# Two-Metal Catalyst System for Redox Isomerization of Propargyl Alcohols to Enals and Enones

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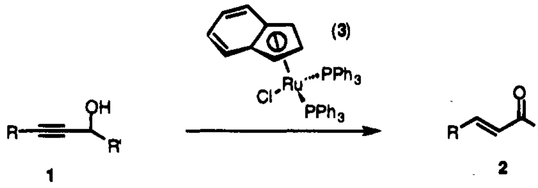
The utility of α,β-unsaturated carbonyl compounds in synthesis and the ease of access to propargyl alcohols make the conversion of the latter into the former a useful transformation. The Meyer–Schuster rearrangement effects such a transformation but with transposition of the oxygen.[1] Methods that avoid such rearrangements of the oxidation pattern are normally multistep processes.[2] The most efficient process involves simple internal redox according to eq 1. Our development of a ruthenium-catalyzed system for redox isomerization of allylic alcohols to saturated carbonyl partners[3] led to our consideration of such systems for this process. Tris(triphenylphosphine)ruthenium dichloride has been reported to effect such a reaction.[4] However, in our hands, applying the reported reaction conditions to **1a** (R = $PhCH_2CH_2CH_2$, R′ = H) led to a 3:1 mixture of enal (**2a**)[5] and 6-phenyl-2,4-hexadienal[6] in only 21% yield after 36 h with most of the remainder being decomposition products. We report a new catalytic system that efficiently effects such an isomerization that operates by a mechanism completely different from that involved in the redox isomerization of allyl alcohols.



(1)

**Table 1.** Redox Isomerization of Alkynols to Enals and Enones

| entry | R | R′ | time (h) | isolated yield (%) | compd no. suffix |
|---|---|---|---|---|---|
| 1 | $Ph(CH_2)_3$ | H | 1.25 | 88 | **a**[a] |
| 2 | $PhC({=}O)(CH_2)_3$ | H | 1.5 | 80 | **b**[b] |
| 3 | $PhCH(OAc)(CH_2)_3$ | H | 1.5 | 87 | **c**[b] |
| 4 | $PhCH(OH)(CH_2)_6$ | H | 1.5 | 86 | **d**[b] |
| 5 | $CH_3(CH_2)_3C{\equiv}C(CH_2)_6$ | H | 1.5 | 83 | **e**[b] |
| 6 | $(CH_3)_2C{=}CH$ | H | 1.5 | 67 | **f**[c] |
| 7 | $CH_3(CH_2)_9$ | $CH_2CH_2Ph$ | 24 | 86 | **g**[b] |
| 8 | $CH_3(CH_2)_3$ | $(CH_2)_8CH{=}CH_2$ | 24 | 83 | **h**[b] |

[a] See ref 5. [b] See ref 9. [c] See ref 10.

Using **1a** (see eq 1 and Table 1) as the test substrate, our studies began with the indenylruthenium complex **3**,[7] which proved very effective for the isomerization of allyl alcohols. Under the normal conditions for the latter reaction, which is cocatalyzed by an ammonium hexafluorophosphate in THF at reflux, **2a** was indeed produced but only in 33% conversion after 4 h. Because of the known sensitivity of the α,β-unsaturated aldehyde products, we envisioned temporarily protecting the aldehyde by the formation of a hydrate or a hemiacetal by performing the reaction in the presence of water or alcohol cocatalyzed by a mild Lewis acid like a lanthanide salt. While this concept failed due to additions to the π-unsaturation, we noted that indium (+3) salts, which we previously had employed as cocatalysts in a palladium reaction to promote carbonyl addition,[8] did however speed up consumption of starting material. Remarkably, simply adding indium trichloride to the original catalyst system in THF at reflux led to complete consumption of starting material within 1 h. In a preparative run, the α,β-unsaturated aldehyde **2a** (see Table 1) was isolated in 88% yield.

Replacing the indenyl complex **3** by the corresponding cyclopentadienyl complex[11] slowed reaction: after 4 h it was 84% complete. Using indium chloride in the absence of an ammonium hexafluorophosphate salt led to only 30–40% completion after 1 h. On the other hand, indium acetate, acetylacetonate, or hexafluoroacetylacetonate did not significantly promote isomerization.

Table 1 summarizes our results. The initial experiments were performed with a batch of triethylammonium hexafluorophosphate prepared from triethylammonium chloride and ammonium hexafluorophosphate which subsequently proved to be a mixture of triethylammonium and ammonium hexafluorophosphate. For the synthesis of the α,β-unsaturated aldehydes (Table 1, entries 1–6), use of 5 mol % of both salts gave slightly better yields in less time than either salt alone. Reaction with internal propargyl alcohols which produced enones proceeded more slowly but still in excellent yield (Table 1, entries 7 and 8). In these cases, use of triethylammonium hexafluorophosphate alone proved beneficial.

The reaction exhibits extraordinary chemoselectivity. The fact that the highly reactive products, α,β-unsaturated aldehydes and ketones, are isolated in excellent yields attests to this fact. An isolated carbonyl group (entry 2), ester (entry 3), unprotected alcohol (entry 4), alkyne (entry 5), and terminal alkene (entry 8) are completely unaffected. The latter is particularly noteworthy since some isomerization of a terminal alkene to an internal alkene had been noted with **3** previously.[3] Complete control of alkene geometry favoring the *E* isomers occurred as shown by GC and NMR analysis. An excellent synthesis of dienals emerges by combining palladium-catalyzed cross cou-

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(2) For some examples, see: Matsuoka, R.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1987**, *28*, 1299. Muzart, J. *Tetrahedron Lett.* **1987**, *28*, 4665. Nakamura, T.; Namiki, M.; Ono, K. *Chem. Pharm. Bull.* **1987**, *35*, 2635. Tanaka, H.; Yoshida, K.; Itoh, Y.; Imanaka, H. *Tetrahedron Lett.* **1981**, *22*, 3421. Wijnberg, B. P.; Speckamp, W. N. *Tetrahedron Lett.* **1981**, *22*, 5079. Corey, E. J.; Park, H.; Barton, A.; Nii, Y. *Tetrahedron Lett.* **1980**, *21*, 4243. Shenvi, A. B.; Gerlach, H. *Helv. Chim. Acta* **1980**, *63*, 2426. Corey, E. J.; Terashima, S. *Tetrahedron Lett.* **1972**, 1815.

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(4) Ma, D.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1989**, 890. For isomerization to a mixture of α,β- and β,γ-enones, see, for Pd: Lu, X.; Ji, J.; Guo, C.; Shen, W. *J. Organomet. Chem.* **1992**, *428*, 259. For Ir: Ma, D.; Lu, X. *Tetrahedron Lett.* **1989**, *30*, 2109. Also see: Minn, K. *Synlett* **1991**, 115. Hirai, K.; Suzuki, H.; Moro-Oka, Y.; Ikawa, T. *Tetrahedron Lett.* **1980**, *21*, 3413.

(5) Takayama, H.; Koike, T. Aimi, N.; Sakai, S. *J. Org. Chem.* **1992**, *57*, 2173.

(6) Yahata, N.; Fujita, M.; Ogura, K. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3601.

(7) Oro, L. A.; Ciriano, M. A.; Campo, M.; Foces-Foces, C.; Cano, F. H. *J. Organomet. Chem.* **1985**, *289*, 117.

(8) Trost, B. M.; Sharma, S.; Schmidt, T. *J. Am. Chem. Soc.* **1992**, *114*, 7903; *Tetrahedron Lett.* **1993**, *34*, 7183.

(9) New compounds have been satisfactorily characterized spectroscopically, and elemental composition has been established by combustion analysis or high-resolution mass spectroscopy.

(10) Skorianetz, W.; Ohloff, G. *Helv. Chim. Acta* **1975**, *58*, 1272.

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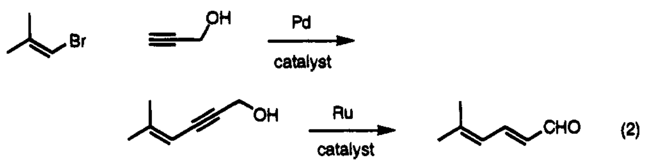
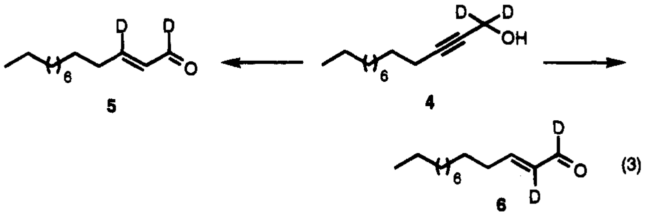
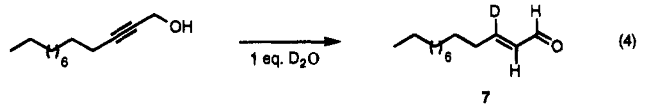
pling[12] with ruthenium-catalyzed redox isomerization (eq 2, Table 1, entry 6).



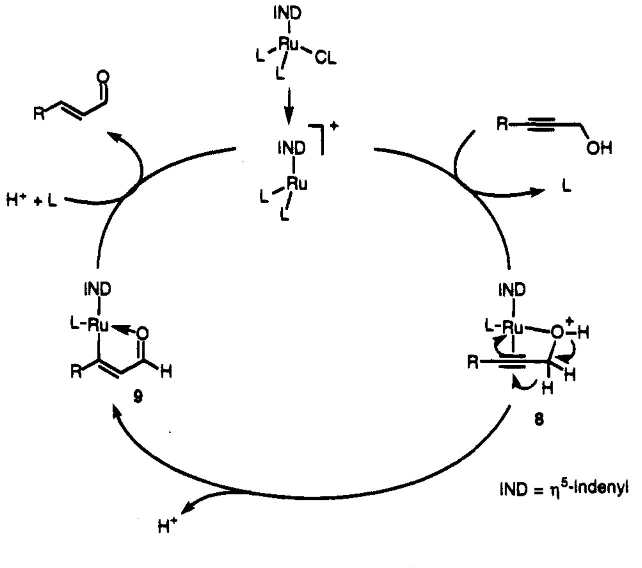
The mechanism of the isomerization was probed by using the deuterated propargyl alcohol **4** (eq 3). If the reaction paralleled that of the ruthenium-catalyzed isomerization of allyl alcohols, the expected product would have the labeling pattern depicted in **5**. NMR spectroscopy clearly reveals that such is not the case and that the labeling corresponds to that depicted in **6**.[13] Performing the reaction in the presence of 1 equiv of $D_2O$ led to 50% incorporation of deuterium at the $\beta$-carbon as shown in **7**. These results strongly implicate a mechanism as shown in Scheme 1. Support for this proposal derives from several observations in stoichiometric ruthenium-catalyzed reactions. As our work neared completion, Dixneuf reported a 1,2-shift of an aryl group in the case of an aryl propargyl alcohol.[14] It would not be unexpected for an electron rich aryl group to migrate in preference to a H,[15] and this supports the concept depicted in **8**. Precedent also exists for the protonation of a vinylruthenium species analogous to **9** as depicted.[16] Left unanswered by this proposal is a role for indium trichloride. It could serve as a chloride scavenger[17] thereby promoting formation of the ruthenium cation. An alternative considers the strain associated with **8**, which could be relieved by invoking an indium-bridged species like **10**.

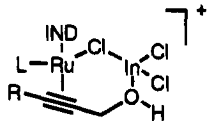




This ruthenium-catalyzed reaction represents an extremely simple, practical, and efficient synthesis of $\alpha,\beta$-unsaturated aldehydes and ketones.[18] Due to the fact that the precursors are normally available via simple additions, the overall sequence is highly atom economical. The elaboration of propargyl alcohols by cross coupling with vinyl halides and pseudohalides extends the sequence to the synthesis of polyunsaturated conjugated carbonyl compounds. The novel mechansim involved suggests several intriguing directions which are currently under active investigation.

**Scheme 1.** Mechanism for Redox Isomerization of Propargyl Alcohols





**10**

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**Supporting Information Available:** Characterization data for **2b–e,g,h**. (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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[12] Magnus, P.; Annoura, H.; Harling, J. *J. Org. Chem.* **1990**, *55*, 1709. Nicolaou, K. C.; Veale, C. A.; Webber, S. E.; Katerinopoulos, H. *J. Am. Chem. Soc.* **1985**, *107*, 7515. For a recent leading reference, see: Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403.

[13] Peaks at $\delta$ 9.51 and 6.12 present in the all protio compound are totally missing. A peak at $\delta$ 6.85 (t, $J = 6.8$Hz, 1H) for $\beta$-vinyl H is present.

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[16] Komiya, S.; Ito, T.; Cowie, M.; Yamamoto, A.; Ibers, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 3874.

[17] Houpis, I. N.; Molina, A.; Douglas, A. W.; Xavier, L.; Lynch, J.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1994**, *35*, 6811.

[18] In a typical experiment, enough freshly distilled THF to make ultimately a solution 0.25 M in substrate was added to a mixture of indium trichloride (20–40 mol %), indenylruthenium complex **3** (5 mol %), triethylammonium hexafluorophosphate (5 mol %), and ammonium hexafluorophosphate (5 mol %). (In the synthesis of enones, 10 mol % of triethylammonium hexafluorophosphate and no ammonium hexafluorophosphate were added.) After addition of the substrate, the homogeneous red solution was stirred for several minutes at room temperature and gradually heated to reflux. After disappearance of starting material, the THF was removed *in vacuo*. The residue was filtered through a short plug of Florisil with ether and then flash chromatographed on silica gel to give the product.