Communication

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Iridium-Catalyzed Enantioselective Fluorination of Racemic, Secondary Allylic Trichloroacetimidates

Qi Zhang, David P. Stockdale, Jason C. Mixdorf, Joseph J. Topczewski, and Hien M. Nguyen*

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242, United States

ABSTRACT: The iridium-catalyzed enantioselective fluorination of racemic, branched allylic trichloroacetimidates with $Et_3N{\cdot}3HF$ is a mild and efficient route for selective incorporation of fluoride ion into allylic systems. We herein describe the asymmetric fluorination of racemic, secondary allylic electrophiles with $Et_3N{\cdot}3HF$ using a chiral diene-ligated iridium complex. The methodology allows for the formation of acyclic fluorine-containing compounds in good yields with excellent levels of asymmetric induction and overcomes the limitations previously associated with the enantioselective construction of secondary allylic fluorides bearing α-linear substituents.

The varied roles that fluorine-containing compounds play in pharmaceuticals, agricultural chemicals, and medical imaging have made syntheses of this class of molecules a major focus in recent years.[1] As a result, methods that allow the selective formation of the allylic carbon-fluorine bond are highly desirable.[2] Traditionally, allylic fluorides were prepared via nucleophilic substitution of allylic alcohols with diethylaminosulfur trifluoride (DAST).[3] Gaining complete regio- and stereocontrol has been a challenging problem associated with DAST-mediated reactions, which typically rely on sterically and electronically biased substrates to facilitate site-selective fluorination.[4] An evolving approach is the utilization of transition metals to catalyze nucleophilic substitution in allylic systems;[5] however, incorporation of fluorine into allylic systems by C-F bond formation via transition metal catalysis has proven difficult.[6] The ability of allylic fluoride to act as an efficient leaving group in transition-metal catalysis has also been reported.[7] Nevertheless, several examples of transition-metal catalyzed nucleophilic fluorination of allylic electrophiles[8] and analogous reactions[9-12] have been reported.

In 2010, Katcher and Doyle reported the first palladium-catalyzed enantioselective fluorination of cyclic allylic chlorides with AgF.[8a] In 2011, Doyle and coworkers extended this work to the transformations of acyclic, allylic chlorides. Excellent asymmetric induction (90 – 97% *ee*) were attained with α-branching or oxygen-substituted allylic chlorides using the commercially available Trost naphthyl ligand **L1** (Figure 1a).[8b] In contrast, the authors found that substrates possessing α-linear substituents provided low to moderate enantioselectivity (21– 71% *ee*) of acyclic, secondary allylic fluorides (Figure 1a). Nevertheless, Doyle's work provides the foundation for the development of new allylic substrates and catalyst systems to overcome the current limitations. Our group recently introduced a new method for the high-yielding regioselective preparation of allylic fluorides from branched allylic trichloroacetimidates with $Et_3N{\cdot}3HF$.[13] Given the paucity of enantioselective allylic fluorination reports via transition-metal catalysis,[14,15] we saw an opportunity to demonstrate the utility of our catalytic system toward this end. Here, we describe the enantioselective fluorination of racemic, secondary allylic trichloroacetimidates with $Et_3N{\cdot}3HF$ using a chiral diene-ligated iridium complex (Figure 1b) to produce allylic fluorides in good yields with excellent asymmetric induction. This process overcomes the challenges associated with the synthesis of secondary allylic fluorides possessing α-linear substituents.

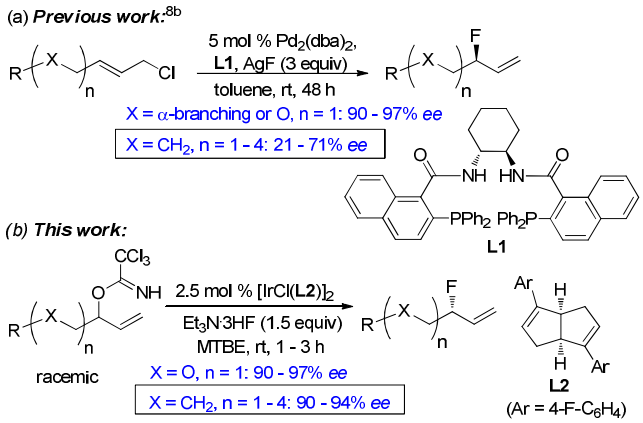
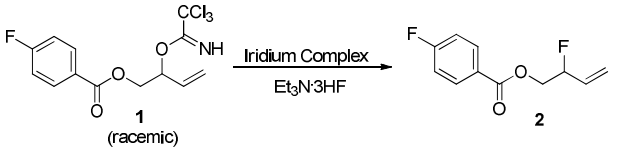


Figure 1. Transition-metal-catalyzed enantioselective synthesis of secondary allylic fluorides bearing α-linear substituents.

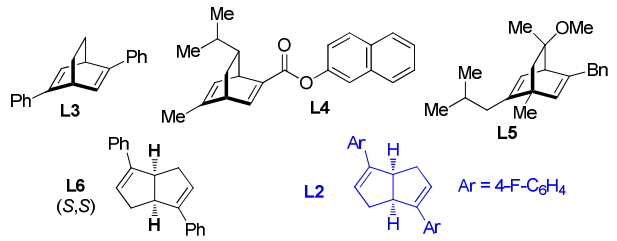
By utilizing the unique features of the trichloroacetimidate as the directing and leaving group at the allylic carbon, we have developed a new program directed toward dynamic kinetic asymmetric transformations (DYKAT) of racemic, branched allylic substrates with anilines. This DYKAT strategy allows the enantioselective preparation of nitrogen-containing tertiary and quaternary carbon centers.[16] We hypothesized that a similar strategy could facilitate the iridium-catalyzed enantioselective fluorination. However, we anticipated some challenges associated with DYKAT of racemic allylic trichloroacetimidates with $Et_3N{\cdot}3HF$. While the DYKAT process could lead to productive fluorination, it might only provide the allylic fluoride products with moderate to low enantioselectivity.[8b] To obtain high levels of asymmetric induction, equilibration of the two possible π-allyl iridium complexes must be rapid and faster than fluoride attack.[17-19] Employing a chiral diene-ligated iridium complex would create a more sterically en-

cumbered environment, which decreases the rate of the fluoride attack and increases the time allowed for interconversion between these two π-allyl iridium complexes.[18,19] Thus, judicious selection of the chiral diene ligand could circumvent the issues associated with the enantioselective synthesis of acyclic, secondary allylic fluorides bearing α-linear substituents.

Table 1. Optimization of Enantioselective Fluorination[a]



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



[a] The diene-ligated iridium complex was generated *in situ* from the reaction of 2.5 mol% $[IrCl(coe)_2]_2$ and 5 mol% ligands (**L3** – **L6**). [b] 2.5 mol% $[IrCl(L_n)]_2$ (**L6** or **L2**) catalyst was used in the reaction. [c] Determined by ^{19}F NMR analysis using $PhCF_3$ as an internal standard. [d] Determined by chiral HPLC.

We previously established that the regioselective fluorination reactions work best with $[IrCl(cod)]_2$ catalyst.[13] Therefore, chelating chiral diene ligands with iridium catalyst would likely allow for the development of an enantioselective variant. We examined several diene ligands in our initial studies (Table 1).[20] Although Hayashi ligands **L3**[21a] and **L4**[21b] (entries 1 and 2) and Carreira ligand **L5**[22] (entry 3) were able to promote the fluorination, the yield and enantioselectivity were low. However, excellent regioselectivity (>20:1 branched:linear) was observed in the formation of the fluoride product **2** after 12 h. We hypothesized that diene ligands with larger bite angles[20] could induce higher asymmetric induction. As expected, the enantioselectivity improved with utilization of 2.5 mol% $[IrCl(coe)_2]_2$ in combination with Lin ligand **L6**[23] (66% *ee*, entry 4) as **L6** has a bite angle similar to that of cyclooctadiene (COD) ligand. We hypothesize that poor ligation of the ligand to the iridium *in situ* may have resulted in moderate observed *ee* values (entry 4). We developed a procedure for better ligation and iridium complexes were isolated and recrystallized before use in the fluorination.[26] Accordingly, utilization of 2.5 mol% $[IrCl(\mathbf{L6})]_2$ complex (entry 5) significantly improved the *ee* value of allylic fluoride **2** (66 → 79% *ee*). Use of fewer equivalents of $Et_3N{\cdot}3HF$ further increased *ee* value of **2** (entry 6). Varying the solvent (entries 7–10) did not have a pronounced effect on the reaction outcome, although MTBE (entry 10) was found to increase the enantioselectivity (84% → 88% *ee*) of the fluoride product **2**. Iridium complex bearing 4-fluorophenyl derivative ligand **L2** (see Figure 2 for X-ray crystallographic structure of $[IrCl(\mathbf{L2})]_2$)[24] was superior to the **L6**-iridium complex in terms of both enantioselectivity and conversion (entry 12), and allylic fluoride **2** was observed in 99% NMR yield after 1 h with 93% *ee* and >20:1 branched:linear selectivity. This result is consistent with our previous report for the rhodium-catalyzed DYKAT of racemic tertiary allylic substrates with anilines.[16a]

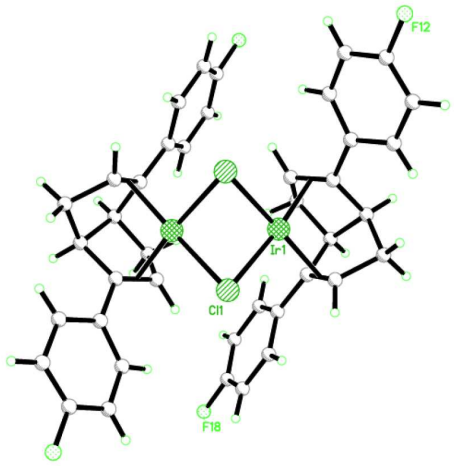
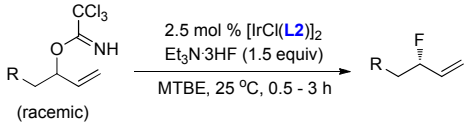


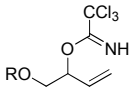
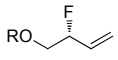
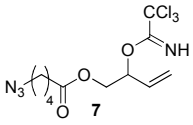
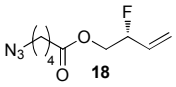
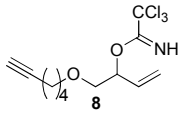
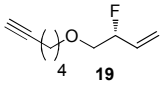
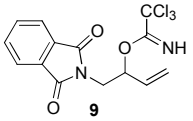
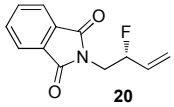
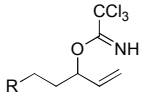
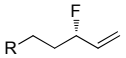
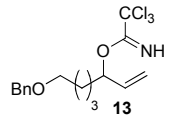
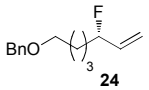
Figure 2. ORTEP Diagram of $[IrCl(\mathbf{L2})]_2$ Catalyst

Next, the optimized fluorination conditions were applied to a number of trichloroacetimidate substrates (Table 2). Gratifyingly, the reaction tolerates a range of functional groups. For instance, allylic imidates **1** and **3**–**6**, bearing both electron-rich and electron-withdrawing β-oxygen substituents, reacted rapidly with $Et_3N{\cdot}3HF$ to provide allylic fluorides **2** and **14**–**17** (entries 1–5) in good yields (61–82%) with excellent levels of enantioselectivity (92–97% *ee*). The mild conditions are also tolerant of the silyl ether group (entry 3) to provide fluoride **15** in 70% and with 97% *ee*. The result obtained with bulky silyl substrate **4** (entry 3) is consistent with what has been observed by Doyle and coworkers[8b] wherein higher asymmetric induction was observed in substrates with greater steric hindrance. The ability to introduce the azide and alkyne functional groups at the β-position provides significant flexibility with our approach. For example, the azide and alkyne substrates **7** and **8** (entries 6 and 7) proceeded with excellent enantioselectivity (90 – 97% *ee*) and offered the functionality for subsequent use in bioorthogonal conjugation.[25] The nitrogen-containing substrate phathamide **9** (entry 8) also imparted good enantioinduction (82% *ee*) in the production of allylic fluoride **20**. This method is not limited to allylic imidate substrates possessing α-heteroatoms. Trichloroacetimidates bearing α-linear substituents **10**–**13** (entries 10–12) proved to be competent allylic electrophiles, giving access to allylic fluoride products **21**–**24** with 90–95% *ee*. Overall, the new method addresses the current limitations for the preparation of the α-linear substituent motif. For example, while the palladium-bisphosphine com-

plex-catalyzed fluorination reaction provided allylic fluorides **21** (21% *ee*) and **24** (58% *ee*) with moderate enantioselectivity,[8b] **21** (entry 9) and **24** (entry 12) were obtained in 92% *ee* and 94% *ee*, respectively, under our DYKAT conditions. To illustrate the reproducibility of the reaction, 1.2 mmol scale of **1** (entry 1) was subjected to similar conditions: **2** was isolated in 83% yield and with 92% *ee*, which are comparable to the use of 0.15 mmol of allylic imidate **1** (82% and 93% *ee*).

Table 2. Survey of Allylic Trichloroacetimidates[a]

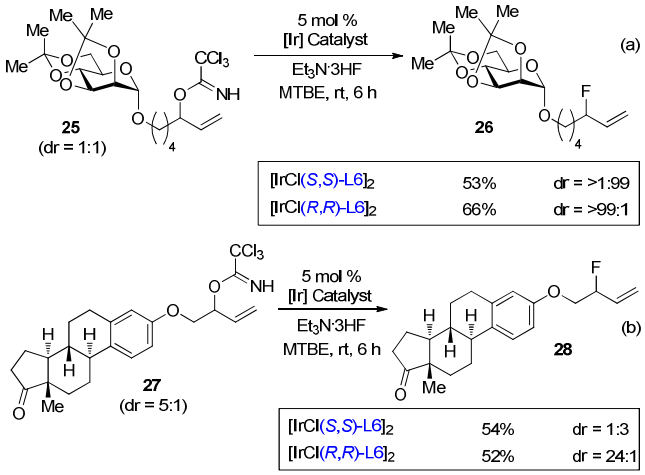


entry	imidates	products	time (h)	yield (%)[c]	ee (%)[d]
					
1	**1** (R = 4-F-Bz)	**2** (R = 4-F-Bz)	1	82(83[b])	93(92[b])
2	**3** (R = Bz)	**14** (R = Bz)	1	75	93
3	**4** (R = TBDPS)	**15** (R = TBDPS)	1.5	70	97
4	**5** (R = 4-MeO-C_6H_4)	**16** (R = 4-MeO-C_6H_4)	1.5	77	95
5	**6** (R = 2-Br-C_6H_4)	**17** (R = 2-Br-C_6H_4)	1	70	92
6	 **7**	 **18**	3	61	95
7	 **8**	 **19**	0.5	74	99
8	 **9**	 **20**	1	73	82
					
9	**10:** R = OBn	**21:** R = OBn	1	90	92
10	**11:** R = OTBDPS	**22:** R = OTBDPS	1	69	95
11	**12:** R = Ph	**23:** R = Ph	1	82	90
12	 **13**	 **24**	1	75	94

[a] All reactions were carried out on a 0.15 – 0.3 mmol scale of imidates and 2.5 mol% [IrCl(**L2**)]$_2$. [b] Reaction was carried out on a 1.2 mmol scale of imidate **1** and 1 mol% [IrCl(**L2**)]$_2$ [c] Isolated yield. [d] Determined by chiral HPLC.

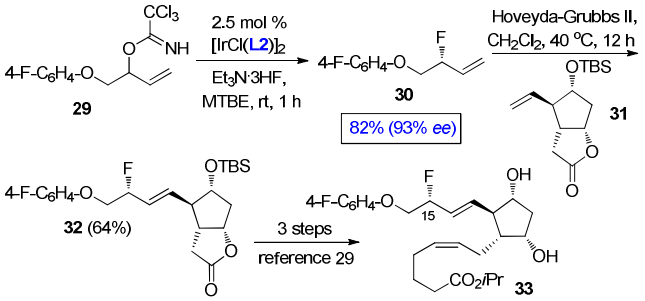
To establish the absolute stereochemistry of the desired allylic fluoride products, compound **2** (93% *ee*) was subjected to cross-metathesis with 4-bromostyrene in the presence of Hoveyda-Grubbs II catalyst because crystallization of **2** proved difficult. The internal allylic fluoride was isolated as a crystalline solid with almost no loss of enantiomeric purity (92% *ee*) and shown to be *R*-configured by X-ray analysis.[26]

Scheme 1. Fluorination of Chiral Allylic Imidate Substrates



We next investigated the ability of the iridium catalyst to control diastereoselectivity in fluorination reactions of chiral allylic trichloroacetimidates (Scheme 1). Because chiral diene ligand **L6** and its enantiomer are commercially available, we chose to investigate the ability of both [IrCl(*R*,*R*)-L6]$_2$ and [IrCl(*S*,*S*)-L6]$_2$ to enhance or overturn the substrate's inherent selectivity preference. Accordingly, the reaction of D-mannose substrate **25** (Scheme 1a) proceeded with excellent catalyst control, providing the desired fluoride product **26** as a single diastereomer.[27] In contrast, a substrate-iridium catalyst matching and mismatching effect was observed with conformationally rigid estrone-derived imidate substrate **27** (Scheme 1b). In the mismatched case with use of [IrCl(*S*,*S*)-L6]$_2$ complex, the fluoride product **28** was produced with low diastereoselectivity (dr = 1:3).[27] In contrast, the matched case with utilization of [IrCl(*R*,*R*)-L6]$_2$ complex resulted in allylic fluoride **28** with excellent diastereocontrol (dr = 24:1).[27]

Scheme 2. Synthesis of 15-Fluoro Prostaglandin Fragment



The allylic fluorides obtained under our DYKAT conditions have potential utility for target-directed synthesis. To illustrate this point, we studied the synthesis of allylic fluoride **32**, an important precursor of 15-fluoro-prostaglandin **33** (Scheme 2). Compound **33** is potentially useful in the treatment of glaucoma, a chronic disease that leads to optic nerve damage and results in blindness.[28] The fluorinated molecule **33** was previously prepared via DAST-mediated dehydroxyfluorination of its 15-allylic alcohol starting material.[29] However, this transformation is neither regioselective nor enantioselective. Under our DYKAT conditions, fluoride **30** (Scheme 2) was obtained in 82% yield and 93% *ee*. Subsequent cross-metathesis of **30** with Corey lactone derivative **31** afforded the desired fluoride

product **32**. Conversion of internal allylic fluoride **32** into **33** follows methods used in previous synthesis.[29]

In summary, we have developed a new method for dynamic kinetic asymmetric fluorination of racemic, secondary allylic trichloroacetimidates with $Et_3N{\cdot}3HF$. Our strategy, promoted by a chiral diene-ligated iridium catalyst, provides acylic allylic fluorides in high yields with enantioselectivity. Furthermore, this method overcomes the limitations previously associated with the asymmetric synthesis of secondary allylic fluorides possessing α-linear substituents. Investigations into the full scope with racemic, branched allylic trichloroacetimidates and further studies to understand the mechanism are ongoing and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website at DOI:

X-ray data (CIF)

X-ray data (CIF)

Experimental procedures and characterization data (NMR, MS, IR, optical rotation) for all new compounds (PDF).

AUTHOR INFORMATION

Corresponding Author

hien-nguyen@uiowa.edu

Notes

The authors declare no competing financial interest.

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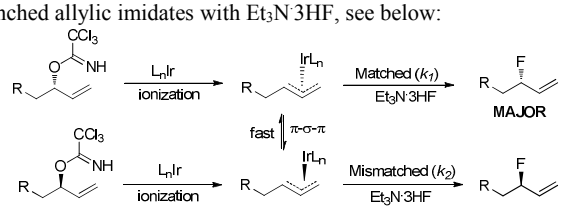

(19) We previously subjected enantioenriched starting imidate (95% *ee*) to our optimized fluorination conditions, and allylic fluoride was generated in only 12% *ee* (see reference #13). The significant degree of racemization of the fluoride product suggested that equilibration of π-allyl iridium complexes occurs faster than fluoride attack.

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(24) The ligation of $[IrCl(coe)_2]_2$ with **L2** to produce $[IrCl(\mathbf{L2})]_2$ was accomplished by heating the mixture in hexane at 50 °C for 48 h. See the Supporting Information for detailed procedure.

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(26) See the Supporting Information.
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