Handbook of Green Chemistry

Edited by Paul T. Anastas

WILEY-VCH

Green Processes

Volume 7: Green Synthesis

Volume Editor:
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Handbook of Green Chemistry

Volume 7
Green Synthesis

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Paul T. Anastas joined Yale University as Professor and serves as the Director of the Center for Green Chemistry and Green Engineering there. From 2004–2006, Paul was the Director of the Green Chemistry Institute in Washington, D.C. Until June 2004 he served as Assistant Director for Environment at the White House Office of Science and Technology Policy where his responsibilities included a wide range of environmental science issues including furthering international public-private cooperation in areas of Science for Sustainability such as Green Chemistry. In 1991, he established the industry-governmentuniversity partnership Green Chemistry Program, which was expanded to include basic research, and the Presidential Green Chemistry Challenge Awards. He has published and edited several books in the field of Green Chemistry and developed the 12 Principles of Green Chemistry.

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Chao-Jun Li (FRSC, UK) received his PhD at McGill University (1992) and was an NSERC Postdoctoral Fellow at Stanford University (1992–1994). He was an Assistant Professor (1994), Associate Professor (1998) and Full Professor (2000–2003) at Tulane University, where he received a NSF CAREER Award (1998) in organic synthesis and the 2001 US Presidential Green Chemistry Challenge Award (Academic). In 2003, he became a Canada Research Chair (Tier I) in Organic/Green Chemistry and a Professor of Chemistry at McGill University in Canada. He serves as the Co-Chair of the Canadian Green Chemistry and Engineering Network, the Director of CFI Infrastructure for Green Chemistry and Green Chemicals, and Co-Director the FQRNT Center for Green Chemistry and

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Preface

Ever since the synthesis of urea by Friedrich Wöhler near two centuries ago, organic synthesis has become the foundation of modern medicines for human health, produced new agrochemicals to boost world food supply, created various synthetic fibers for daily usages, and bestowed a colorful enchantment through synthetic dyes. In spite of these great achievements, the general features of organic syntheses have been, by and large, unchanged over a century: e.g., non-renewable feedstock, batch reactor, and refluxing. In addition, classical organic syntheses often produce stoichiometric amount of waste, use organic solvents and sometimes dangerous reagents, require extensive protection-deprotection of functional groups, need pre-functionalized starting materials, and involve multi-step operations, which resulted in low efficiency in resource utilization and led to various concerns due to waste generations. While, in the past, the primary goal of organic syntheses is " to get the target product", the sustainability of chemical synthesis becomes a more and more important issue. This volume of Green Syntheses illustrated some examples to address this issue ranging from starting materials, reaction design, choice of solvent, energy input, to reactor design. The chapter by Trost describes the general principle of greener synthesis; the chapter by Behr shows examples of using renewable feedstocks for making chemical products; the chapter by Horvath describes the use of alternative solvents for organic synthesis; the chapters by Zhu, Hoffman and Watts describe methods of reducing synthetic steps by running multi-component reactions, avoiding protecting groups, and in flow respectively; the chapters by Ackermann and Li show examples of direct conversion of C–H bonds; the chapters by Varma and Yoshida presents alternative energy input in chemical reactions through light and electricity; the chapters by Tao and Akiyama give examples of using enzymes and organo catalysts for synthetic purposes; and finally the chapter by Andraos uses computation methods to evaluate the relative efficiency of different synthetic routes. We hope that these examples will provide food-for-thought for further innovations in developing greener syntheses.

Montreal, April 2012 C-J Li

1
Atom Economy: a Challenge for Enhanced Synthetic Efficiency

Barry M. Trost

The design of structure for function is the major task for helping to solve problems ranging from material science to human health. The demands and expectations for extremely high levels of performance frequently increases the molecular complexity needed. Thus, a major goal must be to allow the synthesis of such complex molecular arrays in a time-effective manner. The strategic design for the synthesis of complex molecules derives from the available basic tools – the reactions, reagents, and catalysts. Although some might think we have a pretty full toolbox, the reality is that, in most likelihood, only a very small fraction of the true total number of reactions possible is known today. Hence a great unknown awaits us, and chipping away at those unknown processes presents a great opportunity for discovery that will undoubtedly change the practice of the science.

In undertaking a program of discovery for new processes, the characteristics that defines the requirements for these new reactions/reagents/catalysts must be appreciated. In 1983, selectivity was noted as key to evolving reasonable efficiency in the synthesis of complex molecules [1]. The issue of chemoselectivity, defined as discriminating reactivity among various bond types in a molecule without employing activating or blocking groups, was placed at the top of the list! There is no question that problems of chemoselectivity are the single biggest factor in creating synthetic inefficiencies. More than 25 years later, the primacy of this selectivity issue was still noted [2]. It is so pervasive in the science that it undoubtedly will remain the greatest challenge for a long time to come. The second issue is regioselectivity, which is defined as orientational control in the joining of a reagent with an unsymmetrical functional group. Controlling stereochemistry constitutes the third major challenge. There are two fundamentally different issues embodied within this topic – controlling relative stereochemistry or diastereoselectivity and absolute stereochemistry or enantioselectivity.

By and large, selectivity was equated with efficiency. However, just a little further thought makes us realize that we are missing one key aspect of efficiency by focusing only on selectivity, that is, by ignoring an obvious but neglected aspect, which is, simply put, how much of what you put into your pot ends up in your product? In 1991, this fundamental and critical issue was explicitly recognized and referred to as "atom economy" [3]. In 1992, the *E* factor was introduced, which also

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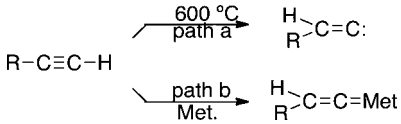
provided a quantitative metric to evaluate the degree of atom economy [4]. Atom economy, which basically emphasizes maximal use of raw materials and minimization of waste, has become one of the 12 principles of Green Chemistry [5]. Making synthetic chemistry more "environmentally benign by design" has become a mantra.

The ideal reaction is one in which 100% of what is introduced into a reaction ends up as product and, if anything else is required, it is needed only catalytically. Thus, a bimolecular reaction should be a single addition and a unimolecular reaction should be an isomerization. Such processes are clearly known and heavily used, such as a Diels–Alder reaction and Claisen and Cope rearrangements. However, such processes constitute only a very small fraction of our toolbox. In the late 1980s, we began a deliberate program to invent processes that theoretically are 100% atom economic. I note this goal as theoretical since to achieve it fully requires the yield to be quantitative, which rarely occurs, but at least the possibility does exist. A reaction of the type $A + B \rightarrow C + D$ suffers from the fact that it theoretically cannot be 100% atom economic and also suffers from the issue of yields typically being less than quantitative. This overview reports the evolution of one of our programs for semi-rationally inventing atom economic processes based upon catalysis with ruthenium complexes.

1.1 Vinylidenes

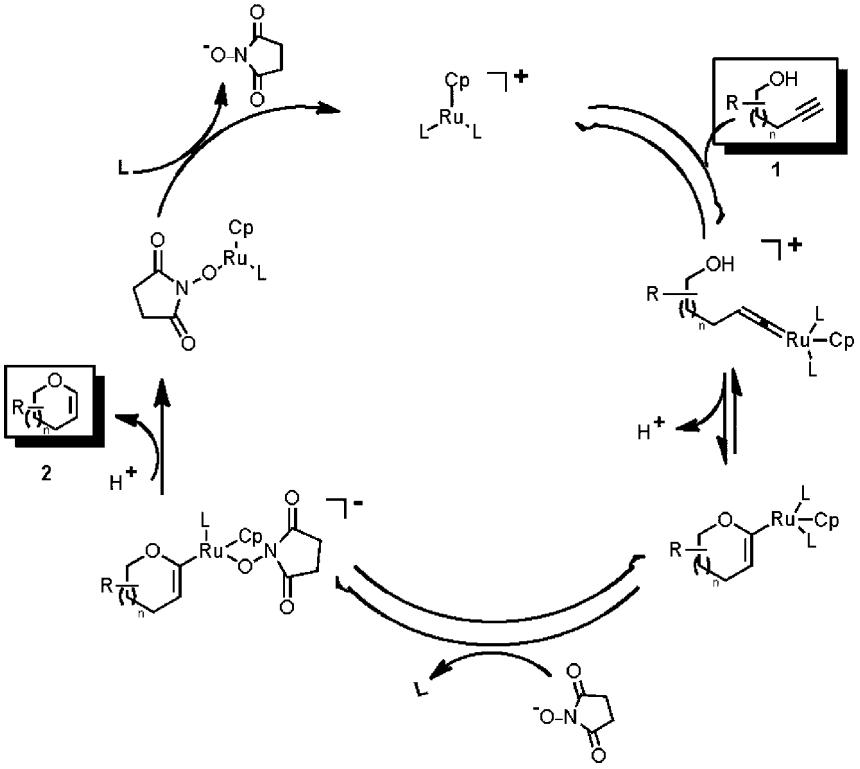
1.1.1 Cycloisomerization of Hydroxyalkynes

The formation of reactive intermediates provides possible opportunities for new reaction design. An attractive highly reactive intermediate, carbenes, which demonstrate numerous useful synthetic pathways, most notably by addition to alkenes and alkynes and also insertion into X–H bonds, where X is both carbon and heteroatoms, suffers from problems associated with their accessibility. Undoubtedly, the most useful class of precursor is the diazo compounds, whose safety problems restrict their use. For the specific case of vinylidenes, an attractive possibility is a terminal alkyne which is isomeric with a vinylidene. Although the thermolysis appears to effect this transformation (Equation 1.1, path a), the extraordinarily high temperatures required make the prospect of a transition metal-catalyzed version (Equation 1.1, path b) attractive. The early studies of Werner [6] using Rh and Bruce and co-workers [7] using Ru proved the facility with which such species would form; however, the studies focused on the formation and isolation of the vinylidene–metal complexes and their stoichiometric reactions.

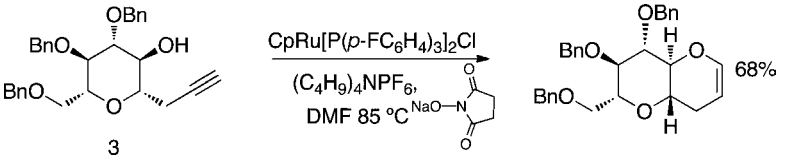


(1.1)

Based on these studies and choosing to focus on Ru for practical considerations such as cost, we envisioned a possible catalytic cycle shown in Scheme 1.1, wherein an ω-alkynyl alcohol **1** would cycloisomerize to the dihydropyran. Although McDonald's group has pioneered the use of molybdenum- and tungsten-mediated processes, several issues related to chemoselectivity and the common need for stoichiometric amounts make the development of other catalysts for such processes desirable [8]. Using $CpRu(PAr_3)_2Cl$-based complexes, less electron-rich arylphosphine ligands such as *m*- or *p*-fluorophenylphosphines promote such processes (Equation 1.2) [9].



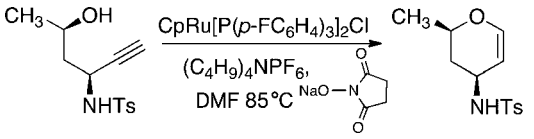
Scheme 1.1 Cycloisomerization of hydroxyalkenes.



(1.2)

While the presence of propargylic hydroxy groups has proven problematic (see below), the presence of a propargylic *N*-tosylamido group is tolerated (Equation 1.3).

Interestingly, the presence of a bis-homopropargylic secondary amide does not lead to insertion into the N–H (as happens with a tungsten catalyst [8c]) competing with formation of the dihydropyran as shown in Equation 1.4 [10]. This reaction extends to the insertion into a phenolic OH to form benzofurans (Equation 1.5). In this case, the presence of an amine such as *n*-butylamine or pyridine appears to be required [11]. It should be noted that insertion into the benzylic OH to form the pyran system does not compete.



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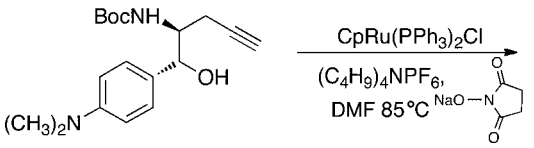

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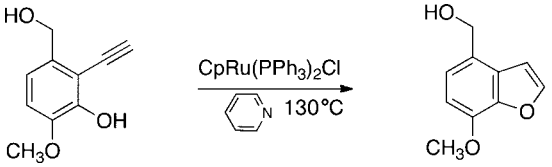
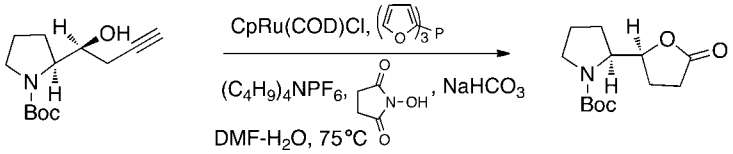
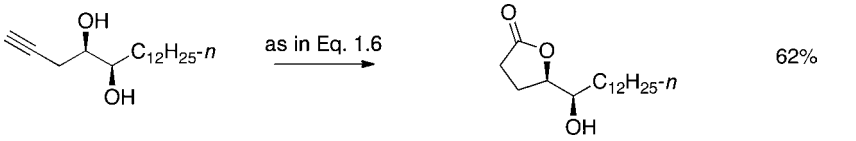


75% (1.5)

Interestingly, making the reaction less basic, increasing the amount of *N*-hydroxysuccinimide to 3 equiv., and changing the phosphine reorients the course of the reaction to an oxidative cyclization to form lactones. For example, γ-butyrolactones form fairly readily from homopropargylic alcohols (Equation 1.6) and even preferentially when the possibility for forming the thermodynamically more stable six-membered ring lactones could occur (Equation 1.7) [12]. The synthesis of the butyrolactones is optimized using trifurylphosphine as the ligand. Nevertheless, bis-homopropargyl alcohols also undergo oxidative cyclization. Thus, the homopropargyl alcohol **3** in Equation 1.2 under the conditions of Equation 1.6 except that the phosphine ligand is changed to tris(*p*-methoxyphenyl) phosphine gives the δ-lactone **4** in 65% yield (Equation 1.8) [9]. As expected, competing a six- versus a seven-membered ring leads exclusively to cyclization to form the six-membered ring (Equation 1.9).



61% (1.6)



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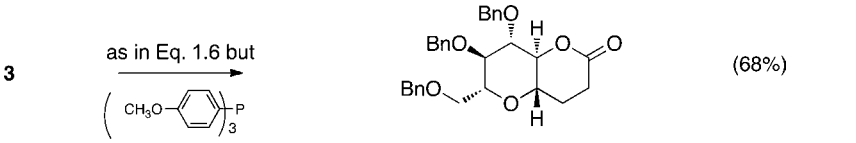
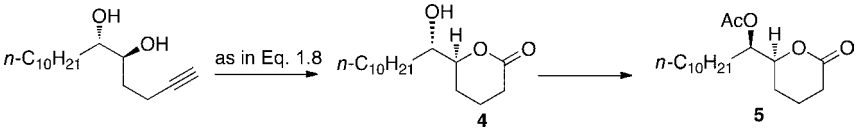
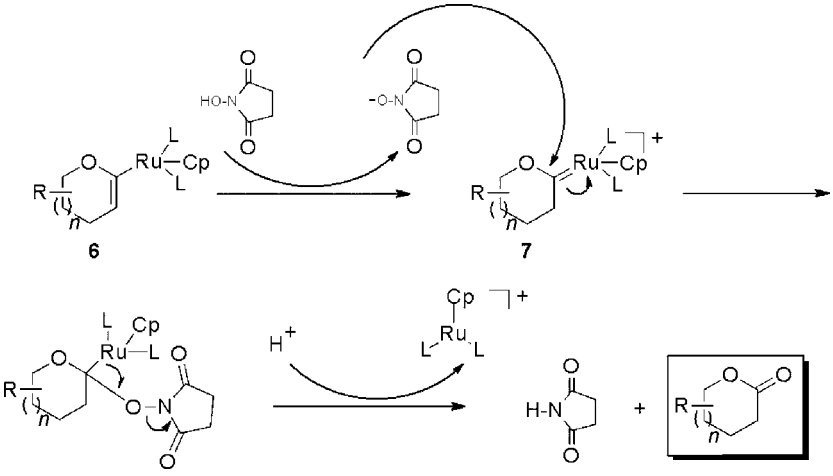


(1.8)



(1.9)

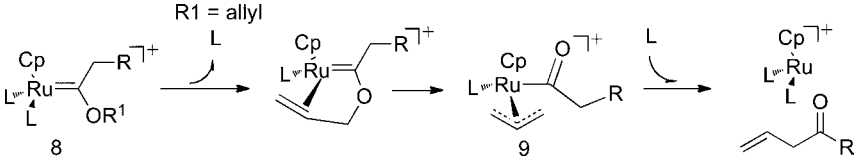
After esterification of alcohol **4** with inversion of configuration, the oviposition attractant pheromone of the mosquito s*Culex pipens fatigans* **5** is formed. The stereochemistry of this sequence originated from the asymmetric dihydroxylation of the *trans*-alkene. Although the oxidative cyclization is significantly less atom economic than the cycloisomerization, since it requires stoichiometric amounts of *N*-hydroxysuccinimide, the recyclability of the resultant succinimide mitigates this defect somewhat. This switch in pathway as a function of pH can be understood by the sequence depicted in Scheme 1.2. In particular, the initially formed vinyl Ru complex **6**, whose coordination with the anion derived from hydroxysuccinimide, thus facilitating protonation to the enol ether, preferentially protonates to form the carbene complex **7**. Now the electrophilic carbene carbon undergoes nucleophilic addition of this same anion, leading ultimately to fragmentation with generation of the lactone.



Scheme 1.2 Mechanistic rationale for oxidative cyclization.

1.1.2
Reconstitutive Condensation

The intermolecular variant of the O–H insertion reaction gets stuck at the stage of the initial adduct **8**. We envisioned that if R^1 = allyl, coordination of the double bond to the metal would initiate a Claisen-type process to form the π-allylruthenium complex **9**, whose reductive elimination would form the allyl ketone starting from terminal alkynes and allyl alcohols (Equation 1.10). Gratifyingly, this prediction was fully realized as shown in Equation 1.11 [13]. A tertiary ester does not undergo elimination under these reaction conditions (Equation 1.12). Dihydroxylation of the double bond and subsequent acidification effect cyclodehydration to form furans in two overall "steps." Subsequent elimination of the elements of acetic acid completes a synthesis of rosefuran **10**, one of the most prized fragrances [14].



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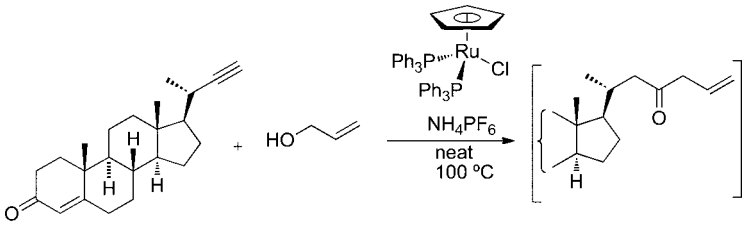

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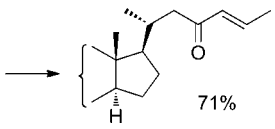
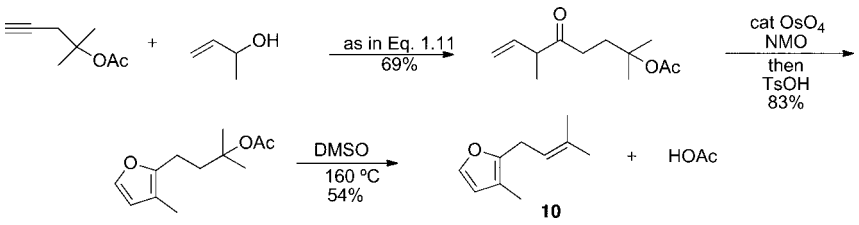
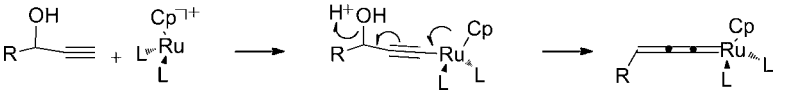




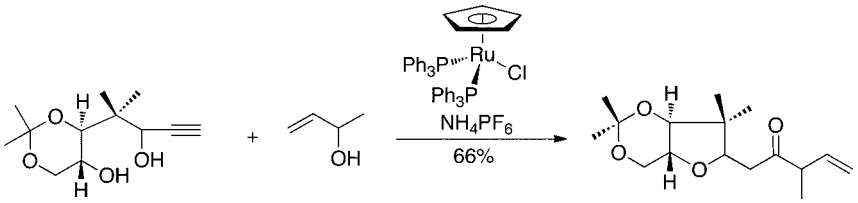
(1.12)

With terminal alkynes bearing propargylic alcohols, formation of the vinylidene is complicated by the competitive formation of the allenylidene as shown in Equation 1.13.

In the case of a substrate bearing a second hydroxyl group, the allenylidene can undergo nucleophilic attack at the γ-carbon to re-form a vinylidene [15]. In such an event, the newly formed vinylidene can then undergo the reconstitutive condensation shown in Equation 1.14 [16]. This reaction provides access to the spiroketal of calyculin A, a nanomolar inhibitor of serine/threonine phosphatases.



(1.13)

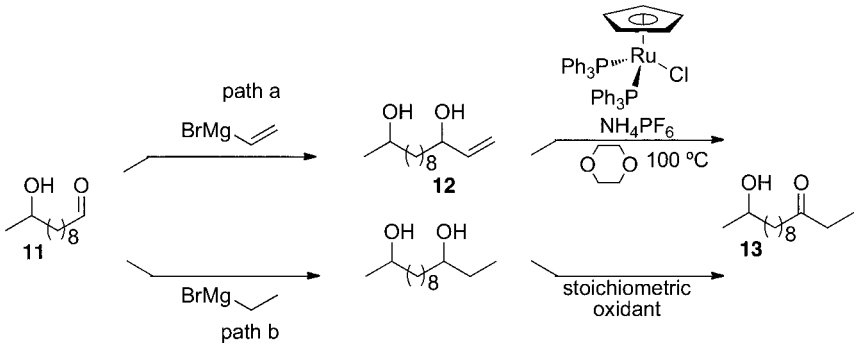


(1.14)

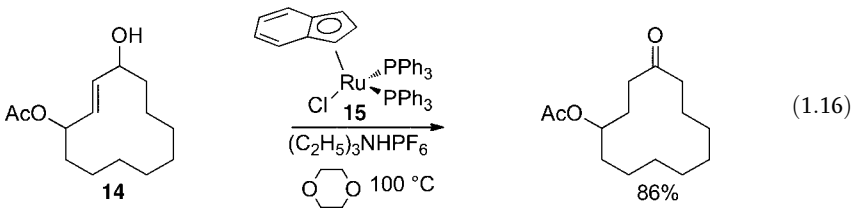
1.2
Redox Isomerization

1.2.1
Allyl Alcohols

In the reconstitutive addition in which we used the allyl alcohol as both reactant and solvent, we noted that propanal was detected as a by-product. This observation led us to consider the use of $CpRuL_2Cl$ as a catalyst for redox isomerization of allyl alcohols in general. Indeed, subjecting allyl alcohol **12** to the standard Ru catalyst effects chemoselective isomerization to the saturated ketone **13** (Equation 1.15) [17]. Normally starting from aldehyde **11**, the typical route to saturated ketone **13**, path b, involves a stoichiometric oxidant for one step. Furthermore, there is also a chemoselectivity issue in this example, thereby further enhancing the inefficiency by requiring a protecting group operation. By simply switching to an unsaturated organometallic for the first step, a stoichiometric oxidant is avoided, as is any need for protecting groups, thereby improving the overall atom economy. For more substituted double bonds, the (indenyl)$Ru(PPh_3)_2Cl$ catalyst, which can slip from an η^5 to an η^3 complex, allows a decrease in steric hindrance in addition to being accompanied by the formation of a coordinatively unsaturated ruthenium which improves the reactivity. Thus, the 1,2-disubstituted alkene substrate **14** (Equation 1.16) undergoes redox isomerization within 3 h, whereas such substrates barely react at all with the $CpRu(PPh_3)_2Cl$ complex.

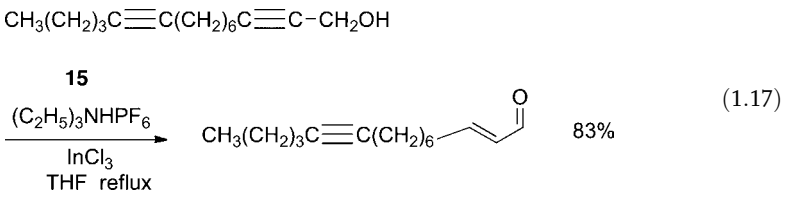


(1.15)

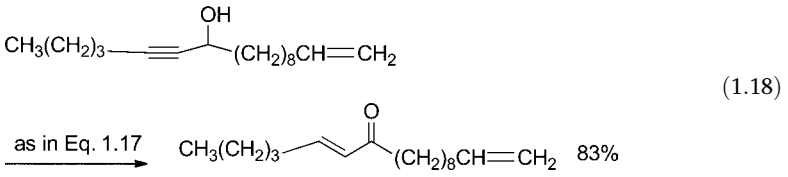


(1.16)

Application of this catalyst system to propargyl alcohols provides α,β-unsaturated aldehydes (Equation 1.17) and ketones (Equation 1.18) [18]. The ease of accessibility of the substrates by simple addition of terminal alkynes to aldehydes followed by this redox isomerization constitutes a highly chemoselective and atom economic strategy to these unsaturated carbonyl compounds. The chemoselectivity problems of the direct aldol condensation and the poor atom economy of olefination methods make this new strategy the most efficient and reliable approach to these units.



(1.17)



(1.18)

A significant improvement in the catalyst adds further utility to this strategy. Using 1–5 mol% of indenyl complex **15** along with indium triflate and camphorsulfonic acid (CSA) as cocatalysts, the redox isomerization in Equation 1.19 was completed in 20 min compared with 1.5 h under the indium chloride cocatalyst conditions.