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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

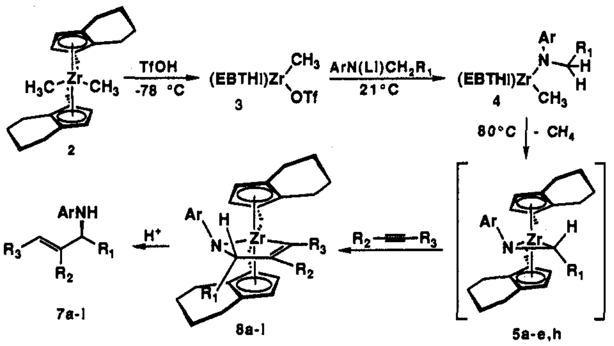
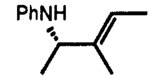
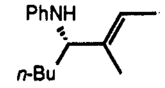
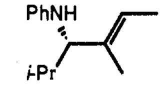
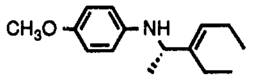
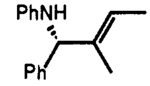
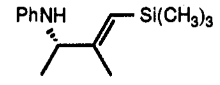
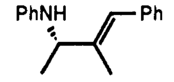
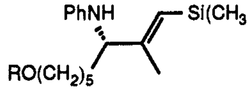
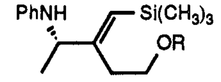
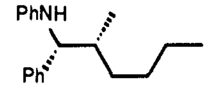
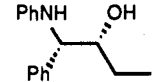


Table I

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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(1) For a collection of reviews, see: *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vols. 1-5.

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(3) Buchwald, S. L.; Watson, B. T.; Wannamaker, M. W.; Dewan, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 4486.

(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]

(5) Synerholm, M. E.; Gilman, N. W.; Morgan, J. W.; Hill, R. K. *J. Org. Chem.* **1968**, *33*, 1111. Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901. Yamamoto, Y.; Shimoda, H.; Oda, J.; Inouye, Y. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3247. Fitzner, J. N.; Shea, R. G.; Fankhauser, J. E.; Hopkins, R. B. *J. Org. Chem.* **1985**, *50*, 417. Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487. Hill, R. K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, Chapter 8 and references therein.

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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]

(9) (a) Waymouth, R.; Pino, P. *J. Am. Chem. Soc.* **1990**, *112*, 4911. (b) Pino, P.; Cioni, P.; Wei, J. *J. Am. Chem. Soc.* **1987**, *109*, 6189. (c) Collins, S.; Kuntz, B. A.; Hong, Y. *J. Org. Chem.* **1989**, *54*, 4154.

(10) Schäfer, A.; Eberhard, K.; Zsolnai, L.; Huttner, G.; Brintzinger, H. H. *J. Organomet. Chem.* **1987**, *328*, 87.

(11) Wild, F. W. R. P.; Zsolnai, L.; Huttner, G.; Brintzinger, H. H. *J. Organomet. Chem.* **1982**, *232*, 233.

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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.

Acknowledgment. This work was supported by the National Institutes of Health (GM-34917). R.B.G. is the recipient of a National Science Foundation Graduate Fellowship (1987–1990), for which he is grateful. S.L.B. acknowledges additional support as a Camille & Henry Dreyfus Teacher-Scholar (1989–1994), a Fellow of the Alfred P. Sloan Foundation (1988–1992), and a Union Carbide Innovation Recognition Awardee. We thank Dr. Ruth A. Doyle for her help in developing the resolution procedure and Dr. Alberto Gutierrez for his aid in solving the crystal structure.

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.

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(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.

(13) Waymouth, R. M.; Bangerter, F.; Pino, P. *Inorg. Chem.* **1988**, *27*, 758.

(14) (a) Kropp, K.; Erker, G. *Organometallics* **1982**, *1*, 1246. (b) Guram, A. S.; Jordan, R. F. *Organometallics* **1990**, *9*, 2190.

(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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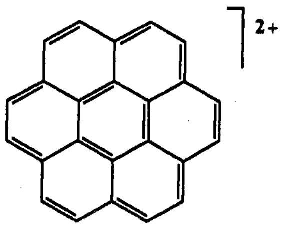
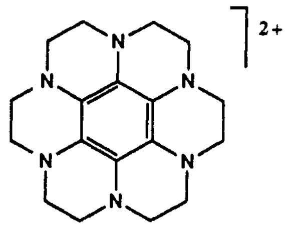
We find that the reaction of coronene (**1**) with strong oxidants yields the ESR spectrum of a thermally accessible triplet associated with the dipositive ion $\mathbf{1}^{2+}$. The triplet arises, by Hund's rule, from the 2-fold degeneracy of the HOMOs of the 6-fold-symmetric framework. The species 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 spectrum, provided a system stable at ambient temperature.[6] A



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



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

[†] Contribution No. 5706.

(1) Glasbeek, M.; van Voorst, J. D. W.; Hoijtink, G. J. *J. Chem. Phys.* **1966**, *45*, 1852.

(2) Cf., e.g.: McLachlan, A. D. *Mol. Phys.* **1959**, *2*, 271. Dewar, M. J. S. *The Molecular Orbital Theory of Organic Chemistry*; McGraw-Hill Book Company: New York, 1969; p 200.

(3) Cf., e.g.: Dougherty, D. A. In *Kinetics and Spectroscopy of Carbenes and Biradicals*; Platz, M. S., Ed.; Plenum Press: New York, 1990; p 117 ff.

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