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A Tandem Olefin Migration and Prins Cyclization Using Cu(OTf)₂-Bisphosphine Complexes: An Improved Synthesis of Functionalized Tetrahydropyrans

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Abstract

In situ-generated (*bis*-DPPMB)-Cu(OTf)₂ complex has been examined to catalyze a tandem olefin migration and Prins cyclization of an alkenol with various aldehydes. The reaction proceeded with electron-rich aromatic aldehydes at room temperature and provided functionalized tetrahydropyrans in good yields. An efficient synthesis of the *bis*-DPPMB ligand has also been described.

Keywords

Phosphine ligand; Prins cyclization; Phosphine-borane adduct; Tetrahydropyrans; Prins chemistry

Functionalized tetrahydropyran derivatives are of considerable interest because of their broad application to synthetic and medicinal chemistry.^{1,2} We recently reported that Cu(OTf)₂-bisphosphine ligand complexes catalyzed a tandem olefin migration and 6-(3,5)-Prins-type cyclization, as shown in Scheme 1.³ This led to the formation of substituted tetrahydropyrans (THP's) in excellent diastereoselectivities and isolated yields. The overall process is attractive, as the chemistry does not involve pericyclic pathways, proceeding instead through an atypical Prins cyclization, and precludes an Oxonia-Cope process.⁴ As shown, we previously utilized *Z*-1,2-bis(diphenylphosphino)ethylene (**L1**) or 1,2-bis(diphenylphosphino)benzene (**L2**) ligand in combination with Cu(OTf)₂, and showed that the reaction is suitable for a variety of aldehydes, such as benzyloxyacetaldehyde **2**, and various aliphatic and aromatic aldehydes. However, the results obtained with electron-rich aromatic aldehydes were less satisfactory. This shortcoming has been reported in related methodologies involving Prins-cyclizations.⁵ In an attempt to expand the scope of our olefin migration and Prins cyclization process, we sought to investigate a new diphosphine ligand (**L3**) with an inter-phosphorus bridge containing four bonds and possessing a σ -donor ability through an electron-neutral triarylphosphine.⁶ We speculated that such a bisphosphine ligand-Cu(OTf)₂ complex may exhibit more effective catalysis due to bite angle change of

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Supplementary Data

Supplementary data (¹H, ¹¹B, ¹³C, and ³¹P NMR spectra for all new compounds.) associated with this article can be found in the online version.

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L3 as compared to metal-ligand complexes made with **L1** or **L2** ligands. Herein, we report the results of this investigation. We have developed an efficient synthesis of 1-(diphenylphosphino)-2-(diphenylphosphinomethyl)benzene (*bis*-DPPMB) from the readily available 2-bromotoluene. The *bis*-DPPMB ligand is easy to handle and can be quickly weighed out without the use of air-sensitive techniques. The Cu(OTf)₂-**L3** complexes provided an improvement of reaction yields with electron-rich aromatic aldehydes. Furthermore, the reaction proceeded at room temperature and the catalytic system worked well with those aliphatic and aromatic conjugated aldehydes examined.

The synthesis of bisphosphine ligand **6** (**L3**) is shown in Scheme 2. There is no satisfactory route to bisphosphine ligand **6** (**L3**) in the literature. We therefore devised an efficient route for the synthesis of this bisphosphine ligand which provided gram quantities. Tolyldiphenylphosphine oxide **7** was readily prepared from commercial 2-bromotoluene as reported by Zhou and co-workers.⁷ Bromination of **7** with NBS in the presence of a catalytic amount of AIBN in benzene at reflux provided a mixture (10:1) of mono- and di-brominated derivatives **8a** and **8b**, respectively, in near quantitative yield. These products were separated by silica gel chromatography. As shown in Table 1, our direct alkylation^{8,9} of **8a** with diphenylphosphine or diphenylphosphine oxide in the presence of triethylamine resulted in no desired product (entries 1 and 2). The corresponding borophosphanylation with a diphenylphosphine-borane adduct resulted in a small amount of the desired product (~5%, entry 3). Formation of the phosphine-borane anion¹⁰ with *n*-BuLi in THF at -78 °C afforded bisphosphine product **9** in 38% yield (entry 4). However, the addition of HMPA (1:1 ratio with THF) after the formation of the phosphine-borane anion, followed by reaction with bromide **8a** provided **9** in 91% yield (entry 5). It is interesting to note that the presence of HMPA during deprotonation with *n*-BuLi resulted in no alkylation product **9**. These results indicated that the addition of HMPA likely facilitated the reaction by assisting in the breakup of unreactive oligomers.

For the reduction of the diphosphine monoxide **9**, we have investigated a variety of conditions. As shown in Table 2, direct reduction with silanes^{11,12} did not result in any desired product (entries 1–2). The attempted reductions with various aluminum reagents provided mixed results (entries 3–5).^{13,14} However, AlH₃ reduction¹⁵ proved to be most effective, furnishing the reduced product **10** in 96% yield (entry 6). While the reduction of phosphine oxides with AlH₃ has been previously reported by Wyatt and co-workers,¹⁶ the present reduction of a phosphine oxide in the presence of a phosphine-borane adduct is unprecedented. The subsequent deprotection of the phosphine-borane adduct was accomplished by treatment with neat diethylamine,¹⁷ providing bisphosphine ligand **6** in near-quantitative yield. Interestingly, this ligand was found to degrade at a rather slow pace upon exposure to atmospheric oxygen (~70% oxidation after 24 h by ³¹P NMR studies). This stability makes it easier to handle and quickly weigh out without the use of air-sensitive techniques. The bisphosphine precursor **10** was recrystallized in acetonitrile under inert atmosphere at 0 °C for 7 days (mp 155–160 °C; decomposition). An ORTEP diagram of the X-ray crystal structure of **10** is shown in Figure 1.^{18,19} The structure clearly shows that the phosphine-borane adduct remained fully intact on the more electron-rich alkyldiphenylphosphine.

We then examined the *bis*-DPPMB-Cu(OTf)₂-catalyzed (15 mol %) reaction of 5-methylhex-5-en-1-ol (**1**) with six representative aldehydes including three electron-rich aromatic aldehydes, an electron-poor aldehyde, a conjugated aromatic aldehyde, and an aliphatic aldehyde. We have compared these results with bisphosphine ligands **L1** and **L2** and results are shown in Table 3. A number of observations are noteworthy here. First of all, the tandem olefin migration and Prins cyclization of alkenol **1** and 4-methoxybenzaldehyde **11** with Cu(OTf)₂ (15 mol %) proceeded sluggishly at 40 °C for 2 h to provide

tetrahydropyran **12** in about 20% yield. Secondly, the reaction does not proceed in the presence of 4 Å MS for 48 h at 40 °C. However, the reaction did proceed once a catalytic amount of triflic acid was added. Thus, it appears that a protic acid is possibly required for the olefin rearrangement step. For the Cu(OTf)₂-**L3** complex catalyzed reaction, we found that the reaction can be carried out at 23 °C.

As can be seen, the reaction of **1** with electron rich 4-methoxybenzaldehyde **11** in the presence of Cu(OTf)₂-**L3** complex proceeded at 23 °C for 18 h to provide **12** in 69% yield with excellent diastereoselectivity (*dr* > 20:1, entry 3). The corresponding reactions with ligands **L1** and **L2** were less satisfactory (entries 1 and 2) and were very slow at room temperature. These reactions were carried out at 40 °C for 2 h (conditions b). Reaction of electron-rich 2-anisaldehyde **13** with Cu(OTf)₂-**L3** complex provided tetrahydropyran **14** in 34% yield at 23 °C for 24 h. The corresponding reaction with **L1** and **L2** Ligands provided lower yields of **14** (entries 4–6). Reaction of piperonal **15** using Cu(OTf)₂-**L3** complex provided tetrahydropyran **16** in 46% yield and the corresponding reaction using **L1** or **L2** ligands afforded **16** in lower yields (entries 8–9). We have surveyed reactions with electron poor 4-nitrobenzaldehyde **17** (entries 10–12). The Cu(OTf)₂-**L3** catalyzed reaction showed similar results as ligand **L2** however, the reaction yield was significantly better with ligand **L1**. The Cu(OTf)₂-**L3** catalyzed reaction with cinnamaldehyde proceeded with improved yields and excellent diastereoselectivity, providing tetrahydropyran **20** in 74% yield and *dr* > 20:1 (entries 13–15). The reaction with isovaleraldehyde also provided improved yields and comparable diastereoselectivity (entries 16–18).

In summary, we have investigated the scope of Cu(OTf)₂-bisphosphine catalyzed reaction in tandem olefin migration and Prins cyclization with a number of aldehydes, particularly with electron-rich aromatic aldehydes. In this context, we prepared a stable bisphosphine ligand, *bis*-DPPMB to further improve these tandem reactions over **L1** and **L2**-ligands. The (*bis*-DPPMB)-Cu(OTf)₂ complex provided some improvement with electron-rich aromatic aldehydes, conjugated aromatic, and aliphatic aldehydes and the reactions proceeded at room temperature. This *bis*-DPPMB ligand is quite stable and can also be handled without the use of air-sensitive techniques. Further improvement of the catalytic system is the subject of ongoing studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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20. All new compounds gave satisfactory spectroscopic and analytical results. *Preparation of 2-(bromomethyl)phenyl diphenylphosphine oxide (8a)*: *O*-tolylidiphenylphosphine oxide **7** (6.83 g, 23.4 mmol) was dissolved in 235 mL benzene. NBS (4.24 g) and AIBN (385 mg) were added, and the solution was refluxed for 40 h, then cooled to 25 °C. The reaction mixture was washed with water and brine, then concentrated, and purified by flash column chromatography to give **8a** (6.27 g, 91%). ¹H NMR (400 MHz, CDCl₃); δ 7.70–7.00 (m, 14H), 5.02 (s, 2H). ¹³C NMR (100 MHz, CDCl₃); δ 142.8–127.4 (Ph), 31.0 (d, ³J_{P-C} = 16.4 Hz). ³¹P NMR (121 MHz, CDCl₃); δ 33.0 (s, 1P). *Preparation of (2-diphenylphosphinoyl)phenylmethyl-diphenylphosphine-borane adduct (9)*: To a solution of Ph₂P(BH₃)H (4.06 g, 20.3 mmol) in THF (200 mL) was added 12.8 mL *n*-BuLi (1.6 M in hexanes) dropwise over 10 min at –78 °C. HMPA (200 mL) was added after 10 min and the resulting solution was stirred for a further 10 min. Phosphine oxide **8a** (6.27 g, 16.9 mmol) was added as a solution in THF (56 mL) *via* cannula. After stirring for 20 min, the solution was warmed to 25 °C over 40 min. The reaction was quenched with aqueous (NH₄)₂SO₄ and the reaction mixture was washed with water and brine. Removal of the solvent provided a residue which was purified by flash column chromatography. Recrystallization of the product from warm diethyl ether furnished **9** (7.53 g, 91%). ¹H NMR (400 MHz, CDCl₃); δ 7.92–6.88 (m, 24H), 4.39 (d, ²J_{PH} = –12.8 Hz, 2H), 1.60–1.20 [q(br), 3H]. ¹¹B NMR (96 MHz, CDCl₃); δ –37.0 [s(br), 1B]. ¹³C NMR (100 MHz, CDCl₃); δ 139.0–126.1 (Ph), 30.8, (d, ¹J_{PC} = 56.9 Hz). ³¹P NMR (121 MHz, CDCl₃); δ 33.9 (s, 1P), 18.3 [s(br), 1P]. LRMS (ESI) (M–H)⁺ = 489, M⁺ = 490, (M–BH₃+ONa)⁺ = 515. *Preparation of (2-diphenylphosphino)phenylmethyl-diphenylphosphine-borane adduct (10)*: Diphosphine-borane monoxide **9** (600 mg, 1.22 mmol) was dissolved in THF (25 mL). Alane-THF adduct (~0.5 M, 1 equiv) was added dropwise over 10 min at 0 °C. After stirring for 30 min, an additional equivalent of alane was added, and the solution was warmed to room temperature over 1 hr. Methanol was added to quench the excess alane, then the mixture was passed through celite. The filtrate was concentrated, and the crude product was purified by flash column chromatography to give pure **10** (560 mg, 96%) as an amorphous solid. ¹H NMR (400 MHz, CDCl₃); δ 7.72–6.78 (m, 24H), 4.03 [d(d), ⁴J_{PH} = –2.4 Hz, ²J_{PH} = –11.6 Hz, 2H], 1.59–0.95 [d(d{br}), 3H]. ¹¹B NMR (96 MHz, CDCl₃); δ –37.3 [s(br), 1B]. ¹³C NMR (100 MHz, CDCl₃); δ 137.4–127.4 (Ph), 31.2, [d(d), ³J_{PC} = 25.2 Hz, ¹J_{PC} = 31.2). ³¹P NMR (121 MHz, CDCl₃); δ 19.8 [s(br), 1P], –14.6 (s, 1P). LRMS (ESI) (M+H)⁺ = 475, (M+Na)⁺ = 497, (M+K)⁺ = 513. *Preparation of 1-(diphenylphosphino)-2-(diphenylphosphinomethyl)benzene (bis-DPPMB) (L3)*: Diphosphine-borane adduct **10** (250 mg, 0.527 mmol) was dissolved in 35 mL diethylamine. After stirring for 12 hrs, 100 ml H₂O was added, and the product was extracted with EtOAc. After concentrating, the crude bisphosphine was purified by silica gel plug filtration to give **L3** in quantitative yield. ¹H NMR (400 MHz, CDCl₃); δ 7.94–6.81 (m, 24H), 3.74 (s, 2H). ¹³C NMR

(100 MHz, CDCl₃); δ 138.4-126.4 (Ph), 34.6. ³¹P NMR (121 MHz, CDCl₃); δ -9.1 (d, 1P, ⁴*J*_{PP} = -24.0 Hz), -15.7 (d, 1P, ⁴*J*_{PP} = -24.0 Hz). HRMS (ESI) *m/z* calcd for C₃₁H₂₆P₂ 461.1588, found 461.1583. *Synthesis of tetrahydropyran derivative 12*: Cu(OTf)₂ (43 mg, 0.12 mmol, 0.15 equiv.) was added to a solution of bisphosphine **L3** (55 mg, 0.12 mmol, 0.15 equiv.) in CH₂Cl₂ (5 mL) under an argon atmosphere. This solution was stirred for 1 h then 4-methoxybenzaldehyde **11** (136 mg, 1 mmol) and alkenol **1** (143 mg, 1.25 mmol) were added to the solution in CH₂Cl₂ (5 mL) via cannula. After stirring for 18 h, the reaction mixture was diluted with CH₂Cl₂ and washed with aq NaHCO₃ (20 mL) and brine (20 mL). The organic layer was dried with Na₂SO₄ and concentrated. Crude THP was purified via column chromatography to provide **12** (160 mg, 69%). ¹H NMR (400 MHz, CDCl₃); δ 7.22 (d, *J* = 5.0 Hz, 2H), 6.82 (d, *J* = 5.0 Hz, 2H), 4.62 & 4.61 (s & s, 1H & 1H), 4.10 (m, 2H), 3.77 (s, 3H), 3.58 [t(d), *J* = 5.0, *J*₂ = 2.3 Hz, 1H], 2.33 [t(d), *J* = 5.0, *J*₂ = 2.4 Hz, 1H], 1.92-1.71 (m, 4H), 1.43 (s, 3H). ¹³C NMR (100 MHz, CDCl₃); δ 159.0, 146.5, 133.5, 128.5, 113.4, 111.9, 84.0, 68.9, 55.2, 50.4, 30.4, 26.4, 21.5. HRMS (EI/CI) *m/z* calcd for C₁₅H₂₀O₂ 232.1463, found 232.1465.

Figure 1. ORTEP drawing of **10**. White = hydrogen, grey = carbon, pink = boron, and orange = phosphorus. Ellipsoids are shown at the 50% probability level.

Scheme 1.

Tandem olefin migration and Prins cyclization routes to functionalized tetrahydropyrans.

Scheme 2. Synthesis of *bis*-DPPMB (**L3**) from *o*-tolyl diphenyl phosphine oxide **7**.

Table 1Conditions for the borophosphnylation of **8a**.

Entry	Conditions	X	Yield (%)
1	Ph ₂ PH, Et ₃ N, CH ₂ Cl ₂	PPh ₂	0
2	Ph ₂ P(O)H, Et ₃ N, CH ₂ Cl ₂	Ph ₂ P=O	0
3	Ph ₂ P(BH ₃)H, Et ₃ N, CH ₂ Cl ₂	Ph ₂ P-BH ₃	5
4	Ph ₂ P(BH ₃)H, <i>n</i> -BuLi, THF	Ph ₂ P-BH ₃	38
5	Ph ₂ P(BH ₃)H, <i>n</i> -BuLi, HMPA/THF	Ph ₂ P-BH ₃	91

Table 2Reduction of bisphosphine monoxide **9** to **10**

Entry	Conditions	Yield (%)
1	Cl_3SiH , Et_3N , Xylene, heat	0
2	PMHS, Et_3N , Xylene, heat	0
3	MeI, LAH, DME, heat	39
4	LAH, CeCl_3 , THF	34
5	DIBAL-H, PCy_3 , CH_2Cl_2	38
6	AlH_3 , THF, THF	96

Table 3

Cu(OTf)₂-bisphosphine catalyzed reactions with aldehydes.

Entry	Aldehyde	Product	Conditions	Ligand	Yield (%) ^a	d ^b
1			a	L1	42	>20:1
2			a	L2	20	>20:1
3			b	L3	69	>20:1
4			a	L1	22	>20:1
5			a	L2	27	>20:1
6			b	L3	34	>20:1
7			a	L1	36	>20:1
8			a	L2	29	>20:1
9			b	L3	46	>20:1
10			a	L1	80	>20:1
11			a	L2	62	>20:1
12			b	L3	63	11:1
13			c	L1	59	>20:1
14			c	L2	53	>20:1
15			b	L3	74	>20:1
16			c	L1	59	>20:1
17			c	L2	62	>20:1
18			b	L3	70	16:1

Reactions were carried out with 5-methylhex-5-en-1-ol (**1**) (1.25 equiv), aldehyde (1 equiv), Cu(OTf)₂ (0.15 eq), ligand (0.15 eq), in 0.1 M in CH₂Cl₂. Conditions, **a**: 40 °C, 2 h; **b**: 23 °C, 18 h; **c**: 40 °C, 40 h.

^a Isolated yield of 2,3-*trans*-THP.