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Enantioselective Cyclopropanation with TADDOL-Derived Phosphate Ligands

Arnaud Voituriez[a] and André B. Charette[a,*]

[a] Département de Chimie, Université de Montréal, P.O. Box 6128, Station Downtown, Montréal, QC H3C 3 J7, Canada
Phone: (+1)-514–343–2432; Fax: (+1)-514–343–5900; e-mail: andre.charette@umontreal.ca

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Abstract: The synthesis of new chiral TADDOL-derived phosphate ligands is described. The ligands were efficiently synthesized on a multi-gram scale in three steps starting from the readily available corresponding TADDOL and were fully characterized. An X-ray structure was obtained and compared to known BINOL-phosphates. Their use in the asymmetric Simmons–Smith cyclopropanation of both functionalized and unfunctionalized olefins gave the desired cyclopropanes in good yields and good to moderate enantioselectivities.

Keywords: asymmetric synthesis; Brønsted acid; cyclopropanes; Simmons–Smith reaction; TADDOL-phosphate

Stereoselective organocatalysis has, over the past few years, become an area of intense investigation worldwide.[1] Among the growing family of organocatalysts, chiral Brønsted acids have emerged as powerful agents in a number of enantioselective transformations. For example, chiral phosphoric acids derived from BINOL,[2] VAPOL[3] and BINAM[4] have been recently shown to catalyze reactions with excellent enantioselectivities. Recently, we reported an alternative use of BINOL-iodomethylzinc phosphates as a new powerful family for zinc carbenoid-mediated cyclopropanation of alkenes[5] (Figure 1).

In order to develop better chiral discriminating reagents and to increase the scope of the cyclopropanation reaction, we engaged in a research program aimed at the development of a new family of chiral phosphates derived from TADDOL.[6] This privileged class of ligands[7] has shown their efficiency in numerous enantioselective reactions such as the titanium-TADDOLate-catalyzed cyclopropanation reaction developed in our group.[8] In this paper, we report the synthesis of new TADDOL-phosphate derivatives and their effectiveness in inducing enantioselectivities in the Simmons–Smith reaction.

Synthesis of TADDOL derivatives and their corresponding chiral phosphates: Most of the TADDOLs used in the present study are known and were synthe-

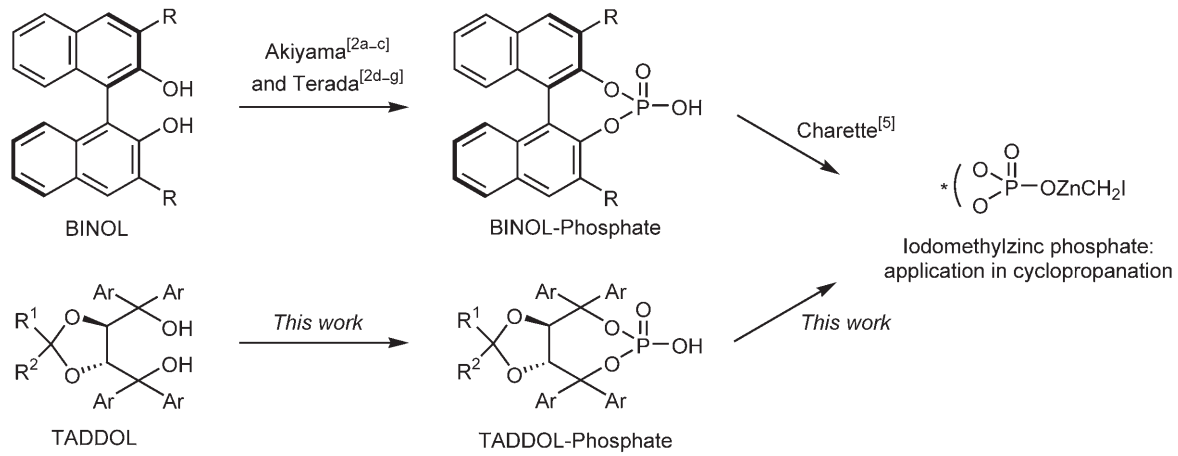
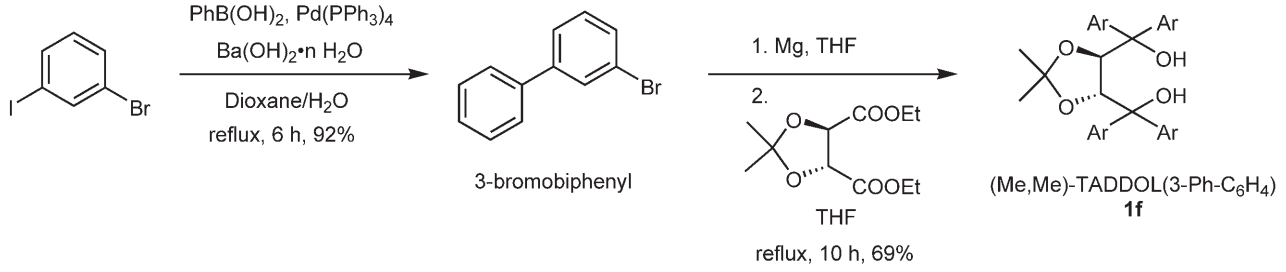


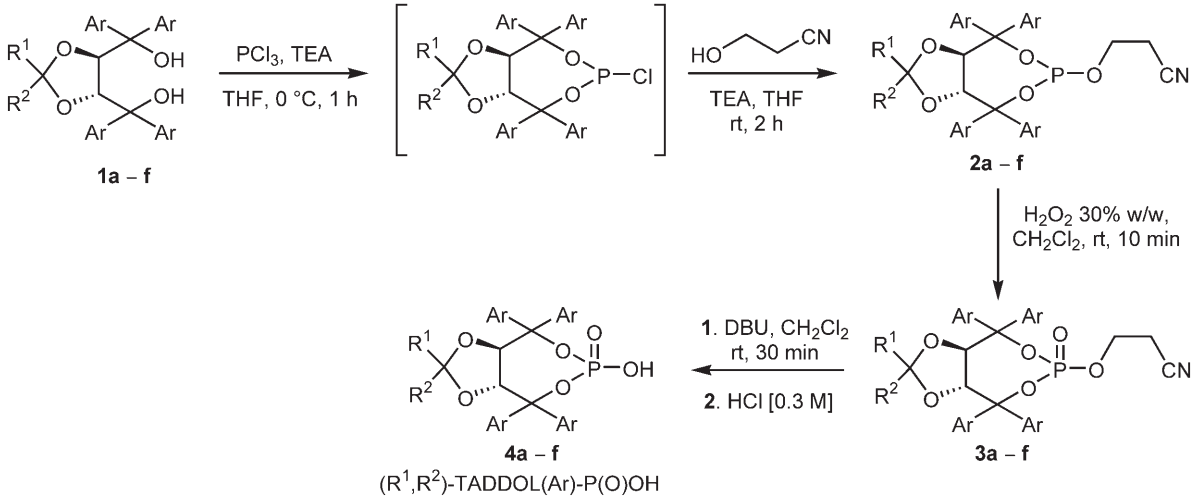
Figure 1.

sized according to literature procedures,[9] except for structure **1f**. The latter was prepared by Grignard addition of the biphenyl (prepared by Suzuki coupling in 92% yield) on the (+)-diethyl tartrate (Scheme 1).

The standard method found in the literature for the synthesis of the BINOL-phosphates, i.e., $POCl_3$, Et_3N and then H_2O failed to produce any of the desired phosphoric acids **4**. In fact, we were able to introduce the phosphorus atom on the diol, but the corresponding phosphochloridate resisted hydrolysis. Inspired by works in the field of oligonucleotide synthesis,[10] we decided to use a protecting group on phosphorus. Accordingly, the new phosphates **4a–f** were synthesized in three steps from the corresponding TADDOL (Scheme 2). To introduce the phosphorus atom, the TADDOL ligand was treated with phosphorus trichloride in the presence of triethylamine, followed by the addition of 3-hydroxypropionitrile to obtain the crude compounds **2a–f**. At this step, purification by flash chromatography could be carried out, (69% isolated yield of **2c**, see Table 1), but no satisfactory results in terms of isolated yields were obtained due to the relative instability of the phosphite. Instead, the phosphorus could be oxidized with a 30% hydrogen peroxide in water, and the more stable ligands **3a** and **3d–f** could be easily purified by flash chromatography. To produce the desired acids **4a–f**, the deprotection of the phosphorus was performed with 1,8-diazabicyclo-



Scheme 1. Synthesis of the new chiral TADDOL **1f**.



Scheme 2. Synthesis of TADDOL-phosphate derivatives.

Table 1. Yields for the synthesis of TADDOL-phosphate derivatives.

(*R*,*R*)-TADDOL	(R^1, R^2)	Ar	**2a–f** Yield [%]	**3a–f** Yield [%]	**4a–f** Yield [%]
1a	(Me, Me)	Ph	-	75	99
1b	(Ph, Me)	Ph	-	-	75
1c	(Me, Me)	(3,5-Me)-C_6H_3	69	-	83
1d	(Me, Me)	2-Naphthyl	-	88	95
1e	(Me, Me)	4-Ph-C_6H_4	-	49	99
1f	(Me, Me)	3-Ph-C_6H_4	-	59	91

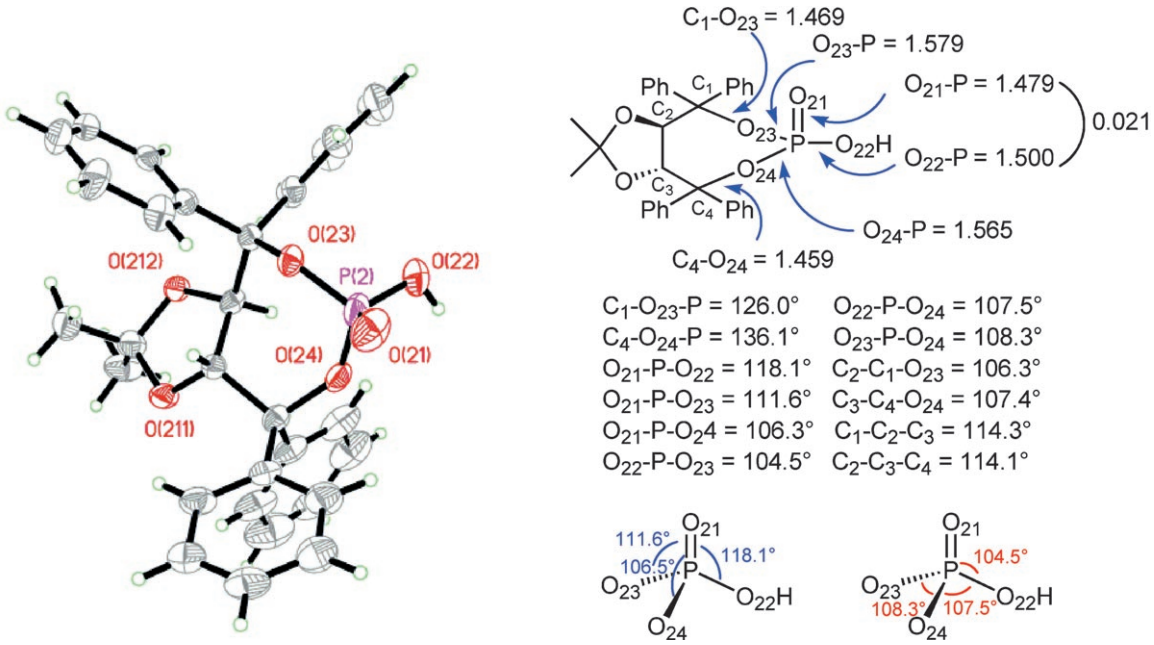
[5.4.0]undec-7-ene (DBU) and this was followed by an acidic work-up. The ligands were obtained with overall yields of 48–84% for the three steps (see Experimental Section for details). Because of the mixture of two diastereoisomers for **2b** and **3b** (arising from the non-symmetrical acetal), their purification was more difficult. Consequently, the synthesis of ligand **4b** was performed without chromatography, and the light yellow solid was recrystallized (CH_2Cl_2/hexane) to provide >95% pure ligand. This practical synthesis of new chiral Brønsted acids has been extented to a multi-gram scale.

Study of the X-ray structure of 4a: An X-ray structure of the ligand **4a** was obtained (Scheme 3). All bond lengths and angles given in Scheme 3 are the average of the data of the two molecules of TADDOL-phosphate in the asymmetric unit.

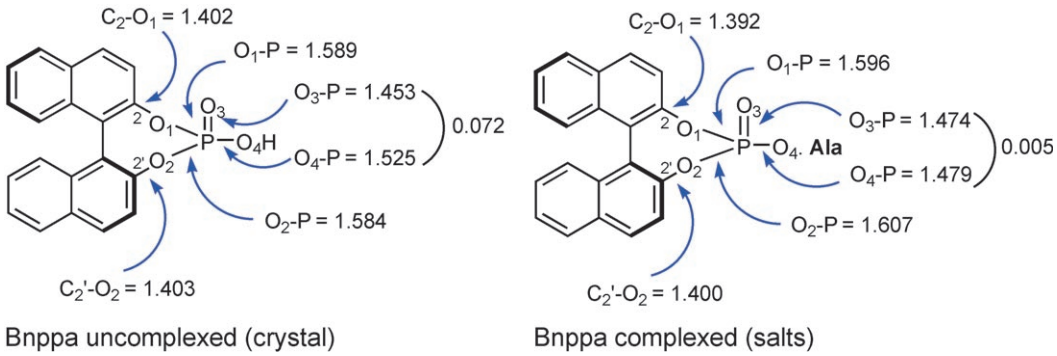
When this crystal was compared to the BINOL-phosphate X-ray structure obtained by Hirayama et al.[11] (Scheme 4), the P–O bond lengths were found to be similar to the TADDOL-phosphate. The difference between the O_3–P and O_4–P distances in the Bnppa (1,1′-binaphthalene-2,2′-diyl hydrogen phosphate) uncomplexed crystal is significantly higher than the corresponding difference in the bnppa salt (a difference 0.072 Å in the acid and 0.005 Å in the salt). In our case, with a difference of 0.023 Å between the P–O_{21} and P–O_{22} bonds, ligand **4a** is a THF and H_2O-complexed phosphate.

Tests of the new chiral auxiliaries in the asymmetric Simmons–Smith cyclopropanation: The Simmons–Smith reaction is a powerful method for the synthesis of cyclopropanes from alkenes.[12] Our group[13] and others[14] have been involved in the past few years in preparing, characterizing and studying new cyclopropanating reagents.

In order to evaluate the potential of our new TADDOL-derived phosphate ligands for asymmetric



Scheme 3. X-ray structure of the ligand **4a**.



Scheme 4. X-ray structures obtained by Hirayama et al.[11]

cyclopropanation, we chose benzyl-protected cinnamyl alcohol as a substrate (Table 2).

We first analyzed the solvent effect on the cyclopropanation (Table 2, entries 1–4). In chlorobenzene or toluene, the reactions were not complete, and the enantioselectivities were modest, up to 54% *ee* (entries 1 and 2). The best result in terms of enantioselectivity was in dichloroethane (DCE) (entry 4, 67% *ee*). Dichloromethane also gave good results, but the enantioselectivity was slightly lower (entry 3, 65% *ee*). With DCE as solvent (entries 4–8), the conversions were always complete and the isolated yields superior to 81%. The order of addition of diethylzinc and the ligand had no effects (entries 4 and 5). For practical purposes, all cyclopropanation reactions were tested as follows: to the ligand and solvent in a flame-dried flask was added sequentially diethylzinc, diiodomethane and finally the substrate. When the reaction was run at 0°C, 69% *ee* was observed (entry 6). At −15°C, the enantiomeric ratio was not improved (entry 7). Increasing the quantity of ligand with respect to the Et_2Zn and CH_2I_2 did not significantly change the enantioselectivity (entry 8). It is noteworthy that the chiral ligand could be readily recovered after the reaction.

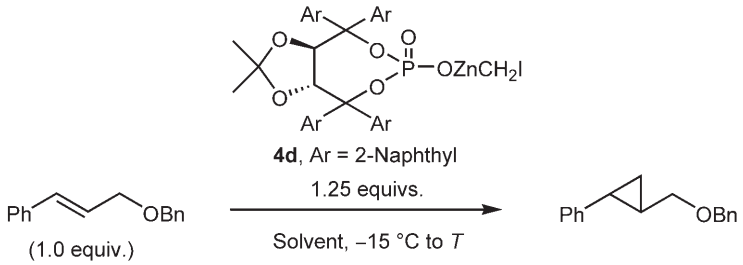
With these optimized conditions (DCE, 0°C) in hand, we turned our attention to the influence of the ligand structure on the activity and the selectivity (Table 3).

In each case, complete conversion in the cyclopropanation reaction was observed, and isolated yields of 75–96% were obtained. The substitution on the acetal moiety of the TADDOL backbone has no interesting influence (entries 1 and 2).[15] The 3,5-dimethylbenzene substituent gave the lowest enantioselectivity (entry 3) while the TADDOL-phosphate with the 2-naphthyl groups (entry 4) was the best ligand in this reaction (69% *ee*). We believed that **4d** was the best ligand tested because of the propensity of the naphthyl groups to project chirality towards the zinc carbenoid, therefore providing the highest enantiodiscrimination. The use of the biphenyl groups did not increase the selectivity (entries 5 and 6).

Finally, the scope of the reaction was explored using ligand **4d** in the cyclopropanation of functionalized (substrates **A**–**E**) and unfunctionalized (substrate **F**) alkenes (Table 4).

The benzyl-protecting group was not necessary for high enantioselectivities in the cyclopropanation reaction with the ligand **4d**. In fact, with a methyl-protected cinnamyl alcohol, a 73% *ee* was obtained (entry 2). A similar enantiomeric excess (69% *ee*, entry 3) was found with an electron-donating group on the aromatic ring (substrate **C**). The best result was obtained with substrate **D** (75% *ee*, entry 4). Even for the cyclopropanation of a non-styrenic substrate (substrate **E**), often recognized as difficult, a 69% *ee* was achieved with ligand **4d** (entry 5). However, it remains a great challenge to cyclopropanate unfunctionalized alkenes, i.e., alkenes which do not contain a directing functional group.[13a,16] To the best of our knowledge, there are no universal ligands for

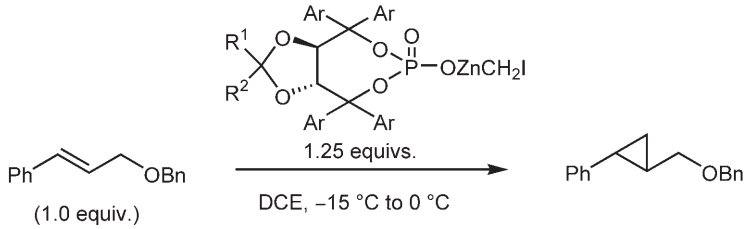
Table 2. Optimization of the benzyl-protected cinnamyl alcohol cyclopropanation with **4d**.

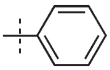
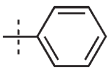
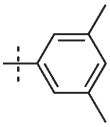
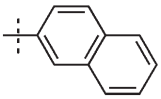
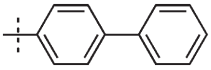
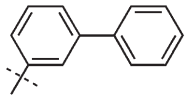


Entry	Solvent	*T* [°C]	Time [h]	Yield [%][a]	*ee* [%][c]
1	PhCl	rt	48	36[b]	46
2	Toluene	rt	49	59[b]	54
3	CH_2Cl_2	rt	48	90	65
4	DCE	rt	49	82	67
5[d]	DCE	rt	49	92	66
6	DCE	0	72	96	69
7	DCE	−15	68	91	68
8[e]	DCE	−15	68	81	70

[a] Isolated yield after flash chromatography.
[b] Determined by ^1H NMR using an internal standard.
[c] Determined by SFC on chiral stationary phase.
[d] Addition of the ligand to $ZnEt_2$.
[e] 1.40 equivs. of ligand/1.25 equivs. of Et_2Zn and CH_2I_2.

Table 3. Ligand screening in the cyclopropanation reaction.



Entry	Ligand	(R^1, R^2)	Ar	Yield [%][a]	*ee* [%][b]
1	**4a**	(Me, Me)		85	42
2	**4b**	(Ph, Me)		77	39
3	**4c**	(Me, Me)		75	24
4	**4d**	(Me, Me)		96	69
5	**4e**	(Me, Me)		89	56
6	**4f**	(Me, Me)		86	65

[a] Isolated yield after flash chromatography.
[b] Determined by SFC on chiral stationary phase.

the Simmons–Smith reaction, in other words ligands that can cyclopropanate functionalized and unfunctionalized substrates. With the previously synthesized chiral ligands and auxiliaries,[5,14] an allylic hydroxy group was essential as a directing group to provide good conversion and stereocontrol for the cyclopropanation. There is only one efficient ligand for the cyclopropanation of unfunctionalized substrates;[16c] however, the scope was limited to the styrenes and silyl enol ethers.[17] In our case, with the ligand **4a**, even though the conversion was modest (15%) with 1.25 equivalents of the chiral carbenoid, an enantiomeric excess of 40% was achieved (entry 6). The conversion was increased to 38% with the use of 2 equivalents of carbenoid, without any change in enantioselectivity (entry 7). For this substrate, the ligand **4d** did not provide better results (entry 8).

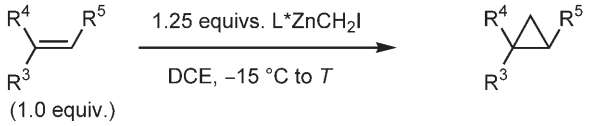
In summary, we have reported a practical synthesis of six new chiral TADDOL-phosphates, which were fully characterized, including an X-ray structure of **4a**. These ligands were used in the Simmons–Smith cyclopropanation reaction and gave excellent yields and good selectivities. For the first time, a single class of ligands has shown enantioselectivities for the cyclopropanation of both functionalized and unfunctionalized alkenes. Further improvement in the design of new chiral phosphate ligands and their application to other asymmetric reactions are currently ongoing in our laboratory.

Experimental Section

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-610459. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336–033; E-mail: deposit@ccdc.cam.ac.uk].

Below is a representative synthesis of ligand **4a**. Syntheses of all other ligands mentioned in this manuscript are available in the Supporting Information.

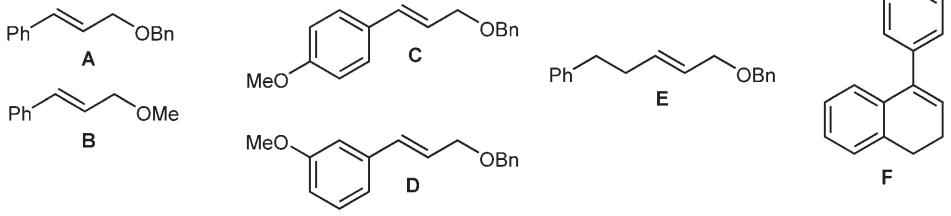
Table 4. Scope of the reaction.



Entry	Ligand	Substrate	T [°C]	Yield [%][a]	*ee* [%][b]
1	**4d**	A	0	96	69
2	**4d**	B	0	69	73[c]
3	**4d**	C	0	87	69
4	**4d**	D	0	97	75
5	**4d**	E	rt	88	69
6	**4a**	F	rt	15[d]	40
7[e]	**4a**	F	rt	38[d]	40
8	**4d**	F	rt	6[d]	31

[a] Isolated yield after flash chromatography.
[b] Determined by SFC on chiral stationary phase.
[c] Determined by HPLC on chiral stationary phase.
[d] Determined by GC analysis.
[e] 2.00 equivs. of L*$ZnCH_2I$.

Substrates:



3-{[(3a*R*,8a*R*)-2,2-Dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepin-6-yl]oxy}propanenitrile (3a)

To a stirred solution of (*R*,*R*)-(Me,Me)-TADDOL-(Ph) **1a** (6.02 g, 12.9 mmol) and triethylamine (6.09 mL, 43.9 mmol, 3.4 equivs.) in dry THF (50 mL) at 0 °C was added dropwise PCl_3 (1.18 mL, 13.6 mmol, 1.05 equivs.). The resulting mixture was stirred at 0 °C for 1 h. A solution of 3-hydroxypropionitrile (969 μL, 14.2 mmol, 1.1 equivs.) in dry THF (50 mL) was then added dropwise *via* cannula. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was diluted with THF and the triethylammonium chloride salts were filtered through a celite pad. The solvent was removed under vacuum. The obtained light yellow solid **2a** was directly used without purification in the oxidation step. To the crude phosphite in CH_2Cl_2 (80 mL) was added 30% aqueous H_2O_2 (8.77 mL, 77.4 mmol, 6.0 equivs.). The biphasic mixture was stirred vigorously for 20 min and then quenched by the addition of 100 mL of saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 and the combined organic extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (hexane/Et_2O: 80/20 to pure Et_2O) afforded **3a** as a white solid; yield: 5.62 g (75% for two steps); $R_f = 0.41$ (Et_2O pure); mp 114–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.61$–7.55 (m, 4H, *H*-Ph), 7.46–7.22 (m, 16H, *H*-Ph), 5.43 (d, $J = 8.1$ Hz, 1H, -C*H*-CPh_2-), 5.15 (d, $J = 8.1$ Hz, 1H, -C*H*-CPh_2-), 3.92–3.85 (m, 1H, -OCH_2C*H*HCN), 3.43–3.35 (m, 1H, -OC*H*HCH_2CN), 2.22–2.14 (m, 1H, -OCH_2C*H*HCN), 2.01–1.91 (m, 1H, -OC*H*HCH_2CN), 0.83 (s, 3H, CH_3), 0.50 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 143.8$, 143.7, 143.2, 143.2, 139.5 (d, $J_{P,C} = 6.7$ Hz), 139.0 (d, $J_{P,C} = 10.0$ Hz), 129.0, 128.6, 128.4, 128.3, 128.0, 128.0, 127.7, 127.3, 126.9, 116.2, 113.9, 88.8 (d, $J_{P,C} = 7.5$ Hz), 88.4 (d, $J_{P,C} = 8.3$ Hz), 80.0, 78.2, 62.0 (d, $J_{P,C} = 4.9$ Hz), 26.9, 26.2, 19.0 (d, $J_{P,C} = 8.5$ Hz); ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = -11.95$; IR: $\nu_{max} =$ 3060, 2989, 2935, 2254 (CN), 1601, 1495, 1447, 1383, 1287, 1215, 1165, 1006, 941, 741, 696 cm^{-1}; HR-MS (ESI): $m/z =$ 604.1843, calcd. for $C_{34}H_{32}NO_6NaP$ $[M+Na]^+$: 604.1859; $[\alpha]_D^{20}$: −196.5 (*c* 1.79, $CHCl_3$).

(3a*R*,8a*R*)-2,2-Dimethyl-4,4,8,8-tetraphenyltetrahydro[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepin-6-ol 6-oxide (4a)

To a stirred solution of **3a** (5.06 g, 8.70 mmol) in dry CH_2Cl_2 (100 mL) was added, dropwise at room temperature, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.39 mL, 9.13 mmol,

1.05 equivs.). The solution was stirred 30 min at room temperature and when the reaction was complete by TLC, AcOH (0.5 mL) was added, followed by H_2O (50 mL). The organic layer was then washed two times with a 0.3 M HCl solution, saturated aqueous NaCl solution, and dried ($MgSO_4$), filtered and concentrated. The resulting white solid **4a** was dried under vacuum, and can be used directly in asymmetric cyclopropanation; yield: 4.56 g (99%); mp 154–156 °C;. This compound was kept several months at −20 °C without degradations. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65–7.60 (m, 4H, *H*-Ph), 7.50–7.40 (m, 4H, *H*-Ph), 7.37–7.22 (m, 12H, *H*-Ph), 5.32 (s, 2H, -C*H*-CPh_2-), 0.74 (s, 6H, 2 × C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.5, 139.6 (d, $J_{P,C}$ = 8.7 Hz), 128.8, 128.2, 128.2, 127.7, 127.3, 127.0, 113.7, 87.9 (d, $J_{P,C}$ = 5.2 Hz), 79.6, 26.7; ^{31}P NMR (162 MHz, $CDCl_3$): δ = −8.13; IR: ν_{max} = 3060, 2989, 2935, 1600, 1495, 1448, 1383, 1287, 1215, 1165, 1009, 997, 733, 695 cm^{-1}; HR-MS (ESI): *m/z* = 551.1589, calcd. for $C_{31}H_{29}O_6NaP$ [M + Na]$^+$: 551.1593; $[\alpha]_D^{20}$: −210.8 (*c* 2.64, $CHCl_3$).

General Procedure for the Cyclopropanation using Chiral Phosphate Ligands Derived from TADDOL 4a–f

To a solution of the ligand (0.31 mmol, 1.25 equivs.) in DCE (1.5 mL) at −15 °C was added $ZnEt_2$ (32 μL, 0.31 mmol, 1.25 equivs.) dropwise. This solution was stirred for 15 min after which CH_2I_2 (25 μL, 0.31 mmol, 1.25 equivs.) was added dropwise. This solution was stirred for an additional 20 min. A solution of substrate (0.25 mmol, 1.0 equiv.) in DCE (1.0 mL) was added and the resulting solution was stirred for 48 h. The reaction was quenched with saturated NH_4Cl solution, washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered and concentrated. It is noteworthy that the chiral ligand could be readily recovered after the reaction by simple precipitation with CH_2Cl_2/hexane and filtration. The crude product was purified by flash chromatography to afford the pure desired cyclopropane derivative. All the cyclopropanes synthesized have spectral and physical data identical to the data reported in the literature.

Acknowledgements

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