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Solvent-Free Benzoin and Stetter Reactions with a Small Amount of NHC Catalyst in the Liquid or Semisolid State

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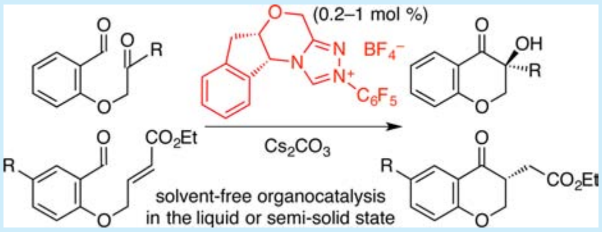
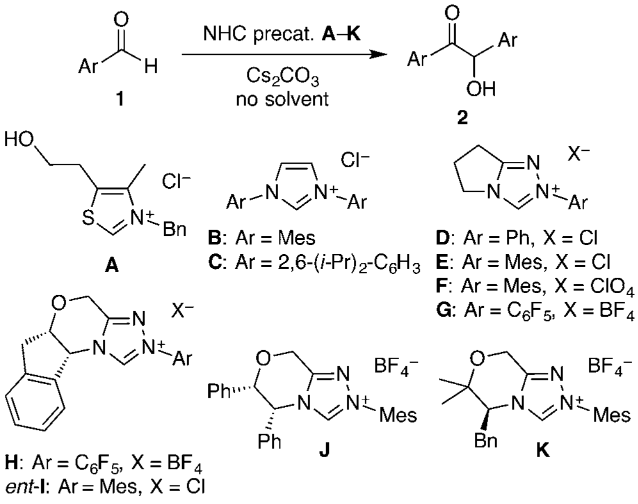
Supporting Information

ABSTRACT: The intermolecular or intramolecular asymmetric benzoin reaction was catalyzed by a small amount of N-heterocyclic carbene (NHC) (0.2−1 mol %) under solvent-free conditions. The solvent-free intramolecular asymmetric Stetter reaction also proceeded efficiently with NHC (0.2−1 mol %). In some cases, even solid-to-solid or solid-to-liquid conversions took place with low catalyst loading (0.2−1 mol %).



N-Heterocyclic carbenes (NHCs) have attracted much attention because of excellent organocatalytic activity.[1−6] Thiazolium, imidazolium, and triazolium salts are used as NHC precatalysts, and the addition of base to the precatalysts generates NHCs, which catalyze various C−C bond formations via polarity inversion (Umpolung). NHC organocatalysis is characterized by reaction diversity as well as high enantioselectivity and broad substrate scope. NHCs catalyze the benzoin reaction,[1a,b,2] the Stetter reaction,[1e,s,3] homoenolate reactions,[1h,i,r,4] acyl azolium reactions,[1k,n,o,5] and other useful reactions.[1,6] The benzoin reaction gives α-hydroxy ketones by combining two aldehyde molecules with high atom efficiency via the Breslow intermediate (Scheme 1).[7] α-Hydroxy ketones are useful building blocks for natural products and pharmaceuticals.[8] We have synthesized bicyclic and tricyclic compounds with contiguous quaternary stereocenters via intramolecular asymmetric cross-benzoin reactions catalyzed by NHC.[9] Catalytic activity and selectivity can be modulated by altering the structure of NHC.[10] Kinetic, thermodynamic, and computational studies on the NHC-catalyzed benzoin reactions have been reported.[11]

Scheme 1. Solvent-Free NHC-Catalyzed Benzoin Reaction



In most organic reactions, a selected solvent is used not only to make a homogeneous solution but also to maximize the reaction yield, stereoselectivity, and chemoselectivity. The solvent is also needed to control a violent exothermic reaction such as that involving a rapid electron transfer from metal and that with a highly reactive species. However, the use of a solvent may decrease the reaction rate according to a kinetic equation such as $v = k[\mathrm{A}][\mathrm{B}]$, produce a waste solvent after the reaction, enhance the production cost, and make a chemical operation risky when a flammable solvent is used. Solvent-free reactions are therefore becoming important from the viewpoint of green chemistry.[12,13] Organocatalysis has great potential in solvent-free reactions because of a high level of safety and utility of organocatalysts.[14]

Except for a few examples,[15] NHC loading of 5−20 mol % is required in most experimental protocols in the literature,[1−6,9] which can be a burden that impedes industrial application, considering the relatively high prices of commercially available NHC precatalysts, especially triazolium salts. In our recent study on CO_2 fixation catalysis, catalyst loading could be reduced to a ppm level under solvent-free conditions.[12] This prompted us to explore the potential of solvent-free NHC-catalyzed reactions. Here we report that in both the benzoin and Stetter reactions, NHC loading could be reduced to 0.2−1 mol % under solvent-free conditions and that the reactions proceeded even in the semisolid state. To the best of our knowledge, this is the first example of solid-to-solid or solid-to-liquid conversions with NHC.

We set precatalyst loading to 0.5 mol % in the optimizing reaction conditions for the benzoin reaction. A mixture of benzaldehyde (**1a**), which was freshly distilled prior to use, NHC

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precatalyst **A**–**K**, and Cs_2CO_3 was stirred under Ar in a Schlenk flask in a thermostatic bath at 30 °C for 1 h (Scheme 1). The results of the solvent-free benzoin reactions are shown in Table 1.

Table 1. Solvent-Free Benzoin Reaction with NHC[a]

entry	NHC precat.	yield (%)[b]	ee (%)[c]
1	**A**	61	
2	**B**	0	
3	**C**	0	
4	**D**	48	
5	**E**	91	
6	**F**	97	
7	**G**	96	
8	**H**	95	87
9	*ent*-**I**	99	2
10	**J**	90	−3
11	**K**	8	77

[a] Conditions: benzaldehyde (**1a**) (5.0 mmol), NHC precatalyst (0.5 mol %), Cs_2CO_3 (0.5 mol %), Ar, 30 °C, 1 h. [b] Determined by ^1H NMR using 2-methoxynaphthalene as an internal standard for entries 1–7. Isolated yield for entries 8–11. [c] Determined by chiral HPLC. Positive sign for (*R*)-**2a**.

Interestingly, a liquid changed into a solid, which was indicative of the reaction progress. The reaction using thiazolium salt **A** gave benzoin (**2a**) in a moderate yield (61%), while imidazolium salts **B** and **C** mediated no reaction (entries 1–3). Among triazolium salts **D**–**G**, pentafluorophenyl-containing **G** most reproducibly afforded **2a** in high yield (96%) (entries 4–7), which is probably due to the sensitivity of **D**–**F** to humidity or a trace amount of impurity (benzoic acid) in **1a**. The difference in the counteranion (Cl^- or ClO_4^-) had little or no influence on the outcome (entries 5 and 6).[10a] Among chiral triazolium salts **H**–**K**, Rovis catalyst **H** gave (*R*)-**2a** in high yield (95%) with the highest enantiomeric purity (87% ee) (entries 8–11). This solvent-free reaction with precatalyst **H** was excellent in both yield and enantioselectivity as compared with the corresponding reaction in THF (1.0 M, 54% yield (73% ee); 0.5 M, 10% yield (67% ee)). Control experiments with solvents indicated the concentration dependence of the reaction rate (Supporting Information).

We further decreased catalyst loading in the solvent-free benzoin reaction of **1a**. Table 2 indicates that the yields in the reaction at 30 °C for 1 h decreased with a decrease in the amount of **H** (entries 1–3). Although catalyst loading of 0.1 mol % afforded a moderate yield (48%) (entry 3), a high yield (88%) was achieved with the catalyst loading of 0.2 mol % (entry 2). When the solvent-free benzoin reaction of **1a** was performed at 0 °C for 24 h using 0.5 mol % **H**, **2a** was isolated in 86% yield with 97% ee (entry 4). These results convinced us of the power of solvent-free NHC organocatalysis.

Table 2. Effect of Catalyst Loading on Solvent-Free Benzoin Reaction.[a]

entry	**H** (mol %)	*t* (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	0.5	30	1	95	87
2	0.2	30	1	88	71
3	0.1	30	1	48	71
4	0.5	0	24	86	97

[a] Conditions: benzaldehyde (**1a**) (5.0 mmol), NHC precatalyst **H** (amount indicated above), Cs_2CO_3 (1 equiv with respect to **H**), Ar. [b] Isolated yield. [c] Determined by chiral HPLC.

A series of aromatic aldehydes **1** were subjected to the solvent-free asymmetric benzoin reaction with precatalyst **H** (0.5 mol %) (Table 3). In all cases where a high conversion was attained, a liquid changed into a solid. Aldehydes having a substituent at the meta or para position were converted into the products in high yields with good to high enantiomeric purities in most cases (entries 3–5, 7, 8, and 10). However, ortho-substituted aldehydes exhibited little or no reactivity (entries 2, 6, and 9). Glorius and co-workers have proposed that the substituent at the ortho position hinders the formation of the Breslow intermediate owing to steric repulsion.[2c] 2-Thienylaldehyde (**1o**) was converted into the benzoin product in high yield (98%) with high enantioselectivity (91% ee) (entry 18), whereas low enantioselectivity was observed for 2-furylaldehyde (**1n**) (28% ee) (entry 17).

Table 3. NHC-Catalyzed Asymmetric Benzoin Reaction under Solvent-Free Conditions[a]

entry	**1**	Ar	*t* (°C)	**2**	yield (%)[b]	ee (%)[c]
1[d]	**1a**	Ph	30	**2a**	95	87
2	**1b**	2-Me-C_6H_4	30	**2b**	0[e]	
3	**1c**	3-Me-C_6H_4	30	**2c**	84	75
4	**1d**	4-Me-C_6H_4	30	**2d**	96	83
5	**1e**	4-Et-C_6H_4	30	**2e**	93	76
6	**1f**	2-MeO-C_6H_4	40[f]	**2f**	13	−31
7	**1g**	3-MeO-C_6H_4	30	**2g**	91	77
8	**1h**	4-MeO-C_6H_4	30	**2h**	70	90
9	**1i**	2-Cl-C_6H_4	30	**2i**	0[e]	
10	**1j**	3-Cl-C_6H_4	30	**2j**	89	69
11	**1k**	4-Cl-C_6H_4	50[f]	**2k**	88	43
12	**1k**	4-Cl-C_6H_4	30[g]	**2k**	98	78
13	**1l**	4-Br-C_6H_4	70[f]	**2l**	84	22
14	**1l**	4-Br-C_6H_4	30[g,h]	**2l**	99	79
15	**1m**	2-naphthyl	70[f]	**2m**	93	76
16	**1m**	2-naphthyl	50[g,h]	**2m**	87	73
17	**1n**	2-furyl	30	**2n**	80	28
18	**1o**	2-thienyl	30	**2o**	98	91

[a] Conditions: aldehyde **1** (5.0 mmol), NHC precatalyst **H** (0.5 mol %), Cs_2CO_3 (0.5 mol %), Ar, 12 h. [b] Isolated yield. [c] Determined by chiral HPLC. Positive sign for (*R*)-**2**. [d] Reaction time of 1 h. [e] The same result was obtained even if catalyst loading was increased to 1 mol %. [f] The reaction temperature was increased to melt the aldehyde. [g] Solid-to-solid conversion. [h] NHC precatalyst **H** (1.0 mol %), Cs_2CO_3 (1.0 mol %).

To melt aldehyde that is a solid at room temperature, the reaction temperature was increased above the melting point, which led to modest or poor enantioselectivities because of the high temperature (Table 3, entries 6, 11, 13, and 15). Obviously, the solvent-free reaction may have limitations when the substrate is a solid. In this situation, we conducted the solvent-free reaction below the melting point even if the reaction mixture was a solid. A finely powdered mixture of aldehyde **1k**, precatalyst **H**, and Cs_2CO_3 was gently stirred under Ar at 30 °C for 12 h, and saturated aqueous NH_4Cl was then added to quench the reaction. Surprisingly, solid **1k** was converted into solid **2k** with a small amount of precatalyst **H** (0.5 mol %) (entry 12). Moreover, the enantiomeric purity of **2k** was higher at 30 °C than at 50 °C (entries 11 and 12). Figure 1 shows the photographs of the reaction mixture before and after the solvent-free benzoin

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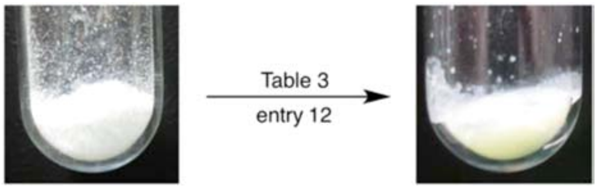
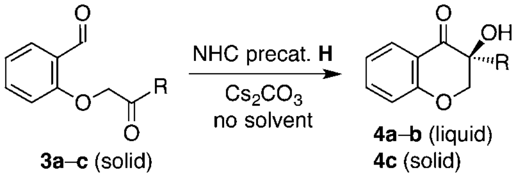


Figure 1. Photographs of a reaction mixture before and after the solvent-free benzoin reaction of **1k**.

reaction of **1k**. Solid aldehyde **1l** was also converted into a solid product more enantioselectively at 30 °C than at 70 °C (entries 13 and 14). In contrast, solid aldehyde **1m** showed poor reactivity at 30 °C (not shown). The molecules of **1m** with the naphthalene ring are likely to be tightly stacked in the crystalline state. When the reaction temperature was increased up to 50 °C, **1m** underwent the benzoin reaction (entry 16). In all cases, a powdery mixture temporarily got damp or slurry (semisolid), which then turned into a solid. This phenomenon may be related to melting-point depression (freezing-point depression); as the reaction proceeds, the substrate becomes impure, which can lower the melting point of the substrate, and the partial melting of the solid (semisolid state) makes the reaction faster. The reaction temperature that is not far below the melting point of substrate may be important for this semisolid-state organocatalysis using no ball mill.[16] In any case, solid-to-solid conversions with such low catalyst loading are quite rare and interesting.[13,14,16]

We also conducted the intramolecular crossed benzoin reaction of **3** under solvent-free conditions because of the fascinating structures of the products **4** (Table 4).[17] When a finely powdered mixture of aldehyde **3a**, precatalyst **H**, and Cs_2CO_3 was gently stirred under Ar in a Schlenk flask (procedure A), 4-chromanone **4a** was obtained in only 47% yield (entry 1). Through trial and error, we found that an excellent outcome (90% yield) (entry 2) could be obtained by procedure B: after a finely powdered mixture of precatalyst **H** and Cs_2CO_3 had been stirred under Ar for 1 h to generate NHC, **3a** was added (Supporting Information). The solvent-free benzoin cyclization of **3b** and **3c** also proceeded efficiently (entries 3 and 4).

Table 4. NHC-Catalyzed Asymmetric Benzoin Cyclization under Solvent-Free Conditions[a]

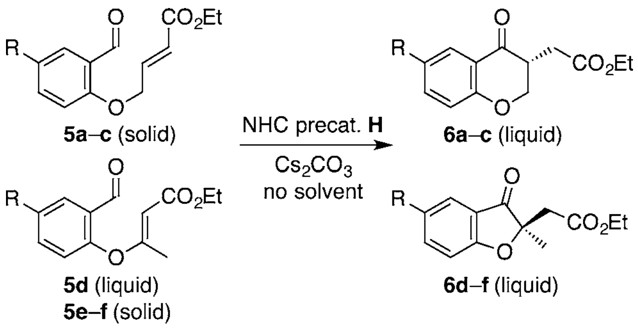


entry	3	R	H (mol %)	time (h)	4	yield (%)[b]	ee (%)[c]
1	**3a**	Me	0.5	24	**4a**	47	68
2[d]	**3a**	Me	0.5	24	**4a**	90	59
3[d]	**3b**	Et	0.5	24	**4b**	89	49
4[d,e]	**3c**	Ph	1	48	**4c**	76	53

[a]Conditions: aldehyde **3** (2.0 mmol), NHC precatalyst **H** (amount indicated above), Cs_2CO_3 (1 equiv with respect to **H**), Ar, 30 °C (procedure A). [b]Isolated yield. [c]Determined by chiral HPLC. [d]Procedure B. [e]At 40 °C.

To further examine the scope of solvent-free NHC organocatalysis, we turned our attention to the Stetter reaction, which often requires 20 mol % NHC in organic solvent.[1e,s,3] The results are shown in Table 5. To our delight, the solvent-free intramolecular asymmetric Stetter reaction of **5a** proceeded with low catalyst loading (0.5 mol %) to give 4-chromanone **6a** in 93% yield with 94% ee according to procedure A (entry 1). Catalyst loading could be reduced to 0.2 mol % although a longer reaction time was needed (entry 2). Because substrate **5a** and product **6a** are solid and liquid, respectively, a solid mixture changed into a liquid as the reaction proceeded. Despite the use of neat (highly concentrated) aldehyde **5a**, there was no sign of the *intermolecular* Stetter or benzoin reaction. In contrast, the solvent-free Stetter reaction of **5b** was somehow slow even when catalyst loading was increased to 1 mol % (43% yield, 94% ee) (entry 3). Eventually, a better result was obtained according to procedure B; **6b** was isolated in 95% yield with 93% ee (entry 4). The solvent-free Stetter reaction of **5c−f** also proceeded successfully (entries 5−9).

Table 5. NHC-Catalyzed Intramolecular Asymmetric Stetter Reaction under Solvent-Free Conditions[a]



entry	5	R	H (mol %)	time (h)	6	yield (%)[b]	ee (%)[c]
1	**5a**	H	0.5	6	**6a**	93	94
2	**5a**	H	0.2	24	**6a**	97	94
3	**5b**	Me	1	12	**6b**	43	94
4[d]	**5b**	Me	1	12	**6b**	95	93
5	**5c**	Br	0.5	12	**6c**	95	94
6[d]	**5d**	H	0.5	48	**6d**	88	97
7[d]	**5d**	H	0.2	48	**6d**	71	98
8[d]	**5e**	Me	0.5	48	**6e**	97	98
9[d]	**5f**	Br	1	48	**6f**	99	94

[a]Conditions: aldehyde **5** (2.0 mmol), NHC precatalyst **H** (amount indicated above), Cs_2CO_3 (1 equiv with respect to **H**), Ar, 30 °C (procedure A). [b]Isolated yield. [c]Determined by chiral HPLC. [d]Procedure B.

In summary, both the benzoin and Stetter reactions were catalyzed by a small amount of NHC (0.2−1 mol %) under solvent-free conditions, and even semisolid state organocatalysis took place. To the best of our knowledge, this is the first example of the solid-to-solid or solid-to-liquid conversions with NHC. These solvent-free reactions are green, efficient, and practical, using approximately 10 to 100 times less catalyst than the typical protocols in the literature. Further work is being done to explore the scope and limitation of solvent-free NHC organocatalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03115.

Synthetic procedures and compound characterizations (PDF)

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Notes

The authors declare no competing financial interest.

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