

Scheme 2.

stereochemistry of **5d** was deduced clearly by means of X-ray crystallography. This tandem cyclization was also applied to allene ketones. Thus allene ketone **4e** was cyclized to give piperidyl-substituted alcohol **5e** in 67% yield (Table 2, entry 5). However, the malonate substrate **4f** gave rise to *cis*-cyclohexanol **5f** (30%) as well as the simple addition product **6** (35%) (Table 2, entry 6).

The exact mechanism of this *cis*-stereoselective tandem reaction has yet to be elucidated. It is presumed that Me₃SiPdSnBu₃ adds initially to the allene moiety to give σ - or π -allyl palladium complexes, which undergo intramolecular carbonyl allyl addition to afford *cis*-cycloalkanols. The *cis* selectivity of the reaction can be ascribed to the fact that intermediate **A**, which leads to the *cis*-cyclopentanol, is energetically more stable than **B**, presumably because of the steric hindrance between TMS and R (R = H, Me) groups (Scheme 2).^[11]

In summary, the palladium-catalyzed regio- and diastereoselective tandem silastannylation/carbonyl allyl addition of allene aldehydes and ketones gives rise to *cis*-cycloalkanols. The process requires a single catalyst and is carried out at constant temperature.

Experimental Section

Typical procedure: trimethyl(tributylstannyl)silane **2** (150 mg, 0.41 mmol) was added to a stirred solution of **1a** (100 mg, 0.38 mmol) and (π -allyl)₂PdCl₂ (6.9 mg, 5 mol %) in THF (3 mL). The reaction mixture was stirred room temperature for 10 min, and the THF solvent was evaporated *in vacuo*. The crude product was separated by means of column chromatography (EtOAc/hexane 1:2) to afford the cyclized product **3a** (91 mg, 71%) as a white solid. M.p. 95 °C; *R*_f = 0.41 (EtOAc/hexane 1:2); ¹H NMR (400 MHz, CDCl₃): δ = 0.00 (s, 9H), 2.35 (s, 3H), 2.89 (m, 1H), 3.29 (dd, 1H, *J* = 9.3, 11.3 Hz), 3.35 (d, 1H, *J* = 11.5 Hz), 3.40 (dd, 1H, *J* = 7.2, 9.3 Hz), 4.05 (m, 1H), 5.59 (d, 2H, *J* = 1.3 Hz), 7.25 (d, 2H, *J* = 8.0 Hz), 7.68 (d, 2H, *J* = 8.0 Hz); ¹³C NMR (125 MHz, CDCl₃): δ = 147.9, 145.0, 135.7, 131.2, 129.7, 129.1, 72.2, 57.7, 50.1, 49.8, 23.1, 0.0; HR-MS: calcd for C₁₆H₂₃NO₃Si: 339.1324, found: 339.1366.

Typical experimental procedures for the preparation of **1a**, **1c**–**1e**, **4c**–**4f**, **3a**, spectroscopic and analytical data for **1a**–**1e**, **4a**–**4f**, **3a**–**3e**, **5a**–**5f**, **6**, and X-ray crystallographic data of **5d** can be found in the Supporting Information.

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IAN-Amines: Direct Entry to a Chiral C₂-Symmetric Zirconium(IV) β -Diketimine Complex**

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The immense utility of metallocene-based catalysts for synthesis^[1] has stimulated the development of non-metallocene complexes that conserve metallocene topographies but offer a greater degree of accessibility and/or improved performance.^[2] A number of recent publications have demonstrated that amidinate ligands,^[3,4] β -diketimines,^[5–7] and other variations on the [1,*n*]-bisimine template are promising in this regard for group IV metals. In general, ligands used as the basis for a non-metallocene complex must 1) bind to the

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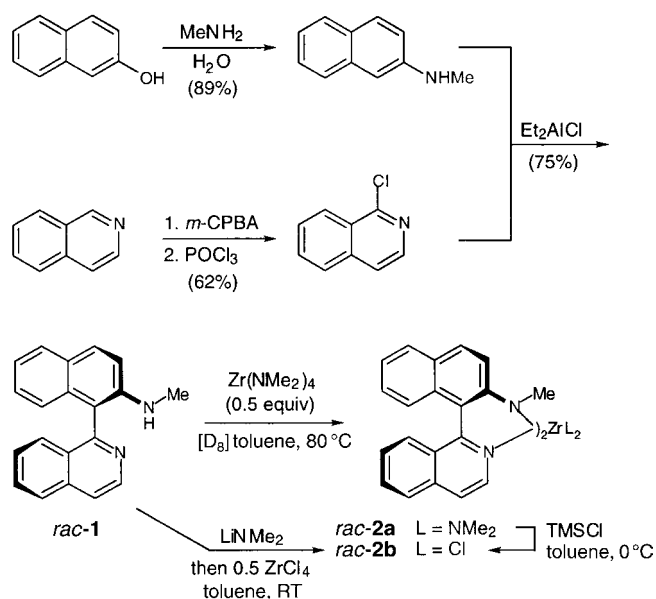
[**] Financial support has been provided by a GAANN Fellowship to S.B.C. (2001) and by Indiana University. IAN-amines are amines that are derived from Isoquinoline and 2-Amino Naphthalene.

Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.

metal organizational center in a manner of high symmetry while 2) leaving the metal with substantial (catalytic) reactivity.^[8]

Chiral β -diketimine **1** (see Scheme 1) and related derivatives are conspicuously absent from the literature^[9] despite the similarity to countless binaphthyl-based ligands that have proven broadly useful in metal-mediated asymmetric synthesis.^[10] As a potential bidentate ligand, this class of β -diketimines is particularly interesting since the usually non-planar binaphthyl backbone prevents a full resonance interaction observed in most β -diketimines. However, the attenuation of resonance and the associated electronic differentiation of the ligating nitrogen atoms might be used to achieve stereocontrol in metal complexation. In this initial report we describe the synthesis of the first two members (**1** and **3**) of this class of amine ligands derived from Isoquinoline and 2-Amino Naphthalene—IAN-amines.^[11] A highly diastereoselective 2:1 complex formation between *rac*-**1** and zirconium(IV) to form a monomeric C_2 -symmetric zirconium(IV) complex is also documented and constitutes a significant advance on the first criterion stated above.

Convergence and expense were two guiding factors in the synthesis development for **1**. Hence, Bucherer reaction of 2-naphthol with aqueous methyl amine in a sealed tube provided 2-methylamino naphthalene in 89% yield as a brown liquid.^[12] 1-Chloroisoquinoline was prepared from isoquinoline according to literature precedent by exposure to *m*-chloroperbenzoic acid (*m*-CPBA) and phosphorus oxychloride (Scheme 1).^[13]



Scheme 1. Synthesis of ligand *rac*-**1** and zirconium complexes *rac*-**2**.

A variety of coupling methods were then investigated. In general, metalation of the amine prior to its addition to a solution of 1-chloroisoquinoline provided only the product of C–N-coupling. Unfortunately, this behavior was found to be independent of solvent and counterion. Similarly, Lewis acids of varying strength and structure failed to deliver the desired C–C-coupled product **1**. Fortunately, diethyl aluminum chlor-

ide was effective and furnished the biaryl amine consistently in 75% yield. Unreacted 2-methylamino naphthalene and 1-chloroisoquinoline could be recovered quantitatively and recycled. Although we continue to optimize this convergent synthesis route, the target amine is easily accessed on multi-gram scale with intermediates that are either crystalline solids or distillable liquids.

In order to indirectly examine the barrier to atropisomerization for **1**,^[14] diastereomeric α -methylbenzylamine derivatives **3** were synthesized, separated by silica gel chromatography, and their thermal integrity independently examined (Table 1). The diastereomers were indefinitely stable to

Table 1. Thermal atropisomerization of enantiopure (*S*)- α -methylbenzyl IAN-amines **3**.

Entry	Conditions 3a/3b	Relative ratio ^[a]
1	toluene, 110 °C, 4 h	100:0
2	xylenes, 145 °C, 5 h	67:33
3	xylenes, 145 °C, 17 h	50:50

[a] Reactions monitored by removing an aliquot from the reaction mixture and examination of the product ratio by 400 MHz ^1H NMR after solvent removal. Relative configurations of the diastereomers are arbitrarily assigned. Identical ratios observed when beginning from either **3a** or **3b** (>95:5).

prolonged refluxing in toluene. It was not until 145 °C that atropisomerization was observed to the extent of 67:33 after 5 hours. Both **3a** and **3b** equilibrated at indistinguishable rates to a 50:50 diastereomeric mixture upon prolonged heating at this temperature, which suggests that it is unlikely that the atropisomerization barrier was significantly affected by the benzylic chiral center. By analogy, **1** is expected to be configurationally stable to a reasonably high temperature.

The complexation of **1** (C_1 -symmetry) to Zr^{IV} was next examined with the hope of obtaining a 2:1 complex of high symmetry based on the analysis provided above. In principle, there are five possible diastereomeric 2:1 complexes in which the two ligands are heterochiral, whereas eight complexes can form with two homochiral ligands. Hence, when using *rac*-**1** in the transformation **1** $\rightarrow$ **2**, thirteen diastereomeric complexes are possible.

In the event, *rac*-**1** and zirconium tetrakis(dimethylamide) were combined in a 2:1 ratio in $[\text{D}_8]$ toluene. When the resulting red solution was examined by ^1H NMR spectroscopy, complete formation of the 1:1 complex was observed. The solution was then heated to 80 °C in a sealed tube for 12 hours. ^1H and ^{13}C NMR spectroscopy revealed the quantitative formation of a single diastereomeric complex in agreement with *rac*-**2**. Orange needles suitable for X-ray diffraction^[15] were grown from the reaction mixture and the structure was solved as depicted in Figure 1.^[16]

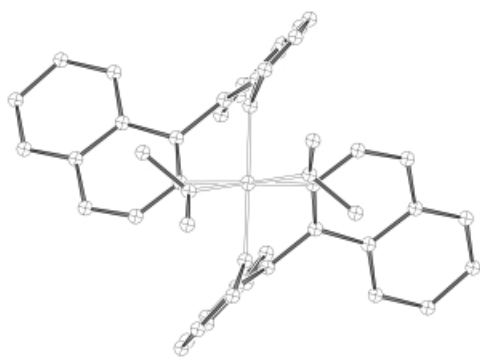


Figure 1. ORTEP diagram of *rac*-**2a** displaying C_2 -symmetry (front view).

Only one 2:1 diastereomeric complex is observed spectroscopically regardless of reaction temperature and time, which suggests that isomerization through amine elimination is not operative.^[17] At present, we cannot fully discount ligand atropisomerization on-metal but are encouraged by our studies of ligand atropisomerization and the lack of intermediates identifiable by NMR spectroscopy during formation of **2**.^[18] It is also significant to note that separate 1:1 complexes formed from **3a** and **3b** with $Zr(NMe_2)_4$ did not atropisomerize during prolonged heating at 90 °C. That the C_2 -symmetric complex is likely the kinetic product is further supported by formation of the same dichloride complex (*rac*-**2b**) by either treatment of *rac*-**2a** with trimethylsilyl chloride (TMSCl), or addition of the lithium salt of *rac*-**1** to zirconium(IV) chloride at room temperature.^[19] Orange single crystals of *rac*-**2b** were obtained and subjected to X-ray analysis (Figure 2).^[20]

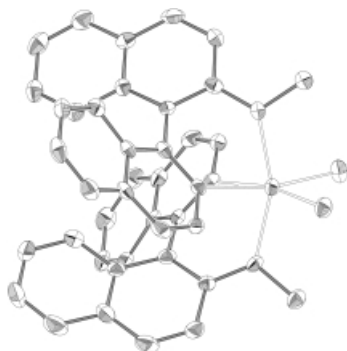


Figure 2. ORTEP diagram of *rac*-**2b** displaying distorted octahedral zirconium coordination geometry (side view).

Several observations are evident from the data.^[21] The most striking feature is the selection of identical ligand antipodes by the metal. The *cis* arrangement of both pyridyl and dimethylamido nitrogen atoms mandates a *trans* arrangement for the anilinic nitrogen atoms. The binaphthyl backbone renders the β -diketimine nonplanar, which results in electronic differentiation of the chelating atoms. Therefore, **1** is better viewed chemically as a β -amido Schiff base.

The favored metal diastereomer possesses the highly desirable C_2 -symmetry^[5] characteristic of many effective metal catalysts used in asymmetric synthesis.^[1] The location of the chelating amido atoms at apical sites of the distorted

octahedron provides the opportunity for steric manipulation above and below the plane of the *cis*-dimethylamido substituents. Additional steric demand is imposed by the isoquinoline rings in opposing quadrants about the metal center.

IAN-Amines are a class of configurationally stable axially chiral β -diketimines that provide direct access to C_2 -symmetric non-metallocene group IV metal complexes. These complexes are remarkably similar, yet truly complementary to the metallocenes by topographical comparison. The high degree of order and symmetry observed in complexation of **1** compares favorably to the traditional use of single polydentate ligands to craft C_2 -symmetric coordination space.^[22]

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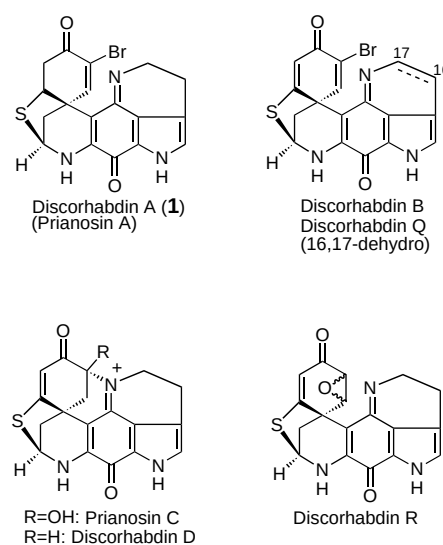
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- [16] Crystal data for *rac-2a*: crystal dimensions $0.30 \times 0.10 \times 0.03$ mm, monoclinic, space group $C2c$, $a = 21.404(4)$, $b = 12.253(3)$, $c = 18.103(4)$ Å, $\beta = 96.27(3)^\circ$; $V = 4719.58$ Å³, $Z = 4$, $\rho = 1.160$ mg mm⁻³; $\mu = 0.71073$ mm⁻¹, $F(000) = 1720$, Bruker Smart6000 CCD diffractometer, $1.92 < \theta < 26.37^\circ$, $\text{MoK}\alpha$ radiation, $\lambda = 0.71073$ Å, Ω scans, $T = 112(2)$ K, 36868 reflections measured, 4813 unique, 1668 with $I > 2\sigma(I)$, $-26 \leq l \leq 25$, $-15 \leq k \leq 14$, $-22 \leq l \leq 22$; $R = 0.0667$, $wR = 0.0644$, $\text{GOF} = 1.565$, $\Delta\rho_{\text{max}} = 0.31$ e Å⁻³.
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- [20] Crystal data for *rac-2b*: crystal dimensions $0.15 \times 0.12 \times 0.10$ mm, monoclinic, space group $P2_1/c$, $a = 20.4685(12)$, $b = 17.3030(10)$, $c = 21.1452(13)$ Å, $\beta = 118.062(2)^\circ$; $V = 6608.52$ Å³, $Z = 8$, $\rho = 1.465$ mg mm⁻³; $\mu = 0.71073$ mm⁻¹, $F(000) = 2976$, Bruker Smart6000 CCD diffractometer, $2.24 < \theta < 27.50^\circ$, $\text{MoK}\alpha$ radiation, $\lambda = 0.71073$ Å, Ω scans, $T = 111$ K, 48532 reflections measured, 15184 unique, 6638 with $I > 2\sigma(I)$, $-24 \leq l \leq 26$, $-21 \leq k \leq 22$, $-27 \leq l \leq 23$; $R = 0.0322$, $wR = 0.0241$, $\text{GOF} = 0.627$, $\Delta\rho_{\text{max}} = 0.36$ e Å⁻³.
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Synthetic Studies on the Sulfur-Cross-Linked Core of Antitumor Marine Alkaloid, Discorhabdins: Total Synthesis of Discorhabdin A**

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Discorhabdins and prianosins have been isolated from marine sponges such as New Zealand sponges of the genus *Latrunculia*, Okinawan sponge *Prianos melanos*, and Fijian sponge *Zyzzya cf. Marsailis*. Among the various discorhabdins (A–R) isolated, discorhabdins A (**1**),^[1a,b,d] B,^[1b] D,^[1c] Q,^[1e] and R^[1f] have a unique sulfur-containing fused-ring system incorporating an azacarbocyclic spirocyclohexadienone and a pyrroloiminoquinone system (Scheme 1), and show potent antitumor activity.^[2] The discorhabdins have



Scheme 1. Sulfur-containing discorhabdins.

attracted the synthetic interest of several groups including ours because of their cytotoxicity and unusual ring structures.^[3] However, to the best of our knowledge, the total syntheses of sulfur-containing discorhabdins have not yet been reported because construction of the labile and highly strained *N,S*-acetal (sulfur-cross-linked) core was difficult. Furthermore, the timing and insertion point for the introduc-

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