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Asymmetric synthesis of 2-substituted 5-, 6- and 7-membered nitrogen heterocycles by oxime addition ring-closing metathesis

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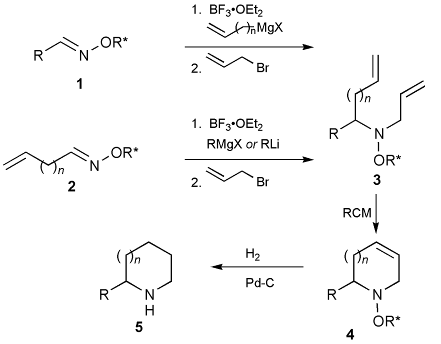
Ring closing metathesis reactions of the dienes 6 and 9 leads to the nitrogen heterocycles 7 and 10, respectively, one of which 10c was converted into (*R*)-(−)-coniine.

The development of methods for the asymmetric synthesis of pyrrolidines and piperidines remains an area of current interest due to the presence of such saturated heterocyclic rings in a large number of biologically important compounds.[1] One possible approach to the synthesis of nitrogen heterocycles involves the ring-closing olefin metathesis (RCM) reaction. The RCM reaction is a powerful synthetic method and, with the development of practical and reliable catalysts by Grubbs and others,[2,3] has been widely used in a number of syntheses in the recent past,[4,5] including examples of nitrogen heterocycles.[6–14] In continuation of our interest in the asymmetric synthesis of saturated nitrogen heterocycles,[15] we decided to investigate the combination of the highly diastereoselective addition reactions of *O*-(1-phenylbutyl) aldoximes with the RCM reaction as a new route to this class of heterocycle. This combination of oxime addition–RCM is shown in outline in Scheme 1, and our preliminary results are described herein.

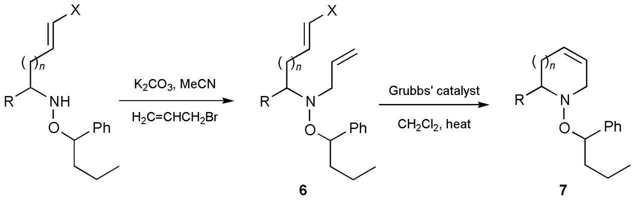
As outlined in Scheme 1, the substrates for the RCM reactions are the dienes **3**, accessible either by the addition of an alkene containing organometallic reagent to the aldoxime ether **1**, or by organometallic addition to an aldoxime **2** derived from an unsaturated aldehyde, followed in both cases by *N*-allylation of the resulting hydroxylamine. Both approaches were successful and a number of dienes **6** were prepared by the highly diastereoselective addition of organolithium reagents to the *O*-(1-phenylbutyl) oximes of cinnamaldehyde or allylmagnesium bromide to the oximes of butyraldehyde or benzaldehyde,[16,17] followed by reaction with allyl bromide in the presence of potassium carbonate (Table 1). The RCM reaction was carried out by heating the dienes **6** in dichloromethane in the presence of Grubbs' catalyst, and gave the required 5- and 6-membered rings **7** in modest to excellent yield (Table 1).

Although the above results indicate that basic or nucleophilic nitrogen atoms are tolerated in the RCM reaction of the hydroxylamine derived substrates, we also investigated the diene substrates **9** in which the nitrogen is rendered non-basic by protection as its benzyloxycarbonyl (Z) derivative. Thus a range of carbamates **8**, prepared as previously described,[16,17] or as indicated in Table 2, was converted into the corresponding *N*-allyl derivatives **9** by reaction with allyl bromide in the presence of sodium hydride. In the case of **8b**, these conditions caused migration of the double bond, and therefore the allyl group was introduced using the palladium catalysed reaction of allyl methyl carbonate.[18] Again the RCM reaction proceeded smoothly and gave the 5- and 6-membered nitrogen heterocycles **10a–10d** in good to excellent yield, with the yield of the 7-membered ring **10e** being slightly lower (Table 2).



Scheme 1 (R* = 1-phenylbutyl).

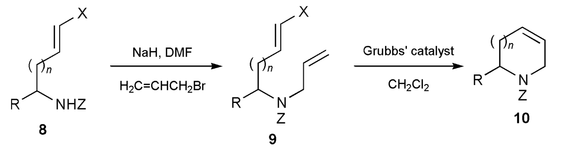
Table 1



(E)-Oxime[a]	Organometallic Addition	Yield (%) (de (%))	R	X	*n*	Diene	Yield (%)	Heterocycle (configuration at C-2)	Yield (%)
(*R*)-PhCH=CHCH=NOR*	MeLi[b]	[c](>95)	Me	Ph	0	**6a**	72[c]	**7a** (*R*)	87
(*R*)-PhCH=CHCH=NOR*	*n*-BuLi[b]	[c](>95)	*n*-Bu	Ph	0	**6b**	66[c]	**7b** (*R*)	78
(*S*)-PhCH=CHCH=NOR*	*i*-BuLi[d]	95 (88)	*i*-Bu	Ph	0	**6c**	83	**7c** (*S*)	74
(*R*)-PhCH=CHCH=NOR*	PhLi[b]	62 (>95)	Ph	Ph	0	**6d**	52	**7d** (*S*)	51
(*S*)-*n*-PrCH=NOR*	$H_2C{=}CHCH_2MgBr$	[c](87)	*n*-Pr	H	1	**6e**	39[c]	**7e** (*R*)	90
(*S*)-PhCH=NOR*	$H_2C{=}CHCH_2MgBr$[e]	[c](94)	Ph	H	1	**6f**	71[c]	**7f** (*S*)	62

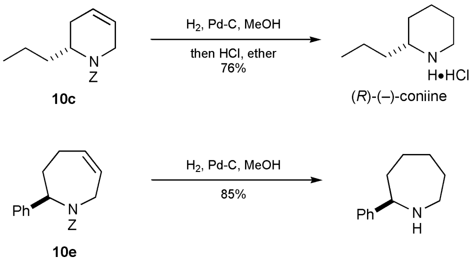
[a] R* = 1-phenylbutyl; configuration as indicated. [b] This addition reaction reported in ref 15. [c] Yield over 2 steps. [d] The addition to the (*R*)-enantiomer of the oxime reported in ref 15. [e] The addition to the (*R*)-enantiomer of the oxime reported in ref 16.

Table 2



Carbamate	Configuration (ee (%))	R	X	*n*	*N*-Allyl carbamate	Yield (%)	Heterocycle (configuration at C-2)	Yield (%)
8a[a]	*S* (89[b])	Me	Ph	0	**9a**	74	**10a** (*S*)	84
8b[c]	*R* (>95[d])	Ph	Ph	0	**9b**	63[e]	**10b** (*R*)	93
8c[f]	*R* (90)	*n*-Pr	H	1	**9c**	90	**10c** (*R*)	88
8d[g]	*S* (98)	4-MeO-C_6H_4	H	1	**9d**	97	**10d** (*S*)	91
8e[h]	*R* (90)	Ph	H	2	**9e**	90	**10e** (*R*)	65

[a] The preparation of the (*R*)-enantiomer is described in ref 15. [b] Enantiomeric excess (ee) of the *N*-allyl derivative **9a** not **8a**. [c] The preparation of the (*S*)-enantiomer is described in ref 15. [d] Refers to the diastereomeric excess (de) of the immediate precursor to **8b**. [e] Allylation using allyl bromide/base caused double bond migration; prepared using allyl methyl carbonate/Pd(0); see text. [f] Prepared by addition of allylmagnesium bromide to the oxime ether (Table 1), followed by cleavage of the N–O bond, and reaction with benzyl chloroformate. [g] Prepared as described in ref 16. [h] Prepared by addition of phenyllithium to the oxime ether, followed by cleavage of the N–O bond, and reaction with benzyl chloroformate.



Scheme 2

Finally two of the heterocycles prepared by the RCM reaction were converted into known compounds for confirmation of structure and configuration. Thus the 6- and 7-membered Z-protected compounds **10c** and **10e** were hydrogenated over palladium-on-charcoal to give (*R*)-(—)-coniine and the known 2-phenylazepane[19] respectively (Scheme 2).

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Notes and references

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