

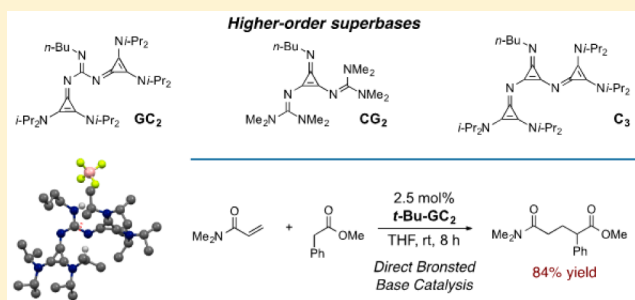
# Higher-Order Cyclopropenimine Superbases: Direct Neutral Brønsted Base Catalyzed Michael Reactions with $\alpha$ -Aryl Esters

Eric D. Nacsa and Tristan H. Lambert\*

Department of Chemistry, Columbia University, New York, New York 10027, United States

**S** Supporting Information

**ABSTRACT:** The synthesis and characterization of six new classes of higher-order superbases, including five that incorporate cyclopropenimine functionality, has been achieved. We propose a nomenclature that designates these as the  $CG_2$ ,  $GC_2$ ,  $PC_3$ ,  $PC_1$ ,  $C_3$ , and  $GP_2$  classes of superbases. The  $pK_{BH^+}$  values were measured to be between 29.0 and 35.6 in acetonitrile. Linear correlations of ten superbase basicities vs that of their substituents demonstrated the insulating effect of the cyclopropenimine core. The molecular structures of several of these materials were obtained by single-crystal X-ray analysis, revealing interesting aspects of conformational bias and non-covalent organization. The types of superbasic cores and substituents were each reliably shown to affect selectivity for deprotonation over alkylation. Higher-order cyclopropenimine and guanidine superbase stability to hydrolysis was found to correlate to basicity. Finally, a  $GC_2$  base was found to catalyze conjugate additions of  $\alpha$ -aryl ester pronucleophiles, representing the first report of a neutral Brønsted base to catalyze such reactions.



## INTRODUCTION

Strong Brønsted bases occupy an important place in the organic chemist's arsenal due to the large number of chemical reactions that involve deprotonation as a key activation step. Within the broader category of Brønsted bases, the so-called superbases are those species derived from the cooperative combination of two or more constituent bases,<sup>1</sup> a synergism that typically results in high thermodynamic basicities.<sup>2</sup> Many superbases, including amidines, guanidines, and phosphazenes, which rely on the combined action of multiple amino substituents, have found important application in organic synthesis, including asymmetric catalysis.<sup>3,4</sup> For obvious reasons, strength of basicity is a key parameter that affects what substrates are amenable to activation with a given Brønsted base. In this regard, the superbase concept can be further extended to species that involve the combination of multiple superbases to form "higher-order superbases",<sup>5–12</sup> and here truly remarkable basicities have been registered. Although such bases have great potential utility,<sup>13</sup> the variety of available functionalities remains limited, and problems of stability and difficulties of preparation make the identification of new higher-order superbases an important goal.

We recently introduced 2,3-diaminocyclopropenimines as a new class of organic superbase.<sup>14</sup> These cyclopropenimines are as basic as the  $P_1$  phosphazenes, but have dramatically improved stability profiles in noninert atmosphere. Given the growing recognition of the utility of cyclopropenimine bases, we sought to develop a number of higher-order cyclopropenimine superbases with the goal of realizing enhanced basicities and unique functional properties. In this work, we describe the synthesis and

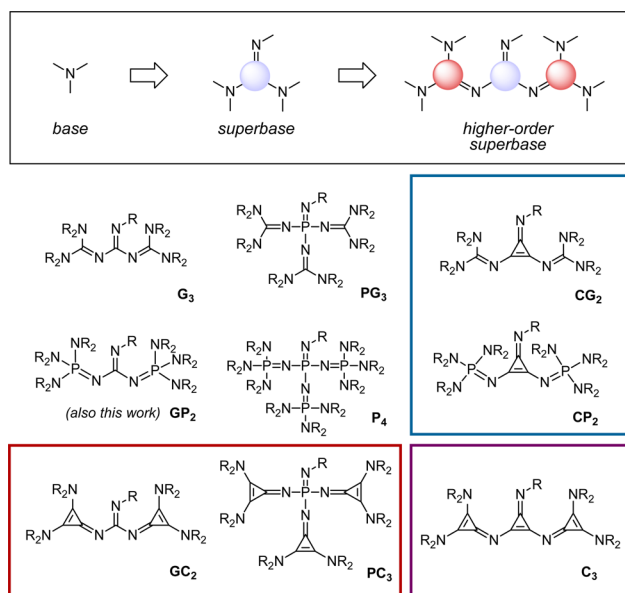
characterization of four new classes of superbases that incorporate cyclopropenimine functionality (Figure 1) as either the core group (blue box), the substituents (red box), or both (purple box). In addition, we report the first example of a bisphosphazenyguanidine higher-order superbase, as well as a monocyclopropeniminyl phosphazene base (not shown).

## NOMENCLATURE

Before beginning the discussion of this work, a brief explanation of the nomenclature for the materials described herein is appropriate. The combination of different superbases offers a variety of possibilities, and so in order to aid in the description of these variants, we propose a classification scheme inspired by the convention already in use for the phosphazene bases.<sup>6</sup> Thus, each base is first assigned a letter according to the functionality that comprises its basic core: "G" for guanidinyl, "P" for phosphazeny, and "C" for cyclopropeniminy. This letter is then followed by the letters corresponding to the superbase substituents on that core (G, P, C), with a numerical subscript indicating the number of substituents. Thus, a trisguanidinyl-phosphazene is a "PG<sub>3</sub>" base, while a biscyclopropeniminyguanidine is a "GC<sub>2</sub>" base. In the cases where the core and substituents are from the same class, the descriptor can be distilled to a single letter, e.g., "P<sub>4</sub>", "G<sub>3</sub>", and "C<sub>3</sub>". Herein we describe the first synthesis of members of the  $CG_2$ ,  $GC_2$ ,  $PC_3$ ,  $PC_1$ ,  $C_3$ , and  $GP_2$  classes of higher-order superbases.

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**Figure 1.** Higher-order superbases, including those with a cyclopropenimine core (blue box), cyclopropenimine substituents (red box), or both (purple box).

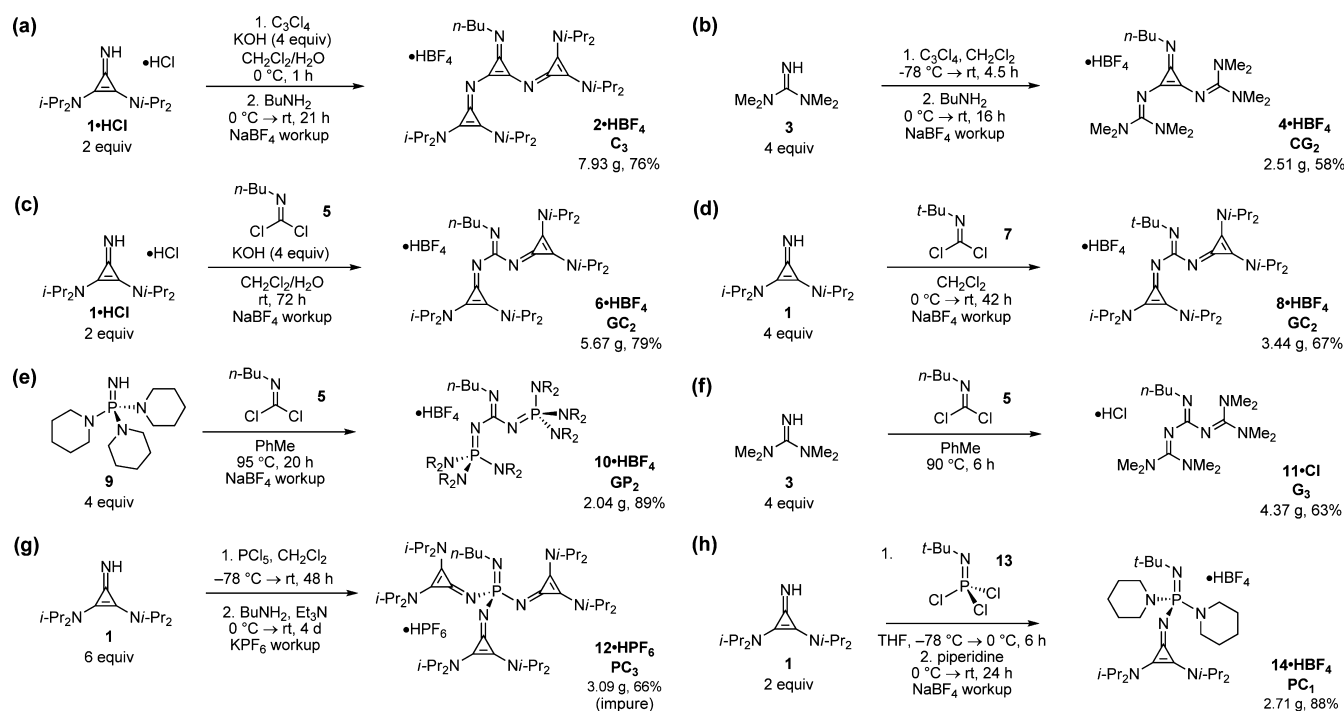
## RESULTS AND DISCUSSION

**Synthesis.** Typically, higher-order superbases are prepared from the reaction of a nucleophilic superbase with an appropriate electrophile. However, such procedures can be complicated by (1) the use of highly moisture-sensitive electrophiles, such as  $\text{PCl}_5$  or chloroformamidinium salts, and (2) the need for twice the equivalents of the nucleophilic superbase in order to neutralize the acid that forms during substitution. Moreover, this type of strategy requires the use of a neutral superbase, which is often less convenient to handle and store than its conjugate acid.

In contrast to the aforementioned electrophiles, cyclopropenimines are generally prepared from tetrachlorocyclopropene ( $\text{C}_3\text{Cl}_4$ ),<sup>15</sup> which is reactive with nitrogen nucleophiles but relatively resistant to hydrolysis. As such, we were able to develop a convenient procedure to prepare the  $\text{C}_3$  base 2: cyclopropenimine 1·HCl (2 equiv) was treated with tetrachlorocyclopropene ( $\text{C}_3\text{Cl}_4$ ) and KOH (4 equiv) in a biphasic mixture of  $\text{CH}_2\text{Cl}_2$  and water at 0 °C (Figure 2a). After 1 h, the layers were separated, *n*-BuNH<sub>2</sub> was added, and the mixture was stirred for 21 h at rt. After aqueous workup, ion exchange with  $\text{NaBF}_4$  and recrystallization, we obtained nearly 8 g of 2 as its  $\text{HBF}_4$  salt in 76% yield. Importantly, this convenient neutralization of HCl by aqueous KOH both enabled the use of the more conveniently handled HCl salt of the cyclopropenimine starting material and obviated the need for any excess of this reactant.

The  $\text{CG}_2$  base 4 was prepared by a similar route, but since we have observed that tetramethylguanidine (3) readily adds three times to tetrachlorocyclopropene at rt, some modifications were needed (Figure 2b). Thus, the guanidine was added in dry  $\text{CH}_2\text{Cl}_2$  at −78 °C to prevent the third substitution, and we employed a sufficient excess of the free base (4 equiv) to neutralize HCl. From this procedure, 2.51 g of 4· $\text{HBF}_4$  was isolated in 58% yield.

We also developed a new route to higher-order guanidine superbases since traditional approaches involving chloroformamidinium<sup>16</sup> or thiuronium<sup>17</sup> salts were consistently problematic in our hands. Compared to these electrophiles, carbonimidic dichloride<sup>18</sup> 5 provided a more desirable balance of reactivity with nucleophiles and ease of handling. The preparation of the  $\text{GC}_2$  base 6 was otherwise comparable to that of the  $\text{C}_3$  base. Cyclopropenimine 1·HCl (2 equiv) and aqueous KOH (4 equiv) was added to 5 in  $\text{CH}_2\text{Cl}_2$  (Figure 2c). After stirring at rt for 3 d, workup and ion exchange furnished 5.67 g of 6· $\text{HBF}_4$  in 79% yield.



**Figure 2.** Syntheses of higher-order superbases.

While the *n*-butyl head groups were selected for most higher-order superbases in this study for structural consistency and to facilitate synthetic procedures, we also sought a more hindered version of a GC<sub>2</sub> base. We therefore reacted *tert*-butyl carbonimidic dichloride **7** with **1**, although in this case 4 equiv of the neutral base were needed since the use of KOH as a base led to significant amounts of hydrolysis byproducts (Figure 2d). Workup similar to that used for the isolation of **6** provided 3.44 g of **8**·HBF<sub>4</sub> in 67% yield.

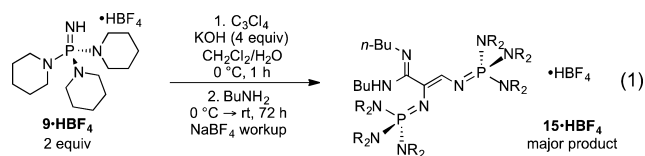
This strategy was also adapted to prepare the first reported example of a GP<sub>2</sub> base **10** (Figure 2e). The reaction was conducted in toluene at a higher temperature (95 °C) to compensate for slower substitution and was again cleaner when using the free phosphazene **9** (4 equiv) as both the nucleophile and the base. After workup and ion exchange, we isolated 2.04 g of **10**·HBF<sub>4</sub> in 89% yield.

The carbonimidic dichloride method similarly provided **11**·HCl in 63% yield (Figure 2f), offering an alternative to the recently reported synthesis of peralkylated triguanides using a sensitive chloroformamidinium salt.<sup>5</sup>

The PC<sub>3</sub> base **12** was prepared by a process used in the synthesis of guanidylphosphazenes<sup>7</sup> (Figure 2g). Isolation of **12** was most convenient as the HPF<sub>6</sub> salt, although purification of this material has thus far proven to be an intractable problem, possibly due to its relative sensitivity, and so the obtained characterization data are of impure material.

In light of our difficulties in obtaining a clean sample of a PC<sub>3</sub> base, we also targeted the synthesis of a monocyclopropenimino-phosphazene (PC<sub>1</sub>) in order to fully characterize the first example of a molecule combining cyclopropenimine and phosphazene moieties. We observed that **1** was reluctant to add more than once to trichloroiminophosphorane **13**,<sup>19</sup> so reaction of these components in a 2:1 ratio at -78 °C followed by treatment with excess piperidine at 0 °C provided 2.71 g of PC<sub>1</sub> base **14** as its HBF<sub>4</sub> salt in 88% yield after the appropriate workup (Figure 2h).

Notably, all attempts at the preparation of a CP<sub>2</sub> base have failed due to facile ring-opening<sup>20</sup> of the cyclopropene core (eq 1). Although we have been unable to purify the major



product, spectroscopic data (NMR, MS) suggest that its structure is the amidine **15**·HBF<sub>4</sub>.

All members of the new classes of superbases that we successfully isolated could be liberated on treatment with KO*t*-Bu (1 equiv) at rt in THF. While we isolated and characterized all of the corresponding free bases in good yields, they were typically sensitive to air and moisture, so these procedures needed to be conducted in a glovebox. Therefore, our catalytic studies with these superbases (vide infra) were performed by deprotonating the base in situ immediately prior to adding the reactants.

**Basicity Measurements.** With robust synthetic routes in hand, we sought to determine the basicities of these new higher-order superbases. The p*K*<sub>BH+</sub> values in acetonitrile are shown in Table 1. Notably, while the basicity trend of the parent superbases is guanidine < cyclopropenimine ≈ phosphazene (**16**, **17**, and **18**), the trend for the higher-order

Table 1. Basicities of Higher-Order Superbases<sup>a</sup>

	<b>16</b> <b>G</b> <sub>1</sub> 24.8		<b>17</b> <b>C</b> <sub>1</sub> 27.6		<b>18</b> <b>P</b> <sub>1</sub> 27.8
	<b>11</b> <b>G</b> <sub>3</sub> 29.5		<b>4</b> <b>CG</b> <sub>2</sub> 29.0		<b>19</b> <b>PG</b> <sub>3</sub> <sup>b</sup> 37.9
	<b>6</b> <b>GC</b> <sub>2</sub> 35.6		<b>2</b> <b>C</b> <sub>3</sub> 31.6		<b>12</b> <b>PC</b> <sub>3</sub> 42.1 (est)
	<b>10</b> <b>GP</b> <sub>2</sub> 34.3		<b>20</b> <b>CP</b> <sub>2</sub> unstable, ring-opens		<b>21</b> <b>P</b> <sub>4</sub> 42.7 <sup>b</sup>

<sup>a</sup>Italicized numbers represent p*K*<sub>BH+</sub> values. Values below 33 were measured in acetonitrile. Values above 33 were extrapolated from measurements in THF. See SI. <sup>b</sup>Literature values, see SI. (NR<sub>2</sub>) = piperidinyl.

superbases is cyclopropenimine < guanidine < phosphazene (compare **11**, **4**, and **19** or **6**, **2**, and **12**). These data indicate that the cyclopropene core is relatively less effective at communicating the basicity of the substituents to the head imino group. The greater insulating character of the cyclopropenimine functionality can be understood by consideration of the conjugate acid form, the core of which is a cyclopropenium ring. As a closed-shell aromatic, the cyclopropenium group gains less in stability from the donation of electron density than other cations, a trend long-established for the chemistry of the cyclopropenium unit.<sup>21</sup>

This phenomenon as it relates to superbasicity can be quantified by plotting the relationship of the p*K*<sub>BH+</sub> values of guanidine, phosphazene, and cyclopropenimine superbases versus the basicities of their substituents (amino, guanidino, cyclopropenimino, and phosphazeno) as shown in Figure 3. The slope of each line is a measure of the degree to which the

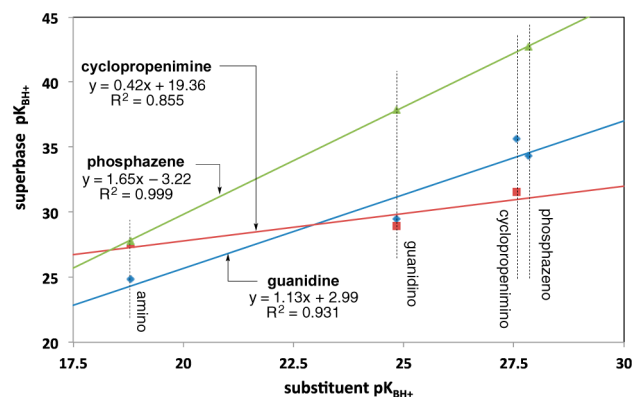


Figure 3. Plot of superbase p*K*<sub>BH+</sub> vs substituent basicities for phosphazene (green ▲), guanidine (blue ◆), and cyclopropenimine (red ■) superbases.

core functionality transmits the electron density of the substituents to the head imino group. For comparison purposes, the slopes must be normalized per substituent; for example, the guanidine slope of 1.13 corresponds to a value of 0.57 for each individual substituent. (A “perfect” normalized value would be 1.00). From this analysis, it can be seen that the phosphazene (0.55) and guanidine (0.57) core groups have approximately the same transmissibility, while the cyclopropenimine (0.21) is less than half as effective. The upshot of these trends is that the CG<sub>2</sub> and G<sub>3</sub> bases have essentially the same basicity.

The y-intercepts of the trend lines in Figure 3 represent the basicity of hypothetical species bearing substituents with pK<sub>BH+</sub> values of 0. In this case, the cyclopropenimine value (19.36) greatly exceeds that of both phosphazene (−3.22) and guanidine (2.99), which again is a reflection of the far greater stability of the aromatic cyclopropenium ion compared to either phosphonium or carbenium ions. From these trends, it can be predicted that cyclopropenimines bearing substituents that are less π-donating than amino groups (e.g., aryl) should maintain a relatively high level of basicity.

**Selectivity: Elimination vs Alkylation.** One potential complication to the use of strong Brønsted bases is their capacity to function instead as nucleophiles (i.e., Lewis bases). A strong preference for Brønsted over Lewis base reactivity is thus a crucial parameter for optimal Brønsted base catalysts. Schwesinger has thoroughly investigated such selectivities in the context of phosphazenes<sup>6</sup> by measuring the extent to which these bases react with alkyl halides via elimination versus alkylation.<sup>6</sup> Using this same approach, we examined the elimination vs alkylation selectivity of the new classes of superbases we have prepared. The superbases were thus treated with *i*-butyl bromide under conditions that completely consumed the free base (10 equiv *i*-BuBr, 60 °C for 6 h), and the selectivity was measured by integrating the ratio of protonated and alkylated products (Table 2). As can be seen from

the cyclopropenimines (compare entries 1 and 4 or 2 and 5), due to the greater congestion of the former. However, the steric demand of the imino substituent appears to have the largest effect on selectivity, as can be seen from comparison of the *n*-Bu-GC<sub>2</sub> and *t*-Bu-GC<sub>2</sub> bases **6** and **8** (entries 2 and 6), with the selectivity of the latter being strongly in favor of protonation.

**Molecular Structures.** The molecular structures of several higher-order superbase salts are shown in Figure 4. Notably, the C<sub>3</sub> salt **2**·HBF<sub>4</sub> (Figure 4a), the CG<sub>2</sub> salt **6**·HBF<sub>4</sub> (Figure 4b), and the GP<sub>2</sub> salt **10**·HBF<sub>4</sub> (Figure 4e) all display gearing of the *n*-butyl and cyclopropeniminyloxy/phosphazenyloxy substituents, due to rather significant steric congestion. For the C<sub>3</sub> salt **2**·HBF<sub>4</sub> and the CG<sub>2</sub> salt **6**·HBF<sub>4</sub>, the cyclopropeniminyloxy substituent that is syn to the N—H group is torqued such that it is significantly out of the plane of the core π-system, at respective angles of 66° and 45°. While these distortions may be partially explained by steric effects, they appear also to enable intramolecular CH—N bonds between the imino nitrogen atom of the torqued cyclopropeniminyloxy substituent and one of the isopropyl CH protons of the adjacent substituent. The CH—N distances are 2.35 Å in the C<sub>3</sub> salt and 2.50 Å in the GC<sub>2</sub> salt, well within the expected range for such an interaction. Notably, the type of conformational organization observed in Figure 4, parts a and b, raises intriguing possibilities for the design of asymmetric catalysts, since it places the H-bonded counterion in close contact with the distal amino groups of the cyclopropeniminyloxy substituent.

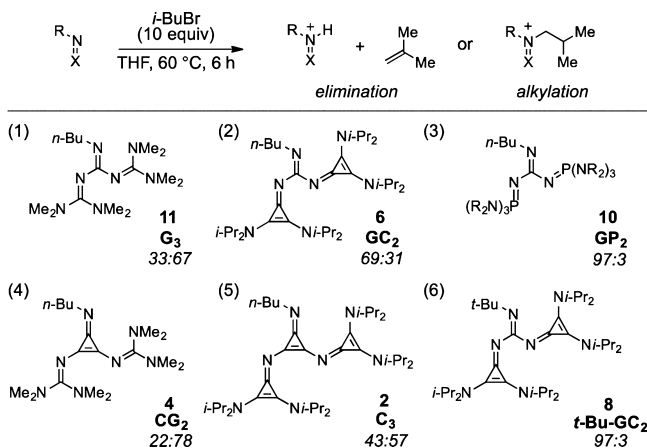
In contrast, the CG<sub>2</sub> salt **4**·HBF<sub>4</sub> (Figure 4c) does not exhibit such a gearing effect, and indeed the guanidinyloxy substituents are arranged syn to one another and appear to be engaged in a π—π interaction. However, the crystal lattice was disordered, so caution should be taken in drawing conclusions from this structure. Interestingly, the GP<sub>2</sub> salt **10**·HBF<sub>4</sub> (Figure 4d) features P=N—C bond angles noticeably larger than the ideal 120° (see the SI), a feature not observed in the other structures shown. Such a distortion most likely arises from steric conflict of the extremely bulky tris(piperidinyloxy)phosphazenyloxy substituents.

**Hydrolytic Stability.** Although higher-order superbases tend to be robust species for most applications, they can be susceptible to nucleophilic attack, especially by solvolysis. To probe the limits of stability of the new superbases, we measured their decomposition rates during heating in aqueous methanol in the presence of 10 equiv of sodium methoxide (Table 3).

The superbases fell roughly into 2 categories. The first encompassed highly robust molecules, which showed no measurable decomposition after 24 h at 140 °C. Among this group were the GP<sub>2</sub>, PC<sub>1</sub>, and the P<sub>1</sub> bases (entries 1–3).<sup>6</sup> The PG<sub>3</sub> base is also quite robust under these conditions (entry 4), but does undergo an observable slow decomposition.

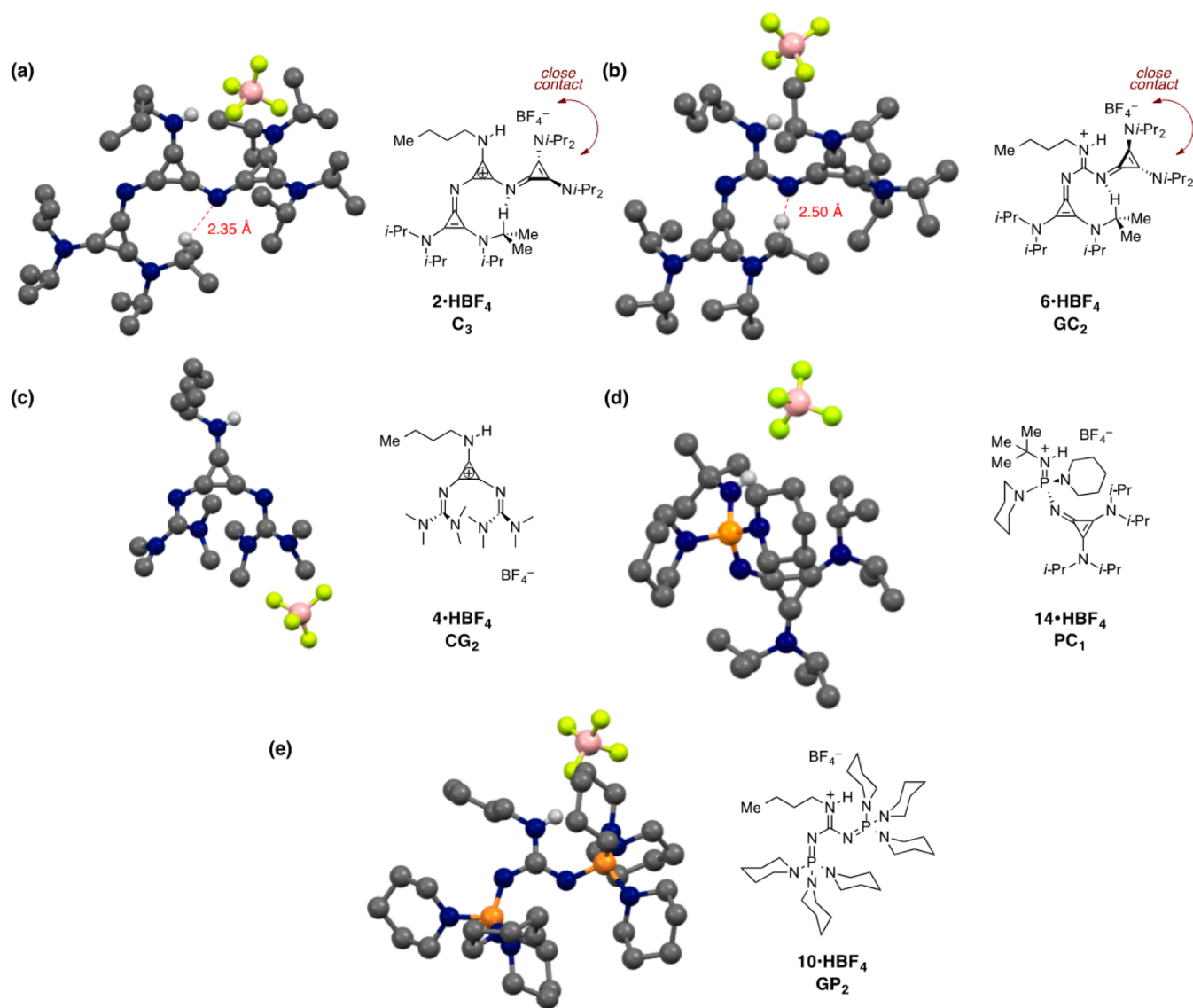
The remaining superbases had a measurable half-life (<10 h) at 140 °C (entries 5 and 6) or 80 °C (entries 7–11) in a sealed tube. For the majority of this group, there is a direct relationship between the basicity and the stability of the molecules under these conditions (entries 5–10). The exception in the CG<sub>2</sub> base (entry 11), which despite its intermediate basicity is the least stable of all the superbases studied. We note that the CG<sub>2</sub> base also displayed the poorest selectivity for elimination vs alkylation (see Table 2), and we speculate that both effects result from the relatively small guanidine substituents coupled with the expanded cyclopropenimine core leaving the imino function relatively open to C-nucleophilic or N-electrophilic attack. The clear conclusion from Table 3 is that the bases in

**Table 2. Elimination vs Alkylation with Higher-Order Superbases and *iso*-Butyl Bromide<sup>a</sup>**



<sup>a</sup>Italicized numbers correspond to ratios of elimination vs alkylation as determined by the ratios of protonated vs alkylated superbases observed by <sup>1</sup>H NMR. See SI.

comparison of guanidine bases with the same *n*-Bu headgroup, the selectivity for protonation increases according to substituent size in the order G<sub>3</sub> < GC<sub>2</sub> < GP<sub>2</sub> (entries 1–3). The effect of the superbase core also reveals a mild size correlation, with the guanidines showing higher protonation selectivity than

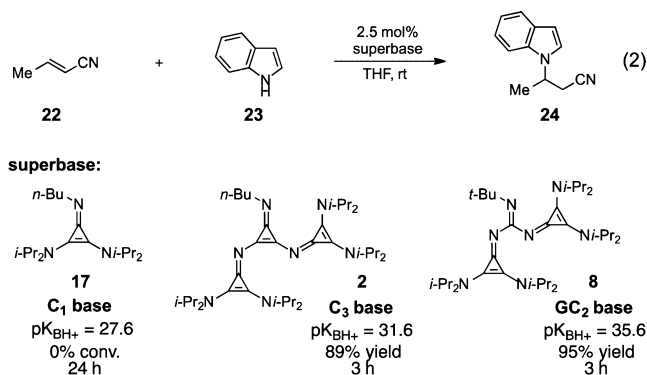


**Figure 4.** Molecular structures of (a)  $2 \cdot \text{HBF}_4$ , (b)  $6 \cdot \text{HBF}_4$ , (c)  $4 \cdot \text{HBF}_4$ , (d)  $14 \cdot \text{HBF}_4$ , and (e)  $10 \cdot \text{HBF}_4$ . Parts (c) and (e) also contain second structures that are qualitatively similar to those shown here (see the SI for complete structures).

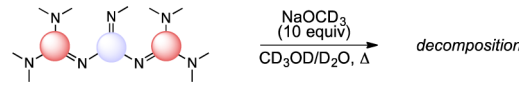
entries 6–11 should be used at temperatures well below 80 °C for maximal effectiveness.

**Catalysis.** The purpose of designing more strongly basic superbases is to enable reactivity with a broader range of less-acidic substrates, and thus the new superbase platforms described here are expected to offer important new opportunities for method development. To illustrate this potential, we examined the conjugate addition of indole (**23**) to crotonitrile (**22**) under superbase catalysis (eq 2). Notably, while the  $\text{C}_1$  base **17** did not catalyze this reaction to any appreciable extent over 24 h, the  $\text{C}_3$  base **2** and  $\text{GC}_2$  base **8**, which are 4 and 8 orders of magnitude more basic, respectively, than **17**, catalyzed the formation of **24** in 89% and 95% yields after 3 h.

In addition, we found the *t*-Bu- $\text{GC}_2$  base **8** to be effective for catalyzing the conjugate addition of  $\alpha$ -aryl esters to Michael acceptors, a reaction that has not been reported using direct neutral Brønsted base catalysis.<sup>22,23</sup> As shown in Table 4, reaction of a range of  $\alpha$ -aryl donors and various Michael acceptors in the presence of 2.5 mol % of **8** produced Michael adducts in excellent yields after 8–12 h. Michael acceptors including an unsaturated ester (entry 1), nitrile (entry 2a), and amide

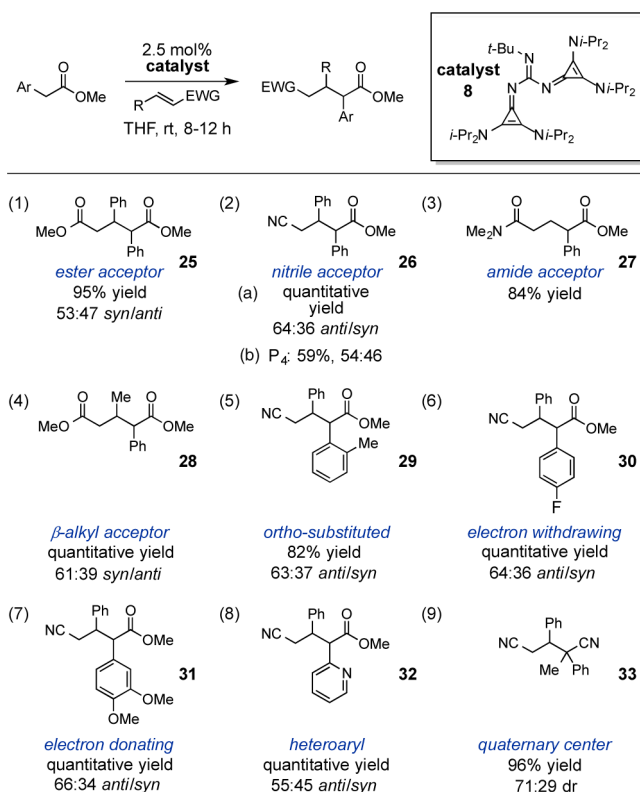


(entry 3) were found to be viable, although in the case of the amide,  $\beta$ -substitution was not compatible. Notably, in a direct comparison, the  $\text{P}_4$  base—the only commercially available higher-order superbase stronger than the  $\text{GC}_2$  base—resulted in only modest conversion (entry 2b) in comparison to the  $\text{GC}_2$  base (entry 2a). Reaction with a  $\beta$ -alkyl Michael acceptor was also productive (entry 4). In terms of the scope of the aryl

**Table 3. Relative Stabilities of Superbases in Basic Aqueous Methanol<sup>a</sup>**


entry	class	compound	temp (°C)	<i>t</i> <sub>1/2</sub> (h)	<i>t</i> <sub>1/2</sub> (rel)	p <i>K</i> <sub>BH+</sub>
1	GP <sub>2</sub>	10	140	≫24	>10 <sup>4</sup>	34.3
2	PC <sub>1</sub>	14	140	≫24	>10 <sup>4</sup>	31.8
3	P <sub>1</sub>	18	140	≫24	>10 <sup>4</sup>	27.8
4	PG <sub>3</sub>	19	140	32	1200	37.9
5	GC <sub>2</sub>	6	140	2.3	81	35.6
6	C <sub>3</sub>	2	140	1.0	36	31.6
7	C <sub>3</sub>	2	80	9.0	36	31.6
8	G <sub>3</sub>	11	80	2.0	8.0	29.5
9	C <sub>1</sub>	17	80	1.0	4.0	27.6
10	G <sub>1</sub>	16	80	0.67	2.7	24.8
11	CG <sub>2</sub>	4	80	0.25	1.0	29.0

<sup>a</sup>Superbase (0.075 mmol) and NaOCD<sub>3</sub> (0.75 mmol) were heated in a mixture of CD<sub>3</sub>OD (0.45 mL) and D<sub>2</sub>O (0.25 mL) in sealed NMR tubes until 50% of the initial amount of superbases remained (vs sodium 3-(trimethylsilyl)propanesulfonate internal standard).

**Table 4. Substrate Scope of Higher-Order Superbase-Catalyzed Conjugate Additions<sup>a</sup>**

<sup>a</sup>Pronucleophile and Michael acceptor (1.0 mmol of limiting reagent) were added to a solution of catalyst (0.025 mmol) in THF (3 mL) and stirred for 8–12 h. See SI for details.

substituent, ortho substituents (entry 5) as well as electron withdrawing (entry 6) and electron donating (entry 7) substituents were well-tolerated. In addition, a heteroaromatic-containing product was accessible in quantitative yield (entry 8). Finally, we found that the generation of a quaternary carbon center could be accomplished in high yield with the use of an  $\alpha$ -branched pronucleophile (entry 9). In all cases,

diastereoselectivity was predictably low, given that the catalyst **8** does not incorporate any of the hydrogen-bonding or other organizational motifs that would be present in chiral analogues. Nevertheless, the ability to engage simple  $\alpha$ -aryl esters and nitriles in direct Brønsted base chemistry represents an important advance for the area of strong neutral base catalysis.

## CONCLUSIONS

Higher-order superbases offer the potential to realize very strong basicities in the context of neutral, organic-soluble reagents. The current work significantly expands the scope of available materials in this category with the introduction of higher-order superbases bearing cyclopropenimine functionality. The enhanced basicity of these new bases coupled with their relatively straightforward synthetic accessibility offer important new opportunities for method development in the area of Brønsted base catalysis.

## EXPERIMENTAL SECTION

**Synthesis of C<sub>3</sub> Base 2·HBF<sub>4</sub>.** A solution of KOH (3 M, 20.25 mL, 60.75 mmol, 4.03 equiv) was added to 1·HCl (8.71 g, 30.3 mmol, 2.01 equiv) and C<sub>3</sub>Cl<sub>4</sub><sup>15</sup> (1.85 mL, 15.1 mmol, 1.00 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (300 mL) at 0 °C. After stirring for 1 h, the layers were separated, and the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and quickly filtered into a second flask at 0 °C. *n*-BuNH<sub>2</sub> (1.4 mL, 14 mmol, 4.8 equiv) was added, and the solution was stirred for 21 h while warming slowly to rt. The reaction was then washed with a combination of 0.5 M Na<sub>2</sub>CO<sub>3</sub> and 0.5 M NaBF<sub>4</sub> (2 × 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was redissolved in EtOAc (300 mL), washed with sat. NH<sub>4</sub>Cl (3 × 50 mL) and a combination of 0.5 M Na<sub>2</sub>CO<sub>3</sub> and 1 M NaBF<sub>4</sub> (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to provide a tan solid (11.75 g). This material was dissolved in hot EtOAc (125 mL), cooled to rt, and hexanes was diffused in for 3 days, followed by standing at –20 °C overnight. The product crystallized as large yellow prisms (8.00 g). The recrystallization was repeated on ~80% of the previous scale and deposited white prisms (7.93 g, 76%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.73 (s, 1H), 3.84 (hept, *J* = 6.7 Hz, 8H), 3.30 (app q, 2H), 1.66 (m, 2H), 1.42–1.18 (overlapping signals, 50H), 0.91 (t, *J* = 7.4 Hz, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  128.0, 124.2, 122.3, 119.7, 50.2, 46.5, 32.7, 21.9, 19.6, 13.6. HRMS (ESI+) for C<sub>37</sub>H<sub>65</sub>N<sub>7</sub> [MH]<sup>+</sup> *m/z* calcd 608.5380, found 608.5383.

**Synthesis of CG<sub>2</sub> Base 4·HBF<sub>4</sub>.** Tetramethylguanidine (3) in CH<sub>2</sub>Cl<sub>2</sub> (5.50 mL TMG diluted to a volume of 19.6 mL, used 18.2 mL, 40.7 mmol TMG, 3.99 equiv) was added at –78 °C over 1 h to a solution of C<sub>3</sub>Cl<sub>4</sub><sup>15</sup> (1.25 mL, 10.2 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL). After stirring for 3 h, the reaction was warmed to rt for 30 min, cooled to 0 °C, and *n*-BuNH<sub>2</sub> (2.5 mL, 25 mmol, 2.5 equiv) was added. After 16 h, the reaction was concentrated, redissolved in 1:1 EtOAc/CH<sub>2</sub>Cl<sub>2</sub> (100 mL), and extracted into sat. NH<sub>4</sub>Cl (3 × 40 mL). The combined aqueous extracts were extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 40 mL), then these combined organic layers were washed with sat. NH<sub>4</sub>Cl (2 × 30 mL) and a combination of 0.5 M Na<sub>2</sub>CO<sub>3</sub> and 1 M NaBF<sub>4</sub> (2 × 20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The resulting brown syrup was purified by flash chromatography (5% → 8% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) on silica gel (250 mL) to provide a yellow semisolid. This material was recrystallized from ~4:1 EtOAc/hexanes (30 mL) while diffusing in further hexanes at –20 °C to provide the HBF<sub>4</sub> salt of the title compound as a yellow solid (2.51 g, 58%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.58 (t, *J* = 5.3 Hz, 1H), 3.36 (app q, 2H), 2.96 (s, 24H), 1.67 (m, 2H), 1.38 (hex, *J* = 7.5 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  167.7, 128.5, 124.4, 123.4, 46.3, 39.8, 32.2, 19.3, 13.5. HRMS (ESI+) for C<sub>17</sub>H<sub>33</sub>N<sub>7</sub> [MH]<sup>+</sup> *m/z* calcd 336.2876, found 336.2881.

**Synthesis of GC<sub>2</sub> base 6·HBF<sub>4</sub>.** A solution of KOH (3 M, 13.75 mL, 41.25 mmol, 4.04 equiv) was added to 1·HCl (5.88 g, 20.4 mmol, 2.00 equiv) and 5<sup>16c</sup> (1.65 g, 10.7 mmol, 1.00 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) at 0 °C. After stirring for 72 h, the CH<sub>2</sub>Cl<sub>2</sub> was evaporated, the residue

was dissolved in EtOAc (250 mL), extracted with 1 M HCl (3 × 75 mL), and extracted from the combined aqueous layers with CH<sub>2</sub>Cl<sub>2</sub> (3 × 75 mL). The combined CH<sub>2</sub>Cl<sub>2</sub> layers were washed with 5% Na<sub>2</sub>CO<sub>3</sub> (75 mL) and concentrated. This residue was dissolved in EtOAc (150 mL), washed with sat. NH<sub>4</sub>Cl (50 mL), 50% sat. NH<sub>4</sub>Cl (2 × 50 mL), and a combination of 5% Na<sub>2</sub>CO<sub>3</sub> and 1 M NaBF<sub>4</sub> (2 × 25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The resulting pale yellow solid was recrystallized from ~10:1 EtOAc/hexanes (125 mL) for 6 days at -20 °C to provide a white solid (5.67 g, 79%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 4.52 (t, J = 5.6 Hz, 1H), 3.89 (hept, J = 6.7 Hz, 8H), 3.31 (dt, J = 7.4, 5.8 Hz, 2H), 1.59 (m, 2H), 1.39–1.18 (overlapping signals, 50H), 0.91 (t, J = 7.4 Hz, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 161.0, 121.9, 120.4, 50.3, 42.9, 32.1, 22.1, 20.3, 14.0. HRMS (ESI+) for C<sub>33</sub>H<sub>65</sub>N<sub>7</sub> [MH]<sup>+</sup> m/z calcd 584.5380, found 584.5374.

**Synthesis of GC<sub>2</sub> base 8-HBF<sub>4</sub> Compound 7.**<sup>16c</sup> (1.17 g, 7.60 mmol, 1.00 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) was added to a solution of **1** (7.68 g, 30.6 mmol, 4.02 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) at 0 °C. After stirring for 42 h, the CH<sub>2</sub>Cl<sub>2</sub> was evaporated, the residue was suspended in EtOAc (200 mL), washed with 50% sat. NH<sub>4</sub>Cl (2 × 75 mL) and a combination of 5% Na<sub>2</sub>CO<sub>3</sub> and 1 M NaBF<sub>4</sub> (2 × 25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. This solid was recrystallized from ~2:1 EtOAc/hexanes (50 mL) for 2 days at -20 °C to provide a white solid (3.44 g, 67%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 4.09 (s, 1H), 3.87 (hept, J = 6.8 Hz, 8H), 1.43 (s, 9H), 1.29 (d, J = 6.8 Hz, 48H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 159.4, 121.5, 120.4, 51.9, 50.3, 29.3, 22.1. HRMS (ESI+) for C<sub>35</sub>H<sub>65</sub>N<sub>7</sub> [MH]<sup>+</sup> m/z calcd 584.5380, found 584.5374.

**Synthesis of PC<sub>1</sub> Base 14-HBF<sub>4</sub> Compound 13.**<sup>19</sup> (1.05 g, 5.04 mmol, 1.00 equiv) in THF (5 mL) was added dropwise to a solution of **1** (2.82 g, 11.2 mmol, 2.23 equiv) in THF (70 mL) at -78 °C. After 4 h, the reaction was warmed to 0 °C, and after 2 h, piperidine (2.5 mL, 25 mmol, 5.0 equiv) was added. After 24 h of warming to rt, the reaction was concentrated, and the residue was suspended in EtOAc (150 mL), washed with sat. NH<sub>4</sub>Cl (2 × 75 mL), 50% sat. NH<sub>4</sub>Cl (75 mL), and a combination of 0.5 M Na<sub>2</sub>CO<sub>3</sub> and 1 M NaBF<sub>4</sub> (2 × 20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The resulting yellow solid (3.21 g) was recrystallized from ~2:1 EtOAc/hexanes (100 mL) while diffusing in further hexanes at -20 °C to provide the phosphazene-HBF<sub>4</sub> as a white solid (2.71 g, 88%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 3.92 (hept, J = 6.9 Hz, 4H), 3.28 (d, J = 12.1 Hz, 1H), 3.19 (m, 4H), 3.08 (m, 4H), 1.63–1.52 (m, 12H), 1.33 (d, J = 7.0 Hz, 24H), 1.29 (s, 9H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 119.4 (d, J<sub>PC</sub> = 22.1 Hz), 118.5, 52.1, 49.7, 46.2, 31.4 (d, J<sub>PC</sub> = 3.9 Hz), 26.1 (d, J<sub>PC</sub> = 5.3 Hz), 24.4, 22.0. <sup>31</sup>P NMR (121 MHz, CDCl<sub>3</sub>) δ 16.18. HRMS (ESI+) for C<sub>29</sub>H<sub>57</sub>N<sub>6</sub>P [MH]<sup>+</sup> m/z calcd 521.4461, found 521.4469.

**Liberation of Higher-Order Superbases.** In a glovebox, KO<sup>t</sup>-Bu (1 M in THF, 1.0 equiv) was added to the superbase conjugate acid salt in THF (~0.2 M) at room temperature. After 5–10 min, the solution was filtered (0.2 μm PTFE), washed with THF, concentrated, redissolved in PhMe, filtered again, and concentrated.

**pK<sub>BH+</sub> Measurements.** Stock solutions of the HX salt of the “substrate” superbase being studied (0.0667 M, 0.60 mL, 0.040 mmol) and a reference free base (0.200 M, 0.20 mL, 0.040 mmol) were mixed in NMR tubes under inert atmosphere. CD<sub>3</sub>CN was employed for all experiments, which were performed using a dual manifold, except for the GC<sub>2</sub> (**6**) and GP<sub>2</sub> (**10**) bases, which employed d<sub>8</sub>-THF and were performed in a glovebox. The mixture was analyzed by <sup>1</sup>H NMR spectroscopy (as well as by <sup>13</sup>C NMR for measurements in d<sub>8</sub>-THF).

The extents of protonation of both the substrate superbase and the reference base were determined by comparison to the spectra of the HX salt and the free base of each component. These data were used to calculate the relative basicities of the substrate superbase and the reference base, and this value was compared to the known pK<sub>BH+</sub> value of the reference base to obtain the pK<sub>BH+</sub> value of the substrate. Measurements were performed in triplicate. Corrections were made for the observed relative NMR integrations and to convert THF data to the acetonitrile scale.

The reference bases used were DBU (pK<sub>BH+</sub> = 24.34, MeCN)<sup>24</sup> for G<sub>1</sub> (**16**); P<sub>1</sub>-tBu(pyr)<sub>3</sub> (pK<sub>BH+</sub> = 28.35, MeCN)<sup>19</sup> for C<sub>1</sub> (**17**), P<sub>1</sub> (**18**), G<sub>3</sub> (**11**), CG<sub>2</sub> (**4**), C<sub>3</sub> (**2**), and PC<sub>1</sub> (**14**); and P<sub>2</sub>-Et (pK<sub>BH+</sub> = 32.94, MeCN)<sup>6c</sup> for GC<sub>2</sub> (**6**), and GP<sub>2</sub> (**10**). The remaining superbases

whose pK<sub>BH+</sub> values discussed herein are literature values, except the PC<sub>3</sub> base **12** which was estimated from Figure 3. See the SI for complete details.

**Preparation of Single Crystals for X-ray Diffraction.** In a 2 dram vial, higher-order superbase salts were dissolved in hot EtOAc, cooled to rt, and then allowed to stand. In some cases, the vial was also placed in a sealed jar containing a layer of hexanes to slowly diffuse these vapors into the EtOAc solution.

C<sub>3</sub> base 2-HBF<sub>4</sub>: salt (150 mg) in EtOAc (3 mL), standing with hexanes diffusion for 3 days.

CG<sub>2</sub> base 4-HBF<sub>4</sub>: salt (100 mg) in EtOAc (3 mL), seeded with a few grains of the salt, then standing alone for 1 day and then with hexanes diffusion for 5 days.

GC<sub>2</sub> base 6-HBF<sub>4</sub>: salt (150 mg) in EtOAc (3 mL), standing with hexanes diffusion for 2 days.

PC<sub>1</sub> base 14-HBF<sub>4</sub>: salt (150 mg) in EtOAc (5 mL), standing alone for 3 days and then with hexanes diffusion for 1 day.

GP<sub>2</sub> base 10-HBF<sub>4</sub>: salt (100 mg) in EtOAc (5 mL), standing alone for 2 days.

**Conjugate Additions of α-Aryl Esters and Nitriles.** KO<sup>t</sup>-Bu (1 M in *t*-BuOH or THF, 25 μL, 0.025 mmol, 0.025 equiv) was added to 8-HBF<sub>4</sub> (20.3 mg, 0.0302 mmol, 0.030 equiv) in THF (3 mL), followed by the α-aryl ester or nitrile and Michael acceptor (1 mmol scale, see SI for details). After stirring for 8–12 h, acetic acid was added (2 drops), and the reaction was concentrated. The residue was purified by chromatography (EtOAc/hexanes) on silica gel (40 mL) to afford the desired adducts. Experiments were also performed using isolated free bases **8** or P<sub>4</sub>-*t*Bu from a glovebox.

## ■ ASSOCIATED CONTENT

### ● Supporting Information

Experimental details, characterization data, pK<sub>BH+</sub> measurements, and crystallographic data (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b05033.

## ■ AUTHOR INFORMATION

### Corresponding Author

\*tl2240@columbia.edu

### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

- (1) Caubere, P. *Chem. Rev.* **1993**, *93*, 2317.
- (2) *Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts*; Ishikawa, T., Ed.; John Wiley & Sons, Ltd: Chichester, UK, 2009.
- (3) Recent reviews: (a) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632. (b) Ishikawa, T.; Kumamoto, T. *Synthesis* **2006**, *2006*, 737. (c) Leow, D.; Tan, C.-H. *Chem. - Asian J.* **2009**, *4*, 488. (d) Sohtome, Y.; Nagasawa, K. *Synlett* **2010**, *2010*, 1. (e) Leow, D.; Tan, C.-H. *Synlett* **2010**, *2010*, 1589. (f) Terada, M. *Yuki Gosei Kagaku Kyokaiishi* **2010**, *68*, 1159. (g) Uruguchi, D.; Ooi, T. *Yuki Gosei Kagaku Kyokaiishi* **2010**, *68*, 1185.
- (4) Seminal publications: (a) Chinchilla, R.; Nájera, C.; Sánchez-Agulló, P. *Tetrahedron: Asymmetry* **1994**, *5*, 1393. (b) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. J. *Am. Chem. Soc.* **1996**,

- 118, 4910. (c) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157. (d) Ishikawa, T.; Araki, Y.; Kumamoto, T.; Isobe, T.; Seki, H.; Fukuda, K.; Isobe, T. *Chem. Commun.* **2001**, 245. (e) Kita, T.; Georgieva, A.; Hashimoto, Y.; Nakata, T.; Nagasawa, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 2832. (f) Allingham, M. T.; Howard-Jones, A.; Murphy, P. J.; Thomas, D. A.; Caulkett, P. W. R. *Tetrahedron Lett.* **2003**, *44*, 8677. (g) Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454. (h) Shen, J.; Nguyen, T. T.; Goh, Y.-P.; Ye, W.; Fu, X.; Xu, J.; Tan, C.-H. *J. Am. Chem. Soc.* **2006**, *128*, 13692. (i) Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* **2006**, *128*, 16044. (j) Yu, Z.; Liu, X.; Zhou, L.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2009**, *48*, 5195. (k) Dong, S.; Liu, X.; Chen, X.; Mei, F.; Zhang, Y.; Gao, B.; Lin, L.; Feng, X. *J. Am. Chem. Soc.* **2010**, *132*, 10650. (l) Misaki, T.; Takimoto, G.; Sugimura, T. *J. Am. Chem. Soc.* **2010**, *132*, 6286. (m) Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392. (n) Wu, L.; Li, G.; Fu, Q.; Yu, L.; Tang, Z. *Org. Biomol. Chem.* **2013**, *11*, 443. (o) Dai, Q.; Huang, H.; Zhao, J. C.-G. *J. Org. Chem.* **2013**, *78*, 4153. (p) Zou, L.; Wang, B.; Mu, H.; Zhang, H.; Song, Y.; Qu, J. *Org. Lett.* **2013**, *15*, 3106. (q) Núñez, M. G.; Farley, A. J. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16348.
- (5) Štrukil, V.; Lekšić, E.; Meštrović, E.; Eckert-Maksić, M. *Aust. J. Chem.* **2014**, *67*, 1129.
- (6) (a) Schwesinger, R.; Schlemper, H. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1167. (b) Schwesinger, R.; Hasenfratz, C.; Schlemper, H.; Walz, L.; Peters, E.-M.; Peters, K.; von Schnering, H. G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1361. (c) Schwesinger, R.; Schlemper, H.; Hasenfratz, C.; Willaredt, J.; Dambacher, T.; Breuer, T.; Ottaway, C.; Fletschinger, M.; Boele, J.; Fritz, H.; Putzas, D.; Rotter, H. W.; Bordwell, F. G.; Satish, A. V.; Ji, G.; Peters, E.-M.; Peters, K.; von Schnering, H. G.; Walz, L. *Liebigs Ann.* **1996**, *1996*, 1055.
- (7) Kolomeitsev, A. A.; Koppel, I. A.; Rodima, T.; Barten, J.; Lork, E.; Rösenthaller, G.-V.; Kaljurand, I.; Kütt, A.; Koppel, I.; Mäemets, V.; Leito, I. *J. Am. Chem. Soc.* **2005**, *127*, 17656.
- (8) Vazdar, K.; Kunetskiy, R.; Saame, J.; Kaupmees, K.; Leito, I.; Jahn, U. *Angew. Chem., Int. Ed.* **2014**, *53*, 1435.
- (9) (a) Lensink, C.; Xi, S. K.; Daniels, L. M.; Verkade, J. G. *J. Am. Chem. Soc.* **1989**, *111*, 3478. (b) Tang, J.; Dopke, J.; Verkade, J. G. *J. Am. Chem. Soc.* **1993**, *115*, 5015.
- (10) Raab, V.; Kipke, J.; Gschwind, R. M.; Sundermeyer, J. *Chem. - Eur. J.* **2002**, *8*, 1682–1693.
- (11) (a) Raab, V.; Gauchenova, E.; Merkoulov, A.; Harms, K.; Sundermeyer, J.; Kovacević, B.; Maksić, Z. B. *J. Am. Chem. Soc.* **2005**, *127*, 15738. (b) Kögel, J. F.; Oelkers, B.; Kovačević, B.; Sundermeyer, J. *J. Am. Chem. Soc.* **2013**, *135*, 17768.
- (12) Belding, L.; Dudding, T. *Chem. - Eur. J.* **2014**, *20*, 1032.
- (13) Takeda, T.; Terada, M. *J. Am. Chem. Soc.* **2013**, *135*, 15306.
- (14) Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2012**, *134*, 5552.
- (15) Tobey, S. W.; West, R. *J. Am. Chem. Soc.* **1966**, *88*, 2481.
- (16) (a) Bredereck, H.; Bredereck, K. *Chem. Ber.* **1961**, *94*, 2278. (b) Eilingsfeld, H.; Neubauer, G.; Seefelder, M.; Weidincer, H. *Chem. Ber.* **1964**, *97*, 1232. (c) Barton, D. H. R.; Elliott, J. D.; Géro, S. D. *J. Chem. Soc. Chem. Commun.* **1981**, 1136. (d) Barton, D. H. R.; Elliott, J. D.; Géro, S. D. *J. Chem. Soc. Perkin Trans. 1* **1982**, 2085. (e) Isobe, T.; Fukuda, K.; Ishikawa, T. *J. Org. Chem.* **2000**, *65*, 7770.
- (17) Short, J. H.; Biermacher, U.; Dunnigan, D. A.; Leth, T. D. *J. Med. Chem.* **1963**, *6*, 275.
- (18) (a) Kühle, E.; Anders, B.; Zumach, G. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 649. (b) Kühle, E.; Anders, B.; Klauke, E.; Tarnow, H.; Zumach, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 20. (c) Gober, C. M.; Le, H. V.; Ganem, B. *Tetrahedron Lett.* **2012**, *53*, 4536.
- (19) Schwesinger, R.; Willaredt, J.; Schlemper, H.; Keller, M.; Schmitt, D.; Fritz, H. *Chem. Ber.* **1994**, *127*, 2435.
- (20) (a) Breslow, R.; Yuan, C. *J. Am. Chem. Soc.* **1958**, *80*, 5991. (b) Breslow, R.; Altman, L. J.; Krebs, A.; Mohacsí, E.; Murata, I.; Peterson, R. A.; Posner, J. *J. Am. Chem. Soc.* **1965**, *87*, 1326. (c) Wu, M. T.; Taub, D.; Patchett, A. A. *Tetrahedron Lett.* **1976**, *17*, 2405.
- (21) (a) Breslow, R.; Chang, H. W. *J. Am. Chem. Soc.* **1961**, *83*, 2367. (b) Chen, W.; Li, H.; Widawsky, J. R.; Appayee, C.; Venkataraman, L.; Breslow, R. *J. Am. Chem. Soc.* **2014**, *136*, 918.
- (22) For a report of direct, neutral base catalysis of aldol reactions using nitriles, see: (a) Kisanga, P.; McLeod, D.; D'Sa, B.; Verkade, J. *J. Org. Chem.* **1999**, *64*, 3090. *tert*-Butoxide has also been reported as an anionic catalyst: (b) Bunlaksananusorn, T.; Rodriguez, A. L.; Knochel, P. *Chem. Commun.* **2001**, 745. (c) Suto, Y.; Kumagai, N.; Matsunaga, S.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3147.
- (23) Kobayashi has recently reported an enantioselective method for direct base catalysis of Michael reactions with amides and esters using an anionic base (KHMDs). (a) Suzuki, H.; Sato, I.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2015**, *137*, 4336. See also: (b) Saito, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, *128*, 8704.
- (24) Kaljurand, I.; Kütt, A.; Sooväli, L.; Rodima, T.; Mäemets, V.; Leito, I.; Koppel, I. A. *J. Org. Chem.* **2005**, *70*, 1019.