

## Iridium-Catalyzed Enantioselective Fluorination of Racemic, Secondary Allylic Trichloroacetimidates

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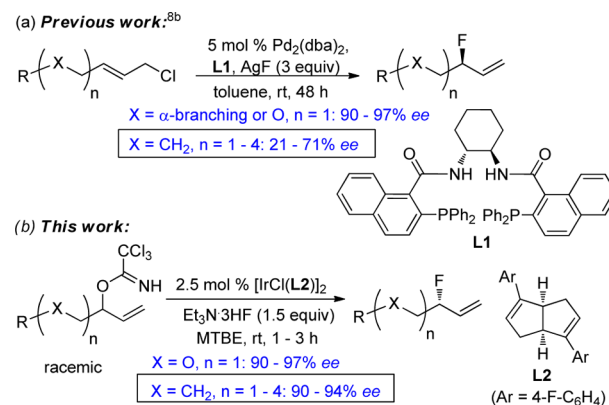
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## Supporting Information

**ABSTRACT:** The Ir-catalyzed enantioselective fluorination of racemic, branched allylic trichloroacetimidates with  $\text{Et}_3\text{N}\cdot 3\text{HF}$  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  $\text{Et}_3\text{N}\cdot 3\text{HF}$  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  $\alpha$ -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.<sup>1</sup> As a result, methods that allow the selective formation of the allylic carbon–fluorine bond are highly desirable.<sup>2</sup> Traditionally, allylic fluorides have been prepared via nucleophilic substitution of allylic alcohols with diethylamino-sulfur trifluoride (DAST).<sup>3</sup> 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.<sup>4</sup> An evolving approach is the utilization of transition metals to catalyze nucleophilic substitution in allylic systems;<sup>5</sup> however, incorporation of fluorine into allylic systems by C–F bond formation via transition-metal catalysis has proven difficult.<sup>6</sup> The ability of allylic fluoride to act as an efficient leaving group in transition-metal catalysis has also been reported.<sup>7</sup> Nevertheless, several examples of transition-metal-catalyzed nucleophilic fluorination of allylic electrophiles<sup>8</sup> and analogous reactions<sup>9–12</sup> have been reported.

In 2010, Katcher and Doyle reported the first Pd-catalyzed enantioselective fluorination of cyclic allylic chlorides with  $\text{AgF}$ .<sup>8a</sup> 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  $\alpha$ -branching or oxygen-substituted allylic chlorides using the commercially available Trost naphthyl ligand **L1** (Figure 1a).<sup>8b</sup> In contrast, the authors found that substrates possessing  $\alpha$ -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  $\alpha$ -linear substituents.

for the high-yielding regioselective preparation of allylic fluorides from branched allylic trichloroacetimidates with  $\text{Et}_3\text{N}\cdot 3\text{HF}$ .<sup>13</sup> Given the paucity of reports on enantioselective allylic fluorination via transition-metal catalysis,<sup>14,15</sup> 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  $\text{Et}_3\text{N}\cdot 3\text{HF}$  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  $\alpha$ -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.<sup>16</sup> 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  $\text{Et}_3\text{N}\cdot 3\text{HF}$ . While the DYKAT process could lead to productive fluorination, it might only provide the allylic fluoride products with moderate to low enantioselectivity.<sup>8b</sup> To obtain high levels of asymmetric induction, equilibration of the two possible  $\pi$ -allyl Ir complexes must be rapid and faster than fluoride attack.<sup>17–19</sup> 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  $\pi$ -allyl Ir complexes.<sup>18,19</sup> 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  $[\text{IrCl}(\text{cod})]_2$  (cod = cyclooctadiene) as the catalyst.<sup>13</sup> 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).<sup>20</sup> Although Hayashi ligands **L3**<sup>21a</sup> and **L4**<sup>21b</sup>

Table 1. Optimization of Enantioselective Fluorination

Reaction scheme: Substrate **1** (racemic) reacts with an Iridium Complex and  $\text{Et}_3\text{N} \cdot 3\text{HF}$  to form product **2**.

entry	Ir complex	solvent	temp (°C)	$\text{Et}_3\text{N} \cdot 3\text{HF}$ (equiv.)	time (h)	NMR yield (%) <sup>c</sup>	ee (%) <sup>d</sup>
1	$[\text{IrCl}(\text{coe})_2]_2/\text{L3}^a$	$\text{Et}_2\text{O}$	25	3	12	51	13
2	$[\text{IrCl}(\text{coe})_2]_2/\text{L4}^a$	$\text{Et}_2\text{O}$	25	3	12	36	13
3	$[\text{IrCl}(\text{coe})_2]_2/\text{L5}^a$	$\text{Et}_2\text{O}$	25	3	12	52	3
4	$[\text{IrCl}(\text{coe})_2]_2/\text{L6}^a$	$\text{Et}_2\text{O}$	25	3	6	95	66
5	$[\text{IrCl}(\text{L6})]_2^b$	$\text{Et}_2\text{O}$	25	3	6	91	79
6	$[\text{IrCl}(\text{L6})]_2^b$	$\text{Et}_2\text{O}$	25	1.5	6	95	84
7	$[\text{IrCl}(\text{L6})]_2^b$	Toluene	25	1.5	6	95	83
8	$[\text{IrCl}(\text{L6})]_2^b$	$\text{CH}_2\text{Cl}_2$	25	1.5	6	95	77
9	$[\text{IrCl}(\text{L6})]_2^b$	THF	25	1.5	6	95	87
10	$[\text{IrCl}(\text{L6})]_2^b$	MTBE	25	1.5	6	95	88
11	$[\text{IrCl}(\text{L6})]_2^b$	MTBE	40	1.5	4	95	86
12	$[\text{IrCl}(\text{L2})]_2^b$	MTBE	25	1.5	1	99	93

Chemical structures of ligands **L3**, **L4**, **L5**, **L6**, and **L2**. **L3**, **L4**, and **L5** are chiral diene ligands. **L6** is a chiral diene ligand with a specific stereochemistry (S,S). **L2** is a chiral diene ligand with an aryl group (Ar = 4-F-C<sub>6</sub>H<sub>4</sub>).

<sup>a</sup>The diene-ligated Ir complex was generated in situ from the reaction of 2.5 mol %  $[\text{IrCl}(\text{coe})_2]_2$  and 5 mol % ligand (**L3**–**L6**). <sup>b</sup>2.5 mol %  $[\text{IrCl}(\text{L})]_2$  (**L** = **L6** or **L2**) was used as the catalyst. <sup>c</sup>Determined by <sup>19</sup>F NMR analysis using  $\text{PhCF}_3$  as an internal standard. <sup>d</sup>Determined by chiral HPLC.

(entries 1 and 2) and Carreira ligand **L5**<sup>22</sup> (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<sup>20</sup> could induce higher asymmetric induction. As expected, the enantioselectivity improved with utilization of 2.5 mol %  $[\text{IrCl}(\text{coe})_2]_2$  (coe = cyclooctene) in combination with Lin ligand **L6**<sup>23</sup> (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.<sup>26</sup> Accordingly, utilization of 2.5 mol %

$[\text{IrCl}(\text{L6})]_2$  (entry 5) significantly improved the ee value of **2** (66 → 79% ee). Using less  $\text{Et}_3\text{N} \cdot 3\text{HF}$  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

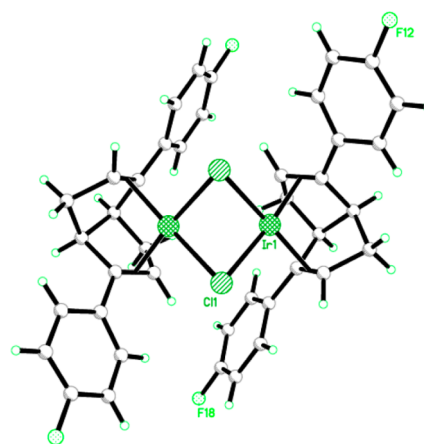


Figure 2. ORTEP diagram of  $[\text{IrCl}(\text{L2})]_2$ .

X-ray structure)<sup>24</sup> 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.<sup>16a</sup>

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  $\text{Et}_3\text{N} \cdot 3\text{HF}$  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,<sup>8b</sup> 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.<sup>25</sup> 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  $\alpha$ -heteroatoms. Trichloroacetimidates **10**–**13** bearing  $\alpha$ -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  $\alpha$ -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,<sup>8b</sup> they were obtained in 92 and 94% ee, respectively, under our DYKAT conditions (entries 9 and 12). To illustrate the

Table 2. Survey of Allylic Trichloroacetimidates<sup>a</sup>

entry	imidates	products	time (h)	yield (%) <sup>c</sup>	ee (%) <sup>d</sup>
	Reaction conditions: 2.5 mol % [IrCl(L2)] <sub>2</sub> , Et <sub>3</sub> N·3HF (1.5 equiv), MTBE, 25 °C, 0.5 - 3 h				
1	<b>1</b> (R = 4-F-Bz)	<b>2</b> (R = 4-F-Bz)	1	82 (83 <sup>b</sup> )	93 (92 <sup>b</sup> )
2	<b>3</b> (R = Bz)	<b>14</b> (R = Bz)	1	75	93
3	<b>4</b> (R = TBDPS)	<b>15</b> (R = TBDPS)	1.5	70	97
4	<b>5</b> (R = 4-MeO-C <sub>6</sub> H <sub>4</sub> )	<b>16</b> (R = 4-MeO-C <sub>6</sub> H <sub>4</sub> )	1.5	77	95
5	<b>6</b> (R = 2-Br-C <sub>6</sub> H <sub>4</sub> )	<b>17</b> (R = 2-Br-C <sub>6</sub> H <sub>4</sub> )	1	70	92
6			3	61	95
7			0.5	74	99
8			1	73	82
9	<b>10</b> : R = OBn	<b>21</b> : R = OBn	1	90	92
10	<b>11</b> : R = OTBDPS	<b>22</b> : R = OTBDPS	1	69	95
11	<b>12</b> : R = Ph	<b>23</b> : R = Ph	1	82	90
12			1	75	94

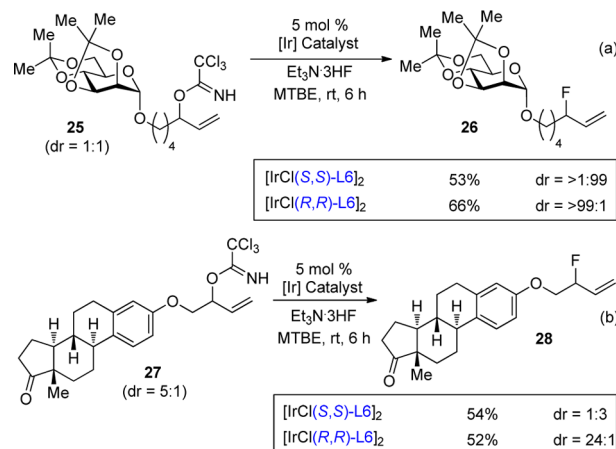
<sup>a</sup>Reactions were carried out using 0.15–0.3 mmol of imide and 2.5 mol % [IrCl(L2)]<sub>2</sub>, unless otherwise noted. <sup>b</sup>The reaction was carried out using 1.2 mmol of imide **1** and 1 mol % [IrCl(L2)]<sub>2</sub>. <sup>c</sup>Isolated yields. <sup>d</sup>Determined by chiral HPLC.

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.<sup>26</sup>

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**)]<sub>2</sub> and [IrCl((*S,S*)-**L6**)]<sub>2</sub> to enhance or overturn the substrate's inherent selectivity preference. Accordingly, the reaction of *D*-mannose substrate **25**

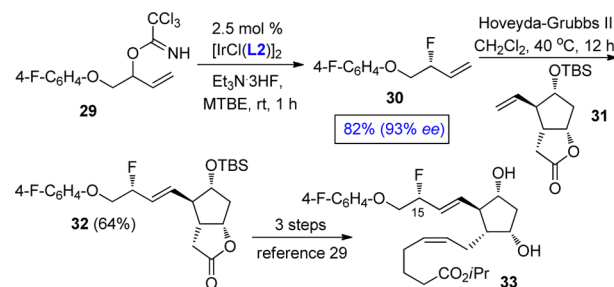
Scheme 1. Fluorination of Chiral Allylic Imidate Substrates



(Scheme 1a) proceeded with excellent catalyst control, providing the desired fluoride product **26** as a single diastereomer.<sup>27</sup> 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**)]<sub>2</sub>, the fluoride product **28** was produced with low diastereoselectivity (dr = 1:3).<sup>27</sup> In contrast, the matched case using [IrCl((*R,R*)-**L6**)]<sub>2</sub> afforded **28** with excellent diastereocontrol (dr = 24:1).<sup>27</sup>

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,<sup>28</sup> was previously prepared via DAST-mediated dehydroxyfluorination of its 15-allylic alcohol starting material.<sup>29</sup> 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.<sup>29</sup>

In summary, we have developed a new method for dynamic kinetic asymmetric fluorination of racemic, secondary allylic trichloroacetimidates with Et<sub>3</sub>N·3HF. Our strategy, promoted by a chiral-diene-ligated Ir catalyst, provides acyclic 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  $\alpha$ -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)

NMR spectra (PDF)

Crystallographic data for  $[\text{IrCl}(\text{L}2)]_2$  (CIF)

Crystallographic data for **35** (CIF)

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

- (1) (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) Miller, P. W.; Long, N. J.; Vilar, R.; Gee, A. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8998. (c) Ametamey, S. M.; Honer, M.; Schubiger, P. A. *Chem. Rev.* **2008**, *108*, 1501. (d) Cai, L.; Lu, S.; Pike, V. W. *Eur. J. Org. Chem.* **2008**, *2008*, 2853. (e) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (f) Gouverneur, V. *Science* **2009**, *325*, 1630. (g) Qiu, X.-L.; Xu, X.-H.; Qing, F.-L. *Tetrahedron* **2010**, *66*, 789. (h) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470.
- (2) (a) Pacheco, M. C.; Purser, S.; Gouverneur, V. *Chem. Rev.* **2008**, *108*, 1943. (b) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev.* **2015**, *115*, 826. (c) Wu, J. *Tetrahedron Lett.* **2014**, *55*, 4289.
- (3) (a) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574. (b) Blackburn, G. M.; Kent, D. E. *J. Chem. Soc., Chem. Commun.* **1981**, 511. (c) Piva, O. *Synlett* **1994**, *1994*, 729. (d) Boukerb, A.; Gree, D.; Laabassi, M.; Gree, R. *J. Fluorine Chem.* **1998**, *88*, 23. (e) Singh, R. P.; Shreeve, J. M. *Synthesis* **2002**, 2561.
- (4) Gree, D. M.; Kermarrec, C. J. M.; Martelli, J. T.; Gree, R. L.; Lellouche, J.-P.; Toupet, L. *J. Org. Chem.* **1996**, *61*, 1918.
- (5) Hollingworth, C.; Gouverneur, V. *Chem. Commun.* **2012**, *48*, 2929.
- (6) (a) Kemmitt, R. D. W.; Peacock, R. D.; Stocks, J. *J. Chem. Soc. A* **1971**, 846. (b) Pagenkopf, B. L.; Carreira, E. M. *Chem. - Eur. J.* **1999**, *5*, 3437. (c) Grushin, V. V. *Chem. - Eur. J.* **2002**, *8*, 1006. (d) Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26. (e) Hintermann, L.; Lang, F.; Maire, P.; Togni, A. *Eur. J. Inorg. Chem.* **2006**, *2006*, 1397. (f) Grushin, V. V. *Acc. Chem. Res.* **2010**, *43*, 160.
- (7) (a) Narumi, T.; Tomita, K.; Inokuchi, E.; Kobayashi, K.; Oishi, S.; Ohno, H.; Fujii, N. *Org. Lett.* **2007**, *9*, 3465. (b) Hazari, A.; Gouverneur, V.; Brown, J. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1296.
- (8) For representative examples of regio- and enantioselective allylic fluorination, see: (a) Katcher, M. H.; Doyle, A. G. *J. Am. Chem. Soc.* **2010**, *132*, 17402. (b) Katcher, M. H.; Sha, A.; Doyle, A. G. *J. Am. Chem. Soc.* **2011**, *133*, 15902. (c) Katcher, M. H.; Norrby, P.-O.; Doyle, A. G. *Organometallics* **2014**, *33*, 2121.
- (9) For other representative examples of regioselective allylic fluorination, see: (a) Hollingworth, C.; Hazari, A.; Hopkinson, M.; Tredwell, M.; Benedetto, E.; Huiban, M.; Gee, A. D.; Brown, J. M.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2011**, *50*, 2613. (b) Lauer, A. M.; Wu, J. *Org. Lett.* **2012**, *14*, 5138. (c) Benedetto, E.; Tredwell, M.; Hollingworth, C.; Khotavivattana, T.; Brown, J. M.; Gouverneur, V. *Chem. Sci.* **2013**, *4*, 89.

(10) For Pd-catalyzed carbofluorination of allenes to generate allylic fluorides, see: Braun, M.-G.; Katcher, M. H.; Doyle, A. G. *Chem. Sci.* **2013**, *4*, 1216.

(11) For Rh-catalyzed regioselective ring opening of vinyl epoxides with  $\text{Et}_3\text{N}\cdot 3\text{HF}$ , see: Zhang, Q.; Nguyen, H. M. *Chem. Sci.* **2014**, *5*, 291.

(12) For Pd-catalyzed allylic C–H fluorination, see: Braun, M.-G.; Doyle, A. G. *J. Am. Chem. Soc.* **2013**, *135*, 12990.

(13) Topczewski, J. J.; Tewson, T. J.; Nguyen, H. M. *J. Am. Chem. Soc.* **2011**, *133*, 19318.

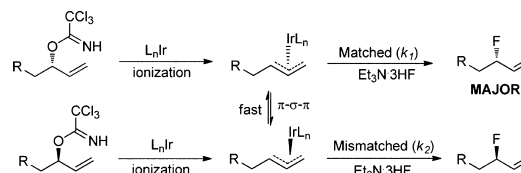
(14) For Rh-catalyzed asymmetric ring opening of oxabicyclic alkenes to form allylic fluorides, see: Zhu, J.; Tsui, G. C.; Lautens, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 12353.

(15) For the enantioselective synthesis of 1,1-disubstituted allylic fluorides using Selectfluor<sup>®</sup> as the electrophilic fluoride source, see: (a) Wu, J.; Wang, Y.-M.; Drljevic, A.; Rauniyar, V.; Phipps, R. J.; Toste, F. D. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110*, 13729. (b) Zi, W.; Wang, Y.-M.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 12864.

(16) Our group has demonstrated that a chiral-diene-ligated Rh catalyst promotes DYKAT of racemic, branched allylic trichloroacetimidates with anilines in high yields with excellent enantioselectivity. See: (a) Arnold, J. S.; Nguyen, H. M. *J. Am. Chem. Soc.* **2012**, *134*, 8380. (b) Arnold, J. S.; Cizio, G. T.; Heitz, D. R.; Nguyen, H. M. *Chem. Commun.* **2012**, *48*, 11531. (c) Arnold, J. S.; Mwenda, E. T.; Nguyen, H. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 3688.

(17) For a recent review of Ir-catalyzed allylic substitution, see: Hartwig, J. F.; Pouy, M. J. *Top. Organomet. Chem.* **2011**, *34*, 169.

(18) A proposed mechanism for Ir-catalyzed DYKAT of racemic, branched allylic imidates with  $\text{Et}_3\text{N}\cdot 3\text{HF}$  is shown below:



(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  $\pi$ -allyl Ir complexes occurs faster than fluoride attack.

(20) (a) Defieber, C.; Grützmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482. (b) Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *Synlett* **2011**, *2011*, 1345.

(21) (a) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584. (b) Okamoto, K.; Hayashi, T.; Rawal, V. H. *Chem. Commun.* **2009**, 4815.

(22) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628.

(23) (a) Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336. (b) Helbig, S.; Sauer, S.; Cramer, N.; Laschat, S.; Baro, A.; Frey, W. *Adv. Synth. Catal.* **2007**, *349*, 2331. (c) Feng, C.-G.; Wang, Z.-Q.; Tian, P.; Xu, M.-H.; Lin, G.-Q. *Chem. - Asian J.* **2008**, *3*, 1511.

(24) The ligation of  $[\text{IrCl}(\text{coe})_2]_2$  with L2 to produce  $[\text{IrCl}(\text{L}2)]_2$  was accomplished by heating the mixture in hexane at 50 °C for 48 h. See the Supporting Information for the detailed procedure.

(25) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (b) Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. *Chem. Rev.* **2013**, *113*, 4905. (c) Sharpless, K. B.; Manetsch, R. *Expert Opin. Drug Discovery* **2006**, *1*, 525.

(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  $[\text{IrCl}((S,S)\text{-L}6)]_2$ . On the other hand, the *S* configuration can be assigned for **26** and **28** with the use of  $[\text{IrCl}((R,R)\text{-L}6)]_2$ .

(28) Sugrue, M. F. *J. Med. Chem.* **2007**, *40*, 2793.

(29) Klimko, P.; Hellberg, M.; McLaughlin, M.; Sharif, N.; Severns, B.; Williams, G.; Haggard, K.; Liao, J. *Bioorg. Med. Chem.* **2004**, *12*, 3451.