

Ruthenium-Catalyzed Reductive
Amination of Allylic Alcohols

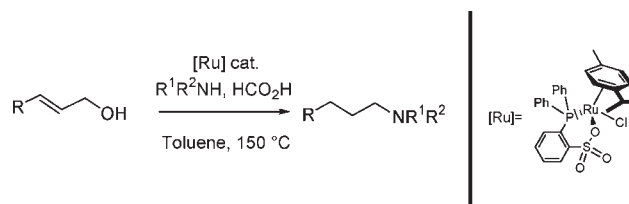
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ABSTRACT



Straightforward access to various saturated amines from allylic alcohols and isostructural mixture can now be achieved in the presence of arene ruthenium catalyst featuring phosphinesulfonate ligand and a hydrogen donor.

Metal-catalyzed tandem and/or cascade processes enable the direct access to functionalized molecules via successive transformations by a precatalyst in the same reaction medium.¹ These synthetic methodologies have attracted considerable attention since they minimize the wastes, the reaction steps and the number of purification processes and fulfill the criteria of sustainability and green chemistry. For this purpose, reactive in situ generated ruthenium-hydride species are of great interest allowing a plethora of transformations involving hydrogen transfers.^{2,3} In the presence of such complexes, allylic alcohols are usually converted into carbonyl compounds via a formal neutral redox process.³ This reactivity has been successfully employed in a cascade process 30 years ago by Watanabe for the formal Friedlander reaction involving isomerization of allylic alcohols.⁴ More recently remarkable results have been obtained by several groups in tandem processes involving allylic alcohols such as the

isomerization/Murai reaction⁵ and isomerization/transfer hydrogenation.⁶ During the N-heterocyclisation of amino arenes with allylic alcohols to produce quinoline in the presence of $\text{RuCl}_2(\text{PPh}_3)_3$ as catalyst, N-alkyl amino arenes were formed as side products in yields up to 27%.⁴ This result revealed that a concomitant isomerization, imine formation followed by reduction occurred. Herein, we report on an efficient catalytic system for reductive amination of allylic alcohols in the presence of various amines

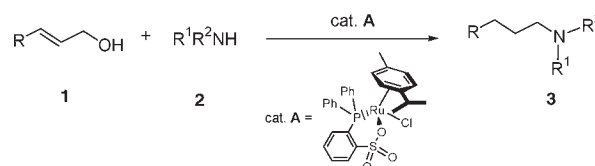


Figure 1. N-Alkylation involving tandem processes.

(Figure 1) and applications in multi hydrogen transfer processes. N-Alkylation of *N*-ethylaniline **2a** was attempted using cinnamyl alcohol **1a** and the results are

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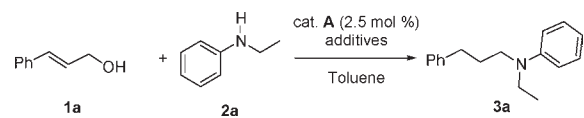
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Table 1. Ruthenium-Catalyzed Reductive Amination of Cinnamyl Alcohol^a



entry	1a ^b	additives ^c	yield ^d
1	1.2	none	41
2	1.4	none	44
3	1.6	none	48
4	1.8	none	62
5	2.0	none	61
6	1.2	<i>i</i> -PrOH (1)	36
7	1.2	HCO ₂ H (1)	75
8	1.2	HCO ₂ H (1.1)	98(82) ^e

^a All reactions were carried out at 0.2 M concentration in toluene at 150 °C for 15 h under an inert atmosphere with **2a**/cat. **A** in 1/0.025 molar ratio. ^b Equivalent of **1a**. ^c Equivalent of additive. ^d Yield determined by GC using *n*-tetradecane as internal standard. ^e Number in parentheses is isolated yield.

described in Table 1. Experiments were performed at 150 °C with 2.5 mol % of precatalyst **A**⁷ for 15 h (Figure 1). The role of cinnamyl alcohol **1a** was first investigated and as expected, **1a** was not only a reactant but also played the role of sacrificial hydrogen donor. Indeed, as shown in entries 1–4 an excess of alcohol led to an increase of the formation of saturated amine **3a** leading to 62% GC yield as the best result in the presence of 1.8 equivalent of **1a** (entry 4). Increasing the amount of alcohol did not improve the yield and resulted in the formation of aldol condensation side products (entry 5). To ensure better results, additional hydrogen donors were then investigated. Thus, the use of stoichiometric amount of *i*-PrOH in the presence of 1.2 equiv of cinnamyl alcohol did not improve the yield (entry 6 as compared to 1). Even worse, the use of isopropanol as solvent afforded no conversion. We then turned out our attention on formic acid as hydrogen donor. Remarkably, the use of equimolar amount of formic acid resulted in complete consumption of *N*-ethyl-aniline **2a** to afford 75% yield (entry 7). Further optimization led to the use of a slight excess of formic acid to give 82% of isolated yield (entry 8). Other ruthenium sources such as Shvo catalyst,⁸ [RuCl₂(*p*-cymene)]₂⁹ afforded lower conversions and yields. With our best conditions in hands, we further enlarged the scope of this transformation. Various amines and allylic alcohols were evaluated (Table 2). Cinnamyl alcohol **1a** was smoothly converted to the expected saturated amines with secondary cyclic amines such as piperidine **2b**, pyrrolidine **2c** and azepane

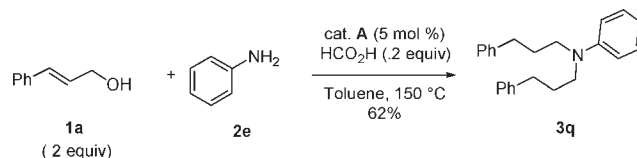
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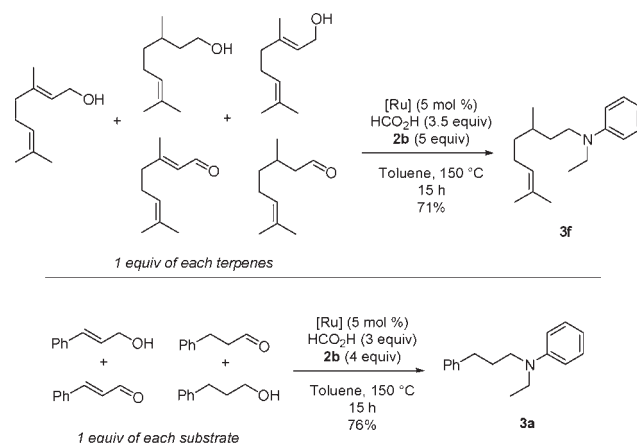
2d in 59, 77 and 87% yields, respectively (entries 1–3). The use of primary amine such as aniline **2e** resulted in the major formation of the expected mono alkylated compound **3e** in 66% yield along with dialkylated amine in 6% yield (entry 4). It is noteworthy, that longer reaction time (24 h) increased the formation of the dialkylated amine based on dealkylation/alkylation via the intervention of hydrogen autotransfer process. Thus, an excess of alcohol resulted in the formation of the dialkylated amine in 62% yield along with 10% of monoalkylated amine (Scheme 1).

Scheme 1. Amination via multi hydrogen transfer processes



Other alcohols were also evaluated. Interestingly, geraniol **1b** which contains additional carbon–carbon double bond was converted into amines **3f–i** in 57–65% isolated yield (entries 5–8). Compounds **3f–i** are formed as major products with only traces of the fully saturated products (less than 10%) highlighting the high chemoselectivity of the reduction process toward the initial allylic alcohol carbon–carbon double bond.

Scheme 2. Amination via Multi Hydrogen Transfer Processes



Similarly, good results were obtained with hex-2-en-1-ol **1c**, crotyl alcohol **1d** and isoprenol **1e** affording alkylated products in 48–82% yield (entries 9–14). Phytol **1f**, a linear diterpene featuring a terminal allylic alcohol functionality was also efficiently converted into the corresponding amine **3p** from **2a** (entry 15). We showed that the reaction is only possible with amines as *N*-protected carbamates and sulfonamides did not react. Taking into account that several hydrogen processes occurred simultaneously, we undertook the challenging preparation of amines **3f** starting from a mixture a substrates. After

Table 2. Ruthenium-Catalyzed Reductive Amination of Allylic Alcohols^a

Reaction scheme: $R-CH=CH-CH_2OH$ (1a-f) + R^1R^2NH (2a-e) $\xrightarrow[\text{Toluene}]{\text{cat. A (5 mol \%), HCO}_2\text{H (1.1 equiv)}}$ $R-CH_2-CH_2-CH_2-NR^1R^2$ (3b-p)

entry	1	2	product	yield ^b
1				59%
2				77%
3				87%
4 ^c				66%
5				64%
6				57%
7				61%
8 ^c				65%
9				82%
10				59%
11 ^c				52%
12				66%
13 ^c				48%
14 ^c				60%
15				90%

^a All reactions were carried out at 0.2 M concentration in toluene for 15 h under inert atmosphere of argon with **1**/**2**/[Ru]/HCO₂H in 1.2/1/0.05/1.1 molar ratio at 150 °C. ^b Isolated yields. ^c Dialkylated side product formed in less than 10%.

adjustment of the amount of formic acid, reaction of *N*-ethyl-aniline in the presence of geraniol, nerol, citronellol,

citronellal and citral resulted in the formation of **3f** in 71% isolated yield (Scheme 2). This result highlights, that

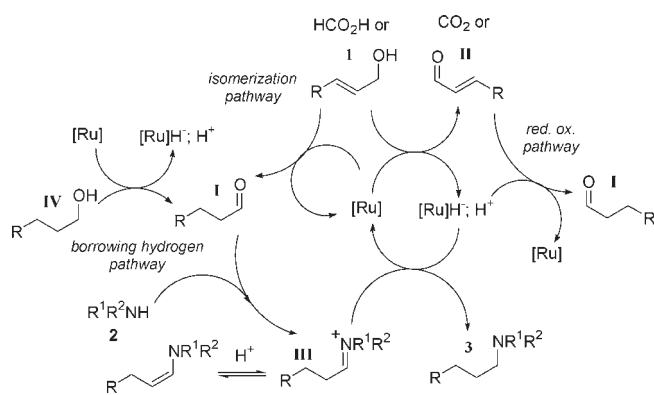


Figure 2. Proposed global mechanism.

concomitant hydrogen transfer and hydrogen autotransfer processes can occur from isostructural alcohols or aldehydes to selectively afford the same compound. A similar result was also obtained with a mixture of cinnamyl alcohol, cinnamaldehyde, 3-phenylpropionaldehyde and 3-phenylpropan-1-ol yielding 76% of **3a** (Scheme 2). The formation of **3f** and **3a** starting from a mixture of substrates can be rationalized according to Figure 2. In the presence of ruthenium catalyst allylic alcohol **1** can be converted to the corresponding aldehyde **I** by ruthenium-catalyzed redox isomerization.³ As demonstrated in Table 1, alcohols **1** can also serve as hydrogen donor to afford α,β -unsaturated aldehydes **II** along with the generation of ruthenium hydride species.¹⁰ To gain some insight into this part of the mechanism, we undertook the reaction of cinnamyl alcohol **1a** in the presence of cat. **A** in the absence of amine and formic acid. After thirty minutes at 130 °C, cinnamaldehyde (minor) and 3-phenylpropionaldehyde (major) were detected by GC/MS along with other side

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products. It should be noted that a similar result was obtained in the presence of formic acid. Then, aldehyde **I** can react with amine to afford imine or iminium intermediates **III** which are readily reduced by the in situ generated ruthenium hydride species to give the expected saturated amines **3**.¹¹ The use of formic acid could completely convert alcohol **1** to **I** by concomitant reduction of **II** and isomerization of **1**.¹² Finally, starting from a mixture of substrates, saturated alcohol **IV** affords the amines via a well-described ruthenium-catalyzed hydrogen autotransfer (hydrogen borrowing) mechanism.¹³ Any substrate **1**, **I**, **II** and **IV** can enter the catalytic cycle to give the final amine **3**. It is noteworthy that no product arising from Michael addition of amine to intermediate enal took place under these conditions, as confirmed by the absence of reaction between cinnamaldehyde and *N*-ethylaniline at 150 °C in the absence of ruthenium catalyst.

Arene ruthenium(II) complex **A** featuring a phosphine sulfonate chelate was efficiently used as a precatalyst for the formal reductive amination of allylic alcohols. Studies demonstrated that allylic alcohol served as hydrogen source by the formation of α,β -unsaturated aldehydes. Formic acid showed the best activity as additional hydrogen source. Current efforts are focused on the extension of the reaction to branched allylic alcohols for the synthesis of chiral amines and application in selective amination of terpene derivatives.

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Supporting Information Available. Experimental procedures and characterization data for compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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