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Enantioselective Synthesis of Pyrrolidine-, Piperidine-, and Azepane-Type *N*-Heterocycles with α-Alkenyl Substitution: The CpRu-Catalyzed Dehydrative Intramolecular *N*-Allylation Approach

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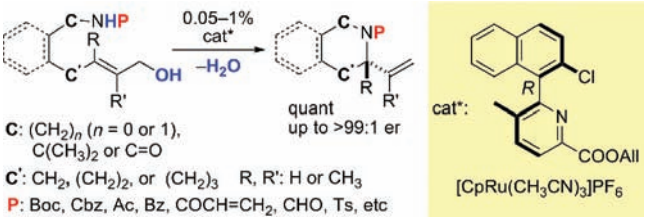
ABSTRACT



A cationic CpRu complex of chiral picolinic acid derivatives [(*R*)- or (*S*)-Cl-Naph-PyCOOCH$_2$CH=CH$_2$] catalyzes asymmetric intramolecular dehydrative *N*-allylation of *N*-substituted ω-amino- and -aminocarbonyl allylic alcohols with a substrate/catalyst ratio of up to 2000 to give α-alkenyl pyrrolidine-, piperidine-, and azepane-type *N*-heterocycles with an enantiomer ratio of up to >99:1. The wide range of applicable *N*-substitutions, including Boc, Cbz, Ac, Bz, acryloyl, crotonoyl, formyl, and Ts, significantly facilitates further manipulation toward natural product synthesis.

Saturated *N*-heterocycles, such as pyrrolidines, piperidines, azepanes, and their benzo-fused compounds, constitute a core part of pharmaceutically important natural alkaloids[1] and have therefore attracted much attention from synthetic chemists for the efficient stereoselective construction of these molecules,[2] particularly in a catalytic enantioselective manner. Among many approaches,[3] installation of an alkenyl group at the α-position via intramolecular enantioselective N–C$_\alpha$ bond formation[3f,4] is

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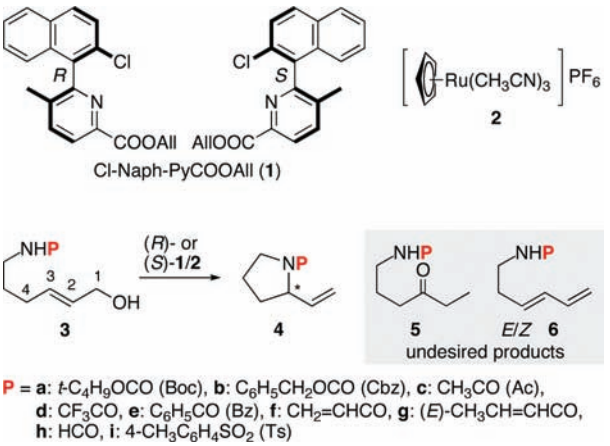
one of the most attractive strategies because of the high utility of the olefinic moiety in subsequent functional transformations.

Scheme 1

Scheme 1 shows one such protocol,[5] in which prochiral ω-amino allylic alcohols masked by an easily removable *N*-protecting group (PG) or modified by a post-transformable moiety dehydratively cyclize. Both Nishizawa/Yamamoto[6] and our[7] groups have recently reported such an atom-economic and operationally simple process in the enantioselective cyclization of ω-sulfonylamino allylic alcohols, although it was limited to specific cases. In this communication, we report a synthetically even more flexible method[8] with high reactivity, selectivity, and generality, which utilizes our previously described Cl-Naph-PyCOOAll (**1**, All: allyl)/$[CpRu(CH_3CN)_3]PF_6$ (**2**) combined catalyst.[9]

N-Boc-protected (*E*)-6-aminohex-2-en-1-ol ((*E*)-**3a**) was selected as a standard substrate because the previously reported methods[6,7] can be applied only to *N*-protected aromatic amine nucleophiles or C(3)-aryl-substituted allylic alcohols. Screening of the reaction conditions was started from [**3a**] = 500 mM; [(*R*)-**1**] = [**2**] = 0.5 mM; DMA; 100 °C; 3 h. The results are shown in Table 1.[10]

Table 1. Dehydrative Intramolecular Asymmetric *N*-Allylation of (*E*)-**3** Using (*R*)-Cl-Naph-PyCOOAll ((*R*)-**1**)/$[CpRu(CH_3CN)_3]PF_6$ (**2**) Combined Catalyst[a]



P = **a**: *t*-C_4H_9OCO (Boc), **b**: $C_6H_5CH_2OCO$ (Cbz), **c**: CH_3CO (Ac), **d**: CF_3CO, **e**: C_6H_5CO (Bz), **f**: CH_2=CHCO, **g**: (*E*)-CH_3CH=CHCO, **h**: HCO, **i**: 4-$CH_3C_6H_4SO_2$ (Ts)

entry	P (substrate)	S/C	time, h	% conv[b]	*S*:*R*[c]
1	*t*-C_4H_9OCO (**3a**)	1000	3	>99 (94)	98:2
2[d]	*t*-C_4H_9OCO (**3a**)	1000	3	>99 (–)	2:98
3[e]	*t*-C_4H_9OCO (**3a**)	2000	6	>99 (–)	98:2
4[f]	*t*-C_4H_9OCO (**3a**)	100	<0.5	>99 (–)	98:2
5	$C_6H_5CH_2OCO$ (**3b**)	1000	3	>99 (99)	98:2
6[f,g,h]	CH_3CO (**3c**)	100	3	>99[i] (90)	(93:7)
7[f]	CF_3CO (**3d**)	100	3	[j]	
8[f]	C_6H_5CO (**3e**)	100	3	>99 (95)	(97:3)
9[f,g]	CH_2=CHCO (**3f**)	100	24	>99 (98)	95:5
10[f,g,h]	(*E*)-CH_3CH=CHCO (**3g**)	100	24	>99 (91)	(93:7)
11[f,g]	HCO (**3h**)	100	24	>99 (97)	(96:4)
12	4-$CH_3C_6H_4SO_2$ (**3i**)	1000	3	>99 (95)	(97:3)

[a] Unless otherwise specified, all of reactions were carried out under the following conditions: [**3**] = 500 mM; [(*R*)-**1**/**2**] = 0.5 mM; solvent, DMA; bath temp, 100 °C. [b] ^{1}H NMR analysis. The value in parentheses: isolated yield of **4**. [c] GC or HPLC analysis. Absolute configuration: comparison of optical rotation with the reported values. Not determined for the parenthesized data. [d] Catalyst: (*S*)-**1**/**2**. [e] [**3a**] = 1 M. [f] [**3**] = 100 mM, [(*R*)-**1**] = [**2**] = 1 mM. [g] 10:1 *t*-C_4H_9OH–DMA mixed solvent. [h] 70 °C. [i] **4c**:**5c** = 95:5. Use of DMA as solvent quantitatively gave **5c**. [j] Only diene **6d** (*E*/*Z* = 2:1) was obtained in either DMA or *t*-C_4H_9OH.

The standard quantitatively afforded (*S*)-**4a** with an enantiomer ratio (er) of 98:2 (Table 1, entry 1), and the enantiomeric product (*R*)-**4a** was obtained by using an *S*-catalyst system (Table 1, entry 2). The substrate concentration could be increased to 1 M [substrate/catalyst (S/C) = 2000 (0.05 mol %)] (Table 1, entry 3). Even with S/C = 10000 (0.01 mol %), the reaction proceeded without loss of er, although it was sluggish (25%, 24 h). In terms of easy lab operation and quickness, S/C = 100 (1 mol %) is recommended (Table 1, entry 4). DMA, THF, and *t*-C_4H_9OH are the solvents of choice. The reaction was slower in CH_3OH (54% conv), C_2H_5OH (71%), *i*-C_3H_7OH (91%), ether (90%), TBME (84%), dioxane (90%), and CH_2Cl_2 (89%), but an er of 96:4 to 97:3 was maintained, whereas toluene deteriorated both the reactivity and selectivity (31% conv, 84:16 er). No reaction occurred in CH_3CN or acetone. The temperature could be lowered to 70 °C (24 h, 88% yield, 98:2 er), but the reaction proceeded little at 50 °C.[10]

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(10) For details, see the Supporting Information.

Not only the BocNH substrate (*E*)-**3a** but also the CbzNH and TsNH substrates **3b** and **3i** could be used with S/C = 1000 (0.1 mol %) to give **4b** and **4i** with a high er (Table 1, entries 5 and 12). Replacement of the alkoxycarbonyl or sulfonyl substitution on N with an acyl group required S/C = 100 (1 mol %) to gain reasonable reactivity and caused undesired reactions, giving ketone **5** or diene **6** in some cases. Thus, **3c** (P = Ac) was quantitatively converted to **5c** in DMA, but change of the DMA solvent to 10:1 *t*-C_4H_9OH−DMA afforded the desired product **4c** in 95% yield (Table 1, entry 6). The benzamide **3e** (P = Bz) smoothly cyclized in DMA to **4e** with a higher yield and without formation of **5e** (Table 1, entry 8). For some reason, **4c** was susceptible to a 1,3-hydrogen shift in DMA to the enamide compound, which was then hydrolyzed to **5c** by water liberated during the course of dehydrative allylation.[11] The reactions with **3f** (P = CH_2=CHCO) and **3h** (P = HCO) were completed under standard conditions to give a 95:5 mixture of **4f** and **6f** (*E*/*Z* = 3:1) and an 80:20 mixture of **4h** and **6h** (*E*/*Z* = 4:1), respectively. Formation of the diene was avoided by using a 10:1 *t*-C_4H_9OH−DMA mixed solvent (Table 1, entries 9 and 11). No cyclization occurred with the CF_3CONH substrate **3d**, while only β-elimination quantitatively proceeded to give **6d** (*E*/*Z* = 2:1) in either DMA or *t*-C_4H_9OH (Table 1, entry 7). Free amine (P = H) and its HX salts (X = TsO, AcO, PF_6) showed no reactivity.

Table 2 shows the scope and limitation of the present asymmetric catalysis for the synthesis of chiral pyrrolidines and piperidines.[10] Not only *E* allylic alcohols but also the *Z*-isomer is the substrate of choice. With the geometrical *Z*-isomer of (*E*)-**3a**, the (*R*)-**1**/**2** catalyst gave **4a** with preference for the *R* enantiomer (Table 2, entry 1). The compound **7a** (*n* = 2), in which one CH_2 is extended from (*E*)-**3a** (*n* = 1), was completely converted to the corresponding 6-*exo*-trig cyclized product **8a** with an er of 97:3 (Table 2, entry 2). The tertiary alkyl-substituted BocNH substrate **7b** could also be used (Table 2, entry 3). Introduction of a methyl group at C(2) of **3a** was tolerable (Table 2, entry 5), but the reaction of the C(3)-methyl substituted substrate **9b** led to generation of the diene (Table 2, entries 5 and 6). With *N*-protected aromatic amines **11**, both 5- and 6-*exo*-trig cyclization proceeded to give the indoline and tetrahydroquinoline derivatives **12** with an er of >99:1 and 95:5, respectively (Table 2, entries 7 and 8). Both the reactivity and enantioselectivity were dramatically decreased with the C(4)−C(5) arene-fused substrate **13a** (Table 2, entry 9),[7] whereas one CH_2 insertion at C(4) led to successful cyclization of **13b** to **14b** (Table 2, entry 10). The *N*-Ts-protected ω-aminocarbonyl allylic alcohol **15a** formed a N−C_α bond with nearly perfect enantioselectivity to give γ-lactam **16a** (Table 2, entry 11). With this *N*-nucleophile, the 3,3-disubstituted allylic alcohol **15b** could also be utilized to give **16b** with high stereocontrol of the tetrasubstituted carbon

Table 2. Asymmetric Synthesis of Pyrrolidines and Piperidines Using (*R*)-**1**/**2**-Combined Catalyst[a]

entry	substrate	product	% yield[b]	er[c]
1[d]	(*Z*)-**3a** (P = Boc; R = H; *n* = 1)	(*R*)-**4a**	92	6:94
2	**7** **a**: P = Boc; R = H; *n* = 2	(*S*)-**8a**	90	97:3
3[e,f]	**b**: P = Boc; R = CH_3; *n* = 1	**8b**	92	97:3
4[g]	**c**: P = (*E*)-CH_3CH=CHCO; R = H; *n* = 2	**8c**	96	94:6
5[e]	**9** **a**: R^1 = CH_3; R^2 = H	(*S*)-**10a**	96	98:2
6[g]	**b**: R^1 = H; R^2 = CH_3	**10b**	—[h]	—
7[f,i,j]	**11** **a**: P = Boc; *n* = 1	(*S*)-**12a**	98	>99:1
8[i,k]	**b**: P = Boc; *n* = 2	**12b**	99	95:5
9	**13** **a**: P = Ts; *n* = 0	**14a**	30	53:47
10[j]	**b**: P = Boc; *n* = 1	**14b**	90	96:4
11	**15** **a**: R = H	**16a**	92	99:1
12[j]	**b**: R = CH_3	(*S*)-**16b**	92	93:7

[a] Conditions: 25−120 mg scale; [substrate] = 100 mM; [(*R*)-**1**] = [**2**] = 1 mM; DMA; 100 °C; 3 h unless otherwise specified. *E* allylic alcohols were used except for (*Z*)-**3a** (entry 1). [b] Isolated yield. [c] GC or HPLC analysis. [d] 1 h. [e] [substrate] = 500 mM; [(*R*)-**1**] = [**2**] = 0.5 mM. [f] 6 h. [g] 24 h. [h] 50% conv, 85:15 mixture of *N*-Boc-protected 6-amino-3-methylhexa-1,3-diene (*E*/*Z* = 3:2) and 6-amino-3-methylenehex-1-ene. [i] 5 g scale. [j] 10:1 *t*-C_4H_9OH−DMA mixed solvent. [k] 1 g scale.

stereogenic center (Table 2, entry 12), which would be a good precursor for α-methyl glutamic acid.[12] Success in the highly enantioselective cyclization of the *N*-alkenoyl allylic alcohols **3f**, **3g**, and **7c** (P = CH_2=CHCO or (*E*)-CH_3CH=CHCO) to **4f**, **4g**, and **8c**, respectively (Table 1, entries 9 and 10; Table 2, entry 4), should shorten the steps to pyrrolizidine and indolizidine alkaloids when combined with subsequent Grubbs intramolecular metathesis.[13]

The Cl-Naph-PyCOOAll/CpRu method could also be applied to the construction of an azepane skeleton, although

(11) For Ru-catalyzed isomerization of the (CO)N-allyl bond to the enamide, see: Krompiec, S.; Krompiec, M.; Penczek, R.; Ignasiak, H. *Coord. Chem. Rev.* **2008**, *252*, 1819–1841.

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not as generally as in the case of five- and six-membered ring formation (Figure 1). The simplest substrate **17a** (E/Z = 97:3) and its imide derivative **17c** underwent only β-elimination to give the diene products **18a** and **18c** (E/Z = 2:1). With the arene-fused substrates **17b** and **17d**, however, the desired cyclization efficiently proceeded to generate the azepane-type *N*-heterocycles **18b** and **18d** with an er of 99:1 and 96:4, respectively. The compounds **18b** and **18d** were high-potential intermediates for the synthesis of tetrahydrobenzazepine alkaloids.[2i,k−m,4d,4e] Introduction of two sp^2 carbons in the carbon tether may enable better HOMO/LUMO orbital interaction between the N atom and the π-allyl C(3) atom. Replacement of Ts group of **17b** with Boc, however, decreased the reactivity and caused β-elimination (29% conv; E/Z = 2:1).[10] The acidity of NH also exerts a significant effect on the reactivity.

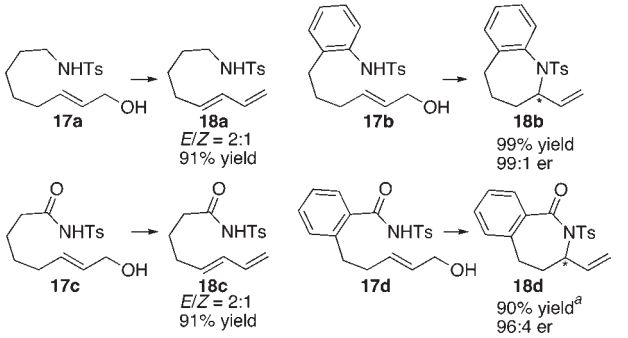

Figure 1. Synthesis of azepane-type *N*-heterocycles ([**17**] = 100 mM; [(*R*)-**1**/**2**] = 1 mM; 10:1 *t*-C_4H_9OH−DMA; 100 °C; 3 h). (a) **18c**-type diene (E/Z = 2:1) was formed in 10% yield.

The present catalysis involves many reaction pathways, such as (i) π-allyl Ru(IV) formation (k_1); (ii) reductive nucleophilic attack of a PNH to the π-allyl ligand to regenerate Cl-Naph-PyCOOH/CpRu(II) (k_2);[9] (iii) β-elimination from the π-allyl complex (k_3); and (iv) 1,3-hydrogen shift of the α-alkenyl *N*-heterocyclic product to the α-exocyclic enamide derivative (k_4), followed by hydrolysis. The rate k_1 would be enhanced by a "redox-mediated donor−acceptor bifunctional catalyst" mechanism,[7,9,14] in which the hard H^+/soft Ru combined catalyst cooperatively activates the allylic alcohol via protonation on the hard hydroxy oxygen and via coordination of the soft double bond to Ru(II). Such a synergetic effect would facilitate the dehydrative π-allyl formation (k_1). The fate of the π-allyl species is determined by the relative rate of k_2 to k_3 and k_4, which is strongly affected by the electronic, steric, stereoelectronic, and molecular orbital properties of PNH. More systematic investigation of the substrate structure/reactivity/selectivity relationship is required for full elucidation of the mechanism. This is an ongoing project in our group.

In summary, by using 0.05−1.00 mol % **1**/**2**, highly enantioselective intramolecular *N*-allylation of *N*-protected ω-amino and -aminocarbonyl allylic alcohols has been realized without activation of allylic alcohols as the esters or halides. Boc-, Cbz-, Ac-, Bz-, CH_2=CHCO-, (*E*)-CH_3CH=CHCO-, HCO-, and Ts-NH can act as nucleophiles, depending on the reaction conditions. Not only 5- and 6-*exo*-trig cyclization but also seven-membered ring formation can be attained. The easily removable PGs, as well as the structurally transformable *N*-substituents, should facilitate the syntheses of pharmaceutically important natural *N*-heterocycles. To the best of our knowledge, the present Cl-Naph-PyCOOAll/CpRu(II) method is the first example showing very high applicability to C(3)-alkyl-substituted allylic alcohols. Furthermore, complementary use of the present method with our other asymmetric catalyst, Naph-diPIM-dioxo-R/CpRu(II)/*p*-TsOH,[7] which has high performance for C(3)-aryl substrates, should significantly widen the scope of substrate patterns in the asymmetric intramolecular dehydrative *N*-allylation approach.

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Supporting Information Available. Experimental details for dehydrative asymmetric cyclization, crystal data for **16b**, and copies of ^{1}H NMR and ^{13}C NMR spectra for substrates and all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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