OL | Organic Letters

pubs.acs.org/OrgLett

Letter

Stereospecific Isomerization of Allylic Halides via Ion Pairs with Induced Noncovalent Chirality

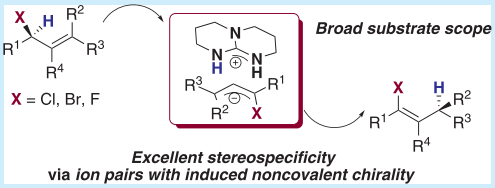
Samuel Martinez-Erro,[†] Víctor García-Vázquez,[†] Amparo Sanz-Marco, and Belén Martín-Matute*

Cite This: *Org. Lett.* 2020, 22, 4123–4128

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A regioselective protocol for the synthesis of substituted allylic chlorides, bromides, and fluorides has been established. Remarkably, the method can be applied to the enantioselective synthesis of challenging chiral allylic chlorides. When the allylic halides are treated with the base triazabicyclodecene as the catalyst, a [1,3]-proton shift takes place, giving the corresponding vinyl halides in excellent yields with excellent *Z*:*E* ratios. Furthermore, the [1,3]-proton shift takes place with an outstanding level of chirality transfer from chiral allylic alcohols (≤98%) to give chiral trifluoromethylated vinyl chlorides.



The direct transfer of a hydrogen atom across an allylic system by a [1,3]-sigmatropic shift is thermally forbidden, both supra- and antarafacially.[1] Thus, when a catalyst promotes this process, the reaction must proceed in a stepwise manner via one or more intermediates.[2] A relevant example of this class of reaction is the isomerization of allylic alcohols into carbonyl compounds, a synthetic transformation in organic chemistry.[3] In recent decades, significant work has been put into the development of methods for performing this isomerization efficiently,[4−6] in some instances even under mild reaction conditions, and with a large substrate scope. Different transition-metal catalysts have been used, in particular, ruthenium, rhodium, palladium, and iridium.[6]

The isomerization of allylic alcohols can be described as a formal [1,3]-hydrogen shift. Under catalytic conditions, we may understand that the reaction proceeds via a series of intermediates. These species could be harnessed and applied in further transformations, opening up new synthetic opportunities. Our group has shown that in the presence of a range of different electrophiles and even nucleophiles, α-substituted ketones are formed as single constitutional isomers.[7,8]

Because of the stepwise nature of the catalytic [1,3]-hydrogen shift reactions, stereospecific examples of this transformation are rare.[9−11] In 2012, Cahard and co-workers reported an outstanding stereospecific isomerization of enantiopure β-trifluoromethylated allylic alcohols catalyzed by an achiral ruthenium complex.[10a] In 2016, we reported the stereospecific isomerization of electron-deficient allylic alcohols and ethers mediated by a simple guanidine-type base, triazabicyclodecene (TBD), thus, in the absence of a metal catalyst.[11] This reaction showed excellent levels of stereospecificity (i.e., chirality transfer), yielding β-substituted ketones and enol ethers with excellent enantiomeric ratios. A similar interaction has also recently been proposed for the stereospecific isomerization of 3-substituted indenols using 1,4-diazabicyclo[2.2.2]octane (DABCO).[12]

For allylic systems, a stereospecific base-catalyzed [1,3]-hydrogen shift has been reported for only allylic alcohols and ethers.[11,12] The application of this approach to other allylic systems would create new synthetic methods and provide access to new chiral scaffolds. For example, the stereospecific isomerization of allylic halides would yield chiral vinyl halides, which are very versatile building blocks in organic chemistry.[13] Examples of the isomerization of allylic halides into vinyl halides are very rare,[14] and no stereospecific examples have been reported. This is due to the difficulty in the synthesis of chiral allylic halides, as they are very prone to racemization.[15]

In this paper, we report a method for the regioselective synthesis of γ-trifluoromethylated allylic chlorides, bromides, and fluorides, and the isomerization of these compounds into vinyl halides using the bicyclic guanidine base TBD as a catalyst (Scheme 1a). Furthermore, we also report the regio- and enantioselective synthesis of allylic chlorides and the first stereospecific base-catalyzed isomerization of these compounds into chiral vinyl chlorides (Scheme 1b).

Several protocols for the synthesis of allylic halides from the corresponding alcohols have been reported in the literature.[16] However, these methods suffer from low regioselectivity due to competing S_N1' and S_N2' pathways.[17] We thus started our investigations by developing a method for the regioselective synthesis of allylic chlorides. We used γ-trifluoromethylated allylic chloride **1a** as a model substrate (Table 1). Treatment of **1a** with $SOCl_2$ (1 equiv) in THF gave a mixture of **2a**, **2a′**, and **2a″** in 78% combined yield (Table 1, entry 1).

Received: April 3, 2020
Published: May 8, 2020

https://dx.doi.org/10.1021/acs.orglett.0c01200
Org. Lett. 2020, 22, 4123–4128

Scheme 1. (a) Regioselective Synthesis and [1,3]-Proton Shift of Allylic Chlorides, Bromides, and Fluorides and (b) Enantioselective Synthesis of Chiral Allylic Chlorides and Stereospecific [1,3]-Proton Shift

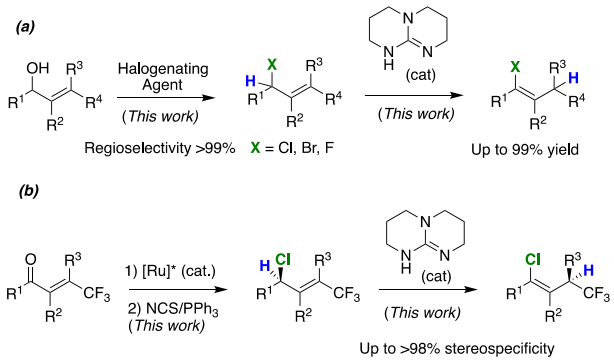
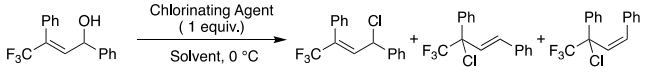


Table 1. Regioselective Synthesis of 2a[a]



entry	Cl source	solvent	yield (%)	2a:2a′:2a″
1	$SOCl_2$	THF	78	82:12:6
2	$SOCl_2$	Et_2O	83	76:16:8
3	$SOCl_2$	CH_2Cl_2	83	88:12:–
4	$SOCl_2$[b]	CH_2Cl_2	47	80:14:6
5	PCl_3	CH_2Cl_2	80	96:4:–
6	PCl_5	CH_2Cl_2	50	98:2:–
7	$POCl_3$	CH_2Cl_2	52	12:–:–[c]
8	NCS/PPh_3[d]	CH_2Cl_2	40	94:6:–
9	NCS/PPh_3[d]	THF	67	>99:–:–

[a]Unless otherwise noted, **1a** (0.1 mmol, 0.1 M) and the chlorinating agent (0.1 mmol) at 0 °C overnight. [b]With 0.1 mmol of pyridine. [c]An unknown product was formed. [d]NCS (0.15 mmol) and PPh_3 (0.15 mmol).

In an attempt to improve the regioselectivity and minimize any *cis*/*trans* isomerization, several reaction parameters were varied. Changing the solvent had little effect on the outcome of the transformation (Table 1, entries 2 and 3). HCl formed in the reaction could promote the formation of carbocationic intermediates, leading to **2a′** and **2a″**. However, when a base was added to suppress the formation of HCl (Table 1, entry 4), significantly lower yields and low selectivity were obtained. Other chlorinating agents were then tested; PCl_3 and PCl_5 gave significantly better results in terms of selectivity (Table 1, entries 5 and 6, respectively), albeit with moderate yields. $POCl_3$ gave similar results, but the reaction also gave an unidentified byproduct (Table 1, entry 7). When the reaction was carried out with NCS (*N*-chlorosuccinimide) and PPh_3 in CH_2Cl_2, we obtained excellent selectivity [94:6 **2a**:**2a′** (Table 1, entry 8)] and a moderate yield.[18] Gratifyingly, when the reaction was performed in THF, **2a** was formed 67% yield with complete regioselectivity (Table 1, entry 9). Moreover, similar conditions (Scheme 2a) using NBS (*N*-bromosuccinimide) gave allylic bromide **3a** in 62% yield (Scheme 2a). Allylic fluoride **4a** was also accessed using DAST (*N*,*N*-diethylaminosulfur trifluoride), with complete regioselectivity (Scheme 2b).[19]

The [1,3]-hydrogen shift of **2a** to give vinyl chloride **5a** was then investigated using various bases at 60 °C (Table 2). With

Scheme 2. Regioselective Synthesis of γ-Trifluoromethylated Allylic Bromide 3a and Fluoride 4a

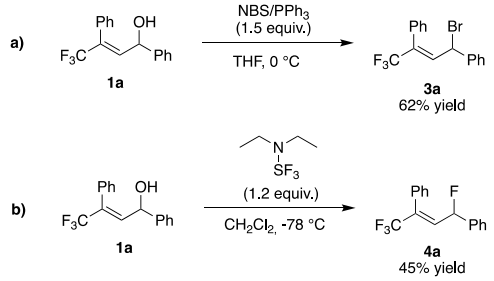
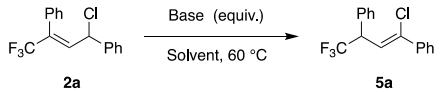


Table 2. Base-Catalyzed Isomerization of 2a[a]



entry	base (equiv)	solvent	conversion[b] (%)	yield[b,c] (%)
1	NEt_3 (1.0)	toluene	<5	–[d]
2	Cs_2CO_3 (1.0)	toluene	<5	–[d]
3	DBU (1.0)	toluene	>99	71[e]
4	TBD (1.0)	toluene	>99	46[e]
5	DBU (0.1)	toluene	86	86[e]
6	TBD (0.1)	toluene	>99	>99
7	MTBD (0.1)	toluene	90	81[e]
8	TBD (0.1)	THF	90	84[e]
9	TBD (0.1)	CH_2Cl_2	67	60[e]
10	TBD (0.1)	dioxane	78	78[e]
11	TBD (0.1)	MeCN	38	20[e]

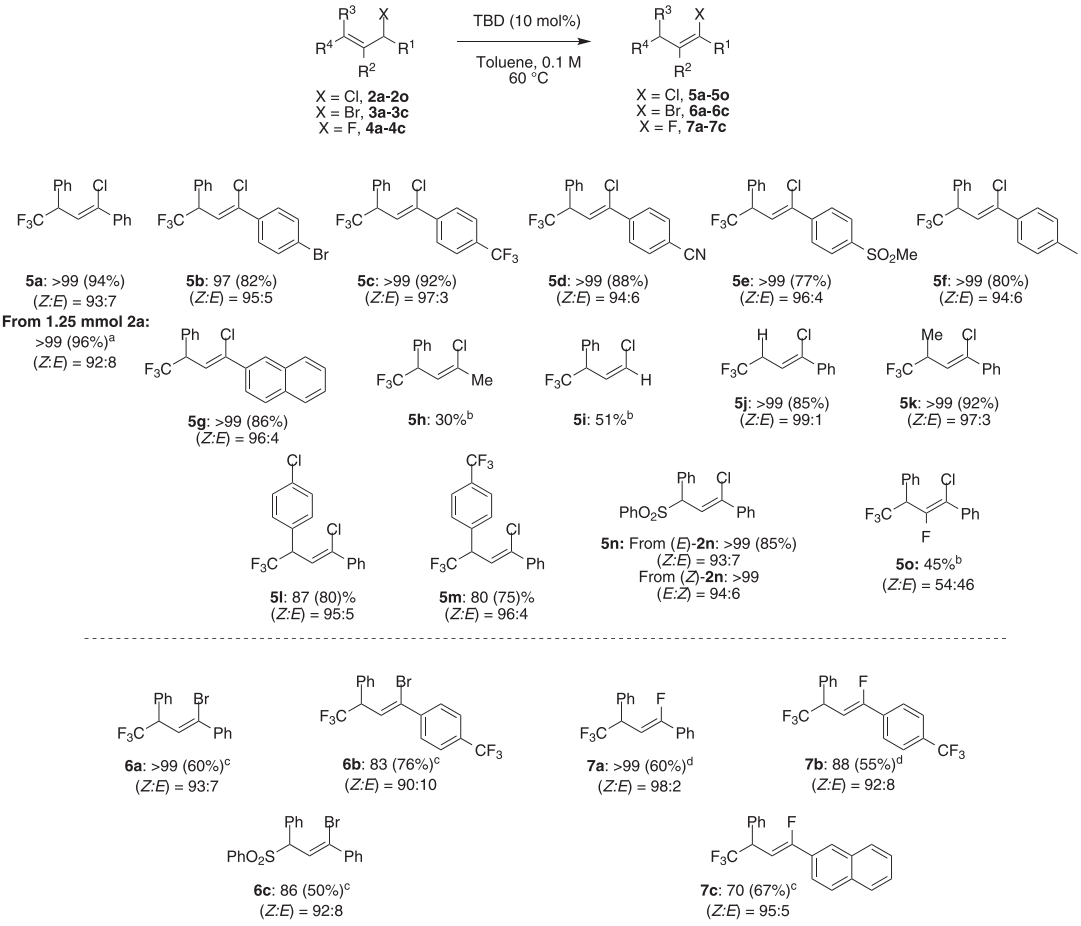
[a]**2a** (0.1 mmol, 0.1 M), base, overnight at 60 °C. [b]Determined by ^{19}F NMR spectroscopy. [c]Against an internal standard. [d]>95% **2a** recovered. [e]Decomposition observed.

NEt_3 or Cs_2CO_3 in a stoichiometric amount, <5% of **5a** was obtained (Table 2, entry 1 or 2, respectively). In contrast, with 1 equiv of the more basic DBU or TBD, full conversions were obtained, giving **5a** in 71% or 46% yield, respectively (Table 2, entry 3 or 4, respectively). In both instances, though, decomposition products were detected. With a smaller amount of base (0.1 equiv), the level of decomposition also decreased (Table 2, entries 5 and 6). DBU gave a good yield of 86%, but TBD gave a >99% yield of **2a** after the same reaction time (18 h). The use of 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene [MTBD (Table 2, entry 7)] afforded **5a** in 81% yield, and full conversion was not achieved. It was also observed that more polar solvents such as CH_2Cl_2 and MeCN always gave lower yields due to the formation of decomposition products (Table 2, entries 8–11).

Next, the scope was studied (Scheme 3) using the optimized reaction conditions (Table 2, entry 6). When an electron-withdrawing or electron-donating group was present at the *para* position of the aryl group at R^1, excellent yields were obtained in all instances (**5b**–**5f**). Even when R^1 was a naphthyl group, **5g** was obtained in very good yield. The products were all formed with very good *Z*:*E* ratios, up to 96:4. Further study of the substituents at R^1 revealed some limitations of the reaction. When R^1 was CH_3 or H, vinyl chlorides **5h** and **5i** were obtained in lower yields (30% and 51%, respectively). Moreover, the introduction of alkyl groups, aryl groups, or even H at R^3 was very well tolerated, and vinyl chlorides **5j**–**5m** were formed in very good yields. Importantly, the CF_3 group at R^4 could be replaced with a sulfonyl group,

https://dx.doi.org/10.1021/acs.orglett.0c01200
Org. Lett. 2020, 22, 4123–4128

Scheme 3. Scope of the Base-Catalyzed Isomerization of Allylic Halides[e]



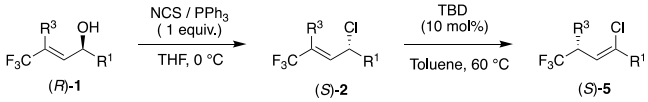
[a]**2a** (1.25 mmol, 371 mg), TBD (0.125 mmol, 17 mg). [b]Conversion measured by ^{19}F NMR. [c]TBD (30 mol %), 100 °C. [d]*o*-Xylene as a solvent at 145 °C. [e]Yields determined by ^{19}F NMR spectroscopy (isolated yields in parentheses).

and **5n** was obtained in excellent yield from both (*E*)-**2n** and (*Z*)-**2n**. Highly substituted allylic chloride **2o** gave a good 45% yield of **5o** with 20 mol % TBD.

We also investigated the isomerization of allylic bromides **3** and fluorides **4**. Both of these allylic substrates proved to be more challenging than the allylic chlorides. After a short optimization (see the Supporting Information), vinyl bromide **6a** could be obtained in a good yield of 60% by using 30 mol % TBD at 100 °C. When an electron-withdrawing group was introduced into the aromatic group at R^1 (**3b**), 83% was obtained with only 10 mol % TBD. Sulfonyl-substituted **3c** isomerized well to **6c** in 86% yield. Allylic fluorides **4a**−**4c** showed lower reactivity, and a higher temperature of 145 °C was needed to reach full conversion. Under these conditions, vinyl fluorides **7a**−**7c** were obtained with excellent *Z*:*E* ratios (≤98:2).

Next the stereospecificity of the reaction was investigated. To do this, a method for the enantioselective preparation of **2a** had to be established.[20] This is a challenging task, as benzyl and allyl groups can both stabilize transient cationic species that may form during the preparation of chiral allylic halides.[21] As a result, S_N1 pathways are favored and racemization occurs. The reaction of chiral (*R*)-**1a** (er of 99:1)[10a] gave allylic chloride (*S*)-**2a** regioselectively with an er of 77:23 (Table 3, entry 1, and Table S4). When the electron density of R^1 was decreased, the racemization also decreased (Table 3, entries 2−5). This effect was more pronounced for the purely inductively electron-withdrawing CF_3 group (**1c**, Table 3, entry 5); (*S*)-**2c** was obtained with an er of 94:6. In addition, a Me group at R^3 also gave allyl chloride (*S*)-**2m**, with an er of 68:32 (Table 3, entry 6). Therefore, the best results are obtained for substrates with substituents that do not stabilize cationic

Table 3. Stereospecific Synthesis and Stereospecific 1,3-Proton Shift of Allylic Chlorides[a]



entry	(*R*)-**1**, R^1/R^3, er	(*S*)-**2** er	(*S*)-**5** er[b]	ss[c] (%)
1	**1a**, Ph/Ph, 99:1	77:23	76:24 (99)	96
2	**1b**, *p*-BrC_6H_4/Ph, 97:3	79:21	77:23 (99)	95
3[d]	**1d**, *p*-CNC_6H_4/Ph, 94:6	82:18	81:19 (92)	98
4[d]	**1e**, *p*-$SO_2MeC_6H_4$/Ph, 93:7	87:13	76:24 (99)	70
5[e]	**1c**, *p*-$CF_3C_6H_4$/Ph, 95:5	94:6	92:8 (99)	95
6	**1m**, Ph/Me, 95:5	68:32	66:34 (99)	94

[a](*S*)-**2** prepared as in Table 1, entry 9, but with 1 equiv of NCS/PPh_3 from (*R*)-**1**. Unless otherwise noted, **5** was obtained as in Table 2, entry 6. er is the enantiomeric ratio. [b]In parentheses, yields by ^{19}F NMR spectroscopy. [c]Stereospecificity = ss = (ee of product **5**/ee of **2**) × 100. [d]**5** prepared at 0 °C for 1 h. [e]**5** prepared at room temperature for 1 h.

https://dx.doi.org/10.1021/acs.orglett.0c01200
Org. Lett. 2020, 22, 4123−4128

species, preventing the chlorination from proceeding by S_N1 pathways. Importantly, the isomerization of (*S*)-**2a** into (*S*)-**5a** took place with an excellent level of chirality transfer of 96% (Table 3, entry 1).

The absolute configuration of (*S*)-**5a** was determined by transforming it into a known β-trifluoromethylated ketone (see the Supporting Information). The stereochemistries of the other products were assigned by analogy. The exceptional transfer of chirality was also achieved for (*S*)-**2b**, (*S*)-**2c**, and (*S*)-**2d** (Table 3, entries 2, 3, and 5, respectively). An exception was (*S*)-**2e**, which bears a polar sulfonyl group; a minor loss of chirality was observed (Table 3, entry 4). Chloride (*S*)-**5m** was also obtained with a high stereosepecificity of 94% (Table 3, entry 6).

The mechanism is proposed to be a suprafacial [1,3]-proton shift (Figure 1), which likely is thermodynamically driven as

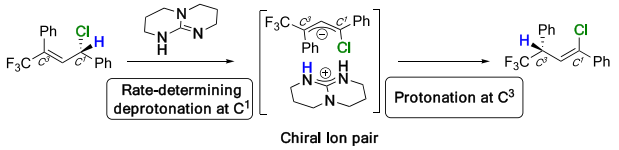


Figure 1. Mechanism through a tight chiral ion pair.

previously observed in related suprafacial proton shifts.[11,12] We carried out parallel isomerization reactions of **2a** and **2a**-d_1 and observed a large kinetic isotope effect of 5.4 ± 0.6 (see the Supporting Information). This suggests that the deprotonation of C^1 is the rate-determining step of the reaction. The high stereospecificity of the reaction indicates a highly efficient transfer of chirality from the starting chiral allylic chloride to the ion pair intermediate. Noncovalent chirality is induced on this ion pair, as interaction of the protonated base with the achiral planar allylic anion occurs exclusively from one specific side. As long as the ion pair remains tight, the chirality can be further transferred stereospecifically to the final product upon protonation of C^3 (Figure 1). In conclusion, we have developed a method for the synthesis of allylic chlorides, bromides, and fluorides from allylic alcohols with full control of the regioselectivity. Furthermore, from enantiopure allylic alcohols, a new stereospecific chlorination reaction has been developed, giving access to γ-trifluoromethylated allylic chlorides in high enantiomeric ratios for the first time. The allylic halides were transformed in a single step into vinyl halides, important intermediates in synthetic organic chemistry. The reaction takes place by a stereospecific [1,3]-proton shift pathway catalyzed by the bicyclic guanidine base TBD. When applied to enantioenriched γ-trifluoromethylated allylic chlorides, the simple base catalyst can transfer the chirality affording vinyl chlorides with a stereogenic center at the allylic position, on a trifluoromethylated carbon. Formation of a very tight ion pair with induced noncovalent chirality, after a rate-determining deprotonation, is responsible for the outstanding levels of chirality transfer.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01200.

Details of experimental procedures and spectroscopic data (PDF)

NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Belén Martín-Matute − *Department of Organic Chemistry, Stockholm University, Stockholm 10691, Sweden;* orcid.org/0000-0002-7898-317X; Email: belen.martin.matute@su.se

Authors

Samuel Martinez-Erro − *Department of Organic Chemistry, Stockholm University, Stockholm 10691, Sweden*

Víctor García-Vázquez − *Department of Organic Chemistry, Stockholm University, Stockholm 10691, Sweden*

Amparo Sanz-Marco − *Department of Organic Chemistry, Stockholm University, Stockholm 10691, Sweden*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01200

Author Contributions

†S.M.-E. and V.G.-V. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are grateful for support from the Swedish Research Council through Vetenskapsrådet and Formas, the Knut and Alice Wallenberg Foundation, and the Göran Gustafsson Foundation. This project was also funded by the European Union's Horizon 2020 research and innovation programme under Grant Agreement 721223.

■ REFERENCES

(1) (a) Woodward, R.; Hoffmann, R. Stereochemistry of Electrocyclic Reactions. *J. Am. Chem. Soc.* **1965**, *87*, 395−397. (b) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, Germany, 1970.

(2) (a) Gauthier, D.; Lindhardt, A. T.; Olsen, E. P. K.; Overgaard, J.; Skrydstrup, T. In Situ Generated Bulky Palladium Hydride Complexes as Catalysts for the Efficient Isomerization of Olefins. Selective Transformation of Terminal Alkenes to 2-Alkenes. *J. Am. Chem. Soc.* **2010**, *132*, 7998−8009. (b) Crossley, S. W. M.; Barabé, F.; Shenvi, R. A. Simple, Chemoselective, Catalytic Olefin Isomerization. *J. Am. Chem. Soc.* **2014**, *136*, 16788−16791. (c) Hassam, M.; Taher, A.; Arnott, G. E.; Green, I. R.; van Otterlo, W. A. L. Isomerization of Allyl Benzenes. *Chem. Rev.* **2015**, *115*, 5462−5569. (d) Kapat, A.; Sperger, T.; Guven, S.; Schoenebeck, F. E-Olefins through intramolecular radical relocation. *Science* **2019**, *363*, 391−396. (e) Molleti, N.; Martinez-Erro, S.; Carretero Cerdán, A.; Sanz-Marco, A.; Gomez-Bengoa, E.; Martín-Matute, B. Base-Catalyzed [1, n]-Proton Shifts in Conjugated Polyenyl Alcohols and Ethers. *ACS Catal.* **2019**, *9*, 9134−9139.

(3) (a) van der Drift, R. C.; Bouwman, E.; Drent, E. Homogeneously catalyzed isomerization of allylic alcohols to carbonyl compounds. *J. Organomet. Chem.* **2002**, *650*, 1−24. (b) Trost, B. M. The atom economy-a search for synthetic efficiency. *Science* **1991**, *254*, 1471−1477.

(4) For reviews of transition-metal-catalyzed isomerization of allylic alcohols, see: (a) Uma, R.; Crevisy, C.; Gree, R. R. Transposition of Allylic Alcohols into Carbonyl Compounds Mediated by Transition Metal Complexes. *Chem. Rev.* **2003**, *103*, 27−52. (b) Cadierno, V.; Crochet, P.; Gimeno, J. Ruthenium-Catalyzed Isomerizations of Allylic and Propargylic Alcohols in Aqueous and Organic Media: Applications in Synthesis. *Synlett* **2008**, *8*, 1105−1124. (c) Lorenzo-

Luis, P.; Romerosa, A.; Serrano-Ruiz, M. Catalytic Isomerization of Allylic Alcohols in Water. *ACS Catal.* **2012**, *2*, 1079−1086.
(5) For examples of the base-catalyzed isomerization of allyic alcohols, see: (a) Johnston, A. J. S.; McLaughlin, M. G.; Reid, J. P.; Cook, M. J. NaH mediated isomerisation-allylation reaction of 1,3-substituted propenols. *Org. Biomol. Chem.* **2013**, *11*, 7662−7666. (b) Zheng, H.-X.; Xiao, Z.-F.; Yao, C.-Z.; Li, Q.-Q.; Ning, X.-S.; Kang, Y.-B.; Tang, Y. Transition-Metal-Free Self-Hydrogen-Transferring Allylic Isomerization. *Org. Lett.* **2015**, *17*, 6102−6105. (c) Mondal, K.; Mondal, B.; Pan, S. C. Organocatalytic Redox Isomerization of Electron-Deficient Allylic Alcohols: Synthesis of 1,4-Ketoaldehydes. *J. Org. Chem.* **2016**, *81*, 4835−4848.
(6) Selected examples: (a) Ito, M.; Kitahara, S.; Ikariya, T. Cp*Ru(PN) Complex-Catalyzed Isomerization of Allylic Alcohols and Its Application to the Asymmetric Synthesis of Muscone. *J. Am. Chem. Soc.* **2005**, *127*, 6172−6173. (b) Cadierno, V.; García-Garrido, S. E.; Gimeno, J. A.; Varela-Álvarez, A.; Sordo, J. A. Bis(allyl)-Ruthenium(IV) Complexes as Highly Efficient Catalysts for the Redox Isomerization of Allylic Alcohols into Carbonyl Compounds in Organic and Aqueous Media: Scope, Limitations, and Theroretical Analysis of the Mechanism. *J. Am. Chem. Soc.* **2006**, *128*, 1360−1370. (c) Larionov, E.; Lin, L.; Guénée, L.; Mazet, C. Scope and Mechanism in Palladium-Catalyzed Isomerizations of Highly Substituted Allylic, Homoallylic, and Alkenyl Alcohols. *J. Am. Chem. Soc.* **2014**, *136*, 16882−16894. (d) Kress, S.; Johnson, T.; Weisshar, F.; Lautens, M. Synthetic and Mechanistic Studies on the Rhodium-Catalyzed Redox Isomerization of Cyclohexadienols. *ACS Catal.* **2016**, *6*, 747−750. (e) Erbing, E.; Vázquez-Romero, A.; Bermejo Gómez, A.; Platero-Prats, A. E.; Carson, F.; Zou, X.; Tolstoy, P.; Martín-Matute, B. General, Simple, and Chemoselective Catalysts for the Isomerization of Allylic Alcohols: The Importance of the Halide Ligand. *Chem. - Eur. J.* **2016**, *22*, 15659−15663. (f) Spiegelberg, B.; Dell'Acqua, A.; Xia, T.; Spannenberg, A.; Tin, S.; Hinze, S.; de Vries, J. G. Additive-Free Isomerization of Allylic Alcohols to Ketones with a Cobalt PNP Pincer Catalyst. *Chem. - Eur. J.* **2019**, *25*, 7820−7825.
(7) (a) Ahlsten, N.; Bermejo Gómez, A.; Martín-Matute, B. Iridium-Catalyzed 1,3-Hydrogen Shift/Chlorination of Allylic Alcohols. *Angew. Chem., Int. Ed.* **2013**, *52*, 6273−6276. (b) Martinez-Erro, S.; Bermejo Gómez, A.; Vázquez-Romero, A.; Erbing, E.; Martín-Matute, B. 2,2-Diiododimedone: a mild electrophilic iodinating agent for the selective synthesis of α-iodoketones from allylic alcohols. *Chem. Commun.* **2017**, *53*, 9842−9845. (c) Sanz-Marco, A.; Martinez-Erro, S.; Martín-Matute, B. Selective Synthesis of Unsymmetrical Aliphatic Acyloins through Oxidation of Iridium Enolates. *Chem. - Eur. J.* **2018**, *24*, 11564−11567.
(8) Sanz-Marco, A.; Martinez-Erro, S.; Pauze, M.; Gómez-Bengoa, E.; Martín-Matute, B. An umpolung strategy to react catalytic enols with nucleophiles. *Nat. Commun.* **2019**, *10*, 5244−5253.
(9) (a) Clark, W. M.; Tickner-Eldridge, A. M.; Huang, G. K.; Pridgen, L. N.; Olsen, M. A.; Mills, R. J.; Lantos, I.; Baine, N. H. A Catalytic Enantioselective Synthesis of the Endothelin Receptor Antagonists SB-209670 and SB-217242. A Base-Catalyzed Stereospecific Formal 1,3-Hydrogen Transfer of a Chiral 3-Arylindenol. *J. Am. Chem. Soc.* **1998**, *120*, 4550−4551. (b) Hedberg, C.; Andersson, P. G. Catalytic Asymmetric Total Synthesis of the Muscarinic Receptor Antagonist (R)-Tolterodine. *Adv. Synth. Catal.* **2005**, *347*, 662−666. (c) Dabrowski, J. A.; Haeffner, F.; Hoveyda, A. H. Combining NHC-Cu and Brønsted Catalysis: Enantioselective Allylic Substitution/Conjugate Additions with Alkynylaluminium Reagents and Stereospecific Isomerization of the Products to Trisubstituted Allenes. *Angew. Chem., Int. Ed.* **2013**, *52*, 7694−7699.
(10) (a) Bizet, V.; Pannecoucke, X.; Renaud, J.-L.; Cahard, D. Ruthenium-Catalyzed Redox Isomerization of Trifluoromethylated Allylic Alcohols: Mechanistic Evidence for an Enantiospeficic Pathway. *Angew. Chem., Int. Ed.* **2012**, *51*, 6467−6470. (b) Bizet, V.; Pannecoucke, X.; Renaud, J.-L.; Cahard, D. J. Synthesis of β-CF3 Ketones from trifluoromethylated allylic alcohols by ruthenium catalyzed isomerization. *J. Fluorine Chem.* **2013**, *152*, 56−61.
(11) Martinez-Erro, S.; Sanz-Marco, A.; Bermejo Gómez, A.; Vázquez-Romero, A.; Ahlquist, M. S. G.; Martín-Matute, B. Base-Catalyzed Stereospecific Isomerization of Electron-Deficient Allylic Alcohols and Ethers through Ion-Pairing. *J. Am. Chem. Soc.* **2016**, *138*, 13408−13414.
(12) Ascough, D. M. H.; Duarte, F.; Paton, R. S. Stereospecific 1,3-H Transfer of Indenols Proceeds via Persistent Ion-Pairs Anchored by NH···π Interactions. *J. Am. Chem. Soc.* **2018**, *140*, 16740−16748.
(13) (a) Shiers, J. J.; Shipman, M.; Hayes, J. F.; Slawin, A. M. Z. Rare Example of Nucleophilic Substitution at Vinylic Carbon with Inversion: Mechanism of Methyleneaziridine Formation by Sodium Amide Induced Ring Closure Revisited. *J. Am. Chem. Soc.* **2004**, *126*, 6868−6869. (b) Corsico, E. F.; Rossi, R. A. Sequential Reactions of Trimethylstannyl Anions with Vinyl Chlorides and Dichlorides by the $S_{RN}1$ Mechanism Followed by Palladium-Catalyzed Cross-Coupliing Processes. *J. Org. Chem.* **2004**, *69*, 6427−6432. (c) Venkat Reddy, C. R.; Urgaonkar, S.; Verkade, J. G. A Highyl Effective Catalyst System for the Pd-Catalyzed Amination of Vinyl Bromides and Chlorides. *Org. Lett.* **2005**, *7*, 4427−4430. (d) Ackermann, L.; Gschrei, C. J.; Althammer, A.; Riederer, M. Cross-coupling reactions of aryl and vinyl chlorides catalyzed by a palladium complex derived from an air-stable H-phosphonate. *Chem. Commun.* **2006**, *13*, 1419−1421. (e) Poulsen, T. B.; Bernardi, L.; Bell, M.; Jørgensen, K. A. Organocatalytic enantioselective nucleophilic vinylic substitution. *Angew. Chem., Int. Ed.* **2006**, *45*, 6551−6554. (f) Bernasconi, C. F.; Rappoport, Z. Recent Advances in Our Mechanistic Understanding for S_NV Reactions. *Acc. Chem. Res.* **2009**, *42*, 993−1003 and references therein.
(14) (a) Oldendorf, J.; Haufe, G. Synthesis of Synthesis of γ-Fluoro-α,β-unsaturated Carboxylic Esters from Saturated α-Fluoro Aldehydes. *J. Prakt. Chem.* **2000**, *342*, 52−57. (b) Guo, R.; Huang, J.; Zhao, X. Organoselenium-Catalyzed Oxidative Allylic Fluorination with Electrophilic N−F Reagent. *ACS Catal.* **2018**, *8*, 926−930.
(15) (a) Zhang, Q.; Mixdorf, J. C.; Reynders, G. J., III; Nguyen, H. M. Rhodium-catalyzed benzylic fluorination of trichloroacetimidates. *Tetrahedron* **2015**, *71*, 5932−5938. (b) Mixdorf, J. C.; Sorlin, A. M.; Zhang, Q.; Nguyen, H. M. Asymmetric Synthesis of Allyl Fluorides via Fluorination of Racemic Allylic Trichloroacetimidates Catalyzed by a Chiral Diene-Iridium Complex. *ACS Catal.* **2018**, *8*, 790−801.
(16) (a) Appel, R. Tertiary Phosphane/Tetrachloromethane, a Versatile Reagent for Chlorination, Dehydration, and P−N Linkage. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801−811. (b) Huy, P. H.; Hauch, T.; Filbrich, I. Lewis Base Catalyzed Nucleophilic Substitution of Alcohols. *Synlett* **2016**, *27*, 2631−2636. (c) Larock, R. C.; Zhang, L. Halogenation of Alcohols. In *Comprehensive Organic Transformations*; Larock, R. C., Ed.; Wiley-VCH: Weinheim, Germany, 2018.
(17) (a) Young, W. G.; Caserio, F. F.; Brandon, D. D. Allylic Rearrangements. XLIX. The Controlled Conversion of α- and γ-Methylallyl Alcohols to Chlorides with Thionyl Chloride. *J. Am. Chem. Soc.* **1960**, *82*, 6163−6168. (b) Snyder, E. I. Conversion of allylic alcohols to chlorides without rearrangement. *J. Org. Chem.* **1972**, *37*, 1466−1466. (c) Corey, E.J.; Kim, C.U.; Takeda, M. New and highly effective method for the oxidation of primary and secondary alcohols to carbonyl compounds. *Tetrahedron Lett.* **1972**, 4339−4344.
(18) (a) Hanessian, S.; Ponpipom, M. M.; Lavallee, P. Procedures for the direct replacement of primary hydroxyl groups in carbohydrates by halogen. *Carbohydr. Res.* **1972**, *24*, 45−56. (b) Bose, A. K.; Lal, B. A facile replacement of hydroxyl by halogen with inversion. *Tetrahedron Lett.* **1973**, 3937−3940. (c) Jaseer, E. A.; Naidu, A. B.; Kumar, S. S.; Rao, R. K.; Thakur, K. G.; Sekar, G. Highly stereoselective chlorination of β-substituted cyclic alcohols using PPh_3-NCS: factors that control the stereoselectivty. *Chem. Commun.* **2007**, 867−869.
(19) Pacheco, M. C.; Purser, S.; Gouverneur, V. The Chemistry of Propargylic and Allylic Fluorides. *Chem. Rev.* **2008**, *108*, 1943−1981.
(20) Synthesis of chiral allylic substrates: Lumbroso, A.; Cooke, M. L.; Breit, B. Catalytic Asymmetric Synthesis of Allylic Alcohols and

https://dx.doi.org/10.1021/acs.orglett.0c01200
Org. Lett. 2020, 22, 4123−4128

Derivatives and their Applications in Organic Synthesis. *Angew. Chem., Int. Ed.* **2013**, *52*, 1890−1932.
(21) (a) Shandala, M. Y.; Waight, E. S.; Weinstock, M. J. The rearrangement of 1-p-fluorophenylallyl, 1-m-tolylallyl, and optically active 1-phenylallyl chlorides in N,N-dimethylformamide. *J. Chem. Soc. B* **1966**, 590−592. (b) Zhang, Q.; Mixdorf, J. C.; Reynders, G. J., III; Nguyen, H. M. Rhodium-Catalyzed Benzylic Fluorination of Trichloroacetimidates. *Tetrahedron* **2015**, *71*, 5932−5938. (c) Mixdorf, J. C.; Sorlin, A. M.; Zhang, Q.; Nguyen, H. M. Asymmetric Synthesis of Allylic Fluorides via Fluorination of Racemic Allylic Trichloroacetimidates Catalyzed by a Chiral Diene-Iridium Complex. *ACS Catal.* **2018**, *8*, 790−801.

https://dx.doi.org/10.1021/acs.orglett.0c01200
Org. Lett. 2020, 22, 4123−4128