

## Design of novel uncharged organic superbases: Merging basicity and functionality

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### Conspectus

One of the constant challenges of synthetic chemistry is the molecular design and synthesis of non-ionic, metal-free superbases as chemically stable neutral organic compounds of moderate molecular weight, intrinsically high thermodynamic basicity, adaptable kinetic basicity, and weak or tunable nucleophilicity at their nitrogen, phosphorus or carbon basicity centers. Such superbases can catalyze numerous reactions, ranging from C-C bond formation to cycloadditions and polymerization, to name just a few. Additional benefits of organic superbases, as opposed to their inorganic counterparts, are their solubility in organic reaction media, mild reaction conditions and higher selectivity. Approaching such superbasic compounds remains a continuous challenge. However, recent advances in synthetic methodology and theoretical understanding have resulted in new design principles and synthetic strategies towards superbases. Our computational contributions have demonstrated that the gas-phase basicity region of 350 kcal mol<sup>-1</sup> and even beyond is well reachable by organosuperbases. However, despite record-high basicities, the physical limitations of many of these compounds become quickly evident. The typically large molecular weight of these molecules and their sensitivity to ordinary reaction conditions prevents them from being practical, even though their preparation is often not too difficult. Thus, obviously structural limitations with respect to molecular weight and structural complexity must be imposed on the design of new synthetically useful organic superbases, but strategies for increasing their basicity remain important.

The contemporary design of novel organic superbases is illustrated by phosphazenyphosphanes displaying gas-phase basicities (GB) above 300 kcal mol<sup>-1</sup> but having molecular weights well below 1000 g·mol<sup>-1</sup>. This approach is based on reconsideration of phosphorus(III) compounds, which goes along with increasing their stability in solution. Another example is the preparation of carbodiphosphanes incorporating pyrrolidine, tetramethylguanidine, or hexamethylphosphazene as substituents. With gas-phase proton affinities of up to 300 kcal

mol<sup>-1</sup> they are among the top non-ionic carbon bases on the basicity scale. Remarkably, the high basicity of these compounds is achieved at molecular weights around 600 g·mol<sup>-1</sup> only. Another approach to achieve high basicity through the cooperative effect of multiple intramolecular hydrogen bonding, which increases stabilization of conjugate acid, has been recently confirmed.

This Account focuses on our efforts to produce superbasic molecules that embody many desirable traits, but other groups' approaches will also be discussed. We reveal the crucial structural features of superbases and place them in known basicity scales. We discuss the emerging potential and current limits of their application and give a general outlook into the future.

## Key references

- Ullrich, S.; Kovačević, B.; Koch, B.; Harms, K.; Sundermeyer, J. Design of Non-Ionic Carbon Superbases: Second Generation Carbodiphosphanes. *Chem. Sci.* **2019**, *10*, 9483–9492.<sup>1</sup> A new generation of carbodiphosphanes (CDPs) is introduced as the most powerful class of non-ionic carbon superbases on the basicity scale to date.
- Kögel, J. F.; Margetić, D.; Xie, X.; Finger, L. H.; Sundermeyer, J. A Phosphorus Bisylide: Exploring a New Class of Superbases with Two Interacting Carbon Atoms as Basicity Centers. *Angew. Chem. Int. Ed.* **2017**, *56*, 3090–3093.<sup>2</sup> The first bisylide superbase exhibiting two interacting carbon-based basicity centers is prepared and investigated.
- Saame, J.; Rodima, T.; Tshepelevitch, S.; Kütt, A.; Kaljurand, I.; Haljasorg, T.; Koppel, I. A.; Leito, I. Experimental Basicities of Superbasic Phosphonium Ylides and Phosphazenes. *J. Org. Chem.* **2016**, *81*, 7349–7361.<sup>3</sup> Self-consistent solution (THF) basicity values for a number of superbases are presented.
- Vazdar, K.; Kunetskiy, R.; Saame, J.; Kaupmees, K.; Leito, I.; Jahn, U. Very Strong Organosuperbases Formed by Combining Imidazole and Guanidine Bases: Synthesis, Structure, and Basicity. *Angew. Chem. Int. Ed.* **2014**, *53*, 1435–1438.<sup>4</sup> Phosphorous free organic superbases with pK<sub>aH</sub> up to 29.3 in THF were synthesized.

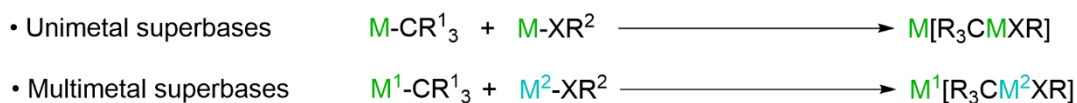
## Introduction

For a long time, the term superbase was restricted to metalorganic species forming weakly solvated and coordinated, sometimes “naked” anions of highest basicity in solution (Figure 1A). This important tool in organic synthesis was reviewed within two subgroups: unimetal superbases in which two organic anions are bound to a single metal ion<sup>5</sup> and multimetal superbases with two different metal centers, both having enhanced thermodynamic and kinetic basicity compared to the strongest single component.<sup>6</sup> Since the discovery of highly basic neutral organic compounds like 1,8-bis(dimethylamino)naphthalene (DMAN) (Figure 1B),<sup>7</sup> much effort was invested in designing organosuperbases with basicities comparable to inorganic or metalorganic bases.<sup>8,9</sup> The threshold of superbasicity was defined in the gas phase (DMAN, GB = 237.8 kcal mol<sup>-1</sup>; bases with higher GB values are called superbases). However, there is no universally accepted definition of superbase in solution. Hereon, we put forward such definitions for acetonitrile (pK<sub>aH</sub> ≥ 25) and THF (pK<sub>aH</sub> ≥ 17) based on 1,8-bis(tetramethylguanidino)naphthalene (TMGN).

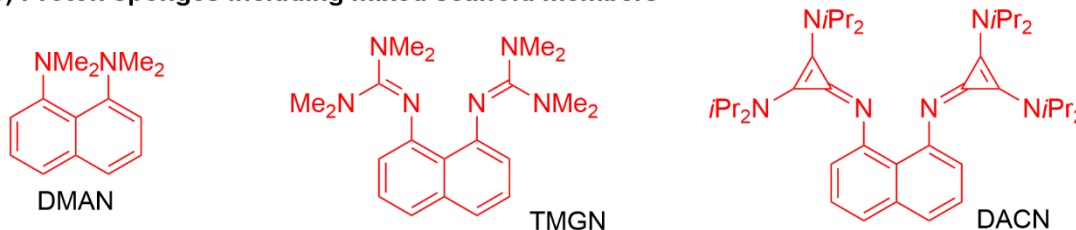
With the rise of Schwesinger's phosphazene bases (Figure 1C),<sup>10</sup> it became apparent that a homologation approach to increase basicity is rewarding, which was subsequently also established in examples of amidines and guanidines (Figure 1D).<sup>11,12</sup> Among all presented

bases Verkade's phosphatranes are unique due to the basicity center residing on phosphorus atom (Figure 1E).<sup>9,13</sup> The syntheses of these bases and applications were thoroughly reviewed in the past.<sup>8,9,14</sup> However, the increase of basicity by homologation results in impractical increase in molecular weight and complexity. To overcome these problems new approaches for creating superbasic compounds must be implemented.

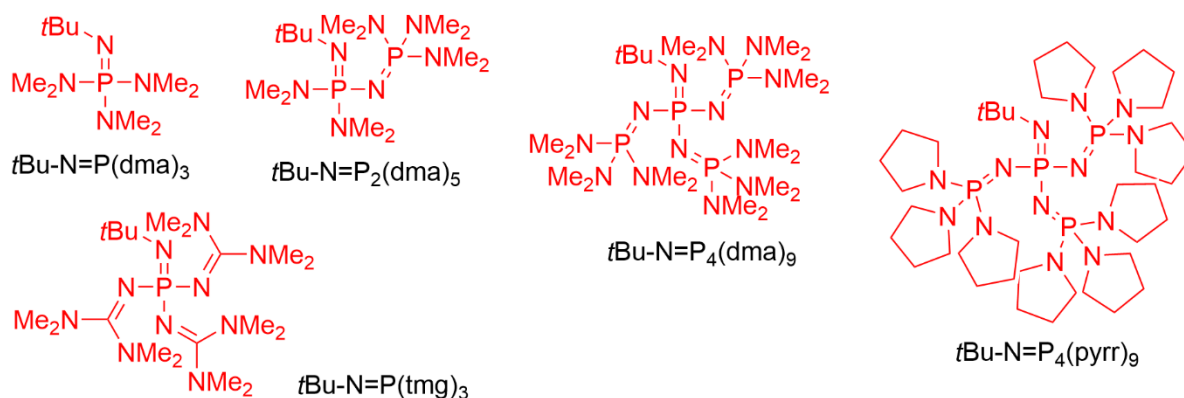
#### A) Classical metalorganic superbases



#### B) Proton sponges including mixed scaffold members



#### C) Phosphazene superbases illustrating homologation and guanidino phosphazenes



#### D) Amidine and guanidine superbases illustrating the homologation principle



#### E) Phosphatrane superbases

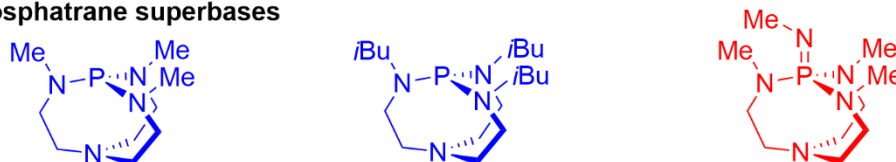


Figure 1. Historically important superbase classes with nitrogen (red) and phosphorous basicity centers (blue).

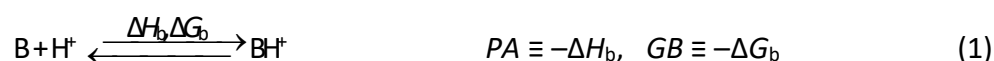
In this Account, we give an overview on novel organosuperbasic molecules since 2010. We outline general approaches to basicity determination, the synergy of theoretical and

experimental investigations, emerging design principles for new organosuperbase scaffolds and synthetic approaches to them, concentrating mostly on results from our own groups but also highlighting important results from others. We briefly summarize significant applications of organosuperbases.

## Basicity determination of organosuperbases

According to the Brønsted-Lowry definition, bases are substances that can accept a proton. Brønsted basicity can be distinguished into gas and solution phase basicity. Although the latter is more important for practical applications, i.e. in organic synthesis, gas phase basicity provides information about the intrinsic properties of bases.

**Gas phase basicity:** Proton affinity (PA) and gas-phase basicity (GB) are quantities describing the intrinsic ability of a molecule to accept a proton. Proton affinity is defined as the negative value of enthalpy change at standard condition (i.e., temperature and pressure) for gas phase reaction:



whereas gas phase basicity is the negative free energy value associated with this reaction (eq. 1).

GB values are typically measured via equilibrium constant  $K$  of proton transfer between two bases  $B_1$  and  $B_2$  according to eq. 2:



Obtaining the  $GB$  from  $\Delta GB$  is straightforward if the  $GB$  of one of the bases (reference base) is known.  $PA$  is usually obtained from  $GB$  by adding the entropy term estimated separately (eq. 3):

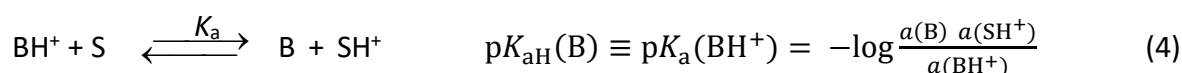
$$PA = GB + T\Delta S \quad (3)$$

The measurement is typically carried out using a mass spectrometer that enables monitoring proton transfer in the gas phase, usually high-pressure mass spectrometry or FT-ICR.<sup>15</sup> The ratio of partial pressures of the neutrals is measured either using a pressure gauge or zero-reaction time mass spectra of the mixture of gaseous bases in the MS vacuum system. The ratio of the amounts of ions in gas phase is approximated by the ratio of their signals in the mass spectrum recorded after a sufficiently long reaction for equilibrium establishment. Different corrections are applied for ionization cross section and isotopic composition.<sup>15</sup>

**Computation of gas phase basicity:** Computational *ab initio* and Density Functional Theory (DFT) approaches can provide reliable values for PA and GB, which are sometimes difficult to determine experimentally. The accuracy of the calculated PA and GB values depends on the applied level of theory. Accurate results are obtained by *ab initio* approaches based on the Coupled Cluster theory – CCSD(T) method, combined with a very large basis sets.<sup>16</sup> Even

better accuracy in calculation of thermochemical data with deviation of only 0.25 kcal mol<sup>-1</sup> from the experimental values can be achieved using the Weizmann-*n ab initio* composite methods (*Wn*, *n* = 1–4).<sup>17</sup> However, both CC and *Wn* methods are computationally extremely expensive and only applicable to small molecules. Organic superbases are usually molecules consisting of *tens to hundreds of atoms*; therefore, accuracy must be sacrificed in calculation of their PA and GB values to make calculations feasible and to reduce computational cost. DFT methods nowadays offer a good compromise between computational accuracy and efficiency and are routinely utilized in calculations of PA and GB values. Bachrach<sup>18</sup> tested three most popular DFT functionals, B3LYP, WB97XD, and M062X employing the 6-311+G(2d,p) basis set, against experimental data for proton affinity of 44 nitrogen bases. The overall performance of all three DFT functionals was reasonably good with absolute mean difference from experiment of 1.10, 1.22 and 3.29 kcal mol<sup>-1</sup>, respectively. The calculated GB data presented here were obtained utilizing one of these functionals in combination with Pople's triple zeta basis sets (Table 1).

**Basicity in solution:** The basicity of base B in solvent S is expressed as p*K*<sub>a</sub> of its conjugate acid BH<sup>+</sup>, termed as p*K*<sub>aH</sub><sup>19</sup> of B (often also as p*K*<sub>BH+</sub>) and is defined according to the following general (simplified and expressing free-ion basicity) equation:

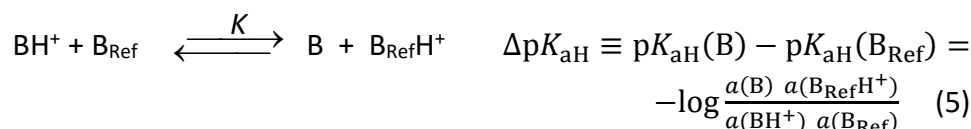


In contrast to gas-phase basicity, basicity in solution is not an intrinsic property of the base but a joint property of base and solvent.<sup>20</sup> Several solvent properties – acidity, basicity, solvation ability (including HB donor and acceptor properties), dielectric permittivity influence the behavior of a base in solvent. Acidity and basicity jointly define the solvent's autoprotolysis constant (p*K*<sub>auto</sub>), the window in which p*K*<sub>aH</sub> values are experimentally accessible in that solvent. The lower they are, the wider is the accessible p*K*<sub>aH</sub> window. In addition, solvent acidity defines the highest p*K*<sub>aH</sub> value that is experimentally accessible in a solvent. Solvent basicity, together with the ability to solvate ions define the offset (zero point) of p*K*<sub>aH</sub> values and the differentiating ability (i.e., how large are p*K*<sub>aH</sub> differences between bases) of the solvent. Dielectric permittivity, together with the solvent's ability to solvate ions, contribute to the differentiating ability and determine whether free-ion or ion-pair equilibria are predominately observed.

For experimental studies of superbases the preferred solvent would enable measurements of high p*K*<sub>aH</sub> values in the widest possible p*K*<sub>aH</sub> range and preferably free ion basicities. A suitable solvent should have therefore most importantly as low as possible acidity as well as high dielectric permittivity. On the practical side, the solvent should be reasonably widely used, available in high purity and stable under strongly basic conditions. Currently acetonitrile (MeCN) and tetrahydrofuran (THF) are widely used,<sup>3,19,21</sup> occasionally also dimethylsulfoxide (DMSO)<sup>22</sup> (DMSO is less widespread because of its long UV cutoff wavelength, less convenient purification and consequently, limited number of reference basicity values available). In acetonitrile free-ion basicities are observed but, because of its limited stability at high basicities, the upper p*K*<sub>aH</sub> limit is around 33, corresponding roughly to phosphazene *t*-Bu-N=P<sub>2</sub>(dma)<sub>5</sub> (Figure 1C, Table 1).<sup>19</sup> THF is not decomposed by strong bases and more than 10 orders of magnitude of p*K*<sub>aH</sub> values are measurable beyond *t*-Bu-N=P<sub>2</sub>(dma)<sub>5</sub>.<sup>3</sup> The downside of THF is its lower permittivity, so that ions exist in it mostly in ion pairs. Thus, neither of these

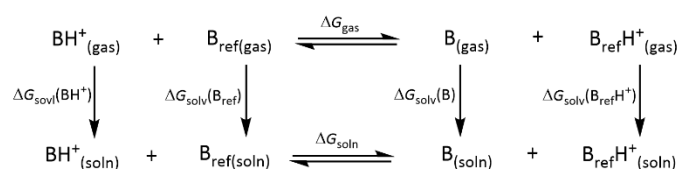
solvents is ideal. However, because of the good correlation between basicities in these solvents,<sup>3,19</sup>  $pK_{aH}$  values measured in one solvent can quite reliably be recalculated into the other and together they form a good set of solvents for  $pK_{aH}$  measurements of superbases.

**Basicity measurements in solution:** For equilibrium basicity measurements of superbases in solution UV-Vis spectrophotometry<sup>3,19</sup> and NMR spectroscopy<sup>23,24</sup> are mostly used. As in gas phase, the measurements are usually relative, i.e. the basicity difference between the investigated base B and a reference base  $B_{Ref}$  with known  $pK_{aH}$  value, both dissolved in the same solution, is determined. The relative basicity expressed as  $\Delta pK_{aH}$  value, is defined as follows:



In practice, ratios of activities  $a$  of the species are usually approximated by ratios of equilibrium concentrations, measured using the respective spectrometric techniques. In case of THF activities of cations are in fact activities of ion pairs with an inert counteranion<sup>3</sup> and basicities are either expressed as “ion-pair  $pK_a$  values” or corrected for ion pairing to obtain ionic  $pK_{aH}$  values (sometimes termed as  $pK_\alpha$  values) (Table 1).<sup>3</sup>

**Basicity computations in solution:** Computations of  $pK_a$  values enable predicting solution basicity of unknown compounds or compounds that are difficult to measure. Although gas phase basicity correlates to some extent with  $pK_a$  values, such correlations cannot be used to obtain reliable data. Assuming the relationship between Gibbs energy of dissociation and  $pK_a$  ( $pK_a = \Delta G_{diss}/2.303RT$ ), it is evident that the calculation of accurate  $pK_a$  values is very demanding, as a 1.36 kcal mol<sup>-1</sup> computation error results in an error of 1  $pK_a$  unit. There are various protocols for  $pK_a$  calculations; the most commonly used is based on the thermodynamic cycle presented in Scheme 1.



Scheme 1. Thermodynamic cycle used for  $pK_a$  computation.

In this cycle, acid species  $BH^+$  (conjugate acid of base B) donates a proton to reference base  $B_{ref}$  to yield base B and conjugate acid of reference base  $B_{ref}H^+$ .  $\Delta G_{gas}$ ,  $\Delta G_{soln}$ , and  $\Delta G_{solv}$  are Gibbs energy of deprotonation in gas phase, solution, and free energy of solvation. Therefore,  $pK_a$  may be calculated using the following equation:

$$pK_a(BH^+) = \frac{\Delta G_{soln}}{2.303RT} + pK_a(B_{ref}H^+)$$

The main advantage of this thermodynamic cycle protocol for  $pK_a$  calculation lays in cancellation of errors in calculated free energy of solvation, which is commonly computed utilizing polarized continuum models. Moreover, this approach provides  $pK_a$  values of  $BH^+$

relative to reference acid  $BH_{ref}^+$ . Therefore, calculated  $pK_a$  values are anchored in the experimental basicity scale, which also increases the accuracy of computed  $pK_a$  data. Using this approach, a slope of  $1/2.303RT$  in linear relationship between calculated  $\Delta G_{diss}$  and  $pK_a$  is assumed. However, several studies reported slopes that are significantly lower than theoretically expected.<sup>25</sup> To avoid this issue, a method modification could be made by correlating larger numbers of experimentally determined  $pK_a$  values with calculated  $\Delta G_{diss}$  for similar types of compounds. Using this approach and utilizing isodensity polarized continuum model for calculation of  $\Delta G_{solv}$  to avoid the arbitrary choice of atomic radii in defining solute cavity, we have calculated  $pK_a$  values of many nitrogen bases in acetonitrile with RMSE values down to 0.3  $pK_a$  units.<sup>12,26</sup> Unfortunately, the correlation obtained for nitrogen bases is not applicable for phosphorus or carbon bases. Therefore, for  $pK_a$  calculation of carbodiphosphorane and phosphane superbases (Figure 2), the thermodynamic cycle was used in combination with CPCM and SMD solvation model and proper selection of reference base that belongs to the same family of studied compounds. The calculated  $pK_a$  values were in good agreement with experimental ones (Table 1) since the maximum absolute error does not exceed 2  $pK_a$  units.

Table 1. Basicities of selected superbases in gas phase, acetonitrile (MeCN) and tetrahydrofuran (THF).<sup>a</sup>

Base <sup>b</sup>	GB (kcal mol <sup>-1</sup> )	$pK_{aH}(\text{MeCN})$	$pK_{aH}(\text{THF})$
<i>Proton sponges</i>			
DMAN <sup>c</sup>	[237.8 <sup>14</sup> ]	18.63 <sup>19</sup>	[11.1 <sup>27</sup> ]
TMGN <sup>c</sup>	256.3 <sup>15</sup>	24.92 <sup>15</sup> , 25.1 <sup>28</sup> , [25.4 <sup>26</sup> ]	16.8 <sup>11</sup>
HMPN <sup>d</sup>	268.8 <sup>15</sup> , [270.1 <sup>15</sup> ]	29.89 <sup>19</sup>	21.9 <sup>15</sup>
TPPN <sup>d</sup>	[274.7] <sup>e</sup>	32.3 <sup>29</sup> , [33.0 <sup>29</sup> ]	
P2-TPPN <sup>d</sup>	[290.1] <sup>e</sup>	42.1 <sup>29</sup> , [40.2 <sup>29</sup> ]	
DACN <sup>c</sup>	[274.6] <sup>e</sup>	[27.0 <sup>30</sup> ]	
<i>Phosphazenes</i>			
<i>t</i> Bu-N=P <sub>4</sub> (dma) <sub>9</sub> <sup>c</sup>	[289.6 <sup>24</sup> ]	42.7 <sup>3</sup> , [41.5 <sup>24</sup> ]	33.9 <sup>3</sup> , [34.5 <sup>24</sup> ]
<i>t</i> Bu-N=P <sub>4</sub> (pyrr) <sub>9</sub> <sup>c</sup>	[295.6 <sup>24</sup> ]	44.0 <sup>3</sup> , [42.8 <sup>24</sup> ]	35.3 <sup>3</sup> , [36.3 <sup>24</sup> ]
<i>t</i> Bu-N=P <sub>2</sub> (dma) <sub>5</sub> <sup>c</sup>	268.8 <sup>15</sup> , [266.6 <sup>15</sup> ]	33.09 <sup>19</sup>	25.0 <sup>3</sup>
<i>t</i> Bu-N=P(dma) <sub>3</sub> <sup>c</sup>	252.9 <sup>15</sup> , [252.1 <sup>11</sup> , 252.0 <sup>31</sup> ]	26.98 <sup>19</sup>	18.9 <sup>32</sup>
<i>t</i> Bu-N=P(tmg) <sub>3</sub> <sup>c</sup>	273.6 <sup>15</sup> , [279.0 <sup>15</sup> ]	37.3 <sup>3</sup>	29.1 <sup>3</sup>
TDMPP <sup>d</sup>	[276.6] <sup>33</sup>	30.4 <sup>33</sup> , [30.6] <sup>33</sup>	22.4 <sup>33</sup> , [21.6] <sup>33</sup>
<i>Amidines and guanidines</i>			
DBU <sup>c</sup>	242.7 <sup>34</sup> , [244.6 <sup>14</sup> ]	24.31 <sup>19</sup> , [24.1 <sup>35</sup> ]	16.9 <sup>11</sup>
MTBD <sup>c</sup>	246.2 <sup>15</sup> , [248.0 <sup>14,15</sup> ]	25.47 <sup>19</sup> , [25.8 <sup>35</sup> ]	18.6 <sup>11</sup>
Me( <i>i</i> -Pr) <sub>4</sub> BIG <sup>d</sup>	[276.6 <sup>4</sup> ]		29.3 <sup>4</sup>
<i>Cyclopropenimines</i>			
<i>t</i> -Bu-CPI( <i>i</i> Pr) <sup>d</sup>	[262.4 <sup>36</sup> ]	26.9 <sup>37</sup> , [29.0 <sup>36</sup> ]	
GC2 <sup>d</sup>		35.6 <sup>23</sup>	27.7 <sup>23</sup>
<i>Phosphanes</i>			
P(N(Me)CH <sub>2</sub> CH <sub>2</sub> ) <sub>3</sub> N <sup>c</sup>	259.1 <sup>15</sup> , [255.0 <sup>15</sup> ]	32.9 <sup>38</sup>	24.1 <sup>3</sup>

P(N( <i>i</i> Bu)CH <sub>2</sub> CH <sub>2</sub> ) <sub>3</sub> N <sup>c</sup>	260.8 <sup>15</sup>	33.5 <sup>38</sup>	
P(N <i>i</i> Pr) <sub>3</sub> <sup>d</sup>	[288.0 <sup>39</sup> , 288.0 <sup>24</sup> ]	38.8 <sup>39</sup> , [40.3 <sup>39</sup> ]	31.0 <sup>39</sup> , [33.8 <sup>39</sup> , 31.4 <sup>24</sup> ]
P(N <i>i</i> Pr) <sub>2</sub> <i>i</i> Pr <sup>d</sup>	[276.2 <sup>39</sup> ]	[33.5 <sup>39</sup> ]	[26.9 <sup>39</sup> ]
[(dma) <sub>3</sub> P=N-] <sub>3</sub> P <sup>d</sup>	[291.3 <sup>24</sup> ]	[41.7 <sup>24</sup> ]	34.9 <sup>24</sup> , [34.9 <sup>24</sup> ]
[(pyrr) <sub>3</sub> P=N-] <sub>3</sub> P <sup>d</sup>	[300.2 <sup>24</sup> ]	[43.8 <sup>24</sup> ]	36.7 <sup>24</sup> , [37.8 <sup>24</sup> ]
[(dma) <sub>3</sub> P=N-] <sub>2</sub> [(dma) <sub>5</sub> P=N-]P <sup>d</sup>	[295.4 <sup>24</sup> ]	[43.8 <sup>24</sup> ]	37.2 <sup>24</sup> , [37.0 <sup>24</sup> ]
<i>Phosphorus ylides</i>			
Me <sub>2</sub> C=P(dma) <sub>3</sub> <sup>d</sup>		[37.7 <sup>3</sup> ]	[29.6 <sup>3</sup> ]
H <sub>2</sub> C=P(2,4,6-(MeO) <sub>3</sub> C <sub>6</sub> H <sub>2</sub> ) <sub>2</sub> Ph <sup>d</sup>		[42.1 <sup>3</sup> ]	[33.5 <sup>3</sup> ]
MHPN <sup>d</sup>		[33.3 <sup>2</sup> ]	
<i>Carbodiphosphoranes</i>			
C[=P(pyrr) <sub>3</sub> ] <sub>2</sub> <sup>d</sup>	[282.2 <sup>1</sup> ]		30.1-32.9 <sup>1</sup> , [32.8 <sup>1</sup> ]
C[=P(dma) <sub>2</sub> (tmg)] <sub>2</sub> <sup>d</sup>	[287.2 <sup>1</sup> ]		34.8-36.8 <sup>1</sup> , [34.9 <sup>1</sup> ]

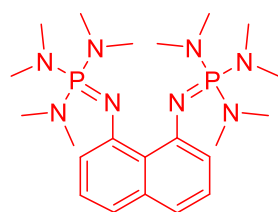
<sup>a</sup> Computational values in square brackets, experimental values without brackets. pK<sub>aH</sub> values refer to the free ion pK<sub>a</sub> of the protonated base. <sup>b</sup> pyrr = 1-pyrrolidino; dma = *N,N*-dimethylamino; Ni*i*Pr = 1,3-diisopropyl-4,5-dimethylimidazolin-2-ylidenamino. <sup>c</sup> Structure in Figure 1. <sup>d</sup> Structure in Figure 2. <sup>e</sup> New data (obtained by B3LYP/6-311+G(2df,p)//B3LYP/6-31G(d) method).

## General strategies of molecular design for superbases

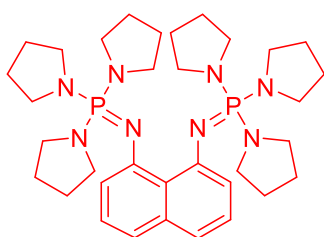
Current superbase design focuses on enhancing the proton affinity of a basicity center, either an extremely electron-rich nitrogen, phosphorus or carbon atom (Figure 2). In the following we discuss design elements enhancing thermodynamic basicity typically measured under equilibrium conditions and design elements influencing kinetic basicity i.e., the rate of proton self-exchange of a superbase and its protonated form. The combination of high thermodynamic and kinetic basicity should be of significant interest for application of superbases, but more work is needed to fully assess this aspect. Evaluating the self-exchange as standard protocol<sup>28</sup> is useful as the rate of proton transfer depends on steric accessibility of both, the base center and of the particular substrate to be deprotonated. Similar arguments are valid for evaluating nucleophilicity versus basicity of a base. The selectivity depends on sterics of the nucleophile and electrophile. As the proton is the smallest and hardest electrophile to be transferred, even despite of a bulky environment, base selectivity typically increases with increasing steric demand of the basicity center.



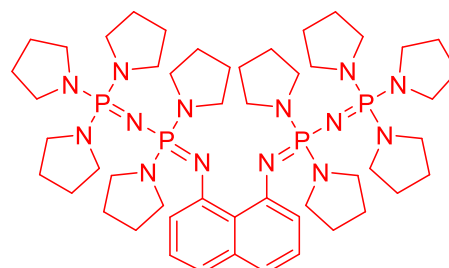
**A) Proton sponges merged with phosphazene units**



HMPN

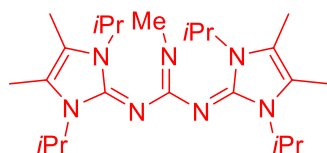


TPPN

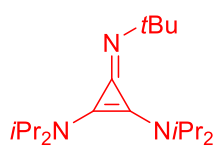


P2-TPPN

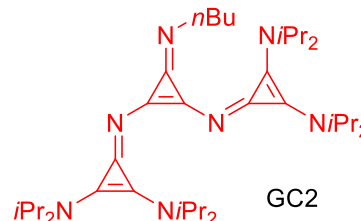
**B) Guanidines and „cyclopropenylogous“ guanidines**



Me(*i*Pr)<sub>4</sub>BIG

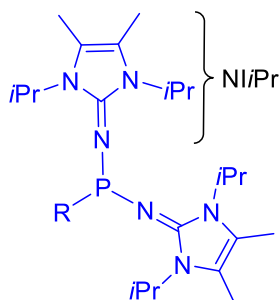


*t*-Bu-CPI(*i*Pr)



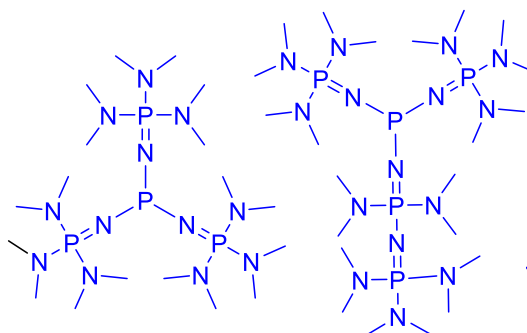
GC2

**C) Phosphane superbases**



R=N/*i*Pr, Ni/*i*Pr

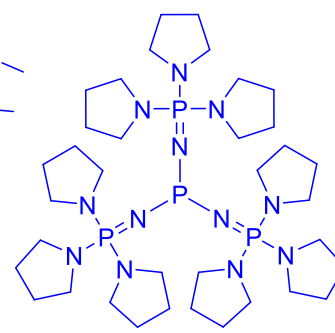
IAP bases



[(dma)<sub>3</sub>P=N-]<sub>3</sub>P

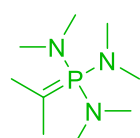
[(dma)<sub>3</sub>P=N-]<sub>2</sub>[(dma)<sub>5</sub>P=N-]P

PAP bases

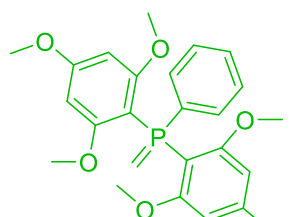


[(pyrr)<sub>3</sub>P=N-]<sub>3</sub>P

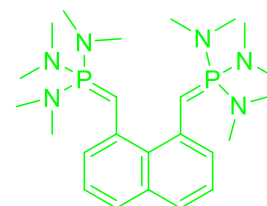
**D) Phosphorus ylide superbases**



Me<sub>2</sub>C=P(dma)<sub>3</sub>

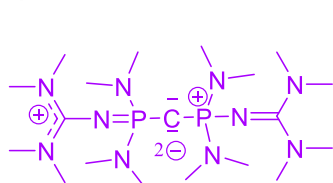


H<sub>2</sub>C=P(2,4,6-(MeO)<sub>3</sub>C<sub>6</sub>H<sub>2</sub>)<sub>2</sub>Ph

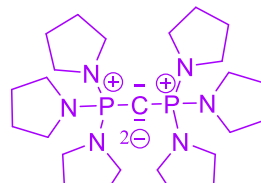


phosphorous bisylide  
MHPN

**E) Carbodiphosphorane superbases**

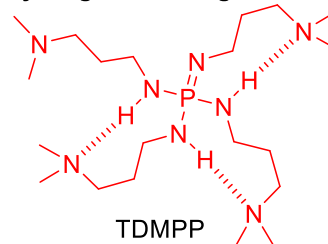


C[=P(pyrr)<sub>3</sub>]<sub>2</sub>  
CDP-TMG



C[=P(dma)<sub>2</sub>(tmg)]<sub>2</sub>  
CDP-PYR

**F) Superbase with cooperative hydrogen bonding effect**

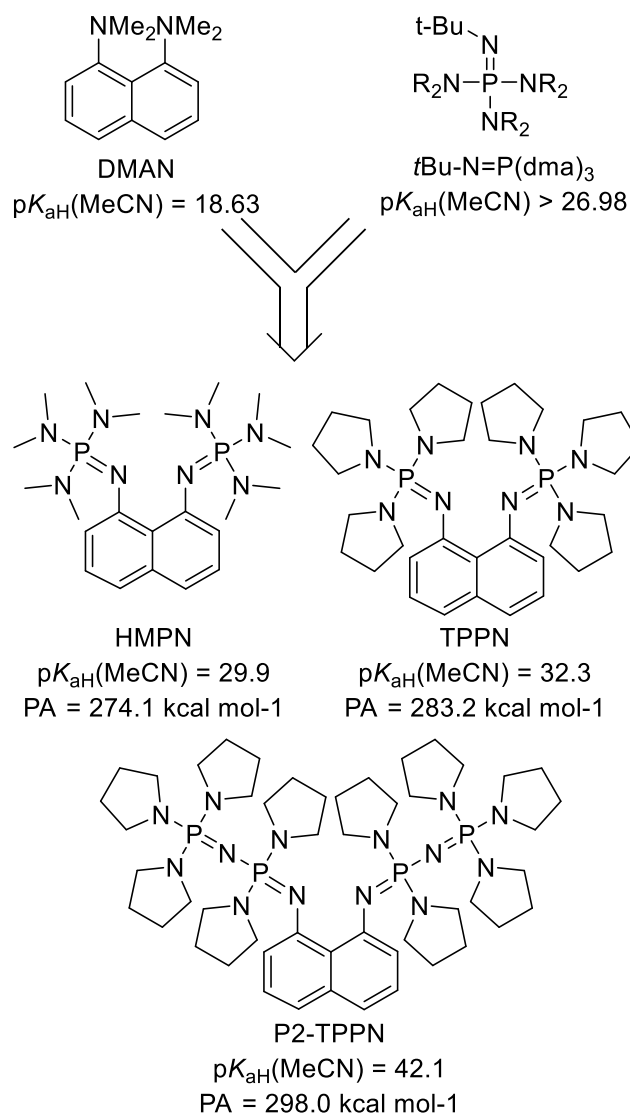


TDMPP

Figure 2. Emerging superbase classes with nitrogen basicity center (red), phosphorous basicity center (blue), and carbon basicity centers (green and purple).

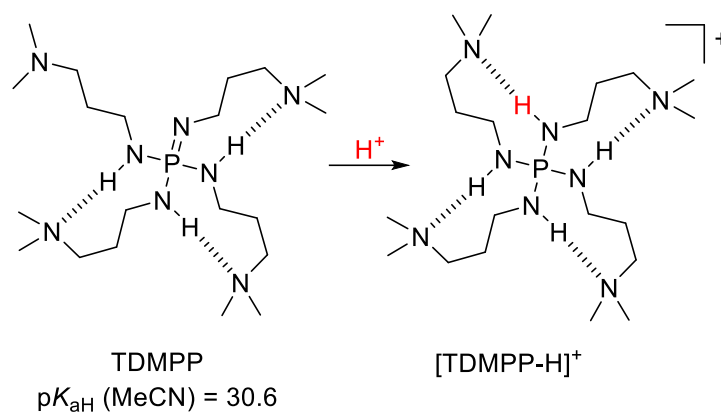
### Nitrogen-centered superbasic phosphazenes (Figure 2A)

Schwesinger's phosphazenes are probably the most established and commercially available class of N-superbases (Figure 1).<sup>10,22,40</sup> The reason for intrinsically high N-basicity of a tris-amino-iminophosphorane is the zwitterionic character of highly polar  $(R_2N)_3P-NR'$  bond. While the anionic charge of the imine functionality is stabilized by  $\pi$ -conjugation to a carbenium center with  $\pi$ -acceptor character in guanidines and other second-row bases, the anionic charge of an iminophosphorane is much less efficiently stabilized by negative hyperconjugation, precisely by LUMO or empty  $\sigma^*$  or  $\pi^*$  orbitals of the phosphonium ion, respectively. Schwesinger discovered the principle of dramatic basicity increase by homologation or higher-order strategy. By stabilizing positive charge of the phosphonium ion attached to the basicity center, e.g. by substituting amino  $-NR_2$  substituents by better donating N-phosphazanyl groups  $-N=P(NR_2)_3$ , more electron density remains at the sterically shielded  $^tBuN$ -basicity center of oligophosphazenes  $^tBuN=P(NR_2)_{3-x}(N=P(NR_2)_3)_x$ . A similar effect has been described for trisguanidinophosphazene superbases (Figure 1).<sup>11</sup> This makes phosphazanyl units ideally suited for coupling with other basicity centers. Merging two phosphazanyl or two bisphosphazanyl groups on 1,8-positions of the rigid naphthalene backbone of DMAN, the entropic proton chelation effect adds to the intrinsic thermodynamic phosphazene basicity and creates new generations of hybrid phosphazene proton sponges HMPN, TPPN, and P<sub>2</sub>-TPPN (Scheme 2).<sup>29,41-43</sup>



Scheme 2. Phosphazene-based proton sponges.

Another design element enhancing superbasicity of a low-molecular weight monophosphazene base consists in multiple intramolecular hydrogen bond (IHB)<sup>44,45</sup> network in the superbase  $\text{N,N',N'',N'''}\text{-tetrakis(3-(dimethylamino)propyl) triaminophosphazene}$  (TDMPP) (Scheme 3). Not only one very strong IHB as observed in highly rigid proton sponges, but the cooperative (“corona”) effect<sup>46</sup> of a multiple IHB network gives rise to considerable basicity enhancement during formation of symmetrical  $[\text{TDMPP-H}]\text{BPh}_4$ .<sup>33</sup>



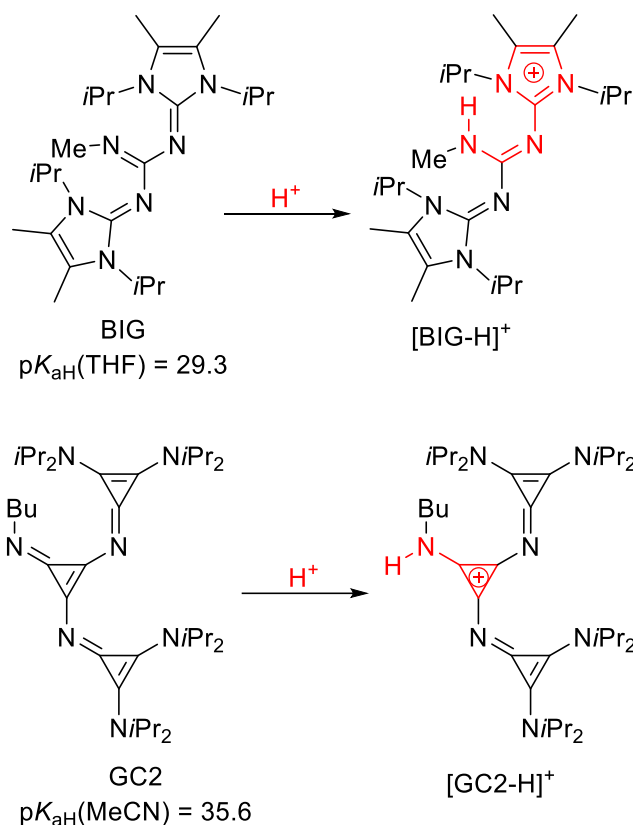
Scheme 3. Cooperative effect of multiple hydrogen bonds in TDMPP base.

### Guanidine superbases (Figure 2B)

TMGN ( $pK_{\text{aH}} = 25.0$ , MeCN, Figure 1) was the first superbasic proton sponge of low molecular weight, cheap and easy to synthesize, crystalline, air stable and kinetically more active than DMAN.<sup>26,28</sup> It combines an enthalpic add-on of several orders of magnitude intrinsically higher thermodynamic basicity of pentaorganoguanidine functionalities (pentamethylguanidine  $pK_{\text{aH}} = 25.0$ , MeCN) or planar amidine DBU ( $pK_{\text{aH}} = 24.3$ , MeCN) with the entropically favorable proton pincer design elements of DMAN (Figure 1).

Cyclic constraints also influence basicity: in MTBD the bicyclic ring system with planar guanidine functionality forces two tertiary amino groups into conjugation with the *N*-alkylimino basicity center. Consequently, the basicity of MTBD is higher ( $pK_{\text{aH}} = 25.4$ , MeCN) compared to DBU with only one tertiary amine group in conjugation with the *N*-alkylimino basicity center. However, the champions of basicity in amidine class are obtained by forcing even more nitrogen atoms into conjugation with the *N*-alkylimino functionality, an impressive example being Schwesinger's vinamidine (VA,  $pK_{\text{aH}} = 31.9$ , MeCN, Figure 1).<sup>47</sup>

An effective strategy for enhancing the  $\pi$ -donor strength or +M character of a  $sp^2$ -nitrogen substituent is to incorporate the imine carbon atom as carbenium atom into a cyclic aromatic ring system, intrinsically required to achieve  $2\pi$  or  $6\pi$  Hückel aromaticity.<sup>48,49</sup> This polarizes the exocyclic imine  $\text{C}=\text{N}$  functional group into a zwitterionic  $\text{C}^{(+)}\text{-N}^{(-)}$  bonding situation, thus enhancing the N-donor character. Typical examples following this idea are higher-order tris(cyclopropeneimino)guanidine,<sup>23</sup> the cyclopropeneimino proton sponge DACN<sup>30,50</sup> and the bis-*N,N'*-(1,3-dialkyl-4,5-dimethyl-1H-imidazol-2(3H)-ylidene)guanidine bases (BIG bases) (Scheme 4).<sup>4,51</sup>



Scheme 4. Aromatization-driven superbasicity of cyclic imines.

### Phosphorus-centered superbases – tris(imino)phosphanes and phosphazeny phosphanes (Figure 2C)

Verkade's proazaphosphatrane 2,8,9-trimethyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane was the first organic superbase involving a P(III) basicity center (*cf.* Figure 1).<sup>38,52</sup> The basicity of Verkade's bases is comparable to those of Schwesinger-type P<sub>2</sub>-phosphazene bases <sup>t</sup>BuN=P(NR<sub>2</sub>)<sub>2</sub>(N=P(NR<sub>2</sub>)<sub>3</sub>). The approach used by Verkade is stabilization of the forming phosphonium group P-H<sup>+</sup> via a transannular N→P-H<sup>+</sup> dative bond of an intramolecular N-donor at appropriate tripodal P-chelation position. But why should a single entropically favored intramolecular dative bond guarantee better stabilization to a phosphonium center than one, two or even three σ bonds of much stronger donor substituents, e.g. -N=P(NR<sub>2</sub>)<sub>3</sub> compared to -NRR' in Verkade's base?

Based on previous theoretical investigation<sup>53</sup> we demonstrated recently that Schwesinger's phosphazene N-superbases are in fact less basic than corresponding phosphazeny phosphanes (PAP) having the same number of phosphorus atoms and P substituent pattern (Figure 3). The message is that formal reductive elimination of a nitrene [<sup>t</sup>BuN] from a Schwesinger N-base <sup>t</sup>BuN=P<sup>V</sup>(NR<sub>2</sub>)<sub>3-x</sub>(N=P(NR<sub>2</sub>)<sub>3</sub>)<sub>x</sub> gives an even more electron rich, more extreme P-base P<sup>III</sup>(NR<sub>2</sub>)<sub>3-x</sub>(N=P(NR<sub>2</sub>)<sub>3</sub>)<sub>x</sub>.<sup>24</sup>

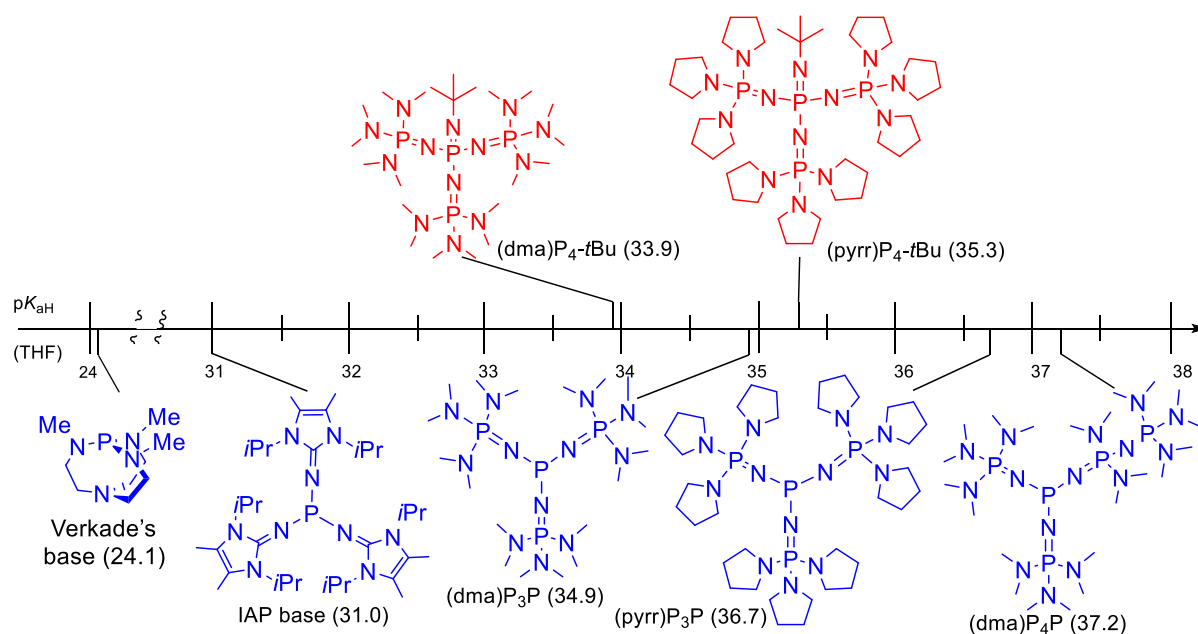


Figure 3. Basicity comparison of superbases with phosphorus basicity centers.

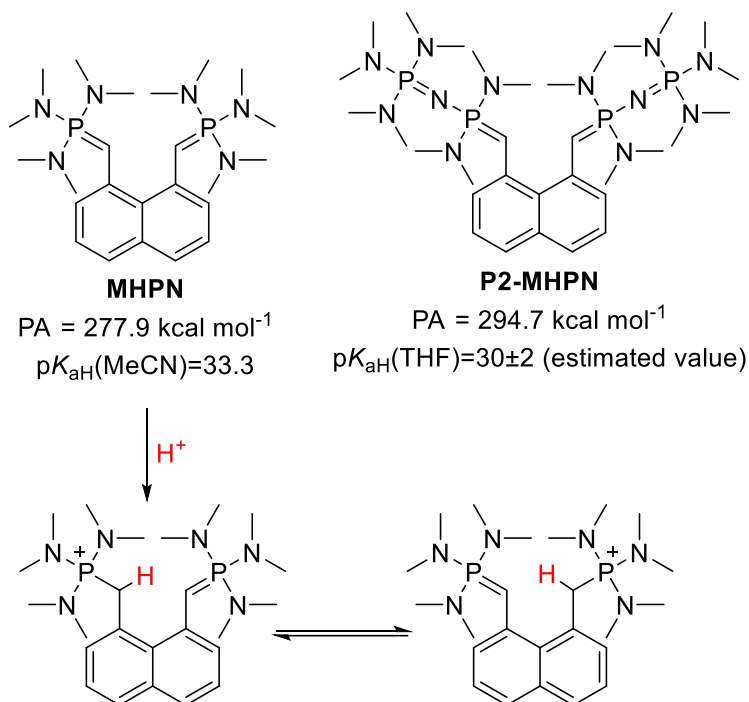
PAPs can also act as nucleophiles or extremely strong  $\sigma$  donor ligands, which is useful in transition metal chemistry and catalysis. Simple, easily synthesized mono-phosphazanyl phosphanes of low molecular weight such as  $P^{III}(NR_2)_2(N=P(NR_2)_3)$ ,  $P^{III}(tBu)_2(N=P(NR_2)_3)$  or  $P^{III}(NR_2)_2(N=P^tBu_3)$  display not only basicities comparable or higher than the corresponding Schwesinger bases but a donor strength, measured as Tolman electronic parameter (TEP)<sup>54</sup> towards transition metal centers comparable with N-heterocyclic carbenes and Verkade's base.<sup>55,56</sup> The aspect of designing extremely strong P-donor ligands instead of extremely strong P-bases is predominantly applied in related tris(imidazol-2-ylidenamino)phosphanes (IAP) in the Dielmann group<sup>57</sup> and in P-ylidyl-substituted phosphanes (YPhos) in the Gessner group.<sup>58</sup> A review on electron abundant phosphines and phosphazenes as superbases was published very recently highlighting the attractiveness of the topic.<sup>59</sup>

### Carbon-centered superbases - phosphorus ylides and carbodiphosphoranes (Figure 2D,E)

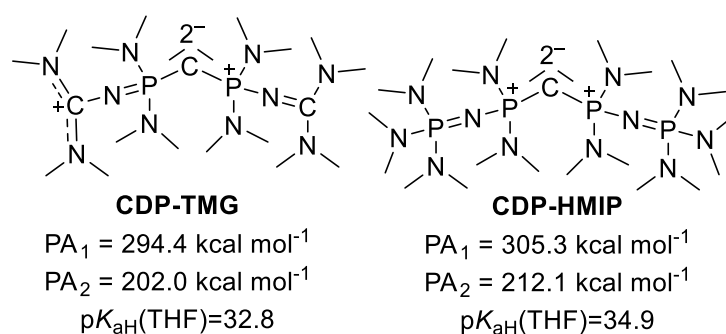
Whereas simple P-ylides display moderate basicity,<sup>3</sup> those carrying P-NR<sub>2</sub> substituents are known to be even more basic than the corresponding aminophosphazenes.<sup>31</sup> The reason is again inefficient stabilization of the negative ylidic charge by negative hyperconjugation (but not conjugation) of the aminophosphonium group. This insight was used to prepare the first proton sponge with two chelating aminophosphonium ylide functionalities, MHPN and its higher homologue P<sub>2</sub>-MHPN.<sup>2</sup> In contrast to classical proton sponges with their characteristic intramolecular [N-H...N] hydrogen bond interaction, no such static [C-H...C] bridges are observed in MHPN, instead fast proton transfer between ylidic centers and as a consequence delocalization of positive charge is responsible for the extra basicity in the gas phase and solution (Scheme 5A). The strongest non-ionic, metal-free carbon bases are double ylides with carbodiphosphorane (CDP) backbone and pyrrolidinyl, tetramethylguanidino and phosphazanyl substituents at both phosphonium centers, e.g. CDP-PYR and higher-order derivatives CDP-TMG and CDP-HMIP (Scheme 5B).<sup>1</sup> Here,  $\pi$ -conjugation also does not contribute to basicity enhancement, only less effective negative hyperconjugation in the bent bisylidic backbone is present. In turn, superbasicity originates from the two electron pairs

mainly located at the central carbon atom of formal charge  $C^{2-}$ , the HOMO of highest PA and HOMO-1 of much lower second PA.

### A) Phosphorus bisylides and their monoprotonation



### B) Carbodiphosphorane superbases

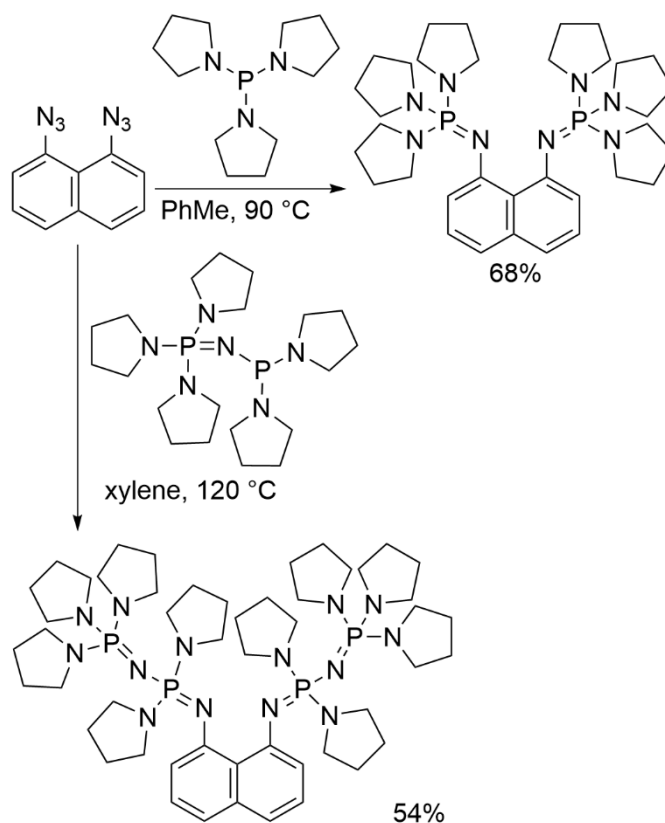


Scheme 5. Phosphorus ylide and carbodiphosphorane superbases.

## Synthesis of organosuperbases

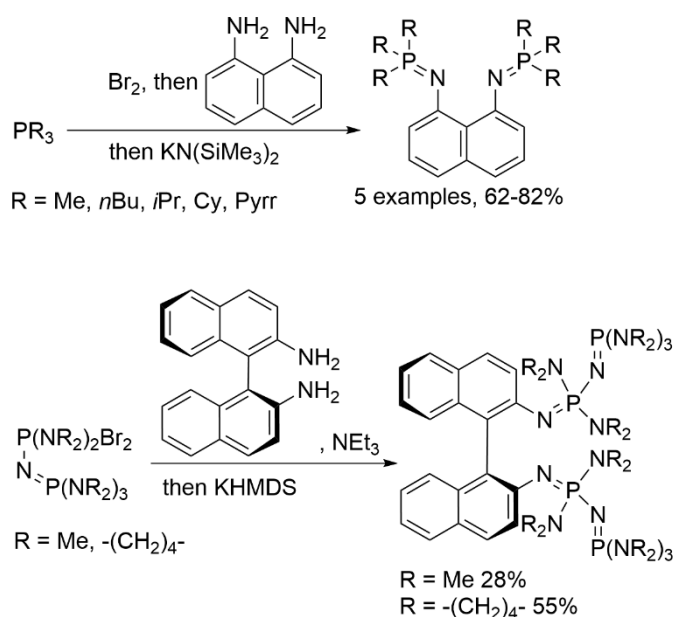
### Nitrogen-centered superbases

Significant effort was dedicated to the synthesis of phosphazene bases, mostly via the Staudinger and Kirsanov reactions. Kögel et al.<sup>29</sup> reported in 2013 two new biposphazene proton sponges 1,8-bis(pyrrolidinophosphazenylnaphthalene (TPPN) and its P<sub>2</sub>-analogue P<sub>2</sub>-TPPN prepared by Staudinger reaction (Scheme 6). 1,8-Diazidonaphthalene was reacted with the corresponding phosphane and heated in toluene or xylene giving the desired TPPN and P<sub>2</sub>-TPPN bases. Here, as in many other preparation methods for superbases the free bases are obtained. However, the free bases require storage under inert conditions due to air and moisture sensitivity. Though data on stability in aqueous solution for novel superbases are still scarce, for CO<sub>2</sub> it is known that its presence usually leads to formation of base-CO<sub>2</sub> adducts.<sup>60</sup>



Scheme 6. New bisphosphazene sponges containing the 1,8-diaminonaphthalene motif.

The Kirsanov procedure, which allows large scale synthesis of superbases was used to synthesize superbasic proton sponges (Scheme 7).<sup>42</sup> The corresponding phosphanes were *in situ* oxidized by bromine followed by addition of 1,8-bisphosphazenylnaphthalene and triethylamine. The free bases were obtained by reaction with  $\text{KN}(\text{SiMe}_3)_2$  in 62-82% yields.

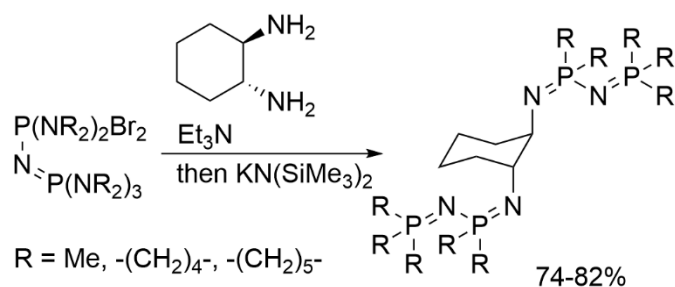


Scheme 7. Superbasic phosphazene proton sponges and related BINAM phosphazenes.



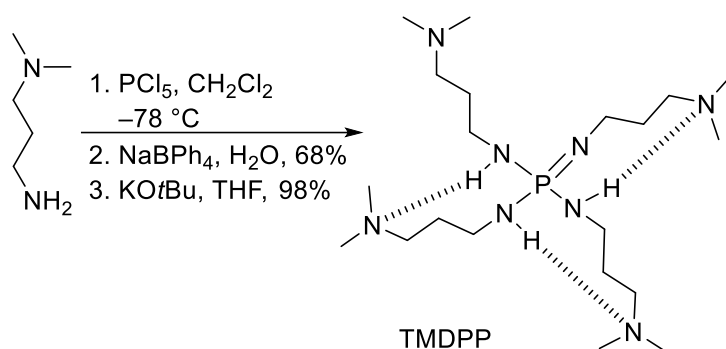
Kögel et al. also connected two P2-phosphazeny groups through a binaphthyl backbone having  $C_2$  symmetry in order to assess their basicity and coordination chemistry (Scheme 7).<sup>61</sup> Bromophosphazeny bromides were treated with (*S*)-(-)-1,1'-binaphthyl-2,2'-diamine in the presence of triethylamine and the phosphazene base was subsequently liberated in 28% and 55% yields, respectively. The chiral bases form dimethylaluminum complexes, indicating possible applications as chiral superbases or chiral ligands in asymmetric catalysis.

Moreover, Kögel et al. employed aliphatic (*R,R*)-1,2-diaminocyclohexane unit as backbone for the preparation of new chiral bis(phosphazene) superbases (Scheme 8).<sup>43</sup> The same bromophosphazeny bromides as above reacted with (*R,R*)-1,2-diaminocyclohexane in the presence of triethylamine giving chiral bis(phosphazene) salts, which were liberated using  $\text{KN}(\text{SiMe}_3)_2$ . Monoprotonated salts can be obtained by subsequent reaction with *p*-TsOH, which leads to diequatorial arrangement.



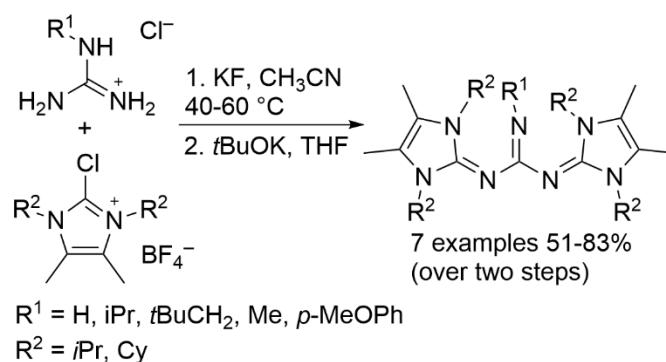
Scheme 8. Chiral P2 phosphazene base with a (*R,R*)-1,2-diaminocyclohexane backbone.

Ullrich et al.<sup>33</sup> prepared *N,N',N'',N'''*-tetrakis(3-(dimethylamino)propyl)triaminophosphazene (TMDPP), the first phosphazene base with intramolecular hydrogen bonding enhancement of basicity (Scheme 9). In the reaction of 3-(dimethylamino)propylamine with  $\text{PCl}_5$  TMDPPH<sup>+</sup>Cl<sup>-</sup> was initially formed, which was precipitated as its tetraphenylborate salt. The free base was liberated using KO<sup>t</sup>Bu.



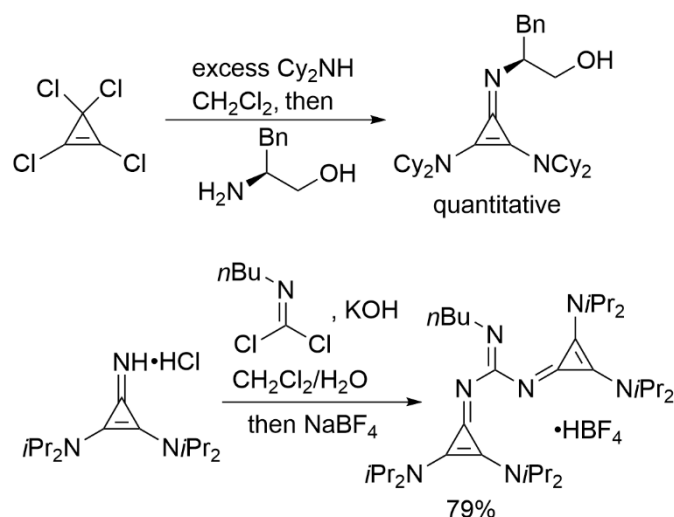
Scheme 9. Synthesis of TMDPP base.

In 2014, Vazdar et al. merged the guanidine and imidazolidinimine<sup>51</sup> motifs to form BIG bases.<sup>4</sup> The reaction of 2-chloroimidazolium salts with guanidines or guanidinium chlorides and subsequent liberation by *t*-BuOK provided the BIG bases in good yields (Scheme 10).



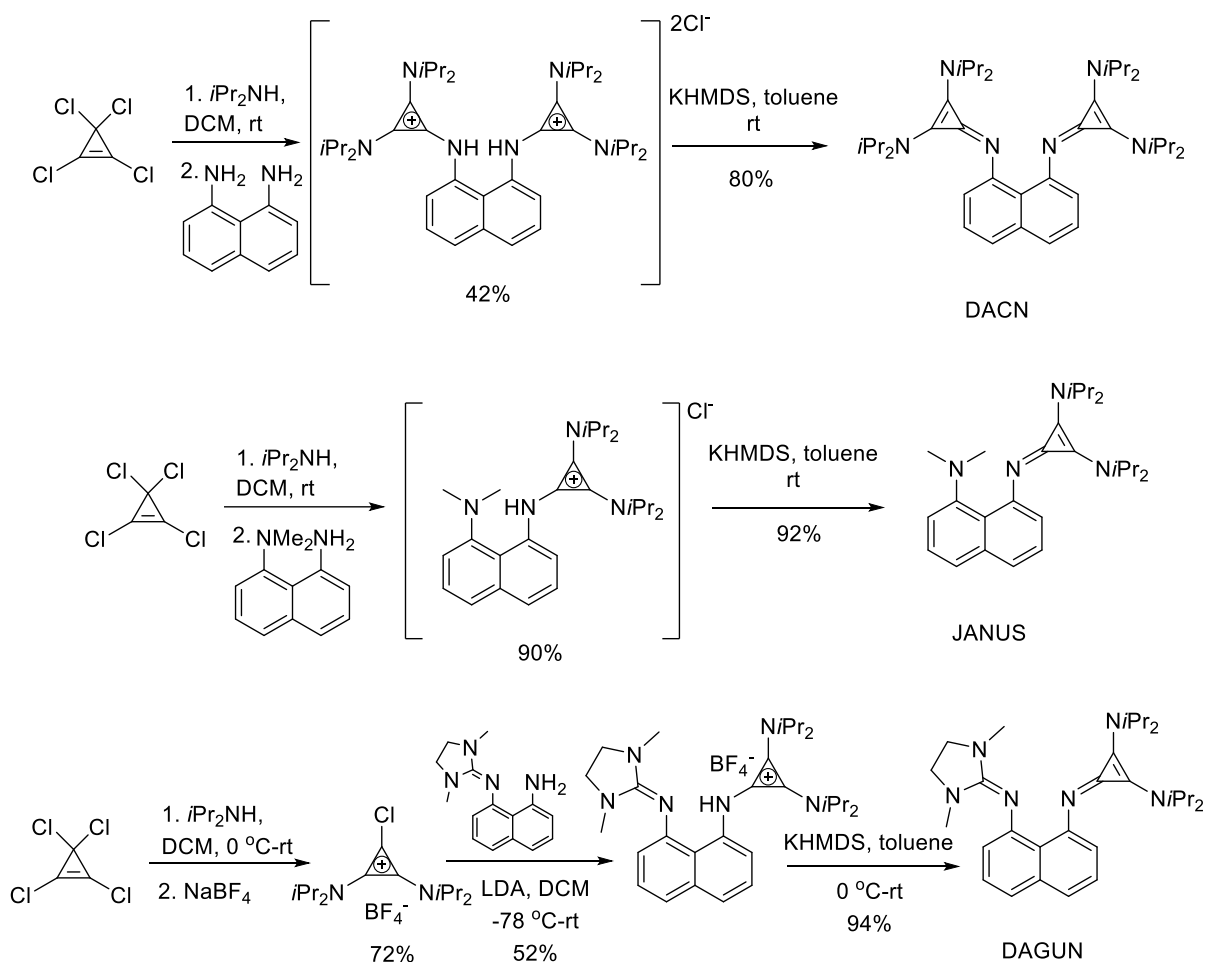
Scheme 10. Synthesis of BIG superbases.

Lambert and co-workers efficiently synthesized chiral cyclopropenimine superbases by substitution reactions (Scheme 11).<sup>37</sup> In 2015 higher order cyclopropenimine superbases were obtained by guanylation of diaminocyclopropenimines with phosgeneimines.<sup>23</sup>



Scheme 11. Chiral cyclopropenimine and higher order cyclopropenimine superbases.

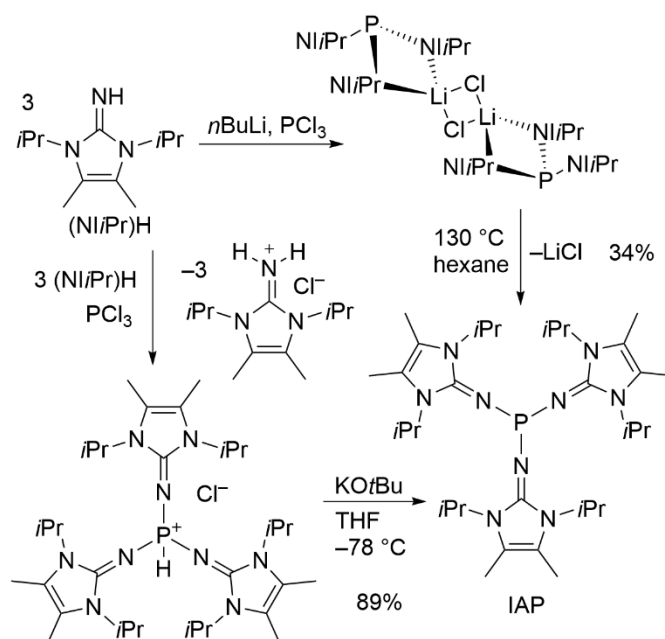
Dudding and coworkers merged the cyclopropenimine and DMAN structural motifs affording the proton sponge 1,8-bis(bis(diisopropylamino)cyclopropeniminyl)naphthalene (DACN)<sup>30</sup> and its unsymmetrical counterparts JANUS and DAGUN.<sup>50,62</sup>



Scheme 12. Synthesis of cyclopropenimine proton sponges.

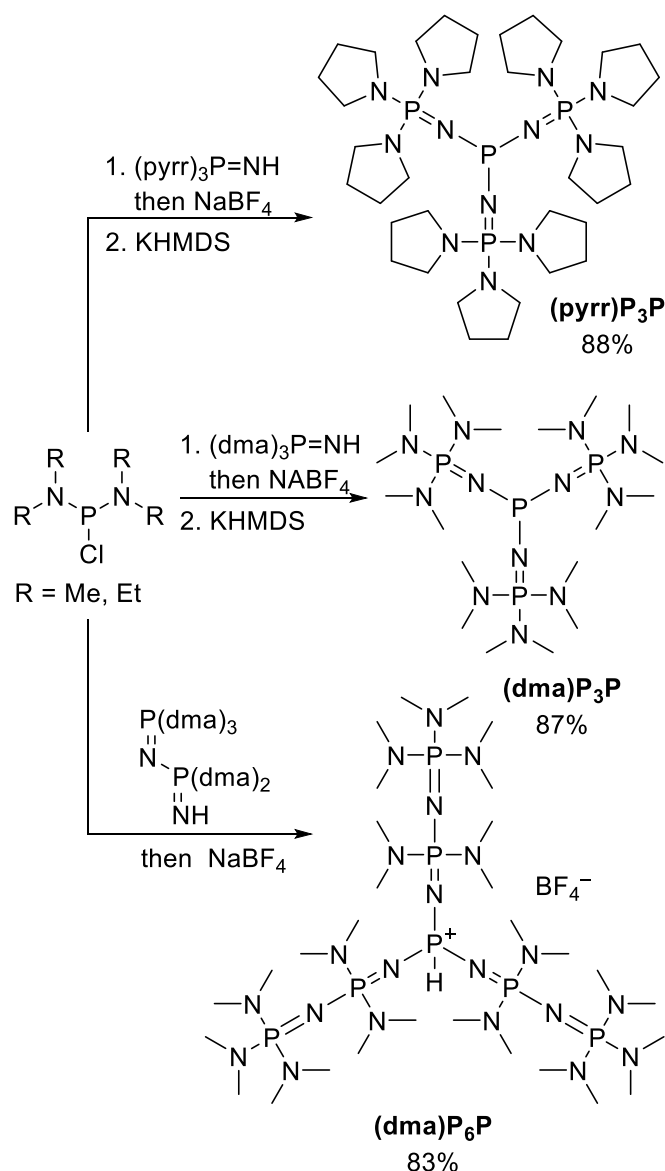
### Phosphorus-centered superbases

Diemann and coworkers accomplished the synthesis of tris(imidazolin-2-ylidenamino)phosphanes (IAP) in 2017 starting from 1,3-diisopropyl-4,5-dimethylimidazolin-2-ylidenamine ( $\text{NiPrH}$ ),  $n\text{-BuLi}$  and  $\text{PCl}_3$  furnishing the IAP- $\text{LiCl}$  adduct.<sup>39</sup> Heating in hexane at  $130\text{ }^\circ\text{C}$  precipitated  $\text{LiCl}$  and gave the free base in 34% yield. A  $\text{LiCl}$ -free approach using an excess of  $\text{NiPrH}$  with  $\text{PCl}_3$  and liberating the IAP base with  $\text{KOtBu}$  proceeded in 89% yield (Scheme 13).



Scheme 13. Synthesis of tris(imidazolin-2-ylidnamino)phosphane (IAP) base.

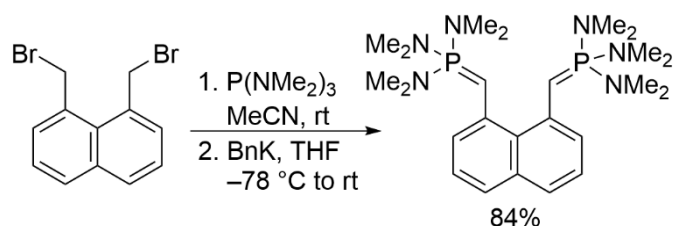
In 2019, Ullrich et al. published the first experimental paper on phosphazenylium phosphanes,<sup>24</sup> which were prepared by reaction of corresponding phosphazenes and  $(\text{Me}_2\text{N})_2\text{PCl}$  or  $(\text{Et}_2\text{N})_2\text{PCl}$  and precipitated with  $\text{NaBF}_4$  (Scheme 14). The desired phosphazenylium phosphane bases were liberated by using  $\text{KHMDS}$  in toluene or THF in high yields. Similarly, to Schwesinger's phosphazene base  $(\text{dma})\text{P}_7\text{-tBu}$ , liberation of  $\text{PAP}$   $(\text{dma})\text{P}_6\text{P}$  remains a challenge for future studies.



Scheme 14. Synthesis of phosphazenyly phosphane superbases.

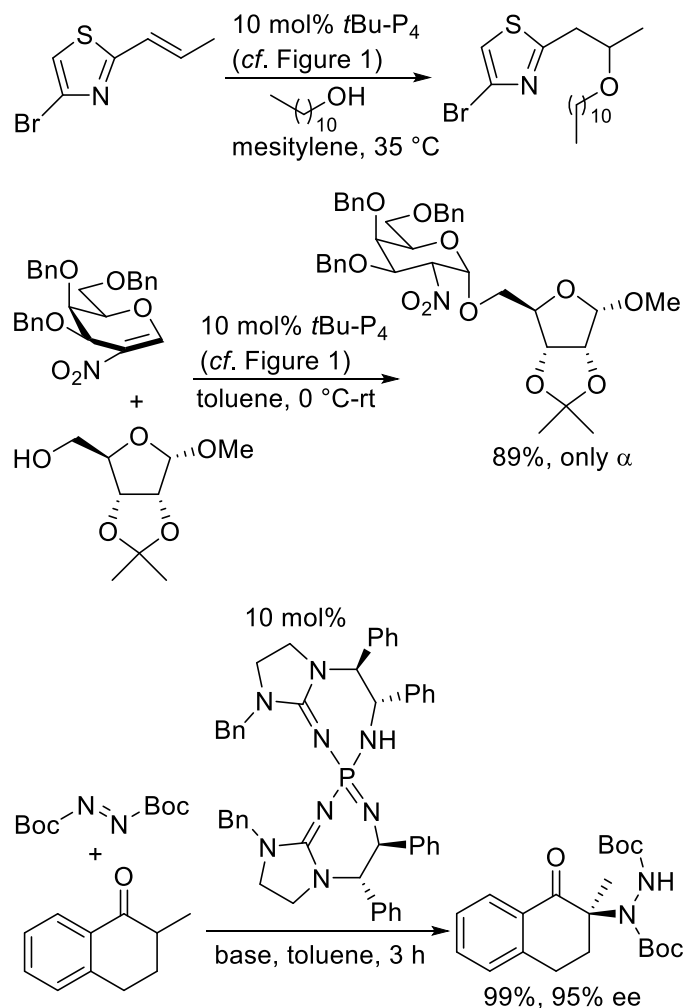
### Carbon centered superbases

Phosphazene-derived phosphorus ylide sponges, which are related to proton sponges, were easily synthesized by classical substitution reaction of  $\text{P}(\text{NMe}_2)_3$  and 1,8-bis(bromomethyl)naphthalene; the base was liberated with benzylpotassium in THF (Scheme 15). They show high reactivity and are very air sensitive. A selective monoprotection is possible (not shown).



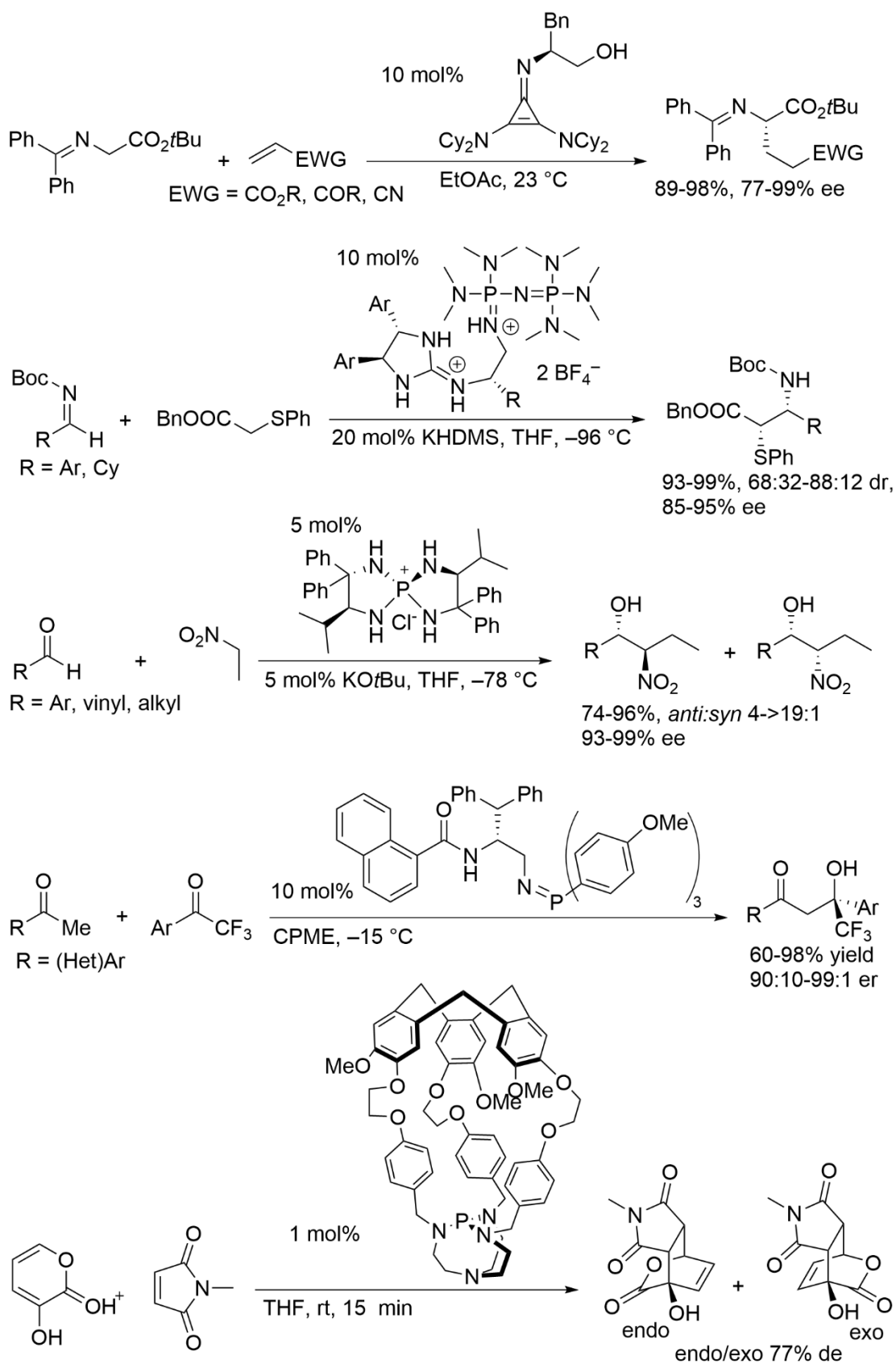
Scheme 15. Approach to phosphorus ylide superbases.





Scheme 17. Superbase-catalyzed C-O and C-N bond-forming reactions.

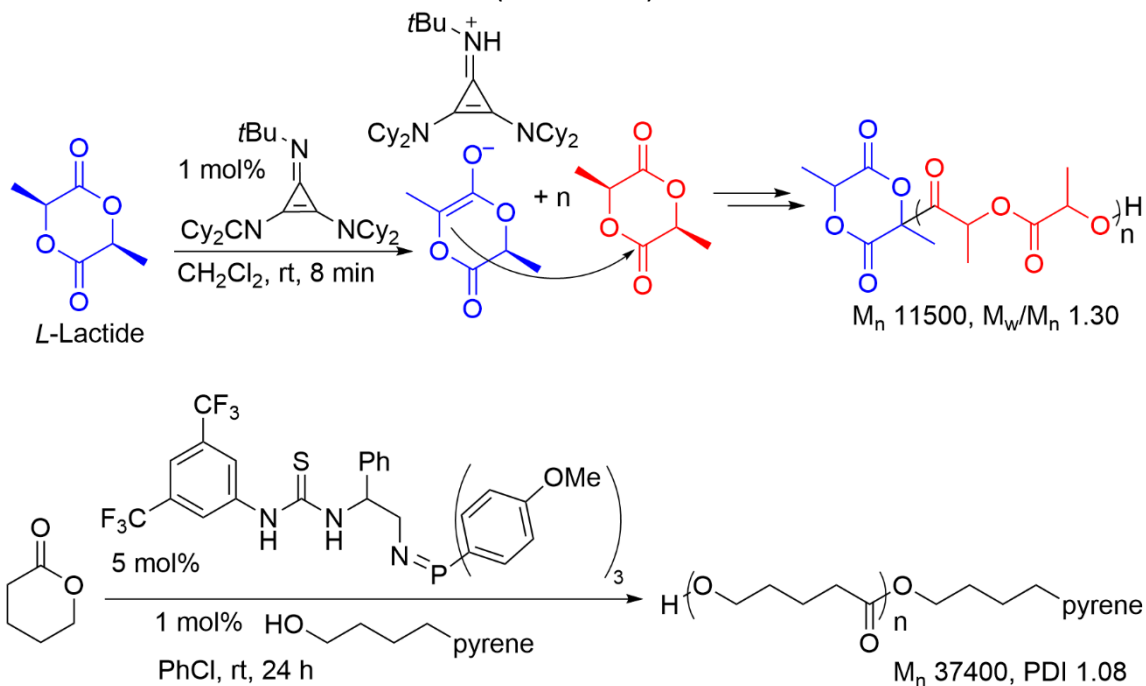
The C-C bond forming reactions catalyzed by organosuperbases attract significant interest (Scheme 18). Bandar and Lambert reported asymmetric Michael additions using chiral a cyclopropenimine catalyst.<sup>37</sup> Mannich reactions have been catalyzed by cyclopropenimine,<sup>69</sup> and iminophosphorane bases.<sup>70</sup> Recently Terada et al. designed a superbasic organocatalyst consisting of a phosphazene and a chiral guanidine unit.<sup>71</sup> The cooperative effect of these two units leads to unprecedented enantioselectivity in direct aza-Mannich reaction of less acidic pronucleophiles, such as  $\alpha$ -phenylthioacetate. Uraguchi and Ooi<sup>70</sup> applied chiral aminophosphonium salts for catalysis of the Henry and other reactions. Dixon et al. succeeded in catalyzing direct aldol additions by difunctional iminophosphorane superbases,<sup>72</sup> which were recently reviewed.<sup>72</sup> Verkade-type superbases were applied by Martinez et al. in base-catalyzed Diels-Alder reactions,<sup>73</sup> for the preparation of chiral derivatizing agents,<sup>74</sup> or Strecker reactions at very low catalyst loading (0.1 mol%).<sup>75</sup>



Scheme 18. Superbase-catalyzed C-C bond formation reactions.



A growing field for superbase application are also ring opening polymerization processes. Waymouth et al.<sup>76</sup> used Lambert's cyclopropenimine superbase to catalyze the ring opening polymerization of lactide with good conversion and moderate polydispersity, while Dixon et al.<sup>77</sup> employed iminophosphoranes to catalyze ring opening polymerization of valerolactone, which showed well-controlled behavior (Scheme 19).



Since novel superbases are still not widely used as catalysts in organic synthesis, we hope that the excellent results presented here will serve as encouragement to the scientific community to expand the superbasic catalyst toolbox.

## Conclusions and perspectives

Over the last decade, it became obvious that surpassing the known limit of basicity for organic compounds is indeed possible. In addition to determining their intrinsic basicities, novel basicity centers other than nitrogen are increasingly utilized. Phosphorus as basicity center experiences a renaissance in the form of new phosphanes, including phosphazeny phosphanes. Carbon has emerged by recognizing phosphorous ylides and carbodiphosphoranes as superbases. By combining theoretical and experimental efforts, superbases displaying arrays of intramolecular hydrogen bonding were discovered and pave the way for low-molecular weight bases. Chiral organic superbase derivatives were designed, which await exploration of their full application potential as catalysts or ligands. Despite the presented success in the design and preparation of organosuperbases, challenges remain. Venturing in the area of novel superbases represents a challenge for molecular design with respect to size and stability. The synthetic approaches to superbases must be rendered more efficient and modular to allow tailoring of their properties and three-dimensional arrangement for synthetic and catalytic applications. The synergy of theory and experiment is more than ever needed for overcoming the presented challenges and for providing a toolbox of superbases that will allow new applications.

## Biographies

**Katarina Vazdar** received her PhD in 2010 from Faculty of Natural Sciences, University of Zagreb, Croatia. From 2010-2012 she conducted postdoctoral research in the group of Dr. Ullrich Jahn at IOCB, Prague. From 2012-2020 she worked as research associate at RBI, Zagreb and currently is a scientist in the Jahn group, IOCB Prague.

**Davor Margetić** received his PhD in 1993 from Faculty of Natural Sciences, University of Zagreb, Croatia. From 1994-2002 he conducted postdoctoral research in the group of Professor Ron Warrener at the Central Queensland University, Australia. Currently he is a senior scientist at RBI and head of Division of organic chemistry and biochemistry. His research interests encompass physical organic chemistry, green organic synthesis and computational chemistry.

**Borislav Kovačević** received his PhD in 2001 from Faculty of Natural Sciences, University of Zagreb, Croatia. In 2007/08, he was a visiting scholar of Professor Leo Radom's group at the University of Sydney, Australia. He is currently a senior research associate at RBI and head of Division of physical chemistry. Core topics of his research are computational design of organic superbases and computational study of reaction mechanisms in radical enzymes.

**Jörg Sundermeyer** received his PhD in 1988 from the University of Göttingen, after a postdoctoral period at the CSIR, University of Natal, RSA, he moved to University of Würzburg, where he developed his independent research interests (habilitation). In 1996 he accepted a call as professor to University of Marburg. Among his interests are topics such as the design of superbases and (Lewis) superacids, of polyaromatic electron acceptors and electron donors, organometallics and redox catalysis, finally the design of molecular materials for energy conversion and storage.

**Ivo Leito** received his PhD in 1998 from the University of Tartu where he now works as professor of analytical chemistry. Research of strong acids and bases, especially measuring their strengths ( $pK_a$  and  $pK_{aH}$  values) in different solvents, is among the core topics of the group led by him (<https://analytical.chem.ut.ee/>).

**Ullrich Jahn** has been a senior group leader at IOCB Prague since 2007, after receiving his PhD at the University of Halle (1992), a postdoctoral stay at the University of Pittsburgh (1993-1995), and habilitation at Technical University of Braunschweig (2002). His interests cover synthetic methodology using basic compounds, radical and electron transfer chemistry and the total synthesis of natural products.

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