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ARTICLE TYPE

Enantioselective *6-endo* Bromoaminocyclization of 2,4-Dienyl *N*-Tosylcarbamates Catalyzed by a Chiral Phosphine Oxide-Sc(OTf)$_3$ Complex. A Dramatic Additive Effect

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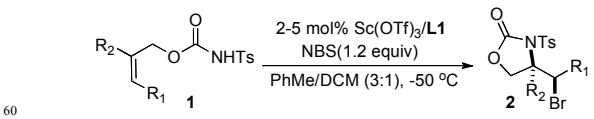
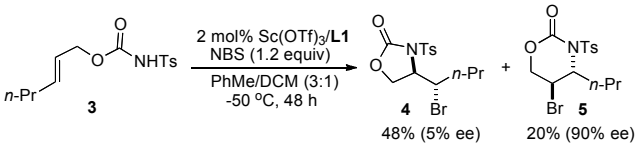
An effective enantioselective 6-endo bromoaminocyclization of 2,4-dienyl *N*-tosylcarbamates catalyzed by a chiral phosphine oxide-Sc(OTf)$_3$ complex is described. A wide variety of optically active 5-bromo-1,3-oxazinan-2-ones containing various functional groups can be obtained in 61-91% yields and 92-99% ee's. An additive, such as NaCl, has been found to be crucial for the reaction process.

Asymmetric electrophilic halogenation of olefins provides an effective approach to simultaneously install two chiral C-X bonds, and has received extensive attention particularly in recent years.[1] A number of effective systems have been developed for both intramolecular[2-4] and intermolecular[5] processes. In our own studies, we have recently shown that a chiral Sc(OTf)$_3$-**L1** (Trost ligand)[6] complex is a highly effective catalyst for enantioselective bromoaminocyclization of (*Z*)-allyl *N*-tosylcarbamates (**1**), providing a variety of optically active 5-exo bromoaminocyclization products **2** in high ee's (Scheme 1) (Fig. 1).[7] When a trans substrate **3** was subjected to the reaction conditions, a mixture of 5-exo and 6-endo isomers was obtained (Scheme 2). While as a minor isomer, the 6-endo product **5** was formed with higher enantioselectivity (90% ee).[7] Optically active 5-bromo-1,3-oxazinan-2-ones **5** resulting from the 6-endo cyclization are potentially useful chiral building blocks and not readily available, which prompted us to search for suitable substrates favorable for the 6-endo cyclization. Along this line, we investigated the bromoaminocyclization of 2,4-dienyl *N*-tosylcarbamates with hope that the 6-endo cyclization could be electronically favored by a conjugating double bond (Scheme 3). Herein, we wish to report our preliminary studies on this subject.

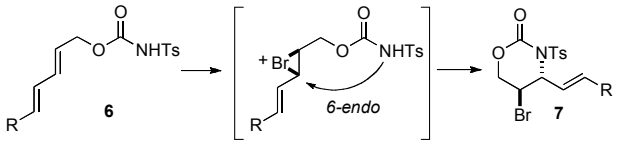
Our initial studies were carried out with (2*E*,4*E*)-hexa-2,4-dienyl tosylcarbamate (**6a**) as test substrate in the presence of 5 mol% Sc(OTf)$_3$-**L1** complex. No cyclization products were obtained with most of the bromine reagents examined such as *N*-bromosuccinimide (NBS), *N*-bromophthalimide (NBP), and 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCO) (Table 1, entries 1-3). When 1,3-dibromo-5,5-dimethylhydantion (DBDMH) was used, optically active 5-bromo-1,3-oxazinan-2-one **7a** could be isolated along with other unidentified isomers (Table 1, entry 4). To our delight, the 6-endo cyclization proceeded with high regioselectivity when chiral phosphine oxide **L2** (prepared by the oxidation of Trost ligand **L1**) was used as ligand (Fig. 1). The desired 6-endo product **7a** was isolated in 93% yield and 96% ee with 5 mol% Sc(OTf)$_3$-**L2** catalyst in $CHCl_3$ at -50 °C (Table 1, entry 7). These results show that the phosphine oxide ligand **L2** is superior to the phosphine ligand **L1** for the current bromoaminocyclization for the reason that is currently unclear. Among the solvents examined, $CHCl_3$ was found to be optimal (Table 1, entries 6, 9, 10, & 11). When the amount of DBDMH was reduced to 0.6 equiv, **7a** was obtained in lower yield (65%) and ee (90%) (Table 1, entry 12 vs entry 7), suggesting that the two Br in DBDMH do not have the same reacting properties for the bromoaminocyclization. Both Sc(OTf)$_3$ and the ligand were required for the reaction. Compound **7a** was not obtained with Sc(OTf)$_3$ alone (Table 1, entry 13). A messy mixture was formed with ligand **L2** in the absence of Sc(OTf)$_3$ (Table 1, entry 14).



Scheme 1

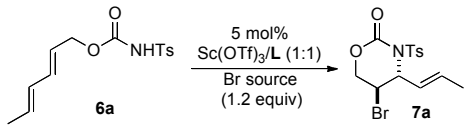


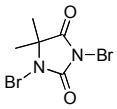
Scheme 2



Scheme 3

Table 1 Studies of the reaction conditions.[a]



Entry	Br source	Solvent	T (°C)	L	Yield(%)[b]	ee(%)[c]
1	NBS	$CHCl_3$	-40	**L1**	-	-
2	NBP	$CHCl_3$	-40	**L1**	-	-
3	TBCO	$CHCl_3$	-40	**L1**	-	-
4		$CHCl_3$	-40	**L1**	28[d]	84
5[e]		$CHCl_3$	-40	**L1**	messy mixture	
6		$CHCl_3$	-40	**L2**	74	96
7		$CHCl_3$	-50	**L2**	93	96
8		$CHCl_3$	-60	**L2**	88	97
9		DCM	-40	**L2**	74	91
10		THF	-40	**L2**	-	-
11		EtOAc	-40	**L2**	-	-
12[e]		$CHCl_3$	-50	**L2**	65	90
13		$CHCl_3$	-50	-	-	-
14[f]		$CHCl_3$	-50	**L2**	messy mixture	-

[a] The reactions were carried out with substrate **6a** (0.20 mmol), Br source (0.24 mmol), and Sc(OTf)$_3$-**L** (1:1) (0.010 mmol) in solvent (2.0 mL) for 18 h unless otherwise noted. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] A mixture of isomers. [e] The amount of DBDMH was 0.12 mmol. [f] Without Sc(OTf)$_3$

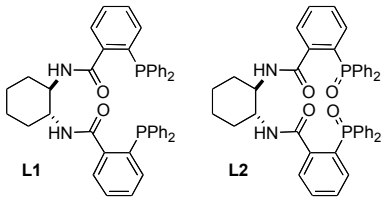


Fig. 1 Chiral ligands examined.

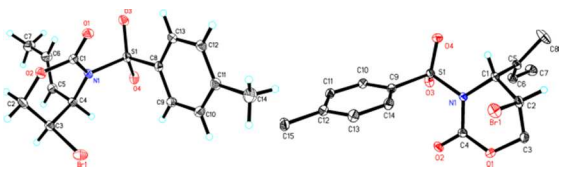
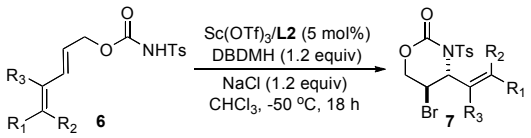
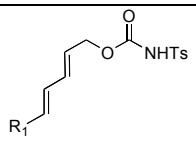
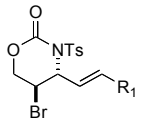
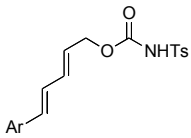
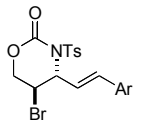
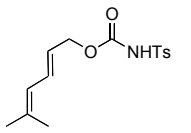
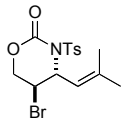
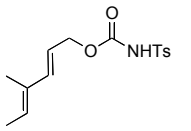
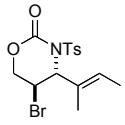
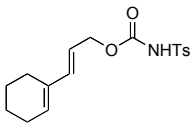
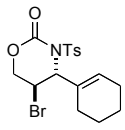


Fig. 2 The X-ray structure of compound **7a** and **7m**.

The substrate scope with the Sc(OTf)$_3$-**L2** system was subsequently investigated. To our surprise, no desired cyclization product was obtained with (2*E*,4*E*)-hepta-2,4-dienyl tosylcarbamate (**6b**) in stark contrast to (2*E*,4*E*)-hexa-2,4-dienyl tosylcarbamate (**6a**) (Table 2, entry 1). The earlier observation on the sensitivity of

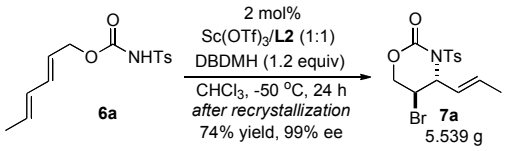
Table 2 Enantioselective bromoaminocyclization of 2,4-dienyl *N*-tosylcarbamates.[a]



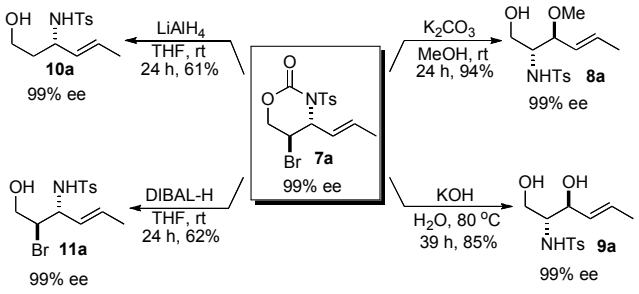
Entry	Substrate	Product[c]	Yield (%)[d]	ee (%)[e]
				
1[b]	R_1 = Me, **6a**	**7a** (X-ray)	91	97
2	R_1 = Et, **6b**	**7b**	83	96
3	R_1 = Pr, **6c**	**7c**	87	95
4	R_1 = Bu, **6d**	**7d**	79	93
5	R_1 = *i*-Pr, **6e**	**7e**	84	95
6	R_1 = CH_2OMe, **6f**	**7f**	77	97
7	R_1 = CH_2OAc, **6g**	**7g**	71	95
8	R_1 = CH_2N_3, **6h**	**7h** (X-ray)	65	95
				
9	Ar = Ph, **6i**	**7i** (X-ray)	61	95
10	Ar = 4-ClPh, **6j**	**7j**	71	95
11	Ar = 4-FPh, **6k**	**7k**	68	97
				
12	**6l**	**7l** (X-ray)	79	92
				
13	**6m**	**7m** (X-ray)	81	98
				
14	**6n**	**7n**	64	99

[a] The reactions were carried out with substrate **6** (0.50 mmol), Sc(OTf)$_3$-**L2** (1:1) (0.025 mmol), NaCl (0.60 mmol), and DBDMH (0.60 mmol) in $CHCl_3$ (5.0 mL) at -50 °C for 18 h unless otherwise noted. [b] The reaction was carried out in the absence of NaCl. [c] The absolute configurations of **7a**, **7h**, **7i**, **7l**, and **7m** were assigned based on their X-ray structures. The absolute configurations of the others were tentatively proposed by analogy. [d] Isolated yield. [e] Determined by chiral HPLC analysis.

the bromoaminocyclization to the source of DBDMH with **L1** (Table 1, entry 4) made us surmise that different batches of DBDMH might contain varying amounts of salts, which could play a role in the reaction. After much experimentation, it was found that the reaction can be greatly promoted by the addition of NaCl.[8] The desired product **7b** was isolated in 83% yield and 96% ee with 5 mol% $Sc(OTf)_3$-**L2** in the presence of 1.2 equiv. of NaCl in $CHCl_3$ at -50 °C (Table 2, entry 2). As shown in Table 2, this new condition can be extended to a variety of 2,4-dienyl tosylcarbamates to give the corresponding 5-bromo-1,3-oxazinan-2-ones in 61-87% yields and 92-99% ee's (Table 2, entries 2-14) (the X-ray structures of **7a** and **7m** are shown in Fig. 2). The substituents on the diene can be linear (Table 2, entries 2-4) or branched (Table 2, entry 5) alkyl groups. Various functional groups such as OMe, OAc, and N_3 can be tolerated (Table 2, entries 6-8). Aryl-substituted (Table 2, entries 9-11) and trisubstituted dienes (Table 2, entries 12-14) were also effective substrates for the reaction.



Scheme 4 Bromoaminocyclization on a gram scale

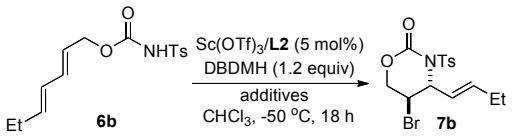


Scheme 5 Synthetic transformations of bromide **7a**

The reaction can be carried out on a relatively large scale. As exemplified by **7a**, over 5 g of the compound was obtained in 74% yield with 99% ee after recrystallization using 2 mol% $Sc(OTf)_3$-**L2** (Scheme 4). As illustrated in Scheme 5, 5-bromo-1,3-oxazinan-2-one **7a** can serve as versatile synthetic intermediate. Treating **7a** with K_2CO_3-MeOH or KOH-H_2O led to compound **8a** or **9a** in 94% and 85% yield, respectively. The reaction process likely proceeded via an aziridine intermediate,[5m] which was opened under the reaction conditions by a nucleophile at the allylic position with inversion of the configuration. When **7a** was treated with $LiAlH_4$ or DIBAL-H, compounds **10a** and **11a** were obtained in 61% and 62% yield, respectively. Compounds **8a**, **9a**, **10a**, and **11a** are also potentially useful building blocks. For example, 2-aminopent-4-ene-1,3-diol fragment of compound **9a** is the core functional moiety contained in various biologically important sphingosine and related analogues.[9]

The effect of NaCl is very intriguing. Additional studies were carried out with various additives (Table 3). A catalytic amount

Table 3 The effect of additives.[a]



Entry	Additive	equiv	Yield(%)[b]	ee(%)[c]
1	NaCl	1.2	85	95
2	NaCl	0.5	78	94
3	NaCl	0.1	84	96
4	NaBr	1.2	75	91
5	NaI	1.2	messy mixture	-
6	LiCl	1.2	42[d]	43
7	KCl	1.2	77	93
8	CsCl	1.2	76	92
9	K_2CO_3	1.2	65	82
10	Na_2SO_4	1.2	-	-

[a] The reactions were carried out with substrate **6b** (0.20 mmol), $Sc(OTf)_3$-**L2** (1:1) (0.010 mmol), DBDMH (0.24 mmol), and additive in $CHCl_3$ (2.0 mL) at -50 °C for 18 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] A mixture of isomers.

of NaCl was found to be sufficient to promote the reaction (Table 3, entries 1-3). The exact role of NaCl is not clear at this moment.[10] Compound **7b** was isolated in slightly lower yield and ee with NaBr (Table 3, entry 4). A messy mixture was obtained with NaI (Table 3, entry 5). The counter cation was also found to be important for the reaction. LiCl gave the poorest result as compared to NaCl, KCl, CsCl (Table 3, entry 6 vs entries 1, 7, & 8). With K_2CO_3, compound **7b** was obtained in 65% yield and 82% ee (Table 3, entry 9). No desired compound was obtained with Na_2SO_4 (Table 3, entry 10).

Conclusion

In summary, we have developed an efficient enantioselective 6-endo bromoaminocyclization of 2,4-dienyl *N*-tosylcarbamates using DBDMH as bromine source and chiral phosphine oxide-$Sc(OTf)_3$ complex as catalyst. Additive, such as NaCl, has been found to be crucial for the reaction. A wide variety of optically active 5-bromo-1,3-oxazinan-2-ones containing various functional groups can be obtained in good yields and high enantioselectivities. The reaction is amenable to gram scale. The resulting 5-bromo-1,3-oxazinan-2-one can be further transformed into various useful compounds containing diverse functional groups. Further efforts will be devoted to understanding the reaction mechanism and the effect of additives, developing more efficient catalytic systems, and expanding the substrate scope.

Acknowledgements

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental, characterization data, X-ray structures of compounds **7a** (CCDC 1038311), **7h** (CCDC 1038312), **7i** (CCDC 1038321), **7l** (CCDC 1038313), **7m** (CCDC 1038314), **9a** (CCDC 1038315), **10a** (CCDC 1038316) **12a** (CCDC 1038318), **13a** (CCDC 1038317), and NMR spectra. See DOI: 10.1039/b000000x/

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