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A one-pot process for the enantioselective preparation of saturated secondary alcohols from propargyl ketones under hydrogen transfer conditions

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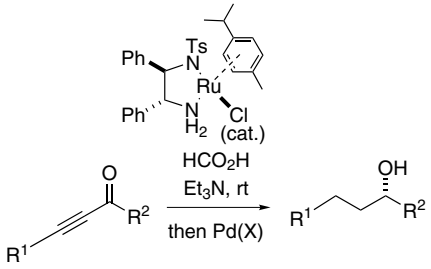
Abstract—Propargyl ketones can be directly transformed to enantio-enriched saturated secondary alcohols in a one-pot reaction using chiral RuCl[*N*-(tosyl)-1,2-diphenylethylenediamine)(*p*-cymene) and Pd/$BaSO_4$ as catalysts, under transfer hydrogenation conditions.

Chiral ruthenium(arene)(L) complexes have emerged as major tools in the enantioselective reduction of ketones.[1] Impressive level of enantio-control has been achieved either under hydrogen transfer conditions or under hydrogen pressure to reduce aryl and propargyl ketones, as well as α- and β-dicarbonyl compounds.[1,2] The preparative usefulness of these reactions was amply demonstrated in a number of syntheses of biologically relevant products.[3] While cyclic ketones can be converted to alcohols in high enantiomeric excess without the presence of stereodirecting groups,[1b] acyclic substrates require adjacent aryl, alkynyl or ester groups for the process. These stereodirecting groups are usually removed or transformed afterwards into other functions. Most commonly, the alkyne function is hydrogenated to afford the corresponding saturated compound. We were interested in examining the enantioselective reduction of propargyl ketones under hydrogen transfer conditions, catalyzed by chiral Ru(II)L_n and by attempting the reduction of the alkyne function in a one-pot reaction without hydrogen. This strategy would take advantage of the reductive conditions of the first reaction, to achieve the hydrogenation of the alkyne. Ruthenium complexes, which were developed for the reduction of ketones are, however, poor hydrogen donors toward olefins and alkynes.[4,5] This shortcoming can be easily overcome by the addition of metals such as palladium, iridium or platinum. The compatibility of the catalysts in a one-pot reaction is the key factor for the success of this transformation. The present study is dedicated in finding conditions, allowing the one-pot reaction using compatible Ru/Pd catalyst system (Scheme 1).[6,7]



Scheme 1. General scheme of transformation.

At first, the reduction of propargyl ketone **1** was studied in the presence of a catalytic amount (2.5 mol %) of (*R*,*R*)-RuCl[*N*-(tosyl)-1,2-diphenylethylenediamine)(*p*-cymene)], [(*R*,*R*)-**I**], formic acid (10 equiv), and triethylamine (4 equiv) at rt.[8] After 2 h, the starting material was converted to the corresponding alcohol **2** in 94% yield and in 90% ee (Scheme 2).[9] The absolute configuration of **2** was assigned by analogy with the literature data.[10]

Keywords: Alcohols; Alkynes; Asymmetric synthesis; Catalysis; Hydrogenation; Reduction.
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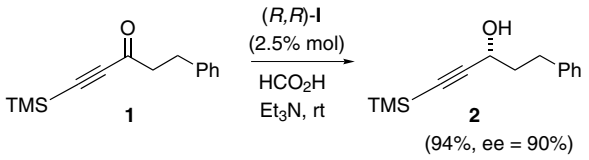
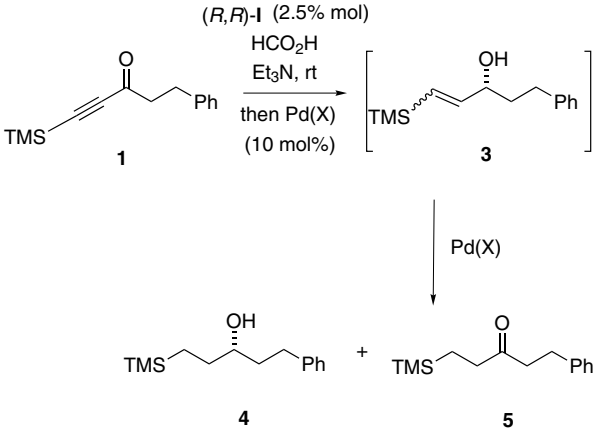


Scheme 2. The one-pot reduction/hydrogenation of propargylic ketone **1**.

The feasibility of the tandem reduction/hydrogenation was tested on compound **1**. After treatment of **1** for 2 h with formic acid (10 equiv), Et_3N (4 equiv) in the presence of catalyst (*R*,*R*)-**I** (2.5 mol %) and stirring at rt until complete disappearance of ketone **1**, a catalytic amount of palladium catalyst (10 mol %) was added and the solution was stirred at rt overnight (15 h). The results are reported in Table 1.

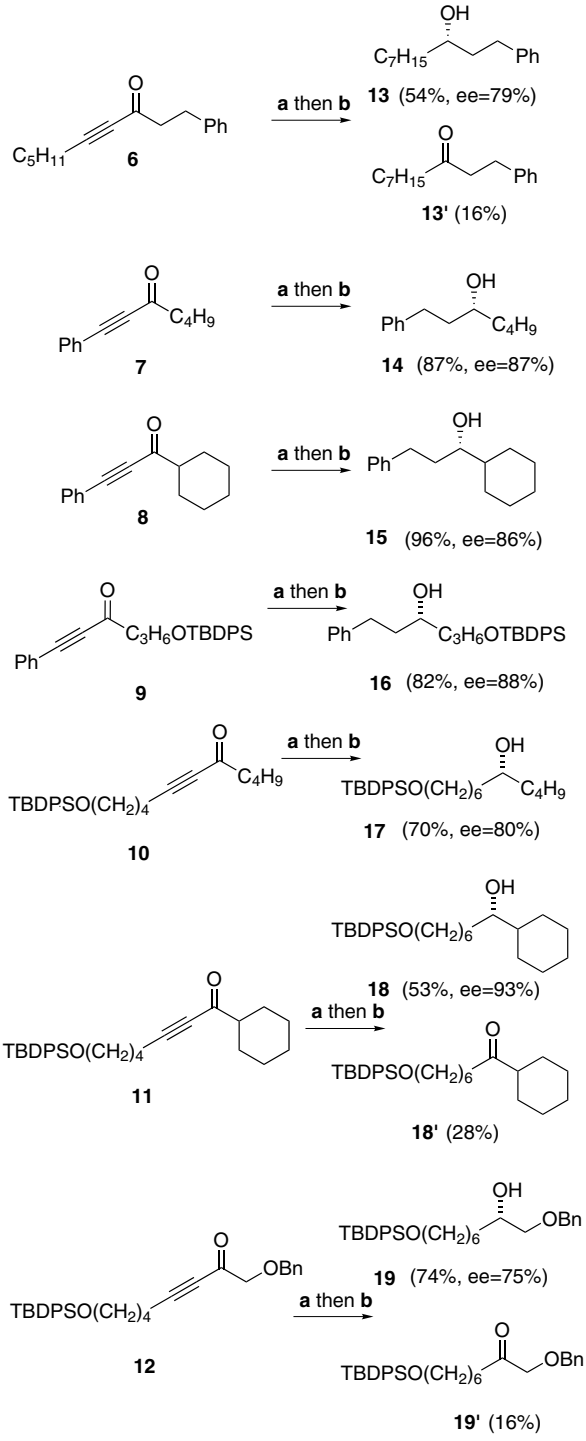
When $Pd(Pb)/CaCO_3$ was added to the reaction mixture, compound **2** was the only product which was isolated in 59% yield (Table 1, entry 1). Similar results were obtained in the presence of $Pd(PPh_3)_4$ (Table 1, entry 2).[11] On the contrary, when $Pd(OH)_2/C$ (Pearlman's catalyst) was added to the reaction mixture, the saturated alcohol **4** and ketone **5** were obtained in 27% yield and in a ratio of 52:48 (Table 1, entry 3). Other palladium catalysts, such as $Pd(acac)_2$ (Table 1, entry 4) or $PdCl_2$ (Table 1, entry 5), afforded similar results as **4** and **5** were isolated in 52% (ratio 55:45) and in 53% (ratio 77:23), respectively. Likewise, the use of Pd/C (10%) afforded modest yield (44%) and selectivity as the desired alcohol **4** and ketone **5** were obtained in a ratio of 84:16 (Table 1, entry 6).[12] The best results were obtained with Rosemund catalyst ($Pd/BaSO_4$) (Table 1, entry 7). In the presence of this catalyst, the desired alcohol **4** was obtained accompanied with a small amount of ketone **5** (ratio **4**/**5** = 93:7, yield: 80%). Whatever the reaction conditions used, the enantiomeric

Table 1. Reduction/hydrogenation of **1** under hydrogen transfer conditions



Entry	Pd(X)	Ratio			Global yield (%)
		2	**4**	**5**	
1	$Pd(Pb)/CaCO_3$ (5%)	100	—	—	59
2	$Pd(PPh_3)_4$	100	—	—	40
3	$Pd(OH)_2/C$ (20%)	—	52	48	27
4	$Pd(acac)_2$	—	55	45	52
5	$PdCl_2$	—	77	23	53
6	Pd/C (10%)	—	84	16	44
7	$Pd/BaSO_4$ (10%)	—	93	7	80

Conditions: HCO_2H (10 equiv), Et_3N (4 equiv), (*R*,*R*)-**I** (2.5 mol %), rt, 2 h; then Pd(X) (10 mol %), rt, 15 h.



Scheme 3. Generalization of the one-pot reduction/hydrogenation reaction. Conditions: (a) (*R*,*R*)-**I** (2.5 mol %), HCO_2H (10 equiv), Et_3N (4 equiv), rt; (b) $Pd/BaSO_4$, (10 mol %) rt, 15 h.

excess of the obtained alcohol **4** is always 75%.[13] It is worth noting that ketone **5** is probably the result of the isomerization of the intermediate allylic alcohol **3** to the corresponding enol (vide infra).

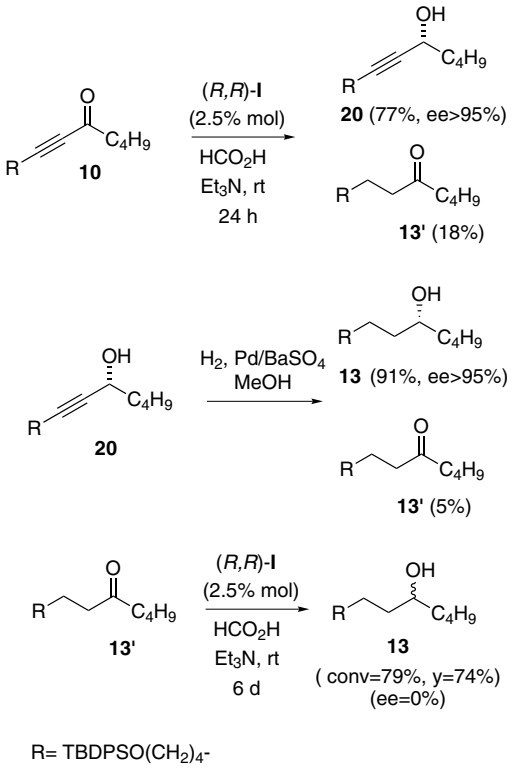
Substrates **6**–**12** were examined and the results are presented in Scheme 3. For each propargylic ketone, a clean conversion to the corresponding saturated secondary alcohol was obtained after 2–15 h of reaction with the (*R*,*R*)-RuCl[*N*-(tosyl)-1,2-diphenylethylenediamine)(*p*-cymene)] complex and $Pd/BaSO_4$ under transfer hydrogenation conditions at rt. The evolution of the reaction was monitored by TLC, and the palladium catalyst was added after consumption of the starting materials **6**–**12**. After adding the palladium catalyst, and stirring the mixture overnight at rt the corresponding alcohols **13**–**19** were obtained.[14] The configuration of **14** was assigned by comparing the $[\alpha]_D$ value with the literature data.[15]

For compounds **6**, **11**, and **19**, the formation of ketones **13′**, **18′**, and **19′** were observed, respectively, as side products in variable amounts (0–28%). This was probably due to the isomerization of the allylic alcohol of type **3** to the corresponding ketone. It is worth noting that this isomerization is suppressed when the C=C bond is conjugated to an aryl substituent (substrates **7**–**9**).

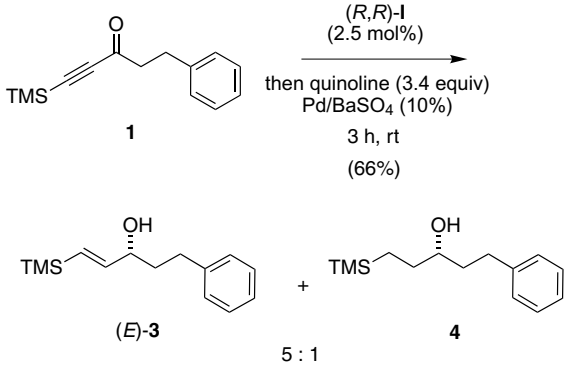
The slight erosion of the enantioselectivity, which was observed in the case of **13** and **19** in the one-pot protocol compared to the two steps transformation, was intriguing. In order to check the raison of this decrease of enantioselectivity, the transformation of **10** to **13** was realized stepwise.

At first compound **10** was reduced with a catalytic amount of (*R*,*R*)-**I** under transfer hydrogenation conditions (Scheme 4).[1] The reaction afforded, after 24 h, the desired propargylic alcohol **20** in 77% yield and in ee >95%.[16] The secondary product of this transformation was ketone **13′**, isolated in 18% yield. Compound **20** was then hydrogenated over $Pd/BaSO_4$ catalyst under H_2 atmosphere in MeOH at rt. The reaction afforded **13** in 91% yield with no detectable epimerization (ee >95%), and also a trace amount of ketone **13′** (5%). In a parallel experience, ketone **13′** was submitted to reduction under Noyori's conditions [(*R*,*R*)-**I**, (2.5 mol %), HCO_2H, TEA, rt],[1] and transformed to **13** in 74% yield as a racemic mixture (79% conversion, 6 days). This experience showed that the non-selective production of alcohol **13** via the reduction of the ketone byproduct **13′** may compromise the overall selectivity of the process in this one-pot protocol. Noteworthy, only marginal difference in the ee was observed between the one-pot and the two steps protocols, when ketone byproducts were not formed. For example, the stepwise reduction of **8** resulted in the formation of **15** in 88% ee versus 86% ee in the one-pot reduction.

The reaction can be stopped at the allylic alcohol level by adding an excess of quinoline (3.4 equiv) in complement with the palladium catalyst (Scheme 5). However, when compound **1** was reduced under these conditions,



Scheme 4. Studies concerning the decrease of enantioselectivity in the one-pot reduction.



Scheme 5. The selective preparation of (*E*)-allyl alcohol (*E*)-**3** from propargyl ketone **1**.

the reaction afforded a mixture of (*E*)-**3**[17] and of the saturated compound **4** in a ratio of 5:1. It is worth noting that the chemoselectivity depends on the reaction conditions, in particular on the reaction time and the amounts of the quinoline additive used.

In this study, we have established conditions for a tandem reduction/hydrogenation sequence, which combines the homogeneous chiral RuCl[*N*-(tosyl)-1,2-diphenylethylenediamine)(*p*-cymene)] catalyst mediated carbonyl reduction and a heterogeneous $Pd/BaSO_4$-mediated hydrogenation reaction in one pot, under transfer hydrogenation conditions. This reaction allows the direct preparation of enantio-enriched saturated sec-

ondary alcohols from propargyl ketones in an experimentally simple procedure, without potentially hazardous gaseous hydrogen. The application of this one-pot sequence in the synthesis of natural products is underway in the laboratory.

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8. Starting materials **1**, **6**–**8** and **10**–**12** were prepared from the corresponding aldehyde and the lithiated acetylene derivative followed by oxidation of the propargyl alcohol by PCC. Compound **9** was prepared according to Huang, P.-Q.; Zheng, X.; Deng, X.-M. *Tetrahedron Lett.* **2001**, *42*, 9039–9041.
9. The enantiomeric purity was determined by chiral HPLC: Column: Daicel CHIRALCEL OD-H; eluent: *n*-hexane/2-propanol: 98:2; flow rate: 0.5 mL/min^{-1}; $l = 220$ nm; retention times: 35.8 min (minor), 57.6 min (major).
10. The reduction of propargylic ketones with complex (*R*,*R*)-**I** affords systematically the corresponding propargylic alcohols with the (*R*) absolute configuration according to Ref. 1b.
11. Prepared from $Pd(dba)_2$ and PPh_3 (5 equiv) in CH_2Cl_2, stirred for 10 min and added to the mixture via cannula.
12. The low yield observed in these entries is essentially due to the partial desilylation of **1**.
13. The lower enantioselectivity of the products **4** (75%) compared to **2** (90%) is probably due to the formation of **5**, which was reduced to the corresponding alcohol in low ee.
14. Typical procedure: To a mixture of propargyl ketone (0.81 mmol) in formic acid (304 μL, 8.05 mmol, 10 equiv) and triethylamine (453 μL, 3.22 mmol, 4 equiv) were added at rt an aliquat amount of the stock solution of the RuCl[*N*-(tosyl)-1,2-diphenylethylenediamine)(*p*-cymene) complex 0.03 M in CH_2Cl_2 (670 μL, 0.02 mmol, 0.025 equiv), prepared according to Ref. 18. The evolution of the reaction was monitored by TLC. When the starting material was totally consumed (2–15 h), the Rosemund catalyst (Pd on $BaSO_4$, 10%, 85 mg, 0.081 mmol, 0.1 equiv) was added and the mixture was stirred overnight at rt. Then, the mixture was diluted with CH_2Cl_2 (3 mL), filtered on a cake of silica gel and the volatile residues were evaporated under reduced pressure. The crude product was purified by chromatography on silica gel using a gradient of solvent (petroleum ether/ethyl acetate 95:5 to 90:10).
15. Sumida, S.-i.; Ohga, M.; Mitani, J.; Nokami, J. *J. Am. Chem. Soc.* **2000**, *122*, 1310–1313. (3*R*)-Phenylheptan-3-ol (**14**): $[\alpha]_D$: −12.0 (*c* 1.0, $CHCl_3$); $[\alpha]_D^{lit}$: −11.6 (*c* 3.9, $CHCl_3$).
16. The alcohol was converted to the corresponding (*R*)-Mosher' ester, and the enantioselectivity of the transformation was established by ^1H NMR.
17. Established by ^1H NMR. The kinetic product of the reaction is the corresponding (*Z*)-olefin, which is converted slowly to the (*E*)-product.
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