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The Lithiation Reactivity and Selectivity of Differentially Branched Alkyldiphenylphosphine Oxides – A Simple and Versatile Approach to *ortho*-Functionalized Arylphosphine Oxides

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Abstract: Alkyldiphenylphosphine oxides typically undergo α-deprotonation with alkyllithium reagents. Here, the lithiation of differentially branched alkyldiphenylphosphine oxides was investigated and a diverse, but predictable reactivity was found. γ-Branched derivatives undergo selective directed *ortho*-metalation (DoM) using butyllithium and TMEDA as an additive. With decreasing degree of γ-branching α-lithiation becomes predominant. The *ortho*-phosphinoyllithium intermediates are subject to functionalization and C–C bond forming reactions, thus providing a convenient approach to new phosphine oxides and phosphine-borane complexes, which have a good potential for an approach to new ligands for catalysis.

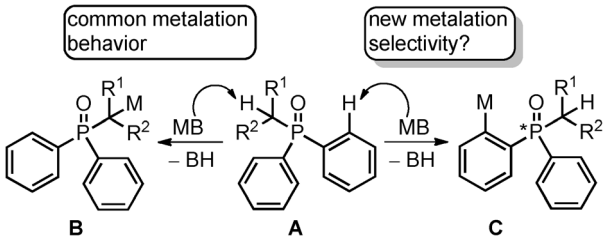
Keywords: lithiation; nucleophilic substitution; organolithium reagents; phosphine oxides; phosphine-borane complexes

Introduction

Phosphines and phosphine oxides are important compound classes in many areas of organic chemistry, catalysis, and material sciences.[1] Phosphines are undisputedly the most important class of ligands in modern metal catalysis research[2] but they are becoming more and more important as Lewis basic nucleophilic organocatalysts.[3] Whereas achiral phosphines have been previously predominately applied, P-chiral derivatives have become the focus of research more recently. Phosphine oxides are equally important. They serve on one hand as stable precursors for the often oxidation-labile phosphines, on the other hand they are also applied as reagents in Wittig–Horner reactions,[4] as ligands[5] and Lewis bases.[6]

Nucleophilic substitution reactions using phosphorus nucleophiles or electrophiles,[7] transition metal-catalyzed phosphinoylation of aryl halides,[7,8] radical[9] or transition metal-catalyzed[10] additions to alkenes, Michael-type additions to vinylphosphine oxides[11] and the α-functionalization of alkylphosphine (oxides) by deprotonation and subsequent reaction with electrophiles[4,12] are the most important methods for the preparation of (chiral) phosphine (oxide)s. Directed *ortho*-metalation (DoM)[13] of arylphosphine oxides can in principle also be used to introduce functionality, but has been employed only for substrates bearing no acidic hydrogen atoms in aliphatic substituents.[14]

It is common wisdom that deprotonation of alkyl-aryl-substituted carbonyl compounds, sulfones, sulfoxides and also phosphine oxides **A** takes place at the thermodynamically most acidic α-position leading to α-lithiated intermediates **B** (Scheme 1). Recent work in our group demonstrated that α,γ-branched alkyl phenyl sulfones undergo selective DoM even in the presence of a significantly more acidic α-proton. The resulting aryllithiums rearrange subsequently on warming to the α-carbanion.[15] We hypothesized that branched alkyldiarylphosphine oxides **A** may behave similarly and that this represents an attractive and simple approach to aryl-functionalized phosphine oxides *via ortho*-phosphinoylphenyllithium intermedi-



Scheme 1. Metalation regioselectivity of phosphine oxides.

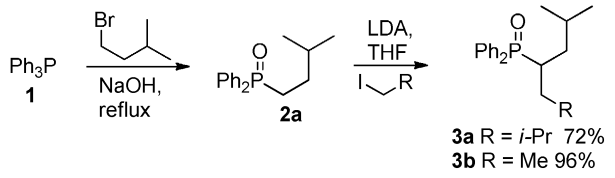
ates **C**, which may subsequently serve as ligands or Lewis bases.

We report here that γ-branched alkyldiphenylphosphine oxides display a unique and distinct metalation behavior toward organolithium compounds. We show that DoM indeed takes place, but compared to sulfones, phosphine oxides show a more diverse reactivity, which is strongly dependent on the reaction conditions and the presence of additives. Optimized conditions allow for the efficient preparation of diverse new aryl-functionalized alkyl(diaryl)phosphine oxides in good yields with high *ortho*/α-selectivities.

Results and Discussion

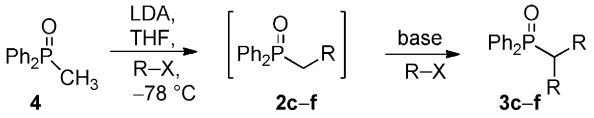
Branched alkyldiphenylphosphine oxides **3** were prepared using two methodologies. α,γ,γ-Branched alkyldiphenylphosphine oxides **3a** and **3b** were synthesized in two steps (Scheme 2). An oxidative substitution of triphenylphosphine with isoamyl bromide in the presence of NaOH, gave isopentyldiphenylphosphine oxide **2a**,[16] which was deprotonated by LDA and the resulting α-phosphinoylalkyllithium was alkylated by isobutyl or ethyl iodide to give differentially branched phosphine oxides **3a** and **3b** in 72% and 96% yield, respectively.

The branched phosphine oxides **3c–e** were prepared by a one-pot dialkylation of commercially available methyldiphenylphosphine oxide **4** (Table 1, entries 1–3). Initial deprotonation by LDA and alkylation gave the intermediates **2c–e**, which were again deprotonated by regenerating LDA by addition of BuLi followed by addition of another batch of alkyl halide or TMSCl providing phosphine oxides **3c–e** in good yields. When 2.6 equiv. of LDA and electrophile were



Scheme 2. Synthesis of branched phosphine oxides with isopropyl group(s).

Table 1. Dialkylation of methyl diphenylphosphine oxide.[a]

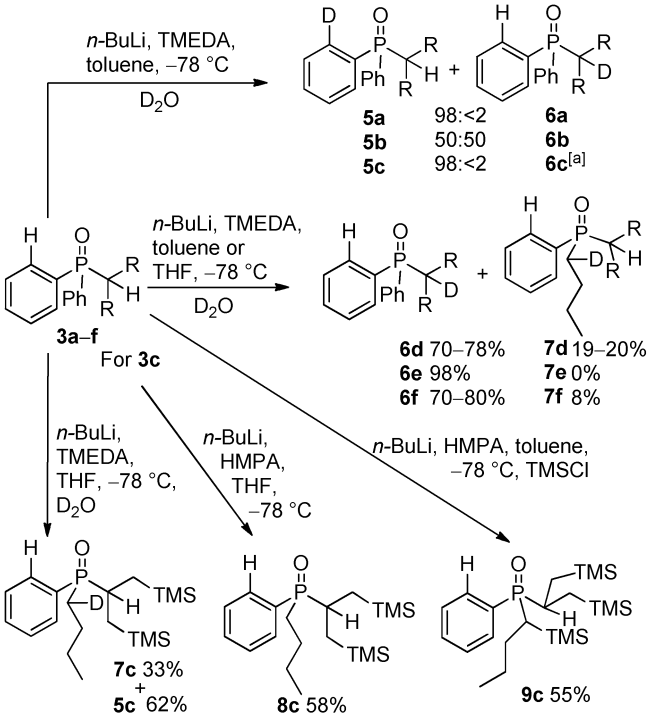


Entry	Base	R–X	**2** [%]	**3** [%]
1	*n*-BuLi	$TMSCH_2Cl$	**c** 5	**c** 82
2	*n*-BuLi	BnBr	**d** –	**d** 87
3	*n*-BuLi	TMSCl	**e** 7	**e** 75
4	–[b]	EtI	**f** –	**f** 95

[a] *Reaction conditions:* **4** (1.0 mmol), LDA (1.3 mmol), electrophile (1.3 mmol) in THF at –78 °C, addition of *n*-BuLi (1.2 mmol) and electrophile (1.3 mmol).
[b] LDA (2.6 mmol) and EtI (2.6 mmol).

used at once the reaction stopped after some time and a mixture of phosphine oxides **2** and **3** was isolated in reduced yield. However, **3f** could be obtained in good yield by a double alkylation using 2.6 equiv. of LDA and ethyl iodide (Table 1, entry 4).

The metalation selectivity of alkyldiphenylphosphine oxides **3a–f** was initially investigated by using butyllithium and different additives and solvents followed by deuteration or silylation (Scheme 3). Phosphine oxides **3a** and **3c** underwent selective DoM



[a] Small amounts of **7c** or **8c** detected.

Scheme 3. The divergent reactivity of branched phosphine oxides toward butyllithium in the presence of different additives and solvents.

with BuLi in the presence of TMEDA in toluene as the solvent despite the presence of the α-proton as determined by the isolation of **5a** and **5c** after deuteration of the reaction mixture with D_2O at low temperature. LDA was in contrast unreactive as a base (see the Supporting Information). Unsymmetrical **3b** having only one γ-branch gave a mixture of **5b** and **6b** in a 1:1 ratio.

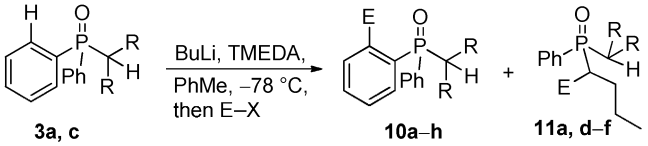
Phosphine oxides **3d–f** bearing benzylic groups **(3d)**, branching in the closer β-position **(3e)** or no additional branching **(3f)** undergo predominately α-deprotonation and provided α-deuterated phosphine oxides **6d–f** both in toluene or THF. However, a substitution reaction at phosphorus surprisingly competed with α-deprotonation providing butylphosphine oxides **7d** and **7f** to a non-negligible extent, whereas the α,α-disilylated derivative **3e** furnished exclusively the α-deuterated compound **6e**.

The DoM selectivtiy was lost on switching the solvent in the metalation reaction of **3c** to THF. The *ortho*-deuterated compound **5c** was isolated only in 62% yield and the α-monodeuterated butylphosphine oxide **7c** resulting from replacement of a phenyl group in **3c** was formed in 33% yield. Remarkably, no deuteration at the aryl units was observed in **7c**, but deprotonation at the newly introduced butyl group becomes the most facile process. When 2.2 equivalents of BuLi in THF and 6 equivalents of HMPA was used instead of TMEDA the substitution reaction at phosphorus becomes the exclusive pathway furnishing phosphine oxide **8c** in 58% yield together with 42% recovered **3c**.[17] To learn more about the relative facility of these competing reaction channels chlorotrimethylsilane was added to a similar reaction performed in toluene with HMPA as an additive, which led to exclusive isolation of the α-silylated phosphine oxide **9c** in 55% yield. These results and the not observed otherwise facile formation of the *ortho*-silylated products **10a**, **g** (*vide infra*, Table 2, entries 1 and 7) show that nucleophilic substitution at phosphorus is faster than both DoM or α-deprotonation in the presence of HMPA and that the subsequent deprotonation at the newly generated acidic butyl group predominates in the sequence under these conditions.

The generated *ortho*-phosphinoylphenyllithium intermediates are highly stable toward *ortho*→α transmetalation. This represents a significant difference compared to the previously studied sulfones.[15] Whereas *ortho*-sulfonylphenyllithiums transmetalate between −40 and −20 °C to the corresponding α-carbanions, their phosphinoyl analogs are stable up to room temperature and show no tendency at all to transmetalation.

The synthetic applicability of the aryllithium intermediates generated by DoM of **3a** and **3c** was investigated in detail. Metalation by *n*-BuLi/TMEDA in toluene at −78 °C for 30 min and subsequent treatment

Table 2. DoM/electrophilic substitution of γ,γ′-dibranched phosphine oxides **3a** and **3c**.[a]



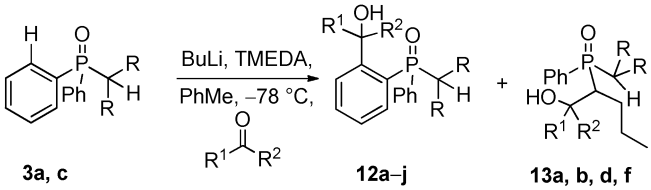
3a, c **10a–h** **11a, d–f**

Entry	E–X	R	**10** [%]	**11** [%]	**3a**, **c** [%][b]
1	TMS–Cl	$TMSCH_2$	**a** 74	5	–
2	PhS–SPh	$TMSCH_2$	**b** 67	–	16
3	Cl–*p*-Ts	$TMSCH_2$	**c** 73	–	15
4	Br–C_2H_4Br	$TMSCH_2$	**d** 76	3	8
5	I–C_2H_4I	$TMSCH_2$	**e** 85	5	–
6	Bu_3Sn–Cl	$TMSCH_2$	**f** 82	6	4
7	TMS–Cl	$(CH_3)_2CHCH_2$	**g** 66	–	31
8	I–C_2H_4I	$(CH_3)_2CHCH_2$	**h** 77	–	21

[a] *Reaction conditions:* **3a** or **3c** (0.5 mmol), *n*-BuLi (0.65 mmol), TMEDA (0.65 mmol), electrophile (for amounts, see the Supporting Information) in toluene (3.0 mL) at −78 °C.
[b] Recovered **3a**, **c**.

with several typical electrophiles provided compounds **10a–h** in good yields (Table 2, entries 1–8). Small amounts of substitution products **11** were detected as side products (entries 1 and 4–6). This reflects the selectivity observed in the DoM-deuteration experiment

Table 3. C–C bond formation reactions of *ortho*-phosphinoylphenyllithiums with aldehydes and ketones.[a]



3a, c **12a–j** **13a, b, d, f**

Entry	**3**	R^1	R^2	**12** [%] (*dr*)[b]	**13** [%]	**3a**, **c** [%][c]
1	**c**	Ph	H	**a** 63 (3:1)	11	–
2	**c**	4-BrC_6H_4	H	**b** 72 (1:1)	11	4
3	**c**	*n*-C_5H_{11}	H	**c** 71 (1:1)	–	25
4	**c**	CH_3CH=CH	H	**d** 81 (2.4:1)	5	11
5	**c**	PhCH=CH	H	**e** 90 (1:1)	–	–
6	**c**	Ph	Ph	**f** 74 (–)	6	7
7	**c**	Fc	Ph	**g** 71 (1.9:1)	–	14
8	**c**	-$(CH_2)_5$-		**h** 65 (–)	–	32
9	**a**	Ph	H	**i** 84 (1.3:1)	–	9
10	**a**	CH_3CH=CH	H	**j** 77 (3.3:1)	–	17

[a] *Reaction conditions:* **3a** or **3c** (0.5 mmol), *n*-BuLi (0.65 mmol), TMEDA (0.65 mmol), aldehyde or ketone (for amounts, see the Supporting Information) in toluene (3.0 mL) at −78 °C.
[b] Determined by ^1H NMR.
[c] Recovered **3a**, **c**.

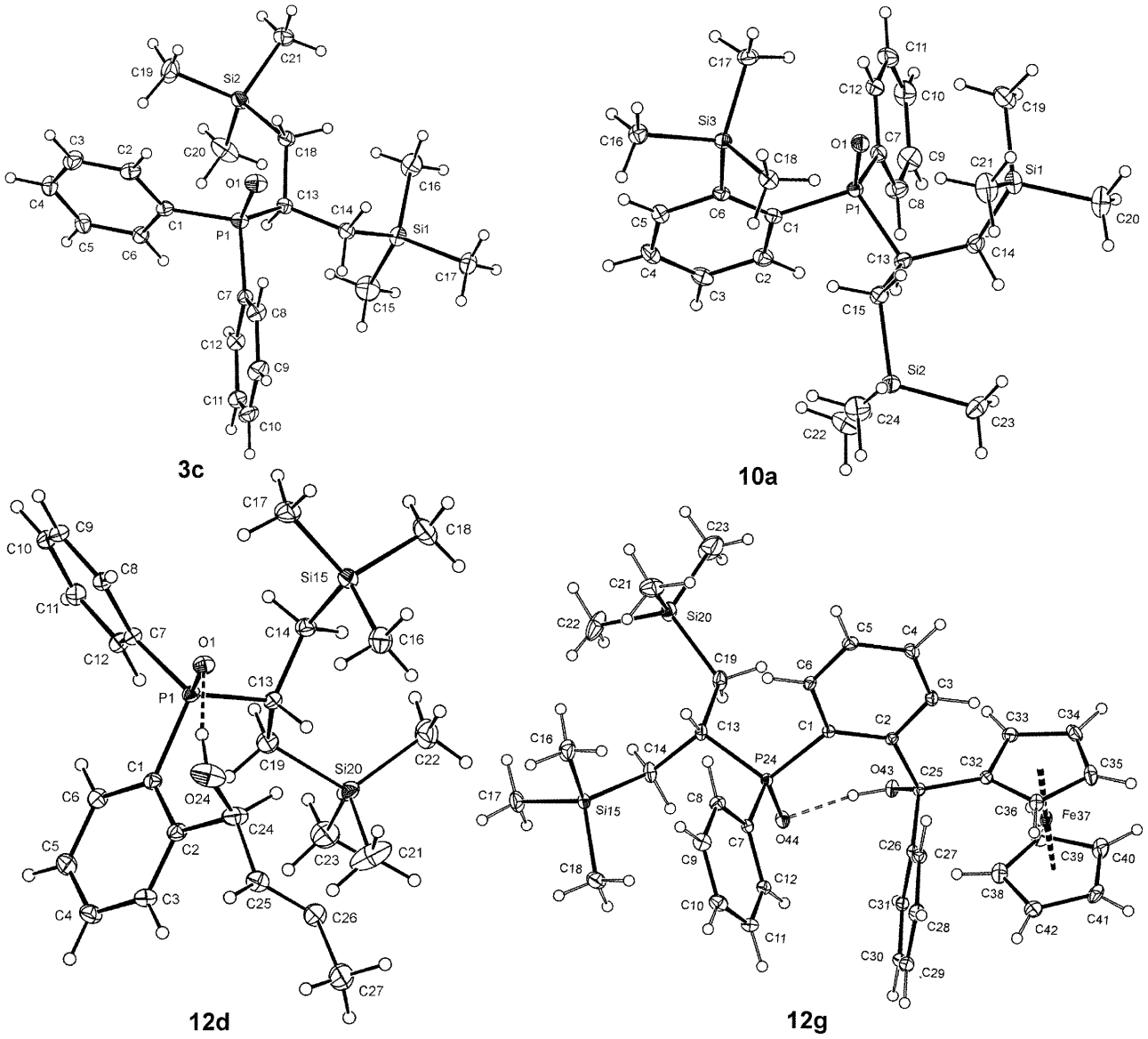


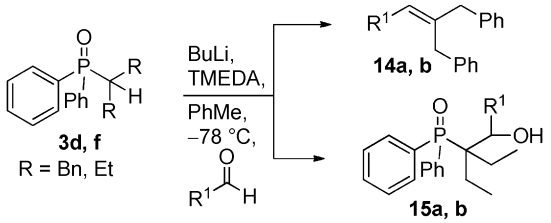
Figure 1. X-Ray crystal structures of compounds **3c**, **10a**, and the major diastereomers of **12d** and **12g**. The displacement ellipsoids are drawn at 30 % probability level.

of **3c** (*vide supra*). Moreover, some starting material was recovered (entries 2–4 and 6–8). The methodology is especially suited to provide precursors, which can be in the future applied as electrophiles or nucleophiles in subsequent cross-coupling reactions (entries 4, 5, 8 and 1, 6, 7, respectively), thus allowing further diversification.[18]

Phosphine oxides **3a**, **c** easily engaged in C–C bond formation reactions by nucleophilic addition to carbonyl compounds after DoM (Table 3). Aromatic, aliphatic, and α,β-unsaturated aldehydes reacted in good yields giving functionalized phosphine oxides **12a–e**, **i**, **j** (entries 1–5, 9 and 10). Even ketones were applicable as substrates (entries 6–8). Sometimes small amounts of substitution/addition products **13** were detected (entries 1, 2, 4, 6). The diastereoselectivity of the addition in these examples remained however low.

The structure of compounds **3c**, **10a**, and the relative configuration of the major diastereomers of addition products **12d** and **12g** were proven by X-ray crystallography (Figure 1).[19] In structure **3c** (and also in **10a**, **12d** and **12g**) an *ortho*-hydrogen atom is in plane with the oxygen atom, thus probably facilitating DoM over deprotonation of the antiperiplanar α-proton, provided the solution conformation of the sterically crowded compounds is similar. The structures of **12d** and **12g** are dominated by an intramolecular hydrogen bond between the hydroxy and phosphine oxide groups. Based on the unequivocal determination of the configuration of the major diastereomers of **12d** and **12g**, the configuration of the major diastereomers

Table 4. Divergent Wittig–Horner reactions of **3d** and **3f**.[a]



Entry	3	R^1	Product	Yield [%]
1	**d**	Ph	**14a**	50
2	**d**	$C_{11}H_{23}$	**14b**	44
3	**f**	Ph	**15a**	69
4	**f**	C_5H_{11}	**15b**	50

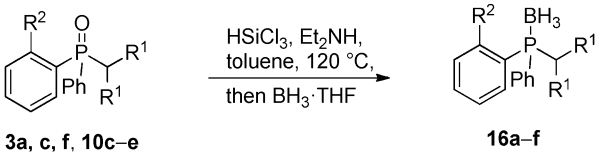
[a] *Reaction conditions:* **3d** or **3f** (1.0 mmol), *n*-BuLi (1.3 mmol), TMEDA (1.3 mmol), aldehyde (1.3 mmol) in toluene (6.0 mL) at −78 °C.

of all other compounds **12** can be assigned on the basis of their ^{1}H and ^{13}C NMR chemical shifts.

The Wittig–Horner reaction as the most important application for α-phosphinoylalkyllithiums[4] was briefly tested for substrates **3d** and **3f** amenable to α-deprotonation to demonstrate their applicability (Table 4). Benzylated phosphine oxide **3d** gave trisubstituted alkenes **14a**, **b** directly after deprotonation by *n*-BuLi/TMEDA and reaction with benzaldehyde or dodecanal between −78–0 °C (entries 1 and 2), whereas the ethylated phosphine oxide **3f** provided β-hydroxy phosphine oxides **15a**, **b** under identical conditions (entries 3 and 4).

As a prerequisite to obtain new potential phosphine ligands the reduction of the phosphine oxide unit to the phosphine-borane complexes was studied.[20] The trichlorosilane/diethylamine system proved to be most reliable to transform phosphine oxides **3a**, **c**, **f** and **10c–e** into the corresponding phosphines, which were not stable to air and were thus converted *in situ* to the corresponding phosphine-borane complexes **16a–f** (Table 5).[21]

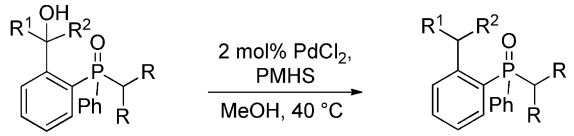
Table 5. Reduction of tertiary phosphine oxides.[a]



Entry	Substrate	R^1	R^2	**16** [%]
1	**3a**	$(CH_3)_2CHCH_2$	H	**a** 81
2	**3c**	$TMSCH_2$	H	**b** 62
3	**3f**	CH_3CH_2	H	**c** 62
4	**10c**	$TMSCH_2$	Cl	**d** 62
5	**10d**	$TMSCH_2$	Br	**e** 62
6	**10e**	$TMSCH_2$	I	**f** 64

[a] *Reaction conditions:* **3a**, **c**, **f**, **10c–e** (0.5 mmol), Et_2NH (2.10 mmol), $HSiCl_3$ (1.94 mmol) in toluene (3.0 mL) at 120 °C. After completion addition of BH_3·THF (1.0 mmol).

Table 6. Reduction of alcohols **12a**, **f**, **i**.[a]



Entry	Substrate	R	R^1	R^2	**17** [%]
1	**12a**	$TMSCH_2$	Ph	H	**a** 85
2	**12f**	$TMSCH_2$	Ph	Ph	**b** 86
3	**12i**	$(CH_3)_2CHCH_2$	Ph	H	**c** 83

[a] *Reaction conditions:* **12a**, **f**, **i** (0.115 mmol), $PdCl_2$ (0.0023 mmol), PMHS (0.345 mmol) in dry MeOH (2.0 mL) at 40 °C.

Since the nucleophilic addition to aldehydes gives diastereomeric mixtures and to check the stability and robustness of the obtained phosphine oxides towards functional group modification, the selective reductive removal of the hydroxy group in selected adducts **12a**, **f**, and **i** was performed (Table 6). Optimized conditions using 2 mol% $PdCl_2$ as a catalyst and poly(methylhydrosiloxane) (PMHS) as the reducing agent[22] gave *ortho*-benzylic phosphine oxides **17a–c** in good yields. No reduction of the phosphine oxide unit was observed under these conditions.

Conclusions

In summary, γ,γ′-branched phosphine oxides undergo selective DoM even in the presence of more acidic α-protons. The resulting aryllithiums are stable up to room temperature and can be functionalized by diverse electrophiles. From all these reactions, P-chiral but so far racemic phosphine oxides result. These compounds can be reduced to the corresponding phosphine-borane complexes, whereas hydroxylated phosphine oxides can be selectively deoxygenated at the benzylic position furnishing (*ortho*-benzylphenyl)-phosphine oxides. The metalation of phosphine oxides is strongly dependent on the conditions. In the presence of HMPA a selective substitution of a phenyl group by butyllithium took place, which leads to another class of P-chiral compounds. Current efforts are directed toward devising asymmetric approaches to phosphine oxides.[23] The potential of the resulting optically enriched compounds in asymmetric transformations, such as cross-coupling reactions, or as Lewis bases will be explored. Investigations along these lines are ongoing in these laboratories.

Experimental Section

Directed *ortho*-Metalation of γ,γ′-Dibranched Phosphine Oxides 3a, c and Functionalization; General Procedure

n-BuLi (0.41 mL, 0.65 mmol, 1.6 M in hexane) was added to a stirred solution of phosphine oxide **3a** (164 mg, 0.5 mmol) or **3c** (194 mg, 0.5 mmol) and TMEDA (0.098 mL, 0.65 mmol) in toluene (3.0 mL) at −78 °C. After 30 min at this temperature, the electrophile (for amounts see the Supporting Information at the individual compounds) was added at −78 °C. The reaction mixture was stirred at −78 °C for 3–4 h, quenched by addition of water and diluted with an organic solvent (Table 2, for entries 1, 3–6 EtOAc; for entries 2, 7–8 CH_2Cl_2). The layers were separated and the aqueous one was extracted with the respective solvent. The combined organic fractions were dried over Na_2SO_4 and evaporated to give the crude product, which was purified by flash column chromatography.

Directed *ortho*-Metalation of γ,γ′-Dibranched Phosphine Oxides 3a, c and their Reaction with Aldehydes and Ketones; General Procedure

n-BuLi (0.41 mL, 0.65 mmol, 1.6 M in hexane) was added to a stirred solution of phosphine oxide **3a** (164 mg, 0.5 mmol) or **3c** (194 mg, 0.5 mmol) and TMEDA (0.098 mL, 0.65 mmol) in toluene (3 mL) at −78 °C. After 30 min at this temperature, the aldehyde or ketone (for amounts see the Supporting Information at the individual compounds) was added at −78 °C. The reaction mixture was stirred at −78 °C and quenched by addition of water after 3–4 h. A solvent was added (Table 3, for entries 1, 3–5 EtOAc; for entries 2, 6–10 CH_2Cl_2), the layers were separated and the aqueous one was extracted with the same solvent. The combined organic fractions were dried over Na_2SO_4 and evaporated to give the crude product, which was purified by flash column chromatography.

Horner–Wittig Reaction of 3d, f; General Procedure

n-BuLi (0.81 mL, 1.3 mmol, 1.6 M in hexane) was added to a stirred solution of phosphine oxide **3d** (396 mg, 1.0 mmol) or **3f** (272 mg, 1.0 mmol) in toluene (6.0 mL) and TMEDA (0.196 mL, 1.3 mmol) at −78 °C. After 30 min at this temperature, the aldehyde was added at −78 °C and the reaction mixture was slowly warmed to 0 °C. The reaction was quenched by addition of water after 4 h and 24 h for **14a** and **14b**, and 3 h for **15a** and **15b**, respectively. The reaction mixture was diluted with EtOAc (Table 4, entries 1 and 2) or CH_2Cl_2 (Table 4, entries 3 and 4), the layers were separated and the aqueous one was extracted with the same solvent. The combined organic fractions were dried over Na_2SO_4 and evaporated to give the crude product, which was purified by flash column chromatography.

Phosphine·Borane Complexes 16; General Procedure

Diethylamine (0.216 mL, 2.10 mmol) was added to a solution of the corresponding phosphine oxide (0.5 mmol) in toluene (3.0 mL) and cooled at 0 °C before dropwise addition of trichlorosilane (0.195 mL, 1.94 mmol). After refluxing the reaction mixture for 5–8 h and monitoring by TLC, the borane·THF complex (0.250 mL, 1.0 mmol) was added. The reaction mixture was stirred for 45 min and quenched by addition of MeOH (5.0 mL). After concentration under reduced pressure the residue was purified by flash column chromatography.

Reduction of Alcohols 12; General Procedure

$PdCl_2$ (0.4 mg, 0.0023 mmol) and PMHS (0.021 mL, 0.345 mmol) were added to a solution of the corresponding hydroxy phosphine oxide **12** (0.115 mmol) in dry MeOH (2.0 mL). The mixture was stirred at 40 °C for 1 h. After completion the reaction mixture was diluted with EtOAc, filtered through a pad of celite, which was washed with EtOAc, and evaporated to give the crude product, which was purified by flash column chromatography.

Acknowledgements

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References

[1] Selected reviews: a) Y. Tao, C. Yang, J. Qin, *Chem. Soc. Rev.* **2011**, *40*, 2943–2970; b) J. Crassous, R. Réau, *Dalton Trans.* **2008**, 6865–6876; c) T. Baumgartner, R. Réau, *Chem. Rev.* **2006**, *106*, 4681–4727.

[2] *Phosphorus Ligands in Asymmetric Catalysis*, Vols. 1–3 (Ed.: A. Börner), Wiley-VCH, Weinheim, **2008**.

[3] Recent reviews: a) *Top. Curr. Chem.* **2013**, *334*; b) C. Gomez, J.-F. Betzer, A. Voituriez, A. Marinetti, *ChemCatChem* **2013**, *5*, 1055–1065; c) S. Xu, Z. He, *RSC Adv.* **2013**, *3*, 16885–16904; d) Y. Hu, X. P. Zhang, *Top. Curr. Chem.* **2012**, *327*, 147–162; e) Z. Zhou, Y. Wang, C. Tang, *Curr. Org. Chem.* **2011**, *15*, 4083–4107; f) S. E. Denmark, G. L. Beutner, *Angew. Chem.* **2008**, *120*, 1584–1663; *Angew. Chem. Int. Ed.* **2008**, *47*, 1560–1638.

[4] Selected reviews: a) Y. Gu, S. Tian, *Top. Curr. Chem.* **2012**, *327*, 197–238; b) J. Clayden, S. Warren, *Angew. Chem.* **1996**, *108*, 261–291; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 241–270.

[5] Recent reviews: a) T. M. Shaikh, C.-M. Weng, F.-E. Hong, *Coord. Chem. Rev.* **2012**, *256*, 771–803; b) V. V. Grushin, *Chem. Rev.* **2004**, *104*, 1629–1662.

[6] Reviews: a) M. Benaglia, S. Rossi, *Org. Biomol. Chem.* **2010**, *8*, 3824–3830; b) S. Kotani, M. Sugiura, M. Nakajima, *Chem. Rec.* **2013**, *13*, 362–370. For a very recent example, see: c) M. Ogasawara, S. Kotani, H. Nakajima, H. Furusho, M. Miyasaka, Y. Shimoda, W.-Y. Wu, M. Sugiura, T. Takahashi, M. Nakajima, *Angew. Chem.* **2013**, *125*, 14043–14047; *Angew. Chem. Int. Ed.* **2013**, *52*, 13798–13802.

[7] Recent review: M. M. Pereira, M. J. F. Calvete, R. M. B. Carrilho, A. R. Abreu, *Chem. Soc. Rev.* **2013**, *42*, 6990–7027.
[8] Recent review: F. M. J. Tappe, V. T. Trepohl, M. Oestreich, *Synthesis* **2010**, 3037–3062.
[9] Selected reviews: a) H. Yorimitsu, *Beilstein J. Org. Chem.* **2013**, *9*, 1269–1277; b) S.-I. Kawaguchi, A. Ogawa, *Synlett* **2013**, *24*, 2199–2215; c) S. N. Arbuzova, N. K. Gusarova, B. A. Trofimov, *Arkivoc* **2006**, *Pt. 5*, 12–36; d) D. Leca, L. Fensterbank, E. Lacôte, M. Malacria, *Chem. Soc. Rev.* **2005**, *34*, 858–865.
[10] Recent reviews: a) M. Tanaka, *Top. Organomet. Chem.* **2013**, *43*, 167–202; b) S. A. Pullarkat, P.-H. Leung, *Top. Organomet. Chem.* **2013**, *43*, 145–166.
[11] Review: D. Enders, A. Saint-Dizier, M.-I. Lannou, A. Lenzen, *Eur. J. Org. Chem.* **2006**, 29–49.
[12] Recent reviews: a) O. I. Kolodiazhnyi, *Tetrahedron: Asymmetry* **2012**, *23*, 1–46; b) J. S. Harvey, V. Gouverneur, *Chem. Commun.* **2010**, *46*, 7477–7485; c) J. Holz, M.-N. Gensow, O. Zayas, A. Börner, *Curr. Org. Chem.* **2007**, *11*, 61–106.
[13] Reviews: a) M. Schlosser, *Angew. Chem.* **2005**, *117*, 380–398; *Angew. Chem. Int. Ed.* **2005**, *44*, 376–393; b) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem.* **2004**, *116*, 2256–2276; *Angew. Chem. Int. Ed.* **2004**, *43*, 2206–2225; c) R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, *Angew. Chem.* **2007**, *119*, 3876–3899; *Angew. Chem. Int. Ed.* **2007**, *46*, 3802–3824.
[14] DoM of: triarylphosphine oxides: a) M. Gray, B. J. Chapell, N. J. Taylor, V. Snieckus, *Angew. Chem.* **1996**, *108*, 1609–1611; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1558–1560; b) J. M. Brown, S. Woodward, *J. Org. Chem.* **1991**, *56*, 6803–6809, and references cited therein; di-*tert*-butylphenylphosphine oxide: c) M. Gray, B. J. Chapell, J. Felding, N. J. Taylor, V. Snieckus, *Synlett* **1998**, 422–424.
[15] a) B. Puget, U. Jahn, *Synlett* **2010**, 2579–2582; b) L. Řehová, I. Císařová, U. Jahn, *Eur. J. Org. Chem.* **2014**, 1461–1476; c) L. Řehová, U. Jahn, *Eur. J. Org. Chem.* **2014**, 4610–4623.
[16] A. D. Buss, S. Warren, *J. Chem. Soc. Perkin Trans. 1* **1985**, 2307–2325.
[17] Substitution of carbon groups was observed before at phosphine oxides bearing no acidic hydrogen atoms: aryl groups in triarylphosphine oxides: a) D. Seyferth, D. E. Welch, J. K. Heeren, *J. Am. Chem. Soc.* **1964**, *86*, 1100–1105; b) B. Schaub, T. Jenny, M. Schlosser, *Tetrahedron Lett.* **1984**, *25*, 4097–4100; c) N. Furukawa, S. Ogawa, K. Matsumura, H. Fujihara, *J. Org. Chem.* **1991**, *56*, 6341–6348; d) T. Shimada, H. Kurushima, Y.-H. Cho, T. Hayashi, *J. Org. Chem.* **2001**, *66*, 8854–8858; chlorovinyl group in (chlorovinyl)diarylphosphine oxides: e) C. Cardellicchio, V. Fiandanese, F. Naso, K. M. Pietrusiewicz, W. Wiśniewski, *Tetrahedron Lett.* **1993**, *34*, 3135–3138; f) C. Cardellicchio, V. Fiandanese, F. Naso, S. Pacifico, M. Koprowski, K. M. Pietrusiewicz, *Tetrahedron Lett.* **1994**, *35*, 6343–6346; alkynyl group in (alkynyl)diarylphosphine oxides: g) W. Smadja, M. Simalty-Siemiatycki, C. Prevost, *Bull. Soc. Chim. Fr.* **1966**, 971–972; methoxymethyl diphenylphosphine oxide is the only example where selective substitution of the alkyl group over the phenyl group has been observed as the primary reaction: h) C. Cardellicchio, G. Fracchiolla, F. Naso, P. Tortorella, W. Holody, K. M. Pietrusiewicz, *Tetrahedron Lett.* **1999**, *40*, 5773–5776.
[18] For DoM/functionalization reactions and subsequent cross-couplings of other compound classes, see: E. J.-G. Anctil, V. Snieckus, *J. Organomet. Chem.* **2002**, *653*, 150–160.
[19] X-ray crystallographic data of compounds **3c**, **10a**, and the major diastereomers of **12d** and **12g** can be found in the Supporting information. CCDC 997785, 997786, 997787 and 997788 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.
[20] Review: A. Staubitz, A. P. M. Robertson, M. E. Sloan, I. Manners, *Chem. Rev.* **2010**, *110*, 4023–4078, and reviews cited therein.
[21] K. Shioji, Y. Oyama, K. Okuma, H. Nakagawa, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3911–3915.
[22] H. Wang, L. Li, X.-F. Bai, J.-Y. Shang, K.-F. Yang, L.-W. Xu, *Adv. Synth. Catal.* **2013**, *355*, 341–347.
[23] For complementary recent asymmetric DoM reactions of other classes, see: diphenylaminophosphazenes: a) M. Casimiro, L. Roces, S. García-Granda, M. J. Iglesias, F. López Ortiz, *Org. Lett.* **2013**, *15*, 2378–2381; diphenylphosphinamides: b) C. Popovici, P. Oña-Burgos, I. Fernández, L. Roces, S. García-Granda, M. J. Iglesias, F. López Ortiz, *Org. Lett.* **2010**, *12*, 428–431; c) D. B. G. Williams, S. J. Evans, H. de Bod, M. S. Mokhadinyana, T. Hughes, *Synthesis* **2009**, 3106–3112; alkyldiphenylphosphazenes: d) J. García-López, I. Fernández, M. Serrano-Ruiz, F. López Ortiz, *Chem. Commun.* **2007**, 4674–4676; diphenylphosphinic acids: e) V. Y. Rodríguez, M. A. del Águila, M. J. Iglesias, F. López Ortiz, *Tetrahedron* **2012**, *68*, 7355–7362.

