

N-Heterocyclic Carbene Catalyzed Enantioselective Annulation of Benzothiazolyl Ethyl Acetates with 2-Bromoaldehydes

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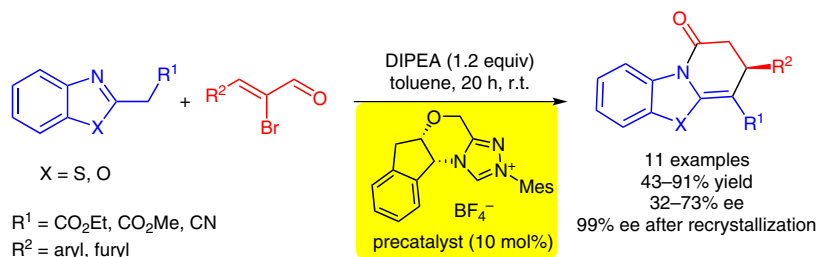
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Abstract An N-heterocyclic carbene catalyzed enantioselective [3+3] annulation of benzothiazolyl acetates with 2-bromoaldehydes has been developed. The protocol provides a direct asymmetric synthesis of dihydro-1H-benzothiazolopyridinones in good to very good yields and medium ee values. In many cases, the virtually enantiopure heterocycles are available through a single recrystallization (99% ee).

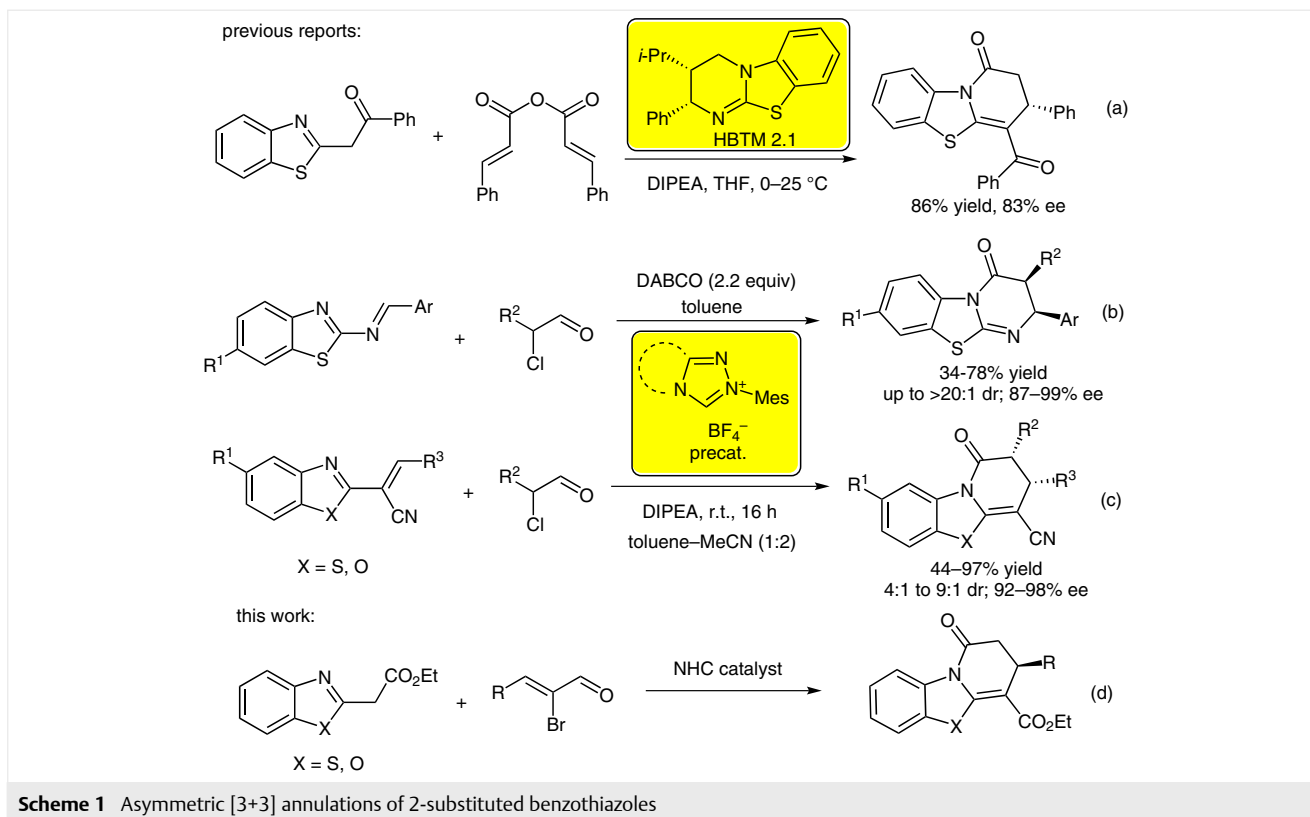
Key words asymmetric synthesis, N-heterocyclic carbene, organocatalysis, annulation, dihydrobenzothiazolopyridinones

Since the seminal reports by the groups of Glorius and Bode in 2004¹ much attention has been paid to develop novel N-heterocyclic carbene (NHC)-catalyzed cyclization/annulation methods.² Especially NHC-based α,β -unsaturated acylazolium intermediates turned out to be excellent electrophiles,³ which could undergo stepwise Michael-acylation or sigmatropic rearrangement-acylation reactions with a variety of dinucleophiles such as 1,3-diketones,⁴ enamines,⁵ naphthols,⁶ or enolizable aldehydes.⁷ Recently, the Ye group reported a [3+3] cyclocondensation of bromoaldehydes with ketimines in the asymmetric synthesis of dihydropyridinones.⁸ Very recently our group developed NHC-catalyzed enantioselective annulations of indolin-3-ones with 2-bromoaldehydes to form dihydropyranoindolones.⁹ In view of the importance of such heterocycles as potentially bioactive compounds the research for further suitable nucleophiles in these annulation protocols is highly desirable.

The dihydro-1H-benzothiazolopyridine core is present in various biologically active natural products and has found widespread applications in numerous pharmaceuticals, such as antitumor¹⁰ and antibacterial drugs.¹¹ However,

only a few asymmetric syntheses have been investigated. In 2013 Smith and co-workers reported an asymmetric annulation of benzothiazolyl ketones with α,β -unsaturated anhydrides catalyzed by the isothiourea HBTM 2.1 (Scheme 1, a).¹² Very recently, we reported a Mannich-lactamization domino reaction of N-(benzothiazolyl)imines with 2-chloroaldehydes for the synthesis of benzothiazolo-pyrimidinones (Scheme 1, b)¹³, followed by an extended work on 1-azadiene-Diels-Alder reactions of styrylbenzo[d]thiazoles with α -chloroaldehydes (Scheme 1, c).¹⁴ Herein, we report the asymmetric synthesis of dihydro-1H-benzothiazolopyridine-2-ones via the formal [3+3] annulation reaction of 2-bromoaldehydes with 2-substituted benzo[d]thiazoles (Scheme 1, d).

Initially, we performed the model reaction of 2-(benzothiazol-2-yl) ethyl acetate (**1a**) with 2-bromocinnamaldehyde (**2a**) at room temperature in toluene in the presence of *N,N*-diisopropyl ethylamine (DIPEA) and 10 mol% of the triazolium pre-catalyst **A**, which proceeded smoothly and gave a 45% yield of the product **3a** (Table 1, entry 1). Chiral triazolium salts **B–F** were also screened and a good yield of 83% and an enantiomeric excess of 80% were obtained with the triazolium salt **C** (Table 1, entry 3). Next we screened a series of bases, however, organic bases such as DABCO, TMEDA, TBD, or DBU and inorganic bases such as K_3PO_4 and K_2CO_3 gave inferior results (Table 1, entries 7–12). We then tested a series of solvents in the presence of pre-catalyst **C** and DIPEA at room temperature. Unfortunately, no improvement was obtained (Table 1, entries 13–17), even with the mixed solvents of toluene–THF (Table 1, entry 18) and toluene–MeCN (Table 1, entry 19). Inspired by recent reports on the NHC–Lewis acid strategy¹⁵ we examined some Lewis acids as additives in our protocol. The strong Lewis acid $Sc(OTf)_3$ lowered the reactivity and enantioselectivity (Table 1, entry 20), and the use of the weak Lewis acid LiCl even inversed the asymmetric induction (Table 1, entry 21).



Finally, we lowered the reaction temperature, however, no further improvement on enantioselectivity was obtained at 5 °C (Table 1, entry 22) and –20 °C (Table 1, entry 23).

We then amplified the scale of the model reaction to 0.5 mmol, which afforded **3a** in 77% yield and 65% ee.¹⁶ Fortunately, a single recrystallization allowed to access the virtually enantiopure product (99% ee, Table 2, entry 1). Next we investigated the substrate scope of this protocol by variation of the 2-substituted benzo[d]thiazole component **1**. A methyl ester and a cyano group as R¹ gave the desired adducts in good to excellent yields and moderate ee values (Table 2, entries 2 and 3). Gratifyingly, 2-(benzoxazol-2-yl)acetonitrile underwent the transformation smoothly and furnished the desired [3+3] annulation product in moderate yield and ee (Table 2, entry 4). Furthermore, various electron-donating and electron-withdrawing groups, as well as *ortho* substituents attached to the aryl group of the bromoenals (R²) were well tolerated, leading to the desired products in good yields and moderate enantiomeric excess (Table 2, entries 5–10). Notably, several products could be obtained as virtually enantiopure compounds (99% ee) after a single recrystallization. Additionally, a heterocyclic 2-furyl substituent R² can be used resulting in a 77% yield and 58% ee (Table 2, entry 11).

The absolute configuration was unambiguously determined to be *S* by X-ray crystal-structure analysis of the methyl acetate **3b** (Figure 1).¹⁷

A plausible reaction mechanism for this NHC-catalyzed formal [3+3] annulation is shown in Scheme 2. The addition of the NHC **C'** to the 2-bromoenal **2** leads to the Breslow intermediate **I**, also drawn as its mesomeric zwitterionic form. After tautomerization to **II**, the subsequent loss of bromide generates the α,β -unsaturated acylazolium key intermediate **III**. The base-mediated Michael addition of the benzothiazolyl ethyl acetates **1** affords the adduct **IV**, followed by proton transfer and lactamization via **V** to furnish the final product **3** and to return the NHC catalyst.

In summary, we have developed a novel NHC-catalyzed asymmetric annulation of 2-(benzothiazol-2-yl) acetates with 2-bromoaldehydes. The protocol tolerates quite a range of substrates including a benzoxazolyl acetonitrile and give

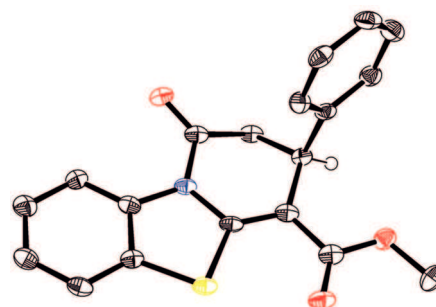
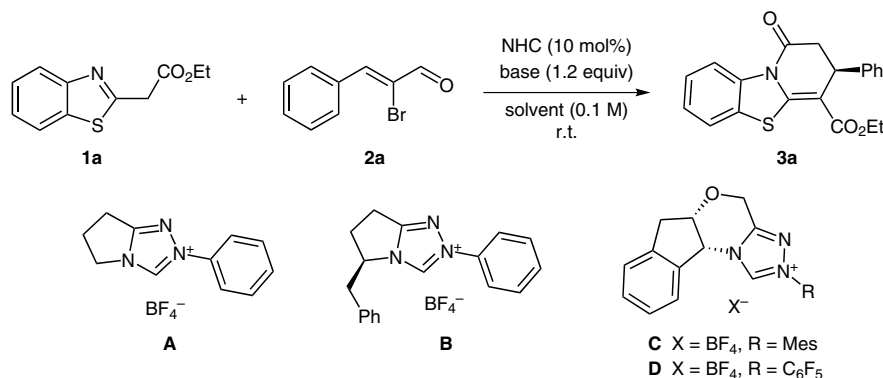


Figure 1 Absolute configuration [X-ray, $x_{\text{abs}} = 0.078$ (32)] of **3b**

Table 1 Optimization of the Reaction Conditions^a

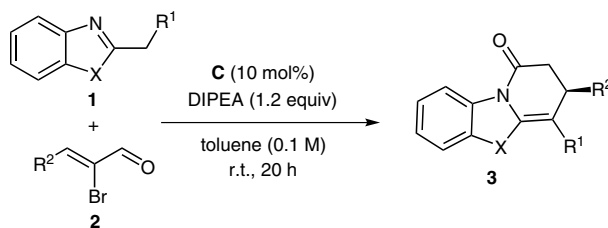
Entry	NHC	Solvent	Base	Additive	Yield (%) ^b	ee (%) ^c
1	A	toluene	DIPEA	–	45	–
2	B	toluene	DIPEA	–	29	–26
3	C	toluene	DIPEA	–	83	80
4	D	toluene	DIPEA	–	61	75
5	E	toluene	DIPEA	–	71	1
6	F	toluene	DIPEA	–	n.r.	–
7	C	toluene	DABCO	–	66	79
8	C	toluene	TMEDA	–	86	68
9	C	toluene	TBD ^d	–	trace	–
10	C	toluene	DBU	–	23	–22
11	C	toluene	K ₃ PO ₄	–	20	63
12	C	toluene	K ₂ CO ₃	–	9	68
13	C	MeCN	DIPEA	–	80	73
14	C	CH ₂ Cl ₂	DIPEA	–	80	32
15	C	THF	DIPEA	–	26	41
16	C	MTBE	DIPEA	–	57	73
17	C	mesitylene	DIPEA	–	46	82
18	C	toluene–THF (10:1)	DIPEA	–	70	79
19	C	toluene–MeCN (10:1)	DIPEA	–	82	69
20	C	toluene	DIPEA	Sc(OTf) ₃	29	66
21	C	toluene	DIPEA	LiCl (1 equiv)	29	–18
22 ^e	C	toluene	DIPEA	–	76	76
23 ^f	C	toluene	DIPEA	–	76	77

^a Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), precatalyst (0.02 mmol), base (0.24 mmol), solvent (2 mL), r.t., under argon, 20 h.^b Yield of isolated product **3a** after column chromatography.^c The ee was determined by HPLC on a chiral stationary phase.^d TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene.^e Performed at 5 °C for 4 d.^f Performed at –20 °C for 4 d.

rise to the corresponding dihydro-1*H*-benzothiazolopyridinones in moderate to very good yields and medium ee values. However, in several cases virtually enantiopure products (99% ee) could be obtained via a single recrystallization.

Acknowledgment

We thank the European Research Council (ERC Advanced Grant 320493 ‘DOMINOCAT’) for financial support. Q.N. and X.S. are grateful to the China Scholarship Council for a fellowship.

Table 2 Substrate Scope^a

Entry	3	R ¹	R ²	X	Yield (%) ^b	ee (%) ^{c,d}
1	3a	CO ₂ Et	Ph	S	77	65 (99)
2	3b	CO ₂ Me	Ph	S	91	64
3	3c	CN	Ph	S	74	32
4	3d	CN	Ph	O	43	55
5	3e	CO ₂ Et	4-MeC ₆ H ₄	S	64	68
6	3f	CO ₂ Et	4-MeOC ₆ H ₄	S	69	62 (99)
7	3g	CO ₂ Et	2-MeO-5-BrC ₆ H ₃	S	80	65 (92)
8	3h	CO ₂ Et	2-MeOC ₆ H ₄	S	86	66 (99)
9	3i	CO ₂ Et	4-ClC ₆ H ₄	S	72	73
10	3j	CO ₂ Et	4-BrC ₆ H ₄	S	83	70 (99)
11	3k	CO ₂ Et	2-furyl	S	77	58

^a Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), precatalyst **C** (0.05 mmol), DIPEA (0.6 mmol), toluene (5 mL), r.t., under argon, 20 h.

^b Yield of isolated product **3** after column chromatography.

^c The ee was determined by HPLC on a chiral stationary phase.

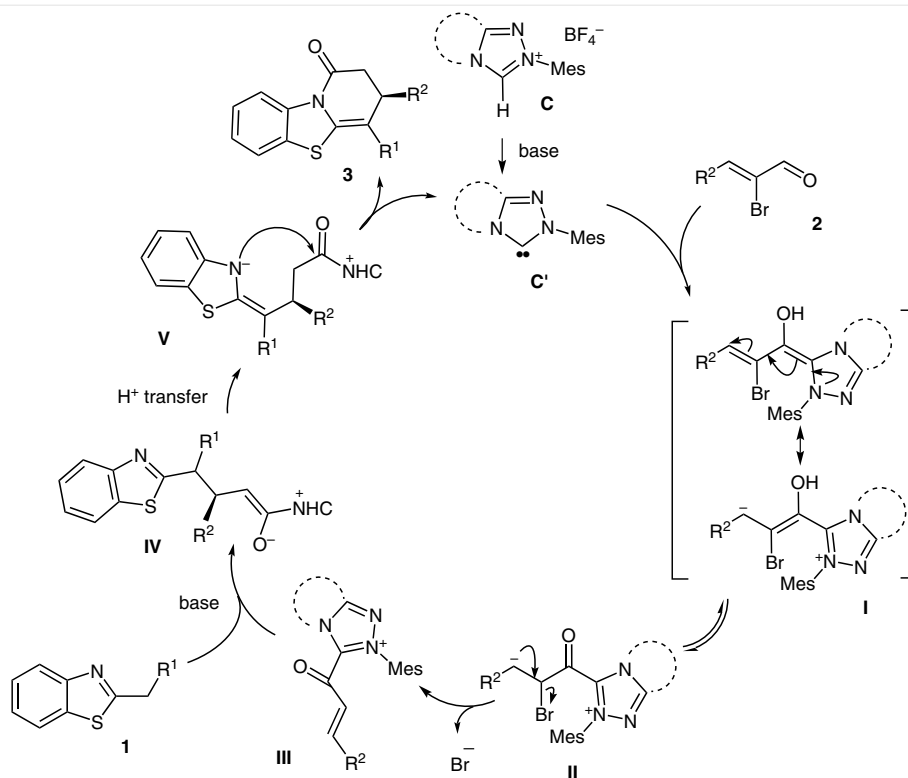
^d The value in parentheses refers to the ee after recrystallization.

Supporting Information

Supporting information for this article is available online at <http://dx.doi.org/10.1055/s-0034-1381004>.

References and Notes

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Scheme 2 Proposed reaction pathway

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- (16) **General Procedure for the Synthesis of Dihydro-1H-benzothiazolopyridinones 3a-k**

To an oven-dried and argon-filled Schlenk tube was added 2-substituted benzo[d]thiazole component **1** (0.5 mmol), 2-bromoaldehyde **2** (0.75 mmol, 1.5 equiv), triazolium salt **C** (0.05 mmol, 10 mol%), and DIPEA (0.6 mmol, 1.2 equiv) in toluene (5 mL). The mixture was stirred at r.t. and monitored by TLC until completion of the reaction. The residue was purified by flash chromatography on silica gel [*n*-pentane–Et₂O (10:1) or *n*-pentane–CH₂Cl₂ (1:1 to 1:2)] to afford the products **3a–k** as orange or yellow solids.

Ethyl (S)-1-Oxo-3-phenyl-2,3-dihydro-1H-benzo[4,5]thiazolo[3,2-a]pyridine-4-carboxylate (3a)

Yield: 135.6 mg (77%), mp 125–127 °C. The ee (65%, 99% after recrystallization) was measured by HPLC using a chiral stationary phase [Daicel IC, *n*-heptane–EtOH = 7:3, 0.7 mL/min], *t_R* = 4.53 min (major), 5.35 min (minor). [α]_D²³ = +236.9 (c 1.0, CHCl₃). ¹H NMR (600 MHz, CDCl₃): δ = 8.44 (d, *J* = 8.4 Hz, 1 H), 7.45 (dd, *J* = 7.2, 1.2 Hz, 1 H), 7.30–7.18 (m, 7 H), 4.33–4.32 (m, 1 H), 4.28–4.16 (m, 2 H), 3.24 (dd, *J* = 16.2, 8.4 Hz, 1 H), 3.02 (dd, *J* = 16.2, 1.8 Hz, 1 H), 1.23 (t, *J* = 7.2 Hz, 3 H). ¹³C NMR (150 MHz, CDCl₃): δ = 168.2, 166.6, 152.3, 141.4, 136.8, 128.9 (2 C), 127.2, 127.0, 126.5 (2 C), 126.5, 125.5, 121.4, 117.4, 100.4, 60.7, 40.1, 36.8, 14.3. MS (EI, 70 eV): *m/z* (%) = 351 (100) [M⁺], 322 (36), 278 (40), 249 (44), 236 (71), 115 (19), 77 (17). IR (ATR): 3851, 3613, 3401, 3060, 2980, 2921, 2645, 2325, 2037, 1903, 1803, 1707, 1660, 1556, 1455, 1359, 1305, 1263, 1194, 1146, 1106, 1034, 939, 906, 853, 795, 748, 697 cm^{−1}. ESI-HRMS: *m/z* calcd for C₂₀H₁₇NO₃S [M]⁺: 351.0924; found: 351.0933.

- (17) CCDC 1056458 contains the supplementary crystallographic data for the compound **3b** reported in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.