Brønsted acid catalyzed regioselective aza-Ferrier reaction: a novel synthetic method for α-(*N*-Boc-2-pyrrolidinyl) aldehydes†

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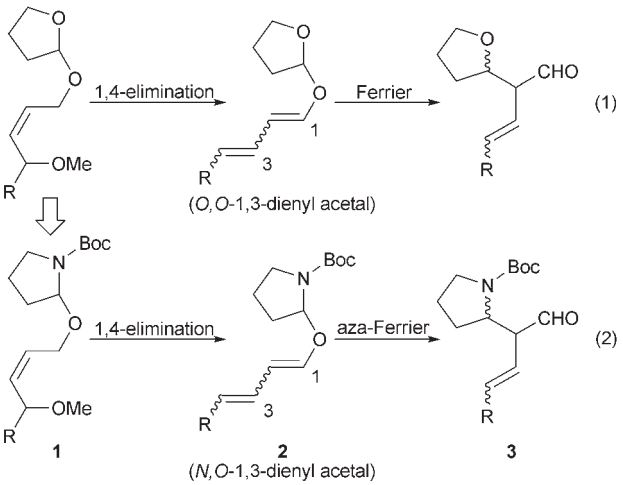
The 1,4-elimination reaction of (*Z*)-*N*-Boc-2-(4-methoxy-2-alkenyloxy)pyrrolidines (1) is shown to proceed with high (1*E*,3*E*)-stereoselectivity to afford *N*-Boc-2-(1,3-dienyloxy)pyrrolidines (2); the Brønsted acid catalyzed aza-Ferrier reaction of the *N*-Boc-2-(1,3-dienyloxy)pyrrolidines (2) provides α-(*N*-Boc-2-pyrrolidinyl) aldehydes (3) in excellent yields with high α-regioselectivities.

The Ferrier reaction[1] of *O*-alkenyl acetals is a unique and powerful synthetic transformation since it can easily convert an O–C bond into a new C–C bond; hence, it has found wide application in the synthesis of oxygen-containing heterocycles such as tetrahydropyranyl derivatives and *C*-glycosides.[2,3] The reaction proceeds *via* Lewis acid catalyzed cleavage of an O–C bond of an *O*,*O*-alkenyl acetal to generate the oxocarbenium ion and an enolate. Their recombination then affords the corresponding β-alkoxy carbonyl compound, but the reaction *via* an *N*-acyliminium ion intermediate (aza-Ferrier reaction) generated from *N*,*O*-alkenyl acetals has been quite limited.[4,5]

Recently, we have reported a stereoselective synthetic method for *O*-1,3-dienyl acetals by 1,4-elimination of (*Z*)-4-methoxy-*O*-alkenyl acetals and the regio- and stereoselective Ferrier reaction of the *O*-1,3-dienyl acetal products (Scheme 1, eqn (1)).[6] With this method in hand, we tried to extend the reaction protocol to *O*-(*N*-Boc-2-pyrrolidinyl) derivatives **1**, which would afford the corresponding *N*-Boc-2-(1,3-dienyloxy)pyrrolidines **2** by 1,4-elimination, and α-(*N*-Boc-2-pyrrolidinyl) aldehydes **3** by an acid catalyzed aza-Ferrier reaction (eqn (2)).

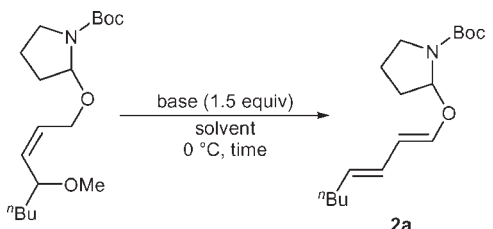
First, we carried out the 1,4-elimination reaction of (*Z*)-*N*-Boc-2-(4-methoxyoct-2-en-1-yloxy)pyrrolidine (**1a**)[7] with lithium diisopropylamide (LDA) in THF (Table 1, entry 1) at 0 °C. The corresponding 1,4-elimination product, (1*E*,3*E*)-*N*-Boc-2-(octa-1,3-dien-1-yloxy)pyrrolidine (**2a**) was obtained in 74% yield as a single stereoisomer (6 : 4 mixture of rotamers). The C_1–C_2 stereochemistry of **2a** was assigned to be *E* by ^{1}H NMR analysis of the 1H-proton [δ 6.70 (d, $J_{1H,2H}$ = 11.6 Hz) for the minor rotamer; δ 6.52 (d, $J_{1H,2H}$ = 11.6 Hz) for the major rotamer].[8] The C_3–C_4 stereochemistry was assigned to be *E* after conversion to aza-Ferrier product **3a** (*cf*. Table 3). Use of *n*-butyllithium in THF or ether did not give **2a** because of decomposition of the substrate **1a** or product **2a** (entries 2, 3).[9] Use of lithium 2,2,6,6-tetramethylpiperidide (LiTMP) in THF, however, provided high yields (entry 4, 1.5 h, 79% yield; entry 5, 15 h, 81% yield) without formation of undesirable side products.



Scheme 1 Application of 1,4-elimination and the Ferrier reaction to *O*-(*N*-Boc-2-pyrrolidinyl) derivatives.

To define the scope and limitations of the present 1,4-elimination reaction of **1**, we prepared a series of substrates **1b–1h** and carried out their reactions with LiTMP (Table 2). Though the corresponding *N*-Boc-2-(1,3-dienyloxy)pyrrolidines **2b–2f** were obtained in reasonable yields with excellent stereoselectivities (entries 1–5), 2-substituted substrates such as 2-methyl- (entry 6, R^3 = Me, **1g**) and 2-butyl- (entry 7, R^3 = ^{n}Bu, **1h**) derivatives were found to be unreactive, producing **2g** and **2h** in lower yields.[10]

Table 1 Stereoselective 1,4-elimination reaction of **1a**



Entry	Base	Solvent	Time/h	Yield (%)[a]
1	LDA	THF	1	74
2	^{n}BuLi	THF	1	0
3	^{n}BuLi	Et_2O	1	0
4	LiTMP	THF	1.5	79
5	LiTMP	THF	15	81

[a] Isolated yield.

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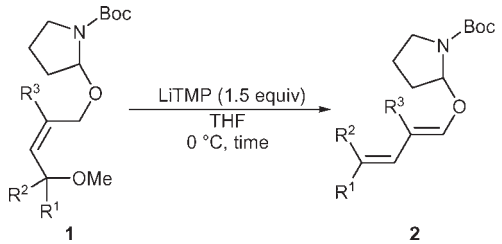
Table 2 1,4-Elimination reaction of various types of **1**



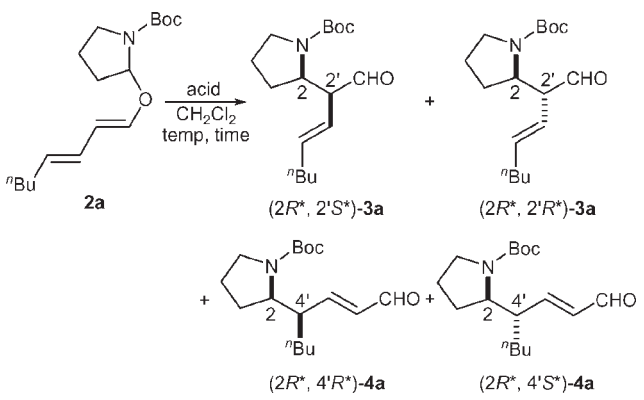
1 **2**

Entry	R^1	R^2	R^3		Time/h	Yield (%)[a]
1	CH_2CH_2Ph	H	H	**b**	17	77
2	Et	H	H	**c**	13	73
3	Me	Me	H	**d**	18	79
4	$-(CH_2)_5-$		H	**e**	2	76
5	H	H	H	**f**	15	61
6	^{n}Bu	H	Me	**g**	22	55
7	^{n}Bu	H	^{n}Bu	**h**	22	<10

[a] Isolated yield.

Next, we investigated the aza-Ferrier reaction of *N*-Boc-2-(1,3-dienyloxy)pyrrolidine **2a** in the presence of Lewis acid catalysts (Table 3). Both the stoichiometric and catalytic use of boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) and titanium tetrachloride ($TiCl_4$) were found to provide the corresponding aza-Ferrier product in excellent yields as a mixture of α-adduct **3a** and γ-adduct **4a** (entries 1–4).[11] The α- and γ-regioisomers were assigned by ^{1}H NMR analysis (olefinic protons: 5.61–5.33 ppm for **3a**; 6.69–6.11 ppm for **4a**). The α-adduct **3a** was obtained as a mixture of diastereomers [(2*R**,2′*S**) and (2*R**,2′*R**)], and the relative stereochemistry of **3a** was determined by ^{1}H NMR analysis after conversion to the corresponding cyclic carbamate.[12] The γ-adduct **4a** was obtained as a single stereoisomer [(2*R**,4′*R**)], and the relative stereochemistry of **4a** was determined by ^{1}H NMR comparison with an authentic sample.[13] The double bond geometries of **3a** and **4a** were determined to be *E* by ^{1}H NMR analysis (J = 15.7 Hz). Significantly, when the reaction of **2a** was catalyzed by Brønsted acids such as *p*-toluenesulfonic acid (*p*-TsOH), *dl*-camphorsulfonic acid, or pyridinium *p*-toluenesulfonate (PPTS), the α-regioisomer **3a** was obtained exclusively (entries 5–7, 76–96% yield).[14] No detectable γ-regioisomer **4a** was observed. At present, the exact origin of the high α-regioselectivity is unclear.[15]

Table 3 Aza-Ferrier reaction of **2a** promoted by several representative acid catalysts



2a

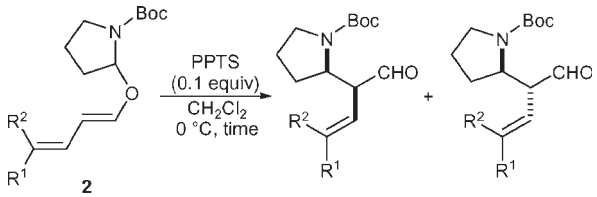
(2*R**, 2′*S**)-**3a** (2*R**, 2′*R**)-**3a**

(2*R**, 4′*R**)-**4a** (2*R**, 4′*S**)-**4a**

Entry	Acid (equiv.)	Temp., time (°C, h)	Yield (%)[a] **3a** (dr)[bc]	**4a** (dr)[cd]
1	$BF_3{\cdot}OEt_2$ (1.1)	−78, 1	59 (8 : 2)	21 (>20 : 1)
2	$BF_3{\cdot}OEt_2$ (0.2)	−78, 1	71 (8 : 2)	4 (>20 : 1)
3	$TiCl_4$ (1.1)	−78, 1	40 (6 : 4)	51 (>20 : 1)
4	$TiCl_4$ (0.2)	−78, 1	64 (7 : 3)	22 (>20 : 1)
5	*p*-TsOH·H_2O (0.1)	0, 3	76 (6 : 4)	0
6	*dl*-Camphorsulfonic acid (0.1)	0, 3	80 (6 : 4)	0
7	PPTS (0.1)	0, 3	96 (7 : 3)	0

[a] Isolated yield. [b] (2*R**,2′*S**) : (2*R**,2′*R**). [c] The diastereomeric ratios were determined by ^{1}H NMR assay. [d] (2*R**,4′*R**) : (2*R**,4′*S**).

Table 4 The α-regioselective aza-Ferrier reaction of various types of **2**



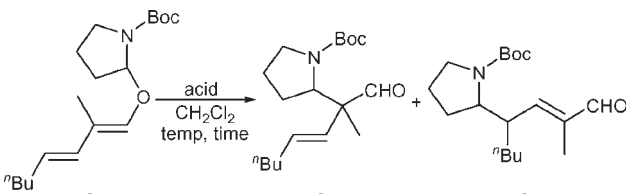
2 (2*R**, 2′*S**)-**3** (2*R**, 2′*R**)-**3**

Entry	R^1	R^2		Time/h	Yield (%)[a]	dr[b]
1	CH_2CH_2Ph	H	**b**	3	92	6 : 4
2	Et	H	**c**	3	93	7 : 3
3	Me	Me	**d**	3	93	8 : 2
4	$-(CH_2)_5-$		**e**	3	87	7 : 3
5	H	H	**f**	5	64	6 : 4

[a] Isolated yield. [b] (2*R**,2′*S**) : (2*R**,2′*R**). The ratios were determined by ^{1}H NMR assay. The relative stereochemistries of **3c**, **3d**, and **3f** were determined by the same procedures described in ref. 12. The relative stereochemistries of **3b** and **3e** were determined by analogy.

To further expand the scope of the α-regioselective aza-Ferrier reaction, we carried out the reactions of *N*-Boc-2-(1,3-dienyloxy)pyrrolidines **2b–2f** with PPTS in dichloromethane. As shown in Table 4, various types of α-(*N*-Boc-2-pyrrolidinyl) aldehydes **3** were obtained with excellent yields and high

Table 5 Formation of a quaternary carbon stereocenter by the aza-Ferrier reaction of **2g**



2g **3g** **4g**

Entry	Acid (equiv.)	Temp., time (°C, h)	Yield (%)[a] **3g** (dr)[b]	**4g** (dr)[b]
1	PPTS (0.1)	0, 3	0	0
2	*p*-TsOH·H_2O (0.1)	0, 3	63 (8 : 2)	17 (7 : 3)
3	*p*-TsOH·H_2O (0.1)	−20, 3	68 (8 : 2)	11 (7 : 3)
4	*dl*-Camphorsulfonic acid (0.1)	−20, 3	79 (8 : 2)	15 (7 : 3)

[a] Isolated yield. [b] The ratios were determined by ^{1}H NMR assay.

α-regioselectivities (entries 1–5). Interestingly, the aza-Ferrier reaction of γ-unsubstituted substrate **2f** catalyzed by PPTS also showed an equally high α-regioselectivity to afford **3f** (entry 5, 64% yield).[16]

Finally, the α-regioselective aza-Ferrier reaction of the 2-methyl-substituted-1,3-dienyl substrate **2g** was attempted to form an α-quaternary carbon stereocenter (Table 5). Unfortunately, however, the reaction of **2g** with PPTS did not give the aza-Ferrier products **3g** and **4g** (entry 1), and the starting material **2g** was recovered in 49% yield. Thus, we carried out the reaction using more acidic Brønsted acid catalysts (entries 2–4). The best result was obtained by using *dl*-camphorsulfonic acid (entry 4) to afford α-adduct **3g** (79% yield) and γ-regioisomer **4g** (15% yield).[17]

In summary, we have demonstrated that the stereoselective 1,4-elimination reaction of (*Z*)-*N*-Boc-2-(4-methoxy-2-alkenyloxy)-pyrrolidines (**1**) with LiTMP proceeded to give *N*-Boc-2-(1,3-dienyloxy)pyrrolidines (**2**) in good yields with high (1*E*,3*E*)-stereoselectivities. Application to the aza-Ferrier reaction of *N*-Boc-2-(1,3-dienyloxy)pyrrolidines in the presence of Brønsted acids such as PPTS or *dl*-camphorsulfonic acid afforded the corresponding α-(*N*-Boc-2-pyrrolidinyl) aldehydes (**3**) in excellent yields with high α-regioselectivities. While further mechanistic studies on the regioselectivity are needed, this method expands the synthetic scope of the Ferrier-type reaction. Further work to develop the asymmetric aza-Ferrier reaction is in progress.

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7 Prepared from *N*-Boc-2-hydroxypyrrolidine and (*Z*)-4-methoxyoct-2-en-1-ol by acetal exchange reaction [$Sc(OTf)_3$, 3 Å MS, CH_2Cl_2]. For more details, see ESI†.

8 When the 1,4-elimination of the 2*E*-isomer of **1a** was carried out under the same conditions, (1*Z*)-**2a** was obtained exclusively (79% yield) as a 5 : 5 mixture of (1*Z*,3*E*) : (1*Z*,3*Z*). ^{1}H NMR analysis of (1*Z*)-**2a** showed four chemical shifts for the 1H-proton because of the formation of rotamers ($J_{1H,2H}$ = 6.0 Hz for each isomer). Similar selectivities were reported in ref. 6.

9 Small amounts of aza-Ferrier product **3a** and decomposition material (allylic alcohol) were observed.

10 The 1,4-elimination of 2-alkyl substituted substrate **1g** or **1h** proceeded slower than **1a–1f** and the starting material was recovered (21% recovery of **1g**; 49% recovery of **1h**).

11 Similar selectivities were observed in our previous report (ref. 6); the use of $TiCl_4$ improved γ-regioselectivities.

12 Reduction of **3a** ($NaBH_4$, MeOH) followed by intramolecular cyclization (NaH, THF) gave the corresponding cyclic carbamate as a mixture of diastereomers. The relative stereochemistries were determined from ^{1}H NMR analysis, which showed *syn* or *anti* coupling constants of 5 Hz and 11 Hz, respectively. For more details, see ESI†.

13 Oxidation of **4a** (OsO_4, $NaIO_4$, CH_3CN–H_2O) afforded the corresponding aldehyde, and an authentic sample of the aldehyde was prepared from **3c** by hydrogenation (Pd/C, H_2, EtOAc). The relative stereochemistry of **3c** was determined by the same procedures described in ref. 12. For more details, see ESI†.

14 When the product **3a** (dr = 8 : 2, obtained from entry 1 or 2) was treated with *dl*-camphorsulfonic acid (0.1 equiv.) in dichloromethane at room temperature for 3 h, **3a** was recovered in 69% yield and the diastereomeric ratio was changed to 6 : 4. The diastereomeric ratios in Table 4 may be determined after epimerization.

15 Formation of α-regioisomer **3a** from γ-regioisomer **4a** *via* a reversible process was not observed. When **4a** was treated with PPTS (0.1 equiv., CH_2Cl_2, rt for 3 h), no detectable amount of **3a** was observed and **4a** was recovered in 91% yield without any isomerization (*trans*-aldehyde only).

16 When the reaction of **2f** was carried out with a stoichiometrica-mount of $TiCl_4$, the corresponding γ-adduct [γ-(*N*-Boc-2-pyrrolidinyl)-α,β-unsaturated aldehyde] was obtained exclusively in 79% yield.

17 The α-regioselectivity was not improved when the reaction was carried out under lower temperatures (−40 and −60 °C).

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