

Atroposelective Ni^{II}-Catalyzed Cross-Coupling Reactions Enable a Deeper Understanding of Negishi Couplings: Isolation and Application of Solid Aryl Higher-Order Zincates

Damian Groß,^[a] Willem A. L. van Otterlo,^{*,[c]} Oliver Trapp,^{*,[b]} and Dino Berthold^{*,[a]}

The Negishi cross-coupling reactions involves the application of organozinc reagents and is a highly versatile reaction in synthetic organic chemistry. The transmetalation step plays a pivotal role in the mechanism of these types of cross-coupling reactions. In this study, mechanistic investigations are presented indicating that higher-order zincates are the transmetalating active species in Pd- and Ni-catalyzed Negishi cross-coupling reactions. These findings are supported by halide salt

addition experiments and by obtaining a single X-ray crystal structure of the solid monoaryl higher-order zincate $[1\text{-NaphthylZnX}_3]^{2-}\text{Mg}(\text{THF})_2^{2+}$. The procedure developed in this work was further applied to the synthesis of various monoaryl higher-order zincates, after which their synthetic usefulness in terms of high reactivity towards transmetalation in Negishi cross-couplings, as well as stability, was exemplified in several reactions.

Introduction

Since its discovery by Negishi in 1977, the Negishi cross-coupling reaction comprising the transition metal-catalyzed reaction of organozinc reagents with organohalides has been recognized as a useful tool for the construction of C–C bonds.^[1] Although organozinc reagents are not as stable against air and moisture as their organotin and organoboron counterparts employed in Stille and Suzuki–Miyaura cross-coupling reactions, they nonetheless offer certain benefits including low toxicity, facile preparations^[2a] and high functional group tolerance.^[2] Usually, of the various organometallic compounds (B, Sn, Al, Zr,

Cu) employed in transition metal-catalyzed cross-coupling reactions the organozinc reagents are recognized as the most reactive in Pd-catalyzed cross-coupling reactions.^[3] Furthermore, the expensive Pd-base catalysts can be replaced by alternative metals, first and foremost Ni, as well as Fe, Co or Cu.^[4] For Ni- and Pd-catalyzed coupling reactions it is generally accepted that the Negishi cross-coupling reaction, as well as the above mentioned other Pd-catalyzed cross-coupling reactions, proceeds via a generic three-stage mechanism involving oxidative addition (OA), transmetalation (TM) and reductive elimination (RE) (Scheme 1). However, recent studies have unveiled that this catalytic cycle is oversimplified regarding the apparent additives, which often results as salts from the synthesis of the zinc reagents, and their essential role in Negishi cross-coupling reactions. The latter has been extensively investigated in the recent past by a number of groups. From 2009, Koszinowski and Organ, respectively, reported of the discovery of lower-order $[\text{R-ZnX}_2]^- \text{M}^+$ and higher-order zincates $[\text{R-ZnX}_3]^{2-} \text{M}^{n+}$

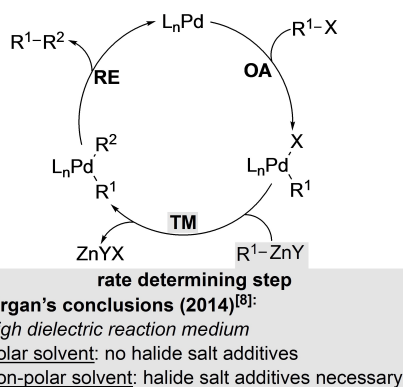
[a] D. Groß, Dr. D. Berthold
Department Chemie
Ludwig-Maximilians-Universität München
Butenandtstraße 5–13, Haus F, 81377 München (Germany)
E-mail: dino.berthold@cup.lmu.de

[b] Prof. Dr. O. Trapp
Department Chemie
Ludwig-Maximilians-Universität München
Butenandtstraße 5–13, Haus F, 81377 München (Germany)
E-mail: oliver.trapp@cup.uni-muenchen.de
Homepage: <http://www.cup.lmu.de/oc/trapp>

[c] Prof. W. A. L. van Otterlo
Department of Chemistry and Polymer Sciences
Stellenbosch University
Private Bag XI, Matieland 7602, Stellenbosch (South Africa)
ORTEP
E-mail: wvo@sun.ac.za
Homepage: <http://willemvanotterlo.co.za>

Supporting information for this article is available on the WWW under <https://doi.org/10.1002/chem.202302841>

© 2023 The Authors. Chemistry - A European Journal published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution Non-Commercial NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.



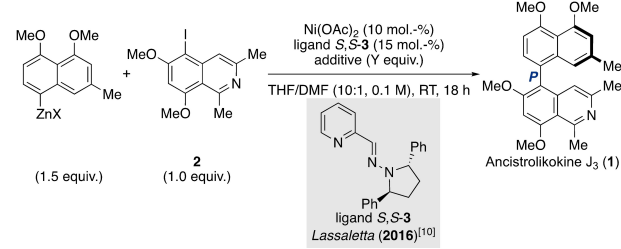
Scheme 1. Organ's proposed catalytic cycle for the Negishi cross-coupling reaction involving arylzinc reagents including the role of salt additives and polarity of reaction media.

obtained via the titration of alkyl and aryl reagents by means of MS and NMR investigations.^[5] Furthermore, it was observed in titration studies by Organ and Clyburne that for the Pd-catalyzed alkyl-alkyl Negishi cross-coupling reactions the higher-order mono-zincate is the only transmetallating active species.^[6,7] Although the transmetalation of sp^2 -hybridized zinc reagents is considered to be faster and therefore easier than their sp^3 -hybridized counterparts, significant inconsistencies became apparent in further titration studies by Organ in 2014.^[8] In contrast to alkylzinc reagents, their aryl substituted counterparts demonstrated the following different reactivities in Pd-catalyzed Negishi cross-coupling reactions: 1. diarylzinc reagents are capable of mono-transmetallating in low dielectric solvents in the absence of salt additives, 2. heteroleptic $ArZnX$ reagents require either a high dielectric solvent (e.g. DMI) or the addition of salt additives in lower dielectric solvents (e.g. THF). The latter observation was attributed to the fact, that sufficient amounts of salt is required to increase the medium's polarity to break down $ArZnX$ aggregates and not for the formation of higher-order monoaryl zincates (Scheme 1).^[8]

Results and Discussion

Herein, we report of our contrary observations that higher-order zincates are actually the transmetallating active species for monoaryl zincates – as well as monoalkyl zincates. Our first indication on the special role of salts present in the Negishi cross-coupling reaction was due to our observations during the optimization of an atroposelective,^[9] $Ni^{II}/N,N$ -ligand-catalyzed cross-coupling reactions employing Lassaletta's ligand^[10] reaction towards the synthesis of the two naphthylisoquinoline enantiomers Ancistrolikokine J_3 (**1**) and Ancistrobreveine D (*ent*-**1**).^[11] To our surprise, the outcome of the synthesis of either of these two enantiomeric natural products was dependent on the method applied for the synthesis of the zinc reagent and its accompanying salt additives, rather than the added salt additives alone. As it is depicted in Table 1, we only obtained the desired natural products **1** or *ent*-**1**, respectively, if the zinc reagent was prepared via the transmetalation of an previously generated organolithium or Grignard reagent (Table 1, entry 6 and 7).^[12] However, the stoichiometric addition of salt additives, such as LiBr and $MgBr_2 \cdot OEt_2$, to the final coupling conditions

Table 1. Initial observations regarding the nature of the applied zinc reagent in $Ni^{II}/N,N$ -ligand-catalyzed, atroposelective Negishi cross-coupling reactions.^{[a],[14]}



entry	zincate ($X =$) ^[b]	additive	yield	ee (1) ^[g]
1	I via direct Zn-insertion ^[c]	–	–	–
2	I via direct Zn-insertion ^[c]	LiBr (2.0 equiv.)	–	–
3	I via direct Zn-insertion ^[c]	LiBr (10 equiv.)	–	–
4	I via direct Zn-insertion ^[c]	$MgBr_2 \cdot OEt_2$ (1.0 equiv.)	–	–
5	I via direct Zn-insertion ^[c]	$MgBr_2 \cdot OEt_2$ (10 equiv.)	–	–
6	Br-LiBr-Li via transmetalation from organolithium ^[d]	–	23 %	92 %
7	Br-MgBr ₂ via transmetalation from Grignard ^[e]	–	70 %	96 %
8	OPIv via transmetalation from Grignard ^[f]	–	41 %	85 %

[a] All couplings were performed on a 0.2 mmol scale. [b] All zinc reagents were titrated against I_2 prior their application. [c] Zinc reagent was prepared from 5-iodo-1,8-dimethoxy-3-methylnaphthalene (**4**) via insertion of Zn dust in DMF. [d] Zn reagent was prepared from 5-bromo-1,8-dimethoxy-3-methylnaphthalene (**5**) via Br–Li-exchange and subsequent transmetalation to $ZnBr_2$. [e] Zn reagent was prepared from 5-bromo-1,8-dimethoxy-3-methylnaphthalene (**6**) via Grignard reaction and subsequent transmetalation to $ZnBr_2$. [f] Zn reagent was prepared from 5-bromo-1,8-dimethoxy-3-methylnaphthalene (**6**) via Grignard reaction, subsequent transmetalation to $Zn(OPiv)_2$ and evaporation of all volatiles. [g] Enantiomeric excesses were determined by chiral HPLC analysis. The absolute configuration of **1** was determined by comparing the rotation values with the literature. For further details, see the Supporting Information.

with a zinc reagent derived directly from the insertion of Zn to aryl iodide in DMF did not lead to product formation (Table 1, entry 2-5). This suggests that our developed coupling was dependent on the nature of the zinc reagent rather than the polarity of the reaction's media. Finally, we tested Knochel's bench-stable zinc pivalate reagent, which was synthesized from the Grignard reagent according to zinc reagent solution in entry 7.^[13] Interestingly, this zinc reagent (entry 8) did not provide similar reactivity as the latter, which might be attributed to the impact of the pivalate counter anion, in contrast to the bromide for the zinc reagent as part of the reaction conditions in entry 7.

To further investigate this interesting behavior, we decided to switch to more general and accessible substrates to eliminate effects of possible heteroatom ligation as well. First, we focused on the reactivity of the zinc reagent derived from the direct insertion of Zn dust into 1-iodonaphthalene (7) in DMF. Again, we observed no coupling with 1-bromo-2-methoxynaphthalene (8) at rt (Table 2, entry 1). Next, we treated the reaction mixture with different stoichiometric amounts (1.0 equiv., 2.0 equiv. and 10 equiv.) of commonly involved salt additives (Table 2, entries 2-4) observing no product formation. We then employed zinc reagents derived either from an I-Li or Br-Li exchange, as well as a Grignard derived reagent to the Ni-catalyzed cross-coupling conditions. To our delight, upon addition of these reagents to the cross-coupling reactions significant product formation was observed, thus confirming our hypothesis that these reagents are capable of transmetallation. Admittedly, the yields were rather low with organolithium derived zinc reagents (Table 2, entry 6 and 7), but similar in terms of iodide or bromide, apparently indicating that the counter anion does not play a crucial role in terms of reactivity towards the transmetallation process. Remarkably, we again obtained the desired product in 79% yield for the Grignard-derived zinc reagent (entry 8). Furthermore, we were interested to see, if preforming the directly derived zinc reagent with different stoichiometries of LiBr and MgBr₂·OEt₂ results in the formation of a reactive zinc species. However, preforming different amounts of salt additives with directly derived zinc reagent at rt for 1 h was not successful (Table 2, entry 9 and 10). In contrast to that, preforming the zinc reagent under refluxing conditions proved to be successful in providing a reactive reagent for the cross-coupling reactions (Table 2, entries 11-15). Furthermore, it became apparent that for the additive LiBr a minimum of 2 equivalents was required, whilst for MgBr₂·OEt₂ only 1.0 equivalent was required for a high conversion.

These experimental findings clearly underline that the reactivity of the zinc reagent in our catalytic system is not dependent on the salt additives increasing the polarity of the reaction medium. In contrast, our results provide strong evidence that by preforming the solution of salt-free zinc reagent under refluxing conditions a new transmetallating species is formed, which we investigated further.

These results were already accompanied by our observation, that during the synthesis of a Grignard-derived zinc reagent, as displayed in Table 2, entry 8, no solution was formed, but a thick, grey suspension was obtained and then directly applied

in the Ni-catalyzed Negishi cross-coupling reactions. Since our interest was piqued in terms of what the precipitated solid was, we examined it further (Scheme 2a). To do so, the solvent was removed by evaporation followed by drying under high vacuum to give in hand an off-white solid, which was recrystallized from a mixture of THF/CH₂Cl₂/n-pentane under inert conditions in a glove-box. The resulting crystals were suitable for single crystal structure analysis revealing its nature as a higher-order zincate [1-NaphthylZnX₃]²⁻Mg(THF)₂²⁺ (**12**).^[15] Noteworthy, its stoichiometric composition corresponded to the transmetallating higher-order ate-species postulated by Böhrer and Organ (Scheme 2b).^[5] Applying this procedure for different aryl zinc reagents several other higher-order zincates (**11-19**) have been isolated as solids in general high yields (Scheme 2c).^[16,17]

In our experience, it was reasonably simple to store these higher-order zincate reagents in a glove-box under inert conditions, however, we were also interested in evaluating their stabilities under air, as we handled them usually during reaction set-up. Therefore, we did a short stability screening with **12**, which showed that the higher-order zincate was stable to oxygen and atmospheric moisture for at least one hour without significant decomposition becoming evident. This characteristic is of course relevant for the practical application of these types of solid higher-order zincates (Figure 1).

With these readily applicable, highly reactive higher-order zincates in hand, we examined further cross-coupling reactions with these to exemplify their synthetic advantages. First, we conducted our Ni^{II}-catalyzed, atroposelective Negishi cross-coupling reaction with the solid higher zincate **12** in order to determine, whether it is superior to the applied zincate suspension in Table 2, entry 8. To our delight, we obtained the desired product in higher yield (82%) and higher enantioselectivity (91%) in comparison to our previous results (Scheme 3a). An advantage of the direct application of solid higher-order zincates is the possibility to carry-out cross-coupling reactions in pure, highly polar solvents or concentrated solutions

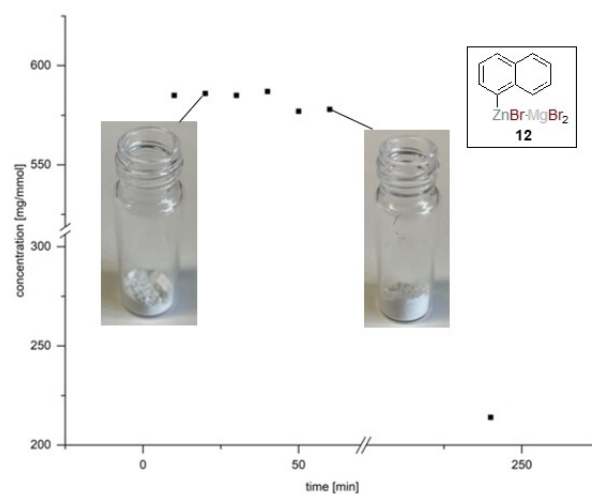
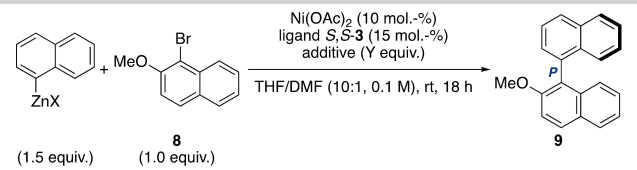


Figure 1. Determination of stability of higher-order zincate **12** via titration against iodine.

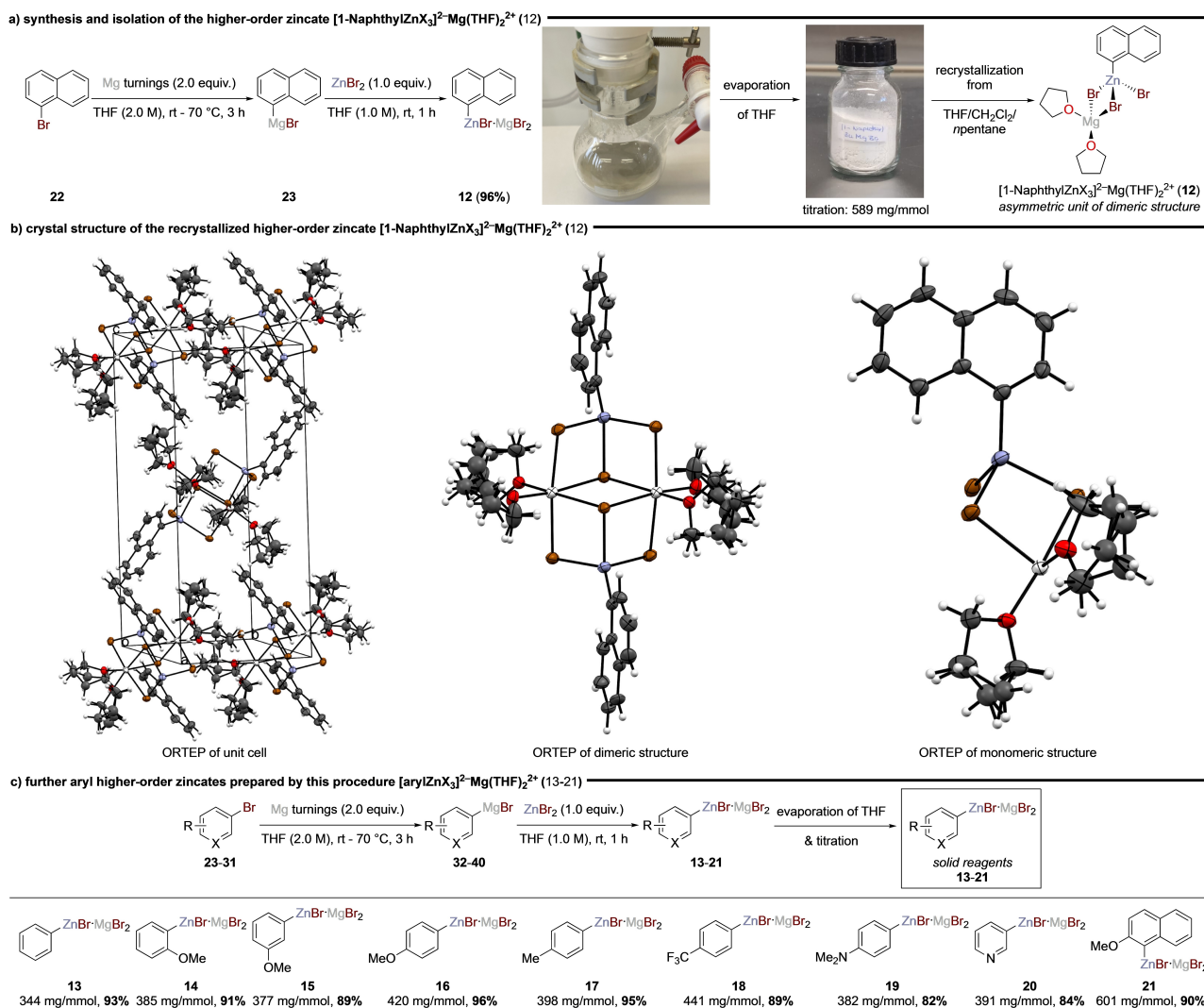
Table 2. Further investigations regarding the nature of the applied zinc reagent in Ni-catalyzed, atroposelective Negishi cross-coupling reactions.^{[a][14]}


entry	zincate (X=) ^[b]	additive	yield	ee (9) ^[f]
1	I via direct Zn-insertion ^[c]	–	–	–
2	I via direct Zn-insertion ^[c]	LiBr (1.0–10 equiv.)	–	–
3	I via direct Zn-insertion ^[c]	LiCl (1.0–10 equiv.)	–	–
4	I via direct Zn-insertion ^[c]	MgBr ₂ ·OEt ₂ (1.0–10 equiv.)	–	–
5	I via direct Zn-insertion ^[c]	ZnBr ₂ (1.0–10 equiv.)	–	–
6	Br·LiBr via transmetalation from organolithium ^[d]	–	19%	87%
7	I·LiBr via transmetalation from organolithium ^[d]	–	20%	85%
8	Br·MgBr ₂ via transmetalation from Grignard ^[e]	–	79%	89%
9	I via direct Zn-insertion ^[c] & preformed at rt for 1 h	LiBr (1.0–10 equiv.)	–	–
10	I via direct Zn-insertion ^[c] & preformed at rt for 1 h	MgBr ₂ ·OEt ₂ (1.0–10 equiv.)	–	–
11	I via direct Zn-insertion ^[c] & preformed at 80 °C for 1 h	LiBr (1.0 equiv.)	22%	90%
12	I via direct Zn-insertion ^[c] & preformed at 80 °C for 1 h	LiBr (2.0 equiv.)	60%	88%
13	I via direct Zn-insertion ^[c] & preformed at 80 °C for 1 h	LiBr (10 equiv.)	58%	84%
14	I via direct Zn-insertion ^[c] & preformed at 80 °C for 1 h	MgBr ₂ ·OEt ₂ (1.0 equiv.)	77%	91%
15	I via direct Zn-insertion ^[c] & preformed at 80 °C for 1 h	MgBr ₂ ·OEt ₂ (2.0 equiv.)/(10 equiv.)	78%/73%	89%/86%

[a] All couplings were performed on a 0.2 mmol scale. [b] All zinc reagents were titrated against I₂ prior their application. [c] Zinc reagent was prepared from 1-iodonaphthalene (10) via insertion of Zn dust in DMF. [d] Zn reagent was prepared from 1-bromonaphthalene (11) via Br–Li-exchange and subsequent transmetalation to ZnBr₂. [e] Zn reagent was prepared from 1-bromonaphthalene (11) via Grignard reaction and subsequent transmetalation to ZnBr₂. [f] Enantiomeric excesses were determined by chiral HPLC analysis. The absolute configuration of 1 was determined by comparing the rotation values with the literature. For further details, see the Supporting Information.

increasing their reactivity even further. To exemplify this, we conducted three Negishi cross-coupling reactions employing a standard catalyst such as Pd(PPh₃)₂Cl₂ either in pure THF, THF/DMA (1:1) or pure DMA at rt. In contrast to the aryl-aryl cross-coupling reactions in THF and THF/DMA (1:1), which showed only low conversion, the desired product was obtained in high yield (94%) for the reaction in DMA at elevated concentration (Scheme 3b). Next, we conducted a Co-catalyzed oxidative

homocoupling employing higher-order zincate **43** and benzoquinone. To our satisfaction, the desired homocoupled product **43** was obtained in 98% yield (Scheme 3c). We also conducted a Negishi cross-coupling reaction in THF and under air at rt, this time employing a less oxygen-prone Pd-catalyst to see if our thus obtained higher-order zincate would undergo coupling before succumbing to decomposition. Although in this case, the desired cross-coupled product was obtained in a lower



Scheme 2. Discovery and isolation of stable higher-order zincates: a) procedure for the synthesis of solid [1-NaphthylZnX₃]²⁻Mg(THF)₂²⁺ (12); b) ORTEP of crystal structures of [1-NaphthylZnX₃]²⁻Mg(THF)₂²⁺ (12); c) syntheses of different higher-order aryl zincates 13–21.^[15]

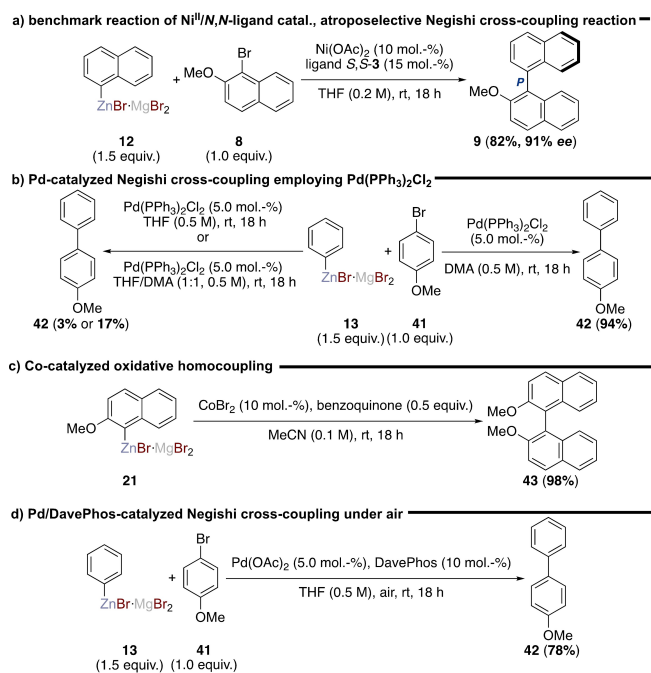
yield, when compared to the result from the application of Pd(PPh₃)₂Cl₂ in DMA under inert conditions, the 78% yield is still respectable (Scheme 3d).

Finally, we were interested, if our solid higher-order zincates prove to be more reactive than a zinc reagent and a lower-order zincate under Organ's conditions applying a Pd-PEPPSI-IPent catalyst.^[6] Therefore, we conducted three experiments employing directly derived PhZnI (44), a lower-order zincate [PhZnBr₂]⁻Li⁺ (45), which was synthesized via Br–Li exchange and subsequent transmetalation to zinc, and higher-order zincate [PhZnBr₃]²⁻Mg²⁺ (13). We were pleased that only the latter reagent 13 resulted in significant product formation supporting our hypothesis that the higher-order zincate is the major transmetalating species (Scheme 4a). Furthermore, we performed two competition experiments under the catalytic conditions employing directly derived PhZnI (44) or lower-order zincate [PhZnBr₂]⁻Li⁺ (45) versus higher-order zincate [4-Me-PhZnBr₃]²⁻Mg²⁺ (17). Employing 44 and 17 only cross-coupling product 46, which results exclusively from the higher-order

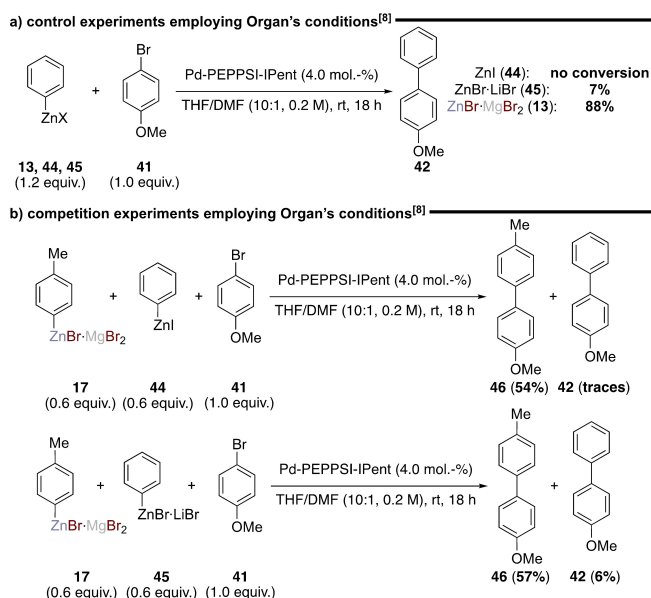
zincate 17, was obtained in 54% yield. Conducting the same experiment with 45 and 17, we obtained the product 46, resulting from the higher-order zincate 17, in 57% yield and 42 in a minor yield of 6%. In our opinion it remains unclear, if the latter outcome results from the minor reactivity of the lower-order zincate itself or from a preceding equilibrium between the lower-order and the higher-order zincate. However, the results of these two experiments clearly indicate that there is no direct or subsequent equilibrium between the zinc reagent or the lower-order zincate, respectively, and the higher-order zincate or the byproduct, respectively (Scheme 4b).

Conclusions

In conclusion, our research has revealed that apparent higher-order zincates were the reason behind our observed high reactivity of Grignard-derived zinc reagents in Negishi cross-coupling reactions. These aryl higher-order zincates, obtained



Scheme 3. Examples for the application of solid higher-order zincates to cross- and homo-coupling reactions.



Scheme 4. Control and competition experiments employing different zinc reagents including lower-order and higher-order zincates in Organ's initially reported catalytic system.

by the transmetalation from Grignard reagents or by heating a mixture of the unactivated zinc reagent with stoichiometric MgBr₂·OEt₂, are already solid and reasonable stable under atmospheric conditions. Furthermore, we are of the opinion that our observations cast doubt on Organ's assertions that the dependence of the reactivity on present salts is solely due to an increase in polarity of the reaction mixture. In addition, our straightforward protocol for the isolation of highly reactive,

higher-order zincates allows for the subsequent application in Negishi cross-coupling reactions exploiting certain advantages over general zinc reagents, namely: 1. providing free choice of solvent and flexibility in terms of the concentration of reaction mixture; 2. option of performing reactions at rt providing improved premises for asymmetric reactions; 3. no additive has to be applied to increase the reactivity of zinc reagents simplifying the overall procedure for Negishi cross-coupling reactions employing aryl higher-order zincates. In order to take advantage of these reaction improvements and flexibility, we are planning to further expand the synthetic values of these reagents in the near future. For instance, we will report in due course on the application of our herein discovered higher-order zincates in the further refinement and application of the Ni^{II}/*N,N*-ligand-catalyzed, atroposelective coupling methodology.

Supporting Information

The authors have cited additional references within the Supporting Information (Ref. [30,31]).

Acknowledgements

DB is very grateful for a Feodor-Lynen *Rückkehrstipendium* from the Alexander von Humboldt Foundation awarded to DB. We thank the analytical department of the Ludwigs-Maximilian-Universität München and especially Dr. Peter Mayer for the X-ray analysis. Open Access funding enabled and organized by Projekt DEAL.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

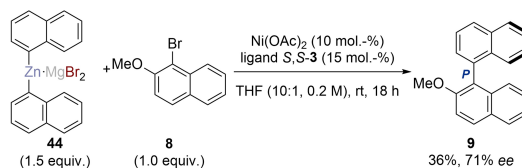
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: Negishi cross-coupling reaction · Nickel · organozinc reagent · salt effects · structure elucidation

[1] a) A. O. King, N. Okukado, E.-i. Negishi, *J. Chem. Soc. Chem. Commun.* **1977**, 683–684; b) E.-i. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821–1823.

[2] For recent reviews and book chapters concerning the Negishi cross-coupling reaction, see: a) E.-i. Negishi, F. Liu, *Palladium- or nickel-catalyzed cross-coupling with organometals containing zinc, magnesium, aluminum, and zirconium*. in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**, Germany, pp. 1–47; b) P. Knochel, P. Jones, F. Langer, *Organozinc Reagents* **1999**, 179–212; c) E.-i. Negishi, *J. Organomet. Chem.* **2002**, *653*, 34–40; d) E.-i. Negishi, Y. Dumond, *Handbook of Organopalladium Chemistry for Organic Synthesis* **2002**, *1*, 767–789; e) G. Lessene, *Aust. J. Chem.* **2004**, *57*, 107–107; f) V. B. Phapale, D. J. Cárdenas, *Chem. Soc. Rev.* **2009**, *38*,

- 1598–1607; g) E.-i. Negishi, *Angew. Chem. Int. Ed.* **2011**, *50*, 6738–6764; h) D. Haas, J. M. Hammann, R. Greiner, P. Knochel, *ACS Catal.* **2016**, *6*, 1540–1552; i) Y. Li, J. Long, G. Yin, *Recent Advances in Nickel-Catalyzed C–C Cross-Coupling. in C–C Cross-couplings with 3d Base Metal Catalysts. Topics in Organometallic Chemistry* (Eds.: X.-F. Wu), Springer Cham, Basel, **2023**, Switzerland, pp. 181–231.
- [3] a) L. Kürti, B. Czakó, *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier Academic Press, Burlington-San Diego-London, **2005**, pp. 310–312; b) C. A. Quesnelle, V. Snieckus, *Synthesis* **2018**, *50*, 4395–4412.
- [4] For examples of Fe, Co and Cu-catalyzed Negishi cross-coupling reactions, see: a) T. Hatakeyama, N. Nakagawa, M. Nakamura, *Org. Lett.* **2009**, *11*, 4496–4499; b) D. Haas, J. M. Hammann, F. H. Lutter, P. Knochel, *Angew. Chem. Int. Ed.* **2016**, *55*, 3809–3812; c) S. Thapa, A. Kafle, S. K. Gurung, A. Montoya, P. Riedel, R. Giri, *Angew. Chem. Int. Ed.* **2015**, *54*, 8236–8240.
- [5] a) K. Koszinovski, P. Böhler, *Organometallics* **2009**, *28*, 771–779; b) G. T. Achonduh, N. Hadei, C. Valente, S. Avola, C. J. O'Brien, M. G. Organ, *Chem. Commun.* **2010**, *46*, 4109–4111; c) H. N. Hunter, N. Hadei, V. Blagojevic, P. Patschinski, G. T. Achonduh, S. Avola, D. K. Bohme, M. G. Organ, *Chem. Eur. J.* **2011**, *17*, 7845–7851.
- [6] a) I. S. MacIntosh, C. N. Sherren, K. N. Robertson, J. D. Matsuda, C. C. Pye, J. A. C. Clyburne, *Organometallics* **2010**, *29*, 2063–2068; b) N. Hadei, G. T. Achonduh, C. Valente, C. J. O'Brien, M. G. Organ, *Angew. Chem. Int. Ed.* **2011**, *50*, 3896–3899; c) L. C. McCann, H. N. Hunter, J. A. C. Clyburne, M. G. Organ, *Angew. Chem. Int. Ed.* **2012**, *51*, 7024–7027.
- [7] In addition, Clyburne reported of the first X-ray crystal structure of a higher-order monoalkyl zincate $[\text{EtZnBr}_3]^-[\text{PPh}_3]^+$ by short circuiting the Schlenk equilibrium.^[5a] Applying this species in Pd-catalyzed Negishi cross-coupling reactions, significant product formation was observed without additional salts and polar co-solvents (e.g. DMI).^[5b]
- [8] L. C. McCann, M. G. Organ, *Angew. Chem. Int. Ed.* **2014**, *53*, 4386–4389.
- [9] a) M. C. Kozlowski, B. J. Morgan, E. C. Linton, *Chem. Soc. Rev.* **2009**, *38*, 3193–3207; b) G. Bringmann, T. Gulder, T. A. M. Gulder, M. Breuning, *Chem. Rev.* **2011**, *111*, 563–639; c) P. Loxq, E. Manoury, R. Poli, E. Deydier, A. Labande, *Coord. Chem. Rev.* **2016**, *308*, 131–190; d) G. Hedouin, S. Hazra, F. Gallou, S. Handa, *ACS Catal.* **2022**, *12*, 4918–4937; e) N. Tajuddeen, D. Feineis, H. Ihmels, G. Bringmann, *Acc. Chem. Res.* **2022**, *55*, 2370–2383.
- [10] Y. Álvarez-Casao, B. Estepa, D. Monge, A. Ros, J. Iglesias-Sigüenza, E. Álvarez, R. Fernández, J. M. Lassaletta, *Tetrahedron* **2016**, *72*, 5184–5190.
- [11] D. Berthold, W. A. L. van Otterlo, *Chem. Eur. J.* **2023**, *accepted article* 10.1002/chem.202302070.
- [12] However, directly prepared (4,5-dimethoxy-7-methylnaphthalen-1-yl)zinc iodide and 1-naphthylzinc iodide were reactive in the Ni^{II}/N,N-ligand catalyzed Negishi cross-coupling reaction, if the reaction was heated at 60 °C, at least.
- [13] a) C. I. Stathakis, S. M. Manolikakes, P. Knochel, *Org. Lett.* **2013**, *15*, 1302–1305; b) A. Hernán-Gómez, E. Herd, E. Hevia, A. R. Kennedy, P. Knochel, K. Koszinovski, S. M. Manolikakes, R. E. Mulvey, C. Schnegelsberg, *Angew. Chem. Int. Ed.* **2014**, *53*, 2706–2710; c) S. M. Manolikakes, M. Ellwart, C. I. Stathakis, P. Knochel, *Chem. Eur. J.* **2014**, *20*, 12289–12297;
- d) Y.-H. Chen, M. Ellwart, V. Malakhov, P. Knochel, *Synthesis* **2017**, *49*, 3215–3223; e) M. Ellwart, Y.-H. Chen, C. P. Tuellmann, V. Malakhov, P. Knochel, *Org. Synth.* **2018**, *95*, 127–141.
- [14] For the different Ni^{II}/N,N-ligand-catalyzed Negishi cross-coupling reaction displayed in Table and , as well as Scheme we observed two side products in generally minor yields (<10%) resulting from the protonation and the oxidative homo-coupling of the zinc reagent. However, side products resulting from the dehalogenation or homo-coupling of the electrophilic substrates were never detected, which means for cross-coupling reactions with incomplete conversion the corresponding halide starting material could be isolated in yields according to the corresponding conversions.
- [15] Deposition Number 2282094 (for **12**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.
- [16] Purity of the obtained aryl zinc reagents was determined via titration against I₂. For further information see the Supporting Information.
- [17] Diorganozinc reagents (R₂Zn), such as diaryl zinc reagents, have been observed to be more reactive towards cross-coupling than heteroleptic zinc reagents (RZnX).^[8] However, these reagents were not applicable for our Ni^{II}/N,N-ligand-based system, since the cross-coupled product was only obtained in low yield and enantiomeric purity.



- [18] J. Suffert, *J. Org. Chem.* **1989**, *54*, 509–510.
- [19] B. E. Love, E. G. Jones, *J. Org. Chem.* **1999**, *64*, 3755–3756.
- [20] M. Ellwart, Y.-H. Chen, C. P. Tuellmann, V. Malakhov, P. Knochel, *Org. Synth.* **2018**, *95*, 127–141.
- [21] a) Y. Fan, P. Feng, M. Liu, H. Pan, Y. Shi, *Org. Lett.* **2011**, *13*, 4494–4497; b) F. Wu, J. Zhang, F. Song, S. Wang, H. Guo, Q. Wie, H. Dai, X. Chen, X. Xia, X. Liu, L. Zhang, J.-Q. Yu, X. Lei, *ACS Cent. Sci.* **2020**, *6*, 928–938.
- [22] S. Fayeiz, D. Feineis, L. Aké Assi, E.-J. Seo, T. Efferth, G. Bringmann, *RSC Adv.* **2019**, *9*, 15738–15748.
- [23] D. Shen, Y. Xu, S.-L. Shi, *J. Am. Chem. Soc.* **2019**, *141*, 14938–14945.
- [24] Y. Wang, J. Luo, Z. Liu, *Appl. Organomet. Chem.* **2013**, *27*, 601–605.
- [25] K. Wongma, N. Bunbamrung, T. Thongpanchang, *Tetrahedron* **2016**, *72*, 1533–1540.
- [26] L. Wang, Z.-X. Wang, *Org. Lett.* **2007**, *9*, 4335–4338.

Manuscript received: August 31, 2023
 Accepted manuscript online: September 4, 2023
 Version of record online: October 17, 2023