Heterocycle Functionalization

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Full Functionalization of the Imidazole Scaffold by Selective Metalation and Sulfoxide/Magnesium Exchange**

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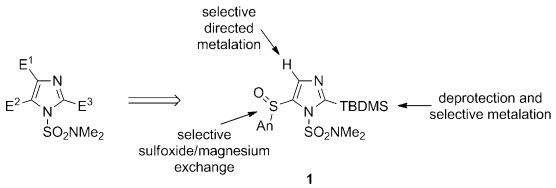
Abstract: *A simple, flexible, and straightforward method for the functionalization of all the positions of the imidazole heterocycle through regioselective arylations, allylations, acylations, and additions to aldehydes is disclosed. Starting from the readily available key imidazole* ***1****, highly functionalized imidazole derivatives have been synthesized in a regioselective manner from directed metalations and a sulfoxide/magnesium exchange. Moreover, the selective N3-alkylation followed by deprotection of N1 (trans-N-alkylation) allows the regioselective N-alkylation of complex imidazoles.*

The imidazole scaffold is present in a plethora of biological relevant molecules displaying a variety of pharmaceutical properties.[1] This makes the full functionalization of the imidazole ring an important target in organic synthesis.[2] Recently, we demonstrated that a combination of metalation and sulfoxide/magnesium exchange allows the 7-azaindole skeleton to be fully functionalized.[3] Herein, we report a simple, flexible, and straightforward method for the functionalization of all the positions of the imidazole ring through regioselective arylations, allylations, acylations, and additions to aldehydes via zinc and magnesium intermediates.

Thus, we have constructed imidazole **1** bearing an *N,N*-dimethylsulfamoyl group at N1, a *tert*-butyldimethylsilyl (TBDMS) group at C2, and a 4-methoxy-3,5-dimethylbenzenesulfinyl (AnS(O)) group at C5 (Scheme 1).



Scheme 1. Imidazole **1** as the key intermediate for full functionalization. An = 4-methoxy-3,5-dimethylphenyl.

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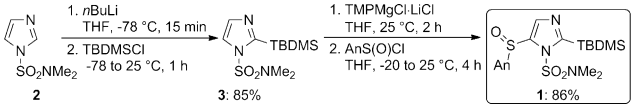
The *N,N*-dimethylsulfamoyl group is known to direct metalations to the *ortho* position.[2c,4] The TBDMS group protects the highly acidic C2-position and ensures a selective metalation at position C5. The AnS(O) group has been chosen for both its ability to direct the metalation to position 4 and its replacement through a sulfoxide/magnesium exchange[3,5] to furnish the corresponding magnesium species.

The preparation of **1** is straightforward and accomplished in two steps from the protected imidazole **2** in 73% overall yield. Thus, the lithiation of the N1-protected imidazole **2**[6] in THF (−78 °C, 15 min) and subsequent silylation with TBDMS-Cl afforded the 2-silylated imidazole **3** in 85% yield.[7] Magnesiation with TMPMgCl·LiCl[8] (TMP = 2,2,6,6-tetramethylpiperidyl) in THF (25 °C, 2 h) followed by reaction with AnS(O)Cl[9] produced the key intermediate **1** in 86% yield (Scheme 2).

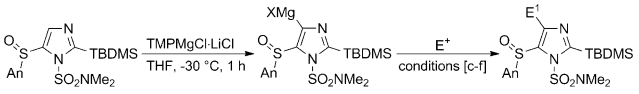


Scheme 2. Synthesis of the key imidazole **1**.

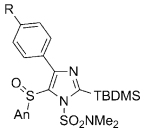
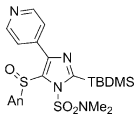
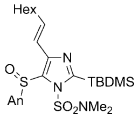
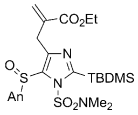
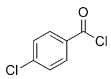
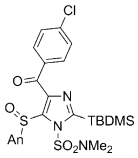
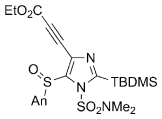
The sulfoxide substituent enables the selective metalation of imidazole **1** in position 4 with TMPMgCl·LiCl (1.1 equiv, −30 °C, 1 h) in quantitative yield.[10] The resulting Mg reagent **4** can be readily functionalized by reaction with various electrophiles of type **5** to furnish 4-substituted imidazoles **6** (Table 1).

After transmetalation with $ZnCl_2$ (1.1 equiv, −30 °C, 15 min), Mg reagent **4** undergoes smooth Pd-catalyzed Negishi cross-coupling reactions.[11] Various electron-rich and electron-poor electrophiles (0.9 equiv) can be used in the cross-coupling reactions at 50 °C in the presence of $[Pd(PPh_3)_4]$ (5 mol%) as the catalyst to afford the 4-substituted imidazoles **6a–d** in high yields (Table 1, entries 1–4). A pyridyl (**5e**, entry 5) and a vinylic iodide (**5f**, entry 6) also led to the expected products **6e** and **6f**, respectively.[12] Moreover, after transmetalation with $ZnCl_2$ (1.1 equiv), Mg reagent **4** undergoes a Cu^I-catalyzed allylation[13] with **5g** (0.9 equiv) to give the desired product **6g** in 98% yield (entry 7). Furthermore, the Cu^I-catalyzed acylation[12] of Mg reagent **4** with benzoyl chloride **5h** (0.9 equiv) affords the corresponding ketone **6h** in 82% yield (entry 8). The Cu^I-catalyzed alkynylation[13] of Mg reagent **4** with bromoacetylene **5i**[14] (0.9 equiv) provides the highly functionalized acetylene **6i** in 53% yield (entry 9).

Table 1: Functionalization at position 4 of imidazole **1**.



1 **4**: >95% **6**

Entry	Organomagnesium reagent[a]	Electrophile	Product (yield [%])[b]
			
1	**4**	**5a**, R = CO_2Et	**6a**: 84[c]
2	**4**	**5b**, R = CF_3	**6b**: 72[c]
3	**4**	**5c**, R = Cl	**6c**: 71[c]
4	**4**	**5d**, R = OMe	**6d**: 60[c]
			
5	**4**	**5e**	**6e**: 60[c]
			
6	**4**	**5f**	**6f**: 83[c]
			
7	**4**	**5g**	**6g**: 98[d]
			
8	**4**	**5h**	**6h**: 82[e]
			
9	**4**	**5i**	**6i**: 53[f]

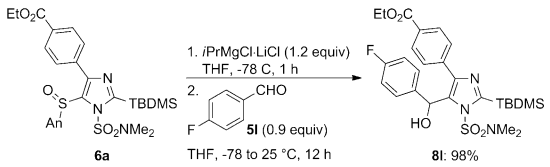
[a] Metalation with TMPMgCl·LiCl (1.1 equiv). [b] Yield of isolated product. [c] Negishi cross-coupling: $ZnCl_2$ (1.1 equiv); then $[Pd(PPh_3)_4]$ (5 mol%) with R-I (0.9 equiv). [d] Allylation: 1 equiv CuCN·2 LiCl with allyl bromide (0.9 equiv). [e] Acylation: CuCN·2 LiCl (1 equiv) with ArC(O)Cl (0.9 equiv). [f] Alkynylation: CuCN·2 LiCl (1 equiv) with alkynyl bromide (0.9 equiv)).

The next functionalization was performed in position 5 by a sulfoxide/magnesium exchange.[3,5] Treatment of imidazoles **6** with *i*PrMgCl·LiCl[15] (1.2 equiv) at −78 °C led within 1 h to the corresponding Mg species **7** in quantitative yield.[10,16] Subsequently, various functionalization reactions were carried out to furnish the corresponding 4- and 5-substituted imidazoles **8** (Table 2).

After transmetalation with $ZnCl_2$ (1.2 equiv, −78 °C, 15 min), the Mg reagents **7** readily undergo Pd-catalyzed Negishi cross-coupling reactions. Thus, the allyl-substituted imidazole-magnesium derivative **7a** reacts with **5a** and **5j** (0.9 equiv) in the presence of $[Pd(PPh_3)_4]$ (5 mol%) at 50 °C to afford the corresponding cross-coupling products **8a** and **8b** in 71 and 90% yield, respectively (Table 2, entries 1 and 2). The alkenyl-imidazole **6f** also readily undergoes Pd-catalyzed Negishi cross-coupling reactions after the sulfoxide/magnesium exchange to produce the Mg reagent **7b** and a subsequent transmetalation with $ZnCl_2$ (1.2 equiv; entries 3 and 4). Similarly, Pd-catalyzed Negishi reactions of Mg species **7c–e** furnish the corresponding cross-coupling products **8f,g** and **8i–k** in high yields (entries 6, 7, 9–11).

The Cu^I-catalyzed acylation of Mg reagents **7** furnished only protonated products. However, the Pd-catalyzed acylation developed by Negishi et al.[17] leads to the desired ketones. Thus, the magnesiated imidazole **7b** reacts with benzoyl chloride **5h** (0.9 equiv) and $[Pd(PPh_3)_4]$ (5 mol%) after transmetalation with $ZnCl_2$ (1.2 equiv) to afford the corresponding ketone **8e** in 79% yield (entry 5). The imidazole **7c** also furnishes the corresponding ketone **8h** in 66% yield under the same reaction conditions (entry 8).

As anticipated, the magnesiated imidazoles undergo not only arylations, allylations, and acylations, but also direct addition to aldehydes. Thus, the magnesium species **7c** of imidazole **6a** reacts with 4-fluorobenzaldehyde (**5l**, 0.9 equiv) to afford the hydroxyarylated imidazole **8l** in 98% yield (Scheme 3).



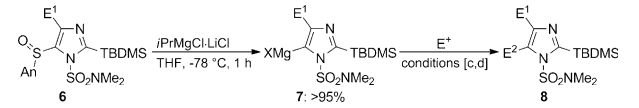
6a **8l**: 98%

Scheme 3. Selective sulfoxide/Mg exchange in position 5 of the imidazole ring by using *i*PrMgCl·LiCl, and subsequent addition to aldehyde **5l**.

To functionalize position 2, the TBDMS group was selectively removed by treatment with tetra-*n*-butylammonium fluoride (TBAF, 1 equiv) at 0 °C, which furnished the unprotected imidazoles **9** quantitatively while leaving the *N*,*N*-dimethylsulfamoyl group at N1 untouched. Both TMPMgCl·LiCl and $TMP_2Zn{\cdot}2\,MgCl{\cdot}2\,LiCl$ have been employed for the metalation of imidazoles **9**. Fully functionalized imidazoles **11** were obtained after quenching the resulting metalated imidazole derivatives **10** and **10′**[10] with a broad range of electrophiles.

The Cu^I-catalyzed allylation reaction of the Zn reagent **10a** with **5g** (1.1 equiv) leads to the desired fully functionalized imidazole **11a** in 81% yield (Table 3, entry 1). Additionally, a Pd-catalyzed Negishi cross-coupling with **5k** (0.9 equiv) produces the highly functionalized imidazole **11b** in 76% yield (entry 2). Furthermore, the Zn reagent **10b** undergoes

Table 2: Functionalization at position 5 of imidazoles **6**.



6 **7**: >95% **8**

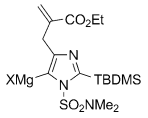
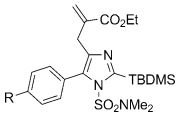
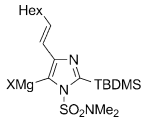
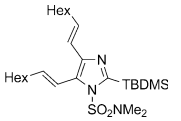
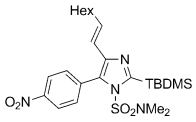
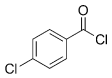
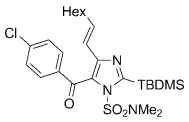
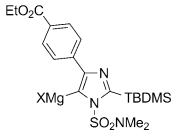
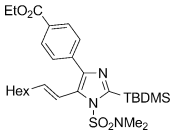
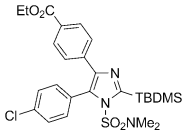
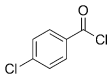
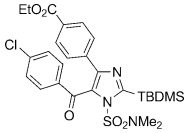
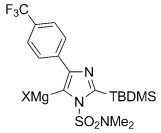
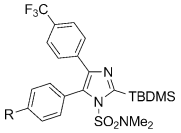
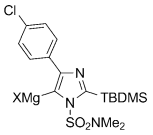
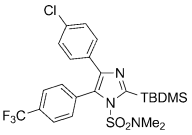
Entry	Organomagnesium Reagent[a]	Electrophile	Product (yield [%])[b]
1	 **7a**	 **5a**, R = CO_2Et	 **8a**: 71[c]
2	**7a**	**5j**, R = CN	**8b**: 90[c]
3	 **7b**	 **5f**	 **8c**: 88[c]
4	**7b**	 **5k**	 **8d**: 98[c]
5	**7b**	 **5h**	 **8e**: 79[d]
6	 **7c**	 **5f**	 **8f**: 60[c]
7	**7c**	 **5c**	 **8g**: 70[c]
8	**7c**	 **5h**	 **8h**: 66[d]
9	 **7d**	 **5a**, R = CO_2Et	 **8i**: 85[c]
10	**7d**	**5c**, R = Cl	**8j**: 80[c]

Table 2: (Continued)

Entry	Organomagnesium Reagent[a]	Electrophile	Product (yield [%])[b]
11	 **7e**	 **5b**	 **8k**: 68[c]

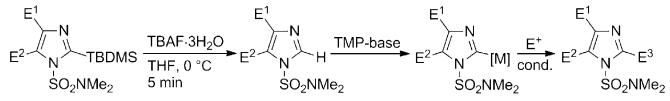
[a] Exchange with *i*PrMgCl·LiCl (1.2 equiv). [b] Yield of isolated product. [c] Negishi cross-coupling: $ZnCl_2$ (1.1 equiv); then $[Pd(PPh_3)_4]$ (5 mol%) with R-I (0.9 equiv). [d] Negishi acylation: $ZnCl_2$ (1.1 equiv); then $[Pd(PPh_3)_4]$ (5 mol%) with ArC(O)Cl (1.1 equiv).

a smooth Cu^I-catalyzed allylation with **5g** (0.9 equiv) to furnish imidazole **11c** in 86% yield (entry 3). The Pd-catalyzed Negishi cross-coupling reactions with **5a** (1.1 equiv) and **5j** (0.9 equiv) produce the highly functionalized imidazole derivatives **11d** and **11e** in 72 and 95% yield, respectively (entries 4 and 5). To demonstrate the higher reactivity of the Mg reagent **10b′** compared to the diimidazolylzinc reagent **10b**, the Grignard reagent **10b′** was submitted to an addition reaction with aldehyde **5l** (1.1 equiv), which furnished alcohol **11f** in 92% yield (entry 6). Moreover, **10b′** reacts smoothly with **5m** (0.9 equiv) to afford thioether **11g** in 93% yield (entry 7). Interestingly, the corresponding diimidazolylzinc reagent **10b** does not undergo the two reactions mentioned above, but leads only to the hydrolyzed species. The Mg reagent **10b'** reacts with benzoyl chloride **5h** (1.1 equiv) and $[Pd(PPh_3)_4]$ (5 mol%) after transmetalation with $ZnCl_2$ (1.2 equiv) to give the corresponding ketone **11h** in 58% yield (entry 8). Furthermore, after transmetalation with $ZnCl_2$ (1.2 equiv), Mg species **10c** successfully undergoes a Pd-catalyzed Negishi cross-coupling reaction to furnish imidazole **11i** in 75% yield (entry 9). Moreover, **10c** also reacts readily with **5m** (0.9 equiv) to afford the thioether **11j** in 70% yield (entry 10).

Depending on the substitution pattern, N-protected imidazoles have shown the tendency to tautomerize, thereby leading to mixtures of isomers after deprotection (triggered by steric factors).[18] *N*-Sulfamoyl-protected imidazoles are known to react with alkylating reagents exclusively through their unsubstituted N atom.[19] Hence, we have used a slightly amended method to that developed by Sames and co-workers,[2a] and treated the fully functionalized imidazole derivatives of type **11** with the Meerwein reagent (trimethyloxonium tetrafluoroborate, 1 equiv) to generate the corresponding imidazolium salts **12**. The *N*,*N*-dimethylsulfamoyl group at the N1-position is then cleaved by the addition of HCl (conc.) to furnish the alkylated imidazoles **13** as only one isomer.[20] Noteworthy, this method allows the selective preparation of regioisomers **13a/b** as well as **13c/13d** (Scheme 4).

In summary, we have developed a general, selective, and flexible synthetic method to prepare complex substituted imidazoles in a regioselective manner starting from key intermediate **1** through directed metalations and a sulfoxide/magnesium exchange. Moreover, we demonstrated the selec-

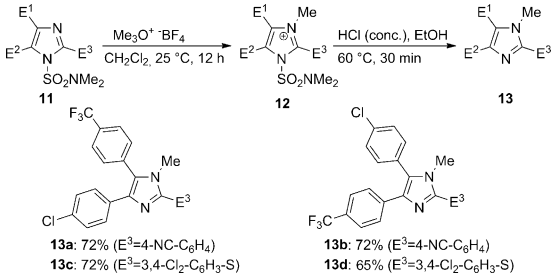
Table 3: Functionalization at position 2 of imidazoles **8**.



cond. = conditions [d-i]

Entry	Organometallic reagent[a,b]	Electrophile	Product (yield [%])[c]
1	**10a**	**5g**	**11a**: 81[d]
2	**10a**	**5k**	**11b**: 76[e]
3	**10b**	**5g**	**11c**: 86[d]
4	**10b**	**5a**, R = CO_2Et	**11d**: 72[e]
5	**10b**	**5j**, R = CN	**11e**: 95[e]
6	**10b′**	**5l**	**11f**: 92[f]
7	**10b′**	**5m**	**11g**: 93[g]
8	**10b′**	**5h**	**11h**: 58[h]
9	**10c**	**5j**	**11i**: 75[i]
10	**10c**	**5m**	**11j**: 70[g]

[a] Metalation with $TMP_2ZnCl{\cdot}2\,MgCl_2{\cdot}2\,LiCl$ (1.2 equiv). [b] Metalation with TMPMgCl·LiCl (1.2 equiv). [c] Yield of isolated product. [d] Allylation: CuCN·2 LiCl (1 equiv) with allyl bromide (1.1 equiv). [e] Negishi cross-coupling: $[Pd(PPh_3)_4]$ (5 mol%) with Ar-I (0.9 or 1.1 equiv). [f] Addition to aldehyde (1.1 equiv). [g] Addition to *S*-arylbenzene thiosulfonate (0.9 equiv). [h] Negishi acylation: $ZnCl_2$ (1.1 equiv); then $[Pd(PPh_3)_4]$ (5 mol%) with ArCOCl (1.1 equiv). [i] Negishi cross-coupling: $ZnCl_2$ (1.1 equiv); then $[Pd(PPh_3)_4]$ (5 mol%) with Ar-I (0.9 equiv).



Scheme 4. Selective methylation with the Meerwein reagent at N3 of the imidazole ring and subsequent deprotection at N1.

tive N3-alkylation followed by deprotection of N1 (trans-N-alkylation), thus allowing the regioselective N-alkylation of complex imidazoles. Further extensions of this work are currently underway in our laboratories.

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[1] a) *The Chemistry of Heterocycles* (Eds.: S. Hauptmann, T. Eicher), Wiley-VCH, New York, **2003**; b) K. Shalini, P. K. Sharma, N. Kumar, *Chem. Sin.* **2010**, *1*, 36; c) S. H. Cohen, D. N. Gerding, S. Johnson, C. P. Kelly, V. G. Loo, L. C. McDonald, J. Pepin, M. H. Wilcox, *Infect. Control Hosp. Epidemiol.* **2010**, *31*, 431; d) N. Xi, Q. Huang, L. Liu, *Comprehensive Heterocyclic Chemistry*, *Vol. 4* (Eds.: A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor), Elsevier, Oxford, **2008**, p. 143; e) L. D. Luca, *Curr. Med. Chem.* **2006**, *13*, 1.

[2] For the synthesis and properties of imidazole derivatives, see a) J. M. Joo, B. B. Touré, D. Sames, *J. Org. Chem.* **2010**, *75*, 4911; b) F. Shibahara, T. Yamauchi, E. Yamaguchi, T. Murai, *J. Org. Chem.* **2012**, *77*, 8815; c) B. Delest, P. Nshimyumukiza, O. Fasbender, B. Tinant, J. Marchand-Brynaert, F. Darro, R. Robiette, *J. Org. Chem.* **2008**, *73*, 6816; d) B. Lipshutz, W. Hagen, *Tetrahedron Lett.* **1992**, *33*, 5865; e) B. H. Lipshutz, B. Huff, W. Hagen, *Tetrahedron Lett.* **1988**, *29*, 3411; f) B. H.

Lipshutz, W. Vaccaro, B. Huff, *Tetrahedron Lett.* **1986**, *27*, 4095; for reviews, see g) F. Bellina, R. Rossi, *Adv. Synth. Catal.* **2010**, *352*, 1223; h) T. Satoh, M. Miura, *Chem. Lett.* **2007**, *36*, 200; i) M. Schnürch, R. Flasik, A. F. Khan, M. Spina, M. D. Mihovilovic, P. Stanetty, *Eur. J. Org. Chem.* **2006**, 3283; j) H. Du, Y. He, R. Sivappa, C. J. Lovely, *Synlett* **2006**, *7*, 965; k) B. H. Lipshutz, *Chem. Rev.* **1986**, *86*, 795.

[3] N. M. Barl, E. Sansiaume-Dagousset, K. Karaghiosoff, P. Knochel, *Angew. Chem.* **2013**, *125*, 10278; *Angew. Chem. Int. Ed.* **2013**, *52*, 10093.

[4] a) S. L. MacNeil, O. B. Familoni, V. Snieckus, *J. Org. Chem.* **2001**, *66*, 3662; b) H. Watanabe, R. A. Schwarz, C. R. Hauser, J. Lewis, D. W. Slocum, *Can. J. Chem.* **1969**, *47*, 1543.

[5] a) T. Satoh, D. Taguchi, C. Suzuki, S. Fujisawa, *Tetrahedron* **2001**, *57*, 493; b) T. Satoh, K. Takano, H. Someya, K. Matsuda, *Tetrahedron Lett.* **1995**, *36*, 7097; c) T. Satoh, K. Takano, H. Ota, H. Someya, K. Matsuda, K. Yamakawa, *Tetrahedron* **1998**, *54*, 5557; d) for a review, see T. Satoh, *Chem. Soc. Rev.* **2007**, *36*, 1561; e) T. Satoh, K. Akita, *Chem. Pharm. Bull.* **2003**, *51*, 181; f) T. Satoh, M. Miura, K. Sakai, Y. Yokoyama, *Tetrahedron* **2006**, *62*, 4253; g) S. Sugiyama, H. Shimizu, T. Satoh, *Tetrahedron Lett.* **2006**, *47*, 8771; h) L. Melzig, C. B. Rauhut, P. Knochel, *Chem. Commun.* **2009**, 3536; i) L. Melzig, C. B. Rauhut, N. Naredi-Rainer, P. Knochel, *Chem. Eur. J.* **2011**, *17*, 5362.

[6] For the preparation of **2**, see D. J. Chadwick, R. I. Ngochindo, *J. Chem. Soc. Perkin Trans. 1* **1984**, 481.

[7] Y. Lee, P. Martasek, L. J. Roman, B. S. S. Masters, R. B. Silverman, *Bioorg. Med. Chem.* **1999**, *7*, 1941.

[8] a) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem.* **2006**, *118*, 3024; *Angew. Chem. Int. Ed.* **2006**, *45*, 2958; b) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem.* **2011**, *123*, 9968; *Angew. Chem. Int. Ed.* **2011**, *50*, 9794.

[9] For the preparation of 4-methoxybenzenesulfinyl chloride, see M. Peyronneau, N. Roques, S. Mazieres, C. Le Roux, *Synlett* **2003**, 631.

[10] The yield of the organometallic intermediates has been quantified by the method of Paquette (H.-S. Lin, L. A. Paquette, *Synth. Commun.* **1994**, *24*, 2503), or the method developed in our laboratory (A. Krasovskiy, P. Knochel, *Synthesis* **2006**, 890).

[11] a) E.-i. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821; b) E.-i. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340; c) E.-i. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298.

[12] *E*/*Z* ratio of product **6 f** > 99:1.

[13] a) M. C. P. Yeh, S. C. Berk, J. Talbert, P. Knochel, *J. Org. Chem.* **1988**, *53*, 2390.

[14] a) M. C. P. Yeh, P. Knochel, *Tetrahedron Lett.* **1989**, *30*, 4799; b) G. Cahiez, O. Gager, J. Buendia, *Angew. Chem.* **2010**, *122*, 1300; *Angew. Chem. Int. Ed.* **2010**, *49*, 1278.

[15] a) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem.* **2003**, *115*, 4438; *Angew. Chem. Int. Ed.* **2003**, *42*, 4302; b) I. Sapountzis, P. Knochel, *Angew. Chem.* **2002**, *114*, 1680; *Angew. Chem. Int. Ed.* **2002**, *41*, 1610; c) A. Krasovskiy, P. Knochel, *Angew. Chem.* **2004**, *116*, 3396; *Angew. Chem. Int. Ed.* **2004**, *43*, 3333; d) H. Ren, P. Knochel, *Chem. Commun.* **2006**, 726; e) C.-Y. Liu, P. Knochel, *Org. Lett.* **2005**, *7*, 2543; f) N. Boudet, P. Knochel, *Org. Lett.* **2006**, *8*, 3737; g) F. Kopp, A. Krasovskiy, P. Knochel, *Chem. Commun.* **2004**, 2288.

[16] Remarkably, in contrast to many sulfoxide/magnesium exchanges,[5] no hydrolysis side products were detected.

[17] E.-i. Negishi, V. Bagheri, S. Chatterjee, F.-T. Luo, J. A. Miller, A. T. Stoll, *Tetrahedron Lett.* **1983**, *24*, 5181.

[18] a) C. J. Lovely, H. Du, R. Sivappa, M. R. Bhandari, Y. He, H. V. R. Dias, *J. Org. Chem.* **2007**, *72*, 3741; b) Y. He, Y. Chen, H. Du, L. A. Schmid, C. J. Lovely, *Tetrahedron Lett.* **2004**, *45*, 5529.

[19] a) H. K. Lee, M. Bang, C. S. Pak, *Tetrahedron Lett.* **2005**, *46*, 7139; b) S. Beaudoin, K. E. Kinsey, J. F. Burns, *J. Org. Chem.* **2003**, *68*, 115.

[20] The addition of concentrated HCl to imidazole derivatives of type **11** without prior treatment with the Meerwein reagent led to a 1:1 mixture of the two possible free imidazole isomers.

