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Regioselectivity Control in the Metal-Catalyzed O–C Functionalization of γ-Allenols, Part 1: Experimental Study[#]

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Dedicated to Professor Franco Fernández on the occasion of his 65th birthday

Abstract: We describe versatile regiocontrolled metal-catalyzed heterocyclization reactions of γ-allenol derivatives leading to a variety of fused enantiopure tetrahydrofurans, dihydropyrans, and tetrahydrooxepines. Regioselectivity control in the O–C functionalization of γ-allenols can be achieved through the choice of catalyst: use of $AuCl_3$ exclusively affords tetrahydrofurans, use of $La[N(SiMe_3)_2]_3$ usually favors the formation of dihydropyrans, whereas use of $PdCl_2$ solely gives tetrahydrooxepines. In addition, it has been observed that for the Au-catalyzed cycloisomerization, the presence of a methoxymethyl protecting group not only masks a hydroxy functionality, but also exerts directing effects as a controlling unit in a regioselectivity reversal (7-*endo* versus 5-*exo* cyclization). In addition, the regioselectivity of the La-catalyzed cycloetherification can be tuned (5-*exo* versus 7-*endo*) simply through a subtle variation in the substitution pattern of the allene component (Ph versus Me). Thus, for the first time the regiocontrolled heterocyclization of γ-allenol derivatives is both catalyst- and substrate-directable. These metal-catalyzed heterocyclization reactions have been developed experimentally (Part 1, this paper), and their mechanisms have additionally been investigated by a theoretical study (Part 2, accompanying paper).

Keywords: allenes · cyclization · gold · heterocycles · palladium

Introduction

β-Lactams are among the most important pharmacophores for treatment of diseases caused by bacterial infections.[1] Additionally, there are many important non-antibiotic uses of azetidin-2-ones in fields ranging from enzyme inhibition[2] to gene activation.[3] These biological activities, combined with the use of these products as starting materials in the preparation of α- and β-amino acids, alkaloids, heterocycles, taxoids, and other types of compounds of biological and medicinal interest,[4] provide the motivation to explore new methodologies for the synthesis of substances based on the β-lactam core.

In addition, tetrahydrofuran, dihydropyran, and oxepane ether rings are ubiquitous structural units extensively encountered in a number of biologically active natural products and functional molecules, and their stereocontrolled synthesis therefore remains an intensively investigated research area.[5]

On the other hand, allene chemistry has attracted considerable attention in recent years.[6] In particular, the transition-metal-catalyzed cyclization of allene derivatives bearing nucleophilic substituents—such as hydroxy, carbonyl, carboxy, thio, and amino groups—has led to many synthetically useful transformations.[7] Regioselectivity problems (*endo-trig* versus *exo-dig* versus *exo-trig* cyclization) are significant, however. In a preliminary study,[8] the metal-catalyzed regiocontrolled cyclization of azetidin-2-one-tethered methyl-γ-allenols to give tetrahydrofurans and tetrahydrooxepines

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[#] For Part 2, see ref. [10].

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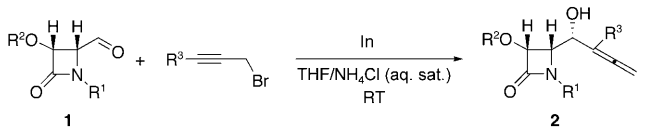
was accomplished. The regioselectivities observed in these reactions were substantially different, when applicable, from those reported for related simple reactants and suggested that the regioselectivity was strongly modulated both by the nature of the metal (gold versus palladium) and by the status of the hydroxy group (i.e., free or protected) in the methyl-γ-allenol. In continuation of our investigations into heterocyclic and allene chemistry,[9] here we report a systematic study of the metal-catalyzed (Au, Ag, Pt, Pd, and La) heterocyclization reactions of methyl- and phenyl-γ-allenols, which fully confirms and extends our earlier conclusions and establishes versatile and regiocontrolled routes to a variety of enantiopure fused tetrahydrofuran-, dihydropyran-, and tetrahydrooxepine-β-lactams. In addition, the mechanisms of these metal-catalyzed cycloetherification reactions have also been investigated theoretically (Part 2, accompanying paper, see ref. [10]).

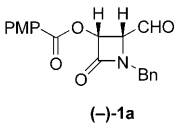
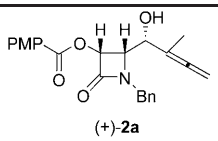
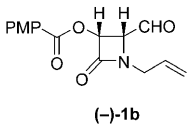
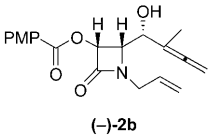
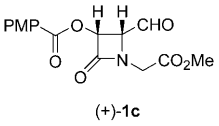
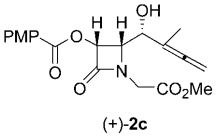
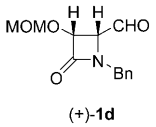
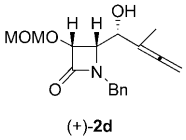
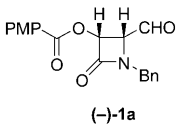
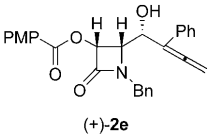
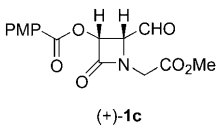
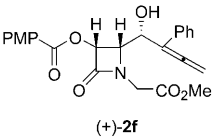
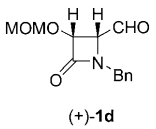
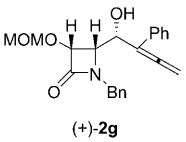
Results and Discussion

Precursors for the formation of five-, six-, and seven-membered oxacycles—the enantiopure γ-allenols **4a–g**—were readily prepared in good overall yield from the appropriate starting carbaldehydes **1a–d** through regiocontrolled indium-mediated Barbier-type carbonyl-allenylation reactions in aqueous media to give α-allenols **2a–g** (Table 1),[11] followed by protecting group manipulation. α-Allenols **2** were protected as the corresponding ethers (methoxymethyl and *tert*-butyldimethylsilyl) or esters (acetate and benzoate) **3a–j**, which were easily converted into γ-allenols **4a–g** (Table 2). Because of steric hindrance, phenyl-α-allenols **2e–g** could not be protected as their corresponding *tert*-butyldimethylsilyl ethers.

Table 1. Preparation of α-allenic alcohols **2**.



1 **2**

Aldehyde	α-Allenol	Yield [%][a]
 **(–)-1a**	 **(+)-2a**	68
 **(–)-1b**	 **(–)-2b**	61
 **(+)-1c**	 **(+)-2c**	65
 **(+)-1d**	 **(+)-2d**	63
 **(–)-1a**	 **(+)-2e**	74
 **(+)-1c**	 **(+)-2f**	55
 **(+)-1d**	 **(+)-2g**	60

[a] Yield of pure, isolated product with correct analytical and spectral data. α-Allenols **2** were obtained as single isomers (de >95%), except in the case of compound **2b** (de 70%). PMP = 4-MeOC$_6$H$_4$, MOM = MeOCH$_2$.

Firstly, the general reactivity of γ-allenols toward the regioselective hydroalkoxylation reaction was tested with substrate **4a** in the presence of $[PtCl_2(CH_2{=}CH_2)]_2$, $AgNO_3$, AuCl, and $AuCl_3$ as catalysts (Table 3). $[PtCl_2(CH_2{=}CH_2)]_2$ and $AgNO_3$ afforded rather low yields or disappointing diastereomeric mixtures of bicycle **5a**.[12,13] Although $AgNO_3$ was less diastereoselective than $[PtCl_2(CH_2{=}CH_2)]_2$ (60:40 vs 100:0), it was a more efficient catalyst, affording adduct **5a** in reasonable yield. Gratifyingly, we found that Au salts were effective as 5-*exo*-selective hydroalkoxylation catalysts.[14] $AuCl_3$ was selected as catalyst of choice because of

Abstract in Spanish: *La reacción de heterociclación de γ-alenoles catalizada por metales es un proceso regiocontrolado que da lugar a una amplia variedad de tetrahidrofuranos, tetrahidropiranos y tetrahidrooxepinas fusionadas enantiopuras. La regioselectividad en la funcionalización O–C se puede controlar y dirigir con la elección del catalizador: la utilización de $AuCl_3$ exclusivamente da lugar a tetrahidrofuranos, La[N(SiMe$_3$)$_2$]$_3$ normalmente genera dihidropiranos, mientras que $PdCl_2$ favorece la formación de tetrahidrooxepinas. Además, se ha observado que un grupo protector metoximetil no sólo enmascara una funcionalidad hidroxilo, sino que también controla un cambio regioquímico (ciclación* 7-endo *frente* a 5-exo*). Por otra parte, la regioselectividad de la cicloeterificación catalizada por La se puede revertir (*5-exo frente a 7-endo*) con un simple cambio en la sustitución del aleno (Ph frente a Me). Así, por primera vez la heterociclación regiocontrolada de derivados de γ-alenol se puede modular tanto por el catalizador como por el sustrato. Estas heterociclaciones catalizadas por metales se han desarrollado experimentalmente (Parte 1, este artículo) y además sus mecanismos han sido investigados teóricamente en detalle (Parte 2, artículo siguiente).*

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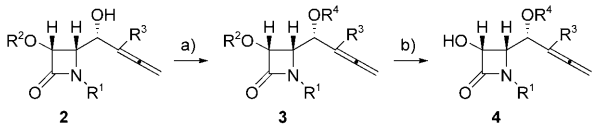
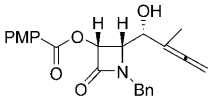
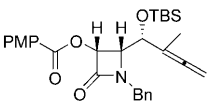
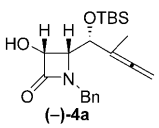
Table 2. Preparation of protected γ-allenols **3** and free γ-allenols **4**.



2 **3** **4**

Substrate	Protected γ-allenol	Yield [%][a]	γ-Allenol	Yield [%][a]
 (+)-**2a**	 (−)-**3a**	70	 (−)-**4a**	quant.
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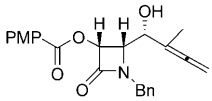
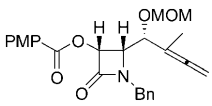
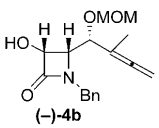
 (+)-**2a**	 (−)-**3b**	79	 (−)-**4b**	quant.
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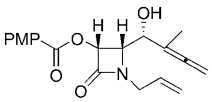
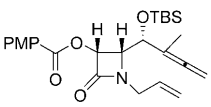
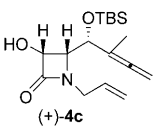
 (−)-**2b**	 (−)-**3c**	71	 (+)-**4c**	quant.
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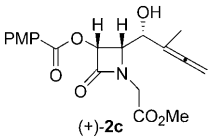
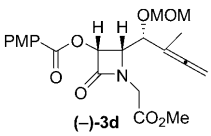
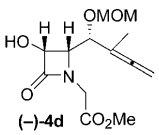
 (+)-**2c**	 (−)-**3d**	61	 (−)-**4d**	quant.
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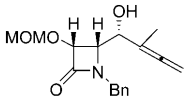
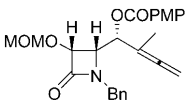
 (+)-**2d**	 (−)-**3e**	60		
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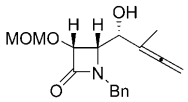
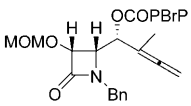
 (+)-**2d**	 (−)-**3f**	60		
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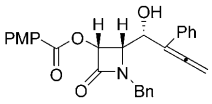
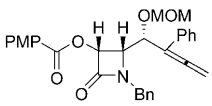
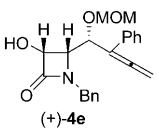
 (+)-**2e**	 (+)-**3g**	77	 (+)-**4e**	quant.
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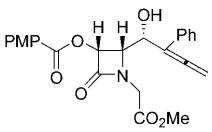
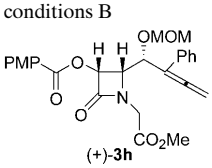
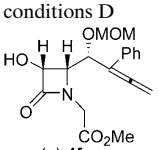
 (+)-**2f**	 (+)-**3h**	56	 (+)-**4f**	quant.
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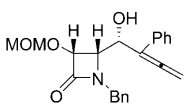
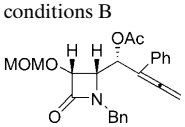
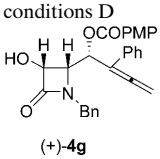
 (+)-**2g**	 (+)-**3i**	77	 (+)-**4g**	60
	conditions C		conditions E	

its superior performance. No regioisomeric products were detected, the fused five-membered oxacycle being obtained exclusively. Compounds **5** are remarkable because they each bear a quaternary stereocenter.[15] Qualitative homonuclear NOE difference spectra allowed us to assign the stereochemistry at the newly formed stereocenters of tetrahydrofurans **5**.

One of the challenges for modern synthesis is to create distinct types of complex molecules from identical starting materials solely through selection of catalyst. Thus, having found a solution for the 5-*exo*-selective hydroalkoxylation, we next examined the more intricate heterocyclizative problem associated with tuning of the regioselectivities of γ-allenols. Specifically, subjection of the γ-allenol **4a** to the lanthanide amide-catalyzed protocol did afford dihydropyran **6a** (Scheme 1), with the nucleophilic attack taking place at the central allene carbon through a 6-*endo* cyclization.[16] In addition, partial epimerization was observed through the isolation of *epi*-**6a**. Notably, the Pd^{II}-catalyzed cyclizative coupling reactions between γ-allenols **4a**, **4c**, and **4g** and allyl halides gave impressive yields (up to 94%) of the desired seven-membered adducts **7a**–**e** (Scheme 2), the results of 7-*endo* oxycyclization, as the sole products.[17] Particularly, judicious choice of catalyst (Au, La, or Pd) allows the ring size (five, six, or seven) of the fused oxacycle to be modulated.

Having demonstrated the stabilities of the benzoate and TBS protecting groups to the Au^{III}- or Pd^{II}-catalyzed conditions, we decided to see whether methoxymethyl substitution would have a beneficial impact on the cyclization reactions. In

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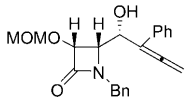
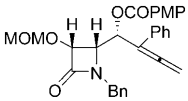
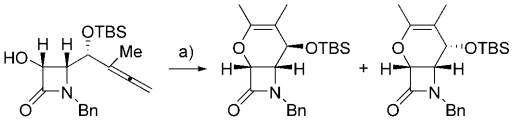
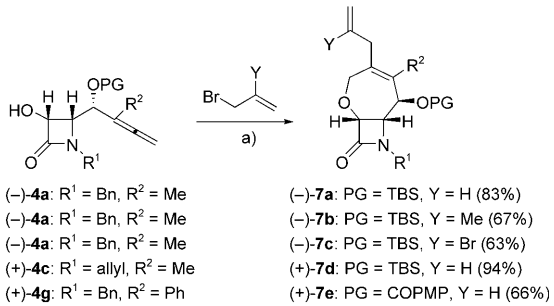
Table 2. (Continued)

Substrate	Protected γ-allenol	Yield [%][a]	γ-Allenol	Yield [%][a]
 (+)-**2g**	 (+)-**3j**	71		
conditions C				

[a] Yield of pure, isolated product with correct analytical and spectral data; PMP = 4-$MeOC_6H_4$, PBrP = 4-BrC_6H_4, MOM = $MeOCH_2$, TBS = *tert*-butyldimethylsilyl.

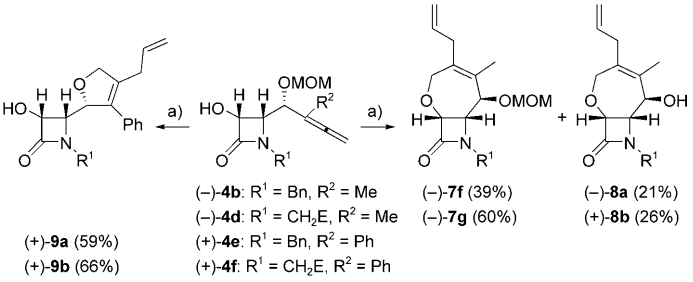


Scheme 1. Lanthanum-promoted preparation of six-membered oxacycles **6a** and *epi*-**6a**. a) 5 mol% $La[N(SiMe_3)_2]_3$, toluene, reflux; TBS = *tert*-butyldimethylsilyl.



Scheme 2. Palladium-promoted preparation of seven-membered oxacycles **7a–e**. a) $PdCl_2$ (5 mol%), DMF, RT; PMP = 4-$MeOC_6H_4$.

the event, appreciable extents of MOM cleavage were observed during the reactions of methyl-γ-allenols **4b** and **4d** with allyl bromide in the presence of $PdCl_2$ (Scheme 3). Surprisingly, though, the $PdCl_2$-catalyzed reactions between allyl bromide and phenyl-γ-allenols **4e** and **4f** afforded the dihydrofurans **9a** and **9b**, corresponding to the heterocyclizative coupling of the MOM-deprotected α-allenols (Scheme 3). Interestingly, when the two methyl-γ-allenols **4b** and **4d** and the

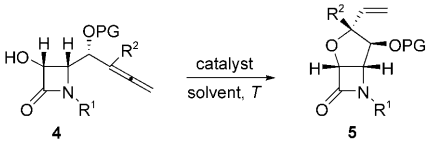


Scheme 3. Palladium-catalyzed heterocyclization reactions of γ-allenol derivatives **4b** and **4d–f**. a) $PdCl_2$ (5 mol%), allyl bromide, DMF, RT; MOM = $MeOCH_2$, E = CO_2Me.

phenyl-γ-allenol **4e** were treated with $AuCl_3$ the 2,5-dihydrofurans **10a–c** were the sole products (Scheme 4). These transformations may involve a chemoselective (5-*endo-trig* versus 7-*endo-trig*) allenol oxycyclization with concomitant MOM ether removal.[18]

In view of the above results, we decide to examine whether the metal-catalyzed preparation of bicycles **5** and **7** could be directly accomplished from MOM-protected γ-allenol derivatives **3**. In the event, MOM ethers **3e**, **3f**, **3i**, and **3j** remained unchanged in the presence of $PdCl_2$ and allyl bromide. Much to our delight though, when allenic MOM ethers **3e**, **3f**, **3i**, and **3j** were treated with $AuCl_3$, the 5-*exo* mode was completely abolished and replaced by a 7-*endo*

Table 3. Heterocyclization of γ-allenol derivatives **4** under modified metal-catalyzed hydroalkoxylation conditions.[a]



4 **5**

Allenol	R^1	R^2	PG	Catalyst	Bicycle	dr	Yield [%][b]
(–)-**4a**	Bn	Me	TBS	[Pt][c]	(+)-**5a**	100:0	12
(–)-**4a**	Bn	Me	TBS	$AgNO_3$[d]	(+)-**5a**	60:40	54
(–)-**4a**	Bn	Me	TBS	AuCl	(+)-**5a**	100:0	37
(–)-**4a**	Bn	Me	TBS	$AuCl_3$	(+)-**5a**	100:0	57
(–)-**4b**	Bn	Me	MOM	$AgNO_3$[d]	(+)-**5b**	100:0	47
(+)-**4c**	allyl	Me	TBS	$AuCl_3$	(+)-**5c**	100:0	58
(+)-**4g**	Bn	Ph	COPMP	$AuCl_3$	(+)-**5d**	100:0	50

[a] Reactions were conducted in CH_2Cl_2 at room temperature, except when otherwise stated. [b] Yield of pure, isolated product with correct analytical and spectral data. [c] [Pt] = $[PtCl_2(CH_2{=}CH_2)]_2$. [d] Reactions were conducted in acetone/H_2O 4:1 at reflux temperature; PMP = 4-$MeOC_6H_4$, MOM = $MeOCH_2$, TBS = *tert*-butyldimethylsilyl.

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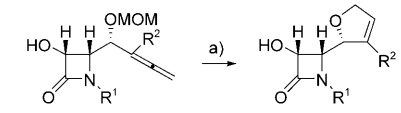
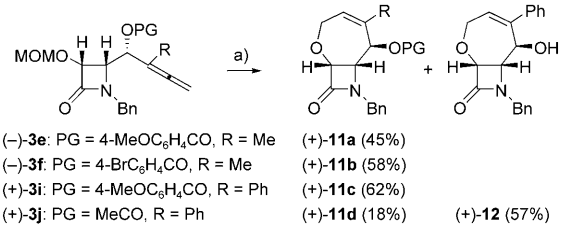


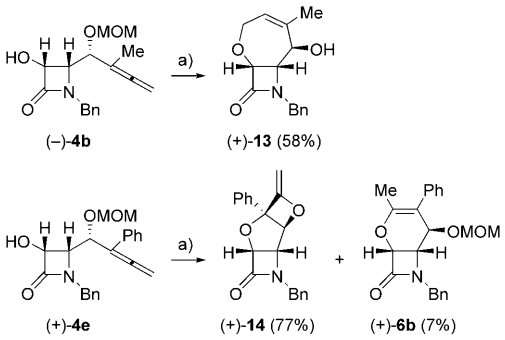
Scheme 4. Gold-catalyzed heterocyclization of γ-allenol derivatives **4b**, **4d**, and **4e**. a) $AuCl_3$ (5 mol%), CH_2Cl_2, RT; E = CO_2Me.

cyclization to afford bicycles **11a–c** and **12** in fair yields (Scheme 5). To the best of our knowledge, this observation is unprecedented. It seems that the reactivity in these classes of Au^{III}-catalyzed reactions is determined by the presence or absence of a methoxymethyl protecting group at the γ-allenol oxygen atom, because the free γ-allenols **4a–c** and **4g** gave 5-*exo* hydroalkoxylation, while the MOM-protected γ-allenol derivatives **3e**, **3f**, **3i**, and **3j** exclusively underwent 7-*endo* oxycyclization. We have thus demonstrated that regioselectivity control in the metal-catalyzed O–C functionalization of γ-allenols can be achieved both through the choice of catalyst (Au versus La versus Pd) and also through the nature of the γ-allenol (free versus protected).[19] This appears to be the first time that such an effect has been reported.



Scheme 5. Au^{III}-catalyzed heterocyclization reaction of MOM-protected γ-allenol derivatives **3e**, **3f**, **3i**, and **3j**. a) $AuCl_3$ (5 mol%), CH_2Cl_2, RT.

From the Au- and Pd-catalyzed results, the heterocyclization reaction is very sensitive to the presence of the MOM ether functionality. To expand the utility of the metal-catalyzed cycloetherification further, allenes incorporating methoxymethyl groups were studied with the lanthanide amide methodology. Accordingly, the La-catalyzed reactions of MOM-protected γ-allenols **3e**, **4b**, and **4e** were investigated. When compound **3e** was subjected to the lanthanide amide conditions, the starting material still remained unaltered even after 2 days of reaction time. Fortuitously, however, when the reaction of methylallene **4b** was conducted in the presence of a catalytic amount of $La[N(SiMe_3)_2]_3$, the MOM-free seven-membered adduct **13** was obtained exclusively (Scheme 6).[20] Intrigued by this unusual outcome, we set out to investigate the lanthanum-catalyzed reaction of phenylallene **4e**, in which the *C*-methyl group on allene was replaced by a sterically more demanding *C*-phenyl group,



Scheme 6. La^{III}-catalyzed heterocyclization reactions of γ-allenol derivatives **4b** and **4e**. a) $La[N(SiMe_3)_2]_3$ (5 mol%), toluene, reflux.

which from the above results with Au and Pd was anticipated not to change the electronic properties of the propa-1,2-dienyl moiety significantly. Much to our delight, however, the reaction proceeded smoothly to afford the strained tricycle **14** in a remarkably high isolated yield of 77%; additionally, a small amount (7% yield) of the dihydropyran **6b** was observed (Scheme 6). Thus, through a subtle variation in the substitution pattern of the allene component (Ph versus Me) the preference for La-catalyzed formation of the seven-membered regioisomer can be reversed.

It should be noted that some of the metal-based catalysts—such as $AgNO_3$, $AuCl_3$, or $PdCl_2$—are not dependent on the use of absolute solvents, whereas others such as $La[N(SiMe_3)_2]_3$ often do need absolute solvents.

To understand the highly regio- and diastereoselective natures of these metal-catalyzed transformations, a computational study on the ring-closure steps of free and protected γ-allenols **3** and **4** was undertaken (Part 2, accompanying paper).

Conclusion

In conclusion, efficient metal-controlled regiodivergent preparations of bicyclic tetrahydrofurans, dihydropyrans, and tetrahydrooxepines also incorporating β-lactam moieties—key structural motifs in biologically relevant compounds such as antibiotics and enzyme inhibitors—from starting enantiopure γ-allenols have been developed. In addition, it has been observed that the presence of a methoxymethyl protecting group not only masks a hydroxy functionality, but also exerts directing effects as a controlling unit in a regioselectivity reversal. In addition, the regioselectivity of the La-catalyzed cycloetherification can be tuned (5-*exo* versus 7-*endo*) simply through subtle variation in the substitution pattern of the allene component (Ph versus Me). Regiocontrolled heterocyclization reactions of γ-allenol derivatives are thus for the first time both catalyst- and substrate-directable. The mechanisms of these metal-catalyzed heterocyclization reactions were also analyzed by calculation-based methods (Part 2, accompanying paper).[10]

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Experimental Section

General methods: ^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker Avance 300, Varian VRX 300S, or Bruker AC 200 instruments. NMR spectra were recorded in $CDCl_3$ solutions, except when otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm) or $CDCl_3$ (^{13}C, 76.9 ppm). Low- and high-resolution mass spectra were taken with a HP 5989 A spectrometer in electronic impact (EI) or electrospray (ES) modes unless otherwise stated. Specific rotations ($[\alpha]_D$) are given in 10^{-1} deg cm^2 g^{-1} at 20 °C, and concentrations (c) are expressed in g per 100 mL. All commercially available compounds were used without further purification.

General Procedure for the Au^{III}-catalyzed cyclizations of γ-allenols (−)-4a, (+)-4c, and (+)-4g—preparation of fused tetrahydrofurans 5: $AuCl_3$ (0.05 mmol) was added under argon to a stirred solution of the corresponding γ-allenol **4** (1.0 mmol) in dichloromethane (1.0 mL). The resulting mixture was stirred at room temperature until disappearance of the starting material (TLC). The reaction was then quenched with brine (1.0 mL), the mixture was extracted with ethyl acetate (3×5 mL), and the combined extracts were washed twice with brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue with elution with ethyl acetate/hexanes mixtures gave analytically pure tetrahydrofuran adducts **5**. Spectroscopic and analytical data for a representative compound of type **5** follow.[21]

Fused tetrahydrofuran (+)-5c: γ-Allenic alcohol (+)-**4c** (50 mg, 0.15 mmol), after chromatography of the residue with hexanes/ethyl acetate 4:1, gave the tetrahydrofuran (+)-**5c** (28 mg, 58%) as a colorless oil. $[\alpha]_D$ = +68.6 (c = 0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 5.96 (dd, J = 17.6, 11.0 Hz, 1H), 5.76 (m, 1H), 5.29 (m, 1H), 5.23 (m, 2H), 5.16 (d, J = 3.7 Hz, 1H), 5.08 (dd, J = 11.0, 0.7 Hz, 1H), 4.11 (s, 1H), 3.93 (d, J = 3.7 Hz, 1H), 3.90 and 3.54 (m, each 1H), 1.31 (s, 3H), 0.92 (s, 9H), 0.11 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 162.1, 142.2, 131.6, 119.5, 113.4, 91.7, 86.6, 75.2, 66.1, 43.6, 25.8, 25.7, 24.0, −4.8, −5.0 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1746 cm^{-1}; MS (ES): m/z (%): 324 (100) $[M+H]^+$, 323 (10) $[M]^+$; elemental analysis calcd (%) for $C_{17}H_{29}NO_3Si$ (323.5): C 63.12, H 9.04, N 4.33; found: C 63.00, H 8.99, N 4.36.

General procedure for the La^{III}-catalyzed cyclization of γ-allenols 4: $La[N(SiMe_3)_2]_3$ (0.05 mmol) was added under argon to a stirred solution of the corresponding γ-allenol **4** (1.0 mmol) in toluene (10.0 mL). The resulting mixture was stirred at reflux temperature until disappearance of the starting material (TLC). The reaction was then filtered through a celite plug before being concentrated under reduced pressure. Chromatography of the residue with elution with ethyl acetate/hexanes mixtures gave analytically pure adducts **6**, **13**, and **14**.

La^{III}-catalyzed cyclization of γ-allenol (−)-4a—preparation of fused dihydropyrans (+)-6a and (+)-*epi*-6a: γ-Allenic alcohol (−)-**4a** (99 mg, 0.31 mmol), after chromatography of the residue with hexanes/ethyl acetate 4:1, afforded the less polar compound (+)-**6a** (52 mg, 44%) and the more polar compound *epi*-**6a** (5 mg, 4%).

Fused dihydropyran (+)-6a: Colorless oil; $[\alpha]_D$ = +33.2 (c = 0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.31 (m, 5H), 5.05 (d, J = 5.0 Hz, 1H), 4.47 and 4.31 (d, J = 15.0 Hz, each 1H), 3.83 (dd, J = 5.0, 1.5 Hz, 1H), 3.75 (d, J = 1.5 Hz, 1H), 1.80 and 1.44 (d, J = 0.9 Hz, each 3H), 0.81 (s, 9H), −0.06 and −0.08 ppm (s, each 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 165.9, 146.8, 135.7, 129.0 (2C), 128.4 (2C), 128.1, 106.8, 78.1, 67.1, 61.3, 44.8, 25.9, 25.7, 18.0, 16.9, −4.6, −4.8 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1746 cm^{-1}; MS (ES): m/z (%): 374 (100) $[M+H]^+$, 373 (11) $[M]^+$; elemental analysis calcd (%) for $C_{21}H_{31}NO_3Si$ (373.6): C 67.52, H 8.36, N 3.75; found: C 67.65, H 8.31, N 3.79.

Fused dihydropyran (+)-*epi*-6a: Colorless oil; $[\alpha]_D$ = +14.6 (c = 0.2 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.28 (m, 5H), 4.94 (d, J = 5.0 Hz, 1H), 4.78 and 4.33 (d, J = 15.5 Hz, each 1H), 4.48 (m, 1H), 4.12 (dd, J = 5.0, 3.8 Hz, 1H), 1.84 (m, 3H), 1.63 (t, J = 1.2 Hz, 3H), 0.90 (s, 9H), 0.07 and −0.01 ppm (s, each 3H); IR ($CHCl_3$): $\tilde{\nu}$ = 1746 cm^{-1}; MS (ES): m/z (%): 374 (100) $[M+H]^+$, 373 (9) $[M]^+$; elemental analysis calcd (%) for $C_{21}H_{31}NO_3Si$ (373.6): C 67.52, H 8.36, N 3.75; found: C 67.66, H 8.42, N 3.70.

General Procedure for Pd^{II}-catalyzed coupling of γ-allenols 4 with allyl bromides—preparation of fused tetrahydrooxepines 7: $PdCl_2$ (0.005 mmol) was added to a stirred solution of the corresponding γ-allenol **4** (0.10 mmol) and the appropriate allyl bromide (0.50 mmol) in *N*,*N*-dimethylformamide (0.6 mL). The reaction mixture was stirred under argon until disappearance of the starting material (TLC). Water (0.5 mL) was added before extraction with ethyl acetate (3×4 mL). The organic phase was washed with water (2×2 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue with elution with hexanes/ethyl acetate mixtures gave analytically pure fused tetrahydrooxepines **7**.

Fused tetrahydrooxepine (+)-7d: γ-Allenic alcohol (+)-**4c** (20 mg, 0.06 mmol), after chromatography of the residue with hexanes/ethyl acetate 3:1, gave the tetrahydrooxepine (+)-**7d** (22 mg, 94%) as a colorless oil. $[\alpha]_D$ = +5.2 (c = 2.3 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 5.74 (m, 2H), 5.17 (m, 2H), 5.08 (m, 2H), 5.04 (m, 1H), 4.53 (d, J = 4.4 Hz, 1H), 4.52 (m, 1H), 4.25 (dt, J = 5.1, 1.5 Hz, 1H), 3.96 (dt, J = 16.3, 1.7 Hz, 1H), 3.63 (dd, J = 9.3, 4.4 Hz, 1H), 3.62 (m, 1H), 2.66 and 2.48 (dd, J = 16.0, 6.0 Hz, each 1H), 1.69 (s, 3H), 0.96 (s, 9H), 0.12 and 0.07 ppm (s, each 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 166.1, 134.2, 131.5, 131.3, 126.3, 118.3, 115.2, 81.3, 74.0, 72.5, 61.8, 44.3, 34.2, 25.7, 18.0, 14.1, −4.8, −4.9 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1744 cm^{-1}; MS (ES): m/z (%): 364 (100) $[M+H]^+$, 363 (17) $[M]^+$; elemental analysis calcd (%) for $C_{20}H_{33}NO_3Si$ (363.6): C 66.07, H 9.15, N 3.85; found: C 66.20, H 9.10, N 3.82.

Fused tetrahydrooxepine (+)-7e: γ-Allenic alcohol (+)-**4g** (34 mg, 0.07 mmol), after chromatography of the residue with hexanes/ethyl acetate 2:1, gave the tetrahydrooxepine (+)-**7e** (23 mg, 66%) as a colorless oil. $[\alpha]_D$ = +39.0 (c = 1.3 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.39 and 6.73 (d, J = 8.5 Hz, each 2H), 7.07 (m, 10H), 6.62 (d, J = 9.8 Hz, 1H), 5.53 (m, 1H), 4.89 (m, 3H), 4.84 (d, J = 4.4 Hz, 1H), 4.66 and 3.96 (d, J = 15.4 Hz, each 1H), 4.20 (m, 1H), 4.11 (dd, J = 9.8, 4.4 Hz, 1H), 3.83 (s, 3H), 2.40 ppm (d, J = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 165.2, 164.7, 163.3, 137.5, 135.3, 135.0, 134.9, 132.9 (2C), 131.3 (2C), 129.0, 128.6 (2C), 128.0 (2C), 127.6 (2C), 126.8 (2C), 121.8, 116.4, 113.1 (2C), 113.0, 82.6, 73.8, 73.5, 61.6, 55.3, 45.2, 35.8 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1745, 1730 cm^{-1}; MS (ES): m/z (%): 496 (100) $[M+H]^+$, 495 (15) $[M]^+$; elemental analysis calcd (%) for $C_{31}H_{29}NO_5$ (495.6): C 75.13, H 5.90, N 2.83; found: C 75.27, H 5.85, N 2.80.

General Procedure for the Au^{III}-catalyzed cyclization of (methoxymethyl)-oxy allenes 3—preparation of fused tetrahydrooxepines 11: $AuCl_3$ (0.025 mmol) was added under argon to a stirred solution of the corresponding methoxymethyl-substituted allene **3** (0.5 mmol) in dichloromethane (0.5 mL). The resulting mixture was stirred at room temperature until disappearance of the starting material (TLC). The reaction was then quenched with brine (0.5 mL), the mixture was extracted with ethyl acetate (3×3 mL), and the combined extracts were washed twice with brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue with elution with ethyl acetate/hexanes mixtures gave analytically pure tetrahydrooxepine adducts **11**.

Fused tetrahydrooxepine (+)-11b: Methoxymethyl-substituted allene (−)-**3f** (55 mg, 0.11 mmol), after chromatography of the residue with hexanes/ethyl acetate 2:1, gave the tetrahydrooxepine (+)-**11b** (27 mg, 58%) as a colorless oil. $[\alpha]_D$ = +26.3 (c = 0.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.80 and 7.60 (d, J = 8.5 Hz, each 2H), 7.20 (m, 3H), 7.04 (m, 2H), 6.33 (d, J = 9.8 Hz, 1H), 5.27 (m, 1H), 4.76 (d, J = 4.4 Hz, 1H), 4.62 and 4.13 (d, J = 15.4 Hz, each 1H), 4.64 and 4.12 (m, each 1H), 3.99 (dd, J = 9.5, 4.4 Hz, 1H), 1.60 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 164.6, 162.2, 135.3, 132.2, 131.7, 131.8 (2C), 131.3 (2C), 128.7 (2C), 127.9, 127.7, 127.6 (2C), 122.7, 82.5, 75.1, 70.9, 61.3, 45.3, 20.3 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1744, 1728 cm^{-1}; MS (ES): m/z (%): 443 (100) $[M+2+H]^+$, 441 (11) $[M+H]^+$; elemental analysis calcd (%) for $C_{22}H_{20}BrNO_4$ (442.3): C 59.74, H 4.56, N 3.17; found: C 59.62, H 4.53, N 3.20.

Fused tetrahydrooxepine (+)-11c: Methoxymethyl-substituted allene (+)-**3i** (40 mg, 0.08 mmol), after chromatography of the residue with hexanes/ethyl acetate 3:1, gave the tetrahydrooxepine (+)-**11c** (23 mg, 62%) as a colorless oil. $[\alpha]_D$ = +27.5 (c = 0.7 in $CHCl_3$); ^{1}H NMR (300 MHz,

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$CDCl_3$, 25 °C): $\delta = 7.63$ and 6.80 (d, $J = 9.0$ Hz, each 2H), 7.23 (m, 5H), 7.10 (m, 5H), 6.58 (d, $J = 9.3$ Hz, 1H), 5.52 (dd, $J = 4.5$, 2.8 Hz, 1H), 4.89 (d, $J = 4.4$ Hz, 1H), 4.83 and 4.35 (m, each 1H), 4.71 and 4.02 (d, $J = 15.1$ Hz, each 1H), 4.18 (dd, $J = 9.0$, 4.4 Hz, 1H), 3.85 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 165.4$, 164.7, 163.4, 139.3, 138.4, 131.6 (2C), 128.7 (2C), 128.1 (2C), 128.0 (2C), 127.8, 127.7 (2C), 127.5, 127.1, 121.6, 113.4 (2C), 83.2, 77.2, 73.1, 70.9, 61.6, 55.4, 45.3 ppm; IR ($CHCl_3$): $\tilde{\nu} = 1746$, 1731 cm^{-1}; MS (ES): *m/z* (%): 456 (100) $[M+H]^+$, 455 (9) $[M]^+$; elemental analysis calcd (%) for $C_{28}H_{25}NO_5$ (455.2): C 73.83, H 5.53, N 3.08; found: C 73.70, H 5.49, N 3.11.

La^{III}-catalyzed cyclization of γ-allenol (+)-4e—preparation of fused dihydropyran (+)-6b and tricycle (+)-14: γ-Allenic alcohol (+)-**4e** (30 mg, 0.07 mmol), after treatment by the General Procedure for the La^{III}-catalyzed cyclization of γ-allenols **4** and chromatography of the residue with hexanes/ethyl acetate 3:1, afforded the less polar compound (+)-**6b** (2 mg, 7%) and the more polar compound (+)-**14** (17 mg, 77%).

Fused dihydropyran (+)-6b: Colorless oil; $[\alpha]_D = +96.7$ ($c = 0.3$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.27$ (m, 8H), 7.05 (m, 2H), 5.18 (d, $J = 4.9$ Hz, 1H), 4.57 (dd, $J = 14.9$, 7.1 Hz, 2H), 4.49 and 4.33 (d, $J = 14.9$ Hz, each 1H), 4.19 (d, $J = 4.9$ Hz, 1H), 4.18 (m, 1H), 3.23 (s, 3H), 1.92 ppm (s, 3H); IR ($CHCl_3$): $\tilde{\nu} = 1746$ cm^{-1}; MS (ES): *m/z* (%): 374 (100) $[M+H]^+$, 373 (11) $[M]^+$; elemental analysis calcd (%) for $C_{22}H_{23}NO_4$ (365.4): C 72.31, H 6.34, N 3.83; found: C 72.44, H 6.29, N 3.87.

Tricycle (+)-14: Colorless oil; $[\alpha]_D = +58.3$ ($c = 0.3$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.33$ (m, 8H), 7.06 (m, 2H), 5.76 (ddd, $J = 4.5$, 1.7, 0.7 Hz, 1H), 5.29 (d, $J = 5.1$ Hz, 1H), 4.97 (t, $J = 1.6$ Hz, 1H), 4.47 (s, 2H), 4.43 (t, $J = 0.6$ Hz, 1H), 4.17 ppm (dd, $J = 5.1$, 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 167.5$, 152.7, 138.7, 135.6, 129.0, 128.8 (2C), 128.5 (2C), 128.3, 128.1 (2C), 127.4 (2C), 122.2, 101.1, 78.7, 66.1, 49.1, 45.2 ppm; IR ($CHCl_3$): $\tilde{\nu} = 1751$ cm^{-1}; MS (ES): *m/z* (%): 320 (100) $[M+H]^+$, 319 (11) $[M]^+$; elemental analysis calcd (%) for $C_{20}H_{17}NO_3$ (319.3): C 75.22, H 5.37, N 4.39; found: C 75.08, H 5.32, N 4.43.

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[21] Experimental procedures as well as full spectroscopic and analytical data for compounds not included in this Experimental Section are described in the Supporting Information. It contains as well copies of NMR spectra for all new compounds.

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