

Organophosphorus-Catalysed Staudinger Reduction

Henri A. van Kalkeren,^a Jorick J. Bruins,^a Floris P. J. T. Rutjes,^a
and Floris L. van Delft^{a,*}^a Institute for Molecules and Materials, Radboud University Nijmegen, Heyendaalseweg 135, NL-6525 AJ Nijmegen, The Netherlands
Fax: (+31)-24-365-3393; phone: (+31)-24-365-2373; e-mail: f.vandelft@science.ru.nl

Received: December 13, 2012; Revised: February 16, 2012; Published online: ■■■, 0000

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/adsc.201100967>.

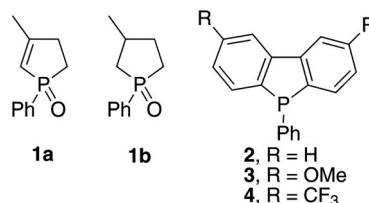
Abstract: The first Staudinger reduction that is catalytic in phosphine has been developed, showing excellent yields and functional group selectivity. To this end we utilised dibenzophosphole catalysts and mild *in situ* reduction of the intermediate iminophosphoranes. We could avoid the necessity of water during the reduction, obtained no phosphine oxides as waste and thus enabled facile purification of the product. A range of azides was converted into amines with good to excellent yields and high functional group tolerance.

Keywords: azides; homogeneous catalysis; phosphorus heterocycles; Staudinger reduction; synthetic methods

a phosphine oxide. For example, in 2008 Marsden et al. showed that this strategy can be applied in an aza-Wittig reaction.^[8a] To this end, the cyclic phospholane oxide **1a** was reacted with isocyanates to generate an iminophosphorane that subsequently reacts with a carbonyl group. Denton et al. have demonstrated a catalytic Appel reaction using a similar approach through activation with oxalyl chloride.^[8b-d] Furthermore, the group of O'Brien showed that *in situ* mild reduction of phosphine oxides is nevertheless possible,^[9] in particular by combination of phospholane oxide **1b** and diphenylsilane [or (trimethoxy)silane] to enable a catalytic Wittig reaction. Finally, Woerpel et al. have used a similar concept by a triphenylphosphine-catalysed reduction of silyl peroxides with *in situ* generated titanium hydride.^[10]

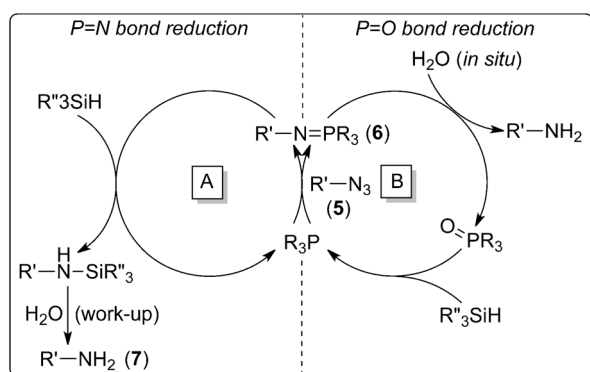
The oxidation of phosphine reactants to the corresponding phosphine oxides serves as an essential driving force to enable a range of synthetic transformations, such as Wittig^[1], Mitsunobu^[2], Appel^[3] and Staudinger^[4] reactions. These reactions are well-established and find wide application, despite the fact that the formation of phosphine oxides gives rise to significant waste production and purification difficulties.^[5] Both from environmental and economic perspectives, it is therefore desirable to develop novel variants of the aforementioned reactions that proceed with better phosphorus atom economy.^[6] Ideally, in such processes the phosphorus species is used in substoichiometric amounts.

In the last few years, organophosphorus catalysis has made notable progress, based on two general strategies.^[7] One strategy involves the *in situ* activation of an intermediate phosphine oxide, either with isocyanates or with a strong dehydration agent like oxalyl chloride.^[8] Throughout the catalytic cycle, the phosphorus species remains in the P(V) oxidation state, thereby avoiding the challenging reduction of



We have recently found that dibenzophospholes (**2** and **3**) are particularly useful for the mild *in situ* reduction strategy, as demonstrated in a catalytic variant of the Appel reaction.^[11] We here report a new application of dibenzophospholes in a catalytic variant of phosphine-based chemistry, i.e., the Staudinger reduction of azides.

The introduction of azides in organic compounds is well established and various methods have been developed.^[12] Azide functionalities may subsequently engage in specific synthetic transformations, in particular 1,3-dipolar cycloadditions, but azides can also simply serve as a protected form of amines.^[13] One practical method to induce the transformation of azide **5** to amine **7** is by treatment with a phosphine



Scheme 1. In a catalytic Staudinger reduction, either the P=N (pathway A) or the P=O bond (pathway B) is reduced. Through pathway A, involving *in situ* reduction of intermediate **6** with silanes, water is required only during work-up to afford the desired amine.

in the presence of water, commonly known as Staudinger reduction (Scheme 1). The overall process involves the formation of an intermediate iminophosphorane **6** that is subsequently hydrolysed to the corresponding amine and phosphine oxide.^[4] One option to develop a catalytic variant of the Staudinger reduction therefore involves *in situ* reduction of phosphine oxide back to phosphine. We realised, however, that the known reducing agents (silanes) for phosphine oxides are incompatible with the water present (Scheme 1, route B). We therefore aimed at a strategy involving direct reduction of the P(V)-iminophosphorane intermediate **6** back to phosphine, with concomitant formation of amine **7**, to avoid the necessity of *in situ* water (Scheme 1, route A). The temporarily formed N–Si bond, by virtue of its high moisture sensitivity, rapidly hydrolyses during work-up.^[14]

We initiated our attempts by using a similar system as used in the development of the catalytic Appel reaction.^[11] Hence, in dioxane, benzyl azide was com-

bined with 10 mol% of **2** and diphenylsilane (Ph_2SiH_2) as reducing agent. The reaction mixture was refluxed, leading to full conversion within 19 h (Table 1, entry 1). Conveniently, a much faster reduction was obtained by utilizing phenylsilane ($PhSiH_3$), i.e., full conversion was obtained within 3 h (entry 2). The influence of electron-donating or electron-withdrawing substituents as in dibenzophospholes **3** and **4**, respectively, was also tested (entries 3 and 4). We found these substituents have a small, but distinct effect on the required reaction time. Remarkably, both elements decrease the required reaction time. Other solvents were tolerated as well and full conversion was obtained in both toluene and acetonitrile (entries 5 and 6). We attribute the different reaction times mainly to the difference in boiling points (i.e., reflux temperatures) of the individual solvents. Furthermore, we established that the optimal protocol involves 5 mol% catalyst loading with overnight reflux. The essential role of the dibenzophosphole catalyst **2** was established by treatment of benzyl azide with phenylsilane in the absence of **2** (entry 8), which did not lead to any detectable conversion. Finally, the advantage of the dibenzophosphole **2** becomes apparent by comparison with triphenylphosphine. First of all, it is clear that the reaction for **2** is much faster (entry 9). Secondly, the catalytic Staudinger reduction with **2** is less sensitive to traces of water and oxygen, both of which would lead to formation of phosphine oxide, thereby shutting off the catalytic cycle. Dibenzophosphole oxide is also formed upon hydrolysis or oxidation, but is, in contrast to phosphine oxide, easily reduced by diphenylsilane (*vide infra*). As a consequence, careful exclusion of water and oxygen is not required and lower catalyst loadings are possible.

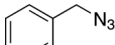
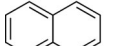
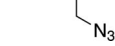
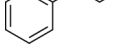
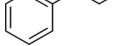
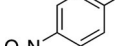
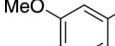

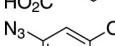
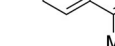
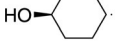
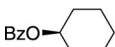
Having established optimal conditions for the catalytic Staudinger reduction with phosphole **2**, a range of substrates was screened. To this end, several azides were subjected to 5 mol% dibenzophosphole **2** and

Table 1. Catalytic Staudinger reduction by variation of catalyst, solvent, silane and temperature.

Entry	Catalyst	Silane (1.5 equiv.)	Catalyst (mol%)	Solvent	Temperature [°C]	Time [h]	Conversion [%] ^[a]
1	2	Ph_2SiH_2	10	dioxane	101	19	97
2	2	$PhSiH_3$	10	dioxane	101	3	100
3	3	$PhSiH_3$	10	dioxane	101	2	100
4	4	$PhSiH_3$	10	dioxane	101	2	100
5	2	$PhSiH_3$	10	toluene	110	2	100
6	2	$PhSiH_3$	10	MeCN	82	16	99
7	2	$PhSiH_3$	5	dioxane	101	16	100
8		$PhSiH_3$		dioxane	101	20	0
9	PPh_3	$PhSiH_3$	10	dioxane	101	21	100

^[a] Conversion as determined by GC with tetradecane as an internal standard.

Table 2. Substrate scope of the catalytic Staudinger reduction.

Entry	Substrate	Yield ^[a] (cat.)
1		63% ^[b]
2		99%
3		71%
4		74%
5		80%
6		99%
7		99%
8		93%
9		99%
10		85%
11		51% ^[c]
12		— ^[d]

^[a] isolated yields.

^[b] Volatility of the product lowered the isolated yield.

^[c] 5-Methoxyfurozane was isolated as well (49%).

^[d] Full conversion of azide into a complex mixture of products.

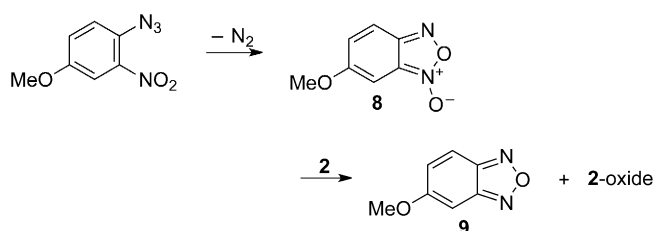
phenylsilane (1.5 equiv.) in refluxing dioxane. We were pleased to find that both aromatic and aliphatic azides were cleanly converted with good to excellent yields (Table 2). Functional groups like nitro (entry 5), carboxylic acid (entry 7), alcohol (entry 6), ester (entry 10) and olefins (entry 4) were all fully compatible with the reaction conditions employed, thereby further demonstrating the versatility of the reaction. Both electron-rich and electron-poor aryl azides could be converted to anilines in high yields (entry 5 and 6). In addition to the high yields, the practical execution of the procedure is extremely

simple. After 16 h reaction time, water is added to quench remaining silane and hydrolyse the N–Si bond. Next, the reaction mixture is concentrated and flushed over a short silica column. By eluting with dichloromethane (DCM), first the dibenzophosphole catalyst is recovered.^[15] Subsequent switching of solvent to DCM/MeOH affords the desired amine with high yield and purity.

An interesting observation was made for 1-azido-4-methoxy-2-nitrobenzene (entry 11). In the case of this particular substrate it was found that, although the azide was fully converted, only 51% aniline product was formed and 5-methoxybenzofurazane (**9**) was isolated as a main by-product (49%). Formation of furazane can be rationalised by dibenzophosphole reduction of the 5-methoxyfuroxane intermediate (**8**) (Scheme 2).^[16] The concomitantly formed dibenzophosphole oxide is subsequently *in situ* reduced by phenylsilane and continues to reduce remaining azide. This reaction clearly demonstrates the power of catalyst **2** over PPh₃ as the formation of triphenylphosphine oxide would terminate further azide reduction.

No amine was isolated from 2-azidophenol (entry 12) as a complex mixture of products was formed.

To verify the catalytic action of dibenzophosphole, we designed a series of experiments involving subjection of the iminophosphorane to several reducing agents or water and monitoring these reactions by NMR (Figure 1).^[17] Thus, first dibenzophosphole **2** (1 equiv.) was reacted with benzyl azide (1.1 equiv.) in dioxane-*d*₈, leading to the formation of iminophosphorane as observed by ¹H and ³¹P NMR (Figure 1, a). Subsequent addition of H₂O led, as expected, to hydrolysis and yielded benzylamine and the oxide derivative of **2**. Addition of diphenylsilane to the iminophosphorane gave a much slower reaction than phenylsilane, in correspondence with the rate of the catalytic Staudinger reduction (Table 1, entries 1 and 2). Not unexpectedly, the phenylsilane reduction of iminophosphorane derived from triphenylphosphine took more than 5 h under similar conditions (Figure 1, b).



Scheme 2. Intermediate **8** is reduced by **2** leading to 5-methoxybenzofurazane (**9**) and **2**-oxide. In contrast to triphenylphosphine oxide, **2**-oxide can be reduced by PhSiH₃ back to **2**. This catalyst regeneration enables continuation of the Staudinger reduction.

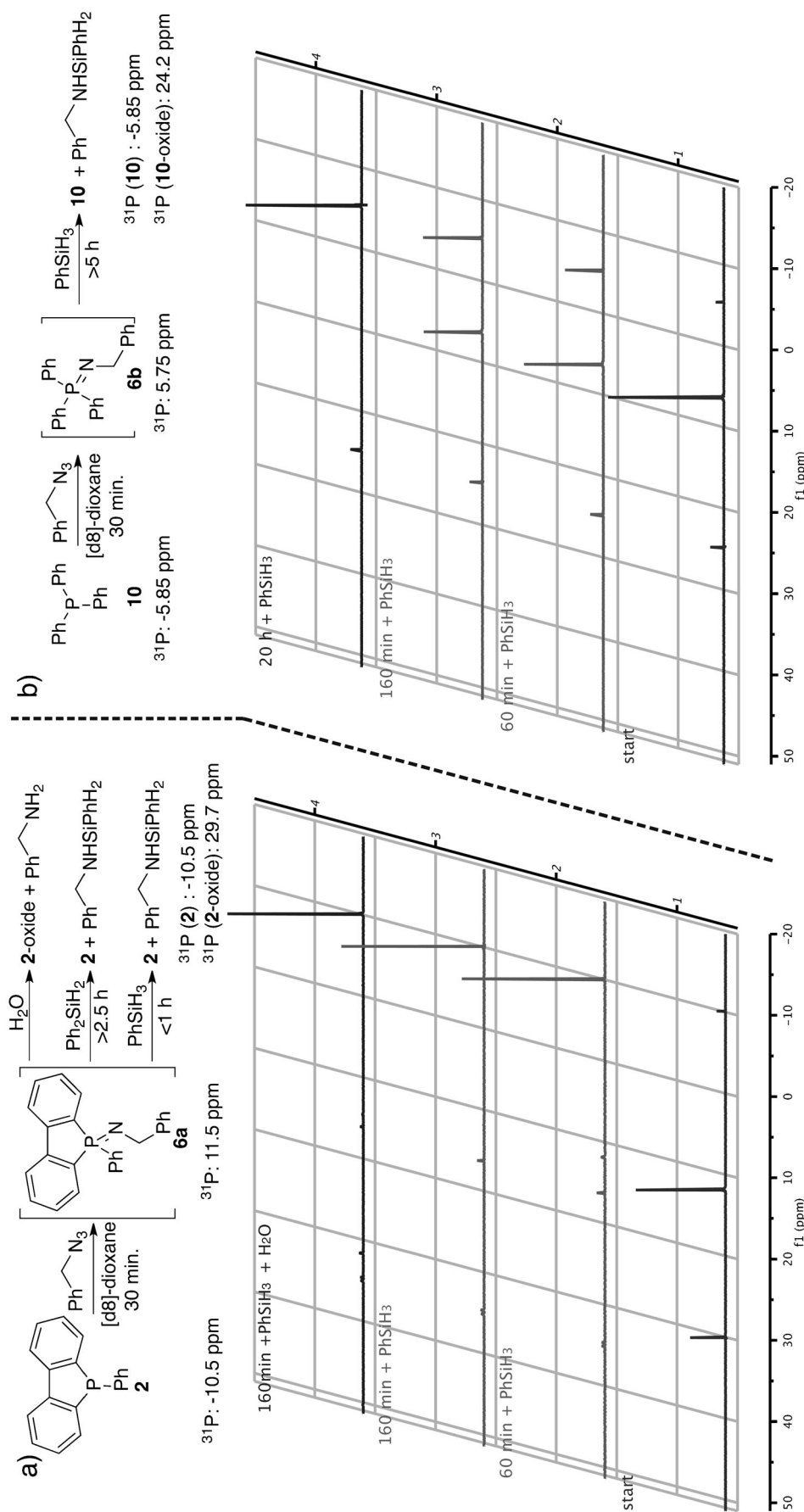


Figure 1. Stoichiometric formation of **6a** (left) or **6b** (right) and subsequent reduction with PhSiH_3 followed by ^{31}P NMR. The bottom spectra show crude iminophosphoranes **6a** and **6b** with chemical shifts around 12 and 6 ppm, respectively. In both cases, some phosphine oxide is also visible (around 30 and 25 ppm, respectively), formed *via* hydrolysis of **6a** or **6b** by residual water. Then, from bottom to top subsequent reduction stages upon reaction with phenylsilane are represented with stacked NMR spectra. Note that **6a** is fully reduced within one hour, and also no traces of phosphine oxide remain. In contrast, full reduction of iminophosphorane **6b** requires > 5 h of reaction time, and **6-oxide** remains present even after 20 h.

In summary, we have developed the first Staudinger reduction that is catalytic in phosphine, involving *in situ* P=N bond reduction. Our procedure offers the advantage of less waste, with catalyst loading down to 5%. In addition, the reaction is practically simple and displays high functional group tolerance. Currently, we are exploring yet other catalytic variants of phosphine-based transformations for application in organic chemistry, an exciting and versatile research area that has remained dormant for more than a long period but is now finally providing sustainable tools for a range of highly practical synthetic transformations.

Experimental Section

General Procedure

The azide was dissolved in dry dioxane (0.2M) and phenylsilane (1.5 equiv.) and 1-phenyl-dibenzophosphole (5 mol%) were added. The reaction mixture was refluxed for 16 h and then water (2 equiv.) was added and the mixture was stirred at room temperature until the evolution of gas had ceased. The solvent was evaporated and the crude product was purified by flash column chromatography to yield the amine.

Acknowledgements

C. A. Hommersom is kindly acknowledged for her analytical contributions. This research has been performed within the framework of the CatchBio program. The authors gratefully acknowledge the support of the Smart Mix Program of the Netherlands Ministry of Economic Affairs and the Netherlands Ministry of Education, Culture and Science.

References

- [1] A. W. Johnson, *Ylides and imines of phosphorus*, Wiley, New York, **1993**.
- [2] K. C. K. Swamy, N. N. B. Kumar, E. Balaraman, K. V. P. P. Kumar, *Chem. Rev.* **2009**, *109*, 2551–2651.
- [3] R. Appel, *Angew. Chem.* **1975**, *87*, 863–874; *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 801–811.
- [4] a) H. Staudinger, J. Meyer, *Helv. Chim. Acta* **1919**, *2*, 635–646; b) Y. G. Gololobov, I. N. Zhmurova, L. F. Kasukhin, *Tetrahedron* **1981**, *37*, 437–472.
- [5] a) J. I. G. Cadogan, *Organophosphorus reagents in organic synthesis*, Academic Press, London, New York, **1979**; b) D. H. Valentine, J. H. Hillhouse, *Synthesis* **2003**, 317–334.
- [6] a) D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer Jr, R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks, T. Y. Zhang, *Green Chem.* **2007**, *9*, 411–420; b) B. M. Trost, *Science* **1991**, *254*, 1471–1477.
- [7] a) S. P. Marsden, *Nature Chemistry* **2009**, *1*, 685–687; b) I. J. S. Fairlamb, *ChemSusChem* **2009**, *2*, 1021–1024.
- [8] a) S. P. Marsden, A. E. McGonagle, B. McKeever-Abbas, *Org. Lett.* **2008**, *10*, 2589–2591; b) R. M. Denton, J. An, B. Adeniran, *Chem. Commun.* **2010**, 3025–3027; c) R. M. Denton, X. Tang, A. Przeslak, *Org. Lett.* **2010**, *12*, 4678–4681; d) R. M. Denton, J. An, B. Adeniran, A. J. Blake, W. Lewis, A. M. Poulton, *J. Org. Chem.* **2011**, *76*, 6749–6767.
- [9] a) C. J. O'Brien, J. L. Tellez, Z. S. Nixon, L. J. Kang, A. L. Carter, S. R. Kunkel, K. C. Przeworski, G. A. Chass, *Angew. Chem.* **2009**, *121*, 6968–6971; *Angew. Chem. Int. Ed.* **2009**, *48*, 6836–6839; b) H. Fritzsche, F. Korte, U. Hasserodt, *Chem. Ber.* **1964**, *97*, 1988–1993; c) K. L. Marsi, *J. Org. Chem.* **1974**, *39*, 265–267; d) L. McKinstry, T. Livinghouse, *Tetrahedron* **1994**, *50*, 6145–6154.
- [10] J. R. Harris, M. T. Haynes, A. M. Thomas, K. A. Woerpel, *J. Org. Chem.* **2010**, *75*, 5083–5091.
- [11] H. A. van Kalker, S. H. A. M. Leenders, C. R. A. Hommersom, F. P. J. T. Rutjes, F. L. van Delft, *Chem. Eur. J.* **2011**, *17*, 11290–11295.
- [12] a) E. D. Goddard-Borger, R. V. Stick, *Org. Lett.* **2007**, *9*, 3797–3800; b) T. M. V. D. Pinho e Melo, in: *Organic Azides: Syntheses and Applications*, (Ed.: K. B. S. Bräse), John Wiley & Sons, Chichester, **2010**, pp 53–94.
- [13] a) V. D. Bock, H. Hiemstra, J. H. van Maarseveen, *Eur. J. Org. Chem.* **2006**, 51–68; b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2708–2711; *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599; c) S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem.* **2005**, *117*, 5320–5374; *Angew. Chem. Int. Ed.* **2005**, *44*, 5188–5240.
- [14] a) N. W. Mitzel, K. Angermaier, H. Schmidbaur, *Chem. Ber.* **1994**, *127*, 841–844; b) N. W. Mitzel, A. Schier, H. Beruda, H. Schmidbaur, *Chem. Ber.* **1992**, *125*, 1053–1059.
- [15] Reuse of the catalyst gave identical results as with the fresh catalyst. See the Supporting Information for more details on catalyst recovery.
- [16] a) R. J. Gaughran, J. P. Picard, J. V. R. Kaufman, *J. Am. Chem. Soc.* **1954**, *76*, 2233–2236; b) M. L. Gross, I. M. Takakis, G. G. Tsantali, G. W. Haas, D. Giblin, *J. Mass Spectrom.* **1999**, *34*, 1137–1153.
- [17] Stacked ¹H and ³¹P NMR spectra for all reaction are present in the Supporting Information.

6 Organophosphorus-Catalysed Staudinger Reduction

Adv. Synth. Catal. **2012**, 354, 1–6

Henri A. van Kalkeren, Jorick J. Bruins,
Floris P. J. T. Rutjes, Floris L. van Delft*

