EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Organocatalytic enantioselective decarboxylative protonation reaction of Meldrum's acid derivatives under PTC conditions

Authors: Fabien Legros, Thomas Martzel, Jean-François Brière, Sylvain Oudeyer, and Vincent Levacher

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201800331

Link to VoR: http://dx.doi.org/10.1002/ejoc.201800331

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

WILEY-VCH

FULL PAPER

Organocatalytic enantioselective decarboxylative protonation reaction of Meldrum's acid derivatives under PTC conditions

Fabien Legros,[a] Thomas Martzel,[a] Jean-François Brière,[a] Sylvain Oudeyer[a]* and Vincent Levacher[a]

Dedication ((optional))

Abstract: An original organocatalyzed enantioselective protonation sequence of transient quaternary ammonium enolate species was developed starting from readily available disubstituted Meldrum's acid derivatives and phenols. Chiral non-racemic 2-aryl propionic ester derivatives were obtained in good isolated yields and up to 70% *ee* under PTC conditions. The usefulness of the reaction was demonstrated in the course of the synthesis of enantioenriched (*S*)-ibuprofen.

Introduction

Enantioselective protonation (EP) of enolates for accessing enantiomerically enriched α,α-disubstituted carbonyl compounds remains a challenging area of research due to the difficulty of introducing the smallest element of the periodic classification in a stereocontrolled manner. Nevertheless, this methodology gives access to ubiquitous enantiomerically enriched α,α-disubstituted carbonyl motifs and, consequently, several research groups have developed elegant and efficient strategies based on either enzymatic, organometallic or organocatalytic approaches over the years.[1] The usefulness of such strategies has been demonstrated during the course of the total synthesis of natural products such as (*S*)-α-Damascone,[2] or homoisoflavones isolated from *Chlorophytum Inornatum* and *Scilla Nervosa*[3] together with drugs derived from 2-aryl propionic acid such as (*S*)-Naproxen.[4] The later architecture is of particular interest due to its wide range of biological properties.[5] Thus, organocatalyzed EP reaction is a synthetic approach of choice for the 2-aryl propionic acid derivatives despite the catalytic formation of transient acyclic ketene enolate for which the complete control of the configuration remains challenging.[6] Several organocatalytic EP approaches were developed providing highly reactive non-cyclic intermediates (Figure 1a). From an historical point of view, enantioselective decarboxylative protonation of alkyl aryl substituted malonic or hemi-malonic acids was first tackled (Figure 1a, upper part).[7] These approaches suffered from a lack of enantioselectivity (*ees* below 40%) and generally required the use of stoichiometric amount of a chiral base. Several years later, the two steps 1,2-addition-protonation sequence of protic nucleophiles such as phenol or benzhydrol derivatives to ketenes was developed. Using either Brønsted or Lewis base catalysts provided 2-aryl propionic acid derivatives in high yields and enantioselectivities up to 95% (Figure 1a, left part).[8] Nevertheless, the use of reactive ketene precursors, that are by nature quite unstable, limit the attractiveness of this approach.

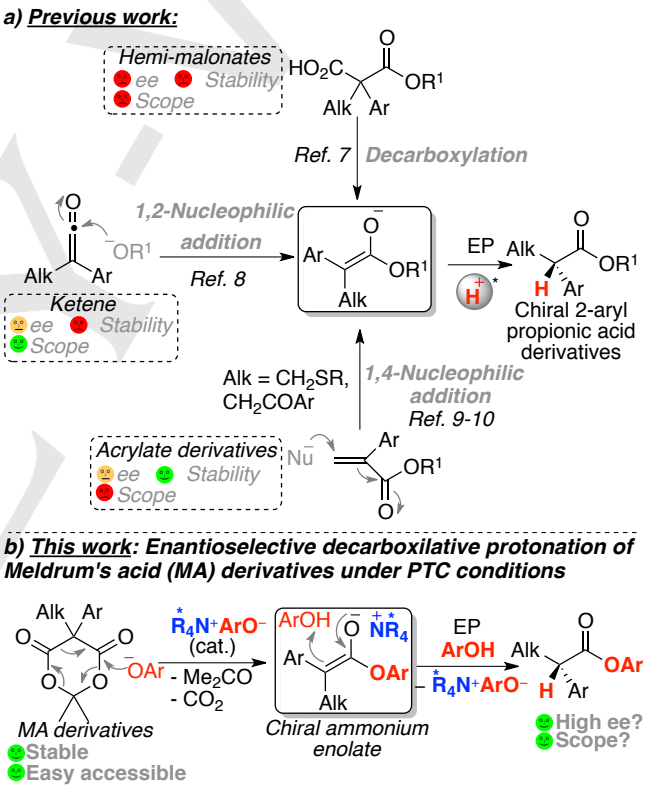


Figure 1. Context of this work.

Lastly, the domino 1,4-addition-protonation sequence of thiol [9] or aldehydes[10] (under the form of Breslow intermediate) nucleophiles to α-aryl acrylates furnished the corresponding products in modest to high enantioselectivities by implementing Brønsted base or NHC organocatalysts respectively (Figure 1a, lower part). Noteworthy, the major limitation relies on the lack of reactivity of α-aryl acrylates derivatives which requires the use of a strong nucleophile such as benzenethiol or Breslow intermediate thus hampering the scope of this approach. In this context, the development of an enantioselective and more general protonation approach for the synthesis of a large array of

[a] F. Legros, T. Martzel, J.-F. Brière, S. Oudeyer* and V. Levacher
Normandie Université, Université de Rouen, INSA Rouen, CNRS, COBRA, 76000 Rouen, France
E-mail: sylvain.oudeyer@univ-rouen.fr
http://www.lab-cobra.fr/thematique/lorganocatalyse

Supporting information for this article is given via a link at the end of the document.

scope of 2-aryl propionic acid derivatives using stable and readily accessible substrates is still of particular interest.

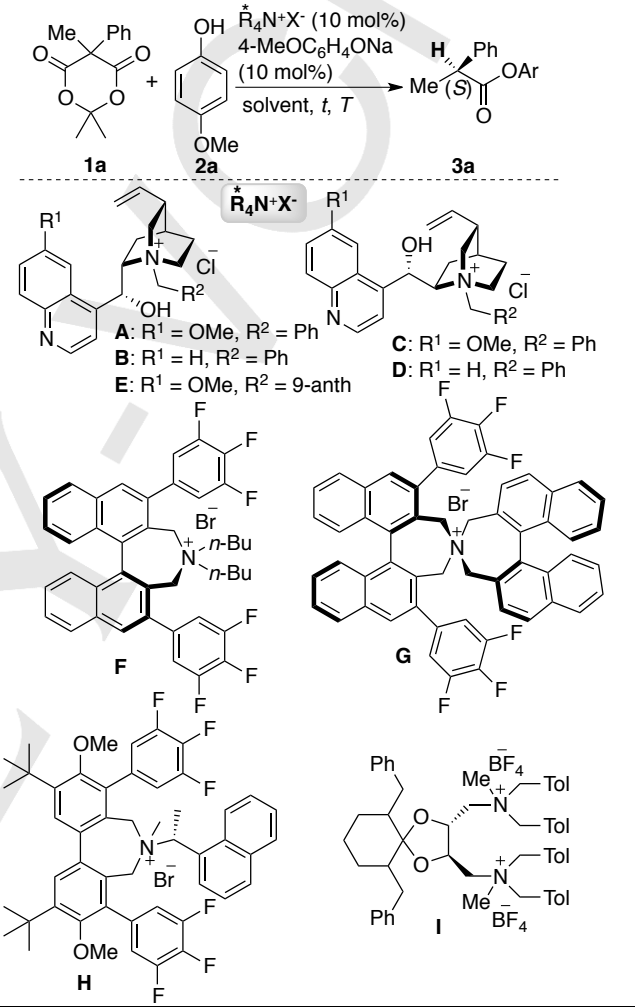
Meldrum's acid (MA) has emerged as a readily available, bench stable and versatile building block in organocatalysis.[11] In line with our recent work dealing with the synthesis and applications of chiral ammonium aryloxides (R_4^*NOAr)[12] as cooperative ion pairs organocatalysts,[13] we reasoned that aryloxides could add to non-symmetrical 5,5-disubstituded MA derivatives in order to trigger a domino fragmentation-decarboxylation-EP sequence to afford enantioenriched 2-aryl propionic derivatives. In the presence of stoichiometric amount of phenol, the key enantioselective protonation of a transient chiral quaternary ammonium enolate[14, 13a] occurs along with the regeneration of the catalytically active R^*_4NOAr species (Figure 1b). Although mono-substituted MA derivatives have been already used as nucleophiles in enantioselective organocatalytic protonation reaction,[15],[16] Worthy of note, the 5,5-disubstituted MA derivatives with two different substituents remain unexplored in organocatalytic processes, and this despite opportunity afforded by the markedly electrophilic properties of their carbonyl functional groups.[11] To the best of our knowledge, a single example described the enantioselective desymmetrisation of 5,5-disubstitued MA by means of the nucleophilic addition of a stoichiometric amount of chiral ammonium alkoxides to form chiral hemi-malonate derivatives with fair level of enantioselectivity up to 51%.[17]

Results and Discussion

At the onset, we studied the addition of 4-methoxyphenol **2a** to MA derivatives **1a** in the presence of 10 mol% of quaternary ammonium halide ($R^*_4N^+X^-$) and 10 mol% of sodium 4-methoxyphenoxide in THF at -20 °C for 24 h. We sought thereby to firstly generate *in situ* the required chiral ammonium phenoxide through an ion metathesis event thus avoiding its tedious and time-consuming preparation (Table 1).

Several catalysts derived from *Cinchona* alkaloids were screened under these conditions but unfortunately low yields and almost racemic mixtures of ester **3a** were obtained (entries 1-5). We thus turned our attention to the 2nd generation of Maruoka's catalyst **F** (5 mol%) for which a promising 46% *ee* could be reached albeit in a poor 10% NMR yield providing that the reaction was performed at room temperature (entries 6-7). We observed that the yields gradually increased with the temperature without any loss of the *ee* allowing to reach 47% NMR yield and 45% *ee* at 50 °C (entries 8-9). The reaction time was increased to 48 h furnishing the product **3a** in 66% NMR yield (54% isolated yield) and 43% *ee* (entry 10). Among other catalysts such as tartrate-derived catalyst **I** (entry 13) or axially chiral ammonium salts **G** and **H** (entries 11-12), the Lygo's catalyst **H** allowed to reach a 49% *ee* along with a 62% NMR yield. Having in hands two suitable catalysts (entries 10 and 12), we studied the influence of the solvent using commercially available Maruoka's catalyst **F** (entries 14-17). Whereas polar aprotic solvents such as ACN led to a better yield, the product was obtained in a racemic form (entry 14). Less polar solvents such as toluene provided decent NMR yield but at the expense of the *ee*, which dropped to 22%. Finally, moving to other ethereal solvents raised the enantioselectivity up to 54% *ee* in CPME but in low NMR yield of around 20% (entries 16-17).

Table 1. Initial attempts for the addition of 4-methoxyphenoxide **2a** to Meldrum's acid derivative **3a**.[a]



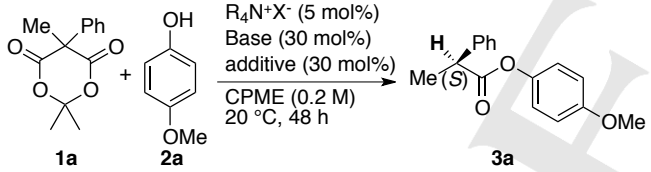
entry	solvent	R*$_4$NX	*t* (h)	*T* (°C)	NMR yield (%)[b]	ee (%)[c]
1	THF	**A**	24	-20	19	14
2	THF	**B**	24	-20	9	6
3	THF	**C**	24	-20	18	5
4	THF	**D**	24	-20	17	1
5	THF	**E**	24	-20	14	16
6	THF	**F**[d]	24	-20	3	-
7	THF	**F**[d]	24	rt	10	46
8	THF	**F**[d]	24	30	23	45

9	THF	**F**[d]	24	50	47	45
10	THF	**F**[d]	48	50	66	43
11	THF	**G**[d]	48	50	52	0
12	THF	**H**[d]	48	50	62	49
13	THF	**I**[d]	48	50	56	4
14	ACN	**F**[d]	48	50	86	0
15	toluene	**F**[d]	48	50	68	22
16	dioxane	**F**[d]	48	50	21	51
17	CPME	**F**[d]	48	50	23[e]	54

[a] The reaction was performed on 0.2 mmol scale using 1 equivalent of **1a** and **2a**. [b] Yield determined by NMR using Bn_2O as internal standard. [c] Measured by HPLC equipped with column containing chiral stationary phase. The absolute configurations were established by comparison with literature data (see supporting information). [d] 5 mol% of catalyst was used. [e] 16% isolated yield.

Then, we moved to a solid-liquid phase transfer (PT) catalysis starting from 4-methoxyphenol **2a** in the presence of a mineral base in order to secure a more convenient generation of the phenoxide species by deprotonation (Table 2).

Table 2. Optimization of the PT catalyzed addition of 4-methoxyphenoxide to Meldrum's acid derivative **3a**.[a]



1a **2a** **3a**

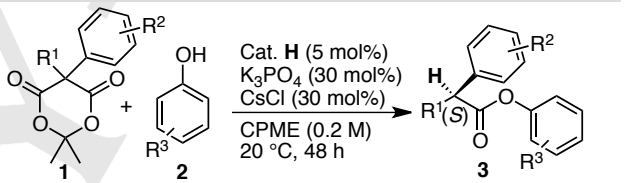
entry	R*$_4$NX	base	additive	yield (%)[b]	ee (%)[c]
1	**F**	K_2CO_3	-	11	59
2	**F**	Cs_2CO_3	-	39	54
3	**F**	K_3PO_4	-	24	62
4	**F**	K_3PO_4	CsCl	35	62
5	**H**	K_3PO_4	CsCl	79	64
6	**H**[d]	K_3PO_4	CsCl	57	65

[a] The reaction was performed on 0.2 mmol scale using 1 equivalent of **1a** and **2a**. [b] Isolated yields. [c] Measured by HPLC equipped with column containing chiral stationary phase. The absolute configurations were established by comparison with literature data (see supporting information). [d] 2 mol% of catalyst were used.

By performing the reaction in CPME (0.2 M) at 20 °C for 48 h in the presence of Maruoka's catalyst **F** (5 mol%) and K_2CO_3 (30 mol%), we were able to improve the level of enantioselectivity to 59% (Table 2, entry 1 *vs* Table 1, entry 17) but at the expense of the isolated yield. Encouraged by this result, Cs_2CO_3 was also tested providing **3a** in 39% yield and 54% *ee* (Table 2, entry 2). Lastly, by using K_3PO_4 as a base, a 62% *ee* could be reached along with a 24% yield (Table 2, entry 3). In order to improve the yield, we turned our attention to the use of additives. By adding a catalytic amount of CsCl, previously reported by Maruoka to enhance the rate of PT catalyzed reaction,[18] we observed a slight improvement of the yield to 35% with a comparable level of enantioselectivity (Table 2, entry 4). As previously observed (Table 1, entry 10 *vs* 12), the Lygo's catalyst **H** gave similar results to those obtained with Maruoka's catalyst **F**, we thus decided to evaluate its performance under PT conditions. Pleasingly, we were able to double the yield (79%) compared to the use of Maruoka's catalyst **F** (Table 2 entry 5 *vs* 4) while maintaining comparable level of enantioselectivity (64% *ee*). The catalyst loading could be decreased to 2 mol% without affecting the *ee* while providing acceptable 57% yield (Table 2, entry 6).

Having in hands our optimized conditions, we then moved to the survey of the scope and limitations of this methodology (Table 3).

Table 3. Scope and limitations.[a]



1 **2** **3**

entry	**1**:R^1/R^2	**2**:R^3	**3**:yield (%)[b]	ee (%)[c]
1	**1a**:Me/H	**2a**:4-MeO	**3a**:79	64
2	**1b**:Et/H	**2a**:4-MeO	**3b**:30	58
3	**1c**:Bn/H	**2a**:4-MeO	**3c**:25	44
4	**1d**:Me/4-F	**2a**:4-MeO	**3d**:99	67
5	**1e**:Me/4-Cl	**2a**:4-MeO	**3e**:91	66
6	**1f**:Me/4-Br	**2a**:4-MeO	**3f**:88	65
7	**1g**:Me/3-Br	**2a**:4-MeO	**3g**:96 (83)[d]	30 (58)[d]
8	**1h**:Me/4-Me	**2a**:4-MeO	**3h**:59	66
9	**1i**:Me/2-Me	**2a**:4-MeO	**3i**:34	25
10	**1j**:Me/4-*i*Bu	**2a**:4-MeO	**3j**:64	59
11	**1k**:Me/4-*t*Bu	**2a**:4-MeO	**3k**:64	57
12	**1l**:Me/4-OMe	**2a**:4-MeO	**3l**:68	65
13	**1m**:Me/4-CF_3	**2a**:4-MeO	**3m**:92 (84)[d]	27 (53)[d]
14	**1a**:Me/H	**2b**:H	**3n**:52	68
15	**1e**:Me/4-Cl	**2b**:H	**3o**:72	70
16	**1e**:Me/4-Cl	**2c**:2-Me	**3p**:79	52

[a] The reaction was performed on 0.15 or 0.2 mmol scale using 1 equivalent of **1** and **2**. [b] Isolated yields. [c] Measured by HPLC equipped with column containing chiral stationary phase. [d] Reaction time: 8 h.

We first studied the influence of the alkyl group on the Meldrum's acid derivatives (Table 3, entries 1-3). The replacement of a methyl by an ethyl or a benzyl resulted in a dramatic drop in the yields along with an erosion of the *ees* from 64% to 44% for the benzyl group. We then examined the influence of the substitution pattern in the aromatic ring (Table 3, entries 4-13). The substitution at the para position by an halogen atom (F, Br or Cl) gave the corresponding products **3d-f** in high yields (88-99%), meanwhile maintaining the enantiomeric excesses around 64% (Table 3, entries 4-6 *vs* 1). Derivatives **1g** possessing a *meta*-bromo substituted phenyl underwent a smooth reaction yielding product **3g** in 83% yield and 58% *ee* as long as the reaction time was shortened to 8 hours (Table 3, entry 7). Otherwise a drastic drop of the *ee* to 30% was observed in 48 hours, likely due to racemization issue caused by the presence of residual K_3PO_4 or phenoxide. Whereas the introduction of a methyl group at the *para* position was well-tolerated (**3h**, 59%, 66% *ee*), the introduction of this substituent at the ortho-position was detrimental to both yield and *ee* (Table 3, entry 9 *vs* 8). Interestingly, these conditions tolerated other alkyl chains at the para position such as *i*Bu or *t*Bu (Table 3, entry 10 and 11) without influencing the outcome of the reaction (**3j-k**, 64%, 57-59% *ee*). Product **1l** with an electro-donating functional group such as a *p*-OMe afforded the corresponding product **3l** with acceptable 68% yield and 64% *ee* (Table 3, entry 12). On the other hand, substrate **1m** with *p*-CF_3 phenyl pendant was also well tolerated provided that the reaction time was reduced to 8 hours furnishing the desired product **3m** in 84% yield and 53% *ee* (Table 3, entry 13). Lastly, we briefly examined the influence of the substitution pattern in the phenol derivatives. Whereas phenol **2b** gave the best level of enantioselectivity (68 and 70% *ee*, Table 3, entries 14-15), phenol **2c** bearing a bulky substituent at the *ortho* position afforded the corresponding product **3p** in 52% *ee* (Table 3, entry 16).

Aware of a possible racemization issue, we decided to follow the *ee* during the course of the formation of compound **3a** was realized (Figure 2).

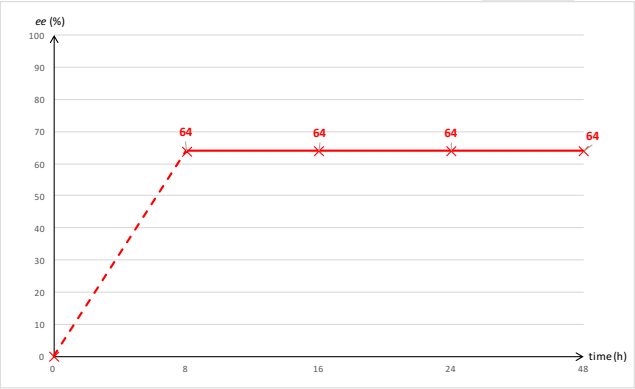
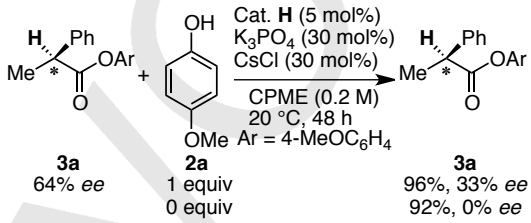


Figure 2. Evolution of the *ee* (%) during the course of the formation of **3a**.

The enantiomeric excess rapidly reached a plateau (*i.e.* 64% after 8 h) and remained at this level until the end of the reaction after 48 h while conversion was ranged from 52 to 79%. In consequence, one may assume that there is no racemization during the course of the reaction.

In order to push forward our investigation, the enantioenriched product **3a** (64% *ee*) was engaged into the classical reaction conditions for 48 h with 1 equivalent of 4-MeOphenol but in the absence of Meldrum's acid derivative (Scheme 1).



Scheme 1. Racemization issue.

After 48 h, the initial enantiomeric excess was divided by two reaching 33% *ee*. Moreover, the same reaction in the absence of phenol resulted in a complete racemization after 48 h. Accordingly, there is a clear competition between the deprotonation of 4-methoxyphenol and the product **3a** in favour of the former one. Then, during the course of the reaction, the generated phenoxide species is more prone to attack the markedly electrophilic MA derivatives **1** rather than acting as a Brønsted base thus preventing any racemization reaction. Such an explanation is in agreement with the fact that **3g** and **3m** that are formed quantitatively in 8 h due to the better reactivity of their corresponding Meldrum's acids **1g** and **1m** (and likely better electrophilic character) start to racemize during the last 40 h in the absence of **1** (Table 3, entries 7 and 13 respectively).

Regarding the mechanism of this reaction, we propose that a solid-liquid PT-catalyzed deprotonation of the phenol **2** occurs in order to generate *in situ* a chiral ammonium aryloxide reactive species (Figure 3, step a), which subsequently adds to the electrophilic carbonyl of the MA derivatives **1**, thus triggering the fragmentation along with the elimination of a molecule of acetone to provide an hemi-malonate derived ion pair (Figure 3, step b). Then, a decarboxylation step (Figure 3, step c) provides a more basic enolate flanked by the chiral ammonium which undergoes an asymmetric protonation by an incoming molecule of phenol derivative **2** thus providing the product **3** with the concomitant regeneration of the chiral ammonium phenoxide that is actually the catalytically active species (Figure 3, step d).

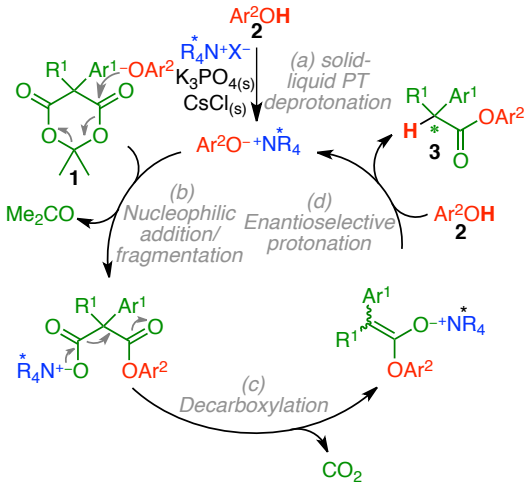
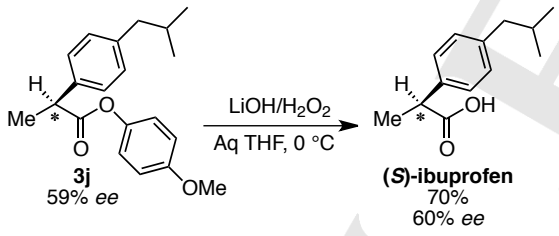


Figure 3. Mechanism proposal for the nucleophilic addition / fragmentation / decarboxylation / enantioselective protonation sequence.

Finally, in order to demonstrate the synthetic utility of this methodology, we turned our attention to the synthesis of enantioenriched ibuprofen, a commercially available anti-inflammatory drug. Starting from compound **3j** (59% *ee*), a simple saponification step in the presence of LiOH and H_2O_2[8b] afforded the ibuprofen in 70% yield without racemization (Scheme 2). A comparison of the optical rotation with literature value allowed us to establish a *S*-configuration of the ibuprofen (see supporting information for transition state proposal).



Scheme 2. Synthesis of enantioenriched (*S*)-ibuprofen starting from ester **3j**.

Conclusions

In conclusion, we have developed an original organocatalyzed enantioselective protonation reaction of acyclic enolates leading to several enantioenriched 2-aryl propionic derivatives **3** with good isolated yields and *ees* up to 70%. This process takes advantage of the readily availability of 5,5-disubstituted MA derivatives as stable starting materials with a marked electrophilic character. This poorly exploited reactivity allows a domino addition-fragmentation-decarboxylation-protonation reaction triggered by a chiral ammonium phenoxide cooperative ion pair. The synthetic usefulness of this methodology was demonstrated in the course of the synthesis of enantioenriched (*S*)-ibuprofen. We feel this original methodology might find further applications in organocatalysis.

Experimental Section

General information: Reactions were performed using oven dried glassware under inert atmosphere of argon. Unless otherwise noticed, all reagent-grade chemicals were commercially available and used as received. THF, Toluene and CH_2Cl_2 were dried over MBRAUN MB SPS-800 apparatus. Dry acetonitrile, dry 1,4-Dioxane, dry DMF and dry methanol were purchased from Aldrich, CPME was purchased from TCI and all were used as received. Reactions were monitored by thin-layer chromatography with silica gel 60 F254 pre-coated aluminium plates (0.25 mm). Visualization was performed under UV light and phosphomolybdic acid or KMO_4 staining. Flash chromatographic purifications of compounds were achieved with 60 silica gel (40-63 µm) or with C18-HP 15 µm F0004 Flash Column on an Interchim Puriflash 430 apparatus. Melting points were measured on a WME Köfler hot-stage (Stuart SMP3). Infrared spectra (IR) were recorded on a PerkinElmer Spectrum 100 Series FT-IR spectrometer. Liquids and solids were applied on a Single Reflection Attenuated Total Reflectance (ATR) accessory. Data are reported in cm^{-1}. Optical rotations were determined with a Perkin Elmer 341 mircropolarimeter with a 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g per 100 mL. ^1H NMR spectra (300 MHz), ^{13}C NMR spectra (75 MHz) and ^{19}F NMR (282 MHz) were recorded on a Bruker Advance300. Data appear in the following order: chemical shift in ppm (referenced to the internal solvent signal for ^1H and ^{13}C NMR, or to $CFCl_3$ as internal standard for ^{19}F NMR), multiplicity (*s*, singlet; *d*, doublet; *t*, triplet; *q*, quadruplet; *m*, multiplet) and coupling constant *J* in Hertz. Accurate Mass measurements (HRMS) were performed with a Waters LCP 1er XR spectrometer. HPLC analyses were performed using a Daicel Chiralpak® column (250 mm x 4.6 mm, 5 µm or 3 µm) on a ThermoFisher Scientific Dionex Ultimate 3000 apparatus with UV-vis diode array detector. Elemental analyses were performed on a Thermo Fisher Flash 2000 Series apparatus.

General procedure for the synthesis of enantioenriched 2-aryl propionic ester derivatives 3

In a glass vial were sequentially introduced K_3PO_4 (30 mol%), CsCl (30 mol%), catalyst **H** (5 mol%), phenol **2** and 5,5-disubstituted Meldrum's acid **1** (0.15 or 0.2 mmol, 1 equiv). CPME (0.2 M) was added, and the resulting heterogeneous mixture was stirred under argon atmosphere at 20 °C for 8 or 48 h. The reaction mixture was then diluted with CH_2Cl_2 (5 mL) and filtered over a silica gel pad (eluent: CH_2Cl_2). The filtrate was concentrated under vacuum, and the crude product was purified by silica gel column chromatography to give the desired enantioenriched phenolic ester **3**.

4-methoxyphenyl 2-phenylpropanoate (3a): Following the general procedure, Meldrum's acid **1a** (46.8 mg, 0.2 mmol, 1 equiv.), 4-methoxyphenol **2a** (24.8 mg, 0.2 mmol, 1 equiv.), K_3PO_4 (12.7 mg, 0.06 mmol, 30 mol%), CsCl (10.1 mg, 0.06 mmol, 30 mol%) and catalyst **H** (8.8 mg, 0.01 mmol, 5 mol%) were stirred in CPME (1 mL) for 48 h. The title compound was obtained as a white solid (40.5 mg, 79%) after silica gel flash column chromatography (Petroleum ether/EtOAc 95:5). R_f = 0.37 (Petroleum ether/EtOAc 95:5). mp = 52-54 °C. IR (neat) ν_{max} = 2985, 2953, 2828, 1744, 1596, 1504, 1453, 1246, 1191, 1141, 1075, 1028, 1007, 935, 889, 818, 751, 702, 538, 525, 507 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.43-7.25 (m, 5H), 6.95-6.80 (m, 4H), 3.94 (q, 1H, *J* = 7.1 Hz), 3.77 (s, 3H), 1.61 (d, 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5, 157.3, 144.4, 140.3, 128.9 (2 C), 127.7 (2 C), 127.5, 122.3 (2 C), 114.5 (2 C), 55.7, 45.7,

18.7. HRMS (EI^+) m/z: $[M]^+$ Calcd for $C_{16}H_{16}O_3$ 256.1094; Found: 256.1090. HPLC analysis: 64% *ee* (column DAICEL Chiralpak IA 3µm, heptane/*i*-PrOH 98:2, flow rate 1 mL/min, 20 °C, UV 230 nm, t_{major} = 11.4 min, t_{min} = 13.5 min). $[\alpha]_D^{20}$ +67.8 (*c* 0.50, $CHCl_3$).

4-methoxyphenyl 2-phenylbutanoate (3b): Following the general procedure, Meldrum's acid **1b** (49.7 mg, 0.2 mmol, 1 equiv.), 4-methoxyphenol **2a** (24.8 mg, 0.2 mmol, 1 equiv.), K_3PO_4 (12.7 mg, 0.06 mmol, 30 mol%), CsCl (10.1 mg, 0.06 mmol, 30 mol%) and catalyst **H** (8.8 mg, 0.01 mmol, 5 mol%) were stirred in CPME (1 mL) for 48 h. The title compound was obtained as a colourless oil (16.3 mg, 30%) after silica gel flash column chromatography (Cyclohexane/EtOAc 95:5). R_f = 0.28 (Cyclohexane/EtOAc 95:5). IR (neat) ν_{max} = 2966, 2935, 1749, 1598, 1505, 1455, 1442, 1298, 1248, 1191, 1132, 1101, 1031, 947, 907, 840, 797, 744, 698, 509 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.43-7.25 (m, 5H), 6.95-6.80 (m, 4H), 3.78 (s, 3H), 3.68 (t, 1H, *J* = 7.7 Hz), 2.30-2.13 (m, 1H), 1.98-1.82 (m, 1H), 0.99 (t, 3H, *J* = 7.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0, 157.3, 144.4, 138.8, 128.8 (2 C), 128.1 (2 C), 127.5, 122.3 (2 C), 114.5 (2 C), 55.7, 53.6, 26.9, 12.3. HRMS (ESI^+) m/z: $[M + NH_4]^+$ Calcd for $C_{17}H_{22}NO_3$ 288.1600; Found: 288.1594. HPLC analysis: 58% *ee* (column DAICEL Chiralpak IA 3µm, heptane/*i*-PrOH 98:2, flow rate 1 mL/min, 20 °C, UV 220 nm, t_{major} = 12.2 min, t_{min} = 13.6 min). $[\alpha]_D^{20}$ +48.2 (*c* 0.50, $CHCl_3$).

4-methoxyphenyl 2,3-diphenylpropanoate (3c): Following the general procedure, Meldrum's acid **1c** (62.1 mg, 0.2 mmol, 1 equiv.), 4-methoxyphenol **2a** (24.8 mg, 0.2 mmol, 1 equiv.), K_3PO_4 (12.7 mg, 0.06 mmol, 30 mol%), CsCl (10.1 mg, 0.06 mmol, 30 mol%) and catalyst **H** (8.8 mg, 0.01 mmol, 5 mol%) were stirred in CPME (1 mL) for 48 h. The title compound was obtained as a white solid (16.9 mg, 25%) after silica gel flash column chromatography (EP/EtOAc 95:5) and C18-HP 15 µm F0004 Flash Column chromatography using an Interchim Puriflash apparatus (gradient ACN/H_2O 20:80 to 100:0). R_f = 0.29 (EP/EtOAc 95:5). mp = 79-82 °C. IR (neat) ν_{max} = 2988, 2936, 2839, 1752, 1593, 1503, 1455, 1355, 1278, 1242, 1192, 1138, 1087, 1031, 860, 821, 753, 703, 521 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.46-7.18 (m, 10H), 6.84-6.70 (m, 4H), 4.08 (dd, 1H, *J* = 9.4, 6.3 Hz), 3.76 (s, 3H), 3.49 (dd, 1H, *J* = 13.7, 9.4 Hz), 3.12 (dd, 1H, *J* = 13.7, 9.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.4, 157.3, 144.2, 138.9, 138.4, 129.2 (2 C), 128.9 (2 C), 128.6 (2 C), 128.1 (2 C), 127.7, 126.7, 122.2 (2 C), 114.4 (2 C), 55.7, 53.8, 40.1. HRMS (ESI^+) m/z: $[M + NH_4]^+$ Calcd for $C_{22}H_{24}NO_3$ 350.1751; Found: 350.1759. HPLC analysis: 44% *ee* (column DAICEL Chiralpak IA 3µm, heptane/*i*-PrOH 98:2, flow rate 1 mL/min, 20 °C, UV 215 nm, t_{major} = 22.7 min, t_{min} = 23.9 min). $[\alpha]_D^{20}$ +16.8 (*c* 0.50, $CHCl_3$).

4-methoxyphenyl 2-(4-fluorophenyl)propanoate (3d): Following the general procedure, Meldrum's acid **1d** (50.4 mg, 0.2 mmol, 1 equiv.), 4-methoxyphenol **2a** (24.8 mg, 0.2 mmol, 1 equiv.), K_3PO_4 (12.7 mg, 0.06 mmol, 30 mol%), CsCl (10.1 mg, 0.06 mmol, 30 mol%) and catalyst **H** (8.8 mg, 0.01 mmol, 5 mol%) were stirred in CPME (1 mL) for 48 h. The title compound was obtained as an off-white solid (54.5 mg, 99%) after silica gel flash column chromatography (Petroleum ether/EtOAc 95:5). R_f = 0.27 (Petroleum ether/EtOAc 95:5). mp = 37-38 °C. IR (neat) ν_{max} = 2980, 2938, 1750, 1602, 1504, 1457, 1298, 1222, 1191, 1132, 1102, 1070, 1033, 890, 837, 819, 788, 761, 724, 535, 520 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.42-7.31 (m, 2H), 7.12-7.01 (m, 2H), 6.95-6.80 (m, 4H), 3.93 (q, 1H, *J* = 7.2 Hz), 3.78 (s, 3H), 1.60 (d, 3H, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.4, 162.2 (d, ^1J = 246 Hz), 157.4, 144.3, 135.9 (d, ^4J = 3 Hz), 129.3 (d, 2 C, ^3J = 8 Hz), 122.2 (2 C), 115.8 (d, 2 C, ^2J = 21 Hz), 114.5 (2 C), 55.7, 44.9, 18.8. $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$, $CFCl_3$) δ_F -115.85 (tt, 1F, *J* = 8.6, 5.3 Hz). HRMS (EI^+) m/z: $[M]^+$ Calcd for $C_{16}H_{15}FO_3$ 274.1000; Found: 274.1006. HPLC analysis: 67% *ee* (column DAICEL Chiralpak IA 3µm, heptane/*i*-PrOH 98:2, flow rate 1 mL/min, 20 °C, UV 220 nm, t_{major} = 13.0 min, t_{min} = 14.2 min). $[\alpha]_D^{20}$ +51.6 (*c* 0.50, $CHCl_3$).

4-methoxyphenyl 2-(4-chlorophenyl)propanoate (3e) : Following the general procedure, Meldrum's acid **1e** (53.7 mg, 0.2 mmol, 1 equiv.), 4-methoxyphenol **2a** (24.8 mg, 0.2 mmol, 1 equiv.), K_3PO_4 (12.7 mg, 0.06 mmol, 30 mol%), CsCl (10.1 mg, 0.06 mmol, 30 mol%) and catalyst **H** (8.8 mg, 0.01 mmol, 5 mol%) were stirred in CPME (1 mL) for 48 h. The title compound was obtained as a white solid (53.2 mg, 91%) after silica gel flash chromatography (Petroleum ether/EtOAc 95:5). R_f = 0.27 (Petroleum ether/EtOAc 95:5). mp = 57-60 °C. IR (neat) ν_{max} = 2982, 2936, 1750, 1597, 1504, 1492, 1456, 1248, 1191, 1134, 1092, 1071, 1033, 1014, 890, 834, 820, 769, 521 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.34 (s, 4H), 6.93-6.81 (m, 4H), 3.92 (q, 1H, *J* = 7.2 Hz), 3.78 (s, 3H), 1.59 (d, 3H, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1, 157.4, 144.3, 138.7, 133.3, 129.1 (2 C), 129.0 (2 C), 122.1 (2 C), 114.5 (2 C), 55.6, 45.1, 18.6. HRMS (ESI^-) m/z: $[M - H]^-$ Calcd for $C_{16}H_{15}ClO_3$ 289.0637; Found: 289.0627. HPLC analysis: 66% *ee* (column DAICEL Chiralpak IA 3µm, heptane/EtOH 98:2, flow rate 1 mL/min, 20 °C, UV 220 nm, t_{min} = 10.6 min, t_{major} = 13.0 min). $[\alpha]_D^{20}$ +61.6 (*c* 0.50, $CHCl_3$).

4-methoxyphenyl 2-(4-bromophenyl)propanoate (3f) : Following the general procedure, Meldrum's acid **1f** (62.6 mg, 0.2 mmol, 1 equiv.), 4-methoxyphenol **2a** (24.8 mg, 0.2 mmol, 1 equiv.), K_3PO_4 (12.7 mg, 0.06 mmol, 30 mol%), CsCl (10.1 mg, 0.06 mmol, 30 mol%) and catalyst **H** (8.8 mg, 0.01 mmol, 5 mol%) were stirred in CPME (1 mL) for 48 h. The title compound was obtained as an off-white solid (59.2 mg, 88%) after silica gel flash column chromatography (Petroleum ether/EtOAc 95:5). R_f = 0.26 (Petroleum ether/EtOAc 95:5). mp = 52-54 °C. IR (neat) ν_{max} = 2980, 2936, 1751, 1596, 1505, 1489, 1463, 1298, 1248, 1192, 1162, 1136, 1074, 1010, 891, 820, 769, 520 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.54-7.46 (m, 2H), 7.32-7.23 (m, 2H), 6.94-6.81 (m, 4H), 3.83 (q, 1H, *J* = 7.2 Hz), 3.70 (s, 3H), 1.51 (d, 3H, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1, 157.4, 144.3, 139.2, 132.0 (2 C), 129.4 (2 C), 122.2 (2 C), 123.4, 114.5 (2 C), 55.7, 45.2, 18.6. HRMS (EI^+) m/z: $[M]^+$ Calcd for $C_{16}H_{15}BrO_3$ 334.0199; Found: 334.0201. HPLC analysis: 65% *ee* (column DAICEL Chiralpak IA 3µm, heptane/EtOH 95:5, flow rate 1 mL/min, 20 °C, UV 220 nm, t_{min} = 8.8 min, t_{major} = 10.6 min). $[\alpha]_D^{20}$ +54.0 (*c* 0.50, $CHCl_3$).

4-methoxyphenyl 2-(3-bromophenyl)propanoate (3g): Following the general procedure, Meldrum's acid **1g** (62.6 mg, 0.2 mmol, 1 equiv.), 4-methoxyphenol **2a** (24.8 mg, 0.2 mmol, 1 equiv.), K_3PO_4 (12.7 mg, 0.06 mmol, 30 mol%), CsCl (10.1 mg, 0.06 mmol, 30 mol%) and catalyst **H** (8.8 mg, 0.01 mmol, 5 mol%) were stirred in CPME (1 mL) for 8 h. The title compound was obtained as a yellowish oil (55.4 mg, 83%) after silica gel flash column chromatography (Petroleum ether/Et_2O 9:1). R_f = 0.31 (Petroleum ether/Et_2O 9:1). IR (neat) ν_{max} = 2980, 2936, 2836, 1750, 1594, 1569, 1503, 1464, 1298, 1190, 1135, 1102, 1073, 1033, 892, 821, 765, 692, 519, 438 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.57-7.53 (m, 1H), 7.47-7.40 (m, 1H), 7.36-7.30 (m, 1H), 7.27-7.20 (m, 1H), 6.95-6.81 (m, 4H), 3.91 (q, 1H, *J* = 7.2 Hz), 3.78 (s, 3H), 1.60 (d, 3H, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9, 157.4, 144.2, 142.4, 130.8, 130.6, 130.5, 126.3, 127.9, 122.2 (2 C), 114.5, 55.7, 45.3, 18.6. HRMS (EI^+) m/z: $[M]^+$ Calcd for $C_{16}H_{15}O_3$ 334.0199; Found: 334.0210. HPLC analysis: 58% *ee* (column DAICEL Chiralpak IA 3µm, heptane/EtOH 98:2, flow rate 1 mL/min, 20 °C, UV 220 nm, t_{major} = 8.1 min, t_{min} = 9.7 min). $[\alpha]_D^{20}$ +44.8 (*c* 0.50, $CHCl_3$).

4-methoxyphenyl 2-(*p*-tolyl)propanoate (3h): Following the general procedure, Meldrum's acid **1h** (49.7 mg, 0.2 mmol, 1 equiv.), 4-methoxyphenol **2a** (24.8 mg, 0.2 mmol, 1 equiv.), K_3PO_4 (12.7 mg, 0.06 mmol, 30 mol%), CsCl (10.1 mg, 0.06 mmol, 30 mol%) and catalyst **H** (8.8 mg, 0.01 mmol, 5 mol%) were stirred in CPME (1 mL) for 48 h. The title compound was obtained as a white solid (31.8 mg, 59%) after silica gel flash column chromatography (Petroleum ether/Et_2O 10:1). R_f = 0.33 (Petroleum ether/Et_2O 10:1). mp = 77-80 °C. IR (neat) ν_{max} = 2982, 2931, 1750, 1594, 1506, 1454, 1343, 1250, 1193, 1150, 1075, 1025, 891, 814,

784, 762, 532, 487 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.26 (m, 2H), 7.17 (m, 2H), 6.94-6.79 (m, 4H), 3.91 (q, 1H, *J* = 7.1 Hz), 3.77 (s, 3H), 2.35 (s, 3H), 1.58 (d, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz; $CDCl_3$): δ = 173.7, 157.2, 144.4, 137.3, 137.0, 129.6 (2 C), 127.5 (2 C), 122.2 (2 C), 114.4 (2 C), 55.6, 45.3, 21.2, 18.7. HRMS (EI^+) m/z: $[M]^+$ Calcd for $C_{17}H_{16}O_3$ 270.1250; Found: 270.1262. HPLC analysis: 66% *ee* (column DAICEL Chiralpak IA 3µm, heptane/*i*-PrOH 98:2, flow rate 1 mL/min, 20 °C, UV 220 nm, t_{major} = 14.3 min, t_{min} = 15.0 min). $[\alpha]_D^{20}$ +66.0 (*c* 0.50, $CHCl_3$).

4-methoxyphenyl 2-(*o*-tolyl)propanoate (3i): Following the general procedure, Meldrum's acid **1i** (49.7 mg, 0.2 mmol, 1 equiv.), 4-methoxyphenol **2a** (24.8 mg, 0.2 mmol, 1 equiv.), K_3PO_4 (12.7 mg, 0.06 mmol, 30 mol%), CsCl (10.1 mg, 0.06 mmol, 30 mol%) and catalyst **H** (8.8 mg, 0.01 mmol, 5 mol%) were stirred in CPME (1 mL) for 48 h. The title compound was obtained as a colourless oil (18.6 mg, 34%) after silica gel flash column chromatography (Petroleum ether/EtOAc 95:5). R_f = 0.26 (Petroleum ether/EtOAc 95:5). IR (neat) ν_{max} = 2978, 2936, 2837, 1751, 1597, 1504, 1463, 1248, 1191, 1146, 1109, 1074, 1032, 890, 823, 750, 727, 541, 519, 452 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.37-7.31 (m, 1H), 7.27-7.15 (m, 3H), 6.94-6.80 (m, 4H), 4.18 (q, 1H, *J* = 7.2 Hz), 3.78 (s, 3H), 2.45 (s, 3H), 1.56 (d, 3H, *J* = 7.2 Hz). ^{13}C NMR (75 MHz; $CDCl_3$): δ = 173.9, 157.2, 144.4, 138.9, 135.8, 130.8, 127.2, 126.8, 126.5, 122.2 (2 C), 114.4 (2 C), 55.6, 41.6, 19.8, 18.0. HRMS (EI^+) m/z: $[M]^+$ calcd for $C_{17}H_{16}O_3$ 270.1250; Found: 270.1262. HPLC analysis: 25% *ee* (column DAICEL Chiralpak IA 3µm, heptane/*i*-PrOH 95:5, flow rate 1 mL/min, 20 °C, UV 220 nm, t_{major} = 7.7 min, t_{min} = 10.0 min). $[\alpha]_D^{20}$ +29.4 (*c* 0.50, $CHCl_3$).

4-methoxyphenyl 2-(4-*iso*-butylphenyl)propanoate (3j): Following the general procedure, Meldrum's acid **1j** (58.1 mg, 0.2 mmol, 1 equiv.), 4-methoxyphenol **2a** (24.8 mg, 0.2 mmol, 1 equiv.), K_3PO_4 (12.7 mg, 0.06 mmol, 30 mol%), CsCl (10.1 mg, 0.06 mmol, 30 mol%) and catalyst **H** (8.8 mg, 0.01 mmol, 5 mol%) were stirred in CPME (1 mL) for 48 h. The title compound was obtained as a colourless oil (40.1 mg, 64%) after silica gel flash column chromatography (Petroleum ether/Et_2O 9:1). R_f = 0.38 (Petroleum ether/Et_2O 9:1). IR (neat) ν_{max} = 2955, 2869, 2838, 1752, 1504, 1464, 1249, 1193, 1162, 1135, 1071, 1036, 890, 842, 766, 546, 520 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.33-7.26 (m, 2H), 7.17-7.10 (m, 2H), 6.95-6.80 (m, 4H), 3.91 (q, 1H, *J* = 7.1 Hz), 3.78 (s, 3H), 2.47 (d, 2H, *J* = 7.2 Hz), 1.97-1.80 (m, 1H), 1.59 (d, 3H, *J* = 7.1 Hz), 0.91 (d, 6H, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7, 157.3, 144.5, 140.9, 137.5, 129.6 (2 C), 127.3 (2 C), 122.3 (2 C), 114.4 (2 C), 55.7, 45.3, 45.2, 30.3, 22.5 (2 C), 18.7. HRMS (AP^+) m/z: $[M + H]^+$ Calcd for $C_{20}H_{25}O_3$ 313.1798; Found 313.1789. HPLC analysis: 59% *ee* (column DAICEL Chiralpak IA 3µm, heptane/*i*-PrOH 95:5, flow rate 0.5 mL/min, 20 °C, UV 220 nm, t_{min} = 16.9 min, t_{major} = 17.9 min). $[\alpha]_D^{20}$ +60.0 (*c* 0.10, $CHCl_3$).

4-methoxyphenyl 2-(4-(*tert*-butyl)phenyl)propanoate (3k): Following the general procedure, Meldrum's acid **1k** (58.1 mg, 0.2 mmol, 1 equiv.), 4-methoxyphenol **2a** (24.8 mg, 0.2 mmol, 1 equiv.), K_3PO_4 (12.7 mg, 0.06 mmol, 30 mol%), CsCl (10.1 mg, 0.06 mmol, 30 mol%) and catalyst **H** (8.8 mg, 0.01 mmol, 5 mol%) were stirred in CPME (1 mL) for 48 h. The title compound was obtained as a white solid (40.1 mg, 64%) after silica gel flash column chromatography (Petroleum ether/Et_2O 9:1). R_f = 0.33 (Petroleum ether/Et_2O 9:1). mp = 58-60 °C. IR (neat) ν_{max} = 2960, 2906, 2871, 2835, 1748, 1596, 1504, 1456, 1250, 1191, 1138, 1070, 1029, 891, 832, 777, 744, 574, 554, 520 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.42-7.28 (m, 4H), 6.96-6.80 (m, 4H), 3.92 (q, 1H, *J* = 7.2 Hz), 1.59 (d, 3H, *J* = 7.2 Hz), 1.33 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7, 157.2, 150.2, 144.5, 137.1, 127.2 (2 C), 125.8 (2 C), 122.3 (2 C), 114.4 (2 C), 55.67, 45.2, 34.6, 31.5 (3 C), 18.8. HRMS (AP^+) m/z: $[M + H]^+$ Calcd for $C_{20}H_{25}O_3$ 313.1798; Found 313.1807. HPLC analysis: 57% *ee* (column DAICEL Chiralpak IA 3µm, heptane/*i*-PrOH 98:2, flow rate 1 mL/min, 20 °C, UV 220 nm, t_{min} = 8.2 min, t_{major} = 9.7 min). $[\alpha]_D^{20}$ +48.4 (*c* 0.50, $CHCl_3$).

4-methoxyphenyl 2-(4-methoxyphenyl)propanoate (3l): Following the general procedure, Meldrum's acid **1l** (52.9 mg, 0.2 mmol, 1 equiv.), 4-methoxyphenol **2a** (24.8 mg, 0.2 mmol, 1 equiv.), K_3PO_4 (12.7 mg, 0.06 mmol, 30 mol%), CsCl (10.1 mg, 0.06 mmol, 30 mol%) and catalyst **H** (8.8 mg, 0.01 mmol, 5 mol%) were stirred in CPME (1 mL) for 48 h. The title compound was obtained as a pale yellow oil (39.2 mg, 68%) after silica gel flash column chromatography (Petroleum ether/EtOAc 9:1). R_f = 0.24 (Petroleum ether/EtOAc 9:1). IR (neat) ν_{max} = 2936, 2837, 1749, 1611, 1504, 1463, 1442, 1301, 1245, 1192, 1178, 1133, 1072, 1031, 889, 834, 820, 784, 759, 540, 520 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35-7.28 (m, 2H), 7.95-7.86 (m, 2H), 6.94-6.80 (m, 4H), 3.89 (q, 1H, *J* = 7.2 Hz), 3.81 (s, 3H), 3.77 (s, 3H), 1.58 (d, 3H, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8, 158.9, 157.3, 144.5, 132.3, 128.7 (2 C), 122.3 (2 C), 114.4 (2 C), 114.3 (2 C), 55.7, 55.4, 44.8, 18.7. HRMS (ESI^+) m/z: $[M + NH_4]^+$ calcd for $C_{17}H_{22}NO_4$ 304.1543; Found: 304.1557. HPLC analysis: 65% *ee* (column DAICEL Chiralpak IA 3µm, heptane/EtOH 95:5, flow rate 1 mL/min, 20 °C, UV 225 nm, t_{min} = 11.6 min, t_{major} = 12.6 min). $[\alpha]_D^{20}$ +65.5 (*c* 0.20, $CHCl_3$).

4-methoxyphenyl 2-(4-(trifluoromethyl)phenyl)propanoate (3m): Following the general procedure, Meldrum's acid **1m** (60.5 mg, 0.2 mmol, 1 equiv.), 4-methoxyphenol **2a** (24.8 mg, 0.2 mmol, 1 equiv.), K_3PO_4 (12.7 mg, 0.06 mmol, 30 mol%), CsCl (10.1 mg, 0.06 mmol, 30 mol%) and catalyst **H** (8.8 mg, 0.01 mmol, 5 mol%) were stirred in CPME (1 mL) for 8 h. The title compound was obtained as a colourless oil (54.2 mg, 84%) after silica gel flash column chromatography (Petroleum ether/Et_2O 9:1). R_f = 0.27 (Petroleum ether/Et_2O 9:1). IR (neat) ν_{max} = 2936, 2845, 1752, 1619, 1504, 1323, 1249, 1190, 1162, 1114, 1067, 1034, 1018, 891, 842, 822, 761, 603, 518 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, 2H, *J* = 8.2 Hz), 7.52 (d, 2H, *J* = 8.2 Hz), 6.95-6.81 (m, 4H), 4.01 (q, 1H, *J* = 7.2 Hz), 3.78 (s, 3H), 1.63 (d, 3H, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.8, 157.5, 144.2 (m, 2 C), 129.8 (q, ^2J = 32 Hz), 128.1 (2 C), 125.9 (q, 2 C, ^3J = 4 Hz), 124.2 (q, ^1J = 270 Hz), 122.1 (2 C), 114.5 (2 C), 55.6, 45.6, 18.6. $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$, $CFCl_3$) δ_F -61.03 (s, 3F). HRMS (ESI^-) m/z: $[M - H]^-$ Calcd for $C_{17}H_{14}F_3O_3$ 323.0901; Found: 323.0898. HPLC analysis: 53% *ee* (column DAICEL Chiralpak IA 3µm, heptane/EtOH 98:2, flow rate 1 mL/min, 20 °C, UV 220 nm, t_{min} = 9.7 min, t_{major} = 10.3 min). $[\alpha]_D^{20}$ +40.0 (*c* 0.50, $CHCl_3$).

phenyl 2-phenylpropanoate (3n): Following the general procedure, Meldrum's acid **1a** (46.8 mg, 0.2 mmol, 1 equiv.), phenol **2b** (18.8 mg, 0.2 mmol, 1 equiv.), K_3PO_4 (12.7 mg, 0.06 mmol, 30 mol%), CsCl (10.1 mg, 0.06 mmol, 30 mol%) and catalyst **H** (8.8 mg, 0.01 mmol, 5 mol%) were stirred in CPME (1 mL) for 48 h. The title compound was obtained as colourless crystals (23.4 mg, 52%) after silica gel flash column chromatography (Petroleum ether/Et_2O 9:1). R_f = 0.29 (Petroleum ether/Et_2O 9:1). mp < 30 °C. IR (neat) ν_{max} = 3031, 2980, 2935, 1752, 1592, 1492, 1454, 1327, 1193, 1161, 1136, 1072, 917, 774, 748, 729, 689, 540, 496 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45-7.27 (m, 7H), 7.23-7.16 (m, 1H), 7.03-6.95 (m, 2H), 3.97 (q, 1H, *J* = 7.2 Hz), 1.62 (d, 3H, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2, 150.9, 140.2, 129.5 (2 C), 128.9 (2 C), 127.7 (2 C), 127.5, 125.9, 121.5 (2 C), 45.8, 18.7. HRMS (EI^+) m/z: $[M]^+$ Calcd for $C_{15}H_{14}O_2$ 226.0988; Found: 226.0985. HPLC analysis: 68% *ee* (column DAICEL Chiralpak IA 3µm, heptane/*i*-PrOH 99:1, flow rate 1 mL/min, 20 °C, UV 215 nm, t_{major} = 6.8 min, t_{min} = 8.1 min). $[\alpha]_D^{20}$ +58.8 (*c* 0.58, $CHCl_3$).

phenyl 2-(4-chlorophenyl)propanoate (3o): Following the general procedure, Meldrum's acid **1e** (53.7 mg, 0.2 mmol, 1 equiv.), phenol **2b** (18.8 mg, 0.2 mmol, 1 equiv.), K_3PO_4 (12.7 mg, 0.06 mmol, 30 mol%), CsCl (10.1 mg, 0.06 mmol, 30 mol%) and catalyst **H** (8.8 mg, 0.01 mmol, 5 mol%) were stirred in CPME (1 mL) for 48 h, the title compound was obtained as a colourless oil (37.5 mg, 72%) after silica gel chromatography (Petroleum ether/Et_2O 9:1). R_f = 0.49 (Petroleum ether/Et_2O 9:1). IR (neat)

ν_{max} = 2982, 2936, 1752, 1593, 1492, 1456, 1331, 1193, 1135, 1092, 1070, 1015, 918, 830, 766, 744, 691, 528, 499 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.31-7.21 (m, 6H), 7.24-7.16 (m, 1H), 7.02-6.94 (m, 2H), 3.94 (q, 1H, *J* = 7.2 Hz), 1.60 (d, 3H, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 172.8, 190.8, 138.6, 133.4, 129.5 (2 C), 129.1 (4 C), 126.0, 122.4 (2 C), 45.2, 18.6. HRMS (EI^+) m/z: $[M]^+$ Calcd for $C_{15}H_{13}ClO_2$ 260.0599; Found: 260.0614. HPLC analysis: 70% *ee* (column DAICEL Chiralpak IA 3µm, heptane/EtOH 95:5, flow rate 0.5 mL/min, 20 °C, UV 220 nm, t_{min} = 10.1 min, t_{major} = 10.6 min). $[\alpha]_D^{20}$ +54.5 (*c* 0.49, $CHCl_3$).

***o*-tolyl 2-(4-chlorophenyl)propanoate (3p):** Following the general procedure, Meldrum's acid **1e** (53.7 mg, 0.2 mmol, 1 equiv.), *o*-cresol **2c** (21.6 mg, 0.2 mmol, 1 equiv.), K_3PO_4 (12.7 mg, 0.06 mmol, 30 mol%), CsCl (10.1 mg, 0.06 mmol, 30 mol%) and catalyst **H** (8.8 mg, 0.01 mmol, 5 mol%) were stirred in CPME (1 mL) for 48 h. The title compound was obtained as a colourless oil (43.3 mg, 79%) after silica gel flash column chromatography (Petroleum ether/EtOAc 96:4). R_f = 0.35 (Petroleum ether/EtOAc 96:4). IR (neat) ν_{max} = 2981, 2935, 1750, 1490, 1457, 1330, 1220, 1172, 1135, 1110, 1091, 1070, 1043, 1014, 940, 894, 833, 778, 746, 712, 527, 448 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.41-7.31 (m, 4H), 7.22-7.07 (m, 3H), 6.95-6.87 (m, 1H), 3.98 (q, 1H, *J* = 7.2 Hz), 1.95 (s, 3H), 1.63 (d, 3H, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.2, 149.3, 138.6, 133.4, 131.3, 130.2, 129.2 (2 C), 129.0 (2 C), 127.0, 126.2, 127.7, 45.1, 18.4, 16.0. HRMS (EI^+) m/z: $[M]^+$ Calcd for $C_{16}H_{15}ClO_4$ 274.0755; Found: 274.0758. HPLC analysis: 52% *ee* (column DAICEL Chiralpak IA 3µm, heptane/EtOH 99:1, flow rate 1 mL/min, 20 °C, UV 220 nm, t_{min} = 6.2 min, t_{major} = 7.5 min). $[\alpha]_D^{20}$ +40.6 (*c* 0.50, $CHCl_3$).

Synthesis of (*S*)-ibuprofen: To a solution of ester **3j** (33.7 mg, 0.12 mmol, 1 equiv.) in THF (0.8 mL) and water (0.12 mL) were successively added LiOH (2.0 M, 0.2 mL) and H_2O_2 (30% in water, 0.1 mL) at 0 °C. The reaction mixture was stirred for 8 h at 0 °C, then quenched by the addition of $Na_2S_2O_3$ (0.7 M, 1 mL) and $NaHCO_3$ (0.5 M, 1.6 mL). The resulting mixture was allowed to stir for 15 minutes, and HCl (20%) was added until the mixture was acidic. The organic layer was extracted with EtOAc (3 x 10 mL), and the combined organic layers were dried over Na_2SO_4 then concentrated. The crude product was purified by silica gel flash column chromatography (Petroleum ether/Acetone/AcOH 90:10:1) to give the title compound as a white solid (18.1 mg, 70%). R_f = 0.22 (Petroleum ether/Acetone/AcOH 90:10:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.25-7.19 (m, 2H), 7.14-7.07 (m, 2H), 3.71 (q, 1 H, *J* = 7.2 Hz), 2.44 (d, 2H, *J* = 7.2 Hz), 1.92-1.76 (m, 1H), 1.50 (d, 3 H, *J* = 7.2 Hz), 0.89 (d, 6 H, *J* = 6.6 Hz). HPLC analysis: 59% *ee* (column DAICEL Chiralpak IA 5µm, MeOH/H_2O (0.1% AcOH) 75:25, flow rate 1mL/min, 20 °C, UV 220 nm, t_{min}= 8.6 min, t_{major} = 9.6 min). $[\alpha]_D^{20}$ +34.0 (*c* 0.50, $CHCl_3$).

Acknowledgements

This work has been partially supported by Rouen University, INSA Rouen, CNRS, EFRD and Labex SynOrg (ANR-11-LABX-0029) and region Normandie (CRUNCh network). F.L. thanks the MESR for a doctoral fellowship.

Keywords: Asymmetric catalysis • Meldrum's acid • Nucleophilic addition • Organocatalysis • Protonation

[1] For reviews, see: a) C. Fehr, *Angew. Chem. Int. Ed.* **1996**, *35*, 2566-2587; b) L. Duhamel, P. Duhamel, J.-C. Plaquevent, *Tetrahedron: Asymmetry* **2004**, *15*, 3653-3691; c) J. Blanchet, J. Baudoux, M. Amere, M.-C. Lasne, J. Rouden, *Eur. J. Org. Chem.* **2008**, 5493-5506; d) J. T. Mohr, A. Y. Hong, B. M. Stoltz, *Nat. Chem.* **2009**, *1*, 359-369; e) T. Poisson, S. Oudeyer, J.-F. Brière, V. Levacher, in *Enantioselective Organocatalyzed Reactions I* (Ed.: R. Mahrwald), Springer, Dordrecht Heidelberg London New York, **2011**, pp. 67-106; f) A. Claraz, S. Oudeyer, V. Levacher, *Curr. Org. Chem.* **2012**, *16*, 2192-2205; g) S. Oudeyer, J.-F. Brière, V. Levacher, *Eur. J. Org. Chem.* **2014**, 6103-6119; h) J. P. Phelan, J. A. Ellman, *Beilstein J. Org. Chem.* **2016**, *12*, 1203-1228; i) N. Fu, L. Zhang, S. Luo, *Org. Biomol. Chem.* **2018**, *16*, 510-520.

[2] C. Fehr, J. Galindo, *Angew. Chem. Int. Ed.* **1994**, *33*, 1888-1889.

[3] T. Poisson, V. Gembus, V. Dalla, S. Oudeyer, V. Levacher, *J. Org. Chem.* **2010**, *75*, 7704-7716.

[4] H. Brunner, P. Schmidt, *Eur. J. Org. Chem.* **2000**, 2119-2133.

[5] a) N. Bodor, R. Woods, C. Raper, P. Kearney, J. J. Kaminski, *J. Med. Chem.* **1980**, *23*, 474-480; b) M. Landoni, A. Soraci, *Curr. Drug Metab.* **2001**, *2*, 37-51.

[6] For a discussion on the influence of the double bond geometry of enolate in protonation reactions, see: P. Duhamel, *Bull. Soc. Chim. Fr.* **1996**, *133*, 457-459.

[7] a) L. Verbit, T. R. Halbert, R. B. Patterson, *J. Org. Chem.* **1975**, *40*, 1649-1650; b) O. Toussaint, P. Capdevielle, M. Maumy, *Tetrahedron Lett.* **1987**, *28*, 539-542; c) H. Brunner, J. Müller, J. Spitzer, *Monatsh. Chem.* **1996**, *127*, 845-858.

[8] a) H. Pracejus, *Justus Liebigs Ann. Chem.* **1960**, *634*, 9-22; b) S. L. Wiskur, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 6176-6177; c) C. Concellón, N. Duguet, A. D. Smith, *Adv. Synth. Catal.* **2009**, *351*, 3001-3009; d) X.-N. Wang, H. Lv, X.-L. Huang, S. Ye, *Org. Biomol. Chem.* **2009**, *7*, 346-350.

[9] a) K. M. Johnson, M. S. Rattley, F. Sladojevich, D. M. Barber, M. G. Nunez, A. M. Goldys, D. J. Dixon, *Org. Lett.* **2012**, *14*, 2492-2495; b) A. J. Farley, C. Sandford, D. J. Dixon, *J. Am. Chem. Soc.* **2015**, *137*, 15992-15995.

[10] N. E. Wurz, C. G. Daniliuc, F. Glorius, *Chem. Eur. J.* **2012**, *18*, 16297-16301.

[11] For reviews, see: a) A. M. Dumas, E. Fillion, *Acc. Chem. Res.* **2010**, *43*, 440-454; b) E. Pair, T. Cadart, V. Levacher, J.-F. Brière, *Chem. Cat. Chem.* **2016**, *8*, 1882-1890.

[12] For reviews, see : a) J.-F. Brière, S. Oudeyer, V. Dalla, V. Levacher, *Chem. Soc. Rev.* **2012**, *41*, 1696-1707; b) J. Godemert, S. Oudeyer, V. Levacher, *Chem. Cat. Chem.* **2016**, *8*, 74-85.

[13] For selected examples, see : a) A. Claraz, G. Landelle, S. Oudeyer, V. Levacher, *Eur. J. Org. Chem.* **2013**, 7693-7696; b) A. Claraz, S. Oudeyer, V. Levacher, *Adv. Synth. Catal.* **2013**, *355*, 841-846; c) A. Claraz, S. Oudeyer, V. Levacher, *Tetrahedron: Asymmetry* **2013**, *24*, 764-768; d) M. Decostanzi, J. Godemert, S. Oudeyer, V. Levacher, J.-M. Campagne, E. Leclerc, *Adv. Synth. Catal.* **2016**, *358*, 526-531; e) J. Godemert, S. Oudeyer, V. Levacher, *ChemistrySelect* **2016**, *1*, 3184-3188.

[14] For enantioselective protonation reactions of transient chiral quaternary ammonium enolates, see : a) E. Yamamoto, A. Nagai, A. Hamasaki, M. Tokunaga, *Chem. Eur. J.* **2011**, *17*, 7178-7182; b) E. Yamamoto, D. Gokuden, A. Nagai, T. Kamachi, K. Yoshizawa, A. Hamasaki, T. Ishida, M. Tokunaga, *Org. Lett.* **2012**, *14*, 6178-6181.

[15] For Michael addition-protonation reactions, see: a) K. L. Kimmel, J. D. Weaver, M. Lee, J. A. Ellman, *J. Am. Chem. Soc.* **2012**, *134*, 9058-9061; b) S. Luo, N. Fu, Y. Guo, L. Zhang, *Synthesis* **2015**, *47*, 2207-2216.

[16] For a domino (2+3) annulation-protonation with nitrones, see: T. Tite, M. Sabbah, V. Levacher, J.-F. Brière, *Chem. Commun.* **2013**, *49*, 11569-11571.

[17] J. Hiratake, K. Shibata, N. Baba, J. Oda, *Synthesis* **1988**, 278-280.

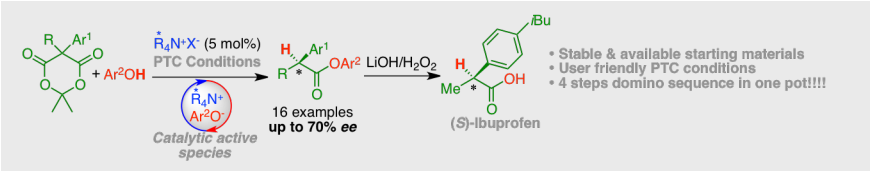
[18] T. Kano, T. Kumano, K. Maruoka, *Org. Lett.* **2009**, *11*, 2023-2025.

10.1002/ejoc.201800331

WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

FULL PAPER



An original organocatalyzed enantioselective protonation sequence starting from readily available disubstituted Meldrum's acid derivatives and phenols was developed providing chiral non-racemic 2-aryl propionic ester derivatives in good isolated yields and up to 70% *ee* under PTC conditions. The usefulness of the reaction was demonstrated in the course of the synthesis of enantioenriched (*S*)-ibuprofen.

Enantioselective protonation

F. Legros, T. Martzel, J.-F. Brière, S. Oudeyer and V. Levacher*

Page No. – Page No.

Organocatalytic enantioselective decarboxylative protonation reaction of Meldrum's acid derivatives under PTC conditions