

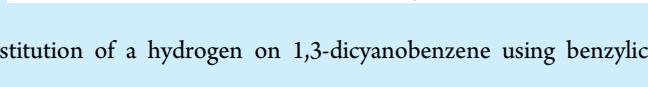
Transition-Metal-Free Cross-Coupling of Aryl and N-Heteroaryl Cyanides with Benzylic Zinc Reagents

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Supporting Information

ABSTRACT: Functionalized 4-benzylated pyridines can be efficiently prepared by a transition-metal-free cross-coupling between various benzylic zinc chlorides and substituted 4-cyanopyridines in THF/DMPU under microwave irradiation ($40\text{ }^{\circ}\text{C}$, 0.5–1.5 h). Selective benzylations on polycyanoaromatics have also been achieved under these mild conditions. We also report a novel oxidative nucleophilic substitution of a hydrogen on 1,3-dicyanobenzene using benzylic zinc reagents.



Transition-metal-catalyzed cross-couplings are standard methods for forming carbon–carbon bonds between aryl and heteroaryl organometallics and electrophiles.^{1,2} By far, the most common electrophiles ($\text{Ar}-\text{X}$) are organic halides ($\text{X} = \text{Cl}, \text{Br}, \text{I}$) and sulfonates ($\text{X} = \text{OTf}, \text{ONf}^3, \text{OTs}$ or OMs). Nevertheless, other leaving groups such as diazonium salts,⁴ trimethylammonium salts,⁵ and cyanides^{6–8} have been used. Most cross-coupling reactions involving cyanides require either transition metal catalysts,⁶ strong Lewis acids,⁷ or polar organometallics.⁸ Additionally, photoredox and photoinduced substitution reactions of aryl and *N*-heteroaryl cyanides have been reported.⁹ The performance of transition-metal-free cross-couplings is a valuable synthetic goal, and pioneering advances reported by E. Shirakawa and T. Hayashi,¹⁰ as well as M. Uchiyama¹¹ and M. J. Ingleson,¹² show the feasibility and significance of such reactions. Unfortunately, high temperatures and a somewhat reduced reaction scope limit in some cases synthetic applications. Our previous results on $\text{BF}_3\cdot\text{OEt}_2$ -mediated substitutions of cyanopyridines⁷ with alkylmagnesium reagents have demonstrated that a cyano group may be a better leaving group compared to a chloride. This led us to explore the scope of such substitutions further. Since benzylic zinc reagents are readily prepared and tolerate a range of functional groups,¹³ we anticipated that the enhanced ionic character of the benzylic carbon–zinc bond (compared to alkyl or aryl carbon–zinc bonds)¹⁴ may allow transition-metal-free cross-couplings. Herein, we report an efficient cross-coupling between various benzylic zinc reagents and aryl or *N*-heteroaryl cyanides under mild conditions, leading to 4-benzylated pyridines and cyano-substituted aromatics.

Preliminary results show that the treatment of 4-cyanopyridine (1a) with 3-(trifluoromethyl)benzylzinc chloride 3a¹⁵ in THF did not provide any substitution product ($25\text{ }^{\circ}\text{C}$, 16 h; entry 1 of Table 1). However, the use of a polar solvent such as DMPU¹⁶ (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) led to the formation of the 4-benzylated pyridine (2a)

Table 1. Optimization of the Reaction Conditions for the Cross-Coupling of 4-Cyanopyridine (1a) with the Benzylic Zinc Chloride (3a) Affording Pyridine (2a)

entry	solvent (ratio) ^a	conditions ($^{\circ}\text{C}$, h)	yield (%) ^b
1	THF	25, 16	<1
2	DMPU	25, 16	43
3	THF/DMPU (1:1)	25, 16	57
4	THF/DMPU (1:2)	25, 16	81
5	THF/TMU (1:2)	25, 16	52
6	THF/DMPU (1:2)	μW , 40, 0.5 h	>95 (94) ^c

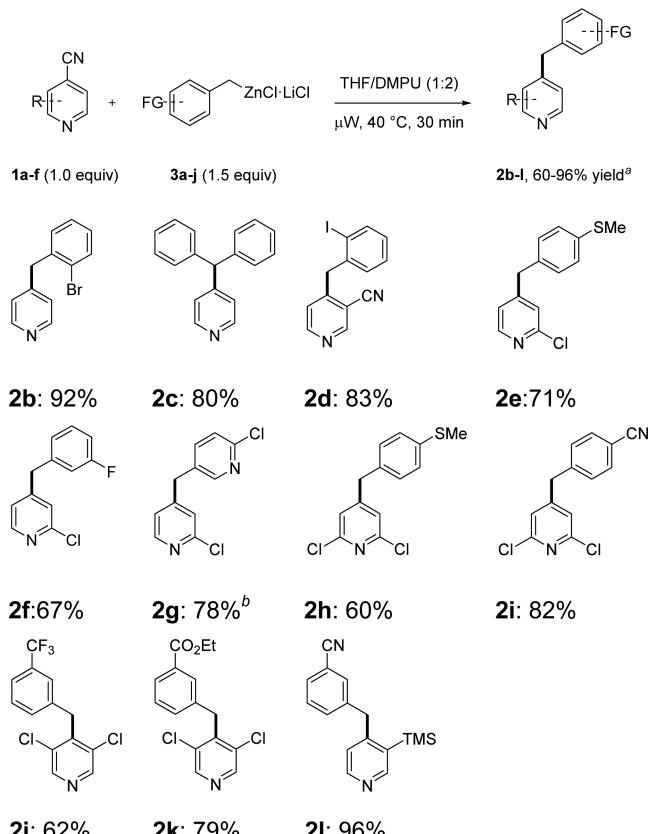
^aFor clarity, the ratio is given before the addition of the benzylic zinc reagent. ^b¹H NMR yield using 1,3,5-trimethoxybenzene as internal standard. ^cIsolated yield (TMU = tetramethylurea, μW = microwave irradiation).

in 43% yield (as determined by ¹H NMR analysis; entry 2). Variation of the solvent mixture allowed a boost in the reaction yield to 81% (entries 3–5). In addition, the reaction time could be considerably shortened by microwave irradiation^{17,18} (μW , $40\text{ }^{\circ}\text{C}$, 30 min; entry 6)¹⁹ leading to the 4-benzylated pyridine (2a) in 94% isolated yield.²⁰

Since a broad range of benzylic zinc reagents are available,¹³ a variety of 4-substituted pyridines of type 2 were readily prepared (Scheme 1). Thus, 2-bromobenzylzinc chloride (3b, 1.5 equiv) adds to 4-cyanopyridine (1a) in a 1:2 mixture of

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Scheme 1. Cross-Coupling between Functionalized 4-Cyanopyridines of Type 1 and Various Benzylid Zinc Chlorides of Type 3 Using Microwave Irradiation



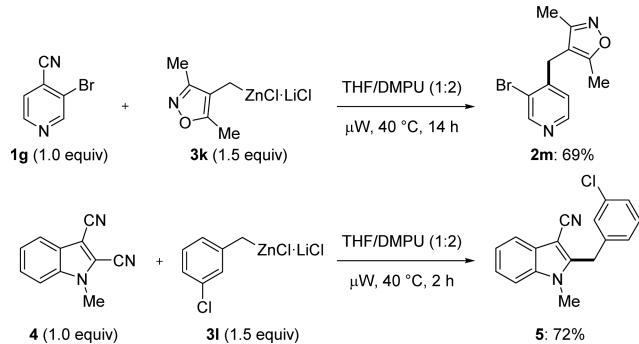
^aIsolated yield. ^bThe reaction was heated for 1 h.

THF/DMPU within 0.5 h at 40 °C using microwave irradiation and leading to the pyridine (**2b**) in 92% yield. Similarly, the addition of benzhydrylzinc chloride (**3c**) provides the 4-substituted pyridine (**2c**) in 80% yield. Substitution at the C(4)-position of the pyridine ring is strongly favored. Thus, the reaction of 3,4-dicyanopyridine (**1b**) with 2-iodobenzylzinc chloride (**3d**) furnishes the 4-benzylid pyridine (**2d**) as the only product in 83% yield.²¹ Remarkably, the substitution of the 4-cyano group is highly preferred compared to the 2-chloro substituent. This is a rather unusual selectivity, since 2-chloropyridines readily undergo substitution reactions.²² Hence, 2-chloro-4-cyanopyridine (**1c**) reacts with various benzylid zinc reagents (**3e-f**) and a heterobenzylid zinc chloride^{13d} (**3g**), leading to the corresponding 4-substituted pyridines (**2e-g**) in 67–78% yield. Even 2,6-dichloro-4-cyanopyridine (**1d**) prefers to undergo a substitution of the 4-cyano group with benzylid zinc reagents (**3e, 3h**), affording 4-benzylated pyridines (**2h-i**) in 60–82% yield. Furthermore, the reaction of 3,5-dichloro-4-cyanopyridine (**1e**) with benzylid zinc chlorides **3a** and **3i** furnishes the expected pyridines (**2j-k**) in 62–79% yield. A smooth addition of 3-cyanobenzylid zinc chloride (**3j**) occurs also to 3-trimethylsilyl-4-cyanopyridine (**1f**), leading almost quantitatively (96% yield) to the desired pyridine **2l**.

In addition, the substitution reaction allows linking two heterocyclic scaffolds in an efficient manner, avoiding the necessity of transition metal catalysis. Thus, 3-bromo-4-cyanopyridine (**1g**) reacts with the heterobenzylid zinc chloride

(**3k**) prepared from 4-(chloromethyl)-3,5-dimethyl-isoxazole²³ providing the isoxazole (**2m**) in 69% isolated yield (Scheme 2).

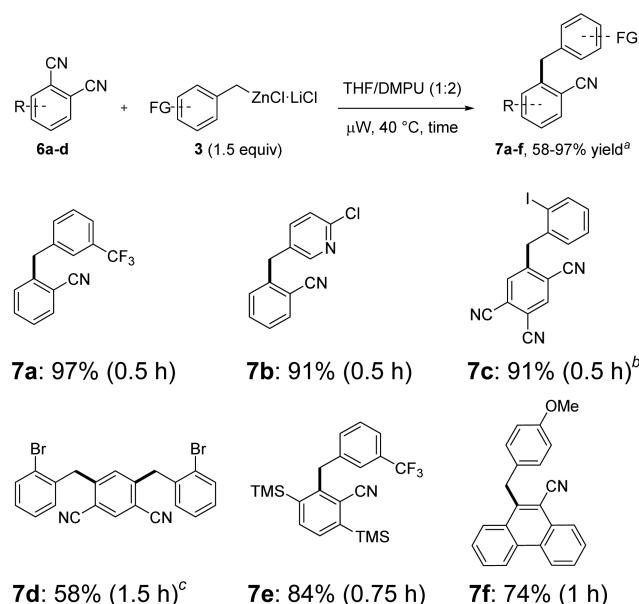
Scheme 2. Synthesis of Isoxazole (**2m**) and Regioselective Preparation of Indole (**5**) via Cross-Coupling with Benzylid Zinc Reagents under Microwave Irradiation



In addition, the 2,3-dicyano-indole **4** reacts regioselectively at the C(2)-position with the benzylid zinc chloride (**3l**), leading to 3-cyanoindole **5** (X-ray diffraction analysis)²⁴ in 72% yield (Scheme 2).²⁵

To expand the reaction scope, substitutions on various polycyano-aromatics were examined. It was found that 1,2-dicyanobenzene (**6a**) undergoes a smooth substitution with benzylid and heterobenzylid reagents **3a** and **3h**, providing the products of monocyano substitution (**7a-b**) in 91–97% yield (Scheme 3). In addition, the reaction of tetracyanobenzene (**6b**) with benzylid zinc chloride (**3c**; 1.0 equiv) furnishes solely the monosubstituted product (**7c**) in 91% yield. However, by treating **6b** with an excess of the benzylid zinc reagent (**3b**; 3.0 equiv; 1.5 h), 1,3-disubstituted dicyanide (**7d**) is obtained as the major product in 58% yield.

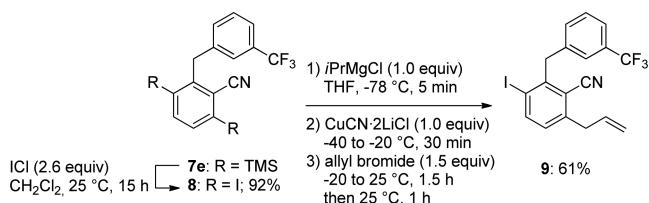
Scheme 3. Cross-Coupling between Aromatic Nitriles of Type 6 and Various Benzylid Zinc Chlorides of Type 3 under Microwave Irradiation



^aIsolated yield of analytically pure product. ^b1.0 equiv of benzylid zinc chloride **3c** was used. ^c3.0 equiv of benzylid zinc chloride **3b** were used.

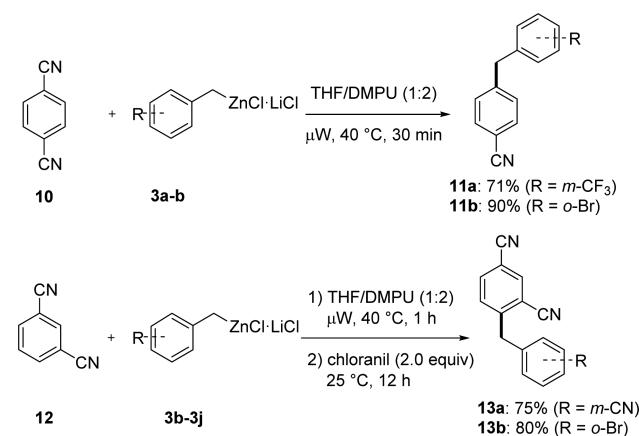
The structure of **7d** has been established unambiguously by X-ray diffraction analysis.²⁴ The regioselectivity obtained in the second substitution can be rationalized by considering the stability of the mesomeric structures obtained after nucleophilic addition.²⁴ The readily prepared 1,4-bis(trimethylsilyl)-2,3-dicyanobenzene (**6c**) undergoes a smooth benzylation with **3a**, leading to the 1,2,3,4-tetrasubstituted aryl cyanide (**7e**) in 84% yield. Finally, 9,10-dicyanophenanthrene (**6d**) reacts with 4-methoxybenzylzinc chloride (**3n**), affording the corresponding substituted product (**7f**) in 74% yield. The products of type **7** can be readily converted into regioselectively functionalized arenes, difficult to prepare otherwise. Thus, the bis-TMS-arene (**7e**) is reacted with ICl, leading to the bis-iodide (**8**) in 92% yield. Treatment with *iPrMgCl* at -78 °C triggers a regioselective I/Mg-exchange, which, after a copper-mediated allylation, produces the 2,3,6-trisubstituted benzonitrile **9** in 61% yield in a one-pot sequence (Scheme 4).

Scheme 4. Preparation of 2,3,6-Trisubstituted Benzonitrile (9)



Whereas Scheme 3 demonstrates that 1,2-dicyanoarenes readily undergo the benzylation, we next examined the influence of the substitution pattern of cyano groups on the reaction outcome. It was found that 1,4-dicyanobenzene (**10**) also undergoes the selective monosubstitution (1.5 times faster than 1,2-dicyanobenzene)²⁴ leading to the benzonitriles (**11a–b**) in 71–90% yield (Scheme 5). Surprisingly, 1,3-dicyano-

Scheme 5. Cross-Coupling Reactions between 1,4-Dicyanobenzene (10) or 1,3-Dicyanobenzene (12) with Benzyl Zinc Chlorides of Type 3



benzene (**12**) did not undergo a cyano substitution, but the major pathway was a new type of oxidative nucleophilic substitution of a hydrogen²⁶ at the C(4)-position giving, after chloranil oxidation, the 1,3,4-trisubstituted products (**13a–b**) in 75–80% yield.²⁷

ICP-AES analysis of zinc powder and lithium chloride excluded the presence of transition metal impurities as catalysts

for the substitutions.²⁰ Compared to the work of E. Shirakawa and T. Hayashi,¹⁰ where the addition of catalytic single electron donors such as SmI₂ or LiDBB (lithium di-*tert*-butylbiphenyl) provided a significant increase in the product yield, this effect was not observed in our reaction. In contrast, a slight yield decrease was observed when catalytic amounts of SmI₂ or LiDBB were added to the reaction of 1,2-dicyanobenzene (**6a**) with a benzylic zinc reagent.²⁴ The reaction also proceeds in the dark at room temperature, discounting the involvement of light in the homolysis of the C–Zn bond. Our results are better mechanistically rationalized by assuming an addition–elimination pathway typical of an S_NAr reaction.²⁸ This mechanism explains especially well the formation of regiosomer **7d** (Scheme 3) as well as the regiosomer obtained in the oxidative nucleophilic substitution of a hydrogen (Scheme 5).²⁴ Additionally, a high electrophilicity of the aromatic or heteroaromatic substrates seems to be required for this new benzylic substitution.^{9a}

In summary, we have developed a novel nucleophilic benzylation of 4-cyanopyridines and polycyano-aromatics using readily available zinc reagents, providing polyfunctional pyridines and cyano-substituted aromatics. Furthermore, we found an unexpected new oxidative nucleophilic substitution of a hydrogen using 1,3-dicyanobenzene. The full reaction scope and further synthetic applications are currently being investigated in our laboratories.

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.5b02380](https://doi.org/10.1021/acs.orglett.5b02380).

Full experimental details and NMR data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (a) Miyaura, N. In *Cross-Coupling Reactions, A Practical Guide*; Miyaura, N., Ed.; Springer: Berlin, 2002. (b) de Meijere, A.; Diederich, F. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim: 2004; Vol. 1. (c) Hartwig, J. F. In *Organotransition Metal Chemistry: From Bonding to Catalysis*; Hartwig, J. F., Ed.; University Science Books: Sausalito, CA, 2010.
- For the transition-metal-catalyzed direct functionalization of pyridines, see: (a) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (b) Larivée, A.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 52. (c) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 2448. (d) Tobisu, M.; Hyodo, I.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 12070. (e) Nakao, Y.; Yamada, Y.; Kashihara, N.; Hiyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 13666. (f) Wasa, M.; Worrell, B. T.; Yu, J.-Q. *Angew. Chem., Int. Ed.*

- 2010**, **49**, 1275. (g) Xiao, B.; Liu, Z.-J.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, **135**, 616.
- (3) Högermeier, J.; Reissig, H.-U. *Adv. Synth. Catal.* **2009**, **351**, 2747.
- (4) (a) Darses, S.; Michaud, G.; Genêt, J.-P. *Tetrahedron Lett.* **1998**, **39**, 5045. (b) Darses, S.; Michaud, G.; Genêt, J.-P. *Eur. J. Org. Chem.* **1999**, **1999**, 1875. (c) Andrus, M. B.; Song, C.; Zhang, J. *Org. Lett.* **2002**, **4**, 2079. (d) Taylor, R. H.; Felpin, F.-X. *Org. Lett.* **2007**, **9**, 2911. (e) Liu, C.-Y.; Gavryushin, A.; Knochel, P. *Chem. - Asian J.* **2007**, **2**, 1020. (f) Felpin, F.-X.; Fouquet, E. *Adv. Synth. Catal.* **2008**, **350**, 863.
- (5) (a) Blakey, S. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, **125**, 6046. (b) Buszek, K. R.; Brown, N. *Org. Lett.* **2007**, **9**, 707. (c) Zhang, X.-Q.; Wang, Z.-X. *J. Org. Chem.* **2012**, **77**, 3658. (d) Maity, P.; Shacklady-McAtee, D. M.; Yap, G. P. A.; Sirianni, E. R.; Watson, M. *P. J. Am. Chem. Soc.* **2013**, **135**, 280.
- (6) (a) For a review, see: Wen, Q.; Lu, P.; Wang, Y. *RSC Adv.* **2014**, **4**, 47806. For Ni-catalyzed cross-couplings, see: (b) Miller, J. A. *Tetrahedron Lett.* **2001**, **42**, 6991. (c) Garcia, J. J.; Brunkan, N. M.; Jones, W. D. *J. Am. Chem. Soc.* **2002**, **124**, 9547. (d) Miller, J. A.; Dankwardt, J. W. *Tetrahedron Lett.* **2003**, **44**, 1907. (e) Penney, J. M.; Miller, J. A. *Tetrahedron Lett.* **2004**, **45**, 4989. (f) Nakao, Y.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2004**, **126**, 13904. (g) Nakao, Y.; Yada, A.; Ebata, S.; Hiyama, T. *J. Am. Chem. Soc.* **2007**, **129**, 2428. (h) Yu, D.-G.; Yu, M.; Guan, B.-T.; Li, B.-J.; Zheng, Y.; Wu, Z.-H.; Shi, Z.-J. *Org. Lett.* **2009**, **11**, 3374. (i) Nakai, K.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2011**, **133**, 11066. For a Pd-catalyzed cross-coupling, see: (j) Tang, S.; Li, S.-H.; Yan, W. *Tetrahedron Lett.* **2012**, **53**, 6743. For Rh-catalyzed cross-couplings, see: (k) Tobisu, M.; Kita, Y.; Ano, Y.; Chatani, N. *J. Am. Chem. Soc.* **2008**, **130**, 15982. (l) Kita, Y.; Tobisu, M.; Chatani, N. *Org. Lett.* **2010**, **12**, 1864.
- (7) Chen, Q.; León, T.; Knochel, P. *Angew. Chem., Int. Ed.* **2014**, **53**, 8746.
- (8) (a) Poccia, M.; Picci, N.; Gugliuzza, A.; Puoci, F.; De Munno, A.; Iemma, F.; Bertini, V. *Heterocycles* **2001**, **55**, 2075. (b) Penney, J. M. *Tetrahedron Lett.* **2004**, **45**, 2667. (c) Thompson, A. D.; Huestis, M. P. *J. Org. Chem.* **2013**, **78**, 762.
- (9) For photoredox catalysis, see: (a) McNally, A.; Prier, C. K.; MacMillan, D. W. C. *Science* **2011**, **334**, 1114. (b) Cuthbertson, J. D.; MacMillan, D. W. C. *Nature* **2015**, **519**, 74. For photoinitiated substitutions, see: (c) Yoshino, A.; Yamasaki, K.; Yonezawa, T.; Ohashi, M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 735. (d) Bernardi, R.; Caronna, T.; Morrocchi, S.; Traldi, P.; Vittimberga, B. M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1607. (e) Lan, J. Y.; Schuster, G. B. *J. Am. Chem. Soc.* **1985**, **107**, 6710. (f) Tsujimoto, K.; Nakao, N.; Ohashi, M. *J. Chem. Soc., Chem. Commun.* **1992**, 366. (g) Ito, Y.; Endo, S.; Ohba, S. *J. Am. Chem. Soc.* **1997**, **119**, 5974. (h) Horspool, W. M.; Hynd, G.; Ixkes, U. *Tetrahedron Lett.* **1999**, **40**, 8295. (i) Tsuji, M.; Higashiyama, K.; Yamauchi, T.; Kubo, H.; Ohmiya, S. *Heterocycles* **2001**, **54**, 1027. (j) Tang, J.; Yue, J.-J.; Tao, F.-F.; Grampp, G.; Wang, B.-X.; Li, F.; Liang, X.-Z.; Shen, Y.-M.; Xu, J.-H. *J. Org. Chem.* **2014**, **79**, 7572.
- (10) (a) Shirakawa, E.; Hayashi, Y.; Itoh, K.; Watabe, R.; Uchiyama, N.; Konagaya, W.; Hayashi, T. *Angew. Chem., Int. Ed.* **2012**, **51**, 218. (b) Shirakawa, E.; Tamakuni, F.; Kusano, E.; Uchiyama, N.; Konagaya, W.; Watabe, R.; Hayashi, T. *Angew. Chem., Int. Ed.* **2014**, **53**, 521.
- (11) Minami, H.; Wang, X.; Wang, C.; Uchiyama, M. *Eur. J. Org. Chem.* **2013**, **2013**, 7891.
- (12) Dunsford, J. J.; Clark, E. R.; Ingleson, M. J. *Angew. Chem., Int. Ed.* **2015**, **54**, 5688.
- (13) (a) Metzger, A.; Schade, M. A.; Manolikakes, G.; Knochel, P. *Chem. - Asian J.* **2008**, **3**, 1678. (b) Metzger, A.; Argyo, C.; Knochel, P. *Synthesis* **2010**, **2010**, 882. (c) Cho, K.-H.; Kim, S.-H. *Bull. Korean Chem. Soc.* **2013**, **34**, 983. (d) Barl, N. M.; Sansiaume-Dagoussset, E.; Monzon, G.; Wagner, A. J.; Knochel, P. *Org. Lett.* **2014**, **16**, 2422.
- (14) (a) Knochel, P.; Millot, N.; Rodriguez, A. L.; Tucker, C. E. *Org. React.* **2001**, **58**, 417. (b) Knochel, P.; Leuser, H.; Gong, L.-Z.; Perrone, S.; Kneisel, F. F. In *Handbook of Functionalized Organometallics*; Knochel, P., Ed.; Wiley-VCH: Weinheim, 2005. (c) Knochel, P.; Almena Perea, J. J.; Jones, P. *Tetrahedron* **1998**, **54**, 8275. (d) Knochel, P.; Jones, P. In *Organozinc Reagents*; Knochel, P.; Jones, P., Eds.; Oxford University Press: New York, 1999. (e) Knochel, P.; Langer, F.; Rottländer, M.; Stüdemann, T. *Chem. Ber.* **1997**, **130**, 1021. (f) Knochel, P.; Vettel, S.; Eisenberg, C. *Appl. Organomet. Chem.* **1995**, **9**, 175.
- (15) The benzylic zinc reagent **3a** was obtained by the insertion of zinc powder (1.5 equiv) in the presence of LiCl (1.5 equiv) to the corresponding benzylic chloride; 25 °C, 9 h, >90% yield (ref 13a).
- (16) Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, **65**, 385.
- (17) For the use of microwaves in organic synthesis, see: (a) Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. *Tetrahedron Lett.* **1986**, **27**, 279. (b) Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, **27**, 4945. (c) Hayes, B. L. In *Microwave Synthesis: Chemistry at the Speed of Light*; CEM Publishing: Matthews, NC, 2002. (d) Lidström, P.; Tierney, J. P. In *Microwave-Assisted Organic Synthesis*; Lidström, P., Tierney, J. P., Eds.; Wiley-Blackwell: 2009. (e) de la Hoz, A.; Loupy, A. In *Microwaves in Organic Synthesis*, 3rd ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2012. (f) Larhed, M.; Olofsson, K. In *Microwave Methods in Organic Synthesis*; Larhed, M. Olofsson, K., Eds.; Springer: Berlin, 2006.
- (18) For a review about organometallic reactions under microwave irradiation, see: (a) Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, **107**, 2563. (b) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, **43**, 6250. (c) Tsukamoto, H.; Matsumoto, T.; Kondo, Y. *J. Am. Chem. Soc.* **2008**, **130**, 388. (d) Shore, G.; Morin, S.; Organ, M. G. *Angew. Chem., Int. Ed.* **2006**, **45**, 2761. (e) Fustero, S.; Jiménez, D.; Sánchez-Roselló, M.; del Pozo, C. *J. Am. Chem. Soc.* **2007**, **129**, 6700. (f) Constant, S.; Tortoilo, S.; Müller, J.; Linder, D.; Buron, F.; Lacour, J. *Angew. Chem., Int. Ed.* **2007**, **46**, 8979. (g) Wunderlich, S.; Knochel, P. *Org. Lett.* **2008**, **10**, 4705.
- (19) Heating the reaction mixture at 40 °C for 30 min without microwave irradiation led to 46% of **2a** and 21% of recovered **1a**, suggesting that some decomposition has occurred.
- (20) ICP-AES analysis of zinc powder and LiCl showed that there were less than the respective detection limits of the following metals: Fe (1.5 ppm); Cu (2.0 ppm); Ag (3.0 ppm); Ir (3.5 ppm); Co, Rh (5.0 ppm); Au, Ni, Ru (5.5 ppm).
- (21) We noticed that benzylic zinc reagents bearing an electron-rich substituent (such as methoxy group) react more sluggishly; in the case of the addition of the 3,4,5-trimethoxybenzylzinc chloride, the 4-substituted product is obtained in 74% yield (but as a mixture of regioisomers 92:8; see *Supporting Information*).
- (22) (a) Bonnet, V.; Mongin, F.; Trécourt, F.; Quéguiner, G.; Knochel, P. *Tetrahedron* **2002**, **58**, 4429. (b) Tagata, T.; Nishida, M. *J. Org. Chem.* **2003**, **68**, 9412. (c) Korn, T. J.; Cahiez, G.; Knochel, P. *Synlett* **2003**, **12**, 1892. (d) Schlosser, M.; Rausis, T. *Helv. Chim. Acta* **2005**, **88**, 1240. (e) Kuzmina, O. M.; Steib, A. K.; Flubacher, D.; Knochel, P. *Org. Lett.* **2012**, **14**, 4818. (f) Steib, A. K.; Fernandez, S.; Kuzmina, O. M.; Corpet, M.; Gosmini, C.; Knochel, P. *Synlett* **2015**, **26**, 1049.
- (23) Klier, L.; Diène, C. R.; Schickinger, M.; Metzger, A.; Wagner, A. J.; Karaghiosoff, K.; Marek, I.; Knochel, P. *Chem. - Eur. J.* **2014**, **20**, 14096.
- (24) See *Supporting Information*.
- (25) The presence of the two cyano groups of **4** is necessary since both 2-cyano- and 3-cyano-N-methylindoles did not undergo the reaction with benzylic zinc reagents.
- (26) (a) Makosza, M.; Winiarski, J. *Acc. Chem. Res.* **1987**, **20**, 282. (b) Makosza, M.; Wojciechowski, K. *Heterocycles* **2014**, **88**, 75.
- (27) We also observed traces of minor products; see *Supporting Information*.
- (28) (a) Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, **49**, 273. (b) Buncel, E.; Dust, J. M.; Terrier, F. *Chem. Rev.* **1995**, **95**, 2261.