Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

Sequential Alkylation of Tröger's Base. An Approach to New Chiral Ligands

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To cite this Article Harmata, Michael , Rayanil, Kanok-On and Barnes, Charles L.(2006) 'Sequential Alkylation of Tröger's Base. An Approach to New Chiral Ligands', Supramolecular Chemistry, 18: 7, 581 — 586
To link to this Article: DOI: 10.1080/10610270600853477
URL: http://dx.doi.org/10.1080/10610270600853477

Supramolecular Chemistry, October–November 2006 Vol. 18 (7), pp. 581–586

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Sequential Alkylation of Tröger's Base. An Approach to New Chiral Ligands

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(Received 2 March 2006; Accepted 9 June 2006)

Heterocycles derived from Tröger's base were shown to complex with metal salts in 2:1 ligand:salt ratios as monodentate or bidentate ligands depending on structure.

Keywords: Tröger's base; Chiral ligands; Diamine ligands; Metal complexation

INTRODUCTION

Ten years ago, we reported the benzylic metalation and alkylation of Tröger's base [1]. In developing that chemistry, we took advantage of the activating effect of Lewis acid coordination to a bridgehead nitrogen in order to facilitate deprotonation [2]. Thus, treatment of Tröger's base with BF_3–Et_2O followed by n-BuLi gave an organolithium species that reacted with a number of electrophiles. An example is given in Scheme 1.

We undertook the present study to begin to explore the possibility of using Tröger's base derivatives as chiral ligands, either as structural building blocks or in catalysis. There have been only a few reports on the use of Tröger's base or its derivatives as ligands in asymmetric catalytic processes or simply as ligands for metals [3–6]. We recently demonstrated that certain ligands derived from Tröger's base were effective in the asymmetric addition of diethylzinc to aromatic aldehydes [7]. For example, treatment of 4-bromobenzaldehyde with diethylzinc in the presence of 5 mol % of ligand **4** (toluene, rt, 48 h) afforded a 79% yield of alcohol **5** in 86% ee (Scheme 2). The stereochemical outcome was rationalized on the basis of the model shown in Fig. 1.

In spite of this favorable outcome, we were concerned that ligands like **4** actually have two binding sites, based on the number of nitrogen atoms in the molecule. It would ultimately be more straightforward if the molecule had symmetry, at least for the purpose of evaluating whether the two binding sites really competed with each other in various reactions. To that end, we decided to see if we could regioselectively deprotonate and alkylate analogues of Tröger's base that had already been through one deprotonation/alkylation sequence. This report documents our successful attempts to do so, as well as some related chemistry.

RESULTS AND DISCUSSION

Our plan was based on the idea that monoalkylated Tröger's base derivatives would coordinate with Lewis acids at the least hindered position, namely at the nitrogen adjacent to the remaining methylene group. This would activate the methylene group, assuring regioselective alkylation. Thus, treatment of a THF solution of **6** with 1.1 equivalents of BF_3–Et_2O at 0°C presumably afforded **7**. Cooling to −78°C and deprotonation with n-BuLi gave an organolithium species, which was trapped with benzyl bromide to afford **8** in 57% yield (Scheme 3). The structure of **8** was established from spectral and X-ray data (Fig. 2) [8]. The structure suggests that an interaction takes place between the benzyl group of one molecule and the cleft of the Tröger's base substructure of another such that both an offset stacking and edge-face interaction are occurring.

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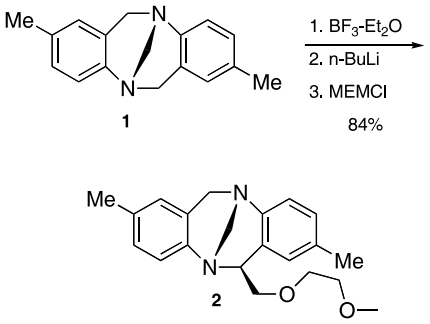
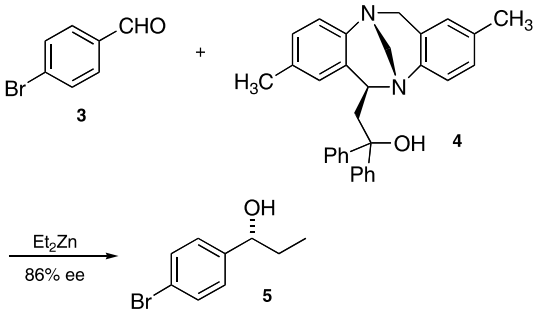
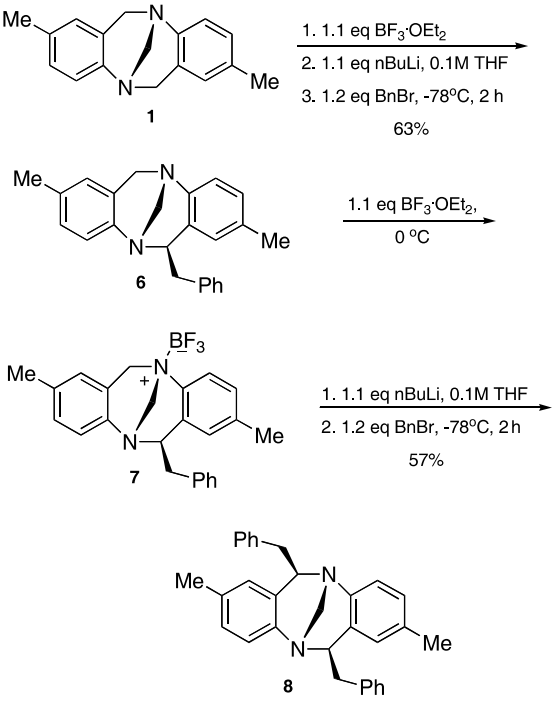
ISSN 1061-0278 print/ISSN 1029-0478 online © 2006 Taylor & Francis
DOI: 10.1080/10610270600853477



SCHEME 1 Metallation and alkylation of Tröger's base.



SCHEME 2 Use of a chiral ligand derived from Tröger's base.



SCHEME 3 Double alkylation of Tröger's base.

Two other compounds, **9** and **10** [8], were prepared using the same procedure [9]. Interestingly, the crystal structure of **10** (Fig. 3) is quite different from **8** and resembles that of racemic **1**, though the latter crystallizes as a racemate and **10** forms a conglomerate [10,11]. It appears as though there may be a CH interaction between the bridging methylene group of one molecule of **10** and the benzene rings of the Tröger's base substructure of another. The distance between the hydrogens of the bridging methylene group and the nearest carbon atom of the benzene ring of the adjacent molecule is calculated to be 2.91 Å.

We wondered whether we could successfully cleave the methylene bridge in these new Troeger's base analogues to produce compounds that were still chiral, but less rigid [10,11]. To that end, **8** was treated with methyl triflate in dichloromethane and the resulting salt was hydrolyzed with aqueous sodium hydroxide in DMF to give **11** in 74% yield. The reaction of **11** with formalin in the presence of sodium cyanoborohydride produced **12** in 98% yield (Scheme 4).

A section (2 molecules) of the crystal structure of **12** is shown in Fig. 4. A methyl group of each molecule of **12** is within the cleft of its neighbor and it appears that an edge-face interaction between one benzyl group from each molecule of **12** is occurring with a aryl ring of the Tröger's base portion of the adjacent molecule [12].

Compound **9** was alkylated with dimethyl sulfate and then hydrolyzed to produce **13** in 89% yield (Scheme 5). We attempted a reductive amination with formalin as used in the synthesis of **12**. However, this reaction failed and our attempts to

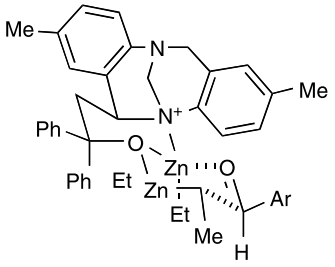


FIGURE 1 Transition state model for process in Scheme 2.

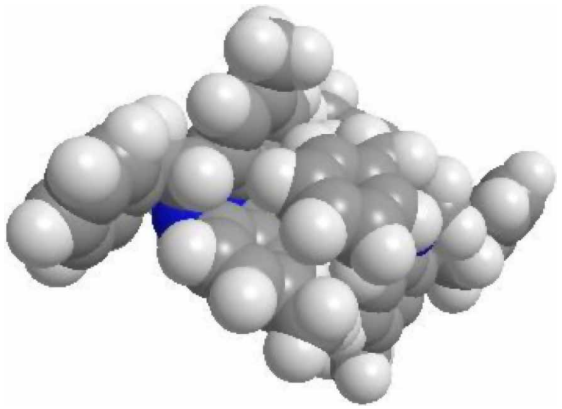


FIGURE 2 A portion of the crystal structure of **8**.

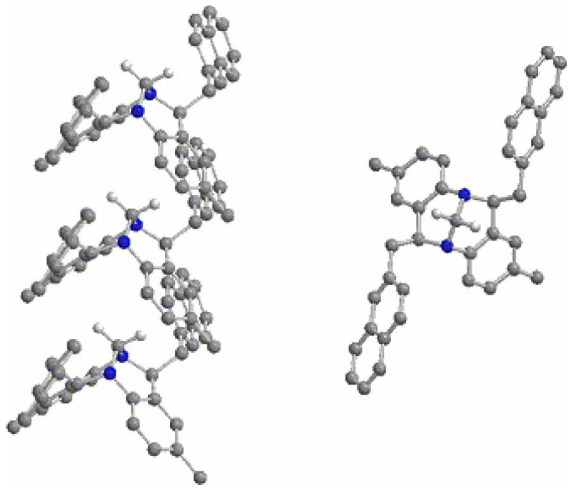


FIGURE 3 Side and top views of a portion of the crystal struture of **10**.

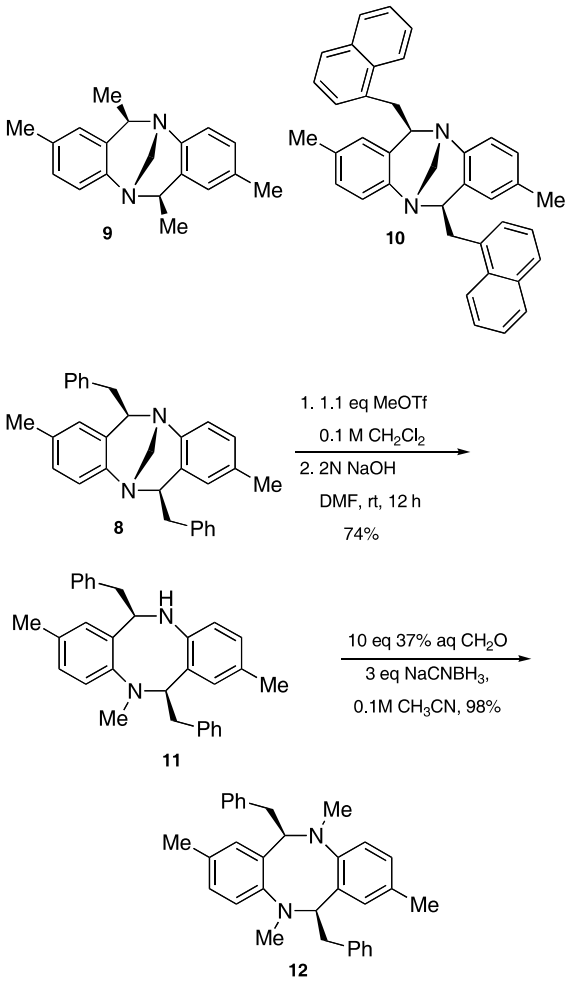
methylate the secondary nitrogen in **13** have thus far been unsuccessful, for reasons that are not clear.

In order to explore the potential of these new diamine ligands to bind metals and thus serve as chiral ligands, we combined a series of metal salts with certain substrates and evaluated the reaction outcomes using NMR. Treatment of **12** with copper (II) chloride and triflate in dichloromethane gave no indication of the formation of a complex. This is somewhat surprising in that heterocycles related to **12** have been reported to serve as bidentate ligands for a variety of metals [13–16]. However, it appears that no relatively congested systems like **12** have ever been studied. Indeed, the X-ray structure of **12** indicated that the nitrogen atoms are in a relatively deep cavity [8].

We thus turned our attention to **13**, a relatively less hindered ligand. Exposure of **13** to a number of metal salts in either methanol or butanol gave no indication of the formation of a complex. Interestingly, of the metal salts chosen, only $CdCl_2$ and CdI_2 appeared to demonstrate binding to **13**. A crystal could be obtained for the complex from CdI_2 and it showed a ligand:salt ratio of 2:1 (**14**, Fig. 5) [8]. In this case, the ligand was monodentate, each secondary nitrogen binding to the cadmium. Attempts to bind **13** to some copper (II) salts again gave no evidence for the formation of a complex of any kind. This suggests that the use of chiral heterocycles derived from Tröger's base as ligands might require modifications to increase interactions with metal ions and move the binding site further away from the chiral scaffold.

For such possibilities to be examined in the future, we needed to be able to alkylate Tröger's base and then cleave the bridging methylene group to leave a chiral compound that had two nitrogens for functionalization. Cleavage of the methylene group in Tröger's base is not trivial, but we were able to show that the method of Johnson could be used in the case of **9** [17]. Thus, treatment of **9** with excess sodium nitrate in acetic acid at 50°C resulted in the formation of **15**, which was solvolyzed using copper chloride and hydrochloric acid in acetic acid at room temperature to yield **16** in 85% yield over two steps (Scheme 6).

A preliminary investigation of the behavior of **16** in the presence of metal salts suggested that the diamine was consumed to form a product. Proton NMR revealed changes, particularly in the aromatic region, to suggest that some interaction was taking place. The complex with $NiCl_2$ was isolated as crystals and characterized by X-ray analysis. The structure is shown in Fig. 6. Interestingly, the complex contains two molecules of **16** possessing the same stereochemistry in a racemic crystal. Each binds to the nickel in a unique way; one using nitrogen lone pairs *cis* to its benzylic methyl groups and the other using those *trans* to its methyl groups. Cavities of different sizes are created around the ligand sphere as illustrated by the angle measurements shown in Fig. 6. This suggests the possibility of creating chiral cavities of varying size and shape if



SCHEME 4 Hydrolysis/N-alkylation of **8**.

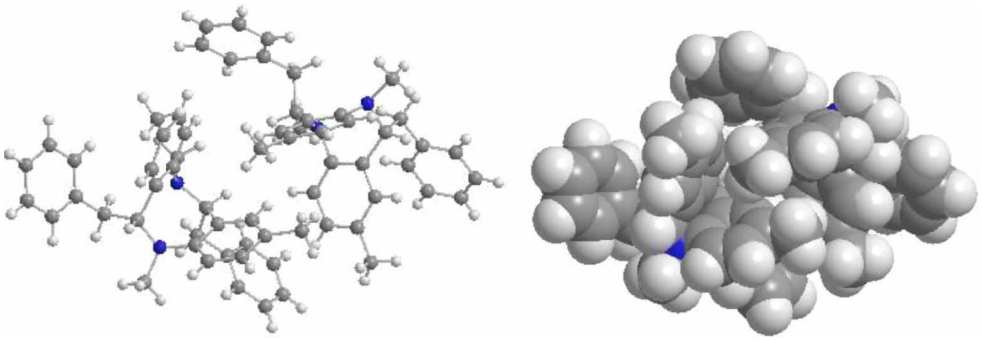
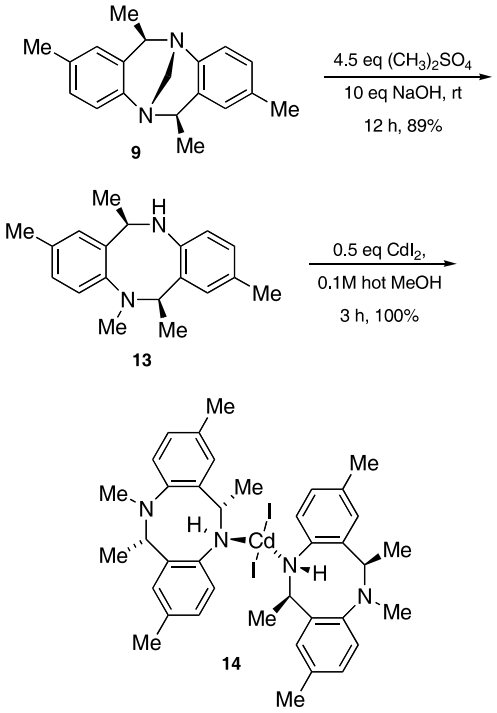


FIGURE 4 Crystal structure of **12**.

larger, non-racemic versions of the complex were to be made. Such investigations are currently being pursued.

In summary, we have demonstrated that sequential alkylation of Tröger's base with stereocontrol and regiocontrol is possible. The products can be manipulated to prepare chiral diamines. Metal binding studies gave two unique outcomes. The application of this chemistry is potentially very broad in scope and we anticipate that the incorporation of appropriate design features into Tröger's base derivatives will lead to the development of new chiral ligands, chiral bases and chiral solid state coordination complexes, among others. Further results will be reported in due course.



SCHEME 5 Complexation of CdI_2 by **13**.

EXPERIMENTAL

Synthesis of Compound 8

A solution of **6** (0.5530 g, 1.624 mmol) in 16 mL of THF under N_2 in a 50 mL flame-dried flask equipped with a magnetic stirring bar was cooled at 0°C for 10 min. The pale yellow solution was added BF_3 OEt_2 (0.210 mL, 1.705 mmol) and the resultant mixture was stirred at 0°C for 20 min. An ice bath was changed to a dry ice/acetone bath and the mixture was stirred at −78°C for 10 min. n-BuLi (2.25 M, 0.794 mL, 1.786 mmol) was added dropwise to the mixture and stirring was continued at this temperature for 30 min. A solution of benzyl bromide (0.232 mL, 1.950 mmol) in 2.0 mL of THF was slowly added and the reaction mixture was stirred for 2 h. Water was added and the resultant aqueous layer was further extracted by CH_2Cl_2. Organic layers were combined together, washed by brine, dried over $MgSO_4$ and filtered. The solvent was removed under vacuum and the extract was purified by flash chromatography (hexanes:EtOAc/4:1) affording (0.399 g, 57%) of a colorless solid; mp 206–208°C; IR (neat): 3080, 3060, 3027, 2941, 2921, 2855, 1605, 1491, 1450, 1360, 1237, 1213, 1119, 1033 cm^{-1}; ^1H NMR (300 Mz, $CDCl_3$): 7.45–7.37 (m, 8H), 7.33–7.27 (m, 2H), 6.85–6.76 (m, 4H), 6.39 (d, $J = 8.0$ Hz, 2H),

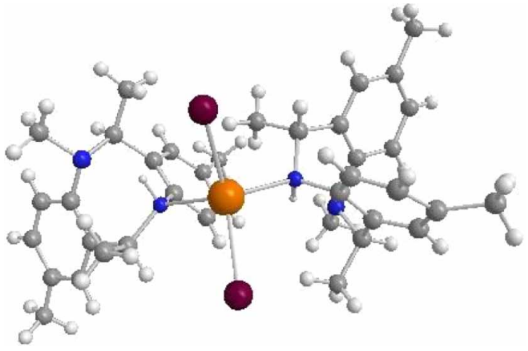
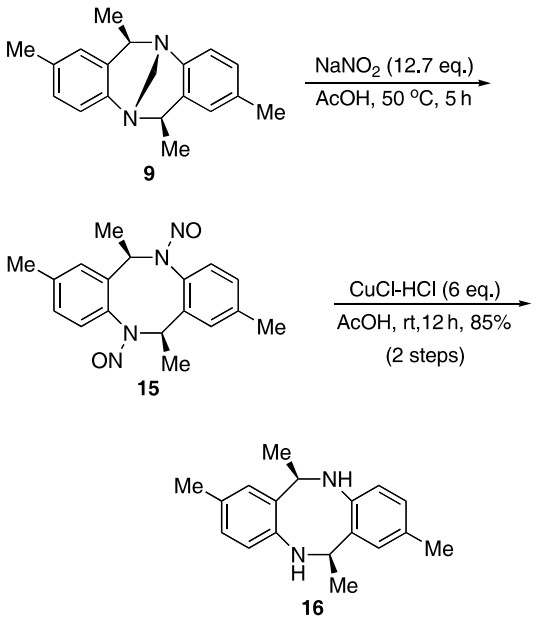


FIGURE 5 Crystal structure of **14**.



SCHEME 6 Preparation of ligand **16**.

4.37 (s, 2H), 4.15 (dd, $J = 4.5, 9.6$ Hz, 2H), 3.19–3.04 (m, 4H), 2.16 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): 146.5, 140.2, 132.7, 130.6, 129.6, 128.3, 128.2, 128.1, 126.3, 124.4, 130.6, 129.6, 128.3, 128.2, 128.1, 68.9, 56.0, 43.0, 20.9; HRMS Calcd for $C_{31}H_{30}N_2Na[M + Na]^+$: 453.2301, Found: 453.2316.

Compound 9

Procedure as for **8**: a colorless oil; 49%; IR (neat): 2967, 2926, 2862, 1613, 1572, 1491, 1446, 1404, 1327, 1340, 1295, 1234, 1205, 1119, 1066, 1029 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): 6.98–6.92 (m, 4H), 6.75–6.74 (m, 2H), 4.24 (s, 2H), 4.16 (q, $J = 7.1$ Hz, 2H), 2.21 (s, 6H), 1.67 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 146.0, 133.0, 132.2, 128.1, 128.1, 124.9, 62.3, 55.7, 23.6, 20.9; HRMS calcd for $C_{19}H_{22}N_2Na[M+Na]^+$: 301.1675, Found: 301.1680.

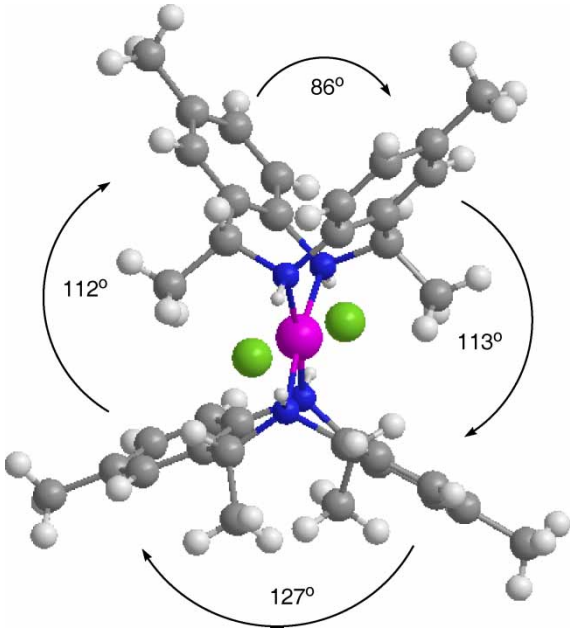


FIGURE 6 X-ray structure of **16**/$NiCl_2$ complex.

Compound 10

Procedure as for **8**: a colorless solid; 47%; mp 273–275°C; IR (neat): 3051, 3011, 2921, 2856, 1601, 1486, 1360, 1343, 1233, 1119, 1033 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): 7.92–7.87 (m, 8H), 7.64 (d, $J = 8.3$ Hz 2H), 7.53–7.44 (m, 4H), 6.82 (s, 2H), 6.75 (d, $J = 8.0$ Hz, 2H), 6.38 (d, $J = 8.0$ Hz, 2H), 4.47 (s, 2H), 4.28 (q, $J = 4.2$ Hz, 2H), 3.34–3.27 (m, 4H), 2.16 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$): 146.5, 137.7, 133.7, 132.8, 132.3, 130.7, 128.3, 128.1, 128.0, 127.8, 127.7, 125.9, 125.3, 124.5, 68.9, 56.1, 43.2, 20.9; HRMS calcd for $C_{39}H_{34}N_2Na[M + Na]^+$: 553.2614, Found: 553.2634.

Synthesis of Compound 13

A 50 mL round-bottom flask equipped with a magnetic stirring bar was purged with N_2 and charged with compound **9** (0.5715 g, 2.0529 mmol). $(CH_3)_2SO_4$ (0.876 mL, 9.24 mmol) was added and the reaction mixture was stirred for 30 min at room temperature. 2N NaOH (2 mL) was added and the mixture was stirred at room temperature overnight. The mixture was extracted by CH_2Cl_2 and the combined organic layers were washed by brine, dried over $MgSO_4$ and filtered. Removal of solvent under vacuum provided a crude product that was purified by flash chromatography (hexane:EtOAc / 1:1) affording 0.5121 g (89%) of a colorless solid.; mp 122–124°C; IR (neat): 3321, 2970, 2917, 2864, 2749, 1613, 1576, 1495, 1442, 1364, 1221, 1172, 1131, 1066, 1017 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): 7.09 (d, $J = 8.1$ Hz, 1H), 6.93 (d, $J = 8.1$ Hz, 1H), 6.88 (dd, $J = 1.7, 4.1$ Hz, 1H), 6.83 (dd, $J = 1.6, 5.0$ Hz, 1H), 6.58 (s, 1H), 6.51 (d, $J = 1.3$ Hz, 1H), 4.07 (q, $J = 5.1$ Hz, 1H), 3.73 (q, $J = 1.3$ Hz, 1H), 2.83 (s, 3H), 2.13 (s, 3H), 2.12 (s, 3H), 1.59 (d, $J = 6.8$ Hz, 3H), 1.50 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 149.4, 144.6, 140.5, 138.8, 134.9, 132.9, 129.1, 128.8, 128.1, 127.9, 126.1, 122.7, 69.3, 64.8, 40.9, 24.1, 22.9, 20.9, 20.8; HRMS calcd for $C_{19}H_{24}N_2Na$ $[M + Na]^+$: 303.1832, Found: 303.1827.

Preparation of a Cadmium Iodide Complex 14

A 5.0 mL flame-dried flask equipped with a magnetic stirring bar was placed under an atmosphere of nitrogen and charged with CdI_2 (0.0131 g, 0.0357 mmol) and 0.2 mL of hot MeOH. A solution of **13** (0.0200 g, 0.0714 mmol) in 0.5 mL of hot MeOH was slowly added into the metal salt solution.

The reaction mixture was stirred for 3 h and then solvent was removed under vacuum. Recrystallization from MeOH afforded 0.0331 g (100%) of a colorless solid; mp 215–220°C; IR (neat): 3207, 2970, 2917, 2860, 2802, 1499, 1442, 1368, 1335, 1262, 1172, 1131, 1070, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 7.07 (d, $J = 8.1$ Hz, 4H), 6.90 (dd, $J = 1.5$, 5.6 Hz, 4H), 6.52 (d, $J = 1.5$ Hz, 4H), 4.38–4.30 (m, 2H), 3.75 (q, $J = 6.7$ Hz, 2H), 2.82 (s, 6H), 2.11 (s, 3H), 2.01 (s, 3H), 1.66 (d, $J = 6.7$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): 148.6, 137.7, 135.9, 135.3, 129.1, 128.8, 128.8, 124.9, 122.7, 69.1, 66.3, 40.6, 24.4, 23.3, 20.9, 20.8.

Preparation of Compound 16

A solution of $NaNO_2$ (0.661 g, 0.958 mmol) in water (5 mL) was added dropwise to a stirred, cold (ice bath) solution of compound **9** (0.21 g, 0.754 mmol) in acetic acid (6 mL). The solution was stirred at 50°C for 5 h and it was poured into ice and made alkaline by the careful addition of 50% aqueous NaOH. The aqueous mixture was extracted with CH_2Cl_2 and the extracts were dried ($MgSO_4$), filtered, and concentrated affording compound **15**. This compound was used directly in the next step. A solution of cuprous chloride (0.366 g, 3.699 mmol) in conc. aqueous HCl (1 mL) was added to a solution of **15** in glacial acetic acid (20 mL). A dark, thick precipitate formed. The mixture was warmed for 5 min on a steam bath, additional concentrate HCl (1 mL) was added, and the mixture was warmed another 10 min. TLC (40% EtOAc in Hexane) indicated that the starting material was consumed. The mixture was poured onto ice, made alkaline by careful addition of aqueous NaOH, and extracted with CH_2Cl_2 (emulsion). The emulsion was filtered through Celite, and the filter pad and aqueous phase of the filtrate were further extracted with EtOAc. The organic extracts were dried ($MgSO_4$), filtered, and concentrated. The extract was purified by flash column (40% EtOAc in hexanes) afforded 0.170 g (85%) of a yellow oil; IR (neat): 3332, 2971, 2920, 2750, 1580, 1496, 1442, 1172, 1131, 1066, 1017 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 6.84–6.80 (m, 2H), 6.75–6.69 (m, 4H), 4.57 (q, $J = 6.6$ Hz, 2H), 2.16 (s, 6H), 1.56 (d, $J = 6.7$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): 144.4, 135.8, 132.5, 128.4, 128.1, 124.4, 60.5, 23.9, 20.7; HRMS calcd for $C_{18}H_{22}N_2Na$ $[M + Na]^+$: 267.1856, Found: 267.1860.

Preparation of a Nickel Chloride Complex of 16

A solution of $NiCl_2$ (4.87 mg, 0.0375 mmol) in 0.5 ml of n-butanol was slowly added to a solution of compound **16** (20 mg, 0.0751 mmol) in 0.5 ml of n-butanol. The mixture was stirred at room temperature for 2 h. TLC indicated that the starting material was consumed. The solvent was removed under vacuum and the residue was recrystallized from methanol and pentane to afford 24.8 mg (100%) of an orange solid.

Acknowledgements

This work was supported by the National Science Foundation, to whom we are grateful.

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[8] Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 275364 (**8**), 275365 (**10**), 275366 (**12**), 275367 (**14**) and 297235 (**16**/$NiCl_2$). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)-1223-336033 or E-mail: deposit@ccdc.cam.ac.uk)
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