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Iridium catalyzed three component cycloaddition cascades to fused ring heterocycles

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ABSTRACT

A three component iridium-catalyzed 1,3-dipolar cycloaddition reaction has been used for the synthesis of fused ring heterocycles as *endo/exo* isomers, in good yields with the formation of three new bonds and four stereo centers.

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Bicyclic pyrrolidines are important heterocycles and form the structural skeletons of a wide range of compounds which exhibit bioactivities for a variety of medical conditions. Some of these medicinal properties include HIV inhibitors,¹ as well as antifungal, antibacterial,² and antithrombotic activities³ (Fig. 1).

It has become increasingly more important in the drug discovery process that new facile methods are developed in which more complex variants of these heterocyclic scaffolds may be produced in 'greener' ways. This can be achieved by using more selective methods where the number of steps involved and the amount of solvents used and waste produced are reduced, allowing the process to be more efficient and environmentally friendly.

Nonstabilized azomethine ylides are highly reactive intermediates. Classical methods to generate nonstabilized azomethine ylides include desilylation of the methyl iminium ion,⁴ reaction of *N*-oxides with strong base,⁵ and condensation of α -amino acids with carbonyl compounds.⁶

Our group and others have been involved in generating stabilized and non-stabilized azomethine ylides and subsequent 1,3-dipolar cycloaddition reactions either via a metal catalyzed route or a thermal decarboxylation pathway.^{6,7}

Indirect functionalization of alcohols using catalytic amounts of a metal complex and base which generates only water as a by-product is an attractive green alternative to standard C–C and C–N bond forming reactions. These cascades are termed as redox–neutral,

hydrogen auto transfer or hydrogen borrowing processes. Our group and others have been involved in the alkylation of amines and active methylene compounds using alcohols catalyzed by iridium, rhodium, and ruthenium complexes, to form new C–N and C–C bonds.⁸

In this communication we report a novel one-pot three component iridium catalyzed dehydrogenation/1,3-dipolar cycloaddition cascade utilizing alcohols to generate fused-ring heterocycles with the formation of three new bonds and four stereo centers (Scheme 1, path A).

The initial reaction was performed using 3,4-dimethoxybenzylalcohol (1 mmol), *L*-proline (1.5 mmol), *N*-methylmaleimide (2 mmol), Cs₂CO₃ (0.2 mmol), and [IrCp*Cl₂]₂ (0.05 mmol) in

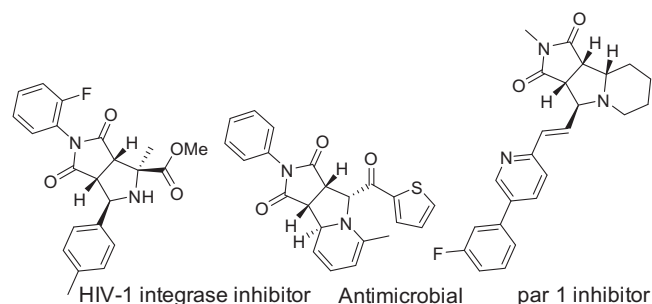
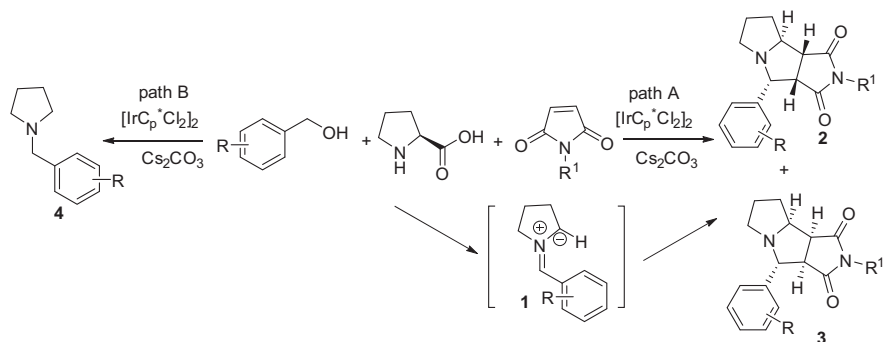


Figure 1. Bioactive bicyclic pyrrolidines.

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Scheme 1. Ir-catalyzed three component cycloaddition cascade.

Table 1
Iridium catalyzed three component cycloaddition reaction^a

Entry	Alcohol	Product	Yield ^b (%)
1			73
2			60
3			52
4			60
5			38
6			51 ^c

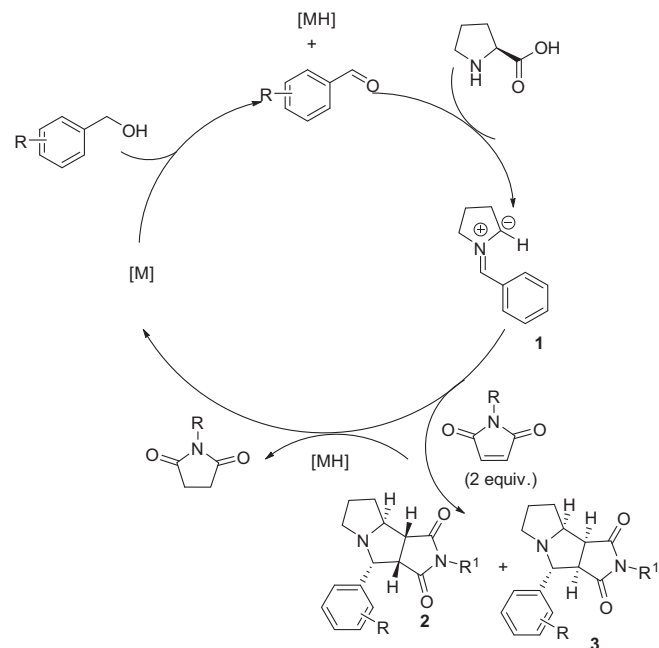
^a Dipolarophile (2 mmol), L-proline (1.2 mmol), an alcohol (1 mmol), Cs₂CO₃, (20 mol %), and [IrCp^{*}Cl₂]₂ (5 mol %) toluene (10 mL) were stirred under reflux (110 °C 24 h).

^b Isomers were separated and isolated total yield.

^c Only major isomer was isolated.

toluene (10 mL) at reflux for (110 °C, 24 h) affording the *endo* and *exo* cycloadducts, **5** and **6**, in 73% total yield and a ratio of 0.6:1 (Table 1, entry 1). *endo/exo* ratios were determined by NMR of the crude reaction mixture. Two equivalents of maleimide were used to regenerate the active iridium catalyst by acting as a recipient for the hydrogen removed from 3,4-dimethoxybenzylalcohol during the dehydrogenation process. The relative stereochemistry of cycloadducts **5** and **6** were assigned using NOE studies and confirmed by single crystal X-ray crystallography (Fig. 2).⁹ The cycloaddition occurred via the *endo/exo* transition states of the *anti* dipole **1** (with respect to the aryl ring and maleimide) (Scheme 1, path A). In the above process none of product **4** was formed from the redox-neutral pathway (Scheme 1, path B). Moreover no reaction took place in the presence of Cs₂CO₃ alone, indicating that the combination of the iridium complex and base was necessary for the reaction.

Benzyl alcohols substituted with electron donating groups readily underwent cycloaddition reaction to afford the *endo/exo* products **5–12** in good yields (40–77%) (Table 1, entries 1–4). The *endo/exo* selectivity trends were similar throughout the series. However, benzyl alcohols substituted with an electron withdrawing group resulted in a low yield of the cycloadducts (Table 1, entry



Scheme 2. Proposed mechanism for Ir-catalyzed 3-component reaction.

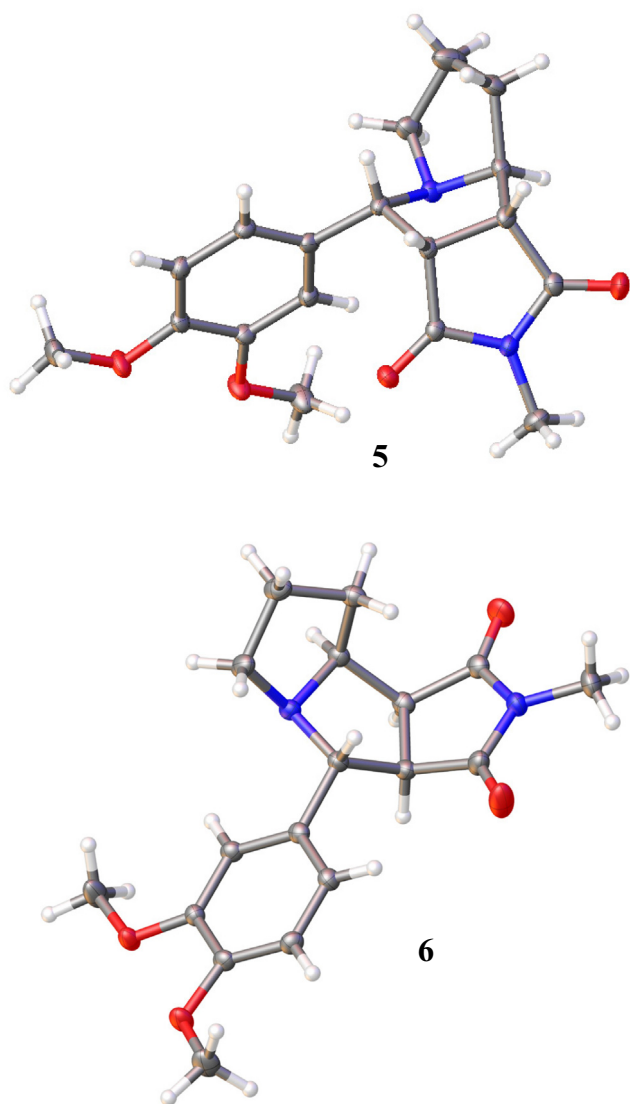


Figure 2. Single crystal structures determined by X-ray diffraction.

5). The heteroaromatic alcohol, thiophene-2-methanol, was also used in the above reaction to give the desired product (Table 1, entry 6) in good yield.

The proposed mechanism for the formation of the fused ring cycloadducts is shown in Scheme 2.

Iridium catalyzed oxidation of the benzylic alcohol to the corresponding aldehyde followed by condensation with proline generates the azomethine ylide **1** which undergoes 1,3-dipolar cycloaddition reaction with *N*-methylmaleimide or *N*-phenylmaleimide to produce the *endo* and *exo* cycloadducts **2** and **3**.

In conclusion we have developed a novel one-pot, three component iridium catalyzed dehydrogenation/1,3-dipolar cycloaddition cascade utilizing alcohols to generate fused-ring heterocycles with the formation of three new bonds and four stereo centers in good yields.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2016.05.029>.

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 9. Deposition numbers for compounds **5** and **6** CCDC 1473013–1473014 contains the supplementary crystallographic data for this structures. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.