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An Enantioselective Route to α-Methyl Carboxylic Acids via Metal and Enzyme Catalysis

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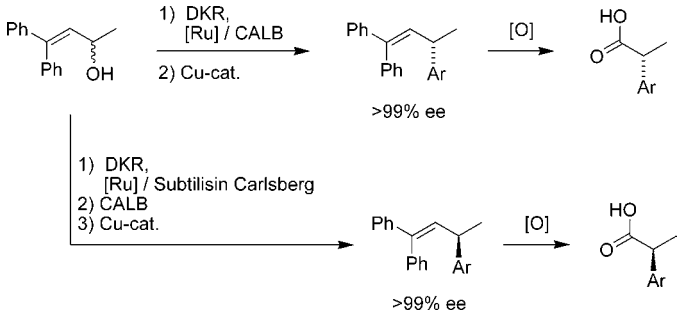
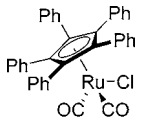
ABSTRACT



Dynamic kinetic resolution of allylic alcohols to allylic acetates followed by copper-catalyzed allylic substitution gave alkenes in high yields and high optical purity. Subsequent oxidative C–C double bond cleavage afforded pharmaceutically important α-methyl substituted carboxylic acids in high ee.

Dynamic kinetic resolution (DKR) has become an active area of research and is of importance in organic synthesis as a powerful tool to prepare enantiomerically enriched compounds in high yields.[1] Recently, a highly efficient ruthenium catalyst (**1**) for room-temperature racemization of secondary alcohols was developed in our laboratories.[2] This catalyst, combined with (*R*)- and (*S*)-selective enzymes, successfully provided an efficient chemoenzymatic catalytic system for the preparation of both possible enantiomerically pure alcohol esters in high yield at ambient temperature in short reaction times.[2b,c,3]



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We report on a strategy to prepare enantiomerically pure α-methyl-substituted carboxylic acids (**IV**), starting from readily available α-methyl-substituted allylic alcohols (**I**) as substrates. A ruthenium- and enzyme-catalyzed DKR in tandem with a highly stereoselective copper-catalyzed allylic α-substitution afforded alkenes (**III**), which upon oxidative C−C double bond cleavage gave the target acids (**IV**) in high ee (Scheme 1). By employing either *Candida antarctica* lipase B (CALB) or Subtilisin Carlsberg in the DKR step, the (*R*)- or (*S*)-ester of **II**, respectively, can be obtained, (only the (*R*)-ester of **II** is shown in Scheme 1). In this way, both

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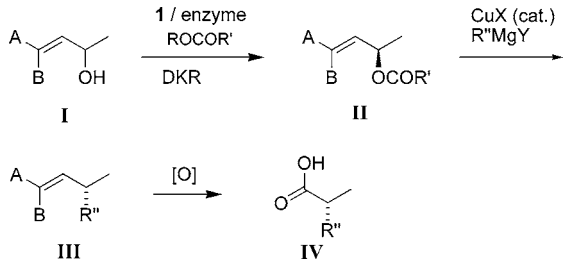
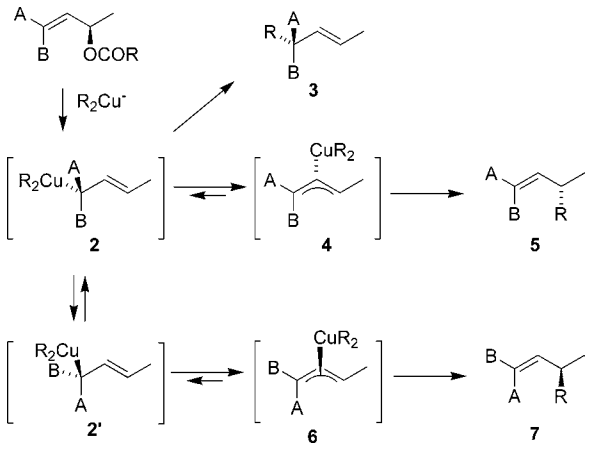
Scheme 1. Enantioselective Synthesis of α-Methyl Carboxylic Acids via Metal and Enzyme Catalysis



enantiomers of the final product can be prepared with high optical purity.

There are several examples of copper(I)-mediated substitutions of enantiomerically pure allylic substrates that occur with high 1,3-chirality transfer in an *anti*-S_N2'manner (γ-selective).[4] On the other hand, the formation of α-product (*anti*-S_N2 reaction) with conserved chiral information is less studied. To the best of our knowledge, only cyclic allylic substrates have been employed,[4c] except for one case[5] where the α-substitution of an acyclic substrate proceeded with 88% conservation of chiral information. However, no further studies or synthetic applications of this reaction have been reported.

Scheme 2. Isomerization of the Allyl Intermediates, Leading to Different Products



Oxidative addition of allylic esters to copper(I) is assumed to occur with high stereoselectivity.[5−8] The substrate adds to copper in a γ-selective manner and with *anti* stereochemistry, giving σ-allyl complex **2** (Scheme 2).[7,8] A fast reductive elimination from intermediate **2** would lead to product **3**. However, if conversion of **2** to **4** is faster than reductive elimination of **2** to **3**, selective formation of product **5** is expected, provided that the equilibration between rotamers **2** and **2′** is slow.

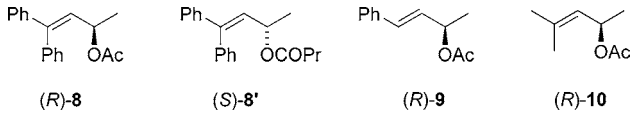


Figure 1. Substrates investigated in the copper-catalyzed allylic substitution.

If substituents A and B are identical, intermediates **4** and **6** will be enantiomers. Thus, fast equilibration of these reaction intermediates (via **2** and **2′**) prior to product formation would lead to formation of a racemic α-product, (i.e., **5** + **7**).[9] If substituents A and B are different, intermediates **4** and **6** are diastereoisomers and under full equilibration between **4** and **6** (via **2** and **2′**) a Curtin-Hammet situation would be at hand. The reactivity of these diastereoisomers as well as their stability would determine the ratio between **5** and **7**.

The substrates investigated for allylic substitution are depicted in Figure 1. Substrates **8** and **8′** have identical substituents in the γ-position and for this reason loss of chiral information according to Scheme 2 may occur. In a previous study we found that loss of chiral information indeed takes place in the copper-catalyzed cross-coupling of **8** with alkyl Grignard reagents at low temperature.[9] However, with aryl Grignard reagents high conservation of chiral information was obtained. Since the efficiency of the reaction of **8** with aliphatic Grignard reagents was moderate, we also investigated **9** and **10** as possible substrates for a selective α-substitution with retained chiral information in the copper-catalyzed allylic substitution reaction.

DKR of alcohol **11** was carried out using ruthenium complex **1** and CALB to afford (*R*)-**8**. An elevated temperature was required to obtain an acceptable rate of product formation, and at 80 °C product (*R*)-**8** was obtained in 97% yield and >99% ee (Scheme 3).[3b] Isomerization of similar allylic alcohols in the presence of ruthenium complexes such as **1** is known to occur;[10] however, the formation of a ketone from the isomerization of **11** was not observed. The ester with the opposite configuration at carbon, (*S*)-**8′**, was obtained in 83% yield and 95% ee in an (*S*)-selective DKR[3a,11] of **11** using the protease Subtilisin Carlsberg and

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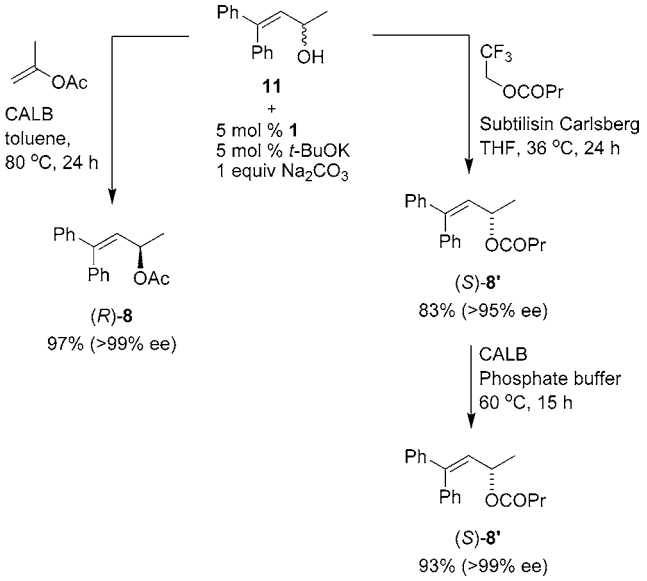
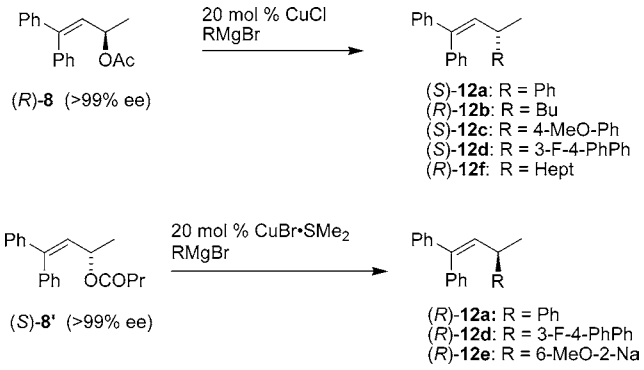
Scheme 3



catalyst **1**. The enantiomeric purity was subsequently enhanced by enzymatic hydrolysis of the undesired enantiomer to give (*S*)-**8′** in >99% ee and 93% yield (77% overall yield from **11**) (Scheme 3). Compound (*R*)-**9** was obtained in 89% yield and >99% ee in an analogous DKR using **1** and CALB.[2c] Allylic acetate (*R*)-**10** was obtained in enantiomerically pure form by kinetic resolution of the corresponding alcohol.[9]

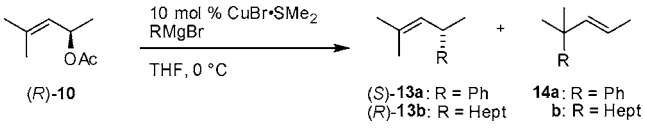
Table 1. Reactions with Substrates (*R*)-**8** and (*S*)-**8′**[a]



entry	substr	R′	rxn time (h)	prod.	yield (%)[b]	ee (%)[c]
1	(*R*)-**8**	Ph	4.5	(*S*)-**12a**	91	>99
2	(*S*)-**8′**	Ph	18	(*R*)-**12a**	88	>99
3	(*R*)-**8**	Bu	1.8	(*R*)-**12b**	67	69
4[d]	(*R*)-**8**	Bu	18	(*R*)-**12b**	48[e]	>99
5	(*R*)-**8**	4-MeO−Ph	12	(*S*)-**12c**	79	>99
6	(*R*)-**8**	3-F-4-PhPh	16	(*S*)-**12d**	95	>99
7	(*S*)-**8′**	3-F-4-PhPh	16	(*R*)-**12d**	89	>99
8	(*rac*)-**8**	6-MeO-2-Na	4.5	**12e**	74	*f*
9	(*S*)-**8′**	6-MeO-2-Na	18	(*R*)-**12e**	75	95
10	(*R*)-**8**	Hept	2	(*R*)-**12f**	74	80

[a] Unless otherwise noted, the Grignard reagent (0.75 mmol) was added to a mixture of the substrate (0.5 mmol) and copper salt in THF at 0 °C. [b] Isolated yields, except for entry 4. [c] Determined by HPLC. [d] Reaction run at −20 °C in Et_2O. [e] Determined by ^1H NMR using 2-decanol as internal standard. [f] Racemic substrate was used.

Table 2. Reactions with Substrate (*R*)-**10**[a]



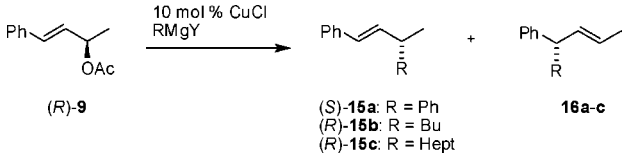
entry	R	time (h)	**13** + **14** (%)[b]	α/γ ratio[b]	ee (%)[c]
1	Ph	14.5	>99	92:8	98
2	Hept	14.5	91	93:7	97

[a] Reaction conditions: allylic acetate (0.5 mmol) and CuBr·SMe_2 were mixed in THF. After cooling, Grignard reagent (0.75 mmol) was added. [b] Determined by GC using decane as internal standard. [c] Determined by GC analysis of the corresponding carboxylic acid obtained by Sharpless oxidation.[13]

When aryl Grignard reagents were used in the copper-catalyzed substitution of substrates (*R*)-**8** and (*S*)-**8′** in THF, the α-products (*S*)-**12a,c,d** and (*R*)-**12a,d,e** were formed in high yields and in excellent ee (Table 1, entries 1, 2, 4−7, and 9). When aliphatic Grignard reagents were used under the same reaction conditions with (*R*)-**8**, products (*R*)-**12b** and (*R*)-**12f** were obtained in moderate stereoselectivity (69 and 80% ee, respectively) (Table 1, entries 3 and 10). Changing the solvent from THF to ether resulted in a dramatic improvement of the stereoselectivity, and (*R*)-**12b** was obtained in >99% ee although in moderate yield (48%) (Table 1, entry 4). All reactions were highly α-selective, and the γ-product was not observed.[12]

Substrate **10** is similar to substrate **8** in the sense that the γ-carbon is not a prochiral center. Thus, loss of chiral information as described in Scheme 2 may occur. However, no significant loss of chiral information was observed in the formation of α-products **13a** and **13b** (Table 2, entries 1 and 2). In both experiments the desired α-product was produced in high yields, accompanied by small amounts of γ-product **14**. The reaction temperature was decreased to −40 °C in

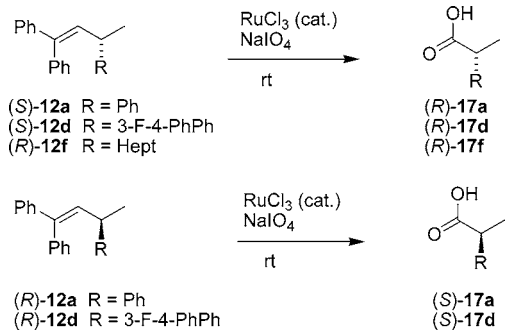
Table 3. Reactions with Substrate (*R*)-**9**[a]



entry	RMgY	time (h)	solvent	temp (°C)	**15** + **16** (%)[b]	α/γ ratio[b]	ee (%)
1	PhMgBr	6	THF	0	≥95	100:0	>99[c]
2	BuMgCl	24	THF	−20	59	89:11	90[d]
3	HeptMgBr	16	Et_2O	0	65	90:10	96[d]

[a] Reaction conditions: allylic acetate (0.5 mmol) and CuBr·SMe_2 were mixed in THF. After cooling, Grignard reagent (0.75 mmol) was added. [b] Determined by ^1H NMR using 2-decanol as internal standard. [c] Determined by HPLC. [d] Determined by GC analysis of the corresponding carboxylic acid obtained by Sharpless oxidation.[13]

Table 4. Oxidation of Olefins to Carboxylic Acids[a]



entry	substrate (% ee)	R	product	yield (%)	ee (%)
1	(*S*)-**12a** (>99)	Ph	(*R*)-**17a**	84	>97[b]
2	(*R*)-**12a** (>99)	Ph	(*S*)-**17a**	90	>97[b]
3	(*S*)-**12d** (>99)	3-F-4PhPh	(*R*)-**17d**	88	>97[c]
4	(*R*)-**12d** (>99)	3-F-4PhPh	(*S*)-**17d**	88	>97[b]
5	(*R*)-**12f** (80)	Hept	(*R*)-**17f**	71	80[b]

[a] Reactions were run on a 0.4−0.6 mmol scale. [b] Determined by GC. [c] Determined by HPLC analysis of the corresponding anilide.

an attempt to favor the formation of α-product **13**; however, no product formation was observed.

Cross-coupling of (*R*)-**9** with PhMgBr in THF led to a quantitative yield of α-product (*S*)-**15a** in >99% ee (Table 3, entry 1). In order to obtain a high chirality transfer in the cross-coupling with an aliphatic Grignard reagent, Et_2O was found to be the better solvent, and in this way α-product (*R*)-**15c** was obtained in high optical purity (Table 3, entry 3).

Some of the olefins obtained as described in Scheme 1 were oxidized according to the Sharpless procedure (Table 4).[13] In this way both enantiomers of α-phenylpropionic acid, **17a**, and flurbiprofen, **17d**, were obtained in good to high yields and with high optical purities (>97% ee). Flurbiprofen is an important anti-inflammatory drug. Oxidation of olefin (*R*)-**12a** and (*R*)-**12d** to to their corresponding acids confirmed that the absolute configurations of the acids were (*S*)-(+)-**17a** and (*S*)-(+)-**17d** by comparison with literature data.[14]

In conclusion, a straightforward route to α-methyl carboxylic acids via metal and enzyme catalysis has been developed. DKR of allylic alcohol **11** proceeded with an excellent yield and optical purity to produce (*R*)-**8** (97%, >99% ee), and no isomerization to the corresponding ketone was observed. Likewise, DKR of **11** followed by enzymatic hydrolysis afforded (*S*)-**8′** in high yield and optical purity (77%, >99% ee). Copper-catalyzed S_N2 substitution of the allylic esters was accomplished in high yield and high enantioselectivity, and subsequent ruthenium-catalyzed oxidation proceeded with conservation of chiral information, to give pharmaceutically important α-methyl arylacetic acids.

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Supporting Information Available: Synthesis and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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