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Stereoselective Synthesis of Bicyclic Tertiary Alcohols with Quaternary Stereocenters via Intramolecular Crossed Benzoin Reactions Catalyzed by *N*-Heterocyclic Carbenes

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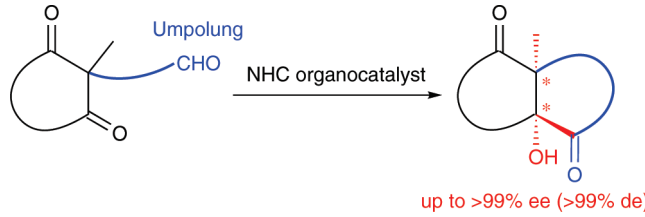
ABSTRACT



Bicyclic tertiary alcohols 1 bearing quaternary stereocenters at the two adjacent bridgehead positions were synthesized with high stereoselectivity via the intramolecular crossed benzoin reactions catalyzed by NHC organocatalysts.

Asymmetric organocatalysis is a rapidly growing area in organic synthesis.[1] Among various kinds of organocatalysts, *N*-heterocyclic carbenes (NHCs), which can catalyze the C−C bond formation via polarity inversion (Umpolung), are one of the most powerful and useful organocatalysts.[2] NHCs are known to catalyze the benzoin reaction,[3,4] the Stetter reaction,[5] the aza-Morita−Baylis−Hillman reaction,[6] the generation of homoenolate species followed by a C−C bond formation,[7] the cycloaddition of ketenes,[8] the acylation of alcohols,[9] and other useful reactions.[10,11]

We envisioned that the NHC-catalyzed intramolecular crossed benzoin reactions of cyclic diketones **2** would give bicyclic compounds **1** as shown in Scheme 1. The target compounds **1** are tertiary alcohols having quaternary stereo-

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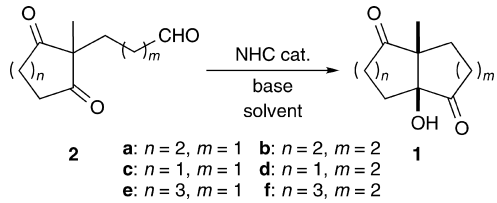
Scheme 1. Intramolecular Crossed Benzoin Reaction Catalyzed by NHC Organocatalyst



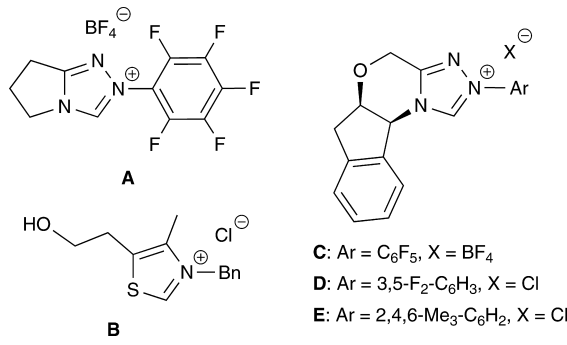


Figure 1. NHC organocatalysts **A**−**E**.

centers at the two adjacent bridgehead positions. Interestingly, a series of homologues **1**, except for racemic **1d**,[12] are new compounds, which may suggest that they are difficult to prepare by other synthetic methods. Further conversions of **1** into other new compounds can also be expected. Because of these features, compounds **1** are the fascinating chiral building blocks worthy of synthetic study. Here, we report the facile stereoselective synthesis of **1** using NHC precursors **A**−**E** (Figure 1).

Table 1. NHC-Catalyzed Benzoin Cyclization of **2**[a]

entry	temp (°C)	substrate **2**	Et_3N (mol %)	product **1**	yield[b] (%)
1	25	**2a**	20	**1a**	65
2	25	**2a**	15	**1a**	46
3	25	**2a**	10	**1a**	42
4	66	**2a**	20	**1a**	81
5[c]	66	**2a**	20	**1a**	29
6	66	**2b**	20	**1b**	59
7	66	**2c**	20	**1c**	82
8	66	**2d**	20	**1d**	76
9	66	**2e**	20	**1e**	73
10	66	**2f**	20	**1f**	40

[a] Conditions: **2** (0.300 mmol), NHC cat. **A** (0.060 mmol, 20 mol %), Et_3N (quantity indicated above), THF (1 mL), 24 h. [b] Isolated yield of **1**. [c] NHC cat. **B** (20 mol %) was used.

We first explored the annulation of **2a**, which can be prepared most easily according to the literature,[13a] by using achiral NHC precatalysts, triazolium salt **A** and thiazolium salt **B**. The results are shown in Table 1. The reaction was initially performed with 20 mol % of triazolium salt **A** and Et_3N in THF at 25 °C for 24 h to give **1a** as a single diastereomer in 65% (entry 1). The *cis*-configuration of **1a** was confirmed by the NOE experiment after **1a** had been converted into **3** (Scheme 2); a positive NOE was observed for the signal of the TMS group upon irradiation of the methyl group at the bridgehead position (Supporting Information). The addition of 1 equiv of Et_3N was necessary for generating NHC most efficiently (entries 1−3). Increasing the reaction temperature up to 66 °C afforded **1a** in 81% (entry 4). In contrast, the use of thiazolium salt **B** resulted in a lower yield (entry 5). The substrate scope was then investigated by using triazolium salt **A**. The homologues **2b**, **2c**, and **2e**, which were prepared according to the literature,[13b−d] and newly synthesized **2d** and **2f** were subjected to the NHC-catalyzed reaction. In all cases, bicyclic compounds **1b**−**f** were obtained completely diastereoselectively in moderate to high yields (entries 6−10).

Next, we examined the asymmetric desymmetrization of **2** using chiral NHCs. Chiral triazolium salt **D** prepared according to the literature,[14] and commercially available chiral triazolium salts **C** and **E** were employed. NHC precatalyst **C**, which has been reported by Rovis to show high catalytic activity and enantioselectivity in the intramolecular Stetter reactions,[5b−e] was initially used to optimize the reaction conditions for **2a**. The results are summarized in Table S1 (Supporting Information), and the best result is shown in Table 2 (entry 1). Despite various attempts, 38%

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Scheme 2. Derivatization of **1a** To Determine Relative Configuration

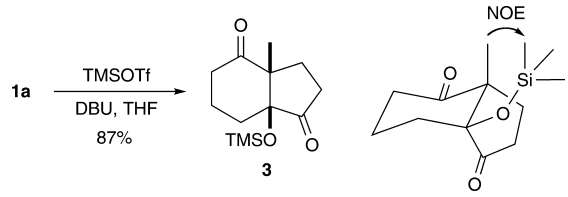


Table 2. NHC-Catalyzed Asymmetric Benzoin Cyclization of **2a**[a]

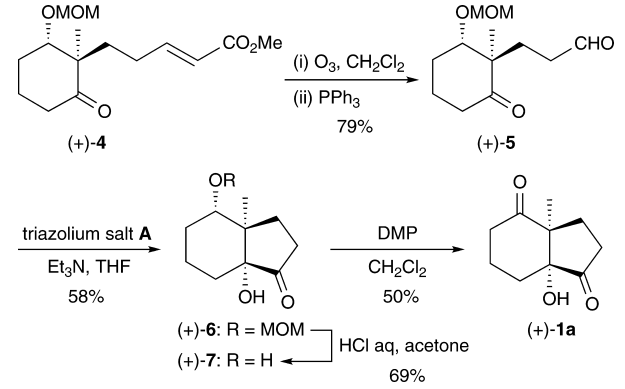
entry	temp (°C)	NHC (mol %)	base (mol %)	solvent	yield[b] (%)	ee[c] (%)
1	rt	**C**(20)	Et_3N (20)	THF	61	−38
2	rt	**D**(20)	Et_3N (20)	THF	12	30
3	rt	**E**(20)	Et_3N (20)	toluene	trace	*d*
4	rt	**E**(20)	DBU (20)	toluene	15	69
5[a]	rt	**E**(20)	DBU (20)	toluene	19	58
6[a]	rt	**E**(20)	DBU (20)	toluene	12	78
7	23	**E**(30)	DBU (30)	toluene	25	75
8	30	**E**(30)	DBU (30)	toluene	41	65
9	60	**E**(30)	DBU (30)	toluene	64	25
10	23	**E**(30)	*i*-Pr_2NEt (30)	toluene	trace	*d*
11	23	**E**(30)	K_2CO_3 (30)	toluene	29	76
12	23	**E**(30)	Cs_2CO_3 (30)	toluene	48	70
13	23	**E**(30)	Cs_2CO_3 (30)	THF	42	71
14	23	**E**(30)	Cs_2CO_3 (30)	MeCN	*e*	*d*
15	23	**E**(30)	Cs_2CO_3 (30)	CH_2Cl_2	50	78

[a] Conditions: **2a** (0.300 mmol), NHC cat. (quantity indicated above), base (quantity indicated above), solvent (1 mL for entries 1−4, 6 mL for entries 5−15), 24 h. NHC was generated after **2a** had been added (entries 1−5), or **2a** was added after NHC had been generated (entries 6−15). [b] Isolated yield of **1a**. [c] Determined by chiral GC (CP-cyclodextrin-β-2,3,6-M-19 column). The sign of the enantiomeric purity is that of the specific rotation. [d] Not determined. [e] Complex mixture.

ee was the highest value, which forced us to change the NHC catalyst. The use of triazolium salt **D** also resulted in a low enantioselectivity (entry 2), although Suzuki and Takikawa have reported that triazolium salt **D** functions as an excellent catalyst for an asymmetric benzoin cyclization.[14] NHC precatalyst **E**, developed by Bode and co-workers,[10a] was then examined. When Et_3N was used as a base, almost no reaction proceeded (entry 3). The acidity of triazolium salt **E** with the *N*-substituted mesityl group is considered to be much lower than that of **C** and **D**. When DBU was used as a base, the reaction proceeded to give **1a** in 69% ee (entry 4).

Encouraged by this result, we decided to optimize the reaction conditions. To suppress side reactions such as the *intermolecular* benzoin reaction, the substrate concentration was changed from 0.3 to 0.05 M, with the result that the isolated yield was improved slightly (entry 5). Another side reaction that we supposed was the base-catalyzed aldol reaction of **2a**. To minimize this possibility, NHC was allowed to generate before the addition of **2a**; after a solution of triazolium salt **E** and DBU in toluene had been stirred for 30 min, **2a** was added. Surprisingly, the enantiomeric purity, but not the yield, increased up to 78% ee (entry 6). To improve both yield and enantioselectivity, the reaction temperature (entries 7−9), base (entries 7, 10−12), and solvent (entries 12−15) were surveyed. The highest enantiomeric purity of **1a** was achieved at 23 °C, although the yield needed to be improved (entry 7). Curiously, neither substrate **2a** nor distinct byproduct could be isolated throughout this survey even when **1a** was obtained in a low yield. The use of Cs_2CO_3 as a base gave the highest yield (entry 12). When the reaction was performed in the presence of Cs_2CO_3 in CH_2Cl_2 at 23 °C, (+)-**1a** was obtained in 50% yield with 78% ee (entry 15).

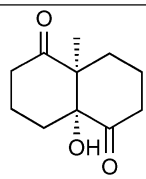
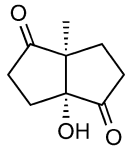
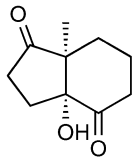
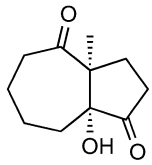
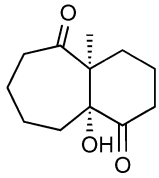
Scheme 3. Determination of Absolute Configuration of (+)-**1a**



The absolute configuration of (+)-**1a** was determined by chemical correlation as shown in Scheme 3. The chiral intermediate (+)-**4**, whose relative and absolute configurations had been established, was prepared from 2-methyl-1,3-cyclohexanedione in four steps according to the literature.[13a] Ozonolysis of (+)-**4** gave aldehyde (+)-**5**, which was converted into bicyclic compound (+)-**6** by using triazolium salt **A** in Figure 1. Deprotection of the MOM group in (+)-**6** followed by the Dess−Martin oxidation of the hydroxy group in (+)-**7** resulted in (+)-**1a** with >99% ee.

To examine the substrate scope, the reaction conditions optimized for **2a** (conditions I) were applied to **2b**−**f**. The results are summarized in Table 3. To our delight, **1b**, **1d**, and **1f** were obtained in 97, 98, and 81% ee, respectively (entries 1, 5, and 9), which indicates that the reaction conditions optimized for **2a** are suitable for the enantioselective formation of the six-membered ring. When we increased the reaction temperature to improve the yield (conditions II), we found that the enantiomeric purities of **1b** and **1f** increased (entries 2 and 10) although that of **1d** decreased slightly (entry 6). In particular, it should be noted that **1b** was obtained completely stereoselectively (>99% ee, >99% de) in a higher yield at a higher temperature. On the other hand, **1c** and **1e** were obtained in much lower enantiomeric purities under conditions I (entries 3 and 7), which indicates that in the case of the five-membered ring formation, enantioselectivity is sensitive to the size of the

Table 3. Substrate Scope of the NHC-Catalyzed Asymmetric Benzoin Cyclization of **2**[a]

entry	**2**	product **1**[b]	conditions	yield[c] (%)	ee[d] (%)
1	**2b**	 **1b**	I	24	97
2			II	67	>99
3	**2c**	 **1c**	I	32	26
4			III	90	13
5	**2d**	 **1d**	I	21	98
6			II	43	95
7	**2e**	 **1e**	I	78	~0
8			III	83	69
9	**2f**	 **1f**	I	12	81
10			II	47	86

[a] Conditions I: **2** (0.300 mmol), NHC cat. **E** (30 mol %), Cs_2CO_3 (30 mol %), CH_2Cl_2 (6 mL), 23 °C, 24 h. Conditions II: the same as conditions I except that the reaction was done under reflux. Conditions III: condition in entry 1 of Table 2 (23 °C). [b] The major enantiomer of **1** obtained under conditions I is shown, in which absolute configuration is tentatively assigned by the analogy of that of (+)-**1a**. [c] Isolated yield of **1**. [d] Determined by chiral GC (CP-cyclodextrin-β-2,3,6-M-19 column). The major enantiomer eluted second in all cases.

adjacent ring. In view of this trend, we employed catalyst **C** under the reaction conditions optimized for **2a**, which is shown in entry 1 of Table 2 (conditions III). As a result, the enantiomeric purity of **1e** showed an improvement (entry 8), whereas that of **1c** did not (entry 4).

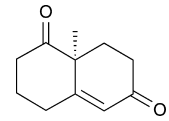


Figure 2. Wieland−Miescher ketone.

Although the aldehyde−ketone crossed benzoin reactions are unfavorable as compared with conventional aldehyde−aldehyde benzoin reactions, a quaternary stereocenter can be installed in the former case.[2b−e,3d,4,14,15] Here we have synthesized bicyclic tertiary alcohols **1** with two consecutive quaternary stereocenters via the NHC-catalyzed intramolecular crossed benzoin reactions. We expect the utility of the products **1** as chiral synthons; for example, **1b** is reminiscent of an important compound, Wieland−Miescher ketone (Figure 2), which has been used in the total synthesis of more than 50 natural products including taxol.[16] The exploitation of the synthetic utility of **1** is currently in progress.

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Supporting Information Available: Synthetic procedures, optimization of the reaction conditions for asymmetric cyclization of **2a** using NHC cat. **C**, determination of relative and absolute configurations of (+)-**1a**, and copies of NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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