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Double Bond Isomerization/Enantioselective Aza-Petasis−Ferrier Rearrangement Sequence as an Efficient Entry to Anti- and Enantioenriched β-Amino Aldehydes

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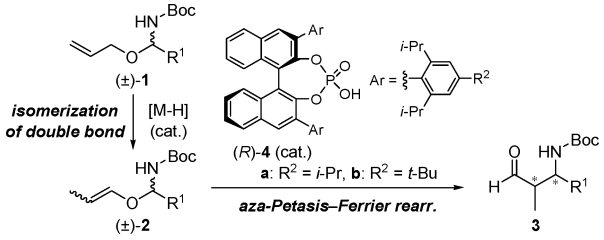
Considerable efforts have been devoted to the development of *syn*- or *anti*-selective synthesis of β-amino aldehydes in an optically active form, which are versatile synthetic precursors of amino alcohols, amino acids, β-lactams, and amino sugars, among others. Organocatalysis in direct Mannich reactions of aldehydes with aldimines using chiral secondary amine catalysts has emerged as a powerful method to provide β-amino aldehydes in high diastereo- and enantioselectivities.[1] However, one critical drawback inherent in the methodologies reported to date is that aromatic or glyoxylate-derived aldimines are employed as adaptive substrates in most cases.[1c] The enantioselective direct Mannich reaction of aliphatic aldimines has largely been unexploited because these aldimines are readily isomerized to their enamine form. To overcome this intrinsic problem, we envisioned an alternative strategy to furnish optically active β-amino aldehydes having an aliphatic substituent (R^1) at the β-position by a combination of two catalytic reactions (Scheme 1). The sequence involves initial metal-

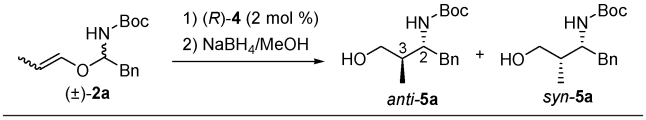
Scheme 1. Catalytic Sequence for Providing Optically Active β-Amino Aldehydes Having an Alkyl Substituent at the β-Position



catalyzed isomerization of a double bond followed by a chiral Brønsted acid-catalyzed aza-Petasis−Ferrier rearrangement,[2] using readily available hemiaminal allyl ethers (**1**) as the initial substrate. Herein we report the sequential transformation of racemic **1** to optically active β-amino-β-alkylaldehydes (**3**) via intermediary vinyl ethers (**2**) in a highly diastereo- and enantioselective manner.

The aza-Petasis−Ferrier rearrangement proceeds via C−O bond cleavage of the hemiaminal ether moiety by an acid catalyst, generating a reactive iminium intermediate and an enol form of the aldehyde.[2] Subsequent recombination with C−C bond formation results in rearranged products, thus providing the β-amino aldehydes (**3**). However, to the best of our knowledge, no previous reports have described enantioselective catalysis in aza-Petasis−Ferrier rearrangement, even considering chiral metal complexes, despite the wide applicability of **3** to the synthesis of a diverse array of nitrogen containing compounds. We therefore began by investigating diastereo- and enantioselective aza-Petasis−Ferrier rearrangement of hemiaminal vinyl ethers (**2**) using chiral phosphoric acids (**4**) as catalysts.[3,4] An initial experiment was performed using an (*E*)/(*Z*)-mixture of **2a** and 2 mol % of (*R*)-**4a** in toluene at 30 °C (Table 1, entry 1). Delightfully, **2a** was transformed cleanly to the desired β-amino aldehyde (**3a**) within 1 h. After reduction of the

Table 1. Diastereo- and Enantioselective Aza-Petasis−Ferrier Rearrangement of (±)-**2a** Catalyzed by (*R*)-**4**[a]



entry	**2a** (*Z*/*E*)	solvent	**4**	conditions	yield (%)[b] (*anti*/*syn*)	ee (%)[c] (*anti*/*syn*)
1	74:26	toluene	**4a**	30 °C, 1 h	89 (80:20)	73/68
2	>99:<1	toluene	**4a**	30 °C, 1 h	90 (97:3)	84/25[d]
3	>99:<1	CH_2Cl_2	**4a**	30 °C, 1 h	90 (98:2)	86/59[d]
4	>99:<1	CH_3CN	**4a**	30 °C, 45 min	95 (>99:<1)	90/39
5	>99:<1	Et_2O	**4a**	30 °C, 3.5 h	78 (>99:<1)	93/50[d]
6	>99:<1	acetone	**4a**	30 °C, 5 h	87 (99:1)	93/4
7	>99:<1	AcOEt	**4a**	30 °C, 1.5 h	95 (98:2)	93/32[d]
8	>99:<1	AcOEt	**4b**	30 °C, 2 h	91 (98:2)	94/25[d]
9	>99:<1	AcOEt	**4b**	0 °C, 18 h	89 (99:1)	89/65[d]
10	>99:<1	AcOEt	**4b**	40 °C, 1.5 h	93 (97:3)	95/6
11	>99:<1	acetone	**4b**	40 °C, 6 h	82 (99:1)	95/13[d]
12	<1:>99	AcOEt	**4b**	40 °C, 1.5 h	94 (23:77)	17/88
13	<1:>99	acetone	**4b**	40 °C, 6 h	69 (8:92)	37/88

[a] All reactions were carried out using 0.002 mmol of (*R*)-**4** (2 mol %), 0.1 mmol of **2a** in 0.5 mL of the indicated solvent. [b] Combined yield of *anti*/*syn*-**5a**. [c] Determined by chiral HPLC analysis. Absolute stereochemistries of **5a** were determined to be 2*R*,3*R* for *anti*-**5a** and 2*R*,3*S* for *syn*-**5a**. See Supporting Information for details. [d] Opposite enantiomer of *syn*-**5a** (2*S*,3*R*).

aldehyde (**3a**), the alcohol (**5a**) was obtained in high yield albeit with moderate *anti*- and enantioselectivity. It is obvious that the geometrical purity of **2a** affects not only *anti*- but also enantioselectivity as shown when pure (*Z*)-**2a** was used (entry 2),[5] in which the *anti*-isomer was obtained exclusively with an increase in enantioselectivity to 84% ee. Further screening of solvents revealed that higher enantioselectivities were obtained with more basic solvents while a high level of *anti*-selectivity was maintained (entries 2−7). Among the solvents examined, AcOEt and acetone were the best in terms of both chemical yields and enantioselectivities (entries 6,7). Catalyst **4b**, having a *tert*-butyl group instead of an isopropyl group at the *para*-position of the phenyl ring, had a beneficial effect on the enantioselectivity (entry 8 vs 7). Further optimization of reaction conditions exhibited an interesting temperature effect; the enantioselectivities increased with increasing reaction temperature up to 40 °C (entries 8−10). With the optimal catalyst (**4b**) and reaction conditions in hand, we also examined the reaction of pure (*E*)-**2a** (entries 12,13). The stereochemistries resulted in the alternative *syn*-isomer as the major product albeit with lower diastereo- and enantioselectivities.

In an effort to establish a sequential protocol that combined the two catalytic reactions without the need for separation of the geometrical isomers of **2**, we next attempted (*Z*)-selective isomerization of **1** using a Ni(II) complex. $NiCl_2$ complexes having a phosphine ligand, such as PPh_2Me and dppb, can be utilized as efficient catalysts

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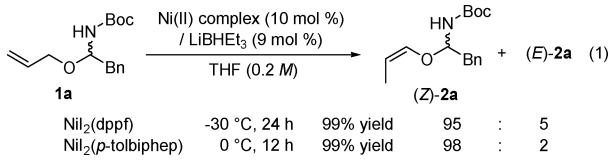
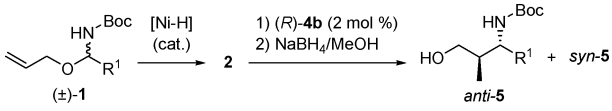
for isomerization of double bonds.[6] However, the typical $NiCl_2$ complexes were not effective in our case and **2a** was obtained with insufficient (*Z*)-selectivity.[7] After thorough optimization of the ligands, counteranions of the nickel salts, and reaction temperature, a NiI_2 complex having a bidentate phosphine ligand, dppf or *p*-tolbiphep, was found to be the best, giving **2a** in high (*Z*)-selectivity (eq 1).



Having identified (*Z*)-selective isomerization, we combined this with an enantioselective aza-Petasis−Ferrier rearrangement to develop a sequential transformation without the need for separation of the geometrical isomers of **2**.[8] As shown in Table 2, the present

Table 2. Substrate Scope of Sequential Transformation of **1** to Amino Alcohols[a]



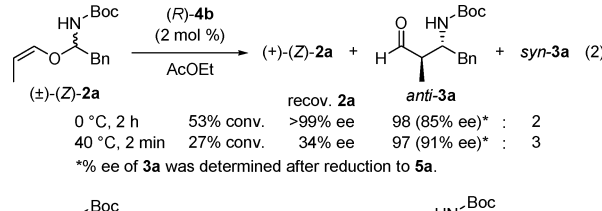
entry	**1** (R^1)	**2** (*Z*)/(*E*)	conditions[b]	**5**	yield (%)[c] (*anti*/*syn*)	ee (%)[d]
1	**1a**: Bn	98:2[e]	acetone, 40 °C, 7 h	**5a**	70 (95:5)	94
2	**1b**: Me	97:3[f]	AcOEt, 40 °C, 2 h	**5b**	86 (91:9)	76
3	**1c**: *n*-pentyl	96:4[f]	acetone, 40 °C, 7 h	**5c**	76 (93:7)	97
4	**1d**: isobutyl	96:4[f]	AcOEt, 40 °C, 3 h	**5d**	55 (95:5)	97
5	**1e**: *c*-hexyl	95:5[f]	AcOEt, 40 °C, 3 h	**5e**	75 (95:5)	>99
6	**1f**: Ph	96:4[f]	AcOEt, 40 °C, 3 h	**5f**	87 (93:7)	98

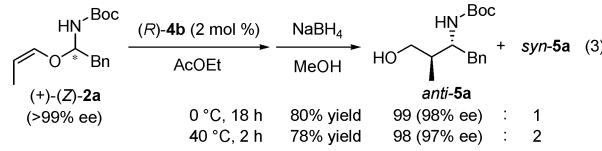
[a] All reactions were carried out using 0.25 mmol of **1**. [b] Reaction conditions of enantioselective aza-Petasis−Ferrier rearrangement. [c] Combined yield of *anti*/*syn*-**5** from **1** (3 steps). [d] For major *anti*-**5**. Determined by chiral HPLC analysis. [e] Isomerization of **1** using NiI_2(*p*-tolbiphep). [f] Isomerization of **1** using NiI_2(dppf).

sequential protocol is applicable to a variety of hemiaminal allyl ethers (**1**). The corresponding products (**5**) having a branched or linear aliphatic substituent were obtained in high *anti*- and enantioselectivities (entries 1, 3−5), with the exception of the less sterically hindered methyl substituent, **1b** (entry 2). The present protocol is also effective for the aromatic hemiaminal ether (**1f**), giving **5f** in high stereoselectivity (entry 6).

The present aza-Petasis−Ferrier rearrangement shows an intriguing temperature effect; that is, a higher temperature resulted in higher enantioselectivity (see Table 1, entries 8−10). It was presumed that this temperature effect would originate from the use of racemic **2**.[9] We therefore investigated the kinetic resolution of racemic (*Z*)-**2a** under the influence of (*R*)-**4b** (eq 2). As a result, (+)-**2a** was recovered in an optically pure form at 0 °C, even with ∼50% conversion of (±)-**2a**, indicating that (±)-**2a** could be efficiently resolved by (*R*)-**4b**.[10] However, the rearranged product, *anti*-**3a**, was obtained in lower enantioselectivities than that obtained under full conversion of (±)-**2a** at both 0 and 40 °C, which gave 89% ee and 95% ee, respectively (see Table 1, entries 9, 10). The lower enantioselectivities obtained for *anti*-**3a** under this resolution reaction imply that the chiral information derived from (−)-**2a** is partially maintained, and this information is unfavorable for the subsequent C−C bond forming step under the influence of (*R*)-**4b**. This unfavorable chiral information is apt to be lost at the higher temperature, because the enantioselectivities increase in this case.

Finally, we attempted the rearrangement of (+)-(*Z*)-**2a** which was recovered under kinetic resolution (eq 3). On the basis of the





above considerations, the chiral information derived from (+)-(*Z*)-**2a** is favorable for the subsequent C−C bond forming step under the influence of (*R*)-**4b** and, hence, would give rise to a much higher enantioselectivity. As expected, **5a** was obtained in excellent *anti*- and enantioselectivity and, in addition, the enantioselectivity observed at 40 °C was as high as that observed at 0 °C.

In conclusion, we have demonstrated highly *anti*- and enantioselective synthesis of β-amino aldehydes having an aliphatic substituent at the β-position by combining two catalytic reactions, a Ni(II) complex-catalyzed isomerization of a double bond and a chiral phosphoric acid-catalyzed aza-Petasis−Ferrier rearrangement. In addition, the chiral phosphoric acid was found to function as an efficient resolving catalyst of racemic hemiaminal ethers. Further studies on the kinetic resolution of racemic compounds using chiral phosphoric acids are in progress with the aim of developing further efficient enantioselective transformations.

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Supporting Information Available: Representative experimental procedure, spectroscopic data for hemiaminal allyl ethers (**1**), hemiaminal vinyl ethers (**2**), and products (**5**), determination of relative and absolute stereochemistry of **5a**. This material is available free of charge *via* the Internet at http://pubs.acs.org.

References

(1) (a) Yang, J. W.; Stadler, M.; List, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 609−611. (b) Zhang, H.; Mitsumori, S.; Utsumi, N.; Imai, M.; Garcia-Delgado, N.; Mifsud, M.; Albertshofer, K.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2008**, *130*, 875–886. (c) Kano, T.; Yamaguchi, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 1838–1840, and references cited therein.

(2) (a) Frauenrath, H.; Arenz, T.; Raabe, G.; Zorn, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 83–85. (b) Arenz, T.; Frauenrath, H.; Raabe, G.; Zorn, M. *Liebigs Ann. Chem.* **1994**, 931–942. (c) Tayama, E.; Otoyama, S.; Isaka, W. *Chem. Commun.* **2008**, 4216–4218.

(3) For recent reviews, see: (a) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713–5743. (b) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744–5758. (c) Terada, M. *Chem. Commun.* **2008**, 4097–4112.

(4) (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566–1568. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357. Activation of hemiaminal ethers, see: (c) Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 2553–2556.

(5) Geometrical isomers of **2a** were separated by HPLC.

(6) (a) Wille, A.; Tomm, S.; Frauenrath, H. *Synthesis* **1998**, 305–308. (b) Yamamoto, Y.; Kurihara, K.; Yamada, A.; Takahashi, M.; Takahashi, Y.; Miyaura, N. *Tetrahedron* **2003**, *59*, 537–542.

(7) See Supporting Information for details of nickel complex-catalyzed isomerization. Isomerization of hemiaminal crotyl ether provided the corresponding vinyl ether in low yield under the optimal conditions.

(8) After isomerization was completed, the reaction mixture was quenched by a few drops of hydrogen peroxide to oxidize the phosphine ligand. The mixture was then passed through a short column to remove nickel salts and the phosphine oxide. Exchange of the solvent from THF to AcOEt or acetone allowed subsequent rearrangement without the need for purification and separation of the geometrical isomers of **2**.

(9) Mohr, J. T.; Ebner, D. C.; Stoltz, B. M. *Org. Biomol. Chem.* **2007**, *5*, 3571–3576.

(10) Partial epimerization at the stereogenic center of **2a** cannot be ruled out.

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