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## Accepted Manuscript

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Robert Lowe, Shereen Fathy, Visuvanathar Sridharan

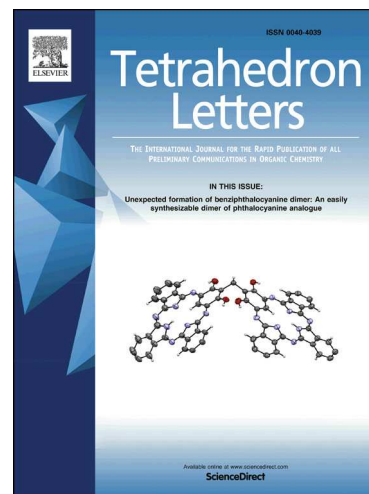
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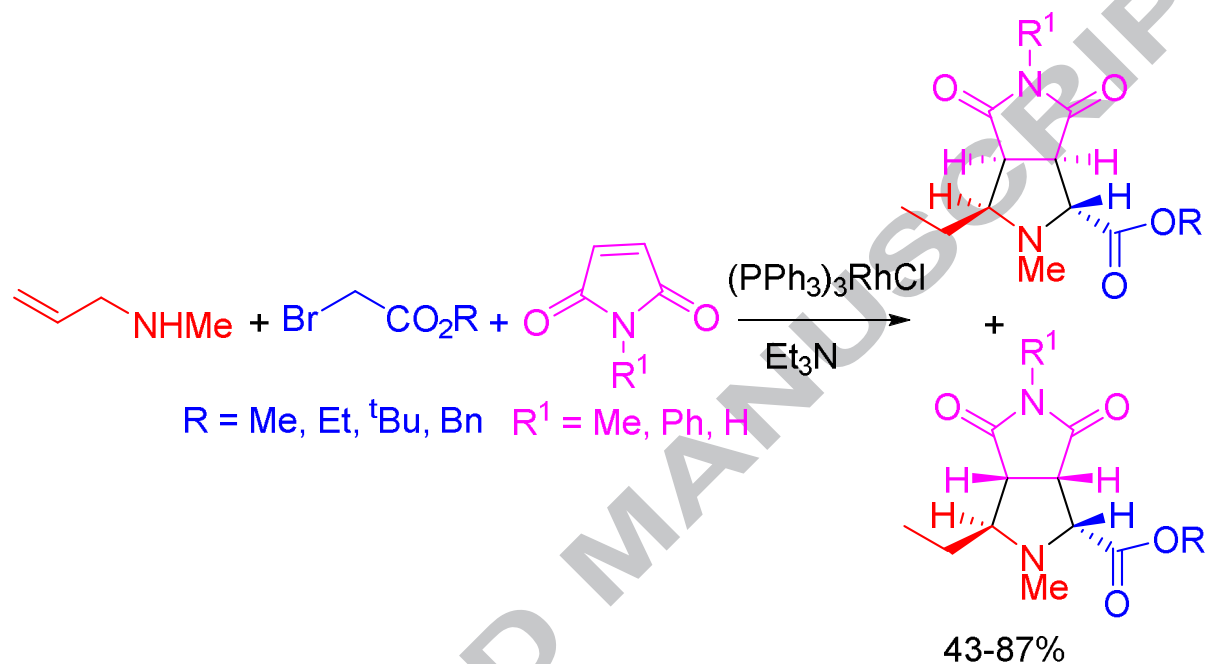
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## Rhodium catalyzed, one-pot, three component redox-neutral process towards fused ring heterocycles

Robert Lowe, Shereen Fathy and Visuvanathar Sridharan\*

School of Chemistry, University of Leeds, LS2 9JT, UK

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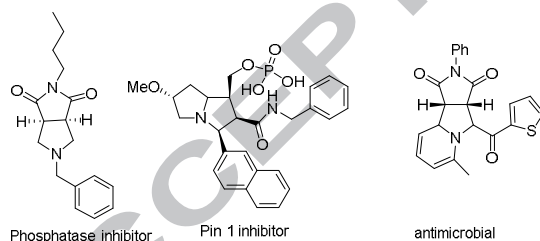
Multicomponent Reaction

## ABSTRACT

A three component, rhodium-catalyzed isomerisation/1,3-dipolar cycloaddition reaction is described for the synthesis of fused ring heterocycles as *endo/exo* isomers, with the formation of three new bonds and four stereocenters.

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Bicyclic pyrrolidine scaffolds are found in various bioactive molecules, possessing medicinal properties such as potent protein phosphatase 1 and 2A inhibition, high levels of anticancer activity against a broad range of tumour cells lines,<sup>1</sup> anti-tumour Pin1 inhibition,<sup>2</sup> and antimicrobial activity<sup>3</sup> (Fig. 1).



**Figure 1.** Selected bioactive bicyclic pyrrolidines

Recently, there has been strong interest in cascade reactions<sup>4</sup> (multiple consecutive, one-pot reactions - also named domino reactions) because of their operational simplicity, the minimization of chemical waste, energy conservation and high atom economy, which make this approach attractive for the fine chemical and pharmaceutical industry.

The large number of possible transformations, wide functional group tolerance and the catalytic nature of these processes make rhodium chemistry an ideal basis for the development of new cascade reactions, enabling rapid entry to highly complex molecules.

\* Corresponding Author: [V.Sridharan@leeds.ac.uk](mailto:V.Sridharan@leeds.ac.uk); Tel +44-1133436520

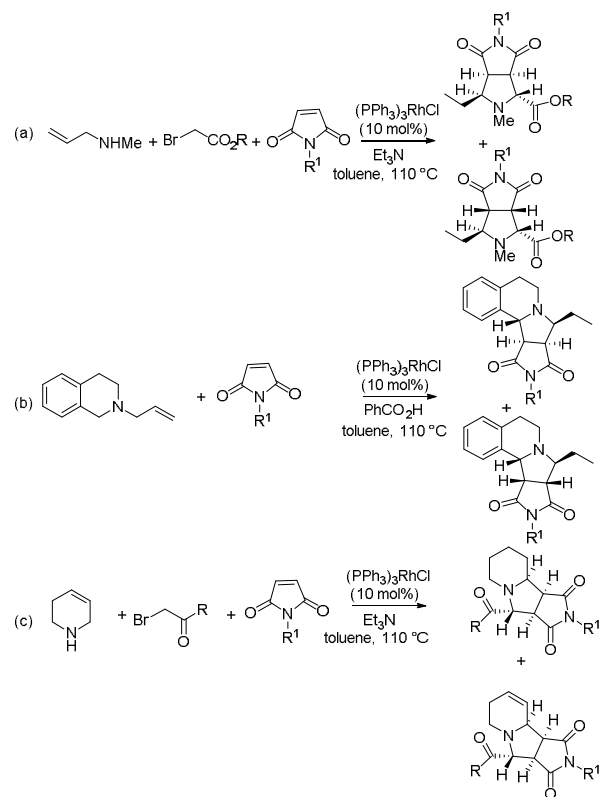
Metals such as Rh, Ru, Ir, Co, Mo, Fe and Cr have been reported to catalyze the double bond isomerization of allylic amines to enamines.<sup>5</sup> Nielsen and co-workers have reported a ruthenium/Brønsted acid catalyzed tandem isomerization/*N*-acyliminium ion cyclisation sequence for the synthesis of tetrahydro- $\beta$ -carbolines whilst Sorimachi and Terada have reported ruthenium/Brønsted acid catalyzed cascade isomerization/Friedel-Crafts type reactions.<sup>6,7</sup> We have been involved in generating azomethine ylides *via* a rhodium catalyzed isomerization process using either two or three component processes.<sup>8</sup>

Herein, we report a novel three component rhodium catalyzed isomerization/1,3-dipolar cycloaddition cascade for the synthesis of fused-ring cycloadducts as *endo/exo* isomers, with the formation of three new bonds and four stereocenters using either acyclic allylamines (Scheme 1a) or cyclic allylamines (Scheme 1b, c).

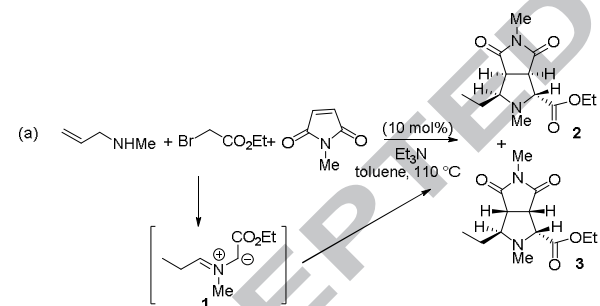
This rhodium catalyzed process has significant advantages over traditional methods to generate azomethine ylides from aliphatic aldehydes and sarcosine alkylesters since aliphatic aldehydes with enolisable hydrogens undergo aldol condensation/enamine formation which subsequently results in lower yields of the corresponding cycloadducts.<sup>9</sup>

The initial reaction was carried out using ethylbromoacetate (1 mmol), *N*-allylmethylamine (1 mmol) and triethylamine (1 mmol) in toluene (15 mL), stirring at room temperature until the alkylation was complete as shown by TLC. Subsequent addition of *N*-methylmaleimide (1 mmol) and (PPh<sub>3</sub>)<sub>3</sub>RhCl (10 mol%), and heating at 110 °C for 16 h afforded the *endo* and *exo*

cycloadducts **2** and **3** in 63% yield with a 1.7:1 ratio, proceeding *via* the *anti*-dipole **1** (Scheme 2, Table 1, entry 1).



**Scheme 1.** Rhodium catalyzed, three component cycloaddition cascades



**Scheme 2.** Three component, 1,3-dipolar cycloaddition reaction

The relative stereochemistry of cycloadducts **2** and **3** were assigned by n.O.e (ESI). The rhodium catalyzed cycloaddition reaction of symmetrical dipolarophiles such as *N*-phenylmaleimide and maleimide with a range of alkyl bromoacetates and *N*-methylallylamine was also explored and gave mixtures of *endo* and *exo* cycloadducts in good to high yields (Table 1 entries 2-8). Cycloadduct **2** was not converted into cycloadduct **3** under the reaction conditions.

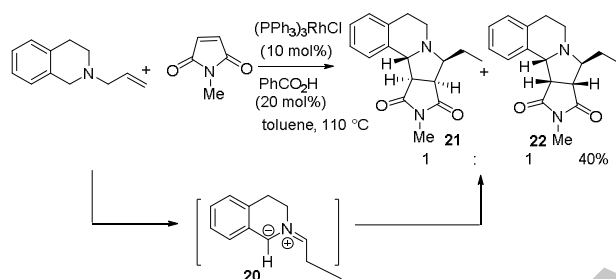
**Table 1.** Rhodium catalyzed three component cycloaddition cascade reaction using *N*-allylmethylamine<sup>a</sup>

Entry	Alkylbromide	Product	Yield (%) <sup>b</sup>
1	Br-CH <sub>2</sub> -CO <sub>2</sub> Et	2 : 3 1.7 : 1	63
2	Br-CH <sub>2</sub> -CO <sub>2</sub> Et	4 : 5 1.4 : 1	85
3	Br-CH <sub>2</sub> -CO <sub>2</sub> Me	6 : 7 1.4 : 1	57
4	Br-CH <sub>2</sub> -CO <sub>2</sub> Me	8 : 9 1.3 : 1	46
5	Br-CH <sub>2</sub> -CO <sub>2</sub> Bu	10 : 11 1.7 : 1	48
6	Br-CH <sub>2</sub> -CO <sub>2</sub> Bn	12 : 13 1 : 0.5	77
7	Br-CH <sub>2</sub> -CO <sub>2</sub> Bn	14 : 15 1 : 0.6	43
8	Br-CH <sub>2</sub> -CO <sub>2</sub> Bn	16 : 17 1 : 0.2	58
9	Br-CH <sub>2</sub> -CO <sub>2</sub> Bn	18 : 19 1 : 0.2	37

<sup>a</sup> Reagents and conditions: alkyl bromide (1 mmol), *N*-allylmethylamine (1 mmol), triethylamine (1 mmol), toluene, room temperature, 16 h, then dipolarophile (1 mmol), (PPh<sub>3</sub>)<sub>3</sub>RhCl (10 mol%), 110 °C, 17-24 h. <sup>b</sup> Isolated yield.

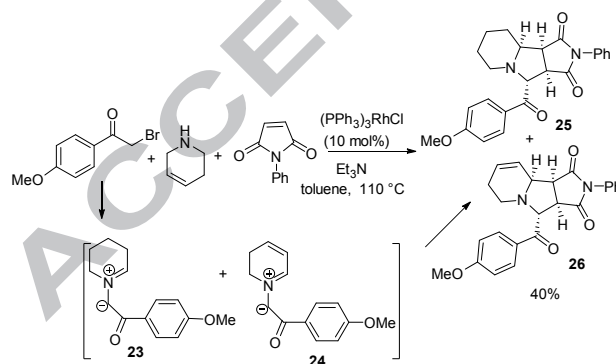
Next, we briefly examined unsymmetrical dipolarophiles in the described cascade reaction. Thus benzyl bromoacetate (1 mmol), *N*-allylmethylamine (1 mmol) and triethylamine (1 mmol) in toluene (15 mL) were stirred at room temperature until alkylation completion, followed by the addition of phenylvinylsulphone (1 mmol) and heating at 110 °C for 24 h to afford *endo*-cycloadduct **18** (30%) together with the Michael adduct **19** (7%). In this case the cycloaddition was both stereo- and regioselective (Entry 9).

The two component cycloaddition reaction of *N*-allyl-1,2,3,4-tetrahydroisoquinoline (1 mmol) and *N*-methylmaleimide (1 mmol), using benzoic acid (20 mol%) and (PPh<sub>3</sub>)<sub>3</sub>RhCl (10 mol%) in toluene (15 mL) at 110 °C, afforded the *endo* **21** (with respect to the ethyl group and maleimide) and *exo* **22** cycloadducts in 40% yield (Scheme 3). In this case benzoic acid was required as an additive to aid the formation of *anti*-dipole **20**; the reaction was unsuccessful in its absence. Seidel and co-workers previously reported that benzoic acid facilitates amine  $\alpha$ -functionalization *via* an intermediate azomethine ylide.<sup>10</sup>



**Scheme 3.** Two component, 1,3-dipolar cycloaddition reaction

Finally, we briefly explored the cycloaddition reaction of 1,2,3,6-tetrahydropyridine (1 mmol) and 2-bromo-4'-methoxyacetophenone (1 mmol) with triethylamine (1 mmol) in toluene (15 mL) for 16 h, followed by the addition of *N*-phenylmaleimide and (PPh<sub>3</sub>)<sub>3</sub>RhCl (10 mol%) and heating at 110 °C for 16 h to afford two *endo* (with respect to the piperidine ring and maleimide) cycloadducts **25** and **26** in 40% yield with a 0.5:1 ratio, proceeding *via* the *anti*-dipoles **23** and **24** (Scheme 4).



**Scheme 4.** Tetrahydropyridine cycloaddition cascade.

The relative stereochemistry of cycloadducts **25** and **26** were assigned by n.O.e (ESI). Regiospecific dehydrogenation occurred during the above cycloaddition reaction.

In summary we have successfully carried out a one-pot, three component, rhodium-catalyzed isomerization/1,3-dipolar cycloaddition cascade to give fused ring heterocycles as *endo/exo* isomers in good yields, with the formation of three new bonds and four stereocenters.

## Acknowledgments

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**Highlights**

- Readily available starting materials were used to increase the molecular complexity of the scaffolds in one-step
- Atom economical process
- Synthesis of biologically important motifs

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