

Article

Iminoiodane- and Brønsted Base-Mediated Cross Dehydrogenative Coupling of Cyclic Ethers with 1,3-Dicarbonyl Compounds

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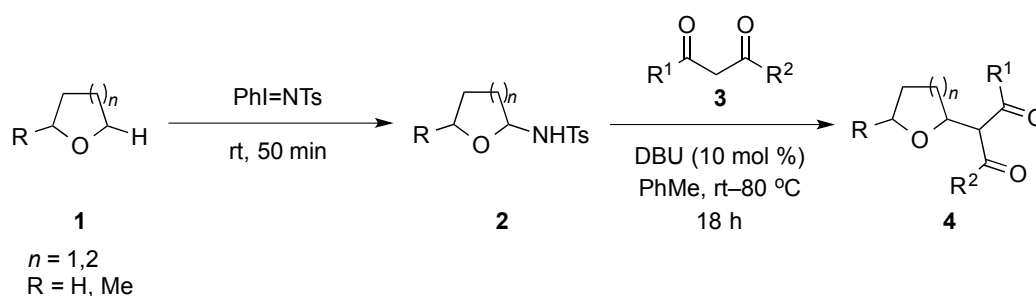
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Abstract: A one-pot, two-step approach to prepare 2-tetrahydrofuran and -pyran substituted 1,3-dicarbonyl compounds by PhI=NTs-mediated amination/Brønsted base-catalyzed cross dehydrogenative coupling (CDC) reaction of the cyclic ether and 1,3-dicarbonyl derivative under mild conditions is reported. The reaction is compatible with a variety of cyclic ethers and 1,3-dicarbonyl compounds, affording the corresponding coupled products in moderate to good yields of up to 80% over two steps.

Keywords: C–C bond formation; cross dehydrogenation coupling; 1,3-dicarbonyl compounds; iminoiodanes; metal-free catalysis

1. Introduction

Recently, there has been an increasing amount of attention toward the ultimate goal of the establishment of more sustainable organic transformations, owing to increased concerns over the impact of present chemical methods and processes on the living environment [1–4]. In this regard, the direct activation of carbon–hydrogen bonds in carbon–carbon bond forming CDC reactions has emerged as one of the most powerful and atom-economical methods in modern organic chemistry [5–9]. A number of transition metal salts, mainly those of Pd, Rh, Ru and Cu, in the presence of an oxidant, to effect these transformations at a variety of C–H bonds such as those at the benzylic, aryl, and alkyl C(sp³)–H positions have often been targeted [10–35]. In the case of the latter, this has included CDC reactions at the α -C–H bond of the heteroatom in ethers, amines, and sulfides with nucleophiles catalyzed by Fe or Cu salts [36–61]. More recently, the development of these reactions mediated by non-metal based catalysts has come under increasing scrutiny [62–71]. In the presence of an oxidant such as a peroxide, DDQ, TEMPO, dioxygen or hypervalent iodide reagent, a variety of carbon nucleophiles were shown to functionalize the α -carbon position of the heteroatom in amines and ethers [65–81]. As part of our interest in the chemistry of iminoiodanes, we wondered whether this class of I(III) compounds could mediate the α -functionalization of cyclic ethers by a carbon nucleophile under basic conditions. In doing so, we discovered THF, 2-methyl tetrahydrofuran and THP shown in Scheme 1 to undergo α -C–H bond amination by PhI=NTs [82–109]. This was followed by substitution at the aminal carbon center by 1,3-dicarbonyl compounds under the basic conditions. Herein, we report the details, this chemistry that provides access to 2-tetrahydrofuran and -pyran substituted 1,3-dicarbonyl compounds in up to 80% yield over two steps.



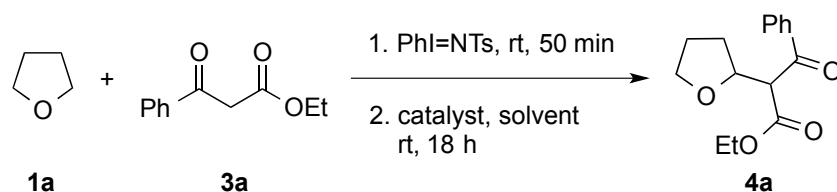
Scheme 1. Iminoiodane-mediated CDC reaction of cyclic ethers with 1,3-dicarbonyl compounds.

2. Results and Discussion

Our investigations began with the *in situ* generation of 2-tosylaminotetrahydrofuran **2a** from THF **1a** and PhI=NTs, which was obtained in 90% yield based on ¹H-NMR measurements [95]. Subsequent treatment of this adduct with 3 equiv of ethyl benzoylacetate **3a** and 10 mol % of DBU as the catalyst in THF at room temperature for 18 h gave ethyl 3-oxo-3-phenyl-2-(tetrahydrofuran-2-yl)propanoate **4a** in 41% yield (Table 1, entry 1) [103,110–112]. Changing the solvent from THF to diethyl ether in the second step gave a comparable product yield (Table 1, entry 2). Our subsequent studies found that the use of dichloromethane and toluene in place of THF led to higher product yields of 79% and 78%, respectively (Table 1, entries 3 and 4). However, other bases, such as Et₃N, DABCO, and MTBD, in place of DBU as the catalyst, afforded lower product yields of 61% or no reaction (Table 1, entries 5–7).

With DBU as the base and toluene as the solvent, decreasing the amount of **3a** from 3 to 2 or 1 equiv led to comparable product yields of 80% and 73%, respectively (Table 1, entries 8 and 9). On the other hand, a lower product yield of 67% was observed on lowering the catalyst loading of DBU from 10 to 5 mol % (Table 1, entry 10). From these results, the one-pot reaction of **1a** and PhI=NTs at room temperature for 50 min followed by treating with 2 equiv of **3a** in the presence of 10 mol % of DBU catalyst in toluene at room temperature for 18 h was deemed to provide the optimal reaction conditions.

Table 1. Optimization of reaction conditions ^a.

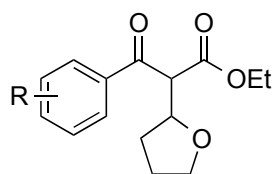
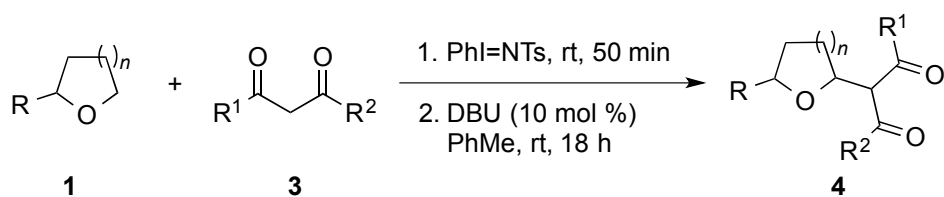


Entry	Catalyst (mol %)	Solvent	Yield (%) ^b
1	DBU (10)	THF	41
2	DBU (10)	Et ₂ O	54 ^c
3	DBU (10)	CH ₂ Cl ₂	79
4	DBU (10)	PhMe	78
5	Et ₃ N (10)	PhMe	- ^d
6	DABCO (10)	PhMe	- ^d
7	MTBD (10)	PhMe	61
8 ^e	DBU (10)	PhMe	80
9 ^f	DBU (10)	PhMe	73 ^c
10 ^e	DBU (5)	PhMe	67

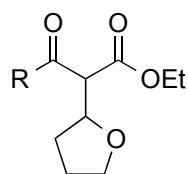
^a All reactions were carried out under N₂(g) with 0.25 M of PhI=NTs in THF for 50 min followed by treatment with the appropriate reaction condition. ^b Isolated yield over two steps. ^c Yield was determined by ¹H NMR analysis of crude mixture. ^d No reaction observed based on TLC and ¹H NMR analysis of the crude mixture. ^e Two equiv of **3a** was used. ^f One equiv of **3a** was used.

To define the generality of the present procedure, a series of cyclic ethers **1** and 1,3-dicarbonyl compounds **3** were tested and the results are summarized in Figure 1. These experiments revealed that reaction of **1a** with a range of aryl-substituted β-ketoesters bearing electron-donating (**3b–d**) and electron-withdrawing (**3e–h**) groups proceeded well to afford the corresponding adducts **4b–h** in good yields of 40%–78%. Likewise, aliphatic-substituted β-ketoesters (**3i–k**) were well tolerated, furnishing the corresponding targets **4i–k** in yields of 32%–63%. The present methodology was also applicable to dialkyl malonates (**3l–o**), as well as the 1,3-dimethyl dione **3p** with the corresponding products **4l–p** provided in good yields of 42%–71%. This is notable, as existing transition metal-catalyzed CDC reactions of these types of 1,3-dicarbonyl compounds have been previously reported to be incompatible [60].

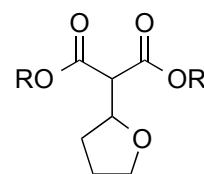
The influence of the cyclic ether coupling partner on the efficiency of the reaction was then assessed. For 2-methyltetrahydrofuran **1b** and THP **1c**, the reaction of these cyclic ethers with **3a** gave the corresponding adducts **4q** and **4r** in 43% and 57% yield, respectively. However, no reaction was observed when either 2,3-dihydrobenzofuran **1s** or dibutyl ether **1t** was treated with **3a**, under the standard conditions, with PhI=NTs and DBU. In the case of **1t**, decomposition of the α-aminated ether intermediate was observed by both TLC and ¹H-NMR analysis of the crude reaction mixture.



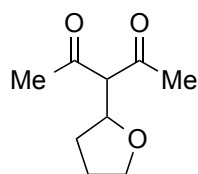
4b R = 2-Me (59%)
4c R = 4-Me (72%)
4d R = 4-OMe (40%)
4e R = 4-F (76%)
4f R = 4-Cl (71%)
4g R = 4-Br (78%)
4h R = 4-I (73%)



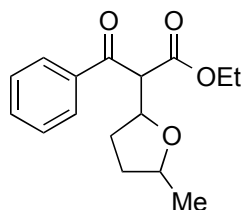
4i R = Me (32%)
4j R = Et (63%)
4k R = *i*-Pr (61%)



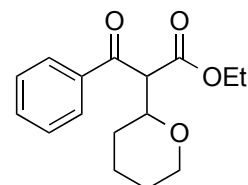
4l R = Me (51%)
4m R = Et (42%)
4n R = *i*-Pr (67%)^b
4o R = Bn (71%)^b



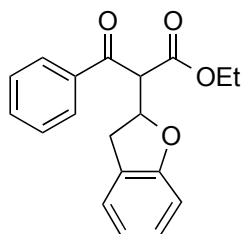
4p (65%)



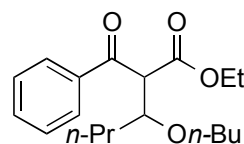
4q (43%)^{b,c}



4r (57%)^{c,d}



4s -^e



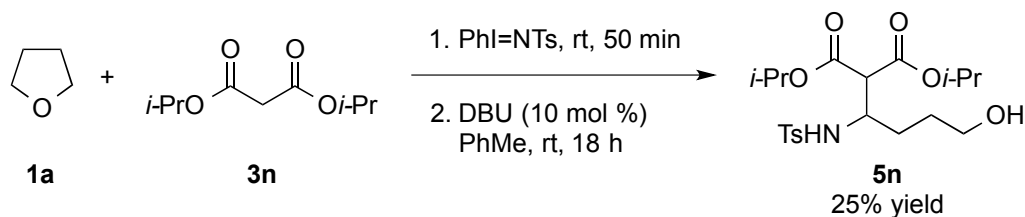
4t -^f

^a All reactions were carried out under N₂(g) with 0.25 M of PhI=NTs in ether for 50 min followed by treatment with 2 equiv of **3** and of 10 mol % DBU in toluene for 18 h. Isolated yields over two steps are in parentheses. ^b Reaction temperature = 40 °C. ^c Isolated yield is calculated based on the conversion of step one. Refer to experimental section for details. ^d Reaction temperature = 80 °C. ^e No reaction observed based on TLC and ¹H-NMR analysis of the crude mixture. ^f Decomposition of starting material based on TLC and ¹H-NMR analysis of the crude mixture.

Figure 1. Iminoiodane-mediated CDC reactions of cyclic ethers **1** and 1,3-dicarbonyl compounds **3** ^a.

At room temperature, reaction of **1a** with diisopropyl malonate **3n** was found to lead to **5n** being isolated in 25% yield (Scheme 2). The structure of compound **5n** was confirmed by single crystal X-ray analysis (Figure 2). The isolation of this acyclic adduct led us to speculate its possible involvement as an intermediate in the α -functionalization reaction. This was further supported by re-subjecting **5n** to 10 mol % of DBU under the standard conditions at 40 °C (Scheme 3, eq. 1). This test gave **4n** along with a 1:1 mixture of **2a** and **3n** in 35% and 43% yield, respectively, with the latter two adducts being obtained, presumably, from a competitive retro-Mannich-type pathway [113–118]. The role of DBU

in mediating the cyclization of the 1,4 amino aldol was also supported by our findings showing the recovery of the substrate on treating it to the standard conditions in the absence of the Schiff base (Scheme 3, Equation (2)).



Scheme 2. Reaction of **3n** under optimum conditions at room temperature.

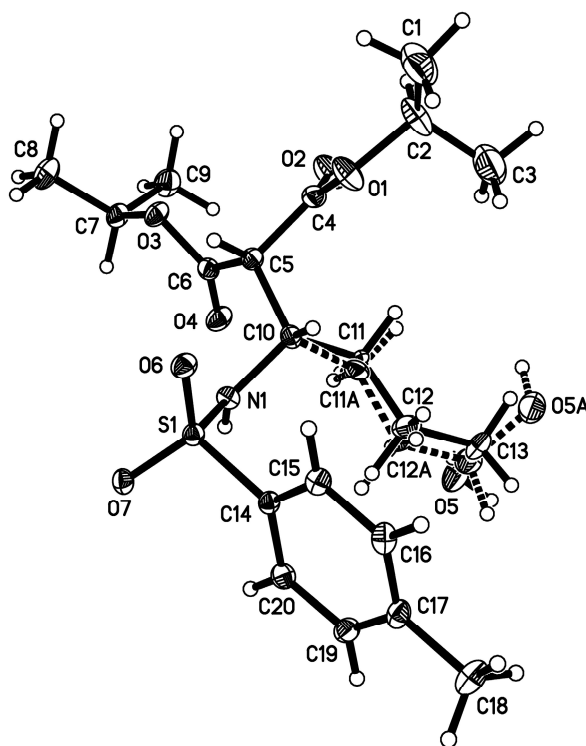
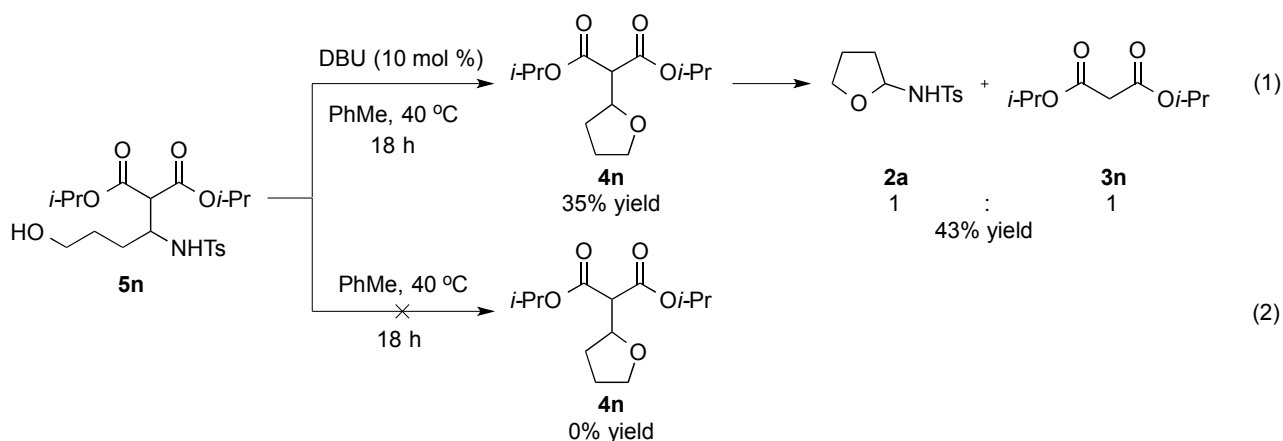
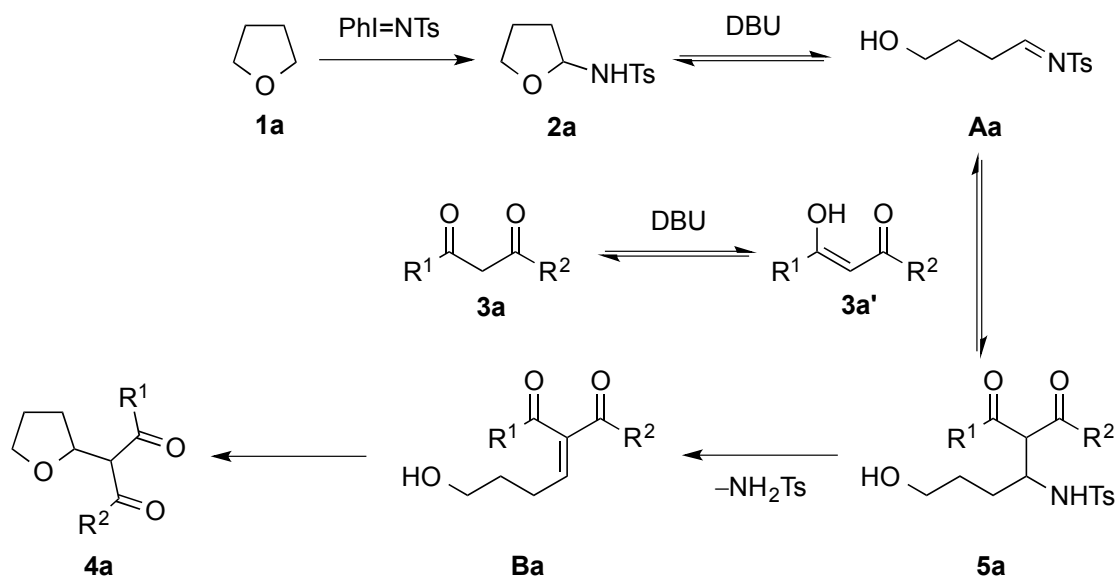


Figure 2. ORTEP drawing for **5n** with thermal ellipsoids at 50% probability level [119].



Scheme 3. Control experiments with **5n** in the absence and presence of DBU.

A tentative mechanism for the present iminoidane-mediated transformation under basic conditions is illustrated in Scheme 4. Using the reaction **1a** with **3a** as a representative example, this could involve formation of **2a** on treating the cyclic ether with the $\text{PhI}=\text{NTs}$ [95,96]. While the possible amination pathway of this step remains presently unclear, the basic conditions provided by DBU may promote ring-opening of the adduct to give the 1,4-imino alcohol intermediate **Aa**. Nucleophilic attack at the imino carbon center of this substrate by the enolate of **3a** would deliver the amino alcohol **5a**. On base-mediated deamination, the ensuing 3-methylene β -keto ester **Ba** might undergo 5-exo-trig cyclization involving addition of the hydroxyl moiety to the alkene bond in the adduct to provide the product **4a**.



Scheme 4. Proposed mechanism of CDC of cyclic ethers **1a** and 1,3-dicarbonyl compounds **3a**.

3. Experimental Section

General Information

All reactions were performed in oven-dried glassware, under a $\text{N}_2(\text{g})$ atmosphere at ambient temperatures, unless otherwise stated. Unless specified, all reagents and starting materials were purchased from commercial sources and used as received. $\text{PhI}=\text{NTs}$ was prepared following literature procedures [120]. Toluene and THF were distilled over sodium/benzophenone, and 2-methyltetrahydrofuran, tetrahydropyran, CH_2Cl_2 and MeCN were purified prior to use by distilling over CaH_2 . Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 pre-coated silica gel plates (Merck, Darmstadt, Germany). Visualization was achieved by UV-Vis light (254 nm) followed by treatment with ninhydrin stain and heating. Flash chromatography was performed using Merck silica gel 60 and a gradient solvent system (EtOAc/*n*-hexane as eluent). Unless otherwise stated, ^1H - and ^{13}C -NMR spectra were measured on a Bruker AV300 or AV400 NMR spectrometer (Bruker, Fällanden, Switzerland), and chemical shifts (ppm) were recorded in CDCl_3 solution with tetramethylsilane (TMS) as the internal reference standard. ^1H -NMR product yields were determined with CH_2Br_2 as the internal reference standard. Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), dt (doublet of triplets), or m (multiplet). The number of protons (*n*) for a given resonance is indicated by *n*H, and coupling

constants are reported as a J value in Hz. Infrared spectra were recorded on a Shimadzu IR Prestige-21 FTIR spectrometer (Shimadzu, Kyoto, Japan). Solid samples were examined as a thin film between NaCl salt plates. Low resolution mass spectra were determined on a LCQ XP MAX mass spectrometer (ThermoFisher Scientific, San Jose, CA, USA) and reported as a ratio of mass to charge (m/z). High resolution mass spectra (HRMS) were obtained using a Finnigan MAT95XP LC/HRMS Q-TOF mass spectrometer (Waters, Manchester, UK). The ^1H - and ^{13}C -NMR spectra of products **4a–r** and compound **5n** is available in the Supplementary Materials.

Representative procedure for CDC of tetrahydrofuran **1a** with 1,3-dicarbonyl compounds **3a**: Tetrahydrofuran **1a** (1 mL) was added to PhI=NTs (93 mg, 0.25 mmol) in a 5 mL round-bottomed flask and stirred for 50 min at room temperature. The solvent was then removed under reduced pressure and the flask back filled with $\text{N}_2(\text{g})$. To the crude mixture, 1,3-dicarbonyl compound **3a** (0.50 mmol, 2 equiv), DBU (4 μL , 0.025 mmol), and PhMe (1 mL) was subsequently added. The reaction was stirred for 18 h at room temperature or 40 $^\circ\text{C}$. Upon completion of the reaction, as judged by TLC analysis, the crude mixture was purified by flash column chromatography (eluent: *n*-hexane/EtOAc, 5:1–4:1) to give the corresponding product **4a**.

Ethyl 3-oxo-3-phenyl-2-(tetrahydrofuran-2-yl)propanoate (4a) [60]. Wt 52.2 mg; yield 80%; obtained as two diastereomers with ratio of 1.3:1; yellow oil; ^1H -NMR (400 MHz, CDCl_3) δ 1.15–1.20 (m, 6H), 1.47–1.56 (m, 1H), 1.74–1.81 (m, 1H), 1.83–1.98 (m, 4H), 2.16–2.27 (m, 2H), 3.70–3.91 (m, 4H), 4.11–4.20 (m, 4H), 4.41 (d, $J = 8.8$ Hz, 1H), 4.46 (d, $J = 8.8$ Hz, 1H), 4.65–4.73 (m, 2H), 7.45–7.50 (m, 2H), 7.56–7.61 (m, 1H), 8.02–8.05 (m, 2H); ^{13}C -NMR (100 MHz, CDCl_3) δ 13.9, 14.0, 25.4, 25.5, 29.7, 30.0, 30.2, 59.3, 60.2, 61.4, 61.6, 68.1, 68.2, 77.7, 78.1, 128.6, 128.7, 128.7, 133.4, 133.7, 136.4, 136.8, 167.5, 167.9, 193.3, 193.6.

Ethyl 3-oxo-2-(tetrahydrofuran-2-yl)-3-(o-tolyl)propanoate (4b). Wt 41.1 mg; yield 59%; obtained as two diastereomers with ratio of 1.2:1; yellow oil; ^1H -NMR (300 MHz, CDCl_3) δ 1.14 (t, $J = 5.6$ Hz, 3H), 1.93 (t, $J = 5.6$ Hz, 3H), 1.52–1.64 (m, 1H), 1.68–1.80 (m, 1H), 1.86–1.97 (m, 4H), 2.17–2.27 (m, 2H), 2.49 (s, 3H), 2.50 (s, 3H), 3.69–3.91 (m, 4H), 4.09–4.21 (m, 4H), 4.31 (d, $J = 2.7$ Hz, 1H), 4.34 (d, $J = 3.0$ Hz, 1H), 4.58–4.66 (m, 2H), 7.24–7.30 (m, 4H), 7.35–7.42 (m, 2H), 7.74–7.89 (m, 2H); ^{13}C -NMR (75 MHz, CDCl_3) δ 13.9, 14.0, 20.9, 21.1, 25.5, 30.1, 30.2, 61.3, 61.4, 61.8, 62.3, 68.0, 68.1, 78.1, 78.1, 125.5, 125.7, 128.7, 129.0, 131.5, 131.8, 131.9, 132.0, 138.8, 138.9, 167.6, 167.9, 196.7, 197.2; IR (NaCl, neat) ν 2979, 2930, 1740, 1688, 1456 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{20}\text{NaO}_4$ $[\text{M} + \text{Na}]^+$ 299.1259, found 299.1268.

Ethyl 3-oxo-2-(tetrahydrofuran-2-yl)-3-(p-tolyl)propanoate (4c). Wt 49.9 mg; yield 72%; obtained as two diastereomers with ratio of 1.2:1; yellow oil; ^1H -NMR (300 MHz, CDCl_3) δ 1.15–1.20 (m, 6H), 1.44–1.56 (m, 1H), 1.71–1.81 (m, 1H), 1.83–1.98 (m, 4H), 2.13–2.27 (m, 2H), 2.40 (s, 3H), 2.41 (s, 3H), 3.68–3.91 (m, 4H), 4.10–4.20 (m, 4H), 4.38 (d, $J = 9$ Hz, 1H), 4.42 (d, $J = 9$ Hz, 1H), 4.62–4.73 (m, 2H), 7.25–7.28 (m, 4H), 7.91–7.95 (m, 4H); ^{13}C -NMR (75 MHz, CDCl_3) δ 14.0, 21.7, 25.4, 25.5, 30.0, 30.2, 59.2, 60.1, 61.4, 61.5, 68.1, 68.1, 77.7, 78.1, 128.9, 129.0, 129.3, 129.4, 134.0, 134.4, 144.4, 144.7, 167.7, 168.0, 192.8, 193.1; IR (NaCl, neat) ν 2980, 1732, 1682, 1607 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{21}\text{O}_4$ $[\text{M} + \text{H}]^+$ 277.1440, found 277.1439.

Ethyl 3-(4-methoxyphenyl)-3-oxo-2-(tetrahydrofuran-2-yl)propanoate (4d). Wt 31.6 mg; yield 40%; obtained as two diastereomers with ratio of 1.4:1; yellow oil; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.16–1.21 (m, 6H), 1.47–1.54 (m, 1H), 1.74–1.81 (m, 1H) 1.85–2.00 (m, 4H), 2.14–2.24 (m, 2H), 3.70–3.88 (m, 10H), 4.11–4.20 (m, 4H), 4.36 (d, $J = 9.2$ Hz, 1H), 4.40 (d, $J = 9.2$ Hz, 1H), 4.64–4.73 (m, 2H), 6.93–6.96 (m, 4H), 8.01–8.04 (m, 4H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 14.0, 14.0, 25.4, 25.5, 30.0, 30.2, 55.5, 55.5, 59.0, 60.0, 61.4, 61.5, 68.1, 68.2, 77.7, 78.2, 113.8, 113.9, 129.5, 129.8, 131.2, 131.3, 163.9, 164.1, 167.8, 168.2, 191.6, 191.9; IR (NaCl, neat) ν 2978, 2938, 1736, 1674, 1601, 1574, 1512 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{21}\text{O}_5$ $[\text{M} + \text{H}]^+$ 293.1389, found 293.1400.

Ethyl 3-(4-fluorophenyl)-3-oxo-2-(tetrahydrofuran-2-yl)propanoate (4e). Wt 53.1 mg; yield 76%; obtained as two diastereomers with ratio of 1.1:1; yellow oil; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.16–1.22 (m, 6H), 1.46–1.58 (m, 1H), 1.72–1.82 (m, 1H), 1.84–1.99 (m, 4H), 2.17–2.27 (m, 2H), 3.69–3.91 (m, 4H), 4.12–4.21 (m, 4H), 4.37 (d, $J = 8.7$ Hz, 1H), 4.39 (d, $J = 9.0$ Hz, 1H), 4.62–4.72 (m, 2H), 7.11–7.18 (m, 4H), 8.04–8.10 (m, 4H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 13.9, 25.4, 30.1, 30.2, 59.4, 60.2, 61.5, 61.7, 68.1, 68.2, 77.7, 78.0, 115.6, 115.8, 115.9, 116.0, 131.4, 131.5, 131.6, 131.6, 167.4, 167.8, 191.8, 192.1; IR (NaCl, neat) ν 2980, 1735, 1684, 1597 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{17}\text{FNaO}_4$ $[\text{M} + \text{Na}]^+$ 303.1009, found 303.0999.

Ethyl 3-(4-chlorophenyl)-3-oxo-2-(tetrahydrofuran-2-yl)propanoate (4f). Wt 52.9 mg; yield 71%; obtained as two diastereomers with ratio of 1:1; yellow oil; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.16–1.21 (m, 6H), 1.46–1.58 (m, 1H), 1.69–1.79 (m, 1H), 1.8–1.99 (m, 4H), 2.15–2.27 (m, 2H), 3.69–3.90 (m, 4H), 4.11–4.21 (m, 4H), 4.36 (d, $J = 8.7$ Hz, 1H), 4.38 (d, $J = 9.3$ Hz, 1H), 4.61–4.72 (m, 2H), 7.43–7.47 (m, 4H), 7.95–8.00 (m, 4H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 14.0, 25.4, 30.1, 30.2, 59.4, 60.2, 61.6, 61.7, 68.1, 68.2, 77.7, 77.9, 128.9, 129.1, 130.2, 130.2, 134.7, 135.2, 140.0, 140.3, 167.3, 167.7, 192.2, 192.5; IR (NaCl, neat) ν 2980, 1736, 1684, 1589 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{17}\text{ClNaO}_4$ $[\text{M} + \text{Na}]^+$ 319.0713, found 319.0723.

Ethyl 3-(4-bromophenyl)-3-oxo-2-(tetrahydrofuran-2-yl)propanoate (4g). Wt 66.1 mg; yield 78%; obtained as two diastereomers with ratio of 1.2:1; yellow oil; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.16–1.21 (m, 6H), 1.46–1.58 (m, 1H), 1.69–1.79 (m, 1H) 1.81–1.99 (m, 4H), 2.15–2.27 (m, 2H), 3.68–3.90 (m, 4H), 4.10–4.21 (m, 4H), 4.36 (d, $J = 8.7$ Hz, 1H) 4.37 (d, $J = 9.3$ Hz, 1H), 4.61–4.71 (m, 2H), 7.60–7.64 (m, 4H), 7.87–7.92 (m, 4H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 14.0, 25.4, 30.1, 30.2, 59.4, 60.1, 61.6, 61.7, 68.1, 68.2, 77.7, 77.9, 128.8, 129.1, 130.2, 130.3, 131.9, 132.1, 135.1, 135.6, 167.3, 167.7, 192.4, 192.8; IR (NaCl, neat) ν 2980, 1738, 1682 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{17}^{79}\text{BrNaO}_4$ $[\text{M} + \text{Na}]^+$ 363.0208, found 363.0222.

Ethyl 3-(4-iodophenyl)-3-oxo-2-(tetrahydrofuran-2-yl)propanoate (4h). Wt 70.4 mg; yield 73%; obtained as two diastereomers with ratio of 1.2:1; yellow oil; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.16–1.21 (m, 6H), 1.45–1.57 (m, 1H), 1.69–1.80 (m, 1H), 1.84–1.98 (m, 4H), 2.14–2.27 (m, 2H), 3.68–3.90 (m, 4H), 4.05–4.25 (m, 4H), 4.34 (d, $J = 8.7$ Hz, 1H), 4.36 (d, $J = 9.0$ Hz, 1H), 4.60–4.71 (m, 2H), 7.71–7.75 (m, 4H), 7.82–7.86 (m, 4H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 14.0, 25.4, 30.1, 30.2, 59.4, 60.0, 61.6, 61.7, 68.1, 68.2, 77.7, 77.9, 101.7, 102.1, 130.1, 130.2, 135.6, 136.1, 138.0, 138.1, 167.3, 167.6, 192.7,

193.1; IR (NaCl, neat) ν 2978, 1732, 1682, 1582 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{17}\text{INaO}_4$ $[\text{M} + \text{Na}]^+$ 411.0069, found 411.0086.

Ethyl 3-oxo-2-(tetrahydrofuran-2-yl)butanoate (4i) [60]. Wt 16.0 mg; yield 32%; obtained as two diastereomers with ratio of 1.7:1; yellow oil; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.25–1.31 (m, 6H), 1.55–1.69 (m, 2H), 1.88–1.95 (m, 4H), 2.11–2.22 (m, 2H), 2.25 (s, 3H), 2.31 (s, 3H), 3.51 (d, $J = 9.2$ Hz, 1H), 3.58 (d, $J = 8.4$ Hz, 1H), 3.72–3.86 (m, 4H), 4.16–4.26 (m, 4H), 4.41–4.48 (m, 2H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 14.0, 25.3, 25.5, 29.7, 29.8, 29.9, 30.4, 61.4, 61.5, 65.0, 65.4, 68.0, 68.2, 77.2, 167.5, 167.9, 201.5, 202.1.

Ethyl 3-oxo-2-(tetrahydrofuran-2-yl)pentanoate (4j). Wt 33.8 mg; yield 63%; obtained as two diastereomers with ratio of 1.7:1; yellow oil; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.03–1.10 (m, 6H), 1.23–1.30 (m, 6H), 1.52–1.67 (m, 2H), 1.85–1.95 (m, 4H), 2.08–2.24 (m, 2H), 2.52–2.68 (m, 4H), 3.55 (d, $J = 9.6$ Hz, 1H), 3.61 (d, $J = 8.7$ Hz, 1H), 3.72–3.87 (m, 4H), 4.13–4.26 (m, 4H), 4.40–4.48 (m, 2H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 7.37, 7.46, 14.0, 25.3, 25.5, 29.8, 30.4, 36.2, 36.3, 61.3, 61.4, 64.0, 64.3, 68.0, 68.1, 77.2, 77.4, 167.6, 168.0, 204.1, 204.6.

Ethyl 4-methyl-3-oxo-2-(tetrahydrofuran-2-yl)pentanoate (4k). Wt 35.0 mg; yield 61%; diastereomer ratio could not be determined; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.10–1.16 (m, 6H) 1.23–1.29 (m, 3H), 1.47–1.66 (m, 1H), 1.85–1.94 (m, 2H), 2.09–2.23 (m, 1H), 2.75–2.87 (m, 1H), 3.69–3.87 (m, 3H), 4.10–4.24 (m, 2H), 4.40–4.49 (m, 1H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 14.0, 14.0, 17.7, 17.8, 17.8, 18.2, 25.3, 25.5, 29.9, 30.3, 41.2, 41.7, 61.2, 61.4, 62.0, 62.5, 68.0, 68.0, 77.5, 77.8, 167.4, 167.7, 207.4, 207.7; IR (NaCl, neat) ν 2976, 2938, 1744, 1713, 1636 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{20}\text{NaO}_4$ $[\text{M} + \text{Na}]^+$ 251.1259, found 251.1262.

Dimethyl 2-(tetrahydrofuran-2-yl)malonate (4l) [121]. Wt 25.7 mg; yield 51%; yellow oil; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.66–1.78 (m, 1H), 1.88–1.97 (m, 2H), 2.11–2.22 (m, 1H), 3.49 (d, $J = 9$ Hz, 1H), 3.74 (s, 3H), 3.77 (s, 3H), 3.79–3.88 (m, 1H), 4.46 (dt, $J = 8.7, 6.9$ Hz, 1H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 25.4, 29.9, 52.5, 52.6, 57.1, 68.3, 77.0, 167.6, 170.0.

Diethyl 2-(tetrahydrofuran-2-yl)malonate (4m) [121]. Wt 24.2 mg; yield 42%; colourless oil; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.24–1.30 (m, 6H), 1.68–1.79 (m, 1H), 1.88–1.97 (m, 2H), 2.11–2.22 (m, 1H), 3.44 (d, $J = 9.3$ Hz, 1H), 3.74–3.90 (m, 2H), 4.16–4.27 (m, 4H), 4.54 (dt, $J = 9.0, 6.9$ Hz, 1H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 14.0, 25.4, 29.9, 57.5, 61.4, 61.4, 68.2, 77.0, 167.2, 167.6.

Diisopropyl 2-(tetrahydrofuran-2-yl)malonate (4n). Wt 43.5 mg; yield 67%; colourless oil; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.23–1.27 (m, 12H), 1.68–1.79 (m, 1H), 1.87–1.96 (m, 2H), 2.09–2.20 (m, 1H), 3.37 (d, $J = 9.0$ Hz, 1H), 3.74–3.89 (m, 2H), 4.39–4.47 (dt, $J = 9.0, 6.9$ Hz, 1H), 4.99–5.16 (m, 2H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 21.5, 21.6, 21.6, 25.4, 29.8, 57.8, 68.1, 68.8, 68.9, 76.9, 166.8, 167.1; IR (NaCl, neat) ν 2982, 2878, 1748, 1732, 1636 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{22}\text{NaO}_5$ $[\text{M} + \text{Na}]^+$ 281.1365, found 281.1365.

Dibenzyl 2-(tetrahydrofuran-2-yl)malonate (4o). Wt 63.3 mg; yield 71%; colourless oil; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.67–1.76 (m, 1H), 1.84–1.90 (m, 2H), 2.07–2.15 (m, 1H), 3.57 (d, $J = 9.2$ Hz,

1H), 3.72–3.85 (m, 2H), 4.50 (dt, $J = 9.2, 6.8$ Hz, 1H) 5.13 (s, 2H), 5.18 (s, 2H), 7.28–7.35 (m, 10H); ^{13}C -NMR (100 MHz, CDCl_3) δ 25.5, 29.9, 57.4, 67.1, 68.3, 77.0, 128.1, 128.2, 128.2, 128.4, 128.5, 128.6, 135.2, 135.5, 166.9, 167.3; IR (NaCl, neat) ν 3065, 3034, 2955, 2876, 1732, 1636 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{22}\text{NaO}_5$ $[\text{M} + \text{Na}]^+$ 377.1365, found 377.1375.

3-(Tetrahydrofuran-2-yl)pentane-2,4-dione (4p) [121]. Wt 27.5 mg; yield 65%; yellow oil; ^1H -NMR (400 MHz, CDCl_3) δ 1.40–1.49 (m, 1H), 1.87–1.94 (m, 2H), 2.10–2.20 (m, 1H), 2.21 (s, 3H), 2.26 (s, 3H), 3.70–3.74 (m, 2H), 3.81–3.86 (m, 1H), 4.50 (m, $J = 9.2, 6.8$ Hz, 1H); ^{13}C -NMR (100 MHz, CDCl_3) δ 25.3, 29.5, 30.2, 30.4, 67.9, 74.3, 77.5, 202.2, 202.8.

Ethyl 2-(5-methyltetrahydrofuran-2-yl)-3-oxo-3-phenylpropanoate (4q). 2-Methyltetrahydrofuran **1b** (2 mL) was added to $\text{PhI}=\text{NTs}$ (186 mg, 0.50 mmol) in a 5 mL round-bottomed flask and stirred for 50 min at room temperature (50% conversion based on ^1H -NMR analysis). The solvent was removed under reduced pressure and the flask back filled with $\text{N}_2(\text{g})$. To the crude mixture, ethyl benzoylacetate **3a** (87 μL , 0.50 mmol) and DBU (4 μL , 0.025 mmol) were subsequently added. In the absence of solvent, the reaction was stirred at 40 $^\circ\text{C}$ for 18 h. Upon completion of the reaction, as judged by TLC analysis, the crude mixture was purified by flash column chromatography (*n*-hexane/EtOAc, 5:1) to give four diastereomers of the corresponding product **4q** with ratio of 1.4:1.3:1.2:1 (22.7 mg, 41%) as yellow oil; ^1H -NMR (400 MHz, CDCl_3) δ 1.13–1.28 (m, 24H), 1.30–1.65 (m, 8H), 1.81–1.91 (m, 2H), 1.95–2.30 (m, 6H), 3.96–4.23 (m, 12H), 4.41 (d, $J = 4.4$ Hz, 1H), 4.44 (d, $J = 4.4$ Hz, 1H), 4.45 (d, $J = 2.8$ Hz, 1H), 4.48 (d, $J = 2.8$ Hz, 1H), 4.63–4.72 (m, 2H), 4.82–4.88 (m, 2H), 7.45–7.49 (m, 8H), 7.56–7.61 (m, 4H), 8.01–8.05 (m, 8H); ^{13}C -NMR (100 MHz, CDCl_3) δ 14.0, 14.0, 21.0, 21.1, 21.2, 29.8, 30.1, 30.5, 30.9, 32.6, 32.6, 33.3, 33.4, 59.6, 59.9, 60.2, 60.6, 61.4, 61.5, 75.2, 75.4, 75.8, 77.2, 77.7, 77.7, 78.0, 128.6, 128.6, 128.7, 128.7, 128.8, 128.8, 128.9, 133.4, 133.7, 136.5, 136.9, 167.6, 167.9, 168.0, 193.6, 193.7; IR (NaCl, neat) ν 2976, 2872, 1734, 1684 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{20}\text{NaO}_4$ $[\text{M} + \text{Na}]^+$ 299.1259, found 299.1263.

Ethyl 3-oxo-3-phenyl-2-(tetrahydro-2H-pyran-2-yl)propanoate (4r) [60]. Tetrahydropyran **1c** (2 mL) was added to $\text{PhI}=\text{NTs}$ (186 mg, 0.50 mmol) in a 5 mL round-bottomed flask and stirred for 50 min at 65 $^\circ\text{C}$ (40% conversion based on ^1H -NMR analysis). The solvent was removed under reduced pressure and the flask back filled with $\text{N}_2(\text{g})$. To the crude mixture, ethyl benzoylacetate **3a** (69 μL , 0.40 mmol) and DBU (3 μL , 0.025 mmol) were subsequently added. In the absence of solvent, the reaction was stirred at 80 $^\circ\text{C}$ for 18 h. Upon completion of the reaction, as judged by TLC analysis, the crude mixture was purified by flash column chromatography (*n*-hexane/EtOAc, 5:1) to give two diastereomers of the corresponding product **4r** with ratio of 1.7:1 (31.2 mg 57%) as yellow oil; ^1H -NMR (300 MHz, CDCl_3) δ 1.16–1.20 (m, 6H), 1.40–1.70 (m, 8H), 1.73–1.89 (m, 4H), 3.40–3.46 (m, 1H), 3.48–3.54 (m, 1H), 3.83–3.86 (m, 1H), 3.99–4.02 (m, 1H), 4.09–4.23 (m, 6H), 4.46 (d, $J = 9.2$ Hz, 1H), 4.47 (d, $J = 9.2$ Hz, 1H), 7.44–7.50 (m, 4H), 7.54–7.61 (m, 2H), 8.01–8.05 (m, 4H); ^{13}C -NMR (75 MHz, CDCl_3) δ 14.0, 23.1, 23.2, 25.8, 25.8, 29.7, 29.9, 59.9, 60.7, 61.4, 61.5, 68.8, 68.9, 76.9, 77.1, 128.6, 128.8, 133.3, 133.8, 136.4, 136.6, 137.2, 167.2, 167.8, 192.7, 193.7.

Diisopropyl 2-(4-hydroxy-1-(4-methylphenylsulfonamido)butyl)malonate (5n). THF **1a** (2 mL) was added to $\text{PhI}=\text{NTs}$ (186 mg, 0.50 mmol) in a 5 mL round-bottomed flask and stirred for 50 min at

room temperature. The solvent was then removed under reduced pressure and the flask back filled with $N_2(g)$. To the crude mixture, diisopropyl malonate **3n** (0.19 mL, 1.0 mmol) and DBU (8 μ L, 0.05 mmol) and PhMe (2 mL) were subsequently added. The reaction was stirred at room temperature for 18 h. Upon completion of the reaction, as judged by TLC analysis, the crude mixture was purified by flash column chromatography (*n*-hexane/EtOAc, 1:1) to give the corresponding product **5n** (50.5 mg, 25%) as white solid; mp 108–114 °C; 1H -NMR (400 MHz, $CDCl_3$) δ 1.18 (t, J = 6.0 Hz, 6H), 1.23 (d, J = 6.0 Hz, 6H), 1.37–1.56 (m, 2H), 1.65 (q, J = 7.6 Hz, 2H), 2.41 (s, 3H), 3.48 (d, J = 4.0 Hz, 1H), 3.51–3.54 (m, 2H), 3.87–3.94 (m, 1H), 4.86–4.92 (m, 1H), 4.99 (m, J = 6.0 Hz, 1H), 5.03 (m, J = 6.0 Hz, 1H), 5.71 (d, J = 9.6 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H); ^{13}C -NMR (100 MHz, $CDCl_3$) δ 21.4, 21.5, 21.5, 21.6, 21.6, 28.7, 29.6, 53.1, 55.2, 61.8, 69.4, 69.7, 127.0, 129.6, 138.4, 143.3, 167.0, 167.6; IR (NaCl, neat) ν 3362, 3310, 2983, 2936, 1732, 1722, 1599 cm^{-1} ; HRMS (ESI) calcd for $C_{20}H_{32}NO_7S$ $[M + H]^+$ 430.1899, found 430.1892.

4. Conclusions

In summary, a mild transition metal-free cross dehydrogenative coupling (CDC) synthetic route to 2-tetrahydrofuran and -pyran substituted 1,3-carbonyl compounds from commercially available cyclic ethers and 1,3-dicarbonyl derivatives has been developed. Achieved in moderate to excellent yields of 32%–80%, the synthetic method was shown to tolerate β -ketoesters, dialkyl malonates and 1,3-diones, which complements and supplements the existing transition metal approaches. The present method also shows the promising utility of other hypervalent iodine reagents other than diaryliodonium salts for transition metal-free CDC reactions. Further exploration on the utility of iminoiodanes is currently underway.

Supplementary Materials

Supplementary materials can be accessed at: <http://www.mdpi.com/1420-3049/20/07/13336/s1>.

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Author Contributions

C.T., X.R.S., B.R.L. and B.J.A. performed the synthetic experiments and analyzed the data. C.-H.L. and D.-L.M. analyzed the data. P.W.H.C. conceived, designed and supervised the study. All the authors contributed to the writing of the paper and supplementary materials.

Conflicts of Interest

The authors declare no conflict of interest.

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