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An Efficient Kinetic Resolution of Racemic Betti Base Based on an Enantioselective *N*,*O*-Deketalization

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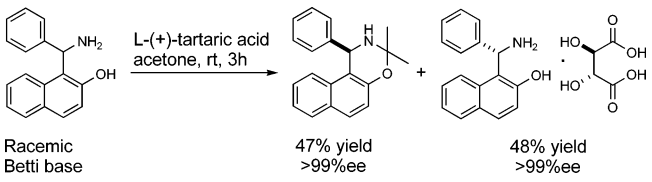
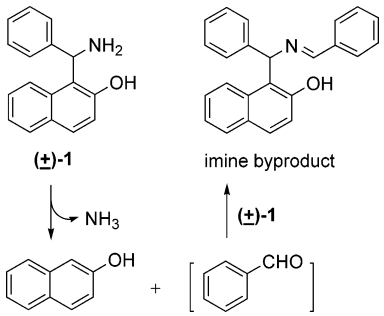


An efficient kinetic resolution of racemic Betti base with L-(+)-tartaric acid in acetone was developed based on a novel enantioselective *N*,*O*-deketalization, by which the enantiopure *R*- and *S*-enantiomers of Betti base were obtained as the corresponding *N*,*O*-ketal compound and salt with L-(+)-tartaric acid, respectively, in excellent yields with a practically foolproof operation.

The catalytic and auxiliary-based asymmetric syntheses have been recognized as two major methods for the preparation of an enantioenriched compound in modern organic synthesis, in which a chiral compound is essential to serve as a ligand or an auxiliary in practice. Many chiral aminohydroxy compounds are excellent ligands in catalytic asymmetric synthesis,[1] but only a few chiral benzylaminohydroxy compounds are also excellent auxiliaries in auxiliary-based asymmetric synthesis due to their ability to dissociate benzyl residue from the induced products under *N*-debenzylation conditions.[2−5] Prominent among them is the artificial chiral pool compound Betti base, which is gaining progressive importance.[4,5]

SCHEME 1



Structurally, Betti base [(±)-**1**] is a 1,3-benzylaminohydroxy compound and is available in bulk as hydrochloride salt [(±)-**1**·**HCl**].[6] Its nonracemic derivatives have been proven to be both excellent ligands and auxiliaries in asymmetric syntheses featuring its unique structure, bulky size, and high reactivity.[4,5] Although its classic resolution has been described in two similar procedures with L-(+)-tartaric acid in alcohols,[4a,7] however, most nonracemic Betti base derivatives reported in the literature were prepared by resolution of the corresponding racemate or by Mannich condensation with chiral amines rather than derived from Betti base enantiomers [(***R***)-**1** and (***S***)-**1**].[4] This unusual result strongly implies that the resolution of racemic Betti base [(±)-**1**] may encounter some obstacles that are difficult to overcome thus far.

When we repeated the published procedures for the resolution of (±)-**1**, the enantiomers (***R***)-**1** and (***S***)-**1** were obtained in unsatisfactory chemical and optical yields. The controlled experiments revealed that Betti base [(±)-**1**] automatically carried out a *retro*-Mannich reaction in protonic solvents at room temperature. For example, an imine byproduct 1-[phenyl[(*E*)-(phenylmethylene)amino]-methyl]-2-naphthalenol in about 5% yield was detected in MeOH within 1 h (monitored by ^{1}H NMR, Scheme 1). Herein, we report an efficient kinetic resolution of racemic Betti base [(±)-**1**] with L-(+)-tartaric acid in acetone based on a novel enantioselective *N*,*O*-deketalization, by which the enantiopure *R*- and *S*-enantiomers of Betti base were obtained as the corresponding *N*,*O*-ketal (***R***)-**2** and salt (***S***)-**3** in excellent yields with a practically foolproof operation.

To avoid using protonic solvents in the resolution of (±)-**1**, some nonprotonic solvents, such as THF, CH_3CN or acetone, were scanned. When acetone was used as a solvent in the presence of 1.0 equimolar of L-(+)-tartaric acid at room temperature for 6 h, the desired enantiopure salt (***S***)-**3** as white crystal was collected in 48% yield by

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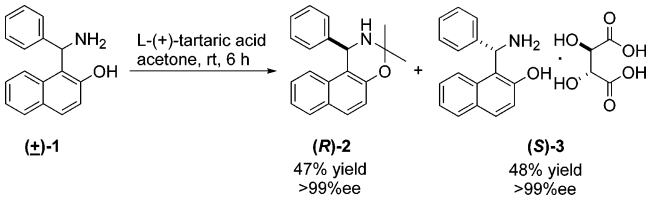
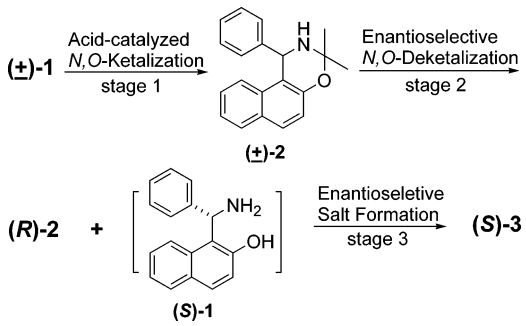
SCHEME 2



SCHEME 3



filtration. Its structure and configuration were confirmed by single-crystal X-ray analysis. Interestingly, instead of the expected salt **(*R*)-3**, the enantiopure *N*,*O*-ketal compound **(*R*)-2** was obtained from the filtrate in 47% yield (Scheme 2).

By carefully monitoring the whole process, we observed that two white precipitates appeared successively in the course of the resolution. The first appeared immediately after the acetone solution of L-(+)-tartaric acid was dropped into the acetone solution of **(±)-1**. The other formed once the first precipitate disappeared (about 30 min) and was easily recognized as the salt **(*S*)-3**. To our great surprise, the first precipitate structure was assigned as racemic *N*,*O*-ketal compound **(±)-2** by its NMR spectra and optical rotation.

Thus far, all the results have shown clearly that the resolution of **(±)-1** carried out in acetone followed a kinetic resolution mechanism[8] based on a novel enantioselective *N*,*O*-deketalization rather than a classic resolution mechanism. We hypothesized that the resolution may go through three stages, and L-(+)-tartaric acid played a different role in each stage (Scheme 3). (1) As a normal acid, L-(+)-tartaric acid promoted an acid-catalyzed *N*,*O*-ketalization between **(±)-1** and acetone to yield **(±)-2** as the first precipitate. (2) As a chiral acidic reagent, L-(+)-tartaric acid enantioselectively catalyzed the *N*,*O*-deketalization of **(*S*)-2** to give **(*S*)-1** as an intermediate. (3) As a chiral acid, L-(+)-tartaric acid enantioselectively captured **(*S*)-1** to form the salt **(*S*)-3** as the second precipitate.

To prove our hypothesis, a resolution using racemic *N*,*O*-ketal [**(±)-2**] (prepared in 96% yield from **(±)-1·HCl**) as an initial substrate was tested in both anhydrous acetone and aqueous acetone. As was expected, no precipitate was found after stirring the solution of **(±)-2** and L-(+)-tartaric acid in anhydrous acetone for 3 h. However, a white precipitate appeared approximately 10 min after 0.5 equimolar H_2O was added. Six hours later,

SCHEME 4

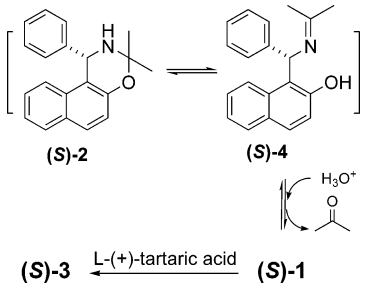


TABLE 1. Effect of L-(+)-Tartaric Acid on the Resolution[a]

entry	L-(+)-tartaric acid (mol)	(*R*)-2 yield (%)	(*R*)-2 ee (%)[b]	(*S*)-3 yield (%)	(*S*)-3 ee (%)[c]
1	1.0	47	>99	48	>99
2	0.75	47	>99	48	>99
3	0.55	59	82	38	>99
4	0.55	52	88	45	>99[d]

[a] With 0.5 equimolar H_2O for 6 h at room temperature. [b] ee was determined by HPLC analysis using a chiral phase column [Hypersil Pirkle(S) Napht]. [c] ee was determined as **(*S*)-1** by ^1H NMR in the presence of (*R*)-(−)-3,5-(dinitrobenzoyl)-α-methylbenzylamine. [d] 12 h was used.

enantiopure **(*R*)-2** and **(*S*)-3** were obtained in 47 and 48% yields, respectively. As shown in Scheme 4, we propose that *N*,*O*-ketal **(*S*)-2** is initially converted into imine **(*S*)-4** by a ring-chain tautomeric equilibrium[9] (see NMR spectra of **(±)-2** in the Supporting Information). Then, another equilibrium between imine **(*S*)-4** and (*S*)-Betti base [**(*S*)-1**] was achieved in the presence of water under acidic conditions. Since the salt **(*S*)-3** is formed as an extremely low soluble crystal immediately after **(*S*)-1** appeared, it causes those two equilibriums to irreversibly shift to the right. As a result, the **(*S*)-2** is *N*,*O*-deketalized enantioseletively in high yield.

Since *N*,*O*-ketalization of **(±)-1** into **(±)-2** promoted by L-(+)-tartaric acid is very clear, the details for the resolution of **(±)-2** to **(*R*)-2** and **(*S*)-3** in acetone were further studied. We observed that the resolution with 0.55 equimolar L-(+)-tartaric acid gave **(*R*)-2** in low enantiomeric excess and **(*S*)-3** in low yield, even though 0.5 equimoles were theoretically required (entry 3, Table 1). Clearly, the problem must result from the uncompleted *N*,*O*-deketalization of **(*S*)-2** because the concentration of L-(+)-tartaric acid in the reaction decreased sharply as the salt **(*S*)-3** precipitated out. Therefore, the resolution result can be improved by using excess L-(+)-tartaric acid or prolonged reaction time (entries 1, 2 and 4). Luckily, the excess amount of L-(+)-tartaric acid did not affect the enantioselectivity of *N*,*O*-deketalization at all.

Unlike most routine kinetic resolutions, kinetic resolution of **(±)-2** is not sensitive to reaction time. As shown in Table 2, the desired resolution not only can be achieved in as short as 3 h (entry 1), but also can be kept for up to another 9 h (entries 2 and 3). The enantioselective *N*,*O*-deketalization of **(±)-2** catalyzed by L-(+)-tartaric acid was so efficient that the relative rate k_S/k_R of this kinetic resolution should be considered to be infinity.

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TABLE 2. Effect of Reaction Time on the Resolution[a]

		(*R*)-2		(*S*)-3	
entry	time (h)	yield (%)	ee (%)	yield (%)	ee (%)
1	3	47	>99	48	>99
2	6	47	>99	48	>99
3	12	47	>99	48	>99
4	96	37	>99	52	90

[a] With 0.75 equimolar L-(+)-tartaric acid and 0.5 equimolar H_2O at room temperature.

TABLE 3. Effect of Amount of H_2O on the Resolution[a]

		(*R*)-2		(*S*)-3	
entry	H_2O (mol)	yield (%)	ee (%)	yield (%)	ee (%)
1	0.5	47	>99	48	>99
2	1.0	47	>99	48	>99
3	10.0	46	>99	48	>99

[a] With 0.75 equimolar L-(+)-tartaric acid at room temperature for 3 h.

TABLE 4. Effect of Temperature on the Resolution[a]

		(*R*)-2		(*S*)-3	
entry	temp (°C)	yield (%)	ee (%)	yield (%)	ee (%)
1	0	47	>99	48	>99[b]
2	25	47	>99	48	>99
3	35	47	>99	48	>99
4	45	37	>99	43	>99

[a] With 0.75 equimolar L-(+)-tartaric acid and 0.5 equimolar H_2O for 3 h. [b] 6 h was used.

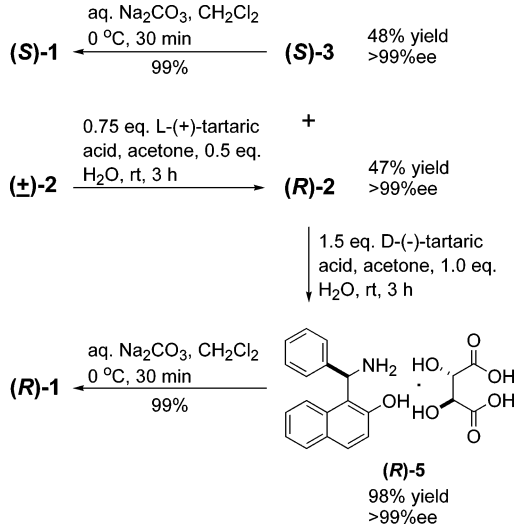
Theoretically, the enantioselective *N*,*O*-deketalization of **(±)-2** required 0.5 equimolar H_2O only. In practice, the tests in Table 3 proved that an excess amount of H_2O did not have any bad effects on the kinetic resolution. The enantioselective ability of the *N*,*O*-deketalization for enantiomer **(*S*)-2** was so strong that enantiomer **(*R*)-2** stayed intact even in the presence of 20 times more H_2O (entry 3). Thus, commercially available acetone in different grades can be used directly for the resolution.

Finally, the effect of temperature on the resolution was tested. As shown in Table 4, the excellent resolution results were obtained at a wide range of temperatures. Room temperature gave the best results, while prolonged time was noted when the resolution ran at 0 °C.

According to the above experimental results, the optimized conditions were established in Scheme 5. The method offered an excellent procedure for the kinetic resolution of racemic Betti base [**(±)-1**] under very mild and undemanding conditions. Since the salt **(*S*)-3** is more suitable for storage than **(*S*)-1** and can be used as an equivalent of **(*S*)-1** in most cases, it usually is not necessary to convert salt **(*S*)-3** into **(*S*)-1**. However, when the suspension of salt **(*S*)-3** in CH_2Cl_2 was neutralized with saturated aqueous solution of Na_2CO_3 at 0 °C, the desired product **(*S*)-1** was obtained conveniently in 99% yield without any loss of enantiomeric excess. Under the same conditions, enantiopure **(*R*)-1** was obtained in almost quantitative yield by the conversion of **(*R*)-2** into salt **(*R*)-5** with D-(−)-tartaric acid followed by neutralization with aqueous Na_2CO_3.

In summary, an efficient kinetic resolution of racemic Betti base [**(±)-1**] with L-(+)-tartaric acid in acetone was developed based on a novel enantioselective *N*,*O*-deketalization, by which the enantiopure *R*- and *S*-enantiomers were obtained as *N*,*O*-ketal compound **(*R*)-2** and L-(+)-tartaric acid salt **(*S*)-3**, respectively, in excellent chemical and optical yields with a practically foolproof operation.

SCHEME 5



Experimental Section

Kinetic Resolution of (±)-1. To a stirred solution of **(±)-1** (49.9 g, 200 mmol) in acetone (300 mL) was added a solution of L-(+)-tartaric acid (22.6 g, 150 mmol) in acetone (400 mL). After the resultant mixture was stirred at room temperature for 3 h, the white solid was collected by filtration and was washed with acetone (2 × 50 mL) to give **(*S*)-3** (38.3 g, 48%); mp 186−188 °C; $[\alpha]^{25}_D$ +44.1 (*c* 1.0, DMSO); IR: *ν* 3489, 3264, 3139, 3040, 2936, 1618, 1522, 1507, 1438 cm^{-1}; ^1H NMR (DMSO-d_6): *δ* 7.95−7.99 (d, 1H), 7.78−7.80 (m, 2H), 7.15−7.48 (m, 9H), 6.18 (s, 1H), 4.05 (s, 2H); ^{13}C NMR (DMSO-d_6): *δ* 174.3 (2C), 155.1, 139.3, 131.9, 130.1, 128.7 (2C), 128.5, 127.9, 127.8, 127.3 (2C), 126.9, 122.6, 121.7, 119.5, 114.7, 72.0 (2C), 52.1; MS *m/z* (%): 249 (1.5), 232 (37), 231 (100), 144 (89), 105 (39), 104 (61); Calcd for $C_{21}H_{21}NO_7$: C, 63.15%; H, 5.30%; N, 3.51%. Found: C, 63.01%; H, 5.37%; N, 3.51%.

To the filtrate was added a saturated aqueous solution of Na_2CO_3 (20 mL). After most of the acetone was removed by rotavapor, the residue was diluted with CH_2Cl_2 (200 mL) and H_2O (200 mL). The separated aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with H_2O and brine and dried over Na_2SO_4. Removal of the solvent gave crude product, which was purified by recrystallization (EtOAc) to give compound **(*R*)-2** (27.2 g, 47%) as colorless crystals; mp 148−150 °C; $[\alpha]^{25}_D$ +33.7 (*c* 1.0, $CHCl_3$), $[\alpha]^{25}_D$ +63.5 (*c* 4.0, C_6H_6).

Preparation of (±)-3,3-Dimethyl-1-phenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine [(±)-2]. To a stirred suspension of **(±)-1·HCl** (57.2 g, 200 mmol) in acetone (500 mL) was added Et_3N (20.2 g, 200 mmol) at 0 °C. Twenty minutes later, H_2SO_4 (98%, 0.1 mL) was added. The resultant mixture was stirred at room temperature for 1 h (monitored by TLC), and saturated aqueous solution of Na_2CO_3 (10 mL) was added. After most acetone was removed by rotavapor, the residue was diluted with CH_2Cl_2 (200 mL) and H_2O (200 mL). The separated aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with H_2O and brine and dried over Na_2SO_4. Removal of the solvent gave crude product, which was purified by recrystallization (EtOAc) to give compound **(±)-2** (55.6 g, 96%) as colorless crystals; mp 124−126 °C; IR: *ν* 2986, 1620, 1512, 1454 cm^{-1}; ^1H NMR ($CDCl_3$): *δ* 7.69−7.72 (m, 2H), 7.06−7.25 (m, 9H), 5.57 (s, 1H), 1.54 (s, 3H), 1.53 (s, 3H); ^{13}C

NMR: δ 152.3, 143.5, 131.3, 129.2, 129.1, 128.8 (2C), 128.3 (2C), 128.2, 127.4, 125.7, 123.9, 122.7, 119.7, 114.0, 86.7, 54.0, 28.9, 23.2; MS *m/z* (%): 289 (M^+, 6.7), 232 (42), 231 (100), 202 (20), 42 (24); Calcd for $C_{20}H_{17}NO$: C, 83.01%; H, 6.62%; N, 4.84%. Found: C, 83.23%; H, 6.85%; N, 4.36%.

Kinetic Resolution of (±)-2. To a stirred solution of **(±)-2** (55.0 g, 190 mmol) in acetone (300 mL) was sequentially added a solution of L-(+)-tartaric acid (21.4 g, 142.5 mmol) in acetone (400 mL) and H_2O (1.71 g, 95 mmol). After the resultant mixture was stirred at room temperature for 3 h, the white solid was collected by filtration and was washed with acetone (2 × 50 mL) to give **(*S*)-3** (36.4 g, 48%). By using the exact same procedure in the kinetic resolution of **(±)-1**, compound **(*R*)-2** was obtained (25.8 g, 47%).

Preparation of (*S*)-(+)-Betti Base [(*S*)-1]. To a stirred suspension of **(*S*)-3** (6.0 g, 15 mmol) in CH_2Cl_2 (30 mL) was added an aqueous solution of Na_2CO_3 (10%, 30 mL) at 0 °C. The resultant mixture was stirred until the solid disappeared completely (30 min). The separated aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with H_2O and brine and dried over Na_2SO_4. Removal of the solvent gave compound **(*S*)-1** (3.7 g, 99%) as colorless crystals; mp 133−134 °C (lit.[3a] 136−137 °C); $[\alpha]^{25}_D$ +94.1 (*c* 1.0, $CHCl_3$), $[\alpha]^{25}_D$ +56.6 (*c* 4.0, C_6H_6); [lit.[3a] +56 °C (*c* 4.4, C_6H_6)]; IR: ν 3360, 3290, 3010, 1620, 1600, 1462, 1450 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.60−7.70 (m, 3H), 7.10−7.40 (m, 8H), 5.95 (s, 1H), 2.39 (br. s, 2H); ^{13}C NMR ($CDCl_3$): δ 156.9, 142.3, 131.9, 129.6, 128.9 (2C), 128.7, 128.4, 127.8, 127.2 (2C), 126.4, 122.4, 121.2, 120.4, 115.1, 55.8; MS *m/z* (%): 249 (M^+, 0.05), 232 (37), 231 (100); Calcd for $C_{17}H_{15}NO$: C, 81.90%; H, 6.06%; N, 5.62%. Found: C, 81.72%; H, 5.88%; N, 5.70%.

Preparation of (*R*)-(−)-Betti Base [(*R*)-1]. To a stirred solution of **(*R*)-2** (5.8 g, 20 mmol) in acetone (30 mL) was sequentially added a solution of D-(+)-tartaric acid (4.5 g, 30 mmol) in acetone (40 mL) and H_2O (36 mg, 20 mmol). After the resultant mixture was stirred at room temperature for 3 h, the white solid was collected by filtration and was washed with acetone (2 × 20 mL) to give **(*R*)-5** (7.8 g, 98%); mp 186−189 °C; $[\alpha]^{25}_D$ −44.5 (*c* 1.0, DMSO). Its spectra data are same as those of **(*S*)-3**.

To a stirred suspension of **(*R*)-5** (4.0 g, 10 mmol) in CH_2Cl_2 (30 mL) was added an aqueous solution of Na_2CO_3 (10%, 30 mL) at 0 °C. The resultant mixture was stirred until the solid disappeared completely (30 min). The separated aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with H_2O and brine and dried over Na_2SO_4. Removal of the solvent gave compound **(*R*)-1** (2.46 g, 99%) as colorless crystals; mp 133−135 °C; $[\alpha]^{25}_D$ −94.3 (*c* 1.0, $CHCl_3$). Its spectra data are same as those of **(*S*)-1**.

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for all compounds and CIF file for single-crystal X-ray analysis structures of **(*S*)-3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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