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Asymmetric Catalysis

Catalytic, Enantioselective, and Highly Chemoselective Bromocyclization of Olefinic Dicarbonyl Compounds**

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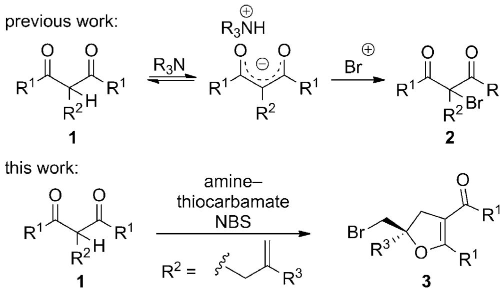
Dedicated to Professor E. J. Corey on the occasion of his 85th birthday

Catalytic enantioselective halocyclization of olefinic substrates attracted much attention over the past few years.[1] The resulting enantioenriched heterocycles form the core of many natural products and pharmaceutically important intermediates.[2] In addition, the halogen atoms can be manipulated readily to give various functional building blocks.[3] Most of the reported catalytic enantioselective halocyclization reactions involve the use of a nitrogen- or an oxygen-containing nucleophilic partner that has an N–H or a O–H moiety (e.g., amides or alcohols/carboxylic acids, respectively).[4] The catalysts can then interact with the R–H functionalities (R = N, O) through hydrogen bonds and/or salt bridges. Such interactions allow for an effective enantioinduction, resulting in highly enantioselective transformations.

1,3-Dicarbonyl compounds **1**, which contain an acidic proton in α-position to the carbonyl funtionalities, are also potential nucleophiles for halocyclizations (when R^2 is an olefinic side chain), furnishing highly functionalized cyclic ethers **3** (Scheme 1).[5] However, this type of nucleophile is also highly susceptible to halogenation in α-position to the carbonyl functionalities, which is a well-known process.[6] The resulting α-halogenated dicarbonyl compound **2** is not a good halogenating reagent and not usually used in the halocyclization of olefinic substrate **1**.[6b,m,7] Nonetheless, herein we report an efficient, catalytic, and highly enantioselective bromocyclization of olefinic 1,3-dicarbonyl compounds, giving rise to highly functionalized furans (see below). A protocol that employs an amine–thiocarbamate as catalysts was developed for the chemoselective bromination at the olefinic moiety over the carbon atom in α-position to the carbonyl functionalities.



Scheme 1. Comparison of previous and present studies.

At the outset of this study, we screened several catalysts that are commonly used in halocyclizations. Olefinic 1,3-dicarbonyl compound **1a** and *N*-bromosuccinimide (NBS) were used as substrate and stoichiometric source of the halogen atom, respectively. Reactions with simple catalysts, including DABCO (**4**), DBU, and DMAP, gave significant amounts of 2-bromo 1,3-dicarbonyl compound **2a**, while the reaction with NEt$_3$ gave a mixture of unidentified products (Table 1, entries 1–4).[8] In particular, when DBU was used as the catalyst, cyclized product **3a** was not obtained and **2a** was isolated in 98% yield.

During further investigations, we found that catalysts with Lewis basic sulfur atoms preferably mediate the bromination at the olefinic moiety instead of at the carbon atom in α-position to the carbonyl functionalities, and thus facilitate the cyclization process. The reaction with triphenylphosphine sulfide (**5**) gave the desired product **3a** with only trace amounts of **2a** (Table 1, entry 5). When the reaction was catalyzed by thiocarbamate **6**, **3a** was obtained as the only product in 78% yield (Table 1, entry 6). To our delight, **3a** was obtained in an excellent yield (92%) and with only a negligible amount of **2a** when amine–thiocarbamate catalyst **7a** was used (Table 1, entry 7). Encouraged by these preliminary results, we proceeded to optimize the reaction conditions and to develop the asymmetric version of the reaction.

A systematic screening of various halogen sources and solvents showed that toluene and NBS gave the best results (see the Supporting Information for details). The influence of the reaction temperature was also examined. At −60 °C, the reaction of **1a** with quinidine-derived amine–thiocarbamate **7a** gave product **3a** in 34% yield and 16% *ee* (Table 2, entry 1, footnote c). The *ee* value and yield improved when the reaction was conducted at −40 °C (Table 2, entry 1). Unexpectedly, reactions with thiocarbamate catalysts that contain other cinchona alkaloid frameworks, including quinine, cinchonine, and cinchonidine, were sluggish and no

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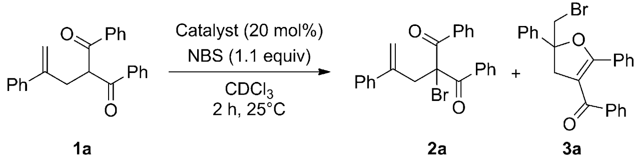
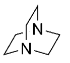
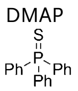
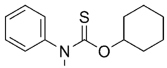
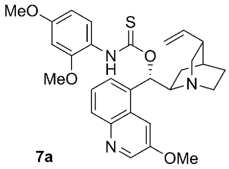
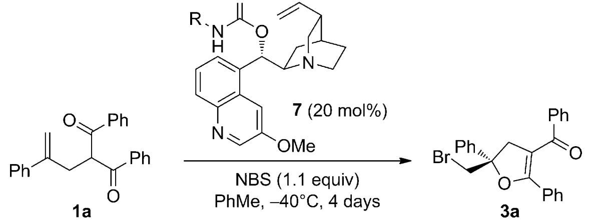
Table 1: Reaction of **1a** with NBS using various catalysts.[a]



Entry	Catalyst	Yield [%][b]		
		1a	2a	3a
1	 4	12	67	22
2[c]	NEt_3	trace	trace	trace
3	DBU	0	98	0
4	DMAP	10	28	60
5	 5	75	trace	20
6	 6	15	trace	78
7	 7a	**0**	**trace**	**92**

[a] Reactions were carried out with **1a** (0.01 mmol), catalyst (0.002 mmol), and NBS (0.011 mmol) in $CDCl_3$ (0.3 mL) at 25 °C for 2 h in the absence of light. [b] Determined by ^1H NMR analysis. [c] Significant amounts of other unidentified side products were detected. Entry in bold marks optimized reaction conditions. DABCO = 1,4-diazabicyclo-[2.2.2]octane; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DMAP = *N*,*N*-dimethylaminopyridine.

Table 2: Screening of catalysts with different thiocarbamate substituents.[a]



Entry	7	R	Yield [%][b]	*ee* [%]
1[c]	**7a**	2,4-$(MeO)_2C_6H_3$	82	20
2	**7b**	4-$MeOC_6H_4$	67	6
3	**7c**	2,5-$(MeO)_2C_6H_3$	72	14
4	**7d**	3,4,5-$(MeO)_3C_6H_2$	74	7
5	**7e**	2,6-$(EtO)_2C_6H_3$	78	18
6	**7f**	2,6-$(i\text{PrO})_2C_6H_3$	57	4
7	**7g**	C_6H_5	75	8
8	**7h**	2-naphthyl	64	0
9	**7i**	C_6F_5	32	0
10	**7j**	**2,4,6-$(MeO)_3C_6H_2$**	**89**	**96**
11[d]	**7j**	2,4,6-$(MeO)_3C_6H_2$	85	94

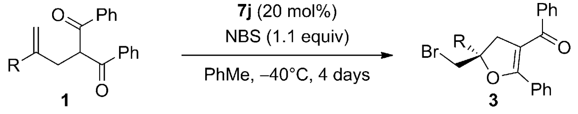
[a] Reactions were carried out with **1a** (0.03 mmol), catalyst **7** (0.006 mmol) and NBS (0.033 mmol) in toluene (1.0 mL) at −40 °C in the absence of light. [b] Yields of isolated products. [c] When this reaction was performed at −60 °C for 5 days, **3a** was obtained in 34 % yield and 16 % *ee*. [d] The reaction was conducted on a 0.3 mmol scale. Entry in bold marks optimized reaction conditions.

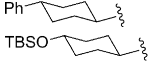
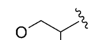
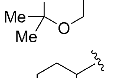
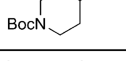
cyclized products were detected after five days at −60 °C. Reactions with an (*S*)-BINOL-derived phosphoric acid or a proline-derived thiocarbamate as catalysts could not furnish the desired product under the same conditions, either.[9]

Next, catalysts with different substituents at the thiocarbamate moiety were examined. Catalysts with electron-rich (Table 2, entries 2–6), bulky (Table 2, entry 8), and electron-deficient (Table 2, entry 9) aryl moieties did not lead to better enantioselectivities than that obtained with 2,4-dimethoxyphenyl-substituted catalyst **7a**. Surprisingly, 2,4,6-trimethoxyphenyl thiocarbamate **7j** was an excellent catalyst and **3a** was furnished in 89 % yield and 96 % *ee* (Table 2, entry 10). These results suggest that the substituents at the 2, 4, and 6 positions of the aryl moiety of the catalyst might have a synergistic effect in inducing high enantioselectivity, although the reason for this effect remains unclear. The reaction with catalyst **7j** was readily scalable without loss of efficiency and enantioselectivity (Table 2, entry 11).[10]

Once the optimized conditions were identified, we examined the substrate scope of the reaction (Table 3). The reactions of different olefinic 1,3-dicarbonyl compounds **1** proceeded smoothly to give aryl- and alkyl-substituted products **3** with high yields and *ee* values. Dicarbonyl substrates with electron-deficient aryl substituents gave products with good to excellent enantioselectivity (from 98 % to 84 % *ee*; Table 3, entries 1–3). In comparison, substrates with electron-rich aryl substituents generally gave products with lower enantioselectivities, which could be ascribed to the enhanced background reaction (Table 3,

Table 3: Substrate scope of bromocyclization of **1** catalyzed by **7j**.[a]

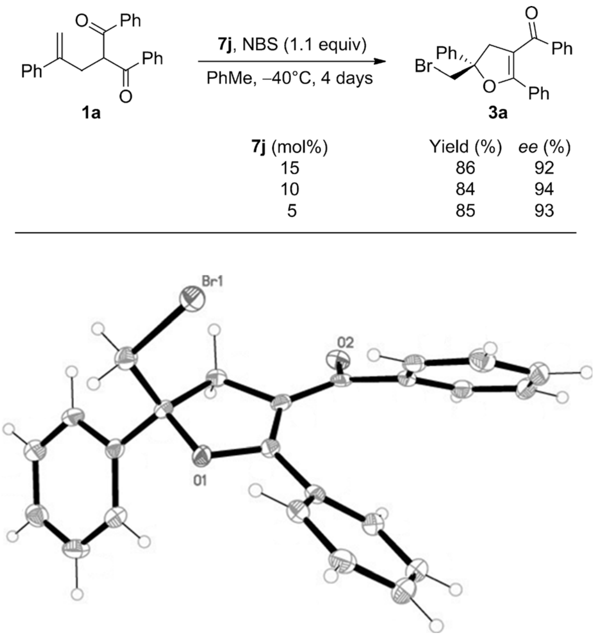


Entry	Subst.	R	Yield [%][b]	*ee* [%]
1	**1b**	4-F-C_6H_4	89	98
2	**1c**	4-Cl-C_6H_4	87	90
3	**1d**	4-Br-C_6H_4	86	84
4	**1e**	4-Me-C_6H_4	86	74
5	**1f**	3-MeO-C_6H_4	89	78
6	**1g**	2-naphthyl	87	81
7	**1h**	Me	80	55
8	**1i**	CH_2OMOM	83	64
9	**1j**	*i*Pr	87	90
10	**1k**	*t*Bu	86	92
11	**1l**	cyclopentyl	88	86
12	**1m**	cyclohexyl	92	90
13	**1n**		89	76
14	**1o**		91	91
15	**1p**		86	90
16	**1q**		92	99

[a] Reactions were carried out with **1** (0.03 mmol), catalyst **7j** (0.006 mmol), and NBS (0.033 mmol) in toluene (1 mL) in the absence of light. [b] Yields of isolated products. Boc = *tert*-butoxycarbonyl, MOM = methoxymethyl, TBS = *tert*-butyldimethylsilyl.

entries 4–6). Notably, alkyl-substituted substrates gave products with good *ee* values in most cases (Table 3, entries 7–16). This result is in sharp contrast with our previous studies and some other reports, in which low to moderate *ee* values were generally reported for alkyl-substituted substrates in asymmetric halocyclization processes.[1,11] Moreover, this catalytic protocol was compatible with various protecting groups, including OTBS, OMOM, isopropyldene, and N-Boc (see Table 3). The absolute configuration of **3** was established by X-ray crystallography of compound **3a**.[12]

After studying the substrate scope of this reaction, we investigated the required catalyst loading of **7j**. Interestingly, the catalyst was highly efficient, and product **3a** was obtained with comparable yields and *ee* values, even when the catalyst loading was reduced to 5 mol% (Scheme 2).

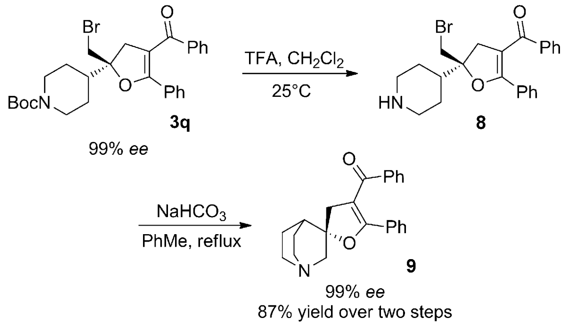


7j (mol%)	Yield (%)	ee (%)
15	86	92
10	84	94
5	85	93

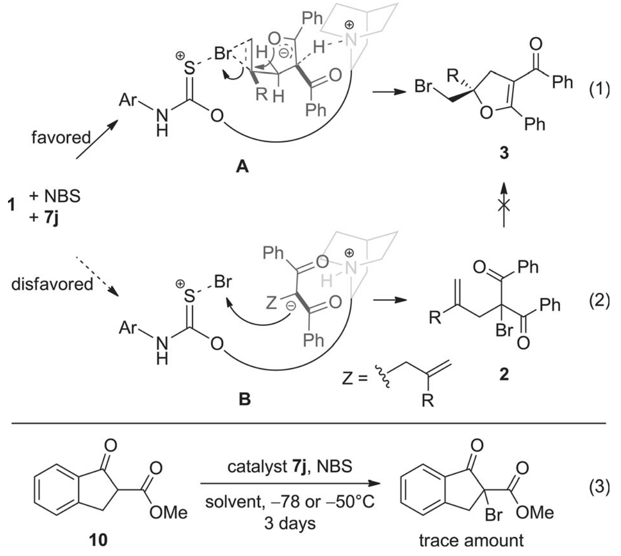
Scheme 2. Examination of catalyst loading required for bromocyclization and crystal structure of compound **3a** (thermal ellipsoids drawn at 50% probability).

The cyclized products can be further manipulated to give various functional building blocks. For instance, removal of the Boc protecting group of **3q** with TFA gave amine **8**. Treatment of **8** with $NaHCO_3$ in toluene at reflux furnished quinuclidine **9**, which can potentially act as a chiral organocatalyst scaffold (Scheme 3).[13]

Based on our previous studies on thiocarbamate catalysis,[11] we believe that the quinuclidine moiety of **7j** might act as a nitrogen base to deprotonate the 1,3-dicarbonyl unit, while the Lewis basic sulfur atom of the thiocarbamate moiety of **7j** might coordinate to Br. We attempted to convert **2a** into **3a** with **7j** as the catalyst, but the reaction did not occur. This result implies that the Br atom in dicarbonyl compounds **2** is not readily exchangeable under the reaction conditions, thus suggesting that **2** and **3** might be formed through two independent pathways. During the formation of cyclized products **3**, a possible transition state **A** might involve a bifunctional interaction/activation of the substrate with/by the catalyst, resulting in an efficient bromocyclization process [Scheme 4, Eq. (1)].[14]



Scheme 3. Synthesis of **9** from **3q**. TFA = trifluoroacetic acid.



Scheme 4. Proposed mechanism of the cyclization.

We speculate that the exceptionally strong preference for the cyclization over the bromination in α-position to the carbonyl functionalities can be attributed to the limited pocket size of the bifunctional catalyst, and transition state **A** might be energetically more favorable than transition state **B** (with regard to steric demand; Scheme 4). We also examined the bromination of dicarbonyl compound **10**, a substrate that is known to smoothly undergo asymmetric halogenation using cinchona alkaloid catalysts.[6c] However, the reaction was sluggish and only a trace amount of the product was detected when amine–thiocarbamate catalyst **7j** was used at −78 or −50 °C in CH_2Cl_2 or toluene for 3 days. This result is in agreement with the speculation that the pocket of the bifunctional amine–thiocarbamate catalyst might not be suitable for the bromination at the α-position of 1,3-dicarbonyl compounds. A possible explanation is that the carbonyl anion might not come into close proximity to S-Br at the thiocarbamate, thus not allowing for an effective bromination through transition state **B** [Scheme 4, Eq. (2)]. The hypothesis is also consistent with the results shown in Table 1, in which the ratio of cyclized product **3a** over α-brominated dicarbonyl compound **2a** increases dramatically when an amine and a thiocarbamate are used together in a bifunctional catalytic system.

In summary, a facile and highly enantioselective bromocyclization of olefinic dicarbonyl compounds has been developed using an amine–thiocarbamate as the catalyst. The use of such a catalyst resulted in the formation of the desired cyclized products with high enantioselectivities and an excellent ratio of cyclization to bromination in α-position to the carbonyl functionalities.

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[12] CCDC 935968 (**3a**) contains the supplementary crystallographic data for 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.

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[14] The bifunctional system appears to be responsible for the high reaction efficiency, as indicated by the results shown in Table 1, entries 6 and 7 (higher efficiency was observed when the amine–thiocarbamate catalyst was used).