Synthesis of Substituted Mandelic Acid Derivatives *via* Enantioselective Hydrogenation: Homogeneous versus Heterogeneous Catalysis

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Dedicated to Joe P. Richmond, the motor behind ASC, on the occasion of his 60th birthday.

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Abstract: An extensive screening of both homogeneous and heterogeneous catalysts was carried out for the enantioselective hydrogenation of *p*-chlorophenylglyoxylic acid derivatives. For *p*-chlorophenylglyoxylic amides only homogeneous Rh-diphosphine complexes gave satisfactory results, ees up to 87% were observed for the cy-oxo-pronop ligand. For methyl *p*-chlorophenylglyoxylate both a homogeneous as well as a heterogeneous catalyst performed with ees >90%. A Pt catalyst modified with cinchona derivatives achieved 93% ee for the *(R)*- and 87% ee for the *(S)*-methyl *p*-chloromandelate. A Ru-MeObiphep catalyst also reached 93% ee with TONs up to 4000 and TOFs up to 210 h^{-1}. For all catalytic systems the effects of the metal, the nature of the chiral auxiliary and the solvent as well as of the reaction conditions were investigated. The homogeneous process was scaled up to the kg scale and the enantiomeric purity of the product was enhanced to >99% ee by two recrystallizations of the free *p*-chlorophenylmandelic acid.

Keywords: cinchona alkaloids; enantioselective hydrogenation; α-keto esters; mandelamide derivatives; MeObiphep; platinum; ruthenium

Introduction

Specifically substituted mandelamides such as SX 623509 (**1**) (Fig. 1) constitute a new class of agrochemical fungicides, acting specifically against the oomycetes family of phytopathogenic fungi like *Phytophthora infestans* (potato late blight) and *Plasmopara viticola* (grape downy mildew).[1,2] There are indications in the literature that the two enantiomers of **1** do not contribute equally to the biological efficacy of the racemate.[2] To check this hypothesis novel concise approaches to enantiopure mandelamides were needed.

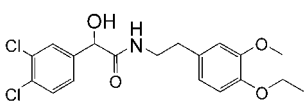

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Figure 1. SX 623509 (**1**), a fungicidally active mandelamide.

Of the several approaches possible, two were explored in more detail. The first is an enantioselective Passerini three-component condensation of a carbonyl compound, an isocyanide and a chiral carboxylic acid, leading directly to the desired amides. As a model reaction, aldehyde **2** and isocyanide **3** were transformed with good stereoselectivity to the chiral mandelamide **5** by using 1,2,3,4-tetra-*O*-acetyl-α-D-galacturonic acid (**4**) as chiral auxiliary (see Fig. 2).[3]

The second approach involves the enantioselective reduction of suitable α-keto acid derivatives as depicted in

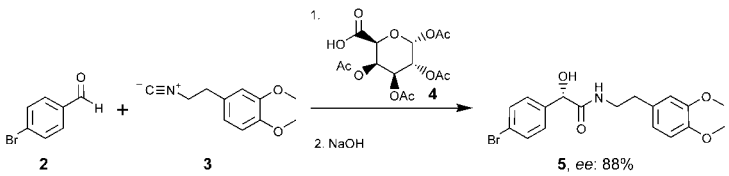

Figure 2. Substituted mandelamides via a Passerini three-component condensation.

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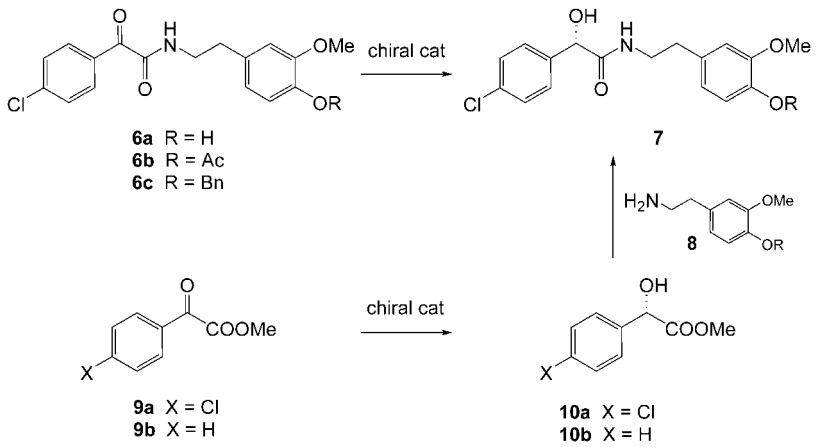

Figure 3. Pathways to substituted mandelic amides *via* enantioselective reduction of the corresponding phenylglyoxylic acid derivative.

Figure 3. Three catalytic methods described in the literature for the enantioselective hydrogenation of α-keto acid derivatives were investigated: Homogeneous hydrogenation,[4] homogeneous transfer hydrogenation[5] and hydrogenation with modified heterogeneous catalysts.[6]

In this contribution we describe our efforts to find a technically feasible access to the desired mandelic amides in >90% ee. We report screening results for the enantioselective reduction of methyl *p*-chlorophenylglyoxylate (**9**) and the analogous amide derivatives **6a–c** as well as the scale-up of the most effective method to the kg scale. Furthermore, the enrichment of the free *p*-chloromandelic acid from approximately 90% ee to >99% ee is described.

Results and Discussion

Some General Remarks

When developing a process for a new biologically active compound, there is usually a rather tight schedule since the time-to-market is a very important aspect. For the development chemists this means that he or she cannot spend too much time searching for the perfect process; rather it is important to be able to give "yes" or "no" answers within a defined time. In a recent concept paper[7] we described our approach in more detail. It is useful to divide the development of a manufacturing process into four different phases:

Phase 1: Outlining and assessing possible synthetic routes on paper.

Phase 2: Demonstrating the chemical feasibility of the key step, usually the enantioselective catalytic reaction.

Phase 3: Optimizing the key catalytic reaction.

Phase 4: Optimizing the over-all process.

Here we will focus on the Phase 2, demonstrating the feasibility of the key enantioselective catalytic step for the two routes sketched in Figure 3. In this context it is important to realize that four elements are critical for a timely result:

1. To have a suitable library of chiral ligands and/or auxiliaries as well as of soluble metal precursors and/or heterogeneous hydrogenation catalysts. There will be no time to procure or synthesize complex chiral structures.
2. To have access to modern laboratory equipment allowing very rapid screening of various catalytic systems preferably in parallel and with very small substrate samples.
3. To have very good analytical equipment (especially chiral GLC or HPLC).
4. Last but not least to have specialists with much hands-on-experience since finding enantioselective catalysts is still very much an empirical business where personal experience is the key to success.

Hydrogenation of Phenylglyoxylic Amides

The most elegant solution to the problem at hand would be the asymmetric reduction of the substituted amides **6**, which, at least in principle, could be prepared *via* Pd-catalyzed double carbonylation of the corresponding aryl bromide or iodide in presence of amines **8**. For this reason, much emphasis was put on investigating the enantioselective hydrogenation of the keto amides **6** with the aim to find a catalyst with >90% ee followed by further optimization for activity. There are only few but quite encouraging reports on the enantioselective hydrogenation of aryl α-keto amides. Chiba et al.[4b] obtained 96% ee for *N*-benzylglyoxylic amide, using Rubichep complexes (for ligand structures, see Fig. 4) while Rh-amidophosphine-phosphinite (ampp) catalysts were

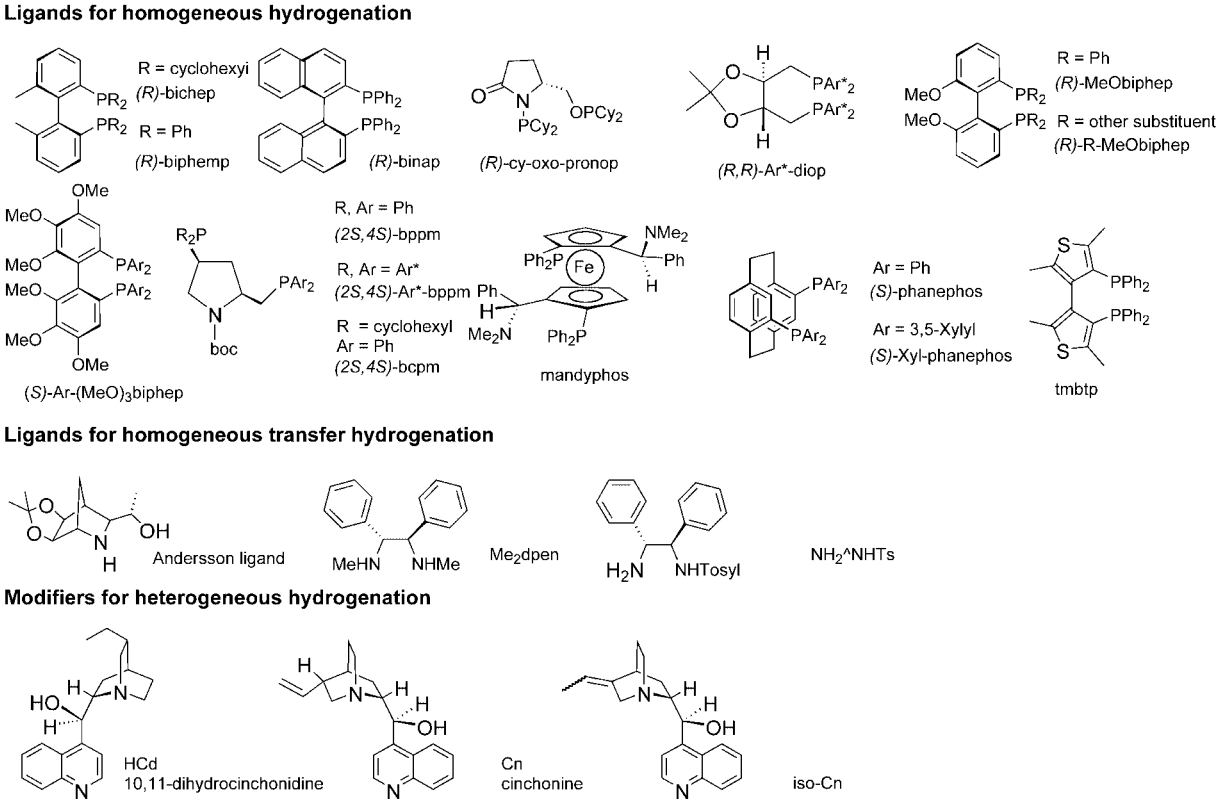

Figure 4. Structures of chiral ligands and modifiers listed in Tables 1–3.

reported to give 99% ee for the same substrate[4c] and 87% ee for the *p*-chloro derivative thereof.[4d] In all cases, rather low TONs (20–200) and TOFs of (3– $<100\ h^{-1}$) were achieved. The hydrogenation of aliphatic α-keto amides using a heterogeneous cinchona-modified Pt catalyst was reported to occur with ees below 60%.[6b]

Based on these literature precedents, we decided to screen the three keto amides **6a–c**, applying both Rh and Ru catalysts with a broad array of privileged, electron-rich ligands (e.g., of the type: MeObiphep, biphep, binap, duphos, josiphos, walphos, plus one available ampp). In total 80 experiments were carried out on a scale of 0.5 mmol substrate in 5 mL solvent (46 for **6a**, 25 for **6b**, and 9 for **6c**) and selected positive results are compiled in Table 1. The highest enantiomeric excess (87%, just short of the required 90% ee) was obtained for **6a** with an Rh catalyst generated *in situ* in dichloromethane from the neutral precursor $[Rh(nbd)Cl]_2$ and the ligand *(R)*-cy-oxo-pronop. However, the catalyst had a rather low activity, and at 40 °C full conversion could only be obtained with a substrate to catalyst ratio (s/c) of =100. In analogy with the results of Mortreux,[4d] we tentatively assigned the *(S)* configuration to the major product.

Except for **6b**, Rh complexes generally achieved better enantioselectivities than Ru complexes. Rh complexes of several ligand classes afforded ees >50% for

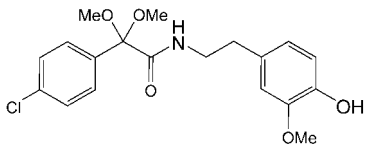

Figure 5. Structure of the byproduct formed in methanol.

all three substrates, but especially for **6a** incomplete conversions were observed even after a reaction time of >15 h. We thought that the free phenolic OH, which is able to coordinate to the metal center, might be responsible for this fact. This interpretation is at least partly supported by the higher conversions observed for **6b** and **6c**. The results with the Ru complexes of atropisomeric diphosphines (especially bichep) were rather disappointing and interestingly, Ru-phanephos (with planar chirality) gave the best results here. Of the solvents tested, dichloromethane was optimal for Rh catalysts while methanol (often requiring 1 N HCl as additive) was found to be the best for Ru catalysts. In the latter case, the formation of a by-product was observed which, based on ^1H NMR, is the α-amido-acetal **11** (Fig. 5), resulting from the acid-catalyzed addition of methanol to the keto group of the starting material.

A few experiments were carried out with cinchona-modified heterogeneous Pt catalysts as described by

Table 1. Screening results for the hydrogenation of **6a–c** (effect of metal, ligand, solvent, pressure, temperature).

Amide	Catalyst[a]	Solvent	*P/T* [bar/°C]	ee [%]	TON	TOF[b] [h^{-1}]	Abs. conf.	Comments[c]
6a	Rh-*(R)*-cy-oxo-pronop	CH_2Cl_2	20/40	87	100	5	*(R)*	BF_4 complex 32% ee
6a	Rh-*(2S,4S)*-bcpm	THF	10/20	74	100	5	*(S)*	in CH_2Cl_2 67% ee
6a	Rh-*(S)*-R-MeObiphep	CH_2Cl_2	20/40	65	100	5	*(S)*	R = cyclopentyl
6a	Ru-*(S)*-phanephos	MeOH	80/60	61	120[d]	8	*(R)*	60 μL HCl, bp 15%
6a	Ru-*(S)*-Ar-$(MeO)_3$biphep[e]	MeOH	80/60	57	115[d]	7	*(S)*	60 μL HCl, bp 10%
6a	Ru-*(S)*-*i*-Pr-MeObiphep	MeOH	80/60	55	55	3	*(S)*	400 μL HCl, bp 15%
6a	Rh-*(R)*-bichep	CH_2Cl_2	20/40	47	100	5	*(R)*	Ru complex 12% ee
6a	Rh-*(2S,4S)*-Ar*-bppm[f]	THF	10/20	47	89	5	*(S)*	
6a	Rh-*(R,R)*-Ar*-diop[f]	CH_2Cl_2	20/40	44	37	2	*(S)*	
6b	Ru-*(S)*-Xyl-phanephos	MeOH	80/60	67	100	6	*(R)*	at 30 °C ee 53%
6b	Rh-*(S)*-*i*-Pr-MeObiphep	CH_2Cl_2	20/40	62	96	5	*(S)*	
6b	Ru-*(R)*-bichep	MeOH	80/60	44	93	6	*(S)*	
6c	Rh-*(2S,4S)*-bcpm	THF	10/20	64	93	2	*(S)*	
6c	Rh-*(S)*-*i*-Pr-MeObiphep	CH_2Cl_2	20/40	54	95	2	*(S)*	
6c	Ru-*(S)*-phanephos	-[g]	80/60	53	100	2	*(R)*	
6c	Rh[h]-mandyphos	THF	60/25	40	25	1	*(R)*	

[a] Reaction conditions: s/c 100 (Rh catalysts: PP + $[Rh(nbd)Cl]_2$; Ru catalysts: PP + $[Ru(p\text{-cymene})I_2]_2$), 0.5 mmol **6**, 5 mL solvent
[b] TOF = TON/reaction time.
[c] μL HCl: addition of 1 N HCl, bp: byproduct (see text).
[d] s/c 200.
[e] Ar = 3,4,5-$(MeO)_3$-C_6H_2.
[f] Ar* = 3,5-*t*-Bu_2-4-MeO-C_6H_2.
[g] MeOH/CH_2Cl_2 (3/1).
[h] $[Rh(nbd)TFA]_2$.

Baiker[6b] for aliphatic α-keto amides but even with the best catalytic system, ees never exceeded 34%.

Hydrogenation of Methyl Phenylglyoxylates

The hydrogenation of aromatic α-keto ester derivatives has also been described in the literature.[4] For the parent compound methyl phenylglyoxylate (**9b**) enantioselectivities of >95% were reported for several catalytic systems. Chiba et al.[4b] achieved >99% ee for an Ru-bichep complex, Carpentier and Mortreux[4c] reached 95% ee using an Rh-ampp catalyst and Lemaire et al.[5b] claimed to have achieved 99% ee for an Rh-Me_2dpen-catalyzed transfer hydrogenation. In addition, a Pt catalyst modified with dihydrocinchonidine was reported to give 98% ee.[6c] For the hydrogenation of substrate **9b**, Mashima et al.[4e] obtained an ee of 93% with Ru-binap. In all cases, TON and TOF were too low to be of technical interest.

Based on these findings three catalyst systems were screened with **9a** as substrate: on the one hand homogeneous Ru complexes with various atropisomeric diphosphines and the Rh-Me_2dpen catalyst and on the other hand the heterogeneous Pt-cinchona system. For the homogeneous catalysts, relevant results are listed in Table 2, for the Pt-cinchona in Table 3. While the efficacies of the Ru-PP and the Pt-cinchona catalysts were confirmed, the Rh-catalyzed transfer hydrogenation could not be reproduced at all.

Homogeneous hydrogenation: The highest enantioselectivities (up to 94% ee, surpassing the target of >90% ee) were obtained with an Ru catalyst generated *in situ* from $[RuI_2(p\text{-cymene}]_2$ and MeObiphep. The observed absolute configuration is in agreement with those reported by Mashima et al[4e] but opposite to the correlation of Chiba et al.[4b] Other aryl derivatives of the MeO-biphep ligand family and atropisomeric ligands such as binap or TMBTP gave medium ees while alkyl-substituted MeObiphep ligands gave very poor results. For the Ru-MeObiphep catalyst, the addition of catalytic amounts 1 N HCl was essential both for good activity as well as for achieving ees >90%. Other acids, like HBF_4, HBr, H_3PO_4 or CF_3COOH gave lower ees and/or activities; racemic product was obtained in presence of Cs_2CO_3.

Homogeneous transfer hydrogenation of 9a and 9b: The results with the Rh-Me_2dpen hydrogen transfer catalysts and isopropyl alcohol as reducing agent were a (negative) surprise. Instead of the expected products **10a** or **10b** (results not shown), only the corresponding isopropyl phenylglyoxylate, i.e., the transesterified ketone, was obtained. Since a blank experiment without metal catalysts also afforded 90% of the same product, we suspect that the literature results might be based on a wrong assignment of the reaction product. With

Table 2. Screening results for the homogeneous hydrogenation of **9a** (effect of metal, ligand, reducing agent).

Catalyst[a, b]	**10a** [%]	ee [%]	s/c	TOF[c] [h^{-1}]	Conf.	Comments
Ru-*(R)*-MeObiphep[a]	99.5	94[d]	200	3	*(R)*	without HCl ee 66%
Ru-*(S)*-Tol-MeObiphep[a]	>99.5	93	200	12	*(S)*	at 30 °C 65% conv.
Ru-*(S)*-Ar-MeObiphep[a]	94–100	64–89	200	10–12	*(S)*	various aryl substituents on P
$[Ru_2Cl_4(R)\text{-binap})_2(NEt_3)(xylene)]$[a]	100	88	200	11	*(R)*	
Ru-*(R)*-biphemp[a]	98	87	200	11	*(R)*	
Ru-*(S)*-tmbtp[a]	100	62	200	10	*(S)*	
Rh-Me_2dpen[b]	<1	–	20		-	>90% *i*-Pr keto ester
Ru-Andersson ligand[b]	2–5	60	100	100	*(S)*	95% *i*-Pr hydroxy ester, ee 6%
Ru-NH_2NTs[b]	3	30	100	80	*(R)*	80% *i*-Pr hydroxy ester, ee 23%
Ru-NH_2NTs[e]	>99	32	100	5	*(R)*	

[a] 1.5 mmol **9a**; catalyst PP + $[Ru(p\text{-cymene})I_2]_2$, 10 mL MeOH, 60 μL 1 N HCl, 80 bar, 60 °C.
[b] Transfer hydrogenation: $[RuCl_2(p\text{-cymene})]_2$ + ligand or isolated complex, *i*-PrOH/KOH, r.t.
[c] TOF = TON/reaction time.
[d] At 30 °C.
[e] With HCOOH/NEt_3 5:2 in CH_2Cl_2.

Table 3. Screening results for the heterogeneous hydrogenation of **9a** (effect of solvent and modifier).

Solvent	Modifier	**9a** [g]	Solvent [mL]	Cat.[a] [mg]	ee [%]	Abs. conf.	Comments
Toluene[b]	HCd	0.1	1	10	90	*(R)*	in AcOH ee 76%
Toluene[b]	iso-Cn	0.1	1	10	85	*(S)*	in AcOH ee 71%
Toluene[a]	HCn	0.1	1	10	75	*(S)*	in AcOH ee 59%
Toluene/AcOH 1/1[b]	HCd	0.1	1	10	80	*(R)*	
Toluene/AcOH 1/1[b]	iso-Cn	0.1	1	10	73	*(S)*	with HCn 62%
Toluene[c]	iso-Cn	3	27	120	87	*(S)*	reaction time 45 min
Toluene[c]	iso-Cn	3	27	60[d]	67	*(S)*	at 5 bar ee 36%
Toluene[c]	HCd	15	135	600	93	*(R)*	reaction time 60 min

[a] 5% Pt/Al_2O_3 JM 94.
[b] Reaction conditions: 2 mg modifier, 60 bar, r.t., 30 min.
[c] Reaction conditions: modifier/catalyst 1/10 (w/w), 60 bar, 25 °C.
[d] Reaction time 180 min.

more active catalysts such as Ru-NH_2NHTs or with the exceedingly active Anderson ligand[5a] reduction was achieved but transesterification could still not be suppressed, and in addition, only ees of 23–60% (for **10a**) and 6–23% (for the isopropyl ester) were observed. When the reaction was performed with HCOOH/NEt_3 as reductant, **10a** was obtained in good yields but with only 32% ee.

Heterogeneous hydrogenation: From the literature,[6a] and our own experience, it is well known that only a few catalysts, modifier and solvent combinations are suitable for the heterogeneous enantioselective hydrogenation of α-keto esters. Based on our vast experience with this catalyst system we chose AcOH and toluene as solvents and screened a limited number of cinchona alkaloids using a Pt catalyst from Johnson Matthey (JM 94). The most important results are listed in Table 3. Furthermore, 12 synthetic modifiers from the group of Pfaltz[6d] were screened, but all of them showed lower ees than HCd and iso-Cn (results not shown).

Under these reaction conditions, full conversion was obtained. As expected, higher ees were obtained for dihydrocinchonidine (HCd) forming preferentially the *(R)*-product than for the pseudo-enantiomeric cinchonine (Cn) derivatives where an excess of *(S)*-hydroxy ester was produced. In this case, a newly discovered isomeric cinchona derivative (iso-Cn)[6d] gave the highest ees. As observed for aromatic ketones,[6a] toluene gave better results than AcOH (the solvent of choice for aliphatic analogs). To our disappointment, we could not reproduce the 98% ee claimed by the group of Bartók[6c] for the hydrogenation of **9b** in a mixture of AcOH and toluene as solvent.

A brief optimization of the reaction conditions was carried out for iso-Cn in toluene. A maximum of 88% ee was reached at relatively low substrate concentrations (≤10%) and a catalyst/modifier ratio of 1/10 w/w. Lowering the temperature to 5–10 °C did not affect the enantioselectivity but led to very viscous reaction solutions which were difficult to stir. Lowering the cata-

lyst loading to 2% relative to substrate had a detrimental effect on both reaction time and ee, especially at 5 bar hydrogen pressure. Increasing the catalyst loading from 2% to 4% increased the initial rate from 0.8 to 6.6 mmol/min · $g_{catalyst}$, a clear indication of catalyst poisoning probably caused by impurities in the substrate. This observation confirms the experience that the Pt-cinchona system is quite sensitive to the quality of the starting material.[6e] A similar effect was observed with HCd where catalyst loading of 4% was needed to reach 93% ee of the (*R*)-enantiomer (i.e., the goal of >90% ee was also met with the heterogeneous system).

Preparative and Scale-Up Aspects

For the production of kg amounts of highly enriched *(S)*-*p*-chloromandelic acid we used the Ru-*(R)*-MeObiphep catalyst. Scale-up experiments showed that s/c up to 4,000 are feasible giving methyl 4-chloromandelate with 90–93% ee with TOFs up to 210 h^{-1}. Despite the fact that this hydrogenation was not fully optimized, the achieved catalyst performance (ee, TON, TOF) indicate that this hydrogenation might be feasible for the production of an agrochemical intermediate both from a technical and an economical point of view.

For the Pt-cinchona system, a scale-up from 100 mg to 15 g **9a** presented no problems. The non-optimized system with HCd showed 93% ee with an estimated TON of about 2000 and TOF of $\geq$2000 h^{-1} (assuming that all surface platinum atoms on the heterogeneous catalyst are active), indicating that the Pt-cinchona system might be a viable alternative for the production of the *(R)*-enantiomer.

Methyl *p*-chloromandelate **10a** should be crystalline (mp 36 °C) but an extensive screening of more than 10 solvents and combinations thereof covering a wide range of solvent properties showed no success: We therefore hydrolyzed the ester using 0.2 M NaOH and were able to crystallize the free acid from dibutyl ether without any problem. In two crystallizations, the ee increased from about 90 to >99% and 150 g of the free *p*-chloromandelic acid with 99.3% ee were produced. At this stage the project was terminated.

Conclusions

The enantioselective hydrogenation of phenyl glyoxylate esters is a technically feasible method to produce the corresponding mandelic acid derivatives with enantioselectivities >90%. Two catalytic systems were found for the specific case of methyl *p*-chlorophenylglyoxylate **9a**: A homogeneous Ru catalyst with the atropisomeric MeObiphep ligand achieved ees of 90–93% with TONs up to 4,000 and TOFs up to 210 h^{-1}. A heterogeneous Pt catalyst modified with dihydrocinchonidine gave up to 93% ee, albeit at rather high catalyst loadings. While the resulting mandelic ester could not be enriched further, the free acid was successfully recrystallized to give material of >99% ee.

Reproduction of several literature results proved to be difficult and, especially, the high enantioselectivity claimed for an Rh-diamine-catalyzed homogeneous transfer hydrogenation could not be confirmed. Also, despite some literature precedents it was not possible to find a suitable catalyst for the hydrogenation of several phenylglyoxylic amides. In all cases, the resulting ees were below the required 90% and in addition, catalyst activities were much too low.

Both for the homogeneous as well as the heterogeneous catalyst system the nature of the chiral auxiliary was the decisive factor. For the homogeneous system, both the choice of an Ru catalyst and of the use of methanol with traces of HCl were important factors, while for the heterogeneous catalyst the choice of toluene as solvent and the catalyst loading had a major effect on the catalyst performance.

Experimental Section

Materials

Substrates: Methyl phenylglyoxylates (**9a** and **9b**) were prepared according to standard Friedel–Crafts acylation procedures,[8,9] 4-chlorophenylglyoxylic acid amide (**6a**; mp 119–120 °C) was obtained from 4-chlorophenylglyoxylic acid[9] and 2-(4-hydroxy-3-methoxyphenethyl)amine[10] under standard peptide coupling conditions with the aid of Castro's reagent and Hünig's base. Subsequent acetylation with acetic anhydride and potassium carbonate or benzylation with benzyl chloride led to the amides **6b** (mp 131–133 °C) and **6c**, respectively.

Catalysts and chiral auxiliaries: 5% Pt/Al_2O_3 JMC 94[6a] (Johnson Matthey, pretreated for 2 h at 400 °C under hydrogen, dispersion ca. 0.25), $[Rh(nbd)Cl]_2$ (Degussa), $[Ru(p\text{-cymene})I_2]_2$ (OMG/Umicore), $[Ru(p\text{-cymene})Cl_2]_2$ (Strem).

Biphep derivatives and cy-oxo-pronop (Roche), binap, phanephos, NH_2NHTs (Strem), diop derivatives (Kanto Chemicals), bcpm, bppm derivatives (Fuji Chemical Industries), tmbtp (Chemi), Me_2dpen (Acros), all other ligands are available from Solvias. Cinchona alkaloids were either purchased from Fluka or prepared as described.[6d]

Analytics

Hydroxy ester 10a: ee determination: HP 1100, column Chiracel ODH, 0.46 × 25 cm, solvent 95% *n*-hexane, 5% isopropyl alcohol, flow 0.7 mL/min, detection at 220 nm. Retention times: **9a** 9.4 min, **10a** (*S*)-enantiomer 15.1 min, **10a** (*R*)-enantiomer 17.2 min.

Amides 7a–c: Conversion was determined by ^1H NMR; byproducts formed in MeOH were estimated by preparative thin layer chromatography (silica gel with dichloromethane/ethyl acetate 1/1). R_f values were as follows: Starting material **6a**/

6b): $R_f = 0.9/0.9$; product **7a**/**7ba**: $R_f = 0.4/0.3$; ee determination: HP 1100, column Chirapak AD, 0.46 × 25 cm, solvent 50% *n*-hexane, 50% isopropyl alcohol, flow 0.5 mL/min, detection at 210 nm. Retention times: **6a**: 12.0 min; **7a** enantiomer 1:8.4 min, **7a** enantiomer 2:11.1 min; **6b**: 17.5 min; **7b** enantiomer 1:14.4 min, **7b** enantiomer 2:21.7 min; **6c**: 16.6 min; **7c** enantiomer 1:10.2 min, **7c** enantiomer 2:17.7 min.

Procedures

Here we only describe the screening experiments, for a description of the preparative experiments (hydrogenation, hydrolysis and recrystallization) see Supporting Information.

Homogeneous hydrogenation: *Standard procedure.* Two solutions, prepared under argon atmosphere (a) catalyst and (b) substrate, were transferred under argon with a cannula to an autoclave. After purging, the desired hydrogen pressure was applied and the autoclave heated to the desired temperature. After a defined time (usually 15–21 h) the reaction was stopped and conversion and ee of were determined.

Heterogeneous hydrogenation: All screening experiments were carried out in 3-mL glass vials with magnetic stirring, placed in a steel autoclave (4 per 50 mL autoclave). After purging, the desired hydrogen pressure was applied and the reaction started. After 30 minutes the reaction was stopped and conversion and ee were determined.

Transfer hydrogenation: *Reducing agent* i-*PrOH/*i-*PrOK*. The catalysts were either prepared *in situ* from the metal precursor and the ligand (*i*-PrOH, reaction time 1 h, room temperature) or an isolated complex was used.[11] The hydrogenation was carried out using 1 mmol of ketone in 10 mL of isopropyl alcohol in the presence of 0.06 mL of a 1 M solution of *i*-PrOK in *i*-PrOH. After 1 h stirring at room temperature, the reaction was quenched with 0.05 mL of acetic acid, the product extracted with 2 mL of ethyl acetate and the organic phase analyzed.

Reducing agent HCOOH/NEt$_3$: RuCl(*p*-cymene)(*R,R*-NH_2NHTs)] and 1 mmol of ketone were dissolved in 2 mL CH_2Cl_2, 1 mL of HCOOH/NEt_3 (5:2) was added and stirred for 16 h at room temperature. The reaction was quenched with saturated $NaHCO_3$ aqueous solution, extracted with 2 mL of ethyl acetate and the organic phase analyzed.

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