Notes

Inverse Enantioselectivity with Catalyst Loading in Enantioselective Self-Benzoin Condensation using Triazolium-based *N*-Heterocyclic Carbene Catalyst

Hui Mao,[a] **Shu Lan An,**[a] **Sun Min Kim, and Jung Woon Yang**[*]

*Department of Energy Science, Sungkyunkwan University, Suwon 440-746, Korea. *E-mail: jwyang@skku.edu*
*Received October 4, 2011, Accepted October 8, 2011*

Asymmetric organocatalysis is a rapidly growing and important field of organic chemistry.[1] *N*-heterocyclic carbenes (NHCs),[2] which are Lewis base catalysts, represent a versatile class of organocatalysts that allow the addition of a variety of different electrophiles to carbonyl or Michael acceptors *via* Umpolung or Breslow intermediates. The benzoin condensation (BC) reaction is a representative example of the Umpolung process in which a NHC is used to generate an acyl anion *via* polarity reversal of aldehydes that can react with other aldehydes. Ugai and co-workers reported in 1943 that thiazolium salts, NHC precatalysts, can catalyze the self-condensation of benzaldehyde to give benzoin.[3] Later, Sheehan and Hunnenman reported the first example of an asymmetric BC reaction of benzaldehyde using a chiral thiazolium salt to yield chiral benzoin.[4] However, these reactions exhibited fairly low enantioselectivities. A highly enantioselective version of the BC reaction was accomplished by the Enders research group in 2002. This group focused on a structural variation of the catalyst through switching thiazolium salt[5] to triazolium salt as the NHC precatalyst.[6] Inspired by Enders' pioneering works, other research groups attempted to design and synthesis of a variety of chiral triazolium salts for asymmetric BC reactions.[7] However, catalytic activities of the catalysts are not sufficiently high, and generally required substoichiometric amounts (e.g., 10-20 mol %) of catalyst to attain reasonable chemical yields. Therefore, organocatalysts with enhanced activity and selectivity are of great interest. Herein, we report our findings that the catalytic activity of *cis*-2-aminoindanol-based chiral triazolium NHC salt **3c** is increased as decrease the loading amounts of catalyst, and achieved high enantioselectivity (up to 90% ee) for the asymmetric self-BC reaction of aldehydes (with only 0.25-5 mol % of catalyst loading).[8] The facts that lower catalyst loading produced significantly higher yields and enantioselectivity than higher catalyst loading are quite unusual behaviors in common catalysis.

We initially examined the efficiency of Rovis' NHC catalysts[9] **3a-c** for the reaction of 4-chlorobenzaldehyde **1d** in 1,4-dioxane [0.5 M] at room temperature (Table 1).

The catalytic activities of the *N*-mesitylated triazolium salts **3a** and *N*-phenylated triazolium salts **3b** were not sufficiently high (Table 1, entries 1-2). Gratifyingly, the electron-withdrawing *N*-pentafluorophenyl substituent on the triazolium ring **3c** significantly increased both the chemical yield and enantioselectivity (Table 1, entry 3).[7d] Encouraged by this promising result, we further optimized the reaction conditions by changing the solvent, base,

Table 1. Optimization of the reaction conditions[a]
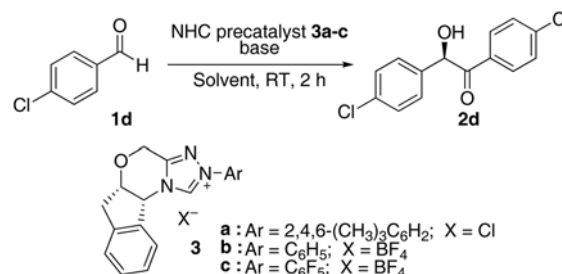
Entry	NHC salt-base (mol %)	Solvent [M]	Yield (%)[b]	Ee (%)[c]
1	**3a**-Cs$_2$CO$_3$ (10 mol %)	1,4-Dioxane [0.5]	39	20
2	**3b**-Cs$_2$CO$_3$ (10 mol %)	1,4-Dioxane [0.5]	64	38
3	**3c**-Cs$_2$CO$_3$ (10 mol %)	1,4-Dioxane [0.5]	84	79
4	**3c**-Cs$_2$CO$_3$ (5 mol %)	1,4-Dioxane [0.5]	82	83
5	**3c**-Cs$_2$CO$_3$ (10 mol %)	THF [0.5]	81	56
6	**3c**-Cs$_2$CO$_3$ (10 mol %)	Et$_2$O [0.5]	54	43
7	**3c**-Cs$_2$CO$_3$ (10 mol %)	CH$_3$CN [0.5]	53	40
8	**3c**-Cs$_2$CO$_3$ (10 mol %)	EtOAc [0.5]	70	30
9	**3c**-Et$_3$N (10 mol %)	1,4-Dioxane [0.5]	< 5	-
10	**3c**-DBU (10 mol %)	1,4-Dioxane [0.5]	30	39
11	**3c**-K$_2$CO$_3$ (10 mol %)	1,4-Dioxane [0.5]	66	54
12	**3c**-KHMDS (10 mol %)	1,4-Dioxane [0.5]	76	67
13	**3c**-Cs$_2$CO$_3$ (10 mol %)	1,4-Dioxane [1.0]	75	64
14	**3c**-Cs$_2$CO$_3$ (5 mol %)	1,4-Dioxane [1.0]	87	85

[a]General conditions: **1d** (0.5 mmol), NHC precatalyst **3a-c**/base (5-10 mol %), rt. [b]Isolated yield. [c]Determined by chiral HPLC column.

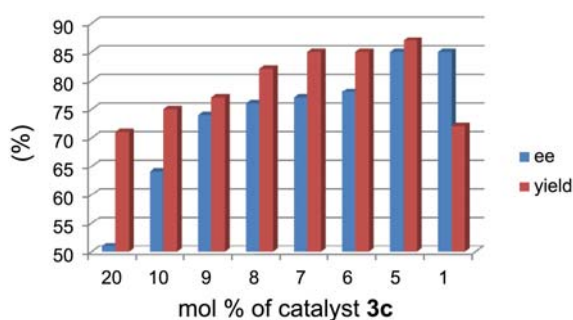[a]These authors contributed equally to this work.

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Bull. Korean Chem. Soc. **2011**, Vol. 32, No. 12   4409

Figure 1. Enantioselectivity *vs* catalyst loading in the asymmetric benzoin condensation of 4-chlorobenzaldehyde **1d**.

Table 2. Substrate scope for the enantioselective self-benzoin condensation using chiral triazolium salt **3c**[a]

a : Ar = Ph   f : Ar = 4-NC-C_6H_4
b : Ar = 2-Naphthyl g : Ar = 4-Me-C_6H_4
c : Ar = Biphenyl   h : Ar = 3-Me-C_6H_4
d : Ar = 4-Cl-C_6H_4 i : Ar = 4-^{t}Bu-C_6H_4
e : Ar = 4-F-C_6H_4 j : Ar = 3-MeO-C_6H_4

Entry	Substrate	Product	Cat. Loading (mol %)	Time (h)	Yield (%)[b]	Ee (%)[c]
1	**1a**	**2a**	5	2	86	86
2	**1a**	**2a**	0.5	12	77	88
3	**1a**[e]	**2a**	0.25	24	46	90
4	**1b**	**2b**	5	2	86	81
5	**1c**	**2c**	5	2	90	88
6	**1d**	**2d**	5	2	87	85
7	**1d**[d]	**2d**	1	6	87	86
8	**1d**	**2d**	0.5	12	86	88
9	**1e**	**2e**	5	2	96	80
10	**1f**	**2f**	5	2	59	51
11	**1g**	**2g**[f]	5	2	77	85
12	**1h**	**2h**	5	5	73	78
13	**1i**	**2i**	5	2	66	80
14	**1j**	**2j**	5	2	95	82

[a]General reaction conditions: **1a-j** (0.5 mmol), NHC precatalyst **3c**/ Cs_2CO_3 (0.025 mmol), 1,4-dioxane [0.5 mL], rt, 2 h. [b]Isolated yield. [c]Determined by chiral HPLC column. [d]The reaction was performed on a 1 mmol scale of the aldehyde. [e]The reaction was performed on a 2 mmol scale of the aldehyde. [f]The absolute configuration of **2g** was determined to be *R* by correlation of its optical rotation with literature data (in ref 5a).
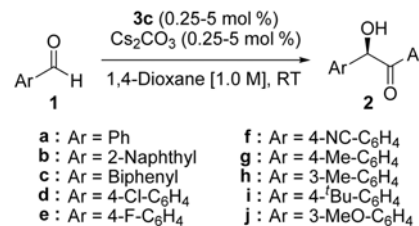
concentration and catalyst loading. Switching the solvent from 1,4-dioxane to THF, Et_2O, CH_3CN, or EtOAc did not improve the enantioselectivity (Table 1, entries 5-8). Realizing that the choice of base was critical to both reactivity and enantioselectivity, we next screened various bases in the BC reaction promoted by the triazolium salt **3c**. Only a trace amount of the desired product was observed when Et_3N was used as the base (Table 1, entry 9). In the presence of DBU, the reaction was sluggish and the enantioselectivity was low (39% ee; Table 1, entry 10). The effect of alkali-cation of the carbonate on the catalytic activity was also investigated. Cs_2CO_3 performed better than K_2CO_3 in terms of enantioselectivity (Table 1, entries 3 and 11). The use of KHMDS slightly improved the enantioselectivity (67% ee; Table 1, entry 12). The enantioselectivity was also affected by changing catalyst loading. For instance, a higher enantioselectivity (85% ee) was observed when 5 mol % catalyst was employed in 1.0 M 1,4-dioxane compared to the reaction conducted with 10 mol % catalyst (Table 1, entries 13 and 14). Taking into account organocatalyst loading, we decided to reduce the amount of NHC organocatalyst **3c** even though the enantioselectivity of the reaction under high concentration conditions was not yet satisfactory. A graph of the observed enantiomeric excess versus the amount of catalyst is shown in Figure 1.[10]

As shown in Figure 1, significantly higher enantioselectivity was obtained with lower catalyst loading, which is a quite unusual phenomenon in asymmetric catalysis.[11] For example, 51% ee was obtained at a catalyst loading of 20 mol %, while the ee value increased to 85% when 5 mol % catalyst loading was employed. Remarkably, even when the catalyst loading was reduced to 1 mol %, a comparable enantioselectivity (85%) was still achieved with a slightly lower chemical yield (72%). It is not clear why this inverse relationship between enantioselectivity and catalyst loading was observed.

The scope and generality of the self-BC reaction of a variety of aromatic aldehydes with electron-withdrawing and electron-donating substituents on the aromatic ring were investigated. The results are listed in Table 2.

In general, the reaction with most aromatic aldehydes progressed smoothly, resulting in a high yield (up to 96%) of the corresponding benzoin product with high enantio-

selectivity (up to 90% ee). An exception, to this was 4-cyanobenzaldehyde **1f**, which showed moderate chemical yield and enantioselectivity (Table 2, entry 10). Electron-deficient aldehydes gave better conversion than electron-rich aldehydes, while the level of enantioselectivity was mostly maintained, regardless of the substituent's electron-withdrawing or electron-donating properties. The position of the substituent also influenced the enantioselectivity and yield. For instance, para-substituent led to a slightly better enantioselectivity and yield compared to meta-substituent (Table 2, entries 11-12).[12] Here again, ee values increased with decreasing catalyst loading from 5 mol % to 0.5 mol % (Table 2, entries 1-2 and entries 6-8). Even though the catalyst loading was reduced to 0.25 mol %, the enantioselectivity (90% ee) was maintained with reasonable yield (Table 2, entry 3). To the best of our knowledge, this is the lowest amount of catalyst reported to be required for an asymmetric self-BC reaction.

In summary, we have developed an efficient self-BC reaction of aromatic aldehydes catalyzed by a *cis*-2-amino-indanol-based chiral triazolium catalyst. High yields of benzoin derivatives with high enantioselectivities were obtained. Remarkably, lower catalyst loading gave higher enantioselectivity.

Experimental Section

Typical procedure for self-benzoin condensation reaction of 4-chlorobenzaldehyde **1d** using *N*-heterocyclic carbene precatalyst **3c**: Anhydrous Cs_2CO_3 (0.025 mmol) was added to a suspension of 4-chlorobenzaldehyde (0.5 mmol) and triazolium salt **3c** (0.025 mmol) in 0.5 mL of dry 1,4-dioxane at room temperature. The reaction was stirred for 2 h, then quenched with distilled water, and extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexanes/ethyl acetate, 8:1 to 4:1) to self-benzoin product **2d** as a solid.

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8. Recently, Connon and co-workers reported that the triazolium-based NHC catalyst derived from pyroglutamic acid can promote self-BC reactions of aromatic aldehydes in high to excellent enantioselectivities (84-95% ee) and moderate to excellent chemical yields (41-95%) with 4-8 mol % catalyst loading. However, a long reaction time (20 h) is still required (see ref. 7d).

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10. The reaction time was fixed at 2 h compare the enantioselectivity of **2d** with different catalytic loadings (20 mol % to 1 mol %).

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12. *Ortho*-substituted aldehyde is known to be a tedious substrate for asymmetric self-BC reactions. Therefore, we investigated 2-chlorobenzaldehyde as an *ortho*-substituted aldehyde under optimal conditions. Unfortunately, we failed to isolate 2,2'-chlorobenzoin in pure form as it was rapidly converted into 2,2'-chlorobenzil during chromatographic purification.