doi:10.2533/chimia.2016.48 Chimia 70 (2016) 48–52

Long-range Effect of Bromine in the Deprotonative Metalation of Aromatic Compounds

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Dedicated to Professor Manfred Schlosser

Abstract: Deprotonative metalation has been largely used to functionalize aromatic compounds. The efficiency of such reactions, as well as their regioselectivity, depends on the substituents connected to the rings. In contrast with other groups such as fluorine and methoxy, bromine exhibits a long-range acidifying effect. Here we try to depict this particular effect of bromine through different examples in which deprotometalation takes place at a remote position.

Keywords: Acidity · Aromatic compounds · Deprotonative metalation · Long-range effects · Substituent effects

Among the existing methods to functionalize aromatic compounds including heterocycles, deprotonative lithiation followed by reaction with electrophiles has been widely used, in particular because of its high regioselectivity.[1] The reactivity of the aromatic substrates involved in this reaction, as well as the regioselectivity of the reaction, largely depends on the substituents connected to the ring.

Among the different *ortho*-directing groups that can be employed in aromatic deprotonative metalation, bromine is far from the best. Indeed, if its ability to acidify the adjacent hydrogens is good, both from a kinetic and a thermodynamic point of view,[2] the *ortho*-bromoarylmetals formed are prone to benzyne formation. Such a limitation can be overcome either by using lithium-metal bases such as TMP-zincate (^{t}Bu$_2$Zn(TMP)Li, TMP = 2,2,6,6-tetramethylpiperidino),[3] or using *in situ* electrophilic trapping,[4] or even in the presence of another substituent (*e.g.* CF_3[5]), capable of stabilizing the arylmetal compound. Nevertheless, if bromine is not the best *ortho*-directing group, it is useful as a *meta*- or even *para*-directing group. Herein, we showcase selected deprotometalation reactions in which bromine exhibits such a long-range acidifying effect.[6]

To explain how substituent effects (*e.g.* acidifying effect) propagate on benzene from the *ortho* to the *meta* and to the *para* position, it has been suggested that two kinds of electronic perturbation operate simultaneously: (i) the inductive effect due to the electronegativity of the hetero-element connected to the ring (such a σ-polarization diminishes with the distance from the electron-withdrawing substituent) and (ii) the modification of the π-electron cloud (π-polarization) either through aspiration (in the case of a tetravalent and electron-deficient element connected to the ring such as CF_3) or through repulsion (in the case of a lone-pair containing element connected to the ring such as F and OMe).[7]

On aromatic compounds, fluorine enhances the acidity of neighboring hydrogens by the inductive effect (through the σ-bond) but not by aspiration of the π-electron cloud. In contrast, due to increased bond lengths, the heavier halogens can modify the π-electron density of the ring. Indeed, its flow is possible toward the highly polarizable halogen (σ/π coupling). This makes chlorine and bromine good long-range electron attractors.[8]

Also due to their longer bond, the heavier halogens have a weaker donor capacity than fluorine when present as arene substituents (poorer π-n overlap). Thus, in contrast to fluorine and other groups (*e.g.* alkoxy), chlorine and, above all, bromine do not exhibit donor/acceptor dualism.[8] This feature makes bromine at the origin of a specific behavior when used as a substituent in deprotonative metalation of aromatic compounds. It is worth noting that only lithium (or lithium-metal) dialkylamides can be used to effect such reactions, as organometals (and, in particular, polar alkylmetals) can cause bromine/metal exchange.

Long-range Effect of Bromine in the Deprotometalation of Benzenes

The long-range acidifying effect of bromine can be easily evidenced from two experiments. If an equimolar mixture of fluorobenzene (**1a**) and 1,3-dibromobenzene (**2a**) is treated with 1 equiv. of LiTMP in tetrahydrofuran (THF) in a competitive reaction, the dibromide **2a** is the only substrate converted, as shown by trapping with carbon dioxide.[9] This result shows that two bromo groups are stronger *ortho*-directing than one fluoro. However, when submitted to the same conditions, 2,4-dibromo-1-fluorobenzene (**3a**) reacts to afford 3,5-dibromo-2-fluorobenzoic acid **3b** in 82% yield (Scheme 1).[10]

1-Bromo-2-fluorobenzene (**4a**) and 1-bromo-4-fluorobenzene (**5a**) can be functionalized next to fluorine upon consecutive treatment with LiDA (DA = diisopropylamino) in THF at –75 °C and dry

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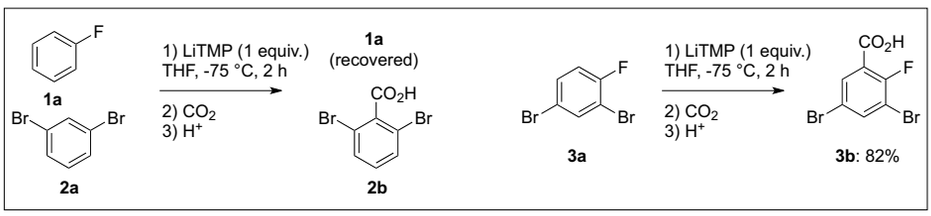
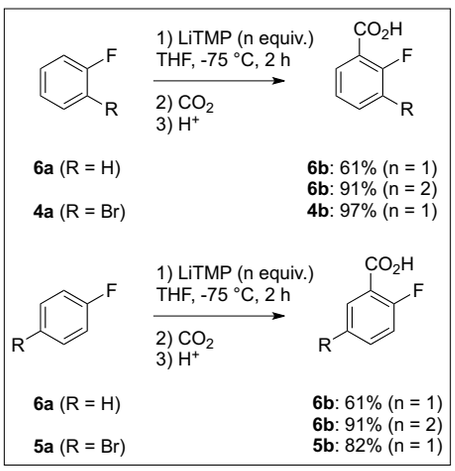


Scheme 1. Reactions demonstrating the long-range acidifying effect of bromine.



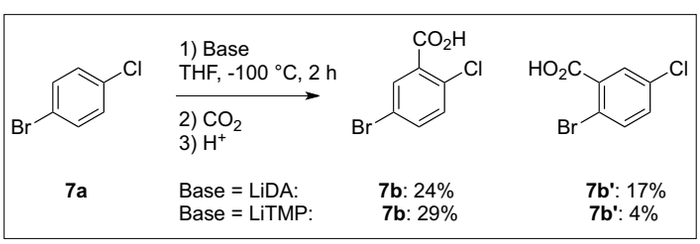
Scheme 2. Deprotonative lithiation of 1-bromo-2-fluorobenzene and 1-bromo-4-fluorobenzene compared with that of fluorobenzene.

ice. In the former reaction, 3-bromo-2-fluorobenzoic acid (**4b**) is the only product, isolated in 73% yield.[11] In the latter reaction, 5-bromo-2-fluorobenzoic acid (**5b**, formed in 72% yield) is accompanied by traces of 2-bromo-5-fluorobenzoic acid.[12] Using LiTMP leads to improved yields, 97% and 82% respectively, and regioselectivity.[10] To identify a possible effect of bromine in such reactions, fluorobenzene (**6a**) was similarly reacted with LiTMP (1 equiv.) in THF at –75 °C for 2 hours before quenching. Under these conditions, 2-fluorobenzoic acid (**6b**) was obtained in a 61% yield, lower than those obtained from the *meta*-bromo substituted derivatives; a high yield (91%) could be reached, but by employing 2 equiv. of base (Scheme 2).[9]

When reacted with a lithium amide at low temperatures in THF, 1-bromo-4-chlorobenzene (**7a**) gives a mixture of 5-bromo-2-chlorophenyllithium and 2-bromo-5-chlorophenyllithium, as demonstrated by subsequent trapping with carbon dioxide. After deprotonative metalation for 2 hours at –100 °C, 5-bromo-2-chlorobenzoic acid (**7b**) and 2-bromo-5-chlorobenzoic acid (**7b'**) are respectively formed in 24 and 17% yield using LiDA, and 29 and 4% yield using LiTMP (Scheme 3).[13] Chlorobenzene and bromobenzene cannot afford the corresponding carboxylic acids in similar yields. Indeed, only traces of 2-chlorobenzoic acid are obtained by using LiTMP in THF for 2 hours at –100 °C before subsequent carboxylation[9,14] whereas bromobenzene fails to yield 2-bromobenzoic acid due to degradation whatever the conditions used.[9,15] This result shows that chlorine and bromine, even when located at a position *meta* to the deprotonation site, exhibit a stabilizing effect. In addition, this regioselectivity is not due to a higher *ortho*-directing power of chlorine over bromine (these effects are similar), but rather arises from a slightly higher *meta*-acidification of bromine over chlorine. Such a claim can be deduced from a recent article on the relative thermodynamic stabilities between different aryllithiums (Table 1).[2,16]

Owing to this long-range acidifying effect, 1,4-dibromobenzene (**8a**) (but not bromobenzene) can be deprotolithiated in THF using LiTMP at –75 °C[17] or –80 °C for 40 min, as evidenced by subsequent reaction with various electrophiles. 2,5-Dibromophenyllithium can be stored at this temperature for at least 1 to 2 hours before degradation (darkening), the latter occurring at temperatures above –75 to –70 °C.[18] After interception with carbon dioxide and acidification, the functionalized derivative **8b** is isolated in 84% yield; using the slightly weaker base LiDA instead of LiTMP affords the same benzoic acid in 68% yield. Iodine proves to exhibit a similar long-range acidifying/stabilizing effect, as shown in Scheme 4.[18] Provided that the reaction temperature with LiDA is maintained at –85 °C, extension of the reaction to 2,5-dibromoanisole is possible, giving 2,5-dibromo-3-methoxybenzaldehyde in a moderate 47% yield after DMF quench and hydrolysis.[19]

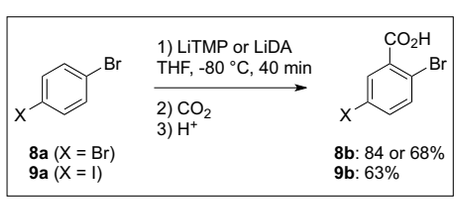
Similarly, 2- and 4-bromobenzonitrile (**10a** and **11a**) benefit from the long-range *meta*-acidifying effect of bromine. In contrast with bare benzonitrile, both substrates can be converted to stable lithio derivatives at the position *ortho* to nitrile when treated with LiTMP in THF at –80 °C. Such a result can be evidenced by subsequent derivatization to the corresponding boronic acids **10b** and **11b** by trapping with trimethylborate followed by hydrolysis (Scheme 5).[18]



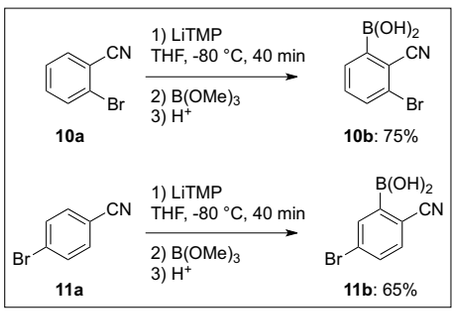
Scheme 3. Deprotonative lithiation of 1-bromo-4-chlorobenzene.

Table 1. Substituent effects on the equilibrium positions between different aryllithiums (prepared using LiTMP, THF, –75 °C): thermodynamic stabilities relative to the unsubstituted lithiated substrates; ΔG° (kcal mol^{-1}) = 0.9067 x (lg K_X – lg K_H).

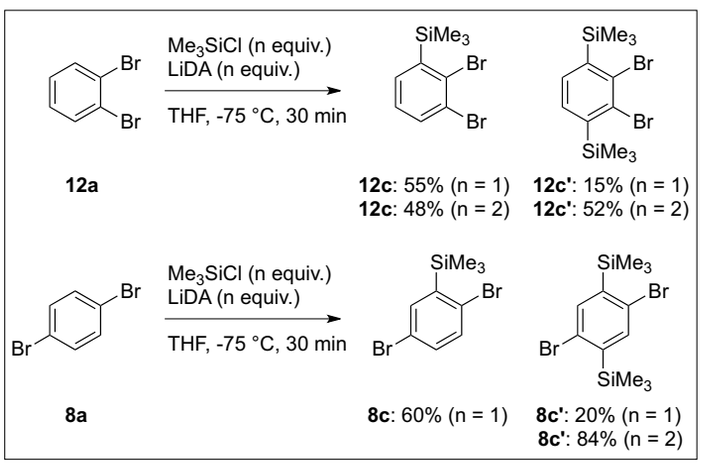
X	*ortho*-X	*meta*-X	*meta*-X	*para*-X
H	0.00	0.00	0.00	0.00
OMe	+1.8	+0.46	+0.29	–0.48
F	+7.4	+2.2	+1.9	+0.48
Cl	+6.4	+2.5	+2.7	+1.3
Br	**+6.4**	**+2.7**	**+3.0**	**+1.2**
I	+5.5	+2.4	+2.9	+1.1
CF_3	+5.2	+3.2	+3.2	–



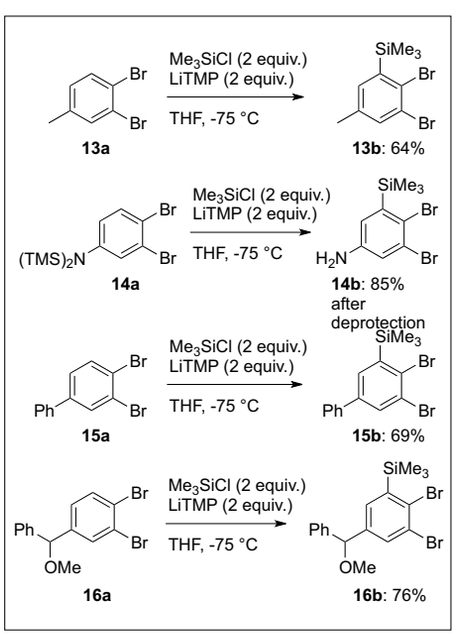
Scheme 4. Deprotolithiation of 1,4-dibromobenzene and 1-bromo-4-iodobenzene.



Scheme 5. Deprotolithiation of 2- and 4-bromobenzonitrile.



Scheme 6. Deprotolithiation of 1,2- and 1,4-dibromobenzene using *in situ* trapping.



Scheme 7. Deprotolithiation of 4-substituted 1,2-dibromobenzenes using *in situ* trapping.

Concerning 1,2-dibromobenzene (**12a**) (or 1-bromo-2-chlorobenzene), such a deprotolithiation using hindered lithium dialkylamides takes place, but 2,3-dibromophenyllithium (or 2-bromo-3-chlorophenyllithium/3-bromo-2-chlorophenyllithium) easily rearranges through bromine migration into thermodynamically more stable 2,6-dibromophenyllithium (or 2-bromo-6-chlorophenyllithium).[13,17,20] It is possible to avoid this rearrangement using LiDA in the presence of chlorotrimethylsilane as *in situ* trap (indeed, LiDA reacts with the aromatic halide more rapidly than it does with chlorotrimethylsilane). Nevertheless, a second deprotolithiation-silylation cannot be avoided, leading to mixtures containing both 1,2-dibromo-3-(trimethylsilyl)benzene (**12c**) and 2,3-dibromo-1,4-bis(trimethylsilyl) benzene (**12c'**). Similarly, 1,4-dibromobenzene (**8a**) can be converted into 1,4-dibromo-2-(trimethylsilyl)benzene (**8c**) and 1,4-dibromo-2,5-bis(trimethylsilyl)benzene (**8c'**) (Scheme 6).[20]

In the case of the 1,2-dibromobenzenes **13a**–**16a**, the presence of bulky substituents at the ring 4 position allows a monosilylation at the sterically less congested position to be observed. When combined with chlorotrimethylsilane as *in situ* trap, LiTMP proves a better alternative than LiDA, and the best results are noted using 2 equiv. of each (Scheme 7).[21]

Experiments performed at –75 °C under irreversible conditions using LiTMP as base and chlorotrimethylsilane as *in situ* trap lead to the relative reaction rates (kinetic acidities) of different substituted benzenes (Table 2).[2] Even if it is less pronounced here at the transition state (kinetic) than at the ground state (thermodynamic), bromine (and it is quite similar for chlorine and iodine) enhances the proton mobility more strongly than fluorine and methoxy do when located at the *meta* and *para* position.

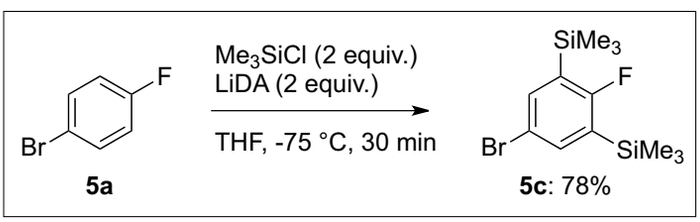
As a consequence, using LiDA in the presence of chlorotrimethylsilane (2 equiv. each) in THF at –70 °C with 1-bromo-4-fluorobenzene (**5a**) furnishes 5-bromo-2-fluoro-1,3-bis(trimethylsilyl)benzene (**5c**) in high yield (Scheme 8).[22]

When bromobenzenes are *ortho*-substituted by bulky trialkylsilyl groups (*e.g.* in the case of **17a**), the bromo group is less capable of inducing lithiation at the neighboring position due to a buttressing effect.[23] In this case, metalation no longer takes place at the halogen-adjacent position, but solely at the halogen-remote *meta* position owing to the long-range acidifying effect of the heavy halogen (Scheme 9).[24]

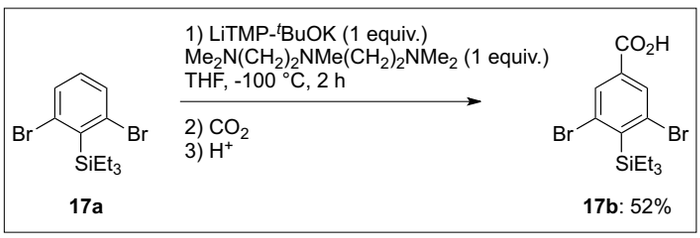
Besides chlorotrimethylsilane, it is possible to intercept arylmetal species generated by deprotonative metalation through

Table 2. Substituent effects on the free activation energies (reaction with LiTMP in the presence of Me_3SiCl at –75 °C); $\Delta\Delta G^{\ddagger}$ (kcal mol^{-1}) = 0.9067 x (lg k_X – lg k_H).

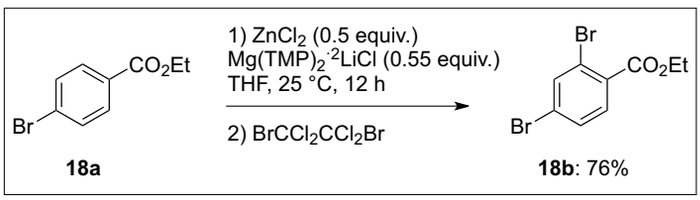
X	*ortho*-X	*meta*-X	*meta*-X	*para*-X
H	0.00	0.00	0.00	0.00
OMe	+2.0	+0.42	+0.44	–0.14
F	+2.9	+1.5	+1.5	+0.013
Cl	+2.8	+1.8	+2.0	+0.46
Br	**+2.6**	**+1.9**	**+2.3**	**+0.44**
I	+2.6	+1.9	+2.3	+0.39
CF_3	+2.0	+2.1	+1.9	–



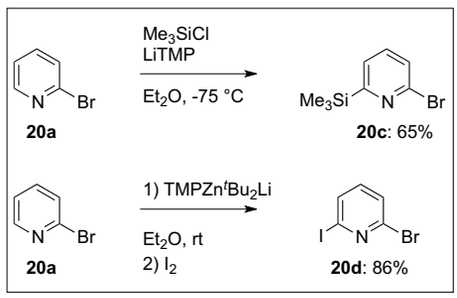
Scheme 8. Consecutive deprotolithiation-silylations of 1-bromo-4-fluorobenzene using *in situ* trapping.



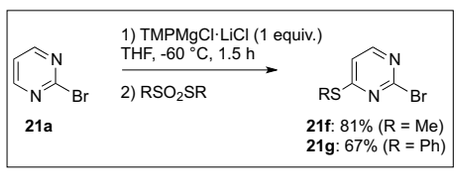
Scheme 9. Reaction showing the long-range acidifying effect of bromine.



Scheme 10. Deprotometalation of ethyl 4-bromobenzoate.



Scheme 12. Deprotometalation of 2-bromopyridine in Et_2O.



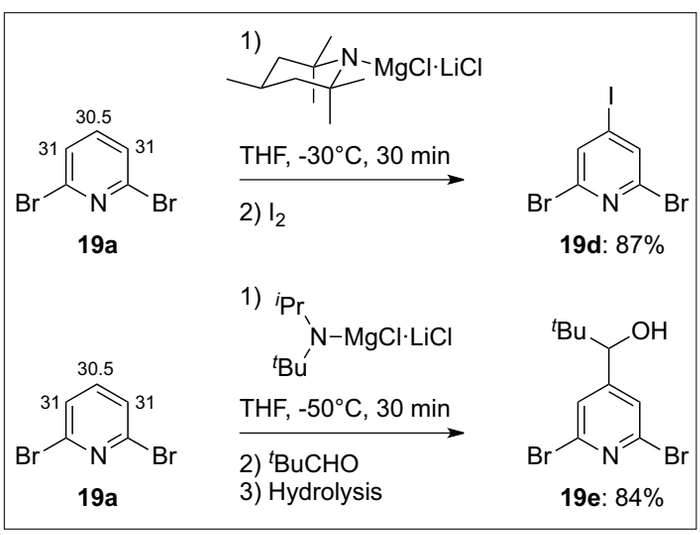
Scheme 13. Deprotometalation of 2-bromopyrimidine.

transmetalation. Thus, aromatic compounds bearing sensitive groups such as **18a** were functionalized through a deprotometalation step using $Mg(TMP)_2{\cdot}2LiCl$ in the presence of $ZnCl_2$ (Scheme 10).[24]

Long-range Effect of Bromine in the Deprotometalation of Aromatic Heterocycles

The most convincing example of the long-range effect of bromine in the dered magnesium amides in THF at lower temperatures (Scheme 11).[28]

From 2-bromopyridine (**20a**), proton abstraction at the 4 or 6 position ('*meta*' to the bromo group) is described in some cases. Thus, even if the 3-functionalized derivative is the main product, the 4-silylated compound also forms when 2-bromopyridine (**20a**) is submitted to the action of LiDA in THF at –75 °C in the presence of chlorotrimethylsilane (*in situ* trapping).[29] More importantly, if THF is replaced by diethyl ether, the reaction also occurs at a position '*meta*' to the bromo group, but this time at the 6 position of the pyridine ring. A similar result also takes place using TMP-zincate (^{t}Bu$_2$Zn(TMP)Li) in this less coordinating solvent (Scheme 12).[30]



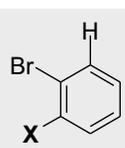
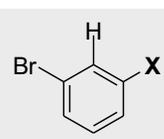
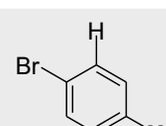
Scheme 11. Calculated pK_a (THF) values and deprotometalation of 2,6-dibromopyridine.

Bromine also plays an important role in the deprotometalation of 2-bromopyrimidine (**21a**), a substrate prone to nucleophilic attacks, using a LiCl-activated hindered magnesium amide. The heteroarylmetal species can be accumulated in THF at –60 °C without degradation, as shown by its quenching after 1.5 hours (Scheme 13).[31]

Conclusions

Thus, compared with other substituents such as fluorine and methoxy, bromine exhibits a different behavior by acidifying differently the aromatic hydrogens of the ring to which it is connected. Whereas fluorine and methoxy tend to acidify the protonative metalation of pyridines is possibly the reaction of 2,6-dibromopyridine (**19a**) with hindered metal amides. Upon treatment at room temperature for 2 hours with the base *in situ* prepared in THF from $ZnCl_2{\cdot}$TMEDA (0.5 equiv.) and LiTMP (1.5 equiv.),[25] and postulated to be 1:1 LiTMP-Zn(TMP)$_2$(±TMEDA),[26] 2,6-dibromopyridine (**19a**) is attacked at its 4 position. The 4-iodo derivative **19d** is isolated in 87% yield after iodolysis. The regioselectivity corresponds to combined acidifying and congesting effects of the bromo groups.[27] A clean C(4) deprotonation of 2,6-dibromopyridine (**19a**) can be performed by using LiCl-activated hin-

Table 3. Substituent effects on the rates of benzyne formation from *ortho*-, *meta*-, and *para*-substituted bromobenzenes (k_{rel}, relative to bromobenzene for which k_{rel} = 1).

X			
Br	140	940	83
F	34	1700	25
OMe	1.4	600	1.2
NMe_2	0.58	7.3	0.23
Ph	1.9	1.8	2.0
Me	0.50	0.35	0.45
^{i}Pr	0.37	0.19	0.53

neighboring hydrogens, bromine exhibits an acidifying effect at a longer range. If we consider the relative rates of formation of benzyne (obtained from haloarenes upon treatment by lithium piperidide in diethyl ether)[32] as a measure of the 2-haloaryl stability,[33] we can once more evidence this behavior at the origin of numerous functionalizations (Table 3).

Received: April 10, 2015

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[14] 2-Chlorobenzoic acid is isolated in 21% yield using LiTMP (1 equiv.) at –75 °C for 2 hours, in 43% yield using LiTMP (2 equiv.) at –75 °C for 2 hours, 45% yield using LiTMP (2 equiv.) at –75 °C for 6 hours.

[15] 2-Bromophenyltrimethylsilane can be obtained in about 40% yield, but using 10 equiv. of LiTMP at –75 °C in the presence of chlorotrimethylsilane as *in situ* trap.

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