ChemComm

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c5cc07504a

Received 7th September 2015,
Accepted 29th September 2015

DOI: 10.1039/c5cc07504a

www.rsc.org/chemcomm

Stereospecific S_N2@P reactions: novel access to bulky P-stereogenic ligands†‡

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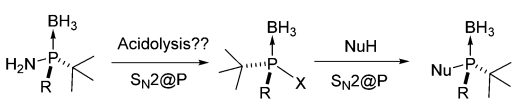
The stereospecific hydrolysis of bulky aminophosphine boranes is reported for the first time. The resulting phosphinous acid boranes, upon activation, undergo stereospecific nucleophilic substitution reaction at the phosphorous center with amine nucleophiles. The combination of these two processes provides a novel access to bulky P*-ligands.

Chiral phosphines are the cornerstone of asymmetric metal catalysis.[1] Among this class of ligands, bulky P-stereogenic phosphines have proved to be highly efficient in asymmetric hydrogenation and other relevant processes.[2,3] However, their synthesis in the optically pure form is often not straightforward. The stereoselective synthesis of *tert*-butyl P-stereogenic phosphines has relied mostly on the selective deprotonation of *tert*-butyldimethylphosphine borane complexes[4] and on the reaction of borane lithium phosphides with electrophiles.[5] Nucleophilic substitution reactions at the "bulky" P-center (S_N2@P) are generally avoided since it is overly unreactive. Furthermore, when forced to react, it usually provides non-stereospecific substitution processes.[6,7] A relevant exception to this behavior is the reaction of halo-*tert*-butylmethylphosphine-boranes with alkynyllithium reagents.[8] However, halophosphines are configurationally unstable and have to be generated and reacted *in situ* at low temperature.

Jugé and others showed that P-stereogenic aryl and alkyl aminophosphine boranes undergo stereospecific acid-promoted methanolysis to yield the resulting methyl phosphinites with inversion at the P-center.[9] The acidolysis can also be carried out with HCl/toluene, in this case yielding the optically enriched chlorophosphine boranes.[10] However, these reactions directly fail or provide reduced optical purity when a bulky group (*e.g.*, *tert*-butyl) is attached to phosphorus.

We recently reported the stereospecific synthesis of aminophosphines **1a** and **1b** which have been used by us in the preparation of MaxPHOS and SIP type ligands.[11] We considered that these compounds were ideally suited to evaluate whether the acidolysis of bulky aminophosphines could be performed in a stereospecific manner, and whether the resulting products could be further transformed into valuable ligand structures (Scheme 1). Herein we report on the stereospecific hydrolysis of bulky aminophosphine boranes and how the resulting phosphinous acids can be transformed into P*-ligands through S_N2@P reactions.

The initial acidolysis studies on **1a** and **1b** were conducted in H_2SO_4/MeOH (Table 1). Methanolysis of **1a** at 50 °C for 16 h did not afford the expected methyl phosphinite borane **2a** but the corresponding phosphinous acid borane **3a** and the secondary phosphine oxide **4a** that results from borane deprotection and P(III)/P(V) tautomerization of **3a** (Table 1, entry 1). We attributed the formation of **3a** to the residual content of water in the solvent used. To confirm this hypothesis, we next ran the acidolysis reaction of **1a** in a MeOH/H_2O (20 : 1) mixture. This solvent mixture and heating to 40 °C for 16 h afforded exclusively phosphine oxide **4a** in low enantiomeric excess (Table 1, entry 2). By simply reducing the reaction time to 2 h, we were able to isolate the corresponding phosphinous acid **3a** with an excellent yield and optical purity (>99% ee, Table 2, entry 3).



(S_P)-**1a**, R=Me
(R_P)-**1b**, R=Ph

Scheme 1 Novel stereospecific route to bulky P-stereogenic phosphines.

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† Dedicated to Stephen L. Buchwald on the occasion of his 60th birthday.

‡ Electronic supplementary information (ESI) available: Experimental procedures, characterization data and NMR spectra for new compounds. CCDC 1412790. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5cc07504a

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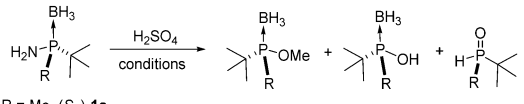
Table 1 Acidolysis of optically pure aminophosphines



R = Me, (S_P)-**1a**
R = Ph, (R_P)-**1b**

2 **3** **4**

Entry	R	Conditions[a]	**2a**/**2b**	**3a**/**3b**[b]	**4a**/**4b**
1	Me	MeOH 50 °C, 16 h	—	75%[c]	25%[c]
2	Me	MeOH/H_2O (20 : 1) 40 °C, 16 h	—	—	83% (53% ee)[e]
3	Me	MeOH/H_2O (20 : 1) 50 °C, 2 h	—	97% (>99% ee)[d]	—
4	Ph	MeOH/H_2O (2 : 1) 50 °C, 7 h	—	63% (>99% ee)[d]	—

[a] Aminophosphine (7.5 mmol), H_2SO_4 (30 mmol) and 42 mL of solvent were used. [b] Isolated yield after flash column chromatography. [c] Conversion data based on ^{1}H NMR crude reaction. [d] Enantiomeric excess determined by chiral GC or HPLC analysis of the corresponding methylated derivative **2a**/**2b**. [e] Enantiomeric excess determined by optical rotation.

The hydrolysis of **1b** was also carried out stereospecifically to yield the corresponding phosphinous acid **3b** in >99% ee and 63% yield (Table 1, entry 4). Hydrolysis of **1a** and **1b** took place with inversion of the configuration at the P-center as confirmed by X-ray crystallography of the corresponding benzoyl derivative (see ESI‡).[12] The opposite enantiomer of **3a** and and **3b** were obtained when starting from (R_P)-**1a** and (S_P)-**1b** thus confirming that the process is completly stereospecific. These results indicate that the acidolysis of bulky aminophosphines is extremely sensitive to the nature of the incoming nucleophile. We believe that the minimal steric differences between methanol and water allow the latter to act as an efficient nucleophile, while making the former unreactive.

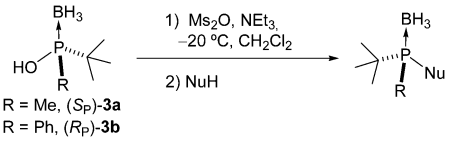
To further explore the scope of this transformation we submitted diastereomerically pure aminophosphines **5a** and **5b** (the synthetic precursors of aminophosphines **1a** and **1b**) to acidic hydrolysis in MeOH/H_2O mixtures (Scheme 2). The reaction was slower than that achieved using the parent compounds **1a** and **1b**;[13] however, again, an increase in the reaction temperature and a longer reaction time produced the enantiomerically pure phosphinous acids **3a** and **3b** in 84% and 66% yields respectively. The hydrolysis of **5a** and **5b** is a practical approach to prepare the corresponding phosphinous acids; furthermore, it allows the recovery of the chiral auxiliary.

Optically pure P-stereogenic phosphinous acid boranes are attractive synthetic intermediates; however, they have barely been used in ligand synthesis.[14] While optically enriched **3b** has been prepared independently by Pietrusiewicz and Buono *via* resolution or H-menthylphosphinate technology, this is the first time that phosphinous acid **3a** has been reported. It is known that mesyl-activated phosphinous acids undergo effective nucleophilic reductions in the presence of $NaBH_4$ with inversion at the phosphorus center,[14] and we speculated whether this process could be extended to nucleophiles larger than hydride. Hence, phosphinous acid (S_P)-**3a** was treated with Ms_2O in the presence of triethylamine, and the reactions of the resulting mixed anhydride with several nucleophiles were studied (Table 2).[15]

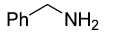
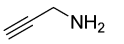
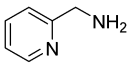
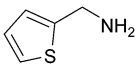
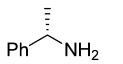
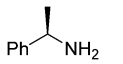
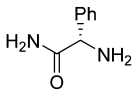
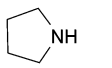
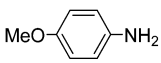
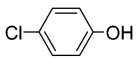
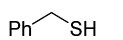
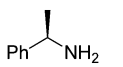
Initial experiments using ammonia as the nucleophile indicated that, in solution, the phosphinyl-mesyl anhydride underwent slow racemization. Fortunately, a judicious choice of solvent and lowering of the reaction temperature to −20 °C permitted the nucleophilic substitution with ammonia in an almost completely stereospecific fashion. This produced (R_P)-**1a** in 99% yield and 96% ee with the inverted configuration at the P-center (Table 2, entry 1). Importantly, primary amines also acted as efficient nucleophiles in this process, producing the corresponding aminophosphines in satisfactory yield and excellent enantiomeric excess (Table 2, entries 2–5). Chiral primary α-branched amines like (*S*) and (*R*)-1-phenylethylamine and phenylglycinamide also yielded the substitution products (R_P)-**10**, (R_P)-**11** and (R_P)-**12** in 95–98% diastereomeric excess (Table 2, entries 6–8). A cyclic secondary amine like pyrrolidine and an aromatic amine like *p*-anisidine also efficiently produced the substitution products in 98 and 91% ee (Table 2, entries 9 and 10). In contrast, dibenzylamine was not good enough as a nucleophile and did not afford the expected aminophosphine (Table 2, entry 11). Also, oxygen nucleophiles failed to provide substitution products (Table 2, entry 12). In contrast, benzylthiol and thiophenol did provide the corresponding sulfides **17** and **18**, albeit in low yield (22 and 36% respectively) (Table 2, entries 13 and 14). We attributed these low yields of isolation to the instability of these molecules. Finally, we tested the *tert*-butylphenylphosphinous acid borane **3b** as the electrophile. Reaction with ammonia and (*R*)-phenylethylamine provided the corresponding aminophosphines **1b** and **19** with excellent optical and diastereomeric purity (Table 2, entries 15 and 16).

The hydrolysis of aminophosphine boranes combined with the substitution on the resulting phosphinous acid represents a novel means of obtaining P*-ligands. To highlight the beneficial impact that this methodology could have in asymmetric catalysis, we followed the procedure shown in Table 2 to prepare a novel P-stereogenic *N*-phosphinooxazoline ligand and its corresponding cationic iridium complex (Scheme 3). Activation of (S_P)-**3a** with mesyl anhydride and triethylamine and reaction with aminooxazoline **20** provided the borane-protected ligand **21** in 43% yield and in >98% dr, as determined by ^{1}H NMR. Borane was removed in neat pyrrolidine at 90 °C.[16] We found that the approach of using neat pyrrolidine was superior to that of existing borane-deprotection methods like DABCO or neat diethylamine. Thus, from **21** and using a one pot-three reaction sequence, the cationic iridium complex **22** was obtained as an orange solid in 89% yield.

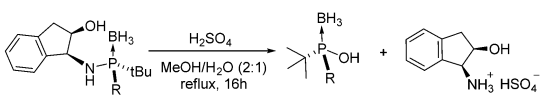
Table 2 Substitution reactions with several nucleophiles



R = Me, (S_P)-**3a**
R = Ph, (R_P)-**3b**

Entry	SM	Nucleophile	Product	Yield[a] (%)	ee/de[b] (%)
1	**3a**	NH_3	(R_P)-**1a**	99	96 ee
2	**3a**		(R_P)-**6**	60	98 ee
3	**3a**		(R_P)-**7**[c]	64	>95 ee
4	**3a**		(R_P)-**8**	87	99 ee
5	**3a**		(R_P)-**9**	73	96 ee
6	**3a**		(R_P)-**10**	76	98 de
7	**3a**		(R_P)-**11**	71	95 de
8	**3a**		(R_P)-**12**	63	97 de
9	**3a**		(R_P)-**13**	65	98 ee
10	**3a**		(R_P)-**14**	42	91 ee
11	**3a**	$HNBn_2$	(R_P)-**15**	0	—
12	**3a**		(R_P)-**16**	0	—
13	**3a**		(R_P)-**17**[d]	22	nd
14	**3a**	PhSH	(R_P)-**18**[e]	36	nd
15	**3b**	NH_3	(S_P)-**1b**	99	99 ee
16	**3b**		(S_P)-**19**	72	96 de

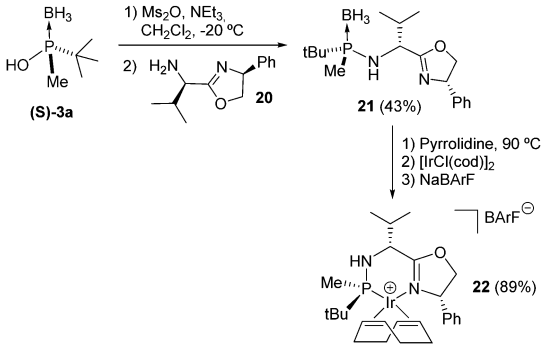
[a] Isolated yield after flash column chromatography. [b] Enantiomeric excess determined by either chiral GC or HPLC analysis, diastereomeric excess determined by ^{1}H NMR of the crude reaction. [c] Optical purity of **7** was assigned tentatively by analogy with similar primary amines tested. [d] Determination of optical purity by chromatographic methods failed. $[\alpha]_D = -23.5^\circ$ (c 1.00, $CHCl_3$). [e] Determination of optical purity by chromatographic methods failed. $[\alpha]_D = -2.1^\circ$ (c 1.49, $CHCl_3$). nd = not determined.



R = Me, (S_P)-**5a** (R_P)-**3a** (84%, 99% ee)
R = Ph, (R_P)-**5b** (S_P)-**3b** (66%, 99% ee)

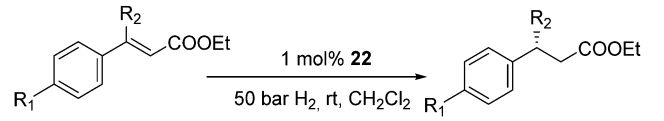
Scheme 2 Acidolysis of *N*-secondary aminophosphines and recovery of the chiral auxiliary.

With the iridium complex **22** in hand, we tested its performance in the asymmetric hydrogenation of α,β-unsaturated esters (Table 3).[17,18] Reduction of ethyl *trans*-β-methylcinnamate under



Scheme 3 Synthesis of the P-stereogenic *N*-phosphino-oxazoline iridium complex.

Table 3 Asymmetric hydrogenation of olefins using complex **22** as the catalyst



Entry	R_1	R_2	Conv.[a] (%)	ee[b] (%)
1	H	Me	100	95 (*R*)
2	H	iPr	100	97 (*R*)
3	H	Cy	100	97 (*R*)
4	Me	Me	100	>99 (*R*)

[a] Conversion was determined by ^{1}H NMR analysis of the crude reaction. [b] Enantiomeric excesses were determined by chiral HPLC analysis.

standard non-optimized conditions (50 bar of hydrogen in dichloromethane with 1 mol% of **22** as the catalyst) produced the (*R*) hydrogenated product in 95% ee (Table 3, entry 1). Under the same reaction conditions, hydrogenation of the isopropyl and cyclohexyl β-substituted cinnamates afforded the reduced products in 97% ee (Table 3, entries 2 and 3). Finally, *para*-methyl-substituted methylcinnamate afforded the reduced compound with complete selectivity (>99% ee, Table 3, entry 4).

In summary, we have shown that the acid hydrolysis of bulky primary and secondary aminophosphine boranes occurs in a completely stereospecific manner with inversion of the configuration at the P-center to yield the corresponding optically pure phosphinous acid boranes. Also, we have demonstrated that, upon activation, phosphinous acid boranes undergo stereospecific nucleophilic substitution reactions at the P-center with amine nucleophiles. The potential of this process has been demonstrated with the synthesis of a P-stereogenic phosphino-oxazoline ligand which has been applied to the asymmetric Ir-catalyzed hydrogenation of *trans*-β-alkylcinnamates, achieving selectivities of up to 99% ee.

We thank financial support from the Spanish Ministerio de Economia y Competividad (CTQ2014-56361-P and CTQ2013-40568P), the IRB Barcelona, the Generalitat de Catalunya (2014SGR670), the ICREA Foundation (M. Diéguez and O. Pàmies ICREA Academia awards). S.O. thanks the Generalitat de Catalunya for a FI fellowship. A. F.-G. thanks the CONACYT for a postdoctoral fellowship.

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