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Generation of Axially Chiral Fluoroallenes through a Copper-Catalyzed Enantioselective β-Fluoride Elimination

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Abstract

Herein we report the copper-catalyzed silylation of propargylic difluorides to generate axially chiral, tetrasubstituted monofluoroallenes in both good yields (27 examples >80%) and enantioselectivities (82–98% ee). Compared to previously reported synthetic routes to axially chiral allenes (ACAs) from prochiral substrates, a mechanistically distinct reaction has been developed: the enantiodiscrimination between enantiotopic fluorides to set an axial stereocenter. DFT calculations and vibrational circular dichroism (VCD) suggest that β-fluoride elimination from an alkenyl copper intermediate likely proceeds through a *syn*-β-fluoride elimination pathway rather than an *anti*-elimination pathway. The effects of the C1-symmetric Josiphos-derived ligand on reactivity and enantioselectivity were investigated. Not only does this report showcase that alkenyl copper species (like their alkyl counterparts) can undergo β-fluoride elimination, but this elimination can be achieved in an enantioselective fashion.

Graphical Abstract

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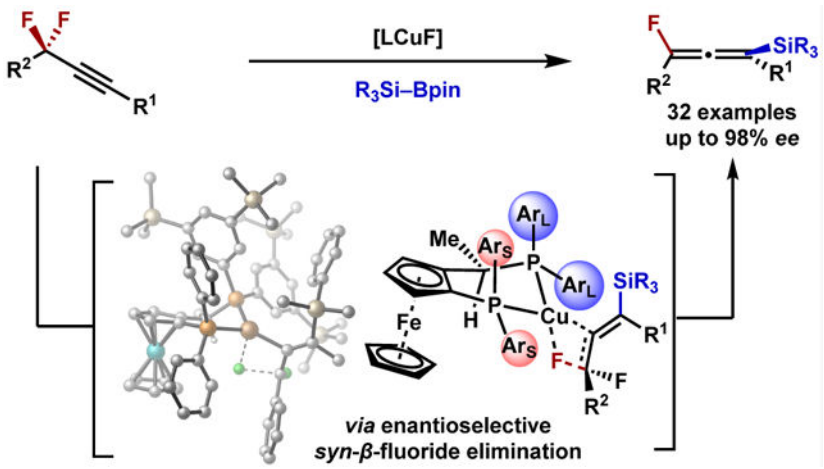
Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c05769.

Synthesis procedures, characterization data for all new compounds, additional optimization data, computational details, and Cartesian coordinates of all computed structures (PDF)

The authors declare no competing financial interest.



INTRODUCTION

The pursuit of synthetic methods to access structurally diverse allenes stems from their applications in both medicinal and materials chemistry as well as their ability to serve as a reactive functional group for further synthetic manipulations.[1,2] These cumulenes can exhibit axial chirality, and most of the naturally occurring allenic compounds that have been isolated are nonracemic.[1a-c] Although enantiopure bromoallenes have been discovered in nature (Scheme 1a) and axially chiral bromo-, chloro-, and iodoallenes have been synthesized, the corresponding axially chiral fluoroallenes are largely unknown.[3,4] Specifically, to the best of our knowledge, there is a single report where an enantioenriched tetrasubstituted, axially chiral monofluoroallene has been prepared, albeit in modest enantioselectivity.[4c] Due to a lack of general synthetic routes toward this chiral, fluorinated motif, their potential applications have remained unexplored.

An emerging route toward the catalytic synthesis of ACAs has been from prochiral substrates.[5] This strategy overcomes the requirement for a stoichiometric amount of a chiral auxiliary and/or enantioenriched substrates. Prochiral substrates that have been transformed into ACAs include propargylic electrophiles, 1,3-enynes, terminal alkynes, 1,3-dienes, racemic allenes, and vinyl triflates.[6] In the case of vinyl triflates, it was demonstrated that β-hydride elimination occurred in an enantioselective fashion, revealing a new mechanistic route for the synthesis of ACAs.[6f] Of the classes of ACAs (1,3-di-, tri-, and tetrasubstituted), tetrasubstituted ACAs remain difficult to synthesize in high enantiopurity.[7]

Moreover, the incorporation of a functional group directly attached to ACAs that permits further transformations has gained popularity as evidenced by recent reports of boryl and silyl substituted ACAs.[8,9] Access to tetrasubstituted, boryl, or silyl monofluoro ACAs would permit an array of further transformations that could generate quaternary, fluorine-containing stereocenters by way of axial-to-point chirality transfer.[3a,10]

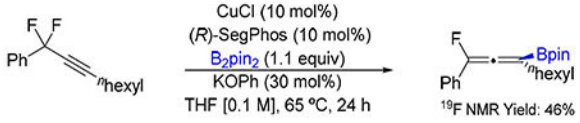
The development of defluorination methods of (poly)-fluorinated compounds has emerged as a complementary strategy to access complex, fluorine-functionalized motifs that have typically been accessed from nonfluorinated substrates.[11] Of the metals that catalyze such

defluorination reactions, copper has been shown to be exceptionally competent, as evidenced by the numerous reports of catalytic hydrodefluorinations, defluoroborylations, and defluorosilylations of fluoroarenes and fluoroolefins.[12] An emerging trend in this field is the enantioselective defluorination of allylic CF_3 or CF_2R groups, forging stereocenters adjacent to mono- and difluoroolefins (Scheme 1b).[13] Recently, a rare example of enantioselective defluorination via oxidative addition to a *gem*-difluoride has been reported as a method to generate products with a fluorine-containing stereogenic unit.[14] We envisioned that a mechanistically different approach to the desymmetrization of difluoromethylene groups, proceeding through an enantioselective β-fluoride elimination reaction, might be employed in the enantioselective synthesis of monofluoro ACAs (Scheme 1c).

To this end, we hypothesized that reaction of propargylic difluorides with a suitable chiral copper nucleophile would form an alkenyl copper species that could undergo an enantioselective β-fluoride elimination to generate tetrasubstituted monofluoro ACAs (Scheme 1c). Potential obstacles toward achieving this transformation included controlling both the regioselectivity[15] and enantioselectivity of the process, avoiding undesired reactivity of the alkenyl copper intermediate,[16] and preventing further silylation of the product.[17] Herein we demonstrate that β-fluoride elimination from an alkenyl copper species is possible and the discrimination of enantiotopic fluorides is a viable elementary process to achieve asymmetric synthesis of ACAs. DFT studies predict that this elimination proceeds through a *syn*-elimination pathway, which is in contrast to some studies of alkyl copper species that undergo β-fluoride elimination.[12b,g-i,13b,c,f,g]

RESULTS AND DISCUSSION

We began our investigation by determining if β-fluoride elimination was feasible from a vinyl copper intermediate. In the presence of a suitable base, the borylation of **1a** with B_2pin_2 generated the desired boryl monofluoroallene in 46% NMR yield (eq 1); however, attempts at isolating this product were



(1)

unsuccessful.[8b] We hypothesized that the corresponding silyl monofluoroallene of **1a** would be isolable and gratifyingly discovered that the silylation of **1a** with $PhMe_2SiBpin$ (**2**) led to **1b**. After a brief optimization of conditions, over 40 chiral ligands were examined for this transformation. Of the chiral ligands employed, only four gave the desired allene in greater than 20% ee.

Fortunately (*R,S*)-Josiphos afforded **1b** in a modest yield (71%) and promising enantioselectivity (20% ee). A series of Josiphos ligands were generated to evaluate their steric and electronic effects (see Supporting Information Tables S1 and S2) on the

reaction. Josiphos ligands containing aryl groups on both phosphorus atoms demonstrated good reactivity and enantioselectivity, specifically when the alkyldiarylphosphorus moiety possessed bulky 3,5-substituted arenes (Table 1, compare entries 2 and 3; Supporting Information Tables S2 and S3). However, once the 3,5-substituents became sterically too demanding, for example, with the TTB derivative, the reactivity dropped significantly (entry 5). Moreover, it appeared that steric rather than electronic factors played a decisive role in determining the enantioselectivity of the transformation (compare entries 3 and 8).

Further optimization led to simplified reaction conditions (Table 2). By lowering the temperature and changing the solvent, the enantiomeric excess of **1b** improved to 90%, but the overall conversion of **1a** dropped (entry 1). Increasing the amount of phenoxide base resulted in decoordination of the ligand, determined by ^{31}P NMR spectroscopy, and erosion of the ee of **1b**.[18] By use of an insoluble source of fluoride (CsF), an increase in the chemical yield of **1b** was achieved (83%, entry 2). Possible roles of CsF could be either trapping FBpin[19] and/or releasing CsOAr from ArOBpin.[20] Fortunately, the transformation proceeded with CsF as the sole base, removing the chance of phosphine decoordination due to excess phenoxide.[21] The reaction proceeded well in nonpolar, low coordinating solvents (entries 4–7), and the removal of MeCN led to in an increase in catalytic activity (entries 8, 9). Switching to $CuOTf\cdot{}^{1}/_{2}C_6H_6$ as the copper source afforded the desired allene in almost quantitative yield (entry 10).

With the optimal conditions established, an alternative synthetic route employing readily available material to prepare propargylic difluorides was developed (Scheme 2). The decarboxylative bromination of difluorocarboxylic acids and the copper-catalyzed Sonogashira cross-coupling of terminal alkynes with difluorobenzyl bromides afforded difluoroalkynes, which were subjected to defluorosilylation under the optimized conditions. A range of functional groups were tolerated in the copper catalyzed transformation, affording the desired allenes **1–24b** in high yields (83–98%) and in good enantioselectivities (82–98%) after isolation (Table 3). Notably, alkynes (**19b**), alkenes (**20b**), enynes (**24b**), aldehydes (**8b**), ketones (**9b**), propargylic acetates (**23b**) as well as alkyl and aryl halides (**3b** and **6b**) were tolerated. Coordinating heterocycles (**14–16b**, **18b**, and **25b**), amides (**7b**, **11–13b**), and nitriles (**5b** and **10b**) also did not hamper catalysis. Although changing the electronics of the aryl ring slightly decreased the enantiomeric excess of the reaction (**1–6b**), increasing the steric bulk of the aryl group was well tolerated (**25b**). Although many functional groups were tolerated, the reaction proved more sensitive to alterations of the substituents directly attached to the allene, which could affect the barrier of silylation of the alkyne (**26–27b**) or impact the C—F bond strength (**28–29b**).

To explore the scalability of this method, **1b** was synthesized on a 6 mmol scale without a significant loss in enantioselectivity or chemical yield. It was discovered that other silylboranes could be utilized for this transformation when (*R,S*)-3,5-Trip-Josiphos was employed as the ligand (**1b-BnMe$_2$Si**, **1b-CyMe$_2$Si**, and **1b-Et$_3$Si**). These allenyl silanes were synthesized on gram scales with comparable yields and enantioselectivities to **1b-PhMe$_2$Si**.

Determination of the absolute configuration of allene **10b** was achieved using vibrational circular dichroism (VCD).[22] After a careful conformational search (see Supporting Information for details) at four levels of theory, B3LYP/6-31G(d), B3PW91/6-31G(d), B3LYP/cc-pVTZ, and B3PW91/cc-pVTZ,[23] the resulting conformers were Boltzmann averaged and plotted with a line width of 5 cm^{-1} to produce the final theoretical spectra. The IR and VCD spectra were then frequency scaled[23] for comparison to the experimental data. Calculations at all four levels of theory matched well, proving the absolute configuration of **10b** to be *S*. Of the four methods employed, the best agreement with experimental data was from the B3PW91/cc-pVTZ level. The comparison of experimental and theoretical spectra was quantified[24] using BioTools (Jupiter, FL) CompareVOA software, with high neighborhood similarity for IR (90.4) and VCD (69.6), ESI (enantiomeric similarity index) for VCD (62.9), and a confidence level of 99%. Of particular note was the asymmetric allene C—C—C stretch observed at 1933 cm^{-1}, which was one of many closely correlated bands between experiment and theory. In addition to allene **10b**, the absolute configuration of **1b-Et$_3$Si, 12b, 17b**, and **25b** were also determined to be S by VCD analysis (see Supporting Information).

On the basis of previous reports regarding CuF[12c,e,16a,21,25] and copper silyl species,[15b,f,17d,26] we propose the following mechanism for the copper-catalyzed reaction (Figure 1). First, a complex between Josiphos and [CuOTf] undergoes salt metathesis with CsF to generate JosiphosCuF (**Cu1**).[16a,21,25d] σ-Bond metathesis with PhMe$_2$SiBpin (**2**) generates JosiphosCuSiMe$_2$Ph (**Cu2**) and releases FBpin.[12c-e] Subsequent coordination and silylation of the triple bond generates an alkenyl Cu species (**Cu3**).[15a,e,27] A β-fluoride elimination[12g] regenerates **Cu1**, which is trapped by FBpin,[19,28] **2**[15c] or decomposes the formed allenylsilane (**c**). As FBpin is more Lewis acidic than B$_2$pin$_2$,[28] the same is likely true with **2**. By using a judicious amount of CsF and a nonpolar solvent, we propose that the precipitation of Cs[F$_2$Bpin][19,20] drives this reaction forward. ^{1}H, ^{19}F, and ^{11}B NMR studies have identified **Cu1**, **Cu2**, LCuF$_2$Bpin, as well as LCuOH and confirmed the generation of **Cu2** from both **Cu1** and LCuF$_2$Bpin (see Supporting Information section 7). **Cu2** was also shown to react with alkyne **1a**, generating both allene **1b** and FBpin. It appears that LCuF$_2$Bpin acts as a reservoir of Cu^{I}F, and under catalytic conditions, a monomeric or dimeric CuF was not observed. Over the course of the reaction only **Cu2**, LCuF$_2$Bpin, and LCuOH were observed, which converged to **Cu2** after the alkyne has been consumed (see Supporting Information section 7). Although the exact structure of **Cu1** is unknown, the speciation of **Cu1** appears to be both solvent and temperature dependent, in which the former has been observed for other Josiphos copper halide complexes (see Supporting Information section 7).[29] On the basis of our experiments, we propose that the silylation of the alkyne and the β-fluoride elimination reactions are the rate- and selectivity-determining steps, respectively. Using (*R*,*S*)-3,5-TES-JosiphosCuF$_2$Bpin as a catalyst, the desired allene **1b** was obtained in a similar yield and enantiomeric excess, demonstrating its catalytic competence (see Supporting Information section 7).

Density functional theory (DFT) calculations were performed to investigate the reaction mechanism and origin of enantioselectivity of this Cu-catalyzed asymmetric silylation of propargylic difluorides. The DFT calculations were performed at the M06/

SDD(Cu,Fe,Cs)-6-311+G(d,p)/SMD-(toluene)//B3LYP-D3(zero)/SDD(Cu,Fe,Cs)-6-31G(d) level of theory using difluoroalkyne **27a** and $PhMe_2SiBpin$ (**2**) as model substrates. The (*R*,*S*)-3,5-TMS-Josiphos ligand was used in the DFT calculations for simplicity because the use of this ligand in the ligand screening provided only slightly lower ee than using (*R*,*S*)-3,5-TES-Josiphos (Table 1, entries 6 and 7). On the basis of the proposed catalytic cycle, the computed reaction energy profile is shown in Figure 2. The association of FBpin to monomeric LCuF (**26**) to form a heterodimer (**29**) is exergonic by 4.0 kcal/mol, suggesting that the more stable complex **29** can be an off-cycle reservoir of $Cu^{I}F$. Although the dimerization of LCuF is exergonic by 7.3 kcal/mol, its formation is expected to be less favorable than forming **29** due to the low concentrations of LCuF under catalytic conditions (see Figure S1 for detailed discussions about the equilibrium of **26**, **29**, and the dimer of LCuF).

The σ-bond metathesis between monomeric LCuF (**26**) and $PhMe_2SiBpin$[30] (**2**) takes place via a four-membered cyclic transition state (**TS-1**) to form silyl copper intermediate **30** and FBpin. This step requires a low activation barrier of 6.7 kcal/mol with respect to **26** and is exergonic by 24.7 kcal/mol. Migratory insertion of alkyne **27a** into the silyl copper (**TS-2**) gives alkenyl copper species **31**. This migratory insertion is highly regioselective for the formation of Cu—C bond at the alkyne terminus adjacent to the difluoromethylene. The transition state leading to the other regioisomer, *TS-2′*, is 10.9 kcal/mol higher in energy than **TS-2**. The high level of regioselectivity is due to steric repulsions between the silyl and the more hindered alkyne terminus (C1) in **TS-2′** as well as inductive effects of the difluoro substituents that stabilize the building of negative charge at C1 in **TS-2**. From **31**, both *syn*[12g-i] and *anti*[13b] β-fluoride elimination pathways were calculated. The *syn*-elimination of either of the two diastereotopic β-F in **31** (via **TS-3** and **TS-4**) involves a four-membered cyclic transition state, while the *anti*-β-fluoride elimination is facilitated by CsF as a Lewis acid (via **TS-5** and **TS-6**). The FBPin-facilitated *anti*-elimination was also computed and is also less favorable than the *syn*-elimination (see Figure S3). The *syn*-elimination pathways require much lower barriers than the *anti*-elimination, which is in contrast to a computational study by Hoveyda and Torker that suggested the β-fluoride elimination from alkyl copper species favors the *anti*-pathway due to Lewis acid (i.e., Na^+) coordination to the F^- leaving group and the Bpin group on the substrate.[13b] In the present study, the lack of such chelating Lewis-acid coordination in the *anti*-pathway, the weaker Lewis acidity of CsF, and the strain release effect that alleviates steric repulsions between the $SiMe_2Ph$ group and the Cu in the *syn*-elimination transition state changed the reaction mechanism to favor the *syn*-elimination.[31]

Among the three key elementary steps in the catalytic cycle, the alkyne migratory insertion (**TS-2**) has the highest activation free energy ($\Delta G^{\ddagger}$ = 19.9 kcal/mol with respect to **30**). This finding is consistent with our experimental results that suggest this step being the rate-determining step (*vide supra*). The enantioselectivity-determining step is the *syn*-β-fluoride elimination. **TS-3**, which leads to the (*S*)-enantiomer of the monofluoroallene product, is 1.9 kcal/mol more stable than **TS-4** that leads to the (*R*)-enantiomer. The predicted enantioselectivity is consistent with the absolute configuration of the product identified by the VCD analysis.

Next, we performed a detailed analysis to investigate the effects of the Josiphos ligand on the reactivity and enantioselectivity of the β-fluoride elimination. Because of the conformational flexibility of the (*R*,*S*)-3,5-TMS-Josiphos ligand,[32] a careful conformational search was performed for all intermediates and transition states in the catalytic cycle. These calculations revealed at least four different conformers of the 3,5-TMS-Josiphos-supported copper complexes. The two most stable and catalytically active ligand conformations **A** and **B** are shown in Table 4 (see Figures S4-S6 for all possible ligand conformations). Ligand conformation **A** involves a twist-boat-type six-membered ring and is more favorable in the copper fluoride (**26**), the σ-bond metathesis transition state (**TS-1**), and the silyl copper intermediate (**30**). In more sterically encumbered structures, including the migratory insertion transition state (**TS-2**), alkenyl copper (**31**), and the β-fluoride elimination transition states (**TS-3** and **TS-4**), ligand conformation **B** becomes more favorable. This ligand conformation involves a half-chair type six-membered ring, which points the Ar and Ph groups in quadrants I and II away from the Cu center. As such, the bulky $SiMe_2Ph$ group is placed between these unoccupied quadrants to minimize steric repulsions between the ligand and the $SiMe_2Ph$ group on the substrate.

Ligand conformation **B** not only stabilizes the silylalkenyl copper species but also plays a significant role in controlling the enantioselectivity of the β-fluoride elimination. The *P*-phenyl group in quadrant III and the *P*-3,5-TMS-phenyl group in quadrant IV point toward the Cu center and thus occupy these quadrants. The larger size of the 3,5-TMS-phenyl compared to phenyl indicates that the ligand–substrate repulsions in quadrant IV would be more pronounced than those in quadrant III. Indeed, quadrant diagrams of the β-fluoride elimination transition states (Figure 3) support this hypothesis. In the less favorable transition state **TS-4**, the phenyl group on the substrate is located in the more occupied quadrant IV, leading to steric repulsion with a TMS group on the ligand. By contrast, in the more favorable β-fluoride elimination transition state **TS-3**, the much smaller fluoro group is located in quadrant IV, and thus the ligand–substrate steric repulsions are diminished. Next, we performed energy decomposition analysis (EDA)[33] calculations to quantitatively analyze the ligand–substrate noncovalent interactions in **TS-3** and **TS-4** (see Supporting Information for computational details). The EDA calculations revealed that the dominant factor controlling the enantioselectivity is the Pauli repulsion (*i.e.*, steric repulsion) between the (*R*,*S*)-3,5-TMS-Josiphos ligand and the substrate. The Pauli repulsion energy (ΔE_{Pauli}) in **TS-4** is 1.7 kcal/mol higher than that in **TS-3** and thus destabilizes the former transition state.

Finally, we calculated the enantioselectivity-determining *syn*-β-F elimination transition states of the reaction of the same substrate (**27a**) catalyzed by a SegPhos-supported Cu complex. The computed enantioselectivity is diminished ($\Delta\Delta G^{\ddagger}$ = 0.2 kcal/mol, Figure S7), indicating the C2-symmetric SegPhos ligand is not effective for asymmetric induction. This prediction is consistent with the low ee of 12% obtained experimentally at 65°C with 5 mol % CuCl, 40 mol % sodium phenoxide, and 6 mol % SegPhos ligand. Taken together, these ligand effect analyses revealed the unique roles of the conformationally flexible C1-symmetric Josiphos ligand, where it lowers the activation barrier for the rate-determining alkyne migratory insertion step and improves the enantioselectivity of the β-F elimination.

CONCLUSION

The first copper-catalyzed, enantioselective β-fluoride elimination has been achieved. The resulting monofluoro ACAs represent the first examples of fluorine-containing, chiral tetrasubtituted allenes.[34] It is expected that such a motif will find value in pharmaceutical and agrochemical chemistry in addition to being a valuable building block for the generation of more elaborate fluorine-containing stereocenters. DFT calculations of the reaction mechanisms predicted that this elimination occurs in a *syn*-fashion, which is promoted by strain release of the *Z*-β-silylalkenyl copper intermediate. The unique roles of the C1-symmetric Josiphos-derived ligand in promoting the reactivity and enantioselectivity were investigated. It is believed that lessons learned from this desymmetrization could be leveraged for the creation of other fluorine-containing stereocenters via defluorination pathways.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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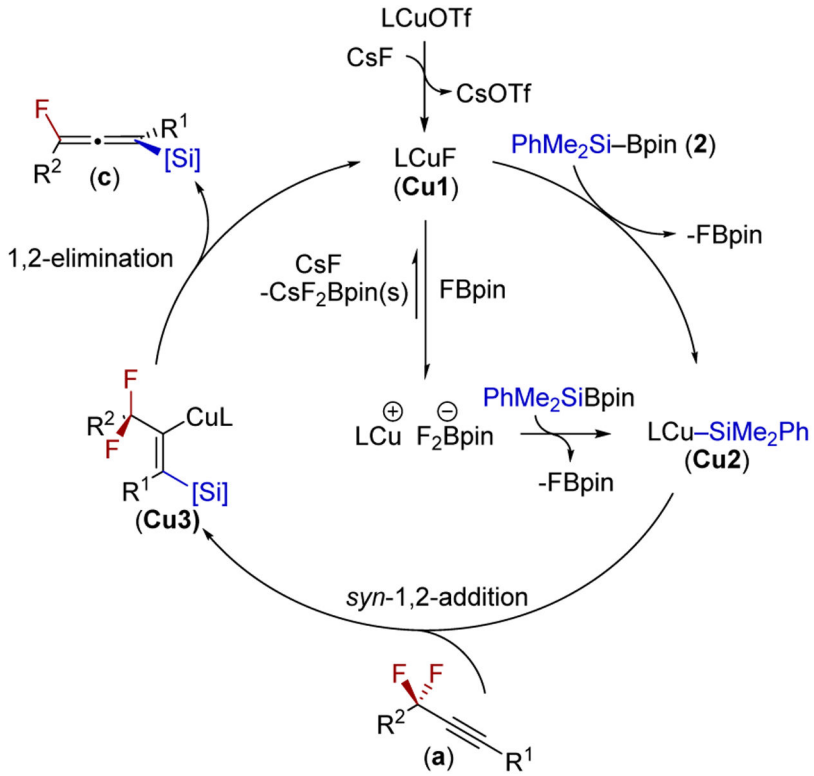


Figure 1.
Proposed catalytic cycle.

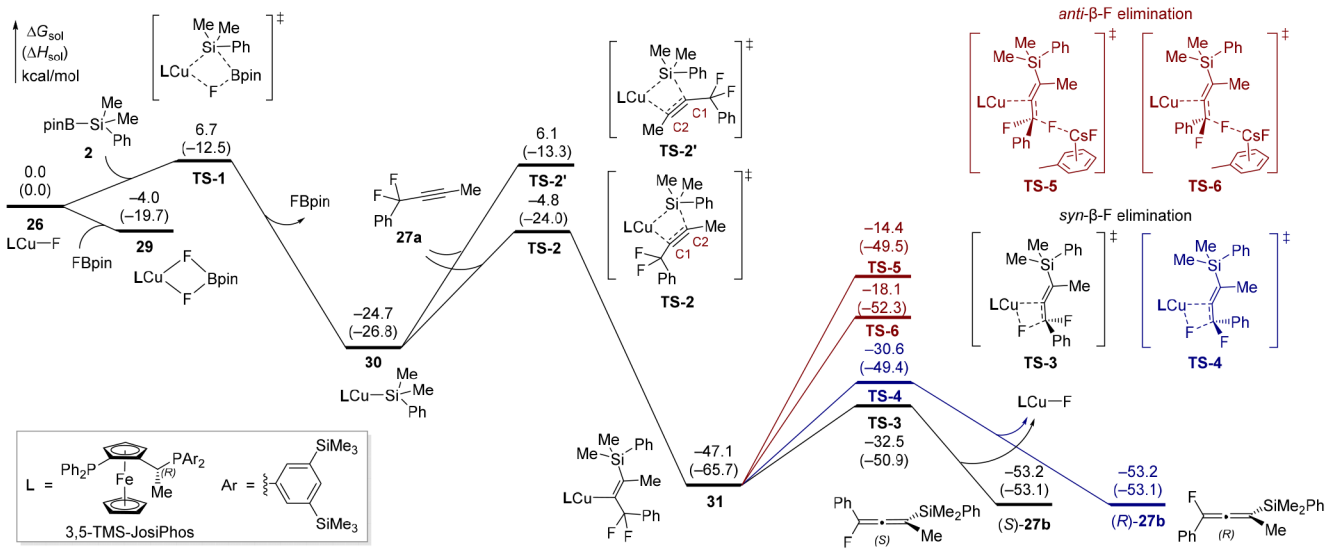


Figure 2.

Computed reaction energy profiles of the Cu-catalyzed silylation and asymmetric β-fluoride elimination. Gibbs free energies and enthalpies (in kcal/mol) are with respect to the monomeric copper fluoride **26**.

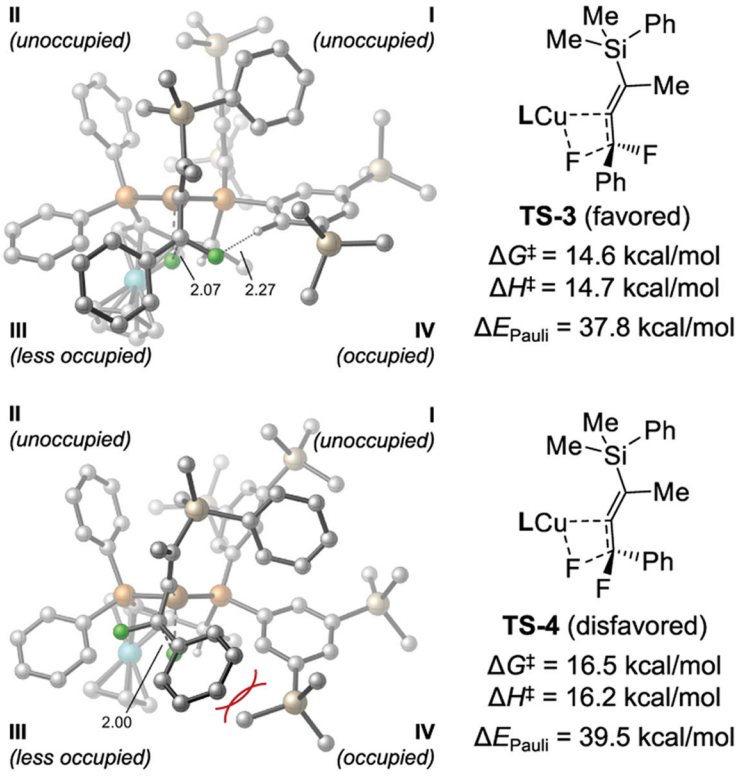
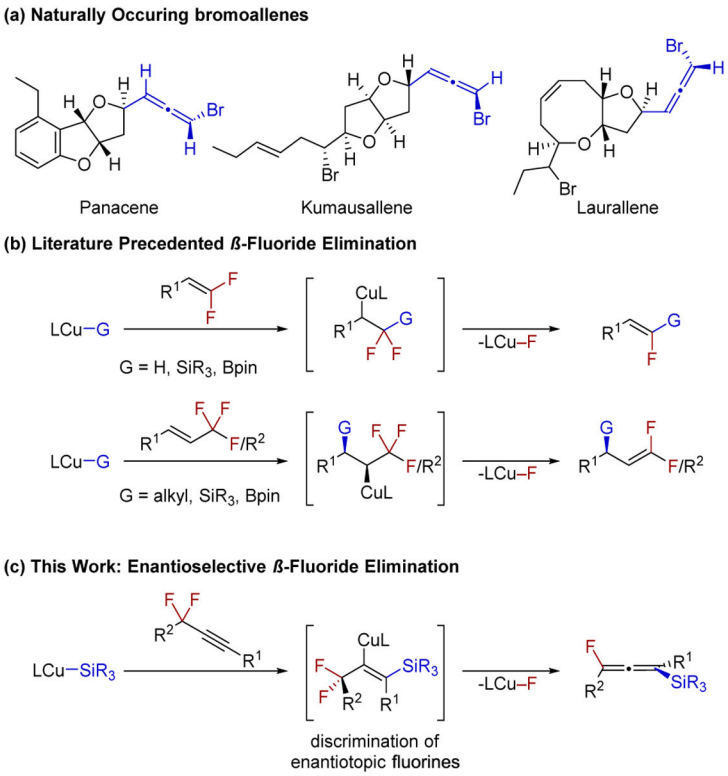


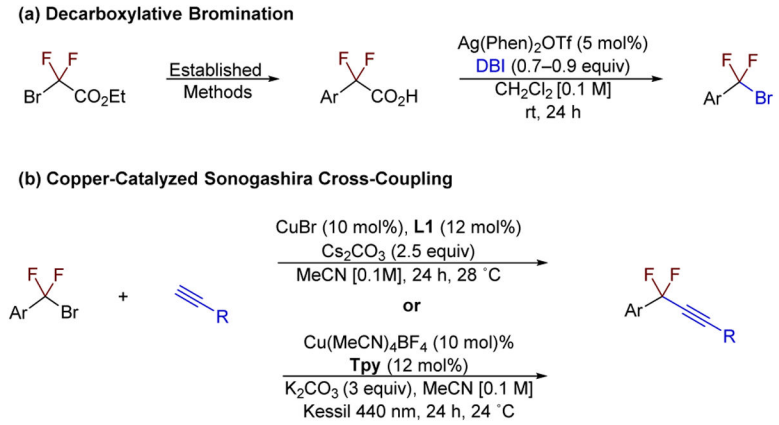
Figure 3.

Origin of enantioselectivity in *syn*-β-fluoride elimination. Most hydrogen atoms are omitted for clarity. Gibbs free energies and enthalpies are with respect to **31**. ΔE_{Pauli} is the Pauli repulsion energy between the substrate and the Josiphos ligand from EDA calculations.



Scheme 1.

Allenyl Halide Natural Products and Synthesis of Monofluoro ACAs *via* Enantioselective *β*-Fluoride Elimination

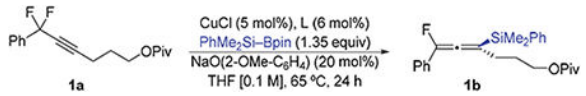


Scheme 2.

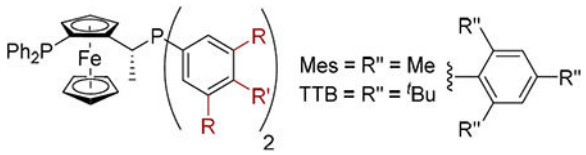
Improved Synthesis of Propargylic Difluorides

Table 1.

Structural Effect of Josiphos on Transformation[a]



entry	R; R'	yield (SM %)[b]	*ee* (%)[c]
1	Me; H	59% (23)	45
2	Me; OMe	31% (14)	44
3	^{t}Bu; OMe	41% (<1)	70
4	Mes; H	58% (38)	75
5	TTB; H	3% (79)	nd
6	TMS; H	73% (<1)	75
7	TES; H	66% (<1)	83
8	CF_3; H	43% (<2)	71
9	^{i}Pr$^{(F7)}$; H	44% (43)	86



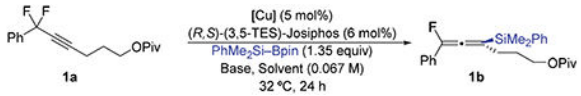
[a]Standard conditions: **1a** (0.10 mmol, 1.0 equiv), **2** (0.135 mmol, 1.35 equiv), CuCl (5 mol %), L (6 mol %), THF (1.0 mL), 65 °C, 24 h.

[b]Yield was determined by ^{19}F NMR of crude reaction, using PhF as an internal standard.

[c]Determined by HPLC with a chiral stationary phase.

Table 2.

Reaction Optimization[a]



entry	Cu	base (mol %)	solvent	yield (SM %)[b]	ee (%)[c]
1	$Cu(MeCN)_4BF_4$	A (20)	PhMe	50% (49)	90
2	"	A (20), CsF (100)	"	83% (13)	90
3	"	CsF (150)	"	75% (11)	91
4	$Cu(MeCN)_4BF_4$	"	THF	39% (48)	74
5	"	"	dioxane	65% (20)	91
6	"	"	cyclohexane	50% (31)	87
7	"	"	MTBE	75% (10)	92
8	"[d]	"	"	74% (<1)	91
9	$Cu(MeCN)_4OTf$[d]	"	"	82% (4)	90
10	$CuOTf \cdot {}^1/_2C_6H_6$	CsF (160)		98% (–)	90

[a]Standard conditions: **1a** (0.10 mmol, 1.0 equiv), **2** (0.135 mmol, 1.35 equiv), [Cu] (5 mol %), L (6 mol %), solvent (1.5 mL), 32 °C, 24 h. A = $NaO(2\text{-}OMeC_6H_4)$.

[b]Yield was determined by ^{19}F NMR of crude reaction, using PhF as an internal standard.

[c]Determined by HPLC with a chiral stationary phase.

[d]MeCN removed before reaction.

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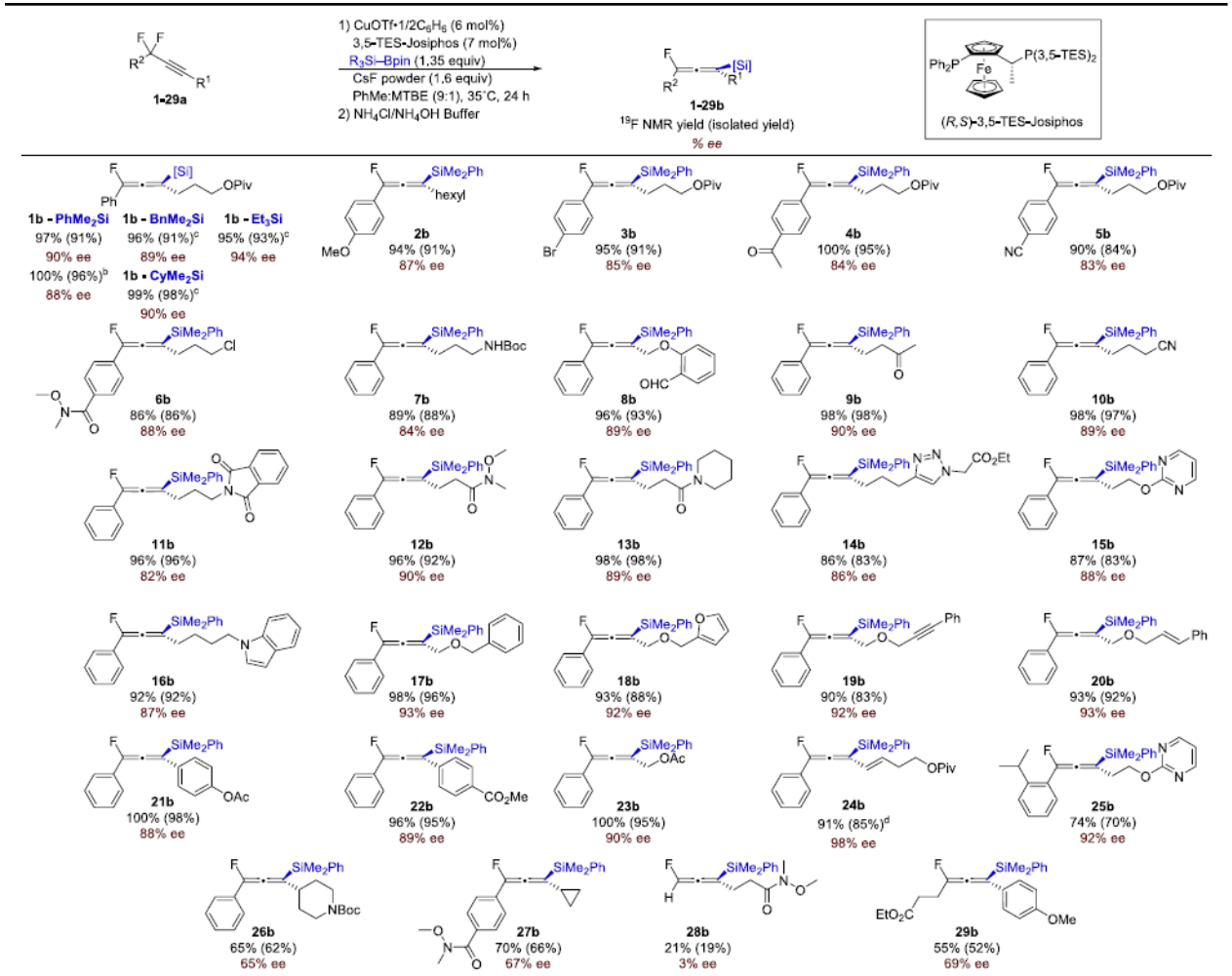
Table 3.

Scope of Asymmetric β-Fluoride Elimination[a]



[a]Standard conditions: **1–25a** (0.20 mmol, 1.0 equiv), 2 (0.27 mmol, 1.35 equiv), CuOTf·½C6H6 (6 mol %), L (7 mol %), CsF (1.6–1.8 equiv), 9:1 PhMe:MTBE or MTBE (3.0 mL), 35–45 °C, 24 h. Reported yields are of isolated allene. Enantiomeric excess was determined by HPLC with a chiral stationary phase.

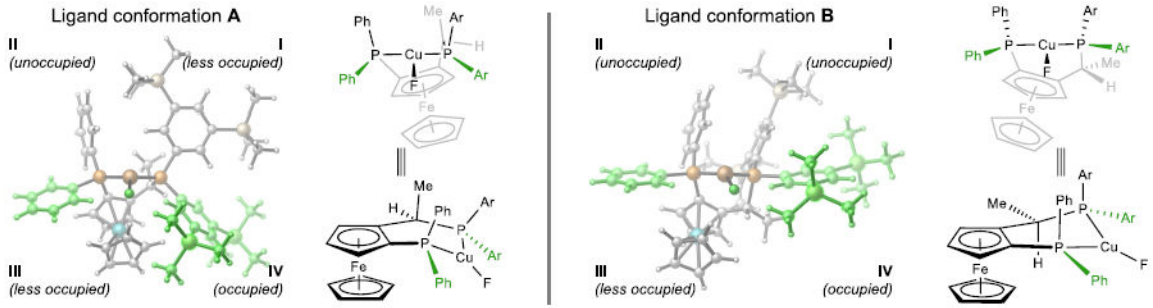
[b] **1a** (6.0 mmol), CsF(25%)–CaF_2 (1.6 equiv), 30 h.

[c] **1a** (2.5–3.0 mmol), $R_3SiBpin$ (1.35–1.45 equiv), Cu (8–9 mol %), 3,5-Triplosiphos (9–10 mol %), CsF(25%)–CaF_2 (1.8–2.5 equiv), MTBE, 28–45°C, 30–48 h.

[d] $NaO(2\text{-}OMeC_6H_4)$ (30 mol %), CsF (1.0 equiv), PhMe, 27 °C.

Table 4.

Relative Free Energies of Conformers of (*R,S*)-3,5-TMS-Josiphos-Supported Copper Complexes and Transition States[a]



						syn-**β**-fluoride elimination	
ligand conformation	**LCuF (26)**	**σ-bond metathesis (TS-1)**	**silyl copper (30)**	**migratory insertion (TS-2)**	**alkenyl copper (31)**	**TS-3**	**TS-4**
A	**0.0**	**6.7**	**−24.7**	2.9	−42.8	−26.7	−28.4
B	4.8	10.8	−23.5	**−4.8**	**−47.1**	**−32.5**	**−30.6**

[a]All Gibbs free energies are in kcal/mol with respect to the monomeric copper fluoride **26**. Bold numbers indicate the favorable ligand conformation.