$P(RNCH_2CH_2)_3N$-Catalyzed Synthesis of β-Hydroxy Nitriles

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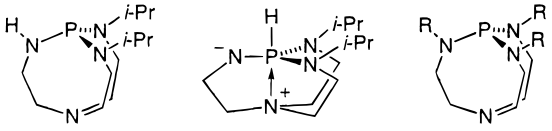
We herein report the successful synthesis of β-hydroxy nitriles in very good to excellent yields from aldehydes and ketones in a simple reaction that is promoted by strong nonionic bases of the title type. The reaction occurs in the presence of magnesium salts which activate the carbonyl group and stabilizes the enolate thus produced.

Introduction

β-Hydroxy nitriles are useful intermediates in organic synthesis as, for example, in the synthesis of 1,3-amino alcohols.[1] As a result, several methods have been developed for their synthesis. The most common methods for preparing β-hydroxy nitriles involve the reaction of a 1,2 epoxide[2] with a nitrile in the presence of metal salts such as $LiClO_4$/KCN,[3] using lanthanide(III) alkoxides as catalysts,[4] or with acetone cyanohydrin under mildly basic conditions.[5] However, these approaches succeed only with simple aliphatic epoxides and the yields range from poor (35%) to very good (95%) with the exception of the $LiClO_4$/KCN reagent that leads to yields ranging from 80 to 98%. Another recent method for the synthesis of β-hydroxy nitriles includes the use of a manganese−lead system to promote the coupling of an alkyl iodide, an acrylonitrile, and a ketone.[6] The toxicity of lead and DMF (used as the solvent) makes this method environmentally unsafe. A mercury-assisted reaction has also been reported. In this process an electron deficient alkene is treated with mercury fulminate and lithium bromide and the reaction mixture is heated at 50 °C to afford the β-hydroxy nitriles in low to moderate yields.[7] However, the toxicity of mercury, the explosive nature of mercury fulminate, and the lengthy reaction times required render this method unattractive. Bahradi *et al.*[8] utilize aryl halides as the precursors of electrogenerated bases which are then used to deprotonate acetonitrile. The anion thus produced can add to acetone or aldehydes in DMF to produce the title compounds in 52−74% yield. β-Hydroxy nitriles can also be synthesized by ionization of an hydrogen of acetonitrile by *n*-butyllithium (sold as a flammable hydrocarbon solution) or alkali amides followed by condensation with ketones and aldehydes.[9] When *n*-butyllithium is employed, a temperature of −80 °C is required to give the best yields (47−89%), and if alkali amides are employed, a temperature of −33 °C is required to provide yields up to 93%. A simple room-temperature procedure was developed by Maasalu *et al.*[10] which involves reacting acetonitrile with carbonyl compounds in the presence of powdered KOH. However, the yields were only moderate, ranging from 43 to 68%. Although several other methods exist for the preparation of β-hydroxy nitriles, they involve a multistep synthesis,[11,12] they make use of highly toxic compounds,[13−15] they proceed with poor to moderate overall yields,[16] or they require low[17] temperatures.

The proazaphosphatranes **1a**/**1a′**,[18] **1b**,[19] and **1c**[20] have recently been shown to be strong nonionic bases capable of deprotonating acetonitrile,[21] benzyl nitrile,[21] nitroalkanes,[22] and other activated methylenes,[23] thereby providing access to anions that we have successfully employed in useful transformations. In our continued search for reactions in which these bases provide improved synthetic methodology over conventional approaches, we have found that compounds of type **1** are efficient catalysts for the preparation of β-hydroxy nitriles.



Results and Discussions

We reported previously that ketones do not react with acetonitrile in the presence of bases of type **1**.[21] In hopes

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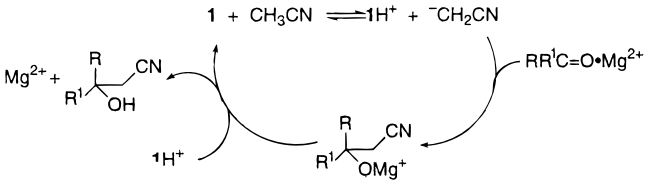
Table 1. Reaction of Carbonyl Compounds with Acetonitrile in the Presence of 1a[a] and 2.2 Equiv of Magnesium Sulfate at 25 °C for 4 Hours

substrate	β-hydroxy nitrile % yield	α,β-unsaturated nitrile % yield	% starting material[b]
acetone (**2**)[c]	94	0	2
cyclohexanone (**3**)[c]	94	0	4
2-methylcyclohexanone (**4**)[c]	91	0	8
5, **7**, **11**, **18**	0	0	100
2-cyclohexenone (**6**)[d]	0	0	0
3-pentanone (**8**)	87	0	9
2-butanone (**9**)	88	0	10
benzaldehyde (**10**)	79	6	13
p-chlorobenzaldehyde (**12**)	71	3	21
2-methylbutyraldehyde (**13**)	95	0	0
cyclohexanecarboxaldehyde (**14**)	76	<1	20
p-anisaldehyde (**15**)	36[b]	10[b]	54[b]
trimethylacetaldehyde (**16**)	83	15	<1
2,5-dimethoxybenzaldehyde (**17**)	62	<1	36

[a] The amount of the catalyst was 10 mol % unless stated otherwise. [b] Estimated by ^{1}H NMR integration. [c] The amount of catalyst used was 15 mol %. [d] Only the dimer of the α,β-unsaturated enone was isolated in 95% yield.

Scheme 1

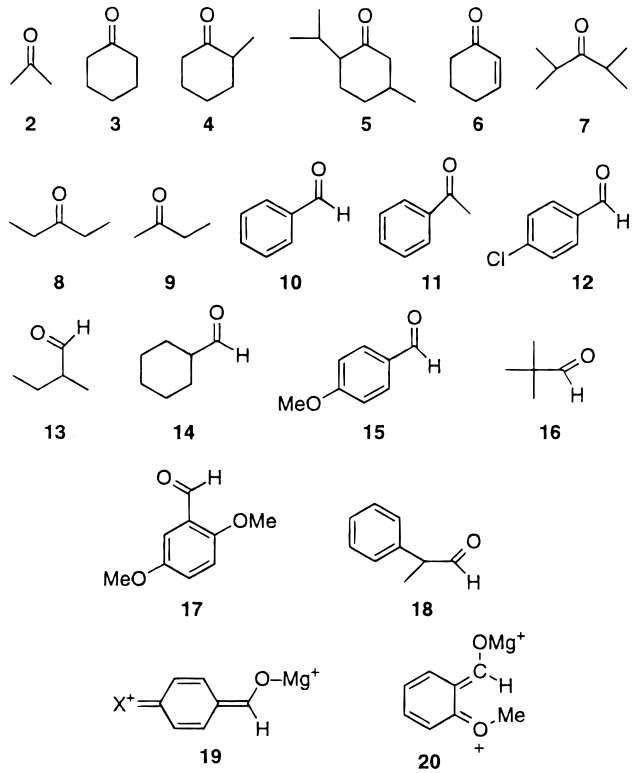


of activating the carbonyl function of this class of compounds to attack by $^-CH_2CN$, we investigated the use of Lewis acids such $AlCl_3$, BF_3, BF_3·OEt_2, $MgBr_2$, and HgI_2. Thus, we were able to detect the formation of 1−2% of β-hydroxy nitriles (estimated by ^{1}H NMR spectroscopic integration) in the reaction of cyclohexanone with acetonitrile in the presence of 1 equiv of BF_3·OEt_2 or HgI_2 and 30 mol % of **1a**. The other Lewis acids either induced no detectable reaction or produced complicated reaction mixtures. When the reaction was repeated in the presence of 1 equiv of magnesium sulfate or magnesium bromide and 30 mol % of **1a**, the reaction mixture produced about 40% of the α,β-unsaturated nitrile in addition to 59% of the products identified by ^{1}H NMR spectroscopy as β-hydroxy nitrile. When the concentration of the base was reduced to 15 mol % in the same reaction, the conversion to β-hydroxy nitrile increased to 72%. At 10 mol % in another repetition of this reaction, 88% of the products produced was observed to be the β-hydroxy nitrile while 11% was identified by ^{1}H NMR spectroscopy as the α,β-unsaturated nitrile. Increasing the amount of the magnesium compound to 2.2 equiv led to the production of 96% of the β-hydroxy nitrile in 4 h and no ^{1}H NMR-detectable unsaturated nitrile. Seventeen carbonyl compounds were then treated under these optimized conditions, and the results are shown in Table 1. The reaction is assumed to proceed through the pathway shown in Scheme 1.

Table 1 shows that ketones participating in this reaction afford β-hydroxy nitriles as the only products. This is due to the sterically hindered nature of the tertiary alcohols produced which prevents further deprotonation by the bulky base **1a**. β-Hydroxy nitriles formed from aldehydes on the other hand (i.e., secondary alcohols) are less sterically hindered and can be deprotonated by **1a** (Scheme 2) leading to α,β-unsaturated nitriles.

Scheme 2

Chart 1



Sterically hindered ketones **5** (menthone) and **7** (2,4-dimethyl-3-pentanone) did not react with acetonitrile in the presence of **1a** under our conditions (Chart 1). This is because the approach of the nucleophilic $^-CH_2CN$ ion to the ketonic carbonyl is hampered by the bulk of the alkyl groups. Acetophenone (**11**) was unreactive, presumably as a result of its resonance stabilization. The enolizable aldehyde **18** (2-phenylpropionaldehyde) produced no detectable β-hydroxy nitrile. The presence of protonated **1a** (detected in the reaction mixture by ^{31}P

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Table 2. Reaction of Carbonyl Compounds with Acetonitrile in the Presence of 1b[a] and 2.2 Equiv of Magnesium Sulfate at 25 °C for 4 Hours

substrate	β-hydroxy nitrile % yield	α,β-unsaturated nitrile % yield	starting material % conversion[b]
acetone (**2**)	99	0	0
cyclohexanone (**3**)	99	0	0
2-methylcyclohexanone (**4**)	54	22	20
5, **7**, **11**, **18**	0	0	100
2-cyclohexenone (**6**)[c]	0	0	0
3-pentanone (**8**)	98	0	0
2-butanone (**9**)	97	0	0
benzaldehyde (**10**)	68	7	20
p-chlorobenzaldehyde (**12**)	50[b]	0	50
2-methylbutyraldehyde (**13**)	97[d]	0	0
cyclohexanecarboxaldehyde (**14**)	95	0	<1
p-anisaldehyde (**15**)	33[b]	33[b]	33
trimethylacetaldehyde (**16**)	95[d]	3	0

[a] The ratio of catalyst used was 20 mol % unless stated otherwise. [b] Estimated by ^{1}H NMR integration. [c] The only product isolated was the dimerized enone in 99% yield. [d] The concentration of **1b** was 10 mol %.

NMR spectroscopy) is attributable to the protonation of **1a** that occurs in the preequilibrium shown for the general case in Scheme 1. However, the $^-CH_2CN$ that is formed here apparently does not attack the carbonyl. Combination of a solution of 2-phenylpropionaldehyde (**18**) with a solution of **1a** in acetonitrile leads to deprotonation of 2-phenylpropionaldehyde (**18**) by either **1a** or $^-CH_2CN$ to give a resonance-stabilized enolate. The involvement of $^-CH_2CN$ in the deprotonation of 2-phenylpropionaldehyde (**18**) was shown by carrying out the reaction in CD_3CN. ^{1}H NMR analysis of the reaction mixture after 2 h revealed the presence of a substantial amount of CHD_2CN. The dimerization of 2-cyclohexenone (**6**) in the presence of catalysts of type **1** is under further investigation in our laboratories. The reaction of primary aldehydes (represented in this study by *n*-heptanal) to form the corresponding aldol product isolated in 99% yield had been reported previously in a separate study.[21] The reaction of 2-methylcyclohexanone (**4**) to form the corresponding novel β-hydroxy nitrile in 91% yield testifies to the efficiency of our methodology.

Both **1b** and **1c** are also catalysts for the preparation of β-hydroxy nitriles. The results of the reaction of carbonyl compounds with acetonitrile in the presence of **1b** and magnesium sulfate are given in Table 2. Contrary to our observation with **1a**, the reaction of acetonitrile with trimethylacetaldehyde in the presence of **1b** and 2.2 equiv of magnesium sulfate does not produce substantial amounts of the corresponding undesired α,β-unsaturated nitrile and gives higher yields of the corresponding β-hydroxy nitrile. This is rationalized by the relatively stronger basicity of **1a** (resulting from its ability to exist in a zwitter ionic amide form **1a′**) which is less sterically hindered.[18,22] Base **1a′** is thus better capable of effecting dehydration of the desired product.

The reaction of aromatic aldehydes produces a mixture of β-hydroxy nitriles and α,β-unsaturated nitriles. This is attributed to resonance stabilization of the α,β-unsaturated nitriles derived from the aryl ring compared with that of the corresponding β-hydroxy nitriles. We reasoned that this propensity of aromatic aldehydes is probably due to the presence of the alkoxide anion that deprotonates the α-methylene in the products, thus leading to the elimination of water during workup. We therefore decided to quench the reaction of benzaldehyde (**10**) with acetonitrile in the presence of 20 mol % of **1b**, with MeOH prior to workup. However, this resulted in only a modest improvement in the distribution of products (i.e., an 82% conversion to the desired β-hydroxy nitrile in addition to 5% of the α,β-unsaturated nitrile). We finally decided to use the less basic **1c** instead of **1b** in the reaction of **10** with acetonitrile and then quenched the reaction with MeOH prior to workup. This produced the β-hydroxy nitrile and the α,β-unsaturated nitrile in conversions of 83% and 3%, respectively, as estimated by ^{1}H NMR integration of the reaction mixture. When the reaction was carried out at 0 °C for 6 h and then quenched at this temperature with MeOH before passing through a silica gel column, the production of β-hydroxy nitrile from benzaldehyde (**10**) increased to 86%. Upon increasing the concentration of **1c** to 30 mol %, a 92% conversion to the desired product was observed with only a trace amount of the α,β-unsaturated nitrile formed. The results of the reactions of aromatic aldehydes with CH_3CN in the presence of **1a**−**1c** are shown in Table 3. The data in this table demonstrate that the dependence of this reaction on the base used (**1a**, **1b**, or **1c**) is minimal. This table also shows that increasing the reaction time to 18 h at 0 °C increases the conversion by an average of 5% while the amount of the α,β-unsaturated nitriles increases by only 1−2%. Therefore, the rate of water elimination is effectively suppressed at this temperature.

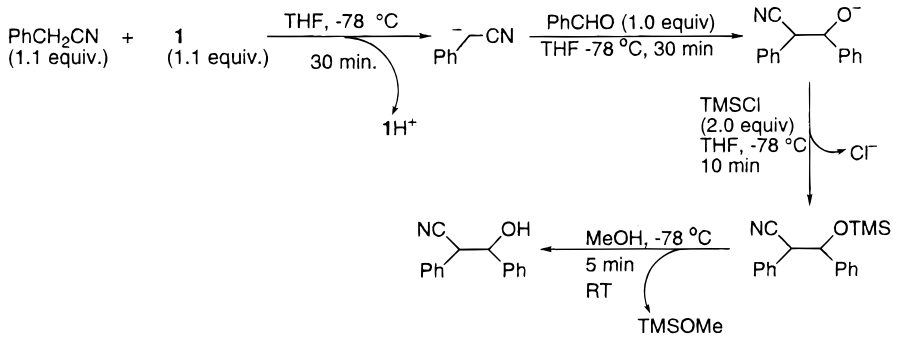
The reactions of *p*-chlorobenzaldehyde (**12**) and *p*-anisaldehyde (**15**) proceeded in an unexpected manner. On the basis of inductive effects, we expected **12** to be more reactive than benzaldehyde (**10**) which in turn would be more reactive than **15**. However, we find that while **10** reacts quantitatively, both **12** and **15** have lower reactivities. The cause of this apparent anomaly is unclear. Since both **10** and **12** have proven to be highly reactive toward $^-CH_2CN$ in the absence of magnesium ion,[21] we suspected that coordination of Mg^{2+} to the carbonyl group may induce greater resonance stabilization (as depicted in **19** and **20**) which offsets the $-I$ effects in *p*-chlorobenzaldehyde (**12**), *p*-anisaldehyde (**15**), and 2,5-dimethoxybenzaldehyde (**17**), thereby reducing the reactivity of these compounds. The $-I$ effects due to the *p*-chloro, *p*-methoxy, and *o*-methoxy groups are expected to activate these compounds toward nucleophilic attack by $^-CH_2CN$ whereas the $+R$ effects are expected to deactivate them. Since deactivation is observed, it may be assumed that the $+R$ effect predominates. To support this assumption, 4-fluorobenzaldehyde and *o*-anisaldehyde were reacted under the same conditions. Conversions of 85% and 83% to the corresponding β-hydroxy

Table 3. Reaction of Aldehydes with Acetonitrile in the Presence of 1a−1c[a] and 2.2 Equiv of Magnesium Sulfate at 0 °C

starting material[c]	base	β-hydroxy nitrile % yield[b]	% α,β-unsaturated nitrile[c]	starting material[c]
benzaldehyde (**10**)	**1a**	96 (98)[d]	2	0
benzaldehyde (**10**)	**1a**	(98)	2	0
benzaldehyde (**10**)	**1b**	(98)	2	0
benzaldehyde (**10**)	**1c**	88 (92)	3	5
benzaldehyde (**10**)	**1c**	(97)[d]	3	0
p-chlorobenzaldehyde (**12**)	**1b**	82 (84)	4	12
p-chlorobenzaldehyde (**12**)	**1c**	77 (80)	4	16
cyclohexanecarboxaldehyde (**14**)	**1a**	88 (92)	4[e]	0
p-anisaldehyde (**15**)	**1a**	71 (75)[d]	6	19
p-anisaldehyde (**15**)	**1b**	(78)	5	17
p-anisaldehyde (**15**)	**1c**	78 (80)	4	16
2,5-dimethoxybenzaldehyde (**17**)	**1a**	81 (85)	0	15
2,5-dimethoxybenzaldehyde (**17**)	**1c**	84 (87)[d]	0	13

[a] The amount of **1c** used was 30 mol %. The reaction time was 6 h unless stated otherwise. [b] Values in parentheses are conversions estimated by ^{1}H NMR integration. [c] Estimated by ^{1}H NMR integration. [d] The reaction time was 18 h. [e] A small amount of unidentified material was observed.

Scheme 3



nitrile were observed, respectively, which are in accord with a $+R$ resonance effect. Despite steric hindrance of the carbonyl group in 2,5-dimethoxybenzaldehyde (**17**), the corresponding β-hydroxy nitrile is formed in 84% yield. Although the *o*-OMe group is expected to deactivate the carbonyl group by a resonance effect, the yields with **17** and *o*-anisaldehyde are slightly higher, since resonance would produce the sterically unfavorable geometry shown in **20**. The aforementioned yields are lower than with benzaldehyde (**10**) as a result of a $+R$ effect.

When the reaction of benzyl cyanide was attempted with PhCHO in the presence of 1 mol % of **1c** and 2.2 equiv of $MgSO_4$, the quantitative production of the corresponding α,β-unsaturated nitrile was recorded in less than 1 h in a ^{1}H NMR experiment. However, preparation of the desired β-hydroxy nitrile was achieved in 99% yield by carrying out the reaction at −78 °C in THF as indicated in Scheme 3.

Conclusion

Nonionic superbases of type **1** are superior catalysts for the synthesis of β-hydroxy nitriles under mild conditions using CH_3CN and sterically unhindered carbonyl substrates that are not easily enolized. The advantages of such catalysts are the following: (1) The yields of the desired products are high. (2) The reaction occurs at room temperature in a relatively short period of time. (3) The catalyst can be recovered in high yields. (4) The reaction consists of one step. (5) Except for two of the catalysts, which are easily synthesized, all materials are commercially available including **1c** (Strem). (6) Reagents known to be toxic are avoided.

Experimental Section

CH_3CN was distilled from calcium hydride and stored over 4 Å molecular sieves under nitrogen. $MgSO_4$ was purchased from Fischer and used as received. All the substrates were purchased from Aldrich Chemical Co. and were used as received. The bases **1a**−**1c** were prepared according to our previously published methods.[18−20]

General Procedure for the Preparation of β-Hydroxy Nitriles Using Acetonitrile. In a round-bottom flask, 3 mL of CH_3CN, 528 mg of $MgSO_4$ (4.39 mmol), and 2 mmol of carbonyl substrate were mixed under nitrogen. In a second round-bottomed flask, 3 mL of CH_3CN and **1** (0.4 equiv) was mixed. The contents of the latter flask were then added to the first, and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was then loaded directly onto a silica gel column and flash chromatographed with 100% ethyl acetate, with the exceptions of 3-hydroxy-3-methylpentanenitrile and 3-hydroxy-3,3-dimethylpentanenitrile which were eluted with MeOH/Et_2O (5:95).

Preparation of β-Hydroxy Nitriles from Aromatic Aldehydes. To a mixture of the aldehyde (2.0 mmol) and anhydrous magnesium sulfate (528 mg 4.39 mmol) contained in a round-bottom flask was added 2.0 mL of dry acetonitrile under nitrogen. The suspension was placed in a constant-temperature bath at 0 °C, and the mixture was stirred for 5 min. A solution of **1** (0.6 mmol) in acetonitrile was added, and the mixture was stirred for 6 h at the end of which 1.0 mL of MeOH was added, and stirring continued for 5 more min. The reaction mixture was then loaded on to a silica gel column and eluted with 100% ethyl acetate. The crude product was purified (when necessary) by column chromatography (vide infra).

Preparation of PhCH(OH)CH(CN)Ph Using 1c and Benzyl Nitrile. In a round-bottom flask, 1.2 g (5.5 mmol) of **1c** was dissolved in 10 mL of dry THF under nitrogen, and the solution was cooled to −78 °C. To the clear solution was added 0.6 mL (5 mmol) of benzyl nitrile followed by stirring for 0.5 h. To the resulting yellow solution was added 0.5 mL (5 mmol) of benzaldehyde, and the mixture was stirred for an additional 10 min. At this point 1.0 mL (8.0 mmol) of TMSCl was added and the mixture was stirred for 10 min. This was followed by the addition of 2.0 mL of MeOH at −78 °C, and then the reaction mixture was allowed to warm slowly to room temperature over 2 h. Most of the THF was evaporated under

reduced pressure, and then 20 mL of dry ether was added to precipitate [H**1c**]Cl that was isolated by filtration. After the removal of ether from the filtrate under reduced pressure, the crude product was eluted through a silica gel column using EtOAc:hexane (70:30) to obtain 1.1 g (99% yield) of the product.

Purification of *β*-Hydroxy Nitriles. The crude *β*-hydroxy nitriles were loaded onto a silica gel column, and the starting materials and α,*β*-unsaturated nitriles eluted with 60 mL of 30% ether in hexanes. The *β*-hydroxy nitriles were then eluted with ethyl acetate in hexane (70:30). The products from the reactions of isobutyraldehyde and trimethylacetaldehyde with acetonitrile were first eluted with Et_2O/hexane (30:70) followed by 80 mL of MeOH/Et_2O (30:70).

(1-Hydroxy-2-methylcyclohexyl)acetonitrile: isolated as a mixture of diastereomers; ^{1}H NMR ($CDCl_3$) δ 0.93 (d, 3H), 1.3−1.95 (m, 9H), 2.01 (bs, 1H), 2.56 (ABq, 2H); ^{13}C NMR ($CDCl_3$) δ 14.9, 15.5 (CH_3), 21.5 (C-5), 23.0 (C-4), 25.3 (C-3), 30.1, 30.2 (CH_2CN), 37.1 (C-6), 38.4 (C-2), 71.3, 72.2 (C-1), 117.9 (CN); mp 77−78 °C; HR MS (EI) *m*/*e* (M^+) calcd for $C_9H_{15}NO$ 153.11536, obsd 153.11551.

Catalyst Recovery. After the reaction, magnesium sulfate was filtered from the reaction mixture and the residue on the filter paper was washed with 10 mL of chloroform. The solvents were removed under vacuum, and 5 mL of water was added. The products were then extracted with 4 × 10 mL portions of ether. The organic layer was then dried over anhydrous magnesium sulfate, and the volatiles were removed under reduced pressure to afford the *β*-hydroxy ntriles. To the aqueous solution containing [**1**H]OH was added 0.1 mL of 37% aqueous HCl, and the mixture was extracted with 4 × 10 mL portions of methylene chloride to afford [**1**H]Cl which was then purified and converted to **1** according to previously published methods.[18−20]

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Supporting Information Available: ^{1}H and ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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