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COMMUNICATION

α,β-Unsaturated imines *via* Ru-catalyzed coupling of allylic alcohols and amines†‡

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A convenient synthesis of α,β-unsaturated imines requiring only an allylic alcohol, an amine and a Ru catalyst has been developed. The use of large excesses of oxidant and the purification of sensitive intermediates can be avoided.

Unsaturated imines are valuable substrates for a number of C–C and C–N bond formations, including hetero-Diels–Alder, electrocyclization and C–H activation/coupling reactions.[1] They are typically prepared by oxidation of an allylic alcohol to the corresponding α,β-unsaturated aldehyde, followed by immediate condensation of the sensitive intermediate with an amine in the presence of a dehydrating agent.[2] Isolated examples of one-pot conversions of allylic alcohols directly to unsaturated imines have been reported; however, these methods often require large excesses of oxidants and dehydrating reagents.[3] In this communication, we report a convenient synthesis of α,β-unsaturated imines that requires only an allylic alcohol, an amine, and a Ru catalyst. The simplicity of the method allows for the possibility of direct use of the imine products without the losses typically associated with the purification of these sensitive compounds.

Catalysts capable of coupling simple alcohols and amines without prior functionalization represent "green methods" for preparing esters, ethers, amides, and amines.[4–7] These reactions may proceed *via* "hydrogen borrowing", where dehydrogenation of the substrate is followed by eventual return of the H_2 to the product. For example, catalyst system **1ac** (Fig. 1) can yield secondary amines from primary alcohols and amines using 1,1′-bis (diphenylphosphino)ferrocene (dppf) as a ligand.[7a] Oxidative coupling is also possible if H_2 can be eliminated from the reaction mixture. Catalyst **1ab** yields amides from the reaction of a primary alcohol and an amine if a sacrificial hydrogen acceptor (acetophenone) is used with 1,4-bis(diphenylphosphino)butane (dppb) as the ligand.[4d] Catalyst **1b** typically forms amides from primary alcohols and primary or secondary amines.[4c] The PNP pincer **1c** and the PNN pincer **1d** catalysts developed by the Milstein group are particularly useful and give quite different reactivities due to the increased hemi-lability of the diethylamino ligand of **1d** compared to the di-*tert*-butyl phosphine ligand of **1c**. Catalyst **1c** gives the imine from primary alcohols and amines, while **1d** yields the same amide product that would be obtained using catalyst **1b**.[4b,6]

Our interest in utilizing dehydrogenative couplings in the context of complex molecule synthesis prompted us to examine more highly functionalized alcohol substrates in these reactions. For example, treatment of a primary allylic alcohol with a primary amine could potentially yield six different products (Table 1, **2a–f**) depending on the catalyst (**1a–d**) employed, as well as the reaction conditions. The use of allylic alcohols with

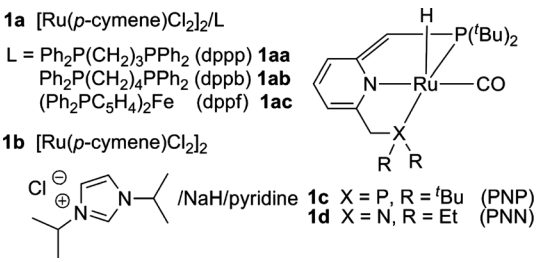
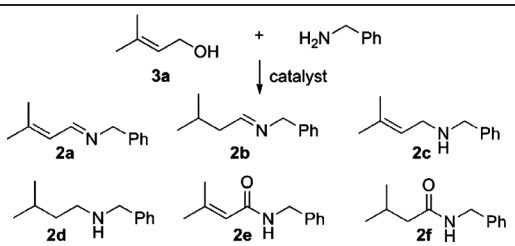


Fig. 1 Common catalysts for coupling alcohols and amines.

Table 1 Catalysts explored for coupling allylic alcohols with amines



entry	catalyst/ligand	results[a]
1	**1ab** [Ru(*p*-cymeme)Cl_2]$_2$/dppf	21% **2a**; 21% **2b**
2	**1b** [Ru(*p*-cymeme)Cl_2]$_2$/^{i}Pr_2NHC	53% **2f**
3	**1ac** [Ru(*p*-cymeme)Cl_2]$_2$/dppf	—
4	**1c** (Milstein's PNP)	50% **2a**; 33% **2b**
5	**1d** (Milstein's PNN)	78% **2a**

[a] NMR yields using mesitylene as internal standard.

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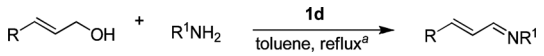
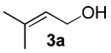
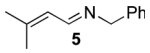
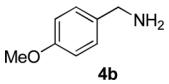
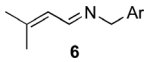
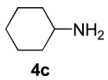
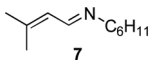
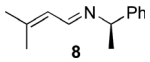
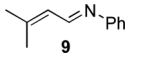
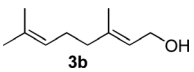
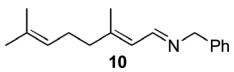
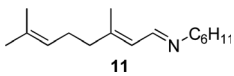
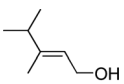
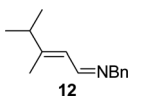
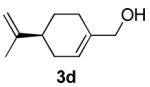
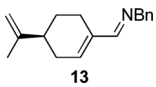
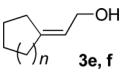
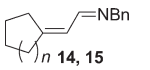
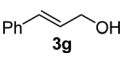
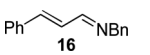
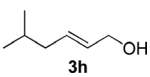
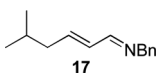
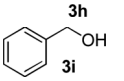
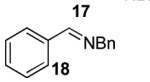
‡Electronic supplementary information (ESI) available: Experimental procedures, NMR, and MS data. See DOI: 10.1039/c2ob06921k

Table 2 RuPNN-catalyzed coupling of allylic alcohols and amines to unsaturated imines



entry	alcohol	amine	product	yield[a] (conversion) (*E* : *Z*)
1	 **3a**	 **4a**	 **5**	78% (100%)
2	**3a**	 **4b**	 **6**	63% (100%)
3	**3a**	 **4c**	 **7**	77% (100%)
4	**3a**	 **4d**	 **8**	74% (95%)
5	**3a**	$PhNH_2$ **4e**	 **9**	22% (57%)[b]
6	 **3b**	**4a**	 **10**	72% (100%) (1.8 : 1)
7	**3b**	**4c**	 **11**	83% (100%) (2 : 1)
8	 **3c** *E*:*Z* 4:1	**4a**	 **12**	61% (100%) (6 : 1)
9	 **3d**	**4a**	 **13**	70% (100%)
10 11	 **3e, f**	**4a**	 **14, 15**	*n* = 2; 38% (30%)[c] *n* = 1; 15% (51%)[c]
12	 **3g**	**4a**	 **16**	46% (85%)
13	 **3h**	**4a**	 **17**	26% (86%)
14	 **3i**	**4a**	 **18**	49% (17%)[d] (95%)

[a] Standard conditions: 3 M solution of amine (1 mmol) and alcohol (1 mmol) in toluene-d_8, 0.2 mmol mesitylene as an internal standard to determine NMR yields, 1 mol% catalyst, reflux, 24 h under a flow of N_2; 100% conversion of the alcohol unless otherwise noted. [b] The low yield resulted from incomplete conversion of the substrates. [c] Exocyclic double bond migrated to give the internal olefin. [d] Product is the amide.

Ru catalysts also poses several additional challenges; namely, competing isomerization and further reduction of the unsaturated imine/amide product.[8,9] Indeed, the reaction of 3-methyl-but-2-enol **3a** with benzylamine in the presence of a Ru-dppb based system **1ab** (entry 1, acetophenone as a hydrogen acceptor) yielded both **2a** and a by-product **2b** in low yields, instead of the expected products **2e** or **2f**.[4d]

The catalyst system **1b** (entry 2) gave the saturated amide **2f**, consistent with the previous reactivity reported for **1b**.[4c] Catalyst **1ac**, using dppf as the ligand instead of dppb (entry 3) gave a complex mixture of unidentified products instead of the expected **2c** or **2d**.[7a] Despite the fact that the PNP catalyst (**1c**, entry 4) has been reported to yield imines from primary alcohols and amines, the desired α,β-unsaturated imine **2a** was formed in only 50% yield, along with significant amounts of **2b** from undesired reduction of the olefinic double bond. Finally, to our surprise, Milstein's PNN catalyst (**1d**, entry 5) produced **2a** as the only product in 78% yield, with no competing formation of the expected amides **2e** or **2f**.

Encouraged by the result obtained using the PNN version of Milstein's catalyst **1d**, the scope of unsaturated imine formation was explored using a variety of allylic alcohols and primary amines (Table 2). The allylic alcohol 3-methyl-but-2-enol **3a**, gave good yields of the α,β-unsaturated imines when electron-rich primary amines **4a–d** were used (entries 1–4). The less nucleophilic aniline (entry 5) gave lower yields of the unsaturated imine due to slow conversion.[4b] Geraniol (**3b**) gave good yields of the corresponding unsaturated imines (entries 6 and 7), but significant *cis* : *trans* isomerization of the proximal olefin occurred to yield approximately a 2 : 1 mixture of *E* and *Z* isomers, the same ratio observed when **10** and **11** are prepared *via* conventional methods.[10] In contrast, when the trisubstituted allylic alcohol **3c** was used, the initial 4 : 1 mixture of *E* : *Z* isomers improved to a 6 : 1 ratio of *E* : *Z* isomers (entry 8).

(*S*)-Perillyl alcohol **3d** (entry 9) also gave good yields of the unsaturated imine **13**. Importantly, the use of the geraniol and perillyl alcohol substrates **3b** and **3d** demonstrated that other isolated olefins were not prone to reduction under the reaction conditions.

Ru catalysts are well-known to promote olefin migration.[11] Isomerization of the exocyclic double bonds of **3e** and **3f** to the internal olefins competed with the formation of the desired unsaturated imines **14** and **15** (entries 10–11). The chiral center of **3d** provided us an opportunity to determine if internal olefin migration could also occur under the reaction conditions. The absolute configuration of the stereocenter would be inverted if isomerization occurred, resulting in degradation of the optical purity of the substrate. However, when **13** was rapidly hydrolyzed back to the aldehyde and reduced to **3d**, the degradation in the *ee* was minimal, indicating that migration of the double bond was not occurring to any significant extent (see the Supporting Information for details‡).

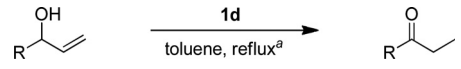
Finally, while trisubstituted allylic alcohols provided high yields, decreased substitution on the olefin (entries 12–13) led to lower yields of unsaturated imine products. The decrease in steric bulk around the olefin gave competing side reactions, including homocoupling of two molecules of amine to form the imine.[6]

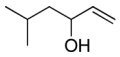
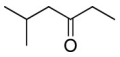
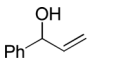
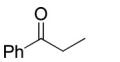
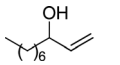
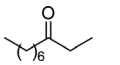
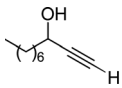
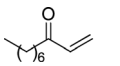
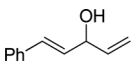
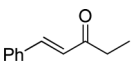
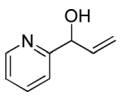
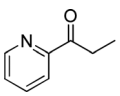
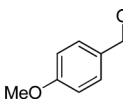
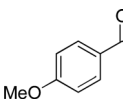
The propensity for primary allylic alcohols to yield α,β-unsaturated imines, rather the amide products typically seen with catalyst **1d**, was initially rather surprising. The increase in conjugation upon forming the unsaturated imine may drive the loss of water more readily than in cases involving typical aliphatic alcohols; however, we did not explore the mechanism of the reaction in any detail. Nonetheless, treatment of benzyl alcohol and benzylamine with **1d** (entry 14), a condition that by inference to previously reported results should give mainly amide product, gave 49% of the imine and only 17% of the amide.[4b,6]

The reasons for the disparity between the use of **1c** (previously reported to give saturated imines from primary alcohols and amines) and **1d** are not clear to us. Neither catalyst gave the amide product, but **1c** did yield substantial amounts of the saturated imine **2b** (Table 1, entry 4). This product could result from either reduction of the α,β-unsaturated imine with H_2 released in the reaction, or from a Ru-promoted redox isomerization of the allylic alcohol to the saturated aldehyde, followed by condensation with the amine. Attempts to promote the redox isomerization of a primary allylic alcohol in the absence of amine led to mixtures of products, potentially due to homocoupling of the alcohol and acetal formation.[5] However, secondary allylic alcohols (Table 3) did yield ketones under the reaction conditions.[8,9] Alkyl and aryl-substituted allylic alcohols **19–21** and **25** smoothly gave the ketone products in good yields (entries 1–3, 7). The propargyl alcohol **22** (entry 4) was not a competent substrate, while the redox isomerization of a bis-allylic alcohol **23** (entry 5) gave predominately the product **23a** resulting from isomerization at the terminal olefin. The presence of a pyridine nitrogen slowed the reaction significantly (entry 6), giving only 28% of **24a** after 24 h.

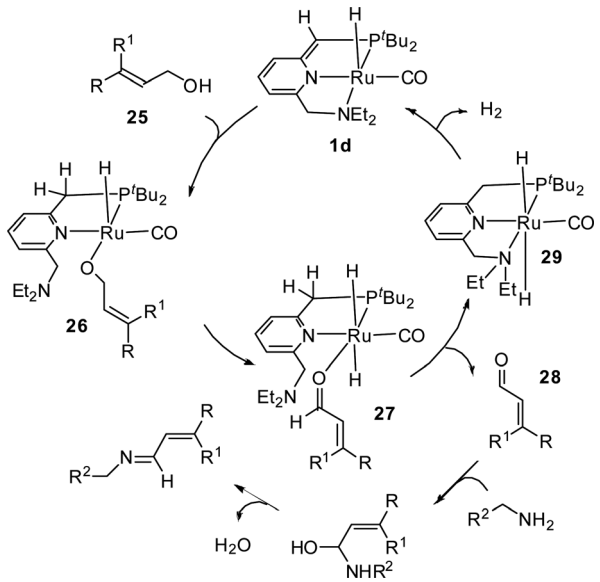
Although the mechanistic details are unclear at this point, it is likely that the reaction pathway for primary alcohols follows a similar one to that proposed by Milstein.[4,6] The allylic alcohol

Table 3 Redox isomerization of secondary allylic alcohols using **1d**



entry	alcohol		product		yield
1		**19**		**19a**	95%
2		**20**		**20a**	89%
3		**21**		**21a**	80%
4		**22**		**22a**	trace
5		**23**		**23a**	52%
6		**24**		**24a**	28%
7		**25**		**25a**	73%

[a] Standard conditions: 3 M solution of amine (1 mmol) and alcohol (1 mmol) in toluene-d_8, 1 mol% catalyst, reflux, 24 h under a flow of N_2; 100% conversion of the alcohol unless otherwise noted.



Scheme 1 Proposed mechanism for the preparation of α,β-unsaturated imines from Ru-catalyzed coupling of allylic alcohols and amines.

25 (Scheme 1) can coordinate to the catalyst **1d** after deprotonation to give **26**. Loss of the hemi-labile NEt_2 ligand, followed by β-hydride elimination would yield an intermediate α,β-unsaturated aldehyde **27** still coordinated to the metal center. At this point, we envisage two different pathways. First, the unsaturated aldehyde **28** could be released from the metal by re-coordination of the NEt_2 ligand to give **29**, which could lose H_2 to regenerate the active catalyst **1d**. Condensation of the unsaturated aldehyde

28 with an amine would yield the desired unsaturated imine. A second possibility is attack of the coordinated aldehyde by the amine to give an intermediate hemiaminal, which could either undergo β-hydride elimination to give the unsaturated amide (not observed), or rapidly lose water to yield the imine. Further mechanistic studies are needed to distinguish between these two potential pathways and rationalize the differences in reactivity between **1c** and **1d** in the coupling of primary allylic alcohols and amines.

In conclusion, we have demonstrated a mild and atom-economical approach towards the synthesis of α,β-unsaturated imines from primary allylic alcohols and amines using a commercially available ruthenium catalyst. No suprastoichiometric amounts of oxidants or dehydrating reagents are required. The reaction performs best with trisubstituted allylic alcohols and the reaction conditions are mild enough to preserve other unsaturated functional groups in the molecule from reduction. The ability of **1d** to catalyze the efficient redox isomerization of secondary allylic alcohols to the corresponding ketones was also demonstrated for the first time. Future efforts will focus on utilizing these atom-economical approaches in complex molecule synthesis and in convenient tandem reactions.

Notes and references

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