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Transition metal catalyzed stereodivergent synthesis of *syn*- and *anti*-δ-vinyl-lactams: formal total synthesis of (−)-cermizine C and (−)-senepodine G†

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A stereodivergent and diastereoselective transition-metal-catalyzed intramolecular hydroamidation of allenes and alkynes furnishing δ-vinyl-lactams is reported. Employing a rhodium catalyst allowed for the selective synthesis of the *syn*-δ-lactam. Conversely, a palladium catalyst led to the formation of the *anti*-δ-lactam in high selectivity. The new method shows high functional group compatibility and assorted synthetic transformations were demonstrated as well as its utility for the enantioselective formal total syntheses of (−)-cermizine C and (−)-senepodine G.

Transition metal-catalyzed intramolecular hydroamination reactions starting from aminoalkenes,[1] aminoallenes,[2] aminodienes[3] and aminoalkynes[4] have been reported frequently for the synthesis of nitrogen-containing heterocycles. Although the δ-lactam moiety is of equally high interest, to date reports of inter- and intramolecular hydroamidations are still rare and stereoselective and stereodivergent variants are unknown.[5] Thus, δ- (and γ-) lactams are found as pharmacophores in a number of drugs and bioactives, such as (+)-ebmamonin (antiarrhythmic agent), rhynchophylline (treatment of disorder of the central nervous system) and BMD 188 (induces the apoptotic death of prostate cancer cells). Furthermore δ-lactams have been used as key intermediates for the synthesis of piperidine type alkaloids such as cermizine C & D and as senepodine G (Fig. 1).[6]

Our group recently reported a series of inter- and intramolecular addition reactions of various nucleophiles and pronucleophiles to allenes and alkynes covering regio-, enantio- and diastereoselective C–O, C–S, C–N and C–C bond formations.[7,8] Thus, these new methods represent atom-economic alternatives to the transition-metal-catalyzed allylic substitution[9] and allylic oxidation.[10] We herein disclose an unprecedented stereodivergent rhodium- and palladium-catalyzed intramolecular hydroamidation to gain selective access to either *syn*- or *anti*-vinyl-δ-lactams.

Our studies commenced by employing the phenyl-β-substituted tosyl amide model substrates **1** (Table 1).

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After a first successful reactivity test using a Rh/dppf catalytic system (d.r. 85/15), an optimization of the reaction parameters was undertaken (Table 1). Employing [Rh(COD)Cl]$_2$/dppf enabled us to selectively obtain the *syn*-configured product albeit in low conversion (entry 2). Fortunately, utilizing chloroacetic acid as a Brønsted acid additive could improve the conversion dramatically to 96% (entry 3). Furthermore, lowering the reaction temperature from 80 °C to room temperature led to optimal results (92% isolated yield) and diastereoselectivity of 91 : 9 in favor of the *syn*-diastereomer (entry 4). Conversely, by altering the metal source to palladium, a complete inversion of the diastereoselectivity in favor of the *anti*-diastereomer was observed. The combination of [Pd(dba)$_2$], dppf and chloroacetic acid at 80 °C led to the best results in terms of diastereoselectivity (6/94) and yield (96%) (entry 8). Further modifying the reaction temperature or examining different additives and ligands showed no improvement.[11]

With optimized conditions in hand, the scope and limitations of this reaction were explored (Table 2). Alkyl-, vinyl- and cyclic-functionalized amides behaved well and furnished the
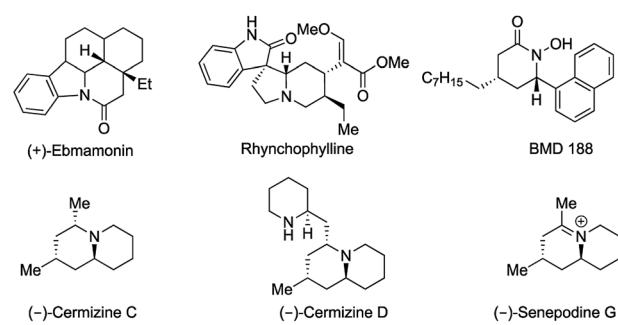

Fig. 1 Bioactives and natural products.

Table 1 Optimization of the transition-metal catalyzed intramolecular hydroamidation[11,12a]
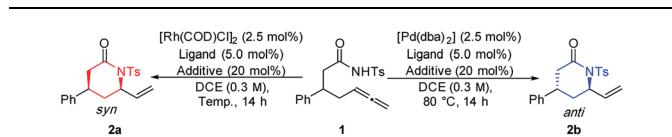
#	Ligand	Additive	Temp./°C	Yield[b] [%]	syn : anti[c]
Optimization towards *syn*-lactam employing[11] [Rh(COD)Cl]₂					
1	dppf	—	80	20	15/85
2	dppf	Acetic acid	80	55	75/25
3	dppf	Chloroacetic acid	80	96	84/16
4	dppf	Dichloroacetic acid	80	82	80/20
5	dppf	Chloroacetic acid	RT	92	91/9
Optimization towards *anti*-lactam employing[11] [Pd(dba)₂]					
6	dppf	—	80	15	18/82
7	dppf	Acetic acid	80	42	29/71
8	dppf	Chloroacetic acid	80	96	6/94
9	dppf	Dichloroacetic acid	80	81	16/84

[a] All reactions were performed on a 0.3 mmol scale; dppf = (1,1-bis(diphenylphosphino)ferrocene); temp. = temperature. [b] Combined yield. [c] Selectivity determined by ¹H-NMR analysis of the crude reaction mixture.

corresponding *syn*- and *anti*-lactams **3a** to **6a** and **3b** to **6b** in good to excellent yields and d.r. Next an assorted variety of different functionalized, aromatic β-substituted amides was investigated. Substrates bearing phenyl, biaryl, naphthyl and

vinyl groups provided the corresponding lactams in yields up to 95% and d.r. up to 96/4 (**2a, 7a, 8a** and **2b, 7b, 8b**). Compounds **2a** and **2b** were also synthesized *via* large scale catalysis without any decline in yield and d.r., respectively.[11] Sensitivity towards steric hindrance was tested employing *meta* and *para* substituted derivatives.[13] Functional groups like thioethers and halides attached to the aromatic ring were compatible and afforded the desired products **12a** & **13a** and **12b** & **13b** in good to excellent yields. Besides β-substituted amides also α-substituted amides could be cyclized in good yields, though with lower diastereoselectivities (**14a** & **14b**).

Overall the Pd-catalyzed reaction towards the *anti*-product showed slightly better results in terms of d.r. in case of aliphatic- and cyclic-functionalized amides compared to the Rh-catalyzed protocol. The relative configuration of *syn*- and *anti*-configured products were determined by NOE-experiments and confirmed by X-ray diffraction analysis (Fig. 2).[11]

To extend the use of this reaction even further, alkyne substrates bearing isopropyl, phenyl and anisole as substituents were subjected to rhodium catalysis conditions (Table 3). The alkyne substrates needed higher reaction temperatures in order to obtain the δ-lactams in sufficiently high yields. Thus, yields up to 88% and diastereoselectivities up to 87/14 in favor of the *syn*-diastereomer were obtained (Table 3). Unfortunately, the palladium catalyst system did not show any reactivity for the terminal alkyne substrates.[11]

To demonstrate that the reaction does not just provide access to highly diastereoselective lactams but also enables their stereoselective synthesis, enantiomerically enriched

Table 2 Scope of the catalytic diastereoselective intramolecular amidation towards *syn*- and *anti*-configured δ-lactams[11abc]
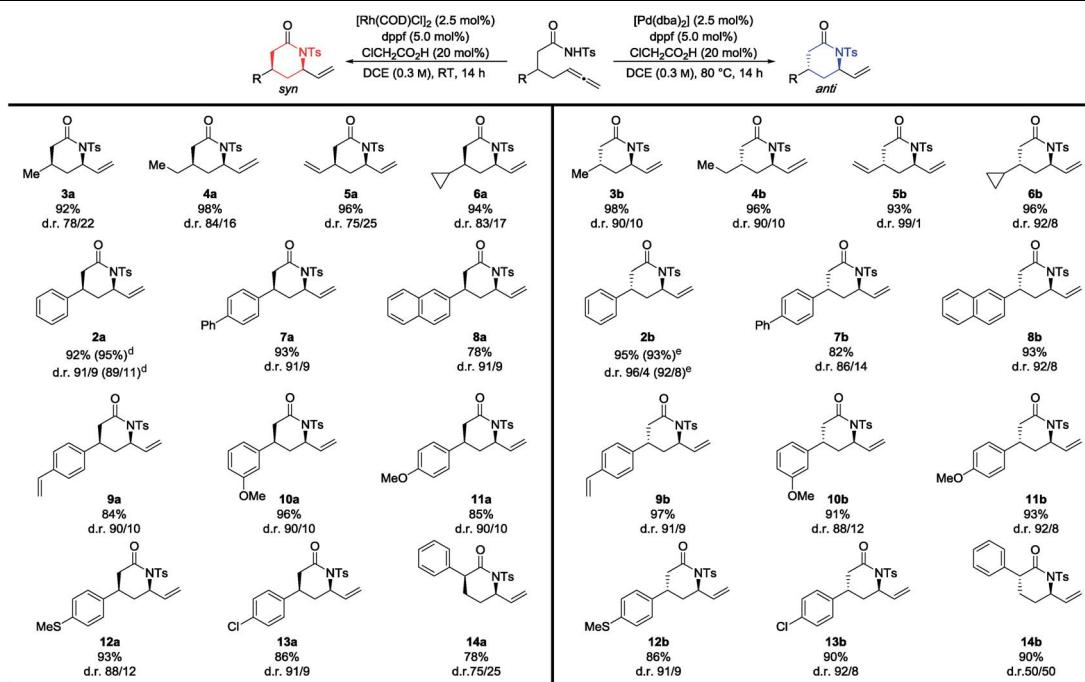
[a] All reactions were performed on a 0.3 mmol scale; dppf (1,1-bis(diphenylphosphino)ferrocene); ClCH₂CO₂H = chloroacetic acid; DCE = 1,2-dichloroethane. [b] Combined yield. [c] Selectivity determined by ¹H-NMR analysis of the crude reaction mixture. [d] Yield and d.r. of large scale Rh-reaction (1.4 mmol). [e] Yield and d.r. of large scale Pd-reaction (3.1 mmol).
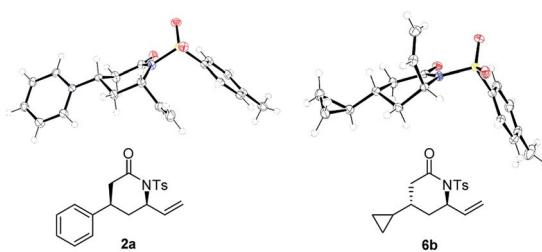
Fig. 2 Crystal structure of **2a** and **6b**.

Table 3 Scope of the catalytic diastereoselective intramolecular amidation towards *syn*-configured compounds employing alkynes as substrate[11abc]
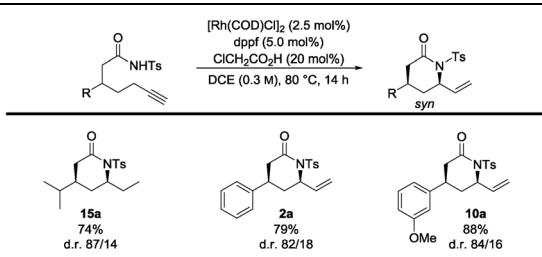
[a] All reactions were performed on a 0.3 mmol scale; dppf (1,1-bis(diphenylphosphino)ferrocene); ClCH$_2$CO$_2$H = chloroacetic acid; DCE = 1,2-dichloroethane. [b] Combined yield. [c] Selectivity determined by ^{1}H-NMR analysis of the crude reaction mixture.

starting material **16** was subjected to the catalysis conditions.[11,13]

We were satisfied to observe that the enantiomeric purity was maintained under both the *syn*-**3a**- and *anti*-**3b**-catalysis conditions (Scheme 1).

To investigate the reversibility of the reaction, both products were subjected to the contrary conditions.

The *anti*-lactam subjected to the "*syn*-conditions" showed no change of relative configuration. Conversely, the *syn*-lactam exposed to the "*anti*-conditions" resulted in an inversion of the relative configuration (Scheme 2).[11] To gain insight into the respective stabilities of the *syn*- and the *anti*-product, DFT calculations (BP86/def2SVP) were performed. The calculations showed that the *anti*- is approximately 1.4 kcal mol^{-1} more stable than the *syn*-diastereomer.[11]

In conclusion, we posit that in presence of rhodium the reaction is driven by kinetic control, whereas in presence of palladium the reaction towards the *syn*-diastereomer is

Scheme 1 Enabling the stereoselective synthesis of *syn*- (**3a**) and *anti*-lactam (**3b**), by employing enantiomerically enriched starting material (**16**).
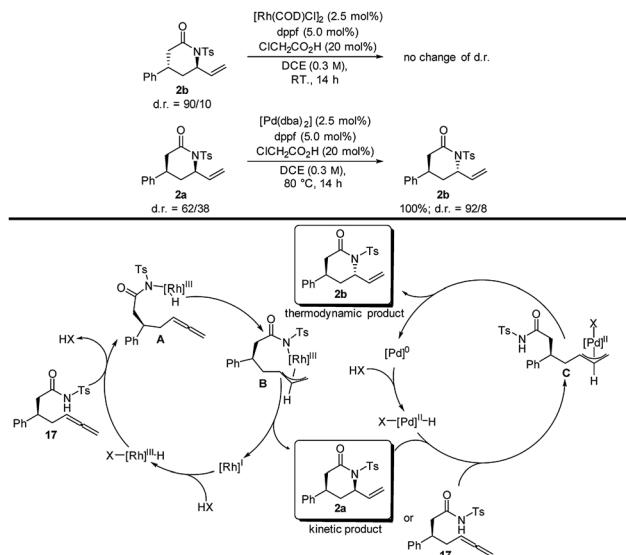

Scheme 2 Reversibility investigations.

reversible and the formation of the more stable *anti*-diastereomer either under thermodynamic control or under product development control.[11] The mechanism of the rhodium-catalyzed addition of nucleophiles to allenes and alkynes was investigated by our group recently.[14] Based on those results, we propose the following mechanistic rationale for the formation of the *syn*-product (Scheme 2, left-hand cycle). First, the active rhodium species is generated *via* oxidative addition, followed by a ligand exchange to form intermediate **A**. Hydrometalation then gives rise to the key allylrhodium species **B**. In the configuration-determining step, a reductive elimination *via* an inner sphere mechanism takes place favoring the *syn*-product **7a**.[15] For the palladium-mediated reaction (Scheme 2, right-hand cycle) we suggested a similar mechanism to the Tsuji–Trost reaction.[16] First the active palladium species undergoes hydrometalation to form the π-allyl species **C**. Then the C–N bond is formed by nucleophilic attack on to the π-allyl intermediate **C**, *via* an outer sphere mechanism, favoring the *anti*-product.

The utility of **2b** as scaffold in the synthesis of more complex molecules was demonstrated by performing assorted transformations (Scheme 3). Ozonolysis of the allylic moiety delivered the C$_1$-shortened aldehyde **18** in excellent yield (99%). The C$_1$-chain-elongated aldehyde **19** was accessed through hydroformylation, employing the self-assembly ligand 6-diphenylphosphinopyridine (6-DPPon) in excellent yield (98%) and regioselectivity. Cleaving the tosyl group under reductive conditions yielded the unprotected lactam **20**. Finally, a hydrolysis was performed as a gateway to access diastereomerically enriched δ-amino acid **21**.

Inspired by the variety of functionalization, the newly developed lactam synthesis was applied in the formal total synthesis of cermizine C and senepodine G (Scheme 4). Both natural products were isolated for the first time in 2004 from the club moss *lycopodium carnuum* and *chinense* by KOBAYASHI.[17]
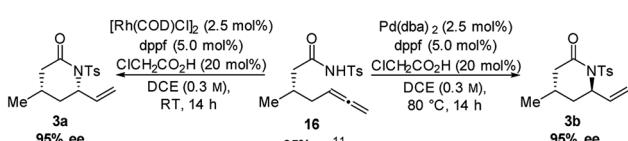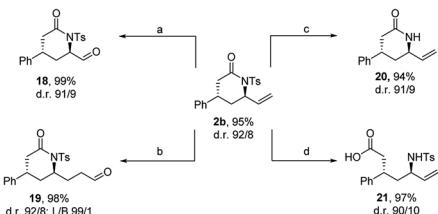
Scheme 3 Follow-up chemistry; *was synthesized in a gram scale catalysis; (a) (i) O₃, MeOH, −78 °C; (ii) SMe₂, MeOH, −78 °C to RT, 99%; (b) [{Rh(CO)₂acac}] (0.5 mol%), 6-DPPon (10 mol%), CO/H₂ (1 : 1, 10 bar), toluene, 80 °C, 21 h, 98% (L/B > 95 : 5); (c) Li, naphthalene, THF, −78 °C to RT; (d) H₂O/IPA, LiOH, reflux, 17 h.

This representative from the lycopodium family as well as even more complex alkaloids were often targeted in the total synthesis, due to their high variety, unusual skeletons and biological properties.[18–20] Some efforts were made to find an easy access to these alkaloids and especially to form the main core unit.[21] A first synthesis was reported by Snider starting from (S)-piperidine ethanol.[22] Even though the synthesis was efficient and elegant, the starting material is expensive and its synthesis not trivial. Other attempts were either based on long reaction sequencesor used auxiliary chemistry to introduce the desired stereochemistry.[23,24]

Our interest in cermizine C and senepodine G was initially stimulated by the quinolizidine core, which is accessible in a straightforward fashion by applying the present methodology (Scheme 4). The attempt for the enantioselective formal total synthesis of this compounds was therefore started from (S)-methyltosylamide (16) which was accessed in two steps from an α,β-unsaturated ester 22.[11]

The enantiomerically enriched starting material 16 was subjected to a gram-scale catalytic cyclization and delivered the tosyl-protected lactam 3b in excellent yield (98%), diastereoselectivity (d.r. = 90/10) and enantioselectivity (95% ee). Next was the deprotection of tosyl–lactam 3b followed by an alkylation reaction to obtain 24 in a good yield. With precursor 24 in hand, a Grubbs ring closing metathesis followed by catalytic hydrogenation furnished the quinolizidine core 25, which was previously converted into cermizine C and senepodine G by Snider et. al.[22] Hence, we have realized a highly efficient stereoselective formal total synthesis of these alkaloids (7 steps,
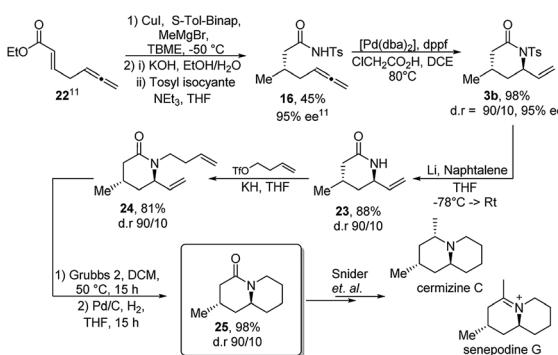
31% overall yield) starting from compound 22. In comparison Snider was able to synthesis compound 25 in 5 steps and an overall yield of 41%, starting from (S)-piperidine ethanol.[25] However, our method compares favorably, in terms of starting material accessibility and costs, to the procedure developed by Snider.

Conclusions

In conclusion, we have established a general and efficient stereodivergent and highly diastereoselective procedure to gain selective access to syn- and anti-vinyl-δ-lactams by using either a rhodium or palladium-based catalytic system. The reaction tolerates a wide range of functional groups which enables the synthesis of a variety of different δ-lactams. Assorted transformations allowed the functionalization of both the alkene and lactam moiety. Furthermore, we successfully utilized the new developed methodology in a highly stereospecific and atom economic formal total synthesis of cerminzin C and senepodine G.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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11 For further information see ESI.†

12 Due to the hazardous nature of DCE different solvents like DCM, THF, toluene, acetonitrile, ethanol and PhF were screened during the optimization of the Rh-catalyzed reaction. Unfortunately, DCE showed the best result and was therefore chosen. See ESI† for further information.

13 Synthesis of **17** see ESI† or Scheme 4.

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