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Metalated Nitriles: Organolithium, -magnesium, and -copper Exchange of α-Halonitriles

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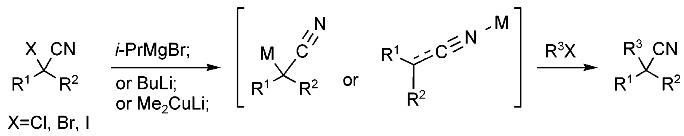

α-Halonitriles react with alkyllithium, organomagnesium, and lithium dimethylcuprate reagents generating reactive, metalated nitriles. The rapid halogen−metal exchange with alkyllithium and Grignard reagents allows selective exchange in the presence of reactive carbonyl electrophiles, including aldehydes, providing a high-yielding alkylation protocol. Lithiated and magnesiated nitriles react with propargyl bromide by S_N2 displacement whereas organocopper nitriles react by S_N2' displacement, correlating with the formation of a *C*-metalated nitrile.

Introduction

α-Metalated nitriles are powerful nucleophiles, ideally suited for sterically demanding alkylations.[1] The exceptional nucleophilicity stems from the powerful inductive stabilization[2] of metalated nitriles that localizes negative charge density on carbon to the virtual exclusion of *N*-alkylation.[3] Augmenting the nucleophilicity of metalated nitriles is the extremely small steric demand of the CN unit, with an *A*-value of only 0.2 kcal mol^{-1}.[4] Collectively, the exceptional nucleophilicity of metalated nitriles,[1] the facile installation of hindered centers,[5] and the conversion of nitriles into a range of functional groups[6] have resulted in the extensive use of metalated nitriles in synthesis.

Metalated nitriles are typically synthesized by deprotonating the parent nitriles with metal amides.[1] Computationally, deprotonating acetonitrile with lithium amide leads directly to *N*-lithiated acetonitrile,[7] which correlates with numerous X-ray[8] (**1**, **2**) and solution[9] structures (**2**, **3**) of metalated nitriles (Figure 1). Remarkably, X-ray analyses[8] consistently show metalated nitriles as having partial double bond character for the C=CN bond and only slight weakening of the C≡N triple bond (1.15−1.20 Å), relative to the C≡N bond length of neutral nitriles (1.14 Å)![10] Another characteristic feature of metalated nitriles is the persistent coordination of amide[11] or amine ligands[12] in X-ray and solution structures, which feature in both *N*- and *C*-coordinated complexes as gauged by the rapid equilibration between **3a** and **3b** in Et_2O at −100 °C.[13]

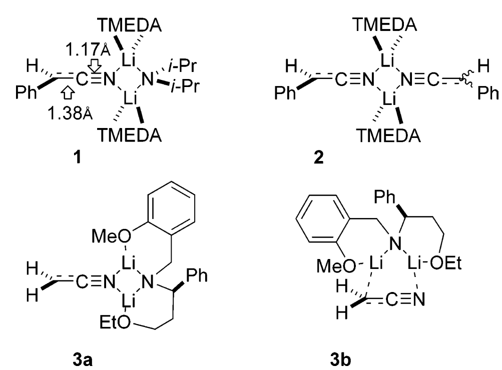

FIGURE 1. Prototypical solution and X-ray structures of metalated nitriles.

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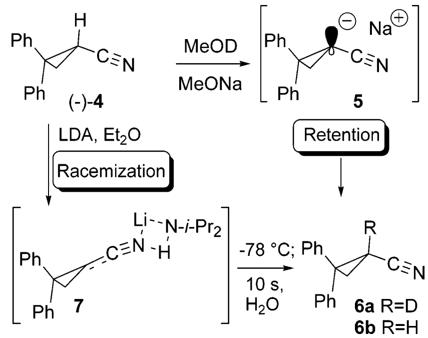
C-Metalated nitriles were experimentally inferred[14] during pioneering deuterations of the chiral cyclopropanecarbonitrile **4**.[15] MeONa−MeOD deuteration proceeds with greater than 99.9% stereochemical retention in generating **6a**, presumably through the intermediacy of the transient ion pair **5**.[16] In contrast, sequential deprotonation−protonation with LDA causes complete racemization (**4** → **6b**) of the putative[9b,c] intermediate *N*-metalated nitrile **7** (Scheme 1).

SCHEME 1. Stereochemical Integrity of *C*- and *N*-Metalated Nitriles



The absence of lithium as the counterion may facilitate maintaining the stereochemical integrity since almost all[17] subsequent examples of *C*-metalated nitriles are with alkaline earth or transition metals.[18] For example, solution NMR of the magnesiated nitrile **8**[19] and the zincated nitrile **9**[20] (Figure 2) imply metalation on carbon in a trend that is maintained within numerous crystal structures of transition metal complexes.[18] Particularly dramatic are the seminal heat-induced interconversions of the crystalline ruthenium *C*- and *N*-phenylsulfonylacetonitriles **10** and **11**, in which the preference for *C*- or *N*-coordination depends on the phosphine ligand.[21]

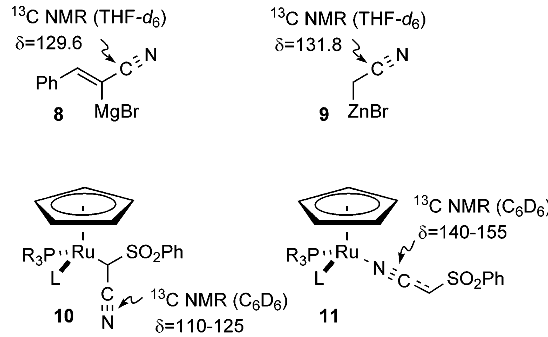


FIGURE 2. Solution and X-ray structures of *C*- and *N*-metalated nitriles.

Selective formation of *C*- and *N*-metalated nitriles offers the possibility for controlling regio- and stereoselective alkylations in previously undeveloped ways. Precedent for divergent reactivity of *C*- and *N*-metalated nitriles stems from metal-dependent cyclization[22] and carbonyl addition[23] stereoselectivities, and metal-dependent alkylation chemoselectivities.[24] Efforts to harness reactivity differences between *C*- and *N*-metalated nitriles stimulated a general route to metalated nitriles having a variety of metal counterions, that, indeed, exhibit reactivities which complement metal amide deprotonation−electrophilic alkylation of nitriles.[25]

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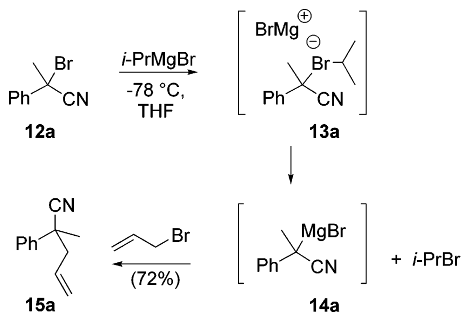
Results and Discussion

Despite extensive halogen−metal exchange[26] of functionalized organometallics, only recently has halogen−metal exchange been achieved with α-halonitriles.[25,27] Historically, α-chloronitriles were serendipitously subjected to chlorine−lithium exchange with BuLi,[28] or LDA,[29] during the previously perplexing oxidative conversion to ketones. Presumably the perceived difficulty[30] in performing chlorine−metal exchange prevented the reaction mechanism from being identified. The requisite α-halonitriles are readily synthesized by brominating (PBr_3, Br_2)[31] or chlorinating (PCl_5, pyridine)[32] the parent nitriles, through organomercury conjugate additions to α-chloroacrylonitrile,[33] and through Diels−Alder cycloadditions with α-chloroacrylonitrile.[34]

Exploratory reactions of bromonitrile **12a** with *i*-PrMgBr demonstrated the viability of accessing magnesiated nitriles through bromine−magnesium exchange (Scheme 2). Initial optimization was complicated by the

SCHEME 2. Prototypical Bromine−Magnesium Exchange



competitive formation of a dimeric material (vide infra), which led to dramatically reducing the time before addition of the electrophile. Sequential addition of *i*-PrMgBr to **12a** followed, 1 min later, by the electrophile causes rapid alkylation, implying a fast bromine−magnesium exchange at −78 °C. A rapid exchange correlates with the immediate color change that occurs upon addition of the Grignard reagent, although the yellow color may potentially be due to formation of the bromate complex **13a**.[35] Fragmentation[35] of the bromate complex **13a** generates *i*-PrBr and the magnesiated nitrile **14a**, which then reacts with the electrophile to furnish the alkylated nitrile **15a**.

TABLE 1. Halogen−Magnesium and −Lithium Exchange-Alkylations of α-Halonitriles

entry	α-halonitrile	reaction	nitrile	yield[a] A	yield[a] B
1	**12a**[b]	*i*-PrMgBr,	**15a**	72%	
2	**12a**[b]	*i*-PrMgBr,	**15b**		71%
3	**12b**	*i*-PrMgBr,	**15c**	62%	82%
4	**12b**	*i*-PrMgBr,	**15d**	58%	80%
5	**12b**	*i*-PrMgBr,	**15e**	52%	70%
6	**12b**	*i*-PrMgBr,	**15f**		65%
7	**12b**	*i*-PrMgBr,	**15g**		73%
8	**12b**	*i*-PrMgBr,	**15h**		70%
9	**12b**	*i*-PrMgBr,	**15i**		63%
10	**12c**	*i*-PrMgBr,	**15j**		79%
11	**12d**	*i*-PrMgBr,	**15j**		60%[c]
12	**12e**	BuLi,	**15c**	72%	
13	**12e**	BuLi,	**15e**	54%	
14	**12c**	*n*-BuLi,	**15j**		51%

[a] Isolated yields for sequential metalation−alkylation, procedure A, and with an in situ metalation−alkylation, procedure B. [b] Prepared by free radical bromination with NBS.[39] [c] Contains 6% of the hydroxynitrile resulting from deprotonation and carbonyl addition.

Diverse α-halonitriles efficiently alkylate an array of electrophiles using the optimized exchange-electrophile addition procedure (Table 1, column A). Bromine−magnesium exchange generates magnesiated nitriles that efficiently alkylate representative alkyl halide and carbonyl electrophiles (Table 1, entries 1−11), whereas the corresponding chloronitriles react significantly less ef-

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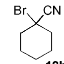
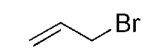
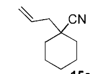
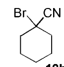
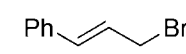
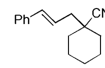
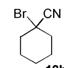
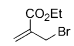
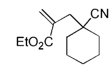
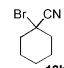
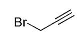
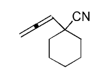
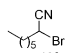
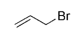
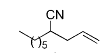
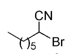
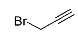
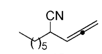
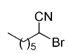
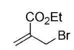
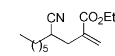
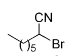
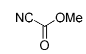
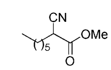
fectively. Chloronitriles exchange more slowly with *i*-PrMgBr resulting in considerable dimerization between the magnesiated nitrile and unreacted chloronitrile, which is conveniently avoided by performing the exchange with BuLi (Table 1, entries 12−14). The efficient lithium−chlorine exchange attests to the activation of the carbon−chlorine bond by the nitrile since chlorine−metal exchange is particularly difficult and seldom observed.[30]

The extremely rapid chlorine−lithium and bromine−magnesium exchanges stimulated a more daring in situ protocol where *i*-PrMgBr or BuLi is added to a solution containing the halonitrile and the electrophile.[36] Remarkably, the in situ protocol is successful even with particularly electrophilic functionalities such as acyl cyanide and aldehyde electrophiles. Comparing the exchange-alkylation and in situ alkylations reveals the latter to be the method of choice, affording consistently a 20% higher yield of alkylnitrile (Table 1, column B). Presumably the increased yield of the in situ procedure is partly due to rapid capture of the magnesiated nitrile with the electrophile, which effectively circumvents prior single electron transfer between the magnesiated nitrile **14** and the electrophilic halonitrile **12**.[37]

Key regio- and chemoselectivity preferences of magnesiated nitriles were probed with the in situ protocol. Alkylations with cinnamyl and propargyl bromide occur exclusively through S_N2 alkylation, analogous to alkylations of lithiated nitriles obtained by metal amide deprotonation.[1b] Perhaps not surprisingly, iodine−magnesium exchange is faster than the corresponding bromine−magnesium exchange as gauged by the increased yield for comparable exchange reactions of *i*-PrMgBr with iodoacetonitrile and bromoacetonitrile (Table 1, entries 10 and 11). Even for the magnesium−bromine exchange of bromoacetonitrile, only 6% of the hydroxynitrile arising from deprotonation of bromoacetonitrile is obtained, indicating that the metal−halogen exchange is faster than the competitive deprotonation.[38]

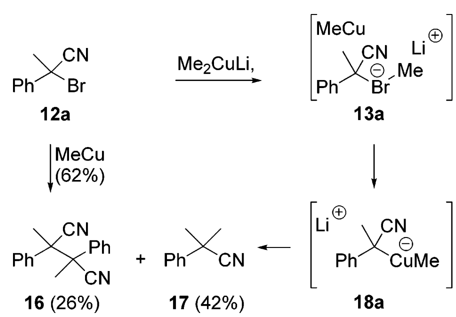
Dramatic advances in copper−halogen exchange[40] stimulated developing an analogous copper−halogen exchange with α-halonitiles.[41] Optimization experiments with bromonitrile **12b** revealed that a facile copper−bromine exchange with Me_2CuLi is complete within 1.5 h at 0 °C. Subsequent addition of allylic electrophiles generates alkylated nitriles (Table 2, entries 1−3), with complete S_N2' displacement occurring for the alkylation with propargyl bromide (Table 2, entry 4).[42] Analogous cuprate exchange-alkylations of the bromonitrile **12f** proceed without any observable deprotonation, affording high yields of the alkylated nitriles with allylic and carbonyl electrophiles (Table 2, entries 5−8).

TABLE 2. Me_2CuLi-Induced Exchange-Alkylations of α-Bromonitriles

entry	α-bromonitrile	electrophile	nitrile	yield
1	 12b		 15c	69%
2	 12b		 15h	54%
3	 12b		 15k	70%
4	 12b		 15l	73%
5	 12f		 15m	85%
6	 12f		 15n	77%
7	 12f		 15o	78%
8	 12f		 15p	87%

Key mechanistic insight was gleaned from copper−halogen exchange reactions with the bromonitrile **12a** (Scheme 3). Me_2CuLi-induced exchange of **12a** generates the dimer **16**[43] (26%) and dimethylphenylacetonitrile (**17**, 42%), even when the exchange was performed with an electrophile in situ at −78 °C. Presumably[35] Me_2CuLi reacts with **12a** to generate the bromate **13a** that

SCHEME 3. Organocopper Exchange of Bromonitrile 12a



(36) For an excellent survey of halogen−metal exchange reactions in the presence of electrophiles see: ref 30, pp 116 and 284−287.

(37) (a) Werry, J.; Stamm, H.; Sommer, A. *Chem. Ber.* **1990**, *123*, 1553. (b) Šindelá, K.; Holubek, J.; Svátek, E.; Schlanger, J.; Dlabač, A.; Valchář, M.; Hurbantová, M.; Protiva, M. *Collect. Czech. Chem. Commun.* **1990**, *55*, 782. (c) Chauffaille, J.; Hebert, E.; Welvart, Z. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1645. (d) Seux, R.; Morel, G.; Foucaud, A. *Tetrahedron* **1975**, *31*, 1335.

(38) Only a trace of the iodo alcohol arising from the deprotonation of **12c** and addition of the resulting anion to cyclohexenone was detected.

(39) Rouz-Schmitt, M.-C.; Petit, A.; Sevin, A.; Seyden-Penne, J.; Anh, N. T. *Tetrahedron* **1990**, *46*, 1263.

(40) (a) Yang, X.; Rotter, T.; Piazza, C.; Knochel, P. *Org. Lett.* **2003**, *5*, 1229. (b) Piazza, C.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 3263.

(41) For a pioneering exchange of a sulfonyl ketone with Me_2CuLi see: Posner, G. H.; Switzer, C. *J. Am. Chem. Soc.* **1986**, *108*, 1239. For a related exchange with a trifluorosulfonyl ester see: Petit, Y.; Sanner, C.; Larchevêque, M. *Tetrahedron Lett.* **1990**, *31*, 2149.

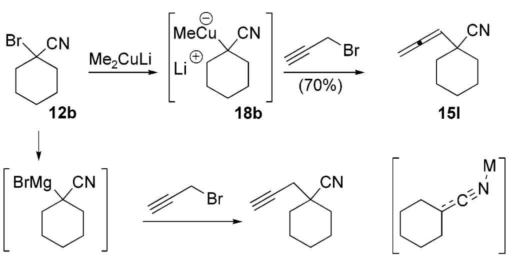
(42) For excellent regioselectivity analyses see: (a) Yamanaka, M.; Kato, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 6287. (b) Breit, B.; Demel, P. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, Germany, 2002; pp 188−223.

(43) Obtained as a mixture of *dl* and *meso* isomers

fragments to the *C*-cuprated nitrile **18a**.[44] Reductive elimination of **18a** leads to **17** whereas competitive alkylation of **18a** with the electrophilic bromonitrile **12a**, through single electron transfer, affords **16**.[37,39,45] Bromine−copper exchange of **12a** with the less reactive MeCu[46] affords **16** (62%), but without the formation of **17** since collapse of the bromate **13a** leads to an organocopper species and not a cuprate.[47]

Formation of dimethylphenylacetonitrile (**17**) by reductive elimination identifies *C*-cuprated nitriles as the key intermediates resulting from Me_2CuLi exchange. The formation of *C*-cuprated nitrile **18b** (Scheme 4) is consistent with the S_N2' displacement of propargyl bromide and difficult to rationalize if copper were coordinated to nitrogen (**19**).[48] Halogen−magnesium exchange of bromonitrile **12b** through an ate complex may initially lead to the *C*-magnesiated nitrile **14b**, although progression to an *N*-metalated nitrile is equally conceivable. The ambiguity is not resolved during alkylation with propargyl bromide since *N*- and *C*-magnesiated nitriles are both anticipated to react by S_N2 alkylation,[1b] leaving the site of magnesium coordination an open question (Scheme 4).

SCHEME 4. Divergent S_N2 and S_N2' Alkylations with Propargyl Bromide



Lithiated nitriles are, almost without exception,[17] *N*-coordinated.[9b,c] Alkylation of the, presumed, *N*-lithiated nitrile **19b** with propargyl bromide causes exclusive S_N2 displacement (Scheme 5). The preference of the cuprate **18b** for S_N2' alkylation (Scheme 4) stimulated an intriguing $N \rightarrow C$ transmetalation of the lithiated nitrile **19b** with MeCu. Sequential LDA deprotonation of **20** and addition of MeCu generates the putative *C*-cuprated nitrile **18b**, which reacts with propargyl bromide to give exclusively the S_N2' allenylnitrile **15*l***. Collectively, these alkylations indicate a high propensity of copper for coordination on carbon.

(44) For the synthesis of *C*-cuprated nitriles see: (a) Kondo, J.; Ito, Y.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 106. (b) Tsuda, T.; Nakatsuka, T.; Hirayama, T.; Saegusa, T. *J. Chem. Soc., Chem. Commun.* **1974**, 557. (c) Corey, E. J.; Kuwajima, I. *Tetrahedron Lett.* **1972**, 487.

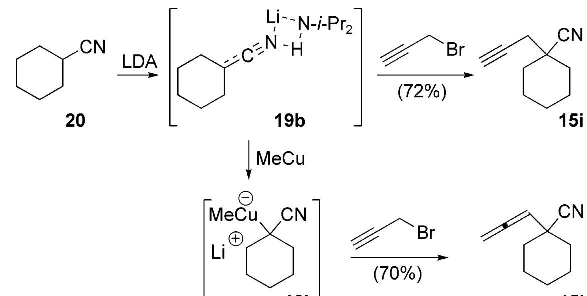
(45) Aryl- and α-aminomethyl cuprates couple in the presence of electrophiles: (a) Dieter, R. K.; Li, S. J.; Chen, N. *J. Org. Chem.* **2004**, *69*, 2867. (b) Kronenburg, C. M. P.; Amijs, C. H. M.; Wijkens, P.; Jastrzebski, J. T. B. H.; van Koten, G. *Tetrahedron Lett.* **2002**, *43*, 1113. (c) Lipshutz, B. H.; Kayser, F.; Liu, Z.-P. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1842. (d) Lipshutz, B. H.; Siegmann, K.; Garcia, E. *J. Am. Chem. Soc.* **1991**, *113*, 8161.

(46) MeCu does not cause bromine−copper exchange with **12b**.

(47) The absence of **17** requires that no alkylation occurs between the organocopper and organocuprate **18a**, with the bromomethane generated from fragmentation of the bromate **13a**.

(48) Potentially, the transition state for reductive elimination could arise from either an *N*- or *C*-cuprated nitrile ground state.

SCHEME 5. Comparative Alkylations of *N*- and *C*-Metalated Nitriles



Conclusion

Halogen−metal exchange of α-halonitriles with organometallics generates diverse metalated nitriles. Grignard and alkyllithium reagents trigger the rapid metal−halogen exchange of α-halonitriles whereas the exchange with lithium dimethylcuprate is considerably slower. An array of electrophiles efficiently intercept the intermediate metalated nitriles either through sequential addition of the electrophile to the metalated nitrile or by performing the exchange in the presence of the electrophile. The reactivities of organocopper- and halomagnesium-substituted nitriles imply *C*-metalated nitrile intermediates, at least in the former instance, with complementary regioselectivity preferences in comparable alkylations with propargyl bromide. Synthetically, the organocopper-substituted nitriles are efficiently accessed by sequential deprotonation followed by the addition of MeCu. Collectively the metal−halogen exchange allows tuning of the metal coordination site with *N*- and *C*-metalated nitriles exhibiting reactivity trends complementary to those of metalated nitriles obtained through deprotonation with metal amide bases.

Experimental Section

General Nitrile Bromination Procedure. Neat bromine and nitrile were sequentially added to ice-cooled PBr_3. After the addition, the ice bath was removed and the reaction was heated at 60 °C. After 5 h the mixture was poured onto ice and extracted with ether (3×), and then the crude extracts were washed with $NaHCO_3$ (3×) and water and then dried ($MgSO_4$). Concentration and purification of the crude product by radial chromatography afforded analytically pure material.

General Alkylation Procedure A. A THF solution of *i*-PrMgBr (1.05 equiv) was added to a −78 °C, THF solution of the bromonitrile (1.0 equiv) and, after 1 min, neat electrophile (1.05 equiv) was added. After 2 h saturated, aqueous NH_4Cl solution was added, and the crude product was extracted with EtOAc, dried ($MgSO_4$), concentrated, and purified by radial chromatography to afford analytically pure material.

General in Situ Alkylation Procedure B. A THF solution of *i*-PrMgBr (1.05 equiv) was added to a −78 °C, THF solution of the bromonitrile (1.0 equiv) and the electrophile (1.05 equiv). After 2 h saturated, aqueous NH_4Cl solution was added, and the crude product was extracted with EtOAc, dried ($MgSO_4$), concentrated, and purified by radial chromatography to afford analytically pure material.

General Bromine−Copper Exchange Procedure. A THF solution of the bromonitrile was added to a 0 °C, ether solution of Me_2CuLi [generated by adding methyllithium (2.2 equiv) to copper iodide (1.2 equiv)]. After 1 h, neat electrophile (1.30 equiv) was added and, after a further 2 h at 0 °C, saturated, aqueous NH_4Cl solution was then added. The mixture was stirred vigorously with exposure to air for 30 min, and the crude product was then extracted with ethyl ether and dried ($MgSO_4$). Concentration of the crude product and purification by radial chromatography afforded analytically pure material.

Acknowledgment. Financial support of this research, and travel funds, from NSF is gratefully acknowledged as are insightful discussions with Dr. Paul Carlier.

Supporting Information Available: Experimental procedures and ^1H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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