2-IMIDAZOLIDINONES AND EPIMERIC PYRROLOIMIDAZOLONES IN ASYMMETRIC SYNTHESIS: FROM CLASSICAL TO NON-CLASSICAL CHIRAL AUXILIARIES

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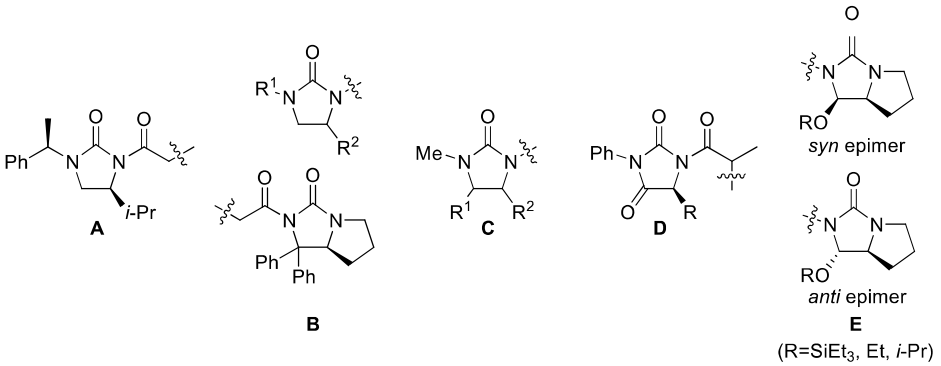
Abstract. *This chapter presents an overview of chiral imidazolone auxiliaries in asymmetric synthesis since 2012 within two sections. The first involves the use of "classical" 2-imidazolidinones in the synthesis of fluoxetine and furoindoline natural products, in addition to β-lactams, γ-lactones, and aziridines. Aspects of solid-phase or ionic liquid recoverability of these auxiliaries are also discussed. The second section covers the development of epimeric pyrroloimidazolones for the asymmetric synthesis: i) planar chiral ferrocenes and η^6-arene chromium tricarbonyl complexes; ii) central chiral cyclohexa-1,4-dienes, N-benzyl and N-propargyl derivatives; iii) axial chiral allenamides. Pyrroloimidazolones are "non-classical" auxiliaries because their epimeric forms behave as pseudo-enantiomers despite being prepared from a single L-proline-derived starting material. The presence of a labile hemiaminal ether moiety allows for their conversion into other nitrogen-containing functional groups.*

Contents

1. Introduction

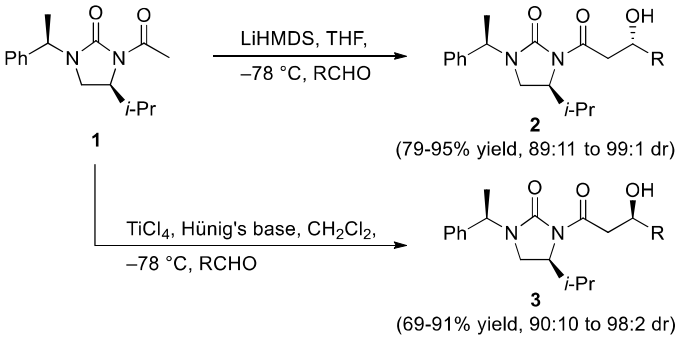
The development of 2-imidazolidinone chiral auxiliaries for asymmetric synthesis, based on the seminal work of Close in 1950,[1] have been the subject of extensive reviews by Roos[2] in 1998 and more recently by Chen in 2012.[3] This chapter is intended to provide an overview of developments in this field since 2012 on two fronts. First, it will give an update on applications of "classical" 2-imidazolidinones and its congeners for the diastereoselective synthesis of products **A-D** with new chiral centers (Scheme 1). These derivatives include *N*-acetyl-(*S*)-4-isopropyl-1-[(*R*)-1-phenylethyl]imidazolidin-2-one **A**, 2-imidazolidinones with one **B** or two **C** chiral centers, and related hydantoin auxiliaries **D**. Second, it will serve as a personal account for the parallel development of related epimeric pyrroloimidazolones **E** for induction of planar, central and axial chirality within our research group, for which preliminary results were coincidentally first reported in 2012.[4] Pyrroloimidazolones may be considered to be "non-classical" auxiliaries in the sense that their epimeric forms often behave as pseudo-enantiomers, which allows for the preparation of enantiomeric products from a single L-proline-derived starting material.[5] In addition, pyrroloimidazolones contain a labile hemiaminal ether substituent that enables their conversion into other nitrogen-containing functional groups after asymmetric induction (*vide infra*). Examples of how both aspects of pyrroloimidazolone chemistry may be exploited will be summarized.



Scheme 1

2. *N*-Acetyl-(*S*)-4-isopropyl-1-[(*R*)-1-phenylethyl]imidazolidin-2-ones

In 2012, Nair and co-workers reported that *N*-acetyl-(*S*)-4-isopropyl-1-[(*R*)-1-phenylethyl]imidazolidin-2-one **1** (Scheme 2) serves as a precursor to secondary alcohols with opposite stereochemistry **2** and **3** depending on whether a lithium or titanium enolate is generated prior to addition of an aldehyde.[6] The change in product stereochemistry was attributed to an open versus closed transition state for the lithium and titanium enolates, respectively. The method was later applied to the synthesis of both enantiomers of fluoxetine.



Scheme 2

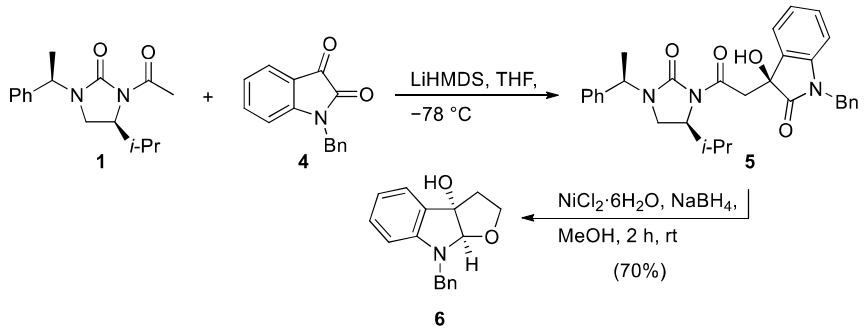
This work was extended to the stereoselective formation of isatin adducts (**1**+**4**→**5**) *via* the lithium enolates, which were produced in good yields favoring secondary alcohols with *S* configuration (Scheme 3).[7] Stereoselectivity of these reactions ranged from 75:25 to 92:2 diastereomeric ratio (dr) depending on the *N*-alkyl group and/or the presence of a 5-aryl substituent in the electrophile. The method was subsequently applied to the synthesis of furoindoline natural product derivatives (*e.g.* **6**) by employing a nickel-promoted reductive cyclization reaction.

In contrast, interception of the same lithium enolate with imines **7** in the presence of tetramethylethylenediamine (TMEDA) results in formation of chiral β-lactams **8** in 78:22 to >99:1 enantiomeric ratio (er) with concomitant loss of the chiral auxiliary (Scheme 4).[8]

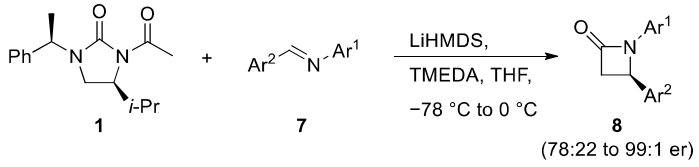
3. 2-Imidazolidinones with one chiral center

Despite the utility of 2-imidazolidinones in asymmetric synthesis, their cost may be prohibitive for some applications unless the auxiliary can be conveniently recovered. To improve ease of recovery, solid-phase synthesis methods have been developed[9] such as polystyrene-supported 2-imidazolidinone **9** (Scheme 5).[10] Deprotonation of this substrate with sodium hexamethyldisilazane (NaHMDS) affords

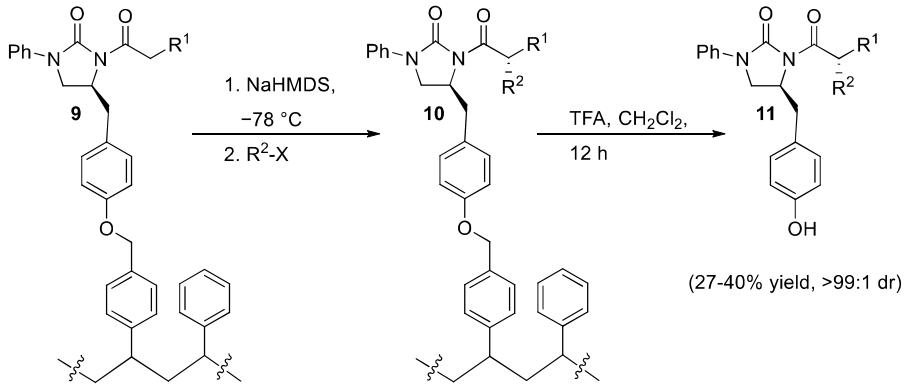
alkylated products **10**, isolated as phenols **11** in >99:1 dr upon cleavage of the product from the solid support.



Scheme 3



Scheme 4

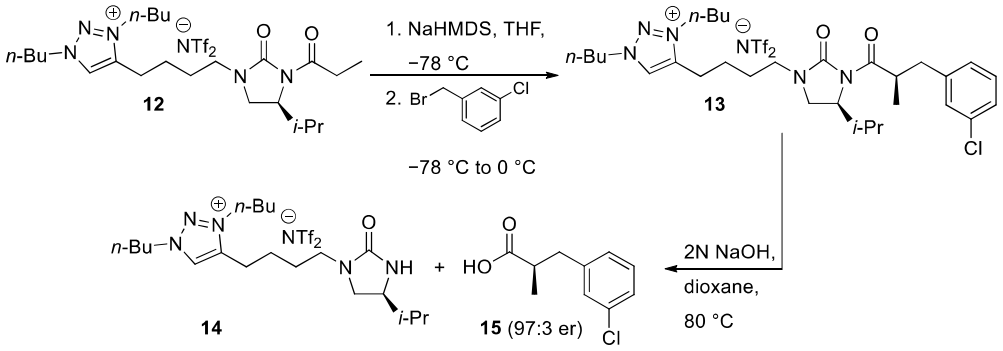


Scheme 5

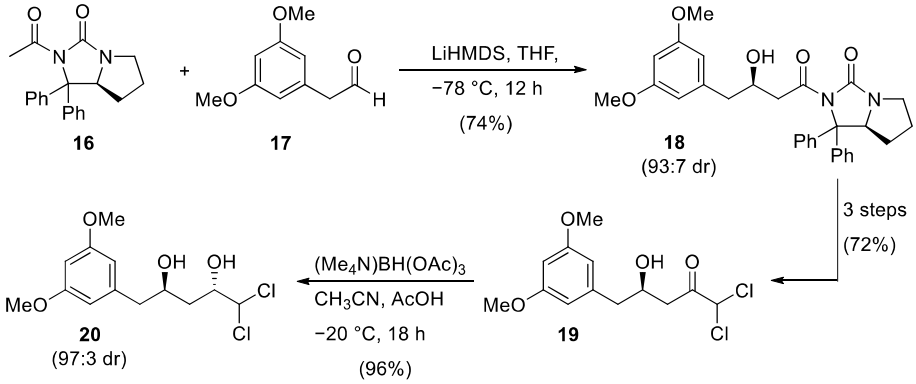
Polymer-supported reactions sometimes pose their own challenges such as poor substrate solubility,[11] and low diastereoselectivity[12] compared to their solution-phase counterparts. Ryu and co-workers have circumvented these challenges by developing a 1,2,3-triazolium ionic liquid-supported chiral 2-imidazolidinone **12** (Scheme 6) for asymmetric alkylation.[13] Thus, sequential deprotonation with NaHMDS and alkylation gives products **13** that can be isolated as carboxylic acid **15** in up to 95:5 to 98:2 er upon hydrolysis, leaving auxiliary **14** within the ionic liquid phase. This approach alleviates the issue of poor solubility while simultaneously improving recovery of products and the chiral auxiliary component for subsequent synthetic cycles.

In 2020 Rajendar and co-workers reported the total synthesis of (−)-(2*S*,4*R*)-3′-methoxy citreochlorol **20** (Scheme 7).[14] Key to this asymmetric synthesis was the need to install the required chiral center by use of the established *N*-acetyl thiozolidenethione auxiliary, which gave poor levels of diastereoselectivity under

several reaction conditions. An alternative *N*-acetyl starting material **16** was synthesized in 8 steps from L-proline, which alleviated problems associated with the enolizeability of aldehyde **17** to give adduct **18** in up to 93:7 dr. Successive steps afforded the geminal dichloride **19** *via* a Weinreb amide, and ultimately **20** using an *anti*-selective reduction.



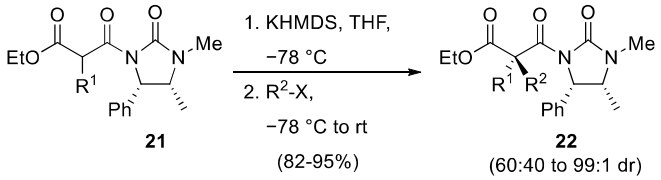
Scheme 6



Scheme 7

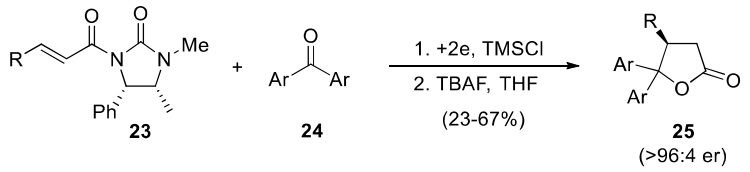
4. 2-Imidazolidinones with 4,5-chiral centers

A new method for stereoselective formation of quaternary chiral centers in α-alkylated malonate imidazolidinones **21** was reported by Hunter and co-workers in 2015 (Scheme 8).[15] The protocol uses potassium hexamethyldisilazane (KHMDS) for enolate formation, a critical point because the potassium ion serves to stabilize the *Z*-enolate for the reaction to proceed *via* a six-membered ring transition state with the substrate in an s-*trans*$_{C\text{-}N}$ conformation. The stereochemistry of products **22** was crystallographically verified.



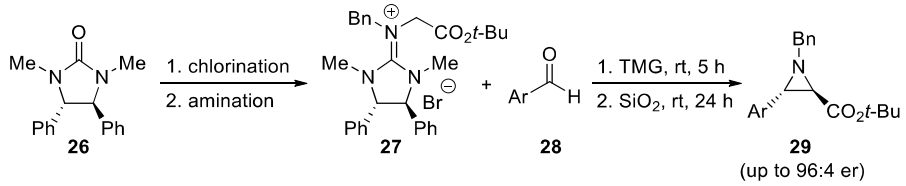
Scheme 8

A different approach has been reported by Kise and co-workers for the asymmetric synthesis of 4,5,5-trisubstituted γ-butyrolactones **25** (Scheme 9).[16] Instead of enolate formation, stereoselective electro-reductive coupling was employed to add substrate **23** to a series of biaryl ketones **24** in the presence of chlorotrimethylsilane (TMSCl). Subsequent hydrolysis and base-induced cyclization afforded the γ-butyrolactones in >96:4 er.



Scheme 9

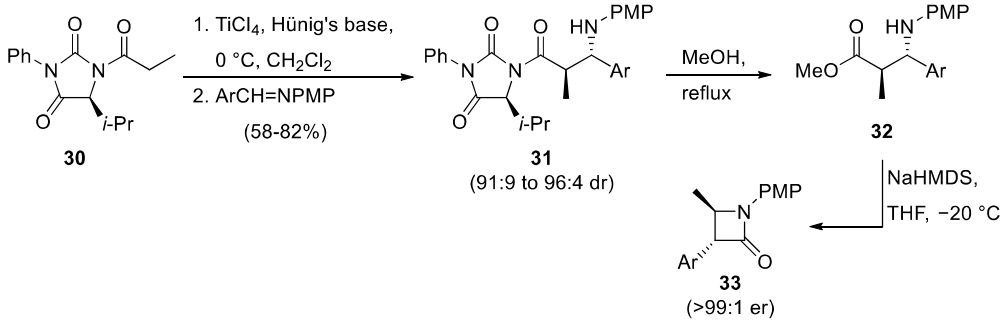
Another unconventional process was reported by Ishikawa and co-workers wherein a C_2-symmetric 2-imidazolidinone **26** (Scheme 10) serves as a precursor to guanidinium salt **27** for the tetramethylguanidine (TMG) induced reaction of benzaldehydes **28** to afford chiral aziridines **29**.[17] In general, the reaction sequence favors aziridines with *anti* stereochemistry and in variable enantiomeric purity of up to 96:4 er.



Scheme 10

5. Hydantoin auxiliaries

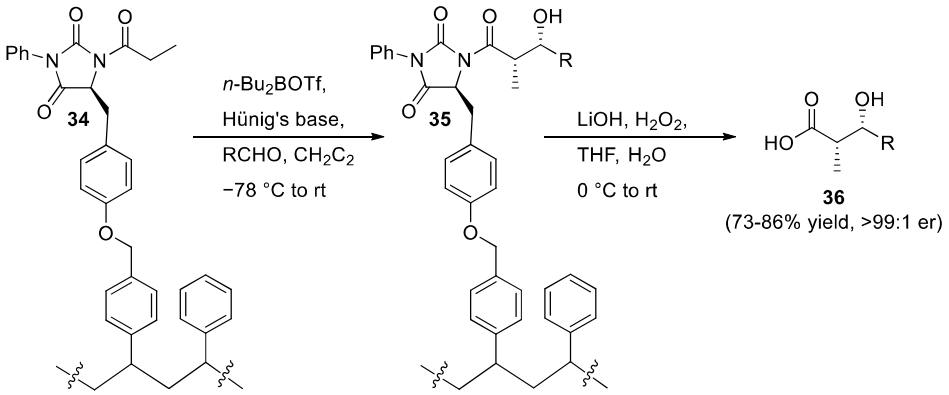
One recent trend is to use five-membered chiral hydantoins directly as chiral auxiliaries, despite the risk posed by racemization of the chiral center α to the carbonyl. In this manner, titanium enolates of hydantoin **30** were trapped with *p*-methoxyphenyl (PMP) protected aldimines in a Mannich reaction to afford adducts **31** that could be isolated in >91:9 dr (Scheme 11).[18] Alcoholysis to esters **32** and cyclization of the intermediates gave access to chiral β-lactams **33** in high enantiomeric purity (>99:1 er). A microgel-supported version of this process has also been reported.[19]



Scheme 11

The preceding method was adapted to a polymer-supported sequence in which stereoselective condensation of aldehydes in the presence of Lewis acids such as *n*-Bu_2BOTf and Hünig's base **34→35**

furnished α,β-chiral carboxylic acids **36** in >99:1 er (Scheme 12).[20] Release of the product from the solid support permits recycling of the chiral auxiliary component with minor loss of its stereochemical integrity.



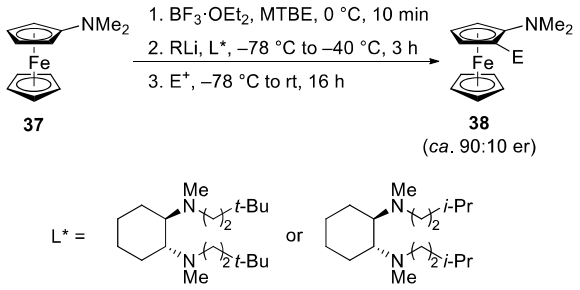
Scheme 12

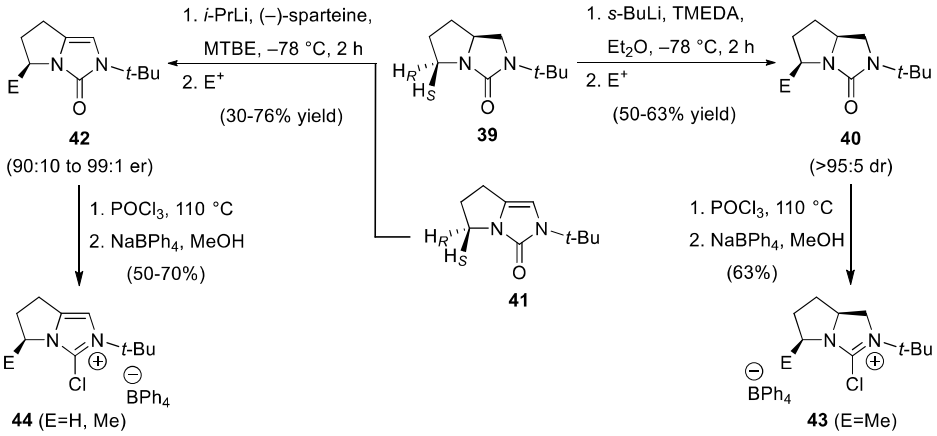
6. Epimeric pyrroloimidazolones

The development of L-proline-derived pyrroloimidazolones for asymmetric synthesis has its origins in two older related projects in the Metallinos research group. The first was development of an enantioselective synthesis of planar chiral 1,2-disubstituted aminoferrocenes,[21,22] which involved asymmetric lithiation of BF_3-activated tertiary amine **37** in the presence of various chiral diaminocyclohexane ligands, followed by quench with a variety of electrophiles (E^+) to give products **38** (Scheme 13). Several 1-amino-2-phosphino ferrocenes were prepared with this method[23] (E=PAr_2) and used in enantioselective hydrogenation reactions.[24] The second project involved the diastereoselective **39→40** or (−)-sparteine-mediated enantioselective **41→42** synthesis of 5-substituted pyrrolo[1,2-c]imidazol-3-ones as a route to chloroimidazolium precursors to *N*-heterocyclic carbenes (NHCs) **43** and **44**.[25]

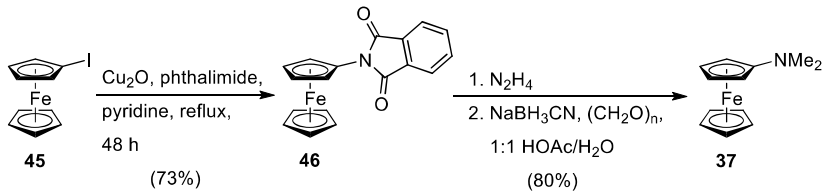
The tertiary aminoferrocenes were synthesized by cuprous oxide mediated coupling of iodoferrocene **45** with phthalimide in refluxing pyridine to give the known *N*-ferrocenyl phthalimide **46** (Scheme 14).[26] Standard deprotection with hydrazine to the primary amine followed by reductive amination afforded dimethylaminoferrocene **37**, among other starting materials.[24] In contrast, the required chiral **39** and achiral **41** pyrrolo[1,2-c]imidazol-3-ones were prepared from the Cbz-protected secondary amide **47**, easily synthesized from L-proline.[27,28] A notable feature in the preparation of the unsaturated achiral material **41** was the partial reduction of an intermediate hydantoin to hemiaminal **48**, which readily underwent dehydration with dilute acid.[25]

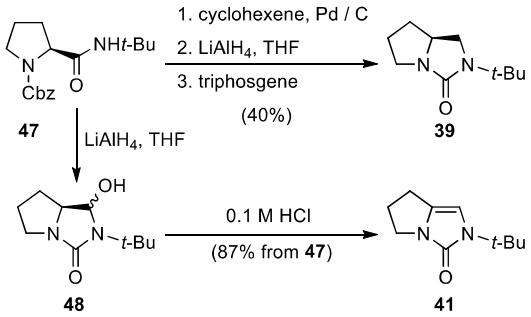
Given the similarities of phthalimides and hydantoins, it was envisioned that partial reduction of *N*-ferrocenyl phthalimide **46**, followed by protection of the resulting hemiaminal hydroxyl, would give a racemic product with a configurationally stable chiral center. The question arose as to whether such a substrate would undergo diastereoselective lithiation-substitution in the cyclopentadienyl (Cp.) ring of ferrocene. To answer this question, phthalimide **46** was reduced with sodium borohydride ($NaBH_4$) to give the isolable hemiaminal **49**, which upon *O*-silylation with chlorotrimethylsilane (TMSCl) or chlorotriethylsilane (TESCl) gave the corresponding phthalimidines **50** and **51** (Scheme 15). The TMS-protected product was found to be unstable to silica gel chromatography, therefore the TES-protected variant **51** was chosen for further experiments. Exposure of **51** to a mixture of lithium diisopropylamide (LDA) and TMSCl at −78 °C for 3 hours, followed by a hydrolytic workup, afforded the Cp.-ring silylated product **52** in 30% yield, along with a mixture of phenyl-substituted by-products **53** and **54** in <5% combined yield.[29] Of critical importance was the observation that the ^1H and ^{13}C NMR spectra of **52** consisted of a single set of signals, indicating highly diastereoselective lithiation-silylation of the Cp. ring (>95:5 dr). Non-selective lithiation would have resulted in two sets of NMR peaks, arising from planar chiral diastereomers. In other words, racemic **51** had given rise to a mixture of **52** plus its enantiomer, which have identical NMR spectra.





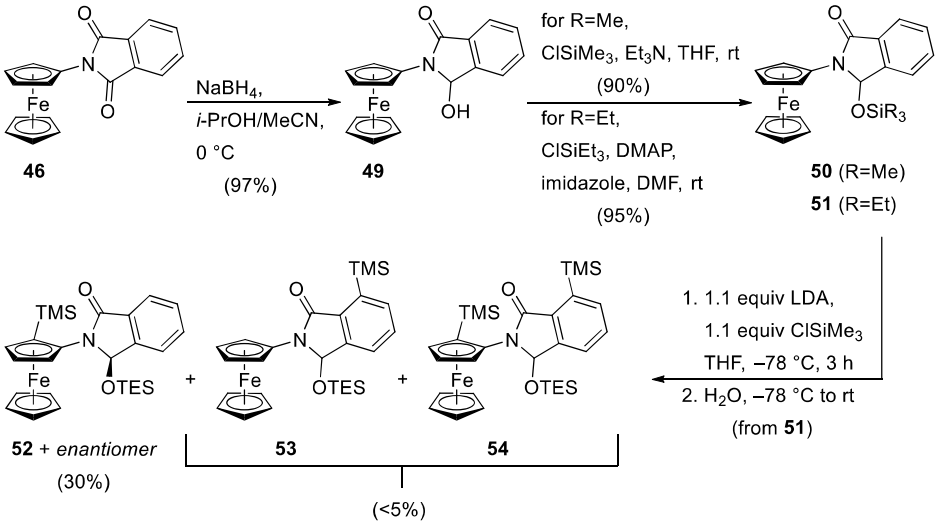
Scheme 13





Scheme 14

Unfortunately, phthalimidine **51** was not stable to alkyllithium bases and required metalation with lithium amide bases that were compatible only with *in situ* electrophiles. This fact limited the number of accessible derivatives. In addition, efforts to perform enantioselective reduction of **46** were unsuccessful (Scheme 15).[29]



Scheme 15

6.1. Planar chiral ferrocenes

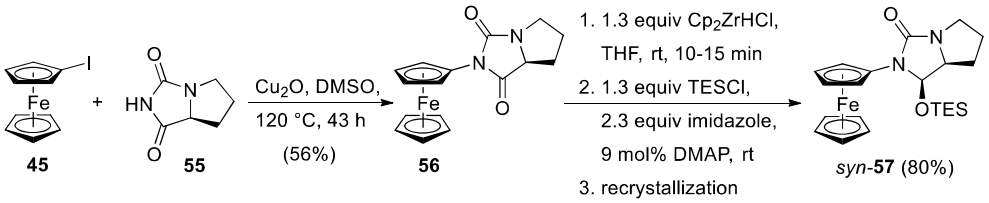
An implication of the preceding results (Scheme 15) was that control of absolute stereochemistry in a starting material containing an analogous hemiaminal ether moiety as **51** may provide access to planar chiral ferrocenes in high enantio- and diastereo-meric purity. A practical *N*-based chiral auxiliary for planar chiral induction in ferrocenes needed to fulfill five design criteria to offer tangible improvements to the previous enantioselective aminoferrocene route (Scheme 13):

1. It needed to be prepared in ample quantities from readily available starting materials;
2. It needed to be stable to strong bases used in lithiation, including alkyllithiums;
3. It needed to provide products in high diastereomeric ratio;
4. It needed to provide access to both planar chiral configurations and/or enantiomers;
5. It needed to be convertible to other *N*-functional groups, potentially including amines.

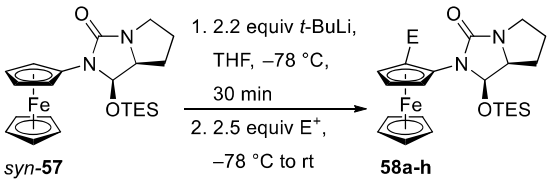
The obvious choice was to make an analogue of **51** by coupling iodoferrocene with L-proline hydantoin (or D-proline hydantoin) instead of phthalimide. L-Proline hydantoin is easy to prepare in ample quantities by condensation of L-proline with potassium cyanate under acidic conditions.[30] Stereoselective reduction and *O*-silylation would afford a substrate to test in diastereoselective lithiation-substitution of ferrocenes. Thus, cuprous oxide mediated coupling of iodoferrocene **45** with L-proline hydantoin **55** in hot DMSO gave ferrocenyl hydantoin **56** (Scheme 16). It was important to use DMSO as the solvent in this reaction because coupling of **45** with **55** in pyridine resulted in racemization of **56**. In any case, the "amido" carbonyl of **56** needed to be partially and stereoselectively reduced to the hemiaminal, a reaction for which sodium borohydride was insufficient. The advent of Schwartz's reagent (Cp_2ZrHCl) for the reduction of tertiary amides to aldehydes, as reported by Georg and co-workers in 2007,[31] provided a feasible alternative considering that aminoalkoxides have been proposed as intermediates in this transformation. To our delight, one-pot reduction of **56** with Cp_2ZrHCl followed by immediate silylation of the putative aminoalkoxide intermediate with TESCl afforded *syn*-**57** in 80% yield after recrystallization.[4]

Optimization experiments revealed that lithiation of *syn*-**57** with 2.2 equivalents of *t*-BuLi at low temperature, followed by electrophile (E^+) quench with a variety of reagents, gave planar chiral products in

70-94% yield and in >95:5 dr, as determined by ^{1}H NMR spectroscopy (Scheme 17). The use of weaker bases such as *n*-BuLi or *i*-PrLi, or fewer than 2.2 equivalents of *t*-BuLi, afforded 2-substituted products **58a-h** in lower yield but invariably high diastereomeric purity. The stereochemistry of the products was determined by X-ray crystallography of boronic acid **58b**, which indicated that the pro-S_p Cp. ring hydrogen of *syn*-**57** had been selectively deprotonated.[4]



Scheme 16



E^+	E	**58a-h**	yield, %
MeI	Me	**d**	91
TMSCl	TMS	**a**	84
$B(OEt)_3$	$B(OH)_2$	**b**	80
Bu_3SnCl	Bu_3SnCl	**c**	87
DMF	CHO	**e**	70
Ph_2CO	$Ph_2C(OH)$	**f**	87
$(MeS)_2$	MeS	**g**	94
$(ICH_2)_2$	I	**h**	91

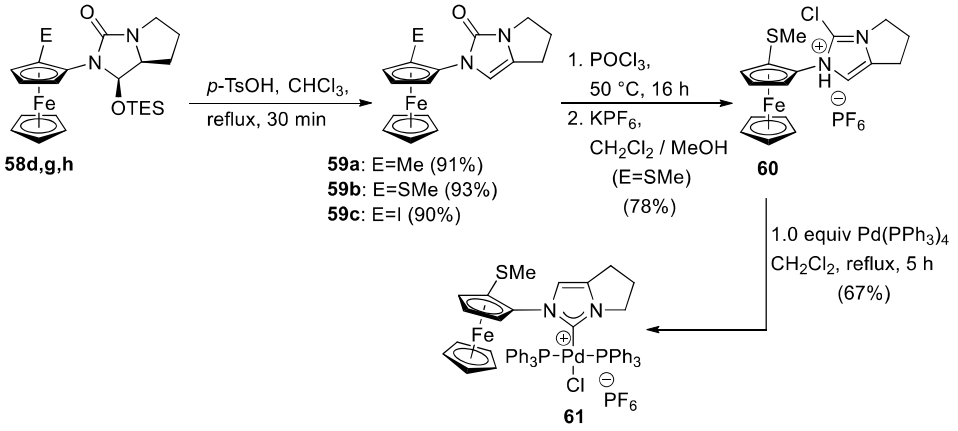
Scheme 17

A key feature of the *syn*-pyrroloimidazolone auxiliary is the lability of the triethylsilyloxy group under various conditions. For example, exposure of products **58d,g,h** to *p*-toluenesulfonic acid (*p*-TsOH) induces clean elimination to afford the solely planar chiral unsaturated imidazolones **59a,b,c** in good yields (Scheme 18).[4] Heating a solution of urea **59b** in phosphorus oxychloride within a sealed tube at 50 °C gave the chloroimidazolium salt **60**, an NHC ligand precursor that was isolated as the hexafluorophosphate salt. Standard oxidative addition[32] of planar chiral imidazolium salt **60** with $Pd(PPh_3)_4$ gave the crystallographically verified Pd(II) complex **61**.[33]

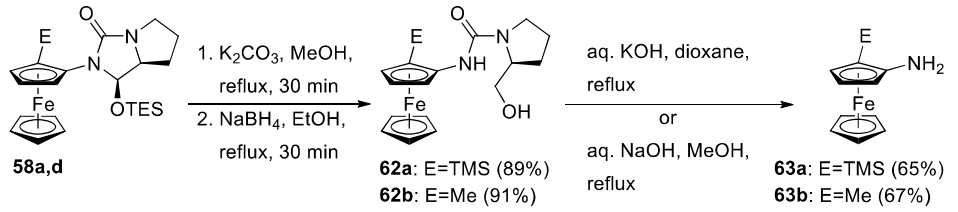
Products **58** were also amenable to manipulation under basic conditions. Treatment of **58a,d** with potassium carbonate provided intermediate hemiaminals that were immediately reduced to secondary ureas **62a,b** containing pendant prolinol groups (Scheme 19). Further hydrolysis of the "open" ureas with KOH in dioxane, or methanolic NaOH, gave the homochiral primary aminoferrocenes **63a,b**.[4]

The observation that lithiation diastereoselectivity of *syn*-**57** was insensitive to steric bulk of the alkyllithium used in the reaction, combined with the high stereoselectivity observed in lithiation of phthalimidine **51**, made us hypothesize that the proximal β-silyloxy stereogenic center of *syn*-**57** was more

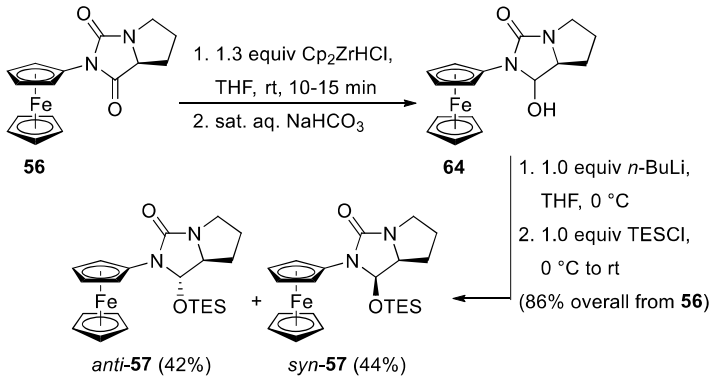
important to reaction selectivity than the γ-pyrrolidine stereocenter. These results suggested that preparation of a β-silyloxy epimer (*anti*-**57**) may result in reversal of the planar chirality in the products of lithiation-electrophile quench compared to *syn*-**57**. Epimer *anti*-**57** was simple to prepare by modification of the original synthesis. Rather than one-pot hydrosilylation, reduction of hydantoin **56** with Schwartz's reagent was followed by mild base workup to give a mixture of configurationally unstable hemiaminals **64** (Scheme 20). Subsequent deprotonation of the hydroxy group with *n*-butyllithium followed by addition of TESCl gave a chromatographically separable mixture of *anti*- and *syn*-**57** in almost equal amounts.[5] The epimeric products could be recrystallized individually to ensure purity.



Scheme 18

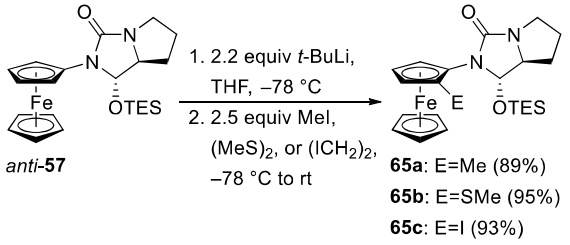


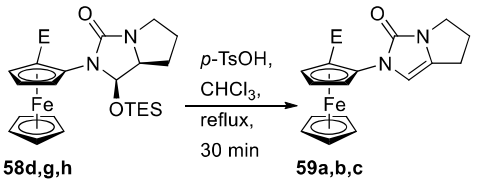
Scheme 19



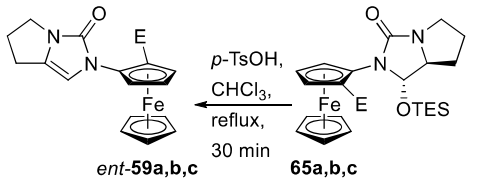
Scheme 20

Metalation and electrophile quench of *anti*-**57** under the same conditions as *syn*-**57** gave methyl, thiomethyl and iodine adducts **65a,b,c** in excellent yields and as single diastereomers (>95:5 dr) (Scheme 21).[5] X-Ray crystallography of **65a** showed the product to have opposite planar chirality to products **58** previously by virtue of selective lithiation of the pro-R_p Cp. ring hydrogen. Reversal of planar chiral stereochemistry was further confirmed by elimination of silyloxy imidazolones **65a,b,c** to the exclusively planar chiral derivatives *ent*-**59a,b,c**, which were shown to be enantiomers[5] of *syn*-derived **59a,b,c** from their specific rotations. These results are of practical significance because *anti*-**57** behaved as a pseudo-enantiomer of *syn*-**57**, which countered the need to synthesize a separate pyrroloimidazolone starting material from more expensive D-proline to access enantiomeric products. The generality of using the β-*syn* versus the β-*anti* epimeric pyrroloimidazolones to prepare enantiomers has been applied to other substrates (*vide infra*).





E	yield, %	er (% ee)	$[\alpha]_D^{20}$
Me	91	99:1 (98)	–29.2
SMe	93	98:2 (96)	–129
I	90	99:1 (98)	–38.9



E	yield, %	er (% ee)	$[\alpha]_D^{20}$
Me	95	97:3 (94)	+31.0
SMe	92	95.5:4.5 (91)	+136
I	85	99:1 (98)	+40.3

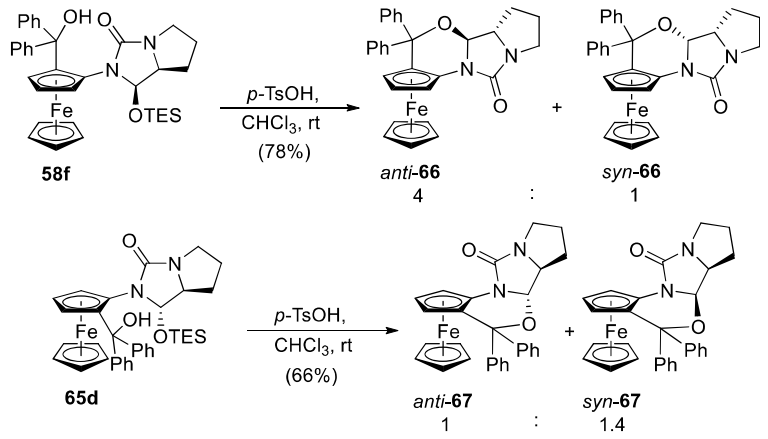
Scheme 21

The presence of nucleophiles in the 2-position of products such as **58** and **65** offered possibilities for new functional group manipulations. Specifically, alcohols **58f** or **65d** undergo cyclization to **66** and **67** (Scheme 22) by intramolecular addition to the putative iminium ion that is generated under acidic conditions, instead of elimination to the unsaturated imidazolones **59a,b,c** or *ent*-**59a,b,c**.[34]

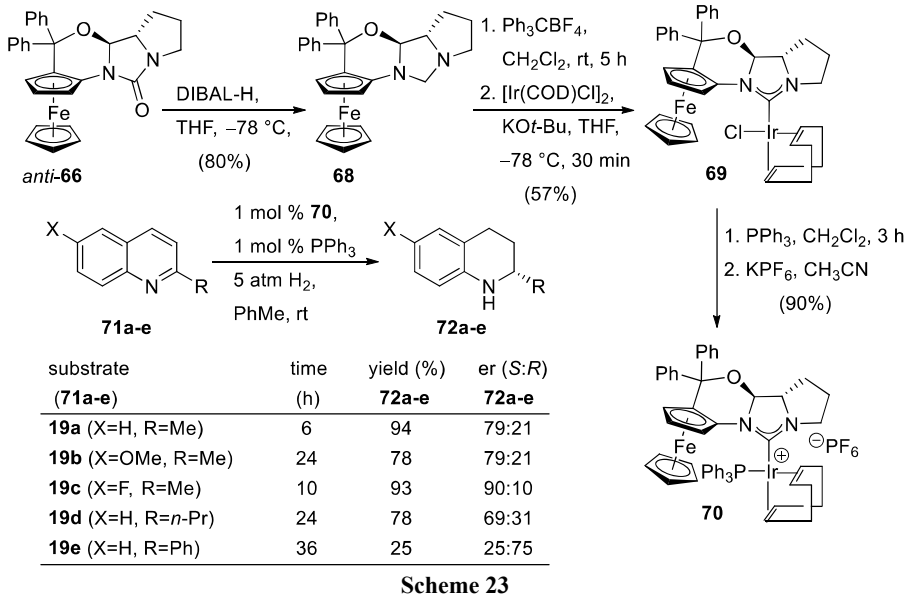
The resulting tetracyclic annulated ureas with differing planar and central chiral configurations *anti*/*syn*-**66** and *anti*/*syn*-**67** (Scheme 22) may be converted to unusual NHC ligands for asymmetric catalysis. For example, reduction of *anti*-**66** with diisobutylaluminum hydride (DIBAL-H) gave stable aminal **68** (Scheme 23), which was converted to an imidazolinium salt NHC ligand precursor with trityl tetrafluoroborate. Coordination to iridium(I) yielded the crystallographically verified neutral complex **69**. Addition of triphenylphosphine produced the cationic complex **70**, which was found to catalyze the enantioselective hydrogenation of variously substituted quinolines **71**→**72** in up to 90:10 er under mild conditions.[34]

6.2. η^6-Arene chromium tricarbonyl complexes

The use of *syn*- and *anti*-pyrroloimidazolones to selectively introduce planar chirality was extended to η^6-arene chromium tricarbonyl complexes (Scheme 24).[35] These starting materials were prepared from *N*-phenyl hydantoin **73**, available by condensation of phenyl isocyante with L-proline. Reduction with Schwartz's reagent gave the intermediate hemiaminal **74**, which was converted to the isopropoxy hemiaminal ethers *anti*- and *syn*-**75**. Complexation of the individual epimers to $Cr(CO)_6$ in refluxing octane gave the corresponding η^6-arene chromium tricarbonyl complexes *anti*-**76** and *syn*-**76**. The use of isopropoxy or ethoxy[36] hemiaminal ethers in this sequence was needed because attempts to *ortho*-lithiate the triethylsilyloxy analogue of *syn*-**75** resulted in elimination to give the unsaturated imidazolone.[35]



Scheme 22

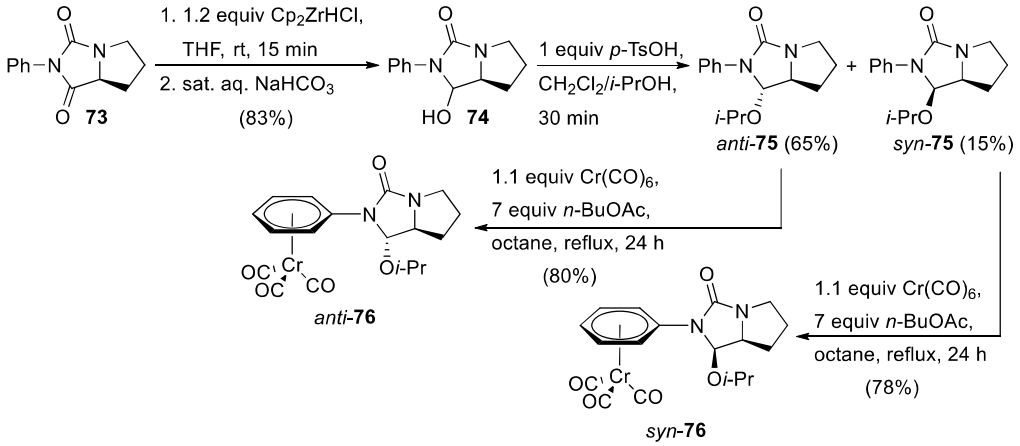


substrate (**71a-e**)	time (h)	yield (%) **72a-e**	er (*S*:*R*) **72a-e**
19a (X=H, R=Me)	6	94	79:21
19b (X=OMe, R=Me)	24	78	79:21
19c (X=F, R=Me)	10	93	90:10
19d (X=H, R=*n*-Pr)	24	78	69:31
19e (X=H, R=Ph)	36	25	25:75

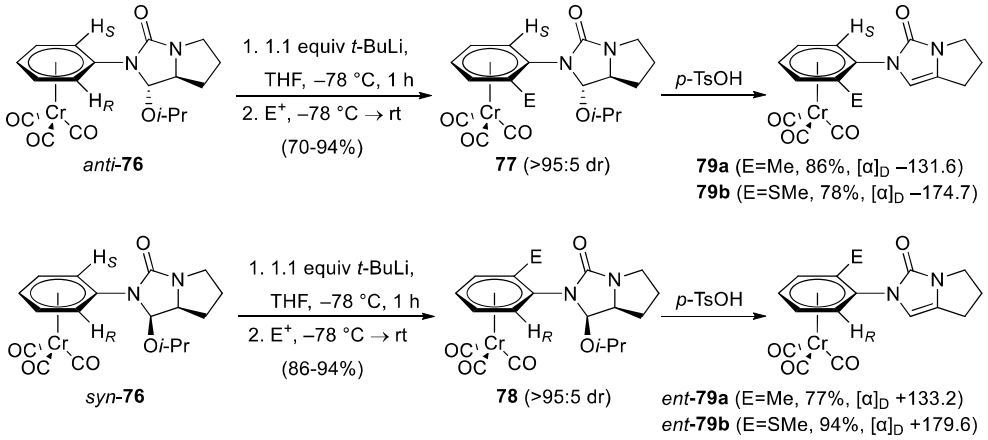
Scheme 23

As in the case of ferrocenes, lithiation followed by quench with a range of electrophiles gave *ortho*-substituted products **77** and **78** in >95:5 dr and with opposite planar chiral configurations, as

confirmed by X-ray crystallography of **77** (E=SMe), and by comparison of specific rotations of the solely planar chiral unsaturated imidazolones **79a,b** and *ent*-**79a,b** (Scheme 25).[35]



Scheme 24



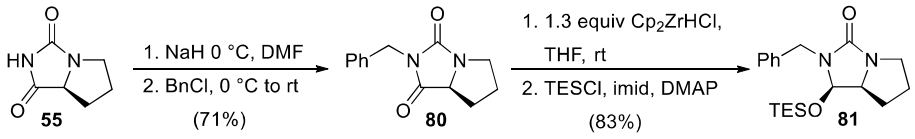
Scheme 25

6.3. *N*-Benzyl pyrroloimidazolones

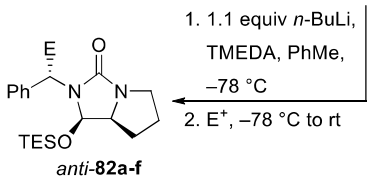
The preceding sections (6.1 and 6.2) described installation of planar chirality by selective lithiation of sp^2-hybridized prochiral positions in aromatic organometallics. While the levels of stereoselectivity were high, it remained to be seen if epimeric pyrroloimidazolones could be successfully applied to lithiation at prochiral sp^3 positions. Unlike ferrocenes and η^6-arene chromium tricarbonyl complexes where the reaction involves asymmetric lithiation to give configurationally stable carbanions before electrophile quench, the same is not always true of sp^3-positions. Lithiation at sp^3 carbons can also proceed by an asymmetric substitution pathway.[37] To determine the feasibility of sp^3-substrates, *N*-benzyl hydantoin **80** was prepared and subjected to stepwise hydrosilylation (Scheme 26) as done for ferrocenes. Benzylic lithiation of **81** followed by electrophile quench gave products **82a-f** in 82:18 to 91:9 dr depending on the electrophile.[38] X-Ray crystallography of benzophenone adduct **82e** showed it to have *anti* relative stereochemistry.

To determine if the stereochemistry of the major diastereomers among products **82a-f** were consistent, transmetalation experiments were performed on stannanes **82b** and **82c**, followed by quench with TMSCl,

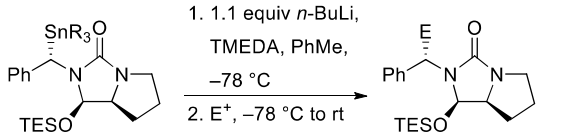
benzophenone, or iodomethane (Scheme 27). The major diastereomers obtained from these experiments were identical to products of direct lithiation-electrophile quench, as depicted in Scheme 26.[38] These results also indicated that the carbanion generated by deprotonation of **81**, or from stannanes **82b,c** *via* transmetalation, had configurational stability at low temperatures.



product	E^+	E	yield, %, **82**	dr **82**, *anti*:*syn*
82a	TMSCl	TMS	65	88:12
82b	$SnBu_3Cl$	$SnBu_3$	57	91:9
82c	$SnMe_3Cl$	$SnMe_3$	72	89:11
82d	$(SMe)_2$	SMe	86	90:10
82e	Ph_2CO	$Ph_2C(OH)$	76	91:9
82f	MeI	Me	81	82:18



Scheme 26



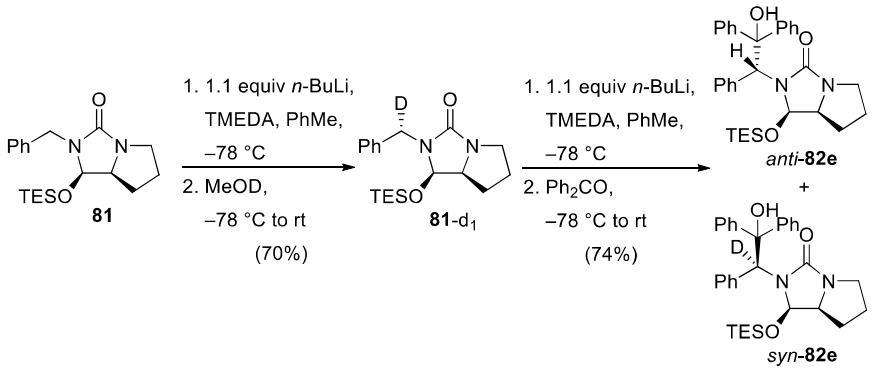
stannane	E^+	E	yield, %, **82**	dr **12**, *anti*:*syn*
82b	TMSCl	TMS	54	89:11
82b	Ph_2CO	$Ph_2C(OH)$	50	91:9
82c	MeI	Me	73	83:17

Scheme 27

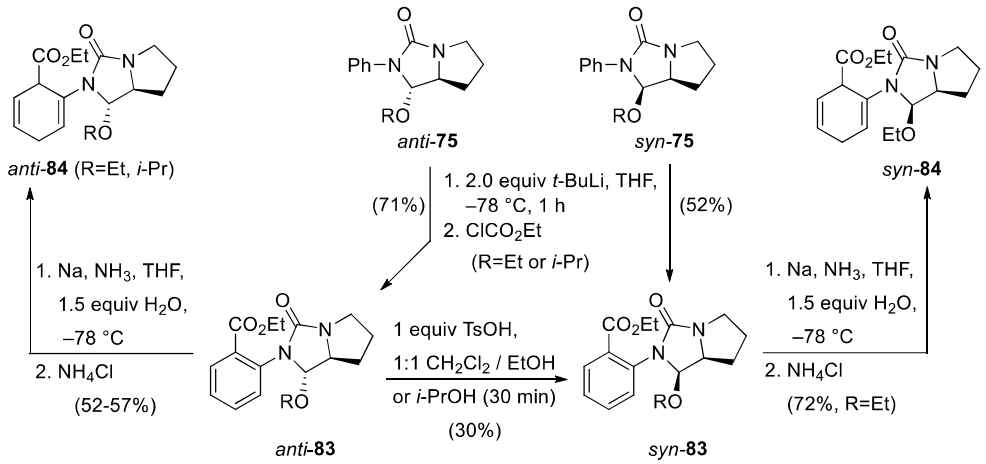
These results further supported that the lithiation step was stereo-determining, as in ferrocenes. This hypothesis was tested by preparation of the deuterated analogue **81**-d_1 (Scheme 28). Lithiation of **81**-d_1 under identical conditions as **81** followed by addition of benzophenone gave *anti*- and *syn*-**82** in almost identical amounts (53:47 dr) because a primary kinetic isotope effect counters the preferred stereoselectivity of lithiation.[38]

6.4. Cyclohexa-1,4-dienes with quaternary chiral centers

Based on the results with *N*-benzyl derivatives, we were interested in exploring the potential of pyrroloimidazolones in diastereoselective Birch reduction-alkylation sequences. The required substrates were synthesized from *anti*- and *syn*-**75** (R=Et, *i*-Pr, Scheme 29), the same derivatives used in the synthesis of η^6-arene chromium tricarbonyl complexes (Scheme 24). Directed *ortho* metalation of the individual epimers, followed by addition of ethyl chloroformate to the reaction mixture, gave benzoate esters *anti*- and *syn*-**83**.[39] The more plentiful epimer *anti*-**83** could be converted to *syn*-**83** by exposure to acidic ethanol or isopropanol, which provided an alternate route to the minor starting material. Birch reduction of each starting material gave the dearomatized intermediates *anti*- and *syn*-**84** that could be stored in a freezer under inert atmosphere for at least two weeks.



Scheme 28



Scheme 29

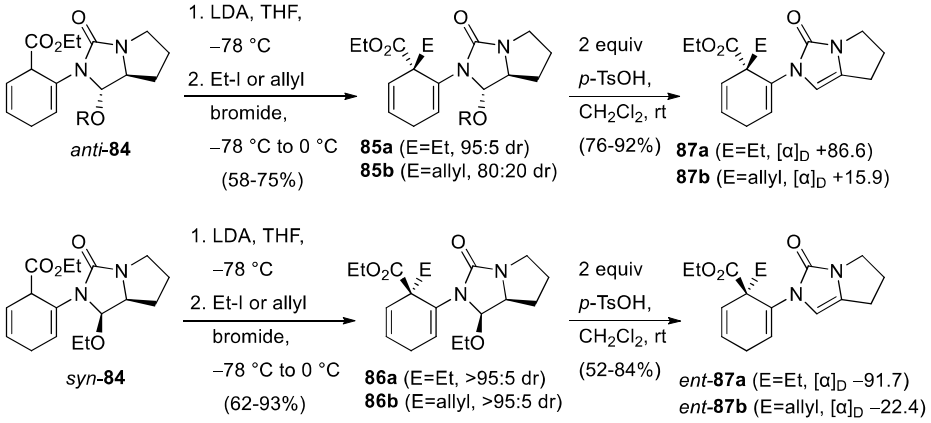
Treatment of *anti*-**84** with LDA at low temperature followed by alkylation with iodoethane or allyl bromide gave products **85a,b** in 95:5 and 80:20 dr, respectively. Reduction of **85a** with $LiAlH_4$ in a separate experiment afforded the primary alcohol, which was found to have *S* configuration at the quaternary chiral center from X-ray crystallography. Analogous generation of the enolate from *syn*-**84** gave ethyl and allyl adducts in comparable yields but >95:5 dr for both cases (only two electrophiles are shown for brevity). The intermediacy of enolates in lithiation of *anti*- and *syn*-**84** assures that the preceding reactions proceed by an asymmetric substitution pathway, rather than asymmetric lithiation as in *N*-benzyl derivative **81**. Alkylated products **85a,b** and **86a,b** were shown to have opposite configurations at the quaternary chiral centers by elimination to imidazolones **87a,b** and *ent*-**87a,b**, given their reversed specific rotations (Scheme 30).[39]

Partial hydrolysis of **85a** with citric acid in aqueous THF furnished the hemiaminal **88** (Scheme 31) with minimal formation of the eliminated product **87a**. In contrast, heating a toluene solution of the minor diastereomer from the mixture of **85b** (R=*i*-Pr) in a sealed tube gave the interesting Cope rearrangement product **89** with concomitant elimination to the unsaturated imidazolone.[39]

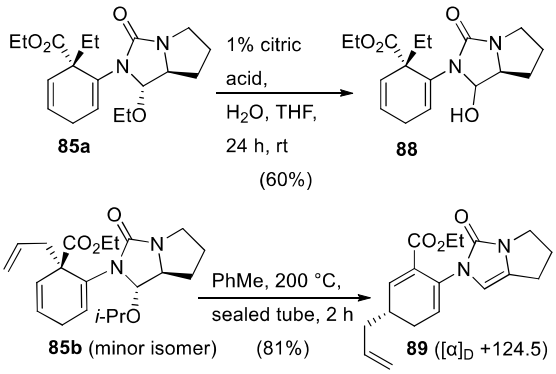
6.5. *N*-Propargyl pyrroloimidazolones and axial chiral allenamides

N-Propargyl alkynes and axial chiral *N*-allenes (allenamides and allenamines) have been studied extensively as valuable synthetic intermediates in organic synthesis.[40,41] Despite their utility it has been challenging to prepare these two classes of molecules consistently and with high stereoselectivity from a

single general starting material. The advent of epimeric pyrroloimidazolones offered a potential solution to this reaction dichotomy.



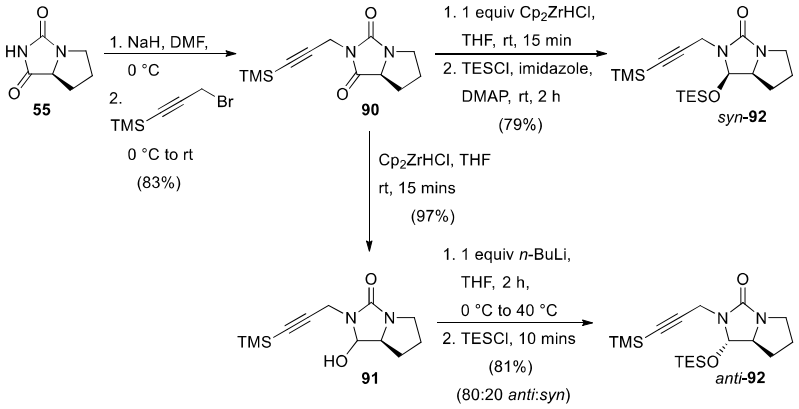
Scheme 30



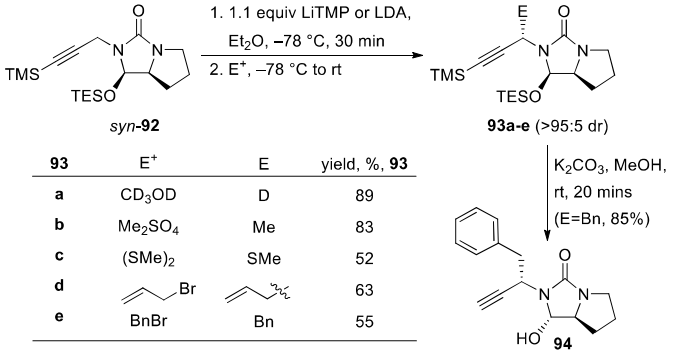
Scheme 31

As in previous examples, *N*-substitution of L-proline hydantoin with TMS-propargyl bromide gave hydantoin **90** (Scheme 32). This material was amenable to one-pot diastereoselective reduction and silylation by sequential addition of Schwartz's reagent and TESCl to give *syn*-**92** without the competing reduction of the alkyne.[42] Alternatively, isolation of the configurationally mobile hemiaminal **91** after reduction, followed by heating the lithium alkoxide to promote equilibration before *O*-silylation, gave mainly the epimeric starting material *anti*-**92**.

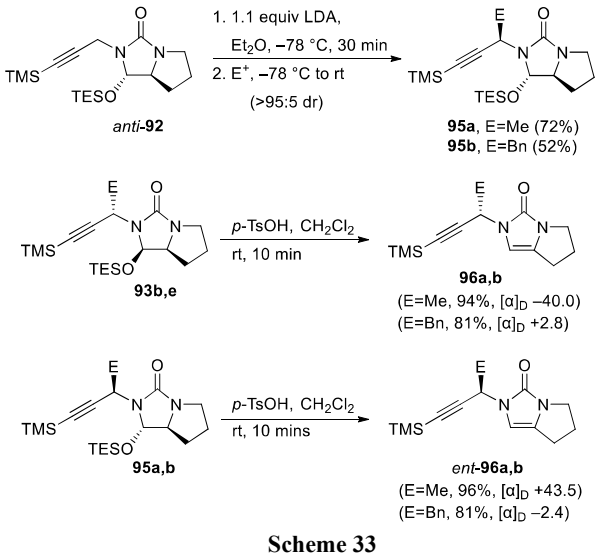
Lithiation of *syn*-**92** with LDA or lithium tetramethylpiperidide (LiTMP) furnished products **93a-e** (Scheme 33) in good yields and excellent diastereoselectivity (>95:5 dr) upon electrophile quench. The high stereoselectivity of the reaction was evident by comparison of the ^{1}H NMR spectrum of deuterium adduct **93a** (E=D) to that of *syn*-**92**, which showed disappearance of a single propargyl proton at 4.3 ppm. Treatment of benzyl adduct **93e** with potassium carbonate afforded alkyne **94**, a derivative that was recrystallized for X-ray diffraction to reveal *S* configuration at the propargyl position, in addition to *anti*-stereochemistry of the hemiaminal moiety.[42] To determine if lithiation-electrophile quench of *anti*-**92** would proceed with reversal of propargyl stereochemistry, methyl and benzyl adducts **95a,b** were prepared under identical conditions and isolated as single diastereomers (>95:5 dr).



Scheme 32



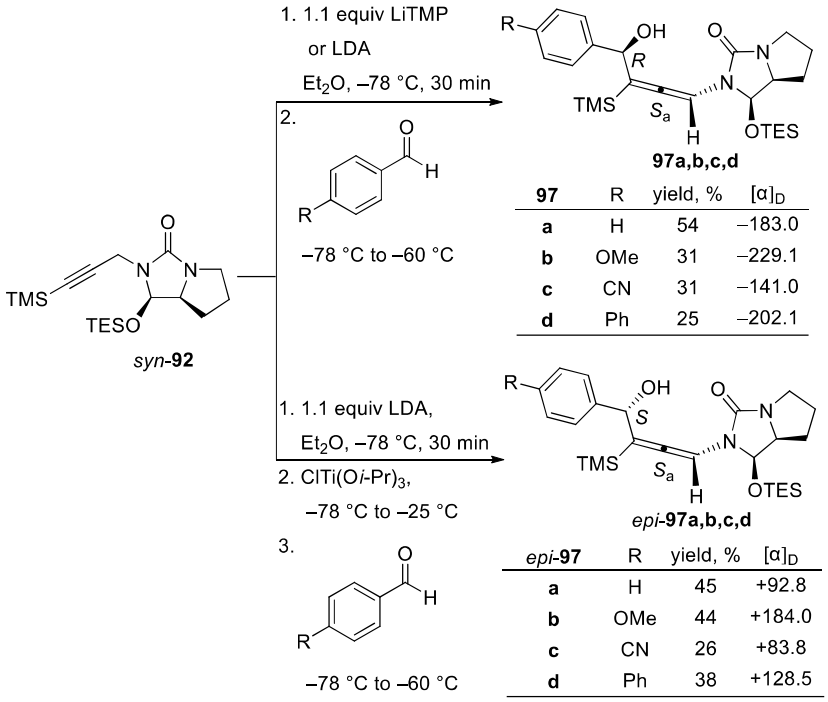
93	E^+	E	yield, %, **93**
a	CD_3OD	D	89
b	Me_2SO_4	Me	83
c	$(SMe)_2$	SMe	52
d			63
e	BnBr	Bn	55



Scheme 33

Elimination of *syn*-derived methyl and benzyl adducts **93b,e** and *anti*-derived **95a,b** with *p*-TsOH gave products **96a,b** and *ent*-**96a,b** that were enantiomers of each other, as verified by their opposite specific rotations (Scheme 33).[42]

Starting material *syn*-**92** also served as a precursor to axial chiral allenes. Lithiation according to established conditions, followed by electrophile quench with a series of prochiral benzaldehydes, gave secondary alcohols **97a,b,c,d** (Scheme 34) in high diastereoselectivity (>95:5 dr) and without the need for an intervening transmetalation using ClTi(O*i*-Pr)$_3$. These results represented the first examples of stereoselective allenamide synthesis *via* direct quench of the lithiated intermediate. X-Ray crystallography of alcohol **97a** showed that the product had S_a axial chirality and *R* configuration of the benzylic alcohol.[42] The latter configuration was atypical, considering that previous allenamides prepared with an intervening transmetalation to titanium had opposite stereochemistry of the benzylic alcohol.[43] This observation prompted us to perform a parallel set of experiments with a deliberate transmetalation after lithiation of *syn*-**92** to see if the epimeric series benzylic alcohols could also be prepared. For this purpose, lithiation of *syn*-**92** with LDA was followed by transmetalation using ClTi(O*i*-Pr)$_3$ before additon of the benzaldehydes. In every case, products *epi*-**97a,b,c,d** were isolated as single diasteromers (>95:5 dr) but with *S* configuration of the benzylic alcohol. The change in stereochemistry of the secondary alcohols was explained by DFT computational studies, which showed a difference in stereofacial attack towards the benzaldehydes in the transition states from the lithiated intermediate (6,5-bicyclic) versus the Ti(IV) intermediate (6-membered).[42]



97	R	yield, %	$[\alpha]_D$
a	H	54	–183.0
b	OMe	31	–229.1
c	CN	31	–141.0
d	Ph	25	–202.1

epi-**97**	R	yield, %	$[\alpha]_D$
a	H	45	+92.8
b	OMe	44	+184.0
c	CN	26	+83.8
d	Ph	38	+128.5

Scheme 34

7. Conclusions

Imidazolone chiral auxiliaries continue a steadfast evolution in asymmetric synthesis. Among "classical" 2-imidazolidinones, new methods employing standard enolate and aldol chemistry have been applied to the stereoselective synthesis of fluoxetine and furoindoline natural products, in addition to β-lactams, γ-lactones, and aziridines. The ease of chiral auxiliary recovery and cost mitigation has been

addressed by development of solid supported or ionic liquid versions of 2-imidazolidinones and related hydantoins. In contrast, the parallel development of epimeric pyrroloimidazolones as "non-classical" auxiliaries permits the stereoselective induction of planar, central, and axial chirality in substrates such as ferrocenes, η^6-arene chromium tricarbonyl complexes, cyclohexa-1,4-dienes, plus *N*-benzyl, *N*-propargyl, and *N*-allenyl derivatives. In many cases, the *syn* versus *anti* epimeric forms of pyrroloimidazolones behave as pseudo-enantiomers, allowing for the stereoselective synthesis of enantiomeric products from a single and less expensive L-proline-derived starting material. The hemiaminal ether moiety of pyrroloimidazolones makes them amenable to manipulation into other nitrogen-containing functional groups after asymmetric induction, giving access to potentially valuable secondary ureas, primary amines, and *N*-heterocyclic carbene ligands. The ease of elimination of *syn* and *anti* pyrroloimidazolones to unsaturated ureas that retain only the newly installed chirality, after asymmetric induction, simplifies the comparison of enantiomeric products from the various reactions in which they are used. Our research group plans to develop pyrroloimidazolone chemistry for additional *N*-derivatives as we simultaneously exploit the products from established methods in the stereoselective synthesis of more complex targets. These efforts will ensure growth of the pyrroloimidazolone subset of imidazolone chiral auxiliaries well into the future.

Acknowledgements

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