JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Study of the Lithiated Phenylacetonitrile Monoanions and Dianions Formed According to the Lithiated Base Used (LHMDS, LDA, or *n*-BuLi). 2. Alkylation and Deuteriation Mechanism Study by Vibrational and NMR Spectroscopy and Quantum Chemistry Calculations

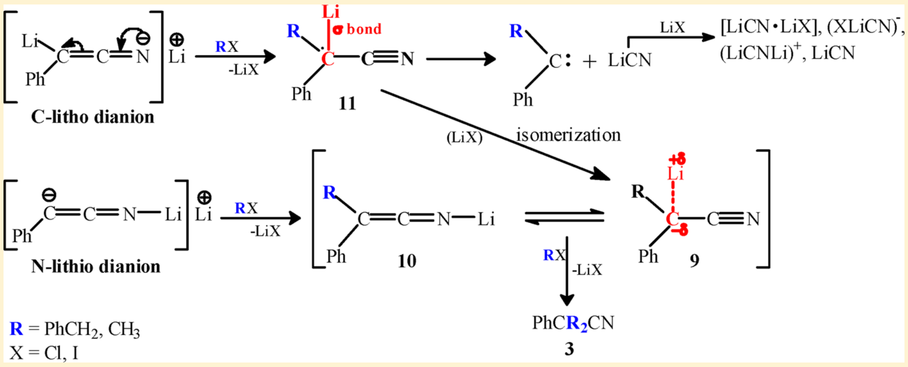
Tekla Strzalko,[†] Lya Wartski,[†] Jacques Corset,[‡] Martine Castellà-Ventura,*[,§] and Françoise Froment[‡]

[†]LSOM - CNRS/U-PSUD, Institut de Chimie Moléculaire et des Matériaux d'Orsay, 15 Rue Georges Clémenceau, 91405 Orsay Cedex, France

[‡]LADIR - CNRS/UPMC, 4 Place Jussieu, 75252 Paris Cedex 05, France

[§]LCT - CNRS/UPMC, 4 Place Jussieu, 75252 Paris Cedex 05, France

Supporting Information



ABSTRACT: Mechanisms of alkylation by $PhCH_2Cl$ or CH_3I in THF and of deuteriation by DCl (4 N in D_2O) in THF or THF−toluene of lithiated phenylacetonitrile monoanions and dianions obtained with LHMDS, LDA, or *n*-BuLi are studied by vibrational and NMR spectroscopy and quantum chemistry calculations. Dialkylation of the three dilithio dianions generated with *n*-BuLi (2.0−2.7 equiv, THF−hexane) depends on their structure: N-lithio $(PhCCNLi)^-Li^+$ and (C,N)-dilithio PhCLiCNLi dianions afford $PhCR_2CN$ (R = $PhCH_2$, CH_3) from the intermediate N-lithio monoalkylated monoanion PhCRCNLi **10**; C-lithio dianion $(PhCLiCN)^-Li^+$ leads to a carbenoid species, the C-lithio monoalkylated nitrile PhCLiRCN **11**, which either eliminates carbene Ph−C̈−R and different LiCN species or isomerizes to PhCRCNLi in the presence of LiX (X = Cl, I). Dialkylation or dideuteriation of monoanions (monomers, dimers, and heterodimers [PhCHCNLi·LiR′], R′ = $(SiMe_3)_2N$, $(i\text{-}Pr)_2N$) obtained with LHMDS or LDA (2.4 equiv, THF) proceeds via a sequential mechanism involving monometalation-monoalkylation (or monodeuteriation) reactions. Some carbene and $(LiCNLi)^+$ are also observed, and explained by another mechanism implying the C-lithio monoalkylated monoanion PhCLiRCN **9** in the presence of LiX. These results show the ambiphilic behavior of PhCLiRCN as a carbenoid (**11**) or a carbanion (**9**) and the importance of LiX formed in situ in the first alkylation step.

INTRODUCTION

Carbanions α to nitrile are useful reagents for C−C bond formation in organic synthesis. The structure of these anionic species (monoanions and dianions) may play an important role in the selectivity of alkylation or deuteriation reactions. In a previous paper,[1] we have shown that a heterodimer **6** (M = Li) is formed with an excess of base (LHMDS, LDA, or *n*-BuLi) added to $PhCH_2CN$ **1** in THF, THF−hexane, or THF−toluene in different amounts depending on the pK_{H_a} and on the base concentration. When a large excess of base is used, dianionic species are obtained almost quantitatively with *n*-BuLi, while only a very small amount of dianion is observed with LDA and no dianion is detected with LHMDS. While the mechanism of alkylation of monoanions of $PhCH_2CN$ has been well documented, that of its dianions has not yet been studied.

The species obtained from reaction of phenylacetonitrile $PhCH_2CN$ **1** with more than 2 equiv of a lithiated base were deuteriated by D_2O, alkylated by different alkyl halides, acylated by diethyl carbonate, or benzoylated with methyl benzoate.[2−4]

Received: April 29, 2012
Published: June 28, 2012

Scheme 1

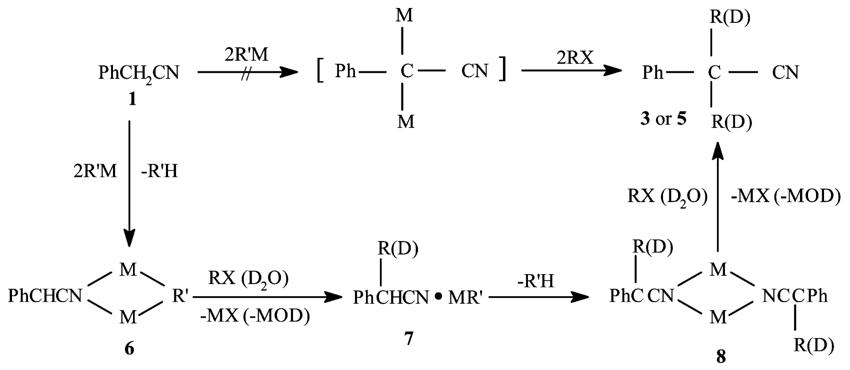
a

$$\underset{\mathbf{1}}{PhCH_2CN} \xrightarrow[\text{THF-hexane}]{n\text{-BuLi, 2.3 equiv}} PhCLi_2CN \xrightarrow{D_2O} \underset{\mathbf{5}}{PhCD_2CN}$$

b

$$\underset{\mathbf{1}}{PhCH_2CN} \xrightarrow[\text{then } D_2O]{n\text{-BuLi, 2.3 equiv}} PhCHLiCN \longrightarrow \underset{\mathbf{4}}{PhCHDCN} \longrightarrow PhCLiDCN \longrightarrow \underset{\mathbf{5}}{PhCD_2CN}$$

Scheme 2. Boche's Deprotonation/Alkylation or Deuteriation Cycle for the Formation of α-Carbon Disubstituted Nitriles[11]



Treatment with oxalic acid bis(imidoyl) chlorides[5] or epibromohydrin[6−8] led to new cyclization reactions affording, respectively, 2-alkylidene-3-iminoindoles and functionalized cyclopropanes.

In 1971, Kaiser et al.[2] concluded that a *gem*-dialkali salt $PhCLi_2CN$ is formed by means of *n*-BuLi excess in THF−hexane from the results of deuteriations and alkylations which take place only at the benzylic carbon atom (Scheme 1a). Thus, they put aside the other possible mechanism that consists of sequential monometalations−monodeuteriations (or monoalkylations) involving only the monoanions (Scheme 1b).

Later on, Crowley et al.[9] and Boche et al.[10,11] did not observe dianion formation. Thus, they gave up Scheme 1a and developed Scheme 1b on the basis of ^{13}C NMR and X-ray structure analysis. They proposed a new scheme (Scheme 2) in which a heterodimer ("Quadac", i.e., "Quasi dianion complex") **6** is on the way to the dialkylated $PhCR_2CN$ **3** or dideuteriated $PhCD_2CN$ **5** for LHMDS and *n*-BuLi[9] or LDA,[10] when 2 equiv of base are used. The existence of a relatively stable complex [PhCHR(D)CN·MR′] **7** between the monoalkylated or monodeuteriated phenylacetonitrile (PhCHRCN **2** or PhCHDCN **4**, respectively) and the base R′M was also proved by X-ray crystal analysis and ab initio calculations.[11] This complex leads through a new deprotonation and a dimerization to the monoanion dimer **8**,[12] which is finally transformed into $PhCR_2CN$ **3** or $PhCD_2CN$ **5**. This reaction pathway was supported by the theoretical study of the deprotonation of nitriles.[13]

Mono- versus dialkylation of phenylacetonitrile monoanions by benzyl or methyl halides (RX) was reported.[3,14,15] These reactions are poorly selective and give rise generally to mixtures of mono- and dialkylated products according to eqs 1−5 (Scheme 3).

To shed some light on the alkylation and deuteriation mechanisms in THF with *n*-BuLi, LHMDS, and LDA, we have performed alkylations by benzyl chloride ($PhCH_2Cl$) and methyl iodide (CH_3I) in THF and deuteriation in THF or THF−toluene with DCl (4 N in D_2O) of the lithiated monoanions and dianions of phenylacetonitrile. We have also identified by IR spectroscopy and calculated by quantum chemistry methods some species that are observed or may be formed during the different steps of the alkylation reactions.

Scheme 3

$$PhCH_2CN + R'Li \longrightarrow PhCHCNLi + R'H \tag{1}$$

$$PhCHCNLi + RX \longrightarrow PhCHRCN + LiX \tag{2}$$

$$PhCHRCN + PhCHCNLi \rightleftharpoons PhCH_2CN + PhCRCNLi \tag{3}$$

$$PhCHRCN + R'Li \longrightarrow PhCRCNLi + R'H \tag{4}$$

$$PhCRCNLi + RX \longrightarrow PhCR_2CN + LiX \tag{5}$$

■ RESULTS AND DISCUSSION

1. Alkylation and Deuteriation of Monoanions and Dianions. Table 1 gathers the results of alkylation of $PhCH_2CN$ anions generated with less than 1.2 equiv (entries 1−3, 6−12, 23, and 24) or more than 2 equiv (entries 4, 5, 13−22, 25, and 26) of base (LHMDS, *n*-BuLi, or LDA) by $PhCH_2Cl$ or CH_3I in THF. The percentage of alkylation at the benzylic position is expressed by $R = 1/2$ (% PhCHRCN) + % $PhCR_2CN$. The rates of the products ($PhCH_2CN$ **1**, PhCHRCN **2**, and $PhCR_2CN$ **3**) are determined either from integration of ^1H NMR spectra of the crude reaction mixture after hydrolysis and extraction or from IR determination of the concentration of each product in solution before treatment. A fairly good agreement is observed between the two spectroscopic methods. IR spectrometry allows us to verify that all of the starting phenylacetonitrile anions are transformed into the three possible products **1**, **2**, or **3**. Since all the initial

Table 1. Mono- vs Dialkylation of Mono- and Dianions Derived from $PhCH_2CN$ **1** in THF

entry	spectroscopic method used for analysis	base (equiv)	RX (equiv)	R^a (%)	products^b **1** (%)	**2** (%)	**3** (%)	yield^c (%)
1	NMR	LHMDS (1.0)	$PhCH_2Cl$ (1.2)	50	23	55	22	
2	NMR	LHMDS (1.2)	$PhCH_2Cl$ (1.2)	58	17	51	32	84
3	IR	LHMDS (1.2)	$PhCH_2Cl$ (1.2)	53	24	46	30	100
4	NMR	LHMDS (2.4)	$PhCH_2Cl$ (2.4)	100	0	0	100	88
5	IR	LHMDS (2.4)	$PhCH_2Cl$ (2.4)	100	0	0	100	88
6	NMR	*n*-BuLi (1.0)	$PhCH_2Cl$ (1.2)	51	24	51	25	92
7	NMR	*n*-BuLi (1.0)	CH_3I (1.2)	51	16	67	17	
8	IR	*n*-BuLi (1.1)	$PhCH_2Cl$ (1.1)	49	25	53	22	100
9	NMR	*n*-BuLi (1.1)	$PhCH_2Cl$ (1.2)	55	20	51	29	88
10[d]	NMR	*n*-BuLi (1.1)	$PhCH_2Cl$ (1.2)	54	21	50	29	92
11	IR	*n*-BuLi (1.1)	CH_3I (1.2)	57	15	57	28	100
12	NMR	*n*-BuLi (1.2)	$PhCH_2Cl$ (1.2)	61	15	49	36	84
13	NMR	*n*-BuLi (2.0)	$PhCH_2Cl$ (2.4)	81	5	28	67	
14	IR	*n*-BuLi (2.0)	$PhCH_2Cl$ (2.4)	80	6	29	65	79
15	NMR	*n*-BuLi (2.2)	$PhCH_2Cl$ (2.4)	92	1	15	84	
16	IR	*n*-BuLi (2.2)	$PhCH_2Cl$ (2.4)	86	4	21	75	82
17	NMR	*n*-BuLi (2.4)	$PhCH_2Cl$ (2.4)	100	0	0	100	
18	IR	*n*-BuLi (2.4)	$PhCH_2Cl$ (2.4)	100	0	0	100	70
19	NMR	*n*-BuLi (2.4)	CH_3I (2.4)	100	0	0	100	
20	IR	*n*-BuLi (2.4)	CH_3I (2.4)	100	0	0	100	56
21	NMR	*n*-BuLi (2.7)	$PhCH_2Cl$ (2.4)	100	0	0	100	
22	IR	*n*-BuLi (2.7)	$PhCH_2Cl$ (2.4)	90	10	0	90	75
23	NMR	LDA (1.2)	$PhCH_2Cl$ (1.2)	52	22	52	26	81
24	IR	LDA (1.2)	$PhCH_2Cl$ (1.2)	57	20	46	34	98
25	NMR	LDA (2.4)	$PhCH_2Cl$ (2.4)	66	9	50	41	
26	IR	LDA (2.4)	$PhCH_2Cl$ (2.4)	65	13	44	43	90

[a] Percentage of alkylation at the benzylic carbon atom. [b] Product percentages after hydrolysis when determined by ^1H NMR and before hydrolysis when determined by IR spectroscopy. [c] Reaction yield in products including $PhCH_2CN$ **1** formed according to equilibrium 3 (Scheme 3). [d] 3.0 equiv of HMDS added.

Table 2. Mono- vs Dideuteriation of Mono- and Dianions Derived from $PhCH_2CN$ **1**

entry	solvent (v/v)		base (equiv)		D^a (%)	products^b
1	THF		LHMDS	1.1	67	**4**~**5** ≫ **1**
2	THF−toluene	30/70		1.1	48[c]	**4**~**1** > **5**
3	THF			2.4	95	**5** ≫ **4**
4	THF−toluene	30/70		2.2	72	**5** > **4** ≫ **1**
5	THF		LDA	1.1	37	**4**~**1** ≫ **5**
6	THF−toluene	30/70		1.1	52	**4**~**1**−**5**
7	THF			2.2	57	**4** > **5** > **1**
8	THF−toluene	30/70		2.2	63	**4**~**5** ≫ **1**
9	THF−hexane[d]	82/18	*n*-BuLi	1.1	55	**4** > **5** > **1**
10	THF−hexane[d]	65/35		2.2	88	**5** ≫ **4**
11	THF−hexane[d]	62/38		2.4	87	**5** ≫ **4**
12	THF−hexane[d]	57/43		2.7	96	**5** ≫ **4**[e]

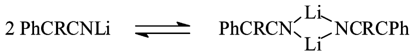
[a] Percentage of deuteriation at the benzylic carbon atom from ^1H NMR spectroscopy in CD_2Cl_2−CCl_4 (50/50 v/v). [b] $PhCHDCN$ **4**: $\delta = 23.1$ ppm (t, $J_{CD} = 20.8$ Hz); $PhCD_2CN$ **5**: $\delta = 22.9$ ppm (quint, $J_{CD} = 20.8$ Hz). [c] From ^{13}C NMR spectroscopy in $CDCl_3$. [d] Hexane comes from the *n*-BuLi commercial solution (1.6 M). [e] Presence of some degradation products.

$PhCH_2CN$ **1** is transformed into monoanions or dianions before alkylation or deuteriation, the observed $PhCH_2CN$ **1** is considered as a product. The reaction yield is also determined.

The results of deuteriation of the mono- and dianionic species formed from $PhCH_2CN$ **1** with different equivalents of base in THF and THF−toluene solutions are reported in Table 2. Three species may be observed by ^1H and ^{13}C NMR spectroscopy: dideuteriated $PhCD_2CN$ **5**, monodeuteriated $PhCHDCN$ **4**, and $PhCH_2CN$ **1**. The percentage of deuteriation *D* is calculated in the same way as *R*.

1.1. Alkylation and Deuteriation of Monoanions.

1.1.1. With 1.0−1.2 equiv of LHMDS, LDA, or n-BuLi. As we have shown previously,[1] with 1.1 equiv of LHMDS, LDA, and *n*-BuLi, only monoanions (monomers and dimers) of PhCHCNLi are present in the solution (equilibrium 6, R =



$$2\ PhCRCNLi \rightleftharpoons PhCRCN\overset{Li}{\underset{Li}{\diamond}}NCRCPh \qquad [6]$$

R = H, CH_3, $PhCH_2$ or D

H). As expected, with 1.0 equiv of LHMDS or *n*-BuLi and 1.2 equiv of $PhCH_2Cl$ (Table 1, entries 1 and 6), *R* ∼ 50%. Moreover, the same proportion (∼24%) of $PhCH_2CN$ **1** and of dialkylated compound $PhCR_2CN$ **3** (R = $PhCH_2$) is obtained with ∼53% of monoalkylated product PhCHRCN **2**. Indeed, PhCHRCN **2** may be deprotonated by PhCHCNLi (equilibrium 3, Scheme 3), leading to $PhCH_2CN$ **1** and to the monoanion PhCRCNLi. Then PhCRCNLi is alkylated through reaction 5 (Scheme 3) to give $PhCR_2CN$ **3**. A similar behavior has already been observed in alkylation reactions of lithioacetonitrile $LiCH_2CN$.[16]

When CH_3I is used as alkylating agent (Table 1, entry 7), less $PhCH_2CN$ **1** and $PhCR_2CN$ **3** (∼17%) and more PhCHRCN **2** are observed (67%). Thus, equilibrium 3 is less displaced to the right than with $PhCH_2Cl$. This is due to the lower acidity of $PhCH(CH_3)CN$ relative to $PhCH(PhCH_2)CN$. The first alkylation reaction 2 may also be faster and the second alkylation reaction 5 slower with CH_3I than with $PhCH_2Cl$ because of the greater steric hindrance at the benzylic carbon atom in PhCRCNLi when R = CH_3 compared to R = $PhCH_2$.

With a slight excess (1.1−1.2 equiv) of LHMDS or *n*-BuLi (Table 1, entries 2, 3, 9, and 12), a slightly higher percentage of alkylation is reached (*R* ∼ 57%), the proportion of $PhCR_2CN$ **3** increases (∼32%), and that of $PhCH_2CN$ **1** decreases (∼19%). The slight excess of base contributes to the deprotonation of PhCHRCN **2** according to reaction 4 (Scheme 3) and to the formation of $PhCR_2CN$ **3** according to reaction 5. Thus, the deprotonation of PhCHRCN **2** by the base through reaction 4 becomes faster than its deprotonation by PhCHCNLi via equilibrium 3.

The results with 1.2 equiv of LDA (Table 1, entries 23 and 24) are comparable to those with 1.2 equiv of LHMDS (Table 1, entries 2 and 3).

In our previous paper,[1] we have shown that the amine R′H (R′ = $(i\text{-}Pr)_2N$ or $(SiMe_3)_2N$) formed through reaction 1 (Scheme 3) shifts the monomer−dimer equilibrium 6 toward the dimer through a solvation entropic effect. When 3.0 equiv of amine HMDS is added to PhCHCNLi formed with 1.1 equiv of *n*-BuLi, an important shift of the equilibrium toward the dimer is observed. However, the selectivity of the alkylation is the same with or without HMDS (Table 1, entries 10 and 9, respectively). Other experiments, not reported in Table 1, have been performed in order to increase the dimer concentration in the medium either by raising the initial concentration of $PhCH_2CN$ **1** (from 0.25 to 0.5 M) with LHMDS (1.2 equiv) or by replacing THF by toluene with *n*-BuLi (1.2 equiv). In all cases, the alkylation selectivity remains unchanged.

A yield of ∼100% (Table 1) is determined by IR studies in all cases. This indicates a total transformation of PhCHCNLi into products. The yields obtained by ^1H NMR vary from 81 to 92% because of loss of products during extraction.

The deuterium incorporation depends on the solvent, the nature of the base used, as already indicated for the C_α deuteration of endocyclic enolates,[17] and on the amount of base.

With 1.1 equiv of base in THF or in THF−hexane (hexane is present in the *n*-BuLi commercial solution; see the Experimental Section) (Table 2, entries 1, 5, and 9), some dideuteriation is observed at the benzylic carbon atom. The percentage of deuteriation *D* is higher with LHMDS (67%), lower with LDA (*D* = 37%), or equal with *n*-BuLi (*D* = 55%) when compared to alkylation (*R* ∼ 55%) (Table 1). As alkylation, the deuteriation is described by reactions 2−5 (Scheme 3, R = D), but for LHMDS and LDA, supplementary mechanisms are involved.

The over-incorporation of deuterium observed with LHMDS is explained by a proton abstraction mechanism related to the hydrolysis of bis trimethylsilylamine $(SiMe_3)_2NH$ in acidic medium, which gives trimethylsilanol $SiMe_3OH$ and NH_4Cl.[18,19] $(SiMe_3)_2NH$ is initially present inside the solvation shell of PhCHCNLi monomers and dimers. Deuteriation of PhCHCNLi solvated by the amine leads to the formation of an intermediate species LiCl solvated by PhCHDCN **4** and $(SiMe_3)_2NH$. In acidic medium (DCl/D_2O), the amine within this complex may abstract rapidly a proton from PhCHDCN **4** to form $PhCD_2CN$ **5**, together with $SiMe_3OD$ and $SiMe_3NH_2$.

The influence of the initial concentration of $PhCH_2CN$ on this process is demonstrated in Figure 1. The variations of *D* determined by ^1H NMR spectroscopy, and the proportions of $PhCH_2CN$ **1** and $PhCD_2CN$ **5** obtained by IR and Raman spectrometry, respectively, for increasing initial concentrations of $PhCH_2CN$ **1** from 0.12 to 0.5 M with 1.1 equiv of LHMDS in THF are shown. *D* and the amount of $PhCD_2CN$ **5** formed at the expense of $PhCH_2CN$ **1** increase with the initial concentration of $PhCH_2CN$. The over-incorporation of *D* is thus directly related to the concentration of PhCHCNLi, generated from $PhCH_2CN$ (reaction 1, Scheme 3). The increase of its concentration corresponds to an equal increase of the amine $(SiMe_3)_2NH$ concentration in the medium and consequently to an increase of the proportion of the intermediate species LiCl solvated by both PhCHDCN **4** and $(SiMe_3)_2NH$.

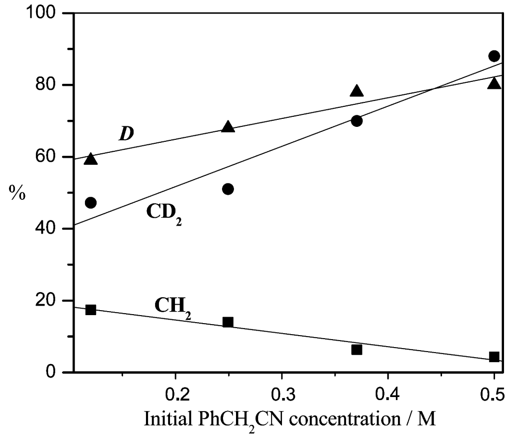
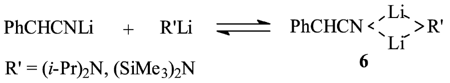


Figure 1. Variations of the percentage (%) of deuterium incorporation *D* at the benzylic carbon atom obtained by ^1H NMR, of the proportions (%) of $PhCH_2CN$ **1** (CH_2) and $PhCD_2CN$ **5** (CD_2) determined by IR and Raman spectrometry, respectively, as a function of the initial $PhCH_2CN$ **1** concentration (0.12, 0.25, 0.37, and 0.5 M) with 1.1 equiv of LHMDS in THF.

In THF−toluene (30/70 v/v) (Table 2, entry 2), *D* is slightly lower than what is expected from base proton abstraction (48% instead of 55%). Thus, the hydrolysis of $(SiMe_3)_2NH$ is less efficient or does not take place at all because of the low solubility of D_2O in this medium.

With 1.1 equiv of LDA in THF (Table 2, entry 5), deuteriation is less efficient than alkylation (*D* = 37% instead of *R* ∼ 55%). With this base, the monomers and dimers of PhCHCNLi are solvated by the free amine $(i\text{-}Pr)_2NH$.[1] During the deuteriation reaction in acidic medium, the formation of deuteriated ammonium salt ($(i\text{-Pr})_2NHD^+Cl^-$) may be responsible for some proton internal return[20−23] which prevents a good deuterium incorporation, while alkylation is not affected by the presence of the amine (Table 1, entries 23 and 24). In THF−toluene (Table 2, entry 6), *D* increases to 52%. Thus, in this solvent, the proton internal return is much less efficient.

1.1.2. With 2.2−2.4 equiv of LHMDS or LDA. With 2.4 equiv of LHMDS or LDA,[1] heterodimers [PhCHCNLi·LiR′] (R′ = $(SiMe_3)_2N$ or $(i\text{-Pr})_2N$) **6** are present in the solution (equilibrium 7) in addition to monomers and dimers of PhCHCNLi (equilibrium 6, R = H). Traces of dianions are also observed with LDA.[1] The concentration of the heterodimer **6** is much more important with LDA than with LHMDS. This is consistent with the greater stability calculated by B3LYP/6-31+G* method for [PhCHCNLi·LDA] compared to [PhCHCNLi·LHMDS] (association energies of −52 and −48 kcal mol^{-1}, respectively), in agreement with less sophisticated calculations of Carlier et al.[24]



$$\mathrm{PhCHCNLi} + \mathrm{R'Li} \rightleftharpoons \mathrm{PhCHCN}\overset{\mathrm{Li}}{\underset{\mathrm{Li}}{<\;>}}\mathrm{R'} \qquad [7]$$

R′ = $(i\text{-Pr})_2N$, $(SiMe_3)_2N$

6

With 2.4 equiv of LHMDS and 2.4 equiv of $PhCH_2Cl$ (Table 1, entries 4 and 5), the percentage of alkylation *R* is of 100%, and only $PhCR_2CN$ **3** is formed with a yield of ∼88%. A very good incorporation of deuterium (*D* = 95%) is also obtained in THF (Table 2, entry 3). *D* decreases to 72% in THF−toluene (Table 2, entry 4). It is to be noted that a smaller amount of LHMDS was used in this solvent (2.2 equiv) than in THF (2.4 equiv) and that more heterodimer **6** is present.[1]

With 2.4 equiv of LDA (Table 1, entries 25 and 26), *R* decreases to ∼66%, and the three products $PhCR_2CN$ **3** (∼ 42%), PhCHRCN **2** (∼ 47%), and $PhCH_2CN$ **1** (∼ 11%) are observed with a yield of 90% similar to the one with LHMDS. The deuterium incorporation in THF (Table 2, entry 7) is a little lower (*D* = 57%) than the percentage of alkylation, as only 2.2 equiv of LDA are employed in deuteriation. In THF−toluene, a slightly better result is obtained (*D* = 63%) (Table 2, entry 8) due to the lower efficiency of the proton internal return in this medium.

1.2. Alkylation and Deuteriation of Dianions. Dianions are prepared with 2.0−2.7 equiv of *n*-BuLi. As we have shown previously (Figure 5 in ref 1), their proportion increases progressively with the amounts of *n*-BuLi (from 2.0 to 2.7 equiv) added to a THF solution of $PhCH_2CN$ **1**. The results of alkylation by an excess of $PhCH_2Cl$ or CH_3I (2.4 equiv) are given in Table 1 (entries 13−22) and Figures 2 and 3 and those of deuteriation in Table 2 (entries 10−12).

With 2.0 and 2.2 equiv of *n*-BuLi, some monoanions (monomers, dimers, and heterodimers **6**) are still present in the solution besides dianions. Monoalkylated **2** (15−29%), dialkylated **3** (65−84%), and only a small amount of $PhCH_2CN$ **1** (1−6%) are formed with a yield of ∼80% (Table 1, entries 13−16). With 2.2 equiv of *n*-BuLi, the percentage of deuteriation (*D* = 88%) (Table 2, entry 10) is similar to the percentage of alkylation by $PhCH_2Cl$ (*R* ∼ 89%) (Table 1, entries 15 and 16). Dideuteriated product **5** is generated in larger amounts than monodeuteriated product **4**.

With 2.4 and 2.7 equiv of *n*-BuLi, the percentage of alkykation is ∼100% (Table 1, entries 17−21). Only dialkylated $PhCR_2CN$ **3** is observed. However, the yield in dialkylated product **3** falls to 70% for R = $PhCH_2$ and to 56% for R = CH_3 with 2.4 equiv of *n*-BuLi (Table 1, entries 18 and 20), indicating the formation of other species which have been characterized by IR spectrometry (Figures 2 and 3). The percentage of deuteriation is of 87 and 96%, respectively (Table 2, entries 11 and 12).

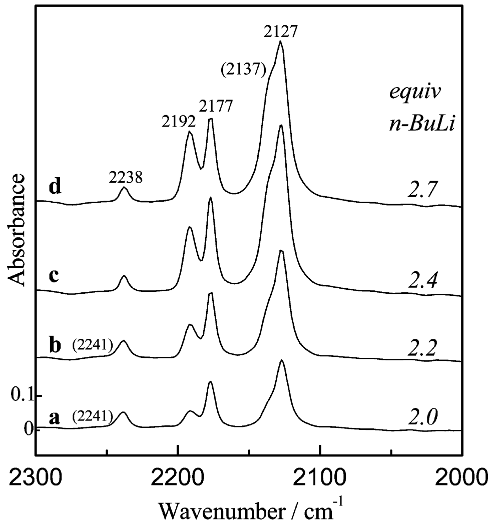


Figure 2. Evolution of the IR spectra (ν(CN) region) of an initial 0.25 M solution of $PhCH_2CN$ **1** (1.0 equiv) in THF−hexane [(a) 67.5/32.5 v/v; (b) 65/35 v/v; (c) 62.5/37.5 v/v; (d) 57.5/42.5 v/v] with increasing amounts of *n*-BuLi after alkylation by $PhCH_2Cl$ (2.4 equiv) and before hydrolysis. Wavenumbers in parentheses correspond to shoulders. Cell thickness: 0.021 cm.

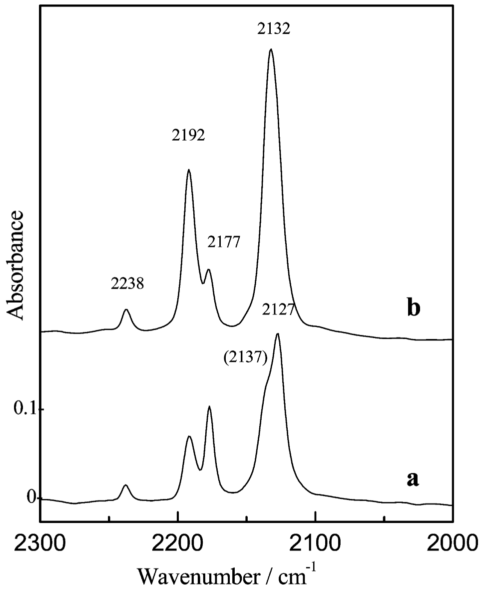


Figure 3. IR spectra (ν(CN) region) of an initial 0.25 M solution of $PhCH_2CN$ **1** (1.0 equiv) with *n*-BuLi (2.4 equiv) in THF−hexane (62.5/37.5 v/v) after alkylation by (a) $PhCH_2Cl$ (2.4 equiv) and (b) CH_3I (2.4 equiv) and before hydrolysis. The wavenumber in parentheses corresponds to a shoulder. Cell thickness: 0.021 cm.

Figure 2 shows the IR spectra of the anionic solutions prepared with increasing amounts of *n*-BuLi after alkylation by 2.4 equiv of $PhCH_2Cl$ and before hydrolysis of the reaction products (Table 1, entries 14, 16, 18, and 22). $PhCR_2CN$ **3** is related to the ν(CN) band at 2238 cm^{-1} and PhCHRCN **2** to the shoulder at 2241 cm^{-1}. The traces of $PhCH_2CN$ **1**, determined from analysis of the spectra, corresponds to a component at 2251 cm^{-1} contributing to the absorption on the high frequency side of the shoulder at 2241 cm^{-1}. Three new bands at 2127, 2177, and 2192 cm^{-1} and a shoulder at 2137 cm^{-1} also appear, with much larger absorption coefficients than that of the CN nitrile group. These bands are assigned to lithium cyanide LiCN associated with lithium or chloride ions, or with lithium chloride LiCl (equilibria 8−12, Scheme 4).

Scheme 4

$$\mathrm{LiCN} + \mathrm{Li}^{+} \rightleftharpoons (\mathrm{LiCNLi})^{+} \qquad [8]$$

$$\mathrm{LiCN} + \mathrm{X}^{-} \rightleftharpoons (\mathrm{XLiCN})^{-} \qquad [9]$$

$$\mathrm{LiCN} + \mathrm{Li\,X} \rightleftharpoons [\mathrm{LiCN{\bullet}LiX}] \qquad [10]$$

$$(\mathrm{LiCNLi})^{+} + \mathrm{X}^{-} \rightleftharpoons [\mathrm{LiCN{\bullet}LiX}] \qquad [11]$$

$$(\mathrm{XLiCN})^{-} + \mathrm{Li}^{+} \rightleftharpoons [\mathrm{LiCN{\bullet}LiX}] \qquad [12]$$

X = Cl, I

The IR spectra of the anionic solutions prepared with 2.4 equiv of *n*-BuLi after alkylation by 2.4 equiv of $PhCH_2Cl$ and CH_3I and before hydrolysis of the reaction products (Table 1, entries 18 and 20) are compared in Figure 3. In the ν(CN) spectral region around 2250 cm^{-1}, only the band at 2238 cm^{-1}, assigned to $PhCR_2CN$ **3**, is observed. With CH_3I, the bands of the lithium cyanide species are observed at 2132, 2177, and 2192 cm^{-1} and are more intense than with $PhCH_2Cl$.

The species corresponding to the bands observed in Figures 2 and 3 have been accurately identified through comparison with the calculated ν(CN) wavenumbers of the lithium cyanide LiCN and isocyanide CNLi species and of their complexes with Li^+, Cl^-, I^- ions, or LiCl or LiI molecules, which are listed in Table S1 in the Supporting Information. Thus, the most intense band of Figure 2 at 2127 cm^{-1} and calculated at 2127 cm^{-1} is related to the anionic lithium cyanide complex $(ClLiCN)^-$. The band observed at 2177 cm^{-1} and calculated at 2184 cm^{-1} is assigned to the cationic lithium cyanide complex $(LiCNLi)^+$, in good agreement with the experimental results of Huang et al.[25] They characterized by IR spectrometry cyanocuprates and described the IR spectrum of a dilute solution of LiCN in THF. This spectrum is dominated by two peaks at 2174 and 2178 cm^{-1} and also contains a relatively weak band at 2068 cm^{-1}. It is interpreted as "arising from a mixture of linear (or zig-zag Li-solvated) CNLi oligomers $Li(NC{-}Li)_n{-}NC$, with 2068 cm^{-1} end group isocyanides (LiNC) and several similar but not identical internal cyanides $(LiCNLi)^+$ in the 2174−2178 cm^{-1} region". In our spectra (Figures 2 and 3), the formation of $(LiCNLi)^+$ species correspond to monomeric ones as compared to those observed by Huang et al.,[25] which are more or less aggregated. The $(LiCNLi)^+$ entity was observed by X-ray crystallography of cyanocuprates $[R_2CuLi{\cdot}LiCN]$ and $[LiCN{\cdot}(pyridine)_2]$.[26−29] The shoulder observed at 2137 cm^{-1} (Figure 2) and calculated at 2156 cm^{-1} corresponds to lithium cyanide LiCN. This species is calculated to be less stable by ~3 kcal mol^{-1} than lithium isocyanide CNLi, in accordance with Snyder et al.[30] The lithium isocyanide CNLi calculated at 2073 cm^{-1} corresponds to the band observed at 2070 cm^{-1} in DMF[31,32] and at 2068 cm^{-1} in THF,[25] i.e., at a significantly lower frequency than lithium cyanide LiCN. Free CN^- is characterized by a calculated wavenumber of 2054 cm^{-1} in good agreement with the experimental value of 2054 cm^{-1} (Table S1, Supporting Information) obtained for $As(Ph)_4CN$ in DMF and NaCN in DMF in the presence of 18-crown-6.[31] The band observed at 2192 cm^{-1} (Figure 2) and calculated at 2193 cm^{-1} is attributed to the linear complex $[LiCN{\cdot}LiCl]$.

In Figure 3, the 2132, 2177, and 2192 cm^{-1} bands correspond to the anionic lithium cyanide $(ILiCN)^-$, $(LiCNLi)^+$, and the linear complex $[LiCN{\cdot}LiI]$, respectively.

The lithium cyanide species are formed in larger concentrations with CH_3I than with $PhCH_2Cl$. This is in line with the much lower yield in dialkylated **3** obtained with CH_3I (56%) (Table 1, entry 20) than with $PhCH_2Cl$ (70%) (Table 1, entry 18), indicating that the alkylation of dianions leads to a side reaction.

In order to get insight into the alkylation mechanism, we have examined by IR spectrometry the distribution of products obtained from a solution of dianions prepared from 1.0 equiv of $PhCH_2CN$ **1** and 2.4 equiv of *n*-BuLi in THF after alkylation by only 1 equiv of $PhCH_2Cl$ or CH_3I (Figures 4a and 4b, respectively). The decomposition of the IR spectra into their components is also shown in parts a and b of Figure 4. Without alkylating agent, the initial spectra of dianions solution is dominated by bands at 1890 and 1930 cm^{-1} attributed to the two main dilithio dianionic species (Figure 5 in ref 1) and corresponding respectively to calculated bridged (C-lithio) $(PhCLiCN)^-$ (Figure 3D in ref 1) and linear (N-lithio) $(PhCCNLi)^-$ dianions (Figure 3C in ref 1). With $PhCH_2Cl$ or CH_3I (Figure 4), these bands have almost disappeared and only traces of C,N-dilithio PhCLiCNLi are observed around 1915 cm^{-1}; the intense bands correspond to lithiated monoanions PhCRCNLi (R = H, CH_3, or $PhCH_2$) and their complexes with

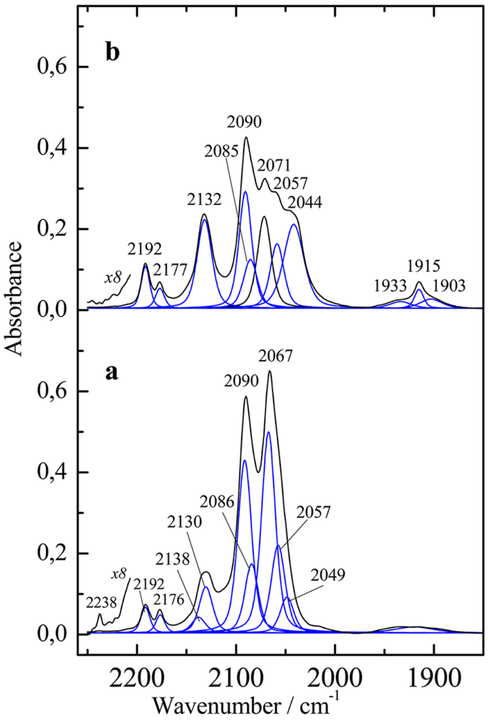
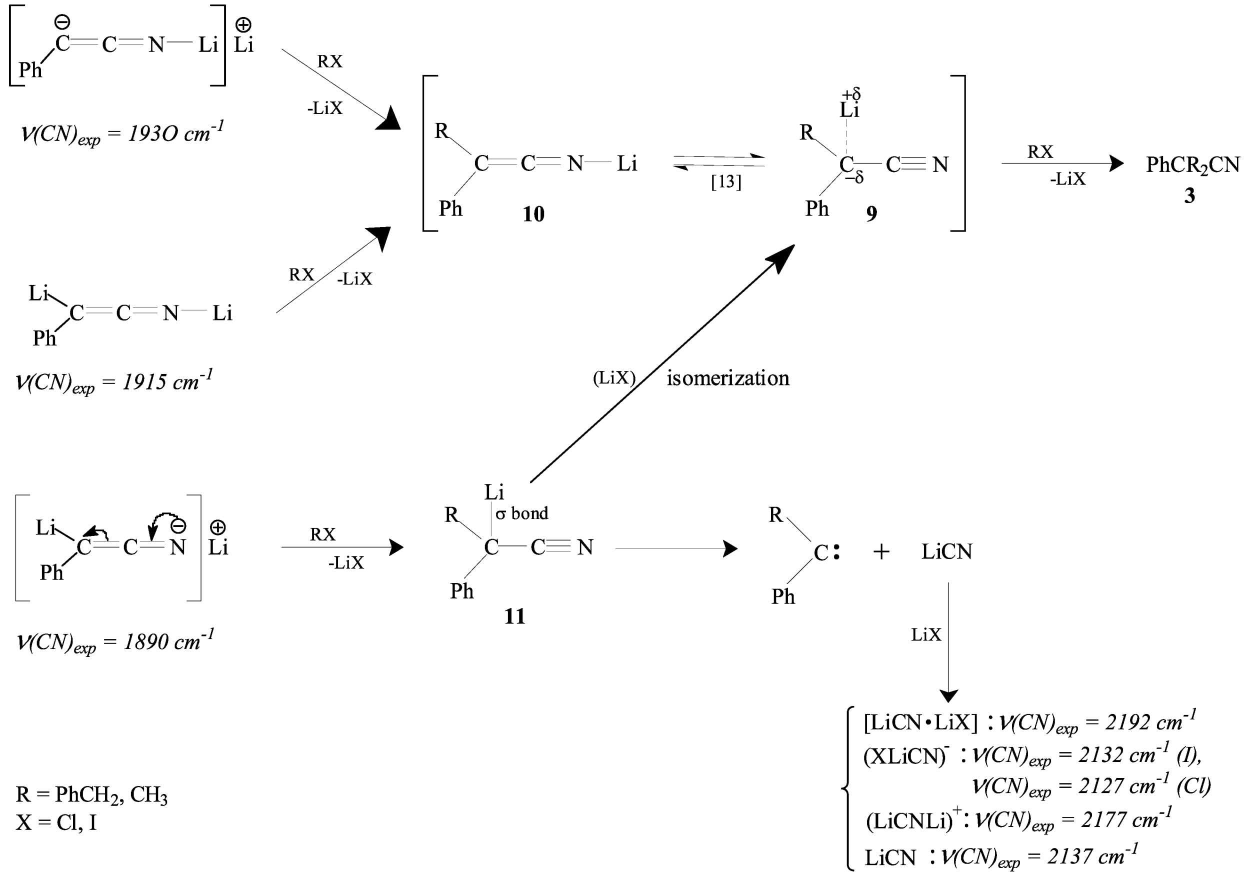


Figure 4. IR spectra (ν(CN) region) of an initial 0.25 M anionic species solution formed with $PhCH_2CN$ **1** (1.0 equiv) and *n*-BuLi (2.4 equiv) in THF−hexane 70/30 v/v after alkylation by only 1.0 equiv of (a) $PhCH_2Cl$ and (b) CH_3I before hydrolysis. Cell thickness: 0.0043 cm.

Scheme 5. Alkylation Mechanism of Dilithiated Dianions



LiCl or LiI in the 2040–2100 cm^{-1} region,[33] and to lithium cyanide species above 2120 cm^{-1} (Figures 2 and 3).

With $PhCH_2Cl$ (Figure 4a), a very small band is also observed at 2238 cm^{-1} indicating the formation of the dialkylated compound $PhC(PhCH_2)_2CN$ **3**. Other bands observed at 2192, 2176, 2138, and 2130 cm^{-1} are related to the lithium cyanide species. The bands at 2090 and 2057 cm^{-1} are due to the ν(CN) vibration of the N-lithio PhCHCNLi monoanion and to the asymmetric ν(CN) vibration of its dimer, respectively.[33] Two other bands at 2086 and 2049 cm^{-1} are also observed, indicating the formation of the N-lithio monoalkylated monoanion $PhC(PhCH_2)CNLi$ (2086 cm^{-1}) and of its dimer (2049 cm^{-1}).[33] The most intense band at 2067 cm^{-1} characterizes the formation of a heterodimer [PhCHCNLi·LiCl] between PhCHCNLi monoanion and LiCl and also that of another heterodimer $[PhC(PhCH_2)CNLi{\cdot}LiCl]$ between the alkylated mononanion and LiCl.[33] After hydrolysis of the solutions, we have determined by ^1H NMR the percentage of the different products formed: 36% of $PhCH_2CN$ **1**, 44% of $PhCH(PhCH_2)CN$ **2** and 20% of $PhC(PhCH_2)_2CN$ **3**.

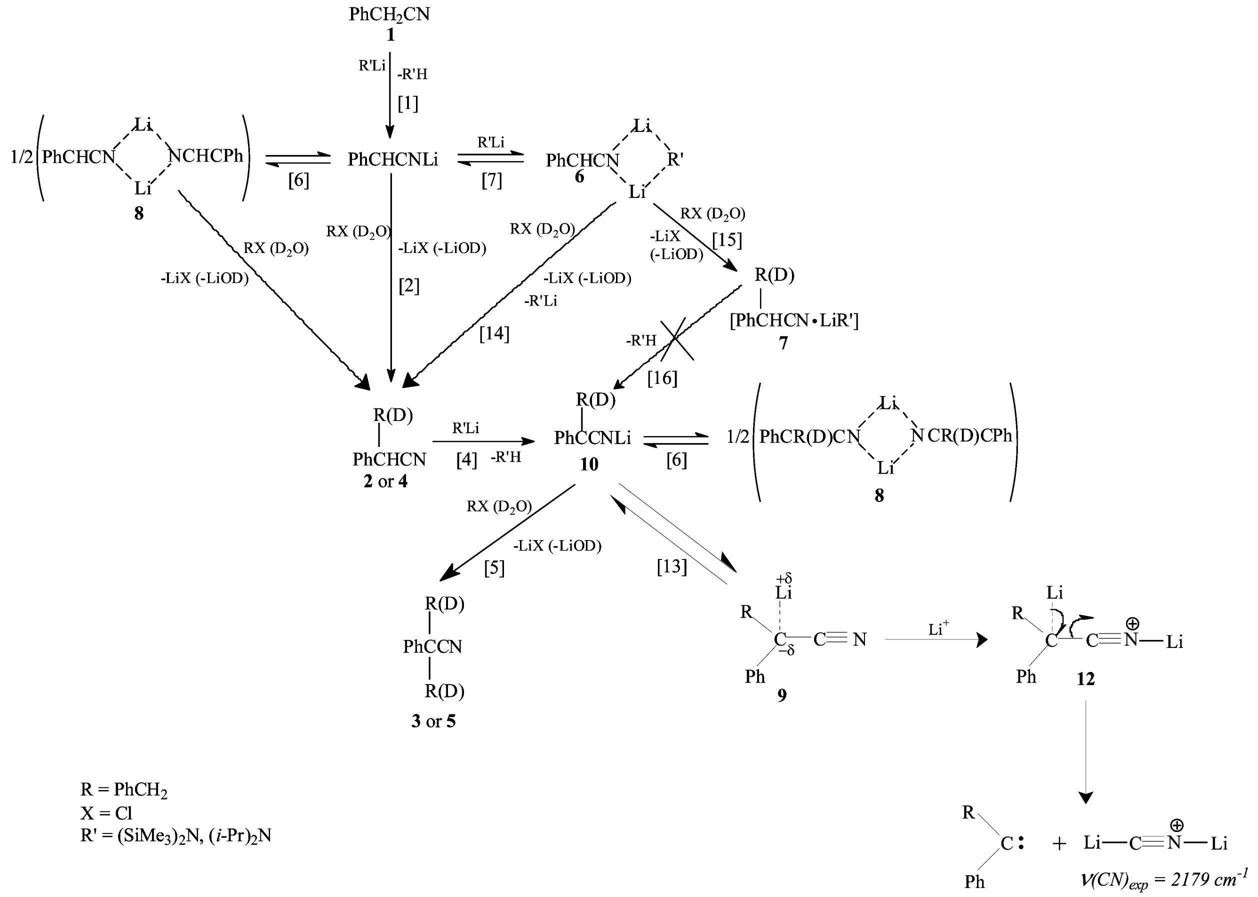
With CH_3I (Figure 4b), no band is observed at 2238 cm^{-1}, indicating that dialkylated product $PhC(CH_3)_2CN$ **3** is not formed. The lithium cyanide bands at 2192, 2177, and 2132 cm^{-1} are more intense than with $PhCH_2Cl$, as mentioned above (Figure 3). The bands of the N-lithio monoanion PhCHCNLi at 2090 cm^{-1} and of its dimer at 2057 cm^{-1} are observed with a smaller intensity than with $PhCH_2Cl$. The ν(CN) vibration of the N-lithio monoalkylated monoanion $PhC(CH_3)CNLi$ and the asymmetric ν(CN) of its dimer are respectively observed at 2085 and 2044 cm^{-1}.[33] The intense band at 2071 cm^{-1} is attributed to both heterodimers [PhCHCNLi·LiI] and $[PhC(CH_3)CNLi{\cdot}LiI]$ by analogy with the heterodimers formed with LiCl (Figure 4a).[33] ^1H NMR study of the solution after hydrolysis gives 32% of $PhCH_2CN$ **1** and 68% of $PhCH(CH_3)CN$ **2**.

The comparison of the IR and NMR results with $PhCH_2Cl$ and CH_3I (1 equiv) allows the following remarks: (i) a noticeable quantity of N-lithio monoanion PhCHCNLi is present in the medium with both alkylating agents. PhCHCNLi monoanion comes either from monoanionic species which were not transformed into dianions, or from dianionic species which, in the absence of sufficient amounts of $PhCH_2Cl$ or CH_3I, may abstract a proton from THF to form it.[1,34,35] (ii) formation of dialkylated compound $PhCR_2CN$ **3** takes place only with $PhCH_2Cl$ and not with CH_3I; (iii) only complexes of N-lithio monoanions with either LiCl or LiI are observed; (iv) with both alkylating agents RX, the elimination of lithium cyanide species in larger amounts with CH_3I than with $PhCH_2Cl$ is observed.

2. Alkylation and Deuteriation Mechanism of Monoanions and Dianions.

2.1. Alkylation Mechanism of Dianions (Scheme 5). From the above results, we propose the following mechanism for the alkylation by RX ($PhCH_2Cl$ or CH_3I) of dilithiated dianionic species in THF–hexane. The species calculated without solvent[1] at 1883 and 1914 cm^{-1} and, respectively, observed at 1890 and 1915 cm^{-1} contain a Li bridged atom between C_1 and C_2. If solvation is taken into account, theses species are probably C–Li ones, as already

Scheme 6. Alkylation and Deuteriation Mechanism of Monoanions



demonstrated by calculations of different THF solvates of PhCLiHCN monoanion.[24]

The N-lithio dianion $(PhCCNLi)^-Li^+$ and the (C,N)-dilithio one $PhCLiCNLi^1$ (which may be present in small amounts) give, through a first alkylation step, the N-lithio monoalkykated monoanion **10**, which is in equilibrium with the C-lithio monoalkylated monoanion **9** (equilibrium 13, Scheme 5). Then, through a second alkylation step, these monoanions lead to $PhCR_2CN$ **3**.

In the first alkylation step, the C-lithio dianion $(PhCLiCN)^-Li^+$ generates a carbenoid species, the C-lithio monoalkylated nitrile **11**.[36−39] Then this carbenoid species either eliminates carbene Ph−C̈−R and lithium cyanide LiCN, which recombines with X^-, Li^+, or LiX to give more stable species (Scheme 4) or isomerizes to the N-lithio monoalkylated monoanion **10**. The α LiCN elimination from the carbenoid **11** may be compared to the α LiX or LiOR′ elimination from analoguous carbenoid compounds like Li−CHR−X (X = Cl, F, I, Br) or Li−CHR−OR′, respectively.[36,37] The complexation of LiX with the thermolabile carbenoid **11** favors ionization of the carbon−lithium σ bond and formation of the more stable N-lithio monoalkylated monoanion **10**, probably through a cyclic six-membered transition state. This ionization is more efficient with LiCl than with LiI, so more **10**, and thus more dialkylated $PhCR_2CN$ **3** and less carbene Ph−C̈−R and LiCN species are obtained with $PhCH_2Cl$ than with CH_3I (yield of 70% for $PhC(PhCH_2)_2CN$ and of 56% for $PhC(CH_3)_2CN$). This is in line with Figure 4 which shows that the band at 2238 cm^{-1} characteristic of $PhCR_2CN$ is only observed with $PhCH_2Cl$. The amount of carbene and LiCN species increases with the dilithio dianion concentration from 2.2 to 2.7 equiv of *n*-BuLi (Figure 2). Both carbenes are unstable species that decompose rapidly in the medium.[40,41]

2.2. Alkylation and Deuteriation Mechanism of Monoanions. 2.2.1. With 2.2–2.4 equiv of LHMDS or LDA in THF (Scheme 6). Monomers, dimers and heterodimers **6** are in equilibrium in the solution (equilibria 6 and 7). Kim and Streitwieser[42] have determined the equilibrium constants and the kinetics of alkylation by benzyl bromide of [lithium enolates·LHMDS] heterodimers in THF by UV−vis spectroscopy. They have shown that heterodimers of lithium enolates are less reactive in alkylation reactions than monomers. In the same way, alkylation of monoanions of enolates proceeds through monomeric species, which are more reactive than dimeric ones.[43−45] Thus, with 2.4 equiv of LHMDS and 2.4 equiv of $PhCH_2Cl$, a sequential process involving mainly monomers of PhCHCNLi and PhCRCNLi monoanions as the more reactive species is proposed to account for the exclusive formation of $PhCR_2CN$ **3** (Table 1, entries 4 and 5). The first alkylation step (reaction 2) affords the monoalkylated product PhCHRCN **2**. This species is further deprotonated by the excess of base present in the medium to give the corresponding lithiated monoalkylated monoanions PhCRCNLi (reaction 4), as monomers in equilibrium with dimers (equilibrium 6).[33] In the second alkylation step (reaction 5), these monoanions lead to $PhCR_2CN$ **3**. $PhCH_2CN$ **1** eventually formed according to equilibrium 3 (Scheme 3) is also converted to $PhCR_2CN$ **3** by the excess of base through steps 1, 2, 4, and 5.

The formation of only $PhCR_2CN$ **3** shows that the heterodimers **6** (R′ = $(SiMe_3)_2N$), although present in small amounts,[1] dissociate easily either by displacement of equilibrium 7 toward monomers or by reaction with $PhCH_2Cl$ (reaction 14) to give the monoalkylated compound **2** and further **3**.

The same reasoning holds for deuteration.

With 2.4 equiv of LDA and 2.4 equiv of $PhCH_2Cl$, the heterodimer **6** is more stable and in greater amount than with LHMDS, which prevents the complete transformation of $PhCH_2CN$ **1** into $PhCR_2CN$ **3** (Table 1, entries 25 and 26) according to the sequential process depicted for LHMDS. Due to the formation of [PhCHCNLi·LiR′] **6**, the concentration of base available in the medium for deprotonation of PhCHRCN **2** into its anions (reaction 4) decreases. The heterodimers [PhCHCNLi·LiR′] **6**, as in the case of enolates,[42] dissociate into monomers (equilibrium 7) much more slowly than with LHMDS, react with $PhCH_2Cl$ much more slowly than monomers to give PhCHRCN **2** (reaction 14) or lead to a stable complex [PhCHRCN·LiR′] **7** between the monoalkylated PhCHRCN **2** and LDA (reaction 15), as proposed by Boche et al.[11]

As about 47% of PhCHRCN **2** (Table 1, entries 25 and 26) were not transformed into $PhCR_2CN$ **3**, the deprotonation within complex **7** (reaction 16) does not take place. If deprotonation could operate within heterodimer **6**, more dianions and hence $PhCR_2CN$ should be observed, which is not the case. Some $PhCH_2CN$ **1** and $PhCR_2CN$ **3** may also result from deprotonation of the monoalkylated compound PhCHRCN **2** by PhCHCNLi (equilibrium 3, Scheme 3), followed by reaction 5. The traces of dianions lead to the formation of the dialkylated species $PhCR_2CN$ **3** according to Scheme 5.

With 2.0 to 2.2 equiv of *n*-BuLi, some monoanions (monomers, dimers, and heterodimers **6**, R′ = *n*-Bu) are present in the solution (Table 1, entries 13−16), and less dialkylated **3** is observed for the same reasons as for LDA.

Smaller yields were generated in THF with 2.4 equiv of LHMDS or LDA (∼89%) (Table1, entries 5 and 26) than with 1.2 equiv of both bases (∼99%) (Table 1, entries 3 and 24). Only $(LiCNLi)^+$, characterized by a ν(CN) band observed in IR before hydrolysis of the reaction products at 2179 cm^{-1} (as in Figure 5), as will be commented below, and calculated at 2177 cm^{-1} (Table S1, Supporting Information) is obtained, indicating that carbene $Ph-\ddot{C}-CH_2Ph$ (∼ 10%) is simultaneously formed. Thus, in THF, another mechanism of formation of carbene is proposed ($R = PhCH_2$) from monoalkylated monoanion monomers particularly from the C-lithio monoalkylated anion **9** which is in equilibrium with the N-lithio monoalkylated anion **10** (equilibrium 13). In THF, the formation of carbene essentially depends on the concentration of **9**. Effectively, Carlier et al.[24] have shown by calculation of explicit THF solvates of anion **9** with R = H that equilibrium 13 is displaced toward **10** with a free energy of isomerization ΔG of −6.8 kcal mol^{-1}. This is probably also the case of anion **9** with $R = PhCH_2$, as ΔG would not differ greatly in this solvent.[33] In case of $PhCH_2Cl$, the first alkylation step of PhCHCNLi leads to the monoalkylated product PhCHRCN **2** and LiCl. This salt formed in situ may complex the C···Li bond of **9** to form either $C\cdots Li\cdots Cl^-$ or [C···Li·LiCl] complexes with a complete displacement of equilibrium 13 toward **10** as calculated already for CH_3Cl instead of $PhCH_2Cl$.[33] Only Li^+ complexation with the C≡N group of **9**[46] somewhat displaces equilibrium 13 toward the C-lithio monoalkylated monoanion **9**. The complexation of **9** with Li^+ leads to a dilithio complex **12**, which then favors carbene $Ph-\ddot{C}-R$ formation and $(LiCNLi)^+$ α-elimination.

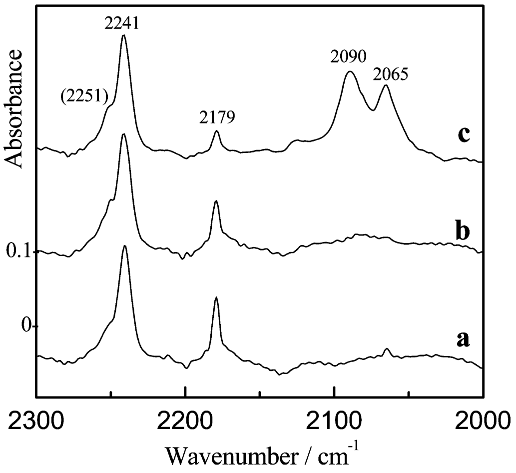


Figure 5. IR spectra (ν(CN) region) of an initial 0.25 M solution of $PhCH_2CN$ **1** (1.0 equiv) in THF [(a) and (b)] or in THF−hexane 82/18 v/v (c) with (a) LDA (1.2 equiv); (b) LHMDS (1.2 equiv); (c) *n*-BuLi (1.1 equiv) after alkylation by $PhCH_2Cl$ [(a) and (b) 1.2 equiv; (c) 1.1 equiv] and before hydrolysis. The wavenumber in parentheses corresponds to a shoulder. Cell thickness: 0.055 cm.

2.2.2. With 1.0−1.2 equiv of LHMDS, LDA, or n-BuLi in THF.

As mentioned above, only monoanions are present in the medium as monomers and dimers (equilibrium 6). Alkylation of monoanions (reaction 2, Scheme 3) proceeds probably through monomeric species which are the more reactive ones, as in the case of alkylation of enolates.[43−45] With strictly 1.0 equiv of base, the alkylation reaction should lead to the exclusive formation of PhCHRCN **2** ($R = PhCH_2$ or CH_3) (reaction 2, Scheme 3). In fact, $PhCH_2CN$ **1** and $PhCR_2CN$ **3** ($R = PhCH_2$ or CH_3) are present in relatively important equal amounts (Table 1, entries 1, 6, and 7), indicating that the competitive reaction 3 followed by reaction 5 (Scheme 3) takes place.

It is interesting to notice that traces of $(LiCNLi)^+$ are also formed during the alkylation of monoanions. Figure 5 shows the IR spectra of a solution of $PhCH_2CN$ **1** (1.0 equiv) with 1.2 equiv of LDA or LHMDS and 1.2 equiv of $PhCH_2Cl$ in THF (Figure 5a and 5b) or with 1.1 equiv of *n*-BuLi and 1.1 equiv of $PhCH_2Cl$ in THF−hexane (82/18 v/v) (Figure 5c) before hydrolysis of the reaction products. With the three bases, the ν(CN) bands characterizing $PhCH_2CN$ **1**, PhCHRCN **2**, and $PhCR_2CN$ **3** are observed through decomposition of the spectra into components at 2251, 2241, and 2238 cm^{-1}, respectively. A small band at 2179 cm^{-1} is due to only traces of $(LiCNLi)^+$, since the yields determined by IR spectrometry before treatment are ∼100% (Table 1, entries 3, 8, and 24). This indicates that the absorption cross-sections of lithium cyanide species are much larger than those of the neutral species $PhCH_2CN$ **1**, $PhCH(PhCH_2)CN$ **2**, and $PhC(PhCH_2)_2CN$ **3**. These traces of $(LiCNLi)^+$ are formed by α-elimination from the small amount of C-lithio monoalkylated monoanion PhCLiRCN **9** absorbing at ∼2067 cm^{-1}.[33] Compound **9** may be formed either by the small excess of base or by reaction 3. With 1.1 of equiv of *n*-BuLi and 1.1 equiv of $PhCH_2Cl$ (Figure 5c), i.e., with a little less of base and alkylating agent than with LDA and LHMDS (Figures 5a and 5b), two bands at 2090 and 2065 cm^{-1} assigned respectively to the N-lithio monoanion PhCHCNLi and to the heterodimer

$[PhCHCNLi{\cdot}LiCl]$[33] are observed, showing that the alkylation process in THF−hexane (82/18 v/v) is slower than in THF (LDA or LHMDS) due to the formation of this heterodimer which alkylates more slowly than monomers and dimers of PhCHCNLi.[47,48]

■ CONCLUSION

Alkylation in THF by $PhCH_2Cl$ and CH_3I or deuteriation by DCl (4 N in D_2O) in THF or THF−toluene of PhCHCNLi monoanions (monomers and dimers) formed with 1.0−1.2 equiv of base (LHMDS, LDA, or *n*-BuLi) leads to mixtures of $PhCH_2CN$ **1**, PhCHRCN **2** (R = $PhCH_2$, CH_3), or PhCHDCN **4** and $PhCR_2CN$ **3** (R = $PhCH_2$, CH_3) or $PhCD_2CN$ **5**. Deuteriation is perturbed by side reactions in acidic media due to the presence of the amine formed with LHMDS or LDA in THF. The importance of these side reactions decreases in THF−toluene.

With 2.4 equiv of LHMDS in THF, only $PhC(PhCH_2)_2CN$ **3** or almost only $PhCD_2CN$ **5** are obtained through a sequential process (Scheme 6) involving essentially PhCRCNLi monomers (R = H, $PhCH_2$) or PhCDCNLi. With 2.2−2.4 equiv of LDA in THF, the sequential process reaches a lower percentage of dialkylated **3** or dideuteriated **5** products. The presence of the heterodimer **6** which affords through alkylation or deuteriation a stable complex **7** is mainly responsible for this lower percentage of dialkylation or dideuteriation (R = $PhCH_2$: 65%; D: 57%). With both bases LHMDS and LDA, about 10% of carbene $Ph{-}\ddot{C}{-}R$ (R = $PhCH_2$) and $(LiCNLi)^+$ ($\nu(CN)_{exp}$ = 2179 cm^{-1}, $\nu(CN)_{calc}$ = 2177 cm^{-1}) are formed from the intermediate C-lithio monoalkylated monoanion **9**. Displacement of equilibrium 13 (Scheme 6) toward **9** is only possible by complexation of Li^+ with the CN group.

Alkylation by $PhCH_2Cl$ or CH_3I of dilithio dianions prepared with more than 2.2 equiv of *n*-BuLi in THF−hexane (Scheme 5) gives only $PhCR_2CN$ **3** (R = $PhCH_2$ or CH_3) but with a lower reaction yield due to formation of carbene $Ph{-}\ddot{C}{-}R$ (R = $PhCH_2$: 70%; CH_3: 56%) and LiCN species. Dialkylation of dilithio dianions depends on their structure. (C,N)-dilithio dianion PhCLiCNLi ($\nu(CN)_{exp}$ = 1915 cm^{-1}) and N-lithio dianion $(PhCCNLi)^-$ Li^+ ($\nu(CN)_{exp}$ = 1930 cm^{-1}) afford $PhCR_2CN$ (R = $PhCH_2$ or CH_3) from the intermediate N-lithio monoalkylated monoanion PhCRCNLi **10**. C-Lithio dianion ($\nu(CN)_{exp}$ = 1890 cm^{-1}) $(PhCLiCN)^-Li^+$ alkylates first to C-lithio monoalkylated nitrile **11**, which either gives carbene $Ph{-}\ddot{C}{-}R$ and LiCN and complexed LiCN species ($(XLiCN)^-$, $(LiCNLi)^+$, and $[LiCN{\cdot}LiX]$, X = Cl or I), which are more stable than LiCN itself, or leads to the N-lithio monoalkylated anion **10** by isomerization in the presence of LiX. The α LiCN elimination is more important with CH_3I (44%) than with $PhCH_2Cl$ (30%) and increases with the dilithiated dianions concentration (from 2.2 to 2.7 equiv of *n*-BuLi).

The lithium cyanide LiCN or isocyanide CNLi species and their complexes with LiCl, LiI, Cl^-, I^-, and Li^+ were characterized by IR spectrometry. Their $\nu(CN)$ frequencies were validated by quantum chemical calculations at B3LYP/6-31+G* level. The association energies of heterodimers **6** $[PhCHCNLi{\cdot}LiR']$ (R′ = $(i\text{-}Pr)_2N$, $(SiMe_3)_2N$) were also computed at the same level.

All these results show the ambiphilic behavior of the C-lithio monoalkylated compound PhCLiRCN (R = $PhCH_2$ or CH_3), as a carbenoid (**11**) when obtained from the C-lithio dianion in THF−hexane (*n*-BuLi, 2.4 equiv) or a carbanion (**9**) in THF when prepared from $PhCH_2CN$ and $PhCH_2Cl$ (LHMDS or LDA, 2.4 equiv) and the importance of LiX (X = Cl or I), formed in situ in the first alkylation step, in this carbene formation.

■ CALCULATION METHODS

All quantum chemical calculations were performed with the DFT approach at the B3LYP level, as in our previous papers.[35,49] For the compounds that do not contain iodine atom, the 6-31+G* basis set was used. For the systems including I, the LanL2DZ basis set was employed. Indeed, for very large nuclei, the internal electrons are treated via effective core potentials (ECPs). This procedure includes some relativistic effects, important in these atoms.[50] In the LanL2DZ basis set, the first row atoms (H, Li, C, N) are treated with the D95 basis,[51] and the atoms from Na to Bi (including Cl and I) are treated with the Los Alamos ECP plus a double-ξ (DZ) basis.[52−54] For the compounds containing a Cl atom, the calculations were performed with both basis sets for comparison. Complete geometry optimizations without any constraint were carried out employing the analytical gradient procedure contained in the Gaussian 09 program.[55] The optimization is complete when the default convergence criteria used by the program are met.

The force constants in Cartesian coordinates were computed at fully optimized geometries by analytical differentiation techniques implemented within the Gaussian 09 program. They were used to determine the harmonic vibrational wavenumbers. The absence of imaginary wavenumber (negative value) for any optimized structure ensures that the stationary points found during the optimization procedure correspond to minima on the potential energy surface.

For the heterodimers $[PhCHCNLi{\cdot}LiR']$ **6** (R′ = $(i\text{-}Pr)_2N$, $(SiMe_3)_2N$), the association energy was computed as the difference between the energy of the optimized heterodimer **6** and the sum of the energies of the optimized isolated PhCHCNLi and LiR′ molecules.

B3LYP/6-31+G* vibrational wavenumbers being usually slightly overestimated relative to the experimental values, they were corrected by applying an empirical scaling factor adjusted to fit the observed wavenumbers.[35,49] A scaling factor of ∼0.964 obtained for lithium isocyanide CNLi allowed to scale the computed wavenumbers of all free and associated cyanide and isocyanide species (except of those involving iodine). The wavenumbers calculated with the LanL2DZ basis set are compared without any scaling procedure to experimental values.

Solvation effects were not taken into account in the calculations. Indeed, for strongly delocalized lithiated anions, a small influence of the solvent on the internal structural parameters of the anion is expected, as has been observed for the 4-alkylpyridines.[56] The solvent only appreciably affects the anion−cation interactions.

■ EXPERIMENTAL SECTION

1. Preparation of Anionic Solutions.[57,58] THF was distilled under argon atmosphere from sodium/benzophenone immediately before use. Toluene was distilled over CaH_2. $PhCH_2CN$ **1** and $PhCH_2Cl$ were distilled prior to use. CH_3I was dried for 24 h over molecular sieves 4 Å. $PhCH(PhCH_2)CN$, $PhC(PhCH_2)_2CN$, and $PhC(CH_3)_2CN$ were purified by liquid chromatography over silica gel. *n*-BuLi (1.6 M in hexane) was a fresh commercial solution checked against salt content.[59]

The preparation of the solutions was performed under argon at 20 °C. To 10^{-3} mol of $PhCH_2CN$ **1** dissolved in the required amount of THF was added 1.0−2.7 equiv of *n*-BuLi so that the final concentration of the solution was 0.25 M.

The LHMDS and LDA solutions in THF were prepared from the corresponding amines, freshly distilled over CaH_2, and *n*-BuLi (1.6 M in hexane). The hexane and THF were evaporated under argon until a white powder was obtained. To 1.0−2.4 equiv of dry LHMDS or LDA dissolved in 4 mL of THF or THF−toluene solvent mixture (30/70 v/v) was added 10^{-3} mol of $PhCH_2CN$ **1**.

2. Alkylation Reactions. After 30 min stirring the anionic solutions when 1.0−1.2 equiv of base was used or 45 min when more than 2.0 equiv of base was employed, 1.2 or 2.4 equiv, respectively, of

PCH_2Cl or CH_3I dissolved in 1 mL of THF was added dropwise. The solution was stirred for 2 h 30 min and hydrolyzed by 1.2−2.0 mL of HCl 10%. After 30 min stirring, the solution was extracted twice with ether and washed to neutrality with a NaCl saturated solution. The organic layers were evaporated, and the residue was examined by NMR in $CDCl_3$ solution.

3. Deuteriation. The anionic solutions were stirred during 30 min and were then deuteriated by dropwise addition of 1−2 mL of a DCl solution (4 N in D_2O) diluted by the same amount of THF. After 30 min of stirring at 20 °C, the solution was extracted twice by 20 mL of ether. The organic layer was dried over anhydrous $MgSO_4$. The solvents were removed under reduced pressure to afford oil with about 90% yield, which was examined by NMR. We have verified that in this acidic medium no exchange between the benzylic protons and deuterium atoms in the absence of base occurs, by stirring $PhCH_2CN$ **1** (0.25 M) in THF during 2 h in the presence of an aliquot DCl (4 N) in D_2O solution at 20 °C. The starting material $PhCH_2CN$ **1** was recovered unchanged.

4. NMR Spectra. The ^1H and ^{13}C NMR spectra of the products were recorded on a spectrometer operating at 200 or 250 and 62.9 MHz, respectively.

5. IR Spectra. IR spectra were measured on a Bruker 1720 spectrometer. The spectra resolution was 4 cm^{-1}. Cells with CaF_2 windows were used, and their thickness was 0.0043 cm for anion solutions and 0.021 or 0.055 cm for solutions after alkylation and before hydrolysis of the reaction products. The filling of the cells was performed under argon in glove bag. The solvent bands were subtracted from the spectra.

After using Origin software, selected parts of the IR spectra were fitted using Gaussian and Lorentzian functions in order to characterize the IR bands of the different species present in the solutions (anions and products $PhCH_2CN$ **1**, PhCHRCN **2**, and $PhCR_2CN$ **3**). The determination of the integrated molar absorption coefficients of **1**, **2**, and **3** by quantitative analysis allowed us to estimate the concentration of these products formed in the solutions after alkylation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Calculated ν(CN) wavenumbers of the lithium cyanide LiCN and isocyanide CNLi species and of their complexes with Li^+, Cl^-, I^- ions, LiCl, or LiI molecules (Table S1). Cartesian coordinates and energetic characteristics of all these species (Tables S2−S21). Cartesian coordinates and energetic characteristics of PhCHCNLi, LHMDS, LDA, and of the heterodimers [PhCHCNLi·LHMDS] and [PhCHCNLi·LDA]-(Tables S22−S26). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*To whom correspondence should be addressed. Fax: 33 (1) 44 27 41 17. E-mail: martine.ventura@lct.jussieu.fr.

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) Corset, J.; Castellà-Ventura, M.; Froment, F.; Strzalko, T.; Wartski, L. *J. Org. Chem.* **2003**, *68*, 3902−3911.
(2) Kaiser, E. M.; Solter, L. E.; Schwarz, R. A.; Beard, R. D.; Hauser, C. R. *J. Am. Chem. Soc.* **1971**, *93*, 4237−4242.
(3) Arseniyadis, R.; Kyler, K. S.; Watt, D. S. *Organic Reaction*; John Wiley and Sons: New York, 1984; Vol. *31*.
(4) Marek, I.; Normant, J. F. *Chem. Rev.* **1996**, *96*, 3241−3268.
(5) Langer, P.; Wuckelt, J.; Döring, M.; Görls, H. *J. Org. Chem.* **2000**, *65*, 3603−3611.
(6) Langer, P.; Freifeld, I. *Org. Lett.* **2001**, *3*, 3903−3905.
(7) Langer, P.; Freiberg, W. *Chem. Rev.* **2004**, *104*, 4125−4150.
(8) Albrecht, U.; Freifeld, I.; Reinke, H.; Langer, P. *Tetrahedron* **2006**, *62*, 5775−5786.
(9) Crowley, P. J.; Leach, M. R.; Meth-Cohn, O.; Wakefield, B. J. *Tetrahedron Lett.* **1986**, *27*, 2909−2912.
(10) Zarges, W.; Marsch, M.; Harms, K.; Boche, G. *Angew. Chem., Int. Ed.* **1989**, *28*, 1392−1394.
(11) Boche, G.; Langlotz, I.; Marsch, M.; Harms, K.; Frenking, G. *Angew. Chem., Int. Ed.* **1993**, *32*, 1171−1173.
(12) Boche, G.; Marsch, M.; Harms, K. *Angew. Chem., Int. Ed.* **1986**, *25*, 373−374.
(13) Koch, R.; Wiedel, B.; Anders, E. *J. Org. Chem.* **1996**, *61*, 2523−2529.
(14) Selva, M.; Marques, C. A.; Tundo, P. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1889−1893.
(15) Ridvan, L.; Závada, J. *Tetrahedron* **1997**, *53*, 14793−14806.
(16) Taber, D. F.; Kong, S. *J. Org. Chem.* **1997**, *62*, 8575−8576.
(17) Eames, J.; Weerasooriya, N.; Coumbarides, G. S. *Eur. J. Org. Chem.* **2002**, 181−187.
(18) Sauer, R. O. *J. Am. Chem. Soc.* **1944**, *66*, 1707−1710.
(19) Sauer, R. O.; Hasek, R. H. *J. Am. Chem. Soc.* **1946**, *68*, 241−244.
(20) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390−5398.
(21) Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1373−1393.
(22) Seebach, D. *Angew. Chem., Int. Ed.* **1988**, *27*, 1624−1654.
(23) Vedejs, E.; Lee, N. *J. Am. Chem. Soc.* **1995**, *117*, 891−900.
(24) Carlier, P. R.; Madura, J. D. *J. Org. Chem.* **2002**, *67*, 3832−3840.
(25) Huang, H.; Alvarez, K.; Lui, Q.; Barnhart, T. M.; Snyder, J. P.; Penner-Hahn, J. E. *J. Am. Chem. Soc.* **1996**, *118*, 8808−8816.
(26) Boche, G.; Bosold, F.; Marsch, M.; Harms, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 1684−1686.
(27) Krause, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 79−81.
(28) Kronenburg, C. M. P.; Jastrzebski, J. T. B. H.; Spek, A. L.; van Koten, G. *J. Am. Chem. Soc.* **1998**, *120*, 9688−9689.
(29) Purdy, A. P.; Houser, E.; George, C. F. *Polyhedron* **1997**, *16*, 3671−3679.
(30) Snyder, J. P.; Spangler, D. P.; Behling, J. R.; Rossiter, B. E. *J. Org. Chem.* **1994**, *59*, 2665−2667.
(31) Loupy, A.; Corset, J. *C. R. Hebd. Seances Acad. Sci. Ser. C* **1974**, *279*, 713−716.
(32) Loupy, A.; Corset, J. *J. Solution Chem.* **1976**, *5*, 817−831.
(33) Corset, J.; Castellà-Ventura, M.; Froment, F.; Strzalko, T.; Wartski, L. *Spectrochim. Acta, Part A* **2007**, *68*, 1340−1346.
(34) Clayden, J.; Yasin, S. A. *New J. Chem.* **2002**, *26*, 191−192.
(35) Corset, J.; Castellà-Ventura, M.; Froment, F.; Strzalko, T.; Wartski, L. *J. Raman Spectrosc.* **2002**, *33*, 652−668.
(36) Boche, G.; Lohrenz, J. C. W. *Chem. Rev.* **2001**, *101*, 697−756.
(37) Hermann, H.; Lohrenz, J. C. W.; Kühn, A.; Boche, G. *Tetrahedron* **2000**, *56*, 4109−4115.
(38) Braun, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 430−451.
(39) Capriati, V.; Florio, S. *Chem.—Eur. J.* **2010**, *16*, 4152−4162.
(40) Zhang, Y.; Burdzinski, G.; Kubicki, J.; Platz, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 16134−16135.
(41) Zhang, Y.; Kubicki, J.; Platz, M. S. *Org. Lett.* **2010**, *12*, 3182−3184.
(42) Kim, Y. J.; Streitwieser, A. *Org. Lett.* **2002**, *4*, 573−575.
(43) Abu-Hasanayn, F.; Stratakis, M.; Streitwieser, A. *J. Org. Chem.* **1995**, *60*, 4688−4689.
(44) Streitwieser, A.; Kim, Y. J.; Wang, D. Z. R. *Org. Lett.* **2001**, *3*, 2599−2601.
(45) Streitwieser, A. *J. Org. Chem.* **2009**, *74*, 4433−4446.
(46) Loupy, A.; Tchoubar, B. *Salt Effects in Organic and Organometallic Chemistry*; VCH: Weinheim, 1992.
(47) Abu-Hasanayn, F.; Streitwieser, A. *J. Am. Chem. Soc.* **1996**, *118*, 8136−8137.
(48) Pratt, L. M.; Streitwieser, A. *J. Org. Chem.* **2003**, *68*, 2830−2838.
(49) Corset, J.; Castellà-Ventura, M.; Froment, F.; Strzalko, T.; Wartski, L. *Spectrochim. Acta, Part A* **2002**, *58*, 1971−1986.

(50) Foresman, J. B.; Frisch, A. *Exploring Chemistry with Electronic Structure Methods*, 2nd ed.; Gaussian, Inc.: Pittsburgh, 1996.

(51) Dunning, T. H., Jr.; Hay, P. J. *Modern Theoretical Chemistry*; Schaefer, H. F., Ed.; Plenum: New York, 1976, Vol. *3*.

(52) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270−283.

(53) Wadt, W. R.; Hay, P. J. *J. Chem. Phys.* **1985**, *82*, 284−298.

(54) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299−310.

(55) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, Revision A.02; Gaussian, Inc.: Wallingford, CT, 2009.

(56) Anders, E.; Opitz, A.; van Eikema Hommes, N. J. R.; Hampel, F. *J. Org. Chem.* **1993**, *58*, 4424−4430.

(57) Strzalko, T.; Seyden-Penne, J.; Wartski, L.; Corset, J.; Castellà-Ventura, M.; Froment, F. *J. Org. Chem.* **1998**, *63*, 3287−3294.

(58) Croisat, D.; Seyden-Penne, J.; Strzalko, T.; Wartski, L.; Corset, J.; Froment, F. *J. Org. Chem.* **1992**, *57*, 6435−6447.

(59) Corset, J.; Froment, F.; Lautié, M. F.; Ratovelomanana, N.; Seyden-Penne, J.; Strzalko, T.; Roux-Schmitt, M. C. *J. Am. Chem. Soc.* **1993**, *115*, 1684−1694.