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## Taking advantage of lithium monohalocarbenoid intrinsic $\alpha$ -elimination in 2-MeTHF: controlled epoxide ring-opening *en route* to halohydrins†

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The intrinsic degradative  $\alpha$ -elimination of Li carbenoids somehow complicates their use in synthesis as C1-synthons. Nevertheless, we herein report how boosting such an  $\alpha$ -elimination is a straightforward strategy for accomplishing controlled ring-opening of epoxides to furnish the corresponding  $\beta$ -halohydrins. Crucial for the development of the method is the use of the eco-friendly solvent 2-MeTHF, which forces the degradation of the incipient monohalolithium, due to the very limited stabilizing effect of this solvent on the chemical integrity of the carbenoid. With this approach, high yields of the targeted compounds are consistently obtained under very high regiocontrol and, despite the basic nature of the reagents, no racemization of enantiopure materials is observed.

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Lithium monohalocarbenoids (LiCH<sub>2</sub>X, X = halogen) constitute highly versatile C1-synthons for accomplishing homologation processes in both nucleophilic and electrophilic regimes, the former being the usual mode of action for lithium derivatives.<sup>1</sup> Accordingly, upon releasing the CH<sub>2</sub>X unit onto a proper electrophilic manifold, a plethora of useful synthetic transformations could be designed.<sup>2</sup> The coexistence of C–Li and C–halogen bonds on the same carbon atom promotes an extremely high tendency to induce degradative Kirmse's  $\alpha$ -elimination phenomenon, triggered by the strong Li–X internal coordination, with the final result of making the carbenoid unproductive for homologation purposes (Scheme 1a).<sup>1c,3</sup> This constitutive aspect of carbenoid chemistry is profoundly reflected in the strict operational details requested for their correct use in batch mode:<sup>1e,4</sup> (1) to overcome the intrinsic instability, the carbenoid generation event from a given precursor (dihalomethane, stannane, or sulfox-

ide) must be conducted under Barbier conditions to ensure that no degradation takes place; (2) running the process in coordinative solvents (THF and diethyl ether) in the presence of lithium halide salts contributes to attenuating (if not eliminating) Kirmse's  $\alpha$ -elimination to a free carbene and a LiX species (Scheme 1b).<sup>5</sup> Notably, these paradigms represent the

### a) Generation and degradation of lithium monohalocarbenoids



### b) Stabilizing Li carbenoids



### c) Compatibility with electrophiles



### d) This work:



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Scheme 1 General context of the presented work.

necessary guidelines for the convenient application of carbenoid-mediated strategies in synthetic methodologies.<sup>6</sup>

Due to our continued interest in this chemistry over the years, we wondered if Kirmse's elimination could have a synthetic significance behind the well-known degradative effect on the chemical integrity of these C1-synthons. The current state-of-the-art of carbenoid-guided processes, clearly evidences that sp<sup>2</sup>-hybridized carbon electrophiles are privileged platforms for accomplishing homologation-type transformations, as well as various heteroatoms (*e.g.* B,<sup>7</sup> Sn,<sup>8</sup> *inter alia*). Unfortunately, the corresponding sp<sup>3</sup>-hybridized carbon electrophiles remain elusive materials for accomplishing homologations with LiCH<sub>2</sub>X, as documented in the seminal work by Huisgen<sup>9</sup> and Hahn (Scheme 1c).<sup>10</sup> In this context, our group very recently documented the formal homologation of C–X functionalities through a sequential installation of the carbenoid into a carbonyl group followed by Si–H-mediated deoxygenation.<sup>11</sup>

Herein, we report the controlled ring-opening of epoxides with the lithium halide liberated during Kirmse's α-elimination for obtaining a high-yield of β-halohydrins (Scheme 1d). Pivotal for the success of the method is the generation and rapid degradation of the carbenoid in 2-MeTHF<sup>12</sup> (a green solvent increasingly becoming more useful in classical organic chemistry and biotransformations, as well as for polymerization or extractive purposes),<sup>13</sup> therefore leading to the degradation of the monohalolithium. We anticipate the genuine regioselectivity of the transformation harnessed on the formation of LiX which plays the dual role of Lewis acid (facilitating the C–O cleavage) and source of the attacking halide.<sup>14</sup>

We selected the enantiomerically pure epoxide-containing phthalimide (*S*)-**1** as the starting material to gather, additionally, information on the stereochemical outcome of the process. LiCH<sub>2</sub>Cl was generated under our previously established reaction conditions<sup>6d</sup> from ICH<sub>2</sub>Cl (3.0 equiv.) and MeLi–LiBr (2.8 equiv.) in THF at –78 °C (Table 1). Surprisingly, no attack of the nucleophile leading to the homologated adduct (*S*)-**1a** was observed, but rather a mixture of two enantiopure halohydrins [(*S*)-**2**] and [(*S*)-**3**] was recovered in an 84 : 16 ratio (entry 1). The subsequent HPLC analysis of both reaction products indicated the full preservation of the stereochemical information embodied, thereby confirming our previous findings on the retention of configuration in reactions involving basic α-substituted methyllithiums.<sup>2a,12k,15</sup> This initial experiment was indicative of the ring-opening of the epoxide with a LiX salt.<sup>16</sup> On the other hand, the simultaneous presence of the chloro (*S*)-**2** and bromo-(*S*)-**3** derivatives points towards a ring-opening mediated by two different species, namely LiCl and LiBr. Presumably, LiCl was formed during Kirmse's α-elimination of the carbenoid, thus yielding the chlorohydrin, whereas LiBr, complexing the metalating agent MeLi (*i.e.* MeLi–LiBr complex in Et<sub>2</sub>O), directly furnished bromohydrin (*S*)-**3**. To ascertain this hypothesis, LiX-free MeLi (MeLi in Et<sub>2</sub>O) was employed for generating the carbenoid under identical conditions: exclusively the chlorohydrin (*S*)-**2** was formed, thus confirming that LiCl (carbenoid degradation product) was responsible for the attack on the oxirane (entry

2). Some important aspects of the process were deduced by running the reaction in different solvents: thus, decreasing the medium-coordination effect on the carbenoid allowed an increase of the yield of the chlorohydrin, as a consequence of a positive modulating effect on Kirmse's elimination. Accordingly, the formation of (*S*)-**2** increased when using Et<sub>2</sub>O, CPME,<sup>17</sup> and TBME (entries 3–5) and it was maximized in 2-MeTHF, giving an excellent yield of 93% (entry 6). Some additional points merit mention: (a) decreasing the loading of carbenoid to 2.0 equiv. has practically no effect (91% yield), thus suggesting that it is optimal in terms of efficiency-costs (entries 7 and 8); (b) the presence of the additive TMEDA did not improve the process (entry 9); (c) the reaction conducted in toluene considerably lowered the yield (entry 10); (d) by running the process at higher temperatures (–40 °C and –10 °C), the effectiveness decreased, probably because of the non-optimal generation of the carbenoid (prior to its decomposition, entries 11 and 12); (e) the process is independent of the pro-carbenoid source, as evidenced using a stannane or a sulfoxide for accomplishing the corresponding metal exchange (entries 13 and 14), though the procedure on ICH<sub>2</sub>Cl afforded the best results; (f) the other Kirmse's elimination product, CH<sub>2</sub> (free carbene), had no effect on the whole transformation (*vide infra*); and (g) the adoption of non-Barbier-type conditions for forming the carbenoid did not provide any material because of the inadequate formation of the carbenoid (entry 15). Collectively, these results confirmed the previous evidence that LiCH<sub>2</sub>Cl is not a competent nucleophile for C-sp<sup>3</sup> hybridized electrophiles.

Having established the reaction conditions, we then studied the scope of the reaction (Scheme 2). The use of the other enantiomer of **1**, *i.e.* [(*R*)-**1**], afforded the corresponding epimeric halohydrin (*R*)-**2** with analogous efficiency and enantiomeric purity. This aspect was further evidenced in the case of different halocarbenoids, such as LiCH<sub>2</sub>Br [(*S*)-**3** and (*R*)-**3**] and LiCH<sub>2</sub>I [(*S*)-**4** and (*R*)-**4**], thus indicating the flexibility of the methodology. The procedure was then extended to *rac*-**1** with the three different carbenoids confirming the average yields obtained with the chiral platform. Unfortunately, the methodology could not be applied for the LiF ring-opening *en route* to a fluorohydrin. Considering the key role of the solvent in generating LiCH<sub>2</sub>F,<sup>6b,c,18</sup> the use of the optimal mixture THF : Et<sub>2</sub>O (1 : 1 v/v) was tested as an alternative to the herein employed 2-MeTHF, without observing the formation of the desired compound. Therefore, regardless of the proper generation of the unstable carbenoid, the degradation salt LiF may not be efficient in promoting the ring opening.<sup>19</sup> Epoxides derived from aldehydes could also be subjected to the reaction conditions leading to decorated aromatic β-chlorohydrins (5–6). Analogously, disubstituted epoxides (derived from ketones) easily underwent the ring-opening despite the substitution pattern on the aromatic ring. Notably, the carbenoid formation was not affected by the presence of functionalities sensitive to the organolithium environment. Thus, bromo-(7), iodo-(8), fluoro-(9, 11, 12), chloro-(10) and trifluoromethyl-(13) β-chlorohydrins were smoothly prepared in 2-MeTHF. The

Table 1 Reaction optimization



Entry	Solvent	LiCH <sub>2</sub> Cl (equiv)	Ratio 2/3 <sup>a</sup>	Yield of (S)-2 <sup>b</sup> (%)	er of (S)-2
1 <sup>c</sup>	THF	2.8	84 : 16	66	>99 : 1
2	THF	2.8	>99 : 1	74	>99 : 1
3	Et <sub>2</sub> O	2.8	>99 : 1	78	>99 : 1
4	CPME	2.8	>99 : 1	81	98 : 2
5	TBME	2.8	>99 : 1	85	97 : 3
6	2-MeTHF	2.8	>99 : 1	93	>99 : 1
7	2-MeTHF	1.8	>99 : 1	91	>99 : 1
8	2-MeTHF	1.5	>99 : 1	77	>99 : 1
9 <sup>d</sup>	2-MeTHF	2.0	>99 : 1	87	>99 : 1
10	Toluene	2.0	>99 : 1	61	>99 : 1
11 <sup>e</sup>	2-MeTHF	2.0	>99 : 1	67	>99 : 1
12 <sup>f</sup>	2-MeTHF	2.0	>99 : 1	48	>99 : 1
13 <sup>g</sup>	2-MeTHF	2.0	>99 : 1	85	>99 : 1
14 <sup>h</sup>	2-MeTHF	2.0	>99 : 1	79	>99 : 1
15 <sup>i</sup>	2-MeTHF	2.0	—	—	—

Unless otherwise stated, the carbenoid was generated under Barbier-type conditions starting from ICH<sub>2</sub>X and MeLi (Et<sub>2</sub>O solution 1.6 M) in THF at -78 °C. <sup>a</sup>The ratio has been calculated by <sup>1</sup>H-NMR analysis using 1,3,5-trimethylbenzene as an internal standard. <sup>b</sup>Isolated yield. <sup>c</sup>MeLi-LiBr complex (Et<sub>2</sub>O solution 1.5 M) was used; compound (S)-3 was obtained in 12% yield and >99 : 1 er. <sup>d</sup>TMEDA (2.0 equiv.) was added. <sup>e</sup>Reaction was run at -40 °C. <sup>f</sup>Reaction was run at -10 °C. <sup>g</sup>The carbenoid was prepared from (*n*-Bu)<sub>3</sub>SnCH<sub>2</sub>Cl. <sup>h</sup>The carbenoid was prepared from PhS(O)CH<sub>2</sub>Cl. <sup>i</sup>The carbenoid was generated under *non*-Barbier conditions.

additional presence of an acidic aromatic alcohol did not constitute a limitation for the method when deprotonation (with the same MeLi) was carried out prior to carbenoid formation (14). Epoxides formally derived from benzo- or acetophenones were amenable substrates for the reaction furnishing derivatives 15–16 and 17–18, respectively, in high yields. The use of an  $\alpha$ -trifluoromethyl-epoxide enabled the straightforward formation of analogue 19, while, much to our delight, even a labile ester group was tolerated during the carbenoid generation–degradation sequence, giving compound 20. The installation of unsaturated fragments (alkyne and alkene) on the epoxide core was particularly attractive not only for the synthetic importance of the so-obtained halohydrins (21–22) but, more importantly, for constituting unambiguous proof of the lack of reactivity of the free carbene generated during the carbenoid degradation. <sup>18b,20</sup> No cyclopropanation-like process was detected, as judged by NMR analysis of the crude product, thus confirming the initial hypothesis of the higher reactivity of the lithium halide salt.

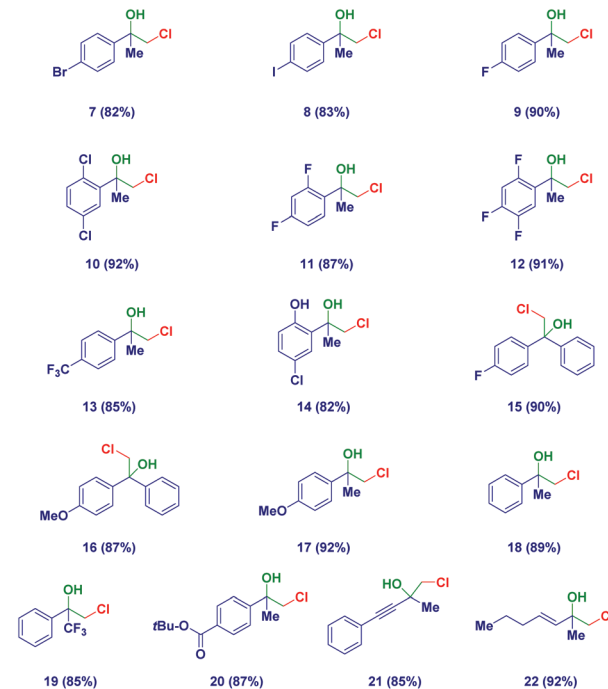
With the aim to gather useful insights into the mechanistic aspects of the transformation, a 1 : 1 molar mixture of epoxide *rac*-1 and an aromatic aldehyde was reacted with LiCH<sub>2</sub>Cl (1.8 equiv.) in 2-MeTHF (Scheme 3a). Two halohydrins were obtained upon the attack of the carbenoid on the aldehyde (major compound, 5) and the attack of the degradation product (LiCl) on the epoxide (minor compound, *rac*-2). This



## From Aldehydes

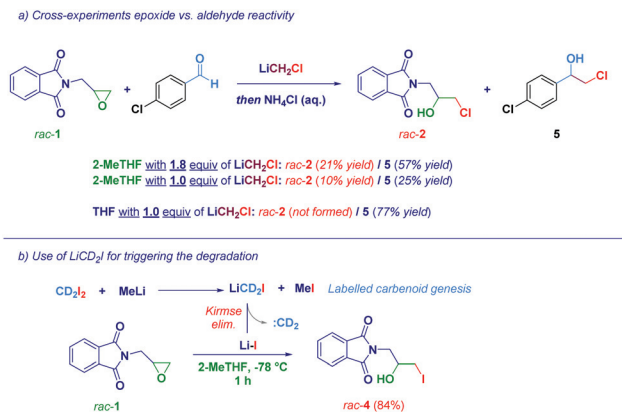


## From Ketones



Scheme 2 Scope of the reaction.

fact can be rationalized taking into account the higher electrophilicity of the carbonyl group compared to that of the epoxide: although not optimal for stabilizing LiCH<sub>2</sub>Cl, the carbonyl nucleophilic addition still takes place, as the predominant process, in 2-MeTHF. Concomitantly, the epoxide ring-



Scheme 3 Additional mechanistic proof.

opening product was observed, though in a lesser yield (21% yield of *rac-2*), promoting itself the degradation of the carbenoid. Notably, when only 1 equiv. of LiCH<sub>2</sub>Cl was used, no significant differences in the ratio of *rac-2* and **5** were observed, probably indicating that, due to its short life, the carbenoid reacted (again) with the more activated substrate (aldehyde) before the decomposition took place, so that the degradation product (LiCl) attacked the epoxide. However, when the reaction was carried out in the carbenoid stabilizing THF, the attack of 1 equiv. of LiCH<sub>2</sub>Cl on the aldehyde was a practically uniquely occurring phenomenon, since no significant Kirmse's elimination took place. Finally, as an additional proof of the formation of LiX, we carried out an experiment using the labelled carbenoid LiCD<sub>2</sub>I (formed upon treatment of CD<sub>2</sub>I<sub>2</sub> with MeLi),<sup>6d</sup> observing the iodohydrin *rac-4*, as the sole product (Scheme 3b). This could be explained considering that Kirmse's elimination of LiCD<sub>2</sub>I provided CD<sub>2</sub> (unreactive) and LiI, responsible for the oxirane opening.

In summary, we have developed a straightforward preparation of different β-halohydrins (chloro, bromo, and iodo) through boosted Kirmse's elimination of the corresponding lithium monohalocarbenoids starting from epoxide. The degradative process – usually conceived as problematic in canonical homologation chemistry – is herein implemented in the eco-friendly and non-coordinating solvent 2-MeTHF. Accordingly, the controlled formation of LiX salts is triggered, leading ultimately to the ring-opening of the epoxides. The uniformly high-yield, the full preservation of the embodied stereochemical information and the high chemocontrol – deduced by selectively preparing variously decorated motifs – further document the potential of this operationally simple and intuitive methodology.

## Experimental part

### General procedure 1

To a cooled (−78 °C) solution of the suitable epoxide (1.0 equiv.) in dry 2-MeTHF was added iodochloromethane (2.0

equiv.). After 2 min, an ethereal solution of MeLi (1.8 equiv., 1.6 M) was added dropwise, using a syringe pump (flow: 0.200 mL min<sup>−1</sup>). The resulting solution was stirred for one hour at −78 °C. A saturated solution of NH<sub>4</sub>Cl was added (2 mL mmol<sup>−1</sup> substrate), and then extracted with Et<sub>2</sub>O (2 × 5 mL) and washed with water (5 mL) and brine (10 mL). The organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and, after removal of the solvent under reduced pressure, the so-obtained crude mixture was subjected to chromatography on silica gel to afford pure compounds.

**2-(3-Chloro-2-hydroxypropyl)-1H-isoindole-1,3(2H)-dione (*rac-2*).** By following the general procedure 1, starting from 2-[(oxiran-2-yl)methyl]-1H-isoindole-1,3(2H)-dione (203 mg, 1.0 mmol, 1.0 equiv.), ICH<sub>2</sub>Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv.), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv.) and 2-MeTHF (3 mL), the desired product was obtained in 91% yield (218 mg) as a white solid (m.p.: 95 °C) after chromatography on silica gel (50 : 50 v/v, *n*-hexane/diethyl ether). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.81 (m, 2H, Phthal H-4,7), 7.70 (m, 2H, Phthal H-5,6), 4.16 (brs, 1H, CHOH), 3.91 (dd, *J* = 14.3, 7.4 Hz, 1H, NCH<sub>2</sub>), 3.83 (dd, *J* = 14.3, 4.4 Hz, 1H, NCH<sub>2</sub>), 3.64 (dd, *J* = 11.5, 4.7 Hz, 1H, CH<sub>2</sub>Cl), 3.59 (dd, *J* = 11.5, 5.5 Hz, 1H, CH<sub>2</sub>Cl), 3.18 (brs, 1H, OH). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 168.6 (Phthal C-1,3), 134.2 (Phthal C-5,6), 131.7 (Phthal C-3a,7a), 123.4 (Phthal C-4,7), 69.5 (CHOH), 47.2 (CH<sub>2</sub>Cl), 41.5 (NCH<sub>2</sub>). HRMS (ESI), *m/z*: calcd for C<sub>11</sub>H<sub>11</sub>ClNO<sub>3</sub><sup>+</sup>: 240.0422 [M + H]<sup>+</sup>; found: 240.0426.

**1-Chloro-2-(4-iodophenyl)-2-propanol (**8**).** By following the general procedure 1, starting from 2-(4-iodophenyl)-2-methyl-oxirane (260 mg, 1.0 mmol, 1.0 equiv.), ICH<sub>2</sub>Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv.), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv.) and 2-MeTHF (3 mL), the desired product was obtained in 83% yield (246 mg) as a colourless oil after chromatography on silica gel (90 : 10 v/v, *n*-hexane/diethyl ether). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.70 (m, 2H, Ph H-3,5), 7.21 (m, 2H, Ph H-2,6), 3.79 (A-part of an AB-system, <sup>2</sup>*J*<sub>AB</sub> = 11.2 Hz, 1H, CH<sub>2</sub>Cl), 3.73 (B-part of an AB-system, <sup>2</sup>*J*<sub>AB</sub> = 11.2 Hz, 1H, CH<sub>2</sub>Cl), 2.60 (brs, 1H, OH), 1.60 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 144.0 (Ph C-1), 137.5 (Ph C-3,5), 127.1 (Ph C-2,6), 93.2 (Ph C-4), 73.7 (COH), 55.0 (CH<sub>2</sub>Cl), 27.3 (CH<sub>3</sub>). HRMS (ESI), *m/z*: calcd for C<sub>9</sub>H<sub>11</sub>ClIO<sup>+</sup>: 296.9538 [M + H]<sup>+</sup>; found: 296.9542.

**1-Chloro-2-(2,4,5-trifluorophenyl)-2-propanol (**12**).** By following the general procedure 1, starting from 2-methyl-2-(2,4,5-trifluorophenyl)oxirane (188 mg, 1.0 mmol, 1.0 equiv.), ICH<sub>2</sub>Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv.), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv.) and 2-MeTHF (3 mL), the desired product was obtained in 91% yield (204 mg) as a colourless oil after chromatography on silica gel (90 : 10 v/v, *n*-hexane/diethyl ether). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.52 (ddd, *J* = 11.5, 9.0, 7.3 Hz, 1H, Ph H-6), 6.91 (m, 1H, Ph H-3), 4.01 (d, *J* = 11.2 Hz, 1H, CH<sub>2</sub>Cl), 3.86 (dd, *J* = 11.2, 1.1 Hz, 1H, CH<sub>2</sub>Cl), 2.79 (brs, 1H, OH), 1.64 (d, *J* = 1.2 Hz, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 153.8 (ddd, *J* = 244.1, 9.3, 2.9 Hz, Ph C), 149.3 (ddd, *J* = 251.5, 14.6, 12.8 Hz, Ph C), 146.8 (ddd, *J* = 244.6, 12.0, 3.4 Hz, Ph C), 127.9 (dt, *J*<sub>d</sub> = 15.0 Hz, *J*<sub>t</sub> = 4.4 Hz, Ph C-1), 116.4 (ddd, *J* = 21.4, 5.9, 1.3 Hz, Ph C-6), 106.4 (dd, *J* = 29.9, 21.0 Hz,

Ph C-3), 72.6 (d,  $J = 4.7$  Hz, COH), 53.4 (d,  $J = 6.5$  Hz, CH<sub>2</sub>Cl), 25.8 (d,  $J = 3.5$  Hz, CH<sub>3</sub>). <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$ : -141.9 (m, F), -134.7 (m, F), -115.7 (m, F). HRMS (ESI),  $m/z$ : calcd for C<sub>9</sub>H<sub>9</sub>ClF<sub>3</sub>O<sup>+</sup>: 225.0289 [M + H]<sup>+</sup>; found: 225.0286.

**2-Chloro-1-(4-fluorophenyl)-1-phenylethanol (15).** By following the general procedure 1, starting from 2-(4-fluorophenyl)-2-phenyloxirane (214 mg, 1.0 mmol, 1.0 equiv.), ICH<sub>2</sub>Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv.), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv.) and 2-MeTHF (3 mL), the desired product was obtained in 90% yield (225 mg) as a colourless oil after chromatography on silica gel (90 : 10 v/v, *n*-hexane/diethyl ether). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.43 (m, 2H, Ph2 H-2,6), 7.42 (m, 2H, Ph1 H-2,6), 7.36 (m, 2H, Ph2 H-3,5), 7.30 (m, 1H, Ph2 H-4), 7.03 (m, 2H, Ph1 H-3,5), 4.18 (A-part of an AB-system, <sup>2</sup>*J*<sub>AB</sub> = 11.7 Hz, 1H, CH<sub>2</sub>Cl), 4.16 (B-part of an AB-system, <sup>2</sup>*J*<sub>AB</sub> = 11.7 Hz, 1H, CH<sub>2</sub>Cl), 3.17 (brs, 1H, OH). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 162.2 (d,  $J = 246.9$  Hz, Ph1 C-4), 143.0 (Ph2 C-1), 139.1 (d,  $J = 3.2$  Hz, Ph1 C-1), 128.4 (Ph2 C-3,5), 128.3 (d,  $J = 8.2$  Hz, Ph1 C-2,6), 127.9 (Ph2 C-4), 126.3 (Ph2 C-2,6), 115.2 (d,  $J = 21.4$  Hz, Ph1 C-3,5), 77.5 (COH), 53.1 (CH<sub>2</sub>Cl). <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$ : -114.7 (m, F). HRMS (ESI),  $m/z$ : calcd for C<sub>14</sub>H<sub>13</sub>ClFO<sup>+</sup>: 251.0633 [M + H]<sup>+</sup>; found: 251.0659.

## Conflicts of interest

There are no conflicts to declare.

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