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Ruthenium(II)-catalysed direct synthesis of ketazines using secondary alcohols†

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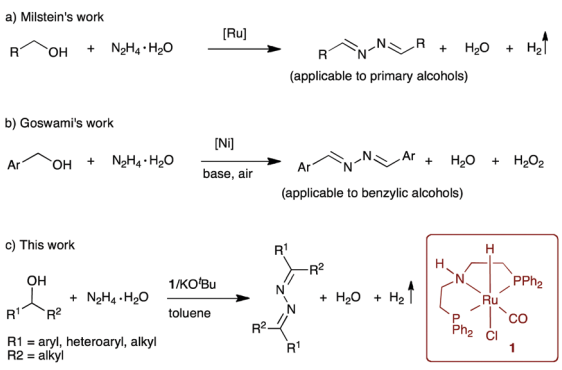
Direct one-pot synthesis of ketazines from secondary alcohols and hydrazine hydrate catalyzed by a ruthenium pincer complex is reported, which proceeds through O–H bond activation of secondary alcohols *via* amine–amide metal–ligand cooperation in the catalyst. Remarkably, liberated molecular hydrogen and water are the only byproducts.

Azines ($R_2C{=}N{-}N{=}CR_2$) are versatile building blocks for the synthesis of various nitrogen containing natural products and molecules of pharmacological relevance.[1,2] They are a class of compounds with interesting chemical properties and undergo a wide variety of chemical transformations.[3] Azines have attracted considerable attention in cycloaddition reactions due to the presence of two conjugated double bonds. For example, azines can be used for the synthesis of N-heterocyclic compounds *via* cycloaddition reactions.[4] Azines display interesting physical properties and are used as ion-selective optical sensors,[5] conductive materials,[6] NLO materials,[7] dye lasers, and image recording materials.[8] The reducing tendency of azines makes them suitable for application as hole-transport materials in optoelectronic devices.[9] Additionally, azines can be used in the construction of covalent organic frameworks (COFs)[10] and chemosensing detectors[11] and as building blocks in supramolecular chemistry.[12] Recently, azines have also been utilized in the synthesis of isoquinoline derivatives.[13]

Conventional methods for the synthesis of azines involve the treatment of carbonyl compounds with hydrazine hydrate or hydrazones.[1a,14] Alternative methods have been developed to synthesize azines from diazo compounds, alkynes, isocyanates and azides.[15,16] Synthesis of azines directly from alcohols by the traditional method is not known. In general, alcohols have to be oxidized to the carbonyl compounds, which involves the excess use of toxic inorganic salts, and further reaction with hydrazine hydrate provides azine products. This multistep synthesis of azines produces waste and requires workup methods and isolation procedures. Thus, developing a direct one-pot synthesis of azines from alcohols can be valuable in organic synthesis. Catalytic dehydrogenation of feedstock chemicals such as alcohols to value-added products with the concomitant generation of dihydrogen is of much interest in the context of the hydrogen economy and is an effective alternative to the classical oxidation reactions. In this direction, acceptorless dehydrogenation of alcohols has become an important paradigm to afford atom-economical and sustainable chemical transformations[17] as the oxidation of alcohols is achieved without using toxic oxidizing reagents and sacrificial hydrogen acceptors. Recently, Milstein and Goswami reported the catalytic one-pot direct synthesis of azines using primary alcohols and hydrazine hydrate (Scheme 1a and b).[18] However, reactions remain applicable to the synthesis of aldazines using primary and benzylic primary alcohols. Direct synthesis of ketazines using secondary alcohols is unknown and challenging due to the lower reactivity and higher steric hindrance of secondary alcohols in comparison to primary alcohols. Recently, using ruthenium PNP pincer complex **1** we have developed the α-alkylation and



Scheme 1 Direct catalytic synthesis of azines using alcohols.

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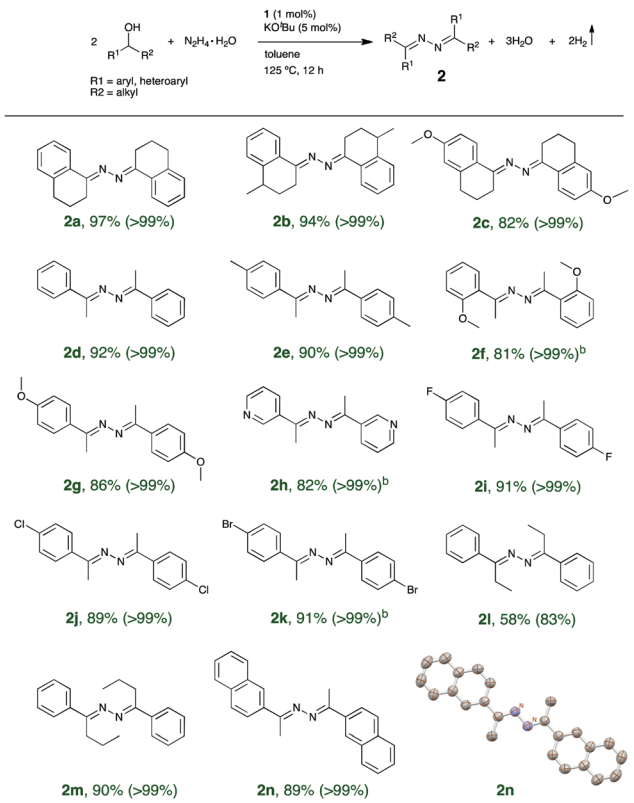
† Electronic supplementary information (ESI) available: Experimental procedures, NMR spectra of ketazines and their spectral data; and X-ray data for **2d**, **2n**, and **3m**. CCDC 1889888–1889890. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9cc01383k

α-olefination of nitriles[19a,b] using primary and secondary alcohols, respectively, and also the cross-coupling of secondary alcohols.[19c] Facile activation of the O–H bonds of alcohols and water through amine–amide metal–ligand cooperation was established from our previous studies.[19,20] Herein, we report a new catalytic protocol for the synthesis of ketazines directly from secondary alcohols and hydrazine hydrate (Scheme 1c).

Using tetralin-1-ol as a benchmark substrate along with hydrazine hydrate, the optimization studies were carried out to find the suitable experimental conditions for ketazine synthesis (see Table S1, ESI†). When the reaction between tetralin-1-ol (0.5 mmol), hydrazine hydrate (0.75 mmol), catalyst **1** (1 mol%) and base (5 mol%, KO^{t}Bu) in toluene with molecular sieves (4 Å) was performed at 125 °C, the quantitative conversion of the secondary alcohol occurred to provide an azine product **2a** in 97% yield (Table 1). Notably, no desired azine (**2a**) formation was observed upon reaction of the Milstein PNP-Ru catalyst with tetralin-1-ol under reported conditions.[18b] Using the optimal reaction conditions for the synthesis of ketazine, we examined the scope of different benzylic secondary alcohols in catalysis. Remarkably, in all cases, we observed almost quantitative conversions and the corresponding ketazine products were obtained in good to excellent yields (Table 1).

Table 1 Ruthenium catalysed synthesis of ketazines using benzylic secondary alcohols[a]



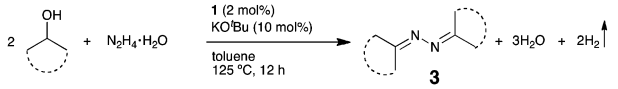
[a] Catalytic conditions: catalyst **1** (1 mol%), base (5 mol%), secondary alcohol (0.5 mmol), $N_2H_4{\cdot}H_2O$ (0.75 mmol) and toluene (2 mL) with molecular sieves (4 Å) were heated at 125 °C in a Schlenk flask for 12 h. Conversion of alcohols was determined by GC analysis and are given within parentheses. Yields correspond to isolated products after column chromatography. [b] Reaction was conducted with 2 mol% catalyst **1** and 10 mol% base.

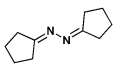
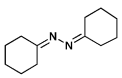
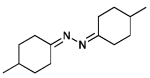
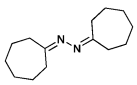
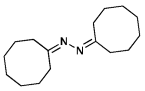
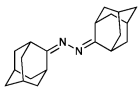
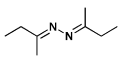
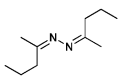
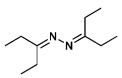
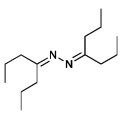
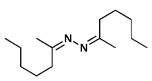
In general, simple cyclic and benzylic secondary alcohols with methyl substituents provided the corresponding products in good yields. The reaction of 4-methyl tetralin-1-ol, 1-phenyl-1-ethanol and 1-(*p*-tolyl)ethanol substrates provided the ketazine products **2b**, **2d** and **2e**, respectively, in more than 90% isolated yields. Further, the reaction of 6-methoxytetralin-1-ol, 1-(2-methoxyphenyl)ethanol, and 1-(4-methoxyphenyl)ethanol provided the ketazine products **2c**, **2f** and **2g** in 81–86% yields, indicating that the catalytic azine formation is sensitive to steric hindrance in the proximity as well as electronic factors. Notably, azine product **2f** can be used in the synthesis of aphrodisiac drugs[22a] and is also used as dielectric and photosemiconductor materials.[22b] In addition, 1-(pyridin-3-yl)ethanol reacted with hydrazine hydrate to form an azine in good yield (**2h**, Table 1). Interestingly, electron withdrawing groups containing benzylic alcohols are well tolerated and afforded the symmetrical azines **2i**, **2j** and **2k** in 89–91% yields. The reaction also proceeded smoothly with 1-phenylpropan-1-ol and 1-phenylbutan-1-ol to afford the azine products **2l** and **2m** in 58% and 90% yields, respectively (Table 1). 1-(Naphthalen-2-yl)ethanol exhibited >99% conversion and provided product **2n** in 89% yield. Single-crystal X-ray analyses of compounds **2d** (see the ESI†) and **2n** (Table 1) confirmed their ketazine structures.

The scope of aliphatic secondary alcohols was explored in direct catalytic ketazine synthesis. A variety of cyclic as well as acyclic aliphatic secondary alcohols afforded good to excellent yields (Table 2). When cyclohexanol was examined under the optimized reaction conditions, 70% conversion was observed and product **3b** was isolated in 65% yield. Thus, increased loadings of catalyst **1** (2 mol%) and base KO^{t}Bu (10 mol%) were used, which resulted in the complete conversion of cyclohexanol and product **3b** in 84% isolated yield (Table 2). A wide variety of cyclic alcohols such as cyclopentanol, 4-methyl cyclohexanol, cycloheptanol and cyclooctanol were reacted with hydrazine hydrate, which provided the quantitative conversion of alcohols to afford symmetrical ketazine products **3a–3e** in very good yields (entries 1–5, Table 2). A sterically hindered substrate such as 2-adamantanol also afforded ketazine product **3f** in 78% yield (entry 6, Table 2). Further, acyclic symmetrical as well as unsymmetrical aliphatic secondary alcohols were explored in this catalytic transformation. When low boiling point secondary alcohols such as isopropanol and 2-butanol were subjected to the reaction, ketazine products **3g** and **3h** were obtained in 50% and 73% yields, respectively (entries 7 and 8, Table 2). Further, higher order acyclic secondary alcohols were used, leading to the formation of ketazine products **3i–3l** in excellent yields (entries 9–12, Table 2). Unsymmetrical acyclic secondary alcohols provided *E*/*Z* mixtures of ketazine products.

Notably, ketazines from natural products can also be synthesized using this methodology. Catalytic reaction of cholesterol with hydrazine hydrate under the standard conditions used in Table 2 provided the ketazine product **3m** in 45% yield in which isomerization of the homoallylic double bond was observed (Scheme 2). The diminished yield of **3m** may be attributable to

Table 2 Ruthenium catalyzed synthesis of ketazines using aliphatic secondary alcohols by catalyst **1**[a]

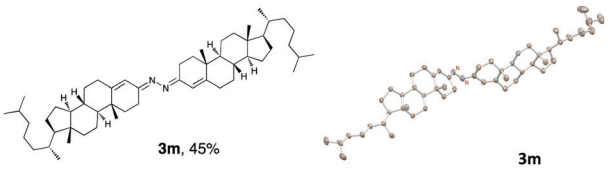


Entry	Product		Conv.[b] (%)	Yield[c] (%)
1		**3a**	>99	74
2		**3b**	>99	84
3		**3c**	>99	92
4		**3d**	>99	89
5		**3e**	>99	87
6[d]		**3f**	90	78
7[e]		**3g**	n.d.	50
8[e,f]		**3h**	>99	73
9[e,f]		**3i**	>99	90
10		**3j**	>99	83
11		**3k**	>99	84
12[f]		**3l**	>99	90

[a] Catalytic conditions: catalyst **1** (2 mol%), base (10 mol%), secondary alcohol (0.5 mmol), hydrazine hydrate (1.5 mmol) and toluene (2 mL) with molecular sieves (4 Å) were heated at 125 °C in a Schlenk flask for 12 h. [b] The conversion of alcohols was determined by GC analysis. [c] The yields correspond to isolated products after column chromatography. [d] The reaction was carried out for 18 h. [e] The yield of the product was calculated from ^{1}H NMR analyses using mesitylene as an internal standard. [f] The product isolated as a mixture of *E*/*Z* isomers. n.d.: not determined.

the low solubility of cholesterol in the reaction medium. The structure of ketazine **3m** is unequivocally corroborated by single-crystal X-Ray analyses.

To understand the reaction pathways, kinetic analysis was carried out. GC monitoring of the reaction progress for tetraline-1-ol with hydrazine hydrate catalyzed by **1** (1 mol%) confirmed that the reaction followed first-order kinetics with respect to the consumption of tetraline-1-ol. The formation of the corresponding 1-tetralone and hydrazone intermediates was observed in GC and ^{1}H NMR of the reaction mixture



Scheme 2 Direct synthesis and single crystal X-ray structure of ketazine **3m** using cholesterol.

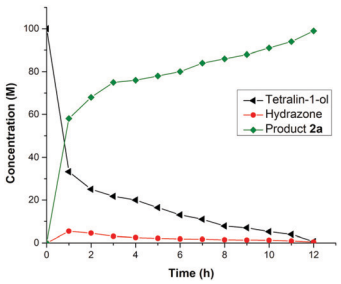
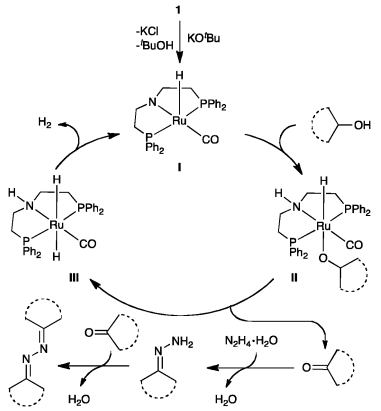


Fig. 1 GC monitoring of ketazine formation using tetralin-1-ol and hydrazine hydrate using ruthenium pincer catalyst **1**. The concentrations of tetralin-1-ol (black line), intermediate hydrazone (red line) and product **2a** (green line) are plotted for direct catalytic synthesis of ketazines from secondary alcohols.

(see the ESI†). ^{1}H NMR analysis of the reaction mixture showed a broad singlet at δ 5.20 ppm, indicating the formation of a hydrazone intermediate (Scheme S1, ESI†). Rapid reaction progress was observed at the outset of the reaction, then it slowed down gradually and exhibited complete conversion within 12 h (Fig. 1).

Based on these experimental studies and our previous work,[19–21] the catalytic cycle for the synthesis of ketazines using secondary alcohols catalyzed by **1** is proposed in Scheme 3. On treatment of catalyst **1** with KO^{t}Bu, a 16-electron unsaturated amide-ligated intermediate (**I**) is obtained. Reaction of unsaturated intermediate **I** with a secondary alcohol leads to the formation of an alkoxy ligand-coordinated intermediate (**II**) *via* O–H bond activation[20c] in which the central amide donor of **I** is converted into an amine donor in intermediate **II**. Further, β-hydride elimination in **II** provides the corresponding ketone compound and a ruthenium dihydride complex (**III**) *via* amine–amide metal–ligand cooperation. Complex **III** can liberate dihydrogen and regenerate the catalytically active intermediate **I**, thus closing one loop in a catalytic cycle. Finally, the *in situ* formed ketone undergoes a condensation reaction with hydrazine hydrate to provide a hydrazone intermediate, which upon subsequent condensation with another molecule of ketone provided the desired symmetrical ketazine products.

In summary, we have developed an efficient protocol for ruthenium(II)-catalyzed direct synthesis of ketazines using secondary alcohols. Several aromatic as well as aliphatic secondary alcohols underwent facile reaction to provide the corresponding ketazine products in good to excellent yields. Using this strategy, we have synthesized the cholesterol azine product directly from cholesterol. Kinetic and NMR studies strongly suggest that the reaction follows first order kinetics and proceeds *via* hydrazone



Scheme 3 Proposed mechanism for the direct synthesis of ketazines using ruthenium pincer complex **1**.

and ketone intermediates. The reactions follow acceptorless dehydrogenation of secondary alcohols *via* amine–amide metal–ligand cooperation in catalyst **1** to provide ketones followed by a consecutive condensation reaction with hydrazine hydrate to provide the corresponding ketazine products. Remarkably, H_2O and H_2 are the only byproducts in this environmentally benign catalytic transformation.

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Conflicts of interest

There are no conflicts to declare.

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