Additions of Allenyl/Propargyl Organometallic Reagents to 4-Oxoazetidine-2-carbaldehydes: Novel Palladium-Catalyzed Domino Reactions in Allenynes

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Abstract: Metal-mediated carbonyl allenylation and propargylation of 4-oxoazetidine-2-carbaldehydes were investigated in aqueous environment. Different propargyl bromide and metal promoters showed varied regio- and stereoselectivities on product formation. In addition, an unprecedented one-pot stereoselective synthesis of β-chlorinated allylic alcohols, which can also be considered as functionalized allylsilanes, has been developed, which involves tin(IV) chloride-mediated reaction of propargyltrimethylsilane and 4-oxoazetidine-2-carbaldehydes. Some of the resulting coupling products were submitted to transition metal catalyzed reactions, such as the allenic Pauson–Khand and palladium-catalyzed reactions, leading to novel fused or bridged tricyclic β-lactams. Remarkably, a novel domino process, namely the allene cyclization/intramolecular Heck reaction was found. A likely mechanism for the cascade reaction should involve an intramolecular cyclization on a (π-allyl)-palladium complex and a Heck-type reaction.

Keywords: allenes · asymmetric synthesis · domino reactions · β-lactams · transition metals

Introduction

The efficient formation of carbon–carbon bonds with good, and preferably predictable, stereocontrol is still a synthetic challenge in organic chemistry. Among the most fundamental and important reactions for constructing carbon–carbon bonds are the allylation and the propargylation/allenylation of aldehydes and ketones (carbonyls) with organometallic reagents. For example, Sakurai, Grignard, and Barbier-type reactions have been widely used for the allylation of carbonyls.[1] Allenes, alkynes, and their derivatives have established a reputation as increasingly popular intermediates in modern organic synthesis because of their unique structural characteristics and reactivities, which include ionic, radical, or concerted processes. The reactions of allenyl and propargyl organometallic reagents with carbonyl compounds provide useful synthetic intermediates.[2] The major drawback of this methodology comes from the tendency of such ambident nucleophiles to produce mixtures of both homopropargylic and allenic species. Normally, propargyl and allenyl metal compounds furnish allenyl and propargylic alcohols, respectively, through an addition reaction to carbonyls. In recent years, pertinent synthetic strategies for the introduction of propargyl or allenyl groups into carbonyl groups have been described. In such procedures, the regiochemical selection was elegantly tuned towards either acetylenic or allenyl adducts. Thus, the synthesis of homopropargyl alcohols from propargylpalladium by the umpolung approach,[3] reported by Tamaru et al., and the preparation of homopropargyl and allenyl alcohols from transient allenylindium reagents or propargylic stannanes, respectively, described by Marshall et al.,[4] deserve special mention.

Organometallic reactions in aqueous media have been the subject of considerable study because of their potential as environmentally benign chemical processes, and because of their synthetic advantages, particularly the unique reactivities and selectivities, which are often exhibited in water.[5] β-Lactam antibiotics represent the most widely prescribed drugs in medicine because of their high antibacterial activities against many pathogenic bacteria, as well as their exceptionally low toxicity toward hosts.[6] Additionally, β-lactams show other interesting biological properties, especially in enzyme inhibition, and from a synthetic point of view the development of new methodologies based on the 2-azetidinone nucleus has reached considerable importance.[7] As part of a continuing commitment to the synthesis and synthetic applications of chiral, functionalized 2-azetidinones,[8] we decided

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Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/chemistry/ or from the author. It contains spectroscopic and analytical data for compounds (+)-**3b**, (+)-**3c**, (±)-**3f**, (+)-**4b**, (+)-**4c**, (±)-**4f**, (+)-**7a**, (+)-**7d**, **7f**, **g**, **13b–e**, **13j**, **13l–n**, (+)-**17**, (+)-**18b**, (−)-**20**, (+)-**26b**, and acetylmandelates of alcohols (+)-**3a**, (+)-**7f**, and (+)-**13f**; as well as experimental procedures for compounds (+)-**17**, (−)-**20**, and acetylmandelates of alcohols (+)-**3a**, (+)-**7f**, and (+)-**13f**.

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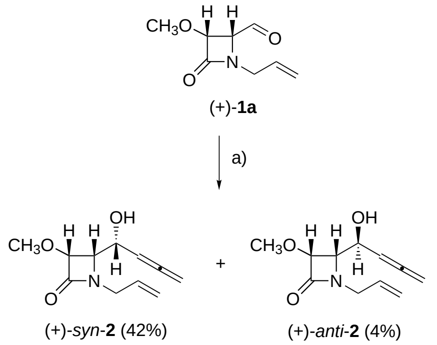
to pursue metal-based approaches for the stereoselective incorporation of new substituents, which retain versatile and useful unsaturated groups capable of future transformations, into the β-lactam ring. We report here a general study of the additions of allenyl/propargyl organometallic compounds to 4-oxoazetidine-2-carbaldehydes, together with further interesting new synthetic transformations.

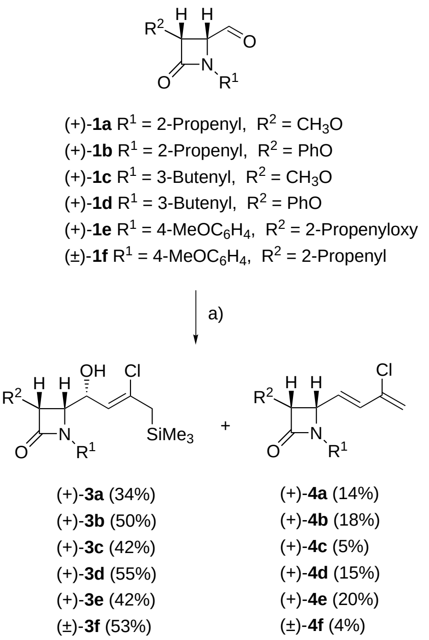
Results and Discussion

One might think that propargyl organometallic compounds would serve as allenyl reagents, with propargyltrimethylsilane being a well-documented reagent for regioselective carbonyl allenylation.[9] In this context, we began this work by investigating the effect of various Lewis acids, such as tin(IV) chloride, titanium(IV) chloride, and boron trifluoride diethyl etherate, on the diastereoselectivity of the allenylation of 4-oxoazetidine-2-carbaldehyde (+)-**1a** with propargyltrimethylsilane. In the event, the expected allenyl alcohol was obtained for the boron trifluoride diethyl etherate induced reaction, whereas the titanium-promoted reaction was messy. The α-allenic alcohol (+)-**2** was obtained in 46% yield as a mixture (90:10) of chromatographically separable *syn*/*anti* isomers (Scheme 1).



Scheme 1. Preparation of α-allenic alcohol (+)-**2**: a) propargyltrimethylsilane, $BF_3 \cdot Et_2O$, dichloromethane, −78 °C, 12 h.

To our delight, we found that the tin(IV) chloride promoted reaction between propargyltrimethylsilane and (+)-**1a** produced the isomerically pure functionalized β-chlorinated allylic alcohol (+)-**3a**. Similarly, the tin-catalyzed reaction of 4-oxoazetidine-2-carbaldehydes **1b–f**, produced 2-azetidinone β-chlorovinyl alcohols **3b–f** as single isomers in moderate to reasonable yields (42–55%) (Scheme 2).

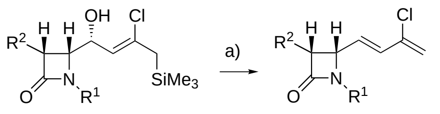


Scheme 2. Preparation of 2-chloro-3-silapropenyl alcohols **3**: a) propargyltrimethylsilane, $SnCl_4$, dichloromethane, −78 °C, 1 h.

Compounds **3** can also be considered as multifunctionalized allylsilanes, exhibiting a valuable manifold reactivity, which could potentially be used in a broad range of synthetic applications.[10] Also, adducts **3** are protected β-amino alcohols,which constitute an important class of biologically interesting compounds.[11] In all cases, by-products **4a–f** were detected in the ^1H NMR spectra of the crude reaction mixtures, accounting for approximately 7–30% of the products formed. Compounds **4a–f** were isolated as pure compounds by gravity flow chromatography in a similar ratio (4–20% yield). Modification of the reaction of a propargylsilane with an aldehyde so that a diene can be made rather than an allenyl alcohol would be a useful extension.[12] β-Chlorovinyl alcohols **3** were transformed into β-lactam-tethered chlorodienes **4** in one step ($SnCl_4/CH_2Cl_2/-78\,^{\circ}C$ or $CH_3SO_2Cl/Et_3N/CH_2Cl_2/0\,^{\circ}C$). This reaction confirms that by-products **4** arise from hydroxy elimination in adducts **3** with concomitant trimethylsilyl cleavage under the reaction conditions. For synthetic purposes, we chose the slightly higher yielding methanesulfonyl chloride procedure (Scheme 3).

Not unexpectedly, only the *trans*-olefin was formed in compounds **4**.[13] Our production of chlorodienes closely resembles a result obtained by Pornet in the titanium(IV) chloride induced reaction of propargyltrimethylsilane with

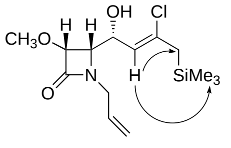
Abstract in Spanish: *Se investigaron la alenilación y propargilación de 4-oxoazetidin-2-carbaldehidos promovidas por metales en medios acuosos. Los diferentes metales produjeron regio- y estereoselectividades variadas. Además, se ha desarrollado una síntesis sin precedentes de alcoholes alílicos β-clorados, que pueden considerarse también como alilsilanos funcionalizados, mediante la reacción de propargiltrimetilsilano y 4-oxoazetidin-2-carbaldehidos catalizada por tetracloruro de estaño. En los productos de acoplamiento resultantes se realizaron transformaciones sintéticas catalizadas por metales de transición, como por ejemplo la variante alénica de la ciclación de Pauson-Khand y reacciones catalizadas por Pd(II). De esta forma, se han obtenido diferentes sistemas β-lactámicos tricíclicos fusionados o puenteados, con diferentes conectividades de anillos y estructuralmente muy novedosos. Hay que resaltar el descubrimiento de un nuevo proceso dominó, que se ha denominado ciclación de alenos/reacción intramolecular de Heck. Un mecanismo razonable para esta reacción en cascada debería involucrar la ciclación intramolecular de un complejo de (π-alil)paladio y una reacción intramolecular de tipo Heck.*



(+)-**3a**	(+)-**4a** (80%)
(+)-**3b**	(+)-**4b** (81%)
(+)-**3c**	(+)-**4c** (80%)
(+)-**3d**	(+)-**4d** (79%)
(+)-**3e**	(+)-**4e** (90%)
(±)-**3f**	(±)-**4f** (88%)

Scheme 3. Synthesis of chlorodienes **4**: a) CH_3SO_2Cl, Et_3N, dichloromethane, 0 °C, 30 min.

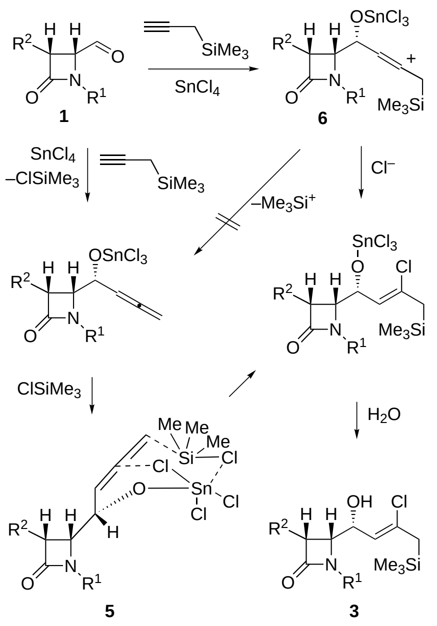
carbonyls.[14] However, his interpretation of the pathway to the chlorodienes may be needs amending, because he postulated that an allenyl carbinol is the intermediate. We think that this reaction actually goes through an intermediate such as compounds **3**. These are the first examples of the reaction of propargyltrimethylsilane to give β-chlorinated allylic alcohols, in either thermal or metal-mediated additions. The configuration at the carbinolic chiral center of the product (+)-**3a** was established by comparison of the ^{1}H NMR chemical shifts of its acetylmandelates,[15] and was assumed to be the same for the rest of β-lactams **3**. The stereochemistry of the double bond in compounds **3** was assigned by qualitative homonuclear NOE difference spectra, as depicted in Figure 1 for compound (+)-**3a**. Similar values of NOE enhancements for compounds **3b–f** were observed, in agreement with the proposed stereochemistry.



(+)-**3a**

Figure 1. Selected NOE effects and stereochemistry of chlorosilapropenyl alcohol (+)-**3a**.

The high selectivity observed in the formation of β-chlorovinyl alcohols **3** could point to a concerted mechanism. According to this theory, the whole process from **1** to **3** could be explained by an initial carbonyl-allenylation, followed by a chlorotrimethylsilane transfer. The formation of 2-chloro-3-silapropenyl alcohols **3** could be consistent with participation of the six-membered, cyclic, chairlike transition structure **5**, which controls both the regio- and the stereochemistry of the reaction (Scheme 4). To probe the above mechanism we had to show that the intermediate α-allenic alcohol does give the corresponding chlorodiene in the presence of tin(IV) chloride and chlorotrimethylsilane. Treatment of the α-allenic alcohol (+)-**2** with tin(IV) chloride and chlorotrimethylsilane in dichloromethane at −78 °C was informative in that compound (+)-**2** remained unaltered after several hours at the above conditions. This experiment leads us to suggest an alternative explanation, which involves a change in mechanism for the formation of the β-chlorovinyl alcohols. We believe the reaction is a stepwise process with the chlorination proceeding via a silicon-stabilized carbocation. Thus, the propargylsilane attacks the aldehyde (coordinated to the tin chloride), but instead of losing the trimethylsilyl group, the intermediate β-silyl-stabilized cation **6** accepts a nucleophile, the chloride ion (Scheme 4).



Scheme 4. Mechanistic explanation for the formation of 2-chloro-3-silapropenyl alcohols **3**.

There are several reported reactions of propargyltrimethylsilane in which the intermediate cation is captured without loss of the silyl group. They include the intramolecular capture of the cation by oxygen nucleophiles[16] and carbon nucleophiles,[17] as well as the capture of the cation after a silyl shift.[18] What makes the present reaction unprecedented is the capture of the cation by an external nucleophile. The observed stereochemistry is not in conflict with this stepwise mechanism, because the chlorine ion must attack *anti* to the silyl group, which will almost certainly be placed *anti* to the incoming electrophile when the C–C bond is being formed. Although it looks as though the chlorine ion has attacked the more hindered site, *syn* to the carbinol atom, it is actually the less hindered side at the time of attack, because the silyl group is larger. The high preference for the formation of the 4,1′-*syn* products **3** in the tandem proccess must be set up at the carbonyl addition step. The observed *syn* stereochemistry could be elucidated as the consequence of a Felkin addition, as shown in the transition state model depicted in Figure 2. The large substituent (the amino group of the four-membered ring) is assumed to be arranged perpendicular to the carbonyl group, the propargyltrimethylsilane group attacks the C=O bond in the most favored conformation, explaining the preference for the *syn*-configured products.

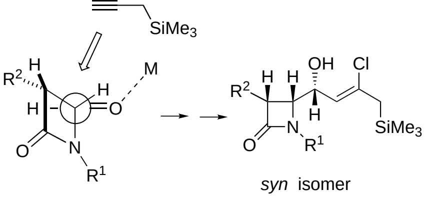
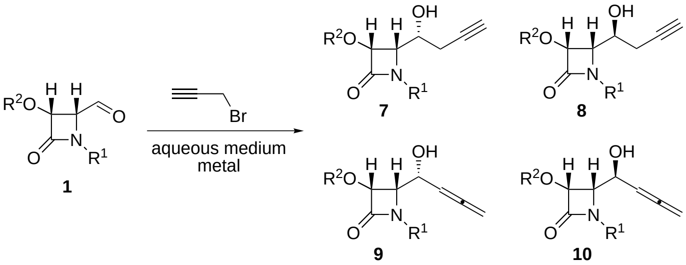


Figure 2. Model to explain the observed 4,1′-*syn* stereochemistry.

In a previous report we described additions to α-keto lactans of allenyl/propargylzinc, tin, and indium reagents, prepared in situ through metal-mediated reaction of propargyl bromides in aqueous media.[8e,f] It was found that these additions proceed with full regioselectivity under certain conditions. We were particularly interested in probing the degree of reagent versus substrate regio- and stereocontrol in such reactions with other relevant classes of nonracemic carbonyl compounds. We thus evaluated the feasibility of metal-mediated Barbier-type carbonyl-propargylation/allenylation reactions of 4-oxoazetidine-2-carbaldehydes in eco-friendly media, studying the diastereochemistry (*syn* vs. *anti*) and the regiochemistry of the connection (e.g., allenylation vs. propargylation). Since alkynes and allenes possess a rich chemistry, the resulting coupled products are prone to undergo further transformations, making them versatile synthetic tools. Since we recently reported that the ionic strength enhancement of the reaction solvent provided by the addition of ammonium chloride accelerated the carbonyl additions in aqueous media, the propargylation/allenylation reactions were conducted in the presence of a saturated solution of NH_4Cl.[8e] Results from the metal-promoted reactions between aldehydes **1** and propargyl bromide (Scheme 5) are summarized in Table 1. The tin- and indium-promoted reactions proceeded with total diastereocontrol, but poor regiocontrol. The results in Table 1 show that the zinc-mediated reaction is the best method for the regio- and stereoselective addition of propargyl bromide to aldehydes **1**, affording the *syn* adducts with complete regioselectivity and 85:15–98:2 diastereoselectivity. Fortunately, the diastereomeric homopropargylic alcohols **7** and **8** were easily separated by gravity flow chromatography in all cases.

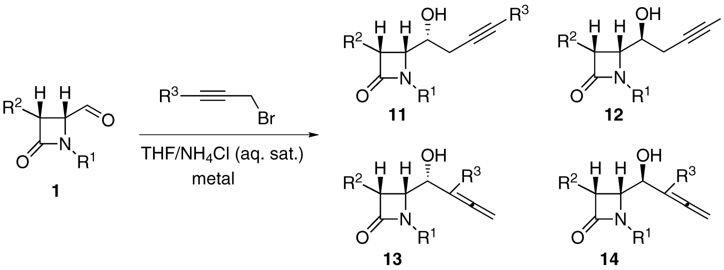


Scheme 5. Regioselective preparation of homopropargylic alcohols **7** in aqueous media.

Table 1. Regio- and stereoselective propargylation of 4-oxoazetidine-2-carbaldehydes **1**.[a]

Aldehyde	R^1	R^2	M	System solvent	**7**:**8**:**9**:**10** ratio[b]	Yield [%][c]
(+)-**1a**	2-propenyl	Me	Zn	THF/NH_4Cl (aq. sat.)	85:15:0:0	55 (**7a**)
(+)-**1a**	2-propenyl	Me	In	THF/NH_4Cl (aq. sat.)	55:0:45:0	72 (**7a**)
(+)-**1c**	3-butenyl	Me	Zn	THF/NH_4Cl (aq. sat.)	90:10:0:0	50 (**7b**)
(+)-**1g**	2-propynyl	Me	Zn	THF/NH_4Cl (aq. sat.)	90:10:0:0	64 (**7c**)
(+)-**1g**	2-propynyl	Me	In	THF/NH_4Cl (aq. sat.)	57:0:43:0	65 (**7c**)
(+)-**1h**	2-propynyl	Ph	Zn	THF/NH_4Cl (aq. sat.)	98:2:0:0	57 (**7d**)
(+)-**1i**	4-pentynyl	Me	Zn	THF/NH_4Cl (aq. sat.)	92:8:0:0	60 (**7e**)
(+)-**1i**	4-pentynyl	Me	In	THF/NH_4Cl (aq. sat.)	55:0:45:0	66 (**7e**)
(+)-**1j**	PMP	Me	Zn	THF/NH_4Cl (aq. sat.)	90:10:0:0	65 (**7f**)
(+)-**1j**	PMP	Me	Zn	MeOH/NH_4Cl (aq. sat.)	90:10:0:0	28 (**7f**)
(+)-**1j**	PMP	Me	In	THF/NH_4Cl (aq. sat.)	80:0:20:0	74 (**7f**)
(+)-**1j**	PMP	Me	In	THF/H_2O	65:0:35:0	69 (**7f**)
(+)-**1j**	PMP	Me	Sn	THF/NH_4Cl (aq. sat.)	57:0:43:0	65 (**7f**)
(+)-**1j**	PMP	Me	Sn	THF/H_2O	54:0:46:0	59 (**7f**)
(+)-**1k**	PMP	Ph	Zn	THF/NH_4Cl (aq. sat.)	90:10:0:0	75 (**7g**)

Next, we needed to find a metal-mediated carbonyl-allenylation method that proceeds in a highly regio- and diastereoselective fashion. Thus, we used propargyl bromides bearing an aliphatic or an aromatic substituent at the terminal position. Reactions of aldehydes **1** with 3-substituted prop-2-ynyl bromides afforded the corresponding α-allenic alcohols **13** as regioisomerically pure products in diastereomeric ratios of about 90:10–100:0 (Scheme 6). The diastereomeric *syn*- and *anti*-alcohols were amenable to separation by bench chromatography. This regiochemical preference is in sharp contrast to the behavior of propargyl bromide itself in metal-mediated reactions in aqueous media. The results are summarized in Table 2.



Scheme 6. Regioselective preparation of α-allenic alcohols **13** in aqueous media.

It may be reasonable to postulate a metallotropic rearrangement between the propargyl- and allenylmetallic species. Both intermediates from this equilibrium can react with the aldehydes **1**. In our case, depending on the structure of the parent halide and the reaction conditions, either the α-allenic or homopropargylic alcohols could be synthesized. It may be inferred that different steric effects in the organometallic reagents derived from differently substituted propargyl bromides may be responsible for the different regiochemical preference of the propargyl/allenyl metals involved in the reaction, by stabilizing one of the intermediates of the metallotropic equilibrium rather than the other. Probably, the isomerization of propargylmetal to allenylmetal is restricted by the steric effect of a substituent ($R^1 = CH_3$ or C_6H_5) in the bromopropyne. Thus, allenyl alcohols **13** are produced almost exclusively. Isomerization of the initially formed propargylmetal species to the corresponding allenyl organometallic can be induced by the absence of substituent ($R^1 = H$) at the propargyl bromide. Then, the allenylmetal undergoes nucleophilic addition to afford homopropargylic alcohols **7** selectively. The formation of alcohols **7** and **13** is consistent with participation of

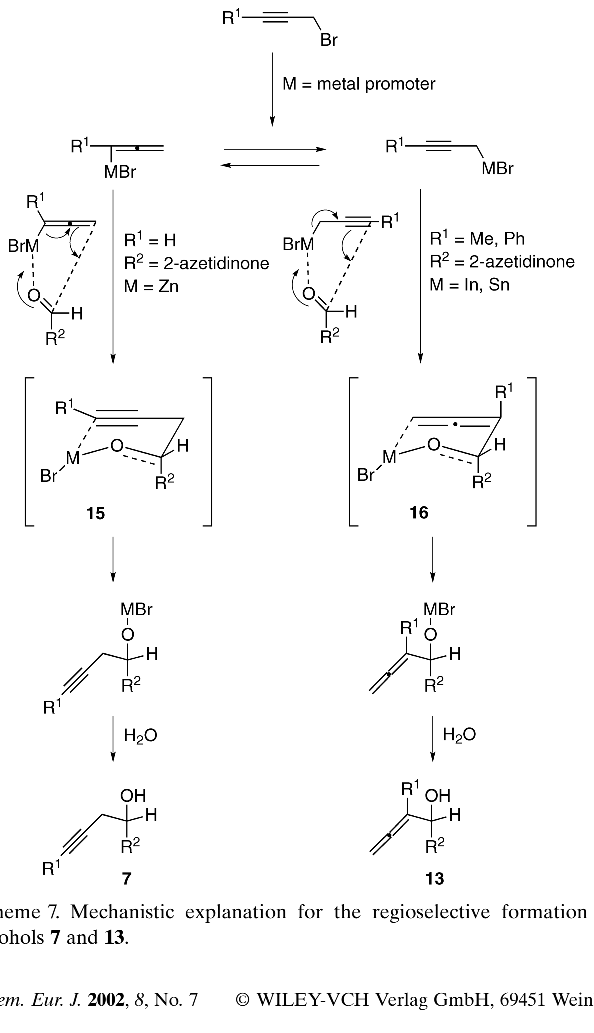
Table 2. Regio- and stereoselective allenylation of 4-oxoazetidine-2-carbaldehydes **1**.[a]

Aldehyde	R^1	R^2	R^3	Metal	**11**:**12**:**13**:**14** ratio[b]	Yield [%][c]
(+)-**1a**	2-propenyl	MeO	Me	In	0:0:95:5	75 (**13a**)
(+)-**1c**	3-butenyl	MeO	Me	In	0:0:97:3	77 (**13b**)
(+)-**1d**	3-butenyl	PhO	Me	In	0:0:90:10	92 (**13c**)
(+)-**1e**	PMP	2-propenyloxy	Me	In	0:0:90:10	80 (**13d**)
(±)-**1f**	PMP	2-propenyl	Me	In	0:0:90:10	90 (**13e**)
(+)-**1g**	2-propynyl	MeO	Me	In	0:0:98:2	75 (**13f**)
(+)-**1g**	2-propynyl	MeO	Me	Zn	0:0:92:8	40 (**13f**)
(+)-**1h**	3-butynyl	MeO	Me	In	0:0:93:7	69 (**13g**)
(+)-**1j**	PMP	MeO	Me	In	0:0:91:9	77 (**13h**)
(+)-**1j**	PMP	MeO	Me	Zn	0:0:90:10	55 (**13h**)
(±)-**1l**	PMP	ethenyl	Me	In	0:0:90:10	60 (**13i**)
(±)-**1m**	PMP	2-propynyl	Me	In	0:0:90:10	90 (**13j**)
(+)-**1a**	2-propenyl	MeO	Ph	In	0:0:100:0	64 (**13k**)
(+)-**1g**	2-propynyl	MeO	Ph	In	0:0:95:5	60 (**13l**)
(+)-**1j**	PMP	MeO	Ph	In	0:0:90:10	84 (**13m**)
(+)-**1j**	PMP	MeO	Ph	Zn	18:2:75:5	80 (**13m**)
(±)-**1l**	PMP	ethenyl	Ph	In	0:0:90:10	89 (**13n**)

[a] All reactions were carried out on 1 mmol scale. PMP = 4-$MeOC_6H_4$. [b] The 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 product with correct analytical and spectral data.

the six-membered, cyclic transition structures **15** and **16**. From a mechanistic point of view, our results could be explained as illustrated in Scheme 7.

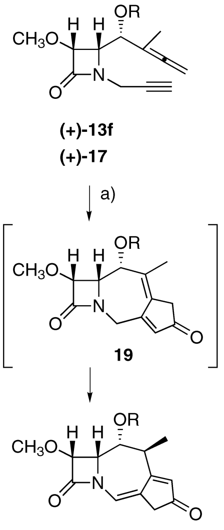
Derivatization of the alcohols **7** and **13** with (*R*)- and (*S*)-acetylmandelic acids allowed assignment of the configuration at the carbinolic stereocenter. Again, the stereochemical result can be interpreted by the Felkin–Anh model.



Scheme 7. Mechanistic explanation for the regioselective formation of alcohols **7** and **13**.

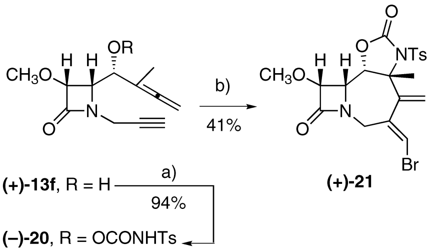
The allene moiety represents a versatile and useful building block in organic synthesis.[19] However, selectivity problems are significant. Intramolecularization of the reactions, usually caused by placement of the group at such a distance that five- or six-membered rings are formed, should automatically solve the positional selectivity problems, because larger rings are unfavored. Considering that the use of allenes in transition metal catalyzed cyclization reactions is of great current interest,[20] we turned our attention to transition metal catalyzed reactions in our β-lactam-tethered α-allenic alcohols.[21] Thus, we tried the less exploited allenic variant of the Pauson–Khand type cycloaddition with the allenynes (+)-**13f** and (+)-**17**.[22] In a previous study in our group on the use of the Pauson–Khand cyclization as an entry to fused tricyclic 2-azetidinones, attempts at generating central ring systems larger than six proved unsuccessful.[23] This result was expected because until recently the intramolecular variant of this reaction was largely restricted to the construction of bicyclo[3.3.0]octenones and bicyclo[4.3.0]nonenones.[24] Substitution patterns on allenynes (+)-**13f** and (+)-**17** were selected in order to direct the regiochemical outcome of the cycloaddition to the six-membered central ring formation. However, we found that the [2+2+1] cycloaddition produced tricycles **18** bearing a central seven-membered ring as the only isomer. Cycloadducts **18** presumably arise from the isomerization of the initially formed adducts **19** (Scheme 8). Conjugation of the dienone moiety with the lone pair of the nitrogen atom is believed to promote the formation of compounds **18**.

The tandem or domino reactions are versatile methods for constructing complex structures in one step, offering a convenient and economical way to prepare desired organic molecules.[25] A requirement for successful tandem reactions is the compatibility of all reactions



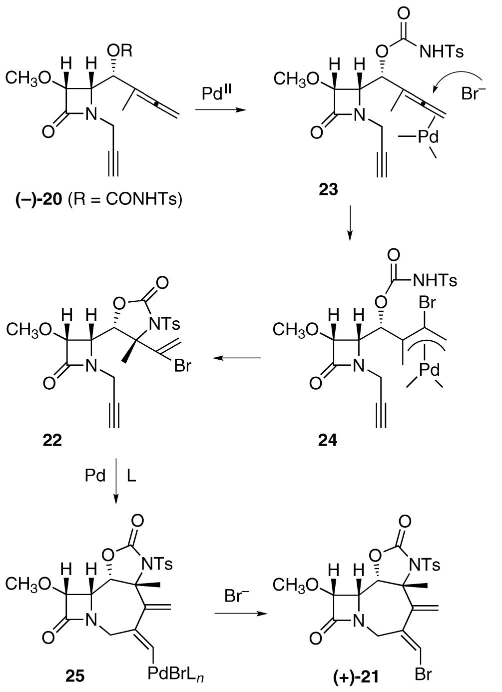
Scheme 8. Synthesis of fused tricyclic β-lactams **18** by a [2+2+1] cyclization of 2-azetidinone-tethered allenynes **13** and CO: a) $[Co_2(CO)_8]$, Me_3NO, dichloromethane, room temperature.

involved in such processes. Transition metal catalysts are ideally suited for this, and palladium catalysts have attracted special interest because of their tolerance of many functional groups.[26] However, one of the major problems associated with the combination of two Pd-catalyzed reactions is the differentiation of the reacting functional groups; thus a fine adjustment of their reactivity is necessary. In contrast to 1,3-dienes, the corresponding 1,2-dienes (allenes) have found limited use in palladium(II)-catalyzed oxidations.[27] We were interested in exploring the 1,2-functionalization of the allene moiety in our allenynol derivatives. The carbamate (−)-**20** was selected as the starting material for the palladium(II)-catalyzed reaction. The above carbamate was prepared from the α-allenic alcohol (+)-**13f** by treatment with tosyl isocyanate (Scheme 9). Reaction of compound (−)-**20** was carried out at room temperature in acetonitrile in the presence of 10 mol% of [Pd(OAc)$_2$], five equivalents of LiBr, two equivalents of [Cu(OAc)$_2$], and 1.2 equivalents of K$_2$CO$_3$ under an atmospheric pressure of oxygen. The ^{1}H NMR spectrum of the crude material displayed no signal corresponding to the allene or alkyne moieties. To our delight, the resulting product was identified after purification as the tricycle (+)-**21**(Scheme 9). Compound (+)-**21** was isolated in moderate yield as the only isomer, indicating that both the regio- and stereoselectivity are extremely high.



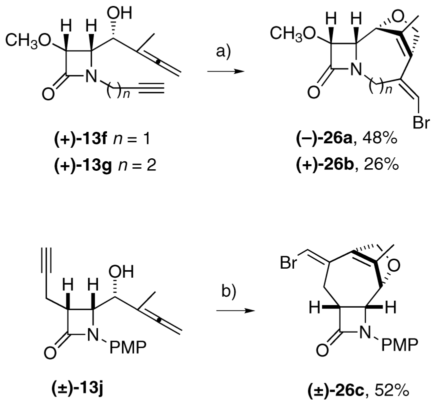
Scheme 9. Synthesis of fused tricyclic β-lactam **21** from α-allenic alcohol **13f** through palladium(II)-catalyzed domino cyclization reaction of 2-azetidinone-tethered allenyne carbamate **20**: a) TsNCO, THF, room temperature; b) [Pd(OAc)$_2$] 10 mol% , LiBr, [Cu(OAc)$_2$], K$_2$CO$_3$, O$_2$, acetonitrile, room temperature.

The formation of compound **21** could be rationalized in terms of an unprecedented domino allene amidation/intramolecular Heck-type reaction.[28] Compound **22** must be the nonisolable intermediate (see Scheme 10). A likely mechanism for **22** would involve a (π-allyl)palladium intermediate as proposed by Bäckvall and co-workers.[27b] The allenepalladium complex **23** is formed initially and undergoes a nucleophilic attack by the bromide to produce a σ-allylpalladium intermediate, which rapidly equilibrates to the corresponding (π-allyl)palladium intermediate **24**. Then, an intramolecular amidation reaction on the (π-allyl)palladium complex must account for the formation of intermediate **22**. Compound **22** evolves to tricycle **21** through a Heck-type coupling reaction. The alkenylpalladium intermediate **25**, generated in the *7-exo-dig* cyclization of bromoenyne **22**, is trapped by the bromide anion to yield the fused tricycle **21** (Scheme 10). Thus, the same catalytic system is able to promote two different but sequential catalytic cycles.



Scheme 10. Rationalization for the formation of fused tricyclic β-lactam **21** by domino allene carbamate insertion/intramolecular Heck reaction.

Encouraged by this interesting result, we decided to explore the reactivity of the allenynol moiety itself under these cascade conditions. To our delight, treatment of allenynols (+)-**13f**, (+)-**13g**, and **13j** under the above palladium-catalyzed domino reaction conditions afforded the bridged medium-sized ring tricycles **26a–c** as single isomers, albeit in moderate yields (Scheme 11). Although complete conversion was observed by TLC and ^{1}H NMR analysis of the crude reaction mixtures, the high polarity of adducts **26** may be responsible for the modest yields of isolated products. Compounds **26** are remarkable since they possess an unusual pyramidalized bridgehead structure.[29] A cascade process



Scheme 11. Synthesis of bridged tricyclic β-lactams **26** from 2-azetidinone-tethered allenynols **13** through palladium(II)-catalyzed domino cyclization reactions: a) [Pd(OAc)$_2$] 10 mol%, LiBr, [Cu(OAc)$_2$], K$_2$CO$_3$, O$_2$, acetonitrile, room temperature; b) [Pd(OAc)$_2$] 10 mol% , LiBr, [Cu(OAc)$_2$], K$_2$CO$_3$, O$_2$, acetonitrile, reflux temperature.

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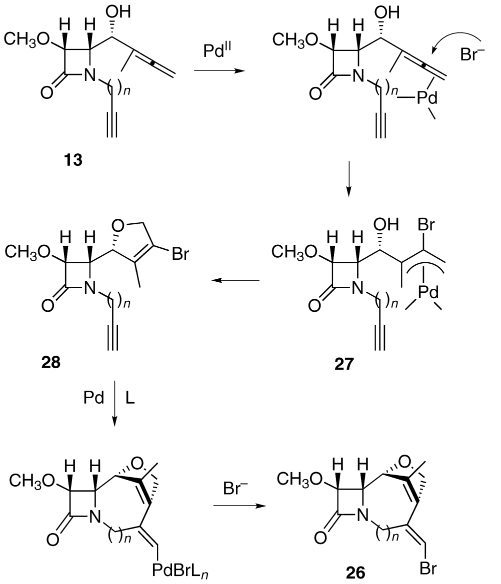
analogous to the formation of compound **21** seems to be taking place in this transformation. However, a dramatic change in the regioselectivity of the nucleophilic insertion into the (π-allyl)palladium intermediate **27** was observed when the bridged dihydrofurans were formed as the exclusive products. The thermochemically more stable five-membered intermediate **28** must be involved in the reaction rather than the corresponding regioisomeric oxirane. Taking into account the precedent explanation for formation of fused compound **21**, Scheme 12 outlines a mechanistic hypothesis for the achievement of bridged compounds **26**.



Scheme 12. Rationalization for the formation of bridged tricyclic β-lactams **26** through domino allenynol cyclization/intramolecular Heck reaction.

The tricyclic structure (by DEPT, HETCOR, and COSY) and the stereochemistry (by vicinal proton couplings and NOE experiments) of compounds **18**, **21**, and **26** were established by NMR mono- and two-dimensional techniques. Selected NOE effects and stereochemistry of some of the above trycicles are shown in Figure 3.

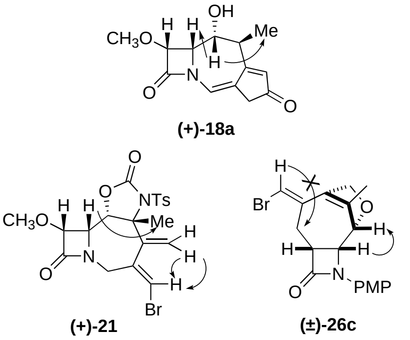


Figure 3. Selected NOE experiments of compounds (+)-**18a**, (+)-**21**, and (±)-**26c**.

Conclusion

In conclusion, we have demonstrated the first direct preparation of β-chlorovinyl alcohols from aldehydes, together with a study on the regio- and stereoselective manner in which enantiopure 4-oxoazetidine-2-carbaldehydes undergo coupling with a variety of propynyl-, and allenylmetal reagents in aqueous media. Some of the resulting coupling products are amenable to transition metal catalyzed reactions, such as the allenic variant of the Pauson–Khand type cycloaddition, and an unprecedented tandem allene cyclization/intramolecular Heck reaction, with high regio- and stereoselectivity controlability, leading to novel fused or bridged tricyclic β-lactams. These results open up the possibility of future application to chiral building blocks other than 2-azetidinones. Other aspects of this chemistry are currently under investigation in our laboratory.

Experimental Section

General methods: ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX-500, Bruker Avance-300, Varian VRX-300S, or Bruker AC-200 spectrometer. NMR spectra were recorded in CDCl$_3$ solutions, except when stated otherwise. Chemical shifts are given in ppm relative to TMS ($\delta = 0$, ^{1}H), or CDCl$_3$ ($\delta = 76.9$, ^{13}C). Low- and high-resolution mass spectra were recorded on a HP5989A spectrometer using the chemical ionization mode (CI) unless otherwise stated. Electrospray ionization (ESI) was performed on a Bruker ESQUIRE LC at 400 eV. Specific rotation $[\alpha]_D$ is given in deg per dm at 20°C, and the concentration (c) is expressed in g100 mL^{-1}. All commercially available compounds were used without further purification. The starting substrates, 4-oxoazetidine-2-carbaldehydes **1**, were prepared both in racemic and in optically pure forms using our previously described methodologies. Enantiomerically pure 2-azetidinones **1a–e** and **1g–k** were obtained as single *cis* enantiomers from imines of (R)-2,3-O-isopropylideneglyceraldehyde, through Staudinger reaction with the corresponding acid chlorides in the presence of Et$_3$N, followed by sequential acidic acetonide hydrolysis and oxidative cleavage.[8] Racemic compounds (±)-**1f**, (±)-**1l**, and (±)-**1m** were obtained from *N,N*-di-(p-methoxyphenyl)glyoxal diimine in one pot as single *cis*-diastereoisomers.[30]

Tin(IV) chloride promoted reactions between propargyltrimethylsilane and 4-oxoazetidine-2-carbaldehydes 1; general procedure for the synthesis of 2-chloro-3-silapropenyl alcohols 3: A solution of the appropriate 4-oxoazetidine-2-carbaldehyde **1** (0.5 mmol) in dichloromethane (1.0 mL) was added dropwise to a stirred solution of tin(IV) chloride (0.75 mmol) in dichloromethane (0.75 mL) at −78°C. After 5 min, propargyltrimethylsilane (1.0 mmol) was added and the mixture was stirred for 1 h at −78°C. Saturated aqueous sodium hydrogen carbonate (5 mL) was added and the mixture was allowed to warm to room temperature before being partitioned between dichloromethane and water. The organic extract was washed with brine and dried (MgSO$_4$). The solvent was removed under reduced pressure and after flash chromatography with ethyl acetate/hexanes mixtures as eluent, compounds **3** were obtained in analytically pure form. Variable amounts of the isomerically pure more polar compounds **4** were isolated in all cases. Spectroscopic and analytical data for some representative pure forms of **3** follow.[31]

(3*R*,4*S*)-4-[(*R*)-1-Hydroxy-3-chloro-4-trimethylsilyl-2-butenyl]-3-methoxy-1-(2-propenyl)-2-azetidinone ((+)-3a): Starting with 4-oxoazetidine-2-carbaldehyde (+)-**1a** (96 mg, 0.568 mmol), and after chromatography of the residue with hexanes/ethyl acetate (1:1) as eluent, two fractions were obtained. The more polar fraction contained the chlorodiene (+)-**4a** (18 mg, 14%). The less polar fraction contained the allylic alcohol (+)-**3a** (61 mg, 34%) as a colorless oil. $[\alpha]_D = +11.8$ ($c = 1.2$ in CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$, 25°C): $\delta = 5.76$ (m, 1H), 5.42 (d, $J = 7.6$ Hz, 1H), 5.22 (m, 2H), 4.82 (dd, $J = 7.6$, 2.9 Hz, 1H), 4.54 (d, $J = 4.9$ Hz, 1H), 4.13 (ddt, $J = 15.9$, 5.1, 1.5 Hz, 1H), 3.90 (dd, $J = 4.9$, 2.9 Hz, 1H), 3.69 (dd, $J = 6.8$, 1.5 Hz, 1H), 3.63 (s, 3H), 2.70 (brs, 1H), 1.91 (s, 2H), 0.09 (s, 9H); ^{13}C NMR

(75 MHz, $CDCl_3$, 25 °C): $\delta = 167.2$, 135.8, 131.6, 121.9, 118.4, 83.7, 68.2, 59.9, 59.6, 44.0, 30.9, −1.4; IR ($CHCl_3$): $\tilde{\nu} = 3422$, 1751 cm^{-1}; MS (CI): m/z (%): 320 (10) $[M + 3]^+$, 318 (22) $[M + H]^+$, 57 (100); elemental analysis calcd (%) for $C_{14}H_{24}NO_3SiCl$ (317.9): C 52.90, H 7.61, N 4.41, Cl 11.15; found: C 52.81, H 7.65, N 4.45, Cl 11.10.

(3*R*,4*S*)-1-(3-Butenyl)-4-[(*R*)-1-hydroxy-3-chloro-4-trimethylsilyl-2-butenyl]-3-phenoxy-2-azetidinone ((+)-3d): Starting with 4-oxoazetidine-2-carbaldehyde (+)-**1d** (92 mg,0.376 mmol), and after chromatography of the residue with hexanes/ethyl acetate (2:1) as eluent, two fractions were obtained. The more polar fraction contained the chlorodiene (+)-**4d** (17 mg, 15 %). The less polar fraction contained the allylic alcohol (+)-**3d** (81 mg, 55 %) as a colorless oil. $[\alpha]_D = +67.7$ ($c = 1.4$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.31$ (m, 2H), 7.07 (m, 3H), 5.79 (m, 1H), 5.43 (d, $J = 7.6$ Hz, 1H), 5.23 (d, $J = 4.9$ Hz, 1H), 5.14 (m, 2H), 4.94 (m, 1H), 4.09 (t, $J = 4.9$ Hz, 1H), 3.69 (dt, $J = 13.9$, 7.6 Hz, 1H), 3.21 (dt, $J = 13.9$, 7.1 Hz, 1H), 2.39 (m, 3H), 1.89 (s, 2H), 0.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 165.9$, 157.3, 136.5, 134.8, 129.6, 122.6, 121.9, 117.2, 115.8, 80.3, 68.6, 60.4, 40.9, 31.6, 30.9, −1.4; IR ($CHCl_3$): $\tilde{\nu} = 3426$, 1748 cm^{-1}; MS (CI): m/z (%): 396 (42) $[M + 3]^+$, 394 (100) $[M + H]^+$; elemental analysis calcd (%) for $C_{20}H_{28}NO_3SiCl$ (393.9): C 60.97, H 7.16, N 3.56, Cl 8.00; found: C 60.90, H 7.18, N 3.55, Cl 8.02.

(3*R*,4*S*)-4-[(*R*)-1-Hydroxy-3-chloro-4-trimethylsilyl-2-butenyl]-1-(*p*-methoxyphenyl)-3-(2-propenyloxy)-2-azetidinone ((+)-3e): Starting with 4-oxoazetidine-2-carbaldehyde (+)-**1e** (94 mg,0.36 mmol), and after chromatography of the residue with hexanes/ethyl acetate (2:1) as eluent, two fractions were obtained. The more polar fraction contained the chlorodiene (+)-**4e** (23 mg, 20 %). The less polar fraction contained the allylic alcohol (+)-**3e** (62 mg, 42 %) as a colorless oil. $[\alpha]_D = +67.7$ ($c = 1.4$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.43$ (d, $J = 9.1$ Hz, 2H), 6.89 (d, $J = 9.1$ Hz, 2H), 5.96 (m, 1H), 5.47 (d, $J = 7.6$ Hz, 1H), 5.35 (m, 2H), 5.10 (m, 1H), 4.82 (d, $J = 5.2$ Hz, 1H), 4.49 (ddt, $J = 12.6$, 5.3, 1.5 Hz, 1H), 4.29 (ddt, $J = 12.6$, 5.0, 1.2 Hz, 1H), 4.28 (dd, $J = 5.2$, 2.9 Hz, 1H), 3.79 (s, 3H), 3.00 (d, $J = 10.6$ Hz, 1H), 1.93 (s, 2H), 0.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 164.1$, 156.6, 135.4, 132.9, 130.2, 122.5, 119.0, 118.8, 114.5, 81.2, 72.8, 67.2, 59.3, 55.5, 30.7, 30.9, −1.5; IR ($CHCl_3$): $\tilde{\nu} = 3423$, 1750 cm^{-1}; MS (CI): m/z (%): 412 (43) $[M + 3]^+$, 410 (100) $[M + H]^+$; elemental analysis calcd (%) for $C_{20}H_{28}NO_4SiCl$ (409.9): C 58.59, H 6.88, N 3.42, Cl 8.65; found: C 58.66, H 6.86, N 3.43, Cl 8.68.

General methods for the preparation of chlorodienes 4 from 2-chloro-3-silapropenyl alcohols 3, method A: A solution of tin(IV) chloride (0.75 mmol) in dichloromethane (0.75 mL) was added dropwise to a stirred solution of the corresponding allylic alcohol **3** (0.5 mmol) at −78 °C in dichloromethane (1.0 mL), and the mixture was stirred for 2 h at −78 °C. Saturated aqueous sodium hydrogen carbonate (5 mL) was added, and the mixture was allowed to warm to room temperature before being partitioned between dichloromethane and water. The organic extract was washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure and after flash chromatography with ethyl acetate/hexanes mixtures as eluent, chlorodienes **4** were obtained in analytically pure form.

Method B: Methanesulfonyl chloride (0.60 mmol) and triethylamine (1.20 mmol) were sequentially added dropwise to a stirred solution of the corresponding allylic alcohol **3** (0.50 mmol), in dichloromethane (5 mL) at 0 °C, and the mixture was stirred for 30 minutes at 0 °C. The organic phase was washed with water (2 × 2 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue with ethyl acetate/hexanes mixtures as eluent, gave analytically pure chlorodienes **4**.

(3*R*,4*S*)-4-[(1*E*)-3-Chloro-1,3-butadienyl]-3-methoxy-1-(2-propenyl)-2-azetidinone ((+)-4a), method A: Starting with 2-chloro-3-silapropenyl alcohol (+)-**3a** (29 mg, 0.091 mmol), and after chromatography of the residue with hexanes/ethyl acetate (2:1) as eluent, the chlorodiene (+)-**4a** (9 mg, 45 %) was obtained as a colorless oil.

Method B: Starting with 2-chloro-3-silapropenyl alcohol (+)-**3a** (29 mg, 0.091 mmol), and after chromatography of the residue with hexanes/ethyl acetate (2:1) as eluent, the chlorodiene (+)-**4a** (17 mg, 80 %) was obtained as a colorless oil. $[\alpha]_D = +56.5$ ($c = 0.7$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 6.40$ (d, $J = 15.0$ Hz, 1H), 6.14 (dd, $J = 15.0$, 8.8 Hz, 1H), 5.72 (m, 1H), 5.46 (brs, 1H), 5.42 (brs, 1H), 5.23 (q, $J = 1.2$ Hz, 1H), 5.10 (dq, $J = 6.6$, 1.2 Hz, 1H), 4.61 (d, $J = 4.4$ Hz, 1H), 4.27 (dd, $J = 8.8$, 4.4 Hz, 1H), 4.05 (ddt, $J = 15.6$, 5.4, 1.5 Hz, 1H), 3.54 (m, 1H), 3.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 166.3$, 137.4, 132.9, 131.2, 128.5, 118.9, 117.0, 85.5, 59.1, 58.7, 42.8; IR ($CHCl_3$): $\tilde{\nu}$ 1749 cm^{-1}; MS (CI): m/z (%): 230 (40) $[M + 3]^+$, 228 (100) $[M + H]^+$; elemental analysis calcd (%) for $C_{11}H_{14}NO_2Cl$ (227.7): C 58.03, H 6.10, N 6.15, Cl 15.57; found: C 58.13, H 6.14, N 6.11, Cl 15.51.

(3*R*,4*S*)-1-(3-Butenyl)-4-[(1*E*)-3-chloro-1,3-butadienyl]-3-phenoxy-2-azetidinone ((+)-4d), method A: Starting with 2-chloro-3-silapropenyl alcohol (+)-**3d** (36 mg, 0.108 mmol), and after chromatography of the residue with hexanes/ethyl acetate (1:1) as eluent, the chlorodiene (+)-**4d** (11 mg, 46 %) was obtained as a colorless oil.

Method B: Starting with 2-chloro-3-silapropenyl alcohol (+)-**3d** (30 mg, 0.075 mmol), and after chromatography of the residue with hexanes/ethyl acetate (2:1) as eluent, the chlorodiene (+)-**4d** (18 mg, 79 %) was obtained as a colorless oil. $[\alpha]_D = +66.3$ ($c = 0.6$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 6.41$ (d, $J = 15.0$ Hz, 1H), 6.15 (dd, $J = 15.0$, 8.8 Hz, 1H), 5.78 (m, 1H), 5.41 (m, 2H), 5.32 (d, $J = 4.4$ Hz, 1H), 5.14 (m, 2H), 4.48 (dd, $J = 8.5$, 4.4 Hz, 1H), 3.52 (dt, $J = 14.4$, 7.3 Hz, 1H), 3.17 (dt, $J = 13.9$, 6.8 Hz, 1H), 2.34 (m, 2H); IR ($CHCl_3$): $\tilde{\nu} = 1750$ cm^{-1}; MS (CI): m/z (%): 306 (42) $[M + 3]^+$, 304 (100) $[M + H]^+$; elemental analysis calcd (%) for $C_{17}H_{18}NO_2Cl$ (303.8): C 67.21, H 5.97, N 4.61, Cl 11.67; found: C 67.29, H 5.95, N 4.60, Cl 11.70.

(3*R*,4*S*)-4-[(1*E*)-3-Chloro-1,3-butadienyl]-1-(*p*-methoxyphenyl)-3-(2-propenyloxy)-2-azetidinone ((+)-4e), method A: Starting with 2-chloro-3-silapropenyl alcohol (+)-**3e** (27 mg, 0.066 mmol), and after chromatography of the residue with hexanes/ethyl acetate (2:1) as eluent, the chlorodiene (+)-**4e** (11 mg, 50 %) was obtained as a colorless oil.

Method B: Starting with 2-chloro-3-silapropenyl alcohol (+)-**3e** (27 mg, 0.066 mmol), and after chromatography of the residue with hexanes/ethyl acetate (2:1) as eluent, the chlorodiene (+)-**4e** (19 mg, 90 %) was obtained as a colorless oil. $[\alpha]_D = +66.3$ ($c = 0.6$ in $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta = 7.35$ (dd, $J = 6.8$, 2.2 Hz, 2H), 6.86 (dd, $J = 6.8$, 2.2 Hz, 2H), 6.52 (d, $J = 15.0$ Hz, 1H), 6.28 (dd, $J = 15.0$, 8.0 Hz, 1H), 5.92 (m, 1H), 5.46 (brs, 1H), 5.44 (brs, 1H), 5.30 (m, 2H), 4.87 (d, $J = 4.8$ Hz, 1H), 4.72 (dd, $J = 7.9$, 4.8 Hz, 1H), 4.16 (m, 2H), 3.79 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta = 163.4$, 156.5, 137.4, 133.3, 132.6, 130.9, 128.8, 118.6, 118.4, 117.2, 114.4, 82.9; IR ($CHCl_3$): $\tilde{\nu} = 1748$ cm^{-1}; MS (CI): m/z (%): 322 (40) $[M + 3]^+$, 320 (100) $[M + H]^+$; elemental analysis calcd (%) for $C_{17}H_{18}NO_3Cl$ (319.8): C 63.85, H 5.67, N 4.38, Cl 11.09; found: C 63.92, H 5.65, N 4.39, Cl 11.06.

Zinc-promoted reaction between propargyl bromide and 4-oxoazetidine-2-carbaldehydes 1; general procedure for the synthesis of homopropargylic alcohols 7: Propargyl bromide (3.0 mmol) was added to a well stirred suspension of the corresponding aldehyde (1.0 mmol) and zinc dust (6.0 mmol) in THF/NH_4Cl (aq. sat.) (1:5, 5 mL) at 0 °C. After disappearance of the starting material (TLC), the mixture was extracted with ethyl acetate (3 × 5 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue with ethyl acetate/hexanes mixtures gave analytically pure compounds. Spectroscopic and analytical data for some representative pure forms of **7** follow.

(3*R*,4*S*)-1-(3-Butenyl)-4-[(*R*)-1-hydroxy-3-butynyl]-3-methoxy-2-azetidinone ((+)-7b): Starting with aldehyde (+)-**1c** (59 mg, 0.322 mmol), and after chromatography of the residue with hexanes/ethyl acetate (1:1) as eluent, compound (+)-**7b** (36 mg, 50 %) was obtained as a colorless oil. $[\alpha]_D = +57.5$ ($c = 0.6$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 5.76$ (m, 1H), 5.10 (m, 2H), 4.46 (d, $J = 4.6$ Hz, 1H), 3.99 (m, 1H), 3.94 (d, $J = 5.0$ Hz, 1H), 3.63 (m, 1H), 3.59 (s, 3H), 3.22 (ddd, $J = 13.9$, 6.8, 5.9 Hz, 1H), 2.69 (d, $J = 3.7$ Hz, 1H), 2.53 (ddd, $J = 6.3$, 2.7, 1.2 Hz, 1H), 2.39 (m, 2H), 2.12 (t, $J = 2.7$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 167.6$, 134.9, 117.1, 82.8, 79.7, 71.6, 69.2, 59.3, 59.0, 40.8, 31.8, 24.1; IR ($CHCl_3$): $\tilde{\nu} = 3424$, 1748 cm^{-1}; MS (CI): m/z (%): 224 (100) $[M + H]^+$, 223 (18) $[M]^+$; elemental analysis calcd (%) for $C_{12}H_{17}NO_3$ (223.3): C 64.55, H 7.67, N 6.27; found: C 64.61, H 7.64, N 6.25.

Preparation of homopropargylic alcohols (+)-7c and (+)-8c: Starting with aldehyde (+)-**1g** (68 mg, 0.407 mmol), and after chromatography of the residue with hexanes/ethyl acetate (1:1) as eluent, 49 mg (58 %) of the less polar compound (+)-**7c** and 5 mg (6 %) of the more polar compound (+)-**8c** were obtained.

(3*R*,4*S*)-4-[(*R*)-1-Hydroxy-3-butynyl]-3-methoxy-1-(2-propynyl)-2-azetidinone ((+)-7c): Colorless oil. $[\alpha]_D = +1.5$ ($c = 0.8$ in $CHCl_3$); ^1H NMR

(300 MHz, $CDCl_3$, 25°C): $\delta = 4.50$ (d, $J = 4.7$ Hz, 1H), 4.34 (dd, $J = 17.6$, 2.4 Hz, 1H), 4.02 (d, $J = 4.7$ Hz, 1H), 4.01 (s, 1H), 3.97 (dd, $J = 17.6$, 2.4 Hz, 1H), 3.59 (s, 3H), 2.56 (dt, $J = 5.6$, 2.7 Hz, 1H), 2.32 (t, $J = 2.7$ Hz, 1H), 2.11 (t, $J = 2.7$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta = 166.7$, 83.1, 79.7, 76.7, 72.9, 71.4, 68.9, 59.4, 59.1, 30.9, 24.1; IR ($CHCl_3$): $\tilde{\nu} = 3422$, 1747 cm^{-1}; MS (CI): *m/z* (%): 208 (100) [*M* + H]$^+$, 207 (13) [*M*]$^+$; elemental analysis calcd (%) for $C_{11}H_{13}NO_3$ (207.2): C 63.76, H 6.32, N 6.76; found: C 63.59, H 6.31, N 6.77.

(3*R*,4*S*)-4-[(*S*)-1-Hydroxy-3-butynyl]-3-methoxy-1-(2-propynyl)-2-azetidinone ((+)-8c): Colorless oil. $[\alpha]_D = +107.3$ ($c = 1.4$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 4.64$ (d, $J = 4.9$ Hz, 1H), 4.29 (dd, $J = 17.8$, 2.7 Hz, 1H), 4.07 (d, $J = 4.9$ Hz, 1H), 3.88 (dd, $J = 17.8$, 2.4 Hz, 1H), 3.64 (s, 3H), 2.95 (d, $J = 7.8$ Hz, 1H), 2.61 (dt, $J = 6.1$, 2.7 Hz, 1H), 2.31 (t, $J = 2.7$ Hz, 1H), 2.10 (t, $J = 2.7$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta = 166.4$, 84.3, 78.5, 73.2, 70.9, 68.4, 59.5, 58.5, 30.0, 24.2; IR ($CHCl_3$): $\tilde{\nu} = 3421$, 1748 cm^{-1}; MS (CI): *m/z* (%): 208 (100) [*M* + H]$^+$, 207 (16) [*M*]$^+$; elemental analysis calcd (%) for $C_{11}H_{13}NO_3$ (207.2): C 63.76, H 6.32, N 6.76; found: C 63.82, H 6.31, N 6.75.

(3*R*,4*S*)-4-[(*R*)-1-Hydroxy-3-butynyl]-3-methoxy-1-(4-pentynyl)-2-azetidinone ((+)-7e): Starting with aldehyde (+)-**1i** (62 mg, 0.315 mmol), and after chromatography of the residue with hexanes/ethyl acetate (1:1) as eluent, compound (+)-**7e** (45 mg, 60%) was obtained as a colorless oil. $[\alpha]_D = +68.6$ ($c = 0.6$ in $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$, 25°C): $\delta = 4.47$ (d, $J = 4.7$ Hz, 1H), 4.03 (m, 1H), 3.89 (d, $J = 4.7$ Hz, 1H), 3.60 (s, 3H), 3.57 (m, 1H), 3.32 (ddd, $J = 13.9$, 7.6, 6.3 Hz, 1H), 2.68 (d, $J = 3.9$ Hz, 1H), 2.54 (dd, $J = 6.3$, 2.7 Hz, 2H), 2.25 (m, 2H), 2.12 (t, $J = 2.7$ Hz, 1H), 1.99 (t, $J = 2.7$ Hz, 1H), 1.88 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C): $\delta = 167.6$, 83.0, 82.8, 79.7, 71.6, 69.2, 69.1, 59.4, 59.3, 41.1, 26.4, 24.1, 16.2; IR ($CHCl_3$): $\tilde{\nu} = 3423$, 1748 cm^{-1}; MS (CI): *m/z* (%): 236 (100) [*M* + H]$^+$, 235 (19) [*M*]$^+$; elemental analysis calcd (%) for $C_{13}H_{17}NO_3$ (235.3): C 66.36, H 7.28, N 5.95; found: C 66.43, H 7.31, N 5.93.

Indium-promoted reaction between 1-bromo-2-butyne and 4-oxoazetidine-2-carbaldehydes 1; general procedure for the synthesis of *α*-allenic alcohols 13: 1-Bromo-2-butyne (3.0 mmol) was added to a well stirred suspension of the corresponding 4-oxoazetidine-2-carbaldehyde **1** (1.0 mmol) and indium powder (6.0 mmol) in THF/NH_4Cl (aq. sat.) (1:5, 5 mL) at 0°C. After disappearance of the starting material (TLC) the mixture was extracted with ethyl acetate (3 × 5 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue with ethyl acetate/hexanes or dichloromethane/ethyl acetate mixtures gave analytically pure compounds. Spectroscopic and analytical data for some representative pure forms of **13** follow.

(3*R*,4*S*)-4-[(*R*)-1-Hydroxy-2-methyl-2,3-butadienyl]-3-methoxy-1-(2-propenyl)-2-azetidinone ((+)-13a): Starting with aldehyde (+)-**1a** (50 mg, 0.298 mmol), and after chromatography of the residue with hexanes/ethyl acetate (1:2) as eluent, compound (+)-**13a** (50 mg, 75%) was obtained as a colorless oil. $[\alpha]_D = +99.1$ ($c = 0.7$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 5.76$ (m, 1H), 5.18 (m, 2H), 4.80 (m, 2H), 4.47 (d, $J = 5.0$ Hz, 1H), 4.24 (s, 1H), 4.13 (ddt, $J = 15.6$, 5.1, 1.7 Hz, 1H), 3.95 (t, $J = 4.9$ Hz, 1H), 3.73 (ddt, $J = 15.6$, 6.8, 1.2 Hz, 1H), 3.57 (s, 3H), 2.58 (d, $J = 4.4$ Hz, 1H), 1.78 (td, $J = 3.2$, 0.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta = 205.5$, 167.4, 132.1, 118.0, 99.7, 83.6, 77.3, 70.3, 59.6, 59.2, 43.9, 16.0; IR ($CHCl_3$): $\tilde{\nu} = 3424$, 2991, 1940, 1748 cm^{-1}; MS (CI): *m/z* (%): 224 (100) [*M* + H]$^+$, 223 (21) [*M*]$^+$; elemental analysis calcd (%) for $C_{12}H_{17}NO_3$ (223.3): C 64.55, H 7.67, N 6.27; found: C 64.62, H 7.65, N 6.29.

(3*R*,4*S*)-4-[(*R*)-1-Hydroxy-2-methyl-2,3-butadienyl]-3-methoxy-1-(2-propynyl)-2-azetidinone ((+)-13f): Starting with aldehyde (+)-**1g** (54 mg, 0.324 mmol), and after chromatography of the residue with hexanes/ethyl acetate (2:3) as eluent, compound (+)-**13f** (54 mg, 75%) was obtained as a colorless oil. $[\alpha]_D = +58.1$ ($c = 0.9$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 4.86$ (m, 2H), 4.49 (d, $J = 4.9$ Hz, 1H), 4.36 (dd, $J = 17.6$, 2.4 Hz, 1H), 4.26 (m, 1H), 4.06 (t, $J = 4.9$ Hz, 1H), 3.89 (dd, $J = 17.6$, 2.4 Hz, 1H), 3.57 (s, 3H), 2.57 (d, $J = 4.9$ Hz, 1H), 2.26 (t, $J = 2.4$ Hz, 1H), 1.82 (td, $J = 3.2$, 0.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta = 205.4$, 166.8, 99.5, 83.8, 77.4, 72.3, 70.3, 59.6, 59.1, 30.8, 15.9; IR ($CHCl_3$): $\tilde{\nu} = 3425$, 2990, 1941, 1747 cm^{-1}; MS (CI): *m/z* (%): 222 (100) [*M* + H]$^+$, 221 (14) [*M*]$^+$; elemental analysis calcd (%) for $C_{12}H_{15}NO_3$ (221.3): C 65.14, H 6.83, N 6.33; found: C 65.21, H 6.81, N 6.35.

(3*R*,4*S*)-1-(3-Butynyl)-4-[(*R*)-1-hydroxy-2-methyl-2,3-butadienyl]-3-methoxy-2-azetidinone ((+)-13g): Starting with aldehyde (+)-**1h** (137 mg, 0.756 mmol), and after chromatography of the residue with hexanes/ethyl acetate (1:1) as eluent, compound (+)-**13g** (123 mg, 69%) was obtained as a colorless oil. $[\alpha]_D = +40.2$ ($c = 1.0$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 4.84$ (td, $J = 3.2$, 1.0 Hz, 1H), 4.48 (d, $J = 4.8$ Hz, 1H), 4.25 (m, 1H), 4.03 (t, $J = 4.8$ Hz, 1H), 3.59 (m, 1H), 3.58 (s, 3H), 3.36 (dt, $J = 13.7$, 6.8 Hz, 1H), 2.59 (d, $J = 4.6$ Hz, 1H), 2.50 (td, $J = 7.3$, 2.7 Hz, 1H), 1.99 (t, $J = 2.7$ Hz, 1H), 1.81 (t, $J = 3.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta = 205.4$, 167.6, 99.7, 83.5, 81.2, 77.3, 70.4, 70.0, 59.9, 59.6, 40.2, 17.9, 16.1; IR ($CHCl_3$): $\tilde{\nu} = 3424$, 2989, 1940, 1745 cm^{-1}; MS (CI): *m/z* (%): 236 (100) [*M* + H]$^+$, 235 (17) [*M*]$^+$; elemental analysis calcd (%) for $C_{13}H_{17}NO_3$ (235.3): C 66.36, H 7.28, N 5.95; found: C 66.43, H 7.26, N 5.94.

Preparation of *α*-allenic alcohols (+)-13h and (+)-14h: Starting with aldehyde (+)-**1j** (55 mg, 0.234 mmol), and after chromatography of the residue with dichloromethane/ethyl acetate (9:1) as eluent, 47 mg (70%) of the less polar compound (+)-**13h** and 5 mg (7%) of the more polar compound (+)-**14h** were obtained.

(3*R*,4*S*)-4-[(*R*)-1-hydroxy-2-methyl-2,3-butadienyl]-3-methoxy-1-(*p*-methoxyphenyl)-2-azetidinone ((+)-13h): Colorless solid. m.p. 117–119°C; $[\alpha]_D = +213.8$ ($c = 0.7$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 7.33$ (d, $J = 9.0$ Hz, 2H), 6.87 (d, $J = 9.0$ Hz, 2H), 4.48 (d, $J = 4.9$ Hz, 1H), 4.65 (m, 3H), 4.40 (dd, $J = 4.9$, 3.4 Hz, 1H), 3.79(s, 3H), 3.67 (s, 3H), 3.07 (d, $J = 40.0$ Hz, 1H), 1.83 (t, $J = 3.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta = 205.5$, 164.2, 156.7, 129.9, 119.6, 114.4, 99.1, 84.1, 81.2, 76.3, 69.3, 59.9, 59.1, 55.5, 15.7; IR ($CHCl_3$): $\tilde{\nu} = 3422$, 2990, 1940, 1748 cm^{-1}; MS (CI): *m/z* (%): 290 (100) [*M* + H]$^+$, 289 (16) [*M*]$^+$; elemental analysis calcd (%) for $C_{16}H_{19}NO_4$ (289.3): C 66.42, H 6.62, N 4.84; found: C 66.50, H 6.60, N 4.83.

(3*R*,4*S*)-4-[(*S*)-1-hydroxy-2-methyl-2,3-butadienyl]-3-methoxy-1-(*p*-methoxyphenyl)-2-azetidinone ((+)-14h): Colorless oil. $[\alpha]_D = +753.5$ ($c = 0.8$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 7.31$(d, $J = 9.0$ Hz, 2H), 6.88 (d, $J = 9.0$ Hz, 2H), 4.68 (m, 2H), 4.59 (d, $J = 5.0$ Hz, 1H), 4.48 (t, $J = 5.0$ Hz, 1H), 4.39 (s, 1H), 3.79(s, 3H), 3.64 (s, 3H), 2.42 (d, $J = 4.6$ Hz, 1H), 1.78 (t, $J = 3.0$ Hz, 3H); IR ($CHCl_3$): $\tilde{\nu} = 3420$, 2993, 1940, 1747 cm^{-1}; MS (CI): *m/z* (%): 290 (100) [*M* + H]$^+$, 289 (21) [*M*]$^+$; elemental analysis calcd (%) for $C_{16}H_{19}NO_4$ (289.3): C 66.42, H 6.62, N 4.84; found: C 66.35, H 6.64, N 4.83.

Preparation of *α*-allenic alcohols (±)-13i and (±)-14i: Starting with aldehyde (±)-**1l** (48 mg,0.208 mmol), and after chromatography of the residue with hexanes/ethyl acetate (1:1) as eluent, 32 mg (54%) of the less polar compound (±)-**13i** and 4 mg (6%) of the more polar compound (±)-**14i** were obtained.

(3*RS*,4*SR*)-4-[(*RS*)-1-hydroxy-2-methyl-2,3-butadienyl]-3-methoxy-1-(*p*-methoxyphenyl)-2-azetidinone ((±)-13i): Colorless oil. ^1H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 6.87$ (dd, $J = 6.8$, 2.4 Hz, 2H), 7.31 (dd, $J = 6.8$, 2.4 Hz, 2H), 6.19 (ddd, $J = 17.3$, 10.3, 7.8 Hz, 1H), 5.49 (dt, $J = 17.3$, 1.5 Hz, 1H), 5.32 (m, 1H), 4.74 (m, 1H), 4.62 (m, 1H), 4.58 (m, 1H), 4.37 (dd, $J = 5.6$, 4.2 Hz, 1H), 4.05 (m, 1H), 3.79 (s, 3H), 2.07 (d, $J = 5.4$ Hz, 1H), 1.76 (t, $J = 3.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta = 205.8$, 165.6, 156.5, 130.2, 130.1, 120.4, 119.8, 114.3, 98.7, 77.3, 69.3, 58.0, 55.5, 15.5; IR ($CHCl_3$): $\tilde{\nu} = 3425$, 2993, 1942, 1746 cm^{-1}; MS (CI): *m/z* (%): 286 (100) [*M* + H]$^+$, 285 (23) [*M*]$^+$; elemental analysis calcd (%) for $C_{17}H_{19}NO_3$ (285.3): C 71.56, H 6.71, N 4.91; found: C 71.50, H 6.73, N 4.89.

(3*RS*,4*SR*)-4-[(*SR*)-1-hydroxy-2-methyl-2,3-butadienyl]-3-methoxy-1-(*p*-methoxyphenyl)-2-azetidinone ((±)-14i): Colorless oil. ^1H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 7.32$ (dd, $J = 6.8$, 2.4 Hz, 2H), 6.89 (dd, $J = 6.8$, 2.4 Hz, 2H), 5.43 (dt, $J = 17.3$, 1.2 Hz, 1H), 5.32 (dq, $J = 10.2$, 1.0 Hz, 1H), 4.81 (ddd, $J = 10.3$, 3.2, 2.4 Hz, 1H), 4.63 (ddd, $J = 10.3$, 3.2, 2.4 Hz, 1H), 4.44 (dd, $J = 7.3$, 5.9 Hz, 1H), 3.96 (m, 1H), 4.17 (m, 1H), 3.78 (s, 3H), 2.08 (d, $J = 6.1$ Hz, 1H), 1.79 (t, $J = 3.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta = 205.8$, 165.9, 156.3, 131.3, 128.9, 121.0, 120.4, 113.9, 99.0, 77.6, 72.8, 58.4, 55.4, 55.0, 15.6; IR ($CHCl_3$): $\tilde{\nu} = 3424$, 2991, 1941, 1745 cm^{-1}; MS (CI): *m/z* (%): 286 (100) [*M* + H]$^+$, 285 (15) [*M*]$^+$; elemental analysis calcd (%) for $C_{17}H_{19}NO_3$ (285.3): C 71.56, H 6.71, N 4.91; found: C 71.63, H 6.72, N 4.93.

(3*R*,4*S*)-4-[(*R*)-1-Hydroxy-2-phenyl-2,3-butadienyl]-3-methoxy-1-(2-propenyl)-2-azetidinone ((+)-13k): Starting with aldehyde (+)-**1a** (56 mg, 0.331 mmol), and after chromatography of the residue with hexanes/ethyl acetate (2:1) as eluent, compound (+)-**13k** (60 mg, 64%) was obtained as a colorless oil. $[\alpha]_D = +70.6$ ($c = 1.0$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 7.39$ (m, 5H), 5.78 (m, 1H), 5.24 (m, 3H), 4.94 (m, 1H), 4.47 (d,

$J = 4.9$ Hz, 1 H), 4.16 (ddt, $J = 15.5$, 5.3, 1.6 Hz, 1 H), 4.04 (dd, $J = 5.6$, 4.9 Hz, 1 H), 3.82 (ddt, $J = 15.5$, 6.7, 1.0 Hz, 1 H), 3.63 (d, $J = 4.9$ Hz, 1 H), 3.53 (s, 3 H), 2.58 (d, $J = 5.1$ Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 207.7$, 167.4, 133.9, 132.0, 128.6, 127.4, 126.7, 118.2, 107.0, 83.6, 80.6, 68.7, 59.8, 59.6, 44.1; IR ($CHCl_3$): $\tilde{\nu} = 3424$, 2991, 1940, 1748 cm^{-1}; MS (CI): m/z (%): 286 (100) $[M + H]^+$, 285 (31) $[M]^+$; elemental analysis calcd (%) for $C_{17}H_{19}NO_3$ (285.3): C 71.56, H 6.71, N 4.91; found: C 71.48, H 6.69, N 4.92.

General procedure for the synthesis of tricyclic 2-azetidinones 18: Solid $[Co_2(CO)_8]$ (0.21 g, 0.6 mmol) was added to a solution of the corresponding allenyne (0.5 mmol) in anhydrous CH_2Cl_2 (7 mL) under argon. The dark solution thus obtained was stirred at room temperature until complete complex formation by TLC (ca 1 h) The resulting solution of $[Co_2(CO)_6]$–alkyne complex was cooled to 0 °C and solid anhydrous TMANO (0.08 g, 1 mmol) was added. The reaction flask was warmed to room temperature by immediate removal of the ice bath. After 30 min, the reaction was again cooled to 0 °C, solid anhydrous TMANO (0.08 g, 1 mmol) was added, and the solution was warmed again to room temperature by immediate removal of the ice bath. This sequence was repeated until a total of 3 mmol (0.24 g) of anhydrous TMANO was added. After that, the solution was stirred for 1 h at room temperature. The crude mixture was diluted with AcOEt (20 mL), filtereed through a short path of Celite, and the solvent was removed under reduced pressure. Chromatography of the residue with hexanes/ethyl acetate mixtures as eluent gave analytically pure tricycles **18**.

Tricyclic azetidinone (+)-18a: Starting with allenyne (+)-**13f** (49 mg, 0.222 mmol), and after chromatography of the residue with ethyl acetate as eluent compound (+)-**18a** (22 mg, 40%) was obtained as a colorless oil. $[\alpha]_D = +183.1$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6, 25 °C): $\delta = 6.09$ (s, 1 H), 5.89 (s, 1 H), 3.79 (d, $J = 5.0$ Hz, 1 H), 3.44 (m, 1 H), 3.23 (d, $J = 5.0$ Hz, 1 H), 3.09 (m, 1 H), 3.03 (s, 3 H), 2.87 (d, $J = 2.0$ Hz, 1 H), 2.52 (t, $J = 10.1$ Hz, 1 H), 0.60 (d, $J = 7.7$ Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6, 25 °C): $\delta = 203.4$, 172.9, 162.5, 136.1, 120.9, 116.9, 85.9, 69.4, 59.8, 56.9, 41.4, 40.6, 20.8; IR ($CHCl_3$): $\tilde{\nu} = 3325$, 1746, 1705 cm^{-1}; MS (CI): m/z (%): 250 (100) $[M + H]^+$, 249 (19) $[M]^+$; elemental analysis calcd (%) for $C_{13}H_{15}NO_4$ (249.3): C 62.64, H 6.07, N 5.62; found: C 62.72, H 6.09, N 5.60.

Procedure for the palladium-catalyzed domino allene amidation/intramolecular Heck reaction of compound 20: Palladium(II) acetate (2.5 mg, 0.011 mmol), lithium bromide (51.2 mg, 0.59 mmol), potassium carbonate (20.2 mg, 0.146 mmol), and copper(II) acetate (46.5 mg, 0.256 mmol) were sequentially added to a stirred solution of the α-allenic tosylcarbamate **20** (51 mg, 0.122 mmol) in acetonitrile (5 mL). The resulting suspension was stirred at room temperature under an oxygen atmosphere for 16 h at room temperature. The organic phase was diluted with brine (2 mL), extracted with ethyl acetate (5 × 5 mL), washed with brine (2 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting first with hexanes/ethyl acetate (2:1) and later with ethyl acetate gave 25 mg (41%) of analytically pure compound **21**.

Tricyclic azetidinone (+)-21: Colorless oil. $[\alpha]_D = +14.0$ ($c = 0.9$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 7.95$ (d, $J = 8.5$ Hz, 1 H), 7.35 (d, $J = 8.5$ Hz, 1 H), 6.56 (dd, $J = 1.9$, 0.7 Hz, 1 H), 5.62 (s, 1 H), 5.42 (s, 1 H), 4.89 (dd, $J = 15.1$, 0.98 Hz, 1 H), 4.60 (dd, $J = 4.9$, 1.5 Hz, 1 H), 4.33 (s, 1 H), 3.94 (d, $J = 4.6$ Hz, 1 H), 3.58 (dt, $J = 15.1$, 1.7 Hz, 1 H), 3.55 (s, 3 H), 2.46 (s, 3 H), 1.97 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): $\delta = 165.8$, 150.9, 145.8, 144.6, 136.0, 135.3, 129.7, 128.7, 121.3, 111.3, 83.4, 79.3, 69.1, 59.3, 54.7, 45.2, 23.0, 21.7; IR ($CHCl_3$): $\tilde{\nu} = 1746$, 1740, 1348 cm^{-1}; MS (ESI): m/z (%): 521 (100) $[M\ (^{81}Br) + Na]^+$, 519 (88) $[M\ (^{79}Br) + Na]^+$; elemental analysis calcd (%) for $C_{20}H_{21}N_2SO_6Br$ (497.4): C 48.30, H 4.26, N 5.63; found: C 48.37, H 4.28, N 5.60.

General procedure for the palladium-catalyzed domino allene cyclization/intramolecular Heck reaction of allenols 13: Palladium(II) acetate (0.009 mmol), lithium bromide (0.49 mmol), potassium carbonate (0.12 mmol) and copper(II) acetate (0.21 mmol) were sequentially added to a stirred solution of the α-allenic alcohols **13** (0.10 mmol) in acetonitrile (5 mL). The resulting suspension was stirred at room temperature under an oxygen atmosphere for 16 h at room temperature. Compound **26c** needs an extra hour at reflux temperature. The organic phase was diluted with brine (2 mL), extracted with ethyl acetate (5 × 5 mL), washed with brine (2 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting first with hexanes/ethyl acetate (1:1) and later with ethyl acetate gave analytically pure compounds **26**.

Bridged tricyclic azetidinone (−)-26a: Starting with allenynol (+)-**13f** (67 mg, 0.305 mmol), compound (−)-**26a** (43 mg, 48%) was obtained as a colorless oil. $[\alpha]_D = +14.0$ ($c = 0.9$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 6.56$ (t, $J = 1.5$ Hz, 1 H), 4.61 (dd, $J = 4.6$, 1.2 Hz, 1 H), 4.56 (d, $J = 4.0$ Hz, 1 H), 4.47 (dd, $J = 15.0$, 1.5 Hz, 1 H), 4.32 (d, $J = 11.2$ Hz, 1 H), 4.07 (d, $J = 11.2$ Hz, 1 H), 3.88 (t, $J = 4.6$ Hz, 1 H), 3.87 (d, $J = 15.0$ Hz, 1 H), 3.64 (s, 3 H), 2.00 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): $\delta = 167.0$, 141.7, 139.6, 130.0, 109.2, 84.4, 71.8, 55.1, 45.8, 43.4, 16.5; IR ($CHCl_3$): $\tilde{\nu} = 1745$ cm^{-1}; MS (ESI): m/z (%): 324 (100) $[M\ (^{81}Br) + Na]^+$, 322 (86) $[M\ (^{79}Br) + Na]^+$; elemental analysis calcd (%) for $C_{12}H_{14}NO_3Br$ (300.2): C 48.02, H 4.70, N 4.67; found: C 48.09, H 4.72, N 4.65.

Bridged tricyclic azetidinone (±)-26c: Starting with allenynol (±)-**13j** (42 mg, 0.141 mmol), compound (±)-**26c** (28 mg, 52%) was obtained as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 7.30$ and 6.85 (dd, $J = 6.8$, 2.2 Hz, each 2 H), 5.81 (d, $J = 2.4$ Hz, 1 H), 4.30 (t, $J = 6.0$ Hz, 1 H), 3.89 (d, $J = 6.0$ Hz, 1 H), 3.84 (d, $J = 9.5$ Hz, 1 H), 3.78 (s, 3 H), 3.65 (ddd, $J = 12.0$, 6.0, 1.5 Hz, 1 H), 3.43 (d, $J = 9.5$ Hz, 1 H), 2.92 (dt, $J = 15.9$, 1.2 Hz, 1 H), 2.40 (m, 1 H), 1.31 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): $\delta = 165.3$, 155.9, 146.4, 146.0, 134.1, 132.0, 130.2, 117.8, 114.3, 75.4, 70.8, 55.4, 50.2, 45.3, 20.4, 14.5; IR ($CHCl_3$): $\tilde{\nu} = 1747$ cm^{-1}; MS (ESI): m/z (%): 400 (100) $[M\ (^{81}Br) + Na]^+$, 398 (88) $[M\ (^{79}Br) + Na]^+$; elemental analysis calcd (%) for $C_{18}H_{18}NO_3Br$ (376.3): C 57.46, H 4.82, N 3.72; found: C 57.53, H 4.80, N 3.71.

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[31] Full spectroscopic and analytical data for compounds not included in the Experimental Section are described in the Supporting Information.

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