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Highly Regioselective Preparation of Heteroaryl–Magnesium Reagents by Using a Br/Mg Exchange

Christoph Sämann, Benjamin Haag, and Paul Knochel*[a]

Abstract: Disubstituted thienyl-, furyl- and pyridylmagnesium derivatives are regioselectively prepared from a Br/Mg exchange of the corresponding dibromo compounds by using either *i*PrMgCl·LiCl or hindered arylmagnesium reagents, such as isitylmagnesium bromide·lithium chloride (isityl = 2,4,6-triisopropylphenyl) complexed with a diamine ligand, in difficult cases. The selective functionalisations of these heterocyclic scaffolds by using Negishi cross-coupling reactions, acylations or addition to aldehydes were readily achieved.

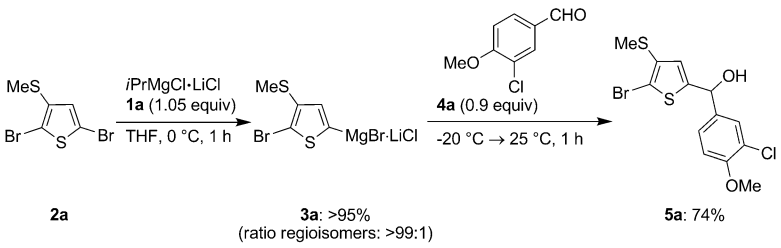
Keywords: copper · cross-coupling · Grignard reaction · palladium · regioselectivity

Introduction

The functionalisation of heterocycles is of key importance for the preparation of pharmaceuticals, agrochemicals and materials (regioregular polymers) and has attracted a lot of attention in recent years.[1] Especially important is the regioselective preparation of metalated five- and six-membered heterocycles. Recently, we reported that *i*PrMgCl·LiCl (**1a**) is a powerful reagent for performing Br/Mg-exchange reactions at various aromatic bromides.[2] The presence of LiCl was shown to enhance the Br/Mg exchange rates by generating reactive ate-intermediates of the type $iPrMgCl_2^-\cdot Li^+$. Herein, we now report a regioselective Br/Mg-exchange reaction of unsymmetrically substituted dibromoheterocycles by using either *i*PrMgCl·LiCl (**1a**) or, in difficult cases, hindered arylmagnesium reagents, such as 2,4,6-trimethylphenylmagnesium bromide (**1b**) or 2,4,6-triisopropylphenylmagnesium bromide (**1c**) complexed with a diamine ligand, to allow the preparation of various thienyl-, furyl- and pyridylmagnesium derivatives. The further selective functionalisation of these heterocyclic scaffolds is also disclosed.

Results and Discussion

Preliminary experiments have shown that the treatment of unsymmetrically substituted dibromoheterocycles, such as 2,5-dibromo-3-(methylthio)thiophene (**2a**), with *i*PrMgCl·LiCl (**1a**; 1.05 equiv) in THF at 0 °C leads to the corresponding magnesium reagent (**3a**) in > 95 % yield and with a regioselectivity of > 99:1 within 1 h. The addition of **1a** to 3-chloro-4-methoxybenzaldehyde (**4a**, 0.9 equiv) at −20 °C provided the corresponding alcohol **5a** in 74 % yield (Scheme 1). With these conditions in hand, several unsymmetrically substituted dibromothiophenes and -thienothiophenes (**2b–j**) were converted into their corresponding magnesium species (Table 1) and subsequently functionalised by using a range of electrophiles, such as aldehydes, aryl iodides or acyl chlorides, in the presence of an appropriate catalyst (Table 1).



Scheme 1. Regioselective Br/Mg exchange on unsymmetrical 2,5-dibromothiophenes of type **2** by using *i*PrMgCl·LiCl (**1a**).

This regioselective exchange has been performed with a number of unsymmetrically substituted dibromothiophenes and -thienothiophenes with good to excellent regioselectivities, even on 10 and 15 mmol scales (Table 1, entries 7 and 17). Thio substituents [MeS (**2a**; Table 1, entries 1–4), PhS (**2b**; Table 1, entries 5–7) and PyrS (**2c**; Table 1, entry 8)] or a trimethylsilyl substituent on the thiophene (**2i**; Table 1, entries 16–18) directed the Br/Mg exchange at position 5

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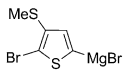
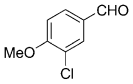
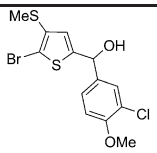
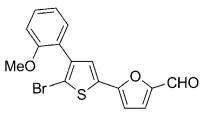
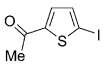
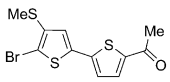
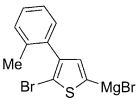
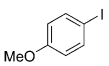
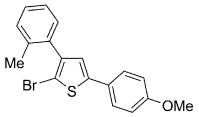
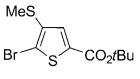
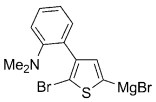
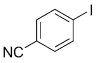
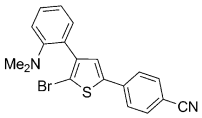
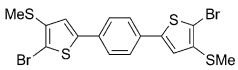
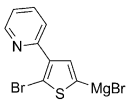
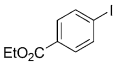
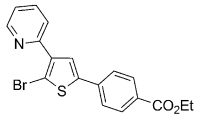
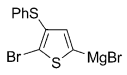
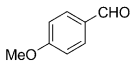
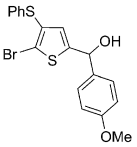
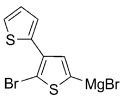
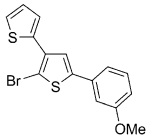
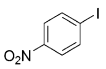
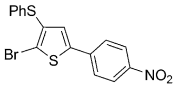
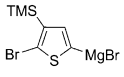
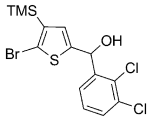
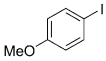
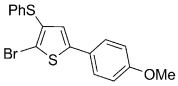
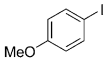
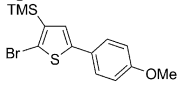
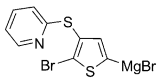
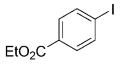
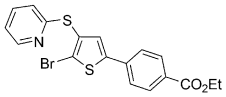
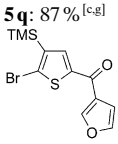
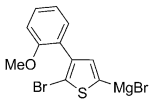
Table 1. Preparation of functionalised thiophenes and thienothiophenes of type **5** by reaction with heteroarylmagnesium reagents of type **3**.

Entry	Mg Reagent: Regioselectivity[a]	Electrophile	Product: Yield[b]	Entry	Mg Reagent: Regioselectivity[a]	Electrophile	Product: Yield[b]
							
1	**3a**: >99:1	**4a**	**5a**: 74%	11	**3d**: >99:1	**4j**	**5k**: 76%[c]
							
2	**3a**: >99:1	**4b**	**5b**: 82%[c]	12	**3e**: 22:1	**4g**	**5l**: 96%[c]
		$(t\mathrm{BuO_2C})_2\mathrm{O}$					
3	**3a**: >99:1	**4c**	**5c**: 82%	13	**3f**: 39:1	**4i**	**5m**: 91%[c]
							
4	**3a**: >99:1	**4d**	**5d**: 84%[c]	14	**3g**: 20:1	**4h**	**5n**: 89%[c]
							
5	**3b**: >99:1	**4e**	**5e**: 91%	15	**3h**[f]: 20:1	**4k**	**5o**: 83%[c]
							
6	**3b**: >99:1	**4f**	**5f**: 86%[c]	16	**3i**: >99:1	**4l**	**5p**: 86%
							
7	**3b**: >99:1	**4g**	**5g**: 96%[c,d]	17	**3i**: >99:1	**4g**	**5q**: 87%[c,g]
							
8	**3c**: >99:1	**4h**	**5h**: 92%[c]	18	**3i**: >99:1	**4m**	**5r**: 72%[h]
							
9	**3d**: >99:1	**4i**	**5i**: 90%[c]	19	**3j**: >99:1	**4e**	**5s**: 81%
10	**3d**: >99:1	**4j**	**5j**: 60%[e]	20	**3j**: >99:1	**4g**	**5t**: 96%[c]

[a] Obtained after exchange reaction with *i*PrMgCl·LiCl (**1a**; 1.05 equiv) in THF at 0 °C for 1 h. Ratio of regioisomers determined by ^{1}H NMR analysis of the quenched crude reaction mixture (HOAc, 10 equiv). [b] Yield of analytically pure isolated product as determined by ^{1}H NMR analysis. [c] Obtained after a Negishi cross-coupling reaction [$ZnCl_2$ (1 equiv) then [$Pd(PPh_3)_4$] (4%)] with ArI (0.9 or 1.1 equiv). [d] The reaction was performed on a 15 mmol scale. [e] Transmetalation with $ZnCl_2$ (0.5 equiv) before addition to the aldehyde. [f] The exchange reaction was performed at −20 °C for 1 h. [g] The reaction was performed on a 10 mmol scale. [h] Obtained after an acylation reaction [$ZnCl_2$ (1 equiv) then CuCN·2LiCl (10%)] with ArCOCl (0.9 equiv).

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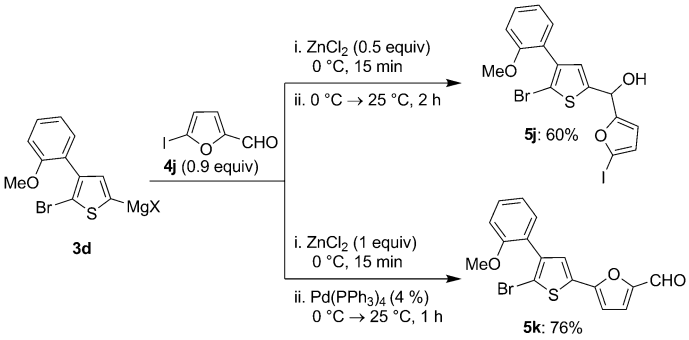
with a regioselectivity of >99:1.[3] Interestingly, by using 2,5-dibromo-3-phenylthiophene, no regioselective Br/Mg exchange could be achieved under various conditions. However, by introducing a substituent at the *ortho* position of the phenyl group [MeO (**2d**; Table 1, entries 9–11), Me (**2e**; Table 1, entry 12) and Me_2N (**2f**; Table 1, entry 13)] selectivities from 20:1 up to >99:1 could be obtained. This effect may be explained by assuming a conformational change by moving the aryl group out of the plane due to the substituent on position 2′, and therefore shields the bromine at position 2. It is worth noting that a satisfactory regioselectivity of 20:1 has been also achieved with the use of heterocyclic substituents such as a 2-pyridyl or a 2-thienyl group (**2g** and **h**; Table 1, entries 14 and 15).

Additionally, no chelating effect with the MeO- or Me_2N-substituent of the phenyl ring, nor with the pyridyl- or the thienyl-substituents, could be observed. We assume that this might be due to the too-long distance between the bromine at position 2 of the thiophene ring and the heteroatom of the MeO or Me_2N group of the phenyl ring (or the pyridyl or thienyl substituent) caused by the almost perpendicular orientation of the thiophene ring and the substituents at position 3. Because thienothiophenes are important building blocks for the preparation of organic materials,[4] we also performed regioselective functionalisations of this scaffold by using *i*PrMgCl·LiCl (**1a**) (Table 1, entries 19 and 20).

As mentioned above, a wide range of electrophiles have been used for the selective functionalisation of the heterocyclic magnesium reagents. It was possible to directly add the Mg species to aldehydes to form the corresponding alcohols in 60–91% yield (Table 1, entries 1, 5, 10,[5] 16 and 19). Furthermore, the thienylmagnesium reagent **3a** reacted with di-*tert*-butyl dicarbonate (**4c**) to provide the *tert*-butyl carboxylate **5c** in 82% yield (Table 1, entry 3). After transmetalation with $ZnCl_2$ (1 equiv), Negishi cross-coupling reactions[6] with various electron-withdrawing and electron-donating aryl iodides and $Pd(PPh_3)_4$ (4%) as the catalyst were performed at 25°C to give the products in high yields (76–96%; Table 1, entries 2, 4, 6–9, 11–15, 17 and 20). Moreover, transmetalation of **3i** with $ZnCl_2$ (1 equiv) followed by a Cu^I-catalysed[7] acylation (10% CuCN·2LiCl) with furan-3-carbonyl chloride (**4m**) gave the functionalised ketone **5r** in 72% yield (Table 1, entry 18).

By the reaction of magnesium species, such as **3d**, with formyl-substituted heterocyclic iodides (**4j**), we were able to perform either an addition to an aldehyde or a Negishi cross-coupling at the iodide substituent (Table 1, entries 10 and 11). After transmetalation with $ZnCl_2$ (0.5 equiv), the reaction with 5-iodofuran-2-carbaldehyde (**4j**) rapidly gave the corresponding alcohol **5j** in 60% yield.[5] By the addition of $Pd(PPh_3)_4$ (4%), the formyl group remained untouched and the Negishi cross-coupling took place to provide **5k** in 76% yield (Scheme 2).



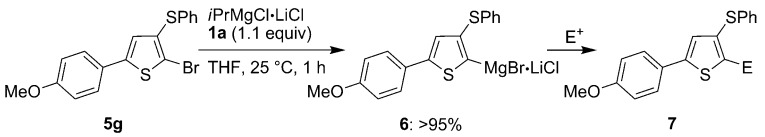
Scheme 2. The tuneable reactivity of the heteroarylmagnesium reagent **3d** towards **4j** by the presence or absence of $Pd(PPh_3)_4$.

In order to exemplify the further functionalisation of monobromothiophenes of type **5** that were obtained after the selective Br/Mg exchange (Table 1), the previously prepared mono-bromothiophene **5g** was submitted to a second Br/Mg-exchange reaction by using *i*PrMgCl·LiCl (**1a**; 1.1 equiv) at ambient temperature. The resulting magnesium reagent **6** was readily used in different types of quenching reactions (Scheme 3 and Table 2).

The thienylmagnesium reagent **6** reacted easily with aldehyde **4n** to provide the alcohol **7a** in 77% yield (Table 2, entry 1). After transmetalation with $ZnCl_2$ (1 equiv), a Negishi cross-coupling reaction with aryl iodide **4h** and $Pd(PPh_3)_4$ (5%) as the catalyst gave the expected product in 73% yield (**7b**; Table 2, entry 2). Moreover, transmetalation with $ZnCl_2$ (1 equiv) followed by a Cu^I-catalysed acylation (10% CuCN·2LiCl) with the acyl chloride **4o** gave the functionalised ketone **7c** in 70% yield (Table 2, entry 3).

The regioselective Br/Mg exchange was also extended to various 3,5-dibromopyridine derivatives (Scheme 4). The corresponding magnesium species **9a–d** were obtained in satisfactory regioselectivities of up to 28:1 (Table 3). Subsequent Negishi cross-coupling reactions, after transmetalation with $ZnCl_2$, led to the formation of the trisubstituted pyridine derivatives **10a–d** in good yields (60–88%; Table 3, entries 1–4). Both electron-poor and electron-rich aryl iodides were used successfully. The cross-coupling reactions were usually complete within a reaction time of one hour at 25°C.

Preliminary experiments showed that the regioselectivity of the Br/Mg-exchange reaction on 2,5-dibromothiophenes with an alkyl substituent at position 3 was poor with the use of *i*PrMgCl·LiCl (**1a**). Therefore, we envisioned that increasing the steric hindrance of the Grignard reagent



Scheme 3. Further functionalisation of the cross-coupling product **5g** by Br/Mg exchange and subsequent reactions with different electrophiles.

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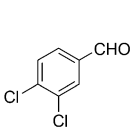
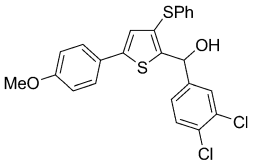
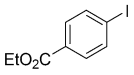
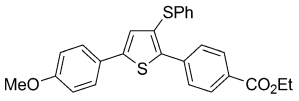
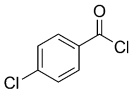
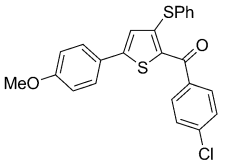
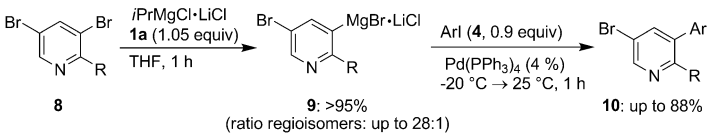
Table 2. Preparation of functionalised thiophenes of type **7** by reaction with the regioselectively generated heteroarylmagnesium reagent **6**.

Entry	Electrophile	Product: Yield[a]
1	 **4n**	 **7a**: 77 %
2	 **4h**	 **7b**: 73 %[b]
3	 **4o**	 **7c**: 70 %[c]

[a] Yield of analytically pure isolated product as determined by ^{1}H NMR analysis. [b] Obtained after a Negishi cross-coupling reaction [$ZnCl_2$ (1 equiv) then $Pd(PPh_3)_4$ (5 %)] with ArI (0.9 equiv). [c] Obtained after an acylation reaction [$ZnCl_2$ (1 equiv) then CuCN·2LiCl (10 %)] with ArCOCl (0.9 equiv).

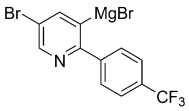
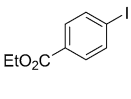
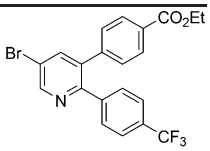
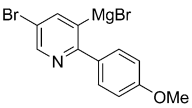
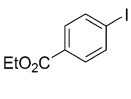
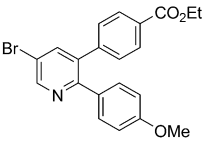
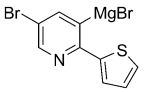
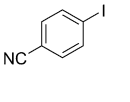
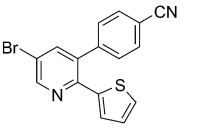
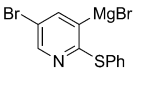
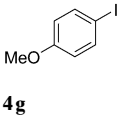
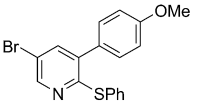


Scheme 4. Regioselective Br/Mg exchange on unsymmetrical 2,5-dibromopyridines of type **8** by using *i*PrMgCl·LiCl (**1a**).

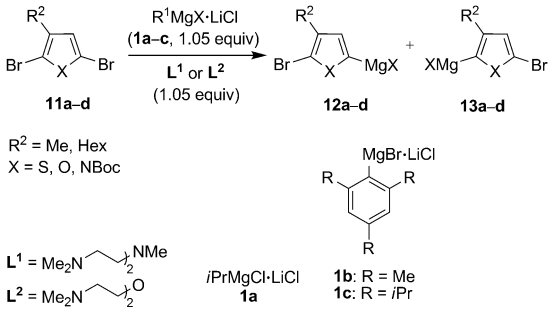
R^1MgX·LiCl of type **1** and its aggregation in solution, by adding typical chelating amines such as ligand $\mathbf{L^1}$ or $\mathbf{L^2}$, would improve the regioselectivity of the Br/Mg-exchange reaction (Scheme 5).[8]

Thus, the treatment of 2,5-dibromo-3-methylthiophene (**11a**) with *i*PrMgCl·LiCl (**1a**; 1.05 equiv) gave a regioisomeric mixture of the thienylmagnesium chlorides **12a** and **13a** in a ratio of 80:20 (Table 4, entry 1). However, the addition of a tridentate ligand, such as *N*-[2-(dimethylamino)ethyl]-*N*,*N*′,*N*′-trimethylethane-1,2-diamine ($\mathbf{L^1}$; 1.05 equiv) or 2,2′-oxy-*bis*(*N*,*N*-dimethylethanamine)[9] ($\mathbf{L^2}$; 1.05 equiv), which led to the formation of the sterically more hindered complexes **1a**·$\mathbf{L^1}$ and **1a**·$\mathbf{L^2}$, significantly improved the regioisomeric ratio of the resulting magnesium reagents in favour of **12a** (85:15 and 87:13; Table 4, entries 2 and 3). Moreover, lower temperatures (−60 °C, 1 h) further increased the regioisomeric ratio up to 90:10 in favour of the formation of **12a** (Table 4, entry 4). Additives such as TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethan-1,2-diamine), DABCO (1,4-diazabicyclo[2.2.2]octane) or NEt_3 showed little influence on the regioselectivity of the Br/Mg-exchange reaction with **11a**. In comparison to secondary alkylmagnesium reagents such as **1a**, arylmagnesium bromides, such as **1b** or **1c**, displayed lower exchange reaction rates but led to a better regioselectivity, increasing from 84:16 to 96:4 (compare Table 4, entry 1 with entries 5 and 7). Remarkably, the addition of $\mathbf{L^2}$ (1.05 equiv) to LiCl-solubilised mesitylmagnesium bromide (**1b**, 1.05 equiv; −20 °C, 12 h) predominantly converted **11a** into the Grignard species **12a** with a regioisomeric ratio of 97:3 (Table 4, entry 6). The reaction of **11a** with the even more sterically hindered ex-

Table 3. Preparation of functionalised pyridines of type **10** by reaction with regioselectively generated heteroarylmagnesium reagents of type **9**.

Entry	Mg Reagent (conditions [*T*, *t*]): Regioselectivity[a]	Electrophile	Product: Yield[b,c]
1	 **9a** (−55 °C, 2 h): 27:1	 **4h**	 **10a**: 88 %
2	 **9b** (−78 °C, 2 h): 13:1	 **4h**	 **10b**: 64 %
3	 **9c** (0 °C, 1 h): 28:1	 **4i**	 **10c**: 74 %
4	 **9d** (−65 °C, 1 h):[d] 17:1	 **4g**	 **10d**: 60 %

[a] Obtained after exchange reaction with *i*PrMgCl·LiCl (**1a**; 1.05 equiv) in THF. The ratio of regioisomers was determined by ^{1}H NMR analysis of the quenched crude reaction mixture (HOAc, 10 equiv). [b] Yield of analytically pure isolated product as determined by ^{1}H NMR analysis. [c] Obtained after a Negishi cross-coupling reaction [$ZnCl_2$ (1 equiv) then $Pd(PPh_3)_4$ (4 %)] with ArI (0.9 equiv). [d] The exchange reaction was performed by using iPr_2Mg·LiCl (0.55 equiv).



Scheme 5. Regioselective Br/Mg-exchange on unsymmetrical 2,5-dibromohetero-cycles of type **11**. Hex = *n*-hexyl.

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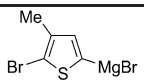
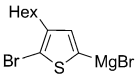
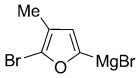
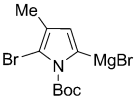
Table 4. Regioselective Br/Mg exchange on unsymmetrical 2,5-dibromoheterocycles by using various complexed and uncomplexed Grignard reagents of type **1**.

Entry	$R^1MgX{\cdot}LiCl{\cdot}\mathbf{L}^{1,2}$	Conditions [*T*, *t*][a]	Product of Type **10**: Regioselectivity[b]
			
1	**1a**	−20 °C, 20 min	**12a**: 80:20
2	**1a**·**L**^{1}	−20 °C, 20 min	**12a**: 85:15
3	**1a**·**L**^{2}	−20 °C, 20 min	**12a**: 87:13
4	**1a**·**L**^{2}	−60 °C, 1 h	**12a**: 90:10
5	**1b**	−20 °C, 12 h	**12a**: 84:16
6	**1b**·**L**^{2}	−20 °C, 12 h	**12a**: 97:3
7	**1c**	−10 °C, 12 h	**12a**: 96:4
8	**1c**·**L**^{2}	−10 °C, 16 h	**12a**: >99:1[c] 
9	**1a**·**L**^{2}	−10 °C, 20 min	**12b**: 85:15
10	**1c**·**L**^{2}	−10 °C, 16 h	**12b**: >99:1[c] 
11	**1a**·**L**^{2}	−10 °C, 6 h	**12c**: 80:20
12	**1c**·**L**^{2}	−10 °C, 16 h	**12c**: 95:5 
13	**1a**·**L**^{2}	−10 °C, 6 h	**12d**: 75:25
14	**1c**·**L**^{2}	−10 °C, 16 h	**12d**: 91:9

[a] Complete conversion as determined by GC analysis of an iodolysed reaction aliquot. [b] Determined by ^{1}H NMR anaylsis of the quenched crude reaction mixture (HOAc, 10 equiv). [c] The regioisomer of type **13** was not observed in ^{1}H NMR analysis of the hydrolysed crude reaction mixture (HOAc, 10 equiv, −20 to 25 °C).

change reagent 2,4,6-triisopropylphenylmagnesium bromide (**1c**) furnished with **L**^{2} (1.05 equiv) at −10 °C in 16 h the products **12a**/**13a** in a ratio of >99:1 (Table 4, entry 8).[10]

These results were extended to the reaction of various 2,5-dibromoheterocycles (**11b–d**; Table 4, entries 9–14). In each case, the use of the sterically hindered Grignard reagent **1c** in combination with **L**^{2} (1.05 equiv) gave the best results (compare Table 4, entries 9, 11 and 13 with 10, 12 and 14). However, the use of the bulky reagent **1c**·**L**^{2} led to significantly lower exchange rates and the Br/Mg exchange required a reaction time of about 16 h compared to 1–6 h.

With these conditions in hand (**1c**·**L**^{2}, −10 °C, 16 h) we have selectively formed the magnesium derivatives of various five-membered heterocyclic species with a regioselectivity of >99:1 (Table 5). The newly generated magnesium species reacted readily with aldehydes to provide the corresponding alcohols **14e**, **14i**, **14l** and **14n** in 71–88 % yield (Table 5, entries 5, 9, 12 and 14). Furthermore, the thienylmagnesium derivative **12a** reacted with di-*tert*-butyl dicarbonate (**4c**) to give the *tert*-butyl carboxylate **14a** in 83 % yield (Table 5, entry 1). Transmetalation of **12a** with $ZnCl_2$ (0.5 equiv) followed by the addition of CuCN·2LiCl (0.5 equiv) and chloranil (1.5 equiv) generated the substituted thiophenyl dimer **14d** in 87 % yield (Table 5, entry 4).[11]

Table 5. Preparation of functionalised five-membered heterocycles of type **14** by reaction with regioselectively generated heteroarylmagnesium reagents of type **12**.

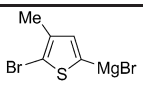
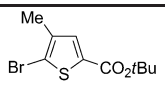
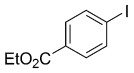
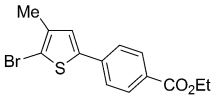
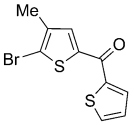
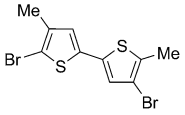
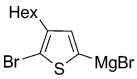
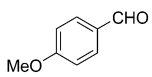
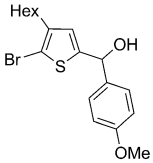
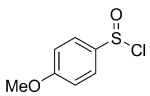
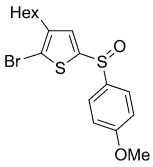
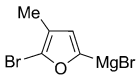
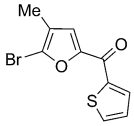
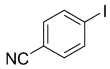
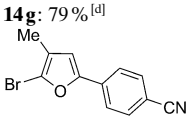
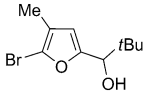
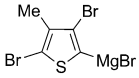
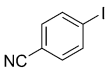
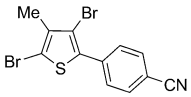
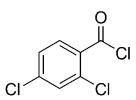
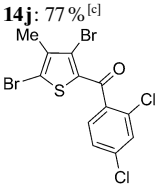
Entry	Mg Reagent: Regioselectivity[a]	Electrophile	Product: Yield[b]
		$(tBuO_2C)_2O$	
1	**12a**: >99:1	**4c** 	**14a**: 83 % 
2	**12a**: >99:1	**4h** 	**14b**: 86 %[c] 
3	**12a**: >99:1	**4p**	**14c**: 85 %[d] 
4	**12a**: >99:1 	– 	**14d**: 87 %[e] 
5	**12b**: >99:1	**4e** 	**14e**: 71 % 
6	**12b**: >99:1 	**4q** 	**14f**: 70 % 
7	**12c**: >99:1	**4p** 	**14g**: 79 %[d] 
8	**12c**: >99:1	**4i** *t*BuCHO	**14h**: 78 %[c] 
9	**12c**: >99:1 	**4r** 	**14i**: 73 % 
10	**12e**:[f] >99:1	**4i** 	**14j**: 77 %[c] 

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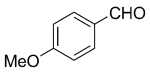
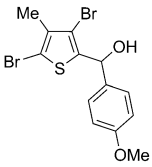
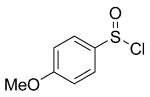
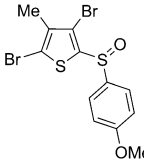
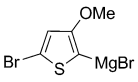
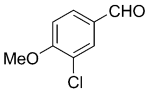
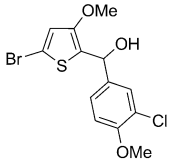
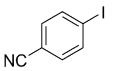
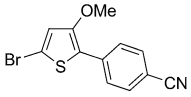
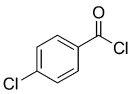
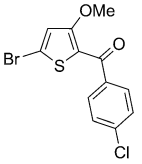
Table 5. (Continued)

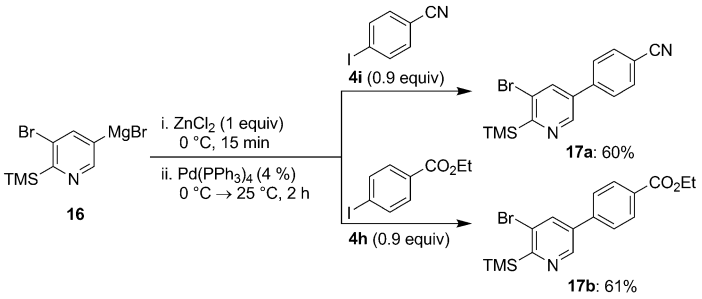
Entry	Mg Reagent: Regioselectivity[a]	Electrophile	Product: Yield[b]
11	**12e**:[f] >99:1	**4s** 	**14k**: 86%[d] 
12	**12e**:[f] >99:1	**4e** 	**14l**: 88% 
13	**12e**:[f] >99:1 	**4q** 	**14m**: 94% 
14	**12f**: >99:1	**4a** 	**14n**: 73% 
15	**12f**: >99:1	**4i** 	**14o**: 69%[c] 
16	**12f**: >99:1	**4o**	**14p**: 66%[d]

[a] Ratio of regioisomers determined by ^{1}H NMR analysis of the quenched crude reaction mixture (HOAc, 10 equiv). [b] Obtained after an exchange reaction with **1c** (1.05 equiv) and **L^2** (1.05 equiv) in THF at −10 °C in 16 h. Yield of analytically pure isolated product as determined by ^{1}H NMR analysis. [c] Obtained after a Negishi cross-coupling reaction [$ZnCl_2$ (1 equiv) then $Pd(PPh_3)_4$ (4%)] with ArI (0.9 or 1.2 equiv). [d] Obtained after an acylation reaction [$ZnCl_2$ (1 equiv) then CuCN·2LiCl (10 mol%)] with ArCOCl (0.9 or 1.2 equiv). [e] Obtained after transmetalation with $ZnCl_2$ (0.5 equiv) and a copper-mediated oxidative dimerisation [CuCN·2LiCl (0.5 equiv) then addition of chloranil (1.5 equiv)]. [f] Exchange reaction performed at 0 °C for 1 h.

Similarly, after transmetalation with $ZnCl_2$ (1 equiv), Negishi cross-coupling reactions with various aryl iodides and $Pd(PPh_3)_4$ (4%) as the catalyst at 25 °C led to the expected products in 69–86% yield (Table 5, entries 2, 8, 10 and 15). By transmetalation with $ZnCl_2$ (1 equiv) followed by a Cu^I-catalysed acylation (10% CuCN·2LiCl) with a range of acyl chlorides, the functionalised ketones **14c**, **14g**, **14k** and **14p** were obtained in 66–86% yield (Table 5, entries 3, 7, 11 and 16). The direct reaction of 4-methoxybenzenesulfinyl chloride (**4q**) with the heterocyclic magnesium species furnished the sulfoxides **14f** and **14m** in 70–94% yield (Table 5, entries 6 and 13).[12]

It is worth mentioning that the Br/Mg-exchange reaction of 2,5-dibromo-3-methoxythiophene with the bulky reagent **1c·L^2** led to the formation of the 2-magnesium-substituted thiophene (**12f**; Table 5, entries 14–16) and not to the 5-magnesium-substituted product (as occurs for the reactions of the other dibromothiophene derivatives **11a–c** and **11e**). We assume that this selectivity resulted from a preliminary coordination of the bulky magnesium reagent to the oxygen of the methoxy substituent. This complexation seemed to be essential for the Br/Mg-exchange reaction to proceed. In contrast, by using *i*PrMgCl·LiCl (**1a**) in the Br/Mg-exchange reaction, the opposite selectivity has been observed (4:1 ratio in favour of the 5-magnesium-substituted thiophene).[13] This might be a result of the high reactivity of *i*PrMgCl·LiCl (**1a**), which allows the exchange reaction to proceed without prior chelation in an etheral solvent such as THF.

The regioselective Br/Mg exchange with **1c·L^2** was also extended to 3,5-dibromo-2-(trimethylsilyl)pyridine (**15**) leading to the corresponding magnesium reagent **16** at −25 °C in 2 h (Scheme 6). The subsequent Negishi cross-coupling reactions, after transmetalation with $ZnCl_2$, led to the formation of the trisubstituted pyridine derivatives **17a–b** in satisfactory yields (60–61%, Scheme 6).



Scheme 6. Preparation of functionalised pyridines of type **17** by reaction with the regioselectively generated heteroarylmagnesium reagent **16**. TMS = trimethylsilyl.

Conclusions

We have described a highly regioselective preparation of five- and six-membered heteroarylmagnesium derivatives by using the efficient Br/Mg-exchange reagents *i*PrMgCl·LiCl (**1a**) and isitylmagnesium bromide·lithium chloride (**1c**). *i*PrMgCl·LiCl (**1a**) underwent highly regioselective Br/Mg-exchange reactions with dibromoheterocycles derived from thiophenes, thienothiophenes and pyridines. Ring substituents, such as thioether or trimethylsilyl groups, as well as pyridyl and thienyl groups or *ortho*-substituted aryl groups, directed the Br/Mg exchange at position 5 with a regioselectivity of up to >99:1.

In the case of alkyl-substituted dibromothiophene or -furan derivatives, the sterically hindered Grignard reagent 2,4,6-triisopropylphenylmagnesium bromide (**1c**) in combination with the chelating diamine 2,2′-oxy-*bis*(*N*,*N*-dimethy-

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lethanamine) ($\mathbf{L^2}$) gave the best results. The bulky complex **1c**·$\mathbf{L^2}$ gave regioselectivities of >99:1 in the Br/Mg-exchange reactions.

All selectively formed, heterocyclic magnesium-derivative scaffolds were subsequently funtionalised with a broad range of electrophiles, such as aldehydes, aryl iodides, acyl chlorides or aryl sulfinyl chlorides. This gave access to a wide range of highly functionalised thiophene or pyridine derivatives from readily available dibromo-precursors. Moreover, the resulting mono-bromoheterocycles could readily be submitted to a second Br/Mg-exchange reaction followed by further functionalisation reactions.

This method is very versatile and one example of its possible application is the synthesis of poly(3-hexylthiophene) (P3HT),[14] in which the regioregularity determines macroscopic physical properties of the polymers.[15]

Experimental Section

Regioselective Br/Mg exchange on unsymmetrical 2,5-dibromothiophenes of type 2:

*Synthesis of 2-bromo-5-(4-nitrophenyl)-3-(phenylthio)thiophene (**5f**)*: A dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with *i*PrMgCl·LiCl (**1a**; 1.2 M in THF, 0.88 mL, 1.05 mmol). 2,5-Dibromo-3-(phenylthio)thiophene (**2b**; 350 mg, 1 mmol) was added as a solution in THF (1.0 M) at 0 °C and stirred continuously for 1 h (the completion of the Br/Mg exchange was monitored by GC analysis of iodolysed reaction aliquots with the use of undecane as an internal standard). $ZnCl_2$ (1.0 mL, 1.0 M in THF, 1 mmol) was added to the freshly prepared heteroarylmagnesium reagent **3b** and the reaction mixture was stirred for 15 min at 0 °C. $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and 1-iodo-4-nitrobenzene (**4f**; 224 mg, 0.9 mmol) were added and the reaction mixture was warmed to 25 °C. After stirring for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted three times with EtOAc, dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatographic purification on silica gel (pentane/Et_2O = 100:3) gave **5f** (302 mg, 86%) as a yellow solid. M.p.: 129.0–130.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.21–8.29 (m, 2H), 7.62–7.69 (m, 2H), 7.42 (s, 1H), 7.25–7.39 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.3, 144.5, 138.7, 135.2, 132.1, 129.4, 129.3, 128.9, 127.5, 125.9, 124.5, 119.9 ppm; MS (EI, 70 eV): *m*/*z* (%): 395 (M^+, 10), 393 (M^+, 100), 391 (95), 312 (13), 267 (15), 266 (72), 265 (24), 234 (14), 221 (36), 189 (13), 121 (11), 113 (15), 77 (14), 43 (14); IR (ATR): $\tilde{\nu}$ = 3092, 3076, 3061, 2932, 2842, 1591, 1578, 1516, 1506, 1477, 1341, 1332, 1108, 1022, 851, 819, 740, 726, 687 cm^{-1}; HRMS (EI): *m*/*z* calcd for $C_{16}H_{10}BrNO_2S_2$: 390.9336 (M^+); found: 390.9333.

Regioselective Br/Mg exchange on unsymmetrical 2,5-dibromopyridines of type 8:

*Synthesis of ethyl 4-(5-bromo-2-(4-(trifluoromethyl)phenyl)pyridin-3-yl)-benzoate (**10a**)*: A dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with *i*PrMgCl·LiCl (**1a**; 1.2 M in THF, 0.88 mL, 1.05 mmol). 3,5-Dibromo-2-(4-(trifluoromethyl)-phenyl)pyridine (**8a**; 381 mg, 1 mmol) was added as a solution in THF (1.0 M) at −55 °C and stirred continuously for 1 h (the completion of the Br/Mg exchange was monitored by GC analysis of iodolysed reaction aliquots with the use of undecane as an internal standard). $ZnCl_2$ (1.0 mL, 1.0 M in THF, 1 mmol) was added to the freshly prepared heteroarylmagnesium reagent **9a** and the reaction mixture was stirred for 15 min at −20 °C. $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and ethyl 4-iodobenzoate (**4h**; 249 mg, 0.9 mmol) were added and the reaction mixture was warmed to 25 °C. After stirring for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted three times with EtOAc, dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatographic purification on silica gel (pentane/Et_2O = 9:1 + 1% NEt_3) gave **10a** (354 mg, 88%) as a white solid. M.p.: 97.5–99.1 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.80 (d, *J* = 2.2 Hz, 1H), 7.99–8.02 (m, 2H), 7.92 (d, *J* = 2.2 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.23–7.26 (m, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.41 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.0, 154.0, 150.0, 142.4, 142.2 (q, *J* = 1.1 Hz), 140.7, 136.8, 130.3 (q, *J* = 32.8 Hz), 130.2, 130.0, 129.9, 129.4, 125.1 (q, *J* = 3.7 Hz), 123.9 (q, *J* = 272.4 Hz), 119.9, 61.2, 14.3 ppm; MS (EI, 70 eV) *m*/*z* (%): 451 (M^+, 97), 450 (M^+, 100), 449 (M^+, 95), 448 (M^+, 85), 421 (32), 419 (35), 406 (21), 404 (21), 378 (15), 376 (17), 297 (31), 296 (15), 228 (11), 227 (11); IR (ATR): $\tilde{\nu}$ = 3055, 2982, 2940, 2904, 1705, 1608, 1426, 1368, 1323, 1310, 1288, 1273, 1166, 1120, 1111, 1101, 1068, 1024, 1009, 854, 783, 769, 715, 706 cm^{-1}; HRMS (EI): *m*/*z* calcd for $C_{21}H_{15}BrF_3NO_2$: 449.0238 (M^+); found: 449.0231.

Regioselective Br/Mg-exchange on unsymmetrical 2,5-dibromoheterocycles of type 11:

*Synthesis of (5-bromo-4-methylthiophen-2-yl)(thiophen-2-yl)methanone (**14c**)*: A dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with 2,4,6-triisopropylmagnesium bromide (**1c**; 0.7 M in THF, 3.0 mL, 2.1 mmol) and 2,2′-oxy-*bis*(*N*,*N*-diethylethanamine) ($\mathbf{L^2}$; 337 mg, 2.1 mmol). After stirring for 15 min at 25 °C, 2,5-dibromo-3-methylthiophene (**11a**; 512 mg, 2 mmol) was added as a solution in THF (1.0 M) at −10 °C and stirred continuously for 16 h (the completion of the Br/Mg exchange was monitored by GC analysis of iodolysed reaction aliquots with the use of undecane as an internal standard). $ZnCl_2$ (1.0 mL, 1.0 M in THF, 1 equiv) was added to the freshly prepared heteroarylmagnesium reagent **12a** and the reaction mixture was stirred for 15 min at −10 °C. CuCN·2LiCl (0.2 mL, 1.0 M in THF, 0.2 mmol) and thiophene-2-carbonyl chloride (**4p**; 352 mg, 2.4 mmol) were added and the reaction mixture was warmed to 25 °C. After stirring for 4 h, the reaction mixture was quenched with saturated aqueous NH_4Cl/NH_3 solution (10:1), extracted three times with EtOAc, dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatographic purification on silica gel (pentane/Et_2O = 95:5) gave **14c** (488 mg, 85%) as an off-white solid. M.p.: 100.2–101.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.69 (dd, *J* = 4.9, 1.1 Hz, 1H), 7.57 (s, 1H), 7.17 (dd, *J* = 5.0, 3.8 Hz, 1H), 2.25 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.6, 142.2, 141.8, 138.7, 134.6, 133.6, 133.0, 128.0, 120.0, 15.4 ppm; MS (EI, 70 eV) *m*/*z* (%): 289 (11), 288 (M^+, 100), 287 (11), 286 (M^+, 93), 207 (13), 205 (37), 203 (36), 111 (77), 96 (11); IR (ATR): $\tilde{\nu}$ = 3004, 2362, 2340, 1740, 1658, 1582, 1522, 1432, 1366, 1228, 1222, 1204, 1098, 1056, 780, 706 cm^{-1}; HRMS (EI): *m*/*z* calcd for $C_{10}H_7BrOS_2$: 285.9122 (M^+); found: 285.9117.

Regioselective Br/Mg exchange on 3,5-dibromo-2-(trimethylsilyl)pyridine (15):

*Synthesis of ethyl 4-(5-bromo-6-(trimethylsilyl)pyridin-3-yl)benzoate (**17b**)*: A dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with 2,4,6-triisopropylmagnesium bromide (**1c**; 0.7 M in THF, 1.5 mL, 1.05 mmol) and 2,2′-oxy-*bis*(*N*,*N*-diethylethanamine) ($\mathbf{L^2}$; 168 mg, 1.05 mmol). After stirring for 15 min at 25 °C, 3,5-dibromo-2-(trimethylsilyl)pyridine (**15**; 309 mg, 1 mmol) was added as a solution in THF (1.0 M) at −25 °C and stirred continuously for 2 h (the completion of the Br/Mg exchange was monitored by GC analysis of iodolysed reaction aliquots with the use of undecane as an internal standard). $ZnCl_2$ (1.0 mL, 1.0 M in THF, 1 mmol) was added to the freshly prepared heteroarylmagnesium reagent **16** and the reaction mixture was stirred for 15 min at −20 °C. $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and ethyl 4-iodobenzoate (**4h**; 249 mg, 0.9 mmol) were added and the reaction mixture was warmed to 25 °C. After stirring for 2 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted three times with EtOAc, dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatographic purification on silica gel (pentane/Et_2O = 95:5) gave **17b** (208 mg, 61%) as a pale-yellow solid. M.p.: 88.2–89.8 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.02 (d, *J* = 2.0 Hz, 1H), 8.25 (d, *J* = 2.0 Hz, 1H), 7.95–8.03 (m, 2H), 7.84–7.90 (m, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 0.37 ppm (s, 9H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 165.8, 165.7, 146.7, 140.4, 136.5, 135.8, 130.3, 130.2, 129.3, 127.9, 61.3, 14.6, −0.5 ppm; MS (EI, 70 eV) *m*/*z* (%): 379 (M$^+$, 44), 377 (M$^+$, 44),

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365 (22), 364 (100), 363 (20), 362 (94), 334 (31), 332 (17), 299 (47), 298 (79), 284 (30), 270 (12), 139 (11), 137 (11), 44 (32), 43 (30); IR (ATR): $\tilde{\nu}$ = 3045, 3041, 2976, 2953, 2899, 1701, 1608, 1573, 1479, 1410, 1365, 1355, 1288, 1274, 1244, 1226, 1184, 1115, 1103, 1046, 1022, 1012, 855, 838, 807, 724, 699 cm^{-1}; HRMS (EI): m/z calcd for $C_{17}H_{20}BrNO_2Si$: 379.0426 (M^+); found: 379.0417.

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