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Organocatalytic α-amination–allylation-RCM strategy: enantioselective synthesis of cyclic hydrazines

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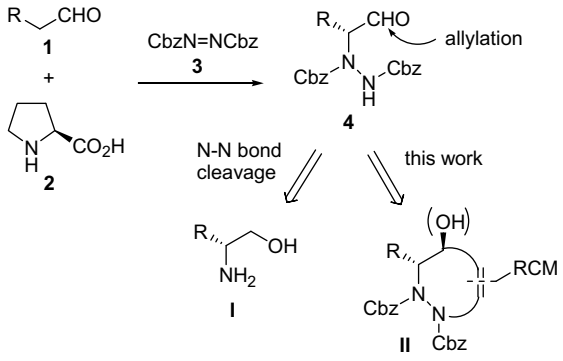
ABSTRACT

A highly enantioselective method for the synthesis of cyclic hydrazines by using organocatalytic α-amination–allylation-RCM strategy is described. Proline-catalyzed α-amination of aldehydes followed by indium-mediated one-pot allylation of the crude α-hydrazino aldehydes produces 1,2-aminoalcohols in high enantio- and diastereoselectivities. The 1,2-aminoalcohols are further converted into cyclic hydrazines by using ring-closing metathesis (RCM) reaction.

1. Introduction

For the past few years, organocatalytic asymmetric synthesis[1] has gained great attention, complementing bio- and metal-catalysis. Several synthetic methods have been developed as practical tools for asymmetric organic synthesis. Especially, the enantioselective α-amination of aldehydes and ketones using proline[2] and its derivatives has been extensively utilized to introduce amino groups enantioselectively. Cleavage of the N–N bond introduced by dialkyl azidodicarboxylate ($RCO_2N{=}NCO_2R$) leads to synthetically useful α-amino alcohol (**I**)[2] or α-amino acid[2a] derivatives (Scheme 1). In other ways, the α-amino aldehydes were further utilized in the subsequent tandem reactions such as aldol,[3] Passerini,[4] and Horner–Wadsworth–Emmons reactions.[5] While allylation reactions of proline-catalyzed aldol products[6] and aminoxylation adducts[7] are known, allylation reaction of the organocatalytic α-amination adducts has not been reported up to now. Although few examples have shown that the N–N bond of **4** could be utilized for the synthesis of cyclic hydrazine derivatives; however, they are limited only to 6-membered piperizine derivatives, where the cyclization step involves either intramolecular alkylation reaction[8] or Wittig reaction.[9]

Herein, we report indium-promoted one-pot allylation of **4** and enantioselective synthesis of cyclic hydrazines (**II**) via an organocatalytic α-amination–allylation-RCM strategy. Synthetic methods for small to medium heterocycles containing an N–O[10] or N–N[11] bond by using ring-closing metathesis (RCM) reaction as the key step have been reported in our group. As an asymmetric version of these methodologies, we envisioned that organocatalytic α-hydrazidination reaction followed by RCM could be synthetically useful for enantioselective synthesis of functionalized cyclic hydrazines.



Scheme 1. Strategy for asymmetric synthesis of cyclic hydrazines.

First, we examined the feasibility of the one-pot α-amination–allylation sequence. After treating aldehydes with 10 mol % of L-proline and dibenzyl diazodicarboxylate (CbzN=NCbz, **3**) in acetonitrile at −20 °C for 12 h, the reaction mixture was diluted with THF/H_2O (3:1) and then reacted with indium powder and allyl bromide at room temperature for 12 h (Table 1). The overall transformation turned out to be highly enantioselective and

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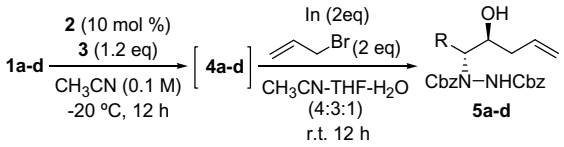
Table 1
One-pot proline-catalyzed α-amination and indium-promoted allylation reactions



Entry	1	5		
		% Yield	dr (*anti*:*syn*)	% ee[a] (*anti*/*syn*)
1	**1a** (R = Me)	**5a** (70)	>99:1	99/(—)[b]
2	**1b** (R = *i*-Pr)	**5b** (88)	98:2	98/(—)[b]
3	**1c** (R = *n*-Bu)	**5c** (67)	81:19	99/>98[c]
4	**1d** (R = $(CH_2)_2CH{=}CH_2$)	**5d** (83)	87:13	98/>98[c]

[a] The % ee's were determined using Chiralcel OD-H column (1% *i*-PrOH in hexanes).
[b] The % ee's for the *syn* isomers of **5a** and **5b** were not determined.
[c] The minor enantiomers of the *syn* isomers of **5c** and **5d** were not observed.

diastereoselective. When R is small (R = Me, entry 1, Table 1), complete diastereoselective allylation is observed, but relatively bulky R groups show decreased diastereoselectivities (entries 3 and 4, Table 1).

The stereochemistries of the allylation step are determined after conversion of **5** to 1,3-oxazolidin-2-ones where the ^{1}H NMR chemical shifts of the methine protons[12] were compared with the known compounds.[13] According to the assigned stereochemistries of **5**, the indium-promoted allylation step proceeds through the Felkin–Ahn transition state (Fig. 1). It seems that the sterically bulky –NCbzNHCbz group prevents chelation of the allylindium reagent to give the Cram product.[14]

Next, the RCM substrates were prepared according to the known procedures (Scheme 2). The dienes **8a**–**c** were prepared using standard alkylation or acylation conditions[10,11] from **6**, which was synthesized from aldehyde **4d** in 63% yield. Substrates **7a**–**d** were prepared from **5a**–**d** in two steps.

The substrates **7a**–**d** and **8a**–**c** were reacted with 10 mol % Grubbs' catalysts (**11** or **12**) under refluxing dichloromethane or toluene solution (0.02 M) (Table 2). Sterically bulky substrate (entry 2) and less reactive acryl amide substrate (entry 6) were reacted using 2nd-generation catalyst (**12**). Cyclization yields are good for most substrates to give 8-membered cyclic hydrazine compounds. The triene substrate **7d** yielded 7-membered product **13d** only instead of the corresponding 8-membered cyclic hydrazine (entry 4). Facile ring-closure to cycloheptene rings was further confirmed from the reaction of substrates **9** and **10**, which were prepared from **5d** (Scheme 3). Under the condition **A**, **9** produced functionalized cycloheptene **13h** in 85% yield in less than 2 h (entry 8). Interestingly, the dieneyne **10** gave only the diene-RCM product **13i** with no enyne-RCM products (entry 9).

In conclusion, we have shown that the indium-promoted in situ allylation of organocatalytic α-amination adducts could introduce 1,2-aminoalcohols with high enantio- and diastereoselectivities. In addition, we have demonstrated that functionalized cyclic hydrazine derivatives could be readily accessed by using the organocatalytic α-amination–allylation-RCM strategy.

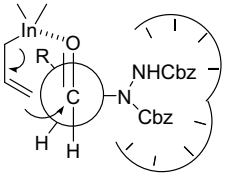
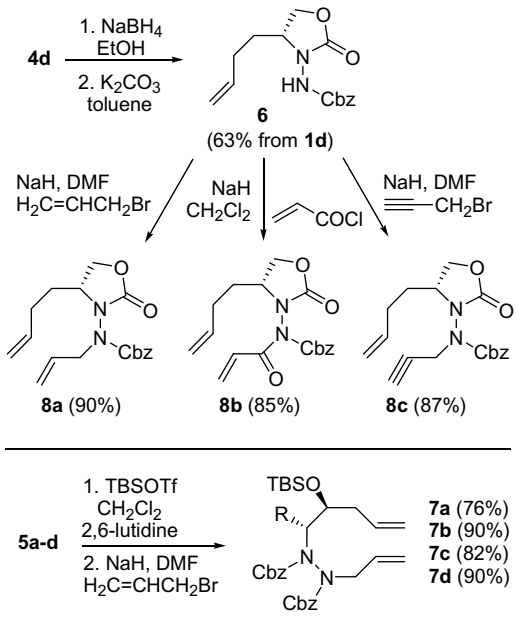


Figure 1. A proposed transition state for the allylation reaction.



Scheme 2. Synthesis of RCM substrates from L-proline-catalyzed α-amination adducts.

2. Experimental procedures

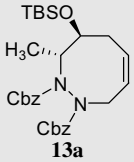
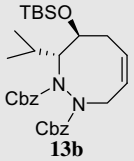
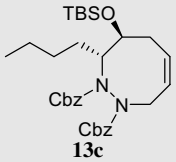
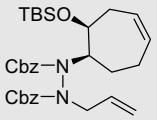
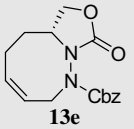
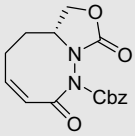
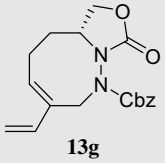
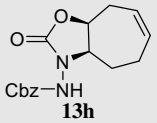
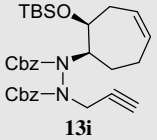
2.1. General procedure for the organocatalytic α-amination–allylation reaction

To a mixture of **1a** (100 mg, 1.72 mmol) and L-proline (18 mg, 0.17 mmol) in acetonitrile (17 mL) was added the dibenzyl azodicarboxylate (616 mg, 2.07 mmol) and the reaction mixture was stirred for 12 h at −20 °C. The reaction mixture was diluted with 17 mL of THF/H_2O (3:1) and indium powder (−100 mesh indium powder purchased from Aldrich; 395 mg, 3.44 mmol) and allyl bromide (2.99 mL, 3.44 mmol) were added. The reaction mixture was stirred for 12 h at room temperature, quenched with saturated 2 N HCl (10 mL), extracted with EtOAc (10 mL × 3). The combined organic solutions were dried over anhydrous $MgSO_4$, and the residue was chromatographed on silica gel (hexanes/EtOAc = 2:1) to give **5a** (479 mg, 70%) as a white solid; R_f = 0.4 (hexanes/EtOAc = 2:1); mp 74–76 °C; $[\alpha]_D^{20}$ +2.28 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.25 (m, 10H), 6.71(br s, 1H), 5.80 (br s, 1H), 5.14–5.08 (m, 7H), 4.19–3.99 (m, 2H), 2.20 (m, 2H), 1.15–1.14 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 156.6, 155.8, 135.8, 135.6, 135.4, 134.8, 128.6, 128.5, 128.4, 127.9, 117.5, 72.4, 68.8, 68.1, 67.9, 57.8, 57.0, 38.1, 29.7, 9.9, 0.0; IR (film, cm^{-1}) 3292, 3062, 3030, 2935, 2355, 1712, 1528, 1498, 1454, 1408, 1262, 1056, 1027; HRMS calcd for $C_{22}H_{26}N_2O_5$ (M^+): 398.1842; found: 398.1840.

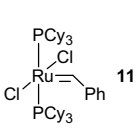
2.2. General procedure for the synthesis of RCM substrates 7

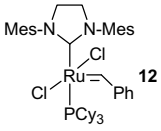
To a solution of **5a** (238 mg, 0.598 mmol) in CH_2Cl_2 (15 mL) were added 2,6-lutidine (0.10 mL, 0.89 mmol) and TBSOTf (0.20 mL, 0.89 mmol) at 0 °C under argon atmosphere. The resulting mixture was stirred at 0 °C for 20 min, warmed to room temperature, and quenched with saturated aqueous $NaHCO_3$. The aqueous solution was extracted with CH_2Cl_2 (10 mL × 3) and the combined organic solutions were dried over anhydrous $MgSO_4$ and the residue was flash chromatographed on silica gel (hexanes/EtOAc = 10:1) to give TBS-protected compound. This product was dissolved in DMF (15 mL) and treated with NaH (47 mg,

Table 2
RCM reactions of compounds **7–10**

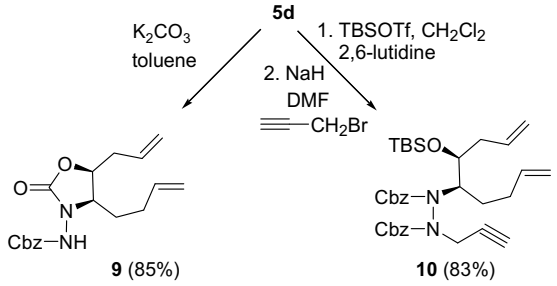
Entry	Substrate	Conditions[a]	**13**	Yield[b] (%)
1	**7a**	**A** 4 h	 **13a**	92
2	**7b**	**12** (10 mol %) toluene reflux, 6 h	 **13b**	88
3	**7c**	**A** 8 h	 **13c**	59
4	**7d**	**A** 2 h	 **13d**	66
5	**8a**	**A** 4 h	 **13e**	85
6	**8b**	**12** (10 mol %) CH_2Cl_2 reflux, 8 h	 **13f**	82
7	**8c**	**A** 4 h	 **13g**	75
8	**9**	**A** 2 h	 **13h**	85
9	**10**	**A** 2 h	 **13i**	23

[a] Condition **A**: **11** (10 mol %), CH_2Cl_2, reflux, argon.

 **11**

 **12**

[b] Isolated yields.



Scheme 3. Synthesis of RCM substrates **9** and **10**.

1.2 mmol) followed by allyl bromide (0.10 mL, 1.2 mmol) at 0 °C. The solution was stirred for 30 min at 0 °C and warmed to room temperature for 2.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL), extracted with CH_2Cl_2 (10 mL × 3). The combined organic solutions were dried over anhydrous $MgSO_4$ and the residue was chromatographed on silica gel (hexanes/EtOAc = 6:1) to give **7a** (250 mg, 76%) as a colorless oil; R_f = 0.4 (silica gel, hexanes/EtOAc = 6:1); $[\alpha]_D^{20}$ +7.33 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.23 (m, 10H), 5.89 (m, 1H), 5.26–4.91 (m, 9H), 4.19–3.85 (m, 2H), 2.45–2.03 (m, 2H), 1.25–0.86 (m, 14H), 0.05–0.00 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 156.9, 156.4, 135.9, 135.8, 134.4, 133.5, 128.5, 128.2, 128.0, 127.9, 117.4, 72.4, 68.2, 67.9, 67.7, 59.8, 58.7, 56.5, 56.3, 56.0, 39.2, 38.7, 26.0 18.1, 15.5, 11.6, −3.8, −4.1, −4.3; IR (film, cm^{-1}) 2954, 2919, 2848, 1714, 1454, 1399, 1301, 1223, 1145, 1086, 1043, 914; HRMS calcd for $C_{31}H_{44}N_2O_5Si$ (M^+): 552.3020; found: 552.3021.

2.3. General procedure for the RCM reaction

A mixture of **7a** (135 mg, 0.240 mmol) and **11** (16 mg, 0.024 mmol) in CH_2Cl_2 (12 mL) was refluxed for 4 h under argon. After concentration of the solution in vacuo, the residue was chromatographed on silica gel (hexanes/EtOAc = 6:1) to give **13a** (115 mg, 92%) as a colorless oil; R_f = 0.3 (hexanes/EtOAc = 6:1); $[\alpha]_D^{20}$ +8.71 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.32 (m, 10H), 6.05 (m, 2H), 5.30–5.12 (m, 4H), 4.53–4.32 (m, 2H), 3.70–3.80 (m, 1H), 3.22–3.20 (m, 1H), 2.33 (m, 2H) 1.75–1.15 (m, 3H), 0.96–0.91 (m, 9H), 0.18–0.06 (m, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 155.1, 154.1, 136.2, 136.0, 128.7, 128.6, 128.5, 128.2, 128.1, 128.0, 127.9, 127.7, 127.5, 126.4 68,1 67.2, 65.7, 43.8, 33.2, 25.8, 18.0, 15.0, −4.3, −4.4, −4.7, −4.8; IR (film, cm^{-1}) 2954, 2923, 2856, 1711, 1462, 1399, 1356, 1305, 1286, 1258 1231, 1106, 1086, 1027, 933; HRMS calcd for $C_{29}H_{40}N_2O_5Si$ (M^+): 547.2707; found: 547.2707.

Acknowledgments

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Supplementary data

The ^1H NMR copies of 1,3-oxazolidin-2-ones **14** (see Ref. 12) showing diastereomeric ratios are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.06.004.

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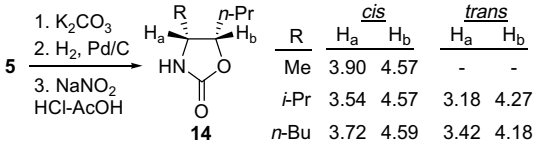
12. The diastereomeric ratios were determined after conversion of **5** to 1,3-oxazolidin-2-ones **14** (for the procedures of the cleavage of the N–N bond in step 3, see: Baumann, T.; Vogt, H.; Bräse, S. *Eur. J. Org. Chem.* **2007**, 266–282). While the chemical shifts of H_a and H_b for cis-isomers in **14** appear at 3.5–3.9 ppm and 4.5–4.7 ppm, respectively, those of *trans*-isomers appear at 3.2–3.4 ppm and 4.2–4.3 ppm (see Ref. 13 and Supplementary data).



	cis		trans	
R	H_a	H_b	H_a	H_b
Me	3.90	4.57	-	-
i-Pr	3.54	4.57	3.18	4.27
n-Bu	3.72	4.59	3.42	4.18

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