Chapter 3

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

3.1 INTRODUCTION

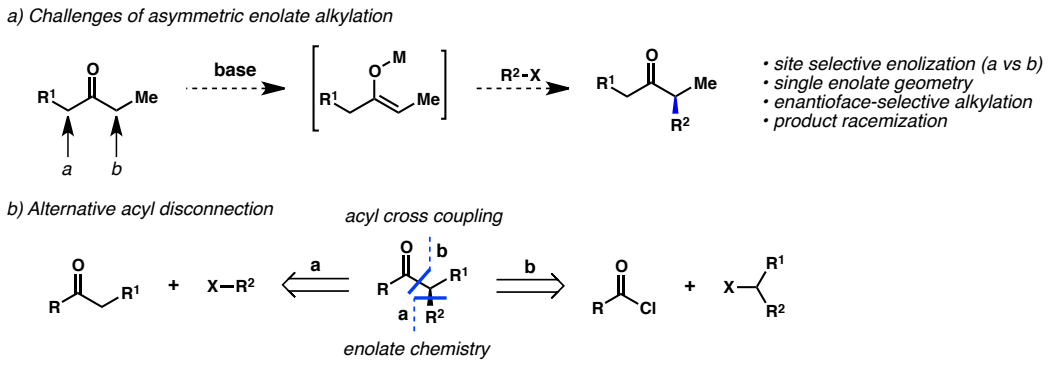
Enantioenriched acyclic α,α-disubstituted carbonyl compounds are versatile synthetic intermediates for the synthesis of natural products and pharmaceutical agents. Due to their ubiquity and utility, the development of new synthetic methods to prepare such compounds has been the subject of intense research. In addition to numerous chiral auxiliary-based strategies,[1] there are an increasing number of catalytic asymmetric α-alkylation,[2] -alkenylation,[3] and -arylation[4] reactions that provide products with α-tertiary

[†] Portions of this chapter have been reproduced from published studies (see reference 21) and the supporting information found therein. The research presented in this chapter was completed in collaboration with Nathaniel T. Kadunce, a graduate student in the Reisman group.

stereogenic centers. Collectively, these methods represent a versatile array of tools that are indispensible to synthetic chemists.

The vast majority of α-functionalization reactions described above proceed via the intermediacy of enolates or enolate equivalents. As a result, the stereochemistry of C–C bond formation is typically influenced by both the enolate geometry and the π-facial selectivity. The synthesis of acyclic α,α-disubstituted *ketones* presents the added requirements of 1) site-selective enolization and 2) mild conditions that prevent racemization of the newly formed tertiary stereogenic center (Figure 3.1, a).[5,6] Strategically, we envisioned that transition metal-catalyzed acyl cross-coupling reactions — which typically occur at low temperatures and circumvent enolate intermediates altogether — could represent an alternative approach to prepare enantioenriched acyclic α,α-disubstituted ketones in a convergent and regioselective fashion (Figure 3.1, b).[7]

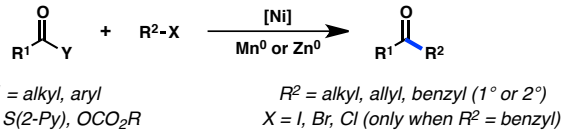
Figure 3.1. *Approach to asymmetric acyl cross-coupling.*



Specifically, we hypothesized that Ni-catalyzed *reductive* coupling reactions[8,9] between carboxylic acid derivatives and secondary alkyl halides[10] could be amenable to asymmetric catalysis. While Ni-mediated reductive homocoupling of organohalide electrophiles was first reported by Semmelhack and coworkers in 1971,[11] a renewed

interest in reductive, or cross-electrophile, methodologies in recent years has been spearheaded by the laboratories of Weix[12] and Gong.[13] Building off of electrochemical studies,[14] Weix and coworkers reported in 2012 the reductive cross-coupling of aliphatic acid chlorides or thioesters with alkyl halides, including benzylic chlorides (Scheme 3.1).[15] Concurrently, Gong and coworkers disclosed a related coupling of aromatic acid chlorides with alkyl halides.[16] Significantly, both transformations demonstrate the ability of Ni catalysts to cross-couple hindered C(sp^3)-hybridized secondary alkyl halides.

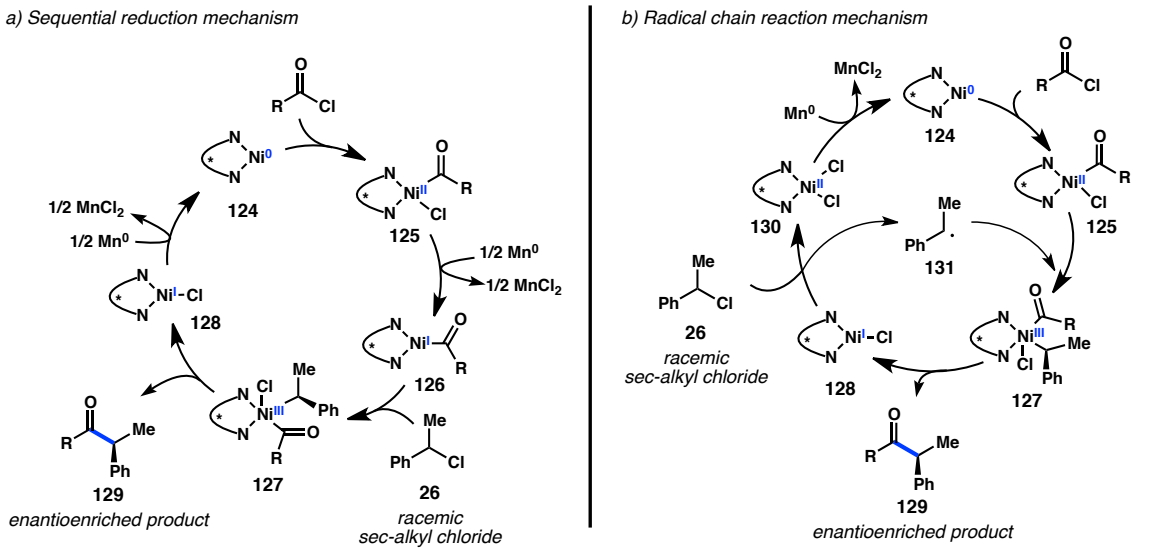
Scheme 3.1. *Racemic Reductive Cross-Coupling of Acyl Electrophiles.*



Although several different mechanisms have been proposed for these reactions, two limiting cases can be considered.[12b] In a sequential reduction mechanism, oxidative addition of the acid chloride could generate Ni^{II}-acyl complex **125**, which could be reduced by Mn^0 to give Ni^{I}-acyl species **126** (Figure 3.2).[17] Subsequent oxidative addition of benzyl chloride **26** by a radical process would then generate Ni^{III} complex **127**, converging both enantiomers of **26** to a single diastereomer.[18] Reductive elimination of ketone **129** from **127** followed by reduction of the Ni^{I}-chloride complex would close the catalytic cycle. An alternative proposal is the radical chain reaction mechanism, wherein Ni^{II}-acyl complex **125**, formed by reaction of Ni^0 with an acid chloride, combines with free benzylic radical **131** to produce Ni^{III} complex **127**. Reductive elimination delivers ketone **129** and Ni^{I}-chloride **128**, which can abstract a halide from starting material **26**. The resultant benzylic radical (**131**) is free to escape the solvent cage, while Ni^{II}-

dichloride **130** is reduced by Mn^0 to reform Ni^0 complex **124**. The key conceptual difference between these two proposed mechanisms is simply the lifetime of benzylic radical **131**. Recent mechanistic studies by Weix and coworkers support a radical chain mechanism for the reductive coupling of aryl and alkyl halides.[12c]

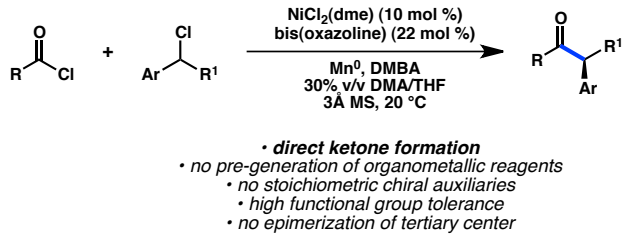
Figure 3.2. *Two potential mechanisms for Ni-catalyzed reductive cross-coupling.*



Regardless of which mechanism is operative under our reaction conditions, we hypothesized that an appropriate chiral catalyst could promote a stereoconvergent transformation of benzyl chloride **26** because of the stereoablative nature with which **26** interacts with Ni. Indeed, Fu and coworkers have shown that Ni catalysts promote stereoconvergent cross-couplings of racemic secondary electrophiles and organometallic reagents under similar reaction conditions.[19] While a stereoconvergent oxidative addition is plausible, Molander and Kozlowski have also recently demonstrated the feasibility of a stereochemistry-determining reductive elimination.[20] Based on this mechanistic understanding, we questioned 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 execution of this plan, which has resulted in the development of the first enantioselective Ni-catalyzed reductive cross-coupling reaction between acid chlorides and secondary alkyl halides (Figure 3.3).[21]

Figure 3.3. *This work: Asymmetric reductive acyl cross-coupling.*



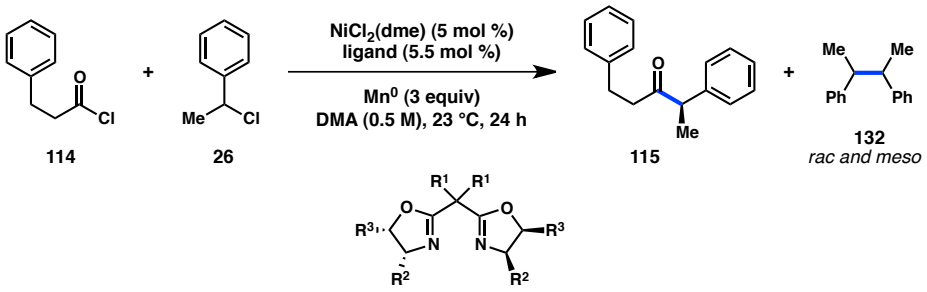
3.2 DEVELOPMENT OF AN ASYMMETRIC REDUCTIVE ACYL CROSS-COUPLING

3.2.1 Identification of a Chiral Catalyst System

Our investigations began with the reductive coupling of hydrocinnamoyl chloride (**114**) and (1-chloroethyl)benzene (**26**). Using catalytic $NiCl_2$(dme) in *N*,*N*-dimethylacetamide (DMA) with Mn^0 as the stoichiometric reductant — conditions previously reported to promote the coupling of acid chlorides and alkyl halides[15a] — a screen of chiral ligands was conducted. Evaluation of a set of bis(oxazoline) ligands revealed that both phenyl substitution and an isopropylidene linker were critical for imparting moderate enantioinduction (entries 1–5). Elaboration to tetrasubstituted ligands (entries 6 and 7) or indanyl-substituted ligands (entries 8–10) produced ketone **115** with reduced enantioselectivity. Other bidentate and tridentate ligand scaffolds (**L38, L105–L108**) delivered the product with little asymmetric induction. While we were encouraged

by the unique activity of bis(oxazoline) **L36**, use of this ligand delivered ketone **115** in only 7% yield, with homocoupled product **132** being the major side product. Nonetheless, we proceeded to investigate other reaction conditions to further increase the enantioselectivity of the transformation.

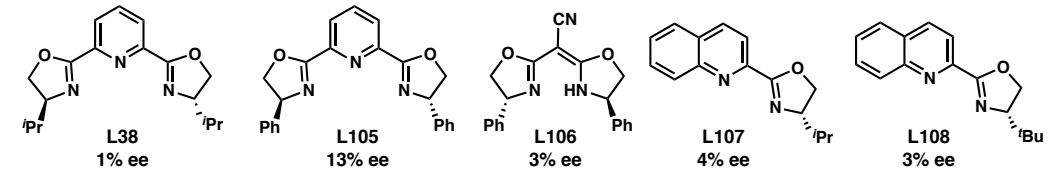
Figure 3.4. *Evaluation of chiral ligand frameworks.*



Bis(oxazoline) Ligand Scaffold

Entry	R^1	R^2	R^3	Ligand	ee (%)
1	Me	^{i}Pr	H	L99	27
2	Me	^{t}Bu	H	L66	5
3	Me	Bn	H	L100	37
4	Me	Ph	H	L36	66
5	H	Ph	H	L101	12
6	H	Ph	Ph	L43	9
7	$-CH_2CH_2-$	Ph	Ph	L102	55
8	H	indanyl		L103	8
9	Me	indanyl		L51	7
10	$-CH_2CH_2-$	indanyl		L104	10

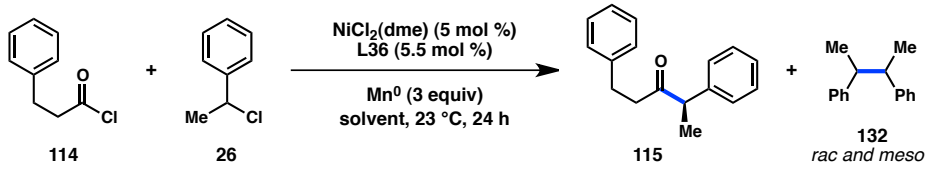
Other Ligand Scaffolds



After conducting a screen of various solvents, we were pleased to observe that less strongly coordinating solvents provided a higher degree of asymmetric induction (Table 3.1). Accordingly, in the presence of THF, ketone **115** was obtained in 92% ee but

only 19% yield (entry 6). Unfortunately, the reaction did not provide full conversion of benzyl chloride **26**, and homocoupling of **26** was competitive.

Table 3.1. *Evaluation of solvents.*



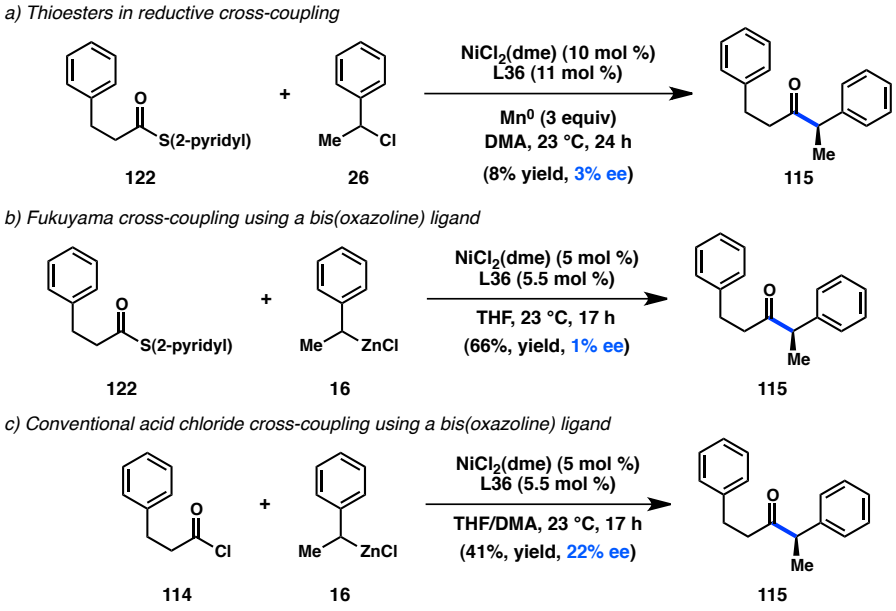
114 26 115 132 *rac and meso*

Entry	Solvent	ee (%)
1	DMPU	37
2	DMF	50
3	DMA	66

Entry	Solvent	ee (%)
4	DME	72
5	EtOAc	82
6	THF	92

At this stage, the role of the leaving group on enantioselectivity was examined. Reductive coupling of benzyl chloride **26** with 2-pyridyl thioester **122** in the presence of **L36** failed to impart any enantioselectivity (Figure 3.5, a). In this case, following oxidative addition, the bidentate thiolate leaving group may inhibit the chiral catalyst, and the poor selectivity may arise from racemic background reactivity. Similarly, as was observed in previous studies on an asymmetric Fukuyama cross-coupling (see Chapter 2), exposure of 2-pyridyl thioester **122** and organozinc halide **16** to $NiCl_2$(dme) and **L36** delivered the desired ketone in 66% yield but only 1% ee (Figure 3.5, b), confirming the non-innocent nature of the thiolate leaving group. We next studied a conventional cross-coupling of acid chloride **114** and organozinc halide **16**, but the reaction did not proceed in THF. Alternatively, a mixed solvent system of THF and DMA allowed ketone **115** to be formed in 22% ee (Figure 3.5, c). This disparity in enantioinduction for the conventional Negishi-type and reductive cross-couplings suggests a difference in the chiral catalyst structure during the enantiodetermining step of the transformation.

Figure 3.5. *Study of enantioselectivity with thioesters and organozinc halides.*

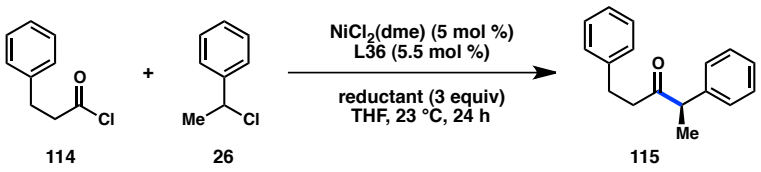


3.2.2 Optimization of Reactivity for an Enantioselective Reaction

Having identified conditions for a highly enantioselective reductive cross-coupling, we proceeded to optimize the yield of the reaction. When THF was utilized as a solvent, the Ni catalyst was poorly reactive, delivering low conversions of benzyl chloride **26** and no selectivity for ketone formation over benzylic homocoupling. Furthermore, the sluggishness of the reactivity induced acid chloride **114** to react with THF, affording ester **133**.[22] We hypothesized that as we transitioned from solvents with high dielectric constants (e.g., DMA, DMPU, and DMF) to THF, the electron-transfer step might become rate-limiting. Unfortunately, a screen of other reductants failed to provide better yields than Mn^0 (Table 3.2, entry 1). Zn^0 provided complete conversion of the starting materials but favored homocoupling over heterocoupling (entry 2). The

soluble reductant cobaltocene ($CoCp_2$) was also ineffective at promoting cross-coupling (entry 6).

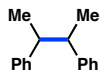
Table 3.2. *Evaluation of stoichiometric reductants.*



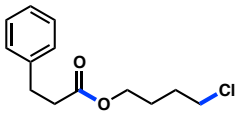
114 26 115

Entry	Reductant	Conversion (%)	Yield (%)	ee (%)
1	Mn^0	43	19	92
2	Zn^0	100	13	46
3	Mg^0	100	trace	20
4	Co^0	0	0	--
5	Fe^0	0	0	--
6	$CoCp_2$	0	0	--

Side Products:



132
rac and meso

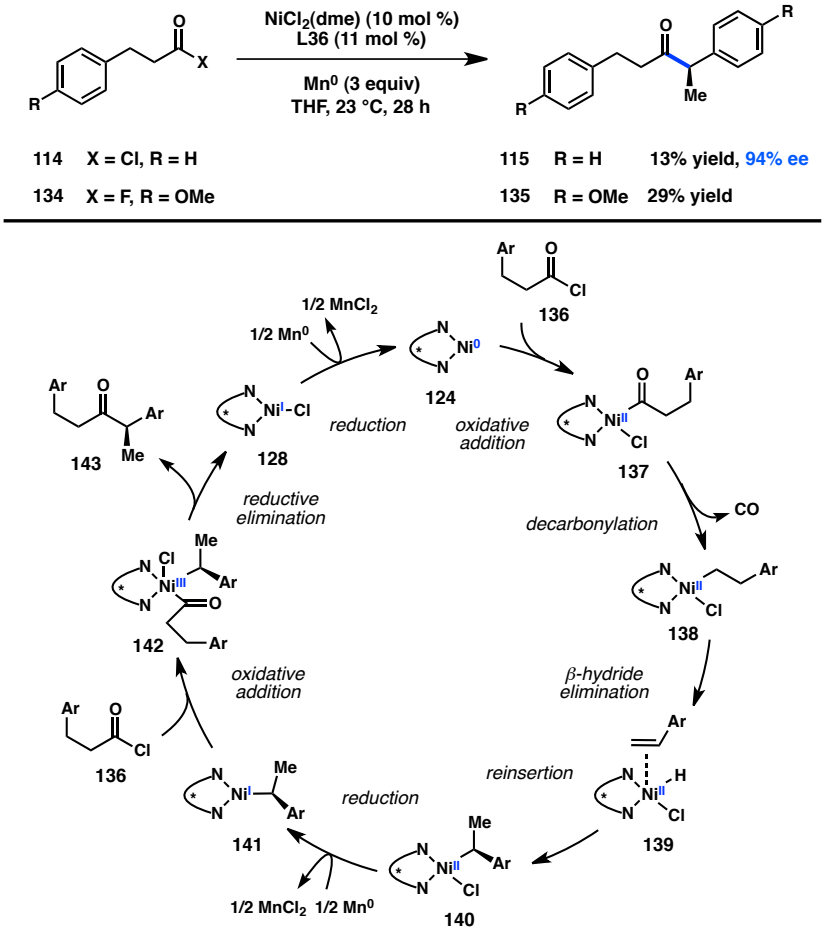


133

The sluggish reactivity toward benzyl chloride **26** in THF also resulted in unexpected rearrangement products. During the course of our studies, we observed that in the absence of benzyl coupling partner **26**, treatment of acid chloride **114** with $NiCl_2$(dme), **L36**, and Mn^0 in THF still produced **115** in 13% yield and 94% ee (Figure 3.6). Further optimization demonstrated that acid fluoride **134** delivers ketone **135** in 29% yield. Surprisingly, no product is detected when the reaction is performed using DMA as a cosolvent. A possible catalytic cycle is displayed in Figure 3.6. Oxidative addition of Ni^0 to acid chloride **136** forms Ni^{II}-acyl complex **137**. If reduction by Mn^0 in THF is slow, then decarbonylation can give Ni^{II}-alkyl **138** and release CO. A β-hydride elimination/reinsertion sequence can provide isomerized Ni^{II}-alkyl **140**, which can then

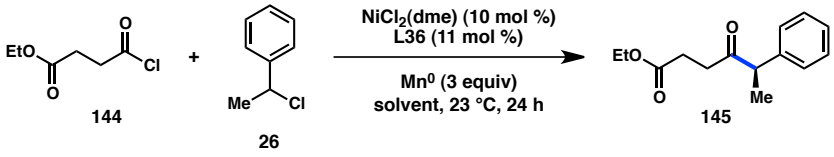
be reduced to a Ni^{I} complex. A second oxidative addition to acid chloride **136** furnishes Ni^{III} complex **142**, intercepting an intermediate from our typical cross-coupling mechanism. Reductive elimination and a subsequent single-electron reduction delivers ketone **143** and reforms Ni^{0}. Interestingly, the acid chloride dimerization proceeds with identical enantioselectivity as the typical cross-coupling reaction. Based on the above results, it is possible that coupling of acid chloride **114** and benzyl chloride **26** can produce ketone **115** by competing heterocoupling and acid chloride dimerizations.

Figure 3.6. *Unexpected dimerization of acid chlorides.*



While the lower dielectric constant of THF compared to DMA may slow down electron transfer events, it is also possible that low conversion of benzyl chloride **26** is the result of dimerization or aggregation of Ni species in less strongly polar solvents, resulting in catalyst inhibition or death.[17] In either case, we reasoned that a mixed solvent system between THF and DMA would maintain high levels of enantioselectivity while also accelerating the rate of product formation. Indeed, using 10 mol % catalyst, THF provides a 24% yield and 86% ee of ketone **145** and DMA delivers a 59% yield and 73% ee of the product (Table 3.3, entries 1 and 8). The cross-coupling proved to be highly sensitive to the amount of DMA that was used as a cosolvent. Lower levels of DMA provided reduced conversion of benzyl chloride **26** (entries 2 and 3), while a higher proportion of DMA resulted in lower asymmetric induction (entries 6 and 7). Gratifyingly, 30% v/v DMA in THF furnishes ketone **145** in 62% yield and 86% ee, preserving the yield seen in DMA and the selectivity seen in THF (entry 4).

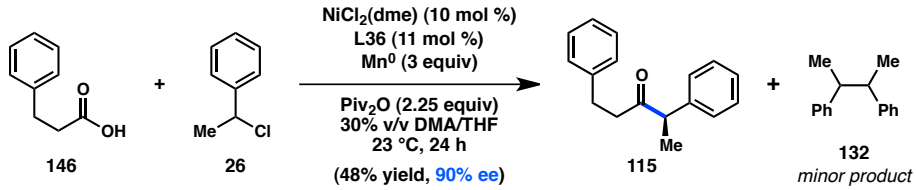
Table 3.3. *Evaluation of mixed solvent systems.*



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

Having increased the reactivity of our system without diminishing the enantioselectivity, we next sought to increase the product yield further by improving the preference for heterocoupling over homocoupling.[23] Previous studies on reductive cross-couplings have minimized homodimer formation through structural modification of the Ni/ligand complex or through statistical manipulation by adding an excess of one reagent.[8a] The sensitivity of our enantioinduction to changes in ligand and a desire to develop an efficient transformation dissuaded us from these approaches. After an extensive analysis of reaction parameters and additives, we became aware of two important considerations: 1) reproducibility of reaction outcomes was hampered because not all trials would exhibit a consistent ratio of product to homocoupling, and 2) the cross-coupling of an in situ-generated mixed anhydride, formed by treatment with pivalic anhydride, proceeded with a low level of homodimer formation (Scheme 3.2).[24]

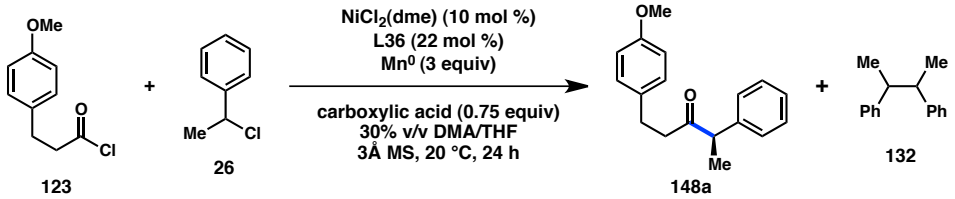
Scheme 3.2. *Reductive cross-coupling of in situ-generated mixed anhydrides.*



To explain these effects, we rationalized that adventitious water might result in irreproducible reaction outcomes because of hydrolysis of the acid chloride to a carboxylic acid. Similarly, we realized that the mixed anhydride cross-coupling resulted in a full equivalent of a free carboxylic acid being present in the reaction medium. Based on these observations, we hypothesized that a free carboxylic acid might be able to modulate the selectivity for ketone formation over homocoupling. A wide screen of

carboxylic acids revealed that 2,6-dimethylbenzoic acid (DMBA, **147**) delivered the greatest selectivity for product formation over homocoupling (Table 3.4). Further optimization of the reaction concentration, the ligand-to-metal ratio, and addition of 3Å molecular sieves permitted ketone **148a** to be obtained in 85% yield and 93% ee, with only a 4% yield of homodimer.

Table 3.4. *Effect of carboxylic acids on the ratio of ketone to homodimer formation.*

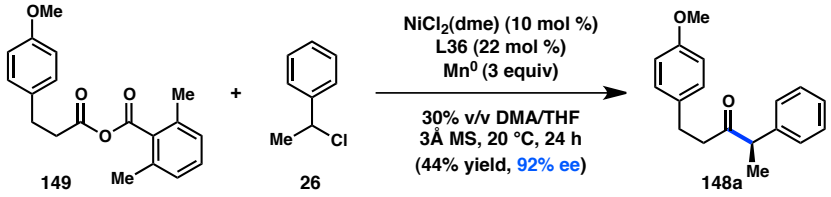


Entry	Acid	Yield 132 (%)	Yield 148a (%)	ee (%)
1	--	22	52	94
2	AcOH	17	65	92
3	BzOH	14	40	92
4	DMBA (147)	4	85	93

The mechanistic role of the carboxylic acid additive is still unclear. We currently speculate that the carboxylic acid can coordinate to the Ni catalyst at some point during the catalytic cycle as opposed to interacting with either substrate. We do not observe formation of the mixed anhydride during the reaction, and the mixed anhydride is not isolated by treatment of the acid chloride with DMBA and mol sieves in DMA/THF. Nonetheless, pregenerated mixed anhydride **149** produces the desired product in 44% yield and 92% ee (Scheme 3.3), suggesting that **149** is a competent starting material but not confirming its role as a reaction intermediate. Interestingly, DMBA displays the greatest inhibitory effect on homocoupling when THF is the sole solvent and has the least activity when DMA is the sole solvent. This may be explained by the reduced

coordinating ability of DMBA in highly polar solvents like DMA, when it has to compete with DMA for open coordination sites on Ni.

Scheme 3.3. *Employing a pregenerated mixed anhydride.*



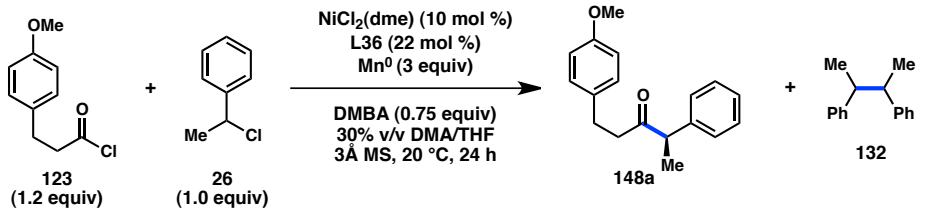
Two possible actions of the carboxylic acid additive are promotion of ketone formation or inhibition of homodimer formation. Given that the enantioselectivity of the cross-coupling is not affected by the choice of acid, it appears that the additive is not coordinated to the catalyst during the stereochemistry-determining step. Instead, the carboxylic acid may assist with initial oxidative addition of Ni^0 to the acid chloride over the benzyl chloride, with addition of Ni^0 to benzyl chloride ultimately resulting in homocoupling. Reactions run in the presence of DMBA generally proceed in lower conversion than in the absence of DMBA, suggesting that the carboxylic acid reduces the rate of the reaction or facilitates catalyst inhibition. While additional mechanistic studies are necessary, we speculate that DMBA might coordinate to Ni^0 and decelerate oxidative addition to benzyl chloride **26** relative to acid chloride **123**, providing greater selectivity for heterocoupling over homocoupling.

At this point, we reevaluated several important reaction parameters. These results are summarized in Table 3.5. Control experiments determined that ketone **148a** is not produced in the absence of Mn^0 or Ni catalyst, although low yields of **148a** can be observed in the absence of ligand (Table 3.5, entries 2–4). Removal of DMBA was found

to increase the formation of homocoupled product **132** and decrease the yield of **148a** (entry 5). Molecular sieves were discovered to further increase the yield of **148a**, although freshly-dried molecular sieves did not provide a yield enhancement (entry 6). Given that Mn^0 mediates homocoupling of benzyl chloride **26** in the absence of Ni (entry 3), several alternative stoichiometric inorganic and organic reductants were investigated with the objective of shutting down this undesired pathway. Unfortunately, Zn^0 was the only reductant that furnished detectable quantities of **148a**, and it did not provide improvements with respect to Mn^0 (entry 7). Use of $Ni(cod)_2$ as a pre-catalyst delivered **148a** with comparable ee (entry 8); however, the yield was reduced relative to $NiCl_2$(dme). The use of other metal salts such as $CoCl_2$ were ineffective (entry 9).

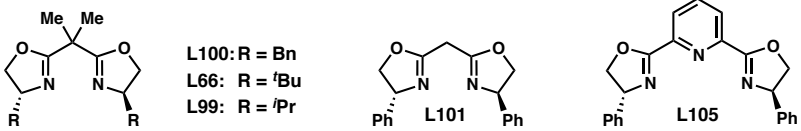
A reinvestigation of ligands under the optimized conditions confirmed that **L36** provides higher ee's than other substituted bis(oxazolines) (entries 10–14). Furthermore, the isopropylidene bridge of **L36** proved to be critical, as **L101** afforded **148a** with no stereoinduction. Use of tridentate ligands such as **L105** led to almost exclusive homocoupling.[25] The mixed solvent system was found to provide the appropriate balance of reactivity and selectivity (entries 16–18). Whereas the best ee's were obtained in THF, the reactivity was poor and the yields were low. On the other hand, DMA provided higher conversions, but also resulted in increased production of homodimer **132**. Reducing the **L36**:Ni ratio to 1.1:1 led to a slight reduction in yield of **148a** (entry 15). Excess ligand might be beneficial to prevent the formation of dimeric Ni^I complexes that can act as a catalyst sink.[17] Coupling of (1-bromoethyl)benzene under otherwise identical reaction conditions provided **148a** in the same ee, but in lower yield due to increased formation of homodimer **132** (entry 19).[26]

Table 3.5. *Impact of reaction parameters on Ni-catalyzed asymmetric reductive coupling.*



Entry	Deviation from standard conditions[a]	Conversion 26 (%)[b]	Yield 132 (%)[b]	Yield 148a (%)[b]	ee 148a (%)[c]
1	none	90	4	85	92
2	no Mn^0	0	0	0	--
3	no $NiCl_2$(dme)	35	35	0	--
4	no L36	73	5	8	--
5	no DMBA (147)	100	22	52	94
6	no 3Å MS	100	7	76	90
7	Zn^0 instead of Mn^0	85	26	31	88
8	$Ni(cod)_2$ instead of $NiCl_2$(dme)	98	18	68	92
9	$CoCl_2$ instead of $NiCl_2$(dme)	73	24	0	--
10	L100 instead of L36	61	24	22	45
11	L66 instead of L36	98	62	14	2
12	L99 instead of L36	89	52	40	69
13	L101 instead of L36	15	1	10	0
14	L105 instead of L36	99	53	4	9
15	11 mol % L36	82	3	72	92
16	DMA as solvent	99	43	30	88
17	THF as solvent	25	<1	26	94
18	MeCN as solvent	28	4	16	45
19	(1-bromoethyl)benzene instead of 26	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.



Several additional experiments were performed to gain additional insight into the observed reactivity. When the reaction between **123** and **26** is conducted in the presence of 0.5 equiv of the radical inhibitor 2,6-bis(1,1-dimethylethyl)-4-methylphenol (BHT),

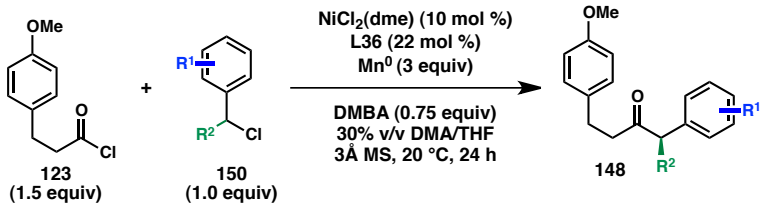
ketone **148a** is isolated in 80% yield and 92% ee. Alternatively, use of the electron transfer inhibitor 1-chloro-2,4-dinitrobenzene completely shuts down the reaction. These findings are consistent with the sequential reduction mechanism proposed in Figure 3.2. Additionally, the ee of ketone **148a** is constant over the course of reaction, whereas the ee of recovered benzyl chloride **26** gradually increases to 17% at 94% conversion. These results suggest that the two enantiomers of **26** react at comparable rates, as only a very modest kinetic resolution occurs. When enantioenriched **26** is employed, ketone **148a** is obtained in 92% ee and **26** is recovered without erosion of ee. Lastly, to assess the intermediacy of organomanganese intermediates, **26** was converted to the corresponding benzylmanganese halide via Grignard formation/transmetalation. Ketone **148a** was not observed after exposure of the organomanganese to our optimized reaction conditions.[27]

3.2.3 Substrate Scope and Further Studies

With optimized conditions in hand, we investigated the scope of the benzyl chloride (Table 3.6). Coupling of **123** with benzyl chlorides bearing electron-releasing substituents furnished the corresponding ketones in high ee; however, these substrates reacted slowly relative to **150a** and required higher **L36**:Ni ratios (3.3:1) to obtain good conversions (entries 2–5). In contrast, benzyl chlorides bearing electron-withdrawing substituents reacted rapidly and proceeded to full conversion. In the case of the trifluoromethyl-substituted substrate (entry 8), the higher reactivity was accompanied by increased side product formation and somewhat reduced enantioselectivity. Both 4-chloro and 4-bromobenzyl chlorides can be coupled with complete chemoselectivity, providing

products suitable for further elaboration. Under our standard conditions, the coupling of **150g** resulted in higher-than-usual levels of homocoupling; this was mitigated via addition of excess DMBA (entry 7). Unfortunately, *o*-substituted benzyl chlorides (e.g. **150d**, entry 4) were poor substrates, providing the ketone products in low yields and ee's.

Table 3.6. *Substrate scope of benzyl chlorides.*



Entry	R^1	R^2	Pdt	Yield (%)[a]	ee (%)[b]
1	H	Me	148a	79	93
2[c]	4-Me	Me	148b	74	93
3[c]	3-Me	Me	148c	75	93
4[c]	2-Me	Me	148d	35	72
5[c]	4-OMe	Me	148e	56	86
6	4-Cl	Me	148f	76	91
7[d]	4-Br	Me	148g	73	86
8[e]	4-CF_3	Me	148h	64	82
9[c]	2-naphthyl	Me	148i	65	91
10	H	Et	148j	50	94
11	Cl	Et	148k	65	90
12	H	Bn	148l	79	92
13[f]	H	CH_2OTBS	148m	51	89
14	H	4-pentenyl	148n	38	92
15	2,3-dihydro-1*H*-inden-1-yl		148o	68	78

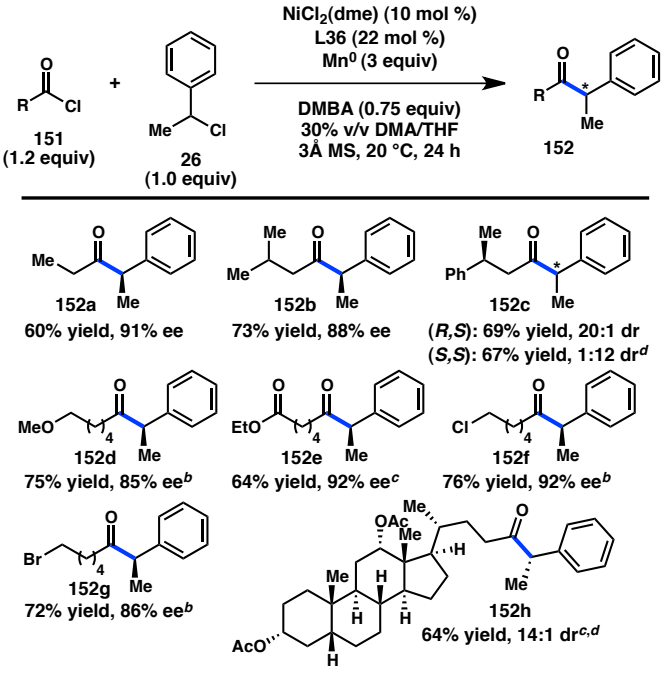
[a] Isolated yield, reactions conducted on 0.2 mmol scale under an N_2 atmosphere in a glovebox. [b] Determined by SFC using a chiral stationary phase. [c] Run with 33 mol % **L36**. [d] Run with 1.25 equiv DMBA [e] Run in 20% v/v DMA/THF. [f] Run in 50% v/v DMA/THF.

We were pleased to discover that β-substituted benzyl chlorides provide access to α-aryl-α-alkyl ketones with high enantioselectivity (entries 10–14). In general, these substrates react more slowly and do not achieve complete conversion; however, they also exhibit low propensity toward homocoupling. Notably, the mild conditions of the

reductive coupling enable formation of **148m** in moderate yield without any observed elimination (entry 13). Interestingly, **148n** was formed without any detectable quantities of the 5-*exo* cyclization product (entry 14). This result suggests that if oxidative addition takes place via a radical pathway, then radical recombination occurs faster than cyclization or that the radical cyclization is reversible.[28] The cyclic substrate 1-chloro-2,3-dihydro-1*H*-indene reacted to provide ketone **148o** in good yield, albeit modest ee (entry 15). The reaction can be run on preparative scale: coupling of acid chloride **123** and benzyl chloride **150a** on a 1.0 mmol scale at the bench top delivered ketone **148a** in 70% yield and 93% ee.

The scope of the acid chloride coupling partner was also investigated (Figure 3.7). Alkyl halide and ester functionalities are well tolerated; these findings are noteworthy because such groups would not be compatible in their native form with the more conventional synthesis involving auxiliary-controlled alkylation followed by Weinreb ketone synthesis.[29] For several of the acid chlorides shown in Figure 3.7, the efficiency of the coupling proved to be sensitive to the DMA:THF ratio, with improved yields often being observed with lower levels of the amide solvent. Depending on the enantiomer of **L36** that is employed, the coupling of benzyl chloride **26** with enantiopure acid chloride **151c** provides access to either diastereomer with high diastereoselectivity. A standard enolate alkylation approach to **152c** would not be anticipated to provide such high levels of 1,4-stereoinduction. The power of this methodology is further demonstrated by the diastereoselective preparation of ketone **152h**. While β-substituted acid chlorides are well-tolerated, α,α-disubstituted acid chlorides result in lower levels of enantioselectivity and increases in benzylic homocoupling.

Figure 3.7. *Substrate scope of acid chlorides.*[a]

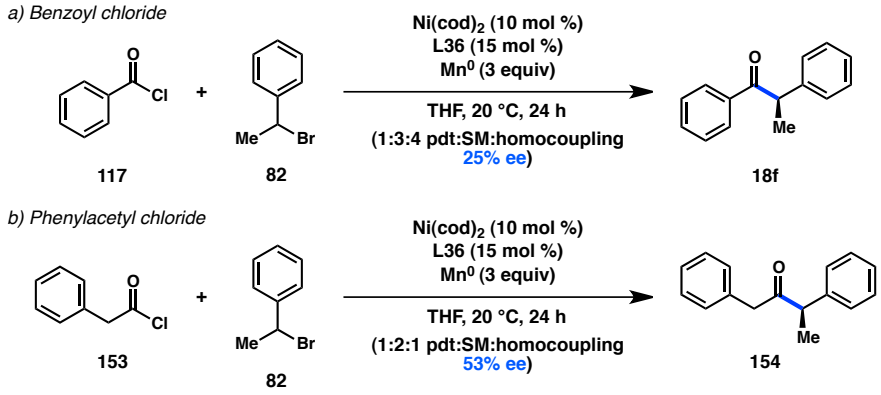


[a] Isolated yield, reactions conducted on 0.2 mmol scale under an N_2 atmosphere in a glovebox. % ee determined by SFC using a chiral stationary phase. [b] Run in 20% v/v DMA/THF. [c] Run in 10% v/v DMA/THF. [d] Run with *ent*-**L36**.

We next attempted to expand our substrate scope from aliphatic acid chlorides to aromatic ones. Unfortunately, under the optimized conditions, no product was observed when benzoyl chloride (**117**) was employed as a starting material. Transitioning to the more reactive benzyl bromide **82**, we realized that only a trace yield of product was detected when DMA was used as a solvent. The yield increased when the reaction was run with $Ni(cod)_2$ in THF, albeit with no enantioinduction. Surprisingly, lowering the concentration from 0.375 M to 0.15 M delivered ketone **18f** in 25% ee (Scheme 3.4). The origin of this concentration-dependent enantioselectivity remains unclear, although a similar concentration effect was also observed for the coupling of phenylacetyl chloride

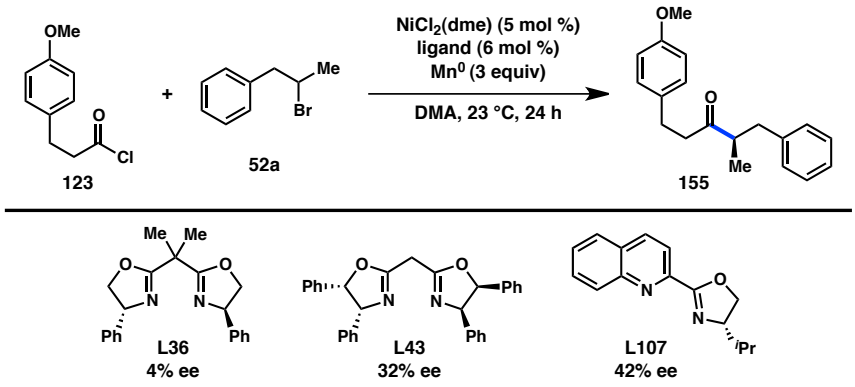
(**153**). Evaluation of other chiral ligands for the couplings of acid chlorides **117** or **153** failed to provide higher levels of enantioinduction

Scheme 3.4. *Expansion of acid chloride substrate scope.*



We questioned whether homobenzylic halides might also undergo an enantioselective reductive cross-coupling. Treatment of acid chloride **123** and bromide **52a** with $NiCl_2$(dme) and **L36** furnished product **155** in 4% ee, demonstrating the critical role that the aryl group plays in our standard cross-coupling (Figure 3.8). A screen of different chiral ligand scaffolds revealed that ketone **155** could be generated in up to 42% ee, highlighting the β-aryl substituent's decreased ability to behave as a directing group in the cross-coupling when compared to an α-aryl substituent.

Figure 3.8. *Reductive cross-coupling of a homobenzylic halide.*



3.3 CONCLUDING REMARKS

In conclusion, the first Ni-catalyzed asymmetric reductive acyl cross-coupling reaction has been developed. This mild, chemoselective reaction provides access to a variety of α-aryl-α-alkyl ketones in good yields and high enantioselectivity. The reaction is highly convergent and functional group-tolerant, which enables the rapid construction of complex ketones from bench stable and easy-to-handle starting 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.

3.4 EXPERIMENTAL SECTION

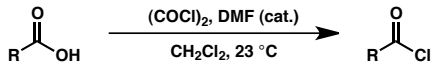
3.4.1 Materials and Methods

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.[30] 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).

3.4.2 Substrate Synthesis

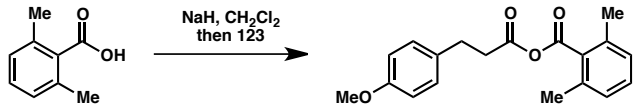
General Procedure 1: Acid Chloride Synthesis



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

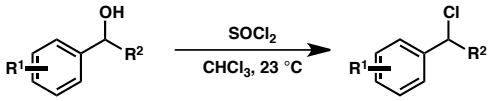
was stirred at 23 °C for 3 h and then concentrated. The crude acid chloride was used without any further purification.

3-(4-methoxyphenyl)Propanoic 2,6-dimethylbenzoic anhydride (149)



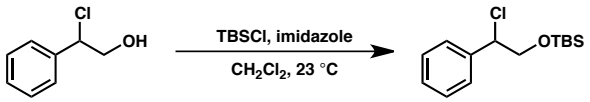
A flame-dried flask was charged with 2,6-dimethylbenzoic acid (1.0 mmol, 1 equiv) and CH_2Cl_2 (0.33 M). To the solution was added NaH (60% dispersion in oil, 1.05 mmol, 1.05 equiv) and the reaction was allowed to stir for 3 h. 3-(4-methoxyphenyl)propanoyl chloride (**123**, 1.0 mmol, 1 equiv) was added dropwise to the reaction mixture and the reaction was stirred overnight. The crude mixture was filtered through a small plug of celite and concentrated to afford 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



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 by 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 (150m).



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.

3.4.3 Enantioselective Reductive Cross-Coupling

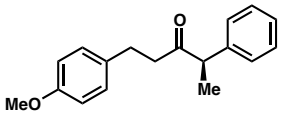
General Procedure 3 (Table 3.5)

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), 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, 0.375 M) followed by benzyl chloride (**26**, 0.2 mmol, 1 equiv), acid chloride (**123**, 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 X 10 mL) and the combined organic layers were washed with brine (1 X 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*)-**L36** (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, 0.375 M) followed by benzyl chloride (**150**, 0.2 mmol, 1 equiv) and acid chloride (**123**, Table 3.6: 0.3 mmol, 1.5 equiv; **151**, Figure 3.7: 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 X 10 mL) and the combined organic layers were washed with brine (1 X 15 mL) and dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by flash chromatography.

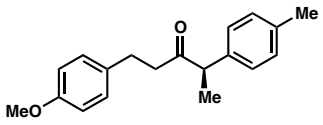
(*R*)-1-(4-methoxyphenyl)-4-Phenylpentan-3-one (148a)



Prepared from (1-chloroethyl)benzene (**150a**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**123**, 0.30 mmol) according to General Procedure 4. The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **148a** (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.

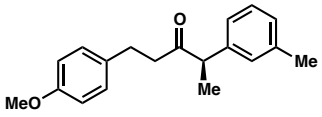
$[\alpha]_D^{25} = -102.3°$ (c = 1.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.21 (m, 3H), 7.22 – 7.14 (m, 2H), 7.05 – 6.96 (m, 2H), 6.84 – 6.75 (m, 2H), 3.79 (s, 3H), 3.72 (q, *J* = 7.0 Hz, 1H), 2.88 – 2.57 (m, 4H), 1.39 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.0, 157.8, 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-(*p*-tolyl)Pentan-3-one (148b)



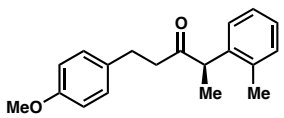
Prepared from 1-(1-chloroethyl)-4-methylbenzene (**150b**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**123**, 0.30 mmol) according to General Procedure 4 except using 33 mol % (*R*,*R*)-**L36** (0.066 mmol). The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **148b** (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-methoxyphenyl)-4-(*m*-tolyl)Pentan-3-one (148c)



Prepared from 1-(1-chloroethyl)-3-methylbenzene (**150c**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**123**, 0.30 mmol) according to General Procedure 4 except using 33 mol % (*R*,*R*)-**L36** (0.066 mmol). The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **148c** (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.

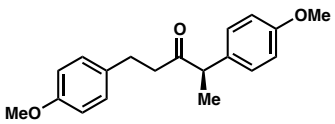
(*R*)-1-(4-methoxyphenyl)-4-(*o*-tolyl)Pentan-3-one (148d)



Prepared from 1-(1-chloroethyl)-2-methylbenzene (**150d**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**123**, 0.30 mmol) according to General Procedure 4 except using 33 mol % (*R*,*R*)-**L36** (0.066 mmol). The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **148d** (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.

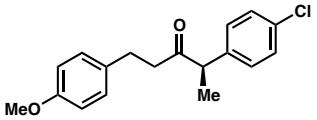
(*R*)-1,4-bis(4-methoxyphenyl)Pentan-3-one (148e)



Prepared from 1-(1-chloroethyl)-4-methoxybenzene (**150e**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**123**, 0.30 mmol) according to General Procedure 4 except using 33 mol % (*R*,*R*)-**L36** (0.066 mmol). The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **148e** (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,

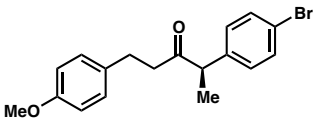
1463, 1301, 1246, 1177, 1034, 827 cm^{-1}; HRMS (MM) calc'd for M^+ 298.1563, found 298.1622.

(*R*)-4-(4-chlorophenyl)-1-(4-methoxyphenyl)Pentan-3-one (148f)



Prepared from 1-chloro-4-(1-chloroethyl)benzene (**150f**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**123**, 0.30 mmol) according to General Procedure 4. The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **148f** (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, $CHCl_3$); ^1H 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.

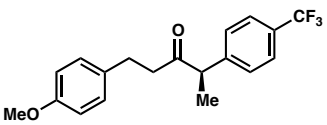
(*R*)-4-(4-bromophenyl)-1-(4-methoxyphenyl)Pentan-3-one (148g)



Prepared from 1-bromo-4-(1-chloroethyl)benzene (**150g**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**123**, 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 **148g** (51.0 mg, 73% yield) in 86% ee as a clear oil. The

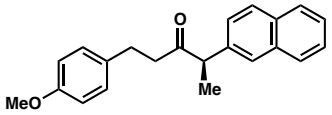
enantiomeric excess was determined by chiral SFC analysis (OD-H, 2.5 mL/min, 5% IPA in CO_2, λ = 210 nm): t_R (minor) = 25.4 min, t_R (major) = 27.0 min. $[\alpha]_D^{25} = -53.5°$ (c = 1.44, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, J = 8.6 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 8.6 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-(4-(trifluoromethyl)phenyl)Pentan-3-one (148h)



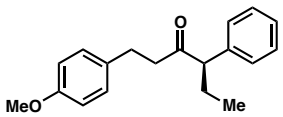
Prepared from 1-(1-chloroethyl)-4-(trifluoromethyl)benzene (**148h**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**123**, 0.30 mmol) according to General Procedure 4 except using 20% v/v DMA/THF. The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **148h** (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, $CHCl_3$); ^{1}H 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*)-1-(4-methoxyphenyl)-4-(naphthalen-2-yl)Pentan-3-one (148i)



Prepared from 2-(1-chloroethyl)naphthalene (**150i**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**123**, 0.30 mmol) according to General Procedure 4 except using 33 mol % (*R*,*R*)-**L36** (0.066 mmol). The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **148i** (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.

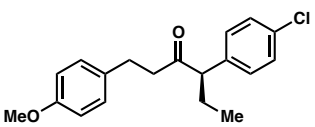
(*R*)-1-(4-methoxyphenyl)-4-Phenylhexan-3-one (148j)



Prepared from (1-chloropropyl)benzene (**150j**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**123**, 0.30 mmol) according to General Procedure 4. The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **148j** (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.

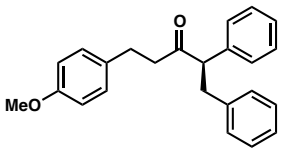
$[\alpha]_D^{25} = -97.9°$ (c = 0.96, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.20 (m, 3H), 7.19 – 7.12 (m, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 3.76 (s, 3H), 3.48 (t, *J* = 7.4 Hz, 1H), 2.84 – 2.56 (m, 4H), 2.11 – 1.99 (m, 1H), 1.77 – 1.64 (m, 1H), 0.80 (t, *J* = 7.4 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*)-4-(4-chlorophenyl)-1-(4-methoxyphenyl)Hexan-3-one (148k)



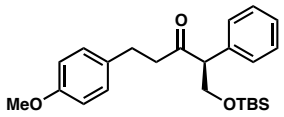
Prepared from 1-chloro-4-(1-chloropropyl)benzene (**150k**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**123**, 0.30 mmol) according to General Procedure 4. The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **148k** (41.2 mg, 65% yield) in 91% 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*)-5-(4-methoxyphenyl)-1,2-Diphenylpentan-3-one (148l)



Prepared from (1-chloroethane-1,2-diyl)dibenzene (**150l**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**123**, 0.30 mmol) according to General Procedure 4. The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **148l** (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.

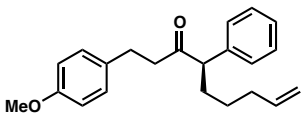
(*S*)-1-((*tert*-butyldimethylsilyl)oxy)-5-(4-methoxyphenyl)-2-Phenylpentan-3-one (148m)



Prepared from [1-chloro-2-(*t*-butyldimethylsiloxy)ethyl]benzene (**150m**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**123**, 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 **148m** (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, $CHCl_3$); ^1H 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.

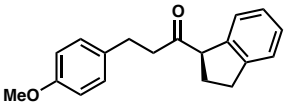
(*R*)-1-(4-methoxyphenyl)-4-Phenylnon-8-en-3-one (148n)



Prepared from (1-chlorohex-5-en-1-yl)benzene (**150n**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**123**, 0.30 mmol) according to General Procedure 4. The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **148n** (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, $CHCl_3$); ^1H 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,

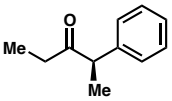
1611, 1583, 1513, 1453, 1300, 1247, 1177, 1036, 824 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 323.2006, found 323.1945.

(*R*)-1-(2,3-dihydro-1*H*-inden-1-yl)-3-(4-methoxyphenyl)Propan-1-one (148o)



Prepared from 1-chloro-2,3-dihydro-1*H*-indene (**150o**, 0.20 mmol) and 3-(4-methoxyphenyl)propanoyl chloride (**123**, 0.30 mmol) according to General Procedure 4. The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **148o** (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, $CHCl_3$); ^1H 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 (152a)

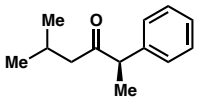


Prepared from (1-chloroethyl)benzene (**26**, 0.20 mmol) and propionyl chloride (**151a**, 0.24 mmol) according to General Procedure 4 except using 20% v/v DMA/THF. The crude residue was purified by silica gel chromatography (2% ethyl acetate/hexanes) to yield **152a** (19.5 mg, 60% yield) in 91% ee 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*)-**L36** 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)[26] and $[\alpha]_D^{21} = -47.2$ (c = 1.00, $CHCl_3$; 73% ee).[5e] Based on the literature precedent, we assign our product as the *R* enantiomer.

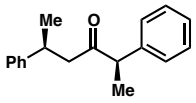
(*R*)-5-Methyl-2-phenylhexan-3-one (152b)



Prepared from (1-chloroethyl)benzene (**26**, 0.20 mmol) and isovaleroyl chloride (**151b**, 0.24 mmol) according to General Procedure 4. The crude residue was purified by silica gel chromatography (2% ethyl acetate/hexanes) to yield **152b** (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

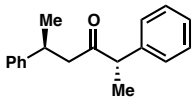
= 6.9 Hz, 1H), 2.29 – 2.16 (m, 2H), 2.10 (hept, J = 6.7 Hz, 1H), 1.38 (d, J = 7.0 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H), 0.75 (d, J = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.5, 140.5, 128.8, 127.9, 127.0, 53.3, 50.0, 24.3, 22.6, 22.2, 17.4; FTIR (NaCl, thin film): 3027, 2957, 2871, 1712, 1600, 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*)-152c)



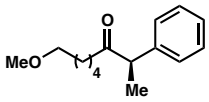
Prepared from (1-chloroethyl)benzene (**26**, 0.20 mmol) and (*S*)-3-phenylbutyryl chloride ((*S*)-**151c**, 0.24 mmol) according to General Procedure 4. The crude residue was purified by silica gel chromatography (2% ethyl acetate/hexanes) to yield (*R*,*S*)-**152c** (34.8 mg, 69% yield) as a clear 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, $CHCl_3$); ^{1}H 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*)-152c)



Prepared from (1-chloroethyl)benzene (**26**, 0.20 mmol) and (*S*)-3-phenylbutyryl chloride ((*S*)-**151c**, 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*)-**152c** (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.

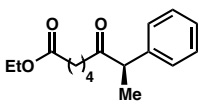
(*R*)-8-Methoxy-2-phenyloctan-3-one (152d)



Prepared from (1-chloroethyl)benzene (**26**, 0.20 mmol) and 6-methoxyhexanoyl chloride (**151d**, 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 **152d** (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, $CHCl_3$); ^{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), 3.74 (q, J = 7.0 Hz, 1H), 3.31 – 3.25 (m,

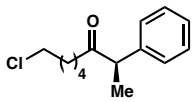
5H), 2.38 – 2.32 (m, 2H), 1.57 – 1.42 (m, 2H), 1.38 (d, J = 7.0 Hz, 3H), 1.26 – 1.17 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.9, 140.7, 128.9, 127.9, 127.1, 72.5, 58.5, 53.0, 40.9, 29.3, 25.6, 23.6, 17.4; FTIR (NaCl, thin film): 2931, 2866, 2360, 1714, 1600, 1494, 1453, 1373, 1119, 1072, 1029, 761 cm^{-1}; LRMS (ESI) calc'd for $[M+H]^+$ 235.2, found 235.2.

(*R*)-Ethyl 6-oxo-7-phenyloctanoate (152e)



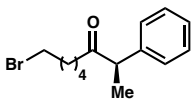
Prepared from (1-chloroethyl)benzene (**26**, 0.20 mmol) and ethyl 6-chloro-6-oxohexanoate (**151e**, 0.24 mmol) according to General Procedure 4 except using 10% v/v DMA/THF. The crude residue was purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield **152e** (33.8 mg, 64% yield) 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-Chloro-2-phenyloctan-3-one (152f)



Prepared from (1-chloroethyl)benzene (**26**, 0.20 mmol) and 6-chlorohexanoyl chloride (**151f**, 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 **152f** (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.

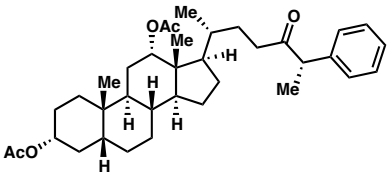
(*R*)-8-Bromo-2-phenyloctan-3-one (152g)



Prepared from (1-chloroethyl)benzene (**26**, 0.20 mmol) and 6-bromohexanoyl chloride (**151g**, 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 **152g** (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, $CHCl_3$); ^{1}H 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.

(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 (152h)

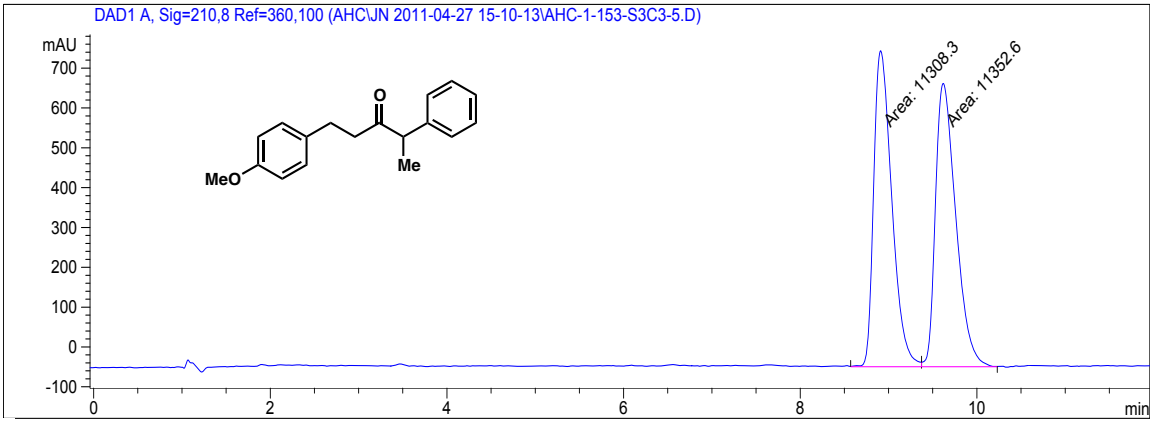


Prepared from (1-chloroethyl)benzene (**26**, 0.20 mmol) and acid chloride **151h** (0.24 mmol) according to General Procedure 4 except using 10% v/v DMA/THF and (*S*,*S*)-**L36.** Following extraction, the combined organic layers were washed with sat. aq. $NaHCO_3$ (1 X 10 mL) and brine (1 X 15 mL). The crude residue was purified by silica gel chromatography (15% ethyl acetate/hexanes) to yield **152h** (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, $CHCl_3$); ^{1}H 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.

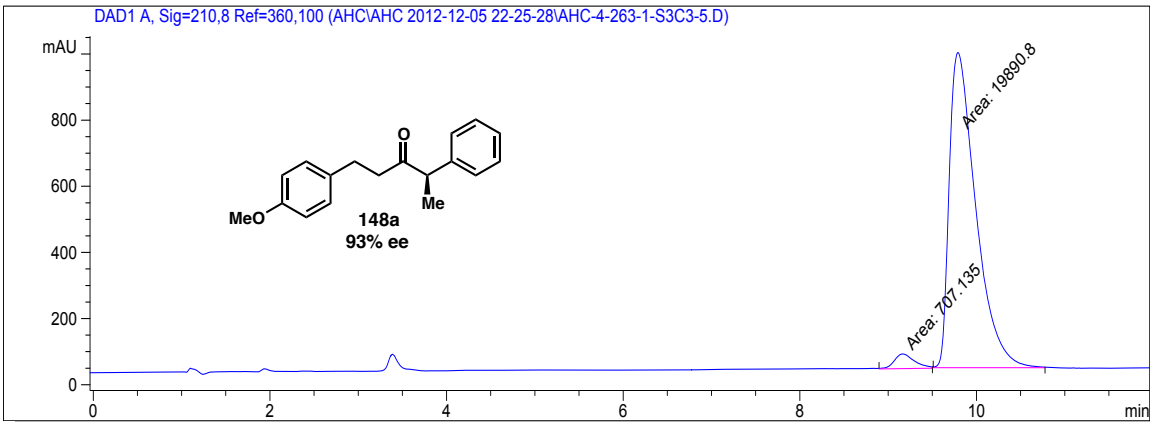
3.4.4 SFC Traces of Racemic and Enantioenriched Ketone Products

148a (Table 3.6, entry 1): racemic



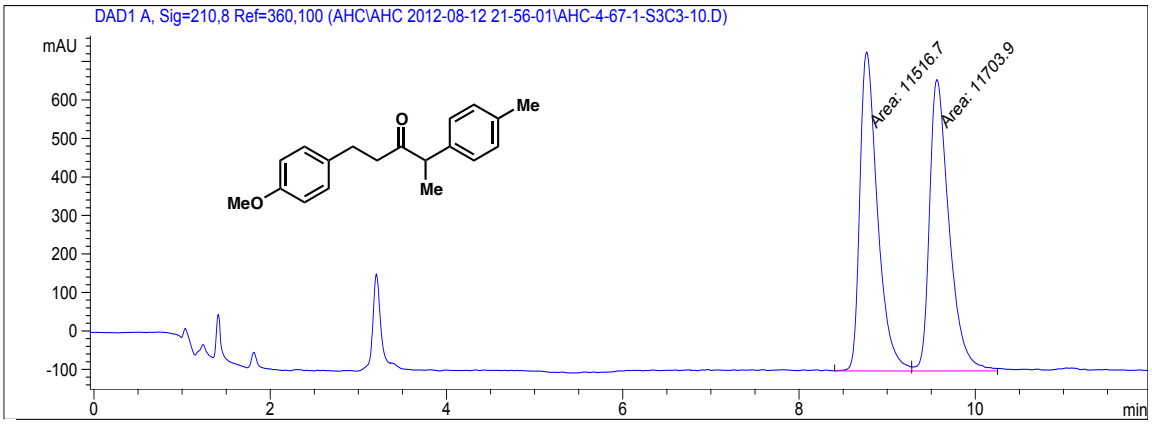
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.911	MM	0.2376	1.13083e4	793.28162	49.9021
2	9.619	MM	0.2660	1.13526e4	711.29791	50.0979

148a (Table 3.6, entry 1): enantioenriched, 93% ee



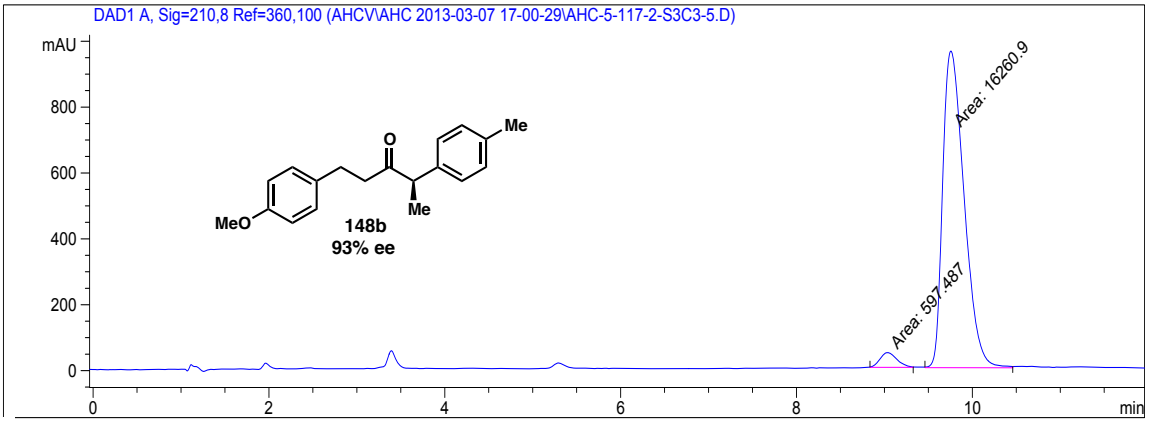
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.164	MM	0.2646	707.13519	44.53406	3.4330
2	9.790	MM	0.3479	1.98908e4	952.85913	96.5670

148b (Table 3.6, entry 2): racemic



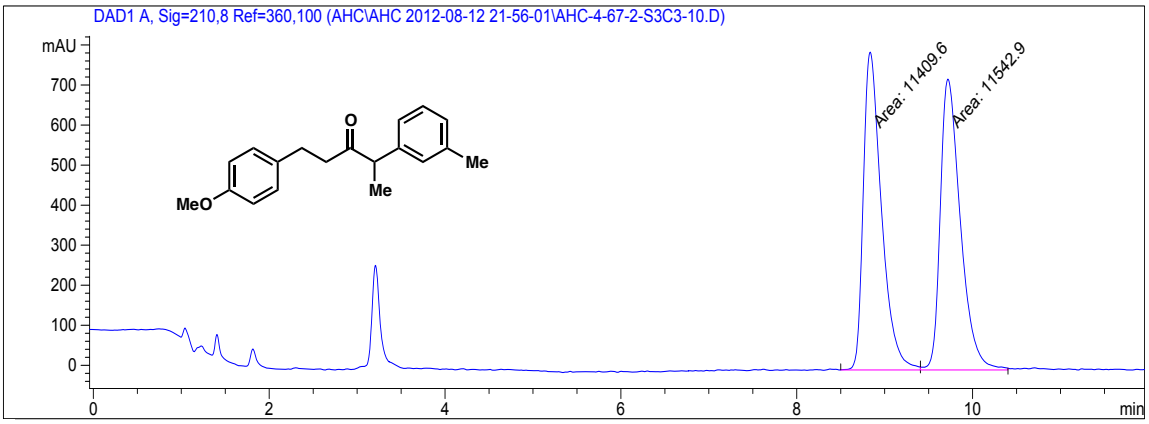
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.766	MM	0.2315	1.15167e4	829.08398	49.5970
2	9.564	MM	0.2576	1.17039e4	757.13312	50.4030

148b (Table 3.6, entry 2): enantioenriched, 93% ee



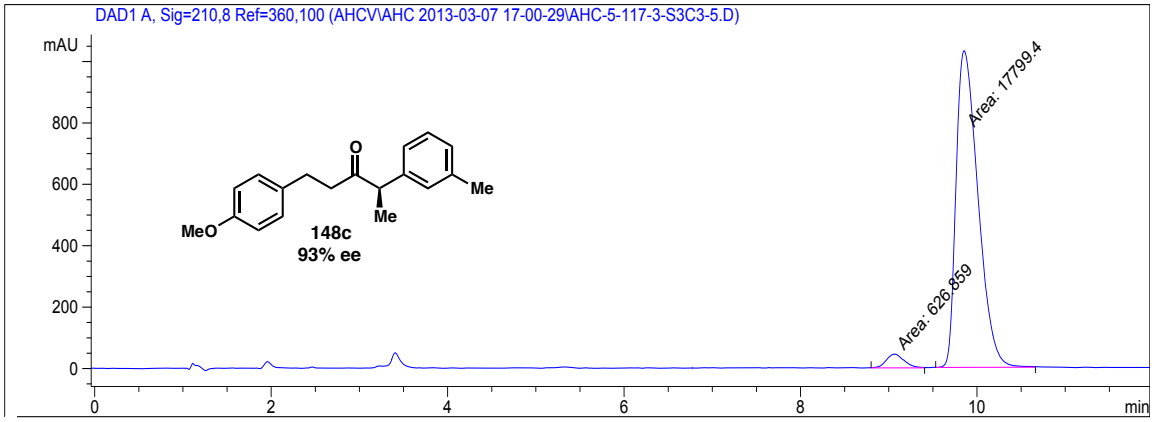
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.036	MM	0.2206	597.48749	45.14814	3.5442
2	9.756	MM	0.2819	1.62609e4	961.42609	96.4558

148c (Table 3.6, entry 3): racemic



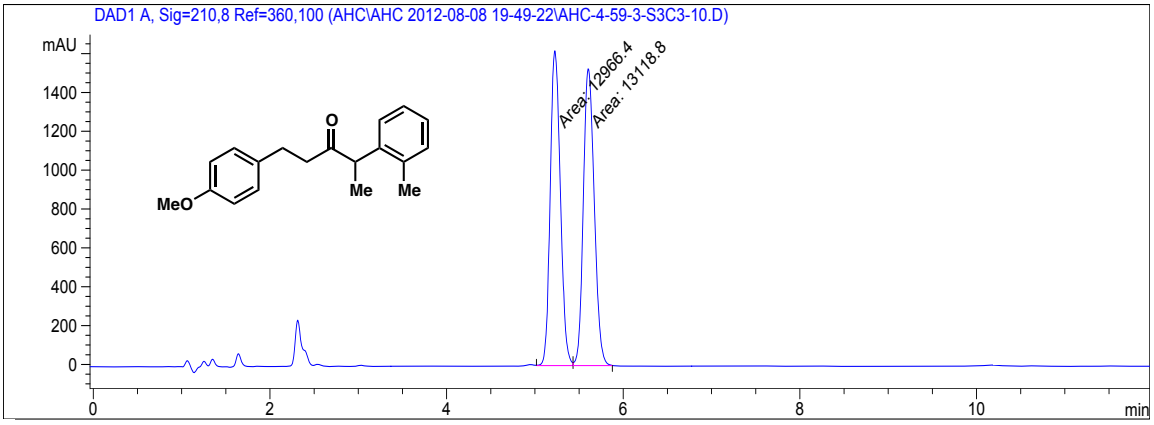
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.835	MM	0.2395	1.14096e4	794.09918	49.7095
2	9.720	MM	0.2647	1.15429e4	726.79602	50.2905

148c (Table 3.6, entry 3): enantioenriched, 93% ee



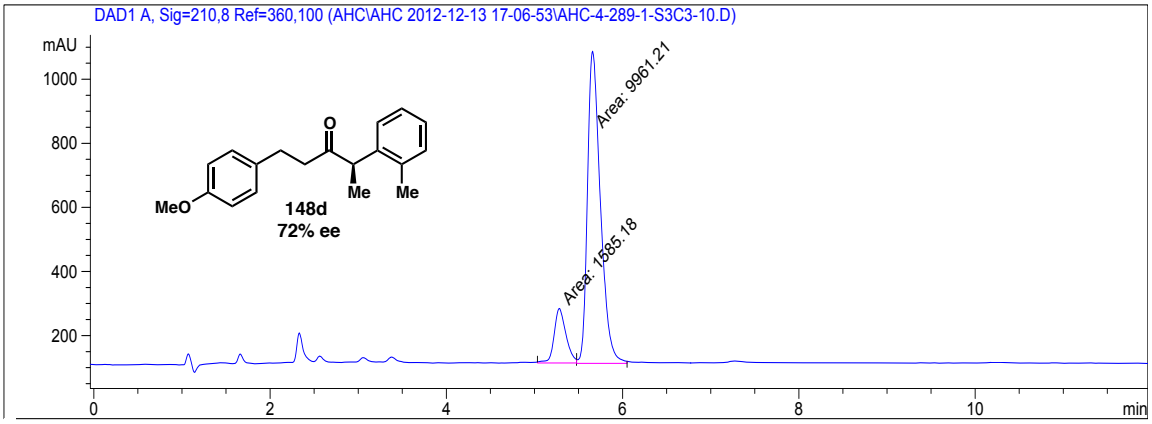
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.064	MM	0.2335	626.85852	44.73974	3.4020
2	9.854	MM	0.2876	1.77994e4	1031.51978	96.5980

148d (Table 3.6, entry 4): racemic



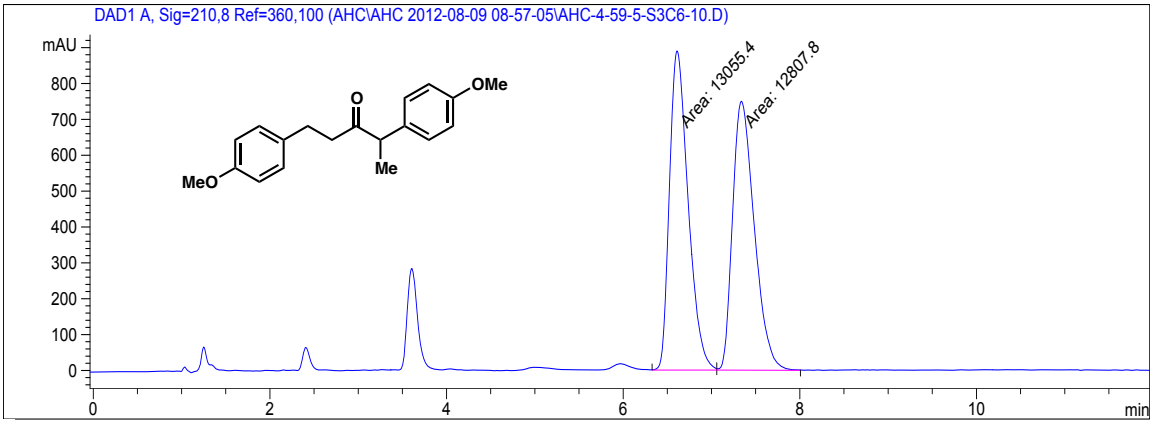
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.225	MM	0.1332	1.29664e4	1622.72693	49.7079
2	5.604	MM	0.1430	1.31188e4	1529.25037	50.2921

148d (Table 3.6, entry 4): enantioenriched, 72% ee



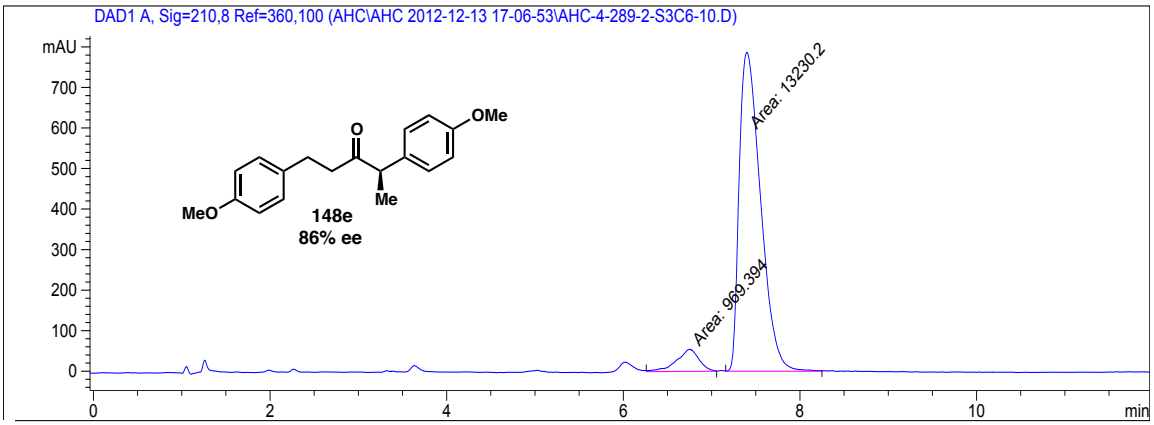
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.282	MM	0.1551	1585.18311	170.37230	13.7288
2	5.659	MM	0.1703	9961.21484	974.66937	86.2712

148e (Table 3.6, entry 5): racemic



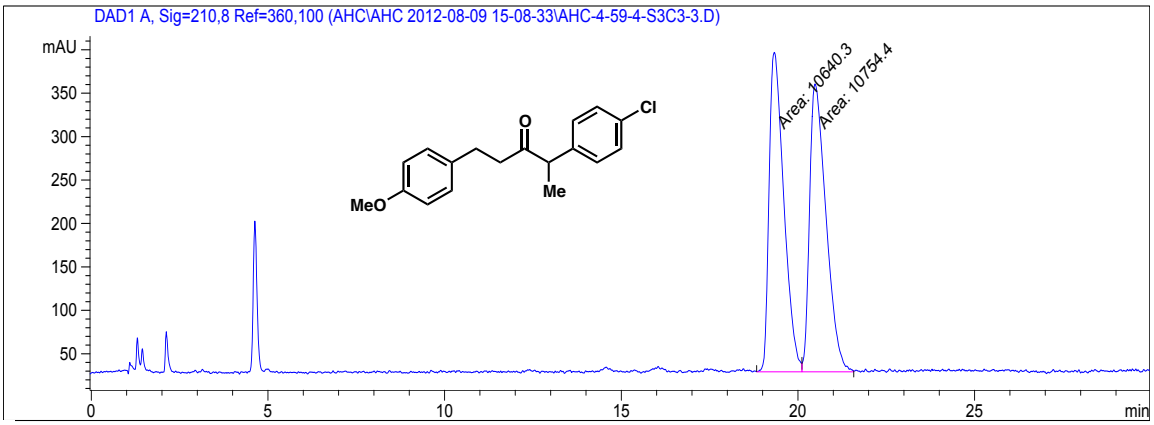
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.610	MM	0.2445	1.30554e4	889.75983	50.4785
2	7.339	MM	0.2848	1.28078e4	749.64392	49.5215

148e (Table 3.6, entry 5): enantioenriched, 86% ee



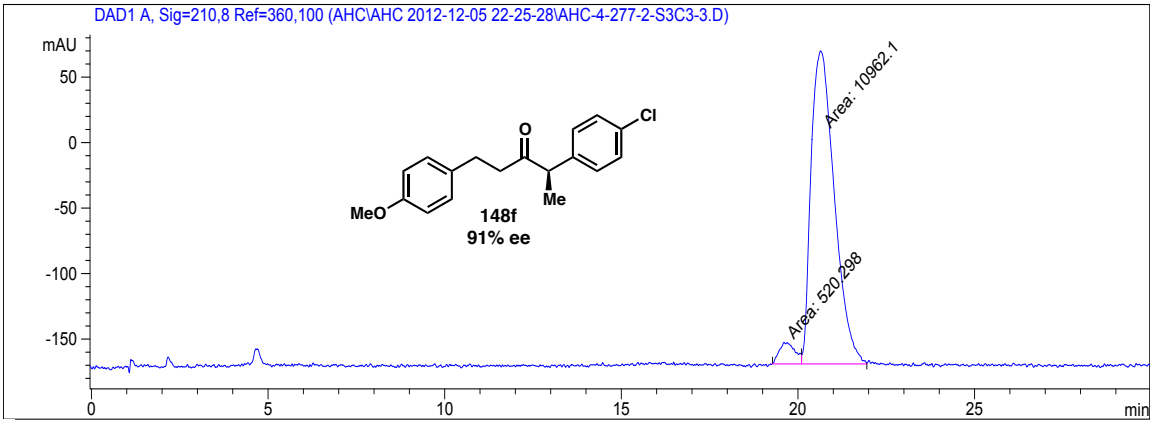
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.750	MM	0.2970	969.39368	54.40509	6.8269
2	7.399	MM	0.2801	1.32302e4	787.11755	93.1731

148f (Table 3.6, entry 6): racemic



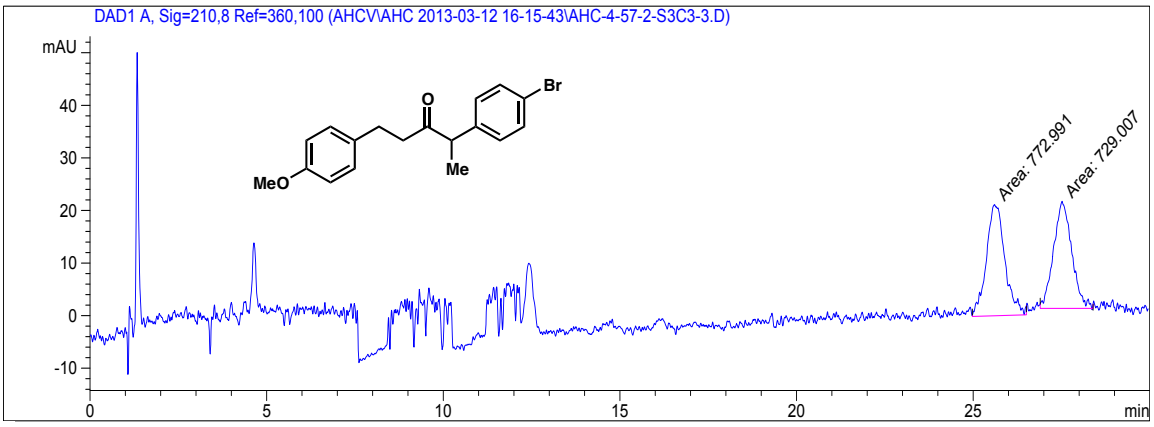
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.330	MM	0.4822	1.06403e4	367.73328	49.7335
2	20.480	MM	0.5409	1.07544e4	331.38272	50.2665

148f (Table 3.6, entry 6): enantioenriched, 91% ee



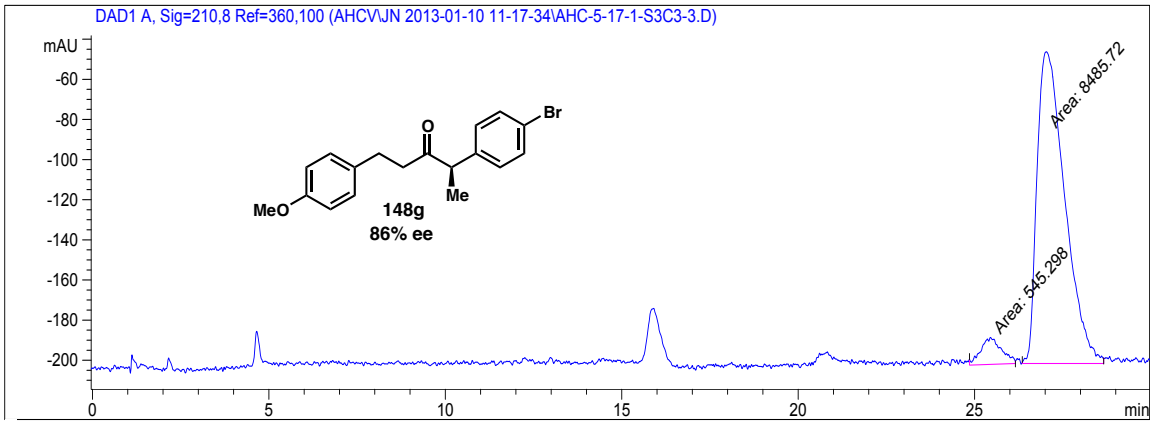
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.605	MM	0.5260	520.29840	16.48751	4.5313
2	20.639	MM	0.7645	1.09621e4	238.97188	95.4687

148g (Table 3.6, entry 7): racemic



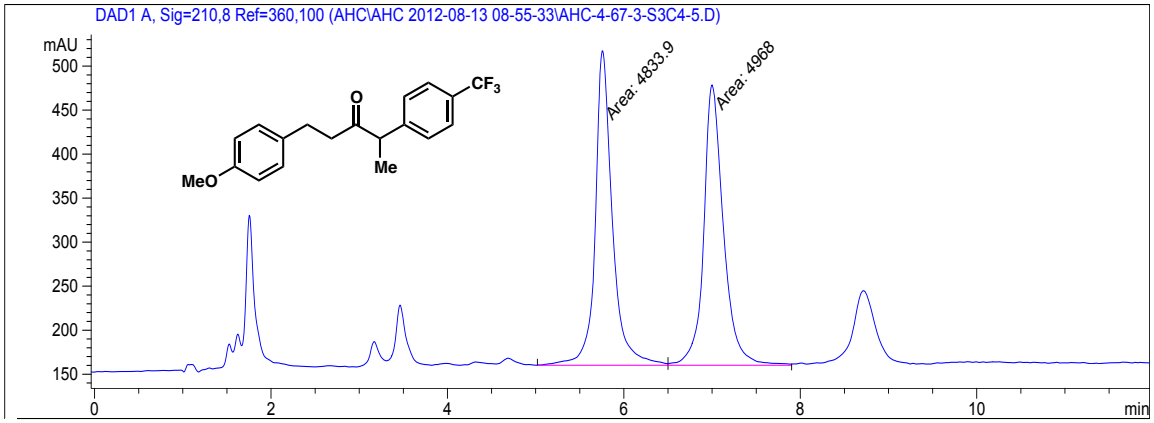
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.604	MM	0.6090	772.99146	21.15472	51.4642
2	27.518	MM	0.5962	729.00677	20.37799	48.5358

148g (Table 3.6, entry 7): enantioenriched, 86% ee



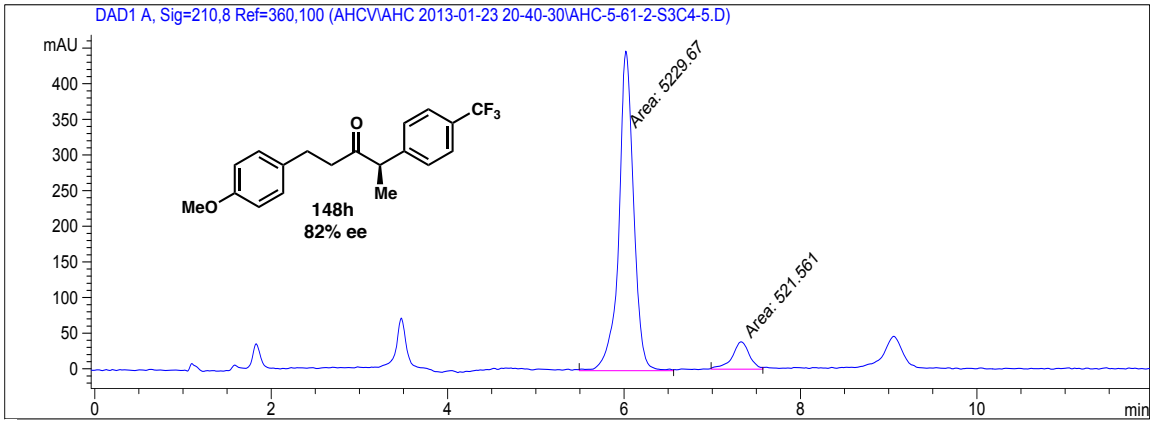
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.449	MM	0.6766	545.29791	13.43136	6.0381
2	27.030	MM	0.9105	8485.72363	155.33823	93.9619

148h (Table 3.6, entry 8): racemic



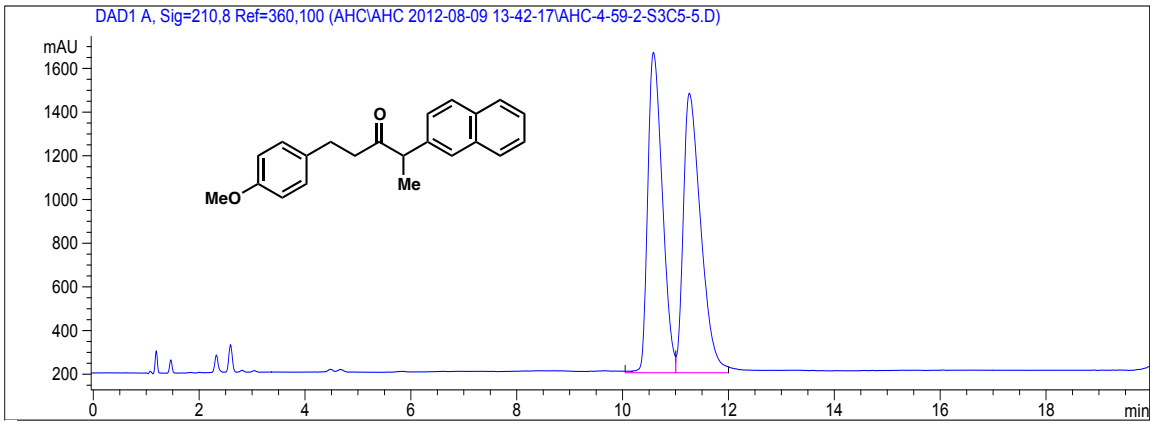
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.757	MM	0.2253	4833.89893	357.65167	49.3159
2	6.999	MM	0.2598	4967.99951	318.66217	50.6841

148h (Table 3.6, entry 8): enantioenriched, 82% ee



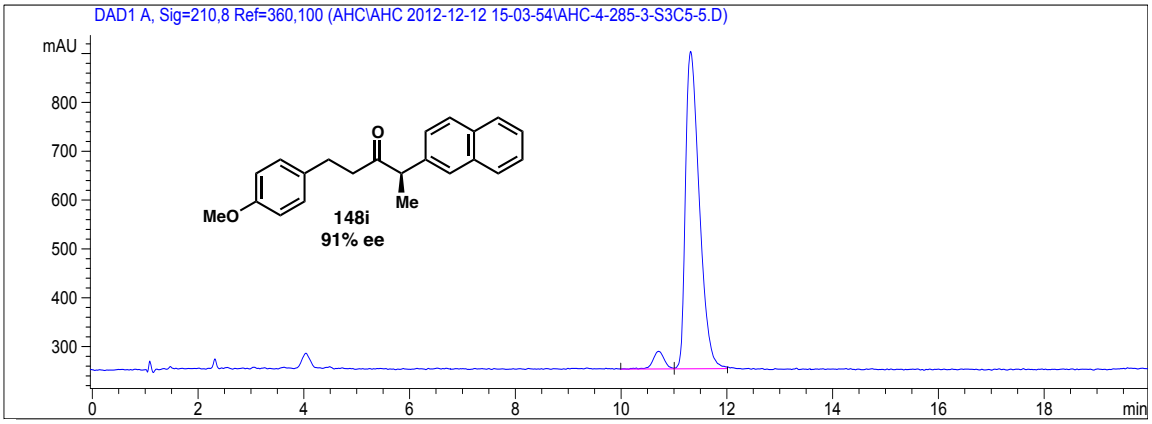
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.020	MM	0.1943	5229.66602	448.69507	90.9313
2	7.327	MM	0.2264	521.56061	38.39449	9.0687

148i (Table 3.6, entry 9): racemic



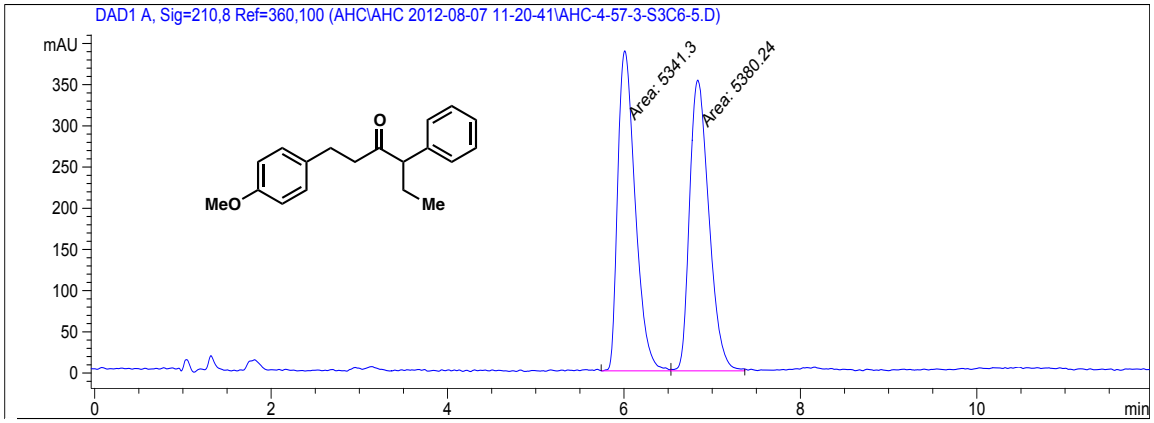
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.584	VV	0.3032	2.80499e4	1465.87903	48.9009
2	11.263	VBA	0.3473	2.93108e4	1279.38000	51.0991

148i (Table 3.6, entry 9): enantioenriched, 91% ee



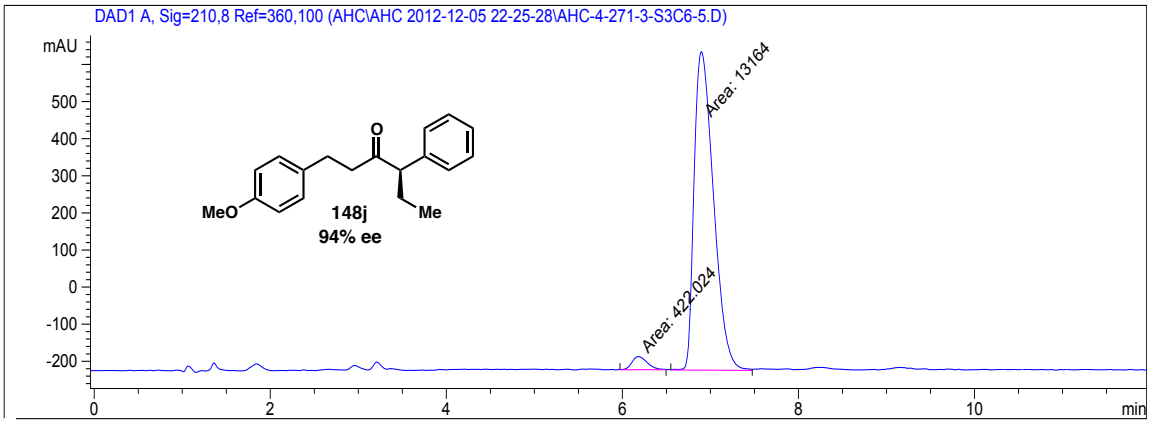
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.708	VV	0.2364	545.21796	36.05198	4.4227
2	11.316	VBA	0.2797	1.17825e4	649.47711	95.5773

148j (Table 3.6, entry 10): racemic



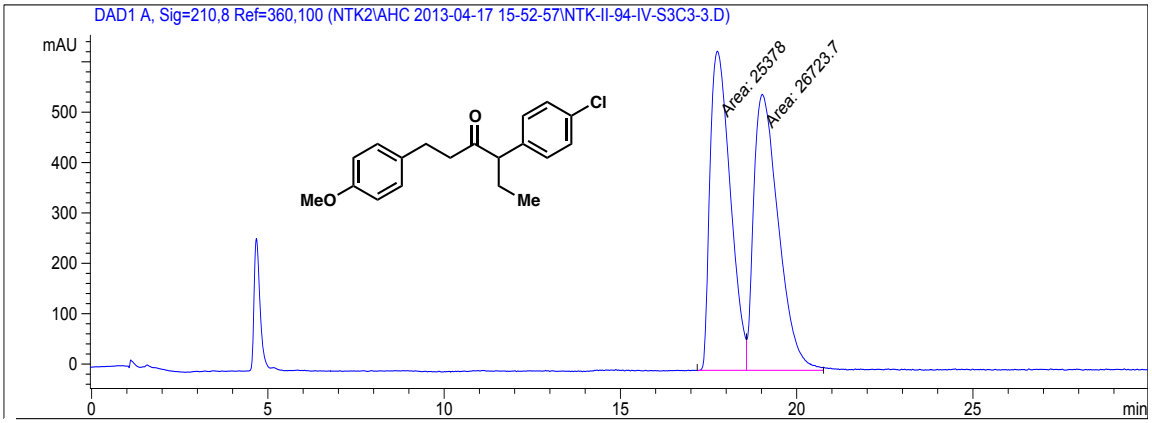
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.009	MM	0.2291	5341.29736	388.53415	49.8184
2	6.837	MM	0.2540	5380.24316	353.03430	50.1816

148j (Table 3.6, entry 10): enantioenriched, 94% ee



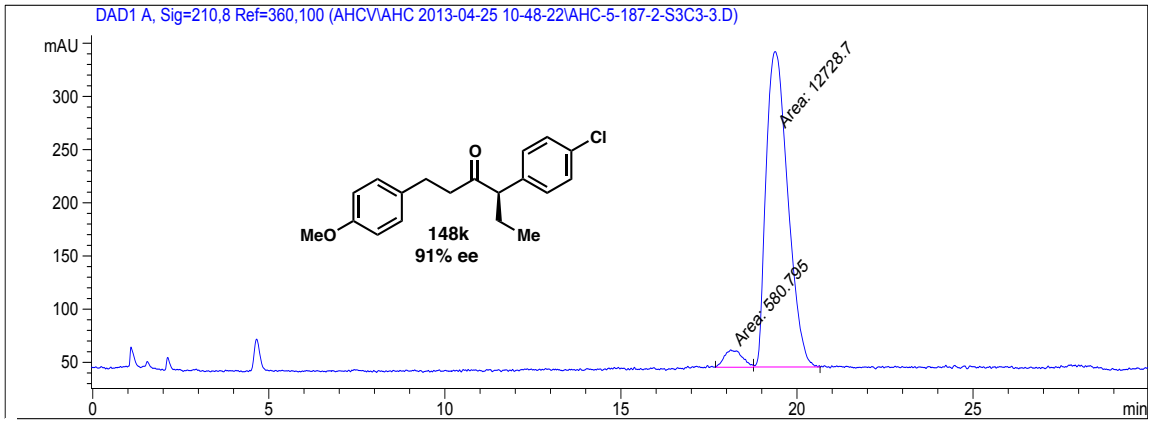
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.179	MM	0.1983	422.02435	35.47295	3.1063
2	6.898	MM	0.2556	1.31640e4	858.35632	96.8937

148k (Table 3.6, entry 11): racemic



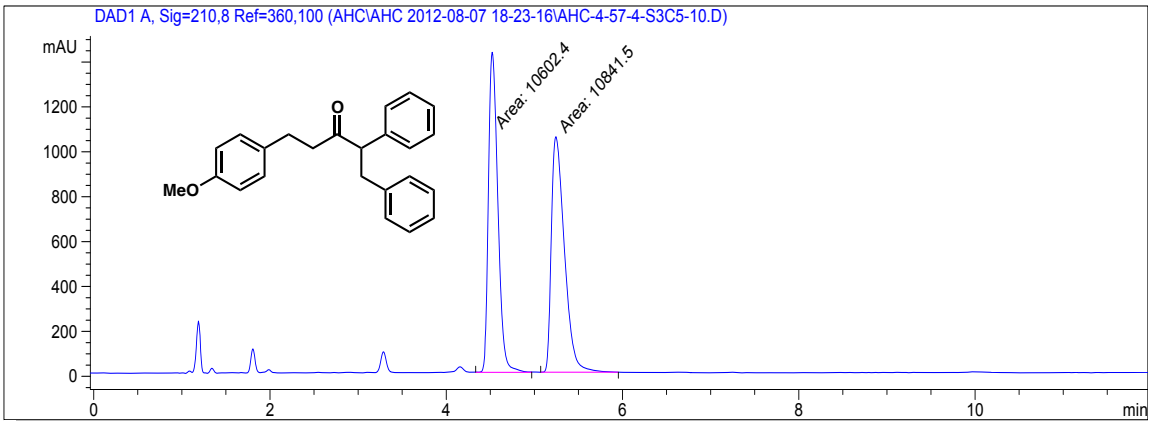
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.749	MM	0.6673	2.53780e4	633.81763	48.7086
2	19.022	MM	0.8126	2.67237e4	548.09839	51.2914

148k (Table 3.6, entry 11): enantioenriched, 91% ee



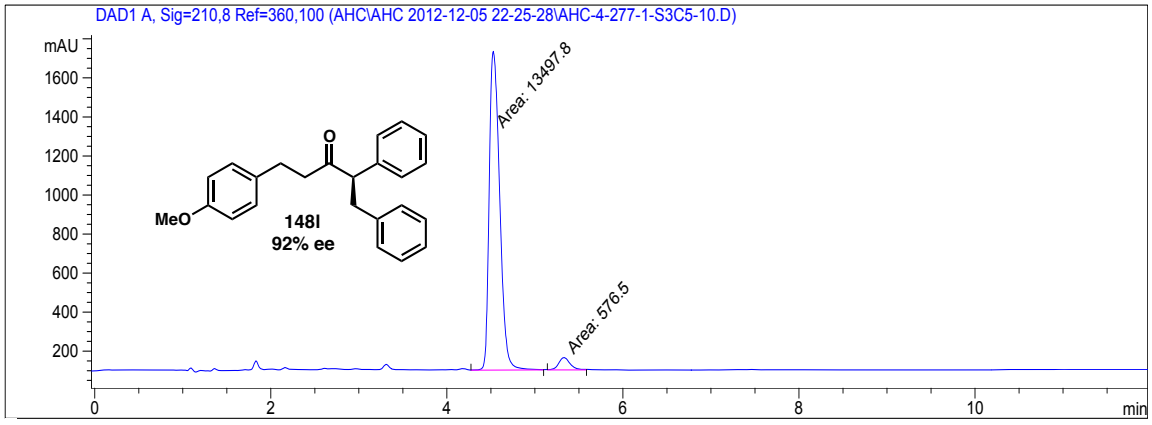
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.118	MM	0.5944	580.79498	16.28630	4.3637
2	19.381	MM	0.7154	1.27287e4	296.55020	95.6363

148l (Table 3.6, entry 12): racemic



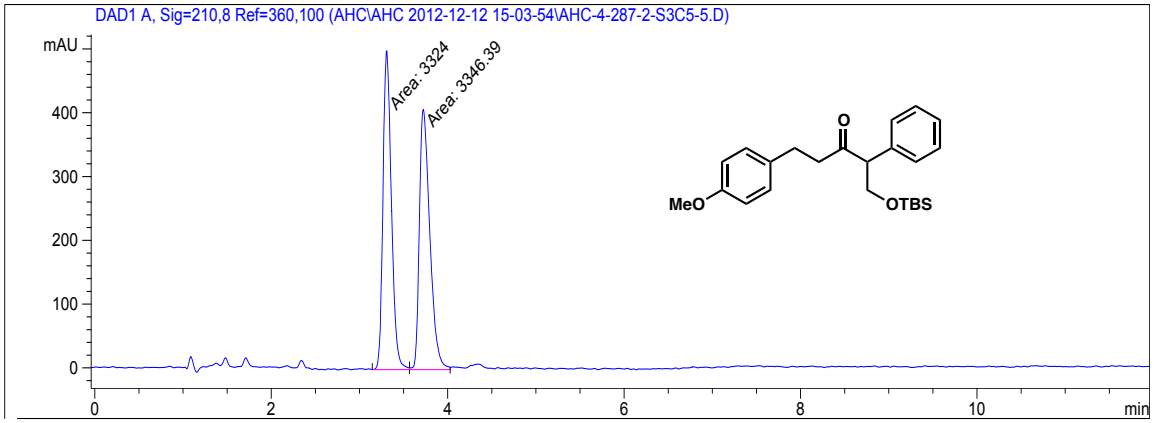
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.522	MM	0.1239	1.06024e4	1426.70251	49.4425
2	5.244	MM	0.1721	1.08415e4	1050.01685	50.5575

148l (Table 3.6, entry 12): enantioenriched, 92% ee



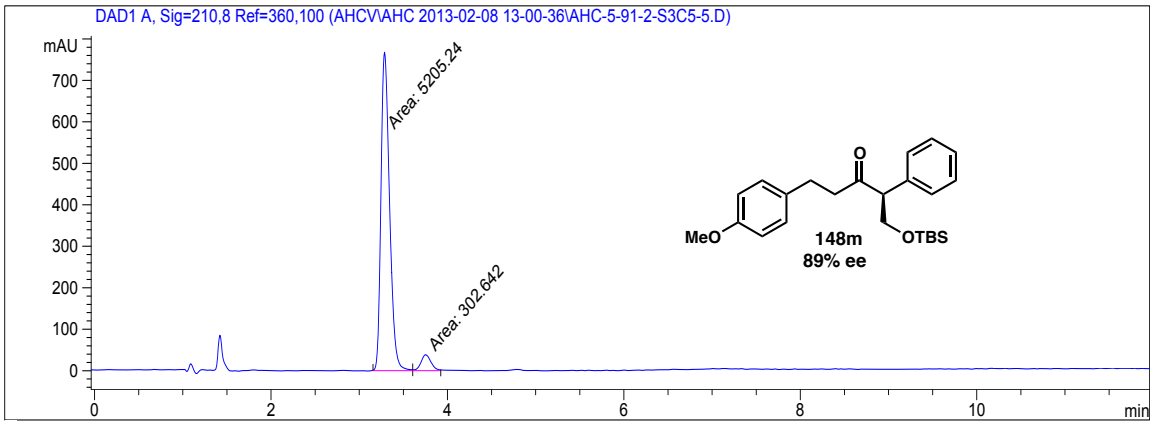
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.528	MM	0.1377	1.34978e4	1634.09204	95.9039
2	5.330	MM	0.1513	576.49988	63.49461	4.0961

148m (Table 3.6, entry 13): racemic



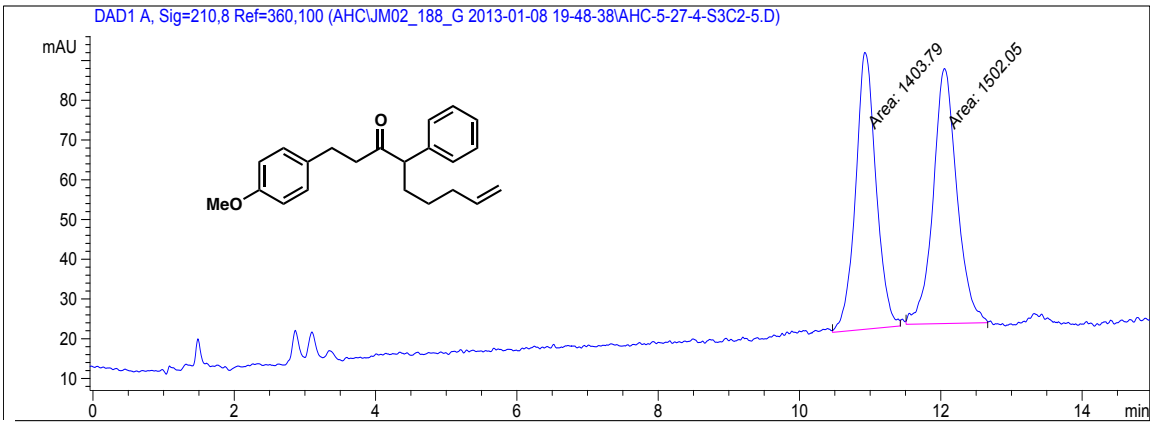
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.308	MM	0.1105	3324.00073	501.56870	49.8322
2	3.723	MM	0.1365	3346.39185	408.55920	50.1678

148m (Table 3.6, entry 13): enantioenriched, 89% ee



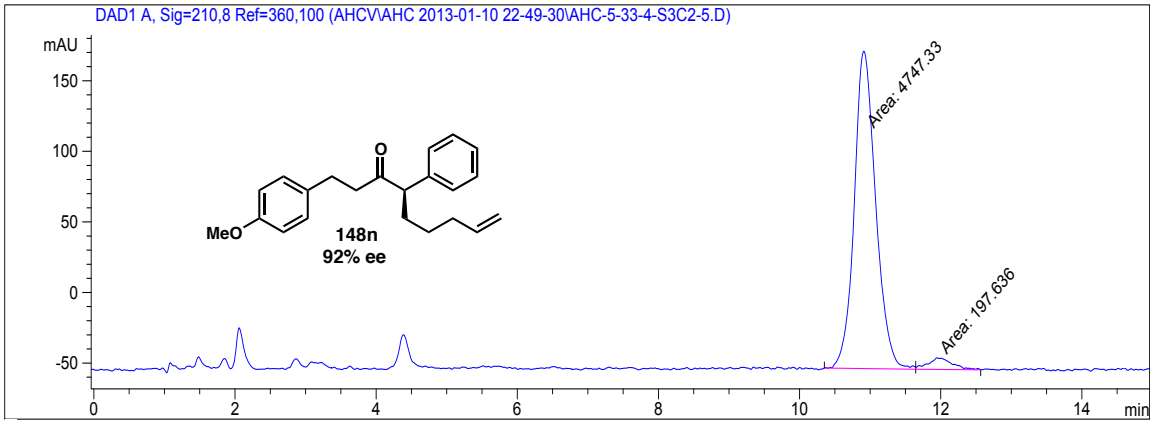
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.287	MM	0.1129	5205.23877	768.54687	94.5053
2	3.754	MM	0.1313	302.64224	38.40394	5.4947

148n (Table 3.6, entry 14): racemic



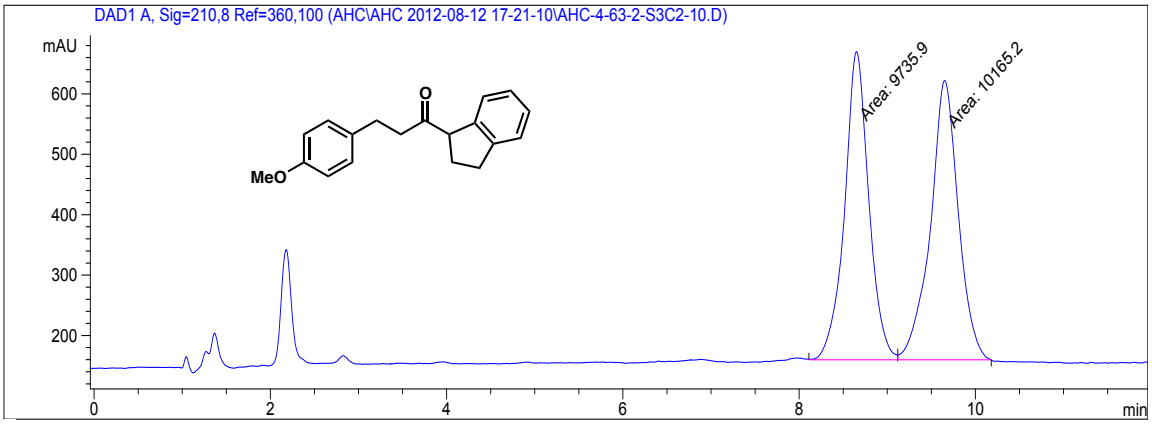
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.925	MM	0.3357	1403.79077	69.69751	48.3093
2	12.051	MM	0.3898	1502.04858	64.21613	51.6907

148n (Table 3.6, entry 14): enantioenriched, 92% ee



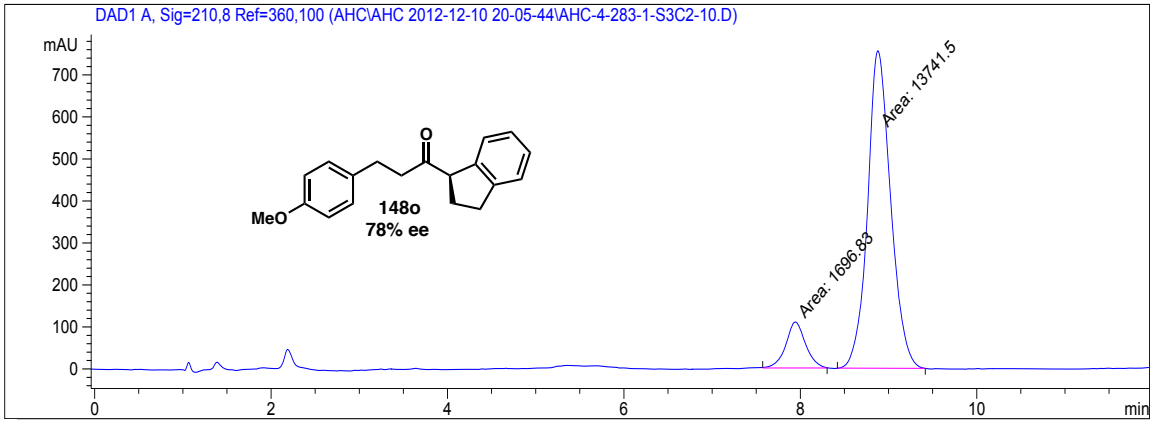
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.911	MM	0.3519	4747.33496	224.86562	96.0033
2	11.946	MM	0.4028	197.63620	8.17804	3.9967

148o (Table 3.6, entry 15): racemic



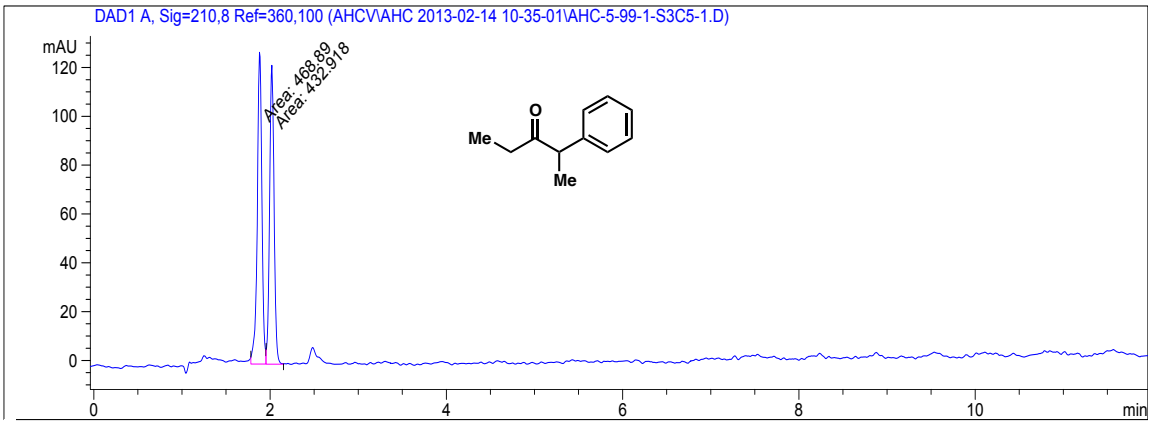
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.651	MM	0.3179	9735.89941	510.35568	48.9213
2	9.651	MM	0.3663	1.01652e4	462.52780	51.0787

148o (Table 3.6, entry 15): enantioenriched, 78% ee



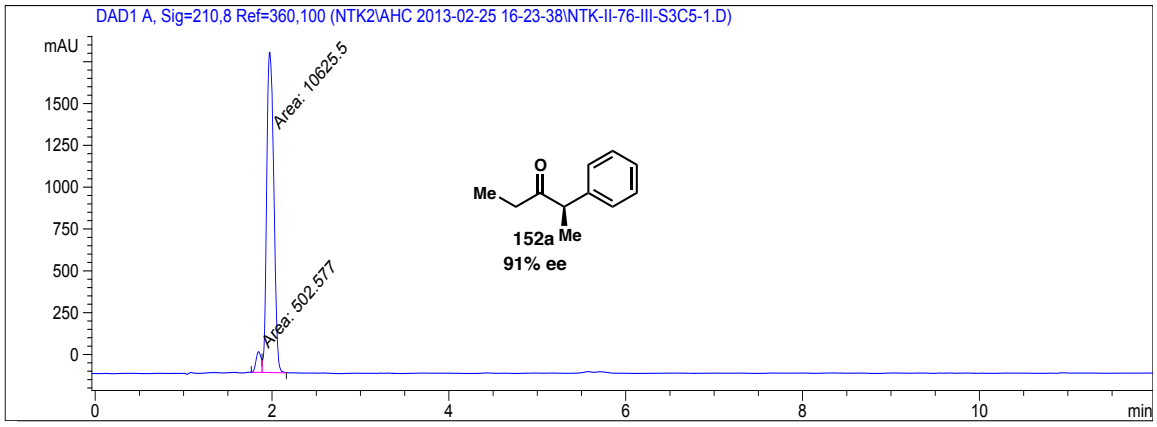
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.943	MM	0.2586	1696.82703	109.37256	10.9910
2	8.880	MM	0.3030	1.37415e4	755.81702	89.0090

152a (Table 3.7): racemic



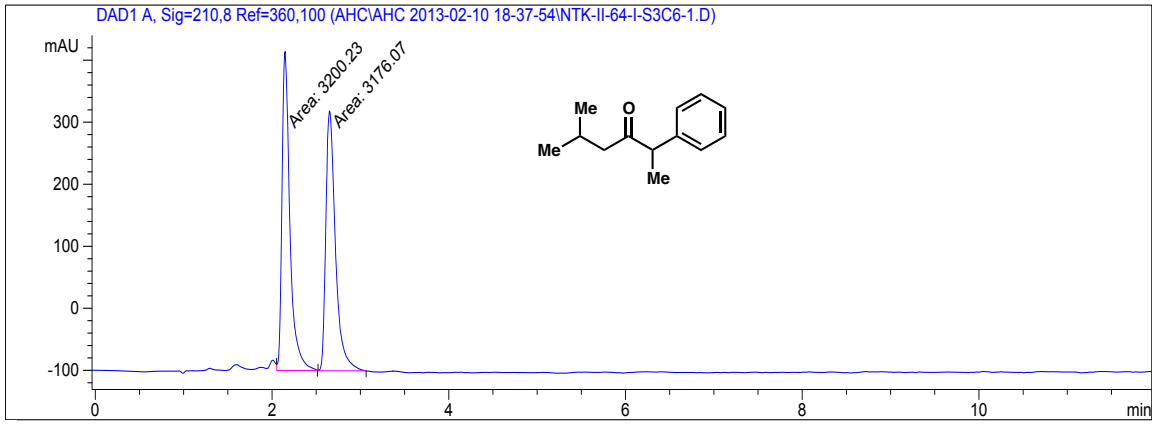
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.882	MM	0.0607	468.89008	128.69202	51.9944
2	2.020	MM	0.0587	432.91794	122.82136	48.0056

152a (Table 3.7): enantioenriched, 89% ee



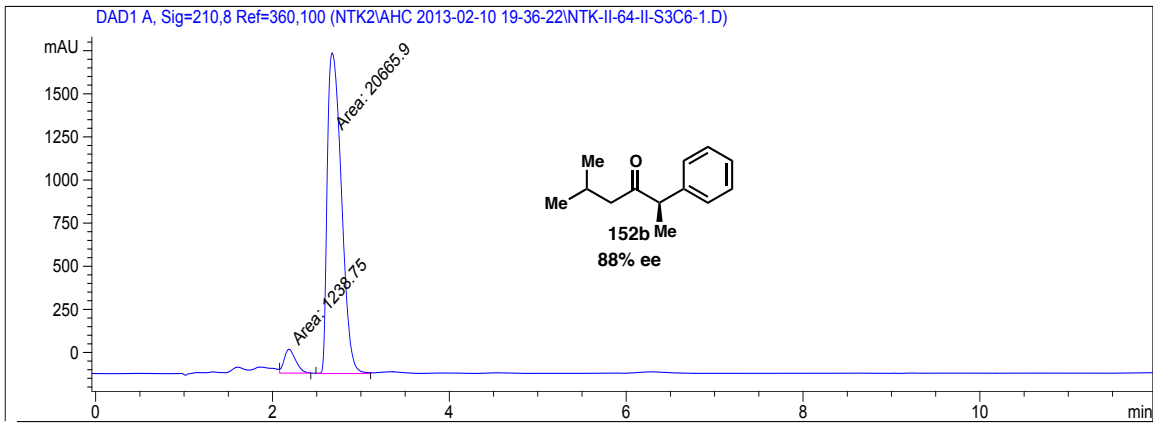
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.848	MM	0.0672	502.57666	124.59120	4.5163
2	1.973	MM	0.0923	1.06255e4	1918.92407	95.4837

152b (Table 3.7): racemic



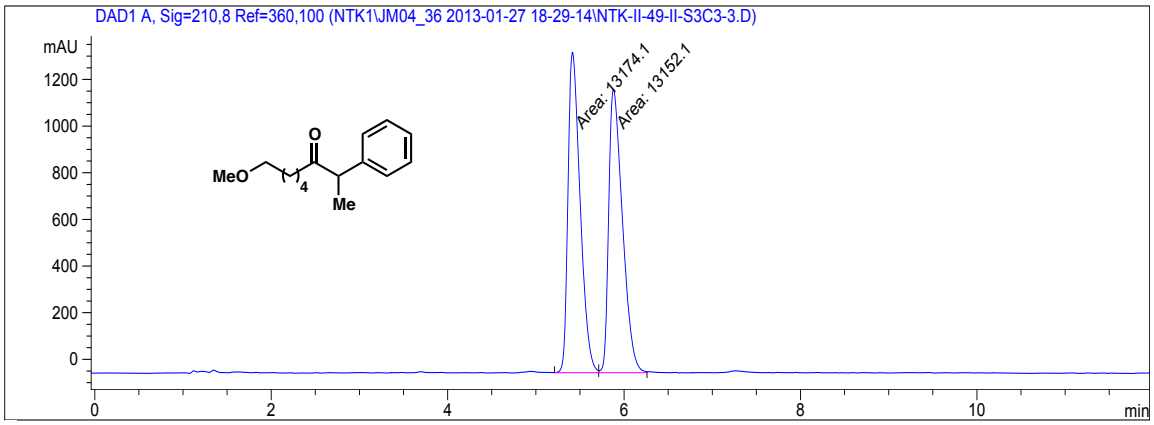
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.147	MM	0.1035	3200.22705	515.47467	50.1894
2	2.651	MM	0.1261	3176.07007	419.70117	49.8106

152b (Table 3.7): enantioenriched, 88% ee



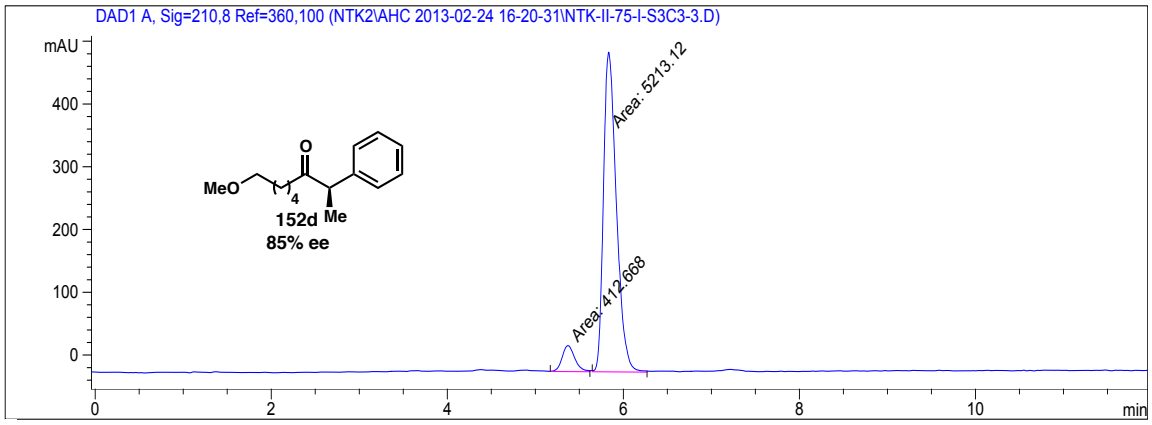
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.186	MM	0.1493	1238.74841	138.30533	5.6552
2	2.675	MM	0.1852	2.06659e4	1859.45630	94.3448

152d (Table 3.7): racemic



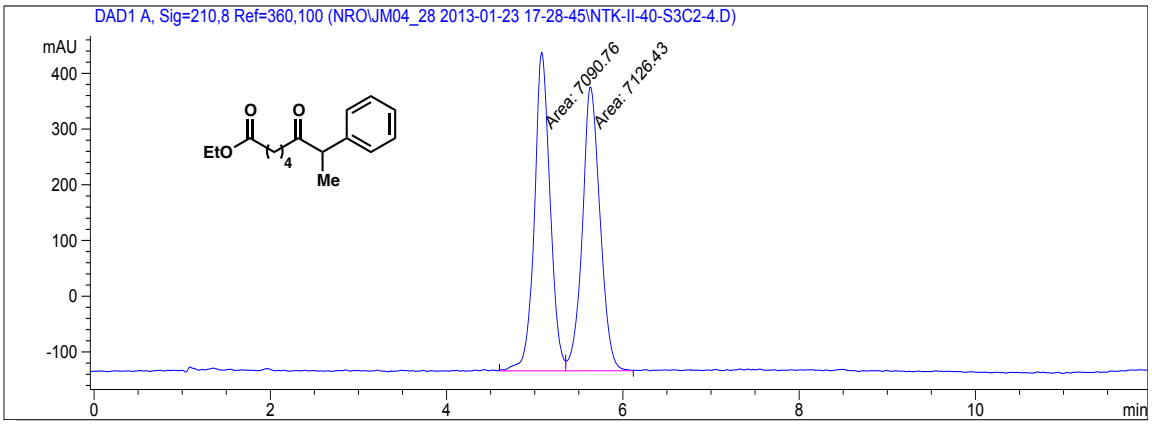
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.415	MM	0.1596	1.31741e4	1375.35034	50.0417
2	5.880	MM	0.1802	1.31521e4	1216.19214	49.9583

152d (Table 3.7): enantioenriched, 85% ee



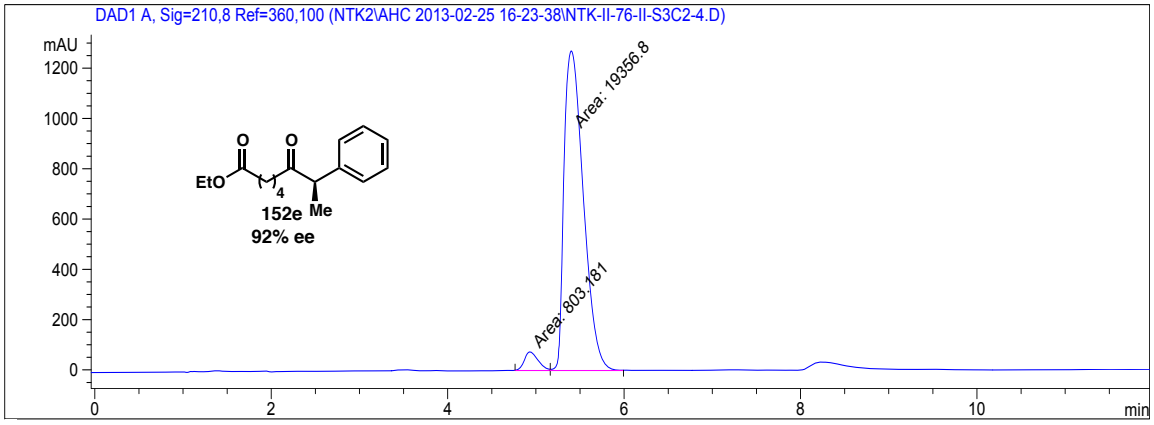
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.371	MM	0.1661	412.66797	41.40784	7.3353
2	5.833	MM	0.1703	5213.12402	510.12839	92.6647

152e (Table 3.7): racemic



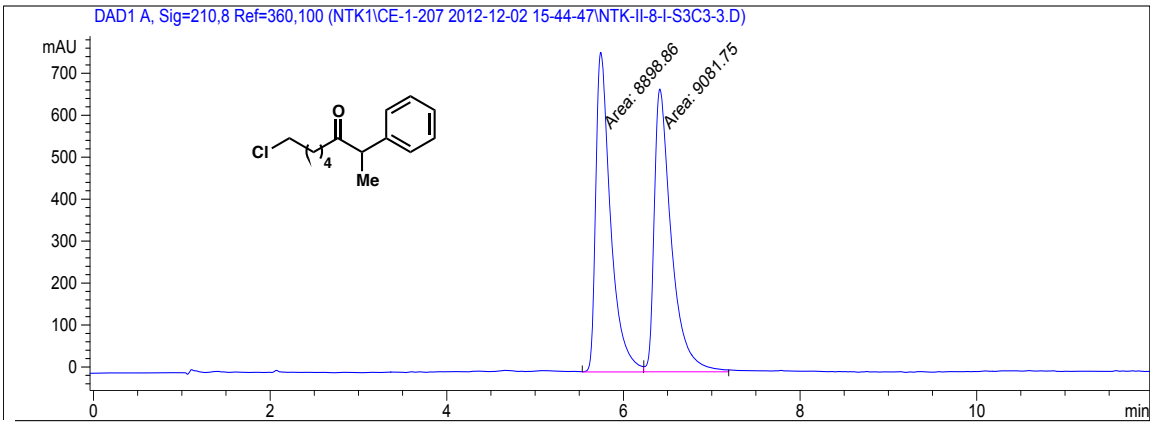
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.079	MM	0.2066	7090.76221	572.01874	49.8746
2	5.631	MM	0.2330	7126.43066	509.79788	50.1254

152e (Table 3.7): enantioenriched, 92% ee



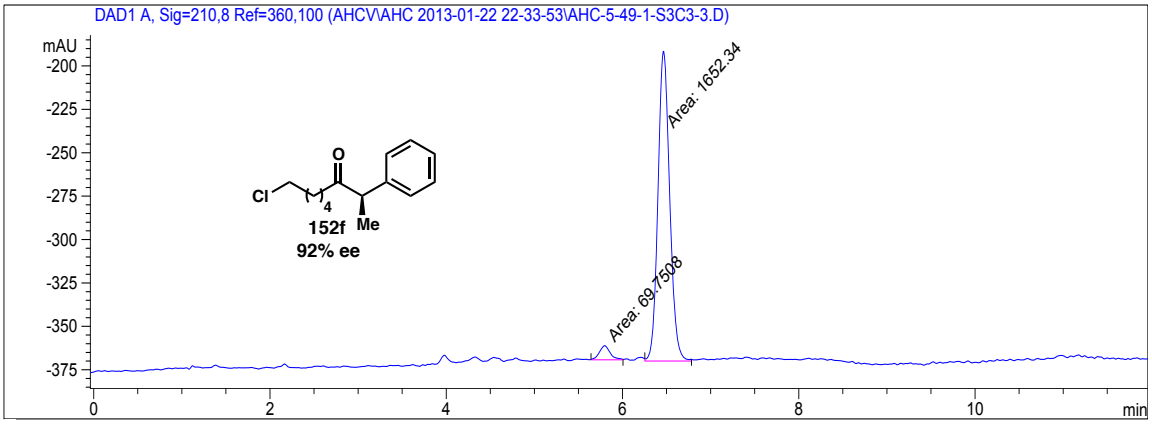
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.932	MM	0.1805	803.18146	74.16300	3.9840
2	5.401	MM	0.2538	1.93568e4	1271.19958	96.0160

152f (Table 3.7): racemic



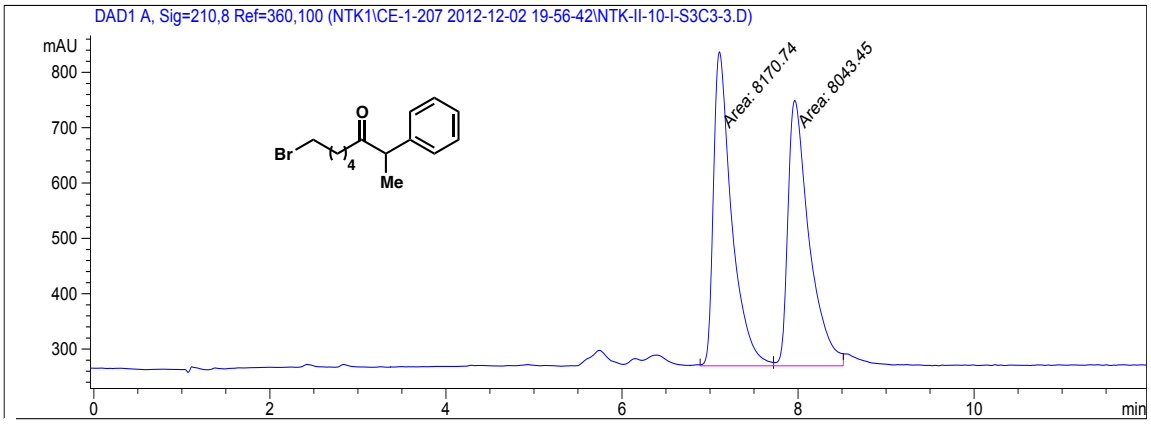
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.744	MM	0.1945	8898.86133	762.63263	49.4914
2	6.413	MM	0.2244	9081.74902	674.62744	50.5086

152f (Table 3.7): enantioenriched, 92% ee



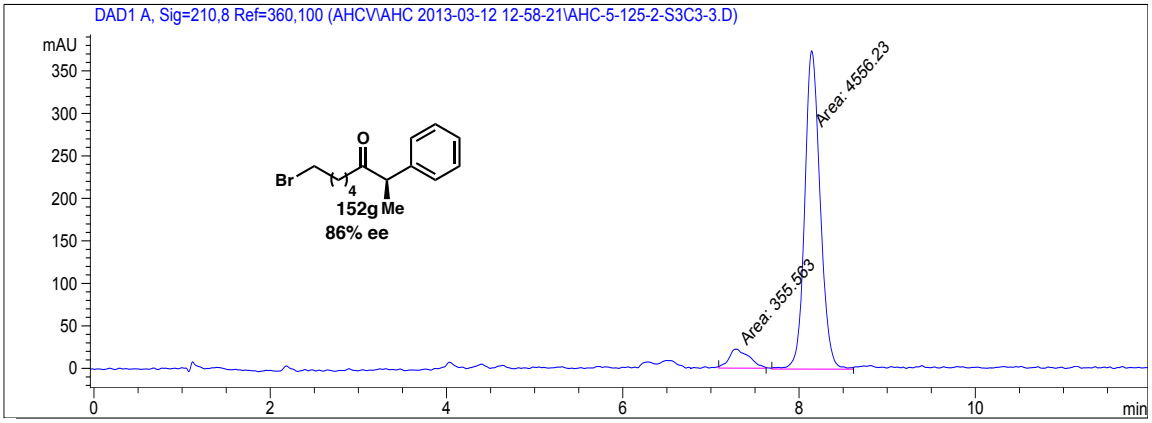
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.798	MM	0.1418	69.75076	8.19656	4.0504
2	6.465	MM	0.1542	1652.33777	178.58195	95.9496

152g (Table 3.7): 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

152g (Table 3.7): 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

3.5 NOTES AND REFERENCES

(1) Seminal reports: (a) Meyers, A. I.; Knaus, G.; Kamata, K. *J. Am. Chem. Soc.* **1974**, *95*, 268. (b) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737. (c) Sonnet, P.; Heath, R. R. *J. Org. Chem.* **1980**, *45*, 3137 (d) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603. (e) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496. (f) A recent example of a "traceless" auxiliary: Stivala, C. E.; Zakarian, A. *J. Am. Chem. Soc.* **2011**, *133*, 11936.

(2) (a) Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582. (b) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77. (c) Shih, H.-W.; Vander Wal, M. N.; Grange, R. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 13600. (d) Chen, J.; Ding, C.; Liu, W.; Hou, X.; Dai, L. *J. Am. Chem. Soc.* **2010**, *132*, 15493.

(3) (a) Kim, H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 398. (b) Dai, X.; Strotman, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 3302. (c) Skucas, E.; MacMillan, D. W. *J. Am. Chem. Soc.* **2012**, *134*, 9090.

(4) (a) Alemán, J.; Cabrera, S.; Maerten, E.; Overgaard, J.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5520. (b) Allen, A. E.; MacMillan, D. W. *J. Am. Chem. Soc.* **2011**, *133*, 4260. (c) Bigot, A.; Williamson, A. E.; Gaunt, M. J. *J. Am. Chem. Soc.* **2011,** *133*, 13778. (d) Harvey, J. S.; Simonovich, S. P.; Jamison, C. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011,** *133*, 13782.

(5) Catalytic asymmetric synthesis of acyclic α,α-disubstituted ketones: (a) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180–17181. (b) Yan, X.-X.; Liang, C.-G.; Zhang, Y.; Hong, W.; Cao, B.-X.; Dai, L.-X.; Hou, X.-L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6544–6546. (c) Zheng, W.-H.; Zheng, B.-H.; Zhang, Y.; Hou, X.-L. *J. Am. Chem. Soc.* **2007**, *129*, 7718. (d) Lundin, P. M.; Esquivias, J.; Fu, G. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 154. (e) Lou, S.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 1264. (f) Lou, S.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 5010. (g) Liang, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 5520.

(6) The catalytic asymmetric synthesis of α-quaternary ketones has been more extensively developed. Selected examples: (a) Åhman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918. (b) Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261. (c) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044. (d) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846. (e) Chen, G.; Kwong, F. Y.; Chan, H. O.; Yu, W.-Y.; Chan, A. S. C. *Chem. Commun.* **2006**, 1413. (f) Doyle, A. G.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2007**, *46*, 3701–3705. (e) Liao, X.; Weng, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 195. (g) Ge, S.;

Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 16330. (h) Evans, P. A.; Oliver, S.; Chae, J. *J. Am. Chem. Soc.* **2012**, *134*, 19314.

(7) Seminal examples of acyl cross coupling: (a) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636. (b) Negishi, E.-i.; Bagheri, V.; Chatterjee, S.; Luo, F.-T.; Miller, J. A.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *24*, 5181. (c) Haddach, M.; McCarthy, J. R. *Tetrahedron Lett.* **1999**, *40*, 3109. For a review, see: (d) Dieter, R. K. *Tetrahedron* **1999**, *55*, 4177.

(8) For reviews on reductive cross-coupling: Everson, D. A.; Weix, D. J. *J. Org. Chem.* **2014**, *79*, 4793; Knappke, C. E. I.; Grupe, S.; Gärtner, D.; Corpet, M.; Gosmini, C.; Jacobi von Wangelin, A *Chem. Eur. J.* **2014**, *20*, 6828; Moragas, T.; Correa, A.; Martin, R *Chem. Eur. J.* **2014**, *79*, 8242.

(9) Co-catalyzed reductive coupling reactions have also been reported: (a) Amatore, M.; Gosmini, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 2089. (b) Amatore, M.; Gosmini, C. *Chem. Eur. J.* **2010**, *16*, 5848. For a related Co-catalyzed reaction proposed to proceed by *in situ* formation of a Grignard reagent, see: (c) Czaplik, W.; Mayer, M.; Jacobi von Wangelin, A. *Synlett* **2009**, 2931.

(10) Reviews on alkyl halides in cross-couplings: (a) Netherton, M. R.; Fu, G. C. *Adv. Synth. & Catal.* **2004**, *346*, 1525. (b) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674. (c) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656.

(11) Semmelhack, M. F.; Helquist, P. M.; Jones, L. D. *J. Am. Chem. Soc.* **1971**, *93*, 5908.

(12) (a) Everson, D. A.; Shrestha, R.; Weix, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 920. (b) Everson, D. A.; Jones, B. A.; Weix, D. J. *J. Am. Chem. Soc.* **2012**, *134*, 6146. (c) Biswas, S.; Weix, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16192.

(13) (a) Yu, X.; Yang, T.; Wang, S.; Xu, H.; Gong, H. *Org. Lett.* **2011**, *13*, 2138. (b) Wang, S.; Qian, Q.; Gong, H. *Org. Lett.* **2012**, *14*, 3352. (c) Xu, H.; Zhao, C.; Qian, Q.; Deng, W.; Gong, H. *Chem. Sci.* **2013**, *4*, 4022.

(14) Metal-catalyzed electrochemical synthesis of ketones: (a) Habeeb, J. J.; Tuck, D. G. *J. Chem. Soc., Chem. Commun.* **1976**, 696. (b) Shono, T.; Nishiguchi, I.; Ohmizu, H. *Chem. Lett.* **1977**, *6*, 1021. (c) Dincan, E.; Sibille, S.; Périchon, J.; Moingeon, M.-O.; Chaussard, J. *Tetrahedron Lett.* **1986**, *27*, 4175. (d) Marzouk, H.; Rollin, Y.; Folest, J. C.; Nédélec, J. Y.; Périchon, J. *J. Organomet. Chem.* **1989**, *369*, 47. (e) Amatore, C.; Jutand, A.; Périchon, J.; Rollin, Y. *Monatsh. Chem.* **2000**, *131*, 1293.

(15) (a) Wotal, A. C.; Weix, D. J. *Org. Lett.* **2012**, *14*, 1476. (b) Wotal, A. C.; Ribson, R. D.; Weix, D. J. *Organometallics* **2014**, *33*, 5874.

(16) (a) Wu, F.; Lu, W.; Qian, Q.; Ren, Q.; Gong, H. *Org. Lett.* **2012**, *14*, 3044. (b) Yin, H.; Zhao, C.; You, H.; Lin, K.; Gong, H. *Chem. Commun.* **2012**, *48*, 7034. (c) Zhao, C.; Jia, X.; Wang, X.; Gong, H. *J. Am. Chem. Soc.* **2014**, *136*, 17645.

(17) Amatore, C.; Jutand, A. *Organometallics* **1988**, *7*, 2203.

(18) (a) Anderson, T. J.; Jones, G. D.; Vicic, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 8100. (b) Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594. (c) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482. (d) Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 13175. (e) Lin, X.; Sun, J.; Xi, Y.; Lin, D. *Organometallics* **2011**, *30*, 3284.

(19) For selected examples see refs 5d–g.

(20) Gutierrez, O.; Tellis, J. C.; Primer, D. N.; Molander, G. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2015**, *137*, 4896.

(21) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 7442.

(22) (a) Cloke, J. B.; Pilgrim, F. J. *J. Am. Chem. Soc.* **1939**, *61*, 2667. (b) Bhar, S.; Ranu, B. C. *J. Org. Chem.* **1995**, *60*, 745

(23) For mechanistic studies on homodimer formation see: (a) Yamamoto, T.; Kohara, T.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2010. (b) Yamamoto, T.; Kohara, T.; Osakada, K.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2147.

(24) Gong and coworkers concurrently published the reductive cross-coupling of in situ-generated mixed anhydrides and alkyl halides: Yin, H.; Zhao, C.; You, H.; Lin, K.; Gong, H. *Chem. Commun.* **2012**, *48*, 7034.

(25) Prinsell, M. R.; Everson, D. A.; Weix, D. J. *Chem. Commun.* **2010**, *46*, 5743.

(26) The absolute stereochemistry was assigned by comparison of the optical rotation to literature reported data. (a) Rodríguez, C.; de Gonzalo, G.; Fraaije, M. W.; Gotor, V. *Tetrahedron: Asymmetry* **2007**, *18*, 1338. The assignment of all other compounds was made by analogy.

(27) Formation of organomanganese reagents: (a) Boucley, C.; Cahiez, G.; Carini, S.; Cerè, V.; Comes-Franchini, M.; Knochel, P.; Pollicino, S.; Ricci, A. *J. Organomet. Chem.* **2001**, *624*, 223. (b) Cahiez, G.; Duplais, C.; Buendia, J. *Chem. Rev.* **2009**, *109*, 1434. (c) Peng, Z.; Knochel, P. *Org. Lett.* **2011**, *13*, 3198.

(28) Choi, J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 9102.

(29) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(30) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923.