Title

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Journal

Journal of the American Chemical Society, 141(33)

ISSN

0002-7863

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Publication Date

2019-08-21

DOI

10.1021/jacs.9b04440

Peer reviewed

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
Cite This: J. Am. Chem. Soc. 2019, 141, 13066−13073
pubs.acs.org/JACS

Stereodivergent Construction of Tertiary Fluorides in Vicinal Stereogenic Pairs by Allylic Substitution with Iridium and Copper Catalysts

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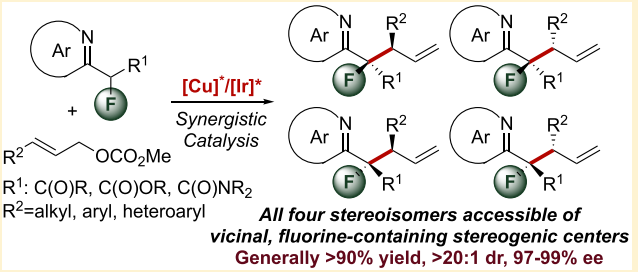
Supporting Information

ABSTRACT: Although much effort has been spent on the enantioselective synthesis of tertiary alkyl fluorides, the synthesis of compounds containing such a stereogenic center within an array of stereocenters, particularly two vicinal ones, remains a synthetic challenge, and no method to control the configuration of each stereogenic center independently has been reported. We describe a strategy to achieve such a stereodivergent synthesis of vicinal stereogenic centers, one containing a fluorine atom, by forming the connecting carbon−carbon bond with a catalyst system comprising an iridium complex that controls the configuration at the electrophilic carbon and a copper catalyst that controls the configuration at the nucleophilic fluorine-containing carbon. These reactions occur with alkyl- and aryl-substituted allylic esters and the unstabilized enolates of azaaryl ketones, esters, and amides in high yield, diastereoselectivity, and enantioselectivity (generally >90% yield, >20:1 dr, 97−99% ee). Access to all four stereoisomers of products demonstrates the precise control of the two configurations independently. This methodology extends to the stereodivergent construction of vicinal quaternary and tertiary stereocenters in similarly high yield and selectivity. DFT calculations uncover the origin of stereoselectivity of copper enolate in allylic substitution.



INTRODUCTION

Enantioselective synthesis of chiral alkyl fluorides has been studied intensively in recent years, due to the favorable physicochemical and biological properties of such structures.[1] The most synthetically challenging fluorine-containing sites to establish are fully substituted, fluorine-containing stereocenters, and many approaches to set such sites are being developed.[1c] However, the construction of such sites in molecules containing multiple stereogenic centers with control of diastereoselectivity is an even greater challenge and is largely unaddressed. Such reactions are important because different relative configurations of stereoisomeric alkyl fluorides can engender distinct properties,[2] and such motifs in which a tertiary fluoride stereocenter is located vicinal to a second stereogenic center are contained in pharmaceuticals, such as dexamethasone, fludrocortisone, fluticasone propionate, and sofosbuvir.[1c]

The most versatile approach to the synthesis of such compounds would provide independent control over the configuration at each of the stereogenic centers to selectively form each of the four stereoisomers, one containing a fluorine atom, but such stereodivergent reactions have not been reported. A few methods have been reported for the enantioselective synthesis of tertiary fluorides bearing an adjacent stereocenter favoring one of two possible relative configurations,[3] but these existing methods have not been amenable to forming all stereoisomers of such fluorine-containing structures. To form such a set of stereoisomers, the catalyst system must control the configuration at two sites separately with two regulating elements.[2]

Enantioselective, iridium-catalyzed allylic substitutions with prochiral enolates can construct compounds containing vicinal stereogenic centers with high diastereo- and enantioselectivity.[4] Recently, Carriera,[5] Jørgensen,[6] Zhang,[7] Wang,[8] and our own group[9] disclosed catalytic systems comprising one catalyst that reacts with carbonyl nucleophiles to form chiral enamine[5,6] or enolate[7−9] intermediates *in situ* and an iridium complex that forms a chiral allyl intermediate to afford products in a stereodivergent fashion containing vicinal stereocenters. All four stereoisomers of the products can be generated by permutation of the enantiomers of the iridium catalyst and the cocatalyst.

We envisioned a strategy to address the unsolved synthetic problem of preparing compounds containing vicinal fluorine-containing stereodyads by enlisting our iridium catalyst to set one stereogenic center and a Lewis acid cocatalyst to set the second fluorine-containing center simultaneously. If unstabilized carbonyl enolates comprising a basic heteroarene, which are common in pharmaceuticals and agrochemicals, and a fluorine atom at the nucleophilic carbon would react, such a system might result. However, reactions of the enolates of α-fluoro ketones, esters, and amides that we envisioned to use as

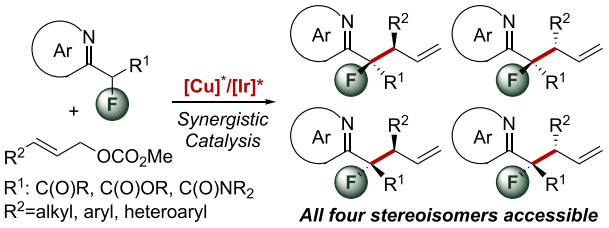
Received: April 24, 2019
Published: July 25, 2019

DOI: 10.1021/jacs.9b04440
J. Am. Chem. Soc. 2019, 141, 13066−13073

nucleophiles are not straightforward to achieve. It is known that α-fluoro carbonyl compounds are much less stable than nonfluorinated enolates,[10] and prior iridium-catalyzed allylic substitutions of fluoroalkyl nucleophiles have occurred only with stabilized nucleophiles containing two carbonyl, nitro, or sulfone groups at the nucleophilic carbon.[11] Because the iridium catalyst alone does not typically control the configuration at a nucleophilic carbon, these reactions form just one of two diastereomers as the major isomer with a diastereoselectivity of less than 5:1, more typically between 1:1 and 4:1.[11] Lewis acids that might control the configuration of the nucleophile could abstract the α-fluorine atom, and the combination of enhanced acidity and weaker Lewis basicity of the fluorine-containing carbonyl compounds than of the parents lacking fluorine[12] makes it possible that reactions with two catalysts could suffer from competing allylations occurring without the involvement of the Lewis acid catalyst, resulting in the low diastereoselectivities of prior work.[11,13]

While cognizant of these issues, we sought to apply a dual catalyst system to this synthetic problem, and we report our results on the stereodivergent synthesis of acyclic compounds containing a fully substituted, fluorine-containing stereocenter vicinal to a second stereocenter by allylic substitution catalyzed by the combination of a chiral cyclometalated iridium catalyst and a chiral, copper enolate catalyst (Scheme 1). The copper

Scheme 1. Our Design for the Stereodivergent Construction of Acyclic Tertiary Fluoride with a Vicinal Stereocenter

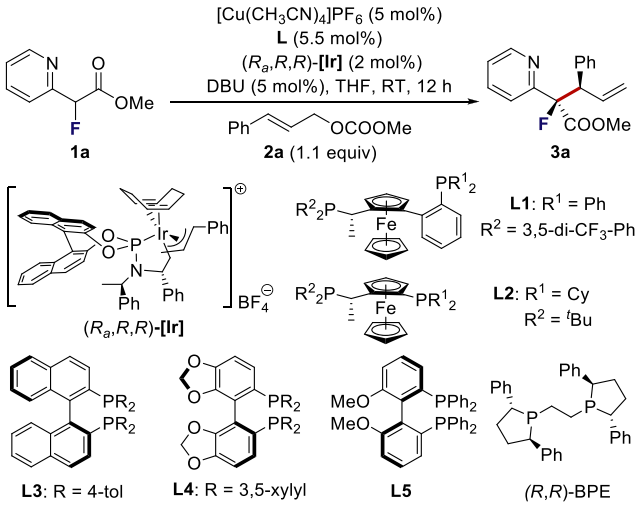


catalyst contains a bisphosphine that provides remarkable control over the configuration at the enolate carbon, and the iridium and copper complexes independently dictate the configurations of the two stereogenic centers in the products arising from the electrophile and nucleophile, respectively. Thus, simple permutations of enantiomers of the iridium and copper catalysts afford all four possible configurations of the two stereogenic centers with excellent diastereo- and enantioselectivity. Computational studies elucidate the origin of the stereoselectivity of the chiral copper enolate in the reaction.

RESULTS AND DISCUSSION

Reaction Development. Our initial studies on the stereodivergent synthesis of products containing a fully substituted, fluorine-containing stereocenter and a vicinal tertiary center began with reactions of α-fluoro pyridinyl acetate **1a** as the nucleophile and cinnamyl methyl carbonate **2a** as the electrophile (Table 1). With the combination of catalysts and base we reported previously[9b] (5 mol % of $[Cu(CH_3CN)_4]PF_6$, 5.5 mol % of Walphos **L1**, 2 mol % of metallacyclic iridium catalyst (R_a,*R*,*R*)-[**Ir**], and 5 mol % of DBU), the allylation occurred in quantitative yield and with a good 14:1 dr (entry 1). Reactions with most other bisphosphine ligands for the copper catalyst gave the product in high yield but low diastereoselectivity (1:1 to 2:1, entries 2−5). Yet, we found that reactions

Table 1. Evaluation of Reaction Conditions for the Allylation of 2-Pyridyl α-Fluoro Acetate (1a)



entry	L	yield (%)[a]	dr[a]	ee (%)[b]
1	**L1**	99	14:1	n.d.
2	**L2**	70	2:1	n.d.
3	**L3**	99	1:1	n.d.
4	**L4**	99	1:2	n.d.
5	**L5**	99	2:1	n.d.
6	(*R*,*R*)-BPE	99 (>99)[c]	>20:1	>99
7	none	86	1:1	n.d.
8[d]	none	18	1:1	n.d.
9[e]	(*R*,*R*)-BPE	<1	n.d.	n.d.
10[f]	(*R*,*R*)-BPE	27	14:1	n.d.

[a]Determined by ^{1}H NMR spectroscopy of the crude reaction with 1,3,5-trimethylbenzene as internal standard. Combined yield of two diastereomers. [b]Determined by chiral SFC analysis of the major isomer. [c]Isolated yield in the parentheses. [d]Without copper catalyst. [e]Without iridium catalyst. [f]Without DBU. n.d., not determined.

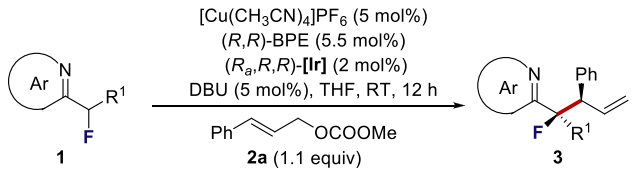
conducted with (*R*,*R*)-BPE as the ligand for copper occurred in quantitative yield (>99%) to give just one detectable diastereomer (>20:1) and enantiomer (>99%) (entry 6).

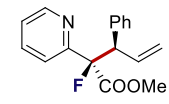
A set of control experiments were conducted to reveal the influence of the dual catalysts on the reaction efficiency and stereoselectivity. Without (*R*,*R*)-BPE ligated to copper, the reaction occurred in 86% yield, but the dr was nearly 1:1, indicating that a competitive background reaction without the copper cocatalyst would lead to lower diastereoselectivity (entry 7). In the absence of both copper and (*R*,*R*)-BPE, only 18% of product **3a** was observed (entry 8). The reaction without the iridium catalyst gave no product (entry 9). The presence of base was important for the reaction to occur; in the absence of DBU, the reaction gave only 27% product, but the observed high 14:1 dr value showed that the product formed in the absence of base resulted from the combination of copper and iridium catalysts (entry 10).

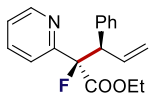
Scope of Fluorinated Nucleophiles for Allylic Substitution. Having identified conditions for reaction of α-fluoro pyridinyl acetate **1a**, we assessed the scope of these conditions for the allylation of a series of fluorinated azaaryl acetates and acetamides for the construction of products containing vicinal tertiary alkyl fluoride and tertiary alkyl stereogenic centers (Table 2). A variety of fluorinated acetates bearing pyridinyl, quinolinyl, and isoquinolinyl moieties underwent allylation

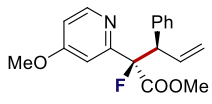
DOI: 10.1021/jacs.9b04440
J. Am. Chem. Soc. 2019, 141, 13066−13073

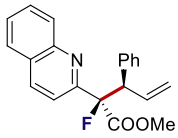
Table 2. Scope of the Fluorinated Nucleophiles That Undergo the Diastereoselective Allylic Substitution[a]

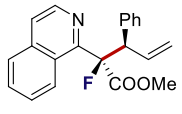


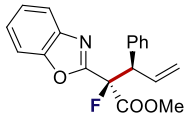

3a, >99% yield
>20:1 dr, >99% ee

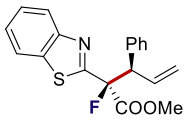

3b, 99% yield
>20:1 dr, 99% ee

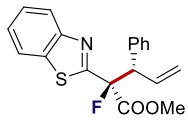

3c, 90% yield
>20:1 dr, 99% ee

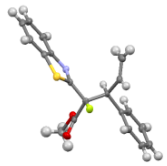

3d, 94% yield
>20:1 dr, 99% ee

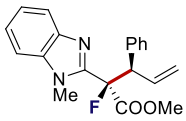

3e, 84% yield
>20:1 dr, 99% ee

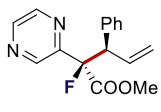

3f, >99% yield
>20:1 dr, 98% ee

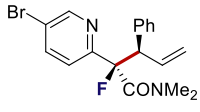

3g, 96% yield
>20:1 dr, 99% ee

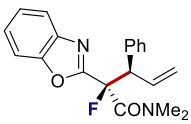

ent-**7g**, 91% yield
20:1 dr, 99% ee

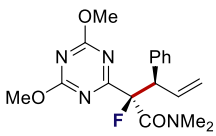

ent-**7g**
(diastereomer of **3g**)

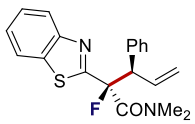

3h, 88% yield
>20:1 dr, 99% ee

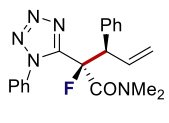

3i, >99% yield
>20:1 dr, >99% ee

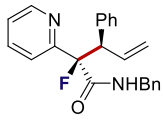

3j, 91% yield
>20:1 dr, >99% ee

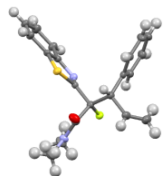

3k, 98% yield
>20:1 dr, 99% ee

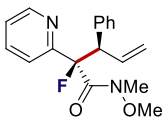

3l, 96% yield
10:1 dr, 97% ee

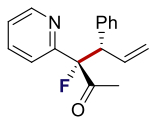

3m, >99% yield
>20:1 dr, 99% ee


3n, 90% yield
>20:1 dr, 99% ee


3o, 83% yield
6:1 dr, 99% ee


ent-**3m**
(enantiomer of **3m**)


3p, 88% yield
>20:1 dr, 99% ee


ent-**3q**, 99% yield
>20:1 dr, 99% ee

[a]Isolated yield. Diastereomeric ratios were determined by ^{1}H NMR spectroscopy of the crude reaction. Enantiomeric excess was determined by chiral SFC or HPLC analysis of the major isomers.

smoothly, providing products **3a**–**3e** with excellent yields and excellent relative and absolute stereoselectivity (84–99% yield, >20:1 dr, 99% ee). Azaaryl units, such as benzoxazolyl, benzothiazolyl, benzimidazolyl, and pyrazinyl, which contain multiple sites that could coordinate to copper, underwent the allylic substitution with high 88–99% yields, >20:1 diastereoselectivity, and 98–99% enantioselectivity (**3f**–**3i**). The absolute configuration of *ent*-**7g**, a diastereomer of **3m** formed from the combination of (*R*,*R*)-BPE and (S_a,*S*,*S*)-[**Ir**], was determined by X-ray analysis.

In addition to α-fluoro azaaryl acetates, the less acidic, but more Lewis basic α-fluoro azaaryl acetamides underwent the allylic substitution (**3j**–**3p**). Products **3j** and **3k** were obtained in >90% yield, >20:1 dr, and 99% ee to form the corresponding fluoro pyridinyl and benzoxazolyl acetamides as nucleophiles. Azaaryl units bearing three and even four nitrogen atoms (**3l**, **3n**) reacted exclusively in excellent yield (90–96%), diastereoselectivity (10:1 → 20:1), and enantioselectivity (96–99%). Fluorinated benzothiazolyl acetamides underwent allylation in essentially perfect yield, dr, and ee (**3m**), and the absolute configuration of its enantiomer was determined by X-ray analysis. The allylic substitution also tolerated secondary amides and Weinreb amides as nucleophiles, greatly extending the scope of transformations of the products and applications of the process (**3o**–**3p**). Finally, α-fluoro pyridinyl ketone **1q** underwent allylic substitution to give compound *ent*-**3q** in excellent yield and selectivity (99% yield, >20:1 dr, 99% ee).

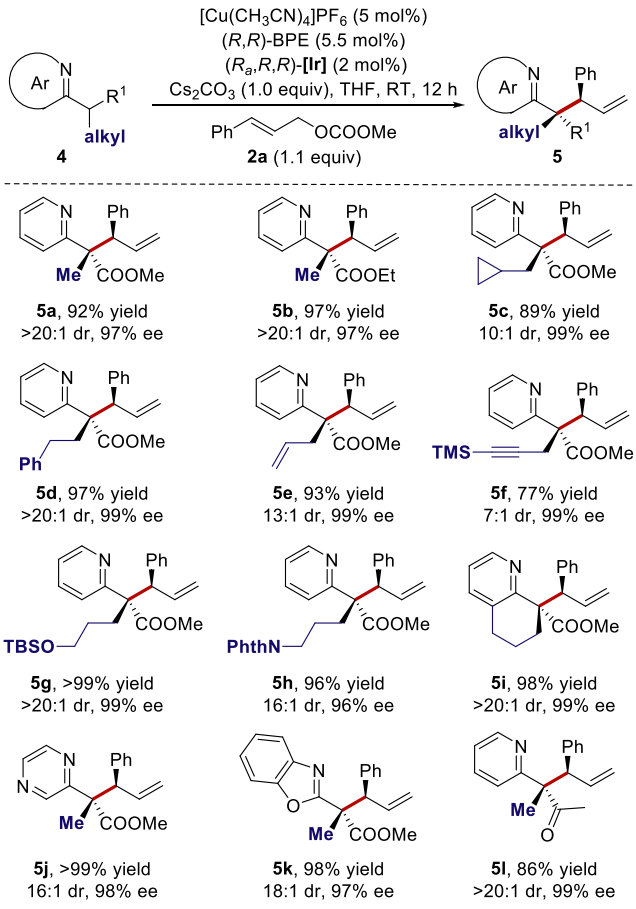
Scope of Alkylated Nucleophiles for Allylic Substitution. Although this work focused on the formation of products containing chiral tertiary fluorides, we did assess whether the scope of the formation of products containing vicinal fully substituted and tertiary stereogenic centers was limited to those containing fluorine at the fully substituted site, particularly because stereodivergent approaches to form products containing acyclic vicinal quaternary and tertiary stereocenters with high diastereoselectivity and enantioselectivity from ester and amide enolates are rare.[5a,14] Indeed, the reaction of alkyl-substituted aza-aryl esters with allylic esters formed the allylation products with high yield and stereoselectivity; modifications of the conditions from those used to form the products containing fluorine at the nucleophilic carbon of the aza-aryl ester increased yields and stereoselectivities. The reaction of methyl 2-pyridyl propionate **4a** with cinnamyl methyl carbonate **2a** under the conditions developed for reaction of the fluorinated substrates in Table 2 gave **5a** in a good 72% yield with 14:1 dr. However, a series of experiments with various bases and ligands (see Supporting Information (SI) for details) showed that reactions with Cs_2CO_3 (1.0 equiv) as the base instead of DBU formed **5a** containing adjacent quaternary and tertiary stereocenters in a high 92% yield as a single detectable (>20:1) diastereomer with 97% enantioselectivity.

A broad range of azaaryl acetates containing various alkyl substituents on the reactive α-carbon also underwent the allylation process, as summarized in Table 3. Alkyl substituents containing cyclopropyl, aryl, alkenyl, alkynyl, OTBS, and imide groups were well tolerated, affording products **5a**–**5h** in 77% to 99% yield, with 7:1 to 20:1 dr, and 96–99% ee.[15] Ester **4i** for which the reactive center lies in a ring reacted in excellent yield and stereoselectivity (98% yield, >20:1 dr, 99% ee). Changes to the structure of the azaaryl units had little effect on the reaction (**5j**–**5k**). Finally, the ketone α-methyl pyridnyl acetone (**4l**) reacted with carbonate **2a** in a similar fashion as the esters to give product **5l** in 86% yield, >20:1 dr, and 99% ee. In this case, allylation of **4l** occurred exclusively at the tertiary α-carbon over the primary α-site.

Scope of Allylic Carbonates as Electrophiles for Allylic Substitution. A series of allylic carbonates containing various

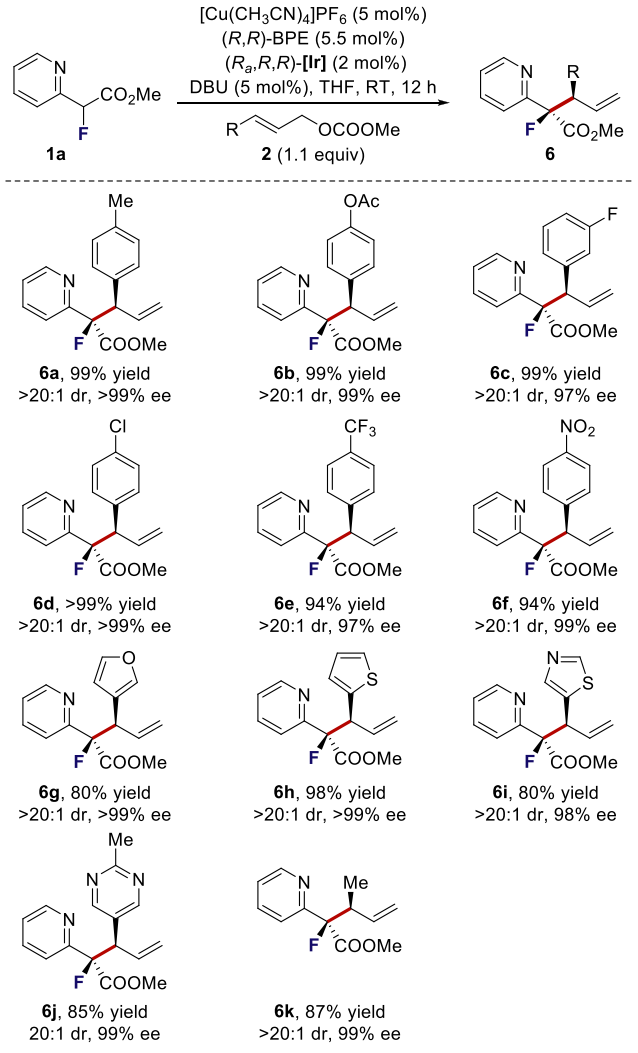
DOI: 10.1021/jacs.9b04440
J. Am. Chem. Soc. 2019, 141, 13066–13073

Table 3. Scope of α-Alkyl Acetates That Undergo the Diastereoselective Allylic Substitution[a]



[a]Isolated yield. Diastereomeric ratios were determined by ^{1}H NMR spectroscopy of the crude reaction. Enantiomeric excess was determined by chiral SFC or HPLC analysis of the major isomers.

Table 4. Scope of Allylic Carbonates That Undergo the Diastereoselective Allylic Substitution with Methyl 2-Pyridyl α-Fluoroacetate (1a)[a]



[a]Isolated yield. Diastereomeric ratios were determined by ^{1}H NMR spectroscopy of the crude reaction. Enantiomeric excess was determined by chiral SFC analysis of the major isomers.

substituted aryl, heteroaryl, and alkyl moieties underwent the allylation with α-fluoro ester **1a** in high 80−99% yields to give a single detectable diastereomer (**6a**−**6i**, **6k**, >20:1 dr) in 97−99% ee (Table 4). Reactions of cinnamyl esters containing both electron-donating and electron-withdrawing groups on the cinnamyl aryl rings occurred to give the substitution product with excellent yields and stereoselectivities (**6a**−**6f**). Carbonates bearing furyl, thienyl, thiazolyl, and pyrimidinyl substituents also reacted with **1a** smoothly forming products containing vicinal stereogeneic centers that contain consecutive heteroaryl groups, as well as the fluorine atom (**6g**−**6j**). The substitution reaction even occurred with the simple crotyl carbonate to give compound **6k** in 87% yield with >20:1 dr and 99% ee.

Stereodivergent Reactions. Having observed high diastereoselectivity from the reactions conducted with the copper catalyst, but nearly 1:1 diastereoselectivity from reactions conducted without the copper catalyst, we conducted experiments to confirm that the configurations of the two stereogenic centers were determined independently by the two catalysts. We conducted these experiments with the fluorine-substituted acetate **1a** and the alkyl-substituted ester **4b**. Indeed, permutation of the enantiomers of iridium and copper complexes gave all four stereoisomers in excellent yields and stereoselectivities (Table 5). For example, the reaction of **1a** with the four combinations of stereoisomers of the catalysts gave all four steroisomers of the α-fluoro esters **3a** in >99% yield, as a single detectable diastereomer with 99% ee. This method provides the first access to all stereoisomers of vicinal fluorine-contained centers and tertiary centers. Likewise, the reaction of ethyl 2-pyridyl propionate **4b** with cinnamyl carbonate catalyzed by the four combinations of stereoisomers of the two catalysts formed the four stereoisomeric products in high yield as a single detectable diastereomer with nearly perfect (97−99%) enantioselectivity. This result, along with the related results to form vicinal quaternary and tertiary stereogenic centers from the α-alkyl esters, indicates the independent control of the configurations of electrophiles and nucleophiles with the iridium and copper catalysts.

The utility and robustness of the present protocol was further demonstrated by conducting the allylic substitution on 0.1 mmol to multimillimole scale. The reaction of 3.0 mmol of fluorinated nucleophile **1a** with cinnamyl carbonate **3a** occurred in an identical fashion as the reaction on 0.1 mmol scale described in Table 5 (Scheme 2A). Likewise, as shown in

DOI: 10.1021/jacs.9b04440
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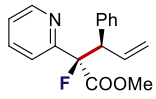
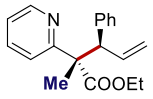
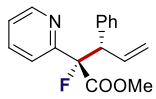
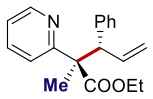
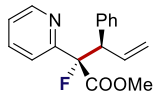
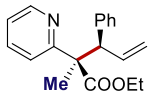
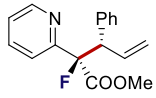
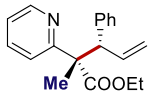
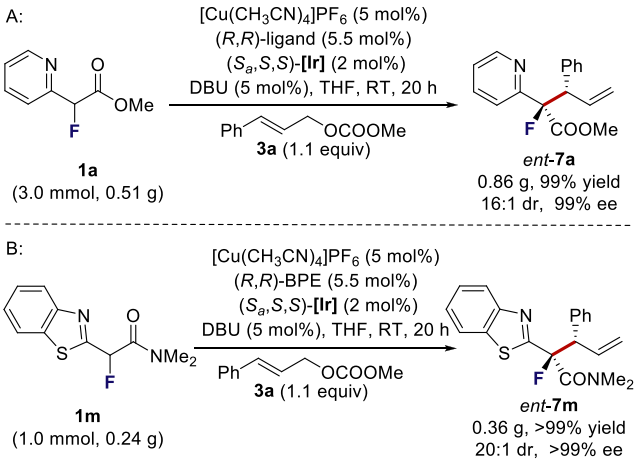
Table 5. Stereodivergent Synthesis of Four Stereoisomers from Reaction of Methyl Cinnamyl Carbonate with an α-Fluoro and α-Methyl Azaaryl Acetate[a]

[Cu]/(*R*,*R*)-BPE + (R_a,*R*,*R*)-[Ir]	 **3a**, >99% yield >20:1 dr, >99% ee	 **5b**, 93% yield >20:1 dr, 97% ee
[Cu]/(*S*,*S*)-BPE + (S_a,*S*,*S*)-[Ir]	 *ent*-**3a**, >99% yield >20:1 dr, 99% ee	 *ent*-**5b**, >99% yield >20:1 dr, 99% ee
[Cu]/(*S*,*S*)-BPE + (R_a,*R*,*R*)-[Ir]	 **7a**, >99% yield >20:1 dr, 99% ee	 **8b**, >99% yield >20:1 dr, 97% ee
[Cu]/(*R*,*R*)-BPE + (S_a,*S*,*S*)-[Ir]	 *ent*-**7a**, >99% yield 20:1 dr, 99% ee	 *ent*-**8b**, 93% yield >20:1 dr, 99% ee

[a]Isolated yield. Diastereomeric ratios were determined by ^{1}H NMR spectroscopy of the crude reactions. Enantiomeric excess was determined by chiral SFC analysis of major isomers. The conditions for reactions of fluorinated substrates were the same as those described for the reactions in Table 2; the conditions for reactions of alkylated substrates were the same as those described for reactions in Table 3.

Scheme 2. Large-Scale Allylation Reactions



Scheme 2B, the reaction of fluorinated nucleophile **1m** with carbonate **3a** on a 1.0 mmol scale catalyzed by the combination of (*R*,*R*)-BPE and (S_a,*S*,*S*)-[**Ir**] formed the diastereomer of **3m**, namely, *ent*-**7m**, in the same high yield and selectivity (>99% yield, 20:1 dr, and >99% ee) as that to form **3m**.

Origin of Stereoselectivity from the Copper Enolate. The allylation reaction is well established to occur by external attack of a nucleophile, in this case a copper enolate (**A**), at the allyl-iridium intermediate (**B**) (Scheme 3a). Previous mechanistic studies demonstrated that the geometry, facial selectivity, and regioselectivity of the allyl moiety in the asymmetric allylic substitution reactions are governed by the metallacyclic iridium catalysts.[16] To understand the origin of stereoselectivity of the copper enolate in the allylation reaction, DFT calculations were performed to elucidate the ground state structure of the α-fluoro copper enolate **Cu-1** derived from **1a** (Scheme 1b). The ωB97X-D/6-31G(d) level of theory was used with the SMD solvation model (THF).

In the optimized structure of **Cu-1**, the enolate carbon **C1** is close to the hydrogen atoms **H1** (3.10 Å) and **H2** (3.21 Å) of one of the phenyl groups of the ligand (Scheme 3c, front view). A top view and side view (Scheme 3c) of the structure clearly show that one face of **C1** (the *re* face) is substantially blocked by **H1** and **H2**, but the opposite face of **C1** (the *si* face) is open. Therefore, the allyl iridium intermediate would approach **C1** preferentially from the face of the enolate opposite to this aryl group. This rationale for the stereochemical outcome is consistent with the absolute configuration of the allylation product obtained by X-ray crystallography analysis.

To further assess the interactions that lead to the steric asymmetricity of the *si* and *re* face of **C1**, we analyzed the overall geometry of the copper complex. In an ideal tetrahedral structure of a copper enolate, the enolate carbon atom should lie in the plane bisecting the plane defined by the two phosphorus atoms and the copper. This geometry is observed for the computed structure of an achiral copper enolate derived from the azaaryl ester **1a** and bearing methyl groups at phosphorus (Scheme 3d). However, in the computed minimum-energy structure of the chiral copper enolate complex **Cu-1** containing BPE-phos, the nucleophilic enolate carbon **C1** lies out of this plane in the fourth quadrant (Scheme 3d, right).

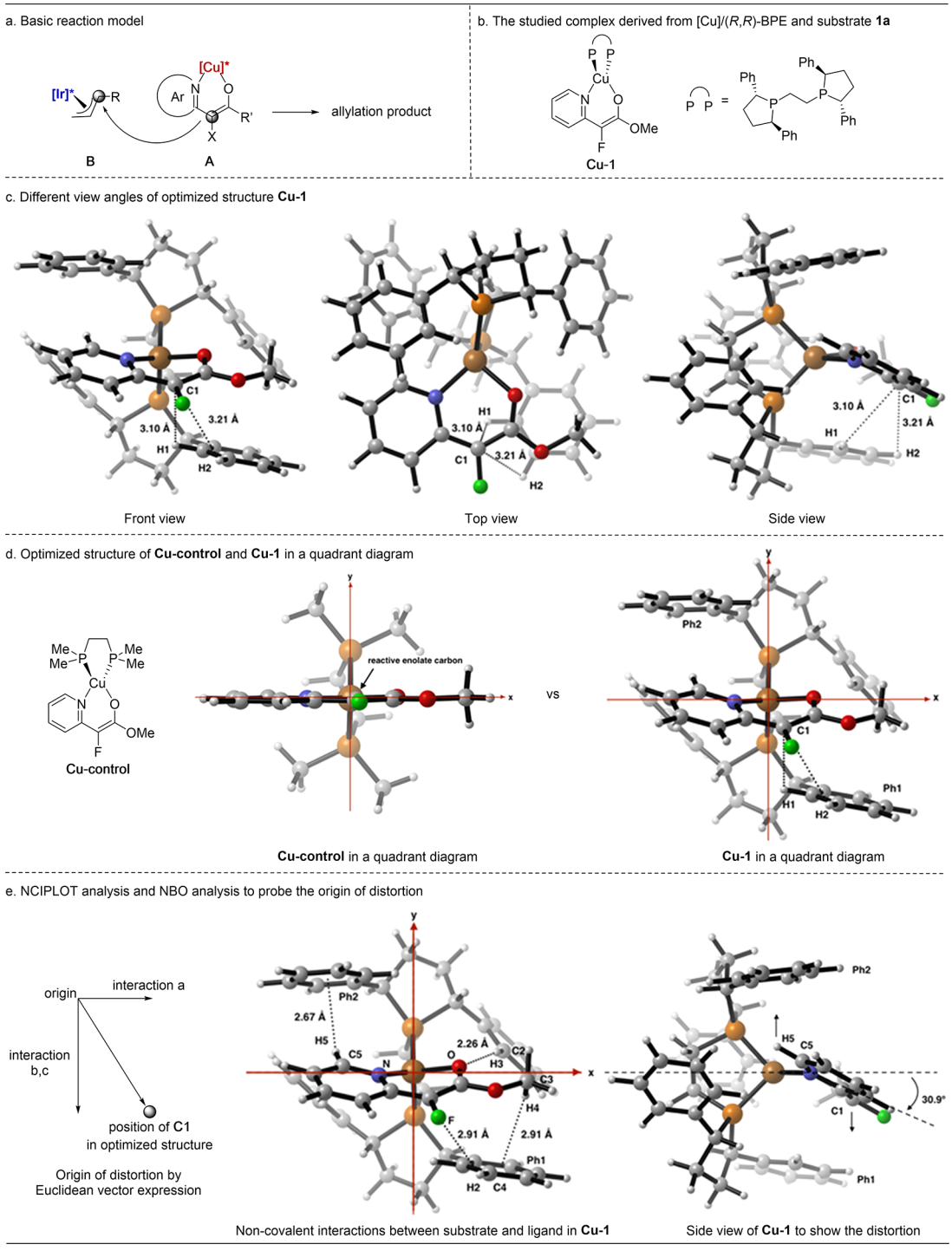
To probe the origin of this distortion, an NCIPLOT analysis[17] and NBO analysis[18] were performed on the minimum-energy structure of **Cu-1** (Scheme 3e; see SI for details). This analysis revealed three substantial interactions that likely lead to rotation of the enolate, such that its *si* face is exposed for reaction with the electrophile. First, the distance between carbonyl oxygen atom **O** and the ortho hydrogen **H3** of a BPE-phos aryl group is 2.26 Å, shorter than the sum of their van de Waals radii (2.72 Å), and an NBO second-order perturbation analysis reveals a substantial stabilizing energy **C2−H3···O** of 2.41 kcal/mol (interaction a, Scheme 3e, left). Second, one of the hydrogen atoms of the methyl ester moiety **H4** is located near the centroid of a second ligand phenyl group **Ph1** (2.91 Å) with a **C3−H4−Ph1** (centroid) angle of 132.1°. The proximity of the hydrogen to the centroid suggests the presence of a **C3−H4···π** interaction (interaction b).[19] Third, the **C5−H5** bond *ortho* to the nitrogen **N** of the pyridine moiety interacts attractively with the π system of a third ligand aryl group **Ph2** (2.67 Å, **C5−H5−Ph2** = 121.4°; interaction c).[20] As the result of these attractive noncovalent interactions between the substrate and the ligand, the distance between **C1** and phenyl group **Ph1** (in the same quadrant) is significantly shorter than that between **C1** and **Ph2** (in the opposite quadrant), and this difference in distance likely leads to the observed high facial selectivity of the copper enolate during the allylation reaction.[21,22]

CONCLUSION

We report a strategy for the stereodivergent construction of products containing fluorine within vicinal stereogenic centers by forming the carbon−carbon bond joining the two sites with an allylic substitution process. The reactions occur with the combination of an iridium catalyst to control the configuration

DOI: 10.1021/jacs.9b04440
J. Am. Chem. Soc. 2019, 141, 13066−13073

Scheme 3. Computational Studies on the Origin of Stereoselectivity by the Copper Enolate



at the electrophilic carbon of an allylic carbonate and a copper catalyst to control the configuration at the nucleophilic carbon of an unstabilized enolate. The fluorine-containing site in the products is fully substituted. The catalytic system also enables the construction of vicinal quaternary and tertiary stereogenic centers. In general, the products are obtained in >90% yield, >20:1 dr, and 97−99% ee. Stereodivergent synthesis of all four isomers of the products from reaction of one α-fluoro and one α-alkyl enolate highlights the high degree of stereocontrol over the nucleophile and electrophile independently. Computational studies suggest that the stereoselectivity of copper enolate during the allylic substitution results from a series of C−H···O and C−H···π interactions, and an analysis of the structure by NBO strongly suggests that these attractive, noncovalent interactions contribute to the distortion from a tetrahedral geometry that leads to asymmetric induction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b04440.

DOI: 10.1021/jacs.9b04440
J. Am. Chem. Soc. 2019, 141, 13066−13073

Experimental details and procedures, spectra for all unknown compounds (PDF)
Crystal structure for *ent*-**3m** (CCDC: 1907850) (CIF)
Crystal structure for *ent*-**7g** (CCDC: 1907851) (CIF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the NSF (CHE-1565886) for support of this work. Dr. Nicholas Settineri is acknowledged for X-ray crystallographic analysis.

REFERENCES

(1) For reviews, see: (a) Cahard, D.; Xu, X.; Couve-Bonnaire, C.; Pannecoucke, X. Fluorine & Chirality: How to Create a Nonracemic Stereogenic Carbon-Fluorine center? *Chem. Soc. Rev.* **2010**, *39*, 558. (b) Lectard, S.; Hamashima, Y.; Sodeoka, M. Recent Advances in Catalytic Enantioselective Fluorination Reactions. *Adv. Synth. Catal.* **2010**, *352*, 2708. (c) Zhu, Y.; Han, J.; Wang, J.; Shibata, N.; Sodeoka, M.; Soloshonok, V. A.; Coelho, J. A. S.; Toste, F. D. Modern Approaches for Asymmetric Construction of Carbon-Fluorine Quaternary Stereogenic Centers: Synthetic Challenges and Pharmaceutical Needs. *Chem. Rev.* **2018**, *118*, 3887.

(2) It is a known fact that stereochemistry might heavily affect the corresponding biological activity. Please see: (a) Caldwell, J. The Importance of Stereochemistry in Drug Action and Disposition. *J. Clin. Pharmacol.* **1992**, *32*, 925. (b) Rentsch, K. M. The Importance of Stereoselective Determination of Drugs in the Clinical Laboratory. *J. Biochem. Biophys. Methods* **2002**, *54*, 1.

(3) For selected examples, see: (a) Wang, L.; Meng, W.; Zhu, C.-L.; Zheng, Y.; Nie, J.; Ma, J.-A. The Long-Arm Effect: Influence of Axially Chiral Phosphoramidite Ligands on the Diastereo- and Enantioselectivity of the Tandem 1,4-Addition/Fluorination. *Angew. Chem., Int. Ed.* **2011**, *50*, 9442. (b) Honjo, T.; Phipps, R. J.; Rauniyar, V.; Toste, F. D. A Doubly Axially Chiral Phosphoric Acid Catalyst for the Asymmetric Tandem Oxyfluorination of Enamides. *Angew. Chem., Int. Ed.* **2012**, *51*, 9684. (c) Yan, L.; Han, Z.; Zhu, B.; Yang, C.; Tan, C.-H.; Jiang, Z. Asymmetric Allylic Alkylation of Morita-Baylis-Hillman Carbonates with α-Fluoro-β-Keto Esters. *Beilstein J. Org. Chem.* **2013**, *9*, 1853. (d) Shang, H.; Li, Y.; Li, X.; Ren, X. Diastereoselective Addition of Metal α-Fluoroenolates of Carboxylate Esters to N-tert-Butylsulfinyl Imines: Synthesis of α-Fluoro-β-amino Acids. *J. Org. Chem.* **2015**, *80*, 8739. (e) Emma, M. G.; Lombardo, M.; Trombini, C.; Quintavalla, A. The Organocatalytic α-Fluorination of Chiral γ-Nitroaldehydes: the Challenge of Facing the Construction of a Quaternary Fluorinated Stereocenter. *Eur. J. Org. Chem.* **2016**, *2016*, 3223. (f) Cosimi, E.; Engl, O. D.; Saadi, J.; Ebert, M. O.; Wennemers, H. Stereoselective Organocatalyzed Synthesis of α-Fluorinated β-Amino Thioesters and Their Application in Peptide Synthesis. *Angew. Chem., Int. Ed.* **2016**, *55*, 13127. (g) Cosimi, E.; Saadi, J.; Wennemers, H. Stereoselective Synthesis of α-Fluoro-γ-nitro Thioesters under Organocatalytic Conditions. *Org. Lett.* **2016**, *18*, 6014.

(4) For recent reviews, see: (a) Shockley, S. E.; Hethcox, J. C.; Stoltz, B. M. Intermolecular Stereoselective Iridium-Catalyzed Allylic Alkylation: An Evolutionary Account. *Synlett* **2018**, *29*, 2481. (b) Cheng, Q.; Tu, H.-F.; Zheng, C.; Qu, J.-P.; Helmchen, G.; You, S.-L. Iridium-Catalyzed Asymmetric Allylic Substitution Reactions. *Chem. Rev.* **2019**, *119*, 1855.

(5) (a) Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M. Enantio- and Diastereodivergent Dual Catalysis: α-Allylation of Branched Aldehydes. *Science* **2013**, *340*, 1065. (b) Krautwald, S.; Schafroth, M. A.; Sarlah, D.; Carreira, E. M. Stereodivergent α-Allylation of Linear Aldehydes with Dual Iridium and Amine Catalysis. *J. Am. Chem. Soc.* **2014**, *136*, 3020. (c) Sandmeier, T.; Krautwald, S.; Zipfel, H. F.; Carreira, E. M. Stereodivergent Dual Catalytic α Allylation of Protected α Amino and α Hydroxyacetaldehydes. *Angew. Chem., Int. Ed.* **2015**, *54*, 14363.

(6) Næsborg, L.; Halskov, K. S.; Tur, F.; Mønsted, S. M. N.; Jørgensen, K. A. Asymmetric γ-Allylation of α,β-Unsaturated Aldehydes by Combined Organocatalysis and Transition-Metal Catalysis. *Angew. Chem., Int. Ed.* **2015**, *54*, 10193.

(7) (a) Huo, X.; He, R.; Zhang, X.; Zhang, W. An Ir/Zn Dual Catalysis for Enantio- and Diastereodivergent α-Allylation of α-Hydroxyketones. *J. Am. Chem. Soc.* **2016**, *138*, 11093. (b) He, R.; Liu, P.; Huo, X.; Zhang, W. Ir/Zn Dual Catalysis: Enantioselective and Diastereodivergent α-Allylation of Unprotected α-Hydroxy Indanones. *Org. Lett.* **2017**, *19*, 5513. (c) Huo, X.; Zhang, J.; Fu, J.; He, R.; Zhang, W. Ir/Cu Dual Catalysis: Enantio- and Diastereodivergent Access to α,α- Disubstituted α-Amino Acids Bearing Vicinal Stereocenters. *J. Am. Chem. Soc.* **2018**, *140*, 2080.

(8) Wei, L.; Zhu, Q.; Xu, S.-M.; Chang, X.; Wang, C.-J. Stereodivergent Synthesis of α,α-Disubstituted α-Amino Acids via Synergistic Cu/Ir Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 1508.

(9) (a) Jiang, X.; Beiger, J. J.; Hartwig, J. F. Stereodivergent Allylic Substitutions with Aryl Acetic Acid Esters by Synergistic Iridium and Lewis Base Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 87. (b) Jiang, X.; Boehm, P.; Hartwig, J. F. Stereodivergent Allylation of Azaaryl Acetamides and Acetates by Synergistic Iridium and Copper Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 1239.

(10) Jiao, Z.; Beiger, J. J.; Jin, Y.; Ge, S.; Zhou, J. S.; Hartwig, J. F. Palladium-Catalyzed Enantioselective α-Arylation of α-Fluoroketones. *J. Am. Chem. Soc.* **2016**, *138*, 15980.

(11) (a) Liu, W.-B.; Zheng, S.-C.; He, H.; Zhao, X.-M.; Dai, L.-X.; You, S.-L. Iridium-Catalyzed Regio- and Enantioselective Allylic Alkylation of Fluorobis(phenylsulfonyl)methane. *Chem. Commun.* **2009**, 6604. (b) Zhang, H.; Chen, J.; Zhao, X.-M. Enantioselective Synthesis of Fluorinated Branched Allylic Compounds via Ir-Catalyzed Allylations of Functionalized Fluorinated Methylene Derivatives. *Org. Biomol. Chem.* **2016**, *14*, 7183. (c) Chen, J.; Zhao, X.; Dan, W. Diasteroselective and Enantioselective Ir-Catalyzed Allylic Substitutions of 1-Substituted 1-Fluoro-1-(arenesulfonyl)methylene Derivatives. *J. Org. Chem.* **2017**, *82*, 10693.

(12) A mono-fluoro substrate is more acidic than a nonfluoro one. Butin, K. P.; Kashin, A. N.; Beletskaya, I. P.; German, L. S.; Polishchuk, V. R. Acidities of Some Fluorine Substituted C-H Acids. *J. Organomet. Chem.* **1970**, *25*, 11.

(13) Cahard, D.; Bizet, V. The Influence of Fluorine in Asymmetric Catalysis. *Chem. Soc. Rev.* **2014**, *43*, 135.

(14) Cruz, F. A.; Zhu, Y.; Tercenio, Q. D.; Shen, Z.; Dong, V. M. Stereodivergent Coupling of Aldehydes and Alkynes via Synergistic Catalysis Using Rh and Jacobsen's Amine. *J. Am. Chem. Soc.* **2017**, *139*, 1029.

(15) When an isopropyl group was the alkyl substituent on the nucleophile, the allylic substitution reaction did not occur.

(16) (a) Madrahimov, S. T.; Markovic, D.; Hartwig, J. F. The Allyl Intermediate in Regioselective and Enantioselective Iridium-Catalyzed Asymmetric Allylic Substitution Reactions. *J. Am. Chem. Soc.* **2009**, *131*, 7228. (b) Madrahimov, S. T.; Hartwig, J. F. Origins of Enantioselectivity during Allylic Substitution Reactions Catalyzed by Metallacyclic Iridium Complexes. *J. Am. Chem. Soc.* **2012**, *134*, 8136. (c) Madrahimov, S. T.; Li, Q.; Sharma, A.; Hartwig, J. F. Origins of Regioselectivity in Iridium Catalyzed Allylic Substitution. *J. Am. Chem. Soc.* **2015**, *137*, 14968.

DOI: 10.1021/jacs.9b04440
J. Am. Chem. Soc. 2019, 141, 13066−13073

(17) (a) Johnson, E. R.; Keinan, S.; Mori-Sanchez, P.; Contreras-Garcia, J.; Cohen, A. J.; Yang, W. Revealing Noncovalent Interactions. *J. Am. Chem. Soc.* **2010**, *132*, 6498. (b) Contreras-Garcia, J.; Johnson, E. R.; Keinan, S.; Chaudret, R.; Piquemal, J.-P.; Beratan, D. N.; Yang, W. NCIPLOT: A Program for Plotting Noncovalent Interaction Regions. *J. Chem. Theory Comput.* **2011**, *7*, 625.

(18) Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. *NBO, version 3.1*; University of Wisconsin: Madison, WI, 1996.

(19) (a) Nishio, M. CH/π Hydrogen Bonds in Crystals. *CrystEngComm* **2004**, *6*, 130. (b) Takahashi, O.; Kohno, Y.; Iwasaki, S.; Saito, K.; Iwaoka, M.; Tomoda, S.; Umezawa, Y.; Tsuboyama, S.; Nishio, M. Hydrogen-Bond-Like Nature of the CH/π Interaction as Evidenced by Crystallographic Database Analyses and Ab Initio Molecular Orbital Calculations. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 2421.

(20) The distance between the fluorine atom **F** and **H2** (2.91 Å) is slightly longer than the sum of their van de Waals radii (2.67 Å), and the NBO analysis implies that this **C4—H2···F** interaction is only very weakly attractive (0.08 kcal/mol).

(21) When (*S*,*S*)-Me-BPE was used as the chiral ligand instead of Ph-BPE for the model reaction under the standard conditions, no product **3a** was observed. These data are consistent with the importance of the phenyl group in the BPE ligand.

(22) The ground-state structure of copper enolates **Cu-2**, **Cu-3**, and **Cu-4** derived from three other substrates and **Cu-5** derived from defluoro pyridyl acetate were also calculated by DFT. Results and corresponding analysis are summarized in the Supporting Information.

DOI: 10.1021/jacs.9b04440
J. Am. Chem. Soc. 2019, 141, 13066−13073