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Bromocyclization

Highly Enantioselective Bromocyclization of Allylic Amides with a P/P=O Double-Site Lewis Base Catalyst

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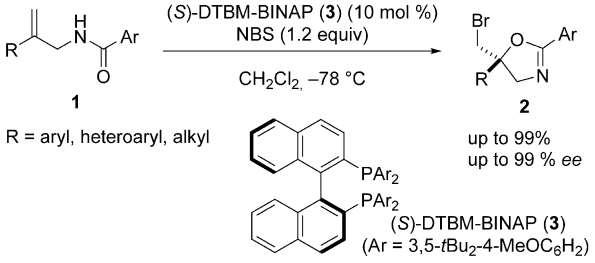
Abstract: The enantioselective bromocyclization of allylic amides catalyzed by phosphorus-containing Lewis bases was examined in detail. A series of control experiments and NMR studies showed that a partially oxidized bis-phosphine generated in situ serves as the actual enantioselective catalyst. The reaction mechanism involves distinct roles of two Lewis basic sites, P and P=O, with P^+Br serving as a fine-tuning element for substrate fixation in the chiral environment, and P^+OBr as the Br^+ transfer agent to the olefin. Catalyst loading could be reduced to as little as 1 mol%, and the reaction affords enantioenriched oxazolines with up to >99.5% *ee*.

Introduction

Electrophilic halofunctionalization of olefins is commonly employed to increase molecular complexity during organic synthesis, since it enables double installation of heteroatoms on a carbon–carbon double bond. Halocyclization by intramolecular attack of pendant nucleophiles, such as carboxylic acid, alcohol, carbamate, and amide, proceeds in a highly stereospecific manner under mild reaction conditions to afford functionalized heterocyclic compounds. Since such reactions have often been utilized as key steps in the synthesis of various useful compounds, the development of catalytic asymmetric variants is of continuing interest.[1] In this context, a wide variety of catalysts have emerged, including chiral amine,[2] Brønsted acid,[3] hydrogen-binding,[4] bifunctional,[5] Lewis acid,[6] phase-transfer,[7] and Lewis base catalysts.[8] Complexation of chiral Lewis bases with haliranium ions would be the most straightforward approach for the generation of chiral halogenating agents, but only a few monofunctional chiral Lewis base catalysts have been identified, probably because soft Lewis bases (P, S, Se, etc.) are generally unstable under halogenation conditions and they readily dissociate from the haliranium ions. In addition, even if a chiral halonium intermediate is efficiently formed, the complex is considered to be racemized through halogen exchange with olefin prior to attack of the pendant nucleophile.[1d,9]

Nevertheless, Yeung and co-workers recently developed optically active dialkyl sulfide and selenide catalysts as single-site Lewis base catalysts for asymmetric bromination of olefins with alcohol or tosyl amide as pendant nucleophile.[8b,c] Concurrently, during the course of our investigations of halogenation reactions,[10] we found that chiral phosphine compounds can catalyze the enantioselective delivery of halogen atoms, and we achieved a highly enantioselective bromocyclization of allylic amides **1** with DTBM-BINAP as a Lewis base catalyst, obtaining chiral oxazolines **2** with a tetrasubstituted carbon center (Scheme 1).[11]



Scheme 1. Enantioselective bromocyclization of allylic amides catalyzed by DTBM-BINAP. DTBM = 3,5-di-*tert*-butyl-4-methoxyphenyl, NBS = *N*-bromosuccinimide.

This reaction is synthetically attractive, not only because the oxazoline substructure frequently occurs in natural products and biologically active compounds,[12] but also because enantiomerically pure oxazolines can serve as useful chiral ligands for asymmetric reactions.[13] Furthermore, oxazoline compounds can be converted to synthetically useful 1,2-amino alcohols under mild reaction conditions.[2c,11] We found that a bis-phosphine structure with axial chirality was essential for achieving high enantioselectivity, but the mechanism has remained elusive.[11] Since this approach might be applicable to other halogenation reactions, we set out to elucidate the reaction mechanism in detail. Herein, we describe a comprehen-

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sive study on the enantioselective bromocyclization of allylic amides catalyzed by double-site Lewis basic phosphorus compounds.

Results and Discussion

The application of soft Lewis base activation of halogens to asymmetric reactions has been considered difficult, because soft Lewis bases are generally unstable and easily oxidized under the conditions of halogenation reactions. Therefore, the co-presence of the oxidant (NBS) and the phosphine compound led us to wonder whether phosphine oxide generated in situ might be involved in the reaction. Sakakura, Ishihara, and co-workers recently reported a chiral phosphate-catalyzed iodolactonization reaction in which the P=O group is presumed to act as a Lewis base catalyst.[8d] Thus, we conducted the reaction of **1a** in CD_2Cl_2 and measured the ^{31}P NMR spectrum of the crude mixture before workup (Figure 1). A signal that can be attributed to phosphine oxide was observed ($\delta =$ 27.8 ppm at 22 °C and $\delta = 29.8$ ppm at −78 °C) in addition to a peak at $\delta \approx 45.5$ ppm (see below).[14] This observation prompted us to investigate the possibility that (partially) oxidized DTBM-BINAP is the actual active species.

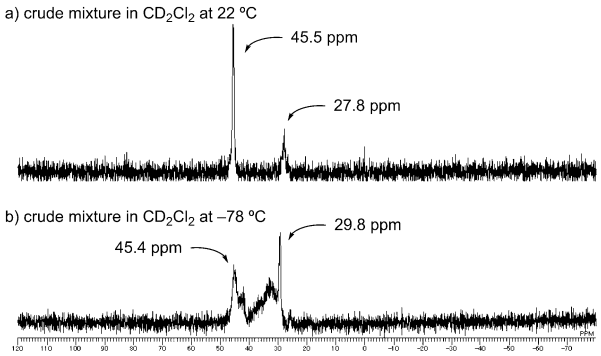
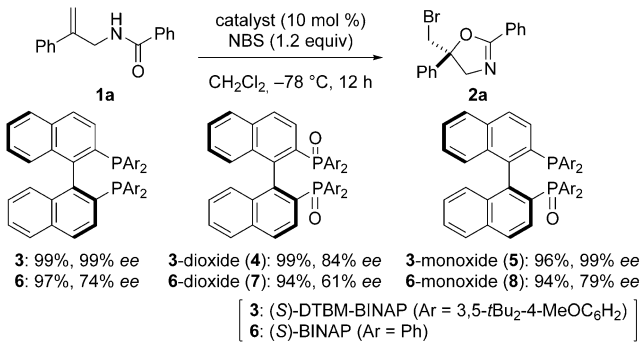


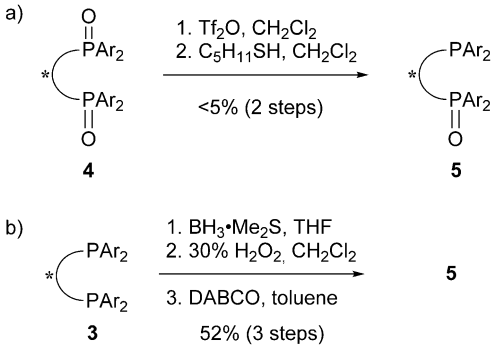
Figure 1. ^{31}P NMR spectra in CD_2Cl_2 at 22 °C (a) and −78 °C (b).

To examine this possibility further, we prepared (partially) oxidized BINAP derivatives and conducted several control experiments using these synthesized compounds as catalysts (Scheme 2). DTBM-BINAP dioxide (**4**), readily obtained by



Scheme 2. Control experiments with oxidized BINAP derivatives.

oxidation with hydrogen peroxide, was able to catalyze the reaction, but with reduced enantioselectivity (84% *ee*).[15] DTBM-BINAP monoxide (**5**) was difficult to synthesize according to a reported procedure for BINAP monoxide (Scheme 3),[16] but



Scheme 3. Synthesis of DTBM-BINAP monoxide **5**. a) Application of reported procedure.[16] b) This study. DABCO = diazabicyclo[2.2.2]octane.

fortunately we managed to obtain **5** in acceptable yield (52%, three steps) by reference to the synthesis of DuPhos monoxide by Charette et al. (Scheme 3).[17] Remarkably, the monoxide catalyst **5** turned out to be as effective as DTBM-BINAP (99% *ee*). Similarly, we found that BINAP monoxide (**8**) was slightly more effective (79% *ee*) than BINAP (74% *ee*), whereas BINAP dioxide (**7**) gave the product with only 61% *ee*.

At this stage, we considered that the monoxide catalyst might be formed by reaction with NBS and a trace amount of contaminating water. If this hypothesis is correct, addition of water should not negatively affect the catalyst activity (Table 1).[18] Thus, reactions of **1a** with DTBM-BINAP (**3**) were

Table 1. Comparable catalyst efficiency in the presence of added water.

Entry	Catalyst		*X* [mol%]	Yield [%][a]	*ee* [%][b]
1	DTBM-BINAP	**3**	0	99	99
2		**3**	10	96	98
3		**3**	20	97	98
4	BINAP	**6**	0	97	74
5		**6**	10	99	79
6		**6**	20	97	79

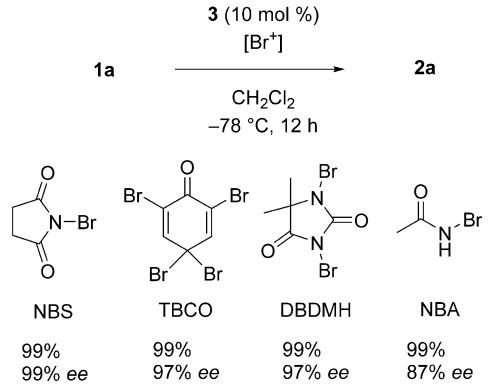
[a] Yield was determined by ^1H NMR analysis with $(CHCl_2)_2$ as internal standard. [b] The *ee* was determined by chiral HPLC analysis.

carried out in the presence of a catalytic amount of water. It was confirmed that the yield and enantioselectivity were comparable with those obtained under the standard conditions (Table 1, entries 1–3). Likewise, BINAP (**6**) in the presence of water afforded **2a** with slightly enhanced enantioselectivity (79% *ee*), equivalent to that obtained in the control experi-

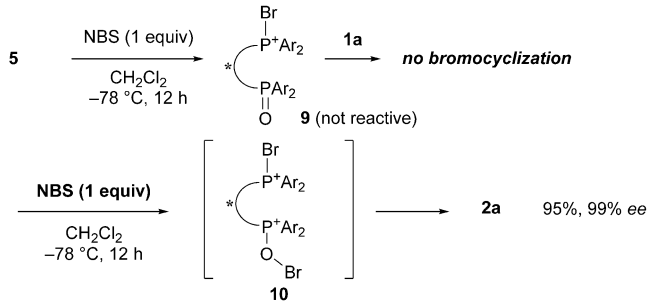
ments with isolated BINAP monoxide (**8**; Table 1, entries 4–6). On the basis of these results, we speculated that DTBM-BINAP monoxide is the enantioselective catalytic species in this reaction.

Next, we turned our attention to the reaction mechanism of the present bromocyclization. As discussed in our previous paper, other brominating reagents had little effect on the enantioselectivity regardless of their different structural and electronic properties, and this result may indicate the generation of a similar chiral brominating species in all cases (Scheme 4). ^{31}P NMR measurements in $CDCl_3$ at $-60\,^{\circ}C$ clearly showed the formation of bromophosphonium salt **9** when DTBM-BINAP monoxide (**5**) was mixed with one equivalent of NBS (Figure 2). Thus, a signal at $\delta = -16.9$ ppm due to P^{III} disappeared on treatment with NBS, and a new signal appeared at $\delta = 45.5$ ppm,[19] which is completely different from that of P=O ($\delta = 30.5$ ppm).

Then, an equimolar amount of **1a** was added to **9**, but the stoichiometric reaction did not proceed at all at $-78\,^{\circ}C$, or even at room temperature, though P^{III} compounds were used as promoters in previous reports.[8a,d,e] Interestingly, however, the desired cyclization occurred after addition of another equivalent of NBS, and **2a** was formed in 95% yield with 99% *ee* (Scheme 5). As shown in Table 2, the reaction of **1a** with PPh_3 as catalyst was retarded with increasing amount of PPh_3, which implies that the bromophosphonium substructure in **9** did not serve as the Br^+ transfer agent.[20] Thus, it is likely that interaction with the second equivalent of NBS enables inactive **9** to form catalytically active species **10**. Considering that the dioxide **5** was also a good promoter, the putative

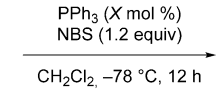


Scheme 4. Effect of brominating reagents on enantioselectivity.



Scheme 5. Stoichiometric reactions.

Table 2. Bromocyclization with various amounts of PPh_3.



Entry	*X* [mol%]	Yield [%][a]
1	0	89
2	10	53
3	50	7
4	100	2

[a] Yield was determined by ^1H NMR analysis with $(CHCl_2)_2$ as internal standard.

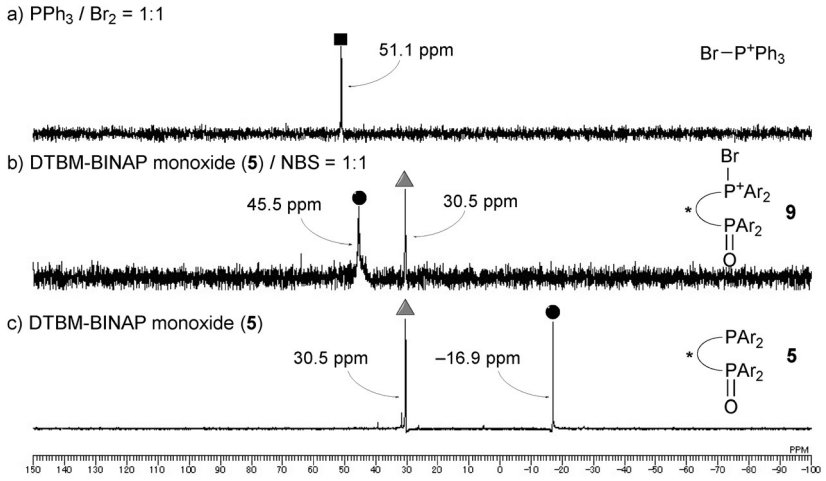
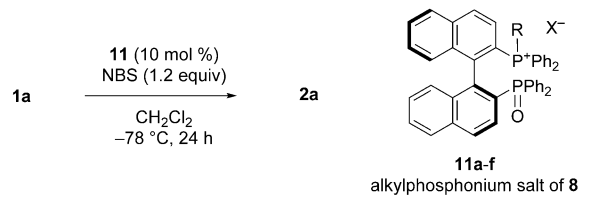


Figure 2. ^{31}P NMR spectra of a) PPh_3/Br_2 (1/1), b) **5**/NBS (1/1), and c) **5** in $CDCl_3$ at $-60\,^{\circ}C$.

coordinatively unsaturated bromooxophosphonium moiety (P^+OBr) would react with the olefin as a Br^+ transfer agent.

Given the assumption that the cationic charge on the bromophosphonium substructure plays a key role, we examined mixed alkyl phosphonium monoxide derivatives **11** and checked the catalytic activity of these compounds (Table 3).

Table 3. Catalytic ability of alkylphosphonium monoxide derivatives.



11a-f
alkylphosphonium salt of **8**

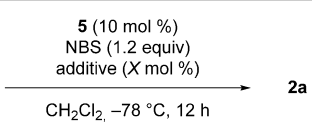
Entry	Cat.	R	X	Yield [%][a]	*ee* [%][b]
1	**11a**	Me	I	53	11
2	**11b**	Me	BF_4	15	2
3	**11c**	Et	I	39	3
4	**11d**	*n*Pr	I	53	9
5	**11e**	*i*Pr	I	49	4
6	**11f**	Bn	Br	64	9

[a] Yield of isolated product. [b] The *ee* was determined by chiral HPLC analysis.

Methyl-substituted phosphonium salts **11a** and **11b** were prepared from BINAP monoxide (**8**) by treatment with MeI or a Meerwein reagent. Unfortunately, however, these salts were far inferior as catalysts, affording **2a** in lower yields and with drastic loss of enantioselectivity, accompanied by recovery of **1a** (Table 3, entries 1 and 2). Other alkylphosphonium phosphine monoxides **11c**–**11f** also failed to promote the reaction efficiently and resulted in low enantioselectivity (Table 3, entries 3–6). In view of our observation that the present bromocyclization could proceed even in the absence of catalyst (Table 2, entry 1), the reason for the low reactivity in the presence of **11** remains unclear. However, these results definitely suggest that the P^+Br substructure in **10** serves as a fine-tuning element to fix the position of the substrate in the chiral environment, and also indicate that the substrate is quite sensitive to small differences in the steric and electronic properties of the phosphonium moiety of the catalyst.[21]

To obtain clearer insight into the role of the two distinct phosphonium ion moieties, we carried out competitive experiments in combination with achiral Lewis base additives under otherwise identical conditions. If the P^+OBr part in **10** is the actual brominating reagent, reaction in the presence of $Ph_3P{=}O$ is anticipated to give a lower enantioselectivity. As summarized in Table 4, however, the desired chiral oxazoline **2a** was obtained essentially without any detrimental effect on catalytic efficiency (Table 4, entries 1–3). On the other hand, drastic loss of yield and enantioselectivity was observed when the amount of PPh_3 additive was increased (Table 4, entries 4–7). From these results, the following conclusions can be drawn: 1) As shown in Table 2, the bromophosphonium salt derived from PPh_3 (Ph_3P^+Br) shows low reactivity as a brominating reagent.

Table 4. Control experiments with $Ph_3P{=}O$ and PPh_3.

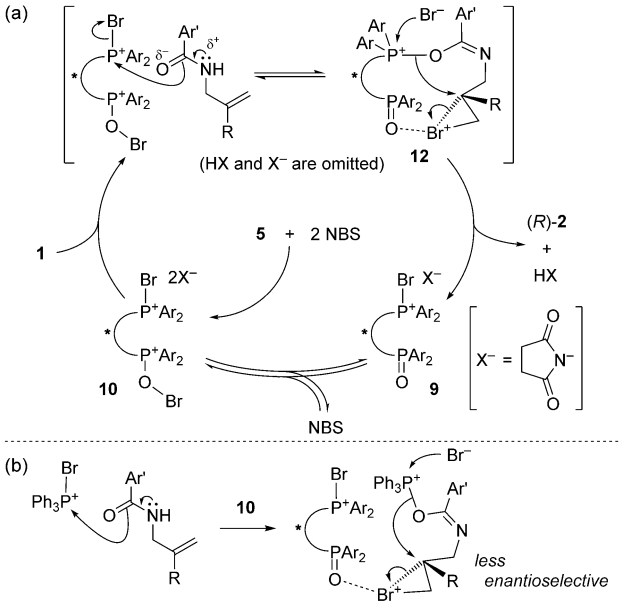


Entry	Additive	*X* [mol%]	Yield [%][a]	*ee* [%][b]
1	$Ph_3P{=}O$	5	99	99
2	$Ph_3P{=}O$	10	99	98
3	$Ph_3P{=}O$	20	89	97
4	PPh_3	5	99	95
5	PPh_3	10	85	88
6	PPh_3	20	65	33
7	PPh_3	40	56	12

[a] Determined by ^1H NMR analysis with $(CHCl_2)_2$ as internal standard. [b] Determined by HPLC analysis.

2) The P^+Br substructure of **10** plays a critical role in enantiocontrol, and decreased enantioselectivity can be explained by competitive inhibition with achiral Ph_3P^+Br in the transition state. 3) Activation of NBS with $Ph_3P{=}O$ alone seems difficult, presumably due to instability of the intermediary P^+OBr species, and this would account for the minimal adverse effect on the catalyst efficiency.

On the basis of these studies, we propose the reaction mechanism shown in Scheme 6a. Coordination of DTBM-BINAP monoxide (**5**) to NBS would generate catalytically active species **10**. This intermediate would then undergo electrophilic attack on the olefin of **1** to afford chiral bromonium intermediate **12**, while the pendant nucleophile would be directed by interaction with the P^+Br moiety. Given the poor enantiocontrol of alkylphosphonium **11**, we speculate that the formation of an oxyphosphonium substructure ($P^+{-}O{-}C{=}N$) might be



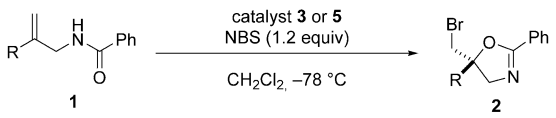
Scheme 6. a) Proposed reaction mechanism. b) Competitive inhibition by achiral phosphine additive.

involved. Substitution of bromide anion on phosphorus, followed by nucleophilic capture of the bromonium ion with the amide oxygen atom, delivers the desired chiral oxazoline (*R*)-**2** with regeneration of **9**. A significant decrease in enantioselectivity in the presence of PPh_3 additive may be attributable to competitive interaction of Ph_3P^+Br with **12** in the transition state (Scheme 6b). Since addition of $Ph_3P{=}O$ had little influence on yield and enantioselectivity, the generation and dissociation of P^+OBr are considered to be in equilibrium in all the processes. Therefore, an appropriate spatial arrangement of P and P=O in **5** would be the key to intramolecular Br^+ transfer from the adjacent P^+OBr species, which enables the cyclization reaction to occur in a highly enantioselective manner.

On the basis of the the above findings, we reinvestigated the optimization of the reaction conditions. Since anhydrous solvent and an inert atmosphere were used in our previous work, the actual amount of **5** in the reaction mixture is likely to have been small. Thus, we became interested in decreasing the catalyst loading (Table 5). As we expected, the new conditions gave results comparable to, or even better than, those obtained under the previously reported conditions, even though as little as 1 mol% of **5** was used; this demonstrates the scalability of this reaction (Table 5, entries 1–3). However, with 0.5 mol% catalyst loading, the enantioselectivity decreased dramatically to 44% (Table 5, entry 4). In the case of **1b**, the *ee* was slightly improved to 97%, even when no more than 1 mol% of **5** was employed (Table 5, entries 5 and 6).[22] These results are consistent with our hypothesis that the monoxide **5** is the actual catalyst. High efficiency of **5** was also observed with other substrate sets (Table 5, entries 7–15). The reaction of bulkier naphthyl-substituted amide **1c** with 2 mol% of **5** afforded similar results to those obtained under the previous conditions (Table 5, entry 7). Substrate **1d** bearing a methoxy substituent at the *meta* position was converted to product **2d** with 94% *ee*, albeit with 3 mol% of catalyst **5** (Table 5, entry 8). Although the reaction of **1e** with 2 mol% of bis-phosphine **3** was not complete after 3 h, the reaction could be run with 2 mol% of monoxide catalyst **5** to afford the corresponding oxazoline **2e** in 97% yield with 99% *ee* (Table 5, entry 9). Compounds with electron-withdrawing 3-CF_3 and 4-CN substituents exhibited particularly high reactivity under the present conditions, affording the desired oxazolines **2f**, **2g** with excellent enantioselectivity at only 1 mol% catalyst loading (Table 5, entries 10 and 11). In addition, medicinally important heteroaromatic substructures, such as a pyridine or thiophene ring, were successfully used in the present reaction, and drug-like products **2h** and **2i** were obtained with high enantioselectivity (Table 5, entries 12 and 13). Alkyl-substituted amide **1j** was also suitable for this reaction, affording **2j** in 85% *ee*.

Finally, with the improved reaction conditions in hand, we turned our attention to the substrate scope of this reaction. The rich chemistry of alkynes[23] prompted us to examine enyne-type substrates (Scheme 7). Whereas the reaction of **1k** with 2 mol% catalyst loading showed poor conversion and enantioselectivity, the cyclization product **2k** was formed with high enantioselectivity at 10 mol% catalyst loading, and the alkyne moiety remained intact (Scheme 7a). In comparison, lower yield and enantioselectivity were observed under the previous conditions (10 mol% of **3**). In the case of substrate **1l** bearing an electron-withdrawing bromo group at the *para* position, the desired bromocyclization was sluggish and afforded **2l** in only 15% yield with moderate enantioselectivity (Scheme 7b). In contrast, the counterpart with an electron-rich *para*-methyl substituent gave the product **2m** in high yield

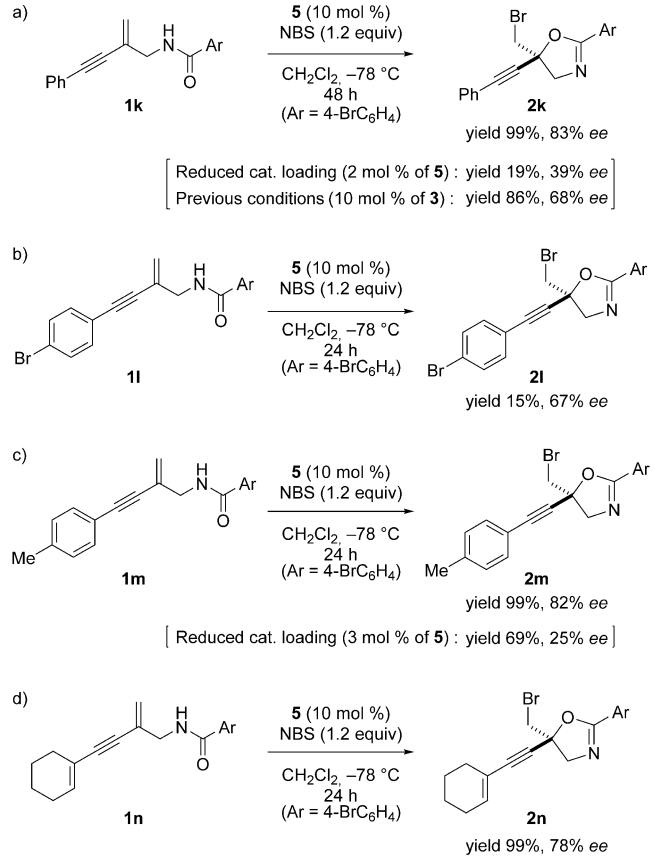
Table 5. Scope of the bromocyclization of allylic amides.[a]



1 2

Entry	R	2	Previous conditions: DTBM-BINAP (**3**)				Current conditions: DTBM-BINAP monoxide (**5**)			
			Cat. [mol%]	*t* [h]	Yield[b] [%]	*ee*[c] [%]	Cat. [mol%]	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1	Ph	**2a**	5	12	99	96	5	12	96	99
2	Ph	**2a**	2	12	99	97	2	12	98	99
3[d]	Ph	**2a**	1	12	99	99	1	12	99	98
4[e]	Ph	**2a**			–		0.5	12	65	44
5[f]	4-MeC_6H_4	**2b**	10	24	91	95	5	12	96	98
6[f]	4-MeC_6H_4	**2b**			–		1	12	91	97
7	2-naphthyl	**2c**	10	12	99	90	2	3	88	89
8	3-$MeOC_6H_4$	**2d**	10	12	85	93	3	12	85	94
9	4-BrC_6H_4	**2e**	2	3	80	95	2	3	98	99
10	3-$F_3CC_6H_4$	**2f**	10	12	94	99	1	12	91	98
11	4-NCC_6H_4	**2g**	10	24	95	98	1	12	90	>99.5
12[f]	3-pyridyl	**2h**	10	24	84	90	2	24	88	93
13[f]	3-thienyl	**2i**	10	24	97	91	3	24	92	87
14[f]	*c*-hexyl	**2j**	10	12	91	86	5	24	99	85

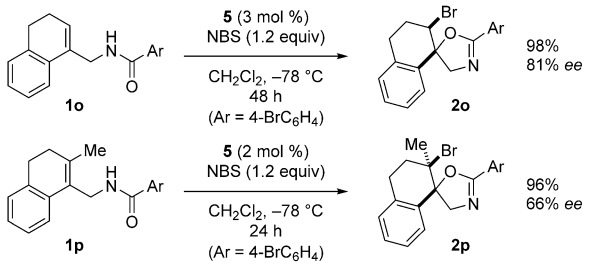
[a] **1**: 0.1 mmol. [b] Yield of isolated product. [c] The *ee* was determined by chiral HPLC analysis. [d] 1.5 mmol of **1a** was used. [e] 1.0 mmol of **1a** was used. [f] The Ph group of **1** was replaced with a 4-BrC_6H_4 group.



Scheme 7. Bromocyclization of enyne-type allylic amides.

and enantioselectivity (Scheme 7c). When cyclohexene-substituted enyne **1n** was used, regioselective bromination occurred on the proximal olefin to the amide functionality, furnishing the corresponding oxazoline **2n** in 78% *ee* (Scheme 7d).[24,5a]

We then explored tri- and tetrasubstituted olefin substrates, which have received less attention in the literature. Dihydronaphthalene-type amide substrates **1o** and **1p** furnished the desired spiro-oxazolines in excellent yield with synthetically acceptable enantioselectivity (Scheme 8). In each case, a single diastereomer was observed in the ^{1}H NMR spectra of the crude mixture. Notably, these are the first examples of the diastereo- and enantioselective synthesis of spiro-oxazolines by bromocyclization of allylic amides.



Scheme 8. Reactions of tri- and tetrasubstituted olefin substrates.

Conclusion

We have reported a detailed mechanistic study on a highly enantioselective bromocyclization of allylic amides recently reported by us. Control experiments and NMR studies indicated that DTBM-BINAP monoxide (**5**) generated in situ serves as the actual enantioselective catalyst. We propose that P^+Br serves as a fine-tuning element that fixes the substrate in the chiral environment, while P^+OBr reacts with the olefin as the Br^+ transfer agent. The catalyst loading could be reduced to as little as 1 mol%, and we obtained a series of chiral oxazolines with up to $>99.5\%$ *ee*. Since our P/P=O compound appears to be a unique double-site Lewis base catalyst, we believe that this work will stimulate further research on halogenation reactions. Application of the present P/P=O catalyst to novel reactions related to vicinal halofunctionalization, including intermolecular reactions, is ongoing.

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[19] A mixture of PPh_3 and NBS exhibited a new peak similar to that seen in Figure 2a. In this case, however, other peaks also appeared at various temperatures, likely due to equilibrium with nucleophilic attack of the succinimide anion on the bromophosphonium ion. See also ^{31}P NMR spectroscopic data of phosphonium salts: E. Krawczyk, A. Skowrońska, J. Michalski, *J. Chem. Soc. Dalton Trans.* **2002**, 4471 – 4478.

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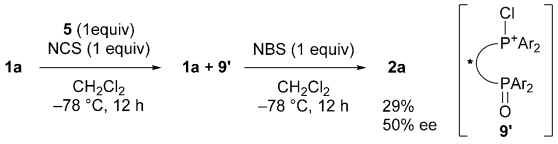
[21] An equimolar amount of **1a** was treated with the chlorophosphonium counterpart **9′**, prepared from the same equivalents of **5** and *N*-chlorosuccinimide (NCS), but no stoichiometric reaction occurred. After further addition of another equivalent of NBS, bromocyclization product **2a** was formed in 29% yield with 50% *ee*.



[22] Various benzoyl-protected allylic amides were tested under the standard conditions. The highest enantioselectivity was observed when the amino group was protected with a 4-Br-benzoyl group. In general, *ee* was improved by an electron-withdrawing group at the *para* position, but decreased by an electron-donating group. See also ref. [11].

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