



Catalytic methoxylation of aryl halides using ^{13}C - and ^{14}C -labeled CO_2 †

Alexia Ohleier,^{abc} Antoine Sallustrau,^{ib} Bouchaib Mouhsine,^b Fabien Caillé,^{ib}*^c
 Davide Audisio^{ib}*^b and Thibault Cantat^{ib}*^a

Cite this: *Chem. Commun.*, 2022, 58, 12831

Received 5th July 2022,
 Accepted 30th September 2022

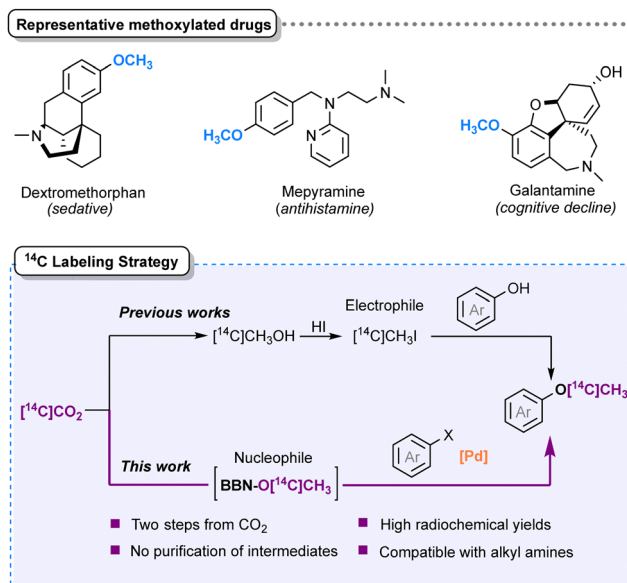
DOI: 10.1039/d2cc03746g

rsc.li/chemcomm

The functionalization of carbon dioxide (CO_2) into high-value building blocks is a relevant topic in carbon isotope labeling, where CO_2 is the primary carbon source. A catalytic methoxylation of aryl halides directly from ^{13}C and ^{14}C CO_2 is reported. Relying on the intermediacy of the methoxyborane BBN-OCH_3 , as a new secondary nucleophilic labeled source, this strategy allowed labeling of a series of substrates, including challenging pharmaceuticals containing tertiary alkyl amine substituents.

The interest in CO_2 transformations has brought tremendous progress in terms of conversion into high-value building blocks and development of mild reaction conditions, especially regarding low temperature and pressure.¹ Such developments are highly relevant for the field of carbon isotope labeling, as CO_2 is the most accessible primary source of carbon-14 (^{14}C).^{2,3} These isotopes have widespread applications from medical imaging to ADME (absorption, distribution, metabolism, excretion) studies for drug development.⁴ However, the thermodynamic stability of CO_2 , has dramatically hampered the availability of ^{14}C -labeled radiotracers. Indeed, ^{14}C CO_2 is generally incorporated at the beginning of costly (^{14}C CO_2 : 1600 € mmol^{-1}) and time-consuming multistep syntheses at the expense of large amounts of long-lived radioactive waste (half-life: 5730 years). In addition, chemoselectivity is an important issue, as most functional groups do not withstand the harsh conditions often required to functionalize CO_2 .⁵ In this context, it becomes essential to develop late-stage labeling strategies relying on fast, selective and mild CO_2 transformations to access a broader range of highly functionalized radiolabeled molecules.

The *O*-methyl group is one of the most popular structural features in medicinal chemistry and in the top-sold pharmaceuticals (see Scheme 1, top).⁶ It is therefore relevant to introduce a ^{14}C radioisotope on the methoxy position. This approach is frequently utilized for preclinical *in vitro* experiments, and in early-stage developments of novel potential drugs.⁵ Access to labeled *O*- ^{14}C methylated substrates is traditionally granted by electrophilic methylation in the presence of ^{14}C methyl iodide.⁷ ^{14}C CH_3I is prepared by LiAlH_4 reduction of ^{14}C CO_2 to ^{14}C CH_3OH , followed by thermic treatment with HI ,⁸ and subsequently employed for the synthesis of methyl ethers through the Williamson reaction. However, this strategy encounters selectivity issues in the presence of nucleophilic aliphatic amines, where the competitive *N*-methylation leads to the formation of quaternary ammonium salts, low yields and



Scheme 1 Representative drugs containing *O*-methyl groups (top) and new strategy to introduce a labeled $-\text{O}^{14}\text{C}\text{CH}_3$ synthon (bottom).

^a Université Paris-Saclay, CEA, CNRS, NIMBE, Gif-sur-Yvette 91191, France. E-mail: thibault.cantat@cea.fr

^b Université Paris-Saclay, Service de Chimie Bio-organique et Marquage (SCBM), CEA/DRF/JOLIOT, Gif sur Yvette 91191, France. E-mail: davide.audisio@cea.fr

^c Université Paris-Saclay, Inserm, CNRS, CEA, Laboratoire d'Imagerie Biomédicale Multimodale Paris-Saclay, Orsay 91401, France. E-mail: fabien.caillé@cea.fr

† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d2cc03746g>



laborious purifications.⁹ For example, the selective O-[¹⁴C]methylation of dextromethorphan required the orthogonal vinyl chloroformate protection of the alcohol and the tertiary amine.¹⁰

These limitations encouraged us to develop a reversed polarity methoxylation strategy starting from labeled [¹⁴C]CO₂.

We previously investigated the organocatalyzed CO₂ reduction into BBN-OCH₃ **2**, using the hydroborane 9-BBN (**1**) as a reductant.¹¹ Among the organic bases catalyzing the reaction, Verkade's proazaphosphatane (VB^{Me}) appeared well-suited as it ensured fast, selective and stoichiometric CO₂ conversion. In the presence of 9-BBN **1** and 5 mol% VB^{Me}, [¹³C]CO₂ was fully converted into BBN-O[¹³C]CH₃ [¹³C]**2** within 30 min at 60 °C or 3 h at RT (Scheme 2A). We reasoned that the nucleophilic secondary carbon source BBN-OCH₃ **2**, might represent an alternative opportunity to insert a methoxy moiety. In this work, we explored the palladium-catalyzed Suzuki coupling between aryl halides and BBN-OCH₃ **2**, acting as a nucleophilic methoxylation source. We further developed a sequential one-pot protocol, which allows inserting methoxy moieties (-OCH₃) starting directly from labeled CO₂, unlocking the O-methylation of substrates bearing *N*-alkyl substituents. The versatility of this approach was first demonstrated using non-radioactive ¹³C on small molecules and pharmaceutical derivatives and subsequently applied to radiosyntheses with ¹⁴C.

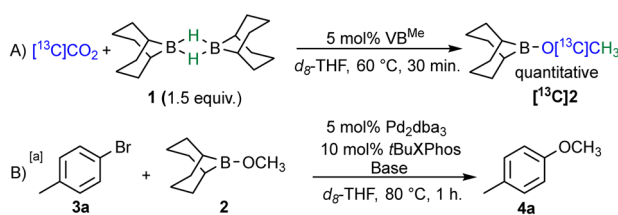
A variety of metal-catalyzed C-O bond forming reactions have emerged over the last two decades.¹² Although couplings involving primary and secondary alcohols are now well-established,¹³ direct methoxylations of aryl halides still remain scarce. Initiated by Buchwald in 2001, the palladium-catalyzed synthesis of anisoles from methanol, was limited to the highly electron deficient 3-nitroanisole.¹⁴ By varying the methanol source and by using bulky ligands, Clarke¹⁵ and Beller¹⁶ managed to improve the reaction conditions and significantly

broadened the scope. However, most protocols require large excess of methanol,¹⁷ which is incompatible with labeling prospects. Interestingly, Novák reported an efficient cross coupling between aryl chlorides and equimolar amounts of tetramethoxyborate salts MB(OR)₄ in the presence of Pd₂dba₃/*t*BuXPhos.¹⁸ Inspired by these achievements, we sought to develop the palladium catalyzed Suzuki coupling reaction between BBN-OCH₃ **2** and aromatic halides **3**.

At first, the reaction conditions were optimized using 4-bromotoluene **3a** and commercially available BBN-OCH₃ **2** in the presence of 10 mol% *t*BuXPhos and 5 mol% Pd₂dba₃ (Scheme 2B). We examined the influence of the base: the addition of 1.5 eq. of KOMe, generating *in situ* K[BBN-(OCH₃)₂], a surrogate of Novák's borate salt, led to 96% conversion within 1 h at 80 °C. Alongside 80% 4-methylanisole **4a**, homocoupled product as well as toluene and formaldehyde, originating from β-hydride elimination, were formed. Though efficient, these conditions are not applicable to ¹³C and ¹⁴C labeling, as the use of unlabeled KOMe would isotopically dilute the desired product. While they differentiate both transmetalating moieties, the use of KO*i*Pr and KO*t*Bu generated 4-methoxyanisole **4a** in only 54% and 62% yield respectively, with small amounts of isopropoxy- and *tert*-butoxyanisole. The use of 2 eq. of CsF turned out to be an efficient alternative, reaching 66% yield without additional side-products. A solvent screening confirmed that THF provided the best conversions, while being fully compatible with the CO₂ reduction conditions into BBN-OCH₃ **2** (see ESI†). Interestingly, as previously observed by Novák,¹⁸ the Suzuki coupling performs better in the presence of aryl chlorides compared to aryl bromides (10% yield improvement) and works sluggishly with iodide derivatives (see ESI† for details), where homocoupling and dehalogenation products are preferentially formed. At present, we speculate that the relative rates between the oxidative addition¹⁹ and β-hydride elimination²⁰ steps might explain this difference in reactivity.

Next, we investigated the feasibility of direct CO₂ reduction into BBN-OCH₃ **2**, followed by palladium-catalyzed Suzuki coupling for the methoxylation of aryl chlorides. Despite extensive optimization, the one-pot procedure could not be implemented, as 9-BBN **1** transmetalates faster than BBN-OCH₃ **2**, thus leading to the formation of large amounts of toluene. Furthermore, both catalytic systems VB^{Me} and *t*BuXPhos/Pd₂dba₃ appear to be incompatible. Decreasing the Verkade's base loading, employing easily removable low boiling point alternatives, as phosphazene BTPP or Suzuki friendly CsF, and performing the active palladium species did not prevent catalyst poisoning.

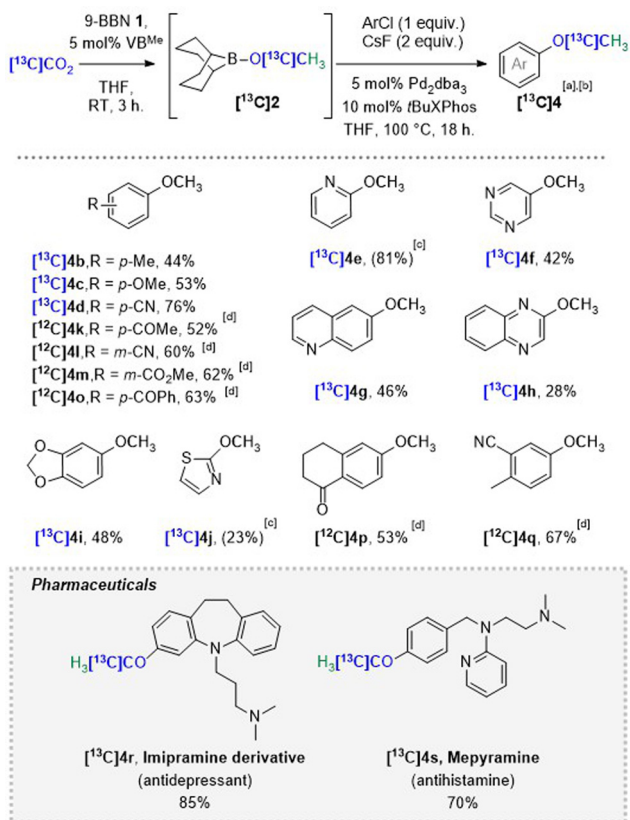
Inspired by Skrydstrup's work on the commercial COWare technology,²¹ we designed a two-chamber system to physically separate both reaction steps. The optimized set-up (Scheme S2, ESI†) is a double chamber, and can be connected to the RC Tritec manifold that allows handling and transferring controlled amounts of [¹³C] and [¹⁴C]CO₂ into a reaction vessel. CO₂ reduction was carried out in the first chamber, a distillation step was introduced to transfer BBN-OCH₃ **2** into the



Entry	Base	Solvent	Conversion (%) ^[b]	Yield (%) ^[b]
1	KOMe (1.5 eq.)	<i>d</i> ₈ -THF	96	80
2	KO <i>i</i> Pr (1.5 eq.)	<i>d</i> ₈ -THF	77	62
3	KO <i>t</i> Bu (1.5 eq.)	<i>d</i> ₈ -THF	75	54
4	Cs ₂ CO ₃ (1.5 eq.)	<i>d</i> ₈ -THF	n.d.	54
5	CsF (2 eq.)	<i>d</i> ₈ -THF	84	66
6	CsF (2 eq.)	CD ₃ CN	83	60

Scheme 2 (A) 9-BBN **1** mediated organocatalyzed [¹³C]CO₂ reduction into BBN-O[¹³C]CH₃ [¹³C]**2**. (B) Pd-catalyzed Suzuki coupling of 4-bromotoluene **3a** with different bases. ^aReaction conditions: 0.1 mmol 4-bromotoluene **3a**, 0.1 mmol BBN-OCH₃ **2**, 0.2 mL solvent. ^bSuzuki coupling followed by ¹H NMR using diphenylmethane as internal standard. Yields are given with respect to **3a**.





Scheme 3 Substrate scope for the palladium catalyzed ¹³C methoxylation of (hetero)aryl chlorides **3** and pharmaceutical compounds starting from [¹³C]CO₂. ^aReaction conditions: (9-BBN)₂ **1** (1.5 mmol, 1.5 eq.), [¹³C]CO₂ (1.0 mmol, 1 eq.) with 4 mL THF, RT, 3 h. in the first chamber and substrate **3** (1.0 mmol, 1 eq.), CsF (2.0 mmol, 2 eq.), tBuXPhos (10 mol%), Pd₂dba₃ (5 mol%) in 2 mL THF in the second chamber, 100 °C, 18 h. ^bIsolated yield. ^c¹H NMR yield determined after two titrations against CH₂Cl₂ (10 μL added at the end of the reaction) D1 = 40. [^d] Reaction performed using a commercial BBN-OCH₃ solution (hexane, 1 M) on 1 mmol scale.

second vessel, pre-charged with the reagents and catalyst of the Suzuki coupling. BBN-OCH₃ **2** being a high boiling point liquid (230 °C < b.p. < 260 °C)²² efficient distillation was performed by heating under static vacuum (0.05 mbar).

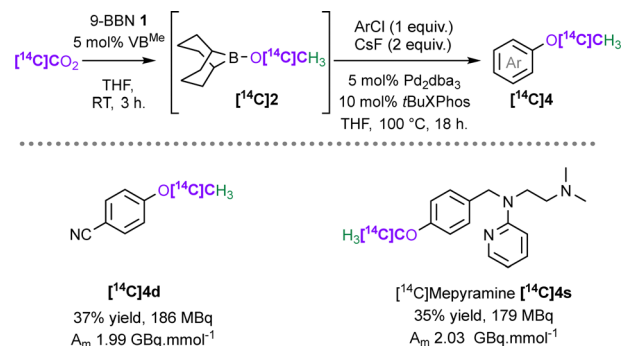
The complete reaction sequence was validated starting from 1 eq. of labeled [¹³C]CO₂, generating *in situ* BBN-O[¹³C]CH₃ [¹³C]**2**, which was reacted with 1 eq. of model substrate 4-chlorotoluene **3b**. After 18 h at 100 °C, 44% isolated yield of 4-methylanisole [¹³C]**4b** was obtained with respect to [¹³C]CO₂ as limiting reagent, thus highlighting the stoichiometric conversion of the labeled starting material. Next, the substrate scope of the reaction sequence was investigated on a 1 mmol scale using the double chamber set-up and [¹³C]CO₂ as a convenient and handy surrogate of [¹⁴C]CO₂. A variety of aryl and heteroaryl chlorides could successfully be coupled in good to excellent yields with *in situ* generated BBN-O[¹³C]CH₃ [¹³C]**2** (Scheme 3). The reaction resulted in a higher yield in the presence of an electron-withdrawing group (76% and 60% for [¹³C]**4d** and [¹²C]**4l**), whereas increasing the strength of

electron-donating substituents gradually decreased it (44% for [¹³C]**4b** and 53% for [¹³C]**4c**).

The developed methodology was applied to nitrogen containing heterocycles.²³ In this way, 2-chloropyridine **3e**, 6-chloroquinoline **3g** and 2-chloroquinoxaline **3h** could all be converted into their methoxylated counterparts with up to 81% yield. The position 5 on the pyrimidine cycle **3f** being the less electron deficient one and thus the less reactive towards nucleophiles, 5-methoxypyrimidine [¹³C]**4f** was obtained with 42% yield. In a similar fashion, electron-rich 5-chlorobenzo[1,3]dioxole **3i** was transformed into [¹³C]5-methoxybenzo[1,3]dioxole [¹³C]**4i**, a sesamol derivative, in 48% isolated yield. Surprisingly, highly activated 2-chlorothiazole **3j** was partially converted and generated only 23% NMR yield [¹³C]**4j**.

Further study of the scope revealed that the presence of substituted ketones was well tolerated. [¹²C]**4k** and **4o** were isolated in 52 and 63%, and 1-tetralone derivative **4p** was obtained in 53% yield. While the presence of free alcohols and carboxylic acids has failed to provide the desired products (see ESI[†]), simple protection of the acid in the form of a methylester restores the reactivity (**4m**, 62%). Finally, when both Csp²-Cl and Csp²-Br substituents are included in the substrate, the reactions provide a mixture of OMe products, difficult to separate. Next, we extend the methodology to drug-like scaffolds. Clomipramine derivative, [¹³C]3-methoxy-imipramine [¹³C]**4r** and FDA approved antihistamine [¹³C]mepyramine [¹³C]**4s** could respectively be obtained in 85% and 70% isolated yield in only two steps starting from [¹³C]CO₂. It is worth noting, that [¹³C]**4r** and [¹³C]**4s** bear tertiary alkyl amine substituents, which makes them both challenging to label by selective *O*-methylation with [¹³C]CH₃I.^{9,10}

This newly developed sequence was applied to ¹⁴C-labeling,²⁴ as proven by the radiosynthesis of substrates **4d** and **4s**, using the same double chamber set-up and the RC Tritec (Scheme 4). Radiosyntheses were conducted on a 0.25 mmol scale to limit the amounts of handled radioactivity. First, as a proof of concept, model substrate [¹⁴C]4-methoxybenzonitrile [¹⁴C]**4d** was generated with 37% yield and a high molar activity (A_m) of 1.99 GBq mmol⁻¹.



Scheme 4 ¹⁴C-Labeling of precursors and pharmaceutically relevant molecules. Reaction conditions: (9-BBN)₂ **1** (0.38 mmol, 1.5 eq.), [¹⁴C]CO₂ (0.25 mmol, 1 eq.) with 1 mL THF in the first chamber and substrate **3** (0.25 mmol, 1 eq.), CsF (0.50 mmol, 2 eq.), tBuXPhos (10 mol%), Pd₂dba₃ (5 mol%) in 0.5 mL THF in the second chamber.



[¹⁴C]mepyramine [¹⁴C]4s was obtained in 35% yield and with an A_m of 2.03 GBq mmol⁻¹ (Scheme 4), which are suitable for use in biological studies. The lower yields can be attributed to the down-scaling, which modifies the liquid gas equilibrium during the distillation step.

In conclusion, we devised a catalytic methoxylation of aryl halides from ¹³C- and ¹⁴C-labeled CO₂. This strategy relies on an inverse polarity strategy using a new secondary nucleophilic source BBN-OCH₃, derived from fast and stoichiometric CO₂ conversion. The development of a palladium catalyzed Suzuki coupling between BBN-OCH₃ and aryl halides and the use of a double chamber set up enabled the late-stage methoxylation of aromatic chlorides, in only two steps under mild conditions.²⁵ A series of substrates, including drug-like scaffolds containing tertiary alkyl amine substituents, could be methoxylated in good to excellent yields starting from equimolar amounts of [¹³C]CO₂. This methodology further proved its relevance and robustness in the radiolabeling of two ¹⁴C-labeled functionalized anisoles with good radiochemical yields and high molar activities, suitable to conduct *in vivo* biological studies.

Financial support was provided by CEA (DRF Impulsion 2017), CNRS, University Paris-Saclay, European Research Council (ERC Consolidator Grant Agreement no. 818260 (to TC) and no. 864576 (to DA)), ANR (ANR-19-CE07-0046). The authors thank D.-A. Buisson, A. Gaudet and S. Lebrequier for the excellent analytical support.

Conflicts of interest

There are no conflicts to declare.

Notes and references

- (a) L. Wu, Q. Liu, R. Jackstell and M. Beller, *Top. Organomet. Chem.*, 2016, **53**, 279–304; (b) S. Bontemps, *Coord. Chem. Rev.*, 2016, **308**, 117–130.
- (a) R. A. Bragg, M. Sardana, M. Artelsmair and C. S. Elmore, *J. Labelled Compd. Radiopharm.*, 2018, **61**, 934–948; (b) C. S. Elmore and R. A. Bragg, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 167–171.
- While for stable isotope carbon-13 (¹³C), the primary building block available is carbon monoxide [¹³C]CO, [¹³C]CO₂ is a very common starting material, as well.
- (a) Z. Tu and R. H. Mach, *Curr. Top. Med. Chem.*, 2010, **10**, 1060–1095; (b) G. Boscutti, M. Huiban and J. Passchier, *Drug Discovery Today: Technol.*, 2017, **25**, 3–10.
- R. Voges, J. R. Heys and T. Moenius, *Preparation of Compounds Labeled with Tritium and Carbon-14*, John Wiley & Sons, New York, 2009, ch. 5, pp. 211–285.
- <https://njarardson.lab.arizona.edu/content/top-pharmaceuticalsposter>: D. T. Smith, M. D. Delost, H. Qureshi and J. T. Njarardson, *J. Chem. Educ.*, 2010, **87**, 1348; Poster information gathered by the Njarardson group with data from DrugTopics & Pharmacompass.
- For selected examples see: (a) D. H. R. Barton, G. W. Kirby, J. B. Taylor and G. M. Thomas, *J. Chem. Soc.*, 1963, 4545–4558; (b) J. Liu, G. G. Miller, L. Huang, Z. Diwu, J. W. Lown, K. Brown, R. B. Moore, J. Tulip and M. S. McPhee, *J. Labelled Compd. Radiopharm.*, 1995, **36**, 815–823; (c) Y. Cai, W. Baer-Dubowska, M. J. Ashwood-Smith, O. Ceska, S. Tachibana and J. DiGiovanni, *Chem. Res. Toxicol.*, 1996, **9**, 729–736; (d) R. T. Brown, V. L. Murrell, A. McMordie, M. Sriram, K. G. Pinney, S. Sharma and D. J. Chaplin, *J. Labelled Compd. Radiopharm.*, 2009, **52**, 567–570.
- (a) A. Murray and A. R. Ronzio, *J. Am. Chem. Soc.*, 1952, **74**, 2408–2412; (b) T. Nagasaki, Y. Katsuyama and M. Yoshioka, *J. Labelled Compd. Radiopharm.*, 1987, **24**, 65–71.
- C. G. M. Janssen, J. B. A. Thijssen and W. J. M. Verluyten, *J. Labelled Compd. Radiopharm.*, 2002, **45**, 841–855.
- S. G. Senderoff, S. W. Landvatter and J. R. Heys, *J. Labelled Compd. Radiopharm.*, 2000, **43**, 1283–1288.
- (a) E. Blondiaux, J. Pouessel and T. Cantat, *Angew. Chem., Int. Ed.*, 2014, **53**, 12186–12190; (b) T. Cantat, C. Gomes, E. Blondiaux and O. Jacquet, *CEA – IRAMIS*, WO 2014162266, 2014.
- (a) S. Enthaler and A. Company, *Chem. Soc. Rev.*, 2011, **40**, 4912–4924; (b) S. Bhadra, W. I. Dzik and L. J. Goossen, *J. Am. Chem. Soc.*, 2012, **134**, 9938–9941; (c) J. P. Stambuli, *RSC Catal. Ser.*, 2015, **21**, 254–275; (d) K. Keerthi Krishnan, S. M. Ujwaldev, K. S. Sindhu and G. Anilkumar, *Tetrahedron*, 2016, **72**, 7393–7407.
- (a) E. Mann and J. F. Hartwig, *J. Am. Chem. Soc.*, 1996, **118**, 13109–13110; (b) M. Palucki, J. P. Wolfe and S. L. Buchwald, *J. Am. Chem. Soc.*, 1997, **119**, 3395–3396; (c) K. E. Torraca, S.-I. Kuwabe and S. L. Buchwald, *J. Am. Chem. Soc.*, 2000, **122**, 12907–12908; (d) A. V. Vorogushin, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 8146–8149; (e) S. Gowrisankar, A. G. Sergeev, P. Anbarasan, A. Spannenberg, H. Neumann and M. Beller, *J. Am. Chem. Soc.*, 2010, **132**, 11592–11598; (f) X. Wu, B. P. Fors and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2011, **50**, 9943–9947; (g) P. E. Maligres, J. Li, S. W. Krska, J. D. Schreier and I. T. Raheem, *Angew. Chem., Int. Ed.*, 2012, **51**, 9071–9074; (h) L. Rotteveel, A. J. Poot, U. Funke, A. Pekosak, U. Filp, A. A. Lammertsma and A. D. Windhorst, *J. Labelled Compd. Radiopharm.*, 2017, **60**, 566–576; (i) H. Zhang, P. Ruiz-Castillo and S. L. Buchwald, *Org. Lett.*, 2018, **20**, 1580–1583.
- K. E. Torraca, X. Huang, C. A. Parrish and S. L. Buchwald, *J. Am. Chem. Soc.*, 2001, **123**, 10770–10771.
- E. J. Milton, J. A. Fuentes and M. L. Clarke, *Org. Biomol. Chem.*, 2009, **7**, 2645–2648.
- S. Gowrisankar, H. Neumann and M. Beller, *Chem. – Eur. J.*, 2012, **18**, 2498–2502.
- (a) P. Dash, M. Janni and S. Peruncheralathan, *Eur. J. Org. Chem.*, 2012, 4914–4917; (b) C. W. Cheung and S. L. Buchwald, *Org. Lett.*, 2013, **15**, 3998–4001; (c) B. T. Inogoglia and S. L. Buchwald, *Org. Lett.*, 2017, **19**, 2853–2856.
- G. L. Tolnai, B. Pethó, P. Králl and Z. Novák, *Adv. Synth. Catal.*, 2014, **356**, 125–129.
- D. Blakemore, *Synthetic Methods in Drug Discovery: Volume 1*, The Royal Society of Chemistry, 2016, vol. 1, pp. 1–69.
- (a) L. M. Martínez-Prieto, E. Ávila, P. Palma, E. Álvarez and J. Cámpora, *Chem. – Eur. J.*, 2015, **21**, 9833–9849; (b) J. A. Mueller, C. P. Goller and M. S. Sigman, *J. Am. Chem. Soc.*, 2004, **126**, 9724–9734.
- P. Hermange, A. T. Lindhardt, R. H. Taaning, K. Bjerglund, D. Lupp and T. Skrydstrup, *J. Am. Chem. Soc.*, 2011, **133**, 6061–6071.
- (a) H. C. Brown and S. U. Kulkarni, *J. Organomet. Chem.*, 1979, **168**, 281–293; (b) H. C. Brown, J. S. Cha, B. Nazer and C. A. Brown, *J. Org. Chem.*, 1985, **50**, 549–553.
- J. Magano and J. R. Dunetz, *Chem. Rev.*, 2011, **111**, 2177–2250.
- (a) N. Penner, I. J. Klunk and C. Prakash, *Biopharm. Drug Dispos.*, 2009, **30**, 185–203; (b) E. M. Isin, C. S. Elmore, G. N. Nilsson, R. A. Thompson and L. Weidolf, *Chem. Res. Toxicol.*, 2012, **25**, 532–542.
- While this work was in preparation, a copper-catalyzed reaction between MeO-9BBN and aryl bromides was reported, see: J.-R. Wang, Z.-Q. Song, C. Li and D.-H. Wang, *Org. Lett.*, 2021, **23**, 8450–8454. Interestingly, aryl chlorides are poorly effective substrates under these reported conditions.

