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Iridium-Catalyzed Enantioselective Fluorination of Racemic, Secondary Allylic Trichloroacetimidates

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Supporting Information

ABSTRACT: The Ir-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 Ir complex. The methodology enables 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 have been 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 Pd-catalyzed enantioselective fluorination of cyclic allylic chlorides with AgF.[8a] In 2011, Doyle and co-workers extended this work to the transformations of acyclic, allylic chlorides. Excellent asymmetric induction (90−97% *ee*) was 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

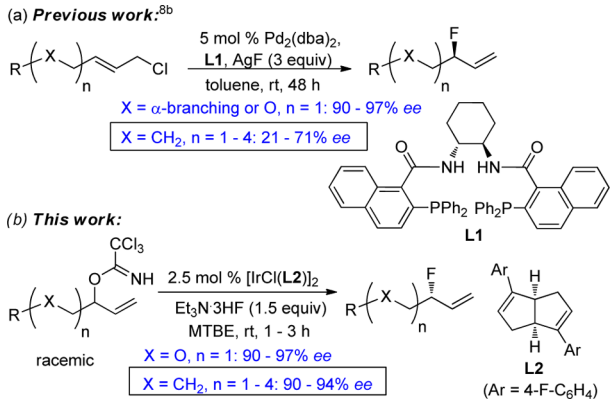

Figure 1. Transition-metal-catalyzed enantioselective syntheses of secondary allylic fluorides bearing α-linear substituents.

for the high-yielding regioselective preparation of allylic fluorides from branched allylic trichloroacetimidates with $Et_3N{\cdot}3HF$.[13] Given the paucity of reports on enantioselective allylic fluorination 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 Ir 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.

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 transformation (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 Ir-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 Ir complexes must be rapid and faster than fluoride attack.[17−19] Employing a chiral-diene-ligated Ir complex would create a more

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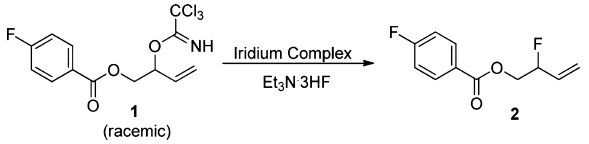
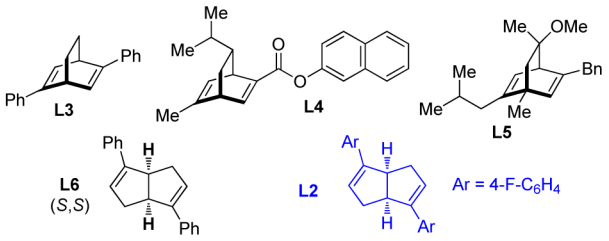
sterically encumbered environment, which would decrease the rate of the fluoride attack and increase the time allowed for interconversion between these two π-allyl Ir complexes.[18,19] Thus, judicious selection of the chiral diene ligand could circumvent the issues associated with the enantioselective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

We previously established that the regioselective fluorination reactions work best with $[IrCl(cod)]_2$ (cod = cyclooctadiene) as the catalyst.[13] Therefore, chelating chiral diene ligands with the Ir catalyst would likely enable 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]

Table 1. Optimization of Enantioselective Fluorination



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	$[IrCl(\mathbf{L6})]_2$[b]	Et_2O	25	3	6	91	79
6	$[IrCl(\mathbf{L6})]_2$[b]	Et_2O	25	1.5	6	95	84
7	$[IrCl(\mathbf{L6})]_2$[b]	Toluene	25	1.5	6	95	83
8	$[IrCl(\mathbf{L6})]_2$[b]	CH_2Cl_2	25	1.5	6	95	77
9	$[IrCl(\mathbf{L6})]_2$[b]	THF	25	1.5	6	95	87
10	$[IrCl(\mathbf{L6})]_2$[b]	MTBE	25	1.5	6	95	88
11	$[IrCl(\mathbf{L6})]_2$[b]	MTBE	40	1.5	4	95	86
12	$[IrCl(\mathbf{L2})]_2$[b]	MTBE	25	1.5	1	99	93



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

(entries 1 and 2) and Carreira ligand **L5**[22] (entry 3) were able to promote the fluorination, the yields and enantioselectivity were low. However, excellent regioselectivity (>20:1 branched:linear) was observed in the formation of the allylic 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 % $[IrCl(coe)_2]_2$ (coe = cyclooctene) in combination with Lin ligand **L6**[23] (66% *ee*; entry 4), as **L6** has a bite angle similar to that of the cod ligand. We hypothesized that poor ligation of the ligand to Ir in situ may have resulted in the moderate observed *ee* values (entry 4). We developed a procedure for better ligation, and Ir complexes were isolated and recrystallized before use in the fluorination.[26] Accordingly, utilization of 2.5 mol % $[IrCl(\mathbf{L6})]_2$ (entry 5) significantly improved the *ee* value of **2** (66 → 79% *ee*). Using less $Et_3N{\cdot}3HF$ further increased the *ee* value of **2** (entry 6). Varying the solvent (entries 7–10) did not have a pronounced effect on the reaction outcome, although methyl *tert*-butyl ether (MTBE) (entry 10) was found to increase the enantioselectivity (84% → 88% *ee*) of the **2**. The Ir complex bearing 4-fluorophenyl derivative ligand **L2** (see Figure 2 for the

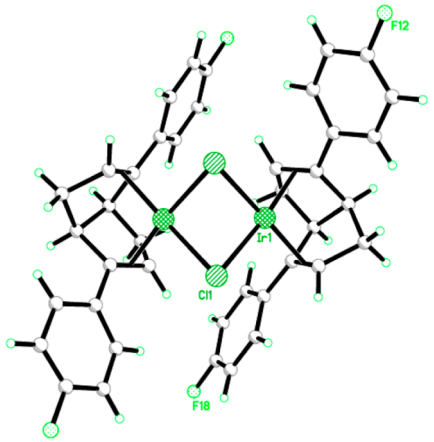


Figure 2. ORTEP diagram of $[IrCl(\mathbf{L2})]_2$.

X-ray structure)[24] was superior to the **L6**–Ir complex in terms of both enantioselectivity and conversion (entry 12), and **2** was obtained 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 Rh-catalyzed DYKAT of racemic tertiary allylic substrates with anilines.[16a]

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), providing fluoride **15** in 70% yield with 97% *ee*. The result obtained with bulky silyl substrate **4** (entry 3) is consistent with what was observed by Doyle and co-workers,[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) reacted with excellent enantioselectivity (95–99% *ee*) and offered the functionality for subsequent use in bioorthogonal conjugation.[25] The nitrogen-containing substrate phthalimide **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 **10**–**13** bearing α-linear substituents (entries 10–12) proved to be competent allylic electrophiles, giving access to allylic fluorides **21**–**24** with 90–95% *ee*. Overall, the new method addresses the current limitations on the preparation of the α-linear substituent motif. For example, while the bis(phosphine)-palladium-complex-catalyzed fluorination reaction provided **21** (21% *ee*) and **24** (58% *ee*) with moderate enantioselectivity,[8b] they were obtained in 92 and 94% *ee*, respectively, under our DYKAT conditions (entries 9 and 12). To illustrate the

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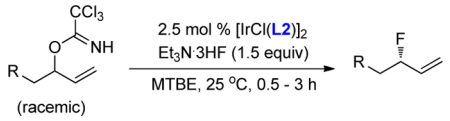
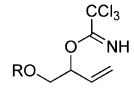
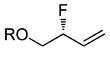
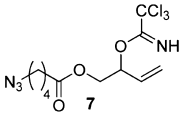
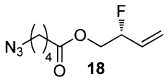
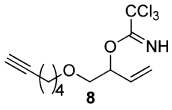
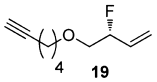
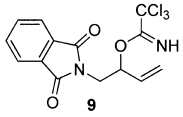
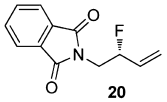
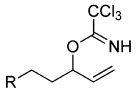
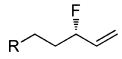
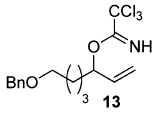
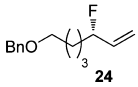
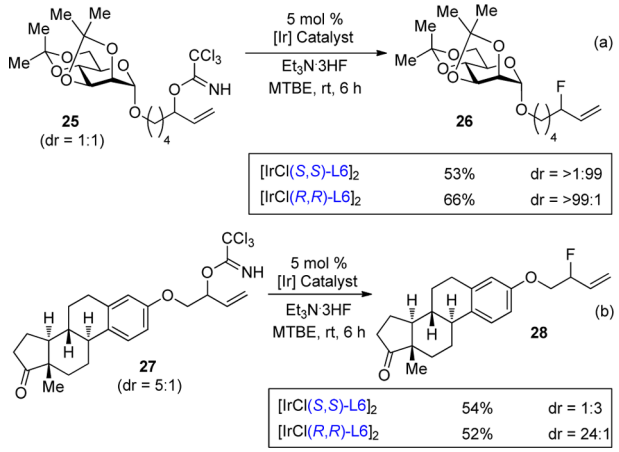
Table 2. Survey of Allylic Trichloroacetimidates[a]



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]Reactions were carried out using 0.15−0.3 mmol of imidate and 2.5 mol % $[IrCl(\mathbf{L2})]_2$, unless otherwise noted. [b]The reaction was carried out using 1.2 mmol of imidate **1** and 1 mol % $[IrCl(\mathbf{L2})]_2$. [c]Isolated yields. [d]Determined by chiral HPLC.

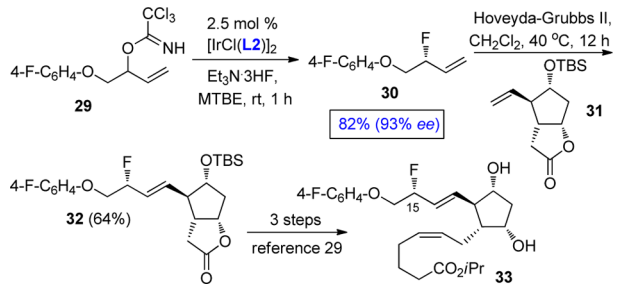
Scheme 1. Fluorination of Chiral Allylic Imidate Substrates



(Scheme 1a) proceeded with excellent catalyst control, providing the desired fluoride product **26** as a single diastereomer.[27] In contrast, a substrate−Ir catalyst matching/mismatching effect was observed with conformationally rigid estrone-derived imidate substrate **27** (Scheme 1b). In the mismatched case using $[IrCl((S,S)\text{-}\mathbf{L6})]_2$, the fluoride product **28** was produced with low diastereoselectivity (dr = 1:3).[27] In contrast, the matched case using $[IrCl((R,R)\text{-}\mathbf{L6})]_2$ afforded **28** with excellent diastereocontrol (dr = 24:1).[27]

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-fluoroprostaglandin (**33**) (Scheme 2).

Scheme 2. Synthesis of a 15-Fluoroprostaglandin Fragment



Compound **33**, which is potentially useful in the treatment of glaucoma, a chronic disease that leads to optic nerve damage and results in blindness,[28] was previously prepared via DAST-mediated dehydroxyfluorination of its 15-allylic alcohol starting material.[29] However, this transformation is neither regio- nor enantioselective. Under our DYKAT conditions, fluoride **30** (Scheme 2) was obtained in 82% yield with 93% *ee*. Subsequent cross-metathesis of **30** with Corey lactone derivative **31** afforded the desired fluoride product **32**. Conversion of **32** into **33** follows methods used in the 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 Ir catalyst, provides acylic allylic fluorides in high yields with excellent enantioselectivity. Furthermore, this method overcomes the limitations previously associated with the asymmetric synthesis of secondary allylic fluorides possessing α-linear substituents. Investigations of the full scope of racemic,

reproducibility of the reaction, 1.2 mmol of **1** (entry 1) was subjected to similar conditions, and **2** was isolated in 83% yield with 92% *ee*, which is comparable to the result when 0.15 mmol of **1** was used (82% yield with 93% *ee*).

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 **35** 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]

We next investigated the ability of the Ir catalyst to control the 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 $[IrCl((R,R)\text{-}\mathbf{L6})]_2$ and $[IrCl((S,S)\text{-}\mathbf{L6})]_2$ to enhance or overturn the substrate's inherent selectivity preference. Accordingly, the reaction of D-mannose substrate **25**

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branched allylic trichloroacetimidates and mechanistic studies 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: 10.1021/jacs.5b07492.

Experimental procedures and characterization data (PDF)
NMR spectra (PDF)
Crystallographic data for $[IrCl(\mathbf{L2})]_2$ (CIF)
Crystallographic data for **35** (CIF)

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Notes

The authors declare no competing financial interest.

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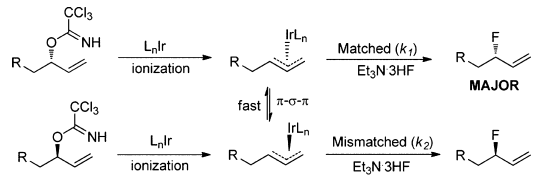

(19) We previously subjected an enantioenriched starting imidate (95% *ee*) to our optimized fluorination conditions, and the allylic fluoride was generated in only 12% *ee* (see ref 13). The significant degree of racemization of the fluoride product suggested that equilibration of π-allyl Ir complexes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

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(26) See the Supporting Information.

(27) On the basis of the X-ray crystal structure analysis establishing the absolute stereochemistry of allylic fluoride **2**, the major diastereomers of **26** and **28** can be analogously assigned to be *R*-configured with use of $[IrCl((S,S)\text{-}\mathbf{L6})]_2$. On the other hand, the *S* configuration can be assigned for **26** and **28** with the use of $[IrCl((R,R)\text{-}\mathbf{L6})]_2$.

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