The Organometallic Approach to Molecular Diversity − Halogens as Helpers

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Strategies to functionalize simple, though structurally challenging, compounds in regiodivergent manner are outlined. The starting materials are inexpensive (5–500 €/mol) arenes or heterocycles bearing heterosubstituents such as Cl, F, CF_3, OCF_3, and OCH_3. A metal is introduced at the targeted position either by direct hydrogen/metal exchange or, if this is not feasible, by use of organometallic precursor species as relay stations. The derivatives thus produced are versatile intermediates that may be employed as building blocks for further elaboration or even as scaffolds in combinatorial synthesis.

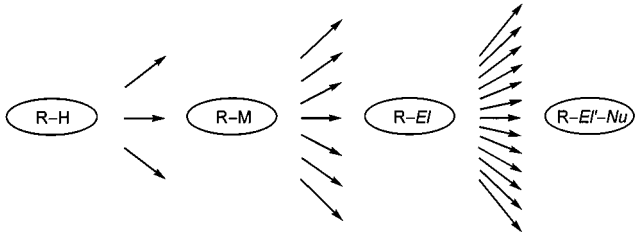
When the work summarized below was started a decade ago, it lacked focus and perspective. Having been pursued only hesitantly and sporadically for quite a while, it has gained momentum only in very recent years. In other words, most of the results reported here still need to be published in detail.

1. The Goal: Multidirectional Elaboration of Core Structures

High-throughput screening[1−2] and more recent offshoots such as DNA-[3−4] and protein-binding[5−6] arrays exhibit a voracious appetite for new organic molecules. Suddenly it looked as if the supply of untested chemical entities would become the bottleneck in the drug discovery chain. Combinatorial synthesis[7−14] was the timely and convincing answer.

However, despite its undeniable merits, this method did not become entirely popular in academic circles. It requires special equipment for automated operation and special expertise relating to solid supports, but relies mainly on standard reactions. In short, combinatorial chemistry has only limited instructive value for undergraduate and graduate students seeking an all-round training.

Is there a didactically more valid, even if technically inferior, approach to molecular diversity? Our laboratory team believes it has identified such a possibility, based on the singular reactivity profile of polar organometallic species.[15] These are known to combine with virtually any kind of carbo- or heterofunctional entity, as long as it is delivered by a suitable electrophile. The functional group (*El*) thus attached to the core structure can be further modified by condensation with a huge variety of nucleophiles, by conversion of, for example, carboxylic acids into esters, carboxamides, nitriles, hydroxamic acids, or amidines (R-*El* → R-*El′*-*Nu*, Scheme 1).



Scheme 1. Breeding molecular diversity by regiodivergent product scattering at three consecutive stages: metalation of a core structure, electrophilic substitution, and possible nucleophilic derivatization

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Professor Schlosser was born in 1934 in Ludwigshafen (Germany). He studied chemistry and, to some extent, medicine, at the University of Heidelberg, graduating in 1957. He carried out his thesis work under the supervision of Professor Georg Wittig and received his doctor's degree in 1960. After a research year in Brussels and his "Habilitation" in Heidelberg (1966), he accepted the position of a group leader ("Oberarzt") at the German Cancer Research Center in Heidelberg. In 1971 he was appointed as the successor to Professor Jiři Sicher at the University of Lausanne. He has lectured as a visiting professor in Italy (Perugia; Firenze), Germany (Berlin), Hungary (Budapest), USA (San Jose; Santa Barbara), and Japan (Kyoto). His research work is characterized by an intimate interplay between novel mechanistic insight and synthetic applications. He coordinates a European network of research in the organofluorine area and is author or editor of three books on organometallic chemistry, a second edition of the most recent one having been released this year ("Organometallics in Synthesis: A Manual", Wiley, Chichester, 2001).

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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Evidently it is not at all difficult to trap an organometallic intermediate with a variety of electrophiles and thus to transform it into an entire population ("library") of first-generation derivatives. Moreover, each of these may itself evolve into a broad range of second generation derivatives through straightforward modification of functional groups. The real problem is at the very beginning. Reductive or permutational halogen/metal exchange, of course, allows an alkali metal to be delivered to any position as long as the latter bears a bromine or iodine atom. However, the introduction of such an element is often complicated and sometimes even impossible, while the direct replacement of a hydrogen atom by a metal is generally confined to the most acidic site. If one wishes to escape such restrictions, one has to learn how to maneuver.

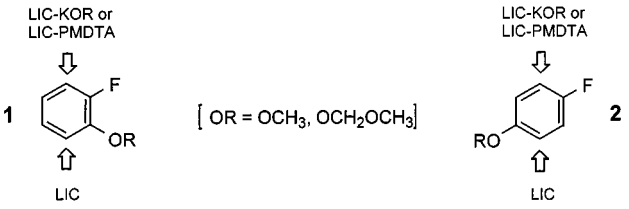
2. Playing Tricks

If one could manage to generate three, four or half a dozen regioisomerically different organometallic intermediates from one and the same starting material (as suggested by Scheme 1), one could legitimately call the entire cascade of derivative formation *Shrapnel reaction sequences*. (Shrapnel's ammunition, used throughout the 19th century, were artillery shells that exploded close to the enemy, though still in the air, and scattered ball-like metallic fragments in many directions.) To achieve such regiodivergency, any of three "tricks", or a combination of them, may be relied on. This means that we have identified three standard reactivity patterns offering opportunities to alter the regioselective outcome of a hydrogen/metal interconversion in a predictable way. As outlined below, we have explored and exploited these systematically.

2.1 Optional Site Selectivity

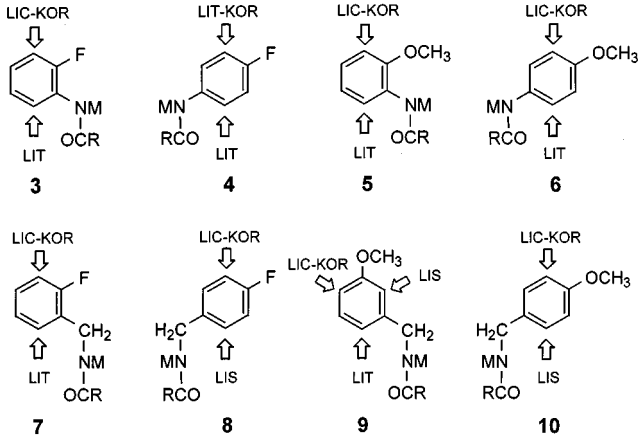
Whatever the base, it may be expected to abstract a proton from the 'most acidic' position of a *CH*-acid. This assumption, though plausible at first sight, has proven to be incorrect in numerous cases. The formation not of the least basic organometallic species, but of a regioisomerically different one, has often been found to be kinetically favored. This has resulted in the concept of *optional site selectivity through mechanism-based substrate reagent matching*.[16]

The first clearcut example of this type has gained the rank of a model. 2- and 4-Fluoroanisole (**1** and **2**, respectively) readily undergo metalation at a halogen-adjacent position when either the superbasic mixture ("LIC-KOR") of butyllithium ("LIC") in the presence of potassium *tert*-butoxide ("KOR") or butyllithium activated with *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine ("PMDTA") act as the base.[17] Butyllithium alone, however, exclusively attacks the position adjacent to oxygen[17] (Scheme 2). In the latter instance, coordination to the better donor atom at the transition state outweighs the acidity-enhancing effect of the more electronegative substituent and lowers the activation energy more significantly. More recently, the same sort of optional site selectivity was established with *O*-methoxymethoxy-protected 2- and 4-fluorophenol.[18]



Scheme 2. Optional site selectivity: proton abstraction at will from positions adjacent to either oxygen or fluorine

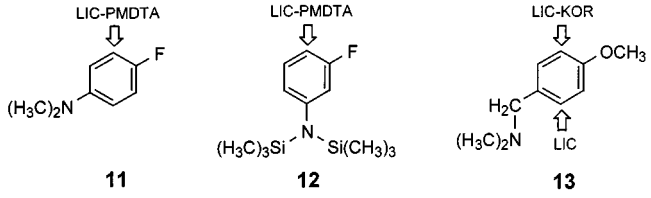
N-*tert*-Butoxy-protected [R = $OC(CH_3)_3$] 2- and 4-fluoroanilines[19] (**3** and **4**) and 2- and 4-anisidines[20] (**5** and **6**) give rise to the same type of adjustable regioselectivity. With *sec*-butyllithium ("LIS") and *tert*-butyllithium ("LIT"), metalation occurs in the immediate vicinity of the nitrogen substituent, while with the butyllithium/potassium *tert*-butoxide mixture it takes place next to the more electronegative heterosubstituent, fluorine or oxygen (Scheme 3). Fluoro- or methoxy-substituted benzylamines (**7**−**10**) can also be made to undergo deprotonation at two different positions. With those substrates, however, reagents and protective groups have to be fine-tuned simultaneously. When carbamates [*N*′-2- and -4-fluorobenzyl-*N*,*N*-dimethylurea and *N*′-3- and -4-methoxybenzyl-*N*,*N*-dimethylurea; R = $N(CH_3)_2$] are treated with *sec*-butyllithium, metalation occurs at the position nearest to nitrogen, whereas the corresponding *O*-*tert*-butyl carbamates [R = $OC(CH_3)_3$] react at a nitrogen-remote site[21] (Scheme 3).



Scheme 3. Optional site selectivity: regioadjustable metalation of fluoro- and methoxy-substituted *N*-acylanilines and *N*-acylbenzylamines (M = Li or K, depending on the reagent used)

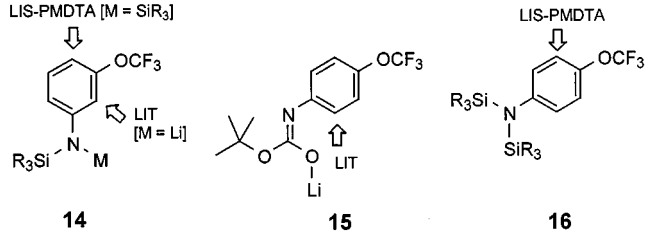
Dialkylamino groups exert only a rudimentary *ortho*-directing effect. Upon treatment with organometallic reagents, 4-fluoro-*N*,*N*-dimethylaniline (**11**) reacts only at the halogen-adjacent position[19] (Scheme 4). *N*,*N*-Dimethyl-*m*-anisidine gives an approximately 9:1 mixture of 2- and 4 deriv-

atives when treated consecutively with butyllithium, benzophenone, and acid.[22,23] A more rigorous steric shielding of the nitrogen surroundings can be achieved by bissilylation of an aniline. 3-Fluoro-*N*,*N*-bis(trimethylsilyl)aniline (**12**) reacts smoothly with PMDTA-activated butyllithium at the 4-position[19] (Scheme 4). 4-Methoxy-*N*,*N*-dimethylbenzylamine (**13**) is lithiated exclusively at the 2-position by butyllithium in diethyl ether at 25 °C[22,24] (Scheme 4). In the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine,[22] however, the 2- and 3-lithiated intermediates are formed in a 1:3 ratio (46%, after trapping with dimethyl sulfate, by gas chromatography[25]). The LIC-KOR superbase in tetrahydrofuran (THF) at −75 °C promotes deprotonation at the 3-position exclusively (71% of trimethylsilylation product, Scheme 4).[25]



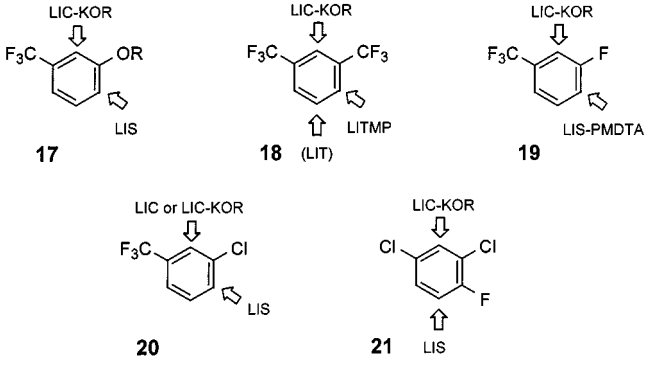
Scheme 4. Optional site selectivity: regiodivergent metalation of 4-fluoro-*N*,*N*-dimethylaniline, 3-fluoro-*N*,*N*-bis(trimethylsilyl)aniline, and 4-methoxy-*N*,*N*-dimethylbenzylaniline

The bulky bis(trialkylsilyl)amino entity also efficaciously shields the positions adjacent to nitrogen in 3-trifluoromethoxy-*N*,*N*-bis(trimethylsilyl)aniline [**14**, M = $Si(CH_3)_3$, R = CH_3] while orienting the attack of PMDTA complexed *sec*-butyllithium to the 4-position (69% carboxylation product), whereas the mono(trimethylsilyl) analogue (**14**, M = Li, R = CH_3) reacts exclusively at the 2-position (33% of the corresponding acid isolated).[26] Similarly, 4-trifluoromethoxy-*N*,*N*-bis(trimethylsilyl)aniline [**16**, R = CH_3] is cleanly deprotonated at a position adjacent to the oxygenated substituent (48% of the acid upon trapping), but *N*-*tert*-butyloxycarbonyl-protected (BOC-protected) 4-(trifluoromethoxy)aniline (**15**) undergoes *C*-metalation solely in the direct vicinity of the nitrogen function (Scheme 5).[26]



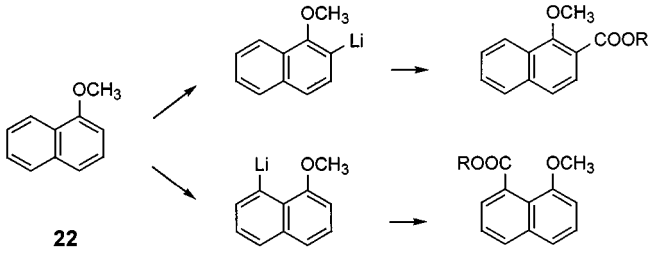
Scheme 5. Optional site selectivity: steric congestion by trialkylsilyl groups to direct metalations from a position adjacent to nitrogen to one remote from nitrogen

Trifluoromethyl- and chloro-substituted substrates often exhibit optional site selectivities. The *O*-methoxymethoxy-protected 3-(trifluoromethyl)phenol (**17**; OR = OCH_2OCH_3),[18] 1,3-bis(trifluoromethyl)benzene,[27,28] 3-fluorobenzotrifluoride,[27,29] 3-chlorobenzotrifluoride,[30] and 2,4-dichloro-1-fluorobenzene,[31] when treated with the superbase, invariably undergo deprotonation at the position flanked by the two acidifying electronegative groups (Scheme 6). On the other hand, *sec*-butyllithium or lithium 2,2,6,6-tetramethylpiperidide ("LITMP") preferentially, if not exclusively, attack the CF_3-remote 4-position [18,27−30] (Scheme 6). 1,3-Bis(trifluoromethyl)benzene (**18**) not only undergoes selective hydrogen/metal exchange at the 2- and 4-positions with LIC-KOR and LITMP, respectively, but also attack concomitantly at the 4- and 5-positions when *tert*-butyllithium is used as the base[27] (Scheme 6). These last findings underscore the relative bulkiness of the trifluoromethyl group as well as its far-reaching activating effect, which is scarcely attenuated by increasing distance. The LIC-KOR superbase deprotonates 3-fluorobenzotrifluoride (**19**) exclusively at the doubly activated 2-position,[27] whereas PMDTA complexed *sec*-butyllithium metalates the 2- and the 4-positions in a ratio of 1:4.[28,29] 3-Chlorobenzotrifluoride (**20**) reacts with butyllithium, either in the presence or in the absence of potassium *tert*-butoxide, at the 2-position and with *sec*-butyllithium at the 4-position.[30] A proton is abstracted from the 3-position of 2,4-dichloro-1-fluorobenzene (**21**) when the superbase is employed (at −75 °C), and from the 6-position when *sec*-butyllithium is used (at −100 °C), the corresponding derivatives being isolated after carboxylation in 74 and 92% yields, respectively, and with regioselectivities exceeding 99% [31] (Scheme 6).



Scheme 6. Optional site selectivity: regiodivergent metalation of 1-methoxymethoxy-3-(trifluoromethyl)benzene, 1,3-bis(trifluoromethyl)benzene, 3-fluoro- and 3-chlorobenzotrifluoride, and 2,4-dichloro-1-fluorobenzene

Years ago, 1-methoxynaphthalene (**22**) featured as the setting for a particularly striking case of optional site-selectivity (Scheme 7). TMEDA-activated butyllithium in cyclohexane was claimed to produce the 2- and 8-metalated intermediates in a 99.7:0.3 ratio, whereas a 1:99 ratio was reported to result if *tert*-butyllithium was employed as the reagent.[32] If these data were exact, the sum of the two differences in free activation energies ($\Delta\Delta G^{\ddagger}$) would total more than 6 kcal/mol. These spectacular data were shown to be false by a recent reinvestigation based on gas chromatographic analysis of the methyl esters (OR = OCH_3). The ratios found with butyllithium/TMEDA and with *tert*-butyllithium were 88:12 and 13:87, respectively.[33,34]

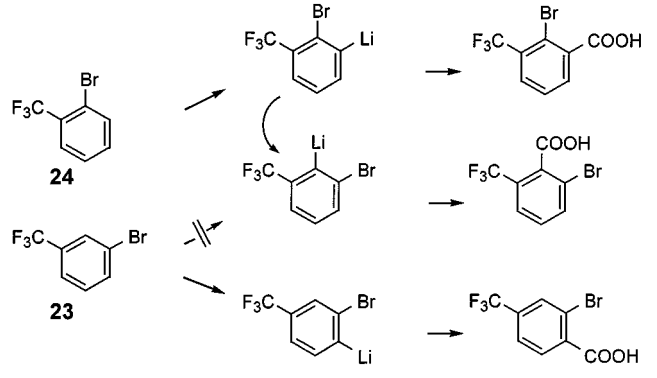


Scheme 7. No practically useful optional site selectivity: the metalation of 1-methoxynaphthalene with butyllithium or *tert*-butyllithium in hydrocarbon media

Competition for metalation between benzylic and aromatic positions[35] is not covered in this review. It should nevertheless be kept in mind that many alkylarenes may give rise to various regiochemical complications. If a heterosubstituent occupies a *meta*-position, as in 3-fluorotoluene[36] or 3-methylanisole,[37] a proton may be abstracted either from an alkyl-adjacent or an alkyl-remote site. Bulky reagents discriminate more rigorously against the sterically hindered angular position. Thus, 3-fluorotoluene is metalated at the 4- and 2-positions in ratios of 9:1 and $\geq$ 99:1, depending on whether LIC-KOR or LIT-KOR (the superbasic mixture composed of *tert*-butyllithium and potassium *tert*-butoxide) is employed as the base.[36]

2.2 Halogen Shuffling

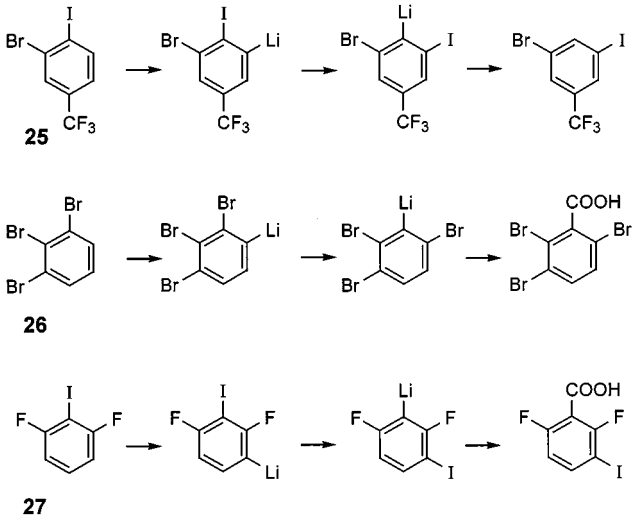
For avoidance of halogen/metal interconversion, only lithium dialkylamides are suited for the promotion of hydrogen/metal exchange with bromoarenes as substrates. Bulky reagents such as lithium diisopropylamide (LIDA) and lithium 2,2,6,6-tetramethylpiperidide (LITMP), being more powerful, are generally employed. Because of steric hindrance, 3-bromobenzotrifluoride (**23**) affords 2-bromo-4-(trifluoromethyl)phenyllithium rather than 2-bromo-6-(trifluoromethyl)phenyllithium.[30] The latter intermediate, obviously the least basic of the entire series, can nevertheless be obtained indirectly. When treated with LITMP at −100 °C, 2-bromobenzotrifluoride (**24**) undergoes clean lithiation at the 6-position.[30] A rise in temperature to −75 °C results in the complete isomerization of the original species to 2-bromo-6-(trifluoromethyl)phenyllithium[30] (Scheme 8). A



Scheme 8. Three organolithium species from two precursors: the indirect isomerization of 2-bromo-3- to 2-bromo-6-(trifluoromethyl)phenyllithium

small amount of incidentally formed 2,3-dibromobenzotrifluoride appears to act as a turntable, allowing lithium and bromine to swap places in the framework of a halogen/metal exchange mechanism.[30]

In general, halogen migration has already started before *ortho*-lithiation is complete. In that case, not the initial but only the isomerized organometallic intermediate can be trapped by the selected electrophile [*El*-X = H_2O, D_2O, CO_2, etc.]. The conversions of 3-bromo-4-iodobenzotrifluoride (**25**) into 3-bromo-5-iodobenzotrifluoride (82%, after neutralization) with LIDA,[38] of 1,2,3-tribromobenzene (**26**) into 2,3,6-tribromobenzoic acid (Li*t*BSA; 50% after treatment with dry ice) with lithium *tert*-butyl(*tert*-butyldimethylsilyl)amide,[38,39] and of 1,3-difluoro-2-iodobenzene (**27**) into 2,6-difluoro-3-iodobenzoic acid (31%) with LITMP[40] represent typical examples (Scheme 9).



Scheme 9. Halogen shuffling in arenes: preconceived counter-current migration of bromine or iodine and lithium

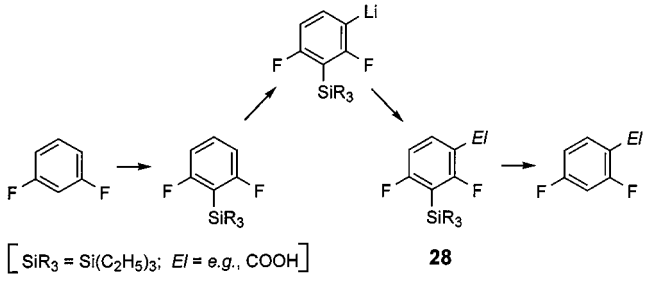
Base-promoted halogen migrations, discovered in the 1950s,[41] were systematically explored by J.F. Bunnett et al.,[42−44] who also coined the euphemistic term of a "halogen dance". Since all these early studies used only moderately strong bases, and sometimes even only catalytic amounts of them, they lacked the driving force to push an organometallic transformation in the direction dictated by a basicity gradient. The halogen atoms were therefore in reality just "scrambled", intra- and intermolecularly redistributed to produce regioisomers of the starting material and also homologues containing a smaller or larger number of halogen atoms. Several synthetically useful base-promoted halogen displacements have previously been reported in the area of five-membered and six-membered heterocycles. 5-Bromo-3-methylisothiazole,[45] 5-bromo-3-methyl-1-phenylpyrazole,[46] 2-bromo-5-methylthiophene,[47−49] 2,3-dibromothiophene,[50−53] 2,5-dibromothiophene,[54] 2,3,5-tribromothiophene,[55] 2-bromo-5-methylfuran,[56,57] 2,3- and 2,5-dibromofuran,[56,57] 3-bromo-2-fluoropyridine,[58] 3-bromo-2-chloropyridine,[59] 3-fluoro-4-iodopyridine,[59] 2-chloro-3-fluoro-4-iodopyridine,[59] and 3-fluoro-4-

iodoquinoline[60] have all been found to isomerize cleanly after metalation.

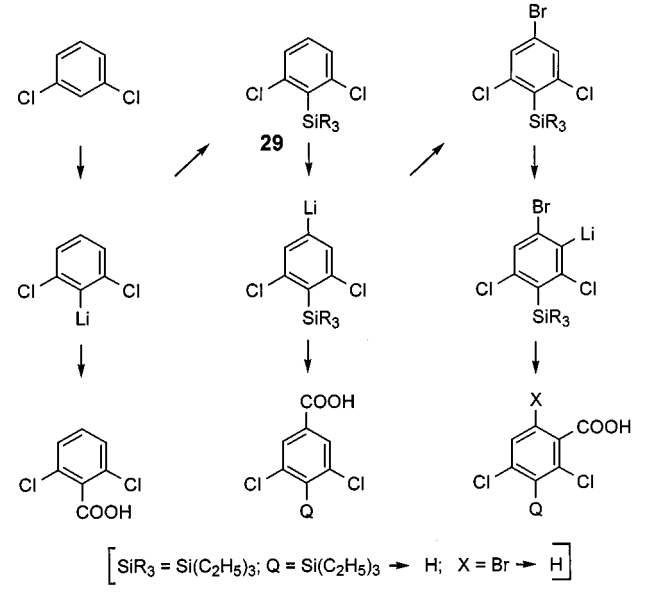
2.3 "Protection" of Carbon-Bound Hydrogen

If optional site-selectivity and basicity-driven halogen shuffling fail to outwit the thermodynamically most acidic position of the substrate, there remains one last chance, which appears at the same time to be the most obvious one. One merely has to bow to the inevitable, deprotonate the most reactive site, and then block it with an atom or group electronegative and slim enough to activate its immediate vicinity for a further deprotonation. The desired electrophilic substitution accomplished, all that remains to be done is to remove the temporary substituent.

The doubly activated angular position in 1,3-dihalobenzenes can also be advantageously protected by a trialkylsilyl group,[39,61,62] as already suggested in another context.[63–65] The electrophilically substituted derivative, for example 2,4-difluoro-3-(triethylsilyl)benzoic acid[62] (**28**), can be desilylated by treatment with strong acids or bases, or, as still another possibility, with anhydrous fluorides (yield: 65% overall; Scheme 10).



Scheme 10. Hydrogen "protection": reorienting the hydrogen/metal exchange in 1,3-difluorobenzene from the silyl-blocked 2-position to the 4-position



Scheme 11. Hydrogen "protection": reorienting the metalation of 1,3-dichlorobenzene from the 2- to the 5-position

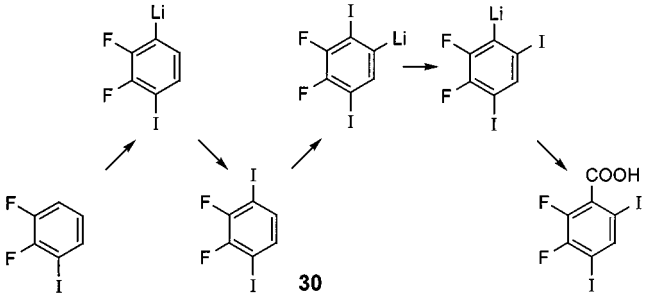
The same proceeding applied to 1,3-dichlorobenzene, resulted in the discovery of an unprecedented remote metalation. (2,6-Dichlorophenyl)trimethylsilane[61] and (2,6-dichlorophenyl)triethylsilane[62] (**29**; 89%) are attacked by *sec*-butyllithium exclusively at the 5-position (carboxylation: 71%; bromination: 63%; subsequent carboxylation followed by desilylation: 93%; Scheme 11). We attribute the inaccessibility of the halogen-adjacent *ortho* positions to the intervention of a buttressing effect.[66–68]

3. Case Studies

Arenes are the most privileged arena in which to create molecular diversity. Heterocycles, five-membered ones in particular, have only a reduced number of vacant sites available, and hence a limited number of options. There are nevertheless lots of opportunities to be exploited, as demonstrated in the second and third subsections.

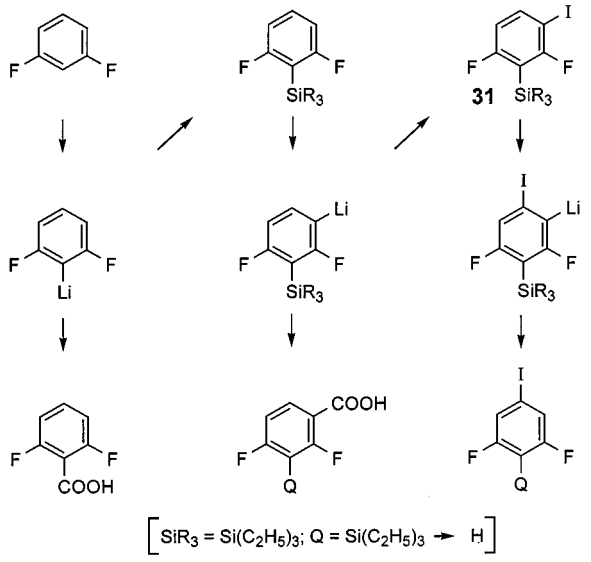
3.1 Manipulation of Arenes

Iodine being arguably the least acidifying electronegative substituent, the deprotonation of 2,3-difluoro-1,4-diiodobenzene (**30**; 87%) by LITMP proceeds only sluggishly. Even so, it does occur and the first organometallic intermediate thus generated instantaneously isomerizes to the less basic isomeric species, which can be trapped by carboxylation[40] (72%; Scheme 12). If it is protonated instead, the resulting 1,2-difluoro-3,5-diiodobenzene can be submitted to a halogen/metal permutation, which takes place selectively at the 3-position, this site benefiting from the activation provided by the vicinal fluorine atom.[38]



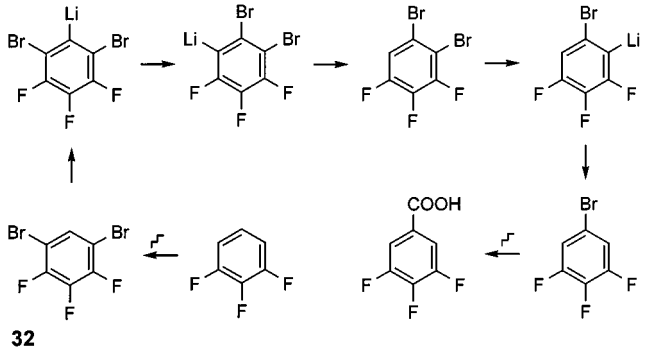
Scheme 12. Halogen relocation: LITMP-mediated iodine migration in 2,3-difluoro-1,4-diiodobenzene

As already mentioned (see Subsection 2.3 above), substituents can readily be introduced into 1,3-difluorobenzene, first at the 2-position and then, after protection by a trialkylsilyl group (yield: 89%), at the 4-position. In this way, 1,3-difluoro-4-iodo-2-(triethylsilyl)benzene (**31**) is readily obtained (yield: 76%). LIDA deprotonates it rapidly and reversibly at the vacant position adjacent to the fluorine and, more sporadically, next to the iodine. In the latter case, immediate migration of the heavier halogen from the 4- to the 5-position ensues. After neutralization and desilylation, 1,3-difluoro-5-iodobenzene is isolated (32%). It can be converted into 3,5-difluorobenzoic acid by halogen/metal exchange and carboxylation.[62] (Scheme 13).



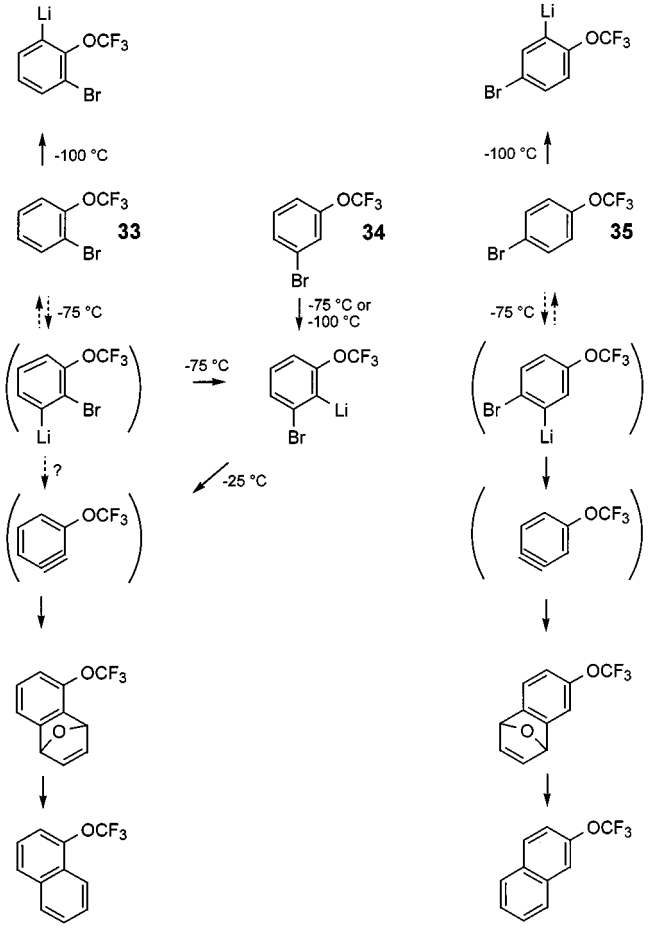
Scheme 13. Protection, halogen migration, and deprotection: the conversion of 1,3-difluorobenzene into 1-iodo-3,5-difluorobenzene

Our favorite "hydrogen protective group" is bromine, since it efficaciously facilitates further *ortho*-lithiation and, in addition, can easily be reductively eliminated using tributyltin hydride, elemental metals, or organolithiums. To illustrate the principle, we have converted 1,2,3-trifluorobenzene into 1,5-dibromo-2,3,4-trifluorobenzene (**32**; 87%).[62] Treatment of the latter with lithium diisopropylamide (LIDA) followed by neutralization gave 2,6-dibromo-3,4,5-trifluorobenzene (86%).[62] After purification, this was submitted to site-selective halogen/metal exchange with butyllithium, followed by quenching with methanol, a further halogen/metal exchange, carboxylation, and neutralization to afford 3,4,5-trifluorobenzoic acid[62] (yield 50% with respect to 1,2-dibromo-3,4,5-trifluorobenzene; Scheme 14).



Scheme 14. Double protection, bromine migration, selective single deprotonation: from 1,2,3-trifluorobenzene through 1,5-dibromo-2,3,4-trifluorobenzene to 5-bromo-1,2,3-trifluorobenzene

According to ab initio calculations[69] at the MP2 level of theory, the trifluoromethoxy substituent belongs to the most powerfully electron-withdrawing groups known. Its outstanding anion-stabilizing capacity is reflected by the extraordinary ease with which (trifluoromethoxy)benzene[70] and its derivatives[26] undergo hydrogen/metal exchange reactions. Thus, LIDA rapidly deprotonates 2-, 3-, and 4-trifluoromethoxy-1-bromobenzene (**33**–**35**) at an oxygen-adjacent position even at −100 °C, as evidenced by high-yield electrophilic trapping[26] (73–82% upon carboxylation; Scheme 15). However, if the mixture containing (together with diisopropylamine) 3-bromo-2-(trifluoromethoxy)phenyllithium is allowed to reach −75 °C, a reversible transmetalation sets in, generating minute stationary concentrations of 2-bromo-3-(trifluoromethoxy)phenyllithium, which either eliminates lithium bromide directly or isomerizes first to 2-bromo-6-(trifluoromethoxy)phenyllithium, a species that can be produced in a more straightforward way by lithiation of 1-bromo-3-(trifluoromethoxy)benzene (**34**) with LIDA. At temperatures around −25 °C, the intermediate loses lithium bromide. If the elimination is carried out in the presence of furan, the dehydroarene ("aryne") thus liberated enters into a Diels–Alder-type [4+2] cycloaddition process to become stabilized as the 1-trifluoromethoxy-1,4-epoxy-1,4-dihydronaphthalene (74%). Zinc-mediated deoxygenation of the latter gives 1-(trifluoromethoxy)naphthalene (71%; Scheme 15), which is readily metalated by *sec*-butyllithium at the 2-position (yield of carboxylation

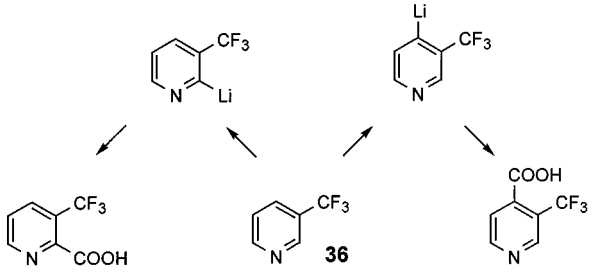


Scheme 15. Competing deprotonation modes with 2-, 3- and 4-(trifluoromethoxy)-1-bromobenzenes: exclusive *O*-adjacent lithiation under irreversible conditions at −75 °C and concomitant deprotonation adjacent to bromine preceding "aryne" formation under reversible conditions at temperatures around −25 °C

product: 80%). Analogously, 1-bromo-4-(trifluoromethoxy)benzene can be converted by way of 2-bromo-5-(trifluoromethoxy)phenyllithium and 1,2-didehydro-4-(trifluoromethoxy)benzene into 2-trifluoromethoxy-1,4-epoxy-1,4-dihydronaphthalene (70%). Reduction of the latter affords 2-(trifluoromethoxy)naphthalene (73%; Scheme 15), which reacts selectively with *sec*-butyllithium at the 3-position by hydrogen/metal exchange (yield: 87% after carboxylation).[26]

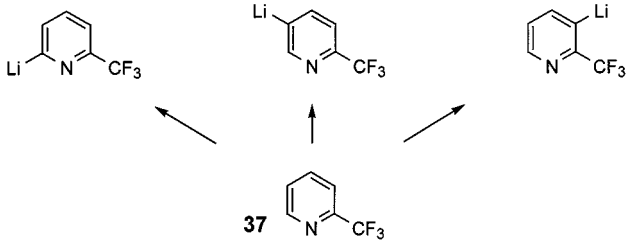
3.2 Manipulation of Pyridines and Quinolines

The butyllithium-promoted metalation of 3-(trifluoromethyl)pyridine (**36**) and a few congeners has been reported by W. Dmowski et al.[71] As we recognized later, selective deprotonation of the 4-position can be accomplished if LIDA is used as the base in tetrahydrofuran at −60 °C (yield: 13% of carboxylation product; Scheme 16).[72]



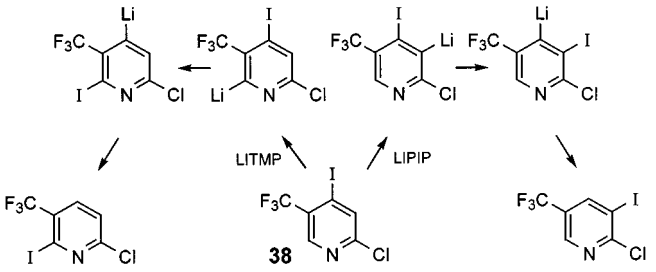
Scheme 16. Optional site selectivity: lithiation of 3-(trifluoromethyl)pyridine at either the 2- or the 4-position

The isomeric 2-(trifluoromethyl)pyridine (**37**) offers an even wider choice of possibilities (Scheme 17). Deprotonation can variously be brought about: selectively at the 3-position by use of LITMP in tetrahydrofuran (73% of carboxylation product), simultaneously at the 5- and 6-positions by use of LITMP in diethyl ether (yields of carboxylic acids: 23% and 18%, respectively), and at the 6-position by use of Caubère's base (butyllithium in the presence of lithium 2-dimethylaminoethoxide; 71% of acid after carboxylation).[72]



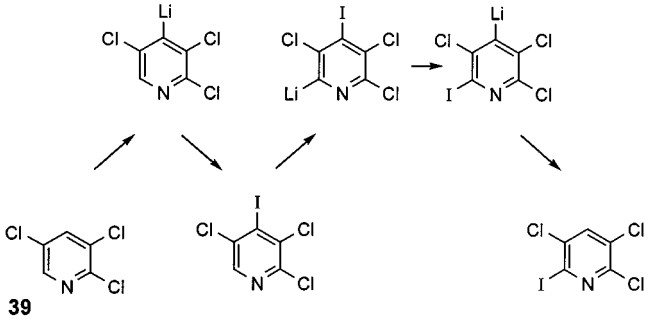
Scheme 17. Optional site selectivity: lithiation of 2-(trifluoromethyl)pyridine at the 3-, 5- or 6-positions

The regioselectivity of the deprotonation step obviously dictates the course of any ensuing halogen migration. In this way, one can understand the different reaction outcomes with 2-chloro-4-iodo-5-(trifluoromethyl)pyridine (**38**), depending on whether lithium piperidide (LIPIP) or LITMP (or LIDA) is employed as the base. After neutralization, 2-chloro-3-iodo-5-(trifluoromethyl)pyridine is isolated in the former case, and the 6-chloro-2-iodo-3-(trifluoromethyl)pyridine isomer in the latter[73] (Scheme 18).



Scheme 18. Optional site selectivity coupled with regiodivergent halogen migration: two-directional isomerization of 2-chloro-4-iodo-5-(trifluoromethyl)pyridine

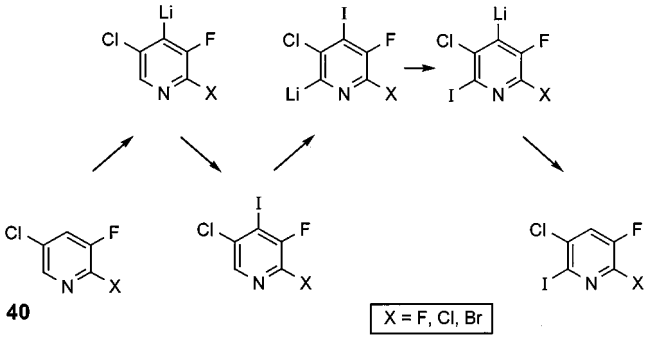
2,3,5-Trichloropyridine (**39**) certainly does not constitute an ideal playground for structural modifications, as from the beginning only two positions are unoccupied. On the other hand, such heterocyclic compounds can be considered as versatile templates for molecular assembly, since halogens in 4- and, even better, 2-positions are extremely prone to substitution by all kinds of nucleophiles. Our attempts to introduce a metal atom alternatively at each vacant position proved successful. Treatment of 2,3,5-trichloropyridine (**39**) with LIDA results in direct lithiation at the 4-position (Scheme 19).[74] Not unexpectedly, the 2,3,5-trichloro-4-iodopyridine obtained upon iodination (yield: 89%) was again found to be labile toward LITMP. Deprotonation followed by migration of the heavy halogen produced an organometallic intermediate, which gave 2,3,5-trichloro-6-iodopyridine upon neutralization (yield: 59%; Scheme 19).[74] 3,5,6-Trichloro-2-pyridyllithium can be generated from the latter compound by butyllithium- or *tert*-butyllithium-promoted halogen/metal exchange (61% of the corresponding acid after carboxylation).[74]



Scheme 19. Halogen shuffling: direct and indirect access to both 2,3,5- and 3,5,6-trichloro-4-pyridyllithium

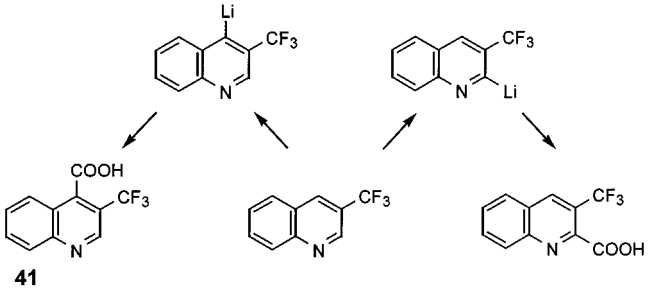
The readily available 2,5-dichloro-3-fluoropyridine (**40**, X = Cl), 5-chloro-2,3-difluoropyridine (**40**, X = F), and 2-bromo-5-chloro-3-fluoropyridine (**40**, X = Br) behave analogously. The first deprotonation invariably occurs exclusively at the 4-position. When the iodination product (yield: 76−84%) is in turn exposed to the action of the base, the heavy halogen shifts to the 6-position, leaving its former location to the lithium (Scheme 20).[74] The resulting organometallic intermediates can be trapped with standard

electrophiles such as water (yield of trihalopyridines: 46−57%) or carbon dioxide (yield of acids: 30−50%).



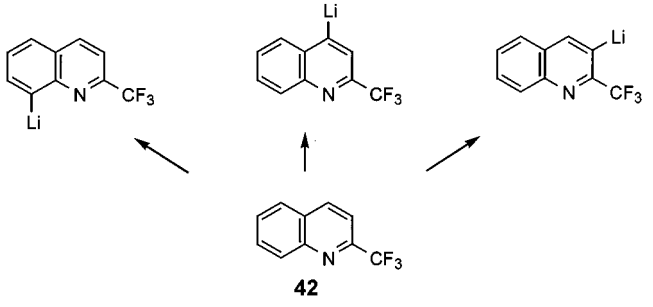
Scheme 20. Halogen shuffling: 2,5-dichloro-3-fluoropyridine (X = Cl), 5-chloro-2,3-difluoropyridine (X = F), and 2-bromo-5-chloro-3-fluoropyridine (X = Br) as starting materials.

Turning now from pyridines to quinolines, certain reactivity features are found to repeat themselves. For example, whether 3-(trifluoromethyl)quinoline (**41**) is attacked at the 2- or at the 4-position depends only on the choice of the base (LITMP or LIDA in tetrahydrofuran; yields after carboxylation: 41% and 32%, respectively; Scheme 21).[72]



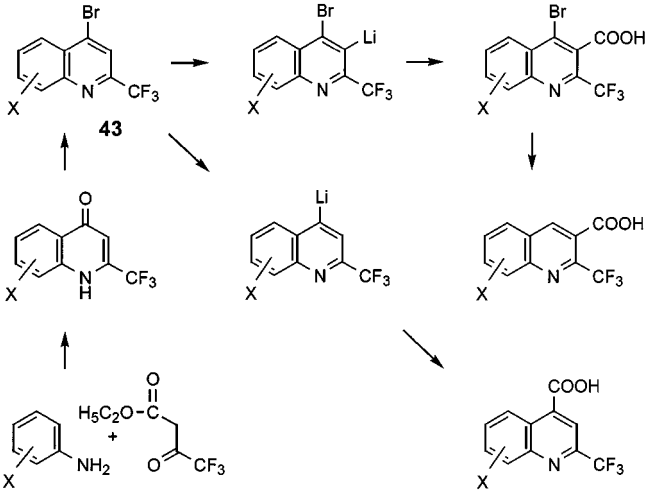
Scheme 21. Optional site selectivity: alternative lithiation of 3-(trifluoromethyl)quinoline at the 2- or the 4-position

The isomeric 2-(trifluoromethyl)quinoline (**42**) even gives rise to three regiochemically distinct organometallic species (Scheme 22). Deprotonation occurs mainly at the 3-position with LIDA in tetrahydrofuran, and at the 4-position with LITMP in tetrahydrofuran (yields of the corresponding carboxylation products: 31 and 27%, respectively), but exclusively at the 8-position with LITMP in diethyl ether (although yields of trapping products are deceptively poor in the last case, amounting to only 20%).[72]

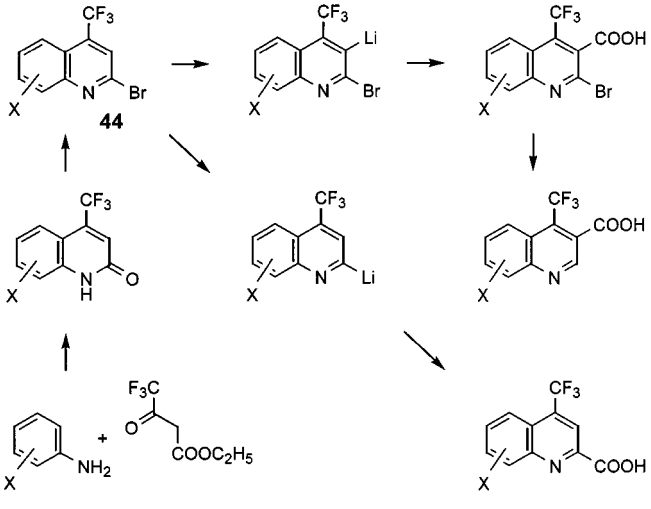


Scheme 22. Optional site selectivity: alternative lithiation of 2-(trifluoromethyl)quinoline at the 3, 4- or 8-positions

The introduction of bromine as both a "protecting" and an activating group still facilitates the juggling with reaction sites. 2-Trifluoromethyl-1*H*-4-quinolones, readily accessible by condensation of aniline or substituted congeners with the inexpensive ethyl 4,4,4-trifluoroacetoacetate, react with phosphorus tribromide to afford the corresponding 4-bromo-2-(trifluoromethyl)quinolines (**43**; 49−88%). Halogen/metal exchange with butyllithium generates 2-trifluoromethyl-4-quinolyllithium, which can then be intercepted by any electrophile such as, for example, carbon dioxide (yield: 57−89%). Another possibility consists of treating the 4-bromo-2-(trifluoromethyl)quinoline with LIDA, which causes proton abstraction from the 3-position (yield of carboxylation products: 62−88%). Finally, bromine may be reductively removed from the products thus obtained (yields of 4-unsubstituted carboxylic acids: 57−68%; Scheme 23).[72]



Scheme 23. Assistance by "hydrogen-protective" groups: controlled functionalization of 4-bromo-2-(trifluoromethyl)quinolines either at the 4- or at the 3-position



Scheme 24. Assistance by "hydrogen-protective" groups: controlled functionalization of 2-bromo-4-(trifluoromethyl)quinolines either at the 2- or at the 3-position

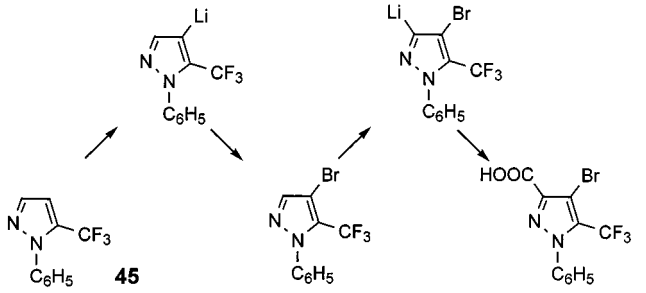
It is possible to proceed in exactly the same way (Scheme 24) when 2-bromo-4-(trifluoromethyl)quinolines (**44**) act as the key intermediates.[75] A relatively minor modification of the working procedure suffices to redirect the condensation between anilines and ethyl 4,4,4-trifluoroacetoacetate from the 4-quinolones shown above to the isomeric 2-quinolones. The same transformations as described in the preceding paragraph then produce 2-bromo-4-(trifluoromethyl)quinolines (**44**; yield: 51−64%), 4-trifluoromethyl-2-quinolinecarboxylic acids (yield: 52−75%), 2-bromo-4-trifluoromethyl-3-quinolinecarboxylic acids (66−89%), and 4-trifluoromethyl-3-quinolinecarboxylic acids (64−67%).[75]

3.3 Manipulation of Pyrazoles

Before any specific class of compounds is addressed, the notorious fragility of deprotonated five-membered heterocycles should be recalled. As long as the metal is attached only to the α-carbon atom, the direct neighbor of the heteroelement in the ring structure, one does not need to worry too much. On the other hand, maintenance of very low temperatures is the only effective precaution that can be taken against the decomposition of β-metalated furans, thiophenes, pyrroles, isooxazoles, oxazoles, triazoles, and tetrazoles by β-elimination, entailing ring-opening to give β-ethynyl or β-cyano enolate-type products.[76] What should also not be overlooked is the ease with which α-metalated heterocycles can mutate by transmetalation either to real β-metalated isomers or to ephemeral incarnations of the latter, in the form of β-elimination-mediating transition states.

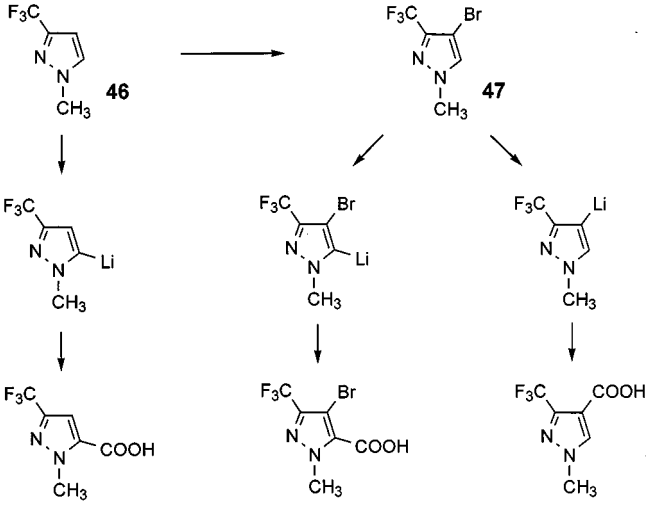
With this as a background, some of the obstacles encountered with 1-phenyl-5-(trifluoromethyl)pyrazole (**45**) should be better appreciated. It nevertheless proved possible to identify suitable conditions for selective organometallic transformations. Unlike the halogen-free congeners 1-benzylpyrazole[77] and 1-propylpyrazole,[78] which are lithiated at the 5-position, substrate **45** readily undergoes hydrogen/metal interconversion at the 4-position. As mentioned above, the reaction temperature has to be kept as low as possible and the metalation time short to prevent excessive ring-opening due to β-elimination. Under such conditions the crucial intermediate can be trapped with electrophiles (such as elemental bromine, in 28% yield, or carbon dioxide). The halogen in 4-bromo-1-phenyl-5-(trifluoromethyl)pyrazole, simultaneously acting as an activating and a protecting group, diverts the base to the 3-position. Neither subsequent functionalization (yield after carboxylation: 11%) nor, if desired, reductive removal of the halogen causes any special problems, although yields are often poor (Scheme 25).[79]

Whoever prepares 1-methyl-5-(trifluoromethyl)pyrazole will receive 1-methyl-3-(trifluoromethyl)pyrazole (**46**) as an extra. Fortunately, the two isomers can readily be separated at the stage of their precursors. This also enabled us to study how the reactivity of such compounds depends on the given substituent pattern. 1-Methyl-3-(trifluoromethyl)-pyrazole can be lithiated at the 5-position with LIDA or butyllithium (yield up to 85% after carboxylation).[79,80]



Scheme 25. Bromine as a "hydrogen-protective" and activating group: shifting the site of deprotonation from the 4- to the 3-position in 1-phenyl-5-(trifluoromethyl)pyrazole

The 4-bromo compound **47** obtained upon bromination reacts with LIDA once more at the 5-position, as evidenced by electrophilic trapping (with carbon dioxide, for example; yield: 89%).[79] With butyllithium, however, a halogen/metal exchange takes place at the 4-position (affording the corresponding acid in 85% yield after carboxylation; Scheme 26).[79]



Scheme 26. 4-Bromo-1-methyl-3-(trifluoromethyl)pyrazole: hydrogen/metal exchange at the 5-position and halogen/metal exchange at the 4-position

As pointed out in the Introduction, the controlled regiodivergent functionalization of core materials constitutes the cornerstone of our Shrapnel sequences concept. The new approach should by no means be considered as a competitor, menacing the triumphant advance of combinatorial synthesis. On the contrary, it supports that approach by providing a great variety of attractive and otherwise inaccessible building blocks.

Acknowledgments

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