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Formation, Alkylation and Hydrolysis of Chiral Nonracemic *N*-Amino Cyclic Carbamate Hydrazones: An Approach to the Enantioselective α-Alkylation of Ketones

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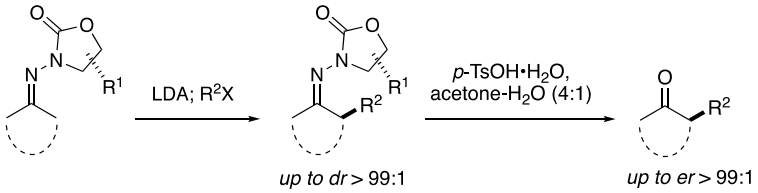

Abstract: The α-alkylation of ketones is a fundamental synthetic transformation. The development of asymmetric variants of this reaction is important given that numerous natural products, drugs, and related compounds exist as α-functionalized ketones or derivatives thereof. We previously reported our preliminary studies on the development of a new enantioselective ketone α-alkylation procedure using *N*-amino cyclic carbamate (ACC) auxiliaries. In comparison to other auxiliary-based

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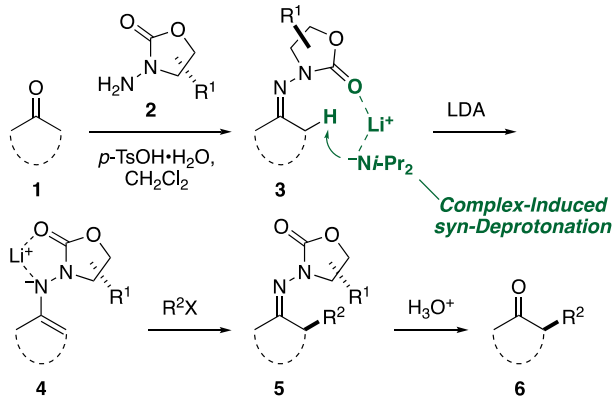
methods, ACC alkylation offers a number of advantages and is both highly enantioselective and high yielding. Herein, we provide a full account of our studies on the enantioselective ACC ketone α-alkylation method.

Introduction

The asymmetric α-alkylation of ketones is an important yet challenging transformation. Remarkably, despite its importance only three methods are available for ketone α-alkylation that have been used in the asymmetric total synthesis of natural products.[1] The use of derived azaenolates has proven more effective in alkylation reactions than enolates in terms of reactivity, product yield, and regioselectivity (C vs. O/N). Azaenolates also provide a means of effecting asymmetric induction through the use of amine-based chiral auxiliaries. In 1969, Yamada provided the first such demonstration along these lines, albeit with an enamine rather than an azaenolate species. In that work, proline-derived enamines were shown to undergo asymmetric conjugate addition to methyl acrylate and acrylonitrile with low yield and asymmetric induction.[2] While the results of these studies left considerable room for improvement, they are highly important in adumbrating not only future work in the context of azaenolate-based ketone alkylation, but also that in the area of enamine-based organocatalysis.[3] With regard to the former, Koga[4] and Meyer[5] subsequently and independently reported the use of acyclic amino acid-derived auxiliaries in the asymmetric α-alkylation of ketones via derived imines, with good to very good diastereoselectivity in the case of cyclic ketones, but poor selectivity for acyclic ketones. SAMP/RAMP dialkyl hydrazones

were introduced by Enders in the late 1970s and were found to undergo alkylation with moderate to excellent diastereoselectivity, and modest to very good yield.[1a,b,6] The introduction of SAMP/RAMP chemistry marked a key advance in the field of asymmetric synthesis. This method has been employed in asymmetric ketone α-alkylation, but is most well established for aldehyde α-alkylation. In the early 2000s, Tunge,[7] Stoltz,[8] and Trost[9] independently reported non-azaenolate-based methods for the catalytic asymmetric α-allylation of ketones, with the Stoltz method finding impressive applications in the synthesis of natural products.[1c-p] These catalytic, asymmetric Tsuji-Trost-based approaches provided the first major advance in the field of asymmetric ketone α-alkylation since the introduction of the SAMP/RAMP auxiliaries, but are each limited to the incorporation of allyl-based substituents.

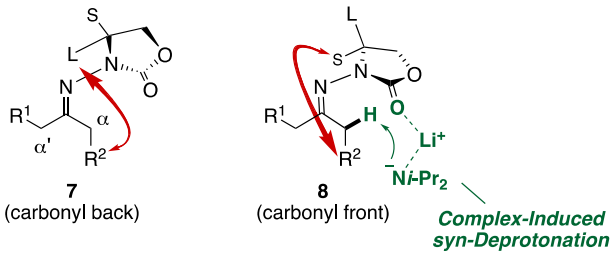


Scheme 1. Enantioselective α-alkylation of ketones using ACC auxiliaries.

In 2008, we reported our initial studies on the development of a method for the enantioselective α-alkylation of ketones using *N*-amino cyclic carbamate (ACC) auxiliaries (Scheme 1, **1** → **6**).[10,11] In contrast to other methods, ACC auxiliaries are both easily introduced into and removed from ketones, with near quantitative recovery. A key design feature of ACC auxiliaries is the placement of a carbonyl group adjacent to the hydrazone moiety. This serves three purposes: 1) it enhances the α-proton acidity leading to rapid deprotonation, even at low temperature, 2) it enables the formation of a rigid five-membered chelate (*cf*. **4**, **9**) such that highly diastereoselective alkylation is possible even at elevated temperature, and, 3) it allows for regioselective deprotonation via complex-induced *syn*-deprotonation (CIS-D) (*vide infra*). The latter effect, which is able to override the inherent selectivity of LDA for removal of the least sterically hindered proton, makes possible the α,α-bisalkylation of ketones having both acidic α-, and α'-protons,[12,13] a previously unattainable transformation. In what follows, we provide a full account of the development of the enantioselective ACC ketone α-alkylation method.

The model that we have developed to rationalize the stereochemical outcome of the ACC alkylation reaction is outlined in Scheme 2.[10,11] Conformational equilibrium favors what we term the carbonyl front form of the hydrazone (**8**) to minimize steric interactions between R^2 and the auxiliary. As indicated above, azaenolate formation occurs upon treatment with LDA via CIS-D, which leads to regioselective deprotonation of the front-facing proton on the same side of the carbon-nitrogen double bond as the auxiliary (**8**→**9**). This results in the formation

of an azaenolate having the *E*-geometry about the C–C bond and the *Z*-geometry about the C–N bond (**9**). The azaenolate exists as a five-membered chelate involving the nitrogen-centered anion, the auxiliary carbonyl, and Li^+, and is configurationally stable at the reaction temperature. In this form, the bottom face of the azaenolate is blocked, causing the electrophile to approach from the top face to give the α-alkylated hydrazone (**9**→**10**). Auxiliary cleavage then provides the desired ketone (**11**) in enantiomerically enriched form.



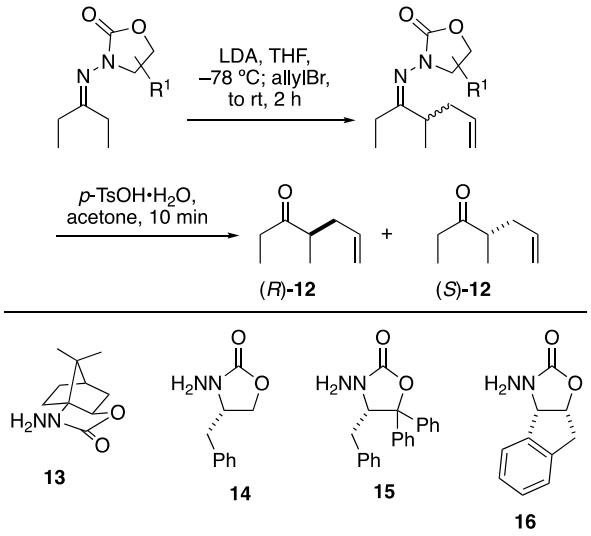
L = large substituent; S = small substituent

Scheme 2. Proposed stereochemical model of ACC alkylation.

Results and Discussion

Our initial report on ACC alkylation centered on auxiliaries **13**-**16** (Table 1).[10] Of these, **13** proved to be the most effective in terms of asymmetric induction,

Table 1. Allylation of 3-Pentanone using ACC Auxiliaries **13-16**.



entry	ACC	hydrazone	allylated hydrazone	alkylation yield (%)	(*R*)-**12**:(*S*)-**12***	hydrolysis yield (%)
1	**13**	**17**	**21**	98	96:4	96
2	**14**	**18**	**22**	92	76:24	90
3	**15**	**19**	**23**	93	91:9	93
4	**16**	**20**	**24**	82	86:14	82

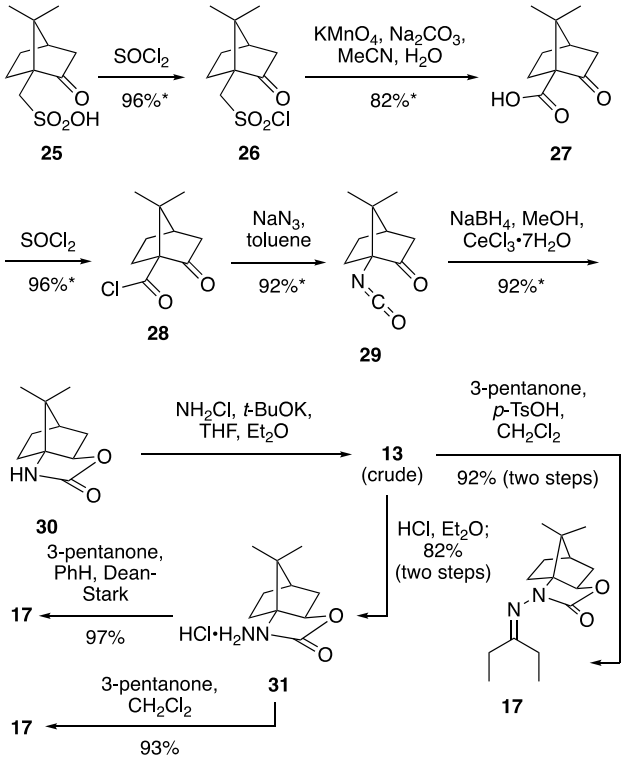
*Determined by chiral GC analysis.

giving an *er* of 96:4 for the α-allylation of **17**.[14] The synthesis of auxiliary **13** is shown in Scheme 3, and begins with readily accessible and inexpensive camphor sulfonic acid (**25**). Sulfonyl chloride **26** is also commercially available and can be used as a starting point for the synthesis of **13**. However, given the simplicity of the conversion of **25** to **26** (vide infra), along with the lower cost of the former, we prefer to begin from the sulfonic acid. **25** is converted into ketopinic acid (**27**) by treatment with thionyl chloride to produce **26**, which is then used in crude form and oxidized by $KMnO_4$. The conversion of **26** to **27** has been described previously[15] and involves the treatment of **26** with an aqueous solution of $KMnO_4$, producing **27** in

38–43% yield. We were able to improve this procedure through the simple modification of adding acetonitrile as a co-solvent to the reaction mixture. This gave consistently high yields (~80%) of **27** at various reaction scales. **27** was used without purification to generate acid chloride **28**, which was used in crude form to prepare the corresponding acyl azide. Curtius rearrangement then led to isocyanate **29**, which was also used without purification to produce oxazolidinone **30** upon treatment with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$. The crude oxazolidinone was converted into the required ACC (**13**) by treatment with NH_2Cl and *t*-BuOK.[16] (If desired, pure **30** could be obtained in 81% yield by recrystallization of the crude amination mixture from EtOAc.) The amination method we used was developed[17] by chemists at the Bristol-Myers Squibb Company as a safe approach for the amination of various nitrogen heterocycles, even in the large scale (75 g) amination of 1*H*-pyrrole-2,4-dicarboxylic acid, 3-methyl-, 2,4-diethyl ester. Conveniently, in both small and large scale applications, the required ACC hydrazones could be obtained in pure form directly from the crude amination mixture [**30** → **13** (crude)] by condensation with the ketone in the presence of *p*-$TsOH \cdot H_2O$ and CH_2Cl_2 at reflux temperature [e.g., **13** (crude) → **17**], followed by silica gel chromatography. At first glance the synthesis of **13** appears rather long. However, since at all stages the crude material generated is very clean[18] and is used directly in the subsequent step, along with the fact that all the transformations are easy to conduct and are complete in a reasonably short time, large amounts of **13** can easily be generated in two days.

An alternative approach to the formation of the ACC hydrazones begins with the acidification of **13** to produce **31** (the HCl salt of **13**) in crude form, which could

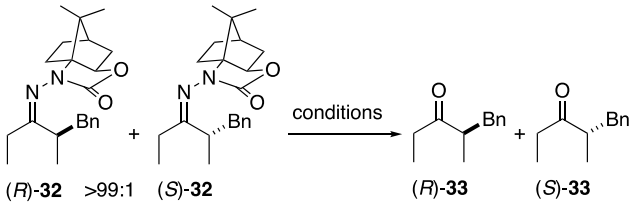
be recrystallized to give pure **31** in 82% yield over the two steps. Pure **31** could be condensed directly with the required ketone by combining it in a 1:1 molar ratio at reflux for 12 h using a Dean-Stark trap (*e.g.*, **13** → **17**), or by condensing it with an excess (10 equiv.) of the required ketone for 12 h at room temperature in CH_2Cl_2. If desired, pure **13** can be obtained by conversion to the corresponding acetone hydrazone, followed by treatment with $NH_2OH{\cdot}HCl$ and silica gel chromatography.[10] Pure **13** can then be condensed with the appropriate ketone in a 1:10 molar ratio, respectively, in the presence of *p*-$TsOH{\cdot}H_2O$ and CH_2Cl_2 at reflux to produce the desired hydrazone in excellent yield (not shown in Scheme 3).



Scheme 3. Synthesis of ACC auxiliary **13**.

As indicated above (Table 1), our original study of the α-alkylation of **17** gave *er*s of up to 96:4.[10] However, subsequent theoretical calculations conducted in collaboration with the Houk group[11] in an effort to confirm our proposed stereochemical model,[10] suggested that the level of asymmetric induction in the alkylation of **17** should have been even greater than we had originally observed. Consequently, we reinvestigated the allylation reaction for auxiliaries **13**-**16** and found that, indeed, in each case the selectivity was better than we had initially found.[19] To do this, we analyzed the level of diastereoselectivity of the allylation products (**21**-**24**) of each ACC hydrazone (**17**-**20**, respectively), and compared that to the level of enantioselectivity of the allylated ketone product (**12**), following hydrolysis of the auxiliary.[20] As it turned out, epimerization at the new stereogenic center was occurring during auxiliary removal. To address this problem, we carried out a survey of auxiliary cleavage conditions using **32** (prepared in the same manner as **21**, but using benzyl bromide), in the hope of being able to remove the auxiliary without causing epimerization (Table 2).[21] After some experimentation we were able to find suitable conditions [*p*-TsOH·H_2O, acetone-H_2O (4:1)] that did not compromise the new stereogenic center, yet gave the desired ketone in excellent yield.

Table 2. Studies on the hydrolysis of ACC hydrazone **32**.

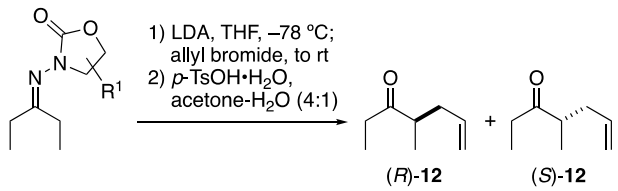


entry	conditions	equiv.	solvent	time (h)	conversion (%)	(*R*)-**33**:(*S*)-**33***
1	*p*-TsOH•H_2O	2	acetone	0.25	>99	97:3
2	*p*-TsOH•H_2O	2	acetone-H_2O (4:1)	3	>99	>99:1
3	*p*-TsOH•H_2O	2	THF-H_2O (4:1)	24	81	98:2
4	BF_3•OEt_2	2	acetone-H_2O (4:1)	12	>99	>99:1
5	$CuCl_2$	1.2	THF-H_2O (4:1)	24	0	na
6	$Cu(OAc)_2$	2	THF-H_2O (4:1)	24	0	na
7	HO_2CCO_2H	2	THF-H_2O (4:1)	24	0	na
8	$NH_4H_2PO_4$	20	THF-H_2O (4:1)	24	0	na
9	10% HCl	2	acetone	24	>99	95:5
10	10% HCl	2	THF	3	88	98:2
11	AcOH	2	acetone-H_2O (4:1)	24	>99	98:2

*Determined by chiral HPLC analysis.

Using these new auxiliary cleavage conditions, the α-allylated ketone (**12**) formed using auxiliaries **13**-**16** could be obtained with *er*s that were a true reflection of the asymmetric induction of each auxiliary (Table 3).[21] In all cases, the level of asymmetric induction was greater than in our original analysis, and was uniformly very high.

Table 3. Allylation and hydrolysis of ACC hydrazones **17-20** using epimerization-free hydrolysis conditions.



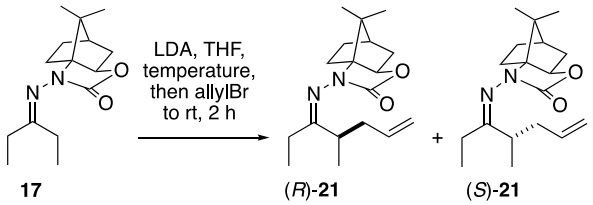
entry	ACC	hydrazone	allylated hydrazone	alkylation yield (%)	(*R*)-**12**:(*S*)-**12***	hydrolysis conversion (%)
1	**13**	**17**	**21**	98	99:1	>99
2	**14**	**18**	**22**	92	93:7	>99
3	**15**	**19**	**23**	93	97:3	>99
4	**16**	**20**	**24**	82	93:7	>99

*Determined by chiral GC analysis.

We next examined the effect of temperature on the alkylation selectivity using ACC hydrazone **17** (Table 4). To do this, **17** was treated with LDA at either –78, –40, –20, or 0 °C for 1 h, followed by addition of allyl bromide. After 5 min the cooling bath was removed and the mixture was allowed to stir for 30 min. Following work up, the ratio of allylated hydrazone diasteroemers [(*R*)-**21**–(*S*)-**21**] was determined by HPLC. In comparison to the result as –78 °C, the level of asymmetric induction was not diminished by increasing the reaction temperature up to –20 °C. However, the selectivity was comprised to a small extent when the reaction was carried out at 0 °C. We attribute the high diasteroselectivity at elevated temperatures to the stability of the five-membered chelate (*cf*. **4**, **9**) that forms following deprotonation of the hydrazone. The structure of this species bears

a strong resemblance to deprotonated hydroxamic acids and related compounds, which are well established as very strong cation chelators.[22] The ability to conduct the transformation with ACC hydrazones at elevated temperature is significant, as it creates the possibility of conducting large-scale enantioselective ketone α-alkylations for the first time. As a preliminary test of this, the allylation of **17** was carried out on a five gram scale at –20 °C, as described above, followed by hydrolysis using *p*-TsOH·H_2O, acetone-H_2O (4:1). This resulted in the production of **12** in 92% yield (over the two steps) with an *er* of >99:1.

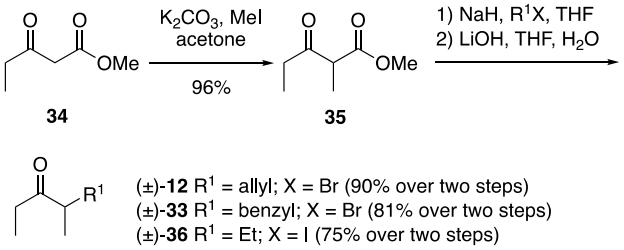
Table 4. Effect of temperature on the allylation of **17**.



entry	temperature (ºC)	(*R*)-**21**: (*S*)-**21***
1	–78	>99:1
2	–40	>99:1
3	–20	>99:1
4	0	97:3

*Determined by HPLC analysis.

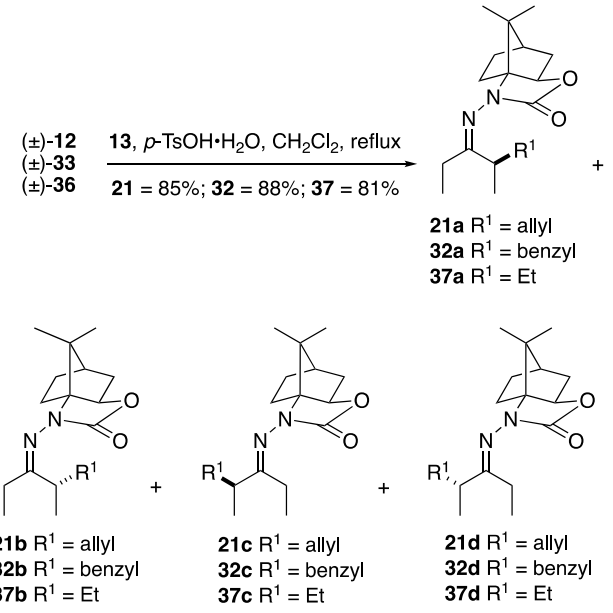
With suitable conditions available for the alkylation procedure, we set out to further refine the data from our preliminary study[10] and extend it to include new alkylating agents. We began by conducting a series of three alkylation reactions in a way that allowed us to further test that the new hydrolysis conditions established



Scheme 4. Synthesis of racemic **12**, **33**, and **36**.

above did not lead to epimerization during auxiliary removal. To do this, racemic 2-allyl-3-pentanone [(±)-**12**], 2-benzyl-3-pentanone [(±)-**33**], and 2-ethyl-3-pentanone [(±)-**36**] were prepared as outlined in Scheme 4. Each of these was condensed with **13** (Scheme 5), which generated a mixture of the four possible diastereomers (**21a-d**, **32a-d**, and **37a-d**, respectively). The chromatographically purified mixtures of diastereomers were analyzed by HPLC under conditions that gave near baseline resolution of the four diastereomers contained within each mixture. Next, **17** was allylated, benzylated, and ethylated using our standard conditions, and the crude reaction mixtures were analyzed under the same HPLC conditions (Table 5). In each instance, the ratio of α-alkylated diastereomers was >99:1, and the α'-alkylated diastereomers were not observed. The alkylated hydrazones were hydrolyzed and the enanitomer ratio of the resulting ketones was determined by either chiral GC or HPLC analysis.[21] In all cases the enantiomer ratio corresponded to the diastereomer ratio of the alkylated hydrazones. This further established that no appreciable epimerization was occurring during auxiliary cleavage. On the basis of these results, for subsequent alkylations the level of

asymmetric induction was determined only from the enantiomer ratio of the ketones produced, thereby simplifying the analysis process.

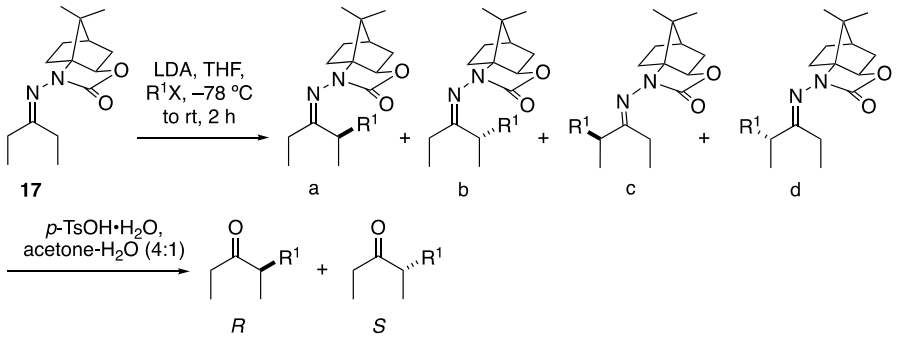


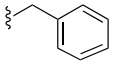
Scheme 5. Synthesis of diastereomers **21a-d**, **32a-d**, **37a-d**.

We continued exploring the scope of the transformation using hydrazone **17** and several different alkylating agents (Table 6). The electrophiles used varied from simple primary alkyl halides with or without bulky substituents, to a secondary alkyl halide. In addition, alkyl halides bearing other functional groups, such as protected alcohols, an epoxide, and an ester, were employed. In all cases, the alkylated hydrazones were obtained in very good to excellent yield. Hydrolysis produced the corresponding ketones with very good to excellent conversion,[21] and with generally excellent *er*s. The only complications that we encountered was

during the hydrolysis of **45** and **46**. Under the acidic conditions the silyl ether of compound **45** was also hydrolyzed, leading to hydroxy ketone **56**. Furthermore, the epoxide moiety of hydrazone **46** did not survive the hydrolysis step, and a complex mixture of products resulted.

Table 5. Diastereoselectivity and enantioselectivity for the alkylation of **17**.

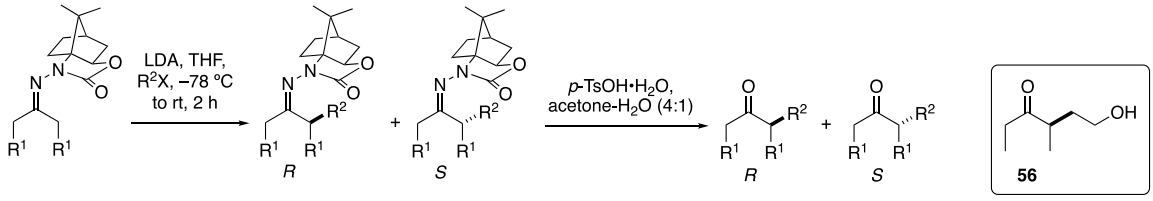


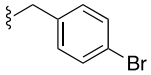
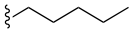
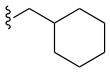
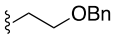
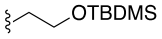
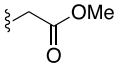
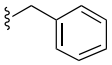
entry	R^1	X	alkylated hydrazone	alkylation regioselectivity α:α' [(a+b):[c+d)]	alkylated hydrazone *dr* (a:b)*	alkylation yield (%)	ketone	ketone *R*:*S*†	hydrolysis conversion (%)
1		Br	**21**	>99:1	>99:1	98	**18**	99:1	>99
2		Br	**32**	99:1	>99:1	97	**40**	99:1	>99
3		I	**37**	99:1	>99:1	92	**41**	99:1	>99

*Determined by HPLC analysis. †Determined by chiral GC or HPLC analysis.

We also tested the alkylation of cyclohexanone using ACC auxiliary **13** (Table 6). 2-Allyl cyclohexanone (**38**) was obtained in excellent yield and *er* (>99:1) from this process (Table 6, entry 10). The corresponding benzylation procedure gave a slightly lower *er* (96:4), but also good yield (entry 11).

Table 6. Alkylation of **17** and **38**.



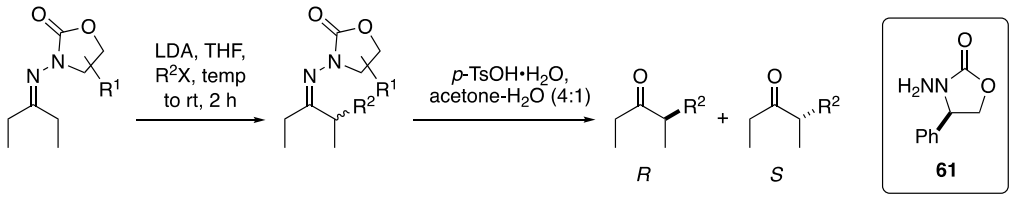
entry	R^1	hydrazone	R^2	X	alkylated hydrazone	alkylation yield (%)	ketone	ketone *R*:*S**	hydrolysis conversion (%)
1	Me	**17**		Br	**39**	92	**50**	>99:1	>99
2	Me	**17**		I	**40**	91	**51**	98:2	>99
3	Me	**17**		I	**41**	98	**52**	99:1	>99
4	Me	**17**		I	**42**	89	**53**	95:5	>99
5	Me	**17**		I	**43**	81	**54**	97:3	>99
6	Me	**17**		I	**44**	90	**55**	>99:1	>99
7	Me	**17**		I	**45**	90	**56**†	>99:1†	>99*
8	Me	**17**		Cl	**46**	97	**57**	n/a	n/a
9	Me	**17**		Br	**47**	99	**58**	99:1	61
10	-$(CH_2)_3$-	**38**		Br	**48**	94	**59**	>99:1	87
11	-$(CH_2)_3$-	**38**		Br	**49**	95	**60**	96:4	92

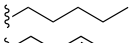
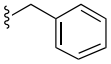
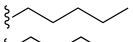
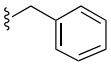
* Determined by chiral GC or HPLC analysis. †The silyl ether hydrolyzed during auxiliary cleavage to give **56**.

In our original ACC alkylation study, we had investigated phenylalanine-derived auxiliary **14** in the allyaltion of 3-pentanone, but found that it gave relatively poor selectivity (*er* = 76:24) in comparison to auxiliary **13** (*er* = 96:4). However, as indicated in Table 3, using the new hydrolysis conditions we developed (*vide supra*), the enantioselectivity for auxiliary **14** was found to be significantly higher (*er* = 97:3).[19] As part of that study we also found that the phenylglycine-derived auxiliary (**61**) gave even higher levels of asymmetric induction (*er* = 3:97) in

the allylation of 3-pentanone (Table 7, entry 5). Given the relatively simple structure of auxiliaries **14** and **61**, along with their corresponding ease of accessibility in comparison to **13**,[16] we wanted to determine if one or both of them might prove to be a viable alternative to the use of **13**. As such, 3-pentanone was alkylated using both **14** and **61**, along with three different alkylating agents (Table 7). For each alkylation tried, the phenylglycine-derived hydrazone (**62**) gave excellent levels of asymmetric induction (*er* = 3:97 to 2:98). The phenylalanine-derived auxiliary produced enantiomer ratios of 95:5 to 93:7. The allylation reaction was also tried at –20 and 0 °C using both **18** and **62** (Table 7, entries 8–11), as had been done previously for hydrazone **17** (Table 4). As with **17**, for both **18** and **62** the selectivity remained equally high at –20 °C, but dropped off slightly at 0 °C. Conveniently, both the *R* and *S* forms of the phenylglycine- and phenylalanine-derived oxazolidinones are commercially available and inexpensive.[23] So, while neither auxiliary **14** or **61** outperformed **13** in the alkylations, given the ease and low cost of their production, they are likely to prove useful in certain synthetic applications.

Table 7. Enantioselectivity for the alkylation of **18** and **62**.



entry	ACC	ACC hydrazone	R^2	X	temp (ºC)	alkylated hydrazone	alkylation yield (%)	ketone	ketone *R*:*S**	hydrolysis conversion (%)
1	**14**	**18**		Br	–78	**22**	92	**12**	93:7	>99
2	**14**	**18**		Br	–78	**63**	98	**52**	95:5	>99
3	**14**	**18**		Br	–78	**64**	95	**33**	93:7	>99
5	**61**	**62**		Br	–78	**65**	93	**12**	3:97	>99
6	**61**	**62**		I	–78	**66**	94	**52**	3:97	>99
7	**61**	**62**		Br	–78	**67**	97	**33**	2:98	>99
8	**14**	**18**		Br	–20	**22**	95	**12**	94:6	>99
9	**61**	**62**		Br	–20	**65**	94	**12**	4:96	>99
10	**14**	**18**		Br	0	**22**	92	**12**	91:9	>99
11	**61**	**62**		Br	0	**65**	93	**12**	7:93	>99

* Determined by chiral GC or HPLC analysis.

Conclusion

In conclusion, we have established that ACC auxiliaries **13**, **14**, and **61** are capable of effecting asymmetric α-alkylation with excellent enantioselectivity and yield. The transformations are highly reliable and easy to carry out. For each auxiliary the allylation reaction can be conducted at temperatures up to –20 °C without compromising asymmetric induction. While auxiliary **13** is clearly superior to all other auxiliaries we have tested, both auxiliary **14** and **61** also deliver

synthetically useful levels of asymmetric induction, and have the advantage of being relatively easy and inexpensive to produce in comparison to **13**.

Experimental Section

General Considerations. Unless stated to the contrary, where applicable, the following considerations apply. Reactions were carried out using dried solvents (see below) under a slight static pressure of Ar (pre-purified quality) that had been passed through a column (5 x 20 cm) of Drierite. Glassware was dried in an oven at 120 °C for at least 12 hours prior to use and then either cooled in a desiccator cabinet over Drierite or assembled quickly while hot, sealed with rubber septa, and allowed to cool under a stream of Ar. Reactions were stirred magnetically using Teflon-coated magnetic stirring bars. Teflon-coated magnetic stirring bars and syringe needles were dried in an oven at 120 °C for at least 12 h prior to use then cooled in a desiccator cabinet over Drierite. Hamilton microsyringes were dried in an oven at 60 °C for at least 24 h prior to used and cooled in the same manner. Commercially available Norm-Jet disposable syringes were used. Dry THF was obtained using an Innovative Technologies solvent purification system. Commercial grade solvents were used for routine purposes without further purification. *i*-Pr_2NH was distilled from CaH_2 under a N_2 atmosphere prior to use. Flash column chromatography was performed using silica gel 60 (230-400 mesh). ^1H and ^{13}C NMR spectra were recorded on a JEOL ECA-500 or ECX-400P spectrometer at ambient temperature. All ^1H chemical shifts are reported in ppm (δ) relative to TMS (0.00),

^{13}C shifts are reported in ppm (δ) relative to $CDCl_3$ (77.16). High-resolution Mass Spectrometry was acquired using an Agilent Technologies 6530 Accurate Mass Q-Tof LC/MS for electrospray ionization (ESI), or a Micromass Autospec Ultima for chemical ionization (CI). Chiral HPLC was performed on a 4.6 x 250 mm Chiralcel OD-H column (Chiral Technologies) using UV detection. Chiral GC was performed on a 20 m x 0.25 mm Chiraldex G-TA column (Advanced Separation Technologies), 40 m x 0.25 mm Chiraldex G-TA column (Advanced Separation Technologies), or 25 m x 0.25mm CP-Cyclodextrin-β-2,3,6-M-19 column (Agilent).

Synthesis of ACC auxiliaries

(1*S*)-(+)-Camphorsulfonyl chloride (26). Thionyl chloride (4.10g, 34.4mmol) was added dropwise with vigorous stirring to a flask containing *l*-10-camphor sulfonic acid (2.01g, 8.61mmol). The resulting mixture was stirred at reflux for 30 min and then allowed to cool and poured over ice. The slurry was partitioned between Et_2O and water and the aqueous phase was extracted with Et_2O (2 x 25 mL), dried ($MgSO_4$), and concentrated in vacuo to yield **26** as a white solid (2.07g; 96%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.30 (d, *J* = 14.7 Hz, 1H), 3.72 (d, *J* = 14.7, 1H), 2.49-2.40 (m, 2H), 2.17-2.12 (t, *J* = 4.6 Hz, 1H), 2.12-2.05 (m, 1H), 1.99 (d, *J* = 18.8 Hz, 1H), 1.80-1.73 (m, 1H), 1.51-1.42 (m, 1H), 1.13 (s, 3H), 0.92 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 212.9, 64.3, 59.8, 48.3, 42.9, 42.4, 27.0, 25.4, 19.9, 19.8. Spectroscopic data was consistent with that previously reported.[24]

(+)-10-Chlorocamphor-10-sulfine (27). A solution of tosyl chloride (186.2 g, .975 mol) in pyridine (216 mL, 2.66 mol) was heated to 100 °C and a solution of *l*-10-camphor sulfonyl chloride (222.2 g, 0.89 mol) in 1,2-dichloroethane (250 mL) was added dropwise over *ca*. 30 min. Upon completion of addition, the reaction was refluxed for 45 min then allowed to cool before being poured into Et_2O (2 L). The resulting dark brown precipitate was then isolated (Et_2O solution saved) and washed with Et_2O (500 mL). The combined organic solutions were then concentrated in vacuo to yield a dark-brown oil. Recrystallization from hexanes yielded **27** as tan crystals (161.6 g; 78%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.63-2.59 (d, *J* = 18.3 Hz, 1H), 2.53-2.48 (t, *J* = 13.8 Hz, 1H), 2.25-2.24 (t, *J* = 4.6 Hz, 1H), 2.17-2.12 (m, 1H), 2.06 (d, *J* = 18.9 Hz, 1H), 1.75-1.70 (m, 1h), 1.54 (td, *J* = 9.7, 2.3 Hz, 1H), 1.13 (s, 3H), 1.1 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 209.3, 181.7, 66.8, 52.0, 44.1, 43.6, 27.6, 27.0, 21.7, 20.1. Spectroscopic data was consistent with that previously reported.[25]

(+)-Ketopinic acid chloride (28). A solution of (+)-10-chlorocamphor-10-sulfine (49.8 g, 211 mmol) in CH_2Cl_2 (625 mL) and pyridine (22.0 mL, 221 mmol) was cooled to –78 °C and treated with ozone until a pale blue solution was observed. The reaction mixture was then partitioned between Et_2O and water, and the aqueous layer was extracted with Et_2O (2 x 100 mL), dried ($MgSO_4$), and concentrated in vacuo to yield **28** as a brown oil. Thionyl chloride (15.4 mL, 211 mmol) and pyridine (0.3 mL, 4 mmol) were then added and the resulting mixture was refluxed for 2h. It was then allowed to cool before benzene was added and the solution concentrated

in vacuo to yield (+)-ketopinic acid chloride (**28**) as a brown solid (39.4 g; 93%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.61-2.53 (m, 1H), 2.52-2.45 (m, 1H), 2.16-1.97 (m, 4H), 1.51-1.41 (m, 1H), 1.17 (d, *J* = 9.6 Hz, 6H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 207.6, 172.1, 76.0, 50.5, 44.3, 43.9, 28.5, 26.4, 21.1, 19.7. Spectroscopic data was consistent with that previously reported.[25]

(+)-1-Isocyanato-7,7-dimethylbicyclo[2.2.1]heptan-2-one (29). A solution of (+)-ketopinic acid chloride (**28**) (4.832g, 24.1 mmol) in acetone (100 mL) was added dropwise over *ca*. 60 min to a stirred solution of sodium azide (4.684 g, 72.1 mmol) in water (100 mL) that was cooled to 0 °C. The reaction was warmed to rt and stirred for 3 h. The solution was then partially concentrated in vacuo, diluted with H_2O, and extracted with Et_2O (3 x 50 mL). The combined organic layers were then washed with 5 % $NaHCO_3$ (2 x 50 mL), dried ($MgSO_4$), and concentrated in vacuo to yield the crude acyl azide. The acyl azide was dissolved in toluene (50 mL), refluxed for 3 h, and then concentrated to yield **29** as a brown solid (4.31 g; >99%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.45 (d, *J* = 18.4 Hz, 1H), 2.12-1.95 (m, 4H), 1.67-1.65 (m, 1H), 1.47-1.45 (m, 1H), 1.04 (s, 3H), 0.90 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 211.6, 128.6, 76.2, 47.3, 41.6, 40.2, 28.5, 26.8, 18.9, 18.7. Spectroscopic data was consistent with that previously reported.[26]

(6*R*,7a*R*)-8,8-Dimethylhexahydro-2*H*-3a,6-methanobenz-o[*d*]oxazol-2-one (30). $CeCl_3 \cdot 7H_2O$ (0.7 g, 1.84 mmol) was added to a solution of isocyanate **29** (3.3 g, 18.4 mmol) in MeOH (135 mL) that was cooled to 0 °C. The solution was stirred at 0

°C for 10 min, and then cooled to –78 °C. $NaBH_4$ (0.99 g, 25.76 mmol) was then added in four portions over a period of *ca*. 20 min. The reaction was warmed to –40 °C and stirred for 2.5 h. After warming to rt, the solvent was evaporated to remove the majority of MeOH and the resulting mixture was diluted with H_2O (110 mL), extracted with EtOAc (3 x 250 mL), dried (MgSO4), and concentrated in vacuo to yield a tan powder. Recrystallization from EtOAc/hexanes yielded **30** as tan crystals (3.07 g; 92%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.67 (bs, 1H), 4.31 (dd, *J* = 8.1, 4.2 Hz, 1H), 2.30-2.25 (m, 1H), 2.01-1.83 (m, 4H), 1.32-1.21 (m, 2H), 1.03 (s, 3H), 0.97 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 161.1, 86.7, 69.6, 47.0, 42.2, 35.5, 27.2, 25.6, 19.3, 19.2. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{10}H_{15}NO_2Na$ 204.09950; Found 204.09970.

(6*R*,7a*R*)-3-Amino-8,8-dimethylhexahydro-2*H*-3a,6-methanobenzo[*d*]oxazol-2-one (13). KOtBu (0.727 g, 6.48 mmol) was added to a stirred solution of **30** (0.587 g, 3.24 mmol) in THF (32.4 mL). The mixture was stirred at rt for 3.5 h. Freshly prepared NH_2Cl[16] (32.4 mL, 4.86 mmol) was then added dropwise over *ca*. 10 min, and the reaction mixture was stirred for 3 h. The reaction was quenched with 1M $Na_2S_2O_3$ (7 mL). The aqueous phase was extracted with Et_2O (2 x 25 mL), and the combined organic layers were dried ($MgSO_4$), and concentrated in vacuo to yield crude **13** (0.642g, 93% conversion) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 4.15 (dd, *J* = 8.1, 4.1 Hz, 1H), 3.81 (s, 2H), 2.25-2.16 (m, 2H), 1.95-1.75 (m, 4H), 1.29-1.25 (m, 1H), 1.67 (s, 3H), 1.00 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 159.7,

82.9, 72.0, 47.2, 42.4, 34.8, 25.5, 25.0, 20.5, 19.1. Spectroscopic data was consistent with that previously reported.[10]

(6*R*,7a*R*)-8,8-Dimethyl-3-(pentan-3-ylideneamino)hexahy-dro-2*H*-3a,6-methanobenzo[*d*]oxazol-2-one (17). Crude **13** (0.642g, approx. 3.24 mmol) was dissolved in CH_2Cl_2 (11 mL). 3-pentanone (2.4 mL, 32.4 mmol) and *p*-TsOH·H_2O (0.04g, 0.194 mmol) were then added and the reaction mixture was stirred for 12 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the aqueous phase was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to yield a yellow oil. Flash chromatography over silica gel using 20:80 EtOAc-hexanes gave **17** (0.789g, 92% over two steps) as a white solid. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 4.25 (dd, *J* = 8.1, 4.0 Hz, 1H), 2.50-2.19 (m, 5H), 2.11-1.79 (m, 3H), 1.73 (t, *J* = 4.3 Hz, 1H), 1.30-1.24 (m, 1H), 1.23 (s, 3H), 1.15-1.07 (m, 7H), 1.05 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 181.1, 155.4, 82.9, 73.3, 48.0, 42.9, 35.5, 29.0, 26.6, 25.7, 25.2, 21.3, 19.2, 10.7, 10.4. Spectroscopic data was consistent with that previously reported.[10]

(6*R*,7a*R*)-3-Amino-8,8-dimethylhexahydro-2*H*-3a,6-methanobenzo[*d*]oxazol-2-onehydrochloride (31). Crude **13** (4.440 g) was dissolved in Et_2O (30 mL) and cooled to 0 °C. Freshly generated HCl gas was bubbled through the solution and HCl salt **31** immediately started to form as yellowish solid. This process was continued for 15 min and then the reaction mixture was filtered and washed with cold Et_2O (3

x 5 mL). Recrystalization from EtOH gave pure **31** as white powder (4.35 g, 82% yield over two steps). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 9.85 (bs, 3H), 4.40 (dd, *J* = 8.0, 4.1 Hz, 1H), 2.74-2.67 (m, 1H), 2.31-2.64 (m, 1H), 2.02-1.97 (m, 1H), 1.88 (dd, *J* = 13.8, 8.0 Hz, 1H), 1.83-1.81 (t, *J* = 4.1 Hz, 1H), 1.40-1.27 (m, 5H), 1.20 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 156.3, 85.5, 72.5, 47.1, 43.5, 34.9, 25.7, 25.3, 20.5, 19.2. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{10}H_{16}N_2O_2Na$ 219.11040; Found 219.1105.

(6*R*,7a*R*)-8,8-Dimethyl-3-(pentan-3-ylideneamino)hexahy-dro-2*H*-3a,6-methanobenzo[*d*]oxazol-2-one (17). To a suspension of **31** (0.506 g, 2.15 mmol) in benzene was added 3-pentanone (0.225 mL, 2.15 mmol), and the solution was heated to reflux for 12 h while attached to a Dean-Stark apparatus. The reaction was quenched with saturated $NaHCO_3$ (5 mL), and the aqueous phase was extracted with Et_2O (2 x 20 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo to yield a yellow oil. Flash chromatography over silica gel using 20:80 EtOAc-hexanes gave **17** (0.551 g, 97%) as a white solid. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 4.25 (dd, *J* = 8.1, 4.0 Hz, 1H), 2.50-2.19 (m, 5H), 2.11-1.79 (m, 3H), 1.73 (t, *J* = 4.3 Hz, 1H), 1.30-1.24 (m, 1H), 1.23 (s, 3H), 1.15-1.07 (m, 7H), 1.05 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 181.1, 155.4, 82.9, 73.3, 48.0, 42.9, 35.5, 29.0, 26.6, 25.7, 25.2, 21.3, 19.2, 10.7, 10.4. Spectroscopic data was consistent with that previously reported.[10]

(6*R*,7a*R*)-8,8-Dimethyl-3-(pentan-3-ylideneamino)hexahy-dro-2*H*-3a,6-methanobenzo[*d*]oxazol-2-one (17). **31** (0.567 g, 2.44 mmol) was dissolved in

CH_2Cl_2 (8 mL), 3-pentanone (2.6 mL, 24.4 mmol) was added, and the resulting mixture was stirred for 12 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the aqueous phase was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo to yield a yellow oil. Flash chromatography over silica gel using 20:80 EtOAc-hexanes gave **17** (0.61 g, 93%) as a white solid. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 4.25 (dd, *J* = 8.1, 4.0 Hz, 1H), 2.50-2.19 (m, 5H), 2.11-1.79 (m, 3H), 1.73 (t, *J* = 4.3 Hz, 1H), 1.30-1.24 (m, 1H), 1.23 (s, 3H), 1.15-1.07 (m, 7H), 1.05 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 181.1, 155.4, 82.9, 73.3, 48.0, 42.9, 35.5, 29.0, 26.6, 25.7, 25.2, 21.3, 19.2, 10.7, 10.4. Spectroscopic data was consistent with that previously reported.[10]

General procedure for the formation of hydrazones 18, 38, and 62

(*S*)-4-Benzyl-3-(pentan-3-ylideneamino)oxazolidin-2-one (18). Crude hydrazide **14**,[16] (0.26 g, 1.468 mmol) was dissolved in CH_2Cl_2 (5.2 mL). 3-pentanone (14.3 mL) and *p*-TsOH·H_2O (0.56, 2.94 mmol) were added, and the resulting mixture was stirred for 14 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to yield a yellow oil. Flash chromatography over silica gel using 20:80 EtOAc-hexanes gave **18** (0.34 g, 88%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.30-7.19 (m, 3H), 7.13-7.11 (m, 2H), 4.33- 4.25 (m, 1H), 4.22 (t, *J* = 8.2 Hz, 1H), 3.98 (t, *J* =

8.3 Hz, 1H), 3.09 (dd, *J* = 13.4, 4.3 Hz, 1H), 2.70 (dd, *J* = 13.6, 8.7 Hz, 1H), 2.49-2.30 (m, 4H), 1.11 (q, *J* = 7.0 Hz, 6H); **^{13}C NMR** ($CDCl_3$, 400 MHz): δ 181.9, 154.9, 135.6, 128.9, 128.5, 126.7. Spectroscopic data was consistent with that previously reported.[16]

(6*R*,7a*R*)-3-(Cyclohexylideneamino)-8,8-dimethylhexahy-dro-2*H*-3a,6-methanobenzo[*d*]oxazol-2-one (38). Crude hydrazide **13** and cyclohexanone were used for formation of **38**. Flash chromatography over silica gel using 20:80 EtOAc-hexanes gave **38** (0.195 g, 85%) as yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 4.23-4.21 (dd, *J* = 8.0, 4.0 Hz, 1H), 2.47-2.25 (m, 5H), 2.06-1.46 (m, 10H), 1.28-1.24 (m, 1H), 1.22 (s, 3H), 1.16-1.14 (m, 1H), 1.12 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 178.4, 156.4, 83.0, 73.1, 48.0, 42.9, 35.8, 35.4, 30.1, 27.5, 26.7, 26.6, 25.7, 21.4, 19.2. **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{16}H_{25}N_2O_2$ 277.19110; Found 277.19160.

(*R*)-3-(Pentan-3-ylideneamino)-4-phenyloxazolidin-2-one (62). Crude hydrazide **61**[16] and 3-pentanone were used for formation of **62**. Flash chromatography over silica gel using 20:80 EtOAc-hexanes gave **62** (0.261 g, 86%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.39-7.13 (m, 5H), 5.13 (dd, *J* = 10.3, 8.5 Hz, 1H), 4.32 (t, *J* = 8.7 Hz, 1H), 4.07 (dd, *J* = 10.1, 8.6 Hz, 1H), 2.51-2.69 (m, 4H), 1.03-0.95 (m, 6H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 182.3, 155.1, 136.9, 128.6, 127.8, 127.1, 68.8, 64.1, 28.1, 24.9, 10.8, 10.1. Spectroscopic data was consistent with that previously reported.[16]

Methyl-2-methyl-3-oxopentanoate (35). K_2CO_3 (25.8 g, 0.187 mol) was added to a solution of methyl-3-oxopentanoate (25 mL, 0.200 mol) in acetone (250 mL), and the mixture was stirred for 5 min. Methyl iodide (60.0 mL, 0.964 mol) was added dropwise over *ca*. 5 min, and stirring was continued for 10 min. The reaction mixture was refluxed for 12 h and allowed to cool to rt. Et_2O (250 mL) was added, the mixture was filtered, dried ($MgSO_4$), and evaporated under reduced pressure to give a yellow liquid (27.1 g, 94%). The crude material was used directly in the next transformation. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 3.61 (s, 3H), 3.46-3.41 (q, *J* = 7.3 Hz, 1H), 2.51-2.39 (m, 2H), 1.22-1.19 (d, *J* = 6.9 Hz, 3H), 0.95-0.90 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 205.1, 169.9, 51.0, 49.8, 33.5, 11.7, 6.8. Spectroscopic data was consistent with that previously reported.[27]

General procedure for the synthesis of racemic mixtures of alkylated ketones

2-Allyl-3-pentanone [(±)-12]. Step 1: NaH (0.099 g, 4.13 mmol) was added to a cooled (ice-H_2O bath) and stirred solution of **35** (0.5 mL, 3.44 mmol) in THF (7.0 mL), and stirring was continued for 10 min. Allyl bromide (0.60 mL, 6.89 mmol) was added dropwise over *ca*. 2 min. Stirring was continued for 3 h, the cold bath was removed, and stirring was continued for an additional 12 h. The reaction mixture was partitioned between saturated aqueous NH_4Cl (5 mL) and Et_2O (5 mL). The aqueous phase was extracted with Et_2O (2 x 5 mL) and the combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo

to yield a colorless liquid (0.59 g, 93%) that was used in the next step without further purification. Step 2: LiOH (0.35 g, 14.4 mmol) was added to a stirred solution of the above crude material (0.59 g, approx. 3.19 mmol) in 3:1 THF-H_2O (18 mL THF and 6 mL H_2O). The resulting suspension was stirred at reflux for 12 h, and then allowed to cool to rt before acidifying with 1.0 M HCl to ~pH 1–2. The mixture was then extracted with Et_2O (2 x 10 mL), dried ($MgSO_4$), and evaporated under weakly reduced pressure (400 torr) to give a pale-yellow liquid. Flash chromatography over silica gel using 2:98 Et_2O-pentane gave (±)-**12** as a colorless liquid (0.36 g, 90%). Spectroscopic data was consistent with that obtained for **12** using the method described above corresponding to Table 5.

2-Methyl-1-phenylpentan-3-one [(±)-33]. Flash chromatography over silica gel using 5:95 Et_2O-pentane gave (±)-**33** as a white solid (0.11 g, 81% over two steps). Spectroscopic data was consistent with that obtained for **33** using the method described in Table 5.

4-Methylhexan-3-one [(±)-36]. Flash chromatography over silica gel using 5:95 Et_2O-pentane gave (±)-**36** as a colorless liquid (1.31 g, 75% over two steps). Spectroscopic data was consistent with that obtained for **36** using the method described in Table 5.

1-(4-Bromophenyl)-2-methylpentan-3-one [(±)-50]. Flash chromatography over silica gel using 5:95 Et_2O-pentane gave (±)-**50** as a white solid (0.46 g, 82% over two

steps). Spectroscopic data was consistent with that obtained for **50** using the method described in Table 6.

4-Methylheptan-3-one [(±)-51]. Flash chromatography over silica gel using 5:95 Et_2O-pentane gave (±)-**51** as a colorless liquid (2.14 g, 71% over two steps). Spectroscopic data was consistent with that obtained for **51** using the method described in Table 6.

4-Methylnonan-3-one [(±)-52]. Flash chromatography over silica gel using 5:95 Et_2O-pentane gave (±)-**52** as a colorless liquid (1.15 g, 81% over two steps). Spectroscopic data was consistent with that obtained for **52** using the method described in Table 6.

1-Cyclohexyl-2-methylpentan-3-one [(±)-53]. Flash chromatography over silica gel using 5:95 Et_2O-pentane gave (±)-**53** as a colorless liquid (0.83 g, 79% over two steps). Spectroscopic data was consistent with that obtained for **53** using the method described in Table 6.

4,5-Dimethylhexan-3-one [(±)-54]. Flash chromatography over silica gel using 5:95 Et_2O-pentane gave (±)-**54** as a colorless liquid (0.83 g, 77% over two steps). Spectroscopic data was consistent with that obtained for **54** using the method described in Table 6.

6-(Benzyloxy)-4-methylhexan-3-one [(±)-55]. Flash chromatography over silica gel using 30:70 EtOAc-hexane gave (±)-**55** as a colorless solid (0.19 g, 82% over two steps). Spectroscopic data was consistent with that obtained for **55** using the method described in Table 6.

6-Hydroxy-4-methylhexan-3-one [(±)-56]. Flash chromatography over silica gel using 70:30 Et_2O-pentane gave (±)-**56** as a colorless solid (1.71 g, 77% over two steps). Spectroscopic data was consistent with that obtained for **56** using the method described in Table 6.

Ethyl 3-methyl-4-oxohexanoate [(±)-58]. A solution of 3-pentanone (0.03 mL, 0.28 mmol) in THF (2.8 mL) was added dropwise over *ca*. 2 min to a stirred solution of freshly prepared LDA (0.25 M, 2.30 mL, 0.57 mmol), rinsed with additional THF (2 x 0.5 mL), and the mixture was stirred for 1 h. Freshly distilled methyl bromoacetate (50 μL, 0.48 mmol) was then added and the mixture was stirred for 5 min at –78 °C. The cold bath was removed and the mixture was stirred for an additional 20 min. It was then partitioned between Et_2O and H_2O. The aqueous phase was extracted with Et_2O (2 x 2mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated under weakly reduced pressure (400 torr) to give crude **58**. ^1H NMR and chiral GC chromatography showed a 61% conversion of 3-pentanone to **58**. Spectroscopic data was consistent with that obtained for **58** using the method described in Table 6.

General procedure of the synthesis of diastereomeric mixtures of alkylated 3-pentanone hydrazones derived from ACCs

Diastereomeric Mixture of (6*R*,7a*R*)-8,8-dimethyl-3-(2-methyl-1-phenylpentan-3-ylidene)amino)hexahydro-2*H*-3a,6-methanobenzo[*d*]oxazol-2-one (32a, 32b, 32c, 32d). *p*-TsOH·H_2O (0.022 mg, 0.12 mmol) was added to a stirred solution of (±)-**33** (0.515 g, 2.92 mmol) and **13** (0.459 g, 2.34 mmol) in CH_2Cl_2 (11.7 mL). The mixture was refluxed for 18 h, cooled to rt, and then partitioned between CH_2Cl_2 (50 mL) and saturated aqueous $NaHCO_3$ (20 mL). The organic phase was washed with brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo to yield a white solid. Flash chromatography over silica gel using 20:80 EtOAc-hexanes gave a mixture of four diastereomers, **32a**, **32b**, **32c**, **32d,** as white solid (0.12 g, 88%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.32-7.13 (m, 35H), 4.24 (q, 1H), 3.03-2.20 (m, 27H), 2.00-1.62 (m, 6H), 1.26-0.90 (m, 45H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 208.4, 183.3, 173.2, 154.6, 141.0, 136.6, 130.2, 129.4, 129.2, 128.3, 128.2, 126.9, 126.0, 82.9, 82.8, 77.5, 77.2, 77.0, 60.7, 52.4, 42.9, 41.5, 40.8, 35.5, 35.4, 32.1, 25.8, 25.7, 19.3, 19.2, 10.7, 10.4, 8.2. **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{22}H_{31}N_2O_2$ 355.2386; Found 355.2383.

Diastereomeric mixture of (6*R*,7a*R*)-8,8-dimethyl-3-(4-methylhept-6-en-3-ylidene)amino)hexahydro-2*H*-3a,6-methanobenzo[*d*]oxazol-2-one (21a, 21b, 21c, 21d) was prepared from (±)-**12.** Flash chromatography over silica gel using 20:80 EtOAc-hexanes gave a mixture of four diastereomers, **21a**, **21b**, **21c**, **21d**,

(0.78 g, 85%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 5.89-5.51 (m, 1H), 5.08-4.91 (m, 2H), 4.27-4.22 (m, 1H), 3.20-2.58 (m, 1H), 2.58-1.74 (m, 10H), 1.30-0.94 (m, 11H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 184.2, 183.7, 183.4, 182.2, 155.4, 155.2, 154.9, 154.7, 136.9, 136.5, 136.4, 135.9, 116.5, 116.3, 116.2, 116.0, 82.8, 82.7, 73.2, 73.16, 73.13, 47.8, 47.7, 42.9, 42.84, 42.8, 39.6, 39.5, 39.3, 39.1, 38.1, 37.4, 35.6, 35.4, 35.3, 34.9, 29.7, 26.7, 26.5, 26.4, 25.7, 25.65, 25.6, 24.7, 24.6, 24.5, 24.1, 21.4, 21.32, 21.3, 19.2, 19.13, 19.1, 17.7, 17.14, 17.1, 10.6, 10.4, 10.2, 10.0. **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{18}H_{29}N_2O_2$ 305.2231; Found 305.2233. Spectroscopic data was consistent with that previously reported.[19]

Diastereomeric Mixture of (6*R*,7a*R*)-3-(1-(4-bromophenyl)-2-methylpentan-3-ylidene)amino)-8,8-dimethylhexahydro-2*H*-3a,6-methanobenzo[*d*]oxazol-2-one (37a, 37b, 37c, 37d) was prepared from (±)-**36**. Flash chromatography over silica gel using 20:80 EtOAc-hexanes gave a mixture of four diastereomers, **37a**, **37b**, **37c**, **37d**, (0.08 g, 81%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 500 MHz): 4.22 (dd, *J* = 8.3, 4.1 Hz, 1H), 2.49-2.16 (m, 4H), 2.04-1.89 (m, 2H), 1.83 (dd, *J* = 13.4, 7.6 Hz, 1H), 1.74-1.57 (m, 2H), 1.46-0.72 (m, 19H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 184.4, 183.2, 180.7, 180.4, 155.3, 155.2, 155.1, 155.0, 82.9, 82.8, 73.2, 48.0, 47.9, 42.9, 41.6, 41.1, 35.5, 27.9, 26.8, 26.6, 25.8, 24.6, 21.4, 19.2, 19.2, 17.8, 11.9, 11.4, 10.8, 10.7. **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{17}H_{29}N_2O_2$ 293.2228; Found 293.2226.

General procedure for conversion of alkyl bromides to alkyl iodides

(Iodomethyl)cyclohexane (68). NaI (10.8 g, 71.7 mmol) was added to (bromomethyl)cyclohexane (6.35 g, 35.8 mmol) in acetone (45 mL). The reaction mixture was stirred at reflux for 48 h and then partitioned between water and Et_2O. The aqueous phase was extracted with Et_2O (2 x 20 mL) and the combined organic extracts were dried ($MgSO_4$), and concentrated in vacuo to yield crude **68**.[28] Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave a colorless liquid (6.98 g, 87%). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 3.08 (t, *J* = 3.4 Hz, 2H), 1.86-1.83 (m, 2H), 1.72-1.69 (m, 2H), 1.61-1.58 (m, 1H), 1.42-1.40 (m, 1H), 1.23-1.10 (m, 3H), 1.00-0.89 (m, 2H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 40.1, 33.6, 31.8, 26.2, 26.1, 26.0, 16.4. **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_7H_{14}I$ 225.0123; Found 225.0122.

Benzyl 2-iodoethyl ether (69) was obtained from benzyl 2-bromoethyl ether. Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave a colorless liquid (2.67 g, 85%). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.45-7.31 (m, 5H), 4.59 (s, 2H), 3.75 (t, *J* = 6.3 Hz, 2H), 3.29 (t, *J* = 6.3 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 138.0, 128.4, 128.0, 127.8, 72.9, 70.8, 3.0. Spectroscopic data was consistent with that previously reported.[28]

(2-Iodoethoxy)-tert-butyldimethylsilane (70) was obtained from (2-bromoethoxy)-*tert*-butyldimethylsilane. Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave a colorless liquid (2.41 g, 81%). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 3.83 (t, *J* = 7.5 Hz, 2H), 3.20 (t, *J* = 6.9 Hz, 2H), 0.90 (s, 9H), 0.07 (s, 6H); **^{13}C**

NMR ($CDCl_3$, 125 MHz): δ 64.3, 26.0, 18.4, 7.2. Spectroscopic data was consistent with that previously reported.[29]

General procedure for hydrazone alkylation of 3-pentanone hydrazones

Hydrazone 32. Lithium diisopropylamide (LDA) was prepared by adding *n*-BuLi (2.50 M in hexanes, 0.5 mL, 1.25 mmol) dropwise over *ca*. 2 min to a stirred and cooled (–78 °C) solution of diisopropylamine (0.19 mL, 1.38 mmol) in THF (4.31 mL). The mixture was transferred to an ice-H_2O bath, stirred for 30 min, and then cooled to –78 °C. A solution of **17** (0.082 g, 0.31 mmol) in THF (3.1 mL) was added dropwise over *ca*. 2 min to a stirred solution of LDA (0.25 M, 1.5 mL, 0.37 mmol), and rinsed with additional THF (2 x 0.5 mL), and the mixture was stirred for 1 h. Freshly distilled benzyl bromide (63 μL, 0.53 mmol) was then added and the mixture was stirred for 5 min at –78 °C. The cold bath was removed and the mixture was stirred for an additional 20 min. It was then partitioned between Et_2O (1 mL) and H_2O (2 mL). The aqueous phases was extracted with Et_2O (2 x 3mL), and the combined organic extracts were washed with brine (3 mL), dried ($MgSO_4$), and concentrated in vacuo to yield crude **32**. The crude material was purified via flash chromatography over silica gel using 20:80 EtOAc-hexane to give **32** as a white solid (0.11 g, 97%). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.46-7.04 (m, 5H), 4.24 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.22-3.07 (m, 2H), 2.48-2.30 (m, 3H), 1.98-1.76 (m, 4H), 1.28-1.03 (m, 12H), 0.86 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 183.5, 155.4, 140.1, 129.7, 128.3, 126.1, 82.9, 73.3, 47.9, 43.0, 39.1, 37.8, 35.5, 26.6, 25.7, 24.9, 21.4, 19.2, 16.5,

10.4. **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{22}H_{31}N_2O_2$ 355.2386; Found 355.2383. HPLC analysis of **32** showed an α:α' ratio of 99:1 and a *dr* of >99:1 [determined by HPLC, chiral OD-H column, 1:99 *i*-PrOH-hexanes, 1 mL/min, λ= 254 nm, t_a = 8.055 min, t_b =11.766 min, t_c or t_d = 13.812 or 15.963 min].

Hydrazone 21. Freshly distilled allyl bromide (1.7 equiv) was used as the alkylating agent. **21** was obtained as light-yellow oil (0.093 g, 98% yield). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 5.87-5.69 (m, 1H), 5.15-4.91 (m, 2H), 4.25 (dd, *J* = 8.1, 4.1 Hz, 1H), 3.16-3.01 (m, 1H), 2.48-2.22 (m, 4H), 2.12-1.78 (m, 4H), 1.75 (t, *J* = 4.4 Hz, 1H), 1.23-1.30 (m, 2H), 1.20 (s, 3H), 1.15 (s, 3H), 1.11 (t, *J* = 7.2 Hz, 3H), 0.92 (d, *J* = 7.0 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 184.1, 155.2, 136.4, 116.3, 82.5, 73.1, 47.6, 42.9, 37.5, 35.3, 34.9, 26.4, 25.5, 24.4, 21.3, 19.1, 17.0, 10.1. **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{18}H_{29}N_2O_2$ 305.2231; Found 305.2233. HPLC analysis of **21** showed an α:α' ratio of >99:1 and a *dr* of >99:1 [determined by HPLC, chiral OD-H column, 0.5:99.5 *i*-PrOH-hexanes, 0.5 mL/min, λ= 254 nm, t_a = 15.642 min, t_c or t_d =19.379 min]. Spectroscopic data is consistent with that previously reported.[19]

Hydrazone 37. Freshly distilled ethyl iodide (15 equiv) was used as the alkylating agent. **37** was obtained as light-yellow oil (0.094 g, 92%). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 4.21 (dd, *J* = 8.2, 4.1 Hz, 1H), 2.94-2.85 (m, 1H), 2.48-2.17 (m, 3H), 1.92-1.54 (m, 5H), 1.34-1.02 9m, 12H), 0.91-0.78 (m, 6H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 185.8, 155.6, 82.4, 73.4, 47.8, 42.9, 36.9, 35.5, 26.6, 25.6, 24.5, 21.4, 19.2, 17.5, 12.3, 10.4. **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{17}H_{29}N_2O_2$ 293.2229; Found 293.2226.

HPLC analysis of **37** showed an α:α' ratio of 98:2 and a *dr* of >99:1 [determined by HPLC, chiral OD-H column, 2:98 *i*-PrOH-hexanes, 1 mL/min, λ= 254 nm, t_a = 7.348 min, t_b = 6.369, t_c or t_d =6.032 or 6.772 min].

Hydrazone 39. Freshly distilled 4-bromobenzyl bromide (1.7 equiv) was used as the alkylating agent. **39** was obtained as white solid (0.85 g, 92%). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.35 (d, *J* = 8.2 Hz, 2H), 7.12 (d, *J* = 7.3 Hz, 2H), 4.24 (dd, *J* = 8.0, 3.7 Hz, 1H), 3.13-3.07 (m, 2H), 2.49-2.29 (m, 3H), 2.01-2.76 (m, 4H), 1.31-1.00 (m, 12H), 0.84 (d, *J* = 6.9, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 182.8, 155.4, 139.1, 131.5, 131.4, 120.0, 83.0, 73.4, 53.5, 48.0, 43.0, 38.6, 37.7, 35.6, 26.6, 25.7, 24.8, 21.4, 19.2, 16.4, 10.3. **HRMS (ESI-TOF)** m/z: $[M]^+$ Calcd for $C_{22}H_{29}BrN_2O_2$ 434.1392; Found 434.1405.

Hydrazone 40. Freshly distilled 1-iodo propane (15 equiv) was used as the alkylating agent. **40** was obtained as light-yellow oil (0.12 g, 91%). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 4.22 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.03-2.94 (m, 1H), 2.33-2.19 (m, 3H), 1.92-1.86 (m, 2H), 1.81 (dd, *J* = 13.8, 8.0 Hz, 1H), 1.71 (t, *J* = 4.0 Hz, 1H), 1.55-1.49 (m, 1H), 1.39-1.25 (m, 1H), 1.29-1.06 (m, 13H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.86-0.83 (m, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 185.8, 155.6, 82.8, 73.4, 47.8, 42.9, 35.6, 35.5, 35.2, 26.6, 25.7, 24.5, 21.4, 20.8, 19.2, 17.9, 14.3, 10.4. **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{18}H_{31}N_2O_2$ 307.2386; Found 307.2383.

Hydrazone 41. Freshly distilled 1-iodo pentane (1.7 equiv) was used as the alkylating agent. **41** was obtained as light-yellow oil (0.13 g, 98%); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 4.23 (dd, *J* = 8.3, 4.6 Hz, 1H), 3.03-2.96 (m, 1H), 2.38-2.20 (m, 3H), 1.95-1.54 (m, 5H), 1.39-1.21 (m, 8H), 1.20 (s, 3H), 1.15 (s, 3H), 1.12 (t, *J* = 7.5 Hz, 4H), 0.94-0.91 (d, *J* = 6.9 Hz, 3H), 0.85 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 185.8, 155.6, 82.9, 73.4, 47.9, 42.9, 35.5, 35.4, 33.3, 32.1, 27.3, 26.6, 25.7, 24.6, 22.6, 21.4, 19.3, 17.9, 14.2, 10.4. **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{20}H_{35}N_2O_2$ 335.2699; Found 335.2702.

Hydrazone 42. Freshly prepared (see above) (iodomehyl)cyclohexane (**68**) (10 equiv) was used as the alkylating agent. **42** was obtained as light-yellow oil (0.86 g, 89%); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 4.23 (dd, *J* = 8.0, 4.6 Hz, 1H), 3.21-3.09 (m, 1H), 2.37-2.19 (m, 3H), 1.95-1.56 (m, 10H), 1.45-1.40 (m, 1H), 1.27-1.07 (m, 16H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.88-0.77 (m, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 186.3, 155.7, 82.8, 73.4, 47.9, 42.9, 35.5, 35.0, 34.4, 32.9, 32.3, 26.6, 26.5, 26.4, 26.3, 25.7, 24.8, 21.4, 19.3, 17.9, 10.5. **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{22}H_{37}N_2O_2$ 361.2855; Found 361.2856.

Hydrazone 43. Freshly distilled 2-iodopropane (15 equiv) was used as the alkylating agent. **43** was obtained as light-yellow oil (0.059 g, 81%). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 4.31 (dd, *J* = 8.1, 3.9 Hz, 1H), 2.82-2.75 (m, 1H), 2.47-2.33 (m, 3H), 2.00-1.65 (m, 4H), 1.39-1.13 (m, 12H), 1.03-0.87 (m, 9H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 187.6, 156.1, 82.9, 73.8, 47.9, 43.0, 42.5, 35.6, 30.6, 26.8, 25.8, 25.0, 22.0, 21.5, 20.5,

19.4, 16.9, 10.8. **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{18}H_{31}N_2O_2$ 307.2386; Found 307.2379.

Hydrazone 44. Freshly prepared (see above) benzyl 2-iodoethyl ether (**69**) (6.5 equiv) was used as the alkylating agent. **44** was obtained as light-yellow oil (0.11 g, 90%). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.37-7.24 (m, 5H), 4.48 (q, *J* = 11.5 Hz, 2H), 4.21 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.53 (t, *J* = 6.9 Hz, 2H), 3.22-3.15 (m, 1H), 2.37 (q, *J* = 7.5 Hz, 2H), 2.32-2.28 (m, 1H), 2.02-1.91 (m, 2H), 1.84 (dd, *J* = 13.5, 8.0 Hz, 1H), 1.75 (t, *J* = 4.0 Hz, 1H), 1.66-1.58 (m, 1H), 1,33-1.25 (m, 1H), 1.21 (s, 3H), 1.16 (s, 3H), 1.13 (t, *J* = 6.9 Hz, 4H), 1.0 (d, *J* = 6.9, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 184.5, 155.2, 138.7, 128.4, 127.9, 127.8, 127.5, 83.0, 73.3, 73.1, 68.2, 47.9, 42.9, 36.3, 35.5, 35.3, 26.6, 25.8, 25.1, 24.7, 21.5, 19.3, 18.9, 10.7. **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{24}H_{33}N_2O_3$ 399.2648; Found 399.2655.

Hydrazone 45. Freshly prepared (see above) (2-iodoethoxy)-*tert*-butyldimethylsilane (**70**) (6.5 equiv) was used as the alkylating agent. **45** was obtained as light-yellow oil (0.097 g, 90%). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 4.22 (dd, *J* = 7.8, 4.1 Hz, 1H), 3.67-3.58 (m, 2H), 3.15-3.08 (m, 1H), 2.39-2.27 (m, 3H), 1.96-1.81 (m, 4H), 1.74 (t, *J* = 3.7 Hz, 1H), 1.57-1.50 (m, 1H), 1.28-1.10 (m, 10H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 185.0, 155.5, 82.9, 73.4, 61.8, 47.8, 44.5, 43.0, 36.2, 35.5, 32.4, 26.6, 26.0, 25.7, 24.7, 21.4, 19.3, 18.4, 18.1. **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{23}H_{43}N_2O_3Si$ 423.3043; Found 423.3040.

Hydrazone 46. Freshly distilled (*R*)-epichlorohydrin (3 equiv) was used as the alkylating agent. **46** was obtained as light-yellow oil (0.17 g, 97%). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 4.24 (dd, *J* = 7.7, 4.0 Hz, 1H), 3.28-3.21 (m, 1H), 2.98-2.89 (m, 1H), 2.76 (t, *J* = 4.6 Hz, 1H), 2.49-2.26 (m, 4H), 2.03-1.72 (m, 5H), 1.44-0.96 (m, 15H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 183.5, 155.4, 83.0, 73.5, 50.7, 47.9, 43.0, 36.0, 35.5, 32.8, 26.6, 25.7, 24.8, 21.4, 19.2, 18.3. **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{18}H_{29}N_2O_3$ 321.2178; Found 321.2179.

Hydrazone 47. Freshly distilled methyl bromoacetate (1.7 equiv) was used as the alkylating agent. **47** was obtained as light-yellow oil (0.056 g, 99%). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 4.25 (dd, *J* = 8.1, 3.9 Hz, 1H), 3.63 (s, 3H), 2.77 (dd, *J* = 15.6, 3.9 Hz, 1H), 2.39-2.24 (m, 4H), 1.95-1.73 (m, 3H), 1.31-1.08 (m, 13H), 1.00 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 181.6, 172.3, 155.3, 82.8, 73.2, 51.7, 47.8, 42.9, 37.2, 35.3, 32.0, 26.4, 25.6, 24.9, 21.3, 19.1, 17.6, 10.2. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{18}H_{28}N_2O_4Na$ 359.19410; Found 359.19470.

Hydrazone 48. Freshly distilled allyl bromide (1.7 equiv) was used as the alkylating agent. **48** was obtained as light-yellow oil (0.028 g, 94%). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 5.74-5.65 (m, 1H), 5.11-4.97 (m, 2H), 4.25 (dd, *J* = 8.3, 4.0 Hz, 1H), 3.03-3.01 (m, H), 2.54-2.28 (m, 5H), 2.00-1.81 (m, 5H), 1.75-1.66 (m, 2H), 1.58-1.38 (m, 2H), 1.36-1.22 (m, 3H), 1.19-1.11 (m, 6H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 184.6, 156.2, 136.3, 116.9, 83.0, 73.4, 48.0, 42.9, 37.2, 35.4, 33.9, 32.6, 29.3, 28.5, 26.5, 25.7, 21.4,

20.0, 19.3. **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{19}H_{29}N_2O_2$ 317.22240; Found 317.22300.

Hydrazone 49. Freshly distilled benzyl bromide (1.7 equiv) was used as the alkylating agent. **49** was obtained as light-yellow oil (0.039 g, 95%). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.29-7.10 (m, 5H), 4.26 (dd, *J* = 8.3, 4.0 Hz, 1H), 3.16-3.09 (m, 2H), 2.83 (t, *J* = 12.0 Hz, 1H), 2.50-2.43 (m, 2H), 2.33-2.30 (m, 1H), 2.12-1.83 (m, 5H), 1.77 (t, *J* = 4.6 Hz, 1H), 1.69-1.67 (m, 1H), 1.59-1.45 (m, 2H), 1.28-1.05 (m, 9H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 183.5, 155.6, 140.3, 129.7, 128.4, 126.2, 83.1, 73.2, 48.0, 43.0, 40.2, 35.4, 34.7, 32.8, 28.8, 28.3, 26.5, 25.7, 21.5, 20.0, 19.2. **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{23}H_{31}N_2O_2$ 367.23800; Found 367.23850.

Hydrazone 22. Freshly distilled allyl bromide (1.7 equiv) was used as the alkylating agent. **22** was obtained as light-yellow oil (0.057 g, 92%). **^{1}H NMR** ($CDCl_3$, 500 MHz): 7.31-7.20 (m, 3H), 7.17- 7.14 (m, 2H), 5.69-5.58 (m, 1H), 5.06-4.95 (m, 2H), 4.34-4.26 (m, 1H), 4.21 (t, *J* = 8.2 Hz, 1H), 4.03-3.98 (m, 1H), 3.20-3.12 (m, 2H), 2.56 (dd, *J* = 13.4, 10.3 Hz, 1H), 2.43- 2.26 (m, 2H), 2.21-2.08 (m, 2H), 1.20 (d, *J* = 6.7 Hz, 3H), 1.15 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 183.3, 155.3, 135.7, 135.5, 128.8, 127.0, 116.6, 67.3, 61.1, 39.3, 38.9, 36.5, 24.1, 17.1, 10.9. **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{18}H_{25}N_2O_2$ 301.19110; Found 301.19110. Spectroscopic data was consistent with that previously reported.[19]

Hydrazone 63. Freshly distilled 1-iodopentane (1.7 equiv) was used as the alkylating agent. **63** was obtained as light-yellow oil (0.15 g, 98 %). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.32-7.02 (m, 5H), 4.37-4.30 (m, 1H), 4.21 (t, *J* = 8.0 Hz, 1H), 4.00 (dd, *J* = 9.7, 8.6 Hz, 1H), 3.16 (dd, *J* = 13.5, 4.0 Hz, 1H), 3.11-3.01 (m, 1H), 2.58 (dd, *J* = 13.8, 10.3 Hz, 1H), 2.43-2.22 (m, 2H), 1.43-1.35 (m, 2H), 1.31-1.24 (m, 6H), 1.23-1.11 (m, 6H), 0.88 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 184.5, 156.5, 135.9, 129.0, 128.9, 127.2, 67.4, 61.4, 39.4, 36.8, 34.7, 32.1, 27.6, 24.2, 22.6, 17.7, 14.2, 11.3. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{20}H_{30}N_2O_2Na$ 353.21990; Found 353.22070.

Hydrazone 64. Freshly distilled benzyl bromide (1.7 equiv) was used as the alkylating agent. **64** was obtained as light-yellow oil (0.171 g, 96 %). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.30-6.88 (m, 10H), 4.20-4.09 (m, 2H), 3.87 (dd, *J* = 9.4, 8.2 Hz, 1H), 3.44-3.30 (m, 1H), 2.80 (dd, *J* = 13.5, 8.2 Hz, 1H), 2.67 (dd, *J* = 13.7, 6.4 Hz, 1H), 2.60-2.46 (m, 3H), 1.86 (dd, *J* = 13.5, 10.1 Hz, 1H), 1.28 (d, *J* = 6.9 Hz, 3H), 1.23 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 182.5, 156.3, 139.9, 136.2, 129.2, 128.9, 128.8, 128.6, 127.0, 126.5, 67.3, 61.1, 41.0, 39.5, 38.1, 24.6, 17.7, 11.4. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{22}H_{26}N_2O_2Na$ 373.18860; Found 373.18890.

Hydrazone 65. Freshly distilled allyl bromide (1.7 equiv) was used as the alkylating agent. **65** was obtained as light-yellow oil (0.13 g, 93%). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.35-7.30 (m, 5H), 5.36- 5.26 (m, 1H), 5.13 (dd, *J* = 10.3, 8.5 Hz, 1H), 4.91-4.85 (m, 1H), 4.79-4.75 (m, 1H), 4.62 (t, *J* = 8.5 Hz, 1H), 4.21 (dd, *J* = 10.5, 8.9 Hz, 1H), 3.16-3.10 (m, 1H), 2.30-2.21 (m, 1H), 2.14-2.05 (m, 1H), 1.97-1.89 (m, 1H), 1.82-1.70 (m,

1H), 1.17 (d, *J* = 6.9 Hz, 3H), 1.00 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 184.0, 155.4, 136.4, 135.3, 128.9, 128.6, 127.4, 116.1, 68.4, 64.2, 38.5, 36.3, 24.1, 16.6, 10.8. **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{17}H_{23}N_2O_2$ 287.1754; Found 287.1758. Spectroscopic data is consistent with that previously reported.[19]

Hydrazone 66. Freshly distilled 1-iodopentane (1.7 equiv) was used as alkylating agent. **66** was obtained as light-yellow oil (0.08 g, 94 %). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.37-7.19 (m, 5H), 5.14 (dd, *J* = 10.9, 8.6 Hz, 1H), 4.64 (t, *J* = 8.6 Hz, 1H), 4.24 (dd, *J* = 8.6, 10.6 Hz, 1H), 3.06-3.00 (m, 1H), 2.30-2.21 (m, 1H), 2.14-2.03 (m, 1H), 1.21-0.98(m, 14H), 0.83 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 185.1, 156.7, 136.8, 129.0, 128.9, 127.8, 68.6, 64.6, 37.1, 34.6, 32.2, 27.2, 24.2, 22.6, 17.3, 14.2, 11.2. **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{19}H_{29}N_2O_2$ 317.22240; Found 317.22310.

Hydrazone 67. Freshly distilled benzyl bromide (1.7 equiv) was used as the alkylating agent. **67** was obtained as light-yellow oil (0.069g, 97%). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.4-6.93 (m, 10H), 5.20 (dd, *J* = 10.3, 8.6 Hz, 1H), 4.67 (t, *J* = 8.6 Hz, 1H), 4.27 (dd, *J* = 10.6, 9.2 Hz, 1H), 3.40-3.34 (m, 1H), 2.37-2.22 (m, 4H), 1.08-1.04 (m, 6H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 184.3, 155.4, 139.1, 137.1, 129.2, 129.1, 129.0, 128.5, 127.5, 126.5, 68.8, 64.7, 40.14, 38.3, 24.9, 51.8, 11.17. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{21}H_{24}N_2O_2Na$ 359.17300; Found 359.17360.

General procedure for hydrolysis of the alkylated hydrazones

(*R*)-2-Methyl-1-phenylpentan-3-one [(*R*)-33]. Benzyl hydrazone **32** (0.058 g, 0.16 mmol) was dissolved in a stirred 4:1 mixture of acetone (1.32 mL) and H_2O (0.33 mL), followed by addition of *p*-TsOH·H_2O (0.07 mg, 0.33 mmol). The reaction was monitored by TLC (5:95 Et_2O-pentane) until complete, and then partitioned between Et_2O (1 mL) and saturated aqueous $NaHCO_3$ (1mL). The aqueous phase was extracted with Et_2O (2 x 2mL), dried ($MgSO_4$), and evaporated under weakly reduced pressure (400 torr) to give crude (*R*)-**33**. Flash chromatography over silica gel using 5:95 Et_2O-pentane gave (*R*)-**33** as a pure, colorless solid (>99% conversion based on ^{1}H NMR of crude product). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.46-6.93 (m, 5H), 2.99-2.94 (m, 1H), 2.84-2.82 (m, 1H), 2.58-2.57 (m, 1H), 2.41-2.39 (m, 1H), 2.28-2.21 (m, 1H), 1.08 (dd, *J* = 6.9, 1.4 Hz, 3H), 0.96 (td, *J* = 6.9, 1.4 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 215.0, 140.0, 129.0, 128.5, 126.3, 48.0, 39.4, 35.3, 16.7, 7.7. Spectroscopic data was consistent to that previously reported.[30] **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{12}H_{17}O$ 177.1279; Found 177.1275. HPLC analysis of (*R*)-**33** showed an *er* of 99:1 [determined by HPLC, chiral OD-H column, 0.5:99.5 *i*-PrOH-hexanes, 0.5 mL/min, λ= 254 nm, t_R = 15.002 min, t_S = 14.274 min].

(*R*)-2-Methyl-1-phenylpentan-3-one [(*R*)-33] (obtained from hydrolysis of hydrazone **64**). Flash chromatography over silica gel using 5:95 Et_2O-pentane gave (*R*)-**33** as a pure, colorless oil (>99% conversion based on ^{1}H NMR of crude product). HPLC analysis (*R*)-**33** showed an *er* of 93:7 [determined by HPLC, chiral

OD-H column, 0.5:99.5 *i*-PrOH-hexanes; 0.41 mL/min, λ= 254 nm, t_R = 21.158 min, t_S = 19.863].

(*S*)-2-Methyl-1-phenylpentan-3-one [(*S*)-33] (obtained from hydrolysis of hydrazone **67**). Flash chromatography over silica gel using 5:95 Et_2O-pentane gave (*S*)-**33** as a pure, colorless oil (>99% conversion based on ^{1}H NMR of crude product). Spectroscopic data was consistent with ketone (*R*)-**33**. HPLC analysis of (*S*)-**33** showed an *er* of 2:98 [determined by HPLC, chiral OD-H column, 0.5:99.5 *i*-PrOH-hexanes; 0.41 mL/min, λ= 254 nm, t_R = 21.090 min, t_S = 19.906].

(*R*)-4-Methylhept-6-en-3-one [(*R*)-12] (obtained from hydrolysis of hydrazone **21**). Flash chromatography over silica gel using 5:95 Et_2O-pentane gave (*R*)-**12** as a pure, colorless oil (>99% conversion based on ^{1}H NMR of crude product). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 5.69 (ddt, J = 17.7, 10.0, 7.1 Hz, 1H), 5.00 -4.94 (m, 2H), 2.60-2.53 (m, 1H), 2.49-2.30 (m, 3H), 2.11-2.06 (m, 1H), 1.06 (d, J = 7.3 Hz, 3H), 1.01 (t, J = 7.3 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 215.2, 135.5, 116.8, 45.8, 37.3, 34.6, 16.3, 7.8. Spectroscopic data was consistent with that previously reported.[9c] GC analysis of (*R*)-**12** showed an *er* of 99:1 [determined by GC, 20 m x 0.25 mm Chiraldex G-TA column, 70.0 °C, 15 psi, 2.9 ml/min, Helium carrier gas, t_R = 5.498 min, t_S = 6.044 min].

(*R*)-4-Methylhept-6-en-3-one [(*R*)-12] (obtained from hydrolysis of hydrazone **22**). Flash chromatography over silica gel using 5:95 Et_2O-pentane gave (*R*)-**12** as a

pure, colorless oil (>99% conversion based on ^{1}H NMR of crude product). GC analysis of (*R*)-**12** showed an *er* of 93:7 [determined by GC, 40 m x 0.25 mm Chiraldex G-TA column, 30.0 °C to 170.0 °C at 1.0 °C/min, hold 5.00 min, 15 psi, 1.5 ml/min, Helium carrier gas, t_R = 42.499 min, t_S = 43.118 min].

(*S*)-4-Methylhept-6-en-3-one [(*S*)-12] (obtained from hydrolysis of hydrazone **65**). Flash chromatography over silica gel using 5:95 Et_2O-pentane gave (*S*)-**12** as a pure, colorless oil (>99% conversion based on ^{1}H NMR of crude product). Spectroscopic data was consistent with ketone (*R*)-**12.** GC analysis of (*S*)-**12** showed an *er* of 3:97. [determined by GC, 40 m x 0.25 mm Chiraldex G-TA column, 30.0 °C to 170.0 °C at 1.0 °C/min, hold 5.00 min, 15 psi, 1.5 ml/min, Helium carrier gas, , t_R = 42.045 min, t_S = 43.628 min].

(*R*)-4-Methylhexan-3-one [(*R*)-36] (obtained from hydrolysis of hydrazone **37**). Flash chromatography over silica gel using 5:95 Et_2O-pentane gave (*R*)-**36** as a pure, colorless oil (>99% conversion based on ^{1}H NMR of crude product). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 2.61-2.37 (m, 3H), 1.75-1.62 (m, 2H), 1.24-0.72 (m, 9H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 214.5, 47.1, 33.9, 25.7, 15.5, 11.2, 7.1. Spectroscopic data was consistent with that previously reported.[6] GC analysis of (*R*)-**36** showed an *er* of 99:1 [determined by 20 m x 0.25 mm Chiraldex G-TA column, 70.0 °C, 15 psi, 2.9 ml/min, Helium carrier gas, t_R = 3.374 min, t_S =3.618 min].

(*R*)-1-(4-Bromophenyl)-2-methylpentan-3-one [(*R*)-50] (obtained from hydrolysis of hydrazone **39**). Flash chromatography over silica gel using 5:95 Et_2O-pentane gave (*R*)-**50** as a pure, colorless oil (>99% conversion based on ^1H NMR of crude product). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.38 (d, *J* = 8.2 Hz, 2H), 7.00 (d, *J* = 7.8 Hz, 2H), 2.92 (dd, *J* = 13.5, 7.8 Hz, 1H), 2.82-2.77 (m, 1H), 2.53-2.41 (m, 2H), 2.27-2.16 (m, 1H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.96 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 214.5, 139.0, 131.5, 130.8, 120.1, 47.8, 38.6, 35.3, 16.8, 7.7. **HRMS (ESI-TOF)** m/z: $[M]^+$ Calcd for $C_{12}H_{16}BrO$ 256.0286; Found 256.0288. HPLC analysis of (*R*)-**50** showed an *er* of >99:1 [determined by HPLC, chiral OD-H column, 0.3:99.7 *i*-PrOH-hexanes, 1 mL/min, λ= 254 nm, t_R = 11.049 min].

4-Methylheptan-3-one [(*R*)-51] (obtained from hydrolysis of hydrazone **40**). Flash chromatography over silica gel using 5:95 Et_2O-pentane gave (*R*)-**51** as a pure, colorless oil (>99% conversion based on ^1H NMR of crude product). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 2.55-2.49 (m, 1H), 2.47-2.40 (m, 2H), 1.64-1.57 (m, 2H), 1.30-1.24 (m, 2H), 1.05-1.01 (m, 6H), 0.88 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 215.8, 46.0, 35.4, 34.3, 20.6, 16.6, 14.2, 7.9. Spectroscopic data was consistent with that previously reported.[6] GC analysis of **51** showed an *er* of 98:2 [determined by 20 m x 0.25 mm Chiraldex G-TA column, 70.0°C, 15 psi, 2.9 ml/min, Helium carrier gas, t_R = 5.513 min, t_S = 6.025 min].

(*R*)-4-Methylnonan-3-one [(*R*)-52] (obtained from hydrolysis of hydrazone **41**). Flash chromatography over silica gel using 5:95 Et_2O-pentane gave (*R*)-**52** as a pure,

colorless oil (>99% conversion based on ^{1}H NMR of crude product). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 2.77-2.26 (m, 3H), 1.63-1.60 (m, 1H), 1.35-1.21 (m, 7H), 1.05-1.01 (m, 6H), 0.86 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 215.8, 46.2, 34.3, 33.2, 32.0, 27.1, 22.6, 16.6, 14.1, 7.9. **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{10}H_{21}O$ 157.1592; Found 157.1592. GC analysis of **52** showed an *er* of 99:1 [determined by 25 m x 0.25mm CP-Cyclodextrin-β-2,3,6-M-19 column, 70.0°C, hold 5 min, 70.0 °C to 160.0 °C at 1 °C/min, 16 psi, 1.57 ml/min, Helium carrier gas, t_R = 22.874 min, t_S = 23.423 min].

(*R*)-4-Methylnonan-3-one [(*R*)-52] (obtained from hydrolysis of hydrazone **63**). Flash chromatography over silica gel using 5:95 Et_2O-pentane gave (*R*)-**52** as a pure, colorless oil (>99% conversion based on ^{1}H NMR of crude product). GC analysis of (*R*)-**52** showed an *er* of 95:5 [determined by 25 m x 0.25mm CP-Cyclodextrin-β-2,3,6-M-19 column, 70.0 °C, hold 5 min, 70.0 °C to 160.0 °C at 1 °C/min, 16 psi, 1.57 ml/min, Helium carrier gas, t_R = 22.940 min, t_S = 23.441 min].

(*S*)-4-Methylnonan-3-one [(*S*)-52] (obtained from hydrolysis of hydrazone **66**). Flash chromatography over silica gel using 5:95 Et_2O-pentane gave (*S*)-**52** as a pure, colorless oil (>99% conversion based on ^{1}H NMR of crude product). Spectroscopic data was consistent with ketone (*R*)-**52.** GC analysis of (*S*)-**52** showed an *er* of 3:97. [determined by 25 m x 0.25mm CP-Cyclodextrin-β-2,3,6-M-19 column, 70.0 °C, hold 5 min, 70.0 °C to 160.0 °C at 1 °C/min, 16 psi, 1.57 ml/min, Helium carrier gas, t_R = 23.042 min, t_S = 23.299 min].

(*R*)-1-Cyclohexyl-2-methylpentan-3-one [(*R*)-53] (obtained from hydrolysis of hydrazone **42**). Flash chromatography over silica gel using 5:95 Et_2O-pentane gave (*R*)-**53** as a pure, colorless oil (>99% conversion based on ^1H NMR of crude product). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 2.67-2.60 (m, 1H), 2.47-2.41 (m, 2H), 1.78-1.31 (m, 7H), 1.21-1.15 (m, 6H), 1.04-1.01 (m, 6H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 215.8, 47.1, 40.5, 36.7, 35.9, 32.9, 27.2, 22.7, 17.5, 7.2. Spectroscopic data was consistent with that previously reported.[6] GC analysis of **53** showed an *er* of 95:5 [determined by 40 m x 0.25 mm Chiraldex G-TA column, 70.0 °C, hold 5 min, 70.0 °C to 170.0 °C at 5 °C/min, 33.8 psi, 2.9 ml/min, Helium carrier gas, t_R = 20.380 min, t_S = 20.540 min].

(*R*)-4,5-Dimethylhexan-3-one [(*R*)-54] (obtained from hydrolysis of hydrazone **43**). Flash chromatography over silica gel using 5:95 Et_2O-pentane gave (*R*)-**54** as a pure, colorless oil (>99% conversion based on ^1H NMR of crude product). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 2.65-2.50 (m, 1H), 2.50-2.43 (m, 4H), 1.11-1.03 (m, 5H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.82 (d, *J* = 6.3 Hz, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 217.5, 52.1, 37.2, 31.8, 20.1, 19.8, 10.3, 7.5. Spectroscopic data was consistent with that previously reported.[31] GC analysis of (*R*)-**54** showed an *er* of 97:3 [determined by 20 m x 0.25 mm Chiraldex G-TA column, 70.0 °C, 15 psi, 2.9 ml/min, Helium carrier gas, t_R = 5.277 min, t_S = 5.559 min].

(*R*)-6-(Benzyloxy)-4-methylhexan-3-one [(*R*)-55] (obtained from hydrolysis of hydrazone **44**). Flash chromatography over silica gel using 70:30 Et_2O-pentane gave (*R*)-**55** as a pure, colorless oil (>99% conversion based on ^1H NMR of crude product). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.40-7.25 (m, 5H), 4.50 (s, 2H), 3.47-3.42 (m, 2H), 2.80-2.71 (m, 1H), 2.52-2.39 (m, 2H), 2.06-1.97 (m, 1H), 1.65-1.57 (m, 1H), 1.08 (d, *J* = 6.8 Hz, 3H), 1.00 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 215.4, 138.6, 128.7, 128.0, 127.9, 73.3, 68.3, 43.2, 34.8, 33.7, 17.1, 8.1. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{14}H_{20}O_2Na$ 243.13560; Found 243.13610. GC analysis of (*R*)-**55** showed an *er* of >99:1 [determined by HPLC, chiral OD-H column, 10:90 *i*-PrOH-hexanes; 0.3 mL/min, λ= 254 nm, t_R =15.533 min].

(*R*)-6-Hydroxy-4-methylhexan-3-one [(*R*)-56] (obtained from hydrolysis of hydrazone **45**). Flash chromatography over silica gel using 70:30 Et_2O-pentane gave **56** as a pure, colorless solid (>99% conversion based on ^1H NMR of crude product). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 3.60-3.56 (m, 2H), 2.82-2.69 (m, 1H), 2.58-2.42 (m, 2H), 1.95-1.55 (m, 3H), 1.10 (d, *J* = 7.3 Hz, 3H), 1.03 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 216.1, 60.7, 43.1, 35.6, 34.5, 16.9, 7.9. **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_7H_{15}O_2$ 131.1072; Found 131.1069. GC analysis of *(R)*-**56** showed an *er* of >99:1 [determined by 40 m x 0.25 mm Chiraldex G-TA column, 70.0°C, hold 10 min, 70.0 °C to 170.0 °C at 5 °C/min, 33.8 psi, 2.9 ml/min, Helium carrier gas, t_R = 28.409 min, t_S =26.510 min].

(*R*)-Ethyl 3-methyl-4-oxohexanoate [(*R*)-58] (obtained from hydrolysis of hydrazone **47**). Flash chromatography over silica gel using 5:95 Et_2O-pentane gave (*R*)-**58** as a pure, colorless oil (>99% conversion based on ^{1}H NMR of crude product). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 3.66 (s, 3H), 3.06-2.97 (m, 1H), 2.78 (dd, *J* = 16.8, 9.3 Hz, 1H), 2.58-2.54 (m, 2H), 2.28 (dd, *J* = 17.1, 5.3 Hz, 1H), 1.32 (d, *J* = 7.3 Hz, 3H), 1.07 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 214.0, 173.0, 51.8, 41.8, 36.9, 34.4, 17.3, 7.8. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_8H_{14}O_3Na$ 181.08350; Found 181.08390. Spectroscopic data was consistent with that previously reported.[32] GC analysis of (*R*)-**58** showed an *er* of 99:1 [determined by 25 m x 0.25mm CP-Cyclodextrin-β-2,3,6-M-19 column, 50.0°C, hold 5 min, 50.0 °C to 160.0 °C @ 1 °C/min, 16 psi, 1.73 ml/min, Helium carrier gas, t_R = 44.829 min, t_S = 45.626 min].

(*R*)-2-Allylcyclohexanone [(*R*)-59] (obtained from hydrolysis of hydrazone **48**). Flash chromatography over silica gel using 20:80 Et_2O-pentane gave *(R)*-**59** as a pure, colorless oil (87% conversion based on ^{1}H NMR of crude product). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 5.79 (m, 1H), 5.11-4.83 (m, 2H), 2.58-2.49 (m, 1H), 2.36-2.24 (m, 2H), 2.16-1.96 (m, 3H), 1.89 (m, 1H), 1.67 (m, 2H), 1.45-1.22 (m, 2H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 212.3, 135.6, 115.9, 49.7, 41.5, 32.2, 31.9, 27.3, 24.6. Spectroscopic data was consistent to that previously reported.[9c] GC analysis of (*R*)-**59** showed an *er* of >99:1 [determined by 25 m x 0.25mm CP-Cyclodextrin-β-2,3,6-M-19 column, 30.0 °C, hold 5 min, 30.0 °C to 160.0 °C at 1.5 °C/min, 16 psi, 1.92 ml/min, Helium carrier gas, t_R = 51.090 min, t_S = 51.565 min].

(*R*)-2-Benzylcyclohexanone [(*R*)-60] (obtained from hydrolysis of hydrazone **49**). Flash chromatography over silica gel using 20:80 Et_2O-pentane gave (*R*)-**60** as a pure, colorless oil (92% conversion based on ^1H NMR of crude product). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.29-7.21 (m, 2H), 7.19-7.10 (m, 3H), 3.20 (dd, *J* = 13.9, 4.8 , 1H), 2.57-2.45 (m, 1H), 2.45-2.35 (m, 1H), 2.38 (dd, *J* = 8.8, 13.9 Hz, 1H), 2.39-2.25 (m, 1H), 2.07-1.95 (m, 2H), 1.89-1.79 (m, 1H), 1.71-1.62 (m, 1H), 1.60-1.49 (m, 1H), 1.41-1.30 (m, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 212.5, 140.1, 129.0, 128.2, 125.8, 52.5, 42.1, 35.3, 33.3, 27.9, 25.0. Spectroscopic data was consistent with that previously reported.[33] GC analysis of **60** showed an *er* of 96:4 [determined by 25 m x 0.25mm CP-Cyclodextrin-β-2,3,6-M-19 column, 70.0°C, hold 5 min, 70.0 °C to 160.0 °C at 0.8 °C/min, hold 50 min, 16 psi, 1.57 ml/min, Helium carrier gas, t_R = 101.583 min, t_S = 102.227 min].

Supporting Information

HPLC, GC, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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References

1) (a) Enders, D. In *Asymmetric Synthesis*; 1st ed.; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 275–339, and references therein. (b) Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. The SAMP-/RAMP-Hydrazone Methodology in Asymmetric Synthesis. *Tetrahedron* **2002**, *58*, 2253–2329, and references therein. (c) Liu, Y.; Han, S.-J.; Liu, W.-B.; Stoltz, B. M. Catalytic Enantioselective Construction of Quaternary Stereocenters: Assembly of Key Building Blocks for the Synthesis of Biologically Active Molecules. *Acc. Chem. Res.* **2015**, *48*, 740–751. (d) Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novák, Z.; Krout, M. R.; McFadden, R. M.; Roizen, J. L.; Enquist Jr., J. A.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz, B. M. Enantioselective Decarboxylative Alkylation Reactions: Catalyst Development, Substrate Scope, and Mechanistic Studies. *Chem.–Eur. J.* **2011**, *17*, 14199–14223, and references therein (e) Garnsey, M. R.; Uteuliyev, M.; Coltart, D. M. Asymmetric Synthesis of Structural Analogues of (+)-Clusianone via Enantioselective ACC Alkylation. *Tetrahedron Lett*. **2015**, *56*, 3183–3185, and references therein. (f) Dey, S.; Wengryniuk, S. E.; Tarsis, E. M.; Robertson, B. R.; Zhou, G.; Coltart, D. M. A Formal Asymmetric Synthesis of Apratoxin D via Advanced-stage Asymmetric ACC α,α-Bisalkylation of a Chiral Nonracemic Ketone. *Tetrahedron Lett*. **2015**, *56*, 2927–2929, and references therein.

2) Yamada, S.; Hiroi, K.; Achiwa, K. Asymmetric Synthesis with Amino Acid I Asymmetric Induction in the Alkylation of Keto-enamine. *Tetrahedron Lett.* **1969**, *10*, 4233–4236.

3) Mahrwald, R. Chiral Imidazolidinone (MacMillan's) Catalyst. In *Comprehensive Enantioselective Organocatalysis: Catalysts*, *Reactions*, *and Applications*; Dalko, K. B., Ed.; Wiley: Weinheim, 2013; pp 69-96.

4) (a) Hashimoto, S.; Koga, K. Asymmetric Synthesis of α-Alkylated Cyclic Ketones via Chiral Chelated Lithioenamines. *Tetrahedron Lett.* **1978**, 573–576. (b) Hashimoto, S.; Koga, K. Strereoselective Reactions 3. Highly Efficient Method for the Asymmetric Synthesis of 2-Alkylcycloalkanones via Chiral Chelated Lithioenamines. *Chem. Pharm. Bull.* **1979**, *27*, 2760–2766.

5) (a) Meyers, A. I.; Williams, D. R.; Druelinger, M. Enantioselective Alkylation of Cyclohexanone via Chiral Lithio-chelated Enamines. *J. Am. Chem. Soc.* **1976**, *98*, 3032–3033. (b) Meyers, A. I.; Williams, D. R. Asymmetric Alkylation of Acyclic Ketones via Chiral Metallo Enamines. Effect of Kinetic vs. Thermodynamic Metalations. *J. Org. Chem.* **1978**, *43*, 3245–3247. (c) Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Druelinger, M. Enantioselective Alkylation of Ketones via Chiral, Nonracemic Lithioenamines. An Asymmetric Synthesis of α-Alkyl and α,α'-Dialkyl Cyclic Ketones. *J. A m. Chem. Soc.* **1981**, *103*, 3081–3087.

6) (a) Enders, D.; Eichenauer, H.; Baus, U.; Schubert, H.; Kremer, K. A. M. Asymmetric Syntheses via Metalated Chiral Hydrazones : Overall Enantioselective α-Alkylation of Acyclic Ketones. *Tetrahedron* **1984**, *40*, 1345–1359. (b) Enders, D.; Eichenauer, H. Asymmetric Synthesis of α-Substituted Ketones by Metalation and Alkylation of Chiral Hydrazones. *Angew. Chem. Int. Ed.*, **1976**, *15*, 549–551. (c) Enders, D.; Eichenauer, H. Asymmetric Synthesis of Ant Alarm Pheromones—α-Alkylation of

Acyclic Ketones with almost Complete Asymmetric Induction. *Angew. Chem. Int. Ed.*, **1979**, *18*, 397–399.

7) (a) Berger, E. C.; Tunge, J. A. Ruthenium-Catalyzed Decarboxylative Allylation of Nonstabilized Ketone Enolates. *Org. Lett.* **2004**, *6*, 2603–2605. (b) Berger, E. C.; Tunge, J. A. Asymmetric Allylic Alkylation of Ketone Enolates: An Asymmetric Claisen Surrogate. *Org. Lett*. **2004**, *6*, 4113–4115. (c) Rayabarapu, D. K.; Tunge, J. A. Catalytic Decarboxylative sp–sp^3 Coupling. J. Am. Chem. Soc. **2005**, *127*, 13510–13511.

8) (a) Behenna, D. C.; Stoltz, B. M. The Enantioselective Tsuji Allylation. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045. (b) Enquist, J. A.; Stoltz, B. M. The Total Synthesis of (-)-Cyanthiwigin F by Means of Double Catalytic Enantioselective Alkylation. *Nature* **2008**, *453*, 1228–1231. (c) Mohr, J. T.; Krout, M. R.; Stoltz, B. M. Natural Products as Inspiration for the Development of Asymmetric Catalysis. *Nature* **2008**, *455*, 323–332.

9) (a) Trost, B. M.; Xu, J. Regio- and Enantioselective Pd-Catalyzed Allylic Alkylation of Ketones through Allyl Enol Carbonates. *J. Am. Chem. Soc*. **2005**, *127*, 2846–2847. (b) Trost, B. M.; Xu, J. Palladium-Catalyzed Asymmetric Allylic α-Alkylation of Acyclic Ketones. *J. Am. Chem. Soc*. **2005**, *127*, 17180–17181. (c) Trost, B. M.; Xu, J.; Schmidt, T. Palladium-Catalyzed Decarboxylative Asymmetric Allylic Alkylation of Enol Carbonates. *J. Am. Chem. Soc*. **2009**, *131*, 18343–18357.

10) Lim, D.; Coltart, D. M. Simple and Efficient Asymmetric α-Alkylation and α,α-Bisalkylation of Acyclic Ketones by Using Chiral N-Amino Cyclic Carbamate Hydrazones. *Angew. Chem. Int. Ed*. **2008**, *47*, 5207–5210.

11) Krenske, E. H.; Houk, K. N.; Lim, D.; Wengryniuk, S. E.; Coltart, D. M. Origins of Stereoselectivity in the α-Alkylation of Chiral Hydrazones. *J. Org. Chem*. **2010**, *75*, 8578–8584.

12) Wengryniuk, S. E.; Lim, D.; Coltart, D. M. Regioselective Asymmetric α,α-Bisalkylation of Ketones via Complex-Induced Syn-Deprotonation of Chiral N-Amino Cyclic Carbamate Hydrazones. *J. Am. Chem. Soc*. **2011**, *133*, 8714–8720.

13) Uddin, Md., N.; Tarsis, E. M.; Wu, C.-H.; Wu, J. I.; Coltart, D. M. A Mismatch-Free Strategy for the Diastereoselective α,α-Bisalkylation of Chiral Nonracemic Methyl Ketones. *Org. Lett*. **2018**, *20*, 3723–3727.

14) For the sterochemical assignment, see references 10 and 11.

15) (a) Bartlett, P. D.; Knox, L. H. D,L-10-Camphorsulphonyl Chloride. *Org. Synth*. **1965**, *45*, 55–56. (b) Bartlett, P. D.; Knox, L. H. D,L-Ketopinic Acid. *Org. Synth*. **1973**, *5*, 689–691.

16) Uyen, H.; Uddin, M. D.; Wengryniuk, S. E.; McDonald, S. L; Coltart, D. M. A Simple and Efficient Approach to the N-amination of Oxazolidinones Using Monochloroamine. *Tetrahedron Lett.* **2016** 57, 4799–4802.

17) Hynes, J., Jr.; Doubleday, W. W.; Dyckman, A. J.; Godfrey, J. D., Jr.; Groso, J. A.; Kiau, S.; Leftheris, K. N-Amination of Pyrrole and Indole Heterocycles with Monochloramine (NH2Cl). *J. Org. Chem.* **2003**, *69*, 1368–1371.

18) See the supporting information for details.

19) Uyen, H.; Uddin, M. D.; Wengryniuk, S. E.; McDonald, S. L; Coltart, D. M. On the Regioselectivity and Diastereoselectivity of ACC Hydrazone Alkylation. *Tetrahedron* **2017**, *73*, 432–436.

20) At the time of our original study, we did not have access to the analytical equipment needed to establish this.

21) Conversion yields were established using 1,3,5-trimethoxy benzene as an internal standard.

22) Agrawal, Y. K. Hydroxamic Acids and Their Metal Complexes. *Russian Chemical Reviews* **1979**, *48*, 948–963.

23) Matrix Scientific prices: (*R*)-4-Benzyl-2-oxazolidinone – $2.05/gram (*R*-**14**); (*S*)-4-Benzyl-2-oxazolidinone – $2.16/gram (*S*-**14**); (*R*)-4-Phenyl-2-oxazolidinone – $0.77/gram (*R*-**65**); (*S*)-4-Phenyl-2-oxazolidinone – $0.95/gram (*S*-**65**). http://www.matrixscientific.com (accessed January 2018).

24) Lewis, F. W.; Egron, G.; Grayson, D. H. Unexpected Formation of 10-Iodo- and 10-Chlorocamphor under Halosulfonylation Conditions, and Convenient Routes to 10-Chloro- and 10-Bromocamphor. *Tetrahdedron: Asymmetry* **2009**, *20*, 1531–1535.

25) Haslanger, M. F.; Heikes, J. An Efficient Preparation Of L Ketopinic Acid Chloride By Ozonolysis Of 10 Chlorocamphor 10 Sulfine. *Synthesis-Stuttgart* **1981,** *10*, 801–802.

26) Joly, M.; Godbout C.; Arbour M.; Claude S. Ti-Catalyzed Reactions of Hindered Isocyanates with Alcohols. *J. Org. Chem.* **2005**, *70*, 6118–6121.

27) Kalaitzakis, D.; Kambourakis, S.; Rozzell, D. J.; Smonou, I.; Stereoselective Chemoenzymatic Synthesis of Sitophilate: a Natural Pheromone. *Tetrahedron: Asymmetry* **2007**, *18*, 2418–2426.

28) Zhao, Y.; Chen, G. Palladium-Catalyzed Alkylation of ortho-C(sp2)–H Bonds of Benzylamide Substrates with Alkyl Halides. *Org. Lett.* **2011**, *13,* 4850–4853.

29) Desroches, C.; Lopes, C.; Kessler, V.; Parola, S. Design and Synthesis of Multifunctional Thiacalixarenes and Related Metal Derivatives for the Preparation of Sol–gel Hybrid Materials with Non-linear Optical Properties. *Dalton Trans.* **2003**, 2085–2092.

30) Lu, S.; Bolm, C. Highly Enantioselective Synthesis of Optically Active Ketones by Iridium-Catalyzed Asymmetric Hydrogenation. *Angew. Chem. Int. Ed.* **2008**, *47*, 8920–8923.

31) Hightower, L. E.; Glasgow, L. R.; Stone, K. M.; Albertson, D. A.; Smith, H. A. *J. Org. Chem.* **1970**, *35*, 1881–1886.

32) Miura, K.; Fujisawa, N.; Saito, H.; Wang, D.; Hosomi, A. Synthetic Utility of Stannyl Enolates as Radical Alkylating Agents. *Org. Lett.* **2001**, *3*, 2591–2594.

33) Kaku, H.; Nakamaru, A.; Inai, M.; Nishii, T.; Horikawa, M.; Tsunoda, T. A Facile and Practical Method of Preparing Optically Active α-Monosubstituted Cycloalkanones by Thermodynamically Controlled Deracemization. *Tetrahedron* **2010**, *66*, 9450–9455.