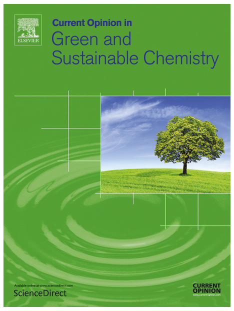

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Organometallic
Chemistry in air

Synthetic Applications of Polar Organometallic and Alkali-Metal Reagents Under Air and Moisture

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Abstract

Recently, there has been an upsurge interest in developing chemoselective and fast processes when working with polar organometallic of s- and d-block elements and alkali-metal reagents under air and moisture, and also in protic bio-based solvents like Deep Eutectic Solvents or water. A discussion is offered highlighting cutting-edge stoichiometric and catalytic synthetic applications in this evolving field, with an accent over the literature published in the last couple of years.

Keywords

Aerobic conditions; Deep Eutectic Solvents; Water chemistry; Polar organometallic chemistry; Alkali-metal reagents.

Graphical abstract

1. Introduction

Since the introduction of the Twelve Principles of Green Chemistry by Anastas and Warner in the early 1990s [1], significant research has been directed towards the design and the development of novel technologies and processes less negatively impacting on human health and the environment, including the adoption of safer and less toxic solvents and reagents [2]. In this perspective, the use of water [3,4**] and other bio-based solvents [e.g., glycerol, 2-methyltetrahydrofuran (2-MeTHF), cyclopentyl methyl ether (CPME), the so-called Deep Eutectic Solvents (DESs)] in organic synthesis [5–9] and in the chemistry of polar organometallic compounds belonging to the s- and d-block elements (e.g., organolithium, organomagnesium, organozinc reagents) [10–12] has been gaining a lot of momentum. The idea of forging novel carbon-carbon bonds by means of highly reactive organometallics in protic media (e.g., water, DESs) and under aerobic conditions might seem counterintuitive, since it goes against the traditional belief that rigorously aprotic and dry volatile organic compounds (VOCs) and inert atmospheres are strictly required for the successful handling of these reagents owing to their polarized metal-carbon bonds, and thus of their high reactivity and air- and moisture-sensitivity. A perusal of the literature, however, reveals not only the intrinsic *slowness* of the reactions between organolithium/organomagnesium compounds and water [7,13–15], but also that the adventitious or even the deliberate addition of water in the reactions of Groups 1/2 metals redirects reactions in interesting and unexpected ways; for example, by speeding up the reaction rate, or by favouring a lithium/halogen exchange reaction, or by enhancing the enantioselectivity in an asymmetric synthesis [15]. By highlighting these phenomena in a review already in 1975 [16], Smith concluded with the question: “Shall we await the day when reactions of organolithiums are routinely performed in aqueous solution?”. Our group embarked on this adventure that would have made this prediction a reality since 2014, by publishing the first examples of regioselective THF-directed *ortho*-lithiation/electrophilic interception reactions of diphenyl tetrahydrofuran triggered by *t*-BuLi in choline chloride (ChCl)-based protic eutectic mixtures [e.g., ChCl/glycerol (Gly), ChCl/urea] at 0 °C or room temperature (RT) in air, which shocked us a lot [17]. One of the reviewers of this work remarked that, on the contrary, we should not have been so shocked of these results, given the precedents in the literature [15,16]. On the other hand, we acknowledged a completely different feeling from another reviewer when we submitted in 2016 [18] the results of an investigation regarding the addition of Grignard and organolithium reagents to γ-chloroketones under air, and using water as a reaction medium, to afford THF derivatives: “The authors present a provocative hypothesis that organometallic reagents (Grignards and organolithiums) are suitable for reactions in water”. The possibility of running routinely the reactions of highly polarized organometallic compounds in bulk water under air is, indeed, quite thought provoking.

Simultaneously and independently from these studies, the groups of Hevia and García-Álvarez reinforced the argument of the feasibility of employment of organolithiums in protic, bio-based solvents like ChCl/Gly, ChCl/H_2O, and Gly by successfully performing the chemoselective addition of these reagents to ketones [19], non-activated imines [20] and nitriles [21] under aerobic ambient temperature conditions, thereby establishing a novel, fast, and sustainable access to secondary alcohols and amines, and ketones, respectively. The reactivity of polar organometallic compounds in unconventional reaction media has been recently in-depth discussed in two reviews [10,15]. Thus, this brief *Opinion* showcases in two Sections recent synthetic applications of polar organometallic and alkali-metal reagents under aerobic conditions and moisture, with a focus over the literature published in the past two years.

2. Synthetic applications of polar organometallic reagents under aerobic conditions and moisture

Directed *ortho* metalation has been traditionally carried out in the presence of bulky bases (e.g., *sec*-BuLi), at low temperature (–78 °C), under inert atmospheres, and in anhydrous VOCs (e.g., THF, Et_2O). Starting from *N*,*N*-diisopropylbenzamide derivatives (**1**), *ortho*-functionalized amides **2** could be obtained in up to 99% yield and within 2 s reaction time, making use of a synergistic combination of a ChCl/Gly-CPME mixture and of *t*-BuLi as a base, working at RT in air. Of note, an half-life of 6.26 s was estimated for **1-Li** in the above eutectic mixture. By simply switching *t*-BuLi for less sterically encumbered organolithium reagents (e.g., MeLi, *n*-BuLi), a nucleophilic acyl substitution reaction was alternatively privileged to afford ketones **3**, however, in combination with the tertiary alcohols **4** in up to a 7:1 ratio, when working at 0 °C in air. (Figure 1a) [22].

The notorious over-addition reaction by organolithiums to the resulting ketones was found to be effectively suppressed by reacting *N*-acylpyrrolidines **5** with commercial solution of organolithiums, when using CPME as a solvent in open air at RT. Under these conditions, a variety of ketones **6** was synthesized. (Figure 1b) [23*].

The regioselective benzylic lithiation of functionalized toluene derivatives **7** took place smoothly and in fast reaction times (2 s) in ChCl/Gly-CPME, at RT under air, to provide valuable educts **8** (up to 90% yield) after interception of the putative **7-Li** with a variety of electrophiles. The estimated half-life for **7-Li** in the aforementioned protic medium was 6.57 s (Figure 1c) [24].

An organo-catalyzed oxidation of secondary alcohols **9** with AZADO (2-azaadamantane *N*-oxyl)/NaClO was successfully combined with a chemoselective and fast (3s) nucleophilic addition of organolithiums to the transiently formed enolizable ketones **10**, at RT in water and in the presence of air, to give alcohols **11** in up to 95% yield (Figure 1d) [25*].

Under heterogeneous conditions, the nucleophilic addition of organolithium and Grignard reagents to esters **12** occurred smoothly in water, or in the biodegradable ChCl/urea eutectic mixture, with a broad substrate scope to deliver tertiary alcohols **13** in 60–95% yield after 20 s reaction time (Figure 1e). Starting from ester **14**, telescoped, one-pot nucleophilic addition/thioetherification processes proved also to be feasible in water, and allowed the straightforward isolation, through the tertiary alcohol **15**, of pharmaceutically relevant *S*-trityl-L-cysteine derivatives **16a**,**b** (Figure 1f) [26].

A novel air- and moisture-compatible methodology that uses organolithium reagents as initiators for the anionic polymerization of different olefins **17** in DESs has been established by Presa Soto, García-Álvarez and Hevia starting from unpurified monomers, and working in ChCl/Gly in air and under sonication at 40 °C. A variety of synthetically relevant organic polymers **19** has been synthesized (up to 90% yield) with low polydispersities (PDI 1.1–1.3). Remarkably, the in situ formed polystyryl lithium **18** (Ar = Ph) exhibited a great resistance to hydrolysis up to 1.5 h (Figure 1g) [27**].

The addition of organolithium and Grignard reagents to chiral nonracemic (S_S)-*N*-*tert*-butanesulfinyl imines **20** proceeded very fast (within 2 min), at RT and under air in D-sorbitol/ChCl, thereby granting access to a mixture of diastereomeric sulfinamides **21**, that could be first separated by column chromatography, and then deprotected to give the enantioenriched (up to 98% ee) secondary amines **22** in high yield (98%). This method was applied to the asymmetric synthesis of both the chiral amine side-chain of (*R*,*R*)-Formoterol **23** (96% ee), and the calcimimetic (*R*)-Cinacalcet **25** (98% ee) from amine (S_S,*R*)-**24** (Figure 1h) [28*].

Highly polar s-block organometallic reagents were found to promote a fast (3 s reaction time) and regiodivergent synthesis of tertiary alcohols **27** (organolithium reagents) or symmetrical ketones **28** (aryl Grignard reagents) or β-hydroxy esters **29** (alkyl Grignard reagents) when added to CO_2-derived cyclic carbonates **26** in 2-MeTHF, at RT and under air (Figure 1i). Hybrid, one-pot/two-step protocols through in situ formed cyclic carbonates from CO_2 and epoxides were successful as well [29].

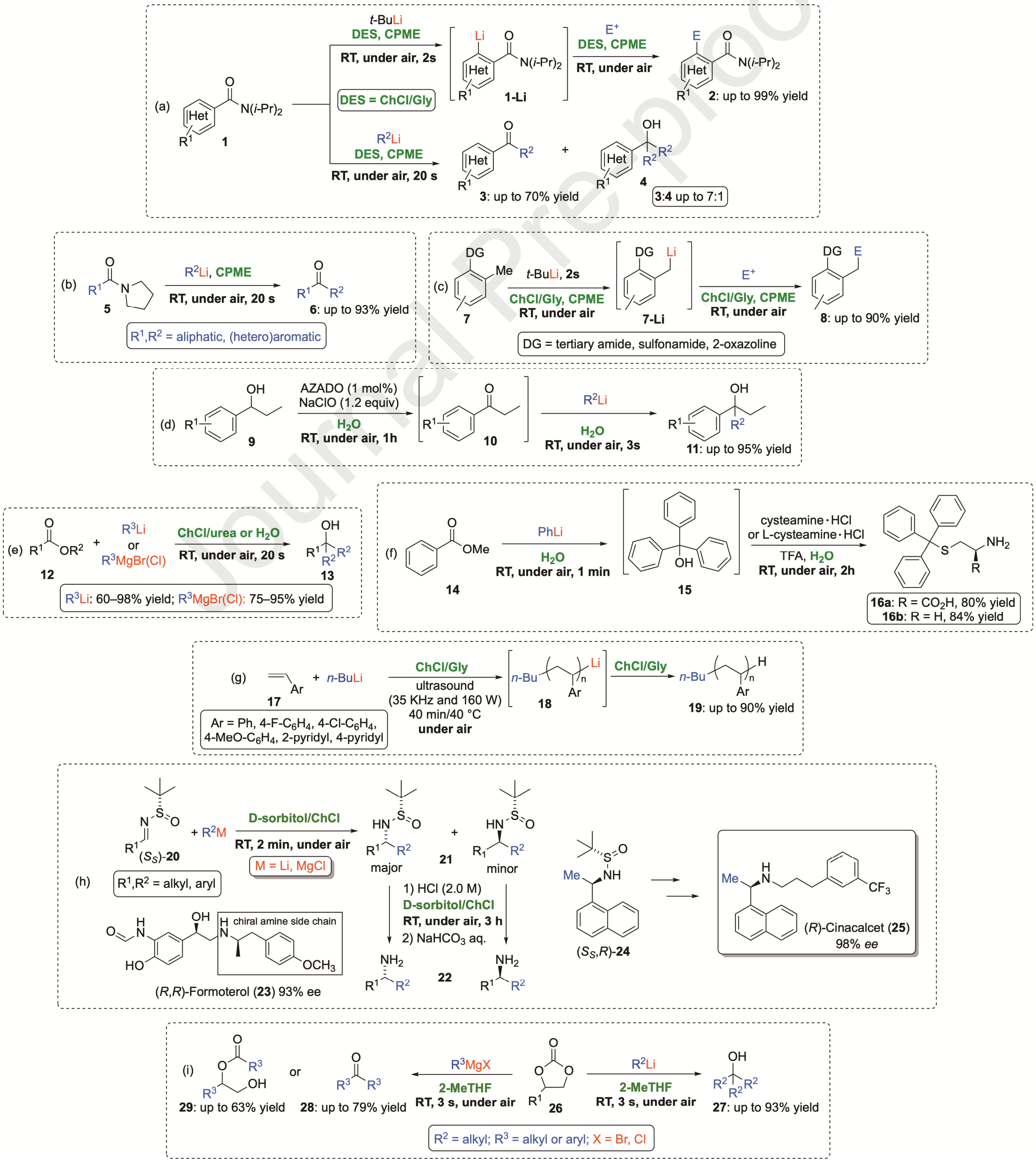

Figure 1. Nucleophilic acyl substitutions on amides (**a**,**b**) and esters (**e**,**f**), directed *ortho* (**a**) and lateral (**c**) lithiation reactions, nucleophilic additions to in situ formed carbonyl compounds (**d**), chiral imines (**h**) and cyclic carbonates (**i**), and anionic polymerization of olefins (**g**) promoted by organolithium and Grignard reagents under air and moisture in DESs, CPME, and H_2O. DESs, Deep Eutectic Solvents. CPME, cyclopentyl methyl ether. DG, directing groups. RT, room temperature.

Scalable highly chemoselective C(sp^2)–C(sp^2) bond-forming reactions between poly(pseudo)halides **30**,**34** and Grignard **31** (Kumada cross-coupling, Figure 2a) or organozinc **35** (Negishi cross-coupling, Figure 2b) reagents have been developed by Schoenebeck and co-workers using the air- and moisture-stable Pd(I) dimer catalyst **32**. Under open-flask conditions, these site-selective (C–Br) couplings are completed within 5 min at RT, furnishing educts **33**,**36** in up to 98% yield (Figures 2a,b) [30]. The bench stable iodide-bridged catalyst **37** was shown also to trigger fast and site-selective Negishi C(sp^2)–C(sp^2) and C(sp^2)–C(sp^3) couplings in NMP (*N*-methyl-2-pyrrolidone) at RT under air between triflate or fluorosulfate substrates **38** and organozinc reagents **39** to give educts **40** in up to 95% yield (Figure 2c) [31*]. Feringa and co-workers reported that direct Pd-catalyzed cross-coupling of organic halides **41** with alkyl- or (hetero)aryllithium reagents **42** proceeded fast (10 min) and selectively by adding the organolithium compound over a neat mixture of organic halide and catalyst [Pd-PEPPSI-IPr or $Pd(Pt\text{-}Bu_3)_2$] (1.5–3 mol%) under air at RT to provide the desired educts **43** in up to 98% yield (Figure 2d) [32].

In 2019, Capriati and co-workers presented the discovery of an ultrafast (20 s) Pd-catalyzed cross-coupling of (hetero)aryl halides **44** with organolithium compounds **45** using bulk water as the reaction medium. In the presence of NaCl, these reactions proceeded selectively at RT and under air giving the expected educts **46** in yields of up to 98%, and competitively with protonolysis (Figure 2e) [33]. Under the same conditions, Negishi couplings between (hetero)aryl bromides **47** and organozinc reagents **48** have also been successfully carried out either “on water” or in ChCl/urea. These two media have been alternatively and complementarily used to include the reactivity of alcohols, esters, carbonyl compounds, phenols, aniline and cyano derivatives. These reactions are scalable, proceed very fast (20 s) at RT or 60 °C, and with a recycling of the eutectic mixture or water and the catalyst, to afford educts **49** in up to 98% yield (Figure 2f) [34*].

Organozinc reagents **51** have also been generated in situ from alkyl/aryl halides **50** and zinc metal under mechanochemical conditions in air, with the subsequent Negishi coupling furnishing educts **52** in up to 98% yield (Figure 2g) [35]. Similarly, mechanochemical zinc-mediated Reformatsky and Barbier-type allylation reactions of carbonyl compounds, under an air atmosphere, delivered β-hydroxycarbonyl and homoallylic alcohol products, respectively [36,37]. The direct conjugate addition of alkyl and aryl organic halides to α,β-unsaturated esters and phosphonates, as well as to acrylonitriles, was also shown to be successfully mediated by zinc dust, and catalyzed by copper, when working at RT under air and in water [38].

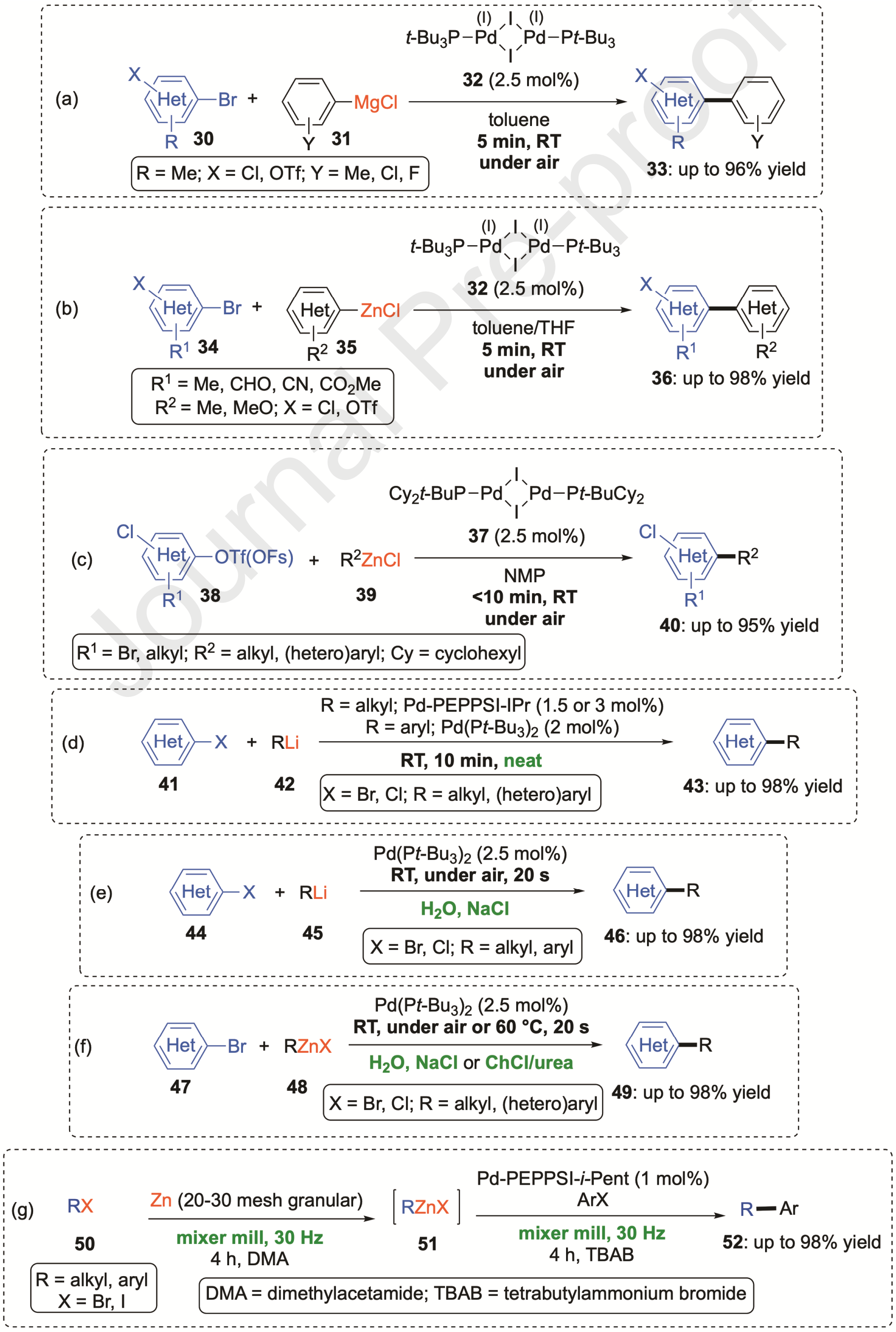

Figure 2. Various Pd-catalyzed cross-coupling reactions promoted by organozinc, organolithium and Grignard reagents, under air and moisture, performed in VOCs, DESs, H_2O, under neat or mechanochemical conditions (**a–g**). OTf, triflate. OFs, fluorosulfate. NMP, *N*-methyl-2-pyrrolidone. RT, room temperature.

3. Synthetic applications of polar alkali-metal reagents under aerobic conditions and moisture

Highly polarized phosphides **54** [$LiP(R^1)_2$] have been prepared in ChCl/Gly through in situ deprotonation with *n*-BuLi of the corresponding secondary phosphines **53** [$HP(R^1)_2$], at RT in air. Intermediates **54** were found to trigger a chemoselective and fast (3 s) nucleophilic addition to aldehydes **55** and epoxides **56** in air to give α- and β-hydroxy phosphine oxides **57** and **58**, respectively, in very good yields (62–94%). After 30 s, lifetime of $LiPPh_2$ was still large enough to allow recovery of educt **57a** in 77% yield (after 3 s: 95% yield) (Figure 3a) [39*].

Amidation and transamidation reactions of ethyl esters **59** and *N*-Boc-substituted benzamides **62** proceeded fast (20 s) and chemoselectively when using lithium amides **60** in the biomass-derived 2-MeTHF, in the presence of air and moisture, to give carboxamides **61** (up to 89% yield) and **63** (up to 77% yield), respectively. (Figures 3b,c) [40].

Hydroamination of styrene derivatives **64** with lithium amides **65-Li**, en route to phenethylamines **67**, was unexpectedly found to be accelerated in 2-MeTHF by the moisture from ambient air, thereby efficiently competing with the polymerization process. Moisture is thought to partially quench **65-Li**, thus generating the free amine **65-H** that could subsequently favor the protonation of intermediate **66** and the regeneration of **65-Li** (Figure 3d) [41**].

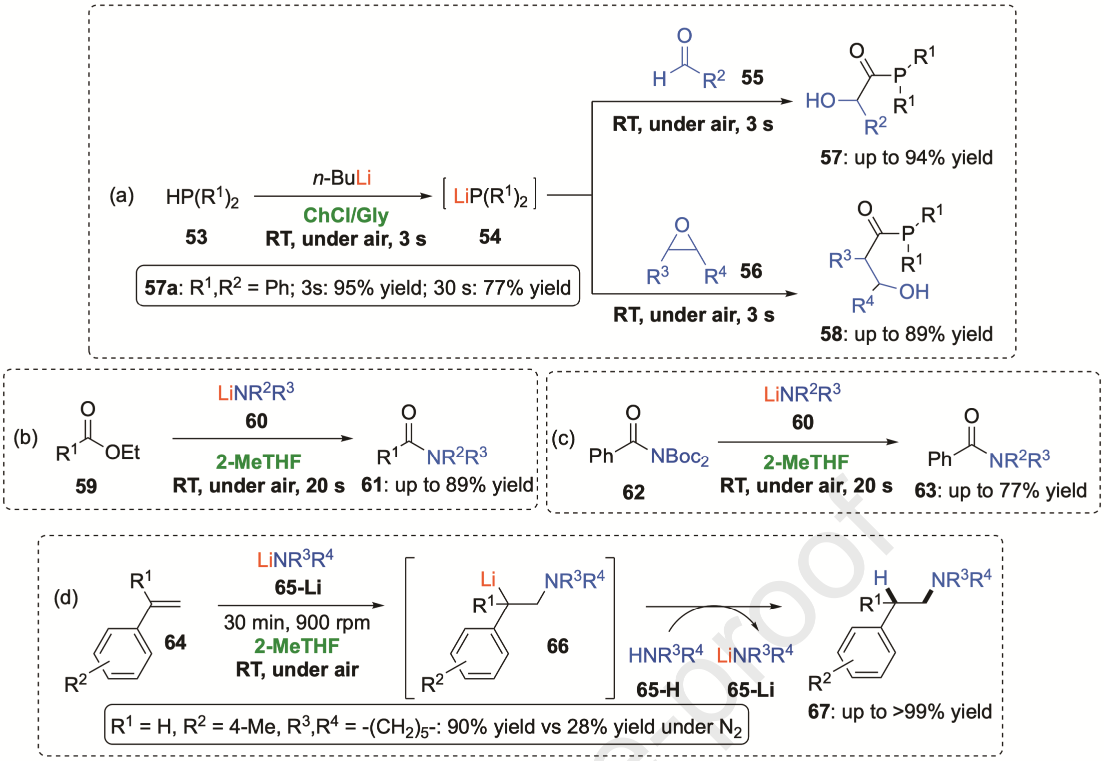

Figure 3. Nucleophilic additions to carbonyl compounds, epoxides (**a**), and styrene derivatives (**d**), and nucleophilic acyl substitution on esters (**b**) and amides (**c**), promoted by polar alkali metal-reagents under air and moisture, and performed in DES or 2-MeTHF. 2-MeTHF, 2-methyltetrahydrofuran. RT, room temperature.

4. Conclusions and opportunities

The successful use of notoriously air- and moisture-sensitive polar organometallic and alkali-metal reagents under mild and aerobic conditions, and their ability to promote very fast reactions in competition with protonolysis when using DESs or water, has opened doors to previously unthinkable perspectives in organometallics. As emerges from the studies discussed herein, it is noteworthy the remarkable kinetic stability exhibited by the aforementioned reagents/intermediates in such strongly hydrogen-bonded associated media, whose properties are undoubtedly unique among other protic solvents [4,9,10]. Hydrogen bonding may be the key to explaining the recalcitrance of these reagents to undergo protonolysis as a first reaction in water or DESs [9,10]. Of note, a recent research has demonstrated that the line between a hydrogen and a covalent bond is blurrier than that suggested by teaching textbooks [42]. To advance this exciting research field further, it is now of great importance to implement this technology on an industrial scale, and to carry out theoretical calculations and spectroscopic investigations for a fundamental understanding of the molecular basis behind this still unexplored chemical space.

Conflict of interest statement

Nothing declared.

Acknowledgements

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In this study, either an aqueous solution of NaCl or a choline chloride/urea eutectic mixture have been used as effective and recyclable reaction media to promote fast (20 s reaction time), operationally simple, chemoselective and scalable (up to 5 g) Pd-catalyzed C(sp^3)–C(sp^2) and C(sp^2)–C(sp^2) cross-coupling reactions of organozinc halides with (hetero)aryl bromides.

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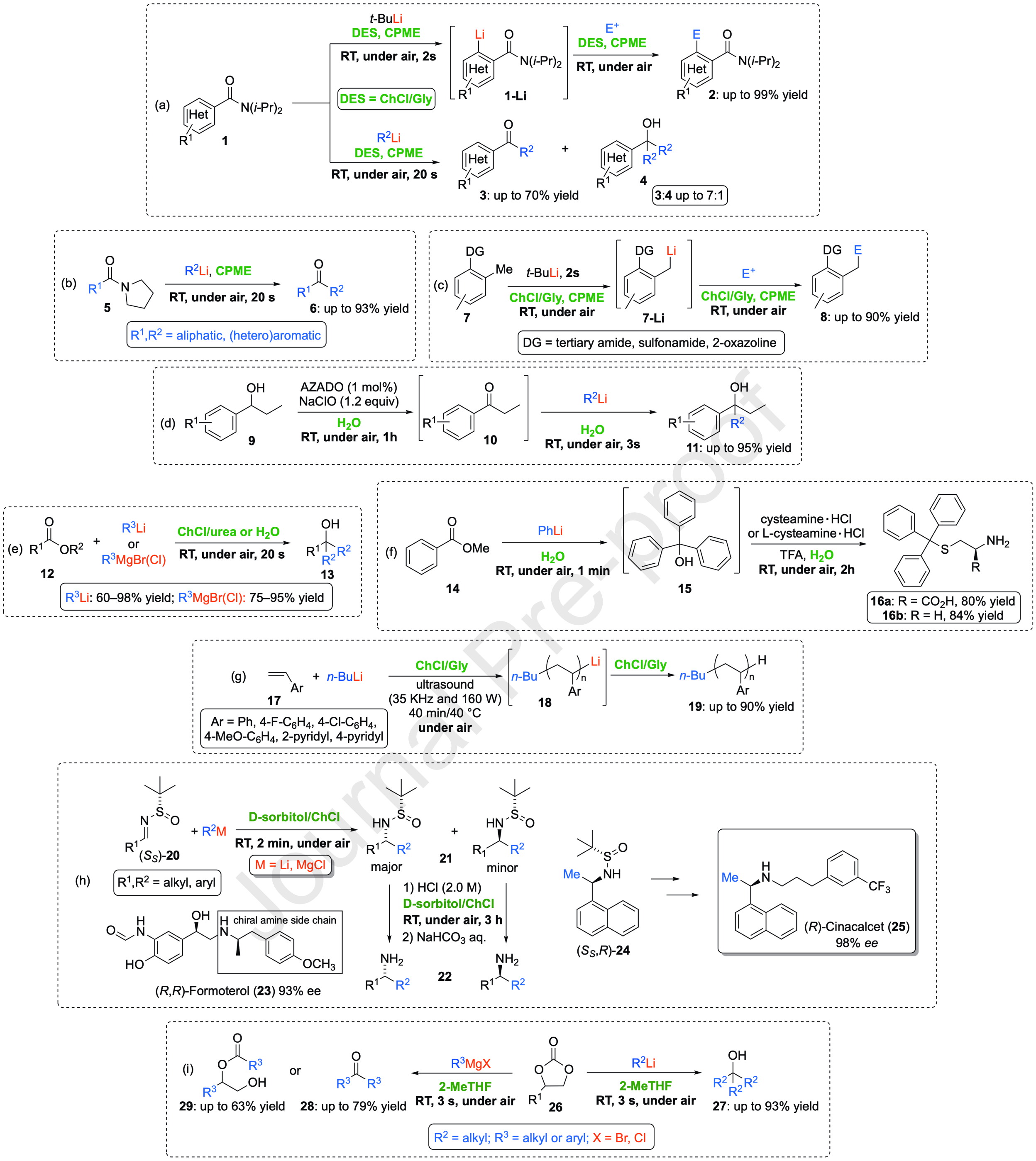
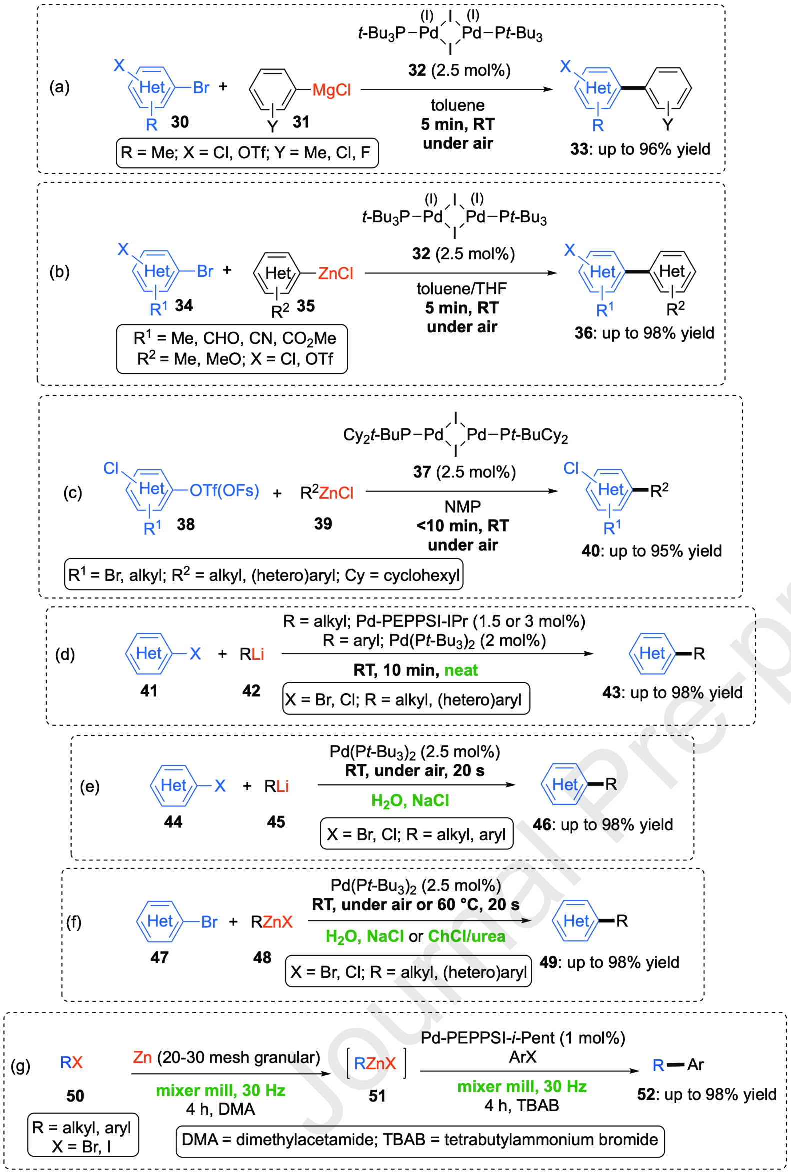
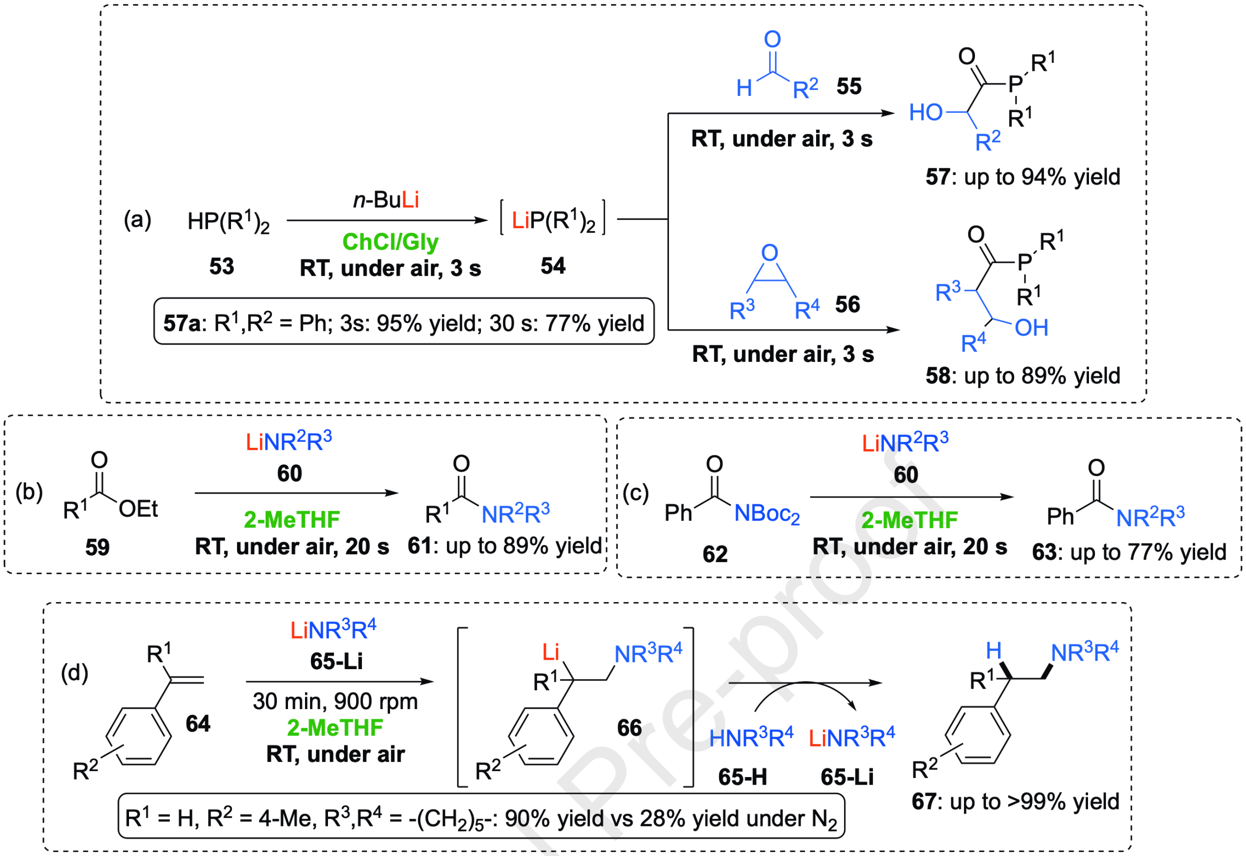

(a)
1
t-BuLi
DES, CPME
RT, under air, 2s
1-Li
E+
DES, CPME
RT, under air
2: up to 99% yield
DES = ChCl/Gly
R2Li
DES, CPME
RT, under air, 20 s
3: up to 70% yield
4
3:4 up to 7:1
(b)
5
R2Li, CPME
RT, under air, 20 s
6: up to 93% yield
R1,R2 = aliphatic, (hetero)aromatic
(c)
7
t-BuLi, 2s
ChCl/Gly, CPME
RT, under air
7-Li
E+
ChCl/Gly, CPME
RT, under air
8: up to 90% yield
DG = tertiary amide, sulfonamide, 2-oxazoline
(d)
9
AZADO (1 mol%)
NaClO (1.2 equiv)
H2O
RT, under air, 1h
10
R2Li
H2O
RT, under air, 3s
11: up to 95% yield
(e)
12
R3Li
or
R3MgBr(Cl)
ChCl/urea or H2O
RT, under air, 20 s
13
R3Li: 60–98% yield; R3MgBr(Cl): 75–95% yield
(f)
14
PhLi
H2O
RT, under air, 1 min
15
cysteamine·HCl
or L-cysteamine·HCl
TFA, H2O
RT, under air, 2h
16a: R = CO2H, 80% yield
16b: R = H, 84% yield
(g)
17
n-BuLi
ChCl/Gly
ultrasound
(35 KHz and 160 W)
40 min/40 °C
under air
18
ChCl/Gly
19: up to 90% yield
Ar = Ph, 4-F-C6H4, 4-Cl-C6H4, 4-MeO-C6H4, 2-pyridyl, 4-pyridyl
(h)
(SS)-20
R2M
D-sorbitol/ChCl
RT, 2 min, under air
M = Li, MgCl
R1,R2 = alkyl, aryl
21
major
minor
1) HCl (2.0 M)
D-sorbitol/ChCl
RT, under air, 3 h
2) NaHCO3 aq.
22
(R,R)-Formoterol (23) 93% ee
chiral amine side chain
(SS,R)-24
(R)-Cinacalcet (25)
98% ee
(i)
29: up to 63% yield
or
28: up to 79% yield
R3MgX
2-MeTHF
RT, 3 s, under air
26
R2Li
2-MeTHF
RT, 3 s, under air
27: up to 93% yield
R2 = alkyl; R3 = alkyl or aryl; X = Br, Cl


(a)
t-Bu3P–Pd(I)(μ-I)2Pd(I)–Pt-Bu3
X
Het
Br
R 30
+
MgCl
Y 31
32 (2.5 mol%)
toluene
5 min, RT
under air
33: up to 96% yield
R = Me; X = Cl, OTf; Y = Me, Cl, F
(b)
X
Het
Br
R1 34
+
Het
ZnCl
R2 35
32 (2.5 mol%)
toluene/THF
5 min, RT
under air
36: up to 98% yield
R1 = Me, CHO, CN, CO2Me
R2 = Me, MeO; X = Cl, OTf
(c)
Cy2t-BuP–Pd–Pd–Pt-BuCy2
Cl
Het
OTf(OFs)
R1 38
+
R2ZnCl
39
37 (2.5 mol%)
NMP
<10 min, RT
under air
R2
40: up to 95% yield
R1 = Br, alkyl; R2 = alkyl, (hetero)aryl; Cy = cyclohexyl
(d)
Het
X
41
+
RLi
42
R = alkyl; Pd-PEPPSI-IPr (1.5 or 3 mol%)
R = aryl; Pd(Pt-Bu3)2 (2 mol%)
RT, 10 min, neat
X = Br, Cl; R = alkyl, (hetero)aryl
43: up to 98% yield
(e)
44
45
Pd(Pt-Bu3)2 (2.5 mol%)
RT, under air, 20 s
H2O, NaCl
X = Br, Cl; R = alkyl, aryl
46: up to 98% yield
(f)
47
RZnX
48
Pd(Pt-Bu3)2 (2.5 mol%)
RT, under air or 60 °C, 20 s
H2O, NaCl or ChCl/urea
X = Br, Cl; R = alkyl, (hetero)aryl
49: up to 98% yield
(g)
RX
50
Zn (20-30 mesh granular)
mixer mill, 30 Hz
4 h, DMA
[RZnX]
51
Pd-PEPPSI-i-Pent (1 mol%)
ArX
mixer mill, 30 Hz
4 h, TBAB
R–Ar
52: up to 98% yield
R = alkyl, aryl
X = Br, I
DMA = dimethylacetamide; TBAB = tetrabutylammonium bromide


(a)
HP(R1)2
53
n-BuLi
ChCl/Gly
RT, under air, 3 s
LiP(R1)2
54
57a: R1,R2 = Ph; 3s: 95% yield; 30 s: 77% yield
O
H
R2
55
RT, under air, 3 s
HO
R2
O
P
R1
R1
57: up to 94% yield
O
R3
R4
56
RT, under air, 3 s
O
P
R1
R1
R3
R4
OH
58: up to 89% yield
(b)
O
R1
OEt
59
LiNR2R3
60
2-MeTHF
RT, under air, 20 s
O
R1
NR2R3
61: up to 89% yield
(c)
O
Ph
NBoc2
62
LiNR2R3
60
2-MeTHF
RT, under air, 20 s
O
Ph
NR2R3
63: up to 77% yield
(d)
R1
R2
64
LiNR3R4
65-Li
30 min, 900 rpm
2-MeTHF
RT, under air
Li
R1
NR3R4
R2
66
HNR3R4
65-H
LiNR3R4
65-Li
H
R1
NR3R4
R2
67: up to >99% yield
R1 = H, R2 = 4-Me, R3,R4 = -(CH2)5-: 90% yield vs 28% yield under N2

- Main-group-metal-mediated organic synthesis can be run under air and moisture, and often at room temperature.
- Pd-catalyzed reactions promoted by organometallic compounds of s- and d-block elements can be performed under air and moisture, and under mild conditions.
- DESs and water represent alternative and effective reaction media to VOCs in the chemistry of s- and d-block elements.
- Polar organometallic and alkali-metal reagents exhibit a remarkable kinetic stability and a recalcitrance to hydrolysis when using in water and DESs.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: