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Molecular Design of Organic Superbases, Azacalix[3](2,6)pyridines: Catalysts for 1,2- and 1,4-Additions

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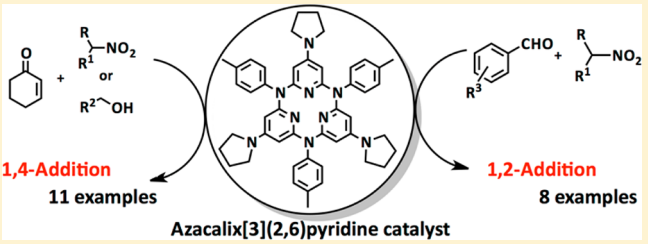
Supporting Information

ABSTRACT: The molecular design, characteristics, and catalytic activity of macrocyclic amino compounds, azacalix[3](2,6)pyridine derivatives, were studied. The introduction of an electron-donating group on the pyridine moiety and bridging amino phenyl group enabled the enhancement of the basicity of azacalix[3](2,6)pyridine up to pK_{BH^+} = 29.5 in CD_3CN. These derivatives were shown to be efficient catalysts for 1,4-addition reactions of nitroalkanes or primary alcohols to α,β-unsaturated carbonyl compounds and 1,2-addition reactions of nitroalkanes to aromatic aldehydes.



INTRODUCTION

Organic superbases have received much attention as, owing to their low environmental burden and the relative ease with which they can be handled, they are used in many organocatalytic reactions. One of the major subjects of organic superbases is enhancement of the basicity.[1] For example, the organic superbase 1,8-bis(hexamethyltriaminophosphazenyl)-naphthalene (HMPN, $^{MeCN}pK_{BH^+}$ = 28.35)[2] was designed by combining the 1,8-bis(dimethylamino)naphthalene (proton sponge, $^{MeCN}pK_{BH^+}$ = 18.2)[3] framework with the highly basic hexamethylphosphoramide unit.[4] However, in general, enhancing the basicity of an organic superbase requires organophosphorus moieties that are known to be toxic and have limited resources.[5]

We previously reported that the macrotricyclic aminopyridine compound azacalix[3](2,6)pyridine derivative **1** (Figure 1) exhibits the synergistic hydrogen bonding ability of three pyridine nitrogen atoms in a cavity that is appropriate for capturing a single proton.[6] Furthermore, we have also clarified that the basicities of azacalix[3](2,6)pyridine derivatives **2** and **3** were enhanced by introducing electron-donating groups on the pyridine units.[7] Since 4-methoxyl substituted aniline (*p*-anisidine) has a basicity ($^{MeCN}pK_{BH^+}$ = 11.86)[8,9] higher than that of aniline ($^{MeCN}pK_{BH^+}$ = 10.62),[9] we can expect that the introduction of an electron-donating group on the bridging amino phenyl group would enhance the basicity of azacalix[3](2,6)pyridine. The insight from the investigation would provide novel and valuable information for the rational molecular design.

From the viewpoint of atom economy, an addition reaction is one of the most effective routes for the formation of C−C bonds. The products of the 1,4-addition reaction of nitroalkanes with α,β-unsaturated ketones have been used as raw materials to prepare azole antifungals,[10] and the 1,2-addition of nitroalkanes is also an extremely useful reaction for organic synthesis.[11] In these reactions, a phosphine-free and nonionic organic superbase such as proton sponge has attracted interest as catalyst because of its low toxicity. A proton sponge organic super base is a promising candidate for the catalyst because the proton sponge is designed to hold a proton selectively. However, because the proton sponge organic superbases generally possess too strong a hold on the proton to serve as a catalyst,[12] most studies involving these compounds are focused on stoichiometric reactions.[1,13] Therefore, both high basicity and weak holding force are required for a catalyst based on the proton sponge structure. Alternatively, azacalix[3](2,6)-pyridine derivatives have a much weaker hold on the proton, despite being classed as a proton sponge type of organic superbase. The moderate holding force of the proton is caused by the high proton affinity and the macrocyclic frameworks of the azacalix[3](2,6)pyridines. This high basicity and moderate proton holding force are the reason why azacalix[3](2,6)-pyridine derivatives **2** and **3** served as effective organic superbase catalysts for the reported 1,4-additions of nitromethane to mesityl oxide and 2-cyclohexenone.[7] Thus, it is expected that the azacalix[3](2,6)pyridine derivatives **2**−**4** will be more powerful and more versatile as organic catalysts than the more commonly used proton sponge organic superbases for various addition reactions.

This study had two aims, the first of which was to achieve expansion of the molecular design of proton sponge organic superbases with enhanced basicity. To achieve this, we investigated newly designed and synthesized the azacalix[3]-(2,6)pyridine derivative **4** bearing electron-donating groups on the bridging amino phenyl group. Following this, we assessed

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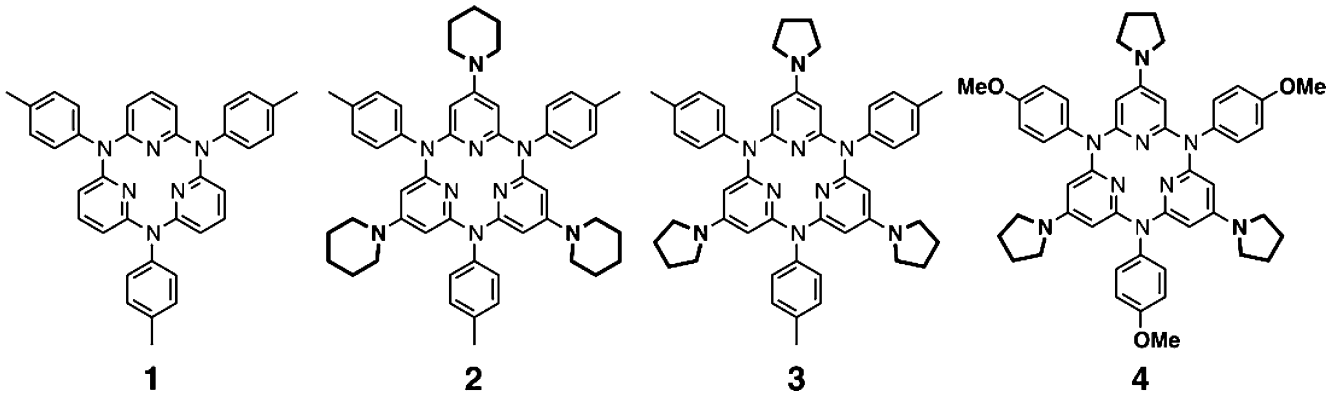
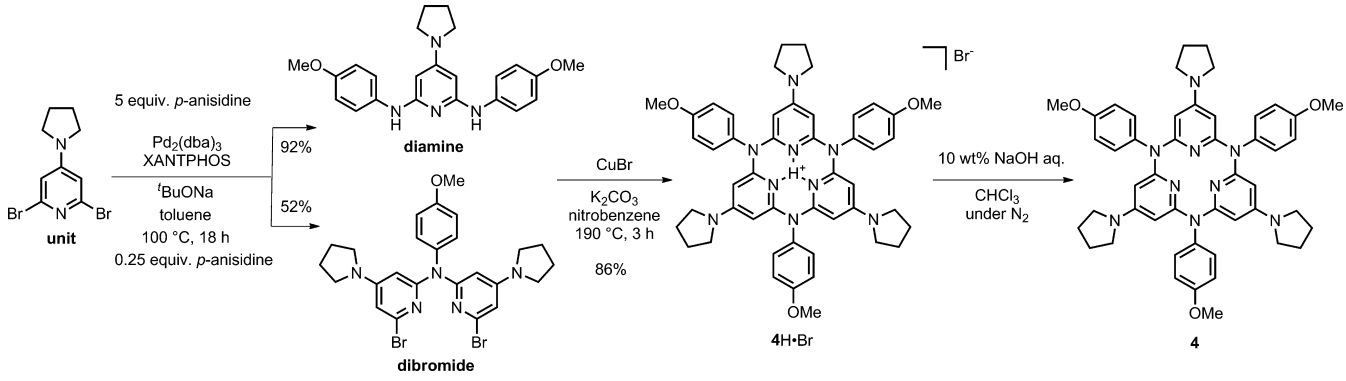


Figure 1. Azacalix[3](2,6)pyridine derivatives.

Scheme 1. Synthesis of Azacalix[3](2,6)pyridine Derivative (4)



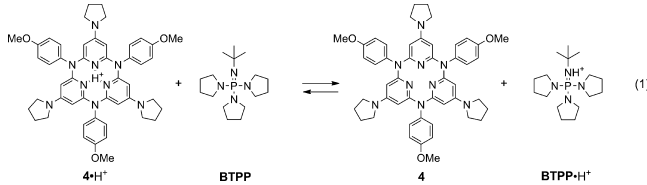
the catalytic activity of **2**–**4** in 1,4- and 1,2-addition reactions in order to demonstrate their superiority in comparison to other compounds.

RESULTS AND DISCUSSION

Synthesis and Characterization of Azacalix[3](2,6)-pyridine Derivative 4. The methoxy-substituted azacalix[3]-(2,6)pyridine derivative **4** was synthesized using a previously reported method (Scheme 1).[7] It was subsequently analyzed using a variety of techniques including NMR, X-ray diffraction, mass spectroscopy, and elemental analysis. The ^{1}H NMR spectrum of **4**H·Br exhibited a singlet signal at 21.1 ppm in $CDCl_3$ (see Supporting Information). This largely downfield-shifted proton signal reflects the synergistic hydrogen bonding ability of the N_{py} atoms in the cavity, which is the same as the previously mentioned monoprotonated azacalix[3](2,6)-pyridine derivatives **1**–**3**H·Br.

Single crystals of **4**H·Br suitable for X-ray diffraction study were obtained by recrystallization from $CHCl_3$ and hexane. The crystal structure of **4**H·Br is shown in Figure 2. There are no significant interactions between the Br anion and the $4H^+$ cation. The dihedral angles between the two N acceptor pyridine rings of **4**H·Br, $Py_{N(1)}\cdots Py_{N(5)}$ and $Py_{N(5)}\cdots Py_{N(3)}$, is twisted by 5.72°. Compared to other previously reported azacalix[3](2,6)pyridine derivatives (**1**, **1**H·PF_6, and **3**H·Br), **4** exhibited a nonbonding distance of 2.510–2.566 Å between the N acceptor atoms N(1)···N(5), N(5)···N(3), and N(1)···N(3), which is appropriate for capturing a single proton. These distances are also close to those of other proton sponge superbases (1,8-bis(dimethylamino)naphthalene (proton sponge)[13,14] = 2.588 Å, 1,8-bis(tetramethylguanidino)-naphthalene (TMGN)[15] = 2.717 Å, HMPN[2] = 2.823 Å). Interestingly, the structure of the azacalix[3](3,6)pyridine derivatives showed that the steric hindrance of the center of the base is significantly reduced in comparison with other proton sponge superbases.[1] It is therefore likely that the azacalix[3](2,6)pyridine derivatives will have an enhanced basicity in addition to a large open space within the molecules. Since azacalix[3](2,6)pyridine possesses a coplanarity of the macrocyclic framework with a slight deviation of the three pyridine rings, the cavity of the compounds should be large enough to enable access to substrates, such as simple nitroalkanes. Thus, the azacalix[3](2,6)pyridine derivatives were expected to be more effective catalysts for reactions involving sterically hindered substrates than the common proton sponge organic superbases.

Basicity $^{MeCN}pK_{BH^+}$ measurements of 4. To estimate the basicity of **4**, transprotonation experiments on **4**H·Br with a known organic superbase were carried out using ^{1}H NMR spectroscopy at room temperature (eq 1). Among the tested organic bases, *tert*-butylimino-tri(pyrrolidino)phosphorane (BTPP, $^{MeCN}pK_{BH^+}$ = 28.4)[16] was found to be the most appropriate compound.



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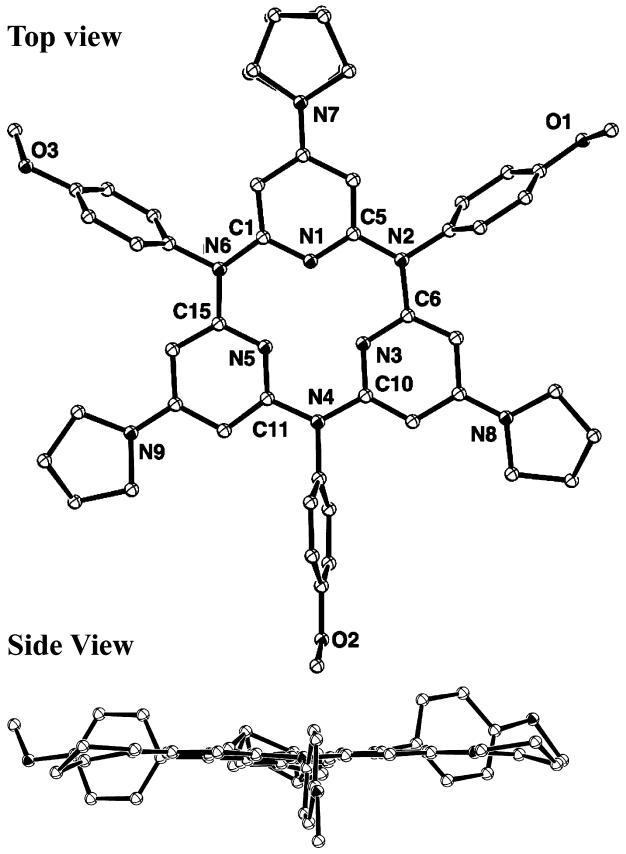
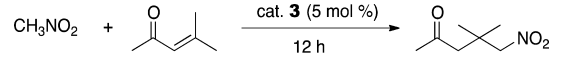


Figure 2. ORTEP drawing of 4H·Br with thermal ellipsoids shown at the 30% probability level. Hydrogen atoms, Br anion, and solvent molecules are omitted for clarity. The position of the proton in the cavity could not be determined by difference Fourier synthesis probably due to the disorder or low quality of crystallographic data.

The basicity of **4** was estimated to be $^{MeCN}pK_{BH^+}$ = 29.5 from the ^{1}H NMR measurements of the mixtures of **4** and BTPP with various molar ratios (see Supporting Information). As expected, the $^{MeCN}pK_{BH^+}$ of **4** was higher than that of **3** because of the enhancement in basicity from the introduction of the electron-donating methoxy groups into the bridging amino phenyl groups in the macrocyclic framework. This value means that the azacalix[3](2,6)pyridine derivative has an enhanced basicity close to that the strongest known phosphine free organic superbase, tricyclic 2,4-diaminovinamidine proton sponge (vinamidine), that has a value of $^{MeCN}pK_{BH^+}$ = 31.9.[17] Figure 3 reveals that the basicities of the azacalix[3](2,6)-pyridine derivatives were systematically enhanced by the introduction of the electron-donating substitutions, not only into the pyridine units but also the bridging amino phenyl groups in the macrocyclic framework. This synthetic strategy is also consistent with a DFT calculation carried out by Maksić and co-workers.[18]

1,4-Addition of Nitroalkanes to Various α,β-Unsaturated Carbonyl Compounds. Prior to comparing the catalytic activity of the azacalix[3](2,6)pyridine derivatives, the appropriate reaction conditions were determined. The 1,4-addition of nitromethane to mesityl oxide was carried out using **3** as a catalyst in various solvents under a nitrogen atmosphere. The reaction did not proceed at room temperature (Table 1, entry 1); however, it was found to be successful at reflux temperature in each of the solvents tested (Table 1, entries 2–6). The desired product of the 1,4-addition, 4,4-dimethyl-5-nitro-2-pentanone, was obtained in 97% yield when isobutyronitrile was employed as the solvent (Table 1, entry 3).

Table 1. 1,4-Addition of Nitromethane to Mesityl Oxide Using 3 as a Catalyst[a]

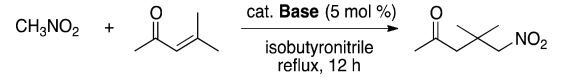


entry	solvent	temp	yield [%][b]
1	1,4-dioxane	rt	no reaction
2	1,4-dioxane	reflux	74
3	isobutyronitrile	reflux	97
4	THF	reflux	72
5	CH_2Cl_2	reflux	trace
6	DMSO	reflux	69

[a]Reaction conditions: 0.20 mmol of mesityl oxide, 0.21 mmol of nitromethane, 1 mL of solvent, 0.01 mmol of **3**, under N_2. [b]Isolated yield.

Under these optimized conditions (Table 1, entry 3), the catalytic activity of azacalix[3](2,6)pyridines **1**–**4** for the 1,4-addition of nitromethane to mesityl oxide was examined (Table 2). The corresponding adducts were obtained in high yield in

Table 2. Catalytic Performance of Azacalix[3](2,6)pyridine Bases 1–4 for 1,4-Addition[a]



	catalyst		
entry	base	$^{MeCN}pK_{BH^+}$	yield [%][b]
1	**1**	23.1	0
2	**2**	27.1	85
3	**3**	28.1	97
4	**4**	29.5	95

[a]Reaction conditions: 0.20 mmol of mesityl oxide, 0.21 mmol of nitromethane, 1 mL of isobutyronitrile, 0.01 mmol of base, reflux, under N_2. [b]Isolated yield.

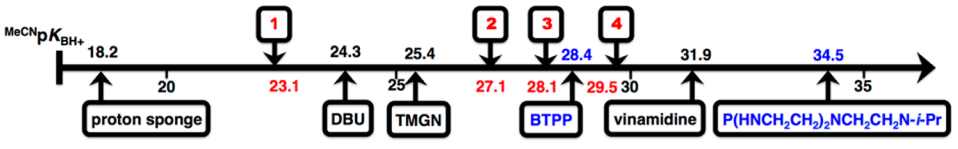


Figure 3. Chart of the basicity of organic superbases in acetonitrile. Red values show the basicity level of the azacalix[3](2,6)pyridine derivatives (**1**–**4**). Black values show the previously reported phosphine-free organic superbases proton sponge, TMGN,[15] 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU),[19] and vinamidine.[17] Blue values show the phosphine-containing organic superbases BTPP and Verkade's base, which are the most basic structures, $P(HNCH_2CH_2)_2NCH_2CH_2N$-*i*-Pr.[1]

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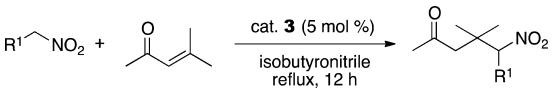
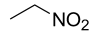
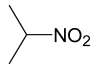
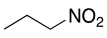
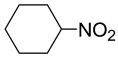
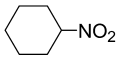
every case except for compound **1**, and the catalytic activity was found to increase with increasing basicity of the azacalix[3](2,6)pyridine derivatives. Since catalysts **3** and **4** gave comparable results, it was deduced that the catalytic activity was saturated at the level of basicity of **3** under these conditions. This result is supported by previous findings for other general organic superbases, such as the proazaphosphatrane base and the phosphazene base.[20]

The 1,4-additions of various nitroalkanes to mesityl oxide were carried out using **3** as a catalyst under the standard conditions (Table 3).[21] The catalyst **3** promoted each reaction

Table 3. 1,4-Addition of Nitroalkane to Mesityl Oxide Using 3 as a Catalyst[a]



entry	cat. base	1,4-addition donor ^{DMSO}pKa	nitroalkane	yield [%][b]
1	**3**	16.7[22]		82
2	**3**	16.9[22]		88
3	**3**	17.0[22]		90
4	**3**	17.2[23]	CH_3NO_2	97
5	**3**	17.9[24]		42
6	**4**	17.9[24]		57

[a]Reaction conditions: 0.20 mmol of mesityl oxide, 0.21 mmol of nitroalkane, 1 mL of isobutyronitrile, 0.01 mmol of **3**, 12 h, reflux, under N_2. [b]Isolated yield.

with nitroalkanes to give the corresponding 1,4-addition adducts. The reaction of 2-nitropropane was slower than that of nitromethane (Table 3, entries 2 and 4). The yield of the reaction with nitromethane was higher than that with nitroethane (entries 1 and 4). From the viewpoint of acidity of the substrates, nitroethane (^{DMSO}pKa = 16.7) has an advantage in the reaction in comparison with nitromethane (^{DMSO}pKa = 17.2). Therefore, steric hindrance of the substrates is likely to determine the reaction efficiency; the reaction with the nitroalkane with a bulky substituent, nitrocyclohexane, provided a moderate yield (entry 5). When **4** was used as a catalyst for the 1,4-addition of nitrocyclohexane, a better yield was obtained compared to that of **3** (Table 3, entry 6). These results indicate that higher basicity of the catalyst **4** promotes the 1,4-addition of nitrocyclohexane smoothly. Therefore, the molecular design of azacalix[3](2,6)pyridine in the present work is effective for the 1,4-addition of nitromethane.

1,4-Addition of Primary Alcohols to Various α,β-Unsaturated Carbonyl Compounds. The alcohol is arguably the most versatile compound in the field of organic synthesis and is used in the Williamson ether synthesis with inorganic bases used for its deprotonation.[25] The proton adducts of the azacalix[3](2,6)pyridine derivatives (**2**–**4**H·Br) were deprotonated by 2.5 wt % aqueous solutions of KOH with a pH of 13.8 or higher.[8] The basicities of such inorganic bases are satisfactory for deprotonating primary alcohols such as methanol and allylalcohol.[2] 4-DMAP, DBU, morpholine (with basicities lower than those of **2**–**4**), and proazaphosphatrane have been reported as useful organic base catalysts for the 1,4-addition of various alcohols to α,β-unsaturated carbonyl compounds.[26,22] However, there are no reports on 1,4-addition of alcohols using proton sponge base catalysts. Thus, as **2**–**4** are a versatile model for base catalysts for the 1,4-addition of primary alcohols, it would be advantageous for the field of synthetic organic chemistry to optimize them. The 1,4-addition reactions of alcohols to α,β-unsaturated carbonyl compounds were carried out using **3** as a catalyst under the same conditions that have been reported for utilizing proazaphosphatrane bases ($^{MeCN}pK_{BH^+}$ = 32.8–33.63).[21] When methanol was used as the donor, **3** showed high catalytic activity in the reactions of each of the α,β-unsaturated carbonyl compounds (Table 4, entries 1 and 2). When allyl alcohol was used as the donor, the corresponding adducts were also obtained in good yields, with the reaction using **3** being clearly superior to that with the reference catalyst. Compound **3** satisfies the basicity requirement for deprotonation of the proton(s) of the hydroxy groups. Moreover, given the difference in amounts of catalyst between **3** and the reference, these results indicate that catalyst **3** has higher catalytic activity.

1,2-Addition of Nitroalkanes to Various Aldehyde Compounds. The activities of the azacalix[3](2,6)pyridine derivatives in the catalysis of the 1,2-addition reaction of nitroalkanes with aromatic aldehydes was also investigated. The 1,2-addition of nitromethane to benzaldehyde was carried out using **3** as a catalyst, in various solvents, at room temperature, under a nitrogen atmosphere (Table 5). The desired product, α-(nitromehyl)benzyl alcohol, was obtained in 97% yield when a neat condition was employed (Table 5, entry 4). Under the optimized conditions, the 1,2-addition reaction of nitromethane with benzaldehyde was carried out using each azacalix[3](2,6)-pyridine catalyst (Table 5, entries 4–7). Compounds **2**, **3**, and **4** all successfully gave the corresponding adducts, with the derivatives with the higher basicities (**3** and **4**) providing the best yields. These results are consistent with those obtained for the 1,4-additions (Table 2).

The 1,2-addition reactions of nitromethane with various aromatic and heterocyclic aldehydes were carried out using **3** as a catalyst (Table 6). Even when aldehydes with electron-donating groups were used as the substrates (*p*-anisaldehyde and *o*,*m*,*p*-tolualdehyde), the corresponding adducts were obtained in good yields (Table 6, entries 1–4). Since the yields of the reactions with the *o*,*m*,*p*-tolualdehydes were comparable, it was clear that the catalytic activity was not affected by steric hindrance of the methyl group. When an aldehyde with electron-withdrawing groups was used as the substrate (*p*-trifluoromethylbenzaldehyde), **3** showed good catalytic activity. Specifically, the reactions of nitromethane with heterocyclic aldehydes show significant advantages over the results of the reference base (Table 6, entries 6 and 7).[27,28] These results suggest that **3** allows approach of heterocyclic aldehydes to the catalytic site because of the high basicity.

■ CONCLUSION

In conclusion, we designed and synthesized a new organic superbase, **4**, that has the highest basicity out of the azacalix[3](2,6)pyridine derivatives described. The introduc-

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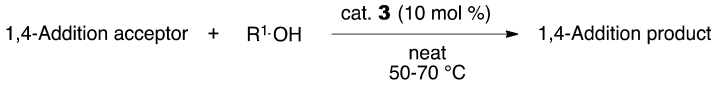
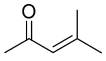
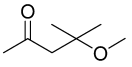
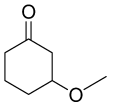
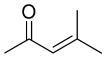
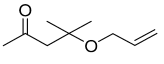
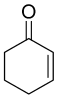
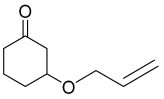
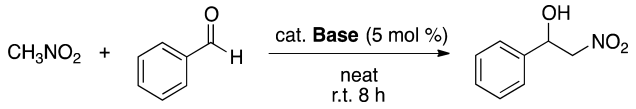
Table 4. 1,4-Addition of Alcohols to α,β-Unsaturated Carbonyl Compounds Using 3 as a Catalyst[a]



entry	1,4-addition acceptor	1,4-addition donor	product	time [h]	temp [°C]	yield [%][b]	ref. [%]
1		CH_3OH		12	50	92	79[c]
2		CH_3OH		6	50	86	89[d]
3		CH_2=$CHCH_2OH$		12	70	82	40[e]
4		CH_2=$CHCH_2OH$		6	70	81	58[f]

[a]Reaction conditions:; 2.0 mmol of α,β-unsaturated carbonyl compounds, 1 mL of alcohol, 0.2 mmol of **3**, neat, under N_2. [b]Isolated yield. [c]Reference 21; cat. 10 mol % of P(*i*-PrNCH$_2$CH$_2$)$_3$N, 0.5 h, 50 °C. [d]Reference 21; cat. 10 mol % of P(*i*-BuNCH$_2$CH$_2$)$_3$N, 3 h, 50 °C. [e]Reference 21; cat. 20 mol % of P(*i*-PrNCH$_2$CH$_2$)$_3$N, 3 h, 70 °C. [f]Reference 21; cat. 20 mol % of P(*i*-BuNCH$_2$CH$_2$)$_3$N, 3 h, 70 °C.

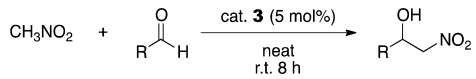
Table 5. Optimization of Reaction Conditions for the 1,2-Addition of Nitromethane to Benzaldehyde Using Azacalix[3](2,6)pyridine Catalysts[a]



	catalyst			
entry	base	$^{MeCN}pK_{BH^+}$	solvent	yield [%][b]
1	**3**	28.1	THF	56
2	**3**	28.1	1,4-dioxane	trace
3	**3**	28.1	DMSO	62
4	**3**	28.1	neat	97
5	**1**	23.1	neat	0
6	**2**	27.1	neat	75
7	**4**	29.5	neat	92

[a]Reaction conditions: 1 mmol of benzaldehyde, nitromethane 1 mL, rt, 8 h, under N_2. [b]Isolated yield.

Table 6. 1,2-Addition of Nitroalkane with Aldehyde Using 3 as a Catalyst



entry	R =	yield [%][a]	yield[b] [%]
1	*p*-MeO-Ph-	93	99[c]
2	*p*-CH_3-Ph-	82	
3	*o*-CH_3-Ph-	91	
4	*m*-CH_3-Ph-	88	
5	*p*-CF_3-Ph-	87	98
6	2-pyridinyl-	91	62
7	2-furanyl-	86	55

[a]Isolated yield. [b]Reference 27; cat. 5 mol % of Cyclen, in THF, 24 h, rt. [c]Reference 28; cat. 10 mol % of P(*i*-PrNCH$_2$CH$_2$)$_3$N,[29] $^{MeCN}pK_{BH^+}$ = 33.63, 40 min, rt.

tion of an electron-donating group on the bridging amino phenyl group enhanced the basicity of azacalix[3](2,6)pyridine. This novel strategy is a promising tool in the development of efficient organic superbase catalysts. Owing to the high basicity, **2**–**4** showed catalytic activities comparable to those of the reported high-performance organic superbases in various 1,4- and 1,2-additions, and **4** exhibited the highest catalytic activity. The experimental results were in accordance with our hypothesis that the level of catalytic activity for these addition reactions is associated with the basicity of the azacalix[3](2,6)-pyridine catalyst used. The major factors involved in achieving high catalytic activity are the high basicities and the moderate holding forces of protons by the macrocyclic framework of the azacalix[3](2,6)pyridine. Thus, catalysts **3** and **4** appear to be well suited to 1,4- and 1,2-addition reactions of various substrates. These results have significant implications concerning novel possibilities for proton sponge organic superbases.

■ EXPERIMENTAL SECTION

General Information. 2,6-Dibromo-4-pyrrolidinopyridine and **1**–**3** were prepared according to previous methods.[7,8] The reagents and solvents were used after distillation.

Synthesis. *Synthesis of N,N-Bis[2-(6-bromo-4-pyrrolidinopyridyl)]-p-anisidine (**Dibromide**).* A mixture of 2,6-dibromo-4-pyrrolidinopyridine (1.20 g, 4.0 mmol), *p*-anisidine (123 mg, 1.0 mmol), sodium-*tert*-butoxide (480.5 mg, 5.00 mmol), tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$] (45.7 mg, 0.050 mmol), and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (XANTPHOS) (86.8 mg, 0.15 mmol) was dissolved in toluene (40 mL). The reaction mixture was stirred for 18 h at 100 °C under a nitrogen atmosphere. After cooling to rt, the mixture was filtered through Celite and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (ethyl acetate/hexane, 1:5) to afford **dibromide** (298.1 mg, 52%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.93–1.96 (m, 8H), 3.18 (t, *J* = 6.4 Hz, 8H), 3.81 (s, 3H), 5.99 (d, *J* = 2.0 Hz, 2H), 6.25 (d, *J* = 1.6 Hz, 2H), 6.85–6.87 (m, 2H), 7.04–7.12 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 25.2, 47.3, 55.4, 97.9, 105.2, 114.5, 128.9, 137.6, 140.3, 154.3, 157.2, 157.8. Anal. Calcd for $C_{25}H_{27}Br_2N_5O$: C, 52.37; H, 4.75; N, 12.22. Found: C,

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52.40; H, 4.92; N, 12.16. ESI-MS positive: 574.12 (m/z). Melting point: 212 °C.

*Synthesis of 2,6-Bis(p-anisylamino)-4-pyrrolidinopyridine (**Diamine**).* A mixture of 2,6-dibromo-4-pyrrolidinopyridine (198 mg, 0.65 mmol), *p*-anisidine (398 mg, 3.2 mmol), sodium-*tert*-butoxide (311 mg, 3.2 mmol), [$Pd_2(dba)_3$] (29.6 mg, 0.030 mmol), and XANTPHOS (56.2 mg, 0.090 mmol) was dissolved in toluene (15 mL). The reaction mixture was stirred for 18 h at 100 °C under a nitrogen atmosphere. After cooling to rt, the mixture was filtered through Celite. The crude product was purified by column chromatography on aminopropylated silica gel (gradient, ethyl acetate/hexane, 5:1 → 2:1) to afford **diamine** (233.5 mg, 92%) as a purple solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.89−1.92 (m, 4H), 3.17 (t, J = 6.6 Hz, 4H), 3.79 (s, 6H), 5.38 (s, 2H), 5.98 (s, 2H), 6.85 (dd, J = 6.4 Hz, 2 Hz, 4H), 7.22 (dd, J = 6.4 Hz, 2 Hz, 4H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 25.3, 47.2, 55.5, 81.3, 114.4, 121.9, 123.9, 134.1, 155.6, 156.6. Anal. Calcd for $C_{23}H_{26}N_4O_2$: C, 70.75; H, 6.71; N, 14.35. Found: C, 70.35; H, 6.70; N, 14.14. ESI-MS positive: 391.78 (m/z). Melting point: 181 °C.

*Synthesis of N,N′,N″-Tris(p-anisyl)azacalix[3](2,6)(4-pyrrolidinopyridine) Hydrogen Bromide (**4**H·Br).* A mixture of **dibromide** (24.2 mg, 0.042 mmol) and **diamine** (16.5 mg, 0.042 mmol), CuBr (7.90 mg, 0.055 mmol), and K_2CO_3 (70.6 mg, 0.51 mmol) was dissolved in nitrobenzene (5 mL). The reaction mixture was stirred for 3 h at 190 °C (oil bath temp; 240 °C) under a nitrogen atmosphere. The solvent was removed under reduced pressure. The crude product was purified by column chromatography on aminopropylated silica gel (gradient, ethyl acetate/hexane 3:7 → chloroform → acetonitrile) to afford **4**H·Br as a brown solid. **4**H·Br was purified by recrystallization from a chloroform/hexane to give white solid (31.9 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.84−1.87 (m, 12H), 2.90−2.93(m, 12H), 3.94 (s, 9H), 4.92 (s, 6H), 7.13−7.15 (m, 6H), 7.29−7.31 (m, 6H), 21.1 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 24.9, 47.2, 55.8, 88.5, 116.1, 131.1, 132.1, 152.4, 154.4, 199.9. Anal. Calcd for $C_{48}H_{52}BrN_9O_3$: C, 65.30; H, 5.94; N, 14.28. Found: C, 65.01; H, 5.81; N, 14.25. ESI-MS positive: 883.65 (m/z). The melting point of **4**H·Br was not observed by melting point apparatus from room temperature to 300 °C.

*Synthesis of N,N′,N″-Tris(p-anisyl)azacalix[3](2,6)(4-pyrrolidinopyridine) (**4**).* **4**H·Br (5.0 mg, 0.0060 mmol) was dissolved in chloroform (1 mL) under a nitrogen atmosphere. The solution was washed with 5.0 wt % NaOH aq (1 mL × 2). After the organic layer was separated, the solvent was removed under reduced pressure. The ^{1}H NMR spectrum of the residual red solid indicates a quantitative formation of **4**. ^{1}H NMR (600 MHz, CD_3CN): δ 1.76 (t, J = 6.6 Hz, 12H), 2.77−2.79 (m, 12H), 3.83 (s, 9H), 4.87 (d, J = 2.4 Hz, 6H), 7.08 (d, J = 9.0 Hz, 6H), 7.32−7.33 (m, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 24.9, 31.6, 47.2, 55.7, 88.6, 116.1, 131.1, 132.1, 152.4, 154.5, 199.9.

Because this compound was protonated in air moisture immediately due to its high basicity, we could not complete other analyses.

General Method of 1,4-Addition of Nitromethane to α,β-Unsaturated Carbonyl Compounds. A mixture of **3** (75.4 mg, 0.10 mmol), nitromethane (112.7 μL, 2.1 mmol), and mesityl oxide (228.8 μL, 2.0 mmol) in dehydrated isobutyronitrile (1 mL) was stirred under a nitrogen atmosphere. After stirring under reflux for 12 h, the mixture poured into water and extracted with ethyl acetate. The crude product was purified by column chromatography on silica gel (gradient, ethyl acetate/hexane = 1:10 to 1:4) to afford corresponding 1,4-adduct (308.8 mg, 97%). The spectral data of the obtained 1,4-adducts were identical to the previous references.[30]

General Method of 1,4-Addition of Primary Alcohol to α,β-Unsaturated Carbonyl Compounds. A mixture of **3** (150.8 mg, 0.20 mmol) and mesityl oxide (228.8 μL, 2.0 mmol) in dehydrated methanol (1 mL) was stirred under a nitrogen atmosphere. After being stirred for the time and temperature indicated in Table 4, the mixture was poured into brine and extracted with diethylether. The crude product was purified by column chromatography on silica gel (gradient, ethyl acetate/hexane = 1:10 to 1:5) to afford corresponding 1,4-adduct (239.5 mg, 92%). The spectral data of the obtained 1,4-adducts were identical to those in previous references.[22,26]

General Method of 1,2-Addition of Nitromethane to Aromatic Aldehydes. A mixture of **3** (37.7 mg, 0.050 mmol), nitromethane (1.0 mL, 18.7 mmol), and benzaldehyde (101.9 μL, 1.0 mmol) was stirred under a nitrogen atmosphere. After being stirred under room temperature for 8 h, the solvent was removed. The crude product was purified by column chromatography on silica gel (chloroform) to afford the corresponding 1,2-adduct (162.2 mg, 97%). The spectral data of the obtained 1,2-adducts were identical to previous results.[31]

Estimation of $^{MeCN}pK_{BH^+}$ of 4 by ^{1}H NMR Transprotonation Studies. The basicity of $^{MeCN}pK_{BH^+}$ of **4** was estimated by ^{1}H NMR transprotonation measurements at 20 °C with BTPP ($^{MeCN}pK_{BH^+}$ = 28.4) and **4**H·Br. The thermodynamic equilibrium constant (K) was determined from integration of the signals of **4** and monoprotonated **4** with several amounts of the organic bases in the spectra. For example, from the ^{1}H NMR experimental data of a 1.61:3.14 mixture of **4**H·Br and BTPP, a 0.38:0.62 mixture of **4** and **4**H$^+$, K for the equilibrium is calculated as

$$K = [\mathbf{4}][\text{BTPP}\cdot\text{H}^+]/[\mathbf{4}\cdot\text{H}^+][\text{BTPP}] = 0.0839$$

The basicity of **4** is estimated as

$$^{\text{MeCN}}pK_{\text{BH}^+}(\mathbf{4}) = {}^{\text{MeCN}}pK_{\text{BH}^+}(\text{BTPP}) - \log K$$
$$= 28.4 - \log(0.0839) = 29.475 \cong 29.5$$

These data reveal that **4** has a basicity stronger than that of BTPP. The average value of $^{MeCN}pK_{BH^+}$ was defined by several attempts.

X-ray Crystal Structure Determinations, Crystal Data. The crystal structure of **4**H·Br was determined by an X-ray diffractional study. Transparent single crystals of **4**H·Br were obtained by the slow diffusion of hexane into a solution in chloroform. Intensity data was collected on a Bruker-APEX-II CCD diffractometer with Mo Kα radiation (λ = 0.71069 Å). A crystal was mounted on MicroMounts. Crystallographic data and details of refinement of the complex are summarized in the CIF data (see Supporting Information). A full matrix least-squares refinement was used for non-hydrogen atoms with anisotropic thermal parameters method by a Direct Methods (SHELXD) program. Hydrogen atoms were placed at the calculated positions and were included in the structure calculation without further refinement of parameters. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-887269.

Selected data for **4**H·Br·3$CHCl_3$: $C_{57}H_{69}BrCl_9N_9O_3$, M = 1327.21, monoclinic, $P2_1/c$, a = 10.364(3) Å, b = 30.543(9) Å, c = 19.545(6) Å, β = 101.745(4)°, V = 6057(3) Å^3, Z = 4, D_{calcd} = 1.455 g/cm^3, μ = 1.129 mm^{-1}, T = 120 K, $F(000)$ = 2744.00, observed reflections 31777 (all data), variables 573, $R1$ = 0.1979 ($I > 2.00\sigma(I)$), R = 0.3537, R_w = 0.5033, GOF = 1.277.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Details of X-ray crystalographic data, NMR spectra, Transporotonations data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) *Superbases for Organic Synthesis: Guanidines, Amidines and Phosphazenes and Related Organocatalysts*; Ishikawa, T., Ed.; Wiley: New York, 2009. (b) Chambron, J.-C.; Meyer, M. *Chem. Soc. Rev.* **2009**, *38*, 1663. (c) Verkade, J. G.; Kisanga, P. B. *Tetrahedron* **2003**, *59*, 7819. (d) Verkade, J. G.; Kisanga, P. B. *Aldrichimica Acta* **2004**, *37*, 1. (e) Pozharskii, A. F.; Ozeryaskii, V. A.; Filatova, E. A. *Chem. Heterocycl. Compd.* **2012**, *48*, 200. (f) Galeta, J.; Potáček, M. *J. Org. Chem.* **2012**, *77*, 1010. (g) Kunetskiy, R. A.; Polyakova, S. M.; Vavřík, J.; Císařová, I.; Saame, J.; Nerut, E. R.; Koppel, I.; Koppel, I. A.; Kütt, A.; Leito, I.; Lyapkalo, I. M. *Chem.—Eur. J.* **2012**, *18*, 3621. (h) Zachovà, H.; Man, S.; Taraba, J.; Potàček, M. *Tetrahedron* **2009**, *65*, 792.

(2) Raab, V.; Gauchenova, E.; Merkoulov, A.; Harms, K.; Sundermeyer, J.; Kovačević, B.; Maksić, Z. B. *J. Am. Chem. Soc.* **2005**, *127*, 15738.

(3) (a) Alder, R. W.; Bowman, P. S.; Steele, W. R. S.; Winterman, D. R. *J. Chem. Soc., Chem. Commun.* **1968**, 723. (b) Alder, R. W. *Chem. Rev.* **1989**, *89*, 1215. (c) Staab, H. A.; Saupe, T. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 865. (d) Llamas-Saiz, A. L.; Foces- Foces, C.; Elguero, J. *J. Mol. Struct.* **1994**, *328*, 297. (e) Howard, S. T. *J. Am. Chem. Soc.* **2000**, *122*, 8238.

(4) Kovačević, B.; Maksić, Z. B. *Tetrahedron Lett.* **2006**, *47*, 2553.

(5) (a) *Phosphorus. The Carbon Copy*; Dillon, K. B., Mathey, F., Nixon, J. F., Eds.; John Wiley & Sons: New York, 1997. (b) *A Guide to Organophosphorus Chemistry*; Quin, L. D., Ed.; John Wiley & Sons: New York, 2000. (c) Kuroda, A.; Takiguchi, N.; Kato, J.; Ohtake, H. *J. Environ. Biotechnol.* **2005**, *4*, 87.

(6) (a) Suzuki, Y.; Yanagi, T.; Kanbara, T.; Yamamoto, T. *Synlett* **2005**, 263. (b) Kanbara, T.; Suzuki, Y.; Yamamoto, T. *Eur. J. Org. Chem.* **2006**, 3314. (c) Miyazaki, Y.; Kanbara, T.; Yamamoto, T. *Tetrahedron Lett.* **2002**, *43*, 7945.

(7) Uchida, N.; Taketoshi, A.; Kuwabara, J.; Yamamoto, T.; Inoue, Y.; Watanabe, Y.; Kanbara, T. *Org. Lett.* **2010**, *12*, 5242.

(8) Bordwell, F. G.; Vanier, N. R.; Matthews, W. S.; Hendrickson, J. B.; Skipper, P. L. *J. Am. Chem. Soc.* **1975**, *97*, 7160.

(9) Kaljurand, I.; Kütt, A.; Sooväli, L.; Rodima, T.; Mäemets, V.; Leito, I.; Koppel, I. A. *J. Org. Chem.* **2005**, *70*, 1019.

(10) Lui, K.-H.; Sammes, M. P. *J. Chem. Soc., Perkin Trans.* **1990**, 457.

(11) (a) Henry, L. *Compt. Rend.* **1895**, *120*, 1265. (b) Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, 2561.

(12) (a) Chan, J. W.; Hoyle, C. E.; Lowe, A. B.; Bowman, M. *Macromolecules* **2010**, *43*, 6381. (b) Hibbert, F.; Phillips, S. *J. Chem. Res., Synop.* **1990**, 90.

(13) (a) Pozharskii, A. F. Russ. *Chem. Rev.* **1998**, *67*, 1. (b) Truter, M. R.; Vickery, B. L. *J. Chem. Soc., Dalton Trans.* **1972**, 395. (c) Wozniak, K.; Krygowski, T. M.; Kariuki, B.; Jones, W.; Grech, E. *J. Mol. Struct.* **1990**, *240*, 111. (d) Kanters, J. A.; Schouten, A.; Kroon, E.; Grech, E. *Acta Crystallogr., Sect. C* **1991**, *47*, 807.

(14) Einspahr, H.; Robert, J. B.; Marsh, R. E.; Roberts, J. D. *Acta Crystallogr.* **1973**, *B29*, 1611.

(15) Raab, V.; Kipke, J.; Gschwind, R. M.; Sundermeyer, J. *Chem.—Eur. J.* **2002**, *8*, 1682.

(16) (a) Schwesinger, R.; Schlemper, H. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1167. (b) 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.-Z.; Peters, E.-M.; Peters, K.; von Schnering, H. G.; Walz, L. *Liebigs Ann.* **1996**, 1055. (c) 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.

(17) Schwesinger, R.; Miβfeldt, M.; Peters, K.; von Schnering, H. G. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1165.

(18) (a) Despotović, I.; Kovačević, B.; Maksić, Z. B. *Org. Lett.* **2007**, *9*, 1101. (b) Despotović, I.; Kovačević, B.; Maksić, Z. B. *Org. Lett.* **2007**, *9*, 4709. (c) Despotović, I.; Maksić, Z. B. *Tetrahedron Lett.* **2011**, *52*, 6263.

(19) Hermann, O.; Moeller; Friedrich, M. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 76.

(20) (a) Ye, W.; Xu, J.; Tan, C.-T.; Tan, C.-H. *Tetrahedron Lett.* **2005**, *46*, 6875. (b) Pahadi, N. K.; Ube, H.; Terada, M. *Tetrahedron Lett.* **2007**, *48*, 8700.

(21) Kisanga, P. B.; Ilankumaran, P.; Fetterly, B. M.; Verkade, J. G. *J. Org. Chem.* **2002**, *67*, 3555.

(22) Bordwell, F. G.; Vanier, N. R.; Matthews, W. S.; Hendrickson, J. B.; Skipper, P. L. *J. Am. Chem. Soc.* **1975**, *97*, 7160.

(23) Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006.

(24) Bordwell, F. G.; Bartmess, J. E.; Hautala, J. A. *J. Org. Chem.* **1978**, *43*, 3113.

(25) (a) Williamson, W. *Liebigs Ann. Chem.* **1851**, *77*, 37. (b) Williamson, W. *J. Chem. Soc.* **1852**, *106*, 229. (c) Dermer, O. C. *Chem. Rev.* **1934**, *14*, 385.

(26) References for 1,4-addition of alcohols: (a) Rulev, A. Y.; Azad, S.; Kotsuki, H.; Maddaluno, J. *Eur. J. Org. Chem.* **2010**, *33*, 6423. (b) Murtagh, J. E.; McCooey, S. H.; Connon, S. J. *Chem. Commun.* **2005**, *2*, 227. (c) Hauser, M. *Chem. Rev.* **1963**, *63*, 311. (d) Ramachary, D. B.; Mondal, R. *Tetrahedron Lett.* **2006**, *47*, 7689. (e) Hayashi, Y.; Nishimura, K. *Chem. Lett.* **2002**, *3*, 296.

(27) Bray, C. V.-L.; Jiang, F.; Wu, X.-F.; Sortais, J.-B.; Darcel, C. *Tetrahedron Lett.* **2010**, *51*, 4555.

(28) Kisanga, P. B.; Verkade, J. G. *J. Org. Chem.* **2002**, *67*, 426.

(29) (a) Kisanga, P. B.; Verkade, J. G. *J. Org. Chem.* **2000**, *65*, 5431. (b) Tang, J.; Dopke, J.; Verkade, J. G. *J. Am. Chem. Soc.* **1993**, *115*, 5015.

(30) References for 1,4-addition of nitroalkanes: (a) Kisanga, P. B.; Verkade, J. G. *Tetrahedron* **2001**, *57*, 467. (b) Ramachary, D. B.; Mondal, R. *Tetrahedron Lett.* **2006**, *47*, 7689.

(31) References for 1,2-addition of nitroalkanes: (a) Kisanga, P. B.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 4298. (b) Han, J.; Xu, Y.; Su, Y.; She, X.; Pan, X. *Catal. Commun.* **2008**, *9*, 2077. (c) Jin, W.; Li, X.; Wan, B. *J. Org. Chem.* **2011**, *76*, 484.