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Selective N-Alkylation of Amines with Alcohols by Using Non-Metal-Based Acid–Base Cooperative Catalysis

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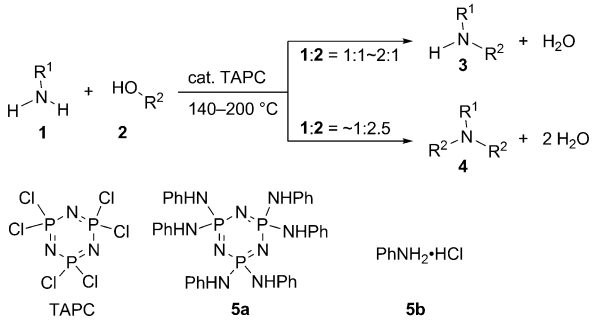
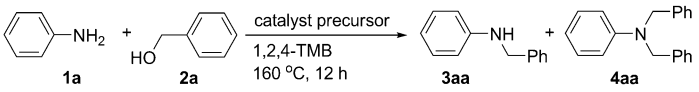
Higher amines are widely used in both the bulk and fine chemical industry for the synthesis of fundamental materials, such as additives, dyes and agrochemicals.[1] Therefore, the development of a selective N-alkylation method that is cost effective, salt free and environmentally benign is of considerable interest. Indeed, reactions involving the N-alkylation of amines with alcohols[2] (R–OH) in place of R–X, where X denotes halide, tosylate, mesylate, or triflate,[1d,e] are well documented. To promote the N-alkylation using R–OH, metal-based catalyses have been developed. These reactions mainly use benzylic-type and saturated alcohols with catalytic Ru,[3] Ir,[4] Cu,[5a–e] Ni,[5f] and Ag[5g,h] species. In addition, Lewis acidic metals[6] and Pd[7] catalysts are also competent mediators of N-alkylation with benzylic-type secondary alcohols and allylic alcohols. Herein, we report a novel and straightforward method for the N-alkylation with R–OH (1°, 2° and 3°) using non-metal-based[8a] catalysis promoted by 1,3,5-triazo-2,4,6-triphosphorine-2,2,4,4,6,6-hexachloride[9] (TAPC). This new reaction involves substitution (S_N) at the alcohols sp^3 carbon atom bearing the hydroxyl group (Scheme 1),[8b] by which selective N-mono- and dialkylation were successfully achieved.

Treatment of aniline (**1a**, 2 equiv) with benzyl alcohol (**2a**, 1 equiv) in the presence of TAPC (5 mol% with respect to **2a**) at 160°C for 12 h in 1,2,4-trimethylbenzene (1,2,4-TMB) under Ar using a sealed reactor,[10] followed by column chromatography on silica gel, gave mono-alkylated amine **3aa** in 92% yield (Scheme 2, Table 1, entry 1).[11] The tertiary amine resulting from N-dialkylation was obtained in about 7% yield, as determined by GC-MS and ^{1}H NMR spectroscopy. Formation of benzyl chloride and dibenzyl ether was found to be negligible[12] by GC-MS analysis. In the absence of solvent, the yield of **3aa** decreased to 75% (entry 1). Addition of water (0.3 and 2.0 equiv with respect to **2a**) to the solute at 25°C prior to reaction initiation did not prevent the reaction from proceeding at 160°C (**3aa** was recovered in 98 and 90%, respectively). Finally, a change in the ratio of **1a**/**2a** from 2:1 to 1:2.5 resulted exclusively in N-dialkylation, giving **4aa** in 80% yield (entry 2).[13]

Control reactions were performed to probe the involvement of Brønsted acid catalysts that might be generated in



Scheme 1. General scheme for TAPC-catalysed selective N-alkylation of amines **1** using alcohols **2**.



Scheme 2. Selective N-mono- and dibenzylation of **1a**.

Table 1. N-Alkylation of **1a** with **2a** under different conditions.[a]

Entry	Catalyst precursor ([mol%])	**1a**:**2a**[b]	Yield[%][c]
1	TAPC (5)	2:1	92 (75)[d]
2	TAPC (4)	1:2.5	<1 (80)[e]
3	TAPC (5)	2:1	45[f]
4	H_3PO_4 (30)	2:1	<1
5	HCl[i] (30)	2:1	23
6	HCl[i] (30) + H_3PO_4 (15)	2:1	51
7	**5a** (5)	2:1	22[g]
8	**5b** (30)	2:1	46[g]
9	**5a** (5) + **5b** (30)	2:1	81[h]
10	**5a** (5) + NMe_4Cl (30)	2:1	26

[a] Unless otherwise specified, the reaction was carried out with **1a** (4 mmol), **2a** (2 mmol) and catalyst precursor (0.1 mmol: 0.09 M) in 1,2,4-TMB (0.5 mL) at 160°C for 12 h. [b] Molar ratio of components **1a** and **2a** in the reaction mixture at $t=0$. [c] Yield of crude product **3aa** determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [d] Without solvent. [e] Isolated yield of **4aa**; **1a**:**2a**:TAPC = 40:100:4 ($[TAPC]_0$ = 0.12 M). [f] 140°C, 12 h. [g] **1a** (3.4 mmol) was used. [h] **1a** (2.8 mmol) was used. [i] 2 M Solution in Et_2O.

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situ, such as H_3PO_4, HCl, or a combination of these two. In fact, these catalysts were found to decelerate the reaction rate (entries 4–6). Convinced that simple Brønsted acid catalysis was not operative, we pursued time profiles of the reaction course using $^{31}P\{^1H\}$ NMR spectroscopy in order to identify the resting state of the P-based catalyst. According to the time-dependent spectra, the singlet signal of TAPC (δ = 20.7 ppm in 1,2,4-TMB/$CDCl_3$ at 25 °C) immediately diminished when mixed with **1a** and **2a** at 25 °C and disappeared completely at elevated temperatures (160 °C, t < 20 min). Instead, only one singlet ($\delta = (1.2 \pm 0.1)$ ppm in 1,2,4-TMB/$CDCl_3$) was detected, which retained the same δ position at all time periods of sampling (up to t = 12 h).

To elucidate the resting state structure of the P species, we attempted its isolation from a solution of **1a** and TAPC. Two chemical entities, **5a**[14] and **5b**, were separated from the mixture through a simple filtration–wash technique, and both were obtained in quantitative yields (calculated based on a molar amount of P and Cl, respectively). When **5a** was added to a reaction mixture containing **1a**, **2a** and the structurally modified TAPC (its structure was not clarified up to that time), the $^{31}P\{^1H\}$ NMR signal of **5a** entirely overlapped at δ = 1.23 ppm with the signal consistently observed throughout the N-alkylation. This strongly suggests that **5a** is the resting state of the catalyst.

Given the understanding gained in our NMR experiments, we examined **5a**, **5b**, or a combined mixture of these two compounds as potential catalysts in the reaction (Table 1, entries 7–9). Of these, **5a + 5b** showed the highest catalytic performance. To get an insight into the kinetic profiles of catalysis promoted by each of these four species, **5a**, **5b**, **5a + 5b** and TAPC, yields of **3aa** were plotted as a function of reaction time (Figure 1). The **5a + 5b** curve has a slope similar to that of the TAPC curve, but with a lower initial reaction rate. When a suspension containing **5a + 5b** was heated to 160 °C, complete dissolution of the solids took about 30 min, suggesting that the induction period (t < 1 h) is partially related to the time required to make the reaction mixture homogeneous. In summary, these experiments clearly demonstrate that TAPC readily generates **5a** in situ with

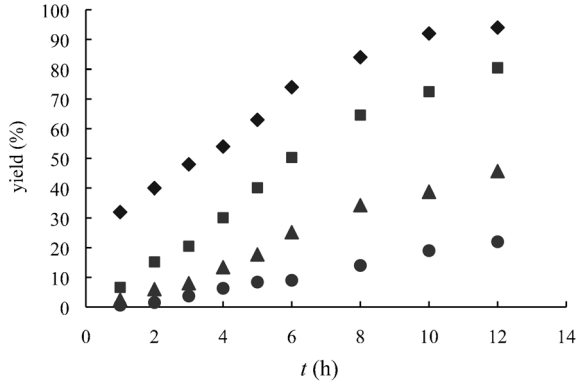
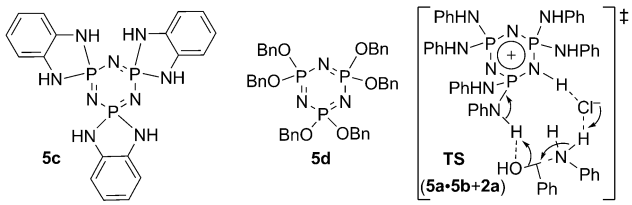


Figure 1. NMR yield (%) of **3aa** obtained from the reaction of **1a** with **2a** (2:1) at 160 °C vs. reaction time (t, h). (◆): with TAPC (5 mol %); (■): with **5a** (5 mol %) + **5b** (30 mol %); (▲): with **5b** (30 mol %); (●): with **5a** (5 mol %). Net $[\mathbf{1a}]_0$ was kept identical for each run.

concomitant liberation of **5b** during N-alkylation. Since Me_4NCl did not enhance the reactivity of **5a** (entry 10) and H_3PO_4 was totally inert (entry 4), **5a** and **5b** (thus $H^+ + Cl^-$) acted synergistically to catalyze the reaction.[12,15]

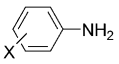
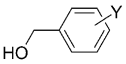
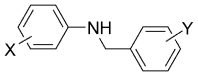
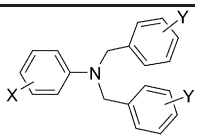
To elucidate the mechanism with which **5b** (HCl) and the resting state P species **5a** catalyzed the reaction of **1a** with **2a**, additional control experiments were carried out (160 °C, 12 h). When $[D_{30}]$**5a** (consisting of 6(C_6D_5NH), 5 mol %) + **5b** (30 mol %) were used with **1a**:**2a** = 1.4:1, **3aa** was obtained in 81 % yield without any incorporation of deuterium. Similarly, **3aa** was obtained from **1a**:**2a** = 1.4:1 in 98 % yield when **5c**[16] (mol %) was used in combination with **5b** (30 mol %). In this case N-alkylation of 1,2-diaminobenzene was not detected by GC-MS. These experiments strongly suggest that **5a** is stable on the reaction timescale. Phosphazene **5a** is much more basic than **1a**, since upon protonation of **5a** with **5b** delocalization of the counterion of Cl^- is reinforced in the six-membered phosphazene ring system. The enhanced catalytic activity of **5a + 5b** (=**5a + 1a** + HCl) being less acidic than **5b** suggests that **5a + 5b** serves as a superior acid–base cooperative catalyst in our reaction. Mechanistically, **1a** in the **5a + 5b** complex could undergo N-alkylation with **2a** (thus bimolecular reaction) giving **3aa** in a concerted fashion (e.g., **TS**) after recombinant of hydrogen bonds[17] in **5a + 5b** may or may not occur at the secondary coordination sphere[18] of **5a**.[19,20] Another important role of HCl is to regenerate the resting state **5a** more effectively. When **5d**[21] (5 mol % with respect to net **2a**) alone was used with **1a**:**2a** = 2.9:1, **3aa** was obtained in 43 % yield. In contrast, the yield of **3aa** was increased to 98 % using **5d** (5 mol %) + **5b** (30 mol %) with **1a**:**2a** = 2.4:1. In this last reaction, **5a** (+**5b**) was again the only species observable by $^{31}P\{^1H\}$ NMR analysis.



Encouraged by these findings, which demonstrate TAPC to be a competent catalyst precursor with easy handling, we next examined the substrate scope of our N-alkylation. The scope was investigated under optimal reaction conditions for both N-mono- (**1**:**2**:TAPC = 2:1:0.05) and dialkylation (**1**:**2**:TAPC = 0.4:1:0.04) in 1,2,4-TMB. The results are summarized in Table 2.

Coupling reactions between anilines **1a–l** and electronically diverse benzylic primary alcohols **2a–m** gave the expected N-mono- or dialkylation products **3ab–ia** or **4ab–ia** selectively in good to high yields (entries 1–20). Furthermore, our results demonstrated that it is feasible to discriminate one NH_2 group from another under the established conditions. Although sulfonamides are readily alkylated with alcohols according to several established methods,[2c,3h,i,5b] the sulfonamide moiety of aniline **1k** re-

Table 2. Selective N-alkylation of various amines **1** with alcohols **2**.[a]

Entry	Amine **1**	Alcohol **2**	**3** (Yield [%])[b,c] conditions A[a]	**4** (Yield [%])[b,d] conditions B[a]
				
1	**1a** (X = H)	**2b** (Y = 4-OMe)	**3ab** (55)	**4ab** (51)
2	**1a**	**2c** (Y = 3-MeO)	**3ac** (83)	**4ac** (95)
3	**1a**	**2d** (Y = 4-Me)	**3ad** (82)	**4ad** (86)
4	**1a**	**2e** (Y = 3-Me)	**3ae** (86)	**4ae** (71)
5	**1a**	**2f** (Y = 2-Me)	**3af** (60)	**4af** (56)
6	**1a**	**2g** (Y = 4-F)	**3ag** (98)	**4ag** (90)
7	**1a**	**2h** (Y = 4-Cl)	**3ah** (81)	**4ah** (82)
8	**1a**	**2i** (Y = 4-Br)	**3ai** (81)	**4ai** (81)
9	**1a**	**2j** (Y = 4-I)	**3aj** (94)	**4aj** (57)
10[e]	**1a**	**2k** (Y = 2-I)	**3ak** (63)	**4ak** (57)
11	**1a**	**2l** (Y = 4-CF_3)	**3al** (83)	**4al** (69)
12	**1a**	**2m** (Y = 4-NO_2)	**3am** (81)[f]	**4am** (34)[h]
13	**1b** (X = 4-OMe)	**2a** (Y = H)	**3ba** (76)	**4ba** (96)
16	**1c** (X = 4-Me)	**2a**	**3ca** (77)	**4ca** (62)
14	**1d** (X = 3-Me)	**2a**	**3da** (98)	**4da** (90)
15	**1e** (X = 2-Me)	**2a**	**3ea** (96)	**4ea** (61)
17	**1f** (X = 4-F)	**2a**	**3fa** (81)[g]	**4fa** (76)
18	**1g** (X = 4-Cl)	**2a**	**3ga** (79)	**4ga** (89)
19	**1h** (X = 3-CF_3)	**2a**	**3ha** (61)	**4ha** (72)[i]
20	**1i** (X = 3-NO_2)	**2a**	**3ia** (78)	**4ia** (71)
21	**1j**	**2a**	**3ja** (99)	**3ja** (99)[j]
22	**1k**	**2a**	**3ka** (81)	**4ka** (47)
23	**1l**	**2a**	**3la** (29)	**4la** (34)

[a] Unless otherwise specified, **1**:**2**:TAPC = 2:1:0.05, $[TAPC]_0 = \sim 0.09$ M (conditions A) or **1**:**2**:TAPC = 0.4:1:0.04, $[TAPC]_0 = \sim 0.11$ M (conditions B) was used in 1,2,4-TMB at 160 °C for 15 h. [b] Isolated yield. [c] Based on **2**. [d] Based on **1**. [e] 36 h. [f] **1**:**2**:TAPC = 2:1:0.1; $[TAPC]_0 = \sim 0.04$ M, 11 h. [g] 180 °C, 24 h. [h] Detected by GC-MS. [i] **1**:**2**:TAPC = 0.4:1:0.08; $[TAPC]_0 = \sim 0.23$ M. [j] No dialkylation.

mained untouched in the presence of the NH_2 of the aniline, which was selectively N-mono- or dialkylated to afford **3ka** and **4ka**, respectively (entry 22).

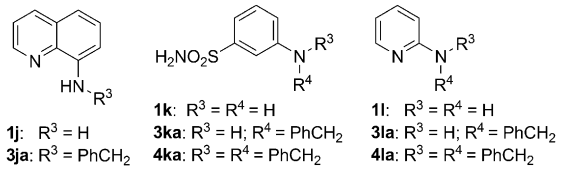
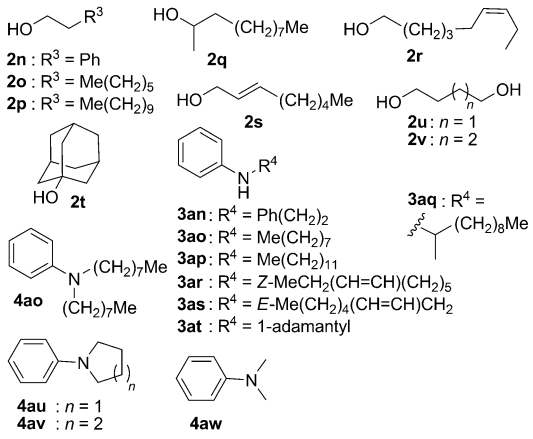


Table 3. Selective N-alkylation of **1a** with various alcohols **2**.[a]

Entry	Alcohol **2**	Conditions T [°C]	Conditions *t* [h]	Product amine	Yield [%][b]
1	**2n**	180	24	**3an**	84
2	**2o**	180	24	**3ao**	94 (74)[e]
3	**2p**	180	24	**3ap**	82
4	**2q**	200	36	**3aq**	75
5	**2r**	160	72	**3ar**	70
6	**2s**	160	36	**3as**	94
7	**2t**	180	72	**3at**	78
8[c]	**2u**	200	36	**4au**	85
9[c]	**2v**	200	36	**4av**	82
10[d]	MeOH (**2w**)	200	36	**4aw**	97

[a] Unless otherwise specified, **1a**:**2**:TAPC = 2:1:0.05 was used in 1,2,4-TMB ($[TAPC]_0 = \sim 0.09$ M). [b] Yield of isolated, purified product, based on **2**. [c] **1a**:**2**:TAPC = 2:1:0.1; $[TAPC]_0 = \sim 0.18$ M. [d] **1a**:**2w**:TAPC = 1:30:0.025; $[TAPC]_0 = \sim 0.017$ M. [e] Isolated yield of **4ao**:**1a**:**2o**:TAPC = 0.4:1:0.04; $[TAPC]_0 = \sim 0.10$ M.

Less reactive alcohols, such as fully saturated alcohols, were also tested (Table 3). By merely elevating the reaction temperature, secondary amines **3an**–**at** and tertiary amines **4au**–**aw**, derived by N-mono- and dialkylation, respectively, were obtained in good to excellent yields (entries 1–10). The carbocation-developing pathway (S_N1) is unlikely to occur with saturated primary alcohols including MeOH. Even at a high temperature, secondary alcohol **2q** and the interior (*Z*)-olefin of **2r** did not undergo β-elimination or isomerization, respectively (entries 4 and 5). The α/γ (>99%) and/or *E*/*Z* (>99%) selectivities of the reaction with allylic alcohol **2s** were excellent (entry 6). Tertiary alcohol **2t** was also compatible with the present reaction (entry 7), which excludes any possibility of a borrowing hydrogen mechanism.[2–5] A second intramolecular alkylation took place smoothly upon reaction of diols **2u** and **2v**, giving pyrrolidine and piperidine derivatives **4au** and **4av**, respectively, in good yields (entries 8 and 9). N-Dimethylation with MeOH proceeded as well using a smaller amount of TAPC to give **4aw** almost quantitatively (entry 10).



The N-benzylation of more basic, aliphatic amines was also examined (Table 4). In the reaction of **1p** (entry 4), no reaction was observed when using Brønsted acid HCl + **1p** (30 mol% each) alone.[12] Although elevated temperatures

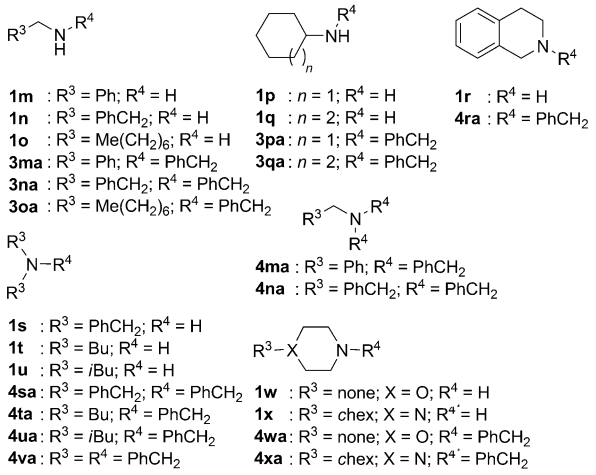


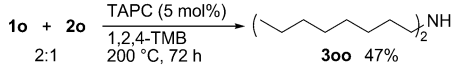
Table 4. N-Mono- and dibenzylation of various aliphatic amines **1** with **2a**.[a]

Entry	Amine **1**	Conditions		Product amine	Yield [%][b]
		T [°C]	t [h]		
1	**1m**	200	36	**3ma**	74 (80)[f]
2	**1n**	200	36	**3na**	98 (65)[f]
3	**1o**	200	36	**3oa**	90
4[c]	**1p**	200	15	**3pa**	80
5[c]	**1q**	200	36	**3qa**	91
6[d,e]	**1r**	180	48	**4ra**	73
7[d]	**1s**	180	36	**4sa**	81
8	**1t**	200	36	**4ta**	91
9	**1u**	200	36	**4ua**	94
10	NH_3(**1v**)/H_2O	200	24	**4va**	16
11[d]	**1w**	200	36	**4wa**	89
12[d]	**1x**	200	36	**4xa**	60

[a] Unless otherwise specified, **1**:**2a**:TAPC = 2:1:0.05 was used in 1,2,4-TMB; $[TAPC]_0 = \sim 0.09$ M. [b] Isolated yield based on **2a**. [c] **1**:**2a**:TAPC = 2:1:0.1; $[TAPC]_0 = \sim 0.18$ M. [d] **1**:**2a**:TAPC = 1:1:0.05; $[TAPC]_0 = \sim 0.1$ M. [e] DMF (5 mol%) was added. [f] Yield of isolated, dialkylation product **4ma** (entry 1) or **4na** (entry 2): **1**:**2a**:TAPC = 0.4:1:0.04; $[TAPC]_0 = \sim 0.09$ M.

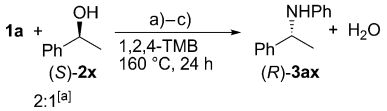
were generally required, primary and secondary amines were well suited for the reaction, giving secondary and tertiary amines in high yields, respectively (entries 1–9, 11, and 12). Aqueous ammonia underwent N-tribenzylation[3k,4i] to give **4va**, albeit in low yield (entry 10). Because of the inherent nature of weak-acid/weak-base cooperative catalysis under fairly neutral pH conditions, elevated temperatures were required to obtain a good product yield. Nonetheless, prolonged heating at 160–200 °C is acceptable at least for an industrial process, because the recovered extra heat energy can be reused for other purposes.

A substrate combination with the least reactive **1o** and **2o** was also tested (Scheme 3). The N-alkylation proceeded to give the product **3oo** in < 50% yield.



Scheme 3. Aliphatic amine–alcohol combination.

Having established the utility of TAPC-based catalysis for the nucleophilic substitution at the COH carbon with amines, we investigated the possibility of a stereospecific S_N2 reaction using optically pure (*S*)-**2x** (Scheme 4). Rather



Scheme 4. Partial Walden inversion of chiral alcohol **2x.** a) TAPC (5 mol%): 92% (9% *ee*); b) **5b** (5 mol%): 77% (6% *ee*); c) **5a** (5 mol%): 30% (51% *ee*). [a] Net ratio, in which **1a** incorporated into **5** is included.

acidic reagents, TAPC and **5b**, furnished N-alkylation product **3ax** in less than 10% *ee*. In contrast, 51% *ee* in favor of (*R*)-**3ax** was obtained in the presence of catalytic **5a** (5 mol%) under milder catalysis. The original absolute configuration maintained in recovered (*S*)-**2x** (> 98% *ee*). Further tuning of the reaction conditions could potentially promote a more satisfactory Walden inversion of chiral alcohols, for which water is the main byproduct. Improvement of catalysts for this salt-free (phosphorus(III)- and azodicarboxylate-free) N-alkylation alternative to the Mitsunobu reaction[22] is now underway. Furthermore, structural diversity of poly(phosphazene)s $(Cl_2P{=}N)_n$[9a–c] and metal complexes of phosphazenes[9d] are available, so that the present basic research has potential to expand to recyclable solid and metal-based catalysts.

Experimental Section

TAPC (34.8 mg, 0.1 mmol), aniline (**1a**) (373 mg, 4 mmol), benzyl alcohol (**2a**) (216 mg, 2 mmol) and 1,2,4-trimethylbenzene (0.5 mL) were added sequentially to a dry and sealed flask, stoppered by a Young's stopcock, under argon atmosphere (*Caution! rigorous exclusion of air from the reaction mixture is strongly recommended for all the N-alkylation reactions using TAPC.*). The reaction mixture was stirred at 160 °C for 15 h and was cooled to room temperature and purified using a middle-pressure preparative LC to give *N*-benzylaniline (**3aa**) as a colorless oil (337 mg, 1.84 mmol, 92%).

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[10] All reactions were carried out in flasks sealed by a Young's stopcock under Ar, so that HCl and water were retained in the reaction vessel.

[11] A large-scale reaction using 60 mmol of **2a** proceeded to give **3aa** in 90% yield.

[12] Involvement of a benzyl or alkyl chloride as a reaction intermediate cannot be fully ruled out. Given that these species are not observed in appreciable quantities and that HCl alone barely catalyzes many of our reactions, participation of a phosphazene such as **5a** seems likely. See also ref. [15].

[13] A good correlation between ratios **1a**:**2a** and product yields of **3aa** and **4aa** was observed, which was visualized by ESI, Figure S1 in the Supporting Information. Selectivity of N-monoalkylation was further improved by using a smaller amount of **1a** with a dummy substrate: when we conducted the reaction at 160°C for 24 h using a ratio of **1a**/**2a**/$PhNMe_2$ = 0.7:1:0.7 in the presence of **5a** (5 mol%) + **5b** (30 mol%), **3aa** and **4aa** were obtained in 85% and 7% yield (based on **1a** + **5b**), respectively, with full conversion of **2a**.

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