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Reaction of 2-alkyl pyridine N-oxide derivatives with Mosher's acyl chloride: first example of stereoselective Boekelheide rearrangement

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Dedicated to the memory of Alessandro Fedeli-Bernardini

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ABSTRACT

Treatment of 2-alkyl pyridine N-oxides with acylating reagents represents an established procedure for the introduction of oxygen functionality into alkyl group at the ortho position of N heteroaromatic rings. We have reported the first example of asymmetric Boekelheide rearrangement applied to a set of 2-alkyl-pyridine N-oxide derivatives using (*R*) Mosher's acyl chloride as activator of the rearrangement to give, after hydrolysis, enantiomerically enriched 1-(2-pyridinyl)alkyl alcohol. Diastereoselectivity of the process was studied at low temperatures in different solvents, and was supported by a preliminary in silico modeling.

1. Introduction

The development of new synthetic methods has reached a level that allows organic chemists to plan and perform almost any kind of functional group transformation. Nevertheless, despite this achievement, advances in the field are still highly desirable particularly if they can solve problems that allow easy and rapid access to chiral pool of compounds.

An interesting and productive way to improve synthetic efficiency, which can give access to a multitude of Csp^3 chiral compounds, is to take a new look at poorly exploited and old pioneer reactions using current knowledge of organic chemistry. In this manner, we re-investigated the so-called Boekelheide rearrangement[1] with the aim of obtaining an asymmetric version of the reaction, and in this way expand the available tools for accessing at enantiomerically enriched 1-(2-pyridinyl)alkyl alcohol derivatives.

Since its discovery in the late 1940s, the reactivity of pyridine N-oxide mediated by activators, such as Ac_2O has attracted the interest of several research groups. The conversion of **1** to the corresponding 2-pyridone **2** with acetic anhydride performed by Katada, Scheme 1, was the first example reported in this field.[2]

Shortly thereafter, it was found that also activation of 2-alkyl pyridine N-oxides **3** either with Ac_2O[3] or with other promoters, such as TFAA[4] and tosyl chloride[5] give access to 1-(2-pyridinyl)-alkyl alcohol derivatives **5**.

Today this is a well established procedure known as the Boekelheide rearrangement,[6] Scheme 1. Under the classical Boekelheide's reaction conditions, the 2-alkyl pyridine N-oxide **3** heated with a large excess of acetic anhydride is converted to **4**, generally in moderate-good yields, and after hydrolysis, the corresponding alcohol **5** is obtained. This can then be resolved using classical techniques[7] to give enantiomers **5-S** and **5-R**.

Despite much research, the mechanism of the rearrangement has not been fully understood, and remains controversial.[6] The most common and accepted explanation is an ion-pair mechanism (see Scheme 2) proposed by Oae[8] and Katritzky[9c,d]. However, we cannot exclude the possibility that other mechanisms, such as a hetero-Claisen rearrangement, in relation to the nature of the substrate, could contribute to the Boekelheide rearrangement.

Until now, the Boekelheide rearrangement has found only limited application, and to the best of our knowledge, there have been reports describing facial diastereoselective rearrangements mediated by chiral promoters. With the aim of expanding the potential of the Boekelheide rearrangement, we investigated the possible development of an asymmetric version of the reaction using a chiral activator.

The easily available, chemically stable and enantiomerically pure (*R*) and (*S*) Mosher's acyl chlorides were chosen as activators, while the 2-alkyl pyridines **8a**, **9a**, **10a**, and **11a** derivatives depicted in Scheme 3 where chosen as substrates. With the

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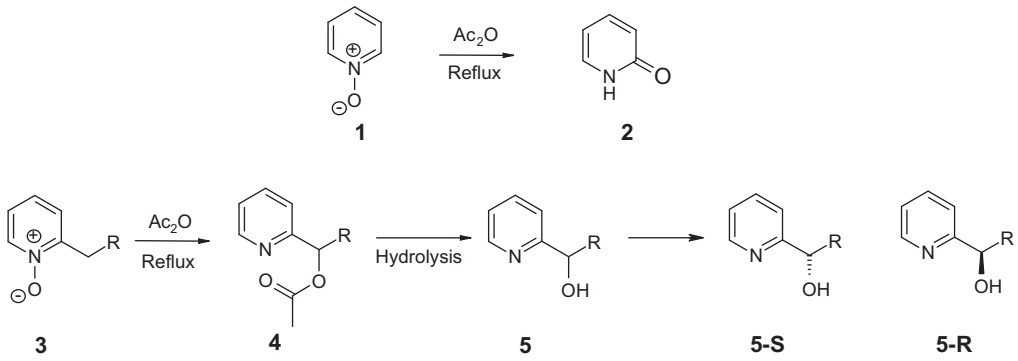
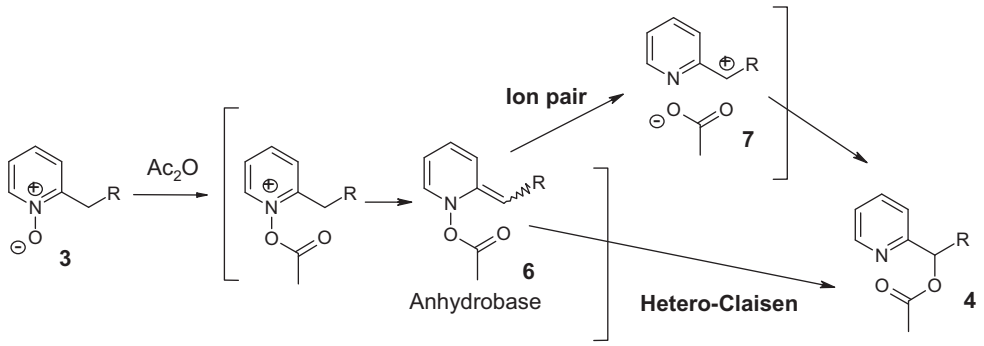
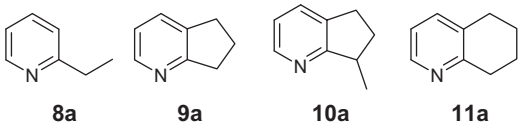


Scheme 1. Katada and Boekelheide rearrangements.



Scheme 2. Boekelheide rearrangement: ion-pair versus intramolecular pathway.



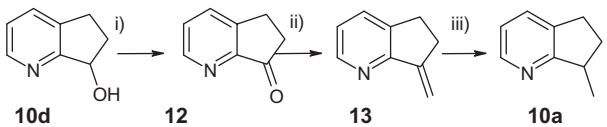
Scheme 3. 2-Alkyl pyridine substrates.

exception of **10a**, all these pyridine derivatives are commercially available.

Since no suitable route has been reported in the literature for compound **10a**, we envisaged the possibility to prepare it starting from **10d** following the chemical route reported in Scheme 4.

Compounds **8a**, **9a**, **10a**, and **11a** were converted to the corresponding N-oxides, respectively, **8b**, **9b**, **10b**, and **11b** in high yields according to literature procedures[9] by means of standard mCPBA conditions or by aqueous hydrogen peroxide in the presence of a catalytic amount of methyl-trioxo-rhenium, Scheme 5.

We found that (*R*)-(−)-α-methoxy-α-(trifluoromethyl) phenylacetyl chloride, (*R*)-(−)MTPA-Cl, is an extremely efficient agent for the Boekelheide rearrangement. In fact, treatment of **8b**, **9b**, and **11b** in ethyl acetate with (*R*)-(−)MTPA-Cl in the presence of TEA as the base, allowed the fast and complete rearrangement to the corresponding esters **8c**, **9c**, and **11c** at reaction temperatures



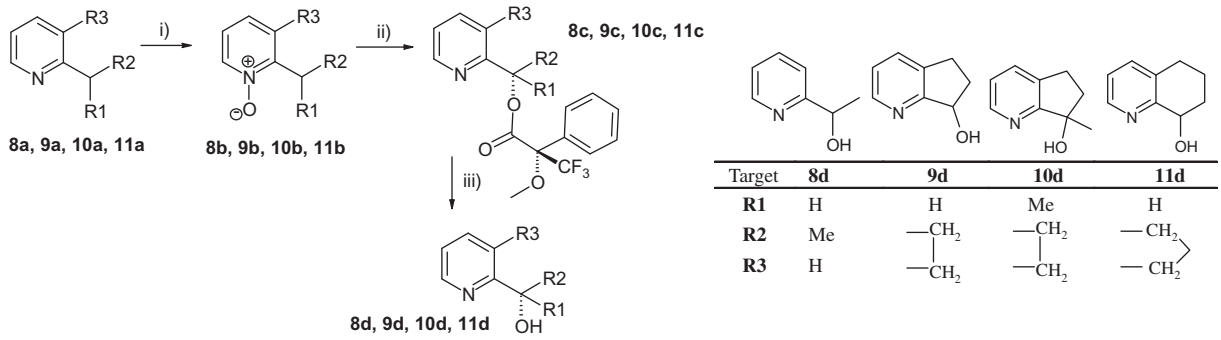
Scheme 4. Synthesis of bicyclic pyridine derivative **10a**. Reagents and conditions: (i) Dess–Martin periodinane, DCM, *y* 85%; (ii) $(Ph)_3P–CH_3Br$, ^tBuOK, THF, *y* 50%; (iii) Pd/C, EtOH, H_2, *y* 80%.

well below 0 °C. Table 1 summarizes the results obtained.[9] The high reactivity exhibited by the (*R*)-(−)MTPA-Cl during the Boekelheide reaction allowed performance of the reaction at temperatures down to −78 °C, entry 5. Interestingly, ester **9c** was obtained in 67% molar yield using 2-propanol as the solvent with an 88:12 diastereomeric ratio with respect to the major isomer. Surprisingly, 2-propanol was found to be fully compatible with (*R*)-(−)MTPA-Cl in the presence of TEA and no formation of the related *i*-Pr MTPA ester was detected when the reaction was carried out at $T \leqslant -30$ °C.

When compound **10b** was reacted under the same conditions adopted in Scheme 5 the expected product **10c** was not observed in spite of the complete consumption of the starting material **10b**. In that case, the main side products detected were pyridine **10a** along with its oxidized form, likely corresponding to the trisubstituted double bond **14**, Scheme 6. We assumed that it could derive from spontaneous elimination of the ester **10c** or proton loss of intermediate **7** like, Scheme 2.

Saponification with LiOH of **8c**, **9c**, and **11c** led to free 1-(2-pyridinyl)alkyl alcohol derivatives **8d**, **9d**, and **11d**. Analysis of their absolute stereochemistry by ORP[9a,b] in comparison with the literature data revealed that all the major isomers of **8c**, **9c**, and **11c** have absolute stereochemistry *S* configuration when (*R*)-(−)MTPA-Cl was used as the promoter. To further support this result, the same reaction was carried out on **9b** with (*S*)-(−)MTPA-Cl producing, as expected, mainly the *R* isomer of **9c** with the same diastereoselectivity ratio in entry 3, Table 1.

Additionally, influence of solvent on the diastereoselection was investigated using **9b** as a model substrate, and results are summarized in Table 2. In this case only a moderate variation in terms of diastereoselectivity was detected when moving from a polar protic solvent, such as 2-propanol (D2/D1 75:25) to apolar solvents, such as toluene (D2/D1 67:33). However, we noticed that the solubility of the reaction mixture highly affects the kinetics as in the case of

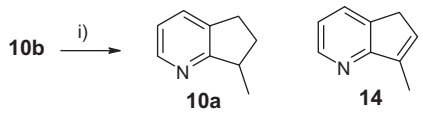


Scheme 5. Rearrangement of different N-oxide substrates promoted by (*R*)-Mosher's acyl chloride and target correlation table. Reagents and conditions: (i) m-CPBA or H_2O_2/CH_3ReO_3 cat.; (ii) solvent, TEA, (*R*)-Mosher's acyl chloride, low T; (iii) LiOH, THF/water, 70 °C.

Table 1
Reaction of different N-oxide substrates with (*R*)-Mosher's acid chloride via Scheme 5[9]

Entry	Substrate	Target	Solvent	*T* (°C)	Time (h)	Conversion[a]	Yield[b]%	D2:D1 ratio[c]	Comments
1	**8b**	**8c**	2-Propanol[d]	−30	<1	Quant.	69	78:22	*i*-Propyl ether in traces
2	**8b**	**8c**	Ethyl acetate	−30	22	Quant.	—	71:29	
3	**9b**	**9c**	Ethyl acetate	−30	22	Quant.	70	70:30	
4	**9b**	**9c**	Ethyl acetate	−78	8	80%	—	80:20	
5	**9b**	**9c**	2-Propanol[d]	−78	4	Quant.	67	88:12	*i*-Propyl ether in traces
6	**11b**	**11c**	Ethyl acetate	−30	4	Quant.	61	72:28	
7	**11b**	**11c**	2-Propanol[d]	−78	2.5	Quant.	—	78:22[e]	*i*-Propyl ether in traces
8	**10b**	—	Ethyl acetate	−30/rt		0%	0	—	

[a] Conversion from HPLC a/a TM/SM.
[b] Isolated yield as sum of D1 + D2.
[c] From HPLC D1/D2 a/a.
[d] No *i*-propyl Mosher's acid ester was detected.
[e] ^{19}F NMR is consistent with HPLC data.



Scheme 6. Reactivity of **10b**. Reagents and conditions: (i) solvent, TEA, (*R*)-Mosher's acyl chloride, −30 °C/rt.

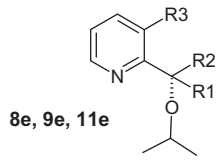
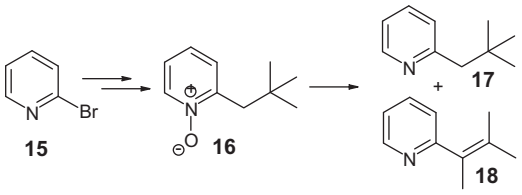


Figure 1. Proposed side products observed using 2-propanol as the solvent.

Table 2
Effect of the solvent on diastereoisomeric ratio[a]

Entry	Solvent	Temperature (°C)	D1:D2[b]
1	Ethyl acetate	−30	70:30
2	THF	−30	70:30
3	Toluene	−30	67:33
4	DCM	−30	63:37
5	DMF	−30	70:30
6	2-Propanol	−30[c]	75:25
7	MeOH	−78	—[d]

[a] Screening was conducted on Substrate **9b** under the following conditions. TEA (3 equiv), (*R*)-Mosher's acid chloride (2 equiv), *C* = 0.025 M.
[b] From HPLC D1/D2 at 2.5 h reaction time.
[c] *i*-Pr ether in traces.
[d] No rearrangement reaction.



Scheme 7. Boekelheide rearrangement on neopentyl derivative **16**.

toluene, where the reaction was found to be very slow. Moreover, as expected MeOH, was not a suitable solvent even at −78 °C, the reaction with acyl chloride to form the corresponding ester was too fast with respect to the Boekelheide reaction.

Ethyl acetate and 2-propanol turned out to be the solvents of choice in terms of conversion and diastereomeric ratio. In particular, 2-propanol accelerated the reaction kinetics with respect to ethyl acetate affording almost the same range of molar yield, Table 1.

In fact, conversion time of **9b** to **9c** was reduced from 22 h at −30 °C down to 4 h at −78 °C changing solvent from ethyl acetate to 2-propanol with a moderately positive effect on the diastereoselectivity, see entries 3 and 5 Table 2 (D2/D1 70:30; D2/D1 88:12). Similar behavior was also observed with substrates **8b** and **11b**, entry 1 and 7 Table 1. The relatively low influence of solvent polarity on selectivity shown in Table 2 provides little support for a complete ion-pair pathway (Scheme 2): 2-propanol only afforded an 8 mol % increase with respect to toluene (75:25 vs 67:33).

It is worth noting that when using 2-propanol as the solvent, entries 1, 5, and 7 Table 1, traces of a compound incorporating 2-propanol, which could fit with the corresponding *i*-propyl ethers **8e**, **9e**, and **11e** were detected by LC–MS (Fig. 1).

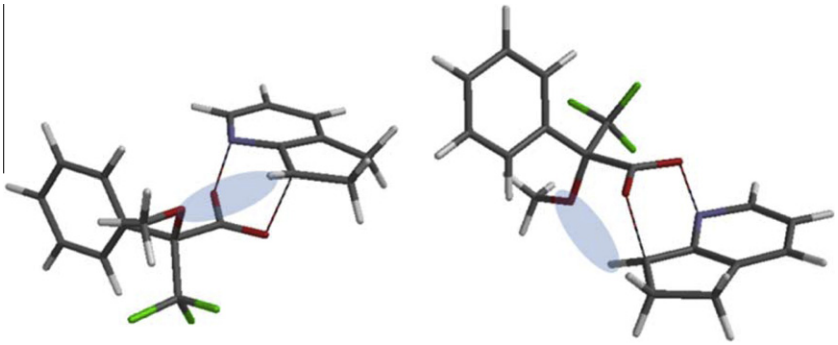


Figure 2. Putative transition states for Boekelheide rearrangement of **9b** promoted by (*R*)-(−)MTPA-Cl; on the left, the transition state leading to the (*S*) isomer, on the right, the transition state leading to the (*R*) isomer.

Intrigued by these results we decided to repeat the same experiment carried out by Katritzky[9c,d] (**16** treated with Ac_2O) to elucidate the mechanism of the Boekelheide rearrangement, Scheme 7. In that case **16**, prepared form **15**,[9c] underwent a [1,2] methyl shift to give alkene **18**, corroborating the cationic hypothesis for the reaction.

In our case, using the procedure described in Scheme 5, only degradation side products were observed where the main compound obtained was pyridine **17**; however, no trace of **18** was detected.

Explanation of the diastereselectivity encountered in the reaction of chiral (*R*)-MTPA-Cl with **8b**, **9b**, and **11b** would be straightforward considering a sigmatropic rearrangement.

However, the facial selectivity could be explained by different energetic levels associated with the transient diastereomeric intermediates both in the case of hetero-Claisen rearrangement[10], or considering a tight ion-pair pathway. For this reason we determined the geometry of the two diastereoisomeric transition states using quantum mechanics calculations.[11]

Having well in mind[12] that (*R*)-MTPA-Cl derives from (*S*)-(−)Mosher's acids, it is worth noting that the geometries observed were apparently characterized by the steric hindrance of the substituent of the (*S*)-(−)Mosher's acids, in the transition states. In the lowest minimum transition state, the methoxy group of the acid is always facing the benzylic proton at position 2 of the pyridine ring (R1, Scheme 5). From the enthalpy point of view, we found that the transition state leading to the (*S*) isomer is slightly more stable than the one leading to the (*R*) isomer (∼1.1 kcal) (see Fig. 2), which is in good agreement with the experimental findings.

2. Conclusions

We have reported the first example of asymmetric Boekelheide rearrangement applied to a set of 2-alkyl-pyridine N-oxide derivatives **8a**, **9a**, and **11a** using (*R*) Mosher's acyl chloride as activator of the rearrangement to obtain enantiomerically enriched 1-(2-pyridinyl)alkyl alcohol derivatives **8d**, **9d**, and **11d**. The reaction was observed to work effectively across a range of low temperatures from −30 to −78 °C, though only a limited effect of temperature was observed on the diastereomeric ratio. Interestingly, the absolute stereochemistry of the major isomers **8d**, **9d**, and **11d** was S in all cases when using (*R*)-MTPA-Cl. We noticed that steric hindrance close to the reaction center had a detrimental effect on the Boekelheide rearrangement, substrates **10b** and **16**. Although, at present it is possible to acquire even large amounts of chiral Mosher's acids at an acceptable price, it is possible to recover the chiral Mosher's acids after hydrolysis without losing optical purity. Additionally, it is worth pointing out that the resulting Mosher ester per se can be used to evaluate the diastereomeric ratio of the reaction, through different techniques HPLC, ^1H or ^{19}F NMR, providing then a further reason for using the chiral Mosher's acyl chloride as the activator.

We believe that future investigations should be focused on the design of alternative quaternary chiral acids, possibly driven by a quantum mechanics analysis, which would be capable of activating 2-alkyl pyridine N-oxide derivatives with increased diastereoselectivity.

Acknowledgments

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9. *Typical experimental procedures*: *Pyridines N-oxides preparation:* Compounds **8b**, **9b**, **10b** and **11b** were synthesized according to: (a) Kaiser, S.; Smidt, S. P.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2005**, *45*, 5194–5197; (b) Drury, W.; Zimmermann, N.; Keenan, M.; Hayashi, M.; Kaiser, S.; Goddard, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2003**, *43*, 70–74; intermediate **16** was synthesized according to: (c) Bodalski, R.; Katritzky, A. R. *Tetrahedron Lett.* **1968**, 257–260; (d) Bodalski, R.; Katritzky, A. R. *J. Chem. Soc. (B)* **1968**, 831–838.
Boekelheide rearrangement: preparation of 1-(2-pyridinyl)ethyl (2S)-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanoate **8c** (entry 1, Table 1). To a solution of 2-ethylpyridine 1-oxide **8b** (100 mg, 0.812 mmol) and TEA (0.340 mL, 2.436 mmol, 3 equiv) in isopropanol (4 mL) under argon at −30 °C, (*R*)-Mosher's acyl chloride (0.304 mL, 1.624 mmol, 2 equiv) dissolved in 0.5 mL of ethyl acetate was added dropwise. The resulting slurry, become thick with formation of yellow solid, was left reacting at −30 °C. After 10 min LC–MS check showed reaction almost complete. After further 40 min, the reaction mixture was taken up with EtOAc/$NaHCO_3$ saturated solution/water. The phases were separated and the aqueous one was back extracted with EtOAc. Combined organics were dried over Na_2SO_4 and evaporated to dryness to get crude material (262 mg as yellow foam). LC–MS showed D2/D1 ratio 22:78 (labels 1 and 2 assigned according to elution order). Crude material was purified by SiO_2 flash chromatography targeting mixture of D1 and D2, eluting with cyclohexane/EtOAc from 95:5 to 60:40 (R_f 0.3 cyclohexane/EtOAc 8:2,

isomers D1and D2 did not separate on SiO_2 TLC). Evaporation of solvent afforded title material (190 mg, 0.560 mmol, 69.0% yield) as pale yellow thick oil. A sample of this material was purified by preparative LC–MS for characterisation purpose to get 2 fractions:

—D1: *(1R)-1-(2-Pyridinyl)ethyl (2S)-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanoate* as colourless thick oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.71 (d, J = 6.53 Hz, 3H), 3.60 (s, 3H), 6.17 (q, J = 6.69 Hz, 1H), 7.13–7.24 (m, 1H), 7.35–7.44 (m, 4H), 7.50–7.57 (m, 2H), 7.62 (td, J = 7.72, 1.63 Hz, 1H), 8.56 (d, J = 4.27 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4, 55.5, 75.4, 84.7, 120.0, 120.5, 122.9, 127.4, 128.4, 129.6, 132.2, 136.8, 149.2, 159.2, 165.6; HRMS (ES+) calcd for $C_{17}H_{16}F_3NO_3$ $[M+H]^+$: 340.1161, found: 340.1162 (Δ 0.3 ppm).

—D2: *(1S)-1-(2-Pyridinyl)ethyl (2S)-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanoate* as colourless thick oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.65 (d, J = 6.53 Hz, 3H), 3.55 (s, 3H), 6.17 (q, J = 6.53 Hz, 1H), 7.24 (m, 1H), 7.33–7.45 (m, 4H), 7.55 (d, J = 6.27 Hz, 2H), 7.66–7.73 (m, 1H), 8.60 (d, J = 4.52 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4, 55.4, 75.5, 85.1, 120.5, 123.0, 124.8, 127.5, 128.4, 129.6, 132.2, 136.9, 149.3, 159.1, 165.8; HRMS (ES+) calcd for $C_{17}H_{16}F_3NO_3$ $[M+H]^+$: 340.1161, found: 340.1147 (Δ −4.1 ppm).

Preparation of 6,7-dihydro-5H-cyclopenta[b]pyridin-7-yl (2S)-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanoate **9c** (entry 3, Table 1). To a solution of 6,7-dihydro-5*H*-cyclopenta[*b*]pyridine 1-oxide **9b** (200 mg, 1.480 mmol) and TEA (0.619 mL, 4.44 mmol, 3 equiv) in dry ethyl acetate (6 mL) under argon at −30 °C, (*R*)-Mosher's acyl chloride (748 mg, 2.96 mmol, 2 equiv) dissolved in 1 mL of dry ethyl acetate was added dropwise. The resulting slurry, become immediately thick and dark brown, was left reacting at −30 °C for 22 h. LC–MS check at 22 h showed reaction complete and a ratio D1/D2 = 30:70 (labels 1 and 2 assigned according to elution order). Reaction mixture was taken up with EtOAc/$NaHCO_3$ saturated solution/water. The phases were separated and the aqueous one was back extracted with EtOAc. Combined organic phases were dried over Na_2SO_4 and evaporated to dryness to get crude material (1.06 g as brownish solid) that was purified by SiO_2 flash chromatography eluting with cyclohexane/EtOAc from 95:5 to 6:4. Evaporation of solvent afforded 3 fractions:

—High running spot (TLC R_f 0.6 cyclohexane/EtOAc 6:4, LC–MS D2): *(7S)-6,7-dihydro-5H-cyclopenta[b]pyridin-7-yl (2S)-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanoate* (130 mg, 0.370 mmol, 25.01% yield) as colourless oil. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.85–2.02 (m, 1H), 2.62 (m, J = 13.70, 6.10 Hz, 1H), 2.84–3.00 (m, 2H), 3.52 (s, 3H), 6.43 (m, J = 7.60, 4.70 Hz, 1H), 7.33 (m, J = 7.60, 4.70 Hz, 1H), 7.35–7.58 (m, 5H), 7.75 (d, J = 8.15 Hz, 1H), 8.49 (d, J = 4.66 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.2, 29.4, 55.2, 79.0, 83.9, 123.3, 123.9, 127.0, 128.5, 129.8, 131.7, 133.4, 137.5, 148.6, 158.9, 165.3; HRMS (ES+) calcd for $C_{18}H_{16}F_3NO_3$ $[M+H]^+$: 352.1161, found: 352.1162 (Δ 0.3 ppm).

—Low running spot (TLC R_f 0.53 cyclohexane/EtOAc 6:4, LC–MS D1): *(7R)-6,7-dihydro-5H-cyclopenta[b]pyridin-7-yl (2S)-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanoate* (43 mg, 0.122 mmol, 8.27% yield) as white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.04–2.20 (m, 1H), 2.58–2.73 (m, 1H), 2.83–3.11 (m, 2H), 3.48 (s, 3H), 6.38–6.45 (m, 1H), 7.27–7.35 (m, 1H), 7.45 (m, J = 2.30 Hz, 5H), 7.74 (d, J = 1.00 Hz, 1H), 8.44 (d, J = 1.00 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.4, 29.4, 55.1, 79.0, 84.0, 123.7, 124.6, 127.3, 128.4, 129.8, 131.6, 133.5, 137.6, 148.6, 159.1, 165.1; HRMS (ES+) calcd for $C_{18}H_{16}F_3NO_3$ $[M+H]^+$: 352.1161, found: 352.1167 (Δ 1.7 ppm).

—Mixed fractions: 6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-7-yl (2*S*)-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanoate (190 mg, 0.541 mmol, 36.5% yield) as brownish oil.

Preparation of 5,6,7,8-tetrahydro-8-quinolinyl (2S)-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanoate **11c** (entry 6, Table 1). To a solution of 5,6,7,8-tetrahydroquinoline 1-oxide **11b** (200 mg, 1.341 mmol) and TEA (0.561 mL, 4.02 mmol) in dry ethyl acetate (8 mL) under argon at −30 °C, (*R*)-Mosher's acyl chloride (0.502 mL, 2.68 mmol) dissolved in 1 mL of ethyl acetate was added dropwise. The resulting thick slurry was left reacting at −30 °C for 4 h. LC–MS check showed reaction complete and a D1/D2 ratio 28:72 (labels 1 and 2 assigned according to elution order). Reaction mixture was taken up with EtOAc/water/$NaHCO_3$ saturated solution. The phases were separated and the aqueous one was back extracted with EtOAc. Combined organics were dried over Na_2SO_4 and evaporated to dryness to get crude material (1.1 g as brown foam) that was purified by SiO_2 flash chromatography eluting with cyclohexane/EtOAc from 95:5 to 1:1. Evaporation of solvent afforded 3 fractions:

—High running spot (TLC R_f 0.55 cyclohexane/EtOAc 7:4, LC–MS D2).
(8S)-5,6,7,8-Tetrahydro-8-quinolinyl (2S)-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanoate (140 mg, 0.383 mmol, 28.6% yield) as colourless thick oil. ^{19}F NMR (376 MHz, $CDCl_3$): δ −71.68; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.79–1.86 (m, 2H), 2.03–2.13 (m, 1H), 2.15–2.23 (m, 1H), 2.69–2.87 (m, 2H), 3.62 (s, 3H), 6.31 (t, J = 4.42 Hz, 1H), 7.18 (dd, J = 7.71, 4.67 Hz, 1H), 7.34–7.41 (m, 3H), 7.44 (d, J = 7.58 Hz, 1H) 7.59–7.67 (m, 2H), 8.51 (d, J = 4.04 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.0, 28.2, 28.8, 55.6, 73.0, 121.9, 123.4, 124.9, 127.6, 128.2, 129.4, 132.7, 133.8, 137.1, 147.7, 152.2, 165.9; HRMS (ES+) calcd for $C_{19}H_{18}F_3NO_3$ $[M+H]^+$: 366.1317, found: 336.1323 (Δ 1.6 ppm).

—Low running spot (TLC R_f 0.5 cyclohexane/EtOAc 7:4, LC–MS D1).
(8R)-5,6,7,8-Tetrahydro-8-quinolinyl (2S)-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanoate (57 mg, 0.156 mmol, 11.64% yield) as pale yellow oil. ^{19}F NMR (376 MHz, $CDCl_3$): δ −72.15; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.87–2.06 (m, 2H), 2.12–2.22 (m, 1H), 2.25–2.34 (m, 1H), 2.75–2.92 (m, 2H), 3.56 (s, 3H), 6.34 (t, J = 4.67 Hz, 1H), 7.15 (dd, J = 7.71, 4.67 Hz, 1H), 7.38–7.41 (m, 3H), 7.43 (d, J = 7.83 Hz, 1H), 7.66 (dd, J = 6.32, 2.78 Hz, 2H), 8.45 (d, J = 4.55 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.8, 28.5, 29.4, 55.7, 73.3, 122.24, 123.6, 125.1, 128.3, 128.4, 129.7, 132.6, 133.7, 137.3, 148.0, 152.5, 166.0; HRMS (ES+) calcd for $C_{19}H_{18}F_3NO_3$ $[M+H]^+$: 366.1317, found: 336.1314 (Δ −0.8 ppm).

—Mixed fractions.
5,6,7,8-Tetrahydro-8-quinolinyl (2S)-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanoate (100 mg, 0.274 mmol, 20.42% yield) as a colourless thick oil.

10. Dalko, P. I.; Langlois, Y. *Tetrahedron Lett.* **1998**, *39*, 2107–2110.
11. Initial guess for the transition states were calculated using the transition state module available within Spartan'02 (www.wavefun.com). STO-3G full transition state optimization was then carried out until convergence. Vibration analysis was also carried out to check consistency amongst the imaginary frequency and the transition state path. The transition state leading to the (*S*) isomer had a total energy of −1251.8706985 au, while the one leading to the (*R*) isomer had a total energy of −1251.8689235 au. The difference in kcal/mol is 1.11 kcal in favour of the transition state leading to the (*S*) isomer.
12. Attention must be paid to the change of the *R* and *S* label when the chiral Mosher's acid is converted to the corresponding chiral Mosher's acyl chloride.