Enantioselective Aryl-Iodide-Catalyzed Wagner–Meerwein Rearrangements

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ABSTRACT: We report a strategy for effecting catalytic, enantioselective carbocationic rearrangements through the intermediacy of alkyl iodanes as stereodefined carbocation equivalents. Asymmetric Wagner–Meerwein rearrangements of β-substituted styrenes are catalyzed by the C_2-symmetric aryl iodide **1** to provide access to enantioenriched 1,3-difluorinated molecules possessing interesting and well-defined conformational properties. Hammett and kinetic isotope effect studies, in combination with computational investigations, reveal that two different mechanisms are operative in these rearrangement reactions, with the pathway depending on the identity of the migrating group. In reactions involving alkyl-group migration, intermolecular fluoride attack is product- and enantio-determining. In contrast, reactions in which aryl rearrangement occurs proceed through an enantiodetermining intramolecular 1,2-migration prior to fluorination. The fact that both pathways are promoted by the same chiral aryl iodide catalyst with high enantioselectivity provides a compelling illustration of generality across reaction mechanisms in asymmetric catalysis.

Introduction

Carbocations are highly reactive intermediates that can undergo skeletal rearrangements through the migration of strong σ bonds, thereby enabling access to valuable carbon frameworks.[1] The energetic barriers to σ-bond migrations in free carbocations are generally low,[2] so control over selectivity in such rearrangement pathways is intrinsically challenging. Successful strategies identified to date for stereochemical control have relied on engagement of electrophiles bearing excellent leaving groups as carbocation surrogates that undergo stereospecific substitutions (Figure 1A).[3] For example, catalytic, enantioselective semipinacol rearrangements have been developed in which transient electrophiles generated stereoselectively by coordination of chiral transition metal complexes or halonium ion equivalents to π-systems undergo stereospecific migration of a C–C or C–H bond from an adjacent carbinol (Figure 1B).[4] The weakly electrophilic nature of the π-adducts generally limits the scope of these reactions to those generating oxocarbenium and iminium ions. In considering approaches to enantioselective catalytic asymmetric Wagner–Meerwein rearrangements, i.e. 1,2-migrations involving non-heteroatom-stabilized carbocations,[5] we were drawn to the possibility of leveraging the configurational stability and extraordinarily high electrophilicity[6] of chiral alkyl iodane intermediates generated via hypervalent iodine catalysis (Figure 1C).[7] Here we report the successful application of this approach to enantioselective catalytic rearrangements of β-substituted styrene derivatives through the 1,2-migration of aryl, methyl, or hydride groups (Figure 1D). These reactions provide a novel approach to chiral 1,3-difluorinated molecules possessing unique conformational properties driven by the minimization of unfavorable 1,3-dipolar interactions.[7k,8] In addition, they offer a powerful tool for evaluation of the distinct mechanistic pathways that have been advanced in hypervalent iodine-catalyzed alkene fluorofunctionalizations (Figure 1E).[7,9]

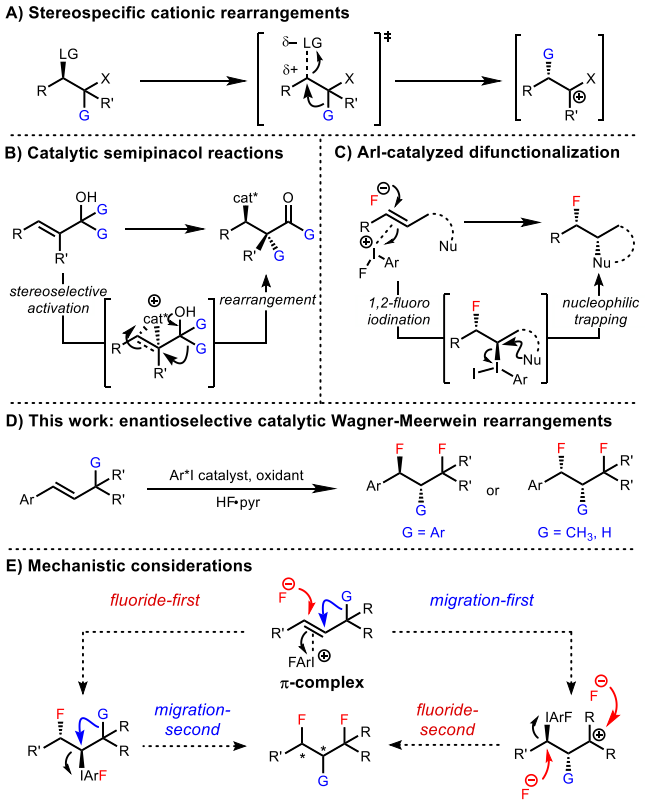


Figure 1. A) Stereospecific cationic rearrangements. B) Successful examples of enantioselective, catalytic rearrangements involve semipinacol rearrangements of allylic alcohol derivatives. C) Aryl iodide-catalyzed enantioselective fluorofunctionalizations. D) Aryl iodide-promoted Wagner–Meerwein rearrangements (this work). E) Mechanistic considerations. LG = leaving group. G = potential migrating group. Ar = aryl.

Results and Discussion

1) Reaction Development

The β-cumyl styrene derivative **2a** was evaluated as a model substrate for the proposed Wagner–Meerwein rearrangement. In the presence of the chiral aryl iodide catalyst **1**, m-CPBA as a stoichiometric oxidant, and pyr·9HF (20 equiv of HF) as the fluoride source **2a** was observed to undergo selective oxidation to generate the corresponding 1,3-difluorinated product **3a** as the anti diastereomer in 90% e.e.

(Figure 2).[10] A larger excess of HF-pyridine (100 equiv) was required to reach full conversion with substrates bearing electron-deficient migrating arenes . The level of 1,2-anti-diastereoselectivity was found to be highly dependent on the electronic properties of the arenes, decreasing with more electron-deficient migrating arenes and more electron-rich stationary arenes. Both the predominant 1,2-anti and minor 1,2-syn diastereomers of **3f** were generated with within 2% e.e. of each other.

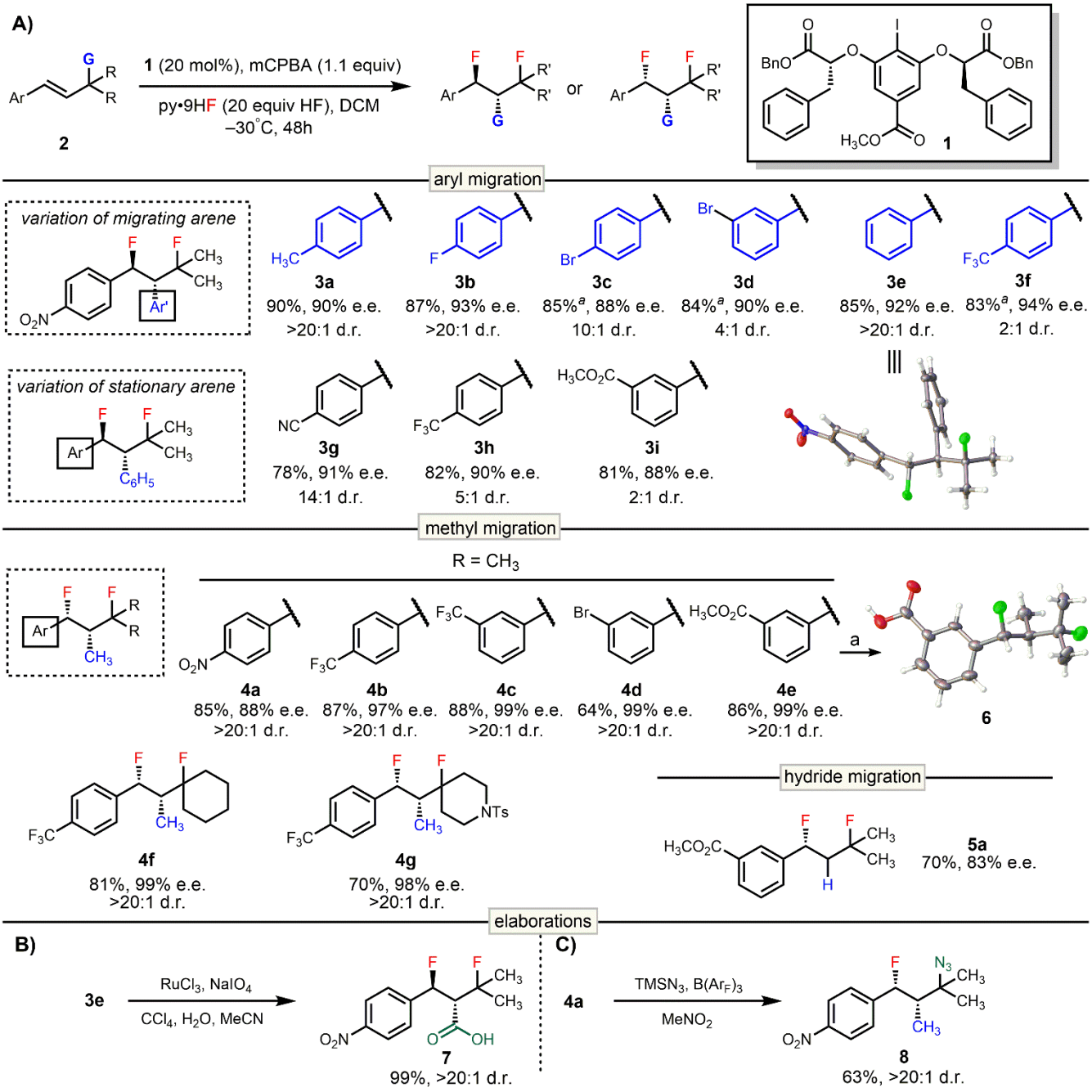


Figure 2. A) Substrate scope for the enantioselective, catalytic Wagner-Meerwein rearrangements. Reactions were carried out using 0.52 mmol scale of styrenyl substrate **2**, catalyst **1** (20 mol%), *m*CPBA (0.57 mmol), and pyr·9HF (10.4 mmol HF) in DCM (3.0 mL). [a]100 equiv HF were employed. Conditions for step a: **4e** (0.45 mmol), KOTMS (0.9 mmol) in Et_2O (2.7 mL) and THF (1.8 mL). B) Oxidative degradation of **3e** to carboxylic acid **7**. Conditions: B) product **2c** (0.25 mmol), $RuCl_3·(H_2O)_3$ (2.5 μmol), and $NaIO_4$ (3.49 mmol) in H_2O (1.3 mL), MeCN (0.65 mL), and CCl_4 (0.65 mL) at room temperature for 18 h C) Azidation of the tertiary fluoride **4a**. Conditions: **4a** (0.185 mmol), $TMSN_3$ (0.37 mmol), and $B(C_5F_5)_3$ (9 μmol) in $MeNO_2$ (93 μL) at room temperature for 90 min. All yields are of isolated products.

The Wagner–Meerwein reactions catalyzed by **1** were extended successfully to rearrangements involving non-aryl migrating groups. For example, β-t-butyl styrene derivatives underwent highly enantioselective 1,3-difluorination reactions

involving methyl migration. In contrast to the aryl-migration reactions described above, uniformly high 1,2-syn, rather than 1,2-anti, diastereoselectivity was observed. A third substrate class bearing β-isopropyl-substitution was also shown to undergo hydride migration (**5a**), albeit with slightly diminished enantioselectivity. Effective enantiocontrol was thus demonstrated migrating groups spanning over three orders of magnitude of migratory aptitude.[11]

The 1,3-difluorinated products of these Wagner–Meerwein rearrangements possess relatively simple structures, but they can be elaborated readily to more highly functionalized molecules. For example, chemoselective oxidation[12] of the more electron-rich phenyl ring of **2e** by $RuCl_3/NaIO_4$ afforded carboxylic acid **7** (Figure 2B). Selective substitution of the more labile tertiary fluoride[13] of **4a** under Lewis-acidic conditions followed by subsequent trapping by azide resulted in the formation of the versatile chiral 1,3-fluoroazide **8** (Figure 2C).

2) Mechanism and enantiodetermining step of the Wagner–Meerwein rearrangements

The Wagner–Meerwein rearrangements described above fall within the growing list of enantioselective oxidative difunctionalizations of alkenes promoted by hypervalent iodine reagents.[7d,f-o,9a] In general, these reactions are understood to proceed via aryl-I(III) intermediates that undergo activation by acid in the presence of alkenes to form highly electrophilic π-complexes (Figure 3). The ordering of the subsequent steps has been a topic of debate in the literature.[7b,d,g,k,m,p,,8] In the scenario depicted as "X^--first", the anionic nucleophile associated with the hypervalent iodine intermediate first attacks the π-complex to generate a chiral alkyl iodane, which then undergoes a second substitution step by an internal or external nucleophile. In the "nucleophile-first" scenario, those steps are reversed with initial attack by an internal or external nucleophile followed by displacement of the alkyl iodane by the anionic nucleophile. In both cases, to the extent that each elementary step is stereospecific, the overall 1,2-addition is predicted to be stereospecific with net syn addition. While both mechanisms produce the same outcome, they differ in the identities of the enantiodetermining events as long as the alkene complexation event is reversible.[14] To date, no experimental investigations into the ordering of these events have been reported for any enantioselective ArI-catalyzed difunctionalization reaction. As noted above, the Wagner–Meerwein rearrangements described herein allow variation of the trapping group (Nu) – in this case the migrating group – over a wide range of nucleophilicities, and therefore offer a unique opportunity to investigate this fundamental mechanistic question.

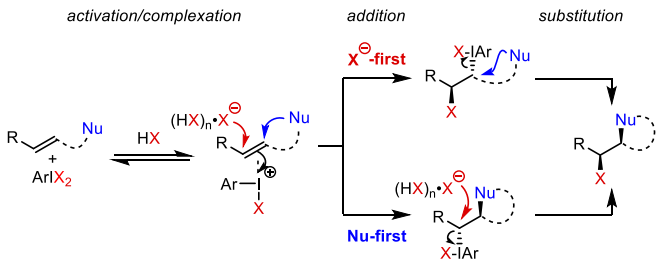


Figure 3. General mechanistic considerations in I(III)-promoted oxidative difunctionalizations of alkenes

a) Aryl migration reactions

The mechanistic dichotomy outlined above is manifest in the aryl migration reactions as fluoride-first and migration-first pathways (Figure 4A). The fluoride-first pathway involves attack of the styrenyl-iodonium π-complex **A** by fluoride to deliver an anti-1,2-fluoroiodane. Subsequent migration of the aryl group should occur invertively via a bridging phenonium[15] intermediate, which would be opened by fluoride at the more substituted position to give the 1,3-difluorinated product. In the migration-first scenario, the activated styrenyl-iodonium π-complex would undergo invertive displacement by the migrating arene to generate a phenonium intermediate with an adjacent benzylic iodane. This putative intermediate possesses two electrophilic sites disposed to fluoride substitution to generate the 1,3-difluoride product. Substitution could occur in either order, with the syn diastereomer expected based on either sequence if all migrations and substitutions are invertive. However, if fluoride attack occurs first on the phenonium ion (pathway b), then the resulting intermediate **C** would be poised to form a second phenonium ion (**D**), as has been documented in other I(III) mediated reactions.[16] Opening of this phenonium intermediate by fluoride at the benzylic position would be expected to lead to the anti diastereomer of 1,3-difluoride.

The anti diastereomer of aryl-migration product **3** is observed to predominate for all substrates examined (Figure 2), so the experimental stereochemical outcomes are thus more readily reconciled with the migration-first mechanism involving phenonium ion intermediates **B** and **D**. The minor syn diastereomer could arise through any of the alternative pathways outlined in Figure 4A. Alternatively, non-stereospecific displacement of the highly labile benzylic C–I(III) bond in intermediates **B** or **C** could also lead to mixtures of syn and anti products.[17] The participation of such SN1 pathways is consistent with the observed electronic effect of the stationary aryl group (**3e**, **g-i**, Figure 2), wherein lower diastereomer ratios are observed with more electron-donating substituents.

The impact of the electronic properties of the migrating aryl group was analyzed in a Hammett study (Figure 4B). Relative rates of reaction of substrates bearing different substituents on the migrating aryl group were determined in one-pot competition experiments. Such one-pot competitions allow assessment of the highest kinetic barrier involving the substrate, even if a step such as catalyst reoxidation that does not involve the substrate is rate-determining. Analysis of the relative rates of **2a** and **2c–f** revealed that substrates bearing electron-rich migrating arenes were consumed more rapidly, with excellent Hammett correlations obtained with both σ ($\rho = -3.7$, $R^2 = 0.99$) and σ+ values ($\rho+ = -2.9$, $R^2 = 0.96$). The large, negative ρ value is consistent with phenonium ion formation accompanied by a high degree of positive charge development in the migrating arene in the first irreversible step involving substrate. Similar correlations have been observed in semi-pinacol rearrangements of tetraaryl diols ($\rho+ = -3.0$), where aryl migration is rate-determining.[18] If either formation of the π-complex **A** or fluoride attack on the π-complex were the substrate-committing step, the migrating arene would be relatively insulated from those events and a small σ value would be predicted. This analysis thus rules out both the fluorination-first pathway and substrate-committing π-complex formation and is consistent instead with a migration-first pathway involving irreversible, and thus enantiodetermining, arene migration.

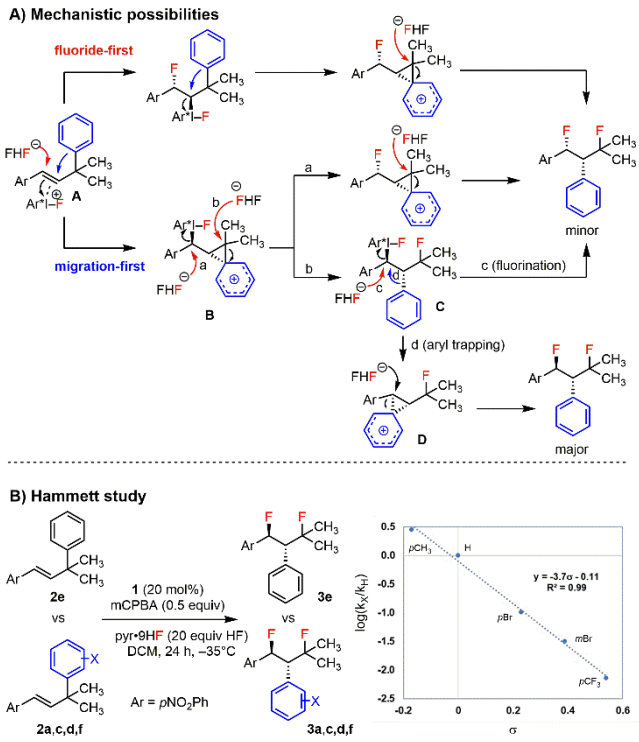


Figure 4. A) Aryl-rearrangement mechanistic possibilities. B) Hammett study of the aryl migration step is the first substrate-committing step and therefore enantiodetermining.

b) Alkyl-migration reactions

In contrast to the aryl migration reactions analyzed above, the methyl migration reactions involve a significantly less nucleophilic, sp^3-hybridized migrating group that cannot form a metastable bridged intermediate,[11] and uniformly high selectivity for the syn diastereomer is obtained in each of the cases examined (**4a-g**, Figure 2). The latter observation is consistent with a sequence of stereospecific steps in the overall process, but it does not allow distinction between fluoride-first or migration-first scenarios (Figure 5A).

The timing of bond-forming and bong-breaking events in the methyl-migration reactions was probed through a set of $^{12}C/^{13}C$ kinetic isotope effect (KIE) studies. The bond between the allylic C2 and the migrating carbon C1 is cleaved in the substrate-committing step in the migration-first mechanism, but it is left essentially unperturbed in the substrate-committing step in the fluoride-first mechanism (Figure 5A). Therefore, a primary intermolecular KIE on C1 is expected in the former case, while a negligible KIE (ca. 1.00) is expected in the latter. As a useful benchmark, a primary KIE on migrating methyl groups of 1.027 was reported in the rearrangement of neopentyl tosylate systems, where methyl migration is rate-determining.[19] The intermolecular KIE in the Wagner–Meerwein methyl rearrangement was evaluated with a β-t-butyl styrene derivative at natural isotopic abundance, where all substrate can be considered to be unlabeled or singly ^{13}C labelled at the C1 or C2 positions. Isotopic enrichment was assessed from fractionation measurements obtained using the DEPT method reported recently by our group.[20] In this manner, a KIE of 0.996(2)[21] was determined, consistent with a fluoride-first pathway and inconsistent with substrate-committing methyl migration. A KIE of 0.999[22] was also determined at C2 using the MQF method recently reported by our group; [23] this negligible KIE is similarly consistent with no change in the C1-C2 bond during the substrate-committing step.[24] The intrinsic primary KIE for the methyl migration was determined in an intramolecular KIE experiment and found to be in the expected range (1.026).[19]

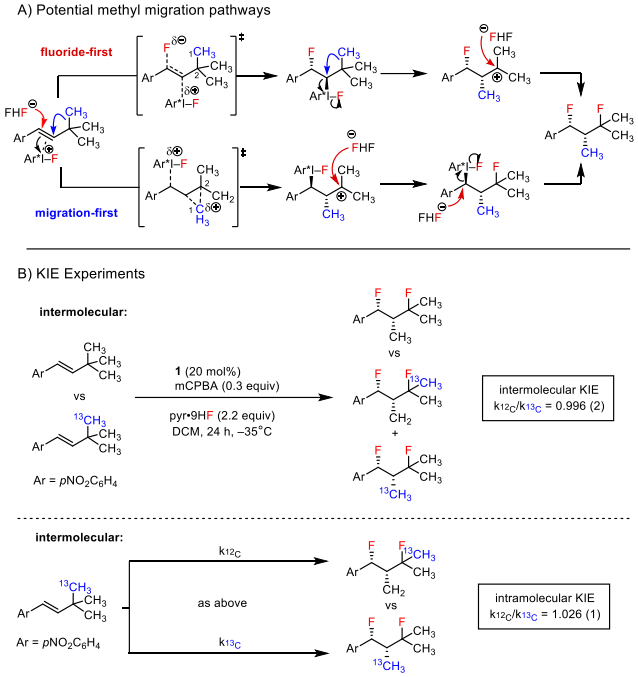


Figure 5. A) Alkyl-rearrangement mechanistic possibilities. B) $^{12}C/^{13}C$ KIE experiments.

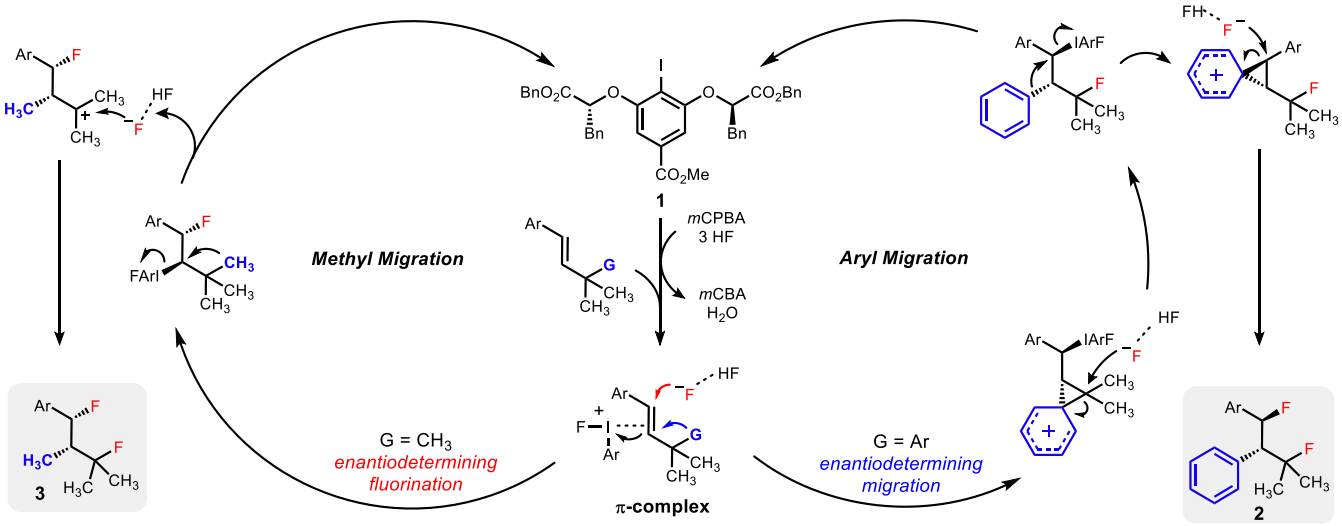
The possibility that formation of the alkene-iodonium complex – which is common to both the fluoride-first and migration-first mechanisms – might be the substrate-committing step in the methyl migration reactions was assessed by determining the KIEs at the alkene carbons. A value of 1.007[25] for the benzylic carbon was determined. Computational modeling of these steps (B3LYP-D3(BJ)/6-31G*/ LANL2DZ/PCM) predicts significant KIEs of 1.01–1.02 for the fluoride-first mechanism, but negligible KIEs for alkene-iodonium complexation (<1.003). It should be added that the rate of π-complexation is expected to be similar for the aryl and methyl rearrangement substrates, and rate-limiting π-complexation was ruled out in the arene migrations by the observation of a large electronic effect of the arene substituents on reaction rate. Thus, all of the available data are most consistent with reversible -complexation followed by irreversible, substrate-committing fluoride addition in the methyl migration reactions.

On the basis of the studies outlined above, two distinct catalytic mechanisms need to be invoked for the aryl-iodide-promoted methyl and aryl rearrangement reactions (Scheme 1). In the methyl rearrangement reaction, the observed syn product results from π-complexation of the substrate followed by irreversible substrate-committing and enantio-determining fluoride attack to form the 1,2-fluoroiodinated adduct. This highly electrophilic intermediate undergoes stereospecific methyl migration to form a tertiary carbocation that is then quenched with fluoride to deliver the observed product. Conversely, in the aryl rearrangement reaction, the experimental observations are only consistent with substrate-committing and enantio-determining aryl migration. The observed anti selectivity can be rationalized by the intermediacy of a second phenonium intermediate, which is opened at the benzylic position by fluoride to give the observed product.

Conclusion

The C2-symmetric aryl iodide **1** was shown to catalyze Wagner–Meerwein rearrangements involving aryl, alkyl, and hydride migrations to afford a variety of 1,3-difluorinated products in good yields and high enantio- and diastereoselectivities. These reactions provide new and compelling illustrations of the remarkably high electrophilicity and versatile reactivity of the intermediate alkene-iodonium π-complexes and alkyl iodanes. The most remarkable conclusion from these studies, however, is that the mechanism of catalysis and identity of the enantiodetermining event are dependent on the identity of the migrating group.

In reactions involving alkyl-group migration, intermolecular fluoride attack is product- and enantio-determining, whereas aryl rearrangement pathways proceed via enantiodetermining intramolecular 1,2-migration. It is noteworthy that both pathways are operative under the same conditions for closely related substrates, and both are promoted by the same chiral aryl iodide catalyst with high enantioselectivity, thereby providing a compelling illustration of generality across reaction mechanisms in asymmetric catalysis.[26]



Scheme 1. Proposed catalytic cycles based on Hammett, KIE, and computational analyses.

ASSOCIATED CONTENT

Supporting Information. Supporting information is available free of charge via the Internet at http://pubs.acs.org.

Experimental procedures, characterization data, and details of mechanistic experiments (PDF)
Crystallographic data for **3e** (CIF)
Crystallographic data for **6** (CIF)

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Notes

The authors declare no competing financial interest.

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