Halogen dance reactions—A review

Michael Schnürch, Markus Spina, Ather Farooq Khan, Marko D. Mihovilovic and Peter Stanetty*

Received 21st December 2006
First published as an Advance Article on the web 6th March 2007
DOI: 10.1039/b607701n

Halogen Dance (HD) reactions are a useful tool for synthetic chemists as they enable access to positions in aromatic and heteroaromatic systems for subsequent functionalization which are often difficult to address by other methods, hence, allowing entry to versatile scaffolds. While the method can be extremely useful, this transformation is often neglected upon designing synthetic sequences. This may be largely attributed to the lack of comprehensive reference works covering the general principles and outlining the versatility and limitations of the technique. The following review tries to present HD reactions in a clear and concise manner in order to convince more chemists of its advantages. It covers the field of HD reactions from their first observation in 1951 until the present. The important contributions leading to the elucidation of the mechanism are briefly outlined followed by a detailed mechanistic section and a discussion of factors which influence HD reactions. Finally, an overview of HD reactions on various carbocyclic and heterocyclic ring systems and its applications in the synthesis of complex compounds is given.

1. Introduction

The Halogen Dance (HD) reaction represents a base induced reaction of a haloaromatic compound in which the position of the halogen atom in the product differs from its position in the starting material. Since the first observation of an HD reaction[1,2] several reports of that process have been published[3–6] referring to this transformation by different names such as halogen scrambling, halogen migration, halogen isomerization, halogen dance, or base catalyzed halogen dance (BCHD). The overall conversion can be described by the general equation depicted in Fig. 1.

Initially, researchers were puzzled by this observation and the mechanism was not fully elucidated until the early 1970s. With our current knowledge the mechanism of HD reactions can be easily understood. It consists of a cascade of deprotonation (metal–hydrogen exchange) and metal–halogen exchange reactions ultimately leading to the most stable organometal species. With this insight HD reactions are today a useful synthetic tool which often enable efficient functionalization of positions which are otherwise difficult to address. Moreover, an HD process potentially allows the introduction

Institute of Applied Synthetic Chemistry, Vienna University of Technology, Getreidemarkt 9/163-OC, 1060 Vienna, Austria. E-mail: peter.stanetty@tuwien.ac.at; Fax: +43 1 58801 15499; Tel: +43 1 58801 15440

Michael Schnürch

Michael Schnürch graduated at Vienna University of Technology (VUT) in 2001, and received his PhD from the same university in 2005 under the supervision of Prof. Peter Stanetty conducting research on Pd-catalyzed cross-coupling strategies in thiazole chemistry. He received an Erwin Schrödinger fellowship in 2006 and is currently on a postdoctoral stay at Columbia University in the research group of Prof. Dalibor Sames.

Markus Spina

Markus Spina graduated at VUT in 2002 and has recently completed his PhD thesis in the group of Prof. Stanetty studying halogen dance and cross coupling reactions on oxazoles.

Ather Farooq Khan

Ather Farooq Khan received his MSc from the University of the Punjab, Lahore, Pakistan, in 2001 and is currently working on his PhD thesis in the research group of Prof. Peter Stanetty investigating cross coupling reactions on thiazole.

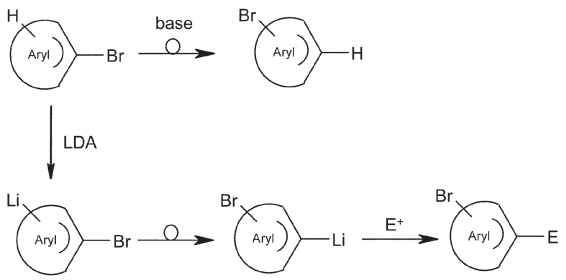
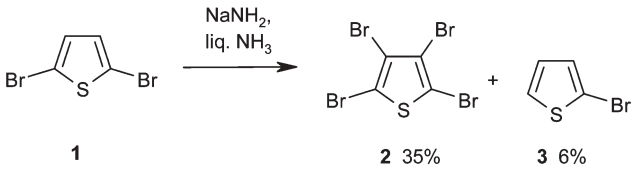


Fig. 1

of an external electrophile at the former position of the halogen by concomitant creation of a new reactive centre at the new position of the halogen (Fig. 1). To enable a versatile application of the methodology, reaction parameters had to be optimized to effectively control the migration process (or prevent it when desired). This required substantial progress in understanding the molecular basis of the reaction, starting with the elucidation of the actual mechanism of HD reactions.

2. Elucidation of the mechanism

In 1951 Vaitiekunas reported isolation of unexpected tetrabromothiophene instead of 2-ethynylthiophene upon reaction of 2-bromothiophene with sodium acetylide in liquid ammonia.[1] Some starting material was recovered and a third tar like fraction was obtained which was believed to be a mixture of di- and tribromothiophenes. Subsequent studies aimed at the investigation of reactions between halogenated thiophenes and sodium amide in liquid ammonia.[2] Using various mono-halo thiophenes as substrates, mixtures of di- and trihalothiophenes were obtained besides recovered starting material. Generally, dibromothiophenes (2,3- or 2,5-) gave tetrabromothiophene and some mono-bromothiophene. For example, starting from excess 2,5-dibromothiophene **1** Vaitiekunas *et al.* isolated up to 35% of tetrabromothiophene **2** and small amounts of 2-bromothiophene **3** (Scheme 1).



Scheme 1

After a series of related observations on various ring systems, it was finally Bunnett who presented the nowadays accepted HD mechanism. He studied reactions of various halobenzenes utilizing different bases (mainly potassium anilide). Initially, he investigated the reaction of 2,4-dibromoiodobenzene **4** with potassium anilide in boiling liquid ammonia (−33 °C) and found the product distribution depicted in Scheme 2.[7]

He was able to rule out an aryne mechanism, maybe the most obvious guess at that time, due to the fact that external halogen ions (*e.g.* from KBr) did not affect the rearrangement process. In addition, within the observed product distribution major compounds were isolated which contradicted the well recognized orientation pattern for the addition of nucleophiles to 3-haloarynes.

Moreover, an aryne mechanism cannot explain the formation of the observed dihalo- and tetrahalo-products. Alternatively, he suggested a mechanism comprising of a series of nucleophilic displacements of phenyl anions on halogen atoms which explained all observed products. Bunnett's hypothesis later became the first correct and ultimately accepted mechanism for an HD reaction.

In a series of articles he summarized his detailed investigations, provided further evidence for his proposed mechanism, and coined the expression of base catalyzed halogen dance (BCHD).[3]

3. The modern mechanism

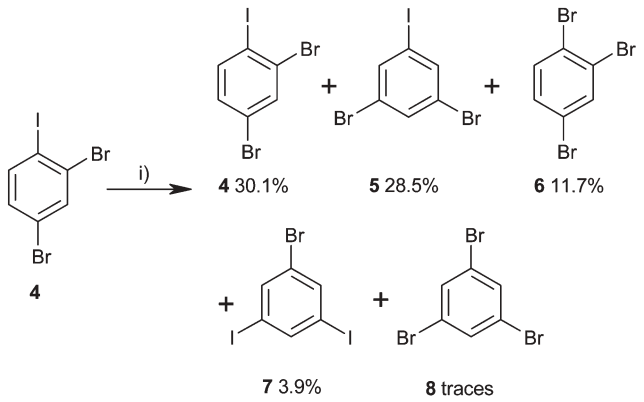
In the following the mechanism of HD reactions will be explained on three simple examples, one for each class of bases which is or was of importance in the context of HD reactions.

Marko D. Mihovilovic

Marko D. Mihovilovic graduated in organic chemistry in 1993 and received his PhD from VUT in 1996. In 1997 he moved to the University of New Brunswick, Saint John, Canada, for a postdoctoral stay within the group of Prof. Margaret M. Kayser as Schrödinger Fellow of the Austrian Science Fund (FWF), followed by a subsequent postdoctoral stay in the group of Prof. Jon D. Stewart at the University of Florida, Gainesville, in 1998. During this time he became strongly acquainted with research in the area of biocatalysis. After his return to VUT, Dr Mihovilovic completed his Habilitation in 2003 in bioorganic chemistry and was appointed Associate Professor in 2004. His current research focuses on enzyme- and metal-assisted methods in bioactive compound and natural product synthesis.

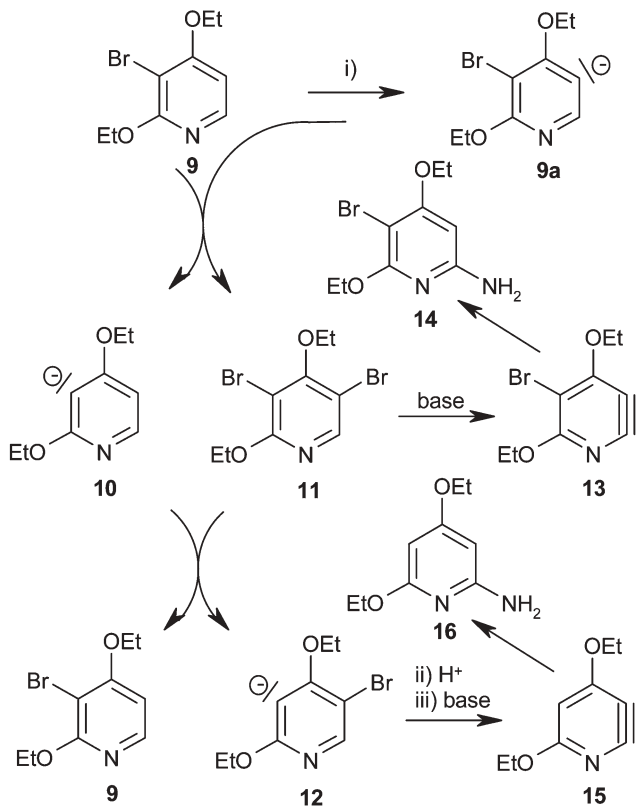
Peter Stanetty

Peter Stanetty graduated in organic chemistry in 1969 and received his PhD from Vienna University of Technology in 1971. He finished his Habilitation in 1981 in the field of heterocyclic spiro compounds and was appointed to Assistant Professor at the Institute of Organic Chemistry in 1983. In 1988 he became Associate Professor and University Professor in 1993. His major research interests cover various aspects of heterocyclic and organometallic chemistry aimed at the synthesis of bioactive compounds for pharmaceutical and agrochemical applications.



Scheme 2 i) C_6H_5NHK in liq. NH_3, reflux, 30 min.

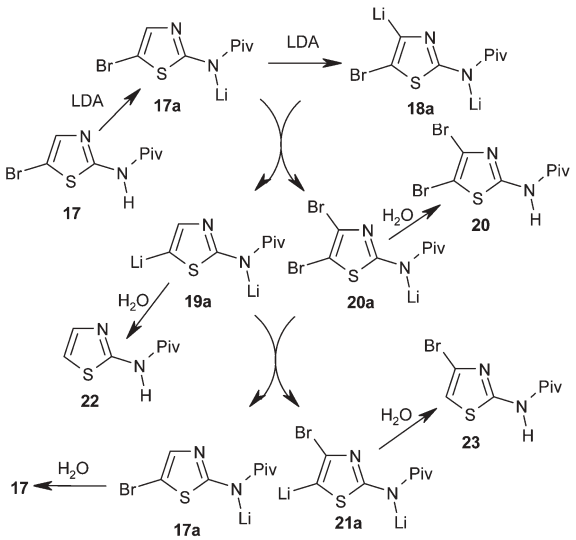
Historically, the first bases applied were amide bases such as KNH_2, $NaNH_2$, or ArNHK and very often liquid NH_3 was the solvent of choice. Such conditions were usually applied in order to obtain aryne formation and initially HD reactions were observed as unwanted side reactions which confronted researchers with puzzling results. In many of these early cases aryne formation and HD operated simultaneously complicating the task of elucidating the HD mechanism. One such case of concomitant aryne formation and HD is depicted in Scheme 3.[8] In fact, in this example aryne formation is only possible if preceded by a halogen migration. Scheme 3 shows one of the first examples where all reaction intermediates of an HD reaction were characterized. This did not lead to the elucidation of the mechanism at that time, however we can now re-visit this example with today's understanding of HD reactions.



Scheme 3

The first step is always formation of an anion, in this particular case through deprotonation of 3-bromo-2,4-diethoxypyridine **9** in 5-position. The resulting anion **9a** can now react with the starting material in a nucleophilic displacement reaction to give 3,5-dibromo-2,4-diethoxypyridine **11** and the newly formed anion **10**. These two species again can react to regenerate starting material **9** and the anion at position 3 of 5-bromo-2,4-diethoxypyridine **12**. Compounds **11** and **12** (after intermediate protonation) now carry a bromine in 5-position which enables aryne formation. After amination of aryne intermediates **13** and **15**, pyridine-2-amines **14** and **16** can be obtained. In conclusion, the complex product distribution can be explained when considering the reaction to proceed *via* an HD mechanism. As it was demonstrated, the HD reaction is an intermolecular process and consequently a dihalogenated species such as **11** is formed from monohalogenated **9**. In fact, such polyhalogenated species further promote the HD reaction and are considered as co-catalysts. Such mediators are usually polyhalogenated species which act as electrophilic halogen donors in HD reactions. The presence of such co-catalysts will always be encountered upon considering the complete HD mechanism. It has to be emphasized that all possible interactions between halogenated species can and do occur during the migration process besides the particular reactions listed above (**9** and **9a**, **10** and **11**, **9** and **12**). However, in those other cases (*e.g.* **11** with **12**) the two species are only interconverted into each other. Additionally, it is of importance that all discussed reaction steps are essentially equilibria. Therefore, depending on the preferred direction of the transformation and the extent of equilibrium position, one product can be formed predominantly or even exclusively as well as mixtures of products can be obtained. In Section 4 it will be discussed how this equilibria can be influenced by tuning certain reaction parameters.

In a representative example from the thiazole ring system aryne formation does not have to be considered as a possible side reaction. Here only two positions of a heteroaryl system are involved in the migration process (Scheme 4).[9] Using *N*-(5-bromothiazol-2-yl)-2,2-dimethylpropanamide as starting material, the halide can only migrate from the 5- into the 4-position. The first step in this reaction sequence is of course the lithiation of the starting material **17** to form the organometal species **18a**. In this particular example an additional equivalent of LDA is required for the initial deprotonation of the amide function. Intermediate **18a** can by itself act as a lithiating agent and reacts with intermediate **17a** to give a metal–halogen exchange forming **19a** and **20a** (= co-catalyst). Note, that the initially formed lithiated species **18a** is capable of undergoing metal–halogen exchange reactions in contrast to LDA. The so formed intermediates **19a** and **20a** can again react with each other to regenerate **17a** and 5-lithiated-4-bromo intermediate **21a**. Quenching the reaction with water could lead to all observed compounds (**17**, **20**, **22** and **23**) in general since all the reactions are equilibria. Indeed, in this specific example all intermediates could be isolated after aqueous workup. Notice that in order to start an HD process, lithiated and unlithiated starting material have to be present at

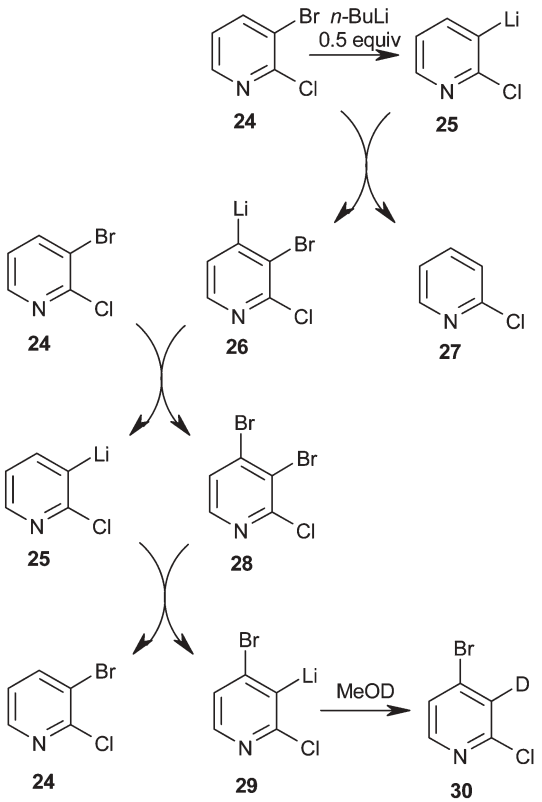


Scheme 4

the same time, a fact which is not only true for this example, but in general for HD reactions: The initially formed anion and yet unconverted starting material have to be present at the same time! As can be seen, the cascade reaction itself proceeded exactly as described in the first case, only the method of anion formation is different. When LDA (or similar bases) are used in HD reactions, the process is much more convenient than in the case of the historically applied amide bases. Therefore LDA is nowadays the most frequently used base for initiation of HD reactions.

The reason why an HD can occur on this thiazole substrate (or in general on an aromatic system) is a difference in the acidity of the various positions and therefore a difference in stability of the different lithiated species. In this particular case, the 5-position is more acidic than the 4-position, therefore favouring lithiatiated species at position 5 relative to the 4-position.

A representative case of initiating an HD reaction by metal–halogen exchange is given in the pyridine series, one of the most accurately studied ring systems in the context of HD reactions. In the particular example 3-bromo-2-chloropyridine **24** was reacted with 0.5 equiv. *n*-BuLi to give 2-chloro-3-lithiopyridine **25** besides starting material (Scheme 5).[10] Note that in this case substoichiometric amounts of *n*-BuLi were used in order to ensure the simultaneous presence of starting material and lithiated species. Compounds **24** and **25** can then react either *via* metal–halogen exchanges simply interconverting the two species into each other (probably the main reaction) or by a deprotonation reaction leading to species **26** and **27** to some extent. 3-Bromo-2-chloro-4-lithiopyridine **26** can then undergo a metal–halogen exchange reaction with **24** to give again **25** and 3,4-dibromo-2-chloro-pyridine **28** (=co-catalyst). Upon reaction of these two species with each other, starting material **24** is regenerated and—more importantly—4-bromo-2-chloro-3-lithiopyridine **29** is formed by halogen migration which was trapped in this example with MeOD. Of course 0.5 equiv. of the halide are sacrificed (in this case formation of 2-chloropyridine **27**) in the course of the reaction



Scheme 5

and a maximum yield of 50% based on halide of HD product can be obtained when HD reactions are started in such a way.

This last example was described in detail by Queguiner who termed this pathway *homotransmetallation*.

After this discussion of the mechanism it is also easy to understand the reason for bromine and iodine undergoing the migration process preferrentially. HD reactions of chlorine have been observed, however only low yields or mixtures of products have been reported.[11,12]

4. Factors influencing HD reactions

So far, the mechanism of HD reactions has been described in detail but only briefly mentioning the driving force behind this rearrangement process. In short, the migration proceeds into the direction of the most stable anion or metalated species. This statement can be illustrated using one of the above examples. In the thiazole case (Scheme 4), the only position available for deprotonation in **17** is the 4-position. However, the 5-lithiated species **21a** is much more stable than its 4-lithiated isomer **18a**, hence leading to fast migration into that direction. Systems which lack such a driving force (*e.g.* 4-bromothiazole **23**) cannot give an HD reaction and will react with bases without showing halogen migrations.

Keeping the above statement in mind it is obvious that the nature of the aromatic systems intended to undergo an HD reaction is of great importance. In carbocyclic systems the position of initial anion formation is solemnly defined by the substituents when the anion is formed by deprotonation. If the initial anion is formed by metal–halogen exchange, the case

is slightly different: With only one exchangeable halide present in the starting material the position of the initial attack is obvious. If more than one exchangeable halide is in the molecule, again the other substituents decide which position is preferentially metalated.

In the case of heteroaromatics, the nature and position of the heteroatoms of course have a very important directing influence regarding initial anion formation. Still the presence of substituents and the position of the halide influence also the position of initial metal–halogen exchange.

As can be seen from this short discussion and also from the mechanistic considerations in Section 3, the most important step in HD reactions is the initial anion formation. The initially formed anion then starts a cascade of metal–halogen exchange reactions generalized in eqn (1). In contrast to the initial reaction between alkylmetalics and arylhalides, in the case of the cascade reaction both sides of the equation

$$\mathrm{Ar–Li + Ar'–X \rightleftarrows Ar–Br + Ar'–Li} \qquad (1)$$

have a considerably higher similarity and therefore small changes in the reaction conditions can have considerable effects on the equilibrium.

By carefully choosing reaction conditions, chemists have a certain degree of influence whether an HD reaction takes place or is prevented. The main factors influencing HD reactions are the nature and amount of the base, the temperature, the order of reagent addition, the electrophile, and the solvent. These factors will be outlined in the following in more detail. Although these parameters are usually in close relationship, and affect each other, a separate discussion was chosen for reasons of greater clarity.

4.1. Choice of base

The reactivity of the base influences the rate of metalation and therefore switching between different bases can also influence the outcome of the reaction. As mentioned earlier, the initially formed anion might derive from a metal–halogen exchange or through a deprotonation reaction, depending on the nature of the base applied. The earliest examples of HD reactions relied on amide bases such as KNH_2, $NaNH_2$ or ArNHK. However, certain disadvantages of these bases render them of no importance nowadays for the initiation (or suppression) of an HD reaction in a controlled fashion. First of all, arylamines can be formed as by-products as already shown in Scheme 3. Additionally, complete conversion of starting materials cannot be achieved, usually due to the relatively low basicity of these reagents, and product mixtures are obtained. Instead, lithiating reagents such as LDA, LTMP, or simply *n*-BuLi are widely used. The prior two bases initiate an HD cascade reaction by deprotonation of the most acidic aryl-position, the latter (mainly) by a metal–halogen exchange reaction. Mechanistic examples for these three types of bases have been discussed in Section 3. Certainly, other bases have been applied but they are of no greater significance for the following discussions. No matter which base is used, reaction conditions have to be chosen which favour the simultaneous presence of metalated (or deprotonated) and unmetalated compounds.

Besides inducing HD reactions by the action of strong bases, the process was also demonstrated to proceed under electrochemical conditions. The mechanism of the HD is of course the same as under the influence of a base, only the method creating the phenyl-anion initiating the cascade is different.[13]

4.2. Temperature

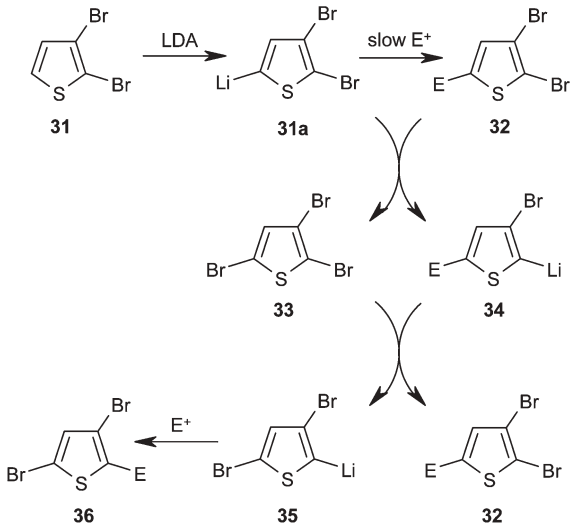
As a consequence of the above discussion the rate of the initial metalation step plays an important role and temperature can be expected to display a considerable effect. Metalated and unmetalated starting material have to be present at the same time in order to start an HD reaction. Lower temperatures, which accordingly means slower metalation, will therefore favour the simultaneous presence of metalated and unmetalated compounds. On the other hand, higher temperatures and therefore faster metalations can often be effectively used to prevent an HD reaction in systems where such a process is possible. At higher temperatures the stability of lithiating reagents is of course limited and HD prevention can therefore be difficult to achieve. In fact, HD-prevention proved to be only successful under special reaction conditions in the already discussed thiazole example (Scheme 4), and only when TMSCl was applied as electrophile replacing H_2O.

4.3. The electrophile

The metalated species formed in HD reactions can of course be trapped by a number of electrophiles as will be seen in the examples in Section 5. As soon as the rearrangement process is completed, the HD intermediate can be trapped with any suitable electrophile. In the case of attempted HD prevention, the nature of the electrophile might play an important role. Upon simple classification electrophiles can generally be divided into two groups: ''fast'' reacting and ''slow'' reacting electrophiles. A fast reacting electrophile will immediately trap a lithiated species in the reaction mixture, thus preventing the simultaneous presence of metalated and unmetalated species and HD-prevention products can be expected. However, if the electrophile reacts slowly with the lithiated species, already quenched product and metalated species can be present simultaneously in the reaction mixture and a migration process might be initiated leading to mixtures of products. This is exemplified in Scheme 6 on 2,3-dibromothiophene as substrate.[14] For example TMSCl, MeOH, ketones and aldehydes can be considered as ''fast'' electrophiles whereas alkyl halides or DMF are ''slow'' electrophiles.

4.4. Amounts and order of reagent addition

One method to favour or prevent an HD reaction is to carefully choose the order of reagent addition (together with the amounts of base, as already outlined). If the base is added slowly to the halide substrate, it can be ensured that unreacted starting material is present besides the metalated species and an HD reaction is preferred. If the reagent addition is performed in reversed sequence and the halide substrate is added to a solution of the base, it is more likely that all the added halide is immediately deprotonated. The two species required for migration are not present at the same time



Scheme 6

ultimately suppressing an HD reaction. The stoichiometry of reagents plays an equally crucial role: If a substoichiometric amount of base is used in the latter case the requirements to start an HD cascade can still be fulfilled. Similarly, when a great excess of base is added quickly to a solution of the halide substrate in the first case the HD process might still be inhibited.

4.5. The solvent

Finally, it was found that in some cases the solvent can play an important role in determining whether an HD takes place or not. The reactivity of the nowadays applied lithio bases is somewhat dependent on the solvent, which explains these observations. In some cases the same reaction leads to HD products in THF, whereas in THP the HD could be prevented (with LDA as base).[4]

Table 1 briefly summarizes the general guidelines for controlling HD reactions.

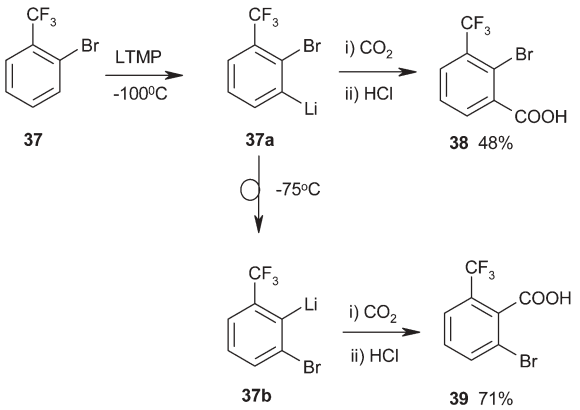
5. Examples for HD reactions

5.1. Benzene derivatives

The group of Schlosser contributed considerably to the investigations of halogen migration processes on benzene. A series of halogenated benzenes was studied to outline simple and efficient access to molecular diversity.[6] In some examples they showed that at very low temperatures (−100 °C) the migration could be prevented and the unscrambled lithiated species was trapped by an electrophile. By "warming" the

Table 1 Guidelines for promoting or preventing an HD

HD Promotion	HD Prevention
Low temperatures	High temperatures
No excess of base	Excess of base
Addition of base to the halide	Addition of halide to the base
THF	THP
Slow reacting electrophile	Fast reacting electrophile



Scheme 7

reaction mixture to −75 °C the HD reaction could be initiated and the isomeric compound was obtained after quenching with an electrophile. The concept is outlined for 2-bromo-trifluoromethylbenzene **37** (Scheme 7): at −100 °C lithiation takes place at the 3-position and intermediate **37a** can be trapped with CO_2 to give the corresponding carboxylic acid **38**. However, when the reaction mixture is warmed to −75 °C migration to form **37b** takes place and **39** is obtained after reaction with the electrophile.[15]

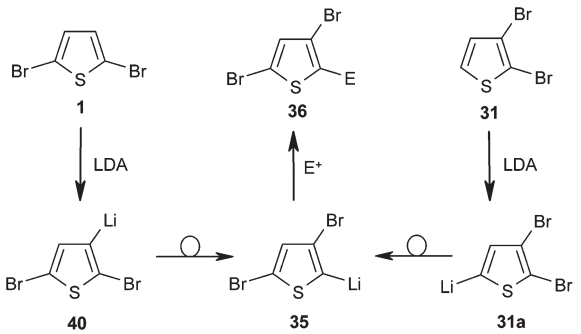
5.2. HD reactions on heterocyclic substrates

Until now, a number of heterocyclic substrates have been studied in HD reactions: thiophene, furan, imidazole, pyrazole, thiazole, isothiazole, oxazole, pyridine, quinoline, pyrimidine, and imidazolopyridine systems successfully gave the halogen migration process. In the following, selected examples will be presented.

5.2.1. Thiophene. Halogenated thiophenes were the first systems on which an HD reaction was observed (see Section 2, Scheme 1)[1] and thiophene remained in the focus of early investigations in the field. Kano found that **1** gave 3,5-dibromo-2-lithiothiophene **35** upon treatment with LDA which was trapped with a number of carbon electrophiles (MeI, H_2O, EtI, allyl bromide, DMF, ethyl chloroformate, propylene oxide, butylene oxide, cyclohexene oxide, cyclohexanone, dimethyl disulfide) to give compounds of the general structure **36** in usually good yields ranging from 45–95% (Scheme 8).[14]

The same substitution pattern can also be obtained starting from 2,3-dibromothiophene **31**, which upon lithiation with LDA rearranges to **35**, as well (Scheme 8).[16]

Taylor then showed that the modalities of reagent addition can determine whether an HD reaction takes place or is prevented.[17] 5-Bromo-4-(methylthio)thiophene-2-carboxylic acid **42** was formed exclusively when 2-bromo-3-(methylthio)thiophene **41** was added slowly to an excess of LDA at −78 °C (followed by addition of CO_2). In contrast, rapid addition of **41** to 1 equiv. of LDA at −78 °C (followed after 1 h by addition of CO_2) yields exclusively rearranged 5-bromo-3-(methylthio)thiophene-2-carboxylic acid **43** (Scheme 9).

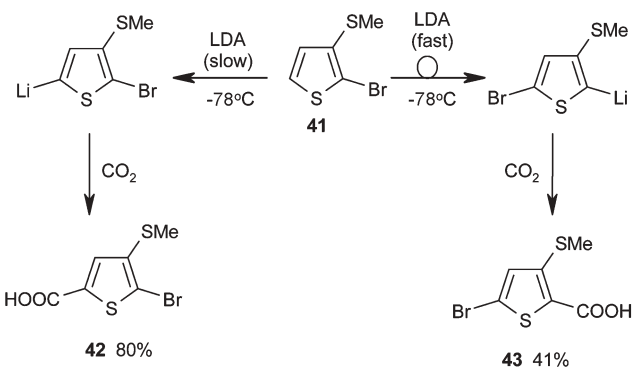


Scheme 8

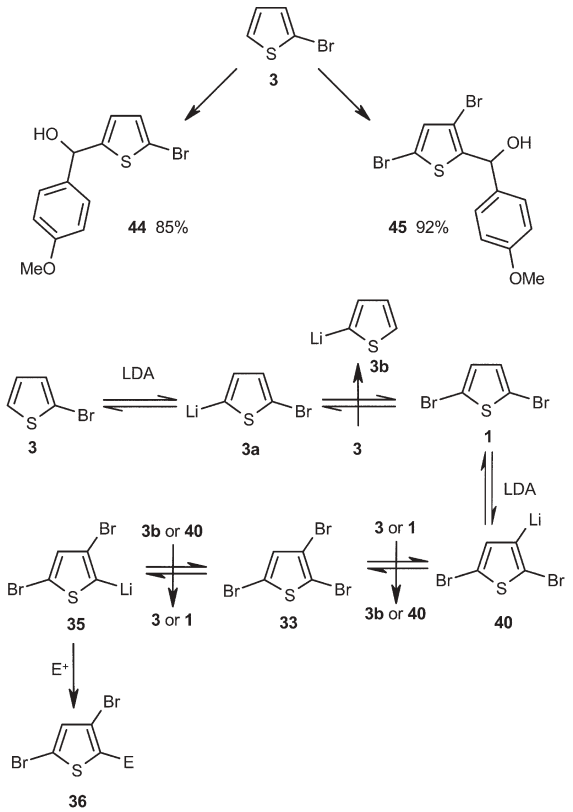
In the latter procedure some unlithiated starting material is present besides initially formed 2-bromo-3-(methylthio)-5-lithiothiophene which starts the HD cascade. Ultimately, 5-bromo-3-(methylthio)-2-lithiothiophene is formed upon reaction with the lithiated species. This species is then trapped by the electrophile. However, slow addition of the starting material to an excess of LDA guarantees that all starting material is immediately lithiated and no HD reaction is possible.

Lately, Benhida and co-workers used the HD reaction of 2-bromothiophene **3** to access 2-substituted 3,5-dibromothiophenes.[18] In this case 2 equiv. of cheap and readily available **3** are applied to obtain good yields of the dibromo compounds. When the reaction was carried out at −78 °C, 2-bromo-5-lithiothiophene **3a** was formed exclusively and could be trapped with a number of electrophiles in high yields (*e.g.* **44**). However, when the reaction was carried out at room temperature, the rearrangement process took place and compounds like **45** were obtained. The HD reaction was found to be a highly ordered and fast process following a typical HD mechanism (Scheme 10).

5.2.2. Furan. In contrast to thiophene, HD reactions on furan have not been studied to a comparable extent. Fröhlich *et al.* described the HD reaction of 2,3-dibromofuran, 2,5-dibromofuran, and 2-bromo-5-methylfuran **46** and the corresponding prevention (Scheme 11).[4,19] For all three substrates, reaction conditions were reported to either prevent or promote the HD and a series of electrophiles was introduced into the metalated position.

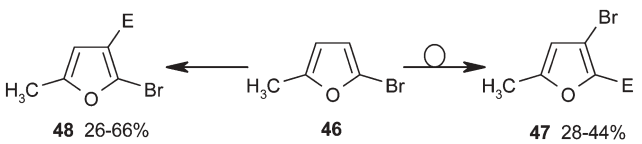


Scheme 9

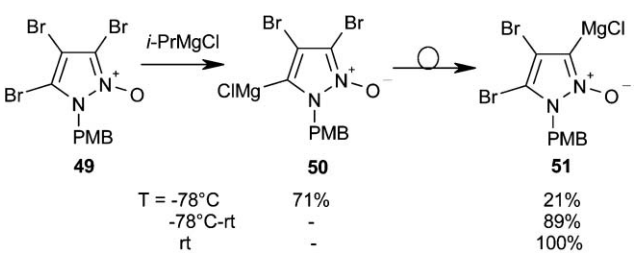


Scheme 10

5.2.3. Pyrazole. 3,4,5-Tribromo-2-(4-methoxybenzyl)pyrazole-1-oxide **49** underwent bromine–magnesium exchange at C-3, predominantly, to give **50**, despite the fact that exchange at C-5 would give a less basic, sterically less hindered and thermodynamically more favoured intermediate **51** (Scheme 12).[20] This regioselectivity was explained by the low solubility of the 3-metalated compound which precipitated at −78 °C. By warming to rt, it was converted to **51**, which was stable at rt and readily soluble in THF even at −78 °C. The HD may involve remaining tribromo compound **49**. It entails



Scheme 11 E = TMS, CHO, 1-OH-1-cyclohexyl, 1-OH-phenylmethyl.

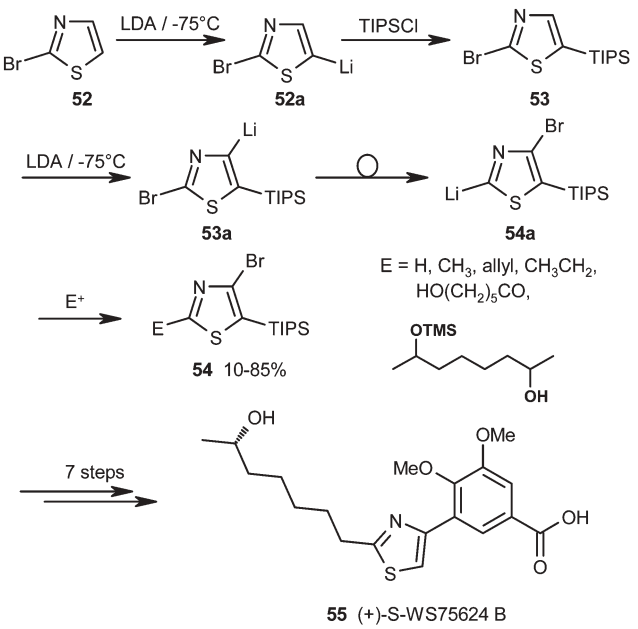


Scheme 12

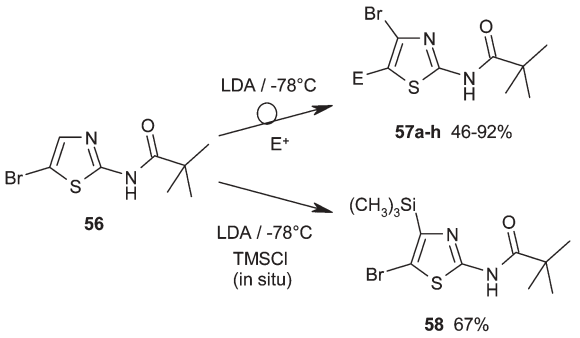
halogen–metal exchange and is therefore somewhat different from most reported HD reactions which involve proton–metal exchange. The process was applied to the synthesis of a series of pyrazolo[3,4-*c*]quinoline-1-oxides.

5.2.4. Thiazole. Thiazole was only recently added to the ring-systems on which an HD reaction was reported. First, Sammakia described the bromine migration from positions 2 or 5 into 4 in combination with the introduction of electrophiles.[21] 2-Triisopropylsilyl-5-bromothiazole smoothly rearranged to the 4-bromo derivative in 86% yield by treatment with LDA at −78 °C. Initial attempts to use 2-bromothiazole **52** as starting material failed due to ring opening of the *in situ* formed 2-lithiothiazole species. However, this problem was solved when the lithiation was carried out in the presence of TIPSCl. In that way, the initially formed 2-bromo-5-lithiothiazole **52a** is trapped by TIPSCl to give **53** before a rearrangement process can take place. By using an excess of 2.2 equiv. of LDA in this reaction, the remaining LDA can now deprotonate the 4-position to give **53a**. Subsequent halogen migration into that position leads to another 2-lithiothiazole intermediate **54a** which proved to be stable at −78 °C and could be trapped with reactive electrophiles to afford compounds **54** (*e.g.* methyl iodide, aldehydes). Hindered lactones and typical alkyl halides were unreactive. This process was applied in the synthesis of (+)-S-WS75624 B **55**, a potential antihypertensive agent (Scheme 13).

Shortly thereafter, a second example was published from our group which has already been discussed in the mechanistic section.[9] Also in this case a series of electrophiles was introduced in 46–92% yield (Scheme 14). The HD process proved to be very fast on this type of substrate and prevention of the migration process was almost impossible. Only when the starting material was lithiated (with LDA) in the *presence* of TMSCl, could the initially formed 4-lithio intermediate be



Scheme 13



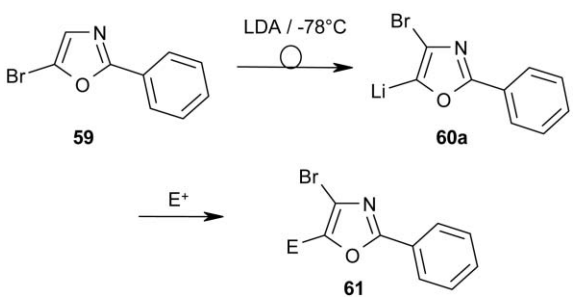
Scheme 14

trapped to give **58** *via* an HD prevention pathway. When benzophenone, a less reactive or ''slower'' electrophile, was used under the same reaction conditions no prevention product was detected and only HD was observed.

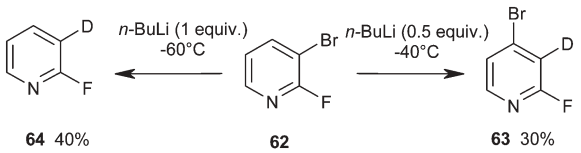
5.2.5 Oxazole. Within a contribution by this laboratory, oxazole was the most recent heterocyclic system on which an HD reaction was reported.[22] Starting from 5-bromo-2-phenyloxazole **59** the migration process was induced by LDA and various electrophiles were introduced at 5-position in 58–78% yield (**61**, Scheme 15). For the incorporation of bromine 1,2-dibromo-1,1,2,2-tetrachloroethane proved to be the best electrophile (76%) since it gave considerably higher yields than Br_2 (30%) and 1,2-dibromoethane (11%). Suppression of the HD failed using the conditions and strategies outlined in Section 4.

5.2.6. Pyridine. As mentioned in Section 3, one of the earliest HD reactions was observed on pyridine.[8] Especially Queguiner and co-workers extensively studied this rearrangement and contributed to HD reactions on this heterocyclic system. We have already discussed in Section 3 the homotransmetallation mechanism found by Queguiner (Scheme 5). Other selected examples of their research will be presented in the following.

They first encountered an HD on pyridine when they investigated the formation of 3,4-pyridynes from 3-bromopyridine or 3-bromo-2-fluoropyridine **62** with *n*-BuLi.[23] Only small amounts of the corresponding Diels–Alder products (15%) were formed upon trapping with furan derivatives. Subsequently, the lithiation of these two substrates was studied in more detail and two different lithiation conditions were applied. In the first protocol the pyridine derivative (1 equiv.)



Scheme 15

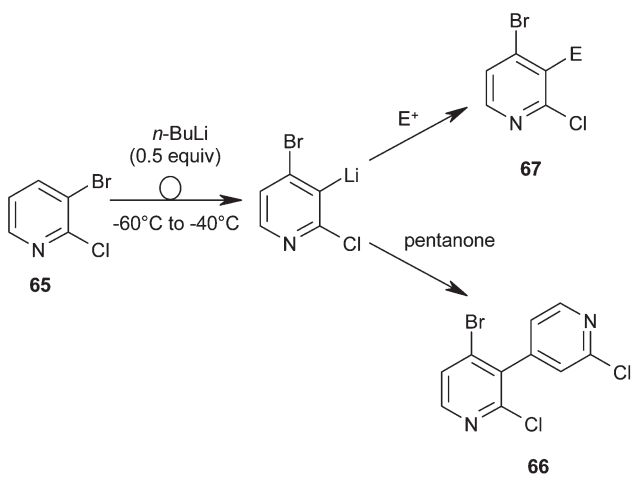


Scheme 16

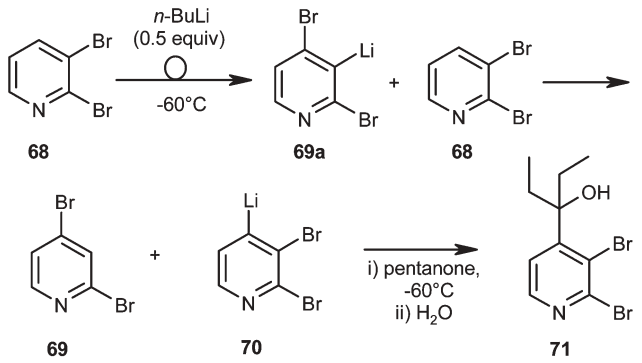
was added at −60 °C to a solution of *n*-BuLi (1 equiv.) in THF or diethyl ether. After warming to rt, the reaction solution was quenched with either D_2O, acetone or pentanone. *Via* this HD prevention method the electrophile was exclusively introduced in 3-position for both substrates (**64**). The second protocol used an inverse order of reagent addition and an excess of halopyridine: *n*-BuLi (0.5 equiv.) was added to a solution of **62** (1 equiv.) in THF at −60 °C and stirred for 15 min at −40 °C. When D_2O was used as electrophile, 30% of 4-bromo-3-deutero-2-fluoropyridine **63** was obtained besides debrominated 2-fluoropyridine (40%). Similar observations were made for pentanone and acetone as electrophile but no yields were given (Scheme 16).

When 3-bromo-2-fluoropyridine **62**, 3-bromo-2-chloropyridine **65**, and 2,3-dibromopyridine **68** were reacted under the same lithiation conditions (0.5 equiv. *n*-BuLi, −60 °C to −40 °C, then 3-pentanone at −60 °C) very different results were obtained.[24] While **62** gave an HD reaction by migration of bromine into the 4-position and incorporation of the electrophile in the 3-position, precursor **65** led to formation of bis-pyridine **66** (Scheme 17).

It was argued that due to the higher steric demand (chlorine > fluorine) the ketone could not be attacked. Instead, two possible mechanisms for formation of the bis-pyridine were given. The first one was again an addition–elimination mechanism *via* a 3,4-pyridyne intermediate. Presumably, 4-bromo-2-chloro-3-lithiopyridine can give rise to the 3,4-pyridyne to some extent. Upon addition of 4-bromo-2-chloro-3-lithiopyridine the bis-pyridine could be formed since the substitution pattern is in accordance with the rules for addition to arynes. The second explanation relies on the *in situ* formation of 4-bromo-2-chloropyridine (eventually from deprotonation of the ketone) which reacts then with



Scheme 17

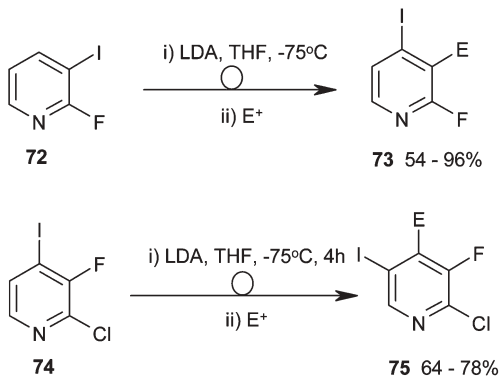


Scheme 18

4-bromo-2-chloro-3-lithiopyridine *via* an S_N mechanism. None of the mechanisms was favoured by the authors and they suggested that they might act simultaneously. However, if less sterically demanding electrophiles are applied, incorporation occurs at position 3 as demonstrated in later work (**67**, Scheme 17).[25]

Finally, 2,3-dibromopyridine **68** gave yet another product since neither the HD derived alcohol nor bis-pyridine formation were observed but alcohol **71** was isolated in 30% yield. The formation of an HD derived alcohol (from quenching of **69a** with pentanone) was indeed quite unlikely based on the argument that steric reasons already prevented this route in the chloro case. The formation of **71** was again explained by a homotransmetalation mechanism. 2,4-Dibromo-3-lithiopyridine **69a** generated *via* the HD process can lithiate the remaining starting material at the 4-position to give **70**. Intermediate **70** is sterically less hindered and can undergo a reaction with 3-pentanone to give the corresponding alcohol **71** (Scheme 18).

Until then, only bromine migrations were investigated on pyridine. The next logical step was replacement with iodine and as expected 2-fluoro-3-iodopyridine **72** gave 2-fluoro-4-iodo-3-lithiopyridine. This intermediate could again be trapped with various electrophiles to give compounds **73**.[26] Starting from 2-chloro-3-fluoro-4-iodopyridine **74** the iodine migrated into position 5 upon reaction with LDA and 2,3,4,5-tetrasubstituted pyridines **75** were obtained (Scheme 19).



Scheme 19

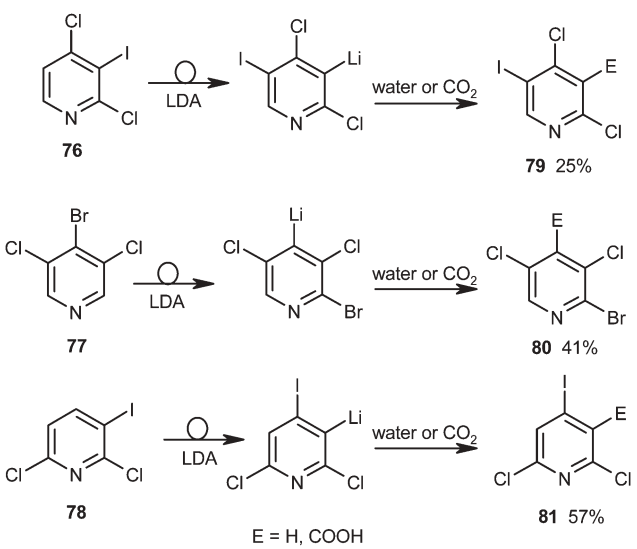
In contrast, 3-fluoro-4-iodopyridine gave 3-fluoro-2-iodopyridine upon reaction with LDA, since the initial metalation was directed into the 2-position by the fluorine. Still, iodine migrated readily into that position and 3-fluoro-2-iodo-4-substituted pyridines were obtained.

Schlosser investigated the selective functionalization of some dichloropyridines.[27] Again, addition of LDA induced halogen migration in compounds **76–78** towards the most stable lithium intermediate which was trapped either with water or CO_2 (Scheme 20, compounds **79–81**).

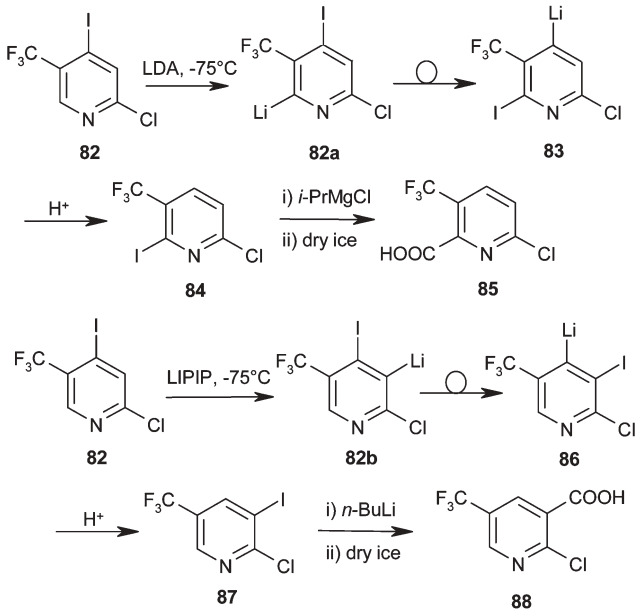
This process was extended to several further halopyridines or trifluoromethyl-halopyridines which essentially all gave the expected migration process upon treatment with LDA.[6,28,29] In the case of 2-chloro-5-(trifluoromethyl)-4-iodopyridine **82** a remarkable regioselectivity for the migration was encountered depending on the nature of base applied. When LDA was used, the iodine migrated into the 6-position (*via* **82a** and **83**), whereas upon lithiation with lithium piperidide (LIPIP) a migration into the 3-position occurred (*via* **82b** and **86**). This observation was rationalized on the basis of the different steric hindrance imposed by these reagents and the differences in their basicities and, hence, capacity for proton abstraction (Scheme 21).[30] Isomeric iodopyridines **84** and **87** and pyridinecarboxylic acids **85** and **88** were finally obtained.

Sammakia and co-workers accomplished the total synthesis of caerulomycin C including even two HD reaction steps (Scheme 22).[31] First, they took advantage of an LDA induced iodine migration from position 3 to 5 (**89** to **90**) which enabled introduction of the second methoxy group at that site *via* nucleophilic substitution with CH_3ONa/CuI. Introduction of bromine at the 3-position and its subsequent migration (again LDA induced) into the 6-position (**91** to **92**) enabled Negishi cross-coupling with 2-pyridyl zinc chloride to give the desired bi-pyridine scaffold. Reduction of the amide to the aldehyde and oxime formation completed the total synthesis of **93**.

Other applications of the HD methodology for the preparation of natural products were the synthesis of the 5-(4-pyridyl)benzo[*c*]-2,7-naphthyridine ring system,[32] a



Scheme 20

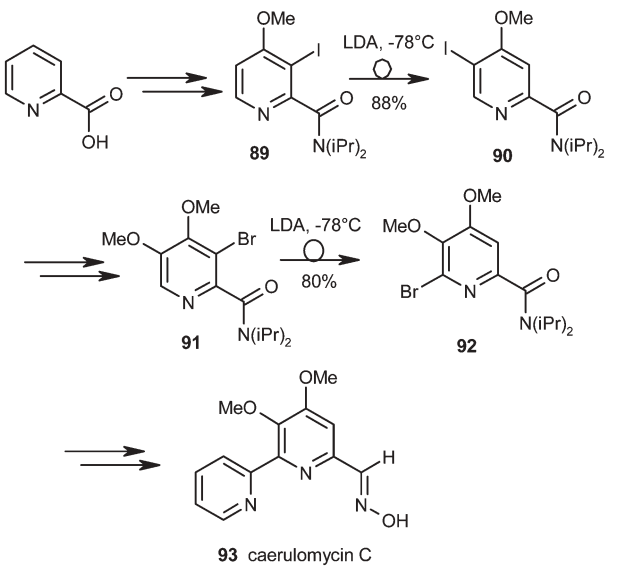


Scheme 21

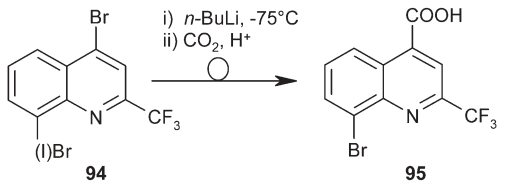
subunit of two marine alkaloids (amphimedine and petrosamine),[33] the asymmetric synthesis of a key camptothecin intermediate,[34] or the synthesis of β-substituted and α,β-disubstituted δ-carbolines.[35] Rault and co-workers utilized the methodology in their synthesis of halogenated pyridineboronic acids and esters.[36] Another application of the already reported reactions is the synthesis of 2,3,4-substituted pyridines as useful scaffolds for tripeptidomimetics.[37,38]

5.2. Quinoline

An interesting example on quinoline was reported by the Schlosser group who demonstrated that the halogen can migrate from the pyridine to the phenyl ring within quinoline.[39] Starting from 4-bromo-8-iodo-2-(trifluoromethyl)quinoline **94** (or the 4,8-dibromo derivative) lithiation with



Scheme 22



Scheme 23

n-BuLi gave a metal halogen exchange in position 8. Subsequently, this 8-lithio intermediate rearranged to the 4-lithio-8-bromo compound which was trapped with CO_2 to give the corresponding carboxylic acid **95** (Scheme 23). When *i*-PrMgCl was used instead of *n*-BuLi the initially formed intermediate metalated in position 8 proved to be stable and electrophiles were introduced at that site.

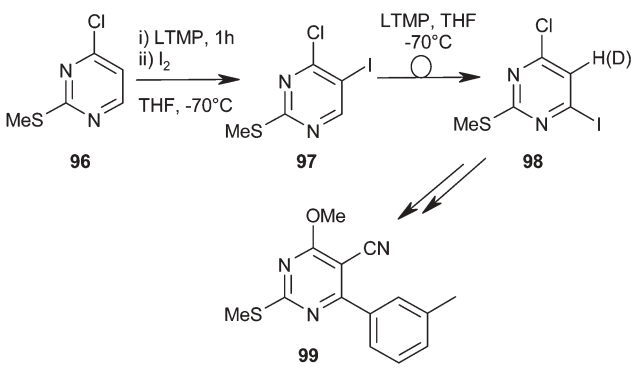
5.4. Pyrimidine

Only one example was reported for an HD reaction in the pyrimidine series.[40] Lithiation of either 2-chloro-4-methoxypyrimidine or 4-chloro-2-(methylthio)pyrimidine **96** with LTMP and subsequent trapping with electrophiles led to the expected 5-substituted derivatives. However, when I_2 was used as electrophile, 6-iodopyrimidines **98** were isolated (Scheme 24).

Since 2.3 equiv. of LTMP and 1.3 equiv. of I_2 were used, the excess of base induced the HD reaction leading to the 6-iodo isomer of **97**. The rearrangement process was utilized for the synthesis of leishmaniacides of the general type **99** and other biologically active compounds.

Conclusions

The Halogen Dance reaction has matured from a peculiar transformation encompassing challenging mechanistic aspects to an important tool in synthetic chemistry. It enables access to certain substitution patterns on both carbo- and heterocyclic systems otherwise difficult to obtain. The extent of functionalization of (hetero-)aromatic systems can be increased *via* the HD reaction by concomitant incorporation of electrophiles and migration of the halogen atom, which remains available for subsequent elaboration. This transformation therefore enables a single-operation multiple-decoration of (het-)aryl cores in a highly efficient manner. The combination of HD promotion and prevention under certain reaction conditions (for which guidelines have become available in recent years) provides a technology platform to access diverse and complementary substitution patterns.



Scheme 24

The versatility and robustness of the methodology provided entry to highly functionalized compounds in only few, simple, and high yielding steps. A variety of ring systems has been investigated in particular during the past decade, however, demonstrating that there are still important contributions to be made to the field. We hope that this review will stimulate the application of the HD reaction in preparative chemistry and inspire future studies on novel systems to further proliferate this powerful synthetic method.

References

1 A. Vaitiekunas and F. F. Nord, *Nature*, 1951, **168**, 875–876.
2 A. Vaitiekunas and F. F. Nord, *J. Am. Chem. Soc.*, 1953, **75**, 1764–1768.
3 J. F. Bunnett, *Acc. Chem. Res.*, 1972, **5**, 139–147 and references cited therein.
4 J. Fröhlich, *Prog. Heterocycl. Chem.*, 1994, **6**, 1–35.
5 X.-F. Duan and Z.-B. Zhang, *Heterocycles*, 2005, **65**, 2005–2012.
6 M. Schlosser, *Angew. Chem., Int. Ed.*, 2005, **44**, 376–393 and references cited therein.
7 C. E. Moyer, Jr. and J. F. Bunnett, *J. Am. Chem. Soc.*, 1963, **85**, 1891–1893.
8 M. J. Pieterse and H. J. den Hertog, *Recl. Trav. Chim. Pays-Bas*, 1962, **81**, 855–863.
9 P. Stanetty, M. Schnürch, K. Mereiter and M. D. Mihovilovic, *J. Org. Chem.*, 2005, **70**, 567–574.
10 M. Mallet and G. Queguiner, *Tetrahedron*, 1979, **35**, 1625–1631.
11 M. H. Mach and J. F. Bunnett, *J. Org. Chem.*, 1980, **45**, 4660–4666.
12 D. A. de Bie and H. C. van der Plas, *Tetrahedron Lett.*, 1968, **36**, 3905–3908.
13 M. S. Mubarak and D. G. Peters, *J. Org. Chem.*, 1996, **61**, 8074–8078.
14 S. Kano, Y. Yuasa, T. Yokomatsu and S. Shibuya, *Heterocycles*, 1983, **20**, 2035–2037.
15 C. Heiss, T. Rausis and M. Schlosser, *Synthesis*, 2005, **4**, 617–621.
16 F. Sauter, J. Fröhlich and W. Kalt, *Synthesis*, 1989, 771–773.
17 E. C. Taylor and D. E. Vogel, *J. Org. Chem.*, 1985, **50**, 1002–1004.
18 C. Peyron, J.-M. Navarre, N. van Craynest and R. Benhida, *Tetrahedron Lett.*, 2005, **46**, 3315–3318.
19 J. Fröhlich and C. Hametner, *Monatsh. Chem.*, 1996, **127**, 435–443.
20 J. Eskildsen, N. Ostergaard, P. Vedso and M. Begtrup, *Tetrahedron*, 2002, **58**, 7635–7644.
21 E. L. Stangeland and T. Sammakia, *J. Org. Chem.*, 2004, **69**, 2381–2385.
22 P. Stanetty, M. Spina and M. D. Mihovilovic, *Synlett*, 2005, **9**, 1433–1434.
23 M. Mallet, F. Marsais, G. Queguiner and P. Pastour, *C. R. Hebd. Seances Acad. Sci., Ser. C*, 1972, **23**, 1439–1442.
24 M. Mallet and G. Queguiner, *Tetrahedron*, 1985, **41**, 3433–3440.
25 M. Mallet, G. Branger, F. Marsais and G. Queguiner, *J. Organomet. Chem.*, 1990, **328**, 319–332.
26 P. Rocca, C. Cochennec, F. Marsais, L. Thomas-dit-Dummont, M. Mallet, A. Godard and G. Queguiner, *J. Org. Chem.*, 1993, **58**, 7832–7838.
27 E. Marzi, A. Bigi and M. Schlosser, *Eur. J. Org. Chem.*, 2001, 1371–1376.
28 F. Cottet and M. Schlosser, *Eur. J. Org. Chem.*, 2004, 3793–3798.
29 E. Marzi, C. Bobbio, F. Cottet and M. Schlosser, *Eur. J. Org. Chem.*, 2005, 2116–2123.
30 S. Takagishi and M. Schlosser, *Synlett*, 1991, 119–121.
31 T. Sammakia, E. L. Stangeland and M. C. Withcomb, *Org. Lett.*, 2002, **4**, 2385–2388.
32 F. Guillier, F. Nivoliers, A. Godart, F. Marsais and G. Queguiner, *Tetrahedron Lett.*, 1994, **35**, 6489–6492.

33 F. Guillier, A. Nivoliers, A. Godard, F. Marsais and G. Queguiner, *Tetrahedron Lett.*, 1994, **35**, 6489–6492.
34 D. L. Comins and K. Saha, *Tetrahedron Lett.*, 1995, **36**, 7995–7998.
35 E. Arzel, P. Rocca, F. Marsais, A. Godard and G. Queguiner, *Heterocycles*, 1999, **50**, 215–226.
36 A. Bouillon, J. C. Lancelot, V. Collot, P. R. Bovy and S. Rault, *Tetrahedron*, 2002, **58**, 4369–4373.
37 S. Saitton, J. Kihlberg and K. Luthman, *Tetrahedron*, 2004, **60**, 6113–6120.
38 S. Saitton, A. L. Del Tredici, N. Mohell, R. C. Vollinga, D. Boström, J. Kihlberg and K. Luthman, *J. Med. Chem.*, 2004, 6595–6602.
39 M. Marull and M. Schlosser, *Eur. J. Org. Chem.*, 2003, 1576–1588.
40 N. Ple, A. Turck, K. Couture and G. Queguiner, *Tetrahedron*, 1994, **50**, 10299–10308.