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Stereoselective synthesis of cyclic hemiacetals from 4-formylbenzoates and α,β-unsaturated aldehydes using a sulfoalkyl-substituted *N*-heterocyclic carbene catalyst

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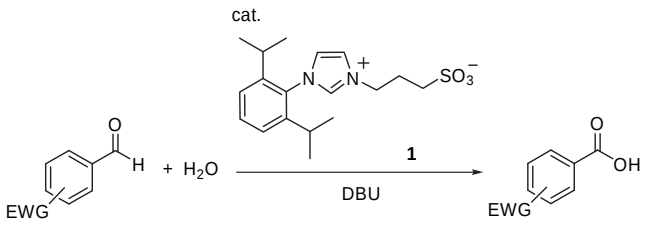
ABSTRACT

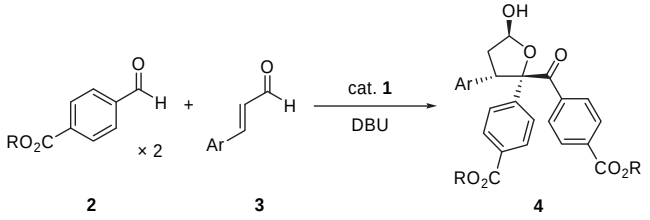
N-Heterocyclic carbene-catalyzed transformation of 4-formylbenzoates and α,β-unsaturated aldehydes to cyclic hemiacetals is described. The reaction proceeded smoothly when the sulfopropyl-substituted imidazolium salt was used as the catalyst. Various substrates were converted to the corresponding cyclic hemiacetals in a stereoselective manner.

1. Introduction

Much attention has centered on the chemistry of *N*-heterocyclic carbene catalysts (NHCs) in organic synthesis.[1–3] Like NHCs, which are widely known as ligands for metal catalysts,[1,2] nucleophilic carbenes have attracted considerable interest as organocatalysts.[1,3] Various types of NHC catalysts have been developed, thus generating a diversity of reactivity in combination with the choice of the substrates. We recently reported an NHC-catalyzed oxidation of arylaldehydes with water, in which the reaction efficiently proceeded when a sulfopropyl-substituted imidazolium salt **1** was used as the catalyst (Scheme 1).[4] The reaction was run in the absence of oxidant, and a variety of arylaldehydes having an electron-withdrawing group were converted to the corresponding carboxylic acids. During the course of our studies on the properties of these catalysts, we focused on their reactions with α,β-unsaturated aldehydes and arylaldehydes.[3d,5] Herein we describe an NHC-catalyzed transformation of 4-formylbenzoates **2** and α,β-unsaturated aldehydes **3**. The reaction produces cyclic hemiacetals **4** in a stereoselective manner when the imidazolium salt **1** is used as the catalyst (Scheme 2).



Scheme 1. NHC-catalyzed oxidation of arylaldehydes with water.



2 **3** **4**

Scheme 2. NHC-catalyzed formation of cyclic hemiacetals **4**.

2. Results and discussion

The initial reactions were carried out using methyl 4-formylbenzoate (**2a**) and cinnamaldehyde (**3a**). When 2 equiv of **2a** and 1 equiv of **3a** were treated with 10 mol % of the imidazolium salt **1** and 1 equiv DBU in THF/H_2O (10/1) at rt for 6 h, the cyclic hemiacetal **4aa** was produced in 31% yield (entry 1, Table 1). The yield of **4aa** was increased to 52% by carrying out the reaction in THF (entry 2). Although trace amounts of the product were obtained in MeOH (entry 3), the reaction in THF/MeOH (10/1) afforded **4aa** in 58% yield (entry 4). Finally, the best result was obtained when 3 equiv of **2a** was subjected to the reaction (92% yield, entry 5).

Our attempts using various imidazolium salts **5**–**10** are shown in Table 2. The imidazolium salts **5** and **6**, containing a 4-sulfobutyl group and a 2-carboxyethyl group, catalyzed the reaction of **2a** with **3a** to produce the cyclic hemiacetal **4aa** in 55% and 54% yield, respectively (entries 1 and 2). However, the yield was decreased to

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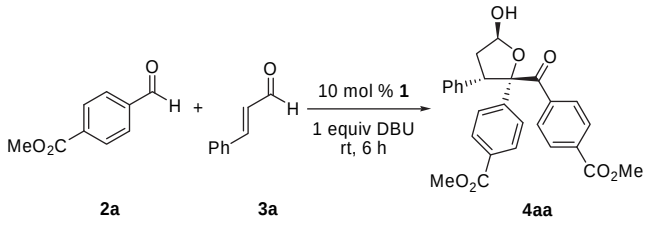
Table 1
Initial attempts using **2a** and **3a**

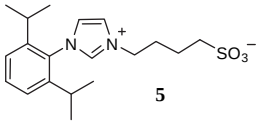
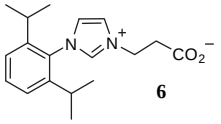
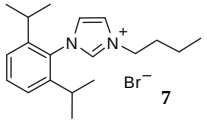
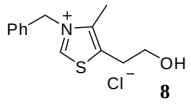
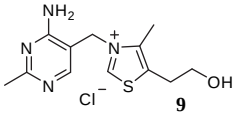
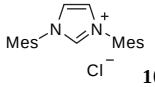


2a **3a** **4aa**

Entry	Solvent	Equiv of **2a**	Yield[a] (%)
1	THF/H_2O (10/1)	2	31
2	THF	2	52
3	MeOH	2	Trace
4	THF/MeOH (10/1)	2	58
5	THF/MeOH (10/1)	3	92

[a] Trace amounts of the anomer of **4aa** were observed in the NMR spectrum.

Table 2
Reactions of **2a** with **3a** using various imidazolium or thiazolium salts **5**–**10**[a]

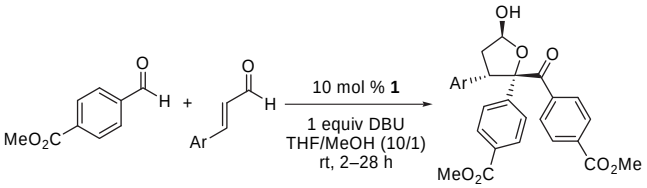
Entry	Catalyst	Yield of **4aa** (%)
1	 **5**	55
2	 **6**	54
3	 **7**	47
4	 **8**	77
5	 **9**	9
6	 **10**	4

[a] Reactions were carried out using **2a** (3 equiv) with **3a** in the presence of 10 mol % catalyst **5**–**10** and DBU (1 equiv) in THF/MeOH (10/1) at rt for 2–7 h.

47% when the imidazolium salt **7**, which does not have an internal counterion, was used (entry 3). This result indicates that the presence of the 4-sulfopropyl moiety in **1** enhances the reactivity. The product **4aa** was obtained in 77% yield when the thiazolium salt **8** was used, but the reactions using the thiamine **9** and the 1,3-dimesityl-substituted imidazolium salt **10** gave poor results (9% and 4% yield, respectively). These findings would suggest that the imidazolium salt **1** is the most suitable catalyst for this reaction.

The results of the reactions of **2a** with various aryl-substituted α,β-unsaturated aldehydes **3b**–**j** in the presence of the imidazolium salt **1** are summarized in Table 3. When the reactions of the 4-methylphenyl- and 2-naphthyl-substituted substrates **3b** and **3c** were carried out, the cyclic hemiacetals **4ab** and **4ac** were obtained

Table 3
Reactions of **2a** with various unsaturated aldehydes **3b**–**j** to give the cyclic hemiacetals **4ab**–**aj**



2a (3 equiv) **3b–3j** **4ab–4aj**

Entry	Ar	Product[a]	Yield (%)
1	4-Methylphenyl (**3b**)	**4ab**	61
2	2-Naphthyl (**3c**)	**4ac**	77
3	2-Methoxyphenyl (**3d**)	**4ad**	55
4	4-Dimethylaminophenyl (**3e**)	**4ae**	66
5	3,4-Methylenedioxy-phenyl (**3f**)	**4af**	60
6	4-Methoxycarbonyl-phenyl (**3g**)	**4ag**	49
7	2-Thienyl (**3h**)	**4ah**	43
8	4-Fluorophenyl (**3i**)	**4ai**	65
9	4-Chlorophenyl (**3j**)	**4aj**	76
10	4-Bromophenyl (**3k**)	**4ak**	79

[a] Trace amounts of the anomers of **4** were observed in the NMR spectrum.

in 61% and 77% yield, respectively (entries 1 and 2). The α,β-unsaturated aldehydes **3d**–**f** having an electron-donating group on the aryl ring were converted to the corresponding products **4ad**–**af** in good yields (entries 3–5). The substrates **3g** and **3h** having an electron-withdrawing 4-methoxycarbonylphenyl group and a heteroaromatic 2-thienyl group also reacted to afford **4ag** and **4ah** in 49%, and 43% yield, respectively (entries 6 and 7). The reactions using the halogen-substituted substrates **3i**–**k** successfully proceeded to afford the corresponding products **4ai**–**ak** in good yields (entries 8–10). The structure of the resulting **4ak**, including the stereochemistry, was confirmed by X-ray crystallographic analysis (Fig. 1).[6] Since in all cases the resulting products **4aa**–**ak** were obtained stereoselectively, it was determined that the reaction with **2a** had proceeded in a highly stereoselective manner.

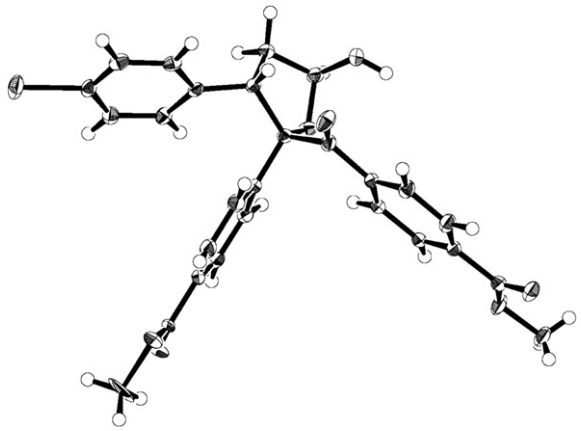
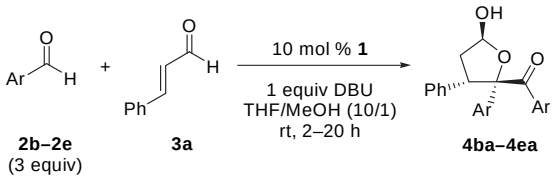


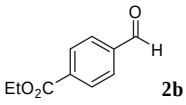
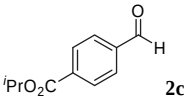
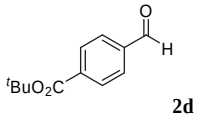
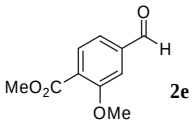
Fig. 1. ORTEP drawing of the cyclic hemiacetal **4ak**.

Table 4 shows the reactions of the various 4-formylbenzoate esters **2b**–**e** with **3a**. The substrates **2b**, **2c**, and **2d** having ethyl, isopropyl, and *tert*-butyl ester groups, reacted to afford the corresponding cyclic hemiacetals **4ba**, **4ca**, and **4da**, respectively (entries 1–3). However, the yields decreased as the electron-withdrawing character of the ester moiety decreased. The reaction of the methoxy-substituted substrate **2e** also proceeded to afford the products **4ea** in 45% yield (entry 4). On the other hand, complex mixtures were produced when 3- and 2-formylbenzoate

Table 4
Reactions of various aldehydes **2b**–**e** with **3a** to cyclic hemiacetals **4ba**–**ea**

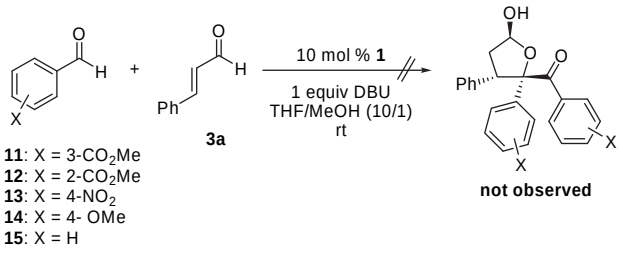


2b–2e (3 equiv) **3a** **4ba–4ea**

Entry	Arylaldehyde	Product[a]	Yield (%)
1	 **2b**	**4ba**	62
2	 **2c**	**4ca**	45
3	 **2d**	**4da**	33
4	 **2e**	**4ea**	45

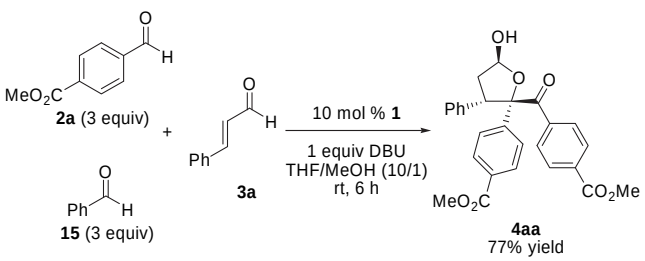
[a] Trace amount of the anomers of **4** were observed on NMR spectrum.

11 and **12** were employed (Scheme 3). Attempts using other arylaldehydes without an ester moiety, **13**–**15**, also failed.[7] These results suggest that the existence of the ester moiety on the *para* position of the arylaldehydes is essential in the formation of the cyclic hemiacetals **4**.



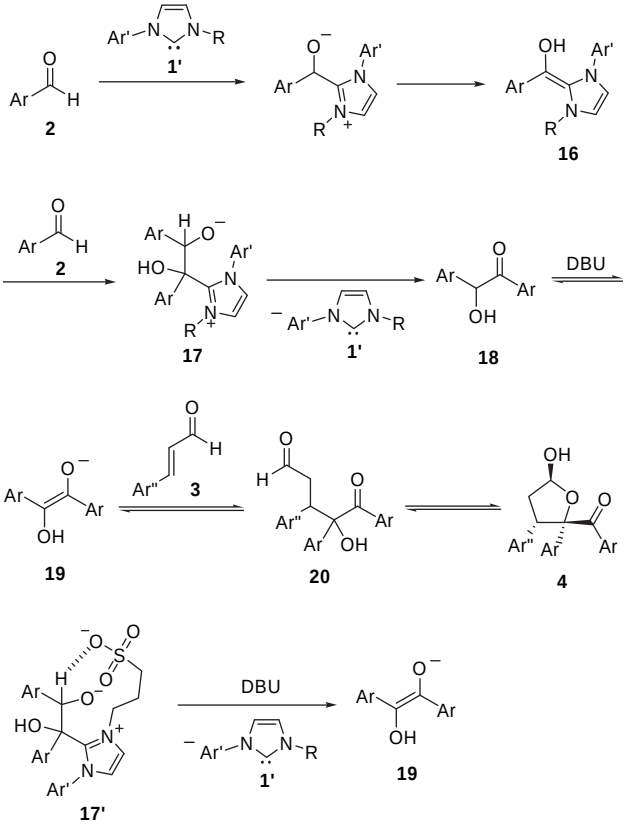
Scheme 3. Attempts using arylaldehydes **11**–**15**.

To further examine the reactivity of the 4-formylbenzoate ester, we next attempted a crossover experiment using methyl 4-formylbenzoate (**2a**) and benzaldehyde (**15**) (Scheme 4). When an equimolar mixture of **2a** and **15** was subjected to the reaction with **3a**, the cyclic hemiacetal **4aa**, derived from **2a**, was produced in 77% yield as the sole product. This result clearly shows that the 4-formylbenzoate reacted selectively with **3a**.



Scheme 4. Crossover experiment using arylaldehydes **2a** and **15**.

A plausible mechanism for the reaction is shown in Scheme 5. The imidazolium carbene **1**′ adds to the arylaldehyde **2** to give the Breslow intermediate **16**, which reacts with another arylaldehyde **2** to provide the benzoin **18** and regenerate the catalyst **1**′ via the intermediate **17**. The resulting benzoin **18** would react with DBU to give the enolate **19**, which undergo the Michael addition with the α,β-unsaturated aldehyde **3** to afford the cyclic hemiacetal **4** via ring closure of the resulting hydroxyaldehyde **20**. Because the process from the benzoin to the cyclic hemiacetal is reversible, the product **4**, which proposed the thermodynamically most stable stereoisomer, would be selectively produced. It is not clear why the presence of the sulfoalkyl moiety in the catalyst **1** increases the yield of the cyclic hemiacetal **4**, but one possible explanation is that presumably there is an intramolecular interaction between the sulfonate oxygen and the benzylic proton in the intermediate **17**, as shown in **17**′, which could enhance the acidity of the benzylic proton to promote the direct formation of the benzoin enolate **19**. As a reason for the necessity of the ester moiety on the *para* position of arylaldehydes **2**, it is expected that the increasing acidity of benzylic proton of the benzoin **18** or the intermediate **17**′ also enhances the formation of the benzoin enolate **19**.

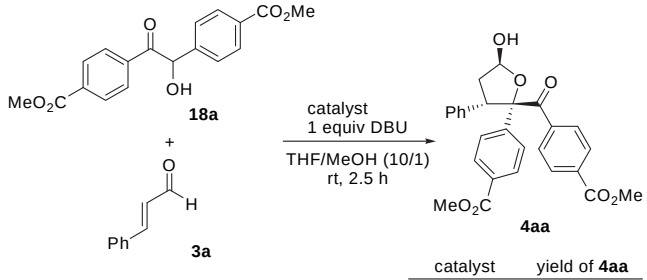


Scheme 5. Proposed reaction mechanism.

Recently, Lüning has reported the formation of cyclic hemiacetals by the NHC-catalyzed reaction of methyl 4-formylbenzoate and cinnamaldehyde.[8,9] However, several differences between our two approaches are noteworthy. First, where Lüning used the bimacrocyclic imidazolium salt as the NHC precursor, we chose the sulfoalkyl-substituted imidazolium salt as the catalyst. Secondly, under his conditions, the product was obtained in 42% yield, whereas under our conditions the yields of the products were up to 92%. Thirdly, we were able to determine the stereochemistry of the product by X-ray crystallographic analysis; in Lüning's report, the stereochemistry was unclear. Finally, Lüning examined only one example of the formation of the cyclic hemiacetal during the course

of his study on the synthesis of γ-butyrolactones, while we have determined the scope and limitations of the reaction, and have reported the synthesis of 15 examples of cyclic hemiacetals.

Moreover when the benzoin **18a** was subjected to the reaction with cinnamaldehyde (**3a**) in the presence of DBU, the corresponding cyclic hemiacetal **4aa** was produced in 28% yield (Scheme 6). Similar result was obtained when the reaction was carried out in the absence of the catalyst **1** (32% yield). These results seem to support the hypothesis that the reaction proceeds via the formation of the benzoin **18**.[10] However, the yields of the resulting **4aa** were very low, which implies the possibility of the direct formation of benzoin enolate **19** from the intermediate **17′** in the reaction of **2** and **3** by the catalyst **1**.



catalyst	yield of **4aa**
10 mol % **1**	28%
none	32%

Scheme 6. Reaction of benzoin **18a** with **3a**.

3. Conclusion

We have developed an NHC-catalyzed reaction of 4-formylbenzoates and α,β-unsaturated aldehydes to give cyclic hemiacetals. The reaction proceeded smoothly when the sulfopropyl-substituted imidazolium salt was used as the catalyst. Various substrates were converted to the corresponding cyclic hemiacetals in a stereoselective manner.

4. Experimental

4.1. General

Materials were obtained from commercial suppliers and used without further purification except when otherwise noted. Solvents were dried and distilled according to standard protocol. Imidazolium salts **1**[4] and **5**–**7**,[4] arylaldehydes **2b**–**e**[11], and α,β-unsaturated aldehydes **3b**–**k**[12] were prepared according to the procedures described in the literature.

4.2. General procedure for the cascade reaction of aromatic aldehyde and unsaturated aldehyde using functionalized imidazolium carbene catalyst (Table 1, entry 5)

To a stirred solution of methyl 4-formylbenzoate (**2a**) (195 mg, 1.19 mmol), *trans*-cinnamaldehyde (**3a**) (50.0 μL, 396 μmol), and the imidazolium catalyst **1** (13.9 mg, 39.6 μmol) in THF (0.7 mL) and MeOH (70 μL) was added DBU (60.0 μL, 396 μmol) at rt. After stirring was continued at rt for 5 h, the reaction mixture was added to H_2O and extracted with AcOEt. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (70:30 v/v) as eluent to provide **4aa** (168 mg, 92%) as colorless crystals.

4.2.1. Methyl 4-[(2S,3S*,5S*)-5-hydroxy-2-{4-(methoxycarbonyl)benzoyl}-3-phenyltetrahydrofuran-2-yl]benzoate (**4aa**).* Colorless crystals; mp 185–189 °C (recrystallized from AcOEt/hexane); IR (KBr) 3516, 2954, 2935, 1727, 1716, 1609 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.39–2.52 (2H, m), 2.62 (1H, br s), 3.83 (3H, s), 3.88 (3H, s), 4.93 (1H, t, *J*=8.4 Hz), 6.08 (1H, br s), 6.91–7.27 (5H, m), 7.12 (2H, d, *J*=7.2 Hz), 7.73 (2H, d, *J*=8.4 Hz), 7.90–7.93 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.2 (CH_2), 49.6 (CH), 52.0 (CH_3), 52.3 (CH_3), 94.8 (Cq), 99.1 (CH), 125.5 (CH), 126.6 (CH), 127.8 (CH), 129.0 (CH), 129.1 (CH), 129.3 (CH), 130.5 (Cq), 130.5 (CH), 133.0 (Cq), 138.6 (Cq), 138.6 (Cq), 142.8 (Cq), 166.2 (Cq), 166.6 (Cq), 198.1 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{27}H_{24}O_7Na$ $[M+Na]^+$ 483.1420, found 483.1421.

4.2.2. Methyl 4-[(2S,3S*,5S*)-5-hydroxy-2-{4-(methoxycarbonyl)benzoyl}-3-(4-methylphenyl)tetrahydrofuran-2-yl]benzoate (**4ab**).* Pale yellow crystals; mp 155–157 °C (recrystallized from AcOEt/hexane); IR (neat) 3470, 2953, 1725, 1689, 1608 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.18 (3H, s), 2.35–2.47 (2H, m), 2.75 (1H, br s), 3.83 (3H, s), 3.87 (3H, s), 4.88 (1H, t, *J*=8.4 Hz), 6.06 (1H, d, *J*=4.0 Hz), 6.80–6.93 (4H, m), 7.12 (2H, d, *J*=7.2 Hz), 7.74 (2H, d, *J*=8.0 Hz), 7.86–7.92 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9 (CH_3), 40.3 (CH_2), 49.2 (CH), 52.0 (CH_3), 52.3 (CH_3), 94.7 (Cq), 99.0 (CH), 125.5 (CH), 128.5 (CH), 129.0 (Cq), 129.0 (CH), 129.3 (CH), 130.4 (CH), 130.4 (CH), 132.9 (Cq), 135.4 (Cq), 136.2 (Cq), 138.7 (Cq), 142.9 (Cq), 166.2 (Cq), 166.7 (Cq), 198.2 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{28}H_{26}O_7Na$ $[M+Na]^+$ 497.1576, found 497.1573.

4.2.3. Methyl 4-[(2S,3S*,5S*)-5-hydroxy-2-{4-(methoxycarbonyl)benzoyl}-3-(naphthalen-2-yl)tetrahydrofuran-2-yl]benzoate (**4ac**).* White solid; mp 126–129 °C (recrystallized from AcOEt/hexane); IR (KBr) 3442, 2952, 1726, 1685, 1609 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.48 (1H, ddd, 1.2, 8.4, and 13.6 Hz), 2.57 (1H, ddd, 4.8, 9.2, and 13.6 Hz), 2.62 (1H, br s), 3.77 (3H, s), 3.88 (3H, s), 5.10 (1H, t, *J*=8.4 Hz), 6.14 (1H, d, *J*=4.8 Hz), 6.91 (1H, dd, *J*=2.4 and 8.4 Hz), 7.16 (2H, d, *J*=7.6 Hz), 7.36–7.40 (2H, m), 7.45 (1H, d, *J*=8.4 Hz), 7.56 (1H, s), 7.66 (4H, d, *J*=9.2 Hz), 7.90–7.94 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.6 (CH_2), 49.7 (CH), 52.0 (CH_3), 52.3 (CH_3), 94.9 (Cq), 99.2 (CH), 125.6 (CH), 125.6 (CH), 125.9 (CH), 126.7 (CH), 127.3 (CH), 127.4 (CH), 127.7 (CH), 128.5 (CH), 129.1 (CH), 129.2 (Cq), 129.3 (CH), 130.5 (CH), 132.1 (Cq), 133.0 (Cq), 136.2 (Cq), 138.6 (Cq), 142.6 (Cq), 166.2 (Cq), 166.5 (Cq), 198.2 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{31}H_{26}O_7Na$ $[M+Na]^+$ 533.1576, found 533.1577.

4.2.4. Methyl 4-[(2S,3S*,5S*)-5-hydroxy-2-{4-(methoxycarbonyl)benzoyl}-3-(2-methoxyphenyl)tetrahydrofuran-2-yl]benzoate (**4ad**).* Colorless crystals; mp 138–140 °C (recrystallized from AcOEt/hexane); IR (neat) 3543, 3435, 2954, 1722, 1690, 1607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.41 (1H, ddd, *J*=2.8, 8.8, and 13.6 Hz), 2.47 (1H, d, 2.8 Hz), 2.66 (1H, dt, *J*=4.8 and 13.6 Hz), 3.52 (3H, s), 3.81 (3H, s), 3.88 (3H, s), 5.40 (1H, dd, *J*=4.8 and 8.8 Hz), 6.12 (1H, t, *J*=2.8 Hz), 6.42 (1H, d, *J*=8.0 Hz), 6.74 (1H, t, *J*=7.6 Hz), 6.95–7.01 (2H, m), 7.25 (2H, d, *J*=8.4 Hz), 7.68 (2H, d, *J*=8.8 Hz), 7.90 (2H, d, *J*=8.8 Hz), 7.94 (2H, d, *J*=8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.6 (CH_2), 43.9 (CH), 51.9 (CH_3), 52.3 (CH_3), 54.6 (CH_3), 95.5 (Cq), 100.1 (CH), 109.8 (CH), 120.0 (CH), 125.4 (CH), 127.9 (CH), 128.5 (CH), 128.5 (CH), 128.7 (Cq), 128.9 (CH), 129.5 (CH), 130.4 (CH), 132.6 (Cq), 139.0 (Cq), 142.5 (Cq), 156.6 (Cq), 166.3 (Cq), 166.7 (Cq), 198.3 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{28}H_{26}O_8Na$ $[M+Na]^+$ 513.1525, found 513.1525.

4.2.5. Methyl 4-[(2S,3S*,5S*)-3-{4-(dimethylamino)phenyl}-5-hydroxy-2-{4-(methoxycarbonyl)benzoyl}tetrahydrofuran-2-yl]benzoate (**4ae**).* Pale yellow solid; mp 103–106 °C (recrystallized from AcOEt/hexane); IR (neat) 3540, 3457, 2952, 2801, 1724, 1684, 1615 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.31–2.59 (2H, m), 2.82 (1H, br s), 3.84 (3H, s), 3.88 (3H, s), 4.82 (1H, t, *J*=8.0 Hz), 6.04 (1H, t, *J*=3.6 Hz), 6.42 (2H, d, *J*=7.6 Hz), 6.78 (2H, d, *J*=8.8 Hz), 7.12 (2H, d, *J*=7.6 Hz), 7.75 (2H, d, *J*=8.8 Hz), 7.86–7.92 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.2 (CH_2), 40.6 (CH_3), 48.8 (CH), 52.0 (CH_3), 52.3 (CH_3), 94.7 (Cq), 99.0 (CH), 112.1 (CH), 125.6 (CH), 129.0 (Cq), 129.0 (CH), 129.2 (CH), 129.8 (Cq), 129.8 (CH), 130.4 (Cq), 130.4 (CH), 132.9 (Cq), 138.8 (Cq), 143.2

(Cq), 166.2 (Cq), 166.8 (Cq), 198.4 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{29}H_{29}NO_7Na$ $[M+Na]^+$ 526.1842, found 526.1846.

4.2.6. Methyl 4-[(2S,3S*,5S*)-3-{benzo[d][1,3]dioxol-5-yl}-5-hydroxy-2-{4-(methoxycarbonyl)benzoyl}tetrahydrofuran-2-yl]benzoate (**4af**).* Pale yellow crystals; mp 176–177 °C (recrystallized from AcOEt/hexane); IR (KBr) 3479, 2953, 1724, 1691, 1608 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.38 (2H, dd, *J*=3.2 and 8.4 Hz), 2.63 (1H, br s), 3.85 (3H, s), 3.88 (3H, s), 4.85 (1H, t, *J*=8.4 Hz), 5.82 (2H, dd, *J*=1.6 and 8.0 Hz), 6.04 (1H, t, *J*=3.2 Hz), 6.41 (1H, dd, *J*=1.6 and 8.0 Hz), 6.46 (1H, d, *J*=1.6 Hz), 6.48 (1H, d, *J*=8.0 Hz), 7.15 (2H, d, *J*=7.6 Hz), 7.78 (2H, d, *J*=8.4 Hz), 7.90–7.92 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.3 (CH_2), 49.2 (CH), 52.0 (CH_3), 52.3 (CH_3), 94.6 (Cq), 98.9 (CH), 100.8 (CH_2), 107.6 (CH), 109.4 (CH), 122.4 (CH), 125.5 (CH), 129.0 (CH), 129.2 (Cq), 129.4 (CH), 130.5(CH), 132.4 (Cq), 133.0 (Cq), 138.6 (CH), 142.8 (Cq), 146.0 (Cq), 147.2 (Cq), 166.2 (Cq), 166.6 (Cq), 198.1 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{28}H_{24}O_9Na$ $[M+Na]^+$ 527.1318, found 527.1315.

4.2.7. Dimethyl 4,4′-[(2S,3S*,5S*)-5-hydroxy-2-{4-(methoxycarbonyl)benzoyl}tetrahydrofuran-2,3-diyl]dibenzoate (**4ag**).* White solid; mp 93.5–95.0 °C (recrystallized from AcOEt/hexane); IR (KBr) 3459, 2953, 1725, 1692, 1611 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.39–2.52 (2H, m), 3.83 (3H, s), 3.85 (3H, s), 3.88 (3H, s), 4.99 (1H, t, *J*=8.4 Hz), 6.10 (1H, dd, *J*=1.2 and 4.6 Hz), 7.03 (2H, d, *J*=8.0 Hz), 7.12 (2H, d, *J*=6.8 Hz), 7.70 (2H, d, *J*=8.0 Hz), 7.73 (2H, d, *J*=8.8 Hz), 7.90–7.92 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.2 (CH_2), 49.5 (CH), 51.9 (CH_3), 52.0 (CH_3), 52.3 (CH_3), 94.7 (Cq), 99.1 (CH), 125.3 (CH), 128.4 (Cq), 129.0 (CH), 129.1 (CH), 129.2 (CH), 129.5 (CH), 130.5 (Cq), 130.5 (CH), 133.0 (Cq), 138.3 (Cq), 142.2 (Cq), 144.3 (Cq), 166.1 (Cq), 166.4 (Cq), 166.8 (Cq), 197.9 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{29}H_{26}O_9Na$ $[M+Na]^+$ 541.1475, found 541.1479.

4.2.8. Methyl 4-[(2S,3S*,5S*)-5-hydroxy-2-{4-(methoxycarbonyl)benzoyl}-3-(thiophen-2-yl)tetrahydrofuran-2-yl]benzoate (**4ah**).* Colorless needles; mp 144–147 °C (recrystallized from AcOEt/hexane); IR (neat) 3461, 2953, 1724, 1688, 1609 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.45 (1H, dd, *J*=4.0 and 8.0 Hz), 2.46 (1H, dd, *J*=2.4 and 8.0 Hz), 2.68 (1H, br s), 3.84 (3H, s), 3.88 (3H, s), 5.18 (1H, t, *J*=8.0 Hz), 6.06 (1H, dd, *J*=2.4 and 4.0 Hz), 6.67 (1H, dd, *J*=1.2 and 3.6 Hz), 6.70 (1H, dd, *J*=3.2 and 5.2 Hz), 6.95 (1H, dd, *J*=1.2 and 5.2 Hz), 7.20 (2H, d, *J*=8.0 Hz), 7.79 (2H, d, *J*=8.0 Hz), 7.91–7.93 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.9 (CH_2), 45.3 (CH), 52.0 (CH_3), 52.3 (CH_3), 94.1 (Cq), 98.7 (CH), 124.6 (CH), 125.2 (CH), 126.3 (CH), 126.5 (CH), 129.1 (CH), 129.3 (CH), 129.4 (Cq), 130.5 (CH), 133.1 (Cq), 138.2 (Cq), 141.8 (Cq), 142.6 (Cq), 166.2 (Cq), 166.7 (Cq), 197.6 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{25}H_{22}O_7Sna$ $[M+Na]^+$ 489.0984, found 489.0982.

4.2.9. Methyl 4-[(2S,3S*,5S*)-3-(4-fluorophenyl)-5-hydroxy-2-{4-(methoxycarbonyl)benzoyl}tetrahydrofuran-2-yl]benzoate (**4ai**).* Colorless crystals; mp 148–151 °C (recrystallized from AcOEt/hexane); IR (neat) 3461, 2953, 1725, 1688, 1607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.40 (2H, dd, *J*=2.8 and 8.4 Hz), 2.63 (1H, br s), 3.84 (3H, s), 3.88 (3H, s), 4.91 (1H, t, *J*=8.4 Hz), 6.06 (1H, dd, *J*=2.8 and 6.0 Hz), 6.72 (2H, dd, *J*=8.8 and 8.8 Hz), 6.90 (2H, dd, *J*=5.2 and 8.8 Hz), 7.09 (2H, d, *J*=7.2 Hz), 7.76 (2H, d, *J*=8.8 Hz), 7.88–7.95 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.1 (CH_2), 49.0 (CH), 52.1 (CH_3), 52.3 (CH_3), 94.5 (Cq), 98.9 (CH), 114.7 (CH, d, *J*=21.5 Hz) 125.4 (CH), 129.1 (CH), 129.3 (Cq), 129.4 (CH), 130.5 (CH), 130.6 (CH, d, *J*=7.4 Hz), 133.0 (Cq), 134.2 (Cq, d, *J*=3.3 Hz), 134.3 (Cq), 138.4 (Cq), 142.6 (Cq), 161.5 (Cq, d, *J*=244.5 Hz), 166.2 (Cq), 166.5 (Cq), 198.1 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{27}H_{23}O_7Fna$ $[M+Na]^+$ 501.1326, found 501.1325.

4.2.10. Methyl 4-[(2S,3S*,5S*)-3-(4-chlorophenyl)-5-hydroxy-2-{4-(methoxycarbonyl)benzoyl}tetrahydrofuran-2-yl]benzoate (**4aj**).* Colorless crystals; mp 156–158 °C (recrystallized from AcOEt/hexane); IR (neat) 3461, 2953, 1725, 1688, 1609 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.40 (2H, dd, *J*=2.8 and 8.4 Hz), 2.86 (1H, br s), 3.84 (3H, s), 3.87 (3H, s), 4.90 (1H, t, *J*=8.4 Hz), 6.07 (1H, d, *J*=2.8 Hz), 6.87 (2H, d, *J*=8.4 Hz), 7.01 (2H, d, *J*=8.4 Hz), 7.11 (2H, d, *J*=6.4 Hz), 7.77 (2H, d, *J*=8.4 Hz), 7.85–7.94 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.1 (CH_2), 49.0 (CH), 52.1 (CH_3), 52.4 (CH_3), 94.5 (Cq), 98.9 (CH), 125.4 (CH), 128.0 (Cq), 128.0 (CH), 129.1 (CH), 129.5 (CH), 130.5 (CH), 130.5 (CH), 132.5 (Cq), 133.1 (Cq), 137.1 (Cq), 138.4 (Cq), 142.5 (Cq), 166.2 (Cq), 166.5 (Cq), 198.0 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{27}H_{23}O_7ClNa$ $[M+Na]^+$ 517.1030, found 517.1030.

4.2.11. Methyl 4-[(2S,3S*,5S*)-3-(4-bromophenyl)-5-hydroxy-2-{4-(methoxycarbonyl)benzoyl}tetrahydrofuran-2-yl]benzoate (**4ak**).* Colorless crystals; mp 162–165 °C (recrystallized from AcOEt/hexane); IR (neat) 3855, 2935, 1713, 1726, 1688, 1609 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.39 (2H, dd, *J*=2.4 and 8.4 Hz), 2.62 (1H, br s), 3.85 (3H, s), 3.88 (3H, s), 4.88 (1H, t, *J*=8.4 Hz), 6.06 (1H, d, *J*=2.4 Hz), 6.82 (2H, d, *J*=8.4 Hz), 7.11 (2H, d, *J*=7.2 Hz), 7.16 (2H, d, *J*=8.4 Hz), 7.77 (2H, d, *J*=8.4 Hz), 7.87–7.94 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.1 (CH_2), 49.0 (CH), 52.1 (CH_3), 52.4 (CH_3), 94.5 (Cq), 98.9 (CH), 120.6 (Cq), 125.4 (CH), 129.0 (CH), 129.5 (CH), 130.5 (CH), 130.8 (CH), 130.9 (Cq), 130.9 (CH), 133.0 (Cq), 137.7 (Cq), 138.4 (Cq), 142.4 (Cq), 166.1 (Cq), 166.5 (Cq), 197.9 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{27}H_{24}O_7Br$ $[M+H]^+$ 539.0705, found 539.0705.

*4.2.12. X-ray crystallographic analysis of compound **4ak**.* A colorless block crystal having approximate dimensions of 0.30×0.40×0.40 mm was mounted on a glass fiber. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo Kα radiation. The structure was solved by direct methods (SIR92) and expanded using Fourier techniques (DIRDIF99). The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement on *F* was based on 11,335 observed reflections ($I>0.00\sigma(I)$) and 339 variable parameters, and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of R=0.060 and R_w=0.167. Crystal data for **4ak**: $C_{27}H_{23}O_7Br$, M=539.38, triclinic, space group $P\bar{1}$, a=7.873(3) Å, b=1.745(4) Å, c=13.899(5) Å, α=81.58(3)°, β=74.33(3)°, γ=69.50(3)°, V=1157.1(7) $Å^3$, Z=2, D_c=1.548 g/cm^3, $F(000)$=552, μ(Mo Kα)=18.29 cm^{-3}.

4.2.13. Ethyl 4-[(2S,3S*,5S*)-2-{4-(ethoxycarbonyl)benzoyl}-5-hydroxy-3-phenyltetrahydrofuran-2-yl]benzoate (**4ba**).* Colorless needles; mp 120–123 °C (recrystallized from AcOEt/hexane); IR (KBr) 3511, 2987, 1718, 1691, 1673, 1609 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (3H, t, *J*=7.2 Hz), 1.35 (3H, t, *J*=7.2 Hz), 2.39–2.52 (2H, m), 2.62 (1H, br s), 4.28 (2H, q, *J*=7.2 Hz), 4.33 (2H, q, *J*=7.2 Hz), 4.92 (1H, t, *J*=8.4 Hz), 6.08 (1H, t, *J*=2.4 Hz), 6.92–7.06 (5H, m), 7.11 (2H, d, *J*=7.2 Hz), 7.73 (2H, d, *J*=8.4 Hz), 7.89–7.95 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (CH_3), 14.2 (CH_3), 40.3 (CH_2), 49.5 (CH), 60.9 (CH_3), 61.3 (CH_3), 94.8 (Cq), 99.1 (CH), 125.4 (CH), 126.6 (CH), 127.8 (CH), 129.0 (CH), 129.2 (CH), 129.2 (CH), 129.5 (Cq), 130.5 (CH), 133.4 (Cq), 138.5 (Cq), 138.7 (Cq), 142.7 (Cq), 165.7 (Cq), 166.2 (Cq), 198.2 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{29}H_{29}O_7$ $[M+H]^+$ 489.1913, found 489.1911.

4.2.14. Isopropyl 4-[(2S,3S*,5S*)-5-hydroxy-2-{4-(isopropoxycarbonyl)benzoyl}-3-phenyltetrahydrofuran-2-yl]benzoate (**4ca**).* White solid; mp 77.0–81.9 °C (recrystallized from AcOEt/hexane); IR (KBr) 3546, 3454, 2980, 1716, 1680, 1611 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29–1.33 (12H, m), 2.39–2.52 (2H, m), 2.64 (1H, br s), 4.92 (1H, t, *J*=8.4 Hz), 5.10–5.25 (2H, m), 6.08 (1H, t, *J*=2.8 Hz), 6.94–7.04 (5H, m), 7.10 (2H, d, *J*=7.6 Hz), 7.72 (2H, d, *J*=8.8 Hz), 7.89–7.92 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8 (CH_3), 21.8 (CH_3), 21.9 (CH_3), 40.3 (CH_2), 49.5 (CH), 68.4 (CH_3), 68.8 (CH_3), 94.9 (Cq), 99.1 (CH), 125.4 (CH), 126.6 (CH), 127.8 (CH), 129.0 (CH), 129.2 (CH), 129.2 (CH), 129.9 (Cq), 130.4 (CH), 133.8 (Cq),

138.4 (Cq), 138.7 (Cq), 165.2 (Cq), 165.7 (Cq), 198.1 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{31}H_{33}O_7$ $[M+H]^+$ 517.2226, found 517.2224.

4.2.15. tert-Butyl 4-[(2S,3S*,5S*)-2-{4-(tert-butoxycarbonyl)benzoyl}-5-hydroxy-3-phenyltetrahydrofuran-2-yl]benzoate (**4da**).* Pale yellow crystals; mp 153–157 °C (recrystallized from AcOEt/hexane); IR (neat) 3569, 2979, 1715, 1691, 1608 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.52 (9H, s), 1.54 (9H, s), 2.38–2.51 (2H, m), 2.62 (1H, br s), 4.92 (1H, t, *J*=8.4 Hz), 6.07 (1H, t, *J*=2.8 Hz), 6.94–7.09 (7H, m), 7.67 (2H, d, *J*=8.8 Hz), 7.85 (2H, d, *J*=8.4 Hz), 7.89 (2H, d, *J*=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1 (CH_3), 28.1 (CH_3), 40.3 (CH_2), 49.5 (CH), 81.0 (Cq), 81.5 (Cq), 94.8 (Cq), 99.1 (CH), 125.3 (CH), 126.6 (CH), 127.8 (CH), 128.8 (CH), 129.1 (CH), 129.2 (CH), 130.4 (CH), 130.9 (Cq), 134.8 (Cq), 138.2 (Cq), 138.8 (Cq), 142.3 (Cq), 164.9 (Cq), 165.3 (Cq), 198.2 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{33}H_{37}O_7$ $[M+H]^+$ 545.2539, found 545.2540.

4.2.16. Methyl 4-[(2S,3S*,5S*)-5-hydroxy-2-{3-methoxy-4-(methoxycarbonyl)benzoyl}-3-phenyltetrahydrofuran-2-yl]-2-methoxybenzoate (**4ea**).* Colorless oil; IR (neat) 3454, 2952, 1716, 1688, 1607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.37–2.49 (2H, m), 2.82 (1H, br s), 3.48 (3H, s), 3.80 (3H, s), 3.80 (3H, s), 3.86 (3H, s), 4.90 (1H, t, *J*=8.0 Hz), 6.07 (1H, t, *J*=2.4 Hz), 6.30 (1H, br s), 6.90–6.98 (3H, m), 7.03–7.10 (3H, m), 7.44 (1H, dd, *J*=1.2 and 8.0 Hz), 7.51 (1H, d, *J*=1.2 Hz), 7.60 (1H, d, *J*=8.0 Hz), 7.64 (1H, d, *J*=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.9 (CH_2), 49.5 (CH), 51.9 (CH_3), 52.2 (CH_3), 55.8 (CH_3), 55.9 (CH_3), 94.4 (Cq), 98.9 (CH), 109.8 (CH), 113.5 (CH), 116.7 (CH), 118.7 (Cq), 122.4 (CH), 123.3 (Cq), 126.8 (CH), 127.9 (CH), 129.3 (CH), 130.8 (CH), 131.7 (CH), 138.6 (Cq), 139.0 (Cq), 143.8 (Cq), 158.2 (Cq), 158.8 (Cq), 166.0 (Cq), 166.1 (Cq), 197.9 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{29}H_{28}O_9Na$ $[M+Na]^+$ 543.1631, found 543.1627.

4.3. Procedure for comparative experiment using methyl 4-formylbenzoate (2a) and benzaldehyde (2f) (Scheme 3)

To a stirred solution of methyl-4-formylbenzoate (**2a**) (188 mg, 1.13 mmol), benzaldehyde (**2f**) (120 μL, 1.13 mmol), *trans*-cinnamaldehyde (**3a**) (50.0 μL, 378 μmol), and the imidazolium catalyst **1** (13.2 mg, 37.8 μmol) in THF (700 μL) and MeOH (70.0 μL) was added DBU (60.0 μL, 396 μmol) at rt. After stirring at rt for 5 h, the reaction mixture was added to H_2O and extracted with AcOEt. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (70:30 v/v) as eluent to provide **4aa** (135 mg, 77%) as colorless crystals.

4.4. Procedure for the reaction of benzoin 14a with cinnamaldehyde (3a) in the absence of imidazolium carbene catalyst (Scheme 5)

To a stirred solution of *trans*-cinnamaldehyde (**3a**) (10.0 μL, 80.0 μmol) and benzoin **18a** (26.3 mg, 80.0 μmol) in THF (200 μL) and MeOH (20.0 μL) was added DBU (10.0 μL, 80.0 μmol) at rt. After stirring was continued for 2.5 h at the same temperature, the reaction mixture was added to H_2O and extracted with AcOEt. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (70:30 v/v) as eluent to provide **4aa** (11.9 mg, 32%) as colorless crystals.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.09.049.

References and notes

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