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Synthesis of Functionalized Pyrazin-2(1H)-ones via Tele-Nucleophilic Substitution of Hydrogen Involving Grignard Reactants and Electrophiles

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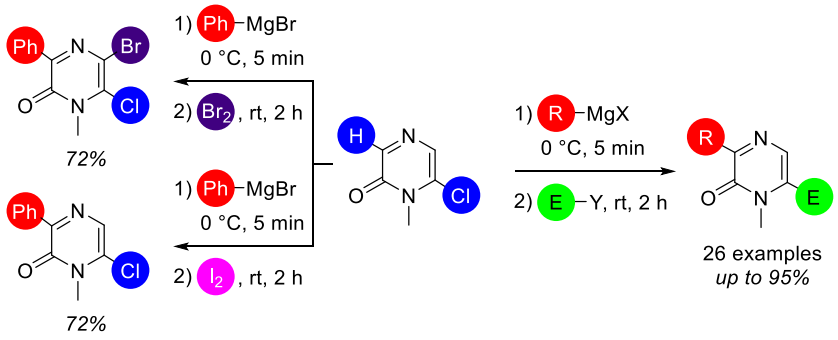
Abstract

The reaction of 6-chloro-1-methylpyrazin-2(1H)-one with Grignard reactants followed by quenchingwith different electrophiles gave access to a variety of 3,6- difunctionalized 1-methylpyrazin-2(1H)-ones. This regioselective three-component reaction represents the first example of a tele-nucleophilic substitution of hydrogen (S_N^H) in which the anionic σ^H adduct is quenched by electrophiles (other than a proton) before elimination takes place. Quenching the reaction with iodine (I_2) or bromine (Br_2) provides an alternative reaction pathway, yielding a 3-functionalized 6-chloro-1-methylpyrazin-2(1H)-one or 5-bromo-6-chloro-1-methylpyrazin-2(1H)-one, respectively. The halogens present offer opportunities for further selective transformations.

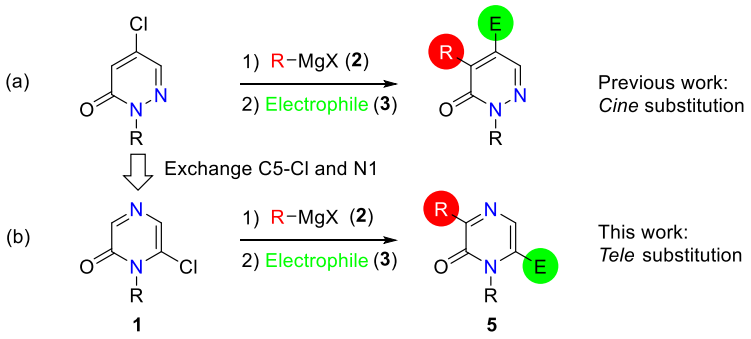


Introduction

Our research group previously reported the *cine* nucleophilic substitution of hydrogen (S_N^H)[1] on 2-substituted 5-chloropyridazin-3(2*H*)-ones via a sequential *one-pot* three-component reaction involving Grignard reactants and electrophiles other than a proton (Scheme 1a).[2] Intrigued by this protocol and the potential of such S_N^H methodology to easily

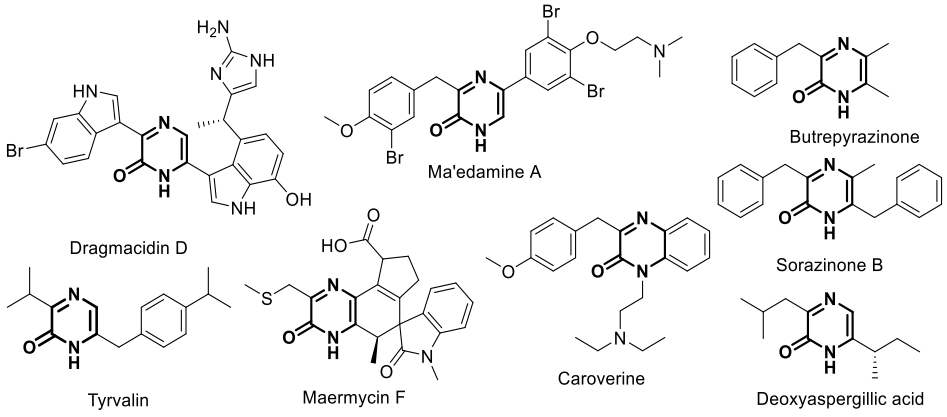
give access to polysubstituted heteroaromatic systems by introducing two substituents in one reaction step, we looked into the extension of this challenging methodology. Especially the hitherto unknown double functionalization via *tele* S_NH caught our attention.[1] We envisioned that by exchanging the C5-Cl and *N*1 in 2-substituted 5-chloropyridazin-3(2*H*)-ones a suitable substrate could be obtained. In this communication, we disclose *tele*-functionalization of 6-chloro-1-methylpyrazin-2-(1*H*)-one (**1**) via a *one*-pot three-component reaction with Grignard reactants (**2**) and electrophiles (**3**) (Scheme 1b).

Scheme 1. Double Functionalization via Nucleophilic Substitution of Hydrogen (S_NH), *Cine* versus *Tele*.



The pyrazin-2(1*H*)-one core constitutes an important class of biologically active compounds as it occurs in a variety of natural products, drugs and (agro)chemicals (Scheme 2).[3] However, so far only limited synthetic methods to perform C-functionalization of the pyrazin-2(1*H*)-one core have been reported.[4] Therefore readily available 6-chloro-1-methylpyrazin-2(1*H*)-one (**1**) was selected to develop *tele* S_NH with Grignard reactants (**2**) and electrophiles (**3**).

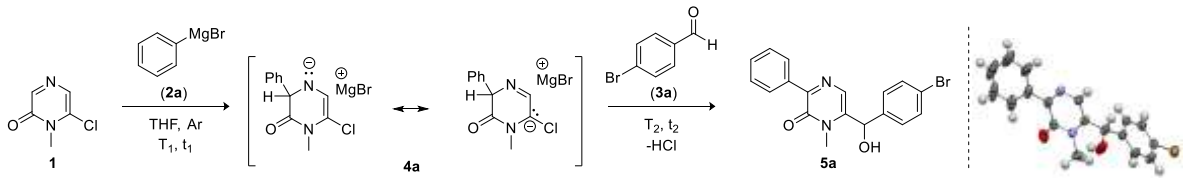
Scheme 2. Selected Examples of Biologically Active Pyrazin-2(1*H*)-ones.



PhMgBr (**2a**) and 4-bromobenzaldehyde (**3a**) were selected as model nucleophile and electrophile, respectively. The intended *tele*-functionalization was successfully achieved when 6-chloro-1-methylpyrazin-2(1*H*)-one (**1**) was treated with **2a** at -78 °C, quenched with **3a** at 0 °C and subsequently stirred for 2 h at room temperature (Table 1, entries 1-2). Interestingly, using 1.1 equiv of the Grignard reactant **2a** at 0 °C and a reaction time of 5 min before the

anionic σ^H-adduct **4** was quenched with 1.3 equiv of the electrophile **3a**, delivered 6-[(4-bromophenyl)hydroxymethyl]-1-methyl-3-phenyl-pyrazin-2(1*H*)-one (**5a**) in 84% isolated yield (entry 6). Altering the ratio between **1**, **2a** and **3a** led to a diminished yield of **5a** (entries 6-9). A lower yield of **5a** was also obtained with 2-MeTHF as solvent (entry 10). A reaction temperature of 0 °C turned out to be important for the stability and reactivity of the anionic σ^H-adduct **4** (entries 11 and 12). The structure of **5a** was also unambiguously established by a single-crystal X-ray measurement (Table 1, top).

Table 1. Model Reaction and Optimization Data[a]



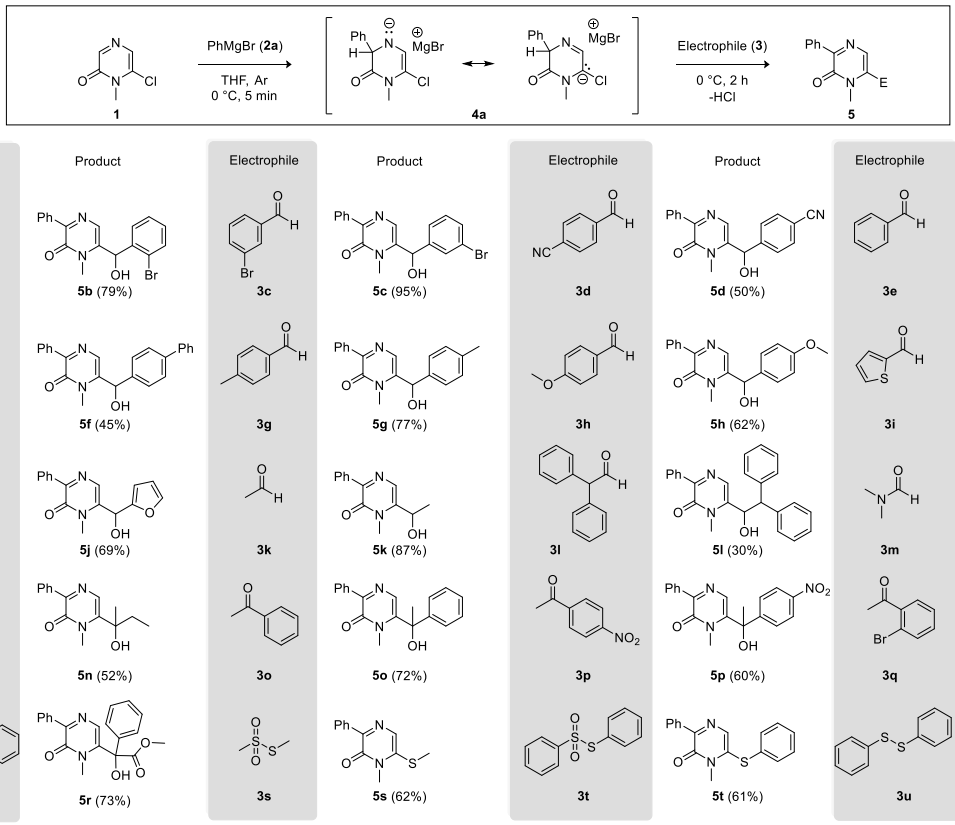
entry	**2a** (equiv)	**3a** (equiv)	T_1 (°C)	t_1 (min)	T_2 (°C)	t_2 (h)	yield **5a** (%)[b]
1	1.1	1.3	-78	15	-78	0.25	0
2[c]	1.1	1.3	-78	15	rt	2	70[d]
3[c]	1.1	1.3	-20	15	rt	2	81[d]
4	1.1	1.3	0	15	rt	2	75
5	1.1	1.3	0	10	rt	2	73
6	**1.1**	**1.3**	**0**	**5**	**rt**	**2**	**81** (**84**)[d]
7	1.0	1.3	0	5	rt	2	75
8	1.3	1.3	0	5	rt	2	60
9	1.1	1.1	0	5	rt	2	70
10[e]	1.1	1.3	0	5	rt	2	6
11	1.1	1.3	0	5	0	2	72
12	1.1	1.3	rt	5	rt	2	54

[a] Reaction conditions: 6-chloro-1-methylpyrazin-2(1*H*)-one (**1**, 1.0 mmol), PhMgBr (**2a**, 1.1 equiv), THF (2 mL, dry), argon, T_1, t_1. Then 4-bromobenzaldehyde (**3a**, 1.3 equiv), T_2, t_2. [b] ^{1}H NMR yield using 1,3,5-trimethoxybenzene as internal standard. [c] **3a** is added at 0 °C before the mixture is stirred at rt for 2 h. [d] Isolated yield. [e] 2-MeTHF (2 mL, dry) as solvent.

With the optimized reaction conditions in hand (Table 1, entry 6), the scope of our three-component reaction with respect to the electrophile (**3**) was investigated with 6-chloro-1-methylpyrazin-2(1*H*)-one (**1a**) and PhMgBr (**2a**) as coupling partners (Scheme 3). Benzaldehydes bearing electron-donating and electron-withdrawing substitutes were generally tolerated well, and the corresponding 3,6-difunctionalized 1-methylpyrazin-2(1*H*)-ones **5b-5h** were obtained in medium to high yield. Heteroaromatic aldehydes, such as 2-thiophenecarboxaldehyde (**3i**) and furfural (**3j**) also delivered the corresponding products (**5i-5j**) in good yield. Aliphatic aldehydes such as acetaldehyde (**3k**) worked smoothly (**5k**). The lower yield for aliphatic aldehyde **3l** can be explained by steric hindrance. Subsequently, a variety of aliphatic and aromatic ketones (**3n-3q**) and methyl oxo(phenyl)acetate (**3r**) were also tested under the optimal reaction conditions, and delivered **5n-5r** in moderate to good

yield, although they are less electrophilic than aldehydes. The resonance and inductive stabilization effects of the σ^H-adduct explain why weak electrophiles such as DMF (**3m**) and PhSSPh (**3u**) cannot be used in our process. However, replacing disulfides by the more electrophilic thiosulfonates **3s** and **3t**, delivered **5s** and **5t** in good yield.[5]

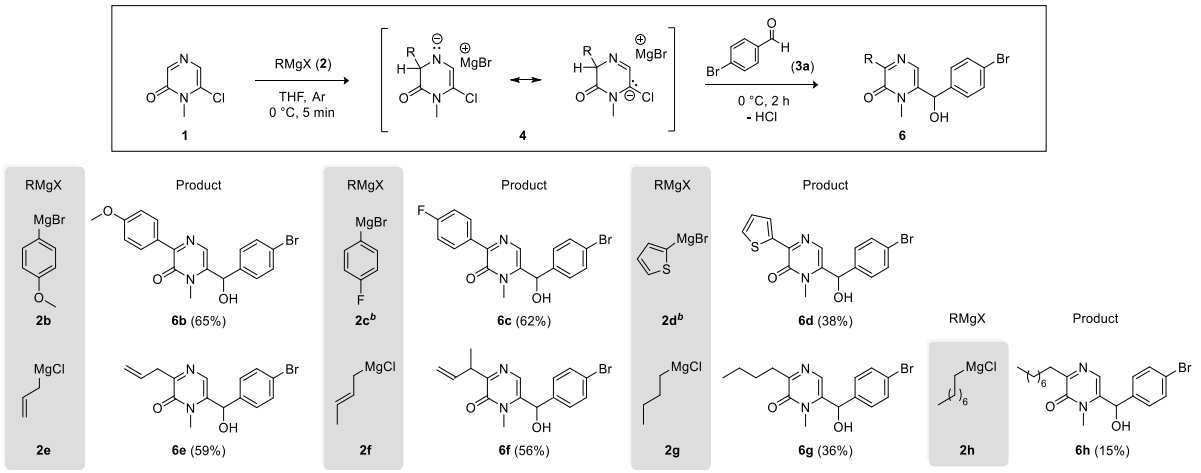
Scheme 3. *Tele*-S_N^H on 6-Chloro-1-methylpyrazin-2(1*H*)-one (1) Involving PhMgBr (2a) and Electrophiles (3)[a]



[a] Reaction conditions: 6-chloropyrazin-2(1*H*)-one (**1a**, 1.0 mmol), PhMgBr (**2a**, 1.0 M in THF, 1.1 equiv), THF (2 mL, dry), argon, 0 °C, 5 min. Then electrophile (**3**, 1.3 equiv), rt, 2 h. Isolated yield.

Besides PhMgBr (**2a**), other organomagnesium reactants were also tested with **1** and **3a** as coupling partners (Scheme 4). (Hetero)aromatic organomagnesium reactants (**2b-2d**) successfully resulted in the corresponding 3,6-difunctionalized 1-methylpyrazin-2(1*H*)-ones (**6b**-**6d**) in moderate yield. We were pleased to observe that allylic organomagnesium reactants, such as allyl- (**2e**) and butenylmagnesium chloride (**2f**) resulted in similar yields for **6e** and **6f**. However, aliphatic butylmagnesium chloride (**2g**) and octylmagnesium chloride (**2h**) resulted in lower yields for **6g** and **6h**. We reasoned that the generated σ^H-adduct is less stable in those cases due to the enhanced nucleophilicity of aliphatic Grignard reactants. Unfortunately, dropwise addition of the nucleophile, lowering of the initial temperature or shortening of the quenching time of the σ^H-adduct, did not significantly improve the yield.

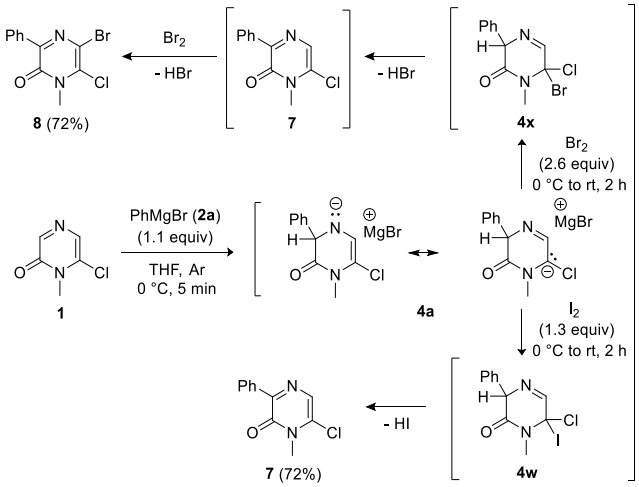
Scheme 4. *Tele*-S_N^H on 6-Chloro-1-methylpyrazin-2(1*H*)-one (1) Involving Grignard Reactants (2) and 4-Bromobenzaldehyde (3a)[a]



[a] Reaction conditions: 6-chloropyrazin-2(1*H*)-one (**1**, 1.0 mmol), commercial Grignard reactant (**2**, 1.1 equiv), THF (2 mL, dry), argon, 0 °C, 5 min. Then 4-bromobenzaldehyde (**3a**, 1.3 equiv), rt, 2 h. Isolated yield. [b] *In situ* formation of Grignard reactant from the corresponding (hetero)aryl bromide and Mg turnings

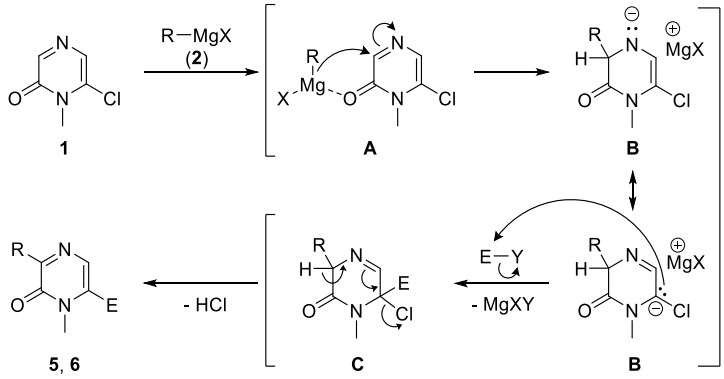
Interestingly, in a reaction of **1** with **2a** as reactant and I_2 as electrophile, 6-chloro-1-methyl-3-phenylpyrazin-2(1*H*)-one (**7**) was obtained in good yield and 6-iodo-1-methyl-3-phenylpyrazin-2(1*H*)-one was not isolated (Scheme 5, bottom). This result can be rationalized in terms of the better leaving group properties of iodine versus chlorine in intermediate **4w**. Mechanistically this is an oxidative nucleophilic substitution of hydrogen.[1] With bromine as the electrophile, an additional electrophilic substitution on **7** occurred, delivering 5-bromo-6-chloro-3-phenylpyrazin-2(1*H*)-one (**8**) (Scheme 5, top). This tandem reaction gave 72% overall yield. The latter reactivity was not observed with I_2, even when using a larger excess. **7** and **8** are very interesting compounds as the C-5 bromine and C-6 chlorine atoms both allow further selective decoration of the pyrazin-2(1*H*)-one via S_NAE and Pd-catalyzed cross-coupling reactions.

Scheme 5. Oxidative *Tele*-S_N^H on 6-Chloro-1-methylpyrazin-2(1*H*)-one (1) with PhMgBr (2a) and Bromine or Iodine



A proposal for the reaction mechanism is depicted in Scheme 6. The carbonyl of the lactam function of 6-chloro-1-methylpyrazin-2(1*H*)-one (**1**) can coordinate to a Grignard reactant (**2**), which favors nucleophilic addition at C-3 of the pyrazin-2(1*H*)-one core. The lactam function acts as a directing group for the nucleophilic addition reaction, which resembles a Directed Metalation Group (DMG) in Directed ortho Metalations (DoMs) with organometallic species.[6,7] The generated anionic σ^H-adduct **B** is resonance stabilized and inductively stabilized by the halogen atom at C-6. This σ^H-adduct is then quenched by an electrophile (other than a proton; **C**) before elimination of hydrochloric acid takes place. In this manner, 3,6-disubstituted 1-methylpyrazin-2(1*H*)-ones (**5** and **6**) are obtained.

Scheme 6. Proposed Reaction Mechanism for *Tele*-S_N^H on 6-Chloro-1-methylpyrazin-2(1*H*)-one (1a)



Conclusions

In summary, we developed a regioselective *one*-pot three-component reaction between 6-chloro-1-methylpyrazin-2(1*H*)-one, organomagnesium reactants and electrophiles affording 3,6-disubstituted 1-methylpyrazin-2(1*H*)-ones in a single step. These represent the first examples of *tele*-S_N^H allowing double functionalization. All compounds reported in this study are unknown based on a Scifinder search, thus justifying the synthetic potential of our procedure. When iodine or bromine are used as the electrophile a 3-substituted 6-chloro-1-methylpyrazin-2(1*H*)-one or 5-bromo-6-chloro-1-methylpyrazin-2(1*H*)-one was respectively obtained, with a large potential for post-functionalization via subsequent reactions involving the halogens (*ipso* substitution, transition metal-catalyzed cross-coupling reaction).

Acknowledgements

This research was financially supported by the University of Antwerp (BOF), the Research Foundation-Flanders (FWO), the Hercules Foundation, COST action CA15106 (CHAOS – C-H Activation in Organic Synthesis), and the Russian Science Foundation (Project no. 18-73-00088). The authors thank Prof. Filip Lemière (University of Antwerp) for HRMS analysis.

References

1. For reviews and books on S_NH, see: (a) Chupakhin, O. N.; Charushin, V. N.; van der Plas, H. C., *Nucleophilic Aromatic Substitution of Hydrogen*; Academic Press: Boston, 1994; (b) Suwiński, J.; Świerczek, K., *Tetrahedron* **2001**, *57*, 1639; (c) van der Plas, H., *Oxidative Amino-Dehydrogenation of Azines* in *Adv. Heterocycl. Chem.*; Academic Press: 2004; Vol. 86, p 1; (d) Mąkosza, M.; Wojciechowski, K., *Chem. Rev.* **2004**, *104*, 2631; (e) Charushin, V. N.; Chupakhin, O. N., *Mendeleev Commun.* **2007**, *17*, 249; (f) Mąkosza, M., *Chem. Soc. Rev.* **2010**, *39*, 2855; (g) Terrier, F., *Nucleophilic Aromatic Substitutions of Hydrogen* in *Modern Nucleophilic Aromatic Substitution*; Wiley-VCH: 2013; (h) Kovalev, I. S.; Kopchuk, D. S.; Zyryanov, G. V.; Rusinov, V. L.; Chupakhin, O. N.; Charushin, V. N., *Russ. Chem. Rev.* **2015**, *84*, 1191; (i) Chupakhin, O. N.; Charushin, V. N., *Tetrahedron Lett.* **2016**, *57*, 2665; (j) Chupakhin Oleg, N.; Charushin Valery, N., *Pure Appl. Chem.* **2017**, *89*, 1195; (k) Suwiński, J. W., *Arkivoc* **2017**, *part i*, 402.
2. Verhelst, T.; Verbeeck, S.; Ryabtsova, O.; Depraetere, S.; Maes, B. U. W., *Org. Lett.* **2011**, *13*, 272.
3. (a) Pawar, V. G.; De Borggraeve, W. M., *Synthesis* **2006**, 2799; (b) Zimmermann, M.; Fischbach, M. A., *Chem. Biol.* **2010**, *17*, 925; (c) Jansen, R.; Sood, S.; Mohr, K. I.; Kunze, B.; Irschik, H.; Stadler, M.; Müller, R., *J. Nat. Prod.* **2014**, *77*, 2545; (d) Kyeremeh, K.; Acquah, K. S.; Camas, M.; Tabudravu, J.; Houssen, W.; Deng, H.; Jaspars, M., *Mar. Drugs* **2014**, *12*, 5197.
4. Sato, N., *Comprehensive Heterocyclic Chemistry III* Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Aitken, A., Eds.; Elsevier: New York, 2008; Vol. 8, p 237.
5. For the use of thiosulfonates, see: (a) Stoll, A. H.; Krasovskiy, A.; Knochel, P., *Angew. Chem. Int. Ed.* **2006**, *45*, 606; (b) Verhelst, T.; Maes, J.; Liu, Z.; Sergeyev, S.; Maes, B. U. W., *J. Org. Chem.* **2011**, *76*, 6670; (c) Mampuys, P.; Zhu, Y.; Vlaar, T.; Ruijter, E.; Orru, R. V. A.; Maes, B. U. W., *Angew. Chem. Int. Ed.* **2014**, *53*, 12849; (d) Mampuys, P.; Zhu, Y.; Sergeyev, S.; Ruijter, E.; Orru, R. V. A.; Van Doorslaer, S.; Maes, B. U. W., *Org. Lett.* **2016**, *18*, 2808; (e) Fang, Y.; Rogge, T.; Ackermann, L.; Wang, S.-Y.; Ji, S.-J., *Nat. Commun.* **2018**, *9*, 2240.
6. For reviews dealing with DoM, see (a) Turck, A.; Plé, N.; Mongin, F.; Quéguiner, G., *Tetrahedron* **2001**, *57*, 4489; (b) Schlosser, M., *Angew. Chem. Int. Ed.* **2005**, *44*, 376; (c) Haag, B.; Mosrin, M.; Ila, H.; Malakhov, V.; Knochel, P., *Angew. Chem. Int. Ed.* **2011**, *50*, 9794; (d) Florio, S.; Salomone, A., *Synthesis* **2016**, *48*, 1993; (e) Miah, M. A. J.; Sibi, M. P.; Chattopadhyay, S.; Familoni, O. B.; Snieckus, V., *Eur. J. Org. Chem.* **2018**, 447.
7. *Metalation of Azines and Diazines* in *Topics in Heterocyclic Chemistry*, Schnürch, M., Mihovilovic, M. D., Eds.; Springer-Verlag: Berlin Heidelberg, 2013; Vol. 31.