Switching stereoselectivity in rhodium-catalysed 1,4-additions: the asymmetric synthesis of 2-substituted pyrrolizidinones†

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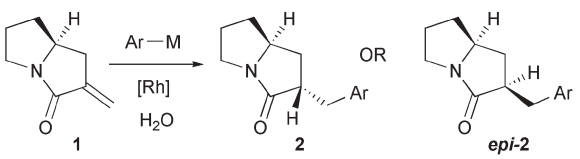
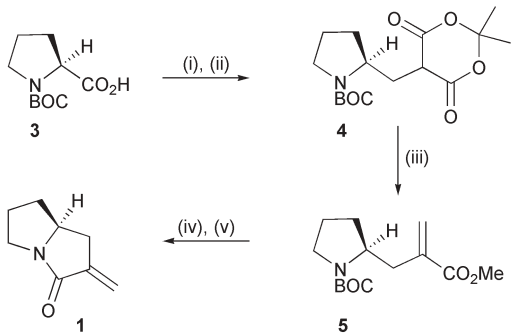
The appropriate choice of organometallic nucleophile enables the straightforward preparation of different stereoisomers of 2-substituted pyrrolizidinones utilising the rhodium-catalysed 1,4-addition reaction.

The stereoselective construction of C–C bonds using the rhodium-catalysed 1,4-addition of organometallics has emerged as fundamental methodology for organic synthesis.[1] Although still relatively rare, an important sub-set of this type of process is the asymmetric arylation of activated alkenes or allenes *via* enantioselective protonation.[2,3] This approach entails the selective protonation of a chiral π-allylrhodium intermediate formed by the reaction of a 1,1′-disubstituted substrate and an arylrhodium species.[4] Here we report a stereoselective route to prepare 2-substituted pyrrolizidinones utilising the rhodium-catalysed 1,4-addition of organometallics to an enantiopure 1,1′-disubstituted activated alkene **1** (Scheme 1).[5] Moreover, we show that the diastereoselectivity of the process can be switched to afford **2** or ***epi*-2** by changing the aryl nucleophile and therefore manner of protonation.

The products from this process are valuable intermediates in the synthesis of compounds related to pyrrolizidine alkaloids. The facility to employ catalysis to modify the structure of a parent pyrrolizidinone and dictate the stereochemistry of the product is a significant addition to existing synthetic approaches.[6] The bicyclic lactam **1** was straightforward to prepare employing the method reported by Tsukamoto *et al.* for the synthesis of α-substituted acrylic esters (Scheme 2).[7] Thus, the DCC mediated coupling of *N*-BOC-L-proline to Meldrum's acid followed by reduction with sodium borohydride afforded **4**, which in the presence of *N*,*N*-dimethylmethyleneammonium iodide (Eschenmoser's iodide salt) and methanol produced the acyclic α-dehydro-γ-amino acid **5** *via* a Mannich-type process. The desired pyrrolizidinone **1** was



Scheme 1

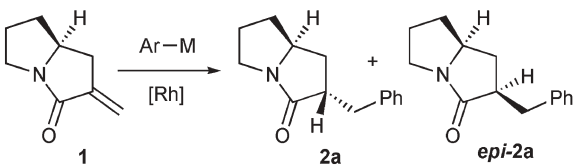


Scheme 2

obtained following TFA deprotection of the BOC group and lactimisation under basic conditions.

A wide range of different organometallics have been reported to participate in the key transmetallation to rhodium and subsequent enantioselective conjugate addition.[1] In all cases the configuration of the newly formed stereocentre is dictated by the nature and configuration of the ligand rather than the organometallic nucleophile used. In our work, initial experiments examined the addition of three different organometallic nucleophiles ($PhSi(OMe)_3$, $PhB(OH)_2$ and PhZnCl) to the enantiopure pyrrolizidinone **1** to afford the two stereoisomers **2a** and ***epi*-2a** as shown in Table 1. In each example, the major stereoisomer could be isolated by flash chromatography. The absolute configuration at C(2) was assigned by comparison of ^{1}H NMR and NOE spectra with literature data.[8]

Table 1 Comparison of organometallic species



Entry	Ph–MX_n	Conversion[a] (Yield %)	Conditions[b]	**2a** : ***epi*-2a**[c]
1	$PhSi(OMe)_3$	100 (69)	A	4 : 1
2	$PhB(OH)_2$	100 (70)	B	3 : 1
3	PhZnCl	95 (68)	C	1 : 3

[a] Determined by NMR conversion. [b] Condition A: $[Rh(cod)_2]BF_4$, dioxane–H_2O (10/1), 110 °C, 24 hours. Condition B: $[Rh(cod)Cl]_2$, dioxane–H_2O (10/1), 110 °C, 24 hours. Condition C: (i) $[Rh(cod)Cl]_2$, TMS–Cl, THF, 20 °C, 24 hours; (ii) H_2O quench. [c] The ratio was determined by integration of signals in the ^{1}H NMR spectra of crude reaction mixtures before purification.

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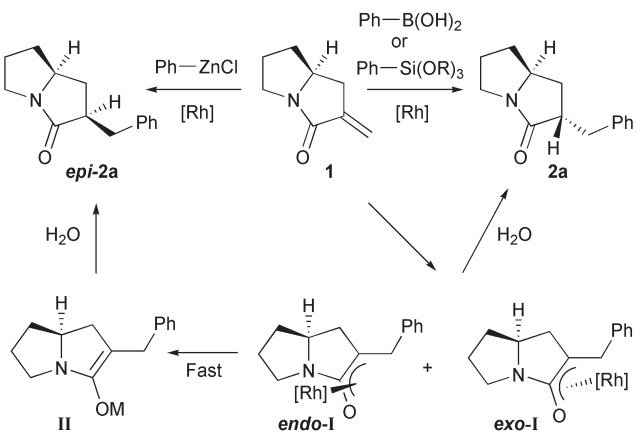
The reaction conditions employed for the addition of the organometallic nucleophiles were based on precedent from previous studies (A, B or C in Table 1).[9] For arylboronic acids and arylsiloxanes, a high temperature and the presence of water in the reaction mixture are crucial for an efficient transmetallation. Under the described conditions the (2*S*,7*S*) stereoisomer **2a** was produced as the major product. Although relatively few examples have been reported, the rhodium-catalysed conjugate addition of arylzinc reagents proceeds at ambient temperatures in the absence of water.[10] This facilitates the synthesis of the (2*R*,7*S*) stereoisomer ***epi*-2a** using the conditions represented in C (Entry 3, Table 1).

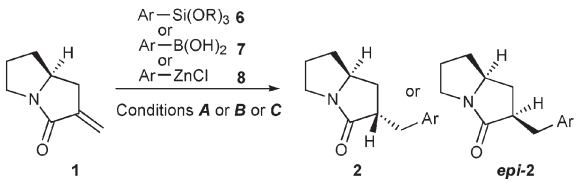
The observed switch in stereoselectivity is attributed to the rate of transmetallation which dictates the reaction temperature and subsequent mode of protonation. Two pathways may be envisioned to account for the observed stereoselectivity (Scheme 3). The insertion of an initial arylrhodium species affords the rhodium oxa-π-allyl species **I**, with the rhodium expected to be situated predominantly on the convex face (***exo*-I**). With arylzinc reagents the transmetallation step is fast, even at room temperature.[11] Thus, the arylrhodium species is regenerated with concomitant conversion of **I** to the zinc enolate **II** (M = Zn) which is trapped with trimethylsilyl chloride. On quenching the reaction with water, protonation of **II** occurs preferentially at the less hindered convex face resulting in the formation of ***epi*-2a**. With arylboronic acids and arylsiloxanes the active [Rh]–OH complex is required for efficient aryl transfer. Hence, the protonation of **I** occurs prior to transmetallation. The mechanism of the protonation step in rhodium-catalysed 1,4-additions has not been fully established, although Hayashi *et al.* have recently suggested that on a chiral π-allylrhodium intermediate generated by the arylation of diphenylphosphinylallenes, protonation occurs on the same face as rhodium.[3] In the presented case, the major stereoisomer **2a** would arise by protonation of ***endo*-I** by prior coordination of water to Rh. Alternatively, if protonation occurs on the opposite face to Rh (from solution) the major stereoisomer **2a** would emerge from ***exo*-I**. Treatment of ***epi*-2a** with potassium *tert*-butoxide in refluxing ethanol effected the equilibration to produce the thermodynamically more stable isomer **2a**.[12]

Following the success of the initial experiments, the scope of the organometallic nucleophile was investigated to establish the versatility of the reaction (Table 2). In all cases the reaction proceeded to afford the (2*S*,7*S*) stereoisomer as the major product



Scheme 3

Table 2 Scope of organometallic nucleophile in selective additions to **1**



Entry	Ar–MX_n	Product[d]	Yield (%)[e]
1[a]	1-naphthyl **6b**	**2b** (4 : 1)	78
2[a]	4-PhC_6H_4 **6c**	**2c** (4 : 1)	71
3[a]	4-$CF_3C_6H_4$ **6d**	**2d** (2 : 1)	51
4[a]	4-$MeOC_6H_4$ **6e**	**2e** (6 : 1)	86
5[a]	4-MeC_6H_4 **6f**	**2f** (4 : 1)	76
6[b]	4-BrC_6H_4 **7g**	**2g** (2 : 1)	53
7[b]	4-$CHOC_6H_4$ **7h**	**2h** (3 : 1)	70
8[c]	1-naphthyl **8b**	***epi*-2b** (1 : 2)	54
9[c]	4-PhC_6H_4 **8c**	***epi*-2c** (1 : 2)	62

[a] Condition A: $[Rh(cod)_2]BF_4$, dioxane–H_2O (10/1), 110 °C, 24 hours. [b] Condition B: $[Rh(cod)Cl]_2$, dioxane–H_2O (10/1), 110 °C, 24 hours. [c] Condition C: (i) $[Rh(cod)Cl]_2$, TMS–Cl, THF, 20 °C, 24 hours; (ii) H_2O quench. [d] The ratio was determined by integration of signals in the ^1H NMR spectra of crude reaction mixtures before purification. [e] Isolated yield of single stereoisomer.

with arylsiloxanes or arylboronic acids and the (2*R*,7*S*) stereoisomer as the major product with arylzinc reagents. The major stereoisomer could be isolated by flash chromatography and the absolute configuration at C(2) was confirmed by ^1H NMR and NOE experiments.

In summary, we have demonstrated that the rhodium-catalysed addition of various organometallic reagents can be utilised in the synthesis of enantiopure 2-substituted pyrrolizidinones. Futhermore, the reaction can be tailored to give predominantly one diastereomer by simply choosing the appropriate nucleophile.

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