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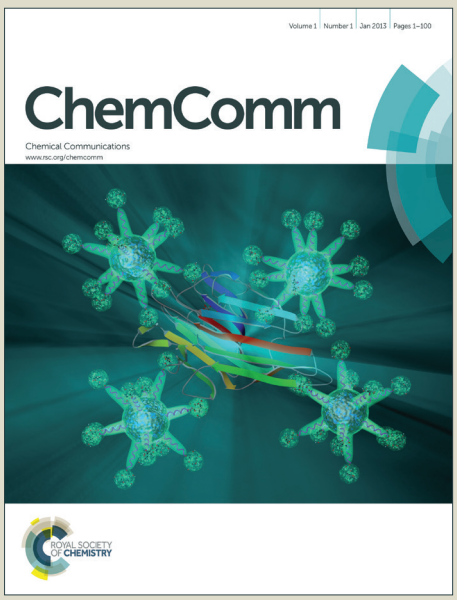

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Regio- and stereoselective synthesis of benzothiazolo-pyrimidinones *via* an NHC-catalyzed Mannich/lactamization domino reaction

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An NHC-catalyzed regio- and stereoselective Mannich/lactamization domino reaction of N-(benzothiazolyl)imines with α-chloroaldehydes has been developed. This new protocol provides a facile approach for the asymmetric synthesis of benzothiazolo-pyrimidinones and a pyrrolo[1,2-*a*]indolone in moderate to good yields (34-78%) and excellent stereoselectivities (87-99% ee, up to >20:1 d.r.).

The tricyclic pyrimido[2,1-*b*]benzothiazole core prevails in a wide range of bioactive molecules with remarkable biological properties,[1] such as the inhibition of *c*-AMP phosphodiesterase, antineoplastic and antimalarial activity. Moreover, the isothiourea-based HBTM is used as an efficient organocatalyst and received great attention in the field of asymmetric catalysis (Figure 1).[2] Although various approaches for the synthesis of the pyrimido[2,1-*b*]benzothiazole motif have been developed, most of them are non-stereoselective and/or need relatively harsh conditions.[3]

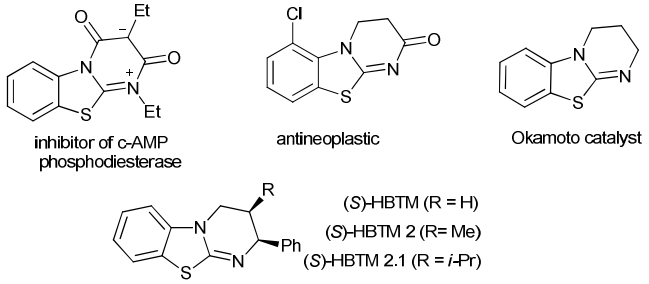
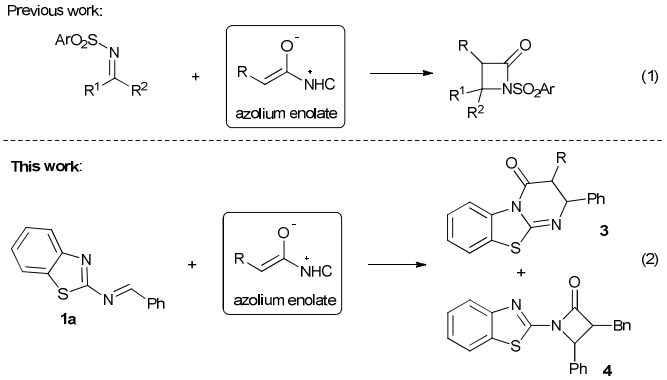


Figure 1 Examples of pyrimido[2,1-*b*]benzothiazole derivatives.

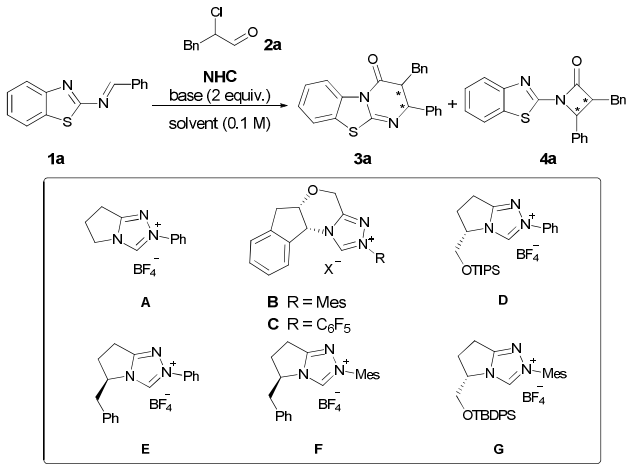
In the past decade, great advances have been achieved in the development of N-heterocyclic carbene (NHC) catalyzed organocatalytic reactions *via* the umpolung of aldehydes.[4] Especially since the seminal works concerning the NHC-catalyzed conjugate umpolung reactions reported by the groups of Glorius and Bode in 2004,[5] NHC organocatalysis has been extended for the activation of the β-carbon (homoenolate intermediate) and α-carbon (enolate intermediate) of enals. These two kinds of intermediates used as nucleophiles reacted with a variety of reactive electrophiles to afford heterocyclic compounds such as lactones, lactams or cyclopentenes.[6] It is noteworthy that aldimines behaved as excellent electrophiles in the reactions of enolate intermediates, providing the corresponding β-lactams (Scheme1, eq 1). Smith *et al.*[7] and Ye *et al.*[8] reported NHC-catalyzed [2+2] cycloadditions of ketenes with N-tosyl imines and N-Boc imines, respectively. Very recently, the Ye group was able to carry out Staudinger reactions of ketenes with isatin-derived ketimines, yielding spirocyclic oxindolo-β-lactams.[9] We envisioned that 2-benzothiazolimine **1a** in combination with an azolium enolate could not only produce the β-lactam **4**, but also provide access to the benzothiazolo-pyrimidinone **3** through a formal [4+2] annulation (Scheme 1, eq 2). Obviously, influencing the regioselectivity of the reaction site of the intermediate ambident anions is the greatest challenge in order to improve the ratio of **3**/**4** in this Mannich/lactamization domino reaction.



Scheme 1 Reactions of imines with NHC-bound enolate intermediates.

To test our hypothesis, we initially checked several triazolium precatalysts **A-C** in the model reaction of 2-benzothiazolimine **1a** with 2-chloro-3-phenylpropanal (**2a**) at room temperature. We found that the chiral triazolium salt **B** resulted in an excellent stereoselectivity for *ent*-**3a** (97% ee, >20:1 d.r.), albeit with a low yield (19%) and regioselectivity (Table 1, entry 2). Attempting to improve the regioselectivity and the yield of *ent*-**3a**, we next tested a

Table 1 Optimization of the reaction conditions[a]



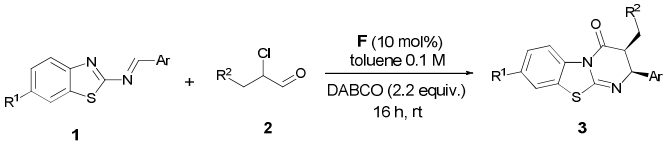
Entry	NHC	Base	Solvent	Yield of **3a** (%)[b]	**3a**/**4a**[c]	dr (**3a**)[d]	ee of **3a** (%)[e]
1	**A**	NEt_3	toluene	43	>20:1	1.3:1	-
2	**B**	NEt_3	toluene	19	1:1.6	>20:1	-97
3	**C**	NEt_3	toluene	-	-	-	-
4	**B**	DIPEA	toluene	30	1.4:1	>20:1	-99
5	**B**	TMEDA	toluene	23	1:1.7	>20:1	-98
6	**B**	DABCO	toluene	31	1:1.6	>20:1	-94
7	**B**	DBU	toluene	-	-	-	-
8	**B**	K_2CO_3	toluene	15	1:1.2	>20:1	-97
9	**B**	NaOAc	toluene	-	-	-	-
10	**B**	DABCO	THF	24	1:1.3	>20:1	-99
11	**B**	DABCO	DCM	22	1:1.4	>20:1	-98
12	**B**	DABCO	EtOAc	30	1:1.2	>20:1	-99
13	**B**	DABCO	PhCl	14	1:1.7	>20:1	-98
14	**B**	DABCO	dioxane	22	1:1.9	>20:1	-97
15	**D**	DABCO	toluene	27	>20:1	>20:1	-90
16	**E**	DABCO	toluene	58	>20:1	>20:1	90
17	**F**	DABCO	toluene	65	7.2:1	>20:1	97
18	**G**	DABCO	toluene	54	>20:1	>20:1	-92
19[f]	**F**	DABCO	toluene	69	14:1	>20:1	93

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), NHC (0.01 mmol), base (0.22 mmol), solvent (1 mL), rt, 16 h. [b] Yields of isolated **3a** after flash column chromatography. [c] Ratio based on isolated yields. [d] Determined by ^{1}H NMR. [e] The ee value was determined by HPLC on a chiral stationary phase. [f] Addition of 4 Å MS. DIPEA = *N*,*N*-diisopropylethylamine, TMEDA = tetramethylethylenediamine, DABCO = 1,4-diazabicyclo[2.2.2]octane, DBU = 1,8-diazabicyclo-[5.4.0]un-dec-7-ene, Mes = 2,4,6-trimethylphenyl, TBDPS = *tert*-butyldiphenylsilyl, TIPS = triisopropylsilyl.

series of bases, but no satisfying improvement was achieved (Table 1, entries 4-9). Solvent screening led to no improvement in yield and selectivity (Table 1, entries 10-14). After the screening of the base and solvent, DABCO in combination with toluene turned out to give the highest yield of *ent*-**3a** (31%), maintaining the excellent stereoselectivity and the low regioselectivity as well (Table 1, entry 6). Notably, the triazolium salt **A** provided *rac*-**3a** in 43% yield exclusively, even though with a drastically decreased d.r. (Table 1, entry 1). Therefore we further screened a series of pyrrolidinone-derived triazolium salts **D-G**. To our delight, a dramatic improvement in both yield and regioselectivity was obtained (Table 1, entries 15-18). The NHC-catalyzed reaction based on the triazolium salt **F** afforded the cycloadduct **3a** in a better yield but with relatively low regioselectivity (Table 1, entry 17). After using 4 Å MS as an additive, the yield (69%) and regioselectivity (14:1) improved further, but the enantioselectivity (93% ee) decreased slightly (Table 1, entry 19).

Next we investigated the substrate scope of this protocol on a 0.5 mmol scale. As shown in Table 2, a wide range of 2-benzothiazolimines **1** with diverse electronic and steric properties were first explored. The use of 2-benzothiazolimines **1a** conducted the desired **3a** in 63% yield with >20:1 d.r. and 90% ee (Table 2, **3a**). Electron-donating substituents such as 4-Me and 4-OMe on the Ar group reduced the electrophilicity of the imine carbon, which led to lower yields and even of the diasteroselectivity in **3c** (Table 2, **3b**,**c**). In the case of electron-withdrawing groups such as 4-Br, 4-Cl and 2-Cl, the reactions gave the desired cycloadducts **3d-f** in good yields and with good to excellent diastereo- and enantioselectivities. The introduction of a heterocyclic furyl group on the Ar position gave compatible results, affording the corresponding product **3g** in 69% yield, 11:1 d.r. and 93% ee under elevated temperature. Several electron-donating and electron-withdrawing substituents as R^1 were also investigated, yielding the cycloadducts **3h-k** in good yields and excellent stereoselectivities. We then varied the α-chloroaldehyde moiety. An aliphatic linear α-chloroaldehyde reacted smoothly with a slight loss of yield and with a reasonable ee value (Table 2, **3l**). When a *para*-nitrophenyl group instead of Ph as R^2 was used, a better result in terms of yield and ee was obtained(Table 2, **3m**).

Table 2 Substrate scope[a]



3	R^1	Ar	R^2	Yield (%)[b]	dr[c]	ee(%)[d]
a	H	Ph	Ph	63	>20:1	90
b[e]	H	4-MePh	Ph	49	>20:1	99
c[f]	H	4-MeOPh	Ph	34	4:1	87
d	H	4-BrPh	Ph	56	11:1	91
e	H	4-ClPh	Ph	61	11:1	89
f	H	2-ClPh	Ph	60	>20:1	97
g[f]	H	2-Furyl	Ph	69	11:1	93
h[e]	Me	Ph	Ph	64	20:1	93
i[g]	MeO	Ph	Ph	56	>20:1	92
j	Cl	Ph	Ph	78	10:1	91
k	F	Ph	Ph	71	17:1	89
l	H	Ph	n-Propyl	51	17:1	87
m	H	Ph	4-$NO_2C_6H_4$	69	13:1	92

[a] Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), **F** (0.05 mmol), DABCO (1.1 mmol), toluene (5 mL), 4 Å MS, rt, 16 h. [b] Yield of isolated **3** after flash column chromatography. [c] Determined by ^{1}H NMR. [d] The ee value was determined by HPLC on a chiral stationary phase. [e] The reaction time is 24 h. [f] Performed at 40 °C. [g] The reaction time is 48 h.

The relative configuration of the major diastereomer **3a** was determined by NOE measurements (see SI), which is in accordance with the absolute configuration of compound **3e** determined by X-ray crystal structure analysis (Figure 2).[10]

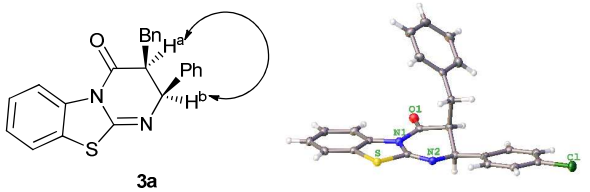
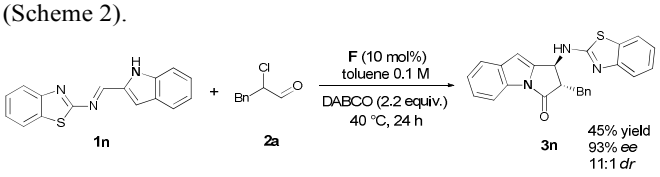


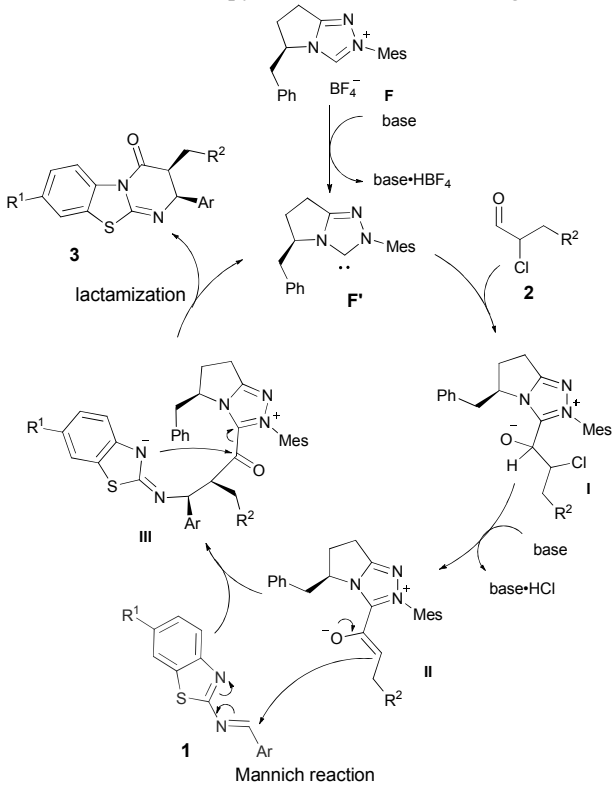
Figure 2 Determination of the relative configuration by NOE (**3a**) and of the absolute configuration by X-ray crystal structure analysis (**3e**).

We then tried to extend the substrate scope by employing a 2-indolyl group on the Ar position. In this case, after the Mannich reaction, there are three nucleophilic N-sites for the subsequent lactamization. Interestingly, only the *trans*-pyrrolo[1,2-*a*]indolone **3n** was obtained *via* cyclization of the indole N-anion with the acylazolium intermediate with acceptable yield (45%) and excellent stereoselectivity (93% ee, 11:1 d.r.) (Scheme 2).



Scheme 2 Asymmetric synthesis of **3n** *via* an NHC-catalyzed [2+3] annulation.

With the substrate scope and stereochemical outcome in hand, we propose a plausible catalytic cycle *via* a stepwise reaction sequence. As shown in Scheme 3, the nucleophilic addition of the NHC to the α-chloroaldehyde gives rise to the intermediate **I**, followed by base assisted HCl-elimination to provide the enolate species **II**. This azolium-enolate then reacts on its *Re*-face with the 2-benzothiazolimine **1** *via* a Mannich reaction to afford the adducts **III** with *cis* selectivity. Finally, the benzothiazole N-anion then cyclizes with the acylazolium intermediate liberating the NHC catalyst and producing the desired benzothiazolopyrimidinone **3** in *cis* configuration.



Scheme 3 Proposed mechanism of the reaction.

In conclusion, we have developed an asymmetric NHC-organocatalyzed annulation of 2-benzothiazolimines with α-chloroaldehydes, producing the desired benzothiazolo-pyrimidinones in moderate to good yields with excellent regio- and stereoselectivities. Particularly noteworthy is the reaction of the indolyl-bound 2-benzothiazolimine with 2-chloro-3-phenylpropanal. This version of the protocol leads to a pyrrolo[1,2-*a*]indolone with high regioselectivity and excellent stereoselectivity. Further applications of this protocol on the scope and application are ongoing in our laboratory.

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Notes and references

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10. CCDC 1029497 contains the supplementary crystallographic data for the compound **3e** 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.

