionaldehyde and 1-hexene, and good ee's were obtained for the resulting organic compounds. We note that the metallacyclic precursors to compounds **8** and **9** contain *two* new stereogenic centers that have been formed with excellent absolute stereoselectivity.

An X-ray crystallographic study of one of the racemic metallacycles, **6b** (Ar = Ph; R_1 = *n*-Bu; $R_2 = R_3 = CH_3$), allowed us to assign the absolute stereochemistry of the enantiomerically pure amines.[18] The allylic carbon atom possessed *RS* configuration with respect to the ligand's *RS,RS* configuration. Thus, the enantiomerically pure allylic amines derived from (*S,S*)-**2** have the *S* absolute configuration, as drawn in Scheme I.

These results demonstate the feasibility of using **1** and its derivatives as starting materials for asymmetric organic synthesis. The availability of enantiomerically pure **1**, the ability to functionalize unactivated substrates, and the very high ee's obtained for the allylic amines at 80 °C make this an ideal system for further study. We are working to develop several other highly enantioselective, catalytic reactions based on the EBTHI ligand system.

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Supplementary Material Available: Detailed experimental procedures for the resolution of **1** and the synthesis and characterization of **6b**, **7a–i**, **8**, and **9**, experimental details for the crystallographic analysis of **6b**, an ORTEP diagram for **6b**, and lists of atom positions, thermal parameters, and bond lengths and angles for **6b** (26 pages). Ordering information is given on any current masthead page.

(12) Mp 92–135 °C (*rac*-**2**:[13] mp 148–162 °C). The ee was determined by treatment with excess (*R*)-(−)-*O*-acetylmandelic acid in C_6D_6. Only one of the two possible diastereomers could be detected by ^{1}H NMR. See the supplementary material for details of the resolution procedure.

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(15) Ee's of **7** were in most cases determined by comparison of the ^{1}H NMR spectra of the racemates with those of the enantioenriched compounds, upon addition of Eu(hfc)$_3$.

(16) Coordination of a second ligand, which is not possible for (EBTHI)Zr–imine complexes but occurs for Cp_2Zr–imine complexes, has been shown to alter the insertion reactivity of at least one other complex of zirconocene. Buchwald, S. L.; Lum, R. T.; Dewan, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 7441.

(17) (a) The de of the metallacycle **6e** (as observed by ^{1}H NMR) is dependent on the reaction conditions, ranging from ca. 50% down to ca. 0%. (b) In contrast to *N*-phenylbenzylamine and dibenzylamine, *N*-(trimethylsilyl)benzylamine does couple diastereoselectively to 2-butyne, as observed by ^{1}H NMR.

(18) Full details are given in the supplementary material.

Coronene Dication: A Thermally Accessible Triplet†

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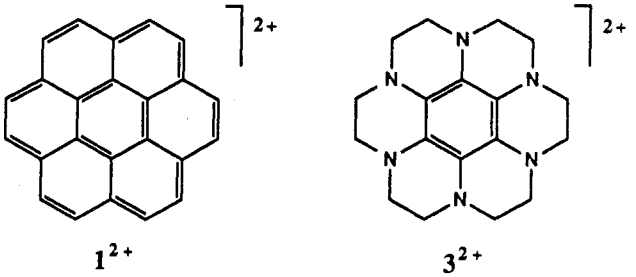
We find that the reaction of coronene (**1**) with strong oxidants yields the ESR spectrum of a thermally accessible triplet associated with the dipositive ion $\mathbf{1}^{2+}$. The triplet arises, by Hund's rule, from the 2-fold degeneracy of the HOMOs of the 6-fold-symmetric framework. The species is surprisingly stable at ambient temperature, decomposing above 50–70 °C. $\mathbf{1}^{2+}$ and the previously reported coronene dianion[1] $\mathbf{1}^{2-}$ provide a pair of aromatic diions to test if the MO-pairing relationships for alternate hydrocarbons[2] can be extended to their triplet states. Dications of benzene derivatives of 3-fold or higher symmetry[3] have also been of recent interest as potential components of molecular ferromagnetic materials.[4]

As an unsubstituted aromatic dication, $\mathbf{1}^{2+}$ may be compared with the substituted cases reported previously. The hexachlorobenzene dipositive ion ($\mathbf{2}^{2+}$) is a ground-state triplet.[5] No evidence for a thermally excited singlet state was found. The species was produced by reaction of **2** with Cl_2/SbF_5 to produce the radical cation; irradiation at 4–100 K yielded the dication. The latter did not survive softening of the SbF_5 matrix at about 180 K. The elegant synthesis of a derivative of hexaaminobenzene by Breslow et al., and its oxidation to a dication ($\mathbf{3}^{2+}$) exhibiting a triplet ESR



$\mathbf{1}^{2+}$ $\mathbf{3}^{2+}$

spectrum, provided a system stable at ambient temperature.[6] A

† Contribution No. 5706.

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