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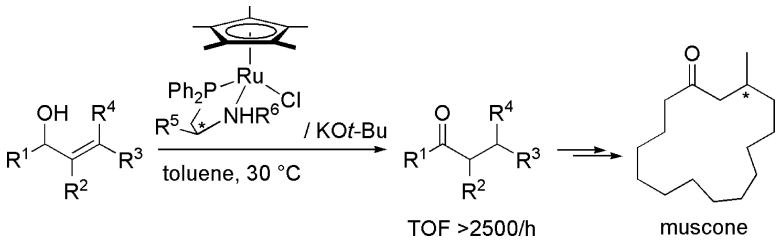

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Cp*Ru(PN) Complex-Catalyzed Isomerization of Allylic Alcohols and Its Application to the Asymmetric Synthesis of Muscone

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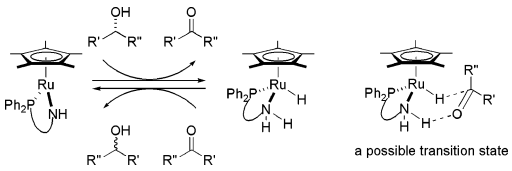
Catalytic selective transformation of allylic alcohols to saturated carbonyls (isomerization of allylic alcohols) is a potentially useful process due to its high atom-economy. Hence, considerable effort has been devoted to the past few decades, developing highly efficient, transition metal, catalyst systems for this reaction.[1a,b] A number of metal hydride catalysts have been known to promote the reaction, in which reversible transposition of the olefinic moiety in the substrate via the metal hydride addition−elimination mechanism leads to the formation of an intermediate enol that tautomerizes to a saturated carbonyl irreversibly. However, the metal hydrides are, in principle, active against most olefinic moieties in a nonselective manner. Hence, they show only poor chemoselectivity in the isomerization of allylic alcohols bearing other olefinic units.[1c,d] Therefore, recent attention has been focused on different mechanisms involving the reaction of the Ru hydride species with the enone ligand derived from Ru allyloxide, leading to high chemoselectivity.[1e−h]

We have recently developed highly efficient half-sandwich Ru catalysts having a metal/NH bifunctionality for hydrogen transfer between alcohols and carbonyls.[2,3] Coordinatively unsaturated Ru amide complexes derived from RuCl(*N*-sulfonyl-1,2-diamine) (η^6-arene)[2] or Cp*RuCl[$Ph_2P(CH_2)_2NH_2$-κ^2-*P*,*N*] (**1a**)[3] (Cp* = η^5-pentamethylcyclopentadienyl) effectively dehydrogenate alcohols possibly through a pericyclic transition state, leading to coordinatively saturated Ru hydride complexes with concomitant formation of carbonyls. In particular, a series of Cp*Ru catalysts bearing tertiary phosphine−primary amine (PN) ligands effect very rapid racemization of chiral nonracemic *sec*-alcohols via *intramolecular* hydrogen transfer[3b] (Scheme 1). We have expanded the scope of the *intramolecular* hydrogen transfer and found that Cp*Ru(PN) catalysts efficiently promote chemo- and stereoselective isomerization of allylic alcohols to give functionalized carbonyls in high yields. Again, the metal/NH bifunctional property of this catalyst plays a crucial role in the excellent catalyst performance.

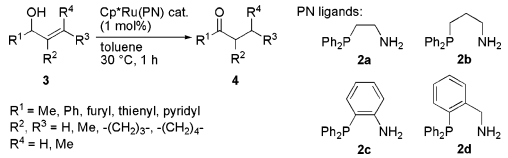
Scheme 1. Racemization Catalyzed by Cp*Ru(PN) Complexes



The ternary catalyst system of Cp*RuCl(cod) (cod = 1,5-cyclooctadiene), PN ligand **2a**, and KO*t*-Bu has proven to smoothly promote isomerization of α-vinylbenzyl alcohol (**3a**) (**3a**:Ru:**2a**:KO*t*-Bu = 100:1:1:1) at 30 °C in toluene ([**3a**] = 0.5 M in toluene) to give propiophenone (**4a**) quantitatively after 1 h (Scheme 2).

The catalyst performance was highly influenced by the structures of the PN ligands employed. Structurally analogous PN ligands with an NH_2 group (**2b**−**d**) also accelerate the reaction (78, 70, and 94% yield, respectively), whereas the rate of the reaction seriously decreased with increasing methyl substitution at the nitrogen (63% yield for $Ph_2P(CH_2)_2NHMe$ and 18% yield for $Ph_2P(CH_2)_2NMe_2$), indicating the crucial importance of the protic amino group in the ligand for determining catalyst performance. Neither a combination of monodentate phosphine or amine ligands nor bidentate diphosphine ligands gave satisfactory results.

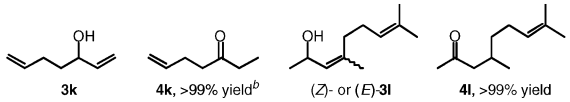
Scheme 2. Cp*Ru(PN)-Catalyzed Isomerization of **3**



Since a binary catalyst system of the preformed complex **1a** with KO*t*-Bu exhibited better catalyst performance[4] than that attained by the ternary system, the binary system was used to examine the scope and limitation of the isomerization.

Table 1. Isomerization of Various Allylic Alcohols[a]

entry	**3**	R^1	R^2	R^3	R^4	yield, %
1	**3a**	Ph	H	H	H	>99
2	**3b**	Ph	Me	H	H	>99
3	**3c**	Ph	H	Me	H	>99
4	**3d**	Ph	H	H	Me	67
5	**3e**	Ph	Me	Me	H	>99
6	**3f**	Ph	$-(CH_2)_3-$		H	>99
7	**3g**	Ph	$-(CH_2)_4-$		H	>99
8	**3h**	Ph	Me	H	Me	37
9	**3i**	Ph	H	Me	Me	>99
10[b]	**3j**	Me	H	H	H	>99
11	**3m**	2-furyl	H	H	H	>99
12	**3n**	3-furyl	H	H	H	>99
13	**3o**	2-thienyl	H	H	H	>99
14	**3p**	3-thienyl	H	H	H	>99
15	**3q**	3-pyridyl	H	H	H	>99



3k **4k**, >99% yield[b] (*Z*)- or (*E*)-**3l** **4l**, >99% yield

[a] [**3**] = 0.5 M in toluene, **3**:**1a**:KO*t*-Bu =100:1:1, 30 °C, 1 h. [b] In C_6D_6.

As listed in Table 1, allylic alcohols with varying substitution pattern on the C═C bond (**3**) are cleanly convertible in the presence of **1a** and KO*t*-Bu to the corresponding ketones **4** within 1 h at 30 °C. The present isomerization is characterized by broad tolerance to multiple substitution on the C═C bond and to a variety of functional groups including an isolated C═C bond. Notably, even allylic alcohols with a trisubstituted C═C bond can be smoothly transformed into their corresponding ketones (entries 5−9). In addition, isolated C═C bonds in **3k** and **3l** or heteroaromatic groups in **3m**−**q** (entries 11−15) do not interfere with the reaction giving

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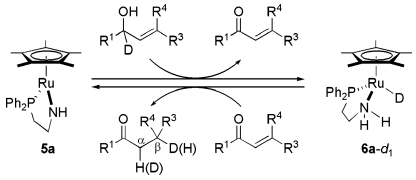
Scheme 3. Isotope-Labeling Experiments



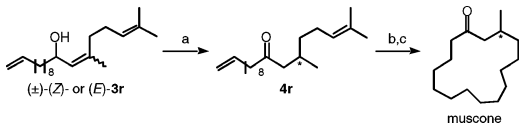
the corresponding ketones **4k**−**q** in quantitative yields within 1 h, suggesting a distinct mechanistic feature associated with metal/NH bifunctionality.

Isomerization of isotope-labeled allylic alcohols using **1a** with KO*t*-Bu provided valuable information on the mechanism. PhCD(OH)CH=CH_2 (**3a**-d_1, >99% D) was catalytically isomerized into $PhCOCH_2CH_2D$ (**4a**-d_1, >99% D) exclusively, and no deuterium was incorporated into the α-carbon of the carbonyl group in the product. Therefore, the present catalyst system may distinguish between the hydrogen on the OH group and that on the OH-bearing carbon in **3a** and relocate them onto the α- and β-carbons in **4a**, respectively. As previously reported,[3] the in situ generated Ru amido complex Cp*Ru[$Ph_2P(CH_2)_2NH$-κ^2-*P*,*N*] (**5a**) should dehydrogenate **3a**-d_1 via a pericyclic transition state to give Cp*RuD[$Ph_2P(CH_2)_2NH_2$-κ^2-*P*,*N*] (**6a**-d_1) and PhCOCH=CH_2 (PVK)[5] (Scheme 3). Then, **6a**-d_1 presumably transfers its deuterium and one of the hydrogens on the N to form C^β−D and C^α−H bonds in **4a**-d_1 regiospecifically due to the latent polarity of the PVK.[6] In sharp contrast, no regiospecificity was observed in the isomerization of $CH_3CD(OH)$-CH=$C(CH_3)(CH_2)_2CH$=$C(CH_3)_2$ (**3l**-d_1, *E*:*Z* = 7:3, >99% D) bearing two alkyl substituents at the distal sp^2 carbon of the allylic alcohol unit. In fact, the deuterium in **3l**-d_1 was distributed almost equally (42:57) at the α- and β-carbons in **4l**, suggesting that H−D scrambling[3b] in **6a**-d_1 should precede the reduction of the intermediary trisubstituted enone, possibly due to its low reactivity for the steric reasons. It is consistent with the fact that enantiomerically enriched (−)-(*E*)-**3l** (50% ee) was isomerized in the presence of **1a** and KO*t*-Bu to give completely racemic **4l** and that the recovered (*E*)-**3l** at an early stage of the reaction was found to be partially racemized.

Encouraged by the highly efficient and unique isomerization with Cp*Ru(PN) catalysts, we have next examined asymmetric isomerization of racemic *sec*-allylic alcohols via dynamic kinetic resolution[7] with a well-defined chiral catalyst Cp*RuCl[(*S*)-Ph_2PCH_2-CHR^5NHR^6-κ^2-*P*,*N*] (R^5, R^6 = $-(CH_2)_3-$) (**1g**) prepared using a chiral PN ligand derived from L-proline.[8] The reaction of (±)-(*Z*)-**3l** or (±)-(*E*)-**3l** in toluene containing **1g** and KO*t*-Bu (**3l**:**1g**:KO*t*-Bu = 20:1:1, [**3l**] = 0.5 M) proceeded smoothly at 30 °C to give the corresponding optically active ketone **4l** with 62% (*S*) and 66% (*R*) ee, respectively, in good yields. It should be noted that the enantioface differentiation is reversed by the geometry of the olefinic unit in **3l** and that enantiomeric excess values of **4l** remain constant throughout the reaction as a result of dynamic kinetic resolution.

This new type of asymmetric isomerization of racemic *sec*-allylic alcohols was applicable to the asymmetric synthesis of muscone.[9] As outlined in Scheme 4, the starting allylic alcohols, (±)-(*Z*)- or (±)-(*E*)-**3r**, which were readily prepared by the addition of 9-decenyllithium to neral and geranial, respectively, were isomerized in toluene containing **1g** and KO*t*-Bu as a catalyst to give the corresponding (*R*)-**4r** with 64% ee and (*S*)-**4r** with 74% ee,

Scheme 4. Asymmetric Synthesis of Muscone[a]



[a] Reaction conditions: (a) **1g** + KO*t*-Bu (5 mol %), toluene, 30 °C. (b) Grubbs 2nd Generation Catalyst (10 mol %), $ClCH_2CH_2Cl$, 65 °C, 68%. (c) Pd/C, H_2 (1 atm), EtOH, 30 °C, 90%.

respectively. These products were subjected to ring-closing olefin metathesis (RCM) using Grubbs 2nd Generation Catalyst and, subsequently, to hydrogenation using a Pd/C catalyst to afford good yields of both antipodes of muscone without any loss of optical purity. Design of better chiral PN ligands for the present asymmetric isomerization is now actively underway.

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Supporting Information Available: Full experimental details including spectral data and determination of enantiomeric excesses. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) Separate experiments with higher **3a**/catalyst ratio revealed that the initial rate of the reaction at 30 °C exceeds over 2500 turnover frequency/h.

(5) Me_3Si protection of the OH group in **3a** completely inhibits the reaction. The reaction of **3a** in the presence of methyl vinyl ketone afforded PVK in addition to **4a** (See Supporting Information). These results also support the intermediacy of enones.

(6) For related 1,4-addition of active methylene compounds across enones, see: (a) Watanabe, M.; Murata, K.; Ikariya, T. *J. Am. Chem. Soc*. **2003**, *125*, 7508−7509. (b) Ikariya, T.; Wang, H.; Watanabe, M.; Murata, K. *J. Organomet. Chem.* **2004**, *689*, 1377−1381. (c) Wang, H.; Watanabe, M.; Ikariya, T. *Tetrahedron Lett.* **2005**, *46*, 963−966. (d) Guo, R.; Morris, R. H.; Song, D. *J. Am. Chem. Soc.* **2005**, *127*, 516−517.

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(8) Single-crystal X-ray analysis confirmed that **1g** adopts the typical three-legged piano-stool structure. Full details will be reported separately.

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