A Predictive Model Towards Site-Selective Metalations of Functionalized Heterocycles, Arenes, Olefins, and Alkanes using TMPZnCl·LiCl

Moritz Balkenohl*, Harish Jangra†, Ilya S. Makarov, Shu-Mei Yang, Hendrik Zipse, and Paul Knochel*  

Abstract: The development of a predictive model towards site-selective deprotonation reactions using TMPZnCl·LiCl is reported (TMP = 2,2,6,6-tetramethylpiperidinyl). The pKₐ values of functionalized N-, S-, and O-heterocycles, arenes, alkenes, or alkynes were calculated and compared to the experimental deprotonation sites. Large overlap (≥80%) between the calculated and empirical deprotonation sites was observed, showing that thermodynamic factors strongly govern the metatation regioselectivity. In the case of olefins, calculated frozen state energies of the deprotonated substrates allowed a more accurate prediction. Additionally, various new N-heterocycles were analyzed and the metatation regioselectivities rationalized using the predictive model.

Introduction

Polyfunctional arenes and heteroarenes are important classes of small molecules, as they find major applications as building blocks in pharmaceutical and agrochemical research today.[8] Almost every newly approved small molecule drug by the United States Food and Drug Administration (FDA) in 2018 contains a (hetero)arene moiety, demonstrating their utmost importance in modern pharmaceutical research.[9] Therefore, the regioselective functionalization of various (hetero)aryl scaffolds is of highest interest and has been addressed by numerous research groups in the past decades.[10]

A straightforward method to selectively introduce a functional group to a (hetero)arene core is its directed metatalsation, followed by electrophilic trapping reactions.[11] Recently, deprotonations of arenes and heteroarenes using metal amide bases have allowed the regioselective introduction of a broad range of functional groups to a plethora of important substrates.[4] Both highly reactive lithium amides, such as LDA[5] or TMPLi[6] (TMP = 2,2,6,6-tetramethylpiperidinyl), or more selective reagents such as TMPMgCl·LiCl[7] or TMPZnCl·LiCl[8] have been used successfully. This gave access to functionalized arenes or heteroarenes, including pharmaceutically relevant scaffolds such as pyrimidines, pyrazines or pyridazines.[8c,9] However, when novel scaffolds were investigated towards directed metalation reactions, the regioselectivity was difficult to anticipate and had to be determined by experimental methods.[7,8] This tedious and inefficient approach hampers a rapid and straightforward systematic functionalization of new heterocycles of the future.

So far, pKₐ calculations have been used to understand experimental results in deprotonation reactions using magnesium or lithium amides.[8c,9] With these theoretical studies, regioselectivities could indeed be explained, whereas a reliable prediction has not yet been possible. The difficulty to selectively predict the deprotonation site in a molecule arises from several competing kinetic and thermodynamic effects which must be considered in the deprotonation process.[10] Thus, thermodynamic considerations mainly focus on the acidity of the proton and the concomitant stability of the resulting anion for determining the deprotonation site. This stability can be influenced by electron donating or electron withdrawing groups, which may destabilize or stabilize the resulting negative charge.[10b] However, kinetic considerations mostly favor a deprotonation adjacent to a coordination site. The base coordinates through its counterion to a Lewis basic direct metalation group (DMG) in the molecule, forming a substrate–base adduct. This brings the base in proximity to a C–H bond, which is subsequently deprotonated (complex induced proximity effect – CIPE).[11] Thus, for many bases both kinetic and thermodynamic effects play a role for determining the metatalsation site.

Considering, that the nitrogen–metal bond in the milder, and functional group tolerant base TMPZnCl·LiCl[12] is of more covalent nature in comparison to the magnesium and lithium analogues due to a smaller difference in electronegativity (ΔEN(N–Zn, Pauling) = 1.39, ΔEN(N–Mg) = 1.73, ΔEN(N–Li) = 2.06),[13] TMPZnCl·LiCl is a base where thermodynamic effects should predominate and the kinetic aspects should play a minor role. In fact, the stronger ionic...
character of the N–Met bond (Met = metal), the more likely is the kinetic control. Therefore, lithium amides are prone to metalate organic substrates under kinetic control.\textsuperscript{[8b,10,13]} Thus, we envisioned, that the site selectivity of the base TMPZnCl·LiCl may go hand in hand with the lowest (calculated) pK\textsubscript{a} values of various arenes or heteroarenes. This would allow the development of a theoretical model\textsuperscript{[14]} using simple pK\textsubscript{a} calculations, bringing forth reliable predictions for site selective deprotonmetalations with the mild base TMPZnCl·LiCl. Herein, we wish to report the development of such a predictive model, which not only rationalizes deprotonmetalations using TMPZnCl·LiCl from the past, but also allows the prediction of the metalation sites on novel, so far unexplored N-heterocycles.

**Computational Details**

Two different modelling approaches were explored to predict the preferred metalation site of the structurally diverse heterocycles as shown below. In Approach 1, relative C–H pK\textsubscript{a} values are calculated for substrates R–H through the proton transfer reaction shown as Equation (1) in Scheme 1 with the furan/furan-2-ide reference system, whose pK\textsubscript{a} value amounts to 35.0 in DMSO.\textsuperscript{[13]} The conformational space of each molecular species is first explored using molecular mechanics (MM) methodology, followed by full geometry optimization with quantum chemical methods in order to obtain Boltzmann-averaged Gibbs free energies over the selected conformational space (see the Supporting Information for more details). All pK\textsubscript{a} values shown in Figures 1–4 and 6, 7 were obtained this way.

A second strategy termed Approach 2 was explored for those substrates, where deprotonation leads to structural rearrangement or fragmentation. For these systems vertical deprotonation energies (VDEs) in terms of \( \Delta E_{\text{tot}} \) were calculated based on the substrate conformer of lowest Gibbs free energy. Deprotonation energies are calculated for the various sites relative to the furan/furan-2-ide reference system, where all anions are kept in a frozen (unrelaxed) state. The VDE values obtained this way are shown in Figure 5 for all alkene substrates and are listed in the Supporting Information for all other systems studied herein.

**Computational Methodology:** As in earlier studies\textsuperscript{[8c]} all geometry optimizations have been performed at the B3LYP\textsuperscript{[15]}-D3\textsuperscript{[16]}/6-31\textsuperscript{++}G(2d,p)\textsuperscript{[17]} level of theory in the gas phase. Thermochemical corrections have been calculated at the same level of theory using the rigid rotor/harmonic oscillator model. Implicit solvation energies for DMSO were calculated for gas phase optimized geometries at the CPCM\textsuperscript{[19]}(DMSO)/B3LYP-D3/6–311\textsuperscript{++}G(2df,2p)//B3LYP-D3/6-31\textsuperscript{++}G(2d,p) level of theory, and subsequently added to gas phase single point energies in order to obtain solution phase energies (see the Supporting Information for more details).

**Results and Discussion**

As mentioned above, we anticipated that for the mild base TMPZnCl·LiCl, kinetic effects are less prone to play a role in the choice of the deprotonation site, whereas a higher importance of thermodynamic effects are expected. Thus, all substrates which have been deprotonated using TMPZnCl·LiCl were investigated and the calculated pK\textsubscript{a} values are listed below. For each substrate class, a representative set of structures was chosen (for full experimental and theoretical details see the Supporting Information). In the following Figures 1–7 the lowest calculated pK\textsubscript{a} value is given in purple color. When the experimental deprotonation site matches the lowest pK\textsubscript{a} value, the proton was marked green. In the case of a mismatch (the deprotonation site did not match the lowest calculated pK\textsubscript{a} value), the proton was marked red.
match with the site of lowest $p_K$ value) the proton was marked black. Also, the reaction conditions and yields for the resulting zinc organometallics after treatment with TMPZnCl-LiCl are given.\[\text{[19]}\]

Azines: First, we focused on a representative set of azines, including pyridines, pyrimidines, pyrazines, and pyridazines bearing various functional groups (12 out of 27 structures are depicted, Figure 1).\[\text{[20]}\] The most acidic proton of pyridine was located at the C4 position ($p_K(H3) = 39.7$), followed by the proton in the C3 position ($p_K(H2) = 40.3$).\[\text{[21]}\] The $p_K$ value at C2 was distinctly higher ($p_K(H1) = 43.0$), which was explained by the neighboring N-atom, since the lone pair destabilizes the anion which formed upon deprotonation.\[\text{[22]}\] When electron-withdrawing groups, such as a halogen or a nitro group, are introduced to the pyridine core, the calculated $p_K$ values of adjacent protons significantly decreased. This is the case for 2-chloro-3-nitropyridine (1a), where the $p_K$ value at C4 was lowest ($p_K(H3) = 25.8$), which is also where deprotonation took place when 1a was treated with TMPZnCl-LiCl (25°C, 45 min), yielding the zinc organometallics 2a in about 80% yield (Figure 1).\[\text{[23]}\] Similarly as in 1a, halogen substituents also decreased the $p_K$ value of ortho-positioned protons significantly (1b–g). Thus, the $p_K$ values in pyrimidines 1b,c,\[\text{[22,28]}\] pyrazines 1d,e,\[\text{[24,26]}\] or pyridazine 1f\[\text{[24]}\] were lowest ortho to the halogen atom, which corresponded to the actual deprotonation sites, producing organozinc reagents 2b–f in 70–95% yield (25–90°C, 0.5–1 h). However, in the case of pyridazine 1g,\[\text{[23]}\] the previously described complex induced proximity effect (CIPE) predominated the thermodynamically favored position, which resulted in a deprotonation ortho to the directing methoxy group ($p_K(H3) = 30.2$, 90°C, 1 h) rather than the site of lowest $p_K$ value ($p_K(H2) = 29.4$). When solely methoxy groups were present (1h,i) the protons with the lowest $p_K$ values ($p_K = 33.5–37.8$) were deprotonated by the zinc amide base under harsher reaction conditions (ca. 80%, 90–100°C, 1 h).\[\text{[23]}\] Additionally, the $p_K$ values of pyridine and pyridazine $N$-oxides were calculated and compared with the experimental deprotonation sites. The N–O bond removes electron density from the heterocycle, acidifying the protons in the aromatic ring. Thus, protons ortho to the N-oxide were acidified most (1j–l), which again matches the experimentally determined deprotonation sites, leading to the corresponding zinc reagents 2j–l in 50–70% yield (Figure 1).\[\text{[24]}\]

Other N-Heterocycles: Next, other nitrogen containing heterocycles were investigated (12 out of 30 structures are depicted in Figure 2).\[\text{[23]}\] A protected indole bearing an aldehyde functional group 3a was deprotonated in the predicted position ($p_K(H1) = 29.5$, 25°C, 0.5 h), which led to the desired organozinc 4a in about 90% yield.\[\text{[23]}\] Other indole derivatives, such as pyrazole[1,5-α]pyridine (3b),\[\text{[25]}\] or indazole 3c\[\text{[25]}\] were also predicted correctly ($p_K(H1) = 31.1–32.4$), producing zinc organometallics 4bc in 80–90% yield. Also, the $p_K$ values of various purine derivatives (3d–f) were analyzed, where deprotonation took place in the predicted C8 position within a small $p_K$ range of TMPZnCl-LiCl (25°C, 5–30 min), the desired purine zinc species 4d–f were obtained in 75–85% yield.\[\text{[25,26]}\] When a 1,2,4-triazole bearing an amide functionality 3g was treated with TMPZnCl-LiCl (2.2 equiv), the two most acidic protons were deprotonated ($p_K(N-H) = 8.3, p_K(C-H) = 26.9$), yielding the zinc reagent 4g in about 90% yield.\[\text{[26]}\] The $p_K$ values for oxazoles 3h–j were also calculated.\[\text{[30]}\] The predictions in oxazole (3h, $p_K(H1) = 27.6$) and a 4-chlorophenyl substituted oxazole 3i ($p_K(H1) = 29.9$) were correct, with the most acidic site being adjacent to the oxygen atom. However, when these two sites are blocked by substituents as in 3j, only the least acidic heterocyclic proton remains ($p_K(H1) = 35.4$).

Despite the calculated acidity adjacent to the chlorine atom being slightly lower ($p_K(H2) = 35.0$), the heterocyclic...
C–H bond was deprotonated owing to coordinative effects.\cite{30}
Similarly, in phthalazine 3k\cite{31} and 1,5-naphthyridine 3l,\cite{32}
electron withdrawing groups (–Cl, –CORBu) acidify adjacent protons (pK_a = 31.5–35.8). Yet, deprotonation occurred at the site of best coordination with the nitrogen atom (pK_a = 36.3–36.6, Figure 2).

**O- and S-Heterocycles**: Inspired by these results, we moved on to investigate oxygen and sulfur heterocycles (7 out of 24 structures are depicted in Figure 3).\cite{20} First, the pK_a values for furan 5a, which bears both a nitrogen and an ester functional group, were calculated (pK_a(H1) = 27.5, pK_a(H2) = 25.3).\cite{22} Similarly to previous cases (1g, 3k–m) the electron withdrawing group leads to a strongly acidified proton in α position. However, deprotonation preferably took place in β-position to the ester group since this carbonyl group is more prone to coordinate the zinc amide base compared to a nitro group. This led to the organozinc 6a in about 80% yield (25°C, 0.5 h). Whereas the metalation site of a substituted 2-pyrone 5b\cite{32} was predicted correctly (pK_a(H1) = 26.6, –78°C, 10 min), the related chromone 5c\cite{33} led to contrasting results. Here, the coordination to the carbonyl group predominated and deprotonation took place in the thermodynamically less favored site (pK_a(H1) = 34.0 versus pK_a(H2) = 29.8). Remarkably, this site selectivity could be switched in the related mercapto derivative under optimized reaction conditions. Thus, when 5d was dissolved in an Et_2O:THF = 1:2 mixture and treated with TMPZnCl-LiCl (–40°C, 10 min), the reduced polarity led to a selective deprotonation at H2, whereas a non-selective deprotonation occurred in pure THF.\cite{34} For other sulfur heterocycles such as benzothiophene 5e\cite{21}, 1,4-dithiin (5f),\cite{35} or 1,4,5,8-tetra-thianaphthalene (5g),\cite{15} pK_a calculations gave surprisingly low values (pK_a = 19.9–24.9). These sites were hence regio-selectively deprotonated using the TMP base (–40–25°C, 0.5 h), to give the corresponding zinc organometallics 6e–g in circa 90% yield (Figure 3).

**Arenes**: With the pK_a value of benzene lying at 44.7,\cite{21} deprotonation of unactivated arenes is difficult to achieve and often require harsh reaction conditions.\cite{36} However, when coordinating (–CO_R, –CO_NR_2, etc.) or electron withdrawing groups (–NO_2, F, etc.) were present, a metatation could be performed using the mild base TMPZnCl-LiCl (6 out of 23 structures are depicted in Figure 4).\cite{20} Thus, pK_a values for electron-poor arenes 7a–e were calculated (pK_a(H1) = 22.6–32.9) and deprotonation occurred at the most acidic sites at 25–160°C within 1–7 h, producing the expected arylic reagents 8a–e in 65–80% yield.\cite{22,23,37,38} A reliable prediction for the tropolone scaffold was difficult (7f), similarly as with chromone 5c due to the carbonyl group, which has proven to strongly coordinate to zinc amide bases, inducing a deprotonation in α-position (Figure 4).\cite{39}

**Alkenes and Allenes**: Next, we investigated the deprotonation of several alkenes and allenes (7 out of 19 structures are depicted in Figure 5).\cite{20} In pK_a calculations following Approach 1, geometry optimizations were accompanied by fragmentation and ring-opening reactions.\cite{36} To prevent these structural rearrangements, vertical deprotonation energies (in kJmol\(^{-1}\)) were calculated according to Approach 2, where the geometry of the neutral parent was not allowed to relax on deprotonation. With these results in hand, we found that for various alkenes and allenes 9a–f, the lowest vertical deprotonation energies matched with the actual deprotonation site. Thus, after treatment with TMPZnCl-LiCl (–50–25°C, 0.25–
1 h), the zincated alkenes and allenes 10a–f were obtained in 65–95% yield. To ensure that these vertical deprotonation energies are representative for the full study, the respective energies for all other structures were calculated as well (see Supporting Information). Interestingly, the prediction fidelity of Approach 2 (vertical deprotonation) is closely similar (>80%) as compared to that of Approach 1 (relaxed deprotonation). In the case of 9g the lowest energy is given for the proton adjacent to the sulfur atom ($E = \text{-}50.6 \text{ kJ mol}^{-1}$), which seems to bring along a strongly acidifying effect as already observed for other S-heterocycles (see 5e–g). However, also a nitro group, in comparison to the sulfur atom, may coordinate stronger to the zinc amide, which eventually led to a deprotonation adjacent to the nitro group (9g, Figure 5).[42]

Alkanes: Finally, various benzylic and alkylic deprotonations were investigated (8 out of 32 structures are depicted in Figure 6).[20] Similarly as in the case of benzene, deprotonations of unactivated alkanes using amide bases occur sluggishly. However, in the presence of stabilizing groups such as nitriles, esters, or amides deprotometalations using TMPZnCl·LiCl may take place.[43] Thus, various benzylic nitriles 11a,b,[44] alkylic nitriles 11c–f,[44,45] an ester 11g,[44] and an amide (11h)[46] were deprotonated at the most acidic position ($p_K_a = 10.8–28.3$), producing alkylzinc organometallics 12a–h in 50–85% yield (Figure 6).

Novel N-Heterocycles: To demonstrate the utility of the developed predictive model, several so far unexplored N-heterocycles were investigated towards metalations using TMPZnCl·LiCl. After having calculated the $p_K_a$ values (see Figure 7), all six N-heterocycles 13a–e were treated with TMPZnCl·LiCl (1.2 equiv) and quenched with various electrophiles (Scheme 2). The deprotonation sites were confirmed by deuteration of the reaction mixtures followed by $^1$H NMR analysis (see Supporting Information). Thus, pyrido[2,3-b]pyrazine (13a), imidazo[1,2-b]pyridazine (13b), [1,2,4]triazolo[4,3-a]pyrazine (13c), and [1,2,4]triazolo[1,5-a]pyrimidine (13d) were readily deprotonated in the predicted most acidic positions ($p_K_a = 24.6–34.6$), leading to organozinc reagents 14a–d in 40–70% yield. After iodolysis or...
Palladium-catalyzed Negishi cross-couplings\(^{[47]}\) the expected N-heterocycles 15a–d were obtained in 42–59% yield (Scheme 2). It is noteworthy, that in the case of 13d, the stronger base TMP\(_2\)Zn·2MgCl\(_2\)·2LiCl was used to achieve zincation, since TMPZnCl·LiCl reacted sluggishly. In imidazo[1,5-a]pyridine (13e), two protons have similar p\(\text{K}_a\) values (p\(\text{K}_a\)(H1) = 33.1, p\(\text{K}_a\)(H2) = 32.7). Since coordination to a nitrogen atom can only take place at position C1, TMPZnCl·LiCl preferably deprotonates proton H1, leading, after cross-coupling, to the functionalized N-heterocycle 15e in 40% yield. The p\(\text{K}_a\) values in quinazoline (13f) are relatively high (p\(\text{K}_a\) = 36.7–40.2), resulting in a deprotonation only at the site of best coordination, which lies in between the two nitrogen atoms (C2). After electrophilic quenching, the biaryl 15f was obtained in 78% yield.

Evaluating the success of the theoretical approaches employed herein, we found that the p\(\text{K}_a\) values calculated according to Approach 1 predict the correct deprotonation site as the site of highest acidity in 81.4% of all cases (Figure 8). The use of vertical deprotonation energies (VDEs) led to improved predictions not only for the alkene substrates, where anion formation triggered larger structural rearrangements untypical for the actual metalated species, but also for the complete dataset study with a prediction fidelity of 82.5%. This result may imply that the unrelaxed anions obtained through vertical deprotonation of the neutral parents are structurally more similar to a metalated species than the structurally relaxed anions obtained after geometry optimization. A final remark should be made for substrates, where the p\(\text{K}_a\) values differed by less than one unit (such as 13e in Figure 7). If these cases are counted as successful predictions, the fidelity of the prediction increased to more than 88% (Figure 8C, the prediction is considered successful if the VDE associated with experimentally determined site lies within 5.69 kJ\(\text{mol}^{-1}\) (1 p\(\text{K}_a\) unit) window to the lowest VDE value in the molecule).

### Conclusion

In summary, we have developed a model which allowed site-selective predictions in deprotometalation reactions of various organic molecules bearing relatively acidic protons using TMPZnCl·LiCl. A wide range of N-, S-, and O-heterocycles as well as functionalized arenes, alkynes and alkanes were investigated and their p\(\text{K}_a\) values calculated. Overall, the predicted site matched well with the empirical results, with a correct prediction in over 80% of the more than 150 investigated substrates, suggesting that for the relatively covalent zinc amide TMPZnCl·LiCl, thermodynamic considerations predominate. It may also be anticipated that in the case of stronger bases, kinetic effects such as the CIPE are of greater importance, which would lead to a more difficult prediction. Finally, the model was used to help predicting the deprotonation site of six so far non-disclosed N-heterocycles.

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### Conflict of interest

The authors declare no conflict of interest.

**Keywords:** acidity · amides · heteroarenes · predictive models · zinc organometalics

\[1\] a) W. R. Pitt, D. M. Parry, B. G. Perry, C. R. Groom, *J. Med. Chem.* 2009, 52, 2952–2963; b) R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem.* 2014, 57, 5845–5859; c) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* 2014, 57, 10257–10274; d) P. Martins, J. Jesus, S. Santos, L. R. Raposo, C. Roma-Rodrigues, P. V. Baptista, A. R. Fernandes, *Molecules*
2019, 57, 128 |
117 |
Angew. Chem. Int. Ed. 2019, 58, 9244–9247; Angew. Chem. 2019, 131, 9344–9348.

[9] a) A. Siggio, F. Chevallier, M. Vautier, F. Mongin, J. Org. Chem. 2007, 72, 6602–6605; b) F. Chevallier, F. Mongin, J. Org. Chem. Soc. Rev. 2008, 37, 595–609; c) M. Mosrin, P. Knochel, Org. Lett. 2008, 10, 2497–2500; d) M. Mosrin, P. Knochel, Chem. Eur. J. 2009, 15, 1468–1477; e) M. Mosrin, T. Bresser, P. Knochel, Organ. Lett. 2009, 11, 3406–3409; f) A. Unissin, M. J. Ford, P. Knochel, Org. Lett. 2015, 17, 1128–1131.

[10] a) F. Chevallier, Y. S. Halauko, C. Peccue, J. F. Narrar, T. U. Dam, T. Roisnel, V. E. Matulis, O. A. Ivashkevich, F. Mongin, Bioorg. Chem. 2011, 9, 4671–4684; b) K. S. Nguen, N. Marquise, Y. S. Halauko, P. J. Harford, T. Roisnel, V. E. Matulis, O. A. Ivashkevich, F. Chevallier, A. E. H. Wheatley, P. C. Gros, F. Mongin, Chem. Eur. J. 2011, 17, 13284–13297; c) R. R. Kadiyala, D. Tilly, E. Nagardaga, T. Roisnel, V. E. Matulis, O. A. Ivashkevich, Y. S. Halauko, F. Chevallier, P. C. Gros, F. Mongin, Chem. Eur. J. 2013, 19, 7944–7960; d) N. Marquise, G. Breteil, F. Lassagne, F. Chevallier, T. Roisnel, V. Dorcet, Y. S. Halauko, O. A. Ivashkevich, V. E. Matulis, P. C. Gros, F. Mongin, RSC Adv. 2014, 4, 19602–19612; e) M. Y. A. Messaoud, G. Bentabed-Ababsa, M. Hedidi, A. Derdour, F. Chevallier, Y. S. Halauko, O. A. Ivashkevich, V. E. Matulis, L. Picot, V. Thiery, T. Roisnel, V. Dorcet, F. Mongin, Beilstein J. Org. Chem. 2015, 11, 1475–1485; f) E. Nagardaga, G. Bentabed-Ababsa, M. Scalabrini, F. Chevallier, S. Philippot, S. Fontanay, R. E. Duval, Y. S. Halauko, O. A. Ivashkevich, V. E. Matulis, T. Roisnel, F. Mongin, Bioorg. Med. Chem. 2015, 23, 6355–6363; g) M. Hedidi, G. Bentabed-Ababsa, A. Derdour, Y. S. Halauko, O. A. Ivashkevich, V. E. Matulis, F. Chevallier, T. Roisnel, V. Dorcet, F. Mongin, Tetrahedron 2016, 72, 2196–2205; h) M. Hedidi, J. Maillard, W. Erb, F. Lassagne, Y. S. Halauko, O. A. Ivashkevich, V. E. Matulis, T. Roisnel, V. Dorcet, M. Hamzé, Z. Fajloun, B. Baratte, S. Ruchaud, S. Bach, G. Bentabed-Ababsa, F. Mongin, Eur. J. Org. Chem. 2017, 5903–5915; For an accurate prediction of pKₐ values using graph convolution neural networks, see: i) R. Roszak, W. Bekker, K. Molga, B. A. Grzybowski, J. Am. Chem. Soc. 2019, 141, 17142–17149.

[11] a) M. C. Whieler, S. MacNeil, V. Snieckus, P. Beak, Angew. Chem. Int. Ed. 2004, 43, 2206–2225; Angew. Chem. 2004, 115, 2226–2227; O. A. Ivashkevich, The Aroyl-exonatal metallo-substituents were observed when well defined template bases were used in deprotonation reactions, see: b) A. J. Martinez-Martinez, A. R. Kennedy, R. E. Mulvey, C. T. O’Hara, Science 2014, 346, 834–837; c) A. J. Martinez-Martinez, D. R. Armstrong, B. Conway, B. J. Fleming, J. Klett, A. R. Kennedy, R. E. Mulvey, S. D. Robertson, C. T. O’Hara, Chem. Sci. 2014, 5, 771–781; d) A. J. Martinez-Martinez, S. Justice, B. J. Fleming, A. R. Kennedy, I. D. H. Oswald, C. T. O’Hara, Sci. Adv. 2017, 3, e1700832.
