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Novel Carbonyl Bromoallylation/Heck Reaction Sequence. Stereocontrolled Access to Bicyclic β-Lactams

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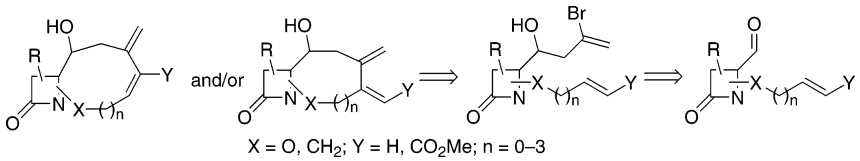

X = O, CH_2; Y = H, CO_2Me; n = 0–3

The reaction of 2,3-dibromopropene with racemic as well as enantiopure 4-oxoazetidine-2-carbaldehydes **1** in aqueous media was promoted by tin in the presence of several additives to afford the corresponding bromohomoallyl alcohols **2** in high diastereoselectivities. However, indium or zinc were unable to promote the bromoallylation reaction of aldehydes **1** under similar Barbier-type conditions. Vinyl bromides **2** bearing an extra alkene tether were used for the preparation of differently sized, fused bicyclic β-lactams of nonconventional structure via Heck cyclization.

Introduction

Besides the utility of β-lactams as biologically active agents,[1] they are used as intermediates in α- and β-amino acid synthesis, as well as building blocks for alkaloids, heterocycles, taxoids, and other types of compounds of biological and medicinal interest.[2] Consequently, the development of new approaches to the stereocontrolled synthesis of β-lactam systems is a subject of great interest. In addition, the chiral β-amino alcohol moiety is present in many biologically important molecules such as dipeptide isosteres and statine and its analogues, and therefore, its stereocontrolled synthesis remains an intensive research area.[3] On the other hand, coupling reactions of organometallic compounds with organic electrophiles have received much attention in the area of synthetic methods for carbon−carbon bond formation. Propenylmetal compounds in particular have been of increasing interest in organic synthesis. In particular, diastereoselective addition of allylmetallic reagents to chiral aldehydes is one of the most important reactions for constructing a carbon skeleton in organic synthesis.[4] In contrast, the analogous reaction involving bromoallylmetals has evolved at a relatively slow pace,[5] despite that the bromovinyl moiety on the bromohomoallylic alcohols can be further functionalized.[6] In connection with our current research interest in the preparation and

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synthetic utility of β-lactams,[7] here we examine the feasibility and efficiency of the metal-mediated bromoallylation of 4-oxoazetidine-2-carbaldehydes in aqueous media, together with further interesting synthetic transformations to structurally novel fused bicyclic β-lactams.

Results and Discussion

Starting substrates, 4-oxoazetidine-2-carbaldehydes **1a**−**m**, were prepared both in the racemic form and in optically pure form using standard methodology. Enantiopure 2-azetidinones **1a**−**d** and **1i**−**m** were obtained as single cis enantiomers from imines of (*R*)-2,3-*O*-isopropylideneglyceraldehyde through Staudinger reaction with the appropriate alkoxyacetyl chloride in the presence of Et_3N, followed by sequential acidic acetonide hydrolysis and oxidative cleavage.[7] Racemic compounds **1e**−**h** were obtained as single cis diastereoisomers by following our one-pot method from *N*,*N*-di-(*p*-methoxyphenyl)glyoxal diimine.[8] Compounds **1** are protected α-amino aldehydes, most of which have been well-known to be both chemically and configurationally labile because of the rather acidic proton positioned α to the carbonyl group.[9]

Aqueous organometallic reactions have several advantages in synthesis over those occurring in dry organic solvents.[10] Unique reactivity and selectivity that are not attained under dry conditions are often observed in aqueous environments. Because indium reagents have emerged as particularly mild organometallic compounds, due to their compatibility with many common organic functional groups and stability under aqueous conditions,[11] we decided to explore the indium-promoted Barbier-type bromoallylation of 4-oxoazetidine-2-carbaldehydes **1** in aqueous media.

A model reaction of 4-oxoazetidine-2-carbaldehyde (+)-**1a** was carried out by mixing in situ indium, 2,3-dibromopropene, and the β-lactam aldehyde in aqueous tetrahydrofuran. Surprisingly, the reaction did not proceed at all, leading to recovery of the starting material unaltered. Different metal mediators were tested with similar unfruitful results. Drastic conditions such as strongly acidic and thermal treatments are undesirable for sensitive substrates **1**. Our idea was to utilize water-stable additives that could improve both the yield and the conversion rate. Thus, we studied the metal-promoted bromoallylation of aldehyde (+)-**1a** in the presence of catalytic amounts of different Lewis or protic acids. The results under various reaction conditions are summarized in Table 1. Indium, cadmium, and samarium were unable to induce the bromoallylation reaction of aldehyde (+)-**1a** even in the presence of several additives, while the bismuth- and zinc-promoted reactions were partially efficient (20% yield of the coupling product). Fortunately, the addition of ammonium chloride (aqueous saturated) to the aqueous medium containing tin, 2,3-dibromopropene, and 4-oxoazetidine-2-carbaldehyde (+)-**1a** was quite effective in this transformation to give the bromohomoallylic alcohol (+)-**2a** in good yield (80%) with high stereoselectivity (dr = 93:7) after 3 days of reaction. Next, using a standard protocol we screened different additives capable of directing the process toward (+)-**2a**. The addition of 20 mol % bismuth(III) chloride, indium(III) chloride, indium(III) triflate, hafnium(IV) chloride, hydrobromic acid, and hydrochloric acid to the aqueous tetrahydrofuran media of the tin-promoted bromoallylation reaction shortened reaction times, exibiting the same facial preference. Lower yields were obtained when the amount of the additives was decreased (5 mol %). The optimized ratio of 4-oxoazetidine-2-carbaldehyde (+)-**1a**, 2,3-dibromopropene, and tin was 1:3:1.5. In terms of achieving good yields and stereoselectivities, $BiCl_3$ was considered the most promising candidate for further reactions. For solvents, aqueous tetrahydrofuran gave the best result, while aqueous ethanol and aqueous DMF were less effective. The reaction hardly proceeded in nonaqueous organic media. Good yields (60−96%) and high diastereoselectivities (de 80−100%) were obtained in the tin-mediated bromoallylation reaction of different 4-oxoazetidine-2-carbaldehydes **1b**−**m** (Scheme 1, Table 1).

In the dilute acidic medium, which provided for the presence of hydrochloric or hydrobromic acids, protonation of the carbonyl occurs, facilitating the addition process by the bromoallylmetal species. It is to be presumed that the ionic strength enhancement of the reaction solvent provided by the ammonium chloride accelerated the process.[12] Although the role of the bismuth-, indium-, and hafnium-derived additives is not completely understood, it may be explained in terms of a Lewis acid that activates the carbonyl group and the softness of the nucleophile reagents. A transmetalation of the initially formed bromoallylorganometallic with bismuth(III) chloride, indium(III) chloride, indium(III) triflate, or hafnium(IV) chloride as a Lewis acid may also be involved.[13]

Configuration at the carbinolic chiral center of the product (+)-**2a** was established by comparison of the ^1H NMR chemical shifts of its acetylmandelates (+)-**3** and (+)-**4** (Scheme 2)[14] and was assumed to be the same for the rest of β-lactams **2**. The metal-promoted addition of 2,3-dibromopropene to 4-oxoazetidine-2-carbaldehydes **1** gave the *syn*-bromohomoallylic alcohols **2a**−**n** practically

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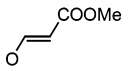
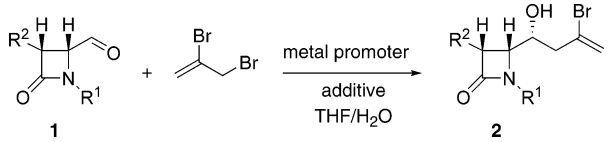
TABLE 1. Bromoallylation Reaction of 4-Oxoazetidine-2-carbaldehydes 1[a]

aldehyde	R^1	R^2	metal	additive	t (h)	product	d.r.[b]	yield (%)[c]
(+)-**1a**	PMP	MeO	In	NH_4Cl	72			
(+)-**1a**	PMP	MeO	Zn	NH_4Cl	72	(+)-**2a**	94:6	20
(+)-**1a**	PMP	MeO	Bi	NH_4Cl	72	(+)-**2a**	92:8	20
(+)-**1a**	PMP	MeO	Sn	NH_4Cl	72	(+)-**2a**	93:7	80
(+)-**1a**	PMP	MeO	Sn	$InCl_3$	4	(+)-**2a**	95:5	64
(+)-**1a**	PMP	MeO	Sn	$In(OTf)_3$	6	(+)-**2a**	95:5	71
(+)-**1a**	PMP	MeO	Sn	$HfCl_4$	4	(+)-**2a**	94:6	80
(+)-**1a**	PMP	MeO	Sn	$BiCl_3$	14	(+)-**2a**	95:5	90
(+)-**1a**	PMP	MeO	Sn	HCl	6	(+)-**2a**	94:6	65
(+)-**1a**	PMP	MeO	Sn	HBr	6	(+)-**2a**	94:6	77
(+)-**1b**	PMP	*O*-allyl	Sn	$BiCl_3$	6	(+)-**2b**	96:4	67
(+)-**1c**	PMP	*O*-propargyl	Sn	$BiCl_3$	6	(+)-**2c**	95:5	66
(+)-**1d**	PMP		Sn	$BiCl_3$	7	(+)-**2d**	99:1	78
(±)-**1e**	PMP	ethenyl	Sn	$BiCl_3$	6	(±)-**2e**	92:8	88[d]
(±)-**1f**	PMP	2-propenyl	Sn	$BiCl_3$	6	(±)-**2f**	95:5	67
(±)-**1g**	PMP	2-propynyl	Sn	$BiCl_3$	6	(±)-**2g**	95:5	62[e]
(±)-**1h**	PMP	isopropenyl	Sn	$BiCl_3$	10	(±)-**2h**	90:10	67[d]
(+)-**1i**	methallyl	PhO	Sn	$BiCl_3$	8	(+)-**2i**	100:0	64
(+)-**1j**	2-propenyl	MeO	Sn	$BiCl_3$	7	(+)-**2j**	97:3	70
(+)-**1k**	3-butenyl	MeO	Sn	$BiCl_3$	7	(+)-**2k**	97:3	91
(+)-**1l**	2-propynyl	MeO	Sn	$BiCl_3$	6	(+)-**2l**	98:2	82
(+)-**1m**	3-butynyl	MeO	Sn	$BiCl_3$	6	(+)-**2m**	100:0	60

[a] All reactions were carried out on 1 mmol scale. PMP = 4-$MeOC_6H_4$. [b] Ratio was determined by integration of well-resolved signals in the ^1H NMR spectra of the crude reaction mixtures before purification. [c] Yield of pure, isolated syn isomer with correct analytical and spectral data. [d] Isolated yield of pure anti isomer was 8%. [e] Isolated yield of pure anti isomer was 4%.

SCHEME 1



as unique diastereomers.[15] This high diastereoselectivity can be explained by bromoallylation from the less hindered *re* face of the carbonyl group following a nonchelated Felkin−Anh model, as depicted in Figure 1.[16]

The palladium-catalyzed arylation or vinylation of alkenes (the Heck reaction) has become one of the most versatile and synthetically useful methods for carbon−carbon bond formation used today.[17] Surprisingly, the information available on the use of β-lactams as building blocks on the Heck reaction is very scarce, and only Grigg has reported the synthesis of racemic tricyclic β-lactams via palladium-catalyzed cyclization of iodoaryl β-lactams.[18] We were interested in studying the regiochemistry of the intramolecular Heck reaction when applied to bromohomoallylic alcohols **2** as a novel entry to bicyclic β-lactams.[19] Compound (+)-**2j**, featuring a 2-bromo-6-aza-1,8-diene moiety amenable to either a 7-*exo*-trig or a

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(15) No partial configuration inversion was involved in the transformation of aldehydes **1** to alcohols **2**. The assignment of the cis stereochemistry to β-lactams **2a**−**m** was based on the observed coupling constants of about 5.0 Hz for methine protons H3 and H4, whereas the trans stereochemistry is consistent with methine coupling constants of ca. 2.0 Hz in their ^1H NMR spectra. The assignment of relative stereochemistry on the basis of the observed coupling constant for methine protons H3 and H4 is a very well-established criterium in β-lactam chemistry. See, for example: Alcaide, B.; Almendros, P.; Salgado, N. R.; Rodríguez-Vicente, A. *J. Org. Chem.* **2000**, *65*, 4453.

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(19) For a review on bi- and tricyclic-β-lactams with nonclassical structures, see: Alcaide, B.; Almendros, P. *Curr. Org. Chem.* **2002**, *6*, 245.

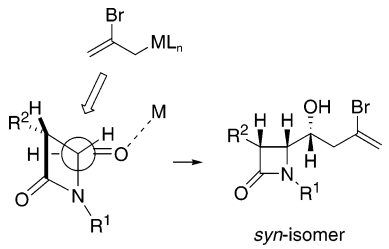
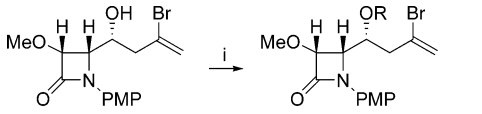


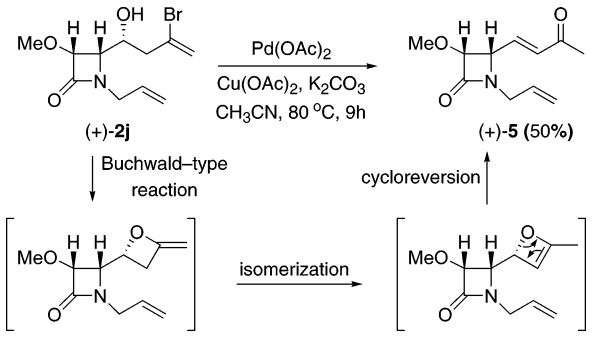
FIGURE 1. Model to explain the observed 4,1′-syn stereochemistry.

SCHEME 2



Key: (i) (*R*)- or (*S*)-acetylmandelic acid, DCC, DMAP.

SCHEME 3



8-*endo*-trig cyclization, was used as starting material in the initial experiment. All attempts to perform the intramolecular coupling reaction of bromodiene (+)-**2j** under Heck-type conditions failed, and more than 95% of (+)-**2j** was recovered. An unexpected result was obtained under palladium−copper-catalyzed conditions: compound (+)-**2j** gave rise to the α,β-unsaturated ketone (+)-**5** as a single isomer.[20] Mechanistically, the formation of compound (+)-**5** could be tentatively explained as depicted in Scheme 3, involving a Buchwald-type reaction, an isomerization, and a cycloreversion reaction.

The low reactivity of the bromodienic system in (+)-**2j** to Heck cyclization was attributed to the acidity of the OH group. As a consequence, in a subsequent reaction the OH group of (+)-**2j** was protected with acetic anhydride to give acetate (+)-**6j**. Using palladium acetate as the palladium source, DMF as the solvent, potassium carbonate as the base, and triphenylphosphine, the reaction occurred at 105 °C, affording as the main product compound (+)-**7a** (Scheme 4, Table 2). Other solvents (acetonitrile and dioxane) were less effective. Different palladium catalysts showed the same results. The intramolecular Heck reaction of compound (+)-**6j** was sensitive to the temperature. Thus, on performing the coupling at

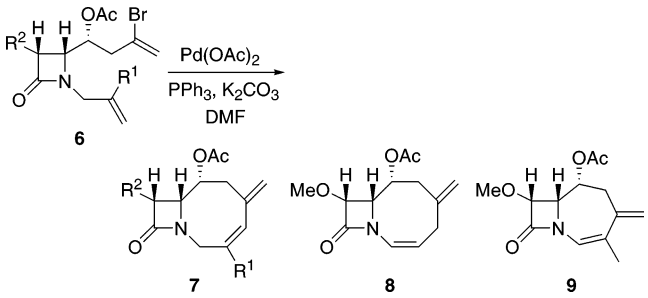
(20) Ketone (+)-**5** was alternatively obtained from the Wittig reaction between the stabilized ylide 1-triphenylphosphoranylidene-2-propanone and the 4-oxoazetidine-2-carbaldehyde (+)-**1h** in a 90% yied but as a mixture of isomers (*E*/*Z* = 86/14).

TABLE 2. Intramolecular Heck Reaction of Compound (+)-6i and (+)-6j[a]

entry	diene	*T* (°C)	*t* (h)	R^1	R^2	products	yield (%)[a] **7/8/9**
1	(+)-**6j**	105	3	H	MeO	(+)-**7a**/(+)-**9**	52/0/9
2	(+)-**6j**	120	1	H	MeO	(−)-**8**/(+)-**9**	0/55/9
3	(+)-**6j**	160	3	H	MeO	(−)-**8**/(+)-**9**	0/46/25
4	(+)-**6i**	105	2	Me	PhO	(−)-**7b**	42/0/0
5	(+)-**6i**	125	1	Me	PhO	(−)-**7b**	48/0/0

[a] Yield of pure, isolated product with correct analytical and spectral data. A similar ratio was detected in the ^{1}H NMR spectra of the crude reaction mixtures.

SCHEME 4



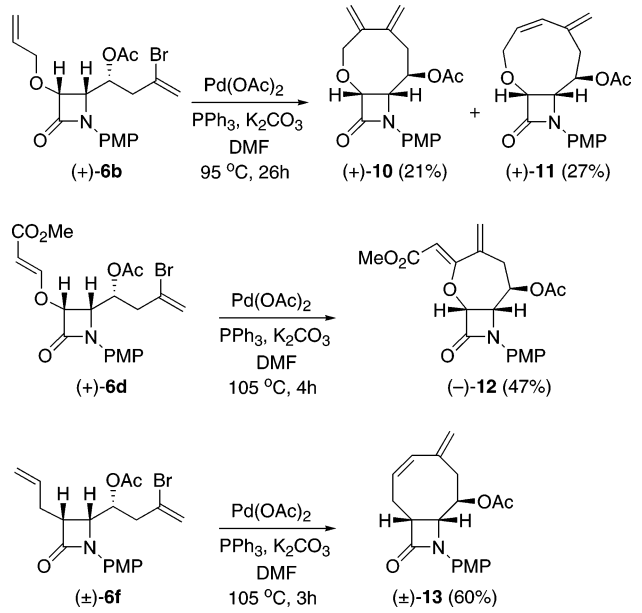
120 °C, isomeric bicycle (−)-**8** became the more important product, and no traces of (+)-**7a** were detected (Table 2, entry 2). At 160 °C, the regiochemistry of the Heck reaction was affected, increasing the importance of the 7-*exo*-trig cyclization with regard to the 8-*endo*-trig (Table 2, entry 3). Adduct (+)-**9** presumably arises from the isomerization of the initially formed 7-*exo*-trig Heck adduct. Interestingly, the palladium-catalyzed cyclization of methallyl acetate (+)-**6i** afforded bicycle (−)-**7b** as the only isomer (Table 2, entries 4 and 5).

Once the Heck reaction was carried out on (+)-**6i** and (+)-**6j**, acetates (+)-**6b**, (+)-**6d**, and (±)-**6f** were selected for the palladium-catalyzed reactions. The reaction conditions were further optimized, and typical results for the preparation of bicyclic β-lactams **10**−**13** are summarized in Scheme 5.

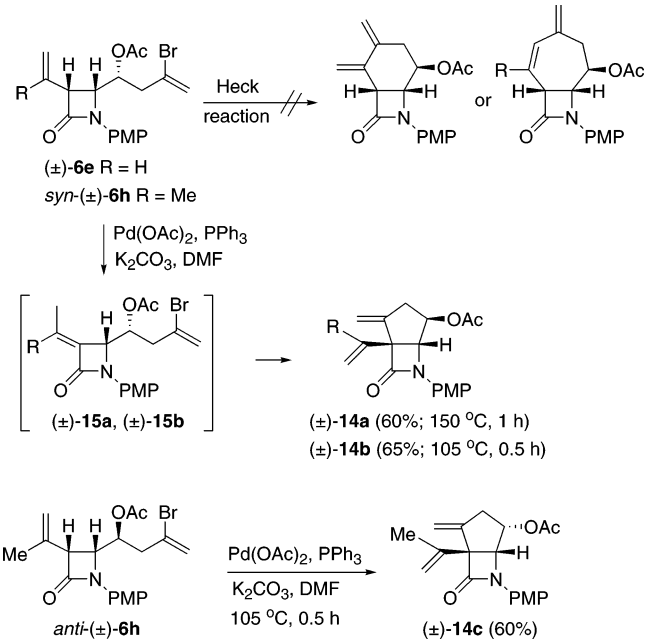
Special mention deserves the Heck reaction of acetate (±)-**6e**. The substitution pattern on bromodiene (±)-**6e** should direct the regiochemical outcome of the cyclization to the six-membered or seven-membered ring formation. Interestingly, we found that the reaction produced the five-membered, fused bicycle (±)-**14a** as the only isomer. As a result of steric congestion, the stereocontrolled construction of carbon atoms having four carbon ligands is a formidable challenge for chemical synthesis. Compound (±)-**14a** is remarkable since it bears a quaternary stereocenter.[21] Adduct (±)-**14a** presumably arises from the Pd-catalyzed 5-*exo* cyclization of the initially formed α,β-unsaturated carbonyl compound (±)-**15a**. A similar

(21) For the enantioselective construction of quartenary centers through intramolecular Heck reaction, see: (a) Busacca, C. A.; Grossbach, D.; Campbell, S. J.; Dong, Y.; Eriksson, M. C.; Harris, R. E.; Jones, P.-J.; Kim, J.-Y.; Lorenz, J. C.; McKellop, K. B.; O'Brien, E. M.; Qiu, F.; Simpson, R. D.; Smith, L.; So, R. C.; Spinelli, E. M.; Vitous, J.; Zavattaro, C. *J. Org. Chem.* **2004**, *69*, 5187. (b) Dounay, A. B.; Hatanaka, K.; Kodanko, J. J.; Oestreich, M.; Overman, L. E.; Pfeifer, L. A.; Weiss, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 6261. For the preparation of fused tricyclic β-lactams bearing a quaternary stereocenter at the same position, see: (c) Shintani, R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 4082.

SCHEME 5



SCHEME 6

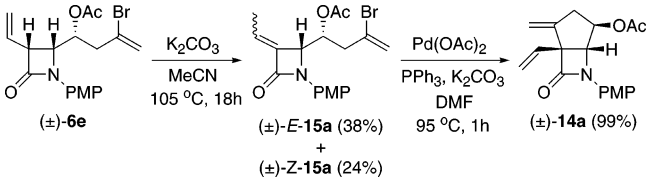


reaction pattern was observed on reacting bromodienes *syn*-(±)-**6h** and *anti*-(±)-**6h**. Thus, bicyclic β-lactams (±)-**14b** and (±)-**14c** were also prepared through essentially the same procedure (Scheme 6).

To probe the above hypothesis, we must show that the intermediate (±)-**15** could be obtained from (±)-**6** and that this new bromodiene does give the corresponding fused β-lactam (±)-**14** under Heck conditions. This mechanistically informative result was provided by the treatment of the bromohomoallylic acetate (±)-**6e** with potassium carbonate in acetonitrile to give a separable mixture of isomeric bromodienes (±)-(*E*)-**15a** and (±)-(*Z*)-**15a**, which under palladium catalysis afforded the expected bicycle (±)-**14a**. The two-step synthesis of compound (±)-**14a** from diene (±)-**6e** is depicted in Scheme 7.

The structure and stereochemistry of compounds **7**−**15** were assigned by NMR studies. The cis stereochemistry

SCHEME 7



of the four-membered ring was set during the cyclization step to form the 2-azetidinone ring, and it was transferred unaltered during the further synthetic steps, except for compounds **14** and **15**. The bicyclic structures (by DEPT, HMQC, HMBC, and COSY) and the stereochemistry (by vicinal proton couplings and qualitative homonuclear NOE difference spectra) of fused β-lactams **7**−**14** were established by NMR one- and two-dimensional techniques.[22]

Conclusion

In conclusion, the present study provides the first insight into the stereoselective manner in which 4-oxoazetidine-2-carbaldehydes and 2,3-dibromopropene undergo a metal-promoted coupling to give bromohomoallylic alcohols. In addition, we have shown that combination of bromoallylation reaction and Heck cyclization is a useful methodology for the preparation of a variety of fused bicyclic β-lactams of nonconventional structure.

Experimental Section

Tin-Promoted Reaction between 2,3-Dibromopropene and 4-Oxoazetidine-2-carbaldehydes 1 in Aqueous Medium. General Procedure for the Synthesis of Bromohomoallylic Alcohols 2. 2,3-Dibromopropene (600 mg, 3 mmol) was added to a well stirred suspension of the appropriate aldehyde **1** (1.0 mmol), tin powder (178 mg, 1.5 mmol), and the corresponding additive (0.2 mmol) in THF/H_2O (1:1, 10 mL) at room temperature. After the disappearance of the starting material (TLC), saturated aqueous sodium hydrogen carbonate (10 mL) was added at 0 °C, and the mixture was allowed to warm to room temperature, before being extracted with ethyl acetate (3 × 10 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds **2**. Spectroscopic and analytical data for some representative forms of **2** follow.[23]

Bromohomoallyl Alcohol (+)-2a. From 54 mg (0.23 mmol) of 4-oxoazetidine-2-carbaldehyde (+)-**1a** was obtained 73 mg (90%) of compound (+)-**2a** as a colorless solid after purification by flash chromatography (hexanes/ethyl acetate, 1/1). Mp: 103−104 °C (hexanes/ethyl acetate). $[\alpha]_D$ +94.0 (*c* 0.6, $CHCl_3$). ^1H NMR: δ 2.62 (s, 1H), 2.65 (d, 1H, J = 2.9 Hz), 2.73 (d, 1H, J = 4.2 Hz), 3.69 (s, 3H), 3.79 (s, 3H), 4.33 (d, 1H, J = 5.1 Hz), 4.41 (m, 1H), 4.65 (d, 1H, J = 5.1 Hz), 5.52 (d, 1H, J = 1.5 Hz), 5.63 (d, 1H, J = 1.2 Hz), 6.87 and 7.38 (d, each 2H, J = 9.0 Hz). ^{13}C NMR: δ 164.9, 156.8, 130.3, 129.6, 120.5, 119.9, 114.2, 82.7, 68.6, 59.7, 55.4, 45.3. IR (KBr, cm^{-1}): ν 3428, 1740. MS (EI), *m/z*: 357 (M^+ + 2, 26), 355

(22) Taking into account that bromohomoallylic alcohols **2** could be obtained and cyclized to bicyclic β-lactams, the stereochemistry at the carbinolic stereogenic center for compounds **2** was immediately deduced by comparison with the NOE results of the bicyclic β-lactams **7**−**14**.

(23) Full spectroscopic and analytical data for compounds not included in this Experimental Section are described in Supporting Information.

(M^+, 26), 149 (100). Anal. Calcd for $C_{15}H_{18}NO_4Br$: C, 50.58; H, 5.09; N, 3.93. Found: C, 50.69; H, 5.11; N, 3.90.

Bromohomoallyl Alcohol (+)-2b. From 132 mg (0.50 mmol) of 4-oxoazetidine-2-carbaldehyde (+)-**1b** was obtained 130 mg (67%) of compound (+)-**2b** as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 2/1). $[\alpha]_D$ +133.1 (*c* 1.1, $CHCl_3$). ^1H NMR: δ 2.66 (d, 2H, J = 6.4 Hz), 3.78 (s, 3H), 4.36 (m, 3H), 4.43 (d, 1H, J = 4.9 Hz), 4.79 (d, 1H, J = 4.6 Hz), 5.29 (d, 1H, J = 10.5 Hz), 5.37 (d, 1H, J = 17.3 Hz), 5.52 (d, 1H, J = 1.5 Hz), 5.63 (s, 1H), 5.96 (m, 1H), 6.86 and 7.38 (d, each 2H, J = 9.0 Hz). ^{13}C NMR: δ 165.0, 156.9, 133.1, 130.5, 129.7, 120.5, 120.0, 118.7, 114.3, 80.6, 72.7, 68.8, 60.0, 55.5, 45.4. IR ($CHCl_3$, cm^{-1}): ν 3428, 1740. MS (EI), *m/z*: 383 (M^+ + 2, 14), 381 (M^+, 14), 149 (100). Anal. Calcd for $C_{17}H_{20}NO_4Br$: C, 53.42; H, 5.27; N, 3.66. Found: C, 53.52; H, 5.24; N, 3.64.

Preparation of Bromohomoallyl Alcohol (±)-2e. From 230 mg (0.996 mmol) of 4-oxoazetidine-2-carbaldehyde (±)-**1e** and after column chromatography eluting with dichloromethane/ethyl acetate (20:1) were obtained 309 mg (88%) of the less polar compound (±)-**2e** and 27 mg (8%) of the more polar compound, its *anti*-epimer.

Bromohomoallyl Alcohol *syn*-(±)-2e. Colorless solid. Mp: 119−120 °C (hexanes/ethyl acetate). ^1H NMR: δ 2.26 (d, 1H, J = 3.9 Hz), 2.53 (dd, 1H, J = 14.5, 8.9 Hz), 2.69 (d, 1H, J = 14.4 Hz), 3.78 (s, 3H), 4.00 (dd, 1H, J = 8.8, 5.6 Hz), 4.21 (m, 2H), 5.43 (ddd, 1H, J = 10.0, 1.5, 0.5 Hz), 5.47 (dt, 1H, J = 17.1, 1.5 Hz), 5.55 (d, 1H, J = 1.5 Hz), 5.69 (s, 1H), 5.99 (ddd, 1H, J = 17.1, 10.0, 8.8 Hz), 6.85 and 7.47 (d, each 2H, J = 9.0 Hz). ^{13}C NMR: δ 165.8, 156.7, 131.2, 129.0, 128.8, 122.8, 120.7, 120.6, 114.1, 70.3, 59.2, 55.6, 55.1, 45.9. IR (KBr, cm^{-1}): ν 3431, 1741. MS (EI), *m/z*: 353 (M^+ + 2, 22), 351 (M^+, 22), 149 (100). Anal. Calcd for $C_{16}H_{18}NO_3Br$: C, 54.56; H, 5.15; N, 3.98. Found: C, 54.65; H, 5.11; N, 4.00.

Bromohomoallyl Alcohol *anti*-(±)-2e. Colorless oil. ^1H NMR: δ 2.17 (d, 1H, J = 5.7 Hz), 2.68 (m, 2H), 3.80 (s, 3H), 4.09 (dd, 1H, J = 8.5, 5.9 Hz), 4.28 (dd, 1H, J = 5.9, 2.9 Hz), 4.53 (m, 2H), 5.38 (dd, 1H, J = 11.0, 1.0 Hz), 5.45 (dt, 1H, J = 18.3, 1.3 Hz), 5.56 and 5.70 (d, each 1H, J = 1.7 Hz), 6.25 (ddd, 1H, J = 17.1, 10.2, 8.9 Hz), 6.90 and 7.41 (d, each 2H, J = 9.0 Hz). ^{13}C NMR: δ 165.4, 156.6, 130.7, 130.0, 129.4, 121.8, 120.5, 119.3, 114.6, 66.9, 58.7, 55.8, 55.6, 44.9. IR ($CHCl_3$, cm^{-1}): ν 3427, 1739. MS (EI), *m/z*: 353 (M^+ + 2, 26), 351 (M^+, 26), 149 (100). Anal. Calcd for $C_{16}H_{18}NO_3Br$: C, 54.56; H, 5.15; N, 3.98. Found: C, 54.46; H, 5.12; N, 3.95.

Bromohomoallyl Alcohol (±)-2f. From 123 mg (0.50 mmol) of 4-oxoazetidine-2-carbaldehyde (±)-**1f** was obtained 123 mg (67%) of compound (±)-**2f** as a colorless solid after purification by flash chromatography (dichloromethane/ethyl acetate, 12/1). Mp: 90−91 °C (hexanes/ethyl acetate). ^1H NMR: δ 2.05 (d, 1H, J = 5.1 Hz), 2.58 (m, 4H), 3.47 (ddd, 1H, J = 8.3, 7.1, 5.4 Hz), 3.78 (s, 3H), 4.23 (t, 1H, J = 5.5 Hz), 4.29 (m, 1H), 5.14 (dq, 1H, J = 9.5, 1.4 Hz), 5.21 (dq, 1H, J = 16.6, 1.5 Hz), 5.56 (d, 1H, J = 1.7 Hz), 5.68 (d, 1H, J = 0.7 Hz), 5.98 (m, 1H), 6.86 and 7.39 (d, each 2H, J = 9.0 Hz). ^{13}C NMR: δ 164.4, 156.7, 135.5, 131.0, 129.2, 121.0, 120.6, 116.8, 114.2, 69.0, 58.3, 55.5, 50.7, 47.3, 29.1. IR (KBr, cm^{-1}): ν 3433, 1742. MS (EI), *m/z*: 367 (M^+ + 2, 11), 365 (M^+, 11), 149 (100). Anal. Calcd for $C_{17}H_{20}NO_3Br$: C, 55.75; H, 5.50; N, 3.82. Found: C, 55.86; H, 5.48; N, 3.79.

Bromohomoallyl Alcohol (+)-2j. From 106 mg (0.63 mmol) of 4-oxoazetidine-2-carbaldehyde (+)-**1j** was obtained 128 mg (70%) of compound (+)-**2j** as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1/1). $[\alpha]_D$ +44.9 (*c* 1.0, $CHCl_3$). ^1H NMR: δ 2.60 (br s, 1H), 2.64 (s, 1H), 2.67 (d, 1H, J = 1.0 Hz), 3.63 (s, 3H), 3.76 (t, 1H, J = 4.5 Hz), 3.83 (dt, 1H, J = 6.8, 1.1 Hz), 4.10 (dt, 1H, J = 5.4, 1.6 Hz), 4.21 (m, 1H), 4.52 (d, 1H, J = 5.1 Hz), 5.22 (d, 1H, J = 1.0 Hz), 5.29 (dq, 1H, J = 7.6, 1.2 Hz), 5.56 (d, 1H, J = 1.7 Hz), 5.72 (d, 1H, J = 1.2 Hz), 5.79 (m, 1H). ^{13}C NMR: δ 167.4, 132.0, 129.5, 120.0, 118.7, 83.3, 68.4, 59.9, 59.5, 45.7, 44.2. IR ($CHCl_3$, cm^{-1}): ν 3430, 1741. MS (EI), *m/z*: 291 (M^+ + 2, 100), 289 (M^+, 98). Anal. Calcd for $C_{11}H_{16}NO_3Br$: C, 45.53; H, 5.56; N, 4.83. Found: C, 45.62; H, 5.54; N, 4.80.

Procedure for the Preparation of Bromohomoallylic Acetate (±)-6e. Acetic anhydride (48 mg, 0.468 mmol), DMAP (catalyst), and triethylamine (95 mg, 0.936 mmol) were sequentially added dropwise to a stirred solution of the bromohomoallylic alcohol (±)-**2e** (138 mg, 0.39 mmol), in dichloromethane (4 mL) at 0 °C, and the mixture was stirred for 2 h at room temperature. The organic phase was washed with water (2 × 2 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with dichloromethane/ethyl acetate (30/1) gave 150 mg (98%) of compound (±)-**6e**. Acetates **6** were prepared in a similar way.

Acetate (±)-6e. Colorless solid. Mp: 106−107 °C (hexanes/ethyl acetate). ^1H NMR: δ 1.64 (s, 3H), 2.71 (br s, 1H), 2.73 (d, 1H, J = 0.7 Hz), 3.78 (s, 3H), 4.06 (dd, 1H, J = 8.8, 5.9 Hz), 4.42 (dd, 1H, J = 9.3, 5.9 Hz), 5.54 (m, 5H), 6.03 (ddd, 1H, J = 17.1, 10.0, 8.8 Hz), 6.86 and 7.32 (d, each 2H, J = 9.0 Hz). ^{13}C NMR: δ 169.5, 165.0, 156.8, 130.2, 128.0, 127.4, 123.3, 121.1, 120.5, 114.1, 71.2, 56.4, 55.6, 55.0, 43.1, 20.5. IR (KBr, cm^{-1}): ν 1740, 1730. MS (EI), *m/z*: 395 (M^+ + 2, 10), 393 (M^+, 10), 149 (100). Anal. Calcd for $C_{18}H_{20}NO_4Br$: C, 54.84; H, 5.11; N, 3.55. Found: C, 54.93; H, 5.09; N, 3.53.

Procedure for Base-Promoted Isomerization of Compound (±)-6e: Preparation of (±)-(*E*)-15a and (±)-(*Z*)-15a. To a solution of 3-vinyl-β-lactam (±)-**6e** (87 mg, 0.22 mmol) in acetonitrile (3.5 mL) was added potassium carbonate (213 mg, 1.44 mmol), and the mixture was heated for 18 h at 107 °C in a sealed tube. After the mixture was cooled at room temperature, the organic phase was washed with water (2 × 1 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate (6:1) gave 17 mg (24%) of the less polar compound (±)-(*Z*)-**15a** and 33 mg (38%) of the more polar compound (±)-(*E*)-**15a**.

Acetate (±)-(*Z*)-15a. Colorless oil. ^1H NMR: δ 2.06 (s, 3H), 2.15 (d, 3H, J = 7.3 Hz), 2.71 (m, 2H), 3.80 (s, 3H), 4.64 (d, 1H, J = 4.1 Hz), 5.50 (d, 1H, J = 2.0 Hz), 5.60 (s, 1H), 5.71 (m, 1H), 5.89 (q, 1H, J = 7.1 Hz), 6.91 and 7.42 (d, each 2H, J = 9.0 Hz). ^{13}C NMR: δ 168.6, 161.4, 155.5, 130.9, 129.5, 128.4, 128.2, 119.9, 118.5, 114.6, 69.9, 58.9, 55.5, 40.5, 20.7, 14.9. IR ($CHCl_3$, cm^{-1}): ν 1741, 1728. MS (EI), *m/z*: 395 (M^+ + 2, 16), 393 (M^+, 16), 149 (100). Anal. Calcd for $C_{18}H_{20}NO_4Br$: C, 54.84; H, 5.11; N, 3.55. Found: C, 54.95; H, 5.14; N, 3.53.

Acetate (±)-(*E*)-15a. Colorless oil. ^1H NMR: δ 1.91 (d, 3H, J = 7.1 Hz), 2.16 (s, 3H), 2.66 (m, 2H), 3.81 (s, 3H), 4.77 (s, 1H), 5.45 (d, 1H, J = 1.9 Hz), 5.59 (d, 1H, J = 1.2 Hz), 5.78 (m, 1H), 6.41 (qd, 1H, J = 7.3, 1.2 Hz), 6.93 and 7.48 (d, each 2H, J = 9.0 Hz). ^{13}C NMR: δ 170.2, 162.5, 156.4, 130.7, 128.3, 125.0, 119.7, 118.5, 114.7, 68.6, 59.9, 55.5, 40.6, 20.9, 14.8. IR ($CHCl_3$, cm^{-1}): ν 1742, 1732. MS (EI), *m/z*: 395 (M^+ + 2, 14), 393 (M^+, 14), 149 (100). Anal. Calcd for $C_{18}H_{20}NO_4Br$: C, 54.84; H, 5.11; N, 3.55. Found: C, 54.94; H, 5.08; N, 3.58.

General Procedure for the Intramolecular Heck Reaction. Preparation of Bicyclic β-Lactams 7−14. Palladium(II) acetate (0.03 mmol), triphenylphosphine (0.07 mmol), and potassium carbonate (7.0 mmol) were sequentially added to a solution of the corresponding bromohomoallylic acetate **6** (1.0 mmol) in dimethylformamide (15 mL), and the mixture was heated at the appropriate temperature (see Table 2 and Schemes 2 and 3) in a sealed tube. After the disappearance of the starting material (TLC), the reaction mixture was cooled at room temperature and diluted with ethyl acetate (10 mL). The organic phase was washed with water (4 × 5 mL) and brine (3 × 5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate or dichloromethane/ethyl acetate mixtures gave analytically pure fused β-lactams **7**−**14**. Spectroscopic and analytical data for some representative forms of **7**−**14** follow.

Intramolecular Heck Reaction of Bromohomoallylic Acetate (+)-6j: Preparation of Bicycles (+)-7a and (+)-9. From 48 mg (0.145 mmol) of bromohomoallylic acetate (+)-**6j** upon heating at 105 °C for 3 h, and after column chromatography eluting with dichloromethane/ethyl acetate (9:1), were obtained 3 mg (9%) of the less polar compound (+)-**9** and 19 mg (52%) of the more polar compound (+)-**7a**.

Bicyclic β-Lactam (+)-7a. Colorless oil. $[\alpha]_D$ +29.6 (*c* 0.5, $CHCl_3$). ^1H NMR: δ 2.03 (s, 3H), 2.46 (dq, 1H, J = 9.8, 1.3 Hz), 2.85 (dd, 1H, J = 9.7, 3.7 Hz), 3.46 (s, 3H), 3.77 (dt, 1H, J = 9.3, 0.9 Hz), 3.84 (dd, 1H, J = 3.1, 0.9 Hz), 4.27 (d, 1H, J = 9.3 Hz), 4.49 (dd, 1H, J = 3.0, 0.9 Hz), 4.90 (td, 1H, J = 1.2, 0.4 Hz), 5.05 (q, 1H, J = 0.9 Hz), 5.07 (t, 1H, J = 0.9 Hz), 5.13 (d, 1H, J = 0.8 Hz), 5.34 (dt, 1H, J = 3.6, 1.1 Hz). IR ($CHCl_3$, cm^{-1}): ν 1741, 1722. MS (EI), *m/z*: 251 (M^+, 100). Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.24; H, 6.79; N, 5.54.

Bicyclic β-Lactam (+)-9. Colorless oil. $[\alpha]_D$ +42.8 (*c* 1.2, $CHCl_3$). ^1H NMR: δ 1.90 (d, 3H, J = 1.2 Hz), 2.00 (s, 3H), 2.39 (dd, 1H, J = 14.2, 3.9 Hz), 2.95 (dd, 1H, J = 14.4, 6.8 Hz), 3.51 (s, 3H), 3.94 (dd, 1H, J = 5.0, 2.1 Hz), 4.61 (dd, 1H, J = 7.4, 5.0 Hz), 4.94 (s, 1H), 5.16 (s, 1H), 5.45 (ddd, 1H, J = 6.8, 3.4, 2.2 Hz), 6.52 (dd, 1H, J = 9.4, 1.8 Hz). ^{13}C NMR: δ 173.5, 167.4, 140.8, 138.5, 118.9, 108.4, 84.6, 66.6, 61.1, 59.8, 41.8, 21.0, 20.9. IR ($CHCl_3$, cm^{-1}): ν 1738, 1723. MS (EI), *m/z*: 251 (M^+, 100). Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.03; H, 6.78; N, 5.60.

Bicyclic β-Lactam (±)-13. From 25 mg (0.061 mmol) of homoallylic acetate (±)-**6f** was obtained 15 mg (60%) of compound (±)-**13** as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 2/1). ^1H NMR: δ 1.59 (d, 3H, J = 3.4 Hz), 2.63 (m, 4H), 3.50 (m, 1H), 3.79 (s, 3H), 4.38 (dd, 1H, J = 8.3, 5.9 Hz), 4.85 (d, 1H, J = 1.9 Hz), 4.93 (s, 1H), 5.07 (t, 2H, J = 2.0 Hz), 5.39 (td, 1H, J = 8.1, 4.1 Hz), 6.86 and 7.36 (d, each 2H, J = 8.8 Hz). ^{13}C NMR: δ 169.6, 161.3, 156.5, 147.1, 145.3, 130.5, 121.2, 120.3, 114.5, 72.8, 56.9, 55.5, 51.1, 39.0, 31.8, 21.0. IR ($CHCl_3$, cm^{-1}): ν 1746, 1730. MS (EI), *m/z*: 327 (M^+, 100). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.81; H, 6.44; N, 4.30.

Bicyclic β-Lactam (±)-14a. Method A. From 14 mg (0.036 mmol) of homoallylic acetate (±)-(*E*)-**15a** was obtained 11 mg (100%) of compound (±)-**14a** as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 3/1). ^1H NMR: δ 2.13 (s, 3H), 2.69 (d, 1H, J = 17.6 Hz), 2.97 (ddt, 1H, J = 17.4, 5.2, 2.7 Hz), 3.81 (s, 3H), 4.22 (d, 1H, J = 1.4 Hz), 5.19 (d, 1H, J = 2.9 Hz), 5.25 (d, 1H, J = 1.9 Hz), 5.31 (d, 1H, J = 5.1 Hz), 5.40 (dd, 1H, J = 10.7, 1.2 Hz), 5.60 (dd, 1H, J = 17.4, 1.2 Hz), 5.97 (dd, 1H, J = 17.5, 10.6 Hz), 6.92 and 7.53 (d, each 2H, J = 9.0 Hz). ^{13}C NMR: δ 170.7, 163.6, 144.3, 131.4, 130.7, 119.1, 118.1, 114.7, 112.7, 71.7, 70.4, 67.4, 55.5, 37.2, 21.1. IR ($CHCl_3$, cm^{-1}): ν 1742, 1729. MS (ES), *m/z*: 336 (M^+ + 23, 100), 313 (M^+, 7). Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.10; H, 6.08; N, 4.49. **Method B.** From 42 mg (0.108 mmol) of homoallylic acetate (±)-**6e** was obtained 20 mg (60%) of compound (±)-**14a** as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 3/1). Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 6.89; H, 6.15; N, 4.45.

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Supporting Information Available: Compound characterization data and experimental procedures for compounds (+)-**2c**, (+)-**2d**, **2g**−**i**, **2k**−**m**, (+)-**3**, (+)-**4**, (+)-**5**, (+)-**6b**, (+)-**6d**, (±)-**6f**, **6h**−**j**, (−)-**7b**, (−)-**8**, **10**−**12**, (±)-**14b**, and (±)-**14c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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