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Enantioselective Route to Ketones and Lactones from Exocyclic Allylic Alcohols via Metal and Enzyme Catalysis

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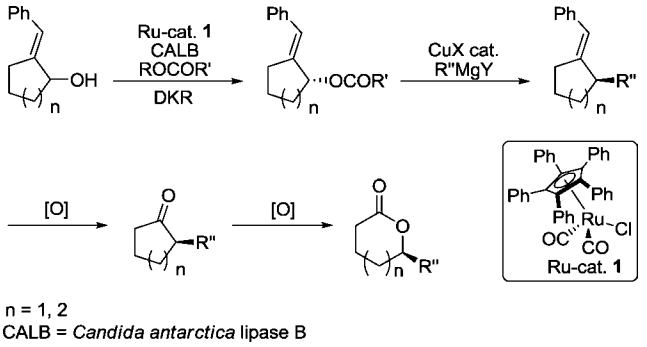
ABSTRACT



n = 1, 2
CALB = *Candida antarctica* lipase B

A general and efficient route for the synthesis of enantiomerically pure α-substituted ketones and the corresponding lactones has been developed. Ruthenium- and enzyme-catalyzed dynamic kinetic resolution (DKR) with a subsequent Cu-catalyzed α-allylic substitution are the key steps of the route. The α-substituted ketones were obtained in high yields and with excellent enantiomeric excess. The methodology was applied to the synthesis of a naturally occurring caprolactone, (*R*)-10-methyl-6-undecanolide, via a subsequent Baeyer–Villiger oxidation.

Ketones and lactones not only are very useful building blocks but also represent structural motifs in a variety of natural products.[1] These natural products have attracted considerable attention because of their biological and medicinal properties.[2] Most of them have substituents in various positions on the ring, which makes them chiral, and this chirality determines their biological activity. For this reason, many methods have been developed to prepare chiral lactones, such as synthesis via chiral auxiliaries[3] and enantioselective variants of catalytic Baeyer–Villiger oxidations,[4] C–H insertion reactions,[5] hydrogenations,[6] 1,4-reduction[7] and 1,4-addition reactions,[8] metal-catalyzed cyclization reactions,[9] and biocatalytic reactions.[10]

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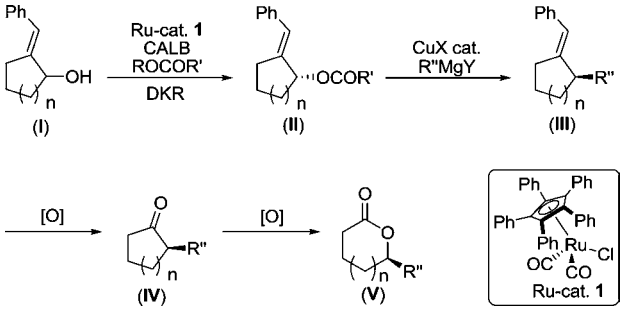
From a green chemistry point of view, enzyme-catalyzed kinetic resolution (KR) of a racemate has proved to be a convenient method to obtain enantiomerically enriched materials.[11] Although lipase-catalyzed resolutions seem to be ideal in both academic and industrial applications, they can only provide the desired enantiomerically enriched product in a maximum theoretical yield of 50%. This limitation can be overcome in dynamic kinetic resolution (DKR) in which the enzyme-mediated enantioselective transformation is integrated with an in situ racemization of the starting material, usually by a metal.[12] Since the fast-reacting enantiomer is never depleted from the reaction mixture, a theoretical yield of 100% can be obtained and this makes DKR a powerful tool for the preparation of enantiomerically enriched compounds in high yields. Over the past decade, we have developed highly efficient DKR protocols for secondary[12c] and primary alcohols[13] as well as for amines,[14] and in some cases we have demonstrated synthetic applications toward biologically interesting compounds.[14a,15] Recently we reported on an efficient DKR for cyclic and acyclic allylic alcohols, utilizing ruthenium catalyst **1** for the racemization and *Candida antarctica* lipase B (CALB) or Subtilisin Carlsberg for the enzymatic kinetic resolution.[16] Both (*R*)- and (*S*)-acetates could be obtained with high enantiopurity and in high yields depending on the enzyme applied.

Here we wish to report on a general route for the enantioselective synthesis of α-alkylated cyclic ketones and their corresponding lactones, utilizing DKR in the enantiodetermining step. Our synthetic strategy begins with DKR of the exocyclic allylic alcohols (**I**), with the use of ruthenium catalyst **1** and CALB, producing the corresponding allylic esters (**II**). Subsequent Cu-catalyzed allylic α-substitution proceeds with inversion of the stereochemistry and forms alkenes (**III**). Further oxidative cleavage of the C=C bond releases the hidden ketone functionality (**IV**). Finally, Baeyer–Villiger oxidation produces the enantiomerically pure lactones (**V**) (Scheme 1).

Scheme 1. Synthetic Strategy Toward Enantioenriched α-Alkylated Ketones (**IV**) and Lactones (**V**) via Tandem DKR and Cu-Catalyzed Allylic Substitution (n = 1, 2)



The cyclic allylic alcohol substrates **2a** and **2b** were synthesized by a straightforward two-step procedure (see Supporting Information for further details). Subsequent DKR of **2a** and **2b** was performed according to the previously published procedure (Table 1).[16] Both acylated products (*R*)-**3a** and (*R*)-**3b** were obtained in good isolated yields and excellent *ee* (>99%) using ruthenium catalyst **1** and *Candida antarctica* lipase B (CALB). A slightly

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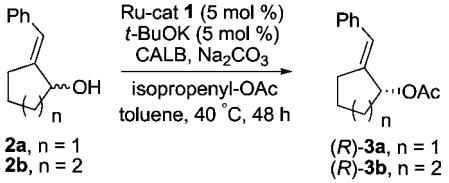
elevated temperature (40 °C) was required to increase the rate of the reaction.

Copper-catalyzed allylic substitution reactions with Grignard reagents are well studied and can proceed via two different pathways, producing either the α- or γ-alkylated product (Scheme 2).[17−19] It is generally accepted that the oxidative addition to allylic esters by Cu(I) proceeds with high γ-regioselectivity, forming σ-allyl complex **4**.[17b,c] The latter reaction proceeds with anti stereochemistry. Fast reductive elimination from intermediate **4** would result in formation of the γ-alkylated product **5** via an S_N2' pathway. However, if rearrangement of complex **4** to α-allyl copper complex **6** is faster, product **III** will be formed via an S_N2 pathway. Intermediate **4** will also be in equilibrium with the rotamer **4′**. If the equilibrium between rotamers **4** and **4′** is fast, this would result in a mixture of products **III** and **III′**. Products **III** and **III′** are diastereoisomers, and therefore the ratio between them will be determined by the Curtin−Hammet principle. In this synthetic approach, selective α-substitution was desired producing product **III** with retained chiral information (Scheme 2).

Table 1. DKR of Allylic Alcohols **2a** and **2b**



2a, n = 1
2b, n = 2

(*R*)-**3a**, n = 1
(*R*)-**3b**, n = 2

entry[a]	substrate	conv (%)[b]	yield (%)[c]	*ee* (%)[d]
1	**2a**	>99	76	>99
2	**2b**	>99	84	>99

[a] 2.0 mmol of **2**, 64 mg of Ru-catalyst **1** (5 mol %), 12 mg of CALB, 5 mol % of *t*-BuOK, 2 mmol of Na_2CO_3, and 3.0 mmol of isopropenyl acetate in dry toluene (4.0 mL) under argon for 48 h. [b] Determined by ^{1}H NMR. [c] Isolated yield. [d] Determined by chiral HPLC.

Scheme 2. Different Pathways for the Cu-Catalyzed Allylic Substitution (n = 1, 2)

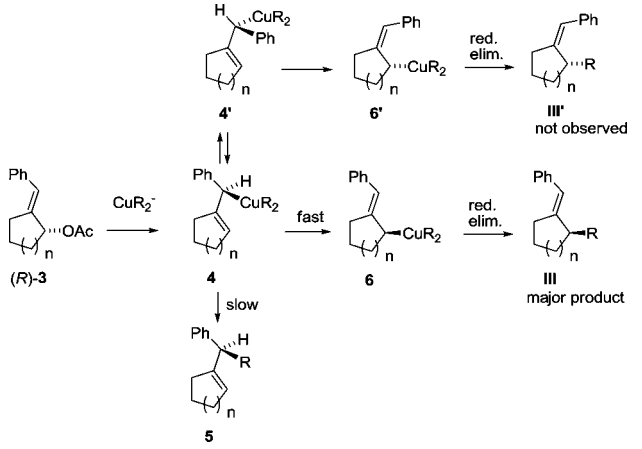
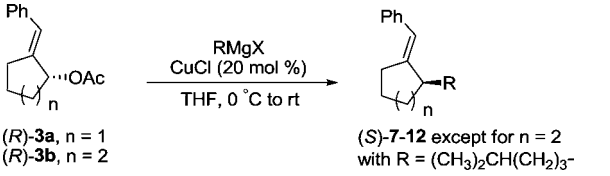


Table 2. Cu-Catalyzed Allylic Substitution Reaction



(*R*)-**3a**, n = 1
(*R*)-**3b**, n = 2

(*S*)-**7-12** except for n = 2 with R = $(CH_3)_2CH(CH_2)_3$-

entry[a]	substrate	RMgX	product	yield (%)[b]
1	(*R*)-**3a**	MeMgBr	(*S*)-**7a**	86
2	(*R*)-**3a**	EtMgBr	(*S*)-**8a**	64
3	(*R*)-**3a**	PhMgBr	(*S*)-**9a**	88
4	(*R*)-**3a**	4-$MeOC_6H_4MgBr$	(*S*)-**10a**	86 (α:γ = 90:10)
5	(*R*)-**3a**	$CH_3(CH_2)_4MgBr$	(*S*)-**11a**	82
6	(*R*)-**3a**	$(CH_3)_2CH(CH_2)_3MgBr$	(*S*)-**12a**	76 (α:γ = 81:19)
7	(*R*)-**3b**	MeMgBr	(*S*)-**7b**	74 (α:γ = 65:35)
8	(*R*)-**3b**	PhMgBr	(*S*)-**9b**	75
9	(*R*)-**3b**	$CH_3(CH_2)_4MgBr$	(*S*)-**11b**	76 (α:γ = 74:26)
10	(*R*)-**3b**	$(CH_3)_2CH(CH_2)_3MgBr$	(*R*)-**12b**[c]	78 (α:γ = 77:23)

[a] The substrate was added to a solution of RMgX (2.5 equiv) and CuCl (20 mol %) in dry THF at 0 °C. [b] Isolated yields. The α:γ ratio was determined by ^{1}H NMR. In the cases not indicated the reactions were α-selective (> 97% α). [c] (*S*) changes to (*R*) because of the sequential rule.

Different conditions for the Cu-catalyzed allylic substitution were screened using a previously published procedure.[19] Some initial optimization was performed with *rac*-(**3b**) and commercially available Grignard reagent MeMgBr. With 1.5 equiv of MeMgBr and 20 mol % of CuCl in dry THF, 35% of the desired product **7b** was formed. Some attack on the ester function in **3b** forming **2b** was observed (15%) under these conditions. Also, 50% of unreacted starting material **3** was observed. When THF was exchanged for Et_2O as solvent, the reaction was much slower and only 4% of the desired product **7b** was formed. Also increased attack on the ester seemed to occur in Et_2O compared to THF. Therefore, THF was chosen as the solvent.

Therefore, instead of adding the Grignard reagent to the substrate mixed with the copper salt we argued that it would be better to first let the Grignard reagent react with the CuCl and then add the substrate, in order to ensure that only dialkylcuprate is present in the solution. This is expected to result in better conversion. The allylic substitution reactions were performed in this manner on the DKR products (*R*)-**3a** and (*R*)-**3b** with different Grignard reagents (Table 2). The Cu-catalyzed allylic substitution reactions proceeded well with moderate to high isolated

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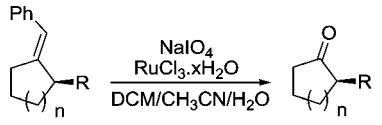
Table 3. Oxidative Cleavage of the C=C Bond



(*S*)-**7-12** except for n = 2 with R = $(CH_3)_2CH(CH_2)_3$- (*S*)-**13-14** and (*R*)-**15-16** (n = 1, 2)

entry[a]	*n*	substrate	R	product	yield (%)[b]	*ee* (%)
1	1	(*S*)-**7a**	Me	(*S*)-**13a**	69[c]	94[d]
2	1	(*S*)-**8a**	Et	(*S*)-**14a**	74	>99[e]
3	1	(*S*)-**11a**	Ph	(*R*)-**15a**	89	97[e]
4	2	(*S*)-**11b**	Ph	(*R*)-**15b**	73	98[d]
5	2	(*R*)-**12b**	$(CH_3)_2CH(CH_2)_3$	(*R*)-**16b**	82	>99[f]

[a] $NaIO_4$ (5 equiv) and $RuCl_3 \cdot xH_2O$ (ca. 1 mol %) were added to the substrate dissolved in a 1:1:2 $DCM/CH_3CN/H_2O$ mixture at rt. [b] Isolated yields except for entry 1. [c] Yield determined by GC. [d] Determined by chiral GC. [e] Determined by chiral HPLC. [f] Determined by chiral GC after transformation to the lactone derivative.

yields. For the more electron-rich and sterically hindered Grignard reagents some of the γ-alkylated products were observed. The α/γ product ratio was found to be slightly better for the five-membered substrate (*R*)-**3a** (Table 2).

The synthetic utility of the Cu-catalyzed allylic substitution reaction was demonstrated by transformation of selected products from Table 2 to the corresponding ketone derivatives (Table 3). Oxidative cleavage of the C=C double bond was performed with $NaIO_4$ using $RuCl_3 \cdot xH_2O$ as the catalyst.[16,20] The ketones were isolated by column chromatography in high yields. A few percent loss in *ee* was observed in some cases. The reactions were quenched at nearly full conversion affording the products (*R*)-**15a** and (*R*)-**15b** with 97 and 98% *ee*, respectively (Table 3, entries 3 and 4). No racemization was observed for substrates (*S*)-**14a** and (*R*)-**16b** (Table 3, entries 2 and 5).

Scheme 3. Synthesis of (*R*)-10-Methyl-6-undecanolide ((*R*)-**17**)

(*R*)-10-Methyl-6-undecanolide ((*R*)-**17**) is a caprolactone recently isolated from a marine streptomycete (isolate B6007).[21] This caprolactone has shown promising activity against different human cancer cell lines such as inhibition of the cell growth of HM02 (gastric adenocarcinoma), HepG2 (hepatocellular carcinoma), and MCF7 (breast adenocarcinoma), with concomitant low general cytotoxicity.[21] As a synthetic application ketone, (*R*)-**16b** was transformed to the lactone derivative (*R*)-**17** in a Baeyer–Villiger oxidation with *m*-CPBA (Scheme 3). (*R*)-**17** was isolated by flash chromatography in 90% yield and with excellent enantiomeric excess (>99% *ee*) in comparison with previously published data (95% *ee*).[22]

In conclusion we have developed a general and efficient route toward enantioselective synthesis of α-alkylated cyclic ketones and the corresponding lactones. This was done via ruthenium- and enzyme-catalyzed DKR of allylic alcohol substrates and subsequent Cu-catalyzed α-allylic substitution. The methodology was applied to the synthesis of a natural product, caprolactone (*R*)-**17**.

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Supporting Information Available. Description of experimental procedures and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.