nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-020-18188-z OPEN

Regioselective functionalization of aryl azoles as powerful tool for the synthesis of pharmaceutically relevant targets

Ferdinand H. Lutter [1], Lucie Grokenberger[1], Luca Alessandro Perego [2], Diego Broggini[2], Sébastien Lemaire [3], Simon Wagschal [2✉] & Paul Knochel [1✉]

Aryl azole scaffolds are present in a wide range of pharmaceutically relevant molecules. Their ortho-selective metalation at the aryl ring is challenging, due to the competitive metalation of the more acidic heterocycle. Seeking a practical access to a key Active Pharmaceutical Ingredient (API) intermediate currently in development, we investigated the metalation of 1-aryl-1*H*-1,2,3-triazoles and other related heterocycles with sterically hindered metal-amide bases. We report here a room temperature and highly regioselective ortho-magnesiation of several aryl azoles using a tailored magnesium amide, TMPMgBu (TMP = 2,2,6,6-tetramethylpiperidyl) in hydrocarbon solvents followed by an efficient Pd-catalyzed arylation. This scalable and selective reaction allows variation of the initial substitution pattern of the aryl ring, the nature of the azole moiety, as well as the nature of the electrophile. This versatile method can be applied to the synthesis of bioactive azole derivatives and complements existing metal-mediated ortho-functionalizations.

[1] Ludwig-Maximilians-Universität München, Department Chemie, Butenandtstrasse 5-13, Haus F, 81377 München, Germany. [2] Discovery Product Development and Supply, Janssen Pharmaceutica, Hochstrasse 201, 8200 Schaffhausen, Switzerland. [3] Discovery Product Development and Supply, Janssen Pharmaceutica, Turnhoutseweg 30, B-2340 Beerse, Belgium. ✉email: swagscha@its.jnj.com; paul.knochel@cup.uni-muenchen.de

N-aryl azole scaffolds are present in several marketed and experimental drugs, such as celecoxib[1], apixaban[2], zibotentan[3], and nesapidil[4] (Fig. 1a). As part of an ongoing development program, we sought a straightforward access to *N*-aryl-1,2,3-triazole **1a**[5]. An attractive and efficient approach to access such heterocyclic motif is the C–H functionalization of 1-aryl-1*H*-1,2,3-triazoles such as **2a** (Fig. 1b). A well-established strategy involves transition metal-catalyzed C–H arylations[6–21]. These reactions usually require harsh conditions and often lead to bis-arylated products, which limits their practicality[6,8,12–17,22,23]. The direct deprotonation with a suitable base may be an alternative for the selective functionalization of aryl azoles. However, the regioselective metalation of the aryl ring linked to a heterocycle is challenging, due to the competitive and often favored metalation of the *N*-heterocycle itself[24].

A potential approach to achieve a regioselective metalation at the aryl ring is the avoidance of coordinating solvents such as THF, which competes with the nitrogen atom of the azole ring in complexation of the base[25]. Sterically hindered metal-amide bases, especially magnesium- and zinc-derived TMP-bases (TMP = 2,2,6,6-tetramethylpiperidyl) have proved to be powerful reagents for the functionalization of various (hetero)arenes[26–33]. The use of hindered metal amides in hydrocarbon solvents should thus be beneficial. In line with this concept, Hagadorn showed that TMP_2Zn is an excellent base for the α-zincation of various carbonyl compounds and the metalation of pyridine-*N*-oxide in toluene[34,35]. Similarly, Mulvey and co-workers[36–43] reported several mixed bimetallic amide bases for metalation reactions in non-coordinating hydrocarbon solvents. Herein we report a highly selective and broadly applicable magnesiation of various aryl azoles using the amide base TMPMgBu in a toluene/hexane solvent mixture and subsequent cross-couplings and electrophilic quench reactions.

Results

Reaction optimization. In preliminary experiments, the reaction of 1-aryl-1*H*-1,2,3-triazole **2a** with various metal-amide bases was examined to assess the selectivity between products **A** and **B**. The use of strong bases like TMPLi or LDA exclusively afforded the undesired metalation at the most acidic 5-position of the triazole together with large amounts of decomposition products (Fig. 2a, entries 1–2). Similarly, mixtures of **A** and **B** were obtained with TMPMgCl·LiCl or TMP_2Mg in THF[44–46] (entries 3–4). We turned our attention to TMPMgBu[47,48], which was conveniently prepared by treating TMP-H with commercially available Bu_2Mg in hexane (25 °C, 48 h), affording a clear 0.74–0.81 M solution in 94–98% yield (Fig. 2b). Unfortunately, performing the metalation of **2a** in THF using TMPMgBu did not yield better results in terms of selectivity between the two metalation sites (Fig. 2a, entry 5). As mentioned above, we anticipated that the use of the highly coordinating solvent THF could hamper a selective coordination at the N(2)-atom of the triazole. We therefore switched to metal bases in hydrocarbons. While TMP_2Mg in toluene proved to be too reactive, leading to extensive decomposition of the starting material **2a** (entry 6), TMPMgBu in toluene turned out to be highly selective, affording the desired metalated triazole **A** in 81% yield within 1 h (**A**:**B** = 96:4, entry 7). However, TMP_2Zn[34,35] or *i*PrMgCl.LiCl were not suitable reagents for the deprotonation of the aryl moiety of **2a** (entries 8–9).

Substrate scope. We then examined the reactivity of the arylmetal species generated via deprotonation with TMPMgBu in the palladium-catalyzed Negishi cross-coupling (Fig. 2c). After transmetalation with $ZnCl_2$, the resulting arylzinc reagent was coupled with 4-chloro-6-methoxypyrimidine using 1 mol% of [$PdCl_2$(dppf)] (dppf = 1,1′-bis(diphenylphosphino)ferrocene) and the desired active pharmaceutical ingredient (API) intermediate **1a** could be isolated in 86% yield. With these results in hand, we examined the scope of the metalation reaction using various substituted aryl triazoles (Fig. 3).

The metalation of the electron-deficient triazole **2b** proceeded smoothly within 1 h at room temperature leading exclusively to the organomagnesium reagent **3b** in 86% yield. The unsubstituted phenyl derivative **2c** was metalated in 4 h affording 72% of the desired metal reagent **3c** along with 6% deprotonation at the triazole 5-position. The electron-rich triazoles **2d–f** required a prolonged metalation time of 4–6 h and furnished **3d–f** in 68–77% yield. The metalation of the ortho-fluoro triazole **2g**

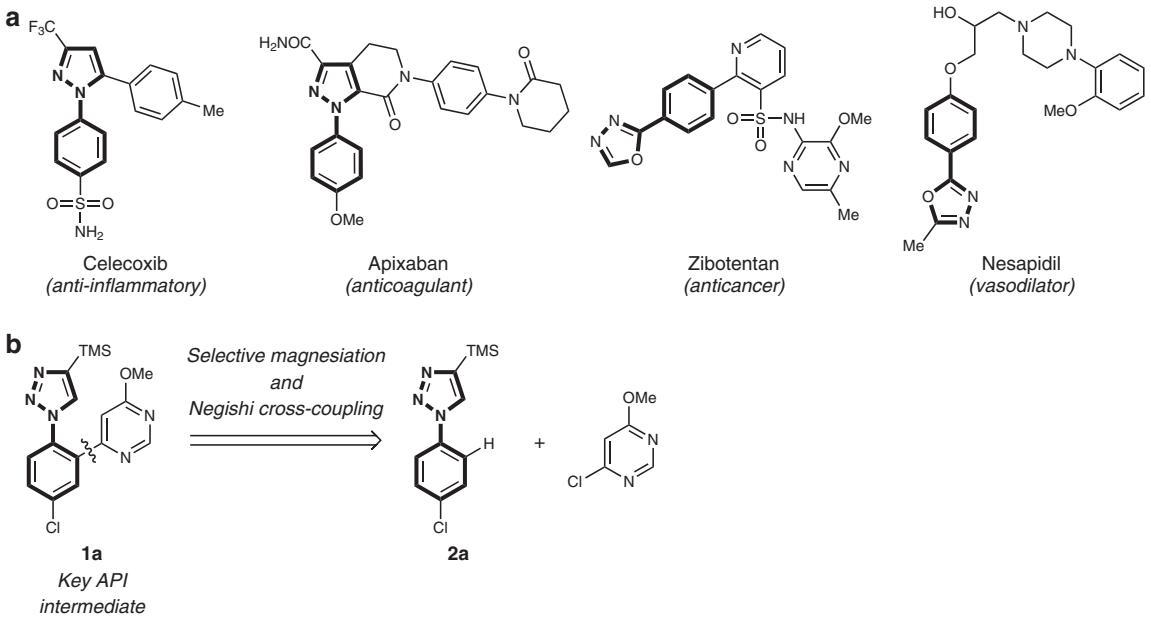
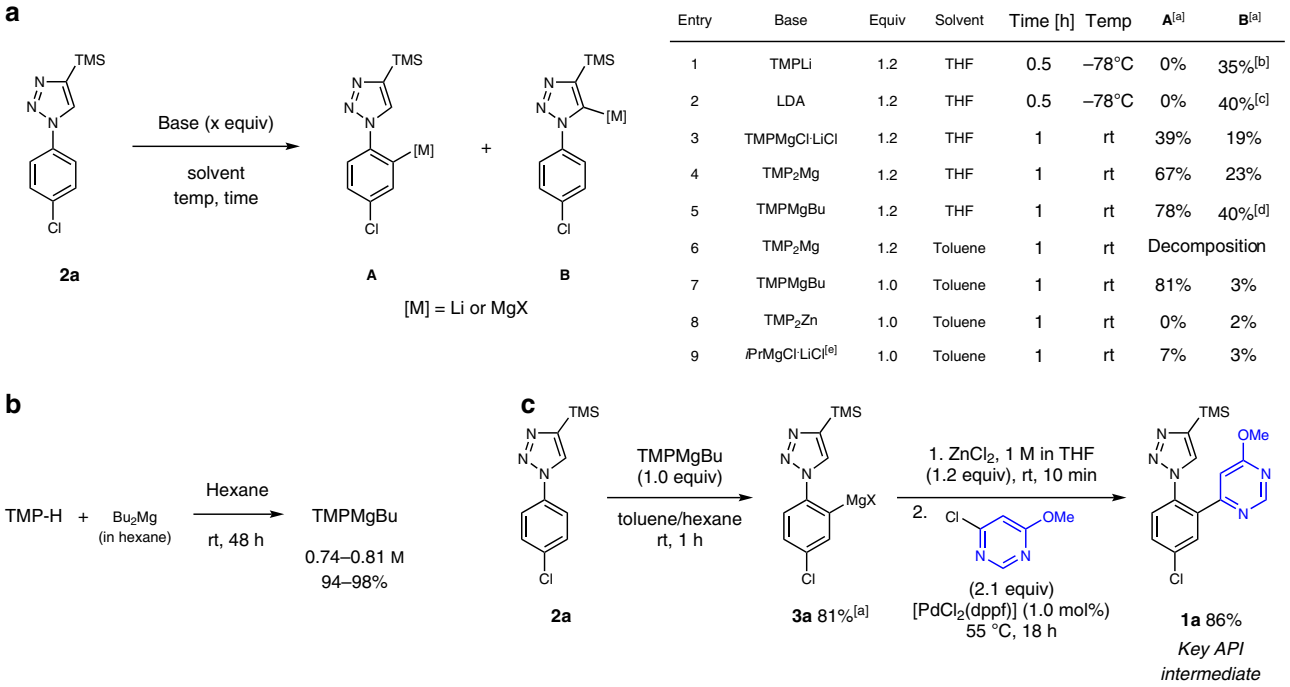


Fig. 1 Background and objective. a Examples of bioactive aryl azole derivatives. **b** Retrosynthetic strategy for API intermediate **1a**.



Entry	Base	Equiv	Solvent	Time [h]	Temp	A[a]	B[a]
1	TMPLi	1.2	THF	0.5	–78°C	0%	35%[b]
2	LDA	1.2	THF	0.5	–78°C	0%	40%[c]
3	TMPMgCl·LiCl	1.2	THF	1	rt	39%	19%
4	TMP_2Mg	1.2	THF	1	rt	67%	23%
5	TMPMgBu	1.2	THF	1	rt	78%	40%[d]
6	TMP_2Mg	1.2	Toluene	1	rt	Decomposition	
7	TMPMgBu	1.0	Toluene	1	rt	81%	3%
8	TMP_2Zn	1.0	Toluene	1	rt	0%	2%
9	*i*PrMgCl·LiCl[e]	1.0	Toluene	1	rt	7%	3%

Fig. 2 Reaction optimization. a Screening of the metalation of **2a**. [a]Metalation yields were determined by ^{1}H-NMR analysis of D_2O-quenched reaction aliquots. [b]Sixty-five percent decomposition. [c]Forty-three percent decomposition. [d]Including bis-metalated species. [e]In THF. **b** Preparation of TMPMgBu. **c** Pd-catalyzed cross-coupling reaction towards **1a**.

afforded **3g** in 80% yield. We did not observe any metalation ortho to either the methoxy or the fluoro moieties, indicating that the triazole unit is a much stronger directing group than those substituents. When testing other substituents at the 4-position of triazole, we found that the TMS group was key to reach high selectivity as the corresponding 4-butyl and 4-phenyl analogs afforded only mixtures of arylmagnesium species (see Supplementary Fig. 13).

Magnesium organometallics **3a–g** were then transmetalated with $ZnCl_2$ prior to their use in the cross-coupling with a variety of functionalized (hetero)aryl bromides. Palladium-catalyzed coupling reactions proceeded smoothly with several electron-rich and -deficient aryl bromides, furnishing the corresponding products **1b–f** in 75–87% yield. Remarkably, the reaction of the sterically demanding 2-bromonaphthalene led to **1g** in 74% yield. Various fluorinated aryl bromides containing a trifluoromethoxy, pentafluorosulfinyl, trifluoromethyl, or fluoro substituent were successfully applied in these couplings affording the desired arylated products **1h–k** in 70–95% yield. Furthermore, a range of heteroaryl bromides, such as pyridyl-, pyrimidyl-, indolyl-, and various thienyl- and furyl bromides were used as coupling partners leading to the corresponding products **1l–s** in 62–96% yield. Next, the metalation was extended to other aryl azoles (Fig. 4a). Treating 1-phenyl-3,5-dimethyl-1*H*-pyrazole **4a** with TMPMgBu (1.0 equiv) for 1 h afforded **5a** in 82% yield and perfect regioselectivity. Unsubstituted pyrazole **4b** was selectively metalated at the aryl moiety leading to the magnesium reagent **5b** (78% yield). Remarkably, no competitive metalation of the azole ring was observed in any case. Furthermore, 2,5-diphenyl-1,3,4-oxadiazole **4c** underwent a selective mono-magnesiation, affording **5c** in 76% yield after 2 h metalation time. The magnesiation of phenyl oxazoline **4d** proceeded within 1 h leading to the metalated product **5d** in 77% yield.

Negishi cross-couplings starting from **5a** afforded the compounds **6a–b** in 68–95% yield under the standard conditions. Substrates containing such a 3,5-dimethylpyrazole group are of special interest, since an oxidative cleavage via ozonolysis affords the corresponding *N*-acetylated anilines[17]. The unsubstituted *N*-aryl pyrazolylmagnesium reagent **5b** was coupled with functionalized aryl bromides bearing a tosylate and nitrile group leading to the products **6c–d** in 89% and 88% yield, respectively. The reaction of **5c** with bromobenzene afforded the corresponding 1,3,4-oxadiazole **6e** in 80% yield, which is a valuable precursor for the synthesis of electroluminescent compounds[49].

Additionally, a more electron-deficient derivative was synthesized following the optimized procedure leading to **6f** in 75% yield. Finally, the cross-coupling of **5d** furnished the corresponding products **6g–h** in 91–96% yield.

The versatility of the method was shown by performing various trapping reactions of the arylmagnesium reagent **3a** with several commonly used electrophiles (Fig. 4b). Thus, a reaction with I_2 afforded **7a** in 98% yield and the addition of benzaldehyde or $MeSSO_2Me$ to **3a** led to the corresponding alcohol **7b** or thioether **7c** in 86% and 75% yield, respectively. A transmetalation with CuCN·2LiCl and subsequent reaction with benzoyl chloride or an allyl bromide derivative afforded **7d–e** in 62–77% yield.

Late-stage diversification. Various late-stage modifications were performed to demonstrate the synthetic utility of the cross-coupling products (Fig. 5). The TMS group could be easily removed using TBAF giving access to unsubstituted triazole **8** in 91% yield. Treating **1h** with TMPMgBu for 2 h in toluene led to the arylmagnesium reagent **9** in 80% yield. After transmetalation with $ZnCl_2$, a palladium-catalyzed cross-coupling with 5-bromo-*N*-methyl indole afforded the bis-arylated triazole **10** in 88% yield. The reaction of **1h** with 1,3-dibromo-5,5-dimethylhydantoin furnished the corresponding bromide **11** in 93% yield. A palladium-catalyzed Suzuki-cross-coupling of **11** with an arylboronic acid allows the smooth functionalization of the triazole moiety, affording **12** in 86% yield.

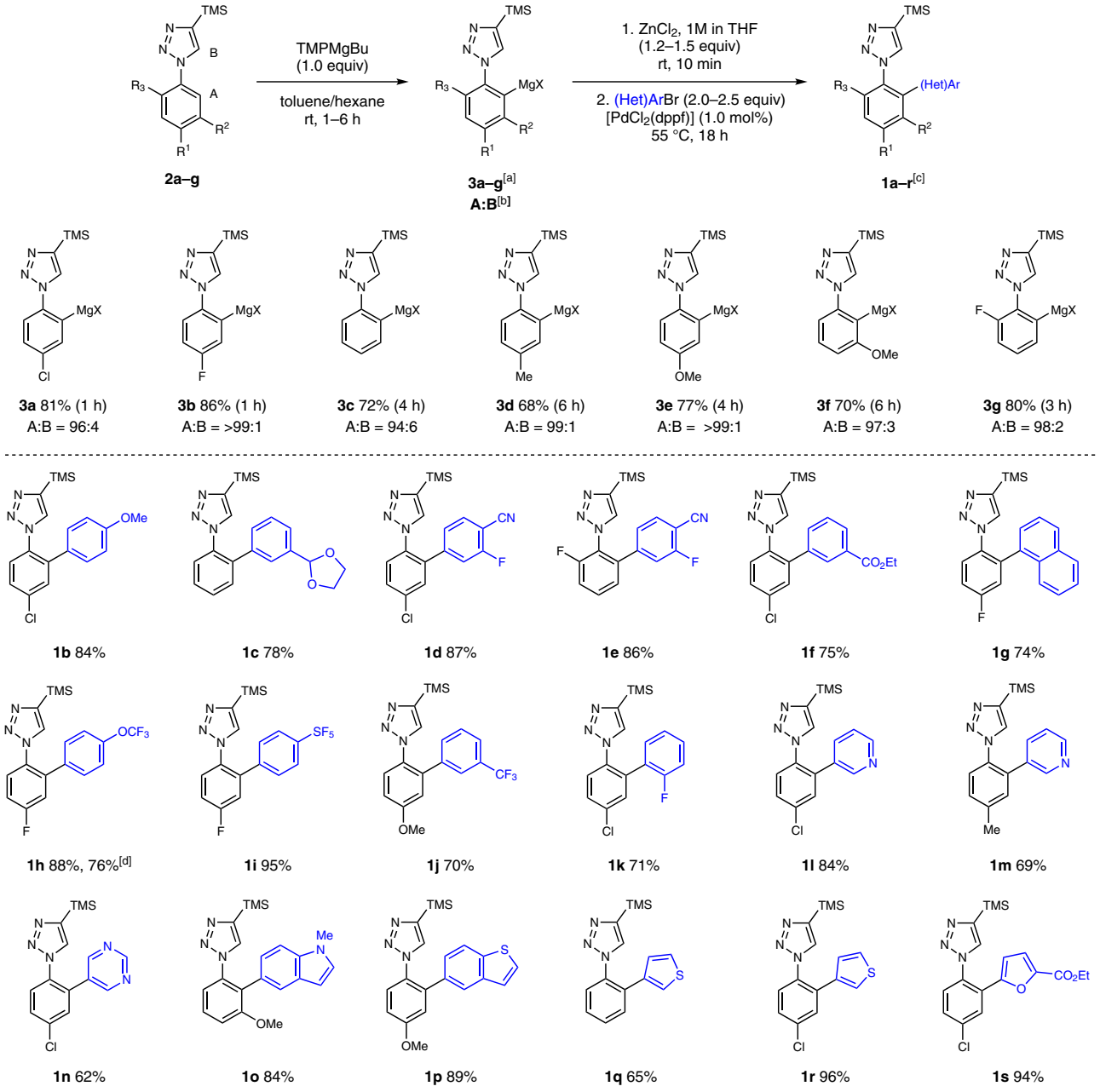


Fig. 3 Metalation of various aryl triazole derivatives and scope of the subsequent palladium-catalyzed cross-coupling. Experiments were performed on a 0.5 mmol scale. [a]Metalation yields were determined by ^{1}H-NMR analysis of D_2O-quenched reaction aliquots. Metalation time in brackets. [b]Metalation ratio in [%] between regioisomers of type A and B. [c]All yields refer to isolated compounds. [d]Reaction performed on a 5 mmol scale.

Mechanistic probes. We then sought to gain a deeper understanding of the metalation and cross-coupling steps. It is known that commercially available Bu_2Mg solutions are mixtures of *n*-butyl and *s*-butyl magnesium species. Analysis of an iodolyzed sample revealed a 60:40 ratio of *n*-butyl and *s*-butyl moieties present in Bu_2Mg, and the same ratio was found in TMPMgBu. Interestingly, Bu_2Mg in toluene/hexane was also an excellent base to selectively deprotonate **2a** affording ortho-magnesiation in 93% yield (Fig. 6). The resulting mixture mainly contained ArMg (*n*-Bu) and ArMg(*s*-Bu) (89% and 4%, respectively). However, after transmetalation with zinc chloride, only 28% of the desired cross-coupling product **1b** were obtained together with 88% of 4-butyl-anisole (**13a**), resulting from the cross-coupling of the *n*-butyl residue. This observation accounts for the superiority of TMPMgBu to Bu_2Mg in the metalation/cross-coupling sequence: the use of TMPMgBu limits the formation of the ArMgBu and thus after transmetalation ArZnBu, which preferentially transfers the butyl group to Ar′Br, forming the byproduct Ar′Bu **13a**.

Discussion

In conclusion, we have described a highly regioselective magnesiation of various aryl azoles using a hindered mixed magnesium amide base, TMPMgBu, in toluene/hexane at room temperature. Subsequent palladium-catalyzed cross-couplings with a variety of (hetero)aryl bromides or trapping with electrophiles afforded polyfunctionalized aryl azoles in good to excellent yields. This methodology could be applied to the synthesis of a key API

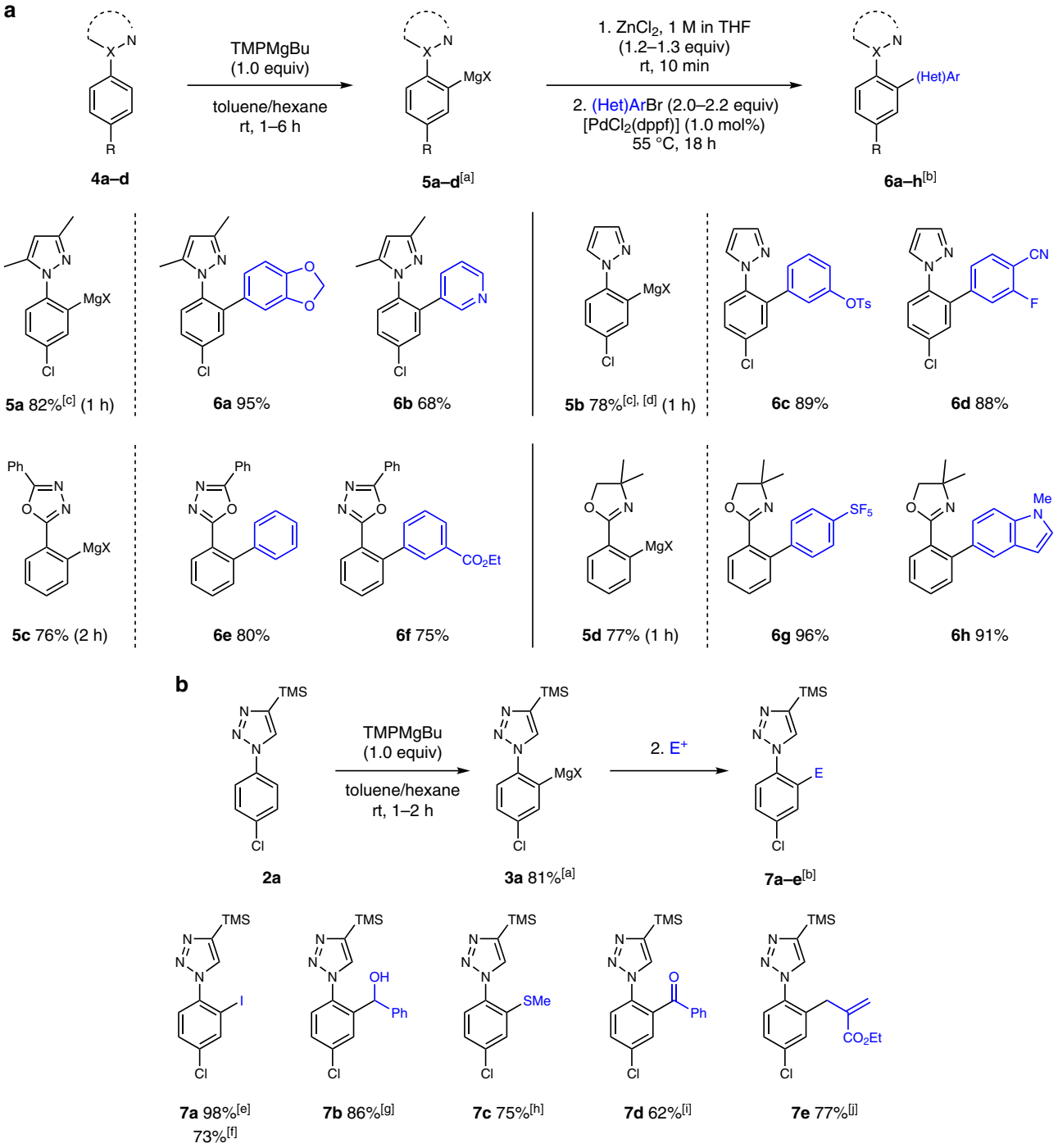


Fig. 4 Substrate scope of aryl azoles and electrophiles. a Metalation of various aryl triazole derivatives and scope of the subsequent palladium-catalyzed cross-coupling. [a]Metalation yields were determined by ^{1}H-NMR analysis of D_2O-quenched reaction aliquots. Metalation time in brackets. [b]All yields refer to isolated compounds. [c]No metalation at the heterocycle was observed. [d]Performing the reaction with TMPLi exclusively led to metalation of the azole moiety. **b** Trapping of magnesium reagent **3a** with various electrophiles. [e]I_2 (4.3 equiv). [f]Metalation of **2a** with Bu_2Mg (vide infra), then I_2 (4.3 equiv). [g]Benzaldehyde (2.5 equiv). [h]$MeSSO_2Me$ (2.5 equiv). [i]Transmetalation with CuCN•2LiCl (3.0 equiv), then benzoyl chloride (2.5 equiv). [j] Transmetalation with CuCN•2LiCl (3.0 equiv), then ethyl 2-(bromomethyl)acrylate (2.5 equiv).

intermediate and several late-stage modifications demonstrated the versatility of the resulting products. Mechanistic experiments highlighted the key role of TMP for the reactivity of the resulting organomagnesium reagents in cross-coupling reactions.

Methods

Preparation of arylmagnesium reagent 3a. Aryl triazole **2a** (126 mg, 0.5 mmol, 1.0 equiv.) was placed in a dry and argon-flushed 10 ml Schlenk tube equipped with a magnetic stirring bar and a septum and was suspended in toluene (0.5 ml, 1.00 M). TMPMgBu (0.67 ml, 0.75 M, 1.0 equiv) was added and the mixture was stirred for 1 h affording the magnesium reagent **3a** in 81% yield.

Palladium-catalyzed cross-coupling. **3a** was transmetalated with a $ZnCl_2$ solution (0.5 ml, 1.00 M in THF) and THF (1.0 ml) was added. A dry and argon-flushed Schlenk tube, equipped with a magnetic stirring bar and a septum, was charged with Pd(dppf)Cl_2 (1.0 mol%, 0.005 mmol, 3.7 mg) and 1-bromo-4-methoxybenzene (0.850 mmol, 159 mg, 2.10 equiv) was added. The freshly

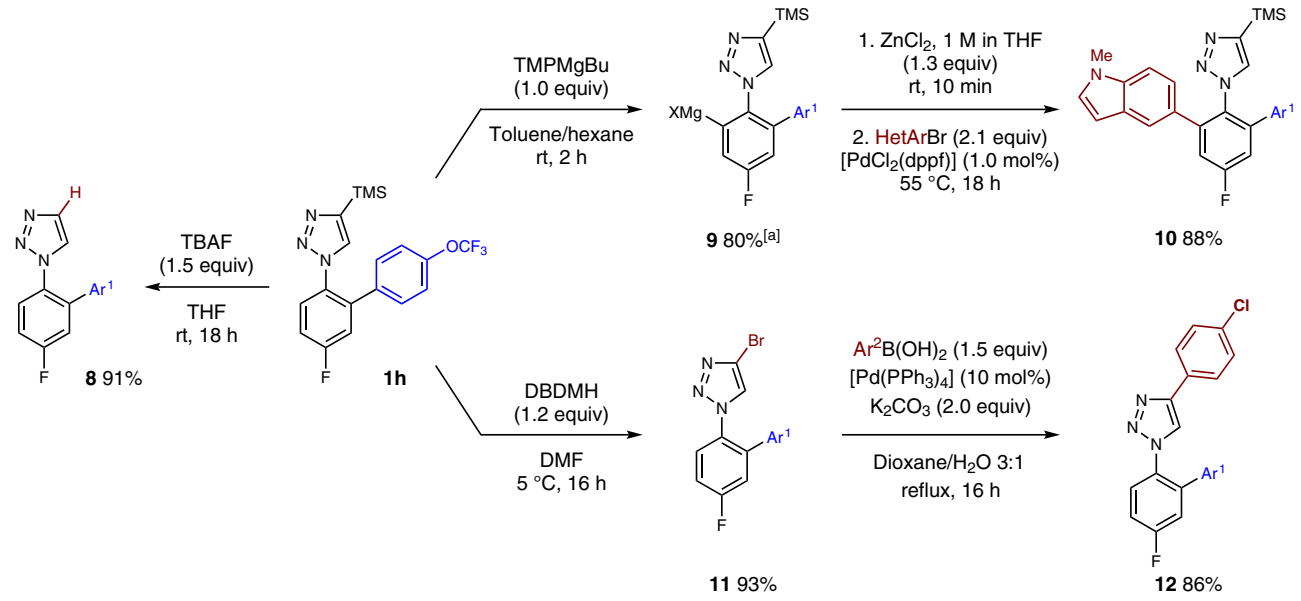


Fig. 5 Late-stage modifications. [a]Metalation yields was determined by ^{1}H-NMR analysis of D_2O-quenched reaction aliquots. All other yields refer to isolated compounds. HetAr = *N*-Me-5-indolyl, Ar^1 = 4-OCF_3-C_6H_4, Ar^2 = 4-Cl-C_6H_4.

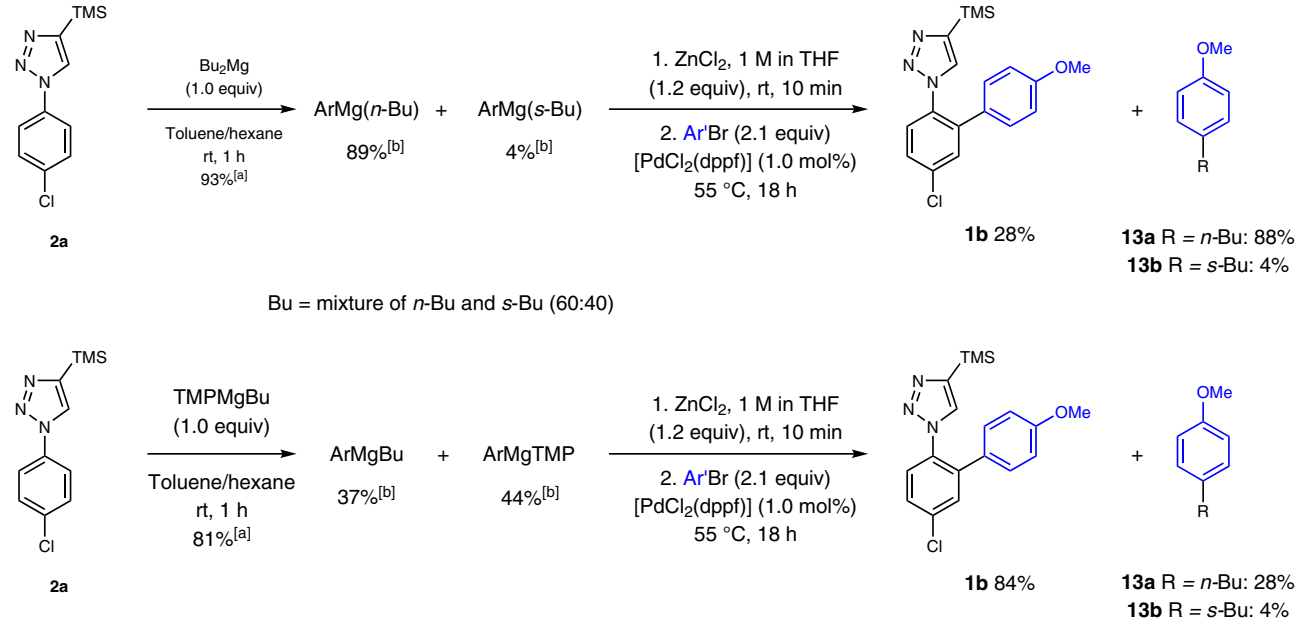


Fig. 6 Mechanistic probes. [a] Metalation yields were determined by ^{1}H-NMR analysis of D_2O-quenched reaction aliquots. [b] Yields were determined by GC analysis of iodolyzed aliquots using undecane as an internal standard. Ar = 5-Cl-2-(4-TMS-1*H*-1,2,3-triazol-1-yl)-C_6H_3. Ar′ = 4-MeO-C_6H_4.

prepared arylzinc reagent was added and the reaction mixture was placed in an oil bath at 55 °C. After 16 h, saturated aq. NH_4Cl solution (5 ml) was added, the phases were separated, and the aqueous phase was extracted with EtOAc (3 × 25 ml). The combined organic layers were dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude product was subjected to column chromatography.

Data availability

The authors declare that the data supporting the findings of this study are available within the paper and its Supplementary Information files.

Received: 14 May 2020; Accepted: 3 August 2020;
Published online: 07 September 2020

References

1. Penning, T. D. et al. Synthesis and biological evaluation of the 1,5-diarylpyrazole class of cyclooxygenase-2 inhibitors: identification of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (SC-58635, Celecoxib). *J. Med. Chem.* **40**, 1347–1365 (1997).
2. Pinto, D. J. P. et al. Discovery of 1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (Apixaban, BMS-562247), a highly potent, selective, efficacious, and orally bioavailable inhibitor of blood coagulation factor Xa. *J. Med. Chem.* **50**, 5339–5356 (2007).
3. Tomkinson, H. et al. Pharmacokinetics and tolerability of zibotentan (ZD4054) in subjects with hepatic or renal impairment: two open-label comparative studies. *BMC Clin. Pharmacol.* **11**, 3 (2011).
4. Schlecker, R. & Thieme, P. C. The synthesis of antihypertensive 3-(1,3,4-oxadiazol-2-yl)phenoxypropanolahines. *Tetrahedron* **44**, 3289–3294 (1988).

5. Ayothiraman, R. et al. Two approaches to a trifluoromethyl triazole: a fit-for-purpose trifluoromethylation in flow-mode and a long-term decarboxylative click approach. *Org. Process Res. Dev.* **24**, 207–215 (2020).
6. Alberico, D., Scott, M. E. & Lautens, M. Aryl−aryl bond formation by transition-metal-catalyzed direct arylation. *Chem. Rev.* **107**, 174–238 (2007).
7. Ackermann, L. Catalytic arylations with challenging substrates: from air-stable haspo preligands to indole syntheses and C-H-bond functionalizations. *Synlett* **2007**, 507–526 (2007).
8. Arockiam, P. B., Bruneau, C. & Dixneuf, P. H. Ruthenium(II)-catalyzed C–H bond activation and functionalization. *Chem. Rev.* **112**, 5879–5918 (2012).
9. Kuhl, N., Schröder, N. & Glorius, F. Formal SN-type reactions in Rhodium(III)-catalyzed C-H bond activation. *Adv. Synth. Catal.* **356**, 1443–1460 (2014).
10. Yang, Y., Lan, J. & You, J. Oxidative C–H/C–H coupling reactions between two (Hetero)arenes. *Chem. Rev.* **117**, 8787–8863 (2017).
11. Gandeepan, P. et al. 3d transition metals for C–H sctivation. *Chem. Rev.* **119**, 2192–2452 (2019).
12. Oi, S., Aizawa, E., Ogino, Y. & Inoue, Y. Ortho-selective direct cross-coupling reaction of 2-aryloxazolines and 2-arylimidazolines with aryl and alkenyl halides catalyzed by ruthenium complexes. *J. Org. Chem.* **70**, 3113–3119 (2005).
13. Ackermann, L., Althammer, A. & Born, R. $[RuCl_3(H_2O)_n]$-catalyzed direct arylations with bromides as electrophiles. *Synlett* **2007**, 2833–2836 (2007).
14. Oi, S., Sasamoto, H., Funayama, R. & Inoue, Y. Ortho-selective arylation of arylazoles with aryl bromides catalyzed by ruthenium complexes. *Chem. Lett.* **37**, 994–995 (2008).
15. Simonetti, M. et al. Cyclometallated ruthenium catalyst enables late-stage directed arylation of pharmaceuticals. *Nat. Chem.* **10**, 724–731 (2018).
16. Ackermann, L., Althammer, A. & Born, R. [RuCl3(H2O)n]-catalyzed direct arylations. *Tetrahedron* **64**, 6115–6124 (2008).
17. Kwak, S. H., Gulia, N. & Daugulis, O. Synthesis of unsymmetrical 2,6-diarylanilines by palladium-catalyzed C–H bond functionalization methodology. *J. Org. Chem.* **83**, 5844–5850 (2018).
18. Oi, S., Sato, H., Sugawara, S. & Inoue, Y. Nitrogen-directed ortho-selective homocoupling of aromatic compounds catalyzed by ruthenium complexes. *Org. Lett.* **10**, 1823–1826 (2008).
19. Ackermann, L., Born, R. & Vicente, R. Ruthenium-catalyzed direct arylations of N-aryl 1,2,3-triazoles with aryl chlorides as electrophiles. *ChemSusChem* **2**, 546–549 (2009).
20. Teskey, C. J. et al. Domino N-/C-arylation via in situ generation of a directing group: atom-efficient arylation using diaryliodonium salts. *Angew. Chem. Int. Ed.* **56**, 5263–5266 (2017).
21. Ackermann, L., Vicente, R. & Althammer, A. Assisted ruthenium-catalyzed C−H bond activation: carboxylic acids as cocatalysts for generally applicable direct arylations in apolar solvents. *Org. Lett.* **10**, 2299–2302 (2008).
22. Daugulis, O. & Zaitsev, V. G. Anilide ortho-arylation by using C-H activation methodology. *Angew. Chem. Int. Ed.* **44**, 4046–4048 (2005).
23. Oi, S., Funayama, R., Hattori, T. & Inoue, Y. Nitrogen-directed ortho-arylation and -heteroarylation of aromatic rings catalyzed by ruthenium complexes. *Tetrahedron* **64**, 6051–6059 (2008).
24. Ballesteros-Garrido, R. et al. The deprotonative metalation of [1,2,3]triazolo [1,5-a]quinoline. Synthesis of 8-haloquinolin-2-carboxaldehydes. *Tetrahedron* **65**, 4410–4417 (2009).
25. Whisler, M. C., MacNeil, S., Snieckus, V. & Beak, P. Beyond thermodynamic acidity: a perspective on the complex-induced proximity effect (CIPE) in deprotonation reactions. *Angew. Chem. Int. Ed.* **43**, 2206–2225 (2004).
26. Haag, B. et al. Regio- and chemoselective metalation of arenes and heteroarenes using hindered metal amide bases. *Angew. Chem. Int. Ed.* **50**, 9794–9824 (2011).
27. Balkenhohl, M. & Knochel, P. Regioselective C–H activation of substituted pyridines and other azines using Mg- and Zn-TMP-bases. *SynOpen* **02**, 78–95 (2018).
28. Lutter, F. H. et al. In *Organic Reactions* (ed. Denmark, S. E.) (Wiley, 2019).
29. Ziegler, D. S. et al. Directed zincation or magnesiation of the 2-pyridone and 2,7-naphthyridone scaffold using TMP bases. *Org. Lett.* **19**, 5760–5763 (2017).
30. Balkenhohl, M. et al. Zn-, Mg-, and Li-TMP bases for the successive regioselective metalations of the 1,5-naphthyridine scaffold (TMP=2,2,6,6-tetramethylpiperidyl). *Chem. Eur. J.* **23**, 13046–13050 (2017).
31. Boga, S. B. et al. Selective functionalization of complex heterocycles via an automated strong base screening platform. *React. Chem. Eng.* **2**, 446–450 (2017).
32. Balkenhohl, M. et al. Regioselective metalation and functionalization of the pyrazolo[1,5-a]pyridine scaffold using Mg- and Zn-TMP bases. *Org. Lett.* **20**, 3114–3118 (2018).
33. Balkenhohl, M. et al. Lewis acid directed regioselective metalations of pyridazine. *Angew. Chem. Int. Ed.* **58**, 9244–9247 (2019).
34. Hlavinka, M. L. & Hagadorn, J. R. $Zn(tmp)_2$: a versatile base for the selective functionalization of C−H bonds. *Organometallics* **26**, 4105–4108 (2007).
35. Hlavinka, M. L. & Hagadorn, J. R. One-step deprotonation route to zinc amide and ester enolates for use in aldol reactions and Negishi couplings. *Tetrahedron Lett.* **47**, 5049–5053 (2006).
36. Blair, V. L. et al. Tuning the basicity of synergic bimetallic reagents: switching the regioselectivity of the direct dimetalation of toluene from 2,5- to 3,5-positions. *Angew. Chem. Int. Ed.* **47**, 6208–6211 (2008).
37. Martínez-Martínez, A. J. et al. Templated deprotonative metalation of polyaryl systems: facile access to simple, previously inaccessible multi-iodoarenes. *Sci. Adv.* **3**, e1700832 (2017).
38. Martínez-Martínez, A. J. et al. Pre-inverse-crowns: synthetic, structural and reactivity studies of alkali metal magnesiates primed for inverse crown formation. *Chem. Sci.* **5**, 771–781 (2014).
39. Mulvey, R. E. Modern ate chemistry: applications of synergic mixed alkali-metal−magnesium or -zinc reagents in synthesis and structure building. *Organometallics* **25**, 1060–1075 (2006).
40. Martínez-Martínez, A. J., Kennedy, A. R., Mulvey, R. E. & O'Hara, C. T. Directed ortho-metá- and meta-meta-dimetalations: a template base approach to deprotonation. *Science* **346**, 834 (2014).
41. Robertson, S. D., Uzelac, M. & Mulvey, R. E. Alkali-metal-mediated synergistic effects in polar main group organometallic chemistry. *Chem. Rev.* **119**, 8332–8405 (2019).
42. Stevens, M. A. et al. Contrasting synergistic heterobimetallic (Na–Mg) and homometallic (Na or Mg) bases in metallation reactions of dialkylphenylphosphines and dialkylanilines: lateral versus ring selectivities. *Chem. Eur. J.* **24**, 15669–15677 (2018).
43. Fuentes, M. Á., Zabala, A., Kennedy, A. R. & Mulvey, R. E. Structural diversity in alkali metal and alkali metal magnesiate chemistry of the bulky 2,6-diisopropyl-*N*-(trimethylsilyl)anilino ligand. *Chem. Eur. J.* **22**, 14968–14978 (2016).
44. Eaton, P. E., Lee, C. H. & Xiong, Y. Magnesium amide bases and amido-grignards. 1. Ortho magnesiation. *J. Am. Chem. Soc.* **111**, 8016–8018 (1989).
45. Eaton, P. E., Xiong, Y. & Gilardi, R. Systematic substitution on the cubane nucleus. Synthesis and properties of 1,3,5-trinitrocubane and 1,3,5,7-tetranitrocubane. *J. Am. Chem. Soc.* **115**, 10195–10202 (1993).
46. Ooi, T., Uematsu, Y. & Maruoka, K. New, improved procedure for the synthesis of structurally diverse *N*-spiro C2-symmetric chiral quaternary ammonium bromides. *J. Org. Chem.* **68**, 4576–4578 (2003).
47. Hevia, E., Kennedy, A. R., Mulvey, R. E. & Weatherstone, S. Synthesis and crystal structure of $[\{n\text{BuMg}(\mu\text{-TMP})\}_2]$ and of a homometallic inverse crown in tetranuclear $[\{n\text{BuMg}_2[\mu\text{-}N(H)\text{Dipp}]2(\mu_3\text{-OnBu})\}_2]$. *Angew. Chem. Int. Ed.* **43**, 1709–1712 (2004).
48. Conway, B. et al. Synthesis and characterisation of a series of alkylmagnesium amide and related oxygen-contaminated "alkoxy" compounds. *Dalton Trans.* **2005**, 1532–1544 (2005).
49. Feldmann, J. et al. Blue luminescent compounds, US 20150236278 A1 (2015).

Acknowledgements

We thank Janssen Pharmaceutica and Bristol-Myers Squibb for the funding of the project. We thank the Deutsche Forschungsgemeinschaft (DFG) and the Ludwig-Maximilians-Universität München for financial support. We also thank Albemarle Lithium GmbH (Hoechst, Frankfurt) for the generous gift of chemicals.

Author contributions

F.H.L., L.G., and L.A.P. performed and analyzed the experiments F.H.L., D.B., S.L., S.W., and P.K. designed the experiments. F.H.L., L.A.P., S.W., and P.K. prepared the manuscript with contributions of all authors.

Funding

Open Access funding provided by Projekt DEAL.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information is available for this paper at https://doi.org/10.1038/s41467-020-18188-z.

Correspondence and requests for materials should be addressed to S.W. or P.K.

Peer review information *Nature Communications* thanks Melodie Christensen, Matthieu Tissot and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Peer reviewer reports are available.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.