

Direct Synthesis of Symmetrical Azines from Alcohols and Hydrazine Catalyzed by a Ruthenium Pincer Complex: Effect of Hydrogen Bonding

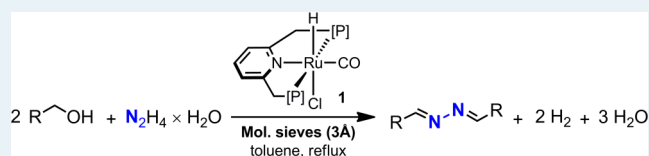
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Supporting Information

ABSTRACT: Azines (2,3-diazabuta-1,3-dienes) are a widely used class of compounds with conjugated C=N double bonds. Herein, we present a direct synthesis of azines from alcohols and hydrazine hydrate. The reaction, catalyzed by a ruthenium pincer complex, evolves dihydrogen and can be run in a base-free version. The dehydrogenative coupling of benzylic and aliphatic alcohols led to good conversions and yields. Spectroscopic evidence for a hydrazine-coordinated dearomatized ruthenium pincer complex was obtained. Isolation of a supramolecular crystalline compound provided evidence for the important role of hydrogen bonding networks under the reaction conditions.

KEYWORDS: azines, homogeneous catalysis, hydrogen bonds, pincer complexes, ruthenium, supramolecular compounds



Azines ($R_2C=N-N=CR_2$), namely, 2,3-diazabuta-1,3-dienes, are an important class of compounds that display diverse reactivity and are useful for many applications, such as the synthesis of N-heterocycles and functional polymers.^{1,2} Metal-promoted transformations of azines have led to new synthetic applications.³ Azine formation has also proven beneficial in studying metal-mediated N_2 activation.⁴ Recently, azines have generated much interest in the construction of covalent organic frameworks (COFs) having photocatalytic activity⁵ or serving as chemosensing detectors.⁶ Because of their unique electronic structure and stereochemical versatility,⁷ azine units give also rise to remarkable chromophoric properties⁸ and are interesting as nonlinear optical materials.⁹ Applications as ferroelectric liquid crystals were also described.¹⁰ The biological activity of azine derivatives holds promise for pharmacological applications.¹¹

Azines are generally synthesized by reaction of carbonyl compounds with hydrazine hydrate or hydrazones,¹² even though some effort in enhancing this general method was undertaken in recent years.¹³ Aside from that, only a small number of alternative routes were reported,^{3b,14–16} such as the reaction of diazoalkanes with carbenes or carbenoids^{3b,14b,c,15} or the transformation of a tetrazole with cyclooctyne.^{14d} However, all of these methods lack generality and are limited to a few very specific substrates. Recently, Chiba reported the conversion of vinyl azides to α -trifluoromethyl azines, which are precursors to various fluorinated compounds.¹⁶

One of the major challenges in the field of catalysis is the development of environmentally benign transformations of widely accessible starting materials into synthetically valuable products. In recent years, our group reported on new catalytic procedures based on the concept of metal–ligand cooperation,¹⁷ which involves reversible aromatization/dearomatization

within the ligand backbone. Using pincer-type complexes, this concept has become an important paradigm in the development of unprecedented one-step reactions toward fundamental building blocks, while avoiding the formation of waste and excessive use of costly or toxic reagents.¹⁸

The dehydrogenative coupling of alcohols and amines catalyzed by pyridine-based pincer ruthenium complexes has led to the synthesis of amides,¹⁹ imines,²⁰ peptides, pyrazines,²¹ and pyrroles.²² Lately, our group reported the development of hydrogen storage systems based on amide bond formation.²³ Ruthenium- and iridium-catalyzed dehydrogenative coupling of alcohols with substituted hydrazines are known as well,²⁴ but the direct use of N_2H_4 in catalysis is very challenging. Very recently, Ru-catalyzed reaction of primary alcohols with hydrazine resulted in alcohol deoxygenation.²⁵

Herein, we present the first direct synthesis of azines from alcohols. The reaction is based on acceptorless dehydrogenative coupling of alcohols and hydrazine catalyzed by a ruthenium pincer complex (Figure 1). This one-step strategy is atom-economical and environmentally benign, forming azines directly from readily available, sustainable starting materials while producing H_2 . Mechanistic insight, including involvement of hydrogen bonding in this process, which has led to the isolation of a supramolecular crystalline compound, and an unexpected role of molecular sieves, is provided.

Exploring the best reaction conditions for the coupling reaction, 4-methoxybenzyl alcohol was chosen as a model system (Table 1). Heating a solution of 4-methoxybenzyl

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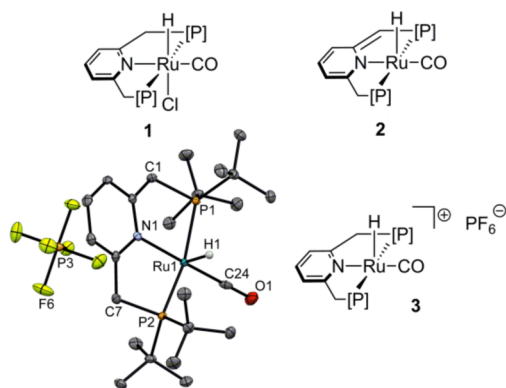
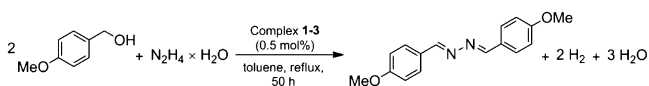


Figure 1. Ruthenium PNP pincer complexes studied for azine synthesis ([P] = P(*t*Bu)₂). Molecular structure of [(*t*BuPNP)Ru(CO)H] [PF₆]⁻ (3) (H atoms at carbon are omitted for the sake of clarity).

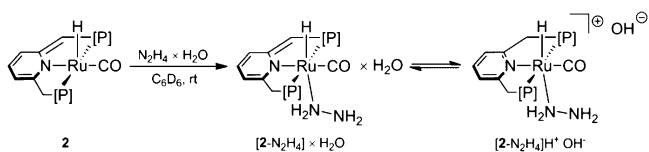
Table 1. Optimization of the Reaction Conditions for Azine Formation^a



entry	complexes 1–3 [0.5 mol %]	KO <i>t</i> Bu [mol %]	Conversion and Yields ^b [%]			
			alcohol	azine	aldehyde	ester
1	1	1.5	94	32	34	25
2	2		50	15	18	10
3 ^c	1	1.5	99	99		
4 ^c	2		62	58		
5 ^c	1		91	91		
6	1		9	6		
7 ^d	1					
8 ^e	1		78	66	5	
9 ^c	3		62	48	2	5
10	3					
11 ^{c,f}	1		89	85	3	

^aReaction conditions: Complexes 1–3, alcohol (2.5 mmol), hydrazine hydrate (0.7 equiv., 1.75 mmol), KO*t*Bu (0–1.5 mol %), and toluene (5 mL) were heated at reflux in a Schlenk flask (oil bath temperature: 130 °C) for 50 h. ^bConversion of alcohol and yields of products were determined by ¹H NMR spectroscopy, using *N,N*-dimethylformamide as an internal standard, supported by GC/MS analysis. ^cIn the presence of molecular sieves (3 Å) (1 g). ^dIn the presence of Na₂SO₄ (1 g). ^eIn the presence of γ-Al₂O₃ (0.6 g). ^fAddition of excess water (0.2 mL).

Scheme 1. Formation of a Coordination Complex from 2 and Hydrazine Hydrate in Solution^a



^a[P] = P(*t*Bu)₂.

alcohol and hydrazine hydrate in the presence of 0.5 mol % **1**²⁰ and 1.5 mol % KO*t*Bu in toluene at reflux for 50 h resulted in only 32% of 4-methoxybenzaldazine, along with 34% aldehyde and 25% ester (Table 1, entry 1). Using the isolated dearomatized complex **2**²⁰ instead of *in situ* deprotonation of

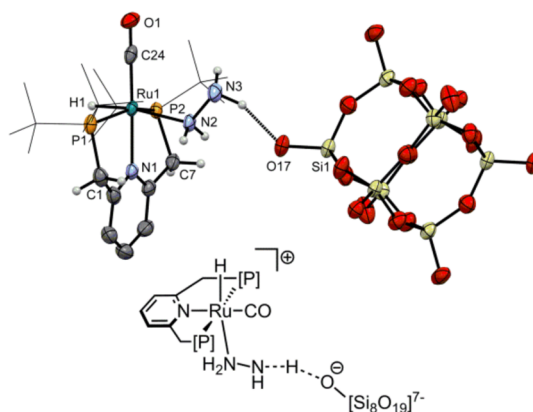
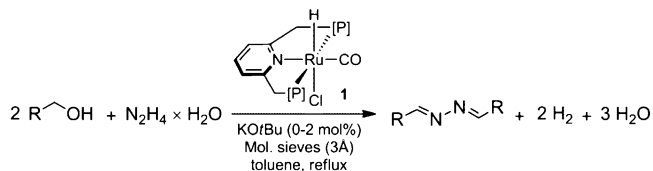


Figure 2. Part of the crystal structure of [(*t*BuPNP)Ru(CO)H-(N₂H₄)⁺]₈[Si₈O₂₀]⁸⁻(C₆H₆)₉(H₂O)₃₇ (**4**): Cationic complex [2-N₂H₄]⁺H⁺ hydrogen-bonded to a [Si₈O₂₀]⁸⁻ cluster (some of the H atoms are omitted for the sake of clarity).

1 with a base, the conversion was lower (50%) but the relative amounts of azine (15%), aldehyde (18%), and ester (10%) remained the same (Table 1, entry 2). Significantly, upon the addition of molecular sieves (3 Å) to the reaction catalyzed by **1** and a base, full conversion was obtained, the desired azine being obtained as the only product under otherwise identical conditions (entry 3). Carrying out the reaction with complex **2** (0.5 mol %) in the presence of molecular sieves but without a base, the azine was also selectively obtained, although in lower conversion (62%) and yield (58%, entry 4 in Table 1). Unexpectedly, in a base-free variant, starting directly from the aromatic complex **1** (0.5 mol %), the coupling reaction of the alcohol and hydrazine proceeded smoothly (91% conversion) with high yield (91%) and without the formation of any side products (entry 5 in Table 1). Performing the same reaction with no molecular sieves and no base using **1** (0.5 mol %), the conversion was negligible (9%), the azine being formed in only 6% yield (entry 6 in Table 1). As shown in entries 7 and 8 in Table 1, we also studied Na₂SO₄ and γ-Al₂O₃ as water-capturing additives in the azine synthesis. Although the reaction was totally inhibited by Na₂SO₄, the use of γ-alumina led to good conversion (78%) and the formation of 66% azine. Even when using the chloride-free cationic complex [(*t*BuPNP)Ru(CO)H]⁺[PF₆]⁻ (**3**) (Figure 1) in the presence of molecular sieves, the reaction proceeded smoothly, albeit the yield of the desired azine was only 48% (entry 9 in Table 1). However, no conversion was observed with **3** in the absence of molecular sieves (entry 10 in Table 1). These findings lead to the conclusion that the presence of molecular sieves or γ-alumina is crucial, and that the hydrazine-containing reaction conditions are capable of forming an active catalyst species directly from complex **1** without the need of added base. Significantly, complexes **1** and **3** were completely inactive toward dehydrogenation of 4-methoxybenzyl alcohol, whereas the dearomatized complex **2** led to full conversion after 50 h of heating at toluene reflux and gave both aldehyde (45%) and ester (54%). These findings suggest that, under the reaction conditions, complex **1** is converted to an active dearomatized catalyst with the assistance of excess hydrazine, prior to the actual catalytic cycle, since dehydrogenation of the alcohol to form the aldehyde is required for condensation with hydrazine to form an azine.

It was of interest to us to get more information regarding the role of molecular sieves. Normally, it is assumed that they act

Table 2. Direct Synthesis of Azines from Alcohols and Hydrazine Hydrate Using the Ruthenium Complex 1^a

entry	R	t [h]	1 [mol %]	KOtBu [mol %]	conversion of alcohol [%] ^b	yield [%] ^b
1	4-(MeO)C ₆ H ₄	50	0.5	1.5	99	99 (91)
		50	0.5		91	91
2	3,4-(MeO) ₂ C ₆ H ₃	66	0.5	1.5	69	66 (56)
		66	0.5		88	69 (59)
3	3-(Me ₂ N)C ₆ H ₄	65	1	2	79	77 (57)
		65	0.5		86	86 (75)
4	3-(MeO)C ₆ H ₄	67	0.5		67	50 (36)
5	4-(Me)C ₆ H ₄	67	1	2	68	61 (46)
		67	0.5		88	82 (70)
6	Ph	67	0.5		88	78 (59)
7	4-(Cl)C ₆ H ₄	69	0.5		58	35 (27)
8	Me(CH ₂) ₄	65	0.5		79	70 (58)

^aReaction conditions: Complex 1, alcohol (2.5 mmol), hydrazine hydrate (0.7 equiv., 1.75 mmol), KOtBu (0–2 mol %), and toluene (5 mL) were heated at reflux in the presence of molecular sieves (3 Å) (1 g) in a Schlenk flask (oil bath temperature: 130 °C). [P] = P(tBu)₂. ^bConversion of alcohols and yields of products were determined by ¹H NMR spectroscopy, using *N,N*-dimethylformamide as an internal standard, supported by GC/MS analysis. Yields of isolated products are given in parentheses.

just as a water scavenger. Surprisingly, an addition of excess water to an experiment under normal conditions, using molecular sieves, had little effect on the reaction (compare entries 5 and 11 in Table 1). Next, a mixture of hydrazine hydrate, complex 1, and molecular sieves in toluene, in the absence of alcohol, was heated at reflux for 17 h. The sieves were then removed and 4-methoxybenzyl alcohol was added to the supernatant solution and the solution was refluxed for 29 h; to our surprise, no azine was formed, although 25% aldehyde was still obtained. 4-Methoxybenzyl alcohol was then added to the removed molecular sieves in fresh toluene and the mixture was refluxed for 50 h, leading to high conversion (85%) of the alcohol to form the azine (58%), along with the aldehyde (23%). Hence, it is obvious that hydrazine remains attached to the molecular sieves, ready for the reaction with an aldehyde, and the catalyst also being partly bound to the molecular sieves, probably by reversible coordination of hydrazine to the ruthenium center.

To gain more insight into possible intermediates, we investigated the interaction between hydrazine and the dearomatized, unsaturated complex 2 (Scheme 1), the latter being considered a key intermediate in the alcohol dehydrogenation process. The addition of hydrazine hydrate (1 equiv) to a freshly prepared solution of 2 in [*d*₆]-benzene led to a color change from dark blue to yellow. ¹H NMR spectroscopy showed a dramatic downfield shift of the metal-hydride triplet signal from –25.76 ppm to –16.16 ppm, which is indicative of coordination *trans* to the hydride ligand of 2. Since water addition to dearomatized ruthenium pincer complexes is likely reversible,^{20,26} it is plausible that hydrazine coordinates to the metal center of 2. Such a complex derived from 2 and an amine was previously observed for ammonia, and is consistent with the general preference of electron-rich amines to coordinate via the lone electron pair rather than undergo N–H bond activation.²⁷ Broad ¹H NMR signals that overlap the chemical shift regions from 2.8 to 3.8 (CH₂P and =CHP) and from 5.3 to 6.4 ppm (Py-H3,5) but the presence of a sharp triplet at 6.51

ppm (Py-H4) indicates an equilibrium between the vinylic and benzylic protons via a symmetric cationic intermediate, such as [2-N₂H₄]H⁺OH[–], in which the PNP ligand underwent protonation by water (Scheme 1). The appearance of sharp ¹³C{¹H} NMR signals for C atoms, which are only marginally affected by such an equilibrium, like Py-C4 (132.6 ppm) and Ru-CO (triplet at 209.2 ppm), is consistent with this equilibrium. The ³¹P{¹H} NMR spectrum showed a broad unsymmetrical splitting pattern at 78.4 and 81.8 ppm that also supports the existence of a dearomatized coordination complex (for details, see the Supporting Information (SI)).²⁸ Such an equilibrium might also occur under the catalytic conditions, the coordinated hydrazine being eventually displaced by an alcohol, enabling the catalytic cycle.

Surprisingly, treating a solution of complex 2 and hydrazine hydrate in benzene with molecular sieves (3 Å) resulted in the formation of single crystals of a unique supramolecular compound. The unit cell consists of eight [(*t*BuPNP)Ru(CO)-H(N₂H₄)]⁺ cations (Figure 2) of the type [2-N₂H₄]H⁺ having an aromatized PNP ligand and coordinated hydrazine. The coordinated hydrazine is part of a sophisticated hydrogen bonding network, together with water molecules and a [Si₈O₂₀]^{8–} cluster, which undoubtedly originated from the molecular sieves (for structural details, including hydrogen bond analysis, see the SI). Most likely, the acidity of silanol groups led to protonation of the dearomatized PNP complex [2-N₂H₄], resulting in stabilization of the cationic complex [2-N₂H₄]H⁺ in the equilibrium of Scheme 1.²⁹ The interesting crystal structure sheds more light on the molecular conditions during the ruthenium-catalyzed azine synthesis and allows for the conclusion that breaking hydrogen-bonded networks between the highly protic reactants, most likely with surface siloxide groups of molecular sieves being involved in hydrogen bonding, might be crucial for releasing the catalyst and enabling the catalytic cycle. This contrasts with imine formation by coupling of amines with alcohols, which generates water as well, but does not require the use of molecular sieves.²⁰

Table 2 shows the substrate scope of the new dehydrogenative coupling reaction of alcohols and hydrazine under slightly basic conditions or in base-free versions using complex 1. The reaction tolerates a variety of substituent patterns of benzylic alcohols. The base-free method can be performed with low catalyst loading (0.5 mol%) to obtain good to high yields (Table 2, entries 1–8). For 3-(dimethylamino)benzyl (75% isolated yield) and 4-methylbenzyl alcohol (70% isolated yield), the base-free version led to significantly better results with lower amounts of catalyst (see entries 3 and 5 in Table 2). The base-free variant also led to good results for benzaldazine (78% yield; entry 6) and can be expanded to halogen-substituted benzyl alcohols as well, as shown for the chloro derivative (entry 7), although in lower yield. The presence of strong electron-withdrawing substituents such as CF₃ or F in *para* position resulted in very little conversion, forming (for CF₃) a mixture of products. Hexanaldazine was synthesized in good yield (70%), demonstrating the applicability for aliphatic alcohols (see entry 8 in Table 2).

In summary, we have developed a general synthetic method for the preparation of symmetrical azines from alcohols and hydrazine hydrate catalyzed by a ruthenium PNP complex in the presence of molecular sieves, which can be performed without added base. This dehydrogenative coupling reaction is an efficient way of forming N–N-linked building blocks that can be used for a variety of subsequent transformations. The use of molecular sieves (or γ -alumina) is essential. Hydrazine is strongly bound to the molecular sieves, and an unusual ruthenium complex bearing coordinated hydrazine hydrogen-bonded to a siloxane cluster was isolated. Studies aimed at further mechanistic insights, and synthetic applications of the hydrazine-based catalytic methodology, are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b02946.

Experimental procedures and spectroscopic details (PDF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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