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Asymmetric catalysis, part 108 [1] Copper catalysts with optically active ligands in the enantioselective Meerwein arylation of activated olefins [2]

Henri Brunner [a,*], Christian Blüchel [a], Michael P. Doyle [b]

[a] *Institut für Anorganische Chemie, Universität Regensburg, D-93040 Regensburg, Germany*
[b] *Department of Chemistry, Trinity University, 715 Stadium Drive, San Antonio, TX 78212-7200, USA*

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Abstract

The copper-catalyzed Meerwein reaction of activated olefins with arenediazonium halides leads to a formal addition of aryl halide to the olefinic double bond. Methyl acrylate, *p*-tolyldiazonium tetrafluoroborate and tetrabutylammonium chloride in anhydrous acetonitrile were used as a model system, the product being methyl α-chloro-β-tolylpropionate. Applying a newly established methodology, the isolated diazonium tetrafluoroborate and an equivalent amount of tetrabutylammonium chloride were added to the olefin and the copper catalyst, containing optically active ligands, such as 2- and 2,6-pyridinyloxazolines and bisoxazolines. The low optical inductions obtained in the room temperature reaction could be raised to 8.7% *ee* in the low temperature variant at -40 °C. Two phenyl substituents in the neighborhood of the chiral centers in the bisoxazoline ligands of the catalyst and increasing steric bulk in the ester group of the substrate (methyl, ethyl, menthyl) increase the stereoselectivity of the Meerwein arylation. Replacement of the *p*-tolyldiazonium salt by the mesityldiazonium salt caused the optical induction in the formation of the corresponding mesityl product rise to 19.5% *ee*. Thus, though considered to be a radical reaction, the Meerwein arylation of activated olefins can be rendered enantioselective by using copper catalysts with optically active ligands. © 1997 Elsevier Science S.A.

Keywords: Meerwein arylation; Copper catalysts; Enantioselectivity; Optically active ligands; Pyridinyloxazoline; Bisoxazoline

1. Introduction

The classical Meerwein reaction [2–4] is the copper-catalyzed arylation of activated unsaturated compounds by arenediazonium halides that leads to the formal addition of aryl halide to the olefinic double bond. It proceeds best when the double bond is activated by an electron-withdrawing group, such as carbonyl, cyano, halogeno, aryl or vinyl. Depending on the reaction conditions, the addition reaction may be followed by the elimination of hydrogen halide.

The regioselectivity of the reaction is determined by the stability of the radical intermediates. Generally, α-halogeno-β-aryl products are formed. These compounds may serve as precursors for a variety of useful substances, e.g. amino acids such as substituted phenylalanines.

Although the Meerwein arylation has been the subject of many studies, its mechanism is still not completely understood. Most observations point to the existence of a free radical chain mechanism [5–10]. However, some facts indicate the presence of complex intermediates [11–15]. The role of copper in the reaction mechanism is twofold [16]. Copper(I) is able to reduce the diazonium salt initiating its decomposition to nitrogen and an aryl radical [17,18]. This reduction may proceed via an inner sphere or an outer sphere mechanism [10,16]. The aryl radical adds to the double bond of the olefin, giving an intermediate arylethyl radical [8]. Subsequent oxidation of this radical by transfer of a halogen ligand from copper(II) leads to the final product [10,16]. Concurrently, copper(II) is reduced to copper(I) and may enter the reaction cycle again. Several suggestions have been made for the mechanism of this last step [19–21]. It might be possible that the Cu–Cl bond breaks up homolytically followed by the transfer of a

* Corresponding author.

[1] For part 107 see Ref. [1].

[2] Dedicated to Professor G. Huttner on the occasion of his 60th birthday.

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free halogen radical. Other mechanisms are formulated via an alkylcopper intermediate. This intermediate might decompose heterolytically to a carbenium ion and copper(I) or by reductive elimination of the reaction product.

Meerwein products obtained under classical reaction conditions are racemic. In the present study we report on our approach to perform an enantioselective catalysis of the Meerwein arylation using optically active copper(I) catalysts [22].

2. Model system

Methyl acrylate (MeAcr) was chosen as the activated olefin and *p*-tolyldiazonium tetrafluoroborate ($TolN_2BF_4$) [23,24] as the arylating agent in our model Meerwein reaction, which gives methyl α-chloro-β-tolylpropionate as the main product (Scheme 1) and methyl β-tolylacrylate as a by-product.

Similar to the procedure of Doyle and Bryker [25] the reaction was carried out in dry acetonitrile. The chloride ions were introduced with tetrabutylammonium chloride (TBACl). A stock solution of $TolN_2BF_4$ in acetonitrile was prepared, which turned out to be stable for weeks at −20 °C. Similar stock solutions were prepared and used for the chloride source TBACl, the procatalyst copper(I) triflate (CuOTf), the optically active ligand L*, and the internal standard ethyl α-chloro-β-tolylpropionate (Scheme 2).

The catalytic reaction was carried out in an inert atmosphere, because it is known that oxygen is an inhibitor of the Meerwein arylation [9] leading to decreased yields and the formation of by-products. However, nitrogen protection was not necessary for the work-up of the reaction.

The olefinic substrate MeAcr, the procatalyst CuOTf and the ligand were dissolved in anhydrous acetonitrile (molar ratio 100:1:1). The catalysts were of the in situ type, e.g. combinations of a copper-containing procatalyst and an optically active ligand as a cocatalyst. The solutions of the copper(I) catalysts with optically active pyridinyloxazolines were brown, whereas those with the optically active bisoxazolines were green. Then, a solution of $TolN_2BF_4$ and TBACl in anhydrous acetonitrile was added within 15–30 min at a temperature of 0–5 °C. Finally, stirring at 0–5 °C was continued for another 30 min.

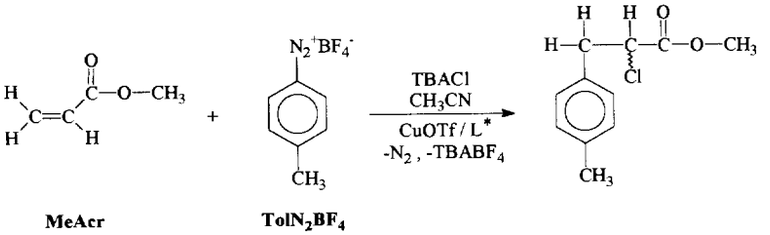
When the TBACl stock solution was added to the brown solution containing MeAcr and a catalyst obtained from CuCl and an equivalent amount of 2,2′-bipyridine, a decoloration was observed, which can be explained by a displacement of the bipyridine ligand by Cl^- ligands in the copper complex. To minimize this displacement of the bipyridine ligand (and other optically active ligands) in the following experiments, TBACl was added together with $TolN_2BF_4$ to the solution of MeAcr and catalyst. This procedure assured that only a small concentration of free chloride was present in the reaction mixture.

For work-up all the volatile compounds were removed in vacuo at room temperature to avoid elimination of HCl from the product. The residue was chromatographed on silical gel with methylene chloride–petroleum ether 20:1.

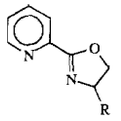
The chemical yield was determined by weighing the product or, alternatively, by GC using an internal standard. Runs in which the yield was determined by weighing were carried out with 5 mmol of MeAcr and 0.5 mmol of $TolN_2BF_4$ and TBACl, respectively, in a total of 8.5 ml of acetonitrile, whereas for runs in which the yield was obtained by GC using an internal standard 1 mmol of MeAcr and 0.1 mmol of $TolN_2BF_4$ and TBACl, respectively, in a total of 5 ml of acetonitrile were sufficient.

For the determination of the chemical yield of the Meerwein arylation by GC an aliquot of the standard ethyl α-chloro-β-tolylpropionate was added to the product before purification by chromatography. An achiral column DB1 was used to separate the methyl ester (product) and the ethyl ester (standard). Calibrations proved that no correlation factor was necessary for the calculation of the quantities of the two esters from their peak areas. We could demonstrate that the product methyl α-chloro-β-tolylpropionate and the standard ethyl α-chloro-β-tolylpropionate are so similar that their ratio did not change during chromatography. These GC analyses showed that after chromatography the products were 93–97% pure.

Enantiomer analysis was carried out with the chiral



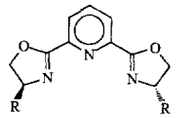
Scheme 1.



1

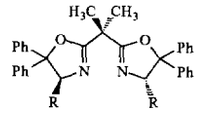
a) R = *n*-Pr [(R)-]

b) R = *n*-Bu [(S)-]



2

R = *i*-Pr



3

a) R = Me

b) R = *i*-Bu

c) R = Bz

Scheme 2.

column G-PN containing propionylated γ-cyclodextrin, which gave base line separation for the scalemic product as well as for the racemic standard. The enantiomeric excess of the product was calculated from the integration areas (reproducibility ± 1%) [22].

The product of the model reaction was also prepared in an optically active form by a classical resolution. To this end the free carboxylic acid α-chloro-β-tolyl-propionic acid was synthesized from acrylic acid and *p*-tolyldiazonium chloride in aqueous hydrochloric acid using CuCl as a catalyst. The resolution was carried out with brucine in ethanol–water. After five fractional crystallizations the optical rotation no longer changed (+5.3°, *c* 4.0, CH_2Cl_2). Esterification of the carboxylic acid with diazomethane gave the optically pure ester methyl α-chloro-β-tolylpropionate ($[\alpha]_D$ = +2.6°, *c* 2.0, CH_2Cl_2). By comparison with (*S*)-(+)-α-chlorohydrocinnamic acid (+6.2°, neat) we assigned the (*S*) configuration to α-chloro-β-tolylpropionic acid having a positive optical rotation at the Na_D-line [26]. In the gas chromatogram of the ester (+)-methyl α-chloro-β-tolylpropionate only the peak with the higher retention time was observed indicating optical purity. Under the conditions of catalysis and work-up, even after distillation at 100 °C, the ester was still optically pure. Thus, racemization during catalysis and work-up can be excluded.

3. Screening of the optically active ligands

In the model reaction of Scheme 1 several types of ligands were tested as chiral cocatalysts together with CuOTf as the procatalyst in the enantioselective Meerwein arylation. Exclusively, yields were determined by weighing. The catalytic efficiency was measured compared to reactions performed with CuOTf without any ligand, which gave 32% yield, and with CuOTf and the optically inactive ligand 2,2′-bipyridine, which gave 45% yield.

The enantioselectivities obtained with more than a dozen of different optically active salicylaldimines, 2-pyridinylaldimines, 2-pyridinylthiazolines, as well as 2- and 4-pyridinylthiazolidines, with varying substituents bound to the asymmetric center were below 2% *ee*, the product yield being between 30 and 50% [22]. Optically active oxazoline derivatives turned out to be the most efficient cocatalysts in the enantioselective Meerwein arylation. Giving good yields, the two 2-pyridinyloxazolines **1a** and **1b** (out of a total of ten ligands tested [22]) raised the enantiomeric excess to 3.5 and 2.4% *ee* in the standard reaction (Table 1, nos. 1, 2).

Nishiyama's 2,6-bispyridinyloxazoline **2** [27] induced 2.7% *ee* with 40% yield (no. 3). The best results were obtained with chiral bisoxazoline ligands. While the application of Evans-type ligands [28] resulted in rather low optical inductions (five ligands tested [22]), the substitution of the oxazoline ring with two phenyl groups in the neighborhood of the chiral center significantly increased the enantioselectivity (no. 4–6). With compound **3a** the enantiomeric excess could be raised to 5.8% *ee* (no. 4), which was the best result achieved in this ligand screening. The two phenyl substituents with their buttressing effect [29,30] activated the reaction. Thus, the catalyst derived from CuOTf and the bis(diphenyloxazoline) **3b** gave a 75% chemical yield of the product (no. 5). The size of the substituent bound to the asymmetric center had no influence on the induced enantioselectivity. With the methyl derivative a better result was obtained than with the benzyl derivative (nos. 4, 6). The isopropyl and the sec-butyl derivatives gave an almost racemic product [22], while the isobutyl

Table 1
Enantioselective Meerwein arylation. The reaction of methyl acrylate with *p*-tolyldiazonium tetrafluoroborate and TBACl was carried out in acetonitrile at 0–5 °C under a nitrogen atmosphere. Chemical yields were determined by weighing

No.	Olefin	Diazo component	Catalyst	Yield (%)	*ee* (%)
1	MeAcr	$TolN_2^+/Cl^-$	CuOTf–**1a**	45	3.5 (*R*)
2	MeAcr	$TolN_2^+/Cl^-$	CuOTf–**1b**	42	2.4 (*S*)
3	MeAcr	$TolN_2^+/Cl^-$	CuOTf–**2**	40	2.7 (*S*)
4	MeAcr	$TolN_2^+/Cl^-$	CuOTf–**3a**	38	5.8 (*R*)
5	MeAcr	$TolN_2^+/Cl^-$	CuOTf–**3b**	75	4.5 (*R*)
6	MeAcr	$TolN_2^+/Cl^-$	CuOTf–**3c**	58	2.4 (*R*)

compound induced 4.5% *ee* (no. 5). The diphenyl-substituted ligands were synthesized starting from the corresponding amino acids which were reduced with phenyl Grignard [29].

A striking observation was the inversion of the sense of optical induction in going from the unsubstituted bisoxazolines to their diphenyl-substituted derivatives. Whereas the unsubstituted ligands having (*S*)-configuration gave predominantly the (*S*)-product enantiomer, substitution of the oxazoline rings with two phenyl groups resulted in the formation of the (*R*)-product.

All the other types of ligand applied in the model reaction gave low optical inductions [22]. Phosphines had a deactivating effect, as the product yields were low. Furthermore, diols, diamines as well as the cinchona alkaloids were tested without success.

4. Variation of procatalyst, concentration, solvent and temperature

All the yields, ranging from 30 to 50%, were determined by GC analysis using an internal standard. In addition to CuOTf the procatalysts CuCl, $CuPF_6$ and $CuCl_2$ were tested in combination with ligand **2** to catalyze the Meerwein arylation of Scheme 1. No substantial change with respect to chemical yield and enantiomeric excess was observed. The same was true for a comparison of the procatalysts CuCl and CuOTf with a series of ligands including **1a**, **3b** and **3d** [22]. An increase in the concentration of the procatalyst and/or the cocatalyst increased the optical induction. A tenfold concentration of the catalyst CuOTf–**2** raised the enantioselectivity of the standard reaction from 2.7 (Table 1, no. 3) to 4.2% *ee*, and a duplication of the ligand concentration in the catalyst CuOTf–**3a** caused an increase from 5.8 (Table 1, no. 4) to 7.0% *ee*.

Increasing the Cl^- concentration in the reaction medium reduced the enantioselectivity without affecting the chemical yield. This was demonstrated for the standard conditions by increasing the ratio $TolN_2BF_4$/TBACl in the series 1:1, 1:2, 1:4, resulting in a drop of the enantiomeric excess in the product from 2.7 (Table 1, no. 3) to 1.5 and 0.5% [22].

Acetone was as good a solvent for the substrates and catalysts of the Meerwein arylation as acetonitrile. The yields were comparable. However, stereoselectivity was better in acetonitrile than in acetone. Using acetone instead of acetonitrile in run 3 of Table 1, the enantiomeric excess dropped from 2.7 to 1.6% *ee*. The presence of water in the reaction medium reduced the chemical yield dramatically [22].

Lowering the reaction temperature and using longer reaction times turned out to be the best choice to increase the stereoselectivity of the Meerwein arylation without affecting the chemical yield. Carrying out the standard reaction not at 0–5 °C but at −40 °C caused the optical induction to rise for the CuOTf–**2** catalyst from 2.7 (Table 1, no. 3) to 6.0% *ee* and for the CuOTf–**3a** catalyst from 5.8 to 8.7 [(*S*) ligand in catalyst] and 9.5% *ee* [(*R*) ligand in catalyst] [22]. On the other hand, the same reactions at +60 °C were less enantioselective (1.5% *ee* and 3.6% *ee*, respectively [22]).

5. Variation of the olefinic substrate and the diazonium component

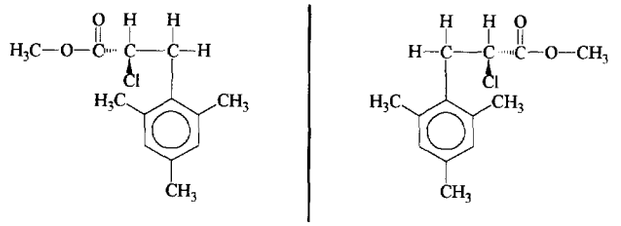
In the variation of the olefinic substrate, the diazonium component $TolN_2BF_4$, the chloride source TBACl and the catalyst CuOTf–**2** remained constant. The experiments were carried out according to the standard procedure (tenfold excess of olefin). The chemical yields were in the range 25–65% [22].

Using ethyl acrylate as the substrate instead of MeAcr gave an appreciable increase of enantioselectivity from 2.7 (Table 1, no. 3) to 4.0% *ee* at 0–5 °C and from 6.0 to 8.4% *ee* at −40 °C. The product was (*S*)-(+)-ethyl α-chloro-β-tolylpropionate (second peak of the enantiomers on the G-PN column). In this system the methyl ester methyl α-chloro-β-tolylpropionate was used as an internal standard.

With the (−)-menthol ester of acrylic acid in the Meerwein arylation with $TolN_2BF_4$ and TBACl two diastereomers arise which differ in the configuration of the asymmetric center at the α-position of the propionic acid chain. With (+)-menthol the enantiomeric compounds are formed. For both series the achiral column DB1, which separates the diastereomers, was used to determine the diastereomeric excess. A configurational assignment of the GC peaks was not carried out.

The Meerwein arylation of (−)-menthyl and (+)-menthyl acrylate at 0–5 °C under achiral conditions gave the same diastereomeric excess of 3.9 and 3.5% (first GC peak dominating). At −40 °C (−)-menthyl acrylate yielded 10% *ee* [22]. Using the optically active catalyst CuOTf–**2** at 0–5 °C, the diastereomeric excess increased for (−)-menthyl acrylate to 6.6 and for (+)-menthyl acrylate to 10.3%.

The use of methyl crotonate and methyl isocrotonate instead of MeAcr turned out to result in the formation of the α-chloro-β-aryl product as well as the α-aryl-β-chloro product. Since both regioisomers separated in two diastereomers, gas chromatography on the achiral column DB1 showed a total of four signals, which were not structurally assigned. Nevertheless, it was possible to make qualitative correlations by comparing the relative intensities of all four peaks. At 0–5 °C the ratio of these peaks remained constant no matter whether methyl crotonate or methyl isocrotonate was used as a substrate and no matter whether the chiral ligand **2** was present or



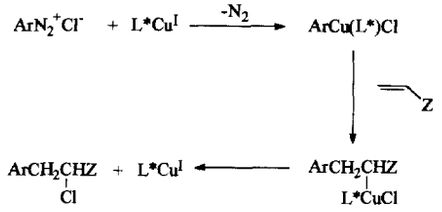
Scheme 3.

not. This indicated that the stereoselectivity of the reaction did not depend on the configuration of the starting material in accord with results published for the Meerwein reaction of maleic acid and fumaric acid derivatives [31] and that the influence of **2** on enantiocontrol cannot be large. At −40 °C reactions catalyzed by CuOTf–**2** showed a somewhat different peak ratio compared to reactions performed without the chiral ligand **2** [22].

Since ester and nitrile groups differ in stabilizing radical or carbenium ion intermediates, acrylonitrile was tested as an olefinic substrate in the enantioselective Meerwein arylation. A reaction performed at −40 °C with CuOTf–**2** as a catalyst produced a racemic mixture of α-chloro-β-tolylpropionitrile (GC analysis on the chiral column Chirasil-DEX CB) in 39% yield.

Replacing TBACl by tetrabutylammonium bromide in the catalysis of Scheme 1 with CuOTf–**2** under standard conditions gave a racemic mixture of methyl α-bromo-β-tolylpropionate in 36% yield, whereas the corresponding chloro compound had been formed in 2.7% *ee* and 40% yield (Table 1, no. 3). The explanation for the loss of enantioselectivity in the formation of the bromo compound could be an increased radical character of the atom transfer [20] in the Meerwein arylation of the bromo system.

In addition to *p*-tolyldiazonium tetrafluoroborate, *o*-tolyldiazonium and mesityldiazonium tetrafluoroborate were used leaving the standard conditions in the reaction of Scheme 1 constant. Surprisingly, the mesityl product gave satisfactory chemical yields (30–50%), in striking contrast to previous experiences. Applying classical Meerwein conditions [3,4] as well as those used by Doyle and Siegfried [24] this reaction hardly takes place. The *p*-tolyl product with the catalyst CuOTf–**2** at 0–5 °C had been formed with 2.7% *ee* (Table 1 no. 3).



Scheme 4.

Scheme 5.

Using the *o*-tolyl product the enantioselectivity rose to 3.7% *ee* and for the mesityl compound methyl α-chloro-β-mesitylpropionate (Scheme 3) to 8.0% *ee* under these conditions.

Using ligand **3a** in the catalyst the *p*-tolyl salt had given 8.7% *ee* at −40 °C [22]. This value increased for the corresponding mesityl compound to 19.5% *ee* at −40 °C, demonstrating that increasing steric hindrance increases the enantioselectivity appreciably. In both cases, for the *o*-tolyl and the mesityl products, the 6-PN column gave base-line separation of the enantiomers.

6. Enantiocontrol

Enantiocontrol in the Meerwein reaction can be explained by formation of an organocopper intermediate followed by reductive elimination (Scheme 4) or by chlorine atom transfer from the chiral chlorocopper(II) complex to the β-arylethyl free radical (Scheme 5).

Although neither can be eliminated from consideration, the low percentage of enantiomeric excesses and high steric demand for selectivity enhancement suggest the atom transfer pathway.

7. Conclusion

The Meerwein arylation is considered to proceed via radical intermediates. Nevertheless, enantiocontrol could be demonstrated by performing the reaction under anhydrous conditions in acetonitrile with optically active copper(I) catalysts.

8. Experimental section

The arenediazonium tetrafluoroborate salts were prepared from corresponding aromatic amines, *tert*-butyl nitrite, and boron trifluoride etherate in anhydrous CH_2Cl_2–ether according to the procedure of Doyle and Bryker [25]. For further use the diazonium salts were dissolved in CH_3CN to give 0.25 M solutions and stored at −20 °C. *tert*-Butyl nitrite was prepared from *tert*-butanol as described by Noyes [23]. Stock solutions were prepared from TBACl (1.00 mol l^{-1}), CuCl (0.05 mol l^{-1}), CuOTf (0.05 mol l^{-1}), ethyl α-chloro-β-tolylpropionate (0.05 mol l^{-1}) and the chiral ligand **2** (0.05 mol l^{-1}). Isocrotonic acid was prepared according to the procedure of Rappe [32]. It was esterified with

diazomethane at 0–5 °C, stabilized by adding hydroquinone and stored at 4 °C.

8.1. Reaction of $TolN_2BF_4$–TBACl with MeAcr. General procedure

The catalysis was performed in an oxygen-free atmosphere. A solution of 0.05 mmol of chiral ligand, 12.6 mg (0.05 mmol) of $CuOTf \cdot 0.5C_6H_6$ and 0.45 ml (0.43 g, 5.0 mmol) of MeAcr in 2 ml of dry acetonitrile were warmed to 60 °C for 30 min and then cooled to 0–5 °C. 139.0 mg (0.5 mmol) of TBACl, 103.0 mg (0.5 mmol) of *p*-toluenediazonium tetrafluoroborate and 3 ml of dry acetonitrile were combined in a dropping funnel and added to the copper–ligand–olefin solution during a 15–30 min period. The reaction mixture was stirred for an additional 30 min at 0–5 °C. Then the volatile compounds were removed under reduced pressure.

If the yield was determined by weighing, the product was purified by column chromatography on silica gel (∅ 2 cm, length 30 cm) with CH_2Cl_2–petroleum ether 20:1 ($R_f \approx 0.7$). In reactions performed using an internal standard the scale could be reduced to 1/5. After completion of the reaction 5.65 mg (0.025 mmol) of ethyl α-chloro-β-tolylpropionate was added to the reaction mixture before removing the volatile compounds in vacuo. The residue was purified by flash chromatography on silica gel with CH_2Cl_2–petroleum ether 20:1.

8.2. Resolution of α-chloro-β-(p-tolyl)propionic acid and methyl α-chloro-β-(p-tolyl)propionate

3.9 g (20 mmol) of α-chloro-β-tolylpropionic acid and 8.6 g (20 mmol) of brucine were dissolved in 20 ml of ethanol. After addition of 250 ml of water the solution was allowed to stand overnight at 4 °C. The precipitating salt was enriched in the (+)-enantiomer of the acid. It was washed with a small amount of water and dissolved in 20 ml of ethanol. Addition of 40 mmol of diluted hydrochloric acid precipitated the free acid. The product was washed twice with diluted hydrochloric acid and dried in vacuo. This procedure was repeated five times to obtain optically pure (+)-α-chloro-β-tolylpropionic acid. Yield: 0.9 g (45%). $[\alpha]_D = +5.3°$ (*c* 4.0, CH_2Cl_2).

Esterification of 0.5 g (2.5 mmol) of (+)-α-chloro-β-tolylpropionic acid with diazomethane gave 0.4 g of (+)-methyl α-chloro-β-tolylpropionate (76%). $[\alpha]_D = +2.6°$ (*c* 2.0, CH_2Cl_2).

8.3. Meerwein arylation products

8.3.1. Methyl α-chloro-β-(p-tolyl)propionate

Colorless liquid. Boiling point: 108 °C/5 mmHg. ^{1}H NMR ($CDCl_3$): δ 7.11 (s, 4H, ArH); 4.43 (dd, J = 7.5 Hz, J = 7.2 Hz, 1H, CH); 3.74 (s, 3H, $COOCH_3$); 3.33 (dd, J = 14.0 Hz, J = 7.2 Hz, 1H, CH_AH_B); 3.13 (dd, J = 14.0 Hz, J = 7.5 Hz, 1H, CH_AH_B); 2.32 (s, 3H, Ar–CH_3). IR (film): 1745 cm^{-1} (C=O). MS (EI, 70 eV): m/e = 212.0 (9, M^+); 177.0 (30); 176.0 (80); 144.9 (57); 116.9 (24), 105.0 (100). Anal. calcd. for $C_{11}H_{13}ClO_2$: C, 62.12; H, 6.17; found: C, 62.04; H, 6.03%.

GC analysis: 30.1 min (*R*); 31.3 min (*S*) [50 m G-PN (Astec), 122 °C, H_2 (2.0 bar)] and 20.2 min (*R*); 21.2 min (*S*) [20 m G-BP (Astec), 115 °C, H_2 (0.6 bar)].

8.3.2. Ethyl α-chloro-β-(p-tolyl)propionate

Colorless liquid. Boiling point: 112 °C/5 mmHg. ^{1}H NMR ($CDCl_3$): δ 7.12 (s, 4H, ArH); 4.40 (t, J = 7.5 Hz, 1H, CH); 4.19 (dq, J = 7.1 Hz, J = 1.2 Hz, 2H, CH_2); 3.32 (dd, J = 14.0 Hz, J = 7.5 Hz, t, 1H, CH_AH_B); 3.13 (dd, J = 14.0 Hz, J = 7.5 Hz, 1H, CH_AH_B); 2.32 (s, 3H, $ArCH_3$); 1.24 (t, J = 7.1 Hz, 3H. CH_2CH_3). IR (film): 1730 cm^{-1} (C=O). MS (EI, 70 eV): m/e = 226.0 (6, M^+); 191.0 (42); 190.0 (91); 161.9 (13); 144.9 (89); 104.9 (100). Anal. calcd. for $C_{12}H_{15}ClO_2$: C, 63.57; H, 6.68, found: C 63.02; H, 6.78%.

GC analysis: 39.3 min (*R*); 40.3 min (*S*) [50 m G-PN (Astec), 122 °C, H_2 (2.0 bar)].

8.3.3. Menthyl α-chloro-β-(p-tolyl)propionate diastereomers

Colorless solid. Melting point: 71–73 °C. ^{1}H NMR ($CDCl_3$): δ 7.12–7.07 (m, 4H, ArH); 4.65 (dt, J = 10.9 Hz, J = 4.4 Hz, 1H, menthyl); 4.37 (dd, J = 8.3 Hz, J = 7.0 Hz, 1H, CH); 3.31 (dd, J = 13.8 Hz, J = 8.3 Hz, 1H, CH_AH_B); 3.12 (dd, J = 13.8 Hz, J = 7.0 Hz, 1H, CH_AH_B); 2.32 (s, 3H, $ArCH_3$); 0.58–2.01 (m, 18H, menthyl). IR (KBr): 1740 cm^{-1} (C=O). MS (EI, 70 eV): m/e = 336.2 (1, M^+); 300.2 (33); 161.9 (80); 139.0 (32); 83.0 (100). Anal. calcd. for $C_{20}H_{29}ClO_2$: C, 71.29; H, 8.69; found: C, 69.81; H, 8.36%.

GC analysis: 21.4 min; 21.7 min [60 m DB1 (J.u.W.), 200 °C, H_2 (2.0 bar)].

8.3.4. α-Chloro-β-(p-tolyl)propionitrile

Colorless liquid. Boiling point: 110 °C/5 mmHg. ^{1}H NMR ($CDCl_3$): δ 7.17 (s, 4H, ArH); 4.53 (dd, J = 7.6 Hz, J = 7.0 Hz, 1H, CH); 3.27 (d, J = 7.6 Hz, 1H, CH_AH_B); 3.26 (d, J = 7.0 Hz, 1H, CH_AH_B); 2.35 (s, 3H, $ArCH_3$). IR (film): 2220 cm^{-1} (C≡N). MS (EI, 70 eV): m/e = 178.9 (35, M^+); 143.9 (9); 104.9 (100). Anal. calcd. for $C_{10}H_{10}ClN$: C, 66.85; H, 5.62; N, 7.80; found: C, 66.76; H, 5.64; N, 8.87%.

GC analysis: 22.0 min; 22.6 min [25 m Chirasil-DEX CB (Chrompack), 125 °C, He (1.2 bar)].

8.3.5. Methyl α-chloro-β-(p-tolyl)butyrate and methyl α-(p-tolyl)-β-chlorobutyrate

Colorless liquid. Boiling point; 115 °C/5 mmHg. ^{1}H NMR ($CDCl_3$): since four diastereomers were present

in the product mixture each resonance occurred as four superimposing signals. The determination of coupling constants was not possible. δ 7.27–7.07 (4dd, 4H, ArH); 4.40–4.30 (4s, 1H, C**H**COOCH$_3$); 3.80–3.55 (4s, 3H, COOCH$_3$); 3.42–3.27 (4dq, 1H, C**H**CH$_3$); 2.36–2.28 (4s, 3H, ArCH$_3$); 1.64–1.26 (4d, 3H, CHC**H**$_3$). IR (film): 1750 cm^{-1} (C=O). MS (EI, 70 eV): m/e = 226.0 (9, M$^+$); 190.0 (23); 118.9 (100). Anal. calcd. for $C_{12}H_{15}ClO_2$: C, 63.57; H, 6.68; found: C, 63.80; H, 6.87%.

GC analysis: 13.7 min; 13.8 min; 14.1 min; 14.8 min [60 m DB1 (J.u.W.), 140 °C (5 min), then up to 180 °C at 2 °C min^{-1}, H_2 (1.5 bar)].

8.3.6. Methyl α-bromo-β-(p-tolyl)propionate

Slightly yellow liquid. Boiling point: 82 °C/10^{-3} mmHg. ^{1}H NMR (CDCl$_3$): δ 7.10 (s, 4H, ArH); 4.38 (dd, J = 8.4 Hz, J = 7.0 Hz, 1H, CH); 3.72 (s, 3H, COOCH$_3$); 3.42 (dd, J = 14.1 Hz, J = 8.4 Hz, 1H, C**H**$_A$H$_B$); 3.20 (dd, J = 14.1 Hz, J = 7.0 Hz, 1H, CH$_A$**H**$_B$); 2.32 (s, 3H, ArCH$_3$). IR (film): 1740 cm^{-1} (C=O). MS (EI, 70 eV): m/e = 256.0 (5, M$^+$); 176.9 (100); 144.9 (96); 116.9 (29); 104.9 (62). Anal. calcd. for $C_{11}H_{13}BrO_2$: C, 51.38; H, 5.11; found: C, 51.09; H, 5.20%.

GC analysis: 31.3 min; 32.6 min [20 m G-BP (Astec), 115 °C, H_2 (0.6 bar)].

8.3.7. Methyl α-chloro-β-(o-tolyl)propionate

Colorless liquid. Boiling point: 110 °C/5 mmHg. ^{1}H NMR (CDCl$_3$): δ 7.20–7.10 (m, 4H, ArH); 4.45 (dd, J = 7.7 Hz, J = 7.2 Hz, 1H, CH); 3.73 (s, 3H, COOCH$_3$); 3.39 (dd, J = 14.2 Hz, J = 7.2 Hz, 1H, C**H**$_A$H$_B$); 3.20 (dd, J = 14.2 Hz, J = 7.7 Hz, 1H, CH$_A$**H**$_B$) 2.35 (s, 3H, Ar–CH$_3$). IR (film): 1740 cm^{-1} (C=O). MS (EI, 70 eV): m/e = 211.9 (9, M$^+$); 176.9 (27); 175.9 (29); 160.8 (7); 144.8 (65); 104.9 (100). Anal. calcd. for $C_{11}H_{13}ClO_2$: C, 62.12; H, 6.17; found: C, 61.01; H, 6.16%.

GC analysis: 49.6 min (*R*); 51.5 min (*S*) [50 m G-PN (Astec), 110 °C, H_2 (2.0 bar)].

8.3.8. Methyl α-chloro-β-mesitylpropionate

Colorless liquid. Boiling point: 80 °C/10^{-3} mmHg. ^{1}H NMR (CDCl$_3$): δ 6.85 (s, 2H, ArH); 4.48 (dd, J = 8.5 Hz, J = 6.5 Hz, 1H, CH); 3.34 (dd, J = 14.3 Hz, J = 6.5 Hz, 1H, C**H**$_A$H$_B$); 3.30 (dd, J = 14.3 Hz, J = 8.5 Hz, 1H, CH$_A$**H**$_B$); 3.17 (s, 3H, COOCH$_3$); 2.32 (s, 6H, o-CH$_3$); 2.25 (s, 3H, p-CH$_3$). IR (film): 1735 cm^{-1} (C=O). MS (EI, 70 eV): m/e = 240.0 (13, M$^+$); 205.0 (3); 204.0 (3); 172.9 (12); 132.9 (100). Anal. calcd. for $C_{13}H_{17}ClO_2$: C, 65.12; H, 6.74; found: C, 64.28; H, 6.71%.

GC analysis: 141.4 min (*R*); 144.4 min (*S*) [50 m G-PN (Astec), 110 °C, H_2 (2.0 bar)].

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