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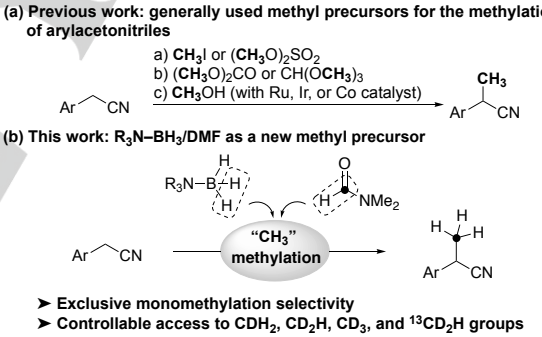
Selective α-Monomethylation by an Amine–Borane/*N*,*N*-Dimethylformamide System as the Methyl Source

Hui-Min Xia,[†] Feng-Lian Zhang,[†] Tian Ye, and Yi-Feng Wang*

Abstract: A new and practical α-monomethylation strategy using an amine–borane/*N*,*N*-dimethylformamide (R_3N–BH_3/DMF) system as the methyl source was developed. This protocol has been found to be effective in the α-monomethylation of arylacetonitriles and arylacetamides. Mechanistic studies revealed that the formyl group of DMF delivered the carbon and one hydrogen atoms of the methyl group, and R_3N–BH_3 donated the remaining two hydrogen atoms. Such a unique reaction pathway enabled controllable assemblies of CDH_2-, CD_2H-, and CD_3- units using Me_2NH–BH_3/d_7-DMF, Me_3N–BD_3/DMF and Me_3N–BD_3/d_7-DMF systems, respectively. Further application of this method to the facile synthesis of anti-inflammatory flurbiprofen and its varied deuterium-labeled derivatives was demonstrated.

The methyl group has become a privileged functionality in medicinal chemistry and the pharmaceutical industry, owing to the magic methyl effect.[1] Furthermore, deuterium-labeled compounds have been gaining increasing interest in medicinal chemistry.[2] Deutetrabenazine is the first deuterated drug that has recently been approved by Food and Drug Administration to treat Huntigton's chorea.[3] Meanwhile, a large number of deuterated drugs have already reached clinic trials.[4] Therefore, the development of robust methylation methods, which are also capable of installing deuterated methyl groups with ease, has been recognized as a highly applicable goal in synthetic and medicinal chemistry. In particular, approaches that can precisely incorporate partially deuterium-labeled methyl groups (CD_2H and CDH_2) into molecules are arguably more desirable, since such functionalities are potentially useful in nuclear magnetic resonance,[5] mass spectroscopy,[6] and mechanistic and metabolic studies.[7] However, their synthesis remains a challenging synthetic problem.[8]

Selective C-monomethylation of active methylene compounds, such as alkyl nitriles and alkyl amides, is an important transformation in chemical synthesis. For example, the α-monomethylation of arylacetonitriles represents one of the most appealing routes to make 2-arylpropionitriles,[9] which are a class of important precursors of anti-inflammatory 2-arylpropionic acids, including ibuprofen, naproxen, and flurbiprofen. However, such a process has been rarely applied in the pharmaceutical industry, largely due to the lack of highly efficient and selective monomethylation methods.[9,10] The classical methylation reactions with electrophilic methylating agents (methyl halides and dimethyl sulfate) and bases often suffered from the formation of dimethylated side products (Scheme 1a).[9] Direct α-monomethylation has previously been achieved with high selectivity using dimethyl carbonate[11] or trimethyl orthoformate[12] as the methyl source. However, high temperatures (150-210 °C) were required, thereby limiting its applicability. Recently, transition metal-catalyzed hydrogen-borrowing reactions using methanol as the methyl source has been reported for methylation reactions.[13] Nevertheless, only limited studies on α-methylation of arylacetonitriles have been described, mainly employing Ru,[14] Ir,[15] or Co[16] complexes as the catalysts. Herein, we report a new α-monomethylation protocol using readily available amine–borane/*N*,*N*-dimethylformamide (R_3N–BH_3/DMF) system as the methyl source. The formyl group of DMF delivers the carbon and one hydrogen atoms of the methyl group, and R_3N–BH_3 donates the remaining two hydrogen atoms (Scheme 1b). Significantly, such a unique reaction pathway allows for the controllable installation of CDH_2-, CD_2H-, CD_3, and $^{13}CD_2H$ motifs into products.



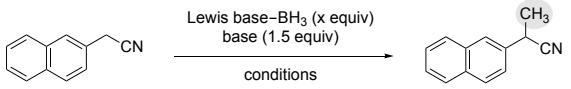
Scheme 1. The α-methylation of arylacetonitriles

During our studies of radical reactions of Lewis base–boryl radicals with nitriles,[17] we serendipitously found that the reaction of 2-naphthylacetonitrile (**1a**) and pyridine–BH_3 in the presence of 2,2-azobis(isobutyronitrile) (AIBN) and *t*-BuOK gave 2-(naphthalen-2-yl)propanenitrile (**2a**) in 53% yield (Table 1, entry 1). The reaction proceeded effectively as well without the addition of AIBN (entry 2), which might exclude the mechanism involving the pyridine–boryl radical.[17c,18] Notably, no product formation was observed when the reaction was carried out in dimethyl sulfoxide (DMSO) as the solvent instead of *N*,*N*-dimethylformamide (DMF) (entry 3) or in the absence of pyridine–BH_3 (entry 4), suggesting that the methyl group should originate from the combination of DMF and pyridine–BH_3. DMF is an abundant raw material and has been shown to be a versatile synthon for a variety of functional groups,[19] whereas its combination with a Lewis base–BH_3 serving as the methyl precursor has not been reported yet. We envisioned that such a unique reaction system could provide a conceptually distinct methylation protocol. Thus, we decided to further optimize the reaction conditions.

[*] H.-M. Xia,[†] Dr. F.-L. Zhang,[†] T. Ye, Prof. Dr. Y.-F. Wang
Hefei National Laboratory for Physical Sciences at the Microscale, Center for Excellence in Molecular Synthesis of CAS, and Department of Chemistry
University of Science and Technology of China
96 Jinzhai Road, Hefei, Anhui 230026 (China)
E-mail: yfwangzj@ustc.edu.cn
Prof. Dr. Y.-F. Wang
State Key Laboratory of Elemento-Organic Chemistry
Nankai University
Tianjin 300071 (China)
[†] These authors contributed equally to this work.
[**] Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

Firstly, a range of Lewis base ligated boranes were examined (Table 1). As a result, PPh_3, Me_2S, and R_3N ligated borane complexes were found to be capable of promoting the methylation of **1a** (entries 5-9), among which $Me_2NH–BH_3$ proved to be the most effective one, giving **2a** in 92% yield (entry 8). Then, the effect and role of bases were tested. At first, to rule out the influence by adventitious transition metal impurities in bases, *t*-BuOK with 99.99% purity (purchased from Sigma-Aldrich) was used, which gave a similar result (entry 9 *vs* entry 10). The utilization of K_2CO_3 as the base was unable to induce the present reaction (entry 11), implying that the deprotonation of arylactonitrile **1a** would be a key step to initiate the reaction process. Switching the base to NaOH led to **2a** in 47% yield (entry 12). Finally, *t*-BuONa was found to be the optimal base that could give **2a** in 92% yield within 10 min of the reaction time (entry 13). Reducing the amount of $Me_2NH–BH_3$ to 1 equiv maintained a good yield (entry 14), and a gram scale reaction afforded **2a** in 90% yield as well (entry 15). Using DMF as a reagent (4 equiv) and DMSO as the solvent, the reaction proceeded smoothly, delivering **2a** in 91% yield (entry 16).

Table 1. Optimization of the α-methylation conditions[a]

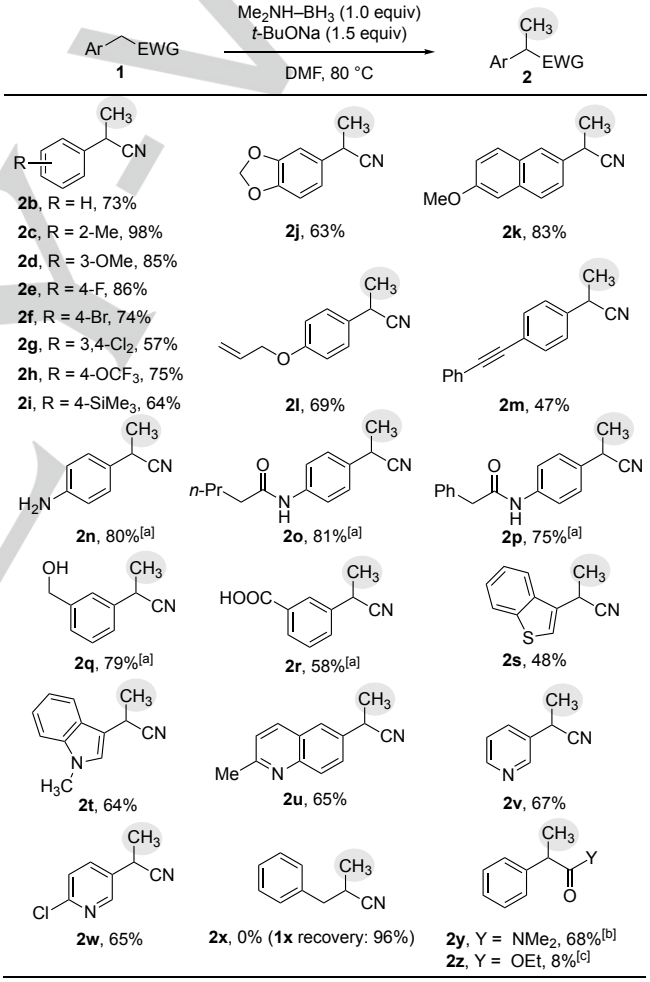


1a **2a**

entry	LB–BH_3 (x equiv)	base	conditions	yield[b] (%)
1[c]	pyridine–BH_3 (1.5)	*t*-BuOK	DMF, 2 h	53 (23)[d]
2	pyridine–BH_3 (1.5)	*t*-BuOK	DMF, 2 h	50 (20)[d]
3	pyridine–BH_3 (1.5)	*t*-BuOK	DMSO, 2 h	0 (87)[d]
4	--	*t*-BuOK	DMF, 2 h	0 (98)[d]
5	$Ph_3P–BH_3$ (1.5)	*t*-BuOK	DMF, 2 h	46 (8)[d]
6	$Me_2S–BH_3$ (1.5)	*t*-BuOK	DMF, 10 min	64
7	$NH_3–BH_3$ (1.5)	*t*-BuOK	DMF, 2 h	78 (15)[d]
8	$Me_2NH–BH_3$ (1.5)	*t*-BuOK	DMF, 1 h	92[f]
9	$Me_3N–BH_3$ (1.5)	*t*-BuOK	DMF, 1 h	71
10	$Me_3N–BH_3$ (1.5)	*t*-BuOK[e]	DMF, 1 h	74
11	$Me_2NH–BH_3$ (1.5)	K_2CO_3	DMF, 27 h	0 (88)[d]
12	$Me_2NH–BH_3$ (1.5)	NaOH	DMF, 7 h	47 (40)[d]
13	$Me_2NH–BH_3$ (1.5)	*t*-BuONa	DMF, 10 min	92[f]
14	$Me_2NH–BH_3$ (1.0)	*t*-BuONa	DMF, 10 min	92[f]
15[g]	$Me_2NH–BH_3$ (1.0)	*t*-BuONa	DMF, 1 h	90[f]
16[h]	$Me_2NH–BH_3$ (1.0)	*t*-BuONa	DMSO, 3 h	91[f]

[a] The reactions were carried out using 0.2-0.3 mmol of **1a** at 80 °C under N_2. [b] ^1H NMR yield using tetrachloroethane as an internal standard. [c] AIBN (20 mol%) was used. [d] Recovery yield of **1a** is shown in parentheses. [e] *t*-BuOK (99.99% purity) was used. [f] Isolated yield. [g] A gram scale reaction of **1a**. [h] DMF (4 equiv) was added.

Using the optimized reaction conditions, we next investigated the generality of this methylation protocol. A variety of arylacetonitriles were methylated with $Me_2NH–BH_3$/DMF system to furnish the desired products (Scheme 2). Noticeably, in all cases only monomethylated products were obtained without the detection of any traces of dimethylated ones. Aryl ring bearing a wide range of functional groups could be converted to methylated products **2b-k** in good to excellent yields. The substrate bearing an alkene (for **1l**) or alkyne (for **1m**) tether was monomethylated in moderate yields, and no hydroboration product was observed in both cases. Remarkably, potentially reactive nucleophilic functional groups, including free aniline (for **2n**), *N*-H amide (for **2o**, **2p**), and alcohol (for **2q**) were well tolerated, without the need for protecting groups. A carboxylic acid (for **2r**) moiety was also tolerated without protection, even though 2.5 equiv of *t*-BuONa was required. Furthermore, a range of 2-heteroarylpropanenitriles bearing benzothiophene (for **2s**), indole (for **2t**), qunioline (for **2u**), and pyridine (for **2v**, **2w**) motifs were produced in good yields. As for the limitation, the methylation of alkylnitrile **1x** was unsuccessful, presumably due to the lower acidity of the α-methylene group.[20] In addition to arylacetonitriles, 2-phenylacetamide could be monomethylated to give the desired product **2y** in 68% yield. However, when ethyl 2-phenylacetate was subjected to the reaction conditions, a facile hydrolysis occurred to afford 2-phenylacetic acid in 70% yield,[21] while the methylated product **2z** was observed in 8% yield.



Scheme 2. Substrate scope. Reaction conditions: **1** (0.4-0.5 mmol), $Me_2NH–BH_3$ (1.0 equiv), *t*-BuONa (1.5 equiv) in DMF at 80 °C under N_2 atmosphere. [a] *t*-BuONa (2.5-3.0 equiv) was used. [b] The reaction was performed using *t*-BuOK (3.0 equiv) and $Me_3N–BH_3$ (2.5 equiv) at 120 °C for 11 h. [c] 2-phenylacetic acid derived from the hydrolysis of **1z** was formed in 70% yield.

To clarify the source of the methyl group, several mechanistic investigations were conducted (Scheme 3). First, to determine whether the methyl group is from the *N*-Me unit,[19c-19f, 22] a control experiment was tested using *N*,*N*-dimethylacetamide

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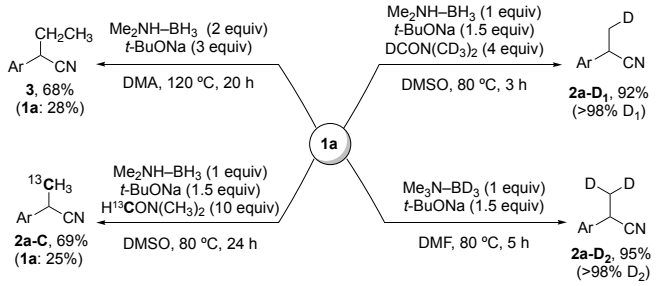
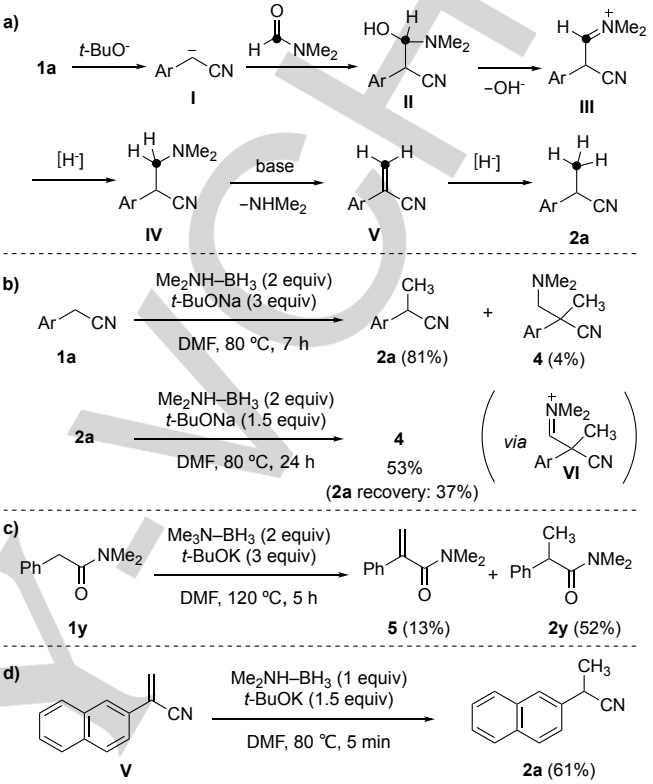
(DMA) as the solvent instead of DMF. As a result, an ethylated product **3** was isolated in 68% yield, and no methylated product **2a** was observed. This implied that the *N*-Me group of DMF and DMA was unlikely to be transferred to the product. When DMF-(carbonyl-^{13}C) was utilized, a ^{13}C-labeled methylated product **2a-C** was formed in 69% yield. This strongly supported that the methyl carbon atom originated from the DMF formyl group. The employment of d_7-DMF as a reagent afforded **2a-D** in 92% yield with the installation of single D atom (>98% D_1-incorporation),[23] suggesting that the formyl hydrogen atom was most likely transferred to the newly formed methyl group. Furthermore, using Me_3N–BD_3[24] as the D source, **2a-D$_2$** having two deuterium atoms (>98% D_2-incorporation)[23] was obtained in 95% yield, which indicated that two hydrogen atoms of the methyl group came from the amine–borane complex.



Scheme 3. Mechanistic studies to clarify the source of the methyl group

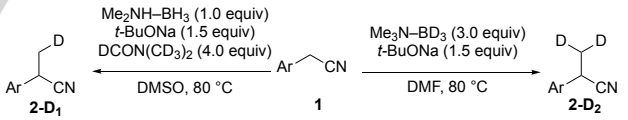
Based on these findings, a plausible mechanism for the methylation reaction is outlined in Scheme 4a. 2-Naphthylacetonitrile (**1a**) is first deprotonated by *t*-BuONa to generate a stabilized carbon anion **I**, which attacks the formyl group of DMF to afford hemiaminal **II**. Removing the hydroxyl group followed by hydride reduction of the resulting iminium intermediate **III** gives α-dimethylaminomethyl substituted arylacetonitrile **IV**. An E1cB elimination of Me_2NH occurs to afford acrylonitrile **V**, a further hydride reduction of which furnishes the methylated product **2a**.

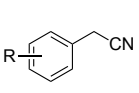
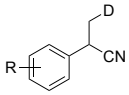
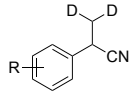
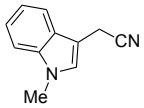
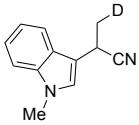
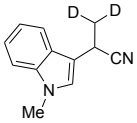
To support this proposed mechanism as well as to rationalize why the dimethylation can be prevented under the optimized reaction conditions, additional mechanistic studies were performed. As shown in Scheme 4b, when the reaction was extended to 7 h, besides **2a** (81% yield), product **4** bearing a dimethylaminomethyl group was formed in 4% yield. A further study showed that **2a** could be partially converted to **4** under the standard reaction conditions with prolonged reaction time. The dimethylaminomethyl group in **4** was derived from the reaction of **2a** with DMF followed by a hydride reduction of the iminium intermediate **VI**. This suggested that a similar reductive dimethylaminomethylation of **1a** might occur to generate intermediate **IV**. In addition, we attempted to detect acrylonitrile **V** in the reaction process, but all were unsuccessful. Fortunately, when the reaction of **1y** was stopped in 5 h, phenylacrylamide **5** was isolated in 13% yield (Scheme 4c).[25] This implied the intermediacy of **V** in the methylation process. Finally, a control experiment showed that reduction of acrylonitrile **V** took place under the standard reaction conditions, giving **2a** in 61% yield (Scheme. 4d), which verified the final hydride reduction reaction in the proposed mechanism.[26] The formation of **4** also indicated that the further reaction of the α-monomethylated product **2a** with amine–borane/DMF system was possible, but it was much slower than the first methylation reaction, probably due to the increased steric hindrance of **2a** that prohibits nucleophilic addition to DMF.



Scheme 4. A proposed mechanism and mechanistic details

Table 2. Selective synthesis of CDH_2- and CD_2H-substituted 2-arylpropionitriles [a][b]

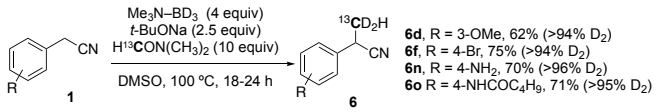


1	2-D_1	2-D_2
		
1d, R = 3-OMe	**2d-D$_1$** 89% (>98% D_1)	**2d-D$_2$**, 73% (>98% D_2)
1f, R = 4-Br	**2f-D$_1$**, 79% (>98% D_1)	**2f-D$_2$**, 53% (>98% D_2)
1n, R = 4-NH_2	**2n-D$_1$**, 42% (>98% D_1)	**2n-D$_2$**, 68% (>98% D_2)
1o, R = 4-$NHCOC_4H_9$	**2o-D$_1$**, 51% (>98% D_1)	**2o-D$_2$**, 65% (>97% D_2)
		
1t	**2t-D$_1$**, 55% (>98% D_1)	**2t-D$_2$**, 57% (>98% D_2)

[a] Reaction conditions for the synthesis of **2-D$_1$**: **1** (0.2-0.3 mmol), Me_2NH–BH_3 (1.0 equiv), *t*-BuONa (1.5 equiv), d_7-DMF (4.0 equiv) in DMSO at 80 °C under N_2 atmosphere. Reaction conditions for the synthesis of **2-D$_2$**: **1** (0.2-0.3 mmol), Me_3N–BD_3 (3.0 equiv), *t*-BuONa (1.5 equiv) in DMF at 80 °C under N_2 atmosphere. [b] Deuterium incorporation was determined by ^{1}H NMR spectroscopic analysis.

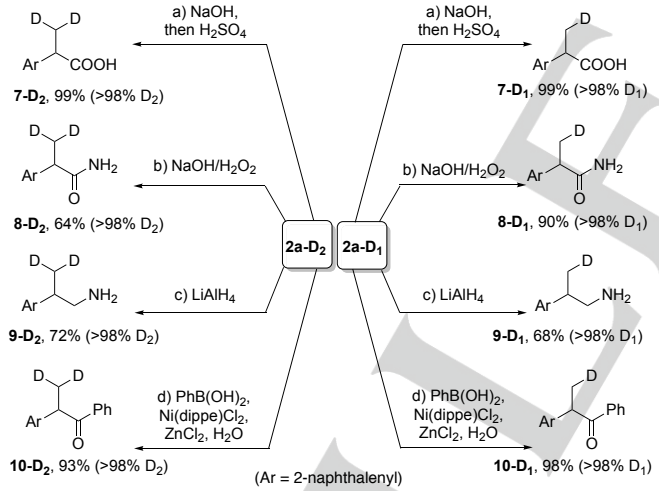
A remarkable advantage of the present methylation method lies in its ability to precisely control the numbers of deuterium atom incorporated into the methyl group. For example, using $Me_2NH–BH_3/d_7$-DMF system affords a CDH_2 unit, while the employment of $Me_3N–BD_3$/DMF delivers a CD_2H motif. As shown in Table 2, both systems worked well for the synthesis of a range of CDH_2- and CD_2H-containing nitriles with exceptionally high levels of D-incorporation.

Notably, the present protocol was also able to make mixed methyl-^{13}C/D isotopologues using DMF-(carbonyl-^{13}C) and $Me_3N–BD_3$ as the methyl source. As depicted in Scheme 5, a series of arylacetonitriles **6** bearing a $^{13}CD_2H$ group were assembled in moderate to good yields with high levels of D-incorporation.



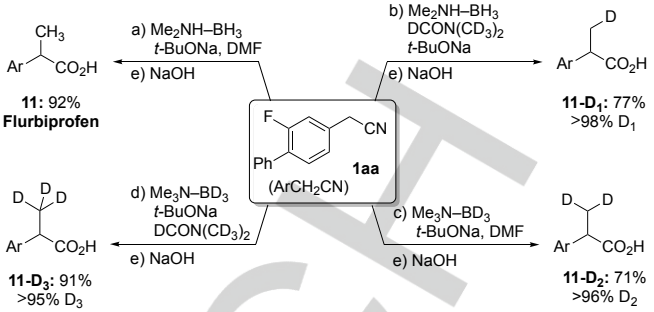
Scheme 5. Synthesis of mixed methyl-^{13}C/D isotopologues

Given the versatility of the cyano group,[27] the formed D-containing nitriles could be easily converted to a broad range of useful D-handled building blocks. Using **2a-D$_1$** and **2a-D$_2$** as model substrates, a variety of CDH_2- and CD_2H-substituted carboxylic acids, amides, amines, and ketones were obtained in good yields with the maintenance of excellent levels of D content (Scheme 6). These D-labeled synthons were difficult to access by existing D-incorporation methods,[8,28] and they may have potential applications in various fields.



Scheme 6. Diversified transformations to produce various CDH_2- and CD_2H-containing building blocks. Reaction conditions: a) NaOH, EtOH/H_2O, 110 °C, 5 h, then 1N H_2SO_4; b) NaOH, H_2O_2 (8 equiv.), MeOH, rt, 6 h; c) $LiAlH_4$ (2 equiv.), Et_2O, rt, 24 h; d) $PhB(OH)_2$ (2 equiv.), $Ni(dippe)Cl_2$ (5 mol%), $ZnCl_2$ (1.5 equiv.), H_2O (1.0 equiv.), 1,4-dioxane, 80 °C, 12 h.

Eventually, we showed the utility of our method in the synthesis of anti-inflammatory flurbiprofen[29] and its D-labeled derivatives (Scheme 7). Arylacetonitrile **1aa** was first monomethylated using the present protocol followed by hydrolysis, giving flurbiprofen in 92% yield (two steps). Furthermore, CDH_2-, CD_2H-, and CD_3-substituted flurbiprofen were selectively accessed in both good yields and high levels of D-incorporation using $Me_2NH–BH_3/d_7$-DMF, $Me_3N–BD_3$/DMF, and $Me_3N–BD_3/d_7$-DMF systems, respectively.



Scheme 7. Synthesis of flurbiprofen and its D-containing analogues. Reaction conditions: a) Me_2NH-BH_3 (1 equiv), *t*-BuONa (1.5 equiv), DMF, 80 °C, 3 h; b) Me_2NH-BH_3 (1 equiv), *t*-BuONa (1.5 equiv), d_7-DMF, 80 °C, 5 h; c) Me_3N-BD_3 (1 equiv), *t*-BuONa (1.5 equiv), DMF, 80 °C, 9 h; d) Me_3N-BD_3 (4 equiv), *t*-BuONa (2.5 equiv), d_7-DMF, 100 °C, 40 min; e) NaOH, EtOH/H_2O, 110 °C, 5 h, then 1N H_2SO_4. Deuterium incorporation was determined by ^{1}H NMR spectroscopic analysis.

In summary, we have developed a new protocol using $R_3N–BH_3$/DMF as the methyl source for the selective monomethylation of arylacetonitriles and arylacetamides. The reaction proceeds under mild reaction conditions with exclusive monomethylation selectivity. Significantly, selective installation of CDH_2, CD_2H, CD_3 and $^{13}CD_2H$ units into the products with high level of D-incorporation has also achieved by tuning the deuterium sources. Using this strategy, varied D-labeled 2-arylpropionic acids have been readily accessed. We are continuously working to explore further methylation reactions using this $R_3N–BH_3$/DMF system as the methyl source.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: synthetic methods • methylation • 2-arylpropionitriles • *N*,*N*-dimethylformamide • deuterium labeling• deuterated methyl groups

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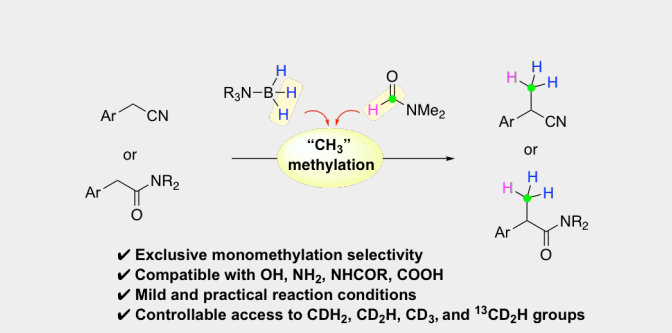

*Hui-Min Xia, Feng-Lian Zhang, Tian Ye, and Yi-Feng Wang**

Page No. – Page No.
Selective α-Monomethylation by an Amine–Borane/*N,N*-Dimethylformamide System as the Methyl Source

An unprecedented and practical methylation protocol using a $R_3N–BH_3$/DMF system as the methyl source has been developed for the selective α-monomethylation of arylacetonitriles and arylacetamides. The formyl group of DMF delivers the carbon and one hydrogen atoms of the methyl group, and $R_3N–BH_3$ donates the remaining two hydrogen atoms. Such a cooperative manner enabled controllable assemblies of CDH_2-, CD_2H-, CD_3-, and $^{13}CD_2H$- units by tuning deuterium sources.