



Organocatalytic diastereoselective dibromination of alkenes

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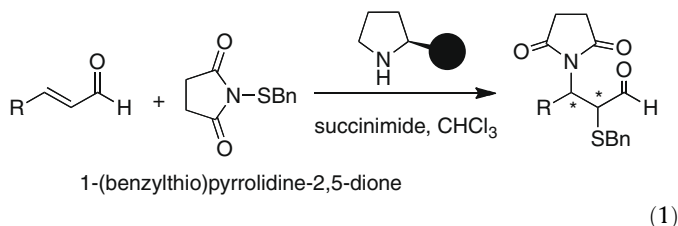
ABSTRACT

A highly diastereoselective pyrrolidine-promoted dibromination of alkenes by combination of NBS and succinimide is presented. The pyrrolidine-mediated dibromination of alkenes is highly *anti*-selective and gives the corresponding products in moderate to high yields and up to >25:1 dr.

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Dihalo derivatives are important compounds in organic synthesis, especially in pharmaceutical chemistry.¹ In the case of dibromination of organic substrates, the electrophilic addition of molecular Br₂ to unsaturated carbon–carbon bonds is still the best choice. However, bromine is hazardous, difficult to handle, and a volatile liquid,² which limits its applications. There have been some recent developments concerning the use of other dibrominating reagents.^{3,4} For example, Salazar et al. developed pentylpyridinium tribromide as the source of Br₂ for mono- or dibrominations.^{3a} Recently, Shi and co-workers^{4a} reported that the combination of *N*-bromosuccinimide (NBS) and LiBr was an efficient method for the dibromination of unsaturated carbon–carbon bonds. Moreover, organic amides have been shown to be potent organocatalysts for the bromoacetoxylation of alkenes using NBS as the electrophilic bromine source.^{4c}

In the research field of organocatalysis, amine-catalyzed domino, cascade and tandem reactions have been developed.⁵ In this context, we recently found that chiral pyrrolidines catalyze enantioselective aminosulfenylation of α,β -unsaturated aldehydes using *N*-(benzylthio)succinimides as both a nucleophilic and an electrophilic reactant (Eq. 1).⁶ The reaction proceeds very well in the presence of a secondary amine catalyst together with a catalytic amount of succinimide providing the corresponding aminosulfenylation products in high yields and enantioselectivities.



Thus, we decided to investigate the reaction between α,β -unsaturated aldehydes and NBS in the presence of a secondary amine catalyst and succinimide. Herein, we present a highly diastereoselective method for the organocatalytic dibromination of alkenes using NBS as the source of bromine.

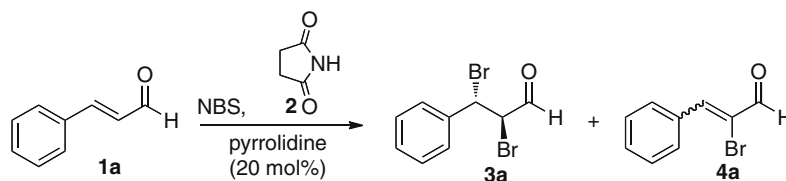
In an initial experiment, we found that pyrrolidine catalyzed the dibromination of *trans*-cinnamaldehyde (**1a**) using pure, freshly recrystallized NBS (2.2 equiv) as the dibrominating reagent in CHCl₃ (Table 1, entry 1). To our delight, the corresponding product **3a** was formed in 17% conversion with excellent *anti*-diastereoselectivity (>25:1 dr). As in our previously reported α -aminosulfenylation reaction, the addition of succinimide (**2**) improved the conversion (entry 2). The reaction did not work in MeOH (entry 3) or in THF. A significant improvement in conversion and reaction time was achieved by increasing the temperature of the reaction mixture. For example, increasing the temperature to 70 °C led to the formation of **3a** in more than 90% conversion with >25:1 dr (*anti/syn*) within 2 h (entry 6). However, a small amount of elimination product **4a** was also formed.

Moreover, decreasing the amount of succinimide (**2**) to 0.2 equiv did not affect the conversion (95%) and product **3a** was obtained with >25:1 dr (*anti/syn*) (entry 8). Replacing pyrrolidine with Et₃N as the organic mediator significantly decreased the conversion (entry 9) and only a trace amount of **3a** was formed when no organic base was added (entry 10). We also compared our method to that reported by Shi and co-workers.⁴ Thus, the addition of LiBr to the reaction mixture was investigated (entries 11 and 12). We found that no reaction occurred when pyrrolidine was not added (entry 11) and 80% conversion was observed in the presence of pyrrolidine and LiBr. However, the diastereoselectivity of the reaction decreased to a moderate 4:1.

Encouraged by these results, we decided to investigate the scope and limitations of the dibromination of α,β -unsaturated aldehydes **1a–f** using 2.2 equiv of NBS, 0.2 equiv of succinimide (**2**), and 0.2 equiv of pyrrolidine (Table 2).

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Table 1Screening of the reaction conditions for the dibromination of *trans*-cinnamaldehyde (**1a**)^a

Entry	NBS (equiv)	2 (equiv)	Concd (M)	Solvent	Time (h)	Temp (°C)	Conv. of 3a ^b (%)	dr of 3a ^b (<i>anti</i> / <i>syn</i>)	3a : 4a ^b
1	2.2	0	0.07	CHCl ₃	15	rt	17	>25:1	>25:1
2	2.2	1.5	0.07	CHCl ₃	15	rt	57	>25:1	>25:1
3	2.2	1.5	0.07	MeOH	15	rt	0	—	—
4	2	0.5	0.5	CHCl ₃	24	rt	58	>25:1	70:30
5	4	0.5	0.5	CHCl ₃	24	rt	71	>25:1	82:18
6	2.2	0.5	0.5	CHCl ₃	2	70	>90	>25:1	83:17
7	2.2	0.5	5	CHCl ₃	4	rt	74	>25:1	85:15
8	2.2	0.2	0.5	CHCl ₃	2	60	95	>25:1	79:21
9 ^c	2.2	0.5	0.5	CHCl ₃	1	60	29	>25:1	>25:1
10 ^d	2.2	0.5	0.5	CHCl ₃	1	60	<5	—	—
11 ^e	2	1.5	0.1	THF	15	rt	0	—	—
12 ^f	2	1.5	0.1	THF	15	rt	80	4:1	>25:1

^a Experimental conditions: To a stirred solution of *trans*-cinnamaldehyde (0.5 mmol) in 1–7 mL of solvent were added successively NBS (recrystallized from boiling water), succinimide, and pyrrolidine. The reaction vial was sealed and the solution was stirred under the conditions displayed in the Table.

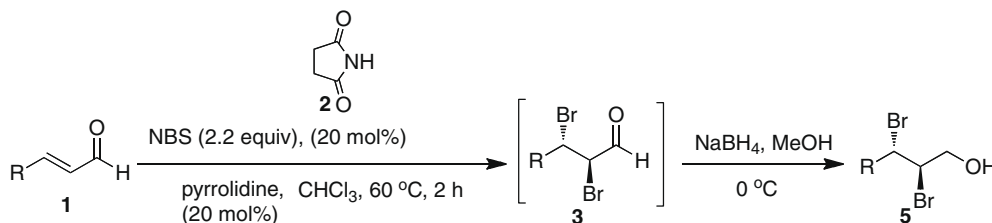
^b Determined by ¹H NMR analyses of the crude reaction mixture.

^c 20 mol % of Et₃N was used instead of pyrrolidine.

^d Reaction run without pyrrolidine.

^e 2 equiv of LiBr added and no pyrrolidine.

^f 2 equiv of LiBr was added.

Table 2Dibromination of α,β-unsaturated aldehydes **1a–1f**^a

Entry	R	Product	Yield ^b (%)	dr ^c (<i>anti</i> / <i>syn</i>)
1 ^d		5a	58	>25:1
2 ^e		5b	30	>25:1
3 ^f		5c	35	>25:1
4	<i>n</i> -Bu	5d	62	>25:1
5	Me	5e	55	>25:1
6	Et	5f	53	>25:1

^a Experimental conditions: To a stirred solution of aldehyde (0.5 mmol) in CHCl₃ (1 mL) were added successively NBS (1.1 mmol, recrystallized from boiling water), succinimide (0.1 mmol), and pyrrolidine (0.1 mmol). The reaction vial was sealed and the solution was heated at 60 °C for 2 h.

^b Isolated yield of the corresponding alcohol **5** after in situ reduction of product **3**.

^c *Anti*/*syn* ratio determined by ¹H NMR analysis.

^d 8% of reduced elimination product **4a** was isolated.

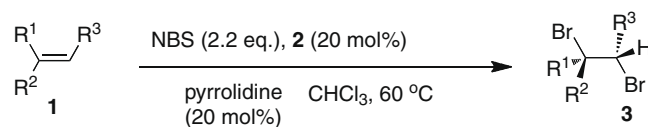
^e 11% of reduced elimination product **4b** was isolated.

^f 16% of reduced elimination product **4c** was isolated.

The dibromination of α,β-unsaturated aldehydes **1a–f** proceeded with excellent diastereoselectivity and the corresponding alcohols **5a–f** were obtained in moderate to good yields after in situ reduction with NaBH₄.⁷ For example, the dibromination of **1a** and subsequent reduction gave the corresponding product **5a** in 58% yield with >25:1 dr (*anti*/*syn*) (entry 1). In the case of the dibromination of α,β-unsaturated aldehydes **1** with an aryl substituent,

a small amount of the corresponding elimination product **4** was also formed (entries 1–3). In the case of enals **1** with aliphatic substituents, only the corresponding dibrominated alcohols **5d–f** were formed (entries 4–6).

With these results in hand, we next investigated whether we could catalyze an enantioselective version of this reaction using chiral pyrrolidine derivatives as catalysts for the dibromination

Table 3Dibromination of simple alkenes **1i–n**^a

Entry	Substrate	Product	Time (h)	Yield ^b (%)	dr ^c (<i>anti</i> / <i>syn</i>)
1	Ph-CH=CH ₂ 1j	Ph-CH(Br)-CH ₂ -Br 3j	1.5	62	—
2 ^d	CH ₃ (CH ₂) ₆ -CH=CH ₂ 1i	CH ₃ (CH ₂) ₆ -CH(Br)-CH ₂ -Br 3i	4	47	—
3	Ph-CH=CH-CH ₃ 1k	Ph-CH(Br)-CH(Br)-CH ₃ 3k	2	90 ^e	9:1
4	Ph-CH=CH-Ph 1l	Ph-CH(Br)-CH(Br)-Ph 3l	3	53	>10:1
5	Ph-C(CH ₃)=CH ₂ 1m	Ph-C(CH ₃) ₂ -CH ₂ -Br 3m Ph-C(CH ₃)=CH-Br 3m' 3m:3m' = 5:6	3	75 ^f	—
6	Cyclohexene 1n	1,2-dibromocyclohexane 3n	6	72	>10:1

^a Experimental conditions: To a stirred solution of alkene **1** (0.5 mmol) in CHCl₃ (1 mL) were successively added NBS (1.1 mmol, recrystallized from boiling water), succinimide (0.1 mmol), and pyrrolidine (0.1 mmol). The reaction vial was sealed and the solution was heated at 60 °C for the time displayed in the Table.

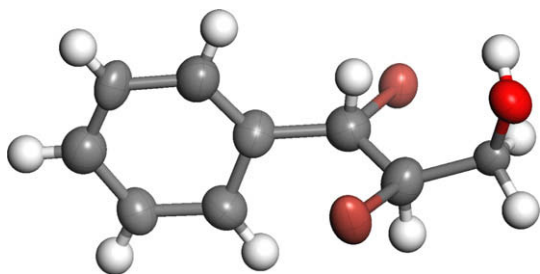
^b Isolated yield of pure *anti*-isomer **3**.

^c *Anti*/*syn* ratio determined by ¹H NMR analysis.

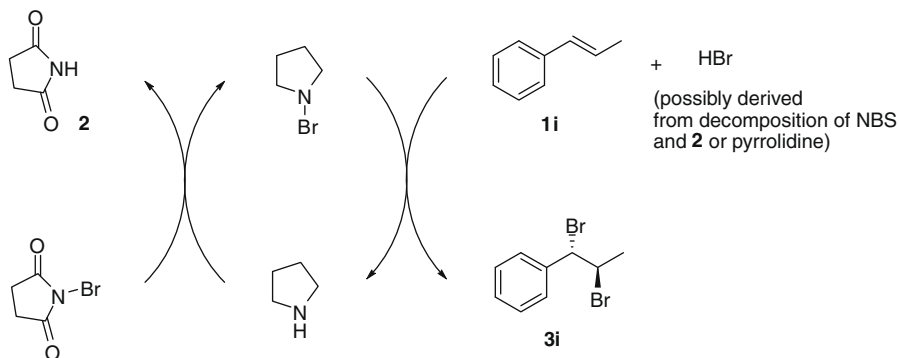
^d 5 equiv of NBS was used.

^e Product **3k** can decompose on silica gel, hence the reaction was purified by extraction with pentane.

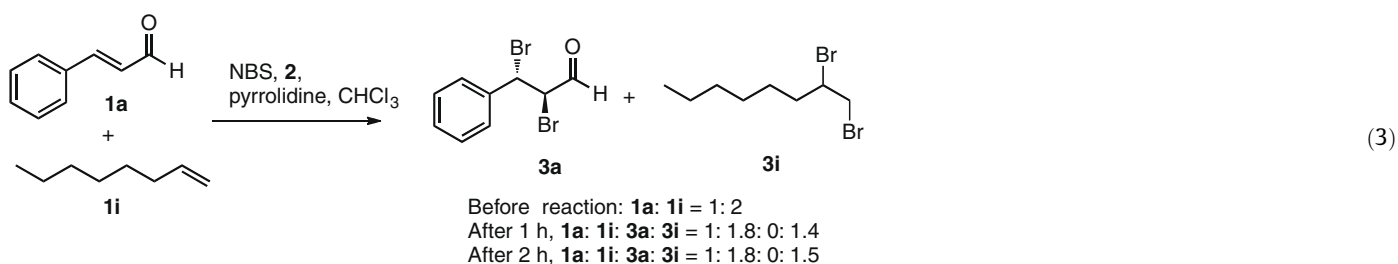
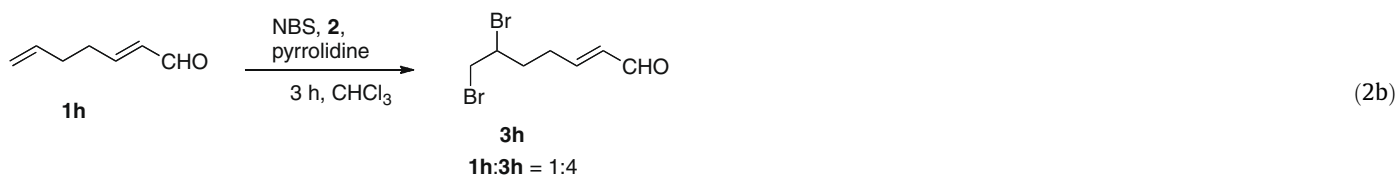
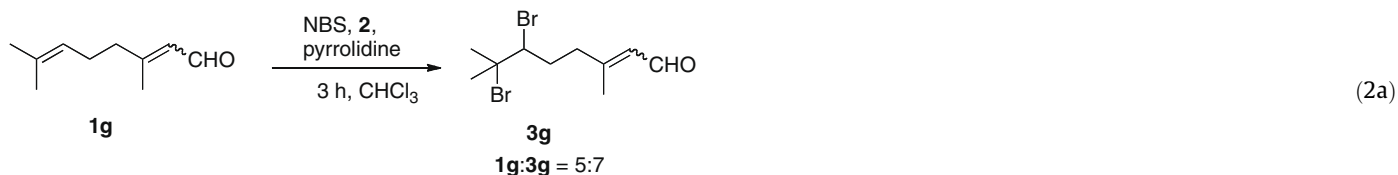
^f Combined yield of compounds **3m** and **3m'**.

**Figure 1.** ORTEP picture of 2,3-dibromo-3-phenylpropan-1-ol **5a**.

of cinnamaldehyde (**1a**) or crotonaldehyde (**1e**). However, the corresponding products were formed in similar yields to those observed when pyrrolidine was used and with only <5% ee. Dibromination of cinnamaldehyde (**1a**) in the presence of (*S*)-2-[diphenyl(trimethylsilyloxy)methyl]pyrrolidine (20 mol %) gave the corresponding product **5a**, after in situ reduction, in 45% yield with >25:1 dr and almost 0% ee. Based on these results, we suggest that the pyrrolidine derivatives were not able to control the stereoselectivity by changing the iminium activation of the enals. We also found that the dibromination process was highly regioselective. As shown in the dibromination of citral (**1g**) (*trans*/*cis* = 1:1), only selective bromination of the electron-rich double bond was

**Scheme 1.** Possible pyrrolidine activation.

achieved (Eq. 2a). This was also the case for the reaction with enal **1h** where only the terminal olefin was dibrominated (Eq. 2b). Moreover, the dibromination of a mixture of olefinic substrates **1a** and **1i** gave only the product **3i** derived from alkene **1i** (Eq. 3).



With this information in hand, we realized that the scope of this organocatalytic reaction could be broadened to other types of alkenes. Thus, we investigated the dibromination of other alkenes **1** using our optimized reaction conditions (Table 3).

Our metal-free system had a broad substrate scope and both acyclic and cyclic alkenes gave the corresponding dibromination products **3i–3n** in moderate to high yields.⁸ For example, the dibrominations of terminal alkenes **1j** and **1i** gave the corresponding dibromo compounds **3j** and **3i** in 62% and 47% yields, respectively (entries 1 and 2). The dibromination of 1,2-disubstituted alkenes **1k** and **1l** gave the corresponding products **3k** and **3l** in 90% and 53% yield and with high diastereoselectivity, respectively (entries 3 and 4). In the case of alkene **1m**, the monobrominated product **3m'** was also formed together with **3m** in a 6:5 ratio (entry 5). Moreover, the dibromination of cyclohexene **1n** gave the corresponding *anti*-product **3n** in 72% yield and >10:1 dr (entry 6).

The relative stereochemistry of compounds **3** was *anti* as established by X-ray analysis of alcohol **5a**⁹ (Fig. 1). The mechanism of this dibromination process is still under investigation. However, molecular Br₂ may be the brominating agent^{4a,10} and can be formed under the present reaction conditions. Moreover, pyrrolidine can activate bromination reagents¹¹ such as NBS by making them more electrophilic. Therefore, another possibility is that pyrrolidine activates NBS via the catalytic cycle shown in Scheme 1. As a comparison, NBS is activated in this manner by organic amidines during bromoacetoxylation of alkenes.^{4c}

In summary, we have reported a convenient and highly diastereoselective organocatalytic method for the dibromination of alkenes using pyrrolidine and its derivatives as catalysts and NBS

as the Br source. The corresponding dibromo products were isolated in moderate to high yields and with up to >25:1 dr (*anti*/*syn*). It is noteworthy that the use of NBS together with an organic catalyst makes it possible to avoid the use of molecular Br₂, which

makes the reaction safer and more environmentally friendly. Further elaboration of this transformation and a study of its mechanistic aspects are ongoing in our laboratory.

Acknowledgements

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7. **Typical experimental procedure:** To a stirred solution of aldehyde **1** (0.5 mmol) in CHCl₃ (1 mL) were successively added NBS (1.1 mmol, recrystallized from boiling water), succinimide (0.1 mmol) and pyrrolidine (0.1 mmol). The reaction vial was sealed and the mixture was stirred at 60 °C for 2 h. Next, the solution was cooled to 0 °C and methanol (1 mL) was added followed by addition of NaBH₄ (1.5 mmol) in portions. The reaction was quenched by addition of satd aq NH₄Cl solution (2 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash silica gel chromatography to give the corresponding dibromo alcohol **5**. Data for **5a**: ¹H NMR (CDCl₃, 400 MHz) δ 7.34–7.43 (m, 5H), 5.31 (d, *J* = 11.0 Hz, 1H), 4.73 (ddd, *J* = 11.1 Hz, *J* = 4.3 Hz, *J* = 2.6 Hz, 1H), 4.36 (ddd, *J* = 12.7 Hz, *J* = 7.8 Hz, *J* = 4.3 Hz, 1H), 4.28 (ddd, *J* = 12.7 Hz, *J* = 6.4 Hz, *J* = 2.6 Hz, 1H), 2.26–2.30 (m, 1H). ¹³C NMR (CDCl₃, 100 MHz) δ 139.8, 128.9, 128.7, 127.8, 65.8, 59.2, 52.3. HRMS (ESI): calcd for [M+Na] (C₉H₁₀Br₂ONa) requires *m/z* 314.8991, found 314.8988. The chiral amine (*S*)-2-[diphenyl-(trimethylsilyloxy)methyl]pyrrolidine (20 mol %) gave the corresponding product **5a**, after in situ reduction, in 45% yield with >25:1 dr and almost 0% ee. The enantiomeric excess was determined by chiral HPLC with an AD-column (iso-hexane/*i*-PrOH = 95:5, λ = 210 nm) 0.5 ml/min, *t*_{R1} = 40.0 min, *t*_{R2} = 45.1 min.
8. **Typical experimental procedure:** To a stirred solution of alkene **1** (0.5 mmol) in CHCl₃ (1 mL) were successively added NBS (1.1 mmol, recrystallized from boiling water), succinimide (0.1 mmol) and pyrrolidine (0.1 mmol). The reaction vial was sealed and the mixture was stirred at 60 °C for the time indicated in Table 3. After the reaction was complete, the corresponding dibromo product **3** was separated by flash chromatography on silica gel. The spectral data were in accordance with the literature: compound **3j**: (a) Dewkar, G. K.; Narina, S. V.; Sudalai, A. *Org. Lett.* **2003**, *5*, 4501–4504. Compound **3i**: (b) Lexa, D.; Saveant, J. M.; Schaefer, H. J.; Binh, S. K.; Vering, B.; Wang, D.-L. *J. Am. Chem. Soc.* **1990**, *112*, 6162–6177. Compounds **3k**, **3l** and **3m**: (c) Butcher, T. S.; Zhou, F.; Detty, M. R. *J. Org. Chem.* **1998**, *63*, 169–176; (d) Ye, C.-F.; Shreeve, J. M. *J. Org. Chem.* **2004**, *69*, 8561–8563. Compound **3m'**: (e) Donohoe, T. J.; Fishlock, L. P.; Procopiou, P. A. *Org. Lett.* **2008**, *10*, 285–288.
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