Catalysis Hot Paper

How to cite: *Angew. Chem. Int. Ed.* **2020**, *59*, 20596–20603
International Edition: doi.org/10.1002/anie.202008866
German Edition: doi.org/10.1002/ange.202008866

Efficient Pd-Catalyzed Direct Coupling of Aryl Chlorides with Alkyllithium Reagents

*Thorsten Scherpf, Henning Steinert, Angela Großjohann, Katharina Dilchert, Jens Tappen, Ilja Rodstein, and Viktoria H. Gessner**

In memory of Professor Hans J. Reich, a pioneer in organolithium chemistry

Abstract: *Organolithium compounds are amongst the most important organometallic reagents and frequently used in difficult metallation reactions. However, their direct use in the formation of C–C bonds is less established. Although remarkable advances in the coupling of aryllithium compounds have been achieved, Csp^2–Csp^3 coupling reactions are very limited. Herein, we report the first general protocol for the coupling or aryl chlorides with alkyllithium reagents. Palladium catalysts based on ylide-substituted phosphines (YPhos) were found to be excellently suited for this transformation giving high selectivities at room temperature with a variety of aryl chlorides without the need for an additional transmetallation reagent. This is demonstrated in gram-scale synthesis including building blocks for materials chemistry and pharmaceutical industry. Furthermore, the direct coupling of aryllithiums as well as Grignard reagents with aryl chlorides was also easily accomplished at room temperature.*

Introduction

Palladium-catalyzed cross-coupling reactions have become a powerful tool for the formation of C–C and C–X bonds in organic synthesis and are nowadays frequently used to produce fine chemicals such as agrochemicals and pharmaceuticals.[1] The success of these methodologies lies in the breadth of electrophiles and nucleophiles which can be used in this protocol and the myriad of reagents which are accessible. Albeit many limitations in coupling chemistry have been overcome over the years by the development of new, more sophisticated and specialized ligands,[2] still many challenges remain, which seem to be related to the intrinsic limitations in the ligand design.[3] In case of C_{sp^2}–C_{sp^2} and C_{sp^2}–C_{sp^3} coupling reactions the Suzuki–Miyaura, Stille, Kumada and Negishi couplings are the most important protocols.[4] Particularly, the Suzuki reaction which makes use of boron nucleophiles has become the method of choice for the formation of biaryl compounds, especially in pharmaceutical industry. This is mainly based on the high group tolerance and the facile access of boronic acids, esters or borates, which are typically generated from readily available organolithium or Grignard reagents. The same is also true for organotin compounds used in Stille couplings, which however are often toxic and thus less frequently applied. To facilitate synthetic protocols by preventing a further transmetallation step the development of reliable protocols with magnesium and lithium nucleophiles would be highly desirable. This would also allow for the reduction of inorganic waste (tin or boron salts) and production costs. While Kumada couplings[5] are routinely used since several years and reliable protocols for sp^2-sp^2 and sp^2-sp^3 couplings have been developed with phosphines[6] as well as *N*-heterocyclic carbenes[7,8] using nickel or palladium as well as base metals,[9,10] the corresponding reactions with organolithium compounds are far less developed. Feringa and co-workers greatly improved the first protocols reported by Murahashi,[11] and in the case of aryl/alkenyl bromides, protocols exist to couple almost any conceivable lithium reagent even at low temperatures (Figure 1).[12] For the more desirable and readily available aryl chlorides, the coupling is much less general. Reagents like aryl/alkenyl lithium or (trimethylsilyl)methyllithium, that cannot undergo β-hydride elimination (BHE) work efficiently, whereas primary and secondary alkyl lithium reagents are problematic.[13] Attempts with nickel-based system were somewhat more successful, but the reaction seems to be

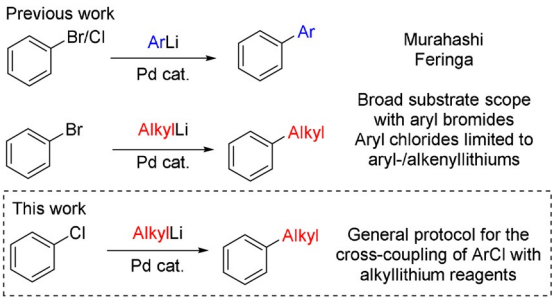


Figure 1. Cross coupling of aryl and alkyl lithium reagents with aryl halides.

[*] Dr. T. Scherpf, M. Sc. H. Steinert, M. Sc. A. Großjohann, Dr. K. Dilchert, M. Sc. J. Tappen, M. Sc. I. Rodstein, Prof. Dr. V. H. Gessner
Faculty of Chemistry and Biochemistry, Chair of Inorganic Chemistry, Ruhr-Universität Bochum
Universitätsstraße 150, 44801 Bochum (Germany)
E-mail: viktoria.gessner@rub.de
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.202008866.

restricted to polyaromatic aryl halides[14] and electron-poor aryl chlorides.[15] Until today, there is no general protocol for the coupling of organolithium reagents with aryl chlorides available.

This limitation is mainly due to two obstacles in the mechanism (Figure 2) of the coupling reaction: i) Aryl chlorides are difficult substrates since oxidative addition of the C–Cl bond is usually rate-limiting and slow at low temperatures. Thus, many side reactions with the highly reactive organolithium reagents can occur (e.g. Cl/Li exchange) prior to the addition step, leading to protodehalogenation and homocoupling. ii) The second limitation concerns the alkyllithium reagents. These reagents are more reactive than aryllithium species and hence more readily undergo the undesired Cl/Li exchange (homocoupling product). This was for example used in the synthesis of symmetric biaryls, where *tert*-butyllithium instead of acting as nucleophile solely enabled lithiation of the aryl halide and hence biaryl formation.[16] Furthermore, the alkyl palladium species formed after the transmetallation step are prone to BHE, which can lead to isomerization and/or protodehalogenation. This competition between "normal" and migratory cross-coupling of alkylmetal reagents has been addressed in recent studies, in particular in the context of Negishi coupling reactions,[17] but remained unexplored with lithium nucleophiles. Thus, the coupling of aryl chlorides with alkyllithium reagents represents the most challenging combination and an unresolved problem.

To promote the coupling of aryl chlorides, very electron-rich ligands are required which facilitate fast oxidative addition at mild temperatures. Therefore, Feringa and co-workers used highly electron-rich phosphines or *N*-heterocyclic carbenes (NHC) to couple aryl and alkenyllithiums.[12,13] Yet, these ligands seem to reach a limit in case of alkyllithium compounds. Recently, we reported on a new class of electron-rich phosphines for homogenous catalysis, the ylide-substituted phosphines, YPhos.[18] Due to the carbanionic charge next to the phosphorus center, these ligands are particularly strong donors, also surpassing the donor strength of NHCs. Accordingly, high activities in Buchwald Hartwig aminations[19] and α-arylations of aryl chlorides at room temperatures were observed.[20,21] This encouraged us to test these ligands for their activities in the coupling of organolithium compounds including alkyllithiums with aryl chlorides, which led us to the development of the first generally applicable reaction protocol.

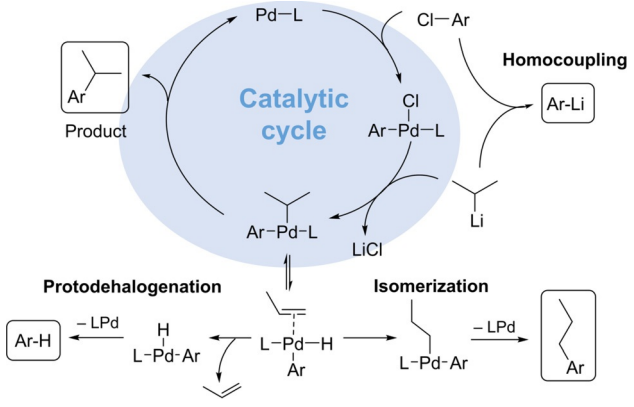


Figure 2. Catalytic cycle of the Murahashi cross-coupling reaction with possible side-reactions.

Results and Discussion

As a first step, the coupling of *sec*-butyllithium with 4-chloroanisole (**1**) was studied using the three YPhos ligands **L1**–**L3** together with Pd_2dba_3·dba as Pd source. The combination of an electron-rich aryl chloride with a secondary alkyllithium reagent represents one of the most challenging reactions and—if being successful—promised a broad applicability of the optimized reaction protocol. We started with reaction conditions similar to those reported by Feringa et al., that is, room temperature and slow addition of the diluted organolithium reagent to a toluene solution of the aryl chloride and the catalyst. Optimization of the reaction conditions showed that 3 mol % catalyst loading are necessary for high conversion (Figure 3, see Supporting Information for details on the optimization). To our delight, YPhos ligand joYPhos (**L3**) gave high conversions of 78 % to the desired coupling product **2a** after only 1 h reaction time. While some protodechlorination product **3** (12 %) was formed, very small amounts of the homocoupling product **4** (4 %) and the isomerized product **2b** (3 %) were obtained. This is especially important, since separation of these isomers are often laborious using standard techniques. Other palladium sources and other YPhos ligands (**L1** and **L2**) also showed high activities in this reaction, albeit with a slightly lower selectivity. In addition, air-stable palladium complexes of **L3**, which are easy to apply showed similar results.[22] Here, [**L3**-Pd(indenyl)Cl] (**L3**–**P3**) showed the highest activity, similar to **L3** and $Pd_2(dba)_3$, and thus represents a convenient alternative to using the free ligand and an additional Pd source.

We compared the activity of the YPhos ligands with that of other catalysts, including those reported in the literature for the coupling of aryl and alkenyllithium compounds. As shown in Figure 3, none of these catalysts delivered comparable good results. While other phosphines ($PtBu_3$, QPhos, XPhos, DavePhos) gave no product at all, the NHC-based PEPPSI catalysts delivered small amounts of product. Presumably, only the NHC catalysts can perform the oxidative addition at room temperature under the coupling conditions. However, conversions and selectivities were low with these catalysts, and for *s*BuLi, several unidentified higher molecular weight products were found, indicating further undesired side reactions. Increasing the reaction temperature to 35 °C to facilitate the oxidative addition of the aryl chloride didn't improve the selectivity or yield of the reaction. The YPhos ligand joYPhos (**L3**) is the only ligand that allows for a sufficiently fast oxidative addition of the aryl chloride at room temperature thus preventing or minimizing the competing homocoupling or protodechlorination, and at the same time minimizes BHE. To our delight, this optimized protocol with **L3** was also capable of effecting the coupling with *n*BuLi (Table 1, Entry 1). In this case, only trace amounts (< 0.1 %)

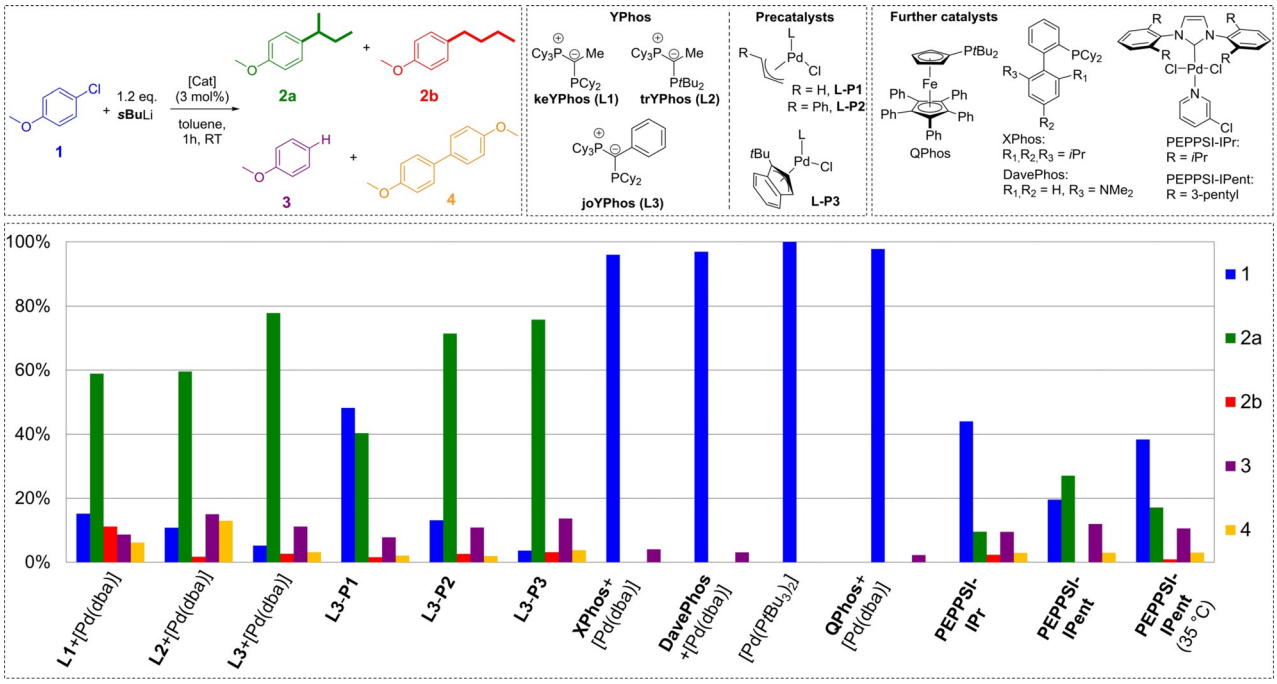
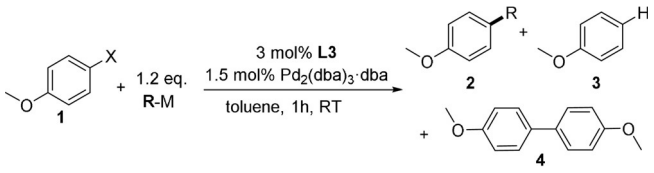


Figure 3. Comparison of catalytic activity of different ligands and palladium complexes in the cross-coupling of *s*-BuLi with 4-chloroanisole. Reaction conditions: 4-Chloroanisole (1 mmol), Pd (3 mol%), ligand (3 mol%) and toluene (1 mL). *s*-Buli (1.3 M in cyclohexane/hexane, 1.2 mmol; diluted with toluene), 1 h addition period at 22 °C (or 35 °C). Yields were determined by GC using *n*-tetradecane as internal standard; Pd(dba) = [$Pd_2(dba)_3$·dba].

Table 1: Results of the reaction of different organometallic reagents with aryl halides.



Entry	X	R–M	Conversion [%]	Product ratio 2	3	4	br:ln ratio
1	Cl	*n*BuLi	93	90	6	4	–
2	Cl	*s*BuLi	95	85	12	3	96:4
3	Br	*n*BuLi	100	90	6	4	–
4	Br	*s*BuLi	100	84	9	7	88:12
5	I	*n*BuLi	100	57	6	37	–
6	I	*s*BuLi	92	3	4	93	78:22
7	Cl	*t*BuLi	99	65	20	16	0:100
8	Cl	*i*PrLi	86	83	12	5	95:5
9	Cl	PhLi	81	95	0	5	–
10	Cl	MeLi	83	98	0	2	–
11	Cl	CyMgCl	96	95	2	3	–
12	Cl	*i*PrMgCl	100	100	0	0	95:5
13	Cl	*t*BuMgCl	100	97	3	0	0:100
14	Cl	*t*BuMgCl[a]	100	94	6	0	0:100
15	Cl	MeMgCl	100	100	0	0	–
16	Cl	PhMgCl	100	100	0	0	–

Reaction conditions: 4-Haloanisole (1 mmol), Pd_2dba_3·xdba (15.62 wt% Pd, 3 mol% [Pd]), **L3** (3 mol%) and toluene (1 mL), lithium/Grignard reagent (see SI, 1.2 mmol) diluted with toluene (0.36 M) and added over 1 h at 22 °C. Yields and br:ln ratios were determined by GC using *n*-tetradecane as internal standard. [a] Addition over 30 s, 1 h reaction time.

of the isomerized product were found, and the amount of protodehalogenation (6%) was likewise small. Again, none of the other catalyst systems (Figure S2) could produce similar good results. Only the NHC-derived catalysts yielded the desired coupling product, but with low selectivities.

Motivated by the initial catalysis results, we turned our attention towards the examination of the generality of the established reaction protocol and a screening of different commercially available alkyllithium and magnesium reagents and aryl halides (Table 1). Aryl bromides were similar efficiently coupled to the desired products (entry 3 and 4), but interestingly the coupling with *s*BuLi showed slightly higher amounts of the isomerized product. Aryl iodides on the other hand showed only low conversion and poor selectivities (entry 5, 6), presumably due to fast iodine/lithium exchange. This suggests that for the successful coupling of alkyllithium reagents, activity towards aryl chlorides is particularly important to obtain high selectivities. While methyllithium and phenyllithium were also efficiently coupled (entry 8, 9), lower selectivities were found with *tert*-butyllithium, which is more reactive towards lithium-halogen exchange. Nonetheless, 65% of product were formed (entry 7). Interestingly, instead of the expected product, complete isomerization to the *iso*-butyl product was observed. No traces of the expected *tert*-butyl product could be detected. Such a complete isomerization has been reported earlier for similar reactions.[22]

Besides C–C couplings with organolithium reagents, **L3**·Pd_2dba_3 is also an extremely efficient catalyst for Kumada coupling reactions (Entries 11–16). Due to the lower reac-

tivity of Grignard reagents higher selectivities for the coupling products were obtained (c.f. entry 8 and 12 or 9 and 116) and secondary alkyl Grignard reagents, like *i*PrMgCl, also gave low amounts of the isomerized products. It is worth mentioning that *t*BuMgCl also selectively provided the isomerization product, but in this case, almost no proto-dehalogenation or biphenyl formation was observed (entry 12). This led us to conclude that the lower selectivities observed wit *t*BuLi were mostly the result of fast side reactions, mainly lithium-halogen exchange, while the complete isomerization of the alkyl group results from an inherent property of the catalytic system. We find it particularly interesting that the same catalyst provides high selectivities for the coupling of secondary alkyllithium and Grignard reagents with little isomerization, while at the same time giving complete isomerization in the coupling of tertiary lithium/Grignard reagents. It is also worth mentioning, that in case of *t*BuMgCl it was not necessary to dilute and slowly add the magnesium reagent. Instant addition of a 1.7 M solution of *t*BuMgCl in THF and stirring for 1 hour only slightly lowered the yield compared to a slow addition over a period of 1 hour. In contrast, instant addition of all other lithium and magnesium nucleophiles resulted in the formation of only small amounts of the desired product.

To gain insight into the reaction process and to understand the observed selectivities, we performed mechanistic studies. At first, we tested the oxidative addition of an aryl chloride to the palladium complex with **L3** by means of a stoichiometric experiment using Pd_2dba_3 and **L3** together with 10 equiv of 4-chlorotoluene. Typically, elevated temperatures are required to reach significant conversion to the Pd^{II} chloride complex. With **L3** however, the oxidative addition complex **L3**·Pd(Tol)Cl was formed at room temperature albeit one day was required for the reaction to complete as evidenced by monitoring of the reaction with ^{31}P NMR spectroscopy. The complex could be isolated in 63 % yield as an air-stable solid, which is poorly soluble in common organic solvents. In the solid state, **L3**·Pd(Tol)Cl forms a dimer (Figure 4) with a planar $(Pd–Cl)_2$ four membered ring as was observed for other phosphine and carbene ligands.[23] Attempts to obtain any information about the transmetallation process revealed to be impossible at room temperature. Addition of *n*-butyllithium to $[\mathbf{L3}\cdot Pd(Tol)Cl]_2$ immediately resulted in the final coupling product. This was also the case when using methyllithium, even though the methyl palladium complex should be less prone to reductive elimination due to the decreased steric bulk. No intermediate compounds could be observed by NMR studies even at low temperature, thus confirming the fast reaction process. It is also important to note that, isolated $[\mathbf{L3}\cdot Pd(Tol)Cl]_2$ can be used as a potent precatalysts. In the coupling of *sec*-butyllithium with 4-chloroanisole under the optimized reaction conditions as discussed above, 87 % conversion with slightly lower selectivities than those found with **L3**-$Pd_2(dba)_3$·dba or precatalyst **L3–P3** were observed.

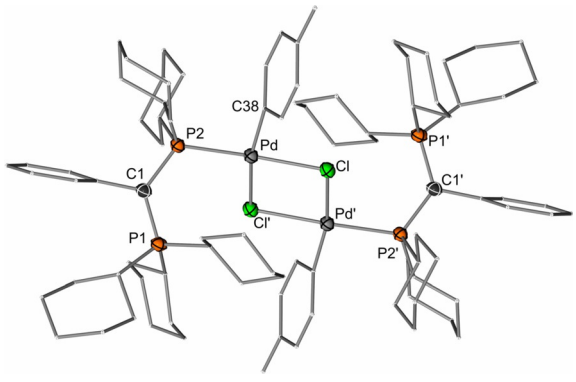


Figure 4. Molecular structure of **L3**·Pd(Tol)Cl.

Since experimental studies could not provide any further information about the mechanism, DFT calculations (PW6B95D3/def2TZVP) were performed to understand the observed selectivities. To this end, we examined the possible reaction steps after transmetallation (Figure 5). From here onwards, complex **I** can either undergo reductive elimination (RE) to the desired product **Pro** or reversible BHE to form the isomerized products **IsoPro**. These reactions steps were calculated with keYPhos (**L1**) and joYPhos (**L3**) with *tert*-butyl (**a**), *sec*-butyl (**b**), *iso*-propyl (**c**) and ethyl (**d**) as alkyl groups. Figure 5 depicts the potential energy surface for the energetically most favored pathways for alkyl complexes **Ia-d** with **L3** (see SI for more details, for example, energies related to rotamers and isomers as well as all results with **L1**). The calculations show that there are three distinct scenarios characterized by the energy differences between the transition states of the two reductive elimination processes ($\mathbf{TS_{RE}}$ and $\mathbf{TS_{Iso\text{-}RE}}$) and the isomerization (olefin rotation $\mathbf{TS_{III\text{-}IV}}$) 1). For the *tert*-butyl palladium complex **Ia** (red line) the BHE and isomerization process is the kinetically most favored pathway, showing a considerably lower activation barrier (22.8 kJ mol^{-1} for $\mathbf{TS_{Iso\text{-}RE}}$) than the RE to the non-isomerized product $\mathbf{TS_{RE}}$ (33.9 kJ mol^{-1}). This energetic difference is in line with the complete isomerization observed in experiment. In contrast, for the ethyl complex **Id**, BHE to the hydrido palladium complex **III** is energetically uphill and rotation of the olefin more energy-consuming than $\mathbf{TS_{RE}}$ ($\Delta\Delta G^{\ddagger} =$ 19 kJ mol^{-1}), resulting in the selective RE without isomerization as observed in experiment for *n*-BuLi.

An intermediate situation to both extremes is found for the *i*Pr and *s*Bu complexes **Ic** and **Ib** (green and purple line, only most favored conformers shown). Here, the barrier for the rotation of the olefin is energetically similar to the RE. Thus, all three transition states determine the product formation. No classical Curtin–Hammett conditions are reached. The activation barriers $\mathbf{TS_{RE}}$, $\mathbf{TS_{III\text{-}IV}}$ and $\mathbf{TS_{Iso\text{-}RE}}$ lie within only 1–5 kJ mol^{-1}, being in line with the observed formation of product mixtures. Although the calculations reflect the trends observed in experiment, the observed selectivities for the secondary alkyl groups should be lower. The reason for this discrepancy is not yet clear. Although inaccuracies of the DFT calculations cannot be ruled out, it might also be possible, that due to the high speed of the reaction (note that all activation barriers are very low) the equilibrium state is not always reached. Therefore, the reaction may simply continue from complex **I** to product **Pro** before equilibrating to the other agostic intermediate **V**.

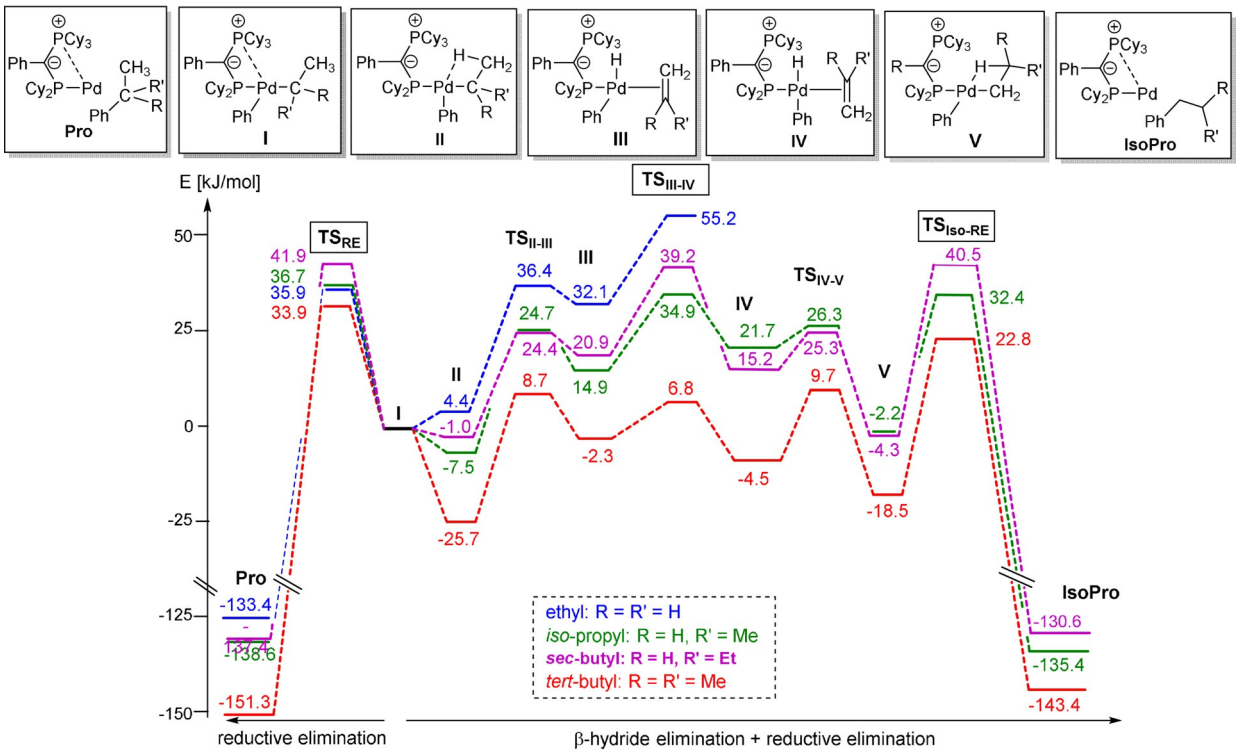


Figure 5. Reaction profile of the reductive elimination and β-hydride elimination from the alkyl Pd complexes **I** with **L3**. Energies (PW6B95D3/def2TZVP) are given relative to the respective alkyl complex **Ia**–**Id**.

Overall, steric effects seem to be the main reason for the observed selectivities since the least sterically demanding alkyl groups provide the highest selectivities for the desired product. However, also the difference in the strengths of the agostic interactions between the Pd center and the PCy_3 moiety of the ligand (complex **I**) and the alkyl group (complex **II**) seem to play a crucial role in this context. The more stable the agostic interaction to the phosphonium group, the less favored the interaction with the alkyl substituent and hence BHE. Since the agostic interaction to the *tert*-butyl group is clearly favored (by 25.7 kJ mol^{-1}), the *tert*-butyl group selectively undergoes isomerization to form **IsoPro**. For the complexes with the primary and secondary alkyl groups, the alkyl palladium species **I** is either more stable or only slightly disfavored over intermediate **II**, suggesting that the agostic interactions by the ligand and the alkyl groups are equally strong. Here, the different activation barriers are decisive. The whole reaction profile with the YPhos ligands contrasts the behavior of NHC-based catalysts, where only the barriers of the reductive elimination and BHE were found to be decisive for the final isomer ratio.[24]

To test the broadness of the reaction protocol, we next addressed a detailed study of the substrate scope (Figure 6). To this end, either a combination of **L3** and $Pd_2(dba)_3$·dba (method **A**) or precatalyst [**L3**-Pd(indenyl)Cl] (**L3**–**P3**) (method **B**) was used. It is important to note that this does not represent an optimization of the reaction conditions. Rather one of the two systems was randomly chosen before the reaction, since both seem to be equally active. Fortunately, a wide variety of aryl chlorides could be coupled via the optimized reaction protocol and the products isolated in moderate to excellent yields. Electron-rich and electron-poor aryl chlorides as well as heteroaryl halides could be alkylated. Likewise, dialkylations such as to **2k** are possible. Most remarkably, also 2-chlorofluorobenzene was coupled in high isolated yields with *n*-hexyllithium (**2m**) and *iso*- and cyclopropyllithium (**2h** and **2i**), respectively, showing no indication of Li/Cl exchange and competing aryne formation. The magnesium compounds also allowed for a surprising group tolerance. Nitriles and esters could be coupled (**2y**, **2z**). For the secondary alkyl reagents, the br:ln ratios were generally good. In general, more electron poor aryl chlorides with substituents in *meta*- and *ortho*-position formed larger amounts of the linear product (**2d**, **2h**), as was previously observed by Organ and co-workers in Negishi coupling reactions.[24a] Most importantly, sp^2-sp^2-bond formations are in general easily achieved using the corresponding aryllithium and magnesium compounds (**2r**–**2u**). Here, isolated yields greater than 80% are obtained also with aryllithium reagent which were produced by direct lithiation, thus allowing the synthesis of more complex biaryls from simple precursors (**2t**, **2u**). Furthermore, aryl bromides were also successfully coupled (**2q**, **2w**), showing that the protocol is not limited to the chlorides.

After having established the successful catalysis protocol, we turned our attention towards the synthesis of substrates useful for the formation of compounds in materials science and pharmaceuticals (Figure 7). The synthesis of these compounds has been described by other routes, sometimes in multiple step procedures. We were pleased to see that for

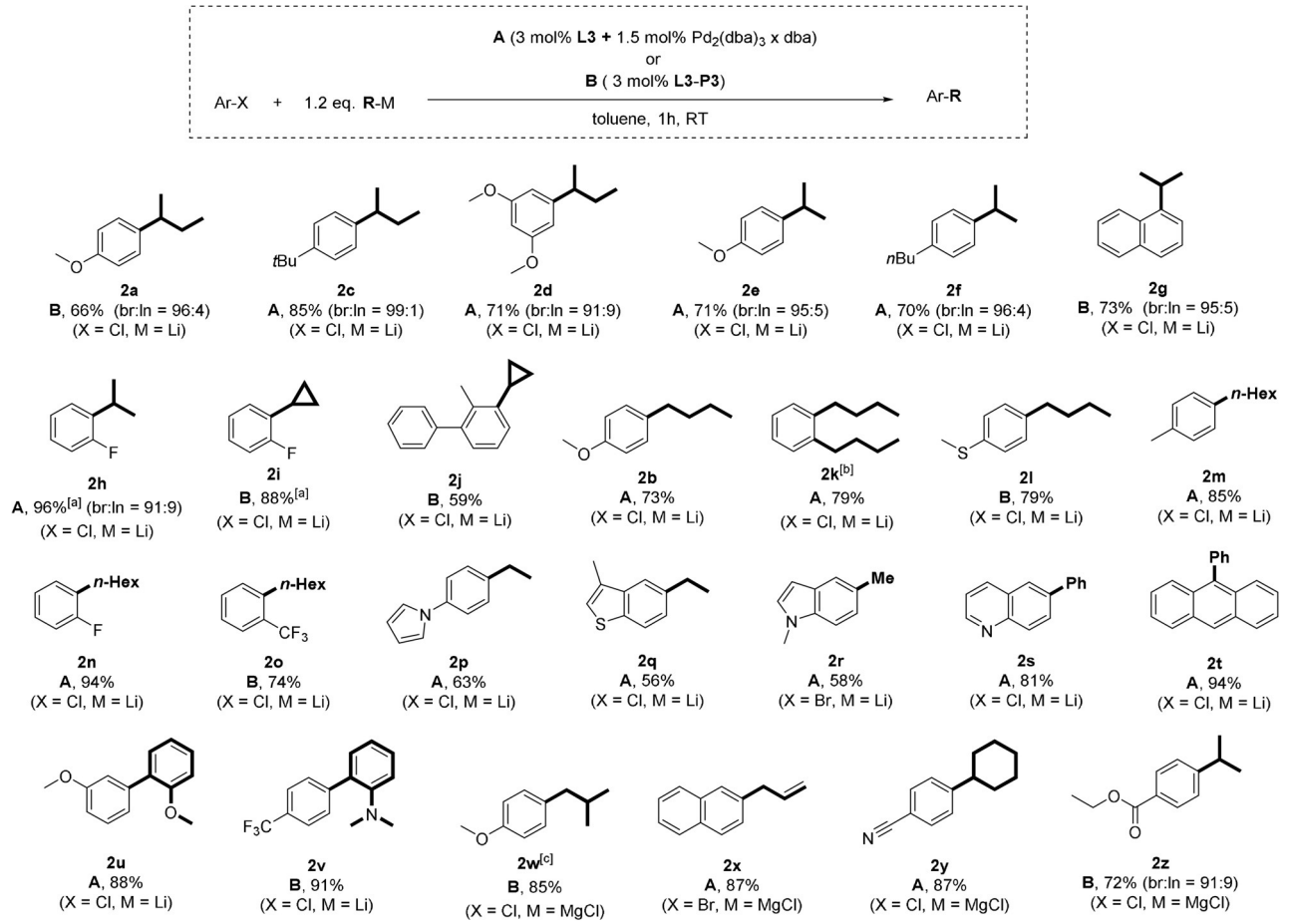


Figure 6. Substrate scope. Reaction conditions: aryl halide (3 mmol), [Pd] (0.09 mmol), nucleophile (3.6 mmol), 1 h, RT. See SI for details. Yields are of the isolated mixture of branched and linear products, if applicable. The br:ln ratios were determined using ^{1}H-NMR-Spectroscopy and GC analysis. [a] GC yield. [b] 7.2 mmol of nucleophile, 2 h addition time. [c] from *t*BuMgCl.

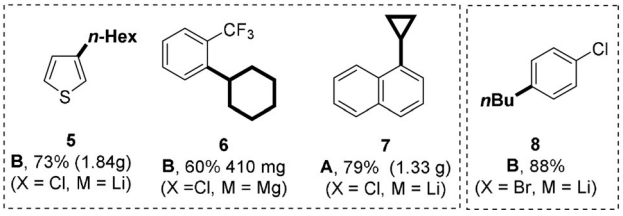


Figure 7. (left) Synthesis of alkylated aromatics which are important building blocks in material science and pharmaceutical industry, yields of isolated products, reaction conditions according to Figure 5. (right) Selective alkylation of 1-bromo-4-chlorobenzene with *n*-butyllithium, GC yield with *n*-tetradecane as internal standard.

example 3-chlorothiophene can be readily alkylated with hexyllithium also in gram-scale to compound **5**, which is a typical precursor for the synthesis of polythiophenes. Likewise, compound **6**, a building block for the synthesis of Siponimod (brand name *Mayzent*; a sphingosine 1-phosphate receptor modulator for treating multiple sclerosis) could be synthesized in one step from *ortho*-trifluoromethylchlorobenzene in 60 % isolated yield. This compound was first prepared via a three-step procedure from cyclohexanone including a Pd-catalyzed hydrogenation reaction[25] and a Negishi-type coupling of the aryl bromide at elevated temperatures with 5 mol % of Pd(P*t*Bu$_3$)$_2$.[26] Additionally, the introduction of the cyclopropyl group could be performed in gram-scale to yield compound **7** which is a building block in the synthesis of Lesinurad, a uric acid salt transport protein 1 (URAT1) inhibitor for the treatment of gout.[27] These examples demonstrate that the Pd-catalyzed alkylation of aryl chlorides with alkyllithium reagents could become a viable method for the synthesis of building blocks in chemical and pharmaceutical industries.

Due to the facile coupling of aryl chlorides at room temperature, we envisioned that the coupling of aryl bromides should readily proceed at low temperatures. This would provide the possibility of two subsequent, different C–C coupling reactions by temperature control. Such a methodology has recently been reported by Feringa and Organ.[12d] However, no dialkylation reactions were possible, due to the reasons highlighted in the introductory section. Fortunately, 1-bromo-4-chlorobenzene was found to be easily alkylated at the bromo position at −40 °C. Subsequent warming to room temperature gave compound **8** in high yields. This shows that the selectivity of the C–C coupling of bromo-substituted aryl chlorides can easily be controlled by temperature, thus allowing step-wise coupling reactions for example, different

C–C couplings[28] (such as to **2 f**) or C–C coupling followed by C–N coupling reactions, for which joYPhos (**L3**) and its palladium complexes also showed high activities.[19]

Conclusion

In conclusion, we reported on the first successful and broadly applicable protocol for the direct sp^2-sp^3 coupling of aryl chlorides with alkyllithium reagents. While all the previously reported catalysts for Murahashi couplings with aryllithium reagents failed in this transformation, catalysts based on ylide-substituted phosphines (YPhos) gave good to excellent yields with high selectivities. The reason for this superior performance is the ability of the catalyst to undergo the oxidative addition of the aryl chloride fast enough to prevent side reactions such as lithium halogen exchange, while also minimizing isomerization due to the ligand architecture. The breadth of application was shown by means of a variety of substrates including *ortho*-fluorinated arenes as well as heteroaromatics. The catalyst was also shown to be highly effective in Kumada couplings as well as in gram-scale isolations and the synthesis of building blocks in materials science and pharmaceutical industry. Overall, the described protocol offers the direct use of readily available aryl and alkyllithium reagents in coupling reactions without the need of a further transmetallation step and thus represents an easily applicable protocol, which reduces the production of additional salt wastes by sp^2-sp^3 couplings in a single reaction step.

Acknowledgements

This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (Starting Grant: YlideLigands 677749) and was supported by RESOLV, funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy—EXC-2033—Projektnummer 390677874. The authors thank UMICORE AG & Co. KG as well as Albemarle Germany GmbH for the donation of chemicals and UMICORE AG & Co. KG for additional financial support. Julian Löffler is acknowledged for his assistance in the synthesis work. Open access funding enabled and organized by Projekt DEAL.

Conflict of interest

The authors have filed patent WO2019030304 covering the YPhos ligands and precatalysts discussed, which is held by UMICORE AG & Co. KG and products will be made commercially available from.

Keywords: catalysis · cross-coupling reactions · organolithium · phosphine ligands · ylides

[1] For reviews, see: a) P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev.* **2016**, *116*, 12564–12649; b) "Palladium-Catalyzed Coupling Reactions": J. G. de Vries in *Organometallics as Catalysts in the Fine Chemical Industry. Topics in Organometallic Chemistry* (Eds.: M. Beller, H. U. Blaser), Springer, Berlin, **2012**; c) J. Magano, J. R. Dunetz, *Chem. Rev.* **2011**, *111*, 2177–2250; d) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489; *Angew. Chem.* **2005**, *117*, 4516–4563; e) J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651–2710.

[2] a) R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461–1473; b) N. Marion, S. P. Nolan, *Acc. Chem. Res.* **2008**, *41*, 1440–1449; c) S. Würtz, F. Glorius, *Acc. Chem. Res.* **2008**, *41*, 1523–1533; d) R. J. Lundgren, K. D. Hesp, M. Stradiotto, *Synlett* **2011**, 2443–2458; e) R. J. Lundgren, M. Stradiotto, *Chem. Eur. J.* **2012**, *18*, 9758–9769; f) L. Chen, P. Ren, B. P. Carrow, *J. Am. Chem. Soc.* **2016**, *138*, 6392–6395; g) L. Ackermann, *Synthesis* **2006**, 1557–1571.

[3] L.-C. Campeau, N. Hazari, *Organometallics* **2019**, *38*, 3–35.

[4] For recent reviewes, see: a) M. M. Heravi, V. Zadsirjan, P. Hajiabbasi, H. Habidi, *Chemical Monthly* **2019**, *150*, 535–591; b) Z. Qureshi, C. Toker, M. Lautens, *Synthesis* **2017**, *49*, 1–16; c) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417–1492.

[5] a) K. Tamao, K. Sumitani, M. Kumada, *J. Am. Chem. Soc.* **1972**, *94*, 4374–4376; b) R. P. J. Corriu, J. P. Masse, *Chem. Commun.* **1972**, 144.

[6] M. E. Limmert, A. H. Roy, J. F. Hartwig, *J. Org. Chem.* **2005**, *70*, 9364–9370.

[7] a) C. Valente, S. Calimsiz, K. H. Hoi, D. Mallik, M. Sayah, M. G. Organ, *Angew. Chem. Int. Ed.* **2012**, *51*, 3314–3332; *Angew. Chem.* **2012**, *124*, 3370–3388; b) G. C. Fortman, S. P. Nolan, *Chem. Soc. Rev.* **2011**, *40*, 5151–5169.

[8] For examples: a) J. Nasielski, N. Hadei, G. Achonduh, E. A. B. Kantchev, C. J. O'Brien, A. Lough, M. G. Organ, *Chem. Eur. J.* **2010**, *16*, 10844–10853; b) J. Huang, S. P. Nolan, *J. Am. Chem. Soc.* **1999**, *121*, 9889–9890; c) C. E. Hartmann, S. P. Nolan, C. S. J. Cazin, *Organometallics* **2009**, *28*, 2915–2919.

[9] a) I. P. Beletskaya, A. V. Cheprakov, *Organometallics* **2012**, *31*, 7753–7808; b) R. B. Bedford, *Acc. Chem. Res.* **2015**, *48*, 1485–1493; c) C. Cassani, G. Bergonzini, C.-J. Wallentin, *ACS Catal.* **2016**, *6*, 1640–1648; d) A. Fürstner, *ACS Cent. Sci.* **2016**, *2*, 778–789; e) J. M. Neely, M. J. Bezdek, P. J. Chirik, *ACS Cent. Sci.* **2016**, *2*, 935–942; f) S. Bhunia, G. G. Pawar, S. V. Kumar, Y. Jiang, D. Ma, *Angew. Chem. Int. Ed.* **2017**, *56*, 16136–16179; *Angew. Chem.* **2017**, *129*, 16352–16397.

[10] For examples: a) A. Piontek, W. Ochędzan-Siodłak, E. Bisz, M. Szostak, *Adv. Synth. Catal.* **2019**, *361*, 2329–2336; b) A. Joshi-Pangu, C.-Y. Wang, M. R. Biscoe, *J. Am. Chem. Soc.* **2011**, *133*, 8478–8481.

[11] S. Murahashi, M. Yamamura, K. Yanagisawa, N. Mita, K. Kondo, *J. Org. Chem.* **1979**, *44*, 2408–2417.

[12] a) M. Giannerini, M. Fañanás-Mastral, B. L. Feringa, *Nat. Chem.* **2013**, *5*, 667–672; b) C. Vila, M. Giannerini, V. Hornillos, M. Fañanás-Mastral, B. L. Feringa, *Chem. Sci.* **2014**, *5*, 1361–1367; c) E. Pinxterhuis, M. Giannerini, V. Hornillos, *Nat. Commun.* **2016**, *7*, 11698; d) N. Sinha, D. Heijnen, B. L. Feringa, M. G. Organ, *Chem. Eur. J.* **2019**, *25*, 9180–9184.

[13] a) V. Hornillos, M. Giannerini, C. Vila, M. Fañanás-Mastral, B. L. Feringa, *Org. Lett.* **2013**, *15*, 5114–5511; b) V. Hornillos, M. Giannerini, C. Vila, M. Fañanás-Mastral, B. L. Feringa, *Chem. Sci.* **2015**, *6*, 1394–1398; c) L. M. Castelló, V. Hornillos, C. Vila, M. Giannerini, M. Fañanás-Mastral, B. L. Feringa, *Org. Lett.* **2015**, *17*, 62–65; d) D. Heijnen, V. Hornillos, B. P. Corbet, M. Giannerini, B. L. Feringa, *Org. Lett.* **2015**, *17*, 2262–2265.

[14] D. Heijnen, J.-B. Gualtierotti, V. Hornillos, B. L. Feringa, *Chem. Eur. J.* **2016**, *22*, 3991–3996.

[15] Y. Yamazaki, N. Arima, T. Iwai, M. Sawamura, *Adv. Synth. Catal.* **2019**, *361*, 2250.
[16] J. Buter, D. Heijnen, C. Vila, V. Hornillos, E. Otten, M. Giannerini, A. J. Minnaard, B. L. Feringa, *Angew. Chem. Int. Ed.* **2016**, *55*, 3620 – 3624; *Angew. Chem.* **2016**, *128*, 3684 – 3688.
[17] For examples, see: a) C. Han, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 7532 – 7533; b) Y. Yang, K. Diedermann, C. Han, S. L. Buchwald, *Org. Lett.* **2014**, *16*, 4638 – 4641; c) S. Çalimsiz, M. Organ, *Chem. Commun.* **2011**, *47*, 5181 – 5183; d) I. Kalvet, T. Sperger, T. Scattolin, G. Magnin, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2017**, *56*, 7078 – 7082; *Angew. Chem.* **2017**, *129*, 7184 – 7188; e) K.-F. Zhang, F. Christoffel, O. Baudoin, *Angew. Chem. Int. Ed.* **2018**, *57*, 1982 – 1986; *Angew. Chem.* **2018**, *130*, 2000 – 2004.
[18] T. Scherpf, C. Schwarz, L. T. Scharf, J.-A. Zur, A. Helbig, V. H. Gessner, *Angew. Chem. Int. Ed.* **2018**, *57*, 12859 – 12864; *Angew. Chem.* **2018**, *130*, 13041 – 13046.
[19] P. Weber, T. Scherpf, I. Rodstein, D. Lichte, L. T. Scharf, L. J. Gooßen, V. H. Gessner, *Angew. Chem. Int. Ed.* **2019**, *58*, 3203 – 3207; *Angew. Chem.* **2019**, *131*, 3235 – 3239.
[20] X.-Q. Hu, D. Lichte, I. Rodstein, P. Weber, A.-K. Seitz, T. Scherpf, L. J. Gooßen, V. H. Gessner, *Org. Lett.* **2019**, *21*, 7558 – 7562.
[21] I. Rodstein, J. Tappen, K. McGuire, A. Großjohann, J. Löffler, T. Scherpf, V. H. Gessner, *Chem. Eur. J.* **2020**, *26*, 4281 – 4288.
[22] a) X. Luo, H. Zhang, H. Duan, Q. Liu, L. Zhu, T. Zhang, A. Lei, *Org. Lett.* **2007**, *9*, 4571 – 4574; b) J. Breitenfeld, O. Vechorkin, C. Corminboeuf, R. Scopelliti, X. Hu, *Organometallics* **2010**, *29*, 3686 – 3689.
[23] a) K. R. Chaudhari, A. P. Wadawale, V. K. Jain, *J. Organomet. Chem.* **2012**, *698*, 15 – 21; b) K. R. Chaudhari, A. P. Wadawale, M. Kumar, V. K. Jain, *J. Organomet. Chem.* **2014**, *760*, 55 – 59; c) L. T. Scharf, I. Rodstein, M. Schmidt, T. Scherpf, V. H. Gessner, *ACS Catal.* **2020**, *10*, 999 – 1009.
[24] a) M. Pompeo, N. Hadei, R. D. J. Froese, M. G. Organ, *Angew. Chem. Int. Ed.* **2012**, *51*, 11354 – 11357; *Angew. Chem.* **2012**, *124*, 11516 – 11519; b) B. Atwater, N. Chandrasoma, D. J. Mitchell, M. Rodriguez, M. Pompeo, R. D. J. Froese, M. G. Organ, *Angew. Chem. Int. Ed.* **2015**, *54*, 9502 – 9506; *Angew. Chem.* **2015**, *127*, 9638 – 9642.
[25] "Process for Preparing N-(4-Cyclohexyl-3-trifluoromethyl-benzyloxy)-acetimidic acid ethyl ester": WO2013113915 A1.
[26] S. Pan, N. S. Gray, W. Gao, Y. Fan, X. Wang, T. Tuntland, J. Che, S. Lefebvre, Y. Chen, A. Chu, K. Hinterding, A. Gardin, P. End, P. Heining, C. Bruns, N. G. Cooke, B. Nuesslein-Hildesheim, *ACS Med. Chem. Lett.* **2013**, *4*, 333 – 337.
[27] Q. Meng, T. Zhao, D. Kang, B. Huang, P. Zhan, X. Liu, *Chem. Cent. J.* **2017**, *11*, 86.
[28] The dialkylation in a one-pot reaction via sequential addition of organolithium reagents only gave poor to moderate yields (4% for 1. *n*BuLi + 2. *s*BuLi; 62% for 1. *n*BuLi + 2. *i*PrLi).

Manuscript received: June 25, 2020
Accepted manuscript online: July 29, 2020
Version of record online: September 3, 2020

