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An Electron-Rich Proazaphosphatrane for Isocyanate Trimerization to Isocyanurates

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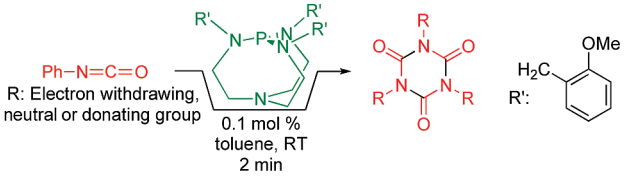
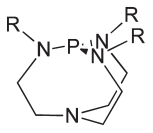


A facile synthesis of the new electron-rich, sterically hindered proazaphosphatrane shown above is described herein. This proazaphosphatrane catalyzes the cyclotrimerization of a wide variety of isocyanates to isocyanurates under mild conditions with unprecedentedly fast reaction times, giving moderate to high product yields. It is also shown that this proazaphosphatrane can be recycled up to 5 times.

Isocyanurates (perhydro-1,3,5-triazine-2,4,6-triones), typically produced by cyclotrimerizing isocyanates, enhance the physical properties of polyurethanes and coating materials.[1] Incorporation of isocyanurates into the framework of polyurethanes enhances their flame retardation and filming characteristics, and commercial products containing polymeric isocyanurates possess increased thermal and chemical resistance.[2] Isocyanurates are also employed in the preparation of copolymer resins which require water-resistance, transparency, and impact resistance,[3] and a novel optically active isocyanurate has been used for chiral discrimination of enantiomeric amino acid units.[4] Selective bonding of chloride anions via a *p*-nitrophenylsulfonamide group connected to an isocyanurate by an ethylene moiety has been reported,[5] and low-toxicity drug delivery has been achieved by tethering drug molecules to an isocyanurate backbone via an amide linker for facilitating subsequent drug release.[6] Triaryl isocyanurates are employed as activators in the continuous anionic copolymerization of ε-caprolactam to nylon-6,[7] and triallyl isocyanurates are useful in the preparation of flame-retardant laminating materials for electrical devices.[1]

The commercial importance of isocyanurates has generated numerous efforts aimed at the development of more effective methods for cyclotrimerizing isocyanates.[8] Problems with some of the known cyclotrimerization procedures include low catalyst activity, diazetidine byproduct formation, lengthy reaction times, product separation difficulties, and the use of toxic solvents.[1,9] Examples of Lewis base cyclotrimerization catalysts that have been reported include phosphines,[3,10] N-heterocyclic carbenes,[1] calcium carbene complexes,[11] amines,[12] NO,[13] fluoride anions,[14] and alkoxyalkenes.[15] Metal-containing cyclotrimerization catalysts include organotin[16] and zirconium[17] compounds, organozinc halides and alkoxides,[18] copper and nickel halides,[13] and palladium(0) systems.[19]

Proazaphosphatranes such as **1**−**5** are strong nonionic bases owing to transannulation of the basal nitrogen to the phosphorus atom upon protonation of the latter, and to the donation of electron density from all three of the P−N nitrogens.[20] In terms of low catalyst loading, fast reaction times, ease of product purification, and optional use of a nontoxic solvent such as toluene, proazaphosphatranes have thus far been shown to be the most effective catalysts so far reported for the cyclotrimerization of isocyanates.[10]



1: R = Me
2: R = *i*-Pr
3: R = *i*-Bu
4: R = Piv
5: R = Bn
6: R = 2-MeOBn
7: R = 2,4-DiMeOBn
8: R = 2,4,6-TriMeOBn

Previously, we showed that with no attempt at temperature control of the reaction, proazaphosphatrane **1** at 0.3 mol %

(1) Duong, H. A.; Cross, M. J.; Louie, J. *Org. Lett.* **2004**, *6*, 4679.
(2) (a) Wirpsza, Z. *Polyurethanes: Chemistry, Technology and Application*; Ellis Horwood: London, UK, 1993. (b) Zitinkina, A. K.; Sibanova, N. A.; Tarakanov, O. G. *Russ. Chem. Rev.* **1985**, *54*, 1866. (c) Nawata, T.; Kresta, J. E.; Frisch, K. C. *J. Cell. Plast.* **1975**, 267. (d) Nicholas, L.; Gmitter, G. R. *J. Cell. Plast.* **1965**, 85.
(3) Tang, J.; Mohan, T.; Verkade, J. G. *J. Org. Chem.* **1994**, *59*, 4931.
(4) Sugimoto, H.; Yamane, Y.; Inoue, S. *Tetrahedron: Asymmetry* **2000**, *11*, 2067.
(5) Hettche, F.; Hoffman, R. W. *New J. Chem.* **2003**, *27*, 172.
(6) Murray, A. P.; Miller, M. J. *J. Org. Chem.* **2003**, *68*, 191.
(7) (a) Bukac, Z.; Sebenda, J. *Chem. Prum.* **1985**, *35*, 361. (b) Horsky, J.; Kubanek, U.; Marick, J.; Kralicek, J. *Chem. Prum.* **1982**, *32*, 599.
(8) For additional information regarding isocyanate trimerization, see the Supporting Information.
(9) (a) Wegener, G.; Brandt, M.; Duda, L.; Hofmann, J.; Klesczewski, B.; Koch, D.; Kumpf, R.-J.; Orzesek, H.; Pirkl, H.-G.; Six, C.; Steinlein, C.; Weisbeck, M. *Appl. Catal. A* **2001**, *221*, 303. (b) Silva, A. L.; Bordado, J. C. *Catal. Rev.* **2004**, *46*, 31.
(10) (a) Tang, J.; Verkade, J. G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 896. (b) Liu, X.; Bai, Y.; Verkade, J. G. *J. Organomet. Chem.* **1999**, *582*, 16.
(11) Orzechowski, L.; Harder, S. *Organometallics* **2007**, *26*, 2144.
(12) (a) Tagachi, Y.; Shibaya, I.; Yasumoto, Y.; Ynoemoto, K. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3486. (b) Moghaddam, F. M.; Dekamin, M. G.; Koozehgari, G. R. *Lett. Org. Chem.* **2005**, *2*, 734.
(13) Villa, J. F.; Powell, H. B. *Synth. React. Met.-Org. Chem.* **1976**, *6*, 59.
(14) Nambu, Y.; Endo, T. *J. Org. Chem.* **1993**, *58*, 1932.
(15) Mizuya, J.; Yokozawa, T.; Endo, T. *J. Polym. Sci., Polym. Chem.* **1991**, *29*, 1544.
(16) (a) Bloodworth, A. J.; Davies, A. G. *J. Chem. Soc.* **1965**, 6858. (b) Foley, S. R.; Yap, G. P. A.; Richeson, D. S. *Organometallics* **1999**, *18*, 4700.
(17) Li, Y.; Matsumura, H.; Yamanaka, M.; Takahashi, T. *Tetrahedron* **2004**, *60*, 1393.
(18) Noltes, J. G.; Boersma, J. *J. Organomet. Chem.* **1967**, *7*, 6.
(19) Paul, F.; Moulin, S.; Piechaczyk, O.; Le Floch, P.; Osborn, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 7294.
(20) (a) Verkade, J. G. New Aspects of Phosphorus Chemistry II, Majoral, J. P., Ed., In *Top. Curr. Chem.* **2003**, *223*, 1−44. (b) Verkade, J. G.; Kisanga, P. *Tetrahedron* **2003**, *59*, 7819–7858. (c) Verkade, J. G.; Kisanga, P. B. *Aldrichim. Acta* **2004**, *37*, 3–14.

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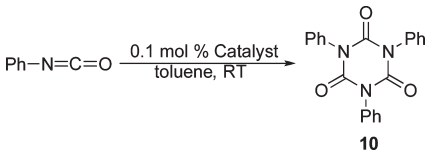
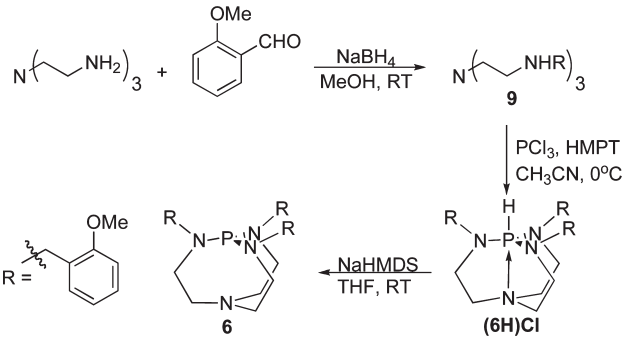
TABLE 1. Comparison of Catalytic Activity of Various Lewis Bases for the Cyclotrimerization of Phenyl Isocyanate[a]



entry	compd	R	pK_a	time[c]	yield (%)[d]
1	**5**	Bn	31.60	169	97
2	**4**	Piv	32.84[b]	135	97
3	**1**	Me	32.90[b]	121	95
4	**3**	^{i}Bu	33.53[b]	117	99
5	**2**	^{i}Pr	33.63[b]	110	97
6	**6**	2-MeOBn	33.70	96	99
7	**7**	2,4-DiMeOBn	34.16	92	98
8	**8**	2,4,6-TriMeOBn	34.25	84	96
9	$P(NMe_2)_3$			5 d	4[e,f]
10	P^tBu_3			24 h	2[f]
11	NEt_3			5 d	3[f]

[a]Reaction conditions: 15 mmol of phenyl isocyanate, 2 mL of toluene, rt. [b]Reference 21. [c]Seconds except were noted. [d]Average of three runs. [e]Heated to 70 °C. [f]1 mol % of promoter used.

SCHEME 1. Synthesis of Proazaphosphatrane 6



loading promoted the exothermic cyclotrimerization of phenyl isocyanate to the corresponding isocyanurate in benzene to give a product yield of 99% in 3 min,[10a] and that at a loading of 0.39 mol %, **2** catalyzes this reaction under the same conditions in 1 min in 97% isolated product yield.[10b] The basicity (pK_a) of the phosphorus appears to rise as electron induction of the alkyl substituent on the P−N nitrogens increases from **1** to **2**, but this trend in pK_a values is apparently reversed in the series **2** to **4** (Table 1). Thus perhaps the size increase in the alkyl substituents on these proazaphosphatranes may be interfering with the bonding of the apical proton and perhaps also with nucleophilic attack of phosphorus on an isocyanate carbon. Proazaphosphatrane **5** is less basic than **3**[21] presumably due to the electron withdrawing nature of the phenyl rings. As expected, the presence of electron donating groups on these rings in **6** to **8** (whose syntheses we report here) increases the pK_a of these compounds. Here we report the pK_a values of **5** to **8** in acetonitrile and the use of **6** as a superior catalyst for the cyclotrimerization of isocyanates to isocyanurates.

Following a known procedure,[21] **6** was synthesized in three steps in 61% overall yield (Scheme 1). The literature

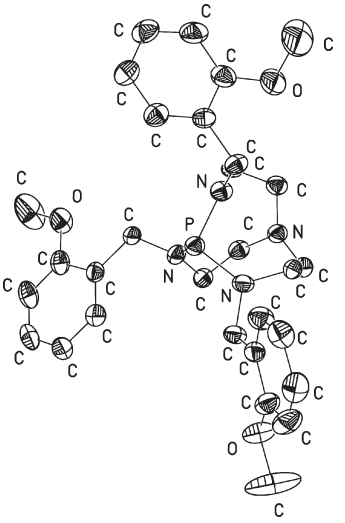


FIGURE 1. Computer drawing of the molecular structure of **6** at a 50% probability level. Hydrogen atoms are omitted for clarity.

procedure was modified, however, by using NaHMDS for the deprotonation step instead of K-O^{t}Bu, which has the advantage of effecting full rather than partial conversion to the desired deprotonated product. The syntheses of proazaphosphatranes **7** and **8** were carried out analogously. The molecular structure of **6** (determined by X-ray means and depicted in Figure 1) confirms its formulation as proposed in Scheme 1. Following a procedure we developed earlier[22] for determining pK_a values of proazaphosphatranes in acetonitrile, these values in the same solvent are shown for the new analogues **6**, **7**, and **8** in Table 1.

For determining the catalytic activity of proazaphosphatrane **6** for isocyanate cyclotrimerization relative to analogues **1**−**5**, 0.1 mol % of catalyst in toluene was used to cyclotrimerize phenyl isocyanate in a water bath at room temperature (Table 1). As shown in this table, excellent yields of product were obtained for **1**−**8** in short times in these exothermic reactions. There does not seem to be any straightforward correlation of reaction times with steric bulk or electron inductive effects from the P−N nitrogen alkyl substituents in **1**−**4**.

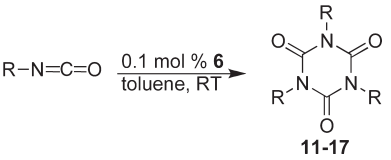
There is an increasing trend in pK_a values from **6** to **8**, however, suggesting that steric crowding of an axial proton by the increasing number of methoxy groups is absent. In fact, axial proton stabilization by hydrogen bonding via six-membered-ring chelation by the oxygens of three *o*-methoxy groups could occur, resulting in an increased pK_a value.

When tri-*tert*-butylphosphine was used in our protocol, only a 2% yield of the desired product was achieved after 24 h with a catalyst loading of 1 mol % (Table 1). Hexamethylphosphorous triamide (HMPT) and triethylamine were also used as catalysts (Table 1) but despite heating the HMPT reaction at 70 °C for 5 days, only 4% of the desired product was observed, and the use of triethylamine under the same conditions led to only 3% of the desired product. The contrasting catalyst performances of **1**−**4**, for example, compared with HMPT, demonstrate the advantageous

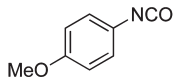
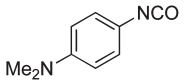
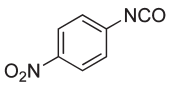
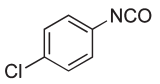
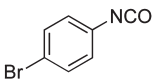
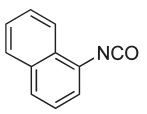
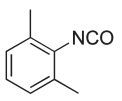
(21) Laramay, M. A. H.; Verkade, J. G. *J. Am. Chem. Soc.* **1990**, *112*, 9421.

(22) Kisanga, P. B.; Verkade, J. G.; Schwesinger, R. *J. Org. Chem.* **2000**, *65*, 5431.

TABLE 2. Substrate Scope of Aryl Isocyanates



11-17

entry	isocyanate	time	product	yield (%)[a,b]
1		7 min	**11**	96 (Lit: 56-96)
2		6 min	**12**	97
3		5 min	**13**	93 (Lit: 85-96)
4		5 min	**14**	91 (Lit: 78-99)
5		5 min	**15**	95
6		6 min	**16**	94 (Lit: 20-91)
7		30 min	**17**	53

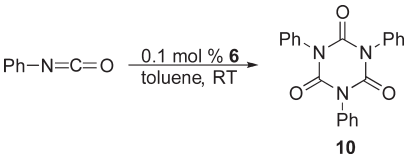
[a]Reaction conditions: 15 mmol of isocyanate, 0.1 mol % of proazaphosphatrane **6**, 2 mL of toluene, rt. [b]Average of two runs.

stereoelectronic features[20a] of the proazaphosphatrane framework for the present catalytic objective.

With these results in hand, the scope of cyclotrimerization using a variety of isocyanates was explored as shown in Table 2. These reactions were carried out with 0.1 mol % of proazaphosphatrane **6** as the promoter in toluene at room temperature. The electron-rich aryl substrate 4-methoxyphenyl isocyanate was trimerized in 7 min in 96% isolated yield (Table 2, entry 1). Such electron-rich substrates typically show low reactivity toward cyclotrimerization with other catalyst systems.[15,23] 4-Dimethylphenyl isocyanate was similarly cyclotrimerized, providing a 97% isolated yield of a new isocyanurate (Table 2, entry 2) in 6 min. Electron-deficient 4-nitrophenyl isocyanate was cyclotrimerized in 5 min in 93% yield (entry 3). Isocyanates such as 4-chlorophenyl isocyanate and 4-bromophenyl isocyanate also cyclotrimerized in fast reaction times giving 91% and 95% isolated yields of product, respectively (Table 2, entries 4 and 5). Our protocol is also effective for sterically hindered isocyanates such as 1-naphthyl isocyanate that provided a 94% isolated product yield (entry 6). In the presence of catalyst **6**, sterically bulky 2,6-dimethylphenyl isocyanate required 30 min to cyclotrimerize in 53% isolated product yield (Table 2, entry 7).

(23) Endo, T.; Suike, J. *Chem. Abstr.* **1990**, *112*, 77236.

TABLE 3. Recyclability of Proazaphosphatrane 6



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entry	cycle	time (min)	yield (%)[a,b]
1	**1**	2	99
2	**2**	2	97
3	**3**	3.5	98
4	**4**	8	98
5	**5**	15	95

[a]Reaction conditions: 15 mmol of phenyl isocyanate, 0.1 mol % of proazaphosphatrane **6**, 5 mL of toluene, rt. [b]Average of two runs.

Previously, we proposed a mechanism in which a proazaphosphatrane attacks the isocyanate carbon atom on phenyl isocyanate, producing an anionic charge on the isocyanate nitrogen and a cationic charge on phosphorus. The anionic site then similarly attacks a second phenyl isocyanate molecule to generate an analogous zwitterion, which in turn attacks a third isocyanate. This process is followed by cyclotrimerization to form product and regenerated catalyst.[10b] In the present work we demonstrate that the catalyst is indeed regenerated for recycling. With use of 0.1 mol % of proazaphosphatrane **6** in 5 mL of toluene for the cyclotrimerization of phenyl isocyanate, the completion of the reaction in 2 min was accompanied by the formation of a white solid (Table 3, entry 1). After filtration of the solid under inert atmosphere, the toluene filtrate (containing only **6**) was subjected to a second cyclotrimerization cycle. Pleasingly, the reaction completed in minutes with a 97% isolated yield of the phenyl isocyanurate (Table 3, entry 2). The proazaphosphatrane could then be recycled up to 3 more times in which the phenyl isocyanurate was isolated in high yields, but with longer formation times (Table 3, entries 3−5).

We suggest that adventitious moisture present in the reaction mixture restricts the number of catalytic cycles of **6**. Evidence for this suggestion was observed in the repetition of the aforementioned recycling experiment with a larger concentration (1 mol %) of **6**. Under those conditions we were able to observe a small peak in the ^{31}P NMR at −10 ppm in the filtrate corresponding to the phosphorus peak of the **6**H$^+$ cation (in addition to the +128 ppm peak corresponding to free **6**). Subsequent recycling of **6** showed that the −10 ppm ^{31}P NMR peak grew in intensity. Attempts to remove the moisture source by distilling phenyl isocyanate onto activated molecular sieves and by using dry solvents under Schlenk techniques were to no avail. ^{1}P NMR monitoring of a toluene solution of a mixture of **6** and phenyl isocyanate in a flame-sealed NMR tube over a period of 1 month revealed that the small ^{1}P peak corresponding to **6**H$^+$ that formed initially remained constant in intensity, thus confirming the likelihood of contamination by moisture during workup procedures.

In conclusion, we have demonstrated that the new proazaphosphatrane **6** is a superior catalyst for the synthesis of isocyanurates from a wide variety of aryl isocyanates. It should be noted that alkyl isocyanates (such as cyclohexylisocyanate) did not form the corresponding isocyanurate

with our protocol. We have also shown that catalyst **6** can be recycled up to 5 times with high product yields but with successively slower reaction times owing to continuous deactivation by moisture. Exploration of additional catalytic applications of **6** is underway.

Experimental Section

Synthesis of Compound 9. To 1.0 equiv of freshly distilled tris(2-aminoethyl)amine in 100 mL of MeOH was added 3.1 equiv of *o*-anisaldehyde. The mixture was allowed to stir at room temperature overnight and then another 100 mL of MeOH was added. The reaction mixture was cooled 0 °C in an ice bath and then $NaBH_4$ (1.5 equiv) was added slowly and portion-wise over 1 h. The reaction mixture was stirred overnight and then the MeOH was removed via rotovap. The addition of 50 mL of water was followed by extraction with 3×100 mL of toluene. The toluene extracts were combined and dried over Na_2SO_4 and then the toluene extract was filtered and removed via rotovap. The crude dark yellow oil was purified by column chromatography (1% MeOH in CH_2Cl_2) to obtain 92% of the desired product as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57−2.58 (d, 6H, J = 5.2 Hz), 2.62−2.63 (d, 6H, J = 4.8 Hz), 3.71 (s, 15H), 4.39 (br, 3H), 6.76−6.78 (d, 3H, J = 8 Hz), 6.80−6.84 (t, 3H, J = 14.8 Hz), and 7.15−7.27 ppm (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 130.1, 128.6, 126.3, 120.4, 110.1, 55.1, 53.5, 47.9, and 46.5 ppm. HRMS m/z 506.32700 (calcd for $C_{30}H_{42}N_4O_3$ 506.32569).

Synthesis of (6H)Cl. Dry CH_3CN (50 mL) was charged to a round-bottomed Schlenk flask, which was then cooled to 0−5 °C. HMPT [$P(NMe_2)_3$, 10.05 g, 2.0 equiv] was added under argon followed by slow addition of PCl_3 (4.19 g, 1 equiv) via syringe. After the reaction mixture was stirred at 0−5 °C for 15 min, **9** (46.53 g, 3.0 equiv) dissolved in 50 mL of dry CH_3CN was added. The reaction mixture was stirred overnight at rt and then solvent was removed via rotovap, leaving a sticky yellow solid. Addition of 5−10 mL of THF to this solid formed a free-flowing solid and addition of ethyl ether (250 mL) to this mixture led to the formation of additional solids. Placing the flask in a freezer for 3 days caused more solids to form. Filtration of the solids followed by drying under reduced pressure produced a light yellow powder (85% isolated yield). ^{1}H NMR (400 MHz, CD_3CN) δ 3.04−3.10 (m, 6H), 3.20−3.25 (m, 6H), 3.76 (s, 9H), 4.07−4.11 (d, 6H, J = 16.8 Hz), 5.09−6.37 (d, 1H, J = 509.2 Hz), 6.9−6.95 (m, 6H), 7.16−7.18 (d, 3H, J = 7.2 Hz), and 7.25−7.29 ppm (t, 3H, J = 15.6 Hz). ^{13}C NMR (400 MHz, CD_3CN) δ 125.4, 129.7, 129.5, 127.0, 121.3, 118.3, 111.6, 56.0, 47.9, 46.8, and 40.0 ppm. ^{31}P NMR (168 MHz, CD_3CN) δ −9.97 ppm.

Synthesis of 6. To a 25 mL round-bottomed flask containing compound **(6H)Cl** (44.54 g, 1 equiv) was added 150 mL of THF followed by stirring for 10 min at room temperature. NaHMDS (28.6 g, 2 equiv) was added to the slurry and then the reaction mixture was stirred overnight. The THF was then evaporated under inert atmosphere and then ether (100 mL) was added to extract **6**. After filtration of the extract, the ether was evaporated under reduced pressure and 10 mL of toluene was added followed by 40 mL of pentane, resulting in precipitation of **6**. Evaporation of the solvent under reduced pressure left 30.46 g of **6** (73% isolated yield). Crystals of **6** suitable for X-ray analysis were obtained by placing a concentrated solution of MeCN in a freezer for 2 days. ^{1}H NMR (400 MHz, C_6D_6) δ 2.69−2.70 (m, 6H), 2.86 (br, 6H), 3.35 (s, 9H), 4.52−4.54 (d, 6H, J = 10 Hz), 6.57−6.59 (d, 3H, J = 8 Hz), 6.93−6.97 (t, 3H, J = 14.8 Hz), 7.11−7.16 (t, 3H, J = 14 Hz), and 7.65−7.67 (d, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, C_6D_6) δ 158.3, 130.2 (d, J = 5.7 Hz), 130.0, 128.1, 55.1, 51.9, 48.0 (d, J = 41.1 Hz), and 46.8 (d, J = 6.6 Hz). ^{31}P NMR (186 MHz, C_6D_6) δ 127.90 ppm. HRMS m/z 534.27714 (calcd for $C_{30}H_{39}N_4O_3P$ 534.27596).

General Procedure for the Synthesis of Isocyanurates with 6 as a Catalyst. To a 100 mL round-bottomed flask with a side arm was added 8 mg (0.1 mol %) of proazaphosphatrane **6** in a glovebox. The flask was capped with a rubber septum and then it was taken out of the glovebox and charged with 2 mL of toluene. The isocyanate (1.78 g, 15 mmol) was added with stirring for the allotted time indicated, using a stopwatch, until the isocyanurate had precipitated. The solids were washed with 5 mL of toluene to extract any impurities and the mixture was then filtered. The solids were dried under reduced pressure and weighed.

Procedure for Recycling 6. To a 100 mL round-bottomed flask with a side arm was added 8 mg (0.1 mol %) of **6** in a glovebox. The flask was capped with a rubber septum and then it was removed from the glovebox and charged with 2 mL of toluene. Phenyl isocyanate (1.78 g, 15 mmol) was added to the flask under an argon flow and then the mixture was stirred for the allotted time. After completion of the reaction, 5 mL of toluene was added followed by stirring for an additional 30 min, after which the solution was filtered under an inert atmosphere through a glass fritted filter tube and then the solution was dried under reduced pressure. This procedure was repeated 4 more times.

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Supporting Information Available: References to known compounds, copies of ^{1}H and ^{13}C NMR spectra for all isocyanurate products, data for unknown compounds, and ^{31}P NMR spectra for proazaphosphatranes **6**, **7**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.