Organozinc Reagents

Air-Stable Solid Aryl and Heteroaryl Organozinc Pivalates: Syntheses and Applications in Organic Synthesis

Sophia M. Manolikakes,^[a] Mario Ellwart,^[a] Christos I. Stathakis,^[b] and Paul Knochel*^[a]

Abstract: A wide range of air-stable, solid, polyfunctional aryl and heteroarylzinc pivalates were efficiently prepared by either magnesium insertion or Hal/Mg exchange followed by transmetalation with $Zn(OPiv)_2$ (OPiv = pivalate). By reducing the amount of LiCl the air stability could be significantly enhanced compared with previously prepared reagents. An alternative route is directed magnesiation using TMPMgCl-LiCl (TMP = 2,2,6,6-tetramethylpiperidyl) followed by transmetala

Introduction

Organozinc reagents play a major role in organometallic chemistry due to their high compatibility with a broad variety of functional groups.^[1] Moreover, they are valuable reagents for transition-metal mediated C–C bond-formation reactions, such as Negishi cross-coupling,^[2] allylation,^[3] or acylation^[4] reactions. However, their limited stability towards air and moisture represents a serious drawback for their practical use in the laboratory and for industrial applications.

To overcome this problem, we recently developed a method for the preparation of aryl and heteroaryl zinc pivalates, which are easy-to-handle solids with exceptional stability when exposed to air.^[5] These zinc reagents can be prepared by magnesium insertion or halogen-magnesium exchange followed by transmetalation with $Zn(OPiv)_2 \cdot 2 \operatorname{LiCl}(1 \mathbf{a}, OPiv = \text{pivalate})$ to give the corresponding aryl, heteroaryl, and benzylic zinc reagents of general formula RZnOPiv·Mg(OPiv)X \cdot 2 \operatorname{LiCl}(X = CI, Br, I).^[5a] A halogen–lithium exchange followed by transmetalation with $Zn(OPiv)_2$ (1 b) proved to be a feasible way to prepare 2pyridylzinc reagents.^[5d] Another possible route is directed metalation using the sterically hindered base TMPMgCI·LiCl^[6] (2, TMP = 2,2,6,6-tetramethylpiperidyl) and subsequent addition of Zn(OPiv)₂ (1 b), giving organozinc reagents of the type

_	
[a]	S. M. Manolikakes, M. Ellwart, Prof. Dr. P. Knochel
	Department Chemie
	Ludwig-Maximilians-Universität München
	Butenandtstrasse 5–13, Haus F, 81377 München (Germany)
	Fax: (+49)89-2180-77680
	E-mail: paul.knochel@cup.uni-muenchen.de
[b]	Dr. C. I. Stathakis
	Pharmathen S.A., 9th km Thermi-Thessaloniki
	Thessaloniki 57001 (Greece)
	Supporting information for this article is available on the WWW under
	http://dx.doi.org/10.1002/chem.201403015.

tion with $Zn(OPiv)_2$ or, for very sensitive substrates, direct zincation by using TMPZnOPiv. These zinc reagents not only show excellent stability towards air, but they also undergo a broad range of C–C bond-formation reactions, such as allylation and carbocupration reactions, as well as addition to aldehydes and 1,4-addition reactions. Acylation reactions can be performed by using an excess of TMSCI to overcome side reactions of the omnipresent pivalate anion.

RZnOPiv·Mg(OPiv)Cl·LiCl. The air-stability of such zinc organometallics was substantially superior to organozinc pivalates prepared by magnesium insertion (or exchange).^[5b] In the presence of sensitive functionalities such as an aldehyde or a nitro group, the milder zinc amide base TMPZnOPiv·Mg(OPiv)-Cl·LiCl^[5c] (**3**) may be used for highly selective metalation reactions to give the desired organozinc reagents, which undergo a range of reactions with various electrophiles.

Previous work describes mainly the behavior of organozinc pivalates in Negishi cross-coupling reactions. Herein, we have expanded the scope of these new air-stable organometallics. We have now investigated the reactivity of organozinc pivalates in 1,4-additions,^[7] carbocuprations^[8] as well as allylations, acylation reactions and their addition to aldehydes.

Results and Discussion

As shown previously, reducing the amount of the hygroscopic lithium chloride from 2.5 to 1.25 equivalent improves the airand moisture-stability of the corresponding zinc reagents.^[5b] Therefore, we have performed the transmetalation step not with $Zn(OPiv)_2 \cdot 2$ LiCl (**1a**) but with the LiCl-free salt $Zn(OPiv)_2$ (**1b**). Thus, the magnesium insertion reaction was performed in the presence of 1.25 equivalent of LiCl^[9] at ambient temperature followed by addition of solid $Zn(OPiv)_2$ (**1b**, 1.2 equiv; Scheme 1, method A). Exchange reactions were performed by using *i*PrMgCl·LiCl (1.1 equiv) at low temperature, and subsequent transmetalation with **1b** gave the desired organozinc pivalates (method B). In both cases, the solid organozinc pivalates were obtained after solvent evaporation in high vacuum (0.1 mm Hg, 3–6 h).

Although, we call these reagents organozinc pivalates and associate these compounds with the formula "RZnOPiv", this is certainly an oversimplification because it does not take account of the magnesium and lithium salts present in these

© 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Chem. Eur. J. 2014, 20, 1–10

Wiley Online Library

These are not the final page numbers! 77



Scheme 1. Synthesis of organozinc pivalates through Mg insertion (method A) or Hal/Mg exchange (method B) followed by transmetalation with $Zn(OPiv)_2$. [a] Mg(OPiv)Hal-LiCl omitted for clarity.

mixtures. Structural studies in solution and on the crystal performed by Mulvey and Hevia indicate that these reagents are actually organozinc halides complexed with magnesium pivalate and lithium chloride.^[10] Therefore, a more accurate way to describe these trimetallic clusters would be the general formula: "RZnHal·Mg(OPiv)₂-LiCl" (Hal = Br, I, Cl). For clarity, we will use the formula RZnOPiv in this manuscript.

By using method A, 2-bromo-4-chloro-1-methoxybenzene (4a) reacted readily with Mg (2.5 equiv) in the presence of LiCl (1.25 equiv) to give, after transmetalation with Zn(OPiv)₂ (1 b), the desired organozinc pivalate 5a in 92% yield (Table 1, entry 1). The more sensitive 4-ethyl iodobenzoate (4b) was converted into the corresponding organozinc reagent by performing a Mg/I exchange using *i*PrMgCl·LiCl (1.1 equiv, -30°C, 30 min) followed by addition of 1b according to method B to furnish the zinc reagent 5b in 92% yield (entry 2). By using the same method at ambient temperature, 4-substituted iodobenzene 4c was converted into zinc reagent 5c in 91% yield (entry 3). The electron-rich halides **4d**-**f** underwent smooth Mg-insertion at 25 $^\circ\text{C}$ in 2–3 h to give, after transmetalation with Zn(OPiv)₂ (1b), zinc pivalates 5d-f in 79-92% yield (entries 4-6). 4-Bromobenzonitrile (4g) as well as bromopyrimidine 4h were converted into the corresponding organozinc species 5g-h by using iPrMgCl·LiCl (1.1 equiv, 0°C, 1-12 h) and subsequent addition of Zn(OPiv)₂ (1b, 1.2 equiv) in 72-84% yield (entries 7 and 8). A Mg-insertion was also performed on 3-bromobenzothiophene (4i, 25 °C, 3 h) leading, after transmetalation with 1b, to the zinc reagent 5i in 91% yield (entry 9).

The resulting solid organozinc reagents showed enhanced air-stability compared with zinc pivalates prepared using Zn-(OPiv)₂•2LiCl.^[5a] When, for instance, reagent **5a** was exposed to air, 91% of the initial activity was retained after 1 h exposure at 25 °C. Even after 4 h air exposure, 81% of the original activity remained.^[11] The zinc reagents not only displayed high stability towards air and moisture, but they also showed high reactivity in copper-catalyzed allylation reactions. Thus, zinc pivalate 5 a reacted readily with 3-bromocyclohexene (6 a, 1.1 equiv, -20° C, 2 h) in the presence of 10 mol% CuCN-2 LiCl^[4b] to give the expected product 7 a in 81% yield (Scheme 2). The organozinc pivalate 5 b showed similar reactivity and furnished, after reaction with 6a (1.1 equiv) in the presence of CuCN-2LiCl (10 mol%) within 1 h at -20 °C, the desired product 7b in 78% yield. By using the same conditions, zincated pyrimidine 5h afforded allylated heterocycle 7c in 81% yield.









Scheme 2. Copper-catalyzed allylation of various zinc reagents with 3-bromocyclohexene (6a). [a] Mg(OPiv)Hal-LiCl omitted for clarity.

Acylation reactions were performed by using stoichiometric amounts of CuCN-2 LiCl (1.1 equiv) and an excess of TMSCI (6.0 equiv). We have observed that in the absence of TMSCI the reactivity of the acyl chlorides dropped significantly. This might be due to competitive formation of a mixed anhydride

Chem. Eur. J. 2014, 20, 1 – 10 www.ch

www.chemeurj.org

2



Scheme 3. Copper-mediated acylation of the zinc reagents 5 a and 5 b.

by the reaction of the pivalate anion (PivO⁻) with the acyl chloride. This mixed anhydride is a weaker acylating reagent, which results in very slow conversion into the desired products. We assume that the role of the TMSCI is to trap the free PivO⁻ in the form of the silyl ester **9**' (Scheme 3). Under optimized reaction conditions, **5a** underwent a smooth acylation reaction with 2-furoyl chloride (**8a**) at 25 °C in 3 h, furnishing ketone **9a** in 96% yield (Scheme 3). The organozinc pivalate **5b** reacted in a similar way with either the perfluorinated benzoyl chloride **8b** or 4-bromobenzoyl chloride (**8c**), producing the desired compounds **9b–c** in 62–84% yield.

Besides allylations and acylations, carbocuprations of alkynes were also performed in the presence of CuCN-2 LiCl (1.1 equiv). Thus, the pyrimidine derivative **5h** reacted with diethyl but-2-ynedioate (**10a**, 1.2 equiv, -30 to -10 °C in THF) to give the copper intermediate **11**, which could be trapped with either water or allyl bromide (**6b**, 1.5 equiv, 2 h) leading to the formation of alkenes **12a** and **12b** in 63 and 72% yield, respectively. In both cases, the *Z*-isomer was the major product (*Z*/*E*=9:1; Scheme 4).^[12] The addition of TMSCI proved to be disadvantageous for carbocupration reactions and led only to decomposition of starting material.

4-(Ethoxycarbonyl)phenylzinc pivalate (**5 b**) reacted under similar conditions in the presence of CuCN-2LiCl (1.1 equiv) with ethyl propiolate (**10 b**, -10 °C, 2 h in THF) to afford, after quenching with water, the *E* alkene **12 c** selectively in 63%



Scheme 4. Carbometalation of diethyl but-2-ynedioate (10a) in the presence of CuCN-2 LiCl by using solid heteroaromatic zinc pivalate 5 h.

Chem. Eur. J. **2014**, 20, 1–10

www.chemeurj.org



yield (Table 2, entry 1). Likewise, silyl ether **5e** reacted with ethyl propiolate (**10b**, -30°C, 5 h) and furnished, after addition of an excess of iodine, trisubstituted alkene **12d** in 60% yield (entry 2). A *syn*-carbocupration was performed by reacting benzothiophene derivative **5i** with diethyl but-2-ynedioate (**10a**, -30°C, 15 h). The generated copper intermediate was then allylated with ethyl 2-(bromomethyl)acrylate (**6c**, 1.5 equiv, -30°C, 2 h) to provide tetrasubstituted alkene **12e** in 60% yield with an *E/Z* ratio of 91:9 (entry 3). The organozinc reagent **5a** also underwent carbocupration with ethyl propiolate (**10b**, 1.2 equiv, -10°C, 6 h) in the presence of CuCN-2LiCI (1.1 equiv) to furnish, after hydrolysis, *E*-alkene **12f** in 48% yield (entry 4).

The addition of an organozinc pivalate to an aldehyde has only been briefly studied.^[5a] In preliminary experiments we have noticed a low reactivity of these organozinc reagents towards aldehydes. This low reactivity can be overcome by the addition of $Ti(O/Pr)_4$.^[13] Best results were obtained by using equimolar amounts of AlMe₃ in toluene/THF at 25 °C, as reported by Woodward et al.^[14] The role of AlMe₃ may be to facilitate conversion of RZnX (X = Br, I, OPiv) species into mixed organozinc reagents of type RZnMe (**13**), which may possess a higher reactivity than the corresponding organozinc halides (Scheme 5). Thus, when zinc reagent **5b** was treated with AlMe₃ (1.0 equiv, 25 °C, 10 min), the addition of the resulting zinc species to benzaldehyde (**14**, 0.8 equiv, 25 °C, 2 h) proceeded smoothly to give alcohol **15a** in 94% yield (Scheme 5).

These are not the final page numbers! 77





Scheme 5. AlMe $_3$ -mediated addition of organozinc pivalates of type 5 to benzaldehyde (14).

Organozinc pivalates 5a,c,f,g reacted similarly and carbinols 15b-e were obtained in 57-72% yield.

1,4-Addition reactions to conjugated double bonds are generally performed with organocuprates.^[7f-I] However, solid functionalized zinc pivalates of type **5** showed only moderate reactivity toward a Michael addition to cyclohex-2-enone in the presence of CuCN-2LiCl and TMSCI. Thus, when zinc reagent **5b** was treated with cyclohex-2-enone (**16**, 0.8 equiv) in the



Scheme 6. 1,4-Addition of functionalized organozinc reagent 5 b to cyclohex-2-enone (16 a). [a] Determined by GC-analysis of hydrolyzed reaction aliquots. [b] Isolated yield of analytically pure product.

presence of CuCN-2 LiCl (1.1 equiv, 25 °C) only a low conversion into the desired product **17a** was observed (Scheme 6). The 1,4-addition of zinc pivalates of type **5** was improved by using a method reported by Frost,^[15] whereby rhodium-catalyzed addition of 2-heteroarylzinc reagents to Michael acceptors was used. This method was derived from the rhodium-catalyzed addition of organoboron reagents to α , β -unsaturated carbonyls, pioneered by Hayashi and Miyaura.^[16] Hence, in the presence of 3 mol% [Rh(COD)Cl]₂, **5b** added readily to the Michael acceptor **16a** to give the desired product **17a** in 95% yield (Scheme 6).

The 4-substituted organozinc pivalates 5c, 5d, and 5g underwent Michael addition with cyclohexe-2-one (**16a**) under the same conditions using 3 mol% [Rh(COD)Cl]₂, and the corresponding cyclohexanone derivatives **17 b**–**d** were obtained in 88–97% yield (Scheme 7). Disubstituted zinc reagent **5a** also underwent a smooth rhodium-catalyzed 1,4-addition to **16a**,



Scheme 7. Rhodium-catalyzed 1,4-addition of functionalized organozinc reagents of type 5 to cyclohex-2-enone (16a) and (*E*)-chalcone (16b).

leading to arylated ketone **17 e** in 91% yield. Heterocyclic reagent **5 i** underwent such Michael-addition to cyclohex-2enone (**16 a**), leading to 3-substituted benzothiophene **17 f** in 91% yield (Scheme 7). Zinc reagent **5 b** also underwent 1,4-addition to the acyclic Michael acceptor (*E*)-chalcone (**16 b**) to give the desired ketone **17 g** in 84% yield. The use of α , β -unsaturated esters led only to decomposition of starting materials and only low conversions into the desired products could be observed by GC-analysis.

Although aryl and heteroaryl halides used for the preparation of solid organozinc pivalates of type **5** are readily available, it was envisioned that these organometallics could be prepared by directed metalation, which would allow the scope of our preparations to be expanded to include various arenes and heteroarenes as convenient starting materials. The sterically hindered base TMPMgCl-LiCl (**2**) was used to deprotonate various carbo- and heterocycles^[6] and the resulting magnesium reagents were transmetalated by using $Zn(OPiv)_2$ (**1 b**) (Table 3).^[5b] This procedure gives access to a range of new solid zinc reagents that show very high stability when exposed to air.

Thus, ethyl 3-fluorobenzoate (18a) was readily metalated by using ${\bf 2}$ (1.1 equiv 0 $^\circ C,$ 2 h) and led, after transmetalation with $Zn(OPiv)_2$ (1 b, 1.2 equiv), to the formation of zinc reagent 19a in 92% yield (Table 3, entry 1). Chloro-substituted derivative 18b and the Boc-protected ester 18c also reacted under similar conditions (0°C, 3-6 h), furnishing, after solvent evaporation, solid organozinc pivalates 19b-c in 93-95% yield (entries 2 and 3). Trisubstituted pyridine 18d was also metalated by using TMPMgCl·LiCl (2, 1.1 equiv) at -40 °C for 2 h and, after subsequent transmetalation with Zn(OPiv)₂ (1b), zinc reagent 19d was obtained in 84% yield. Zincated pyrazine derivatives 19e-f were obtained in the same way in 86-89% yield by treating 18e and 18f with base 2 (1.1 equiv, -20 to -45 °C, 2–4 h) followed by transmetalation with Zn(OPiv)₂ (**1 b**) (entries 5 and 6). Trisubstituted pyrimidine 18g and 2,4-dimethoxypyrimidine (18h) were both metalated by using

www.chemeurj.org

4

© 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



CHEMISTRY A European Journal Full Paper



TMPMgCl·LiCl (2, 1.1 equiv) at 25 °C within 30 min and provided, after transmetalation with 1b, solid organozinc reagents 19g-h in 85-92% yield (entries 7 and 8). Isoquinoline 18i was readily magnesiated by using 2 (1.1 equiv, 25 °C, 1 h) and, after transmetalation to Zn(OPiv)₂ (1b), reagent 19i was obtained in 85% yield (entry 9). Ester substituted bromofuran 18 j required a lower temperature of $-25\,^\circ\text{C}$ for the metalation with 2 (1.1 equiv, 1 h), however, after addition of zinc pivalate (1 b) the perfectly stable zinc species 19 j was obtained in 77% yield (entry 10). Finally, by following this procedure, pyrazole derivatives 18k-I were converted into the corresponding zinc reagents 19 k-l in 83-85% yield (entries 11 and 12). As described in our previous work, aryl and heteroaryl zinc pivalates of type 19 proved to be excellent nucleophiles in Negishi cross-couplings.^[5b] Herein, we report further reactions of the solid zinc reagents of type 19. Thus, zinc reagent 19a was treated with allyl bromide (6b, 1.2 equiv, -20°C, 1h, THF) in the presence of 10 mol% CuCN·2LiCl, which furnished the trisubstituted benzene derivative 20 a in 98% yield (Scheme 7). Acylation was performed under similar conditions used for the reagents of type 5 (Scheme 3). Thus, when organozinc pivalate 19a was treated with benzoyl chloride (8d) and CuCN-2LiCl (1.1 equiv) in the presence of an excess of TMSCI, ketone 20b was obtained in 89% yield. TMSCI is necessary for such an acylation; in its absence only traces of the desired product were obtained (Scheme 8).



Scheme 8. CuCN-2 LiCI-mediated reactions of functionalized organozinc reagent 19a with allyl bromide (6b) and benzoyl chloride (8d).

Chloro-derivative 19b was allylated in a similar way by using 3-bromo-2-methylpropene (6d, 1.2 equiv, -20°C, 1 h) in the presence of 10 mol% CuCN-2LiCl to give the product 20c in 87% yield (Table 4, entry 1). Acylation of 19b by using either 3-chlorobenzoyl chloride (8e, 1.0 equiv, -45 to 25 $^\circ$ C, 2 h) or cyclopropanecarbonyl chloride (8 f, 1.0 equiv, 0 to 25 °C, 2 h), after transmetalation with CuCN-2LiCl (1.1 equiv) and in the presence of an excess of TMSCI, furnished ketones 20 d-e in 71-85% yield (entries 2 and 3). The Boc-protected zinc reagent 19c was allylated with ethyl 2-(bromomethyl)acrylate (6c, 1.0 equiv, -20° C, 5 h) to give the desired product **20 f** in 80% yield (entry 4). The heterocyclic zinc reagents 19d and 19e also underwent smooth acylation reactions with 3,4,5-trimethoxybenzoyl chloride (8g, 1.0 equiv, -20 to 25 °C, 4 h) and cyclohexanecarbonyl chloride (8h, 1.0 equiv, 0 to 25°C, 2h), to give ketones 20g-h in 68-93% yield (entries 5 and 6). Zincated pyrazine derivative **19 f** as well as zincated pyrimidine **19 g** were allylated by using 3-bromocyclohex-1-ene (6a, 1.0 equiv, -20 °C, 2 h) in the presence of 10 mol % CuCN-2 LiCl to provide

www.chemeuri.org

Chem. Eur. J. 2014, 20, 1-10









the desired products 20 i-j in 89-93% yield (entries 7 and 8). Zincated pyrimidine 19g and zincated isoquinoline 19i were also acylated by using cyclopropanecarbonyl chloride (8 f, 1.0 equiv, 25 °C, 2 h) and furnished, after aqueous workup, ketones 20k and 20m in 56-95% yield (entries 9 and 11). Zincated pyrimidine derivative 19h reacted with 3-bromo-2-methylpropene (6 d, 1.2 equiv, -20° C, 1 h) to give allylated product 201 in 93% yield (entry 10). Zincated furan derivative 19j underwent smooth acylation by using 2-furoyl chloride (8 a, 1.0 equiv, 25 °C, 2 h) to furnish the desired ketone 20 o in 74% yield (entry 13). Pyrazole derivative 19k was acylated with benzoyl chloride (8d, 1.0 equiv, -20 °C, 2 h) to give ketone 20 p in 79% yield (entry 14). Finally, zinc reagent 191 underwent smooth allylation reaction with 3-bromocyclohex-1-ene (6a, 1.0 equiv, -20 °C, 2 h) leading to the product **20 q** in 82% yield (entry 15).

The methods described above for the preparation of solid organozinc reagents might be incompatible with the presence of sensitive functionalities such as an aldehyde or related carbonyl groups. To overcome this limitation, we envisioned the use of a milder zinc amide base for preparing the solid zinc pivalates. In his pioneering work, Kondo introduced lithium ditert-butyl-tetramethylpiperidino zincate (tBu₂Zn(TMP)Li) as an excellent base for the directed metalation of aromatics.[17] Other zincates and related ate bases have also been reported.^[18] Recently, we prepared a new base by treating TMPMgCl·LiCl (2) with $Zn(OPiv)_2$ (1b, 1.05 equiv) to give the corresponding zinc amide, tentatively written as TMPZnOPiv·Mg(OPiv)Cl·LiCl (3; Scheme 9).^[5c] This base proved to be compatible with functionalities such as a nitro group, an aldehyde, or sensitive heteroaromatic rings, and gives access to a multitude of new solid organozinc pivalates, which show excellent stability towards air.[11]

Chem. Eur. J. **2014**, 20, 1 – 10

www.chemeurj.org

6





Scheme 9. Preparation of the zinc base 3 by transmetalation of TMP-MgCl·LiCl (2) with $Zn(OPiv)_2$ (1 b). [a] Complexed Mg(OPiv)Cl and LiCl are omitted for clarity.



Thus, when 3,6-dichloropyridazine (**22a**) was treated with zinc base **3** (1.1 equiv) at 25 °C for 30 min, the solid zinc reagent **23a** was obtained in 75% yield after solvent evaporation (Table 5, entry 1). This zincated pyridazine showed excelent stability and, after 4 h exposure to air, 95% of the initial activity remained.^[11] Under microwave irradiation, 2-chloropyrazine (**22b**) was regioselectively metalated with **3** at 90°C within 2 h to give the organozinc pivalate **23b** in 90% yield (entry 2).

Trichlorobenzene **22 d** was also readily deprotonated by TMPZnOPiv (**3**, 1.1 equiv) under microwave irradiation (160 °C, 1 h) to give, after solvent evaporation, zinc species **23 d** in 76% yield (entry 4). This mild base tolerates an aldehyde func-

These are not the final page numbers! **77**

tion present in the benzothiophene derivative **22e**, which was converted into the stable organozinc reagent **23e** in 89% yield (entry 5). Caffeine (**22 f**) was also metalated at 25 °C within 30 min to give zincated caffeine derivative **23 f** in 95% yield (entry 6).

The resulting organozinc reagents of type **23** show a reactivity that was similar to those of type **19** (Table 3). Thus, zinc pivalate **23 a** was iodinated by using an excess of iodine at 25 °C to furnish halogenated pyridazine **24 a** in 92% yield (Scheme 10). Copper-mediated reactions also proceeded readily. When **23 a** was treated with 3-bromocyclohex-1-ene (**6 a**, 1.2 equiv) in the presence of 10 mol% CuCN-2LiCl, the allylat-



Scheme 10. Reactions of functionalized organozinc reagent 23 a with various electrophiles. [a] Only trace amounts of 24 c were observed without the addition of TMSCI.

ed product **24b** was obtained in 90% yield. As described for zinc reagents of type **5** and **19**, the acylation reactions required the presence of an excess of TMSCI. Hence, when **23a** was treated with TMSCI (6.0 equiv), the acylation with benzoyl chloride (**8d**, 2.5 equiv) provided ketone **24c** in 96% yield. The reaction with 2-furoyl chloride (**8a**, 2.5 equiv) also proceeded well and furnished the desired product **25d** in 87% yield.

Zincated pyrazine derivative 23b was also iodinated with iodine (2.0 equiv, 30 min, 25 °C) to give 2-chloro-3-iodopyrazine (24e) in 93% yield (Table 6, entry 1). An allylation reaction using 3-bromocyclohex-1-ene (6a, 1.2 equiv) in the presence of 10 mol% CuCN-2LiCl provided the product 24 f in 91% yield (entry 2). lodolysis of zinc pivalate 23 c furnished tetrasubstituted benzene derivative 24 g in 91% yield (entry 3). Acylation reactions on 23c in the presence of an excess of TMSCI and stoichiometric amounts of CuCN-2LiCl by using cyclobutanecarbonyl chloride (8 i, 2.5 equiv, -30 °C, 30 min) or perfluorinated benzoyl chloride 8b (2.5 equiv, 0°C, 12 h) provided the corresponding ketones 24h and 24i both in 95% yield (entries 4-5). Trichloroarylzinc reagent 23d was allylated by using 3-bromo-2-methylpropene (**6 d**, 1.2 equiv, -20° C, 45 min) to give alkene 24j in 94% yield (entry 6). Acylation of 23d was performed by using cyclobutanecarbonyl chloride (8i, -20°C,





30 min) and ketone **24k** was obtained in 95% yield (entry 7). Benzothiophene **23e** underwent smooth iodolysis to give iodinated heterocycle **24l** in 89% yield (entry 8). An allylation reaction by using **6a** (2.5 equiv, -20°C, 10 h) furnished the corresponding product **24m** in 95% yield (entry 9). Metalated caffeine **23f** reacted readily with allyl bromide **6d** (1.2 equiv, -20°C, 4 h) or with acyl chloride **8j** (2.5 equiv, -20°C, 15 h) to give caffeine derivatives **24n–o** in 73–94% yield (entries 10 and 11).

Conclusion

We have described a set of efficient preparations of solid, airstable zinc reagents by using either Mg insertion or a bromineor iodine-magnesium exchange. Alternatively, directed metalation performed with TMPMgCI·LiCl (2) followed by transmetalation with $Zn(OPiv)_2$ (1b), or directed zincation by using the base "TMPZnOPiv" (3) were used to produce a range of solid zinc pivalates. We have shown that the stability of these zinc reagents can be enhanced by reducing the amount of LiCl present. The reactivity scope of these zinc reagents was investigated. Not only Negishi cross-couplings but also coppermediated carbocupration, acylation, and allylation reactions were efficiently performed with organozinc pivalates. In addition, AIMe₃-mediated addition to aldehydes, or Rh-catalyzed 1,4-addition reactions are also possible. These solid zinc reagents open a range of new potential applications of zinc compounds in organic synthesis. By lowering the sensitivity towards air and moisture, these zinc compounds are much more practical to use in conventional synthesis or in high-throughput screenings. Further investigation of these solid, air-stable organozinc reagents is currently underway in our laboratories.

Experimental Section

(5-Chloro-2-methoxyphenyl)zinc pivalate (5 a)

A dry and argon-flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with magnesium turnings (304 mg, 12.5 mmol), flame-dried anhydrous LiCl (318 mg, 7.50 mmol), and THF (15 mL). 2-Bromo-4-chloro-1-methoxybenzene (1.11 g, 5.0 mmol) was added. If necessary, the Schlenk-flask was placed in a water bath for cooling during the initial heat evolution of the insertion reaction. The progress of the insertion reaction was monitored by GC-analysis of reaction aliquots quenched with aq. sat. NH₄Cl solution and/or I₂. Upon completion of the insertion after 2 h at 25 °C, solid Zn(OPiv)₂ (1.61 g, 6.00 mmol) was added in one portion. After stirring at 25 °C for 15 min, the solvent was carefully removed in vacuo. The arylzinc pivalate **5a** was obtained as a pale-gray solid. Titration with iodine gave a concentration of the active zinc species of 1.01 mmolg⁻¹, which corresponds to a yield of 92%.

(5-Chloro-2-methoxyphenyl)(furan-2-yl)methanone (9a)

(5-Chloro-2-methoxyphenyl)zinc pivalate (**5 a**, 0.99 g, 1.01 mmol g⁻¹, 1.0 mmol) dissolved in anhydrous THF (3 mL) was cooled to -20 °C. TMSCI (652 mg, 6.0 mmol) was added followed by 30 min stirring. CuCN-2 LiCl (1 m in THF, 1 mL, 1 mmol) and furan-2-carbon-yl chloride (**8 a**, 130 mg, 1.0 mmol) were added subsequently and

Chem. Eur. J. **2014**, 20, 1 – 10

www.chemeurj.org

FF These are not the final page numbers!



the reaction mixture was stirred for 3 h at 25 °C. After quenching with an aqueous NH₄Cl/NH₃(conc.) (8:1, 4 mL) the mixture was extracted with ethyl acetate (5×8 mL). The combined organic layers were dried over Na2SO4 and, after filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (silica gel; isohexane/EtOAc=5:1) afforded the product 9a (227 mg, 96%) as a white solid. M.p. 78.6-80.6°C; ¹H NMR (300 MHz, CDCl₃): δ = 7.63 (dd, J = 0.8, 1.7 Hz, 1 H), 7.43–7.34 (m, 2 H), 7.04 (dd, J = 0.8, 3.6 Hz, 1 H), 6.91 (d, J=8.8 Hz, 1 H), 6.53 (dd, J=1.7, 3.6 Hz, 1 H), 3.77 ppm (s, 3 H); ¹³C NMR (75 MHz, CDCl₃): δ = 181.5, 156.3, 152.8, 147.7, 132.0, 129.4, 129.4, 125.7, 120.9, 113.2, 112.6, 56.4 ppm; IR (ATR): $\tilde{\nu} = 2923$, 2853, 1643, 1600, 1561, 1486, 1460, 1403, 1386, 1312, 1301, 1284, 1274, 1252, 1228, 1181, 1153, 1131, 1098, 1077, 1018, 984, 966, 945, 938, 900, 891, 882, 858, 810, 772, 736, 677, 640, 618 cm⁻¹; MS (70 eV, EI): m/z (%) = 236 (100) $[M]^+$, 219 (70), 207 (85), 291 (28), 184 (16), 157 (17), 139 (21), 126 (35), 111 (29), 75 (20), 63 (24); HRMS (EI): *m/z* calcd for C₁₂H₉ClO₃: 236.0240; found: 236.0236.

Acknowledgements

The research leading to these results received funding from the European Research Council under the European Community's Seventh Framework Programme (FP7/2007–2013) ERC grant agreement no. 227763. We thank the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft (DFG) for financial support. We also thank BASF SE (Ludwigshafen), Heraeus Holding GmbH (Hanau), and Rockwood Lithium GmbH (Frankfurt) for generous gifts of chemicals.

Keywords: copper \cdot magnesium \cdot metalation \cdot synthetic methods \cdot zinc

- a) P. Knochel, J. Almena, P. Jones, *Tetrahedron* **1998**, *54*, 8275; b) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem.* **2000**, *112*, 4584–4606; *Angew. Chem. Int. Ed.* **2000**, *39*, 4414–4435; c) P. Knochel, N. Millot, A. L. Rodriguez, C. E. Tucker, *Org. React.* **2004**, *58*, 417–759; d) P. Knochel, H. Leuser, L.-Z. Cong, S. Perrone, F. F. Kneisel in *Handbook of Functionalized Organometallics* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**, pp. 251–333; e) A. Lemire, A. Côté, M. K. Janes, A. B. Charette, *Aldrichimica Acta* **2009**, *42*, 71–83.
- [2] a) E. Negishi, A. O. King, N. Okukado, J. Org. Chem. 1977, 42, 1821; b) E. Negishi, L. F. Valente, M. Kobayashi, J. Am. Chem. Soc. 1980, 102, 3298; c) G. Wang, N. Yin, E. Negishi, Chem. Eur. J. 2011, 17, 4118; d) E. Negishi, X. Zeng, Z. Tan, M. Qian,Q. Hu, Z. Huang in Metal-Catalyzed Cross-Coupling Reactions, 2ednd ed(Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, 2004, pp. 815–877; e) A. A. Zemtsov, N. S. Kondratyev, V. V. Levin, M. I. Struchkova, A. D. Dilman, J. Org. Chem. 2014, 79, 818.
- [3] a) F. Dübner, P. Knochel, Angew. Chem. 1999, 111, 391; Angew. Chem. Int. Ed. 1999, 38, 379; b) F. Dübner, P. Knochel, Tetrahedron 2000, 41, 9233; c) H. Malda, A. W. van Zijl, L. A. Arnold, B. L. Feringa, Org. Lett. 2001, 3, 1169; d) C. A. Falciola, A. Alexakis, Eur. J. Org. Chem. 2008, 3765; e) K. Geurts, S. P. Fletcher, A. W. van Zijl, A. J. Minnaard, B. L. Feringa, Pure Appl. Chem. 2008, 80, 1025; f) E. Erdik, M. Koçoğlu, J. Organomet. Chem. 2009, 694, 1890.
- [4] a) E. Nakamura, I. Kuwajima, J. Am. Chem. Soc. 1984, 106, 3368; b) P.
 Knochel, M. Yeh, S. Berk, J. Talbert, J. Org. Chem. 1988, 53, 2390; c) P.
 Knochel, S. A. Rao, J. Am. Chem. Soc. 1990, 112, 6146.
- [5] a) S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, Angew. Chem. 2011, 123, 9372; Angew. Chem. Int. Ed. 2011, 50, 9205; b) C. I. Stathakis, S. Bernhardt, V. Quint, P. Knochel, Angew. Chem. 2012, 124, 9563; Angew. Chem. Int. Ed. 2012, 51, 9428; c) C. I. Stathakis, S. M. Manolikakes, P. Knochel, Org. Lett. 2013, 15, 1302; d) J. R. Colombe, S. Bernhardt, C. Stathakis, S. L. Buchwald, P. Knochel, Org. Lett. 2013, 15, 5754.

- [6] a) A. Krasovskiy, V. Krasovskaya, P. Knochel, Angew. Chem. 2006, 118, 3024; Angew. Chem. Int. Ed. 2006, 45, 2958; b) S. H. Wunderlich, C. J. Rohbogner, A. Unsinn, P. Knochel, Org. Process Res. Dev. 2010, 14, 339; c) T. Kunz, P. Knochel, Angew. Chem. 2012, 124, 1994; Angew. Chem. Int. Ed. 2012, 51, 1958.
- [7] Rh-catalysis: a) M. Sakai, H. Hayashi, N. Miyaura, Organometallics 1997, 16, 4229; b) T. Hayashi, K. Yamasaki, Chem. Rev. 2003, 103, 2829; c) T. Hayashi, Russ. Chem. Bull. 2003, 52, 2595; d) J. Le Nôtre, D. van Mele, C. G. Frost, Adv. Synth. Catal. 2007, 349, 432; e) J. C. Allen, G. Kociok-Köhn, C. G. Frost, Org. Biomol. Chem. 2012, 10, 32; Cu-catalysis: f) E. Na-kamura, S. Matsuzawa, Y. Horiguchi, I. Kuwajima, Tetrahedron Lett. 1986, 27, 4029; g) V. Wendisch, N. Sewald, Tetrahedron: Asymmetry 1997, 8, 1253; h) M. Kitamura, T. Miki, K. Nakano, R. Noyori, Bull. Chem. Soc. Jpn. 2000, 73, 999; i) A. Wilsily, E. Fillion, Org. Lett. 2008, 10, 2801; j) A. Wilsily, T. Lou, E. Fillion, Synthesis 2009, 2066; k) A. Quintarda, A. Alexakisa, Adv. Synth. Catal. 2010, 352, 1856; l) M. Tissot, A. Pérez Hernández, D. Müller, M. Mauduit, A. Alexakis, Org. Lett. 2011, 13, 1524.
- [8] a) H. Chechik-Lankin, I. Marek, Synthesis 2005, 3311; b) A. Abramovitch, I. Marek, Eur. J. Org. Chem. 2008, 4924; c) J. P. Das, H. Chechik, I. Marek, Nat. Chem. 2009, 1, 128; d) B. Dutta, N. Gilboa, I. Marek, J. Am. Chem. Soc. 2010, 132, 5588; e) C. Dunst, A. Metzger, E. A. Zaburdaeva, P. Knochel, Synthesis 2011, 3453; f) A. Frischmuth, P. Knochel, Angew. Chem. 2013, 125, 10268; Angew. Chem. Int. Ed. 2013, 52, 10084; g) Y. Minko, M. Pasco, H. Chechik, I. Marek, Beilstein J. Org. Chem. 2013, 9, 526; h) W. Gati, F. Couty, T. Boubaker, M. M. Rammah, M. B. Rammah, G. Evano, Org. Lett. 2013, 15, 3122; for reviews on carbocupration reactions, see also: i) J. F. Normant, A. Alexakis, Synthesis 1981, 841; j) N. Krause in Modern Organocopper Chemistry (Ed.: N. Krause), Wiley-VCH, Weinheim 2002; k) N. Chinkov, D. Tene, I. Marek in Metal-Catalyzed Cross-Coupling Reactions, 2ednd ed(Eds.: F. Diederich, A. de Meijere), Wiley-VCH, Weinheim 2004; I) A. Basheer, I. Marek, Beilstein J. Org. Chem. 2010, 6, 77.
- [9] In the absence of LiCl, the solubility dropped significantly, which reduced the reactivity of the corresponding zinc reagent.
- [10] A. Hernán-Gómez, E. Herd, E. Hevia, A. R. Kennedy, P. Knochel, K. Koszinowski, S. M. Manolikakes, R. E. Mulvey, C. Schnegelsberg, *Angew. Chem.* 2014, 126, 2744; *Angew. Chem. Int. Ed.* 2014, 53, 2706.
- [11] See the Supporting Information for more detailed stability studies.
- [12] The Z/E ratio was determined by GC-analysis of the crude hydrolyzed reaction mixture. The stereochemistry was confirmed by a NOESY experiment (see the Supporting Information).
- [13] a) F. Langer, L. Schwink, A. Devasagayaraj, P.-Y. Chavant, P. Knochel, J. Org. Chem. **1996**, *61*, 8229; b) H. Li, P. J. Walsh, J. Am. Chem. Soc. **2005**, *127*, 8355; c) S.-J. Jeon, H. Li, P. J. Walsh, J. Am. Chem. Soc. **2005**, *127*, 16416.
- [14] J. Shannon, D. Bernier, D. Rawson, S. Woodward, *Chem. Commun.* 2007, 3945.
- [15] J. Le Nôtre, J. C. Allen, C. G. Frost, Chem. Commun. 2008, 3795.
- [16] a) Y. Takaya, M. Ogasawara, T. Hayashi, M. Sakai, N. Miyaura, J. Am. Chem. Soc. 1998, 120, 5579; b) see the Supporting Information in: T. Hayashi, Synlett 2001, 0879; c) T. Hayashi, Bull. Chem. Soc. Jpn. 2004, 77, 13; d) K. Yoshida, T. Hayashi in Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine (Ed.: D. G. Hall), Wiley-VCH, Weinheim, 2006, pp. 171–203.
- [17] a) Y. Kondo, H. Shilai, M. Uchiyama, T. Sakamoto, *J. Am. Chem. Soc.* 1999, 121, 3539; b) T. Imahori, M. Uchiyama, Y. Kondo, *Chem. Commun.* 2001, 2450; c) P. F. H. Schwab, F. Fleischer, J. Michl, *J. Org. Chem.* 2002, 67, 443; d) M. Uchiyama, T. Miyoshi, Y. Kajihara, T. Sakamoto, Y. Otami, T. Ohwada, Y. Kondo, *J. Am. Chem. Soc.* 2002, 124, 8514.
- [18] a) E. Hevia, G. W. Honeyman, R. E. Mulvey, J. Am. Chem. Soc. 2005, 127, 13106; b) M. Uchiyama, Y. Matsumoto, D. Nobuto, T. Furuyama, K. Yamaguchi, K. Morokuma, J. Am. Chem. Soc. 2006, 128, 8748; c) W. Clegg, S. H. Dale, A. M. Drummond, E. Hevia, G. W. Honeyman, R. E. Mulvey, J. Am. Chem. Soc. 2006, 128, 7434; d) D. R. Armstrong, W. Clegg, S. H. Dale, E. Hevia, L. M. Hogg, G. W. Honeyman, R. E. Mulvey, Angew. Chem. 2006, 118, 3859; Angew. Chem. Int. Ed. 2006, 45, 3775.

Received: April 9, 2014 Published online on ■■ ■, 0000

Chem.	Eur. J.	2014,	20,	1 –	10	w١
-------	---------	-------	-----	-----	----	----

www.chemeurj.org

9

 $\ensuremath{\mathbb{C}}$ 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

These are not the final page numbers! **77**



FULL PAPER

Organozinc Reagents

S. M. Manolikakes, M. Ellwart, C. I. Stathakis, P. Knochel*

Air-Stable Solid Aryl and Heteroaryl Organozinc Pivalates: Syntheses and Applications in Organic Synthesis $\begin{array}{c|c} Ar-Hal & \underset{exchange}{\text{insertion or}} & R & \underset{exchange}{ \end{array} & Ar & Ar & H \\ Ar-H & \underset{metalation}{\text{directed}} & Ar-ZnOPiv & R'CHO & Ar & OH \\ \hline R'COCI & Ar-COR & R'COCI & Ar-COR \\ \hline R'COCI & Ar-COR & R'COCI & R'COCI \\ \hline R'COCI & Ar-COR & R'COCI & R'COCI \\ \hline R'COCI & R'COCI & R'COCI & R'COCI & R'COCI \\ \hline R'COCI & R'COCI & R'COCI & R'COCI & R'COCI \\ \hline R'COCI & R'COCI & R'COCI & R'COCI & R'COCI & R'COCI \\ \hline R'COCI & R'CO$

Reactive but stable: The preparation of polyfunctional, air-stable, solid aryl and heteroaryl organozinc pivalates by either Mg insertion or Hal–Mg (Hal = Br, I) exchange, followed by transmetalation with $Zn(OPiv)_2$ (OPiv = pivalate) or alternatively by directed metalation is

described. The zinc reagents show excellent stability in air (up to 4 h at 25 °C) and undergo a range of reactions including allylation, acylation, and carbocupration reactions, additions to aldehydes, and 1,4-addition reactions (see scheme).

© 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

