Bronsted acid catalyzed regioselective aza-Ferrier reaction: A novel synthetic method of α-(*N*-Boc-2-pyrrolidinyl)aldehydes

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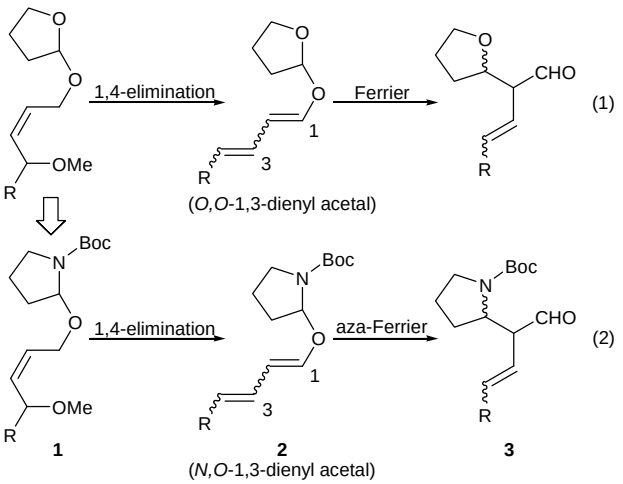
The 1,4-elimination reaction of (*Z*)-*N*-Boc-2-(4-methoxy-2-alkenyloxy)pyrrolidines (1) is shown to proceed with high (1*E*, 3*E*)-stereoselectivities to afford *N*-Boc-2-(1,3-dienyloxy)-pyrrolidines (2). The Bronsted acid catalyzed aza-Ferrier reaction of the *N*-Boc-2-(1,3-dienyloxy)pyrrolidine (2) 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 for 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 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]

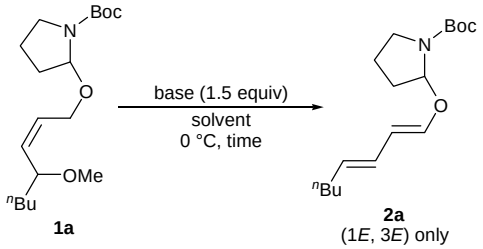
Recently, we have reported a stereoselective synthetic method of *O*-1,3-dienyl acetals by 1,4-elimination of (*Z*)-4-methoxy-*O*-alkenyl acetals and the regio- and stereoselective Ferrier reaction of the *O*-1,3-dienyl acetal products (Scheme 1, eq 1).[6] With this method in hand, we tried to extend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

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

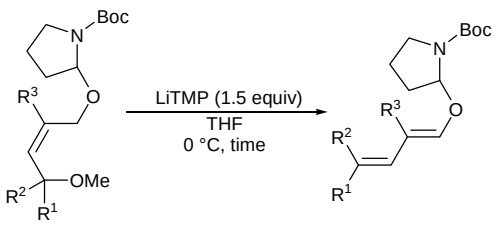


entry	base	solvent	time (h)	yield (%)[a]
1	LDA	THF	1	74
2	^{n}BuLi	THF	1	0
3	^{n}BuLi	Et_2O	1	0
4	LiTMP	THF	1.5	79
5	LiTMP	THF	15	81

[a] Isolated yield.

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.

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



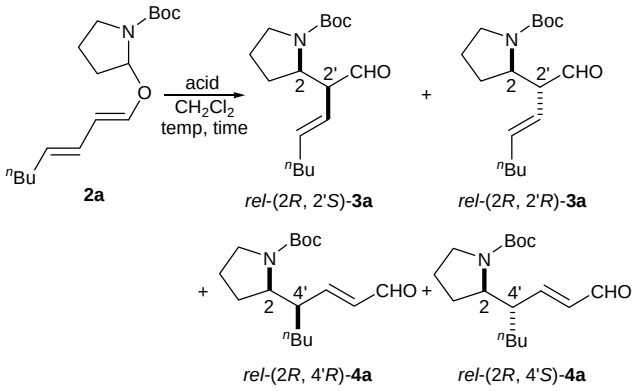
1 **2**

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 the 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).[10] The

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



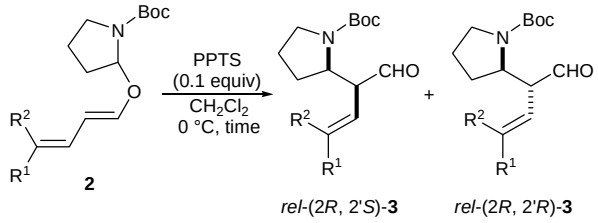
entry	acid (equiv)	temp, time (°C, h)	yield (%)[a] **3a** (dr)[b,c]	**4a** (dr)[c,d]
1	$BF_3{\cdot}OEt_2$ (1.1)	–78, 1	59 (8:2)	21 (>20:1)
2	$BF_3{\cdot}OEt_2$ (0.2)	–78, 1	71 (8:2)	4 (>20:1)
3	$TiCl_4$ (1.1)	–78, 1	40 (6:4)	51 (>20:1)
4	$TiCl_4$ (0.2)	–78, 1	64 (7:3)	22 (>20:1)
5	*p*-TsOH·H_2O (0.1)	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] *rel*-(2*R*, 2'*S*)/*rel*-(2*R*, 2'*R*). [c] The diastereomeric ratios were determined by ^{1}H NMR assay. [d] *rel*-(2*R*, 4'*R*)/*rel*-(2*R*, 4'*S*).

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 [*rel*-(2*R*, 2'*S*) and *rel*-(2*R*, 2'*R*)], and the relative stereochemistry of **3a** was determined by ^{1}H NMR analysis after conversion to the corresponding cyclic carbamate.[11] The γ-adduct **4a** was obtained as a single stereoisomer [*rel*-(2*R*, 4'*R*)], and the relative stereochemistry of **4a** was determined by ^{1}H NMR comparison with an authentic sample.[12] 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 Bronsted acids such as *p*-toluenesulfonic acid (*p*-TsOH), *dl*-camphorsulfonic acid, and pyridinium *p*-toluenesulfonate (PPTS), α-regioisomer **3a** was obtained exclusively with perfect α-regioselectivitiy (entries 5–7, 76–96% yield).[13] No detectable γ-regioisomer **4a** was observed. At present, the exact origin of the high α-regioselectivity is unclear.

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 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).[14]

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



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

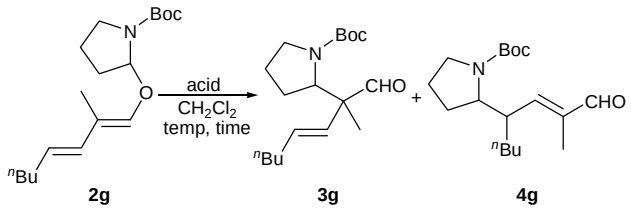
[a] Isolated yield. [b] *rel*-(2*R*, 2'*S*)/*rel*-(2*R*, 2'*R*). The ratios were determined by ^{1}H NMR assay. The relative stereochemistries of **3c**, **3d**, and **3f** were determined by the same procedures described in ref. 11. The relative stereochemistries of **3b** and **3e** were determined by analogy.

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 reactions 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 Bronsted 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).

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 Bronsted 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.

Table 5 Formation of a quaternary carbon stereocenter by 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.

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Notes and references

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

8 When the 1,4-elimination of 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 of 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 Similar selectivities were observed in our previous report (ref. 6); the use of $TiCl_4$ improved γ-regioselectivities.

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

12 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. 11. For more details: see Electronic Supplementary Information.

13 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.

14 When the reaction of **2f** was carried out by stoichiometric amount of $TiCl_4$, the corresponding γ-adduct [γ-(*N*-Boc-2-pyrrolidinyl)-α,β-unsaturated aldehyde] was obtained exclusively in 79% yield.