Studies towards Developing Diastereoselective S_N1 Reactions of α-Keto Carbocations

by

Joshua A. Dubland

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Abstract

Although α-keto carbocations have been demonstrated to be viable intermediates in solvolysis reactions, their applications in synthesis are scarce. These species can be considered to be equivalent to "reversed polarity" enolates and, as such, could be useful for the asymmetric formation of carbon-carbon and carbon-heteroatom bonds. In principle, facial selectivity in additions to α-keto carbocations may be induced using easily removed ester, amide, or imide chiral auxiliaries. Efforts to achieve such diastereoselective S_N1 reactions of α-keto carbocations are described herein.

Acknowledgments

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I am grateful to my parents and sister Elysia for always being there for me and for encouraging me in my endeavors. Finally, I owe my greatest thanks to my fiancée Stephanie for all the support over the course of my masters' studies, my thesis is dedicated to you.

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List of Abbreviations

$AgBF_4$	silver tetrafluoroborate
Ag_2CO_3	silver carbonate
AgMs	silver methanesulfonate
AgOAc	silver acetate
AgOTf	silver trifluoromethanesulfonate
AgOTs	silver *p*-toluenesulfonate
$AgPF_6$	silver hexafluorophosphate
$AlCl_3$	aluminum trichloride
Ar	aryl
$CDCl_3$	deuterated chloroform
DCE	1,2-dichloroethane
DCM	dichloromethane
DIC	*N,N*'-diisopropylcarbodiimide
DMAP	4-*N,N*-(dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
ee	enantiomeric excess
EI	electron impact

equiv.	equivalents
ESI	electrospray ionization
Et_3N	triethylamine
EtOAc	ethyl acetate
FID	flame ionization detector
FT	Fourier transform
g	gram
GC	gas chromatography
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hz	hertz
IR	infrared
J	coupling constant
LDA	lithium diisopropylamine
M	molarity
$MgSO_4$	magnesium sulfate
MHz	megahertz
δ	chemical shift in parts per million
m/z	mass-to-charge ratio
$NaHCO_3$	sodium bicarbonate

Na_2SO_4	sodium sulfate
$NaHSO_4$	sodium bisulfate
NaS_2O_3	sodium thiosulfate
NBS	*N*-bromosuccinimide
NH_4Cl	ammonium chloride
NMR	nuclear magnetic resonance
mmol	millimole
mL	milliliter
µL	microliter
MS	mass spectrometry
ppm	parts per million
r.t.	room temperature
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TOF	time of flight
Tr	trifluoroethanesulfonyl
Ts or tosyl	*para*-toluenesulfonyl
UV	ultraviolet

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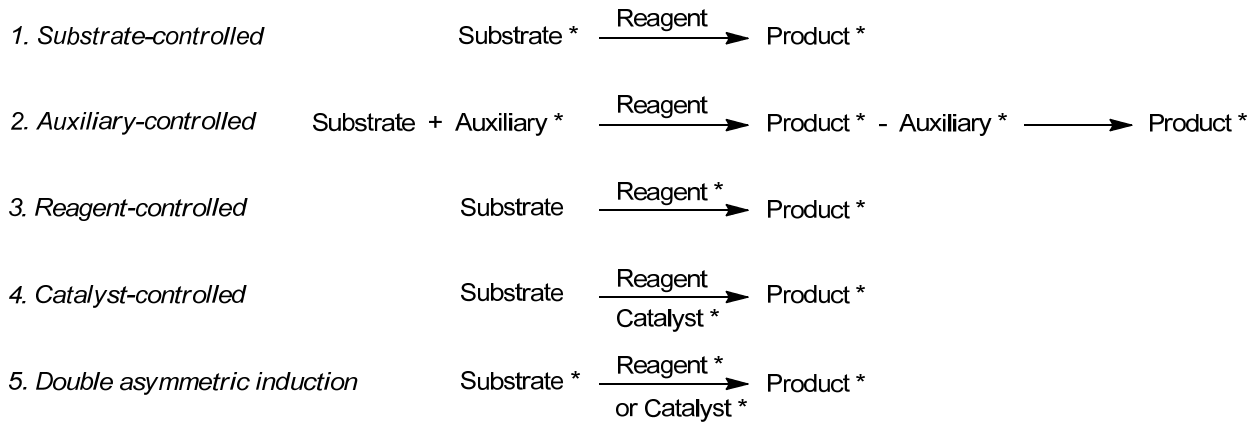
1. Introduction

1.1 Asymmetric synthesis

Asymmetric synthesis, defined as the conversion of an achiral unit under the influence of a chiral group into a chiral centre where one of the possible stereoisomers is formed preferentially, has attracted much attention from the scientific community due to the importance of biologically active chiral compounds. Many pharmaceuticals, flavours, fragrances, food and feed additives, and agrochemicals contain elements of chirality and are required to be in enantiomerically pure forms before they can be utilized. One of the processes which the chemical industry relies on for obtaining enantiomerically pure compounds is asymmetric synthesis. The known methods of asymmetric synthesis have been divided into five general classes based on how the influence of a chiral group is used to induce the stereoisomeric selectivity (Figure 1.1).[1, 2]

Figure 1.1: Classes of asymmetric synthesis



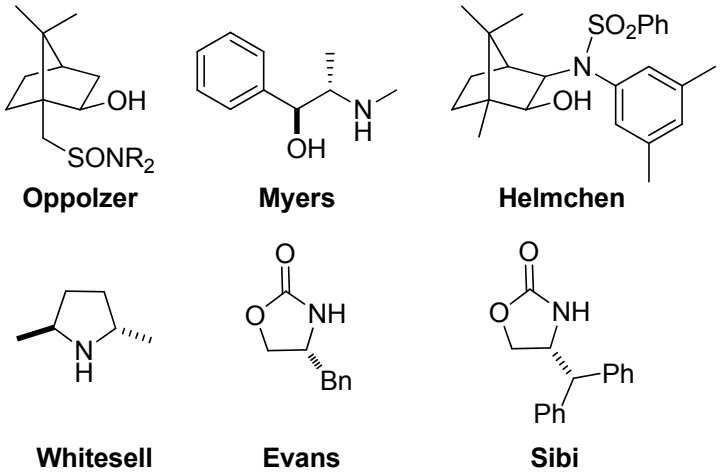
The first class consists of substrate-controlled methods, where the stereoselective formation of the new chiral centre is directed by the preexisting chiral elements in the molecule. The second class consists of auxiliary-controlled methods, whereby a chiral directing group (auxiliary) is deliberately attached to the substrate molecule and is then removed once the stereoselective

reaction has occurred. Different from the first two classes, the third class consists of intermolecular reagent-controlled methods. These methods use chiral reagents to convert non-chiral substrate molecules into chiral products. The fourth class involves catalyst-controlled methods, whereby a chiral catalyst is used to convert a non-chiral substrate molecule into a chiral product in an intermolecular fashion.[1] More recently, methods of double asymmetric induction have also been developed where a chiral substrate reacts with a chiral reagent or chiral catalyst to generate a new chiral centre or centres. This fifth class was first investigated by Horeau[3] and reviewed by Masamune[4] in 1985.[1, 5]

1.2 Chiral auxiliaries

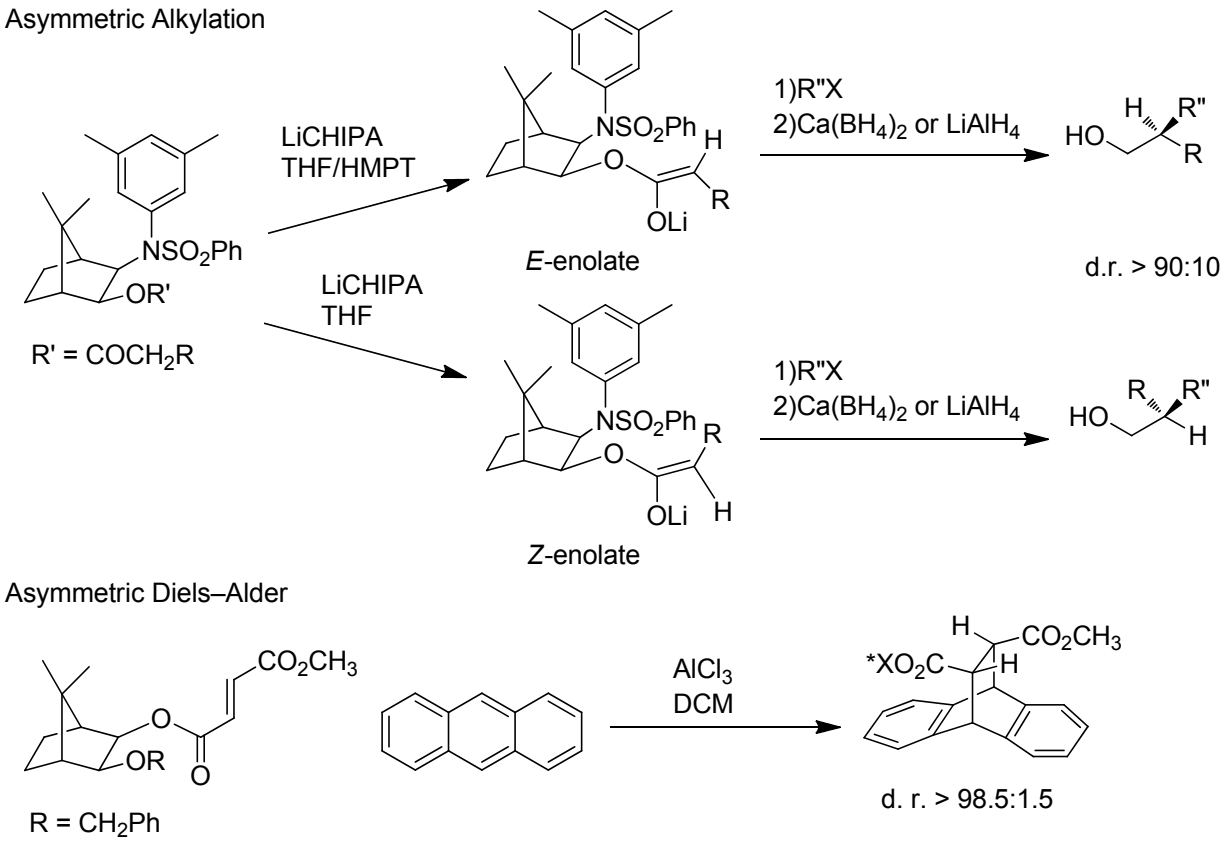
Despite the fact that new catalytic and biocatalytic methods of obtaining compounds in enantiomerically pure form are being discovered and increasingly used by the chemical industry, the use of chiral auxiliaries remains a mainstay of asymmetric synthesis. For many transformations, chiral auxiliaries offer the only means of obtaining high stereoselectivity even though their use requires stoichiometric amounts of chiral material and necessitates two additional synthetic steps. The chiral auxiliary must first be attached to the substrate molecule prior to the stereoselective reaction and removed afterwards in such a way that racemization of the desired product is avoided. A great benefit of this method is that the attachment of the chiral auxiliary allows for the selective formation of a diastereomeric product. Therefore, even if the selectivity is not perfect, the desired product can be separated by standard techniques such as recrystallization or column chromatography before the chiral auxiliary is removed and the desired enantiopure product is obtained. Asymmetric methods that lead to enrichment of enantiomeric products suffer from the fact that unless the reaction leads to an enantiopure product, methods such as chiral chromatography must be employed to separate the desired enantiomer from the undesired enantiomer. Numerous chiral auxiliaries (Figure 1.2) have been developed and several have proved to be generally reliable in various asymmetric transformations. Due to this large knowledge base and high level of stereoselective predictability, the use of chiral auxiliaries remains an important method in asymmetric synthesis.[6, 7]

Figure 1.2: Represenative chiral auxiliaries employed in asymmetric synthesis[7]



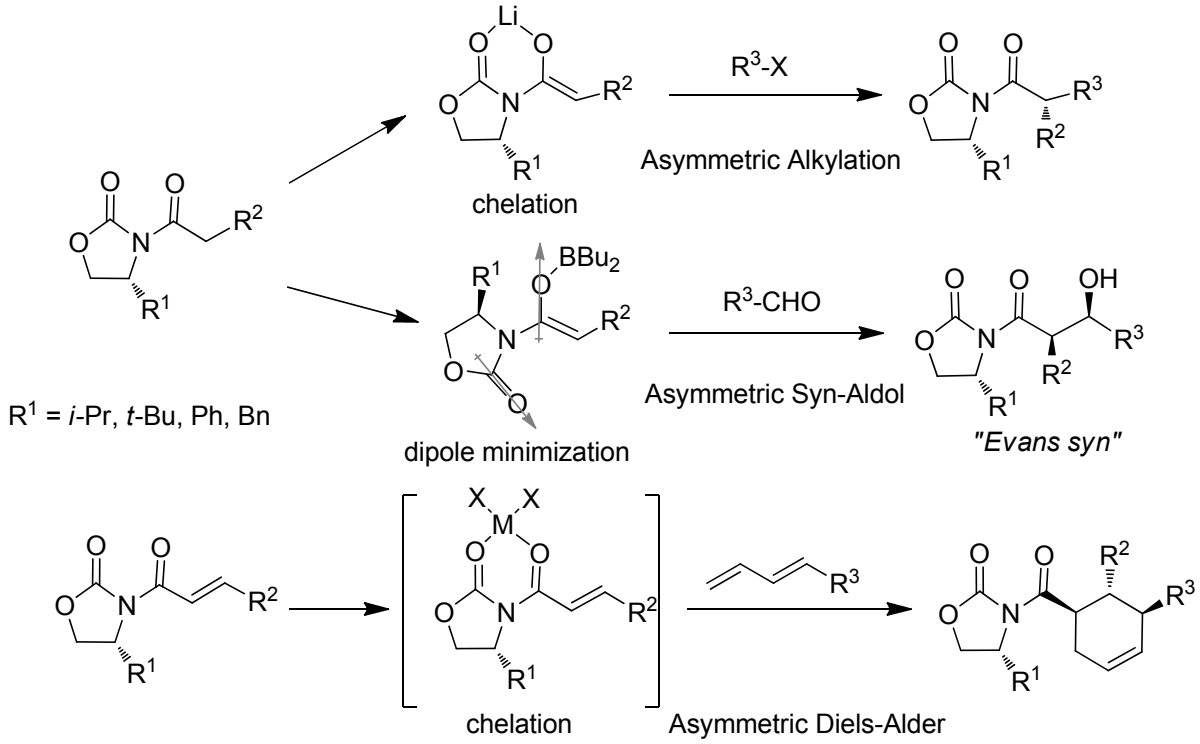
Chemical transformations that have relied most extensively on the use of chiral auxiliaries are asymmetric alkylations, Diels–Alder, and aldol reactions. An early example of chiral auxiliary-controlled asymmetric alkylations and Diels–Alder reactions was reported by Helmchen and coworkers in 1981 using concave camphor-derived chiral auxiliaries (Scheme 1.1).[8] In the asymmetric alkylation reactions, deprotonation by lithium hexylisopropylamide (LiCHIPA) resulted in the formation of the corresponding *E*-enolate in THF and the *Z*-enolate in THF:HMPT (4:1). Upon reaction with an alkyl halide, followed by reduction using calcium borohydride or lithium aluminum hydride, enantiomerically enriched alcohols were obtained (d.r. > 90:10). Under the two sets of conditions employed, alcohols of opposite absolute configuration were obtained as a result of the solvent effects. Diastereoselective Lewis acid-mediated Diels–Alder cylcoadditions of methyl fumarates with anthracene were also reported using a similar camphor-derived auxiliary to induce diastereoselectivity (d.r. > 98.5:1.5).[8]

Scheme 1.1: Asymmetric alkylations and Diels–Alder reactions using a camphor-derived chiral auxiliary[7, 8]



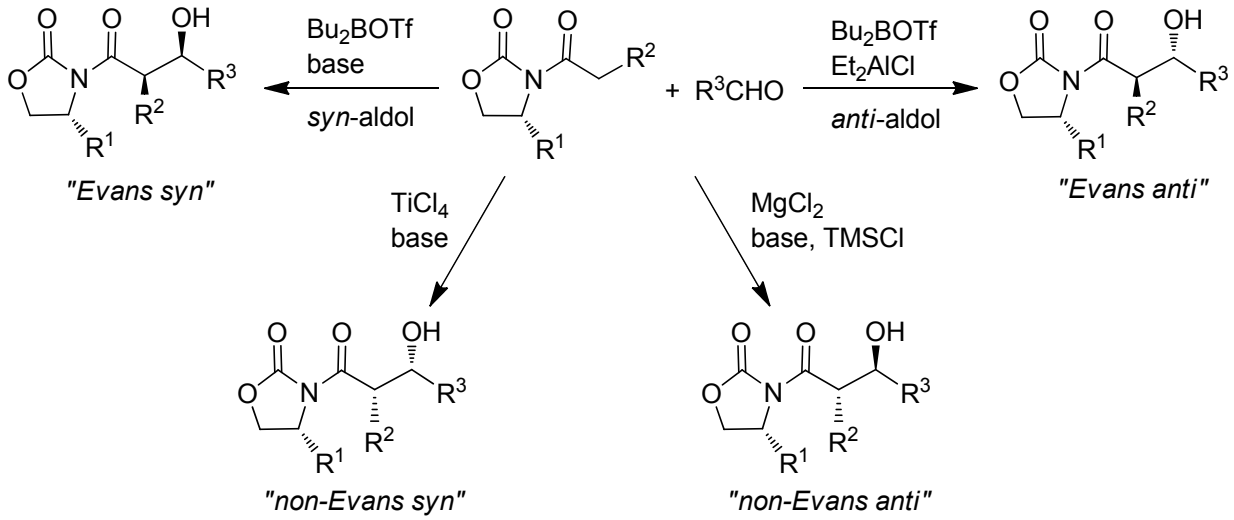
Chiral oxazolidinones are among the most frequently utilized classes of chiral auxiliaries. These types of auxiliaries were first introduced by Evans in 1981[9] and have found extensive applications, mostly notably in the areas of asymmetric alkylations, Diels-Alder, and aldol reactions. Many structural variants of this chiral auxiliary have since been synthesized and utilized for asymmetric transformations, but chiral monosubstituted 2-oxazolidinones first developed by Evans remain the most widely used (Scheme 1.2). They are also referred to as Evans auxiliaries. Chelation or dipole minimization often leads to preferred conformations of the substrate molecule in which the substituent R^1 effectively shields one of the diastereotopic faces of the molecule. Because of this preference for certain rotamers high diastereoselectivities are often achievable.

Scheme 1.2: Representative asymmetric alkylations, aldol, and Diels-Alder reactions using the Evans auxiliary[7, 6]



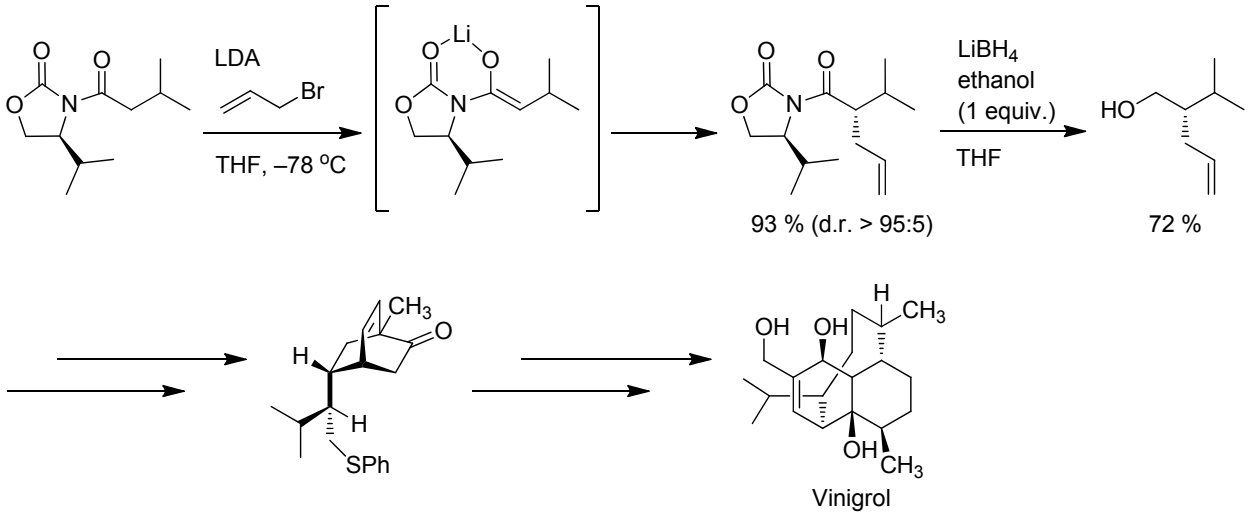
The versatility of the oxazolidinone auxiliary is well illustrated by the aldol reaction (Scheme 1.3). Access to all four possible diastereosomers is possible by the choice of reagents and reagent conditions. *Z*-Enolates are generally generated upon enolization of *N*-acyloxazolidinones due to minimization of $A_{1,3}$ strain. Boron enolates form tight transition states because of the shorter B–C and B–O bonds, which generally leads to high stereochemical selectivity.[6] With *Z*-enolates this leads to the Evans-*syn* aldol product as a result of dipole minimization.[10] Addition of large Lewis acids coordinated to the aldehyde (such as Et_2AlCl) along with the boron enolate lead to the formation of the Evans-*anti* aldol product. Chelation control with appropriate metals gives rise to 'non-Evans' type aldol products. For example titanium enolates yield 'non-Evans *syn*' products.[11] The 'non-Evans *anti*' product has also been reported using magnesium chloride and chlorotrimethylsilane (TMSCl). TMSCl was required to achieve catalyst turnover by silylation of the *anti*-aldol products.[12]

Scheme 1.3: Formation of all possible stereoisomeric aldol products using the Evans auxiliary[6]



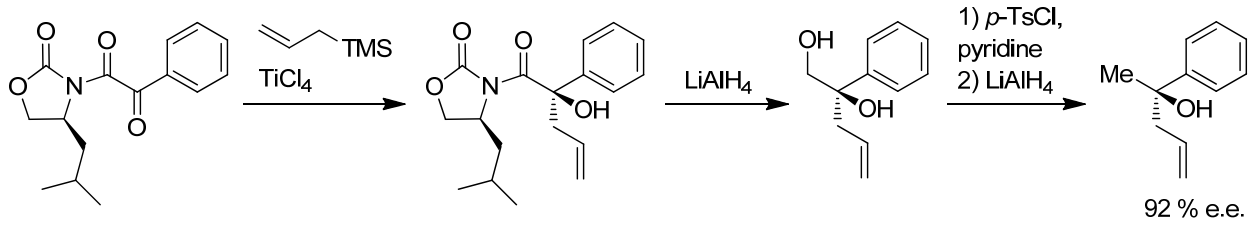
Asymmetric enolate alkylations using chiral 2-oxazolidinones were first described by Evans in 1982 as a method for the stereoselective synthesis of α-substituted carboxylic acid derivatives.[13] These reactions are normally conducted under chelation conditions with the metal coordinated to the oxazolidinone carbonyl group upon formation of the *Z*-enolate (see Scheme 1.2). A nice example of the application of this chemistry was reported by Paquette and coworkers towards the enantioselective total synthesis of the core structure of the diterpenoid vinigrol (Scheme 1.4).[14] Formation of the lithium-chelated *Z*-enolate followed by diastereoselective allylation gave the addition product with a d.r. of 95:5. Reduction using lithium borohydride then afforded the enantiomerically enriched alcohol. Many other conditions for cleaving *N*-acyloxazolidinones have also been developed allowing for the preparation of carboxylic acids, alcohols, esters, thioesters, amides, and other functional groups.[15, 16] A successful synthesis of vinigrol has been recently reported by Baran and coworkers in 23 steps and an overall yield of 3 %.[17]

Scheme 1.4: Asymmetric alkylation using an oxazolidinone auxiliary in the synthesis of vinigrol[14]



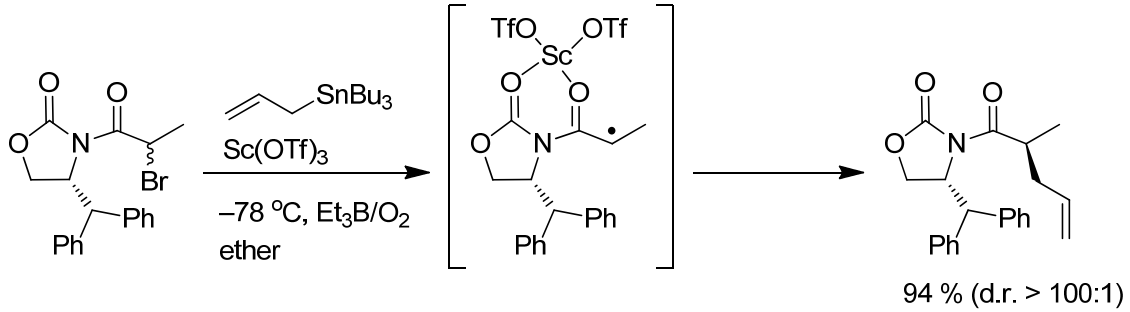
Diastereoselective processes in which the chiral oxazolidinone substrate acts as an electrophile instead of a nucleophile are also possible. Nucleophilic additions of allyltrimethylsilane to chiral α-keto imides mediated by titanium tetrachloride followed by reduction to the corresponding tertiary homoallylic alcohol, have been shown to be highly diastereoselective (Scheme 1.5).[18] Nucleophilic additions of allyltrimethylsilane to a menthol-derived 2-phenyl-2-keto ester under the same conditions showed low stereoselectivity (23 % *ee* after base hydrolysis to the corresponding α-hydroxy acid).[19] In comparison, nucleophilic addition of allyltrimethylsilane to the 2-phenyl-2-keto amide derived from (S)-proline has previously been shown to have a diastereoselectivity of 84:14 with a low yield of 13 % when titanium tetrachloride was used as the Lewis acid. Tin tetrachloride was found to result in higher diastereoselectivities and yields.[20]

Scheme 1.5: Diastereoselective nucleophilic additions of allyltrimethylsilane to chiral α-keto imides[18]



The use of oxazolinone auxiliaries to induce stereoselectivity at the α-keto position in radical allylations has been reported by Sibi and coworkers (Scheme 1.6).[21] A chelating Lewis acid such as scandium (III) triflate was found to be a requirement for high diastereoselectivity (d.r. > 100:1). Without the presence of the Lewis acid, d.r.'s of 1:1 to 1:1.8 were observed. The bulkier diphenylmethyl substituent on the oxazolidinone resulted in much higher diastereoselectivities than when the corresponding isopropyl, phenyl, or benzyl substituents were utilized. Of the four rotamers possible when a radical is present at the α-keto position, chelation first eliminates two rotamers and restricted rotation about the C(radical)–CO bond due to the the bulky size of the oxazolidinone fixes the conformation in the *Z* arrangement. Delocalization of the radical into the carbonyl group results in the C–(CO) bond having some double bond character, therefore, stabilizing the *Z*-arrangement. The *E*-arrangement is destabilized due to $A_{1,3}$ strain.[22]

Scheme 1.6: Diastereoselective radical allylations using Lewis acid-chelated chiral oxazolidinone auxiliaries[21]



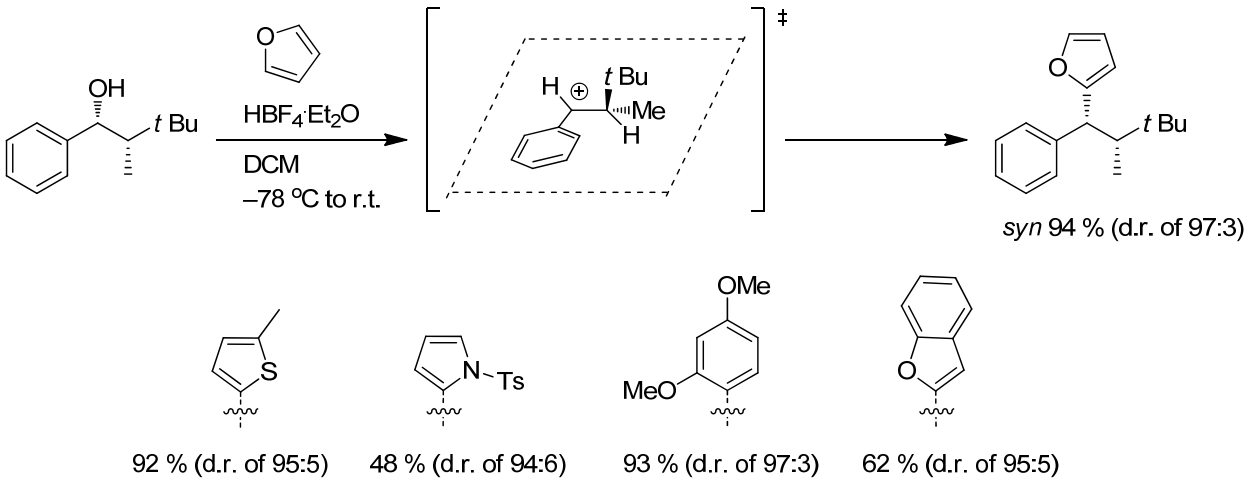
The above examples illustrate that chiral oxazolidinone auxiliaries have been used to induce diastereomeric facial selectivity at the α-keto position in reactions where the substrate acts as the nucleophile (Scheme 1.4) or electrophile (Scheme 1.5), or in radical reactions (Scheme 1.6). Therefore, the carbonyl group is capable of stabilizing negative charge, radical formation, and increasing electrophilicity at the α-position.

1.3 S_N1 reactions

It is well-established that the stability of a carbocation increases as the number of hyperconjugating alkyl groups attached to the carbon is increased ($1^o < 2^o < 3^o$). Allylic and benzylic carbocations show even greater stability due to conjugation with π or lone-pair electrons. Substituent effects on benzylic carbocation stability have been studied using temperature-dependent NMR.[23] Rate and equilibrium constants of various anionic and neutral nucleophiles with aromatic stabilized carbocations in solvents of varying polarity have also been investigated.[24] By definition, in an S_N1 reaction the rate limiting step is the spontaneous, unimolecular dissociation of the leaving group from the substrate to form a carbocation intermediate. By the Hammond postulate, factors that increase the stability of the intermediate carbocation will, therefore, increase the rate of the S_N1 reaction. Polar solvents increase the stability of the carbocation intermediate by solvation, thereby lowering the transition-state energy leading to the carbocation. Leaving groups that form stable anions also increase the reaction rate by lowering the transition-state energy leading to the carbocation intermediate. The rate of the reaction does not depend on the concentration of the nucleophile. In contrast to the S_N1 reaction, the S_N2 reaction is a one-step process where the rate of the leaving group displacement depends both on the concentration of the nucleophile and the substrate and therefore is a bimolecular process.[25] It has been suggested that a definitive distinction between an S_N2 and an S_N1 type mechanism cannot be made because there is a gradual increase in carbocation character in the transition state.[26] Intermediates in the borderline scenarios can be considered nucleophilically solvated ion pairs. Here the transition state has been thought to look like that of a S_N2 reaction, but as energy minimum not maximum. These scenarios are termed S_N2 (intermediate).[27] Nucleophilic solvent assistance in the transition state where heterolysis of

the carbon-leaving group bond occurs decreases going from an S_N2 to an S_N2 (intermediate) to an S_N1 type mechanism. The S_N1 intermediate ion pair may be nucleophilically solvated, but the transition state leading to it is not. The S_N2 (intermediate) mechanism involves an ion pair intermediate that is nucleophilically solvated, and the transition state leading to it is nucleophilically solvated. The purely S_N2 mechanism occurs with nucleophilic solvent assistance and no intermediate formed.[27] Bach and coworkers have recently examined S_N1 reactions of arene nucleophiles with chiral α-branched benzylic carbocations (Scheme 1.7).[28] This is a substrate-controlled method of asymmetric synthesis because the chiral information causing the stereoselectivity is held within the substrate molecule. Nucleophilic additions to a free carbocation that is prostereogenic (meaning the three substituents are different) and not under the influence of any chiral information results in a product that is racemic. The two faces of the plane defined by the three different substituents at the carbocation are, therefore, enantiotopic. If the free carbocation is under the influence of chiral information within the same substrate molecule, the two faces of the plane are diastereotopic and nucleophilic addition to the free carbocation will lead to two diastereomeric products which may be formed in disproportionate amounts.[28]

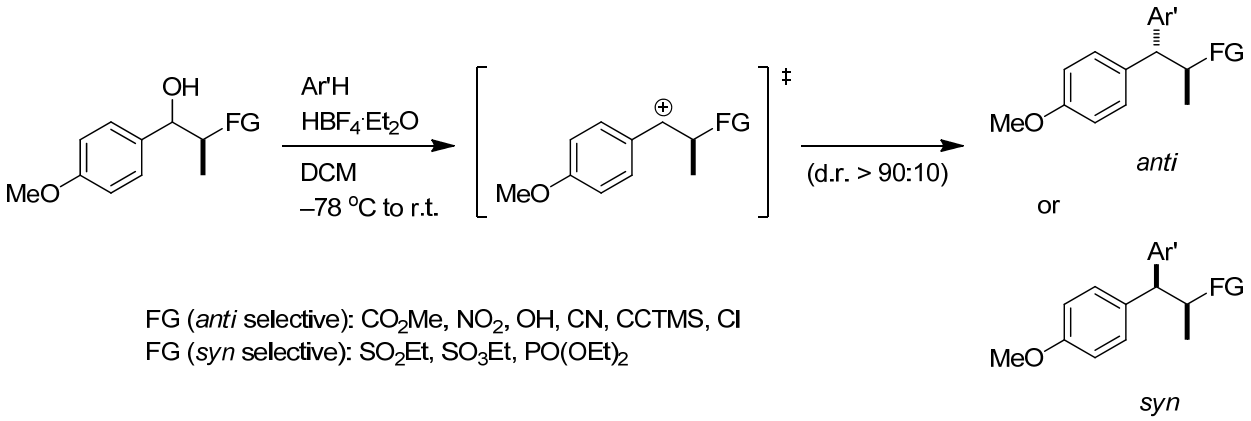
Scheme 1.7: Acid-catalyzed nucleophilic additions of arenes to chiral α-branched benzylic carbocations[28]



The reagents F_3CSO_3H, $BF_3{\cdot}OEt_2$, and $HBF_4{\cdot}OEt_2$ were found to be the best acids for promoting this transformation. Reaction optimizations were conducted with furan as the nucleophile. Temperature (0 ^oC versus ambient temperature) and nucleophile concentration were found to only have a minor influence on the stereoselectivity and yield when F_3CSO_3H was used as the acid. When $HBF_4{\cdot}OEt_2$ was used as the acid, lowering the reaction temperature from ambient temperature to –78 ^oC resulted in only a minimal increase in d.r. from 96:4 to 97:3 (*syn* was the major diastereomer), but a yield increase of 59 % to 94 % was observed. When the configuration of the starting material was changed from *syn* to *anti* the same product distribution was observed, ruling out a S_N2-type displacement and indicating the formation of a carbocation of the type shown in Scheme 1.7.[28] The preferred conformation of the carbocation intermediate was posulated to be a result of 1,3-allylic strain.[29] The arene nucleophiles 2-methylthiophene, *N*-tosylpyrrole, resorcindimethyl ether, and benzofuran, all being of similar nucleophilicity[30, 31] showed diastereomeric ratios ranging from 97:3 to 94:6. The less nucleophilic arenes mesitylene and thiophene did not yield addition products but instead the corresponding elimination products were observed. The possibility of thermodynamic control of the nucleophilic addition reactions was disproved by subjecting diastereomeric mixtures of the 2-methylthiophene addition product to the optimized reaction conditions (4 equiv. of 2-methylthiophene, –78 ^oC to r.t., 1 equiv. of $HBF_4{\cdot}OEt_2$, DCM) and observing no change in d.r. in favour of the *syn* major diastereomer. Therefore, the d.r. of 95:5 was not a result of thermodynamic equilibration.[28]

In extension of the chiral α-branched benzylic carbocation motif Bach and coworkers have examined the influence of various functional groups attached at the chiral 2-position along with methoxy substitution at various positions of the aromatic ring (Scheme 1.8).[32, 33] This work was further extended to gold (III) catalyzed reactions of benzylic acetates having various functional groups attached at the 2-position[34] as well as bismuth (III) triflate-catalyzed reactions of chiral propargylic acetates containing a *t*-butyl group at the 2-position.[35] Intramolecular variants were also investigated and found to give high diastereoselectivities.[36] The nature of the chiral benzylic carbocation was elucidated by low temperature NMR studies and theoretical calculations.[37]

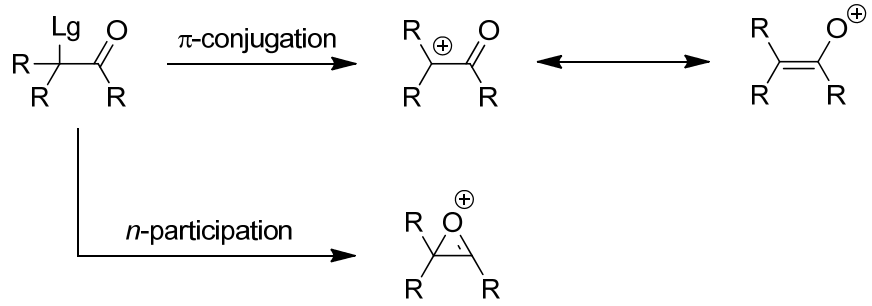
Scheme 1.8: Acid-catalyzed nucleophilic additions of arenes to chiral α-functionalized benzylic carbocations[32, 33]



1.4 α-Keto carbocations

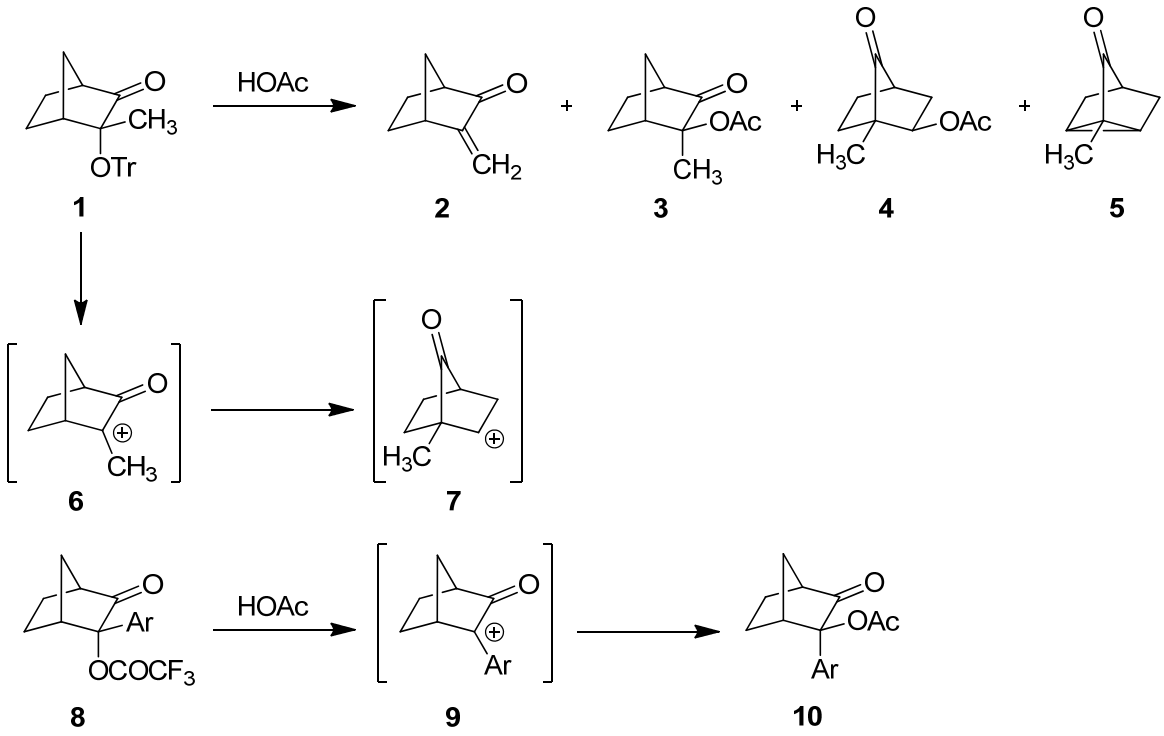
Although not intuitively evident at first, stabilization of carbocations at the α-keto position is also possible. This stabilization arises through π-conjugation, and possible interactions of the lone-pair carbonyl electrons (*n*-participation) with the α-keto carbocation (Figure 1.3). The carbonyl group is also inductively withdrawing (σ-participation), which is destabilizing for carbocation intermediate formation.[38]

Figure 1.3: Stabilization of α-keto carbocation through π-conjugation and *n*-participation



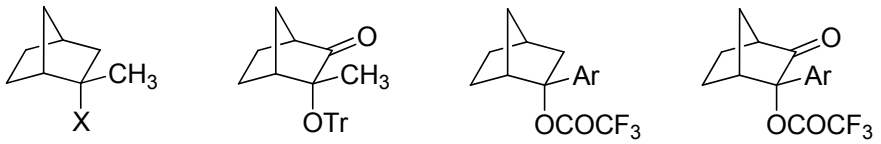
The generation of α-keto carbocations in the norbornyl system under solvolytic conditions was investigated by Creary and coworkers in 1979.[39] The norbornyl system was chosen because of its semipredictable rearrangement patterns. Acetolysis of the methyl substituted tresylate substrate **1** showed the formation of four products (Scheme 1.9). Elimination product **2** and solvent capture product **3** were postulated to arise from the cationic intermediate **6**. Wagner-Meerwein rearrangement from cationic intermediate **6** to **7** then led to the observed formation of products **4** and **5**. This suggested a step-wise process involving both of the proposed cationic intermediates because the endo stereochemistry of the tresylate leaving group prevented concerted Wagner-Meerwein rearrangement. The observance of products **4** and **5**, therefore, support the formation of the distinct intermediate carbocation **6**, but at the same time indicate that the stabilizing ability of the methyl group can be counteracted by the inductive destabilizing ability of the α-keto group. Acetolysis of the aromatic substituted trifluoroacetate substrate **8** as well as the analogous mesylate substrate showed exclusive formation of the *exo*-acetate product **10** through the formation of the carbocation intermediate **9**. In this case no Wagner-Meerwein rearrangement was observed, thereby, indicating the increased stabilization of aryl substituted substrates compared to methyl substituted substrates.[39]

Scheme 1.9: Indication of tertiary and benzylic α-keto carbocation generation in the norbornyl system[39]



The stability of methyl and aryl substituted α-keto carbocations in the norbornyl system was evaluated using solvolytic rate ratios as well as the β-deuterium isotope effect (Figure 1.4). The solvolysis rate ratio for methyl substituted tresylate substrates **11**:**1** in acetic acid was found to be $10^{7.3}$, indicating that the carbonyl group was causing a large rate retarding effect. An analysis of the effect of aryl stabilization on the α-keto cation was also conducted. A solvolysis rate ratio for aryl substituted trifluoroacetate substrates **13**:**14** was found to be $10^{5.8}$, indicating a greater stabilizing influence relative to the methyl substituted substrate. The methyl-d_3 isotope effects for methyl substituted tresylate substrates **1** and **12** were found to be 1.47 ± 0.01 and 1.26 ± 0.01 respectively. The increased methyl-d_3 isotope effect in substrate **1** compared to substrate **12** shows that there is a large destabilizing effect caused by the carbonyl group and indicates that there is a huge demand for hyperconjugative stabilization in the α-keto carbocation intermediate **6** (Scheme 1.9). Tertiary and benzylic α-keto carbocations are feasible intermediates in solvolytic reactions, but are unstable as indicated by the solvolysis rate ratios and the β-deuterium isotope effect study.[39]

Figure 1.4: Investigation of α-keto carbocation stability using solvolysis rates and the β-deuterium isotope effect[39]



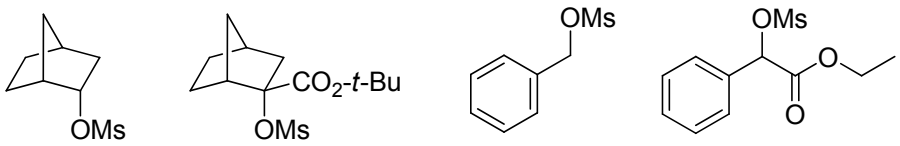
11: X = OTr **1** **13** **14**
12: X = OPNB

$k_{11}:k_1 = 10^{7.3}$ $k_{13}:k_{14} = 10^{5.8}$

12: methyl-d_3 KIE = 1.26 ± 0.01
1: methyl-d_3 KIE = 1.47 ± 0.01

Further solvolysis studies conducted by Creary and coworkers with tertiary α-keto carbocations and secondary benzylic α-keto carbocations indicated a lack of or a negligible rate-retarding effect due to the the presence of the carbonyl group (Figure 1.5).[40] The endo mesylate substrate **16** was in fact found to solvolyze 3.7 times faster than the endo-2-norbornyl mesylate **15** in acetic acid. The solvolysis rate ratio for the mesylate substrates **17**:**18** was found to be 200, indicating only a small rate retarding affect due to the carbonyl group. The ease at which solvolysis occurs was proposed to be a result of carbocation stabilization through π-conjugation, which offsets the inductive destabilizing ability of the carbonyl group. A similar α-cyano carbocation stabilization through π-conjugation was reported by Gassman.[41] Solvolysis of (+)-ethyl 2-((methylsulfonyl)oxy)-2-phenylacetate **18** showed racemization indicating the formation of a intermediate carbocation, which is characteristic of an S_N1 reaction.

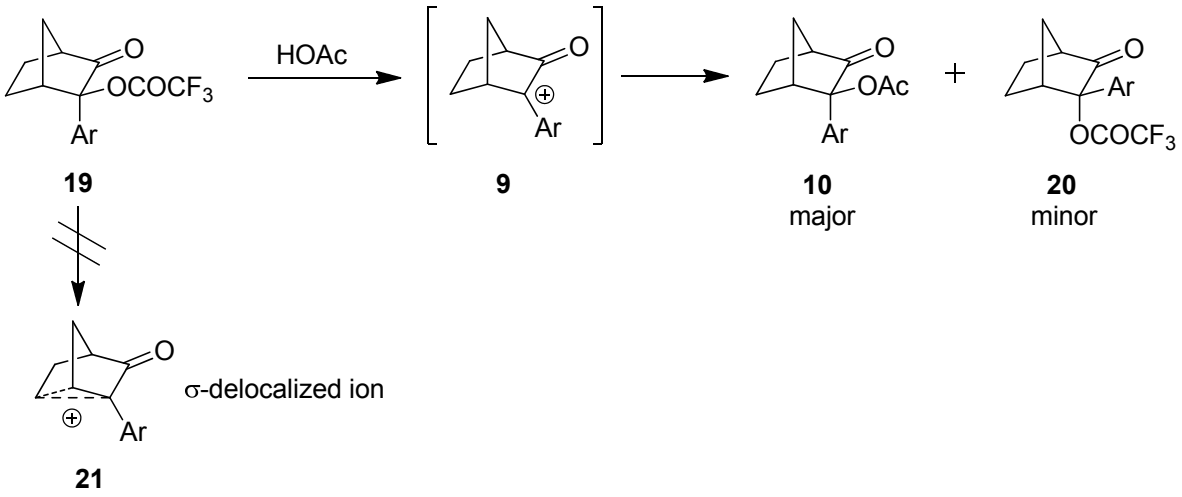
Figure 1.5: Solvolysis rate studies of tertiary and secondary benzylic α-keto carbocations[40]



	15	**16**	**17**	**18**
relative rates	1.0	3.7	~200	1.0
	HOAc		$(CF_3)_2CHOH$	

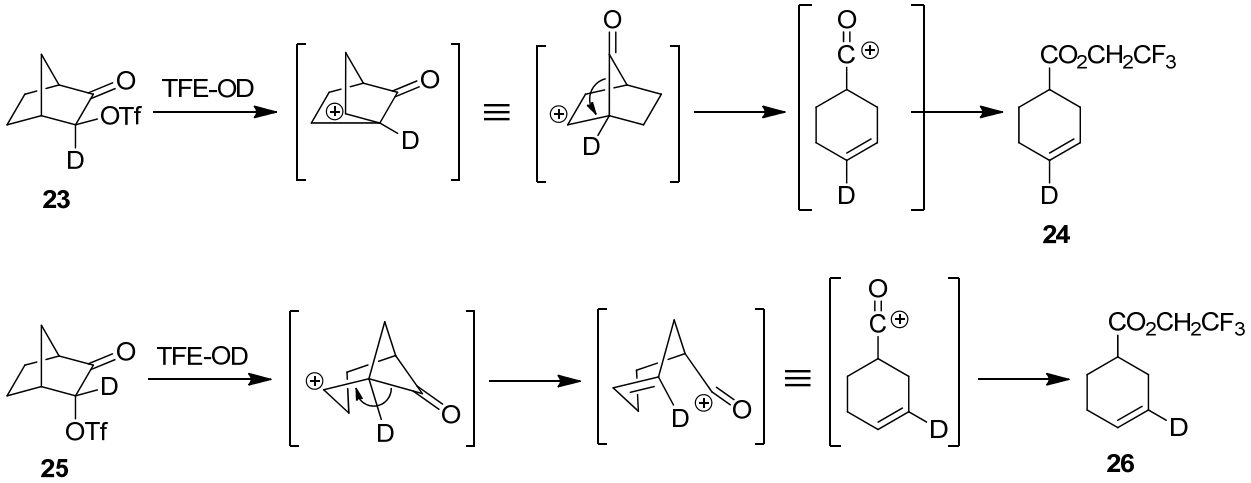
The solvolysis of substrates with the leaving group in the exo position was also investigated along with exo/endo rate ratios. Solvolysis of exo trifluoroacetate **19** resulted in formation of the exo product **10** and a small amount of the inverted trifluoroacetate product **20**, which indicated the involvement of the discrete benzylic α-keto carbocation **9** (Scheme 1.10).[42] The formation of small amounts of **20** ruled out the involvement of σ-delocalized non-classical ion **21**. A further study of the exo/endo solvolysis rate ratio for **8** and **19** gave a ratio of 126, which was comparable to ratios seen by Brown[43] in similar systems. The exo/endo solvolysis rate ratio, therefore, indicated the discrete benzylic α-keto carbocation **9** and no participation of the σ-delocalized non-classical ion **21**.

Scheme 1.10: Evidence for no formation of σ-delocalized ions in the solvolysis of exo trifluoroacetate 19[42]



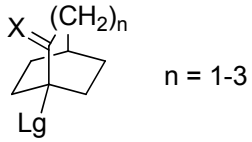
The solvolysis of secondary exo and endo α-keto norbornyl triflates **23** and **25** were studied using deuterium labeling studies which indicated that the exo and endo substrates unraveled to give an ester product by completely different mechanisms (Scheme 1.11).[42] The exo/endo solvolysis rate ratio for **23** and **25** was found to be 4.4×10^4, much larger than that of the exo and endo secondary benzylic α-keto triflates **8** and **19**. This implicates neighboring σ-participation in the secondary exo-norbornyl system **25**. The σ-participation is a result of the increased electron demand due to the inductively withdrawing carbonyl group. Stabilization through π-conjugation is not great enough to allow for the formation of discrete secondary α-keto carbocations.

Scheme 1.11: Analysis of secondary α-keto carbocation formation using deuterium labeling studies[42]



Analysis of π-conjugation stabilization of bridgehead α-keto carbocations was conducted by Takeuchi and coworkers (Figure 1.6).[44] The relative solvolysis rate for **27b**:**27c** was found to increase as the flexibility of the bicyclic ring was increased. This was proposed to be consistent with increased carbocation stabilization by allylic conjugation. The relative solvolysis rate for **27a**:**27c** was found to stay constant as the flexibility of the bicyclic ring was increased, indicating that π-conjugation was not occurring appreciably. As the size of the ring increased more overlap of the filled carbonyl p-orbital with that of empty carbocation p-orbital should have occurred, therefore, leading to greater carbocation stabilization and an increased solvolytic rate.

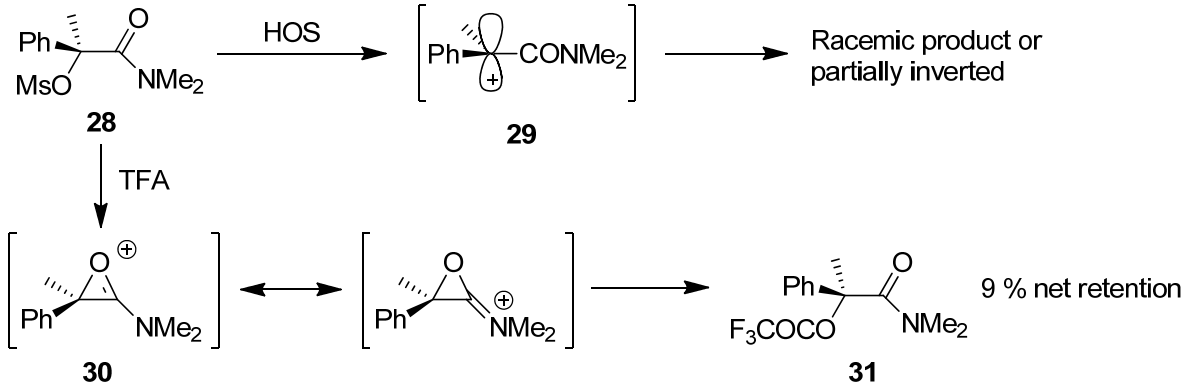
Figure 1.6: Evidence for the unimportance of π-conjugative stabilization in tertiary α-keto carbocations[44]



27a X = O
27b X = CH_2
27c X = H_2

Stabilization of α-keto carbocations can also possibly come from the interaction of the lone pair electrons of the carbonyl group with the developing vacant orbitals of the cationic centre (Scheme 1.12).[45, 38] This type of stabilization was not possible with the norborynl systems because the products indicated Wagner-Meerwein rearrangement as well as net inversion of configuration, both of which are not consistent with *n*-participation. Investigation of substrate **28** showed racemic product in trifluoroethanol and hexafluoroisopropyl alcohol, 33 % net inversion in methanol, and 11 % net inversion in acetic acid. Using trifluoroacetic acid as the solvent resulted in 9 % net retention of configuration, thereby indicating partial *n*-participation and oxiranyl ion **30** formation. This very small *n*-participation in the case of an amide, where bond rotation about the C(CO)–N bond is restricted and the nucleophilicity of the carbonyl is increased by the nitrogen nonbonding electrons, argues in favour of the open carbonyl-substituted cation **29**. In the solvolysis of ester and ketone substrates *n*-participation giving oxiranyl type ions would, therefore, be very unlikely.

Scheme 1.12: *n*-Participation[45]



1.5 Research objectives

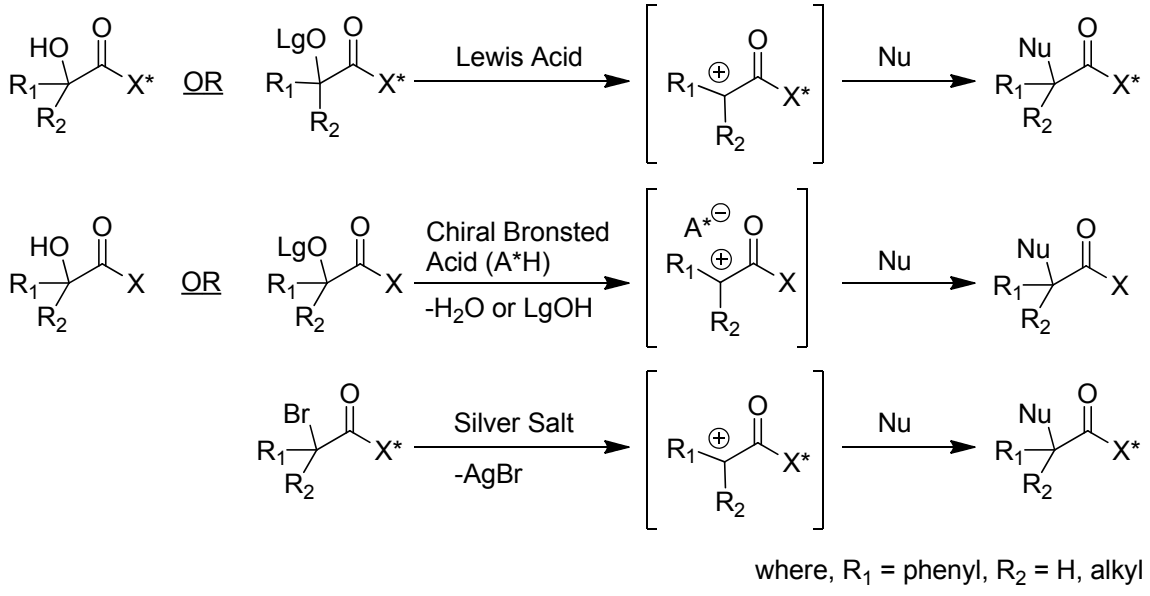
The generation of tertiary α-keto carbocations and benzylic α-keto carbocations under solvolytic conditions has been shown to be possible. Stabilization of the α-keto carbocation through π-

conjugation, and possible *n*-participation of the carbonyl group compete with destabilization caused by the inductively withdrawing nature of the carbonyl group. Generation of discrete secondary α-keto carbocation was shown to not be probable due to neighboring σ-participation in the secondary exo-norbornyl system. Considering previous examples with regards to diastereoselective S_N1 reactions at stabilized chiral benzylic carbocations, it was hypothesized that chiral auxiliaries could be used to induce facial selectivity at stabilized benzylic α-keto carbocations. Here the chiral information would not have to be built into the substrate molecule framework prior to nucleophilic substitution (substrate controlled method). The chiral auxiliary could be attached using a facile ester or amide bond and the intermediate carbocation would potentially be stabilized by the adjacent aromatic group and carbonyl group. Further stabilization of the α-keto carbocation could potentially come from an energetically favourable cation-quadrupole interaction of the chiral auxiliary's face shielding aromatic substituent. Alternatively, facial selectivity at the benzylic α-keto carbocation could also be achieved through non-covalent ion pairing of a chiral Brønsted acid (reagent or catalyst-controlled method). The α-keto group has also previously been shown to be capable of stabilizing negative charge, radical formation, and increasing electrophilicity. The following section describes efforts to use chiral auxiliaries to control facial selectivity in diastereoselective S_N1 reactions of benzylic α-keto carbocations as well as efforts to determine which non-covalent interactions might be useful for control of stereoselectivities in such reactions.

2. Results and discussion

The primary goal of this project was to formulate ways of controlling the facial selectivity in S_N1 reactions of stabilized electron deficient benzylic α-keto carbocations in ester, amide, and imide substrates (Scheme 2.1). These α-keto carbocations would be equivalent to reverse polarity enolates. The asymmetric formation of stereocentres containing newly formed carbon-carbon and carbon-heteroatom bonds is of great value in synthetic organic chemistry. Lewis acids or silver salts could possibly be used to induce carbocation formation at the benzylic α-keto position and then have an easily removed chiral auxiliary induce facial selectivity at the carbocation. Alternatively a chiral Brønsted acid could be used to initiate the formation of the carbocation and then through ion-pairing cause facial selectivity.

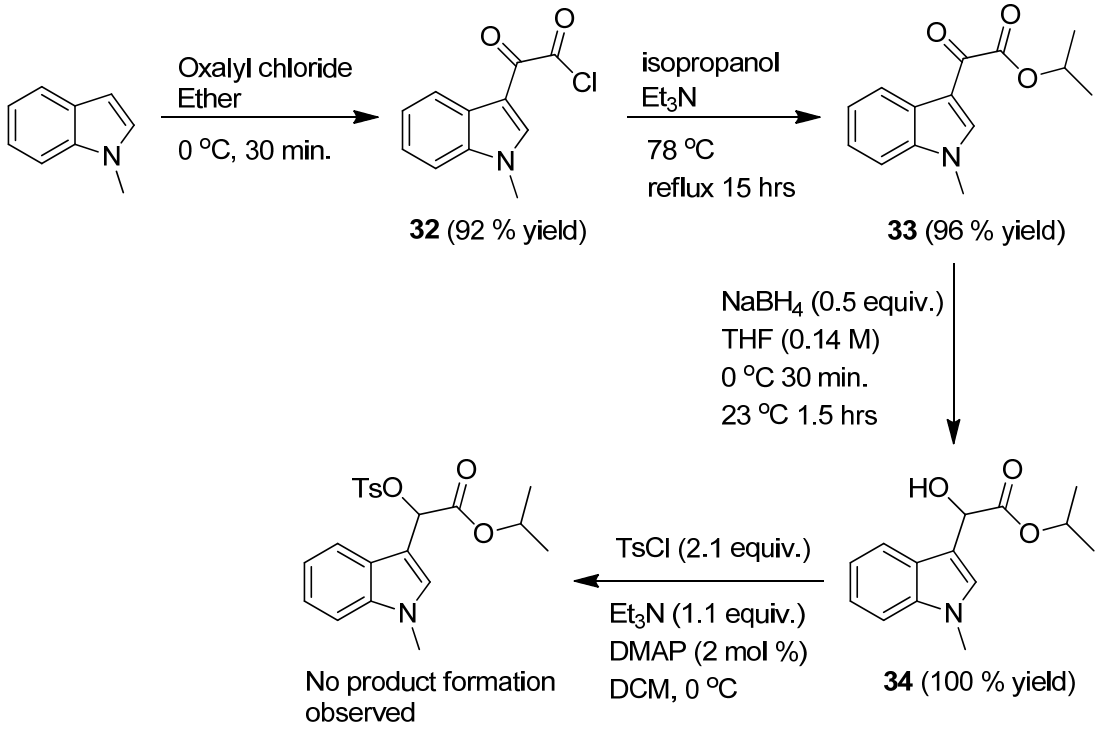
Scheme 2.1: Lewis acid, chiral Brønsted acid, and silver-mediated S_N1 reactions of α-keto carbocations



2.1 Ester substrates

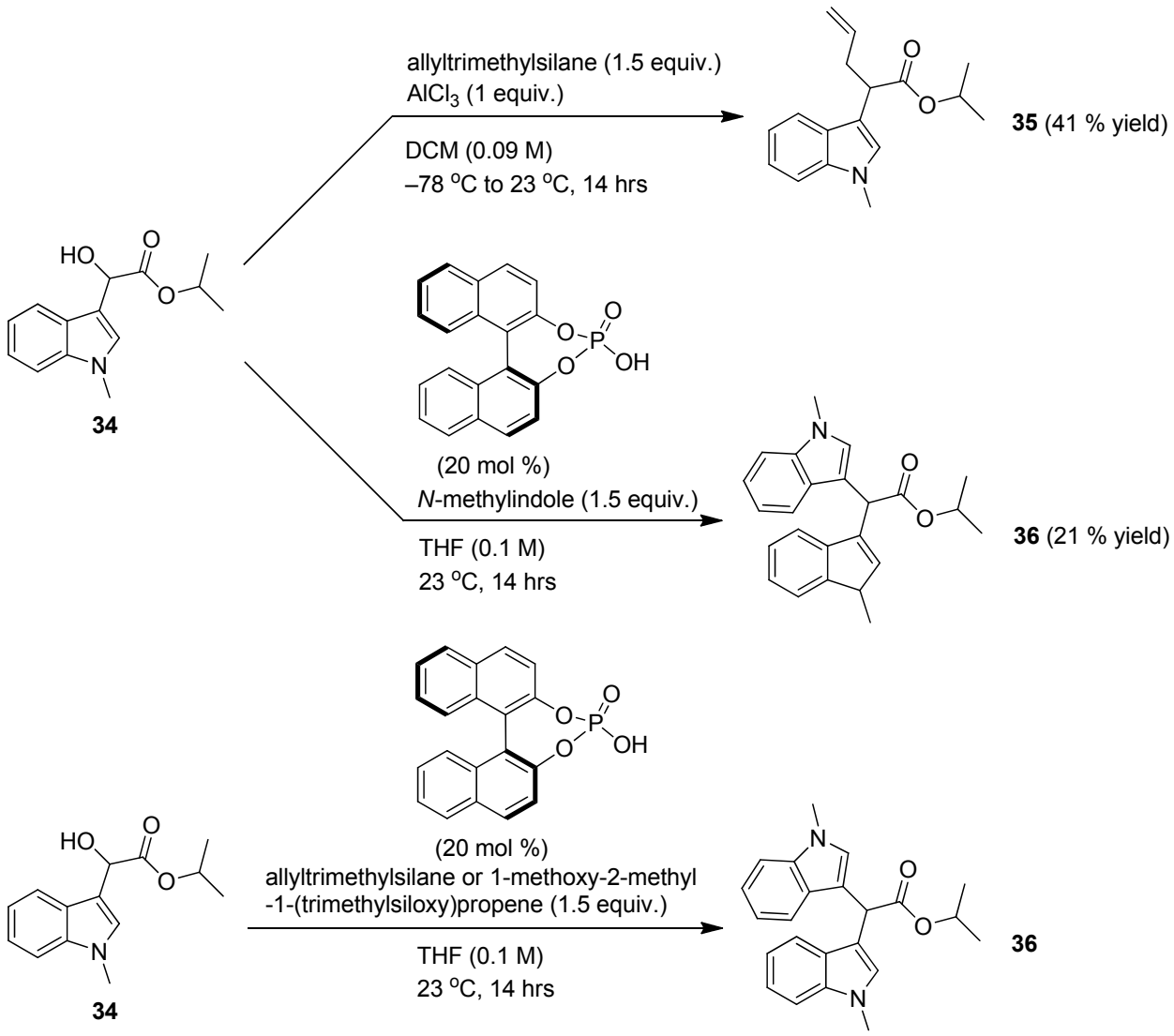
The α-hydroxy ester **34** was first synthesized in order to investigate Lewis acid and Brønsted acid-mediated nucleophilic substitution reactions of resonance-stabilized α-keto carbocation ester substrates (Scheme 2.2). The α-keto acid chloride **32** was formed by an acylation reaction between *N*-methylindole and oxalyl chloride. A second acylation reaction between the α-keto acid chloride **32** and isopropanol promoted by triethylamine gave the α-keto ester **33** in 96 % yield. The first attempt to reduce α-keto ester **33** to the corresponding α-hydroxy ester **34** using methanol as the solvent resulted in transesterification (6.3:1 ratio of isopropyl ester and methyl ester products). To avoid this problem, THF was used as the solvent and the desired α-hydroxy ester **34** product was obtained in 100 % yield. Attempts at synthesizing the corresponding α-tosyloxy ester using *p*-toluenesulfonyl chloride, triethylamine, and DMAP showed no product formation by GC-MS and crude ^{1}H-NMR analysis.

Scheme 2.2: Synthesis of α-hydroxy ester 34 and attempted tosylation



Because the α-tosyloxy ester could not be obtained, nucleophilic substitutions of α-hydroxy ester **34** were conducted (Scheme 2.3). A Lewis acid-mediated nucleophilic substitution reaction of α-hydroxy ester **34** using allyltrimethylsilane and aluminum trichloride gave the substitution product **35** in 41 % yield. The reaction was conducted in DCM from –78 ^{o}C to 23 ^{o}C over 14 hours. A Brønsted acid-mediated nucleophilic substitution reaction of α-hydroxy ester **34** using *N*-methylindole and 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate gave the substitution product **36** in 21 % yield. The reaction was conducted in THF at 23 ^{o}C for 14 hours. Corresponding reactions using the Brønsted acid 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate and the nucleophiles allyltrimethylsilane and 1-methoxy-2-methyl-1-(trimethylsiloxy)propene resulted in no desired product formation. Interestingly, analysis of the crude ^{1}H-NMR spectra and GC-MS spectra of both of these reactions showed formation of the *N*-methylindole substitution product **36**. This indicated that decomposition of a molecule of α-hydroxy ester **34** was yielding free *N*-methylindole which was then attacking another molecule of α-hydroxy ester **34** to form the corresponding *N*-methylindole substitution product **36**. These two reactions were carried out one month after the reactions indicated in Scheme 2.3 were conducted so the decomposition could have happened during the reaction or during the time the material was being stored at 4 ^{o}C.

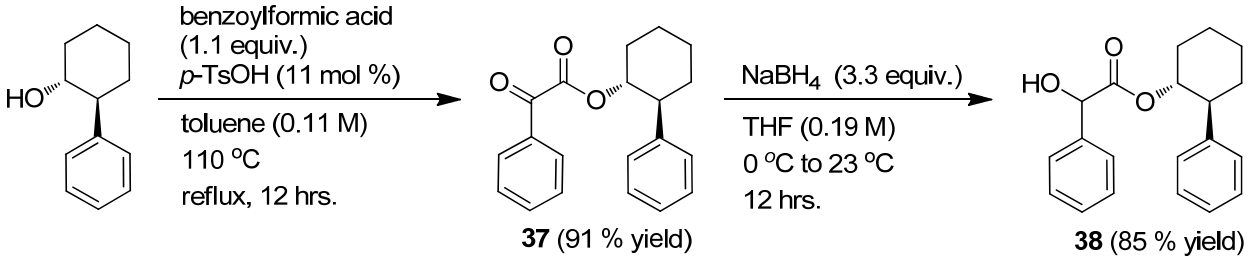
Scheme 2.3: Brønsted acid and Lewis acid-mediated nucleophilic substitution reactions of α-hydroxy ester 34



Next, diastereoselective Lewis acid-mediated nucleophilic substitution reactions of benzylic α-keto carbocation ester substrates were examined. Stereoselective induction at the benzylic α-keto position could be controlled using a chiral auxiliary. The aromatic group of the chiral auxiliary might shield one of the faces of the prostereogenic carbocation centre through an energetically favourable cation-quadrupole interaction. Favourable π-conjugation and potentially *n*-participation of the adjacent carbonyl group could also stabilize the intermediate carbocation. To investigate this method the racemic auxiliary 2-phenylcyclohexanol was first

synthesized from the corresponding cyclohexane epoxide and phenyl Grignard (synthesis of the auxiliary was done by Golam Sarwar). A review of cyclohexyl-based chiral auxiliaries has been previously published by Whitesell.[46] A Fischer esterification using 2-phenylcyclohexanol and benzoylformic acid afforded the α-keto ester **37** in 91 % yield (Scheme 2.4). Reduction using sodium borohydride and THF as the solvent then gave the α-hydroxy ester **38** in 85 % yield.

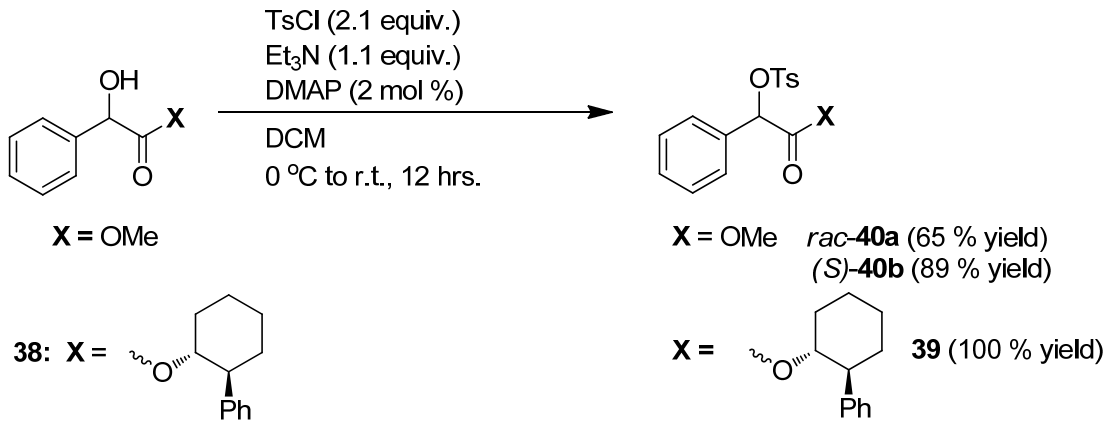
Scheme 2.4: Synthesis of α-hydroxy ester 38



*the racemic auxiliary 2-phenylcyclohexanol was prepared by Golam Sarwar

The α-hydroxy ester **38** was then converted to the corresponding α-tosyloxy ester **39** using *p*-toluenesulfonyl chloride, triethylamine, and DMAP (Scheme 2.5). Racemic and enantiopure methyl mandelate tosylate (*rac*-**40a** and *(S)*-**40b**) were also synthesized by this method using methyl DL-mandelate and (S)-(+)-methyl mandelate respectively.

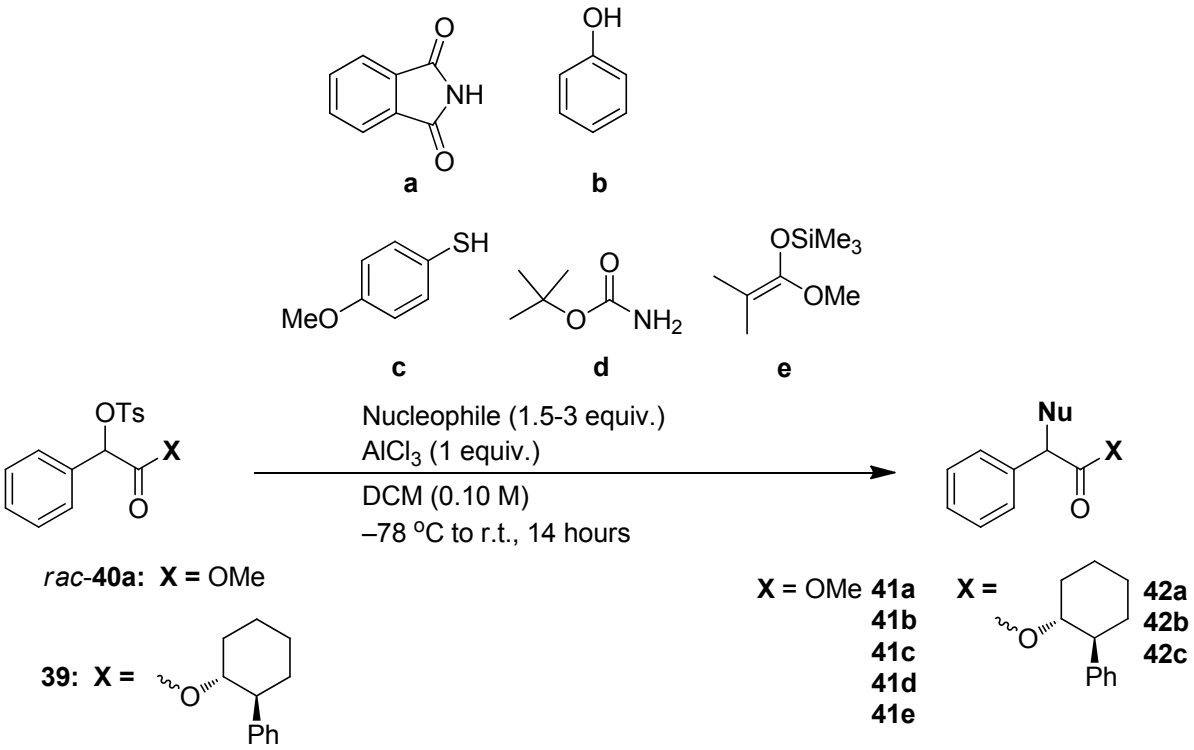
Scheme 2.5: Synthesis of α-tosyloxy esters 39, *rac*-40a, and *(S)*-40b



Lewis acid-mediated substitution reactions of α-tosyloxy esters **39** and *rac*-**40a** with various carbon and heteroatom nucleophilies was then investigated (Table 2.1). All nucleophilic substitution reactions were conducted in DCM (–78 °C to 23 °C over 14 hours), using aluminum trichloride as the Lewis acid. Nucleophilic substitutions were first evaluated using the racemic α-tosyloxy ester *rac*-**40a** substrate. Phthalimide, phenol, and 4-methoxybenzene thiol were found to result in product formation and were, therefore, tested for diastereoselectivity using the chiral α-tosyloxy ester **39**. The sulfur nucleophile 4-methoxybenzene thiol gave the highest diastereoselectivity (d.r. of 2.0:1), followed by the nitrogen nucleophile phthalimide (d.r. of 1.4:1), and then the aromatic carbon nucleophile phenol (d.r. of 1.1:1). A surprising result was that nucleophilic substitutions using the similar nitrogen nucleophiles phthalimide and *t*-butyl carbamate gave very different results using aluminum trichloride as the Lewis acid in DCM. Nucleophilic substitutions of α-tosyloxy ester *rac*-**40a** with phthalimide resulted in clean product formation, where as nucleophilic substitutions of α-tosyloxy ester *rac*-**40a** with *t*-butyl carbamate resulted in no product formation. Even when the more ionizing solvent nitromethane was utilized, nucleophilic substitution of α-tosyloxy ester *rac*-**40a** with *t*-butyl carbamate resulted in no product formation. When nitromethane was used as the solvent, the reaction was conducted at 23 °C because nitromethane has a melting point of –29 °C. Nucleophilic substitution reactions of α-tosyloxy esters **39** and *rac*-**40a** using allyltrimethylsilane were found to be possible as well (M. G. Sarwar, unpublished results). Interestingly the nucleophile 1-methoxy-2-methyl-1-(trimethylsiloxy)propene, which was indicated by Mayr's scale of nucleophilicity[47, 30, 31] to be

more nucleophilic than allyltrimethylsilane, resulted in no product formation with α-tosyloxy ester *rac*-**40a**. This could possibly be a result of a steric issue of the nucleophilic substition or an interfering interaction of the Lewis acid aluminum trichloride with the oxygen containing trimethylsiloxy group of 1-methoxy-2-methyl-1-(trimethylsiloxy)propene.

Table 2.1: Investigation of Lewis acid-mediated nucleophilic substition reactions of α-tosyloxy esters 39 and *rac*-40a

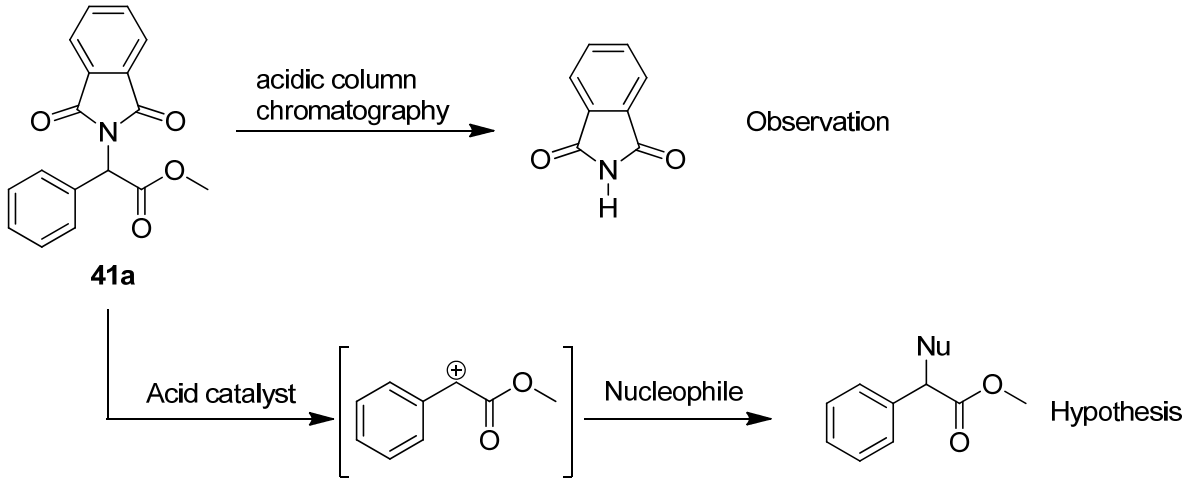


Starting Material	Product	Isolated Product Yield (%)	^{1}H-NMR d.r.
***rac*-40a**	**41a**	**	-
	41b	48	-
	41c	82	-
	41d	-	-
	41e	-	-
39	**42a**	51	1.4:1
	42b	20	1.1:1
	42c	77	2.0:1

**100 % conversion contaminated with 23 % phthalimide determined by ^{1}H-NMR

Interestingly, when column chromatography was attempted in order to purify the α-phthalimido ester **41a**, decomposition was observed and only phthalimide was isolated. Because silica gel is mildly acidic, it was hypothesized that it might be possible to use phthalimide as a leaving group under Brønsted acid conditions to generate α-keto carbocations (Scheme 2.6). It was possible, however, to purify the similar α-phthalimido ester **42a** using a small plug of silica gel (50 % isolated yield).

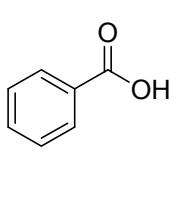
Scheme 2.6: Phthalimide as a possible leaving group

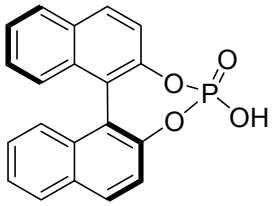


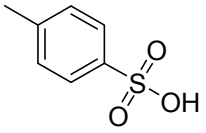
In order to test the hypothesis that phthalimide might act as a leaving group, Brønsted acids of varying acidities were evaluated for their potential to generate α-keto carbocations from α-phthalimido ester **41a** and then undergo S_N1 reactions using allyltrimethylsilane and *N*-methylindole (Table 2.2). The Brønsted acids evaluated were benzoic acid (pKa of 4.25[48]), 1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (pKa of ~1.3[49]), and *p*-toluenesulfonic acid (pKa of -1.0[50]). Using these Brønsted acids, allyltrimethylsilane was first evaluated as a nucleophile in solvents of varying polarity (DCM, nitromethane, and THF). The reactions were conducted at 23 ^{o}C for 24 hours. In all cases GC-MS and ^{1}H-NMR analysis indicated no desired product

formation. The reactions conducted in THF were then heated at 60 ^{o}C for an additional 24 hours, but again no desired product formation was observed. *N*-Methylindole was then evaluated as a nucleophile using the solvents DCE or dioxane, which allowed for higher reaction temperatures because of their high boiling points (83.5 ^{o}C and 101.1 ^{o}C respectively). Again in all cases GC-MS and ^{1}H-NMR showed no desired product formation. These results indicated that α-phthalimido ester **41a** was decomposing by a different mechanism than protonation when exposed to silica gel, and that nucleophilic substitution reactions were not possible under these conditions.

Table 2.2: Brønsted acid-catalyzed nucleophilic substitution reactions of compound 41a using phthalimide as a leaving group







pK_a: 4.25 ~1.3 -1.0

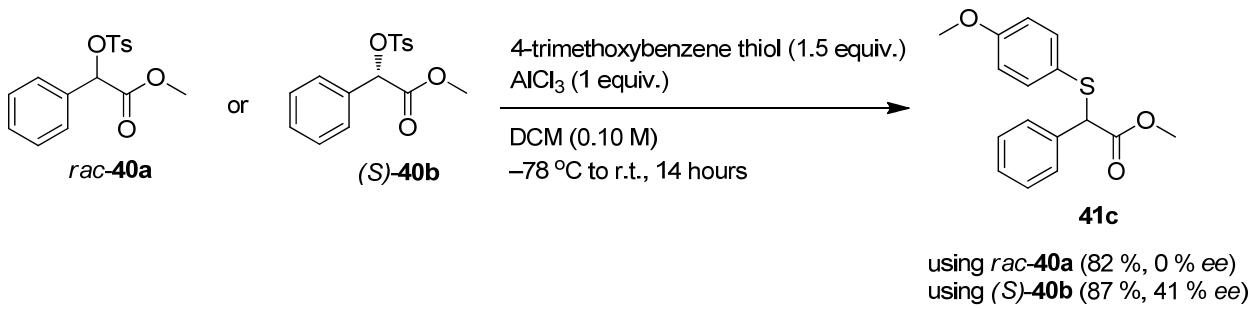
Nucleophile (5 equiv.)	Solvents tested	Reaction conditions	Result
Allyltrimethylsilane	DCM nitromethane THF	23 °C, 24 hrs. all solvents; then 60 °C, 24 hrs. (THF only)	GC-MS and ^{1}H-NMR show no products
N-methylindole	DCE Dioxane	23 °C, 24 hrs., then 70 °C	

*Brønsted acid catalysts (0.5 equiv.) tested were *p*-toluenesulfonic acid, benzoic acid, and 1,1′-binaphthyl-2,2′-diyl hydrogenphosphate

A mechanistic study was also undertaken to determine whether the nucleophile 4-methoxybenzene thiol was reacting with the α-tosyloxy ester substrates via an S_N1 or S_N2 pathway. To determine this, parallel nucleophilic substitution reactions using racemic methyl 2-phenyl-2-(tosyloxy)acetate (**40a**) and enantiopure (S)-methyl 2-phenyl-2-(tosyloxy)acetate (**40b**) (Scheme 2.7) were carried out. Analysis of the enantiomeric products **41c** by chiral HPLC showed 0 % *ee* for the reaction using racemic methyl 2-phenyl-2-(tosyloxy)acetate (**40a**) and 41 % *ee* for the reaction using enantiopure (S)-methyl 2-phenyl-2-(tosyloxy)acetate (**40b**). If the

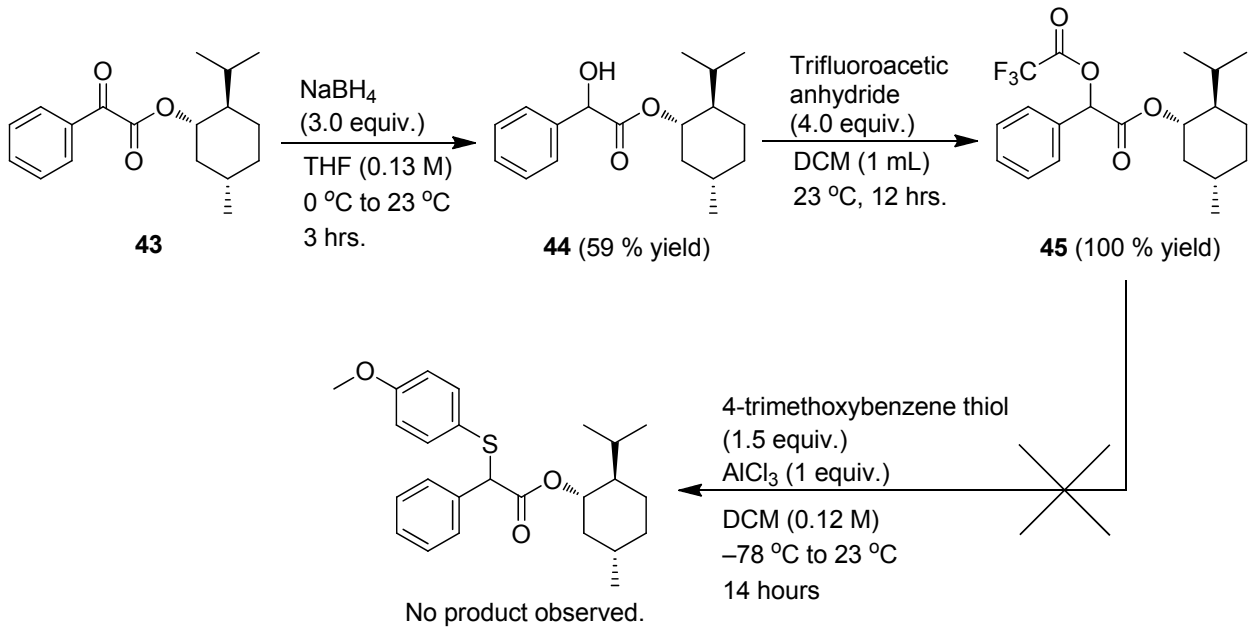
reaction was proceeding by a purely S_N2 like mechanism, inversion of stereochemistry would occur and only one product enantiomer (100 % *ee*) should be observed when using (S)-methyl 2-phenyl-2-(tosyloxy)acetate (**40b**). Therefore, the formation of the product **10c** in 41 % *ee* using enantiopure (S)-methyl 2-phenyl-2-(tosyloxy)acetate (**40b**) indicates that a purely S_N2 mechanism is not occurring and instead a carbocation intermediate is being generated, which is consistent with a S_N1 mechanism. If the reaction was proceeding by a purely S_N1 pathway, where a planar carbocation intermediate was being generated the product should exhibit 0 % *ee* regardless if the starting material is racemic or enantiopure. Therefore, formation of the product **41c** in 41 % *ee* using (S)-methyl 2-phenyl-2-(tosyloxy)acetate (**40b**) indicates that the reaction is proceeding via a pathway that has both S_N1 and S_N2 character. A possible explanation is the S_N2 (intermediate) mechanism, which has been previously mentioned by Schleyer and Bentley.[27] The intermediate carbocation was proposed by Schleyer and Bentley to exist as an ion pair that is nucleophilically solvated, where the transition state leading to the intermediate is nucleophically solvated as well. Another explanation for the formation of product **41c** in 41 % *ee* is that the carbocation intermediate might possibly be stabilized through *n*-participation (see Scheme 1.12).[45] If this was the case, preferential attack of the nucleophile from one side of the partially formed oxiranyl type ion might occur. Nucleophilic substitution reactions of enantioenriched α-tosyloxy esters using allyltrimethylsilane were previously found to react by a purely S_N1 pathway under the same reaction conditions (M. G. Sarwar, unpublished results). In this case the formation of racemic product through non-biased nucleophilic substitution might be explained by stabilization of the intermediate prostereogenic carbocation through π-conjugation of the adjacent carbonyl in addition to the resonance stabilization gained from the aromatic ring.

Scheme 2.7: Mechanistic study of nucleophilic substitution reactions of α-tosyloxy esters *rac*-40a and *(S)*-40b using 4-methoxybenzene thiol



The effect of changing the α-keto leaving group from a tosylate group to a trifluoroacetate group in Lewis acid mediated nuclephilic substitution reactions was also investigated (Scheme 2.8). To do this, the chiral α-keto ester **43** was first synthesized by esterification of benzoylformic acid and menthol using a catalytic amount of *p*-toluenesulfonic acid. Sodium borohydride reduction using THF as the solvent next afforded the corresponding α-hydroxy ester **44**. The α-trifluoroacetoxy ester **45** was obtained using trifluoroacetic anhydride. A nucleophilic substitution reaction of α-trifluoroacetoxy ester **45** using 4-methoxybenzene thiol was then conducted using the same reaction conditions (aluminum trichloride as the Lewis acid) as was employed with the other α-tosyloxy esters previously investigated. Analysis of the crude ^{1}H-NMR showed no product formation, therefore, indicating that a tosylate leaving group is better suited than a trifluoroacetate leaving group for this reaction system.

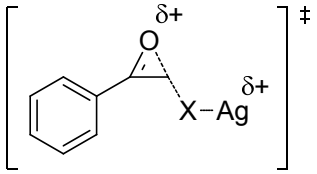
Scheme 2.8: Synthesis of α-trifluoracetoxy ester 45 and attempted nucleophilic substitution reaction using 4-methoxybenzene thiol



*α-keto ester **43** was prepared by Golam Sarwar

Generation of α-keto carbocations from α-bromo esters mediated by cationic silver followed by nucleophilic substitution was then investigated. Previous solvolysis rate studies conducted by Pasto and Serv[51] indicated that silver assisted *n*-participation might have been occurring based evaluation of observed and expected entropies of activation (Figure 2.1). Stabilization by π-conjugation has also been proposed to be important in these systems.[52]

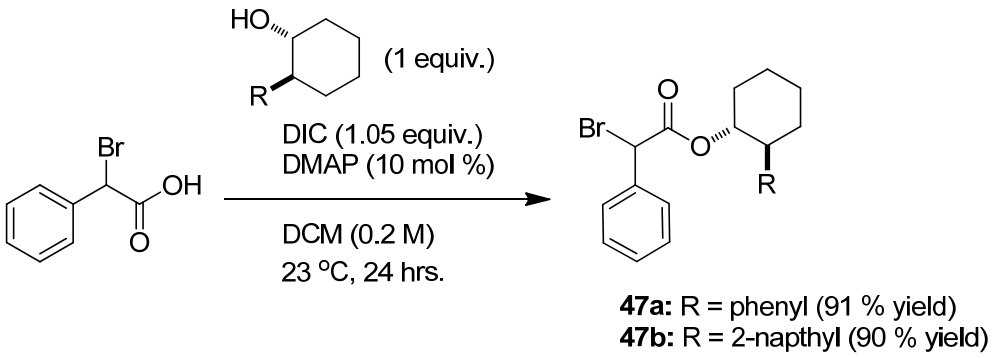
Figure 2.1: Silver-assisted *n*-participation[51]



X = Cl, Br **46**

In order to evaluate the facial selectivity of nucleophilic additions to benzylic α-keto carbocations generated by the precipitation of silver bromide, the 2-bromo-2-phenyl chiral esters **47a** and **47b** were synthesized using a DIC coupling of α-bromophenylacetic acid and the respective chiral alcohol (Scheme 2.9).

Scheme 2.9: Synthesis of α-bromo esters 47a and 47b

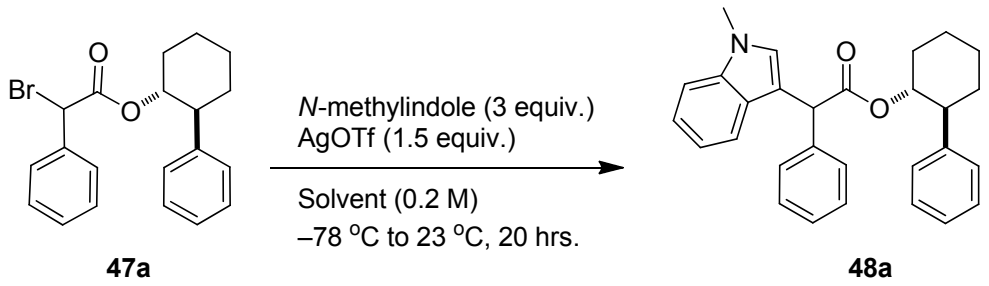


* The racemic auxiliaries' 2-phenylcyclohexanol and 2-(1-naphthalenyl) cyclohexanol were synthesized from the corresponding cyclohexane epoxide and either phenyl Grignard or 2-naphthalenyl Grignard courtesy of Golam Sarwar.

Intially various nucleophiles were evaluated for reactivity in S_N1 reactions of benzylic α-bromo ester **47a**. The nucleophiles *N*-methylindole and 1,3,5-trimethoxybenzene were found to have reactivity in this system, whereas the nucleophiles allyltrimethylsilane and 1-methoxy-2-methyl-1-(trimethylsiloxy)propene were not. Initial experiments indicated that *N*-methylindole was giving slightly higher diastereoselectivities than was 1,3,5-trimethoxybenzene, therefore, optimization of the reaction conditions was conducted using *N*-methylindole. A solvent screen was conducted using α-bromo ester **47a** and silver trifluoromethanesulfonate as the halogen abstractor (Table 2.3). Silver trifluoromethanesulfonate was found to be reactive when the reaction was conducted from –78 °C to 23 °C. Product formation (**47a**) was observed using all the solvents tested with d.r.'s ranging from 1.6:1 in chloroform, to 2.6:1 in ether. GC-MS d.r.'s were found to be higher than those obtained via ^{1}H-NMR and were analyzed as being less accurate due to low signal-to-noise ratios. Using ether as the solvent gave a d.r. of 2.6:1 with a

product yield of 30 %. The low yield of this reaction could possibly have been a result of selective decomposition of one diastereomer over the other one, thus, giving an apparent higher d.r. in comparison to the other solvents used. DCM as the solvent gave the second highest d.r. (2.3:1), with a product yield of 71 %, which was less indicative of selective decomposition of one of the diastereomers than was the experimental result obtained in ether.

Table 2.3: Initial solvent screening for silver trifluoromethanesulfonate-mediated nucleophilic substitution reactions of α-bromo ester 47a using *N*-methylindole



47a **48a**

Solvent	^{1}H-NMR yield (%) *	^{1}H-NMR d.r. **	GC-MS d.r. ***
THF	93	1.8:1	-
Ether	30	2.6:1	-
Acetonitrile	79	1.7:1	2.1:1
Nitromethane	62	2.2:1	2.5:1
Toluene	85	1.9:1	2.7:1
DCM	71	2.3:1	2.7:1
Chloroform	58	1.6:1	2:1
Pentane	70	1.9:1	2.5:1

* 1,3,5-trimethoxybenzene (0.033 mmol) was used as the ^{1}H-NMR internal standard to determined the combined percent yield of both diastereomers; ** ^{1}H-NMR d.r. was determined by integrating the CH_3NC**H** signals of the diastereomers at 6.64 ppm (major) & 6.35 ppm (minor) respectively; *** GC-MS d.r. was determined by integrating the mass spectra of the respective diastereomers

Various silver salts were also tested in order to determine which ones would give higher d.r.'s in nucleophilic substitution reactions of *N*-methylindole with the α-bromo ester **47a** substrate (Table 2.4). It was found that silver hexafluorophosphate and silver methanesulfonate were reactive when reactions were conducted from –78 ^{o}C to 23 ^{o}C. Higher temperatures (70 ^{o}C) were needed when silver *p*-toluenesulfonate, silver acetate, and silver carbonate were used as the halide abstractors. Silver hexafluorophosphate was screened in various different solvents to investigate whether the presence of the large less coordinating hexafluophosphate anion would result in increased diastereoselectivity. It was hoped that the hexafluorophosphate anion would stabilize the carbocation being formed upon precipitation of silver bromide and, therefore, lead to increased facial selectivity. Results obtained in the solvents DCM, ether, and THF with silver hexafluorophosphate indicated increased yields with decreased diastereoselectivities when compared with the results obtained with silver trifluoromethanesulfonate. This could possibly be indicative of selective decomposition of one diastereomer over the other one. When toluene was used as the solvent a small decrease in yield and diastereoselectivity was observed with silver hexafluorophosphate relative to silver trifluoromethanesulfonate. These similar results indicated that a stabilizing cation-quadrupole interaction of cationic silver with the aromatic solvent might have been occurring, in which case, the counter ion of the silver salt may not influence the results as much. The experiment conducted with silver mesylate in ether resulted in a similar yield to that obtained with silver hexafluorophosphate with a small decrease in diastereoselectivity. From the silver salt screening, the highest diastereoselectivity was obtained with silver *p*-toluenesulfonate in DCE at 70 ^{o}C resulting in a d.r. of 2.1:1 with a yield of 96 %. The nucleophile 1,3,5-trimethoxybenzene was also tested using silver *p*-toluenesulfonate in DCE at 70 ^{o}C, but a lower d.r. of 1.5:1 was obtained.

Table 2.4: Silver salt screening for nucleophilic substitution reactions of α-bromo ester 47a using *N*-methylindole

Silver Salt	Solvent	Reaction Conditions	^{1}H-NMR yield (%)	^{1}H-NMR d.r.	GC-MS d.r.
$AgPF_6$	DCM	–78 ^oC to	88	1.8:1	2.5:1
	Ether	23 ^oC *	71	1.8:1	2.6:1
	THF		99	1.7:1	2:1
	Toluene		78	1.8:1	2.4:1
AgMs	Ether		69	1.4:1	1.6:1
AgOTs	DCE	70 ^oC *	96	2.1:1	2.6:1
AgOAc	DCE	23 ^oC then	64	1.2:1	1.4:1
Ag_2CO_3	DCE	70 ^oC **	53	1.2:1	-

* reaction times were 20 hours; ** reaction was stirred at 23 ^oC for 24 hours and then 70 ^oC for 20 hours

Results from the solvent screening (Table 2.3) and silver salt screening experiments (Table 2.4) indicated that the solvents DCM, ether, and DCE along with the halide abstractors silver trifluoromethanesulfonate and silver *p*-toluenesulfonate were giving the highest diastereoselectivities. Various additives were experimented with to try and improve on the observed diastereoselectivities with α-bromo ester **47a** (Table 2.5). An experiment was conducted using the sterically hindered base 2,6-lutidine, which would presumably form an ion pair with the acid generated upon Friedel–Crafts reaction. The reaction was conducted in ether using silver trifluoromethanesulfonate as the halide abstractor. Analysis showed an increase in yield from 30 % to 86 % when 2,6-lutidine was added to the reaction mixture. Conversely, the diastereoselectivity also decreased from 2.6:1 to 2.0:1 upon the observed yield increase. This is indicative that the generated triflic acid from the silver salt may have been causing selective

product degredation, thereby, resulting in a higher observed diastereoselectivity. Next a reaction was conducted under dynamic kinetic resolution conditions using tetrabutyl ammonium iodide, where by the iodine epimerizes the starting material converting the slower reacting diastereomer into the faster reacting diastereomer over the course of the reaction. Asymmetric S_N2 reactions using amine nucleophiles and chiral α-halo esters and α-halo amides under dynamic kinetic resolution conditions have been previously investigated by the research groups of Durst[53], Park[54], and Nunami.[55] Although *N*-methylindole is a softer nucleophile than the amine nucleophiles used by previous groups in dynamic kinetic resolutions, it was thought that increased diastereoselectivity might still be seen due to the ionizability of the bromine at the benzylic α-keto position. Results of this experiment actually showed decreased diastereoselectivity as well as yield, thus indicating that an S_N2 mechanism was not occuring. This result is consistent with the formation of a carbocation intermediate as is seen in a S_N1 reaction and not an S_N2 reaction. The influence of adding various Lewis acids was also investigated with the hopes that coordination would increase the electronic interactions of the aromatic group of the auxiliary with the carbocation intermediate and lead to greater facial selectivity. Previously, additions of Lewis acids in Grignard additions to α-keto carbonyls where 8-phenylmenthol was used chiral auxiliary had showed substantial HOMO-LUMO interaction when studied using fluorescence.[56] Although a slight increase in diastereoselectivity was observed with magnesium (II) triflate, results indicated that increased facial selectivity with the addition of Lewis acids was not occurring. This could be indicative of decreased π-conjugation stabilization of the α-keto carbocation intermediate due to the influence of the Lewis acid.

Table 2.5: Analysis of Lewis acid, Brønsted base, and dynamic kinetic resolution conditions on nucleophilic substitution reactions of α-bromo ester 47a using *N*-methylindole

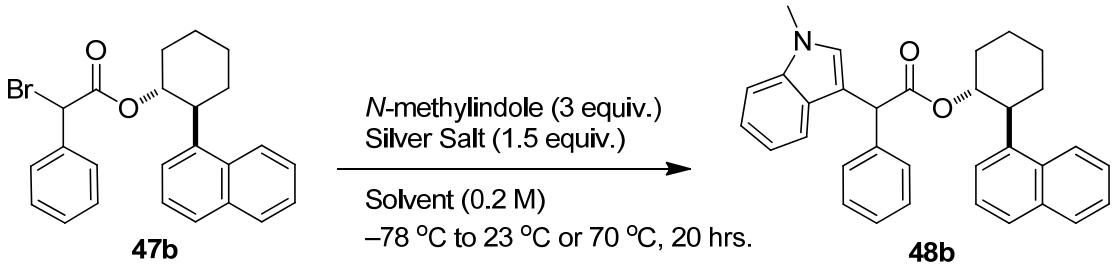
Silver Salt	Solvent	Reaction Conditions *	Additive	^{1}H-NMR yield (%)	^{1}H-NMR d.r.	GC-MS d.r.
AgOTf	Ether	–78 ^{o}C to	-	30	2.6:1	-
		23 ^{o}C	2,6-lutidine	86	2.0:1	2.8:1
AgOTf	DCM	–78 ^{o}C to	-	71	2.3:1	2.7:1
		23 ^{o}C	^{t}BuN$^+$I$^-$	43	1.3:1	1.3:1
AgOTs	DCE	70 ^{o}C	-	96	2.1:1	2.6:1
			$Sc(OTf)_3$	95	1.8:1	2.5:1
			$Zn(OTf)_2$	65	2.1:1	2.8:1
			$Mg(OTf)_2$	73	2.3:1	2.1:1

* reaction times were 20 hours

Next the α-bromo ester **47b** containing the bulkier 2-(1-naphthalenyl) cyclohexanol auxiliary was experimented with (Table 2.6). It was thought that increased face shielding of the α-keto carbocation intermediate due to an energetically favourable cation-quadrupole interaction would occur because of the increased size of the aromatic group. The reaction conducted in ether using silver trifluoromethanesulfonate indicated an increased yield but also a decreased diastereoselectivity when compared to the reaction conducted under the same conditions with the α-bromo ester **47a** containing the chiral auxiliary 2-phenylcyclohexanol. When DCM was used as the solvent a similar yield as that obtained with the α-bromo ester **47a** was seen but with a

lower diastereoselectivity. A reaction conducted in DCE at 70 °C using silver *p*-toluenesulfonate gave a high yield with again low diastereoselectivity. Addition of the sterically hindered base 2,6-lutidine only slightly improved the diastereoselectivity. The 2-phenylcyclohexanol auxiliary resulted in better diastereoselectivities than the bulkier 2-(1-naphthalenyl) cyclohexanol auxiliary, which is unexpected and difficult to interpret.

Table 2.6: Analysis of silver-mediated nucleophilic substitution reactions of α-bromo ester 47b containing a bulkier 2-(1-naphthalenyl) cyclohexanol auxiliary using *N*-methylindole



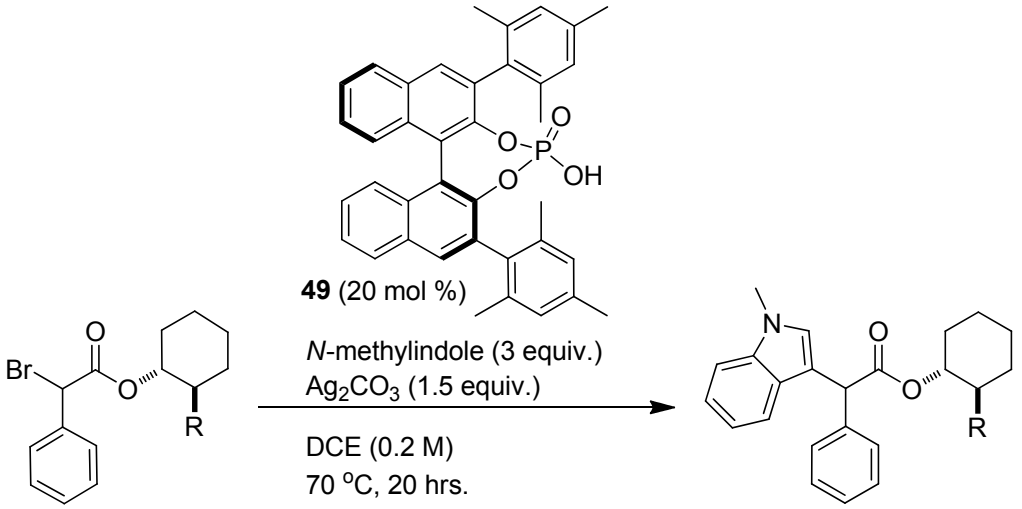
Silver Salt	Solvent	Reaction Conditions*	Additive	^{1}H-NMR yield (%)	^{1}H-NMR d.r.**
AgOTf	Ether	–78 °C to	-	79	1.1:1
	DCM	23 °C	-	77	1.4:1
AgOTs	DCE	70 °C	-	94	1.1:1
			2,6-lutidine	95	1.2:1

* reaction times were 20 hours; ** ^{1}H-NMR d.r. was determined by integrating the $CH_3NC\mathbf{H}$ signals of the diastereomers at, 6.43 ppm (major) and 6.19 ppm (minor) respectively

Toste and coworkers[57] have previously reported the use of an axially chiral phosphate anion for asymmetric ring opening of *meso*-aziridinium ions. The chiral phosphate anion was reported to

first act as a phase transfer catalyst for the silver (I) cation due to its high solubility in organic solvents and then subsequently form a chiral ion pair with the organic substrate upon halide abstraction. Nucleophilic addition of various alcohols to the carbocation intermediate directed by the chiral counteranion then occured in an enantioselective manner. Since the axially chiral phosphate anion was acting as a phase transfer catalyst, interference of the achiral counteranion from the silver (I) source with the cationic organic substrate was avoided. Interference of the achiral counteranion would have the potential to lead to racemic product. Spurred by this report by Toste and coworkers it was thought to apply this type of chiral counteranion mediated nucleophilic addition reaction to the benzylic α-bromo ester substrate systems using the axially chiral phosphate counterion **49** which had been previously synthesized in our lab (Table 2.7). Silver carbonate had been found by Toste and coworkers to be the best silver salt for their nucleophilic additions so it was decided to use silver carbonate in our system. More soluble silver salts such as silver *p*-toluenesulfonate had been found to give decreased selectivity. Analysis of this reaction system using *N*-methylindole as the nucleophile showed excellent formation of the products **48a** and **48b** respectively. ^{1}H-NMR yield and isolated yields showed accurate correlation. Use of the axially chiral phosphate anion with the phenyl-cylcohexanol derived substrate **47a** showed increased yield and diastereoselectivity (2.0:1 vs. 1.2:1) when compared to the reaction conducted without the chiral counter anion (Table 2.4). When the 2-naphthyl derived substrate **47b** was used with the axially chiral phosphate anion a lower diastereoselectivity was obtained. This again implied that a bulkier aromatic auxiliary does not lead to increased selectivity.

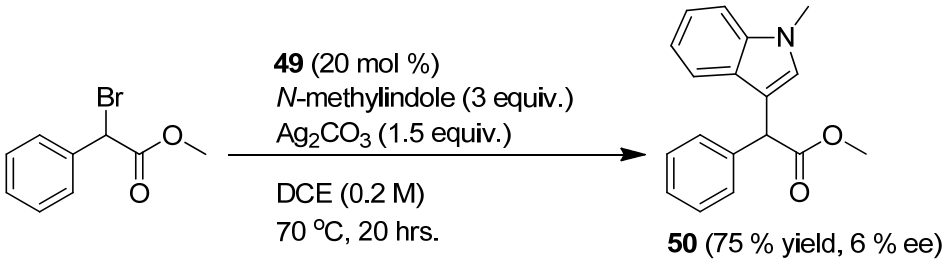
Table 2.7: Analysis of silver-mediated nucleophilic substitution reactions of α-bromo esters 47a and 47b utilizing an axially chiral phosphate counterion 49



Product	^{1}H-NMR d.r.	GC-MS d.r.	^{1}H-NMR yield (%)	Isolated Product Yield (%)
48a	2.0:1	2.7:1	96	95
48b	1.4:1	-	97	98

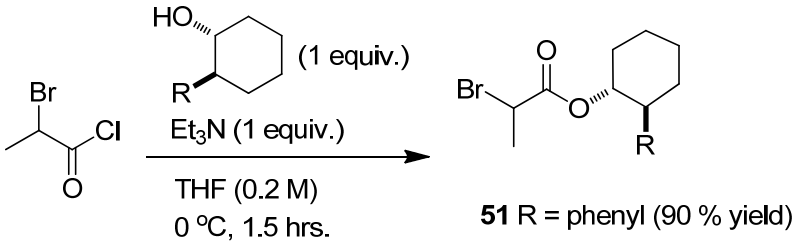
It was then thought to apply the use of the axially chiral phosphate counteranion **49** to a system not containing a chiral auxiliary. Double asymmetric induction was occurring in the systems using **47a** and **47b** (Table 2.7) where the competing souces of chiral information, chiral phosphate counteranion **49** and the repective chiral auxiliaries, might have been interfering with the selectivity. Using the axially chiral phosphate counteranion with racemic α-bromophenyl acetate under the same conditions, the *N*-methylindole substitution product was obtained in 75 % yield and 6 % *ee* (Scheme 2.10). The use of different chiral counteranions and different reaction conditions may increase the selectivity to practical levels.

Scheme 2.10: Analysis of enantioselectivity in a silver-mediated nucleophilic substitution reaction of α-bromophenyl acetate utilizing an axially chiral phosphate counterion 49



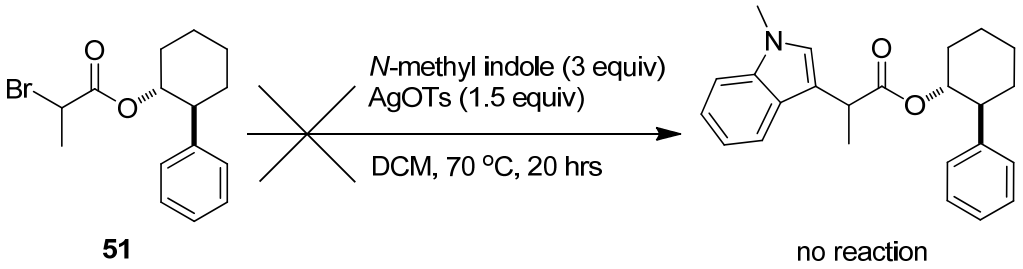
For the analysis of substituent effects at the α-keto position with silver mediated nucleophilic substitution reactions, the 2-bromo-2-methyl ester **51** was synthesized from commercially available 2-bromopropionyl chloride and the corresponding chiral alcohol (Scheme 2.11).[53]

Scheme 2.11: Synthesis of α-bromo ester 51



Nucleophilic substitution of the less sterically hindered and less ionizable 2-bromo-2-methyl ester **51** with *N*-methylindole was then attempted (Scheme 2.12). ^{1}H-NMR analysis of the crude reaction mixture showed no product formation and only recovery of the starting material. The elimination product was not observed. This result can be rationalized by the fact that the ionizability of the bromine is reduced due to the lack of an adjacent phenyl substituent.

Scheme 2.12: Attempted silver *p*-toluenesulfonate-mediated nucleophilic substitution reaction of α-bromo ester 51 using *N*-methylindole

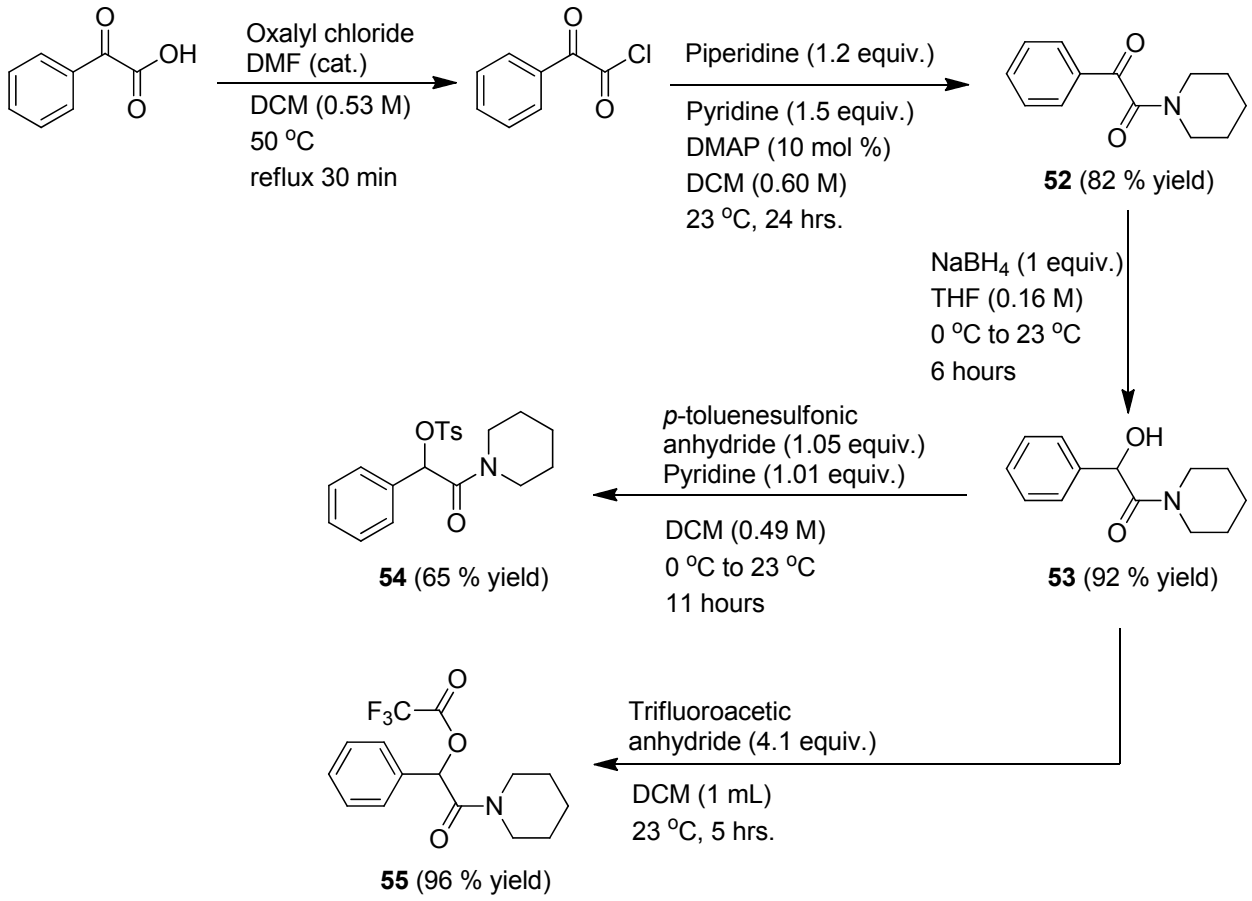


51 no reaction

2.2 Amide substrates

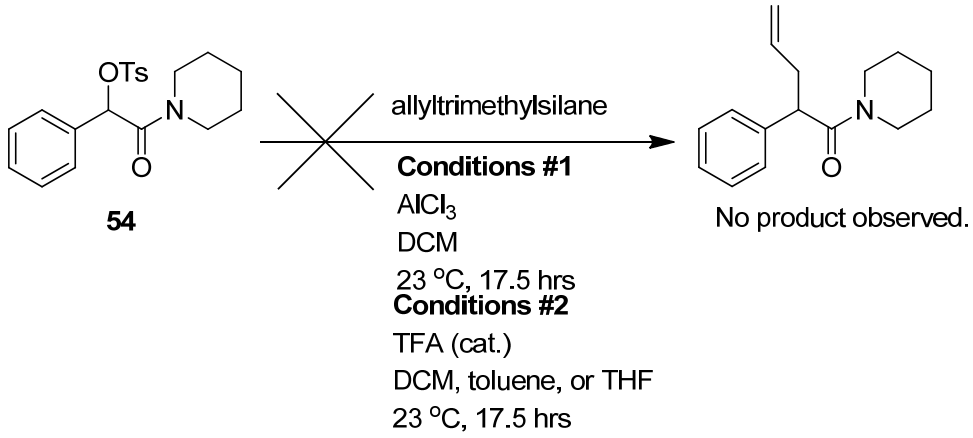
Next, Lewis acid and Brønsted acid-mediated nucleophilic substitution reactions of benzylic α-keto carbocation amide substrates were investigated. The α-tosyloxy amide substrate **54** and α-trifluoroacetate amide **55** served as model substrates for this study (Scheme 2.13). The α-keto amide **52** was first synthesized by conversion of benzoylformic acid to the corresponding acid chloride using oxalyl chloride followed by a subsequent acylation reaction using piperidine. Reduction using sodium borohydride in THF cleanly gave the α-hydroxy amide **53** in 92 % yield. A first attempt at synthesizing α-tosyloxy amide **54** using *p*-toluenesulfonyl chloride, triethylamine, and DMAP showed no product formation. Tosylation using *p*-toluenesulfonyl chloride, *N*-methylimidazole, and triethylamine was then examined but also did not show product formation. Lastly, using the conditions *p*-toluenesulfonic anhydride, and pyridine the α-tosyloxy amide **54** was obtained in 65 % yield. This method had been previously reported by Wessig and coworkers[58] to work in the tosylation of various α-hydroxy ketone substrates. Wessig and coworkers also found that tosylation reactions of α-hydroxy ketones using *p*-toluenesulfonyl chloride led to products that were contaminated with the corresponding α-chloro ketones. Analysis of the crude ^{1}H-NMR of α-tosyloxy amide **54** did not indicate formation of the corresponding α-chloro amide; only unreacted α-hydroxy amide **53** was observed. The corresponding α-trifluoroacetoxy amide **55** was synthesized using trifluoroacetic anhydride.

Scheme 2.13: Synthesis of α-tosyloxy amide 54 and α-trifluoroacetoxy amide 55



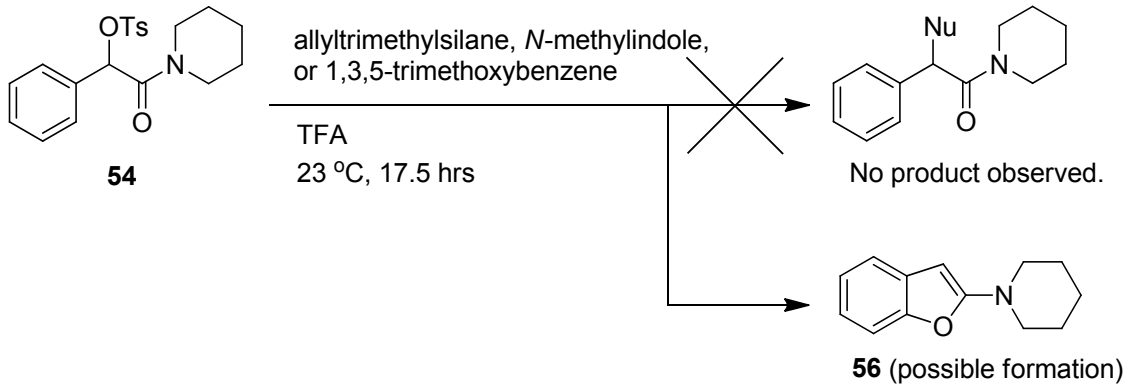
Unlike the ester substrates tested, aluminum trichloride mediated nucleophilic substitution reactions of α-tosyloxyamide **54** using allyltrimethylsilane resulted in no product formation and only clean unreacted starting material was observed by crude ^{1}H-NMR analysis (Scheme 2.14). This might be a result of the increased steric demand of the amide substrate, where restricted rotation of the (CO)–N bond makes it is harder for the Lewis acid to coordinate to the tosylate leaving group. Brønsted acid conditions were then examined using α-tosyloxyamide substrate **54**. Turnbull and coworkers[59] had previously reported that a catalytic amount of trifluoroacetic acid at 25 °C could induce the formation of benzylic α-amido carbocations through the rearrangement of *O*-aryl ethers into *ortho*-hydroxyaryl systems. This rearrangement was indicated to go through a dissociative S_N1 type mechanism. Nucleophilic substitution reactions of α-tosyloxyamide **54** using allyltrimethylsilane showed no product formation when catalytic amounts of trifluoroactic acid in DCM, toluene, or THF were used.

Scheme 2.14: Attempted Lewis acid and Brønsted acid-mediated nucleophilic substitution reactions of α-tosyloxy amide 54



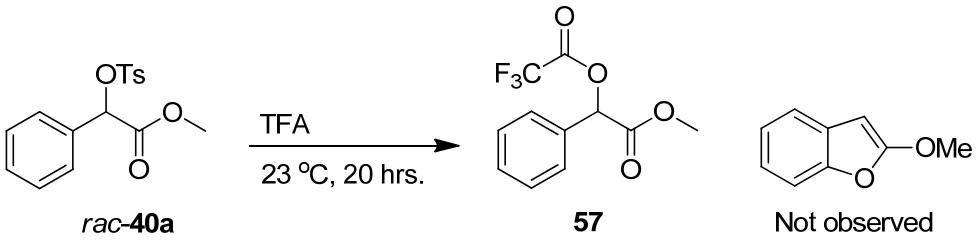
With no product formation observed using a catalytic amount of trifluoroacetic acid, nucleophilic substitution reactions using trifluoroacetic acid as the reaction solvent were then attempted (Scheme 2.15). Nucleophilic substitutions of α-tosyloxy amide **54** using allyltrimethylsilane, *N*-methylindole, and 1,3,5-trimethoxybenzene were attempted by this method, but no desired substitution products were observed. The possible formation of the benzofuran product **56** was indicated by GC-MS and ^{1}H-NMR analysis. The benzofuran product **56** was also indicated when the α-hydroxy amide **53** was treated with excess trifluoroacetic acid. The methine ^{1}H-NMR signal of the observed benzofuran product **56** had a similar chemical shift compared to that of a previously reported 3-(benzofuran-2-yl)oxazolidin-2-one compound.[60] Column chromatography of the benzofuran product **56** was found to be difficult due to decomposition and only a very small impure amount was isolated.

Scheme 2.15: Possible formation of benzofuran product 56



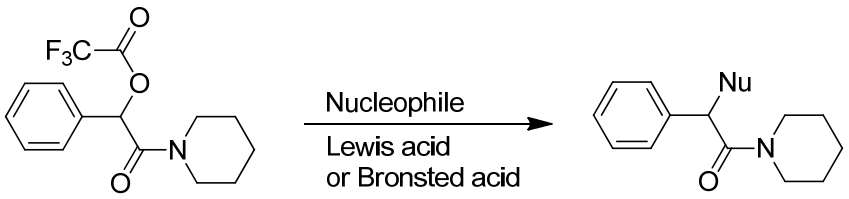
In order to identify reactivity differences between amide and ester substrates, the α-tosyloxy ester *rac*-**40a** was reacted under the same acidic conditions as α-tosyloxy amide **54** (Scheme 2.16). Unlike the amide substrate, where cyclization to form a substituted benzofuran product was observed, α-tosyloxy ester *rac*-**40a** was found to undergo nucleophilic substitution to form the corresponding, α-trifluoroacetatoxy ester as determined by GC-MS, ^{1}H-NMR, and ^{19}F-NMR analysis. The propensity for the amide substrate to undergo cyclization instead of nucleophilic substitution under acidic solvolytic conditions might be a result of the steric differences between esters and amides. It could also indicate that stabilization of an intermediate α-keto carbocation is more preferable with an ester substrate.

Scheme 2.16: Observed displacement of tosylate by trifluoroacetate in α-tosyloxy ester *rac*-40a



Nucleophilic substitutions of α-trifluoroacetoxy amide **55** were also attempted under Lewis acid and Brønsted acid-mediated conditions (Table 2.8). Aluminum trichloride-mediated nucleophilic substitution using allyltrimethylsilane indicated no product formation when conducted in DCM from –78 ^{o}C to 23 ^{o}C. The reaction was then evaluated at higher temperatures (70 ^{o}C) in DCE and the Lewis acids aluminum trichloride, scandium (III) triflate, and zinc (II) bromide were screened. In all cases no desired product formation was observed, but in the reaction where zinc (II) bromide was used as the Lewis acid conversion to the corresponding α-hydroxyamide **53** was seen by ^{1}H-NMR analysis. Brønsted acid conditions were then tested using 1,1'-binaphthyl-2,2'-diyl hydrogenphosphate in THF at 23 ^{o}C. No product formation was observed under these conditions as well. The nucleophile 1,3,5-trimethoxybenzene was then tested in DCE at 60 ^{o}C using scandium (III) triflate as the Lewis acid, but no product formation was observed. Conducting this reaction in the polar solvent nitromethane at 23 ^{o}C and subsequently 40 ^{o}C using scandium (III) triflate did not show desired product formation, but instead hydrolysis to the α-hydroxyamide **53** was observed. These results indicate that the generation of a α-keto carbocation from a α-trifluoroacetoxy amide is difficult both under Lewis acid and Brønsted acid conditions. Similarily, α-trifluoroacetoxy ester **45** (Scheme 2.8) was found to not undergo nucleophilic substitution under the evaluated Lewis acid conditions. Table 2.8 indicates that if a small amount of water was present in the reaction there was a preference for formation of the α-hydroxy amide instead of desired nucleophilic substitution product.

Table 2.8: Attempted nucleophilic substitution reactions of α-trifluoroacetoxy amide 55



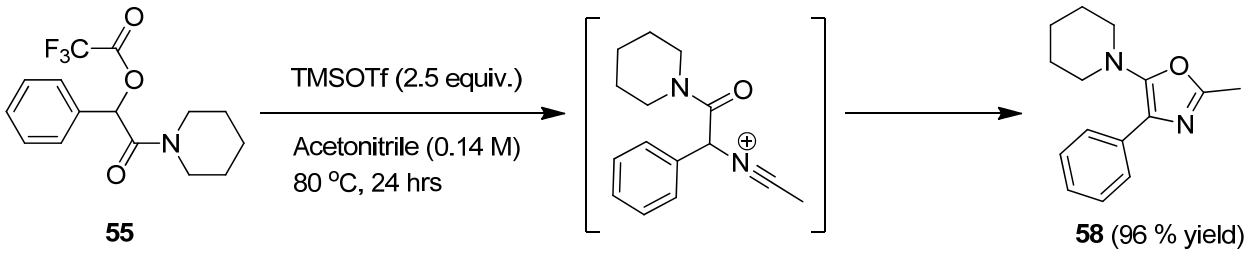
55

Nucleophile	Acid catalyst	Solvent	Reaction time and temp.	Results
Allyltrimethylsilane	$AlCl_3$	DCM	–78 °C to 23 °C, 13 hrs.	Stm only except for $ZnBr_2$ where stm and hydrolsis (~1:2.4) were found
	$AlCl_3$, $Sc(OTf)_3$, or $ZnBr_2$	DCE	60 °C, 13 hrs.	
	1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate	THF	23 °C, 13 hrs.	
1-Methoxy-2-methyl-1-(trimethylsiloxy)propene	$Sc(OTf)_3$	DCE	60 °C, 18 hrs.	Hydrolysis
	$Sc(OTf)_3$	Nitromethane	23 °C, 19 hrs. then 40 °C, 24 hrs.	

It was discovered that cyclization of α-trifluoroacetoxy amide **55** was possible under solvolytic conditions. If the α-trifluoroacetoxy amide **55** was treated with the Lewis acid trimethylsilyl trifluoromethanesulfonate (TMSOTF) using acetonitrile as the solvent at 80 °C, formation of the corresponding oxazole product **58** was observed (Scheme 2.17). This transformation presumably occured by a Ritter reaction to give a nitrilium intermediate, which then under went a cyclization

resulting in the formation of the oxazole product.[61] The oxazole product was not stable to column chromatography so recrystallization was conducted using pentane:ethyl acetate (9:1) resulting in a yield of 96 %. Other methods of synthesizing oxazoles have been reviewed by Turchi and coworkers[62] including methods using isocyanates, 1,3-dipolar additions of carbonylcarbenes to nitriles, and cyclizations using 2-oxo nitrones. The formation of oxazoles via boron trifluoride-catalyzed reactions of diazo carbonyl compounds with nitriles has also been reported.[63]

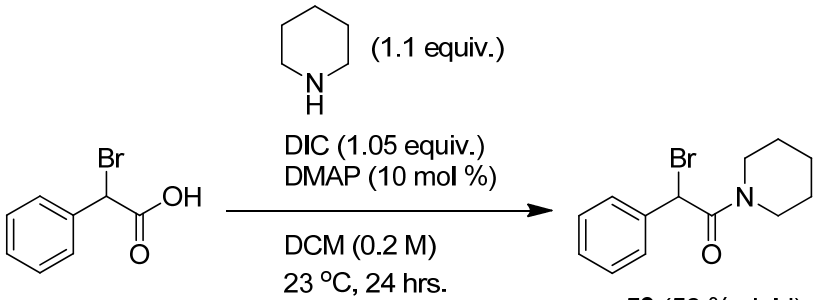
Scheme 2.17: Cyclization to form oxazole 58



55 **58** (96 % yield)

The generation of a α-amido carbocation from a α-bromo amide mediated by cationic silver was then investigated. The α-bromo amide **59** was first synthesized similarly to the α-bromo esters using a DIC coupling (Scheme 2.18).

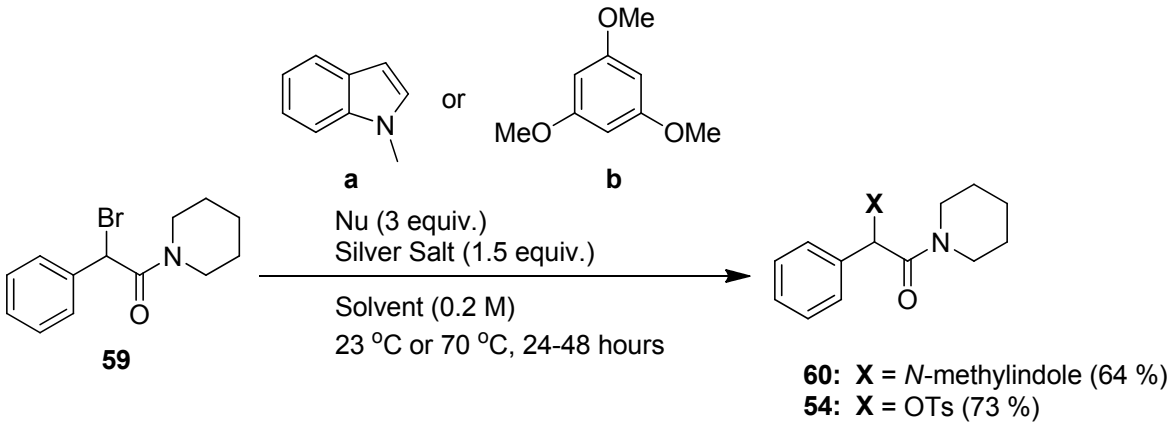
Scheme 2.18: Synthesis of α-bromo amide 59



59 (56 % yield)

Nucleophilic substitution reactions of α-bromo amide **59** mediated by silver trifluoromethanesulfonate and silver *p*-toluenesulfonate were then evaluated using the solvents DCE, acetonitrile, and dioxane (Table 2.9). Experiments conducted with the nucleophile *N*-methylindole resulted in 100 % starting material to product conversion as determined by crude ^{1}H-NMR analysis in all reactions except when DCE was used as the solvent with silver trifluoromethanesulfonate. In that reaction a starting material to product ratio of 1.6:1 was observed. Reactions conducted with silver trifluoromethanesulfonate did not require elevated temperatures, showing reactivity at 23 ^{o}C, where-as reactions conducted with silver *p*-toluenesulfonate required heating at 70 ^{o}C for conversion to be observed. The desired substitution product **60** was isolated in 64 % yield from the experiment conducted in dioxane with silver *p*-toluenesulfonate as the halide abstractor. When nucleophilic substitutions were conducted using 1,3,5-trimethoxybenzene as the nuceophile and silver *p*-toluenesulfonate as the halide abstractor, the formation of the α-tosyloxy amide product **54** was observed by crude ^{1}H-NMR analysis. The α-tosyloxy amide product **54** was isolated in 73 % yield from the reaction conducted in dioxane. The results of these experiments indicate that *N*-methylindole is a better nucleophile than 1,3,5-trimethoxybenzene in nucleophilic substitutions of α-bromo amide substrates, and that a competition between the silver salt counter anion and the nucleophile for substitution at the generated α-amido carbocation occurs.

Table 2.9: Investigation of silver-mediated nucleophilic substitution reactions of α-bromo amide 59 using *N*-methylindole and 1,3,5-trimethoxybenzene



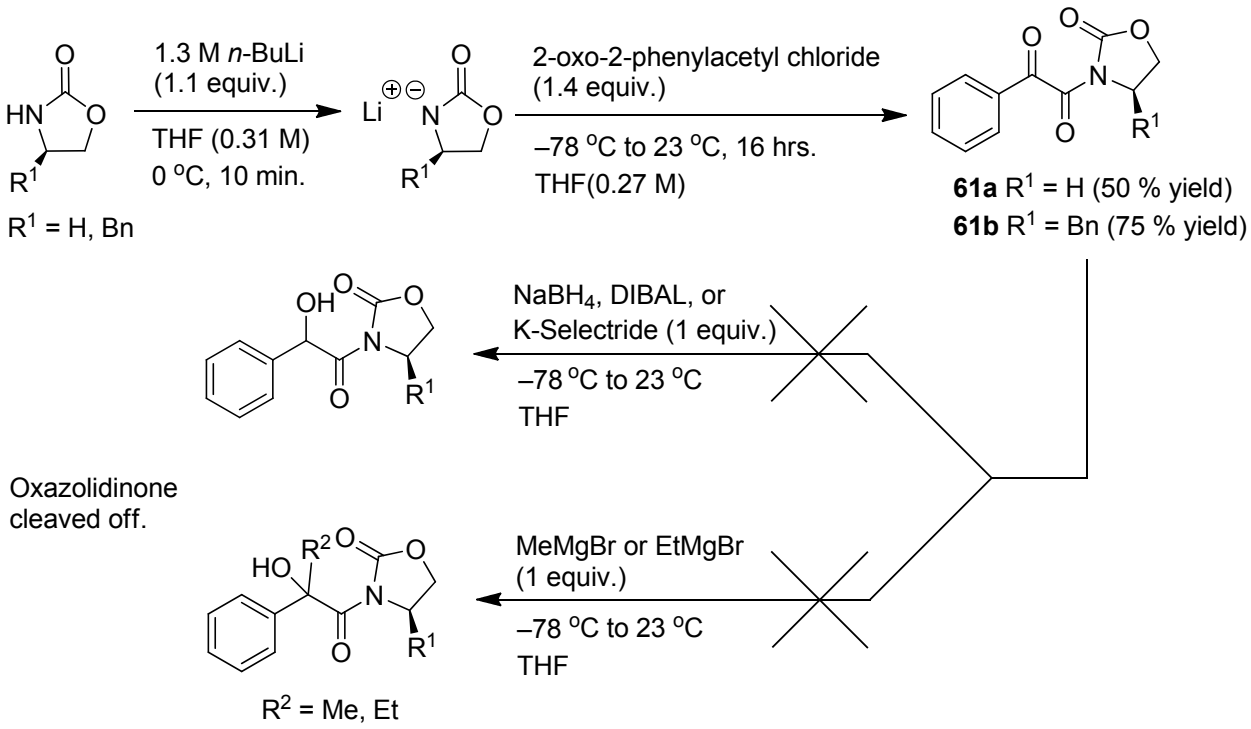
Nucleophile	Product	Silver Salt	Reaction Conditions	Solvent	^{1}H-NMR prod.:stm conv.	Isolated Product Yield (%)
N-methylindole	**60**	AgOTf	23 °C for 48 hrs	DCE	1:1.6 *	-
				Acetonitrile	100 % *	-
				Dioxane	100 % *	-
		AgOTs	23 °C for 24 hrs, then 70 °C for 24 hrs	DCE	100 % *	-
				Acetonitrile	100 % *	-
				Dioxane	100 % *	64
1,3,5-trimethoxybenzene	**54**	AgOTs	23 °C for 24 hrs	DCE	100 %**	73
			23 °C for 24 hrs	Acetonitrile	100 %**	-
			23 °C for 24 hrs, then 70 °C for 24 hrs	Dioxane	100 %**	-

*conversion determined by integrating the starting material ArC**H**Br signal at 5.77 ppm and the product ArC**H**(CO)N signal at 5.48 ppm of the ^{1}H-NMR spectrum; **conversion determined by integrating the starting material ArC**H**Br signal at 5.77 ppm and the product ArC**H**(OTs) signal at 6.15 ppm of the ^{1}H-NMR spectrum

2.3 Imide substrates

Chiral oxazolidinone auxiliaries have found diverse applications in asymmetric synthesis and, therefore, were evaluated for their potential as chiral auxiliaries for diastereoselective S_N1 reaction of α-keto carbocations. Similar to the ester and amide substrates evaluated, placing a leaving group at the α-keto postion was desired. In order to do this the α-keto imides **61a** and **61b** were synthesized by first converting benzoylformic acid to the corresponding α-keto acid chloride using oxalyl chloride. Addition of the α-keto acid chloride to a THF solution of the respective lithiated oxazolidinones at –78 ^{o}C gave the α-keto imides **61a** and **61b** products in 50 % and 75 % yield respectively (Scheme 2.19).[9,18] Reduction of the α-keto group using $NaBH_4$, DIBAL, or K-Selectride all resulted in the oxazolidinone being cleaved off. Grignard additions were also evaluated in order to make tertiary benzylic alcohols, but cleavage of the oxazolidinone auxiliary was also observed. Therefore, placing a leaving group at the α-keto position would have to be accomplished by another method.

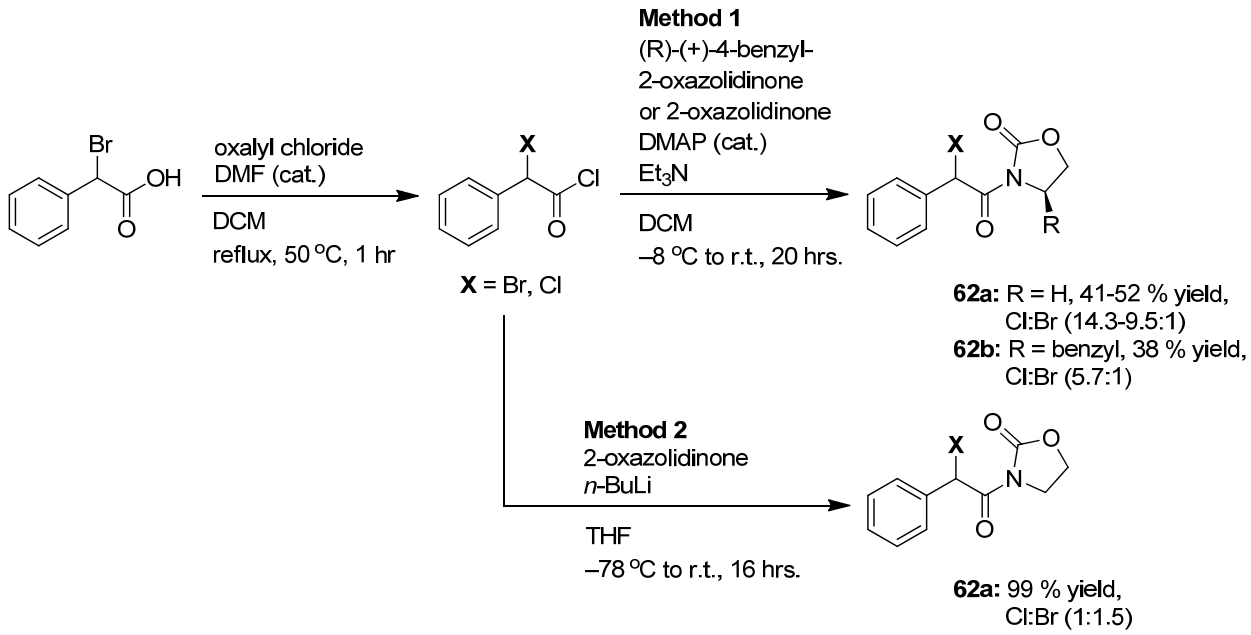
Scheme 2.19: Synthesis of α-keto imides 61a and 61b followed by attempted reduction and Grignard addition



Because reduction of the α-keto imides **61a** and **61b** to the corresponding alcohols was not possible it was decided to try converting a α-bromo imide to a α-tosyloxy imide using silver *p*-toluenesulfonate as a halide abstractor/tosylating agent.[64] The first approach used to prepare the α-bromo imides **62a** and **62b** was based on previous reports[65, 66] that α-bromophenylacetyl chloride, not being commercially available, could be synthesized from the corresponding α-bromophenylacetic acid using thionyl chloride or another chlorinating reagent. Oxalyl chloride was chosen as the chlorinating agent because it is cheaper and also a milder reagent. The α-bromophenylacetyl chloride could then be reacted with the corresponding Brønsted base deprotonated oxazolidinone (Scheme 2.20 – Method 1[65]) or lithiated oxazolidinone (Scheme 2.20 – Method 2[66]) to form the desired α-bromo imide as previously reported. Unfortunately, after using both of the above mentioned methods it was determined by GC-MS that the desired α-bromo imides **62a** and **62b** were actually mixtures of the α-chloro and α-bromo products (Scheme 2.20 & Table 2.10). Although possible to synthesize α-halo imides using DMAP and

triethylamine, much lower yields (38 - 50 % yield) were obtained by this method versus using a lithiated oxazolidinone (99 % yield).

Scheme 2.20: Synthesis of α-halo imides 62a and 62b using α-bromophenylacetic acid



The observed displacement of the bromine by chlorine could have happened either during the formation of the α-bromophenylacetyl chloride using oxalyl chloride, where free chloride ions were generated or during the reaction quench, where a saturated aqueous solution of NH_4Cl was used as previously reported.[65, 66] Further literature searching after this discovery revealed previous reports[67, 68] that *N*-(2-bromoacyl)oxazolidin-2-ones having a phenyl substituent alpha to the bromine atom were obtained as the benzylic α-chloro imide products instead of the desired benzylic α-bromo imide products. The synthetic methods used whereby chlorination was observed were not mentioned, but presumably they involved the formation of an acid chloride using a chlorinating agent. If the substituent alpha to the bromine was alkyl, then the desired α-bromo products were obtained. The displacement of bromine by chlorine in the synthesis of benzylic α-halo imides indicates the expected increase in ionizability of the C–Br bond due to the electron donating ability of the phenyl substituent.

Shown in Table 2.10 is a summary of the reactions conducted using oxalyl chloride as the chlorinating agent where bromide/chloride scrambling was observed. Increasing the equivalents of oxalyl chloride used in the formation of the α-bromophenylacetyl chloride (Table 2.10 – Entries 1-3, 5) resulted in only a small increase in the yield when DMAP and triethylamine were used in the acylation reaction (Scheme 2.20 – Method 1). Interestingly, the chloride to bromide ratio decreased when the equivalents of oxalyl chloride used was increased. The lack of concentration dependence on the chloride nucleophile might indicate a S_N1 type pathway or that chloride displacement was also occurring during the reaction quench when NH_4Cl was used. When the acylation reaction was conducted using a lithiated oxazolidinone (Scheme 2.20 – Method 2), the chloride to bromide ratio was determined to be much lower by crude ^{1}H-NMR analysis (Table 2.10 – Entry 4). The increased chloride displacement observed when the acylation reaction was conducted using DMAP and triethylamine might have been a result of nucleophilic displacement of the α-keto bromide by DMAP.

Table 2.10: Observed bromide displacement by chloride in the synthesis of α-halo imides 62a and 62b using oxalyl chloride

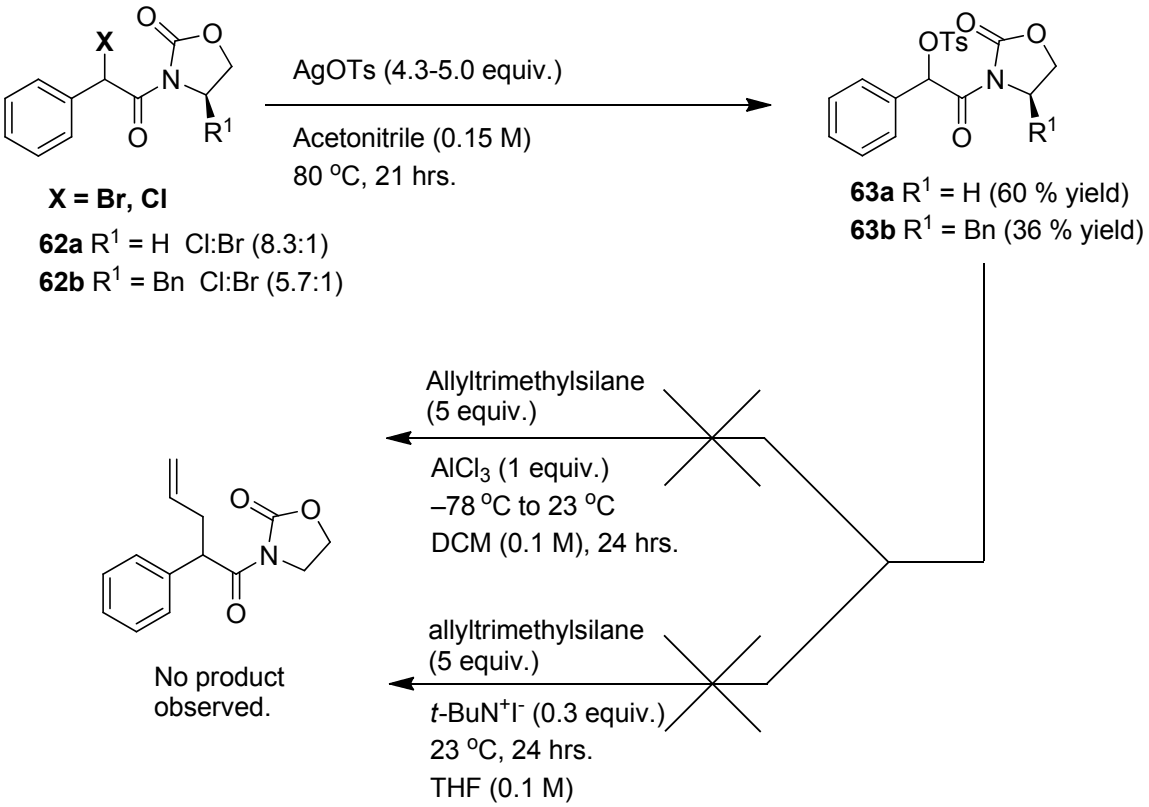
Entry	Product	Synthesis Method*	Oxalyl Chloride Equiv.	Cl:Br Ratio of Crude Product**	Cl:Br Ratio of Pure Product**	Mol % Yield
1	**62a**	1	3	14.3:1	16.7:1	41 %
2		1	5	10.0:1	8.7:1	50 %
3		1	5	9.5:1	10.8:1	52 %
4		2	6	1:1.5	2.5:1	99 %
5	**62b**	1	5	5.3:1	5.7:1	38

* see Scheme 2.20; ** determined by ^{1}H-NMR analysis

The α-halo imides **62a** and **62b** were then converted to the α-tosyloxy imides **63a** and **63b** using silver *p*-toluenesulfonate as a halide abstractor/tosylating agent (Scheme 2.21). The solvents acetonitrile, propionitrile, DMF, DMSO, nitromethane, THF, and DCM were first evaluated using silver *p*-toluenesulfonate (1.2 equiv.). The reaction conducted in DMSO showed no desired product formation and indicated cleavage of the oxazolidinone. Evaluation of the reactions conducted in THF and DCM showed no desired product formation. A product to starting material ratio of 1:6.3 determined by ^{1}H-NMR was observed when nitromethane was used as the solvent. Reactions conducted in acetonitrile, propionitrile, and DMF showed product to starting material ratios determined by ^{1}H-NMR of 1:2.9, 1:1.3, and 1.3:1 after 20 hours. Acetonitrile was chosen because it gave the cleanest crude ^{1}H-NMR spectrum. The low product to starting material ratios can be attributed to the decreased ionizability of the α-chloro imides present in the starting materials **62a** and **62b**. The equivalents of silver *p*-toluenesulfonate used were then increased to optimize the conversion. When 3 equivalents of silver *p*-toluenesulfonate was used, a product to starting material ratio of 5.7:1 was obtained and when 5 equivalents was used a product to starting material ratio of 12.9:1 was obtained.

Aluminum trichloride mediated nucleophilic substitution of α-tosyloxyimide **63a** using allyltrimethylsilane resulted in no product formation and only clean unreacted starting material was observed by crude ^{1}H-NMR analysis (Scheme 2.21). The lack of reactivity of α-tosyloxyimide **63a** might be a result of the steric hindrance of the imide substrate, where restricted rotation of the (CO)–N bond makes it is harder for the Lewis acid to coordinate to the tosylate leaving group. This lack of reactivity under Lewis acid conditions was also observed with the α-tosyloxy amide **54**. Dynamic kinetic resolution conditions were also evaluated using tetrabutylammonium iodide, which showed no product formation.[53, 65]

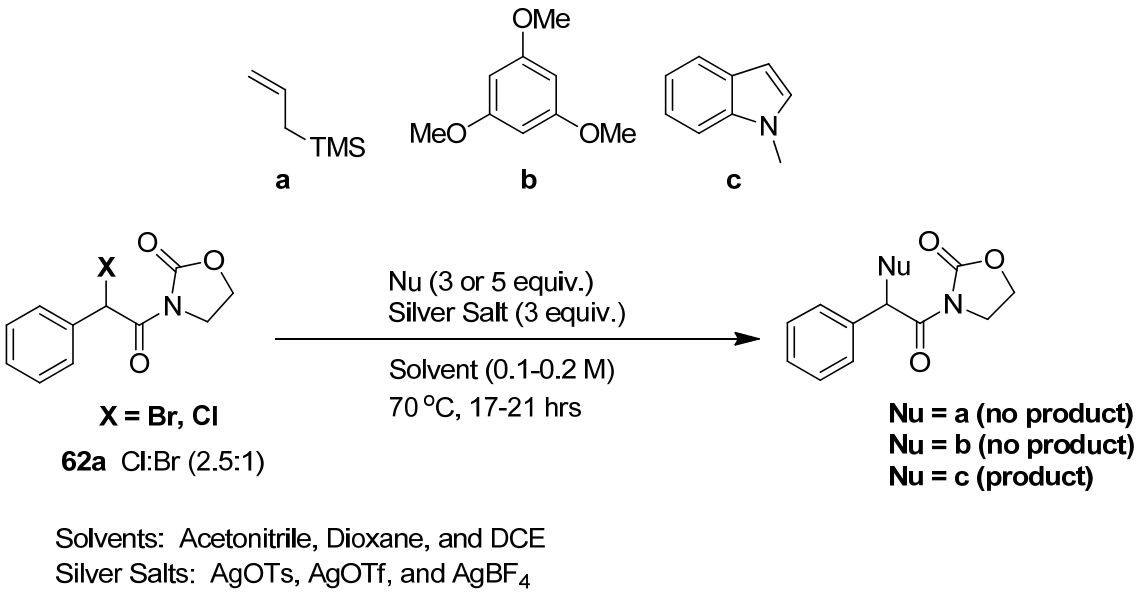
Scheme 2.21: Synthesis of α-tosyloxy imides 63a and 63b followed by attempted nucleophilic substitution reactions



Nucleophilic substitution reactions of α-halo imide **62a** mediated by cationic silver were then investigated. A screening study of various carbon nucleophiles (allyltrimethylsilane, 1,3,5-trimethoxybenzene, and *N*-methylindole) was conducted (Scheme 2.22). The nucleophilic substitution reactions were screened using three different solvents (acetonitrile, dioxane, and DCE) as well as three different silver salts (silver *p*-toluenesulfonate, silver trifluoromethanesulfonate, and silver tetrafluoroborate) at 70 °C. Analysis by ^{1}H-NMR and ^{19}F-NMR for experiments where silver trifluoromethanesulfonate or tetrafluoroborate were used indicated that the respective triflate product and the fluorinated product were possibly being formed instead of the desired nucleophilic addition product. Experiments involving silver *p*-toluenesulfonate and the nucleophiles allyltrimethylsilane and 1,3,5-trimethoxybenzene showed formation of the tosylated product by ^{1}H-NMR analysis when they were conducted in acetonitrile. Nucleophilic substitutions of α-halo imide substrate **62a** by *N*-methylindole were

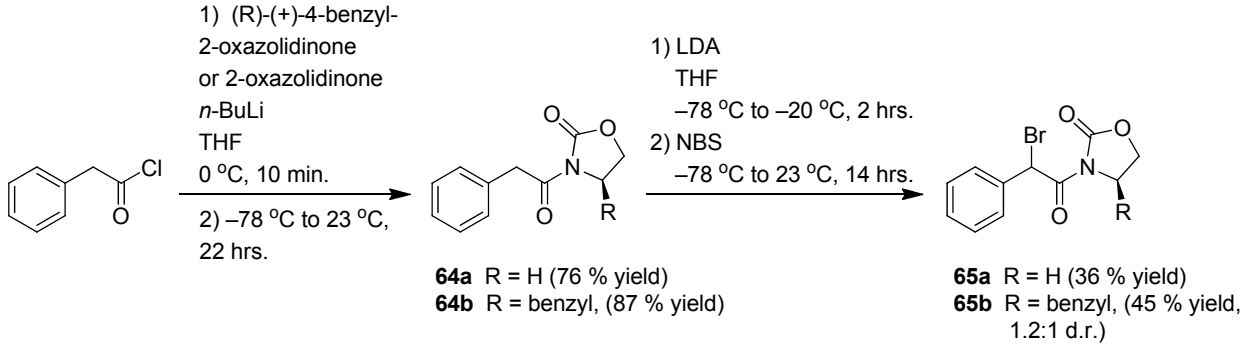
found to work regardless of the solvent or silver salt choice as indicated by GC-MS and ^{1}H-NMR analysis. No tosylation product was observed when *N*-methylindole was used as the nucleophile. Results of this investigation indicated that *N*-methylindole was the best nucleophile to use with the α-halo imide substrate **62a** (Cl:Br, 2.5:1). Product formation was also observed with *N*-methylindole as the nucleophile when the reaction was conducted with *p*-toluenesulfonate at 23 ^{o}C in DCE, acetonitrile, and dioxane. After 24 hours the reaction conducted in dioxane still showed presence of starting material, the reaction in acetonitrile showed only product formation (by TLC the reaction was indicated to be complete after 6 hours), and the reaction in DCE showed dimerization of *N*-methylindole as well as product formation. The results of these experiments indicate that *N*-methylindole is a better nucleophile than allyltrimethylsilane and 1,3,5-trimethoxybenzene in silver mediated nucleophilic substitutions of α-halo imide substrates, and that a competition between the silver salt counter anion and the nucleophile for substitution at the generated α-imido carbocation occurs.

Scheme 2.22: Initial screening of different nucleophiles, solvents, and silver salts for nucleophilic substitution reactions of α-halo imide 62a



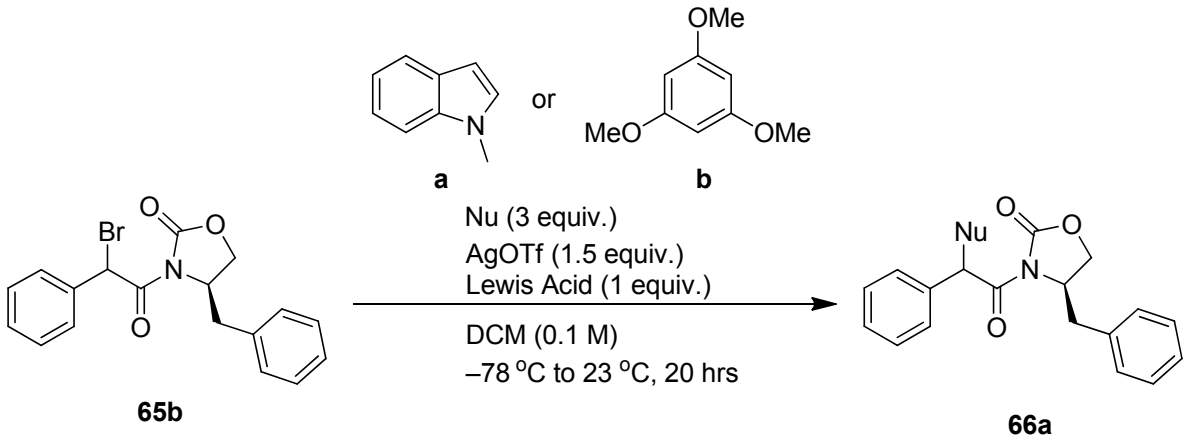
In order to overcome the bromide/chloride scrambling problem that was observed during the conversion of α-bromophenylacetic acid into an acid chloride, a synthetic route not involving chloride anions was desired. The α-bromo imides **65a** and **65b** were, therefore, synthesized using previous reports by Evans concerning diastereoselective bromination reactions of chiral imide enolates (Scheme 2.23).[69, 70] First the (2-phenylacetyl)oxazolidinones **64a** and **64b** were synthesized from phenyl acetyl chloride and the corresponding lithiated oxazolidinones. Next the lithium enolate was formed using a freshly prepared solution of LDA at –78 ^{o}C. At temperatures above 0 ^{o}C the lithium enolate would decompose via a ketene pathway,[71] therefore, the temperature was allowed only to rise to –20 ^{o}C. The lithium enolate was then quickly transferred via cannula to a slurry of NBS in THF at –78 ^{o}C. Evans found that (2-phenylacetyl) oxazolidinones gave lower diastereoselectivity (3.5:1) than other *N*-acyloxazolidin-2-ones in bromination reactions under the optimized enolate formation conditions of dibutylboryl triflate and diisopropylethylamine.[70] Boron enolates were reported to give higher diastereoselectivity than the corresponding lithium enolates, and this is consistent with the d.r. of 1.2:1 observed with α-bromo imide **65b**. For the analysis of S_N1 type reactions a low d.r. in the starting material is desirable in order to rule out an S_N2 inversion process. Synthesis of α-bromo imide **65a** using a DIC coupling of the corresponding α-bromophenyl acetic acid and 2-oxazolidinone was also attempted, but was unsuccessful. This was not surprising considering the decreased nucleophilicity of the 2-oxazolidinone relative to that of alcohols and secondary amines, which were both successfully used in DIC couplings with α-bromophenyl acetic acid.

Scheme 2.23: Synthesis of α-bromo imides 65a and 65b using NBS



After obtaining the desired α-bromo imide without contamination with chloride as determined by NMR and HR-MS, diastereoselective nucleophilic substitution reactions using the chiral α-bromo imide **65b** were evaluated. *N*-methylindole had been found to indicate product formation with the non-chiral α-halo imide **62a**, and was, therefore, used. An initial experiment using *N*-methylindole and silver trifluoromethanesulfonate with the chiral α-bromo imide **65b** at –78 ^{o}C showed a d.r. of 1.3:1 (Table 2.11). Silver *p*-toluenesulfonate was also tested under the same conditions and the product **66a** was obtained with a d.r. of 1.3:1. A previous report by Sibi and coworkers[21] regarding radical allylations conducted using chiral α-bromo imides containing oxazolidinone auxiliaries had shown a d.r. of 1.4:1. Interestingly the d.r. for these radical allylations increased to 100:1 with the addition of chelating Lewis acids, which would restrict the number of possible rotamers of the intermediate α-imido radical substrate. To try and improve on the observed selectivity, experiments with various Lewis acids capable of chelating to the two carbonyl groups of the chiral α-bromo imide **65b** were conducted. This, however, only slightly increased the diastereoselectivity in the experiment where $Zn(OTf)_2$ was used as the Lewis acid. A possible explanation for the lack of selectivity increase observed when chelating Lewis acids were added is that π-conjugation stabilization of the intermediate carbocation is reduced due to the electron withdrawing Lewis acid coordinated to the carbonyl groups. Also, possibly due to steric reasons, the face shielding aromatic group of the oxazolidinone might be orientated away from the α-keto carbocation and a quadrupole-cation interaction not energetically favoured. The nucleophile 1,3,5-trimethoxybenzene was tested as well, but no product formation was observed.

Table 2.11: Silver trifluoromethanesulfonate-mediated nucleophilic substitution reactions of α-bromo imide 65b



Nucleophile	Product	Additive	^{1}H-NMR yield (%)	^{1}H-NMR d.r.
N-methylindole	**66a**	-	31	1.3:1
		$Sc(OTf)_3$	57	1.2:1
		$Zn(OTf)_2$	57	1.4:1
		$Mg(OTf)_2$	43	1.3:1
1,3,5-trimethoxybenzene	**No product**	-	-	-

3. Summary and conclusion

Nucleophilc substitution reactions of α-keto carbocations generated from ester, amide, and imide substrates were evaluated. These represent the first general set of methods for carbon–carbon and carbon–heteroatom bond forming reactions of α-keto carbocations. While conditions for effective carbon–carbon and carbon–heteroatom bond-forming reactions of these intermediates were successfully developed, control of facial selectivity by a chiral auxiliary proved to be very challenging. Experiments with various ester and imide chiral auxiliaries showed similar selectivities despite their different electronic properties. The mechanistic study conducted with the nucleophile 4-methoxybenzene thiol indicated that a S_N2 type mechanism might be involved.

It is surprising that the observed diastereoselectivities of the chiral ester and imide substrates evaluated did not change significantly when extensive reaction optimizations were conducted. Diastereoselectivities for the most part remained constant across a wide range of conditions where α-keto carbocation formation was initiated by various Lewis acids, and silver salts using many different solvents at various temperatures. Experiments conducted using a sterically hindered base or chelating Lewis acids did not indicate large changes in selectivity. When an axially chiral phosphate anion was evaluated, the selectivity increased by a small amount, but was not reflective of the large increases in selectivities seen by Toste and coworkers[57] when an axially chiral phosphate anion was used in their asymmetric ring opening reactions of *meso*-aziridium ions. Dynamic kinetic resolution conditions were also assessed, but an increase in selectivity was not seen. Diffusion control in the nucleophilic substitution reactions might be causing the lack of selectivity increase upon changing conditions. Experiments should also be conducted to determine if these types of reactions are under thermodynamic or kinetic control.

Lewis acid mediated-nucleophilic substitutions with ester substrates were found to be possible if the leaving group was a tosylate but not possible if the leaving group was a trifluoroacetate group. Silver-mediated conditions were found to give higher diastereoselectivities than Lewis

acid-mediated conditions with the ester substrates. Only small changes in selectivity were seen when different silver salts were used. The possibility of selective decomposition of one of the diastereomers might be implicated by the observation that lower yields resulted in higher d.r.'s and higher yields resulted in lower d.r.'s in some experiments. The larger 2-(1-naphthalenyl) cyclohexanol auxiliary was surprisingly found to result in lower diastereoselectivities than that of the phenyl cyclohexanol auxiliary. It was predicted that increased face shielding as well as an increased cation-quadrupole interaction due to the larger aromatic group would give higher selectivities. The observed lower selectivity using the larger 2-(1-naphthalenyl) cyclohexanol auxiliary indicates that the increased steric bulk of the auxiliary is such that it is energetically more favourable for the aromatic group to be in a position away from the benzylic α-keto carbocation. The influence of an axially chiral phosphate counteranion was also investigated, but increased selectivity was not observed. It was also determined that a stabilizing aromatic group was needed to increase the ionizability of C–Br bond in order for reactivity to be seen.

Amide substrates were not reactive under Lewis acid-mediated conditions using either a tosylate leaving group or a trifluoroacetate leaving group. This might be a result of restricted rotational freedom of the (CO)–N bond, which inhibits coordination of the Lewis acid to the leaving group. If a small amount of water was present in the reaction, formation of the α-hydroxy amide instead of the desired nucleophilic substitution product was observed. Cyclization to form an oxazole product using Lewis acid conditions was discovered if acetonitrile was used as the solvent. Under harsh Brønsted acid conditions (TFA as the solvent) cyclizations to form a substituted benzofuran product was indicated. The same conditions using an ester substrate resulted in solvolytic nucleophilic substitution. When silver-mediated nucleophilic substitution reactions of an α-bromo amide substrate were investigated, the arene nucleophile *N*-methylindole was found to indicate product formation. When 1,3,5-trimethoxybenzene was used as the nucleophile the corresponding α-tosyloxy amide substrate was observed, therefore, a competition between the silver salt counter anion and the nucleophile for substitution at the generated α-amido carbocation occurs.

Initial attempts to prepare α-hydroxy imides were thwarted by cleavage of the oxazolidinone auxiliary. The α-tosyloxy imides were successfully synthesized from α-halo imides, but unlike the ester substrates nucleophilic substitution under Lewis acid conditions was not indicated. Silver-mediated nucleophilic substitutions were possible using *N*-methylindole as the nucleophile. Diastereoselectivities observed using a chiral α-bromo imide substrate were lower than with the ester substrates and the influence of chelating Lewis acids on the selectivity was negligible. Restricted rotation of the (CO)–N bond as well as orientation of the face shielding aromatic group of the oxazolidinone away from the carbocation might be implicated. The observed lack of selectivity increase upon using a chelating Lewis acid might be a result of reduced π-conjugation of the carbonyl group to the carbocation.

The possibility that these types of reactions were under thermodynamic control, instead of kinetic control, might indicate the low selectivites of these types of nucleophilic substitution reactions. In retrospect, isolating pure diastereomers and resubjecting them to the reactions conditions could have been an informative experiment. Similar diastereoselectivities were seen at both low temperatures (–78 ^{o}C) as well as at high temperatures (70 ^{o}C). The benzylic carbocation systems investigated by Bach[28] indicated only slight changes in diastereoselectivities when conducted at ambient temperatures versus at low temperatures (–78 ^{o}C). Perhaps an electron donating substituent on the aromatic ring would further stabilize the intermediate α-keto carbocation and increase the selectivity. Alternatively a different chiral auxiliary might be used that would better shield one of the intermediate α-keto carbocation faces. Since a decrease in the diastereselectivity was observed with the ester substrates using the larger 2-(1-naphthalenyl) cyclohexanol auxiliary versus the phenyl cyclohexanol auxiliary, maybe a smaller group on the auxiliary would further increase selectivities. A chiral auxiliary containing a methoxy group might be capable of stabilizing the intermediate α-keto carbocation through an energetically favourable cation–lone pair interaction.

4. Experimental section

General Experimental Details

All reactions were performed under nitrogen using oven dried glassware, unless otherwise noted. The reaction temperatures stated are those of the external oil bath. Dichloromethane, THF, toluene, acetonitrile, ether, and pentane, when used as reaction solvents, were dried using a solvent purification system (PureSolv MD) obtained from Innovative Technology. Chloroform, when used as a reaction solvent, was dried over molecular sieves. All commercial materials were purchased from Sigma Aldrich or Alfa Aesar and were used as received, unless otherwise stated.

Silver trifluoromethanesulfonate, silver hexafluorophosphate, and silver methanesulfonate are hygroscopic and were, therefore, weighed out in an inert atmosphere glove box.

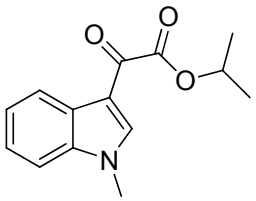
All reactions were monitored by analytical thin-layer chromatography (TLC) using pre-coated aluminum-backed silica gel plates (TLC Silica gel 60 F_{254}) obtained from EMD Chemicals Inc. and were visualized using a UV lamp (254 nm) and potassium permanganate. Purification by flash chromatography was conducted using silica gel (60 Å, 230-400 mesh) obtained from SiliCycle.

Proton, fluorine, and carbon nuclear magnetic resonance spectra (^{1}H, ^{19}F, and ^{13}C NMR respectively) were recorded using a Varian Mercury 300 (300 MHz) or a Varian Mercury 400 (400 MHz) NMR spectrometer. Chemical shifts (δ) for all compounds are listed in parts per million (ppm) downfield from tetramethylsilane (TMS) using the NMR solvent as an internal reference. The reference values for deuterated chloroform ($CDCl_3$) were 7.26 and 77.16 ppm for

^{1}H and ^{13}C NMR spectra respectively. The reference values for deuterated DMSO ($(CD_3)_2SO$) were 2.50 and 39.52 ppm for ^{1}H and ^{13}C NMR spectra respectively. NMR data are represented in the following order: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (*J*, Hz), and assignment. No special notation is used for equivalent carbons. Infrared (IR) spectra were obtained using a Spectrum 100 series FT-IR spectrometer equipped with an attenuated total reflectance (ATR) accessory from Perkin-Elmer as $CDCl_3$ thin films or as neat solids. IR data are represented in the following order: frequency of absorption (cm^{-1}), and intensity of absorption (s = strong, m = medium, w = weak). High resolution mass spectroscopic data (HRMS) were obtained from the University of Toronto's Advanced Instrumentation for Molecular Structure (AIMS) facility. Available spectrometers were as follows: a AB/Sciex QStar mass spectrometer with an ESI source, a AB/Sciex QStarXL mass spectrometer with an ESI source, a Waters GC TOF mass spectrometer with EI/CI sources, and a Sciex API4000 triple quadrupole mass spectrometer with an ESI source. Low resolution mass spectroscopic data was obtained from a Perkin-Elmer Clarus 600C GC-MS instrument. GC-FID analysis was conducted using a Perkin-Elmer Clarus 600 instrument. HPLC analysis was conducted using a Perkin-Elmer series 200 instrument.

4.1 α-Keto ester, amide, and imide substrates

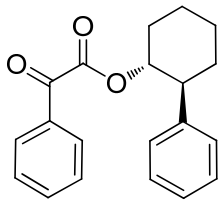
Isopropyl 2-(1-methyl-1H-indol-3-yl)-2-oxoacetate (33)



33

To a stirred solution of *N*-methylindole (477 μL, 3.81 mmol) in ether (10 mL) at 0 ^{o}C was added oxalyl chloride (645 μL, 7.62 mmol) drop wise. After stirring for 30 minutes at 0 ^{o}C the precipitate was filtered, washed with cold ether (15 mL) and the solvent was removed under reduced pressure. The resulting acid chloride **32** product (0.773 g, 3.49 mmol, 92 %) was dissolved in isopropanol (10 mL) followed by the dropwise addition of triethyl amine (50 μL, 0.36 mmol). The reaction mixture was refluxed at 78 ^{o}C for 15 hours, then cooled to room temperature and concentrated under reduced pressure. Ethyl acetate (30 mL) was added to dissolve the residue, which was washed with water (3 x 10 mL), washed with brine (15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was then filtered through a short plug of silica gel (ethyl acetate) to give the purified product **33** (0.822 g, 96 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.45-8.42 (1H, m, Ar**H**), 8.31 (1H, s, CH_3NC**H**), 7.36-7.34 (3H, m, Ar**H**), 5.25 (1H, septet, J = 6.3 Hz, CO_2C**H**$(CH_3)_2$), 3.87 (3H, s, NC**H**$_3$), 1.42 (6H, d, J = 6.3 Hz, $CO_2CH(C$**H**$_3)_2$).

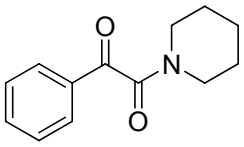
2-Phenylcyclohexyl 2-oxo-2-phenylacetate (37)



37

To a stirred solution of benzoyl formic acid (0.468 g, 3.12 mmol) and 2-phenylcyclohexanol (0.500 g, 2.84 mmol) in toluene (25 mL) was added *p*-toluenesulfonic acid (0.054 g, 0.31 mmol). The reaction mixture was refluxed at 110 ^{o}C for 12 hours, allowed to cool to room temperature and then washed with saturated aqueous $NaHCO_3$ (2 x 20 mL). The aqueous phase was then extracted with toluene (2 x 15 mL) and the combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was then subjected to flash chromatography (pentane:EtOAc, 9:1) to give the purified product **37** (0.795 g, 91 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.46-7.13 (10H, m, Ar**H**), 5.34 (1H, td, *J* = 10.7, 4.5 Hz, CO_2C**H**), 2.69 (1H, m, ArC**H**), 2.21-2.16 (1H, m, -C**H**$_2$-), 1.96-1.84 (2H, m, -C**H**$_2$-), 1.78-1.74 (1H, m, -C**H**$_2$-), 1.64-1.45 (3H, m, -C**H**$_2$-), 1.43-1.24 (1H, m, -C**H**$_2$-); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 187.23, 163.94, 142.82, 134.54, 132.16, 129.83, 128.81, 128.77, 127.95, 126.92, 78.50, 49.97, 34.21, 32.29, 25.72, 24.88. Preparation of the above reported α-keto ester **37** was similar to that previously reported[72] and the obtained spectral properties were also consistent with previously reported data.[73]

1-Phenyl-2-(piperidin-1-yl)ethane-1,2-dione (52)



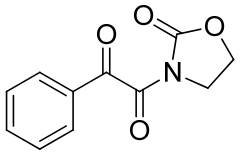
52

To a stirred solution of benzoylformic acid (2.00 g, 13.3 mmol) in DCM (25 mL) was added oxalyl chloride (2.5 mL, 29.3 mmol), and DMF (3 drops). The reaction mixture was refluxed at 50 ^{o}C for 1 hour, after which the solution was cooled to room temperature, and the solvent

removed under reduced pressure. To rid the product of excess oxalyl chloride, DCM (5 mL) was added to the flask and removed under reduced pressure (2 times). The green oily product was dissolved in DCM (22 mL) and then DMAP (0.163 g, 1.3 mmol) and pyridine (1.6 mL, 20.0 mmol) were added sequentially. After stirring for 5 minutes, piperidine (1.6 mL, 16.2 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 24 hours. The reaction was then quenched with water (20 mL), the layers separated, and the aqueous phase extracted with DCM (2 x 20 mL). The combined organic phases were then washed with saturated aqueous NH_4Cl (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was then subjected to flash chromatography (ethyl acetate and pentane mixtures) to give the purified product **52** (2.374 g, 82 %) as a white powder. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.95 (2H, d, *J* = 7.1 Hz, Ar**H**), 7.64 (1H, t, *J* = 7.4 Hz, Ar**H**), 7.51 (2H, m, Ar**H**), 3.71 (2H, m, CONC**H**$_2$-), 3.29 (2H, m, CONC**H**$_2$-), 1.70 (4H, m, -C**H**$_2$-), 1.55 (2H, m, -C**H**$_2$-); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 192.05, 165.55, 134.74, 133.41, 129.68, 129.10, 47.15, 42.26, 26.33, 25.57, 24.51; **IR** (cm^{-1}) ν 2973 (w), 2942 (w), 2861 (w), 1738 (w), 1670 (m), 1639 (s), 1594 (m), 1579 (w), 1448 (s), 1438 (s), 1240 (s), 1214 (s), 1138 (w), 1025 (w), 972 (s), 719 (s), 694 (s). Preparation of the above reported α-keto amide **52** was similar to that previously reported[74] and the obtained spectral properties were also consistent with previously reported data.[75]

General Procedure A: Synthesis of α-keto imides

3-(2-Oxo-2-phenylacetyl)oxazolidin-2-one (61a)

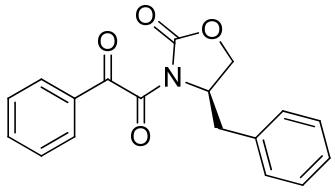


61a

2-Oxo-2-phenylacetyl chloride (13.3 mmol) was prepared as outlined in the preparation of 1-phenyl-2-(piperidin-1-yl)ethane-1,2-dione (**52**). To a stirred solution of 2-oxazolidinone (0.812 g, 9.30 mmol) dissolved in THF (30 mL) at 0 ^oC was added 1.3 M *n*-butyllithium in hexanes (7.89 mL, 10.3 mmol) dropwise. After stirring for 10 minutes the reaction mixture was cooled to

–78 ^{o}C and the previously prepared 2-oxo-2-phenylacetyl chloride dissolved in THF (5 mL) was added dropwise over a 10 minute period. The reaction mixture was allowed to warm to room temperature over 16 hours, diluted with DCM (15 mL) and then quenched with water (30 mL). The resulting mixture was then concentrated on a rotary evaporator to remove the bulk of the THF and hexanes. The layers were then separated and the aqueous phase was extracted with DCM (2 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was then subjected to flash chromatography (ethyl acetate and pentane mixtures) to give the purified product **61a** (1.446 g, 50 %). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* = 7.1 Hz, Ar**H**), 7.65 (1H, m, Ar**H**), 7.51 (2H, m, Ar**H**), 4.59 (2H, m, C**H**$_2$), 4.16 (2H, m, C**H**$_2$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 187.97, 166.59, 153.25, 134.94, 132.47, 129.44, 129.16, 64.16, 41.07; **IR** (cm^{-1}) ν 3073 (w), 2971 (w), 2933 (w), 1783 (s), 1687 (s), 1674(s), 1597 (m), 1467 (m), 1448 (m), 1392 (s), 1374 (s), 1236 (s), 1224 (s), 1202 (s), 1128 (s), 1026 (s), 714 (s). Preparation of the above mentioned α-keto imide **61a** was achieved using previously reported chemistry.[18, 9]

(R)-4-Benzyl-3-(2-oxo-2-phenylacetyl)oxazolidin-2-one (61b)



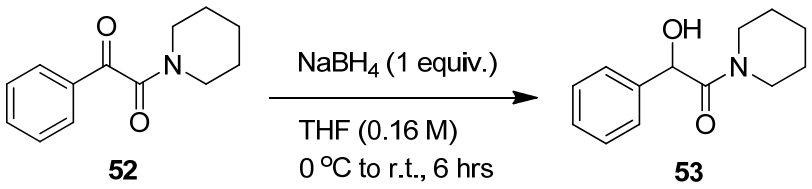
61b

Compound **61b** was prepared following General Procedures **A** outlined above for the synthesis of α-keto imides using (R)-4-benzyl-2-oxazolidinone (0.195 g, 1.10 mmol). Flash chromatography (ethyl acetate and pentane mixtures) afforded the purified product **61b** (0.254 g, 75 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.90-7.88 (2H, m, Ar**H**), 7.66 (1H, t, *J* = 7.4 Hz, Ar**H**), 7.55-7.51 (2H, m, Ar**H**), 7.41-7.29 (5H, m, Ar**H**), 4.85-4.79 (1H, m, NC**H**), 4.45-4.40 (1H, m, CO_2C**H**$_2$), 4.34 (1H, dd, *J* = 9.3, 3.5 Hz, CO_2C**H**$_2$), 3.55 (1H, dd, *J* = 13.5, 3.6 Hz, ArC**H**$_2$), 2.99 (1H, dd, *J* = 13.5, 9.4 Hz, ArC**H**$_2$). Preparation of the above mentioned α-keto imide **61b** was achieved using previously reported chemistry.[18, 9]

4.2 α-Hydroxy amides and esters

General Procedure B: Reduction of 1,2-diketo amides and 1,2-diketo esters

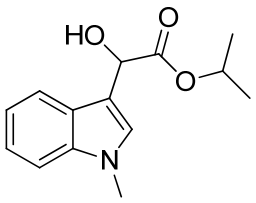
2-Hydroxy-2-phenyl-1-(piperidin-1-yl)ethanone (53)



52 **53**

Compound **52** (1.00 g, 4.60 mmol) was dissolved in THF (28 mL) and cooled to 0 °C. Sodium borohydride (0.174 g, 4.60 mmol) was then added and the reaction mixture was allowed to slowly warm to room temperature. After 6 hours of stirring at room temperature the reaction was diluted with DCM (20 mL), quenched with water (30 mL), and concentrated under reduced pressure to remove the THF. To the concentrated solution was then added water (20 mL) and DCM (15 mL) and the layers were separated. The aqueous phase was then extracted with DCM (3 x 40 mL) and the combined organic phases were dried over Na_2SO_4, and concentrated under reduced pressure. The residue was then subjected to flash chromatography (ethyl acetate and pentane mixtures) to give the purified product **53** (0.932 g, 92 %) as a white powder. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.37-7.28 (5H, m, Ar**H**), 5.19 (1H, d, *J* = 6.2 Hz, ArC**H**OH), 4.87 (1H, d, *J* = 6.2 Hz, ArCHO**H**), 3.81-3.75 (1H, m, CONC**H**$_2$-), 3.48-3.42 (1H, m, CONC**H**$_2$-), 3.17 (2H, t, *J* = 5.6 Hz, CONC**H**$_2$-), 1.61-1.40 (4H, m, -C**H**$_2$-), 1.35-1.25 (1H, m, -C**H**$_2$-), 0.93-0.84 (1H, m, -C**H**$_2$-); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 170.53, 139.86, 129.11, 128.49, 127.54, 71.52, 45.94, 44.13, 25.49, 25.30, 24.32; **IR** (cm^{-1}) ν 3318 (m), 3221 (m), 2935 (m), 2852 (m), 1614 (s), 1470 (m), 1443 (m), 1420 (m), 1355 (w), 1256 (m), 1239 (m), 1188 (m), 1082 (s), 1068 (m), 1011 (s), 763 (m). Preparation of the above reported α-hydroxy amide **53** was similar to that previously reported for related compounds[76, 77] and has also been previously reported.[78-80]

Isopropyl 2-hydroxy-2-(1-methyl-1H-indol-3-yl)acetate (34)

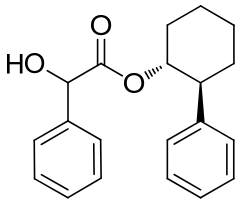


34

Compound **34** was prepared following General Procedure **B** outlined above for the synthesis of α-hydroxy esters using compound **33** (0.100 g, 0.41 mmol), sodium borohydride (0.008 g, 0.20 mmol), and THF (0.14 M). Reaction time was 2 hours. Flash chromatography (pentane: EtOAc, 9:1 then 4:1) afforded the purified product **34** (0.101 g, 100 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.71 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.31 (1H, d, *J* = 8.2 Hz, Ar**H**), 7.24 (1H, t, *J* = 8.2 Hz, Ar**H**), 7.13 (1H, t, *J* = 8.0 Hz, Ar**H**), 7.11 (1H, s, CH_3NC**H**), 5.41 (1H, d, *J* = 5.7 Hz, CC**H**OH), 5.11 (1H, septet, *J* = 6.3 Hz, CO_2C**H**$(CH_3)_2$), 3.77 (3H, s, NC**H**$_3$), 3.22 (1H, d, *J* = 6.0 Hz, CCHO**H**), 1.29 (3H, d, *J* = 6.3 Hz, $CO_2CH(C$**H**$_3)_2$), 1.12 (3H, d, *J* = 6.3 Hz, $CO_2CH(C$**H**$_3)_2$).

*Reduction in methanol resulted in transesterification (6.3:1 ratio of isopropyl ester and methyl ester products).

2-Phenylcyclohexyl 2-hydroxy-2-phenylacetate (38)

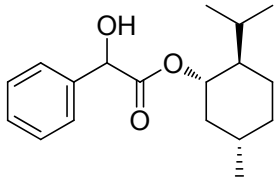


38

Compound **38** was prepared following General Procedure **B** outlined above for the synthesis of α-hydroxy esters using compound **37** (0.500 g, 1.62 mmol), sodium borohydride (0.202 g, 5.34 mmol), and THF (0.19 M). Reaction time was 12 hours. Flash chromatography (pentane:EtOAc, 9:1) afforded the purified product **38** (0.430 g, 85 %; 86 % purity as determined by ^{1}H-NMR) and a small amount of inseparable 2-phenylcyclohexanol. **^{1}H-NMR** (400 MHz,

$CDCl_3$, 1.9:1 mixture of diastereomers, signals corresponding to the major indicated by *) δ 7.36-6.89 (10H, m, Ar**H***, Ar**H**), 5.11-5.00 (1H, m, CO_2C**H***, CO_2C**H**), 4.94 (1H, d, *J* = 6.0 Hz, ArC**H***OH), 4.79 (1H, d, *J* = 5.7 Hz, ArC**H**OH), 3.21 (1H, br s, ArCHO**H***, ArCHO**H**), 2.67 (1H, td, *J* = 11.6, 3.7 Hz, ArC**H**CH_2), 2.57 (1H, td, *J* = 11.7, 3.4 Hz, ArC**H***CH_2), 2.24-2.18 (1H, m, -C**H***$_2$-), 1.95-1.92 (1H, m, -C**H**$_2$-), 1.88-1.75 (3H, m, -C**H***$_2$-, -C**H**$_2$-), 1.61-1.46 (2H, m, -C**H***$_2$-, -C**H**$_2$-), 1.43-1.17 (2H, m, -C**H***$_2$-, -C**H**$_2$-); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 173.04, 172.83, 142.73, 142.34, 138.58, 138.01, 128.59, 128.54, 128.43, 128.40, 128.32, 127.91, 127.56, 127.25, 126.83, 126.65, 126.46, 126.30, 78.44, 78.39, 72.97, 72.86, 49.63, 49.60, 34.20, 33.78, 32.39, 31.84, 25.77, 25.73, 24.80, 24.66. The obtained spectral properties of the above mentioned α-hydroxy ester **38** were consistent with previously reported data.[73]

2-Isopropyl-5-methylcyclohexyl 2-hydroxy-2-phenylacetate (44)



44

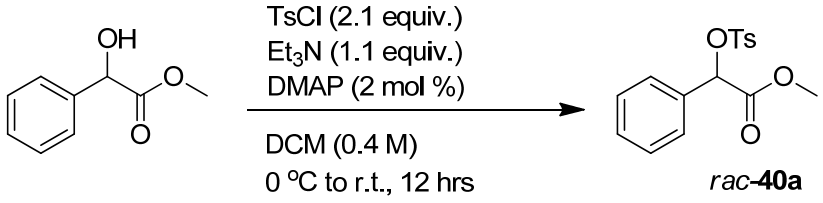
Compound **44** was prepared following General Procedure **B** outlined above for the synthesis of α-hydroxy esters using 2-isopropyl-5-methylcyclohexyl 2-oxo-2-phenylacetate (0.221 g, 0.77 mmol), sodium borohydride (0.087 g, 2.30 mmol), and THF (0.13 M). Reaction time was 3 hours, and the extraction solvent was ethyl acetate. Flash chromatography (ethyl acetate and pentane mixtures) afforded the purified product **44** (0.132 g, 59 %). **^{1}H-NMR** (400 MHz, $CDCl_3$, 1.1:1 mixture of diastereomers, signals corresponding to the major indicated by *, indistinguishable signals indicated by **) δ 7.42-7.28 (5H, m, Ar**H**, Ar**H***), 5.14 (1H, d, *J* = 6.0 Hz, ArC**H**OH), 5.10 (1H, d, *J* = 5.6 Hz, ArC**H***OH), 4.77 (1H, td, *J* = 10.9, 4.4 Hz, CO_2C**H**), 4.65 (1H, td, *J* = 10.9, 4.4 Hz, CO_2C**H***), 3.56 (1H, d, *J* = 5.7 Hz, ArCHO**H***), 3.46 (1H, d, *J* = 6.0 Hz, ArCHO**H**), 2.07-2.02 (1H, m, -C**H****-), 1.86 (1H, m, CH_3C**H****CH_3), 1.75-1.71 (1H, m, -C**H****-), 1.70-1.63 (3H, m, CH_3C**H****CH_3, -C**H****-), 1.59-1.55 (1H, m, -C**H****-), 1.52-1.34 (3H, m, -C**H****-), 1.26-1.19 (2H, m, -C**H****-), 1.14-0.94 (4H, m, -C**H****-), 0.92 (3H, d, *J* = 3.1 Hz, C**H***$_3$CHCH$_3$), 0.90 (3H, d, *J* = 3.7 Hz, C**H**$_3$CHCH$_3$), 0.87-0.73 (2H, m, -C**H****-), 0.82 (3H, d, *J*

= 6.6 Hz, C**H***$_3$CH), 0.78 (3H, d, *J* = 6.9 Hz, C**H**$_3$CH), 0.58 (3H, d, *J* = 7.0 Hz, C**H**$_3$CHCH$_3$), 0.39 (3H, d, *J* = 7.0 Hz, C**H***$_3$CHCH$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 173.64, 173.50, 128.64, 128.53, 128.43, 126.78, 126.59, 73.26, 72.95, 47.20, 46.98, 40.86, 40.20, 34.23, 34.19, 31.56, 31.46, 31.08, 26.52, 25.52, 23.58, 23.13, 22.12, 22.02, 20.83, 20.61, 16.52, 15.73. The above mentioned α-hydroxy ester **44** has been previously reported[81] and the obtained spectral properties were also consistent with previously reported data.[73]

4.3 α-Tosyloxy & α-trifluoroacetoxy esters and amides

General Procedure C: Synthesis of α-tosyloxy esters

Methyl 2-phenyl-2-(tosyloxy)acetate (40a)

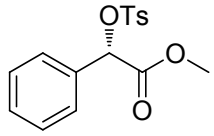


rac-**40a**

To a stirred solution of commercially available methyl DL-mandelate (2.00 g, 12.0 mmol) dissolved in DCM (30 mL) at 0 °C was added *p*-toluenesulfonyl chloride (4.82 g, 25.3 mmol), DMAP (0.029 g, 0.24 mmol), and triethylamine (1.84 mL, 13.2 mmol). The reaction mixture was allowed to warm to room temperature over 12 hours and was then diluted with water (30 mL). The layers were separated and the aqueous phase was then extracted with DCM (2 x 15 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was then subjected to flash chromatography (ethyl acetate and pentane mixtures) to give the purified racemic product **40a** (2.50 g, 65 %) as a white powder. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.76 (2H, d, *J* = 8.4 Hz, Ar**H**), 7.35-7.29 (5H, m, Ar**H**), 7.28 (2H, d, *J* = 7.9 Hz, Ar**H**), 5.80 (1H, s, ArC**H**), 3.68 (3H, s, CO_2C**H**$_3$), 2.42 (3H, s, ArC**H**$_3$). Preparation of the above reported α-tosyloxy ester **9a** was similar to that previously

reported[82] and the obtained spectral properties were also consistent with previously reported data.[83]

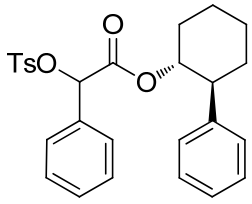
(S)-Methyl 2-phenyl-2-(tosyloxy)acetate (40b)



(S)-**40b**

Compound *(S)*-**40b** was prepared using commercially available (S)-(+)-methyl mandolate (0.150 g, 0.90 mmol) and the above outlined General Procedure **C** for the synthesis of α-tosyloxy esters. Flash chromatography (ethyl acetate and pentane mixtures) afforded the enantiopure product *(S)*-**40b** (0.257 g, 89 %) as a white powder. Spectral properties were consistent with previously reported data.[83]

2-Phenylcyclohexyl 2-phenyl-2-(tosyloxy)acetate (39)

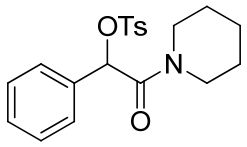


39

Compound **39** was prepared following General Procedure **C** outlined above for the synthesis of α-tosyloxy esters using compound **38** (0.200 g, 0.64 mmol) and DCM (0.1 M). Flash chromatography (pentane, followed by pentane:EtOAc, 9:1) afforded the purified product **39** (0.311 g, 100 % conversion determined by ^{1}H-NMR, contaminated with 14 % ethyl acetate determined by ^{1}H-NMR). **^{1}H-NMR** (400 MHz, $CDCl_3$, 1.8:1 mixture of diastereomers, signals corresponding to the major indicated by *) δ 7.70 (2H, d, J = 8.3 Hz, Ar**H***), 7.64 (2H, d, J = 8.3 Hz, Ar**H**), 2.27-2.15 (4H, m, Ar**H***, Ar**H**), 7.10-7.01 (4H, m, Ar**H***, Ar**H**), 6.95-6.93 (2H, m, Ar**H***, Ar**H**), 6.82-6.78 (2H, m, Ar**H***, Ar**H**), 5.58 (1H, s, ArC**H***), 5.47 (1H, s, ArC**H**), 4.99

(1H, m, CO_2CH^*, CO_2CH), 2.72 (1H, m, $ArCHCH_2$), 2.57 (1H, m, $ArCH^*CH_2$), 2.42 (3H, s, $ArCH_3$), 2.40 (3H, s, $ArCH^*_3$), 2.06-1.70 (4H, m, $-CH^*_2-$, $-CH_2-$), 1.58-1.29 (4H, m, $-CH^*_2-$, $-CH_2-$).

2-Oxo-1-phenyl-2-(piperidin-1-yl)ethyl 4-methylbenzenesulfonate (54)

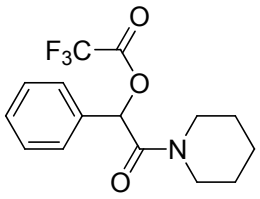


54

Compound **53** (0.300 g, 1.37 mmol) was dissolved in DCM (2.8 mL) and cooled to 0 ^oC. Pyridine (112 μL, 1.38 mmol) and *p*-toluenesulfonic anhydride (0.469 g, 1.44 mmol) were then added and the reaction mixture was allowed to slowly warm to room temperature. After 11 hours of stirring, the reaction was diluted with DCM (15 mL) and washed with aqueous 1 M HCl (20 mL). The layers were separated and the aqueous phase was extracted with DCM (3 x 15 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was then subjected to flash chromatography (DCM:EtOAc, 95:5) to give the purified product **54** (0.331 g, 65 %) as a white powder. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.81 (2H, d, *J* = 8.4 Hz, Ar**H**), 7.37-7.31 (5H, m, Ar**H**), 7.28 (2H, d, *J* = 8.0 Hz, Ar**H**), 6.15 (1H, s, ArC**H**), 3.47-3.44 (2H, m, $CONCH_2-$), 3.28-3.25 (2H, m, $CONCH_2-$), 2.42 (3H, s, $ArCH_3$), 1.55-1.17 (6H, m, $-CH_2-$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 164.52, 144.98, 133.59, 133.37, 129.73, 129.36, 128.96, 128.25, 127.38, 79.39, 46.59, 43.68, 25.67, 25.39, 24.35, 21.76; **IR** (cm^{-1}) ν 3035 (w), 2937 (w), 2858 (w), 1656 (s), 1598 (w), 1444 (s), 1364 (s), 1189 (m), 1174 (s), 1096 (m), 1020 (w), 972 (s), 838 (s). Preparation of the above reported α-tosyloxy amide **54** was similar to that previously reported for related α-tosyloxy ketones[58] and is a known compound.[80]

General Procedure D: Synthesis of α-trifluoroacetoxy amides and esters

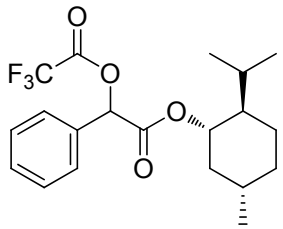
2-Oxo-1-phenyl-2-(piperidin-1-yl)ethyl 2,2,2-trifluoroacetate (55)



55

Trifluoroacetic anhydride (1.3 mL, 9.35 mmol) was added to a round bottom flask containing compound **53** (0.500 g, 2.28 mmol) and a magnetic stir bar. After stirring for 10 minutes at room temperature, DCM (1 mL) was added to fully dissolve the mixture. The reaction mixture was then stirred for 5 hours at room temperature, diluted with DCM (5 mL) and concentrated under reduced pressure. Toluene (3 mL) and DCM (3mL) were then added and the mixture was concentrated under reduced pressure (repeated twice). The product was then placed under high vacuum for 8 hours, affording the product **55** (0.687 g, 96 %) as a fibrous white solid. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.48-7.42 (5H, m, Ar**H**), 6.31 (1H, s, ArC**H**), 3.69-3.64 (1H, m, CONC**H**$_2$-), 3.51-3.45 (1H, m, CONC**H**$_2$-), 3.35-3.22 (2H, m, CONC**H**$_2$-), 1.66-1.50 (4H, m, -C**H**$_2$-), 1.48-1.38 (2H, m, -C**H**$_2$-); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 163.85, 157.46, 157.03, 132.32, 130.23, 129.44, 128.74, 116.01, 113.17, 76.93, 46.59, 44.00, 25.60, 25.48, 24.34; **^{19}F-NMR** (376 MHz, $CDCl_3$) 75.15; **IR** (cm^{-1}) ν 2955 (w), 2937 (w), 2873 (w), 1782 (s), 1641 (s), 1473 (m), 1451 (m), 1382 (m), 1318 (w), 1222 (s), 1169 (s), 1138 (s), 1018 (w), 972 (s), 695 (s).

(1S,2R,5S)-2-Isopropyl-5-methylcyclohexyl 2-phenyl 2,2,2-trifluoroacetate (45)



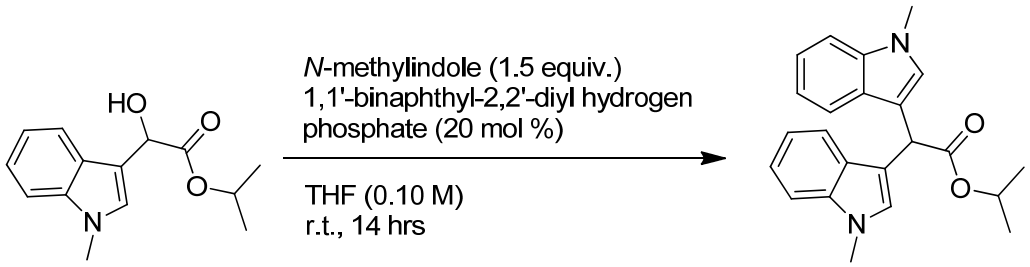
45

Compound **45** was prepared following General Procedure **D** outlined above for the synthesis of α-trifluoroacetoxy esters using compound **44** (0.132 g, 0.46 mmol) and trifluoroacetic anhydride (0.25 mL, 1.82 mmol). Reaction time was 12 hours. Removal of the residual trifluoroacetic acid and trifluoroacetic anhydride was achieved as described in General Procedure **D**, affording the product **45** (0.182 g, 100 % conversion determined by ^{1}H-NMR, contaminated with 6 % trifluoroacetic anhydride determined by ^{19}F-NMR). **^{1}H-NMR** (400 MHz, $CDCl_3$, mixture of diastereomers, indistinguishable signals indicated by **) δ 7.48-7.41 (5H, m, Ar**H***, Ar**H**), 6.01 (1H, s, ArC**H**, ArC**H***), 4.80-4.64 (1H, m, CO_2C**H***, CO_2C**H**), 2.05-2.01 (2H, m, -C**H****-), 1.90-1.78 (2H, m, -C**H****-), 1.68-1.63 (4H, m, -C**H****-), 1.53-1.39 (3H, m, -C**H****-), 1.35-1.33 (1H, m, -C**H****-), 1.29-1.26 (1H, m, -C**H****-), 1.22-1.15 (1H, m, -C**H****-), 1.12-0.98 (3H, m, -C**H****-), 0.96-0.79 (2H, m, -C**H****-), 0.90 (3H, d, *J* = 7.1 Hz, C**H***$_3$CHCH$_3$, C**H**$_3$CHCH$_3$), 0.85 (3H, *J* = 6.6 Hz, C**H***$_3$CH), 0.75 (3H, *J* = 7.0 Hz, C**H**$_3$CH), 0.65 (3H, d, *J* = 7.0 Hz, C**H**$_3$CHCH$_3$), 0.46 (3H, d, *J* = 6.9 Hz, C**H***$_3$CHCH$_3$); **^{19}F-NMR** (376 MHz, $CDCl_3$) δ 75.23.

4.4 Brønsted acid and Lewis acid-mediated nucleophilic substitutions

General Procedure E: Brønsted acid-mediated nucleophilic substitutions

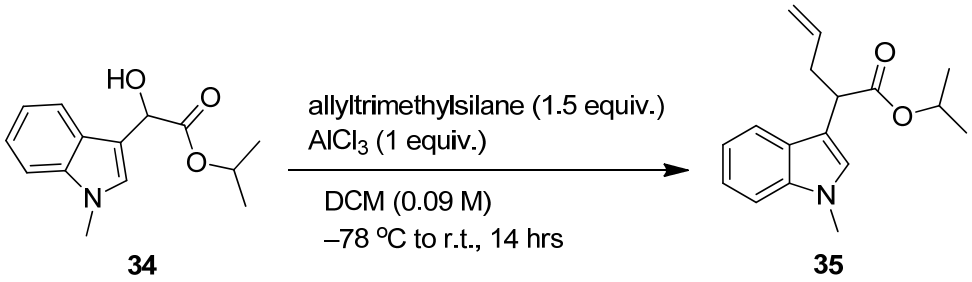
Isopropyl 2,2-bis(1-methyl-1H-indol-3-yl)acetate (36)



To a stirred solution of compound **34** (0.032 g, 0.13 mmol) and *N*-methylindole (24 μL, 0.19 mmol) in THF (1.25 mL) was added 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (0.009 g, 0.03 mmol) at room temperature. After 14 hours the reaction was diluted with ethyl acetate (2 mL), quenched with water (2 mL), and extracted with ethyl acetate (3 x 1.5 mL). The combined organic phases were then dried over Na_2SO_4, and concentrated under reduced pressure. The residue was then subjected to flash chromatography (pentane:EtOAc, 9:1 then 4:1) to give the purified product **36** (0.010 g, 21 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.65 (2H, d, J = 8.0 Hz, Ar**H**), 7.29 (2H, d, J = 8.2 Hz, Ar**H**), 7.22 (2H, m, Ar**H**), 7.09 (2H, m, Ar**H**), 7.01 (2H, s, CH_3NC**H**), 5.46 (1H, s, CC**H**CO_2), 5.08 (1H, septet, J = 6.3 Hz, CO_2C**H**$(CH_3)_2$), 3.73 (6H, s, NC**H**$_3$), 1.24 (6H, d, J = 6.3 Hz, $CO_2CH(C$**H**$_3)_2$).

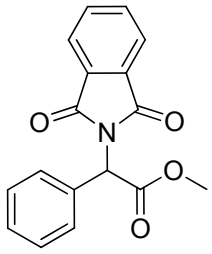
General Procedure F: Lewis acid-mediated nucleophilic substitutions

Isopropyl 2-(1-methyl-1H-indol-3-yl)pent-4-enoate (35)



A stirred solution of compound **34** (0.027 g, 0.11 mmol) and allyltrimethylsilane (26 µL, 0.16 mmol) in DCM (1.25 mL) was cooled to –78 °C and then aluminum trichloride (0.015 g, 0.11 mmol) was added. The reaction mixture was allowed to warm to room temperature over 14 hours and was then diluted with DCM (1 mL) and quenched with water (1.5 mL). The aqueous phase was then extracted with DCM (3 x 1.5 mL) and the combined organic phases were then dried over Na_2SO_4, and concentrated under reduced pressure. The residue was then subjected to flash chromatography (pentane:EtOAc, 25:1 then 9:1) to give the purified product **35** (0.012 g, 41 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.70 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.29 (1H, d, *J* = 8.2 Hz, Ar**H**), 7.22 (1H, m, Ar**H**), 7.11 (1H, t, *J* = 6.9 Hz, Ar**H**), 7.03 (1H, s, CH_3NC**H**), 5.83 (1H, m, CH_2C**H**CH_2CH), 5.12 (1H, dq, *J* = 17.1, 1.6 Hz, C**H**$_2CHCH_2CH$), 5.04-5.01 (1H, m, C**H**$_2CHCH_2CH$), 5.01 (1H, septet, *J* = 6.3 Hz, CO_2C**H**$(CH_3)_2$), 3.92 (1H, dd, *J* = 9.0, 6.3 Hz, CC**H(**$CH_2)CO_2$), 3.76 (3H, s, NC**H**$_3$), 2.86 (1H, m, CCH**(**C**H**$_2$)CH), 2.63 (1H, m, CCH**(**C**H**$_2$)CH), 1.24 (3H, d, *J* = 6.3 Hz, $CO_2CH(C$**H**$_3)_2$), 1.16 (3H, d, *J* = 6.3 Hz, $CO_2CH(C$**H**$_3)_2$).

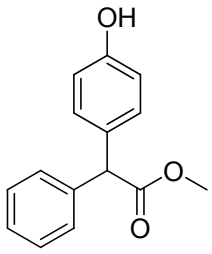
Methyl 2-(1,3-dioxoisoindolin-2-yl)-2-phenylacetate (41a)



41a

Compound **41a** was prepared following General Procedure **F** outlined above using compound *rac*-**40a** (0.050 g, 0.16 mmol), phthalimide (0.034 g, 0.23 mmol), aluminum trichloride (0.021 g, 0.16 mmol), and DCM (0.09 M). The crude ^{1}H-NMR showed only residual phthalimide and complete conversion of the starting material to the desired product **41a** (0.048 g, 100 % conversion determined by ^{1}H-NMR, contaminated with 23 % phthalimide determined by ^{1}H-NMR). Flash chromatography (pentane:EtOAc, 4:1) resulted in decomposition and only phthalimide (0.026 g) was recovered. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.89-7.86 (2H, m, Ar**H**), 7.78-7.75 (2H, m, Ar**H**), 7.51-7.48 (2H, m, Ar**H**), 7.39-7.37 (3H, m, Ar**H**), 5.37 (1H, s, ArC**H**), 3.78 (3H, s, $CO_2C\mathbf{H}_3$); **^{1}H-NMR** (400 MHz, $(CD_3)_2SO$) δ 7.78 (4H, s, Ar**H**), 7.49-7.36 (5H, m, Ar**H**), 5.90 (1H, s, ArC**H**), 3.69 (3H, s, $CO_2C\mathbf{H}_3$); **^{13}C-NMR** (100 MHz, $(CD_3)_2SO$) δ 168.51, 136.23, 132.62, 129.21, 128.88, 128.01, 58.51, 53.24; **IR** (cm^{-1}) ν 3180 (m), 3059 (m), 2957 (w), 2849 (w), 2719 (w), 1773 (m), 1738 (s), 1603 (m), 1497 (w), 1467 (m), 1456 (m), 1436 (m), 1374 (s), 1358 (s), 1306 (s), 1287 (s), 1186 (m), 1165 (m), 1142 (m), 1089 (w), 1070 (w), 1051 (s), 1006 (m), 712 (s). The above mentioned α-phthalimido ester **41a** was previously reported[84, 85] and the obtained spectral properties were consisted with previously reported data.[86]

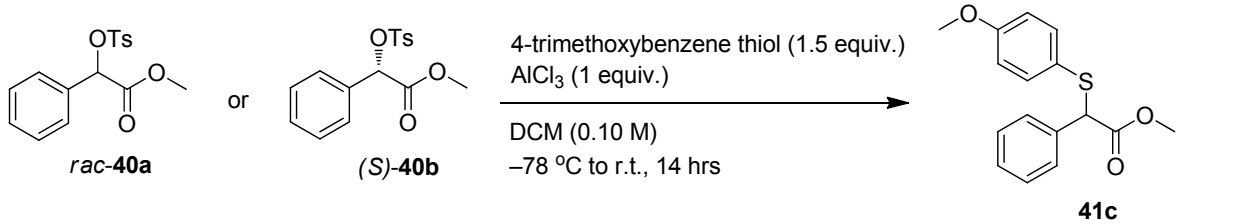
Methyl 2-(4-hydroxyphenyl)-2-phenylacetate (41b)



41b

Compound **41b** was prepared following General Procedure **F** outlined above using compound *rac*-**40a** (0.030 g, 0.18 mmol), phenol (0.085 g, 0.90 mmol), aluminum trichloride (0.024 g, 0.18 mmol), and DCM (0.12 M). The residue was then subjected to flash chromatography (ethyl acetate and pentane mixtures) to give the purified product **41b** (0.011 g, 48 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.33-7.23 (5H, m, Ar**H**), 7.16 (2H, d, *J* = 8.7 Hz, Ar**H**), 6.75 (2H, d, *J* = 8.6 Hz, Ar**H**), 4.99 (1H, br s, ArO**H**), 4.97 (1H, s, ArC**H**), 3.74 (3H, s, $CO_2C\mathbf{H}_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 173.55, 154.96, 138.99, 130.94, 130.01, 128.75, 128.59, 127.37, 115.60, 56.33, 52.50; **IR** (cm^{-1}) ν 3392 (s), 3030 (w), 2953 (w), 1712 (s), 1613 (m), 1596 (m), 1513 (s), 1496 (m), 1436 (m), 1348 (m), 1201 (s), 1153 (s), 1007 (m), 822 (m), 737 (m), 698 (s); **HRMS** (EI) *m/z* for $C_{15}H_{14}O_3$ calculated (M^+) 242.0943, found 242.0946. The above mentioned compound **41b** has been reported in the patent literature.[87]

Methyl 2-(4-methoxyphenylthio)-2-phenylacetate (41c)



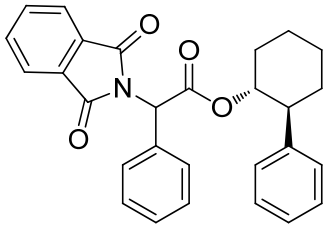
rac-**40a** *(S)*-**40b** **41c**

using *rac*-**40a** (82 %, 0 % *ee*)
using *(S)*-**40b** (87 %, 41 % *ee*)

Compound **41c** was prepared following General Procedure **F** outlined above using racemic compound **40a** (0.050 g, 0.16 mmol), 4-methoxybenzene thiol (29 μL, 0.23 mmol), aluminum trichloride (0.021 g, 0.16 mmol), and DCM (0.10 M). Flash chromatography (pentane:EtOAc,

4:1) afforded the purified product **41c** (0.031 g, 82 %) and chiral HPLC analysis showed 0 % ee. Enantiopure compound *(S)*-**40b** was also used in the same way to prepare compound **41c** (0.033 g, 87 %) and chiral HPLC analysis showed 41 % ee. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.40 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.34-7.28 (5H, m, Ar**H**), 6.79 (2H, d, *J* = 8.8 Hz, Ar**H**), 4.77 (1H, s, ArC**H**S), 3.78 (3H, s, $CO_2C\mathbf{H}_3$), 3.67 (3H, s, $C\mathbf{H}_3OAr$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 171.11, 160.35, 136.34, 135.92, 132.79, 128.70, 128.31, 123.75, 114.74, 114.61, 57.52, 55.42, 52.71; **IR** (cm^{-1}) ν 2951 (w), 2918 (m), 2850 (w), 1736 (s), 1591 (m), 1571 (w), 1492 (s), 1455 (m), 1286 (s), 1246 (s), 1172 (m), 1147 (s), 1030 (m), 829 (m), 697 (m); **HRMS** (ESI) *m/z* for $C_{16}H_{16}O_3NaS$ calculated (MNa^+) 311.0712, found 311.0703. The ethyl ester version of this compound has been reported in the patent literature.[88]

2-Phenylcyclohexyl 2-(1,3-dioxoisoindolin-2-yl)-2-phenylacetate (42a)

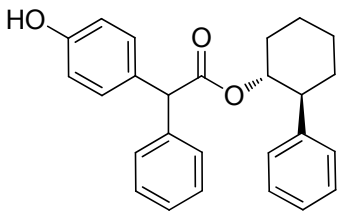


42a

Compound **42a** was prepared following General Procedure **F** outlined above using compound **39** (0.060 g, 0.13 mmol), phthalimide (0.029 g, 0.19 mmol), aluminum trichloride (0.017 g, 0.13 mmol), and DCM (0.09 M). Analysis of the crude ^{1}H-NMR showed a 1.4:1 mixture of diastereomers. An aliquot of the crude product was filtered through a short plug of silica gel (pentane:EtOAc, 4:1) affording the purified product **42a** (0.029 g, 51 %). **^{1}H-NMR** (400 MHz, $CDCl_3$, 1.5:1 mixture of diastereomers, signals corresponding to the major indicated by *) δ 7.29-7.15 (9H, m, Ar**H***, Ar**H**), 7.13-7.08 (3H, m, Ar**H***, Ar**H**), 7.04-7.01 (2H, m, Ar**H***, Ar**H**), 5.12 (1H, s, ArC**H**N), 5.09 (1H, s, ArC**H***N), 5.07-5.01 (1H, m, $ArCO_2C\mathbf{H}^*$, $ArCO_2C\mathbf{H}$), 2.72 (1H, m, ArC**H***CH_2), 2.63 (1H, m, ArC**H**CH_2), 2.20-2.07 (1H, m, -C**H***$_2$-, -C$\mathbf{H}_2$-), 1.98-1.75 (3H, m, -C**H***$_2$-, -C$\mathbf{H}_2$-), 1.61-1.30 (4H, m, -C**H***$_2$-, -C$\mathbf{H}_2$-); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 167.70, 167.61, 142.73, 142.42, 136.12, 135.71, 128.98, 128.79, 128.74, 128.71, 128.60, 128.37, 127.87, 127.62, 127.55, 127.43, 126.72, 126.56, 78.63, 78.48, 59.51, 59.38, 49.73, 49.60, 34.11,

32.25, 31.85, 25.81, 24.81, 24.74; **IR** (cm^{-1}) ν 3030 (w), 2930 (s), 2858 (m), 1749 (s), 1727 (s), 1603 (w), 1495 (m), 1450 (m), 1272 (s), 1163 (s), 1124 (m), 1010 (s), 972 (w), 755 (m), 727 (m), 698 (s); **HRMS** (EI) *m/z* (relative intensity, molecular ion not seen) 293.2 (2), 247.2 (100), 203.1 (4), 132.1 (4).

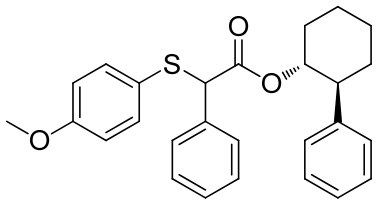
2-Phenylcyclohexyl 2-(4-hydroxyphenyl)-2-phenylacetate (42b)



42b

Compound **42b** was prepared following General Procedure **F** outlined above using compound **39** (0.060 g, 0.13 mmol), phenol (0.061 g, 0.65 mmol), aluminum trichloride (0.017 g, 0.13 mmol), and DCM (0.09 M). Analysis of the crude ^{1}H-NMR showed a 1.1:1 mixture of diastereomers. The residue was then subjected to flash chromatography (ethyl acetate and pentane mixtures) to give the purified product **42b** (0.010 g, 20 %). **^{1}H-NMR** (400 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers, signals corresponding to the major indicated by *) δ 7.25-7.09 (8H, m, Ar**H***, Ar**H**), 7.03-7.01 (1H, m, Ar**H***, Ar**H**), 6.88 (1H, d, *J* = 8.7 Hz, Ar**H***, Ar**H**), 6.77 (1H, m, Ar**H***, Ar**H**), 6.64 (2H, m, Ar**H***, Ar**H**), 6.56 (1H, *J* = 8.6 Hz, Ar**H***, Ar**H**), 5.10 (2H, m, CO_2C**H***, CO_2C**H**), 4.75 (1H, br s, ArO**H***, ArO**H**), 4.70 (1H, s, ArC**H**), 4.69 (1H, s, ArC**H***), 2.65 (2H, m, ArC**H***CH_2, ArC**H**CH_2), 2.12-2.08 (1H, m, -C**H***$_2$-, -C**H**$_2$-), 1.94-1.89 (1H, m, -C**H***$_2$-, -C**H**$_2$-), 1.85-1.75 (2H, m, -C**H***$_2$-, -C**H**$_2$-), 1.60-1.29 (4H, m, -C**H***$_2$-, -C**H**$_2$-); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 172.20, 154.62, 154.40, 143.20, 139.22, 138.80, 131.33, 130.11, 129.74, 128.72, 128.53, 128.37, 128.35, 127.75, 127.03, 126.77, 126.58, 126.55, 115.38, 115.24, 76.96, 76.94, 56.63, 56.58, 49.87, 49.85, 34.31, 34.29, 29.85, 25.90, 24.83; **IR** (cm^{-1}) ν 3400 (m), 3027 (w), 2929 (s), 2858 (m), 1704 (s), 1614(m), 1597 (w), 1514 (s), 1495 (m), 1495 (m), 1449 (m), 1351 (w), 1196 (s), 1174 (s), 1124 (m), 1112 (m), 756 (m), 700 (s); **HRMS** (EI) *m/z* for $C_{26}H_{26}O_3$ calculated (M^+) 386.1882, found 386.1871.

2-Phenylcyclohexyl 2-(4-methoxyphenylthio)-2-phenylacetate (42c)

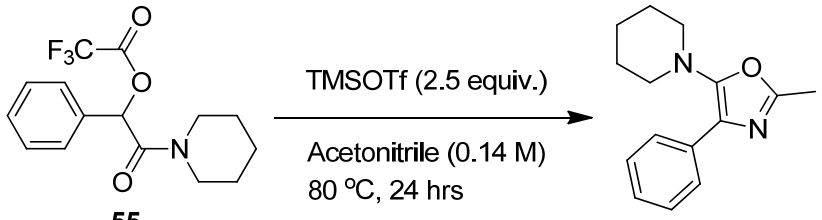


42c

Compound **42c** was prepared following General Procedure **F** outlined above using compound **39** (0.060 g, 0.13 mmol), 4-methoxybenzene thiol (40 μL, 0.32 mmol), aluminum trichloride (0.017 g, 0.13 mmol), and DCM (0.09 M). Analysis of the crude ^{1}H-NMR showed a 2:1 mixture of diastereomers. Flash chromatography (pentane:EtOAc, 9:1, then 4:1) afforded the purified product **42c** (0.043 g, 77 %). **^{1}H-NMR** (400 MHz, $CDCl_3$, 2.0:1 mixture of diastereomers, signals corresponding to the major indicated by *) δ 7.28-7.06 (10H, m, Ar**H***, Ar**H**), 6.98-6.96 (2H, m, Ar**H***, Ar**H**), 6.84 (2H, d, *J* = 8.7 Hz, Ar**H**), 6.70 (2H, d, *J* = 8.7 Hz, Ar**H***), 5.01 (1H, m, CO_2C**H***, CO_2C**H**), 4.52 (1H, ArC**H**S), 4.51 (1H, s, ArC**H***S), 3.80 (3H, s, C**H**$_3$OAr), 3.78 (3H, s, C**H***$_3$OAr), 2.72 (1H, m, ArC**H***CH_2), 2.60 (1H, m, ArC**H**CH_2), 2.22-1.74 (4H, m, -C**H***$_2$-, -C**H**$_2$-), 1.61-1.21 (4H, m, -C**H***$_2$-, -C**H**$_2$-); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 169.99, 169.68, 160.05, 159.86, 143.05, 142.65, 136.13, 135.98, 132.79, 132.55, 129.06, 128.97, 128.78, 128.59, 128.53, 128.47, 128.41, 128.38, 128.31, 128.23, 127.85, 127.79, 127.68, 127.61, 127.52, 127.42, 126.71, 126.55, 126.46, 124.41, 124.19, 119.95, 114.86, 114.75, 77.65, 77.39, 55.48, 55.40, 49.66, 49.55, 34.45, 34.03, 32.18, 31.98, 31.84, 25.88, 25.84, 24.82, 24.77; **IR** (cm^{-1}) ν 3029 (w), 2932 (m), 2858 (w), 1725 (m), 1591 (m), 1572 (w), 1493 (s), 1453 (m), 1285 (m), 1244 (s), 1172 (m), 1151 (m), 1124 (m), 1031 (m), 1011 (m), 972 (w), 822 (m), 699 (m); **HRMS** (EI) *m/z* for $C_{27}H_{28}O_3NaS$ calculated (MNa^+) 455.1651, found 455.1637.

4.5 Lewis acid-mediated oxazole formation

1-(2-Methyl-4-phenyloxazol-5-yl)piperidine (58)



55 **58**

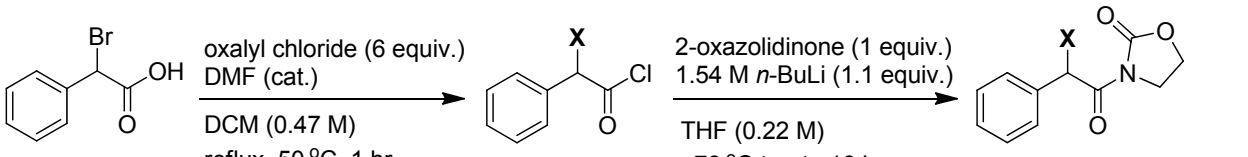
To a stirred solution of compound **55** (0.050 g, 0.2 mmol) in acetonitrile (1.5 mL) at room temperature was added trimethylsilyl trifluoromethanesulfonate (92 µL, 0.5 mmol). The solution was subsequently heated at 80 ^{o}C for 24 hours. Heating was discontinued and the mixture was allowed to cool to room temperature. The reaction mixture was then diluted with ethylacetate (3 mL) and quenched with water (1 mL). After separation of the layers, the aqueous phase was extracted with ethyl acetate (3 x 1 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to yield the crude product **58** as a white/yellow powder. Crude product **58** was then dissolved in a pentane:ethyl acetate (9:1) mixture and allowed to precipitate in the fridge (4 ^{o}C) overnight. The mother liquor was removed and the precipitated product was dissolved in a minimum amount of ethyl acetate and re-precipitated by the addition of pentane. The flask was placed in the fridge (4 ^{o}C) overnight, after which the mother liquor was removed and any remaining solvent residue was taken off *in vacuo* to yield the pure product **58** (0.047 g, 96 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.72 (2H, d, *J* = 7.2 Hz, Ar**H**), 7.49 (2H, m, Ar**H**), 7.42 (1H, m, Ar**H**), 3.15 (4H, m, NC**H**$_2$), 2.91 (3H, s, C**H**$_3$), 1.76-1.71 (4H, m, -C**H**$_2$-), 1.68-1.63 (2H, m, -C**H**$_2$-); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 129.96, 129.71, 129.51, 127.97, 126.43, 123.88, 50.83, 31.08, 25.53, 23.47, 13.43; **IR** (cm^{-1}) ν 2940 (w), 2833 (w), 1663 (m), 1612 (m), 1454 (w), 1400 (w), 1381 (w), 1275 (s), 1232 (s), 1174 (s), 1111 (w), 1031 (s), 898 (m), 772 (m), 696 (m); **HRMS** (EI) *m/z* for $C_{15}H_{18}N_2O$ calculated (M^+) 242.1419, found 242.1420.

4.6 α-Chloro imides

General Procedure G: Synthesis of α-chloroimides

G.1

3-(2-Chloro-2-phenylacetyl)oxazolidin-2-one (62a)



1.940 g (99 mol % yield)
Cl:Br (2.5:1)

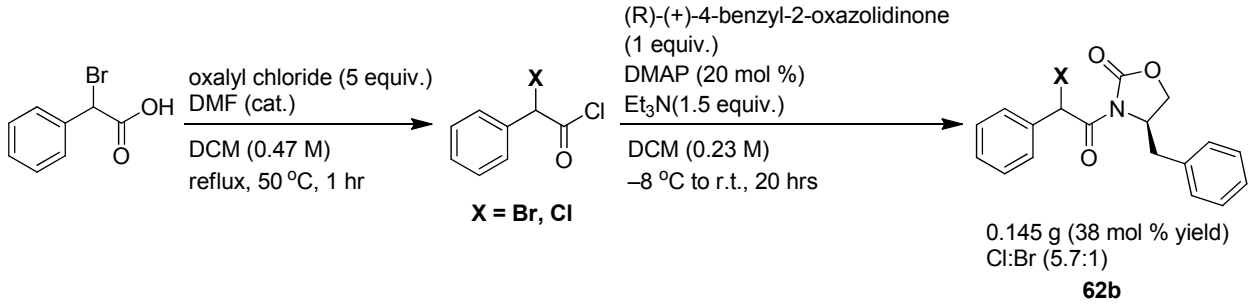
62a

To a stirred solution of α-bromophenylacetic acid (2.00 g, 9.30 mmol) in DCM (20 mL) was added oxalyl chloride (4.7 mL, 55.8 mmol), and DMF (5 drops). The reaction mixture was then refluxed at 50 °C for 1 hour, after which the solution was cooled to room temperature, and the solvent removed under reduced pressure. To rid the product of excess oxalyl chloride, DCM (10 mL) was added to the flask and removed under reduced pressure (2 times). To a stirred solution of 2-oxazolidinone (0.675 g, 7.75 mmol) dissolved in THF (24 mL) at 0 °C was added 1.54 M *n*-butyllithium in hexanes (5.6 mL, 8.62 mmol) drop wise. After stirring for 10 minutes the reaction mixture was cooled to –78 °C and the prepared α-halophenyl acetyl chloride dissolved in THF (6 mL) was added drop wise over a 10 minute period. The reaction mixture was allowed to slowly warm to room temperature over 16 hours, diluted with DCM (15 mL) and then quenched with saturated aqueous NH_4Cl (30 mL). The resulting mixture was then concentrated on a rotary evaporator to remove the bulk of the THF and hexanes. The layers were then separated and the aqueous phase was extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Analysis of the crude ^{1}H-NMR showed a 1:1.5 mixture of the chlorinated and brominated products respectively. The residue was then subjected to flash chromatography (pentane:EtOAc, 4:1 then 2:1) to give as a mixture the chlorinated (1.32 g, 5.49 mmol) and

brominated (0.62 g, 2.20 mmol) product **62a** (1.94 g, 99 mol % yield). **^{1}H-NMR** (400 MHz, $CDCl_3$, 2.5:1 mixture of chlorinated and brominated products, signals corresponding to the chlorinated product indicated by *) δ 7.62-7.59 (2H, m, Ar**H**), 7.58-7.55 (2H, m, Ar**H***), 7.40-7.34 (3H, m, Ar**H***, Ar**H**), 6.88 (1H, s, Ar**H**Br), 6.83 (1H, s, ArC**H**Cl), 4.48-4.34 (2H, m, C**H***$_2$, C**H**$_2$), 4.16-3.95 (2H, m, C**H***$_2$, C**H**$_2$); **^{13}C-NMR** (100 MHz, $CDCl_3$, mixture of chlorinated and brominated products) δ 167.67, 167.48, 152.83, 135.32, 135.29, 129.52, 129.50, 129.43, 128.92, 128.86, 62.40, 62.28, 56.80, 44.80, 43.16, 43.07; **HRMS** (EI) *m/z* for $C_{11}H_{10}NO_3Cl$ calculated (M^+) 239.0349, found 239.0352; **LRMS** (EI) *m/z* (relative intensity, chlorinated product) 241.1 (7.8), 239.1 (20.8), 153.1 (5.4), 155.2 (1.7), 125.1 (80.5), 127.1 (23.9), 89.1 (100); **LRMS** (EI) *m/z* (relative intensity, brominated product) 285.0 (2.0), 283.0 (1.1), 254.8 (0.2), 198.0 (7.6), 196.1 (6.8), 171.1 (3.2), 169.1 (3.5), 90.0 (100). The above mentioned α-chloro imide **62a** was obtained instead of the desired α-bromo imide using previously reported chemistry.[89, 66] Previous reports on chlorination instead of bromination have been made on similar α-halo imides.[68, 67]

G.2

(4R)-4-Benzyl-3-(2-chloro-2-phenylacetyl)oxazolidin-2-one (62b)



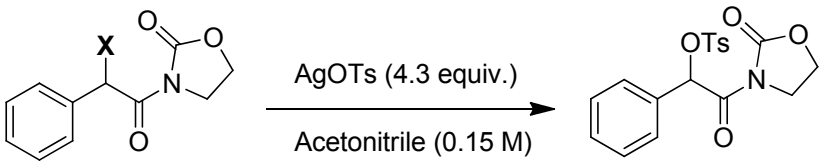
α-Halophenyl acetyl chloride (0.395 g, 1.69 mmol) was prepared at outlined in the General Procedure **G.1**, except oxalyl chloride (5 equiv.) was used. Next, (R)-4-benzyl-2-oxazolidinone (0.200 g, 1.13 mmol), DMAP (0.028 g, 0.26 mmol), and triethyl amine (235 μL, 1.67 mmol) were dissolved in DCM (3.2 mL) and cooled to –8 °C. The prepared α-halophenyl acetyl chloride dissolved in DCM (1.7 mL) was added dropwise over a 10 minute period. The reaction mixture was allowed to warm to room temperature over a period of 20 hours, diluted with DCM

(5 mL) and then quenched with saturated aqueous NH_4Cl (15 mL). After separation of the layers, the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic layers were washed with water (2 x 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Analysis of the crude ^{1}H-NMR showed a 5.3:1 mixture of the chlorinated and brominated products respectively. The residue was then subjected to flash chromatography (pentane:EtOAc, 9:1 and then 4:1) to give as a mixture the chlorinated (0.121 g, 0.37 mmol) and brominated (0.024 g, 0.06 mmol) product **62b** (0.145 g, 38 mol % yield). **^{1}H-NMR** (400 MHz, $CDCl_3$, 1.2:1 mixture of chlorinated diastereomers, signals corresponding to the major indicated by *; 5.7:1 mixture of chlorinated and brominated products, only peaks for ArC**H**Br* and ArC**H**Br are indicated for the brominated product) δ 7.64-7.56 (2H, m, Ar**H***, Ar**H**), 7.43-7.19 (7H, m, Ar**H***, Ar**H**), 6.96-6.93 (1H, m, Ar**H***, Ar**H**), 6.90 (1H, s, ArC**H**Br), 6.89 (1H, s, ArC**H**Br*), 6.85 (1H, s, ArC**H**Cl), 6.84 (1H, s, ArC**H***Cl), 4.83-4.75 (1H, m, NC**H***), 4.67-4.60 (1H, m, NC**H**), 4.31-4.16 (2H, m, $CO_2C\mathbf{H}^*_2$, $CO_2C\mathbf{H}_2$), 3.39 (1H, dd, *J* = 13.4, 3.1 Hz, ArC$\mathbf{H}_2$), 3.10 (1H, dd, *J* = 13.6, 3.3 Hz, ArC$\mathbf{H}^*_2$), 2.88 (1H, dd, *J* = 13.4, 9.5 Hz, ArC$\mathbf{H}_2$), 2.66 (1H, dd, *J* = 13.5, 8.7 Hz, ArC$\mathbf{H}^*_2$); **LRMS** (EI) *m/z* (relative intensity, chlorinated product) 330.9 (0.4), 329.1 (3.0), 211.5 (0.2), 176.9 (0.8), 153.2 (0.8), 127.2 (8.3), 125.1 (49.2), 118.1 (60.8), 91.1 (100); **LRMS** (EI) *m/z* (relative intensity, brominated product) 373.4 (0.5), 253.1 (0.4), 176.9 (0.8), 118.1 (60.8), 91.1 (100). The above mentioned α-chloro imide **62b** was obtained instead of the desired α-bromo imide using previously reported chemistry (oxalyl chloride was used instead of thionyl chloride).[65]

4.7 α-Tosyloxy imides

General Procedure H: Synthesis of α-tosyloxy imides

2-Oxo-2-(2-oxooxazolidin-3-yl)-1-phenylethyl 4-methylbenzenesulfonate (63a)

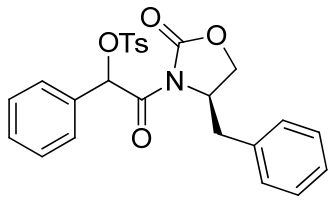


X = Br, Cl
62a Cl:Br (8.3:1)

63a

Silver *p*-toluenesulfonate (1.07 g, 3.84 mmol) was added to a stirred solution of compound **62a** (0.218 g, 0.89 mmol, Cl:Br ratio of 8.3:1) in acetonitrile (6 mL) and heated for 21 hours at 80 °C. The reaction mixture was subsequently cooled to room temperature, filtered through a cotton plug to remove the silver salts that had precipitated during the reaction, and the acetonitrile removed under reduced pressure. The resulting residue was dissolved in toluene, filtered again through a cotton plug to remove the last traces of silver bromide, and the toluene removed under reduced pressure. Flash chromatography (pentane:EtOAc, 4:1 then 2:1) then gave the purified product **63a** (0.202 g, 60 %) as a colourless, transparent oil. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.74 (2H, d, *J* = 8.4 Hz, Ar**H**), 7.45-7.40 (5H, m, Ar**H**), 7.32 (2H, d, *J* = 8.0 Hz, Ar**H**), 5.73 (1H, s, ArC**H**), 4.37-4.27 (2H, m, C**H**$_2$), 3.86 (2H, m, C**H**$_2$), 2.44 (3H, s, ArC**H**$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 170.94, 154.73, 145.42, 132.55, 131.29, 130.11, 130.03, 129.25, 128.10, 126.40, 80.65, 64.82, 39.48, 21.81; **IR** (cm^{-1}) ν 3069 (w), 2922 (w), 1817 (m), 1742 (s), 1597 (w), 1496 (w), 1436 (m), 1408 (m), 1358 (m), 1190 (m), 1174 (s), 1120 (m), 1097 (m), 1018 (m), 981 (m), 899 (m). **HRMS** (EI) *m/z* for $C_{18}H_{17}NO_6S$ calculated (MH^+) 376.0849, found 376.0849. Preparation of the above reported α-tosyloxy oxazolidinone **63a** was accomplished using previously reported chemistry for similar compounds.[64]

2-((R)-4-Benzyl-2-oxooxazolidin-3-yl)-2-oxo-1-phenylethyl 4-methylbenzenesulfonate (63b)



63b

Compound **63b** was prepared following General Procedure **H** outlined above for the synthesis of α-tosyloxy imides using compound **62b** (0.073 g, 0.22 mmol, Cl:Br ratio of 5.7:1) and 5 equivalents of silver *p*-toluenesulfonate. Flash chromatography (pentane:EtOAc, 9:1 then 4:1) then gave the purified product **63b** (0.039 g, 39 %) as a colourless, transparent oil. **^{1}H-NMR** (400 MHz, $CDCl_3$, 1.4:1 mixture of diastereomers, signals corresponding to the major indicated by *) δ 7.77-7.73 (2H, m, Ar**H**, Ar**H***), 7.40-7.32 (4H, m, Ar**H**, Ar**H***), 7.29-7.27 (1H, m, Ar**H**, Ar**H***), 7.25-7.22 (3H, m, Ar**H**, Ar**H***), 7.14-7.10 (2H, m, Ar**H**, Ar**H***), 7.06 (2H, d, *J* = 7.4 Hz, Ar**H**), 6.83 (2H, d, *J* = 7.6 Hz, Ar**H***), 5.50 (1H, s, ArC**H***), 5.42 (1H, s, ArC**H**), 4.75-4.59 (4H, m, NC**H***, NC**H,** $CO_2C\mathbf{H}^*_2$), 4.25-4.21 (2H, m, $CO_2C\mathbf{H}_2$), 3.21-3.12 (2H, m, ArC$\mathbf{H}^*_2$), 3.05-2.99 (2H, m, ArC$\mathbf{H}_2$); **^{13}C-NMR** (100 MHz, $CDCl_3$, diastereomers) δ 171.13, 171.02, 154.53, 154.14, 145.45, 145.40, 135.16, 135.10, 132.58, 132.53, 131.30, 130.16, 130.13, 129.93, 129.11, 129.06, 129.04, 128.99, 128.10, 127.47, 127.45, 126.87, 126.59, 80.43, 79.85, 67.19, 66.87, 53.73, 52.87, 33.48, 33.39, 21.82; **IR** (cm^{-1}) ν 3064 (w), 3032 (w), 2926 (w), 1810 (m), 1740 (s), 1598 (m), 1497 (m), 1456 (m), 1406 (s), 1363 (s), 1293 (m), 1190 (m), 1175 (s), 1096 (m), 981 (s); **HRMS** (EI) *m/z* for $C_{25}H_{23}NO_6S$ calculated (MH^+) 466.1318, found 466.1299.

4.8 α-Bromo esters, amides, and imides

General Procedure I: Synthesis of α-bromo esters and α-bromo amides

Synthesis of the α-bromo esters **47a**, **47b** and **51,** and α-bromo amide **59** were achieved using previously reported chemistry for similar compounds.[53] The racemic auxiliaries' 2-phenylcyclohexanol and 2-(1-naphthalenyl) cyclohexanol were provided courtesy of Golam Sarwar.

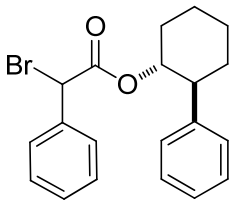
I.1

To a stirred solution of α-bromophenylacetic acid (1 equiv.), the appropriate alcohol or amide (1 equiv.) and DMAP (10 mol %) in DCM (0.2 M) was added DIC (1.05 equiv.). After stirring at room temperature for 24 hours (or until the TLC verified the reaction was complete) the reaction mixture was diluted with ether and filtered through a pad of celite to remove the precipitate. After removing the solvent under reduced pressure, the residue was dissolved in ether and washed sequentially with equal amounts of aqueous 1 M HCl and water (20 mL). The organic phase was then dried over Na_2SO_4, and concentrated under reduced pressure. The crude products were purified using flash chromatography.

I.2

A stirred solution of the appropriate alcohol (1 equiv.) and triethyl amine (1 equiv.) in dry THF (0.2 M) was cooled to 0 ^{o}C. The desired α-bromoacyl halide (1 equiv.) was then added dropwise over a period of 20 minutes. After stirring for 1.5 hours the reaction was quenched with water and then extracted with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified using flash chromatography.

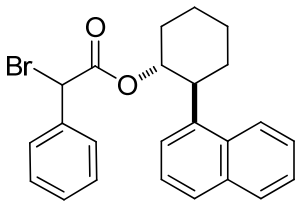
2-Phenylcyclohexyl 2-bromo-2-phenylacetate (47a)



47a

Compound **47a** was prepared following General Procedure **I.1** outlined above for the synthesis of α-bromo esters using α-bromophenylacetic acid (0.54 g, 2.5 mmol) and 2-phenylcyclohexanol (0.44 g, 2.5 mmol). Flash chromatography (pentane:EtOAc, 19:1) afforded the purified compound **47a** (0.85 g, 91%) as a oily yellow solid. **^{1}H-NMR** (400 MHz, $CDCl_3$, 1.8:1 mixture of diastereomers, signals corresponding to the major indicated by *) δ 7.27-7.05 (10H, m, Ar**H***, Ar**H**), 5.11 (1H, s, ArC**H**Br), 5.10 (1H, s, ArC**H***Br), 5.05 (1H, td, J = 10.6, 4.5 Hz, CO_2C**H*,** CO_2C**H**), 2.73 (1H, m, ArC**H***CH_2), 2.65 (1H, m, ArC**H**CH_2), 2.19-1.76 (4H, m, -C**H***$_2$-, -C**H**$_2$-), 1.61-1.29 (4H, m, -C**H***$_2$-, -C**H**$_2$-); **^{13}C-NMR** (100 MHz, $CDCl_3$, mixture of diastereomers) δ 167.49, 167.42, 142.69, 142.43, 136.04, 135.80, 128.91,128.76, 128.71, 128.64, 128.55, 128.46, 128.33, 128.29, 127.61, 127.46, 126.66, 126.54, 78.60, 78.44, 49.70, 49.61, 47.63, 47.26, 34.12, 34.02, 32.05, 31.83, 25.78, 24.75, 24.71; **IR** (cm^{-1}) ν 3062 (w), 3029 (w), 2933 (m), 2858 (m), 1740 (s), 1723 (s), 1603 (w), 1584 (w), 1495 (m), 1450 (m), 1272 (s), 1214 (s), 1144 (s), 1123 (s), 1009 (s), 755 (m), 698 (s). **HRMS** (ESI) *m/z* for $C_{20}H_{21}O_2NaBr$ calculated (MNa^+) 395.0617, found 395.0597.

2-(Naphthalen-1-yl)cyclohexyl 2-bromo-2-phenylacetate (47b)

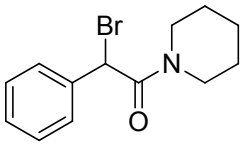


47b

Compound **47b** was prepared following General Procedure **I.1** outlined above for the synthesis of α-bromo esters using α-bromophenylacetic acid (0.38 g, 1.8 mmol) and 2-(1-naphthalenyl)

cyclohexanol (0.40 g, 1.8 mmol). Flash chromatography (pentane:EtOAc, 19:1) afforded the purified compound **47b** (0.670 g, 90%) as a yellow oil. **^{1}H-NMR** (400 MHz, $CDCl_3$, 1.3:1 mixture of diastereomers, signals corresponding to the major indicated by *) δ 8.15 (1H, d, *J* = 8.7 Hz, Ar**H***), 8.08 (1H, d, *J* = 8.4 Hz, Ar**H**), 7.86 (1H, d, *J* = 7.9 Hz, Ar**H***), 7.76 (1H, d, *J* = 7.9 Hz, Ar**H**), 7.70-7.34 (4H, m, Ar**H***, Ar**H**), 7.29-7.23 (1H, m, Ar**H***, Ar**H**), 7.16-6.91 (4H, m, Ar**H***, Ar**H**) 6.84-6.82 (1H, m, Ar**H***, Ar**H**), 5.35-5.22 (1H, m, CO_2C**H***, CO_2C**H**), 4.92 (1H, s, ArC**H***Br), 4.88 (1H, s, ArC**H**Br), 3.68 (1H, m, ArC**H***CH_2), 3.60 (1H, m, ArC**H**CH_2), 2.32-2.19 (1H, m, -C**H***$_2$-, -C**H**$_2$-), 2.10-2.00 (1H, m, -C**H***$_2$-, -C**H**$_2$-), 1.96-1.90 (1H, m, -C**H***$_2$-, -C**H**$_2$-), 1.84-1.80 (1H, m, -C**H***$_2$-, -C**H**$_2$-), 1.67-1.42 (4H, m, -C**H***$_2$-, -C**H**$_2$-); **^{13}C-NMR** (100 MHz, $CDCl_3$, diastereomers) δ 167.77, 167.59, 138.78, 138.65, 135.76, 135.30, 134.17, 133.97, 132.12, 132.07, 129.06, 129.03, 128.83, 128.61, 128.55, 128.31, 128.24, 128.02, 127.00, 126.91, 125.94, 125.79, 125.71, 125.59, 125.49, 125.30, 123.13, 123.06, 122.96, 78.58, 78.39, 47.32, 47.22, 43.29, 34.36, 34.15, 32.43, 32.21, 26.14, 24.89, 24.85; **IR** (cm^{-1}) ν 3045 (w), 2933 (m), 2858 (m), 1740 (s), 1724 (s), 1598 (w), 1511 (w), 1495 (w), 1452 (m), 1272 (s), 1212 (s), 1144 (s), 1120 (s), 1002 (s), 795 (s), 777 (s), 693 (s); **HRMS** (EI) *m/z* for $C_{24}H_{23}O_2Br$ calculated (M^+) 422.0881, found 422.0901.

2-Bromo-2-phenyl-1-(piperidin-1-yl)ethanone (59)

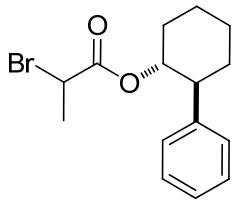


59

Compound **59** was prepared following General Procedure **I.1** outlined above for the synthesis of α-bromo amides using α-bromophenylacetic acid (1.00 g, 4.65 mmol) and piperidine (510 μL, 5.15 mmol). Flash chromatography (pentane:EtOAc, 85:15 then 4:1) afforded the purified compound **59** (0.739 g, 56 %) as a white powder. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.53-7.50 (2H, m, Ar**H**), 7.38-7.29 (3H, m, Ar**H**), 5.77 (1H, s, ArC**H**Br), 3.66-3.54 (2H, m, CONC**H**$_2$-), 3.47-3.35 (2H, m, CONC**H**$_2$-), 1.64-1.20 (6H, m, -C**H**$_2$-); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 165.38, 136.92, 128.91, 128.83, 128.70, 47.88, 47.66, 44.15, 26.05, 25.50, 24.40; **IR** (cm^{-1}) ν 3000 (w), 2936 (m), 2855 (m), 1643 (s), 1435 (s), 1351 (w), 1247 (w), 1221 (m), 1133 (m), 1013 (m), 697

(s); **HRMS** (EI) *m/z* (relative intensity) 202(16), 118(19), 112(100), 91(92), 84(30); **Anal. Calcd.** for $C_{13}H_{16}BrNO$: C, 55.33; H, 5.72; N, 4.96. Found: C, 55.38; H, 5.38; N, 4.95. The above mentioned α-bromo amide **59** was previously reported.[90, 91]

2-Phenylcyclohexyl 2-bromopropanoate (51)



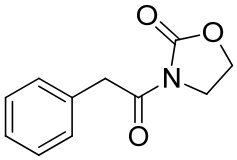
51

Compound **51** was prepared following General Procedure **I.2** outlined above for the synthesis of α-bromo esters using 2-bromopropionyl chloride (86 μL, 0.85 mmol) and 2-phenyl cyclohexanol (0.150 g, 0.85 mmol). Flash chromatography (pentane:EtOAc, 19:1) afforded the purified compound **51** (0.670 g, 90%) as a clear, colourless oil. **^{1}H-NMR** (400 MHz, $CDCl_3$, mixture of diastereomers, signals corresponding to the major indicated by *) δ 7.28-7.15 (5H, m, Ar**H***, Ar**H**), 5.01 (1H, m, CO_2C**H***, CO_2C**H**), 4.08 (1H, q, *J* = 6.9 Hz, CH_3C**H**Br*), 4.07 (1H, q, *J* = 6.9 Hz, CH_3C**H**Br), 2.71 (1H, m, ArC**H***CH_2, ArC**H**CH_2), 2.18-2.12 (1H, m, -C**H***$_2$-, -C**H**$_2$-), 1.99-1.86 (2H, m, -C**H***$_2$-, -C**H**$_2$-), 1.85-1.77 (1H, m, -C**H***$_2$-, -C**H**$_2$-), 1.63-1.50 (2H , m, -C**H***$_2$-, -C**H**$_2$-), 1.48 (3H, d, *J* = 6.9 Hz, C**H**$_3$CHBr*), 1.44 (3H, d, *J* = 7.0 Hz, C**H**$_3$CHBr), 1.43-1.29 (2H, m, -C**H***$_2$-, -C**H**$_2$-); **^{13}C-NMR** (100 MHz, $CDCl_3$, diastereomers) δ 169.47, 169.26, 142.69, 142.62, 128.33, 127.60, 127.57, 126.57, 77.65, 49.78, 49.75, 40.71, 40.51, 33.92, 33.81, 31.89, 31.76, 25.77, 24.71, 21.56, 21.49; **IR** (cm^{-1}) ν 3027 (w), 2932 (s), 2858 (m), 1733 (s), 1602 (w), 1494 (w), 1448 (m), 1332 (m), 1268 (m),1224 (m), 1160 (s), 1057 (m), 1010 (m), 756 (m), 700 (s); **HRMS** (EI) *m/z* (relative intensity) 158(100), 107(6), 77(4).

General Procedure J: Synthesis of α-bromo imides

J.1

3-(2-Phenylacetyl)oxazolidin-2-one (64a)

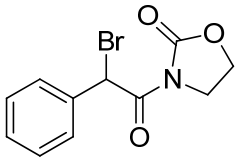


64a

To a stirred solution of 2-oxazolidinone (2.00 g, 23.0 mmol) dissolved in THF (50 mL) at 0 ^{o}C was added 1.19 M *n*-butyllithium in hexanes (21.2 mL, 25.3 mmol) drop wise. After stirring for 10 minutes the reaction mixture was cooled to –78 ^{o}C and phenyl acetyl chloride (4.0 mL, 30.2 mmol) was added dropwise over a 5 minute period. The reaction mixture was allowed to warm to room temperature over 22 hours, diluted with ethyl acetate (20 mL) and quenched with saturated aqueous NH_4Cl (20 mL). The resulting mixture was then concentrated on a rotary evaporator to remove the bulk of the THF and hexanes. Subsequently, the slurry was diluted with ethyl acetate (20 mL) and saturated aqueous NH_4Cl (20 mL) and the layers separated. The aqueous phase was extracted with ethyl actetate (3 x 20 mL) and the combined organic layers were washed with water (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was then subjected to flash chromatography (pentane:EtOAc, 4:1 then 2:1) to give the purified product **64a** (3.58 g, 76 %) as a transparent yellow oil. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.37-7.14 (5H, m, Ar**H**), 4.39 (2H, m, C**H**$_2$), 4.28 (2H, s, ArC**H**$_2$), 4.01 (2H, m, C**H**$_2$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 171.38, 153.59, 133.64, 129.84, 128.64, 127.31, 62.09, 42.80, 41.19. The preparation of the above *N*-acyloxazolidinone **64a** was similar to that previously reported.[89]

J.2

3-(2-Bromo-2-phenylacetyl)oxazolidin-2-one (65a)



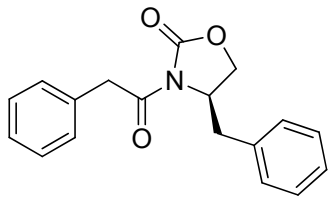
65a

A fresh solution of LDA was first prepared as follows:

To a stirred solution of diisopropyl amine (190 μL, 1.34 mmol) in THF (3 mL) at 0 ^{o}C was added 1.19 M *n*-butyllithium in hexanes (0.90 mL, 1.07 mmol) drop wise. The solution was then allowed to stir at 0 ^{o}C for 30 minutes.

A stirred solution of compound **64a** (0.200 g, 0.98 mmol) dissolved in THF (5 mL) was cooled to –78 ^{o}C and the freshly prepared solution of LDA (1.07 mmol, 0.26 M) was added dropwise. The solution was stirred for 2 hours and the temperature was allowed to rise from –78 ^{o}C to –20 ^{o}C. In a separate round bottom flask *N*-bromosuccinimide (0.191 g, 1.07 mmol) was cooled to –78 ^{o}C followed by the addition of THF (2 mL) to form a slurry. The lithium enolate solution, precooled to –78 ^{o}C, was then rapidly added via cannula to the NBS slurry. The reaction mixture was allowed to warm to room temperature over 14 hours and then quenched by pouring into saturated aqueous sodium bisulfate (20 mL). The solution was extracted with ethyl acetate (2 x 30 mL) and the combined organic layers washed with saturated aqueous sodium thiosulfate (20 mL), and brine (20 mL). The combined organic layers were then dried over Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to flash chromatography (pentane:EtOAc, 9:1 then 4:1) to give the purified product **65a** (0.101 g, 36 %) as a transparent orange oil. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.62-7.59 (2H, m, Ar**H**), 7.39-7.34 (3H, m, Ar**H**), 6.88 (1H, s, ArC**H**Br), 4.49-4.37 (2H, m, C**H**$_2$), 4.16-3.98 (2H, m, C**H**$_2$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 167.47, 152.84, 135.28, 129.51, 129.42, 128.85, 62.28, 44.79, 43.14. The preparation of the above α-bromo oxazolidinone **65a** was similar to that previously reported.[70, 71, 92]

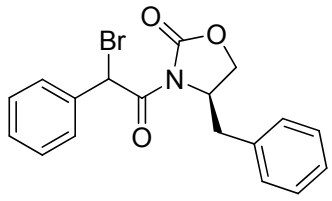
(R)-4-Benzyl-3-(2-phenylacetyl)oxazolidin-2-one (64b)



64b

Compound **64b** was prepared following General Procedure **J.1** outlined above for the synthesis of α-bromo oxazolidinones using (R)-4-benzyl-2-oxazolidinone (0.300 g, 1.69 mmol). Flash chromatography (pentane:EtOAc, 9:1 then 4:1) afforded the purified compound **64b** (0.436 g, 87 %) as transparent colourless oil. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.42-7.23 (8H, m, Ar**H**), 7.14 (2H, d, *J* = 8.0 Hz, Ar**H**), 4.71-4.65 (1H, m, NC**H**), 4.31 (2H, q, *J* = 15.6 Hz, ArC**H**$_2$(CO)N), 4.22-4.15 (2H, m, $CO_2C\mathbf{H}_2$), 3.27 (1H, dd, *J* = 13.4, 3.3 Hz, ArC**H**$_2$CH), 2.76 (1H, dd, *J* = 13.4, 9.4 Hz, ArC**H**$_2$CH); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 171.36, 153.52, 135.25, 133.63, 129.93, 129.56, 129.08, 128.73, 127.48, 127.40, 66.27, 55.48, 41.73, 37.89.

(4R)-4-Benzyl-3-(2-bromo-2-phenylacetyl)oxazolidin-2-one (65b)



65b

Compound **65b** was prepared following General Procedure **J.2** outlined above for the synthesis of α-bromo oxazolidinones using compound (**64b**) (0.333 g, 1.13 mmol). Flash chromatography (pentane:EtOAc, 9:1 then 4:1) afforded the purified compound **65b** (0.191 g, 45 %) as transparent reddish orange oil. The compound was stable at –20 ^{o}C for over 1 month. **^{1}H-NMR** (400 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers, signals corresponding to the major indicated by *) δ 7.66-7.61 (2H, m, Ar**H***, Ar**H**), 7.43-7.34 (4H, m, Ar**H***, Ar**H**), 7.32-7.29 (1H, m, Ar**H***, Ar**H**), 7.24-7.20 (2H, m, Ar**H***, Ar**H**), 7.02-7.00 (1H, m, Ar**H***, Ar**H**), 6.90 (1H, s, ArC**H**Br), 6.89 (1H, s, ArC**H***Br), 4.82-4.74 (1H, m, NC**H***), 4.70-4.64 (1H, m, NC**H**), 4.31-4.15 (2H, m,

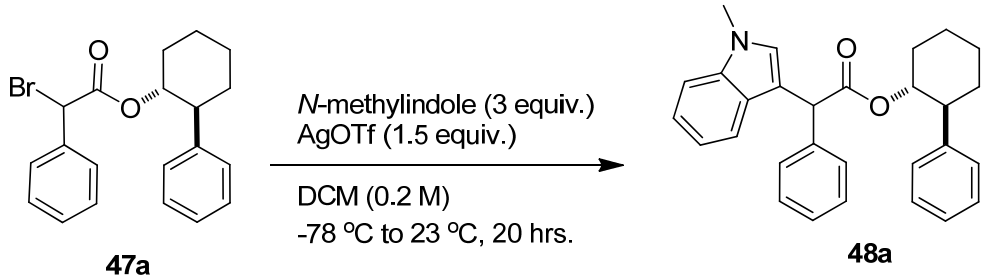
$CO_2CH^*_2$, CO_2CH_2), 3.39 (1H, dd, *J* = 13.4, 3.1 Hz, ArC**H**$_2$), 3.16 (1H, dd, *J* = 13.5, 3.3 Hz, ArC**H***$_2$), 2.88 (1H, dd, *J* = 13.4, 9.5 Hz, ArC**H**$_2$), 2.69 (1H, dd, *J* = 13.5, 9.1 Hz, ArC**H***$_2$); **^{13}C-NMR** (100 MHz, $CDCl_3$, diastereomers) δ 167.41, 167.19, 152.65, 152.59, 135.24, 135.15, 134.78, 134.50, 129.53, 129.51, 129.48, 129.37, 129.35, 129.00, 128.87, 128.74, 127.45, 127.35, 66.32, 66.22, 55.63, 55.51, 45.44, 44.88, 37.22, 37.20; **IR** (cm^{-1}) ν 3028 (w), 2924 (w), 1777 (s), 1705 (s), 1584 (w), 1496 (m), 1455 (m), 1389 (s), 1358 (s), 1212 (s), 1187 (s), 1108 (s), 990 (m), 701 (s); **HRMS** (EI) *m/z* for $C_{18}H_{16}NO_3Br$ calculated (M^+) 373.0314, found 373.0320.

4.9 Silver-mediated nucleophilic substitutions

General Procedure K: Silver-mediated nucleophilic substitutions of α-bromo esters, amides, and imides

K.1 *Experiments conducted using silver trifluoromethanesulfonate, silver hexafluorophosphate, and silver methanesulfonate*

2-Phenylcyclohexyl 2-(1-methyl-1H-indol-3-yl)-2-phenylacetate (48a)

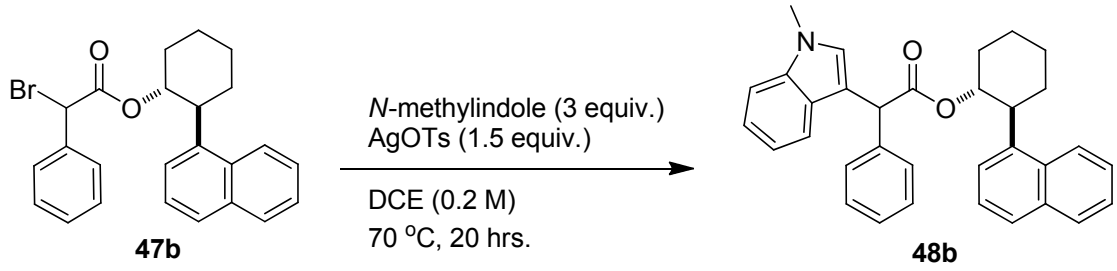


A stirred solution of silver trifluoromethanesulfonate (0.039 g, 0.15 mmol) in DCM (0.2 mL) was first cooled to –78 °C under a positive pressure of argon and then *N*-methylindole (37 μL, 0.30 mmol) was added drop wise. Next, a solution of the α-bromo ester **47a** (0.037 g, 0.10 mmol) dissolved in DCM (0.2 mL) was added drop wise and the syringe was washed with an additional portion of DCM (0.1 mL). Total reaction concentration was 0.2 M. The reaction

mixture was allowed to warm to room temperature over 20 hours, diluted with DCM and filtered through a plug of silica to remove the precipitated silver bromide and any other traces of silver salts. A solution of 1,3,5-trimethoxybenzene (0.033 mmol) in ethyl acetate (0.5 mL) was then added as an internal standard and the solvent was removed under reduced pressure. Analysis of the crude ^{1}H-NMR then gave the product **48a** (71%, 2.3:1 mixture of diastereomers). Flash chromatography (pentane:EtOAc, 19:1 then 9:1) afforded the pure product as a colourless oil. **^{1}H-NMR** (400 MHz, $CDCl_3$, 2.3:1 mixture of diastereomers, signals corresponding to the major indicated by *) δ 7.52-7.13 (9H, m, Ar**H***, Ar**H**), 7.12-7.06 (2H, m, Ar**H***, Ar**H**), 7.03-6.82 (3H, m, Ar**H***, Ar**H**), 6.64 (1H, s, CH_3NC**H***), 6.35 (1H, s, CH_3NC**H**), 5.10 (1H, m, CO_2C**H*,** CO_2C**H**), 5.03 (1H, s, ArC**H***), 4.95 (1H, s, ArC**H**), 3.62 (3H, s, NC**H***$_3$), 3.60 (3H, s, NC**H**$_3$), 2.68 (1H, m, ArC**H***CH_2, ArC**H**CH_2), 2.15-2.08 (1H, m, -C**H***$_2$-, -C**H**$_2$-), 1.93-1.89 (1H, m, -C**H***$_2$-, -C**H**$_2$-), 1.82-1.73 (2H, m, -C**H***$_2$-, -C**H**$_2$-), 1.59-1.30 (4H, m, -C**H***$_2$-, -C**H**$_2$-); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 172.32, 172.27, 143.33, 138.89, 138.75, 137.06, 128.51, 128.44, 128.42, 128.26, 128.12, 127.85, 127.82, 127.77, 127.68, 127.31, 127.12, 126.98, 126.70, 126.51, 126.43, 121.73, 121.62, 119.26, 119.12, 119.07, 112.56, 111.55, 109.25, 109.12, 76.65, 76.58, 49.81, 49.79, 49.31, 49.17, 34.54, 34.34, 32.80, 32.77, 32.23, 25.93, 25.90, 24.82; **IR** (cm^{-1}) ν 3058 (w), 3028 (w), 2930 (s), 2857 (m), 1727 (s), 1602 (w), 1547 (w), 1494 (m), 1474 (m), 1449 (m), 1374 (m), 1331 (m), 1301 (w), 1235 (w), 1187 (m), 1151 (s), 1122 (m), 1060 (w), 1012 (s), 968 (w), 909 (m), 737 (s), 699 (s); **HRMS** (EI) *m/z* for $C_{29}H_{29}NO_2$ calculated (M^+) 423.2198, found 423.2200.

K.2 *Experiments using silver p-toluenesulfonate, silver carbonate, and silver acetate*

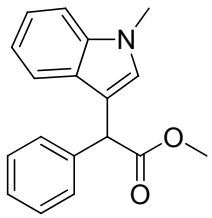
2-(Naphthalen-1-yl)cyclohexyl 2-(1-methyl-1H-indol-3-yl)-2-phenylacetate (48b)



Silver *p*-toluenesulfonate (0.042 g, 0.15 mmol) and the α-bromo ester **47b** (0.042 g, 0.10 mmol) were combined in an oven dried vial that had been cooled under a positive pressure of argon and then dissolved in DCE (0.5 mL). Total reaction concentration was 0.2 M. *N*-methylindole (37 μL, 0.30 mmol) was added and the reaction mixture was heated to 70 °C. After 20 hours of heating, the solution was cooled to room temperature, diluted with DCM and filtered through a plug of silica to remove the precipitated silver bromide and any other traces of silver salts. A solution of 1,3,5-trimethoxybenzene (0.033 mmol) in ethyl acetate (0.5 mL) was then added as an internal standard and the solvent was removed under reduced pressure. Analysis of the crude ^{1}H-NMR then gave the product **48b** (94 %, 1.1:1 mixture of diastereomers). Flash chromatography (pentane:EtOAc, 19:1 then 9:1) afforded the pure product as a colourless oil. **^{1}H-NMR** (400 MHz, $CDCl_3$, 1.1:1 mixture of diastereomers, signals corresponding to the major indicated by *) δ 8.15 (1H, d, *J* = 8.5 Hz, Ar**H***), 8.10 (1H, d, *J* = 8.4 Hz, Ar**H**), 7.86 (1H, d, *J* = 7.7 Hz, Ar**H***), 7.81 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.70 (1H, d, *J* = 8.1 Hz, Ar**H**), 7.66 (1H, d, *J* = 8.1 Hz, Ar**H***), 7.54-7.27 (4H, m, Ar**H***, Ar**H**), 7.22-7.01 (5H, m, Ar**H***, Ar**H**), 6.98-6.79 (3H, Ar**H***, Ar**H**), 6.75-6.73 (1H, m, Ar**H***, Ar**H**), 6.43 (1H, s, CH_3NC**H***), 6.19 (1H, s, CH_3NC**H**), 5.35 (1H, m, CO_2C**H*,** CO_2C**H**), 4.88 (1H, s, ArC**H***), 4.77 (1H, s, ArC**H**), 3.67-3.58 (1H, m, ArC**H***CH_2, ArC**H**CH_2), 3.48 (3H, s, NC**H***$_3$), 3.40 (3H, s, NC**H**$_3$), 2.24-2.17 (1H, -C**H***$_2$-, -C**H**$_2$-), 2.09-2.01 (1H, m, -C**H***$_2$-, -C**H**$_2$-), 1.93-1.86 (1H, m, -C**H***$_2$-, -C**H**$_2$-), 1.81-1.77 (1H, m, -C**H***$_2$-, -C**H**$_2$-), 1.65-1.38 (4H, m, -C**H***$_2$-, -C**H**$_2$-); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 172.34, 139.43, 139.29, 138.63, 138.61, 136.91, 136.90, 134.12, 134.07, 132.21, 132.14, 129.02, 128.86, 128.33, 128.09, 127.97, 127.69, 127.17, 126.97, 126.87, 126.79, 126.77, 126.66, 125.87, 125.84, 125.77, 125.70, 125.46, 125.33, 123.28, 123.25, 121.64, 121.53, 119.13, 119.08, 119.01, 118.96, 112.36, 111.18, 109.16, 109.02, 76.53, 76.46, 49.19, 49.16, 34.54, 34.35, 32.55, 32.53, 32.48,

26.23, 26.22, 24.92; **IR** (cm^{-1}) ν 3057 (w), 2932 (s), 2858 (w), 1725 (s), 1598 (w), 1494 (w), 1474 (m), 1450 (m), 1374 (w), 1331 (m), 1300 (w), 1233 (m), 1151 (s), 1119 (m), 1060 (w), 1004 (m), 908 (m), 795 (m), 777 (s), 732 (s), 699 (m); **HRMS** (EI) *m/z* for $C_{33}H_{31}NO_2$ calculated (M^+) 473.2355, found 473.2355.

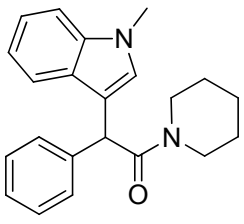
Methyl 2-(1-methyl-1H-indol-3-yl)-2-phenylacetate (50)



50

Compound **50** was prepared following General Procedure **K.2** outlined above using methyl α-bromophenyl acetate (16 μL, 0.10 mmol), silver carbonate (0.041 g, 0.15 mmol), and the axially chiral phosphate counterion **49** (20 mol %). Flash chromatography (pentane:EtOAc, 19:1 then 9:1) afforded the purified product **50** (0.021 g, 75 %, 6 % *ee*). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.45-7.41 (3H, m, Ar**H**), 7.33-7.25 (4H, m, Ar**H**), 7.24-7.19 (1H, m, Ar**H**), 7.08-7.06 (1H, m, Ar**H**), 7.05 (1H, s, CH_3NC**H**), 5.26 (1H, s, ArC**H**), 3.76 (3H, s, C**H**$_3$), 3.75 (3H, s, C**H**$_3$).

2-(1-Methyl-1H-indol-3-yl)-2-phenyl-1-(piperidin-1-yl)ethanone (60)

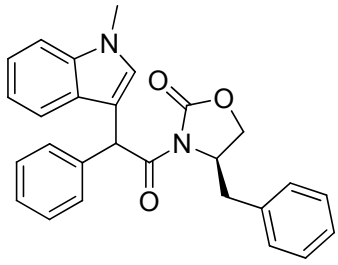


60

Compound **60** was prepared following General Procedure **K.2** outlined above using compound **59** (0.028 g, 0.10 mmol), silver *p*-toluenesulfonate (0.042 g, 0.15 mmol), and dioxane (0.20 M) as the solvent. Flash chromatography (pentane:EtOAc, 9:1 then 3:1) afforded the purified

compound **60** (0.021 g, 64 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.44 (1H, d, *J* = 7.9 Hz, Ar**H**), 7.35-7.33 (2H, m, Ar**H**), 7.30-7.25 (3H, m, Ar**H**), 7.22-7.17 (2H, m, Ar**H**), 7.03 (1H, t, *J* = 7.0 Hz, Ar**H**), 6.97 (1H, s, CH_3NC**H**), 5.48 (1H, s, ArC**H**(CO)N), 3.73 (3H, s, NC**H**$_3$), 3.70-3.58 (2H, m, CONC**H**$_2$-), 3.55-3.44 (2H, m, CONC**H**$_2$-), 1.62-1.31 (6H, m, -C**H**$_2$-).

(4R)-4-Benzyl-3-(2-(1-methyl-1H-indol-3-yl)-2-phenylacetyl)oxazolidin-2-one (66a)



66a

Compound **66a** was prepared following General Procedure **K.1** outlined above using compound **65b** (0.037 g, 0.10 mmol), and silver trifluoromethanesulfonate (0.039 g, 0.15 mmol). Analysis of the crude ^{1}H-NMR using 1,3,5-trimethoxybenzene as the internal standard then gave the product **66a** (31 %, 1.3:1 mixture of diastereomers). Flash chromatography (pentane:EtOAc, 9:1 then 4:1) afforded the purified compound **66a** (0.009 g, 21 %). **^{1}H-NMR** (400 MHz, $CDCl_3$, 1.3:1 mixture of diastereomers, signals corresponding to the major indicated by *) δ 7.63 (1H, d, *J* = 8.0 Hz, Ar**H***), 7.59 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.52 (2H, d, *J* = 7.0 Hz, Ar**H**), 7.49 (2H, d, *J* = 6.9 Hz, Ar**H***), 7.39-7.17 (8H, m, Ar**H***, Ar**H**), 7.15-7.05 (4H, m, Ar**H***, Ar**H,** CH_3NC**H***, CH_3NC**H**), 6.84 (1H, s, ArC**H***(CO)N), 6.81 (1H, s, ArC**H**(CO)N), 4.77-4.66 (1H, m, (CO)NC**H***, (CO)NC**H**), 4.18-4.09 (2H, m, CO_2C**H***$_2$, CO_2C**H**$_2$), 3.77 (3H, s, NC**H***$_3$), 3.76 (3H, s, NC**H**$_3$), 3.27 (1H, m, ArC**H***$_2$, ArC**H**$_2$), 2.76-2.67 (1H, m, ArC**H***$_2$, ArC**H**$_2$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 172.94, 172.90, 153.19, 153.18, 138.62, 137.12, 137.06, 135.35, 135.23, 129.58, 129.56, 129.11, 129.05, 129.02, 128.82, 128.77, 128.71, 128.66, 127.39, 127.37, 127.26, 127.21, 122.04, 121.99, 119.53, 119.48, 119.44, 119.37, 112.05, 111.99, 109.46, 109.44, 65.95, 55.84, 55.65, 46.00, 45.92, 37.92, 37.78, 33.00; **IR** (cm^{-1}) ν 3062 (w), 3027 (w), 2925 (m), 2853 (w), 1773 (s), 1697 (s), 1603 (w), 1584 (w), 1495 (w), 1474 (m), 1454 (m), 1387 (m), 1354 (s), 1333 (m), 1209 (s), 1156 (m), 1105 (m), 909 (m), 737 (s), 701 (s); **HRMS** (EI) *m/z* for $C_{27}H_{24}N_2O_3$ calculated (M^+) 424.1787, found 424.1792.

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