Synthetic Methods

The Indium-Mediated Selective Introduction of Allenyl and Propargyl Groups at the C4-Position of 2-Azetidinones and the $AuCl_3$-Catalyzed Cyclization of 4-Allenyl-2-azetidinones**

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The 2-azetidinone nucleus is the central building block of β-lactam antibiotics, so functionalization of the 2-azetidinone framework is pivotal for the development of new β-lactam antibiotics.[1] The selective introduction of ethynyl,[2] allyl,[3] allenyl,[4] and propargyl[5] groups at the C4-position of 2-azetidinones is an especially intriguing and fundamental problem in the field of carbapenem synthsis because further functionalization of these groups could potentially lead to the construction of the bicyclic nucleus.[6] Therefore, considerable effort has been devoted to the selective introduction of these groups by reaction of 4-acetoxy-2-azetidinones with various organometallic reagents. Although a variety of allylations at the C4-position of 4-acetoxy-2-azetidinone has been reported,[3] there are relatively few methods for selective nucleophilic allenylation or propargylation.[4] Also, it remains a formidable challenge to control the regioselectivity of the reaction of propargyl–metal compounds with 4-acetoxy-2-azetidinones when, for example, applied to the synthesis of either 4-allenyl or 4-propargyl-2-azetidinones. These aspects led us to develop a facile, efficient method for the direct and selective introduction of allenyl or propargyl groups at the C4-position of 4-acetoxy-2-azetidinones.[7] Herein, the selective introduction of allenyl and propargyl groups at the C4-position of 4-acetoxy-2-azetidinones by using organoindium reagents generated in situ from propargyl bromides and indium powder as well as cyclizations of 4-allenyl-2-azetidinones catalyzed by $AuCl_3$ is presented (Scheme 1).

Initally, the optimum conditions for indium-mediated allenylation at the C4-position of 2-azetidinones were examined by the reaction of [3*R*(1′*R*,4*R*)]-(+)-4-acetoxy-3-[1′-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone (**1**) with organoindium reagents generated from indium and 1-bromo-2-butyne (**2**) (Table 1). Treatment of **1** with 1.5 equivalents of

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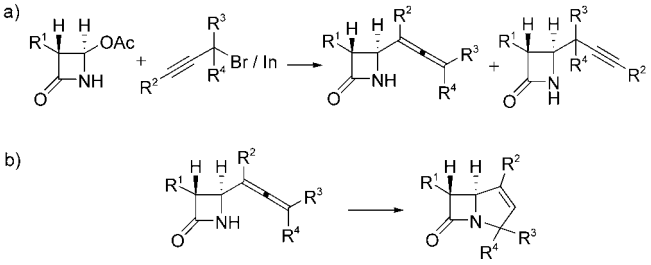
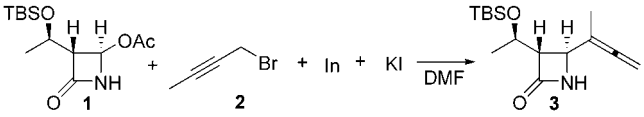


Scheme 1. a) The use of organoindium reagents to selectively introduce allenyl and propargyl groups at the C4-position of 4-acetoxy-2-azetidinones. b) The $AuCl_3$-catalyzed cyclization of 4-allenyl-2-azetidinones.

Table 1: Optimization of allenylation reactions at the C4-position of 2-azetidinone **1**.



Entry	Equivalents			T [°C]	t [h]	Yield [%][a]
	2	In	KI			
1	1.5	1.0	–	60	4	69
2	1.5	1.0	1.5	25	9	73
3	1.5	1.0	3.0	25	3.5	91
4	3.0	2.0	3.0	25	3	95

[a] Yield of isolated product.

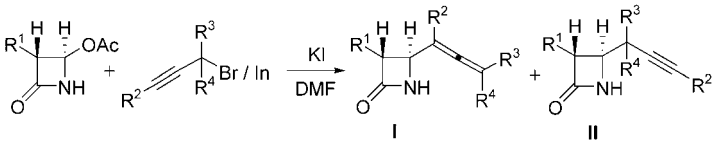
2 and 1.0 equivalents of indium powder selectively produced the allenic product **3** in 69% yield at 60°C in *N*,*N*-dimethylformamide (DMF; entry 1). No propargylic product was obtained in this reaction. When 1.5 equivalents of KI were used as an additive, compound **3** was obtained in 73% yield at 25°C (entry 2). The best results among the several reaction conditions examined were obtained with the organoindium reagent that was generated in situ from the reaction of 2.0 equivalents of indium with 3.0 equivalents of **2** in the presence of 3.0 equivalents of KI; this combination produced **3** in 95% yield (entry 4). DMF was found to be the best solvent from those that were screened (DMF, THF, C_6H_6, and $C_6H_5CH_3$).

We applied the optimum conditions to numerous propargyl bromides to demonstrate the efficiency and scope of this procedure (Table 2). Although treatment of **1** with indium powder and propargyl bromide produced a mixture of 4-allenyl- and 4-propargyl-2-azetidinone derivatives in 14 and 78% yields, respectively (entry 1), propargyl bromides with substituents such as methyl, ethyl, *n*-butyl, $THPOCH_2$ (THP = tetrahydropyran), phenyl, and 2-naphthyl at the γ-position gave 4-allenyl-2-azetidinones selectively in excellent yields (85–97%, entries 2–5, 7, and 8). The reaction of indium powder and 3-bromo-1-propynyltrimethylsilane afforded 4-(1′-trimethylsilylallenyl)-2-azetidinone in 88% yield as the major product (entry 6). 4-Propargyl-2-azetidinone derivatives were produced selectively in excellent yields (entries 9–11) by using propargyl bromides with methyl, phenyl, and 1,1-dimethyl substituents at the α position. Organoindium reagents generated from indium powder and 1-phenyl-3-bromo-1-butyne gave rise to a mixture of 4-allenyl- and 4-propargyl-2-azetidinones in 32 and 48% yields, respectively (entry 12). Treatment of 4-acetoxy-2-azetidinone with organoindium reagents generated from indium powder and various propargyl bromides that had γ-substituents gave 4-allenyl-2-azetidinones selectively in good yields (entries 13–17).

Next, we turned our attention to the cyclization of 4-(1′-methylallenyl)-2-azetidinone derivatives with a variety of catalysts (Table 3). Although many catalysts such as $Pd(OAc)_2$, $PdCl_2$, $[Pd(PPh_3)_4]$, and $[Pd_2(dba)_3]\cdot CHCl_3$ failed to give the desired cyclized products, exposure of 4-(1′-methylallenyl)-2-azetidinone to 5 mol% $AuCl_3$ in CH_2Cl_2 produced the bicyclic β-lactam product in 65% yield (entry 1).[4,8] The desired products were produced in good yields (entries 2–5) for 2-azetidinones with *n*-butyl, $THPOCH_2$, phenyl, and 2-naphthyl substituents.

Although the mechanism of the cyclization reaction has not been established, a possible reaction pathway is described in Scheme 2. $AuCl_3$ activates the allenyl group of **A** and subsequent cyclization affords **B**, which then gives a vinyl gold intermediate **C**.[8] Subsequent protonation of the transient

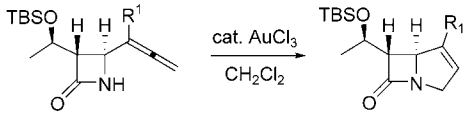
Table 2: Reactions of 4-acetoxy-2-azetidinones with organoindium reagents.[a]



Entry	R^1	R^2	R^3	R^4	T [°C]	t [h]	Yield [%][b]	
							I	**II**
1	(TBSO)(CH_3)CH	H	H	H	30	2	14	78
2	(TBSO)(CH_3)CH	Me	H	H	30	2	95	0
3	(TBSO)(CH_3)CH	Et	H	H	30	4	93	0
4	(TBSO)(CH_3)CH	*n*Bu	H	H	30	3	95	0
5	(TBSO)(CH_3)CH	$THPOCH_2$	H	H	30	3	97[c]	0
6	(TBSO)(CH_3)CH	TMS	H	H	30	6	88	9
7	(TBSO)(CH_3)CH	Ph	H	H	30	4	95	0
8	(TBSO)(CH_3)CH	2-naph[d]	H	H	30	4	85	0
9	(TBSO)(CH_3)CH	H	Me	H	80	4	0	87[e]
10	(TBSO)(CH_3)CH	H	Ph	H	80	5	0	93[f]
11	(TBSO)(CH_3)CH	H	Me	Me	80	5	0	81
12	(TBSO)(CH_3)CH	Ph	Me	H	30	3	32[g]	48[h]
13	H	Me	H	H	30	3	84	0
14	H	Et	H	H	30	3	88	0
15	H	*n*Bu	H	H	30	4	84	0
16	H	TMS	H	H	30	3	85	0
17	H	Ph	H	H	30	5	84	0

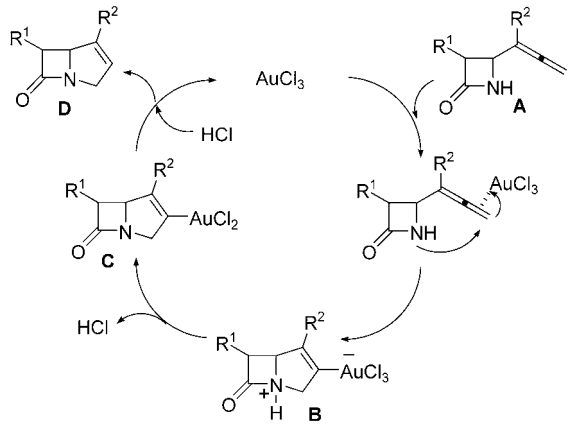
[a] Reaction performed in the presence of 1.0 equivalents of 4-acetoxy-2-azetidinone, 3.0 equivalents of propargyl bromide, 2.0 equivalents of indium powder, and 3.0 equivalents of KI in DMF. [b] Yield of isolated product. [c] d.r. = 1.1:1. [d] 2-naph = 2-napthyl. [e] d.r. = 3.1:1. [f] d.r. = 1.4:1. [g] d.r. = 1.5:1. [h] d.r. = 11.1:1.

Table 3: Cyclization of 4-allenyl-2-azetidinone catalyzed by $AuCl_3$.[a]



Entry	R	*t* [min]	Yield [%][b]
1	Me	15	65
2	*n*Bu	20	81
3	$THPOCH_2$	60	80
4	Ph	15	85
5	2-naph[c]	60	71

[a] Reaction performed in the presence of 5 mol% of $AuCl_3$ in CH_2Cl_2. [b] Yield of isolated product. [c] 2-naph = 2-napthyl.



Scheme 2. A possible reaction pathway for the $AuCl_3$-catalyzed cyclization of 4-allenyl-2-azetidinones.

vinyl gold intermediate **C** produces **D** and regenerates $AuCl_3$ to continue the catalytic cycle.

In summary, we have demonstrated that the reaction of 4-acteoxy-2-azetidinones with organoindium reagents generated in situ from indium powder and γ-substituted propargyl bromides in the presence of KI in DMF selectively produced 4-allenyl-2-azetidinones in good to excellent yields and that α-substituted propargyl bromides gave 4-propargyl-2-azetidinones selectively. Furthermore, treatment of 4-(1-substituted allenyl)-2-azetidinone derivatives with 5 mol% $AuCl_3$ in CH_2Cl_2 produced the corresponding bicyclic β-lactams in good yields.

Experimental Section

Typical experimental procedures for allenylation and cyclization reactions: The allenylindium reagent was prepared by the addition of indium powder (99.99% (Aldrich); 92.0 mg, 0.8 mmol) to a solution of 3-bromo-1-phenyl-1-propyne (234.0 mg, 1.2 mmol) and KI (199.0 mg, 1.2 mmol) in DMF (1.5 mL) and the mixture was stirred for 1 h at 30°C. [3*R*(1′*R*,4*R*)]-(+)-4-Acetoxy-3-[1′-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone (115.0 mg, 0.4 mmol) was added to the reaction mixture, and after stirring the mixture for 4 h, it was poured into saturated ammonium chloride solution (20 mL), extracted with CH_2Cl_2 (3 × 20 mL), and washed with brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude product was purified by column chromatography on silica gel with EtOAc/hexane (1:3, $R_f = 0.4$) as the eluant to afford [3*R*(1′*R*,4*S*)]-4-(1″-phenylallenyl)-3-[(1′-(*tert*-butyldimethylsilyloxy)-ethyl]-2-azetidinone (131.0 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.40$–7.35 (m, 4H), 7.29–7.28 (m, 1H), 5.91 (s, 1H), 5.24 (d, $J =$ 2.00 Hz, 2H), 4.72 (q, $J = 2.53$ Hz, 1H), 4.30–4.28 (m, 1H), 3.23–3.22 (m, 1H), 1.16 (d, $J = 6.27$ Hz, 3H), 0.91 (s, 9H), 0.1 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 207.6$, 168.7, 134.0, 128.8, 127.5, 126.3, 106.2, 80.6, 65.0, 64.7, 48.3, 25.8, 22.7, 18.0, −4.3, −4.9 ppm; IR (film) 3054, 2956, 1758, 1265 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{29}NO_2Si$ [M^+]: 343.1968, found: 343.1967.

$AuCl_3$ (99% (Au = 99.9%; Strem Chemicals); 3.0 mg, 0.01 mmol) was added to a solution of [3*R*(1′*R*,4*S*)]-4-(1″-phenylallenyl)-3-[(1′-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone (69.0 mg, 0.2 mmol) in CH_2Cl_2 (1.0 mL). After stirring the mixture for 15 min, it was poured into saturated ammonium chloride solution (15 mL), extracted with CH_2Cl_2 (3 × 15 mL), and washed with brine (15 mL). The organic layer was dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude product was purified by column chromatography on silica gel using EtOAc/hexane (1:5, $R_f = 0.35$) as the eluant to afford [6*R*(1′*R*,5*S*)]-1-aza-6-[(1′-(*tert*-butyldimethylsilyloxy)ethyl]-4-phenylbicyclo[3.2.0]-3-hepten-7-one (60.0 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.55$ (d, $J = 7.02$ Hz, 2H), 7.36–7.28 (m, 3H), 6.32 (s, 1H), 4.66 (t, $J = 1.81$ Hz, 1H), 4.53 (dt, $J = 16.09$, 5.76 Hz, 1H), 4.31 (quint, $J = 6.12$ Hz, 1H), 3.74 (dd, $J = 15.99$, 2.61 Hz, 1H), 3.17 (dd, $J = 7.93$, 2.04 Hz, 1H), 1.36 (d, $J = 6.11$ Hz, 3H), 0.97 (s, 9H), 0.16 ppm (d, $J = 2.57$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 180.7, 142.1, 132.9, 129.1, 128.7, 126.8, 126.4, 68.1, 66.5, 62.6, 53.9, 26.3, 23.5, 18.5, −4.0, −4.02 ppm; IR (film) 3061, 2929, 1770, 1256 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{29}NO_2Si$ [M^+]: 343.1968, found: 343.1965.

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