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Stereoselective synthesis of substituted *N*-heterocycles via sequential cross metathesis—reductive cyclization

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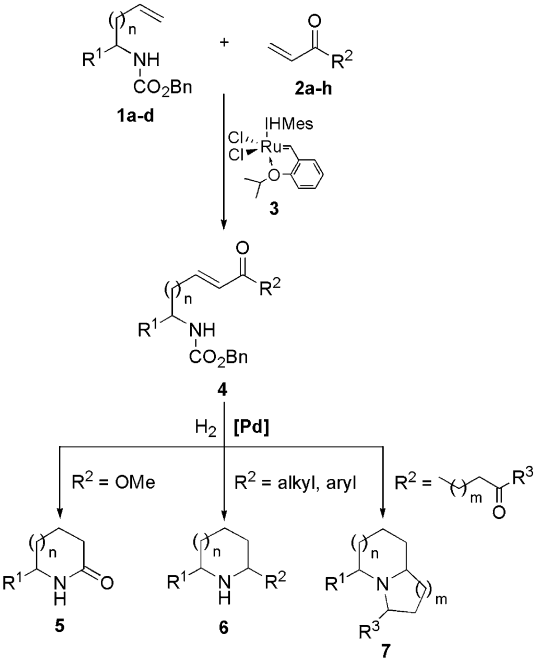
Abstract—A diastereoselective synthesis of substituted mono- and bicyclic-piperidine and pyrrolidine derivatives is presented, employing a highly selective cross metathesis (CM) reaction followed by a domino reduction–cyclization process.

Substituted mono- and bicyclic-piperidine and pyrrolidine derivatives are among the most ubiquitous natural building blocks for which a huge amount of synthetic effort has been spent on their preparation.[1] While numerous examples of ring-closing metathesis (RCM) and ring-rearrangement metathesis (RRM) for the synthesis of *N*-heterocycles are known,[2] the efficiency of cross metathesis (CM) reactions has not yet been explored as much. As an extension of previous work within the group[3] we herein present the highly selective cross-coupling reaction of *N*-protected allylic and homoallylic amines with α,β-unsaturated ketones and acrylates followed by reductive cyclization as a general approach towards their synthesis.

The commercially available phosphine free ruthenium-catalyst **3** was found to efficiently catalyze CM reactions between alkyl-substituted and electron-deficient olefins with high selectivities.[4] Consequently, cross-coupling of *N*-protected allylic and homoallylic amines with enones or acrylates should easily afford aminoenones of type **4**, which upon catalytic hydrogenation are converted into the saturated *N*-heterocycles **5** or **6** in a sequence of double bond reduction, *N*-deprotection and cyclization.[5] While simple reductive aminations affording piperidines and pyrrolidines of type **6** are known to proceed *cis*-selectively under the control of the stereocentre adjacent to the nitrogen,[6] aminoenones containing a second carbonyl group are expected to undergo a further diastereoselective cyclization yielding bicycles of type **7** (Scheme 1).[7]

This tandem sequence should therefore allow flexible and rapid access to *N*-heterocyclic compounds such as pyrrolidines, piperidines, pyrrol-, indol- and quinolizidines.



Scheme 1. Synthesis of substituted *N*-heterocycles.

Keywords: Cross metathesis; Reductive amination; Ruthenium catalyst; Indolizidines; Pyrrolizidines.

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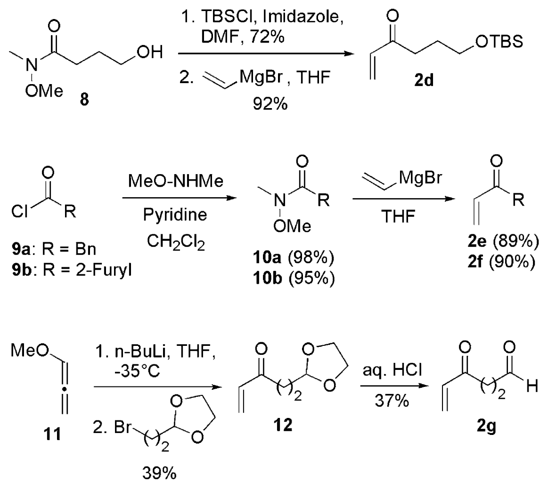
Table 1. Substrates for CM reactions

1a	$R^1 = CO_2Me$	$n = 1$	**2c**	$R^2 = n\text{-Bu}$
1b	$R^1 = CH_2OBn$	$n = 0$	**2d**	$R^2 = (CH_2)_3OTBS$
1c	$R^1 = CH_2OTBS$	$n = 0$	**2e**	$R^2 = Bn$
1d	$R^1 = Bn$	$n = 0$	**2f**	$R^2 = 2\text{-furyl}$
2a	$R^2 = OMe$		**2g**	$R^2 = (CH_2)_2CHO$
2b	$R^2 = Me$		**2h**	$R^2 = (CH_2)_2COMe$



Scheme 2. Synthesis of substrates **2d**–**g**.

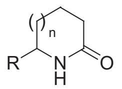
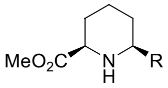
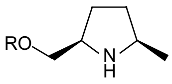
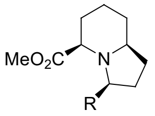
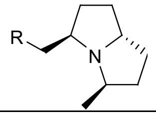
To demonstrate the general applicability of this concept we decided to react the known carbamates **1a**–**d**[8] with methyl acrylate **2a**, methyl vinyl ketone **2b**, *n*-butyl vinyl ketone **2c**[9] and a series of enones **2d**–**h**, (Table 1) prepared as shown in Scheme 2.

Protection of Weinreb amide **8**, which is readily prepared by aluminium promoted amidation of γ-butyrolactone,[10] and treatment with vinyl magnesium bromide in THF at 0 °C furnished enone **2d** in high overall yield after acidic workup. Under the same conditions, **2e**,**f** were obtained in excellent yield from Weinreb amides **10a**,**b** derived from the commercially available acid chlorides **9a**,**b**. While the synthesis of enedione **2h** has been reported by Stetter and Landscheidt,[9] aldehyde **2g** was prepared by condensation of lithiated methoxyallene, serving as an ester homoenolate equivalent,[11] with commercially available 2-(2-bromoethyl)-1,3-dioxolane to provide acetal **12** after acidic workup. Deprotection with aqueous HCl gave the unstable aldehyde **2g**.

The results and conditions of the CM reactions and subsequent catalytic reductions are presented in Table 2.

All CM reactions were carried out in DCM at reflux temperature utilizing 2.5–10% of Ru-catalyst **3**.[12] Except the rather volatile (**2a**,**b**) or less reactive (**2f**) substrates both coupling partners were preferably reacted in a 1:1 ratio giving exclusively the *E*-configurated alkenes (*E*/*Z* > 20:1) in moderate to good yields. The prolonged reaction times and increased amounts of catalyst needed for the cross-coupling of allylic carbamates **1b**,**c** may be

Table 2. Results and conditions of CM and catalytic hydrogenation reactions

Substrates		CM product		Cyclization product	
1a+**2a** (1:2)	$\xrightarrow[\text{DCM, 40°C}]{5\%\ \mathbf{3},\ 3\,\text{h}}$	**4a** (76%)	$\xrightarrow[\text{MeOH, 1 h}]{\text{H}_2\text{, Pd/C}}$	**5a**: R = CO_2Me, $n = 1$ (97%)[a]	
1b+**2a** (1:2)	$\xrightarrow[\text{DCM, 40°C}]{10\%\ \mathbf{3},\ 48\,\text{h}}$	**4b** (71%)		**5b**: R = CH_2OBn, $n = 0$ (91%)[b]	
1a+**2b** (1:2)	$\xrightarrow[\text{DCM, 40°C}]{2.5\%\ \mathbf{3},\ 3\,\text{h}}$	**4c** (85%)	$\xrightarrow[\text{Et}_2\text{O, 3 h}]{\text{H}_2\text{, Pd/C}}$	**6a**: R = Me (85%)	
1a+**2c** (1:1)		**4d** (83%)		**6b**: R = *n*-Bu (83%)	
1a+**2d** (1:1)	$\xrightarrow[\text{DCM, 40°C}]{5\%\ \mathbf{3},\ 16\,\text{h}}$	**4e** (64%)	$\xrightarrow[\text{MeOH, 3 h}]{\text{H}_2\text{, Pd/C}}$	**6c**: R = $(CH_2)_3OTBS$ (96%)	
1a+**2e** (1:1)		**4f** (78%)		**6d**: R = Bn (71%)	
1a+**2f** (1:2)		**4g** (73%)		**6e**: R = 2-furyl (74%)	
1b+**2b** (1:2)	$\xrightarrow[\text{DCM, 40°C}]{10\%\ \mathbf{3},\ 48\,\text{h}}$	**4h** (77%)	$\xrightarrow[\text{MeOH/AcOH}]{\text{H}_2\text{, Pd/C, 5 h}}$	**6f**: R = Bn (72%)[c]	
1c+**2b** (1:2)		**4i** (80%)	$\xrightarrow[\text{MeOH, 5 h}]{\text{H}_2\text{, Pd(OH)}_2}$	**6g**: R = TBS (87%)[d]	
1a+**12** (1:1)	$\xrightarrow[\text{DCM, 40°C}]{5\%\ \mathbf{3},\ 16\,\text{h}}$	**4j** (65%)	$\xrightarrow[\text{MeOH/HCl}]{\text{H}_2\text{, Pd/C, 24 h}}$	**7a**: R = H (81%)	
1a+**2h** (1:1)		**4k** (74%)	$\xrightarrow[\text{MeOH, 16 h}]{\text{H}_2\text{, Pd/C}}$	**7b**: R = Me (77%)	
1c+**2h** (1:1)	$\xrightarrow[\text{DCM, 40°C}]{10\%\ \mathbf{3},\ 72\,\text{h}}$	**4l** (71%)	$\xrightarrow[\text{MeOH, 72 h}]{\text{H}_2\text{, Pd/C}}$	**7c**: R = OTBS (73%)	
1d+**2h** (1:1)		**4m** (62%)		**7d**: R = Ph (68%)	

[a] After 5 h in refluxing glyme.

[b] After 5 h in refluxing MeOH.

[c] *cis*/*trans* = 1:1.

[d] *cis*/*trans* = 4:1.

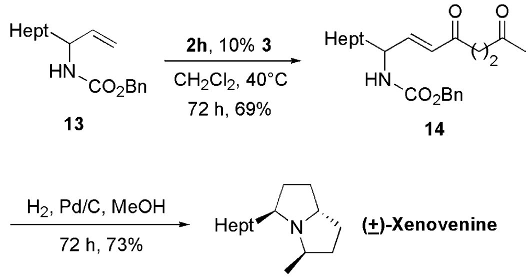
ascribed to the intramolecular chelation of the intermediate ruthenium species.[13] Higher temperatures (toluene, 80 °C) resulted in somewhat lower yields presumably due to the concurrent decomposition of the catalyst.

The subsequent catalytic reductions of aminoenones **4a–m** were performed in MeOH or Et_2O (in case of rather volatile products) at rt with 5 mol% [Pd] under 1 atm of hydrogen.[14] Single cyclizations gave rise to the pipecolates **6a–e** with complete *cis*-selectivity, as determined by NOE experimental analysis, and the lactams **5a**,**b** upon heating. In case of pyrrolidines, the facial selectivities of catalytic hydrogenations have been shown to depend on substrate structure, catalyst and reaction conditions.[6e,f] For example, when the reduction of substrate **4h** was performed in methanol using Pd/C the reaction stopped after formation of the intermediate pyrroline. Complete reduction could be achieved in the presence of acetic acid,[6f] resulting in a 1:1 mixture of diastereomers, or with Pearlman's catalyst causing partial *O*-debenzylation. To rule out simultaneous deprotection, hydrogenation of the corresponding silylether **4i** was investigated. Reduction using Pearlman's catalyst was complete within 5 h affording a 4:1 mixture of diastereomers in favour of the *cis*-isomer **6g** as assigned by ^1H NMR analysis (two doubled-doublets for the CH_2OTBS methylene protons at 3.55 and 3.62 ppm, respectively).[15]

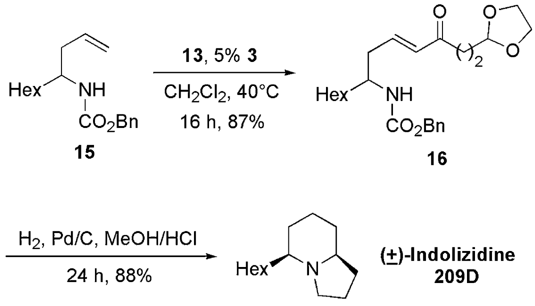
In order to verify the effect of a second reductive amination on the diastereoselectivity of the piperidine formation, the CM product of **1a** and aldehyde **2g** was subjected to hydrogenation. Unfortunately, the first cyclization attempts produced only small amounts of the desired bicycle (20%), probably due to intermolecular side reactions. Alternatively, reduction of protected analogue **4j** in acidic media afforded the stereoisomer **7a** as the only product whose relative configuration was ascertained by comparison with the known ethyl ester.[16]

Since an additional methyl group would simplify the determination of the diastereoselectivity of the second reductive amination, we continued with the hydrogenation of diketone **4k**, which proceeded smoothly yielding the disubstituted indolizidine **7b** exclusively, whose spectroscopical data were identical with the ones reported.[17]

Pleased by these results we turned to the reductive aminations of the pyrrolizidine precursors **4l**,**m**. The disappearance of the imine intermediate was comparably slow in both cases as monitored by TLC. Moreover, the spectroscopical properties of the obtained products were not in accordance with the expected *trans*-fused isomers (*cis*-configuration at both pyrrolidine rings) but with the less strained *cis*-fused isomers (*trans*-configuration at both pyrrolidine rings) lacking the specific Bohlmann bands in their infrared spectra. To confirm this observation we decided to prepare aminoenone **14** via precursor **13**[8d] and compare its cyclization product with (+)-*Xenovenine*, a pyrrolizidine alkaloid found in the thief ant *Solenopsis xenovenum*.[18] As depicted in Scheme 3, the isolated pyrrolizidine was identical with the natural product in all considerable respects. Although mechanistically unexpected, these results are somehow advantageous as access to the more attractive class of naturally occurring (5*Z*,8*E*)-3,5-disubstituted pyrrolizidines[19] is enabled.



Scheme 3. Synthesis of (±)-*Xenovenine*.



Scheme 4. Synthesis of (±)-*Indolizidine 209D*.

Finally, we applied our two-step sequence on the diastereoselective synthesis of the indolizidine alkaloid *209D*, a potent neurotransmitter exuded by the skin of neotropical *dendrobatid* frogs.[20] Starting from precursor **15**, derived from heptaldehyde in a sequence of allylation, azidation and introduction of the benzyl carbamate,[21] (±)-*Indolizidine 209D* could be conveniently obtained in 77% overall yield (Scheme 4).

In conclusion, our proposed CM reaction—reductive cyclization sequence has been successfully applied on the convergent synthesis of various piperidine, pyrrolidine, indolizidine and pyrrolizidine derivatives as well as on the diastereoselective total synthesis of (±)-*Xenovenine* and (±)-*Indolizidine 209D*. Considering the high functional group tolerance of Ru-metathesis catalyst **3**, this concept should as well offer an efficient and stereoselective entry to structurally more diverse natural products. Further applications are therefore under investigation and will be reported in due course.

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