Iridium-Catalyzed Enantioselective Fluorination of Racemic, Secondary Allylic Trichloroacetimidates

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ABSTRACT: The Ir-catalyzed enantioselective fluorination of racemic, branched allylic trichloroacetimidates with Et₃N·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 Et₃N·3HF using a chiral-diene-ligated Ir complex. The methodology enables the formation of acyclic fluoride-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 fluorne-containing compounds play in pharmaceuticals, agricultural chemicals, and medical imaging have made syntheses of this class of molecules a major focus in recent years. As a result, methods that allow the selective formation of the allylic carbon–fluorine bond are highly desirable. Traditionally, allylic fluorides have been prepared via nucleophilic substitution of allylic alcohols with diethylaminosulfur trifluoride (DAST). 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. An evolving approach is the utilization of transition metals to catalyze nucleophilic substitution in allylic systems; however, incorporation of fluorine into allylic systems by C–F bond formation via transition-metal catalysis has proven difficult. The ability of allylic fluoride to act as an efficient leaving group in transition-metal catalysis has also been reported. Nevertheless, several examples of transition-metal-catalyzed nucleophilic fluorination of allylic electrophiles and analogous reactions have been reported.

In 2010, Katcher and Doyle reported the first Pd-catalyzed enantioselective fluorination of cyclic allylic chlorides with AgF. 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). 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 Et₃N·3HF. Given the paucity of reports on enantioselective allylic fluorination via transition-metal catalysis, 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 Et₃N·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. 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 Et₃N·3HF. While the DYKAT process could lead to productive fluorination, it might only provide the allylic fluoride products with moderate to low enantioselectivity. To obtain high levels of asymmetric induction, equilibration of the two possible π-allyl Ir complexes must be rapid and faster than fluoride attack.

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Figure 1. Transition-metal-catalyzed enantioselective syntheses of secondary allylic fluorides bearing α-linear substituents.
sterically encumbered environment, which would decrease the rate of the fluoride attack and increase the time allowed for interconversion between these two $\pi$-allyl Ir complexes.\textsuperscript{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 $\alpha$-linear substituents.

We previously established that the regioselective fluorination reactions work best with $[\text{IrCl(cod)}]_2$ (cod = cyclooctadiene) as the catalyst.\textsuperscript{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).\textsuperscript{20} Although Hayashi ligands L$_3$\textsuperscript{20a} and L$_4$\textsuperscript{21b}

<table>
<thead>
<tr>
<th>entry</th>
<th>Ir complex</th>
<th>solvent</th>
<th>temp (°C)</th>
<th>Et$_3$N 3HF (equiv.)</th>
<th>time (h)</th>
<th>NMR yield (21%$^a$)</th>
<th>ee (21%$^a$)</th>
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<td>1</td>
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<td>6</td>
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<td>84</td>
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The diene-ligated Ir complex was generated in situ from the reaction of 2.5 mol % $[\text{IrCl(coe)}]_2$ and 5 mol % ligand (L$_3$–L$_6$).\textsuperscript{21a} Determined by $^1$F NMR analysis using PhCF$_3$ as an internal standard.\textsuperscript{a} Determined by chiral HPLC.

Table 1. Optimization of Enantioselective Fluorination

X-ray structure\textsuperscript{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.\textsuperscript{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 $\beta$-oxygen substituents, reacted rapidly with Et$_3$N·HCl 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,\textsuperscript{26} wherein higher asymmetric induction was observed in substrates with greater steric hindrance. The ability to introduce the azide and alkyne functional groups at the $\beta$-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.\textsuperscript{25} The nitrogen-containing substrate p-hydroxyphenyl derivative ligand L$_2$ (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 $\alpha$-heteroatoms. Trichloroacetimidates 10–13 bearing $\alpha$-linear substituents (entries 10–13) 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 $\alpha$-linear substrate motif. For example, while the bis(phosphine)-palladium-complex-catalyzed fluorination reaction provided 21 (21% ee) and 24 (58% ee) with moderate enantioselectivity,\textsuperscript{26} they were obtained in 92 and 94% ee, respectively, under our DYKAT conditions (entries 9 and 12). To illustrate the

![Figure 2. ORTEP diagram of $[\text{IrCl(L2)}]_2$.](image)
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)-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–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)-L6)]2, the fluoride product 28 was produced with low diastereoselectivity (dr = 1:3).27 In contrast, the matched case using [IrCl((R,R)-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).

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 Et3N·3HF. Our strategy, promoted by a chiral-diene-ligated Ir catalyst, provides acrylic 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,
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)

Crystallographic data for [IrCl(L2)]_2 (CIF)

Crystallographic data for 35 (CIF)

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**Notes**

The authors declare no competing financial interest.

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**REFERENCES**


(15) A proposed mechanism for Ir-catalyzed DYKAT of racemic, branched allylic imidates with Et,N·3HF is shown below:

![Mechanism](https://example.com/mechanism.png)

(16) We previously subjected an enantioenriched starting imidate (95% ee) to our optimized fluorination conditions, and the allylic fluoride was generated in at least 92% ee (see ref 13). The significant degree of racemization of the fluoride product suggested that equilibration of the allyl fluoride source, see: (a) Zhu, J.; Tsui, G. C.; Lautens, M. Angew. Chem., Int. Ed. 2007, 46, 5138. (b) Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. Chem. Sci. 2010, 5138. (c) Sharpless, K. B.; Green, M. C.; Yokota, K.; Ueyama, K.; Shintani, R.; Hayashi, T. J. Am. Chem. Soc. 2007, 129, 13729.

(17) The ligation of [IrCl(co)2]2 with L2 to produce [IrCl(L2)]2 was accomplished by heating the mixture in hexane at 50 oC for 48 h. See the Supporting Information for the detailed procedure.


(22) For regio- and enantioselective allylic fluorination, see: (a) Gouverneur, V.; Brown, J. M. Angew. Chem., Int. Ed. 2009, 48, 1296.