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Asymmetric Brønsted acid catalyzed carbonyl activation – organocatalytic domino electrocyclization–halogenation reaction†

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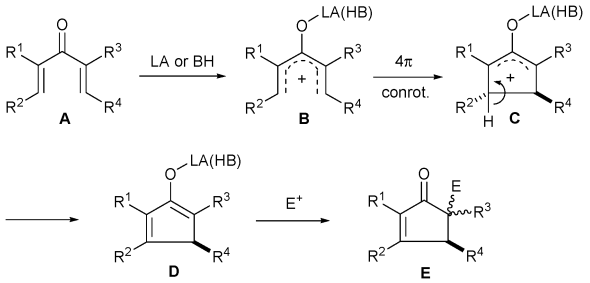
A highly efficient Brønsted acid catalyzed enantioselective Nazarov cyclization–bromination reaction has been developed. The protocol gives access to highly functionalized *trans*-4,5-substituted 5-bromocyclopentenone derivatives in good yields and with excellent enantioselectivities.

The Nazarov reaction has been established as a powerful method for the construction of five membered rings, being widely used for the rapid assembly of cyclopent-2-enone cores.[1] In addition to its utility in the synthesis of various natural products, the Nazarov cyclization has also found widespread application in more complex domino, cascade and sequential reactions. In this regard, two different approaches which take advantage of the intermediates formed at different stages in the classical Nazarov cyclization have been developed: (i) trapping of the carbocation intermediate **C** with different carbon- or heteroatom-based nucleophiles[2,3] or (ii) trapping of enolate **D** formed at a later stage with various electrophiles other than protons (Scheme 1).[4–8] The efficient integration of the Nazarov cyclization into complex domino reactions has significantly broadened the application scope of this transformation. Considerable progress has been made in the field of interrupted Nazarov reactions with nucleophiles. These offer access to valuable polycyclic structures.[2] Regarding the alternative way of functionalization which implies trapping of the enolate with an electrophile, highly diastereoselective Nazarov cyclization/Michael addition[4] and Nazarov cyclization/halogenation[6,7] reactions have been developed. However, examples of enantioselective domino or sequential processes are scarce.[5,9]

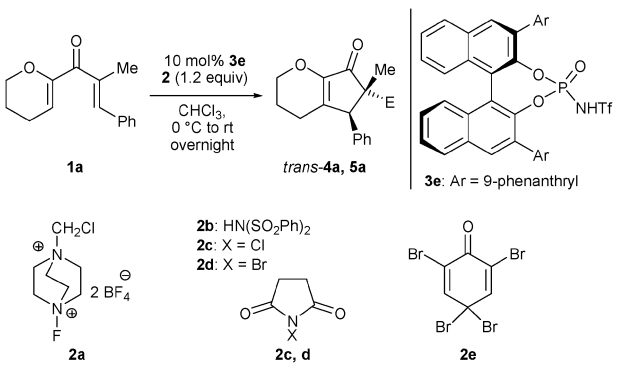


Scheme 1 Nazarov cyclization with subsequent electrophilic trapping.

Based on our experience in the field of Brønsted acid catalyzed enantioselective reactions with carbonyl substrates,[10,11] and inspired by the enzymatic halohydration of soybean peroxidase[12] we decided to investigate an asymmetric Nazarov cyclization/halogenation domino reaction as this would provide access to synthetically useful functionalized cyclopentenones. Recently, we reported an efficient methodology for the Nazarov cyclization of activated dienones which gives access to 4,5-disubstituted cyclopent-2-enones in good yields and with excellent enantioselectivities.[13,14]

However, in order to develop a generally applicable Nazarov cyclization/halogenation protocol, different electrophiles **2a–e** and a wide range of *N*-triflylphosphoramides[15,16] **3a–h** had to be evaluated under different reaction conditions (Tables 1 and 2).

Table 1 Evaluation of different electrophilic halogenating reagents



Entry[a]	Electrophile **2** (E^+)	Product	Yield[b] (%)	ee[c,d] (%)
1	Selectfluor **2a**	—	—	—
2	NFSI **2b**	—	—	—
3	*N*-Chlorosuccinimide **2c**	**4a**	15	47
4	*N*-Bromosuccinimide **2d**	**5a**	16	92
5	TBCHD **2e**	**5a**	44	86

[a] Reactions were performed with dienone **1** and electrophiles **2a–e** (1.2 equiv.) in the presence of **3e** (10 mol%) in $CHCl_3$ at 0 °C to room temperature for overnight. [b] Yield of the isolated major diastereomer (*trans*). [c] Enantiomeric excess for the isolated major diastereomer (*trans*). [d] Determined by chiral HPLC analysis.

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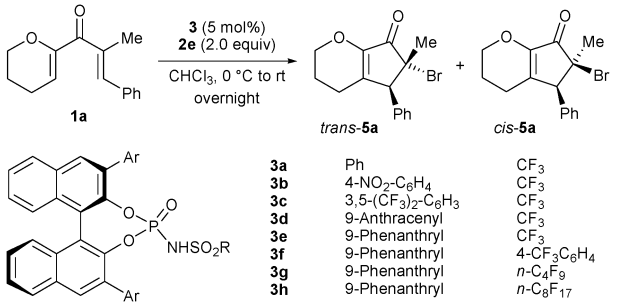
† Electronic supplementary information (ESI) available: Experimental procedures and full characterization data for all new compounds are provided. See DOI: 10.1039/c1cc15289k

Table 2 Evaluation of various Brønsted acids under different reaction conditions



Entry[a]	Catalyst	*trans* : *cis*[b]	Yield[c] (%)	Ee[b,d] (%)
1	**3a**	1 : 1	46	76
2	**3b**	1 : 1	48	58
3	**3c**	1.6 : 1	46	77
4	**3d**	2.3 : 1	35	87
5	**3e**	2.3 : 1	44	90
6	**3f**	4 : 1	5	88
7	**3g**	3 : 1	37	94
8	**3h**	2.8 : 1	40	93
9[e]	**3e**	2.7 : 1	33	94
10[f]	**3e**	2.3 : 1	54	92
11[f,g]	**3e**	2.5 : 1	53	92
12[g]	**3e**	2 : 1	66	89

[a] Reactions were performed with dienone **1**, and TBCHD (**2e**, 2.0 equiv.) in the presence of **3a–h** (5 mol%). [b] Determined by chiral HPLC analysis. [c] Yield of the isolated *trans* diastereomer. [d] Enantiomeric excess for the isolated major diastereomer (*trans*). [e] 1 mol% catalyst. [f] 2 mol% catalyst. [g] Temperature and reaction time: 0 to 10 °C for 60 h.

The evaluation of electrophiles was performed by applying 1.2 equiv. of the halogenating reagent in the presence of 10 mol% of catalyst **3e** in chloroform (Table 1).

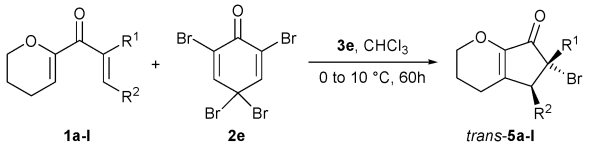
Under these conditions the enolate did not react with electrophilic fluoride sources such as Selectfluor and *N*-fluorobenzenesulfonimide (NFSI) (Table 1, entries 1 and 2). In the case of *N*-chlorosuccinimide **2c** the desired product was obtained in 15% yield and 47% ee (Table 1, entry 3). Better enantioselectivity (92% ee) was obtained in the case of *N*-bromosuccinimide **2d**.

However, the yield was low (Table 1, entry 4). An improved yield was obtained with the 2,4,4,6-tetrabromocyclohexa-2,5-dienone **2e** (TBCHD) as a bromine source (Table 1, entry 5). Hence, TBCHD was selected as a brominating agent to further examine the enantioselective Nazarov cyclization–bromination reaction.

Our subsequent investigation focussed on the evaluation of different chiral Brønsted acids **3a–h**. Most of the investigated catalysts afforded the *trans* isomer as the major product (Table 2, entries 3–12). The highest enantioselectivities (up to 94% ee) were obtained with catalysts **3e–h**, bearing large phenanthryl groups in the 3,3′-positions (Table 2, entries 5–8). With regard to both yield and selectivity, the best results were obtained with catalyst **3e** (Table 2, entry 5). The catalyst loading and the reaction temperature were also examined (Table 2, entries 9–12). The best result was obtained at 0 to 10 °C in the presence of 5 mol% of catalyst **3e** (Table 2, entry 12).

With the optimized conditions in hand we explored the scope of the Brønsted acid-catalyzed asymmetric Nazarov

Table 3 Substrate scope for the Brønsted acid-catalyzed Nazarov cyclization/bromination cascade reaction



Entry[a]	R^1	R^2	*trans*-**5a–l**	*trans* : *cis*[b]	Yield (%)[c]	ee (%)[b,d]
1	Me	Ph	**5a**	2 : 1	66	89
2	Me	4-FC_6H_4	**5b**	20 : 1	50	94
3	Me	4-ClC_6H_4	**5c**	3 : 1	66	94
4	Me	4-BrC_6H_4	**5d**	6.7 : 1	74	92
5	Me	4-$CF_3C_6H_4$	**5e**	8 : 1	55	97
6	Me	4-MeC_6H_4	**5f**	1.7 : 1	61	92
7[e]	Me	4-$MeOC_6H_4$	**5g**	3 : 1	42	85
8	Me	1-Naphthyl	**5h**	5.7 : 1	59	94
9	Me	2-Naphthyl	**5i**	4.8 : 1	63	94
10[e]	Me	3,4-Methylene dioxybenzene	**5j**	8 : 1	43	92
11	Pr	2-Naphthyl	**5k**	15 : 1	82	95
12	Pr	3-BrC_6H_4	**5l**	3 : 1	51	92

[a] Reactions were performed with substrates **1a–l** and **2e** (2.0 equiv.) in the presence of **3e** (5 mol%) in $CHCl_3$ at 0 to 10 °C for 60 h. [b] Determined by chiral HPLC. [c] Yield of the isolated major diastereomer. [d] Enantiomeric excess for the isolated major diastereomer (*trans*). [e] Temperature and reaction time: 0 to 5 °C for 60 h.

cyclization–bromination reaction with various dienones **1a–l** (Table 3). In general, differently disubstituted dienones were successfully converted into the corresponding α-brominated cyclopent-2-enones. Various aryl groups are tolerated at the β position in the dienone substrates and the desired products were obtained in moderate to good yields and with high enantioselectivities (85–97% ee). Whereas the diastereoselectivity was considerably influenced by the electronic and steric effects of the group at the β position, the enantioselectivity was not significantly affected.

The absolute configuration of the major diastereomers was determined by X-ray analysis. The X-ray crystal structure of the major diastereomer *trans*-**5a** (Fig. 1) indicated that the bromination occurred *trans* to the β-substituent (R = Ph) of the Nazarov cyclization intermediate whereas the *cis* attack was sterically restricted by the β-substituent.

In summary, we have developed the first asymmetric Brønsted acid-catalyzed Nazarov cyclization–halogenation reaction. Two chiral centers, a tertiary and a quaternary one, have been established during this transformation. The present method provides, for the first time, a variety of α-brominated cyclopent-2-enones with a wide substrate scope and with excellent enantioselectivities.

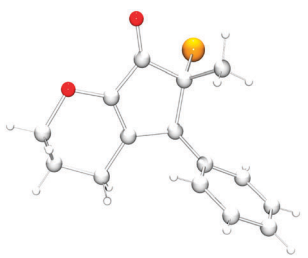


Fig. 1 Crystal structure of *trans*-**5a**.

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