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Copper-catalyzed synthesis of phenol and diaryl ether derivatives *via* hydroxylation of diaryliodoniums†

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A copper-catalysed hydroxylation of diaryliodoniums to generate phenols and diaryl ethers is reported. This method allows the synthesis of diversely functionalized phenols under mild reaction conditions without the need for a strong inorganic base or an expensive noble-metal catalyst. Significantly, convenient application of diaryliodoniums is demonstrated in the preparation of diaryl ethers in a one-pot operation.

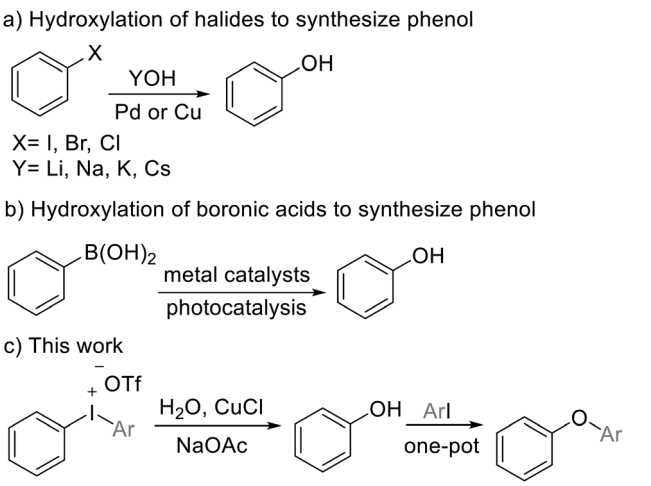
Introduction

Phenols and their derivatives are ubiquitous constituents for constructing bioactive natural products, agrochemicals and pharmaceuticals and serve as important motifs of polymers as well as novel materials.[1] Currently, many useful methods have been developed to prepare these phenol moieties by synthetic researchers.[2] Couplings of aryl halides and nucleophilic hydroxide salts in the presence of palladium or copper complex have been proved to be classical methods to prepare these compounds (Scheme 1a).[3i] In addition, hydroxylation of boronic acids (Scheme 1b) and hydrolysis of diazonium salts are also efficient strategies.[4] Although phenol derivatives are available by different transformations, it is very important to develop novel methodologies with mild reaction conditions, high efficiency and low waste generation.

Diaryliodoniums are air- and moisture-stable versatile electrophilic arylating reagents, which are easily available when iodoarenes are treated with mild oxidants.[5] They have been utilized to arylate a broad scope of nucleophiles in recent years, including aryl/alkyl amines,[6] phenols,[7] aliphatic alcohol and benzoic acid, which afford the corresponding aromatic compounds.[8] Despite this achievement, the use of strong inorganic bases or organic bases is adverse to reaction, especially for basic-sensitive functional groups.[9] Recently, We and other groups reported mild and rapid transformations of cyclic hypervalent iodoniums into oxygen-bridged polycyclic heteroarenes and dibenzofuran derivatives.[10] Owing to these previous work, we envisage a strategy for the synthesis of phenols *via* the hydroxylation of diaryl iodoniums. In terms of the oxygen donor, waster is the most environmentally friendly oxygen source.[11] The arylation of diaryliodoniums with waster as the nucleophile is believed to be a valuable access to phenols. In this study, we develop a one-pot reaction for the synthesis of a wide range of phenols and diaryl ethers from diaryliodoniums. This versatile method operates under mild reaction conditions, with inexpensive CuCl as the catalyst (Scheme 1c).

Results and discussion

At the outset of our studies, the hydroxylation of diaryliodoniums was conducted by the exposure substrate **1a** to $Cu(OAc)_2$ (0.1 equiv.), Na_2CO_3 (2.0 equiv.), H_2O (5.0 equiv.) in DMF at 40 °C for 2 hours, leading to the desired product **2a** in a moderate yield (entry 1). Encouraged by this result, we subsequently screened other copper catalysts (entry 2–5),



Scheme 1 Selected methods for the synthesis of phenols.

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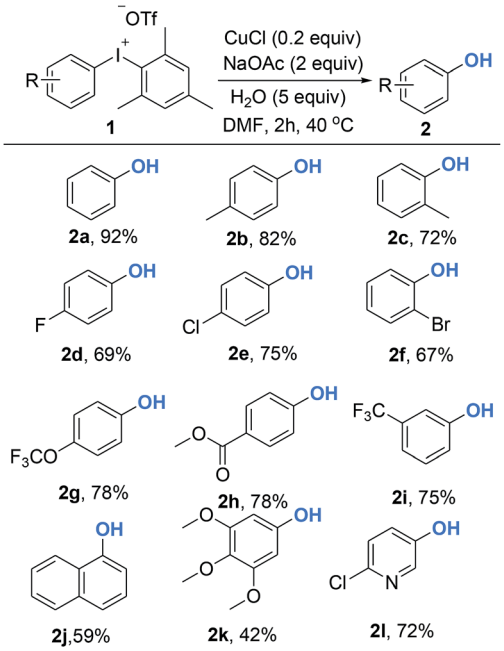
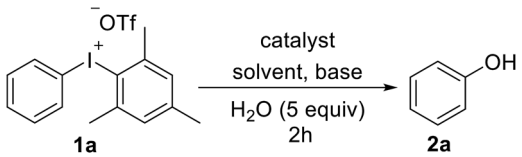
including $Cu(OTf)_2$, $CuCl_2$, $CuSO_4$ and CuI were inferior to $Cu(OAc)_2$, while CuCl showed the best efficiency. Compared with DMF, solvents of toluene, DCE, dioxane and MeCN were not helpful for the reaction conversion (entry 6–9). The examine of bases disclosed that mild NaOAc was ideal choice (entry 10–14). The yields reduced when the reaction was performed in shortened time (entry 15–16). It was observed that only 39% **2a** was yielded at rt (entry 17), which indicated that slight heating was needed for the diaryliodoniums reactivity. Further study revealed that it is not fruitful without the addition of water (entry 18), and even no targeted product was isolated in the absence of CuCl (entry 19) (Table 1).

With optimized reaction conditions in hand, diversely functionalized diaryliodoniums were subjected to the established reaction conditions to explore the efficiency and scope of this copper-catalyzed hydroxylation reaction. As summarized in Scheme 2, this protocol afforded phenols bearing electron-rich, electron-poor, or sterically bulky substituted groups in good yields (**2a–2l**). Electron-neutral phenols were delivered in excellent yields (**2a–2c**). In terms of electron-deficient substrates, *para*-, and *meta*-substituted diaryliodoniums containing –F, $-OCF_3$, $-CF_3$ and $-CO_2Me$ were compatible to produce phenols **2d–2g** in the yield of 56–87%. The reaction also furnished the electron-rich product efficiently (**2h**). Notably, 1-naphthol was available in a 74% yield (**2i**). It is necessary to emphasize that the reaction conditions were tolerant of *ortho*-functional groups such as methyl and bromo to give **2j** and **2k**. Hydroxylated heteroarenes are prevalent bioactive intermediates in medicinal chemistry. To our surprise, it was demonstrated that our strategies were suitable for the synthesis of hydroxylated pyridine **2l**.



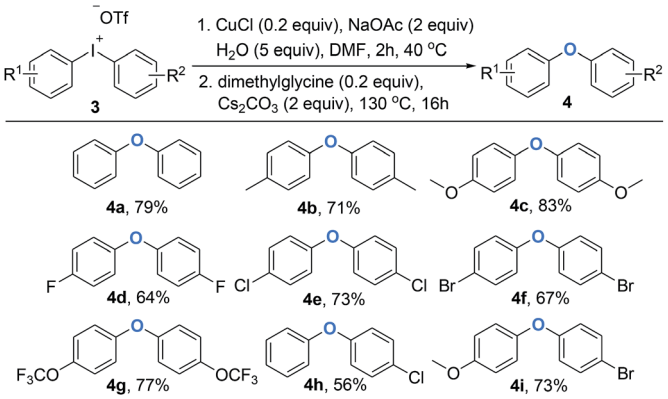
Scheme 2 Copper-catalyzed synthesis of phenols from diaryliodoniums. Reaction conditions: **1** (0.2 mmol), CuCl (10 mol%), NaOAc (2 equiv.), H_2O (5 equiv.), DMF (1.0 mL), Ar, 40 °C, 2 h.

Table 1 Optimization of the hydroxylation of diaryliodoniums. Reaction conditions: **1a** (0.1 mmol), catalyst (10 mol%), base (2 equiv.), H_2O (5 equiv.), solvent (0.5 mL), Ar, 2 h. [a]1.5 h, [b]1 h, [c]12 h, [d]H_2O was not added



Entry	Catalysis	Base	Solvent	T (°C)	Yield (%)
1	$Cu(OAc)_2$	Na_2CO_3	DMF	40	57
2	$Cu(OTf)_2$	Na_2CO_3	DMF	40	0
3	$CuSO_4$	Na_2CO_3	DMF	40	0
4	CuI	Na_2CO_3	DMF	40	50
5	CuCl	Na_2CO_3	DMF	40	85
6	CuCl	Na_2CO_3	Toluene	40	10
7	CuCl	Na_2CO_3	DCE	40	21
8	CuCl	Na_2CO_3	Dioxane	40	0
9	CuCl	Na_2CO_3	MeCN	40	42
10	CuCl	Et_3N	DMF	40	77
11	CuCl	K_2CO_3	DMF	40	85
12	CuCl	NaOAc	DMF	40	92
13	CuCl	K_3PO_4	DMF	40	14
14	CuCl	NaOH	DMF	40	0
15	CuCl	NaOAc	DMF	40	86[a]
16	CuCl	NaOAc	DMF	40	79[b]
17	CuCl	NaOAc	DMF	rt	39(83[c])
18	CuCl	NaOAc	DMF	40	11[d]
19	—	NaOAc	DMF	40	0

Diaryl ethers are significant building blocks and have found wide applications in the preparation of natural products and synthetic compounds with various biological properties and functions.[12] Although diaryliodoniums have been extensively investigated as versatile arylating reagents in recent years, their poor atom economy limits further applications, as one equivalent of iodobenzene was generated as a waste in most of common reactions.[13] Until recently, some examples were reported to overcome the drawback by designing one-pot, tandem reactions that can use the aryl iodide side product in a second arylation process *in situ*.[14] Inspired by this domino arylating strategy, it is appealing to synthesize diaryl ethers directly, which represents a feasibility of using diaryliodoniums in an economic way. As shown in Scheme 3, the access to various aromatic ethers was realized by the addition of Cs_2CO_3 and dimethylglycine at 130 °C. As expected, symmetric diaryl ethers substituted by both electron-donating and electron-withdrawing groups formed smoothly (**4a–4g**). It is notable that the intact chloro (**4e**) or bromo (**4f**) moieties allow potential modification of polymer materials. Besides, unsymmetric diaryl ethers were synthesized efficiently in our method (**4h–4i**). Based on our observation, a copper-catalyzed hydroxylation of linear diaryliodoniums was proposed. Initially, oxidative addition of iodonium **1a** to copper(I) would provide copper(III) intermediate A. This electrophilic species can be attacked by H_2O under basic



Scheme 3 One-pot synthesis of diaryl ethers from diaryliodoniums. Reaction conditions: (1) **1** (0.2 mmol), CuCl (10 mol%), NaOAc (2 equiv.), H_2O (5 equiv.), DMF (1.0 mL), Ar, 40 °C, 2 h; (2) Cs_2CO_3 (2 equiv.) and dimethylglycine (0.2 equiv.) were added, Ar, 130 °C, 16 h.

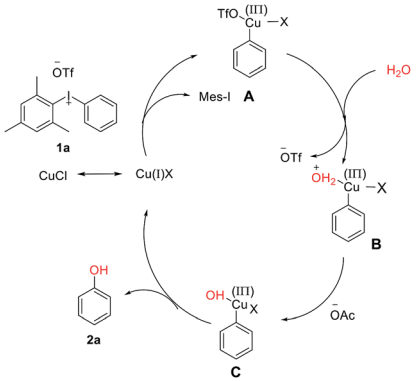


Fig. 1 The proposed mechanism for the hydroxylation of diaryliodoniums.

conditions, and intermediate B and C were formed consequently through this process. Finally, a reductive elimination of C would generate phenol **2a** (Fig. 1).

Conclusions

In summary, we have developed a copper-catalysed hydroxylation diaryliodoniums in a mild reaction conditions. This protocol enables the synthesis of aryl/heteroaryl phenols with various functionalities. Moreover, the one-pot, tandem process to diaryl ethers realizes convenient application of diaryliodoniums. Together with the use of an inexpensive metal catalyst, simple operation and atom economy, featuring the practical value of our protocol. Further study on utilization of this strategy in medicinal chemistry is underway in our lab.

Experimental

General information

All solvents were commercially available and were used without further purification unless stated. The chemicals used were either purchased from commercial sources or prepared according to literature procedures for CDPIs. The ^1H, ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance spectrometer 400 at 400 MHz, 100 MHz respectively. Chemical shifts are given in ppm (δ) referenced to $CDCl_3$ with 7.26 for ^1H and 77.10 for ^{13}C, and to d_6-DMSO with 2.50 for ^1H and 39.5 for ^{13}C. In the case of multiplet, the signals are reported as intervals. Signals are abbreviated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants are expressed in hertz. Mass spectra were recorded on a BRUKER VPEXII spectrometer (ESI mode). The progress of the reactions was monitored by thin-layer chromatography on a glass plate coated with silica gel with fluorescent indicator (GF254). Column chromatography was performed on silica gel (200–300 mesh).

General procedure to synthesize phenols (2)

To a round-bottom flask was added diaryliodonium (0.2 mmol, 1.0 equiv.), NaOAc (2.0 equiv.), CuCl (0.1 equiv.), 5 (0.1 equiv.), DMF (1.0 mL). Then the flask was sealed, degassed and recharged with argon. The reaction proceeded at 40 °C for 2 h under argon atmosphere. Then, the reaction mixture was extracted with EtOAc, the combined organic layers were washed with H_2O and brine and dried over anhydrous Na_2SO_4, evaporated *in vacuo*. The residue was purified by column chromatography on a silica gel (PE/EtOAc) to provide compounds **2**.

General procedure to synthesize diaryl ethers (4)

To a round-bottom flask was added diaryliodonium (0.2 mmol, 1.0 equiv.), NaOAc (2.0 equiv.), CuCl (0.1 equiv.), 5 (0.1 equiv.), DMF (1.0 mL). Then the flask was sealed, degassed and recharged with argon. The reaction proceeded at 40 °C for 2 h under argon atmosphere. Then, Cs_2CO_3 (2 equiv.) and dimethylglycine (0.2 equiv.) were added to the reaction residue, degassed and recharged with argon again. The reaction proceeded at 130 °C for 16 h under argon atmosphere. The reaction mixture was extracted with EtOAc, the combined organic layers were washed with H_2O and brine and dried over anhydrous Na_2SO_4, evaporated *in vacuo*. The residue was purified by column chromatography on a silica gel (PE/EtOAc) to provide compounds **4**.

Phenol (2a). White acicular crystal, yield 94%. ^1H NMR (500 MHz, chloroform-d) δ 7.26 (t, $J = 7.7$ Hz, 2H), 6.95 (t, $J = 7.4$ Hz, 1H), 6.85 (d, $J = 8.3$ Hz, 2H), 4.29 (d, $J = 101.8$ Hz, 1H). ^{13}C NMR (125 MHz, chloroform-d) δ 155.57, 129.82, 120.96, 115.45.

***P*-Cresol (2b).** Pale yellow crystal, yield 82%. Mp: 31–33 °C. ^1H NMR (500 MHz, chloroform-d) δ 7.04 (d, $J = 7.8$ Hz, 2H), 6.74 (d, $J = 7.7$ Hz, 2H), 2.28 (s, 3H). ^{13}C NMR (125 MHz, chloroform-d) δ 153.32, 130.21, 130.13, 115.19, 20.60.

***O*-Cresol (2c).** Colorless clear liquid, yield 72%. ^1H NMR (400 MHz, chloroform-d) δ 7.16–7.05 (m, 2H), 6.85 (td, $J = 7.4$, 1.2 Hz, 1H), 6.77 (d, $J = 8.0$ Hz, 1H), 2.26 (s, 3H). ^{13}C NMR (101 MHz, chloroform-d) δ 153.92, 131.16, 127.26, 123.85, 120.88, 115.03, 15.81.

4-Fluorophenol (2d). Pale yellow crystal, yield 69%, mp: 42–44 °C. ^1H NMR (400 MHz, chloroform-d) δ 7.01–6.88 (m, 2H), 6.85–6.73 (m, 2H), 3.98 (s, 1H). ^{13}C NMR (101 MHz, chloroform-

d) δ 158.63, 156.26, 151.69, 151.67, 116.42, 116.34, 116.24, 116.01.

4-Chlorophenol (2e). Clear crystal, yield 75%. Mp: 42–44 °C. ^{1}H NMR (400 MHz, chloroform-d) δ 7.19 (d, J = 8.9 Hz, 2H), 6.77 (d, J = 8.9 Hz, 2H). ^{13}C NMR (101 MHz, chloroform-d) δ 154.61, 130.00, 126.19, 117.13.

2-Bromophenol (2f). Pale yellow liquid, yield 67%. ^{1}H NMR (400 MHz, chloroform-d) δ 7.47 (dd, J = 8.0, 1.6 Hz, 1H), 7.23 (td, J = 7.7, 1.6 Hz, 1H), 7.03 (dd, J = 8.2, 1.6 Hz, 1H), 6.81 (td, J = 7.7, 1.6 Hz, 1H). ^{13}C NMR (101 MHz, chloroform-d) δ 152.37, 132.15, 129.33, 121.96, 116.27, 110.39.

4-(Trifluoromethoxy)phenol (2g). Brown clear liquid, yield 78%. ^{1}H NMR (400 MHz, chloroform-d) δ 7.09 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H). ^{13}C NMR (101 MHz, chloroform-d) δ 154.33, 142.99, 122.79, 116.31.

Methyl 4-hydroxybenzoate (2h). White solid, yield 78%. Mp: 122–124 °C. ^{1}H NMR (400 MHz, chloroform-d) δ 7.95 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 6.68 (s, 1H), 3.90 (s, 3H). ^{13}C NMR (101 MHz, chloroform-d) δ 167.74, 160.55, 132.12, 122.32, 115.47, 52.26.

3-(Trifluoromethyl)phenol (2i). Yellow clear liquid, yield 75%. ^{1}H NMR (500 MHz, chloroform-d) δ 7.35 (t, J = 8.0 Hz, 1H), 7.20 (d, J = 7.7 Hz, 1H), 7.09 (s, 1H), 7.01 (dd, J = 8.2, 2.4 Hz, 1H). ^{13}C NMR (125 MHz, chloroform-d) δ 156.08, 130.65, 125.31, 123.14, 119.20, 118.08, 118.05, 118.02, 112.79, 112.76.

Naphthalen-2-ol (2j). White solid, yield 59%. Mp: 119–121 °C. ^{1}H NMR (400 MHz, chloroform-d) δ 7.77 (dd, J = 8.2, 6.4 Hz, 2H), 7.69 (d, J = 8.2 Hz, 1H), 7.46–7.40 (m, 1H), 7.33 (ddd, J = 8.1, 6.9, 1.1 Hz, 1H), 7.15 (d, J = 2.4 Hz, 1H), 7.11 (dd, J = 8.8, 2.5 Hz, 1H), 4.87 (s, 1H). ^{13}C NMR (101 MHz, chloroform-d) δ 153.33, 134.60, 129.91, 128.97, 127.81, 126.58, 126.40, 123.68, 117.75, 109.51.

3,4,5-Trimethoxyphenol (2k). Yellowish solid, yield 42%. Mp: 147–148 °C. ^{1}H NMR (400 MHz, chloroform-d) δ 6.09 (s, 2H), 3.82 (s, 6H), 3.78 (s, 3H). ^{13}C NMR (101 MHz, chloroform-d) δ 153.95, 152.41, 107.55, 93.16, 61.18, 56.18.

6-Chloropyridin-3-ol (2l). Pale yellow crystal, yield 88%. Mp: 154–156 °C. ^{1}H NMR (500 MHz, chloroform-d) δ 8.59 (s, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.47 (d, J = 8.2 Hz, 1H). ^{13}C NMR (125 MHz, chloroform-d) δ 151.88, 147.92, 137.19, 124.87.

Oxydibenzene (4a). Colorless liquid, yield 75%. ^{1}H NMR (400 MHz, chloroform-d) δ 7.41–7.28 (m, 4H), 7.14–7.06 (m, 2H), 7.05–6.95 (m, 4H). ^{13}C NMR (101 MHz, chloroform-d) δ 157.43, 129.87, 123.36, 119.04.

4,4′-Oxybis(methylbenzene) (4b). Colorless liquid, yield 64%. ^{1}H NMR (400 MHz, chloroform-d) δ 7.12 (d, J = 8.4 Hz, 4H), 6.89 (d, J = 8.5 Hz, 4H), 2.33 (s, 6H). ^{13}C NMR (101 MHz, chloroform-d) δ 155.49, 132.59, 130.28, 118.75, 20.80.

4,4′-Oxybis(fluorobenzene) (4c). Pale yellow liquid, yield 58%. ^{1}H NMR (400 MHz, chloroform-d) δ 7.08–6.98 (m, 4H), 6.94 (dq, J = 6.7, 2.8, 2.2 Hz, 4H). ^{13}C NMR (101 MHz, chloroform-d) δ 160.10, 157.70, 153.53, 120.11, 120.03, 116.59, 116.36.

4,4′-Oxybis(chlorobenzene) (4d). Pale yellow liquid, yield 56%. ^{1}H NMR (400 MHz, chloroform-d) δ 7.30 (d, J = 9.0 Hz, 4H), 6.93 (d, J = 8.9 Hz, 4H). ^{13}C NMR (101 MHz, chloroform-d) δ 155.74, 130.01, 128.85, 120.25.

4,4′-Oxybis(bromobenzene) (4e). Pale yellow liquid, yield 59%. ^{1}H NMR (500 MHz, chloroform-d) δ 7.44 (d, J = 8.9 Hz, 4H), 6.88 (d, J = 8.9 Hz, 4H). ^{13}C NMR (125 MHz, chloroform-d) δ 156.12, 132.96, 120.70, 116.31.

4,4′-Oxybis(methoxybenzene) (4f). White liquid, yield 45%. ^{1}H NMR (400 MHz, chloroform-d) δ 6.93 (d, J = 9.1 Hz, 4H), 6.86 (d, J = 9.0 Hz, 4H), 3.79 (s, 6H). ^{13}C NMR (101 MHz, chloroform-d) δ 155.50, 151.76, 119.67, 114.92, 55.81.

4,4′-Oxybis((trifluoromethoxy)benzene) (4g). Brown liquid, yield 60%. ^{1}H NMR (500 MHz, chloroform-d) δ 7.21 (d, J = 8.9 Hz, 4H), 7.02 (d, J = 9.0 Hz, 4H). ^{13}C NMR (126 MHz, chloroform-d) δ 155.63, 145.15, 128.79, 123.07, 121.80, 121.66, 120.14, 119.75.

Chloro-4-phenoxybenzene (4h). Colorless liquid, yield 46%. ^{1}H NMR (500 MHz, chloroform-d) δ 7.36 (t, J = 7.3 Hz, 2H), 7.30 (d, J = 7.4 Hz, 2H), 7.14 (t, J = 7.3 Hz, 1H), 7.02 (d, J = 7.8 Hz, 2H), 6.95 (d, J = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, chloroform-d) δ 156.98, 156.07, 130.00, 129.83, 128.30, 123.76, 120.16, 119.06.

1-Bromo-4-(4-methoxyphenoxy)benzene (4i). Pale yellow liquid, yield 44%. ^{1}H NMR (500 MHz, chloroform-d) δ 7.38 (d, J = 8.2 Hz, 2H), 6.97 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.1 Hz, 2H), 3.81 (s, 3H). ^{13}C NMR (126 MHz, chloroform-d) δ 157.93, 156.32, 149.73, 132.63, 121.06, 119.30, 115.10, 114.84, 55.80.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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