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Modular Synthesis of a New Family of Tripodal Ligands, *all-cis*-1,2,3-Tris(diphenylphosphinomethyl)cyclopropane and Relatives†

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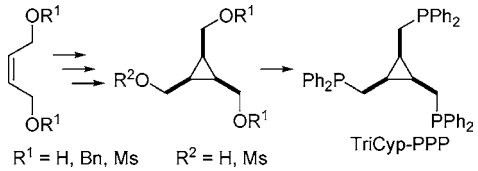
ABSTRACT



Bisbenzyl-protected *all-cis*-1,2,3-tris(hydroxymethyl)cyclopropane has been obtained in three steps from commercially available *cis*-2-butene-1,4-diol (75% overall yield) and used to prepare a number of *all-cis*-1,2,3-trisubstituted cyclopropane derivatives. Among them, the new tripodal ligand *all-cis*-tris(diphenylphosphinomethyl)cyclopropane (TriCyp-PPP) has been demonstrated to furnish—with π-allylpalladium chloride dimer—a highly active catalyst for the allylation of diethyl methylmalonate enolate with allyl acetate.

The lack of sufficiently active catalysts for palladium-catalyzed reactions applicable to a wide range of substrates and reaction conditions to date is one of the predominant reasons why these reactions are not yet frequently applied as industrial processes.[1] Over the past decade, a variety of new and remarkably efficient catalyst systems have been developed using palladacycles,[2] bulky monodentate ligands to form coordinatively highly unsaturated palladium complexes,[3] or carbene ligands[4] to bring about unprecedented activity and the ability to cope with sterically encumbered or deactivated substrates. The classical systems using phosphine ligands had already been written off by several authors for never being appropriate to achieve high turnover numbers (TONs), when 6 years ago a tetrapodal diphenylphosphine

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ligand **1**, in short called "Tedicyp", was introduced (Figure 1).[5a] This ligand performed exceptionally well in several

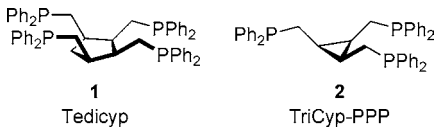
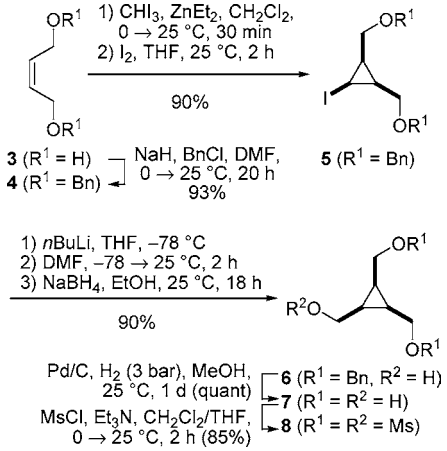


Figure 1. Structural motif for the design of the TriCyp family of ligands.

palladium-catalyzed reactions on a wide range of notoriously poor substrates and brought about quite good TONs.[5] Along a similar line of thought, we envisaged a new "TriCyp" family of ligands containing an *all-cis*-configured trisubstituted cyclopropane backbone[6] for use in palladium-catalyzed transformations. Especially, *all-cis*-1,2,3-tris(diphenylphosphinomethyl)cyclopropane (TriCyp-PPP, **2**) in connection with palladium was hoped to provide an even higher catalytic activity than **1** because the metal center in the palladium complexes of **2** should be slightly less "shielded"[5a,7] by phosphino groups while still maintaining a wide bite angle.[8]

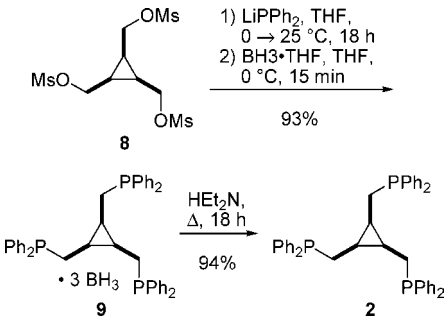
all-cis-1,2,3-Tris(hydroxymethyl)cyclopropane (**7**) was conceived as a suitable intermediate en route to TriCyp-PPP **2**. Besides a synthesis of **7** lacking experimental details,[9] a rather cumbersome seven-step access to the bisbenzyl-protected derivative **6** in around 40% overall yield[10] and an elegant, yet reasonably exotic, access to derivatives of the yet unknown 1,2,3-cyclopropanetriscarbaldehyde by ozonolysis of bullvalene[11] have been reported. Therefore, a much more efficient approach to **7** was developed starting with a diastereoselective iodocyclopropanation[12] of the bisbenzyl ether **4** of commercially available *cis*-butene-1,4-diol (**3**). The *all-cis*-3-iodo-1,2-bis(benzyloxymethyl)cyclopropane (**5**), obtained in 90% yield, was cleanly converted into an aldehyde by iodine−lithium exchange with *n*-butyllithium and subsequent trapping with dimethylformamide. The aldehyde in turn was reduced with sodium borohydride to give the bisprotected triol **6** in an overall yield of 75% starting from **3**. After deprotection of **6**, the triol **7** was converted into the trismesylate **8** in 85% yield (Scheme 1).

Scheme 1



Among several tested phosphorus nucleophiles, lithium diphenylphosphide, generated from diphenylphosphine by deprotonation with *n*-butyllithium, gave the best yields in the conversion of the trismesylate **8** to the corresponding trisphosphine which was in situ protected as the trisborane complex **9** (Scheme 2). This complexation of TriCyp-PPP **2**

Scheme 2



was performed to obtain an air-stable ligand precursor which can be purified and stored easily. The desired *all-cis*-configuration at the cyclopropane moiety was rigorously proved by an X-ray crystal structure analysis (Figure 2). Generation of the free trisphosphine **2** was accomplished by stirring **9** with an excess of diethylamine at reflux overnight.

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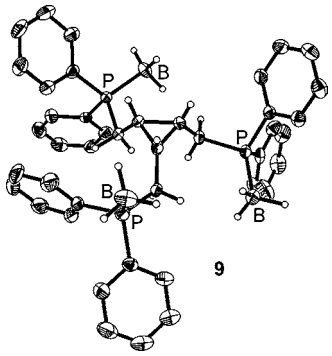


Figure 2. Structure of the *all-cis*-1,2,3-tris(diphenylphosphinomethyl)cyclopropane−trisborane complex [TriCyp-PPP·$(BH_3)_3$, **9**] in the crystal.[20]

Further elaboration of the partially protected precursor **6** provided access to differently substituted analogues of **2** bearing other donor functionalities (Figure 3). Thus, **6** was

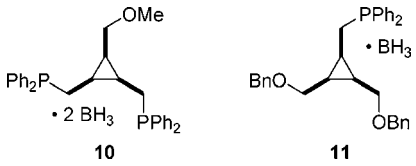


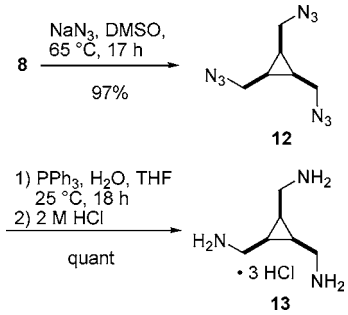
Figure 3. Two differently substituted tripodal ligand precursors.

methylated to its monomethyl ether (97% yield), the latter debenzylated by hydrogenolysis, and the resulting diol was converted to the corresponding bismesylate which was in turn substituted with lithium diphenylphosphide. The monomethoxybisphosphine was isolated as the bisborane complex **10** (18% over three steps). On the other hand, the mesylate of **6** (96% yield) was converted to the borane-protected bisbenzyloxymethylmonodiphenylphosphinomethyl derivative **11** in 78% yield.

The phosphine ligand TriCyp-PPO was liberated from its borane complex **10** by heating in diethylamine. Amino substituents as exemplified in the 1,2,3-trisaminomethylcyclopropane trishydrochloride (**13**) were realized by conversion of the trismesylate **8** to the trisazide by substitution with sodium azide, and the trisazide was reduced by reaction with triphenylphosphine (Staudinger reaction[13]) and subsequent hydrolysis (97% overall yield from **8**, Scheme 3).

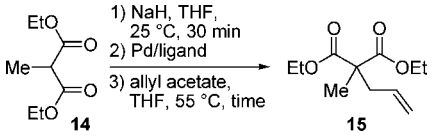
To test the performance of the new ligand **2** in palladium-catalyzed reactions, the allylation of the sodium enolate of diethyl methylmalonate (**14**) with allyl acetate[14] was chosen

Scheme 3



as a first benchmark. In this reaction, applying π-allylpalladium chloride dimer as a precatalyst, the ligand TriCyp-PPP **2** in terms of TON outperformed 1,4-bis(diphenylphosphino)butane (dppb), one of the established bidentate ligands[15] with a slightly smaller bite angle[16] (Table 1).

Table 1. Effects of Different Ligands on the Isolated Yields of Diethyl Allylmethylmalonate (**15**) in the Palladium-Catalyzed Allylation of the Enolate of Diethyl Methylmalonate (**14**) with Allyl Acetate



entry	Pd/ligand[a]	ratio[b] of substrate/ catalyst	time (h)	yield (%)	TON
1	dppb	5000	3	quant	5000
2	dppb	10000	3	91	9100
3	dppb	50000	16	93	46500
4	dppb	200000	16	60	120000
5	TriCyp-PPP	10000	3	93	9300
6	TriCyp-PPP	200000	16	92	184000
7	TriCyp-PPP	1000000	65	0[c]	–
8	TriCyp-PPO	200000	16	76[d]	152000

[a] η^3-$[C_3H_5$-PdCl$]_2$/ligand = 1:2. [b] Calculated for allyl acetate. [c] Only transesterification products observed. [d] Decomposition of the catalyst stock solution after 1 day was observed.

The bisphosphine TriCyp-PPO was tested in the same reaction as well. The yield of **15** was significantly lower (76 vs 92%), and the stock solution of the catalyst decomposed within 1 day. Thus, it is impossible to judge whether the palladium complex of TriCyp-PPO is inherently less active or only less stable than the complex formed with TriCyp-PPP **2**.

In summary, an unprecedented efficient access to the bisbenzyl-protected *all-cis*-1,2,3-tris(hydroxymethyl)cyclo-

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(16) The natural bite angle[18] of **2**, considered in a bidentated complex, was computed by the PM3 semiempirical method[19] to be 101°. This compares with a natural bite angle of 98° for complexes of dppb.[8]

propane **6** has been developed. The latter can serve as a convenient precursor to a variety of *all-cis*-1,2,3-trisubstituted cyclopropane derivatives with ligand properties. Furthermore, the trisazide **12** might serve as a suitable precursor in the formation of heterocycles using the "click" chemistry introduced by Sharpless et al.[17] In a first test, the new trisphosphine **2**, prepared in seven steps (56% overall yield) from inexpensive *cis*-2-butene-1,4-diol, compares favorably with the commercially available dppb and the previously introduced Tedicyp ligand **1**,[5] which has to be prepared in seven steps (33% overall yield) from a more expensive starting material.

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Supporting Information Available: Experimental procedures and product characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Crystallographic data (excluding structure factors) for structure **9** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (+44)1223−336-033, e-mail: deposit@ccdc.cam.ac.uk], on quoting the depository number CCDC 601835.