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Synthesis of Substituted Benzaldehydes via a Two-Step, One-Pot Reduction/Cross-Coupling Procedure

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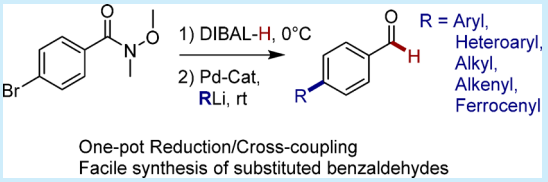
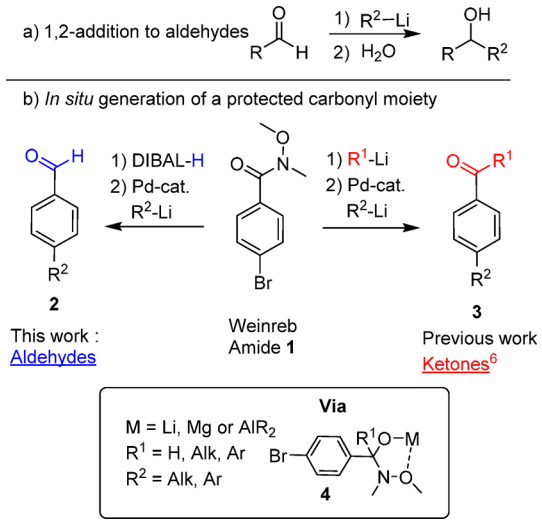
Supporting Information

ABSTRACT: The synthesis of functionalized (benz)aldehydes, via a two-step, one-pot procedure, is presented. The method employs a stable aluminum hemiaminal as a tetrahedral intermediate, protecting a latent aldehyde, making it suitable for subsequent cross-coupling with (strong nucleophilic) organometallic reagents, leading to a variety of alkyl and aryl substituted benzaldehydes. This very fast methodology also facilitates the effective synthesis of a ^{11}C radiolabeled aldehyde. Aluminum−ate complexes enable transmetalation of alkyl fragments onto palladium and subsequent cross-coupling.



The synthesis of small, highly functionalized molecules lies at the basis of many areas of chemistry, ranging from drug design to (hetero)cyclic materials for photovoltaics and ligands for catalytic applications.[1] Transition metal catalyzed cross-coupling methods for derivatization of these compounds, despite their great versatility, frequently rely on rather expensive coupling partners with reduced reactivity requiring higher temperatures and long reaction times. When using highly reactive reagents, traditional protecting group strategies are generally applied.[2] Facing environmental awareness, catalytic methods with lighter reagents that produce less waste and of lower toxicity should be favored according to the principles of green chemistry.[3] The application of cheaper and more reactive organometallic reagents as coupling partners in combination with carbonyl functional groups has some precedence, but still remains a major synthetic challenge.[4] The reactive aldehyde functionality in particular is prone to side reactions with organometallic reagents. On the other hand it is this high reactivity with a range of reagents that make aldehydes such privileged building blocks in organic synthesis, and therefore alternative methodology allowing general and facile synthesis of substituted (benz)aldehydes remains a highly desirable goal. In order to prevent the fast 1,2-addition of an organometallic nucleophile to the aldehyde (Scheme 1a), or over-addition to a synthetic precursor, Weinreb amides **1** have proven themselves to be valuable precursors to aldehydes **2**. By addition of an organometallic compound to **1**, a stable tetrahedral intermediate **4** (Scheme 1b) is created *in situ*, which is not susceptible to further nucleophilic attack.[5] We discovered that these metal chelated intermediates, representing a protected/latent carbonyl functional group, are stable toward organolithium cross-coupling conditions. As a consequence, a method for the synthesis of cross-coupled ketones, with organolithium reagents and bromo-substituted Weinreb amides as the coupling partners via reaction intermediate **4**, was developed (Scheme 1b).[6]

Scheme 1. One-Pot Cross-Coupling Procedures with Weinreb Amides to Ketones[6] and Aldehydes



Adding to the well-known transformations of Weinreb amides, this method provides an easy approach to cross-coupled carbonyl compounds, and we envisioned that reduction with a (aluminum-) hydride source would yield a hemiaminal with similar stability, facilitating a procedure for the cross-coupling of masked aldehydes. Various Weinreb amides are easily prepared on a multigram scale from cheap, commercially available benzoic acids, providing a viable

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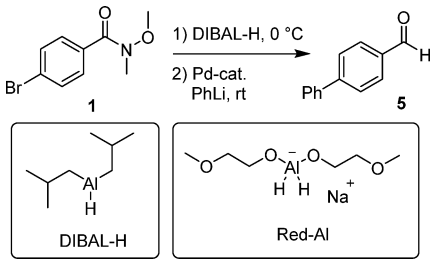
synthetic pathway for the synthesis of aldehyde building blocks.

As the reductant of the Weinreb amide, diisobutylaluminum hydride (DIBAL-H), was chosen, initial screening with Pd-complexes based on carbene and phosphine ligands showed the latter to be the more reactive and selective catalyst for the cross-coupling of aryl bromides with organolithium reagents. A significant acceleration of the reaction was observed upon preoxidation of the Pd-phosphine catalyst by means of molecular oxygen, while preserving excellent conversion and selectivity toward the desired aldehyde (Table 1). A similar

Table 1. Reaction Optimization[a]



entry	catalyst	"H"/solvent	yield[b]
1	$Pd(P^tBu_3)_2$	DIBAL-H (1 equiv)/toluene	85
2	$Pd(P^tBu_3)_2$	DIBAL-H (1 equiv)/toluene	87[c]
3	$Pd(P^tBu_3)_2$	DIBAL-H (1 equiv)/THF	40
4	Ox. $Pd(P^tBu_3)_2$	DIBAL-H (1 equiv)/toluene	92[c]
5	**Ox. $Pd(P^tBu_3)_2$**	**DIBAL-H (1 equiv)/toluene**	**90**[c,d]
6	Ox. $Pd(P^tBu_3)_2$	Red-Al (1 equiv)/toluene	30[e]

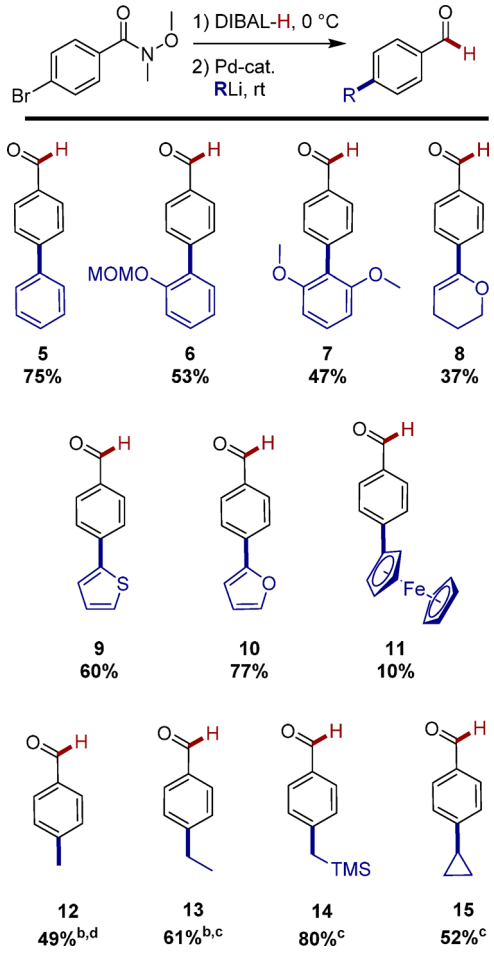
[a]Reaction conditions: Weinreb amide (0.3 mmol) in toluene (2 mL) at 0 °C, hydride source added dropwise over 5 min. Catalyst added as a 10 mg/mL solution. Phenyllithium added over 1 h by means of a syringe pump. Reaction was quenched with sat. aq NH_4Cl. [b]Yield determined by GC/MS analysis of the organic phase. [c]DIBAL-H added over 1 min. [d]The organolithium reagent was added over 5 min. [e]Sodium bis(2-methoxyethoxy)aluminum hydride.

effect was observed in our previous work and was attributed to the *in situ* formation of Pd nanoparticles as the active catalyst resulting in an increase in reactivity.[7] By switching the reductant to Red-Al, the conversion toward the aldehyde remained quantitative, but selectivity in the subsequent coupling reaction dropped due to competing dehalogenation of the aryl bromide. The lithium halogen exchange that leads to the formation of benzaldehyde is expected to be accelerated by the chelating effect of the ether moieties in the Red-Al.[8]

Having the optimal conditions for the reduction/aryl cross-coupling (fast 1 min DIBAL-H addition at 0 °C in toluene, and Ar–Li addition at rt, Table 1, entry 5) in hand, we employed various organolithium reagents (Scheme 2), including phenyllithium, as well as (functionalized) aryllithium reagents to provide **5**, **6**, and **7**, respectively. The coupling of a lithiated enol ether derivative and lithiated heterocycles that are commercially available, or easily prepared via direct deprotonation, led to products **8**, **9**, and **10**, respectively. The direct deprotonation and coupling of ferrocene yielded aldehyde **11**, providing an easy synthetic route toward functionalized ferrocenes, compared to current methods.[9]

Expanding the scope of the organolithium coupling partner to alkyl fragments, we were able to isolate the methyl, ethyl, and trimethylsilylmethylene substituted benzaldehydes **12**, **13**, and **14** with little to no alteration to the previously optimized

Scheme 2. Scope of the One-Pot Reduction/Cross-Coupling Strategy for Substituted Benzaldehydes[a]



[a]Reaction conditions: Weinreb amide (0.5 mmol) in toluene (2 mL) at 0 °C, DIBAL-H added dropwise over 5 min. Pre-oxidized catalyst (5 mol %) added as a 10 mg/mL solution. Organolithium reagent added over 10 min by means of a syringe pump. Reaction was quenched with sat. aq NH_4Cl. Yields refer to isolated yields after column chromatography. [b]Lower yield due to volatile product. [c]Yield corrected for minor isobutylbenzaldehyde impurities. [d]Performed on 1 mmol scale.

procedure. Interestingly the coupling of cyclopropyl lithium yielded benzaldehyde **15** providing a valuable method for the incorporation of this motif in medicinally relevant compounds.[10] Unfortunately, the relatively light and volatile aldehydes showed significant loss in yield upon purification (GC-MS conversion for those compounds are given in the Supporting Information). The Weinreb amide used in this transformation was also varied (Scheme 3), and the less volatile naphthyl-analogue **16** proved to be less prone to evaporation and was isolated in 63% yield. It was found that *meta*-bromo substituted Weinreb amides were also reactive under the standard reaction conditions and provided aldehydes **17** and **18** in good yield, the latter being obtained after a double cross-coupling reaction starting from the 3,5-dibromo-*N*-methoxy-*N*-methylbenzamide. Methoxy substituted aldehydes could also be synthesized illustrated by the preparation of compound **19**. 2,5-Dimethyl substituted Weinreb amide was also subjected to reduction followed by a cross-coupling reaction but afforded compound **20** in low yield. The decrease

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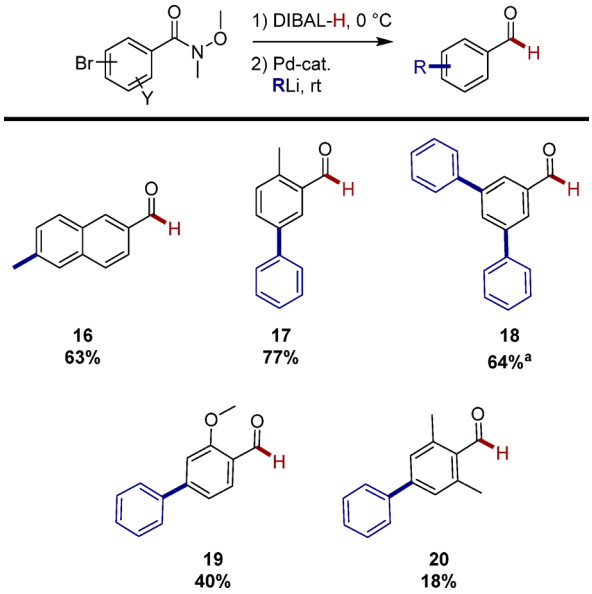
Scheme 3. Variation of the Weinreb Amide[a]



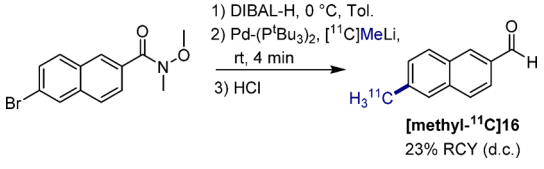
[a]Starting from the corresponding dibromo compounds. Cross-coupling step performed using 3 equiv of PhLi.

in yield was anticipated to be a consequence of the lower stability of the aluminum intermediate, induced by the additional steric bulk from the two *ortho*-methyl substituents.

We have previously successfully incorporated the short-lived ^{11}C isotope ($t_{1/2}$ = 20.3 min) for Positron Emission Tomography (PET) by means of a palladium catalyzed cross-coupling of methyl-lithium with aryl bromides. In expanding the scope of the organolithium cross-coupling, the rapid formation of radiolabeled aldehydes remains a synthetically challenging, but highly desirable, goal.[11] Due to the limited amount of methods available for the preparation or functionalization of radiolabeled aldehydes, we set out to design a method for the incorporation of ^{11}C in (substituted) benzaldehydes for future PET tracer development. By employing the above-described general reduction/cross-coupling strategy, we aimed to synthesize compound [**methyl-^{11}C**]**16** as a model substrate. With our previously described method for making [^{11}C]methyllithium from [^{11}C]methyl iodide by means of an *in situ* lithium halogen exchange with *n*-BuLi, the one-pot procedure described above yields the isolated target molecule [**methyl-^{11}C**]**16** in a 23% decay corrected yield with a radiochemical purity of >99% and a reaction time of only 4 min (Scheme 4).

To the best of our knowledge, this is one of the few examples of the formation of radiolabeled (substituted) benzaldehydes. Radiolabeled aldehydes used as such or followed by rapid transformation,[12] taking advantage of its high reactivity, could play an important role in the synthesis of new PET-tracers, vital for mapping of processes and biological targets in the human body.

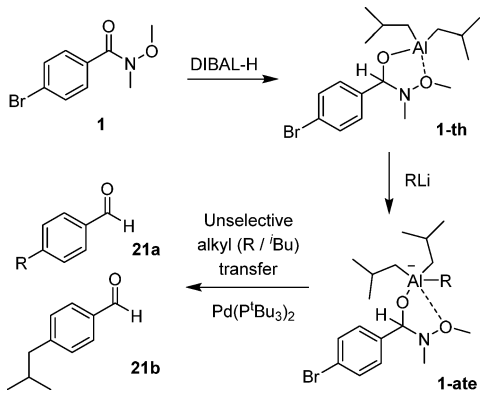
Scheme 4. Synthesis of Radiolabeled [^{11}C]6-Methyl-2-naphthaldehyde



Upon further expansion of the scope to other alkyllithium reagents, we observed the competing coupling of an isobutyl group, originating from the DIBAL-aminal intermediate. It is known that, for cross-coupling reactions, mixed aryl/alkyl aluminum species selectively transmetallate the sp^2 center, and only trialkyl-aluminum species transfer the sp^3 center.[13] We expected the isobutyl to derive from the aluminum−ate complex, which is formed after addition of the alkyllithium reagent.

Table 2 shows the selectivity toward cross-coupling of isobutyl versus that of the added alkyl fragment. Tetrahedral intermediate **1-th** is formed upon DIBAL-H addition and is the precursor to the anionic aluminum-ate complex **1-ate** upon alkyllithium addition. For both *n*-butyl- (entries 1−3) and isopropyl-lithium (entries 4 and 5), varying selectivity for the alkyl substituted benzaldehyde was found, regardless of addition speed or reaction temperature. We were unable to find reaction conditions that gave satisfactory selectivity toward the desired product. In order to force the selectivity toward isobutyl (originating from the DIBAL-H fragment) coupling, the reluctant coupling partner *t*-BuLi was added, which indeed showed full selectivity in the alkyl transfer toward the isobutyl coupled benzaldehyde **21b** (entries 6, 7). Similar to our previous findings on homocoupling reactions of aryl bromides, the lithium halogen exchange is a prominent reaction pathway, and thus a significant amount of 4,4′-bisbenzaldehyde was observed.

Table 2. Scrambling of Alkyl Fragments upon Alkyllithium Addition and Cross-Coupling



entry	R−Li	temp (°C)	selectivity[a] **21a**/**21b**
1	^{n}BuLi	23	95−60[b]/5−40
2	^{n}BuLi	0	65/35
3	^{n}BuLi	45	85/15
4	^{i}Pr−Li	23	68/32
5	^{i}Pr−Li	0	61/39
6	^{t}Bu−Li	23	<1/99[c,d]
7	^{t}Bu−Li	0	<1/99[c,d]

[a]As determined by GC/MS analysis. [b]Selectivity varied under identical reaction conditions. [c]Varying amounts of homocoupling (bis-benzaldehyde) were also observed. [d]Reversed selectivity: only the isobutyl coupled benzaldehyde observed.

In order to check for the formation of free isobutyllithium (displacement of the alkyl fragment by *n*-butyllithium), a range of starting materials and mixtures were subjected to ^{1}H NMR

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analysis (Figure 1). The CH_2 fragment of the isobutyl in DIBAL-H (spectrum 1) is clearly visible at 0.44 ppm and is

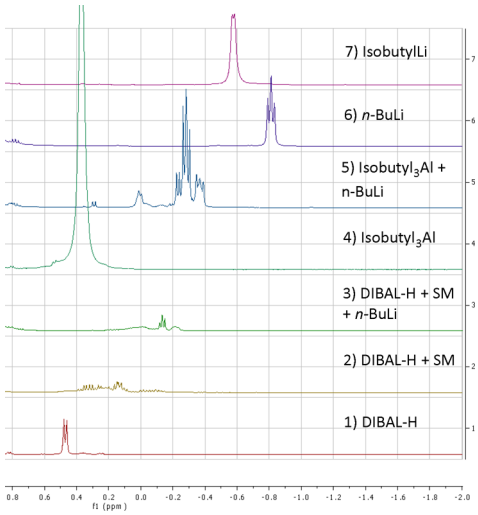


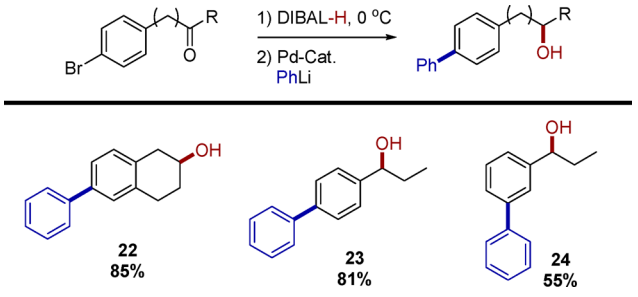
Figure 1. ^{1}H NMR studies of DIBAL-H reduction of Weinreb amides. Conditions: Concentration of all reagents: 0.1 mmol in 0.5 mL of Tol-d_8. Reduction and *n*-BuLi addition performed at 0 °C.

completely consumed upon addition to the Weinreb amide starting material (spectrum 2). The large variety of signals between 0 and 0.4 ppm can be explained by the generation of unequal alkyl fragments on the aluminum center, in combination with diastereotopic protons. Upon addition of *n*-butyllithium, the CH_2 fragment of the linear alkyl chains becomes apparent at −0.17 ppm (spectrum 3). A similar trend is visible when the trialkyl-aluminum complex (doublet at 0.38, spectrum 4) is mixed with *n*-butyllithium (spectrum 5) where an upfield shift is observed that leads to a signal at −0.32 ppm. When this mixture is added to a stirred solution of Pd-catalyst and 1-bromonaphthalene, a similar product distribution to that of Table 2, entry 2 between *n*- and isobutyl coupled naphthalene is observed. Finally, as a control, the pure sample of both *n*-butyllithium (spectrum 6) and isobutyllithium (spectrum 7) provided the reference for the hypothesis that no observable free alkyllithium is present in sample 3 and 5. This, together with literature precedence, supports the hypothesis of the unselective alkyl transmetalation from aluminum to palladium.[14]

The reduction/cross-coupling strategy could be further expanded from Weinreb amides to ketones. Ketones such as acetophenones are easily prepared via Friedel−Craft acetylation and make up an important class of chemical intermediates. In a two-step procedure, the acidic proton of the benzylic alcohol would consume a stoichiometric amount of organolithium reagent. It is therefore determined that this group is suitably protected as a metal alkoxide (for example an aluminum alkoxide), which is conveniently formed upon reduction of the carbonyl by means of DIBAL-H. The transfer of the hydride leads to an aluminum alkoxide, suitable for subsequent cross-coupling with an organolithium reagent. Secondary alcohols **22**, **23**, and **24** were obtained following this strategy, providing a viable route toward both cyclic and linear structures (Scheme 5).

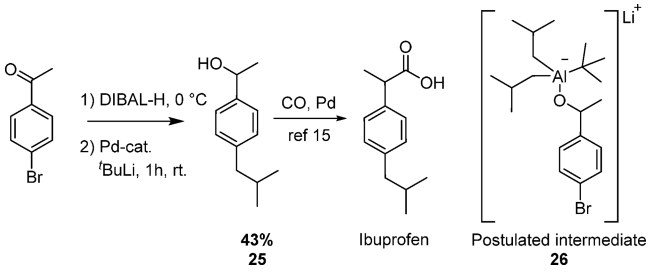
The isobutyl transfer observed in previous examples led us to attempt the twofold use of DIBAL-H in the reaction with 4-bromoacetophenone. Reduction of the acetophenone moiety

Scheme 5. One-Pot Preparation of Secondary Alcohols *via* DIBAL-H Reduction/Cross-Coupling Reaction



yields a substituted benzylic aluminum alkoxide that can be further functionalized. Addition of *tert*-butyllithium is hypothesized to generate **26**, a similar ate complex as shown in the previous section. Selective isobutyl transmetalation from aluminum to palladium and consecutive cross-coupling readily give access to industrially relevant alcohol **25**, a precursor to anti-inflammatory agent Ibuprofen, in 43% yield (Scheme 6).[15]

Scheme 6. Twofold Use of DIBAL-H in the Reduction and Cross-Coupling of 4-Bromoacetophenone



In conclusion, we have shown that the DIBAL-H reduction of Weinreb amides yields a masked aldehyde in the form of a stable aluminum aminal intermediate, providing a platform for subsequent functionalization with nucleophilic cross-coupling partners. The method not only provides an alternative route to aldehydes but also is applicable to ketones, yielding secondary alcohols, as showcased by the twofold use (reducing agent and alkyl transfer agent) of DIBAL-H in the synthesis of an Ibuprofen precursor. ^{1}H NMR studies show the formation of an aluminum−ate complex upon addition of primary and secondary alkyllithium reagents, which is hypothesized to transfer an alkyl fragment on to palladium, followed by cross-coupling. These aluminum aminal intermediates might provide attractive opportunities in other multistep one-pot procedures.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01274.

General, experimental procedures, and characterization of compounds (PDF)

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Notes

The authors declare no competing financial interest.

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