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Ir-Catalyzed Allylic Amination/Ring-Closing Metathesis: A New Route to Enantioselective Synthesis of Cyclic β-Amino Alcohol Derivatives

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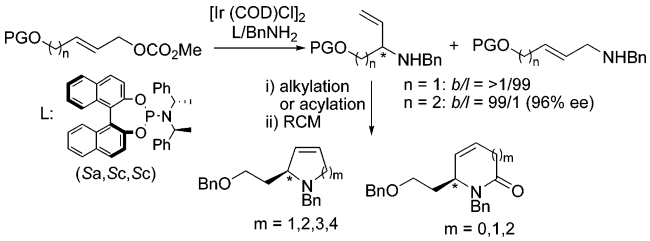

Ir-catalyzed allylic aminations of (*E*)-4-benzyloxy-2-butenyl methyl carbonate with benzylamine using Feringa's (S_a,S_c,S_c)-phosphoramidite as a chiral ligand afforded linear-aminated achiral product *N*,*O*-dibenzyl-4-amino-2-buten-1-ol regioselectively (linear/branched = >99/1), whereas the (*E*)-5-benzyloxy-2-pentenyl methyl carbonate showed completely opposite regioselectivity (linear/branched = >1/99) and afforded the optically active (3*R*)-*N*,*O*-dibenzylated 3-amino-1-penten-5-ol with very high enantioselectivity (96% ee), which was used as a key intermediate for the effective synthesis of various cyclic β-amino alcohol derivatives through ring-closing metathesis in high yields.

Due to their ubiquity in biologically interesting natural and synthetic compounds, the stereoselective synthesis of cyclic β-amino alcohols, particularly 2-hydroxyethylpyrrolidines, has become an increasingly important synthetic target.[1] The most commonly employed method is carboxylic acid reduction of optically active cyclic β-amino acids, which are generally prepared by the homologation of cyclic α-amino acids.[2] However, although a number of interesting and synthetically useful methods for optically active cyclic β-amino acids have been developed,[3,4] they are often specific to a particular ring size (generally 5- and 6-membered rings) and/or stereochemical motif. Hence, cyclic β-amino acid-based approaches include limitations to their utility as general methods for synthesizing optically active 2-hydroxyethyl pyrrolidine and its cyclic analogues. Therefore, the development of more general and flexible enantioselective synthetic methods for cyclic β-amino alcohol derivatives represents a desirable goal.

Over the past few years, Ir-catalyzed asymmetric allylic substitutions of an achiral or racemic allylic ester or carbonate have been extensively studied and utilized to generate new stereogenic carbon centers bonded to carbon,[5] nitrogen,[6] and oxygen atoms.[7] In particular, regio- and enantioselective allylic aminations and etherifications of terminal allylic electrophiles using the Ir complex of chiral phosphoramidite have proven to be an extremely useful method for the synthesis of chiral *N*- and *O*-heterocyclic compounds such as 2-vinylazacycloalkanes,[6d] 2,5-divinylpyrrolidines,[6h,j] disubstituted dehydropyrrolidines,[6k] dihydropyrans, and dihydrofurans.[7b] It has also been reported that the asymmetric Ir-catalyzed allylic alkylation of *O*-protected allylic carbonates **1** (n = 1)[8] or stereospecific Rh-catalyzed allylic amination of enantiomerically pure allylic carbonates,[9]

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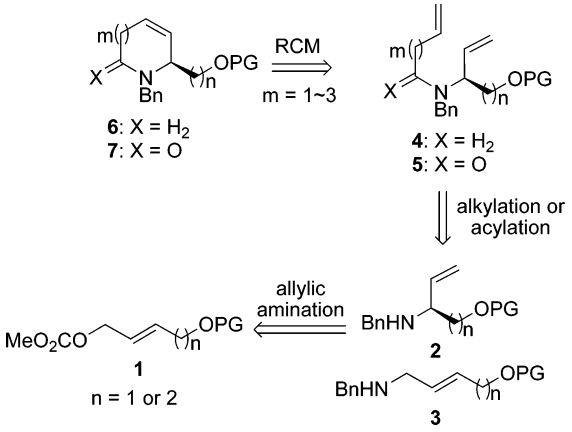
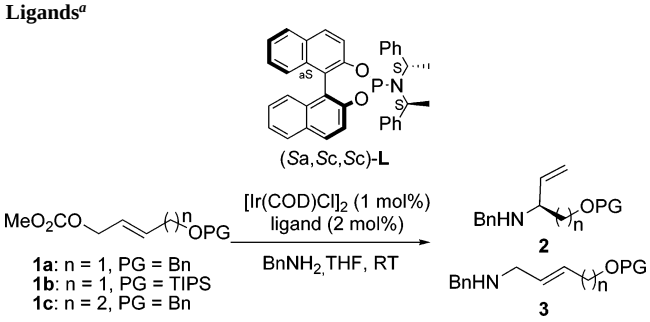
SCHEME 1. Ir-Catalyzed Allylic Amination/Ring-Closing Metathesis for Cyclic Amino Alcohol Derivatives



in combination with ring-closing metathesis (RCM), afforded carbocycles and dihydropyrroles, respectively. Surprisingly, no report on the regio- and enantioselective Ir-catalyzed allylic amination of *O*-protected hydroxyalkyl-substituted carbonates such as **1** has been found in the literature. As shown in Scheme 1, we anticipated that the regio- and enantioselective Ir-catalyzed allylic aminations of *O*-protected hydroxyalkyl-substituted allylic carbonates **1** could provide a new route for the synthesis of optically active *N*,*O*-protected allylamines **2**. In particular, 3-amino-1-penten-5-ol (n = 2 in **2**), which is generally synthesized by multistep synthesis starting from L-cysteine (or after conversion into homoserine),[10] was expected to be a key intermediate for the synthesis of pyrrolidines **6** and pyrrolidinones **7** (Scheme 1). Here, we report the Ir-catalyzed allylic aminations of *O*-protected hydroxyalkyl-substituted allylic carbonates **1** providing a new route for the *N*,*O*-dibenzylated optically active 3-amino-1-penten-5-ol **2** (n = 2), which has been used as a key intermediate for the synthesis of various cyclic β-amino alcohol derivatives through ring-closing metathesis.

It has been generally known that Ir-catalyzed allylic substitutions of the linear allylic carbonates proceed regiospecifically, i.e., the substrates having (*E*)-geometry show much higher selectivity for branched product than the (*Z*)-substrates.[5b,11] Based on these observations, the regioselectivity of the (*E*)-4-benzyloxy-2-butenyl methyl carbonate (**1a**)[12] having (*E*)-geometry was investigated first in an Ir-catalyzed (1 mol % of $[Ir(COD)Cl]_2$) allylic amination with benzylamine using achiral $P(OPh)_3$ (2 mol %) as a ligand at room temperature for 12 h. Unfortunately, the linear-aminated product **3a** was formed regioselectively (**2a**/**3a** = 4:96) in 40% yield (entry 1, Table 1), and most of the starting **1a** remained unreacted. Changing the benzyl protection group to the sterically bulky triisopropylsilyl (TIPS) group (**1c**)[12] did not improve the regioselectivity (**2b**/**3b** = 3:97) and yield at all (entry 2, Table 1). There were no signs for the formation of corresponding branched amines **2a** and **2b** from **1a** and **1b**, respectively, in the ^{1}H NMR analysis.

TABLE 1. Ir-Catalyzed Allylic Amination of *O*-Protected Hydroxyalkyl-Substituted Allylic Carbonates 1 with Benzylamine Using Achiral $P(OPh)_3$ and Chiral (S_a,S_c,S_c)-Phosphoramidite as Ligands[a]



entry	1	ligand	2/3[b]	yield (2 + 3)[c] (%)	% ee (2)[d]
1	**1a**	$P(OPh)_3$	5:95	40	
2	**1b**	$P(OPh)_3$	3:97	32	
3	**1c**	$P(OPh)_3$	>99:1	89	racemic
4[e]	**1c**	(S_a,S_c,S_c)-**L**	2.5:1	59	77
5[f]	**1c**	(S_a,S_c,S_c)-**L**	>99:1	94	96
6[f]	**1a**	(S_a,S_c,S_c)-**L**	>1:99	42	
7[f]	**1b**	(S_a,S_c,S_c)-**L**	>1:99	27	

[a] Reactions were carried out at room temperature using 1 mol % of Ir catalyst ($[Ir(COD)Cl]_2$ and 2 mol % of ligand in THF (0.5 M). [b] Ratio determined by ^{1}H NMR analysis of crude mixture. [c] Isolated yield. [d] Determined by HPLC analysis using a chiral column (Daicel CHIRALCEL OD-H). [e] Catalyst was activated in situ with DABCO (conditions A). [f] Catalyst was pre-activated with *n*-propylamine (conditions B).

Fortunately, under the same reaction conditions, completely opposite regioselectivity was observed from the one-carbon elongated substrate **1c**,[12] and thus, only the branch-aminated racemic **2c** was formed in 89% yield (entry 3, Table 1).

Regioselective formation of the branched allylic amine **2c** suggests the possibility of asymmetric synthesis of optically active **2c** by Ir-catalyzed allylic amination of **1c**. Thus, we next carried out asymmetric allylic amination of the (*E*)-5-benzyloxy-2-pentenyl methyl carbonate (**1c**)[12] using Feringa's (S_a,S_c,S_c)-phosphoramidite ligand (**L**), which is known to be one of the most effective chiral ligands for Ir-catalyzed allylic aminations.[13] As pointed out by Helmchen[5b,6h] and Hartwig,[6f,g] it has been found that the regio- and enantioselectivity were largely dependent on the catalyst preparation. Initially, the $[Ir(COD)Cl]_2$ (1 mol %) was activated in situ by using 10 mol % of 1,2-diazabicyclo[2.2.2]octane (DABCO) to form an activated iridacyclic complex (conditions A), which is known to be an excellent active catalyst for aminations.[6b,f] However, a mixture of branched **2c** (42%) and linear amine **3c** (17%) was formed with low regioselectivity (ca. **2c**/**3c** = 2.5:1) and a moderate enantioselectivity of **2c** (77% ee) (entry 4, Table 1). Gratifyingly, when the catalyst was preactivated with *n*-propylamine,[6g] extremely high regio- and enantioselectivity were observed. The preactivated catalyst was prepared by stirring a solution of $[Ir(COD)Cl]_2$ (1 mol %) and (S_a,S_c,S_c)-**L** (2 mol %) in THF/*n*-propylamine (v/v, 1:1) at 50 °C for 30 min (conditions B). After evaporation of all of the volatiles, the remaining activated catalyst was used directly for allylic aminations. Thus, the allylic carbonate **1c** and benzylamine were added to a solution of the preactivated Ir catalyst (2 mol %) in THF (1.0 M), and the reaction mixture was stirred at room temperature for 10 h to

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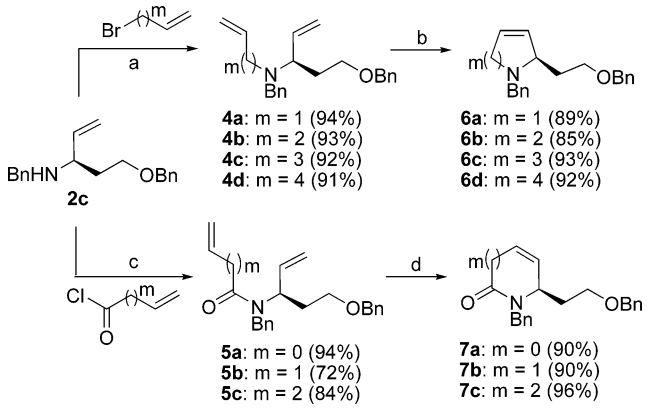
SCHEME 2. Synthesis of Benzyloxyethyl-Substituted Azacycloalkenes 6 and 7 Using 2c as a Key Intermediate[a]



[a] Conditions: (a) $NaHCO_3$/cat. *n*-Bu_4NI, CH_3CN, reflux, 12 h; (b) *p*-toluenesulfonic acid monohydrate (1.0 equiv), Grubbs' second-generation Ru−carbene catalyst (5 mol %)/CH_2Cl_2 (0.05 M), reflux, 10 h; (c) *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 1 h; (d) Grubbs' second-generation Ru−carbene catalyst (5 mol %)/CH_2Cl_2 (0.01 M), reflux, 12 h.

afford the branched amine **2c** with extremely high regio- (>99%, no **3c** was detected in ^{1}H NMR) and enantioselectivity (96% ee) in a yield of 94% (entry 5, Table 1). However, under the optimized asymmetric conditions (conditions B), as observed in nonasymmetric allylic amination, only the linear-aminated product **3a** (**2a**/**3b** = >1:99, 42%) and **3b** (**2b**/**3b** = >1:99, 27%) were formed from **1a** and **1b**, respectively. The reason for the opposite regioselectivity between **1a** (or **1b**) and **1c** is not yet clear and remains to be elucidated.

With a gram quantity of the key intermediate chiral allyl amine **2c** in hand, we next attempted synthesis of various 2-benzyloxyethyl-substituted azacycloalkenes **6** and **7** via ring-closing metathesis (Scheme 2). For this purpose, dienes **4a**−**d** were prepared in a straightforward manner by *N*-alkylation of **2c** with the corresponding bromoalkenes in high yields (90−94%). Due to catalyst inhibition by basic nitrogen, a variety of methods for blocking basic nitrogen function for Ru-based RCM reactions were employed, involving Brönsted or Lewis acids.[10,14] In our case, Wright's protocol employing an equivalent amount of *p*-toluenesulfonic acid (*p*-TsOH·H_2O)[10] as an additive worked best for RCM of amines **4a**−**d**, where the Grubbs' second-generation catalyst showed superior catalytic efficiency compared with the Grubbs' first-generation catalyst.[15] With 5 mol% of Grubbs' second Ru−carbene catalyst, five- to eight-membered azacycles **6a**−**d** were synthesized uneventfully in high yields. The RCM of the amide dienes **5a**−**c**, on the other hand, was carried out in the absence of an acid with 5 mol % of Grubbs second Ru−carbene catalyst, affording the corresponding five- to seven-membered pyrrolidinone analogues **7a**−**c** in high yields. It should be noted that these azacycloalkenes represent a useful platform for a variety of *N*-heterocyclic compounds.

In summary, we have developed a new route for enantioselective synthesis of *N*,*O*-protected 3-amino-1-penten-5-ol through investigation of the Ir-catalyzed allylic amination of *O*-protected hydroxyalkyl-substituted allylic carbonates **1a**−**c**. It was also found that the regioselectivities are largely dependent on the length of the alkyl substituents, and thus, the benzyloxyethyl-substituted allylic carbonate **1c** showed high branch selectivity (linear/branched = >1/99) with very high enantioselectivity (96% ee), whereas completely opposite regioselectivity (linear/branched = >99/1) was observed from the benzyloxymethyl-substituted allylic carbonates **1a** and **1b**. Utilization of the optically active *N*,*O*-dibenzylated 3-amino-1-penten-5-ol **2c** as a key intermediate permits the asymmetric synthesis of various *N*,*O*-dibenzylated cyclic *β*-amino alcohol derivatives **6** and **7** through combination with ring-closing metathesis.

Experimental Section

Asymmetric Allylic Amination of Allylic Carbonates 1. A typical procedure is given for the reaction of (*E*)-5-benzyloxy-2-pentenyl methyl carbonate (**1c**). In a nitrogen-filled drybox, [Ir(COD)Cl]$_2$ (9.4 mg, 14.0 *μ*mol) and (S_a,S_c,S_c)-phosphoramidite **L** (15.1 mg, 28.0 *μ*mol) were diluted in 0.3 mL of THF and 0.3 mL of *n*-propylamine in a 5 mL screw-capped vial. The reaction vial was heated at 50 °C in a preheated oil bath for 30 min and then allowed to cool to room temperature. All of the volatiles were removed by blowing a stream of dry nitrogen gas, and the resulting yellow residue was dried under vacuum. To the residual precatalyst were added allylic carbonate **1a** (350.0 mg, 1.4 mmol), benzylamine (225.0 mg, 2.1 mmol), and 1.4 mL of THF. The vial was sealed with a cap containing a PTFE septum and removed from the drybox, and the reaction was stirred at room temperature for 10 h. After evaporation of all volatiles, the ratio of regioisomers was **2c**/**3c** = >99:1 as determined by ^{1}H NMR analysis of the crude mixture. Silica gel column chromatography using 20% EtOAc/*n*-hexane afforded (*R*)-*N*-[1-(2-benzyloxyethyl)-2-propenyl]benzylamine **2c** (369 mg, 94%). The absolute configuration of **2c** was tentatively assigned as *R* according to Hartwig's model.[6a] The enantiomeric excess of the allylic amination product **2c** was determined to be 95.5% by HPLC analysis using a chiral column [Daicel CHIRALCEL OD-H column (0.46 × 25 cm); eluent: *n*-hexane/2-propanol = 95:5; flow rate = 0.9 mL/min; retention time: 18.3 min (major), 27.3 min (minor)]. **2c**: colorless oil; $[\alpha]_D = -5.56$ (*c* 2.78, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.33−7.23 (m, 10H), 5.65 (ddd, *J* = 17.6, 10.0, 8.3, 1H), 5.14 (d, *J* = 10.0 Hz, 1H), 5.12 (d, *J* = 17.6 Hz, 1H), 4.49 (d of AB pattern, *J* = 12.0 Hz, 1H), 4.45 (d of AB pattern, *J* = 12.0 Hz, 1H), 3.82 (d of AB pattern, *J* = 13.1 Hz, 1H), 3.63 (d of AB pattern, *J* = 13.1 Hz, 1H), 3.60−3.48 (m, 2H), 3.24 (dd, *J* = 6.9, 7.6 Hz, 1H), 1.90−1.81 (m, 1H), 1.76−1.70 (m, 1H), 1.58 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 140.83, 140.61, 138.40, 128.33, 128.17, 127.64, 127.52, 126.77, 116.24, 73.0, 67.72, 58.95, 51.25, 35.63; HRMS *m*/*z* (FAB) calcd for $C_{19}H_{24}NO$ ($M + H^+$) 282.1852, found 282.1854. **3c**: ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.42−7.25 (m, 10H), 5.88−5.81 (m, 1H), 5.71−5.64 (m, 1H), 4.58 (s, 2H), 3.84 (s, 2H), 3.51 (t, *J* = 6.5 H, 2H), 2.38 (q, *J* = 6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 138.2, 133.3, 128.3, 127.6, 127.5, 125.1, 72.9, 69.2, 68.3, 54.6, 52.9, 33.6.

Representative Procedure for the Ring-Closing Metathesis of 4 To Give 6. *p*-Toluenesulfonic acid monohydrate (11.2 mg, 0.059 mmol) was added to a solution of **4a** (19.0 mg, 0.059 mmol) in dichloromethane (5 mL, 0.010 M), and the solution was stirred for 30 min at room temperature until it became a homogeneous solution. Grubbs' monoimidazolinylidene monophosphine carbene complex (second-generation catalyst, 2.5 mg, 2.9 *μ*mol, 5 mol %) was added, and the solution was stirred under reflux for 10 h. After removal of the solvent, the residue was directly loaded on a silica gel (EtOAc/Hex = 1:4, containing 5% Et_3N and 2% MeOH) to afford 15.5 mg (89%) of pure **6a**: pale yellow oil; $[\alpha]_D = -48.2$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.40−7.20 (m, 10H), 5.77−5.70 (m, 2H), 4.49 (s, 2H), 4.03 (d of ABq, *J* = 13.2 Hz,

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1H), 3.75 (m, 1H), 3.71−3.56 m, 3), 3.54 (d of ABq, J = 13.5 Hz, 1H), 3.21−3.14 (m, 1H), 1.94−1.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 138.8, 131.6, 128.8, 128.6, 128.5, 127.8, 127.7, 127.1, 127.0, 73.2, 68.4, 68.0, 60.4, 59.4, 35.3; HRMS *m*/*z* (FAB) calcd for $C_{20}H_{24}NO$ (M + H^+) 294.1852, found 294.1851.

Representative Procedure for the Ring-Closing Metathesis of 5 To Give 7. Grubbs' monoimidazolinylidene monophosphine carbene complex (second-generation catalyst, 2.2 mg, 2.6 μmol, 3 mol %) was added to a solution of **5a** (26.0 mg, 0.078 mmol) in dichloromethane (0.8 mL, 0.1 M), and the solution was stirred at room temperature for 10 h. Then, an additional 3% of Grubbs' second-generation catalyst was added, and the mixture was stirred under reflux for a further 10 h. Thin layer chromatography indicated complete conversion, and the reaction mixture was directly loaded on a silica gel and purified (EtOAc/Hex = 1:1) to afford the ring-closed product **7a**: pale yellow oil (90%); $[\alpha]_D$ = −23.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.15 (m, 10H), 7.10 (dd, J = 1.5, 5.9 Hz, 1H), 6.17 (dd, J = 1.9, 5.8 Hz, 1H), 5.10 (d of ABq, J = 15.0 Hz, 1H), 4.41 (s, 2H), 4.12 (d of ABq, J = 15.0 Hz, 1H), 4.15−4.06 (m, 1H), 3.45−2.36 (m, 2H), 2.15 (m, 1H), 1.78 (m, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 171.6, 148.5, 138.1, 137.7, 128.9, 128.6, 128.05, 128.0, 127.9, 127.7, 126.7, 73.4, 66.0, 60.5, 60.4, 43.8; HRMS *m*/*z* (FAB) calcd for $C_{20}H_{22}NO_2$ (M + H^+) 308.1645, found 308.1647.

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Supporting Information Available: Detailed experimental procedures and spectroscopic data, ^{1}H and ^{13}C spectra of compounds **2c**, **4a**−**d**, **5a**−**c**, **6a**−**d**, and **7a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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