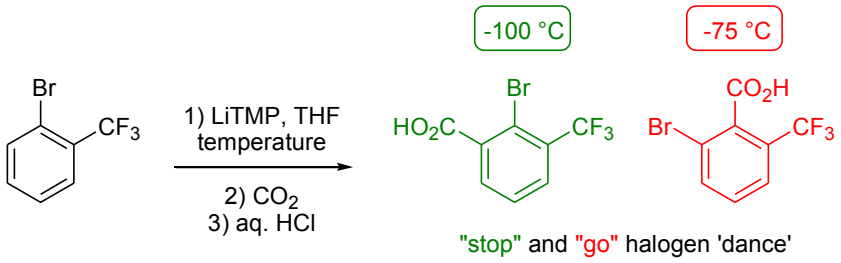
Graphical Abstract



Halogen 'Dance': a Way to Extend the Boundaries of Arene Deprotolithiation

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Dedicated to Professor Manfred Schlosser

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Abstract

Functionalization of aromatic heterocycles using deprotonation-promoted heavy halogen migration has established itself as a powerful tool. The development of clean and synthetically useful halogen 'dance' reactions in the less acidic arene series has been delayed because of

competitive aryne formation and dismutation. The comprehensive studies devoted to this chemistry during the last 20 years brought new insights into this synthetic method extremely useful to access scaffolds that would not otherwise be available.

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1. Introduction

The base-catalyzed arene halogen 'dance' was discovered in 1959 when, upon reaction of sodium amide with polyhalogenobenzenes in liquid ammonia, 1,2,4-tribromobenzene was converted to its 1,3,5-isomer.[1] The group of Bunnett next identified more satisfactory isomerization catalysts, but could not avoid formation of arynes and dismutation, at the origin of a large numbers of unwanted products.[2] In spite of such issues, by showing that the isomerization of available compounds containing heavy halogens into less accessible ones was feasible, this study has attracted interest from chemists.

In the developments that have resulted, halogen 'dance' is related to two essential reactions involving organometallic compounds, namely halogen/lithium exchange[3] and deprotonative lithiation.[4,3b] Indeed, a lithio intermediate has first to be generated by base-mediated arene

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metalation before halogen migration could furnish, through thermodynamic equilibration, the more stable lithio isomer. The method is restricted to compounds bearing heavy halogens (Br, I), fluorine and chlorine atoms being unable to change places under such conditions.

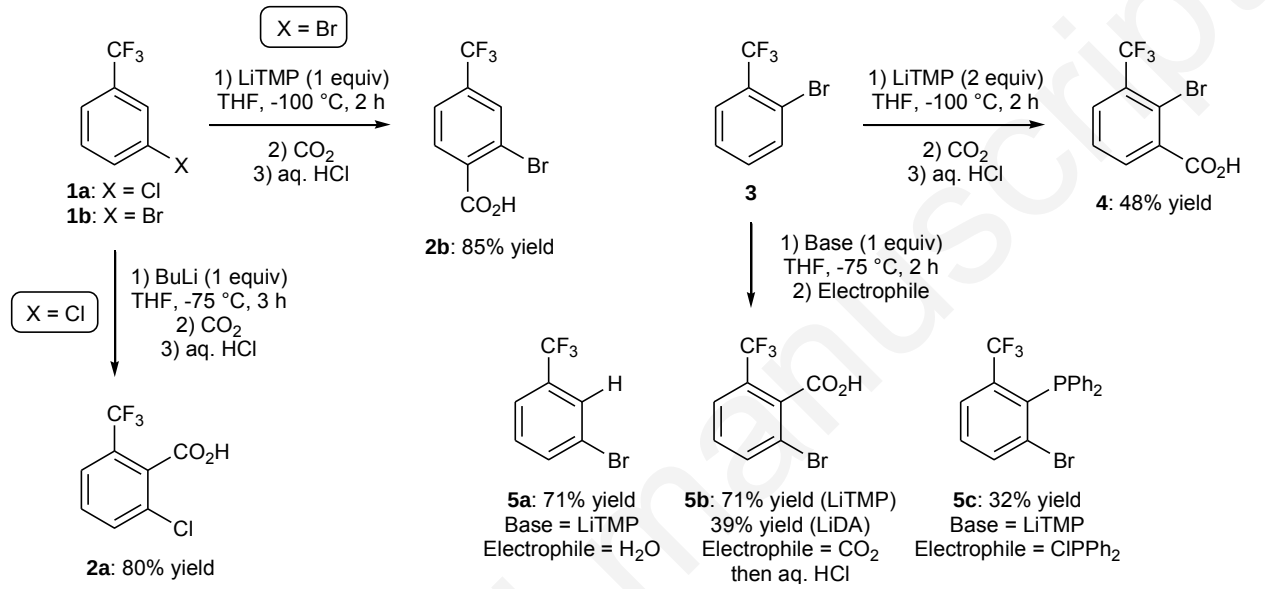
Halogen 'dance' has first been developed for five-[5] and six-[6] membered aromatic heterocycles, which are more acidic than arenes, by using lithium amides.[7] In the arene series, clean and synthetically useful deprotonation-promoted heavy halogen migration emerged about twenty years ago. Even if it established itself as a powerful tool to implement regioflexibility in the functionalization of arenes through organometallic intermediates,[7b,c,7f] such basicity gradient-controlled halogen migration remains under-employed in synthetic pathways. Our goal is thus to focus on arene halogen 'dance' in order to highlight its benefits for the elaboration of scaffolds that would not otherwise be available.

2. (Trifluoromethyl)benzenes

As exemplified in Scheme 1, trifluoromethyl group can be used to induce bromine migration.[8] 1-Chloro-3-(trifluoromethyl)benzene (**1a**) was converted by Schlosser and co-workers to 2-chloro-6-(trifluoromethyl)phenyllithium upon treatment with butyllithium in tetrahydrofuran (THF) at -75 °C, as demonstrated by subsequent quenching with dry ice followed by acidic workup (compound **2a**, 80% yield). It is impossible to employ butyllithium in the case of 1-bromo-3-(trifluoromethyl)benzene (**1b**) due to more favored halogen/metal interconversion.[9] Turning to lithium 2,2,6,6-tetramethylpiperidide (LiTMP, pK_a = 37.3[10]) led to efficient deprotonation of **1b** in THF at -100 °C; subsequent interception with dry ice showed the reaction took place next to bromine, but at the less hindered position, remote from the trifluoromethyl group. 2-Bromo-4-(trifluoromethyl)benzoic acid (**2b**) was therefore isolated in 85% yield. Steric hindrance combined with the capacity of trifluoromethyl to stabilize a remote electron excess[11] can justify this result. Nevertheless, it is possible to obtain 2-bromo-6-(trifluoromethyl)phenyllithium by starting from 1-bromo-2-(trifluoromethyl)benzene (**3**). While the latter is attacked by LiTMP next to bromine in THF at -100 °C, as shown by conversion to 2-bromo-3-(trifluoromethyl)benzoic acid (**4**, 48% yield when 2 equivalents of LiTMP are used), 2-bromo-6-(trifluoromethyl)phenyllithium is formed at -75

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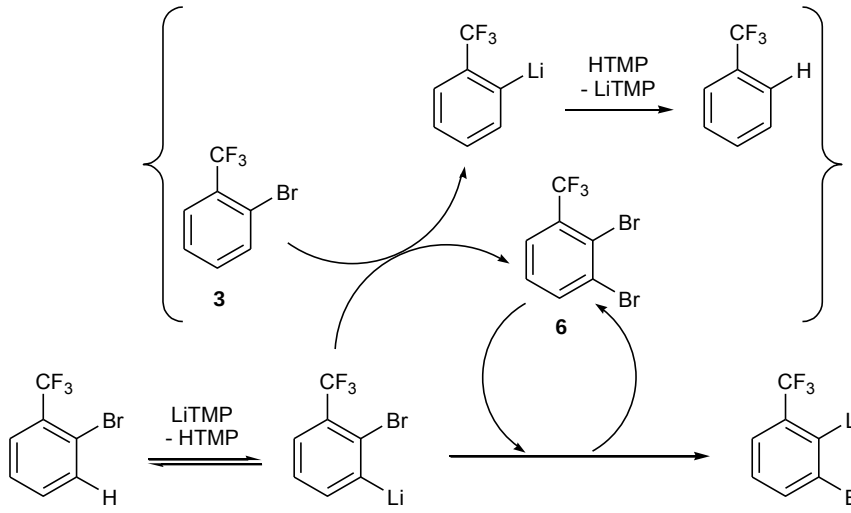
°C, as evidenced by isolation of 1-bromo-3-(trifluoromethyl)benzene (**5a**) or the 2-substituted 1-bromo-3-(trifluoromethyl)benzenes **5b** and **5c**. Lithium diisopropylamide (LiDA, pK_a = 35.7[10]) proved less efficient in performing this 'stop-and-go' isomerization ("stop" at -100 °C, "go" at -75 °C), only affording 2-bromo-6-(trifluoromethyl)benzoic acid (**5b**) in 39% yield due to competitive isomer formation (through deprotonation next to the trifluoromethyl group) under similar conditions.



Scheme 1. Bromine migration using trifluoromethyl as directing group.

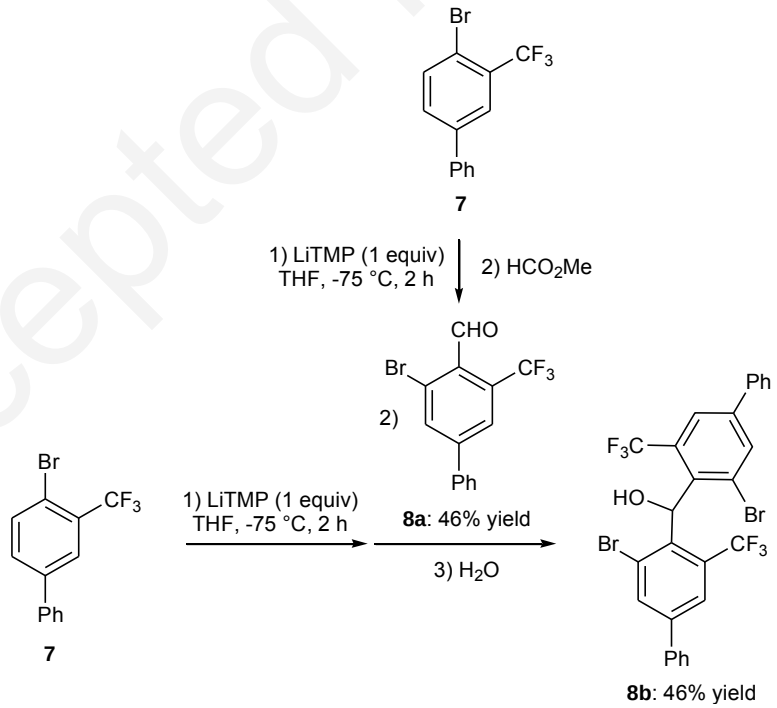
A mechanism involving elimination of lithium bromide followed by readdition to the resulting benzyne with opposite regioselectivity is unlikely as all attempts to intercept the hypothetical benzyne intermediate with nucleophiles and dienes failed. From the data above, it can be assumed that, even if 2-bromo-6-(trifluoromethyl)phenyllithium is stabilized (thermodynamic lithio product), LiTMP is too bulky to abstract at -100 °C the proton flanked by bromine and trifluoromethyl of 1-bromo-3-(trifluoromethyl)benzene (**1b**). On the other hand, since (i) 1,2-dibromo-3-(trifluoromethyl)benzene (**6**) can catalyze the reaction involving 1-bromo-2-(trifluoromethyl)benzene (**3**) and (ii) 2-(trifluoromethyl)phenyllithium cannot survive in the presence of 2,2,6,6-tetramethylpiperidine (attempts to metalate (trifluoromethyl)benzene with LiTMP in THF at -75 °C failed), repetitive halogen/metal exchanges could propagate such an isomerization, as reported previously[12] (Scheme 2).[8]

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Scheme 2. Mechanism proposed for the isomerization of 2-bromo-3-(trifluoromethyl)phenyllithium.

In the course of the synthesis of diphenyldiazomethanes by Tomioka and co-workers, two halogen 'dance' reactions were applied to access bis[2-bromo-4-phenyl-6-((trifluoromethyl)phenyl)]methanol (**8b**) from 1-bromo-4-phenyl-2-(trifluoromethyl)benzene (**7**) (Scheme 3).[13]



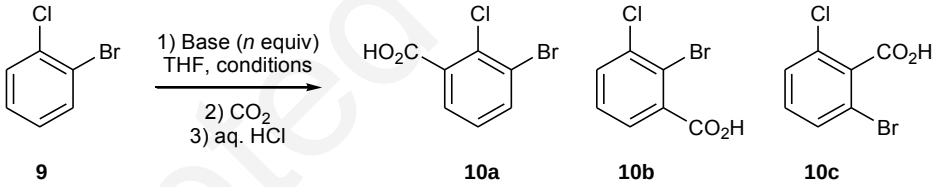
Scheme 3. Bromine migration using trifluoromethyl as directing group.

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3. Chlorobenzenes

Things become more complex with 1-bromo-2-chlorobenzene (**9**, Table 1).[14,8c] Indeed, whereas trifluoromethyl is only a moderate *ortho*-directing group due to its bulkiness,[11b,15] chlorine exerts a stronger short-range acidifying effect,[8a] not very different from that of bromine.[14] As a consequence, metalation can take place rather equally at a position adjacent to chlorine or bromine. Using LiTMP in THF at -75 °C for 2 h to perform the reaction led to a 3:1 mixture of 3-bromo-2-chlorophenyllithium and 2-bromo-6-chlorophenyllithium, evidenced by conversion to the corresponding carboxylic acids **10a** and **10c** (entry 1). Probably in relation with its slightly smaller size, employing LiDA furnished the same lithio derivatives, but in a 5:95 ratio (entry 2). Reducing the contact time with the lithium amide to 30 min was detrimental to both yields and selectivities (entries 3 and 4). Reducing the temperature to -100 °C stopped the isomerization (entries 5 and 6) whereas carrying out the experiment at -50 °C led to degradation through benzyne formation (entry 7).

Table 1. Bromine migration using chlorine as directing group.



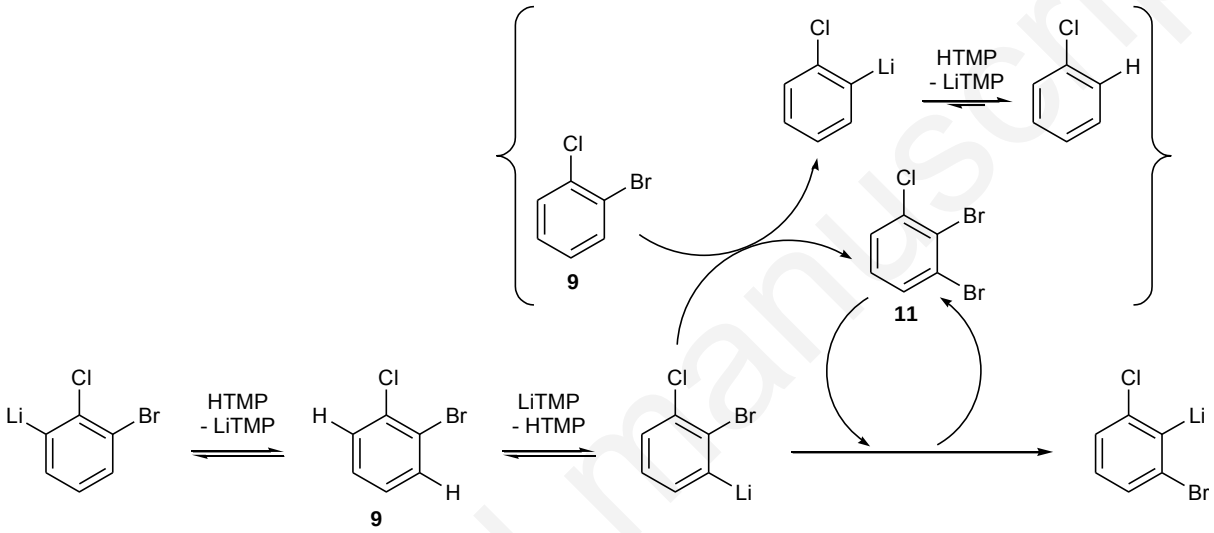
9 **10a** **10b** **10c**

Entry	Base	*n*	Conditions	Yields (%)		
				10a	**10b**	**10c**
1	LiTMP	1	-75 °C, 2 h	50	0	14
2	LiDA	1	-75 °C, 2 h	2	0	38
3	LiTMP	1	-75 °C, 30 min	46	0	15
4	LiDA	1	-75 °C, 30 min	13	3	14
5	LiTMP	1	-100 °C, 2 h	4	2	0
6	LiTMP	2	-100 °C, 2 h	10	5	0
7	LiTMP	1	-50 °C, 40 min	8	0	27

On the basis of the differences in the thermodynamic stabilities relative to the unsubstituted metalated substrates, chlorine and bromine exert similar activating effects when located *ortho* to the metal, and bromine is slightly more stabilizing than chlorine when present at a longer range.[16] As a

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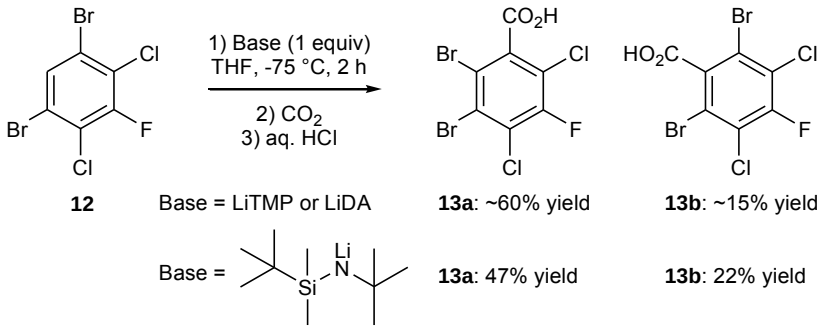
consequence, both positions of **9** *ortho* to halogens are affected by the reaction (with a slight preference for the position next to chlorine), and the equilibria is displaced by isomerization of 2-bromo-3-chlorophenyllithium into the more stabilized 2,6-dihalogenophenyllithium (Scheme 4).[14] Replacing chlorine by fluorine completely changed the outcome of the reaction, as no more halogen 'dance' was observed due to the strong ability of the lighter halogen to stabilize a lithio compound when positioned at the adjacent site.[17] Attempts to obtain 1-chloro-3-iodo derivatives from 1-chloro-2-iodobenzene under similar conditions at -75 or -100 °C only led to complex mixtures.[8c]



Scheme 4. Mechanism proposed for the bromine migration using chlorine as directing group.

Conversion of 2,6-dibromo-3,5-dichloro-4-fluorophenyllithium coming from **12** to 2,3-dibromo-4,6-dichloro-5-fluorophenyllithium only proceeds partially (weaker driving force). Indeed, whatever the lithium amide used among LiTMP, LiDA and lithium *N*-(*tert*-butyldimethylsilyl) *tert*-butylamide, mixtures of **13a** and **13b** were invariably isolated (Scheme 5).[18,8c] Because bromine and chlorine similarly stabilize lithio compounds when present next to lithium onto benzenes,[14,16] one has rather to compare the effects of the substituents located *meta* and *para* to the metal to understand this result. The *meta*-bromo group is slightly more stabilizing than the *meta*-chloro (~ +0.25 kcal.mol^{-1}), the *meta*-fluoro less than the *meta*-chloro (~ -0.55 kcal.mol^{-1}), and the *para*-chloro more than the *para*-fluoro (~ +0.82 kcal.mol^{-1}). The first aryllithium is therefore more stabilized than the second, but with only ~ 0.5 kcal.mol^{-1} difference, in accordance with the results observed.

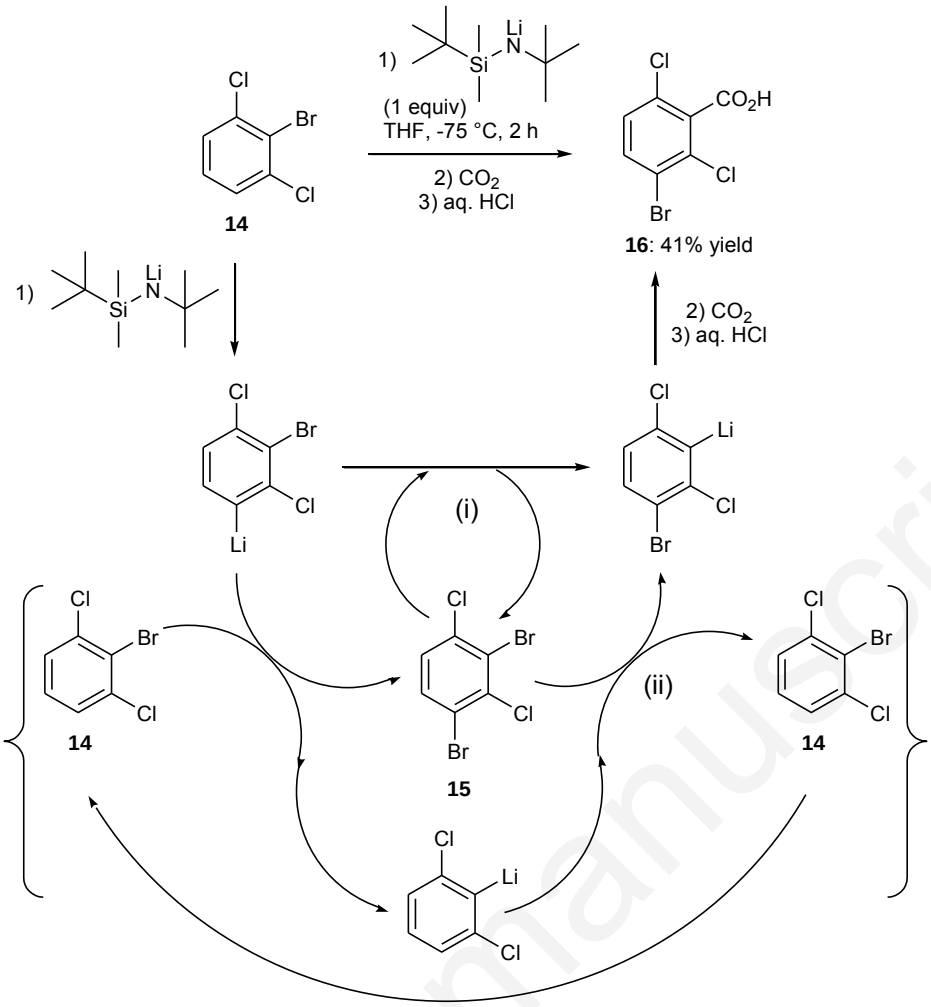
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Scheme 5. Bromine migration using chlorine as directing group.

Bromine can also migrate to a site different from the adjacent one provided that there is stabilization, e.g. through attenuation of the intramolecular steric repulsion, as exemplified below from **14** (Scheme 6).[18,8c] As the two sites involved in the reaction are not neighboring but remote from each other, the halogen migration cannot be rationalized by elimination of lithium bromide followed by readdition to the resulting benzyne with opposite regioselectivity, thus providing additional evidence in favor of two successive bromine/lithium exchanges. Concerning these two successive halogen/metal exchanges,[19,12] because 2,6-dichlorophenyllithium (generated at the same time as the dibromide **15**) has a relatively high stability, notably when compared with 2-(trifluoromethyl)phenyllithium (Scheme 2) and 2-chlorophenyllithium (Scheme 4) and can thus survive in the presence of 2,2,6,6-tetramethylpiperidine in the reaction mixture, two sequence sets should here be considered, namely (i) as before and (ii) using 2,6-dichlorophenyllithium.

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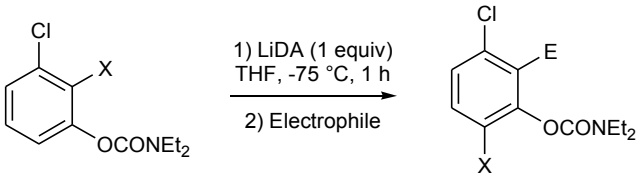


Scheme 6. Bromine migration using chlorine as directing group.

More recently, chlorine was used to drive the migration of heavy halogens on aryl *O*-carbamates.[20] From the 2-halogeno 3-chlorophenyl *O*-carbamates **17a** and **17b**, the deprotolithiation takes place at the position adjacent to the carbamate function before isomerization to lithio compounds in which the metal is surrounded by both the chloro and carbamate groups; trapping was finally performed to afford the derivatives **18** and **19** in high yields (Table 2). Combining halogen 'dance' with anionic *ortho* Fries rearrangement proved successful, as exemplified by the formation of **20** (Scheme 7).

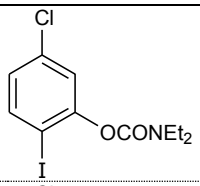
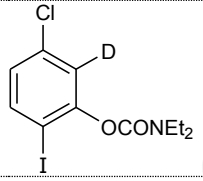
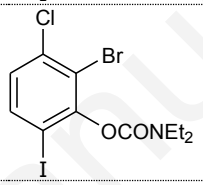
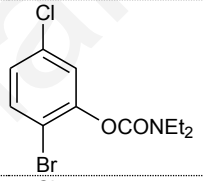
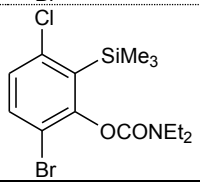
Table 2. Heavy halogen migration using chlorine as directing group.

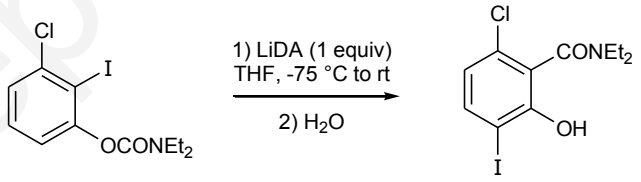
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18: X = I
19: X = Br

Entry	Substrate, X	Electrophile	Products, Yields (%)
1	**17a**, I	MeOH	 **18a**, 89
2	**17a**, I	MeOD	 **18b**, 87
3	**17a**, I	$C_2Br_2F_4$	 **18c**, 73
4	**17b**, Br	MeOH	 **19a**, 86
5	**17b**, Br	$ClSiMe_3$	 **19b**, 79



17

20: 87% yield

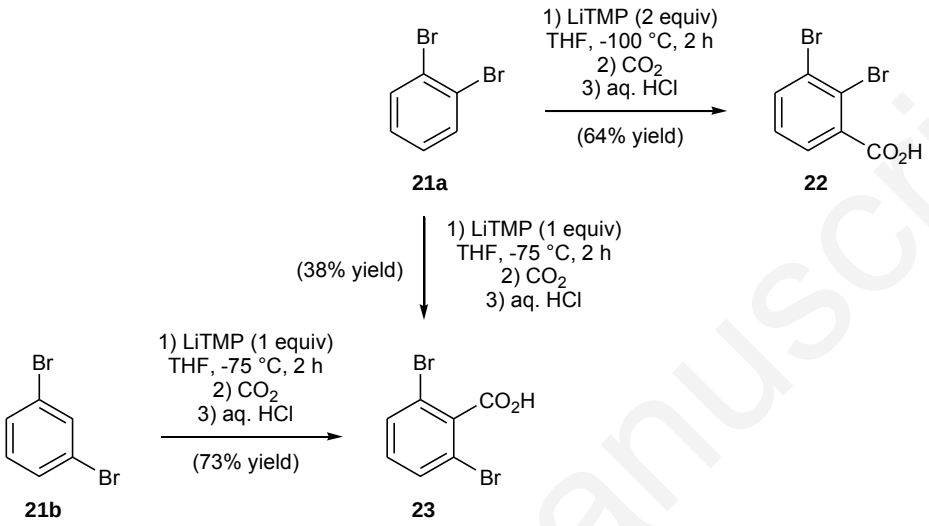
Scheme 7. Iodine migration using chlorine as directing group combined with anionic *ortho* Fries rearrangement.

4. Bromobenzenes

For symmetry reason, halogen 'dance' from 1,2-dibromobenzene (**21a**) is less complex than that of 1-bromo-2-chlorobenzene (**9**). But, whereas the ability of bromine to acidify the adjacent

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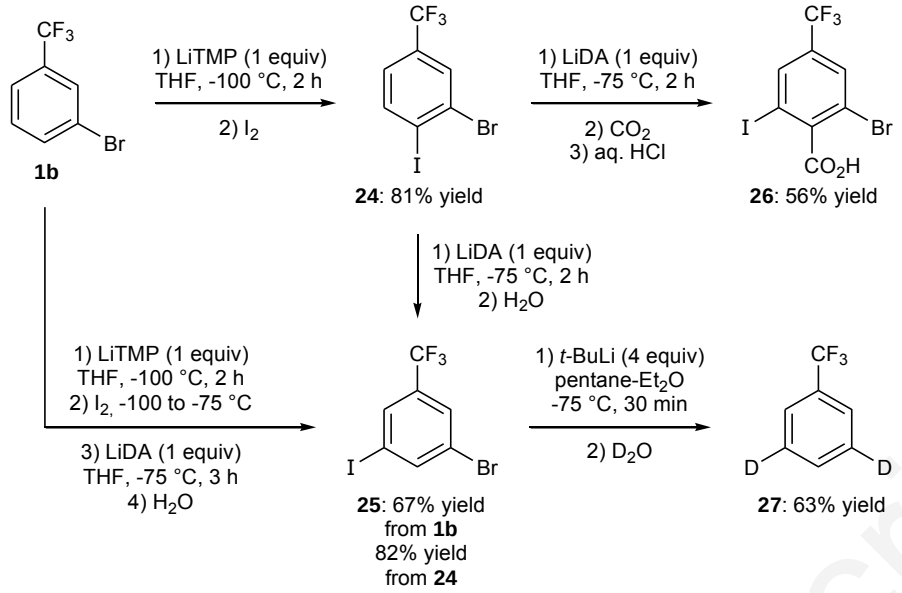
hydrogens is comparable to that of chlorine from a thermodynamic point of view,[16] the 2-bromophenyllithiums formed are prone to benzyne formation.[21] As the halogen migration does not take place at temperatures below -75 °C (as shown by the formation of **22**), low yields are noted due to such degradation before quenching to afford 2,6-dibromobenzoic acid (**23**), a product than can be here more directly formed from 1,3-dibromobenzene (**21b**, Scheme 8).[8c]



Scheme 8. Bromine migration using bromine as directing group.

Iodine migration can also work from 2-bromo-1-iodo-4-(trifluoromethyl)benzene (**24**). Thus, upon treatment by LiDA in THF at -75 °C, deprotometalation occurs next to iodine before isomerization proceeds smoothly to give 1-bromo-3-iodo-5-(trifluoromethyl)phenyllithium, as demonstrated by subsequent trapping to furnish 1-bromo-3-iodo-5-(trifluoromethyl)benzene (**25**) and 2-bromo-6-iodo-4-(trifluoromethyl)benzoic acid (**26**). The conversion of 1-bromo-3-(trifluoromethyl)benzene (**1b**) to 1-bromo-3-iodo-5-(trifluoromethyl)benzene (**25**) can also be carried out in a one-pot procedure. This method was applied to the synthesis of the deuterated (trifluoromethyl)benzene **27** (Scheme 9).[7b,8c]

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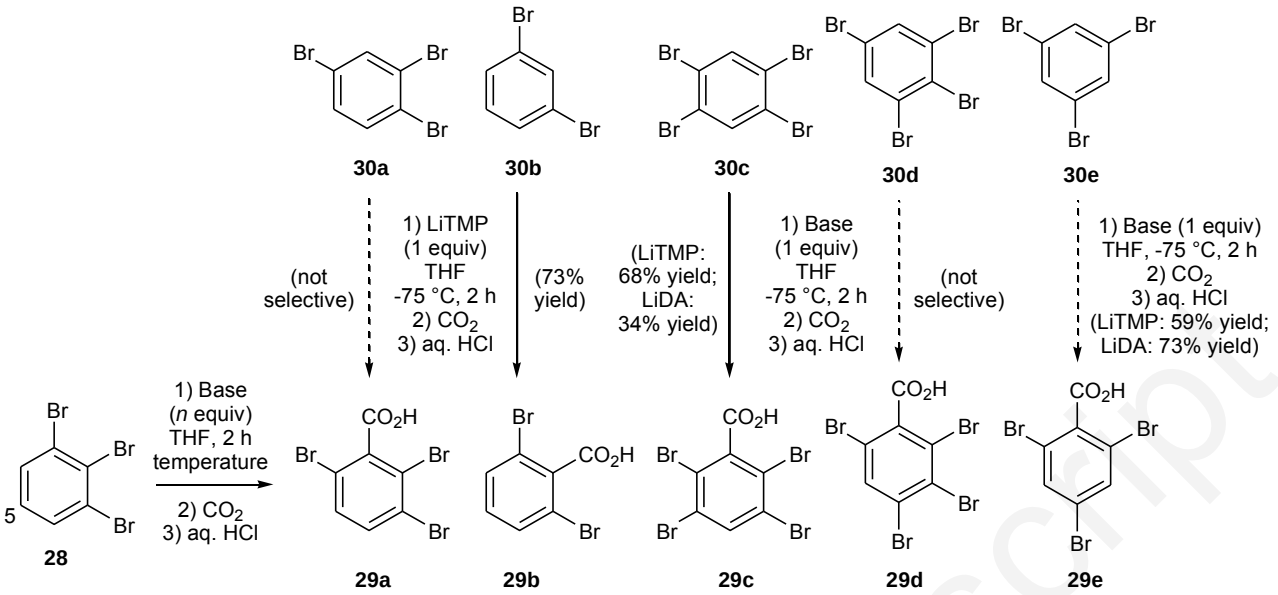
Scheme 9. Iodine migration using bromine as directing group.

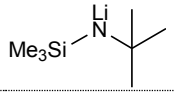
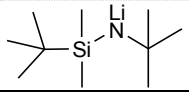
With **28**, a benzene substituted by three contiguous bromines, complications are encountered (Table 3).[18,7b,8c] Indeed, consecutive treatment by LiTMP or LiDA in THF at -75 °C for 2 h and by dry ice followed by acidification led to a mixture containing no fewer than five benzoic acids (compounds **29a-e**). Bromine migration here proceeds anarchically from -100 °C, giving rise to the formation of tri-, but also di- and tetra-brominated benzoic acids through a 'dismutation' process (entries 1-3). As shown by the sluggish deprotolithiation of the corresponding polybromobenzenes **30a-e**, most of the polybrominated phenyllithiums obtained suffer from a lack of stability (e.g. compared with their polychlorinated analogs), probably due to high steric pressure. In addition, the bromine atoms exert two effects that could allow 1,2,3-tribromobenzene (**28**) to be attacked at its 5 position: (i) a long range acidifying effect[16,22] and (ii) a 'buttressing' effect.[23] When the central bromine exerts the latter, its steric effect is propagated through the neighboring halogens, inhibiting *ortho*-deprotonation.[23] All this could explain why such a scrambling halogen migration takes place.

Attempts to employ a catalytic amount of lithium azetidide as less hindered relay failed (entry 4). In contrast, using lithium amides less basic than LiTMP and LiDA such as lithium *N*-(trimethylsilyl) *tert*-butylamide (pK_a = 33.6,[10] entry 5) and, above all, hindered lithium *N*-(*tert*-butyldimethylsilyl) *tert*-butylamide (entry 6) favored the formation of 2,3,6-tribromophenyllithium (and thus compound **29a** after trapping).

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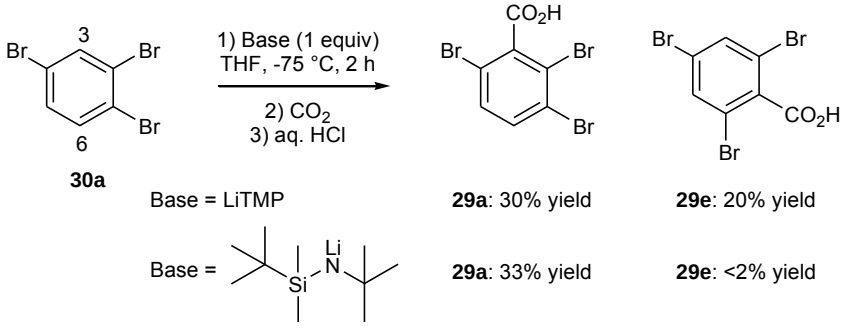
Table 3. Bromine migration using bromine as directing group.



Entry	Base	*n*	Temperature	Total yield (%)	Products, ratios (%)				
					29a	**29b**	**29c**	**29d**	**29e**
1	LiTMP	1	-75 °C	94	43	33	14	6	4
2	LiDA	1	-75 °C	73	28	47	13	7	5
3	LiTMP	2	-100 °C	88	47	28	16	6	3
4	LiTMP[a]	1	-75 °C	48	40	29	15	9	7
5		1	-75 °C	19	78	9	11	2	0
6		1	-75 °C	50	100	0	0	0	0

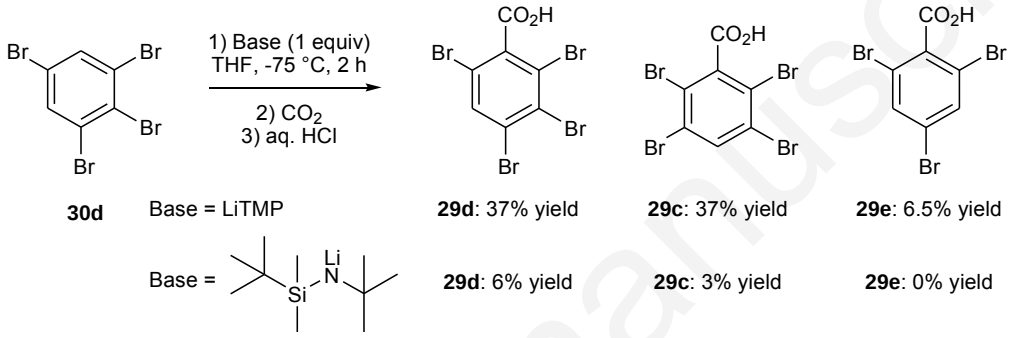
[a] In the presence of 0.1 equiv lithium azetidide.

2,3,6-Tribromophenyllithium was also the main arylmetal generated upon treatment of 1,2,4-tribromobenzene (**30a**) with lithium amides. Similarly, using more basic LiTMP allowed halogen 'dance' to happen, probably initiated by metalation at the 6 position, whereas less basic lithium *N*-(*tert*-butyldimethylsilyl) *tert*-butylamide more selectively abstracted the proton at the 3 position flanked by two bromine atoms (Scheme 10).[18]



Scheme 10. Bromine migration using bromine as directing group.

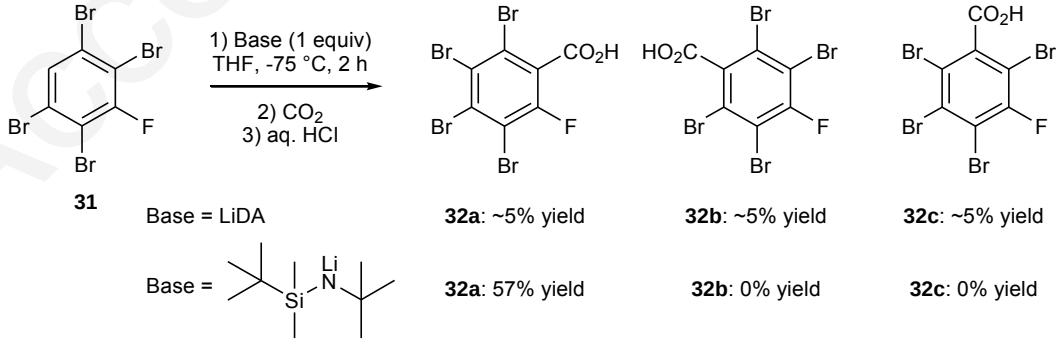
Because of a reduced number of alternatives when compared with 1,2,3-tribromobenzene (**28**), 1,2,3,5-tetrabromobenzene (**30d**) only furnished three benzoic acids (products **29d**, **29c** and **29e**) when submitted to LiTMP and dry ice (Scheme 11). Besides the products coming from direct lithiation at the 4 position (compound **29d**) and subsequent halogen migration (compound **29c**), dehalogenation was also noticed (compound **29e**). Since the lithium amide lacks β-hydrogens, such a dehalogenation cannot proceed by a hydride transfer mechanism;[24] thus, single electron transfer from the base to the polybromobenzene was rather suggested to account for this halogen loss. Similar observations were made concerning iodines placed next to lighter halogens.[18]



Scheme 11. Bromine migration using bromine as directing group.

5. Fluorobenzenes

Starting from 2,3,5,6-tetrabromo-4-fluorobenzene (**31**), the bromine migration occurred satisfactorily by using lithium *N*-(*tert*-butyldimethylsilyl) *tert*-butylamide to afford the acid **32a** (Scheme 12).[18]

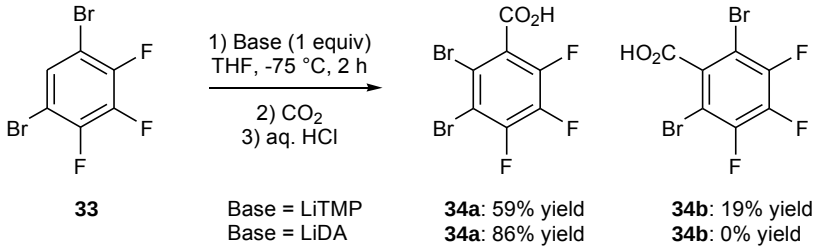


Scheme 12. Bromine migration using fluorine as directing group.

Because of its size, fluorine does not create any 'buttressing' effect.[23] In addition, it is capable of stabilizing lithio compounds when located at the position adjacent to lithium.[25] As a consequence,

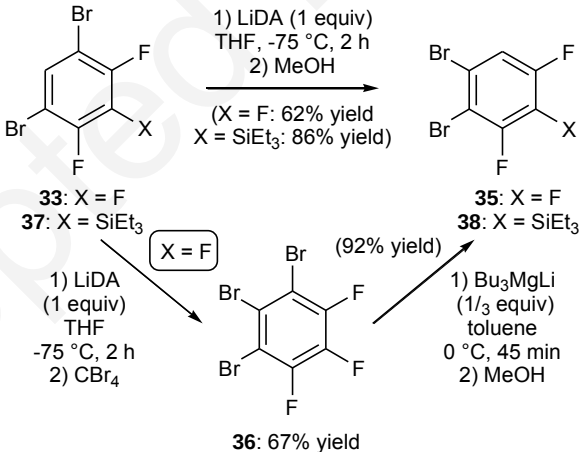
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when 1,5-dibromo-2,3,4-trifluorobenzene (**33**) was submitted to LiDA in THF at -75 °C for 2 h, deprotolithiation and bromine migration readily took place to afford, after interception, 2,3-dibromo-4,5,6-trifluorobenzoic acid (**34a**) in high yield (Scheme 13).[18]



Scheme 13. Bromine migration using fluorine as directing group.

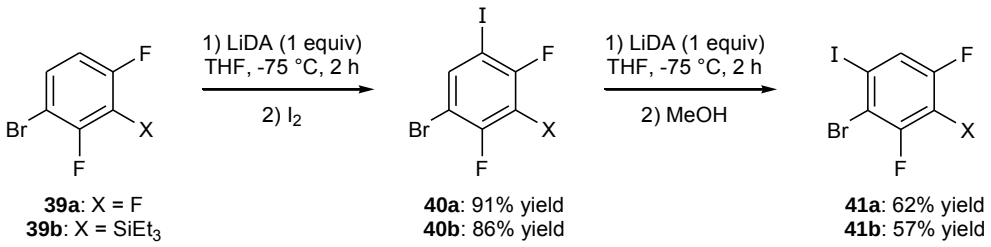
To generate 1,2-dibromo-3,4,5-trifluorobenzene (**35**), this deprotonation-triggered migration of bromine can be either directly used before adding a proton source, or employed to introduce an additional bromine (product **36**) before regioselective bromine/metal exchange and protonation were performed.[26] (3,5-Dibromo-2,6-difluorophenyl)triethylsilane (**37**) similarly underwent a LiDA-mediated rearrangement allowing lithium and bromine to swap places to give after neutralization (3,4-dibromo-2,6-difluorophenyl)triethylsilane (**38**, Scheme 14).[27]



Scheme 14. Bromine migration using fluorine as directing group.

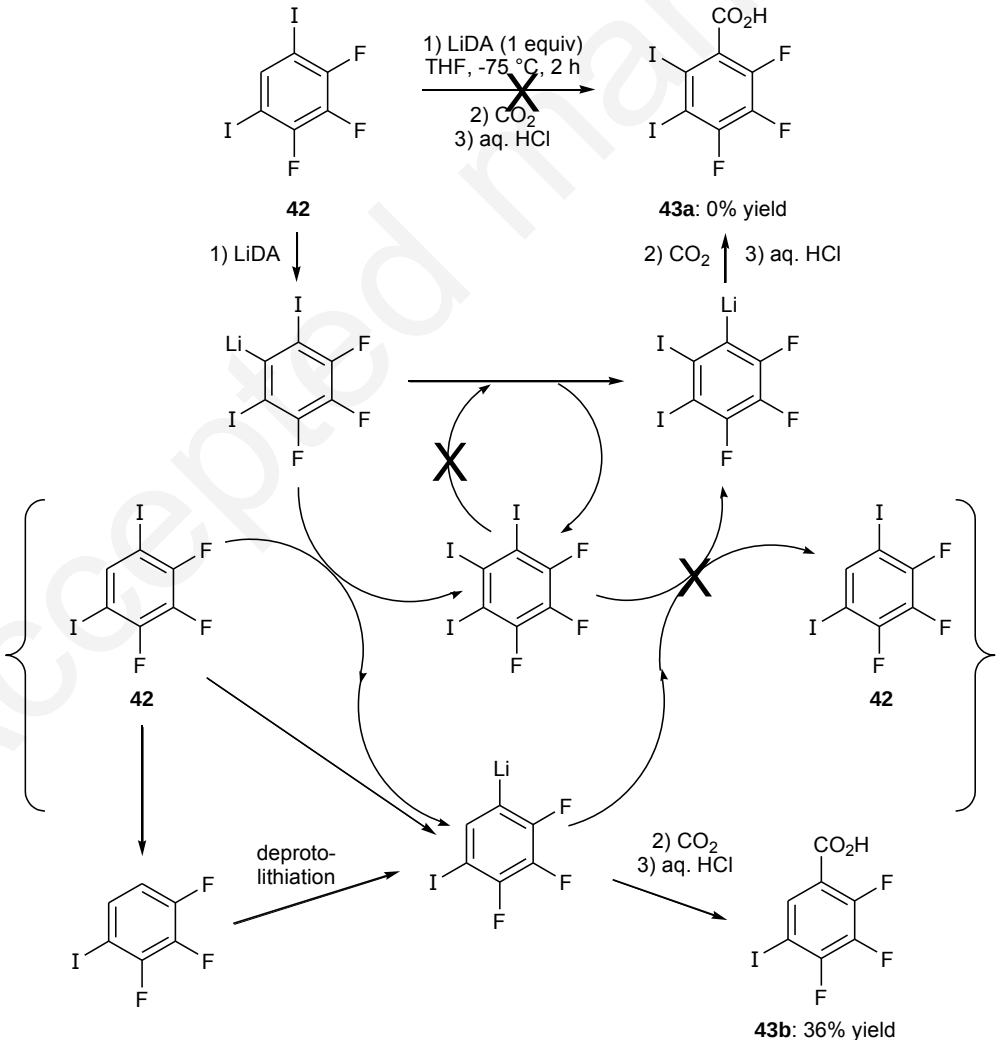
Isomerization of 1-bromo-2,3,4-trifluoro-5-iodobenzene (**40a**) was also found possible, this time by iodine/metal permutation to give 2-bromo-3,4,5-trifluoro-1-iodobenzene (**41a**).[26] The same applied to (3-bromo-2,6-difluoro-5-iodophenyl)triethylsilane (**40b**), which yielded (3-bromo-2,6-difluoro-4-iodophenyl)triethylsilane (**41b**) (Scheme 15).[27]

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Scheme 15. Iodine migration using fluorine as directing group.

It is worth noting that starting from the corresponding trifluorodiiodobenzene **42** did not lead to any diiodinated benzoic acid (e.g. **43a**), but to the iodobenzoic acid **43b**.[18]. Two explanations could be given: (i) either proton abstraction between both iodines does not take place due to high congestion (instead, radical formation should occur, leading to 1,2,3-trifluoro-4-iodobenzene or to 2,3,4-trifluoro-5-iodophenyllithium),[18] or (ii) proton abstraction and first iodine/lithium permutation occur, but the reaction stops at this stage (Scheme 16).

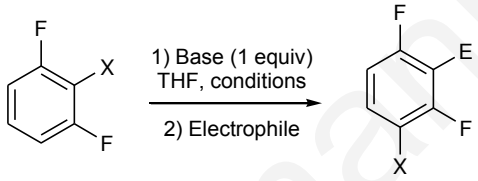


Scheme 16. Unsuccessful iodine migration using fluorine as directing group.

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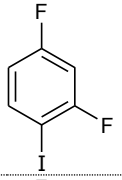
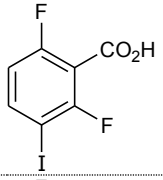
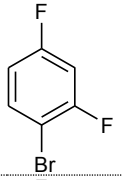
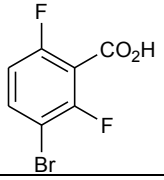
The above example, in which initial deprotolithiation is prevented due to steric congestion, does not reflect the general behavior of fluoroiodoarenes toward hindered lithium amides. Indeed, even if in a moderate yield due to side reactions such as halogen loss, 1,3-difluoro-2-iodobenzene (**44**) was deprotolithiated at its 4 position to afford, after iodine/lithium permutation and subsequent trapping, either 2,4-difluoro-1-iodobenzene (**45a**) or 2,6-difluoro-3-iodobenzoic acid (**45b**) (Table 4, entries 1-4). From 2-bromo-1,3-difluorobenzene (**46**), heavy halogen loss was less noted (products **47a** and **47b**, entries 5-7).[27-28] The gain in energy to go from 3-bromo-2,4-difluorophenyllithium to 3-bromo-2,6-difluorophenyllithium has been evaluated from the basicity difference found at the level of the corresponding free ('naked') benzenide ions,[25] and represents a driving force of ~3.4 kcal.mol^{-1}.[28a]

Table 4. Halogen migration using fluorine as directing group.



44
46

45: X = I
47: X = Br

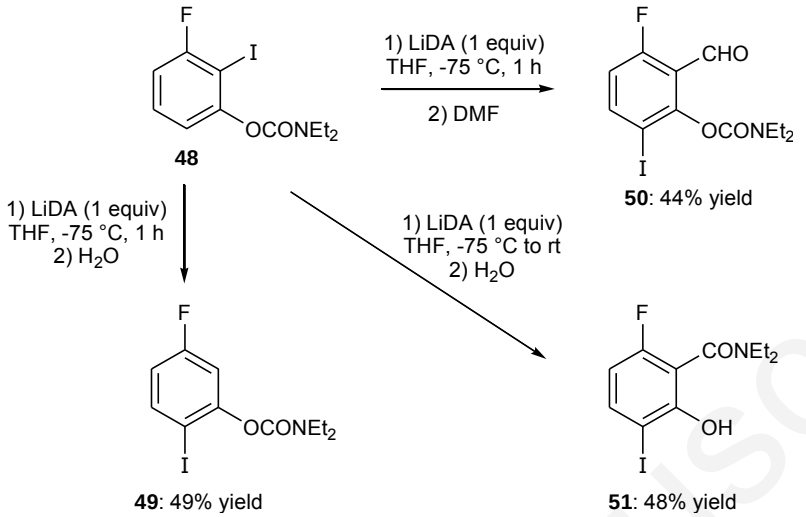
Entry	Substrate, X	Base	Conditions	Electrophile	Product, Yield (%)
1	**44**, I	LiDA	-75 °C, 2 h	H_2O	 **45a**, 48
2	**44**, I	LiDA	-75 °C, 2 h	CO_2 then aq. HCl	 **45b**, 47
3		LiTMP	-75 °C, 2 h		**45b**, 48
4		LiTMP	-125 °C, 2 h		**45b**, 47[a]
5	**46**, Br	LiDA	-75 °C, 2 h	H_2O	 **47a**, 20[b]
6	**46**, Br	LiTMP	-75 °C, 2 h	CO_2 then aq. HCl	 **47b**, 92
7		LiTMP	-125 °C, 2 h		**47b**, 42

[a] Together with 40% of the reduction product, 2,6-difluorobenzoic acid. [b] Starting material was recovered.

The 3-fluoro-2-iodophenyl *O*-carbamate **48** was involved in a similar LiDA-mediated deprotolithiation-isomerization to generate, after interception by an electrophile, either the

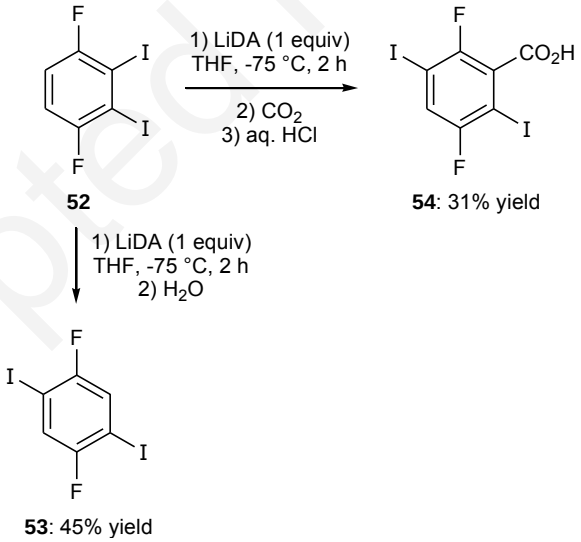
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corresponding 5-fluoro-2-iodophenyl or the 3-fluoro-2-formyl-6-iodophenyl *O*-carbamate (**49** or **50**). Halogen 'dance' was also combined with anionic *ortho* Fries rearrangement to produce a 4-fluoro-2-hydroxy-3-iodobenzamide (**51**, Scheme 17).[20]



Scheme 17. Iodine migration using fluorine as directing group.

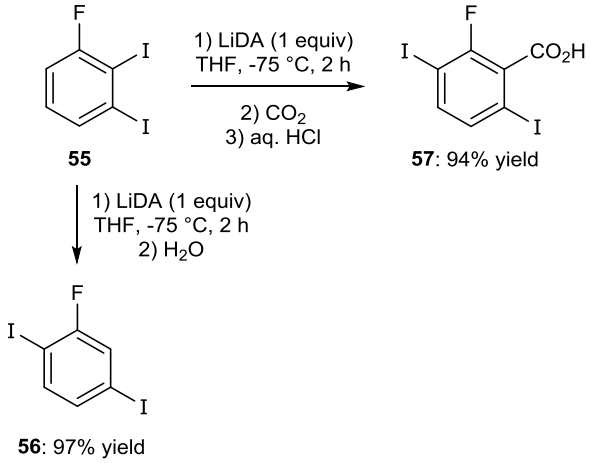
Analogous reactions, albeit in lower yields, were accomplished from 1,4-difluoro-2,3-diiodobenzene (**52**, Scheme 18).[28b]



Scheme 18. Iodine migration using fluorine as directing group.

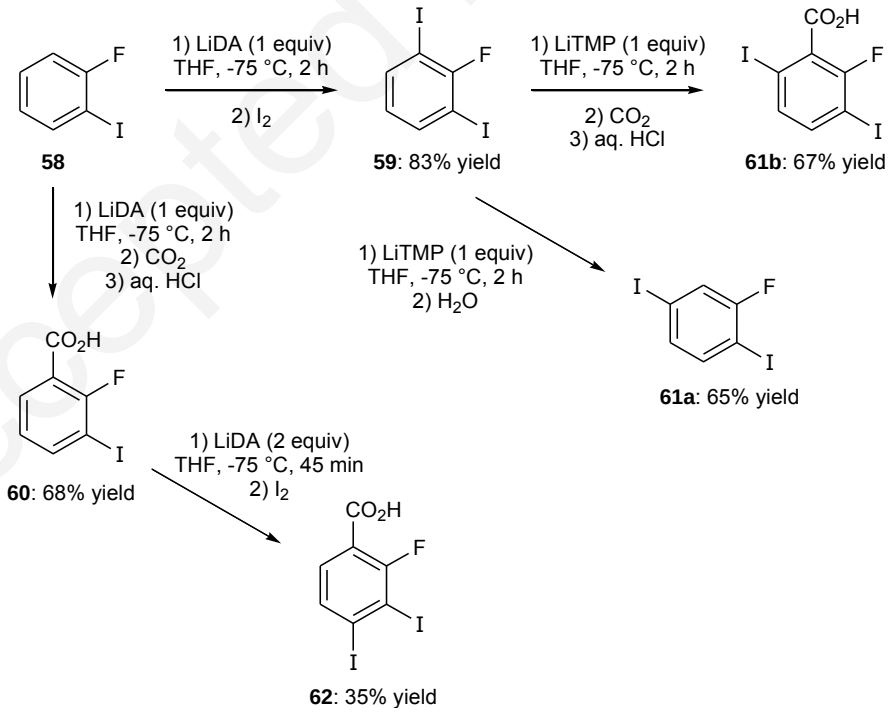
In the case of 1-fluoro-2,3-diiodobenzene (**55**), in spite of the lack of symmetry, high yields were reached. Thus, after deprotolithiation next to fluorine as above, the iodine/lithium permutation occurs in a site-discriminating manner in favor of the fluorine-adjacent iodine (products **56** and **57**, Scheme 19).[28b]

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Scheme 19. Iodine migration using fluorine as directing group.

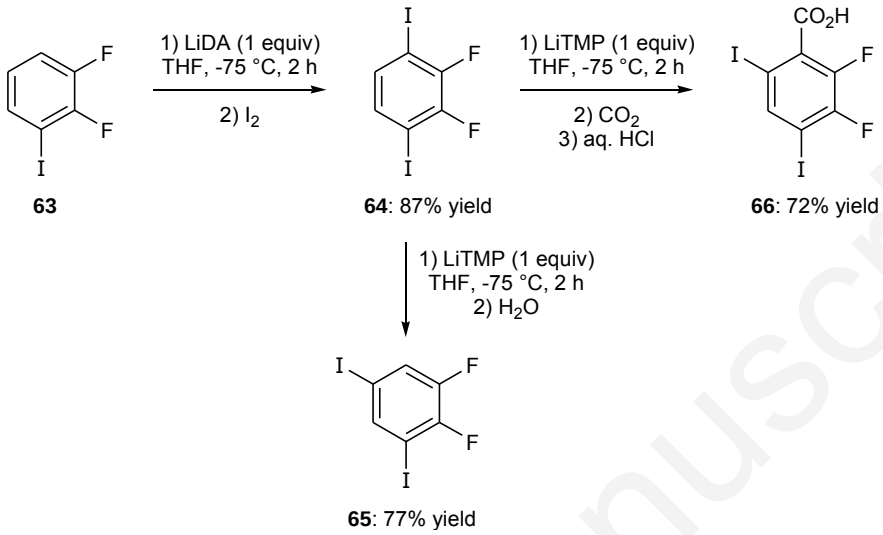
Due to the higher *ortho*-directing power of fluorine over heavy halogens,[16] 1-fluoro-2-iodobenzene (**58**) does not lead to a 2,6-dihalogenated phenyllithium upon treatment with LiDA or LiTMP in THF at -75 °C.[29,28b] Thus, its conversion to 2-fluoro-1,3-diiodobenzene (**59**) can be carried out by LiDA-mediated deprotometalation. In the case of **59** (and 2-fluoro-3-iodobenzoic acid **60**), iodine migration can only take place after deprotolithiation next to iodine, a halogen known as a weak *ortho*-directing group (products **61** and **62**, Scheme 20).[28b]



Scheme 20. Iodine migration using fluorine as directing group.

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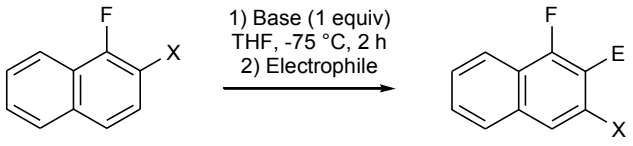
As for 1-fluoro-2-iodobenzene (**58**) above, 1,2-difluoro-3-iodobenzene (**63**) is attacked at its fluorine-adjacent center when subjected to LiDA, giving 2,3-difluoro-1,4-diiodobenzene (**64**) after iodolysis. In this case, LiTMP was also able to trigger deprotolithiation and basicity-gradient relocation of iodine with its subsequent replacement by lithium (products **65** and **66**, Scheme 21).[28b]

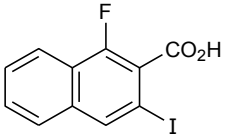


Scheme 21. Iodine migration using fluorine as directing group.

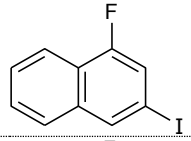
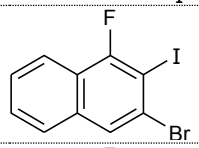
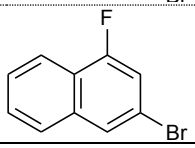
Unlike 1-fluoro-2-iodobenzene (**58**), 1-fluoro-2-iodonaphthalene (**67**) can only react at its iodine-adjacent position with LiTMP in THF at -75 °C to furnish, after isomerization and trapping, the 1,3- and 1,2,3-substituted compounds **68a**,**b** in high yields (Table 5, entries 1 and 2).[28b] 1-Fluoro-2-bromonaphthalene (**69**) worked in a similar way to generate the 1,3- and 1,2,3-substituted derivatives **70a**,**b** (entries 3 and 4).[30]

Table 5. Bromine migration using a fluoroalkoxy directing group.



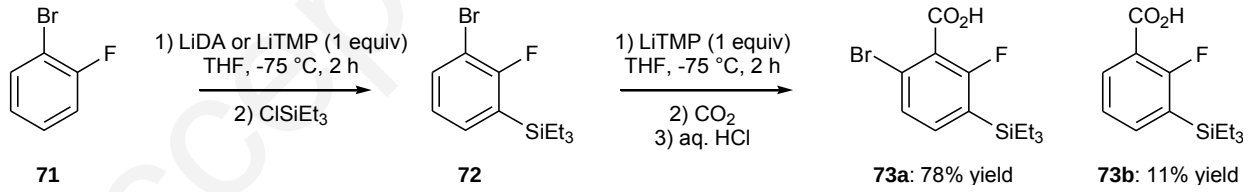
Entry	Substrate, X	Base	Electrophile	Product, Yield (%)
1	**67**, I	LiTMP	CO_2 then aq. HCl	 **68a**, 93

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2	**67**, I	LiTMP	H_2O		**68b**, 78
3	**69**, Br	LiDA	I_2		**70a**, 80
4	**69**, Br	LiTMP[a]	H_2O		**70b**, 89

[a] Conditions: THF, -75 °C, 6 h.

In agreement with the behavior of 1-fluoro-2-iodobenzene (**58**), 1-bromo-2-fluorobenzene (**71**) is attacked by hindered lithium amides next to fluorine without subsequent heavy halogen migration.[17] A protective group can nevertheless be introduced (substrate **72**) in order to functionalize the bromine-adjacent site, as exemplified in Scheme 22. The process here described at -75 °C (product **73a**; 78% yield) already takes place instantaneously at -100 °C (**73a** obtained in 64% yield). The energy gain of roughly 2.5 kcal.mol^{-1} from 2-bromo-3-fluoro-4-(triethylsilyl)phenyllithium to 6-bromo-2-fluoro-3-(triethylsilyl)phenyllithium (fluorine respectively *meta* and *ortho* with respect to the lithiated center) is enough to drive the reaction. 2-Fluoro-3-(triethylsilyl)benzoic acid (**73b**) was also isolated in 11% yield, maybe from 2-fluoro-3-(triethylsilyl)phenyllithium generated at the same time as the catalytic dibromide.[28a]



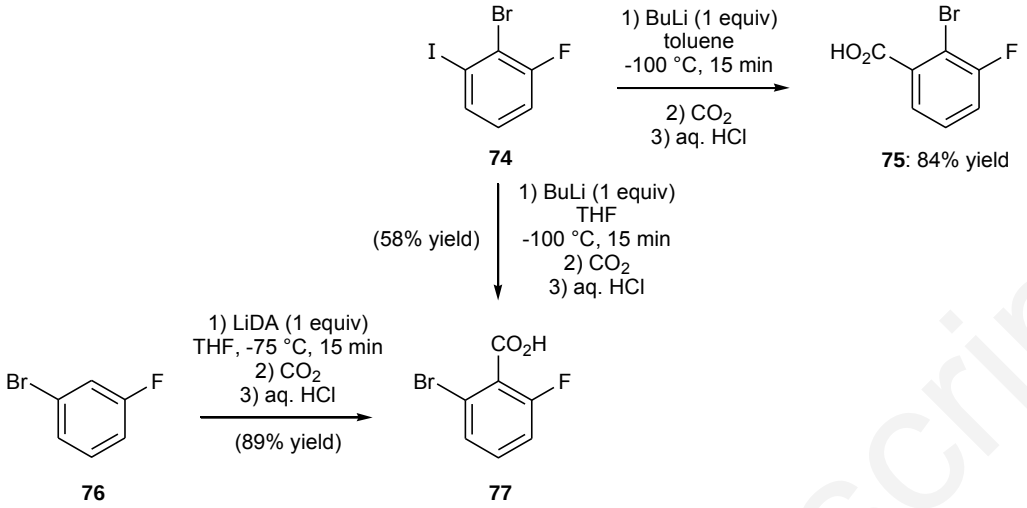
71 **72** **73a**: 78% yield **73b**: 11% yield

Scheme 22. Bromine migration using fluorine as directing group.

Another trick to impose initial formation of 2-bromo-3-fluorophenyllithium is to start from 2-bromo-1-fluoro-3-iodobenzene (**74**). Indeed, after treatment with butyllithium in toluene at -100 °C, the corresponding 2,3-dihalogenobenzoic acid **75** could be isolated in 84% yield. In contrast, replacing toluene by THF or using *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA) as additive allowed the halogen to migrate, as shown by formation of 2-bromo-6-fluorobenzoic acid (**77**,

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Scheme 23).[28a] This result demonstrates that halogen 'dance' can happen either after deprotolithiation or after halogen/lithium exchange.

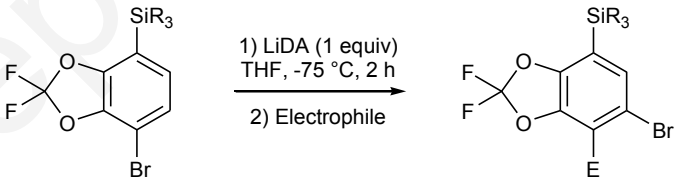


Scheme 23. 'Stop-and-go' bromine migration using fluorine as directing group.

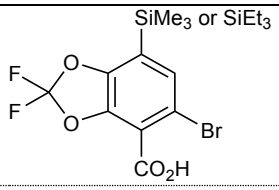
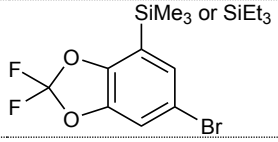
6. Other substituted benzenes

Once protected by a silyl group, 4-bromo-2,2-difluoro-1,3-benzodioxole (**78**) can be isomerized in the presence of LiDA in THF at -75 °C, as evidenced by subsequent carboxylation, neutralization and iodination (products **79a-c**, Table 6). Without protection of the 7 position, this site is regioselectively attacked under similar reaction conditions.[31]

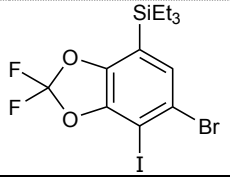
Table 6. Bromine migration using a fluoroalkoxy directing group.



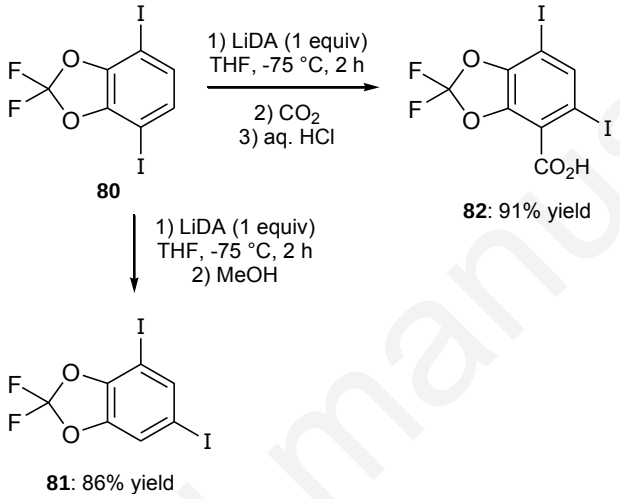
78 **79**

Entry	R	Electrophile	Product, Yield (%)	
1	Me or Et	CO_2 then aq. HCl		**79a**, 82
2	Me or Et	MeOH		**79b**, 86 or 85

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3	Et	I_2		**79c**, 73

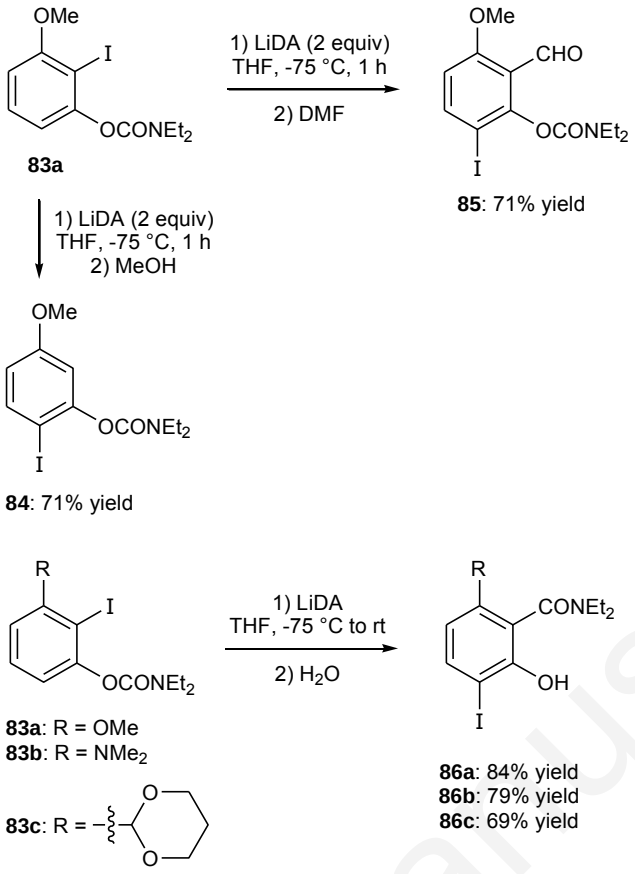
Similarly, starting from 4,7-diiodo-2,2-difluoro-1,3-benzodioxole (**80**), the use of LiDA allowed the heavy halogen to migrate from the 4 to the 5 position (products **81** and **82**, Scheme 24). Since iodine atoms hardly contribute to the stabilization of lithio compounds, when present at the site adjacent to the metal, this result testifies to the acidifying effect of the fluoroalkoxy unit.[31]



Scheme 24. Iodine migration using a fluoroalkoxy directing group.

The 2-iodo-3-methoxyphenyl *O*-carbamate **83a** was also converted into the corresponding 2-iodo-5-methoxyphenyl or the 6-iodo-2-formyl-3-methoxyphenyl *O*-carbamate **84** or **85** in a similar way. By using methoxy (substrate **83a**), dimethylamino (**83b**) and 2-(1,3-dioxanyl) (**83c**) as directing groups, Snieckus and co-workers showed that the aryllithium isomerization proceeds before *ortho* Fries rearrangement, providing 4-substituted 2-hydroxy-3-iodobenzamides (products **86a-c**, Scheme 25).[20]

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Scheme 25. Iodine migration using methoxy, dimethylamino and 2-(1,3-dioxanyl) as directing groups.

7. Conclusion

In the previous parts, we have shown that trifluoromethyl, chlorine, bromine, fluorine, alkoxy, dimethylamino and 2-(1,3-dioxanyl) are groups capable of driving migration of heavy halogens when located onto aryllithiums. Numerous other groups are known to stabilize lithio compounds either by acidification or by metal coordination, and could be used to extend the scope of this halogen 'dance'.

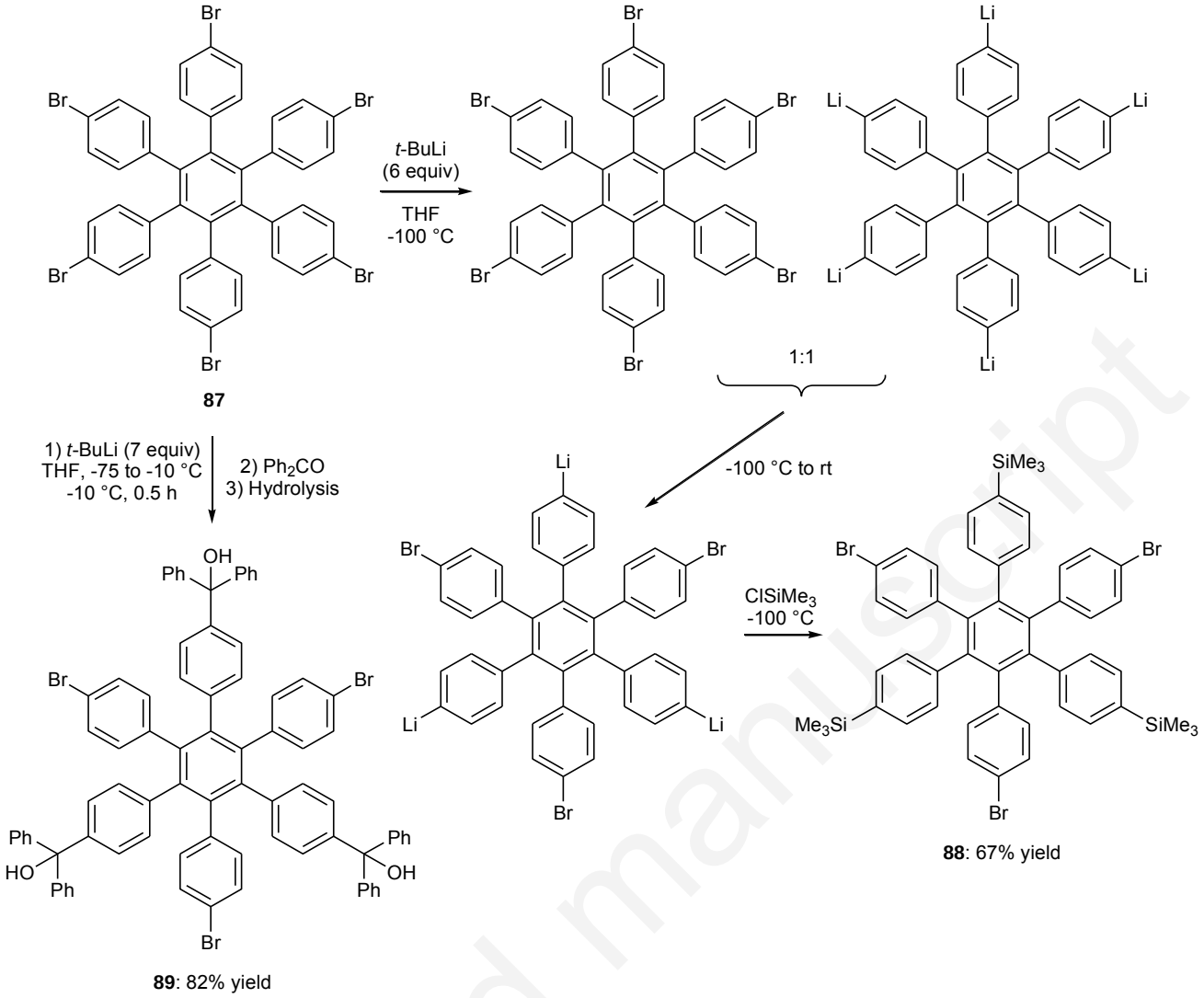
In addition, the concept of basicity gradient-controlled halogen migration can escape not only prior deprotolithiation but also the use of directing groups. For example, Rathore and co-workers in 2004 (Scheme 26, left),[32] as well as Kojima and Hiraoka in 2014 (Scheme 26, right),[33] documented the selective alternate derivatization of C_6-symmetric hexakis(4-bromophenyl)benzene (**87**) by halogen/lithium exchange, provided that the amount of *tert*-butyllithium used is suitably calculated to ensure the formation of trilithiated derivatives. Whereas hexakis(4-lithiophenyl)benzene first

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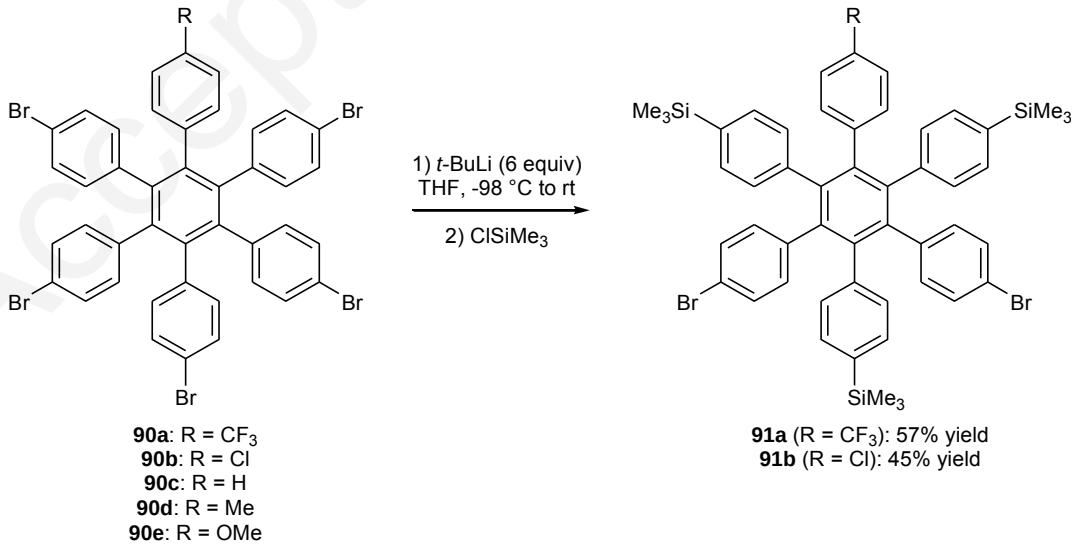
forms in a 1:1 ratio together with the substrate at -100 °C, a result attributed to the slower dissolution rate of the substrate when compared to the rate of the halogen/metal exchange on the dissolved partially lithiated species, the most stable alternate tris(4-bromophenyl)tris(4-lithiophenyl)benzene becomes the main product after warming to rt, as indicated by interception with chlorotrimethylsilane (product **88**).[33]

The different hexaphenylbenzenes **90a-e** possessing one substituent (CF_3, Cl, H, Me or OMe) and five bromine atoms were involved in reactions using similar conditions of trilithiation. As advanced by Winkler, for which the equilibria between aryllithiums and aryl bromides favor the formation of the organolithiums containing the more electron-withdrawing groups,[34] the higher alternate selectivity was noted when trifluoromethyl and chlorine were employed (products **91a**,**b**, Scheme 27). The authors suggested a through-space interaction at the *ipso* carbons to rationalize the impact of the peripheral substituents on the stability of the trilithiated derivatives.[33]

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Scheme 26. Bromine migration without directing group.



Scheme 27. Bromine migration without directing group.

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By equilibrating aryllithiums with the corresponding brominated or iodinated arenes, the relative basicities/stabilities of aryllithiums bearing five different substituents (methoxy, chlorine, fluorine, trifluoromethyl and trifluoromethoxy) at the *ortho*, *meta* and *para* positions were assessed.[35] These thermodynamic substituent effects on aryllithiums correlate well with the kinetic substituent effects determined on a large range of substrates on the almost reversible bromine/metal permutation with *i*-PrMgCl.[36] In the present examples (Schemes 26 and 27), the electron transfer from the lithiated phenyls to the group-substituted phenyls through σ/π polarization has an important impact on the stabilization of the lithio derivatives, and decreases as follows: Br ~ CF_3 > Cl >> H > Me > OMe. In addition, such a stabilization is more efficient in the case of the alternate tris(4-substituted phenyl)tris(4-lithiophenyl)benzene, each lithiated moiety being stabilized by two adjacent 4-substituted phenyl rings.[33]

As the heavy halogens transferred can be used for numerous subsequent functionalizations (e.g. transition-metal-catalyzed couplings),[26,28b] this stability-driven heavy halogen migration is a useful tool that extends the boundaries of arene deprotolithiation toward molecular diversity.

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Biographical sketch



William Erb obtained his PhD in organic synthesis in 2010 under the supervision of Pr. Jieping Zhu on total synthesis and metal-catalyzed reactions. During the next 4 years of post-doctoral studies he works in various laboratories on different research projects (University of Bristol, Pr. Varinder Aggarwal - ESPCI, Pr. Janine Cossy - LCMT, Pr. Jacques Rouden - COBRA, Pr. Géraldine Gouhier, Rouen). He was appointed assistant professor at the University of Rennes in 2015 where he is working on the development of stereoselective syntheses of ferrocenes and their applications.



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