Chiral Auxiliaries for Stereoselective Electrophilic Aromatic Substitutions

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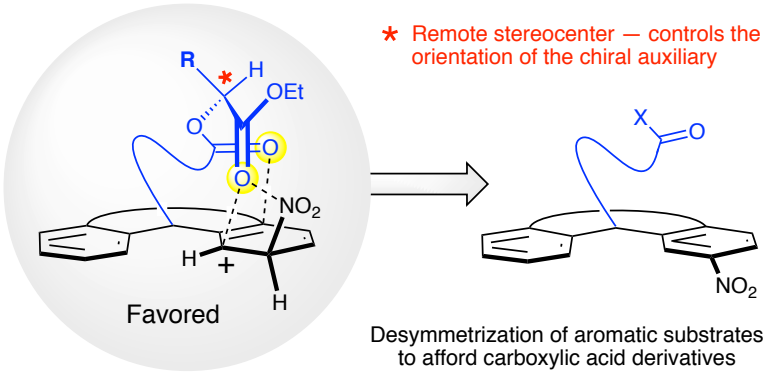


Received:
Accepted:
Published online:
DOI:

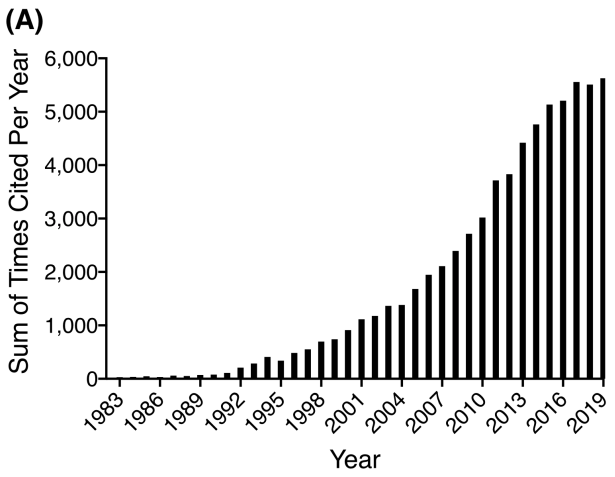
Abstract Electrophilic aromatic substitution reactions are of profound importance for the synthesis of biologically-active compounds and other advanced materials. They represent an important means to activate specific aromatic C–H bonds without requiring transition metal catalysts. Surprisingly, few stereoselective variants are known for electrophilic aromatic substitutions, which limits the utility of these classical reactions for stereoselective synthesis. While many electrophilic aromatic substitutions lead to achiral products (due to the planar nature of aromatic rings), there are important examples where chiral products are produced, including desymmetrization reactions of aromatic cyclophanes and of prochiral substrates with multiple aromatic rings. This *Synpacts* article now illustrates how chiral arms, placed precisely above and underneath delocalized carbocations, can act as chiral auxiliaries to convert classical electrophilic aromatic substitution reactions into powerful diastereo- and enantioselective transformations.

Key words Electrophilic aromatic substitution; enantioselective transformation; chiral auxiliary; density functional theory; Wheland intermediate; polyaromatics; chirality-assisted synthesis; through-space reaction control

Electrophilic aromatic substitution (SEAr) reactions, directed via electron-donating/withdrawing substituents to *ortho*-, *meta*-, and *para*-positions on aromatic rings, have become[4] classical transformations described in nearly every organic chemistry textbook. These reactions are now used frequently by synthetic chemists, and a search for the keyword "electrophilic aromatic substitution reaction" shows (Figure 1A) that the field has been growing substantially for nearly four decades, with steadily increasing total citations per year. Overall, electrophilic aromatic substitution represents a long established[4] method to activate aromatic C–H bonds for further transformations. SEAr reactions are relatively simple to perform as they generally don't require specialized reagents like transition-metal catalysts and/or complex ligands; in fact, many SEAr reactions also readily proceed at or even below room temperature.[4]

Many SEAr reactions achieve excellent regiocontrol (dictated primarily by the relative stabilities of the different possible Wheland intermediates.[4] Yet, it has proven much more difficult to control the stereochemistry of SEAr reactions. While many SEAr reactions lead to achiral products due to the planar nature of aromatic rings, stereochemistry is often introduced[5] at the SEAr step into versatile polyaromatic substrates like tribenzotriquinacenes (TBTQs).[6] TBTQs have emerged as key building blocks for a variety of nanoarchitectures (including, but not limited to large, chiral, self-assembled molecular capsules[7b], trefoil-shaped, porous nanographene,[6j] and enantiopure metallosquares[6e]) with chirality-assisted synthesis[7] and related approaches.[6] Thus, learning how to more efficiently synthesize such structures in a stereocontrolled manner is needed to advance our ability to self-assemble complex nanoscale structures.

Severin T. Schneebeli completed his B.S. degree at the University of Zurich in 2006 and received his Ph.D. degree in 2011 from Columbia University, working jointly with Prof. Ronald Breslow and Prof. Richard Friesner. As an International Institute for Nanotechnology (IIN) Postdoctoral Fellow at Northwestern University with Prof. Sir Fraser Stoddart from 2011 to 1014, Severin's research transitioned to the synthesis and computer-aided design of hierarchical functional nanomaterials. Since Summer 2014, Severin is serving as the PI of the Mesosynthesis Laboratory at the University of Vermont as an Assistant Professor of Chemistry. In 2020, Severin was promoted to Associate Professor. His current research aims to advance the field of soft materials, by investigating how traditional concepts of organic chemistry — like selective recognition and catalysis — can be extended to larger length scales for precision polymer synthesis. Severin is the recipient of a 2018 ARO Young Investigator Award, a 2019 NSF CAREER Award, and a 2020 Thieme Chemistry Journals Award.



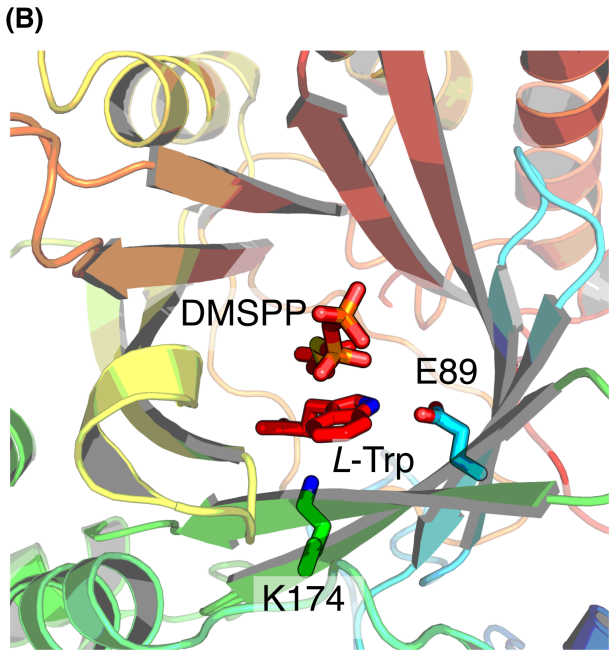
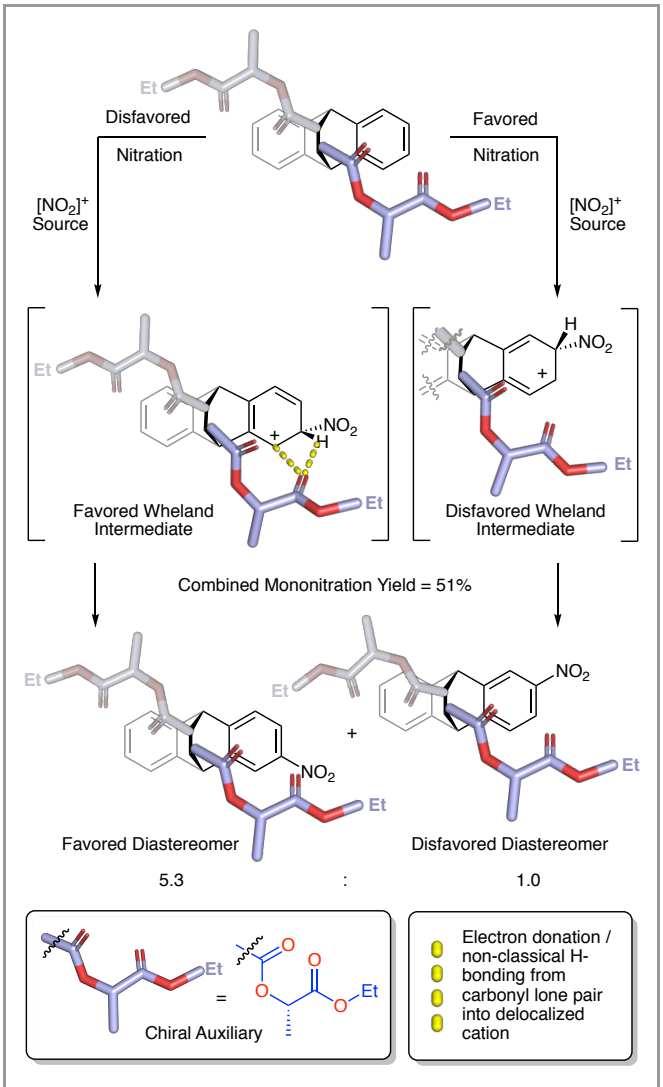


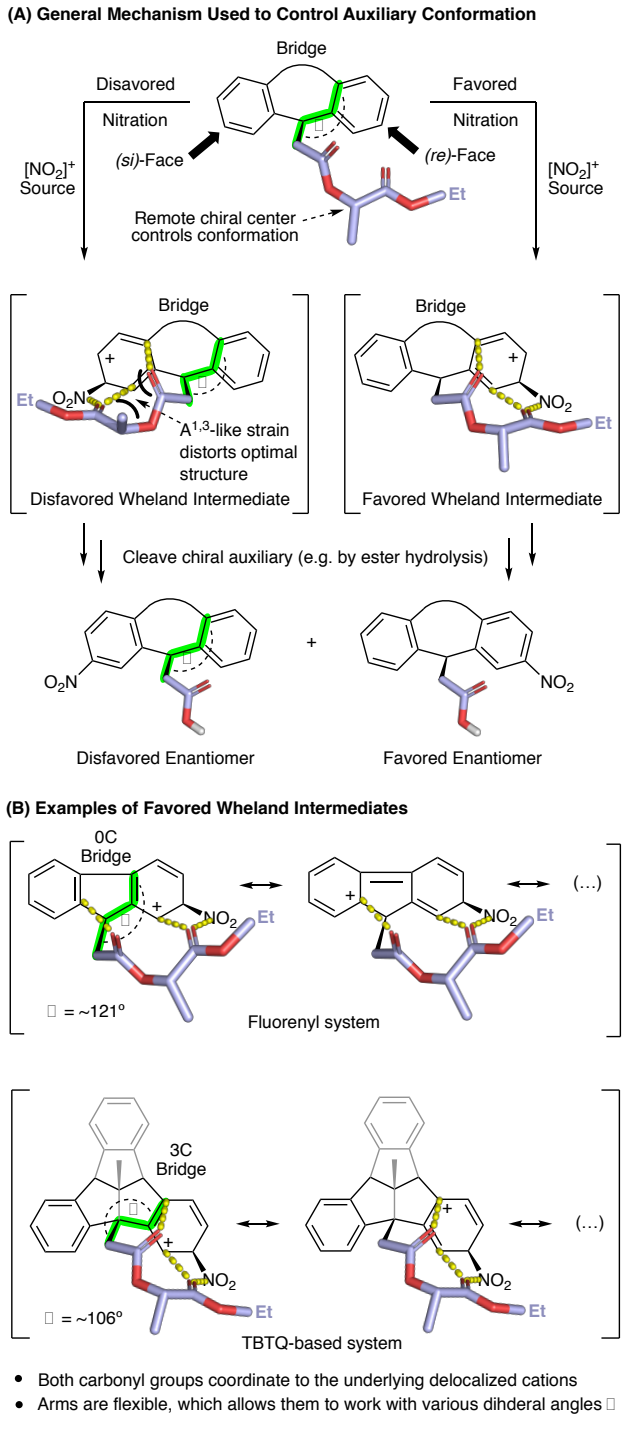
Figure 1 (A) Total citations/year for the search keyword "electrophilic aromatic substitution reaction" in Web of Science.[10] **(B)** An example active site (single crystal X-ray structure, PDBID: 3I4X) of a natural electrophilic aromatic substitution reaction in water, catalyzed by the enzyme dimethallyltryptophane synthase (DMATS). The figure shows how the substrate *L*-tryptophan (*L*-Trp) and the electrophile structural analogue dimethallyl S-thiolodiphosphate (DMSPP) are bound inside the active site of DMATS. The enzyme controls[9a] the regioselectivity of this SEAr reaction with active-site residues like E89 and K174 placed precisely above and underneath the aromatic rings in the *L*-Trp starting material.

In order to meet the challenge of controlling the stereochemistry of SEAr reactions, it is necessary to move the directing groups out of the planes of the aromatic rings, which act as the substrates for the SEAr reactions. This concept, wherein SEAr directing groups are placed precisely above and underneath the reactive aromatic rings or other substrates, is generally referred to as through-space control.[8] Through-space control is well-known in enzymatic systems like dimethallyltryptophane synthase (DMATS), which catalyzes[9] the dimethallylation of *L*-tryptophane via an SEAr reaction in water. In enzymes like DMATS, amino acid residues in the active site are positioned above and underneath the reactive aromatic rings of the substrates to control the outcomes of SEAr reactions.

Notably, the precise placement of such through-space directing residues (in particular K174 in the case of DMATS) can have a profound impact on the regiochemical outcome of enzymatic SEAr reactions. For example, in the case of DMATS, different enzymatic variants are able to generate distinct regioisomeric product distributions, simply by adjusting the positioning of key active site residues like K174, which interact[9a] with the Wheland intermediates of the SEAr reactions through space. See Figure 1B for an example in this regard — a single-crystal X-ray structure[9a] of the DMATS active site in complex with *L*-tryptophane (the SEAr substrate) and dimethallyl S-thiolodiphosphate (DMSPP, a structural analogue of the electrophile). Inspired by how enzymes are able to control SEAr reactions through space, we set out to learn more about how through-space control can be utilized to direct the stereochemical outcome of classical SEAr transformations in the laboratory. We started with electrophilic aromatic nitrations for the following reasons:



Scheme 1 Diastereoselective aromatic nitration directed through-space[8b] by lactate ester-derived chiral auxiliaries. Nitration was accomplished with a mixture of ammonium nitrate and trifluoroacetic anhydride as the $[NO_2]^+$ source at room temperature.



Scheme 2 Electrophilic aromatic nitration reactions directed by chiral diester auxiliaries are able to desymmetrize substrates with multiple aromatic rings.[5b] After cleavage of the chiral auxiliaries, enantioenriched products are obtained. Bonds involved in defining the dihedral angles α are highlighted with a green background. **(A)** General mechanism based on $A^{1,3}$-like strain, which is used to control whether a chiral auxiliary swings to the left or to the right. **(B)** Examples of delocalized Wheland intermediates (both described in reference 5b), which are stabilized by carbonyl-lone-pair to carbocation electron donation from both carbonyl groups of the chiral diester auxiliaries. TBTQ stands for tribenzotriquinacene.

(i) Aromatic nitrations can be performed under relatively mild conditions with a simple nitrate salt (e.g. tetrabutylammonium nitrate) and trifluoroacetic anhydride as the $[NO_2]^+$ source. [8b, 11] This nitration procedure works well[12] in organic solvents (like chloroform or dichloromethane), and it is able to functionalize unactivated aromatic rings at or below room-temperature. In contrast, other popular SEAr reactions (e.g. aromatic halogenations) usually entail harsher conditions (heating and/or the addition of a strong Lewis acid) to achieve reaction of unactivated aromatic rings,[4b, 13] even though these reactions also proceed under mild conditions[13a, 14] with activated aromatic substrates (e.g. phenol derivatives).

(ii) Unlike some other SEAr reactions (e.g. halogenations, where controlling the reaction stoichiometry can challenging due to fast reaction with more than one equivalent of the electrophile) nitration can readily be stopped after a single nitro group has been introduced into an aromatic substrate. This well-known[5] stoichiometric control offered by nitrations, coupled with the fact that nitro groups can readily be converted into many other useful functional groups, has made aromatic nitration a highly popular synthetic transformation over the years.[4]

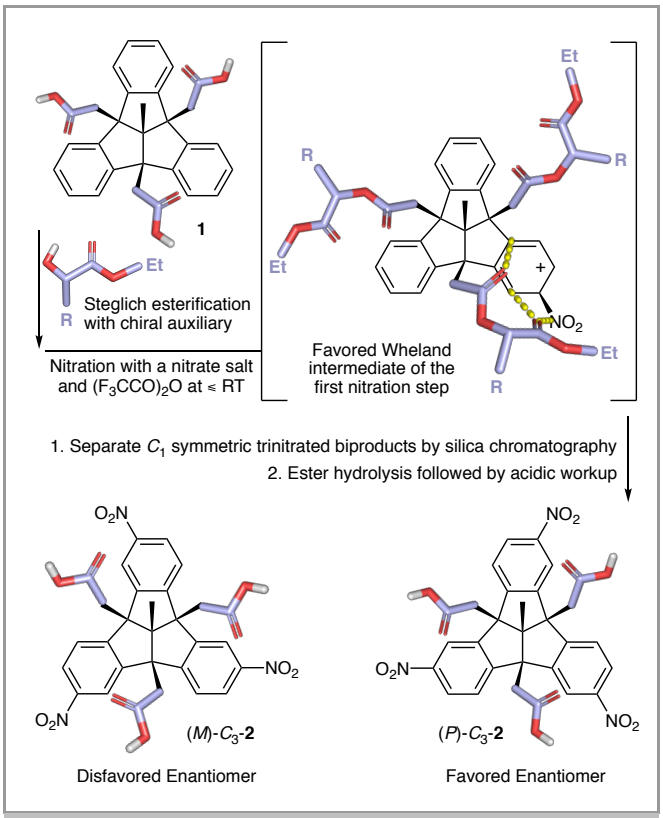
To advance chirality-assisted synthesis,[7] we started to investigate[8b] through space-directed electrophilic aromatic nitrations with 9,10-dihydro-9,10-ethanoanthracene derivatives, with chiral diester arms placed (Scheme 1) above the aromatic rings. ^{1}H-^{1}H NOESY NMR spectroscopy indicated that diastereoselective nitration occurred preferentially at the 2 and 6 positions, which lie directly underneath the chiral diester arms. In contrast, the selectivity mostly disappears with simple ethyl esters as the through space directing groups or in the presence of an ester-based solvent (e.g. ethyl acetate). These findings, which are also supported by DFT calculations, indicate[8b] that the distant carbonyl ester groups on the chiral diester arms are primarily responsible for the observed diastereoselectivity based on the following mechanism:

The overhanging chiral diester arms are able to selectively stabilize (Scheme 1, left Wheland intermediate) the underlying carbocations by (i) carbonyl lone pair-to-carbocation electron-donation. At the same time, the favored Wheland intermediates experience additional stabilization, which arises from (ii) non-classical hydrogen bonding of a carbonyl group with the positively-polarized, acidic protons in the 2 and 6 positions. For nitration in the 3 and 7 positions, the chiral arms are not well positioned to effectively reach over the carbocations and/or the acidic protons of the Wheland intermediates (Scheme 1, right Wheland intermediate), and therefore nitration in the 3 and 7 positions is disfavored. With these experiments, we had established that chiral esters can selectively stabilize specific Wheland intermediates through space to achieve diastereoselective SEAr reactions.

Next, we started to apply[5b] (Scheme 2) the chiral diester auxiliary to achieve SEAr-based, enantioselective aromatic nitration. While catalytic enantioselective aromatic halogenation reactions operating with chiral peptide catalysts are known[15] these catalysts have, to the best of our knowledge, not yet been able to carry out stereoselective SEAr reactions under the more acidic conditions required for aromatic nitrations. As is shown in Scheme 2, our chiral auxiliary is now finally able to meet this long-standing[5b] challenge. Overall, our enantioselective nitration process, which is directed by readily available chiral diester auxiliaries, is implement with the following three synthetic steps:

(i) The chiral auxiliary is introduced into the starting material. This step is accomplished by condensing a carboxylic acid functional group in the starting material with a commercially available lactate ester (e.g. *(S)*- or *(R)*-ethyl lactate) in a straightforward Steglich esterification[16] (see Scheme 3 for an example). (ii) Nitration is carried out at or below room temperature with a nitrate salt (e.g. tetrabutylammonium nitrate) and trifluoroacetic anhydride as the $[NO_2]^+$ source. (iii) The ester-based chiral auxiliary is cleaved, e.g. by simple hydrolysis back to the acid, or by reduction to the alcohol.

Our electrophilic aromatic nitration protocol allows for effective desymmetrization[6] of substrates like fluorenes or TBTQs, which contain two or more equally reactive aromatic rings.



Scheme 3 Regio- and enantioselective synthesis[5b] of C_3-symmetric tribenzotriquinacene (TBTQ) derivatives, based on electrophilic aromatic nitration reactions directed through space by three identical chiral diester auxiliaries.

The key to distinguishing the aromatic rings is $A^{1,3}$-like strain, which arises in the disfavored conformation of the chiral auxiliary between the proximal carbonyl group of the chiral auxiliary and the methyl substituent of the lactate group. This $A^{1,3}$-like strain pushes (Scheme 2A) the diester arm of the chiral auxiliary selectively over the *(re)*-face of the aromatic substrate. Consistent with this mechanism, we have found[5b] (Table 1) that when the methyl substituent on the chiral auxiliaries are substituted with larger isopropyl groups, the enantiomeric ratio (*e.r.*) observed for trinitration of the TBTQ derivative shown in Scheme 3 increases from ~6:1 to ~9:1.

Table 1 Bulkier chiral substituents –R attached to the chiral auxiliaries enhance the regio- and stereocontrol for the trinitration reaction shown in Scheme 3. Increasing the steric bulk of –R offers enhanced $A^{1,3}$-like strain, which is used to control (Scheme 2) the orientation of the chiral auxiliaries.

–R	*e.r.*[a]	C_3 Nitration Yield[b]	C_1 Nitration Yield[c]
$-CH_3$	6:1	34%	55%
$-(CH)(CH_3)_2$	9:1	44%	56%

[a] *(P)*-C_3-**2** : *(M)*-C_3-**2** ratio (determined[5b] by ^{1}H NMR integration)

[b] Combined trinitration yield of all C_3 symmetric products

[c] Combined trinitration yield of all C_1 symmetric products

At the same time, both carbonyl groups of the auxiliaries' ester functionalities coordinate (Scheme 2) to the underlying carbocations in the Wheland intermediates. This chelation-driven dicarbonyl-to-carbocation interaction rigidifies the geometries of the Wheland intermediates, which in turn amplifies[5b] the $A^{1,3}$-like strain to further enhance the diastereoselectivity of the nitration reactions. Overall, the chiral, lactate-derived diester auxiliaries seem to provide a good balance between shape-persistence and flexibility and the auxiliaries are still sufficiently malleable to adopt to different substrate geometries (including fluorenyl derivatives[5b]) with different dihedral angles α (please see Scheme 2 for the definition of α).

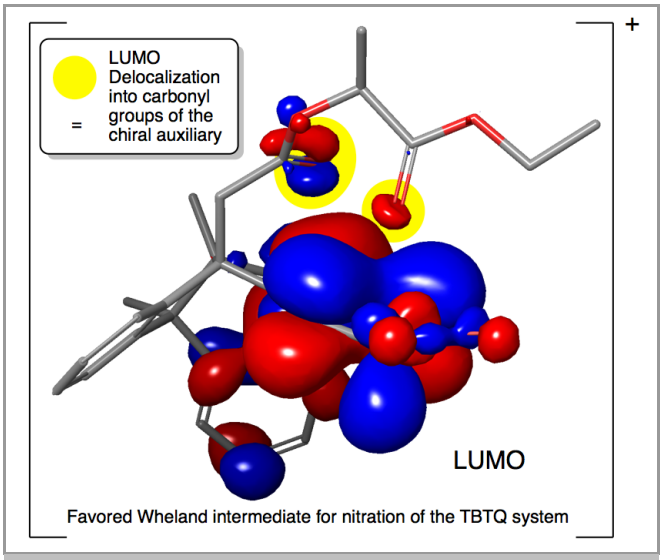


Figure 2 Isosurface plot showing the lowest unoccupied molecular orbital (LUMO) of the favored Wheland intermediate for tribenzotriquinacene (TBTQ) nitration. The LUMO, which was calculated at the B3LYP[17] LACVP* level of theory, is delocalized into both carbonyl groups of the chiral auxiliary.

The chelating dicarbonyl-to-carbocation interaction is clearly shown by DFT calculations of the lowest unoccupied molecular orbital (LUMO, see Figure 2 for an example), which is delocalized into both carbonyl groups. This finding is consistent with electron donation into the carbocation (the LUMO) from both carbonyl groups. Furthermore, the DFT calculations also indicate[5b] hat the selectivity for the nitration reactions will decrease, if the proximal ester group is simply replaced by two $-CH_2-$ groups (which are not able to coordinate as effectively to the underlying carbocations in the Wheland intermediates).

In conclusion, we invented diester-based chiral auxiliaries, which are able to control the stereoselectivity of electrophilic aromatic nitration reactions precisely through space. The chiral auxiliaries are

commercially available and readily installed/removed via simple esterification/ester hydrolysis. While the initial enantioselectivities obtained with these auxiliaries were still modest — in the range of ~2.5:1 (for a single nitration) up to ~6:1 (for three consecutive nitrations) with the commercially-available lactate-derived auxiliaries — we are currently extending our chiral auxiliaries to contain more contact points with the underlying carbocations. This strategy has started to lead to increased selectivities. Furthermore, we have also begun to investigate the use of the chiral diester auxiliaries for other types of electrophilic aromatic substitution reactions, in addition to nitrations. These new results will be reported in due course.

Funding Information

This research was supported by an NSF grant from the Chemistry Division (grant number: CHE-1848444) awarded to S.T.S. R.O.B. was supported by a Summer Undergraduate Research Fellowship at the University of Vermont. Computational resources for this paper were provided by the Vermont Advanced Computing Core (VACC).

Acknowledgment

We thank Prof. Jianing Li at the University of Vermont for helpful discussions.

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