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One-Pot Synthesis of Enantioenriched β-Amino Secondary Amides *via* Enantioselective [4+2] Cycloaddition Reaction of Vinyl Azides with *N*-Acyl Imines Catalyzed by Chiral Brønsted Acid

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Abstract: A catalytic enantioselective synthesis of β-amino secondary amides was achieved using vinyl azides as the enamine-type nucleophile and chiral *N*-Tf phosphoramide as the chiral Brønsted acid catalyst through a five-step sequential transformation in one pot. The established sequential transformation involves an enantioselective [4+2] cycloaddition reaction of vinyl azides with *N*-acyl imines as the key stereo-determining step that is efficiently accelerated by a chiral *N*-Tf phosphoramide catalyst in a highly enantioselective manner in most cases. Further generation of the iminodiazonium ion intermediate through ring opening of the cycloaddition product and subsequent skeletal rearrangement involving Schmidt-type 1,2-aryl group migration followed by recyclization of the resulting nitrilium ion were also initiated by the same acid catalyst. Final acid hydrolysis of the recyclized products in the same pot gave rise to enantioenriched β-amino amides through C-C bond formation at the α-position of the secondary amides.

The amide moiety is ubiquitous in nature as it is present in such molecules as peptides and proteins, and widely embedded in a variety of synthetic molecules, including pharmaceuticals, agrochemicals, and relevant molecules.[1] Consequently, much attention has been devoted to the development of efficient syntheses of amide-containing molecules not only in atom- and step-economical manners but also in enantioenriched forms.[2] Among the efficient methods reported to date, carbon-carbon (C-C) bond formation at the α-position of the amide moiety, namely, the addition of an amide enolate to an electrophile, is a powerful procedure for the construction of a range of enantioenriched amide derivatives. However, in general, the methods require a stoichiometric amount of a strong base or the corresponding pre-formed silyl enol ether because of the low acidity (p*K*a = 35 in DMSO)[3] at the α-position of the amide moiety.[4,5] Hence, the catalytic enantioselective formation of an amide derivative through the C-C bond formation at the α-position of the amide has been a challenging topic.[6] These intrinsic issues have been surmounted as a result of a recent advance in well-designed chiral catalytic systems, including the combination of a transition metal complex and an organobase co-catalyst,[7] an alkaline metal salt derived superbase,[8] and an organosuperbase having iminophosphorane units.[9] These efficient methods have enabled the catalytic enantioselective synthesis of amides through the C-C bond formation.[10] However, the scope of the amide functionality is strictly limited to a tertiary amide that has no hydrogens attached to the amide nitrogen atom because of the involvement of an amide enolate as the reactive intermediate.[6b]

Vinyl azides have been recently utilized as an enamine-type nucleophile[11] and also reported as the synthetic equivalent to the corresponding enols of secondary amides (Figure 1a),[12] the

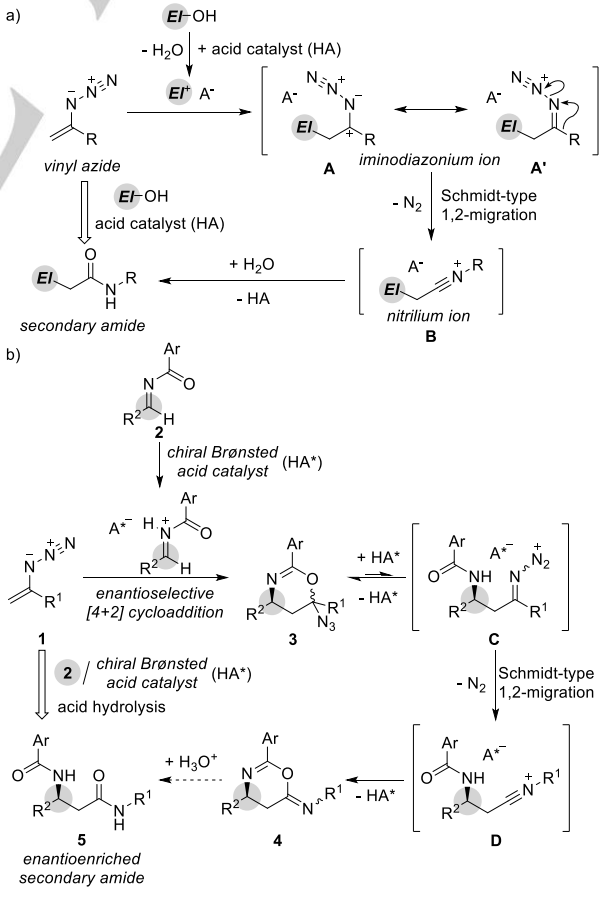

Figure 1. Utilization of vinyl azide as a secondary amide enolate equivalent.

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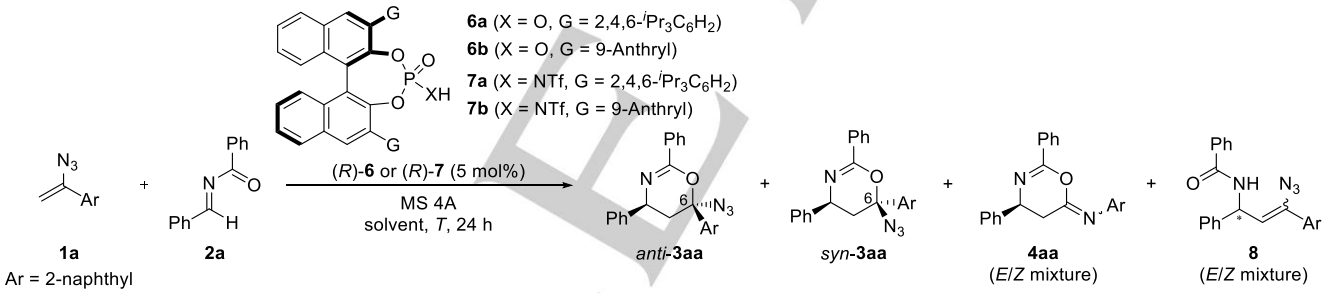
properties of which are completely different from those of tertiary amides because the secondary amides serve not only as a hydrogen bond acceptor site but also as a donor site. Generally, vinyl azide would function as the enamine-type nucleophile and undergo the reaction with a cationic electrophile (***El***$^+$) that is generated by an acid catalyst through the elimination of a leaving group (OH in Figure 1a), affording an iminodiazonium intermediate having resonance structures **A** and **A'**. Subsequent Schmidt-type 1,2-migration of intermediate **A'** would generate nitrilium ion **B** with elimination of dinitrogen (N_2),[13] and the subsequent hydrolysis of nitrilium ion **B** by the eliminated water molecule would furnish the corresponding secondary amide.

Over the past decades, chiral Brønsted acid catalysts have drawn much attention as one of the privileged organocatalysts[14] and a diverse range of enantioselective reactions have been accomplished using them.[15,16] In our continuous efforts to expand the scope of enantioselective reactions using a chiral Brønsted acid catalyst, we envisioned the use of vinyl azides as an enamine-type nucleophile for the synthesis of enantioenriched β-amino secondary amides. We designed a five-step sequential transformation involving a [4+2] cycloaddition reaction of vinyl azides **1** with *N*-acyl imines **2** as the key enantio-determining step.[17,18] Our proposed reaction scheme is shown in Figure 1b. The first step of the [4+2] cycloaddition would be initiated by a chiral phosphoric acid or its derivative as the chiral Brønsted acid catalyst[16] to afford cycloaddition product **3** in an enantioselective fashion. Further treatment of cycloaddition product **3** in the presence of an acid catalyst would result in the partial formation of iminodiazonium ion **C** because the resonance stabilization by the azide functionality would be anticipated in generated cation **C**.[19] Although cation **C** would instantaneously reproduce **3** *via* intramolecular cyclization using the oxygen atom of the *N*-acyl moiety under equilibrium conditions,[20] we expected that cycloaddition product **3** could be used as the resting state of positively charged intermediate **C**. Subsequently, generated **C** would undergo the Schmidt-type 1,2-migration to afford nitrilium ion **D** with elimination of dinitrogen, and subsequent recyclization of the *N*-acyl oxygen atom at the nitrilium carbon atom of **D** would give rise to *N*-(1,3-oxazinylidene)amine derivative **4**. Further acid hydrolysis of recyclized product **4** would provide β-amino secondary amide **5** in an enantioenriched form. Based on this reaction design, we successfully established an efficient one-pot procedure[21] for the synthesis of enantioenriched secondary amides through the five-step sequential transformation utilizing the enantioselective [4+2] cycloaddition as the key stereo-determining step. We report herein the details of our investigation.

To ascertain the viability of the designed sequential process, we began the investigation with the first key reaction, namely, the enantioselective [4+2] cycloaddition reaction of vinyl azide **1a** having a 2-naphthyl moiety with *N*-benzoyl imine **2a** under the influence of chiral Brønsted acid (*R*)-**6** or (*R*)-**7**. Initially, the reaction of **1a** (1.2 eq.) with **2a** was performed in the presence of chiral phosphoric acid (*R*)-**6a** or (*R*)-**6b**[16] and molecular sieves 4A (MS 4A) in dichloromethane at 0 °C for 24 h (Table 1, entries 1 and 2). As expected, cycloaddition product **3aa** was formed albeit in low yield along with a trace amount of recyclized product **4aa**. Fairly good *anti*-diastereoselectivities and moderate enantioselectivities were observed in **3aa** in both cases and minor

Table 1. Optimization of reaction conditions.[a]



Entry	Catalyst	*T* (°C)	Solvent	Yield[b] (%) 3aa	4aa[c]	8[c]	*anti*-**3aa**/*syn*-**3aa**[d]	Ee[e] (%) for *anti*-**3aa**/*syn*-**3aa**
1	(*R*)-**6a**	0	CH_2Cl_2	7	(~2)	(38)	86/14	11/40
2	(*R*)-**6b**	0	CH_2Cl_2	24	(~2)	(32)	90/10	58/61
3	(*R*)-**7a**	0	CH_2Cl_2	50	(~5)	(<1)	78/22	52/31
4	(*R*)-**7b**	0	CH_2Cl_2	68	(~5)	(<1)	81/19	20/62
5	(*R*)-**7a**	0	toluene	63	(10)	(8)	89/11	81/81
6	(*R*)-**7a**	-30	toluene	81	(<1)	(<1)	89/11	90/90
7	(*R*)-**7a**	-60	toluene	72	(<1)	(<1)	22/78	64/38
8[f]	(*R*)-**7a**	-30	toluene	95	(<1)	(<1)	89/11	90/90
9[f,g]	(*R*)-**7a**	-30	toluene	95	(<1)	(<1)	31/69	86/96

[a] Unless otherwise noted, all reactions were carried out using 0.005 mmol of (*R*)-**6** or (*R*)-**7** (5 mol%), 0.12 mmol of **1a** (1.2 eq.), 0.1 mmol of **2a** (1.0 eq.), and MS 4A (50 mg) in the indicated solvent (1.0 mL). [b] Isolated yield, NMR yield in parenthesis using 1,1,2,2-tetrabromoethane as the internal standard. [c] **4aa** and **8** were obtained as an *E*/*Z* mixture. [d] Determined by ^{1}H NMR analysis of the crude materials. [e] Determined by chiral stationary phase HPLC analysis. [f] 0.1 mmol of **1a** (1.0 eq.) and 0.15 mmol of **2a** (1.5 eq.) were used. [g] For 1 h.

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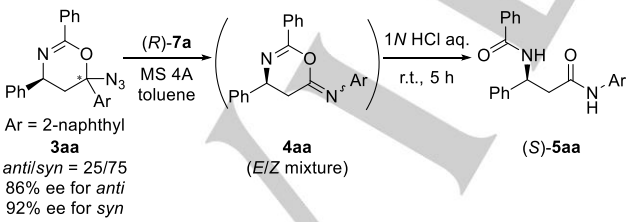
syn-**3aa** exhibited higher enantioselectivity than major *anti*-**3aa**. However, a significant amount of vinyl azide derivative **8**, which was produced by deprotonation at the methylene carbon of the iminodiazonium intermediate, was also formed as an undesirable byproduct. The low chemical yield presumably arose from the low acidity of catalyst **6** and hence, the conjugate base of catalyst **6** having relatively high basicity would function as the deprotonating agent of the cationic iminodiazonium intermediate. Therefore, more acidic *N*-Tf phosphoramide catalysts (*R*)-**7a** and (*R*)-**7b** were employed for further investigation (Table 1, entries 3–9).[22,23] Using either (*R*)-**7a** or (*R*)-**7b**, the formation of undesirable **8** was completely suppressed, the yield of **3aa** was markedly improved, and the yield of **4aa** was slightly enhanced (Table 1, entries 3 and 4). When (*R*)-**7a** was used, major *anti*-**3aa** was obtained in higher enantioselectivity than minor *syn*-**3aa** (Table 1, entry 3). Hence, the reaction solvent and temperature were further examined using (*R*)-**7a**. The use of toluene instead of dichloromethane markedly improved the enantioselectivity of **3aa** and maintained the high *anti*-diastereoselectivity (Table 1, entry 5). Although a small amount of **4aa** and undesirable **8** were generated at 0 °C, reducing the reaction temperature to -30 °C resulted in the exclusive formation of **3aa** and an increase in enantioselectivity of both *anti*- and *syn*-diastereomers with the same 90% ee (Table 1, entry 6). However, further decrease of the reaction temperature to -60 °C led to a marked decrease in enantioselectivity and *syn*-**3aa** was formed as the major diastereomer (Table 1, entry 7). At -30 °C, the chemical yield was improved by changing the equivalent of **2a** to 1.5 eq. (Table 1, entries 8 and 9). More interestingly, the reaction time substantially influenced the stereochemical outcome: a prolonged reaction resulted in a dramatic change of the diastereoselectivity from *syn*-**3aa** to *anti*-**3aa** and the enantioselectivities changed from 86% ee/96% ee (for 1 h) to 90% ee/90% ee (for 24 h). These results clearly suggest that epimerization at the 6-position of **3aa** proceeds through C-O bond cleavage, namely, equilibrium between **3aa** and iminodiazonium intermediate **C** (see Figure 1b), under the reaction conditions.[24] Considering the resonance stabilization of cationic intermediate **C** by the azide functionality,[25] we anticipated that elevating the temperature would lead to efficient generation of iminodiazonium intermediate **C** under the influence of acid catalyst (*R*)-**7a**, and the subsequent Schmidt-type migration of **C** and recyclization of nitrilium ion **D** would afford *N*-(1,3-oxazinylidene)amine derivative **4aa**.

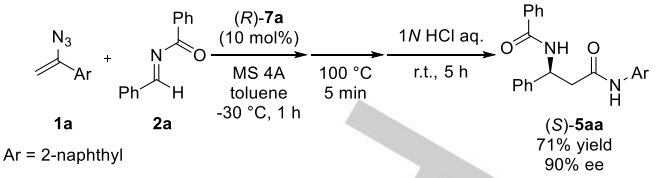
Based on the above considerations, isolated **3aa** was treated with optimized catalyst (*R*)-**7a** under elevated temperatures. To evaluate the formation of recyclized product **4aa**, the generated **4aa** was directly hydrolyzed to β-amino secondary amide **5aa** by adding 1*N* HCl aqueous solution to the reaction mixture without isolating **4aa** because **4aa** was an *E*/*Z* mixture. Initially, the proposed four-step sequence was performed using 5 mol% of (*R*)-**7a** at 40 °C (Table 2). The progress of the recyclization step from **3aa** to **4aa** was monitored by TLC. Although **3aa** was not completely consumed even by prolonged reaction for 26 h, acid hydrolysis of the reaction mixture afforded desired (*S*)-**5aa**[26] with high enantioselectivity that is consistent with the averaged enantioselectivities of initial *anti*- and *syn*-**3aa** (Table 2, entry 1). Elevating the temperature to 100 °C did not markedly improve the yield of **5aa** (Table 2, entry 2),[27] whereas increasing the catalyst loading to 10 mol% efficiently promoted the four-step sequence, affording **5aa** in an acceptable yield without any loss of enantioselectivity (Table 2, entry 3).

Table 2. Transformation of **3aa** into secondary amide **5aa** under the influence of (*R*)-**7a**.[a]



Entry	(*R*)-**7a** (mol%)	*T* (°C)	Time (h)	Yield[b] (%)	Ee[c] (%)
1	5	40	26	45	90
2	5	100	2	56	90
3	10	100	2	74	90

[a] Unless otherwise noted, all reactions were carried out using (*R*)-**7a**, 0.05 mmol of **3aa**, and MS 4A (25 mg) in toluene (0.5 mL). [b] Isolated yield. [c] Determined by chiral stationary phase HPLC analysis.



Scheme 1. One-pot synthesis of enantioenriched secondary amide.

The successful formation of enantioenriched **5aa** from cycloaddition product **3aa** prompted us to accomplish a five-step sequential transformation that starts from enantioselective [4+2] cycloaddition ends with acid hydrolysis in one pot. As shown in Scheme 1, the initial enantioselective [4+2] cycloaddition reaction of **1a** with **2a** (1.5 eq.) was performed using (*R*)-**7a** in accordance with the optimized procedure (Table 1, entry 9) and then the reaction mixture was heated to 100 °C (Table 2, entry 3). Subsequent acid hydrolysis in the same pot gave rise to β-amino secondary amide **5aa** in good yield with the same enantioselectivity as that of the individual enantioselective cycloaddition.

With the optimal one-pot procedure in hand, the generality of the present sequential reaction was demonstrated by exploring several combinations of vinyl azides **1** and *N*-benzoyl imines **2** (Figure 2). As shown in the top portion of Figure 2, the sequential reaction of a series of vinyl azides **1** having different electronic properties of the aryl group with imine **2a** proceeded smoothly to afford enantioenriched amides **5** in acceptable yields,[28] although the enantioselectivities were highly dependent on the electronic nature of the aryl ring of **1**. The introduction of an electron-donating group to the aryl ring, particularly, at the *ortho*- and *para*-positions, led to a significant decrease in enantioselectivity. It is considered that the electronically enriched aryl ring, which would stabilize the positively charged species generated in the transient structure, could influence the [4+2] cycloaddition reaction pathway. Thus, the reaction tends to proceed via a stepwise pathway presumably because of the resonance stabilization of the positively charged species not only by the azide functionality but also by the electronically enriched aryl ring. Further screening for the substrates was performed using vinyl azide **1a** and a series of imines **2**. As shown in the bottom portion of Figure 2, the electronic nature of the aryl ring of imine **2** markedly influenced the yields and the enantioselectivities of amides **5**. Imine **2b** having a strong electron donor, namely, a 4-methoxyphenyl group, underwent the cycloaddition reaction and the formation of cyclized product **3ab** was confirmed by ^{1}H NMR measurement.[29] However, desired amide product **5ab** was not formed at all after the following sequential transformation. Thus, the decomposition of intermediate **3ab** and/or **4ab** was observed when the reaction mixture was heated at 100 °C presumably because of the C-N bond cleavage at C4-position of **3ab** and **4ab**. In contrast, the introduction of a weak electron-donating group, such as **2c** (R^2 = 4-tolyl) and **2d** (R^2 = 4-fluorophenyl), led to the formation of

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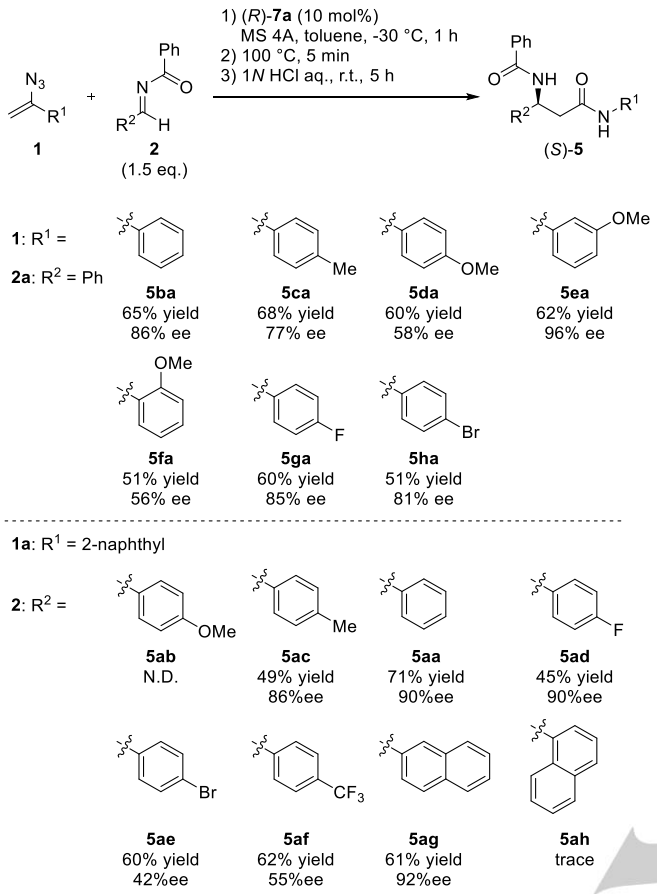

Figure 2. Scope of substrates **1** and **2**.

amides **5ac** and **5ad** in moderate yields with good enantioselectivities. An imine having an aryl ring with an electron-withdrawing group, such as **2e** (R^2 = 4-bromophenyl) and **2f** (R^2 = 4-trifluoromethylphenyl), facilitated the sequential reaction in fairly good yields albeit with marked decreases in the enantioselectivities.[30] Steric congestion also influenced the sequential reaction. Imine **2h** having a 1-naphthyl substituent afforded amide **5ah** in only a trace amount, whereas imine **2g** having a less sterically congested 2-naphthyl substituent underwent the sequential reaction to produce amide **5ag** in good yield with high enantioselectivity.

In conclusion, we have developed a catalytic enantioselective synthesis of chiral amides that is characterized by a five-step sequential transformation in one pot using chiral *N*-Tf phosphoramide as the chiral Brønsted acid catalyst. The method provides enantioenriched β-amino secondary amides through the C-C bond formation at the α-position of the amide using vinyl azides as the enamine-type nucleophile. The established sequential transformation involves an enantioselective [4+2] cycloaddition reaction of vinyl azides with *N*-acyl imines as the key stereo-determining step and the chiral *N*-Tf phosphoramide efficiently accelerates not only the cycloaddition process in a highly enantioselective manner in most cases but also further skeletal rearrangement and recyclization processes involving cationic intermediates in the same pot. Further studies of the development of other enantioselective reactions using vinyl azides as the enamine-type nucleophile will be conducted in due course.

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Keywords: β-amino amide • vinyl azide • Brønsted acid • enantioselective • [4+2] cycloaddition

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[23] The results of screening for a series of catalysts are summarized in Supporting Information (Table S1).

[24] Epimerization at the 6-position of **3aa** was confirmed under the same reaction conditions using *syn*-**3aa** as the major diastereomer. See Supporting Information for details.

[25] When a [4+2] cycloaddition product having a methyl substituent, instead of the azide, at the 6-position was subjected to similar reaction conditions using a chiral phosphoric acid catalyst, no epimerization was observed at the 6-position. See Ref. [17a].

[26] The absolute configuration of enantioenriched **5aa** was assigned to be (*S*)-isomer by analogy of the stereochemical determination of **5ba**. The absolute stereochemistry of **5ba** was determined by derivatization of the stereochemically known compound into **5ba**. See Supporting Information for details.

[27] The results of screening for reaction conditions are summarized in Supporting Information (Table S5).

[28] Aliphatic substituted vinyl azide, R^1 = $(CH_2)_2Ph$, was also used in the present reaction, however the initial cycloaddition reaction did not proceed efficiently. The cycloaddition product was formed in low yield, less than 15%, even at elevated reaction temperature to 0 °C.

[29] The formation of **3ab** was confirmed by ^{1}H NMR analysis. See Supporting Information.

[30] Further optimization of the reaction conditions by changing the reaction temperature was unsuccessful. See Supporting Information.

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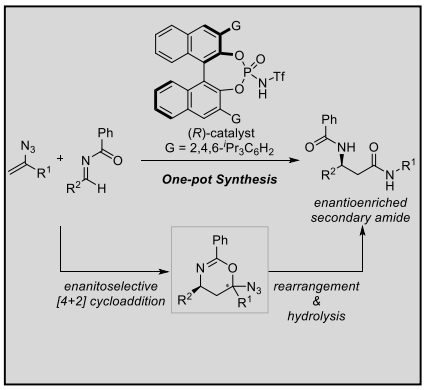

A catalytic enantioselective synthesis of β-amino secondary amides was achieved using vinyl azides and chiral *N*-Tf phosphoramide as the chiral Brønsted acid catalyst through a five-step sequential transformation in one pot. The established sequential transformation involves an enantioselective [4+2] cycloaddition reaction of vinyl azides with *N*-acyl imines as the key stereo-determining step that is accelerated by a chiral *N*-Tf phosphoramide.