



HAL
open science

Zincate-Mediated Remote Functionalisation of p-Iodobenzyl Derivatives Through Metallotropy in 2-Methyltetrahydrofuran as Key Solvent

Alexandre Pierret, Clément Denhez, Philippe Gros, Alexandre Vasseur

► To cite this version:

Alexandre Pierret, Clément Denhez, Philippe Gros, Alexandre Vasseur. Zincate-Mediated Remote Functionalisation of p-Iodobenzyl Derivatives Through Metallotropy in 2-Methyltetrahydrofuran as Key Solvent. *Advanced Synthesis and Catalysis*, 2022, 10.1002/adsc.202200475 . hal-03768996

HAL Id: hal-03768996

<https://hal.science/hal-03768996v1>

Submitted on 15 Nov 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Zincate-Mediated Remote Functionalisation of *p*-Iodobenzyl Derivatives Through Metallotropy in 2-Methyltetrahydrofuran as Key Solvent

Alexandre Pierret,^a Clément Denhez,^b Philippe C. Gros,^a and Alexandre Vasseur^{a,*}

^a Université de Lorraine, CNRS, L2CM, F-54000 Nancy, France
E-mail: alexandre.vasseur@univ-lorraine.fr

^b Université de Reims Champagne Ardenne, CNRS, ICMR UMR 7312, 51097 Reims, France

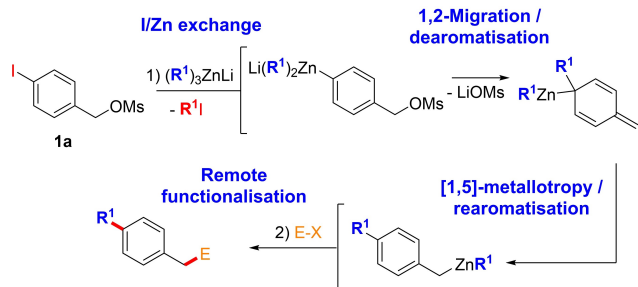
Abstract: 2-MeTHF (2-methyltetrahydrofuran) promotes the zincate-mediated remote functionalisation of *p*-iodobenzyl derivatives through metallotropy with a broad scope. This biosourced solvent remarkably impacted all the key elementary steps involved in the tandem reaction. The method tolerates a wide range of sensitive functionalities within the substrates as well as enolisable and activated or deactivated aromatic aldehydes as reaction partners. A challenging benzyl naphthalene derivative was even reacted through an original dearomatisation/rearomatisation/metallotropy chain.

Keywords: Zincate; Green solvent; Remote functionalisation; metallotropy; metal-shift

Introduction

Metal promoted-remote functionalisation is an elegant synthetic route providing rapid access to added-value molecular architectures with a high degree of structural diversity from simple and readily available substrates.^[1] If perfectly controlled, such an approach allows the selective functionalisation at a site away from a functional group initially interacting with the reagent or catalyst used. Since the pioneering work of Breslow,^[2] 40 years of intensive research efforts produced a myriad of strategies. The original approach proceeds through distant external induction involving tether-directed templates. Although highly selective and efficient, a severe limitation is the required multi-step synthesis of linkers as well as the anchorage and removal steps.^[3] Strategies based either on transient directing group reversibly combined with the substrate or ligand-substrate non-covalent interactions^[4] enable to lessen some above-mentioned drawbacks but are still in their infancy. Alternatively, remote functionalisation through internal induction^[5] relies on through-space metal migration^[6] or intrinsic migration of the metal along a flexible carbon chain *via* unidirectional positional isomerisation sequence of a double bond.^[7]

Along with carbocycle β -fragmentation and 1,*n*-hydrogen atom transfer-based tactics,^[8] the remote functionalisation through internal induction unquestionably respects the principle of step economy. Moreover, when the metal migration precedes the use of an additional catalyst, the overall transformation may result in the selective formation of two distant carbon-carbon bonds in a single operation.^[9] In this context, remote functionalisation through alkene isomerisation is a rapidly developing field. In contrast, metallotropic rearrangements^[10] are relatively underexplored most likely because factors triggering the communication process between the initiation and the remote site remain inside a black box. Harada and co-workers first reported the remote functionalisation of 4-iodobenzyl methanesulfonate **1a** by simple treatment with lithium trialkylzincate and subsequent addition of an electrophile.^[11] This reaction is the result of a perfect orchestration of four chemical events directed by a unique metal reagent as maestro (Scheme 1) : (i) I/Zn exchange, (ii) 1,2-migration of one of the two alkyl ligands of the Zn metal centre and subsequent dearomatisation, (iii) rearomatisation associated with formal [1,5]-metallotropic rearrangement, (iv) selective



Scheme 1. Concept of the remote functionalisation of **1a** through metallotropy.

transfer of the resulting benzyl ligand of Zn to an electrophile.

The beauty of this sequence also lies in the selective formation of a $C(sp^3)-C(sp^2)$ bond and a $C(sp^3)-C(sp^3)$ bond at sites five atoms apart in a single process. Furthermore, the reagent is easily prepared from low toxic, cheap and abundant zinc thus offsetting the drawback of using it in non-catalytic amounts.^[12] This tandem sequence enables the homologation reaction *via* 1,2-migration of a wide range of alkyl ligands. Unfortunately, the synthetic scope was only restricted to **1a** with no substituent on the aromatic ring, except the halogen essential for the metalation step. Additionally, this transformation was proved to proceed smoothly with aliphatic aldehydes as electrophiles. However, no data was provided regarding the compatibility of the reaction with activated and deactivated aromatic aldehydes. This lack of information also applies to the challenging enolisable aldehydes^[13] in the presence of a notorious basic metal reagent such as lithium zincate.^[14] We report herein the remote functionalisation through metallotropy of diversely decorated 4-iodobenzyl derivatives with activated/deactivated aromatic and enolisable aldehydes as reaction partners in 2-MeTHF (2-methyltetrahydrofuran) as solvent by using a range of lithium trialkylzincate reagents. The influence and the role of the solvent on key elementary steps of the process are discussed.

Results and Discussion

We were first delighted to find that the reaction of **1a** with the enolisable isovaleraldehyde **2a** at -85°C yielded the remotely functionalised product **3aa** in 72% under earlier reported conditions,^[11] namely initial treatment of **1a** with *n*-Bu₃ZnLi at -85°C for 30 min and then for 1 hour in THF prior to addition of the electrophile (Table 1, entry 1). Since chloro-substituted iodoarenes were known to successfully undergo zincate-promoted I/Zn exchange,^[15] we pursued our investigations with **1b** so as to provide a first impact evaluation of electron-withdrawing effects on other

Table 1. Optimisation of the remote functionalisation of **1a-b**.^[a]

Entry	Solvent	T ^[b]	1	2	3 ^[c]	4 ^[c]
1	THF	-85	1a	2a	3aa , 72	–
2	THF	-85	1b	2a	3ba , 30	59
3	THF	-85	1b	2b	3bb , 33	59
4	2-MeTHF	-85	1b	2b	3bb , 66	–
5	2-MeTHF	-85	1b	2a	3ba , 40	–
6	2-MeTHF	-95	1b	2a	3ba , 49	–
7	2-MeTHF	-110	1b	2a	3ba , 60	–
8	2-MeTHF	-110	1b	2b	3bb , 40	–

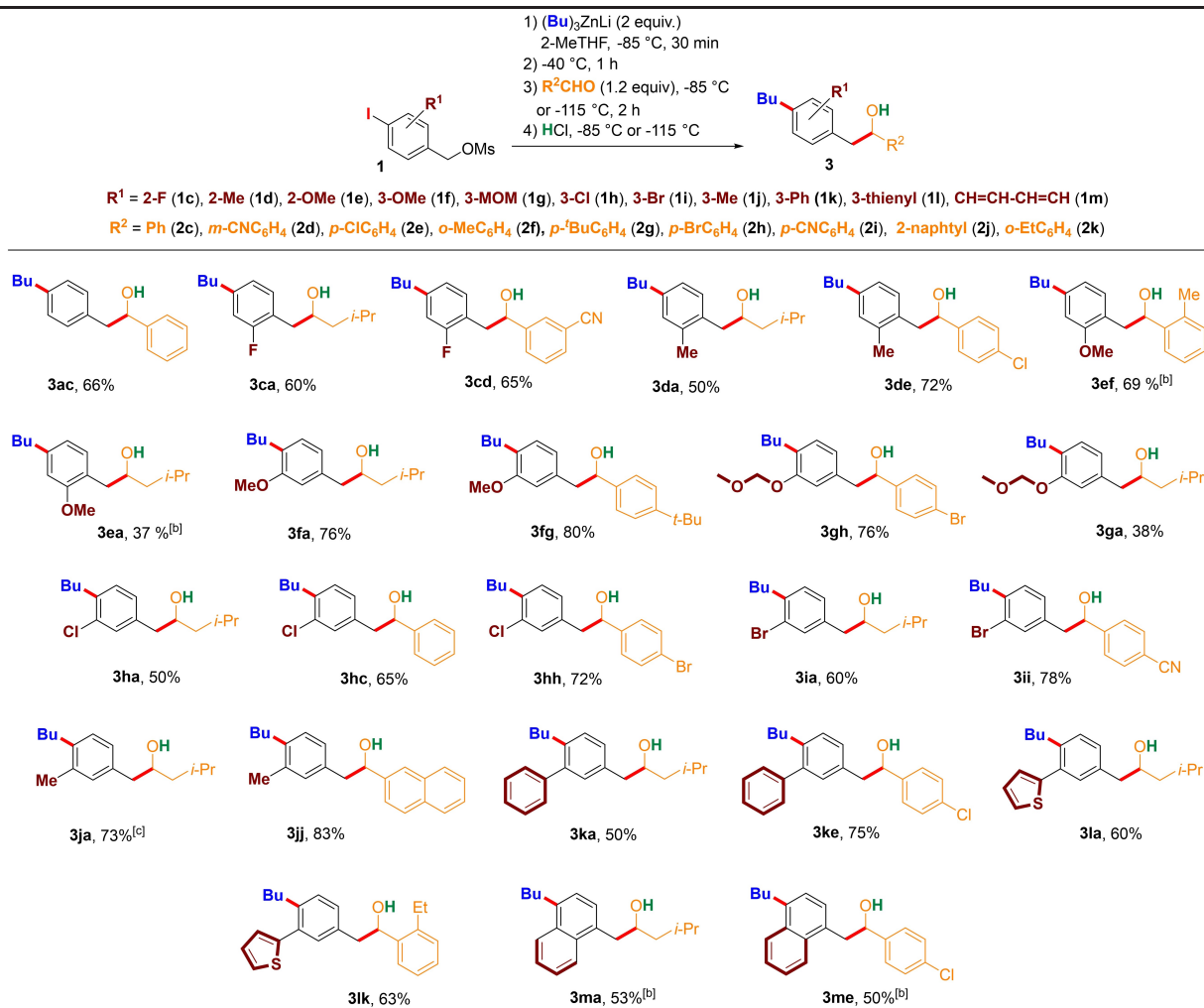
^[a] Conditions: 1) **1** (0.6 mmol), *n*-Bu₃ZnLi (1.2 mmol), -85°C , 30 min, solvent (10 mL); 2) -40°C , 1 h; 3) R²CHO (0.72 mmol), 2 h; 4) HCl, -85°C .

^[b] Expressed in $^\circ\text{C}$.

^[c] Isolated yields (%).

key chemical events of our reaction sequence. The above conditions applied to **1b** led to both the formation of the expected **3ba** (30% yield) and side product **4** (59% yield) arising from I/Zn exchange step with no metal migration (entry 2). The use of 1-naphthaldehyde **2b** instead of **2a** resulted in a similar incomplete migration process (entry 3). Switching from THF to 2-MeTHF exclusively produced **3bb** in good yield (66%) without any trace of **4** (entry 4). This low-toxic biomass-derived solvent^[16] has already been reported to impact positively on several organometallic transformations^[17] but was never applied to such a metallotropic process. The reaction conducted with **2a** in 2-MeTHF enabled the selective production of **3ba**, albeit in a still low yield (40%, entry 5). Harnessing the larger temperature range offered by 2-MeTHF compared with THF^[18] enhanced the isolated yield by 9% and 20% when the temperature was decreased from -85°C to -95°C and -115°C respectively, before addition of the electrophile (entries 6–7). Nevertheless, -85°C remained the most appropriate temperature for the reaction involving the aromatic aldehyde **2b** (entries 8 and 4).

The scope of the process was then examined (Table 2). The remote functionalisation of **1a** with aromatic aldehyde **2c** could be achieved with similar success as observed in Table 1 (compare the yields of **3ac** (Table 2) and **3bb** (Table 1, entry 4)). Other reactions carried out with substrates displaying a 3-substituted aromatic ring **1b–e** also produced the expected products **3** in fair to good yields. Regardless

Table 2. Synthetic scope of the process.^[a]

^[a] Conditions: 1) **1** (0.6 mmol), *n*- Bu_3ZnLi (1.2 mmol), 2-MeTHF (10 mL), -85°C , 30 min; 2) -40°C , 1 h; 3) **2** (0.72 mmol), -115°C for **2a** and -85°C for **2b–k**, 2 h; 4) HCl 1 M (8 mL), -85°C ; Isolated yields are reported.

^[b] Performed with $\text{OPO}(\text{OEt})_2$ as leaving group instead of OMs.

^[c] **2a** (2.5 equiv.) was used. The yield obtained by using 1.2 equiv. of **2a** was 44%.

of the electron-withdrawing or donating nature of the substituent, isolated yields remained above 50% (**3ca**, **3cd**, **3da**, **3de**, **3ef**), even with the 2-F substituted compound **1c**. The 4-event tandem sequence also proceeded smoothly with 2-substituted benzyl derivatives **1f–j**. The yields either reached or substantially exceeded the value of 50% peaking at 83% for **3jj** involving 2-naphthaldehyde **2j** as reaction partner. A plausible explanation for lower yields relating to **3ea** and **3ga** might be the more pronounced enolisable character of **2a** when involved in reactions with electron-enriched organometallic benzyl species resulting from **1e** and **1g** respectively. However, this drawback was substantially overcome by increasing the amount of **2a**. For instance, **3ja** was delivered in 73% yield by using 2.5 equiv. of **2a** instead of 44% with 1.2 equiv. of the same electrophile.

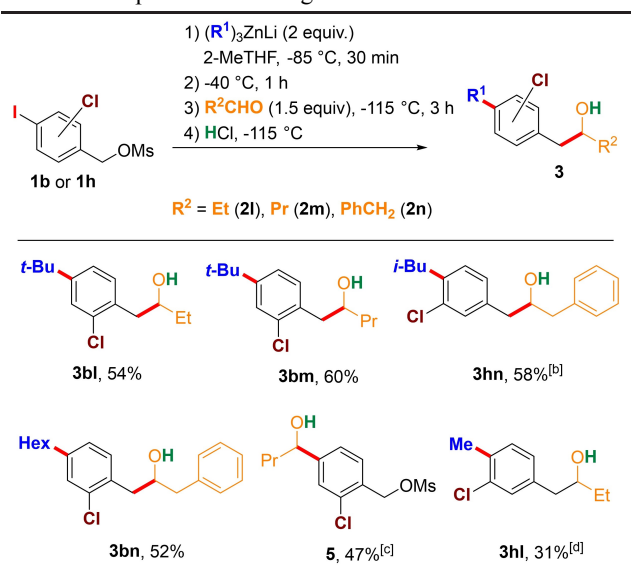
Overall, these results show that the 1,2-migration of Bu/metallotropic rearrangement through dearomatization/rearomatization string is very little sensitive to substituent-induced electronic effects. In addition, it should be stressed that a potentially Zn-chelating MOM group placed in the immediate vicinity of the reaction initiation site did not affect the course of the transformation once the I/Zn exchange step was achieved (see **3gh**). Remarkably, the C–Br bonds in **3ia** and **3ii** were perfectly tolerated showing that (i) a tri-coordinated mono-anionic-type lithium zincate was the operating reagent rather than a tetra-coordinated di-anionic analogue,^[19] (ii) our conditions were not conducive to formation of aryne.^[20] Polyaromatic substrates **1k** and **1l** including a thienyl motif reacted similarly to other previously commented analogues since compounds **3ka**, **3ke**, **3la**, **3lk** were obtained in

a 50–75% yield range depending on the used electrophile **2**. Thus, once the through I/Zn exchange metalation step was achieved, the reactivity of the Zn metal centre was not affected by the neighbouring sulphur atom (see **3la** and **3lk**).^[21] The impact of 2-MeTHF on the promotion of the butyl 1,2-migration was remarkably confirmed when the transformation was conducted with the fused aromatic **1m** as a substrate. Whereas **3ma** and **3me** were selectively produced in fair yields when the reaction was performed in 2-MeTHF with **2a** and **2e** respectively, using THF as solvent considerably dimmed those results since the undesired 4-type product was isolated in 60%. Remote functionalisation of naphthalene derivatives involving dearomatisation/rearomatisation process is very rarely reported.^[22] In this regard, both **3ma** and **3me** represent unique examples derived from remote bis-functionalisation approach allowing the distal formation of both a C(sp³)–C(sp²) and a C(sp³)–C(sp³) bond after metallotropic rearrangement between two sites distant by 5 atoms. The reactivity of the final benzyl zinc-type species formed after the metallotropic rearrangement was not impacted at all by the presence of a CN-substituent on aromatic aldehydes (see **3cd** and **3ii**) even though such a functional group might act as a competitive coordinator of the Zn centre.^[21] This kind of species were also selectively captured through reaction with para or ortho deactivated benzaldehyde derivatives (**3ef**, **3fg**, **3ii** and **3lk**).

We also examined the scope of alkyl zincate reagents. *t*-Bu, *i*-Bu and Hex ligands also underwent smoothly the 1,2-migration reaction once the I/Zn exchange occurred (Table 3). The homologated benzyl anion resulting from the treatment of **1b** or **1h** with (*t*-Bu)₃ZnLi, (*i*-Bu)₃ZnLi or (*n*-Hex)₃ZnLi could be trapped with an additional range of enolisable aldehydes, including the highly enolisable **2n**. Compounds **3bl**, **3bm**, **3hn** and **3bn** were obtained in fair to good yields (up to 60%). In contrast, Me ligand turned out to be very reluctant to undergo 1,2-migration. Whereas the treatment of **1b** with (Me)₃ZnLi at –85 °C for 30 min and then at –40 °C for 1 h only yielded a complex mixture after addition of **2m** at –115 °C, performing the reaction under Barbier-type conditions (namely addition of **2m** at –85 °C after a 15-min-period treatment of **1b** with Me₃ZnLi at that temperature and then warming of the reaction mixture from –85 to –40 °C for 1 h) led to both **5** and **4** in 47% and 38% yield respectively. However, we found that the hybrid zincate Me₂(Ph)ZnLi offered promising opportunities for successful 1,2-migration of Me ligand. Indeed, the reaction carried out with **1h** as substrate and **2l** as electrophile produced **3hl** in 31% yield.

To get a better insight into the influence of the solvent, we performed analytical comparative studies of each elementary key step of the reaction sequence in THF and 2-MeTHF. The positive impact of 2-MeTHF

Table 3. Scope of zincate reagents.^[a]



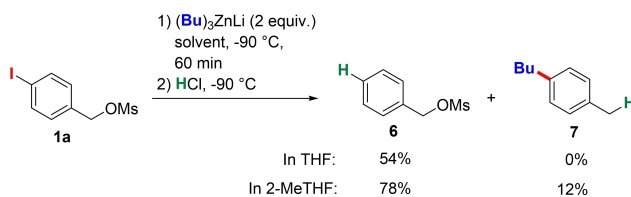
^[a] Conditions: 1) **1** (0.6 mmol), (R¹)₃ZnLi (1.2 mmol), 2-MeTHF (10 mL), –85 °C, 30 min; 2) –40 °C, 1 h; 3) **2** (0.90 mmol), –115 °C to –85 °C, 3 h; 4) HCl 1 M (8 mL), –85 °C; Isolated yields are reported.

^[b] **2n** was added at –85 °C and then, the reaction mixture was stirred at –45 °C for 5 h.

^[c] Barbier-type conditions were used: **2m** was added at –85 °C after a 15-min-period treatment of **1b** with Me₃ZnLi and then, the reaction mixture was stirred at –40 °C for 1 h; **4** was isolated in 38% yield.

^[d] Me₂(Ph)ZnLi, prepared from Me₂Zn 2 M in toluene (1,2 mmol) and PhLi (1,2 mmol) at –10 °C for 20 min, was used as reagent.

on the butyl 1,2-migration step was noticeable to varying degrees in all reactions disclosed in Table 1 and 2, including those performed with **1a** (Scheme 2). Treatment of **1a** with 2 equivalents of *n*-Bu₃ZnLi in THF for 60 min at –90 °C, followed by hydrolysis solely afforded product **6** in 54% GC/MS yield. In contrast, besides the formation product **6** in a considerably enhanced 78% GC/MS yield, the same reaction carried out in 2-MeTHF concomitantly produced **7** in 12% GC/MS yield without the need for warming-up the reaction mixture from –90 °C to –40 °C.



Scheme 2. Effect of 2-MeTHF on both the I/Zn exchange step and the Bu 1,2-migration step.

The conversion of **1a** into **6** on one hand, and **6** + **7** on the other hand, has been studied by GC/MS in THF and 2-MeTHF respectively in order to evaluate the potential solvent impact on the I/Zn exchange step (Figure 1).

GC/MS kinetic monitoring could not be directly performed by successive samplings due to excessive temperature variations during such an operation. As a consequence, each point of both curves is an average result derived from three experiments which have been conducted independently and separately. Regardless of the considered solvent, the conversion at the initial stage was unchanged. In contrast, the solvent has a strong effect on the conversion of **1a** after this initial stage. It is well known that the solvent choice is critical

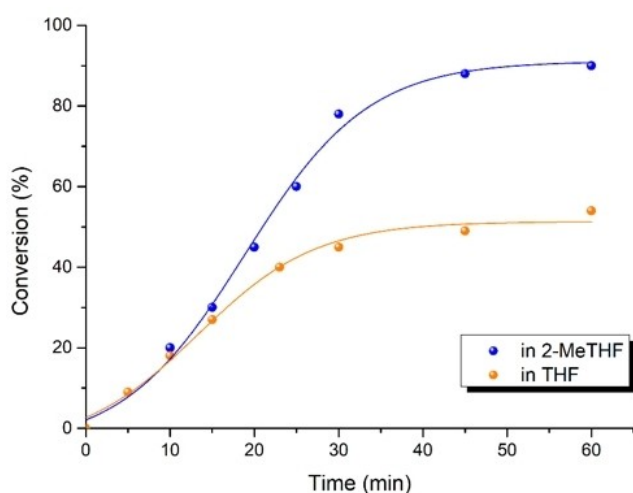
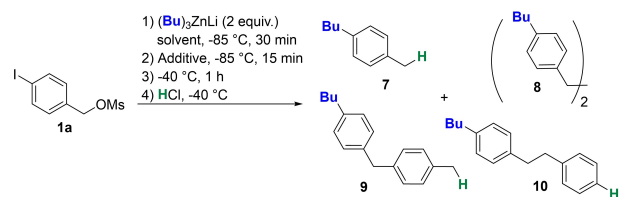


Figure 1. Profiles of the conversion of de **1a** into **6** or **6** + **7**. Conditions: **1a** (0.6 mmol), *n*-Bu₃ZnLi (1.2 mmol), solvent (10 mL), -85°C , time; 2) HCl 1 M (1 mL), -90°C .

Table 4. Inhibitor effect of 2-MeTHF on the formation of **8**–**10**.^[a]



Entry	Solvent	additive	7 ^[b]	8 ^[b]	9 ^[b]	10 ^[b]
1	THF	–	73	13	7	7
2	2-MeTHF	–	89	8	2	1
3	THF	B(OMe) ₃	89	5	3	3

^[a] Conditions: 1) **1a** (0.6 mmol), *n*-Bu₃ZnLi (1.2 mmol), 2-MeTHF (10 mL), -85°C , 30 min; 2) additive (0 or 0.6 mmol, 0–1 equiv.), -85°C , 15 min; 3) -40°C , 1 h; 4) HCl 1 M (8 mL), -85°C ; ratio determined by GC.

^[b] Values expressed in %.

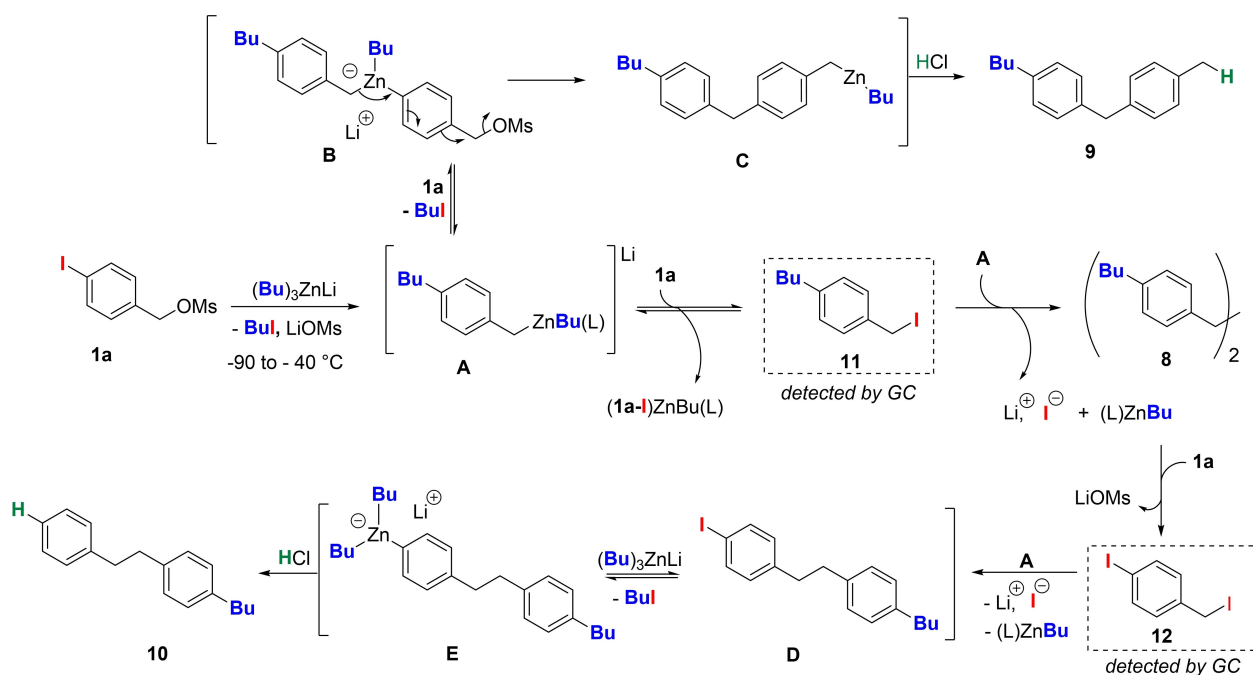
for controlling both efficiency and selectivity in polar organometallic chemistry-based reactions. Examination of the literature data revealed that the solvent could improve not only the stability and/or solubility of organometallic intermediates but also their reactivity through either beneficial changes in their aggregation state or transitions state (or reaction products) stabilisation/destabilisation.^[23]

Lastly, we investigated the impact of 2-MeTHF on the stability of the benzyl organometallic species generated in the last step of our chemical string (Table 4). Treatment of **1a** with 2 equivalents of *n*-Bu₃ZnLi at -85°C in THF for 30 min and then at -40°C for 1 h yielded the products **7/8/9/10** with a 73/13/7/7 distribution after hydrolysis (Table 4, entry 1). The use of 2-MeTHF instead of THF resulted in a substantial decrease of the amount of homocoupling products (Table 4, entry 2). LiOMs released during the 1,2-migration step probably promotes the formation of aggregates favouring side Würtz-type reactions since attempts to trap it with B(OMe)₃ as additive afforded similar results as those obtained in 2-MeTHF (Compare entry 3 with entry 2). Such an inhibitor effect of 2-MeTHF on the formation of Würtz-type product was also observed in the addition reaction of PhMgCl onto butan-2-one. 2-MeTHF-induced favourable changes in the aggregation state of key organometallic species were suspected.^[24]

However, the enhanced stability of the final benzyl organometallic species **A** may also be in connection with the positive influence on the I/Zn exchange process (Scheme 3). Warming-up the reaction medium from -85 to -40°C is instrumental in starting (case of THF) or completing the Bu 1,2-migration step (case of 2-MeTHF). Since, the conversion of **1a** into **6** was only 45% after 30 min at -85°C in THF compared with 75% in 2-MeTHF, the warming of the reaction mixture allows the formation of **A** while **1a** is still far from being totally consumed.

Accordingly, **A** reversibly reacts with **1a** at -40°C to yield **11** detected by GC/MS which provides the homocoupling product **8** after reaction with **A**. The reaction of **1a** with **A** also leads to organometallic **B** and then successively to **C** and **9**, subsequent to benzyl ligand 1,2-migration and final hydrolysis. Ultimately, **1a** is converted into 4-iodobenzyl iodide **12** detected by GC likely through reaction with *in-situ* generated lithium iodide in the presence of *in-situ* produced (L)ZnBu-type Lewis acid. Transformation of **12** into **10** can thereafter occur through transfer of the benzyl ligand of **A**/initial reagent-promoted I/Zn exchange sequence prior to hydrolysis.

Even though the Bu 1,2-migration step was complete in both solvent at -40°C after a 1 h stirring period, the combination of 2-MeTHF-induced booster effect of the I/Zn exchange and the better stability of **A** was mostly enough to access better yields than those



Scheme 3. Proposed mechanistic pathway for the synthesis of homocoupling products.

obtained in THF as evidenced by selected examples showcased in Table 5. For instance, reactions performed in THF with 2-substituted benzyl derivatives **1** afforded corresponding compounds **3** in yields from 12

Table 5. Solvent comparative study.^[a]

1a	1) (Bu) ₃ ZnLi (2 equiv.), THF, -85 °C, 30 min 2) -40 °C, 1 h 3) 2 (1.2 equiv.), -85 °C, 2 h 4) HCl, -85 °C	3
		3ab , 66% (in MeTHF: 81%)
		3ca , 48% (in 2-MeTHF: 60%)
		3da , 38% (in 2-MeTHF: 50%)
		3ef , 55% ^b (in 2-MeTHF: 69%)
		3ea , 69% (in 2-MeTHF: 37%)
		3ga , 50% (in 2-MeTHF: 38%)
		3gh , 62% (in 2-MeTHF: 76%)
		3fa , 50% (in 2-MeTHF: 76%)
		3ia , 51% (in 2-MeTHF: 60%)
		3ma , 22% ^b (in 2-MeTHF: 53%) ^{b,c}

^[a] Conditions: 1) **1** (0.6 mmol), *n*-Bu₃ZnLi (1.2 mmol), THF (10 mL), -85 °C, 30 min; 2) -40 °C, 1 h; 3) **2** (0.72 mmol), -85 °C, 2 h; 4) HCl 1 M (8 mL), -85 °C; Isolated yields; As a reminder, yields in parenthesis are those obtained with 2-MeTHF as solvent (10 mL).

^[b] Performed with OPO(OEt)₂ as leaving group instead of OMs.

^[c] Diethyl (naphthalen-1-ylmethyl) phosphate **13** was isolated in 60% yield.

to 14% below those got in 2-MeTHF (see **3ca**, **3da**, **3ef**). Similar differences were also noticeable for reactions carried out with 3-substituted derivatives **1g** and **1i** (see products **3gh**, **3ia**) and even more pronounced with the substrate **1f** (see the discrepancy of 26% for **3fa**). Yield improvements regarding **3ab** and **3ma** are due to the three above-mentioned combined effects of 2-MeTHF. A reasonable interpretation for lower yields relating to **2a** for enolisation when electron-enriched A-type benzyl derivatives are brought into play.

Conclusion

In conclusion, we have proposed general reaction conditions for the remote functionalisation of *p*-iodobenzyl derivatives through a tandem sequence involving a I/Zn exchange-metalation step, an alkyl 1,2-migration, a reversible dearomatisation and a metallotropic rearrangement. Compared with the previously reported protocol,^[11] our conditions allow for considerable scope expansion involving various linear and branched trialkylzincates and variously substituted substrates including a benzyl naphthalene. The method was also compatible not only with deactivated or activated aromatic aldehydes as reaction partners but also with standard enolisable aldehydes, including highly enolisable phenylacetaldehyde. The process opens access to the formation of both a C(*sp*³)-C(*sp*²) and a C(*sp*³)-C(*sp*³) bond at sites distant by five atoms in a single operation. The method requires a notori-

ously low-toxic, low-priced and abundant zinc-based reagent as unique operator, thus offsetting the need for stoichiometric amount, and 2-MeTHF as well recognised green solvent. 2-MeTHF exerts a ubiquitous positive influence on the overall reaction sequence, namely on (i) the I/Zn exchange, (ii) the alkyl 1,2-migration, (iii) the final functionalisation of the benzylzinc species **A** due to better stabilisation. According to the literature, positive solvent effects on both I/Zn exchange and alkyl 1,2-migration may be ascribable either to beneficial changes in the aggregation state of key organometallic species or destabilization/stabilization effect on involved transition states. The comprehensive mechanism of the entire reaction sequence in both solvents is currently under experimental and theoretical investigation.

Experimental Section

General Information

All reactions were carried out under an atmosphere of argon, with dry oxygen-free organic solvent and using standard Schlenk techniques. All solvents and liquid reagents were transferred using plastic single-use graduated syringes and stainless-steel needles except for electrophiles **2** which were transferred using Microseringues Hamilton. THF (HPLC grade, non-stabilized, BioLab) was dried using Solvent Purifier System (SPS Mbraun 800) (two columns of alumina) and kept under positive pressure of argon (99.9999% purity grade). Progress of the reactions was monitored by analytical TLC using ready-made plates precoated with silica gel on aluminium with F254 indicator (Merck 60 F₂₅₄). Visualization of spots was done using UV-light or phosphomolybdic acid followed by heating. Purification of crude mixtures was accomplished by column chromatography on silica gel 60–200 μm using a mixture of petroleum ether/diethyl ether as eluent (from 90/10 to 60/40, v/v). ¹H, ¹³C and ¹⁹F NMR spectra were measured on Bruker Advance III 400 (400, 100.6 and 376.4 MHz respectively) spectrometer in CDCl₃ and referenced to TMS. Chemical shifts values (δ) are reported in ppm (calibration of spectra to the residual peak of CDCl₃: $\delta = 7.26$ ppm (s) for ¹H NMR; $\delta = 77.16 \pm 0.06$ ppm for ¹³C NMR). All the proton spectra are reported as follows: δ value (multiplicity, J coupling constant in Hz, number of nuclei). Multiplicity contractions used: (bs) – broad singlet, (d) – doublet, (dd) – doublet of doublets, (ddd) – doublet of doublets of doublets, (dddd) – doublet of doublets of doublets of doublets, (dqd) – doublet of quartets of doublets, (dt) – doublet of triplets, (m) – multiplet, (t) – triplet, (td) – triplet of doublets, (tdd) – triplet of doublets of doublets, (tt) – triplet of triplets, (s) – singlet. IR spectra were recorded using a Shimadzu IRAffinity-1 equipped with an ATR PIKE Technologies model gladiAT (Spectral range: 7500 cm⁻¹–375 cm⁻¹; spectral resolution: < 3 cm⁻¹). Wavenumbers are listed in cm⁻¹. Melting points (M.p.) were measured on a Kofler bench and were uncorrected. The values are reported in Celsius degrees. High resolution mass spectra (HRMS) were recorded on a Bruker MicrOTOFq ESI/QqTOF apparatus equipped with an Atmospheric Pressure Ionization (API) source Low-resolution spectra in electronic impact (GC-EI) were recorded on a

Shimadzu QP2010 coupled with a gas chromatography apparatus equipped with a DB5-MS UI column (length: 30 m, width: 0.25 mm, thickness of the film: 0.25 μm).

Reagents and Starting Materials

n-BuLi (1.6 M in hexanes), *t*-BuLi (1.9 M in pentane), *n*-hexLi (2.5 M in hexane), MeLi (1.6 M in diethyl ether) are commercially obtained from Acros and regularly titrated under argon atmosphere by using a dry toluene solution of menthol and 2,2'-bipyridine as indicator. Me₂Zn (2 M in toluene) and PhLi (1.9 M in dibutyl ether) were purchased from Aldrich. Anhydrous ZnCl₂ (>98% reagent grade) and aldehydes **2** are commercially available and were used as received. Stabilised 2-MeTHF (99+ % purity grade), extra dry over Molecular sieve, was purchased from AcroSeal[®] and used as received. All starting materials **1** were prepared by a standard procedure sequence reported in the literature:^[25] (i) reduction of corresponding methyl 4-iodobenzoate derivatives using commercially available DIBAL-1 M solution (1.5 equiv.) in toluene at -60°C for 1 h;^[25a] (ii) mesylation of the resulting benzyl alcohol using DMAP (0.1 equiv.)/Et₃N (2 equiv.)/MsCl at -10°C in DCM for 1 h and subsequent quench with HCl-1 M.^[25b] Because of stability issues, mesylate ester as a leaving group was changed by diethyl phosphate ester for the preparation of **1e** and **1m** according to standard reaction conditions: DMAP (0.1 equiv.)/DIPEA (1.5 equiv.)/diethyl chlorophosphate (1.5 equiv.) at rt in DCM for 2 h and subsequent quench with water.^[25c]

General Procedure for the Synthesis of Products **3**

An oven-dried 50 mL-three-neck flask, equipped with a Teflon-coated magnetic stir bar, a greased gas inlet adaptor with a glass plug, a rubber septum and a low-temperature thermometer with greased glass adaptor, was preliminarily charged with anhydrous ZnCl₂ (164 mg, 1.2 mmol, 2.0 equiv.). The flask was connected to the Schlenk line and the air was pumped out of the flask. ZnCl₂ was heated three times using a heat gun. Once the flask returned to room temperature, the resulting vacuum was replaced with argon. This “vac-refill” operation was performed three times. Dry 2-MeTHF (8 mL) was added and the resulting mixture was stirred at -10°C for 10 min. A solution of *n*-butyllithium (1.6 M in hexanes, 2.13 mL, 3.4 mmol) was then added dropwise under inert atmosphere at that temperature. After a 20 min-stirring period at -10°C , the reaction mixture was cooled down to -85°C . A 2 mL dry 2-MeTHF solution of 4-iodobenzyl mesylate ester **1** (0.6 mmol, 1.0 equiv.) was added dropwise and the reaction mixture was stirred at -85°C for 30 min before warming-up to -40°C for 1 h. The reaction mixture was thereafter cooled down to -85°C (in the case of aromatic aldehydes) or -115°C (in the case of enolisable aldehydes) before addition of the electrophile **2** (0.72 mmol, 1.2 equiv.) and the resulting solution was stirred at that temperature for 2 h. Finally, the reaction mixture was hydrolysed with an aqueous solution of 1 M HCl (1 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 times). The combined organic fractions were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Pure products **3** were obtained after purification of the

corresponding reaction crude by silica-gel chromatography (SiO₂, Petroleum ether/Et₂O, 80:20–60:40).

1-(4-Butyl-phenyl)-4-methyl-pentan-2-ol (3aa). Colorless oil (106 mg, yield 72%). R_f 0.37 (Petroleum Ether:Et₂O, 8:2, v:v). ¹H NMR (400 MHz, CDCl₃) δ 7.13 (s, 4H), 3.88 (tt, *J*=8.5, 4.1 Hz, 1H), 2.79 (dd, *J*=13.6, 4.0 Hz, 1H), 2.63–2.54 (m, 3H), 1.93–1.75 (m, 1H), 1.65–1.53 (m, 3H), 1.51–1.44 (m, 2H), 1.41–1.24 (m, 2H), 0.99–0.87 (m, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 141.0, 135.8, 129.4, 128.6, 70.7, 46.1, 44.3, 35.4, 33.8, 24.8, 23.5, 22.5, 22.1, 14.1; IR (ATR) ν_{max}/cm⁻¹ 3356, 2953, 2922, 2862, 1606, 1504, 1465, 1455, 1028, 821; HRMS (ESI-TOF) *m/z* calcd for C₁₆H₂₆NaO [M+Na]⁺ 257.1881, found 257.1884.

1-(4-Butyl-2-chloro-phenyl)-4-methyl-pentan-2-ol (3ba). Colorless oil (96 mg, yield 60%). R_f 0.40 (Petroleum Ether:Et₂O, 8:2, v:v). ¹H NMR (400 MHz, CDCl₃) δ 7.19 (d, *J*=1.8 Hz, 1H), 7.16 (d, *J*=7.8 Hz, 1H), 7.02 (dd, *J*=7.8, 1.8 Hz, 1H), 3.98 (tt, *J*=8.7, 4.1 Hz, 1H), 2.98 (dd, *J*=13.7, 3.8 Hz, 1H), 2.67 (dd, *J*=13.7, 8.7 Hz, 1H), 2.59–2.53 (m, 2H), 1.91–1.77 (m, 1H), 1.61–1.55 (m, 2H), 1.49–1.43 (m, 2H), 1.42–1.26 (m, 3H), 0.98–0.90 (m, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 143.1, 134.1, 133.6, 131.7, 129.6, 127.0, 69.4, 46.5, 42.0, 35.0, 33.5, 24.9, 23.5, 22.4, 22.2, 14.0; IR (ATR) ν_{max}/cm⁻¹ 3327, 2953, 2926, 2868, 1608, 1490, 1465, 1458, 1049, 819, 690; HRMS (ESI-TOF) *m/z* calcd for C₁₆H₂₅ClNaO [M+Na]⁺ 291.1486, found 291.1477.

2-(4-Butyl-2-chloro-phenyl)-1-naphthalen-1-yl-ethanol (3bb). White solid (133 mg, yield 66%). R_f 0.60 (Petroleum Ether:Et₂O, 8:2, v:v). mp. 76–78 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.33–8.27 (m, 1H), 7.92–7.87 (m, 1H), 7.82–7.75 (m, 2H), 7.56–7.47 (m, 3H), 7.26 (d, *J*=1.9 Hz, 1H), 7.20 (d, *J*=7.7 Hz, 1H), 7.01 (dd, *J*=7.7, 1.8 Hz, 1H), 5.79 (dd, *J*=9.5, 3.7 Hz, 1H), 3.45 (dd, *J*=14.0, 3.7 Hz, 1H), 3.12 (dd, *J*=14.0, 9.5 Hz, 1H), 2.61–2.55 (m, 2H), 1.98 (bs, 1H), 1.64–1.56 (m, 2H), 1.41–1.32 (m, 2H), 0.95 (t, *J*=7.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 143.5, 140.0, 134.1, 133.9, 133.2, 132.2, 130.6, 129.6, 129.0, 128.2, 127.1, 126.2, 125.7, 125.7, 123.4, 123.1, 70.3, 42.8, 35.1, 33.5, 22.4, 14.1; IR (ATR) ν_{max}/cm⁻¹ 3356, 2958, 2922, 2872, 1506, 1456, 1049, 827, 790, 771, 690; HRMS (ESI-TOF) *m/z* calcd for C₂₂H₂₂Cl [M–H₂O+H]⁺ 321.1405, found 321.1397.

2-(4-Butyl-phenyl)-1-phenyl-ethanol (3ac). Colorless oil (123 mg, yield 66%). R_f 0.54 (Petroleum Ether:Et₂O, 8:2, v:v). ¹H NMR (400 MHz, CDCl₃) δ 7.40–7.34 (m, 4H), 7.31–7.27 (m, 1H), 7.13 (s, 4H), 4.89 (dd, *J*=4.5, 8.8 Hz, 1H), 3.03 (dd, *J*=4.5, 13.7 Hz, 1H), 2.94 (dd, *J*=8.8, 13.7 Hz, 1H), 2.60 (t, *J*=7.7 Hz, 2H), 1.80 (bs, 1H), 1.64–1.56 (m, 2H), 1.41–1.32 (m, 2H), 0.93 (t, *J*=7.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 144.0, 141.3, 135.2, 129.4, 128.6, 128.4, 127.6, 125.9, 75.4, 45.8, 35.3, 33.7, 22.4, 14.0; IR (ATR) ν_{max}/cm⁻¹ 3356, 2954, 2924, 2854, 1602, 1508, 1454, 1043, 806, 754, 698; HRMS (ESI-TOF) *m/z* calcd for C₁₈H₂₂NaO [M+Na]⁺ 277.1563, found 277.1602.

1-(4-Butyl-2-fluoro-phenyl)-4-methyl-pentan-2-ol (3ca). Colorless oil (90 mg, yield 60%). R_f 0.49 (in Petroleum Ether:Et₂O, 8:2, v:v). ¹H NMR (400 MHz, CDCl₃) δ 7.12 (t, *J*=7.8 Hz, 1H), 6.92–6.84 (m, 2H), 3.92 (tt, *J*=8.5, 4.2 Hz, 1H), 2.85 (dd, *J*=13.7, 4.2 Hz, 1H), 2.66–2.54 (m, 3H), 1.83 (dddd, *J*=13.3,

12.1, 8.8, 6.6 Hz, 1H), 1.59 (tt, *J*=9.0, 6.9 Hz, 3H), 1.49–1.28 (m, 4H), 0.97–0.88 (m, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 162.6, 160.2, 143.8, 143.7, 131.6, 131.6, 124.1, 124.1, 122.7, 122.5, 115.4, 115.2, 69.9, 46.3, 37.6, 35.2, 33.4, 24.8, 23.5, 22.4, 22.2, 14.0; ¹⁹F NMR (375 MHz, CDCl₃) δ –118.6; HRMS (ESI-TOF) *m/z* calcd for C₁₆H₂₄F [M–H₂O+H]⁺ 235.1857, found 235.1876; IR (ATR) ν_{max}/cm⁻¹ 3334, 2954, 2926, 2868, 1627, 1508, 1465, 1458, 1118, 1026, 819.

3-[2-(4-Butyl-2-fluoro-phenyl)-1-hydroxy-ethyl]-benzotrile (3cd). Colorless oil (115 mg, yield 65%). R_f 0.16 (Petroleum Ether:Et₂O, 8:2, v:v). ¹H NMR (400 MHz, CDCl₃) δ 7.67–7.63 (m, 1H), 7.61–7.54 (m, 2H), 7.44 (td, *J*=7.8, 0.6 Hz, 1H), 7.01 (t, *J*=7.8 Hz, 1H), 6.91–6.84 (m, 2H), 4.98 (dd, *J*=8.5, 4.8 Hz, 1H), 3.06 (dd, *J*=13.8, 4.8 Hz, 1H), 2.92 (dd, *J*=13.8, 8.5 Hz, 1H), 2.61–2.55 (m, 2H), 1.87 (bs, 1H), 1.63–1.55 (m, 2H), 1.39–1.30 (m, 2H), 0.93 (t, *J*=7.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 162.5, 160.1, 145.4, 144.5, 144.4, 131.6, 131.6, 131.2, 130.4, 129.6, 129.1, 124.3, 124.2, 121.1, 121.0, 118.9, 115.4, 115.2, 112.3, 73.2, 39.3, 35.2, 33.3, 22.3, 14.0; ¹⁹F NMR (375 MHz, CDCl₃) δ –118.8; IR (ATR) ν_{max}/cm⁻¹ 3408, 2954, 2927, 2858, 2229, 1627, 1508, 1423, 1109, 1053, 810, 794; HRMS (ESI-TOF) *m/z* calcd for C₁₉H₂₀FNNaO [M+Na]⁺ 320.1421, found 320.1431.

1-(4-Butyl-2-methyl-phenyl)-4-methyl-pentan-2-ol (3da). Colorless oil (74 mg, yield 50%). R_f 0.62 (Petroleum Ether:Et₂O, 8:2, v:v). ¹H NMR (400 MHz, CDCl₃) δ 7.08 (d, *J*=7.6 Hz, 1H), 7.01–6.95 (m, 2H), 3.89 (tt, *J*=8.9, 3.9 Hz, 1H), 2.80 (dd, *J*=13.8, 3.9 Hz, 1H), 2.65–2.52 (m, 3H), 2.31 (s, 3H), 2.02 (bs, 1H), 1.90–1.80 (m, 1H), 1.64–1.48 (m, 4H), 1.40–1.29 (m, 3H), 0.98–0.90 (m, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 141.2, 136.5, 134.1, 130.8, 130.2, 126.1, 69.9, 46.5, 41.6, 35.3, 33.8, 24.9, 23.6, 22.6, 22.2, 19.8, 14.1; IR (ATR) ν_{max}/cm⁻¹ 3354, 2953, 2924, 2866, 1616, 1506, 1465, 1458, 1022, 819; HRMS (ESI-TOF) *m/z* calcd for C₁₇H₂₇ [M–H₂O+H]⁺ 231.2107, found 231.2081.

2-(4-Butyl-2-methyl-phenyl)-1-(4-chloro-phenyl)-ethanol (3de). Colorless oil (130 mg, yield 72%). R_f 0.35 (Petroleum Ether:Et₂O, 8:2, v:v). ¹H NMR (400 MHz, CDCl₃) δ 7.35–7.28 (m, 4H), 7.04 (d, *J*=7.6 Hz, 1H), 7.02–6.94 (m, 2H), 4.86 (dd, *J*=8.6, 4.8 Hz, 1H), 2.99 (dd, *J*=13.9, 4.8 Hz, 1H), 2.91 (dd, *J*=13.9, 8.7 Hz, 1H), 2.56 (t, *J*=7.8 Hz, 2H), 2.27 (s, 3H), 1.69–1.50 (m, 3H), 1.36 (h, *J*=7.3 Hz, 2H), 0.93 (t, *J*=7.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 142.7, 141.6, 136.6, 133.2, 133.0, 130.8, 130.3, 128.6, 127.3, 126.2, 73.8, 43.2, 35.3, 33.8, 22.6, 19.7, 14.1; IR (ATR) ν_{max}/cm⁻¹ 3327, 2956, 2920, 2854, 1618, 1492, 1442, 1051, 825, 690; HRMS (ESI-TOF) *m/z* calcd for C₁₉H₂₂ClO [M–H₂O+H]⁺ 285.1405, found 285.1409.

2-(4-Butyl-2-methoxy-phenyl)-1-o-tolyl-ethanol (3ef). White solid (122 mg, yield 69%). R_f 0.44 (Petroleum Ether:Et₂O, 8:2, v:v). mp. 80–82 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.61–7.55 (m, 1H), 7.24–7.22 (m, 1H), 7.19–7.11 (m, 2H), 7.04 (d, *J*=7.4 Hz, 1H), 6.77–6.69 (m, 2H), 5.16 (dd, *J*=9.3, 3.1 Hz, 1H), 3.86 (s, 3H), 3.06 (dd, *J*=13.7, 3.1 Hz, 1H), 2.80 (dd, *J*=13.7, 9.3 Hz, 1H), 2.63–2.57 (m, 2H), 2.36 (s, 3H), 1.66–1.56 (m, 3H), 1.42–1.33 (m, 2H), 0.94 (t, *J*=7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 157.7, 143.4, 143.0, 134.5, 131.4, 130.3, 127.1, 126.3, 125.2, 124.2, 120.8, 110.9, 70.8, 55.4, 40.2, 35.9, 33.8, 22.6, 19.0, 14.1; IR (ATR) ν_{max}/cm⁻¹ 3346, 2956, 2926,

2873, 2854, 1610, 1508, 1456, 1257, 1128, 1039, 817, 752; **HRMS (ESI-TOF)** m/z calcd for $C_{20}H_{25}O$ $[M-H_2O+H]^+$ 281.1900, found 281.1863.

1-(4-Butyl-2-methoxy-phenyl)-4-methyl-pentan-2-ol (3ea). Colorless oil (58 mg, yield 37%). R_f 0.40 (Petroleum Ether:Et₂O, 8:2, v:v). **¹H NMR** (400 MHz, CDCl₃) δ 7.05 (d, $J=7.5$ Hz, 1H), 6.74 (dd, $J=7.5, 1.6$ Hz, 1H), 6.70 (d, $J=1.6$ Hz, 1H), 3.91 (tdd, $J=8.4, 4.7, 3.5$ Hz, 1H), 3.83 (s, 3H), 2.86 (dd, $J=13.6, 3.5$ Hz, 1H), 2.64–2.57 (m, 3H), 1.88–1.79 (m, 1H), 1.65–1.57 (m, 2H), 1.50–1.26 (m, 5H), 0.97–0.91 (m, 9H); **¹³C NMR** (100 MHz, CDCl₃) δ 157.6, 143.0, 131.2, 124.5, 120.7, 110.9, 70.1, 55.4, 46.6, 39.0, 35.9, 33.8, 24.9, 23.4, 22.6, 22.4, 14.1; **IR** (ATR) ν_{max}/cm^{-1} 3385, 2953, 2926, 2868, 2856, 1612, 1508, 1463, 1458, 1257, 1130, 1039, 815; **HRMS (ESI-TOF)** m/z calcd for $C_{17}H_{27}O$ $[M-H_2O+H]^+$ 247.2056, found 247.2097.

1-(4-Butyl-3-methoxy-phenyl)-4-methyl-pentan-2-ol (3fa). Colorless oil (120 mg, yield 76%). R_f 0.36 (Petroleum Ether:Et₂O, 8:2, v:v). **¹H NMR** (400 MHz, CDCl₃) δ 7.07 (d, $J=7.5$ Hz, 1H), 6.74 (dd, $J=7.5, 1.6$ Hz, 1H), 6.70 (d, $J=1.6$ Hz, 1H), 3.89 (tt, $J=8.7, 4.0$ Hz, 1H), 3.82 (s, 3H), 2.80 (dd, $J=13.5, 4.0$ Hz, 1H), 2.63–2.54 (m, 3H), 1.85 (m, 1H), 1.62–1.44 (m, 4H), 1.42–1.28 (m, 3H), 1.00–0.90 (m, 9H); **¹³C NMR** (100 MHz, CDCl₃) δ 157.6, 137.3, 129.9, 129.5, 121.2, 111.6, 70.7, 55.4, 46.2, 44.7, 32.2, 29.6, 24.8, 23.6, 22.8, 22.2, 14.1; **IR** (ATR) ν_{max}/cm^{-1} 3354, 2953, 2926, 2868, 2858, 1610, 1506, 1463, 1458, 1251, 1134, 1041, 813; **HRMS (ESI-TOF)** m/z calcd for $C_{17}H_{28}NaO_2$ $[M+Na]^+$ 287.982, found 287.1941.

2-(4-Butyl-3-methoxy-phenyl)-1-(4-tert-butyl-phenyl)-ethanol (3fg). Colorless oil (162 mg, yield 80%). R_f 0.42 (Petroleum Ether:Et₂O, 8:2, v:v). **¹H NMR** (400 MHz, CDCl₃) δ 7.41–7.37 (m, 2H), 7.35–7.30 (m, 2H), 7.07 (d, $J=7.5$ Hz, 1H), 6.78 (dd, $J=7.5, 1.6$ Hz, 1H), 6.61 (d, $J=1.6$ Hz, 1H), 4.87 (dd, $J=8.7, 4.5$ Hz, 1H), 3.75 (s, 3H), 3.03 (dd, $J=13.7, 4.5$ Hz, 1H), 2.94 (dd, $J=13.7, 8.7$ Hz, 1H), 2.58 (t, $J=7.6$ Hz, 2H), 1.86 (bs, 1H), 1.59–1.51 (m, 2H), 1.42–1.34 (m, 2H), 1.33 (s, 9H), 0.93 (t, $J=7.3$ Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 157.49, 150.51, 141.08, 136.89, 129.78, 129.61, 125.79, 125.33, 121.34, 111.71, 75.13, 55.26, 46.12, 34.60, 32.18, 31.48, 29.63, 22.74, 14.13; **IR** (ATR) ν_{max}/cm^{-1} 3361, 2953, 2926, 2868, 2860, 1610, 1508, 1458, 1253, 1134, 1041, 829, 804. **HRMS (ESI-TOF)** m/z calcd for $C_{23}H_{31}O$ $[M-H_2O+H]^+$ 323.2369, found 323.2385.

1-(4-Bromo-phenyl)-2-(4-butyl-3-methoxymethoxy-phenyl)-ethanol (3gh). Colorless oil (178 mg, yield 76%). R_f 0.16 (Petroleum Ether:Et₂O, 8:2, v:v). **¹H NMR** (400 MHz, CDCl₃) δ 7.49–7.42 (m, 2H), 7.21 (dt, $J=7.9, 0.7$ Hz, 2H), 7.09 (d, $J=7.6$ Hz, 1H), 6.83 (d, $J=1.6$ Hz, 1H), 6.77 (dd, $J=7.6, 1.6$ Hz, 1H), 5.14 (s, 2H), 4.82 (dd, $J=8.3, 4.9$ Hz, 1H), 3.47 (s, 3H), 2.96 (dd, $J=13.6, 4.9$ Hz, 1H), 2.89 (dd, $J=13.6, 8.3$ Hz, 1H), 2.66–2.58 (m, 2H), 2.22 (bs, 1H), 1.62–1.54 (m, 2H), 1.38 (dt, $J=14.4, 7.3$ Hz, 2H), 0.96 (t, $J=7.3$ Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 155.3, 142.9, 136.2, 131.5, 130.5, 130.1, 127.8, 122.7, 121.3, 115.1, 94.5, 74.6, 56.1, 46.1, 32.4, 29.7, 22.7, 14.1; **IR** (ATR) ν_{max}/cm^{-1} 3327, 2954, 2922, 2856, 2821, 1610, 1506, 1458, 1240, 1151, 1124, 1068, 1004, 923, 821, 807, 516; **HRMS (ESI-TOF)** m/z calcd for $C_{20}H_{24}BrO_2$ $[M-H_2O+H]^+$ 375.0954, found 375.0943.

1-(4-Butyl-3-methoxymethoxy-phenyl)-4-methyl-pentan-2-ol (3ga). Colorless oil (67 mg, yield 38%). R_f 0.28 (Petroleum Ether:Et₂O, 8:2, v:v). **¹H NMR** (400 MHz, CDCl₃) δ 7.08 (d, $J=7.6$ Hz, 1H), 6.91 (d, $J=1.6$ Hz, 1H), 6.80 (dd, $J=7.6, 1.6$ Hz, 1H), 5.23–5.16 (m, 2H), 3.88 (tt, $J=8.5, 4.1$ Hz, 1H), 3.49 (s, 3H), 2.77 (dd, $J=13.6, 4.0$ Hz, 1H), 2.65–2.53 (m, 3H), 1.90–1.78 (m, 1H), 1.70 (bs, 1H), 1.62–1.54 (m, 2H), 1.49–1.27 (m, 4H), 0.97–0.91 (m, 9H); **¹³C NMR** (100 MHz, CDCl₃) δ 155.3, 137.4, 130.2, 130.1, 122.6, 115.1, 94.5, 70.7, 56.1, 46.2, 44.6, 32.4, 29.8, 24.8, 23.6, 22.7, 22.2, 14.1; **IR** (ATR) ν_{max}/cm^{-1} 3404, 2953, 2926, 2868, 2825, 1612, 1506, 1465, 1458, 1246, 1153, 1126, 1072, 1010, 921, 815; **HRMS (ESI-TOF)** m/z calcd for $C_{18}H_{30}NaO_3$ $[M+Na]^+$ 317.2087, found 317.2072.

1-(4-Butyl-3-chloro-phenyl)-4-methyl-pentan-2-ol (3ha). Colorless oil (80 mg, yield 50%). R_f 0.43 (Petroleum Ether:Et₂O, 8:2, v:v). **¹H NMR** (400 MHz, CDCl₃) δ 7.20 (d, $J=1.7$ Hz, 1H), 7.15 (d, $J=7.7$ Hz, 1H), 7.03 (dd, $J=7.7, 1.7$ Hz, 1H), 3.87 (tt, $J=8.5, 4.1$ Hz, 1H), 2.77–2.67 (m, 3H), 2.57 (dd, $J=13.7, 8.5$ Hz, 1H), 1.87–1.76 (m, 1H), 1.63–1.55 (m, 2H), 1.49–1.27 (m, 5H), 0.97–0.90 (m, 9H); **¹³C NMR** (100 MHz, CDCl₃) δ 138.5, 138.0, 134.0, 130.4, 130.3, 127.9, 70.6, 46.2, 43.9, 33.1, 32.1, 24.8, 23.5, 22.6, 22.2, 14.1; **IR** (ATR) ν_{max}/cm^{-1} 3336, 2953, 2926, 2868, 1608, 1490, 1465, 1458, 1047, 817, 690; **HRMS (ESI-TOF)** m/z calcd for $C_{16}H_{25}ClNaO$ $[M+Na]^+$ 291.1486, found 291.1480.

2-(4-Butyl-3-chloro-phenyl)-1-phenyl-ethanol (3hc). Colorless oil (111 mg, yield 65%). R_f 0.54 (Petroleum Ether:Et₂O, 8:2, v:v). **¹H NMR** (400 MHz, CDCl₃) δ 7.36 (d, $J=4.4$ Hz, 4H), 7.33–7.28 (m, 1H), 7.21 (d, $J=1.8$ Hz, 1H), 7.13 (d, $J=7.7$ Hz, 1H), 7.00 (dd, $J=7.7, 1.8$ Hz, 1H), 4.88 (dd, $J=8.2, 5.0$ Hz, 1H), 3.00–2.90 (m, 2H), 2.70 (dd, $J=8.6, 7.0$ Hz, 2H), 1.79 (s, 1H), 1.63–1.55 (m, 2H), 1.43–1.34 (m, 2H), 0.95 (t, $J=7.4$ Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 143.8, 138.6, 137.4, 133.9, 130.4, 130.3, 128.6, 128.0, 127.8, 126.0, 75.2, 45.3, 33.1, 32.1, 22.6, 14.1; **IR** (ATR) ν_{max}/cm^{-1} 3356, 2954, 2926, 2860, 1606, 1490, 1456, 1047, 810, 754, 698, 690; **HRMS (ESI-TOF)** m/z calcd for $C_{18}H_{20}Cl$ $[M-H_2O+H]^+$ 271.1248, found 271.1244.

1-(4-Bromo-phenyl)-2-(4-butyl-3-chloro-phenyl)-ethanol (3hh). Colorless oil (158 mg, yield 72%). R_f 0.36 (Petroleum Ether:Et₂O, 8:2, v:v). **¹H NMR** (400 MHz, CDCl₃) δ 7.47 (d, $J=8.4$ Hz, 2H), 7.24–7.18 (m, 3H), 7.13 (d, $J=7.8$ Hz, 1H), 6.97 (dd, $J=7.8, 1.8$ Hz, 1H), 4.84 (dd, $J=8.3, 4.9$ Hz, 1H), 2.96–2.84 (m, 2H), 2.73–2.66 (m, 2H), 1.83 (bs, 1H), 1.63–1.55 (m, 2H), 1.38 (dt, $J=14.6, 7.3$ Hz, 2H), 0.95 (t, $J=7.3$ Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 142.7, 138.7, 136.9, 133.9, 131.5, 130.3, 130.3, 127.9, 127.7, 121.5, 74.5, 45.1, 33.0, 32.0, 22.6, 14.0; **IR** (ATR) ν_{max}/cm^{-1} 3307, 2958, 2922, 2858, 1593, 1489, 1456, 1049, 821, 690, 594; **HRMS (ESI-TOF)** m/z calcd for $C_{18}H_{19}BrCl$ $[M-H_2O+H]^+$ 349.0353, found 349.0323.

1-(3-Bromo-4-butyl-phenyl)-4-methyl-pentan-2-ol (3ia). Colorless oil (112 mg, yield 60%). R_f 0.52 (Petroleum Ether:Et₂O, 8:2, v:v). **¹H NMR** (400 MHz, CDCl₃) δ 7.40 (d, $J=1.8$ Hz, 1H), 7.15 (d, $J=7.7$ Hz, 1H), 7.08 (dd, $J=7.7, 1.8$ Hz, 1H), 3.87 (tt, $J=8.5, 4.1$ Hz, 1H), 2.77–2.67 (m, 3H), 2.56 (dd, $J=13.7, 8.5$ Hz, 1H), 1.87–1.77 (m, 1H), 1.62–1.55 (m, 2H), 1.49–1.27 (m, 5H), 0.98–0.90 (m, 9H); **¹³C NMR** (100 MHz, CDCl₃) δ 140.2, 138.3, 133.6, 130.4, 128.6, 124.6, 70.7, 46.2, 43.8,

35.6, 32.3, 24.8, 23.6, 22.6, 22.2, 14.1; **IR** (ATR) $\nu_{\max}/\text{cm}^{-1}$ 3336, 2953, 2924, 2860, 1604, 1489, 1465, 1458, 1037, 817, 675; **HRMS (ESI-TOF)** m/z calcd for $\text{C}_{16}\text{H}_{25}\text{BrNaO}$ [$\text{M} + \text{Na}$] $^{+}$ 335.0981, found 335.0966.

4-[2-(3-Bromo-4-butyl-phenyl)-1-hydroxy-ethyl]-benzotriazole (3il). Colorless oil (167 mg, yield 78%). R_f 0.38 (Petroleum Ether: Et_2O , 6:4, v:v). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.64 (d, $J=8.3$ Hz, 2H), 7.48–7.43 (m, 2H), 7.37 (d, $J=1.8$ Hz, 1H), 7.14 (d, $J=7.7$ Hz, 1H), 7.00 (dd, $J=7.7$, 1.8 Hz, 1H), 4.94 (dt, $J=8.6$, 4.5 Hz, 1H), 2.96 (dd, $J=13.8$, 4.5 Hz, 1H), 2.87 (dd, $J=13.8$, 8.6 Hz, 1H), 2.74–2.67 (m, 2H), 2.01 (s, $J=3.2$ Hz, 1H), 1.62–1.54 (m, 2H), 1.44–1.35 (m, 2H), 0.95 (t, $J=7.3$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 148.9, 140.9, 136.5, 133.7, 132.4, 130.5, 128.6, 126.7, 124.7, 118.9, 111.6, 74.5, 45.2, 35.6, 32.2, 22.6, 14.1; **IR** (ATR) $\nu_{\max}/\text{cm}^{-1}$ 3442, 2953, 2926, 2858, 2227, 1606, 1489, 1400, 1037, 831, 673; **HRMS (ESI-TOF)** m/z calcd for $\text{C}_{19}\text{H}_{19}\text{BrN}$ [$\text{M} - \text{H}_2\text{O} + \text{H}$] $^{+}$ 340.0695, found 340.0698.

1-(4-Butyl-3-methyl-phenyl)-4-methyl-pentan-2-ol (3ja). Colorless oil (108 mg, yield 73%). R_f 0.55 (Petroleum Ether: Et_2O , 8:2, v:v). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.08 (d, $J=7.6$ Hz, 1H), 6.97 (d, $J=7.6$ Hz, 2H), 3.87 (ddd, $J=12.8$, 8.8, 3.9 Hz, 1H), 2.76 (dd, $J=13.6$, 3.9 Hz, 1H), 2.63–2.47 (m, 3H), 2.29 (s, 3H), 1.93–1.76 (m, 1H), 1.61–1.53 (m, 3H), 1.50–1.40 (m, 3H), 1.36–1.30 (m, 1H), 0.97–0.91 (m, 9H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 139.3, 136.1, 135.9, 131.3, 129.1, 126.9, 70.7, 46.2, 44.2, 32.8, 32.6, 24.8, 23.6, 22.9, 22.2, 19.4, 14.1; **IR** (ATR) $\nu_{\max}/\text{cm}^{-1}$ 3356, 2953, 2926, 2866, 1616, 1506, 1465, 1458, 1028, 819; **HRMS (ESI-TOF)** m/z calcd for $\text{C}_{17}\text{H}_{27}$ [$\text{M} - \text{H}_2\text{O} + \text{H}$] $^{+}$ 231.2107, found 231.2107.

2-(4-Butyl-3-methyl-phenyl)-1-naphthalen-2-yl-ethanol (3jj). White solid (157 mg, yield 83%). R_f 0.37 (Petroleum Ether: Et_2O , 8:2, v:v). mp. 52–54 °C. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.88–7.81 (m, 4H), 7.54 (dd, $J=8.5$, 1.7 Hz, 1H), 7.51–7.43 (m, 2H), 7.12–6.97 (m, 3H), 5.05 (dd, $J=9.2$, 4.1 Hz, 1H), 3.09 (dd, $J=13.8$, 4.1 Hz, 1H), 2.96 (dd, $J=13.8$, 9.2 Hz, 1H), 2.63–2.53 (m, 2H), 2.29 (s, 3H), 1.61–1.51 (m, 2H), 1.40 (dq, $J=14.3$, 7.2 Hz, 2H), 0.95 (t, $J=7.3$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 141.6, 139.7, 136.3, 135.3, 133.5, 133.1, 131.4, 129.3, 128.3, 128.1, 127.8, 127.0, 126.2, 125.9, 124.7, 124.3, 75.5, 45.93, 32.8, 32.6, 22.9, 19.4, 14.2; **IR** (ATR) $\nu_{\max}/\text{cm}^{-1}$ 3290, 2956, 2920, 2870, 1597, 1506, 1456, 1051, 823, 817, 742; **HRMS (ESI-TOF)** m/z calcd for $\text{C}_{23}\text{H}_{26}\text{NaO}$ [$\text{M} + \text{Na}$] $^{+}$ 341.1876, found 341.1880.

1-(6-Butyl-biphenyl-3-yl)-4-methyl-pentan-2-ol (3ka). Colorless oil (92 mg, yield 50%). R_f 0.54 (Petroleum Ether: Et_2O , 8:2, v:v). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.45–7.29 (m, 5H), 7.25 (d, $J=7.8$ Hz, 1H), 7.17 (dd, $J=7.8$, 1.9 Hz, 1H), 7.08 (d, $J=1.9$ Hz, 1H), 3.93 (tt, $J=8.5$, 4.0 Hz, 1H), 2.83 (dd, $J=13.6$, 4.0 Hz, 1H), 2.66–2.55 (m, 3H), 1.86 (dddd, $J=13.4$, 12.2, 8.7, 6.6 Hz, 1H), 1.53–1.44 (m, 3H), 1.38–1.31 (m, 1H), 1.24 (q, $J=7.4$ Hz, 2H), 0.95 (dd, $J=10.7$, 6.6 Hz, 6H), 0.81 (t, $J=7.3$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 142.2, 142.1, 138.6, 135.8, 131.1, 129.6, 129.4, 128.5, 128.1, 126.8, 70.8, 46.3, 44.3, 33.7, 32.5, 24.9, 23.6, 22.6, 22.2, 14.0; **IR** (ATR) $\nu_{\max}/\text{cm}^{-1}$ 3348, 2953, 2924, 2866, 1600, 1487, 1465, 1458, 1022, 821, 758, 700; **HRMS (ESI-TOF)** m/z calcd for $\text{C}_{22}\text{H}_{29}$ [$\text{M} - \text{H}_2\text{O} + \text{H}$] $^{+}$ 293.2264, found 293.2274.

2-(6-Butyl-biphenyl-3-yl)-1-(4-chloro-phenyl)-ethanol (3ke). Colorless oil (164 mg, yield 75%). R_f 0.41 (Petroleum Ether: Et_2O , 8:2, v:v). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.47–7.25 (m, 10H), 7.16 (dd, $J=7.8$, 2.0 Hz, 1H), 7.03 (d, $J=2.0$ Hz, 1H), 4.92 (dd, $J=8.5$, 4.8 Hz, 1H), 3.03 (dd, $J=13.7$, 4.8 Hz, 1H), 2.96 (dd, $J=13.7$, 8.5 Hz, 1H), 2.63–2.56 (m, 2H), 2.03 (bs, 1H), 1.52–1.44 (m, 2H), 1.29–1.22 (m, 2H), 0.87–0.81 (m, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 142.5, 142.2, 141.9, 139.0, 134.7, 133.3, 131.3, 129.6, 129.3, 128.6, 128.5, 128.1, 127.4, 126.9, 74.7, 45.9, 33.7, 32.5, 22.6, 14.0; **IR** (ATR) $\nu_{\max}/\text{cm}^{-1}$ 3340, 2953, 2924, 2858, 1598, 1487, 1012, 827, 758, 700, 542; **HRMS (ESI-TOF)** m/z calcd for $\text{C}_{24}\text{H}_{25}\text{ClNaO}$ [$\text{M} + \text{Na}$] $^{+}$ 387.1486, found 387.1482.

1-(4-Butyl-3-thiophen-2-yl-phenyl)-4-methyl-pentan-2-ol (3la). Colorless oil (114 mg, yield 60%). R_f 0.44 (Petroleum Ether: Et_2O , 8:2, v:v). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.36 (dd, $J=5.1$, 1.2 Hz, 1H), 7.25 (d, $J=7.8$ Hz, 2H), 7.17 (d, $J=7.8$ Hz, 1H), 7.10 (dd, $J=5.1$, 3.5 Hz, 1H), 7.04 (dd, $J=3.5$, 1.2 Hz, 1H), 3.93 (tt, $J=9.4$, 4.7 Hz, 1H), 2.83 (dd, $J=13.7$, 3.9 Hz, 1H), 2.75–2.68 (m, 2H), 2.63 (dd, $J=13.7$, 8.6 Hz, 1H), 1.91–1.80 (m, 1H), 1.58–1.47 (m, 4H), 1.39–1.28 (m, 3H), 0.96 (dd, $J=10.5$, 6.6 Hz, 6H), 0.89 (t, $J=7.3$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 143.0, 139.6, 136.0, 134.2, 132.1, 130.0, 129.2, 127.1, 126.5, 125.2, 70.7, 46.3, 44.1, 33.9, 33.0, 24.9, 23.6, 22.8, 22.2, 14.0; **IR** (ATR) $\nu_{\max}/\text{cm}^{-1}$ 3381, 2953, 2926, 2866, 1608, 1490, 1465, 1438, 1028, 827, 692; **HRMS (ESI-TOF)** m/z calcd for $\text{C}_{20}\text{H}_{27}\text{S}$ [$\text{M} - \text{H}_2\text{O} + \text{H}$] $^{+}$ 299.1828, found 299.1823.

2-(4-Butyl-3-thiophen-2-yl-phenyl)-1-(2-ethyl-phenyl)-ethanol (3lk). Colorless oil (137 mg, yield 63%). R_f 0.45 (Petroleum Ether: Et_2O , 8:2, v:v). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.58 (dd, $J=7.2$, 2.1 Hz, 1H), 7.34 (dd, $J=5.1$, 1.2 Hz, 1H), 7.29–7.23 (m, 2H), 7.23–7.20 (m, 2H), 7.18 (ddd, $J=6.5$, 3.9, 1.8 Hz, 2H), 7.08 (dd, $J=5.1$, 3.5 Hz, 1H), 6.99 (dd, $J=3.5$, 1.2 Hz, 1H), 5.18 (ddd, $J=7.7$, 4.6, 2.9 Hz, 1H), 3.05–2.91 (m, 2H), 2.72–2.56 (m, 4H), 1.87 (d, $J=2.9$ Hz, 1H), 1.56–1.47 (m, 2H), 1.35–1.27 (m, 2H), 1.20 (t, $J=7.6$ Hz, 3H), 0.86 (t, $J=7.3$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 143.0, 141.5, 140.7, 139.8, 135.8, 134.1, 132.1, 129.9, 129.2, 128.6, 127.7, 127.0, 126.5, 126.4, 125.7, 125.2, 71.2, 45.2, 33.9, 33.0, 25.3, 22.7, 15.7, 14.0; **IR** (ATR) $\nu_{\max}/\text{cm}^{-1}$ 3336, 2954, 2926, 2870, 1608, 1489, 1456, 1037, 829, 754, 692; **HRMS (ESI-TOF)** m/z calcd for $\text{C}_{24}\text{H}_{27}\text{S}$ [$\text{M} - \text{H}_2\text{O} + \text{H}$] $^{+}$ 347.1828, found 347.1888.

1-(4-Butyl-naphthalen-1-yl)-4-methyl-pentan-2-ol (3ma). Colorless oil (90 mg, yield 53%). R_f 0.47 (Petroleum Ether: Et_2O , 8:2, v:v). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.14–8.03 (m, 2H), 7.57–7.49 (m, 2H), 7.31–7.26 (m, 2H), 4.05 (tt, $J=9.0$, 3.8 Hz, 1H), 3.33 (dd, $J=14.0$, 3.8 Hz, 1H), 3.06 (t, $J=7.8$ Hz, 2H), 2.98 (dd, $J=14.0$, 9.0 Hz, 1H), 1.90 (dddd, $J=13.3$, 12.0, 5.9, 3.9 Hz, 1H), 1.78–1.70 (m, 2H), 1.65–1.57 (m, 1H), 1.52–1.43 (m, 4H), 1.02–0.96 (m, 6H), 0.93 (d, $J=6.5$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 138.2, 132.9, 132.7, 132.6, 127.5, 125.6, 125.5, 125.5, 124.8, 124.6, 70.1, 46.7, 41.9, 33.1, 33.0, 24.9, 23.7, 23.0, 22.2, 14.1; **IR** (ATR) $\nu_{\max}/\text{cm}^{-1}$ 3292, 2953, 2924, 2866, 1595, 1508, 1463, 1458, 1026, 817, 748; **HRMS (ESI-TOF)** m/z calcd for $\text{C}_{20}\text{H}_{28}\text{NaO}$ [$\text{M} + \text{Na}$] $^{+}$ 307.2032, found 307.2036.

2-(4-butyl-naphthalen-1-yl)-1-(4-chlorophenyl)ethan-1-ol (3me). White solid (100 mg, yield 50%). R_f 0.41 (Petroleum

Ether:Et₂O, 8:2, v:v). mp. 90–92 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.17–8.05 (m, 2H), 7.61–7.49 (m, 2H), 7.40–7.30 (m, 4H), 7.26–7.20 (m, 2H), 5.04 (dd, *J*=9.0, 4.3 Hz, 1H), 3.49 (dd, *J*=14.1, 4.3 Hz, 1H), 3.30 (dd, *J*=14.1, 9.0 Hz, 1H), 3.06 (t, *J*=7.8 Hz, 2H), 1.92 (bs, 1H), 1.73 (p, *J*=7.8 Hz, 2H), 1.47 (s, *J*=7.4 Hz, 2H), 0.98 (t, *J*=7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 142.7, 138.7, 133.3, 132.6, 132.5, 131.7, 128.7, 127.8, 127.3, 125.8, 125.6, 125.6, 125.0, 124.4, 73.8, 43.6, 33.1, 33.0, 23.0, 14.1; IR (ATR) $\nu_{\max}/\text{cm}^{-1}$ 3365, 2956, 2920, 2854, 1492, 1456, 1051, 827, 777, 540; HRMS (ESI-TOF) *m/z* calcd for C₂₂H₂₂Cl [M–H₂O+H]⁺ 321.1405, found 321.1396.

2-chlorobenzyl methanesulfonate (4).^[26a] Colorless oil (77 mg, yield 59%). R_f 0.08 (Petroleum Ether:Et₂O, 8:2, v:v). ¹H NMR (400 MHz, CDCl₃) δ 7.52–7.49 (m, 1H), 7.45–7.41 (m, 1H), 7.37–7.30 (m, 2H), 5.35 (s, 2H), 3.02 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 134.2, 131.3, 130.9, 130.8, 129.9, 127.4, 68.8, 38.1.

diethyl (naphthalen-1-ylmethyl) phosphate (13).^[26b] Colorless oil (106 mg, yield 60%). R_f 0.03 (in Petroleum Ether:Et₂O, 8:2, v:v). ¹H NMR (400 MHz, CDCl₃) δ 8.14–8.09 (m, 1H), 7.87 (tt, *J*=8.4, 1.0 Hz, 2H), 7.60–7.43 (m, 4H), 5.53 (d, *J*=7.8 Hz, 2H), 4.06 (dq, *J*=7.8, 7.1, 3.1 Hz, 4H), 1.26 (td, *J*=7.1, 1.0 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 133.7, 131.6, 131.6, 131.4, 129.6, 128.6, 127.1, 126.6, 126.0, 125.2, 123.5, 67.5, 67.5, 63.9, 63.8, 16.1, 16.0.

1-(4-(tert-butyl)-2-chlorophenyl)butan-2-ol (3bl). Colorless oil (77 mg, yield 54%). R_f 0.37 (in Petroleum Ether:Et₂O, 8:2, v:v). ¹H NMR (400 MHz, CDCl₃) δ 7.37 (d, *J*=1.8 Hz, 1H), 7.25–7.17 (m, 2H), 3.92–3.76 (m, 1H), 2.99 (dd, *J*=13.7, 4.1 Hz, 1H), 2.71 (dd, *J*=13.7, 8.6 Hz, 1H), 1.66–1.53 (m, 2H), 1.52 (bs, 1H), 1.30 (s, 9H), 1.02 (t, *J*=7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 151.5, 134.1, 133.5, 131.4, 126.8, 124.0, 72.7, 40.9, 34.7, 31.3, 30.0, 10.1; IR (ATR) $\nu_{\max}/\text{cm}^{-1}$ 3211, 2954, 2922, 2870, 1608, 1489, 1462, 1388, 1361, 1056, 873, 813, 621; HRMS (ESI-TOF) *m/z* calcd for C₁₄H₂₁ClNaO [M+Na]⁺ 263.1173, found 263.1169.

1-(4-(tert-butyl)-2-chlorophenyl)pentan-2-ol (3bm). Colorless oil (91 mg, yield 60%). R_f 0.45 (in Petroleum Ether:Et₂O, 8:2, v:v). ¹H NMR (400 MHz, CDCl₃) δ 7.37 (d, *J*=1.8 Hz, 1H), 7.25–7.16 (m, 2H), 3.92 (ddd, *J*=12.5, 5.1, 3.3 Hz, 1H), 2.99 (dd, *J*=13.7, 3.9 Hz, 1H), 2.70 (dd, *J*=13.7, 8.7 Hz, 1H), 1.61–1.45 (m, 5H), 1.30 (s, 9H), 0.95 (t, *J*=6.9 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 151.5, 134.1, 133.5, 131.5, 126.8, 124.0, 71.1, 41.4, 39.4, 34.7, 31.3, 19.0, 14.2; IR (ATR) $\nu_{\max}/\text{cm}^{-1}$ 3242, 2954, 2924, 2868, 1608, 1489, 1462, 1388, 1361, 1047, 875, 813, 623; HRMS (ESI-TOF) *m/z* calcd for C₁₅H₂₂Cl [M–H₂O+H]⁺ 237.1405, found 237.1414.

1-(3-chloro-4-isobutylphenyl)-3-phenylpropan-2-ol (3hn). Colorless oil (105 mg, yield 58%). R_f 0.50 (in Petroleum Ether:Et₂O, 8:2, v:v). ¹H NMR (400 MHz, CDCl₃) δ 7.36–7.28 (m, 2H), 7.26–7.21 (m, 4H), 7.11 (d, *J*=7.7 Hz, 1H), 7.04 (dd, *J*=7.7, 1.8 Hz, 1H), 4.05 (tt, *J*=8.2, 4.6 Hz, 1H), 2.91–2.65 (m, 4H), 2.57 (d, *J*=7.2 Hz, 2H), 2.01–1.91 (m, 1H), 0.92 (d, *J*=6.6 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 138.4, 137.9, 137.4, 134.3, 131.4, 130.3, 129.5, 128.7, 127.6, 126.7, 73.4, 43.6, 42.6, 42.4, 28.9, 22.5, 22.5; IR (ATR) $\nu_{\max}/\text{cm}^{-1}$ 3387, 2953, 2920, 2866, 1604, 1490, 1402, 1382, 1047, 885, 833,

744, 698; HRMS (ESI-TOF) *m/z* calcd for C₁₉H₂₃ClNaO [M+Na]⁺ 325.1330, found 325.1321.

1-(2-chloro-4-hexylphenyl)-3-phenylpropan-2-ol (3bn). Colorless oil (102 mg, yield 52%). R_f 0.33 (in Petroleum Ether:Et₂O, 9:1, v:v). ¹H NMR (400 MHz, CDCl₃) δ 7.34–7.28 (m, 2H), 7.26–7.20 (m, 3H), 7.20–7.16 (m, 2H), 7.01 (dd, *J*=7.8, 1.7 Hz, 1H), 4.16 (tt, *J*=8.5, 4.4 Hz, 1H), 3.03 (dd, *J*=13.7, 4.4 Hz, 1H), 2.90 (dd, *J*=13.7, 4.3 Hz, 1H), 2.81 (ddd, *J*=18.2, 13.7, 8.4 Hz, 2H), 2.59–2.51 (m, 2H), 1.62–1.55 (m, 3H), 1.38–1.22 (m, 6H), 0.92–0.84 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 143.1, 138.4, 134.0, 133.3, 131.5, 129.4, 128.5, 126.9, 126.5, 72.1, 43.6, 40.7, 35.2, 31.7, 31.2, 28.9, 22.6, 14.1; IR (ATR) $\nu_{\max}/\text{cm}^{-1}$ 3385, 2953, 2924, 2854, 1604, 1492, 1454, 1049, 887, 821, 742, 698; HRMS (ESI-TOF) *m/z* calcd for C₂₁H₂₇ClNaO [M+Na]⁺ 353.1643, found 353.1628.

2-chloro-4-(1-hydroxybutyl)benzylmethanesulfonate (5). Colorless oil (82 mg, yield 47%). R_f 0.17 (in Petroleum Ether:EtOAc, 8:2, v:v). ¹H NMR (400 MHz, CDCl₃) δ 7.48–7.44 (m, 2H), 7.28 (dd, *J*=8.0, 1.7 Hz, 1H), 5.33 (s, 2H), 4.71 (dd, *J*=5.5, 2.2 Hz, 1H), 3.02 (s, 3H), 1.84 (bs, 1H), 1.80–1.70 (m, 2H), 1.47–1.39 (m, 2H), 0.94 (t, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 148.4, 134.3, 131.0, 130.1, 127.3, 124.8, 73.4, 68.7, 41.3, 38.1, 18.9, 14.0; IR (ATR) $\nu_{\max}/\text{cm}^{-1}$ 3356, 2956, 2931, 2870, 1608, 1458, 1350, 1170, 1053, 927, 825, 694; HRMS (ESI-TOF) *m/z* calcd for C₁₂H₁₇ClNaO₄S [M+Na]⁺ 315.0428, found 315.0395.

1-(3-chloro-4-methylphenyl)butan-2-ol (3hl). Colorless oil (36 mg, yield 31%). R_f 0.20 (in Petroleum Ether:Et₂O, 9:1, v:v). ¹H NMR (400 MHz, CDCl₃) δ 7.21 (d, *J*=1.8 Hz, 1H), 7.16 (dd, *J*=7.7, 0.8 Hz, 1H), 7.01 (dd, *J*=7.7, 1.8 Hz, 1H), 3.76–3.70 (m, 1H), 2.77 (dd, *J*=13.7, 4.4 Hz, 1H), 2.60 (dd, *J*=13.7, 8.3 Hz, 1H), 2.34 (s, 3H), 1.56–1.48 (m, 3H), 0.99 (t, *J*=7.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 138.1, 134.4, 134.1, 131.1, 130.0, 127.8, 74.0, 42.9, 29.8, 19.7, 10.1; IR (ATR) $\nu_{\max}/\text{cm}^{-1}$ 3338, 2960, 2922, 2875, 1610, 1496, 1442, 1049, 877, 810, 690; HRMS (ESI-TOF) *m/z* calcd for C₁₁H₁₄Cl [M–H₂O+H]⁺ 181.0779, found 181.0776.

Acknowledgements

The authors thank the French “Agence Nationale de Recherche” (ANR-19-CE07-0032) for financial support and grants to A.P. The L2CM is grateful to F. Dupire (MASSLOR Platform) for mass spectrometry analyses as well as the “Plateforme de RMN de l’Institut Jean Barriol, Université de Lorraine”.

References

- [1] a) B. Ramadoss, Y. Jin, S. Asako, L. Ilies, *Science* **2022**, 375, 658–663; b) L. Guillemard, N. Kaplaneris, L. Ackermann, M. J. Johansson, *Nat. Chem. Rev.* **2021**, 5, 522–545; c) S. Bag, T. Patra, A. Modak, A. Deb, S. Maity, U. Dutta, A. Dey, R. Kancherla, A. Maji, A. Hazra, M. Bera, D. Maiti, *J. Am. Chem. Soc.* **2015**, 137, 11888–11891.
- [2] R. Breslow, *Chem. Soc. Rev.* **1972**, 1, 553–580.

- [3] a) H. Shi, Y. Lu, J. Weng, K. L. Bay, X. Chen, K. Tanaka, P. Verma, K. N. Houk, J.-Q. Yu, *Nat. Chem.* **2020**, *12*, 399–404; b) B. Wang, Y. Zhou, N. Xu, X. Xu, X. Xu, Z. Jin, *Org. Lett.* **2019**, *21*, 1885–1889; c) Y. Zheng, W. Song, Y. Zhu, B. Wie, L. Xuan, *J. Org. Chem.* **2018**, *83*, 2448–2454; d) B. F. Van Steijvoort, N. Kaval, A. A. Kulago, B. U. W. Maes, *ACS Catal.* **2016**, *6*, 4486–4490; e) J. Li, S. Warratz, D. Zell, S. De Sarkar, E. E. Ishikawa, L. Ackermann, *J. Am. Chem. Soc.* **2015**, *137*, 13894–13901; f) R.-Y. Tang, G. Li, J.-Q. Yu, *Nature* **2014**, *507*, 215–220; g) D. Leow, G. Li, T.-S. Mei, J.-Q. Yu, *Nature* **2012**, *486*, 518–522.
- [4] W. A. Golding, R. J. Phipps, *Chem. Sci.* **2020**, *11*, 3022–3027, and references cited therein.
- [5] A. Vasseur, J. Bruffaerts, I. Marek, *Nat. Chem.* **2016**, *8*, 209–219.
- [6] a) T. Miyakoshi, N. E. Niggli, O. Baudoin, *Angew. Chem. Int. Ed.* **2022**, *61*, DOI: 10.1002/anie.202116101; *Angew. Chem.* **2022**, *134*, DOI: 10.1002/ange.202116101; b) F. Shi, R. Larock, *Top. Curr. Chem.* **2009**, *292*, 123–164; c) Q. Huang, M. A. Campo, T. Yao, Q. Tian, R. C. Larock, *J. Org. Chem.* **2004**, *69*, 8251–8257.
- [7] a) I. Massad, R. Suresh, L. Segura, I. Marek, *Nat. Synthesis* **2022**, *1*, 37–48; b) H. E. Bonfield, D. Valette, D. M. Lindsay, M. Reid, *Chem. Eur. J.* **2021**, *27*, 158–174; c) H. Sommer, F. Juliá-Hernández, R. Martin, I. Marek, *ACS Cent. Sci.* **2018**, *4*, 153–165; d) I. Franzoni, C. Mazet, *Org. Biomol. Chem.* **2014**, *12*, 233–241.
- [8] a) E. Nobile, T. Castanheiro, T. Besset, *Angew. Chem. Int. Ed.* **2021**, *60*, 12170–12191; *Angew. Chem.* **2021**, *133*, 12278–12299; b) W. Guo, Q. Wang, J. Zhu, *Chem. Soc. Rev.* **2021**, *50*, 7359–7377.
- [9] A. Vasseur, I. Marek, *Nat. Protoc.* **2017**, *12*, 74–87.
- [10] a) H. J. Seo, S. J. Yoon, S. H. Jang, S. K. Namgoong, *Tetrahedron Lett.* **2011**, *52*, 3747–3750; b) Y. Ikeuchi, T. Taguchi, Y. Hanzawa, *J. Org. Chem.* **2005**, *70*, 4354–4359.
- [11] T. Harada, T. Kaneko, T. Fujiwara, A. Oku, *J. Org. Chem.* **1997**, *62*, 8966–8967.
- [12] T. Klatt, J. T. Markiewicz, C. Sämann, P. Knochel, *J. Org. Chem.* **2014**, *79*, 4253–4269.
- [13] For selected papers on reactivity of zincate reagents with varying electrophiles including aldehydes, see: a) S. Cho, E. J. McLaren, Q. Wang, *Angew. Chem. Int. Ed.* **2021**, *60*, 26332–26336; *Angew. Chem.* **2021**, *133*, 26536–26540; b) S. Cho, Q. Wang, *Org. Lett.* **2020**, *22*, 1670–1674; c) K. Shibata, M. Kimura, K. Kojima, S. Tanaka, Y. Tamaru, *J. Organomet. Chem.* **2001**, *624*, 348–353.
- [14] T. Harada, T. Katsuhira, A. Osada, K. Iwazaki, K. Maejima, A. Oku, *J. Am. Chem. Soc.* **1996**, *118*, 11377–11390.
- [15] M. Uchiyama, T. Miyoshi, Y. Kajihara, T. Sakamoto, Y. Otani, T. Ohwada, Y. Kondo, *J. Am. Chem. Soc.* **2002**, *124*, 8514–8515.
- [16] a) P. Parris, J. N. Duncan, A. Fleetwood, W. P. Beierschmitt, *Regul. Toxicol. Pharmacol.* **2017**, *87*, 54–63; b) V. Antonucci, J. Coleman, J. B. Ferry, N. Johnson, M. Mathe, J. P. Scott, J. Xu, *Org. Process Res. Dev.* **2011**, *15*, 939–941.
- [17] a) S. Monticelli, L. Castoldi, I. Murgia, R. Senatore, E. Mazzeo, J. Wackerlig, E. Urban, T. Langer, V. Pace, *Monatsh. Chem.* **2017**, *148*, 37–48; b) V. Pace, P. Hoyos, L. Castoldi, P. Domínguez de María, A. R. Alcántara, *ChemSusChem* **2012**, *5*, 1369–1379.
- [18] D. F. Aycock, *Org. Process Res. Dev.* **2007**, *11*, 156–159.
- [19] Tetra-coordinated di-anionic lithium zincates are able to promote Br/Zn exchanges, see: a) N. T. T. Chau, M. Meyer, S. Komagawa, F. Chevallier, Y. Fort, M. Uchiyama, F. Mongin, P. C. Gros, *Chem. Eur. J.* **2010**, *16*, 12425–12433; b) M. Uchiyama, Y. Kondo, T. Miura, T. Sakamoto, *J. Am. Chem. Soc.* **1997**, *119*, 12372–12373; c) M. Uchiyama, M. Koike, M. Kameda, Y. Kondo, T. Sakamoto, *J. Am. Chem. Soc.* **1996**, *118*, 8733–8734.
- [20] M. Uchiyama, Y. Kobayashi, T. Furuyama, S. Nakamura, Y. Kajihara, T. Miyoshi, T. Sakamoto, Y. Kondo, K. Morokuma, *J. Am. Chem. Soc.* **2008**, *130*, 472–480.
- [21] M. Uchiyama, M. Kameda, O. Mishima, N. Yokoyama, M. Koike, Y. Kondo, T. Sakamoto, *J. Am. Chem. Soc.* **1998**, *120*, 4934–4946.
- [22] a) S. Zhang, J. Cai, Y. Yamamoto, M. Bao, *J. Org. Chem.* **2017**, *82*, 5974–5980; b) S. Zhang, Y. Wang, X. Feng, M. Bao, *J. Am. Chem. Soc.* **2012**, *134*, 5492–5495.
- [23] a) S. Z. Shirejini, A. Mohammadi, *Org. Process Res. Dev.* **2017**, *21*, 292–303; b) U. Azzena, F. Kondrot, L. Pisano, M. Pittalis, *Appl. Organomet. Chem.* **2012**, *26*, 180–184; c) B. Jedlicka, R. H. Crabtree, P. E. M. Siegbahn, *Organometallics* **1997**, *16*, 6021–6023; d) E. Weiss, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1501–1523; *Angew. Chem.* **1993**, *105*, 1565–1587; e) D. B. Collum, *Acc. Chem. Res.* **1992**, *25*, 448–454.
- [24] A. Kadam, M. Nguyen, M. Kopach, P. Richardson, F. Gallou, Z.-K. Wan, W. Zhang, *Green Chem.* **2013**, *15*, 1880–1888.
- [25] a) S.-Y. Cheung, H.-F. Chow, T. Ngai, X. Wei, *Chem. Eur. J.* **2009**, *15*, 2278–2288; b) C. Chardin, J. Rouden, S. Livi, J. Baudoux, *Green Chem.* **2017**, *19*, 5054–5059; c) J. Pahor, S. Stavber, A. Čusak, G. Kosec, H. Petković, A. P. Berke, *Synthesis* **2016**, *48*, 3763–3772.
- [26] a) G. Wu, S. Xu, Y. Deng, C. Wu, X. Zhao, W. Ji, Y. Zhang, J. Wang, *Tetrahedron* **2016**, *72*, 8022–8030; b) G. Pallikonda, R. Santosh, S. Ghosal, M. Chakravarty, *Tetrahedron Lett.* **2015**, *56*, 3796–3798.