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Application of a Recyclable Pseudoephedrine Resin in Asymmetric Alkylations on Solid Phase

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A pseudoephedrine resin has been successfully employed in asymmetric alkylations on solid phase. Immobilized pseudoephedrine amides are conveniently prepared by the one-step attachment of pseudoephedrine to Merrifield resin through the hydroxyl group and subsequent acylation on nitrogen. Deprotonation and alkylation of the resin-bound amides proceeds smoothly. Ketones and alcohols are cleaved from the resin in high enantiomeric excess and moderate to good overall yield. The parallel, asymmetric solid-phase synthesis of a small library of chiral ketones and alcohols has been carried out to illustrate the utility of the approach. Finally, the pseudoephedrine resin can be conveniently recycled and utilized with no significant loss in the yield or enantiomeric excess of the products.

Introduction

Although the use of a supported chiral auxiliary was first reported over 30 years ago, the efficient, asymmetric synthesis of chiral compounds using solid-phase auxiliaries is still a relatively underdeveloped area.[1] Oxazolidinone-based auxiliaries have been most commonly employed; however, these auxiliaries must be prepared, either on or off resin, prior to use, and their efficient recycling has yet to be described. In addition, in one example, the attachment of an oxazolidinone-based auxiliary to solid support was problematic due to side reactions. This had recently led to confusion over the exact nature of an immobilized oxazolidinone auxiliary.[2]

Our interest in new concepts for linker design[3] has led us to develop readily available and inexpensive ephedrine and pseudoephedrine derivatives as "*chiral linkers*" for solid-phase synthesis. These linkers tether substrates to resin and control the stereochemistry of reactions carried out on the substrate. Importantly, the "one-step" attachment of the commercially available ephedrine or pseudoephedrine unit to resin *selectively* through either oxygen or nitrogen is straightforward, leading to robust ether or amine linkages (Figure 1).

We have investigated asymmetric transformations on solid-phase using both modes of linkage: most recently, we have described samarium(II)-mediated asymmetric, intermolecular ketyl-olefin couplings with α,β-unsaturated esters, linked to resin through an ephedrine chiral link (*linkage mode B*), which is the basis of a direct "asymmetric catch-release" approach to γ-butyrolactones.[4] In this paper, we wish to describe in full our studies on the application of a pseudoephedrine linker

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(1) Carbohydrate-based auxiliaries: (a) Kawana, M.; Emoto, S. *Tetrahedron Lett.* **1972**, *48*, 4855. Kawana, M.; Emoto, S. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 160. (b) Oertel, K.; Zech, G.; Kunz, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1431. (c) Zech, G.; Kunz, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 787. (d) Enholm, E. J.; Gallagher, M. E.; Jiang, S.; Batson, W. A. *Org. Lett.* **2000**, *2*, 3355. (e) Enholm, E. J.; Cottone, J. S. *Org. Lett.* **2001**, *3*, 3959. Chiral amines: (f) Worster, P. M.; McArthur, C. R.; Leznoff, C. C. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 221. McArthur, C. R.; Worster, P. M.; Jiang, J.-L.; Leznoff, C. C. *Can. J. Chem.* **1982**, *60*, 1836. Evans oxazolidinones: (g) Allin, S. M.; Shuttleworth, S. J. *Tetrahedron Lett.* **1996**, *37*, 8023. (h) Burgess, K.; Lim, D. *Chem. Commun.* **1997**, 785. (i) Purandare, A. V.; Natarajan, S. *Tetrahedron Lett.* **1997**, *38*, 8777. (j) Phoon, C. W.; Abell, C. *Tetrahedron Lett.* **1998**, *39*, 2655. (k) Winkler, J. D.; M^{c}Coull, W. *Tetrahedron Lett.* **1998**, *39*, 4935. (l) Faita, G.; Paio, A.; Quadrelli, P.; Rancati, F.; Seneci, P. *Tetrahedron Lett.* **2000**, *41*, 1265. Faita, G.; Paio, A.; Quadrelli, P.; Rancati, F.; Seneci, P. *Tetrahedron* **2001**, *57*, 8313. (m) Desimoni, G.; Faita, G.; Galbiati, A.; Pasini, D.; Quadrelli, P.; Rancati, F. *Tetrahedron: Asymmetry* **2002**, *13*, 333. Pyrrolidine-based auxiliaries: (n) Moon, H.-s.; Schore, N. E.; Kurth, M. J. *J. Org. Chem.* **1992**, *57*, 6088. Moon, H.-s.; Schore, N. E.; Kurth, M. J. *Tetrahedron Lett.* **1994**, *35*, 8915. (o) Price, M. D.; Kurth, M. J.; Schore, N. E. *J. Org. Chem.* **2003**, *67*, 7769. Oppolzer's camphorsultam: (p) Miyabe, H.; Konishi, C.; Naito, T. *Org. Lett.* **2000**, *2*, 1443. Miyabe, H.; Konishi, C.; Naito, T. *Chem. Pharm. Bull.* **2003**, *51*, 540. Oxazolines: (q) Colwell, A. R.; Duckwall, L. R.; Brooks, R.; McManus, S. P. *J. Org. Chem.* **1981**, *46*, 3097. Hydrazine auxiliaries: (r) Enders, D.; Kirchhoff, J. H.; Köbberling, J.; Peiffer, T. H. *Org. Lett.* **2001**, *3*, 1241. An alcohol auxiliary: (s) Akkari, R.; Calmes, M.; Mai, N.; Rolland, M.; Martinez, J. *J. Org. Chem.* **2001**, *66*, 5859. Akkari, R.; Calmes, M.; Di Malta, D.; Escale, F.; Martinez, J. *Tetrahedron: Asymmetry* **2003**, *14*, 1223. A sulfinamide auxiliary: (t) Dragoli, D. R.; Burdett, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 10127. An α-hydroxyvaline auxiliary: (u) Savinov, S. N.; Austin, D. J. *Org. Lett.* **2002**, *4*, 1419.

(2) (a) Bew, S. P.; Bull, S. D.; Davies, S. G. *Tetrahedron Lett.* **2000**, *41*, 7577. (b) Bew, S. P.; Bull, S. D.; Davies, S. G.; Savory, E. D.; Watkin, D. J. *Tetrahedron*, **2002**, *58*, 9387.

(3) (a) McKerlie, F.; Procter, D. J.; Wynne, G. *Chem. Commun.* **2002**, 584. (b) McAllister, L. A.; Brand, S.; de Gentile, R.; Procter, D. J. *Chem. Commun.* **2003**, 2380.

(4) Kerrigan, N. J.; Hutchison, P. C.; Heightman, T. D.; Procter, D. J. *Chem. Commun.* **2003**, 1402.

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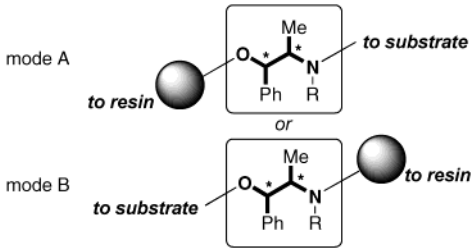
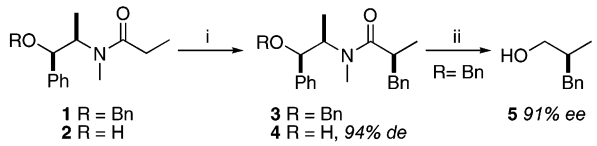


FIGURE 1. Ephedrine and pseudoephedrine chiral linkers.

SCHEME 1[a]



[a] Reagents and conditions: (i) LDA (2.1 equiv), LiCl (6 equiv), THF, −78 °C to rt then BnBr added at 0 °C, 88% (R = Bn); (ii) LDA (3.9 equiv), $BH_3{\cdot}NH_3$, THF, 0 °C to rt, 55%.

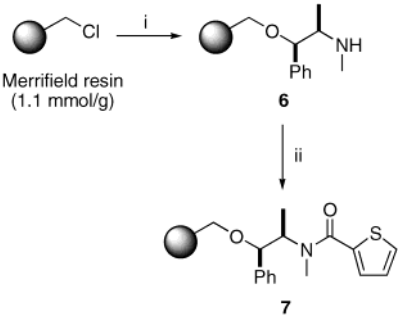
(*linkage mode A*) in a solid-phase adaptation of Myers' pseudoephedrine auxiliary approach[5] for the asymmetric alkylation of amide enolates.[6] Most significantly, we demonstrate the potential of the chemistry for asymmetric library synthesis and the efficient recovery and reuse of the pseudoephedrine resin.

Results and Discussion

In Myers' original pseudoephedrine auxiliary approach, deprotonation generates a dianion as the hydroxyl on the auxiliary is also deprotonated during enolization. The lithium alkoxide on the auxiliary has been implicated in attempts to rationalize the diastereoselectivity of the alkylation reactions.[7] Clearly in our approach, as the hydroxyl group of pseudoephedrine acts as a link to the solid support, formation of an analogous dianion is not possible. To examine whether high diastereoselectivities would still be observed in alkylations of our system, *O*-benzylpseudoephedrine amide **1**, a solution-phase model for an immobilized amide, was prepared and alkylated (Scheme 1).

For the R = H series, diastereoselectivities were determined by conversion of **4** into the corresponding TMS ether and analysis by GC−MS. For the R = Bn series, the diastereoisomeric purity of **3** was obtained indirectly from the enantiomeric excess of **5**, determined by chiral GC. Primary alcohol **5** was obtained by reduction of **3** with lithium amidotrihydroborate. Crucially, only slightly lower diastereoselectivity (91% de) was observed in the case of the *O*-benzylpseudoephedrine amide **1**, compared to the analogous Myers-type substrate **2** (94% de).[5c] Assured that linkage to the resin through oxygen should not greatly effect the diastereoselectivity of alkylation reactions, we next sought to prepare a pseudoephedrine resin.

SCHEME 2[a]



[a] Reagents and conditions: (i) KH, (1*R*,2*R*)-pseudoephedrine, THF, 18 h. Resultant solution then added to resin in THF, rt; (ii) thiophene carbonyl chloride, NEt_3, CH_2Cl_2, rt.

We elected to adapt Welch's procedure for *O*-benzylation to attach (1*R*,2*R*)-pseudoephedrine to Merrifield resin.[8] In our hands, solution-phase benzylation of pseudoephedrine under these conditions was found to give less than 5% of *N*-benzylpseudoephedrine (prepared independently[9]). Thus, similar high selectivity for *O*-alkylation was expected in the immobilization step. The loading of the pseudoephedrine resin **6** (approximately 0.75 mmol g^{-1}) was determined by conversion to the thiophene carboxamide **7** followed by sulfur elemental analysis of the resin (Scheme 2).

Pseudoephedrine resin **6** was acylated (anhydride or acid chloride, NEt_3 CH_2Cl_2, rt) to give the corresponding resin-bound pseudoephedrine amides **8** (ν_{max} 1635−1645 cm^{-1}). In some IR spectra of acylated resins, extremely faint *ester* carbonyl stretches could also be seen. This is in agreement with the expected high selectivity for *O*-alkylation of pseudoephedrine in the immobilization step. Amides **8** were then deprotonated and alkylated to give adducts **9** using Myers' LDA-LiCl conditions (Scheme 3).

Myers has shown that the auxiliary group can be removed from pseudoephedrine amides using a variety of methods to give carboxylic acids, primary alcohols, ketones, and aldehydes.[5c] In our solid-phase approach, the use of different cleavage strategies allows us to introduce further diversity into our collection of compounds during the cleavage process.

One disadvantage of simple immobilization through the hydroxyl group of the pseudoephedrine unit is that hydrolytic cleavage after alkylation, to give enantiomerically enriched carboxylic acids directly, is not possible using Myers' conditions. Myers has clearly shown that hydrolysis of pseudoephedrine amides proceeds through *N*−*O* acyl transfer followed by ester hydrolysis.[5c] This is obviously not possible if the hydroxyl is derivatized. We have, however, been successful in cleaving products from the resin to give primary alcohols and ketones: primary alcohols **5** and **10a** were obtained by reduction of the immobilized pseudoephedrine amides with lithium amidotrihydroborate (LAB, LiH_2NBH_3),[10,5c] while ketones **11**

(5) (a) Myers, A. G.; Gleason, J. L.; Yoon, T. *J. Am. Chem. Soc.* **1995**, *117*, 8488. (b) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 656. (c) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496. (d) Myers, A. G.; McKinstry, L. *J. Org. Chem.* **1996**, *61*, 2428. (e) Myers, A. G.; Schnider, P.; Kwon, S.; Kung, D. W. *J. Org. Chem.* **1999**, *64*, 3322.

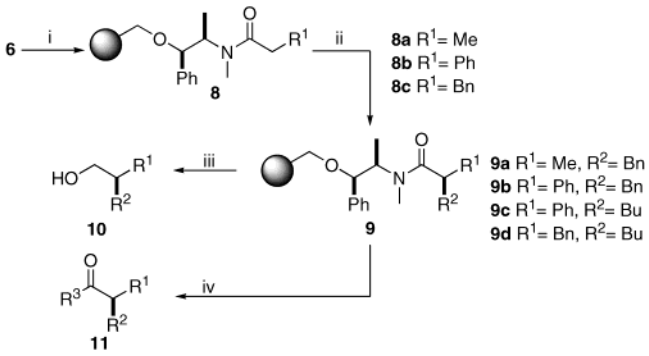
(6) For a preliminary account of this work, see: Hutchison, P. C.; Heightman, T. D.; Procter, D. J. *Org. Lett.* **2002**, *4*, 4583.

(7) For a discussion, see ref 5c.

(8) Näslund, J.; Welch, C. J. *Tetrahedron: Asymmetry* **1991**, *2*, 1123.

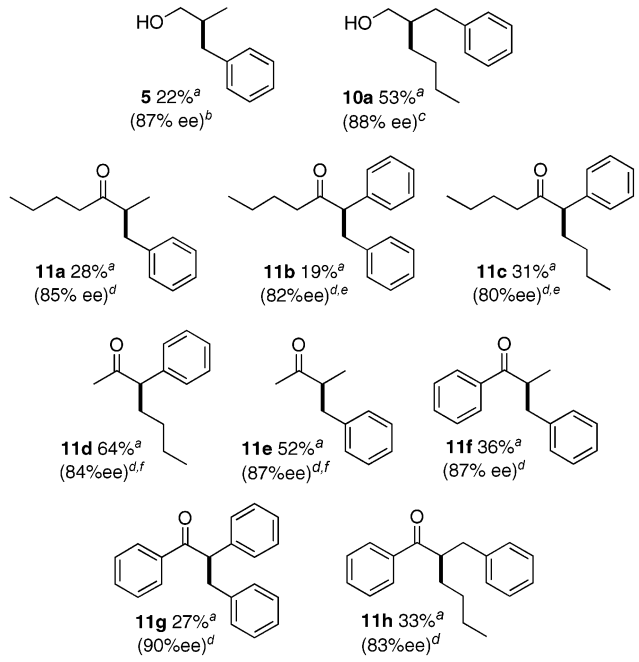
(9) *N*-Benzylation of pseudoephedrine was achieved in 83% yield using the procedure of Gray: Gray, B. D.; Jeffs, P. W. *Chem. Commun.* **1987**, 1329.

SCHEME 3[a]



[a] Reagents and conditions: (i) propionic anhydride/phenylacetyl chloride/3-phenylpropionyl chloride, NEt_3, CH_2Cl_2, rt; (ii) LDA (6.2 equiv), LiCl (36 equiv), THF, −78 °C to rt, then BnBr/BuI (4.5 equiv) added at 0 °C; (iii) LDA (1.2 equiv), $BH_3{\cdot}NH_3$ (1.2 equiv), −78 °C to rt, added to resin at 0 °C and allowed to warm to rt; (iv) R^3Li, Et_2O, −78 to 0 °C.

CHART 1. Preparation of Enantiomerically Enriched Alcohols and Ketones[a]



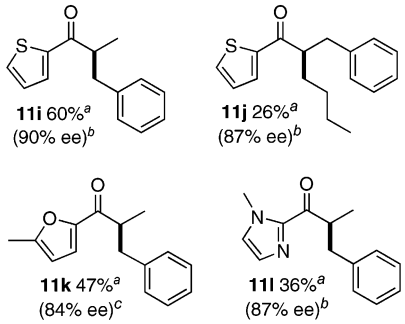
[a] Key: (a) isolated yields based on the loading of **6** and for three steps; (b) ee determined by chiral GC (see the Supporting Information); (c) ee determined by the method outlined in ref 11; (d) ee determined by the procedure outlined in ref 12; (e) ee of the product lowered due to some enolization on cleavage; (f) TMEDA employed as a cosolvent in the cleavage with MeLi.

were prepared by reaction of amides **9** with alkyllithium reagents (R^3Li, Et_2O/THF).[5c]

Moderate to good isolated yields (19−64%) are obtained for the three-step processes, and products are obtained in good enantiomeric excess (80−90% ee) (Chart 1).[11,12] For cleavage with methyllithium to give methyl ketones **11d** and **11e**, TMEDA was found to be essential for high yields of product. In some cases, the cleavage of substrates derived from phenylacetamides gave products

(10) Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623.

CHART 2. Preparation of Enantiomerically Enriched Heteroaromatic Ketones[a]

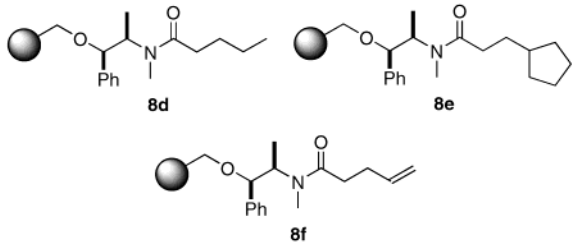


[a] Key: (a) isolated yields based on the loading of **6** and for three steps; (b) ee determined by the procedure outlined in ref 12; (c) ee determined by chiral HPLC.

with lower enantiomeric excesses presumably due to some enolization on cleavage.

The use of heteroaryllithiums in the cleavage step allows efficient access to heteroaromatic ketones. Cleavage of amides **9** with commercially available 2-thienyllithium, 5-methyl-2-furanyllithium, and 1-methyl-2-imidazoyllithium, both readily prepared by lithiation of the parent heterocycle, gives the expected ketones in good yield and high enantiomeric excess (Chart 2).

To illustrate the potential of our approach for the generation of libraries of enantiomerically enriched compounds we have undertaken the parallel synthesis of a small library (3 × 3 × 2) of alcohols and ketones using a reaction carousel with low-temperature bath. Immobilized pseudoephedrine amides **8d**−**f** were alkylated using benzyl bromide or butyl iodide and the products cleaved by reduction to give six primary alcohols, and using thienyllithium or 1-methyl-2-imidazoyllithium to give 12 heterocyclic ketones.



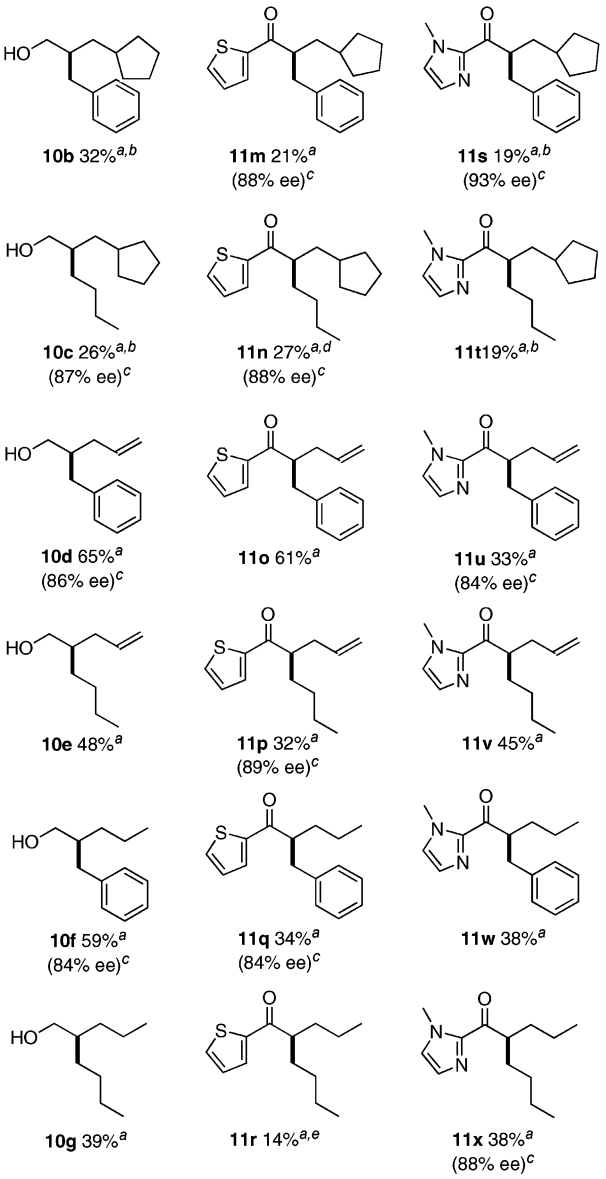
Unoptimized yields ranged from moderate to good for the three-step processes and the enantiomeric excess of selected library members was consistently high (84−93% ee) (Chart 3).

In most cleavage reactions to give ketones, the product could not be detected on TLC until after the reaction was quenched, suggesting a tetrahedral intermediate remains immobilized on resin thus preventing double addition to give the corresponding tertiary alcohol. Only in one case

(11) The enantiomeric excess of alcohols **10a**, **10c**, **10d**, and **10f** was determined by preparation of both the (*R*)- and (*S*)-Mosher's esters and analysis by ^{19}F NMR.

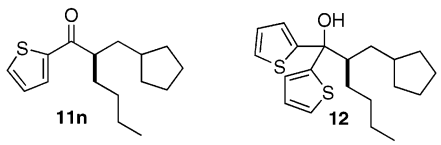
(12) The enantiomeric excess of ketones **11a**−**h** and **11i**, **11j**, **11l**, **11m**, **11n**, **11p**, **11q**, **11s**, **11u**, **11x,** and **11y** was determined by reduction of the ketones with $LiAlH_4$, esterification with both (*R*)- and (*S*)-Mosher's acids and analysis of the resultant diastereoisomeric mixtures of esters by ^{19}F NMR (see ref 5c). The enantiomeric excess of **11k** was determined by chiral HPLC.

CHART 3. Library of Enantiomerically Enriched Alcohols and Ketones[a]



[a] Key: (a) isolated, unoptimized yields based on the loading of **6** and for three steps; (b) approximately 20% of unalkylated material was also obtained; (c) ee determined by the procedure outlined in ref 12; (d) double addition product **12** (17%) also obtained; (e) yield based on crude ^{1}H NMR. **11r** was not isolated and characterized.

has the product of double addition been isolated. In the preparation of **11n**, tertiary alcohol **12** was obtained as a major byproduct (17%) in addition to the desired ketone **11n** (27%).



A key advantage of immobilizing a chiral auxiliary is to aid the recovery and reuse of the auxiliary. Despite this there are few extensive studies on the efficient recycling of immobilized chiral auxiliaries: In Kawano and Emoto's seminal studies on Grignard additions to α-ketoesters of an immobilized sugar auxiliary, they showed that the chiral resin could be recycled for the synthesis of one compound, up to seven times with no loss in yield or enantiomeric excess of the product.[1a] In Leznoff's studies on the asymmetric alkylation of chiral imines prepared using a chiral amine resin, one example of recycling was described. This gave no decrease in the enantiomeric excess of the product and only a slight decrease in yield.[1f] In Faita and Quadrelli's work on Lewis acid mediated 1,3-dipolar cycloadditions employing immobilized oxazolidinone auxiliaries, regio- and enantioselectivities were found to decrease during recycling.[1l] In Kurth and Schore's studies using pyrrolidine-based auxiliaries, one recycle led to no drop in yield or selectivity.[1n] Finally, in the use of an immobilized chiral alcohol to prepare propionic acids, Calmes reported one example of recycling which was found to give a product of undiminished enantiomeric excess in only slightly lower yield.[1s] Of these reports of recycling, only the work of Leznoff[1f] and Kurth[1n] deals with the recycling of chiral resins in diastereoselective alkylations on solid phase.

In our pseudoephedrine chiral-linker approach, we envisaged that cleavage to give both alcohols and ketones should result in clean regeneration of the pseudoephedrine resin. Indeed, MAS NMR studies on resin recovered from both types of cleavage confirmed our ideas and we began studies on the recycling of the pseudoephedrine resin.

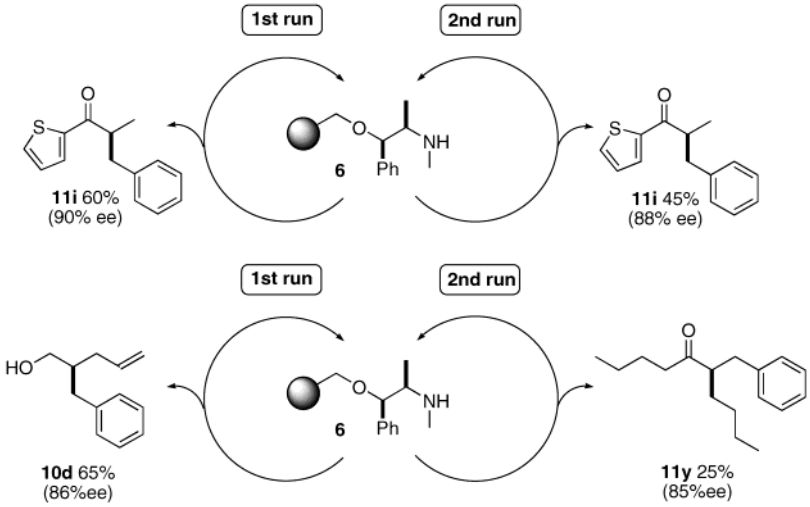
Initially, we began by taking the recovered resin from the preparation of thiophene ketone **11i**, reacylating, alkylating and cleaving to give a second batch of **11i**. Satisfyingly, we obtained **11i** in only slightly lower yield for the three-step sequence and in similar enantiomeric excess. In addition, using the resin from the preparation of alcohol **10d**, we prepared butyl ketone **11y** in a yield and with an enantiomeric excess comparable to that obtained previously for the preparation of butyl ketones **11a**−**c** (Scheme 4).

Finally, employing the resin recovered from the preparation of phenyl ketone **11h**, **11i** has been prepared in good yield and enantiomeric excess. Recycling the same resin a third time gave alcohol **10d** in moderate yield accompanied by alcohol **5**, indicating that incomplete cleavage had occurred in the previous cycle (Scheme 5). These studies show the potential for recycling the pseudoephedrine resin **6** multiple times with no significant loss in the activity of the resin.

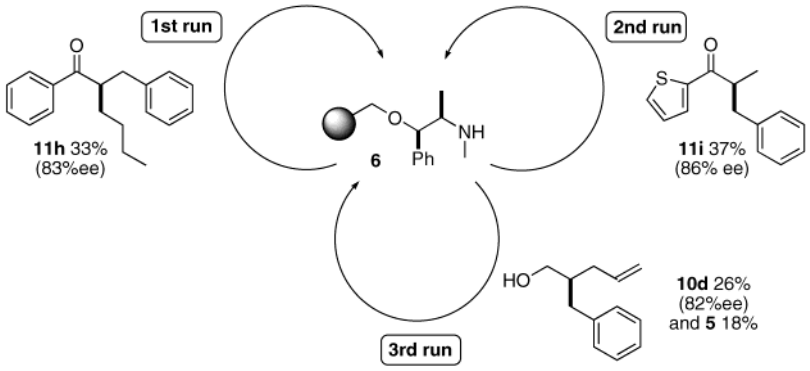
Conclusions

Inexpensive pseudoephedrine can be conveniently immobilized on Merrifield resin in a single step, through a robust ether link. Acylation of nitrogen and diastereoselective alkylations of the resulting immobilized pseudoephedrine amides have been investigated. Cleavage of products from the resin gives ketones and alcohols in moderate to good overall yield and good enantiomeric excess. We have begun to illustrate the potential of this technology for high-throughput synthesis by preparing a small library of enantiomerically enriched alcohols and ketones using parallel synthesis. In all cases, the pseudoephedrine resin can be conveniently recovered from the

SCHEME 4



SCHEME 5



cleavage reactions by filtration and can be recycled. Products obtained using recycled resin show no significant drop in enantiomeric excess or yield when compared to the synthesis of the corresponding compounds using freshly prepared resin.

Experimental Section

(1*R*,2*R*)-*O*-Benzylpseudoephedrine. To a solution of potassium hydride (3.70 g, 92.2 mmol, 1.48 equiv) in THF (100 mL) was added by cannula (1*R*, 2*R*)-pseudoephedrine (10.3 g, 62.0 mmol, 1 equiv) in THF (60 mL) over 5 min. After stirring for 15 h, benzyl bromide (7.02 mL, 58.9 mmol, 0.95 equiv) in THF (10 mL) was added by cannula. After stirring for a further 5 h, the reaction was quenched by the addition of propan-2-ol (50 mL) and water (150 mL). The aqueous layer was separated and extracted into Et_2O (2 × 200 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography on silica (eluting with 10% EtOH/CH_2Cl_2) to give (1*R*, 2*R*)-*O*-benzylpseudoephedrine as a viscous yellow oil (10.6 g, 67%): *m*/*z* (CI^+ mode, isobutane) 256 ($M + H^+$, 100), 254 (10), 148 (28); HRMS calcd for $(M + H)^+$, $C_{17}H_{22}ON$ 256.1701, found 256.1703; ν_{max} (neat)/cm^{-1} 3029s, 2865m, 1453s; $[\alpha]_D$ −87.5 (*c* = 4.63 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.42−7.28 (10H, m, Ar*H*), 4.41 (1H, d, AB system, *J* = 11.3 Hz, 1H of CH_2Ph), 4.26 (1H, d, AB system, *J* = 11.3 Hz, 1H of CH_2Ph), 4.14 (1H, d, *J* = 8.5 Hz, C*H*Ph), 2.85 (1H, dq, J 6.4, 8.5, C*H*CH_3), 2.44 (3H, s, CH_3N), 2.31 (1H, br s, N*H*), 0.81 (3H, d, *J* = 6.4 Hz, CH_3CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1 (Ar*C*), 138.6 (Ar*C*), 128.8 (4 × Ar*C*H), 128.4 (4 × Ar*C*H), 128.1 (2 × Ar*C*H), 86.3 (*C*HPh), 71.1 (*C*H_2Ph), 60.5 (*C*HCH_3), 33.9 (*C*H_3N), 15.7 (*C*H_3CH).

(1*R*,2*R*)-*N*-(2-Benzyloxy-1-methyl-2-phenylethyl)-*N*-methylpropionamide 1. To a solution of (1*R*,2*R*)-*O*-benzylpseudoephedrine (2.00 g, 7.84 mmol, 1 equiv) and Et_3N (1.31 mL, 9.41 mmol, 1.2 equiv) in CH_2Cl_2 (20 mL) was added propionic anhydride (1.08 mL, 8.39 mmol, 1.07 equiv) dropwise. After 24 h, the reaction was quenched with water (10 mL). The organic layer was separated and washed with aqueous saturated $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was then dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified using flash chromatography on silica (eluting with 40% EtOAc/CH_2Cl_2) to give **1** (1.91 g, 78%) as a pale yellow oil: (For major rotamer) *m*/*z* (CI^+ mode, isobutane) 312 ($M + H^+$, 44), 204 (20), 114 (100), 91 (37); HRMS calcd for $(M + H)^+$, $C_{20}H_{26}O_2N$ 312.1964, found 312.1961; ν_{max} (neat)/cm^{-1} 3029m, 2937s, 2873s, 1644s (C═O), 1455s, 1376m; $[\alpha]_D$ −119 (*c* = 0.5 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.11 (10H, m, Ar*H*), 4.34 (1H, d, AB system, *J* = 11.9 Hz, 1H of CH_2Ph), 4.11−4.02 (1H, m, C*H*Ph), 4.06 (1H, d, AB system, *J* = 11.9 Hz, 1H of CH_2Ph), 4.00−3.97 (1H, m, C*H*CH_3), 2.70 (3H, s, CH_3N), 2.46−2.34 (1H, m, 1H of CH_2CH$_3$), 2.32−2.25 (1H, m, 1H of CH_2CH$_3$), 1.05 (3H, t, *J* = 7.5 Hz, CH_3CH$_2$), 0.87 (3H, d, *J* = 6.8 Hz, CH_3CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1 (*C*═O), 139.6 (Ar*C*), 138.2 (Ar*C*), 128.6 (4 × Ar*C*H), 128.1 (4 × Ar*C*H), 128.0 (2 × Ar*C*H), 82.1 (*C*HPh), 70.7 (*C*H_2-Ph), 57.4 (*C*HCH$_3$), 27.4 (*C*H_3N), 26.9 (*C*H_2CH$_3$), 16.1 (*C*H_3-CH), 10.1 (*C*H_3CH$_2$). Anal. Calcd for $C_{20}H_{26}O_2N$: C, 77.14; H, 8.09; N, 4.50. Found: C, 76.90; H, 8.10; N, 4.60.

(1*R*,2*R*)-*N*-(2-Benzyloxy-1-methyl-2-phenylethyl)-2,*N*-dimethyl-3-phenylpropionamide 3. To a solution of LiCl (0.41 g, 9.64 mmol, 6 equiv) and *i*-Pr_2NH (0.51 mL, 3.61 mmol, 2.25 equiv) in THF (7 mL) at −78 °C was added *n*-BuLi (1.25 mL, 2.67 M in hexanes, 3.34 mmol, 2.08 equiv). The reaction was warmed to 0 °C briefly and then cooled to −78 °C for 10

min. The propionamide **1** (0.50 g, 1.61 mmol, 1 equiv) in THF (15 mL) was then added to the reaction by cannula. The reaction was stirred for 1 h at −78 °C, warmed to 0 °C for 15 min, warmed to room temperature for 5 min, and then cooled to 0 °C before the addition of benzyl bromide (0.29 mL, 2.41 mmol, 1.50 equiv) after which the reaction was allowed to warm to room temperature. After 3 h, the reaction was quenched with aqueous saturated NH_4Cl (15 mL). The aqueous layer was separated and washed with EtOAc (2 × 50 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified using flash chromatography on silica (eluting with 30% EtOAc/petroleum ether (40−60 °C)) to give 3 (0.56 g, 88%) as a yellow oil: (for major rotamer) *m/z* (CI^+ mode, isobutane) 402 ($M + H^+$, 33), 294 (17), 204 (100), 119 (11) and 91 (37); HRMS calcd for $(M + H)^+$ $C_{27}H_{32}O_2N$ 402.2433, found 402.2438; ν_{max} (neat)/cm^{-1} 3028m, 2971m, 1644s (C=O) and 1453m; $[\alpha]_D$ −52.7 (*c* = 1.87 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−6.97 (15H, m, Ar*H*), 4.29 (1H, d, AB system, *J* = 11.9 Hz, 1H of CH_2Ph), 4.04 (1H, d, *J* = 7.8 Hz, C*H*Ph), 4.04−4.03 (1H, m, NC*H*CH_3), 4.00 (1H, d, AB system *J* = 11.9 Hz, 1H of CH_2Ph), 3.07−2.77 (2H, m, C*H*Bn and 1H of CH_2Ph), 2.63 (3H, s, CH_3N), 2.58−2.53 (1H, m, 1H of CH_2Ph), 0.95 (3H, d, *J* = 6.8 Hz, CH_3CHBn), 0.84 (3H, d, *J* = 8.9 Hz, CH_3CHN); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5 (*C*=O), 140.8 (Ar*C*), 139.4 (Ar*C*), 138.8 (Ar*C*), 129.8 (2 × Ar*C*H), 129.4 (2 × Ar*C*H), 129.2 (Ar*C*H), 128.6 (2 × Ar*C*H), 128.5 (2 × Ar*C*H), 128.3 (Ar*C*H), 128.0 (2 × Ar*C*H), 127.9 (2 × Ar*C*H), 126.2 (Ar*C*H), 81.5 (*C*HPh), 70.8 (O*C*H_2Ph), 57.1 (*C*HMe), 39.9 (CH*C*H_2Ph), 38.2 (C(O)*C*HCH$_3$), 27.7 (*C*H_3N), 17.9 (*C*H_3CHC=O) 16.1 (*C*H_3CHN). Anal. Calcd for $C_{27}H_{32}O_2N$: C, 80.76; H, 7.78; N, 3.49. Found: C, 80.62; H, 7.82; N, 3.58;

Preparation of (1*R*,2*R*)-*O*-Merrifield Bound Pseudoephedrine 6. To a solution of potassium hydride (4.20 g, 105 mmol, 7.5 equiv) in THF (50 mL) was added dropwise, by cannula, a solution of (1*R*,2*R*)-pseudoephedrine (11.5 g, 69.8 mmol, 5 equiv) in THF (80 mL). After being stirred for 18 h, the reaction mixture was added by cannula to Merrifield resin (12.7 g, 13.9 mmol, 1 equiv) in THF (100 mL). After 24 h, the reaction was quenched with propan-2-ol (30 mL) and filtered. The resin was washed with THF (3 × 50 mL), THF−water, 2:1 (3 × 50 mL), THF−water, 1:1 (3 × 50 mL), THF−water, 1:2 (3 × 50 mL), (MeOH, 50 mL then CH_2Cl_2, 50 mL) × 3, and MeOH (3 × 50 mL). The resin was then dried in vacuo: ν_{max} (KBr)/cm^{-1} 3346w (NHMe amine), 2787m (Me-N).

(1*R*,2*R*)-*O*-Merrifield Bound Thiophene-2-carboxylic Acid (2-Hydroxy-1-methyl-2-phenylethyl)methylamide 7. To a solution of Merrifield bound pseudoephedrine resin (100 mg, 0.10 mmol, 1 equiv) in CH_2Cl_2 (2 mL) were added Et_3N (0.04 mL, 0.25 mmol, 2.6 equiv) and thiophene carbonyl chloride (0.02 mL, 0.23 mmol, 2.3 equiv) at room temperature, and the reaction mixture was stirred slowly for 1 day. The mixture was filtered and washed with THF (3 × 20 mL), THF−water; 2:1 (3 × 20 mL), THF−water; 1:1 (3 × 20 mL), THF−water; 1:2 (3 × 20 mL), (MeOH, 20 mL then CH_2Cl_2, 20 mL) × 3, and MeOH (3 × 20 mL). The resin was then dried in vacuo: ν_{max} (KBr)/cm^{-1} 1624s (C=O). Found: C, 86.40; H, 7.30; N, 1.13; S, 2.07.

Preparation of (1*R*,2*R*)-*O*-Merrifield Bound Pseudoephedrine Amides 8. (1*R*,2*R*)-*O*-Merrifield Bound *N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methylpropionamide 8a. To a solution of Merrifield bound pseudoephedrine (2.00 g, 1.96 mmol, 1 equiv) in CH_2Cl_2 (40 mL) were added Et_3N (0.66 mL, 4.70 mmol, 2.4 equiv) and propionic anhydride (0.54 mL, 4.19 mmol, 2.14 equiv) at room temperature, and the reaction was stirred slowly. After 3 days, the mixture was filtered and washed with THF (3 × 50 mL), (MeOH, 50 mL then CH_2Cl_2, 50 mL) × 3, and THF (3 × 50 mL). The resin was then dried in vacuo: ν_{max} (KBr)/cm^{-1} 1639s (C=O).

(1*R*, 2*R*)-*O*-Merrifield Bound *N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methyl-2-phenylacetamide 8b. To a solution of Merrifield bound pseudoephedrine (2.00 g, 1.96 mmol, 1 equiv) in CH_2Cl_2 (40 mL) were added Et_3N (0.36 mL, 2.55 mmol, 2.6 equiv) and phenyl acetyl chloride (0.30 mL, 2.25 mmol, 2.4 equiv) at room temperature, and the reaction mixture was stirred slowly. After 5 days, the mixture was filtered and washed with THF (3 × 50 mL), (MeOH, 50 mL then CH_2Cl_2, 50 mL) × 3, and THF (3 × 50 mL). The resin was then dried in vacuo: ν_{max} (KBr)/cm^{-1} 1636s (C=O).

(1*R*,2*R*)-*O*-Merrifield Bound *N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methyl-3-phenylpropionamide 8c. To a solution of Merrifield bound pseudoephedrine (4.20 g, 4.12 mmol, 1 equiv) in CH_2Cl_2 (40 mL) were added Et_3N (1.38 mL, 9.88 mmol, 2.4 equiv) and 3-phenylpropionyl chloride (1.29 mL, 8.64 mmol, 2.1 equiv) at room temperature, and the reaction mixture was stirred slowly. After 2 days, the mixture was filtered and washed with THF (3 × 50 mL), (MeOH, 50 mL then CH_2Cl_2, 50 mL) × 3, and THF (3 × 50 mL). The resin was then dried in vacuo: ν_{max} (Golden Gate)/cm^{-1} 1643s (C=O).

(1*R*,2*R*)-*O*-Merrifield Bound Pentanoic Acid (2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methylamide 8d. To a solution of Merrifield bound pseudoephedrine (1.00 g, 0.98 mmol, 1 equiv) in CH_2Cl_2 (20 mL) were added Et_3N (0.29 mL, 2.10 mmol, 2.4 equiv) and valeric anhydride (0.47 mL, 2.35 mmol, 2.14 equiv) at room temperature, and the reaction mixture was stirred slowly. After 2 days, the mixture was filtered and washed with THF (3 × 50 mL), (MeOH, 50 mL then CH_2Cl_2, 50 mL) × 3, and THF (3 × 50 mL). The resin was then dried in vacuo: ν_{max} (Golden Gate)/cm^{-1} 1637s (C=O).

(1*R*,2*R*)-*O*-Merrifield Bound 3-Cyclopentyl-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylpropionamide 8e. To a solution of Merrifield bound pseudoephedrine (2.00 g, 1.96 mmol, 1 equiv) in CH_2Cl_2 (20 mL) were added Et_3N (0.66 mL, 4.70 mmol, 2.4 equiv) and 3-cyclopentyl propionyl chloride (0.72 mL, 4.70 mmol, 2.4 equiv) at room temperature, and the reaction mixture was stirred slowly. After 4 days, the mixture was filtered and washed with THF (3 × 50 mL), (MeOH, 50 mL then CH_2Cl_2, 50 mL) × 3, and THF (3 × 50 mL). The resin was then dried in vacuo: ν_{max} (Golden Gate)/cm^{-1} 1643s (C=O).

(1*R*, 2*R*)-*O*-Merrifield Bound Pent-4-enoic Acid (2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methylamide 8f. To a solution of Merrifield bound pseudoephedrine (2.00 g, 1.96 mmol, 1 equiv) in CH_2Cl_2 (20 mL) were added Et_3N (0.66 mL, 4.70 mmol, 2.4 equiv) and 4-pentenoic anhydride (0.77 mL, 4.19 mmol, 2.14 equiv) at room temperature, and the reaction mixture was stirred slowly. After 4 days, the mixture was filtered and washed with THF (3 × 50 mL), (MeOH, 50 mL then CH_2Cl_2, 50 mL) × 3, and THF (3 × 50 mL). The resin was then dried in vacuo: ν_{max} (Golden Gate)/cm^{-1} 1641m (C=O).

General Procedure A. Alkylation of Merrifield Bound Pseudoephedrine Amides. (1*R*, 2*R*)-*O*-Merrifield Bound *N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methyl-(2*S*)-2-methyl-3-phenylpropionamide 9a. To a solution of LiCl (0.26 g, 6.80 mmol, 18 equiv) and *i*-Pr_2NH (0.36 mL, 2.55 mmol, 6.75 equiv) in THF (5 mL) at −78 °C was added *n*-BuLi (0.82 mL, 2.36 mmol, 6.24 equiv). The suspension was warmed to 0 °C briefly and then cooled to −78 °C. The solution was then added to the immobilized amide (300 mg, 1.26 mmol loading, 0.38 mmol, 1 equiv) and LiCl (0.26 g, 6.80 mmol, 18 equiv) in THF (5 mL) by cannula. The reaction was stirred for 3 h at −78 °C, warmed to 0 °C for 15 min, warmed to room temperature for 5 min, and then cooled to 0 °C before the addition of benzyl bromide (0.20 mL, 1.17 mmol, 4.50 equiv) after which the reaction was allowed to gradually warm to room temperature. After 2 days, the reaction mixture was filtered and washed with THF (3 × 20 mL), (MeOH, 20 mL then CH_2Cl_2, 20 mL) × 3, and THF (3 × 20 mL). The resin was then dried in vacuo: ν_{max} (KBr)/cm^{-1} 1639s (C=O).

(1*R*,2*R*)-*O*-Merrifield Bound *N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methyl-(2*R*)-2,3-diphenylpropionamide 9b. As for general procedure A. The precursor resin

(2.00 g, 1.76 mmol, 1 equiv) on treatment with LDA (6.24 equiv) and BnBr (0.94 mL, 7.92 mmol, 4.50 equiv) and after filtration and washing gave the product resin which was dried in vacuo: ν_{max} (KBr)/cm^{-1} 1643s (C=O).

(1*R*,2*R*)-*O*-Merrifield Bound (2*R*)-2-Benzylhexanoic Acid (2-Hydroxy-1-methyl-2-phenylethyl)methyl Amide 9c. As for general procedure A. The precursor resin (1.00 g, 0.86 mmol, 1 equiv) on treatment with LDA (6.24 equiv) and BuI (0.44 mL, 3.87 mmol, 4.5 equiv) and after filtration and washing gave the product resin which was dried in vacuo: ν_{max} (Golden Gate)/cm^{-1} 1635s (C=O).

General Procedure B. Cleavage from Resin To Give Alcohols. (2*S*)-2-Methyl-3-phenylpropan-1-ol 5.[5c] To a solution of *i*-Pr$_2$NH (0.55 mL, 3.91 mmol, 8.4 equiv) in THF (8 mL) was added *n*-BuLi (1.26 mL, 2.89 M in hexanes, 3.62 mmol, 7.8 equiv) at −78 °C. The resulting mixture was stirred at −78 °C for 10 min and then warmed to 0 °C for 10 min. Borane−ammonia complex (114.8 mg, 3.72 mmol, 8.0 equiv) was then added, and the reaction mixture was stirred at 0 °C for 15 min and then warmed to room temperature. After 15 min, the reaction was cooled to 0 °C and added to the resin (500 mg, 0.47 mmol, 1 equiv) in THF (5 mL) by cannula. The reaction was then warmed to room temperature. After 21 h, the reaction was filtered, washed with distilled THF (300 mL), and concentrated in vacuo. The organic residue was quenched with 3 M HCl (5 mL) and extracted with Et$_2$O (2 × 10 mL). The combined organic layers were washed with 3 M HCl (2 mL), 2 M NaOH (2 mL), and brine (2 mL). The organic layer was dried (MgSO$_4$) and concentrated in vacuo. The crude product was purified by flash chromatography on silica (eluting with 10% EtOAc/petroleum ether (40−60 °C)) to give **5** (10 mg, 22%) as a colorless oil: *m*/*z* (EI$^+$ mode) 150 (M$^+$, 25), 132 (20), 117 (50), 91 (91), 84 (84), 49 (100) and 47 (19); HRMS calcd for M$^+$, $C_{10}H_{14}O$ 150.1045, found 150.1043; ν_{max} (neat)/cm^{-1} 3406s (OH), 2921m, 1602m, 1494m, 1454s; $[\alpha]_D$ −10.0 (*c* = 0.84 in $CHCl_3$) (lit.[13] $[\alpha]_D$ −10.1 (*c* = 0.8 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.09 (5H, m, Ar*H*), 3.46 (1H, dd, *J* = 5.9, 10.6 Hz, 1H of C*H*$_2$OH), 3.40 (1H, dd, *J* = 5.9, 10.6 Hz, 1H of C*H*$_2$OH), 2.68 (1H, dd, *J* = 6.3, 13.4 Hz, 1H of C*H*$_2$Ph), 2.35 (1H, dd, *J* = 8.0, 13.4 Hz, 1H of C*H*$_2$Ph), 1.92−1.82 (1H, m, C*H*), 1.31 (1H, br s, O*H*) and 0.85 (3H, d, *J* = 6.8 Hz, C*H*$_3$-CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0 (Ar*C*), 129.5 (2 × Ar*C*H), 128.7 (2 × Ar*C*H) 126.3 (Ar*C*H), 68.1 (*C*H$_2$OH), 40.1 (*C*H$_2$Ph), 38.2 (*C*H) and 16.9 (*C*H$_3$CH).

(2*R*)-2-Benzylhexan-1-ol 10a.[14] As for general procedure B. The precursor resin (1.32 g, 1.11 mmol, 1 equiv) on treatment with lithium amidotrihydroborate (7.8 equiv) and after purification by flash chromatography on silica (eluting with 80% CH_2Cl_2/petroleum ether (40−60 °C)) gave **10b** (99.1 mg, 58%) as a yellow oil: *m*/*z* (EI$^+$ mode) 192 (M$^+$, 19), 174 (15), 131 (13), 104 (38), 83 (100), and 47 (17); HRMS calcd for M$^+$, $C_{13}H_{20}O$ 192.1514, found 192.1513; ν_{max} (neat)/cm^{-1} 3357s (OH), 2954s, 2927s, 1583w, 1543w, 1454s; $[\alpha]_D$ +3.31 (*c* = 1.30 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17−7.04 (5H, m, Ar*H*), 3.40 (2H, d, *J* = 4.8, C*H*$_2$OH), 2.51 (2H, apparent d, AB system, *J* = 7.2 Hz, C*H*$_2$Ph), 1.71−1.64 (1H, m, C*H*), 1.28−1.13 (6H, m, 3 × C*H*$_2$), 0.76 (3H, t, *J* = 7.0 Hz, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2 (Ar*C*), 129.6 (2 × Ar*C*H), 128.7 (2 × Ar*C*H), 126.2 (Ar*C*H), 65.3 (*C*H$_2$OH), 43.0 (*C*H), 38.1 (*C*H$_2$-Ph), 30.9 (*C*H$_2$), 29.6 (*C*H$_2$), 23.4 (*C*H$_2$), 14.4 (*C*H$_3$).

General Procedure C. Cleavage of Ketones from Resin. (2*S*)-2-Methyl-1-phenylheptan-3-one 11a.[5c] To a solution of the resin (500 mg, 0.44 mmol, 1 equiv) in Et$_2$O (5 mL) at −78 °C was added *n*-BuLi (0.84 mL, 2.09 mmol, 4.8 equiv), and the reaction mixture was warmed to 0 °C. After 4 h, *i*-Pr$_2$NH (0.12 mL, 0.87 mmol, 2 equiv) was added, and the reaction was stirred for 15 min. The reaction mixture was filtered and washed with distilled THF (300 mL) and concentrated in vacuo. The organic residue was partitioned between EtOAc (10 mL) and water (10 mL). The aqueous layer was washed with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (MgSO$_4$) and concentrated in vacuo. The crude product was purified by flash chromatography on silica (eluting with 5% EtOAc/petroleum ether (40−60 °C)) to give **11a** (16.5 mg, 28%) as a yellow oil: *m*/*z* (EI$^+$ mode) 204 (M$^+$, 20), 167 (12), 147 (22), 119 (29), 91 (100), 85 (51), 57 (59) and 41 (26); HRMS calcd for M$^+$, $C_{14}H_{20}O$ 204.1514, found 204.1512; ν_{max} (neat)/cm^{-1} 2960m, 2931m, 1710s (C=O), 1608m, 1454m; $[\alpha]_D$ +54.1 (*c* = 1.12 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22−7.06 (5H, m, Ar *H*), 2.90 (1H, dd, *J* = 7.1, 13.4 Hz, 1H of C*H*$_2$-Ph), 2.76 (1H, apparent sextet, *J* = 7.0 Hz, C*H*), 2.48 (1H, dd, *J* = 7.4, 13.4 Hz, 1H of C*H*$_2$Ph), 2.36−2.28 (1H, m, 1H of C*H*$_2$C-(O)), 2.23−2.15 (1H, m, 1H of C*H*$_2$C(O)), 1.44−1.36 (2H, m, C*H*$_2$CH$_2$CH$_3$), 1.20−1.09 (2H, m, C*H*$_2$CH$_3$), 1.00 (3H, d, *J* = 6.9 Hz, C*H*$_3$CH), 0.78 (3H, t, *J* = 7.3 Hz, C*H*$_3$CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.8 (*C*=O), 140.3 (Ar *C*), 129.3 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 126.6 (Ar*C*H), 48.5 (*C*H), 42.1 (*C*H$_2$C=O), 39.5 (*C*H$_2$Ph), 25.9 (*C*H$_2$CH$_2$CH$_3$), 22.7 (*C*H$_2$CH$_3$), 16.9 (*C*H$_3$CH), 14.2 (*C*H$_3$CH$_2$).

(2*R*)-1,2-Diphenylheptan-3-one 11b.[15] As for general procedure C. The precursor resin (500 mg, 0.41 mmol, 1 equiv) on treatment with *n*-BuLi (0.78 mL, 2.5 M in hexanes, 1.94 mmol, 4.8 equiv) and after purification by flash chromatography on silica (eluting with 5% EtOAc/petroleum ether (40−60 °C)) gave **11b** (14 mg, 19%) as a colorless oil: *m*/*z* (EI$^+$ mode) 266 (M$^+$, 23), 181 (70), 103 (28), 85 (100) and 57 (54); HRMS calcd for M$^+$, $C_{19}H_{22}O$ 266.1671, found 266.1672; ν_{max} (neat)/cm^{-1} 2957m, 2931m, 1713s (C=O), 1600m, 1453m; $[\alpha]_D$ −187.9 (*c* = 0.89 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−6.92 (10H, m, Ar*H*), 3.85 (1H, apparent t, *J* = 7.4 Hz, C*H*), 3.35 (1H, dd, *J* = 7.9, 13.7 Hz, 1H of C*H*$_2$Ph), 2.82 (1H, dd, *J* = 6.9, 13.7 Hz, 1H of C*H*$_2$Ph), 2.29−2.10 (2H, m, C*H*$_2$C(O)), 1.37−1.21 (2H, m, C*H*$_2$CH$_2$CH$_3$), 1.09−0.99 (2H, m, C*H*$_2$CH$_3$), 0.68 (3H, t, *J* = 7.3 Hz, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.9 (*C*=O), 138.8 (Ar*C*), 137.6 (Ar*C*), 128.0 (2 × Ar*C*H), 127.8 (2 × Ar*C*H), 127.3 (2 × Ar*C*H), 127.2 (2 × Ar*C*H), 126.2 (Ar*C*H), 125.0 (Ar*C*H), 59.8 (*C*HPh), 41.1 (*C*H$_2$C(O)), 37.7 (*C*H$_2$Ph), 24.6 (*C*H$_2$CH$_2$CH$_3$), 21.0 (*C*H$_2$CH$_3$), 12.7 (*C*H$_3$).

(6*R*)-6-Phenyldecan-5-one 11c.[16] As for general procedure C. The precursor resin (500 mg, 0.42 mmol, 1 equiv) on treatment with *n*-BuLi (0.80 mL, 2.5 M in hexanes, 1.99 mmol, 4.8 equiv) and after purification by flash chromatography on silica (eluting with 5% EtOAc/petroleum ether (40−60 °C)) gave **11c** (20.2 mg, 31%) as a colorless oil: *m*/*z* (FAB$^+$ mode) 233 ((M + H)$^+$, 100), 147 (47), 91 (82), 86 (29) and 58 (31); HRMS calcd for [M + H]$^+$, $C_{16}H_{25}O$ 233.1905, found 233.1906; ν_{max} (neat)/cm^{-1} 2957m, 2931m, 1713s (C=O), 1599w, 1453w; $[\alpha]_D$ −164.1 (*c* = 1.14 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.12 (5H, m, Ar*H*), 3.53 (1H, t, *J* = 7.4 Hz, C*H*), 2.29−2.25 (2H, m, C*H*$_2$C(O)^A), 1.97−1.92 (1H, m, 1H of C*H*$_2$CHPh^B), 1.65−1.58 (1H, m, 1H of C*H*$_2$CHPh^B), 1.44−1.34 (2H, m, C*H*$_2$-CH$_2$CH$_3^A$), 1.26−1.19 (2H, m, C*H*$_2$CH$_3^B$), 1.17−1.03 (4H, m, C*H*$_2$CH$_3^A$ and C*H*$_2$CH$_2$CH$_3^B$), 0.78 (3H, t, *J* = 7.3 Hz, C*H*$_3$-CH$_2^A$), 0.73 (3H, t, *J* = 7.3 Hz, C*H*$_3$CH$_2^B$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.3 (*C*=O), 139.7 (Ar*C*), 129.3 (2 × Ar*C*H), 128.7 (2 × Ar*C*H), 127.4 (Ar*C*H), 59.4 (*C*H), 42.0 (*C*H$_2$C(O)^A), 32.3 (*C*H$_2$CHPh^B), 30.1 (CH$_2$CH$_2$CH$_3^B$), 26.2 (CH$_2$CH$_2$CH$_3^A$), 23.0 (*C*H$_2$CH$_3^B$), 22.6 (CH$_2$CH$_3^A$)14.3 (CH$_3$CH$_2^A$), 14.2 (*C*H$_3$CH$_2^B$).

(3*R*)-3-Phenylheptan-2-one 11d.[17] To a solution of the resin (500 mg, 0.42 mmol, 1 equiv) in Et$_2$O (5 mL) were added TMEDA (0.16 mL, 1.05 mmol, 2.5 equiv) and MeLi·LiBr (0.70 mL, 1.5 M in Et$_2$O, 1.05 mmol, 2.5 equiv) at −78 °C, and then the reaction warmed to 0 °C. After 4 h, *i*-Pr$_2$NH (0.12 mL, 0.84 mmol, 2 equiv) was added, and the reaction was stirred for 15 min. The reaction mixture was filtered, washed with distilled THF (300 mL), and concentrated in vacuo. The organic residue

(13) Nordin, O.; Nguygen, B.-V.; Vörde, C.; Hedenström, E.; Högberg, H.-E. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 367.
(14) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.*, **1994**, *116*, 9361.
(15) Takeda, T.; Taguchi, H.; Fujiwara, T. *Tetrahedron Lett.* **2000**, *41*, 65.
(16) Meyers, A. I.; Smith, E. M.; Jurjevich, A. F. *J. Am. Chem. Soc.* **1971**, *93*, 2314.

was partitioned between EtOAc (10 mL) and water (10 mL). The aqueous layer was washed with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give **11d** (41.0 mg, 64%) as a yellow oil: *m*/*z* (CI^+ mode, isobutane) 191 ($(M + H)^+$, 100), 147 (10), 134 (17), 91 (20), 81 (16) and 69 (27); HRMS calcd for [M + H^+], $C_{13}H_{19}O$ 191.1436, found 191.1437; ν_{max} (neat)/cm^{-1} 2956s, 2931s, 2860s, 1714s (C=O), 1495m, 1356m, 1163m; $[\alpha]_D$ −222.2 (*c* = 1.18 in cyclohexane) (lit.[18] for (*S*)-enantiomer $[\alpha]_D$ +485 (in cyclohexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.27−7.13 (5H, m, Ar*H*), 3.52 (1H, apparent t, *J* = 7.4 Hz, C*H*), 1.98 (3H, s, CH_3C=O), 2.00−1.91 (1H, m, 1H of CH_2CHPh), 1.67−1.59 (1H, m, 1H of CH_2CHPh), 1.27−1.16 (2H, m, CH_2CH_3), 1.15−1.04 (2H, m, $CH_2CH_2CH_3$), 0.78 (3H, t, *J* = 7.2 Hz, CH_3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.7 (*C*=O), 138.1 (Ar*C*), 127.8 (2 × Ar*C*H), 127.2 (2 × Ar*C*H), 126.1 (Ar*C*H), 58.8 (*C*H), 30.5 (CH_2CH_2-CH_3), 28.6 (CH_2CHPh), 28.0 (CH_3CH), 21.6 (CH_2CH_3), 12.9 (CH_3CH_2).

(2*S*)-3-Methyl-4-phenylbutan-2-one 11e.[19] To a solution of the resin (500 mg, 0.43 mmol, 1 equiv) in Et_2O (5 mL) were added TMEDA (0.16 mL, 1.06 mmol, 2.5 equiv) and MeLi·LiBr (0.71 mL, 1.5 M in Et_2O, 1.06 mmol, 2.5 equiv) at −78 °C, and then the reaction mixture was warmed to 0 °C. After 4 h, *i*-Pr_2-NH (0.12 mL, 0.85 mmol, 2 equiv) was added, and the reaction mixture was stirred for 15 min. The reaction mixture was then filtered, washed with THF (300 mL), and concentrated in vacuo. The organic residue was partitioned between EtOAc (10 mL) and aqueous saturated $NaHCO_3$ (10 mL). The organic layer was separated, washed with aqueous saturated $NaHCO_3$ (5 mL) and H_2O (5 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash chromatography on silica (eluting with 5% EtOAc/petroleum ether (40−60 °C)) to give **11e** (29.3 mg, 52%) as a yellow oil: *m*/*z* (EI^+ mode) 162 (M^+, 37), 147 (24), 119 (16), 91 (100), 83 (14), 65 (10) and 43 (29); HRMS calcd for M^+, $C_{11}H_{14}O$ 162.1045, found 162.1044; ν_{max} (neat)/cm^{-1} 2970s, 1714s (C=O), 1454s, 1360s; $[\alpha]_D$ +40.0 (*c* = 0.79 in EtOH) (lit.[19] $[\alpha]_D$ +45.5 (*c* = 2.00 in EtOH)); ^1H NMR (400 MHz, $CDCl_3$) δ 7.23−7.07 (5H, m, Ar*H*), 2.93 (1H, dd, *J* = 6.7, 13.5 Hz, 1H of CH_2Ph), 2.76 (1H, apparent q, *J* = 7.0 Hz, C*H*), 2.49 (1H, dd, *J* = 7.8, 13.4 Hz, 1H of CH_2Ph), 2.02 (3H, s, CH_3C=O), 1.02 (3H, d, *J* = 6.9 Hz, CH_3CH);^{13}C NMR (100 MHz, $CDCl_3$) δ 211.3 (*C*=O), 138.6 (Ar*C*), 127.9 (2 × Ar*C*H), 127.4 (2 × Ar*C*H), 125.2 (Ar*C*H), 47.8 (*C*H), 37.9 (CH_2Ph), 27.9 (CH_3C=O), 15.2 (CH_3CH).

(2*S*)-2-Methyl-1,3-diphenylpropan-1-one 11f.[5c] As for general procedure C. The precursor resin (500 mg, 0.44 mmol, 1 equiv) on treatment with PhLi (1.16 mL, 1.8 M in cyclohexanes−ether, 2.09 mmol, 4.8 equiv) and after purification by flash chromatography on silica (eluting with 5% EtOAc/petroleum ether (40−60 °C)) gave **11f** (23.7 mg, 36%) as a yellow oil: *m*/*z* (EI^+ mode), 224 (M^+, 30), 105 (100) and 77 (33); HRMS calcd for M^+, $C_{16}H_{16}O$ 224.1201, found 224.1201; ν_{max} (neat)/cm^{-1} 2969m, 2931m, 1681s (C=O), 1596m, 1450m; $[\alpha]_D$ +76.6 (*c* = 1.33 in $CHCl_3$) (lit.[20] for (*R*)-enantiomer $[\alpha]_D$ −71.1 (*c* = 0.84 in $CHCl_3$)); ^1H NMR (400 MHz, $CDCl_3$) δ 7.86−6.92 (10H, m, Ar*H*), 3.68 (1H, apparent sextet, *J* = 6.8, C*H*), 3.10 (1H, dd, *J* = 6.3, 13.8 Hz, 1H of CH_2Ph), 2.62 (1H, dd, *J* = 7.9, 13.8 Hz, 1H of CH_2Ph), 1.13 (3H, d, *J* = 6.9 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.1 (*C*=O), 140.3 (Ar*C*), 136.9 (Ar*C*), 133.3 (Ar*C*H), 129.5 (2 × Ar*C*H), 129.0 (2 × Ar*C*H), 128.8 (2 × Ar*C*H) 128.7 (2 × Ar*C*H), 126.6 (Ar*C*H), 43.1 (*C*H), 39.8 (CH_2Ph), 17.8 (CH_3).

(2*R*)-1,2,3-Triphenylpropan-1-one 11g.[21] As for general procedure C. The precursor resin (460 mg, 0.37 mmol, 1 equiv) on treatment with PhLi (0.99 mL, 1.8 M in cyclohexanes−ether, 1.79 mmol, 4.8 equiv) and after purification by flash chromatography on silica (eluting with 5% EtOAc/petroleum ether (40−60 °C)) gave **11g** (19.4 mg, 27%) as a white solid: *m*/*z* (EI^+ mode) 286 (M^+, 21), 105 (100) and 77 (29); HRMS calcd for M^+, $C_{21}H_{18}O$ 286.1358, found 286.1358; ν_{max} (KBr)/cm^{-1} 2919w, 1675s (C=O), 1595m, 1493m; $[\alpha]_D$ −127.3 (*c* = 1.94 in $CHCl_3$); (lit.[22] for (*S*)-enantiomer $[\alpha]_D$ +155 (*c* = 1.31 in $CHCl_3$)); ^1H NMR (400 MHz, $CDCl_3$) δ 8.02−6.85 (15H, m, Ar*H*), 4.74 (1H, apparent t, *J* = 7.3 Hz, C*H*), 3.49 (1H, dd, *J* = 7.5, 13.7 Hz, 1H of CH_2Ph), 2.99 (1H, dd, *J* = 7.0, 13.7 Hz, 1H of CH_2Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6 (*C*=O), 140.2 (Ar*C*), 139.5 (Ar*C*), 133.3 (Ar*C*), 132.8 (Ar*C*H), 129.4 (2 × Ar*C*H), 129.3 (2 × Ar*C*H), 129.1 (2 × Ar*C*H), 128.9 (2 × Ar*C*H), 128.9 (2 × Ar*C*H), 128.7 (2 × Ar*C*H), 127.5 (Ar*C*H), 126.5 (Ar*C*H), 56.3 (*C*H), 40.5 (CH_2Ph).

(2*R*)-2-Benzyl-1-phenylhexan-1-one 11h.[14] As for general procedure C. The precursor resin (500 mg, 0.42 mmol, 1 equiv) on treatment with PhLi (1.12 mL, 1.8 M in cyclohexanes−ether, 2.02 mmol, 4.8 equiv) and after purification by flash chromatography on silica (eluting with petroleum ether (40−60 °C)) gave **11h** (29.5 mg, 33%) as a yellow oil: *m*/*z* (EI^+ mode) 266 (M^+, 13), 209 (53), 105 (100), 84 (48), 77 (33) and 49 (52); HRMS calcd for M^+, $C_{19}H_{22}O$ 266.1671, found 266.1670; ν_{max} (neat)/cm^{-1} 2956s, 2929s, 1680s (C=O), 1597m, 1448m; $[\alpha]_D$ −30.2 (*c* = 2.67 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.79−6.88 (10H, m, Ar*H*), 3.64 (1H, m, C*H*), 3.02 (1H, dd, *J* = 7.7, 13.6 Hz, 1H of CH_2Ph), 2.70 (1H, dd, *J* = 6.5, 13.6 Hz, 1H of CH_2Ph), 1.74−1.68 (1H, m, 1H of CH_2CH), 1.51−1.42 (1H, m, 1H of CH_2CH) 1.19−1.12 (4H, m, $CH_2CH_2CH_3$ and CH_2CH_3), 0.74 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.4 (*C*=O), 140.4 (Ar*C*), 137.9 (Ar*C*), 133.2 (Ar*C*H), 129.4 (2 × Ar*C*H), 128.9 (2 × Ar*C*H), 128.7 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 126.5 (Ar*C*H), 48.7 (*C*H), 38.6 (CH_2Ph), 32.5 (CH_2CH), 29.9 (CH_2 of Bu), 23.2 (CH_2 of Bu), 14.3 (CH_3).

(2*S*)-2-Methyl-1-(thieny-2′-yl)-3-phenylpropan-1-one 11i. As for general procedure C. The precursor resin (1.00 g, 0.85 mmol, 1 equiv) on treatment with 2-thienyllithium (4.08 mL, 1.0 M in THF, 4.08 mmol, 4.8 equiv) and after purification by flash chromatography on silica (eluting with 40% CH_2Cl_2/petroleum ether (40−60)) gave **11i** (80.6 mg, 60%) as a yellow oil: *m*/*z* (EI^+ mode) 230 (M^+, 65), 215 (25), 118 (12), 11 (100), 91 (61) and 65 (10); HRMS calcd for M^+, $C_{14}H_{14}OS$ 230.0765, found 230.0765; ν_{max} (neat)/cm^{-1} 2958s, 2917s, 2848m, 1659s (C=O), 1517w, 1454m, 1416s, 1376w; $[\alpha]_D$ +89.4 (*c* = 0.90 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (1H, dd, *J* = 1.0, 3.8 Hz, HC=C*H*(S)), 7.53 (1H, dd, *J* = 1.0, 5.0 Hz, *H*C=C−C(O)), 7.20−7.08 (5H, m, Ar*H*), 7.01 (1H, dd, *J* = 3.8, 5.0 Hz, *H*C=CH(S)), 3.47 (1H, apparent sextet, *J* = 7.1 Hz, C*H*), 3.08 (1H, dd, *J* = 6.6, 13.6 Hz, 1H of CH_2Ph), 2.64 (1H, dd, *J* = 7.7, 13.6 Hz, 1H of CH_2Ph), 1.16 (3H, d, *J* = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5 (*C*=O), 143.9 (HC=*C*(S)−C(O)), 139.7 (Ar*C*), 133.7 (*C*H=C−C(O)), 131.7 (HC=*C*H(S)), 129.1 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 128.1 (H*C*=CH(S)), 126.2 (Ar*C*H), 44.7 (*C*H), 39.7 (CH_2Ph), 17.6 (CH_3).

(2*R*)-2-Benzyl-1-(thien-2′-yl)hexan-1-one 11j. As for general procedure C. The precursor resin (500 mg, 0.44 mmol, 1 equiv) on treatment with 2-thienyllithium (2.12 mL, 1.0 M in THF, 2.12 mmol, 4.8 equiv) and after purification by flash chromatography on silica (eluting with 5% EtOAc/petroleum ether (40−60 °C)) gave **11j** (25.2 mg, 26%) as a yellow oil: *m*/*z* (EI^+ mode) 272 (M^+, 30), 215 (100), 111 (91), 83 (100) and 49 (73); HRMS calcd for M^+, $C_{17}H_{20}OS$ 272.1235, found 272.1235; ν_{max} (neat)/cm^{-1} 2956s, 2927s, 1655s (C=O), 1517m, 1415s, 1377w; $[\alpha]_D$ +16.7 (*c* = 1.96 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (1H, s, *H*C=C−C(O)), 7.51 (1H, s, HC=C*H*(S)), 7.19−7.04 (5H, m, Ar*H*), 6.98 (1H, apparent t, *J* = 4.5 Hz,

(17) Scommoda, M.; Gais, H.-J.; Bosshammer, S.; Raabe, G. *J. Org. Chem.* **1996**, *61*, 4379.
(18) Mislow, K.; Hamermesh, C. L. *J. Am. Chem. Soc.* **1955**, *77*, 1590.
(19) Rangaishenvi, M. V.; Singaram, B.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 3286.
(20) Oppolzer, W.; Darcel, C.; Rochet, P.; Rosset, S.; De Brabander, J. *Helv. Chim. Acta* **1997**, *80*, 1319.
(21) Diez-Barra, E.; Merino, S.; Sánchez-Verdú, P.; Torres, J. *Tetrahedron* **1997**, *53*, 11437.

*H*C═CH(S)), 3.44−3.37 (1H, m, C*H*), 3.01 (1H, dd, J = 7.8, 13.6 Hz, 1H of CH_2Ph), 2.71 (1H, dd, J = 6.5, 13.6 Hz, 1H of CH_2Ph), 1.78−1.71 (1H, m, 1H of CH_2CH_2CH), 1.53−1.45 (1H, m, 1H of CH_2CH_2CH), 1.25−1.15 (4H, m, CH_2CH_3 and CH_2-CH_2CH_3), 0.78 (3H, t, J = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6 (*C*═O), 144.1 (HC═*C*-C(O)), 138.8 (Ar*C*), 132.7 (*C*H thiophene), 130.6 (*C*H thiophene), 128.0 (2 × Ar*C*H), 127.3 (2 × Ar*C*H), 127.0 (Ar*C*H), 125.1 (*C*H thiophene), 49.6 (*C*H), 37.7 (CH_2Ph), 31.3 (CH_2CH_2CH), 28.7 (CH_2), 21.8 (CH_2), 13.0 (CH_3).

(2*S*)-2-Methyl-1-(5-methylfuran-2-yl)-3-phenylpropan-1-one 11k. To a solution of 2-methylfuran (0.31 mL, 3.42 mmol, 4.8 equiv) in THF (5 mL) was added *n*-BuLi (1.62 mL, 2.11 M in hexanes, 3.42 mmol, 4.8 equiv) at −25 °C. After 4 h, the 2-methyl-5-furanyllithium reagent was added to a solution of the precursor resin (750 mg, 0.71 mmol, 1 equiv) in Et_2O at −78 °C, and then the reaction mixture was warmed to 0 °C. After 18 h, the reaction was quenched by the addition of *i*-Pr_2NH (0.20 mL, 1.43 mmol, 2 equiv) and stirred for 15 min. The reaction mixture was filtered and washed with distilled THF (300 mL) and concentrated in vacuo. The organic residue was partitioned between EtOAc (20 mL) and aqueous saturated $NaHCO_3$ (20 mL). The organic layer was separated, washed with aqueous saturated $NaHCO_3$ (10 mL) and H_2O (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash chromatography on silica (eluting with 10% EtOAc/petroleum ether (40−60 °C)) to give **11k** (44 mg, 47%) as a yellow oil: m/z (EI$^+$ mode) 228 (M^+, 74), 213 (63), 109 (87), 83 (100), 65 (10) and 47 (30); HRMS calcd for M^+, $C_{15}H_{16}O_2$ 228.1150, found 228.1151; ν_{max} (neat)/cm^{-1} 2969s, 2929s, 1668s (C═O), 1587m, 1517s, 1454s, 1354m; $[\alpha]_D$ +83.5 (c = 2.71 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.08 (5H, m, Ar *H*), 6.97 (1H, d, J = 3.4 Hz, C*H* = CC(O)), 6.04 (1H, d, J = 3.4 Hz, C*H* = CCH_3), 3.41−3.32 (1H, m, C*H*), 3.04 (1H, dd, J = 6.8, 13.6 Hz, 1H, of CH_2Ph), 2.60 (1H, dd, J = 7.7, 13.6 Hz, 1H of CH_2Ph), 2.29 (3H, s, CH_3C═CH), 1.12 (3H, d, J = 6.9 Hz, CH_3CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3 (*C*═O), 158.3 (HC═*C*CH_3), 151.4 (HC═*C*C(O)), 140.3 (Ar*C*), 129.5 (2 × Ar*C*H), 128.7 (2 × Ar*C*H), 126.5 (Ar*C*H), 119.8 (*C*H═C(CO)), 109.3 (*C*H═CCH_3), 43.7 (*C*H), 39.8 (CH_2Ph), 17.7 (CH_3CH), 14.5 (CH_3C═CH).

(2*S*)-2-Methyl-1-(1-methyl-1*H*-imidazol-2-yl)-3-phenylpropan-1-one 11l. To a solution of 1-methylimidazole (0.17 mL, 2.13 mmol, 2.5 equiv) and TMEDA (0.32 mL, 2.13 mmol, 2.5 equiv) in THF (2 mL) at −78 °C was added *n*-BuLi (1.15 mL, 2.78 M in hexanes, 3.19 mmol, 3.75 equiv). After 3 h, the 1-methyl-2-imidazolyllithium reagent was added to a solution of the precursor resin (500 mg, 0.43 mmol, 1 equiv) in Et_2O (5 mL) at −78 °C, and then the reaction mixture was warmed to 0 °C and allowed to gradually warm to room temperature. After 20 h, *i*-Pr_2NH (0.12 mL, 0.85 mmol, 2 equiv) was added, and the reaction mixture was stirred for 15 min. The reaction mixture was then filtered, washed with distilled THF (300 mL), and concentrated in vacuo. The organic residue was partitioned between EtOAc (10 mL) and aqueous saturated $NaHCO_3$ (10 mL). The organic layer was separated, washed with aqueous saturated $NaHCO_3$ (5 mL) and H_2O (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash chromatography on silica (eluting with 30% EtOAc/petroleum ether (40−60 °C)) to give **11l** (28.5 mg, 36%) as a colorless oil: m/z (EI$^+$ mode) 228 (M^+, 15), 200 (47), 185 (38), 110 (24), 91 (58), 82 (100), 58 (17) and 47 (13); HRMS calcd for M^+, $C_{14}H_{16}ON_2$ 228.1263, found 228.1263; ν_{max} (neat)/cm^{-1} 2970m, 1674s (C═O), 1454m, 1408s; $[\alpha]_D$ +1.34 (c = 1.34 in $CHCl_3$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.06 (5H, m, ArH), 7.02 (1H, s, HC═CH), 6.92 (1H, s, HC═CH), 4.17−4.06 (1H, m, CH), 3.89 (3H, s, CH_3N), 3.07 (1H, dd, J = 6.5, 13.6 Hz, 1H of CH_2Ph), 2.60 (1H, dd, J = 8.1, 13.7 Hz, 1H of CH_2-Ph), 1.11 (3H, d, J = 7.0 Hz, CH_3CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1 (*C*═O), 141.5 (N−*C*═N), 138.8 (Ar*C*), 128.2 (2 × Ar*C*H), 127.9 (H*C*═CH), 127.2 (2 × Ar*C*H), 126.0 (Ar*C*H), 125.0 (H*C*═CH), 42.0 (*C*H), 38.0 (CH_2Ph), 35.2 (CH_3N), 16.0 (CH_3CH).

Library Synthesis. Pseudoephedrine resin **6** was acylated, in parallel, with 3-cyclopentyl propionyl chloride, 4-pentenoic anhydride, and valeric anhydride, and the resulting amides were then alkylated using benzyl bromide and butyl iodide using procedures identical to those previously described.

Preparation of a Standard Solution of Lithium Amidotrihydroborate. To a solution of *i*-Pr_2NH (6.14 mL, 43.8 mmol, 1.08 equiv) in THF (120 mL) was added *n*-BuLi (14.6 mL, 2.78 M in hexanes, 40.7 mmol, 1 equiv) at −78 °C. The resulting mixture was stirred at −78 °C for 10 min and then warmed to 0 °C for 10 min. Borane−ammonia complex (1.29 g, 41.8 mmol, 1.06 equiv) was then added and the reaction mixture stirred for 15 min and then warmed to room temperature. After 15 min, the solution of lithium amidotrihydroborate (0.34 M) was cooled to 0 °C, and then aliquots were added to the reaction flasks of a carousel containing the substrate resins.

(2*S*)-2-Benzyl-3-cyclopentyl-propan-1-ol 10b. Cleavage, after purification by flash chromatography on silica (eluting with 10% EtOAc/petroleum ether (40−60 °C)), gave **10b** (38.9 mg, 32%) as a colorless oil: m/z (EI$^+$ mode) 218 (M^+, 13), 118 (23), 104 (43), 84 (100), 83 (58) and 49 (88); HRMS calcd for M^+, $C_{15}H_{22}O$ 218.1671, found 218.1671; ν_{max} (neat/cm^{-1}) 3336s (OH), 2947s, 2865s, 2360m, 2339m; $[\alpha]_D$ −6.22 (c = 1.19 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22−7.09 (5H, m, Ar*H*), 3.47−3.39 (2H, m, CH_2OH), 2.61−2.52 (2H, m, CH_2Ph), 1.87−1.66 (4H, m, C*H*Bn, C*H*, CH_2), 1.53−1.41 (4H, m, 2 × CH_2), 1.36−1.30 (1H, m, 1H of CH_2CHBn), 1.24−1.19 (1H, m, 1H of CH_2CHBn), 1.00−0.79 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8 (Ar*C*), 128.1 (2 × Ar*C*H), 127.3 (2 × Ar*C*H), 124.8 (Ar*C*H), 63.9 (*C*H_2OH), 40.4 (*C*HBn), 36.9 (*C*H_2CH), 36.5 (*C*H), 36.4 (*C*H_2Ph), 32.0 (*C*H_2), 31.9 (*C*H_2), 24.1 (2 × *C*H_2).

(2*R*)-2-Cyclopentylmethylhexan-1-ol 10c. Cleavage, after purification by flash chromatography on silica (eluting with 10% EtOAc/petroleum ether (40−60 °C)), gave **10c** (31.8 mg, 26%) as a colorless oil: m/z (EI$^+$ mode) 214 (M + $(C_4H_9)^+$, 78), 167 (100), 166 (17), 97 (21) and (83 (13); HRMS calcd for (M + $(C_4H_9)^+$, $C_{16}H_{33}O$ 241.2531, found 241.2531; ν_{max} (neat/cm^{-1}) 3446s (OH), 2927s, 2360s, 2339s; $[\alpha]_D$ +0.55 (c = 1.10 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 (2H, dd, J = 1.6, 5.3 Hz, CH_2OH), 1.94−1.86 (1H, m, C*H*Bu), 1.79−1.75 (2H, m, CH_2), 1.65−1.51 (3H, m, 2 × CH_2, C*H*), 1.39−1.25 (8H, m, 4 × CH_2), 1.10−1.06 (2H, m, CH_2), 0.92 (3H, t, J = 6.9 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 66.3 (*C*H_2OH), 39.9 (*C*HBu), 38.1 (*C*H_2), 38.0 (*C*H), 33.5 (*C*H_2), 33.4 (*C*H_2), 31.4 (*C*H_2), 29.4 (*C*H_2), 25.5 (*C*H_2), 25.5 (*C*H_2), 23.5 (*C*H_2), 14.5 (*C*H_3).

(2*S*)-2-Benzylpent-4-en-1-ol 10d.[23] Cleavage, after purification by flash chromatography on silica (eluting with 10% EtOAc/petroleum ether (40−60 °C)), gave **10d** (76.9 mg, 65%) as a colorless oil: m/z (EI$^+$ mode) 176 (M^+, 3), 158 (13), 134 (22), 117 (30), 91 (100), 84 (70), 65 (14) and 49 (68); HRMS calcd for M^+, $C_{12}H_{16}O$ 1 76.1201, found 176.1201; ν_{max} (neat/cm^{-1}) 3365s (OH), 2921s, 2360s, 2339s; $[\alpha]_D$ −12.8 (c = 1.53 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.22 (5H, m, Ar*H*), 5.93−5.82 (1H, m, C*H*═CH_2), 5.15−5.08 (2H, m, CH_2═CH), 3.64−3.48 (2H, m, CH_2OH), 2.73−2.58 (2H, m, CH_2CH═CH_2), 2.21−2.14 (2H, m, CH_2Ph), 2.02−1.91 (1H, m, C*H*), 1.67 (1H, br s, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9 (Ar*C*), 137.2 (*C*H═CH_2), 129.4 (2 × Ar*C*H), 128.9 (2 × Ar*C*H), 126.4 (Ar*C*H), 117.0 (CH_2═CH), 65.1 (*C*H_2OH), 42.8 (*C*H), 37.6 (CH_2CH═CH_2), 35.9 (*C*H_2Ph).

(2*R*)-2-Butylpent-4-en-1-ol 10e. Cleavage, after purification by flash chromatography on silica (eluting with 10% EtOAc/petroleum ether (40−60 °C)), gave **10e** (46.4 mg, 48%)

(22) McKenzie, A.; Roger, R.; Wills, G. O. *J. Chem. Soc.* **1926**, 779.
(23) Kim, D. H.; Li, Z.-H.; Lee, S. S.; Park, J.; Chung, S. J. *Bioorg. Med. Chem.* **1998**, *6*, 239.

as a colorless oil: *m*/*z* (CI$^+$ mode, isobutane) 143 ((M + H)$^+$, 100), 125 (22) and 83 (14); HRMS calcd for (M + H)$^+$, $C_9H_{19}O$ 143.1436, found 143.1433; ν_{max} (neat/cm^{-1}) 3336s (OH), 2927s, 2860s, 2360s, 2339s; $[\alpha]_D$ +1.15 (*c* = 0.78 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75−5.65 (1H, m, C*H* = CH_2), 4.97−4.88 (2H, m, CH_2=CH), 3.47−3.39 (2H, m, CH_2OH), 2.02−1.98 (2H, m, CH_2CH=CH_2), 1.50−1.44 (2H, br m, O*H* and C*H*) 1.25−1.15 (6H, m, 3 × CH_2), 0.78 (3H, t, *J* = 6.7 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5 (*C*H=CH_2), 116.5 (CH_2=CH), 65.9 (CH_2OH), 40.8 (*C*H), 36.2 (CH_2CH=CH_2), 30.7 (CH_2), 29.5 (CH_2), 23.4 (CH_2), 14.4 (CH_3).

(2*S*)-2-Benzylpentan-1-ol 10f.[24] Cleavage, after purification by flash chromatography on silica (eluting with 20% EtOAc/petroleum ether (40−60 °C)), gave alcohol **10f** (60 mg, 59%) as a colorless oil: *m*/*z* (EI$^+$ mode) 178 (M$^+$, 31), 160 (24), 131 (21), 117 (50), 104 (49), 91 (100), 82 (52), 69 (16), 65 (12) and 41 (11); HRMS calcd for M$^+$, $C_{12}H_{18}O$ 178.1358, found 178.1357; ν_{max} (neat)/cm^{-1} 3350s (OH), 2956s, 2927s, 1583w, 1542m, 1454s; $[\alpha]_D$ +0.29 (*c* = 1.39 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21−7.09 (5H, m, Ar*H*), 3.43 (2H, apparent d, *J* = 5.3 Hz, CH_2OH), 2.60−2.51 (2H, m, CH_2Ph), 1.77−1.68 (1H, m, C*H*), 1.37−1.14 (4H, m, CH_2CH_3 and $CH_2CH_2CH_3$), 0.83−0.80 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8 (Ar*C*), 127.9 (2 × Ar*C*H), 127.3 (2 × Ar*C*H), 124.8 (Ar*C*H), 63.8 (CH_2OH), 41.3 ($CHCH_2$Ph), 36.6 (CH_2Ph), 32.0 ($CH_2CH_2CH_3$), 19.1 (CH_2CH_3), 13.3 (CH_3).

(2*S*)-2-Propylhexan-1-ol 10g.[25] Cleavage, after purification by flash chromatography on silica (eluting with 10% EtOAc/petroleum ether (40−60 °C)), gave **10g** (38.5 mg, 39%) as a colorless oil: *m*/*z* (CI$^+$ mode, ammonia) 162 ((M + NH_4)$^+$, 28), 131 (28), 130 (7) and 102 (8); ν_{max} (neat/cm^{-1}) 3336s (OH), 2956s, 2871s, 2360s, 2341s; $[\alpha]_D$ +21.1 (*c* = 0.09 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.41 (2H, apparent d, *J* = 5.5 Hz, CH_2OH), 1.38−1.26 (2H, m, CH_2O*H* and C*H*), 1.26−1.08 (10H, m, 5 × CH_2), 0.78 (6H, 2 × t, *J* = 7.0, 6.9 Hz, 2 × CH_3-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 66.1 (CH_2OH), 40.7 (*C*H), 33.6 (2 × CH_2), 31.0 (CH_2), 29.5 (CH_2), 23.5 (CH_2), 14.8 (CH_3-CH_2), 14.4 (CH_3CH_2).

(2*S*)-2-Cyclopentylmethyl-3-phenyl-1-(thien-2′-yl)-propan-1-one 11m. Cleavage, after purification by flash chromatography on silica (eluting with 5% EtOAc/petroleum ether (40−60 °C)), gave **11m** (22.4 mg, 21%) as a yellow oil: *m*/*z* (EI$^+$ mode) 298 (M$^+$, 5), 216 (40), 215 (44), 111 (52), 91 (29), 85 (64), 83 (100) and 47 (19); HRMS calcd for M$^+$, $C_{19}H_{22}OS$ 298.1391, found 298.1390; ν_{max} (Golden Gate)/cm^{-1} 3103w, 3082w, 3026w, 2933m, 2852w, 1641s (C=O), 1605w, 1516w; $[\alpha]_D$ +62.4 (*c* = 1.61 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51−7.50 (2H, m, 2 × C*H* thiophene), 7.27−7.03 (5H, m, Ar*H*), 6.99−6.96 (1H, m, C*H* thiophene), 3.50−3.43 (1H, m, C*H*Bn), 3.00 (1H, dd, *J* = 8.0, 13.5, 1H of CH_2Ph), 2.70 (1H, dd, *J* = 6.3, 13.5 Hz, 1H, of CH_2Ph), 1.90−1.83 (1H, m, 1H of CH_2), 1.72−1.62 (3H, m, C*H* and CH_2), 1.49−1.35 (5H, m, 2 × CH_2 and 1H of CH_2), 1.02−0.92 (2H, m CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2 (*C*=O), 145.5 (Ar*C*), 140.1 (Ar*C*), 134.2 (*C*H thiophene), 132.0 (*C*H thiophene), 129.3 (2 × Ar*C*H), 128.7 (2 × Ar*C*H), 128.5 (*C*H thiophene), 126.5 (Ar*C*H), 50.3 (*C*HBn), 39.7 (CH_2Ph), 39.4 ($CHCH_2$), 38.6 (*C*H), 33.6 (CH_2), 33.0 (CH_2), 25.5 (2 × CH_2).

(2*R*)-2-Cyclopentylmethyl-1-(thien-2-yl)hexan-1one 11n and (2*R*)-2-Cyclopentylmethyl-1,1-di(thien-2-yl)hexan-1-ol 12. Cleavage, after purification by flash chromatography on silica (eluting with 5% EtOAc/petroleum ether (40−60 °C)), gave **11n** (23.6 mg, 27%) as a yellow oil: *m*/*z* (EI$^+$ mode) 264 (M$^+$, 4), 208 (27), 182 (70), 139 (68), 111 (100), 83 (15), 55 (13) and 41 (14); HRMS calcd for M$^+$, $C_{16}H_{24}OS$ 264.1548, found 264.1549; ν_{max} (neat)/cm^{-1} 2951s, 2858s, 1658s (C=O), 1518m, 1415s, 1236s; $[\alpha]_D$ −14.3 (*c* = 1.81 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (1H, dd, *J* = 1.1, 3.8 Hz, C*H* thiophene), 7.56 (1H, dd, *J* = 1.1, 4.9 Hz, C*H* thiophene), 7.07 (1H, dd, *J* = 3.8, 4.9 Hz, C*H* thiophene), 3.22−3.15 (1H, m, C*H*Bu), 1.84−1.69 (1H, m, 1H of CH_2), 1.69−1.53 (4H, m, CH_2, C*H*, 1H of CH_2), 1.52−1.44 (2H, m, CH_2), 1.43−1.36 (4H, m, CH_2, 1H of CH_2, 1H of CH_2), 1.22−1.16 (4H, m, 2 × CH_2), 1.03−1.00 (2H, m, CH_2), 0.78 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2 (*C*=O), 146.0 (*C* thiophene), 134.0 (*C*H thiophene), 131.8 (*C*H thiophene), 128.5 (*C*H thiophene), 48.1 (*C*HBu), 39.8 (CH_2), 38.6 (*C*H), 33.6 (CH_2), 33.5 (CH_2), 33.1 (CH_2), 30.3 (CH_2), 25.5 (2 × CH_2), 23.2 (CH_2), 14.3 (CH_3).

Further elution then gave **12** (16.1 mg,17%) as a yellow oil: *m*/*z* (EI$^+$ mode) 348 (M$^+$, 2), 195 (100) and 111(40); HRMS calcd for M$^+$, $C_{20}H_{28}OS_2$ 348.1582, found 348.1582; ν_{max} (neat)/cm^{-1} 3537m (OH), 2951s, 2860s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14−7.12 (2H, m, 2 × C*H* thiophene), 6.94−6.86 (4H, m, 4 × C*H* thiophene), 2.14−2.10 (1H, m, C*H*Bu), 1.65−1.64 (3H, m, C*H*, CH_2), 1.55−1.37 (8H, m, 3 × CH_2, 2 × 1H of CH_2), 1.28−1.19 (1H, m, 1H of CH_2), 1.17−1.06 (3H, m, CH_2, 1H of CH_2), 0.94−0.93 (2H, m, CH_2), 0.73 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1 (*C* thiophene), 151.9 (*C* thiophene), 127.0 (*C*H thiophene), 124.6 (*C*H thiophene), 124.2 (*C*H thiophene), 50.3 (*C*OH), 50.3 (*C*HBu), 39.0 (*C*H), 37.9 (CH_2), 34.0 (CH_2), 32.6 (CH_2), 31.9 (CH_2), 31.7 (CH_2), 25.4 (CH_2), 25.3 (CH_2), 14.4 (CH_3).

(2*S*)-2-Benzyl-1-(thien-2-yl)pent-4-en-1-one 11o. Cleavage, after purification using flash chromatography on silica (eluting with 5% EtOAc/petroleum ether (40−60 °C)), gave **11o** (52.5 mg, 61%) as a yellow oil: *m*/*z* (EI$^+$ mode) 256 (M$^+$, 12), 215 (100), 212 (11), 131 (13), 111 (71) and 83 (56); HRMS calcd for M$^+$, $C_{16}H_{16}OS$ 256.0922, found 256.0923; ν_{max} (neat/cm^{-1}) 3077m (C=C), 2921m, 1654s (C=O), 1415s, 993m (C=CH_2), 916s (C=CH_2); $[\alpha]_D$ +82.1 (*c* = 1.33 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.49 (2H, m, 2 × C*H* thiophene), 7.09−7.04 (5H, m, Ar*H*), 6.98−6.95 (1H, m, C*H* thiophene), 5.72−5.61 (1H, m, C*H* = CH_2), 5.00−4.90 (2H, m, CH_2=CH), 3.52−3.43 (1H, m, C*H*), 3.01 (1H, dd, *J* = 7.9, 13.6, 1H of CH_2Ph), 2.74 (1H, dd, *J* = 6.4, 13.6 Hz, 1H of CH_2Ph), 2.51−2.44 (1H, m, 1H of CH_2CH=CH_2), 2.27−2.21 (1H, m, 1H of CH_2CH=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0 (*C*=O), 145.1 (Ar*C* or *C* thiophene), 139.8 (Ar*C* or *C* thiophene), 135.6 (*C*H=CH_2), 134.4 (*C*H thiophene), 132.2 (*C*H thiophene), 129.7 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 128.5 (Ar*C*H), 126.7 (*C*H thiophene), 117.7 (CH_2=CH), 50.6 (*C*H), 38.5 (CH_2Ph), 37.0 (CH_2CH=CH_2).

(2*R*)-2-Butyl-1-(thien-2-yl)pent-4-en-1-one 11p. Cleavage, after purification using flash chromatography on silica (eluting with 5% EtOAc/petroleum ether (40−60 °C)), gave **11p** (24.3 mg, 32%) as a yellow oil: *m*/*z* (EI$^+$ mode) 222 (M$^+$, 2), 166 (15), 111 (59), 83 (100) and 47 (17); HRMS calcd for M$^+$, $C_{13}H_{18}OS$ 222.1078, found 222.1077; ν_{max} (neat/cm^{-1}) 3077m (C=C), 2929s, 1658s (C=O), 1415s, 993m (C=CH_2), 914s (C=CH_2); $[\alpha]_D$ +6.27 (*c* = 1.10 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (1H, dd, *J* = 1.1, 3.8 Hz, C*H* thiophene), 7.57 (1H, dd, *J* = 1.1, 4.9 Hz, C*H* thiophene), 7.06 (1H, dd, *J* = 3.8, 4.9 Hz, C*H* thiophene), 5.73−5.63 (1H, m, C*H* = CH_2), 5.00−4.88 (2H, m, CH_2=CH), 3.24−3.19 (1H, m, C*H*), 2.48−2.40 (1H, m, 1H of CH_2CH=CH_2), 2.24−2.17 (1H, m, 1H of CH_2CH=CH_2), 1.76−1.67 (1H, m, 1H of $CHCH_2$), 1.53−1.44 (1H, m, 1H of $CHCH_2$), 1.27−1.14 (4H, m, 2 × CH_2), 0.78 (3H, t, *J* = 6.9 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9 (*C*=O), 145.6 (*C* thiophene), 136.1 (*C*H=CH_2), 134.2 (*C*H thiophene), 132.0 (*C*H thiophene), 128.6 (*C*H thiophene), 117.1 (CH_2=CH), 48.6 (*C*H), 37.2 (CH_2CH=CH_2), 32.5 ($CHCH_2$), 30.0 (CH_2), 23.2 (CH_2), 14.3 (CH_3).

(2*S*)-2-Benzyl-1-(thien-2-yl)pentan-1-one 11q. Cleavage, after purification using flash chromatography on silica (eluting with 5% EtOAc/petroleum ether (40−60 °C)), gave **11q** (29.1 mg, 34%) as a yellow oil: *m*/*z* (EI$^+$ mode) 258 (M$^+$, 13), 215 (43), 111 (49), 84 (100) and 49 (98); HRMS calcd for M$^+$, $C_{16}H_{18}$-OS 258.1078, found 258.1080; ν_{max} (neat/cm^{-1}) 2929s, 1654s (C=O), 1415s; $[\alpha]_D$ +8.27 (*c* = 1.15 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.50 (2H, m, 2 × C*H* thiophene), 7.18−7.02 (5H, m, Ar*H*), 6.98 (1H, apparent t, *J* = 4.4 Hz, C*H* thiophene), 3.46−3.39 (1H, m, C*H*), 3.02 (1H, dd, *J* = 7.8, 13.6

(24) Meakin, B. J.; Mumford, F. R.; Ward, E. R. *J. Pharm. Pharmacol.* **1959**, 540.

(25) Felkin, H.; Swierczewski, G.; Tambuté, A. *Tetrahedron Lett.* **1969**, *10*, 707.

Hz, 1H of CH_2Ph), 2.70 (1H, dd, J = 6.5, 13.6 Hz, 1H of CH_2-Ph), 1.79−1.69 (1H, m, 1H of CH_2CH$_2$CH$_3$), 1.51−1.42 (1H, m, 1H of CH_2CH$_2$CH$_3$), 1.32−1.15 (2H, m, CH_2CH$_3$), 0.79 (3H, t, J = 7.3 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0 (*C*=O), 145.5 (Ar*C* or *C* thiophene), 140.2 (Ar*C* or *C* thiophene), 134.2 (*C*H thiophene), 132.0 (*C*H thiophene), 129.4 (2 × Ar*C*H), 128.7 (2 × Ar*C*H), 128.5 (Ar*C*H), 126.6 (*C*H thiophene), 50.8 (*C*H), 39.1 (*C*H$_2$Ph), 35.2 (*C*H$_2$CH$_2$CH$_3$), 21.2 (*C*H$_2$CH$_3$), 14.6 (*C*H$_3$).

Preparation of a Standard Solution of 1-Methyl-2-imidazoyllithium. To a solution of 1-methylimidazole (0.52 mL, 6.15 mmol, 1 equiv) and TMEDA (0.93 mL, 6.15 mmol, 1 equiv) in THF (12 mL) at −78 °C was added *n*-BuLi (4.61 mL, 2.0 M in hexanes, 9.22 mmol, 1.5 equiv). The reaction was stirred for 3 h at −78 °C, and then aliquots of the 1-methyl-2-imidazoyllithium (0.51 M) were added to the reaction flasks of the carousel containing the substrate resins.

(2*S*)-2-Benzyl-3-cyclopentyl-1-(1-methyl-1*H*-imidazol-2-yl)propan-1-one 11s. Cleavage, after purification using flash chromatography on silica (eluting with 10% EtOAc/petroleum ether (40−60 °C) to 20% EtOAc/petroleum ether (40−60 °C)), gave **11s** (23.3 mg, 19%) as a colorless oil: *m*/*z* (EI$^+$ mode) 296 (M$^+$, 20), 268 (32), 213 (48), 205 (26), 185 (53), 110 (38), 84 (100) and 49 (88); HRMS calcd for M$^+$, $C_{19}H_{24}ON_2$ 296.1889, found 296.1889; ν_{max} (neat/cm^{-1}) 2949s, 2866s, 1670s (C=O), 1408s; $[\alpha]_D$ +46.2 (c = 1.04 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16−7.04 (5H, m, Ar*H*), 7.03 (1H, s, C*H* imidazole), 6.89 (1H, s, C*H* imidazole), 4.25−4.18 (1H, m, C*H*Bn), 3.86 (3H, s, CH_3N), 2.98 (1H, dd, J = 7.4, 13.6 Hz, 1H of CH_2Ph), 2.69 (1H, dd, J = 7.2, 13.6 Hz, 1H of CH_2Ph), 1.82−1.77 (1H, m, 1H of CH_2CH), 1.70−1.59 (3H, m, CH_2, 1H of CH_2CH), 1.48−1.32 (5H, m, CH, 2 × CH_2), 1.18−0.93 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9 (*C*=O), 143.7 (Ar*C* or *C* imidazole), 140.2 (Ar*C* or *C* imidazole), 129.5 (2 × Ar*C*H), 129.4 (*C*H imidazole), 128.5 (2 × Ar*C*H), 127.3 (Ar*C*H), 126.3 (*C*H imidazole), 48.0 (*C*HBn), 39.0 (*C*H$_2$CH), 38.7 (*C*H$_3$N), 38.4 (*C*H$_2$), 36.6 (*C*H), 33.5 (*C*H$_2$), 33.2 (*C*H$_2$), 25.5 (2 × *C*H$_2$).

(2*R*)-2-Cyclopentylmethyl-1-(1-methyl-1*H*-imidazol-2-yl)hexan-1-one 11t. Cleavage, after purification using flash chromatography on silica (eluting with 10% EtOAc/petroleum ether (40−60 °C)), gave **11t** (21.8 mg, 19%) as a colorless oil: *m*/*z* (EI$^+$ mode) 262 (M$^+$, 8), 193 (10), 84 (100), 77 (26) and 49 (84); HRMS calcd for M$^+$, $C_{16}H_{26}ON_2$ 262.2045, found 262.2044; ν_{max} (neat/cm^{-1}) 2952s, 2860s, 1670s (C=O), 1408s; $[\alpha]_D$ −16.0 (c = 0.91 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (1H, d, J = 0.8 Hz, C*H* imidazole), 6.95 (1H, s, C*H* imidazole), 3.93 (3H, s, CH_3N), 3.89−3.82 (1H, m, C*H*Bu), 1.76−1.59 (5H, m, C*H*, CH_2, 2 × 1H of CH_2), 1.50−1.35 (6H, m, 2 × CH_2, 2 × 1H of CH_2), 1.23−1.17 (4H, m, 2 × CH_2), 1.03−0.99 (2H, m, CH_2), 0.77 (3H, t, J = 7.0 Hz, CH_3CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1 (*C*=O), 143.9 (*C* imidazole), 129.3 (*C*H imidazole), 127.4 (*C*H imidazole), 46.3 (*C*HBu), 39.0 (*C*H$_2$), 38.8 (*C*H$_3$N), 36.7 (*C*H), 33.5 (*C*H$_2$), 33.3 (*C*H$_2$), 33.2 (*C*H$_2$), 30.0 (*C*H$_2$), 25.5 (2 × *C*H$_2$), 23.3 (*C*H$_2$), 14.3 (*C*H$_3$CH$_2$).

(2*S*)-2-Benzyl-1-(1-methyl-1*H*-imidazoly-2-yl)pent-4-en-1-one 11u. Cleavage, after purification using flash chromatography on silica (eluting with 30% EtOAc/petroleum ether (40−60 °C)), gave **11u** (28.3 mg, 33%) as a colorless oil: *m*/*z* (EI$^+$ mode) 254 (M$^+$, 8), 213 (100), 185 (16), 163 (28) 109 (41), 83 (48) and 82 (31); HRMS calcd for M$^+$, $C_{16}H_{18}ON_2$ 254.1419, found 254.1418; ν_{max} (neat/cm^{-1}) 2954m, 2922m, 1674s (C=O), 1408s; $[\alpha]_D$ +61.9 (c = 1.01 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17−7.05 (5H, m, Ar*H*), 7.03 (1H, s, C*H* imidazole), 6.90 (1H, s, C*H* imidazole), 5.75−5.65 (1H, m, C*H* = CH$_2$), 4.97−4.88 (2H, m, CH_2=CH), 4.28−4.21 (1H, m, C*H*), 3.86 (3H, s, CH_3N), 3.01 (1H, dd, J = 7.6, 13.7 Hz, 1H of CH_2Ph), 2.72 (1H, dd, J = 7.1, 13.7 Hz, 1H of CH_2Ph), 2.48−2.41 (1H, m, 1H of CH_2CH=CH$_2$), 2.28−2.21 (1H, m, 1H of CH_2CH=CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4 (*C*=O), 143.4 (Ar*C* or *C* imidazole), 140.0 (Ar*C* or *C* imidazole), 136.0 (*C*H=CH$_2$), 129.6 (2 × Ar*C*H), 129.4 (*C*H imidazole), 128.6 (2 × Ar*C*H), 127.4 (Ar*C*H), 126.4 (*C*H imidazole), 117.1 (*C*H$_2$=CH), 48.2 (*C*H), 37.5 (*C*H$_2$Ph), 36.5 (*C*H$_3$N), 36.2 (*C*H$_2$CH=CH$_2$).

(2*R*)-2-Butyl-1-(1-methyl-1*H*-imidazol-2-yl)pent-4-en-1-one 11v. Cleavage, after purification using flash chromatography on silica (eluting with 20% EtOAc/petroleum ether (40−60 °C)), gave **11v** (33.7 mg, 45%) as a colorless oil: *m*/*z* (EI$^+$ mode) 220 (M$^+$, 2), 191 (8), 177 (40), 163 (17) 149 (16), 149 (16), 136 (10), 109 (22), 83 (100), 82 (25) and 47 (27); HRMS calcd for M$^+$, $C_{13}H_{20}ON_2$ 220.1576, found 220.1575; ν_{max} (neat/cm^{-1}) 2929s, 2860s, 1672s (C=O), 1408s; $[\alpha]_D$ −9.74 (c = 1.01 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (1H, s, C*H* imidazole), 6.95 (1H, s, C*H* imidazole), 5.74−5.64 (1H, m, C*H* = CH$_2$), 4.96−4.85 (2H, m, CH_2=CH), 3.92 (3H, s, CH_3N), 3.90−3.86 (1H, m, C*H*), 2.44−0.237 (1H, m, 1H of CH_2CH=CH$_2$), 2.25−2.18 (1H, m, 1H of CH_2CH=CH$_2$), 1.71−1.62 (1H, m, 1H of CHCH_2), 1.50−1.42 (1H, m, 1H of CHCH_2), 1.27−1.12 (4H, m, 2 × CH_2), 0.78 (3H, t, J = 7.0 Hz, CH_3CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7 (*C*=O), 143.7 (*C* imidazole), 136.4 (*C*H=CH$_2$), 129.4 (*C*H imidazole), 127.4 (*C*H imidazole), 116.7 (*C*H$_2$=CH), 46.5 (*C*H), 36.7 (*C*H$_2$CH), 36.6 (*C*H$_3$N), 31.7 (CH*C*H$_2$), 29.8 (*C*H$_2$), 23.2 (*C*H$_2$), 14.3 (*C*H$_3$CH$_2$).

(2*S*)-2-Benzyl-1-(1-methyl-1*H*-imidazol-2-yl)pentan-1-one 11w. Cleavage, after purification using flash chromatography on silica (eluting with 20% EtOAc/petroleum ether (40−60 °C)), gave **11w** (35.0 mg, 38%) as a colorless oil: *m*/*z* (EI$^+$ mode) 256 (M$^+$, 5), 228 (12), 213 (13), 185 (17) 109 (10), 83 (100), 82 (29) and 47 (27); HRMS calcd for M$^+$, $C_{16}H_{20}ON_2$ 256.1576, found 256.1577; ν_{max} (neat/cm^{-1}) 2958s, 2929s, 1674s (C=O), 1408s; $[\alpha]_D$ +57.6 (c = 1.42 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16−7.04 (5H, m, Ar*H*), 7.03 (1H, s, C*H* imidazole), 6.89 (1H, s, C*H* imidazole), 4.19−4.12 (1H, m, C*H*), 3.86 (3H, s, CH_3N), 2.99 (1H, dd, J = 7.5, 13.6, 1H of CH_2Ph), 2.69 (1H, dd, J = 7.2, 13.6 Hz, 1H of CH_2Ph), 1.73−1.63 (1H, m, 1H of CHCH_2), 1.47−1.39 (1H, m, 1H of CHCH_2), 1.28−1.16 (2H, m, CH_2CH$_3$), 0.78 (3H, t, J = 7.3 Hz, (CH_3CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6 (*C*=O), 143.7 (Ar*C* or *C* imidazole), 140.3 (Ar*C* or *C* imidazole), 129.5 (2 × Ar*C*H), 129.4 (*C*H imidazole), 128.5 (2 × Ar*C*H), 127.4 (Ar*C*H), 126.3 (*C*H imidazole), 48.5 (*C*H), 38.3 (*C*H$_2$Ph), 36.6 (*C*H$_3$N), 34.4 (CH*C*H$_2$), 20.9 (*C*H$_2$CH$_3$), 14.6 (*C*H$_3$CH$_2$).

(2*S*)-1-(1-Methyl-1*H*-imidazol-2-yl)-2-propylhexan-1-one 11x. Cleavage, after purification using flash chromatography on silica (eluting with 10% EtOAc/petroleum ether (40−60 °C)), gave **11x** (36.9 mg, 38%) as a colorless oil: *m*/*z* (EI$^+$ mode) 222 (M$^+$, 39), 193 (44), 179 (69), 165 (41) 137 (57), 109 (82), 84 (100), 82 (93) and 49 (95); HRMS calcd for M$^+$, $C_{13}H_{22}ON_2$ 222.1732, found 222.1732; ν_{max} (neat/cm^{-1}) 2956s, 2929s, 1668s (C=O), 1410s; $[\alpha]_D$ +1.89 (c = 1.43 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (1H, d, J = 0.6 Hz, C*H* imidazole), 6.95 (1H, apparent s, C*H* imidazole), 3.93 (3H, s, CH_3N), 3.84−3.75 (1H, m, C*H*), 1.68−161 (2H, m, 1H of CH_2CH$_2$CH$_3$ and 1H of CHCH_2), 1.46−1.38 (2H, m, 1H of CH_2CH$_2$CH$_3$ and 1H of CHCH_2), 1.25−1.11 (6H, m, 3 × CH_2), 0.80 (3H, t, J = 7.3 Hz, CH_3CH$_2$), 0.77 (3H, t, J = 7.0 Hz, CH_3CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9 (*C*=O), 143.9 (*C* imidazole), 129.3 (*C*H imidazole), 127.4 (*C*H imidazole), 46.8 (*C*H), 36.7 (*C*H$_3$N), 34.9 (*C*H$_2$), 32.4 (*C*H$_2$), 30.0 (*C*H$_2$), 23.9 (*C*H$_2$), 21.1 (*C*H$_2$), 14.7 (*C*H$_3$-CH$_2$), 14.3 (*C*H$_3$CH$_2$).

(2*R*)-6-Benzyldecan-5-one 11y.[5c] As for general procedure C. The recycled resin (865 mg, 0.73 mmol, 1 equiv) on treatment with *n*-BuLi (0.91 mL, 2.0 M in hexanes, 1.82 mmol, 2.5 equiv) and after purification by flash chromatography on silica (eluting with 30% CH_2Cl_2/petroleum ether (40−60 °C)) gave **11y** (35.5 mg, 25%) as a colorless oil: *m*/*z* (EI$^+$ mode) 246 (M$^+$, 12), 189 (78), 161 (15), 148 (23), 105 (13), 91 (100), 85 (40), 57 (31) and 49 (10); HRMS calcd for M$^+$, $C_{17}H_{26}O$ 246.1984, found 246.1983; ν_{max} (neat)/cm^{-1} 2956s, 2931s, 1710s (C=O), 1456m; $[\alpha]_D$ −32.0 (c = 1.02 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20−6.95 (5H, m, Ar*H*), 2.81−2.69 (2H, m, 1H of CH_2Ph, C*H*), 2.58 (1H, dd, J = 5.4, 12.6 Hz, 1H of CH_2-Ph), 2.25−2.17 (1H, m, 1H of CH_2), 2.07−1.99 (1H, m, 1H of CH_2), 1.59−1.54 (1H, m, 1H of CH_2), 1.36−1.28 (3H, m, 1H of

CH_2 and CH_2), 1.24−1.07 (6H, m, 3 × CH_2), 0.79 (3H, t, J = 7.1 Hz, CH_3CH$_2$), 0.74 (3H, t, J = 7.3 Hz, CH_3CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.9 (*C*═O), 140.3 (Ar*C*), 129.3 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 126.5 (Ar*C*H), 54.4 (*C*H), 43.8 (*C*H$_2$), 38.6 (*C*H$_2$), 32.0 (*C*H$_2$), 30.0 (*C*H$_2$), 25.7 (*C*H$_2$), 23.2 (*C*H$_2$), 22.6 (*C*H$_2$), 14.3 (*C*H$_3$CH$_2$), 14.2 (*C*H$_3$CH$_2$).

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Supporting Information Available: General experimental methods, details of the determination of enantiomeric excess including examples of GC and HPLC traces and ^{19}F NMR spectra of Mosher's esters, selected IR and MAS ^{1}H NMR and ^{1}H NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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