

ChemComm

Chemical Communications

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: E. Nelson, R. Bisoyi and C. Wolf, *Chem. Commun.*, 2026, DOI: 10.1039/D6CC02743A.



This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.

COMMUNICATION

Palladium-catalyzed Asymmetric Carbofluorination of *gem*-Difluorostyrenes with Cesium Fluoride and Allylic Acetates

Eryn Nelson, Rajesh K. Bisoyi, and Christian Wolf*

Received 00th January 20xx,
Accepted 00th January 20xx

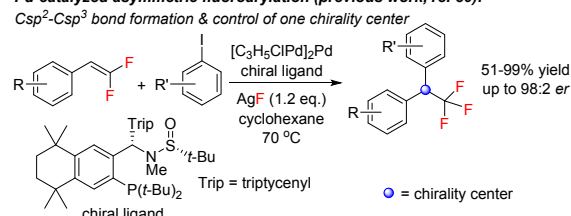
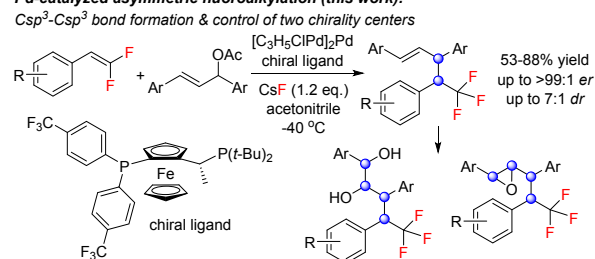
DOI: 10.1039/x0xx00000x

Palladium-catalyzed asymmetric carbofluorination of difluorostyrenes with allylic acetates and CsF gives synthetically versatile products with a trifluoromethyl, a vinyl and two different aryl groups directly attached to a scaffold exhibiting vicinal chirality centers in good yields and with high stereoselectivities. The synthetic usefulness is highlighted with the incorporation of additional functionalities and the formation of products displaying four adjacent chirality centers, a rarely reported accomplishment.

Chiral fluorinated organic compounds have found numerous applications in the last 20 years and are nowadays routinely included in drug and agrochemical development projects due to their unique pharmacological and physicochemical properties which often compare favorably with those of nonfluorinated analogs.¹⁻³ The general importance and the popularity of chiral organofluorines in many academic and industrial laboratories continue to inspire the search for catalytic asymmetric procedures that address the unwavering call for efficient synthetic access to new scaffolds.^{4,5} This is typically achieved by stereoselective carbon-carbon bond construction with commercially available fluorinated building blocks or by the introduction of a carbon-fluorine bond into an existing structure with the help of a fluorinating agent.⁶⁻¹³ Carbofluorination strategies that integrate both transformations into a single reaction and thus allow concomitant C-C and C-F bond formation have also surfaced although asymmetric methods have remained scarce. In 2014, Toste and coworkers showed an early example of a palladium-catalyzed asymmetric fluoroarylation reaction with styrenes carrying a directing group.¹⁴ Since then, intra- and intermolecular variations giving practical access to a variety of fluoroarylation products with excellent regiocontrol and high enantioselectivities have been reported by the same group^{15,16} and others.^{17,18}

Despite these important advances, considerable challenges and opportunities to uncover new chemical reaction space, in particular with regard to catalytic asymmetric fluorinative alkylations, remain. Regioselective carbofluorination of *gem*-difluorostyrenes has received considerable attention,¹⁹ probably at least in part because it can produce a trifluoromethyl group which is undoubtedly among the most prominent organofluorine moieties in the pharmaceutical development realm.^{20,21} Several carbofluorination reactions with

difluorostyrenes have been reported to date but they typically afford racemic products or proceed with marginal enantioselectivity, suggesting that this would not be possible by asymmetric palladium catalysis.²²⁻²⁹

Pd-catalyzed asymmetric fluoroarylation (previous work, ref 30):**Pd-catalyzed asymmetric fluoroalkylation (this work):**

Scheme 1. Pd-catalyzed C-F and C-C bond formation with difluorostyrenes.

A noteworthy exception is Li's and Zhang's enantioselective palladium(sulfonamide phosphine) catalyzed fluoroarylation which utilizes aryl iodides and stoichiometric amounts of silver fluoride in cyclohexane at 70 °C (Scheme 1).³⁰ Two years ago, our laboratory demonstrated regioconvergent substitution and enantioselective asymmetric alkylation of allylic fluorides,³¹ which was elegantly extended by Companyó's group to organocatalytic reactions with difluorostyrenes.³² This protocol affords high stereoselectivities and gives moderate to good yields but requires a threefold molar excess of the precious difluoroalkene compound. We envisioned that atom-economic asymmetric fluorinative alkylations of *gem*-difluorostyrenes should be possible if mild homogeneous reaction conditions compatible with nucleophilic fluoride addition and subsequent transition metal catalyzed C-C bond construction could be identified. Herein, we introduce a palladium catalyzed allylic alkylation procedure that achieves this goal and generates two contiguous chirality centers at

^a Department of Chemistry, Georgetown University, Washington, D.C. 20057, USA.
Email: cw27@georgetown.edu

[†] Electronic Supplementary Information available here:
See DOI: 10.1039/x0xx00000x



once with excellent enantioselectivity and good diastereoselectivity by using cesium fluoride in acetonitrile at low temperatures.

Table 1. Optimization of the asymmetric fluoroalkylation of *gem*-difluorostyrenes.^[a]

Reaction scheme showing the asymmetric fluoroalkylation of *gem*-difluorostyrene (**1a**) with 1,3-diphenylallyl acetate (**2a**) to form product **3aa** and by-product **4**. Conditions: [allylPdCl]₂ (2.5%), ligand (5%), CsF (1.2 eq.), 18-crown-6 (1.2 eq.), MeCN, 25 °C, 48 h.

Chemical structures of ligands L1-L17 are shown below the reaction scheme. L1-L10 are ferrocenyl phosphine ligands with various substituents. L11-L17 are ferrocenyl phosphine ligands with different substituents, including trifluoromethyl groups.

Entry	Ligand	Conversion ^b	3aa : 4 ^c	<i>dr</i> ^c	<i>ee</i> ^d
1	L1	100%	5:1	2.6:1	92%
2	L2	100%	2:1	4.9:1	n.d.
3 ^e	L3	67%	2:1	1.8:1	>99%
4 ^e	L4	66%	3:1	2.2:1	95%
5	L5	100%	3:1	2.0:1	n.d.
6	L6	100%	1:1	2.9:1	n.d.
7	L7	77%	1:1	1.5:1	n.d.
8	L8	89%	1:3	2.7:1	n.d.
9	L9	89%	1:1	2.6:1	n.d.
10	L10	100%	3:1	3.4:1	n.d.
11 ^f	L11	100%	10:1	3.0:1	n.d.
12	L12	100%	5:1	2.7:1	n.d.
13 ^g	L13	100%	12:1	4.4:1	80%
14 ^g	L14	100%	6:1	1.5:1	n.d.
15 ^g	L15	79%	1:1	3.0:1	n.d.
16 ^g	L16	100%	1:7	3.7:1	n.d.
17 ^g	L17	100%	24:1	3.5:1	n.d.
18 ^g	L17	100%	16:1	4.3:1	91%

[a] Reaction conditions: ligand (5 mol%), [allylPdCl]₂ (2.5 mol%), **1a** (0.15 mmol), **2a** (0.3 mmol), CsF (0.18 mmol), and 18-crown-6 (0.18 mmol) in 1.0 mL of acetonitrile at 25 °C. [b] Conversion of **1a** determined by ¹⁹F NMR spectroscopy of the crude reaction. [c] Determined by ¹⁹F NMR spectroscopy. [d] Determined by chiral HPLC using Chiralpak AD-H. [e] Reaction was run in 1.0 mL dichloromethane. [f] Reaction was run at -40 °C. [g] Reaction was run for 24 h. n.d. = not determined.

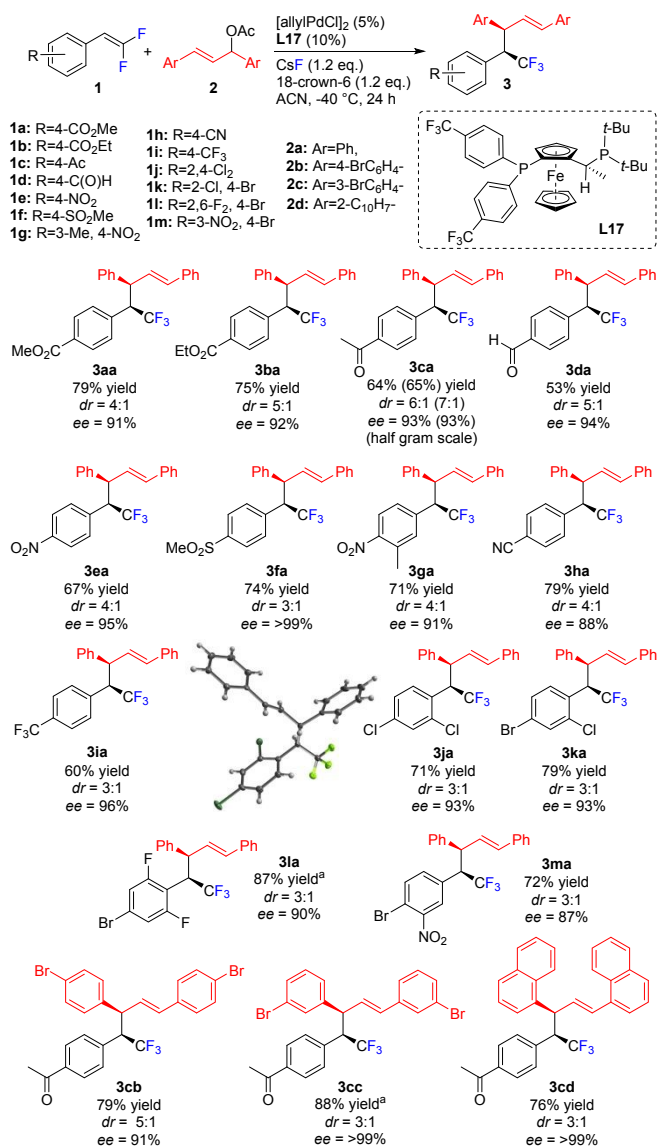
We began our search for an efficient asymmetric fluoroalkylation protocol by screening the reaction between *gem*-difluorostyrene, **1a**, and 1,3-diphenylallyl acetate, **2a**, in the presence of 2.5 mol% of [allylPdCl]₂, 5% (*R*)-BINAP (**L1**), CsF, and 18-crown-6 at 25 °C (Table 1, entry 1). We were pleased to see that the presence of the crown ether allowed efficient fluoride

addition at room temperature, and NMR and chiral HPLC analysis revealed full consumption of **1a** and formation of the desired product **3aa** in 92% *ee* and 2.6:1 *dr*. Screening of various solvents showed that the highest conversions are achieved with polar aprotic solvents such as acetonitrile, acetone, EtOAc, benzonitrile, and DMF, which likely aid in the stabilization of the intermediate carbanion formed *in situ* upon reversible fluoride addition to the difluoroalkene (see SI).²⁴ The best results were obtained using acetonitrile as solvent and we then continued with screening a large group of ligands under these conditions to further improve the diastereoselectivity and yield, which was compromised by the formation of by-product **4**. Unfortunately, the amount of **4** increased when we applied **L2-L10** in our protocol (Table 1, entries 2-10). However, we noticed that the palladium catalysis is accelerated by Segphos and bis(phosphino)ferrocene ligands which allowed us to decrease the temperature to -40 °C while the reactions were typically still complete within 24 hours (entries 11-18). The formation of **4** was most successfully suppressed when we employed ligands **L11**, **L13**, and **L17** which we attribute to a faster consumption of the fluorinated carbanion intermediate in the successive C-C bond forming step. Ultimately, we were able to obtain the highest yields and stereoselectivities using ligand **L17** (entry 18). Attempts to further improve the diastereoselectivity at -78 °C were unsuccessful and resulted in increased formation of by-product **4**. The presence of one equivalent of the crown ether in the final protocol proved important as we observed incomplete conversion and significantly increased formation of **4** in its absence.

With an optimized procedure in hand, we continued with the evaluation of the substrate scope. We first screened a variety of *gem*-difluorostyrenes **1a-m** with 1,3-diphenylallyl acetate **2a** (Scheme 2). As expected, **3aa** was isolated in 79% yield, 91% *ee* and 4:1 *dr*. The presence of other ester, ketone and aldehyde functions is perfectly tolerated and **3ba**, **3ca** and **3da** were produced in 92-94% *ee* and up to 6:1 *dr*. Similar results were obtained with nitro, nitrile, sulfone and methyl derivatives, giving **3ea**, **3fa**, **3ga** and **3ha** in 67-79% yield and with good diastereoselectivity and excellent enantioselectivity. We noticed that the rate of fluoride addition to the difluorostyrene was strongly influenced by the electron-withdrawing strength of its aromatic substituents, as evidenced by an increase in the formation of by-product **4** and overalkylation observed with the *gem*-difluorostyrenes **1e** and **1f**. However, optimal yields and excellent *ee*'s of **3da**, **3ea**, **3fa**, **3ga** and **3ma** could still be obtained with slow addition of the difluorostyrene, leading us to believe that the subsequent allylic alkylation is the rate-limiting step in this case. Furthermore, we found that the reaction is compatible with the placement of various halides, a trifluoromethyl group as well as combinations of several of the above-mentioned functionalities in the *ortho*-, *meta*- or *para*-positions in difluorostyrene, and **3ia-3ma** were formed with the same protocol in 60-87% yield and comparable *ee*'s and *dr*'s. It is noteworthy that fluoride addition under these conditions did not occur with substrates lacking an electron-withdrawing group, which is consistent with previous findings.²⁴ We were also able to expand the reaction scope by including



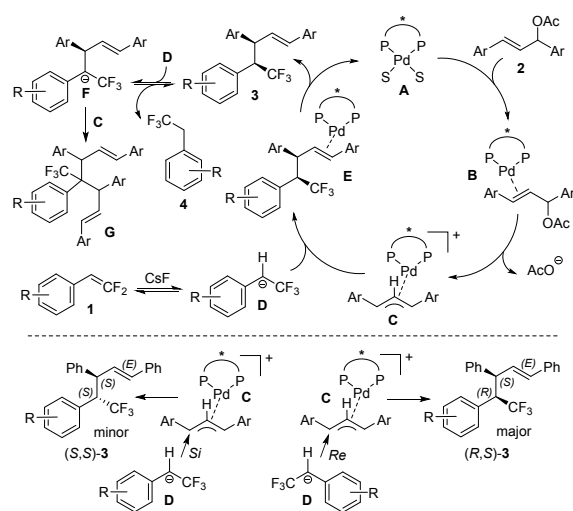
various substituted allylic acetates **2b-c**, producing **3cb**, **3cc**, and **3cd** in 76–88% yield, 91–99% *ee*, and up to 5:1 *dr* (Scheme 2). A single crystal was obtained by slow evaporation of a solution containing **3ja** in dichloromethane and crystallographic analysis revealed (3*S*,4*R*)-configuration, thus providing important insights into the sense of asymmetric induction provided by the palladium catalyst derived from **L17**.



Scheme 2. Reaction scope. See SI for details. ^a48 h. The absolute configuration of **3ja** was determined by X-ray analysis. The stereochemistry of all other products is assigned by analogy.

Literature reports and our own findings are in agreement with the mechanism of the asymmetric carbofluorination shown in Scheme 3.^{33–36} Coordination of the allylic acetate **2** to the palladium catalyst **A** gives species **B** which undergoes oxidative addition to form the η³-allyl palladium complex **C**. Fluoride addition to the difluorostyrene **1** affords nucleophile **D** which then attacks **C** to form the alkyl-alkyl bond in structure **E**. Dissociation of the π-complex finally regenerates **A** and yields product **3**. The challenges of the asymmetric carbofluorination are not only to control the simultaneous formation of two adjacent chirality centers but also to

minimize competitive side reactions. In fact, we found that the byproduct **4** can be generated from unconsumed **D** when the reaction is quenched too early, which suggests that the fluorination with cesium fluoride is faster than the asymmetric C-C bond forming step. Alternatively, **4** can be formed from intermediate **D** via deprotonation of **3** thus generating **F** which undergoes overalkylation to **G**, a problem that we observed in particular with styrenes carrying strong electron-withdrawing groups. We found that this can be effectively mitigated by slow addition of **1** to the reaction mixture which is expected to limit the concentration of **D** and thus favors the desired reaction between the anionic nucleophile and the cationic allyl-loaded palladium catalyst. The stereochemical outcome of the reaction is in agreement with an outer-sphere mechanism in which the η³-allyl palladium complex **C** is preferentially attacked by the *Re*-face of the intermediate carbanion **D**. This pathway yields the major (*R,S,E*)-diastereomer of **3**, while the attack from the *Si*-face of **D** results in the formation of the minor (*S,S,E*)-diastereomer.

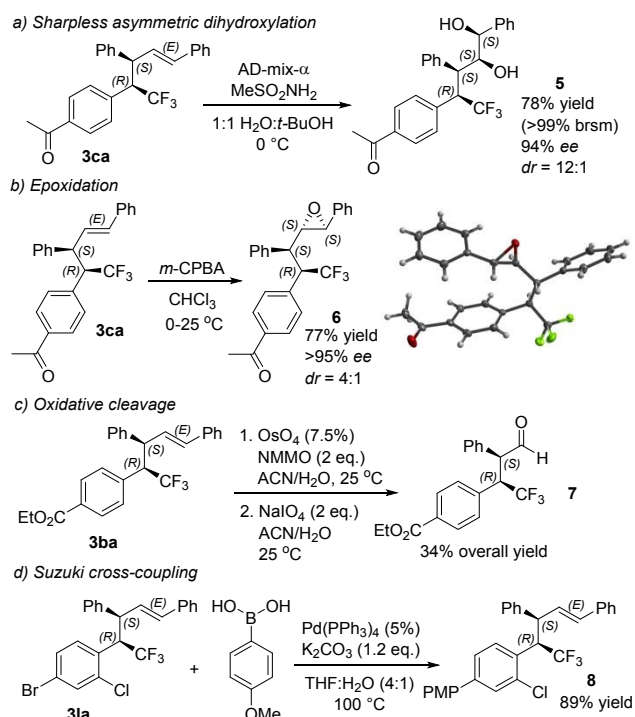


Scheme 3. Proposed mechanism of the asymmetric carbofluorination.

Importantly, the reaction is amenable to scaling, and we were able to prepare more than half a gram of **3ca** which was isolated in 65% yield, 7:1 *dr* and 93% *ee*. As mentioned above, the trifluoromethyl group is of particular importance due to its prominence in many pharmaceuticals, and we anticipated that the incorporation of an allylic group into the *gem*-difluorostyrene scaffold would facilitate further transformations with the possibility of introducing additional chiral centers. To this end, we carried out a variety of transformations at the double-bond of compound (3*S*,4*R*)-**3ca** (Scheme 4). We were pleased to find that Sharpless asymmetric dihydroxylation with AD-mix- α yielded **5** in 78% yield and 94% *ee* thus establishing four contiguous chirality centers along the alkyl sidechain. We previously established that the sense of asymmetric induction of the dihydroxylation of similar structures is controlled by the AD catalyst used and not by the substrate chirality and we can therefore assign the structure as (2*R*,3*S*,4*S*,5*S*)-**5**.³⁷ Additionally, the epoxidation of **3ca** can be carried out efficiently with *m*-CPBA and we obtained **6** in 77% yield. A single crystal of the major diastereomer was obtained by slow evaporation of a dichloromethane solution. The



crystallographic analysis identified **6** as 1-(4-((2*R*,3*S*)-1,1,1-trifluoro-3-phenyl-3-((2*S*,3*S*)-3-phenyloxiran-2-yl)propan-2-yl)phenyl)ethan-1-one, providing another example with four adjacent chirality centers (see SI). Dihydroxylation of (3*S*,4*R*)-**3ba** with osmium tetroxide and *N*-methylmorpholine *N*-oxide (NMMO) followed by diol cleavage with sodium periodate gave aldehyde **7** in 34% overall yield. Finally, we applied (3*S*,4*R*)-**3la** in a Suzuki cross-coupling procedure with 4-methoxyphenylboronic acid and obtained **8** in 89% yield.



Scheme 4. Transformations with fluoroalkylated products **3ca**, **3ba** and **3la**.

In summary, we have developed a catalytic asymmetric fluoroalkylation method that allows efficient C-F and C-C bond formation across an electron-deficient double bond, producing a variety of multifunctional products in 53-79% yield, 88-99% ee, and up to 7:1 dr. This reaction has several noteworthy features. Two contiguous chirality centers are installed at once and with high stereoselectivity, the initiating C-F bond formation proceeds under mild conditions with stoichiometric amounts of inexpensive cesium fluoride which replaces AgF required in asymmetric fluoroarylations, the palladium-catalyzed reaction is accelerated by a commercially available chiral bis(phosphino)ferrocene ligand and can be scaled up without compromising the stereochemical outcome and yield. The synthetic utility of the products exhibiting a unique arrangement of a trifluoromethyl, a vinyl and two different aryl groups directly attached to a scaffold of vicinal chirality centers is demonstrated by the introduction of additional functionalities either at the aryl ring or at the alkene moiety. This allows stereocontrolled introduction of four adjacent chirality centers via asymmetric dihydroxylation and epoxidation reactions as well as other modifications. We believe that these results will be of broad interest to synthetic and medicinal chemists and attract increasing attention to the development of other asymmetric fluoroalkylation reactions.

Conflicts of interest

The authors declare no competing financial interest.

Data availability

The data supporting this article have been included as part of the Supplementary Information.

Acknowledgements

We gratefully acknowledge financial support from the US National Institutes of Health, GM106260. E.N. thanks the Henry Luce Foundation for a Clare Boothe Luce Graduate Fellowship.

Notes and references

- P. Jeschke, *ChemBioChem* **2004**, *5*, 570–589.
- B. R. Smith, C. M. Eastman, J. T. Njardarson, *Med. Chem.* **2014**, *57*, 9764–9773.
- M. Inoue, Y. Sumii, N. Shibata, *ACS Omega* **2020**, *5*, 10633–10640.
- K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886.
- Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Acena, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 422–518.
- T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264.
- D. Cahard, X. Xu, S. Couve-Bonnaire, X. Pannecoucke, *Chem. Soc. Rev.* **2010**, *39*, 558–568.
- X. Yang, T. Wu, R. J. Phipps, F. D. Toste, *Chem. Rev.* **2015**, *115*, 826–870.
- P. A. Champagne, J. Desroches, J.-D. Hamel, M. Vandamme, J.-F. Paquin, *Chem. Rev.* **2015**, *115*, 9073–9174.
- Y. Zhu, J. Han, J. Wang, N. Shibata, M. Sodeoka, V. A. Soloshonok, J. A. S. Coelho, F. D. Toste, *Chem. Rev.* **2018**, *118*, 3887–3964.
- J. Liu, Q. Yuan, F. D. Toste, M. S. Sigman, *Nat. Chem.* **2019**, *11*, 710–715.
- W. Zhu, X. Zhen, J. Wu, Y. Cheng, J. An, X. Ma, J. Liu, Y. Qin, H. Zhu, J. Xue, X. Jiang, *Nature Comm.* **2021**, *12*, 3957.
- A. Pons, L. Delion, T. Poisson, A. B. Charette, P. Jubault, *Acc. Chem. Res.* **2021**, *54*, 2969–2990.
- E. P. A. Talbot, T. de A. Fernandes, J. M. McKenna, F. D. Toste, *J. Am. Chem. Soc.* **2014**, *136*, 4101–4104.
- J. Miró, C. del Pozo, F. D. Toste, S. Fustero, *Angew. Chem. Int. Ed.* **2016**, *55*, 9045–9049.
- Z. Liu, L. J. Oxtoby, M. Liu, Z.-Q. Li, V. T. Tran, Y. Gao, K. M. Engle, *J. Am. Chem. Soc.* **2021**, *143*, 8962–8969.
- Y. He, Z. Yang, R. T. Thornbury, F. D. Toste, *J. Am. Chem. Soc.* **2015**, *137*, 12207–12210.
- Y. Xi, C. Wang, Q. Zhang, J. Qu, Y. Chen, *Angew. Chem. Int. Ed.* **2021**, *60*, 2699–2703.
- J. P. Sorrentino, R. A. Altman, *Synthesis* **2021**, *53*, 3935–3950.
- W. Zhu, J. Wang, S. Wang, Z. Gu, J. L. Aceña, K. Izawa, H. Liu, V. A. Soloshonok, *J. Fluorine Chem.* **2014**, *167*, 37–54.
- A. Abula, Z. Xu, Z. Zhu, C. Peng, Z. Chen, W. Zhu, and H. A. Aisa, *J. Chem. Inf. Model.* **2020**, *60*, 6242–6250.
- B. Gao, Y. Zhao, C. Ni, J. Hu, *Org. Lett.* **2014**, *16*, 102–105.
- B. Gao, Y. Zhao, J. Hu, *Angew. Chem. Int. Ed.* **2015**, *54*, 638–642.
- P. Tian, C.-Q. Wang, S.-H. Cai, S. Song, L. Ye, C. Feng, T.-P. Loh, *J. Am. Chem. Soc.* **2016**, *138*, 15869–15872.
- H.-J. Tang, L.-Z. Lin, C. Feng, T.-P. Loh, *Angew. Chem. Int. Ed.* **2017**, *56*, 9872–9876.



- 26 P. E. Daniel, C. I. Onyeagusi, A. A. Ribeiro, K. Li, S. J. Malcolmson, *ACS Catal.* **2019**, *9*, 205-210.
- 27 H. Liu, L. Ge, D.-X. Wang, N. Chen, C. Feng, *Angew. Chem. Int. Ed.* **2019**, *58*, 3918-3922.
- 28 W.-J. Yoo, J. Kondo, J. A. Rodriguez-Santamara, T. V. Q. Nguyen, S. Kobayashi, *Angew. Chem. Int. Ed.* **2019**, *58*, 6772-6775.
- 29 X. Yu, A. Maity, A. Studer, *Angew. Chem. Int. Ed.* **2023**, *62*, e202310288.
- 30 T.-Y. Lin, Z. Pan, Y. Tu, S. Zhu, H.-H. Wu, Y. Liu, Z. Li, J. Zhang, *Angew. Chem. Int. Ed.* **2020**, *59*, 22957-22962.
- 31 J. S. S. K. Formen, C. C. Lynch, E. Nelson, A. Yuan, S. E. Steber, C. Wolf, *J. Org. Chem.* **2024**, *89*, 10998-11002.
- 32 J. Duran, V. G. Moldoveanu, C. Barroso, G. A. Pereira, B. Limburg, X. Companyó, *Angew. Chem. Int. Ed.* **2026**, *65*, e202520513.
- 33 R. Prétôt, A. Pfaltz, *Angew. Chem., Int. Ed.* **1998**, *37*, 323-325.
- 34 B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395-422.
- 35 G. Helmchen, U. Kazmaier, S. Foerster, Enantioselective allylic Substitutions with Carbon Nucleophiles. In *Catalytic Asymmetric Synthesis*, 3rd ed.; I. Ojima, Ed.; John Wiley & Sons, Inc., Hoboken, **2010**, pp 497-641.
- 36 O. Pàmies, J. Margalef, S. Cañellas, J. James, E. Judge, P. J. Guiry, C. Moberg, J.-E. Bäckvall, A. Pfaltz, M. A. Pericàs, M. Diéguez. *Chem. Rev.* **2021**, *121*, 4373-4505.
- 37 K. Balaraman, C. Wolf, *Angew. Chem. Int. Ed.* **2017**, *56*, 1390-1395.

View Article Online
DOI: 10.1039/D6CC02743A



Data availability

The data supporting this article have been included as part of the Supplementary Information.

