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N-Heterocyclic Carbene-Catalyzed Enantioselective Intramolecular N-Tethered Aldehyde–Ketone Benzoin Reactions

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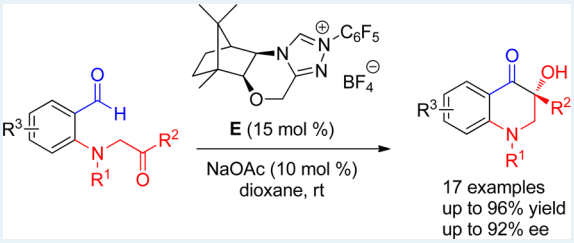
Supporting Information

ABSTRACT: The N-heterocyclic carbene-catalyzed enantioselective intramolecular benzoin reaction of N-tethered substrates was realized. With 15 mol % of D-camphor-derived triazolium salt **E** and 10 mol % of NaOAc, the aldehyde–ketone cross benzoin reactions of various substituted N-tethered substrates proceeded smoothly to afford dihydroquinolinone derivatives with a quaternary carbon stereocenter in moderate to good yields and excellent ee.



KEYWORDS: *benzoin, camphor, dihydroquinolinone, organocatalysis, N-tethered*

The chiral tetrahydroquinoline ring system is a very common structural motif in a number of biologically active natural products and pharmaceuticals (Figure 1).[1,2] Consequently,

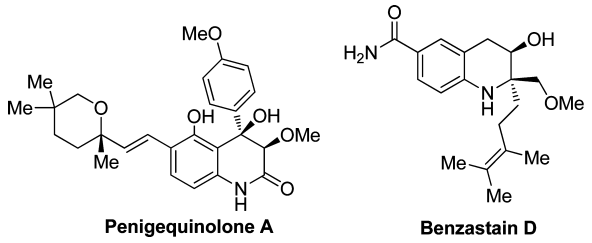


Figure 1. Selected tetrahydroquinoline-derived natural products.

the development of new methodologies for enantioselective synthesis of tetrahydroquinoline derivatives has been an intense research area. In this regard, a few methods have been documented, such as asymmetric hydrogenation of quinolines,[3] aza Diels–Alder reaction,[4] Reissert type reaction,[5] etc. As our continuing interest in NHC catalysis,[6,7] we envisaged that the NHC-catalyzed intramolecular benzoin reaction[8] of an N-tethered aldehyde–ketone[9] would generate the tetrahydroquinoline structural motif. However, the competing intramolecular aldol side reaction induced by a base poses a formidable challenge (Scheme 1). Recently, we found that the utilization of a weak base could minimize the aldol side reaction and lead to an efficient aldehyde–ketone benzoin reaction. Herein, we report our preliminary results on this subject.

Our studies began with the screening of several readily available chiral NHC precursors for the enantioselective intramolecular benzoin reaction of substrate **1a**. In the presence of D-camphor-derived NHC precursors **A**–**D** (Figure 2)[6a,10] and DIEA, only the aldol product **2a′** was observed with no desired benzoin product **2a** (entries 1–4, Table 1). To our delight,

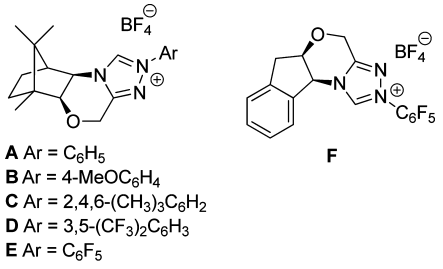


Figure 2. Several readily available chiral NHC precursors.

when the more electron-deficient D-camphor-derived NHC precursor **E** was utilized, the benzoin product **2a** was obtained with 91% ee, although the yield (25%) was moderate (entry 5, Table 1). Notably, the reaction catalyzed by the aminoindanol-derived triazolium salt **F** and DIEA only gave product **2a** in 33% yield and 10% ee (entry 6, Table 1).

With 15 mol % of the triazolium salt **E**, various reaction parameters were further examined. All the tested organic bases, including DBU, Et_3N, DIEA, gave the desired product with excellent enantioselectivity, albeit in low yields (entries 1–3, Table 2). To our great delight, when a weak base, such as NaOAc,[11] was tested, the desired product was obtained in 72% yield and 90% ee (entry 4, Table 2). Other inorganic bases, such as Cs_2CO_3, $NaHCO_3$, PhCOONa, and sodium salicylate, also gave the desired product with excellent enantioselectivity but moderate yields (entries 5–8, Table 2). Various solvents, such as CH_2Cl_2, $CHCl_3$, toluene and dioxane were tested (entries 9–12, Table 2). The reaction in dioxane led to a slightly elevated yield and ee (74% yield, 92% ee, entry 12,

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Scheme 1. Synthetic Protocol and Challenge

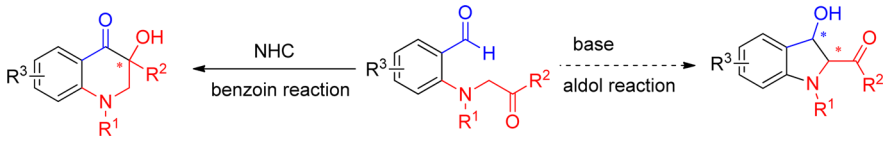
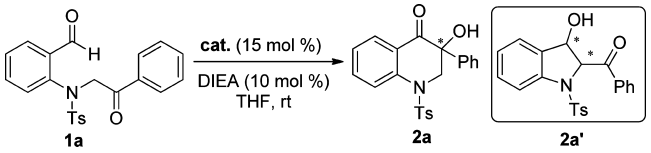


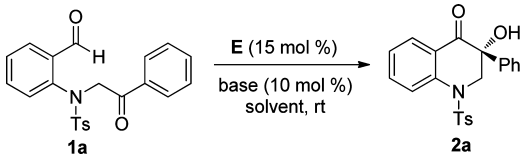
Table 1. Screening of Chiral NHC Catalysts[a]



entry	cat.	time (h)	yield (%)[b]	ee (%)[c]
1	**A**	24	–[d]	–
2	**B**	24	–[d]	–
3	**C**	24	–[d]	–
4	**D**	24	–[d]	–
5	**E**	48	25	91
6	**F**	60	33	−10

[a]Reaction conditions: **1a** (0.1 mmol), 15 mol % of cat., 10 mol % of DIEA, THF (1.0 mL), rt. [b]Yield of isolated **2a**. [c]Determined by HPLC. [d]Aldol product **2a′** was observed.

Table 2. Optimization of the Reaction Conditions[a]



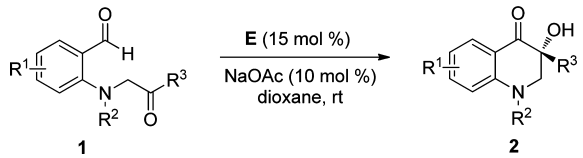
entry	base	solvent	time (h)	yield (%)[b]	ee (%)[c]
1	DBU	THF	48	8	93
2	Et_3N	THF	48	20	91
3	DIEA	THF	48	25	91
4	NaOAc	THF	48	72	90
5	Cs_2CO_3	THF	48	5	91
6	$NaHCO_3$	THF	48	26	93
7	PhCOONa	THF	48	46	88
8	Nasal	THF	48	31	89
9	NaOAc	CH_2Cl_2	48	71	76
10	NaOAc	$CHCl_3$	48	51	74
11	NaOAc	toluene	48	65	54
12	NaOAc	dioxane	12	74	92
13[d]	NaOAc	dioxane	12	71	89
14[e]	NaOAc	dioxane	2	76	90
15[f]	NaOAc	dioxane	12	78	93
16[g]	NaOAc	dioxane	12	64	93

[a]Reaction conditions: **1a** (0.1 mmol), 15 mol % of **E**, and 10 mol % of base in solvent (1.0 mL) at rt, unless noted otherwise. [b]Yield of isolated **2a**. [c]Determined by HPLC. [d]10 mol % of **E** and NaOAc. [e]15 mol % of **E** and 30 mol % of NaOAc. [f]Dioxane: 2 mL. [g]Dioxane: 4 mL. Nasal: sodium salicylate.

Table 2). Further examination of the base loadings and the substrate concentrations led to the following optimized reaction conditions: 15 mol % of **E**, 10 mol % of NaOAc, 0.05 mol/L of substrate **1a** in dioxane, rt (78% yield, 93% ee, entry 15, Table 2).

Under the above optimized conditions, various N-tethered aldehyde−ketone substrates were tested. The results are summarized in Table 3. The influence of the R^3 substituent was first

Table 3. NHC-Catalyzed Enantioselective Intramolecular Benzoin Reaction[a]



entry	R^1	R^2	R^3	product	time (h)	yield (%)[b]	ee (%)[c]
1	H	Ts	Ph	**2a**	5	76	92
2	H	Ts	4-MeC_6H_4	**2b**	32	71	90
3	H	Ts	4-$OMeC_6H_4$	**2c**	16	54	88
4	H	Ts	4-FC_6H_4	**2d**	32	65	91
5	H	Ts	4-ClC_6H_4	**2e**	32	71	91
6	H	Ts	4-BrC_6H_4	**2f**	5	65	91
7	H	Ts	3-ClC_6H_4	**2g**	5	55	92
8	H	Ts	2-naphthyl	**2h**	15	61	90
9	H	Ts	cyclopropyl	**2i**	5	96	68
10[d]	H	Ts	*t*-Bu	**2j**	24	NR	
11	5-F	Ts	Ph	**2k**	40	76	88
12	5-Cl	Ts	Ph	**2l**	2	82	92
13	5-Br	Ts	Ph	**2m**	15	82	87
14	4-Cl	Ts	Ph	**2n**	10	80	92
15	5-Me	Ts	Ph	**2o**	40	66	82
16	5-OMe	Ts	Ph	**2p**	120	51	84
17[e]	H	Ms	Ph	**2q**	4	85	85

[a]Reaction conditions: **1** (0.2 mmol), 15 mol % of **E**, and 10 mol % of NaOAc in dioxane (4.0 mL) at rt, unless noted otherwise. [b]Yield of isolated **2**. [c]Determined by HPLC. [d]Starting material was recovered with 88% yield. [e]Dioxane (2.0 mL) was used.

investigated. Either electron-withdrawing or -donating substituents (4-Me, 4-OMe, 4-F, 4-Cl, 4-Br, 3-Cl) on the phenyl group could be well tolerated, affording their desired products in moderate to good yields and excellent ee (54−76% yields, 88−92% ee, entries 1−7, Table 3). The 2-naphthyl bearing substrate also led to product **2h** in 61% yield and 90% ee (entry 8, Table 3). When a cyclopropyl substituent was introduced, the reaction ran smoothly, affording the product **2i** in 96% yield and 68% ee (entry 9, Table 3). The *t*-butyl group containing substrate **1j** gave no product (entry 10, Table 3).

The influence of the substituent of R^1 was also investigated. When the electron-withdrawing groups, such as F, Cl, and Br, were introduced, the reaction proceeded smoothly in good yields and excellent enantioselectivity (76−82% yields, 87−92% ee, entries 11−14, Table 3), although the electron-donating groups, such as Me and OMe, required a longer reaction time and gave slightly lower enantioselectivity (82−84% ee, entries 15−16, Table 3). The reaction with the *N*-Ms-linked substrate **1q** underwent the benzoin reaction to give product **2q** in 85% yield and 85% ee (entry 17, Table 3). The absolute configuration of the product was determined by an X-ray crystallographic analysis of a crystal of enantiopure **2m** as *R*.[12]

In summary, we have developed an enantioselective N-heterocyclic carbene-catalyzed intramolecular aldehyde−ketone

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benzoin reaction with N-tethered substrates. Various substituted dihydroquinolinone derivatives were obtained with a quaternary carbon stereocenter in moderate to good yields and excellent ee. The mild reaction conditions utilizing a weak base NaOAc are critical for minimizing the aldol side reaction.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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