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Ultrafast reactivity and application in PET tracer synthesis

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DOI:
10.33612/diss.173876639

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Helbert, H. (2021). *Ultrafast reactivity and application in PET tracer synthesis*. University of Groningen. https://doi.org/10.33612/diss.173876639

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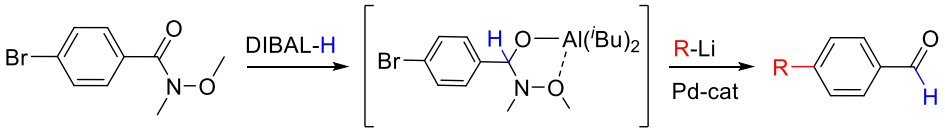
Chapter 4

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

The synthesis of functionalized (benz)aldehydes *via* a two-step, one-pot procedure, is presented. The method employs a stable aluminum hemiaminal as 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 transmetallation of alkyl fragments onto palladium and subsequent cross-coupling.



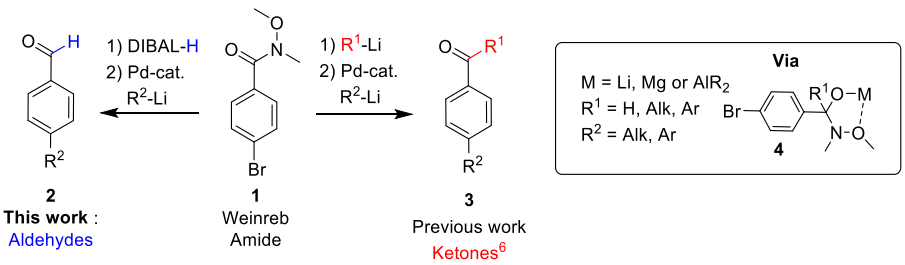
This chapter was published as:
D. Heijnen‡, H. Helbert‡, G. Luurtsema, P. H. Elsinga, B. L. Feringa, *Org. Lett.* **2019**, *21* (11), 4087-4091.

‡: *D. Heijnen and H. Helbert contributed equally to this work*

4.1 Introduction

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 catalysed 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 favoured 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 4.1), 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 4.1) 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 towards 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 4.1).[6]

Scheme 4.1 One pot cross-coupling procedures with Weinreb amides to ketones[6] and aldehydes.

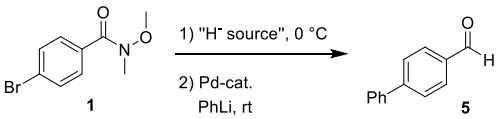


Adding to the well-known transformations of Weinreb amides, this method provides an easy approach to cross-coupled carbonyl compounds, and we envisioned that reduction with a (aluminum-) hydride source would yield a hemiaminal with similar stability, facilitating a procedure for the cross-coupling of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

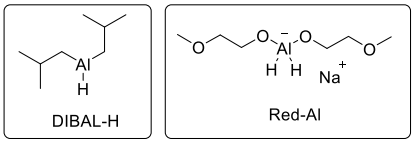
4.2 Optimization

As the reductant of the Weinreb amide, diisobutylaluminum hydride (DIBAL-H) was chosen, and 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 pre-oxidation of the Pd-phosphine catalyst by means of molecular oxygen, while preserving excellent conversion and selectivity towards the desired aldehyde (Table 4.1). A similar 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 towards 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]

Table 4.1 Reaction optimization



Entry	Catalyst	"H source" / solvent	Yield[a]
1	Pd(P^tBu_3)$_2$	DIBAL-H (1 eq.) / toluene	85
2	Pd(P^tBu_3)$_2$	DIBAL-H (1 eq.) / toluene	87[b]
3	Pd(P^tBu_3)$_2$	DIBAL-H (1 eq.) / THF	40
4	Ox. Pd(P^tBu_3)$_2$	DIBAL-H (1 eq.) / toluene	92[b]
5	Ox. Pd(P^tBu_3)$_2$	DIBAL-H (1 eq.) / toluene	90[b,c]
6	Ox. Pd(P^tBu_3)$_2$	Red-Al (1 eq.) / toluene	30[d]

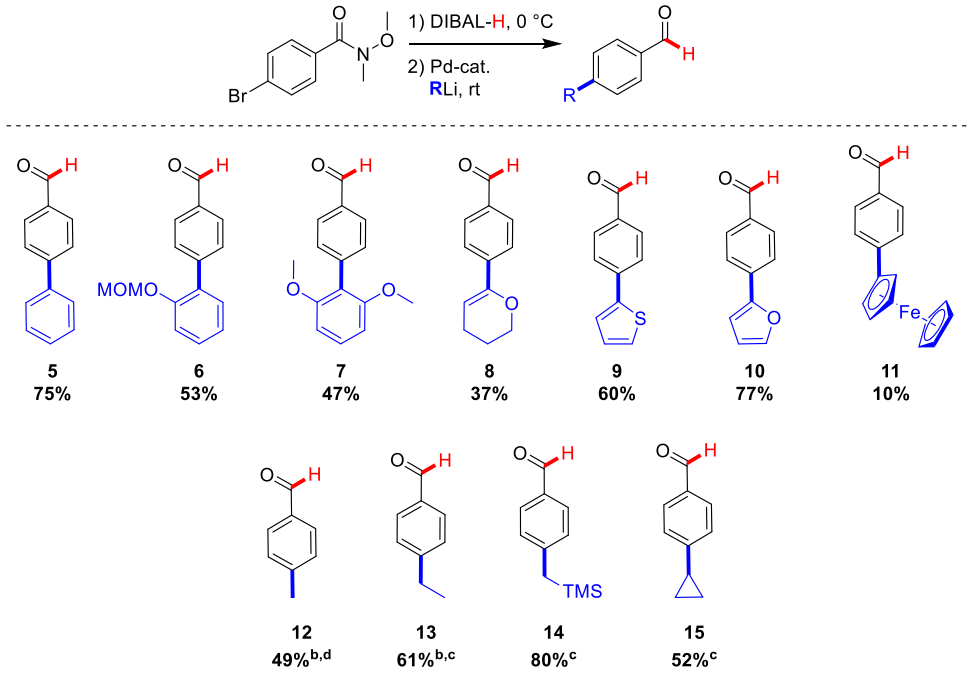


Reaction conditions: Weinreb amide (0.3 mmol) in toluene (2 mL) at 0 °C, hydride source added dropwise over 5 min. Catalyst added as a 10 mg/mL solution. Phenyllithium added over 1 h by means of a syringe pump. Reaction was quenched with sat. aq NH_4Cl. a) Yield determined by GC/MS analysis of the organic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

4.3 Scope of the reaction

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 4.1, entry 5) in hand, we employed various organolithium reagents (Scheme 4.2), including phenyllithium, as well as (functionalized) aryllithium reagents to provide **5**, **6** and **7**, respectively. The coupling of 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 towards functionalized ferrocenes, compared to current methods.[9]

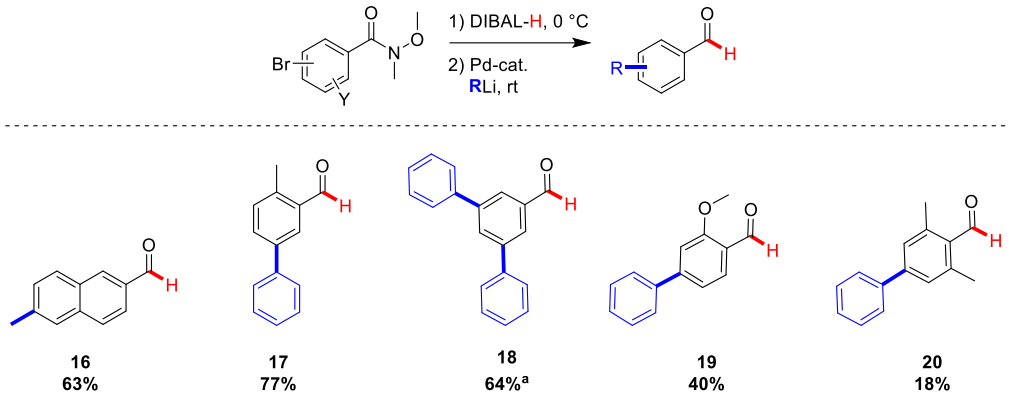
Scheme 4.2 Scope of the one pot reduction/cross-coupling strategy for substituted benzaldehydes.



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. a) Yields refer to isolated yields after column chromatography. b) Lower yield due to volatile product c) Yield corrected for minor *iso*-butylbenzaldehyde impurities. d) Performed on 1 mmol scale.

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 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. The Weinreb amide used in this transformation was also varied (Scheme 4.3) and the less volatile naphthyl-analogue **16** proved 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 cross-coupling reaction but afforded compound **20** in low yield. The decrease 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.

Scheme 4.3 Variation of the Weinreb amide

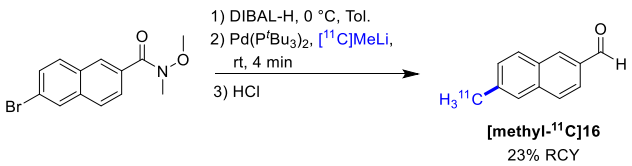


a) Starting from the corresponding dibromo compounds. Cross-coupling step performed using 3 eq. of PhLi.

4.4 Application in radiolabelling

We have previously successfully incorporated the short lived ^{11}C isotope ($t_{½}$ = 20.3 min) for Positron Emission Tomography (PET) by means of a palladium catalysed cross-coupling of methyl-lithium with aryl bromides. Expanding the scope of the organolithium cross-coupling, the rapid formation of radiolabelled aldehydes remains a synthetically challenging, but highly desirable, goal.[11] Due to the limited amount of methods available for the preparation or functionalization of radiolabelled aldehydes, we set out to design a method for the ^{11}C incorporation in (substituted) benzaldehydes for future PET tracer development. 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]methyliodide 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 4.4).

Scheme 4.4 Synthesis of radiolabelled [^{11}C]6-methyl-2-naphthaldehyde

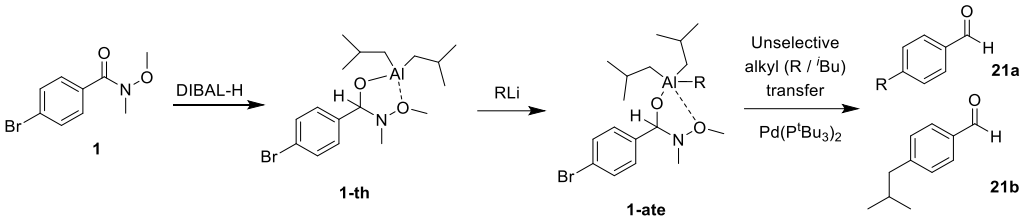


To the best of our knowledge, this is one of the few examples of the formation of radiolabelled (substituted) benzaldehydes. Radiolabelled aldehydes used as such or followed by rapid transformation[12], taking advantage of its high reactivity, could play an important role in the synthesis of new PET-tracers,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

4.5 Investigation on the selectivity of alkyl transfer

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 4.2 Scrambling of alkyl fragments upon alkyllithium addition and cross-coupling.

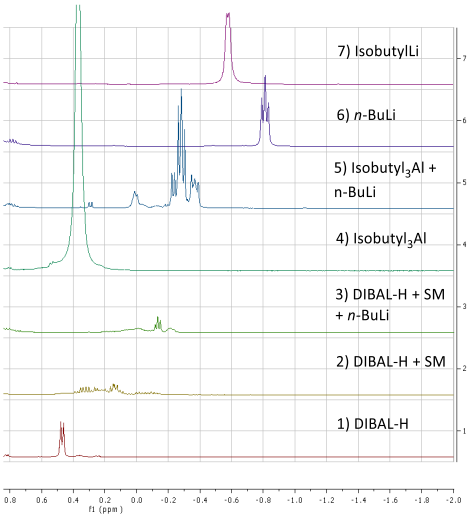


Entry	R-Li	Temp (°C)	Selectivity[a] 21a/21b
1	^{n}BuLi	23	95-60[b]/5-40
2	^{n}BuLi	0	65/35
3	^{n}BuLi	45	85/15
4	^{i}Pr-Li	23	68/32
5	^{i}Pr-Li	0	61/39
6	^{t}Bu-Li	23	<1/99[c,d]
7	^{t}Bu-Li	0	<1/99[c,d]

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.

Table 4.2 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- (entry 1-3), and isopropyl- lithium (entry 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 towards the desired product. In order to force the selectivity towards 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 towards the isobutyl coupled benzaldehyde **21b** (entries 6, 7). Similar to our previous findings on homocoupling reactions of arylbromides the lithium halogen exchange is a prominent reaction pathway, and thus a significant amount of 4,4'-bisbenzaldehyde was observed.

Figure 4.1 ^{1}H-NMR studies of DIBAL-H reduction of Weinreb amides.



Conditions: Concentration of all reagents: 0.1 mmol in 0,5 ml Tol-*d8*, reduction and *n*-BuLi addition performed at 0 °C.

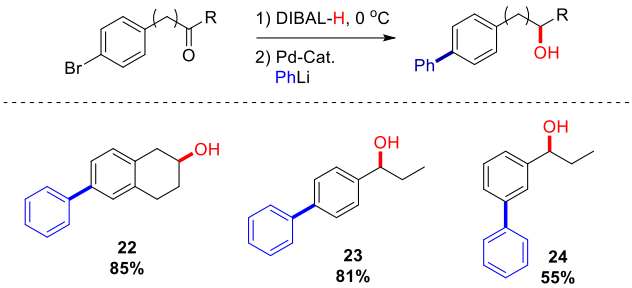
In order to check for the formation of free *iso*-butyllithium (displacement of the alkyl fragment by *n*-butyllithium), a range of starting materials and mixtures was subjected to ^{1}H-NMR analysis (Figure 4.1). The CH_2 fragment of the isobutyl in DIBAL-H (spectrum 1) is clearly visible at 0.44 ppm, and is 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 4.2, entry 2 between *n*- and *iso*- butyl coupled naphthalene is observed. Finally, as a control, the pure sample of both *n*-butyllithium (spectrum 6) and *iso*-butyllithium (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 transmetallation from aluminum to palladium.[14]

4.6 Preparation of secondary alcohols

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 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

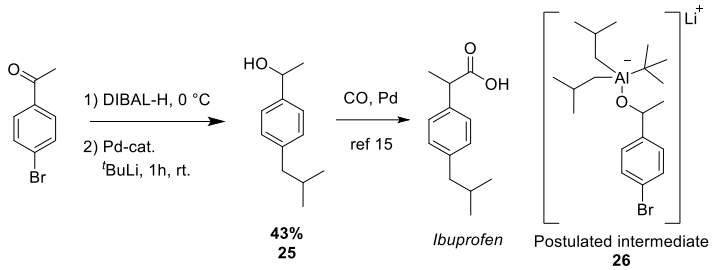
leads to an aluminum alkoxide, suitable for subsequent cross-coupling with an organolithium reagent. Secondary alcohols **22**, **23** and **24** were obtained following this strategy, providing a viable route towards both cyclic and linear structures (Scheme 4.5).

Scheme 4.5 One pot preparation of secondary alcohols *via* DIBAL-H reduction/cross-coupling reaction.



The isobutyl transfer observed in previous examples, led us to attempt the two fold use of DIBAL-H in the reaction with 4-bromoacetophenone. Reduction of the acetophenone moiety 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 transmetallation from aluminum to palladium and consecutive cross-coupling gives readily access to industrially relevant alcohol **25**, a precursor to anti-inflammatory agent Ibuprofen, in 43% yield (Scheme 4.6).[15]

Scheme 4.6 Two fold use of DIBAL-H in the reduction and cross-coupling of 4-bromoacetophenone



4.7 Conclusion

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 is also applicable to ketones, yielding secondary alcohols, as showcased by the two fold use (reducing agent and alkyl transfer agent) of DIBAL-H in the synthesis of an Ibuprofen precursor. ^{1}H-NMR studies show a formation of an aluminum ate complex upon addition of primary and secondary alkyllithium reagents, that 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.

4.8 Author contributions

D. Hejinen and H. Helbert contributed equally to this work. Both performing reaction optimization, substrate scope exploration and writing of the manuscript. D. Hejinen performed the NMR study of the reaction and H. Helbert performed the radiolabelling experiment with ^{11}C.

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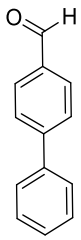
4.10 Experimental section

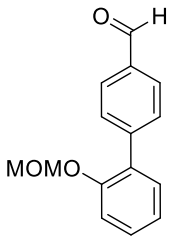
General procedure for the reduction and cross coupling of bromo-substituted Weinreb amides

In a dry Schlenk flask the corresponding Weinreb amide 1 (122 mg, 0.5 mmol) was dissolved in 2 mL of dry toluene, the mixture was cooled down to 0 °C and DIBAL-H 1M in hexanes (1.0 eq., 0.5 mL, 0.5 mmol) was added dropwise over 1 min. After the addition the reaction mixture was allowed to warm to room temperature, and a solution of pre-oxidized $Pd[P(^tBu)_3]_2$ (1.2 ml of 10 mg/ml, stirred vigorously under O_2 atmosphere for 1 h) was added. The corresponding organolithium reagent (1.5 eq., 0.75 mmol) was diluted with toluene to reach a final concentration of 0.45 M, and was added over 10 min by means of a syringe pump. After the addition of the organolithium reagent was completed, the reaction was quenched with 1 ml of 1 M aqueous HCl, and transferred to a separatory funnel. The organic layer was diluted with EtOAc, and washed 3 times with 1 M aqueous HCl. The organic layers were combined, dried with $MgSO_4$, and concentrated *in vacuo* to yield the crude product which was further purified by column chromatography (SiO_2) (pentane/EtOAc).



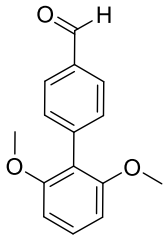
[1,1'-biphenyl]-4-carbaldehyde (5)

Synthesized according to the general procedure, using Weinreb amide **1** and phenyllithium. The product was obtained after column chromatography (SiO_2) using Pentane/EtOAc (0-5 %) The product was isolated as a white solid (68 mg, 75 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.96 (d, J = 8.2 Hz, 2H), 7.76 (d, J = 8.2 Hz, 2H), 7.64 (d, J = 7.2 Hz, 2H), 7.49 (t, J = 7.4 Hz, 2H), 7.43 (d, J = 7.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.02, 147.32, 139.85, 135.33, 130.39, 129.14, 128.60, 127.81, 127.49. The data is consistent with that of the commercially available product.



2'-(methoxymethoxy)-[1,1'-biphenyl]-4-carbaldehyde (6)

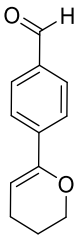
Synthesized according to the general procedure, using Weinreb amide 1 and 2-MOM-phenyllithium prepared *via* a literature procedure.[1] The product was obtained after column chromatography (SiO_2) using Pentane/EtOAc (0-5 %) (61 mg, 50 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.93 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.38 – 7.31 (m, 2H), 7.29 – 7.21 (m, 2H), 7.12 (td, *J* = 7.5, 1.2 Hz, 1H), 5.15 (s, 2H), 3.40 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.22, 154.33, 145.21, 135.03, 130.92, 130.34, 129.85, 129.58, 122.50, 115.71, 115.42, 95.15, 56.36. HRMS (ESI+): Calculated $[M+H]^+$: 243.1016; found: 243.1016. FT-IR: 2962, 2906, 2823, 2733, 1698 cm^{-1}



2',6'-dimethoxy-[1,1'-biphenyl]-4-carbaldehyde (7)

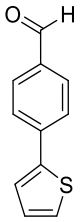
Synthesized according to the general procedure, using Weinreb amide 1 and 2,6-dimethoxy-phenyllithium prepared *via* a literature procedure.[1] The product was obtained after column chromatography (SiO_2) using Pentane/EtOAc (0-5 %) (57 mg, 47%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 7.92 (d, *J* = 8.1 Hz, 2H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.33 (t, *J* = 8.4 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 2H), 3.75 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.34, 157.55, 141.38, 134.91, 131.92, 129.70, 129.18, 118.27, 104.31, 56.00. HRMS (ESI+): Calculated $[M+H]^+$: 243.1016; found: 243.1017. FT-IR: 3011, 2936, 2837, 2744, 1694 cm^{-1}

[1] a) D. Heijnen, J. Gualtierotti, V. Hornillos, B. L. Feringa, *Chem. Eur. J.* **2016**, *22*, 3991-3995. b) V.Hornillos, M. Giannerini, C. Vila, M. Fañanás-Mastral, B. L. Feringa, *Chem. Sci.* **2015**, *6*, 1394-1398.



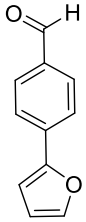
4-(3,4-dihydro-2H-pyran-6-yl)benzaldehyde (8)

Synthesized according to the general procedure, using Weinreb amide 1 and (3,4-dihydro-2H-pyran-6-yl)lithium prepared *via* a literature procedure.[1b] The product was obtained after column chromatography (SiO_2) using Pentane/EtOAc (0-5 %) (35 mg, 37%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.81 (d, *J* = 8.3 Hz, 2H), 7.69 (d, *J* = 8.3 Hz, 2H), 5.54 (t, *J* = 4.1 Hz, 1H), 4.19 (d, *J* = 4.9 Hz, 2H), 2.25 (q, *J* = 6.3 Hz, 2H), 1.92 (dt, *J* = 11.6, 6.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.96, 150.81, 142.00, 135.58, 129.78, 124.71, 100.97, 66.68, 22.30, 21.14. HRMS (ESI+): Calculated $[M+H]^+$: 189.0910; found: 189.0911. FT-IR : 2933, 2871, 1683 cm^{-1}



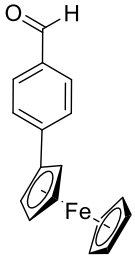
4-(thiophen-2-yl)benzaldehyde (9)

Synthesized according to the general procedure, using Weinreb amide 1 and 2-thienyllithium. The product was obtained after column chromatography (SiO_2) using Pentane/EtOAc (0-5 %) (56 mg, 60%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H), 7.89 (d, *J* = 8.3 Hz, 2H), 7.76 (d, *J* = 6.8 Hz, 2H), 7.46 (d, *J* = 3.5 Hz, 1H), 7.40 (d, *J* = 4.9 Hz, 1H), 7.13 (dd, *J* = 5.0, 3.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.55, 142.84, 140.20, 135.21, 130.58, 128.60, 127.04, 126.15, 125.16. The data are in accordance with literature.[2]



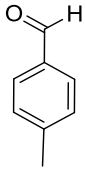
4-(furan-2-yl)benzaldehyde (10)

Synthesized according to the general procedure, using Weinreb amide 1 and 2-furyllithium prepared *via* a literature procedure.[1] The product was obtained after column chromatography (SiO_2) using Pentane/EtOAc (0-5 %) (66 mg, 77%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.88 (d, *J* = 8.3 Hz, 2H), 7.80 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 0.9 Hz, 1H), 6.83 (d, *J* = 3.4 Hz, 1H), 6.57 – 6.49 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.62, 152.72, 143.72, 136.19, 135.01, 130.43, 124.02, 112.34, 108.24. The data are in accordance with literature.[3]



4-(ferrocenyl)benzaldehyde (11)

Synthesized according to the general procedure, using Weinreb amide 1 and ferrocenyllithium prepared *via* a literature procedure. The product was obtained after column chromatography (SiO_2) using Pentane/EtOAc (0-5 %) (15 mg, 10%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.79 (d, *J* = 7.9 Hz, 2H), 7.59 (d, *J* = 7.9 Hz, 2H), 4.74 (s, 2H), 4.43 (s, 2H), 4.05 (s, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.82, 147.46, 134.14, 130.10, 126.25, 82.95, 70.31, 70.06, 67.21. HRMS (ESI+) : Calculated $[M+H]^+$: 291.0472; found: 291.0464. FT-IR: 3085, 2906, 2922, 2819, 2798, 2719, 1692 cm^{-1}.

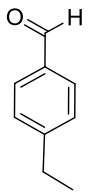


4-methylbenzaldehyde (12)

Synthesized according to the general procedure, using Weinreb amide 1 and methyllithium on a 1 mmol scale (GC-MS conversion: 95%). The product was obtained after column chromatography (SiO_2) using Pentane/EtOAc (0-5 %) (58 mg, 49%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.62, 148.18, 136.86, 132.49, 132.35, 24.53. The data is consistent with the commercially available product.

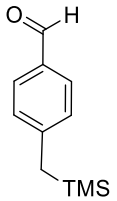
[2] M. Baghbanzadeh, C. Pilger, C. O. Kappe, *J. Org. Chem*. **2011**, *76*, 8138-8142

[3] N. A. Bumagin, I. S. Veselov, D. S. Belov, *Chem. Heterocycl. Compd.* **2014**, *50* (19), 24-31



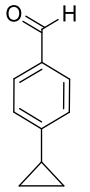
4-ethylbenzaldehyde (13)

Synthesized according to the general procedure, using Weinreb amide 1 and ethyllithium (GC-MS conversion : 87%). The product was obtained after column chromatography (SiO_2) using Pentane/EtOAc (0-5 %) (41 mg, 61%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 2.74 (q, *J* = 7.6 Hz, 2H), 1.27 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.66, 154.33, 137.06, 132.61, 131.18, 31.81, 17.78. The data is consistent with the commercially available product.



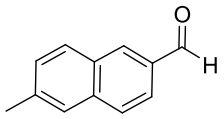
4-((trimethylsilyl)methyl)benzaldehyde (14)

Synthesized according to the general procedure, using Weinreb amide 1 and trimethylsilyl-methyllithium. The product was obtained after column chromatography (SiO_2) using Pentane/EtOAc (0-5 %) (56 mg, 58%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 2.21 (s, 2H), 0.01 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.50, 151.74, 135.63, 132.55, 131.06, 31.08. The data are in accordance with literature.[4]



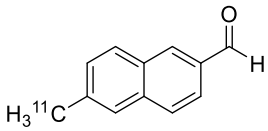
4-((trimethylsilyl)methyl)benzaldehyde (15)

Synthesized according to the general procedure, using Weinreb amide 1 and cyclopropyllithium, which was prepared *via* a literature procedure.[1] The product was obtained as a mixture with isobutyl-benzaldehyde after column chromatography (SiO_2) using Pentane/EtOAc (0-5 %) (52% via NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (s, 1H), 7.76 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 8.3 Hz, 2H), 2.01 – 1.92 (m, 1H), 1.14 – 1.06 (m, 2H), 0.85 – 0.78 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.45, 154.77, 136.75, 135.11, 133.63, 132.56, 128.55, 18.63, 13.32. HRMS (ESI+) : Calculated $[M+H]^+$: 147.08044, found : 147.04037. FT-IR : 3004, 2823, 1697 cm^{-1}



6-methyl-2-naphthaldehyde (16)

Synthesized according to the general procedure, using 6-bromo-N-methoxy-N-methyl-2-naphthamide (147 mg, 0.5 mmol) and methyllithium. The product was obtained after column chromatography (SiO_2) using Pentane/EtOAc (0-5 %) (54 mg, 63%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.13 (s, 1H), 8.30 (s, 1H), 7.91 (t, *J* = 7.9 Hz, 2H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.68 (s, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 2.56 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.88, 142.14, 139.40, 137.00, 136.14, 133.50, 132.01, 131.97, 131.04, 129.81, 125.58, 24.64. The data are in accordance with literature.[5]

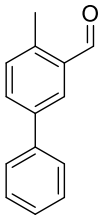


[^{11}C]6-(*methyl-11C*)-2-naphthaldehyde

To an oven dried, argon purged 4 mL vial containing 6-bromo-N-methoxy-N-methyl-2-naphthamide (58.8 mg, 0.2 mmol) in 0.5 mL of dry toluene was added dropwise at 0 °C a solution of DIBAL-H (0.2 mL, 0.2 mmol, 1M in cyclohexane) and stirred at the same temperature for 1h. The reaction mixture was allowed to warm up to room temperature and a solution of fully pre-oxidized $Pd(P^tBu_3)_2$ in toluene (0.5mL, 0.01 mmol) was added. In another oven dried, argon purged 4 mL vial containing a solution of *n*-BuLi (0.125 mL, 0.2 mmol, 1.6M in hexanes) in 0.87 mL of dry toluene was bubbled [^{11}C]MeI for 4 min. This solution was then taken up into a syringe and added at room temperature over 2 min. *via* syringe pump into the reaction mixture with catalyst. After additional 2 min. of stirring, the reaction was quenched by addition of 1 mL of a 1M aq. HCl solution. A sample was taken out from the organic phase and the solvent evaporated at 60 °C under argon flow. The residue was dissolved in 1 mL of eluent (MeCN/H_2O : 65/35 with 0.1% formic acid) and purified HPLC (column : Phenomenex Luna 5µ C18(2) 100Å 250x10mm ; eluent : MeCN/H_2O : 65/35 with 0.1% formic acid ; flow : 5 mL/min). The title product was collected (retention time : 7.5 ± 0.5 min) in 23 ± 4 % Radiochemical yield decay-corrected from [^{11}C]MeI (n= 3).

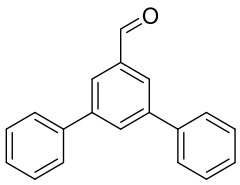
[4] A. Nagaki, Y. Tsuchihashi, S. Haraki, J. Yoshida, *Org. Biomol. Chem*. **2015**, *13*, 7140-7145

[5] L. K. Sydnes, I. C. Burkow, S. H. Hansen, *Tetrahedron* **1985,** *41* (23), 5703-5706



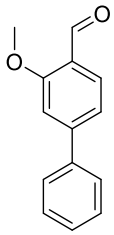
4-methyl-[1,1'-biphenyl]-3-carbaldehyde (17)

Synthesized according to the general procedure, using 5-bromo-N-methoxy-N,2-dimethylbenzamide (129 mg, 0.5 mmol) and phenyllithium. The product was obtained after column chromatography (SiO_2) using Pentane/EtOAc (0-10 %) (75 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.02 (d, J = 2.1 Hz, 1H), 7.70 (dd, J = 7.9, 2.1 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 2H), 7.46 (t, J = 7.5 Hz, 2H), 7.41 – 7.30 (m, 2H), 2.70 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.39, 142.28, 142.18, 142.09, 137.09, 135.02, 134.71, 133.03, 131.60, 131.54, 130.38, 129.55, 21.84. The data are in accordance with literature.[6]



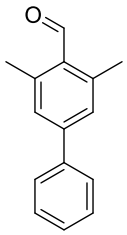
[1,1':3',1''-terphenyl]-5'-carbaldehyde (18)

Synthesized according to the general procedure, using 3,5-dibromo-N-methoxy-N-methylbenzamide (161 mg, 0.5 mmol) and 3 eq. of phenyllithium. The product was obtained after column chromatography (SiO_2) using Pentane/EtOAc (0-10 %) (83 mg, 64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.16 (s, 1H), 8.08 (s, 3H), 7.69 (d, J = 7.2 Hz, 4H), 7.51 (t, J = 7.3 Hz, 4H), 7.44 (t, J = 7.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.28, 142.76, 139.73, 137.45, 131.83, 129.05, 128.14, 127.25, 127.15. The data are in accordance with literature.[7]



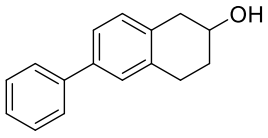
3-methoxy-[1,1'-biphenyl]-4-carbaldehyde (19)

Synthesized according to the general procedure, using 4-bromo-N-2-dimethoxy-N-methylbenzamide (136 mg, 0.5 mmol) and phenyllithium. The product was obtained after column chromatography (SiO_2) using Pentane/EtOAc (0-10 %) (41 mg, 40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.50 (s, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 7.3 Hz, 2H), 7.53 – 7.40 (m, 4H), 7.26 (d, J = 7.3 Hz, 1H), 7.17 (s, 1H), 4.00 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.10, 164.73, 151.69, 142.77, 131.73, 131.62, 131.21, 129.96, 126.33, 122.39, 112.99, 58.36. The data are in accordance with literature.[8]



3,5-dimethyl-[1,1'-biphenyl]-4-carbaldehyde (20)

Synthesized according to the general procedure, using 4-bromo-N-methoxy-N,2,6-trimethylbenzamide (136 mg, 0.5 mmol) and phenyllithium. The product was obtained after column chromatography (SiO_2) using Pentane/EtOAc (0-10 %) (19 mg, 18%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.65 (s, 1H), 7.61 (d, J = 7.1 Hz, 2H), 7.46 (t, J = 7.4 Hz, 2H), 7.40 (t, J = 7.3 Hz, 1H), 7.31 (s, 2H), 2.68 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.72, 148.13, 144.51, 142.44, 133.84, 131.53, 131.06, 130.89, 129.89, 23.42. The data are in accordance with literature.[9]



6-phenyl-1,2,3,4-tetrahydronaphthalen-2-ol (22)

Synthesized according to the general procedure, starting with the corresponding ketone 6-bromo-3,4-dihydronaphthalen-2(1H)-one (112 mg, 0.5 mmol) and phenyllithium. The product was obtained after column chromatography (SiO_2) using Pentane/EtOAc (5-15 %) (95 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.54 (m, 2H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.41 – 7.32 (m, 3H), 7.18 (d, *J* = 7.8 Hz, 1H), 4.32 – 4.06 (m, 1H), 3.15 (dd, *J* = 16.3, 5.0 Hz, 1H), 3.05 (dt, *J* = 17.0, 5.8 Hz, 1H), 2.92 (ddd, *J* = 16.6, 9.0, 6.0 Hz, 1H), 2.83 (dd, *J* = 16.3, 7.8 Hz, 1H), 2.15 – 2.04 (m, 1H), 1.99 – 1.75 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.12, 139.09, 136.04, 133.44, 129.97, 128.72, 127.30, 127.07, 127.02, 124.79, 67.24, 38.13, 31.50, 27.11. HRMS (ESI-): Calculated $[M-H]^-$: 223.1128; found: 223.1121. FT-IR: 3362 (bs), 3028, 2963, 2931, 2874 cm^{-1}.

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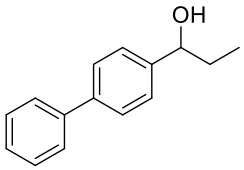
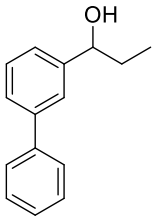


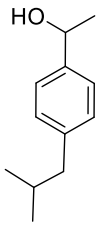
1-([1,1'-biphenyl]-4-yl)propan-1-ol (23)

Synthesized according to the general procedure, starting with the corresponding ketone 1-(4-bromophenyl)propan-1-one (106 mg, 0.5 mmol) and phenyllithium. The product was obtained after column chromatography (SiO_2) using Pentane/EtOAc (5-15 %) (84 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.56 (m, 4H), 7.49 – 7.39 (m, 4H), 7.35 (t, *J* = 7.4 Hz, 1H), 4.66 (t, *J* = 6.6 Hz, 1H), 1.84 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.60, 140.86, 140.42, 128.75, 127.24, 127.15, 127.06, 126.41, 75.76, 31.88, 10.18. The data are in accordance with literature.[10]



1-([1,1'-biphenyl]-4-yl)propan-1-ol (24)

Synthesized according to the general procedure, starting with the corresponding ketone 1-(3-bromophenyl)propan-1-one (106 mg, 0.5 mmol) and phenyllithium. The product was obtained after column chromatography (SiO_2) using Pentane/EtOAc (5-15 %) (59 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.56 (m, 3H), 7.55 – 7.50 (m, 1H), 7.49 – 7.40 (m, 3H), 7.40 – 7.31 (m, 2H), 4.68 (t, J = 6.6 Hz, 1H), 1.93 – 1.74 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.82, 144.04, 143.78, 131.50, 131.42, 129.99, 129.85, 128.99, 127.57, 127.48, 78.73, 34.64, 12.84. HRMS (ESI-): Calculated $[M-H]^-$: 211.1128; found: 211.1125. FT-IR: 3334 (bs), 3030, 2962, 2929 cm^{-1}.



1-(4-isobutylphenyl)ethan-1-ol (25)

Synthesized according to the general procedure, using 4-bromoacetophenone (99 mg, 0.5 mmol) and *tert*-butyllithium. The product was obtained after column chromatography (SiO_2) using Pentane/EtOAc (5-15 %) (38 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 4.87 (q, *J* = 6.5 Hz, 1H), 2.47 (d, *J* = 7.2 Hz, 2H), 1.92 – 1.78 (m, 2H), 1.49 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.05, 140.98, 129.21, 125.19, 70.28, 45.08, 30.24, 25.02, 22.38. The data are in accordance with literature.[11]

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