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Preparation and reactions of polyfunctional magnesium and zinc organometallics in organic synthesis†

Alexander Kremsmair, Johannes H. Harenberg, Kuno Schwärzer, Andreas Hess and Paul Knochel *

Polyfunctional organometallics of magnesium and zinc are readily prepared from organic halides *via* a direct metal insertion in the presence of LiCl or a Br/Mg-exchange using iPrMgCl·LiCl (turbo-Grignard) or related reagents. Alternatively, such functionalized organometallics are prepared by metalations with TMP-bases (TMP = 2,2,6,6-tetramethylpiperidyl). The scope of these methods is described as well as applications in new Co- or Fe-catalyzed cross-couplings or aminations. It is shown that the use of a continous flow set-up considerably expands the field of applications of these methods and further allows the preparation of highly reactive organosodium reagents.

1. Introduction

The compatibility of functional groups with a carbon–metal bond in an organometallic reagent is essential for broad synthetic applications in modern organic synthesis. In this perspective article, we will show that Mg and Zn organometallics are unique for combining an excellent functional group tolerance with a high reactivity toward various classes of electrophiles. Furthermore, magnesium and zinc derivatives are non-toxic and the moderate price of these two elements makes them ideal candidates for industrial applications. Although, some innovative chemistry of lithium, sodium and potassium will be presented considering some remarkable properties of these species, the main part of this article will concern the preparation and reactivity of polyfunctional Mg and Zn reagents. The behaviour of aryl- and heteroaryl organometallics will be especially emphasized because of their importance in material, agrochemical and pharmaceutical research. We will also show that continuous flow set-ups involving such organometallic reactions further expands the application scope, especially by allowing some new Barbier-type procedures.

Department of Chemistry, Ludwig-Maximilans-Universität München, Butenandtstraße 5-13, 81377 München, Germany. E-mail: paul.knochel@cup.uni-muenchen.de

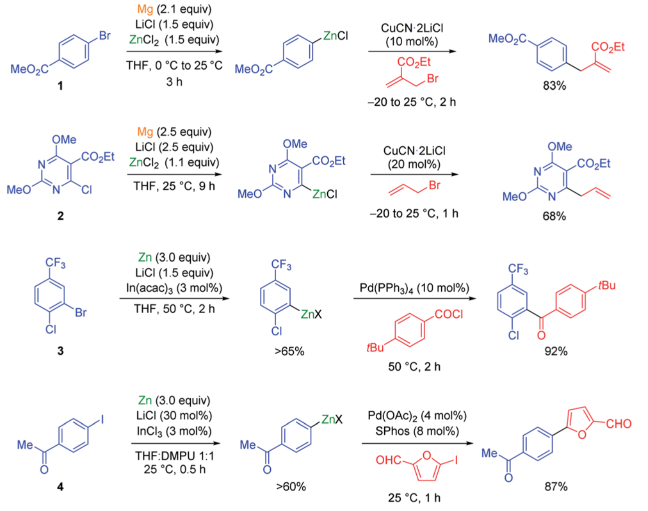
† In memory of Victor Snieckus.

Alexander Kremsmair was born in 1994 in Linz a. d. Donau (Austria). After finishing his high school diploma, he studied chemistry at the Ludwig-Maximilians-Universität in Munich and joined the group of Prof. Paul Knochel for his Master thesis in 2018, where he stayed to pursue his PhD. His research focuses on the preparation of new chiral secondary alkylmetal reagents for asymmetric synthesis and the regioselective metalation of sensitive heterocycles.

Johannes H. Harenberg was born in Berlin (Germany) in 1992. After his undergraduate studies at the Ludwig-Maximilians-Universität (Munich) he joined the research group of Professor Paul Knochel for his Master's thesis and started his PhD in the same group in 2019. His current research work is focused on the application of alkali organometallic species in continuous flow.

2. Preparation of polyfunctional Zn and Mg organometallics

2.1 Direct reaction of magnesium or zinc with organic halides



Scheme 1 Magnesium and zinc insertions to functionalized (hetero)aryl halides mediated by LiCl and indium salts.

The carbon–zinc bond is a covalent carbon–metal bond with moderate intrinsic reactivity. Metallic zinc is a weaker reducing agent compared to magnesium, and therefore a mixed metal synthesis using magnesium dust in the presence of LiCl and $ZnCl_2$ is an advantageous procedure for the preparation of aryl and heteroaryl zinc reagents bearing sensitive functional groups.[1] Under these conditions, methyl 4-bromobenzoate (**1**) underwent a smooth conversion to the corresponding zinc reagent within 3 h at 25 °C (see Scheme 1).

The addition of LiCl was essential for removing the organometallic species on the metal surface by forming a mixed magnesium–lithium complex of the type RMgX·LiCl.[2] Fast magnesium insertion rates were observed with electron-deficient substrates like electron-poor aromatics or heterocyclic chlorides such as **2**.[1] The direct zinc insertion may require the addition of a Lewis-acid catalyst whose role is to facilitate electron transfer steps from the metal surface to the organic halide. Thus, in the presence of In(acac)$_3$ (3 mol%), 2-bromo-1-chloro-4-(trifluoromethyl)-benzene (**3**) was converted to the corresponding zinc reagent at 50 °C within 2 h.[3] The use of a polar co-solvent such as DMPU proved to be helpful.[4] Under these conditions, a sensitive functional group like an acetyl group which is prone to enolization, like in 4-iodoacetophenone (**4**), was perfectly tolerated. The mild conditions required for these insertion reactions are also compatible with the presence of acidic NH-groups.[5] Thus, the iodo-indole derivative **5** was converted to the corresponding zinc reagent at 25 °C.[6] In the presence of a palladium catalyst (2 mol% Pd(OAc)$_2$; 4 mol% SPhos), a Negishi cross-coupling with an N-heterocyclic iodide readily took place at 25 °C. Secondary alkyl iodides usually react faster in these direct insertion reactions. Thus, *cis*-iodo-pyrrole

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Kuno Schwärzer was born in 1992 in Innichen (Italy). After his undergraduate studies at the Ludwig-Maximilians-Universität in Munich he joined the group of Prof. Paul Knochel for his Master's thesis and started his PhD thesis in the same group in 2017. His research focuses on the reaction of [1.1.1]propellane with organometallic reagents and the metalation of nitrogen-containing heterocycles with TMP-bases.

Andreas Hess was born in 1995 in Landshut (Germany). After his undergraduate studies at the Ludwig-Maximilians-Universität (Munich) he joined the research group of Professor Paul Knochel for his Master's thesis and started his PhD in the same group in 2020. His research focuses on the regioselective magnesiation of nitrogen-containing heterocycles and arenes.

Paul Knochel was born in 1955 in Strasbourg (France). He studied at the University of Strasbourg (France) and did his PhD at the ETH-Zürich (D. Seebach). He spent four years at the University Pierre and Marie Curie in Paris (J.-F. Normant) and one year at Princeton University (M. F. Semmelhack). In 1987, he became Professor at the University of Michigan. In 1992, he moved to Philipps-University at Marburg (Germany). In 1999, he then moved to the Chemistry Department of Ludwig-Maximilians-University in Munich (Germany). His research interests include the development of novel organometallic reagents and methods for use in organic synthesis, asymmetric catalysis, and natural product synthesis. Prof. Knochel has received many distinguished prizes including the Berthelot medal of the Academie des Sciences (Paris), the IUPAC Thieme prize, the Otto–Bayer-prize, the Leibniz-prize, the Arthur C. Cope scholar award, Karl-Ziegler-prize, the Nagoya Gold Medal, the H. C. Brown award, and Paul Karrer gold medal. He is member of the Académie des Sciences, the Bavarian Academy of Science and the German Academy of Sciences Leopodina. He is author of over 900 publications.

6, which was readily available from *trans*-2-aminocyclohexanol, underwent a zinc insertion within 10 min at 25 °C leading to a *cis*, *trans*-mixture of zinc reagent **7**. This loss of stereochemistry is characteristic for Mg or Zn insertions which proceed through radical intermediates. However, in the presence of a palladium catalyst, a diastereoselective cross-coupling[7] took place leading exclusively to the *trans*-cyclohexane derivative **8** (84%; 99% ee; dr >99 : 1; see Scheme 2).[6]

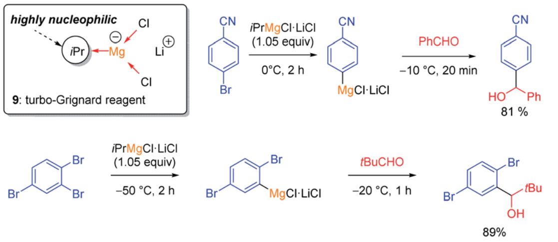
2.2 The halogen/metal exchange

The halogen/lithium exchange (Hal = I, Br) is a fast reaction, independently discovered in 1939 by Gilman and Wittig.[8] In comparison, the halogen/magnesium-exchange is a much slower reaction, which had only found applications in the preparation of some heterocyclic Grignard reagents[9] and magnesium carbenoids.[10] However, by using organomagnesium halides complexed by LiCl such as iPrMgCl·LiCl (**9**, turbo-Grignard reagent) fast I/Mg- and Br/Mg-exchanges took place producing functionalized aryl and heteroaryl magnesium reagents under mild conditions (see Scheme 3).[11]

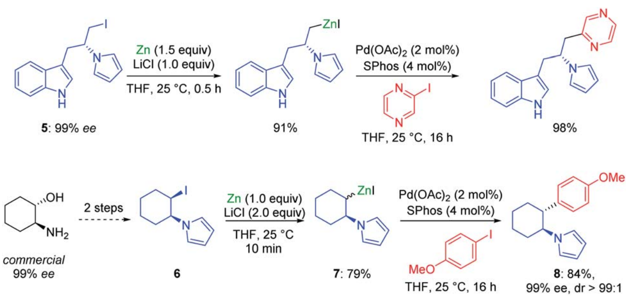
The kinetics of the Br/Mg-exchange[12] as well as the mechanism of the reaction have been well studied.[13] It was postulated that the rate of a halogen/metal exchange depends on the ionic character of the carbon–metal bond: the more electro-positive the metal is, the faster the halogen/metal exchange takes place. This hypothesis led to the discovery of halogen/lanthanide exchange reactions.[14] The replacement of LiCl in the turbo-Grignard reagent (**9**) with lithium alkoxides (LiOR) led to even more powerful exchange reagents (*s*BuMgOR^1·LiOR^1 and *s*Bu$_2$Mg·2LiOR^1; R^1 = 2-ethylhexyl) soluble in toluene. These reagents allowed the performance of some Cl/Mg-exchanges[15] as well as regioselective exchanges on various dibromopyridines such as **10**.[16] Furthermore, the use of the corresponding zinc reagents (*s*Bu$_2$Zn·2LiOR^2 or *p*tol$_2$Zn·2LiOR^2 **11**) allowed the performance of an I/Zn-exchange on functionalized aryl iodides in toluene (see Scheme 4).[17]

2.3 Directed magnesiation and zincation with TMP-bases complexed with LiCl

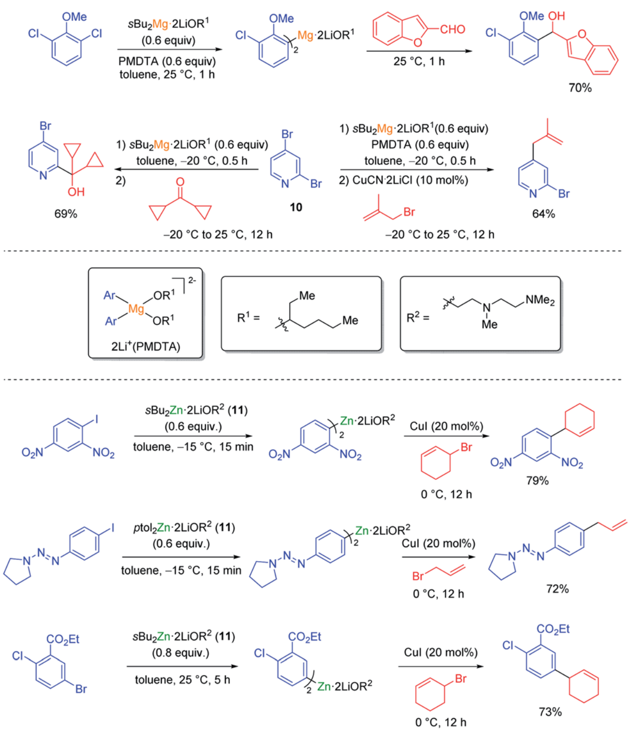
In general, magnesium amides (R$_2$NMgX or (R$_2$N)$_2$Mg) are poorly soluble in THF and display moderate kinetic basicity.[18] However, by using a sterically hindered amine (2,2,6,6-tetramethylpiperidine, TMP-H), it was possible to prepare a series of metallic amides complexed with LiCl (TMPMgCl·LiCl, TMP$_2$Mg·2LiCl, TMPZnCl·LiCl and TMP$_2$Zn·2LiCl) with high solubility in THF (1.2–1.4 M) and exceptional kinetic basicity.[19] The preparation of polyfunctional magnesium reagents became now possible from halide-free precursors. Thus, the highly functionalized arene **12** was magnesiated with TMPMgCl·LiCl at −20 °C leading to an arylmagnesium species **13** bearing several sensitive functional groups (OBoc, CO$_2$Et, COPh).[20] A copper-mediated acylation afforded the penta-substituted arene **14** in 88% yield. By using TMPZnCl·LiCl, aryl and heteroaryl zinc organometallics **15–17** were produced.[21] Since a carbon–zinc bond is much more covalent than a carbon–magnesium bond, the inherent reactivity of the carbon–zinc bond is much lower and therefore it becomes possible to prepare highly



Scheme 3 Br/Mg-Exchange on functionalized aryl bromides using the turbo-Grignard reagent (**9**).



Scheme 2 Zn-Insertion to alkyl iodides bearing an indolyl NH-group and (or) a β-*N*-pyrrolyl group.

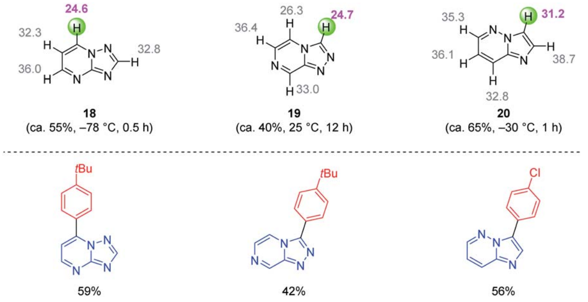


Scheme 4 Halogen/magnesium and zinc exchanges using the exchange reagents *s*Bu$_2$Mg·2LiOR^1, *s*Bu$_2$Zn·2LiOR^2 or *p*Tol$_2$-Zn·2LiOR^2 (**11**).

functionalized organozinc derivatives. Due to the presence of low lying p-orbitals at the zinc centre, various transmetalations with transition metal salts proceeded readily, providing transition metal intermediates which underwent new reaction pathways not possible for main-group organometallics (oxidative addition, reductive elimination, insertion reaction). This behaviour allowed an efficient reaction with numerous electrophiles (see Scheme 5).

In contrast to TMPMgCl·LiCl, TMPZnCl·LiCl is less prone to undergo kinetic metalations and thermodynamic considerations are relevant for predicting the zincation regioselectivity. Thus, the site of metalation can be readily determined by calculation of the pK_a-values of various unsaturated substrates. The zincation of new heterocyclic systems such as **18–20** were predicted by this model and subsequent functionalizations were performed successfully (see Scheme 6).[22] In general, TMPMgCl·LiCl and TMPZnCl·LiCl are valuable reagents for the metalation of various heterocycles.[23] Remarkably, the compatibility of these bases with various Lewis acids including $BF_3 \cdot OEt_2$ has also been observed.[24]

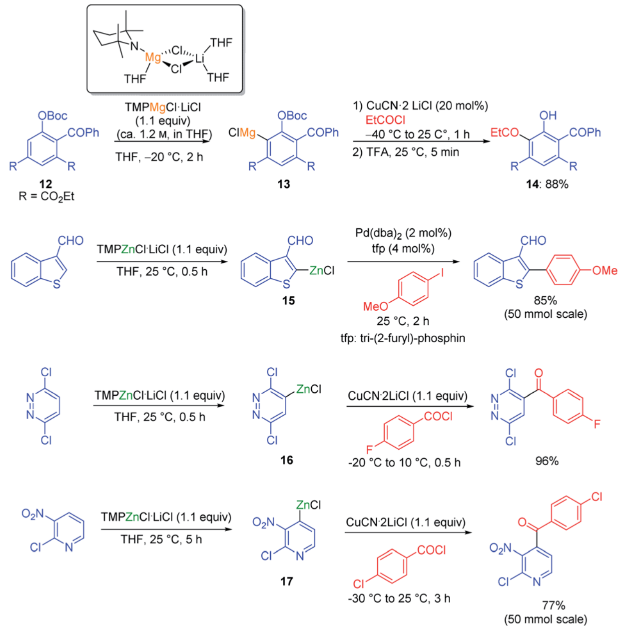
For example, this possibility of forming frustrated Lewis pairs has been exploited for the regioselective functionalization of uridines such as **21**. By using TMPMgCl·LiCl in THF a complexation occurred at the heterocyclic amide function directing the magnesiation at the adjacent position leading to products of type **22a–b**. On the other hand, using $TMP_2Zn \cdot 2LiCl$ in the presence of $MgCl_2$ similarly led to a complexation of $MgCl_2$ at the amide function and hampered the approach of the zinc base which eventually deprotonated at position 6 leading to products of type **22c–d** (see Scheme 7).[25] The performance of kinetically controlled metalations (usually triggered by a precomplexation of the base to a Lewis-basic centre of the substrate)[26] is often amplified by the use of a low polarity solvent such as toluene. Thus, designing a new toluene soluble base (BuMgTMP) allowed a regioselective kinetic metalation of various aryl azoles at the *ortho*-position of the aryl ring resulting in products of great interest for pharmaceutical research (Scheme 7).[27]



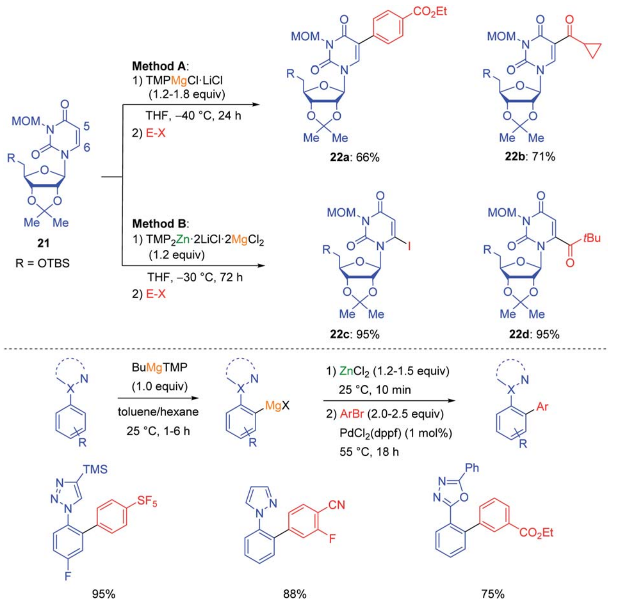
Scheme 6 Calculation of the pK_a-values of condensed N-heterocycles to predict their reactivity with TMPZnCl·LiCl and subsequent quenching with electrophiles.

3. Reactions of polyfunctional organozinc reagents

Cobalt salts are *ca.* 1000 times cheaper than palladium salts and many cobalt-catalyzed cross-couplings require only inexpensive N-ligands such as 2,2′bipyridine (bipy) or 4,4′-di-*tert*-butyl-2,2′-dipyridyl (dtbbpy). Thus, 2-bromopyrimidine underwent diastereoselective cross-couplings with secondary alkylzinc reagents furnishing products in high diastereomeric ratio (see



Scheme 5 Directed magnesiations and zincations using mixed Mg–Li or Zn–Li-TMP-bases.



Scheme 7 Regioselective magnesiations and zincations of uridines with TMP-bases and magnesiations of aryl azoles in toluene with BuMgTMP.

Scheme 8). These cross-couplings were also extended to 1-bromoalkynes.[28]

Furthermore, a range of cobalt catalyzed cross-couplings[29] proceeded well with functionalized organozinc and organomagnesium reagents.[30] For example, highly diastereoselective cross-couplings were achieved with α-bromo lactones (see Scheme 9).[31]

Novel Csp^3–Csp^3 cross-couplings catalyzed by $CoCl_2$ (20 mol%) in the presence of *trans*-1,2-bis-dimethylaminocyclohexane or neocuproine (20 mol%) allowed the preparation of polyfunctional products. Furthermore, ring closures and openings indicated the occurance of radical intermediates in the course of such cross-couplings (see Scheme 10).[32]

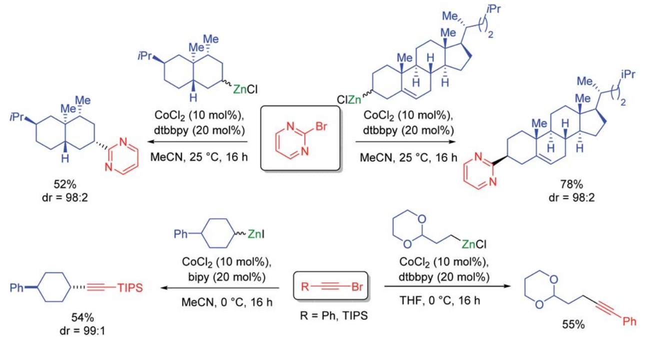
3.1 Preparation of organozinc pivalates with enhanced air and water stability

Organozinc pivalates are mixed zinc–magnesium organometallics bearing a carbon–zinc bond and magnesium or zinc pivalate (OCO*t*Bu) units.[33] These organometallic reagents are readily prepared by various methods and produce, after solvent evaporation, solid organozinc species with enhanced air and water stability.[34] Polyfunctional organozinc pivalates underwent Pd-catalyzed cross-couplings with peptidic aryl halides bearing various acidic protons.[35] They proved also very advantageous for performing other transition metal catalyzed cross-couplings. Thus, a cobalt-catalyzed acylation of thiopyridyl esters allowed the preparation of α-chiral ketones as well as a short synthesis of the pharmaceutical fenofibrate (see Scheme 11).[36]

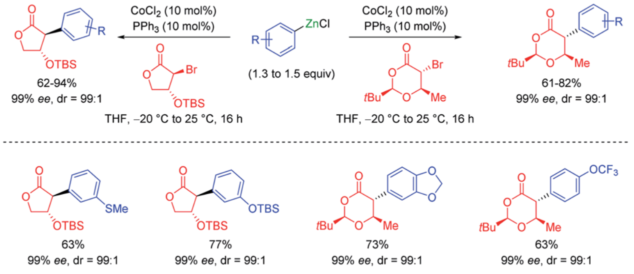
Organozinc pivalates often undergo challenging cross-couplings better than analogous organozinc halides. Therefore, the nickel-catalyzed cross-couplings of various aryl, heteroaryl and alkenyl triflates or nonaflates with aryl- and heteroarylzinc pivalates were achieved in good yields and with high stereoretention (see Scheme 12).[37]

3.2 Transition-metal catalyzed electrophilic aminations using organozinc reagents

Organozinc pivalates[38] and halides[39] are also useful for the performance of cobalt-catalyzed electrophilic aminations. Drugs like paroxetine **24** or sertraline **25** were functionalized by this method and converted into the new valuable derivatives **26** and **27** (see Scheme 13).



Scheme 8 Diastereoselective cobalt-catalyzed cross-couplings.



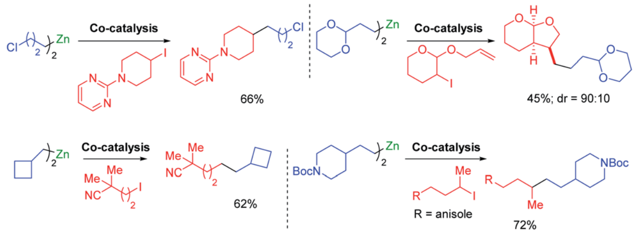
Scheme 9 Cobalt-catalyzed diastereoselective cross-couplings.

Furthermore, organozinc chlorides were converted to secondary amines by iron(III) chloride mediated reactions with various organic azides.[40] For this amination procedure both the organozinc reagent and the aryl azide[41] could be generated *in situ*. In addition, chiral azides with peptidic structures led to the corresponding arylated, chiral secondary amines (see Scheme 14).[40]

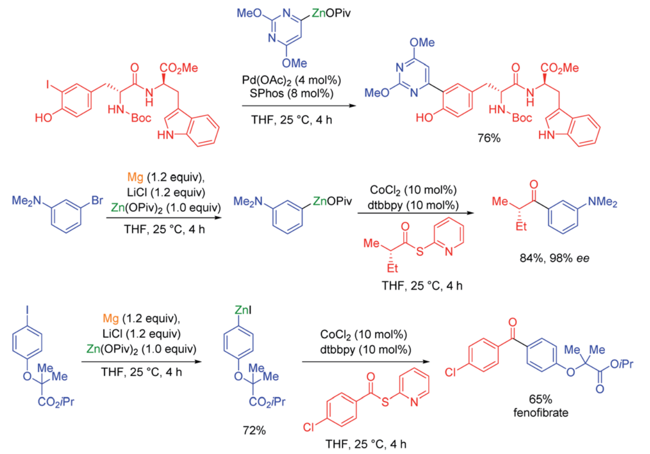
4. Lewis pairs involving organozinc and organomagnesium reagents; new Barbier-reactions

Various magnesium and zinc organometallics are compatible with strong Lewis acids such as $BF_3 \cdot OEt_2$ and this behaviour has already been exploited for performing selective metalations.[24] The field of Barbier reactions remained largely unexplored although remarkable selectivities were achieved.[42] A recent example concerned the regioselective metalation of 2,4-dichlorobenzonitrile **28** (see Scheme 15).[43]

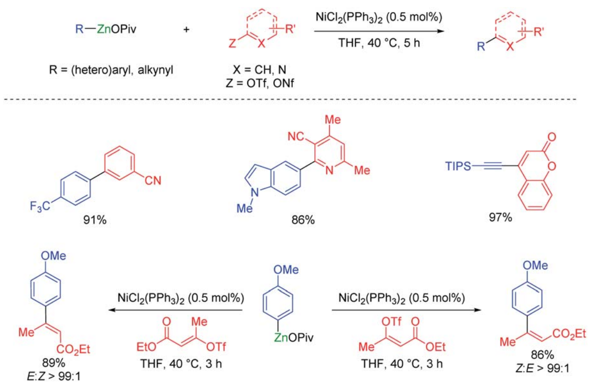
In accordance with the pK_a-values of the ring hydrogens, the most acidic 3-position of benzonitrile derivative **28** was readily zincated by TMPZnCl·LiCl. As indicated above, this base is especially prone to undergo thermodynamically driven metalations.[22] After 12 h at 60 °C and subsequent iodolysis, nitrile **29** was obtained as the only regioisomer. However, with the strong lithium base TMPLi, a complexation driven deprotonation was triggered by coordination of this base to the cyano group inducing an *ortho*-deprotonation. Performing this lithiation only with TMPLi led to extensive decomposition due to the high reactivity of the resulting aryllithium



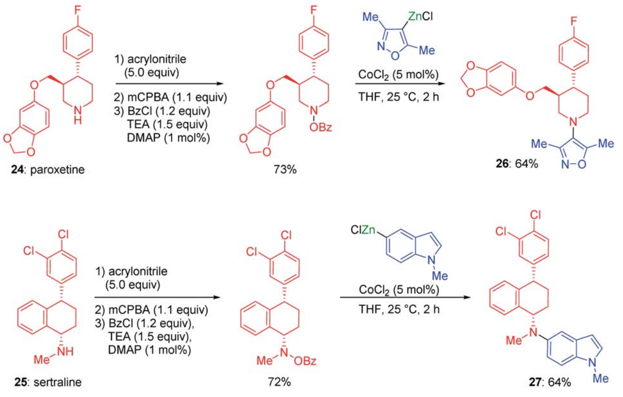
Scheme 10 Cobalt-catalyzed alkyl–alkyl cross-couplings using organozinc reagents.



Scheme 11 Chemoselective cross-couplings and acylations using organozinc pivalates.

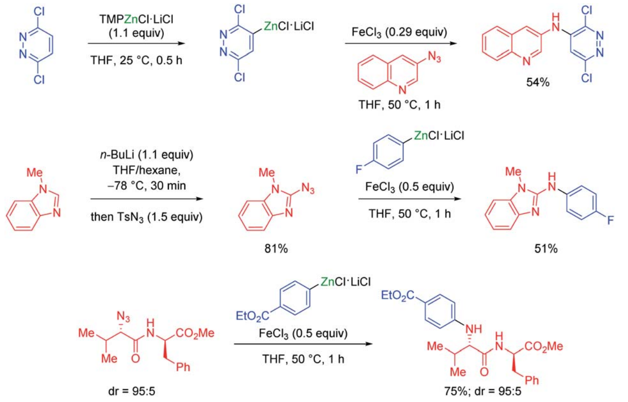


Scheme 12 Stereoselective nickel-catalyzed cross-couplings with organozinc pivalates.



Scheme 13 Cobalt-catalyzed electrophilic aminations for the functionalization of secondary amine pharmaceuticals.

species. However, mixing **29** with the THF-soluble salt $ZnCl_2 \cdot 2LiCl$ and adding TMPLi at −78 °C led to a fast kinetic deprotonation followed by a transmetalation with the zinc(II)-salt, providing a stable arylzinc reagent which after iodolysis produced regioselectively the iodonitrile **30**. This behaviour



Scheme 14 Iron-mediated electrophilic aminations of organic azides with organozinc reagents.

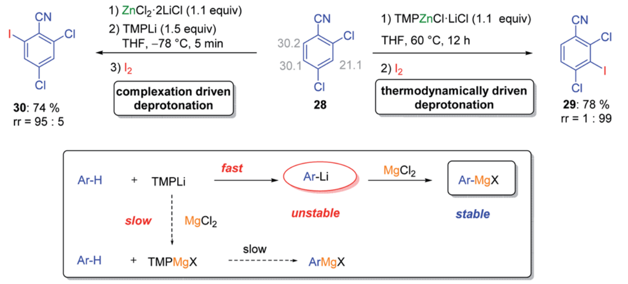
proved to be quite general and $MgCl_2$ or $CuCN \cdot 2LiCl$ allowed similar reactions. However, the scale-up of these reactions proved to be difficult. This problem was solved by performing these metalations in continuous flow using micro-reactors (see Scheme 16).[44]

It was possible to perform a short-cut in such Barbier-reactions by mixing the electrophile (E–X) directly with the substrate bearing an acidic proton avoiding the need of transmetalations. Thus, the treatment of mixtures of various formamides ($HCONR^1R^2$) and electrophiles such as ketones, aldehydes, allylic bromides, disulfides, morpholino- and Weinreb amides in continuous flow provided a very convenient and readily scalable synthesis of functionalized amides (see Scheme 17).[45]

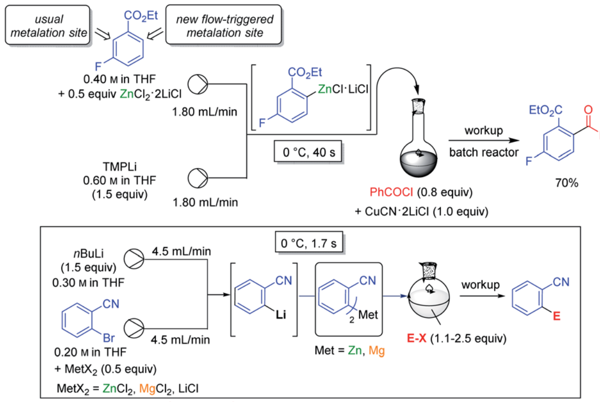
Organosodium chemistry has been mostly of academic interest, despite the low costs and toxicity of metallic sodium as well as its easy handling and recycling.[46] The use of a continuous flow set-up allowed the sodiation of various unsaturated heterocyclic and aromatic substrates (see Scheme 18).[47]

5. Preparative aspects

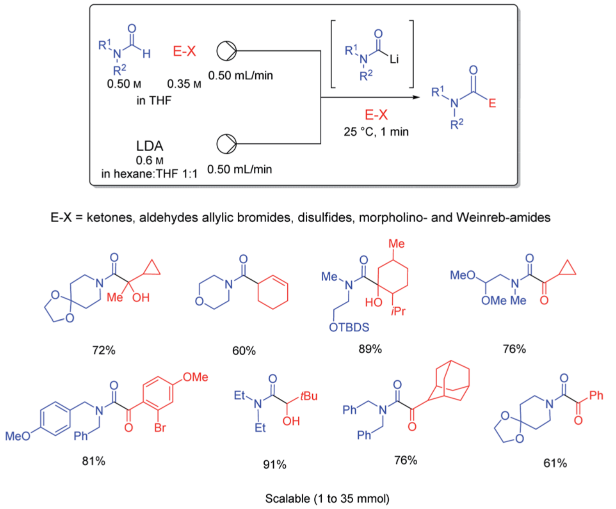
All reactions were performed using standard Schlenk-line techniques under argon atmosphere.[48] $TMPMgCl \cdot LiCl$ and $iPrMgCl \cdot LiCl$ are commercially available (Sigma-Aldrich, Acros Organics, Albemarle, *etc.*) and were as all other organometallic



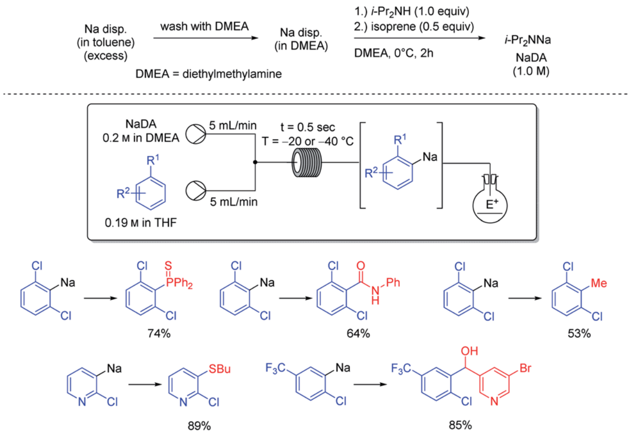
Scheme 15 Kinetic and thermodynamic deprotonation of aryl nitrile **28**.



Scheme 16 Directed lithiations and Br/Li-exchanges in the presence of various metallic salts $MetX_2$.



Scheme 17 Barbier reactions in continuous flow involving an *in situ* generation of carbamoyllithium derivatives.



Scheme 18 Generation of aryl- and heteroaryl-sodium intermediates in continuous flow.

reagents used after titration.[49] No glove-box or special apparatus were required. Only dry solvents and analytically pure starting materials were used.

6. Conclusions

Broadly applicable preparations of functionalized Zn- and Mg-organometallics are now available and described in this perspective article. A range of transition metal catalyzed reactions including Negishi cross-couplings and acylation reactions allow a straightforward functionalization of these polyfunctional organometallics.[50] The use of continuous flow further broadens the scope of these organometallics. Also, the performance of new Barbier-type reactions opens up new synthetic applications. Thus, the chemistry of these functionalized main-group organometallics should pave the way for further discoveries and give an even more prominent place in organic synthesis to these ecologically friendly metals.

Author contributions

A. K. developed and assembled the section on the preparation of polyfunctional organometallics and reactions of polyfunctional organozinc reagents. J. H. H. developed and assembled the section on continuous flow set-ups. K. S. developed and assembled the section on reactions of polyfunctional organozinc reagents. A. H. developed and assembled the section on directed magnesiations and zincations. A. K., J. H. H., K. S., A. H. and P. K. wrote and edited the manuscript.

Conflicts of interest

There are no conflicts to declare.

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References

1 A. Krasovskiy, V. Malakhov, A. Gavryushin and P. Knochel, *Angew. Chem., Int. Ed.*, 2006, **45**, 6040–6044; F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin and P. Knochel, *Chem.–Eur. J.*, 2009, **15**, 7192–7202.
2 C. Feng, D. W. Cunningham, Q. T. Easter and S. A. Blum, *J. Am. Chem. Soc.*, 2016, **138**, 11156–11159.
3 A. D. Benischke, G. Le Corre and P. Knochel, *Chem.–Eur. J.*, 2017, **23**, 778–782.
4 T. Mukhopadhyay and D. Seebach, *Helv. Chim. Acta*, 1982, **65**, 385–391.
5 G. Manolikakes, M. A. Schade, C. M. Hernandez, H. Mayr and P. Knochel, *Org. Lett.*, 2008, **10**, 2765–2768; G. Manolikakes, C. Muñoz Hernandez, M. A. Schade, A. Metzger and P. Knochel, *J. Org. Chem.*, 2008, **73**, 8422–8436; Z. Dong, G. Manolikakes, J. Li and P. Knochel, *Synthesis*, 2009, **2009**, 681–686; G. Manolikakes,

M. S. Z. Dong, H. Mayr, J. Li and P. Knochel, *Chem.–Eur. J.*, 2009, **15**, 1324–1328.

6 M. Leroux, W.-Y. Huang, Y. Lemke, T. J. Koller, K. Karaghiosoff and P. Knochel, *Chem.–Eur. J.*, 2020, **26**, 8951–8957.

7 T. Thaler, B. Haag, A. Gavryushin, K. Schober, E. Hartmann, R. M. Gschwind, H. Zipse, P. Mayer and P. Knochel, *Nat. Chem.*, 2010, **2**, 125–130.

8 H. Gilman, W. Langham and A. L. Jacoby, *J. Am. Chem. Soc.*, 1939, **61**, 106–109; G. Wittig and U. Pockels, *Ber. Dtsch. Chem. Ges.*, 1939, **72**, 884–886.

9 M. Rottländer, L. Boymond, L. Bérillon, A. Leprêtre, G. Varchi, S. Avolio, H. Laaziri, G. Quéguiner, A. Ricci, G. Cahiez and P. Knochel, *Chem.–Eur. J.*, 2000, **6**, 767–770; A. Boudier, L. O. Bromm, M. Lotz and P. Knochel, *Angew. Chem., Int. Ed.*, 2000, **39**, 4414–4435; P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis and V. A. Vu, *Angew. Chem., Int. Ed.*, 2003, **42**, 4302–4320.

10 J. Villiéras, *Bull. Soc. Chim. Fr.*, 1967, **5**, 1520; J. Villiéras, B. Kirschleger, R. Tarhouni and M. Rambaud, *Bull. Soc. Chim. Fr.*, 1986, 470–478; S. Avolio, C. Malan, I. Marek and P. Knochel, *Synlett*, 1999, 1820–1822; L. Boymond, M. Rottländer, G. Cahiez and P. Knochel, *Angew. Chem., Int. Ed.*, 1998, **37**, 1701–1703.

11 A. Krasovskiy and P. Knochel, *Angew. Chem., Int. Ed.*, 2004, **43**, 3333–3336.

12 I. Hiriyakkanavar, O. Baron, A. J. Wagner and P. Knochel, *Chem. Lett.*, 2006, **35**, 2–7; G. Dagousset, C. François, T. León, R. Blanc, E. Sansiaume-Dagousset and P. Knochel, *Synthesis*, 2014, **46**, 3133–3171; N. M. Barl, V. Werner, C. Samann and P. Knochel, *Heterocycles*, 2014, **88**, 827–844.

13 A. Krasovskiy, B. F. Straub and P. Knochel, *Angew. Chem., Int. Ed.*, 2006, **45**, 159–162; L. Shi, Y. Chu, P. Knochel and H. Mayr, *Angew. Chem., Int. Ed.*, 2008, **47**, 202–204; L. Shi, Y. Chu, P. Knochel and H. Mayr, *Org. Lett.*, 2009, **11**, 3502–3505; L. Shi, Y. Chu, P. Knochel and H. Mayr, *Org. Lett.*, 2012, **14**, 2602–2605.

14 A. D. Benischke, L. Anthore-Dalion, G. Berionni and P. Knochel, *Angew. Chem., Int. Ed.*, 2017, **56**, 16390–16394; A. D. Benischke, L. Anthore-Dalion, F. Kohl and P. Knochel, *Chem.–Eur. J.*, 2018, **24**, 11103–11109; L. Anthore-Dalion, A. D. Benischke, B. Wei, G. Berionni and P. Knochel, *Angew. Chem., Int. Ed.*, 2019, **58**, 4046–4050.

15 D. S. Ziegler, K. Karaghiosoff and P. Knochel, *Angew. Chem., Int. Ed.*, 2018, **57**, 6701–6704.

16 A. Desaintjean, T. Haupt, L. J. Bole, N. R. Judge, E. Hevia and P. Knochel, *Angew. Chem., Int. Ed.*, 2021, **60**, 1513–1518.

17 M. Balkenhohl, D. S. Ziegler, A. Desaintjean, L. J. Bole, A. R. Kennedy, E. Hevia and P. Knochel, *Angew. Chem., Int. Ed.*, 2019, **58**, 12898–12902.

18 C. R. Hauser and H. G. Walker, *J. Am. Chem. Soc.*, 1947, **69**, 295–297.

19 A. Krasovskiy, V. Krasovskaya and P. Knochel, *Angew. Chem., Int. Ed.*, 2006, **45**, 2958–2961; S. H. Wunderlich and P. Knochel, *Angew. Chem., Int. Ed.*, 2007, **46**, 7685–7688; B. Haag, M. Mosrin, H. Ila, V. Malakhov and P. Knochel, *Angew. Chem., Int. Ed.*, 2011, **50**, 9794–9824; S. M. Manolikakes, N. M. Barl, C. Sämann and P. Knochel, *Z. Naturforsch., B: J. Chem. Sci.*, 2013, **68**, 411–422.

20 W. Lin, O. Baron and P. Knochel, *Org. Lett.*, 2006, **8**, 5673–5676.

21 M. Mosrin and P. Knochel, *Org. Lett.*, 2009, **11**, 1837–1840; T. Bresser, G. Monzon, M. Mosrin and P. Knochel, *Org. Process Res. Dev.*, 2010, **14**, 1299–1303.

22 M. Balkenhohl, H. Jangra, I. S. Makarov, S.-M. Yang, H. Zipse and P. Knochel, *Angew. Chem., Int. Ed.*, 2020, **59**, 14992–14999.

23 K. Schwärzer, C. P. Tüllmann, S. Graßl, B. Górski, C. E. Brocklehurst and P. Knochel, *Org. Lett.*, 2020, **22**, 1899–1902.

24 M. Jaric, B. A. Haag, A. Unsinn, K. Karaghiosoff and P. Knochel, *Angew. Chem., Int. Ed.*, 2010, **49**, 5451–5455; K. Groll, S. M. Manolikakes, X. M. du Jourdin, M. Jaric, A. Bredihhin, K. Karaghiosoff, T. Carell and P. Knochel, *Angew. Chem., Int. Ed.*, 2013, **52**, 6776–6780; S. M. Manolikakes, M. Jaric, K. Karaghiosoff and P. Knochel, *Chem. Commun.*, 2013, **49**, 2124–2126.

25 L. Klier, E. Aranzamendi, D. Ziegler, J. Nickel, K. Karaghiosoff, T. Carell and P. Knochel, *Org. Lett.*, 2016, **18**, 1068–1071.

26 M. C. Whisler, S. MacNeil, V. Snieckus and P. Beak, *Angew. Chem., Int. Ed.*, 2004, **43**, 2206–2225.

27 F. H. Lutter, L. Grokenberger, L. A. Perego, D. Broggini, S. Lemaire, S. Wagschal and P. Knochel, *Nat. Commun.*, 2020, **11**, 4443.

28 F. H. Lutter, L. Grokenberger, P. Spieß, J. M. Hammann, K. Karaghiosoff and P. Knochel, *Angew. Chem., Int. Ed.*, 2020, **59**, 5546–5550.

29 G. Cahiez and A. Moyeux, *Chem. Rev.*, 2010, **110**, 1435–1462.

30 A. Guérinot and J. Cossy, *Acc. Chem. Res.*, 2020, **53**, 1351–1363.

31 M. S. Hofmayer, A. Sunagatullina, D. Brösamlen, P. Mauker and P. Knochel, *Org. Lett.*, 2020, **22**, 1286–1289.

32 F. H. Lutter, L. Grokenberger, M. Benz and P. Knochel, *Org. Lett.*, 2020, **22**, 3028–3032.

33 A. Hernán-Gómez, E. Herd, E. Hevia, A. R. Kennedy, P. Knochel, K. Koszinowski, S. M. Manolikakes, R. E. Mulvey and C. Schnegelsberg, *Angew. Chem., Int. Ed.*, 2014, **53**, 2706–2710.

34 C. I. Stathakis, S. Bernhardt, V. Quint and P. Knochel, *Angew. Chem., Int. Ed.*, 2012, **51**, 9428–9432; C. I. Stathakis, S. M. Manolikakes and P. Knochel, *Org. Lett.*, 2013, **15**, 1302–1305; S. M. Manolikakes, M. Ellwart, C. I. Stathakis and P. Knochel, *Chem.–Eur. J.*, 2014, **20**, 12289–12297; T. J. Greshock, K. P. Moore, R. T. McClain, A. Bellomo, C. K. Chung, S. D. Dreher, P. S. Kutchukian, Z. Peng, I. W. Davies, P. Vachal, M. Ellwart, S. M. Manolikakes, P. Knochel and P. G. Nantermet, *Angew. Chem., Int. Ed.*, 2016, **55**, 13714–13718; Y.-H. Chen, M. Ellwart, V. Malakhov and P. Knochel, *Synthesis*, 2017, **49**, 3215–3223.

35 M. Leroux, T. Vorherr, I. Lewis, M. Schaefer, G. Koch, K. Karaghiosoff and P. Knochel, *Angew. Chem., Int. Ed.*, 2019, **58**, 8231–8234.

36 F. H. Lutter, L. Grokenberger, M. S. Hofmayer and P. Knochel, *Chem. Sci.*, 2019, **10**, 8241–8245.

37 M. S. Hofmayer, F. H. Lutter, L. Grokenberger, J. M. Hammann and P. Knochel, *Org. Lett.*, 2019, **21**, 36–39.

38 Y.-H. Chen, S. Graßl and P. Knochel, *Angew. Chem., Int. Ed.*, 2018, **57**, 1108–1111.

39 S. Graßl, Y.-H. Chen, C. Hamze, C. P. Tüllmann and P. Knochel, *Org. Lett.*, 2019, **21**, 494–497; S. Graßl and P. Knochel, *Org. Lett.*, 2020, **22**, 1947–1950.

40 S. Graßl, J. Singer and P. Knochel, *Angew. Chem., Int. Ed.*, 2020, **59**, 335–338.

41 S. Ohta, N. Tsuno and S. Nakamura, *Heterocycles*, 2000, **53**, 1939–1955.

42 C. Blomberg, *The Barbier reaction and related one-step processes*, Springer Science & Business Media, 2012, vol. 31.

43 A. Frischmuth, M. Fernández, N. M. Barl, F. Achrainer, H. Zipse, G. Berionni, H. Mayr, K. Karaghiosoff and P. Knochel, *Angew. Chem., Int. Ed.*, 2014, **53**, 7928–7932.

44 M. R. Becker and P. Knochel, *Angew. Chem., Int. Ed.*, 2015, **54**, 12501–12505; M. Ketels, M. A. Ganiek, N. Weidmann and P. Knochel, *Angew. Chem., Int. Ed.*, 2017, **56**, 12770–12773.

45 M. A. Ganiek, M. R. Becker, G. Berionni, H. Zipse and P. Knochel, *Chem.–Eur. J.*, 2017, **23**, 10280–10284.

46 A. Gissot, J.-M. Becht, J. R. Desmurs, V. Pévère, A. Wagner and C. Mioskowski, *Angew. Chem., Int. Ed.*, 2002, **41**, 340–343; P. C. K. Vesborg and T. F. Jaramillo, *RSC Adv.*, 2012, **2**, 7933–7947; Y. Ma, R. F. Algera and D. B. Collum, *J. Org. Chem.*, 2016, **81**, 11312–11315; R. F. Algera, Y. Ma and D. B. Collum, *J. Am. Chem. Soc.*, 2017, **139**, 7921–7930; R. F. Algera, Y. Ma and D. B. Collum, *J. Am. Chem. Soc.*, 2017, **139**, 11544–11549; R. F. Algera, Y. Ma and D. B. Collum, *J. Am. Chem. Soc.*, 2017, **139**, 15197–15204; R. A. Woltornist, Y. Ma, R. F. Algera, Y. Zhou, Z. Zhang and D. B. Collum, *Synthesis*, 2020, **52**, 1478–1497.

47 N. Weidmann, M. Ketels and P. Knochel, *Angew. Chem., Int. Ed.*, 2018, **57**, 10748–10751; J. H. Harenberg, N. Weidmann and P. Knochel, *Angew. Chem., Int. Ed.*, 2020, **59**, 12321–12325; J. H. Harenberg, N. Weidmann, K. Karaghiosoff and P. Knochel, *Angew. Chem., Int. Ed.*, 2021, **60**, 731–735.

48 P. Knochel and P. Jones, *Organozinc reagents: a practical approach*, Oxford University Press, 1999; F. H. Lutter, M. S. Hofmayer, J. M. Hammann, V. Malakhov and P. Knochel, *Organic Reactions*, 2020, pp. 63–120.

49 A. Krasovskiy and P. Knochel, *Synthesis*, 2006, **2006**, 0890–0891.

50 T. Noël and S. L. Buchwald, *Chem. Soc. Rev.*, 2011, **40**, 5010–5029; D. Cantillo and C. O. Kappe, *ChemCatChem*, 2014, **6**, 3286–3305; D. Haas, J. M. Hammann, R. Greiner and P. Knochel, *ACS Catal.*, 2016, **6**, 1540–1552; M. Markovič, P. Lopatka, T. Gracza and P. Koóš, *Synthesis*, 2020, **52**, 3511–3529; B. Heinz, D. Djukanovic, M. A. Ganiek, B. Martin, B. Schenkel and P. Knochel, *Org. Lett.*, 2020, **22**, 493–496.