Chapter 2

Catalytic Asymmetric Reductive Acyl Cross-Coupling: Synthesis of Enantioenriched Acyclic α,α-Disubstituted Ketones[◊]

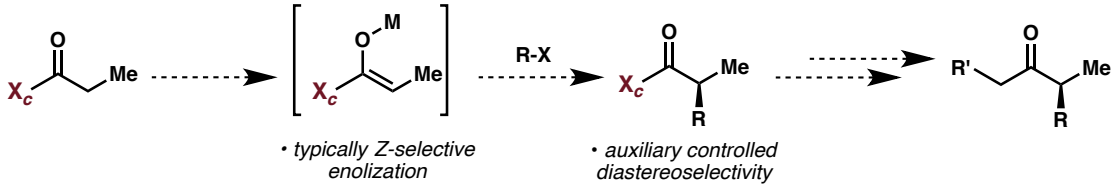
2.1. INTRODUCTION

Enantioenriched α,α-disubstituted carbonyl compounds are versatile intermediates in the synthesis of natural products and pharmaceuticals. As such, their preparation has received ample attention from the organic chemistry community, leading to the development of a rich palette of transformations. With respect to acyclic systems, these largely fall into two categories: the chiral-auxiliary directed α-functionalization of amides,[1] and the more recently-developed direct α-functionalization of carbonyl compounds,[2] frequently via organocatalysis.

◊ Portions of this chapter have been reproduced from published studies (see reference **16**) and the supporting information found therein. The research presented in this chapter was completed in collaboration with Alan H. Cherney, Ph.D., then a graduate student in the Reisman group.

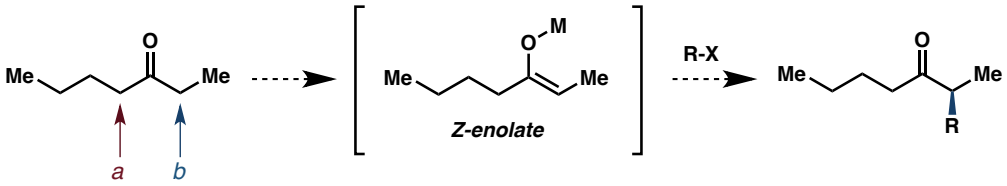
A significant majority of these methods, especially those most widely employed in synthesis, proceed via enolate intermediates. Chiral auxiliaries enable the diastereoselective alkylation of an enolate by controlling the facial selectivity of electrophile approach (**Scheme 2.1**). These methods offer a well-established and robust route to stereogenic carbonyl compounds. However they also require synthetic manipulations to append and cleave the auxiliary. Moreover, ketone products in particular require additional transformations to access following the alkylation event. While organocatalytic methodologies obviate the need to append and cleave auxiliaries, these methods suffer from similar issues of elaboration to ketone products. Neither of these well-established methods provides a direct route to α-stereogenic acyclic ketone products.

Scheme 2.1. *Chiral auxiliary-directed alkylation methodologies.*



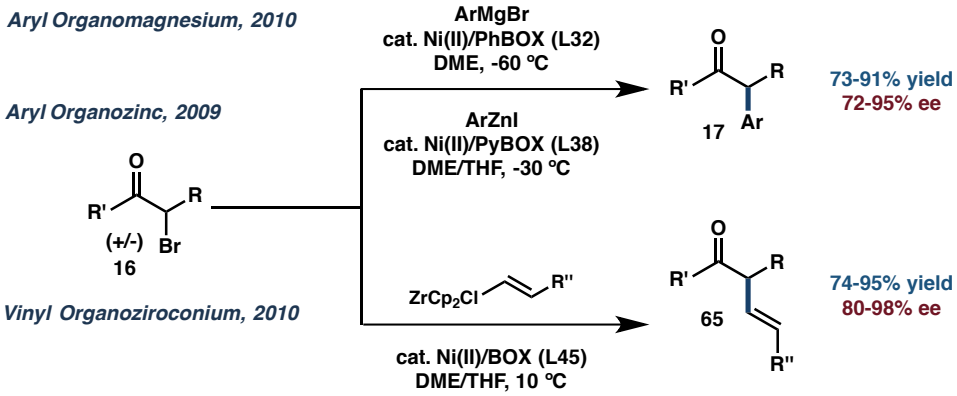
An ideal solution relying on these principles would be the enantioselective alkylation of an acyclic ketone-derived enolate. To obtain a single desired product from such a route would require i) the regioselective generation of the correct enolate (site a vs. b), ii) the stereoselective generation of the *E* or *Z* enolate, and iii) the facially-selective approach of the electrophile (**Scheme 2.2**). Finally, all of this must be accomplished while avoiding racemization of the ketone product under the reaction conditions. While this has been demonstrated in some cyclic systems (eliminating the *E*/*Z* control requirement), no such method exists for the alkylation of acyclic ketones.

Scheme 2.2. *Elements of control in ketone enolate alkylation.*



Metal-catalyzed, asymmetric cross-coupling has recently emerged as a viable strategy to access α,α-disubstituted enantioenriched ketones. While Pd-catalyzed α-allylations have been known for some time,[3] the only catalytic asymmetric methods for broader α-functionalization of acyclic ketones currently available are the Ni-catalyzed reactions developed by Fu and coworkers. These transformations involve the cross-coupling of α-bromoketones (**16**) with vinylzirconium reagents, aryl Grignard reagents, and aryl organozinc reagents (**Scheme 2.3**).[4] This technology represents a major practical and strategic advance in the stereoselective preparation of α-acyl tertiary centers. However these methods still require the preparation of unsymmetrical α-bromoketones, sometimes a nontrivial synthetic operation.

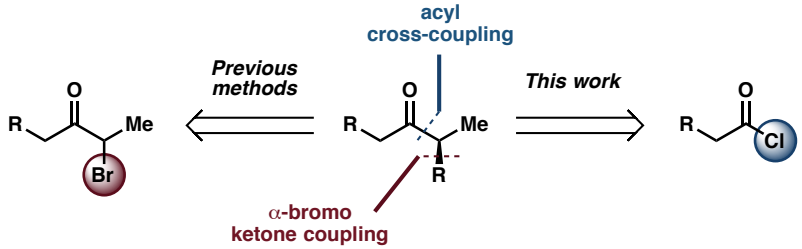
Scheme 2.3. *Fu's catalytic asymmetric ketone α-functionalizations.*



In considering a solution to this problem, we envisioned an alternative disconnection: acyl-alkyl cross-coupling (**Figure 2.1**).[5] This approach avoids the

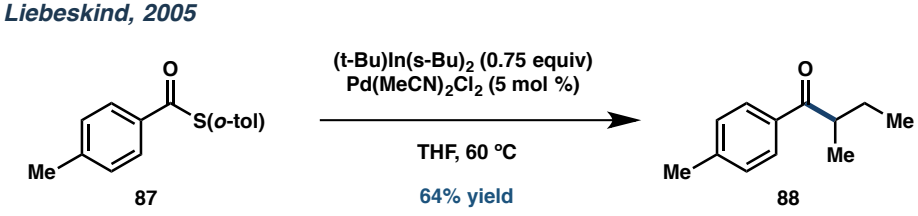
difficulties innate to enolate intermediates and resolves the issue of differentiating the α-positions of a ketone substrate before or during the reaction.

Figure 2.1. *Cross-coupling disconnections to access chiral α-tertiary ketones.*



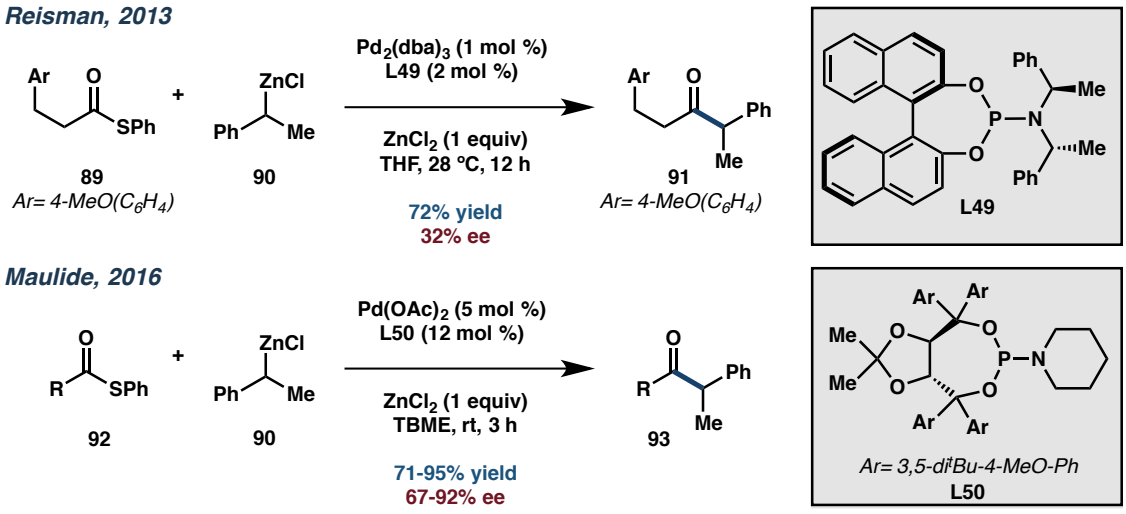
At the time of our research in this area, acyl cross-coupling reactions using secondary organometallic reagents were precedented using only simple nucleophiles.[6] While a variety of acyl electrophiles had be utilized, including carboxylates, thioesters, acyl halides, and anhydrides, only one example had been reported in which the secondary organometallic partner was non-symmetrical.[7] Liebeskind and coworkers reported the selective transfer of a *sec*-butyl group from (*t*-Bu)(*s*-Bu)$_2$In via Pd catalysis to form ketone **88** (**Scheme 2.4**). This dearth of examples reflects the challenge of coupling secondary organometallic reagents. These substrates are prone to β-hydride elimination and rearrangement, leading to a mixture of products. They are also frequently pyrophoric and unstable to long-term storage, making the development of methodology that avoids preformed organometallics a desirable aim.

Scheme 2.4. *Acyl cross-coupling of unsymmetrical nucleophile.*



At this juncture, it is important to note that following the publication of the work described here, two cross-coupling methods employing acyl electrophiles and unsymmetrical secondary organozinc reagents were reported (**Scheme 2.5**). The first, describing earlier work in our laboratory to access this class of products, achieves only a modest 32% ee with the optimal substrate, but affords a wider range of racemic α-tertiary ketones in good to excellent yields.[8] The second, reported in 2016 by the Maulide group, achieves excellent enantioselectivities but employs only one organozinc substrate (**90**), significantly limiting the accessible range of products.[9] These efforts further illustrate the difficulty of cross-coupling secondary organozinc reagents to access highly enantioenriched ketone products.

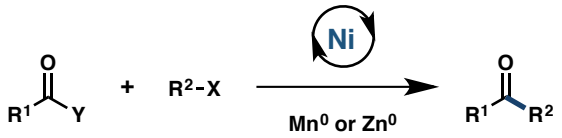
Scheme 2.5. *Asymmetric Negishi couplings of acyl electrophiles.*



With the challenges encountered in the development of asymmetric Fukuyama-type cross-coupling in mind, we turned to recent reports of nickel-catalyzed reductive cross-coupling (see **Chapter 1**). These methodologies couple two electrophiles in the presence of a stoichiometric reductant to turn over the Ni catalyst, obviating the need for organometallic reagents.[10] Specifically, Weix and Gong have reported the racemic

reductive cross-coupling of acyl electrophiles, as shown in **Scheme 2.6**.[11] These reactions show excellent functional-group tolerance due to their mild conditions and demonstrate the feasibility of employing hindered unsymmetrical secondary alkyl electrophiles in cross-coupling to afford ketone products. The absence of base in these reactions is particularly encouraging for asymmetric catalysis, as it minimizes risk of epimerization of the ketone products.

Scheme 2.6. *Racemic Reductive Cross-Coupling of Acyl Electrophiles.*



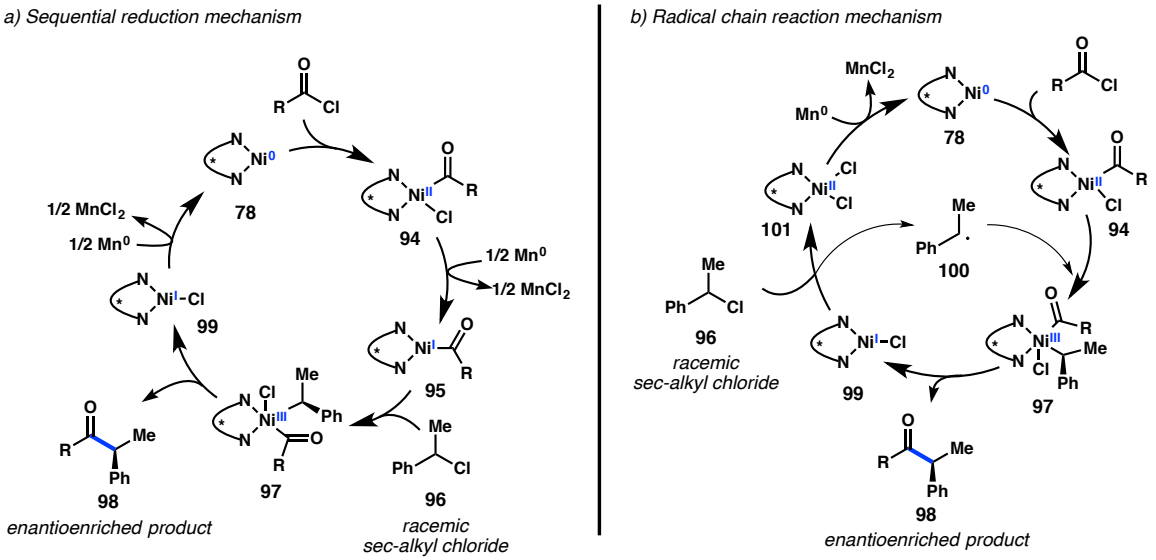
R^1 = alkyl, aryl
Y = Cl, S(2-Py), OCO_2R

R^2 = alkyl, allyl, benzyl (1° or 2°)
X = I, Br, Cl (only when R^2 = benzyl)

Although several mechanisms have been proposed for these reactions, two limiting cases will be considered here.[12] First, in a sequential reduction mechanism, concerted oxidative addition of the acyl chloride to Ni^0 **78** could generate Ni^{II}-acyl complex **94**, which could be reduced by Mn^0 to afford Ni^I-acyl species **95** (**Figure 2.2**). Single-electron oxidative addition of benzyl chloride **96** via a radical rebound process would then generate Ni^{III} complex **97**, converging both enantiomers of **96** to a single diastereomer of **97**. Reductive elimination of ketone **98** from **97** followed by reduction of Ni^I-chloride **99** would close the catalytic cycle. The basis for high cross-selectivity arises from the different rates of oxidative addition of the $C(sp^2)$ and $C(sp^3)$-hybridized electrophiles with Ni^0 and Ni^{II}, respectively, while the single-electron reaction of **96** affords an entry to stereoconvergence.[13]

An alternative proposal is a radical chain mechanism, wherein Ni^{II}-acyl complex **94**, formed by reaction of Ni^{0} with an acyl chloride, combines with free benzylic radical **100** to produce Ni^{III} complex **97**. Reductive elimination delivers ketone **98** and Ni^{I}-chloride **99**, which can abstract the benzylic halide from **96**, resulting in chain propagation. Reduction of Ni^{II}-dichloride **101** by Mn^{0} to reform Ni^{0} complex **78** closes the catalytic cycle. The key mechanistic difference between these two proposed cycles is the lifetime of benzylic radical **100**: If **100** recombines with the Ni center that generated it, then the sequential reduction mechanism is operative, whereas if **100** undergoes solvent cage escape to combine with another Ni center, then the radical chain mechanism is operative. Recent studies by Weix and coworkers support a radical chain mechanism for the related reductive coupling of aryl and alkyl halides.[12b]

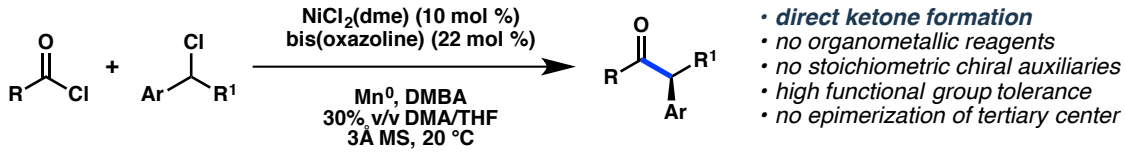
Figure 2.2. *Two potential mechanisms for Ni-catalyzed reductive cross-coupling.*



Regardless of which mechanism is operative under our reaction conditions, we hypothesized that an appropriate chiral catalyst could promote a stereoconvergent cross-coupling of benzyl chloride **96**. Halide abstraction by Ni^{I} in either cycle would generate

the stabilized prochiral radical **100**, facilitating stereoconvergence. Indeed, Fu and coworkers have demonstrated that chiral Ni catalysts can promote stereoconvergent cross-couplings of racemic secondary electrophiles with organometallic reagents under similar reaction conditions.[14] While a stereoconvergent oxidative addition is one possible mechanism of enantioinduction, Molander and Kozlowski have also recently established the feasibility of a stereochemistry-determining reductive elimination.[13b] Based on this mechanistic reasoning, we asked whether the use of a chiral Ni catalyst could enable the stereoconvergent synthesis of enantioenriched α,α-disubstituted ketones from racemic alkyl halides. Herein we report the successful realization of this strategy, leading to the development of the first enantioselective Ni-catalyzed reductive cross-coupling reaction between halide electrophiles (**Scheme 2.7**).

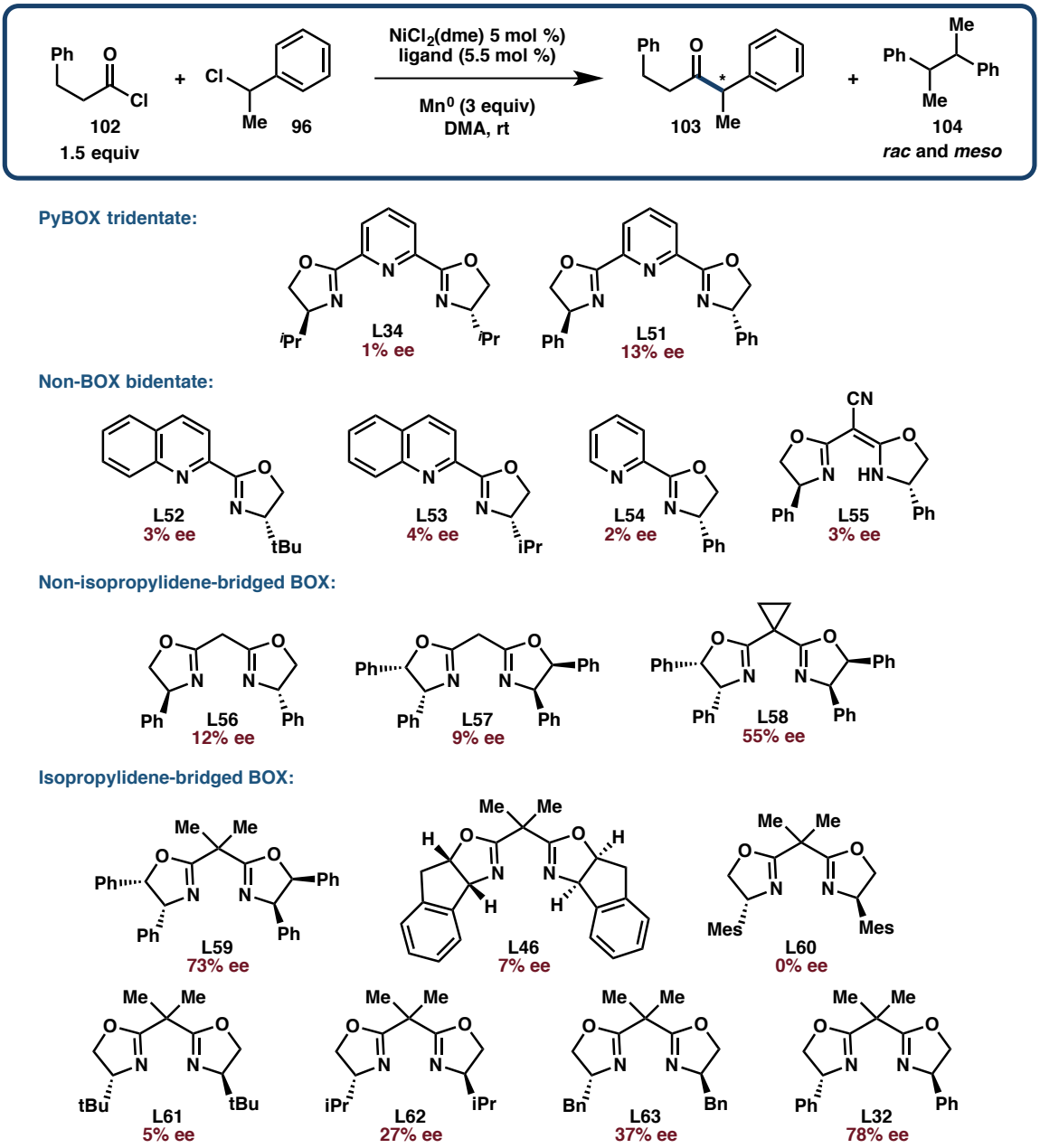
Scheme 2.7. *This work: Asymmetric reductive acyl cross-coupling.*



2.2 REACTION DEVELOPMENT

We began our study employing the racemic conditions reported by Weix *et al.* (**Figure 6**, **entry 3**) and conducting a chiral ligand screen. We selected as our model substrates 3-phenylpropionyl chloride (**55**) as the acyl chloride component and (1-chloroethyl)benzene (**96**) as the C(sp^3) partner. Utilizing 5 mol % $NiCl_2$(dme), 3 equivalents of Mn^0 as the terminal reductant, and DMA as solvent, we evaluated a variety of ligand architectures for enantioinduction (**Scheme 2.8**).

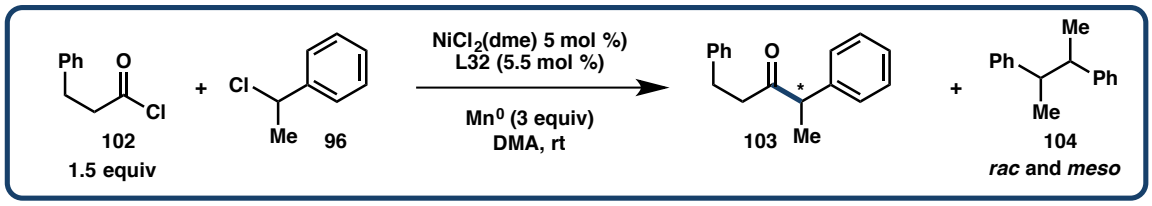
Scheme 2.8. *Initial evaluation of chiral ligands.*



Tridentate PyBOX scaffolds employed in some reductive couplings of alkyl electrophiles were found to give low ee (**L34** and **L51**).[12a] Moving to bidentate ligands, semicorrin (**L55**) and Quin/PyOx ligands (**L52-54**) also gave low enantioinduction. The best ligand family was found to be the bisoxazoline (BOX) ligands, with the

isopropylidene-bridged entries generally giving the highest ee's. Cyclopropylidene (**L58**) and methylidene bridged (**L56-57**) BOX ligands afforded poor results. We were delighted to find that one ligand, PhBOX (**L32**), afforded **103** in an encouraging 78% ee, but only trace yield. The major product of this reaction was observed to be homocoupling of the benzylic chloride partner to afford bibenzyl **104** as a 1:1 mixture of the *rac* and *meso* compounds (45% yield).

Table 2.1. *Solvent and reductant screens.*



a) Solvent screen:

Entry	Solvent	ee (%)
1	DMPU	37
2	DMF	50
3	DMA	66
4	DME	72
5	EtOAc	82
6	THF	92

b) Reductant screen in THF:

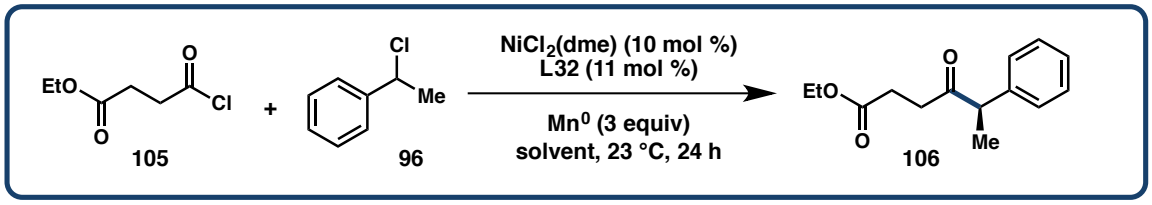
Entry	Reductant	Conversion (%)	Yield (%)	ee (%)
1	Mn^0	43	19	92
2	Zn^0	100	10	88
3	Mg^0	100	trace	20
4	Co^0	0	0	--
5	Fe^0	0	0	--
6	$CoCp_2$	0	0	--

To address the issue of chemoselectivity as well as enantioselectivity, we began a systematic exploration of the other reaction parameters. Beginning with solvent, we explored a range of polar solvents common to reductive cross-couplings (DMPU and DMF shown, **Table 2.1a**, entries 1 and 2). None of these were found to improve ee or reduce side-product formation. Moving to a broader solvent screen, we noted an improvement in ee with decreasing solvent polarity, with THF affording **103** in 92% ee. However, **103** was still produced in only 19% yield due to poor conversion, with

competitive dimerization of the benzylic partner being the major product (**104**). Other ethereal solvents such as *tert*-butyl methyl ether, cyclopentyl methyl ether, and diethyl ether gave no product and failed to suspend the powdered Mn^0 throughout the reaction.

At this stage, control experiments run in the absence of Ni showed that Mn could facilitate the homocoupling side-reaction. Therefore, we investigated other terminal reductants that have been employed in reductive cross-coupling, as well as less commonly used entries (selected results shown in **Table 2.1b**). Soluble reductants were sought especially due to the difficulties inherent in maintaining the heterogeneous Mn suspension. These included tetrakis(dimethylamino)ethylene (TDAE), cobaltocene, chromium dichloride, and $Ru(bpy)_3/h\nu$. Unfortunately none of the homogeneous reductants gave more than trace product in the reaction. Additional heterogeneous reductants screened included zinc, magnesium, gallium, indium, aluminum, and iron. Of all reductants, only Zn was shown to furnish product, albeit in decreased yield (10%) and ee (88%) relative to Mn.

Table 2.2. *Evaluation of binary solvent conditions.*

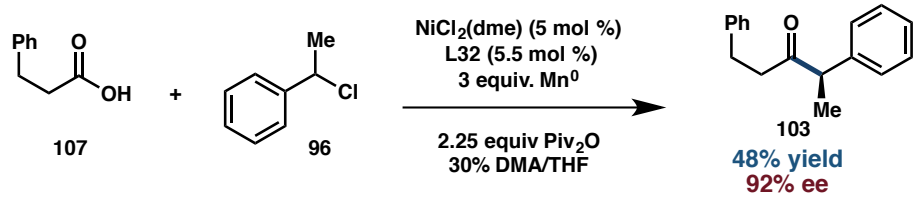


Entry	Solvent	Conversion (%)	Yield (%)	ee (%)
1	THF	72	24	86
2	10% DMA in THF	45	46	87
3	20% DMA in THF	57	47	87
4	30% DMA in THF	90	62	86
5	40% DMA in THF	87	36	82
6	50% DMA in THF	100	43	74
7	75% DMA in THF	100	52	64
8	DMA	100	59	73

With Mn conclusively identified as the optimal reductant, we returned to investigating the solvent system for this reaction. While DMA and other amide solvents had afforded full conversion of the starting materials, these solvents afforded large amounts of homocoupling and lower enantioselectivity. THF afforded **106** in slightly higher yields and excellent ee, but with sluggish reactivity and lower conversions. This led us to hypothesize that a mixed solvent system may be optimal, with polar amide solvents being critical for reactivity and THF being necessary for good enantioinduction. To evaluate this, screens of amide cosolvents (DMF, DMA, N,N-diethylacetamide and N,N-diisopropylacetamide) in a gradient with THF showed that DMA was the optimal amide, with 30% DMA in THF as the best ratio (**Table 2.2**). This combination afforded 62% yield of **106** while maintaining a high 86% ee. The improved reactivity with DMA may suggest that a higher dielectric solvent is required to achieve optimal rates of

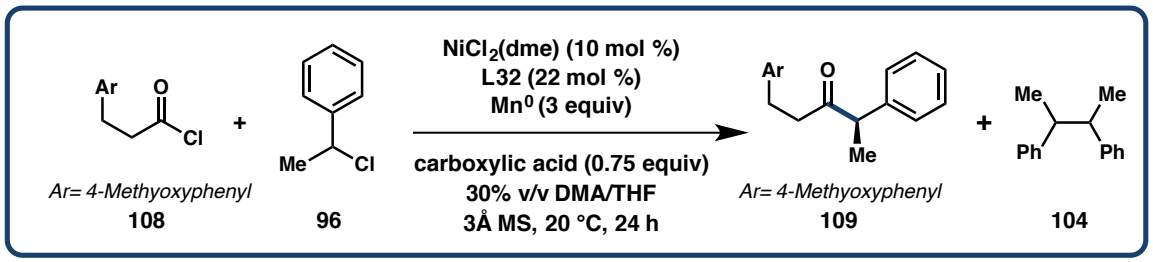
electron transfer events, or it may reflect some solvation of key Ni intermediates and aggregation states.

Scheme 2.9. *Reductive cross-coupling of anhydride acyl electrophiles.*



The use of a binary solvent system led to a significantly improved reaction profile, with modest yields and excellent ee. In an effort to further improve yields, we decided to explore other acyl electrophiles positing that a more reactive acyl partner might outcompete side-reactions such as homocoupling. Carboxylic acids have been shown to undergo reductive cross-couplings in the presence of super-stoichiometric amounts of pivalic anhydride via the intermediacy of mixed anhydrides.[15] Therefore, we explored this cross-coupling under analogous conditions, employing hydrocinnamic acid (**107**), and 2.25 equivalents of pivalic anhydride (**Scheme 2.9**). A similar result in terms of yield and enantioselectivity was observed with this substrate. However the yield based on recovered starting material was substantially improved and less bibenzyl **104** was formed. While it was unclear what led to this improvement, we hypothesized that the presence of carboxylic acid (either starting material or pivalic acid generated as a byproduct) in these reactions may be responsible for this change in reactivity.

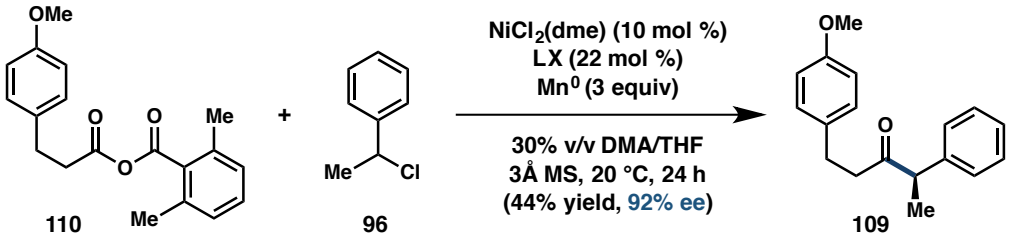
Table 2.3. *Evaluation of carboxylic acid additives.*



Entry	Acid	Yield 104 (%)	Yield 109 (%)	ee 109 (%)
1	--	22	52	94
2	AcOH	17	65	92
3	BzOH	14	40	92
4	DMBA	4	85	93

A screen of carboxylic acid additives was therefore conducted to evaluate their role in attenuating formation of dimer **104**. As an initial control, 1 equivalent of HCl was added to determine if unselective protonation by the carboxylic acid was solely responsible for the observed effects. This resulted in complete decomposition with no observed product formation. From here we turned our attention to carboxylic acid additives exclusively. It became clear that aryl carboxylic acids were the most effective at inhibiting the homocoupling reaction, with benzoic acid emerging as an early lead. More extensive screening indicated that electron-rich benzoic acids gave the best improvements in reactivity. Of these, 2,6-dimethylbenzoic acid (DMBA) provided the best yields. Further optimization of the reaction concentration, the ligand-to-metal ratio, and addition of 3Å molecular sieves permitted ketone **109** to be obtained in 85% yield and 93% ee, with only a 4% yield of homodimer (**Table 2.3**, entry 4). It was also observed that these additives led to slower rates overall, with the reaction of some substrates stalling at incomplete conversion.

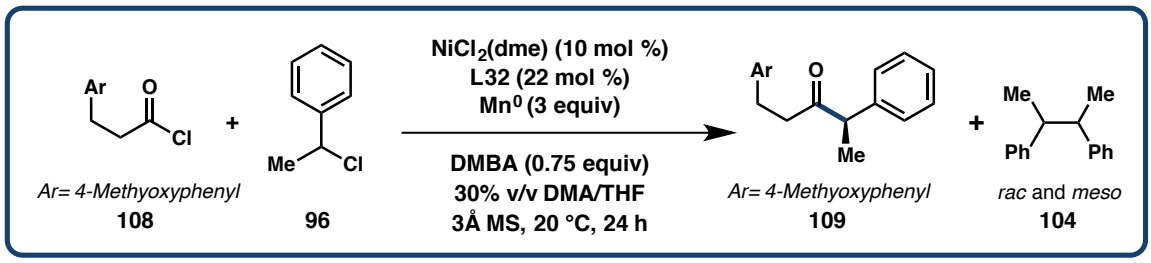
Scheme 2.10. *Reaction of a preformed mixed DMBA anhydride.*



We imagined that a mixed anhydride generated *in situ* from acyl chloride **108** and DMBA may be the active acyl electrophile in this transformation, potentially explaining the change in reaction profile. To explore this, we prepared anhydride **110** and subjected it to the reaction conditions (**Scheme 2.10**). As expected, **110** is a competent electrophile in the reductive cross-coupling. The reaction afforded **109** in identical ee, suggesting that it may intercept the same productive catalytic cycle. However the yield obtained was significantly lower than that observed using exogenous DMBA, indicating that the mixed anhydride is likely not the sole active acyl electrophile.

A mixture of acyl chloride **108** and DMBA under the reaction conditions in the absence of Ni or benzyl chloride does not lead to the formation of **110**, and **110** is not observed during the reaction, leading us to believe the role of DMBA is not simple anhydride formation. Rather, it may coordinate to Ni at some point in the catalytic cycle, altering the relative rates of key steps. It is interesting to note that DMBA exerts the greatest influence over product distribution in neat THF, while it leads to minimal change in neat DMA. This may be explained by DMBA's decreased relative coordination ability in a polar medium, in which it must compete with the amide solvent for coordination of Ni intermediates. However, further investigations are required to determine the role of DMBA in the catalytic reaction.

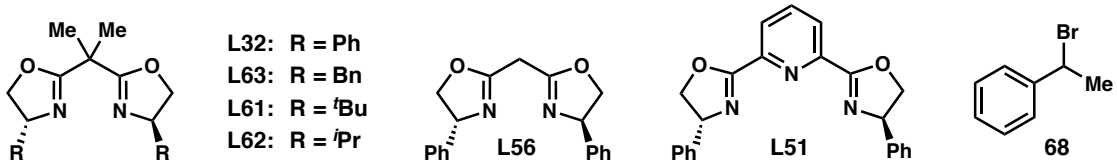
***Table 2.4**. Control experiments for optimized reaction conditions.*



Ar= 4-Methyoxyphenyl **108** | **96** | *Ar= 4-Methyoxyphenyl* **109** | *rac* and *meso* **104**

Entry[a]	Deviation from conditions	Conv. 96[b]	Yield 104[b]	Yield 109[b]	ee[c] 109	Entry[a]	Deviation from conditions	Conv. 96[b]	Yield 104[b]	Yield 109[b]	ee[c] 109
1	none	90	4	85	92	12	L63, no L32	61	24	22	45
2	no Mn^0	0	0	0	--	13	L56, no L32	15	1	10	0
3	no $NiCl_2$(dme)	35	35	0	--	14	L51, no L32	99	53	4	9
4	no L32	73	5	8	--	15	11 mol % L32	82	3	72	92
5	no DMBA	100	22	52	94	16	neat DMA	99	43	30	88
6	No 3 Å MS	100	7	76	90	17	neat THF	25	<1	26	94
7	Zn^0, no Mn^0	85	26	31	88	18	neat MeCN	28	4	16	45
8	$Ni(cod)_2$, no $NiCl_2$(dme)	98	18	68	92	19	AcOH, no DMBA	96	17	65	92
9	$CoCl_2$, no $NiCl_2$(dme)	73	24	0	--	20	PivOH, no DMBA	97	51	33	92
10	L61, no L32	98	62	14	2	21	BzOH, no DMBA	73	14	40	92
11	L62, no L32	89	52	40	69	22	BnBr 68, no 96	100	42	58	92

[a] Reactions conducted on 0.2 mmol scale under an N_2 atmosphere in a glovebox. [b] Determined by GC versus an internal standard. [c] Determined by SFC using a chiral stationary phase.



With the conditions described above in hand, we conducted a series of control experiments to confirm the necessity of all the identified reaction components (**Table 2.4**).[16] As expected, Ni and Mn are required for the cross-coupling to proceed (**Entries 2 and 3**). However, Mn alone is capable of mediating homocoupling of the benzylic partner (**Entry 3**). The desired reaction appears to be ligand-dependent, with the ligand free conditions affording significant decomposition (**Entry 4**). 2,6-DMBA provides a

marked decrease in homocoupling, while other acid additives are less effective (**Entry 5 vs. entries 19-21**). $NiCl_2$(dme) was still shown to be the optimal Ni source, although the use of $Ni(cod)_2$ instead demonstrates that Ni^0 is capable of entering the catalytic cycle (**Entry 8**). In contrast, $CoCl_2$ gave none of the desired **109** (**Entry 9**). A follow-up ligand screen returned the same results as the initial investigation, with phenyl substitution (**L32**) being optimal and the isopropylidene bridge proving necessary for high ee (**Entries 10-15**). The solvent effects determined in the initial evaluation were unchanged by optimization, with DMA being required for reactivity and THF needed for high enantioinduction (**Entries 16-18**). Finally, the benzylic bromide substrate **68** did not lead to an improvement in reactivity, being more prone to homocoupling and affording a lower yield of **109**, albeit in the same ee (**Entry 22**).

Additional variables explored

Over the course of the extensive optimization process, many additional variables and additives were studied that did not generate any productive impact on the reaction. However some of these gave insight into the reaction nonetheless; these are summarized below.

Lewis acid additives: It was hypothesized that activation of the acid chloride partner via Lewis acid coordination could increase its reactivity relative the benzyl chloride partner, reducing homocoupling. Strong Lewis acids such as $TiCl_4$ were found to erode ee and yield while milder ones had no effect. LiCl was singularly found to decrease ee to 3% without significantly impacting yield.

Bases: The Weix group has noted in some of their reductive cross-coupling methodologies that addition of pyridine leads to increased yields and improved

reproducibility.[17] They postulate that pyridine may act to stabilize Ni^{III} intermediates in the catalytic cycle, promoting the desired pathway. To investigate this, coordinating and noncoordinating amine bases as well as inorganic bases were added to the reaction. The addition of K_2CO_3, 2,6-di-t-Bu-pyridine, pyridine, and DIPEA did not significantly impact the reaction. It is notable that these are tolerated in that they do not lead to racemization of the products or intermediates, nor do they inhibit the reaction via undesirable coordination.

π-Acids: The addition of π-acids to catalytic cross-coupling reactions has been shown to facilitate reductive elimination, improving turnover and reaction yields in some cases.[18] While there does not appear to be an issue in this step of the desired catalytic cycle, we conducted the simple experiment of adding maleic anhydride as well as *p*-fluorostyrene to the reaction. These additives served only to promote homocoupling, improving turnover of the undesired pathway with no observed increase in cross-coupled yield.

Halide additives: The Weix and Reisman groups have noted in some of their reductive cross-coupling methods that the addition of sub-stoichiometric NaI leads to an increase in yield.[19] Suggested explanations for this include assistance in electron transport in the catalyst turnover steps, formation of more reactive alkyl iodides *in situ*, or the formation of nickelate complexes. Therefore we screened the addition of catalytic NaI and TBAI as well as TBAB and TBAC as halide sources. None of these significantly impacted the reaction.

Metal-surface activators: Contrary to findings by Durandetti,[20] Weix,[21] and later work by our laboratory (see Chapters 3-5),[22] treatment of the stoichiometric metal reductant

with activating agents such as TMSCl, Brønsted acids, and 1,2-dibromoethane had no effect.

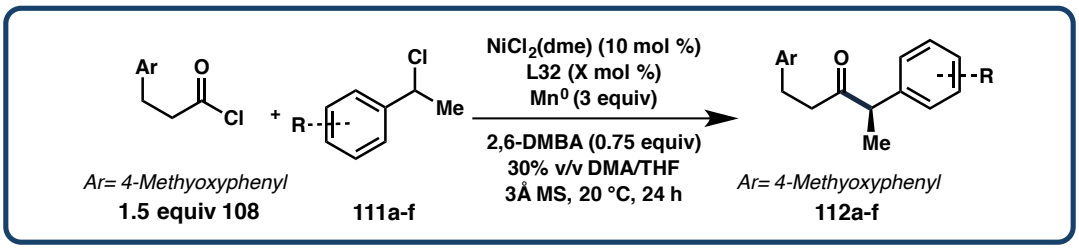
Nickel sources: Most Ni^{II} sources give yields within 10% of $NiCl_2$(dme) ($NiCl_2$, $NiBr_2$•xH_2O, $Ni(BF_4)_2$, $Ni(acac)_2$, $Ni(hfacac)_2$). $Ni(cod)_2$, the only Ni^0 source explored, gave a modest yield, identical ee, and increased homocoupling even in the presence of DMBA. Therefore $NiCl_2$(dme) was used as the Ni source in all substrate screening.

Prestir time: We examined a prestir interval of Ni, ligand, and Mn prior to the addition of substrates. This variable was periodically explored throughout the optimization. Optimized systems showed a decrease in yield with longer prestir time, with no prestir being the optimal condition. We tentatively attribute this effect to catalyst dimerization, with the prestir generating Ni^I halides that can then dimerize in the absence of reactants. No prestir was used in subsequent substrate evaluation.

2.3 SUBSTRATE SCOPE

With optimized conditions in hand, we sought to explore the substrate scope of the reaction with respect to both partners. Beginning with the benzyl chloride component, we examined substitution about the ring as well as the effect of α-substitution.

Table 2.5. *Electron-rich benzyl chloride substrate scope.*



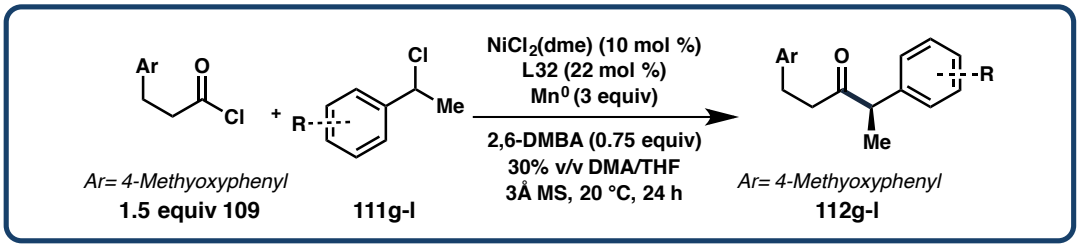
R	Product	L:M	Conversion 111[a]	Yield 112[b]	ee 112[c]
H	112a	2.2: 1	>90	79	93
		3.3: 1	100	80	93
2-Me	112b	2.2: 1	100	35	72
3-Me	112c	2.2: 1	72	51	94
		3.3: 1	81	75	91
4-Me	112d	2.2: 1	77	64	93
		3.3: 1	78	72	93
4-OMe	112e	2.2: 1	69	48	89
		3.3: 1	64	56	86
2-Nap	112f	2.2: 1	74	50	92
		3.3: 1	100	65	91

[a] Determined by GC versus an internal standard. [b] Isolated yield, reactions conducted on 0.2 mmol scale under an N_2 atmosphere in a glovebox. [c] Determined by SFC using a chiral stationary phase.

Electronic perturbations to the benzyl chloride partner were found to exert a significant impact on the reaction. Electron-donating substituents on the phenyl ring generally led to slower reaction rates, with the reactions not reaching full conversion (**Table 2.5**). However the yields and ee's were high for these substrates, with the lowest being for the strongly donating *p*-methoxy substrate (**112e**). Yields for these substrates were found to increase with higher ligand to metal ratios, with 3.3:1 being optimal for all of the substrates. This may simply be the result of the slow reaction rate necessitating

higher ligand loadings to prevent catalyst death over the increased reaction time. *Ortho*-substitution is poorly tolerated (**112b**), leading to only modest ee's and poor yields.

Table 2.6. *Electron-poor benzyl chloride substrate scope.*



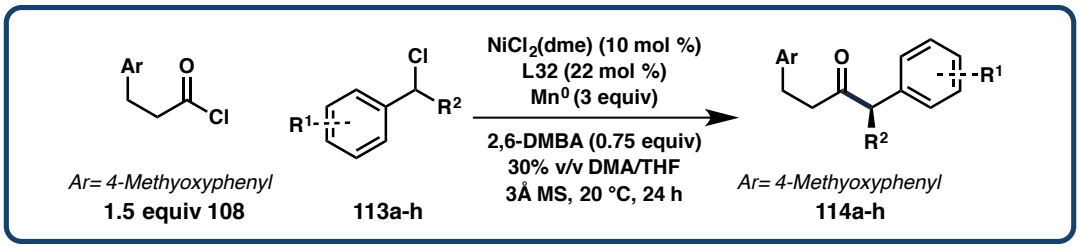
R	Product	Conversion 110[a]	Yield 112	ee 112[c]
4-CN	112g	100	44[a]	66
4-CF_3[d]	112h	100	64[b]	82
4-Cl	112i	100	76[b]	91
4-Br[e]	112j	100	73[b]	86
4-CO_2Et	112k	100	25[a]	70
4-B(pin)	112l	100	52[a]	74

[a] Determined by GC versus an internal standard. [b] Isolated yield, reactions conducted on 0.2 mmol scale under an N_2 atmosphere in a glovebox. [c] Determined by SFC using a chiral stationary phase. [d] Run in 20% v/v DMA/THF. [e] Run with 1.25 equiv DMBA.

Substrates bearing electron-withdrawing substituents on the aryl ring behave rather differently, with conversion occurring more quickly and reaching completion in all cases (**Table 2.6**). Additionally, these reactions did not require or benefit from increased ligand loading. At a 2.2: 1 ligand: metal ratio, many of these substrates gave good yields and ee's. However, these numbers began to decline as strongly withdrawing substituents were introduced, with *p*-trifluoromethyl **112h** giving 86% ee and *p*-boronic acid pinacol ester **112l** giving 75% ee. We were pleased to find that the reaction is completely orthogonal to aryl halides, with the *p*-bromo (**111j**) and *p*-chloro (**111i**) substrates coupling chemoselectively. These substrates provide useful handles for further derivatization of the cross-coupled products.

Unfortunately, benzylic halides bearing conjugated electron-withdrawing groups were not well tolerated. The *p*-carboxaldehyde, *p*-acetyl, and ethyl *p*-carboxylate **111k** substrates produced very messy reactions with only trace to low yields of product obtained. Sufficient *p*-acetyl product was isolated, although not cleanly, to obtain an ee value of 60% for this substrate. Finally, benzonitrile substrate **111g** gave only moderate yield and selectivity. We hypothesize that stabilized radical intermediates generated from these substrates may be sufficiently long-lived to escape the solvent cage and participate in side reactions. These non-inner sphere side reactions may generate racemic product, deteriorating ee, while unproductive side reactions would explain the low yields and messy crude spectra obtained for these substrates.

Table 2.7*. α-Substituted benzyl chloride substrate scope.*



R^1	R^2	Product	Conversion 113[a]	Yield 114[b]	ee 114[c]
H	Et	114a	72	50	94
H	Bn	114b	100	79	92
H	CH_2OTBS	114c[f]	60	51	89
H	*i*Pr	114d	low	trace[a]	82
H	4-pentenyl	114e	100	38	92
H	CO_2Ph	114f	65	38[a]	89
4-Cl	Et	114g	70	65	90
2,3-dihydro-1H-inden-1-yl		114h	100	68	78

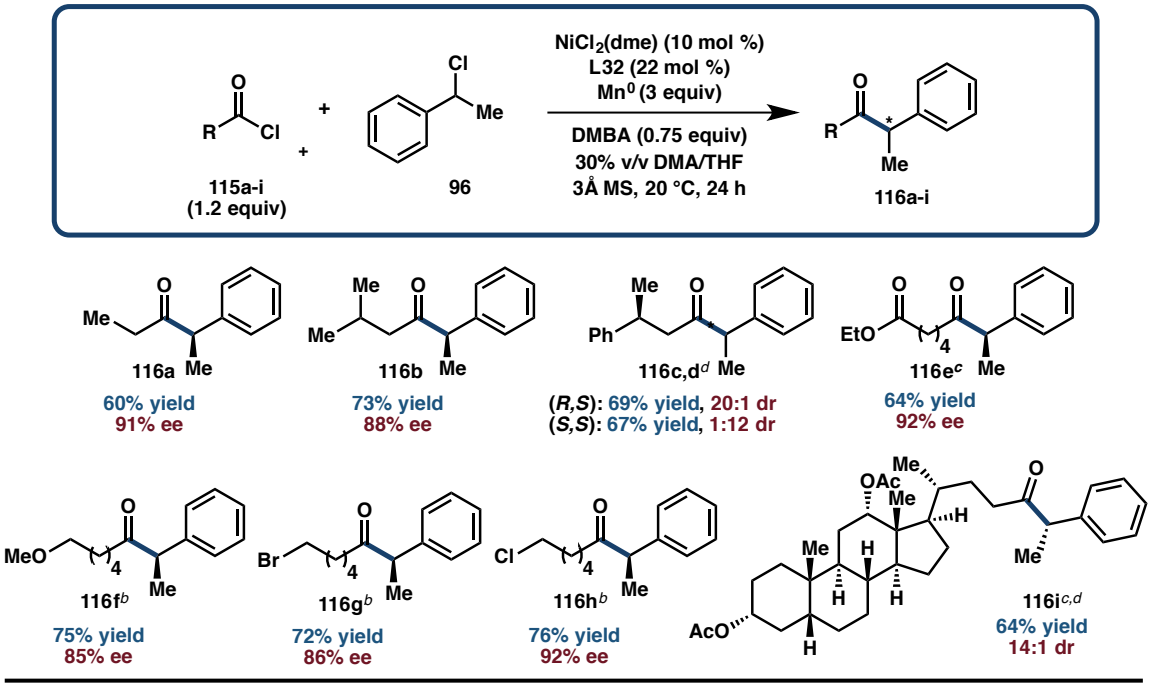
[a] Determined by GC versus an internal standard. [b] Isolated yield, reactions conducted on 0.2 mmol scale under an N_2 atmosphere in a glovebox. [c] Determined by SFC using a chiral stationary phase. [d] Run in 50% v/v THF/DMA.

Lastly, substrates bearing substituents at the benzylic α-position were also shown to cross-couple smoothly, providing the ketone products in good to excellent ee's (**Table**

2.7). These substrates generally reacted more slowly and did not reach full conversion. The exception to this is the anomalously well-performing deoxybenzoin-derived substrate **113b**, bearing an α-benzyl group. Synthetically valuable substrates such as β-silyloxy **113c** and the α-benzoate-substituted **113f** coupled with high ee and no observed elimination under the reaction conditions. The yield of **114c** was improved further by increasing the DMA loading to 50%, although no benefit was obtained beyond that. Increasing the bulk of the α -substituent to an isopropyl group (**113d**) was not tolerated, affording only a trace of detectable **114d**. Finally, a cyclic benzylic chloride, the indanyl **113h,** provided the ketone in more modest selectivity but still high yield.

It is worth noting that the reaction was also conducted employing benzylic bromides. The *p*-fluoro-, α-ethyl-, and unsubstituted model substrates were prepared and explored alongside the chlorides. It was found that while these substrates undergo the cross-coupling with nearly identical enantioselectivity, they afford lower yields of the desired product and undergo homocoupling more readily (see **Table 2.4, entry 22**). Manipulation of DMBA loading and solvent ratio were not found to effectively mitigate this and the benzyl bromides were not pursued further.

Scheme 2.11. *Acid chloride substrate scope.*



[a] Isolated yield, reactions conducted on 0.2 mmol scale under an N_2 atmosphere in a glovebox. % ee determined by SFC using a chiral stationary phase. [b] Run in 20% v/v DMA/THF. [c] Run in 10% v/v DMA/THF. [d] Run with *ent*-**L32.**

We then turned our attention to the substrate scope of the acid chloride coupling partner (**115a-i**) (**Scheme 2.11**). It was quickly determined that increased steric bulk at the α-carbon resulted in poor reactivity, with cyclohexanecarbonyl chloride and *t*-butylacetyl chloride giving only poor ee's and yields (not shown). Interestingly, aroyl chlorides and aryl acetyl chlorides did not afford any cross-coupled products under the reaction conditions. Finally, substrates capable of forming 4- and 5-membered chelates upon oxidative addition to Ni (methoxyacetyl, 3-phenoxyprionyl, and methyl malonyl chloride) were found to be unsuccessful substrates. With these exceptions however, the reaction was found to be functional group- and branching-tolerant. 6-Chloro- (**115h**) and 6-bromohexanoyl chloride (**115g**) behaved well, demonstrating perfect chemoselectivity of the reaction in the presence of unactivated alkyl halides. These, as well as the ester-

containing adipoyl substrate (**115e**), are notable because their products are not directly accessible by chiral auxiliary-directed alkylation followed by Weinreb ketone synthesis. Reaction with either enantiomer of 3-phenylbutyryl chloride (**115c,d**) gave excellent catalyst-controlled diastereoselectivity and good yields. The more highly functionalized steroidal acyl chloride derived from deoxycholic acid (**115i**) also delivered high yields and excellent dr.

2.4 CONCLUSION

A new method has been developed for the direct enantioselective preparation of acyclic α,α-disubstituted ketones. This reaction is the first reported example of a catalytic asymmetric reductive cross-coupling of halide substrates. This approach presents nucleophile-free cross-coupling as a viable alternative to traditional methods of accessing chiral products. It does not require the use of stoichiometric chiral auxiliaries or pregenerated organometallic reagents, marking an advance in both usability and efficiency. The acyl chloride and benzylic chloride substrates are commercially available or easily prepared from carboxylic acids and benzylic alcohols respectively and are bench-stable, enabling the rapid assembly of stereogenic acyclic ketones from accessible materials. The further development and application of this reaction, as well as study of the mechanism, is the focus of ongoing research in our laboratory.

2.5 EXPERIMENTAL SECTION

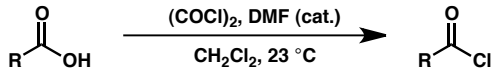
2.5.1 *Materials and Methods*

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), and acetonitrile (MeCN) were dried by passing through activated alumina columns. Anhydrous dimethylacetamide (DMA) was purchased from Aldrich and stored under inert atmosphere. Manganese powder (-325 mesh, 99.3%) was purchased from Alfa Aesar. Unless otherwise stated, chemicals and reagents were used as received. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, *p*-anisaldehyde, or $KMnO_4$ staining. Flash column chromatography was performed as described by Still et al. using silica gel (partical size 0.032-0.063) purchased from Silicycle. Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ^1H and ^{13}C NMR spectra were recorded on a Varian 400 MR (at 400 MHz and 101 MHz, respectively) or a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), and are reported relative to internal $CHCl_3$ (^1H, δ = 7.26) or acetone (^1H, δ = 2.05), and $CDCl_3$ (^{13}C, δ = 77.0) or acetone (^{13}C, δ = 29.8). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI) or mixed (MM) ionization mode, or

obtained from the Caltech Mass Spectral Facility in fast-atom bombardment mode (FAB). Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system with Chiralcel AD-H, OD-H, AS-H, OB-H, and OJ-H columns (4.6 mm x 25 cm) with visualization at 210 nm. Analytical achiral GC was performed with an Agilent 6850 GC utilizing an Agilent DB-WAX (30.0 m x 0.25 mm) column (1.0 mL/min He carrier gas flow).

2.5.2 Substrate Synthesis

General Procedure 1: Acid Chloride Synthesis (115)



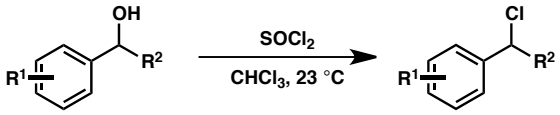
A flask was charged with the appropriate carboxylic acid (1.0 equiv) and CH_2Cl_2 (0.5 M). Two drops of DMF and oxalyl chloride (1.2 equiv) were added dropwise. The solution was stirred at 23 °C for 3 h and then concentrated. The crude acid chloride was used without any further purification.

3-(4-methoxyphenyl)Propanoic 2,6-dimethylbenzoic anhydride (110)

A flame-dried flask was charged with 2,6-dimethylbenzoic acid (1.0 mmol, 1 equiv) and CH_2Cl_2 (0.33 M). To the solution was added NaH (60% dispersion in oil, 1.05 mmol, 1.05 equiv) and the reaction was allowed to stir for 3 h. 3-(4-methoxyphenyl)propanoyl chloride (**108**, 1.0 mmol, 1 equiv) was added dropwise to the reaction mixture and the

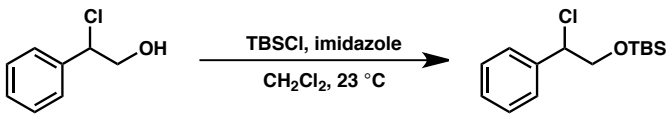
reaction was stirred overnight. The crude mixture was filtered through a small plug of celite with CH_2Cl_2 and concentrated to afford **110** as a light yellow oil (291.1 mg, 93% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (t, *J* = 7.7 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 2H), 7.06 (d, *J* = 7.5 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 4H), 3.79 (s, 3H), 2.97 (t, *J* = 7.6 Hz, 2H), 2.82 (dd, *J* = 4879.7, 7.5 Hz, 4H), 2.37 (d, *J* = 0.7 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 165.1, 158.2, 135.8, 131.7, 131.6, 130.4, 129.3, 127.9, 114.0, 55.3, 37.5, 29.4, 20.0; FTIR (NaCl, thin film): 2955, 2931, 2836, 1811, 1740, 1612, 1595, 1584, 1513, 1466, 1301, 1248, 1179, 1124, 1079, 1036, 990, 827, 775 cm^{-1}; LRMS (ESI) calc'd for $[M+Na]^+$ 335.1, found 335.1.

General Procedure 2: Benzyl Chloride Synthesis (111 and 113)



A flask was charged with the appropriate benzyl alcohol (1.0 equiv) and $CHCl_3$ (1.5 M). Thionyl chloride (1.05 equiv) was added dropwise. Evolved gas was quenched via cannula into aqueous $NaHCO_3$. The solution was stirred at 23 °C for 12 h and then concentrated to afford a yellow oil. The crude residue was purified by Kugelrohr distillation to isolate a clear oil. Spectral data for all compounds matched those reported in the literature.

[1-chloro-2-(*t*-butyldimethylsiloxy)ethyl]benzene (113c).



To a flask was added 2-chloro-2-phenylethanol (8.5 mmol, 1.0 equiv) and CH_2Cl_2 (18 mL, 0.5 M) followed by imidazole (10.2 mmol, 1.2 equiv) and *tert*-butyldimethylsilyl chloride (10.2 mmol, 1.2 equiv). The reaction was stirred at 23 °C for 24 h and then quenched by pouring into water (40 mL). The aqueous and organic layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 X 20 mL). The combined organic layers were washed with brine (1 X 20 mL) and dried (Na_2SO_4), filtered, and concentrated. The crude residue was filtered through a thick pad of silica with hexanes and concentrated to afford a clear oil (2.21 g, 96% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 5H), 4.87 (t, *J* = 6.6 Hz, 1H), 4.00 (dd, *J* = 10.7, 6.8 Hz, 1H), 3.92 (dd, *J* = 10.7, 6.5 Hz, 1H), 0.85 (s, 9H), 0.01 (s, 3H), –0.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0, 128.39, 128.37, 127.6, 68.5, 63.3, 25.7, –5.4, –5.5; FTIR (NaCl, thin film): 2955, 2928, 2884, 2856, 1494, 1472, 1361, 1257, 1123, 1080, 837, 778 cm^{-1}; HRMS (FAB) calc'd for $[M+H]^+$ 271.1279, found 271.1290.

2.5.3 Enantioselective Reductive Cross-Coupling

General Procedure 3 (Variable Screening)

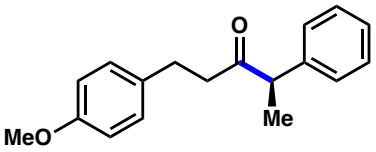
On a bench-top, to a 1/2 dram vial was added the appropriate ligand (0.044 mmol, 22 mol %), carboxylic acid (0.15 mmol, 0.75 equiv), 3 Å mol sieves (30 mg/0.2 mmol benzyl chloride), powdered metal reductant (0.6 mmol, 3 equiv), and nickel source (0.02 mmol, 10 mol %). Under an inert atmosphere in a glovebox, the vial was charged with the appropriate solvent (0.53 mL, 0.38 M) followed by benzyl chloride (0.2 mmol, 1 equiv), acid chloride (0.24 mmol, 1.2 equiv), and dodecane (internal standard). The mixture was stirred at 240 rpm, ensuring that the reductant was uniformly suspended. Stirring

continued at 20 °C under inert atmosphere for 24 h. The black slurry was transferred to a separatory funnel using 1 M HCl (5 mL) and diethyl ether (10 mL). The mixture was diluted with H_2O (10 mL) and the aqueous and organic layers were separated. The aqueous layer was extracted with diethyl ether (2 × 10 mL) and the combined organic layers were washed with brine (1 × 15 mL) and dried ($MgSO_4$), filtered, and concentrated. The crude residue was analyzed by GC.

General Procedure 4: Enantioselective Reductive Coupling of Benzyl Chlorides and Acid Chlorides

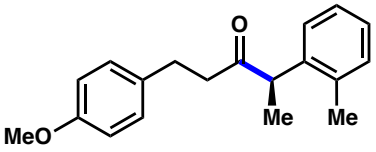
On a bench-top, to a 1/2 dram vial was added (*R*,*R*)-**L32** (0.044 mmol, 22 mol %), 2,6-DMBA (0.15 mmol, 0.75 equiv), 3 Å mol sieves (30 mg/0.2 mmol benzyl chloride), manganese powder (0.6 mmol, 3 equiv), and $NiCl_2$(dme) (0.02 mmol, 10 mol %). Under an inert atmosphere in a glovebox, the vial was charged with 30% v/v DMA/THF (0.53 mL, 0.38 M) followed by benzyl chloride (**111** or **113**, 0.2 mmol, 1 equiv) and acid chloride (**108**, Table 2.5-2.7: 0.3 mmol, 1.5 equiv; **115**, Scheme 2.11: 0.24 mmol, 1.2 equiv). The mixture was stirred at 240 rpm, ensuring that the manganese powder was uniformly suspended. Stirring continued at 20 °C under inert atmosphere for 24 h. The black slurry was transferred to a separatory funnel using 1 M HCl (5 mL) and diethyl ether (10 mL). The mixture was diluted with H_2O (10 mL) and the aqueous and organic layers were separated. The aqueous layer was extracted with diethyl ether (2 × 10 mL) and the combined organic layers were washed with brine (1 × 15 mL) and dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by flash chromatography.

(*R*)-1-(4-methoxyphenyl)-4-Phenylpentan-3-one (112a or **109)**



Prepared from (1-chloroethyl)benzene (**96** or **111a**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**108**, 0.30 mmol) according to General Procedure 4. The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **112a** (42.3 mg, 79% yield) in 93% ee as a clear oil. The enantiomeric excess was determined by chiral SFC analysis (OD-H, 2.5 mL/min, 5% IPA in CO_2, λ = 210 nm): t_R (minor) = 9.2 min, t_R (major) = 9.8 min. $[\alpha]_D^{25} = -102.3°$ (c = 1.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.21 (m, 3H), 7.22 – 7.14 (m, 2H), 7.05 – 6.96 (m, 2H), 6.84 – 6.75 (m, 2H), 3.79 (s, 3H), 3.72 (q, *J* = 7.0 Hz, 1H), 2.88 – 2.57 (m, 4H), 1.39 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.0, 157.8, 140.4, 133.0, 129.2, 128.9, 127.8, 127.1, 113.7, 55.2, 53.2, 42.8, 29.1, 17.3; FTIR (NaCl, thin film): 3060, 3027, 2973, 2931, 2834, 1713, 1611, 1513, 1493, 1452, 1300, 1247 cm^{-1}; HRMS (MM) calc'd for $[M–H]^-$ 267.1391, found 267.1391.

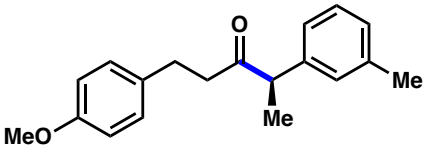
(*R*)-1-(4-methoxyphenyl)-4-(*o*-tolyl)Pentan-3-one (112b)



Prepared from 1-(1-chloroethyl)-2-methylbenzene (**111b,** 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**108**, 0.30 mmol) according to General Procedure 4 except using 33 mol % (*R*,*R*)-**L32** (0.066 mmol). The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **112b** (19.8 mg, 35% yield) in 72% ee as a clear oil. The enantiomeric excess was determined by chiral SFC analysis (OD-H, 2.5 mL/min, 10% IPA in CO_2, λ = 210 nm): t_R (minor) = 5.3 min, t_R (major) = 5.7 min.

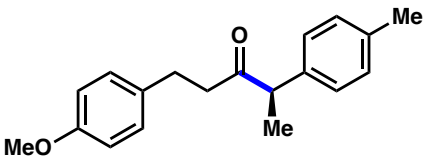
$[\alpha]_D^{25} = -72.3°$ (c = 0.56, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 – 7.09 (m, 3H), 7.02 – 6.92 (m, 3H), 6.77 (d, *J* = 8.6 Hz, 2H), 3.87 (q, *J* = 6.9 Hz, 1H), 3.76 (s, 3H), 2.85 – 2.68 (m, 2H), 2.64 – 2.47 (m, 2H), 2.33 (s, 3H), 1.32 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.4, 157.9, 140.0, 135.7, 133.1, 130.8, 129.2, 127.0, 126.6, 113.8, 55.2, 49.2, 42.8, 29.2, 19.7, 16.7; FTIR (NaCl, thin film): 2931, 2834, 1712, 1611, 1513, 1491, 1463, 1300, 1246, 1171, 1036, 828 cm^{-1}; HRMS (MM) calc'd for M^+ 282.1614, found 282.1543.

(*R*)-1-(4-methoxyphenyl)-4-(*m*-tolyl)Pentan-3-one (112c)



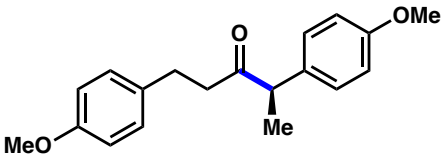
Prepared from 1-(1-chloroethyl)-3-methylbenzene (**111c**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**108**, 0.30 mmol) according to General Procedure 4 except using 33 mol % (*R*,*R*)-**L32** (0.066 mmol). The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **111c** (42.5 mg, 75% yield) in 93% ee as a clear oil. The enantiomeric excess was determined by chiral SFC analysis (OD-H, 2.5 mL/min, 5% IPA in CO_2, λ = 210 nm): t_R (minor) = 9.1 min, t_R (major) = 9.9 min. $[\alpha]_D^{25} = -90.4°$ (c = 1.46, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.5 Hz, 1H), 7.09 – 7.01 (m, 1H), 7.02 – 6.92 (m, 4H), 6.77 (d, *J* = 8.5 Hz, 2H), 3.77 (s, 3H), 3.66 (q, *J* = 6.9 Hz, 1H), 2.84 – 2.56 (m, 4H), 2.31 (s, 3H), 1.36 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.1, 157.8, 140.4, 138.6, 133.1, 129.2, 128.8, 128.6, 127.9, 125.0, 113.8, 55.2, 53.1, 42.8, 29.1, 21.4, 17.3; FTIR (NaCl, thin film): 2931, 2834, 1714, 1611, 1584, 1513, 1453, 1300, 1246, 1178, 1036, 825 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 283.1693, found 283.1557.

(*R*)-1-(4-methoxyphenyl)-4-(*p*-tolyl)Pentan-3-one (112d)



Prepared from 1-(1-chloroethyl)-4-methylbenzene (**111d**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**108**, 0.30 mmol) according to General Procedure 4 except using 33 mol % (*R*,*R*)-**L32** (0.066 mmol). The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **112d** (41.8 mg, 74%% yield) in 93% ee as a clear oil. The enantiomeric excess was determined by chiral SFC analysis (OD-H, 2.5 mL/min, 5% IPA in CO_2, λ = 210 nm): t_R (minor) = 9.0 min, t_R (major) = 9.8 min. $[\alpha]_D^{25} = -84.9°$ (c = 1.37, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, *J* = 7.9 Hz, 2H), 7.05 (d, *J* = 7.9 Hz, 2H), 6.99 (d, *J* = 9.0 Hz, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 3.77 (s, 3H), 3.66 (q, *J* = 6.9 Hz, 1H), 2.84 – 2.55 (m, 4H), 2.33 (s, 3H), 1.35 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.2, 157.8, 137.4, 136.7, 133.1, 129.6, 129.2, 127.7, 113.8, 55.2, 52.8, 42.8, 29.1, 21.0, 17.3; FTIR (NaCl, thin film): 2930, 2834, 1713, 1612, 1584, 1513, 1454, 1300, 1246, 1178, 1036, 824 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 283.1647, found 283.1693.

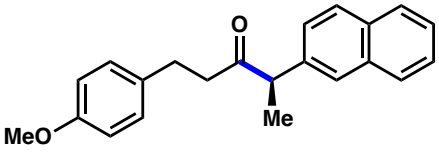
(*R*)-1,4-bis(4-methoxyphenyl)Pentan-3-one (112e)



Prepared from 1-(1-chloroethyl)-4-methoxybenzene (**111e**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**108**, 0.30 mmol) according to General Procedure 4 except using 33 mol % (*R*,*R*)-**L32** (0.066 mmol). The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **112e** (33.4 mg, 56% yield) in 86% ee as a clear oil. The

enantiomeric excess was determined by chiral SFC analysis (OB-H, 2.5 mL/min, 10% IPA in CO_2, λ = 210 nm): t_R (minor) = 6.8 min, t_R (major) = 7.4 min. $[\alpha]_D^{25} = -77.2°$ (c = 1.22, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.3 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 9.0 Hz, 2H), 6.76 (d, *J* = 9.0 Hz, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.64 (q, *J* = 6.9 Hz, 1H), 2.83 – 2.54 (m, 4H), 1.34 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.3, 158.7, 157.9, 133.1, 132.4, 129.2, 128.9, 114.3, 113.8, 55.24, 55.23, 52.3, 42.7, 29.1, 17.3 ; FTIR (NaCl, thin film): 2930, 2834, 1710, 1611, 1582, 1512, 1463, 1301, 1246, 1177, 1034, 827 cm^{-1}; HRMS (MM) calc'd for M^+ 298.1563, found 298.1622.

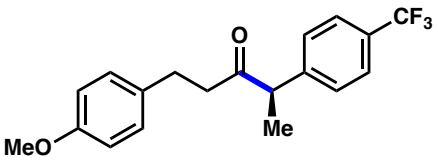
(*R*)-1-(4-methoxyphenyl)-4-(naphthalen-2-yl)Pentan-3-one (112f)



Prepared from 2-(1-chloroethyl)naphthalene (**111f**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**108**, 0.30 mmol) according to General Procedure 4 except using 33 mol % (*R*,*R*)-**L32** (0.066 mmol). The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **112f** (41.7 mg, 65% yield) in 91% ee as a clear oil. The enantiomeric excess was determined by chiral SFC analysis (AS-H, 2.5 mL/min, 5% IPA in CO_2, λ = 210 nm): t_R (minor) = 10.7 min, t_R (major) = 11.3 min. $[\alpha]_D^{25} = -100.4°$ (c = 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 – 7.73 (m, 3H), 7.59 (s, 1H), 7.52 – 7.42 (m, 2H), 7.29 – 7.23 (m, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 8.8 Hz, 2H), 3.86 (q, *J* = 6.9 Hz, 1H), 3.73 (s, 3H), 2.85 – 2.60 (m, 4H), 1.46 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.0, 157.8, 137.9, 133.6, 132.9, 132.5, 129.2, 128.7, 127.7, 127.6, 126.6, 126.2, 125.9, 113.7, 55.2, 53.3,

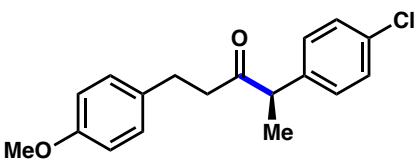
42.9, 29.0, 17.3; FTIR (NaCl, thin film): 3055, 2972, 2931, 2834, 1713, 1611, 1583, 1511, 1455, 1374, 1300, 1245, 1178, 1035, 822, 750 cm^{-1}; LRMS (ESI) calc'd for $[M+H]^+$ 319.2, found 319.2.

(*R*)-1-(4-methoxyphenyl)-4-(4-(trifluoromethyl)phenyl)Pentan-3-one (112h)



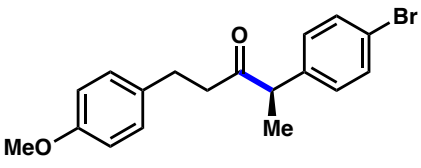
Prepared from 1-(1-chloroethyl)-4-(trifluoromethyl)benzene (**111h**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**108**, 0.30 mmol) according to General Procedure 4 except using 20% v/v DMA/THF. The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **112h** (42.8 mg, 64% yield) in 82% ee as a clear oil. The enantiomeric excess was determined by chiral SFC analysis (OJ-H, 2.5 mL/min, 5% IPA in CO_2, λ = 210 nm): t_R (major) = 6.0 min, t_R (minor) = 7.3 min. $[\alpha]_D^{25} = -50.8°$ (c = 1.01, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.8 Hz, 2H), 7.25 (d, *J* = 7.7 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 9.0 Hz, 2H), 3.80 – 3.74 (m, 4H), 2.85 – 2.60 (m, 4H), 1.38 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.0, 158.0, 144.2, 132.7, 129.3, 129.2, 128.2, 125.8, 113.9, 113.8, 55.2, 53.0, 43.1, 28.9, 17.3; FTIR (NaCl, thin film): 2934, 2837, 1717, 1616, 1584, 1513, 1419, 1326, 1247, 1165, 1124, 1070, 1036, 825 cm^{-1}; HRMS (MM) calc'd for M^+ 336.1332, found 336.1342.

(*R*)-4-(4-chlorophenyl)-1-(4-methoxyphenyl)Pentan-3-one (112i)



Prepared from 1-chloro-4-(1-chloroethyl)benzene (**111i**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**108**, 0.30 mmol) according to General Procedure 4. The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **112i** (45.9 mg, 76% yield) in 91% ee as a clear oil. The enantiomeric excess was determined by chiral SFC analysis (OD-H, 2.5 mL/min, 3% IPA in CO_2, λ = 210 nm): t_R (minor) = 19.6 min, t_R (major) = 20.6 min. $[\alpha]_D^{25}$ = –64.1° (c = 0.79, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.8 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 3.77 (s, 3H), 3.67 (q, *J* = 7.0 Hz, 1H), 2.83 – 2.55 (m, 4H), 1.34 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.4, 157.9, 138.8, 133.0, 132.8, 129.2, 129.0, 113.8, 55.2, 52.5, 42.9, 29.0, 17.3; FTIR (NaCl, thin film): 2932, 1713, 1611, 1513, 1491, 1300, 1247, 1178, 1093, 1036, 1014, 825 cm^{-1}; HRMS (MM) calc'd for M^+ 302.1068, found 302.1001.

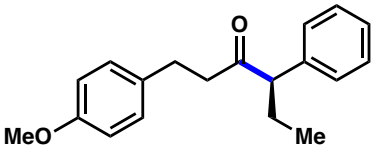
(*R*)-4-(4-bromophenyl)-1-(4-methoxyphenyl)Pentan-3-one (112j)



Prepared from 1-bromo-4-(1-chloroethyl)benzene (**111j**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**108**, 0.30 mmol) according to General Procedure 4 except using 1.25 equiv 2,6-DMBA (0.25 mmol). The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **112j** (51.0 mg, 73% yield) in 86% ee as a clear oil. The enantiomeric excess was determined by chiral SFC analysis (OD-H, 2.5 mL/min, 5% IPA in CO_2, λ = 210 nm): t_R (minor) = 25.4 min, t_R

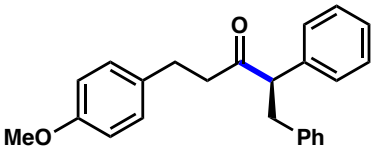
(major) = 27.0 min. $[\alpha]_D^{25} = -53.5°$ (c = 1.44, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.6 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 9.2 Hz, 2H), 3.77 (s, 3H), 3.65 (q, *J* = 7.0 Hz, 1H), 2.83 – 2.55 (m, 4H), 1.34 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.3, 157.9, 139.3, 132.8, 132.0, 129.6, 129.2, 121.1, 113.8, 55.2, 52.6, 42.9, 29.0, 17.3; FTIR (NaCl, thin film): 2932, 2834, 1714, 1611, 1513, 1487, 1453, 1300, 1247, 1178, 1036, 1010, 825 cm^{-1}; HRMS (MM) calc'd for M^+ 346.0563, found 346.0463.

(*R*)-1-(4-methoxyphenyl)-4-Phenylhexan-3-one (114a)



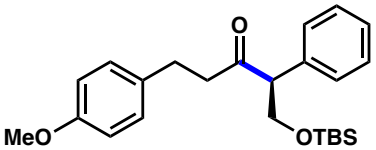
Prepared from (1-chloropropyl)benzene (**113a**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**108**, 0.30 mmol) according to General Procedure 4. The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **114a** (28.1 mg, 50% yield) in 94% ee as a clear oil. The enantiomeric excess was determined by chiral SFC analysis (OB-H, 2.5 mL/min, 5% IPA in CO_2, λ = 210 nm): t_R (minor) = 6.2 min, t_R (major) = 6.9 min. $[\alpha]_D^{25} = -97.9°$ (c = 0.96, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.20 (m, 3H), 7.19 – 7.12 (m, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 3.76 (s, 3H), 3.48 (t, *J* = 7.4 Hz, 1H), 2.84 – 2.56 (m, 4H), 2.11 – 1.99 (m, 1H), 1.77 – 1.64 (m, 1H), 0.80 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.7, 157.8, 138.8, 133.1, 129.2, 128.8, 128.3, 127.1, 113.8, 61.0, 55.2, 43.6, 29.0, 25.1, 12.1; FTIR (NaCl, thin film): 2961, 2932, 1711, 1611, 1513, 1492, 1453, 1300, 1247, 1178, 1036, 821 cm^{-1}; HRMS (MM) calc'd for M^+ 282.1614, found 282.1631.

(*R*)-5-(4-methoxyphenyl)-1,2-Diphenylpentan-3-one (114b)



Prepared from (1-chloroethane-1,2-diyl)dibenzene (**113b**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**108**, 0.30 mmol) according to General Procedure 4. The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **114b** (54.6 mg, 79% yield) in 92% ee as a clear oil. The enantiomeric excess was determined by chiral SFC analysis (AS-H, 2.5 mL/min, 10% IPA in CO_2, λ = 210 nm): t_R (major) = 4.5 min, t_R (minor) = 5.3 min. $[\alpha]_D^{25} = -166.8°$ (c = 0.85, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.08 (m, 8H), 7.06 – 6.96 (m, 2H), 6.92 (d, *J* = 8.3 Hz, 2H), 6.74 (d, *J* = 8.3 Hz, 2H), 3.87 (t, *J* = 7.4 Hz, 1H), 3.77 (s, 3H), 3.42 (dd, *J* = 13.7, 7.7 Hz, 1H), 2.90 (dd, *J* = 13.7, 7.0 Hz, 1H), 2.80 – 2.59 (m, 3H), 2.58 – 2.45 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.0, 157.8, 139.7, 138.3, 132.9, 129.1, 129.0, 128.9, 128.4, 128.2, 127.3, 126.1, 113.8, 61.1, 55.2, 44.1, 38.6, 28.9; FTIR (NaCl, thin film): 3027, 2930, 2834, 1712, 1611, 1583, 1513, 1495, 1453, 1300, 1247, 1178, 1035, 824 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 345.1849, found 345.1831.

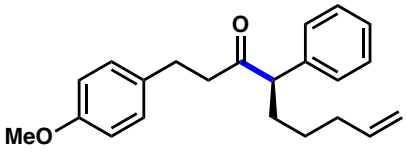
(*S*)-1-((*tert*-butyldimethylsilyl)oxy)-5-(4-methoxyphenyl)-2-Phenylpentan-3-one (114c)



Prepared from [1-chloro-2-(*t*-butyldimethylsiloxy)ethyl]benzene (**113c**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**108**, 0.30 mmol) according to General Procedure 4 except using 50% v/v DMA/THF. The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **114c** (40.4

mg, 51% yield) in 89% ee as a clear oil. The enantiomeric excess was determined by chiral SFC analysis (AS-H, 2.5 mL/min, 5% IPA in CO_2, λ = 210 nm): t_R (major) = 3.3 min, t_R (minor) = 3.8 min. $[\alpha]_D^{25} = -50.0°$ (c = 0.90, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 3H), 7.20 (dd, *J* = 8.1, 1.6 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 4.23 (dd, *J* = 9.7, 8.5 Hz, 1H), 3.92 (dd, *J* = 8.5, 5.7 Hz, 1H), 3.77 (s, 3H), 3.73 (dd, *J* = 9.7, 5.7 Hz, 1H), 2.88 – 2.68 (m, 4H), 0.84 (s, 9H), –0.01 (s, 3H), –0.03 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.8, 157.8, 135.9, 133.1, 129.2, 128.7, 128.5, 127.5, 113.8, 65.0, 61.0, 55.2, 45.1, 28.6, 25.8, 18.2, –5.57, –5.60; FTIR (NaCl, thin film): 2953, 2928, 2855, 1718, 1612, 1583, 1513, 1463, 1361, 1248, 1099, 835 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 399.2350, found 399.2198.

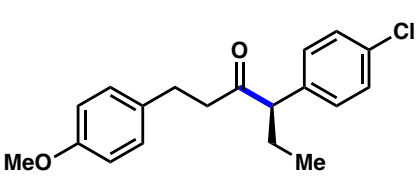
(*R*)-1-(4-methoxyphenyl)-4-Phenylnon-8-en-3-one (114e)



Prepared from (1-chlorohex-5-en-1-yl)benzene (**113e**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**108**, 0.30 mmol) according to General Procedure 4. The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **114e** (24.6 mg, 38% yield) in 92% ee as a clear oil. The enantiomeric excess was determined by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ = 210 nm): t_R (major) = 10.9 min, t_R (minor) = 11.9 min. $[\alpha]_D^{25} = -90.9°$ (c = 0.47, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.20 (m, 3H), 7.18 – 7.11 (m, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 8.9 Hz, 2H), 5.73 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.02 – 4.88 (m, 2H), 3.76 (s, 3H), 3.55 (t, *J* = 7.4 Hz, 1H), 2.84 – 2.54 (m, 4H), 2.09 – 1.93 (m, 3H), 1.74 – 1.63 (m, 1H), 1.37 – 1.15 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ

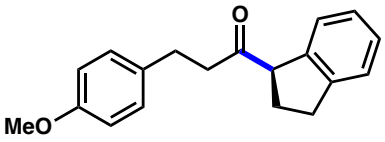
209.6, 157.9, 138.8, 138.4, 133.0, 129.2, 128.9, 128.3, 127.2, 114.7, 113.8, 59.1, 55.2, 43.6, 33.6, 31.4, 29.0, 26.7; FTIR (NaCl, thin film): 2930, 1712, 1640, 1611, 1583, 1513, 1453, 1300, 1247, 1177, 1036, 824 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 323.2006, found 323.1945.

(*R*)-4-(4-chlorophenyl)-1-(4-methoxyphenyl)Hexan-3-one (114g)



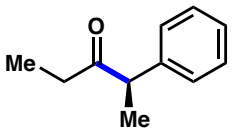
Prepared from 1-chloro-4-(1-chloropropyl)benzene (**113g**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**108**, 0.30 mmol) according to General Procedure 4. The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **114g** (41.2 mg, 65% yield) in 91% ee as a clear oil. The enantiomeric excess was determined by chiral SFC analysis (OD-H, 2.5 mL/min, 3% IPA in CO_2, λ = 210 nm): t_R (minor) = 18.1 min, t_R (major) = 19.4 min. $[\alpha]_D^{25} = -79.7°$ (c = 1.85, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.6 Hz, 2H), 7.06 (d, *J* = 8.9 Hz, 2H), 6.97 (d, *J* = 9.1 Hz, 2H), 6.76 (d, *J* = 8.6 Hz, 2H), 3.77 (s, 3H), 3.48 – 3.41 (m, 1H), 2.83 – 2.55 (m, 4H), 2.01 (dp, *J* = 14.4, 7.3 Hz, 1H), 1.72 – 1.62 (m, 1H), 0.78 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.2, 157.9, 137.1, 133.0, 132.8, 129.6, 129.2, 128.9, 113.7, 60.3, 55.2, 43.7, 28.9, 25.1, 12.0; FTIR (NaCl, thin film): 2962, 2932, 2834, 1711, 1611, 1583, 1512, 1490, 1463, 1300, 1246, 1178, 1092, 1036, 1014, 819 cm^{-1}; LRMS (ESI) calc'd for $[M+H]^+$ 317.1, found 317.1.

(*R*)-1-(2,3-dihydro-1*H*-inden-1-yl)-3-(4-methoxyphenyl)Propan-1-one (114h)



Prepared from 1-chloro-2,3-dihydro-1*H*-indene (**113h**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**108**, 0.30 mmol) according to General Procedure 4. The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **114h** (38.3 mg, 68% yield) in 78% ee as a clear oil. The enantiomeric excess was determined by chiral SFC analysis (AD-H, 2.5 mL/min, 10% IPA in CO_2, λ = 210 nm): t_R (minor) = 7.9 min, t_R (major) = 8.9 min. $[\alpha]_D^{25} = 11.3°$ (c = 0.1.79, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.10 (m, 4H), 7.07 (d, *J* = 8.9 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 3H), 4.08 (t, *J* = 7.1 Hz, 1H), 3.78 (s, 3H), 3.05 (d, *J* = 7.9 Hz, 1H), 2.98 – 2.67 (m, 5H), 2.37 – 2.18 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.0, 157.9, 144.6, 140.8, 133.2, 129.3, 127.5, 124.9, 124.8, 113.9, 113.8, 58.4, 55.3, 42.4, 31.9, 28.9, 28.5; FTIR (NaCl, thin film): 2932, 2849, 1709, 1611, 1583, 1513, 1458, 1300, 1247, 1178, 1036, 826, 755 cm^{-1}; LRMS (ESI) calc'd for $[M+H]^+$ 281.2, found 281.1.

(*R*)-2-Phenylpentan-3-one (116a)

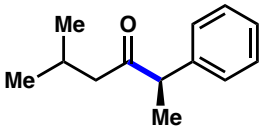


Prepared from (1-chloroethyl)benzene (**96**, 0.20 mmol) and propionyl chloride (**115a**, 0.24 mmol) according to General Procedure 4 except using 20% v/v DMA/THF. The crude residue was purified by silica gel chromatography (2% ethyl acetate/hexanes) to yield **116a** (19.5 mg, 60% yield) in 91% ee as a clear oil. The enantiomeric excess was determined by chiral SFC analysis (AS-H, 2.5 mL/min, 1% IPA in CO_2, λ = 210 nm): t_R (minor) = 1.8 min, t_R (major) = 2.0 min. $[\alpha]_D^{25} = –225.9°$ (c = 0.57, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 2H), 7.28 – 7.23 (m, 1H),

7.23 – 7.19 (m, 2H), 3.76 (q, *J* = 7.0 Hz, 1H), 2.42 – 2.33 (m, 2H), 1.39 (d, *J* = 7.0 Hz, 3H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.5, 140.9, 128.8, 127.8, 127.0, 52.7, 34.2, 17.5, 8.0; FTIR (NaCl, thin film): 3027, 2976, 2935, 1716, 1600, 1494, 1453, 1374, 1130, 1070, 1029, 957, 758 cm^{-1}; LRMS (ESI) calc'd for $[M+H]^+$ 163.1, found 163.1.

The optical rotation of the product generated in the presence of (*R*,*R*)-**L32** was measured as $[\alpha]_D^{25} = -225.9°$ (c = 0.57, $CHCl_3$). Lit: $[\alpha]_D^{25} = -76°$ (c = 1.2, $CHCl_3$, *R* enantiomer, 95% ee) and $[\alpha]_D^{21} = -47.2$ (c = 1.00, $CHCl_3$; 73% ee).[4b] Based on the literature precedent, we assign our product as the *R* enantiomer.

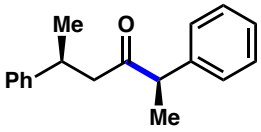
(*R*)-5-Methyl-2-phenylhexan-3-one (116b)



Prepared from (1-chloroethyl)benzene (**96**, 0.20 mmol) and isovaleroyl chloride (**115b**, 0.24 mmol) according to General Procedure 4. The crude residue was purified by silica gel chromatography (2% ethyl acetate/hexanes) to yield **116b** (27.5 mg, 73% yield) in 88% ee as a clear oil. The enantiomeric excess was determined by chiral SFC analysis (OD-H, 2.5 mL/min, 1% IPA in CO_2, λ = 210 nm): t_R (minor) = 2.2 min, t_R (major) = 2.7 min. $[\alpha]_D^{25} = -205.8°$ (c = 0.92, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 2H), 7.28 – 7.23 (m, 1H), 7.23 – 7.18 (m, 2H), 3.72 (q, *J* = 6.9 Hz, 1H), 2.29 – 2.16 (m, 2H), 2.10 (hept, *J* = 6.7 Hz, 1H), 1.38 (d, *J* = 7.0 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H), 0.75 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.5, 140.5, 128.8, 127.9, 127.0, 53.3, 50.0, 24.3, 22.6, 22.2,

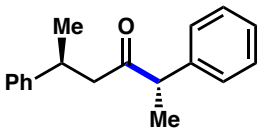
17.4; FTIR (NaCl, thin film): 3027, 2957, 2871, 1712, 1600, 1493, 1453, 1366, 1143, 1071, 1024, 761 cm^{-1}; LRMS (ESI) calc'd for $[M+H]^+$ 191.1, found 191.2.

(2*R*,5*S*)-2,5-Diphenylhexan-3-one ((*R*,*S*)-116c)



Prepared from (1-chloroethyl)benzene (**96**, 0.20 mmol) and (*S*)-3-phenylbutyryl chloride ((*S*)-**115c**, 0.24 mmol) according to General Procedure 4. The crude residue was purified by silica gel chromatography (2% ethyl acetate/hexanes) to yield (*R*,*S*)-**116c** (34.8 mg, 69% yield) as a clear oil and as a 20:1 mixture of diastereomers (determined by NMR analysis of the purified product). $[\alpha]_D^{25} = -122.2°$ (c = 1.71, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.17 (m, 5H), 7.17 – 7.12 (m, 1H), 7.10 – 7.02 (m, 4H), 3.69 (q, *J* = 7.0 Hz, 1H), 3.30 (h, *J* = 7.0 Hz, 1H), 2.70 (dd, *J* = 16.8, 6.8 Hz, 1H), 2.58 (dd, *J* = 16.8, 7.5 Hz, 1H), 1.34 (d, *J* = 6.9 Hz, 3H), 1.20 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.3, 146.1, 140.2, 128.8, 128.3, 127.0, 126.74, 126.73, 126.1, 53.5, 49.2, 35.2, 21.9, 17.2; FTIR (NaCl, thin film): 3061, 3027, 2967, 2930, 1714, 1601, 1493, 1452, 1373, 1125, 1069, 1029, 759 cm^{-1}; LRMS (ESI) calc'd for $[M+H]^+$ 253.2, found 253.2.

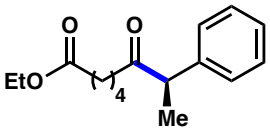
(2*S*,5*S*)-2,5-Diphenylhexan-3-one ((*S*,*S*)-116d)



Prepared from (1-chloroethyl)benzene (**26**, 0.20 mmol) and (*S*)-3-phenylbutyryl chloride ((*S*)-**151d**, 0.24 mmol) according to General Procedure 4 except using (*S*,*S*)-**L36**. The crude residue was purified by silica gel chromatography (2% ethyl acetate/hexanes) to yield (*S*,*S*)-**152d** (33.7 mg, 67% yield) as a clear oil and as a 12:1 mixture of diastereomers (determined by NMR analysis of the

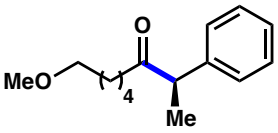
purified product). $[\alpha]_D^{25} = 121.3°$ (c = 1.59, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 2H), 7.31 – 7.24 (m, 3H), 7.22 – 7.13 (m, 5H), 3.54 (q, *J* = 6.9 Hz, 1H), 3.29 (h, *J* = 7.3 Hz, 1H), 2.67 (dd, *J* = 16.3, 6.4 Hz, 1H), 2.56 (dd, *J* = 16.3, 7.9 Hz, 1H), 1.32 (d, *J* = 6.9 Hz, 3H), 1.11 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.5, 146.3, 140.3, 128.9, 128.5, 128.0, 127.1, 126.8, 126.2, 53.4, 49.6, 35.4, 21.5, 17.2; FTIR (NaCl, thin film): 3061, 3027, 2968, 2930, 1714, 1601, 1494, 1452, 1374, 1125, 1068, 1029, 1004, 763 cm^{-1}; LRMS (ESI) calc'd for $[M+H]^+$ 253.2, found 253.1.

(*R*)-Ethyl 6-oxo-7-phenyloctanoate (116e)



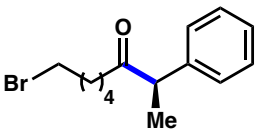
Prepared from (1-chloroethyl)benzene (**96**, 0.20 mmol) and ethyl 6-chloro-6-oxohexanoate (**115e**, 0.24 mmol) according to General Procedure 4 except using 10% v/v DMA/THF. The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **115f** (33.8 mg, 64% yield) in 92% ee as a clear oil. The enantiomeric excess was determined by chiral SFC analysis (AD-H, 2.5 mL/min, 4% IPA in CO_2, λ = 210 nm): t_R (minor) = 4.9 min, t_R (major) = 5.3 min. $[\alpha]_D^{25} = -146.8°$ (c = 0.85, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 2H), 7.28 – 7.23 (m, 1H), 7.22 – 7.18 (m, 2H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.73 (q, *J* = 7.0 Hz, 1H), 2.44 – 2.28 (m, 2H), 2.25 – 2.15 (m, 2H), 1.58 – 1.44 (m, 4H), 1.38 (d, *J* = 7.0 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.4, 173.4, 140.6, 128.9, 127.8, 127.1, 60.2, 53.0, 40.5, 34.0, 24.3, 23.2, 17.4, 14.2; FTIR (NaCl, thin film): 2977, 2932, 1733, 1714, 1600, 1494, 1453, 1375, 1248, 1181, 1029, 761 cm^{-1}; LRMS (ESI) calc'd for $[M+H]^+$ 263.2, found 263.2.

(*R*)-8-Methoxy-2-phenyloctan-3-one (116f)



Prepared from (1-chloroethyl)benzene (**96**, 0.20 mmol) and 6-methoxyhexanoyl chloride (**115f**, 0.24 mmol) according to General Procedure 4 except using 20% v/v DMA/THF. The crude residue was purified by silica gel chromatography (5-10% ethyl acetate/hexanes) to yield **116f** (35.0 mg, 75% yield) in 85% ee as a clear oil. The enantiomeric excess was determined by chiral SFC analysis (OD-H, 2.5 mL/min, 3% IPA in CO_2, λ = 210 nm): t_R (minor) = 5.4 min, t_R (major) = 5.8 min. $[\alpha]_D^{25} = -146.0°$ (c = 1.14, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 2H), 7.28 – 7.23 (m, 1H), 7.22 – 7.18 (m, 2H), 3.74 (q, *J* = 7.0 Hz, 1H), 3.31 – 3.25 (m, 5H), 2.38 – 2.32 (m, 2H), 1.57 – 1.42 (m, 2H), 1.38 (d, *J* = 7.0 Hz, 3H), 1.26 – 1.17 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.9, 140.7, 128.9, 127.9, 127.1, 72.5, 58.5, 53.0, 40.9, 29.3, 25.6, 23.6, 17.4; FTIR (NaCl, thin film): 2931, 2866, 2360, 1714, 1600, 1494, 1453, 1373, 1119, 1072, 1029, 761 cm^{-1}; LRMS (ESI) calc'd for $[M+H]^+$ 235.2, found 235.2.

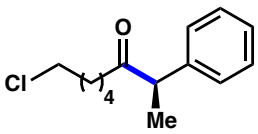
(*R*)-8-Bromo-2-phenyloctan-3-one (116g)



Prepared from (1-chloroethyl)benzene (**96**, 0.20 mmol) and 6-bromohexanoyl chloride (**115g**, 0.24 mmol) according to General Procedure 4 except using 10% v/v DMA/THF. The crude residue was purified by silica gel chromatography (2% ethyl acetate/hexanes) to yield **116g** (40.8 mg, 72% yield) in 86% ee as a clear oil. The enantiomeric excess was determined by chiral SFC analysis (OD-H, 2.5 mL/min, 3% IPA in CO_2, λ = 210 nm): t_R (minor) = 7.3 min, t_R (major) = 8.1 min. $[\alpha]_D^{25} = -146.8°$ (c = 1.57, $CHCl_3$); ^1H NMR (500 MHz,

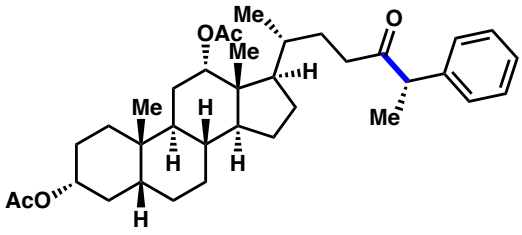
$CDCl_3$) δ 7.37 – 7.30 (m, 2H), 7.29 – 7.24 (m, 1H), 7.23 – 7.18 (m, 2H), 3.74 (q, *J* = 7.0 Hz, 1H), 3.32 (t, *J* = 6.8 Hz, 2H), 2.46 – 2.28 (m, 2H), 1.80 – 1.70 (m, 2H), 1.56 – 1.44 (m, 2H), 1.39 (d, *J* = 7.0 Hz, 3H), 1.37 – 1.24 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.5, 140.6, 128.9, 127.9, 127.2, 53.1, 40.6, 33.6, 32.4, 27.5, 22.9, 17.4; FTIR (NaCl, thin film): 2932, 2867, 1713, 1600, 1494, 1453, 1373, 1252, 1069, 1029, 761 cm^{-1}; LRMS (ESI) calc'd for $[M+H]^+$ 283.1, found 283.1.

(*R*)-8-Chloro-2-phenyloctan-3-one (116h)



Prepared from (1-chloroethyl)benzene (**96**, 0.20 mmol) and 6-chlorohexanoyl chloride (**115h**, 0.24 mmol) according to General Procedure 4 except using 20% v/v DMA/THF. The crude residue was purified by silica gel chromatography (2% ethyl acetate/hexanes) to yield **116h** (36.3 mg, 76% yield) in 92% ee as a clear oil. The enantiomeric excess was determined by chiral SFC analysis (OD-H, 2.5 mL/min, 3% IPA in CO_2, λ = 210 nm): t_R (minor) = 5.8 min, t_R (major) = 6.5 min. $[\alpha]_D^{25}$ = –163.3° (c = 0.78, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 2H), 7.29 – 7.23 (m, 1H), 7.23 – 7.18 (m, 2H), 3.74 (q, *J* = 7.0 Hz, 1H), 3.45 (t, *J* = 6.7 Hz, 2H), 2.46 – 2.28 (m, 2H), 1.73 – 1.61 (m, 2H), 1.57 – 1.44 (m, 2H), 1.39 (d, *J* = 7.0 Hz, 3H), 1.34 – 1.24 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.6, 140.6, 128.9, 127.8, 127.2, 53.1, 44.8, 40.6, 32.3, 26.2, 23.0, 17.4; FTIR (NaCl, thin film): 2932, 2867, 2360, 1711, 1599, 1493, 1452, 1374, 1122, 1069, 1029, 760 cm^{-1}; LRMS (ESI) calc'd for $[M+H]^+$ 239.1, found 239.1.

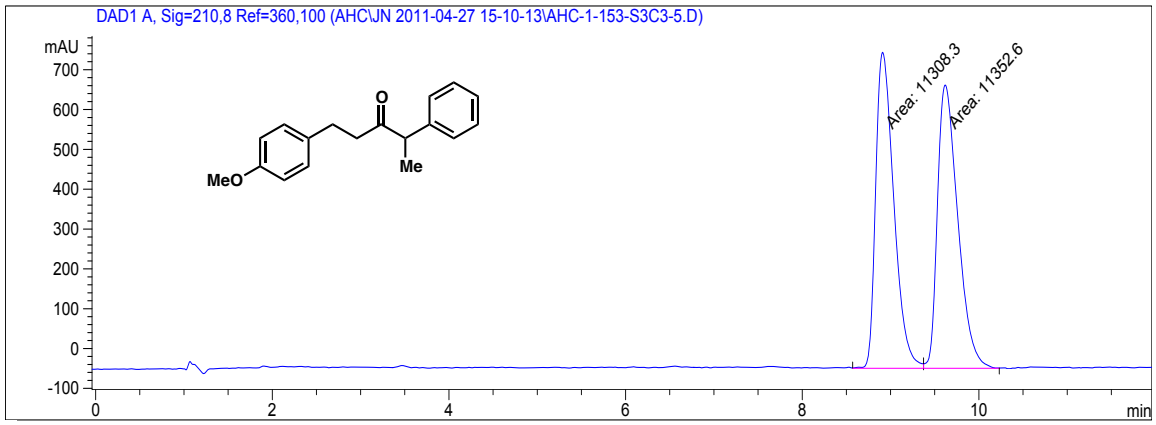
(3*R*,5*R*,8*R*,9*S*,10*S*,12*S*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-((2*R*,6*S*)-5-oxo-6-phenylheptan-2-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthrene-3,12-diyl diacetate (116i)



Prepared from (1-chloroethyl)benzene (**96**, 0.20 mmol) and acid chloride **115i** (0.24 mmol) according to General Procedure 4 except using 10% v/v DMA/THF and (*S*,*S*)-**L32.** Following extraction, the combined organic layers were washed with sat. aq. $NaHCO_3$ (1 X 10 mL) and brine (1 X 15 mL). The crude residue was purified by silica gel chromatography (15% ethyl acetate/hexanes) to yield **116i** (72.5 mg, 64% yield) as a fluffy white solid and as a 14:1 mixture of diastereomers (determined by NMR analysis of the purified product). $[\alpha]_D^{25} = 146.0°$ (c = 2.05, $CHCl_3$); ^1H NMR (500 MHz, Acetone-d_6) δ 7.39 – 7.31 (m, 2H), 7.30 – 7.22 (m, 3H), 4.99 (t, *J* = 3.0 Hz, 1H), 4.63 (tt, *J* = 11.4, 4.6 Hz, 1H), 3.90 (q, *J* = 6.9 Hz, 1H), 2.45 – 2.29 (m, 2H), 2.01 (s, 3H), 1.98 – 1.40 (m, 17H), 1.37 – 0.99 (m, 13H), 0.95 (s, 3H), 0.72 (s, 3H), 0.69 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.8, 169.5, 169.3, 141.3, 128.7, 127.8, 126.9, 75.2, 73.5, 52.4, 49.4, 47.4, 44.9, 41.7, 37.3, 35.6, 34.6, 34.5, 34.3, 33.9, 32.1, 29.6, 27.0, 26.7, 26.4, 25.8, 25.3, 23.2, 22.5, 20.4, 20.3, 17.1, 16.9, 11.8; FTIR (NaCl, thin film): 2937, 2869, 1735, 1493, 1452, 1377, 1363, 1245, 1194, 1029, 971 cm^{-1}; LRMS (ESI) calc'd for $[M+H_2O]^+$ 582.4, found 582.4.

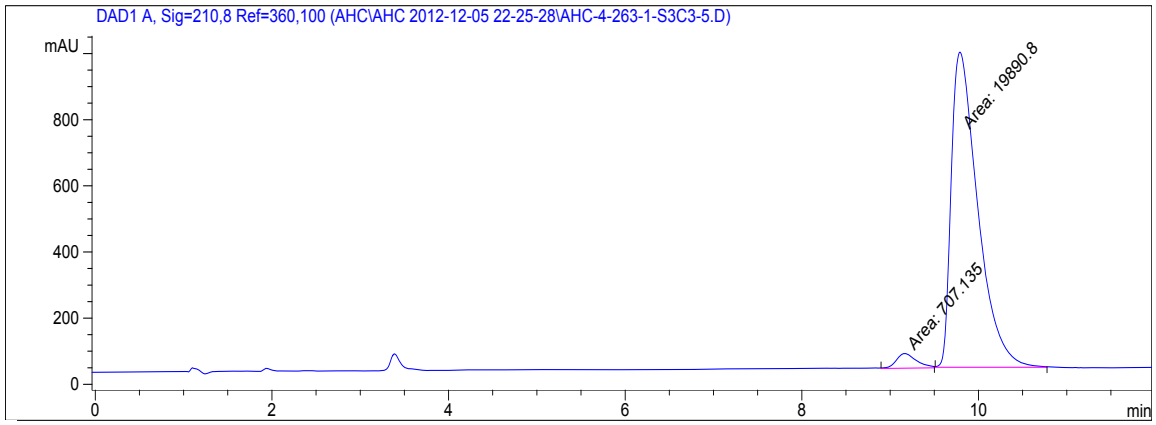
2.5.4 SFC Traces of Racemic and Enantioenriched Ketone Products

112a racemic



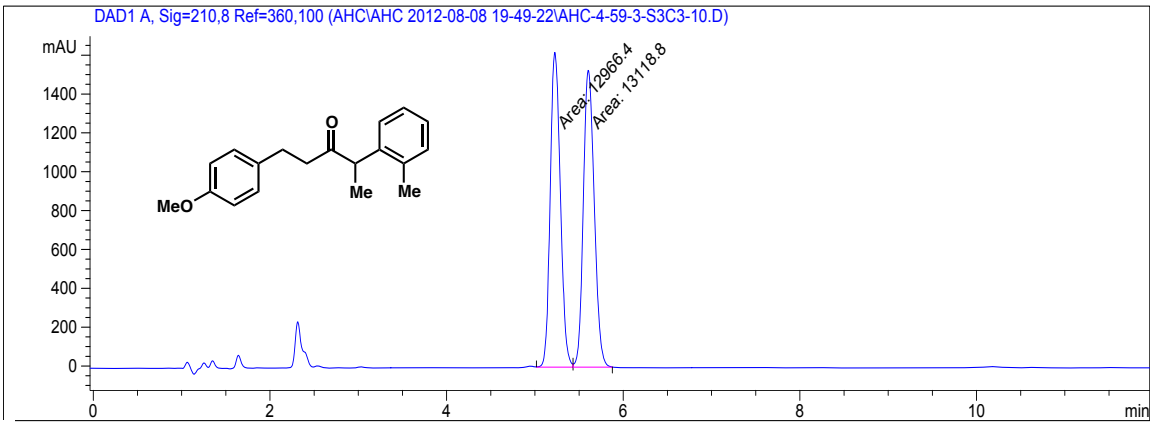
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.911	MM	0.2376	1.13083e4	793.28162	49.9021
2	9.619	MM	0.2660	1.13526e4	711.29791	50.0979

112a enantioenriched, 93% ee



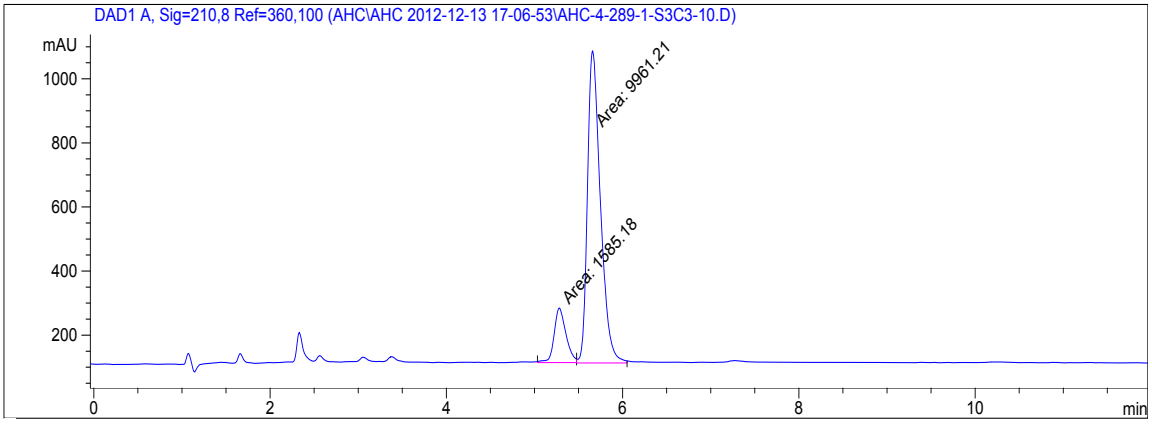
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.164	MM	0.2646	707.13519	44.53406	3.4330
2	9.790	MM	0.3479	1.98908e4	952.85913	96.5670

112b racemic



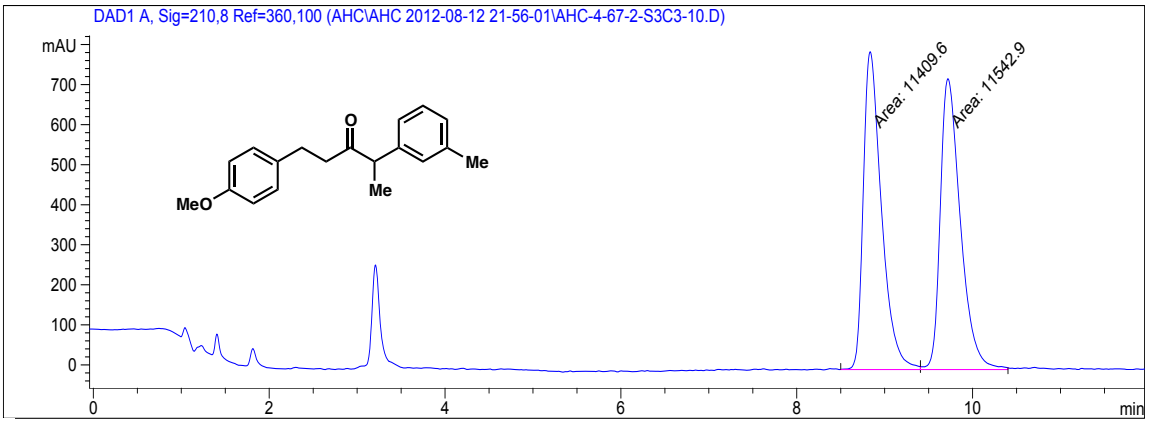
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.225	MM	0.1332	1.29664e4	1622.72693	49.7079
2	5.604	MM	0.1430	1.31188e4	1529.25037	50.2921

112b enantioenriched, 72% ee



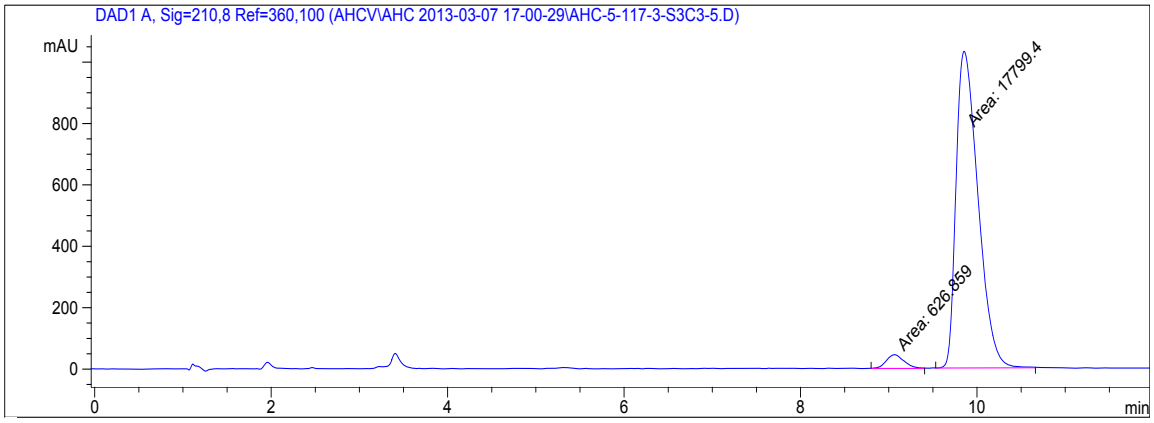
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.282	MM	0.1551	1585.18311	170.37230	13.7288
2	5.659	MM	0.1703	9961.21484	974.66937	86.2712

112c racemic



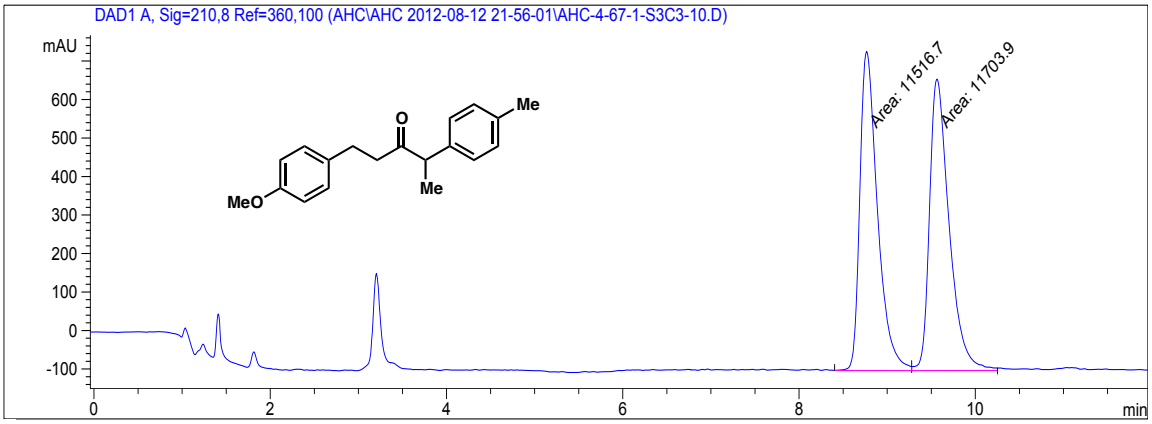
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.835	MM	0.2395	1.14096e4	794.09918	49.7095
2	9.720	MM	0.2647	1.15429e4	726.79602	50.2905

112c enantioenriched, 93% ee



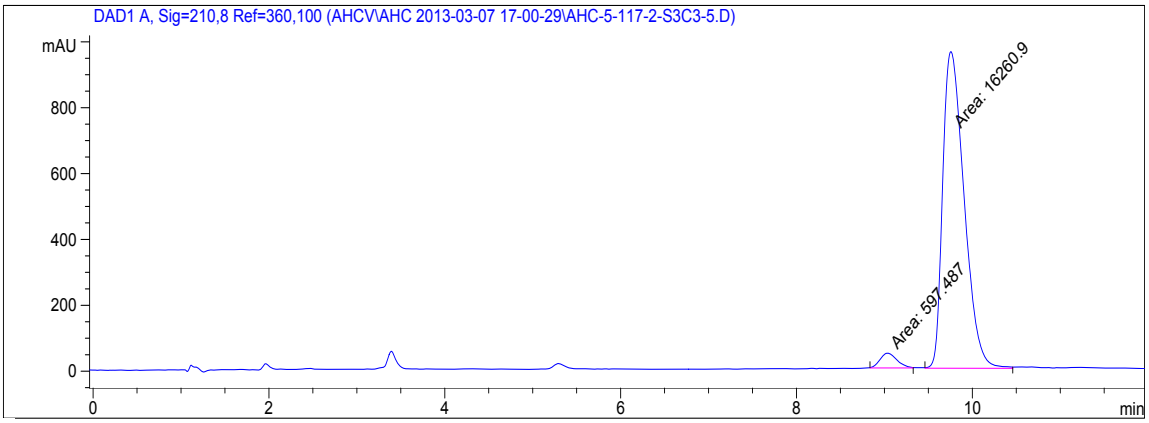
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.064	MM	0.2335	626.85852	44.73974	3.4020
2	9.854	MM	0.2876	1.77994e4	1031.51978	96.5980

112d racemic



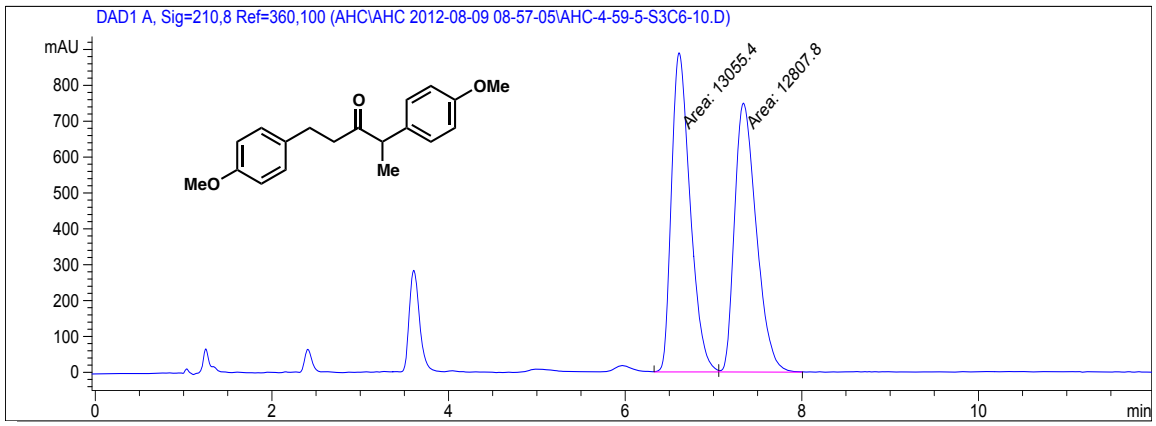
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.766	MM	0.2315	1.15167e4	829.08398	49.5970
2	9.564	MM	0.2576	1.17039e4	757.13312	50.4030

112d enantioenriched, 93% ee



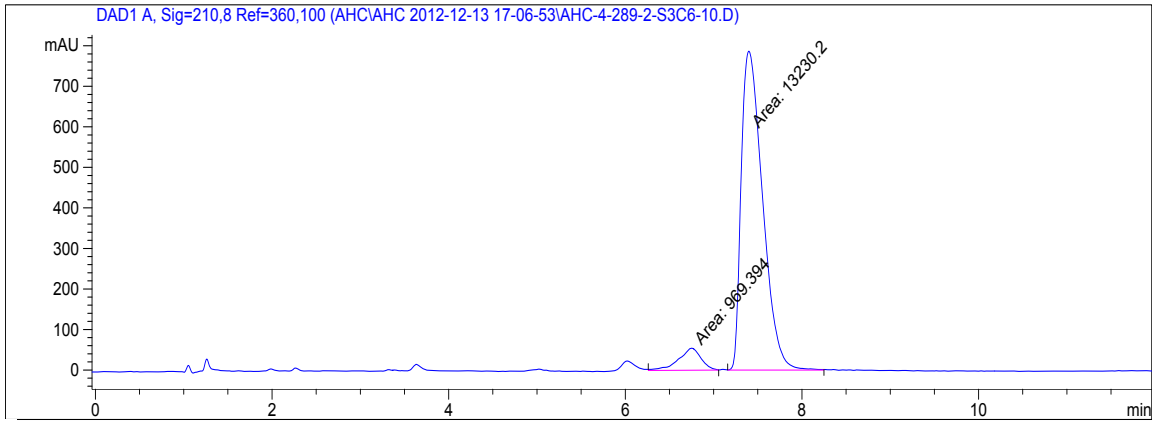
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.036	MM	0.2206	597.48749	45.14814	3.5442
2	9.756	MM	0.2819	1.62609e4	961.42609	96.4558

112e racemic



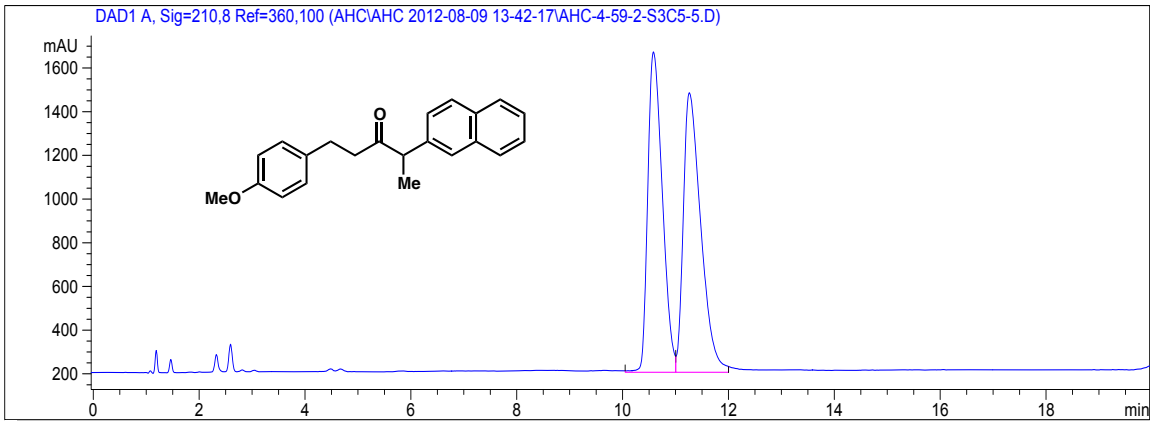
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.610	MM	0.2445	1.30554e4	889.75983	50.4785
2	7.339	MM	0.2848	1.28078e4	749.64392	49.5215

112e enantioenriched, 86% ee



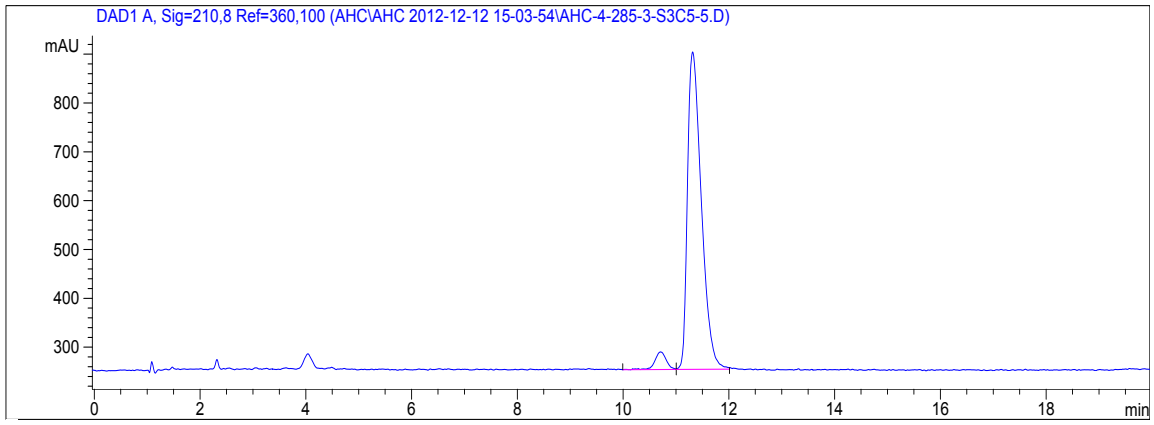
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.750	MM	0.2970	969.39368	54.40509	6.8269
2	7.399	MM	0.2801	1.32302e4	787.11755	93.1731

112f racemic



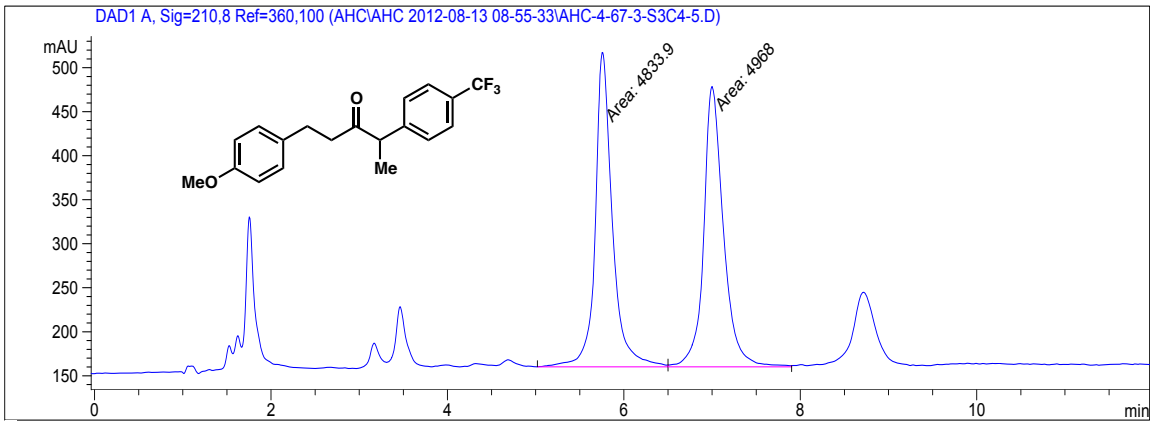
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.584	VV	0.3032	2.80499e4	1465.87903	48.9009
2	11.263	VBA	0.3473	2.93108e4	1279.38000	51.0991

112f enantioenriched, 91% ee



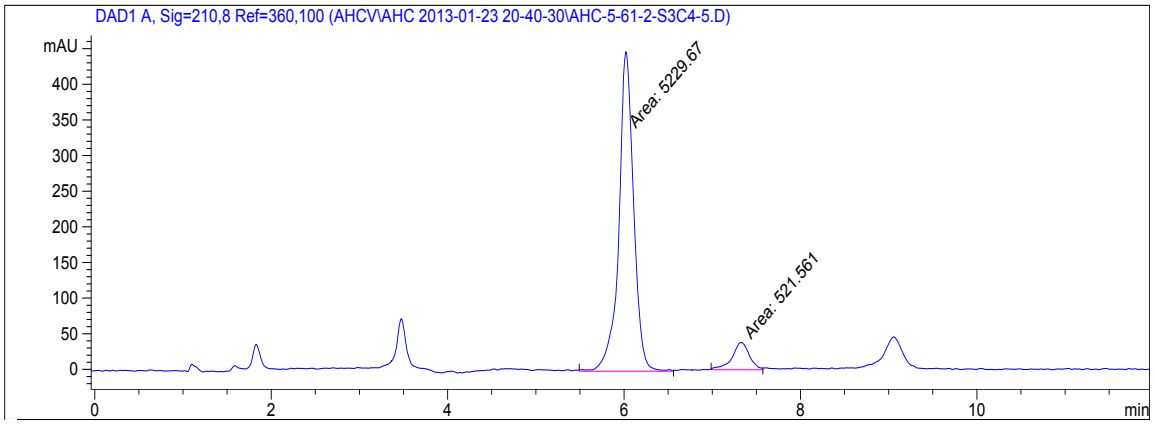
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.708	VV	0.2364	545.21796	36.05198	4.4227
2	11.316	VBA	0.2797	1.17825e4	649.47711	95.5773

112h racemic



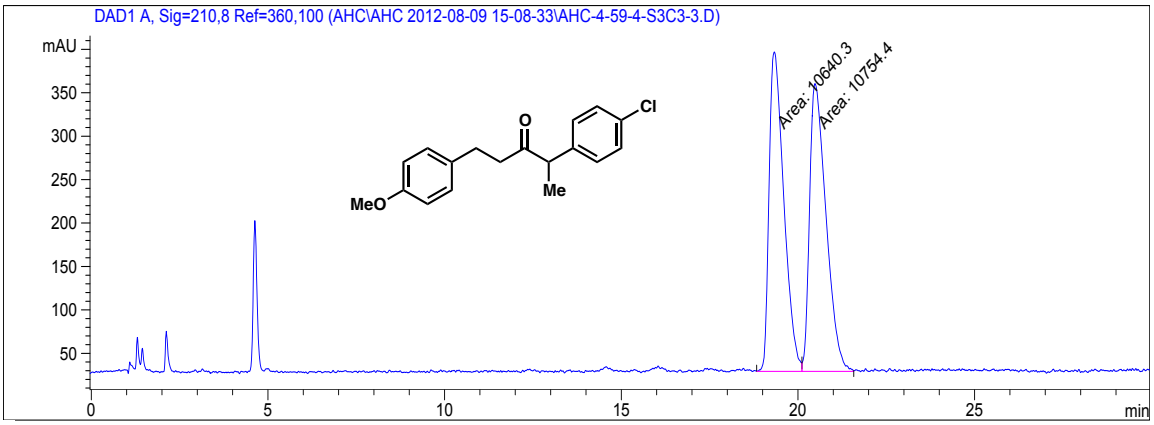
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.757	MM	0.2253	4833.89893	357.65167	49.3159
2	6.999	MM	0.2598	4967.99951	318.66217	50.6841

112h enantioenriched, 82% ee



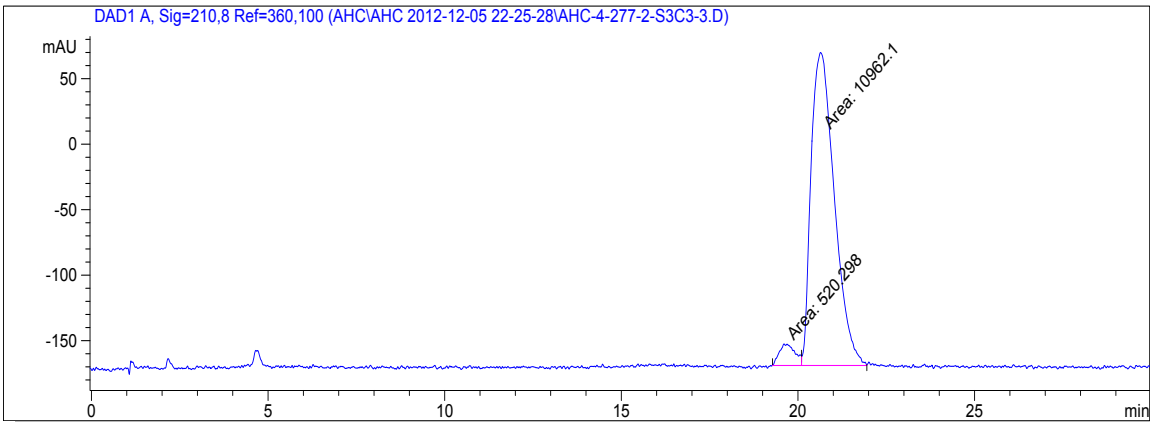
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.020	MM	0.1943	5229.66602	448.69507	90.9313
2	7.327	MM	0.2264	521.56061	38.39449	9.0687

112i racemic



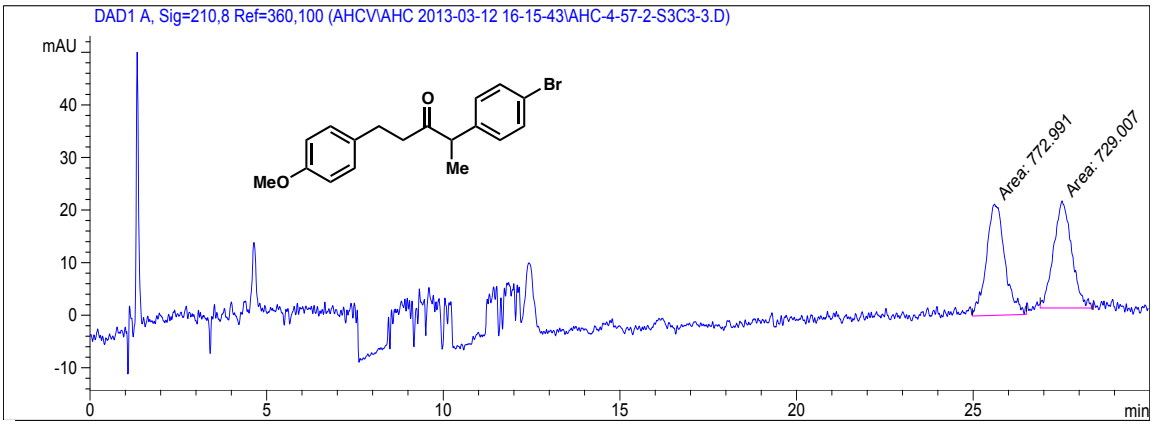
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.330	MM	0.4822	1.06403e4	367.73328	49.7335
2	20.480	MM	0.5409	1.07544e4	331.38272	50.2665

112i enantioenriched, 91% ee



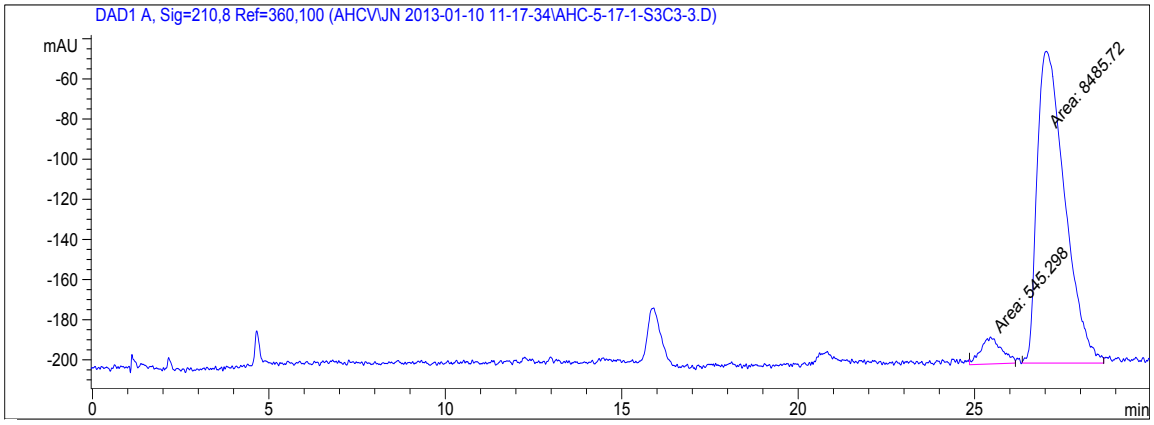
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.605	MM	0.5260	520.29840	16.48751	4.5313
2	20.639	MM	0.7645	1.09621e4	238.97188	95.4687

112j racemic



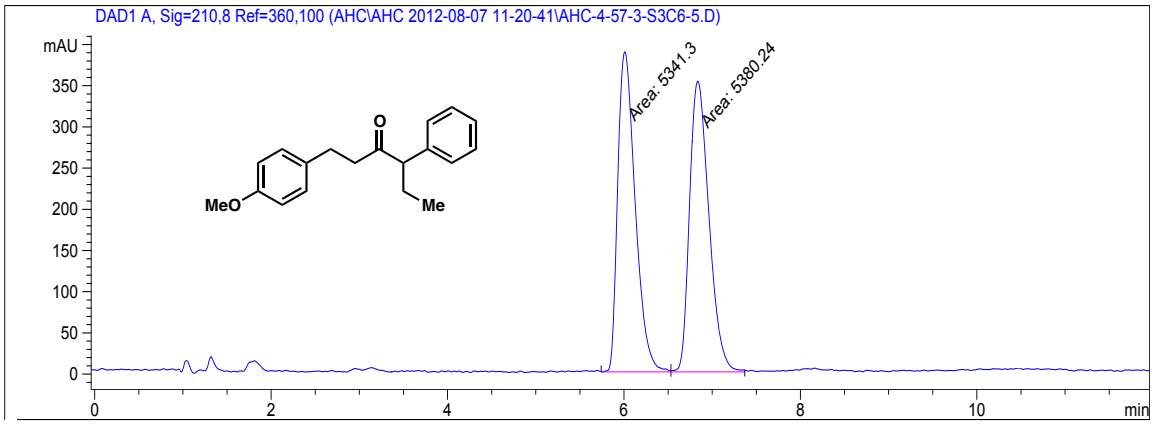
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.604	MM	0.6090	772.99146	21.15472	51.4642
2	27.518	MM	0.5962	729.00677	20.37799	48.5358

112j enantioenriched, 86% ee



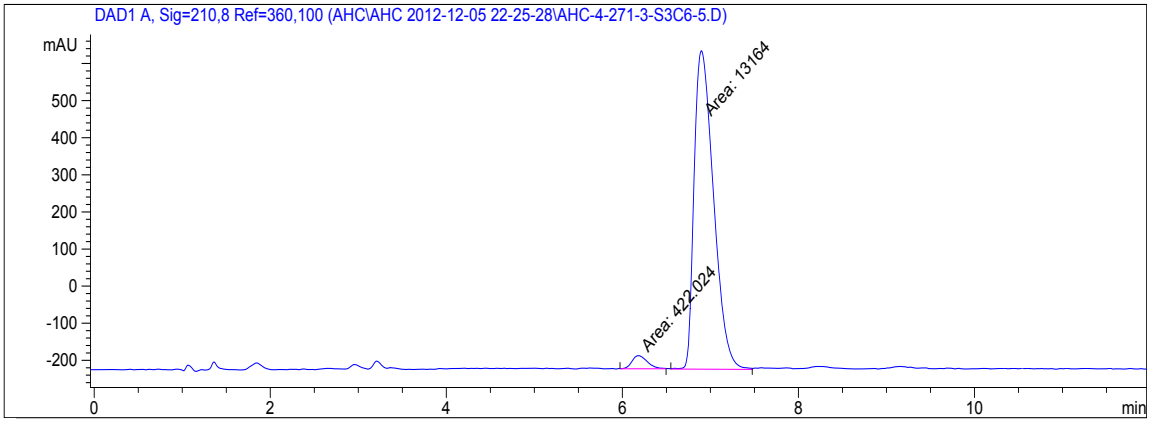
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.449	MM	0.6766	545.29791	13.43136	6.0381
2	27.030	MM	0.9105	8485.72363	155.33823	93.9619

114a racemic



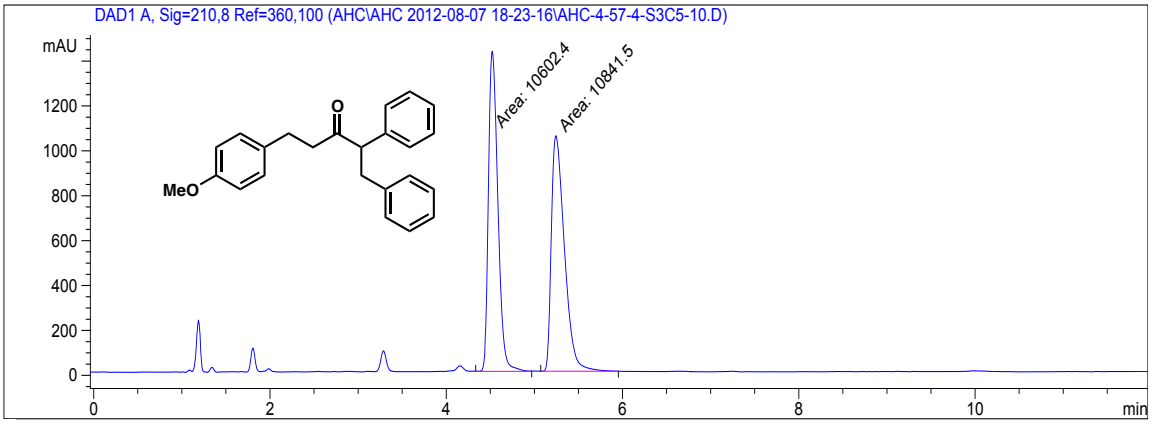
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.009	MM	0.2291	5341.29736	388.53415	49.8184
2	6.837	MM	0.2540	5380.24316	353.03430	50.1816

114a enantioenriched, 94% ee



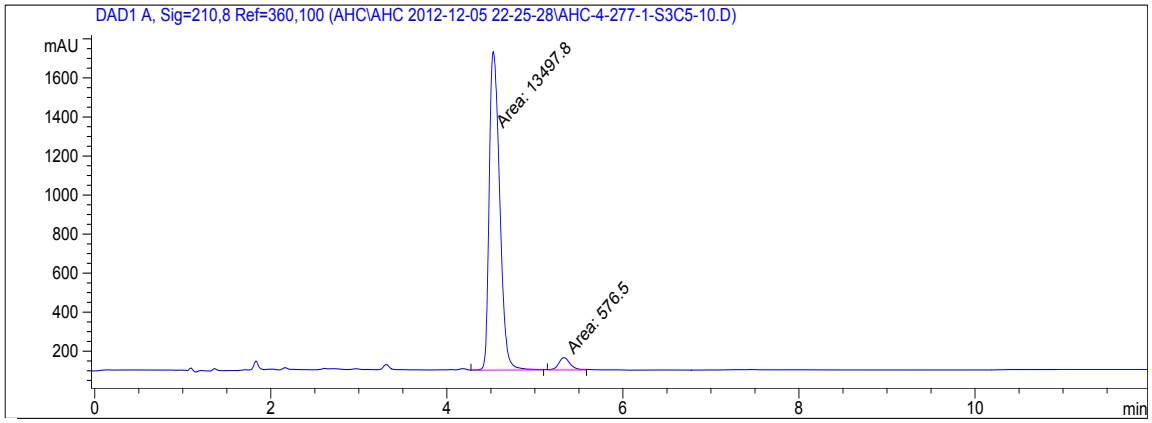
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.179	MM	0.1983	422.02435	35.47295	3.1063
2	6.898	MM	0.2556	1.31640e4	858.35632	96.8937

114b racemic



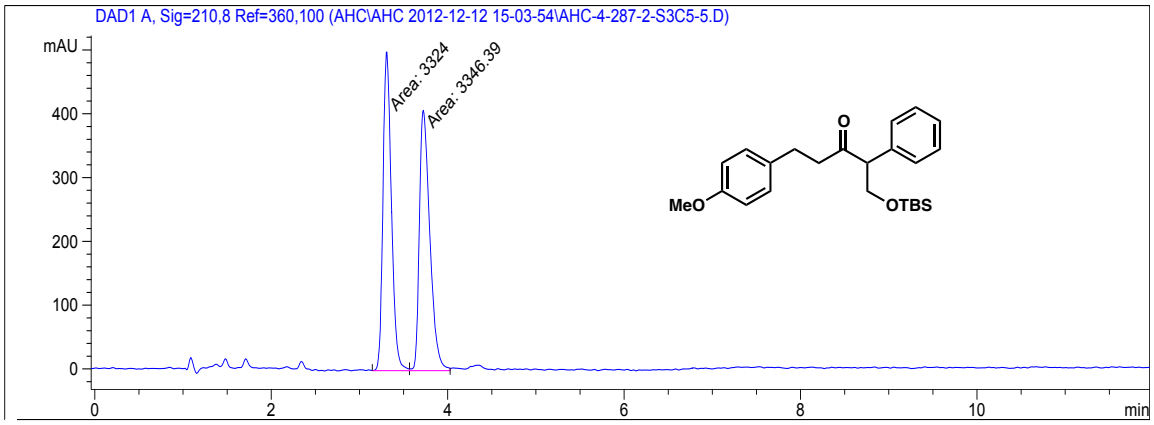
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.522	MM	0.1239	1.06024e4	1426.70251	49.4425
2	5.244	MM	0.1721	1.08415e4	1050.01685	50.5575

114b enantioenriched, 92% ee



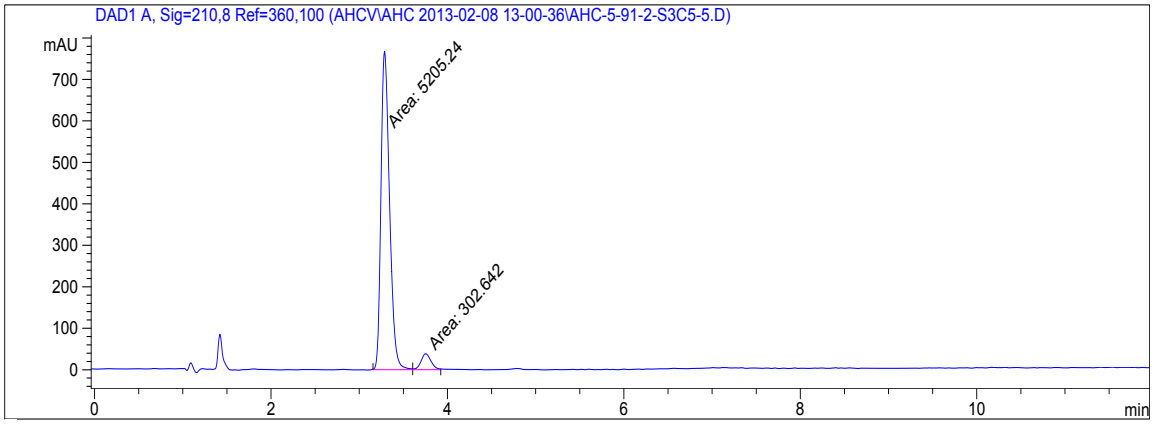
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.528	MM	0.1377	1.34978e4	1634.09204	95.9039
2	5.330	MM	0.1513	576.49988	63.49461	4.0961

114c racemic



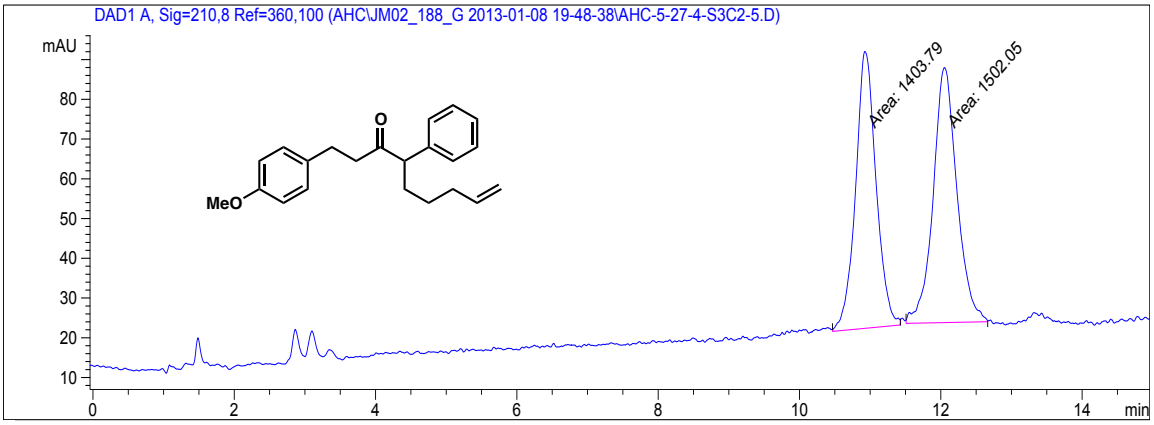
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.308	MM	0.1105	3324.00073	501.56870	49.8322
2	3.723	MM	0.1365	3346.39185	408.55920	50.1678

114c enantioenriched, 89% ee



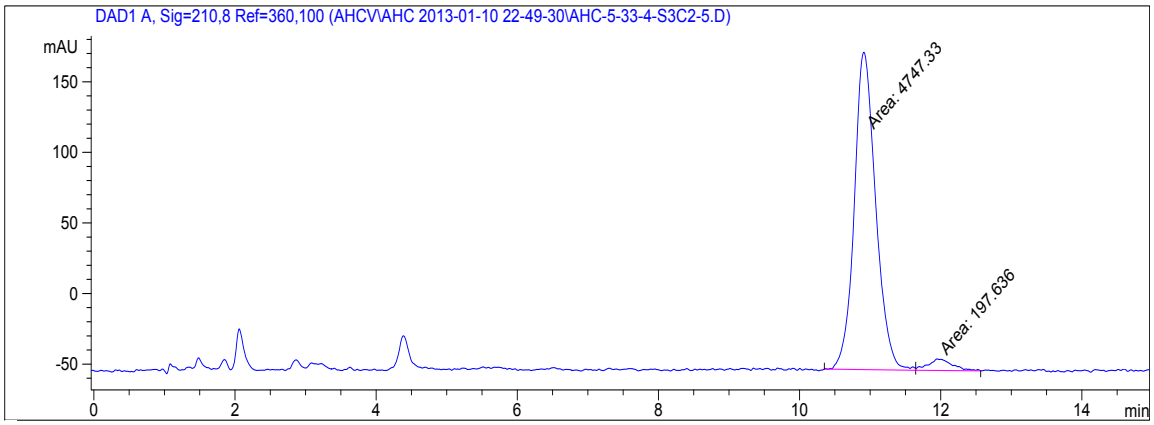
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.287	MM	0.1129	5205.23877	768.54687	94.5053
2	3.754	MM	0.1313	302.64224	38.40394	5.4947

114e racemic



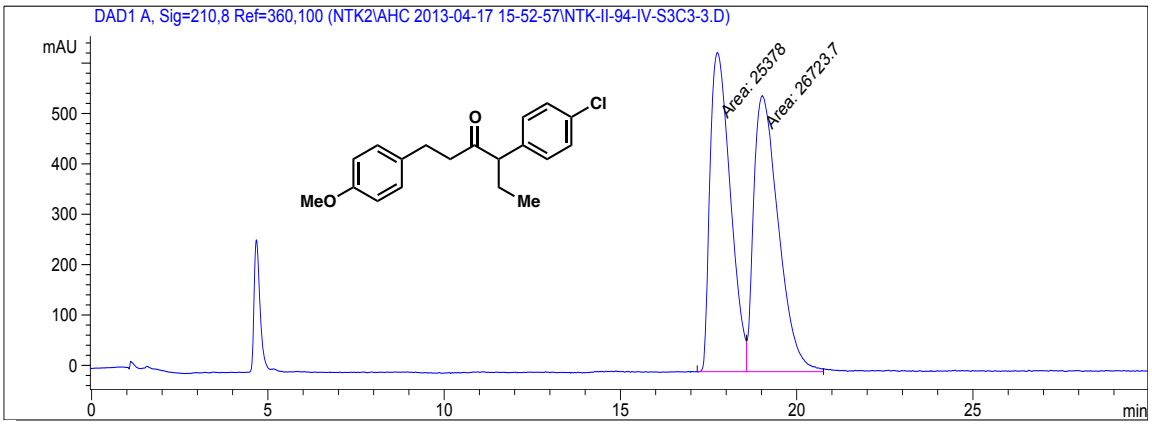
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.925	MM	0.3357	1403.79077	69.69751	48.3093
2	12.051	MM	0.3898	1502.04858	64.21613	51.6907

114e enantioenriched, 92% ee



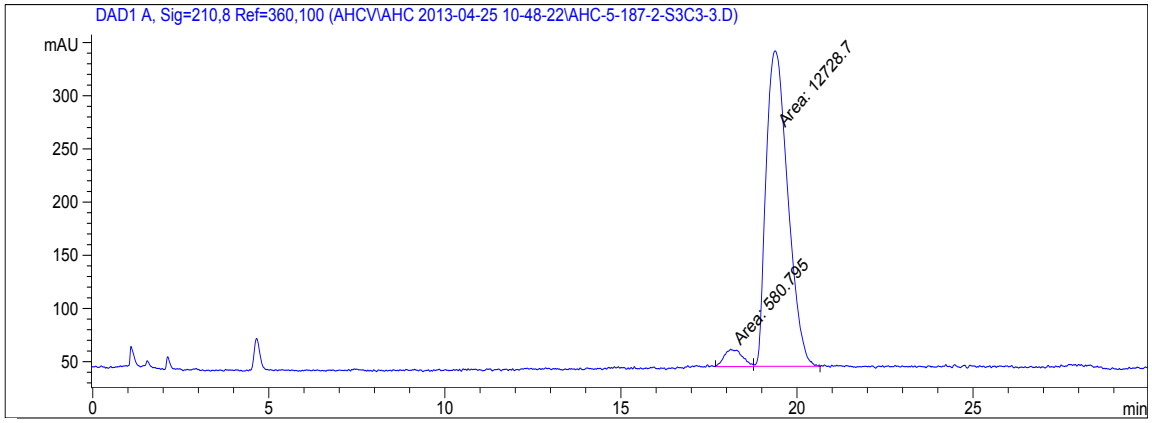
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.911	MM	0.3519	4747.33496	224.86562	96.0033
2	11.946	MM	0.4028	197.63620	8.17804	3.9967

114g racemic



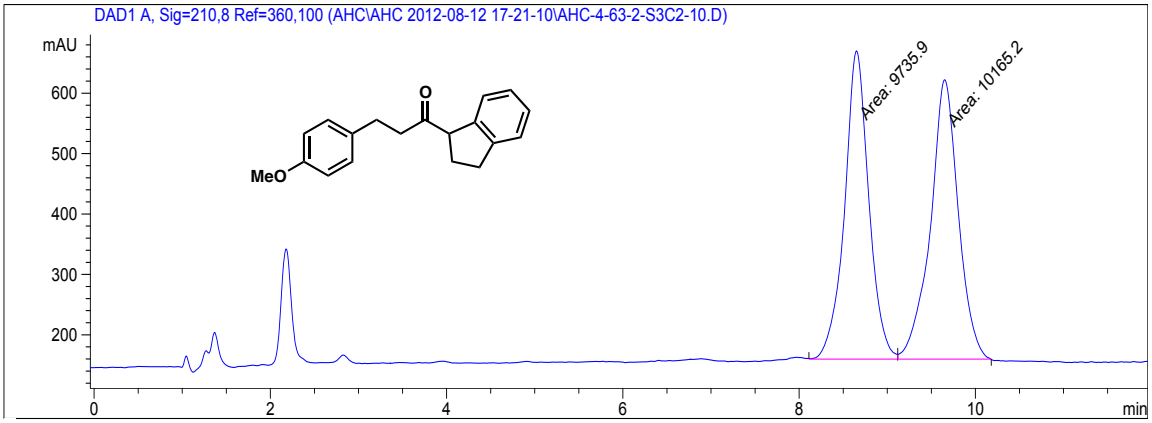
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.749	MM	0.6673	2.53780e4	633.81763	48.7086
2	19.022	MM	0.8126	2.67237e4	548.09839	51.2914

114g enantioenriched, 91% ee



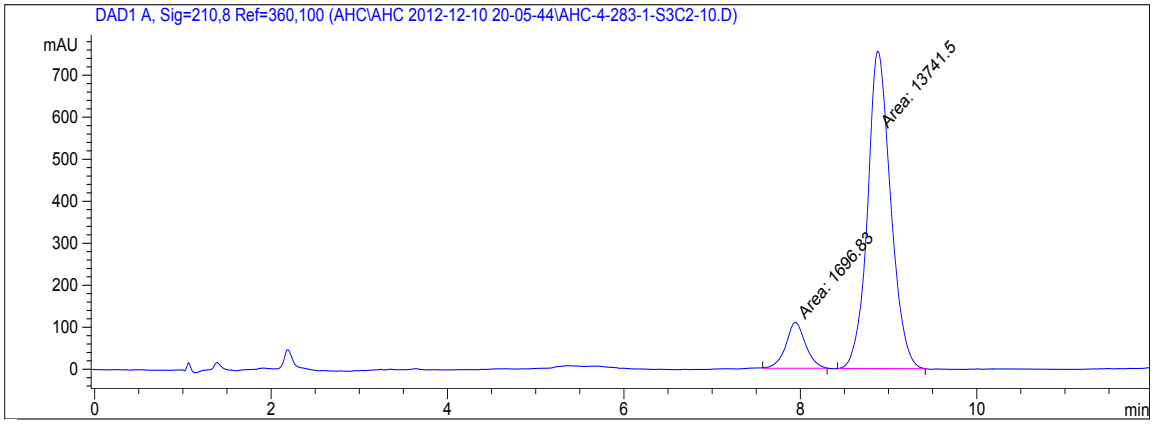
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.118	MM	0.5944	580.79498	16.28630	4.3637
2	19.381	MM	0.7154	1.27287e4	296.55020	95.6363

114h racemic



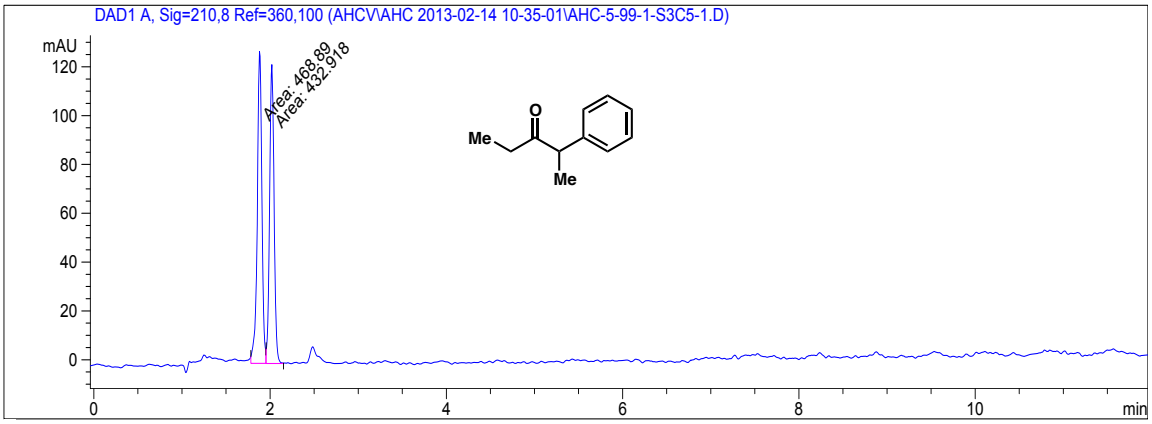
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.651	MM	0.3179	9735.89941	510.35568	48.9213
2	9.651	MM	0.3663	1.01652e4	462.52780	51.0787

114h enantioenriched, 78% ee



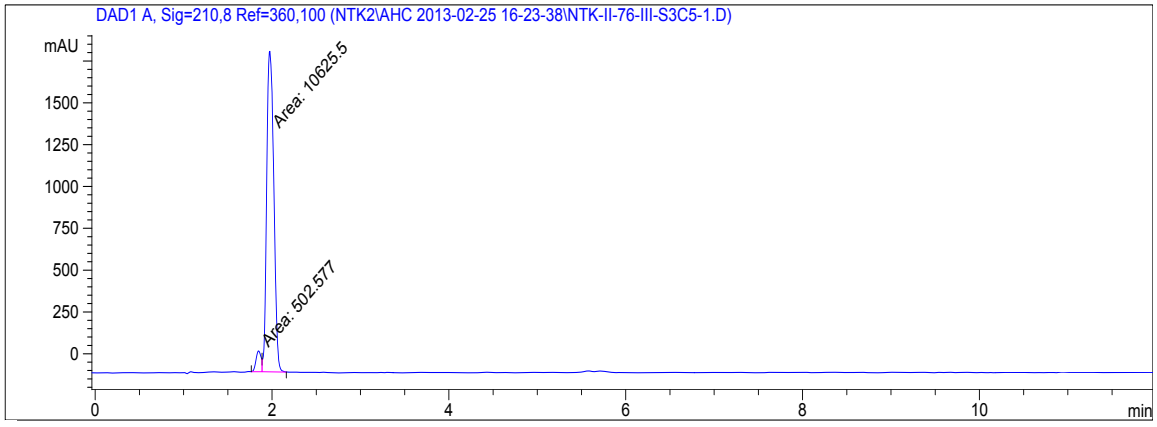
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.943	MM	0.2586	1696.82703	109.37256	10.9910
2	8.880	MM	0.3030	1.37415e4	755.81702	89.0090

116a racemic



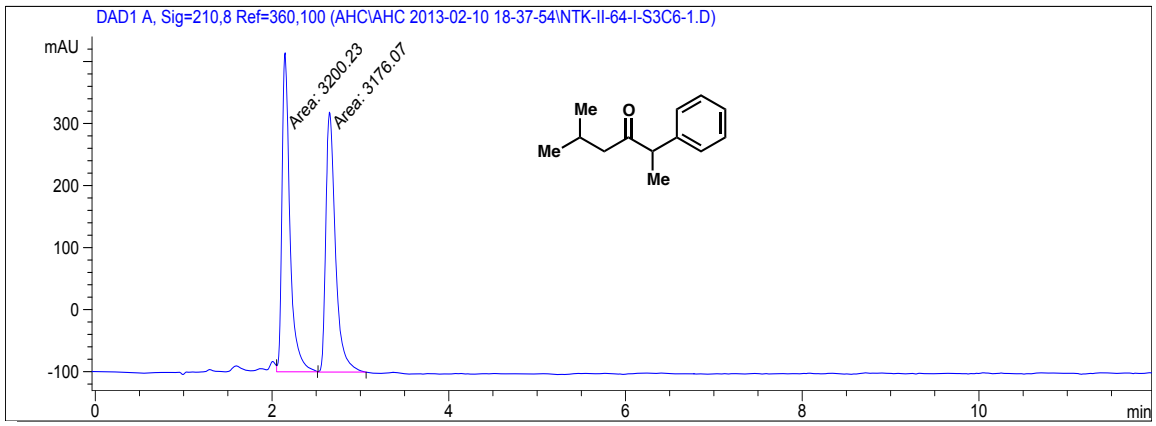
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.882	MM	0.0607	468.89008	128.69202	51.9944
2	2.020	MM	0.0587	432.91794	122.82136	48.0056

116a enantioenriched, 89% ee



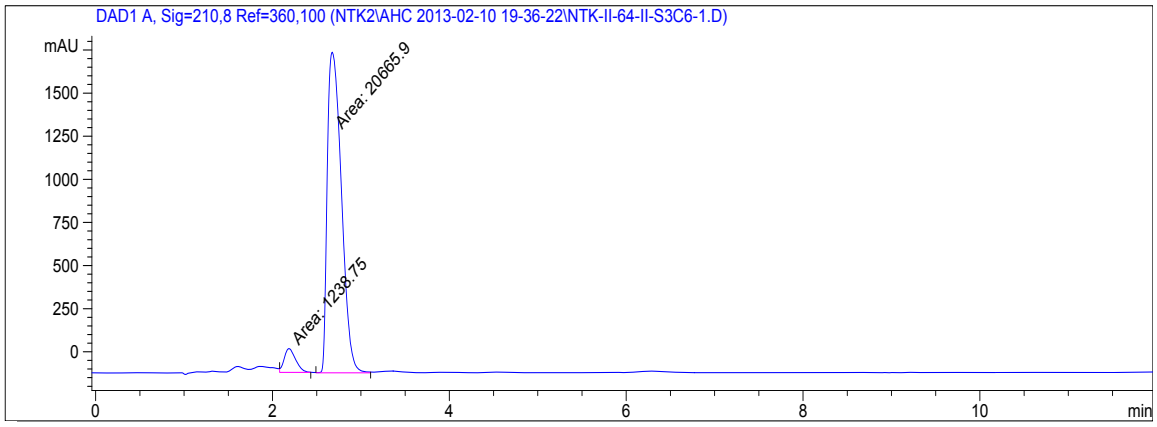
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.848	MM	0.0672	502.57666	124.59120	4.5163
2	1.973	MM	0.0923	1.06255e4	1918.92407	95.4837

116b racemic



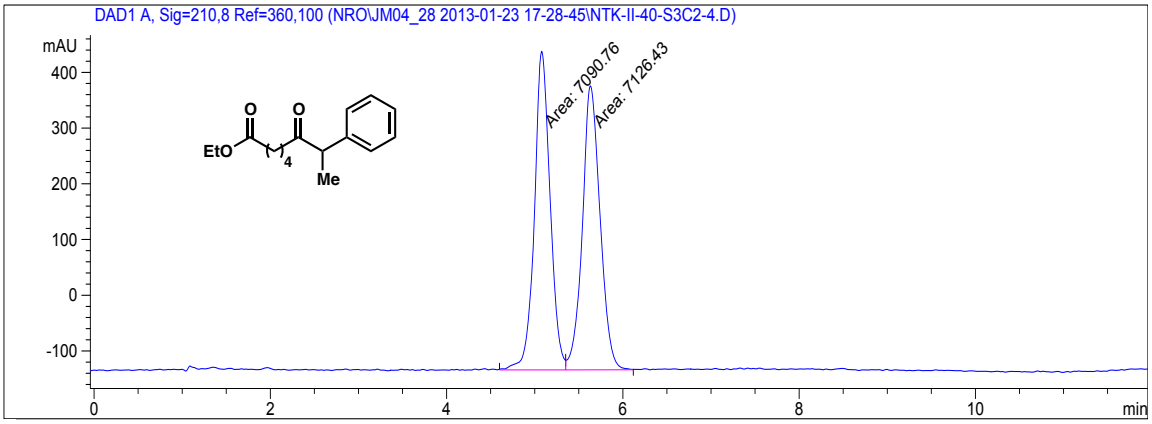
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.147	MM	0.1035	3200.22705	515.47467	50.1894
2	2.651	MM	0.1261	3176.07007	419.70117	49.8106

116b enantioenriched, 88% ee



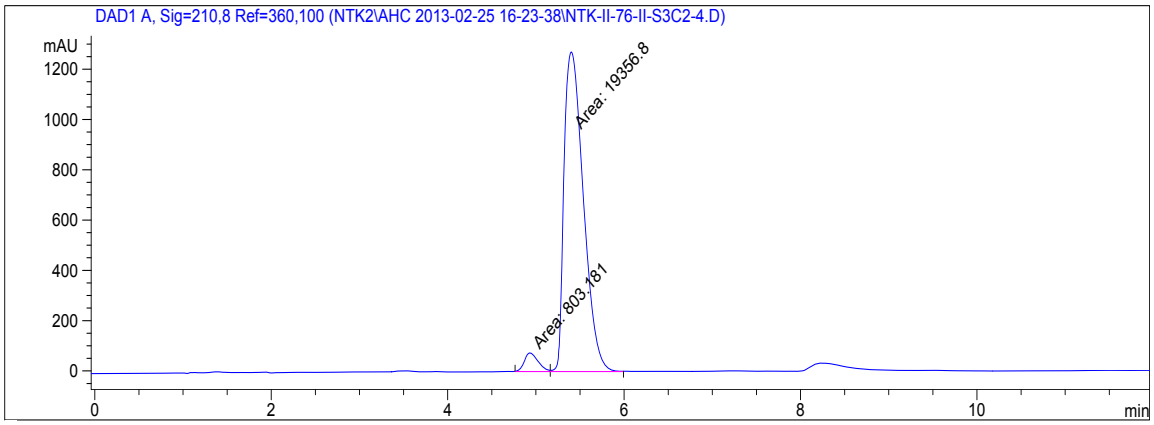
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.186	MM	0.1493	1238.74841	138.30533	5.6552
2	2.675	MM	0.1852	2.06659e4	1859.45630	94.3448

116e racemic



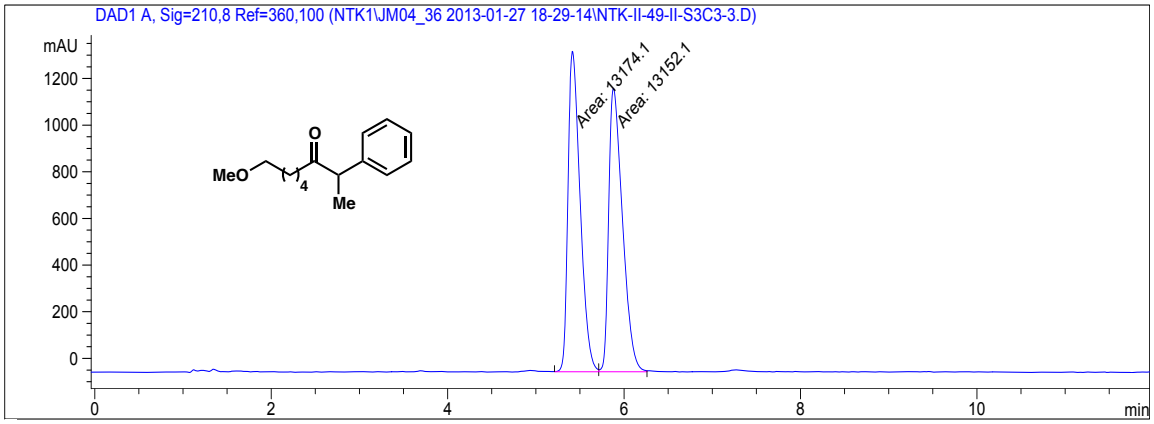
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.079	MM	0.2066	7090.76221	572.01874	49.8746
2	5.631	MM	0.2330	7126.43066	509.79788	50.1254

116e enantioenriched, 92% ee



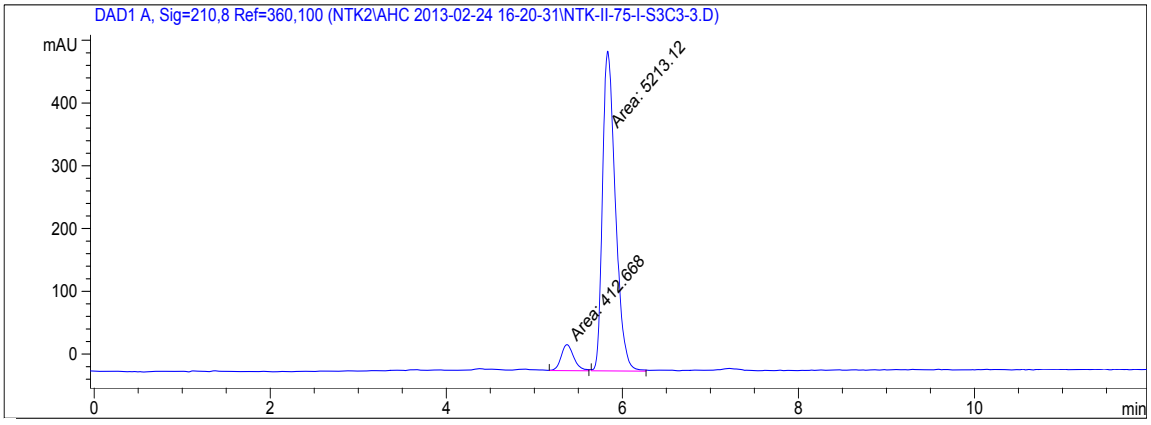
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.932	MM	0.1805	803.18146	74.16300	3.9840
2	5.401	MM	0.2538	1.93568e4	1271.19958	96.0160

116f racemic



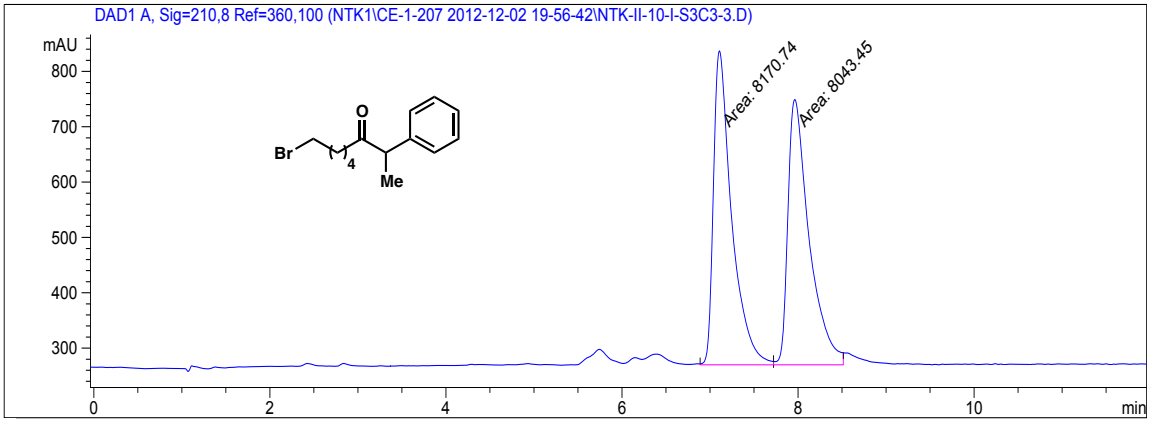
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.415	MM	0.1596	1.31741e4	1375.35034	50.0417
2	5.880	MM	0.1802	1.31521e4	1216.19214	49.9583

116f enantioenriched, 85% ee



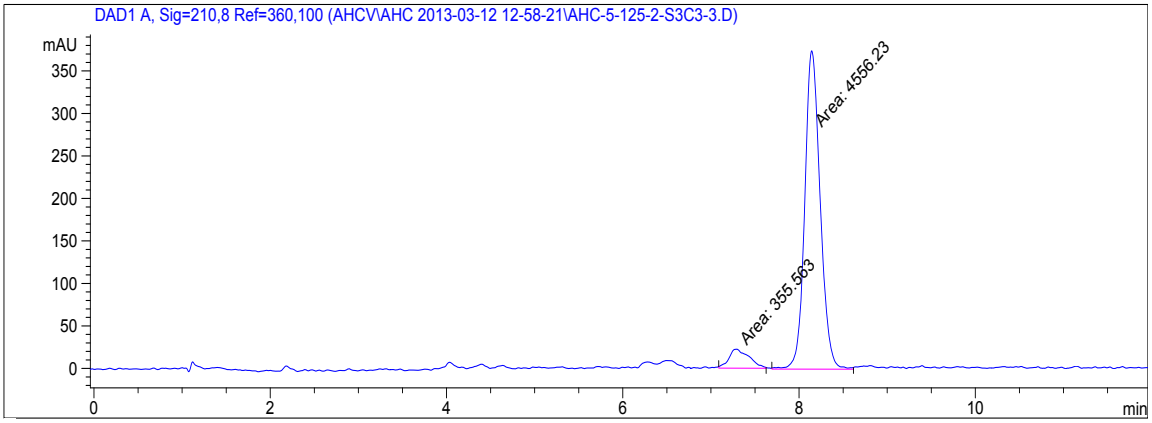
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.371	MM	0.1661	412.66797	41.40784	7.3353
2	5.833	MM	0.1703	5213.12402	510.12839	92.6647

116g racemic



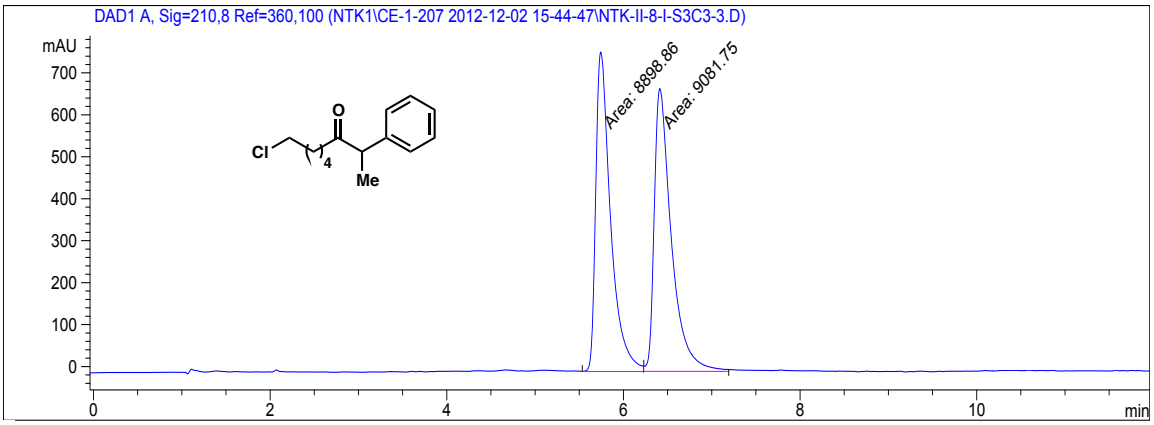
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.107	MM	0.2399	8170.74316	567.72528	50.3925
2	7.963	MM	0.2795	8043.45215	479.56842	49.6075

116g enantioenriched, 86% ee



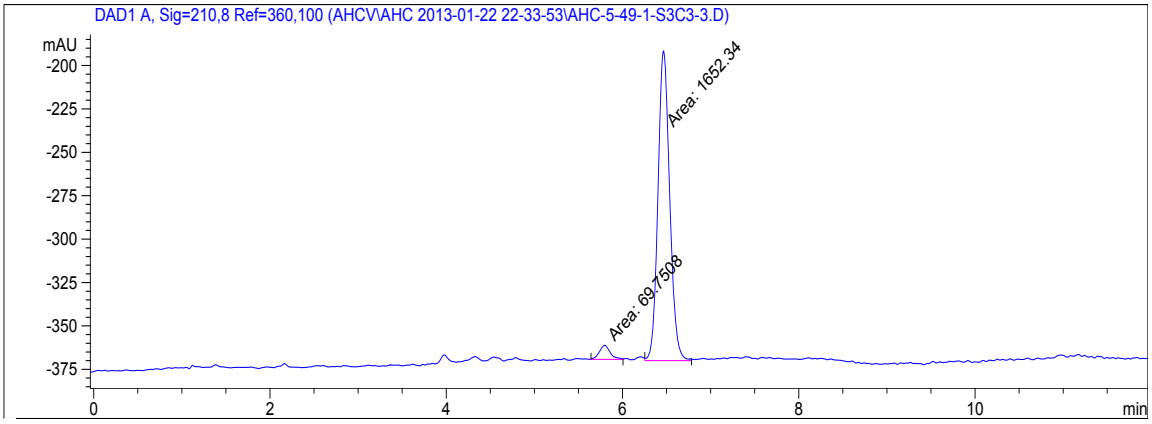
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.295	MM	0.2652	355.56323	22.34372	7.2390
2	8.144	MM	0.2027	4556.22852	374.71005	92.7610

116h racemic



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.744	MM	0.1945	8898.86133	762.63263	49.4914
2	6.413	MM	0.2244	9081.74902	674.62744	50.5086

116h enantioenriched, 92% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.798	MM	0.1418	69.75076	8.19656	4.0504
2	6.465	MM	0.1542	1652.33777	178.58195	95.9496

2.6 NOTES AND REFERENCES

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