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Synthesis of α-amino esters by dynamic kinetic resolution of α-haloacyl imidazolidinones

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Abstract—Dynamic kinetic resolution of α-haloacyl imidazolidinones with a variety of nitrogen and carbon nucleophiles has been achieved with selectivities up to 100% (d.e.). An unusual dichotomy of diastereoselection has been observed whereby metalated nucleophiles preferentially react via the 5*S*,2′*R* diastereomer whilst amine nucleophiles react via the 5*S*,2′*S* diastereomer. Mild procedures are described for the coupling and removal of the ephedrine based chiral auxiliary.

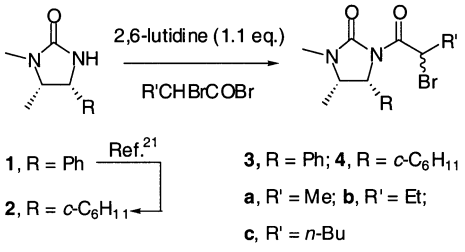
1. Introduction

Dynamic resolution strategies are being increasingly employed in the synthesis of chiral organic molecules.[1–4] The use of α-haloacyl compounds in dynamic kinetic resolution (DKR) reactions has been an active area of interest.[5–18] α-Haloacyl compounds are versatile precursors in DKR reactions because they are easily obtained in racemic form. Configurational lability can be readily induced and the α-haloacyl functionality allows access to a wide range of synthetically useful products via nucleophilic substitution. We herein present a study on the DKR of α-haloacyl compounds using a chiral auxiliary approach which we have generally developed with a view to amino-acid synthesis. We chose to use ephedrine derived imidazolidinones to provide a chiral environment for efficient stereo-differentiation.[19] The chiral auxiliary **1** is readily synthesised by the thermal fusion of ephedrinium chloride and urea.[20] This auxiliary appealed to us because of the availability of both enantiomers of ephedrine. The saturated cyclohexyl adduct, **2**, was furnished efficiently according to the procedure of Roos and Drewes.[21]

2. Results

2.1. Acylation of imidazolidinone auxiliaries with racemic 2-bromoacyl bromides

In order to prepare the desired precursors we required an



Scheme 1.

Table 1. Acylation of imidazolidinone auxiliaries **1** and **2** with racemic 2-bromoacyl bromides

Entry	Auxiliary	Acid bromide		Temp. (°C)	Product	Yield (%)
		R′	Equiv.			
1	**1**	Me	(1.1)	−20	**3a**	96
2	**1**	Et	(1.1)	−20	**3b**	95
3	**1**	*n*-Bu	(1.5)	−10	**3c**	81
4	**2**	Et	(1.1)	−20	**4b**	61[a]

[a] 79% Yield with respect to recovered **2**.

Keywords: resolution; diastereoselection; acylation; cleavage reactions.

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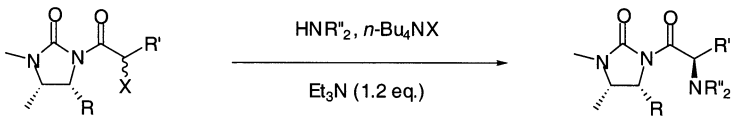


	R	R'	X		R	NR''_2
3a	Ph	Me	Br	**6a-c**	Ph	$NHCH_2Ph$
3b	Ph	Et	Br	**7a-c**	Ph	N*c*-$(CH_2)_4$
3c	Ph	*n*-Bu	Br	**8a-c**	Ph	N*c*-$(CH_2)_5$
4b	*c*-C_6H_{11}	Et	Br	**9b**	Ph	NH*c*-C_6H_{11}
5a	Ph	Me	I	**10b**	*c*-C_6H_{11}	$NHCH_2Ph$

Scheme 2.

Table 2. DKR's on substrates **3a–c**, **4b** and **5a** with amine nucleophiles

Entry	Starting material	Nucleophile (equiv.)[a]	*n*-Bu_4NX (eq.)[b]	Solvent	Temp.[c]	Time	Product[d]	Yield (%)	d.e. (%)[e]
1	**3a**	Benzylamine	Br	THF	rt	77 h	**6a**	87	58
2	**3a**	Benzylamine	Br (2.0)	THF	rt	42 h	**6a**	80	37
3	**3a**	Benzylamine	I	THF	rt	48 h	**6a**	quant.	74
4	**3a**	Benzylamine	I (2.0)	THF	rt	44 h	**6a**	85	62
5	**3a**	Pyrrolidine	Br	THF	rt	62 h	**7a**	62	24
6	**3a**	Pyrrolidine	I	THF	rt	46 h	**7a**	quant.	42
7	**3a**	Piperidine	Br	THF	rt	91 h	**8a**	88	57
8	**3a**	Piperidine	I	THF	rt	91 h	**8a**	93	72
9	**5a**	Benzylamine	I	THF	rt	51 h	**6a**	96	79
10	**5a**	Pyrrolidine	I	THF	rt	69 h	**7a**	79	68
11	**5a**	Piperidine	I	THF	rt	50 h	**8a**	91	81
12	**3a**	Benzylamine	I	THF	−8	7 days	**6a**	70	59[f]
13	**3a**	Benzylamine	I	THF	Δ	24 h	**6a**	90	71
14	**3a**	Benzylamine	I	MeCN	rt	43 h	**6a**	84	6
15	**3a**	Benzylamine	I	DMF	rt	49 h	**6a**	73	8
16	**3a**	Benzylamine	I	MeOH	rt	4 days	**6a**	36	0[g]
17	**3b**	Benzylamine	I	THF	rt	48 h	**6b**	77	59
18	**3b**	Benzylamine	I	THF	Δ	48 h	**6b**	97	76
19	**3b**	Pyrrolidine	I	THF	rt	63 h	**7b**	63	73
20	**3b**	Pyrrolidine	I	THF	Δ	48 h	**7b**	87	89
21	**3b**	Piperidine	I	THF	rt	72 h	**8b**	79[h]	88
22	**3b**	Piperidine	I	THF	Δ	43 h	**8b**	97	94
23	**3b**	Cyclohexylamine	I	THF	Δ	4 days	**9b**	88	81
24	**3b**	Benzylamine	I	BTF	83	48 h	**6b**	98	62
25	**3b**	Benzylamine	I	$BMIBF_4$[i]	83	48 h	**6b**	45	2
26	**3c**	Benzylamine	I	THF	rt	47 h	**6c**	55	58[j]
27	**3c**	Benzylamine	I	THF	Δ	72 h	**6c**	71	82
28	**3c**	Pyrrolidine	I	THF	Δ	6 days	**7c**	99	100
29	**3c**	Piperidine	I	THF	Δ	48 h	**8c**	94	100
30	**4b**	Benzylamine	I	THF	Δ	48 h	**10b**	97	86
31[k]	**3a**	Benzylamine	I	THF	rt	75 h	**6a**	79	65
32[l]	**3a**	Pyrrolidine	Br (5.0)	THF	rt	44 h	**s-7a**	64	−28
33	**3a**	Pyrrolidine	I, NO_3	THF	rt	24 h	**s-7a**	64	−22
34	**3b**	Pyrrolidine	I, NO_3	THF	Δ	47 h	**s-7b**	94	−15
35	**3c**	Pyrrolidine	I, NO_3	THF	Δ	23 h	**s-7c**	80	−13

Amine DKR's carried out at 0.1 M with respect to starting material (unless otherwise stated).

[a] 1.5 equiv. nucleophile used.

[b] 0.2 equiv. *n*-Bu_4NI/*n*-Bu_4NBr used unless otherwise stated in parentheses; 16.0 equiv. *n*-Bu_4NNO_3 used in entries 33–35.

[c] rt=ambient temperature); Δ=reflux temperature; other values relate to oil bath temperature.

[d] Products have the 2′*R* stereochemistry (as depicted in Scheme 2) unless otherwise stated.

[e] d.e. values determined by ^1H NMR signal integrations. Minus (−) prefix denotes opposite sense of stereoselectivity to that depicted in Scheme 2.

[f] 26% recovered **3a** (62% d.e. in 2′*R*), 3% recovered **5a** (50% d.e. in 2′*R*).

[g] 0.08M in **3a**. 44% auxiliary, **1**; 25% ester, **17a**.

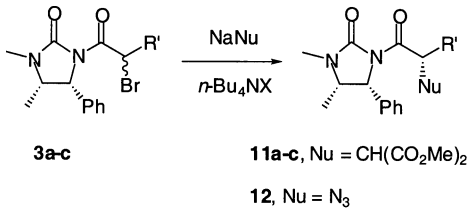
[h] 16% recovered **3b**.

[i] $BMIBF_4$=1-*n*-butyl-3-methylimidazolium tetrafluoroborate.

[j] 0.083 M in starting material, 27% recovered **3a**.

[k] Reaction doped with $Et_3N{\cdot}HBr$ 1.0 equiv.

[l] 0.05 M in **3a**.



Scheme 3.

under non-epimerising conditions simple nucleophilic substitution reactions of diasteroisomerically pure bromides proceed with inversion of configuration. Under epimerising conditions a number of DKR reactions proceeded in excellent yield and with high selectivities. Higher levels of selectivity were generally observed when *n*-Bu_4NI was used in place of *n*-Bu_4NBr as the epimerising agent (entries 1 vs 3; 2 vs 4; 5 vs 6; 7 vs 8). The 2′-iodo substrate **5a** gave higher selectivity than the corresponding 2′-bromo

Table 3. DKR's on substrates **3a–c** with ionic nucleophiles

Entry	Starting material	Nucleophile	*n*-Bu_4NX (equiv.)[a]	Solvent[b]	Temp.[c]	Time	Product[d]	Yield	d.e. %[e]
1[f]	**3a**	SDM	Br (2)	THF	rt	6 days	**11a**	62	54–60
2[g]	**3a**	SDM	Br (2)	THF	rt	66 h	**11a**	78	40–60
3[g]	**3a**	SDM	I (1)	THF	rt	66 h	**11a**	74	20–25
4	**3b**	SDM	Br	THF	Δ	48 h	**11b**	90	35
5	**3b**	SDM	I	THF	Δ	48 h	**11b**	94	14
6	**3b**	SDM (2.7)	Br	BTF	83	48 h	**11b**	93	33
7	**3b**	SDM (2.7)	I	BTF	83	48 h	**11b**	92	28
8	**3c**	SDM (2.7)	Br	THF	Δ	27 h	**11c**	83	52
9	**3c**	SDM (2.7)	I	THF	Δ	27 h	**11c**	99	31
10	**3b**	NaN_3 (1.5)	Br	BTF	83	30 h	**12b**	quant.	31
11	**3b**	NaN_3 (1.5)	I	BTF	83	30 h	**12b**	95	23

Sodium dimethyl malonate (SDM) DKR's carried out by addition of SDM (0.70 M in THF unless otherwise stated) to a solution of starting material (0.1 M in THF).
[a] 0.2 equiv. *n*-Bu_4NI/*n*-Bu_4NBr used unless otherwise stated in parentheses.
[b] BTF=Benzotrifluoride (α,α,α-Trifluorotoluene).
[c] rt=ambient temperature; Δ=reflux temperature; other values relate to oil bath temperature.
[d] Products have the stereochemistry depicted in Scheme 3.
[e] d.e. values determined by ^1H NMR signal integrations except entries **8** and **9** which were isolated.
[f] SDM (0.034 M in THF) added over 28 h to **3a** (0.1 M in THF).
[g] SDM (0.2 M in THF) added over 27 h to **3a** (0.2 M in THF).

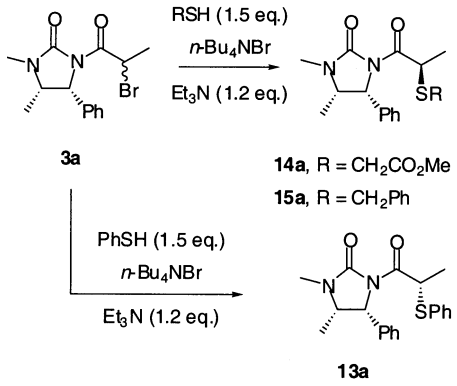
efficient acylation of the imidazolidinone chiral auxiliary.[†] We developed a convenient and reliable method using 2,6-lutidine and an appropriate racemic 2-bromoacyl bromide (Scheme 1, Table 1). The products were isolated as diastereomeric mixtures.[‡] Acyl chlorides are effective reagents in this coupling protocol,[§] but the potential for bromine/chlorine transposition led us to use the corresponding acyl bromides.

2.2. Dynamic kinetic resolution with amine nucleophiles

We examined DKR reactions using amine nucleophiles as a potential synthetic approach to enantiomerically enriched α-amino acid derivatives (Scheme 2, Table 2). Substrate epimerisation was effected using tetra-*n*-butylammonium bromide/iodide (*n*-Bu_4NBr/I).[‖]

Extensive control experiments confirmed that, as expected, analogue under *n*-Bu_4NI catalysis (entries 9 vs 3; 10 vs 6; 11 vs 8). Selectivity tended to increase with chain length (e.g. entries 13 vs 18 vs 27). Also, when the chiral directing group was changed from phenyl to cyclohexyl an increase in selectivity was seen (entry 30 vs 18). The level of stereoselectivity was compromised at lower reaction temperatures (entries 18 vs 17; 20 vs 19; 22 vs 21; 27 vs 26 and 12 vs 3) although once the optimum d.e. has been reached, raising the temperature further appeared to have little influence on the selectivity (entries 13 vs 3). Of the solvents explored, THF consistently gave the best results. Polar solvents resulted in considerable loss of selectivity (entries 14–16). We were surprised to observe appreciable methanolysis when methanol was employed as the solvent (entry 16). In the one example in which the perfluoro solvent BTF was used a modest drop in selectivity resulted (entry 24 vs 18). During the process of optimisation we noticed that increasing the amount of *n*-Bu_4NX or using the ionic liquid 1-*n*-butyl-3-methylimidazolium tetrafluoroborate[27] ($BMIBF_4$) tended to erode the selectivity (entries 2 vs 1, 4 vs 3 and 25 vs 18). In the case of the DKR of **3a** with pyrrolidine this resulted in actual reversal of the sense of stereoselectivity (entry 32 vs 5). These counter-intuitive results led us to probe the effect of ionic strength on the DKR selectivities. The use of an excess of *n*-Bu_4NNO_3 was shown to reverse the sense of selectivity in the pyrrolidine DKR's of **3a**, **3b** and **3c**, albeit with low selectivity (entries 33–35). A mild drop in selectivity was seen when we doped the reaction of **3a** and benzylamine with triethylamine hydrobromide (entry 31 vs 3).

[†] A number of coupling methods were investigated[21–26] but these gave capricious results and frequently poor yields (less then 50%).
[‡] The diastereomer composition sometimes varied in these reactions but the subsequent DKR reactions were performed on substrates with 1:1 d.r. or on mixtures that were at equilibrium under epimerising conditions (3–17% d.e.).
[§] For example acylation of **1** with phenylacetyl chloride proceeded with 66% yield and acylation of **1** with propionyl chloride proceeded with 91% yield using the 2,6-lutidine method.
[‖] We observed epimerisation of individual diastereomers in THF and $CDCl_3$ in the presence of Bu_4NBr/I.



Scheme 4.

2.3. Dynamic kinetic resolution with metalated nucleophiles

The substrates **3a–c** were treated with either sodium dimethyl malonate (SDM) or sodium azide under substrate epimerising conditions (Scheme 3). The results of some of the DKR reactions are summarised in Table 3.

In general, good yields were achieved although selectivity ranged from poor to moderate. Perhaps the most striking facet in these DKR's was the general observation that the sense of stereoselection observed with these ionic nucleophiles was opposite to that seen in the DKR reactions with amine nucleophiles. We also observed that DKR reactions carried out under bromide epimerisation gave higher levels of selectivity than the corresponding iodide catalysed DKR's. Substrate **3a** reacted relatively quickly with SDM and good stereoselectivity was only achieved after optimising the reaction conditions. This was accomplished by employing slow addition of SDM under dilute conditions and by having an excess of epimerising agent (entries 1–3). It is interesting to note that the perfluoro solvent, BTF, gave an improved d.e., over THF, in the DKR of **3b** with SDM (entry 5 vs 7). During the course of our investigation we have attempted to carry out DKR reactions using azide nucleophiles to enable us to access synthetically important α-amino acids. Typically these DKR's have proceeded with no appreciable selectivity, as one might expect from such a small nucleophile. However, encouraged by the malonate DKR's carried out in BTF, we used this solvent in the DKR's with NaN_3 (entries 10 and 11). We were gratified to observe some selectivity albeit modest.

2.4. Dynamic kinetic resolutions with sulfur nucleophiles

The results of DKR reactions using **3a** and sulfur nucleophiles are presented below (Scheme 4, Table 4).

The high reactivity of the sulfur nucleophiles resulted in rapid nucleophilic displacement reactions relative to the epimerisation process and this may explain the lack of selectivity. To overcome this problem these reactions were performed at higher dilutions than the corresponding amine DKR's whilst the concentration of n-Bu_4NBr was kept constant. High levels of selectivity were not achieved which is disappointing from a synthetic point of view. From a mechanistic standpoint it is interesting to note that both methyl thioglycolate and benzylmercaptan gave the 2′*R* products (Table 4, entries 3–5) as the major diastereomer (analogous to the amines), whilst thiophenol gave predominantly the 2′*S* product (analogous to the diastereoselection seen with ionic nucleophiles).

Table 4. DKR's on substrate **3a** with sulfur nucleophiles

Entry	Nucleophile	n-Bu_4NBr (equiv.)	[**3a**] (M)	Time	Product[a]	Yield (%)	d.e. (%)[b]
1	PhSH	2.0	0.01	4 days	*S*-**13a**	78	19
2	PhSH	20.0	0.001	7 days	*S*-**13a**	96	34
3	$MeOCOCH_2SH$	2.0	0.01	48 h	*R*-**14a**	79	9
4	$MeOCOCH_2SH$	20.0	0.001	7 days	*R*-**14a**	80	10
5	$PhCH_2SH$	2.0	0.01	7 days	*R*-**15a**	56	11

Thiol DKR's carried out in THF at rt.
[a] The stereochemistry of the major isomer is indicated by the prefix in the table and is as depicted in Scheme 4.
[b] d.e. values determined by ^1H NMR signal integration.

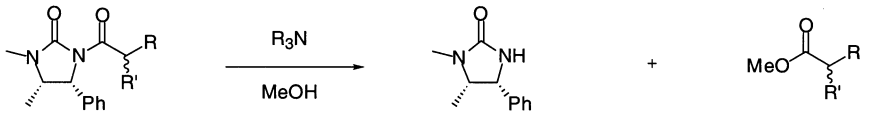
2.5. Methanolysis

The result obtained in the amine DKR carried out in methanol (see Table 2, entry 16) led us to investigate the cleavage of the chiral auxiliary using mild conditions (Scheme 5, Table 5). We ascertained that the substrates used were stable in methanol solutions. However, we discovered that the auxiliary could be removed under remarkably mild cleavage conditions employing a simple amine base in methanol; cleavage of this auxiliary under such mild basic conditions is surprising as conventionally, much harsher conditions are more commonly employed.

The 2-aminopropionyl substrates generally cleaved readily using 1.2 equiv. of Et_3N whilst the 2-aminobutyryl and 2-aminohexanoyl substrates typically required a higher concentration of Et_3N and longer reaction times. The enantiomeric excess of some of the products was shown to be 78–90% implying a degree of racemisation. The relationship between the strength of the base and the efficiency of the methanolysis was implied by the methanolysis of substrate **16** with Et_3N and Hünig's base (Table 5, entries 9 and 10, respectively).

3. Discussion

In this study we have not sought to optimise every DKR but to ascertain the salient features that are important in DKR



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	R	R'
***S*-6a**	Me	$NHCH_2Ph$
***R*-6a**	Me	$NHCH_2Ph$
***R*-6b**	Et	$NHCH_2Ph$
***R*-6c**	*n*-Bu	$NHCH_2Ph$
***R*-7a**	Me	N*c*-$(CH_2)_4$
***R*-7c**	*n*-Bu	N*c*-$(CH_2)_4$
***R*-8a**	Me	N*c*-$(CH_2)_5$
***R*-8c**	*n*-Bu	N*c*-$(CH_2)_5$
16	Ph	H

	R	R'
***S*-17a**	Me	$NHCH_2Ph$
***R*-17a**	Me	$NHCH_2Ph$
***R*-17b**	Et	$NHCH_2Ph$
***R*-17c**	*n*-Bu	$NHCH_2Ph$
***R*-18a**	Me	N*c*-$(CH_2)_4$
***R*-18c**	*n*-Bu	N*c*-$(CH_2)_4$
***R*-19a**	Me	N*c*-$(CH_2)_5$
***R*-19c**	*n*-Bu	N*c*-$(CH_2)_5$
20	Ph	H

Scheme 5.

Table 5. Methanolysis of *N*-acylimidazolidinones

Entry	Substrate		R_3N	Time	Products		
	[substrate]	(M)			Ester[a]	Yield	**1** (Yield)
1	*S*-**6a**	0.11	Et_3N (1.2)	24 h	*S*-**17a**	72	73
2	*R*-**6a**	0.11	Et_3N (1.2)	23 h	*R*-**17a**	75	77
3	*R*-**6b**	0.11	Et_3N (6.0)[b]	6 days	*R*-**17b**	84	85[c]
4	*R*-**6c**	0.12	Et_3N (6.0)[b]	7 days	*R*-**17c**	62	79
5	*R*-**7a**	0.10	Et_3N (1.2)	26 h	*R*-**18a**	39	37
6	*R*-**7c**	0.50	Et_3N (6.1)	16 days	*R*-**18c**	68	49
7	*R*-**8a**	0.10	Et_3N (1.2)	26 h	*R*-**19a**	71	19
8	*R*-**8c**	0.50	Et_3N (6.1)	16 days	*R*-**19c**	65	63[d]
9	**16**	0.10	Et_3N (1.0)	76 h	**20**	39	34[e]
10	**16**	0.10	*i*-Pr_2NEt (1.0)	76 h	**20**	78	47[f]

Reactions carried out in dry methanol at reflux.
[a] The product e.e. was determined by chiral HPLC (Chiralcel® OD) for entries 1–4. Entries 1, 2 and 4 gave 90% e.e; entry 3 gave 78% e.e..
[b] 1.2 equiv. Et_3N followed by 4.8 equiv. after 48 hours.
[c] 5% recovered *R*-**6b**.
[d] 20% recovered *R*-**8c**.
[e] 29% recovered **16**.
[f] 3% recovered **16**.

systems of this type. From our results we can make a number of generalisations. Perhaps the most intriguing aspect of this study is the dichotomy of stereoselectivity observed between the metalated and the neutral nucleophiles. The former can be rationalised utilising a model originally proposed in other related systems.[10,15] To account for the anomalous stereoselectivity observed with amine nucleophiles, we have previously proposed a model based on a hydrogen bonded amine-substrate complex. In this model we postulated that a bifurcated hydrogen bond bridges the imidazolidinone and acyl carbonyl groups thus altering the conformation and hence reversing the stereoselectivity of the DKR reaction (Fig. 1).[1,5] We have used this model as a simple device from which we can predict the stereochemical outcome of our reactions and it can be used to rationalise all DKR results presented thus far. However, as will be discussed in the following paper, we have carried out extensive molecular modelling experiments and feel that the assembly shown in Fig. 2 is probably more accurate. It too relies on a H-bond model in which the amine forms a more conventional H-bond with the strongly basic ring carbonyl group. The stereochemical outcome is governed by

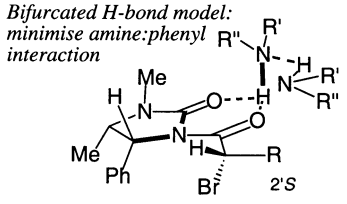

Figure 1.

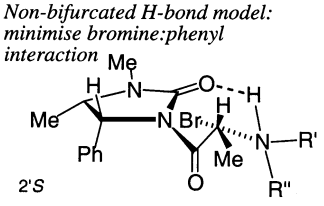

Figure 2.

the steric and/or electrostatic interactions between the bromine leaving group and the phenyl group on the auxiliary. As the amine undergoes substitution a twisting of the C_1–C_2 bond is required which potentiates these interactions in the 2′*R* isomer but not in the 2′*S* isomer, hence its greater reactivity with H-bonding nucleophiles.

The sense of diastereocontrol in the DKR reactions with methyl thioglycolate and benzylmercaptan were analogous to those of the amine DKR's. The poor selectivity may, in part, be a reflection of the relatively poor hydrogen bond donor properties of thiols. The result of the DKR with thiophenol, which reacted preferentially with the 2′*R* diastereomer, is easily understood in that in the presence of Et_3N, thiophenol exists as a salt complex (pK_a PhSH=6.5; pK_a Et_3NH^+=10.7). Hence under the reaction conditions thiophenol will react principally as the thiophenolate anion and the model previously presented for metalated nucleophiles applies in this case.

The diminished selectivity seen with amine DKR's in polar solvents might be attributed to the disruption of hydrogen bonding interactions. Similarly the presence of high concentrations of organic salts lead to selectivity erosions and reversals in some cases. In addition to disrupting hydrogen bonding, the ionic strength media would also provide stabilisation of localised partial charges in the transition state. Hence a formal S_N2 mechanism would become increasingly favourable. This would tend to result in preferential reaction of the 2′*R* diastereomer. This also holds true for the reaction carried out in the ionic solvent $BMIBF_4^-$. The use of *n*-Bu_4NI as the epimerising agent presumably generates the 2′-iodo analogues in-situ. This may account for the enhanced stereoselectivity with amines. Indeed, the use of the stoichiometric 2′-iodo substrate led to higher diastereoselectivities. This behaviour can also be explained using the revised H-bond model which will be presented in detail in the adjoining paper.

4. Conclusion

We have shown that dynamic kinetic resolution of α-haloacyl imidazolidinones can be successfully applied towards the synthesis of a range of enantiomerically enriched products. The use of amine nucleophiles in particular allows access to α-amino acid derivatives, often with excellent yield and stereoselectivity (up to 100%). We have achieved DKR reactions with sodium dimethylmalonate as a carbon nucleophile. The potential for asymmetric carbon–carbon bond homologation is very appealing although further optimisation may be needed if this approach is to be synthetically useful. The poor selectivities observed with sulfur nucleophiles are disappointing. Our use of the ephedrine derived chiral auxiliaries was justified from a practical and economic standpoint. The diastereomeric nature of the products of these DKR reactions greatly assists in the separation and purification of the desired stereoisomer whereas in an enantioselective process one must generate the product with initially high e.e. unless the product can be enriched by crystallisation. The development of facile coupling and cleavage protocols alleviates some of the inherent disadvantages associated with chiral auxiliaries. The acylation utilises the amine base 2,6-lutidine thus obviating the need for organometallic bases and the associated low temperatures that they necessitate. The mild methanolysis reactions have synthetic potential although the usefulness of this protocol may be limited by the accompanying reduction of optical purity. Work is continuing to further extend the scope of dynamic resolutions toward asymmetric synthesis and to probe the reactive properties observed with *N*-acyl imidazolidinones.

5. Experimental

All glasswares were oven dried and cooled in a desiccator (P_2O_5 desiccant) prior to use. Reaction solvents were predried and distilled immediately prior to use. Tetrahydrofuran (THF) was pre-dried over sodium wire and distilled from sodium/benzophenone under a nitrogen atmosphere. Methanol was distilled from iodine/magnesium turnings under a nitrogen atmosphere. *N*,*N*-Dimethyl formamide (DMF), acetonitrile and dichloromethane (DCM) were distilled from calcium hydride powder under a nitrogen atmosphere.

Commercially supplied reagents were used as supplied except for acyl halides which were distilled prior to use. 1-*n*-Butyl-3-methylimidazolium tetrafluoroborate ($BMIBF_4$) was prepared following reported procedure.[28]

Flash column chromatography was carried out using Merck 60 silica gel (70–240 μm) or basic alumina (activated, Brockmann grade II). The non polar liquid phase was either distilled hexanes or petroleum ether 40–60°C boiling fraction unless otherwise stated. Pet_{30-40} refers to petroleum ether 30–40°C boiling fractions which were distilled prior to use. Other eluents were used as supplied. Thin layer chromatography was carried out using Merck Kieselgel 60 F_{254} pre-coated, glass backed plates. The plates were visualised using ultraviolet light (254 nm), $KMnO_4$ solution, ninhydrin or iodine as appropriate. HPLC was carried out using a Chiralcel OD-H (0.46 cm ∅×25 cm) stationary phase.

^{1}H NMR spectra were recorded on Brüker AMX 500, ARX 400, WM 360 or DPX 300 spectrometers. Chemical shifts are reported downfield in parts per million (ppm) from a tetramethyl silane reference. ^{13}C NMR spectra were recorded on Brüker AMX 500, ARX 400 or DPX 300 spectrometers at 125, 100 or 75 MHz, respectively. Infra red spectra were recorded on a Perkin–Elmer FT-IR 1720 spectrometer as thinly dispersed films (from DCM) between sodium chloride plates unless otherwise stated. Low resolution (EI/FAB) mass spectra were recorded using a Fisons Autospec or Kratos mass spectrometer. High resolution accurate mass determinations were carried out by the EPSRC National Mass Spectrometry Service, University of Wales-Swansea, Singleton Park, Swansea, Wales. Optical rotations were carried out using a Perkin–Elmer 241 or Optical Activity Mod. AA-1000 digital polarimeters with a cell path length of 10 or 5 cm, respectively. The mean value for 10 α readings was taken. Melting points were carried out on a Gallenkamp melting point apparatus and are uncorrected. X-Ray crystal structure data was collected

using Enraf–Nonius CAD software. Structure solutions and refinements were carried out using SHELXS-86 and SHELXL-93 programs, respectively.

5.1. Auxiliary coupling reactions

General procedure. To a stirred solution of imidazolidinone in DCM or THF, under an inert atmosphere (argon or N_2), was added 2,6-lutidine. The solution was cooled and 2*RS*-bromoacyl halide was added in a drop wise fashion. The reaction was monitored by TLC and quenched with saturated (aq.) NH_4Cl. The mixture was diluted with DCM and extracted with saturated (aq.) NH_4Cl (4–5 portions). The combined aqueous phase was back extracted with DCM and the combined organic phase was washed once with brine and dried with $MgSO_4$. The crude product was purified by column chromatography.

5.1.1. Preparation of (2′*RS*,4*S*,5*R*)-1-*N*-(2′-bromopropanoyl)-3,4-dimethyl-5-phenylimidazo-lidin-2-one, 2′*RS*-3a (Table 1, entry 1). 1 (100.3 mg, 5.3 mmol), 2,6-lutidine (0.07 mL, 0.60 mmol), 2*RS*-bromopropanoyl bromide (0.06 mL, 0.57 mmol), DCM (3.0 mL). Reaction performed at −20°C. Reaction time 2 h. Purification (SiO_2, Hex/EtOAc 8:2, 7:3 and 6:4) gave the diastereomers 2′*RS*-**3a** as a white crystalline solid (164.3 mg, 96%).

2′*R*-**3a**: mp 144.9–147.5°C; ν_{max} 3031, 2977, 2917, 2352, 1729, 1693, 1651, 1634, 1556, 1515, 1471, 1429, 1387, 1308, 1289, 1239, 1192, 1059, 991, 946, 776, 759, 700, 676 cm^{-1}; δ_H ($CDCl_3$) 7.37–7.22 (5H, m, Ph), 5.98 (1H, q, *J*=6.8 Hz, CO*CH*(Br)CH_3), 5.34 (1H, d, *J*=8.8 Hz, N*CH*(Ph)CH), 3.92 (1H, m, N*CH*(CH_3)CH), 2.86 (3H, s, NCH_3), 1.78 (3H, d, *J*=6.8 Hz, CH(Br)CH_3), 0.82 (3H, d, *J*=6.6 Hz, CHCH_3); δ_C ($CDCl_3$) 170.5, 156.6, 137.3, 130.4, 130.1, 128.9, 60.1, 55.7, 41.6, 30.3, 22.2, 17.1; *m*/*z* (EI) 326 (M^+), 245 (M^+-Br), 189 ($M^+-COCH(Br)CH_3$), 175, 132, 91, 77, 58, 42; Found M^+, 324.0473. $C_{14}H_{17}BrN_2O_2$ requires M, 324.0473; R_f=0.22 Pet/EtOAc (2:1); $[\alpha]^{32}_D$=−82.4° (*c*=6.3, $CHCl_3$).

2′*S*-**3a**: mp 132.5–133.5°C; ν_{max} 3076, 3035, 2989, 2879, 1729, 1688, 1495, 1445, 1422, 1377, 1307, 1289, 1259, 1237, 1188, 1137, 1107, 1082, 1060, 1029, 991, 948, 864, 811, 781, 757, 742, 698, 672 cm^{-1}; δ_H ($CDCl_3$) 7.34–7.27 (3H, m, 3ArH), 7.13 (2H, m, 2ArH), 6.00 (1H, q, *J*=6.7 Hz, CO*CH*(Br)CH_3), 5.29 (1H, d, *J*=8.3 Hz, NC*H*(Ph)CH), 4.00 (1H, m, NC*H*(CH_3)CH), 2.88 (3H, s, NCH_3), 1.75 (3H, d, *J*=6.7 Hz, CH(Br)CH_3), 0.82 (3H, d, *J*=6.5 Hz, CHCH_3); δ_C ($CDCl_3$): 169.4, 155.3, 136.6, 129.0, 128.7, 127.2, 60.4, 54.2, 40.5, 28.6, 21.4, 15.2; *m*/*z* (EI) 324 (M^+), 245, 189, 175, 132, 91, 77, 58, 42; Found M^+, 324.0473. $C_{14}H_{17}BrN_2O_2$ requires M, 324.0473; R_f=0.53 Pet/EtOAc (2:1); $[\alpha]^{32}_D$=−89.2° (*c*=8.9, $CHCl_3$).

5.1.2. Preparation of (2′*RS*,4*S*,5*R*)-1-*N*-(2′-bromobutanoyl)-3,4-dimethyl-5-phenylimidazo-lidin-2-one, 2′*RS*-3b (Table 1, entry 2). 1 (1.00 g, 5.26 mmol), 2,6-lutidine (0.68 mL, 0.58 mmol), 2*RS*-bromobutanoyl bromide (0.68 mL, 5.81 mmol), DCM (30 mL). Reaction performed at −20°C. Reaction time 90 min. Purification (SiO_2, Pet/EtOAc 8:2–6:4) gave 2′*RS*-**3b** (1.70 g, 95%).

2′*R*-**3b**: mp 85–87°C; ν_{max} 3042, 2985, 2946, 2889, 1736, 1690, 1389 cm^{-1}; δ_H ($CDCl_3$) 7.28–7.14 (5H, m, ArH), 5.74 (1H, t, *J*=7.3 Hz, CO*CH*(Br)CH_2), 5.26 (1H, d, *J*=8.8 Hz, NC*H*(Ph)CH), 3.85 (1H, dq, *J*=6.6, 8.8 Hz, NC*H*(CH_3)CH), 2.78 (3H, s, NCH_3), 2.03 (1H, ddq, *J*=7.3, 7.3, 13.8 Hz, CH(Br)C$H_A$$H_B$$CH_3$), 1.92 (1H, ddq, *J*=7.3, 7.3, 13.8 Hz, CH(Br)C$H_A$$H_B$$CH_3$), 0.94 (3H, t, *J*=7.3 Hz, CH_2CH_3), 0.73 (3H, d, *J*=6.6 Hz, CHCH_3); δ_C ($CDCl_3$): 168.1, 154.7, 135.4, 128.4, 128.2, 126.9, 59.2, 53.8, 46.8, 28.3, 27.1, 15.1, 12.0; *m*/*z* (EI) 338 (M^+), 259, 189, 132, 58; Found M^+, 338.0629. $C_{15}H_{19}BrN_2O_2$ requires M, 338.0630; R_f=0.46 Hex./EtOAc (6:4); $[\alpha]^{25}_D$=−79.8° (*c*=1.0, $CHCl_3$).

2′*S*-**3b**: mp 75–77°C; ν_{max} 3031, 2978, 2934, 2877, 1736, 1690, 1389 cm^{-1}; δ_H ($CDCl_3$) 7.28–7.20 (3H, m, ArH), 7.06 (2H, m, ArH), 5.80 (1H, t, *J*=7.2 Hz, CO*CH*(Br)CH_2), 5.24 (1H, d, *J*=8.5 Hz, NC*H*(Ph)CH), 3.91 (1H, dq, *J*=6.5, 8.5 Hz, NC*H*(CH_3)CH), 2.79 (3H, s, NCH_3), 2.00 (1H, ddq, *J*=7.2, 7.3, 14.3 Hz, CH(Br)C$H_A$$H_B$$CH_3$), 1.89 (1H, ddq, *J*=7.2, 7.3, 14.3 Hz, CH(Br)C$H_A$$H_B$$CH_3$), 0.84 (3H, t, *J*=7.3 Hz, CH_2CH_3), 0.75 (3H, d, *J*=6.6 Hz, CHCH_3); δ_C ($CDCl_3$): 168.6, 154.9, 136.3, 128.6, 128.2, 126.8, 59.9, 53.8, 46.9, 28.2, 28.0, 14.8, 11.8; *m*/*z* (EI) 338 (M^+), 259, 149, 132, 57, 41; Found M^+, 338.0638. $C_{15}H_{19}BrN_2O_2$ requires M, 338.0630; R_f=0.58 Hex./EtOAc (6:4); $[\alpha]^{25}_D$=−105.3° (*c*=1.1, $CHCl_3$).

5.1.3. Preparation of (2′*RS*,4*S*,5*R*)-1-*N*-(2′-bromohexanoyl)-3,4-dimethyl-5-phenylimidazolidin-2-one, 2′*RS*-3c (Table 1, entry 3). 1 (426 mg, 2.43 mmol), 2,6-lutidine (0.31 mL, 2.66 mmol), 2*RS*-bromohexanoyl bromide (0.58 mL, 3.65 mmol), DCM (9 mL). Reaction performed at −10°C. Reaction time 25 min. Purification (SiO_2, Pet/EtOAc 4:1–3:1) gave 2′*RS*-**3c** (720 mg, 81%).

2′*R*-**3c**; mp 86.5–88.5°C; ν_{max} 2927, 2857, 1732, 1688, 1457, 1423, 1390, 1313, 1261, 1201, 1071, 757, 701 cm^{-1}; δ_H ($CDCl_3$) 7.30–7.13 (5H, m, Ph), 5.81 (1H, t, *J*=7.4 Hz, CO*CH*(Br)CH_2), 5.27 (1H, d, *J*=8.8 Hz, NC*H*(Ph)CH), 3.86 (1H, m, NC*H*(CH_3)CH), 2.79 (3H, s, NCH_3), 2.06–1.84 (2H, m, CH(Br)CH_2CH_2), 1.39–1.17 (4H, m, $CH_2CH_2CH_2CH_3$), 0.82 (3H, t, *J*=7.0 Hz, $-CH_2CH_3$), 0.74 (3H, d, *J*=6.6 Hz, CHCH_3); δ_C ($CDCl_3$) 167.2, 153.7, 134.3, 127.4, 127.2, 125.9, 58.2, 52.7, 44.0, 32.4, 28.4, 27.3, 21.2, 14.1, 12.8; *m*/*z* (EI) 366 (M^+), 325 ($M^+-C_3H_7$), 287 (M^+-Br), 245, 232, 189 (Aux), 175, 132, 58; Found M^+, 366.0943. $C_{17}H_{23}BrN_2O_2$ requires M, 366.0943; R_f=0.72 Pet/EtOAc (1:1); $[\alpha]^{25}_D$=−44.4° (*c*=0.6, $CHCl_3$).

2′*S*-**3c**; mp 71.2–73.5°C; ν_{max} 3033, 2957, 2872, 1732, 1688, 1457, 1422, 1390, 1313, 1289, 1261, 1201, 1071, 983, 757, 701, 672 cm^{-1}; δ_H ($CDCl_3$) 7.29–7.20 (3H, m, 3ArH), 7.05 (2H, m, 2ArH), 5.89 (1H, t, *J*=7.3 Hz, CO*CH*(Br)CH_2), 5.25 (1H, d, *J*=8.5 Hz, NC*H*(Ph)CH), 3.91 (1H, m, NC*H*(CH_3)CH), δ 2.79 (3H, s, NCH_3), 2.10–1.80 (2H, m, CH(Br)CH_2CH_2), 1.30–1.06 (4H, m, $CH_2CH_2CH_2CH_3$), 0.76 (3H, t, *J*=8.3 Hz, CH_2CH_3; 3H, d, *J*=6.7 Hz, CHCH_3); δ_C ($CDCl_3$) 167.0, 153.2, 134.5, 126.8, 126.5, 125.1, 58.1, 52.0, 43.3, 32.6, 27.6, 26.4, 20.3, 13.1, 12.1; *m*/*z* (EI) 366 (M^+), 325 ($M^+-C_3H_7$), 287 (M^+-Br), 245, 205, 191, 175, 132, 84, 49; Found M^+, 366.0943.

$C_{17}H_{23}BrN_2O_2$ requires M, 366.0943; R_f=0.81 Pet/EtOAc (1:1); $[\alpha]^{25}_D$=−80.0° (c=1.7, $CHCl_3$).

5.1.4. Preparation of (2′*RS*,4*S*,5*R*)-1-*N*-(2′-bromobutanoyl)-3,4-dimethyl-5-cyclohexylimidazo-lidin-2-one, 2′*RS*-4b (Table 1, entry 4). 2 (0.50 g, 2.56 mmol), 2,6-lutidine (0.33 mL, 2.83 mmol), 2*RS*-bromobutanoyl bromide (0.33 mL, 2.82 mmol), DCM (15 mL). Reaction performed at −20°C. Reaction time 70 min. Purification (SiO_2, Hex/EtOAc 9:1–6:4 then EtOAc) gave 2′*RS*-**4b** (0.54 g, 61%) and recovered **2** (0.09 g, 18%).

2′*R*-**4b**: mp 120.5–122°C; ν_{max} 2970, 2930, 2848, 1721, 1679, 1392 cm^{-1}; δ_H ($CDCl_3$) 5.75 (1H, t, J=7.3 Hz, COC*H*(Br)CH_2), 4.35 (1H, dd, J=2.4, 7.3 Hz, NC*H*-(C_6H_{11})CH), 3.63 (1H, dq, J=6.9, 7.3 Hz, NC*H*(CH_3)CH), 2.71 (3H, s, NCH_3), 2.04 (1H, ddq, J=7.3, 7.4, 14.2 Hz, CH(Br)C$H_AH_B$$CH_3$), 1.97 (1H, ddq, J=7.3, 7.4, 14.2 Hz, CH(Br)$CH_AH_B$$CH_3$), 1.73–1.56 (6H, m, –$(CH_2)_3$–), 1.27 (3H, d, J=6.9 Hz, CHCH_3), 1.25–1.04 (5H, m, CH-$(CH_2)_2$–), 0.94 (3H, t, J=7.4 Hz, CH_2CH_3); δ_C ($CDCl_3$): 169.3, 155.4, 60.0, 58.7, 54.4, 47.0, 40.0, 32.2, 27.7, 27.3, 27.1, 26.1, 12.9, 12.0; *m/z* (EI) 344 (M^+), 265, 223, 183, 113, 41; Found M^+, 344.1110. $C_{15}H_{25}BrN_2O_2$ requires M, 344.1099; R_f=0.44 Hex./EtOAc (6:4); $[\alpha]_D$=−6.9° (c=1.0, $CHCl_3$).

2′*S*-**4b**: mp 86.5–90.5°C; ν_{max} (KBρ) 2947, 2925, 2852, 1727, 1683, 1389 cm^{-1}; δ_H ($CDCl_3$) 5.75 (1H, t, J=7.1 Hz, COC*H*(Br)CH_2), 4.28 (1H, dd, J=2.7, 8.1 Hz, NC*H*(C_6H_{11})CH), 3.71 (1H, dq, J=6.9, 7.1 Hz, NC*H*-(CH_3)CH), 2.74 (3H, s, NCH_3), 2.14 (1H, ddq, J=7.1, 7.3, 14.3 Hz, CH(Br)C$H_AH_B$$CH_3$), 2.00 (1H, ddq, J=7.1, 7.3, 14.3 Hz, CH(Br)$CH_AH_B$$CH_3$), 1.69–1.51 (6H, m, –$(CH_2)_3$–), 1.26 (3H, d, J=6.8 Hz, CHCH_3), 1.19–0.95 (5H, m, CH$(CH_2)_2$–), 1.01 (3H, t, J=7.3 Hz, CH_2CH_3); δ_C ($CDCl_3$): 169.3, 155.6, 60.5, 54.4, 47.8, 39.0, 32.5, 28.4, 27.7, 27.6, 26.8, 26.1, 26.0, 12.8, 12.1; *m/z* (EI) 344 (M^+), 265, 223, 183, 113, 41; Found M^+, 344.1131. $C_{15}H_{25}BrN_2O_2$ requires M, 344.1099; R_f=0.60 Hex./EtOAc (6:4); $[\alpha]_D$=−15.1° (c=1.2, $CHCl_3$).

5.1.5. Preparation of (4*S*,5*R*)-1-*N*-(phenylacetyl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one, 16. 1 (500 mg, 2.64 mmol), 2,6-lutidine (0.31 mL, 2.66 mmol), phenylacetyl chloride (0.52 mL, 3.93 mmol), THF (10 mL). Reaction performed at 0°C. Reaction time 4 h. Purification (SiO_2, Pet/Et_2O 3:1–1:2) gave **16** as a white crystalline solid (534 mg, 65.6%).

16; mp 123.5 −124.1°C; ν_{max} 3064, 3030, 2980, 2892, 1953, 1726, 1668, 1602, 1495, 1455, 1422, 1361, 1263, 1176, 1093, 1077, 1031, 999, 951, 934, 873, 844, 819, 793, 704, 640, 600 cm^{-1}; δ_H ($CDCl_3$) 7.24–7.11 (8H, m, ArH), 7.00–7.97 (2H, m, ArH), 5.21 (1H, d, J=8.6 Hz, NC*H*(Ph)CH), 4.27 (2H, s, COCH_2Ph), 3.80 (1H, m, NC*H*(CH_3)CH), 2.75 (3H, s, NCH_3), 0.70 (3H, d, J= 6.6 Hz, CHCH_3); δ_C ($CDCl_3$) 170.8, 156.1, 136.9, 135.0, 130.2, 128.9, 128.7, 128.5, 127.4, 127.1, 59.9, 54.2, 42.2, 28.7, 15.4; *m/z* (EI) 308 (M^+), 217 (M^+−$PhCH_2$), 191 (M^+−$COCH_2Ph$), 175, 135, 118, 91, 58; Found M^+, 308.1525. $C_{19}H_{20}N_2O_2$ requires M, 308.1525; R_f=0.53 Pet/EtOAc (1:1); $[\alpha]^{31}_D$=−60.3° (c=1.4, $CHCl_3$).

5.1.6. Preparation of (2′*RS*,4*S*,5*R*)-1-*N*-(2′-iodopropanoyl)-3,4-dimethyl-5-phenylimidazolidin-2-one, 2′*RS*-5a. To a stirred solution of **3a** (750 mg, 2.31 mmol, 29% d.e. in 2′*S*-**3a**) in acetone (5 mL) was added a solution of sodium iodide (1.23 M, 3.75 mL, 4.62 mmol) in acetone. After 22 h the reaction mixture was filtered through a sinter and the filtrate was reduced in vacuo. The crude residue was dissolved in DCM (20 mL) and was washed with distilled water (4×10 mL) and brine (10 mL). The organic phase was dried with $MgSO_4$ and the crude product was purified by column chromatography (SiO_2, Hex:EtOAc 8:1–2:1) to give the product diastereomers of **5a** as white crystalline solids (796 mg, 92.7%, 50.0% d.e. in favour of 2′*R*-**5a**).

2′*R*-**5a**; mp 138.0–140.4°C; ν_{max} 3031, 2974, 2913, 1728, 1681, 1428, 1398, 1373, 1305, 1288, 1265, 1234, 1209, 1175, 1155, 1087, 1058, 1039, 986, 946, 860, 804, 755, 758, 737, 699, 674 cm^{-1}; δ_H ($CDCl_3$) 7.31–7.17 (5H, m, Ph), 6.03 (1H, q, J=6.9 Hz, COC*H*(I)CH_3), 5.25 (1H, d, J=8.8 Hz, NC*H*(Ph)CH), 3.85 (1H, m, NC*H*(CH_3)CH), 2.78 (3H, s, NCH_3), 1.85 (3H, d, J=6.9 Hz, CH(I)CH_3), 0.73 (3H, d, J=6.6 Hz, CHCH_3); δ_C ($CDCl_3$) 171.7, 156.1, 136.7, 129.8, 129.6, 128.5, 60.5, 55.1, 29.7, 23.6, 17.0, 16.6; *m/z* (EI) 372 (M^+), 245 (M^+−I), 191 (M^+−$COCH(I)CH_3$), 175, 132, 91, 77, 58, 42; Found M^+, 372.0335. $C_{14}H_{17}IN_2O_2$ requires M, 372.0335; R_f=0.30 Pet/EtOAc (2:1); $[\alpha]^{36}_D$= −86.0° (c=1.2, $CHCl_3$).

2′*S*-**5a**; mp 125.6–126.7°C; ν_{max} 3033, 2983, 2919, 2352, 1728, 1681, 1556, 1539, 1495, 1455, 1422, 1373, 1309, 1289, 1259, 1233, 1202, 1172, 1129, 1081, 1060, 1030, 987, 946, 862, 810, 781, 757, 737, 699, 672 cm^{-1}; δ_H ($CDCl_3$) 7.29–7.20 (3H, m, 3ArH), 7.07–7.04 (2H, d, 2ArH), 6.06 (1H, q, J=6.9 Hz, COC*H*(I)CH_3), 5.19 (1H, d, J=8.4 Hz, NC*H*(Ph)CH), 3.94 (1H, m, NC*H*(CH_3)CH), 2.81 (3H, s, NCH_3), 1.81 (3H, d, J=6.8 Hz, CH(I)CH_3), 0.74 (3H, d, J=6.6 Hz, CHCH_3); δ_C ($CDCl_3$) 171.4, 155.4, 136.8, 129.0, 128.7, 127.2, 60.5, 54.1, 28.6, 23.1, 15.8, 15.2; *m/z* (EI) 372 (M^+), 245 (M^+−I), 191 (M^+−$COCH(I)CH_3$), 175, 132, 91, 77, 58, 42; Found M^+, 372.0335. $C_{14}H_{17}IN_2O_2$ requires M, 372.0335; R_f=0.58 Pet/EtOAc (2:1); $[\alpha]^{39}_D$=−54.0° (c=1.2, $CHCl_3$).

5.2. Dynamic kinetic resolutions (DKR) with amine nucleophiles

5.2.1. General procedure. To a stirred solution of 2′-haloacylimidazolidinone, tetra-*n*-butylammonium halide and triethylamine in an appropriate solvent was added the amine nucleophile. Reactions were monitored by TLC and were worked up by dilution in diethyl ether and washed with distilled water. The organic phase was dried with $MgSO_4$ and the crude product was purified by column chromatography unless otherwise stated.

5.2.2. Typical procedure for DKR of 2′*RS*-3a with benzylamine (1.5 equiv.), Bu_4NBr (0.2 equiv.), THF [0.10 M] (Table 2, entry 1, for specific conditions of related experiments see Table 2). 2′*RS*-**3a** (65.0 mg, 0.20 mmol), Bu_4NBr (12.9 mg, 0.040 mmol), Et_3N (0.034 mL, 0.240 mmol), benzylamine (0.033 mL, 0.302 mmol) in THF (2.0 mL). Reaction time 77 h.

Purification (SiO_2, Pet/EtOAc 2:1–1:2) gave 2′*R*-**6a** (61.4 mg, 87.5%, 57.8% d.e.).

5.2.3. DKR of 2′*RS*-5a with benzylamine (Table 2, entry 9). 2′*RS*-**5a** (74.3 mg, 0.200 mmol), Bu_4NI (14.7 mg, 0.040 mmol), Et_3N (0.033 mL, 0.237 mmol), benzylamine (0.033 mL, 0.302 mmol) in THF (2.0 mL). Reaction time 51 h. Purification (SiO_2, Hex/EtOAc 1:1) gave 2′*R*-**6a** (67.5 mg, 96.1%, 78.8% d.e.).

2′*R*-**6a**; ν_{max} 3335, 3063, 3031, 2979, 2935, 2869, 1954, 1729, 1681, 1606, 1587, 1495, 1455, 1423, 1387, 1310, 1288, 1234, 1205, 1155, 1125, 1066, 1029, 966, 948, 910, 858, 810, 735, 701, 628 cm^{-1}; δ_H ($CDCl_3$) 7.38–7.13 (10H, m, 2Ph), 5.33 (1H, d, *J*=8.6 Hz, NC*H*(Ph)CH), 4.80 (1H, q, *J*=6.8 Hz, COC*H*(NHR)CH_3), 3.94 (1H, m, NC*H*(CH_3)CH), 3.48 (1H, d, J_{gem}=12.5 Hz, HNC$H_A$$H_B$Ph), 3.43 (1H, d, J_{gem}=12.5 Hz, HNC$H_B$$H_A$Ph), 2.84 (3H, s, NCH_3), 2.27 (1H, br s, NH), 1.34 (3H, d, *J*=6.8 Hz, CH(NH)CH_3), 0.83 (3H, d, *J*=6.5 Hz, CHCH_3); δ_C ($CDCl_3$) 176.3, 157.3, 140.0, 136.6, 128.4, 128.1, 128.04, 127.99, 126.8, 126.7, 59.4, 55.3, 53.9, 51.4, 28.1, 19.4, 14.8; *m/z* (EI) 351 (M^+), 260 (M^+-PhCH_2), 246 (M^+-NCH_2Ph), 191 (Aux H^+), 175, 134, 91, 58, 42; Found M^+, 351.1947. $C_{21}H_{25}N_3O_2$ requires M, 351.1947; R_f=0.18 Pet/EtOAc (1:1); $[\alpha]^{37}_D=-19.8°$ (*c*=2.7, $CHCl_3$).

2′*S*-**6a**; ν_{max} 3326, 3062, 3031, 2979, 2934, 1729, 1681, 1605, 1495, 1455, 1423, 1387, 1353, 1310, 1289, 1260, 1235, 1205, 1158, 1126, 1065, 1029, 966, 948, 808, 740, 702 cm^{-1}; δ_H ($CDCl_3$) 7.34–7.13 (10H, m, 2Ph), 5.29 (1H, d, *J*=8.7 Hz, NC*H*(Ph)CH), 4.76 (1H, q, *J*=6.7 Hz, COC*H*(NHR)CH_3), 3.92 (1H, m, NC*H*(CH_3)CH), 3.74 (1H, d, J_{gem}=12.3 Hz, HNC$H_A$$H_B$Ph), 3.64 (1H, d, J_{gem}= 12.3 Hz, HNC$H_B$$H_A$Ph), 2.85 (3H, s, NCH_3), 2.18 (1H, br s, NH), 1.30 (3H, d, *J*=6.8 Hz, CH(NH)CH_3), 0.82 (3H, d, *J*=6.4 Hz, CHCH_3); δ_C ($CDCl_3$) 178.5, 157.7, 142.6, 138.9, 131.0, 130.8, 130.7, 129.3, 129.2, 60.5, 58.1, 56.1, 55.0, 30.6, 22.3, 17.5; *m/z* (EI) 351 (M^+), 260 (M^+-PhCH_2), 246 (M^+-NCH_2Ph), 191 (AuxH^+), 134, 91, 77, 58, 42; Found M^+, 351.1947. $C_{21}H_{25}N_3O_2$ requires M, 351.1947; R_f=0.30 Pet./EtOAc (1:1); $[\alpha]^{37}_D=-106.4°$ (*c*=2.6, $CHCl_3$).

5.2.4. Typical procedure for DKR of 2′*RS*-3a with pyrrolidine (1.5 equiv.), *n*-Bu_4NI (0.2 equiv.), THF [0.10 M] (Table 2, entry 6, for specific conditions of related experiments see Table 2). 2′*RS*-**3a** (65.1 mg, 0.200 mmol), Bu_4NI (14.9 mg, 0.040 mmol), Et_3N (0.033 mL, 0.237 mmol), pyrrolidine (0.025 mL, 0.299 mmol) in THF (2.0 mL). Reaction time 46 h. Reaction mixture diluted with DCM (5 mL), washed with distilled water (4×5 mL) and dried with $MgSO_4$. Repeated triteration in Et_2O and drying in vacuo gave 2′*R*-**7a** as a viscous straw oil (64.2 mg, 100%, 42% d.e.).

2′*R*-**7a**; ν_{max} 3033, 2971, 1729, 1457, 1421, 1391, 1310, 1230, 1173, 1077, 1031, 944, 860, 808, 757, 681 cm^{-1}; δ_H ($CDCl_3$) 7.32–7.24 (3H, m, ArH), 7.15 (2H, d, *J*=7.0 Hz, ArH), 5.31 (1H, d, *J*=8.6 Hz, NC*H*-(Ph)CH), 4.77 (1H, q, *J*=6.7 Hz, COC*H*(NR_2)CH_3), 3.88 (1H, m, NC*H*(CH_3)CH), 2.82 (3H, s, NCH_3), 2.60 (2H, d, J_{gem}=5.8 Hz, N($CH_A$$H_B$$CH_2$)$_2$), 2.47 (2H, d, J_{gem}=5.6 Hz, N($CH_B$$H_A$$CH_2$)$_2$), 1.65 (4H, s, N($CH_2CH_2$)$_2$), 1.34 (3H, d, *J*=6.8 Hz, CH(NR_2)CH_3), 0.79 (3H, d, *J*=6.6 Hz, CHCH_3); δ_C ($CDCl_3$) 174.0, 156.0, 137.1, 128.8, 128.4, 127.5, 59.7, 59.0, 54.3, 50.5, 28.7, 23.8, 16.6, 15.4; *m/z* (EI) 315 (M^+), 149, 132, 117, 98, 84, 56, 42; Found M^+, 315.1947. $C_{18}H_{25}N_3O_2$ requires M, 315.1947; Pet/EtOAc (1:2); $[\alpha]^{25}_D=-47.1°$ (*c*=1.2, $CHCl_3$).

2′*S*-**7a**; ν_{max} 2971, 1729, 1689, 1456, 1422, 1391, 1310, 1260, 1230, 1202, 1172, 1070, 945, 860, 758, 701 cm^{-1}; δ_H ($CDCl_3$) 7.28–7.08 (5H, m, Ph), 5.30 (1H, d, *J*=8.6 Hz, NC*H*(Ph)CH), 4.70 (1H, q, *J*=6.9 Hz, COC*H*-(NR_2)CH_3), 3.87 (1H, m, NC*H*(CH_3)CH), 2.78 (3H, s, NCH_3), 2.70 (2H, d, J_{gem}=6.2 Hz, N($CH_A$$H_B$$CH_2$)$_2$), 2.62 (2H, d, J_{gem}=6.4 Hz, N($CH_B$$H_A$$CH_2$)$_2$), 1.70 (4H, s, N($CH_2CH_2$)$_2$), 1.28 (3H, d, *J*=6.9 Hz, CH(NR_2)CH_3), 0.75 (3H, d, *J*=6.6 Hz, CHCH_3); δ_C ($CDCl_3$) 173.5, 155.3, 136.5, 128.2, 127.7, 126.7, 58.9, 58.3, 53.3, 49.9, 28.0, 23.4, 15.0, 14.8; *m/z* (EI) 315 (M^+), 245, 217, 191, 175, 132, 117, 99, 56, 42; Found M^+, 315.1947. $C_{18}H_{25}N_3O_2$ requires M, 315.1947; $[\alpha]^{25}_D=-93.7°$ (*c*=0.6, $CHCl_3$).

5.2.5. Typical procedure for DKR of 2′*RS*-3a with piperidine (1.5 equiv.), *n*-Bu_4NBr (0.2 equiv.), THF [1.0 M] (Table 2, entry 7, for specific conditions of related experiments see Table 2). 2′*RS*-**3a** (65.1 mg, 0.20 mmol), Bu_4NBr (12.9 mg, 0.04 mmol), Et_3N (0.034 mL, 0.24 mmol), piperidine (0.03 mL, 0.30 mmol), in THF (2.0 mL). Reaction time 91 h. Reaction mixture diluted with EtOAc (10 mL), washed with distilled water (4×10 mL) and dried with $MgSO_4$. Repeated triteration in Et_2O and drying in vacuo gave 2′*R*-**8a** as a clear viscous oil (57.7 mg, 88%, 57% d.e.).

2′*R*-**8a**; ν_{max} 3548, 3033, 2934, 2853, 2804, 1729, 1687, 1606, 1495, 1455, 1422, 1392, 1309, 1288, 1261, 1173, 1119, 1101, 1073, 1037, 970, 933, 908, 861, 809, 785, 758, 736, 703, 678, 632 cm^{-1}; δ_H ($CDCl_3$) 7.27–7.12 (5H, m, Ph), 5.26 (1H, d, *J*=8.8 Hz, NC*H*(Ph)CH), 4.82 (1H, q, *J*=6.8 Hz, COC*H*(NR_2)CH_3), 3.78 (1H, m, NC*H*(CH_3)CH), 2.74 (3H, s, NCH_3), 2.38 (4H, m, N(CH_2)$_2$), 1.40 (4H, m, *J*=5.2 Hz, (CH_2)$_2$$CH_2$), 1.24 (2H, m, *J*=5.2 Hz, (CH_2CH_2)$_2$CH_2), 1.10 (3H, d, *J*=6.9 Hz, CH(NR_2)CH_3), 0.72 (3H, d, *J*=6.6 Hz, CHCH_3); δ_C ($CDCl_3$) 173.6, 155.9, 137.3, 128.6, 128.3, 127.6, 59.9, 59.4, 54.1, 50.4, 28.8, 26.9, 25.0, 15.6, 12.0; *m/z* (EI) 329 (M^+), 245, 132, 112, 84, 55, 41; Found M^+, 329.2103. $C_{19}H_{27}N_3O_2$ requires M, 329.2103; $[\alpha]^{25}_D=-48.5°$ (*c*=2.2, $CHCl_3$).2′*S*-**8a**; ν_{max} 3429, 3067, 3035, 2980, 2937, 2856, 2754, 2697, 1723, 1682, 1607, 1497, 1423, 1396, 1311, 1287, 1262, 1237, 1207, 1163, 1116, 1101, 1073, 1037, 1010, 971, 932, 906, 861, 810, 796, 780, 746, 703, 676, 634, 569 cm^{-1}; δ_H ($CDCl_3$) 7.27–7.04 (5H, m, Ph), 5.24 (1H, d, *J*=8.5 Hz, NC*H*(Ph)CH), 4.82 (1H, q, *J*=7.0 Hz, COC*H*(NR_2)CH_3), 3.84 (1H, m, NC*H*(CH_3)CH), 2.75 (3H, s, NCH_3), 2.62 (2H, m, N($CH_A$$H_B$$CH_2$)$_2$), 2.50 (2H, m, N($CH_B$$H_A$$H_2$)$_2$), 1.46 (4H, m, ($CH_2CH_2$)$_2$$CH_2$), 1.34 (2H, m, ($CH_2$)$_2CH_2$), 1.15 (3H, d, *J*=7.0 Hz, CH(NR_2)CH_3), 0.71 (3H, d, *J*=6.6 Hz, CHCH_3); δ_C ($CDCl_3$) 174.1, 155.9, 137.1, 128.9, 128.4, 127.2, 60.3, 59.6, 54.2, 50.9, 28.5, 26.9, 25.1, 15.4, 14.0; *m/z* (EI) 329 (M^+), 245, 132, 112, 91, 56, 41; Found M^+, 329.2103. $C_{19}H_{27}N_3O_2$ requires M, 329.2103; R_f=0.19 Pet/EtOAc (1:1); $[\alpha]^{35}_D=-48.0°$ (*c*=2.3, $CHCl_3$).

5.2.6. Typical procedure for DKR of 2′*RS*-3b with benzylamine (Table 2, entry 17, for specific conditions of related experiments see Table 2). 2′*RS*-**3b** (67.8 mg, 0.20 mmol), Bu_4NI (14.8 mg, 0.04 mmol), Et_3N (0.034 mL, 0.24 mmol), benzylamine (0.033 mL, 0.30 mmol), in THF (2.0 mL). Reaction time 48 h. Purification (SiO_2, Hex/EtOAc 6:4) gave 2′*R*-**6b** (56.0 mg, 77%, 59% d.e.).2′*R*-**6b**: mp 76.5–77.5°C; ν_{max} (KBρ) 3432, 3084, 3063, 3029, 2977, 2937, 2916, 1718, 1678, 1399 cm^{-1}; δ_H ($CDCl_3$) 7.29–7.10 (10H, m, ArH), 5.23 (1H, t, *J*=8.5 Hz, NC*H*(Ph)CH), 4.57 (1H, dd, *J*=5.1, 7.2 Hz, COC*H*-(NHBn)CH_2), 3.83 (1H, dq, *J*=6.6, 8.5 Hz, NC*H*(CH_3)CH), 3.43 (1H, d, J_{gem}=12.8 Hz, NHCH_AH_BPh), 3.33 (1H, d, J_{gem}=12.8 Hz, NHCH_AH_BPh), 2.74 (3H, s, NCH_3), 2.14 (1H, brs, NH), 1.70 (1H, ddq, *J*=5.1, 7.4, 14.4 Hz, CH(NHBn)C$H_AH_BCH_3$), 1.48 (1H, ddq, *J*=7.2, 7.4, 14.4 Hz, CH(NHBn)C$H_AH_BCH_3$), 0.93 (3H, t, *J*=7.4 Hz, CH_2CH_3), 0.73 (3H, d, *J*=6.6 Hz, CHCH_3); δ_C ($CDCl_3$): 175.9, 155.5, 140.3, 136.8, 128.4, 128.11, 128.07, 128.3, 126.9, 126.7, 60.9, 59.5, 54.0, 51.6, 28.1, 26.7, 14.8, 10.4; *m*/*z* (EI) 365 (M^+), 336, 274, 191, 148, 91; Found M^+, 365.2103. $C_{22}H_{27}N_3O_2$ requires M, 365.2103; R_f=0.20 Hex./EtOAc (6:4); $[\alpha]^{25}_D$=−9.7° (*c*=1.0, $CHCl_3$).

2′*S*-**6b**: mp 40–42°C; ν_{max} 3453, 3063, 3032, 2972, 2935, 1731, 1671, 1382 cm^{-1}; δ_H ($CDCl_3$) 7.26–7.13 (8H, m, ArH), 7.06 (2H, d, *J*=6.7 Hz, ArH), 5.18 (1H, t, *J*= 8.7 Hz, NC*H*(Ph)CH), 4.54 (1H, dd, *J*=4.5, 7.2 Hz, COC*H*(NHBn)CH_2), 3.80 (1H, dq, *J*=6.6, 8.7 Hz, NC*H*(CH_3)CH), 3.66 (1H, d, J_{gem}=12.8 Hz, NHCH_AH_BPh), 3.56 (1H, d, J_{gem}=12.8 Hz, NHCH_AH_BPh), 2.75 (3H, s, NCH_3), 2.01 (1H, brs, NH), 1.72 (1H, ddq, *J*=4.5, 7.3, 13.5 Hz, CH(NHBn)C$H_AH_BCH_3$), 1.41 (1H, ddq, *J*=7.2, 7.3, 13.5 Hz, CH(NHBn)C$H_AH_BCH_3$), 0.82 (3H, t, *J*= 7.3 Hz, CH_2CH_3), 0.73 (3H, d, *J*=6.6 Hz, CHCH_3); δ_C ($CDCl_3$): 175.5, 155.3, 140.5, 136.6, 128.5, 128.4, 128.1, 126.9, 126.7, 60.9, 59.1, 54.0, 52.7, 28.1, 27.2, 15.0, 10.8; *m*/*z* (EI) 365 (M^+), 336, 274, 260, 191, 148, 91; Found M^+, 365.2103. $C_{22}H_{27}N_3O_2$ requires M, 365.2103; R_f=0.26 Hex./EtOAc (6:4); $[\alpha]^{25}_D$=−88.3° (*c*=0.8, $CHCl_3$).

5.2.7. Typical procedure for DKR of 2′*RS*-3b with pyrrolidine (Table 2, entry 19, for specific conditions of related experiments see Table 2). 2′*RS*-**3b** (68.4 mg, 0.20 mmol), Bu_4NI (14.9 mg, 0.04 mmol), Et_3N (0.034 mL, 0.24 mmol), pyrrolidine (0.025 mL, 0.30 mmol), in THF (2.0 mL). Reaction time 72 h. Purification (SiO_2, Hex/EtOAc 6:4 then EtOAc) gave 2′*R*-**7b** (42.0 mg, 63%, 73% d.e.) and recovered 2′*RS*-**3b** (8.3 mg, 12%).

2′*R*-**7b**: mp 79–82°C; ν_{max} (KBρ) 3089, 3068, 3028, 2978, 2935, 2895, 2848, 2799, 1716, 1684, 1393 cm^{-1}; δ_H ($CDCl_3$) 7.25–7.19 (3H, m, ArH), 7.11 (2H, d, *J*=6.3 Hz, ArH), 5.26 (1H, d, *J*=8.5 Hz, NC*H*(Ph)CH), 4.79 (1H, dd, *J*=5.8, 8.0 Hz, COC*H*(NR_2)CH_2), 3.81 (1H, dq, *J*=6.7, 8.5 Hz, NC*H*(CH_3)CH), 2.76 (3H, s, NCH_3), 2.58 (2H, m, N(C$H_ACH_BCH_2$)$_2$), 2.44 (2H, m, N($CH_ACH_BCH_2$)$_2$), 1.76 (1H, ddq, *J*=7.4, 8.0, 14.0 Hz, CH(NR_2)C$H_AH_BCH_3$), 1.68–1.54 (5H, m, CH(NR_2)$CH_AH_BCH_3$, N(CH_2CH_2)$_2$), 0.86 (3H, t, *J*=7.4 Hz, CH_2CH_3), 0.74 (3H, d, *J*=6.7 Hz, CHCH_3); δ_C ($CDCl_3$): 173.2, 155.7, 136.9, 128.3, 127.9, 127.2, 62.9, 59.4, 53.8, 49.3, 28.3, 23.4, 23.1, 15.0, 10.6; *m*/*z* (EI) 329 (M^+), 300, 231, 205, 175, 132, 112, 70, 55, 42; Found M^+, 329.2103. $C_{19}H_{27}N_3O_2$ requires M, 329.2103; R_f=0.375 EtOAc/MeOH (1:1); $[\alpha]^{25}_D$=−73.9° (*c*=1.0, $CHCl_3$).

2′*S*-**7b**: mp 108–109.5°C; ν_{max} (KBρ) 3095, 3063, 3033, 2971, 2878, 2812, 1718, 1686, 1393 cm^{-1}; δ_H ($CDCl_3$) 7.26–7.19 (3H, m, ArH), 7.08 (2H, d, *J*=6.6 Hz, ArH), 5.28 (1H, d, *J*=8.5 Hz, NC*H*(Ph)CH), 4.81 (1H, dd, *J*=6.0, 7.4 Hz, COC*H*(NR_2)CH_2), 3.83 (1H, dq, *J*=6.6, 8.5 Hz, NC*H*(CH_3)CH), 2.76 (3H, s, NCH_3), 2.71 (2H, m, N(C$H_ACH_BCH_2$)$_2$), 2.58 (2H, m, N($CH_ACH_BCH_2$)$_2$), 1.77 (1H, ddq, *J*=7.4, 7.5, 13.9 Hz, CH(NR_2)C$H_AH_BCH_3$), 1.67–1.55 (5H, m, CH(NR_2)$CH_AH_BCH_3$, N(CH_2CH_2)$_2$), 0.74 (3H, d, *J*=6.6 Hz, CHCH_3), 0.73 (3H, t, *J*=7.5 Hz, CH_2CH_3); δ_C ($CDCl_3$): 173.1, 155.7, 136.8, 128.4, 128.0, 127.1, 62.8, 59.2, 53.8, 49.5, 28.2, 23.55, 23.53, 15.9, 10.3; *m*/*z* (EI) 329 (M^+), 300, 260, 245, 231, 205, 175, 132, 112, 70, 55, 42; Found M^+, 329.2103. $C_{19}H_{27}N_3O_2$ requires M, 329.2103; R_f=0.27 EtOAc/MeOH (1:1); $[\alpha]^{25}_D$=−92.6° (*c*=1.0, $CHCl_3$).

5.2.8. Typical procedure for DKR of 2′*RS*-3b with piperidine (Table 2, entry 21, for specific conditions of related experiments see Table 2). 2′*RS*-**3b** (68.2 mg, 0.20 mmol), Bu_4NI (15.0 mg, 0.04 mmol), Et_3N (0.034 mL, 0.24 mmol), piperidine (0.030 mL, 0.30 mmol), in THF (2.0 mL). Reaction time 72 h. Purification(SiO_2, Hex/Et_2O 7:3, 6:4 then Et_2O) gave 2′*R*-**8b** (54.0 mg, 78%, 88% d.e.) and recovered 2′*RS*-**3b** (10.8 mg, 16%).2′*R*-**8b**: mp 89–91°C; ν_{max} (KBρ) 3063, 3021, 2979, 2963, 2929, 2854, 2798, 1731, 1686, 1387 cm^{-1}; δ_H ($CDCl_3$) 7.26–7.19 (3H, m, ArH), 7.15 (2H, d, *J*=6.5 Hz, ArH), 5.28 (1H, d, *J*=8.8 Hz, NC*H*(Ph)CH), 4.69 (1H, dd, *J*=5.6, 8.9 Hz, COC*H*(NR_2)CH_2), 3.79 (1H, dq, *J*=6.6, 8.8 Hz, NC*H*(CH_3)CH), 2.76 (3H, s, NCH_3), 2.45–2.34 (4H, m, N(CH_2CH_2)$_2CH_2$), 1.68 (1H, ddq, *J*=7.4, 8.9, 13.5 Hz, CH(NR_2)C$H_ACH_BCH_3$), 1.51 (1H, ddq, *J*=5.6, 7.3, 13.5 Hz, CH(NR_2)$CH_ACH_BCH_3$), 1.41–1.35 (4H, m, N(CH_2CH_2)$_2CH_2$), 1.26–1.21 (2H, m, (CH_2CH_2)$_2CH_2$), 0.80 (3H, d, *J*=7.4 Hz, CH_2CH_3), 0.74 (3H, d, *J*=6.6 Hz, CHCH_3); δ_C ($CDCl_3$): 172.5, 155.7, 137.0, 128.2, 127.9, 127.3, 65.7, 59.2, 53.8, 50.2, 28.4, 26.7, 24.8, 19.6, 15.2, 11.1; *m*/*z* (EI) 343 (M^+), 314, 233, 191, 126, 110, 56, 41; Found M^+, 343.2260. $C_{20}H_{29}N_3O_2$ requires M, 343.2260; R_f=0.40 EtOAc/MeOH (1:1); $[\alpha]^{25}_D$=−72.2° (*c*=1.0, $CHCl_3$).

2′*S*-**8b**: mp 128.5–130°C; ν_{max} (KBρ) 3084, 3063, 3029, 2989, 2938, 2878, 2857, 2796, 1719, 1682, 1393 cm^{-1}; δ_H ($CDCl_3$) 7.25–7.19 (3H, m, ArH), 7.07 (2H, d, *J*=6.6 Hz, ArH), 5.26 (1H, d, *J*=8.4 Hz, NC*H*(Ph)CH), 4.82 (1H, dd, *J*=6.3, 8.3 Hz, COC*H*(NR_2)CH_2), 3.84 (1H, dq, *J*=6.6, 8.4 Hz, NC*H*(CH_3)CH), 2.76 (3H, s, NCH_3), 2.60–2.49 (4H, m, N(CH_2CH_2)$_2CH_2$), 1.77 (1H, ddq, *J*=7.6, 8.3, 13.5 Hz, CH(NR_2)C$H_ACH_BCH_3$), 1.53–1.32 (7H, m, CH(NR_2)$CH_ACH_BCH_3$, N(CH_2CH_2)$_2CH_2$), 0.74 (3H, t, *J*=7.6 Hz, CH_2CH_3), 0.73 (3H, d, *J*=6.6 Hz, CHCH_3); δ_C ($CDCl_3$): 172.8, 155.8, 136.8, 128.4, 128.0, 127.0, 65.3, 59.4, 53.7, 50.4, 28.1, 26.7, 24.9, 21.7, 14.9, 10.7; *m*/*z* (EI) 343 (M^+), 314, 233, 191, 126, 110, 69, 56, 42; Found M^+, 343.2260. $C_{20}H_{29}N_3O_2$ requires M, 343.2260; R_f=0.35 Hex./EtOAc (6:4); $[\alpha]^{25}_D$=−75.4° (*c*=1.0, $CHCl_3$).

5.2.9. DKR of 2′*RS*-3b with cyclohexylamine, reflux (Table 2, entry 23). 2′*RS*-**3b** (68.8 mg, 0.20 mmol), Bu_4NI (15.0 mg, 0.04 mmol), Et_3N (0.035 mL, 0.25 mmol), cyclohexylamine (0.035 mL, 0.31 mmol), in THF (2.0 mL) at reflux. Reaction time 4 days. Purification (SiO_2, Hex/EtOAc 7:3, 1:4 then Et_2O) gave 2′*R*-**9b** (63.6 mg, 88%, 81% d.e.).

2′*R*-**9b**: mp 114–116°C; ν_{max} (KBρ) 3409, 3068, 3035, 2974, 2924, 2851, 1706, 1686, 1395 cm^{-1}; δ_H ($CDCl_3$) 7.26–7.19 (3H, m, ArH), 7.08 (2H, d, *J*=6.7 Hz, ArH), 5.23 (1H, d, *J*=8.5 Hz, NC*H*(Ph)CH), 4.76 (1H, t, *J*=6.1 Hz, COC*H*(NHR)CH_2), 3.84 (1H, dq, *J*=6.5, 8.5 Hz, NC*H*(CH_3)CH), 2.77 (3H, s, NCH_3), 2.11 (1H, brs, NH), 2.00–1.93 (1H, m, NHC*H*(CH_2)$_5$), 1.90–1.83 (1H, m, *c*-C_6H_{11}C*H*), 1.67–1.57 (2H, m, CH(NR_2)C$H_A$$CH_B$$CH_3$, *c*$C_6H_{11}$, CH), 1.51–1.38 (4H, m, CH(NR_2)CH_AC$H_B$$CH_3$, *c*-$C_6H_{11}$, 3C*H*), 1.09–0.83 (5H, m, *c*-C_6H_{11},), 0.90 (3H, t, *J*=7.3 Hz, CH_2CH_3), 0.75 (3H, d, *J*=6.5 Hz, CHCH_3); δ_C ($CDCl_3$): 176.8, 155.5, 136.6, 128.3, 128.0, 126.9, 59.5, 57.4, 55.0, 53.8, 34.2, 32.6, 28.1, 27.6, 26.0, 24.9, 24.8, 14.8, 10.2; *m*/*z* (EI) 357 (M^+), 328, 274, 191, 140, 41; Found M^+, 357.2417 $C_{21}H_{31}N_3O_2$ requires M, 357.2416; R_f=0.26 EtOAc; $[\alpha]^{25}_D$=−39.5° (*c*=1.1, $CHCl_3$).

2′*S*-**9b**: mp 91–95°C; ν_{max} (KBρ) 3448, 3068, 3032, 2964, 2941, 2926, 2851, 1732, 1681, 1391 cm^{-1}; δ_H ($CDCl_3$) 7.26–7.18 (3H, m, ArH), 7.08 (2H, d, *J*=6.7 Hz, ArH), 5.28 (1H, d, *J*=8.8 Hz, NC*H*(Ph)CH), 4.59 (1H, dd, *J*=4.1, 6.6 Hz, COC*H*(NHR)CH_2), 3.88 (1H, dq, *J*=6.7, 8.8 Hz, NC*H*(CH_3)CH), 2.77 (3H, s, NCH_3), 2.33 (1H, brs, NH), 2.19–2.14 (1H, m, NHC*H*(CH_2)$_5$), 1.84–1.49 (6H, CH(NR_2)C$H_A$$CH_B$$CH_3$, *c*-$C_6H_{11}$, 5CH), 1.42–1.31 (1H, m, CH(NR_2)CH_AC$H_B$$CH_3$), 1.20–0.92 (5H, m, *c*-C_6H_{11}), 0.78 (3H, t, *J*=7.4 Hz, CH_2CH_3), 0.75 (3H, d, *J*=6.7 Hz, CHCH_3); δ_C ($CDCl_3$): 176.0, 155.4, 136.6, 128.4, 128.1, 126.9, 59.2, 58.0, 55.3, 54.0, 34.1, 32.9, 28.1, 27.2, 26.0, 25.1, 24.7, 15.0, 9.9; *m*/*z* (EI) 357 (M^+), 328, 274, 191, 140, 58, 41; Found M^+, 357.2418 $C_{21}H_{31}N_3O_2$ requires M, 357.2416; R_f=0.36 EtOAc; $[\alpha]^{25}_D$=−96.3° (*c*=1.0, $CHCl_3$).

5.2.10. DKR of 2′*RS*-4b with benzylamine, reflux (Table 2, entry 30). 2′*RS*-**4b** (70.0 mg, 0.20 mmol), Bu_4NI (15.0 mg, 0.04 mmol), Et_3N (0.036 mL, 0.26 mmol), benzylamine (0.034 mL, 0.31 mmol), in THF (2.0 mL) at reflux. Reaction time 48 h. Purification (SiO_2, Hex/EtOAc 6:4) gave 2′*R*-**10b** (72.9 mg, 97%, 86% d.e.).

2′*R*-**10b**: mp 88–90°C; ν_{max} (KBρ) 3438, 3063, 3032, 2968, 2928, 2854, 1724, 1683, 1389 cm^{-1}; δ_H ($CDCl_3$) 7.29 (2H, d, *J*=7.3 Hz, 2*o*-ArH), 7.23 (2H, t, *J*=7.2, 7.3 Hz, 2*m*-ArH), 7.15 (1H, t, *J*=7.2 Hz, *p*-ArH), 4.58 (1H, dd, *J*=5.3, 7.3 Hz, COC*H*(NHBn)CH_2), 4.28 (1H, dd, *J*=2.8, 7.2 Hz, CHC*H*(C_6H_{11})CH), 3.74 (1H, d, J_{gem}=12.8 Hz, NHC$H_A$$H_B$Ph), 3.64–3.37 (2H, m, NHC$H_A$$H_B$Ph, NC*H*($CH_3$)CH), 2.68 (3H, s, NCH_3), 2.30 (1H, brs, NH), 1.73–1.54 (7H, m, CH(NHBn)C$H_A$$H_B$$CH_3$, CHC*H*(*c*$CH_2$)$_5$), 5(cyclohexyl)CH), 1.44 (1H, ddq, *J*=7.3, 7.3, 13.7 Hz, CH(NHBn)$CH_A$$H_B$$CH_3$), 1.25 (3H, d, *J*=7.0 Hz, CHCH_3), 1.20–1.00 (5H, m, 5(cyclohexyl)CH), 0.89 (3H, t, *J*=7.3 Hz, CH_2CH_3); δ_C ($CDCl_3$): 175.6, 155.9, 139.6, 128.22, 128.18, 126.9, 60.3, 59.6, 54.5, 51.8, 38.7, 32.5, 27.8, 27.4, 26.8, 26.4, 26.1, 26.0, 12.8, 10.1; *m*/*z* (EI) 371 (M^+), 342, 280, 197, 148, 91; Found M^+, 371.2580. $C_{22}H_{33}N_3O_2$ requires M, 371.2573; R_f=0.22 Hex./EtOAc (6:4); $[\alpha]^{25}_D$=−2.2° (*c*=1.0, $CHCl_3$).

2′*S*-**10b**: ν_{max} 3440, 3085, 3062, 3028, 2928, 2853, 1732, 1682, 1386 cm^{-1}; δ_H ($CDCl_3$) 7.26 (2H, d, *J*=6.9 Hz, 2*o*-ArH), 7.19 (2H, t, *J*=6.9, 7.3 Hz, 2*m*-ArH), 7.14 (1H, t, *J*=7.3 Hz, *p*-ArH), 4.47 (1H, dd, *J*=4.5, 7.3 Hz, COC*H*(NHBn)CH_2), 4.22 (1H, dd, *J*=2.2, 7.3 Hz, C*H*-(C_6H_{11})CH), 3.64 (1H, d, J_{gem}=12.8 Hz, NHC$H_A$$H_B$Ph), 3.58 (1H, d, J_{gem}=12.8 Hz, NHC$H_A$$H_B$Ph), 3.55 (1H, dq, *J*=6.9, 7.3 Hz, NC*H*(CH_3)CH), 2.68 (3H, s, NCH_3), 2.44 (1H, brs, NH), 1.84 (1H, m, CHC*H*(*c*CH_2)$_5$), 1.67–1.51 (7H, m, CH(NHBn)C$H_2$$CH_3$, 5(cyclohexyl)CH), 1.15–0.93 (5H, m, 5(cyclohexyl)CH), 1.01 (3H, t, *J*=7.3 Hz, CHCH_3); δ_C ($CDCl_3$): 175.8, 155.8, 140.0, 128.5, 128.2, 126.8, 60.9, 58.8, 54.7, 52.7, 39.3, 32.5, 27.8, 27.7, 27.6, 26.9, 26.2, 26.0, 13.0, 10.3; *m*/*z* (EI) 371 (M^+), 342, 280, 197, 148, 86; Found M^+, 371.2572 $C_{22}H_{33}N_3O_2$ requires M, 371.2573; R_f=0.28 Hex./EtOAc (6:4); $[\alpha]^{25}_D$=−21.3° (*c*=1.3, $CHCl_3$).

5.2.11. DKR of 2′*RS*-3c with benzylamine, reflux (Table 2, entry 27). 2′*RS*-**3c** (167.8 mg, 0.457 mmol), Bu_4NI (33.8 mg, 0.092 mmol), Et_3N (0.076 mL, 0.545 mmol), benzylamine (0.075 mL, 0.686 mmol) in THF (4.6 mL) at reflux. Reaction time 72 h. Purification (SiO_2, Pet/EtOAc 4:1–2:1) gave 2′*R*-**6c** as a white semi-solid (127.8 mg, 71.2%, 82% d.e.).

2′*R*-**6c**; ν_{max} (KBρ) 3335, 3061, 3030, 2954, 2865, 1729, 1679, 1604, 1456, 1423, 1386, 1311, 1231, 1172, 1127, 1074, 1030, 968, 914, 832, 746, 701, 626 cm^{-1}; δ_H ($CDCl_3$) 7.29–7.09 (10H, m, 2Ph), 5.23 (1H, d, *J*=8.5 Hz, NC*H*(Ph)CH), 4.62 (1H, t, *J*=5.6 Hz, COC*H*(NHR)CH_2), 3.83 (1H, m, NC*H*(CH_3)CH), 3.42 (1H, d, J_{gem}=12.8 Hz, NHC$H_A$$H_B$Ph), 3.32 (1H, d, J_{gem}=12.8 Hz, NHC$H_B$$H_A$Ph), 2.74 (3H, s, NCH_3), 2.05 (1H, br s, NH), 1.65 (1H, m, CH(NHR)C$H_A$$H_B$$CH_2$), 1.45–1.19 (5H, m, CH(NHR)-C$H_B$$H_A$$CH_2$, $CH_2CH_2CH_2CH_3$), 0.81 (3H, t, *J*=7.1 Hz, CH_2CH_3), 0.73 (3H, d, *J*=6.6 Hz, CHCH_3); δ_C ($CDCl_3$) 174.7, 154.3, 139.4, 135.6, 127.5, 127.4, 127.1, 126.0, 125.8, 58.8, 58.1, 53.0, 51.8, 32.3, 27.2, 26.5, 21.7, 14.0, 13.0; *m*/*z* (EI) 393 (M^+), 336 ($M^+-C_4H_9$), 302 (M^+-CH_2Ph), 288, 211, 191 (AuxH^+), 176, 132, 91; Found M^+, 393.2416. $C_{24}H_{31}N_3O_2$ requires M, 393.2416; R_f=0.31 Pet/Et_2O (1:1); $[\alpha]^{25}_D$=−19.3° (*c*=3.4, $CHCl_3$).

2′*S*-**6c**; ν_{max} 3333, 3031, 2955, 1732, 1679, 1495, 1455, 1422, 1393, 1311, 1232, 1204, 1173, 1072, 1029, 971, 833, 742, 701 cm^{-1}; δ_H ($CDCl_3$) 7.27–7.05 (10H, m, 2Ph), 5.18 (1H, d, *J*=8.7 Hz, NC*H*(Ph)CH), 4.62 (1H, t, *J*=7.2 Hz, COC*H*(NHR)CH_2), 3.80 (1H, m, NC*H*-(CH_3)CH), 3.65 (1H, d, J_{gem}=12.7 Hz, NHC$H_A$$H_B$Ph), 3.55 (1H, d, J_{gem}=12.7 Hz, NHC$H_B$$H_A$Ph), 2.76 (3H, s, NCH_3), 2.04 (1H, br s, NH), 1.64 (1H, m, CH(NHR)-C$H_A$$H_B$$CH_2$), 1.39 (1H, m, CH(NHR)C$H_B$$H_A$$CH_2$), 1.21 (4H, m, $CH_2CH_2CH_2CH_3$), 0.75 (3H, t, *J*=6.9 Hz, CH_2CH_3), 0.73 (3H, d, *J*=6.6 Hz, CHCH_3); δ_C ($CDCl_3$) 174.7, 154.3, 139.4, 135.6, 127.5, 127.4, 127.1, 126.0, 125.8, 58.8, 58.1, 53.0, 51.8, 32.3, 27.2, 26.5, 21.7, 14.0, 13.0; *m*/*z* (EI) 393 (M^+), 336 ($M^+-C_4H_9$), 302

(M^+-CH_2Ph), 191 ($AuxH^+$), 176, 132, 91, 57; Found M^+, 393.2416. $C_{24}H_{31}N_3O_2$ requires M, 393.2416; R_f=0.15 Pet/Et_2O (1:1); $[\alpha]^{25}_D$=−73.1° (c=1.1, $CHCl_3$).

5.2.12. Typical procedure for DKR of 2′*RS*-3c with pyrrolidine (1.5 equiv.), Bu_4NI (0.2 equiv.), THF [0.10 M], reflux (Table 2, entry 28, for specific conditions of related experiments see Table 2). 2′*RS*-**3c** (73.2 mg, 0.20 mmol), Bu_4NI (15.0 mg, 0.041 mmol), Et_3N (0.034 mL, 0.244 mmol), pyrrolidine (0.025 mL, 0.299 mmol) in THF (2.0 mL) at reflux. Reaction time 143 h. Purification (SiO_2, Pet/Et_2O 2:1–1:1, Et_2O) gave 2′*R*-**7c** as a clear colourless oil (71.1 mg, 99.4%, >98% d.e.).

2′*R*-**7c**; ν_{max} 3033, 2958, 2872, 1729, 1683, 1606, 1456, 1421, 1391, 1310, 1229, 1201, 1172, 1089, 1071, 1031, 972, 942, 904, 865, 829, 755, 683, 633 cm^{-1}; δ_H ($CDCl_3$) 7.25–7.16 (3H, m, ArH), 7.11 (2H, m, ArH), 5.26 (1H, d, J=8.6 Hz, NC*H*(Ph)CH), 4.89 (1H, t, J=6.9 Hz, COC*H*-(NR_2)CH_2), 3.82 (1H, m, NC*H*(CH_3)CH), 2.76 (3H, s, NCH_3), 2.57 (2H, d, J_{gem}=5.5 Hz, N($CH_AH_BCH_2$)$_2$), 2.45 (2H, d, J_{gem}=5.4 Hz, N($CH_BH_ACH_2$)$_2$), 1.77–1.47 (2H, m, CH(NR_2)CH_2CH_2), 1.54 (4H, m, N(CH_2CH_2)$_2$), 1.23 (4H, m, $CH_2CH_2CH_2CH_3$), 0.81 (3H, t, J=6.6 Hz, CH2CH3), 0.74 (3H, d, J=6.6 Hz, CHCH3); δ_C (CDCl3) 173.6, 156.1, 137.3, 128.7, 128.4, 127.6, 61.7, 59.9, 54.2, 49.7, 30.1, 28.8, 28.7, 23.8, 23.3, 15.4, 14.4; m/z (EI) 357 (M^+), 300 ($M^+-C_4H_9$), 245, 191 ($AuxH^+$), 141, 110, 42; Found M^+, 357.2416. $C_{21}H_{31}N_3O_2$ requires M, 357.2416; R_f=0.15 Pet/Et_2O (1:1); $[\alpha]^{32}_D$=−75.4° (c=3.9, $CHCl_3$).

2′*S*-**7c**; ν_{max} 3034, 2957, 2872, 1729, 1683, 1456, 1422, 1392, 1311, 1288, 1260, 1229, 1202, 1171, 1089, 1071, 1031, 972, 942, 864, 828, 737, 702 cm^{-1}; δ_H ($CDCl_3$) 7.23–7.15 (3H, m, ArH), 7.06 (2H, d, J=7.0 Hz, ArH), 5.27 (1H, d, J=8.6 Hz, NC*H*(Ph)CH), 4.87 (1H, t, J=6.6 Hz, COC*H*(NR_2)CH_3), 3.81 (1H, m, NC*H*(CH_3)CH), 2.74 (3H, s, NCH_3), 2.68 (2H, d, J_{gem}=5.4 Hz, N($CH_AH_BCH_2$)$_2$), 2.57 (2H, d, J_{gem}=5.6 Hz, N($CH_BH_ACH_2$)$_2$), 1.77–1.47 (2H, m, CH(NR_2)CH_2CH_2), 1.63 (4H, s, N(CH_2CH_2)$_2$), 1.23 (4H, m, $CH_2CH_2CH_2CH_3$), 0.72 (6H, d, J=6.3 Hz, CHC*H*$_3$, CH_2CH_3); δ_C ($CDCl_3$) 173.0, 155.5, 136.6, 128.3, 128.0, 127.1, 61.3, 59.1, 53.7, 49.4, 30.2, 28.1, 27.8, 23.4, 22.7, 14.9, 13.9; m/z (EI) 357 (M^+), 300 ($M^+-C_4H_9$), 220, 205, 140, 57; Found M^+, 357.2416. $C_{21}H_{31}N_3O_2$ requires M, 357.2416; R_f=0.06 Pet/Et_2O (1:1); $[\alpha]^{33}_D$=−47.3° (c=2.4, $CDCl_3$).

5.2.13. DKR of 2′*RS*-3c with piperidine, reflux (Table 2, entry 29). 2′*RS*-**3c** (0.10M, 2.0 mL, 0.200 mmol), Bu_4NI (14.9 mg, 0.040 mmol), Et_3N (0.034 mL, 0.244 mmol), piperidine (0.030 mL, 0.293 mmol) in THF (2.0 mL) at reflux. Reaction time 48 h. Purification (SiO_2, Pet/Et_2O 1:1) gave 2′*R*-**8c** as a clear colourless oil (69.9 g, 94.1%, >98% d.e.).

2′*R*-**8c**; ν_{max} 3033, 2932, 2856, 2805, 1729, 1682, 1607, 1495, 1421, 1392, 1311, 1288, 1260, 1235, 1204, 1173, 1121, 1072, 1036, 1000, 969, 942, 910, 863, 829, 739, 703, 671, 632 cm^{-1}; δ_H ($CDCl_3$) 7.32–7.07 (5H, m, Ph), 5.27 (1H, d, J=8.8 Hz, NC*H*(Ph)CH), 4.79 (1H, br t, COC*H*(NR_2)CH_2), 3.79 (1H, m, NC*H*(CH_3)CH), 2.75 (3H, s, NCH_3), 2.44 (4H, m, N(CH_2)$_2$), 1.68 (1H, m, CH(NR_2)C$H_AH_BCH_2$), 1.47 (1H, m, CH(NR_2)C$H_BH_ACH_2$), 1.37 (4H, m, N(CH_2CH_2)$_2CH_2$), 1.25–1.10 (6H, m, $CH_2CH_2CH_2CH_3$, (CH_2)$_2CH_2$), 0.80 (3H, t, J=7.0 Hz, CH_2CH_3), 0.73 (3H, d, J=6.6 Hz, CHC*H*$_3$); δ_C ($CDCl_3$) 172.4, 155.5, 136.9, 128.1, 127.8, 127.2, 63.9, 59.1, 53.6, 50.1, 28.7, 28.3, 26.6, 26.0, 24.6, 22.7, 15.1, 14.0; m/z (EI) 371 (M^+), 314 ($M^+-C_4H_9$), 245, 191 ($AuxH^+$), 154, 132, 124, 84, 69, 41; Found M^+, 371.2573. $C_{22}H_{33}N_3O_2$ requires M, 371.2573; R_f=0.54 Pet/Et_2O (1:1); $[\alpha]^{32}_D$=−62.7° (c=4.7, $CHCl_3$).

2′*S*-**8c**; ν_{max} 3033, 2932, 2857, 1729, 1682, 1495, 1456, 1421, 1392, 1310, 1288, 1260, 1228, 1202, 1172, 1123, 1092, 1071, 1033, 967, 942, 863, 756, 739, 702 cm^{-1}; δ_H ($CDCl_3$) 7.26–7.13 (5H, m, Ph), 5.27 (1H, d, J=8.8 Hz, NC*H*(Ph)CH), 4.77 (1H, t, J=8.7 Hz, COC*H*(NR_2)CH_2), 3.79 (1H, m, NC*H*(CH_3)CH), 2.75 (3H, s, NCH_3), 2.38 (4H, m, N(CH_2-)$_2$), 1.65 (1H, m, CH(NR_2)C$H_AH_BCH_2$), 1.43 (1H, m, CH(NR_2)C$H_BH_ACH_2$), 1.45 (4H, m, N(CH_2CH_2)$_2CH_2$), 1.37 (2H, t, J=5.0 Hz, (CH_2)$_2CH_2$), 1.13 (4H, m, $CH_2CH_2CH_2CH_3$), 0.80 (3H, t, J=7.0 Hz, CH_2CH_3), 0.73 (3H, d, J=6.9 Hz, CHC*H*$_3$); δ_c($CDCl_3$) 173.0, 155.3, 136.4, 128.0, 127.6, 126.6, 63.2, 59.0, 53.3, 50.1, 29.3, 27.9, 27.7, 26.2, 24.4, 22.3, 14.4, 13.6; m/z (EI) 371 (M^+), 314 ($M^+-C_4H_9$), 245, 191 ($AuxH^+$), 154, 140, 124, 84, 57, 42; Found M^+, 371.2573. $C_{22}H_{33}N_3O_2$ requires M, 371.2573; R_f=0.13 Pet/Et2O (1:1); $[\alpha]^{35}_D$=−40.7°(c=1.1, $CHCl_3$).

5.3. Dynamic kinetic resolutions with metalated nucleophiles

5.3.1. General procedure using sodium dimethyl malonate. To a stirred solution of 2′-haloacylimidazolidinone and tetra-*n*-butylammonium halide in THF (unless stated otherwise), under N_2, was added a solution of sodium dimethylmalonate (NaDMM) in THF. Reactions were monitored by TLC and were worked up by quenching with saturated, aqueous NH_4Cl and extraction into DCM. The combined organic fractions were then washed with distilled water and dried with $MgSO_4$ and the crude product was purified by column chromatography.

5.3.2. Typical procedure for DKR of 2′*RS*-3a with sodium dimethylmalonate (1.2 equiv.) over 28 h, Bu_4NBr (2.0 equiv.), THF (Table 3, entry 1, for specific conditions of related experiments see Table 3). 2′*RS*-**3a** (200.0 mg, 0.615 mmol), Bu_4NBr (396.9 mg, 1.231 mmol), THF (6.0 mL), NaDMM (0.034 M, 20 mL, 1.231 mmol) added slowly over 28 h. TLC revealed some remaining starting material after 116 h so additional NaDMM (0.034 M, 2.0 mL, 0.069 mmol) was added over 8 h. Reaction quenched after 141 h (in total). Purification (SiO_2, Pet/Et_2O 1:3) gave 2′*R*-**11a** (144.0 mg, 62.3%, 54–60% d.e.).

2′*R*-**11a**; mp 90.7–95.6°C; ν_{max} 2955, 2360, 1734, 1682, 1424, 1392, 1330, 1197, 1071, 1003, 974, 948, 911, 863, 810, 787, 739, 702, 677 cm^{-1}; δ_H ($CDCl_3$) 7.26–7.10 (3H, m, ArH), 7.05 (2H, m, J=6.4 Hz, ArH), 5.22 (1H, d, J=8.7 Hz, NC*H*(Ph)CH), 4.49 (1H, dt, J_A=12.5 Hz, J_B=7.0 Hz, COC*H*(CHR_2)CH_3), 3.89 (1H, m, NC*H*(CH_3)-CHR_2), 3.74 (1H, d, J=11.2 Hz, CHC*H*(CO_2R)$_2$), 3.66

(3H, s, CO_2CH_3), 3.61 (3H, s, CO_2CH_3), 2.77 (3H, s, NCH_3), 1.10 (3H, d, J=7.0 Hz, CH(CHR$_2$)CH_3), 0.72 (3H, d, J=6.5 Hz, CHCH_3); δ_C ($CDCl_3$) 174.2, 169.4, 169.1, 155.5, 137.1, 129.0, 128.7, 128.5, 59.6, 54.7, 54.2, 53.1, 53.0, 38.6, 28.6, 15.9, 15.4; m/z (EI) 376 (M^+), 345, 312, 280, 245, 205, 189, 132, 84; Found M^+, 376.1634. $C_{19}H_{24}N_2O_6$ requires M, 376.1634; R_f=0.49 Pet/EtOAc (1:1); $[\alpha]^{25}_D$=−31.6° (c=0.8, $CHCl_3$).

2′*S*-**11a**; mp 59.0–63.0°C; ν_{max} 2955, 1733, 1683, 1423, 1393, 1197, 1072, 1025, 975, 948, 912, 863, 791, 757, 735, 702, 632 cm^{-1}; δ_H ($CDCl_3$) 7.28–7.11 (5H, m, Ph), 5.18 (1H, d, J=8.6 Hz, NCH(Ph)CH), 4.63 (1H, dt, J_A=12.2 Hz, J_B=6.8 Hz, COCH(CHR$_2$)CH$_3$), 3.84 (1H, m, NCH(CH$_3$)CH), 3.71 (1H, d, J=12.8 Hz, CHCH(CO$_2$R)$_2$), 3.63 (3H, s, CO_2CH_3), 3.39 (3H, s, CO_2CH_3), 2.78 (3H, s, NCH_3), 1.15 (3H, d, J=7.0 Hz, CH(CHR$_2$)CH_3), 0.73 (3H, d, J=6.6 Hz, CHCH_3); δ_C ($CDCl_3$) 174.3, 169.1, 168.7, 155.6, 136.4, 128.7, 128.3, 127.6, 60.0, 54.9, 54.2, 53.0, 52.9, 38.7, 28.6, 16.3, 15.4; m/z (EI) 376 (M^+), 345, 312, 285, 245, 189, 159, 127, 58; Found M^+, 376.1634. $C_{19}H_{24}N_2O_6$ requires M, 376.1634; R_f=0.37 Pet/EtOAc (1:1); $[\alpha]^{25}_D$=−72.8° (c=1.5, $CHCl_3$).

5.3.3. Typical procedure for DKR of 2′*RS*-3b with sodium dimethylmalonate (2.7 equiv.), Bu_4NBr (0.2 equiv.), THF (Table 3, entry 4, for specific conditions of related experiments see Table 3). 2′*RS*-**3b** (68.3 mg, 0.20 mmol), Bu_4NBr (13.1 mg, 0.04 mmol), THF (2.0 mL), NaDMM (0.7 M, 0.80 mL, 0.55 mmol) added at reflux. Reaction time 48 h. Purification (SiO_2, Pet/EtOAc 9:1, 7:3 then 6:4) gave 2′*R*-**11b** (70.8 mg, 90%, 35% d.e.).

2′*R*-**11b**; mp 98–99.5°C; ν_{max} 3037, 3005, 2984, 2963, 2879, 1736, 1721, 1676, 1394, 1326 cm^{-1}; δ_H ($CDCl_3$) 7.25–7.20 (3H, m, ArH), 7.08 (2H, d, J=6.5 Hz, ArH), 5.26 (1H, d, J=8.7 Hz, NCH(Ph)CH), 4.62 (1H, ddd, J=4.6, 7.5, 11.1 Hz, COCH(CHR$_2$)CH$_2$), 3.90 (1H, dq, J=6.5, 8.7 Hz, NCH(CH$_3$)CH), 3.82 (1H, d, J=11.1 Hz, CHCH(CO$_2$R)$_2$), 3.66 (3H, s, CO_2CH_3), 3.61 (3H, s, CO_2CH_3), 2.78 (3H, s, NCH_3), 1.75 (1H, ddq, J=4.6, 7.6, 14.3 Hz, CH(CHR$_2$)CH_ACH$_B$CH$_3$), 1.51 (1H, ddq, J=6.5, 7.6, 14.3 Hz, CH(CHR$_2$)CH$_A$CH_BCH$_3$), 0.74 (3H, d, J=6.5 Hz, CHCH_3), 0.62 (3H, t, J=7.6 Hz, CH$_2$CH_3); δ_C ($CDCl_3$) 172.9, 169.1, 168.6, 155.2, 136.7, 128.3, 128.3, 128.0, 127.0, 59.3, 53.6, 52.5, 42.9, 28.1, 22.9, 14.9, 9.3; m/z (EI) 390 (M^+), 359, 326, 299, 259, 189, 173, 141; Found M^+, 390.1791. $C_{20}H_{26}N_2O_6$ requires M, 390.1791; R_f=0.26 Hex./EtOAc (6:4); $[\alpha]^{25}_D$=−31.6° (c=1.3, $CHCl_3$).

2′*S*-**11b**; ν_{max} 3068, 3037, 2975, 2958, 2881, 1755, 1735, 1677, 1394, 1317 cm^{-1}; δ_H ($CDCl_3$) 7.26–7.12 (5H, m, ArH), 5.19 (1H, d, J=8.4 Hz, NCH(Ph)CH), 4.73 (1H, ddd, J=4.5, 7.3, 10.6 Hz, COCH(CHR$_2$)CH$_2$), 3.84 (1H, dq, J=6.5, 8.4 Hz, NCH(CH$_3$)CH), 3.80 (1H, d, J=10.6 Hz, CHCH(CO$_2$R)$_2$), 3.60 (3H, s, CO_2CH_3), 3.40 (3H, s, CO_2CH_3), 2.77 (3H, s, NCH_3), 1.68 (1H, ddq, J=4.5, 7.5, 14.1 Hz, CH(CHR$_2$)CH_ACH$_B$CH$_3$), 1.55 (1H, ddq, J=7.4, 7.5, 14.1 Hz, CH(CHR$_2$)CH$_A$CH_BCH$_3$), 0.82 (3H, t, J=7.5 Hz, CH$_2$CH_3), 0.73 (3H, d, J=6.5 Hz, CHCH_3); δ_C ($CDCl_3$) 172.7, 168.5, 168.2, 155.2, 136.0, 128.0, 127.7, 127.1, 59.6, 53.6, 52.8, 52.34, 52.29, 43.1, 28.0, 22.9, 14.8, 9.8; m/z (EI) 390 (M^+), 359, 326, 299, 259, 189, 173, 141; Found M^+, 390.1791. $C_{20}H_{26}N_2O_6$ requires M, 390.1791; R_f=0.274 Hex./EtOAc (6:4); $[\alpha]^{25}_D$=−104.4° (c=1.4, $CHCl_3$).

5.3.4. Typical procedure for DKR of 2′*RS*-3c with sodium dimethylmalonate (2.7 equiv.), Bu_4NBr (0.2 equiv.), THF (Table 3, entry 8, for specific conditions of related experiments see Table 3). 2′*RS*-**3c** (0.250 mmol), Bu_4NBr (16.2 mg, 0.050 mmol), THF (2.5 mL), NaDMM (0.692 M, 1.0 mL, 0.692 mmol), heated at reflux under N_2. Reaction quenched after 27 hours. Purification (SiO_2, Pet/Et_2O 2:1–1:2) gave 2′*R*-**11c** (86.9 mg, 83.2%, 52.1% d.e.).

2′*R*-**11c**; ν_{max} 3456, 2956, 2873, 1735, 1678, 1423, 1393, 1317, 1265, 1195, 1073, 1034, 988, 944, 898, 865, 801, 738, 702, 632 cm^{-1}; δ_H ($CDCl_3$) 7.26–7.12 (5H, m, Ph), 5.18 (1H, d, J=8.5 Hz, NCH(Ph)CH), 4.76 (1H, dt, J=6.5, 7.5 Hz, COCH(CHR$_2$)CH$_2$), 3.82 (1H, m, NCH(CH$_3$)CH), 3.79 (1H, d, J=10.4 Hz, CHCH(CO$_2$R)$_2$), 3.58 (3H, s, CO_2CH_3), 3.41 (3H, s, CO_2CH_3), 2.78 (3H, s, NCH_3), 1.53 (2H, m, CH(CHR$_2$)CH_2CH$_2$), 1.18 (4H, m, CH$_2$CH_2CH_2CH$_3$), 0.78 (3H, t, J=6.6 Hz, CH$_2$CH_3), 0.73 (3H, d, J=6.6 Hz, CHCH_3); δ_C ($CDCl_3$) 173.5, 169.0, 168.7, 155.7, 136.5, 128.6, 128.2, 127.6, 60.2, 54.2, 53.7, 52.8, 42.8, 30.2, 28.6, 28.2, 23.2, 15.3, 14.2; m/z (EI) 418 (M^+), 387, 354, 330, 303, 287, 201, 189, 169, 132, 113, 58; Found M^+, 418.2104. $C_{22}H_{30}N_2O_6$ requires M, 418.2104; R_f=0.42 Pet/Et_2O (1:2); $[\alpha]^{34}_D$ −94.4° (c=1.9, $CHCl_3$).

2′*S*-**11c**; ν_{max} 3457, 3063, 3034, 2956, 2872, 1734, 1681, 1606, 1495, 1456, 1423, 1392, 1319, 1193, 1089, 1074, 1034, 987, 945, 899, 854, 829, 737, 703, 472 cm^{-1}; δ_H ($CDCl_3$) 7.26–7.15 (3H, m, ArH), 7.08 (2H, m, ArH), 5.26 (1H, d, J=8.7 Hz, NCH(Ph)CH), 4.66 (1H, m, COCH(CHR$_2$)CH$_2$), 3.90 (1H, m, NCH(CH$_3$)CH), 3.81 (1H, d, J=11.1 Hz, CHCH(CO$_2$R)$_2$), 3.66 (3H, s, CO_2CH_3), 3.60 (3H, s, CO_2CH_3), 2.79 (3H, s, NCH_3), 1.59 (1H, m, CH(CHR$_2$)CH_AH$_B$CH$_2$), 1.43 (1H, m, CH(CHR$_2$)CH_BH$_A$CH$_2$), 1.10 (4H, m, CH$_2$CH_2CH_2CH$_3$), 0.74 (3H, d, J=6.6 Hz, CHCH_3), 0.68 (3H, t, J=7.0 Hz, CH$_2$CH_3); δ_C ($CDCl_3$) 173.6, 169.6, 169.2, 155.7, 137.2, 128.8, 128.5, 128.6, 59.7, 54.1, 53.4, 53.0, 42.6, 30.3, 28.7, 27.5, 23.3, 15.4, 14.2; m/z (EI) 418 (M^+), 387, 354, 330, 303, 287, 220, 205, 189, 169, 132, 57; Found M^+, 418.2104. $C_{22}H_{30}N_2O_6$ requires M, 418.2104; R_f=0.17 Pet/Et_2O (1:2); $[\alpha]^{35}_D$=−10.3° (c=2.3, $CHCl_3$).

5.3.5. General procedure using sodium azide. 2′-Haloacylimidazolidinone was stirred in benzotrifluoride (α,α,α-Trifluorotoluene, BTF) with tetra-*n*-butylammonium halide and sodium azide at 83°C. Reactions were monitored by TLC and were worked up by dilution with DCM and extraction with distilled water and brine. The organic phase was dried with $MgSO_4$ and the crude product was purified by column chromatography.

5.3.6. Typical procedure for DKR of 2′*RS*-3b with sodium azide (1.5 equiv.), Bu_4NBr (0.2 equiv.), BTF, 83°C (Table 3, entry 10, for specific conditions of related experiments see Table 3). 2′*RS*-**3b** (68.1 mg, 0.20 mmol), Bu_4NBr (13.0 mg, 0.040 mmol), NaN_3 (19.8 mg,

0.30 mmol), BTF (2.0 mL) heated at 83°C. Reaction quenched after 30 h. Purification (SiO_2, Hex/EtOAc 8:2, 6:4) gave 2′*R*-**12b** (60.5 mg, 100%, 31.0% d.e.).

2′*R*-**12b**; mp 113–114°C; ν_{max} 3068, 3053, 3032, 2970, 2928, 2879, 2105, 1727, 1685, 1394, 1231 cm^{-1}; δ_H ($CDCl_3$) 7.30–7.21 (3H, m, ArH), 7.09–7.07 (2H, m, ArH), 5.21 (1H, d, *J*=8.5 Hz, NC*H*(Ph)CH), 4.99 (1H, dd, *J*=4.7, 9.0 Hz, COC*H*(N_3)CH_2), 3.87 (1H, dq, *J*=6.6, 8.5 Hz, NC*H*(CH_3)CH), 2.77 (3H, s, NCH_3), 1.87 (1H, ddq, *J*=4.7, 7.3, 14.2 Hz, CH(N_3)CH_AC$H_B$$CH_3$), 1.72 (1H, ddq, *J*=7.3, 9.0, 14.2 Hz, CH(N_3)CH_AC$H_B$$CH_3$), 1.02 (3H, t, *J*=7.3 Hz, CH_2CH_3), 0.75 (3H, d, *J*=6.6 Hz, CHCH_3); δ_C ($CDCl_3$) 170.1, 155.1, 135.9, 128.7, 128.3, 126.8, 62.0, 59.6, 54.1, 28.2, 24.7, 14.9, 10.8; *m*/*z* (EI) 302 (MH^+), 274, 259, 217, 190, 132, 58; Found MH^+, 302.1613. $C_{15}H_{20}N_5O_2$ requires *MH*, 302.1617; R_f=0.31 Hex./EtOAc (6:4); $[\alpha]^{25}_D$=−180.8° (*c*=0.8, $CHCl_3$).

2′*S*-**12b**; mp 109–110°C; ν_{max} 3089, 3036, 2989, 2938, 2881, 2102, 1709, 1681, 1384, 1211 cm^{-1}; δ_H ($CDCl_3$) 7.28–7.20 (3H, m, 3ArH), 7.07–7.05 (2H, m, 2ArH), 5.27 (1H, d, *J*=8.6 Hz, NC*H*(Ph)CH), 4.97 (1H, dd, *J*=4.4, 8.9 Hz, COC*H*(N_3)CH_2), 3.89 (1H, dq, *J*=6.7, 8.6 Hz, NC*H*(CH_3)CH), 2.76 (3H, s, NCH_3), 1.89 (1H, ddq, *J*=4.4, 7.3, 14.1 Hz, CH(N_3)CH_AC$H_B$$CH_3$), 1.64 (1H, ddq, *J*=7.3, 8.9, 14.1 Hz, CH(N_3)CH_AC$H_B$$CH_3$), 0.95 (3H, t, *J*=7.3 Hz, CH_2CH_3), 0.73 (3H, d, *J*=6.7 Hz, CHCH_3); δ_C ($CDCl_3$) 170.3, 155.0, 136.0, 128.5, 128.2, 126.8, 61.6, 59.2, 54.0, 28.1, 24.9, 14.8, 10.5; *m*/*z* (EI) 302 (MH^+), 259, 217, 190, 132, 28; Found MH^+, 302.1615. $C_{15}H_{20}N_5O_2$ requires *MH*, 302.1617; R_f=0.39 Hex./EtOAc (6:4); $[\alpha]^{25}_D$=−52.9° (*c*=1.0, $CHCl_3$).

5.4. Dynamic kinetic resolutions with sulfur nucleophiles

5.4.1. General procedure. To a stirred solution of 2′-haloacylimidazolidinone, tetra-*n*-butylammonium bromide and triethylamine in THF was added thiol. Reactions were monitored by TLC and were worked up by removal of THF in vacuo. The crude mixture was taken up in DCM and washed with distilled water. The organic phase was dried with $MgSO_4$ and the crude product was purified by column chromatography.

5.4.2. Typical procedure for DKR of 2′*RS*-3a with thiophenol (1.5 equiv.), Bu_4NBr (2.0 equiv.), THF [0.010 M] (Table 4, entry 1, for specific conditions of related experiments see Table 4). 2′*RS*-**3a** (65 mg, 0.20 mmol), Bu_4NBr (129 mg, 0.40 mmol), Et_3N (0.033 mL, 0.24 mmol), thiophenol (0.031 mL, 0.30 mmol) in THF (20 mL). Reaction time 4 days. Purification (SiO_2, Pet/EtOAc 5:1) gave 2′*S*-**13a** (5 6 mg, 78%, 19% d.e.).

2′*R*-**13a**; ν_{max} 2974, 1726, 1683, 1422, 1372, 1235, 1201, 753, 701 cm^{-1}; δ_H ($CDCl_3$) 7.25–6.92 (10H, m, Ar*H*), 5.31–5.22 (2H, m, NC*H*(CH_3)C*H*(Ph)N), 3.91–3.81 (1H, m, COC*H*(SPh)CH_3), 2.80 (3H, s, NCH_3), 1.20–1.15 (3H, d, *J*=6.8 Hz, NCHCH_3), 0.75 (3H, d, *J*=6.6 Hz, CH(SPh)CH_3); δ_C ($CDCl_3$) 172.4, 157.0, 137.6, 136.4, 132.5, 129.9, 129.8, 129.5, 129.5, 129.0, 60.7, 55.3, 43.3, 29.8, 17.6, 16.5; *m*/*z* (EI) 354 (M^+), 245; Found M^+, 354.1358. $C_{20}H_{22}N_2O_2S$ requires M, 354.1402; $[\alpha]^{25}_D$=−63° (*c*=1.0 Hz, $CHCl_3$).

2′*S*-**13a**; ν_{max} 2976, 1728, 1686, 1429, 1380, 1241, 1201, 755, 700 cm^{-1}; δ_H ($CDCl_3$) 7.45–7.00 (10H, m, 10Ar*H*), 5.45–5.35 (1H, q, *J*=6.5 Hz, NC*H*(CH_3)CH), 5.1 (1H, d, *J*=6.8 Hz, NC*H*(Ph)CH), 3.74–3.65 (1H, m, COC*H*(SPh)CH_3), 2.65 (3H, s, NCH_3), 1.25 (3H, d, *J*=6.8 Hz, NCHCH_3), 0.65 (3H, d, *J*=6.6 Hz, CH(SPh)CH_3); δ_C ($CDCl_3$) 172.0, 155.7, 136.9, 134.6, 133.1, 129.3, 129.1, 129.0, 128.9, 128.6, 128.5, 128.4, 127.2, 126.3, 126.2, 60.2, 54.2, 43.5, 28.5, 17.4, 15.2; *m*/*z* (EI) 354 (M^+), 245; Found M^+, 354.1405. $C_{20}H_{22}N_2O_2S$ requires M, 354.1402; $[\alpha]^{25}_D$=−156° (*c*=1.0, $CHCl_3$).

5.4.3. Typical procedure for DKR of 2′*RS*-3a with methyl thioglycolate (1.5 equiv.), *n*-Bu_4NBr (2.0 equiv.), THF [0.01 M] (Table 4, entry 3, for specific conditions of related experiments see Table 4). 2′*RS*-**3a** (65.0 mg, 0.20 mmol), Bu_4NBr (130 mg, 0.40 mmol), Et_3N (0.033 mL, 0.24 mmol), methyl thioglycolate (0.027 mL, 0.30 mmol) in THF (20 mL). Reaction time 48 h. Purification (SiO_2, Pet/EtOAc 5:1) gave 2′*R*-**14a** (55 mg, 79%, 9% de).

2′*R*-**14a**; ν_{max} 3431, 2102, 1728, 1646, 1424, 1374, 1291 cm^{-1}; δ_H ($CDCl_3$) 7.25–7.05 (5H, m, ArH), 5.20–5.05 (2H, m, NC*H*(CH_3)C*H*(Ph)N), 4.0–3.90 (1H, m, COC*H*(SR)CH_3), 3.60 (3H, s, OCH_3), 3.30 (2H, s, SCH_2CO), 2.75 (3H, s, NCH_3), 1.35 (3H, d, *J*=6.8 Hz, CHCH_3), 0.70 (3H, d, *J*=6.6 Hz, CHCH_3); δ_C ($CDCl_3$) 171.6, 171.3, 155.9, 137.0, 129.0, 128.5, 127.2, 60.2, 54.2, 52.9, 39.7, 31.6, 28.6, 17.2, 15.3; *m*/*z* (EI) 350 (M^+), 277, 246; Found M^+, 350.1292. $C_{17}H_{22}N_2O_4S$ requires M, 350.1300; $[\alpha]^{25}_D$=−58° (*c*=1.0, $CHCl_3$).

2′*S*-**14a**; ν_{max} 2976, 1729, 1682, 1424, 1291, 1200 cm^{-1}; δ_H ($CDCl_3$) 7.25–7.15 (5H, m, ArH), 5.31 (1H, d, *J*=8.5 Hz, NC*H*(Ph)CH), 5.10 (1H, q, *J*=6.7 Hz, NC*H*(CH_3)CH), 4.0–3.9 (1H, m, COC*H*(SR)CH_3), 3.55 (3H, s, OCH_3), 3.05–2.85 (2H, m, SCH_2CO), 2.75 (3H, s, NCH_3), 1.35 (3H, d, *J*=6.8 Hz, CHCH_3), 0.70 (3H, d, *J*=6.6 Hz, CHCH_3); δ_C ($CDCl_3$) 171.1, 155.6, 136.6, 128.8, 128.5, 127.4, 59.6, 54.2, 52.7, 39.4, 30.9, 28.8, 16.6, 15.6; *m*/*z* (EI) 350 (M^+), 277, 246; Found M^+, 350.1292. $C_{17}H_{22}N_2O_4S$ requires M, 350.1300; $[\alpha]^{25}_D$=−70° (*c*=1.0, $CHCl_3$).

5.4.4. DKR of 2′*RS*-3a with benzyl mercaptan (1.5 equiv.), Bu_4NBr (2.0 equiv.), THF [0.010 M] (Table 4, entry 5, for specific conditions of related experiments see Table 4). 2′*RS*-**3a** (65.0 mg, 0.20 mmol), Bu_4NBr (129 mg, 0.40 mmol), Et_3N (0.033 mL, 0.24 mmol), benzyl mercaptan (0.027 mL, 0.30 mmol) in THF (20 mL). Reaction time 7 days. Purification (SiO_2, Pet/EtOAc 5:1) gave 2′*R*-**15a** (41 mg, 56%, 11% d.e.).

2′*R*-**15a**; ν_{max} 3447, 2974, 2933, 1725, 1680, 1422, 1372, 1235, 1201, 1060, 757, 701 cm^{-1}; δ_H ($CDCl_3$) 7.25–7.00 (10H, m, Ar*H*), 5.30–5.25 (1H, d, *J*=8.4 Hz, NC*H*(Ph)CH), 5.10–5.00 (1H, m, NC*H*(CH_3)CH), 3.85–3.75 (1H, m, COC*H*(SR)CH_3), 3.5–3.2 (2H, m, SCH_2Ph), 2.70 (3H, s, NCH_3), 1.35 (3H, d, *J*=6.8 Hz, NCHCH_3), 0.70 (3H, d, *J*=6.6 Hz, CH(SR)CH_3); δ_C ($CDCl_3$) 171.1, 155.8, 137.8,

136.9, 129.6, 128.9, 128.7, 128.5, 127.5, 127.3, 59.6, 54.2, 39.7, 32.9, 28.8, 16.6, 15.6; *m/z* (EI) 368 (M^+), 277, 246; Found M^+, 368.1576. $C_{21}H_{24}N_2O_2S$ requires M, 368.1558; $[\alpha]^{25}_D=-7.7°$ (c=1.0, $CHCl_3$).

2′*S*-**15a**; ν_{max} 1728, 1682, 1455, 1423, 1375, 1236, 1200 cm^{-1}; δ_H ($CDCl_3$) 7.25–7.00 (5H, m, Ar*H*), 5.10–4.95 (2H, m, NC*H*(Ph)C*H*(Ph)N), 3.86–3.75 (2H, d, J=8.5, SCH_2Ph), 3.75–3.65 (1H, m, COC*H*(SR)CH_3), 2.70 (3H, s, NCH_3), 1.30 (3H, d, J=6.8 Hz, NCHCH_3), 0.65 (3H, d, J=6.6 Hz, CH(SR)CH_3); δ_C ($CDCl_3$) 171.3, 154.9, 137.8, 136.2, 128.7, 128.1, 127.8, 127.6, 126.4, 126.3, 59.2, 53.1, 39.3, 33.9, 27.7, 16.9, 14.4; *m/z* (EI) 368 (M^+), 277, 246; Found M^+, 368.1551. $C_{21}H_{24}N_2O_2S$ requires M, 368.1558; $[\alpha]^{25}_D=-140°$ (c=1.0, $CHCl_3$).

5.5. *N*-Acylimidazolidinone methanolysis reactions

General procedure. *N*-acylimidazolidinone was stirred in methanol. Triethylamine was added to the solution and the reaction and the progress of the reaction was monitored by TLC. Work-up was effected by removal of the methanol in vacuo. The crude product was taken up in DCM and the organic phase was washed with distilled water and brine. The organic phase was dried with $MgSO_4$ and the product purified by column chromatography (SiO_2) using Pet_{30-40}/Et_2O in view of the volatility of many of the products.

5.5.1. Methanolysis of 2′*S*-6a with triethylamine (1.2 equiv.), *MeOH* [0.11 M] (Table 5, entry 1). 2′*S*-**6a** (103.8 mg, 0.296 mmol), Et_3N (0.050 mL, 0.355 mmol), MeOH (2.6 mL) at reflux. Reaction time 24 h. Purification (SiO_2, Pet_{30-40}/Et_2O 4:1 then Pet/EtOAc 1:1–2:1) gave 2*S*-**17a** as a colourless liquid (40.5 mg, 71.7%). Chiral auxiliary **1** was recovered (41.2 mg, 73.3%).

5.5.2. (*S*)-Methyl 2-(benzylamino)-propionate, 2*S*-17a. ν_{max} 3419, 3054, 2927, 2854, 1729, 1455, 1266, 1148, 1029, 896, 737, 703 cm^{-1}; δ_H ($CDCl_3$) 7.34–7.25 (5H, m, Ph), 3.81 (1H, d, J_{gem}=12.8 Hz, NCH_AH_BPh), 3.74 (3H, s, OCH_3), 3.68 (1H, d, J_{gem}=12.8 Hz, NCH_BCH_APh), 3.41 (1H, q, J=17.0 Hz, COC*H*(NHBn)CH_3), 1.87 (1H, br s, NH), 1.34 (3H, d, J=7.0 Hz, $CHCH_3$); δ_C ($CDCl_3$) 176.6, 140.1, 128.9, 128.7, 127.5, 56.3, 52.4, 52.2, 19.6; *m/z* (FAB) 194 (MH^+), 134, 91, 55, 43; Found MH^+, 194.1181. $C_{11}H_{16}NO_2$ requires M, 194.1181; R_f=0.78 Pet/EtOAc (1:7); $[\alpha]^{25}_D=-37.2°$ (c=0.7, MeOH); Lit.[29] $[\alpha]^{21}_D=-41.0°$; HPLC: (Chiralcel OD-H); detection λ 254 nm; temp. 25°C; flow rate 0.50 mL $^{-1}$; eluent-hexane/isopropanol, Et_2NH (95:5, 1%); R.T.-10.10 mins; 89.8% e.e.

5.5.3. Methanolysis of 2′*R*-6a with triethylamine (1.2 equiv.), MeOH [0.11 M] (Table 5, entry 2). 2′*R*-**6a** (110.7 mg, 0.315 mmol), Et_3N (0.053 mL, 0.380 mmol), MeOH (2.75 mL) at reflux. Reaction time 23 h. Purification (SiO_2, Pet_{30-40}/Et_2O 4:1 then Pet/EtOAc 1:1) gave 2*R*-**17a** as a clear, colourless oil (44.6 mg, 74.5%) and 1 (46.5 mg, 77.3%).

5.5.4. (*R*)-Methyl 2-(benzylamino)-propionate, 2*R*-17a. Spectral data (IR, ^1H- and ^{13}C NMR) identical to the enantiomer 2*S*-**17a**; *m/z* (FAB) 194 (MH+), 134, 91, 55, 43; Found MH^+, 194.1181. $C_{11}H_{16}NO_2$ requires M, 194.1181; $[\alpha]^{25}_D=+39.5°$ (c=1.15, $CHCl_3$); Lit.[30] $[\alpha]^{29}_D=+45.0°$ (c=1.0, MeOH); HPLC: (Chiralcel OD-H); detection λ 254 nm; temp. 25°C; flow rate 0.50 mL $^{-1}$; eluent hexanes/isopropanol, Et_2NH (95:5, 1%); R_T 11.23 mins; 89.8% e.e.

5.5.5. Methanolysis of 2′*R*-6b with triethylamine (1.2 equiv.), MeOH [0.11 M] (Table 5, entry 3). 2′*R*-**6b** (196.7 mg, 0.54 mmol), Et_3N (0.090 mL, 0.65 mmol), MeOH (4.7 mL) at reflux. Reaction time 6 days. Purification (SiO_2, Pet_{30-40}/Et_2O 9:1 then Pet/EtOAc 6:4) gave 2*R*-**17b** as a clear, colourless oil (94.2 mg, 84%) and **1** (86.7 mg, 85%).

5.5.6. (*R*)-Methyl 2-(benzylamino)-butanoate, 2*R*-17b. ν_{max} 3337, 3086, 3028, 2966, 2878, 1735, 1454, 1197 cm^{-1}; δ_H ($CDCl_3$) 7.22–7.08 (5H, m, Ph), 3.68 (1H, d, J_{gem}=13.0 Hz, NCH_AH_BPh), 3.57 (3H, s, OCH_3), 3.51 (1H, d, J_{gem}=13.0 Hz, NCH_BH_APh), 3.10 (1H, t, J=6.5 Hz, COC*H*(NHBn)CH_2), 1.81 (1H, s, N*H*), 1.58 (1H, ddq, J=6.5, 7.5, 13.0 Hz, CH(NHBn)C$H_AH_BCH_3$), 1.54 (1H, ddq, J=6.5, 7.5, 13.0 Hz, CH(NHBn)C$H_AH_BCH_3$), 0.82 (3H, t, J=7.5 Hz, CH_2CH_3); δ_C ($CDCl_3$) 175.5, 139.7, 128.0, 127.9, 126.7, 61.7, 51.8, 51.2, 26.3, 9.9; *m/z* (FAB) 208 (MH^+), 148, 91, 51; Found MH^+, 208.1338. $C_{12}H_{18}NO_2^+$ requires MH^+, 208.1338; R_f=0.52 Pet_{30-40}/Et_2O (6:4); $[\alpha]^{25}_D=+34.7°$ (c=4.95, $CHCl_3$), Lit. [12] $[\alpha]_D=+42.4°$ (c=1.0, MeOH); HPLC: (Chiralcel ODH); detection λ 254 nm; temp. 25°C; flow rate 0.50 mL $^{-1}$; eluent hexane/isopropanol (97:3); R_T 12.92 mins; 78% e.e.

5.5.7. Methanolysis of 2′*R*-6c with triethylamine (1.2–6.0 equiv.), MeOH [0.12 M] (Table 5, entry 4). 2′*R*-**6c** (91.8 mg, 0.233 mmol), Et_3N (0.039 mL, 0.280 mmol) then additional Et_3N (0.156 mL, 1.12 mmol) added after 48 h, MeOH (2.0 mL) at reflux. Reaction time 7 days in total. Purification (SiO_2, Pet_{30-40}/Et_2O 14:1 then Pet/EtOAc 1:1) gave 2*R*-**17c** as a colourless liquid (33.8 mg, 61.7%). Chiral auxiliary 1 was recovered (34.9 mg, 78.8%).

5.5.8. (*R*)-Methyl 2-(benzylamino)-hexanoate, 2*R*-17c. ν_{max} 3328, 3029, 2955, 2860, 1737, 1496, 1455, 1378, 1196, 1028, 991, 736, 699 cm^{-1}; δ_H ($CDCl_3$) 7.26–7.17 (5H, m, Ph), 3.65 (3H, s, OCH_3), 3.73 (1H, d, J_{gem}=12.9 Hz, NCH_AH_BPh), 3.55 (1H, d, J_{gem}=12.9 Hz, NCH_BH_APh), 3.19 (1H, t, J=6.7 Hz, COC*H*(NHBn)CH_2), 1.73 (1H, br s, NH), 1.56 (2H, m, $CHCH_2CH_2$), 1.24 (4H, m, $CH_2CH_2CH_2CH_3$), 1.34 (3H, t, J=6.9 Hz, CH_2CH_3); δ_C ($CDCl_3$) 176.6, 140.3, 128.8, 128.7, 127.5, 61.1, 52.6, 52.1, 33.8, 28.3, 22.9, 14.4; *m/z* (EI) 235 (M^+), 176, 106, 91, 65, 28; Found M^+, 235.1572. $C_{14}H_{21}NO_2$ requires M, 235.1572; R_f=0.63 Pet/Et_2O (5:1); $[\alpha]^{37}_D=+26.5°$ (c=1.02, $CHCl_3$); HPLC: (Chiralcel ODH); detection λ 254 nm; temp. 23°C; flow rate 0.50 mL $^{-1}$; eluent hexanes/isopropanol (98:2); R_T 15.50 mins; 90.8% e.e.

5.5.9. Methanolysis of 2′*R*-7a with triethylamine (1.2 equiv.), MeOH [0.10 M] (Table 5, entry 5). 2′*R*-**7a** (216.4 mg, 0.687 mmol), Et_3N (0.115 mL, 0.825 mmol), MeOH (6.9 mL) at reflux. Reaction time 26 h. Purification (SiO_2, Pet_{30-40}/Et_2O 5:1–3:1 then Pet/EtOAc 1:1–0:1) gave 2*R*-**18a** as a colourless liquid (42.9 mg, 39.2%). Chiral auxiliary **1** was recovered (47.6 mg, 36.5%).

5.5.10. (*R*)-Methyl 2-(pyrrolidinyl)-propionate, 2*R*-18a. ν_{max} 3391, 2926, 2361, 1739, 1683, 1456, 1379, 1265, 737 cm^{-1}; δ_H ($CDCl_3$) 3.66 (3H, s, OCH_3), 3.90 (1H, q, J=6.9 Hz, $CO(NR_2)CHCH_3$), 2.24 (4H, m, $N(CH_2CH_2)_2$), 1.74 (4H, s, $N(CH_2CH_2)_2$), 1.30 (3H, d, J=7.0 Hz, $CHCH_3$); δ_C ($CDCl_3$) 174.7, 62.6, 52.0, 51.4, 23.8, 17.7; *m/z* (EI) 157 (M^+), 142, 98, 56, 28; Found M^+, 157.1103. $C_8H_{15}NO_2$ requires M, 157.1103; R_f=0.29 Pet/EtOAc (1:7); $[\alpha]^{31}_D$=+30.3° (*c*=0.03, $CHCl_3$).

5.5.11. Methanolysis of 2′*R*-7c with triethylamine (6.1 equiv.), MeOH [0.50 M], (Table 5, entry 6). 2′*R*-**7c** (334.4 mg, 0.935 mmol), Et_3N (0.790 mL, 5.668 mmol), MeOH (1.9 mL) at reflux. Reaction time 16 days. Purification (SiO_2, Pet_{30-40}/Et_2O 5:1–3:1 then Pet/EtOAc 1:1–0:1) gave 2*R*-**18c** as a colourless liquid (127.4 mg, 68.4%). Chiral auxiliary **1** was recovered (87.6 mg, 49.3%).

5.5.12. (*R*)-Methyl 2-(pyrrolidinyl)-hexanoate, 2*R*-18c. ν_{max} 2956, 2873, 1735, 1460, 1378, 1192, 1149, 736 cm^{-1}; δ_H ($CDCl_3$) 3.58 (3H, s, OCH_3), 3.02 (1H, q, J=7.1 Hz, $CO(NR_2)CHCH_2$), 2.49 (4H, m, $N(CH_2CH_2)_2$, 1.62 (6H, m, $N(CH_2CH_2)_2$); $CHCH_2CH_2$), 1.22 (4H, m, $CH_2CH_2CH_2CH_3$), 0.81 (3H, t, J=6.9 Hz, CH_3); δ_C (CD_2Cl_2) 173.8, 66.5, 51.2, 50.5, 31.5, 28.5, 23.8, 23.0, 14.0; *m/z* (EI) 199 (M^+), 140, 110, 96, 84, 69, 55, 41, 28; Found M^+, 199.1572. $C_{11}H_{21}NO_2$ requires M, 199.1572; R_f=0.69 Pet/EtOAc (1:1); $[\alpha]^{25}_D$=+0.81° (*c*=3.2, $CHCl_3$).

5.5.13. Methanolysis of 2′*R*-8a with triethylamine (1.2 equiv.), MeOH [0.10 M] (Table 5, entry 7). 2′*R*-**8** (213.7 mg, 0.649 mmol), Et_3N (0.109 mL, 0.782 mmol), MeOH (6.5 mL) at reflux. Reaction time 26 h. Purification (SiO_2, Pet_{30-40}/Et_2O 10:1 then Pet/EtOAc 1:1–1:2) gave 2*R*-**19a** as a colourless oil (78.9 mg, 71.0%). Chiral auxiliary **1** was recovered (23.4 mg, 19.0%).

5.5.14. (*R*)-Methyl 2-(piperidyl)-propionate, 2*R*-19a. ν_{max} 3451, 2936, 2854, 2809, 2758, 1736, 1451, 1380, 1343, 1309, 1229, 1163, 1133, 1098, 1055, 1029, 981, 944, 908, 862, 838, 789, 751 cm^{-1}; δ_H ($CDCl_3$) 3.67 (3H, s, OCH_3), 3.24 (1H, q, J=7.0 Hz, $CO(NR_2)CHCH_3$), 2.50 (4H, m, $N(CH_2CH_2)_2CH_2$), 1.55 (4H, m, $(CH_2CH_2)_2CH_2$), 1.44 (2H, m, $(CH_2)_2CH_2$), 1.24 (3H, d, J=6.9 Hz, $CHCH_3$); δ_C ($CDCl_3$) 173.4, 63.4, 51.2, 50.9, 26.8, 24.9, 14.7; *m/z* (EI) 171 (M^+), 156, 112, 96, 84, 69, 56, 41, 28; Found M^+, 171.1259. $C_9H_{17}NO_2$ requires M, 171.1259; R_f=0.66 Pet/EtOAc (1:1); $[\alpha]^{31}_D$=+20.5° (*c*=4.2, $CHCl_3$).

5.5.15. Methanolysis of 2′*R*-8c with triethylamine (6.1 equiv.), MeOH [0.50 M] (Table 5, entry 8). 2′*R*-**8c** (481.2 mg, 1.295 mmol), Et_3N (1.10 mL, 7.892 mmol), MeOH (2.6 mL) at reflux. Reaction time 16 days. Purification (SiO_2, Pet_{30-40}/Et_2O 10:1 then Pet/EtOAc 10:1–0:1) gave 2*R*-**19c** as a colourless liquid (178.1 mg, 64.5%). Chiral auxiliary **1** was recovered (155.8 mg, 63.3%) and 2′*R*-**8c** was recovered (96.0 mg, 20.0%).

5.5.16. (*R*)-Methyl 2-(piperidyl)-hexanoate, 2*R*-19c. ν_{max} 2934, 2858, 1737, 1454, 1344, 1191, 1161, 1134, 1103, 1035, 998, 861 cm^{-1}; δ_H ($CDCl_3$) 3.63 (3H, s, OCH_3), 3.05 (1H, dd, J=5.9 Hz, $CO(NR_2)CHCH_2$), 2.44 (4H, m, $N(CH_2CH_2)_2CH_2$), 1.69–1.13 (12H, m, $N(CH_2CH_2)_2CH_2$; $CHCH_2CH_2$; $N(CH_2CH_2)_2CH_2$; $CH_2CH_2CH_2CH_3$), 0.82 (3H, t, J=6.9 Hz, CH_3); δ_C ($CDCl_3$) 173.5, 68.9, 51.3, 51.2, 29.7, 28.9, 26.8, 25.0, 23.0, 14.4; *m/z* (EI) 213 (M^+), 154, 124, 110, 98, 84, 69, 55, 41, 29; Found M^+, 213.1729. $C_{12}H_{23}NO_2$ requires M, 213.1729; R_f=0.90 Pet/EtOAc (1:1); $[\alpha]^{25}_D$=+29.5° (*c*=1.9, $CHCl_3$).

5.5.17. Methanolysis of 16 with triethylamine (1.0 equiv.), MeOH [0.10 M] (Table 5, entry 9). 16 (101.7 mg, 0.330 mmol), Et_3N (0.045 mL, 0.323 mmol), MeOH (3.2 mL) at reflux. Reaction time 76 h. Purification (SiO_2, Pet_{30-40}/Et_2O 5:1–1:1 then EtOAc) gave **20** as a colourless liquid (19.3 mg, 38.9%). Chiral auxiliary **1** was recovered (21.0 mg, 33.5%) and **16** was recovered (29.2 mg, 28.7%).

5.5.18. Methyl phenylacetate 20. ν_{max} (liquid film) 3065, 3031, 2952, 2843, 1740, 1603, 1497, 1455, 1436, 1256, 1161, 1076, 1013, 843, 762, 697 cm^{-1}; δ_H ($CDCl_3$) 7.37–7.27 (5H, m, Ph), 3.71 (3H, s, OCH_3), 3.65 (2H, s, $COCH_2Ph$); δ_C ($CDCl_3$) 171.9, 133.9, 129.2, 128.5, 127.0, 51.9, 41.1; *m/z* (EI) 150 (M^+), 91, 65, 28; Found M^+, 160.0681. $C_9H_{10}O_2$ requires M, 160.0681; R_f=0.97 Pet/EtOAc (1:1).

5.5.19. Methanolysis of 16 with ethyl diisopropylamine (1.0 equiv.), MeOH [0.10 M] (Table 5, entry 10). 16 (100.4 mg, 0.325 mmol), ethyl diisopropylamine (0.057 mL, 0.327 mmol), MeOH (3.2 mL) at reflux. Reaction time 76 h. Purification (SiO_2, Pet_{30-40}/Et_2O 5:1–1:1 then EtOAc) gave **20** (38.2 mg, 78.3%). Chiral auxiliary **1** was recovered (28.8 mg, 46.6%) and **16** was recovered (2.5 mg, 2.5%).

5.6. Structure elucidation

The absolute stereochemistry of the diastereomers 2′*S*-**3a**, 2′*R*-**3a**, 2′*R*-**3c**, 2′*S*-**3b**, 2′*R*-**4b**, 2′*S*-**5a**, 2′*S*-**12b** were confirmed by X-ray crystallography. Details of these structures have been lodged at the Cambridge Crystallographic Database (CIF 155713, 155714, 155715, 155716, 155717, 155718, 155719).

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