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# Asymmetric Synthesis of Allylic Fluorides via Fluorination of Racemic Allylic Trichloroacetimidates Catalyzed by a Chiral Diene-Iridium Complex

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## ABSTRACT

The ability to use racemic allylic trichloroacetimidates as competent electrophiles in a chiral bicyclo[3.3.0]octadiene-ligated iridium-catalyzed asymmetric fluorination with $Et_3N{\cdot}3HF$ is described. The methodology represents an effective route to prepare a wide variety of α-linear, α-branching, and β-heteroatom substituted allylic fluorides in good yields, excellent branched-to-linear ratios, and high levels of enantioselectivity. Additionally, the catalytic system is amendable to the fluorination of optically active allylic trichloroacetimidate substrates to afford the fluorinated products in good yields with exclusively branched selectivity. Excellent levels of catalyst-controlled diastereoselectivities using either (*R*,*R*) or (*S*,*S*)-bicyclo[3.3.0]octadiene ligand are observed. The synthetic utility of the fluorination process is illustrated in the asymmetric synthesis of 15-fluorinated prostaglandin and neuroprotective agent P7C3-A20.

**Keywords:** *Enantioselective, Allylic Fluorination, Iridium, Transition-Metal, Trichloroacetimidate, Catalysis*

## INTRODUCTION

Over the past decade, fluorine-containing molecules have become increasingly important in several fields including medicinal chemistry, positron emission tomography (PET) imaging, agriculture, and materials science.[1] The introduction of carbon-fluorine bonds into organic molecules can lead to improved bioavailability and, in turn, the efficacy of fluorinated drug candidates over their non-fluorinated parent compounds by affecting a wide variety of properties including $pK_a$, lipophilicity, metabolic stability, and binding affinity.[2] Roughly 30% of agrochemicals and 20% of pharmaceutical targets currently on the market contain at least one fluorine atom.[3] As a result, numerous methods have been developed to address the unmet challenges previously associated with the syntheses of aryl fluorides[4,5] and enantioenriched aliphatic fluorides[6,7,8] via nucleophilic fluorination.

Allylic fluorides are biologically important and can be found in many pharmaceuticals **1**–**3** and PET radiotracers **4** (Figure 1).[9,10,11] However, catalytic asymmetric methods for the direct nucleophilic incorporation of fluoride into allylic systems remain significantly underdeveloped.[12,13,14] A transition-metal-catalyzed asymmetric substitution of allylic electrophiles with nucleophilic fluoride sources could be an ideal approach for the enantioselective synthesis of allylic fluorides.[15,16] This strategy has proven difficult in part due to strong metal-fluoride bonding[17] and a high basicity of desolvated fluoride.[18] Additionally, the ability of allylic fluorides to act as a leaving group has been reported in a palladium-catalyzed allylic substitution reaction,[19] allowing for a reversible reaction thus resulting in a loss of

enantioselectivity. As a result, nucleophilic allylic fluorination has only been harnessed in the context of enantioselective catalysis much more recently when compared to the aliphatic counterparts. [20,21,22,23]

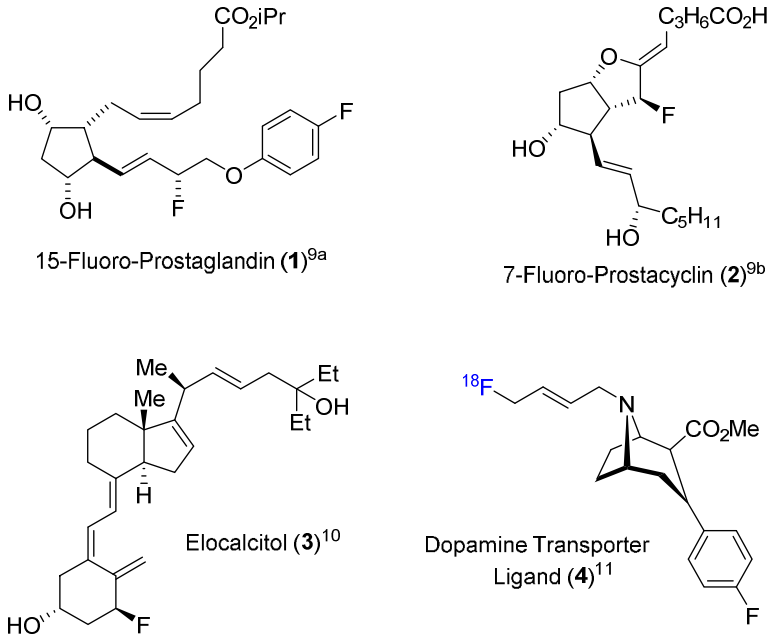
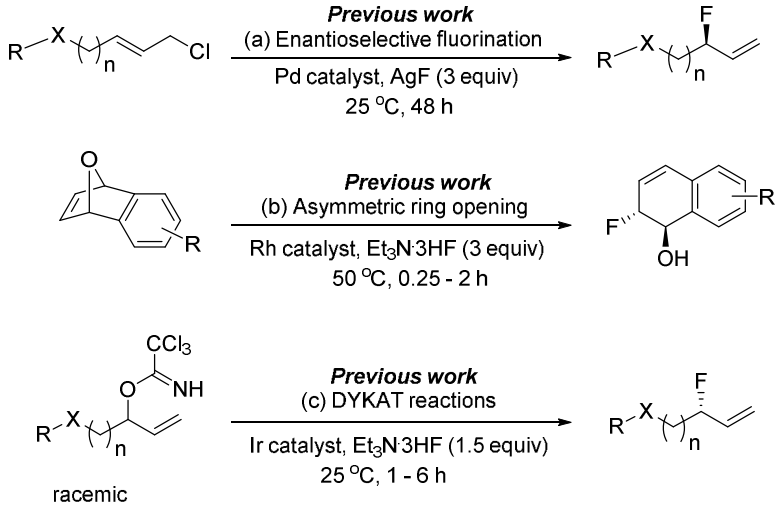



**Figure 1.** Bioactive molecules and PET tracer possessing allylic fluoride unit

In 2010, Katcher and Doyle reported the first enantioselective synthesis of cyclic allylic fluorides in excellent enantiomeric excess (85-96% *ee*) via a chiral bisphosphine-ligated palladium-catalyzed fluorination of cyclic allylic chlorides with silver fluoride as the nucleophilic fluorinating reagent.[24a] In the following year, Doyle and coworkers extended their fluorination method to acyclic allylic halides (Scheme 1a). The α-branching and β-oxygen-substituted allylic halides are effective substrates to provide allylic fluorides with excellent asymmetric induction (90–97% *ee*).[24b] However, fluorination of α-linear substituted halide substrates only provided the branched allylic fluoride products with moderate to low enantioselectivity (21–71% *ee*) despite high regioselectivity.[24b] In 2012, Lautens and coworkers reported the rhodium-catalyzed asymmetric ring-opening of oxabicyclic alkenes using $Et_3N{\cdot}3HF$ as the nucleophilic fluoride source (Scheme 1b).[25] The ring-opening products possess both allylic fluorides and fluorohydrin moieties and were obtained in excellent enantiomeric excess (94–99% *ee*). A variety of substituents on the aryl ring were tolerated except for substrates bearing electron-donating groups. For unsymmetrical oxabicyclic alkene substrates, both regioisomers were obtained with high levels of enantioselectivities. The work of Doyle and Lautens demonstrates the ability of transition metal catalysts to enable enantioselective access to branched allylic fluorides. Nevertheless, there is still a need to develop a more general catalytic asymmetric platform for access to various classes of branched allylic fluorides which could be valuable building blocks for bioactive molecule syntheses.

In 2015, we described a new method for the catalytic enantioselective fluorination via dynamic kinetic asymmetric transformations (DYKAT) of racemic allylic trichloroacetimidates (Scheme 1c). In this process, trichloroacetimidate derivatives of secondary allylic alcohols were illustrated to react with $Et_3N{\cdot}3HF$ (1.5 equiv.) in the presence of 2.5 mol% chiral diene-ligated iridium complex to generate secondary allylic fluorides, bearing α-linear and β-oxygen-substituents, in high yields with excellent enantiomeric purity (Scheme 1c).[26] The fluorination reactions proceeded at room temperature with excellent branched-to-linear ratios (b:l >99:1). The process overcame several of the limitations previously associated with the enantioselective syntheses of α-linear substituted allylic fluorides along with improved branched-to-linear ratios.[24b] Herein, we delineate the scope of this novel catalytic system

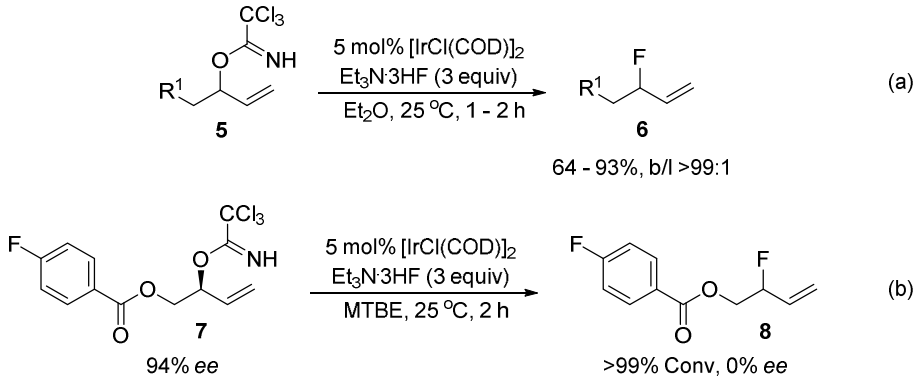
for the asymmetric syntheses of different classes of branched allylic fluorides and the ability of the chiral iridium catalyst to control the diastereoselectivities of the fluorinated products.




**Scheme 1. Asymmetric Allylic C-F Bond Formation**

## RESULTS AND DISCUSSION

**Initial Studies.** In 2011, we investigated regioselective fluorination reactions with allylic substrates **5** (Scheme 2a) bearing a branched trichloroacetimidate, which is used as both a leaving group and a directing group at the allylic carbon.[27] Cyclooctadiene iridium chloride dimer, $[IrCl(COD)]_2$, was identified as an effective catalyst at promoting the fluorination of **5** with $Et_3N{\cdot}3HF$ as the preferred fluoride source to form allylic fluorides **6** in moderate to high yields and excellent branched-to-linear ratios. These reactions performed optimally at room temperature and proceeded within 1 – 2 h in the presence of 5 mol% $[IrCl(COD)]_2$. In the absence of the iridium complex, no conversion was found to occur towards the desired allylic fluoride product. In addition, only trace amounts of Overman rearrangement,[28] forming allylic trichloroacetamides, and elimination-forming diene products were observed.




**Scheme 2**. **Discovery of Iridium-Catalyzed Regioselective Allylic Fluorination**

To clarify the stereochemical outcome of our allylic fluorination process, a control experiment with enantioenriched trichloroacetimidate **7** (94% *ee*) was conducted (Scheme 2b). The fluorination reaction was not enantiospecific, as evidence by the racemization of the fluorinated product **8** (0% *ee*). Based on this result, we explored the possibility of converting racemic allylic trichloroacetimidate

substrates **9** and **12** to enantioenriched fluoride products through a DYKAT pathway (Figure 2).[29] Such a process is highly desirable as both enantiomers (**9** and **12**) of the starting material are transformed into a single optically active fluorinated product, in contrast to a kinetic resolution which involves conversion of only one enantiomer (**9** or **12**) of the starting material. For a DYKAT process to be realized, a Curtin-Hammett situation must be established such that equilibration of the π-allyliridium intermediates **10** and **14** must be faster than the subsequent nucleophilic fluoride attack. We hypothesize that the utilization of a chiral bulky ligand could establish a highly congested steric environment around the iridium metal, and subsequently slow down the rate of fluoride addition to allow more time for a rapid π-σ-π interconversion of the diastereomeric π-allyliridium complexes **10** and **14** via σ-complex **13**. An unfavorable interaction between one of the two π-allyliridium intermediates would determine which enantiomer of the fluoride product (**11** or **15**) is formed preferentially.[30]

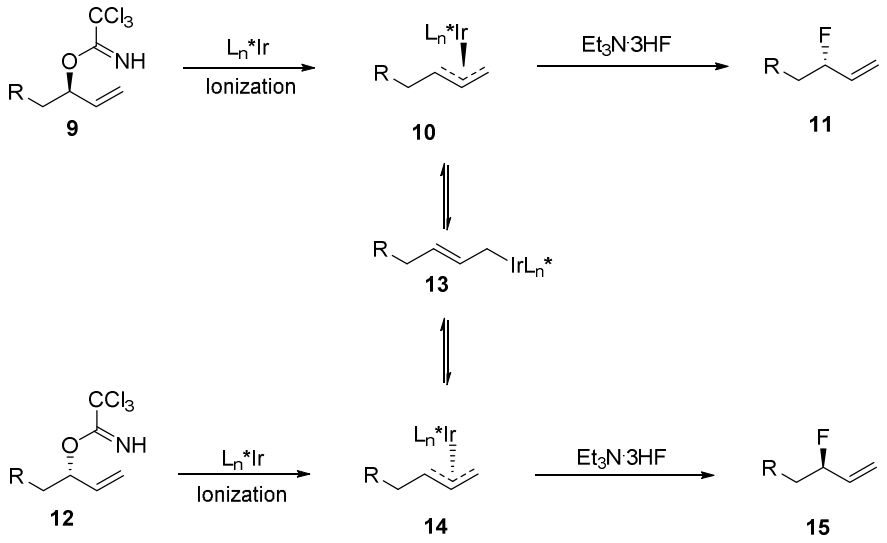
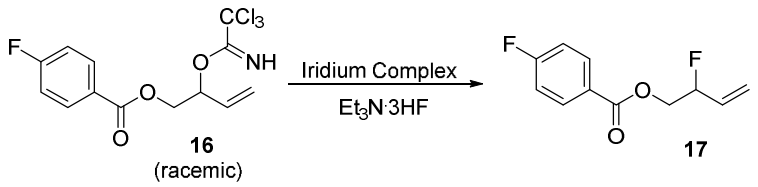


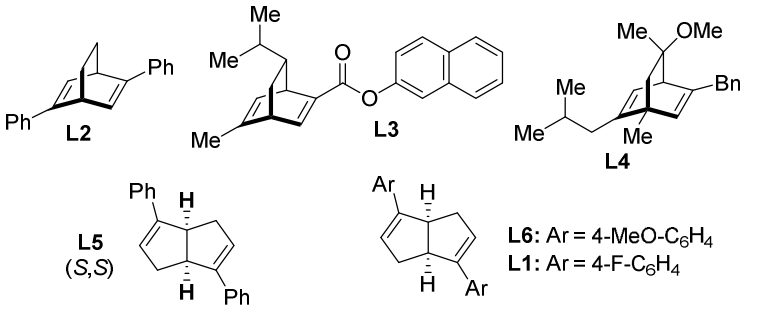

**Figure 2.** Proposed DYKAT-based synthesis of allylic fluorides.

**Reaction Development.** With these considerations in mind, the 4-fluorobenzoyl protected allylic trichloroacetimidate **16** was chosen as a model substrate in our reaction development (Table 1). Based on our previous regioselective fluorination results (Scheme 2a),[27] we hypothesized that the use of chiral diene ligands would enable access to enantioselective allylic fluorides. Our group has previously developed a DYKAT type reaction for the synthesis of enantioenriched allylic amines using a chiral diene-ligated rhodium complex;[31] therefore, we reasoned that Hayashi's bicyclo[2.2.2]octadiene ligand, **L2**,[32a] would be a good starting point (entry 1). Although the reaction with *in situ* generated **L2**-ligated iridium complex provided the desired allylic fluoride **17** in good conversion (51%) and excellent branched selectivity (b:l > 99:1), the enantiomeric excess of **17** was low (13% *ee*). Further Hiyashi ligand **L3**[32b] and Carreira ligand **L4**[33] (entries 2 and 3) proved ineffective. We hypothesized that chiral diene ligands with larger bite angles could induce higher asymmetric induction as they could bind more tightly to the iridium center.[34] Accordingly, fluorination of substrate **16** using Lin ligand **L5** (entry 4)[35] significantly improved the enantioselectivity of **17** (66% *ee*). Having established commercially available Lin ligand, **L5**, as the most effective ligand at promoting the fluorination, we next investigated the electronic effects by changing substituents on the phenyl ring (**L6** and **L1**). While use of 4-methoxyphenyl diene **L6** did not result in improved enantiomeric excess (62% *ee*, entry 5), use of 4-fluorophenyl diene **L1** significantly induced higher asymmetric induction (81% *ee*, entry 6). Similar diene ligand trends have been observed with our previous results for the rhodium-catalyzed DYKAT of racemic tertiary allylic substrates with anilines.[31a]

**Table 1. Reaction Optimization**




| entry | Ir complex | solvent | temp (°C) | $Et_3N{\cdot}3HF$ (equiv.) | time (h) | NMR yield (%)[c] | *ee* (%)[d] |
|---|---|---|---|---|---|---|---|
| 1 | $[IrCl(COE)_2]_2$/**L2**[a] | $Et_2O$ | 25 | 3 | 12 | 51 | 13 |
| 2 | $[IrCl(COE)_2]_2$/**L3**[a] | $Et_2O$ | 25 | 3 | 12 | 36 | 13 |
| 3 | $[IrCl(COE)_2]_2$/**L4**[a] | $Et_2O$ | 25 | 3 | 12 | 52 | 3 |
| 4 | $[IrCl(COE)_2]_2$/**L5**[a] | $Et_2O$ | 25 | 3 | 6 | 95 | 66 |
| 5 | $[IrCl(COE)_2]_2$/**L6**[a] | $Et_2O$ | 25 | 3 | 6 | 95 | 62 |
| 6 | $[IrCl(COE)_2]_2$/**L1**[a] | $Et_2O$ | 25 | 3 | 6 | 95 | 81 |
| 7 | $[IrCl(\mathbf{L5})]_2$[b] | $Et_2O$ | 25 | 3 | 6 | 91 | 79 |
| 8 | $[IrCl(\mathbf{L5})]_2$[b] | $Et_2O$ | 25 | 1.5 | 6 | 95 | 84 |
| 9 | $[IrCl(\mathbf{L5}]_2$[b] | Toluene | 25 | 1.5 | 6 | 95 | 83 |
| 10 | $[IrCl(\mathbf{L5})]_2$[b] | $CH_2Cl_2$ | 25 | 1.5 | 6 | 95 | 77 |
| 11 | $[IrCl(\mathbf{L5})]_2$[b] | THF | 25 | 1.5 | 6 | 95 | 87 |
| 12 | $[IrCl(\mathbf{L5})]_2$[b] | MTBE | 25 | 1.5 | 6 | 95 | 88 |
| 13 | $[IrCl(\mathbf{L5})]_2$[b] | MTBE | 40 | 1.5 | 4 | 95 | 86 |
| 14 | $[IrCl(\mathbf{L1})]_2$[b] | MTBE | 25 | 1.5 | 1 | 99(82)[e] | 93(93)[e] |




[a] The diene-ligated iridium complex was generated *in situ* from 2.5 mol% $[IrCl(COE)_2]_2$ with 5 mol% ligands, **L1** – **L6**. [b] 2.5 mol% $[IrCl(L_n)]_2$ complex (**L6** or **L1**) was utilized in the reaction. [c] Determined by $^{19}F$ NMR analysis using $PhCF_3$ as an internal standard. [d] Determined by chiral HPLC. [e] Isolated Yield.

Since **L5** is commercially available, it was chosen as the model ligand to further optimize the reaction conditions (Table 1, entries 7-13). To exclude the possibility that unbound cyclooctene (COE) reversibly binds to the iridium catalyst resulting in degradation of the enantioselectivity, we developed a procedure for superior ligation by heating a mixture of $[IrCl(COE)_2]_2$ with diene **L5** in hexane at 50°C for 48 h. The resulting iridium complex, $[IrCl(\mathbf{L5})]_2$, was isolated and used in the fluorination without further purification. As expected, use of 2.5 mol% $[IrCl(\mathbf{L5})]_2$ complex (entry 7) resulted in much higher asymmetric induction (66 → 79% *ee*). Higher enantioselectivity was also observed when fewer equivalents of $Et_3N{\cdot}3HF$ (entry 8) were used (79 → 84% *ee*). Varying the solvents (entries 9–12) did not have a pronounced effect on the outcome of the reaction, although MTBE (entry 12) was found to slightly increase the selectivity (84% → 88% *ee*) of **17**. Additional efforts at reaction optimization (higher temperature, ligands,[36] additive,[37] and concentration) provided similar levels of selectivity. With these optimal conditions at hand, we ligated iridium with the most enantioselective 4-fluorophenyl diene **L1** to produce $[IrCl(S,S)\text{-}\mathbf{L1}]_2$ complex (see Figure 3 for its X-ray crystallographic structure), which was

found to be superior to [IrCl(**L5**)]$_2$ complex in terms of both yield and enantioselectivity (entry 14). The fluorination proceeded to completion within 1 h to provide allylic fluoride **17** in 82% isolated yield with excellent enantiomeric excess (93% *ee*).

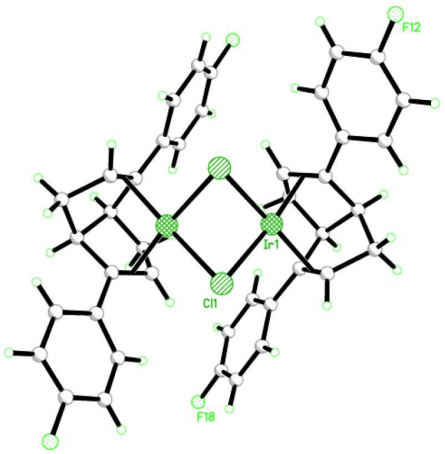
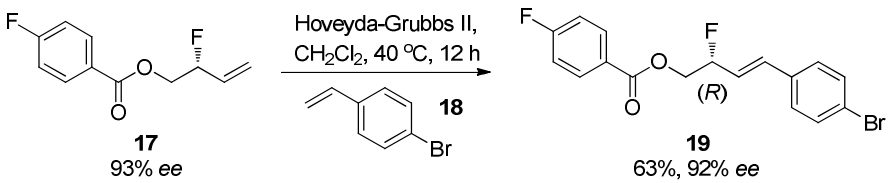



**Figure 3.** ORTEP diagram of [IrCl(*S*,*S*)-**L1**]$_2$

Attempts to crystallize allylic fluoride **17** were unsuccessful; therefore, to establish the absolute stereochemistry of the allylic fluoride product, **17** was subsequently subjected to cross-metathesis with 4-bromostyrene **18** in the presence of Hoveyda-Grubbs II catalyst (Scheme 3). Internal allylic fluoride **19** was isolated as a crystalline solid in 63% yield with no loss of enantiomeric purity (92% *ee*). Subsequent crystallographic analysis showed allylic fluoride **19** to be *R*-configured (Figure 4).

**Scheme 3. Derivatization of Allylic Fluoride 17 for X-ray Analysis**



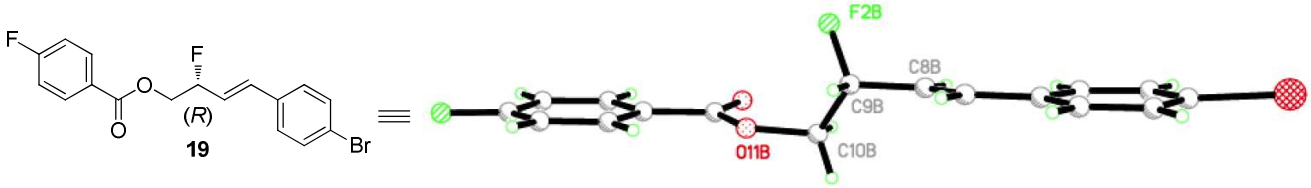
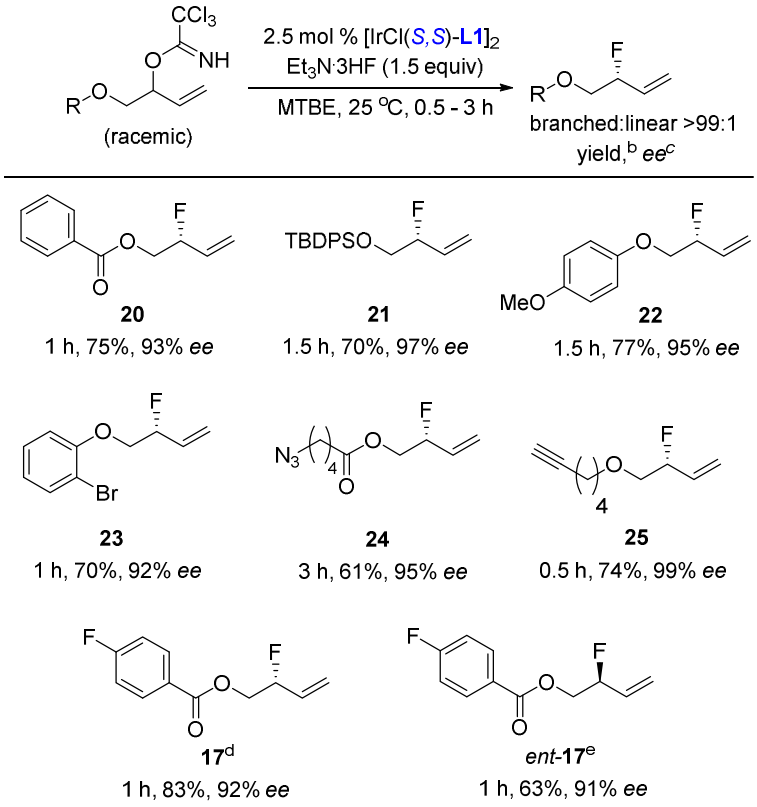




**Figure 4.** ORTEP diagram of internal allylic fluoride **19**.

**Substrate Scope.** With the optimized conditions in hand, we next sought to investigate the scope of the fluorination reaction with respect to the β-oxygen-substituted trichloroacetimidate substrates (Table 2). The fluorination reaction tolerates a range of functional groups and provides the fluorinated products **20**–**25** in good yields (61–75%) with excellent enantioselectivity (91–99% *ee*) and regioselectivity (b:l >99:1). The mild conditions are also tolerant of the silyl ether group (TBDPS) to provide fluoride **21** in 70% yield and 97% *ee*. These results are consistent with what has been observed by the Doyle group wherein higher asymmetric induction was observed with substrates bearing β-oxygen substituents.[24b]

The ability to introduce the azide and alkyne functional groups (**24** and **25**) highlights the significant flexibility of this method. Both the azide and alkyne-containing fluoride products offer the functionality of subsequent incorporation into a variety of biologically relevant molecules.[38] Having examined the scope of β-oxygen substituted substrates, we sought to probe the effects of increasing the scale of the fluorination while simultaneously decreasing the chiral iridium catalyst loading. Accordingly, allylic trichloroacetimidate **16** was fluorinated on a 1.2 mmol scale using 1 mol% [IrCl(*S*,*S*)-**L1**]$_2$ to afford allylic fluoride **17** in good yield (83%) with high levels of enantiocontrol (92% *ee*), similar to the result obtained in a small scale (82% and 93% *ee*, Table 1). We also conducted the reaction with [IrCl(*R*,*R*)-**L1**]$_2$ and *ent*-**17** was isolated in comparable yield and enantiomeric excess (Table 2).

**Table 2. Scope of β-Oxygen-Substituted Imidate Substrates**[a]

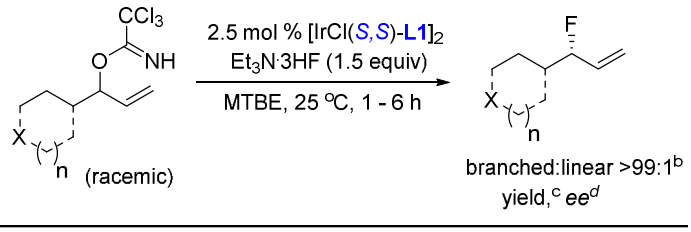


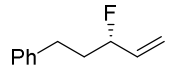

[a] All reactions were carried out on a 0.04 – 0.3 mmol scale of allylic trichloroacetimidates. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Reaction was conducted on a 1.2 mmol scale of imidate substrate **16**. [e] Reaction was conducted 2.5 mol% [IrCl(*R*,*R*)-**L1**]$_2$.

In addition to β-oxygen-substituted trichloroacetimidates, we found that substrates bearing α-linear and α-branching substituents readily participated in catalytic fluorination process to deliver the allylic fluoride products **26** – **33** (Table 3) in high yields (77 – 90%) and enantioselectivity (88 – 94% *ee*). Importantly, our fluorination process is also suited for α-linear substituted substrates, providing the corresponding allylic fluorides **26**–**29** (Table 3) with excellent levels of asymmetric induction (90 – 95% *ee*). Our method addresses the current limitation associated with the asymmetric synthesis of this motif. For example, while our reaction affords **27** and **29** in 92% *ee* and 94% *ee*, respectively, a chiral bisphosphine-palladium complex-catalyzed fluorination of acyclic allylic chlorides provided moderate enantiomeric excess of **27** (21% *ee*) and **29** (58% *ee*).[24b] The six-membered ring substituted products (**30** and **31**) induced higher enantiocontrol than their 4-membered ring counterparts (**32** and **33**).

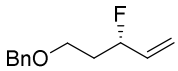
Furthermore, it has been determined that longer reaction times are necessary for substrates (**30** – **33**) containing α-branching unit. Interestingly, α-naphthyl substituted allylic trichloroacetimidate provided the branched product **34** preferentially albeit in reduced regioselectivity (b:l = 4:1) as a racemate (0% *ee*). In previous reports by both the Gouverneur and Doyle groups, under palladium catalysis, cinnamyl 4-nitrobenzoate[20a] and cinnamyl chloride[24b] produced linear allylic fluorides preferentially over the branched allylic fluoride. Under our iridium conditions, we hypothesize that the α-naphthyl substituted substrate is more likely to proceed through a discreet benzylic and allylic cation, as previously reported under our rhodium catalyzed benzylic fluorination conditions,[39] to provide allylic fluoride **34**.

**Table 3. Scope of α-Linear and α-Branching Substituted Imidates**[a]

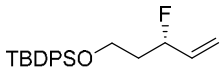


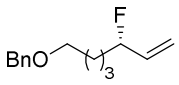

**26**
1 h, 82%, 90% *ee*



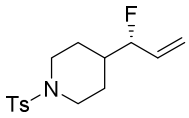

**27**
1 h, 90%, 92% *ee*



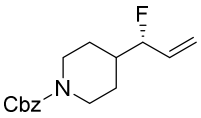

**28**
1 h, 69%, 95% *ee*



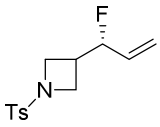

**29**
1 h, 75%, 94% *ee*



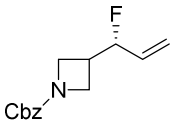

**30**
6 h, 89%, 93% *ee*



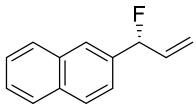

**31**
6 h, 90%, 94% *ee*




**32**
6 h, 78%, 86% *ee*



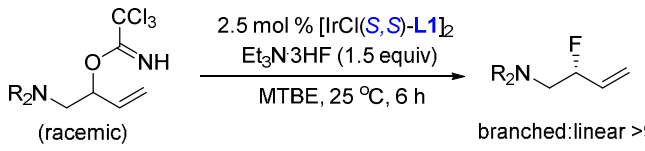

**33**
6 h, 77%, 88% *ee*

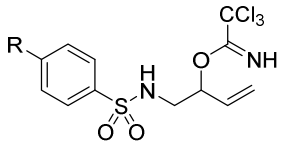
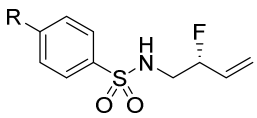
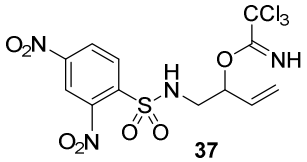
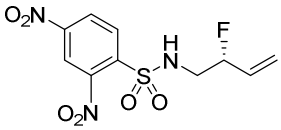
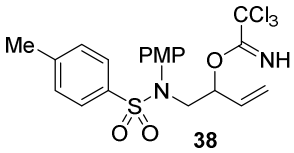
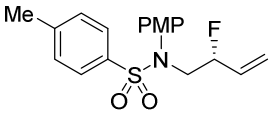
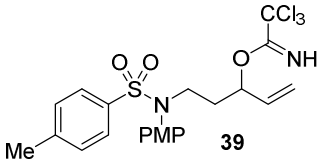
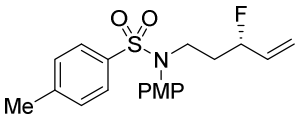



**34**[e]
2 h, 65%, 0% *ee*

[a] All reactions were carried out on a 0.04 – 0.3 mmol scale of allylic imidate substrates, 2.5 mol% [IrCl(*S*,*S*)-**L1**]$_2$ complex, and 1.5 equiv. of $Et_3N{\cdot}3HF$. [b] **34** isolated with b:l = 4:1 [c] Isolated yield.
[d] Determined by chiral HPLC. [e] Isolated after hydrogenation.

**Table 4. Scope of Nitrogen-Containing Imidate Substrates**[a]



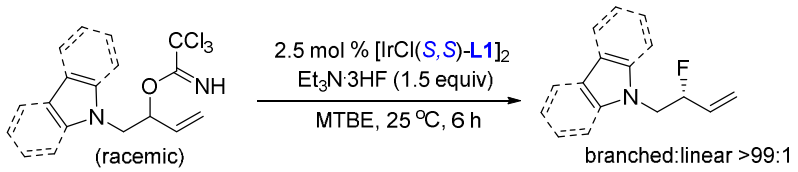

| entry | imidates | products (yield[b], *ee*[c]) |
|---|---|---|
| 1 |  **35:** R = Me |  **40:** 88%, 49% *ee* |
| 2 | **36:** R = $NO_2$ | **41:** 95%, 82% *ee* |
| 3 |  **37** |  **42** 90%, 91% *ee* |
| 4 |  **38** |  **43** 79%, 90% *ee* |
| 5 |  **39** |  **44** 93%, 91% *ee* |

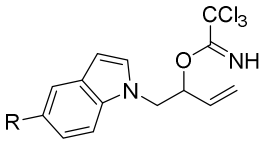
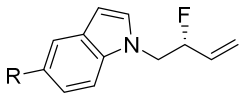
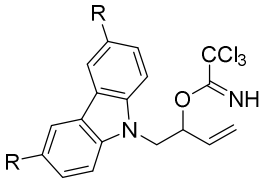
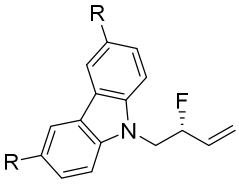
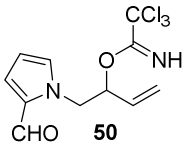
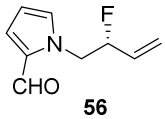
[a] All reactions were carried out on a 0.04 – 0.3 mmol scale of allylic imidate substrates, 2.5 mol% [IrCl(*S*,*S*)-**L1**]$_2$ complex, and 1.5 equiv. of $Et_3N{\cdot}3HF$. [b] Isolated yield. [c] Determined by chiral HPLC.

Next, we studied the scope of the reaction conditions with respect to β-nitrogen containing substituents (Table 4). The allylic β-fluoroamine products generated from this reaction are valuable building blocks for the synthesis of medicinally relevant molecules.[40] A fluorine atom beta to an amine provides a 1-2 log reduction in pKa while retaining bioactivity and improving the metabolic stability of the targets.[41] Only a few approaches to access enantioenriched β-fluoroamines have been reported.[42] Transition-metal-catalyzed asymmetric allylic substitutions to generate allylic β-fluoroamines remains underdeveloped as amines can bind to metal centers effectively preventing catalyst turnover. To overcome this challenge, we postulated that judicious choice of the protecting groups is critical to attenuate the nitrogen basicity thus preventing catalyst deactivation. As a result, the *p*-toluenesulfonyl (Ts) protected amine substrate **35** was first investigated (Table 4, entry 1). Although allylic β-fluoroamine **40** was isolated in 88% yield, its enantiomeric excess was only moderate (49% *ee*). We hypothesize that upon generating π-allyliridium complex from **35**, due to an amino group proximal to the electrophilic site of π-allyliridium complex, both the competing vinyl aziridine and the desired product **40** (Table 4, entry 1) could be generated.[43,44] Rapid interconversion of the vinyl aziridine

intermediate and π-allylmetal complex, as proposed by Ibuka and coworkers in their studies of palladium-catalyzed equilibrated reactions of vinyl aziridines,[45] results in loss of enantioselectivity in the product **40**. To suppress competing vinyl azidirine formation, we aimed to explore the protecting groups that either decrease nitrogen nucleophilicity and/or make nitrogen less accessible. Consequently, substrate **36**, bearing the more electron-withdrawing *para*-nitro-benzenesufonyl group (Table 4, entry 2), was studied. As expected, the fluoride product **41** was obtained in higher enantioselectivity (82% *ee*) than **40** bearing the tosyl group (49% *ee*, entry 1). Substrate **37** bearing the dinitro-benzensulfony group was the most effective, providing allylic fluoride **42** (entry 3) in 90% yield with excellent asymmetric induction (91% *ee*). Similarly, use of the sterically and doubly protected amine-containing allylic trichloroacetimidate **38** (entry 4) provided β-fluoroamine **43** in 79% yield with 90% *ee*. We also investigated a γ-nitrogen containing substrate **39** (entry 5). Allylic γ-fluoroamine **44** was isolated in excellent yield (93%) and showed excellent enantioselectivity (91% *ee*).

**Table 5. Scope of Nitrogen-Heterocycle Substituted Substrates**[a]



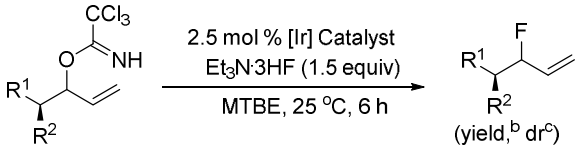

| entry | imidates | products (yield[b], *ee*[c]) |
|---|---|---|
| |  |  |
| 1 | **45:** R = H | **51:** 73%, 88% *ee* |
| 2 | **46:** R = F | **52:** 55%, 90% *ee* |
| 3 | **47:** R = OMe | **53:** 67%, 91% *ee* |
| |  |  |
| 4 | **48:** R = H | **54:** 65%, 94% *ee* |
| 5 | **49:** R = OMe | **55:** 62%, 84% *ee* |
| 6 |  **50** |  **56** 57%, 96% *ee* |

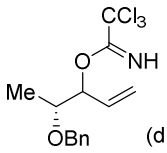
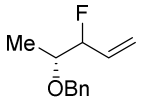
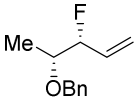
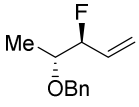
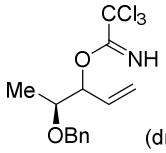
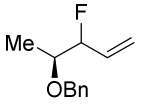
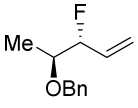
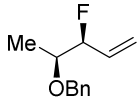
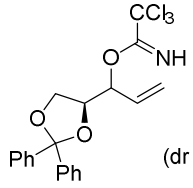
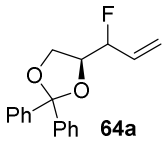
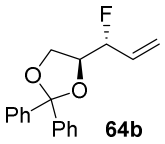
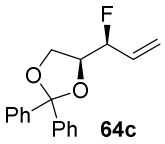
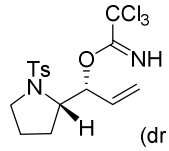
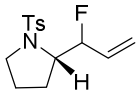
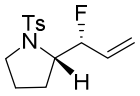
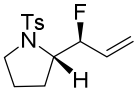
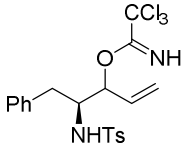
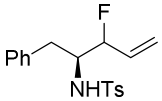
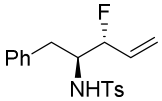
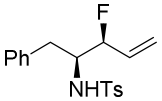
[a] All reactions were carried out on a 0.04 – 0.3 mmol scale of allylic imidate substrates, 2.5 mol% [IrCl(*S*,*S*)-**L1**]$_2$ complex, and 1.5 equiv. of $Et_3N{\cdot}3HF$. [b] Isolated yield. [c] Determined by chiral HPLC.

Expanding the scope of enantioselective fluorination to other families of nitrogen-containing allylic trichloroacetimidates is another important objective. We chose to pursue nitrogen-containing

heterocycles (Table 5, entries 1–6) as their architectures have been used as promising lead compounds in medicinal chemistry.[11,46] We speculate that heterocycles such as indole, carbazole, and pyrrole could potentially suppress vinyl aziridine formation as their nitrogen lone pair are comprised in the aromatic π-system. As postulated, fluorination of indole-containing allylic substrates **45**–**47** (entries 1–3) proceeded smoothly to furnish the desired fluorinated products **51**–**53** in moderate yields (55–73%) and high enantioselectivity (88–91% *ee*). A similar trend was observed with carbazole-containing allylic imidates **48** and **49** (entries 4 and 5), and their corresponding fluoride products **54** and **55** were formed in 94% *ee* and 84% *ee*, respectively. We discovered that pyrrole-2-carboxaldehyde **50** was the most effective electrophile (entry 6), providing allylic β-fluoroamine **56** with excellent enantiomeric excess (96% *ee*).

**Table 6. Scope of Allylic Imidate Substrates Bearing α-Stereocenter**[a]



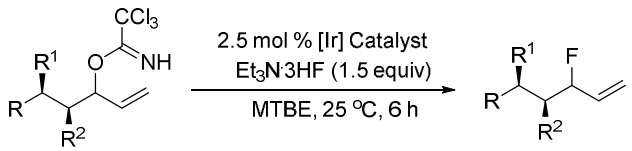

| entry | imidates | fluorinated products (major diastereomer) [IrCl(COD)]$_2$ | [IrCl(*S*,*S*)-**L1**]$_2$ | [IrCl(*R*,*R*)-**L1**]$_2$ |
|---|---|---|---|---|
| 1 |  **57** (dr = 1.5:1) |  **62a** 99% (dr = 1:1) |  **62b** 52% (dr = 14:1) |  **62c** 98% (dr = 43:1) |
| 2 |  **58** (dr = 1.5:1) |  **63a** 82% (dr = 1:1) |  **63b** 55% (dr = 17:1) |  **63c** 63% (dr = 13:1) |
| 3 |  **59** (dr = 1:1) |  **64a** 67% (dr = 1:1) |  **64b** 67% (dr >99:1) |  **64c** 62% (dr = 52:1) |
| 4 |  **60** (dr > 25:1) |  **65a** 77% (dr = 1:1) |  **65b** 62% (dr = 17:1) |  **65c** 71% (dr > 99:1) |
| 5 |  **61** (dr = 2:1) |  **66a** 52% (dr = 1:1) |  **66b** 62% (dr = 22:1) |  **66c** 80% (dr = 49:1) |

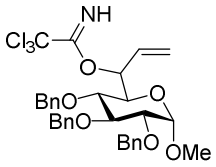
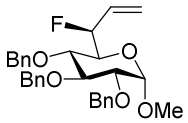
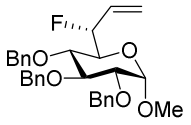
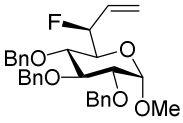
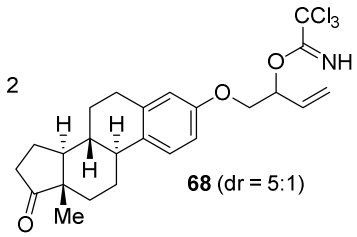
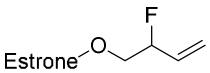
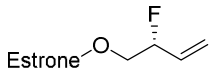
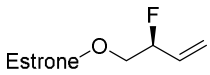
[a] All reactions were carried out on a 0.04 – 0.3 mmol scale of chiral allylic imidate substrates **57**– **61**, 2.5 mol% [Ir] complex, and 1.5 equiv. of $Et_3N{\cdot}3HF$. [b] Isolated yield. [c] Determined by $^1H$ NMR.

To this point, the substrates which have been studied bear only one stereocenter, set via iridium-catalyzed asymmetric fluorination. The applicability of the new synthetic methodology in more complex molecular settings is highly desirable, especially a method that can produce the desired product without interference from the pre-existing stereocenter of the molecule. As a result, we studied the influence of both [IrCl(*R*,*R*)-**L1**]$_2$ and [IrCl(*S*,*S*)-**L1**]$_2$ on the diastereoselective reactions with trichloroacetimidate substrates **57** – **61** bearing an α-stereocenter (Table 6). A wide range of allylic fluorides **62** – **66** were formed in moderate to good yields (52 – 99%) with excellent catalyst-controlled diastereoselectivities. The following trends were observed in the diastereoselective fluorination reactions: (1) use of achiral [IrCl(COD)]$_2$ catalyst provided the fluorinated products **62** – **66** as a 1:1 mixture of diastereomers; (2) use of [IrCl(*S*,*S*)-**L1**]$_2$ provided the products with (*R*)-configured at the allylic carbon (*vide infra*, Figure 5); and (3) use of [IrCl(*R*,*R*)-**L1**]$_2$ provided the products with (*S*)-configured at the allylic carbon (Figure 5). For enantiomeric trichloroacetimidate substrates **57** and **58** (entries 1 and 2), the α-stereochemistry of the starting materials did not influence the stereochemical outcome of the desired fluoride products **62** and **63**. For *N*-tosyl-proline substrate **60** (entry 4),[47] the ability of chiral diene-ligated iridium complexes to effectively control diastereoselective fluorination outweighed the directing ability of the tosyl (Ts) group, as proposed by Liu and coworkers in their studies of copper-catalyzed regioselective fluorination of allylic halides.[48] Importantly, the *N*-tosyl protected phenylalanine trichloroacetimidate **61** (entry 8) is a suitable substrate to deliver allylic β-fluoroamine **66** with high catalyst-controlled diastereoselectivity using either [IrCl(*S*,*S*)-**L1**]$_2$ (dr = 22:1) or [IrCl(*R*,*R*)-**L1**]$_2$ (dr = 49:1) catalysts.

Encouraged by the results obtained in Table 6 with substrates bearing α-stereocenter, we extended the applicability of the asymmetric fluorination method with carbohydrate- and estrone-derived allylic trichloroacetimidates **67** and **68** carrying multiple stereocenters (Table 7). For carbohydrate substrate **67** (entry 1), use of [IrCl(COD)]$_2$ catalyst provided the fluoride product **69a** (entry 1) as a 4:1 mixture, favoring the diastereomer with the (*S*)-configuration at the allylic carbon. This results shows the nature of the substrate to influence the selectivity of the fluorination. In stark contrast, a substrate-iridium catalyst matching and mismatching effect was observed with chiral diene-iridium complexes. In the mismatched case, with use of [IrCl(*S*,*S*)-**L1**]$_2$ catalyst, fluorinated glucoside **69b** was obtained with moderate diastereoselectivity (dr = 4:1), opposite to the result obtained with use of [IrCl(COD)]$_2$ (dr = 4:1). In the matched case, use of [IrCl(*R*,*R*)-**L1**]$_2$ resulted in the major diastereomer **69a** with excellent levels of diastereocontrol (dr > 99:1). For estrone starting material **68** (entry 2), its major diastereomer was not established (dr = 5:1). Nevertheless, use of [IrCl(COD)]$_2$ resulted in the fluorinated product **70a** in 46% yield as a racemic mixture. On the other hand, excellent catalyst-controlled diastereoselectivities were observed with use of both [IrCl(*S*,*S*)-**L1**]$_2$ and [IrCl(*R*,*R*)-**L1**]$_2$ catalysts, and the fluorinated products **70b** and **70c** were obtained with dr = 13:1 – 24:1 (entry 2).

**Table 7. Fluorination of Carbohydrate- and Estrone-Derived Substrates**[a]




| entry | imidates | products [major diastereomer (yield,[b] dr[c])] |
|---|---|---|
| 1 |  **67** (dr = 1:1) |  **69a:** [IrCl(COD)]$_2$ 67% (dr = 4:1)  **69b:** [IrCl(*S*,*S*)-**L1**]$_2$ 62% (dr = 4:1)  **69a:** [IrCl(*R*,*R*)-**L1**]$_2$ 81% (dr > 99:1) |
| 2 |  **68** (dr = 5:1) **Estrone** |  **70a:** [IrCl(COD)]$_2$ 46% (dr = 1:1)  **70b:** [IrCl(*S*,*S*)-**L1**]$_2$ 75% (dr = 13:1)  **70c:** [IrCl(*R*,*R*)-**L1**]$_2$ 61% (dr = 24:1) |

[a] All reactions were carried out on a 0.04 – 0.3 mmol scale of allylic imidate substrates **67** and **68**, 2.5 mol% [Ir] complex, and 1.5 equiv. of $Et_3N{\cdot}3HF$. [b] Isolated yield. [c] Determined by chiral HPLC or $^1H$ NMR.

To validate the fluoride products obtained as a function of the absolute configuration of the diene ligand, X-ray crystallography was then performed to establish the absolute stereochemistry of the major diastereomers of the allylic fluoride products (Tables 6 and 7). The major diastereomer of fluoride **64b**, with use of [IrCl(*S*,*S*)-**L1**]$_2$ could be recrystallized, allowing the absolute stereochemistry at its allylic carbon to be determined as the *R*-configuration (Figure 5).[41] The major diastereomer of proline-containing allylic fluoride **65b** with use of [IrCl(*S*,*S*)-**L1**]$_2$ could also be recrystallized; X-ray analysis showed that the stereochemistry at the allylic carbon of **65b** was determined to be *R*-configured (Figure 5). On the other hand, use of [IrCl(*R*,*R*)-**L1**]$_2$ to generate estrone-containing product **70c** whose stereochemistry at the allylic carbon was determined to be *S*-configured by X-ray analysis (Figure 5).

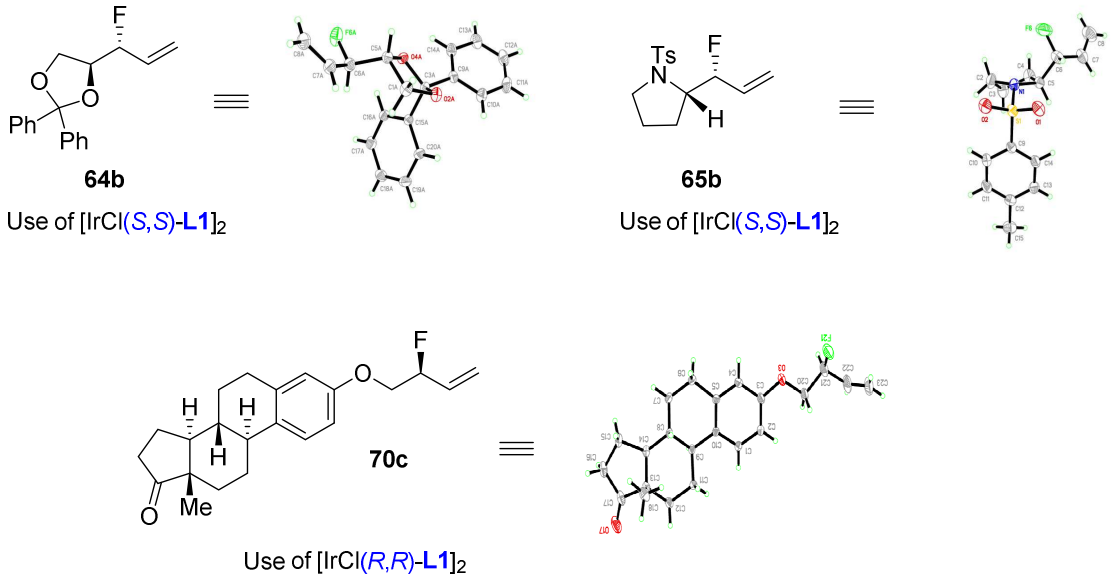
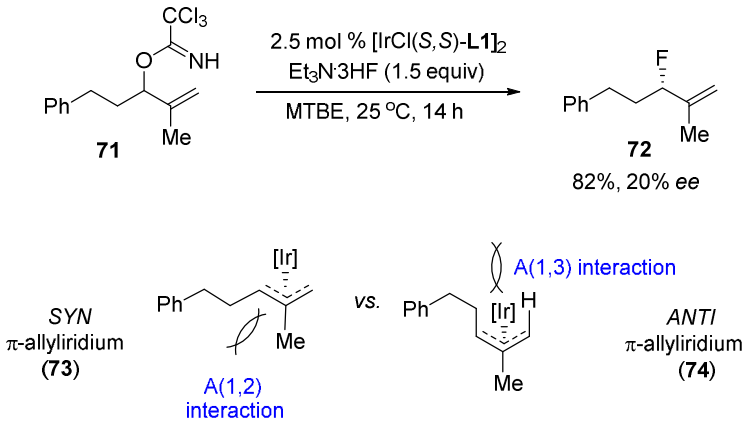


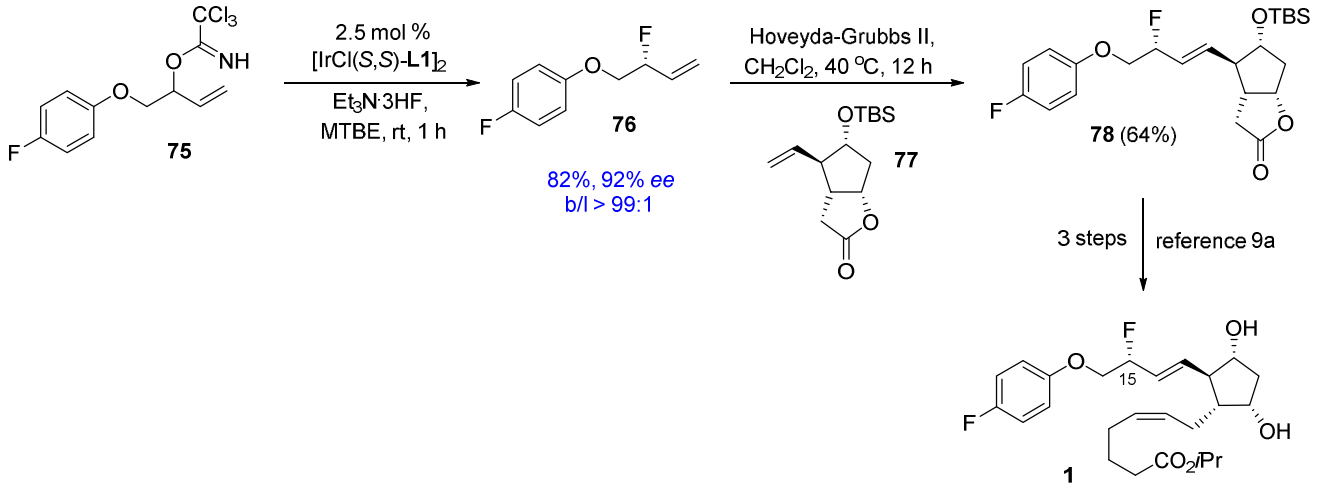

**Figure 5.** ORTEP diagram of diastereoselective allylic fluorides **64b**, **65b**, and **70c**.

In addition to monosubstituted allylic trichloroacetimidates described previously, we attempted the fluorination of disubstituted substrate to test the limitation of our methodology. We found that allylic imidate **71** (Scheme 4) with additional methyl substitutent at C(2) underwent fluorination to provide **72** in high yield (82%) with low enantioselectivity (20% *ee*). Unlike the monosubstituted allylic imidate substrates, disubstittued allylic substrate **71** offers an additional hurdle in that both *syn* (**73**) and *anti* (**74**) π-allyiridium complexes are likely to be generated in the reaction upon ionization of **71**.[49] In the case of monsubstituted substrates, the *anti* π-allyiridium complex is much less stable than the *syn* complex counterpart due to unfavorable A(1,3) interactions.[50] However, in the case of disubstituted substrate **71**, the C(2)-methyl substituent on the allyl destabilizes the *syn* π-allyiridium complex through unfavorable A(1,2) steric interactions. Since the chiral diene-ligated iridium catalyst was not effective at controlling the relative population of complexes **73** and **74**, the fluorinated product **72** (Scheme 4) was obtained with poor enantiocontrol.



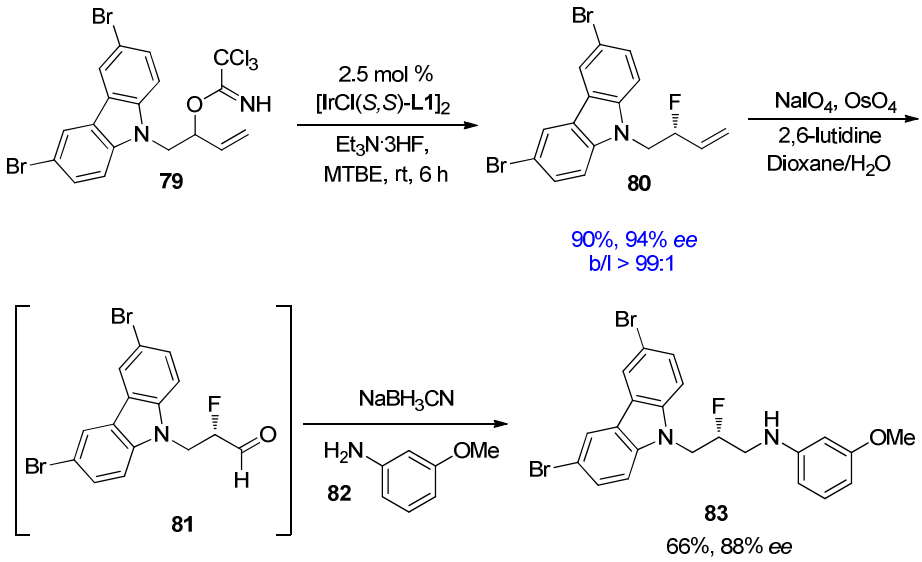

**Scheme 4. Attempted Asymmetric Synthesis of Disubstituted Allylic Fluoride**

**Synthetic Applications.** The allylic fluorides obtained in our study have far reaching utility in target-directed synthesis. To illustrate the point, we explored the asymmetric synthesis of allylic fluoride **76**, an important precursor of 15-fluoro-prostaglandin (**1**, Scheme 5). Compound **1** can be potentially useful for treating glaucoma, a chronic disease that leads to optic nerve damage and results in blindness, and was derived from the internal allylic fluoride precursor **78**.[51] The fluoride intermediate **78** was previously synthesized via nucleophilic substitution of its 15-allylic alcohol starting material with DAST.[9a] However, the DAST-mediated dehydrofluorination process is not regio- or enantioselective. We envisioned developing an asymmetric route to **78** by utilizing our fluorination reaction. Accordingly, fluorination of trichloroacetimdiate substrate **75** with $Et_3N{\cdot}3HF$ (1.5 equiv) in [IrCl(*S,S*)-**L1**]$_2$ (2.5 mol%) provided allylic fluoride **76** in high yield (82%) with excellent enantiomeric excess (93% *ee*). Subsequent cross-metathesis of **76** with Corey lactone derivative **77** afforded the fluorinated product **78** as a single diastereomer (Scheme 5), suggesting that there is no loss of enantiomeric purity. Transformation of the internal fluoride intermediate **78** into the corresponding 15-fluoro-prostaglandin (**1**) follows methods used in previous synthesis.[9a]




**Scheme 5. Asymmetric Synthesis of a 15-Fluoro-Prostaglandin Fragment**

Finally, access to enantioenriched allylic fluorides by iridium-catalyzed asymmetric fluorination provides an opportunity to further derivatize them into biologically relevant molecules. To illustrate this point, the olefin moiety of the fluorinated compound **80** was elaborated to furnish P7C3-A20 (**83**, Scheme 6), a neuroprotective molecule which protects mature neurons from cell death.[52] In addition, compound **83** is orally available and non-toxic and can readily cross the blood-brain barrier. The racemic synthesis of **83** has been previously reported[51] via ring opening of 3,9-dibromo-carbazole containing epoxide with aniline followed by conversions of the alcohol intermediate into the corresponding fluorinated product with morpholinosulfur trifluoride (MORPHO-DAST) reagent.[52] Under our asymmetric conditions, allylic β-fluroamine **80** was prepared in 90% yield with excellent enantioselectivity (94% *ee*) and regiocontrol from trichloroacetimidate **79** (Scheme 6). Next, using an improved procedure for the oxidative cleavage of the olefin in β-fluroamine **80**,[53] followed by condensation of the aldehyde intermediate **81** with 3-methoxylaniline **82** and subsequent reductive amination, provided the corresponding P7C3-A20 (**83**) in 66% yield over 2 steps with slight loss of enantiomeric excess (88% *ee*).




**Scheme 6. Asymmetric Synthesis of Bioactive P7C3-A20 Target**

## Conclusions

A useful catalytic enantioselective synthesis of branched allylic fluorides, from the reaction of racemic allylic tricloroacetimidate substrates with a mild $Et_3N{\cdot}3HF$ reagent, has been developed utilizing chiral bicyclo[3.3.0]octadiene-ligated iridium complexes. We propose this catalytic process is likely to operate through dynamic kinetic asymmetric transformation (DYKAT) of racemic secondary allylic substrates. The scope is suitable for a wide variety of allylic trichloroacetimidates bearing α-branching, α-linear, β-oxygen, and β-nitrogen substituents, providing the fluorinated products in good yields with excellent branched-to-linear ratios and enantioselectivities. The current fluorination methodology is also suitable to generate allylic fluorides possessing two contiguous stereocenters with excellent catalyst-controlled diastereoselectivities using either [IrCl(*S*,*S*)-**L1**]$_2$ and [IrCl(*R*,*R*)-**L1**]$_2$ catalysts. Importantly, the fluorination of carbohydrate- and estrone-derived substrates, bearing multiple stereocenters, proceeds with excellent diastereocontrol. The methodology is, however, limited to allylic imidate substrates having 1,1-disubstituted double bonds. The utility of the fluorination process has been demonstrated in the rapid and asymmetric synthesis of biologically relevant 15-fluoro-prostaglandin and neuroprotective P7C3-A20. We anticipate that these findings have important future implications for designing other catalytic enantioselective processes utilizing racemic allylic trichloroacetimidate substrates and transforming this methodology to radiofluorination.

The detailed mechanistic studies of the iridium-catalyzed asymmetric fluorination with racemic trichloroacetimdiates are under investigation and will be reported in due course.[30]

## ASSOCIATED CONTENT

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**Notes:** The authors declare no competing financial interest.

## Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: Full experimental procedures and characterization data for all new compounds (PDF).

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(44) To further validate our hypothesis that the competing vinyl aziridine intermediate is generated in the reaction, a control experiment was conducted in the presence of $Et_3N{\cdot}3HF$. Only vinyl aziridine was isolated in the reaction. See supporting information Scheme S2.

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## Table of Contents