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SHORT COMMUNICATION

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Tandem α-Alkylation/Asymmetric Transfer Hydrogenation of Acetophenones with Primary Alcohols

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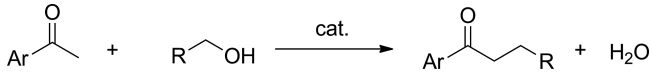
A tandem α-alkylation/asymmetric transfer hydrogenation of acetophenones with primary alcohols, mediated by a single ruthenium catalyst, is described. Under optimized reaction conditions and with use of $[Ru(p\text{-cymene})Cl_2]_2$ in combination with an amino acid hydroxyamide ligand, the chiral secondary alcohol products were isolated in moderate yields and in moderate to good enantiomeric excess (up to 89 % *ee*).

Introduction

A significant amount of drugs available on the pharmaceutical market contain stereocenters, which play important roles for the bioactivity of these compounds. Certain isomers are simply inactive, like (*R*)-Ibuprofen; however, others are harmful, like (*R*)-Naproxen.[1] Therefore, the development of selective methods for the formation of single-enantiomer drugs is highly important. One example of such a method is the transition-metal-catalyzed formation of enantiomerically enriched secondary alcohols by asymmetric transfer hydrogenation of ketones, which represents one of the most common asymmetric reduction methods in modern organic chemistry.[2] Among the available catalytic systems, the use of ruthenium-based catalysts have attracted significant attention due to generally high activity, enabling low catalyst loadings and mild reaction conditions.[2,3]

The α-alkylation of methyl aryl ketones with primary alcohols as alkylating agents (Scheme 1), is frequently described in the literature with different homo- and heterogeneous catalysts based on Ru,[4] Rh,[5] Pd,[6] Os,[7] Ir,[8] Ni,[9] Cu,[10] as well as Ag–Pd[11] and Ag–Mo[12] mixed-metal materials. The transformation is a nice example of the borrowing hydrogen methodology, where the hydrogen source in the transfer hydrogenation also acts as one of the reactants.[13]



Scheme 1. α-Alkylation of methyl aryl ketones with primary alcohols.

A similar process, where the α-alkylated ketone is reduced in the final step to furnish a secondary alcohol, is also reported in the literature. Shim and co-workers developed a ruthenium-catalyzed procedure that yielded the racemic alcohol products in moderate to good yields, using an excess of the primary alcohol.[14] In addition, Yus and co-workers demonstrated that either alkylated ketones or the corresponding racemic secondary alcohols could be obtained, depending on the stoichiometry between the reactants in the presence of a ruthenium–DMSO complex.[15] Furthermore, the transformation has been described with catalysts based on Rh, Pd, and Fe,[16] and, recently, even under catalyst-free conditions.[17]

To the best of our knowledge, there is only one communication that describes the asymmetric reductive α-alkylation transformation of acetophenones into enantiomerically enriched alcohols with an elongation of the alkyl chain (Scheme 2).[18] However, this method, reported by Uemura and co-workers, is an example of a sequential reaction, which requires the use of two different catalysts to carry out the transformation.

During the last decade, we have investigated a series of Ru and Rh complexes containing different chiral ligands based on amino acids, and employed these as catalysts for the asymmetric transfer hydrogenation (ATH) of aryl ketones in 2-propanol.[19] For the most efficient ruthenium half-sandwich catalyst, the scope was successfully expanded to allow for ethanol as hydrogen donor for the asymmetric reduction of substituted acetophenones.[20] However, in this ethanol ATH protocol, the appearance of a small amount of a byproduct was observed along with the desired secondary alcohol. Analyzing the nature of this impurity, we found that it consisted of a different enantiomerically enriched alcohol, resulting from the full reduction of the condensation product of the corresponding acetophenone with acet-

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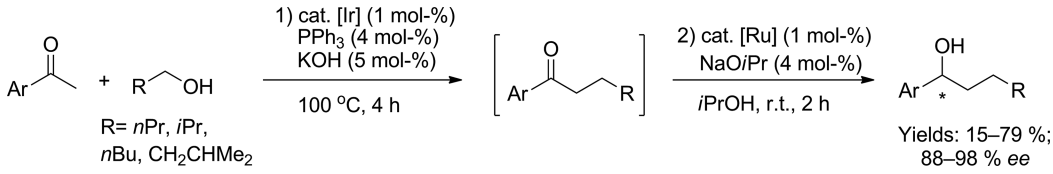
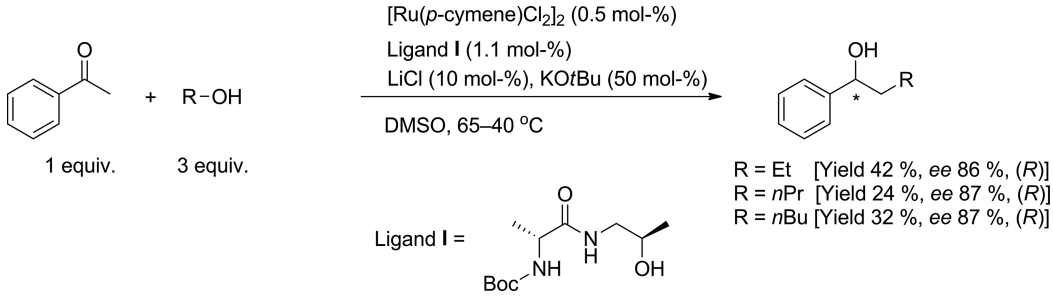


Scheme 2. One-pot sequential reactions of acetophenones with alcohols in the presence of an achiral iridium catalyst, followed by a chiral ruthenium complex, developed by Uemura and co-workers.[18]

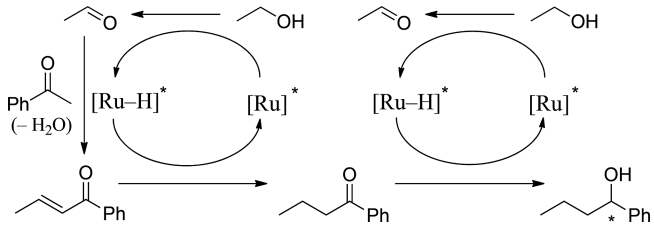


Scheme 3. Tandem α-alkylation/ATH reaction of acetophenone with primary alcohols.

aldehyde, which forms in situ when the hydride donor ethanol is oxidized by the metal catalyst. This was intriguing, not only in view of the asymmetric tandem process, which appeared to have occurred, but also since acetaldehyde can be a troublesome coupling partner in regular aldol chemistry, because of self-condensation. In the current communication, we present the optimized catalytic protocol, which – to the best of our knowledge – is the first example of the direct formation of enantiomerically enriched secondary alcohols from ketones and primary alcohols by a tandem α-alkylation/asymmetric transfer hydrogenation process with one single catalyst (Scheme 3).

Results and Discussion

Starting from the conditions used in our previous work,[20] amino acid hydroxyamide ligand **I** and [Ru(*p*-cymene)Cl_2]$_2$ were applied in catalytic amounts in the optimization of the tandem process, with acetophenone as model substrate and ethanol as hydrogen donor and source of the condensing aldehyde. Different bases were evaluated, and KO*t*Bu was found to be the most proficient with a loading of 50 mol-%; these conditions were maintained for all further reactions in the study. We had previously found that the reaction rate increased when THF was used as co-solvent for the asymmetric transfer hydrogenation of acetophenones, using catalytic amounts of [Ru(*p*-cymene)Cl_2]$_2$ in combination with ligand **I**.[21] In contrast, DMSO was found to decrease the rate for the acetophenone reduction, and it was therefore chosen as solvent for the tandem α-alkylation/ATH reaction.[21,22] A schematic reaction mechanism for the process is depicted in Scheme 4, indicating that the reaction requires a minimum of 2 equiv. of alcohol to reach full conversion. In practice, we found that the best result was obtained by using 3 equiv. of ethanol, conducting the experiments in 1 M solutions in a DMSO/EtOH mixture. An evaluation of the optimal concentration was performed by changing the amount of DMSO while keeping the quantity of EtOH constant at 3 equiv. relative to acetophenone. It was found that the best yield of 1-phenyl-1-butanol was obtained at a concentration of 2 M, which corresponds to an approximate molar ratio of 4:3 for DMSO/EtOH. This molar ratio of DMSO to primary alcohol was further employed in the reactions using *n*PrOH and *n*BuOH as hydride source and coupling agent. We have previously reported that the addition of LiCl has a positive effect on the catalytic activity and the enantioselectivity in ATH of ketones with this class of ruthenium catalysts.[21] The same beneficiary effect was obtained also in the tandem α-alkylation/ATH process when 10 mol-% of LiCl was used as an additive.



Scheme 4. Schematic reaction mechanism for the tandem α-alkylation/ATH reaction.

As expected, increasing the temperature and reaction time led to higher conversion of the product alcohol, but unfortunately also resulted in a decrease in enantioselectivity.[19h] Optimization of the procedure with respect to chemoselectivity and enantioselectivity led to the following conditions: the reaction mixture was kept at 65 °C for 30 min, thereafter the temperature in the oil bath was decreased to 40 °C, and the solution was stirred for an additional 4.5 hours. By this procedure, 1-phenyl-1-butanol was isolated in 42% yield with 86% *ee*.[23]

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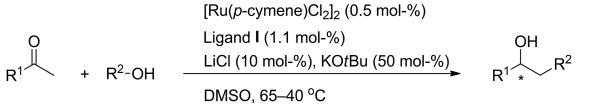
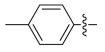
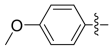
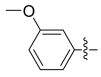
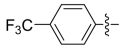
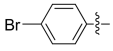
Acetophenones containing either electron-rich or electron-poor substituents were evaluated under the optimized conditions. The results in Table 1 show that electron-donating groups in the phenyl ring of acetophenone promote better yields, whereas electron-deficient rings give rise to lower yields (Table 1, entries 1–3 vs. 4–5). These results are in accordance with what is expected for enolate condensation reactions. The *ee* of the products was found to follow the same trend, being higher for substrates with electron-rich aryl substituents.

Table 1. Tandem α-alkylation/ATH of acetophenones with primary alcohols.[a]



Entry	R^1	R^2 = Et		R^2 = *n*Bu	
		Yield [%][b]	*ee* [%]	Yield [%][b]	*ee* [%]
1		35	84[c]	34	88[d]
2		31	84[c]	28	83[c]
3		43	86[c]	32	89[d]
4		17	65[d]	19	57[d]
5		9	79[c]	18	65[c]

[a] For the reaction conditions, see the Experimental Section. [b] Isolated yields. [c] Determined by HLPC (CHIRALCEL OB or CHIRALCEL OJ). [d] Determined by GLC (CP Chirasil DEX CB).

All obtained alcohols have positive optical rotation values when the *R*,*R*-diastereomer of ligand **I** was used. Comparisons with literature data confirmed that this corresponds to the *R*-isomers for 1-phenyl-1-butanol, 1-phenyl-1-pentanol, and 1-phenyl-1-hexanol.[24]

Performing the tandem α-alkylation/ATH reaction between acetophenone and ethanol in [D_6]DMSO resulted in the isolation of a mixture of 1-phenylethanols with deuterium incorporated in positions 2 and 4. The result shows that, under the basic conditions employed for the tandem process, a deuterium/proton exchange occurs between the deuterated solvent and the various carbonyl-containing species present in the reaction mixture, that is, acetophenone, acetaldehyde, and possibly also butyrophenone. The lack of deuterium present in position 1 and 3 of the product clearly suggests that the reaction proceeds via the monohydride route, which has previously been demonstrated for half-sandwich Ru and Rh complexes containing amino acid hydroxyamide ligands.[19f,21]

Conclusions

We have demonstrated that the in situ generated catalyst based on [Ru(*p*-cymene)Cl_2]$_2$ and amino acid hydroxyamide ligand **I** mediates the tandem α-alkylation/asymmetric transfer hydrogenation process. A series of differently substituted acetophenones were successfully alkylated with simple primary alcohols, which served as both alkylating and reducing agents. The resulting secondary alcohols were isolated in moderate yields with enantioselectivities up to 89%.

Experimental Section

General Procedure for the Catalytic Tandem α-Alkylation/Asymmetric Transfer Hydrogenation Reaction: To a 20 mL vial equipped with a septum and stirring bar, were added [Ru(*p*-cymene)Cl_2]$_2$ (0.0153 g, 0.025 mmol), ligand **I** (0.0135 g, 0.055 mmol), and LiCl (0.0212 g, 0.500 mmol). The atmosphere in the vial was exchanged by means of three consecutive vacuum/Ar cycles. Dry DMSO (1.6 mL), ROH (R = Et, *n*Pr, *n*Bu; 15.0 mmol), and substrate (5.0 mmol) were added. The mixture was allowed to stir for 10 min, thereafter KO*t*Bu (0.280 g, 2.5 mmol) was added. The vial was subsequently sealed and placed in an oil bath at 65 °C with vigorous stirring for 30 min. Thereafter, the temperature in the bath was decreased to 40 °C, and the stirring was continued for additional 4.5 h. Brine (20 mL) was added, and the mixture was extracted with EtOAc (4 × 20 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The resulting oily residue was purified by column chromatography (for details, see Supporting Information).

Supporting Information (see footnote on the first page of this article): Experimental procedures and compound characterizations.

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[22] In addition, Yus and co-workers have demonstrated that DMSO complexes of ruthenium act as efficient catalysts for the α-alkylation of ketones; see ref.[15]

[23] At 99% acetophenone conversion, a chemoselectivity of 47% in favor of 1-phenyl-1-butanol was determined by using ^{1}H NMR spectroscopy with anisole as external standard. In addition to the target alcohol, the reaction mixture contained a complex mixture of different compounds in small amounts.

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