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

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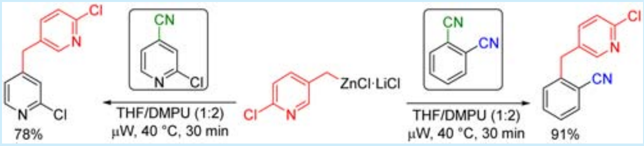
Supporting Information

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 °C, 0.5−1.5 h). Selective benzylations on polycyano-aromatics 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.

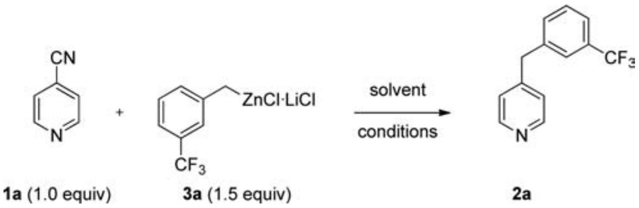


Transition-metal-catalyzed cross-couplings are standard methods for forming carbon−carbon bonds between aryl and heteroaryl organometallics and electrophiles.[1,2] By far, the most common electrophiles (Ar−X) are organic halides (X = Cl, Br, I) and sulfonates (X = OTf, ONf,[3] OTs or OMs). Nevertheless, 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. Uchiyama[11] 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 BF$_3$·OEt$_2$-mediated substitutions of cyanopyridines[7] 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 **3a**[15] in THF did not provide any substitution product (25 °C, 16 h; entry 1 of Table 1). However, the use of a polar solvent such as DMPU[16] (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) led to the formation of the 4-benzylated pyridine (**2a**) in 43% yield (as determined by ^{1}H 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 °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

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 (°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]

[a]For clarity, the ratio is given before the addition of the benzylic zinc reagent. [b]^{1}H NMR yield using 1,3,5-trimethoxybenzene as internal standard. [c]Isolated yield (TMU = tetramethylurea, μW = microwave irradiation).

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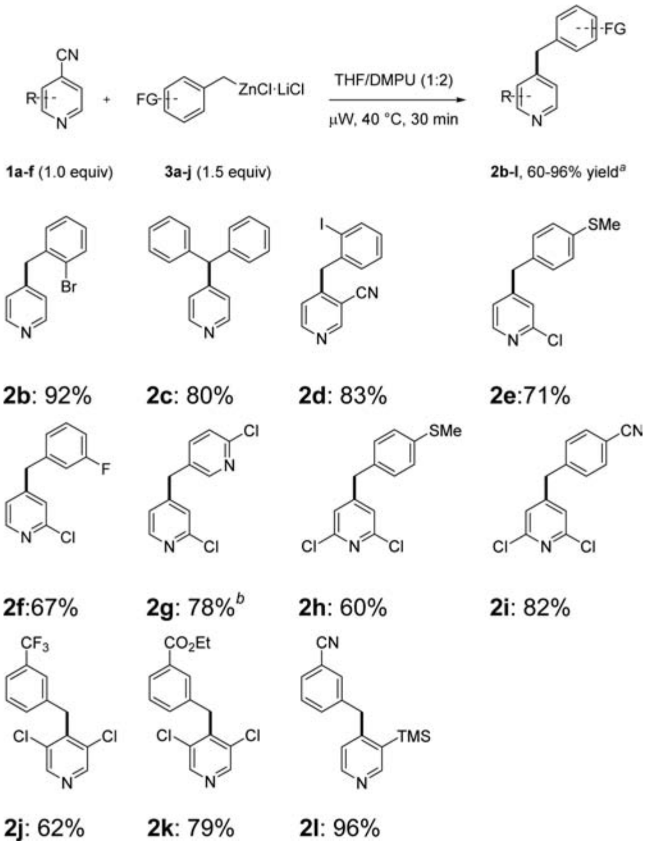
Scheme 1. Cross-Coupling between Functionalized 4-Cyanopyridines of Type 1 and Various Benzylic Zinc Chlorides of Type 3 Using Microwave Irradiation

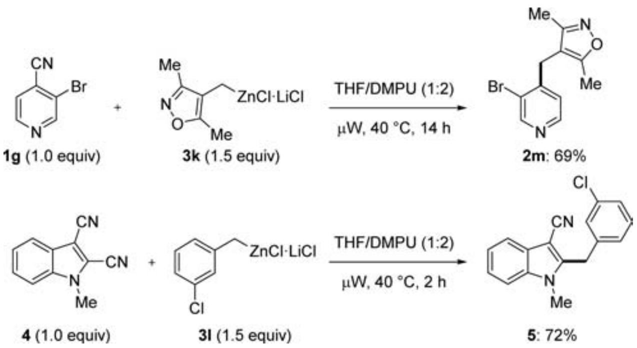


[a]Isolated yield. [b]The reaction was heated for 1 h.

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-benzylic 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 benzylic zinc reagents (**3e**−**f**) and a heterobenzylic 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 benzylic 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 benzylic zinc chlorides **3a** and **3i** furnishes the expected pyridines (**2j**−**k**) in 62−79% yield. A smooth addition of 3-cyanobenzylic 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 heterobenzylic zinc chloride (**3k**) prepared from 4-(chloromethyl)-3,5-dimethyl-isoxazole[23] providing the isoxazole (**2m**) in 69% isolated yield (Scheme 2).

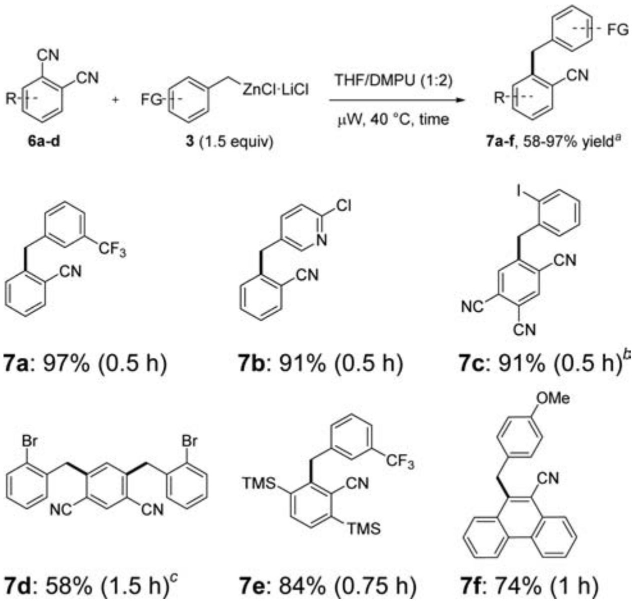
Scheme 2. Synthesis of Isoxazole (2m) and Regioselective Preparation of Indole (5) *via* Cross-Coupling with Benzylic Zinc Reagents under Microwave Irradiation



In addition, the 2,3-dicyano-indole **4** reacts regioselectively at the C(2)-position with the benzylic 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 benzylic and heterobenzylic 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 benzylic zinc chloride (**3c**; 1.0 equiv) furnishes solely the monosubstituted product (**7c**) in 91% yield. However, by treating **6b** with an excess of the benzylic zinc reagent (**3b**; 3.0 equiv; 1.5 h), 1,3-disubstituted dicyanide (**7d**) is obtained as the major product in 58% yield.

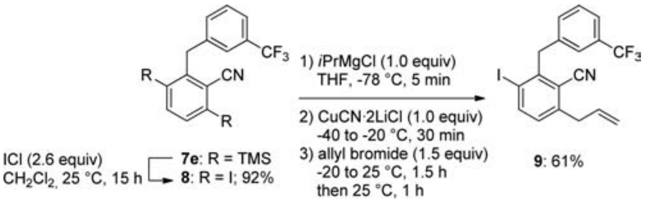
Scheme 3. Cross-Coupling between Aromatic Nitriles of Type 6 and Various Benzylic Zinc Chlorides of Type 3 under Microwave Irradiation



[a]Isolated yield of analytically pure product. [b]1.0 equiv of benzylic zinc chloride **3c** was used. [c]3.0 equiv of benzylic zinc chloride **3b** were used.

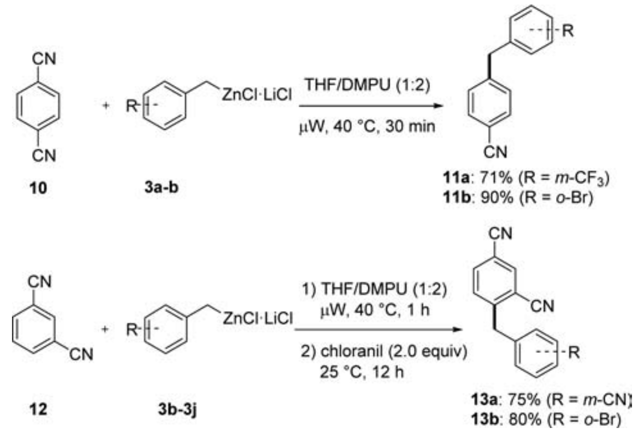
The structure of **7d** has been established unambiguously by X-ray diffraction analysis.[24] The regioselectivity obtained in the second substitution can be rationalized by considering the stability of the mesomeric structures obtained after nucleophilic addition.[24] The readily prepared 1,4-bis-trimethylsilyl-2,3-dicyanobenzene (**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 *i*PrMgCl 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-dicyanobenzene (**12**) did not undergo a cyano substitution, but the major pathway was a new type of oxidative nucleophilic substitution of a hydrogen[26] at the C(4)-position giving, after chloranil oxidation, the 1,3,4-trisubstituted products (**13a–b**) in 75–80% yield.[27]

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



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 SmI_2 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 SmI_2 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 regioisomer **7d** (Scheme 3) as well as the regioisomer 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

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 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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(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).

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(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).

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(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.

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