Asymmetric Catalysis

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Kinetic Resolution of Azomethine Imines by Brønsted Acid Catalyzed Enantioselective Reduction

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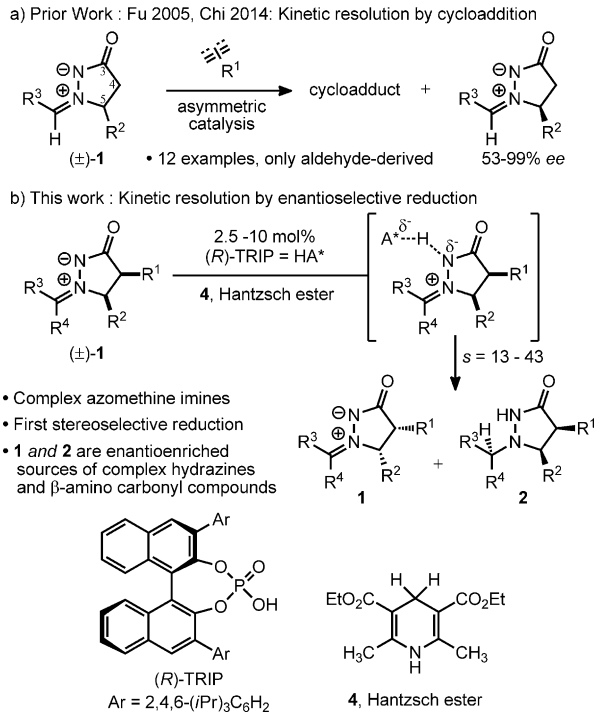
Abstract: *Azomethine imines are valuable substrates in asymmetric catalysis, and can be precursors to β-amino carbonyl compounds and complex hydrazines. However, their utility is limited because complex and enantioenriched azomethine imines are often unavailable. Reported herein is a kinetic resolution of N,N′-cyclic azomethine imines by enantioselective reduction (s = 13–43). This resolution was accomplished using a Brønsted acid catalyst, and represents the first example of the asymmetric reduction of azomethine imines. The pyrazolidinone product (up to 86 % ee) and the recovered azomethine imine (up to 99 % ee) can both be used to access the opposite enantiomers of valuable products.*

In the past decade, azomethine imines have been intensely studied in the field of asymmetric catalysis. These versatile compounds are well known as substrates in 1,3-dipolar cycloadditions and nucleophilic additions, as well as directing groups and bifunctional catalysts.[1] In 2003, Shintani and Fu reported the first example of asymmetric catalysis with azomethine imines, where they described the enantioselective cycloaddition of prochiral N,N′-cyclic azomethine imines.[2] Since this report, there have been many examples of catalytic stereoselective reactions with N,N′-cyclic azomethine imines (**1**; see Scheme 1),[3] thus establishing their value as precursors to pyrazolidinones, hydrazines, and β-aminocarbonyl compounds. However, because of the difficult synthesis of structurally diverse azomethine imines, the scope of these reactions is limited to simple and achiral substrates. While simple azomethine imines can be synthesized by the condensation of pyrazolidinones onto aldehydes, the complex and ketone-derived **1** are typically inaccessible.[4] There are only two reports on the access to enantioenriched **1**, that is, the kinetic resolution of a small scope of substrates (Scheme 1 a).[5] In both cases, the selective cycloaddition of one enantiomer provides resolution, but at the cost of half the starting material going to the cycloadduct. These reaction conditions are only amenable to aldehyde-derived azomethine imines, with limited substitutions at C5 and no substitution at C4. Herein, we report a kinetic resolution of the complex ketone- and aldehyde-derived **1** by enantioselective reduction (*s* = 13–43),[6] where both the products and recovered starting materials are valuable enantioenriched compounds containing the β-aminocarbonyl motif (Scheme 1 b).



Scheme 1. Access to enantioenriched azomethine imines.

We recently reported a cycloaddition of simple alkenes with imino isocyanates, to give azomethine imines (±)-**1** of unprecedented complexity.[7,8] Because examples of intermolecular alkene aminocarbonylations are rare,[7,9] and enantioselective variants have not been developed,[10] we aimed to find a general kinetic resolution procedure to resolve these azomethine imines. An attractive strategy is enantioselective reduction, to afford two enantioenriched compounds of opposite stereochemistry and differing simply by their oxidation state. This approach would provide access to enantioenriched pyrazolidinones, hydrazines, and β-amino carbonyl compounds. Azomethine imines are commonly reduced with hydrides, but to the best of our knowledge there are no reports of enantioselective reduction.[11] Furthermore, there are only two examples of enantioselective nucleophilic additions to **1**.[3h,i]

We explored several methods for the enantioselective reduction of imines, and became interested in chiral phosphoric acid catalysis.[12,13] We envisioned that the Brønsted acid catalyst would activate the dipole at the negative nitrogen center, and selectively deliver the hydride to one

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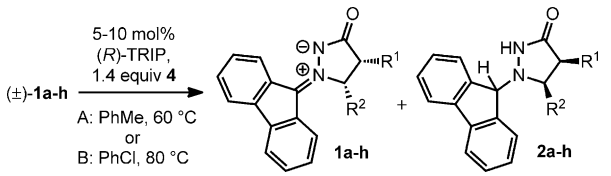
enantiomer. While chiral phosphoric acids are well-known for the reduction of imines, the binding mode of these catalysts with azomethine imines is unique and has not been shown to provide efficient control of enantioselective 1,2-additions.[14] After testing several chiral phosphoric acid organocatalysts, reducing agents, and reaction conditions (see Tables S1–S4 in the Supporting Information for selected optimization data), we identified (*R*)-TRIP as an excellent catalyst for selective reduction, with the Hantzsch ester (**4**) as a mild reductant (Scheme 1b). We first investigated the use of these reaction conditions with fluorenone-derived azomethine imines [(±)-**1a–h**], which are the products of our alkene aminocarbonylation process (Table 1).[7]

Gratifyingly, several substrates could be resolved with high selectivity using this catalyst system (Table 1). Our initial investigations identified reaction conditions (A) which allowed access to several C5-aryl-substituted azomethine imines (**1a–d**, 95–96% *ee*) and pyrazolidinones (**2a–d**, 73–77% *ee*) in high yields (entries 1–4). When the kinetic resolution of (±)-**1d** was stopped at lower conversion (entry 5), the pyrazolidinone **2d** was isolated in 83% *ee*. Bulky alkyl- and naphthyl-substituted azomethine imines [(±)-**1e–h**] were less reactive and also sparingly soluble in toluene, and chlorobenzene was a more suitable solvent (conditions B; entries 6–9). The kinetic resolution of the *syn*-disubstituted (±)-**1e** (entry 6) proceeded with high selectivity at 80°C, thus the providing azomethine imine **1e** (93% *ee*) and pyrazolidinone **2e** (79% *ee*). The 2-naphthyl substituted (±)-**1f** (entry 7) was also effectively resolved under these reaction conditions. In contrast, reactions of the more hindered 1-naphthyl (entry 8) and cyclohexyl (entry 9) azomethine imines proceeded with low conversion but with high selectivity to give **2g** (81% *ee*) and **2h** (83% *ee*), respectively, and recovered **1g** (82% *ee*) and **1h** (72% *ee*), respectively. In addition, bulkier fluorenone-derived azomethine imines could not be resolved, thus providing no pyrazolidinone product even at elevated temperatures. To address this limitation, we decided to explore aldehyde-derived azomethine imines to improve the reactivity of the C=N bond and increase tolerance of bulkier groups at C4 and C5.

Aldehyde-derived N,N′-cyclic azomethine imines [(±)-**1i–l**] showed high reactivity towards the reduction compared to the fluorenone-derived substrates, thus requiring lower catalyst loading and temperatures (Table 2). These kinetic resolutions proceeded selectively at 40–60°C to provide enantioenriched azomethine imines (**1i–l**) and pyrazolidinones (**2i–l**) in high yields (entries 1–5). In addition to solving the lack of reactivity observed with some of the substrates in Table 1, this protocol allowed us to assign the absolute configuration of the products (resolved **1i** was compared to previous reports).[5] The benzaldehyde-derived substrates (±)-**1k** and (±)-**1l** were synthesized by a one-pot net transimidation protocol from the fluorenone-derived aminocarbonylation products [Eq. (1)].[15] These azomethine imines were now easily reduced (entries 3–4), compared to the fluorenone-derived precursors (e.g. **1g**, Table 1, entry 8). The resolution of (±)-**1l** was effectively scaled up to 1 mmol, thus affording the azomethine imine in greater than 99% *ee* (Table 2, entry 5).

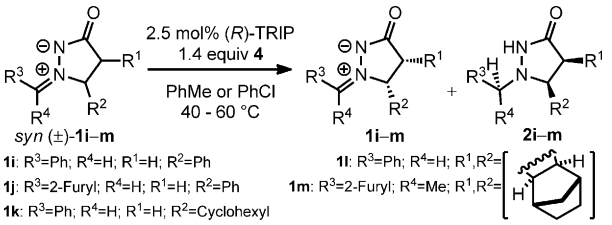
Table 1: Kinetic resolutions of fluorenone-derived azomethine imines by enantioselective reduction.[a]



Entry	(±)-**1** (R^1, R^2)	Cond.[a]	*t* [h]	Conv. [%]	*ee* (Yield) [%][b] **1**	**2**	*s*[c]
1	(±)-**1a** (H, Ph)	A	6	54	96 (45)	73 (41)	38
2	(±)-**1b** (H, 4-(F)C_6H_4)	A	6	58	96 (32)	76 (32)	21
3	(±)-**1c** (H, 4-(Me)C_6H_4)	A	6	57	95 (42)	74 (48)	22
4	(±)-**1d** (H, 4-(MeO)C_6H_4)	A	16	55	95 (43)	77 (43)	29
5	(±)-**1d**	A	5	49	82 (50)	83 (46)	35
6	(±)-**1e** (Me, Ph)	B	24	54	93 (43)	79 (52)	29
7	(±)-**1f** (H, 2-naphthyl)	B	24	53	95 (45)	74 (45)	43
8	(±)-**1g** (H, 1-naphthyl)	B	24	50	82 (48)	81 (45)	26
9	(±)-**1h** (H, *c*-C_6H_{11})	B[d]	24	46	72 (47)	83 (38)	26

[a] Azomethine imine (0.1–0.2 mmol, 1 equiv), **4** (1.4 equiv). Conditions A: (*R*)-TRIP (5 mol%) in toluene (0.02-0.04 M) at 60°C. Conditions B: (*R*)-TRIP (10 mol%) in PhCl (0.01–0.02 M) at 80°C. Conversion determined from ^{1}H NMR analysis of crude reaction mixture. [b] The *ee* value was determined by HPLC using a Diacel ChiralPak AD-H column. Yield is that of the isolated product. [c] Selectivity factor = k_{fast}/k_{slow} [d] 2.0 equiv of **4** were used.

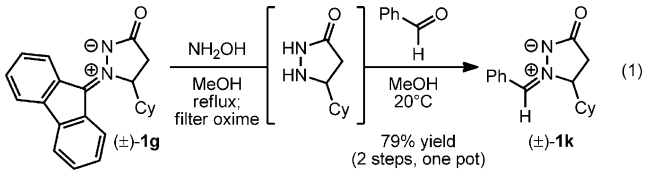
Table 2: Kinetic resolution of unsymmetrical azomethine imines by enantioselective reduction.[a]

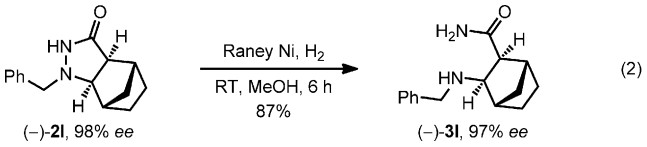


Entry		Solvent	*T* [°C]	*t* [h]	Conv. [%]	*ee* (Yield) [%][b] **1**	**2**	*s*[c]
1	(±)-**1i**	PhMe	40	6	57	95 (41)	86 (43)	22
2	(±)-**1j**	PhMe	60	6	56	94 (45)	75 (54)	23
3[d]	(±)-**1k**	PhCl	60	6	61	93 (35)	76 (41)	13
4	(±)-**1l**	PhMe	60	6	63	99 (32)	66 (52)	18
5[e]	(±)-**1l**	PhCl	60	4	61	>99 (39)	67 (50) 98 (29)[f]	25
6	(±)-**1m**	PhCl	80	24	56	85 (37)	78 (51)[g]	13

[a] Azomethine imine (0.1–0.2 mmol, 1 equiv), **4** (1.4 equiv), (*R*)-TRIP (2.5 mol%) in toluene (0.025 M) or PhCl (0.05 M). Conversion determined from ^{1}H NMR analysis of crude reaction mixture. [b] The *ee* value was determined by HPLC using a Diacel ChiralPak AD-H column. Yield is that of the isolated product. [c] Selectivity factor = k_{fast}/k_{slow}. [d] 5 mol% (*R*)-TRIP [e] 1 mmole scale. [f] After recrystallization. [g] Mixture of two diastereomers (2:1); the *ee* value is that of the major diastereomer.

Fortunately, the pyrazolidinone **2l** (67% *ee*) produced in this experiment could be recrystallized to 98% *ee*. After separation, both **1l** and **2l** [Eq. (2)] underwent reductive ring opening to give the corresponding β-amino amides in good yields with no loss in enantiopurity.





The proposed pre-transition state complex for selective reduction of **1i** is shown in Figure 1. This model features both Brønsted acid activation of the azomethine imine and Brønsted base activation of the Hantzsch ester by the chiral phosphoric acid.[16] The observed selectivity is rationalized by orienting the large substituent of the azomethine imine (Ph) in the most accessible quadrant.

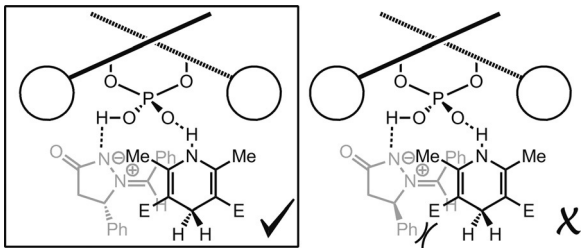


Figure 1. Pre-transition-state complexes for stereoselective reduction of the azomethine imine (±)-**1**. E = CO_2Et.

In summary, we developed a kinetic resolution of complex N,N′-cyclic azomethine imines (±)-**1** by selective reduction of one enantiomer (s = 13–43) by using the Brønsted acid organocatalyst (*R*)-TRIP. This protocol demonstrates the first example of stereoselective reduction of azomethine imines. The enantioenriched azomethine imines **1** and pyrazolidinones **2** are both valuable precursors to β-amino carbonyl compounds and complex hydrazine derivatives, as well as attractive substrates for asymmetric synthesis. Combined with our previously reported intermolecular alkene aminocarbonylation reaction to synthesize (±)-**1**,[7] this work provides a versatile approach to enantioenriched compounds possessing the β-aminocarbonyl motif.

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Keywords: asymmetric catalysis · azo compounds · Brønsted acids · kinetic resolution · reduction

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