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Titanocene(III) Chloride Mediated Radical Induced Allylation of Aldimines: Formal Synthesis of C-Linked 4′-Deoxy Aza-disaccharide

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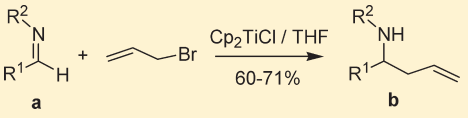
Supporting Information

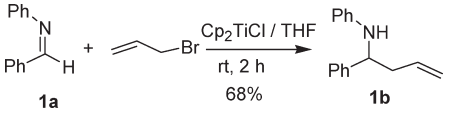
ABSTRACT: Titanocene(III) chloride (Cp_2TiCl) mediated radical induced allylation of aldimines for the preparation of homoallyl amines is described. The radical was generated from the allyl bromide using Cp_2TiCl as the radical source. Formal synthesis of C(4)−C(5′)-linked 4′-deoxy aza-disaccharide is demonstrated and a study toward the bicyclic skeleton of alkaloids was also accomplished. The radical initiator Cp_2TiCl was prepared *in situ* from commercially available titanocene dichloride (Cp_2TiCl_2) and Zn dust in THF under argon.



Homoallyl amines are versatile intermediates for the preparation of widely used compounds for the synthesis of naturally occurring targets such as β-amino acids or esters, 1,3-amino alcohols, and 1-amino-3,4-epoxides.[1,2] For instance, β-amino acids used for the synthesis of β-lactam antibiotics such as antimicrobial 1β-methyl carbapenem and α-branched amines, e.g., cinacalcet, can also be obtained from homoallyl amines.[3] Homoallyl amines proved to be eminent building units for the asymmetric synthesis of pyrrolidines and piperidines via a ring-closing metathesis (RCM).[4] Moreover, it has also been assayed that homoallyl amines containing aryl rings at C-4 of butene moiety exhibit considerable antimicrobial activity against some infective dermatophytes.[5]

The usual approach for the preparation of homoallyl amines is a nucleophilic addition of allyl-metal compounds to aldimines in the presence of a Lewis acid.[6] There are also several other methods for the synthesis involving metals in association with ionic liquids, poly(ethylene glycol) (PEG) and some other metal salts.[7] Recently, Gall and his co-workers reported[3b] similar types of reactions using only Zn metal but failed to produce allylated products using Zn and allyl bromide. However, most of the reported methods suffer from functional group intolerance, substrate variation, and the use of expensive and toxic catalysts, implying the need for a more efficient method especially in chiral molecules. The mildness and efficiency of bis-cyclopentadienyl titanocene(III) chloride (Cp_2TiCl) mediated radical induced reactions have significantly inspired synthetic chemists in recent years to utilize radical technology in developing synthetic strategy and its application in natural product synthesis.[8] In continuation of our studies for the synthesis of natural products involving radical-induced reactions,[9] we report here a mild and efficient Cp_2TiCl mediated radical induced synthesis of homoallyl amines. Titanocene(III) chloride (Cp_2TiCl) was prepared *in situ* from commercially available titanocene dichloride (Cp_2TiCl_2) using Zn dust in THF.[8a] Thus, freshly prepared Cp_2TiCl in THF was added dropwise at room temperature to the aldimine (prepared by mixing the aldehyde and amine under vacuum) and allyl bromide, furnishing the homoallyl amines in excellent yield. There are several one-pot strategies for the synthesis of homoallylic amines reported in the literature where most likely the reaction goes via the formation of imines as an intermediate.[10] In a preliminary experiment, Cp_2TiCl in THF was added dropwise to the solution of phenyl aldimine **1a** in THF. The resulting solution was stirred at room temperature for additional 2 h to furnish the allylated product **1b** in 68% yield (Scheme 1). In the ^{1}H NMR spectrum of **1b**, allylic methylene protons appeared at δ 2.5 and the olefinic protons appeared at δ 5−6.

Scheme 1. Cp_2TiCl Mediated Allylation of Aromatic Aldimines



Thus, a series of aromatic aldimines were subjected to allylation reaction; the results are summarized in Table 1. When the aromatic amine was replaced by a *N*-aliphatic amine (Table 1, entry 11), a trace amount of product was observed in the ^{1}H NMR. This indicates that although the allylic titanocene would act as reactive species generated via one-electron transfer process, the subsequent allylation step to imine might go through an ionic process (Scheme 2) stabilized by the adjacent aromatic ring.

Next, some chiral aldimines were subjected to allylation reaction; the results are summarized in Table 2. The corresponding desired homoallyl amines were isolated with better yield compared to the aromatic aldimines. The optically pure aldimines (Table 2, entry 13−17) yielded a mixture of isomers, although the formation of one isomer was found to dominate. Only two isomers of **17b** could be separated by chromatographic methods, but the structures of the two isomers **17b**^{1} (major) and **17b**^{2} (minor) were confirmed in the later stage. Isomers in the

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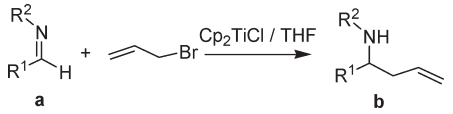
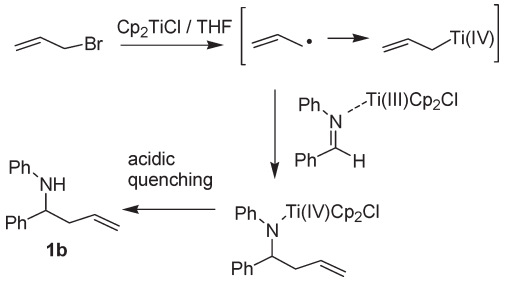
Table 1. Cp_2TiCl Mediated Allylation of Aromatic Aldimines



entry	R^1	R^2	yield (%)[a]	ref
1	C_6H_5	C_6H_5	68	6b
2	C_6H_5	4-MeO-C_6H_4	62	6f
3	C_6H_5	4-Cl-C_6H_4	65	6b
4	C_6H_5	1-naphthyl	64	6b
5	C_6H_5	4-Me-C_6H_4	65	6b
6	4-Me-C_6H_4	C_6H_5	65	6b
7	4-Cl-C_6H_4	C_6H_5	64	6b
8	4-MeO-C_6H_4	C_6H_5	65	6b
9	2-naphthyl	C_6H_5	60	6f
10	2-OH-C_6H_4	C_6H_5	63	6f
11	C_6H_5	$PhCH_2$	tr	

[a] Isolated yield.

Scheme 2. Plausible Reaction Pathway of Allylation



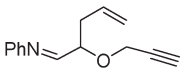
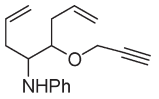
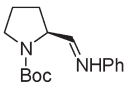
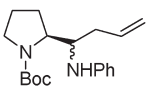
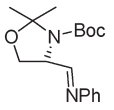
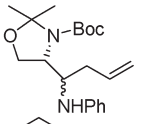
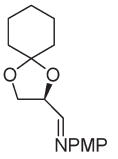
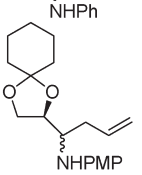
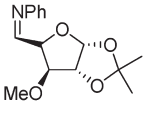
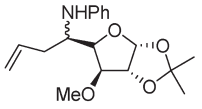
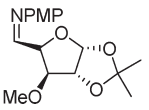
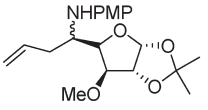
other compounds **13b**−**16b** could not be separated by usual chromatographic methods.

The better diastereoselectivity observed for compounds **13b**−**17b** at room temperature compared to reported literature[11] encouraged us to apply the methodology to the synthesis of heterocyclic natural products and related compounds. Aza-sugars are important analogues in sugar chemistry, and their inhibitory activity[12] against glycosidases or glycosyl transferases are well-known. There are several reports on the synthesis of aza-sugar derivatives,[11] but still advancement is required for a better stereoselective synthetic protocol with fewer number of steps and satisfactory yield.

To focus this idea, the major isomer of homo allyl amine **17b**[1] was acylated[13] with acryloyl chloride in the presence of Et_3N to afford the acylated product **17c**. Finally, compound **17c** was subjected to RCM[14] using second generation Grubbs catalyst to obtain the cyclic amide **17d** (Scheme 3). The 4-methoxy phenyl group in compound **17d** was deprotected[15] by CAN in aqueous CH_3CN to furnish compound **17e**. Compound **17e** has already been transformed to C(4)−C(5′)-linked 4′-deoxy aza-D-disaccharide **17f** in one step.[12a] So, we report here a formal synthesis of C(4)−C-(5′)-linked 4′-deoxy aza-D-disaccharide **17f**.

The structure of the compound **17d** was confirmed by X-ray crystallographic study (Figure 1). The three-dimensional X-ray structure of **17d** showed that the methyl protons of the methoxy group attached to the furanose ring came into the shielding zone

Table 2. Cp_2TiCl Mediated Allylation of Chiral Aldimines

Entry	Aldimine (a)	Product (b)	yield (%)[a]
12			65 (ratio not dtectable)
13			69 (9.5:0.5)[b]
14			70 (12:1)[b]
15			71[c] (9:1)[b]
16			69 (3:1)[b]
17			70 (3:1)[b]

[a] Isolated yield. [b] Distereomeric ratio determined by GC. [c] PMP = 4-methoxy phenyl.

of the benzene ring (anisotropic effect). As a result, the methoxy protons of the cyclic amide **17d** appeared at δ 2.46, whereas the same protons appeared at δ 3.27 for the acyclic amide **17c**. So, by analogy with the X-ray structure of **17d**, assignment of stereochemistry of the major isomer of homoallyl amine **17b**[1] as shown in Scheme 3 could easily be determined.

Compound **15b** was converted to the cyclic amide **15d** through acylation followed by RCM (Scheme 4). It is expected that compound **15d** could easily be converted to bicyclic skeletons[16] related to alkaloids through some classical transformations as shown in Scheme 4, which is under progress and will be reported elsewhere.

In conclusion, we have demonstrated a titanocene(III) chloride mediated radical induced mild and convenient allylation of aldimines and its application toward the synthesis of some important aza-sugar molecules and alkaloid skeletons.

EXPERIMENTAL SECTION

Representative Procedure for the Preparation of Aldimine 1a. Benzaldehyde (106 mg, 1 mmol) and aniline (93 mg, 1 mmol) were mixed in a small round-bottom flask. The crude oil was left under vacuum (4×10^{-4} mbar) for 10 min, until all of the oil was solidified. The crude solid aldimine **1a** (170 mg, 90%) was subjected to allylation reaction without further purification.

All other aldimines **2a**−**17a** were prepared following the same procedure as stated above for **1a**.

Representative Procedure for Cp_2TiCl Mediated Allylation of Aldimine 1a: Preparation of Phenyl-(1-phenyl-but-3-enyl)-amine (1b). A solution of titanocene dichloride (370 mg, 1.5 mmol)

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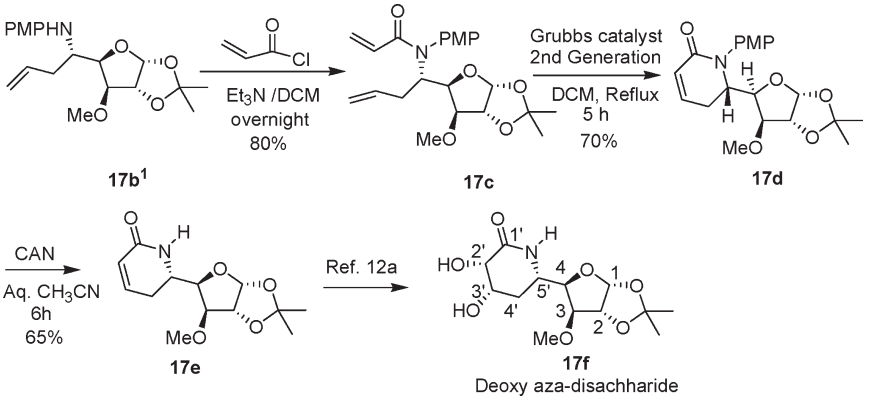
Scheme 3. Formal Synthesis of Deoxy Aza-disaccharide



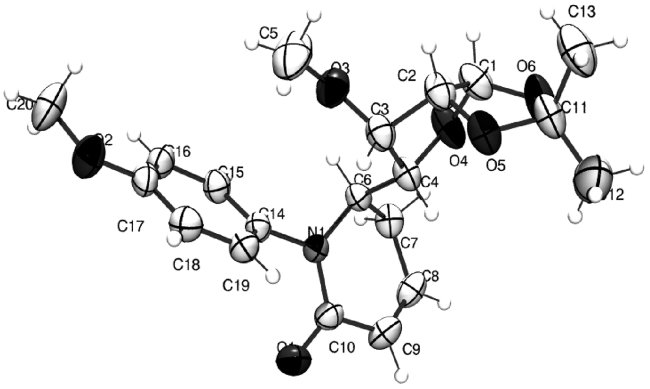
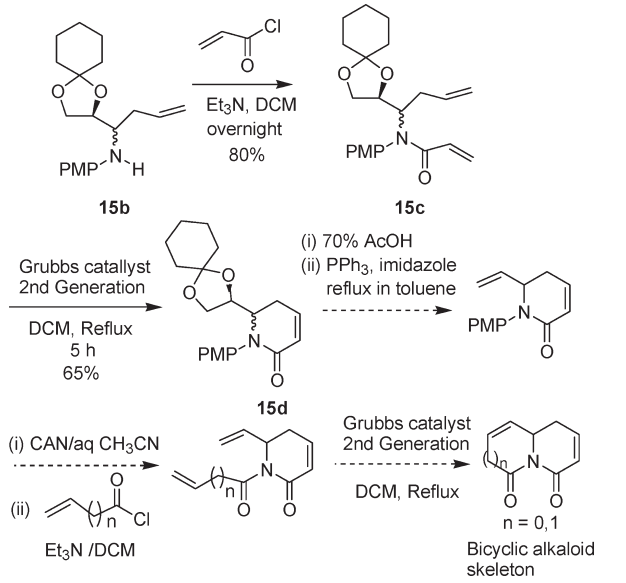


Figure 1. X-ray structure of **17d**.

Scheme 4. Synthesis toward Bicyclic Skeleton of Alkaloids



in dry THF (25 mL per mmol of reagent) was stirred with activated zinc dust (250 mg, 3.75 mmol) for 1 h under argon (activated zinc dust was prepared by washing 20 g of commercially available zinc dust with 60 mL of 4 M HCl and thorough washing with water and finally with dry acetone and then drying in vacuo). The resulting green solution was then added dropwise to a stirred solution of the aldimine **1a** (140 mg, 0.75 mmol) and allyl bromide (1.5 equiv) in dry THF (25 mL per mmol of compound) at room temperature under argon during 1 h. The reaction mixture was further stirred for 2 h. After completion of the reaction (monitored by TLC) the mixture was quenched with 10% aqueous Na_2HPO_4 until complete precipitation. Most of the solvent was removed under reduced pressure, and the residue was extracted with diethyl ether (4 × 30 mL). The combined ether extract was washed with water (10 mL) and brine (10 mL) and finally dried (Na_2SO_4). After removal of the solvent the crude residue obtained was purified by column chromatography over silica gel (10% ethyl acetate in light petroleum) to afford phenyl-(1-phenyl-but-3-enyl)-amine (**1b**) as a viscous liquid in 68% yield. IR (neat): 3053, 2978, 2931, 1600, 1506 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.35−2.54 (m, 2H), 4.29 (t, J = 6.0 Hz, 1H), 5.03−5.12 (m, 2H), 5.60−5.71 (m, 1H), 6.39−6.41 (m, 2H), 6.53−6.57 (m, 1H), 6.96−7.00 (m, 2H), 7.12−7.15 (m, 1H), 7.15−7.28 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 43.4, 57.3, 113.6, 117.5, 118.4, 126.4, 127.1, 128.7, 129.2, 134.7, 134.8, 143.6, 147.4.

(4-Methoxy-phenyl)-(1-phenyl-but-3-enyl)-amine (2b). IR (neat): 3400, 3061, 2931, 1514, 1240, 1037 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.46−2.65 (m, 2H), 3.72 (s, 3H), 4.33−4.35 (m, 1H), 5.16−5.24 (m, 2H), 5.74−5.85 (m, 1H), 6.50 (d, J = 7.5 Hz, 2H), 6.72 (d, J = 7.5 Hz, 2H), 7.27−7.41 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 43.5, 55.8, 58.1, 114.8, 118.3, 118.3, 126.5, 127.0, 128.7, 134.9, 141.7, 143.9, 152.1.

(4-Chloro-phenyl)-(1-phenyl-but-3-enyl)-amine (3b). IR (neat): 3390, 3050, 2920, 1530, 1250, 1040 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 2.47−2.53 (m, 1H), 2.60−2.64 (m, 1H), 4.35 (dd, J = 5.0, 8.0 Hz, 1H), 5.16−5.21 (m, 2H), 5.73−5.80 (m, 1H), 6.40−6.43 (m, 2H), 7.00−7.04 (m, 2H), 7.31−7.32 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 43.3, 57.4, 114.8, 118.6, 126.4, 127.3, 128.8, 129.0, 134.5, 143.0, 145.9.

Naphthalen-1-yl-(1-phenyl-but-3-enyl)-amine (4b). IR (neat): 3410, 3043, 2920, 1510, 1320,1250 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.63−2.84 (m, 2H), 4. 60 (dd, J = 5.0, 7.8 Hz, 1H), 5.25−5.39 (m, 2H), 5.81−5.95 (m, 1H), 7.20−7.40 (m, 3H), 7.48−7.59 (m, 6H), 7.68−7.90 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 43.7, 57.0, 106.3, 117.4, 118.8, 119.9, 123.6, 124.9, 125.8, 126.7, 128.8, 128.9, 129.0, 134.4, 135.0, 142.2, 143.3.

(1-Phenyl-but-3-enyl)-*p*-tolyl-amine (5b). IR (neat): 3410, 3026, 2916, 1519, 1301, 1265, 1040 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 2.22 (s, 3H), 2.51−2.56 (m, 1H), 2.63−2.66 (m, 1H), 4.40 (dd, J = 5.0, 8.0 Hz, 1H), 5.17−5.24 (m, 2H), 5.76−5.81 (m, 1H),

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6.45−6.48 (m, 2H), 6.92−6.94 (m, 2H), 7.34−7.41 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.4, 43.4, 57.6. 113.7, 118.3, 126.4, 126.6, 127.0, 128.7, 129.1, 129.7, 134.9, 143.9, 145.2.

Phenyl-(1-*p*-tolyl-but-3-enyl)-amine (6b). IR (neat): 3406, 3051, 2920, 1504, 1305, 1267, 1168 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.23 (s, 3H), 2.37−2.43 (m, 1H), 2.49−2.52 (m, 1H), 4.26−4.27 (m, 1H), 5.03−5.10 (m, 2H), 5.63−5.71 (m, 1H), 6.41−6.42 (m, 2H), 6.54−6.56 (m, 1H), 6.97−7.04 (m, 4H), 7.13−7.23 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.2, 43.4, 57.1, 113.7, 117.5, 118.2, 129.2, 129.4, 129.8, 130.0, 134.9, 136.6.

[1-(4-Chloro-phenyl)-but-3-enyl]-phenyl-amine (7b). IR (neat): 3412, 3051, 2910, 1505, 1315, 1205, 1089 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.37−2.43 (m, 1H), 2.48−2.53 (m, 1H), 4.27 (dd, *J* = 5.5, 8.0 Hz, 1H), 5.06−5.11 (m, 2H), 5.60−5.66 (m, 1H), 6.39−6.40 (m, 2H), 6.58−6.61 (m, 1H), 6.99−7.02 (m, 2H), 7.20−7.23 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 43.2, 57.0, 113.9, 118.8, 127.9, 128.9, 129.3, 129.6, 130.1, 131.0, 132.8, 134.3.

[1-(4-Methoxy-phenyl)-but-3-enyl]-phenyl-amine (8b). IR (neat): 3410, 3051, 2906, 2835, 1506, 1246, 1033 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.40−2.44 (m, 1H), 2.48−2.52 (m, 1H), 3.70 (s, 3H), 4.26 (dd, *J* = 5.5, 7.5 Hz, 1H), 5.04−5.10 (m, 2H), 5.64−5.70 (m, 1H), 6.42 (d, *J* = 8.5 Hz, 2H), 6.56 (t, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 2H), 6.98−67.01 (m, 2H), 7.06−7.20 (d, *J* = 11.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 43.4, 55.4, 57.0, 113.8, 114.1, 117.7, 118.3, 127.5, 129.2, 134.9, 147.4, 158.8.

(1-Naphthalen-2-yl-but-3-enyl)-phenyl-amine (9b). IR (neat): 3412, 3051, 2910, 1507, 1313,1271 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.54−2.76 (m, 2H), 4.56 (dd, *J* = 5.5, 8.0 Hz, 1H), 5.16−5.24 (m, 2H), 5.76−5.80 (m, 1H), 6.58−6.60 (m, 2H), 6.66−6.69 (m, 1H), 7.07−7.10 (m, 2H), 7.31−7.49 (m, 3H), 7.67−7.84 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 29.9, 57.9, 114.1, 118.6, 124.8, 125.3, 125.7, 126.2, 127.8, 128.0, 128.8, 129.7, 133.0, 133.7, 135.2.

2-(1-Phenylamino-but-3-enyl)-phenol (10b). IR (neat): 3400, 3335, 3057, 2933, 2858, 1573, 1485, 1352, 1280, 1230, 1186 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.67−2.70 (m, 2H), 4.33 (t, *J* = 7.0 Hz, 1H), 5.27−5.30 (m, 2H), 5.82−5.87 (m, 1H), 6.77−6.78 (m, 2H), 6.82−6.84 (m, 1H), 6.89−6.92 (m, 2H), 7.14−7.18 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 41.5, 60.1, 116.9, 117.3, 119.8, 120.2, 127.9, 128.7, 129.4, 134.4, 156.7.

(1-Allyl-2-prop-2-ynyloxy-pent-4-enyl)-phenyl-amine (12b). IR (neat): 3304, 3076, 2976, 2926, 2247, 1600, 1506, 1259, 1082 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.21−2.30 (m, 3H including the acetylinic proton), 2.32−2.41 (m, 2H), 3.44−3.50 (m, 1H), 3.60−3.66 (m, 1H), 4.08 (dd, *J* = 2.3, 18.2 Hz, 1H), 4.20 (dd, *J* = 2.5, 15.9 Hz, 1H), 4.93−5.16 (m, 4H), 5.72−5.87 (m, 2H), 6.49−6.67 (m, 2H), 7.05−7.15 (m, 2H), 7.17−7.19 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.9, 35.7, 54.9, 57.9, 74.5, 79.7, 80.3, 113.6, 117.4, 118.0, 129.0, 134.3, 135.7, 147.7. HRMS: calcd for $C_{17}H_{22}NO$ [M + H$^+$] 256.1701; found 256.1719.

2-(1-Phenylamino-but-3-enyl)-pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (13b). IR (neat): 3365, 2972, 2926, 2854, 1672, 1600, 1396, 1317, 1165 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35−1.65 (m, 9H), 1.74−1.86 (m, 4H), 2.10−2.38 (m, 2H), 2.85−3.60 (m, 2H), 3.70−3.9 (m, 1H), 4.02−4.06 (m, 1H), 4.95−5.03 (m, 2H), 5.74−5.80 (m, 1H), 6.49−6.61 (m, 3H), 7.01−7.06 (m, 2H). HRMS: calcd for $C_{19}H_{28}N_2O_2Na$ [M + Na$^+$] 339.2048; found 339.2048.

2,2-Dimethyl-4-(1-phenylamino-but-3-enyl)-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (14b). IR (neat): 3404, 3055, 2978, 2933, 1693, 1602, 1498, 1392, 1367, 1257, 1172 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33−1.45 (m, 15H), 2.06−2.43 (m, 2H), 3.73−3.89 (m, 1H), 3.90−4.02 (m, 1H), 4.03−4.07 (m, 1H), 4.15−4.18 (m, 1H), 4.97−5.08 (m, 2H), 5.77−5.79 (m, 1H), 6.48−6.61 (m, 3H), 7.05−7.08 (m, 2H). HRMS: calcd for $C_{20}H_{30}N_2O_3Na$ [M + Na$^+$] 369.2154; found 369.2155.

[1-(1,4-Dioxa-spiro[4.5]dec-2-yl)-but-3-enyl]-(4-methoxy-phenyl)-amine (15b). IR (neat): 3400, 2936, 2862, 1512, 1236, 1099 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26−1.40 (m, 2H), 1.59−1.65 (m, 8H), 2.33−2.40 (m, 2H), 3.35−3.42 (m, 1H), 3.74 (s, 3H), 3.83−3.95 (m, 1H), 3.97−4.05 (m, 2H), 5.06−5.14 (m, 2H), 5.81−5.90 (m, 1H), 6.57−6.62 (m, 2H), 6.75−6.78 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.1, 23.9, 25.3, 34.8, 36.7, 54.7, 55.8, 56.8, 66.1, 109.8, 110.0, 115.0, 115.6, 117.7, 118.3, 134.4, 134.5, 135.1, 141.6. HRMS: calcd for $C_{19}H_{28}NO_3$ [M + H$^+$] 318.2069; found 318.2065.

[1-(6-Methoxy-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]-dioxol-5-yl)-but-3-enyl]-phenyl-amine (16b). IR (neat): 3387, 3055, 2985, 2937, 1602, 1498, 1438, 1373 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.45 (s, 3H), 2.42−2.49 (m, 2H), 3.27 (s, 3H), 3.71 (s, 1H), 3.99−4.01 (m, 2H), 4.55 (d, *J* = 4.0 Hz, 1H), 5.10 (m, 2H), 5.83−5.87 (m, 1H), 5.91 (d, *J* = 3.5 Hz, 1H), 6.67−6.70 (m, 3H), 7.13−7.16 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.4, 27.0, 50.9, 57.7, 81.5, 81.6, 83.8, 105.1, 111.7, 114.3, 117.7, 118.6, 129.3, 134.2, 147.6. HRMS: calcd for $C_{18}H_{26}NO_4$ [M + H$^+$] 320.1862; found 320.1875.

[1-(6-Methoxy-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]-dioxol-5-yl)-but-3-enyl]-(4-methoxy-phenyl)-amine (17b[1], major isomer). IR (neat): 3385, 3052, 2985, 2937, 1602, 1490, 1431, 1370 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.49 (s, 3H), 2.37−2.49 (m, 2H), 3.27 (s, 3H), 3.71−3.72 (m, 1H), 3.74 (s, 3H), 3.86−3.90 (m, 1H), 3.96 (dd, *J* = 3.0, 9.0 Hz, 1H), 4.55 (d, *J* = 3.5 Hz, 1H), 5.09−5.12 (m, 2H), 5.81−5.84 (m, 1H), 5.87 (d, *J* = 2.5 Hz, 1H), 6.63 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.3, 14.3, 36.3, 51.9, 55.9, 57.8, 81.2, 817, 83.7, 105.1, 111.7, 114.9, 115.8, 118.6, 134.2. HRMS calcd for $C_{19}H_{28}NO_5$ [M + H$^+$] 350.1967; found 350.1962.

Preparation of *N*-[1-(6-Methoxy-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxol-5-yl)-but-3-enyl]-*N*-(4-methoxy-phenyl)-acrylamide (17c). To a stirred solution of the homoallyl amine **17b**[1] (350 mg, 1 mmol) and Et_3N (0.2 mL, 1.5 mmol) in DCM (2 mL) was added acryloyl chloride (120 mg, 1.3 mmol) in DCM (2 mL) at 0 °C. The reaction mixture was stirred for 1 h at this temperature and then at room temperature for 3 h. Then the reaction mixture was quenched with saturated $NaHCO_3$ solution (10 mL) and extracted with DCM (3 × 30 mL). The combined organic layer was washed with water (3 × 10 mL) and brine (5 mL) and finally dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and crude product obtained was subjected to column chromatography to furnish the desired acetylated product **17c** (330 mg, 80%) as a colorless liquid. IR (neat): 3074, 2985, 2935, 2835, 1735, 1647, 1510, 1408 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 1.23 (s, 3H), 1.45 (s, 3H), 2.61−2.74 (m, 2H), 3.27 (s, 3H), 3.72−3.75 (m, 1H), 3.81 (s, 3H), 4.39−4.44 (m, 1H), 4.52 (d, *J* = 4.0 Hz, 1H), 5.04−5.09 (m, 2H), 5.44 (dd, *J* = 1.5, 10.5 Hz, 1H), 5.82−5.91 (m, 3H), 6.28 (dd, *J* = 1.5, 17.0 Hz, 1H), 6.86 (d, *J* = 9.0 Hz, 2H), 7.10 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.4, 26.9, 33.6, 55.6, 57.6, 80.7, 81.4, 84.4, 104.8, 111.7, 114.3, 116.9, 127.3, 129.8, 136.2, 159.1, 166.7. HRMS: calcd for $C_{22}H_{29}NO_6Na$ [M + Na$^+$] 426.1893; found 426.1893.

Preparation of 6-(6-Methoxy-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxol-5-yl)-1-(4-methoxy-phenyl)-5,6-dihydro-1*H*-pyridin-2-one (17d). The second generation Grubbs catalyst (37 mg, 5 mol %) was added to a solution of **17c** (320 mg, 0.80 mmol) in CH_2Cl_2 (20 mL) under an Ar atmosphere. After being stirred under reflux for 5 h, the resulting solution was exposed to air with stirring for 1 h, concentrated, and purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:2) to give cyclic amide **17d** (210 mg, 70%) as a colorless crystalline solid. IR (KBr): 2924, 1662, 1512, 1246, 1078 cm^{-1}. ^{1}H NMR (500 Mz, $CDCl_3$): δ 1.22 (s, 3H), 1.41 (s, 3H), 2.46 (s, 3H), 2.71−2.78 (m, 2H), 3.34 (d, *J* = 2.5 Hz, 1H), 3.72 (s, 3H), 4.24 (dd, *J* = 2.5, 9.5 Hz, 1H), 4.37 (d, *J* = 3.5 Hz, 1H), 4.40−4.43 (m, 1H), 5.66 (d, *J* = 4.0 Hz, 1H), 6.01

(dd, J = 2.5, 8.0 Hz, 1H), 6.54−6.57 (m, 1H), 6.83−6.86 (m, 2H), 7.20−7.22 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.2, 26.3, 26.9, 55.2, 55.7, 56.2, 78.0, 81.3, 82.2, 104.3, 112.1, 114.1, 125.6, 128.0, 134.4, 138.9, 157.9, 163.4. $[\alpha]^{27.0}_D$ = 7.95 (c 1.12 in $CHCl_3$). HRMS calcd for $C_{20}H_{25}NO_6Na$ $[M + Na]^+$ 398.1580; found 398.1581.

Preparation of 6-(6-Methoxy-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxol-5-yl)-5,6-dihydro-1*H*-pyridin-2-one (17e). A solution of **17d** (190 mg, 0.5 mmol) in acetonitrile (2 mL) was cooled to 0 °C. A solution of CAN (960 mg, 1.75 mmol) in water (1 mL) was added to it dropwise at 0 °C. Then the reaction mixture was stirred for 5 h at room temperature. The mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic extract was washed with water (3 × 5 mL) and brine (10 mL) and finally dried over Na_2SO_4. The crude product was subjected to column chromatography to furnish the desired deprotected cyclic amide **17e** (90 mg, 65%). $[\alpha]^{27.0}_D$ = −33.7 (c 0.02, $CHCl_3$). IR (neat): 3212, 2953, 2854, 1683, 1557, 1457, 1374 cm^{-1}. ^{1}H NMR (500 Mz, $CDCl_3$): δ 1.32 (s, 3H), 1.47 (s, 3H), 2.63−2.68 (m, 2H), 3.45 (s, 3H), 3.83 (d, J = 3.5 Hz, 1H), 3.85−3.87 (m, 1H), 4.28 (dd, J = 3.5, 9.5 Hz, 1H), 4.63 (d, J = 3.5 Hz, 1H), 5.87 (d, J = 4.0 Hz, 1H), 5.93−5.95 (m, 1H), 6.61−6.62 (m, 1H). HRMS: calcd for $C_{13}H_{19}NO_5Na$ $[M + Na]^+$ 292.1161; found 292.1161.

Preparation of *N*-[1-(1,4-Dioxa-spiro[4.5]dec-2-yl)-but-3-enyl]-*N*-(4-methoxy-phenyl)-acrylamide (15c). To a stirred solution of the homoallyl amine **15b** (320 mg, 1 mmol) and Et_3N (0.2 mL, 1.5 mmol) in DCM (2 mL) was added acryloyl chloride (120 mg, 1.3 mmol) in DCM (2 mL) at 0 °C. The reaction mixture was stirred for 1 h at this temperature then at room temperature for 3 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution (10 mL) and extracted with DCM (3 × 30 mL). The organic layer was washed with water (3 × 10 mL) and brine (5 mL) and finally dried over Na_2SO_4. The solvent was evaporated, and the crude product was subjected to column chromatography to furnish the desired acetylated product **15c** (300 mg, 80%) as a pale yellow liquid. IR (neat): 3076, 2937, 2862, 1732, 1643, 1512, 1410, 1251, 1101 cm^{-1}. ^{1}H NMR (500 Mz, $CDCl_3$): δ 1.35−1.45 (m, 2H), 1.58−1.67 (m, 8H), 1.81−2.25 (m, 2H), 2.81−2.85 (m, 1H), 3.72−3.76 (m, 1H), 3.83 (s, 3H), 3.87−3.97 (m, 1H), 4.10−4.17 (m, 1H), 5.08−5.12 (m, 2H), 5.44−5.48 (m, 1H), 5.79−5.87 (m, 2H), 6.29−6.33 (m, 1H), 6.87−6.89 (m, 2H), 7.03−7.05 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.0, 24.1, 25.3, 32.8, 33.9, 35.0, 35.3, 36.2, 37.4, 38.7, 55.6, 67.3, 67.4, 75.2, 76.6, 109.9, 110.4, 114.5, 117.1, 117.8, 127.6, 128.1, 129.3, 131.6, 134.7, 135.7, 159.5, 159.5, 167.2, 174.7. HRMS: calcd for $C_{22}H_{29}NO_4Na$ $[M + Na]^+$ 394.1994; found 394.1993.

Preparatoin of 6-(1,4-Dioxa-spiro[4.5]dec-2-yl)-1-(4-methoxy-phenyl)-5,6-dihydro-1*H*-pyridin-2-one (15d). The second generation Grubbs' catalyst (75 mg, 10 mol %) was added to a solution of **15c** (300 mg, 0.80 mmol) in CH_2Cl_2 (20 mL) under an argon atmosphere. After being stirred under reflux for 5 h, the resulting solution was exposed to air with stirring for 1 h, concentrated, and purified by flash column chromatography on silica gel to give cyclic amide **15d** (160 mg, 65%) as a pale yellow liquid. IR (neat): 2935, 2862, 1668, 1510, 1413, 1246, 1103 cm^{-1}. ^{1}H NMR (500 Mz, $CDCl_3$): 1.35−1.37 (m, 2H), 1.47−1.56 (m, 8H), 2.78−2.89 (m, 2H), 3.28 (dd, J = 6.5, 8.5 Hz, 1H), 3.81 (s, 3H), 3.82−3.90 (m, 2H), 4.24−4.28 (m, 1H), 6.07 (dd, J = 2.0, 10.0 Hz, 1H), 6.58−6.92 (m, 1H), 6.89−6.92 (m, 2H), 7.18−7.21 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.9, 24.1, 25.2, 26.3, 35.0, 36.5, 55.6, 62.0, 67.6, 74.5, 109.7, 114.6, 125.6, 128.6, 134.6, 138.6, 158.3, 163.6. HRMS: calcd for $C_{20}H_{25}NO_4Na$ $[M + Na]^+$ 366.1681; found 366.1618.

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H NMR spectra of **2b**−**10b**, **11b**−**17b**, **17c**, **17e**, **15c**, and **15d** and ^{13}C NMR spectra of **2b**−**10b**, **11b**−**17b**, **17c**, **17e**, **15c**, and **15d**. Crystallographic data including CIF file of compound **17d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) (a) Laschat, S.; Kunz, H. *J. Org. Chem.* **1991**, *56*, 5883–5889. (b) Graf, E.; Boeddeker, H. *Liebigs Ann. Chem.* **1958**, *613*, 111–120. (c) Yoshioko, T.; Kuraoka, Y.; Tikita, T.; Maeda, K.; Umezawa, H. *J. Antibiot.* **1972**, *25*, 625–626. (d) Wakamiya, T.; Shiba, T.; Kaneko, T. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3668–3669.

(2) (a) Juaristi, E.; Leon−Romo, J. L.; Reyes, A.; Escalante, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2441. (b) Alvaro, G.; Savoia, D. *Tetrahedron: Asymmetry* **1996**, *7*, 2083. (c) Moody, C. J.; Hunt, J. C. *Synlett* **1998**, 733. (d) Polniaszek, R. P.; Belmont, S. E.; Alvarez, R. *J. Org. Chem.* **1990**, *55*, 215. (e) Laschat, S.; Kunz, H. *Synlett.* **1990**, 51. (f) Hua, D. H.; Miao, S. W. M.; Chen, J. S.; Iguchi, S. *J. Org. Chem.* **1991**, *56*, 4.

(3) (a) Hashihayata, T.; Sakoh, H.; Goto, Y.; Yamada, K.; Morishima, H. *Chem. Pharm. Bull.* **2002**, *3*, 423. (b) Gall, E. L.; Haurena, C.; Sengmany, S.; Martens, T.; Troupel, M. *J. Org. Chem.* **2009**, *74*, 7970.

(4) (a) Hunt, J. C. A.; Laurent, P.; Moody, C. J. *Chem. Commun.* **2000**, 1771. (b) Ovaa, H.; Stragies, R.; Marel, G. A. V.; Boom, J. H. V.; Blechert, S. *Chem. Commun* **2000**, 1501.

(5) (a) Barrio, A, G.; Pereira, D, M.; Ruiz, J. J. N.; Escario, J. A.; Serrano, S. M.; Kouznetsov, V. V.; Mendez, L. Y. V.; Gonzales, J. M. U.; Ochoa, C. *Acta Parasitol.* **2006**, *51*, 73. (b) Mendez, L. Y. V.; Zacchino, S. A.; Kouznetsov, V. V. *J. Braz. Chem. Soc.* **2010**, *21*, 105.

(6) (a) Hatano, M.; Suzuki, S.; Ishihara, K. *J. Am. Chem. Soc.* **2006**, *128*, 9989. (b) Yuan, Y.; Chen, F.; Zhao, D. *Appl. Organometal. Chem.* **2009**, *23*, 485. (c) Wei, X. N.; Liu, L. Y.; Wang, B.; Chang, W. X.; Li *J. Chin. Chem. Lett.* **2009**, *20*, 40. (d) Deng, D. S.; Liu, Ping.; Cai, J. *Eur. J. Org. Chem.* **2007**, 1594. (e) Yin, Y.; Zhao, G.; Li, G. L. *Tetrahedron* **2005**, *61*, 12042. (f) Zhengfeng, X.; Guilong, L.; Gang, Z.; Jide, W. *Chin. J. Chem.* **2009**, *27*, 925.

(7) (a) Law, M. C.; Cheung, T. W.; Wong, K. Y.; Chan, T. H. *J. Org. Chem.* **2007**, *72*, 923. (b) Shen, K. H.; Yao, C. F. *J. Org. Chem.* **2006**, *71*, 3980. (c) Andrews, P. C.; Peatt, A. C.; Raston, C. L. *Green Chem.* **2004**, *6*, 119. (d) Shibata, I.; Nose, K.; Sakamoto, K.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2004**, *69*, 2185. (e) Han, R.; Choi, S. H.; Son, K. I.; Jun, Y. M.; Lee, B. M.; Kim, B. H. *Synth. Commun.* **2005**, *35*, 1725. (f) Shibata, I.; Miyamoto, S.; Tsunoi, S.; Sakamoto, K.; Baba, A. *Eur. J. Org. Chem.* **2009**, 3508. (g) Andrews, P. C.; Peatt, A. C.; Raston, C. L. *Tetrahedron Lett.* **2004**, *45*, 243. (h) Sugiura, M.; Robvieux, F.; Kobayashi, S. *Synlett.* **2003**, 1749.

(8) (a) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986 and references therein. (b) Gansauer, A.; Pierobon, M.; Bluhm, H. *Synthesis* **2001**, 2500 and references therein. (c) Justicia, J.; Oller-Lopez, J. L.; Campana, A. G.; Oltra, J. E.; Cuerva, J. M.; Bunuel, E.; Cardenas, D. J. *J. Am. Chem. Soc.* **2005**, *127*, 14911. (d) Estevez, R. E.; Lopez, J. L. O.; Robles, R.; Melgarejo, C. R.; Gansauer, A.; Cuerva, J. M.; Oltra, J. E. *Org. Lett.* **2006**, *8*, 5433. (e) Rodriguez, M. M.; Farnandez, R. G.; Escribano, A. M.; Bermezo, F. A. *J. Org. Chem.* **2009**, *74*, 1798. (f) Rasales, A.; Oller-Lopez, J. L.; Justicia, J.; Gansauer, A.; Oltra, J. E.; Cuerva, J. M. *Chem. Commun.* **2004**, 2628. (g) Campana, A. G.; Bazdi, B.; Fuentes, N.; Robles, R.; Cuerva, J. M.; Oltra, J. E.

Angew. Chem. Int. Ed. **2008**, *47*, 7515. (h) Sancho-Sanz, I.; Miguel, D.; Millan, A.; Estevez, R. E.; Oller-Lopez, J. L.; Alvarez-Manzaneda, E.; Robles, R.; Cuerva, J. M.; Justicia, J. *J. Org. Chem.* **2011**, *76*, 732. (i) Millan, A; Alvarez de Cienfuegos, L.; Martin-Lasanta, A.; Campana, A. G.; Cuerva, J. M. *Adv. Synth. Catal.* **2011**, *353*, 73.(j) Millan, A.; Campana, A. G.; Bazdi, B.; Miguel, D.; Alvarez de Cienfuegos, L.; Echavarren, A. M.; Cuerva, J. M. *Chem. Eur. J.* **2011**,17,3985 and references therein.

(9) (a) Roy, S. C.; Rana, K. K.; Guin, C. *J. Org. Chem.* **2002**, *67*, 3242. (b) Jana, S.; Guin, C.; Roy, S. C. *Tetrahedron Lett.* **2004**, *45*, 6575. (c) Jana, S.; Guin, C.; Roy, S. C. *Tetrahedron Lett.* **2005**, *46*, 1155. (d) Mandal, S. K.; Jana, S.; Roy, S. C. *Tetrahedron Lett.* **2005**, *46*, 6115.

(10) Saggiormo, V.; Luning, U. *Tetrahedron Lett.* **2009**, *50*, 4663.

(11) Chattopadhyay, S. K.; Biswas, T.; Biswas, T. *Tetrahedron Lett.* **2008**, *49*, 1365.

(12) (a) Sharma, G. V. M.; Pendem, N.; Reddy, K. R.; Krishna, P. R.; Narsimulu, K.; Kunwar, A. C. *Tetrahedron Lett.* **2004**, *45*, 8807. (b) Sundaraju, B.; Sridhar, T.; Achard, M.; Sharma, G. V. M. *Eur. J. Org. Chem.* **2010**, 6092.

(13) Lam, H. W.; Murry, G. J.; Firth, J. D. *Org. Lett.* **2005**, *7*, 5743.

(14) (a) Ma, S.; Ni, B. *Org. Lett.* **2002**, *4*, 639. (b) Dhavale, D. D.; Jachak, S. M.; Karche, N. P.; Trombini, Claudio. *Tetrahedron* **2004**, *60*, 3009.

(15) Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P. G. *J. Org. Chem.* **1992**, *57*, 4155.

(16) (a) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398. (b) Nomura, H; Richards, C. J. *Org. Lett.* **2009**, *11*, 2892.