A family of cis-macrocyclic diphosphines: modular, stereoselective synthesis and application in catalytic CO$_2$/ethylene coupling†

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A family of cis-macrocyclic diphosphines was prepared in just three steps from white phosphorus and commercial materials using a modular synthetic approach. Alkylation of bicyclic diphosphane 3,4,8,9-tetramethyl-1,6-diphosphabicyclo(4.4.0)deca-3,8-diene, or P$_2$(dmb)$_2$, produced phosphonium salts R-P$_2$(dmb)$_2$X, where R is methyl, benzyl and isobutyl, in yields of 90–96%. Treatment of these salts with organolithium or Grignard reagents yielded symmetric and unsymmetric macrocyclic diphosphines of the form cis-1-R-6-R’-3,4,8,9-tetramethyl-2,5,7,10-tetrahydro-1,6-DiPhospeCine, or R,R’-DPC, in which R’ is methyl, cyclohexyl, phenyl or mesityl, in yields of 46–94%. Alternatively, symmetric diphosphine Cy$_2$-DPC was synthesized in 74% yield from the dichlorodiphosphine Cl$_2$P$_2$(dmb)$_2$. As a first application, these cis-macrocyclic diphosphines were used as ligands in the nickel-catalyzed synthesis of acrylate from CO$_2$ and ethylene, for which they showed promising catalytic activity.

While chelating diphosphines have established a wide range of uses in areas from fundamental chemistry to catalysis,1 macrocyclic diphosphines are an underrepresented class of ligands. Their scarcity is primarily due to challenges associated with their synthesis. Macrocycles containing two or more phosphorus atoms exhibit multiple stereoisomers since the phosphines, which are locked in place by the cyclic framework, have a high barrier to inversion. Typically, syntheses of macrocyclic diphosphines yield mixtures of diastereomers;2,3 stereoselective syntheses of either cis or trans macrocyclic diphosphines are rare.4,5 While synthetically challenging, embedding one or more phosphorus atoms in a cyclic framework is desirable as it leads to more rigid and robust structures compared to their acyclic phosphine counterparts.6

cis-Macrocyclic diphosphines have been postulated to be “interesting ligands for transition metal complexes, comparable to, but perhaps usefully different from, the familiar range of chelating diphosphines”,7 yet their coordination chemistry is essentially unexplored.8 In this context, it is useful to distinguish between medium-sized (7–12-membered rings) and large (>12 membered rings) macrocyclic diphosphines. Complexes of large macrocyclic diphosphines have been synthesized as mixtures of diastereomers via ring closing metathesis and hydrogenation of preassembled metal complexes of trans-spanning monophosphines with pendant olefins.9 This synthetic strategy was also extended to prepare metal complexes of large trans-spanning macrobicyclic diphosphines.9 While both cis and trans isomers of a diphosphine embedded in a very large macrocycle can bind to a metal center, only the cis isomer can bind to a single metal center in medium-sized ring systems. The only medium-sized macrocyclic diphosphine with structurally characterized metal complexes is cis-1,5-diphenyl-1,5-diphosphacyclooctane, a ligand obtained after tedious separation of the cis and trans diastereomers produced by the lithium aluminum hydride reduction of the corresponding phosphine oxides.10

The only stereoselective synthetic route to cis medium-sized macrocyclic diphosphines was reported by Alder et al.7 We were surprised to find no coordination complexes reported for these diphosphines, despite them being synthesized two decades ago. In the Alder synthesis, the desired cis-macrocyclic diphosphines are obtained by stereoselective cleavage of the P–P bond in alkylated diphosphabicyclo[k.l.0]alkanes (k = 3–5, l = 3–4) by organometallic reagents. These diphosphabicyclo[k.l.0]alkanes are prepared via a tedious procedure from diphosphinoalkanes H$_2$P–(CH$_2$)$_i$–PH$_2$, which in turn are prepared in two steps from the corresponding dibromoalkanes. While the bicyclic diphosphane framework is key to the stereoselectivity of the entire

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process, its assembly represents the most cumbersome part of the synthesis. Our group has recently accessed bicyclic diphosphines in only one step from white phosphorus and commercial dienes under photochemical conditions.\textsuperscript{11,12} For example, diphosphane \(3,4,8,9\)-tetramethyl-1,6-diphosphabicyclo[4.4.0]deca-3,8-diene or \(P_2(dmb)_2\) (1) is obtained in gram quantities directly from white phosphorus and 2,3-dimethylbutadiene.\textsuperscript{11} This synthesis is part of a greater endeavor pursued by our group\textsuperscript{13} and others\textsuperscript{14} to prepare phosphorus-containing compounds in an atom economical fashion directly from \(P_4\),\textsuperscript{15} the precursor to the more widely used phosphorus source \(PCl_3\).

We envisioned that alkylating 1 would yield phosphino-phosphonium salts that would be prone to reacting with nucleophiles to break the P–P bond. This process would afford \(cis\)-macrocyclic diphosphines in a stereoselective manner in only three steps from white phosphorus! We describe herein an expedited synthetic route to a family of \(cis\)-macrocyclic diphosphines that will facilitate investigating the coordination chemistry of these molecules and enable their use as ligands in catalysis.

We began this synthetic endeavor by investigating the alkylation of diphosphane 1 with methyl iodide [MeI]. Previous studies have shown excellent selectivity in functionalizing only one of the phosphorus atoms in 1.\textsuperscript{16} As expected, phosphino-phosphonium salt [Me-P\(_2(dmb)_2\)]I (2) was obtained in 90% yield after treatment of 1 with methyl iodide in diethyl ether at room temperature overnight. The structure of [Me-P\(_2(dmb)_2\)]I was confirmed by X-ray crystallography (Fig. 2), and displayed a typical P–P single bond distance of 2.1862(17) \(\text{Å}\). Treatment of 1 with benzyl bromide (BnBr) also proceeded smoothly to give [Bn-P\(_2(dmb)_2\)]Br (3) in 96% yield after 2 hours at room temperature in dichloromethane (Fig. 1). The reaction of 1 with isobutyl bromide (iBuBr) was more sluggish and required heating at 100 °C for 20 h in the presence of an excess of the alkyl halide in order to achieve full conversion to [iBu-P\(_2(dmb)_2\)] Br (4).\textsuperscript{17} All of these phosphino-phosphonium salts have characteristic \(^{31}\text{P}\{\text{H}\}\) NMR spectra that show strong coupling between the two phosphorus atoms. For example, the \(^{31}\text{P}\{\text{H}\}\) NMR shifts of [Me-P\(_2(dmb)_2\)]I are +44.7 ppm and −69.3 ppm, with a \(J_{PP}\) = 276 Hz (see Table S1 in ESI for a summary of all the \(^{31}\text{P}\{\text{H}\}\) NMR chemical shifts and coupling constants).

With these salts in hand, we began investigating their reactivity with organometallic reagents. Upon adding a methyl-lithium solution to a slurry of 2 in THF or diethyl ether at room temperature, a new signal indicative of \(cis\)-1,3,4,6,8,9-hexamethyl-2,5,7,10-tetrahydro-1,6-DiPhosphateine, or Me\(_2\)DPC (5), was observed by \(^{31}\text{P}\{\text{H}\}\) NMR spectroscopy. A potential side reaction we had considered was deprotonation of the phosphino-phosphonium salt by methyl lithium and formation of the Wittig reagent (\(CH_2\)P\(_2(dmb)_2\)). However, no evidence was found for the formation of such an ylide by \(^{31}\text{P}\{\text{H}\}\) NMR spectroscopy. Diphosphine 5 was also characterized by X-ray crystallography (Fig. 3), revealing a conformation with nearly \(C_{2v}\) symmetry in which the phosphorus lone pairs are pointed away from each other.

Treatment of phosphino-phosphonium salts 2, 4, and 3 with cyclohexylmagnesium chloride led to the formation of Me,Cy-DPC (6), iBu,Cy-DPC (7), and Bn,Cy-DPC (8), respectively (Fig. 1). All of these diphosphines can be isolated in yields of 90–94% and they each show two distinct signals in their \(^{31}\text{P}\{\text{H}\}\) NMR spectra, with small \(J_{PP}\) coupling constants of ca. 5 Hz. For example, the \(^{31}\text{P}\{\text{H}\}\) NMR spectrum of 6 shows two signals at −38.9 and −60.8 ppm. In order to demonstrate the versatility of this synthetic strategy, 3 was also treated with two aryl Grignard reagents, phenylmagnesium bromide and mesitylmagnesium bromide. The resulting diphosphines, Bn,Ph-DPC (9) and Bn,Mes-DPC (10), showed similar spectroscopic features to the dialkyl diphosphines described above.

While this modular approach had already enabled the synthesis of a variety of macrocyclic diphosphines, the initial alkylation step was limited to primary halide substrates. In order to overcome this limitation, we sought to add a dihalodiphosphine to our synthetic toolbox. This intermediate would

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**Fig. 1** Synthetic routes to phosphino-phosphonium salts 2–4, dichloride 11, and macrocyclic diphosphines 5–10 and 12.

**Fig. 2** Solid-state structure of [Me-P\(_2(dmb)_2\)]I (2) with ellipsoids at the 50% probability level and disordered THF omitted for clarity. Representative interatomic distances [Å] and angles [°]: P2–C4 1.813(5), P2–C5 1.817(5), P2–C9 1.791(5), P1–P2 2.1862(17), C9–P2–C4 1.117(2), C9–P2–C5 106.9(2), C4–P2–C5 110.0(2), C9–P2–P1 114.0(19).
provide access to a symmetrical diphosphine upon addition of two equivalents of organometallic reagent. Treatment of 1 with iodine, a mild oxidant, did not yield a diiododiphosphine, but rather an iodine adduct, I$_2$·1, which we were able to characterize by X-ray crystallography (Fig. 4). The elongated I–I distance of 3.4169(12) Å is similar to metrical data reported for other phosphine–iodine adducts. While several monophosphine–iodine adducts have been structurally characterized and described in the literature, this is an unusual example of a diphosphane–iodine adduct in which the P–P bond is still intact.

The reaction of 1 with many potent halogenating agents (e.g. bromine, N-bromosuccinimide, xenon difluoride) proved to be unselective, yet oxidation of 1 with hexachloroethane produced the desired Cl$_2$P$_2$(dmb)$_2$ (11) in good purity. We expected this product to have a symmetrical open structure, as the P–P bond would have been cleaved upon oxidation. However, NMR spectroscopy suggests that 11 is best described as a chloronium chloride salt in equilibrium with the open form. At room temperature, signals are broad in both the $^1$H NMR and $^{31}$P{$^1$H} NMR ($\Delta$F$_{1/2}$ ≈ 1700 Hz) spectra of 11; upon cooling to $-40$ °C, the $^{31}$P{$^1$H} NMR spectrum shows two distinct phosphorus environments at +143.4 ppm and $-48.7$ ppm with a $^{1}J_{PP} = 291$ Hz. In order to elucidate whether the broad NMR signals were due to chloride association/dissociation at the same phosphorus center versus chloride-mediated P–P bond scission/reformation, a 2D EXSY (EXchange SpectroscopY) experiment was performed. In the first pathway, the two phosphorus centers would remain distinct throughout the exchange process, while in the second pathway the two phosphorus centers would become chemically equivalent in the open form. The $^{31}$P{$^1$H} 2D EXSY spectrum of 11 (Fig. 5) clearly shows the presence of exchange cross peaks, thus supporting the chemical exchange pathway depicted in the same figure. The proposed role of free chloride in the exchange was corroborated by treatment of 11 with GaCl$_3$, which sequestered the chloride into the tetra-chlorogallate [GaCl$_4$]$^-$ anion; this inhibited the exchange process and “froze” the compound in the chloronium salt form with sharp $^{31}$P{$^1$H} NMR resonances at room temperature.

Addition of two equivalents of cyclohexylmagnesium chloride to a suspension of 11 in diethyl ether or THF results in the formation of the desired Cy$_2$-DPC (12). The $^{31}$P{$^1$H} NMR spectrum of this product reveals a characteristic singlet resonance at $-38.7$ ppm for 12, but also a small amount of 1 (ca. 2%). This by-product is likely due to the reduction of 11 under the reaction conditions. While reduction was not a major reaction pathway during the formation of 12, it became problematic when attempting to prepare tBu$_2$-DPC. Treatment of 11 with tert-butylmagnesium chloride resulted in a roughly equimolar mixture of tBu$_2$-DPC and 1. Due to their similar solubility properties, these two products could not be separated.

While all syntheses were conducted under inert atmosphere, we wondered if these new diphosphines had any stability to air
and moisture. Exposing a benzene-\(d_6\) solution of 12 to air led to no visible changes by \(^{13}\)P NMR spectroscopy even after 24 hours. This diphosphine proved to be remarkably robust, as less than 10% of the material had decomposed to the phosphine-phosphine oxide after 48 hours in solution.

Having accessed a family of new chelating macrocyclic diphosphines, we were interested in exploring their use as supporting ligands in a catalytic process. Given our interest in diphosphines, we were interested in exploring their use as such. Notably, 93.91(4) \(\alpha\) observed for the lactone of diphenylphosphinobutane (dppb), DPC)Ni(CH\(_2\)CH\(_2\)COO) (13) (Fig. 7). The Ni1–C3 and Ni1–O1 distances of 1.982(6) and 1.899(4) \(\text{Å}\), respectively, are similar to those reported for other nickelalactones.\(^{29}\) The bite angle of the diphosphine in complex 13 is 91.46(5)\(^{\circ}\), a value intermediate between that observed for the lactone of dicyclohexylphosphinoethane (dcpe), namely 88.07(5)\(^{\circ}\),\(^{26}\) and that observed for the lactone of diphenylphosphinobutane (dppb), namely 93.91(4)\(^{\circ}\).\(^{26}\) The smaller bite angle compared to dppb, a ligand that also has a four carbon atom bridge, might be due to the increased backbone rigidity of 12.

While helpful for comparing 12 with other ligands previously used to support nickelalactones, bite angle is an insufficient metric for describing the steric profile of 12. The cyclic backbone of this ligand renders an unusual placement of the cyclohexyl substituents in the P–Ni–P plane, a feature best described by the P1–Ni1–P2–C41 and P2–Ni1–P1–C31 torsion angles of \(-173.1(2)\)\(^{\circ}\) and 175.33(18)\(^{\circ}\), respectively. In contrast, a ligand such as dcpe places its backbone linker in the P–Ni–P plane, and the cyclohexyl substituents above and below that plane (Fig. 8). The absolute values of the corresponding P–Ni–P–C torsion angles in (dcpe)Ni(CH\(_2\)CH\(_2\)COO) range from 96.6\(^{\circ}\) to 136.7\(^{\circ}\), and average 117.2\(^{\circ}\). In effect, 12 has its cyclohexyl substituents rotated by 60\(^{\circ}\) compared to a typical diphosphine such as dcpe.

In order to further probe the comparison between dcpe and 12, their \(V_{\text{bur}}\) values defined as the percent

![Fig. 6 Synthesis of (Cy\(_2\)-DPC)Ni(CH\(_2\)CH\(_2\)COO) (13) from 12 via two complementary routes (see ESI† for details).](image)

![Fig. 7 Solid-state structure of nickelalactone (Cy\(_2\)-DPC)Ni(CH\(_2\)CH\(_2\)COO) (13) with ellipsoids at the 50% probability level and hydrogen atoms omitted for clarity. Representative interatomic distances [\(\text{Å}\)] and angles ['\(\circ\)']: Ni1–P1 2.2454(15), Ni1–P2 2.1283(15), Ni1–C3 1.982(6), Ni1–O1 1.899(4), O1–C1 1.283(6), O2–C1 1.225(6); O1–Ni1–P1 90.86(12), O1–Ni1–C3 85.3(2), C3–Ni1–P2 92.56(19), P2–Ni1–P1 91.46(5), P1–Ni1–P2–C41–173.1(2), P2–Ni1–P1–C31 175.33(18).](image)

![Fig. 8 Ball and stick models of dcpe (top) and Cy\(_2\)-DPC (bottom) with hydrogen atoms omitted for clarity, highlighting the differences in steric profiles between these two diphosphines. Both ligands are viewed along the Z axis, defined using SambVca 2.0 as the P–Ni–P angle bisector in their respective nickelalactone complexes.](image)
volume occupied by the ligand out of the total volume of a sphere centered at the metal and typically set to have a 3.5 Å radius\(^{43}\) were calculated\(^{44}\) using the SambVca 2.0 web application developed by Cavallo and coworkers.\(^{22}\) Even though dcpp has four cyclohexyl substituents and 12 has only two, these ligands have almost identical % buried volumes: 54.5% and 54.8%, respectively. This result can be in part attributed to the unusual placement of the cyclohexyl groups in 12 with respect to the metal center, but also to the significant bulk added by the protruding methyl groups of the tetramethyltetrahydroDiPhosphateCine (DPC) backbone.

Having determined that nickelalactones are accessible with this new ligand platform, we proceeded in measuring the catalytic activity of diphosphines 5-10 and 12. In doing so, we used two different protocols: one adapted from the work of Vogt et al. (method A),\(^{25}\) and one adapted from Limbach et al. (method B).\(^{27}\) In a typical catalytic run, Ni(COD)\(_2\) was mixed with the ligand, along with a base, Lewis acid, and zinc as an additive. For runs using method A, the base was NE\(_3\) and the Lewis acid was LiI, whereas for runs using method B, sodium 2-fluorophenoxide served as both the base and source of Lewis acid.

As shown in Table 1, all of the new ligands but the bulky Bn,Mes-DPC (10) showed catalytic activity in this transformation. Dicyclohexylphosphinoethane (dcppe), dicyclohexylphosphinopropane (dcpp) and dicyclohexylphosphinobutane (dcbp) were used as benchmarks, as they are some of the best performing ligands reported in the literature so far.\(^{25,27}\) We found the turnover numbers of our most active ligands such as 12 to be comparable to or better than those of the benchmark ligands. Notably, 12 performed significantly better than dcpb, a ligand that has a similar 4-carbon atom backbone.

Employing this new family of cis-macrocyclic diphosphines in CO\(_2\)/ethylene coupling is only the first step in exploring the catalytic relevance of these compounds. We plan to expand this ligand family using the synthetic methods disclosed herein, which have laid the groundwork for accessing phosphorus-based ligands with unique structures and steric profiles in a modular fashion. Asymmetric ligands will be easily accessible by installing chiral groups on the phosphorus centers, thus enabling numerous applications in the realm of asymmetric catalysis. Given the unusual steric profiles of the cis-macrocyclic diphosphines reported herein, our group is also actively pursuing the synthesis and characterization of a variety of metal complexes supported by these ligands in order to learn more about their coordination chemistry.

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### References


### Table 1

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<td>Cy2P-(CH2)3–PCy2 (dcbp)</td>
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\(^{a}\) Ni(COD)\(_2\) (0.05 mmol), ligand (0.05 mmol), Zn (2.5 mmol), LiI (1.25 mmol), NE\(_3\) (2.5 mmol), PhCl (2 mL), pressurized with C\(_2\)H\(_4\) (25 bar) and CO\(_2\) (5 bar) and heated to 50 °C for 24 h. The TONs listed are averages of two independent runs. \(^{b}\) Ni(COD)\(_2\) (0.07 mmol), ligand (0.077 mmol), Zn (3.5 mmol), sodium 2-fluorophenoxide (3.5 mmol), THF (10 mL), pressurized with C\(_2\)H\(_4\) (10 bar) and CO\(_2\) (10 bar) and heated to 100 °C for 20 h. \(^{c}\) Complex 13 (0.07 mmol) was used as the starting nickel source in lieu of the typical mixture of Ni(COD)\(_2\) and ligand.
8 The 1998 review article cited above mentions unpublished observations vis-à-vis the ligand behaviour of the cis-macrocyclic diphenosphines synthesized by Alder et al.


17 Secondary halides such as cyclohexyl bromide did not react with 1 under similar conditions.


31 The %Vbar for both dcpb and 12 was calculated using the default settings in SambVca 2.0, namely bond radii scaled by 1.17, sphere radius of 3.5 Å, Ni as the center of the sphere, mesh spacing for numerical integration of 0.1 Å, and H atoms not included.