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General and user-friendly protocol for the synthesis of functionalized aryl- and heteroaryl-cyclopropanes by Negishi cross-coupling reactions

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ABSTRACT

The introduction of an unsubstituted cyclopropyl moiety was efficiently accomplished via Negishi cross-coupling of cyclopropylzinc bromide with functionalized aryl halides in high yields and fast reaction rates. The stability and the efficient one-step synthesis of cyclopropylzinc bromide make this protocol very valuable in particular for commercial applications.

Molecules bearing cyclopropyl groups as structural motifs have emerged as important synthetic intermediates and pharmaceutical active molecules.[1] In particular, the higher metabolic stability of the cyclopropyl group compared to aliphatic residues toward microsomal oxidation enables applications of these derivatives in structure–activity relationship studies.[2,4]

The introduction of a cyclopropyl group can be accomplished by several methods such as radical substitution on arenes by cyclopropyl radicals,[3] cyclopropanation of vinyl arenes with diazomethane,[4] the classical Simmons–Smith reaction,[5] transformations with sulfonium ylids,[6] or reactions with ferrocenyl carbenes.[7] Although the cyclopropanation toolbox provides versatile methods, the required vinyl arenes for the transformations are usually obtained from aryl halides.

To circumvent this reaction sequence, the direct introduction of the cyclopropyl group by cross-coupling reactions of the corresponding cyclopropyl nucleophile with organic halides has been reported by several groups from academia and industry.[8] Kumada coupling reactions with cyclopropylmagnesium halides can be performed with nickel and palladium catalysts, however, the high reactivity of organomagnesium reagents limits this technology to substrates without sensitive functional groups.[9,10] Knochel published the in situ generation of functionalized cyclopropylmagnesium halides via Br–Mg exchange reactions using *i*-PrMgCl·LiCl.[11] Most impressively, an ester group adjacent to the Grignard center was tolerated when conducting the reactions at low temperatures of −50 °C. Organotin compounds like cyclopropyl(tri-*n*-butyl)stannane have not been frequently applied because of low reactivity and limited scope.[12] Gagnon et al. recently reported tricyclopropylbismuth, generated from cyclopropylmagnesium bromide and bismuth chloride, as a cyclopropanation reagent. Although the cross-coupling with this novel reagent has a broad scope and tolerates a broad variety of functional groups, the tricyclopropylbismuth reagent is pyrophoric. This is a major drawback, especially for applications at commercial scale.[13]

Wallace and Chen described the cross-coupling of cyclopropylboronic acid with aryl and vinyl halides employing an in situ catalyst generated from $Pd(OAc)_2$ and PCy_3.[14] Since cyclopropylboronic acid is prone to protodeboronation, which limits its stability and shelf life, Molander and Gormisky developed a cross-coupling protocol using the stable potassium cyclopropyltrifluoroborate as a nucleophile.[15] Soderquist reported a method which takes advantage of an in situ generation of a cyclopropylborate complex from propargylic bromide and 9-borabicyclo[3.3.1]nonane.[16,17] Although good to high yields and tolerance to a broad variety of functional groups were observed under Suzuki conditions,[18] the multistep synthesis of cyclopropylboronic acid derivatives often causes diminished yields of the nucleophile.

In 1996, Weichert et al. published a Negishi cross-coupling[19] with cyclopropylzinc chloride, which was generated by cyclopropylmagnesium chloride and zinc chloride by transmetallation, and aryl bromides bearing functional groups such as methyl ester, sulfone, or trifluoromethyl group. Reactions were conducted in the presence of 5 mol % $PdCl_2$dppf and the addition of 6–11 mol % of CuI as co-catalyst was essential for high conversions and yields.[20]

Although the discussed protocols enable the direct introduction of a cyclopropyl group by cross-coupling technology, to the best of our knowledge there is no organometallic nucleophile which consolidates the following highly desirable properties: (1) synthesis of the compound in high yield and few steps, (2) shelf life of several months, (3) broad substrate scope and tolerance to sensitive functional groups in cross-coupling reactions, and (4) convenient and safe handling.

With the purpose to design a reagent which addresses these desirable requirements and is in addition scalable for manufacturing of commercial quantities, we investigated cyclopropylzinc bromide in more detail.[21] The reagent is known in the literature but applications are rare and often it is generated in situ by transmetallation.[2b]

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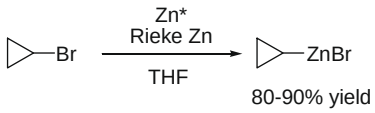
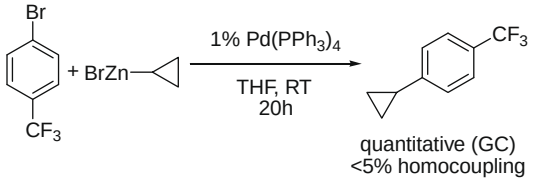


Scheme 1.



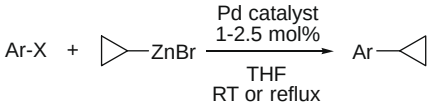
Scheme 2.

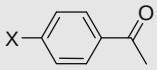
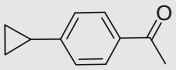
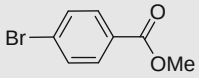
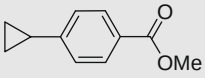
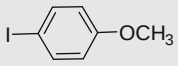
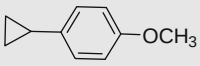
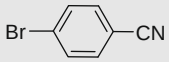
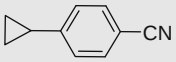
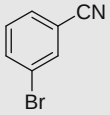
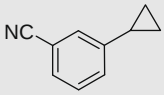
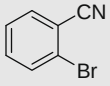
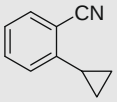
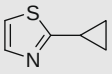
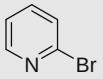
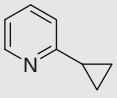
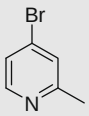
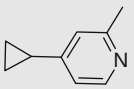
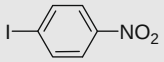
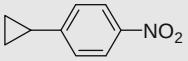
As depicted in Scheme 1, cyclopropylzinc bromide was conveniently prepared in one step by employing the Rieke active zinc technology.[22] We conducted the synthesis on multikilogram scale, which provided the product as 1M solution in THF in excellent yields of 80–90%.

The excess of Zn* was filtered off and the organozinc compound obtained as a solution in THF. In contrast to other nucleophiles, we were able to demonstrate in ongoing room temperature shelf life studies for the first time that cyclopropylzinc bromide is stable over six months and can be stored under an inert atmosphere without loss of reactivity.[23] In addition we found that the organozinc reagent is non-pyrophoric as a 1 M solution in THF.

In order to evaluate the full scope and limitations of cyclopropylzinc bromide in the Negishi cross-coupling reaction, we started

Table 1
Palladium-catalyzed cross-coupling reactions of aryl halides with cyclopropylzinc bromide[c]



Entry	Substrate	Catalyst[b]	Reaction time (h)/temperature	Product	Yield[a]
					
1	X=I	$Pd(PPh_3)_4$, 2.5%	1/65 °C		99 (GC)
2	X=Br	PEPPSI, 1%	1/65 °C		75
3	X=Cl	PEPPSI, 1%	4/65 °C		75
4		PEPPSI, 1%	1/rt		97 (GC)
5		PEPPSI,1%	4/65 °C		92 (GC)
6		$Pd(PPh_3)_4$, 2.5%	18/65 °C		99 (GC)
7		$Pd(PPh_3)_4$, 2.5%	18/65 °C		91
8		$Pd(PPh_3)_4$, 2.5%	24/65 °C		75
9		PEPPSI, 1%	8/65 °C		99 (GC)
10		$Pd(PPh_3)_4$, 2.5%	24/65 °C		56
11		PEPPSI, 0.1%	24/rt		99 (GC)
12		$Pd(PPh_3)_4$, 2.5%	4/65 °C		62
13		$Pd(PPh_3)_4$, 2.5%	1/rt		77
14		PEPPSI, 1%	4/rt		5 (GC)

[a] Isolated yields unless stated otherwise. Reactions conducted in THF on 10 mmol scale.
[b] Catalyst loadings are not optimized.
[c] Cyclopropylzinc bromide was prepared as 1 M solution in THF by BASF.

our studies with the conversion of 4-bromobenzotrifluoride in the presence of 1% $Pd(PPh_3)_4$ in THF (Scheme 2). Very satisfyingly, we observed a complete conversion of the aryl bromide to the desired cross-coupling product after 20 h at room temperature. The reaction proceeded cleanly and only a trace amount of the homocoupling by-product (<5%) of the electrophile was observed. Interestingly, copper salts as co-catalyst, as reported by Weichert et al., were not required to obtain high conversions.[20]

We evaluated the substrate scope using $Pd(PPh_3)_4$ and PEPPSI, which was developed by Organ and co-workers,[24] as catalysts. As depicted in Table 1, a broad variety of aryl halides bearing sensitive functional groups such as ketone, methyl ester, ether, nitrile, and nitro group can be tolerated under the described reaction conditions.[25] No side products by an uncatalyzed nucleophilic attack of the organozinc reagent on these functionalities were observed. In the case of 4-chloro-acetophenone, PEPPSI was applied as catalyst to accomplish high conversions (Table 1, entry 3). In other reactions, PEPPSI was employed due to its good stability to air and moisture, making its handling under an inert atmosphere unnecessary (Table 1, entries 2–5 and 9).[26] In the case of 2-bromo pyridine, the cross-coupling could be conducted efficiently with 0.1 mol % PEPPSI at room temperature. Interestingly, 1-iodo-4-nitrobenzene showed low conversions with PEPPSI whereas $Pd(PPh_3)_4$ gave complete conversion after 1 h and the final product was isolated in 77% yield (Table 1, entries 13 and 14). The influence of the substitution pattern of the aryl halide had no significant impact on the reaction rate. For example, 2-, 3-, and 4-bromo benzonitrile were converted with comparable high reaction rates providing isolated yields up to 91% (Table 1, entries 6–8). The reaction with heterocycles like 2-bromo-thiazole, 2-bromo-pyridine, and 2-methyl-4-bromopyridine gave good yields (56–99%) of the corresponding cross-coupling product (Table 1, entries 9–12).

In conclusion, we have developed a powerful protocol for the Negishi cross-coupling of functionalized aryl halides with cyclopropylzinc bromide. The method outperforms competitive technologies because the organozinc reagent can be synthesized in excellent yields in only one step on multikilogram scale, shows high reactivity, is compatible to sensitive functional groups and convenient to apply. To the best of our knowledge, we are reporting for the first time, thermal stability data of cyclopropylzinc bromide. In ongoing stability studies, no significant loss of reactivity or decomposition of this non-pyrophoric reagent was observed. This is of particular interest for applications at commercial scale. The cyclopropyl Negishi cross-coupling protocol is very user friendly and no diligent optimization of catalysts, additives, or solvents was required to obtain high yields of the final products.

Acknowledgments

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References and notes

1. (a) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117–3179; (b) Brackmann, F.; de Meijere, A. *Chem. Rev.* **2007**, *107*, 4493–4537; (c) Patai, S. In *The Chemistry of the Cyclopropyl Group, Part 2*; John Wiley & Sons: New York, 1987; Vol. 1; (d) Salaün, J. *Top. Curr. Chem.* **2000**, *207*, 1; (e) Doucet, H. *Eur. J. Org. Chem.* **2008**, 2013.
2. (a) Todo, Y.; Takagi, H.; Iino, F.; Fukuorka, Y.; Ikeda, Y.; Tanaka, K.; Saikawa, I.; Narita, H. *Chem. Pharm. Bull.* **1994**, *42*, 2049; (b) Gagnon, A.; Amad, M.; Bonneau, P.; Coulombe, R.; DeRoy, P. L.; Doyon, L.; Duan, L.; Garneau, M.; Guse, I.; Jakalian, A.; Jolicoeur, E.; Landry, S.; Malenfant, E.; Simoneau, B.; Yoakim, C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4437–4441.
3. Shono, T.; Nishiguchi, I. *Tetrahedron* **1974**, *30*, 2183.
4. Turner, W. R.; Suto, M. J. *Tetrahedron Lett.* **1993**, *34*, 281.
5. (a) Kawabata, N.; Naka, M.; Yamashita, S. *J. Am. Chem. Soc.* **1976**, *98*, 2676; (b) Yang, Z.; Lorenz, J. C.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 8621; (c) Lorenz, J. C.; Long, J.; Yang, Z.; Xue, S.; Xie, Y.; Shi, Y. *J. Org. Chem.* **2004**, *69*, 327.
6. (a) Gai, Y.; Julia, M.; Verpeaux, J.-N. *Synlett* **1991**, 56; (b) Cimetière, B.; Julia, M. *Synlett* **1991**, 271; (c) Gibson, S. E.; Jefferson, G. R.; Prechtl, F. *J. Chem. Soc., Chem. Commun.* **1995**, 1535.
7. Du, H.; Yang, F.; Hossain, M. M. *Synth. Commun.* **1996**, *26*, 1371.
8. (a) For general recent cross coupling reviews see: *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Meijere, A., Eds.; Wiley-VCH: Weinheim, 2004; (b) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469; (c) *Top. Curr. Chem.*; Miyaura, N., Ed.; Springer: New York, 2002; Vol. 219, (d) Corbet, J.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651–2710; (e) Leitner, A. Iron Catalyzed Cross Coupling Reactions. In *Iron Catalysis in Organic Chemistry*; Plietker, B., Ed.; Wiley-VCH Verlag GmbH & Co. KgaA: Weinheim, Germany, 2008; pp 147–176; (f) Sherry, D. B.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500–1511; (g) Knochel, P.; Calaza, M. I.; Hupe, E. Carbon–Carbon Bond-Forming Reactions Mediated by Organozinc Reagents, 2nd ed.. In *Metal-Catalyzed Cross-Coupling Reactions*; De Meijere, A., Diederich, F., Eds.; Wiley-VCH Verlag GmbH & Co. KgaA: Weinheim, Germany, 2004; Vol. 2, pp 619–670; (h) Knochel, P.; Leuser, H.; Gong, L.; Perrone, S.; Kneisel, F. Functionalized Organozinc Compounds. In *Chemistry of Organozinc Compounds*; Rappoport, Z., Marek, I., Eds.; John Wiley & Sons Ltd: Chichester, UK, 2006; Pt. 1, pp 287–393.
9. (a) Ng, D. K. P.; Luh, T. *J. Am. Chem. Soc.* **1989**, *111*, 9119–9121; (b) Ornstein, P. L.; Bleisch, T. J.; Brian, M.; Kennedy, A. J. H.; Wright, R. A.; Johnson, B. G.; Tizzano, J. P.; Helton, D. R.; Kallman, M. J.; Schoepp, D. D.; Hrin, M. *J. Med. Chem.* **1998**, *41*, 358–378.
10. For a Kumada coupling of cyclopropylmagnesium bromide with aryl tosylates see: Limmert, M. E.; Roy, A. H.; Hartwig, J. F. *J. Org. Chem.* **2005**, *70*, 9364.
11. (a) Rauhut, C. B.; Cervino, C.; Krasovskiy, A.; Knochel, P. *Synlett* **2009**, 67–70; (b) Vu, V. A.; Marek, I.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 351–352.
12. (a) Schmitz, W. D.; Romo, D. *Tetrahedron Lett.* **1996**, *37*, 857; (b) Piers, E.; Jean, M.; Marrs, P. S. *Tetrahedron Lett.* **1987**, *28*, 5075.
13. Gagnon, A.; Duplessis, M.; Alsabeh, P.; Barabe, F. *J. Org. Chem.* **2008**, *73*, 3604.
14. Wallace, D. J.; Chen, C.-Y. *Tetrahedron Lett.* **2002**, *43*, 6987.
15. Molander, G. A.; Gormisky, P. E. *J. Org. Chem.* **2008**, *73*, 7481–7485.
16. Soderquist, J. A.; Huertas, R.; Leon-Colon, G. *Tetrahedron Lett.* **2000**, *41*, 4251.
17. Fürstner, A.; Leitner, A. *Synlett* **2001**, *73*, 209.
18. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1992**, *95*, 2457.
19. (a) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821–1823; (b) Negishi, E. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 233–257.
20. Weichert, A.; Bauer, M.; Wirsig, P. *Synlett* **1996**, 473; See also Campbell, J. B., Jr.; Wawerchak Firor, J.; Davenport, T. W. *Synth. Commun.* **1989**, *19*, 2265.
21. For further information see: www.RZnX.basf.com.
22. Rieke, R. D. *Science* **1989**, *246*, 1260.
23. Cyclopropylzinc bromide is commercially available as 1 M solution from BASF. The reagent was tested by iodometric titration as published by: Krasovskiy, A.; Knochel, P. *Synlett* **2006**, 890–891.
24. (a) O'Brien, C. J.; Kantchev, E. A. B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.; Hopkinson, A. C.; Organ, M. G. *Chem. Eur. J.* **2006**, *12*, 4743; (b) Organ, M. G.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Valente, C. *Eur. J. Chem.* **2006**, *12*, 4749.
25. Representative procedure: In a glove box under nitrogen, $Pd(PPh_3)_4$ (0.29 g, 0.25 mmol), 4-iodonitrobenzene (2.49 g, 10 mmol), and THF (3 ml) were added to a 50 ml two necked round-bottomed flask with a magnetic stir bar. The mixture was stirred for 0.5 h at room temperature. Cyclopropylzinc bromide (15 ml, 1 M in THF, 15 mmol) was added and the reaction was stirred at 65 °C for 1 h. After cooling down to room temperature, the reaction was quenched with HCl (3 ml, 3 M). After addition of NaOH (3 ml, 22 wt %), the product was extracted with diethyl ether (3 × 30 ml). The combined organic phases were washed with saturated aqueous KCl solution, dried over $MgSO_4$, and concentrated. Purification by flash column chromatography (hexanes/ether = 10:1) delivered the final product 4-nitrophenylcyclopropane in 77% isolated yield. ^1H NMR (300 MHz, $CDCl_3$): δ 8.10 (2H, d), 7.2 (2H, d), 2.0 (1H, m), 1.1 (2H, m), 0.8 (2H, M). ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.8, 145.7, 125.9, 123.5, 15.8, 11.1. The analytical data are in accord to the literature: Lemhadri, M.; Doucet, H.; Santelli, M. *Synth. Commun.* **2006**, *36*, 121.
26. Sase, S.; Jaric, M.; Metzger, A.; Malakhov, V.; Knochel, P. *J. Org. Chem.* **2008**, *73*, 7380–7382.