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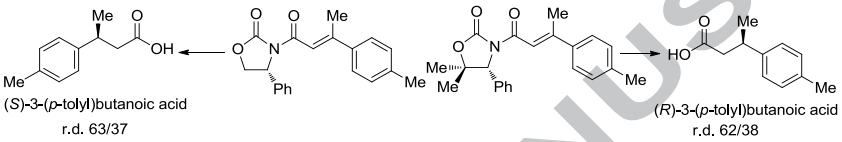
Jacqueline Jiménez,[a] Mildred López,[a] Vladimir Carranza,[b] Angel Mendoza,[b] Jenaro Varela,[c] Estibaliz Sansinenea[a], Aurelio Ortiz[a] *.

[a] *Facultad de Ciencias Químicas,* [b]*Instituto de Ciencias,* [c]*Centro de vinculación y transferencia de tecnología, Benemérita Universidad Autónoma de Puebla, Pue. 72570, México.*



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Diastereoselective hydrogenation of α,β-unsaturated but-2-enamides to access the chiral 3-(*p*-tolyl) butanoic acids.

Jacqueline Jiménez,[a] Mildred López,[a] Vladimir Carranza,[b] Angel Mendoza,[b] Jenaro Varela,[c] Estibaliz Sansinenea [a], Aurelio Ortiz [a] *

[a] *Facultad de Ciencias Químicas, Benemérita Universidad Autónoma de Puebla, Pue. 72570, México.*
[b] *Instituto de Ciencias, Benemérita Universidad Autónoma de Puebla, Pue. 72570, México.*
[c] *Centro de vinculación y transferencia de tecnología, Benemérita Universidad Autónoma de Puebla, Pue. 72570, México*

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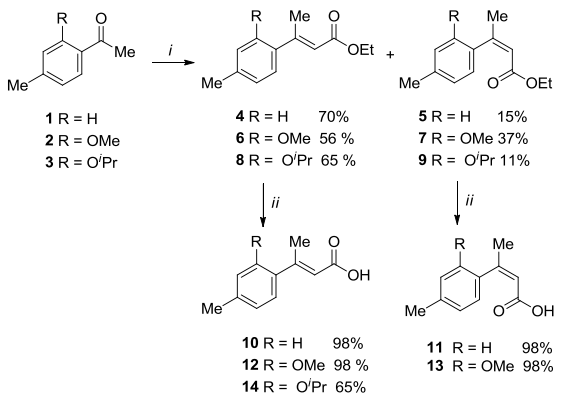
ABSTRACT

An alternative methodology for the synthesis of chiral 3- (*p*-tolyl) butanoic acids is presented. This was accomplished through the diastereoselective hydrogenation reaction of different chiral *N*-3-(*p*-tolyl) but-2-enamides, using Pd/C in EtOH, to produce the corresponding chiral *N*-3-(*p*-tolyl) butanamides with high chemical yields and moderate diastereomeric ratios. Removal of the chiral auxiliary from *N*-3-(*p*-tolyl) butanamides gave the respective enantiomerically pure acids.

* Corresponding author. Tel.: +00-52-222-2295500 ext 7518; fax: +00-52-222-2295584; e-mail: aurelioom@yahoo.com

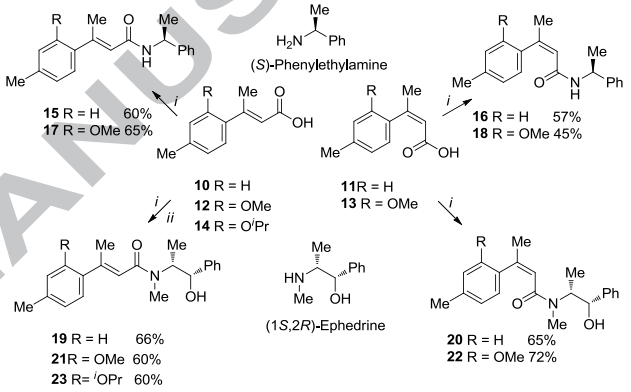
The asymmetric synthesis of 3-(*p*-tolyl) butanoic acid derivatives has been the subject of interest for many research groups. It is widely known that these compounds have been versatile chiral building blocks for the synthesis of bioactive aromatic sesquiterpenes and diterpenes[1]. There are different types of asymmetric methods for introduction of a stereogenic center in the benzylic position. Asymmetric hydrogenation of α,β-unsaturated carboxylic acid derivatives has been an efficient method for the obtaining of chiral 3-(*p*-tolyl)butanoic acid derivatives with high yields and high enantioselectivities.[2] However, the high economic or synthetic cost of most commercial chiral ligands, difficults their use. Organometallic reagents additions to α,β-unsaturated carboxylic acids attached to chiral auxiliaries have been another method described.[3] An enzymatic process such as, lipase-mediated kinetic resolution has furnished the enantiomerically enriched chiral 3-(*p*-tolyl)butanoic acids, although its disadvantage is that chemical yield does not exceed 50%.[4] The diastereoselective alkylation carried out in *N*-acetyloxazolidinone delivers chiral molecules that easily can be transformed to 3-(*p*-tolyl)butanoic acids.[5] Recently two organocatalytic methods have been described for the synthesis of 3-(*p*-tolyl) butanoic acid derivatives.[6] The aim of this work is to describe an alternative method for easy accessibility to chiral 3-(*p*-tolyl)butanoic acids. We described a diastereoselective hydrogenation reaction of different chiral *N*-3-(*p*-tolyl) but-2-enamides, using Pd/C in EtOH, to produce the corresponding chiral *N*-3-(*p*-tolyl) butanamides, where the (*S*)-phenylethylamine, (1*S*, 2*R*)-ephedrine and oxazolidinones act as chiral auxiliaries.

Our alternative method to the synthesis of chiral 3-(*p*-tolyl)butanoic acids, started with the protection of hydroxyl group of commercially available 2'-hydro-4'-methylacetophenone with MeI in the presence of KOH gave **2** with 95% yield[7a]. The protection of 2'-hydro-4'-methylacetophenone with 2-iodopropane and NaOH in DMF at 70 °C for 18 hours[7b] gave the compound **3** in 98 % yield. The acetophenones **1-3** were transformed to their respective ethyl 3-(*p*-tolyl)butanoates **4-9** using NaH and triethyl phosphonoacetate in THF to give the *trans*-isomers **4, 6** and **8** as the major products in 56-70 % yield and the *cis*-isomers **5, 7** and **9** in 11-37 % yield. The geometric isomers were separated by column chromatography using hexane: ethyl acetate (99:1) as eluent. A change in the stereoselectivity was observed when this reaction was carried out at reflux giving *trans*-isomer **6** (35%) and *cis*-isomer **7** (57%). The hydrolysis reaction of the ethyl 3-(*p*-tolyl)butanoates **4-7** was carried out with 0.5 N aq. NaOH in methanol at room temperature to give the carboxylic acids **10-13** with high yields after their purification by column chromatography using silica gel and hexane : ethyl acetate (8:2) as eluent[8]. The compound **8** was treated with KOH in DMF-H_2O at reflux for 15 hours to give the carboxylic acid **14** in 65% yield after its purification as above mentioned, as shown in Scheme 1.



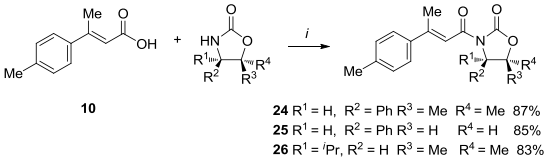
Scheme 1. *Reagents and conditions*. *i*) NaH, $(EtO)_2POCH_2CO_2Et$, THF, rt, 24 h; *ii*) 0.5N aq. NaOH, MeOH, rt, 12 h, 1M HCl pH 1; to **8**, KOH, DMF-H_2O, reflux, 15 h, 1M HCl.

The carboxylic acids **10-13** were linked to (*S*)-phenylethylamine, using *N, N´*-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) in DCM at room temperature for 16 hours to give the chiral *N*-3-(*p*-tolyl) but-2-enamides **15-18**, in 45%-65% isolated yield[3f]. On the other hand, these carboxylic acids **10-13** also were treated under the same reaction conditions in the presence of (1*S*,2*R*)-ephedrine to deliver the chiral *N*-3-(*p*-tolyl) but-2-enamides **19-22**, in 65%-72% yield. The chiral *N*-3-(*p*-tolyl) but-2-enamide **23** was accomplished via formation of its respective acyl chloride, treating the carboxylic acid **14** with oxalyl chloride and a catalytic amount of DMF at room temperature for 6 hours. Then, the acyl chloride was treated with (1*S*,2*R*)-ephedrine in the presence of Et_3N to afford the compound **23** in 60% yield[11], as shown in Scheme 2.



Scheme 2. *Reagents and conditions*. *i*) DCC, DAMP, DCM, 16h, rt; *ii*) to **23**, $Cl_2(CO)_2$, catalytic amount DMF, 6 h, rt, ephedrine, Et_3N, DCM, 12 h, rt.

Treatment of chiral oxazolidinones with *n*-butyllithium in THF at -78 °C for 30 minutes and subsequent addition of the corresponding acyl chloride (described above) and stirring for 18 hours gave the compounds **24-26** in 83-87% yield,[10] as shown in Scheme 3.



Scheme 3. *i*) *Reagents and conditions*. $Cl_2(CO)_2$, catalytic amount DMF, 6 h, rt, *n*BuLi, THF, -78 °C, 45 min., 18 h, rt.

The chiral *N*-3-(*p*-tolyl) but-2-enamides **15-26** were exposed to hydrogenation reaction conditions using a catalytic amount of Pd/C in EtOH at room temperature for 16 hours to deliver the chiral *N*-3-(*p*-tolyl) butanamides **27a-34b** in high yield (>98%) and with moderated diastereoselectivity (Tables 1 and 2). The hydrogenation reaction of **15-*E*** (Table 1, entry 1) afforded the chiral *N*-3-(*p*-tolyl) butanamides **27a** and **27b** in high yield and with a diastereomeric ratio of 70:30 (40% d.e.). Both products **27a** and **27b** were isolated by column chromatography using hexane/AcOEt (8:2), where the isomer **27a** was the major product. The configuration at newly formed stereogenic center is (*R*) for compound **27a** as established by X-ray analysis[11] (Fig. 1). Hydrogenation reaction of **16-*Z*** (Table 2, entry 1) proceeded similarly giving the compounds **27a** and **27b** in high yield and with the same diastereomeric ratio of 70:30 (40% d.e.). Surprisingly the compound **27a** was also the major product. For this case the stereoselectivity was unalterable by change in the geometry of alkenes (**15-*E***, to **16-*Z***).

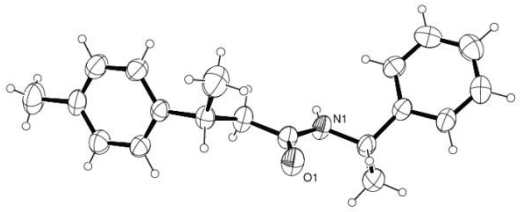


Figure 1. Molecular structure of the chiral *N*-3-(*p*-tolyl) butanamide **27a**.

Hydrogenation reaction of **21-*E*** (Table 1, entry 4), under the same reaction conditions described above, gave the chiral *N*-3-(*p*-tolyl) butanamides **30a** and **30b** in (>98% yield) and with a diastereomeric ratio of 70:30 (40% d.e.). The compound **30a** (*R* configuration) was the mayor product. This was established by X-ray analysis of **30b** where the configuration at the newly formed stereogenic center is (*S*)[12] (Fig. 2). The hydrogenation for **22-*Z*** (Table 2, entry 4) gave the compounds **30a** and **30b** in high yield and with an opposite diastereomeric ratio of 40:60 (20% d.e.). In this reaction, the compound **30b** (*S* configuration) was the mayor product.

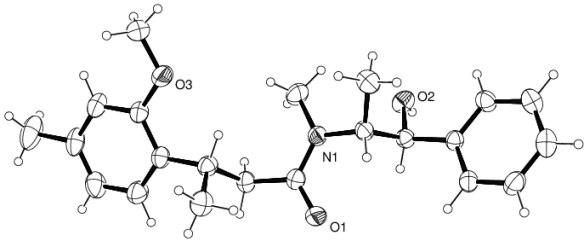


Figure 2. Molecular structure of the chiral saturated butanamide **30b**.

Hydrogenation of **17-*E***, **18-*Z***, **19-*E*** (Table 1, entries 2 and 3, Table 2, entry 2) and **23-*E*** (Table 1, entry 5) were carried out under the same reaction conditions to produce the corresponding chiral *N*-3-(*p*-tolyl) butanamides in high yields and with poor diastereoselectivity. The hydrogenation of **17-*E*** (Table 1, entry 2) and **18-*Z*** (Table 2, entry 2) delivered *N*-3-(*p*-tolyl) butanamides **28a**, **b** 44:56 (12% d.e.) and **28a**, **b** 47:53 (6% d.e.) respectively. The relative configuration at newly formed stereogenic center for compound **28a** was confirmed unambiguously as (*S*) via single crystal X-ray analysis[13] (Fig. 3).

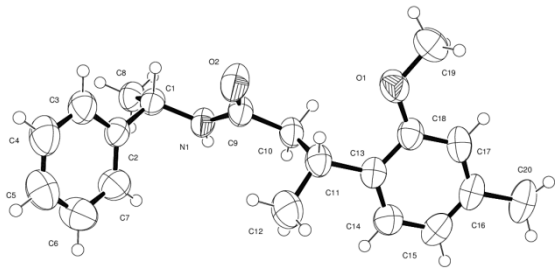
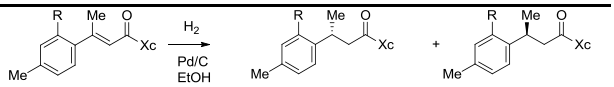
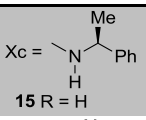
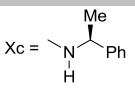
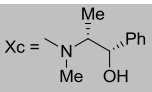
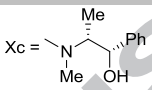
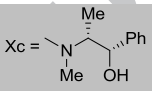
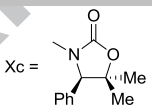
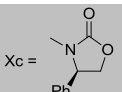
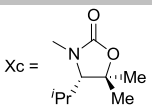


Figure 3. Molecular structure of the *N*-3-(*p*-tolyl) butanamide **28a**.

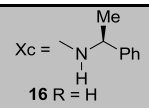
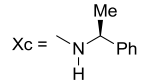
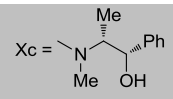
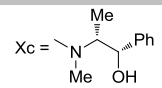
Hydrogenation of **19-*E*** (Table 1, entry 3) and **20-*Z*** (Table 2, entry 3) gave an inseparable mixture of butanamides **29a** and **29b** in high yield (>98%) and with no diastereoselectivity, for **19-*E*** 53:47 (6% d.e.) and for **20-*Z*** 60:40 (20% d.e.). The configuration of the new stereogenic center of the mayor product **29a** was established via comparison of the chemical shifts in the ^{1}H-NMR spectra of compounds **30a** and **30b**. An isopropyl group was placed in the aromatic ring in order to observe any change in the diastereomeric ratio of the hydrogenation; however, hydrogenation of **23-*E*** (Table 1, entry 5) gave the *N*-3-(*p*-tolyl) butanamides **31a** and **31b** in high yield and with a poor diastereoselectivity, compared to the *N*-3-(*p*-tolyl) butanamides **30a** and **30b**.

Table 1. Diastereoselective hydrogenation of chiral (*E*)- *N*-3-(*p*-tolyl) but-2-enamides.

Entry			
1	 **15** R = H	**27a** (70)[a]	**27b** (30)[a]
2	 **17** R = OMe	**28a** (44)	**28b** (56)
3	 **19** R = H	**29a** (53)	**29b** (47)
4	 **21** R = OMe	**30a** (70)	**30b** (30)
5	 **23** R = O^{i}Pr	**31a** (50)	**31b** (50)
6	 **24** R = H	**32a** (62)	**32b** (38)
7	 **25** R = H	**33a** (37)	**33b** (63)
8	 **26** R = H	**34a** (33)	**34b** (67)

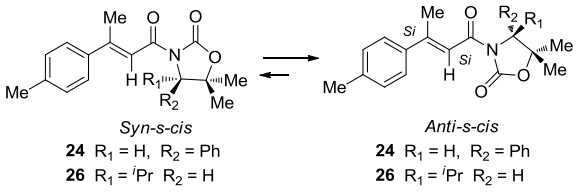
[a] diastereomeric ratios were determined by ^{1}H NMR on crude of reaction

Table 2. Diastereoselective hydrogenation of chiral (*Z*)- *N*-3-(*p*-tolyl) but-2-enamides

Entry			
1	Xc =  **16** R = H	**27a** (70)[a]	**27b** (30)[a]
2	Xc =  **18** R = OMe	**28a** (47)	**28b** (53)
3	Xc =  **20** R = H	**29a** (60)	**29b** (40)
4	Xc =  **22** R = OMe	**30a** (40)	**30b** (60)

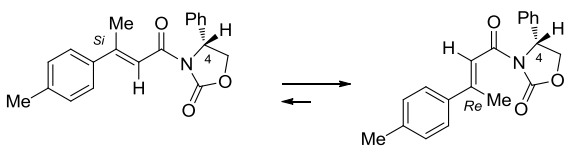
[a] diastereomeric ratios were determined by ^{1}H NMR on crude of reaction

Hydrogenation reaction of *N*-3-(*p*-tolyl)butenoyl oxazolidinones **24-26** was carried out under the same reaction conditions with a catalytic amount of Pd/C in EtOH at room temperature for 16 hours to deliver the chiral *N*-3-(*p*-tolyl)butanoyl oxazolidinones **32a**-**34b** in high yield (>98%) and with a moderated diastereoselectivity. The compound **24-*E*** (Table 1, entry 6) gave the products **32a** and **32b** with a diastereomeric ratio of 62:38 (24% d.e.) The configuration of new stereogenic center of the mayor product **32a** is (*R*). Although both chiral oxazolidinone moieties within **24-*E*** and **25-*E*** have the same phenyl substituent group and the same configuration at C(4), an unexpected result was observed for hydrogenation of compound **25-*E*** (Table 1, entry *7*), which gave the products **33a**-(*R*) and **33b**-(*S*) as white solids in high yield (>98%) and with a diastereomeric ratio of 37:63 (26% d.e.). Hydrogenation of **25-*E*** gave the product **33b**-(*S*) as mayor compound, therefore the gem-dimethyl groups at C(5) within the oxazolidinone structure in **25-*E*** have an important role in the stereocontrol of the hydrogenation.[14] The compound **26-*E*** (Table 1, entry 8) afforded the products **34a**-(*R*) and **34b**-(*S*) in high yield and with a diastereomeric ratio of 33:67 (34% d.e.) The mayor product is the compound **34b**-(*S*). The stereoselectivity of the major products **32a**-(*R*) and **34b**-(*S*) can be rationalized by the conformational preference of *anti-s-cis* rotamers,[15] where hydrogenation of **24-*E*** is carried out in the *Si*-face, which is opposite to the phenyl group substituent at C4. Hydrogenation for ***26-E*** was carried out in the *Re*-face, which is opposite side to the isopropyl group substituent at C4, as shown in Scheme 4.



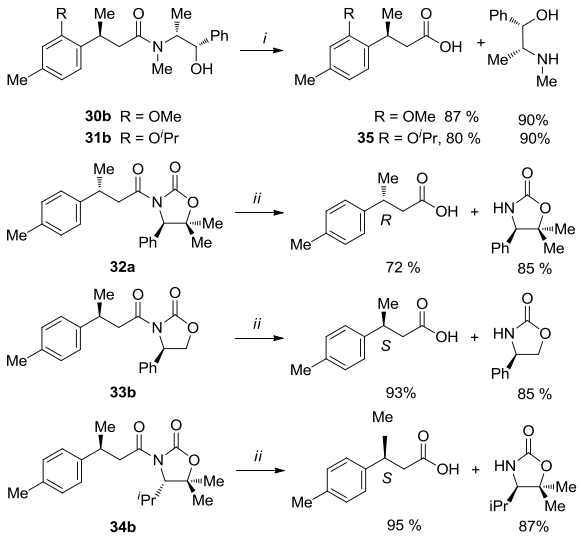
Scheme 4. Conformers of **24-*E*** and **26-*E***.

Hydrogenation of **25-*E*** can be rationalized by the conformational preference of *anti-s-trans* rotamer, where its hydrogenation is carried out in the *Re*-face, which is opposite to the phenyl group substituent at C4, as shown in Scheme 5.



Scheme 5. Conformers of **25-*E*.**

The chiral auxiliary ephedrine was removal from **30b** and **31b** under acid hydrolysis conditions described by Myers.[11] Compound **30b** was treated with 9N aq. H_2SO_4 solution/dioxane 1/1, reflux for 6 hours and a subsequent addition of saturated aq. NaOH solution for the extraction of ephedrine and addition of 3M aq. HCl solution to give the known (*S*)-3-(2-methoxy-4-methylphenyl) butanoic acid[4b,4d] in 87% yield, $[\alpha]^{20}_D$ = +16.6 (*c* 2, $CHCl_3$). To avoid degradation of compound **31b**, it was treated with 4N aq. H_2SO_4 solution /dioxane 1/1, reflux for 4 hours and subsequent addition of saturated aq. NaOH solution for the extraction of ephedrine and addition of 3M aq. HCl solution to give the new (*S*)-3-(2-isopropyl-4-methylphenyl) butanoic acid **35** in 80% yield, which its absolute configuration was assigned by comparison with the carboxylic acid above described, $[\alpha]^{25}_D$ = +10.4 (*c* 0.94, $CHCl_3$). On the other hand, the compounds **32a**, **33b**, and **34b** were treated under hydrolysis conditions described by Evans,[16] using LiOH, H_2O_2 in THF/H_2O at 0 °C for 2 hours to furnish the known (*R*)-3-(*p*-tolyl)butanoic acid in 72% yield, $[\alpha]^{25}_D$ = -36.4 (*c* 1.92, $CHCl_3$), lit. $[\alpha]^{25}_D$ = -31.1 (*c* 3.1, $CHCl_3$)[5a], and (*S*)-3-(*p*-tolyl)butanoic acids in 93% and 95% respectively, $[\alpha]^{25}_D$ = +34.8 (*c* 1.92, $CHCl_3$), lit. $[\alpha]^{25}_D$ = +34.2 (*c* 1.92, $CHCl_3$).[4b,4c] The recovery of the chiral auxiliaries oxazolinedines and ephedrine was in high yield 85% to 90%, as shown in Scheme 6.



Scheme 6. *Reagents and conditions*: *i*) **30b**, 9N aq. H_2SO_4 soln. dioxane, reflux 6h, NaOH soln. pH 10, HCl pH 1. **31b**, 4.0 N aq. H_2SO_4 soln. dioxane, reflux 4h, NaOH soln. pH 10, HCl pH 1. *ii*) LiOH, H_2O_2 30%, THF/H_2O, 0 °C to rt, 2h, HCl soln. pH 1.

We realized a study of the hydrogenation reaction of *N*-3-(*p*-tolyl) but-2-enamides carring (*S*)-phenylethylamine, (1*S*,2*R*)-ephedrine and oxazolidinones as chiral auxiliaries. (*S*)-phenylethylamine produced the highest diastereoselectivity (40% d.e.); however, its removal from chiral *N*-3-(*p*-tolyl) butanamides, under soft reaction conditions was not possible. Hydrogenation of both geometric isomers (*Z*)-*N*-3-(*p*-tolyl) but-2-enamides or (*E*)- *N*-3-(*p*-tolyl) but-2-enamides joined to (*S*)-phenylethylamine or (1*S*,2*R*)-ephedrine gave the same diastereoselectivity. The best reaction conditions to achieve chiral 3-(*p*-tolyl)butanoic acids are those in which the oxazolidinones were used as chiral auxiliaries. Hydrogenation of their *Z*-*N*-3-(*p*-tolyl) but-2-enamides produced the chiral *N*-3-

(*p*-tolyl) butanamides in high yield > 98 % and with moderated diastereoselectivity. This methodology has the advantage that the products were crystalline and easy to separate by column chromatography. In addition, mild reaction conditions were used to remove the oxazolidinone moiety.

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References and notes

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Highlights

- Alternative methodology for the synthesis of chiral 3- (p-tolyl) butanoic acids is described
- Diastereoselective hydrogenation reaction
- Easy removal of chiral auxiliaries.