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Synthetic Methods

Alcohols as Electrophiles in C–C Bond-Forming Reactions: The Hydrogen Autotransfer Process**

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The hydrogen autotransfer process involves an initial oxidative hydrogen elimination, followed by different types of reactions, and is completed with a reductive hydrogen addition to give the final product. The sequence allows the alkylation of different nucleophilic agents using environmentally benign alcohols as electrophiles, mild conditions, and soft bases, with water produced as the only waste material. Recent examples of modulating the organometallic catalyst have also lent themselves to expansion of the range of available substrates, as described in this Minireview.

1. Introduction

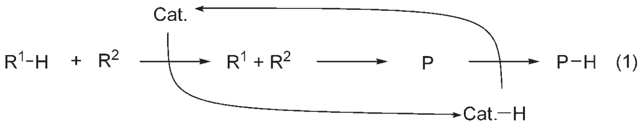
To increase the molecular complexity of a simple organic substrate[1] using efficient, selective, high-yielding, and environmentally benign methods is one of the contemporary challenges for synthetic organic chemists.[2] C–C bond formation is a pivotal method to achieve this goal, with the electrophilic alkylation of a given substrate being one of the most useful procedures.

In this field, one of the most used methods is the coupling of enolate derivatives with alkyl halides.[3] However, this synthetic approach suffers great disadvantages, such as the required use of strong bases with high molecular weights, the large amount of weight lost with the leaving group of the alkylating agent, thus decreasing the atom efficiency[4] of the process (usually less than 20%), as well as the problem of generating waste.

The ideal electrophilic agent should have a low-molecular-weight leaving group, and the environmental impact of this group should be minimum. On these grounds, alcohols are a good choice and they offer the extra advantage of being cheap and easy to handle and store. However, alcohols are generally not used as alkylating agents due to the high energy of C–O bonds ($\approx 90\ \text{kcal}\,\text{mol}^{-1}$); this energy is then increased as a result of their deprotonation under the basic conditions of the reaction. Despite these facts, several strategies have been developed to change the usual nucleophilic reactivity of alcohols.[5] Among them, the hydrogen autotransfer process is probably one of the best possibilities not only from a chemical point of view but also from economical and environmental aspects, as we demonstrate herein.

2. General Definition

The hydrogen autotransfer process is a type of domino reaction[6] [Eq. (1)]. The process involves initial hydride



(1)

abstraction from one of the reagents (R^1–H) by the catalyst (Cat.), followed by the reaction of the two generated reagents (R^1 and R^2) to form a new stable compound (P), which in turn is the hydrogen acceptor for the previously hydrogenated catalyst (Cat.–H), thereby renewing the catalyst and giving the final product (P–H).

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With this new concept, a nucleophilic alcohol can be transformed in situ into a highly electrophilic aldehyde, which can react with different nucleophiles to give the desired alkylated products with water as the only waste material. Therefore, in principle, it is a more efficient (only OH or H_2O is the leaving group lost) and cheaper strategy (no need for anhydrous bases and anhydrous solvents) and can be considered as a "greener" approach than the traditional alkylation process.

3. Electrophilic α-Alkylation of Ketones

Although the alkylation of ketones with alcohols in the presence of mixed metal oxide catalysts at very high temperatures is well known,[7] its synthetic applicability was decreased as a result of the very low chemical yields obtained and the presence of many by-products. However, in 1969 a French patent revealed the possible usefulness of this approach.[8] The reaction between different ketones **1**, such as acetone, acetophenone, and butanone, and primary alcohols **2** was undertaken in an autoclave using ruthenium(III) acetylacetonate as catalyst and NaOH as base to afford the corresponding α-alkylated ketones **3** in moderate to good yields and with interesting atom efficiencies (Table 1, entry 1).

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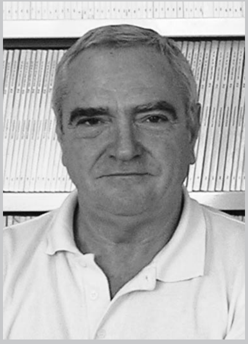
Diego J. Ramón was born in Alicante (Spain) in 1965 and completed his BSc (1988), MSc (1989), and PhD (1993) at the University of Alicante. In 1994, he was awarded the Prize for Young Scientists of the Spanish Royal Society of Chemistry. After a two-year postdoctoral stay at the ETH Zurich (Switzerland), he returned to the University of Alicante, where, after a short stay at Miguel Hernández University, he was appointed Associate Professor in 2000. His research interests focus on organometallic chemistry and asymmetric synthesis.



Miguel Yus received his PhD in 1973 from the University of Zaragoza (Spain). Following a two-year postdoctoral stay at the Max Planck Institut für Kohlenforschung (Mülheim a.d. Ruhr, Germany), he joined the University of Oviedo (Spain), where he was appointed Associate Professor in 1977 and promoted to full Professor in 1987. A year later, he moved to the University of Alicante, where he is currently Head of the Organic Synthesis Institute. His research interests encompass the development of new methodologies involving organometallic intermediates.

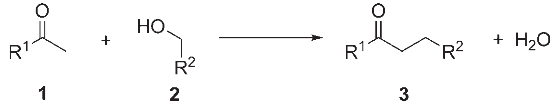
A further improvement of the reaction was observed by introducing the catalyst $[RuCl_2(PPh_3)_3]$.[9] However, in this case the use of a hydrogen acceptor (1-dodecene) was compulsory to prevent the over-reduction of the final alkylated ketone to the corresponding alcohol of type **8** (see Scheme 2; 1,4-dioxane was the source of the extra hydrogen for this final over-reduction[10]). With this ruthenium complex, not only alkyl aryl ketones but also dialkyl ketones could be successfully alkylated (Table 1, entry 2). In the case of using substituted aryl alkyl ketones, yields were not affected by either the position or the electronic properties of the substituents at the aromatic ring. The yields for dialkyl ketones were lower than those for the related aryl compounds. In the case of dialkyl ketones, alkylation took place exclusively at the less-hindered position. Although the alkylation of benzo-fused cyclic ketones could be accomplished satisfactorily, the alkylation of simple cyclohexanone gave a complicated product mixture.

The use of $[RuCl_2(dmso)_4]$ allowed the reaction to be performed in the absence of any type of additive, and a relatively high value for the atom efficiency was therefore reached (Table 1, entry 3). The low reactivity of this catalytic system permitted the use of heteroaromatic ketones and alcohols, and even the selective alkylation of methyl aryl ketones in the presence of either aryl alkyl or alkyl methyl ketones.[11] Surprisingly, the alkylation of benzo-fused cyclic ketones gave only α,β-unsaturated ketones of type **6** (Scheme 1).

Other metals have also been used in this new alkylation process. For example, palladium on charcoal has been used as a heterogeneous catalyst in the presence of a large excess of 1-decene and base (Table 1, entry 4), with the ratio of the starting ketone and alcohols being critical to prevent the over-reduction of product **3**.[12] More interesting results were obtained using palladium nanoparticles entrapped in aluminum hydroxide (Table 1, entry 5).[13] In this way, the catalyst could be sixfold recycled without lessening its activity; another advantage was the use of a weak base such as potassium phosphate. However, to maintain the reaction rate, the addition of one equivalent of base was required in each cycle. Furthermore, one of the biggest disadvantages was the necessity of inert-gas conditions to avoid the oxidation of the palladium hydride intermediate; otherwise the reaction stops at the formation of the α,β-unsaturated ketone. By using this protocol, aryl methyl and dialkyl ketones were alkylated in high yields and with high regioselectivities. The alkylation of steroidal 5-pregnen-3β-ol-20-one illustrated the compatibility of the protocol with the presence of different functional groups and stereogenic centers.

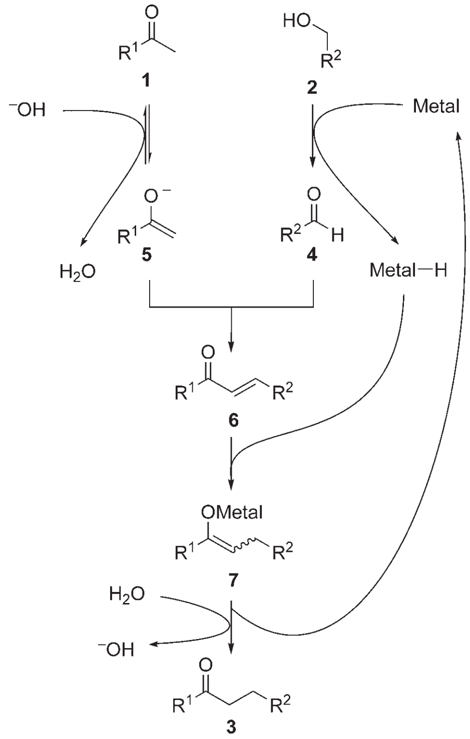
Also, nanoparticles of palladium occluded in a main-chain viologen polymer showed to be effective for this alkylation process (Table 1, entry 6). This catalyst was prepared by treating the main-chain viologen polymer with an aqueous

Table 1: Comparison of the α-alkylation of ketones by different methods.



Entry	Catalyst (loading [mol %])	Conditions (reagent loading [mol %])	Yield [%]	Atom efficiency for **3a** [%] (yield [%])[a]	Ref.
1	$[Ru(acac)_3]$ (0.2)[b]	**1** (147), **2** (100), NaOH (15), H_2O, 145 °C, 2 h	29–93	30 (42)	[8]
2	$[RuCl_2(PPh_3)_3]$ (2)	**1** (100), **2** (100), KOH (100), 1-dodecene (100), dioxane, 80 °C, 20 h	48–86	36 (82)	[9]
3	$[RuCl_2(dmso)_4]$ (2)[c]	**1** (100), **2** (100), KOH (100), dioxane, 80 °C, 24 h	41–93	51 (72)	[11]
4	Pd/C (5)	**1** (100), **2** (200), KOH (300), 1-decene (400), dioxane, 100 °C, 20 h	40–88	11 (66)	[12]
5	Pd/AlO(OH) (0.2)	**1** (100), **2** (120), K_3PO_4 (300), toluene, 110 °C, 8 h	80–98	22 (97)	[13]
6	Pd/viologen polymers (5)	**1** (100), **2** (200), $Ba(OH)_2{\cdot}H_2O$ (100), H_2O (700), neat, 100 °C, 24 h	82–95	26 (83)	[14]
7	$[IrCl(cod)]_2$ (0.1)[d]	**1** (100), **2** (200), KOH (10), PPh_3 (4), neat, 100 °C, 4 h	47–96	50 (86)	[15]

[a] **3a**: $R^1 = R^2 = Ph$. Atom efficiency [%] = Yield (**3a**) [%] × M_w(**3a**)/($\Sigma_i m_i \times M_{w_i}$) ($i$ = all reagents and additives). Chemical yields [%] are given in parentheses. [b] acac = acetylacetonate. [c] dmso = dimethyl sulfoxide. [d] cod = 1,5-cyclooctadiene.



Scheme 1. Proposed catalytic cycle.

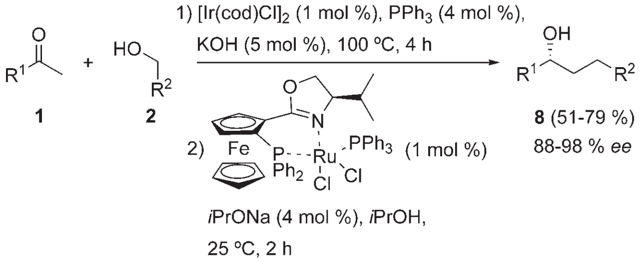
solution of Na_2PdCl_4. Treatment of the resultant assembly with $NaBH_4$ gave a black polymeric palladium catalyst, which was insoluble in water. In this case, the reaction could be performed with a variety of ketones and alcohols in the absence of organic solvents—a clear environmental advantage—and under atmospheric conditions, but in the presence of a large excess of water.[14] As in the case of the previous heterogeneous catalyst, it could be recycled threefold without affecting the yield.

The dimeric complex $[IrCl(cod)]_2$ has also been used as catalyst for the α-alkylation of ketones using alcohols as electrophiles.[15] The reactions could be performed in the absence of organic solvents using PPh_3 as ligand and only substoichiometric amounts of base to afford the expected products (Table 1, entry 7). The only major disadvantage was the necessity to use a large excess of the primary alcohol. Under these conditions, several alkyl aryl and dialkyl ketones could be alkylated selectively with excellent yields and atom efficiencies. The catalytic system is so active that the reaction between acetone and two molar equivalents of alcohol gave the α,α′-dialkylated ketone in very high yield.

Regarding the possible mechanistic pathway, in all cases the reaction starts with the oxidation of the primary alcohol **2** to give the corresponding aldehyde **4** and a metal hydride (or dihydride) intermediate. This is followed by an aldol condensation with the in situ formed enolate **5** to give the α,β-unsaturated ketone **6** (Scheme 1), and finishes with reduction of the double bond by the previously formed hydride intermediate. With $[RuCl_2(dmso)_4]$, the reaction using deuterium-labeled reagents revealed interesting results.[11b] When the labeled reagents were the base, the ketone, or the hydroxy group (i.e. KOD, $ArCOCD_3$, or ROD, respectively), the product ketone of type **3** contained deuterium atoms only at the α-position with different levels of deuterium incorporation. In contrast, when the reaction was performed using the labeled alcohol RCD_2OH, the product ketone **3** presented two deuterium atoms at the β-positions, with a very high level of deuterium incorporation (> 94 %). The absence of deuterium scrambling in these experiments seems to indicate that the reduction of the double bond takes place by a hydride addition in a Michael-type mode and not by a standard hydrogenation of this double bond. The final hydrolysis of the enolate **7** affords the alkylated ketone **3** and renews the active catalytic metal complex.

Alternatively, trialkylamines can be used instead of primary alcohols for the alkylation process, and, as in the previous case, the alkylation takes place at the less-hindered position of the dialkyl ketone.[16] When an excess of the primary alcohol was used as the source of electrophile, the corresponding secondary alcohol of type **8** (see below) was obtained as the main product. This product resulted from a sequential α-alkylation process followed by a Meerwein–Ponndorf–Verley reduction.[17] When $[RuCl_2(PPh_3)_3]$ (5 mol %) was used as catalyst, the reaction proceeded well with aryl methyl and dialkyl ketones; in the latter case, high regioselectivity was observed, with the alkylation taking place at the methyl group.[18] When [RuCl(dmso)$_4$] (2 mol %) was used as catalyst for this sequential process, the best results were obtained with the addition of PPh$_3$.[11]

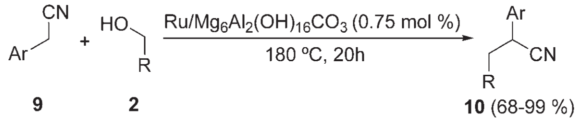
This sequential strategy has been successfully used to produce chiral secondary alcohols simply by adding chiral ruthenium complexes following the electrophilic alkylation in a one-pot process. Thus, whilst the alkylation process was catalyzed by an iridium complex at 100 °C without solvents (Scheme 2), the final enantioselective reduction was performed at room temperature in the presence of a ruthenium complex and a catalytic amount of sodium 2-propoxide, with 2-propanol as the solvent and the source of the reducing agent.[19] The whole process proceeded with good to excellent yields and enantioselectivities. Note that only moderate enantioselectivities were observed when the sequential process was performed using only the chiral ruthenium complex. Moreover, the use of other catalysts for the first alkylation step did not give satisfactory results. Therefore, the compatibility between both catalysts, namely [Ir(cod)Cl]$_2$ and the chiral ruthenium complex, is an essential factor in the success of this transformation.



Scheme 2. One-pot sequential α-alkylation and enantioselective Meerwein–Ponndorf–Verley reduction process.

4. Electrophilic α-Alkylation of Nitriles

Another interesting source of nucleophile for this alkylation is nitrile compounds. Although the α-alkylation of phenylacetonitrile using alcohols is known at extremely high temperatures in the presence of alkaline metals,[20] Grigg et al. showed that it was possible to use milder reaction conditions through a hydrogen autotransfer process. The reaction of aryl acetonitriles **9** with a large excess of alcohol gave the expected alkylated products **10** with yields of 38–78 %, using [RuH$_2$(PPh$_3$)$_4$] as catalyst and stoichiometric amounts of Na$_2$CO$_3$.[21] However, better results were obtained using a ruthenium-grafted hydrotalcite [Mg$_6$Al$_2$(OH)$_{16}$CO$_3$], which contains both active Ru^{IV} species and surface base sites (Scheme 3).



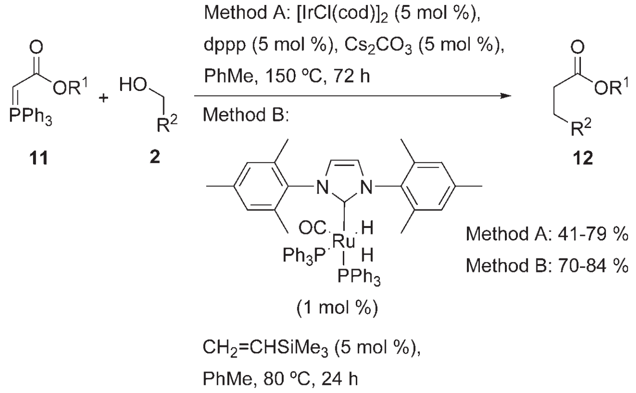
Scheme 3. α-Alkylation of nitriles.

While the nature of the alcohol has no influence on the results, the range of nitriles seemed to be limited to arylacetonitriles or the corresponding heteroaryl derivatives.[22] The reaction had to be performed under argon atmosphere, otherwise the product isolated was the corresponding alkylated α,β-unsaturated nitrile derivative. The reaction rates were not affected by the nature of the substituent at the aromatic ring of the nitrile, thus the deprotonation of nitrile **9** is not the rate-limiting step. Finally, note that the cooperative catalysis of the grafted ruthenium species and the surface base sites permitted the synthesis of α,α-dialkylated phenylacetonitrile derivatives through an alkylation using a hydrogen autotransfer strategy followed by a Michael-type reaction of the in situ formed monoalkylated derivative **10** with different acrylates.

5. Electrophilic Alkylation of α,α-Difunctionalized Methylene Derivatives

5.1. Indirect Wittig-type Process

The hydrogen autotransfer or hydrogen-borrowing process is not limited to the alkylation of ketones and nitriles, as was elegantly pointed out by Williams and co-workers, and has been expanded to the indirect Wittig-type process (Scheme 4). The reaction can be performed using arylmethanol derivatives and catalytic amounts of [IrCl(cod)]$_2$ in the presence of diphosphane ligands (method A).[23] The use of other inactivated alcohols as well as secondary alcohols gave accountably lower results. Better yields were obtained under milder conditions when a ruthenium N-heterocyclic carbene was used as catalyst (method B).[24] In this latter case, vinyltrimethylsilane (5 mol %) was added to accomplish the initial dehydrogenation of the catalyst required to initiate the reaction.

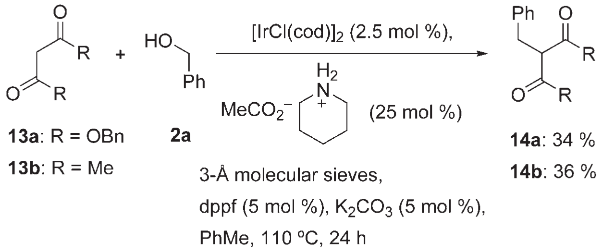


Scheme 4. Indirect Wittig-type process. dppp = 1,2-bis(diphenylphosphanyl)propane.

Instead of phosphane-ylides derived from ester functionality **11**, other ylides from amide, nitrile, and even non-functionalized alkyl and aryl derivatives could be also used in this hydrogen autotransfer process catalyzed by [IrCl(cod)]$_2$, although slightly lower yields were obtained.[25] The related indirect Horner–Wadsworth–Emmons reaction was performed with different phosphonates derived from esters as the source of nucleophile to give slightly lower yields than with the related Wittig process.[23,26] These results were attributed to the coordination of the β-carbonyl phosphonate derivative to the metal, thus inhibiting its activity.

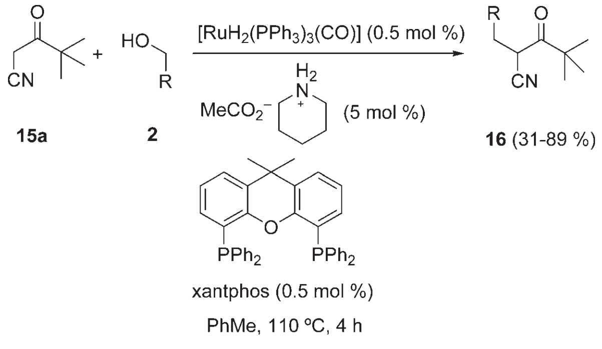
5.2. Electrophilic Alkylation of 1,3-Dicarbonyl Nucleophiles

The Knovenagel reaction can also be performed using dibenzyl malonate (**13a**) but with low yields. Similar results were obtained by using acetylacetone (**13b**) as the source of the nucleophile to afford the alkylated 1,3-dicarbonyl compound **14b** in up to 36 % yield (Scheme 5).[26] Similar reaction conditions were used in the alkylation of different nitroalkanes with benzyl alcohol to give the corresponding alkylated products with variable conversions (14–70 %).[26]



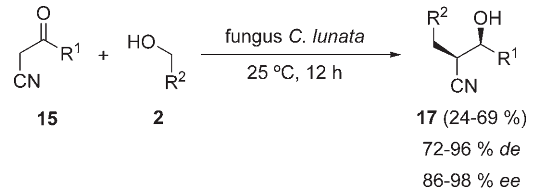
Scheme 5. α-Alkylation of 1,3-dicarbonyl compounds. Bn = benzyl, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene.

β-Ketonitriles proved to be an ideal source of nucleophiles as they do not suffer from the problems mentioned before with 1,3-dicarbonyl compounds such as metal coordination, transesterification, decarboxylation, and decarbonylation processes. Thus, the reaction of compound **15a** with different arylmethanol derivatives catalyzed by $[IrCl(cod)]_2$ gave the expected products **16** (30–89 %).[26] These results have recently been improved using a xantphos-ruthenium complex (Scheme 6).[27] The wide bite angle of this ligand led to enhanced reactivity of the ruthenium active species. Besides functionalized benzyl alcohol derivatives, other primary alcohols such as aliphatic alcohols and heteroarylmethanol derivatives could be used successfully as alkylating agents.



Scheme 6. α-Alkylation of β-ketonitrile **15a**.

Besides metal catalysts, enzymes also are able to perform these alkylating hydrogen autotransfer processes. For example, cells of the *Curvularia lunata* fungus have been used as the catalytic system in the α-alkylation of aryl and heteroaryl β-ketonitriles **15** with alcohols (Scheme 7). The product hydroxy nitriles **17** arise from the expected alkylation process, followed by reduction of the ketone of type **16** (Scheme 6) with the excess of alcohol used. The whole process showed a moderate chemical yield but very high diastereo- and enantioselectivity.[28]



Scheme 7. Enzymatic α-alkylation of β-ketonitriles.

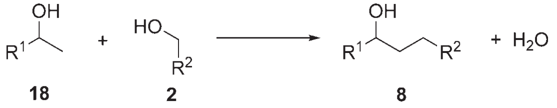
6. Electrophilic β-Alkylation of Alcohols

The auto-β-alkylation of primary alcohols under basic conditions is an established process,[29a] which usually gives low yields and several by-products.[29] The reaction is not restricted to this dimerization process, and either methanol or benzyl alcohol derivatives can be used as alkylating agents for other primary alcohols.[30] However, a more interesting application appears to be the β-alkylation of secondary alcohols with primary alcohols—a process that is impossible to perform in a direct way by other strategies as outlined in Table 2. When the reaction was performed using $[RuCl_2(PPh_3)_3]$ as catalyst, a large excess of 1-dodecene was necessary to obtain good results but led to a drastic reduction in the atom efficiency (Table 2, entry 1).[31] Aryl methyl carbinols **18** could be alkylated successfully with different primary alcohols. However, the related reaction using alkyl methyl carbinols gave accountably lower yields; alkylation took place always at the methyl position although no dialkylation was observed.

Use of the Grubbs' catalyst permitted the omission of the sacrificial hydrogen acceptor as well as the excess of primary alcohol (Table 2, entry 2). Only one example was reported in which the yield of product **8a** was slightly inferior, as a result of the formation of the corresponding ketone **3a** (26 %).[32] The employment of $[RuCl_2(dmso)_4]$ as catalyst was more successful as the product **8** was obtained with a very high yield and atom efficiency (Table 2, entry 3). An extra advantage is that the reaction can be also performed in the absence of organic solvents.[33] The yields were consistently high for aromatic or heteroaromatic alcohols (either **18** or **2**). However, the use of aliphatic secondary (**18**) or primary (**2**) alcohols led to decreased chemical yields.

Not only ruthenium complexes can be used for this unusual reaction; highly active iridium complexes have also been shown to be efficient (Table 2, entry 4).[34] In this case,

Table 2: Comparison of the β-alkylation of secondary alcohols by different methods.

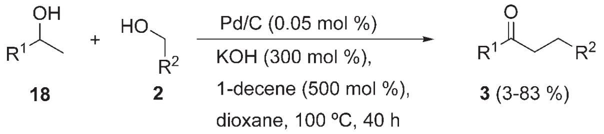


Entry	Catalyst (loading [mol %])	Conditions (reagent loading [mol %])	Yield [%]	Atom efficiency for **8a** [%] (yield [%])[a]	Ref.
1	$[RuCl_2(PPh_3)_3]$ (5)	**18** (100), **2** (200), KOH (300), 1-dodecene (500), dioxane, 80 °C, 40 h	34–90	12 (82)	[31]
2	$[RuCl_2{=}CHPh(PCy_3)_2]$ (5)[b]	**18** (100), **2** (100), $LiOH{\cdot}H_2O$ (15), toluene, 110 °C, 48 h	74	56 (74)	[32]
3	$[RuCl_2(dmso)_4]$ (2)	**18** (100), **2** (100), KOH (200), neat, 100 °C, 74 h	47–98	58 (91)	[33]
4	$[IrCp^*Cl_2]_2$ (2)[c]	**18** (100), **2** (120), NaO*t*Bu (300), toluene, 110 °C, 17 h	58–88	29 (75)	[34]

[a] **8a**: $R^1 = R^2 = Ph$. Atom efficiency [%] = Yield (**8a**) [%] × M_w (**8a**)/($\Sigma_i m_i \times M_{w_i}$) ($i$ = all reagents and additives); Chemical yields [%] are given in parentheses. [b] PCy_3 = tricyclohexylphosphane. [c] Cp* = pentamethylcyclopentadienyl.

the yields were very high when aryl methyl carbinols **18** were used, independent of the nature of the primary alcohol. However, the results were lower for aliphatic secondary alcohols.

The reaction of secondary alcohols **18** with aliphatic primary alcohols **2** can be driven to obtain the related α-alkylated ketones of type **3** by the use of palladium on charcoal as catalyst and a large excess of 1-decene as sacrificial hydrogen acceptor. The best results were obtained using aromatic secondary alcohols (Scheme 8).[35]



Scheme 8. β-Alkylation of secondary alcohols to give ketones.

7. Conclusion and Outlook

The hydrogen autotransfer process is a more efficient and cleaner strategy than some classical alkylation protocols, substituting hazardous and expensive alkyl halides, sulfonates, or sulfates, strong bases, and extreme conditions by simple alcohols, metal hydroxides, and very mild conditions. Furthermore, the only waste generated through the overall process is water. Moreover, with the range of available starting reagents and the changes recently introduced to the structures of the metallic catalysts, both the range of synthesized products and the selectivity of the process has been increased. Also, the use of certain catalysts under heterogeneous conditions allows them to be reused. These aspects, together with the absence of organic solvents for some protocols, make this new strategy interesting from an economical and environmental point of view. In the future,[36] the application of this new process to other substrates and the development of chiral catalysts will provide a powerful tool for the synthesis of complex molecules not only on the laboratory scale but also in industrial processes.

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