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Iodine-catalyzed oxidative functionalization of purines with (thio)ethers or methylarenes for the synthesis of purin-8-one analogues†

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An efficient oxidative functionalization of purine-like substrates with (thio)ethers or methylarenes under mild conditions is described. Using I_2 as the catalyst, and TBHP as the oxidant, this protocol provides a valuable synthetic tool for the assembly of a wide range of 9-alkyl(benzyl)purin-8-one derivatives with high atom- and step-economy and exceptional functional group tolerance.

The purine skeleton, is widely found in many natural compounds.[1] Among them, purin-8-ones are well-known as scaffolds to form target drugs against immune disease,[2] as bioreceptor agonists or antagonists,[3] and cancer cell inhibitors.[4] The purin-8-ones Loxoribine,[5] XBD173[6] and GRC0321[4a] are used as active pharmaceutical ingredients (Fig. 1). Research on such analogues is of great interest to organic chemists.[7] Traditionally, C–N and C–O bonds[8,9] are constructed using a metal catalyst through an oxidative dehydrogenation cross coupling process. However, problems with transition metal catalysts are increasingly apparent. They are expensive, require special conditions (anhydrous and/or oxygen free, *etc.*) and are environmental pollutants. Therefore, metal-free methods of purin-8-one synthesis are desired. Recently, to investigate pharmaceutical applications, diverse methods were developed for the synthesis of purin-8-one analogues.[10] Maki's group used a quaternary ammonium iodide salt intermediate to obtain purin-8-one derivatives (Scheme 1A).[10a] However, this iodide salt intermediate severely limited the range of 8-oxo-purine nucleosides. Sugimura's group reported the regio- and stereo controlled synthesis of 8-oxo-purine nucleosides based on intramolecular glycosylation (Scheme 1B).[10b] This method suffered from a limited substrate scope and required the activation of C_8–H *via* bromination. In addition, Guo's group developed a one-pot copper catalyzed method for the N-7 alkylation of 9-alkylpurin analogues using a halogenated alkane (Scheme 1C).[10c] The copper salt is economical but may be a biological toxin and the halogenated substrates are environmentally unfriendly. In the literature[11] and in our previous work,[12] a cross dehydrogenation coupling reaction occurred linking the nitrogen heterocycle or purine with the ether or toluene derivative *via* a new C–N bond. This paper extends that work to a bifunctionalization process with both a coupling and an oxidation occurring in one pot. In addition, sulfur analogues of the ethers were investigated. Herein, we developed a novel method to construct new C–N and C=O bonds in a one-pot synthesis of 9-alkyl(benzyl)purin-8-one analogues using I_2 as the catalyst.

Initially, the reaction conditions for the model substrates, 7-benzyl-6-chloro-7*H*-purine (**1a**) and tetrahydrofuran (THF) (**2a**), were investigated. The reaction of **1a** in the presence of the oxidant, TBHP, the base, K_2CO_3, and the solvent/reactant, **2a**, in air at 90 °C provided no desired product (Table 1, entry 1). Different commercially available transition metal salts $CuCl_2$, $FeCl_2$ and $Pd(OAc)_2$ were examined, but they gave unsatisfactory results (entries 2–4). Instead of metal catalysts, the iodine catalysts, TBAI, KI and I_2 were used and provided the desired product **3a** in 54%, 50% and 75% yield (entries 5–7). An increased or decreased amount of I_2 did not improve the yield (entries 8 and 9). Next, the reaction was carried out with different oxidants: TBHP (in decane), DTBP, H_2O_2, $K_2S_2O_8$, DDQ, BPO, TBPB and no oxidant (entries 10–17). TBHP pro-

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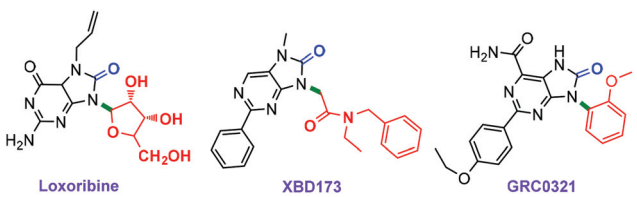
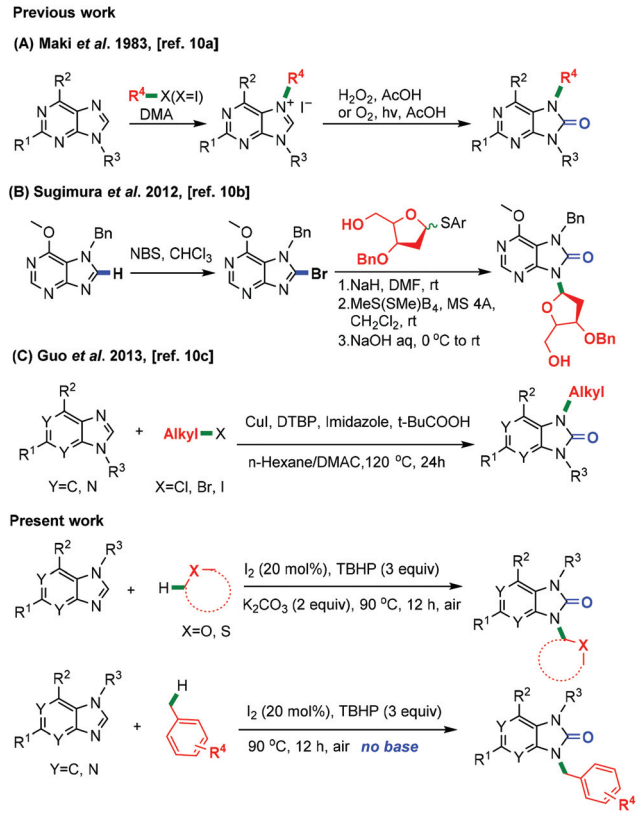


Fig. 1 Examples of biologically active purin-8-one.

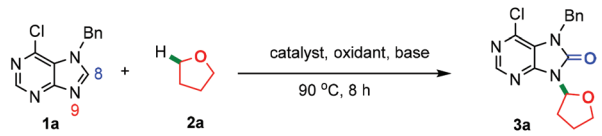


Scheme 1 Synthesis methods for purin-8-one analogues.

vided the best yield. Increasing the amount of oxidant, TBHP, from 2 to 3 equiv., improved the yield to 82% (entry 18), but using 4 equiv. lowered the yield (entry 19). The reaction was further explored using the bases Na_2CO_3 and Cs_2CO_3, but the yield did not improve (entries 20 and 21). When no base was added, the yield was only 10% (entry 22). Increasing the amount of base provided a similar yield (86% to 80%, entries 23 and 24). While slightly extending the reaction time (12 h) provided a better yield of 89% (entry 25), but a longer reaction time (24 h) reduced the yield (entry 26). Furthermore, the N_2 atmosphere had little influence on the yield (entry 27). Raising or lowering the temperature did not give better results (entries 28 and 29). In addition, experiments on the amounts of reactant **2a** were carried out (entries 30–34). The results indicated that the use of excess **2a** as the reactant and solvent helps ensure the solubility of the other reactant and makes the reaction more complete. Based on the above results, the optimized conditions were set as 0.1 mmol **1a**, 20 mol% I_2, 3 equiv. TBHP and 2 equiv. K_2CO_3 in 4 mmol **2a**, at 90 °C for 12 h.

Using the optimized conditions, the substrate scope of purines and alkyl ethers was investigated (Table 2). Purine substituted at the 2 and 6 position with the weak electron-withdrawing group (–Cl) and the electron-donating substituent (–OMe) provided the desired products in good yield (**3a–3c**). In addition, a small non-bulky group at the 7 position (–Et) provided good yields of the corresponding products (**3d–3f**). Next,

Table 1 Optimization of the reaction parameters[a]



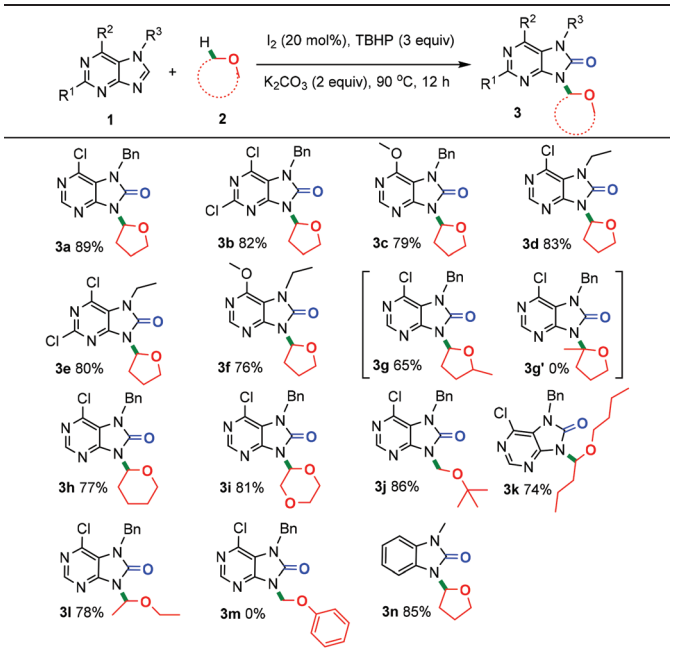
Entry	Catalyst (mol%)	Oxidant[b] (equiv.)	Base (equiv.)	Yield[c] (%)
1	—	TBHP (2)	K_2CO_3 (1.5)	0
2	$CuCl_2$ (20)	TBHP (2)	K_2CO_3 (1.5)	0
3	$FeCl_2$ (20)	TBHP (2)	K_2CO_3 (1.5)	0
4	$Pd(OAc)_2$ (20)	TBHP (2)	K_2CO_3 (1.5)	0
5	TBAI (20)	TBHP (2)	K_2CO_3 (1.5)	54
6	KI (20)	TBHP (2)	K_2CO_3 (1.5)	50
7	I_2 (20)	TBHP (2)	K_2CO_3 (1.5)	75
8	I_2 (30)	TBHP (2)	K_2CO_3 (1.5)	70
9	I_2 (10)	TBHP (2)	K_2CO_3 (1.5)	40
10[d]	I_2 (20)	TBHP (2)	K_2CO_3 (1.5)	71
11	I_2 (20)	DTBP (2)	K_2CO_3 (1.5)	0
12	I_2 (20)	H_2O_2 (2)	K_2CO_3 (1.5)	0
13	I_2 (20)	$K_2S_2O_8$ (2)	K_2CO_3 (1.5)	0
14	I_2 (20)	DDQ (2)	K_2CO_3 (1.5)	0
15	I_2 (20)	BPO (2)	K_2CO_3 (1.5)	40
16	I_2 (20)	TBPB (2)	K_2CO_3 (1.5)	15
17	I_2 (20)	—	K_2CO_3 (1.5)	0
18	I_2 (20)	TBHP (3)	K_2CO_3 (1.5)	82
19	I_2 (20)	TBHP (4)	K_2CO_3 (1.5)	59
20	I_2 (20)	TBHP (3)	Na_2CO_3 (1.5)	32
21	I_2 (20)	TBHP (3)	Cs_2CO_3 (1.5)	55
22	I_2 (20)	TBHP (3)	—	10
23	I_2 (20)	TBHP (3)	K_2CO_3 (2)	86
24	I_2 (20)	TBHP (3)	K_2CO_3 (3)	80
25[e]	**I_2 (20)**	**TBHP (3)**	**K_2CO_3 (2)**	**89**
26[f]	I_2 (20)	TBHP (3)	K_2CO_3 (2)	84
27[g]	I_2 (20)	TBHP (3)	K_2CO_3 (2)	90
28[h]	I_2 (20)	TBHP (3)	K_2CO_3 (2)	63
29[i]	I_2 (20)	TBHP (3)	K_2CO_3 (2)	51
30[j]	I_2 (20)	TBHP (3)	K_2CO_3 (2)	5
31[k]	I_2 (20)	TBHP (3)	K_2CO_3 (2)	8
32[l]	I_2 (20)	TBHP (3)	K_2CO_3 (2)	26
33[m]	I_2 (20)	TBHP (3)	K_2CO_3 (2)	58
34[n]	I_2 (20)	TBHP (3)	K_2CO_3 (2)	77

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (4 mmol), catalyst (20 mol%), oxidant (2 equiv.) and base (1.5 equiv.) were heated in a sealed tube, 90 °C, 8 h. [b] TBHP (70% aq. solution). [c] GC yield. [d] TBHP (in decane). [e] Reaction time 12 h. [f] Reaction time 24 h. [g] Under a N_2 atmosphere. [h] Reaction temperature 60 °C. [i] Reaction temperature 120 °C. [j] **2a** (1 equiv.), CH_3CN (1 mL). [k] **2a** (2 equiv.), CH_3CN (1 mL). [l] **2a** (3 equiv.), CH_3CN (1 mL). [m] **2a** (20 equiv.), CH_3CN (1 mL). [n] **2a** (30 equiv.).

the scope of the alkyl ether substrates with 7-benzyl-6-chloro-7*H*-purine (**1a**) under the optimized conditions was explored. Cyclic and straight chain ethers were found to be suitable substrates for this transformation (**3g–3l**). When 2-methyltetrahydrofuran was used, the product **3g**, with two chiral carbon atoms, was obtained in 65% yield, but **3g′** was not detected. This result shows that the primary carbon is more reactive than the secondary carbon, indicating that steric hindrance has a significant effect on the reaction. The desired product **3m** was not detected when using PhOMe as the substrate. In addition to purines, 1-methylbenzimidazole as the substrate provided **3n** in 85% yield.

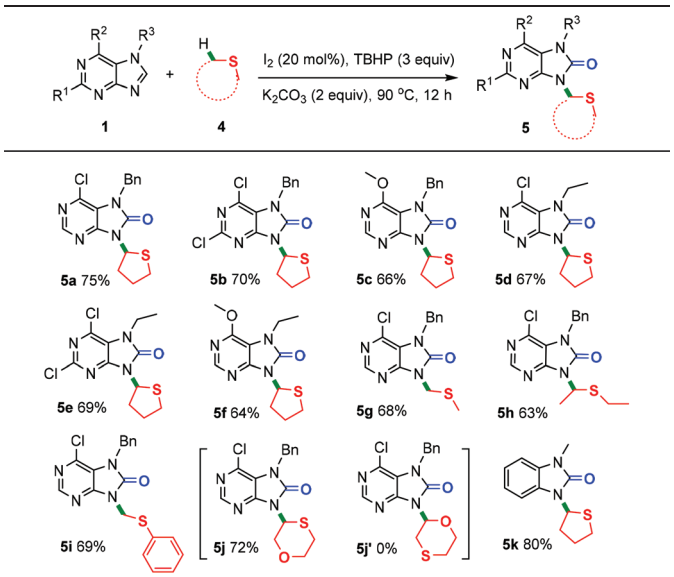
These results prompted us to investigate the reaction of heterocycle substrates with thioethers (Table 3). The corres-

Table 2 Substrate scope of purines and alkyl ethers[a]



[a] Reaction conditions: **1** (0.1 mmol), **2** (4 mmol), I_2 (20 mol%), TBHP (70% aq. solution, 3 equiv.), and K_2CO_3 (2 equiv.) were heated in a sealed tube under air at 90 °C for 12 h. Isolated yields are shown.

Table 3 Substrate scope of purines and thioethers[a]

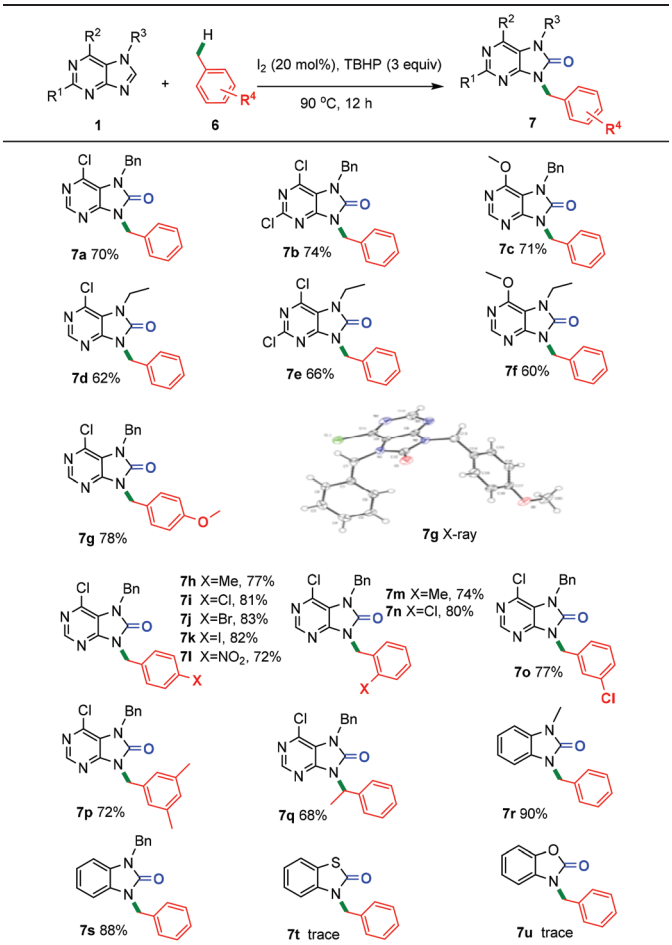


[a] Reaction conditions: **1** (0.1 mmol), **4** (4 mmol), I_2 (20 mol%), TBHP (70% aq. solution, 3 equiv.), and K_2CO_3 (2 equiv.) were heated in a sealed tube under air at 90 °C for 12 h. Isolated yields are shown.

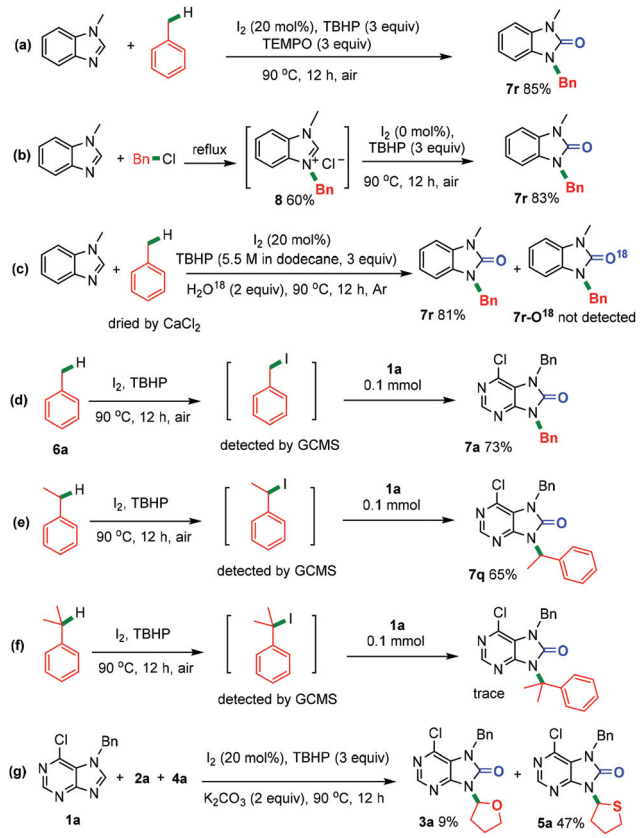
ponding products (**5a–5k**) were generated in moderate yields. An interesting result was found using 1,4-oxathiane as the substrate. The product was determined using DEPT spectra to be **5j** and not **5j′**. A competition reaction using THF and THT provided the THT adduct as the major product further confirming the result (Scheme 2g).

To further explore the potential of this methodology, toluene derivatives were investigated. The optimized conditions showed that there was no requirement of a base. Products from various substituted purines and toluene (**7a**[13]–**f**) were formed in good yield (Table 4). Methylarenes bearing electron-donating or withdrawing substituents such as methoxy (**7g**), methyl (**7h, m, p**), halo (**7i–k, n**,[14] **o**), nitro (**7l**) were successfully transformed into the desired purin-8-one products in good yield. When methylanisole (**6g**) was reacted under both sets of optimized conditions, with and without a base, the methylarene substituted product (**7g**) was obtained. The structure of **7g** was clearly certified by single-crystal X-ray diffraction analysis.[15] Ethylbenzene was also a suitable substrate, producing the corresponding product (**7q**) in medium yield. In addition to purines, the optimized reaction conditions were also applied to other heterocycles, 1-methylbenzimidazole (**7r**) and 1-benzylbenzimidazole (**7s**) products

Table 4 Substrate scope of purines and methylarenes[a]



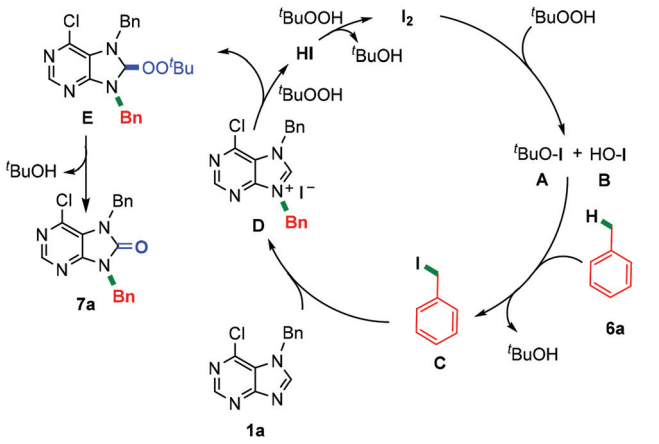
[a] Reaction conditions: **1** (0.1 mmol), **6** (4 mmol), I_2 (20 mol%), and TBHP (70% aq. solution, 3 equiv.) were heated in a sealed tube under air at 90 °C for 12 h. Isolated yields are shown.



Scheme 2 Control experiments.

were obtained in high yields, but, benzothiazole (**7t**) and benzoxazole (**7u**) products were only obtained in trace amounts.

To gain insights into the mechanism of this methodology, several control experiments were carried out. In Scheme 2a, when a radical inhibitor, TEMPO (2,2,6,6-tetra-methyl-piperidine-*N*-oxyl) was added to the reaction, the formation of the desired product **7r** was not affected. It was obtained in 85% yield. In Scheme 2b, the quaternary ammonium salt **8** was synthesized by the reaction of 1-methylbenzimidazole and benzyl chloride. In the absence of the iodine catalyst, **8** was transformed into the product (**7r**) in 83% yield. The carbonylation step did not require iodine, which implied that the function of iodine was the conversion of benzyl C–H to benzyl C–I. In Scheme 2c, the addition of $\mathbf{H_2O^{18}}$ (2 equiv.) did not yield the corresponding **7r-O^{18}**, indicating that the oxygen atom came from TBHP, not from water. In Scheme 2d, using toluene under the standard conditions, benzyl iodide was detected by GCMS (see the ESI†), and subsequent addition of **1a** provided **7a** in a yield of 73%. In Scheme 2e, similarly, using ethylbenzene, (1-iodoethyl)benzene was detected by GCMS, and the addition of **1a** gave **7q** in 65% yield. In Scheme 2f, when using cumene, the (2-iodopropan-2-yl)benzene was detected by GCMS, and the addition of **1a** gave only trace amounts of the product. These results may indicate that the reaction does not proceed through a cation or radical intermediate, because cumene should provide the most stable cation or radical. In Scheme 2g, a reaction of 7-benzyl-6-chloro-7*H*-purine (**1a**) with equal amounts of THF and THT under the optimized conditions was carried out, products **3a** and **5a** in a 1 : 5 ratio were obtained, indicating that thioethers are more reactive than alkyl ethers.



Scheme 3 Proposed reaction mechanism.

A possible reaction path based on previous literature reports and our results is proposed (Scheme 3).[10c,16] Initially, ^{t}BuO-I **A** and HO-I **B** are generated by molecular iodine and TBHP.[17] The benzylic C(sp^3)–H bond performs an iodination reaction *via* ^{t}BuO-I **A** or HO-I **B** to generate **C**. Then **C** undergoes nucleophilic attack by purine **1a** to provide the quaternary ammonium salt **D**. Subsequently, the addition of TBHP gives the peroxide **E**, which undergoes O–O bond cleavage to afford the product **7a**.[16,18] The iodine is regenerated by TBHP, recycling the catalyst.[19]

Conclusions

In conclusion, we have developed a concise, I_2-catalyzed C–N and C=O bifunctionalization protocol for the construction of 9-alkyl(benzyl)purin-8-one analogues *via* nucleophilic substitution and sp^{2}C–H oxidation. This method provides a simple and direct way for the synthesis of C_8=O/N_9 substituted purine compounds in one pot. These compounds have significant potential as biological and pharmacological agents. Moreover, the method is environmentally friendly since no pollutant is generated in the reaction process. Further investigations to understand the mechanism for this reaction are currently underway in our laboratory.

Author contributions

Juanping Zhuge – conceptualization, investigation, writing – original draft; Ziyang Jiang – conceptualization, investigation; Wei Jiang – investigation; Gary Histand – writing – review and editing; Dongen Lin – conceptualization, project administration, supervision, funding acquisition, writing – review and editing.

Conflicts of interest

There are no conflicts to declare.

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