

Figure 3. Color changes observed upon exposing aqueous solutions of chloride ions to dichloromethane phases containing 2,2'-bis(3-hydroxy-1,4-naphthoquinone) (1×10^{-3} M). A) Control experiment. The aqueous phase is distilled water (pH 7.41). B) The aqueous phase contains NaCl at a concentration of 1×10^{-1} M. C) The aqueous phase contains NaCl (1×10^{-1} M) and benzo[15]crown-5. D) The aqueous phase is Gulf of Mexico sea water (pH 7.34) and benzo[15]crown-5.

ability to sense qualitatively in a naked-eye-detectable fashion chloride anions is not limited to laboratory samples but was also found to work for sea water obtained from the Gulf of Mexico.^[14] This observation leads us to suggest that this particular species could prove useful as a chloride anion sensor.^[15]

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- [10] The change in color for 1,8-diaminoanthraquinone was smaller than for 1,2-diaminoanthraquinone. For example, the color of a solution of 1,8-diaminoanthraquinone in dichloromethane (1×10^{-4} M) changed from orange ($\lambda_{max} = 487$ nm) to red ($\lambda_{max} = 503$ nm) upon the addition of 500 equivalents of fluoride ions.
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Resolution and Kinetic Stability of a Chiral Supramolecular Assembly Made of Labile Components**

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The importance of chirality for recognition processes in nature is impressively exemplified by the different tastes of (*R*)- and (*S*)-asparagine,^[1] and the vastly different pharmacological effects of the two enantiomers of thalidomide.^[2] Chirality is not the exclusive domain of organic chemistry, many metals can also serve as centers of chirality.^[3] The most frequent case is an octahedral arrangement of three bidentate ligands around a metal center to form Δ or Λ absolute configurations. Chirality at metal centers has been found to play an important role in nature, for example, for the siderophore-mediated iron uptake in many organisms.^[4]

Δ/Λ Isomerization of tris-bidentate complexes of the labile high-spin ferric ion or its closely related gallium(III) analogues is rapid in aqueous solution. Tris(catecholate)gallium(III) complexes, model compounds of iron siderophores, usually racemize fast. Racemization rates of $10(1) s^{-1}$ for a mononuclear complex^[5] and $0.10(1) s^{-1}$ for a dinuclear helix^[6] were determined by NMR studies. The isomerization was found to

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be unimolecular and to proceed through a Bailar twist mechanism. The combination of two chiral metal centers to form a helicate substantially slows the isomerization rate as a result of strong mechanical coupling through the rigid ligands.

Larger supramolecular clusters based on metal–ligand interactions have been designed,^[7–10] many of which are intrinsically chiral. In particular, tetrahedral $[M_4L_6]$ assemblies have been prepared from C_2 -symmetric bis-catecholate or bis-hydroxamate ligands and octahedral metal ions, which form trigonally symmetric vertices (Figure 1).^[11–15] In $[Ga_4L_6]$

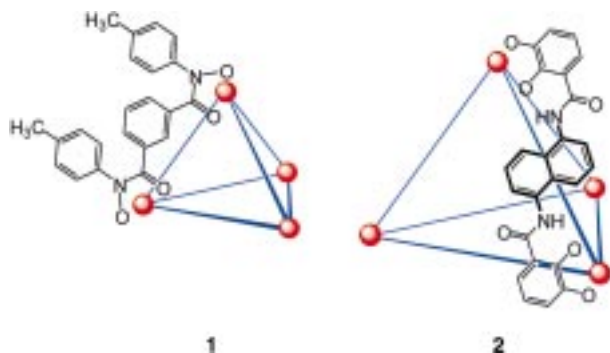


Figure 1. Tetrahedral clusters $[Ga_4L_6]$ and $[Ga_4L_6]$ formed by bis-catecholate ligands and Ga^{III} ions at the corners of a tetrahedron.

the metal vertices are bridged by a ligand that does not discriminate between the Δ - Δ or Λ - Λ configuration across an edge but does discriminate against the Bailar-twist transition state required for inversion.^[11, 12] The result is the formation in solution of all possible isomers (with point group symmetry): $\Delta\Delta\Delta\Delta$ (T), $\Delta\Delta\Delta\Delta$ (C_3), $\Delta\Delta\Delta\Delta$ (S_4), and their mirror images. In contrast, the tetrahedral complex $[Ga_4L_6]$ has strongly coupled metal centers, such that if one metal center initially has a Δ configuration, the metal center across an edge from it must necessarily also be Δ . In this case the result is the formation of a racemic mixture of homoconfigurational clusters ($\Delta\Delta\Delta\Delta$ or $\Lambda\Lambda\Lambda\Lambda$).^[13] The activation energy for interconversion of a tris(catecholate)gallium(III) center from Δ to Λ is $67(1) \text{ kJ mol}^{-1}$.^[6] If the tetrahedral structure is truly rigid and the metal centers cannot racemize independently from each other, the activation barrier for isomerizing a $[M_4L_6]$ cluster through a Bailar-twist mechanism would be expected to be much higher. Herein we report the resolution of $[Ga_4L_6]$ and show that the enantiomers are indeed exceedingly stable towards racemization.

Complete resolution of the chiral anionic cluster is accomplished in the presence of the chiral *N*-methylnicotinium cation (Nic) derived from natural (–)-nicotine and designed to interact stereospecifically with the vertices of the tetrahedron. Interestingly, the cation is encapsulated in the cavity of the

cluster $[(Nic) \subset Ga_4L_6]^{11-}$, as shown by the large upfield shift of the resonances of the cation in the 1H spectrum (Figure 2), which is characteristic of encapsulation and has been observed previously for related clusters and guests.^[13, 16] The encapsulated chiral cation is an ideal probe to determine the diastereomeric excess (*de*) of the resolved cluster. The

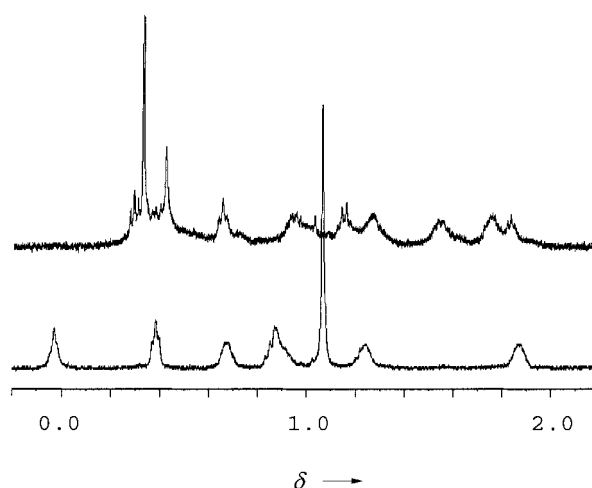
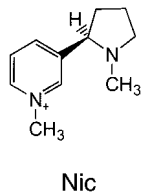


Figure 2. NMR spectra (D_2O) of the resolved tetrahedral clusters $\Delta\Delta\Delta\Delta$ - $[(Nic) \subset Ga_4L_6]^{11-}$ (bottom) and $\Lambda\Lambda\Lambda\Lambda$ - $[(Nic) \subset Ga_4L_6]^{11-}$ (top) showing the strongly upfield shifted resonances of the encapsulated chiral guest (Nic).

NEt_4^+ ion readily displaces the chiral guest to form enantiopure $\Delta\Delta\Delta\Delta$ - and $\Lambda\Lambda\Lambda\Lambda$ - $[Et_4N]_{11}[(Et_4N) \subset Ga_4L_6]$ clusters with complete retention of chirality of the metal centers. Remarkably, an alkaline, aqueous solution of $\Delta\Delta\Delta\Delta$ - $[(Et_4N) \subset Ga_4L_6]^{11-}$ retained its enantiopurity for at least eight months, and even extended boiling of the solution did not lead to racemization!^[17]

The absolute configuration and enantiopurity of the clusters was determined from their CD spectra (Figure 3): the π – π^* transitions in the catechol moiety at each metal center give rise to a strong exciton couplet from which the absolute configuration can be determined.^[18]

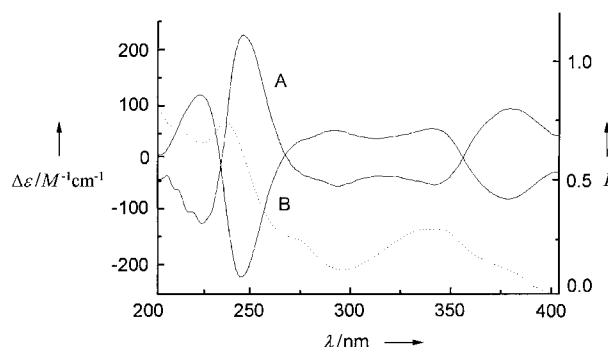


Figure 3. CD and absorption spectrum of the resolved tetranuclear cluster $[(Nic) \subset Ga_4L_6]^{11-}$: $\Delta\Delta\Delta\Delta$ (A) and $\Lambda\Lambda\Lambda\Lambda$ (B) forms.

An X-ray crystallographic analysis^[19] of $\Delta\Delta\Delta\Delta$ - $[(Et_4N) \subset Ga_4L_6]$ confirmed the absolute configuration at the metal center (Figure 4). The gallium ions are coordinated in a distorted octahedral fashion (average Ga–O bond length $1.966 \text{ \AA}$, with a twist angle at the Ga center of 40.2° and Ga...Ga distances of $12.663 \text{ \AA}$). These values are very similar to those found in the crystal structure of the same compound in racemic form.^[13]

Chirality at octahedral metal centers can be imposed by chiral ligands,^[3] and a tetrahedral bis-catecholate cluster with

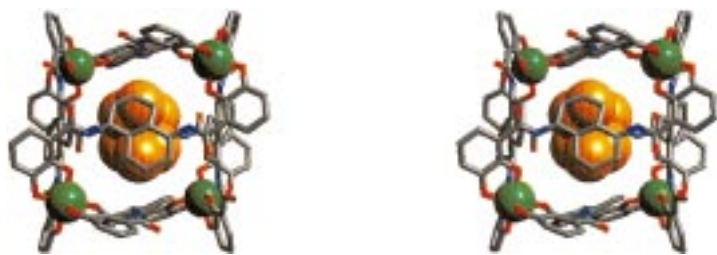


Figure 4. Crystal structure of $\Delta\Delta\Delta\Delta$ -[(Et₄N)⊂Ga₄2₆] (stereoview). View along the twofold axis of the molecule showing its overall crystallographic *T*-symmetry. The disorder of the naphthyl backbone and counterions have been omitted for clarity.

exclusive Δ configurations at the Ga^{III} metal centers has been reported.^[20] To the best of our knowledge, the $\Delta\Delta\Delta\Delta$ - and $\Delta\Delta\Delta\Delta$ -[Et₄N]₁₁[(Et₄N)⊂Ga₄2₆] clusters are the first examples of enantiopure, nonracemizing clusters formed quantitatively from achiral labile components.^[21] Like a wooden house, the rigidity of this molecular tetrahedron results from not the individual components but the way they are assembled. Dissociation of one board followed by reattachment does not change the structure.

In summary, we have shown that a racemic mixture of homoconfigurational tetrahedral clusters with labile metal ions can be resolved into its $\Delta\Delta\Delta\Delta$ and $\Delta\Delta\Delta\Delta$ enantiomers, which are stable towards racemization even though related mononuclear or dinuclear metal complexes (helicates) racemize quickly. “Mechanical stiffness” that prevents racemization is provided through the interconnection of all four labile metal centers in a rigid three-dimensional tetrahedral arrangement. We are currently investigating the use of such chiral capsules for enantioselective catalysis and diastereoselective encapsulation of other chiral molecules.

Experimental Section

General: All NMR spectra were measured with a Bruker 500 MHz spectrometer. Chemical shifts are reported as δ downfield from sodium [D₄]2,2,3,3-[3-(trimethylsilyl)]propionate. Absorption spectra were recorded on a Hewlett–Packard 8450A UV/Vis diode array spectrophotometer. Circular dichroism (CD) spectra were measured with a Jasco J-500C spectropolarimeter equipped with an IF-500 II A/D converter. Mass spectral data were acquired using a Bruker Apex II actively shielded FT-ICR mass spectrometer equipped with an Analytica electrospray source (off-axis probe). H₂2^[13] and *N*-methylnicotinium iodide^[24] (NicI) were synthesized according to published procedures. Solvents and commercially available reagents were used without further purification.

Enantiopure tetrahedral clusters: [Ga(acac)₃] (37.0 mg, 0.101 mmol), H₄2 (66.7 mg, 0.155 mmol), and NicI (94.3 mg, 0.310 mmol) were suspended in degassed, dry CH₃OH (20 mL). A 0.508 N KOH solution in CH₃OH (610 μ L) was slowly added through a syringe whereupon the ligand dissolved, and a clear solution was obtained. After 1 h, an orange-yellow powder started to precipitate. The precipitate ($\Delta\Delta\Delta\Delta$ form) was collected after 24 h by centrifugation, washed with a small portion of methanol, and dried under high vacuum (55 mg, 100%, *de* > 98%). The remaining methanolic solution was concentrated to about 1 mL and an excess of acetone (20 mL) added to quantitatively precipitate the remaining $\Delta\Delta\Delta\Delta$ -form, which was collected by centrifugation, washed with acetone, and dried under high vacuum (49 mg, 100%, *de* > 98%). Enantiopure Al^{III}, In^{III}, and Fe^{III} complexes were obtained using the same procedure starting with the corresponding [M(acac)₃] salts. The enantiopure [(Nic)⊂Ga₄2₆]¹¹⁻ clusters precipitated with various unstoichiometric mixtures of Nic and K⁺ ions, with quantitative yields of both $\Delta\Delta\Delta\Delta$ and $\Delta\Delta\Delta\Delta$ enantiomers (50% each). The same cluster was previously found to precipitate with mixtures

of Et₄N⁺ and K⁺ ions.^[13] The *de* values were determined by NMR spectroscopy and exceeded 98% in all cases, since no trace of the other diastereomer could be found (Figure 2). The encapsulated Nic ions were exchanged quantitatively against Et₄N⁺ by elution with 1 N basic Et₄NCl on a cation exchange column (Amberlite IRC-50) and precipitation of the complex by addition of acetone after elution to yield $\Delta\Delta\Delta\Delta$ -[Et₄N]₁₁[(Et₄N)⊂Ga₄2₆] and $\Delta\Delta\Delta\Delta$ -[Et₄N]₁₁[(Et₄N)⊂Ga₄2₆]. Crystals suitable for analysis by X-ray diffraction were obtained by slow vapor diffusion of acetone into an aqueous solution of $\Delta\Delta\Delta\Delta$ -[(Et₄N)⊂Ga₄2₆]¹¹⁻ with a mixture of K⁺/NEt₄⁺/Nic ions present.

The following abbreviations have been employed: Nic_H for free nicotinium protons, Nic_E for encapsulated nicotinium protons, Ar_nH for the ligand naphthyl protons and Ar_EH for the ligand catecholate protons.

$\Delta\Delta\Delta\Delta$ -K₄[Nic]₅[(Nic)⊂Ga₄2₆]: ¹H NMR (500 MHz, D₂O): δ = 13.35 (s, 12 H), 7.86 (s, 12 H, Nic_H), 7.71 (d, 5 H, Nic_H), 7.66 (d, 5 H, Nic_H), 7.55 (s, 12 H, Ar_nH), 7.35 (t, 1 H, Nic_H), 7.31 (d, 12 H, Ar_EH), 7.12 (t, 5 H, Nic_H), 6.83 (t, 12 H, Ar_nH), 6.75 (d, 12 H, Ar_EH), 6.61 (t, 12 H, Ar_EH), 6.20 (d, 1 H, Nic_H), 5.21 (d, 1 H, Nic_H), 4.22 (s, 1 H, Nic_H), 3.77 (s, 15 H, Nic_H), 2.97 (t, 5 H, Nic_H), 2.89 (t, 5 H, Nic_H), 2.21 (dd, 5 H, Nic_H), 2.01 (d, 5 H, Nic_H), 1.88 (s, 15 H, Nic_H), 1.85 (s, 3 H, Nic_H), 1.71 (d, 5 H, Nic_H), 1.68 (dd, 5 H, Nic_H), 1.32 (m, 5 H, Nic_H), 0.02 (m, 1 H, Nic_H), -0.38 (t, 1 H, Nic_H), -0.83 (m, 1 H, Nic_H), -0.88 (m, 2 H, Nic_H), -1.07 (s, 3 H, Nic_H), -1.28 (m, 1 H, Nic_H), -1.89 (m, 1 H, Nic_H); UV/Vis (H₂O, *c* = 4.85 × 10⁻⁶ M): 229 (15 500), 271 (5400, sh), 340 (12 400), 365 nm (4700); CD (H₂O, *c* = 4.85 × 10⁻⁶ M): 221 (340), 242 (-680), 288 (150), 337 nm (150), 374 (-240). ESI-FTMS (410 pmol μ L⁻¹ in methanol, samples prepared with NaOH instead of KOH): Matching isotope distributions of Na₈[(Nic)⊂Ga₄2₆]³⁻ and Na₇[(Nic)⊂Ga₄2₆]⁴⁻ were found; *m/z* observed for Na₈[(Nic)⊂Ga₄2₆]³⁻: 1065.424, 1065.759, 1066.092, 1066.425, 1066.759, 1067.094, calcd for Ga₄C₁₅₅H₁₀₁N₁₄O₃₆Na₈: 1065.425, 1065.759, 1066.092, 1066.426, 1066.759, 1067.093.

$\Delta\Delta\Delta\Delta$ -K₄[Nic]₅[(Nic)⊂Ga₄2₆]: ¹H NMR (500 MHz, D₂O): δ = 13.10 (s, 12 H), 7.91 (t, 1 H, Nic_H), 7.81 (d, 12 H, Ar_nH), 7.77 (s, 5 H, Nic_H), 7.61 (d, 12 H, Ar_nH), 7.55 (d, 5 H, Nic_H), 7.52 (d, 12 H, Ar_EH), 7.20–7.30 (m, 3 H, Nic_H), 7.25 (t, 12 H, Ar_EH), 7.08 (t, 5 H, Nic_H), 6.84 (t, 12 H, Ar_nH), 6.74 (d, 12 H, Ar_EH), 6.57 (t, 12 H, Ar_EH), 4.89 (d, 1 H, Nic_H), 3.64 (s, 15 H, Nic_H), 2.87 (t, 5 H, Nic_H), 2.68 (t, 5 H, Nic_H), 2.10 (dd, 5 H, Nic_H), 1.87 (s, 3 H, Nic_H), 1.86 (d, 5 H, Nic_H), 1.75 (s, 15 H, Nic_H), 1.64 (m, 10 H, Nic_H), 1.38 (m, 5 H, Nic_H), -0.39 (s, 3 H, Nic_H), -0.39 (m, 1 H, Nic_H), -0.75 (m, 1 H, Nic_H), -1.00 (m, 1 H, Nic_H), -1.29 (m, 1 H, Nic_H), -1.18 (m, 1 H, Nic_H), -1.51 (m, 1 H, Nic_H), -1.71 (m, 1 H, Nic_H).

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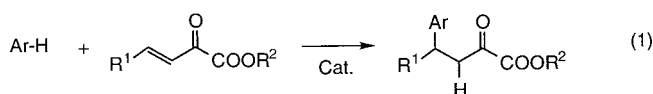
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- [19] Crystal structure of $\Delta\Delta\Delta\Delta\text{-(Et}_4\text{N)}\text{C}(\text{Ga}_2\text{Zr})\cdot x(\text{solvent})$: Crystal data were collected using a Siemens SMART diffractometer equipped with a CCD area detector^[25], crystal size $0.30 \times 0.20 \times 0.15$ mm, $T = -125^\circ\text{C}$, graphite-monochromated $\text{MoK}\alpha$ radiation ($\lambda = 0.71073$ Å), cubic, space group $I23$ (No. 197), $a = 22.572(1)$ Å, $V = 11500.5(9)$ Å³, $Z = 2$, $\mu = 0.528$ cm⁻¹, $F(000) = 3706$, $\rho_{\text{calc}} = 1.07$ Mg m⁻³, $2\theta_{\text{max}} = 37.64^\circ$. Of the 15524 reflections measured, 1510 were unique ($R_{\text{int}} = 0.087$). The structure was solved by direct methods and refined on F^2 using SHELXTL.^[26] Data were corrected for Lorentz and polarization effects. A semi-empirical absorption correction was applied using XPREP (ellipsoidal model, $R_{\text{int}} = 0.0486$, $T_{\text{max}} = 0.812$, $T_{\text{min}} = 0.755$).^[26] The carbonyl oxygen atom of the ligand is disordered over two positions with 1/2 occupancy, and the naphthalene backbone of the ligand is disordered across an imaginary line connecting the two carbon atoms affixed to the nitrogen atoms of the amide. This disorder was modeled as a twist of this backbone around its center with both orientations having 1/2 occupancy. A disordered NEt_4^+ ion is present in the cavity of the cluster. The nitrogen atom is located on the 23 special position, and the methylene groups are disordered over two sites with 1/2 occupancy. The methyl carbon atoms were disordered over the threefold axes and 12 sites with 1/3 occupancy. There was also a high degree of disorder among the other cations and solvent molecules present. As a result, only the encapsulated NEt_4^+ ion was found and constrained to be rigid in the disorder model described. The other 11 cations and solvent molecules are included as "x(solvent)" in the chemical formula and accounted for by a SWAT parameter. As a result of the lack of high angle data (1.2 Å resolution) only the gallium atoms, amide nitrogens, and catecholate oxygen atoms were refined anisotropically. All other atoms were refined isotropically. Hydrogen atoms were included on all appropriate atoms of the ligand that were not disordered but were not refined. Weighting scheme: $1/[\sigma^2(F_o^2) + (0.1763p)^2 + 2.7183p]$, where $p = (F_o^2 + 2F_c^2)/3$. Final $R_1 = 0.0837$ for 1022 reflections with $F_o > 4\sigma(F_o)$ (1162 Friedel unique data, 157 parameters, 6 restraints); for all 1510 data, $wR_2 = 0.269$, GOF = 1.118; Flack^[27] parameter = 0.08(8); max/min residual density +0.28/−0.27 e Å⁻³. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-145431. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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Catalytic Asymmetric Friedel–Crafts Alkylation of β,γ -Unsaturated α -Ketoesters: Enantioselective Addition of Aromatic C–H Bonds to Alkenes**

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Aromatic compounds are very important molecules in chemistry and the addition of these compounds to alkenes in the Friedel–Crafts alkylation constitutes one of the fundamental reactions in synthetic chemistry.^[1]

The catalytic enantioselective addition of aromatic C–H bonds to alkenes leading to formation of a new C–C bond is of considerable interest and remains a long-term challenge for chemists. Such a reaction would provide a simple and attractive method for the formation of optically active aryl-substituted compounds from easily available starting materials. Recently, the first examples of catalytic enantioselective addition reactions of aromatic and heteroaromatic compounds to activated carbonyl compounds,^[2] α -dicarbonyl compounds,^[3] and imines were reported.^[4] However, the development of a catalytic enantioselective version of the corresponding Friedel–Crafts alkylation reaction has, to the best of our knowledge, not been reported, although numerous examples can be given for the non-enantioselective version of this reaction.^[1, 5] This paper presents the first catalytic highly enantioselective Friedel–Crafts alkylation, that is, the addition of aromatic C–H bonds to β,γ -unsaturated α -ketoesters catalyzed by chiral Lewis acids [Eq. (1)].



The reaction of indole (**1a**) with methyl 4-phenyl-2-oxo-3-butenate (**2a**) can be catalyzed by various metal complexes, and the application of the chiral bisoxazoline (BOX) complexes^[6, 7] $[(S)\text{-}i\text{Bu-BOX}]\text{M}$ ($(S)\text{-4a-c}$; $\text{M} = \text{Cu}(\text{OTf})_2$, $\text{Cu}(\text{SbF}_6)_2$, and $\text{Zn}(\text{OTf})_2$, respectively) and $[(S)\text{-Ph-BOX}]\text{M}$ ($(S)\text{-4d}$; $\text{M} = \text{Cu}(\text{OTf})_2$) gives the optically active Friedel–Crafts alkylation product **3a**. Some representative screening results are presented in Table 1. The Friedel–Crafts alkylation reactions with $(S)\text{-4a-c}$ and $(S)\text{-4d}$ proceed with high conversion. For the reaction catalyzed by $(S)\text{-4a}$, product **3a** is formed with up to 88 % *ee* in CH_2Cl_2 (entry 3), while 74 % *ee* is found in THF (entry 6). In Et_2O , with 2 mol % of the catalyst,

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