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Organoselenium-catalyzed enantioselective *syn*-dichlorination of unbiased alkenes

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ABSTRACT

The enantioselective dichlorination of alkenes is a continuing challenge in organic synthesis owing to the limitations of selective and independent antarafacial delivery of both electrophilic chlorenium and nucleophilic chloride to an olefin. Development of a general method for the enantioselective dichlorination of isolated alkenes would allow access to a wide variety of polyhalogenated natural products. Accordingly, the enantioselective *suprafacial* dichlorination of alkenes catalyzed by electrophilic organoselenium reagents has been developed to address these limitations. The evaluation of twenty-three diselenides as precatalysts for enantioselective dichlorination is described, with a maximum e.r. of 76:24 Additionally, mechanistic studies suggest an unexpected Dynamic Kinetic Asymmetric Transformation (DyKAT) process may be operative.

1. Introduction

The vicinal dihalogenation of alkenes is familiar to every organic chemist and is taught in every introductory organic chemistry course. This special stature is a consequence of its generality for a wide variety of alkenes and the predictable diastereoselectivity associated with it. The relative configuration of the dihalide products and the mechanistic explanation for the diastereoselectivity observed were a matter of great debate in the early 20th century [1,2]. The intermediacy of haliranium ions and the stereochemical requirement of invertive opening eventually gained acceptance, and much later the isolation and characterization of stable bromiranium ions established their existence with certainty [3,4].

Despite this foundational mechanistic understanding and the high diastereoselectivity obtained with many electrophilic halogen sources, methods available for catalytic, enantioselective vicinal halogenation of alkenes are distinctly lacking when compared to the myriad other vicinal, difunctionalization reactions of alkenes such as epoxidation [5–7], dihydroxylation [8–10], hydrogenation [11–13], and intramolecular halofunctionalization [14–16].

This deficiency is not for a lack of necessity; several classes of vicinally polyhalogenated (usually marine) natural products could be efficiently prepared were a selective alkene dihalogenation available (Fig. 1) [17]. Owing in part to this limited synthetic accessibility, much less is known about the biological activities of these natural products compared to terrestrial bacterial, plant, and fungi isolates.

Synthetic approaches to these natural products involve diastereo- and enantioselective generation of oxygen-bearing stereocenters through historically well-developed asymmetric oxidations and subsequent stereospecific replacement of oxygen with chlorine or alcohol-directed diastereoselective dichlorination [18–22]. Although several of these natural products have been obtained in what are undoubtedly impressive feats of total synthesis, the multiple steps required to enantioselectively transform an alkene into a vicinal dichloride highlight a major shortcoming in the synthetic organic chemist's toolkit.

Although several attempts have been made to address this challenge in the last decade (*vide infra*), all are reliant on halenium ion (or equivalent) delivery to an alkene, resulting in a haliranium ion, which is subsequently opened by a halide anion to afford the vicinal dihalide in an overall antarafacial fashion. Numerous hurdles must be overcome to design an alkene dihalogenation by this approach (Scheme 1) [23,24]. In a simplified system, chiral catalyst (**Cat***), coordinated by either hydrogen bonding, Lewis base association, or ion pairing to the electrophilic halogen source ($\mathbf{X}^+$), delivers the halenium ion to the olefin with enantiofacial selectivity. The possibility for enantiofacial selectivity in this transfer may be attenuated by the stereoelectronic requirement of

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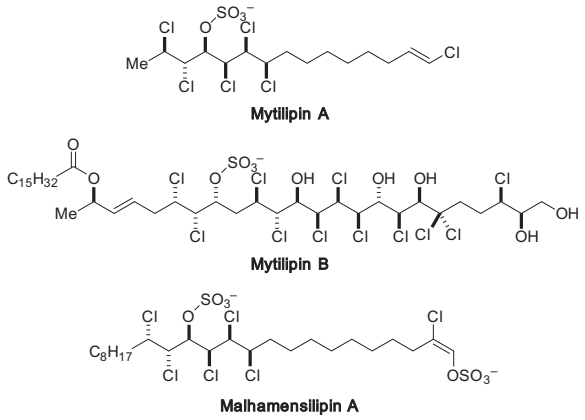


Fig. 1. Representative chlorosulfolipids, a subclass of halogenated natural products.

interaction between the alkene π-orbital and the **Cat***–**X** σ* orbital, placing the most significant steric effects of the chiral catalyst far from the alkene, axially opposite the halenium ion (Scheme 1, right). The haliranium ion thus formed is opened by halide ($\mathbf{X}^-$) to afford the dihalide product. To achieve high enantioselectivity (assuming high enantiofacial selectivity), first, halenium ion transfer to the alkene should be irreversible [25]. Second, the haliranium ion thus formed should be configurationally stable. Finally, nucleophilic trapping of the haliranium ion must be biased toward one carbon terminus of the ion, as the two possible ring-opened products are enantiomeric. *Consequently, both haliranium ion formation and capture must be highly selective to afford highly enantioenriched vicinal dihalide product*.

In spite of the hurdles to the development of an enantioselective *anti*-dihalogenation [23], four methods for catalytic, enantioselective dichlorination following this process have been developed (Fig. 2) [26–30].

Nicolaou and coworkers first achieved moderate to good enantioselectivities for the dichlorination of cinnamyl alcohols **1** [26]. This method employs Lewis base (ligand-accelerated) catalysis to activate an iodosobenzene dichloride derivative as the chlorenium ion and chloride source. Both the alcohol and aromatic ring on the substrate alkene are necessary to achieve good selectivity, most likely due to the requirement for hydrogen-bonded ligand association to the substrate and a strong electronic bias for selective chloriranium ion opening.

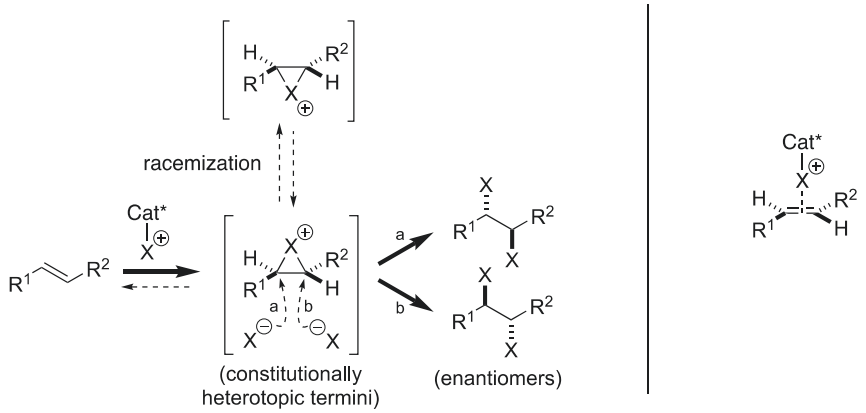
Adaptation of these conditions by Borhan and coworkers to the dichlorination of allylic amides **3** afforded a wide variety of *E* and *Z*-disubstituted alkenes with excellent yields and selectivities [27]. In contrast to the method of Nicolaou and coworkers, Cinnamyl and 3,3-dialkyl (trisubstituted) alkene substrates afforded dichloride products with lower enantiomeric ratios, suggesting that the electronic bias of chloriranium opening generally favors the carbon proximal to nitrogen, and stabilization of partial positive charge at the distal carbon reduces that selectivity.

Most recently, Hennecke and coworkers have further adapted this method, through modification of cinchona alkaloid-derived ligand, to afford dichloride products in modest to excellent selectivities from alkenes **5** not bearing allylic hydrogen-bonding functional groups [28]. The method does nonetheless still rely on styrenyl substrates to bias chloriranium opening toward the carbon proximal to the benzene ring. Furthermore, the substrate scope was limited to *Z*-olefins and only a select few electron-poor dihydronaphthalenes gave dichloride products with e.r. greater than 90:10.

Perhaps the most general method, developed by Burns and coworkers, requires allylic alcohol substrates **7** but has a much broader scope. Here, a halotitanium triisopropoxide complex and a halenium ion source (*t*-BuOCl or NBS) with catalytic amounts of a Salen-type ligand provide vicinal *anti*-dihalide products. Exquisite selectivity is obtained in bromochlorination, dibromination, and dichlorination across a wide variety of 1,1-di-, 1,2-*E*- and *Z*-di-, and trisubstituted olefins. The scope and selectivity of the method rivals the Sharpless asymmetric epoxidation (Scheme 2) [29,30].

Similar to the method of Nicolaou et al., this transformation is suggested to operate within a similar manifold of Lewis base, or ligand accelerated, catalysis. The halenium ion source is only reactive enough to oxidize the alkene once it has been coordinated to a ligated titanium center (coordination to chlorotriisopropoxytitanium is insufficient as little background reaction is observed in the absence of ligand). A structural limitation to the scope of this antarafacial dihalogenation is the requirement for an allylic alcohol to direct halenium ion and halide addition to the double bond. Although this feature can be leveraged to their advantage as evidenced by the presence of simple alkenes left untouched in a variety of products, the limitation does emphasize the need to overcome unselective haliranium ion opening by tethering the halide source, tightly bound to titanium, to the alcohol.

In contrast to these antarafacial vicinal dihalogenations, suprafacial dihalogenation (pictured below as proceeding through a different *–iranium* ion intermediate but true for all suprafacial dihalogenations) [31–34] converges to a single enantiomer, or does not proceed through an intermediate that could diverge (Scheme



Scheme 1. Symmetry analysis of stereochemical transformations in enantioselective *antarafacial*-vicinal dihalogenation. Enantiodetermining steps are highlighted with bold arrows. Cat* = chiral catalyst, X = halogen.

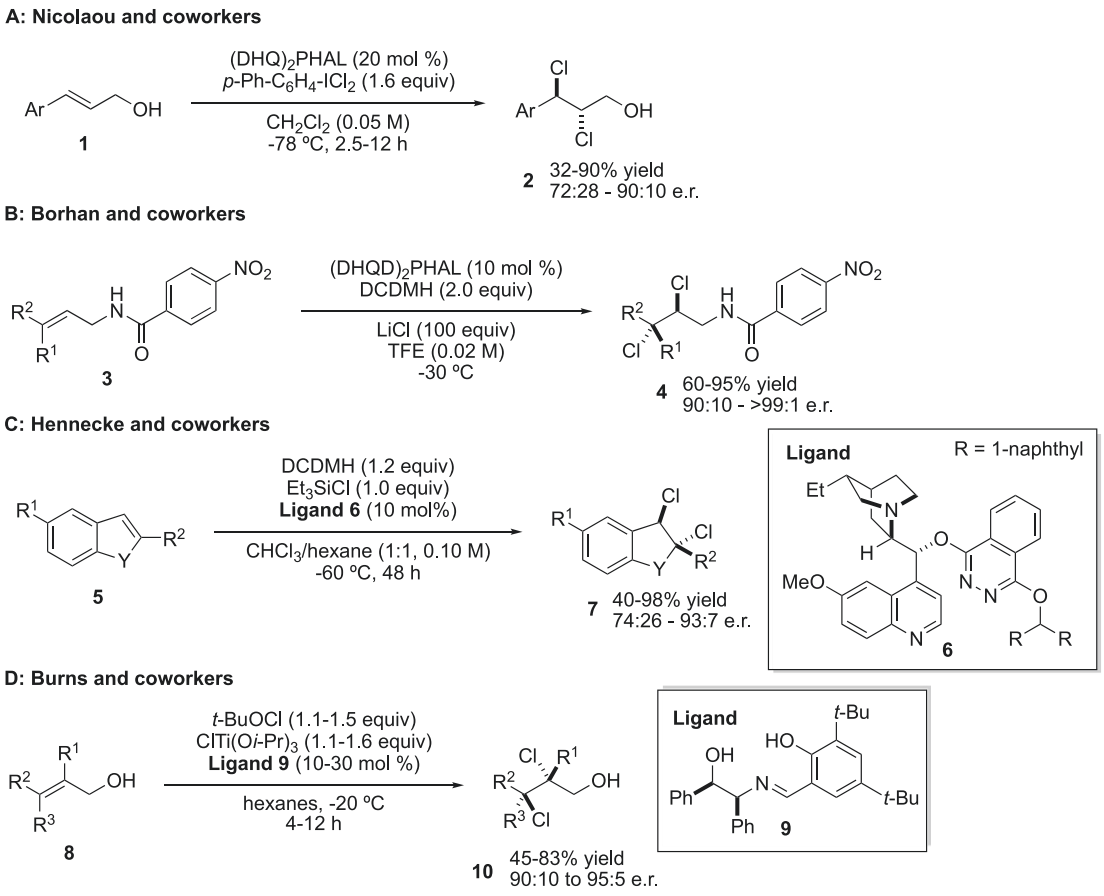
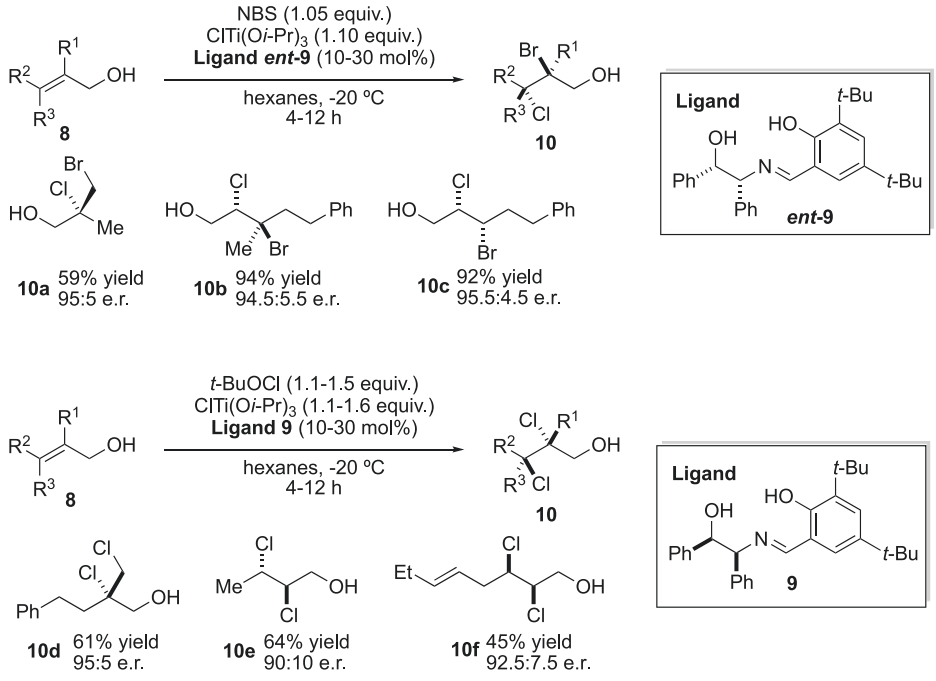
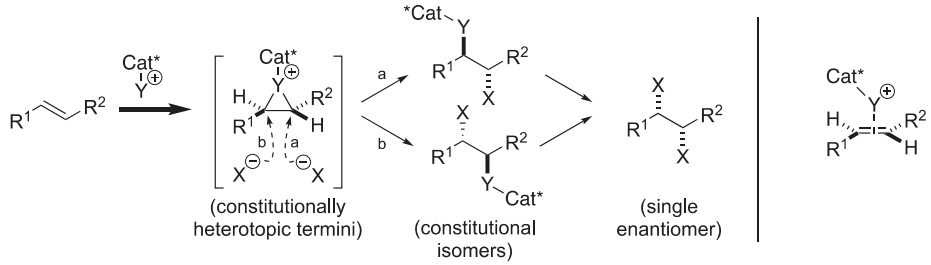


Fig. 2. State of the art for catalytic enantioselective dichlorination.



Scheme 2. Enantioselective dihalogenation of allylic alcohols developed by Burns et al.

3). Here, an electrophilic complex **Cat***–**Y** reacts with the alkene to form a non-halo –*iranium* ion. This intermediate is then opened at either constitutionally heterotopic carbon to afford a mixture of isomers. This isomeric mixture converges to a single dihalide



Scheme 3. Symmetry analysis of stereochemical transformations in enantioselective *suprafacial*-vicinal dihalogenation. Enantiodetermining step is highlighted with a bold arrow. Cat* = chiral catalyst (or ligand), X = halogen.

product by displacement of **Cat***–**Y** (now in reduced form) from the alkane backbone of the product. Thus, the only requirements for a selective process are now irreversible –*iranium* ion formation and configurational stability of that intermediate.

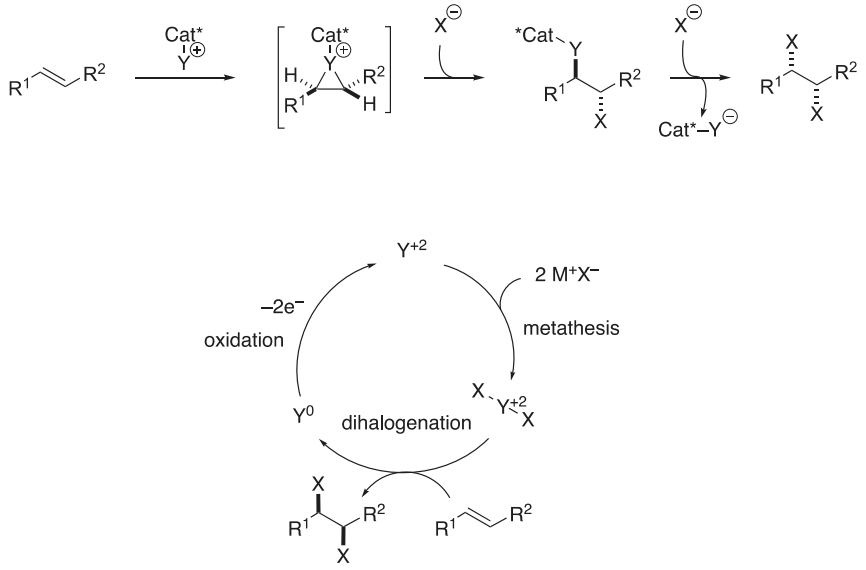
This alternative approach is distinguished by the presence of the chiral, enantioenriched catalyst backbone **Cat*** in the –*iranium* ion and ring-opened intermediates, as **Y** is, unlike **X,** an atom with valence greater than 1. This higher valence also allows for greater variety in the transition state geometry of –*iranium* ion formation (Scheme 3, right) and the portion of the catalyst bearing features that convey stereochemical information can be brought in closer proximity to the olefin than in the necessarily linear **Cat***–**X**–**alkene** complex (Scheme 1, right).

The mode by which two halogen atoms are incorporated into the product molecule is also unique compared to the antarafacial dihalogenations, as both equivalents of **X** are introduced as halide anions. The second halide equivalent displaces **Cat***–**Y** from the product and results in the formation of anionic **Cat***–**Y**$^-$ (Scheme 4). This catalyst must be reoxidized for the cycle to turn over, standing in contrast to the requirement of separate halide and halenium ion sources in conjunction for antarafacial vicinal dihalogenations. This type of transformation has been previously categorized as a member of the larger group of "group-transfer catalysis," [35] but could be more precisely referred to as "redox catalysis."

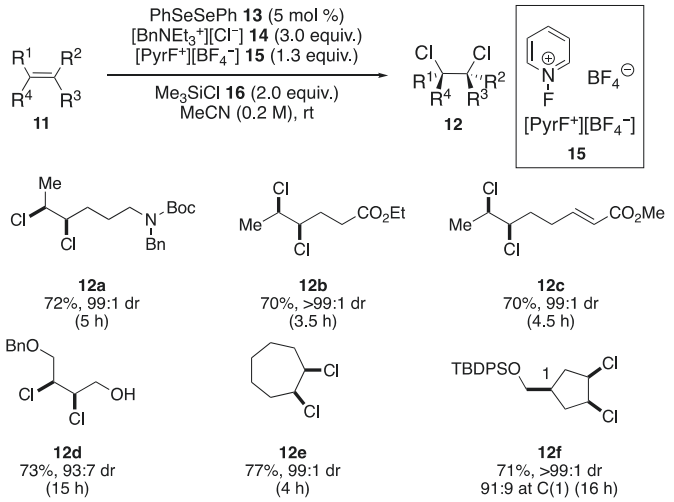
The structural limitations to the scope of antarafacial enantioselective dichlorination reactions could be overcome by employing a suprafacial dichlorination wherein the alkene need not be electronically (or otherwise) biased. In the case of a catalytic, enantioselective *syn*-dichlorination proceeding through an alternative –*iranium* ion, and provided that –*iranium* ion formation is irreversible, then formation of that ion alone would be stereodetermining. The ring-opening of this cationic intermediate is inconsequential to the final enantiomeric ratio, simplifying the challenge in simultaneous installation of adjacent halogenated stereocenters.

2. Background

As a prelude to the development of an enantioselective vicinal dihalogenation, these laboratories recently disclosed the stereospecific *syn*-dichlorination of alkenes using redox catalysis (Scheme 5) [24]. The reaction employs diphenyl diselenide (PhSeSePh **13**) as the precatalyst, with benzyltriethylammonium chloride ([BnNEt$_3$]$^+$[Cl]$^-$ **14**) as the chloride source and *N*-fluoropyridinium tetrafluoroborate ([PyF]$^+$[BF$_4$]$^-$ **15**) as the oxidant. Trimethylsilyl chloride (Me$_3$SiCl **16**) was also employed in stoichiometric amounts to serve as a trap for the fluoride generated as a byproduct of oxidation. The reaction shows good functional group tolerance, proceeding smoothly in the presence of neighboring nucleophilic groups that would often be expected to participate in anchimeric assistance (**12b, d**), and leaving electron-poor olefins untouched (**12c**). Diastereoselectivity was excellent with respect to stereocenters already present on the alkene substrate (**12f**).



Scheme 4. Net transformation for suprafacial dihalogenation and redox catalytic cycle. Y = transition metal or main group element; oxidation states are relative, not absolute.



Scheme 5. Stereospecific *syn*-dichlorination of olefins: representative scope.

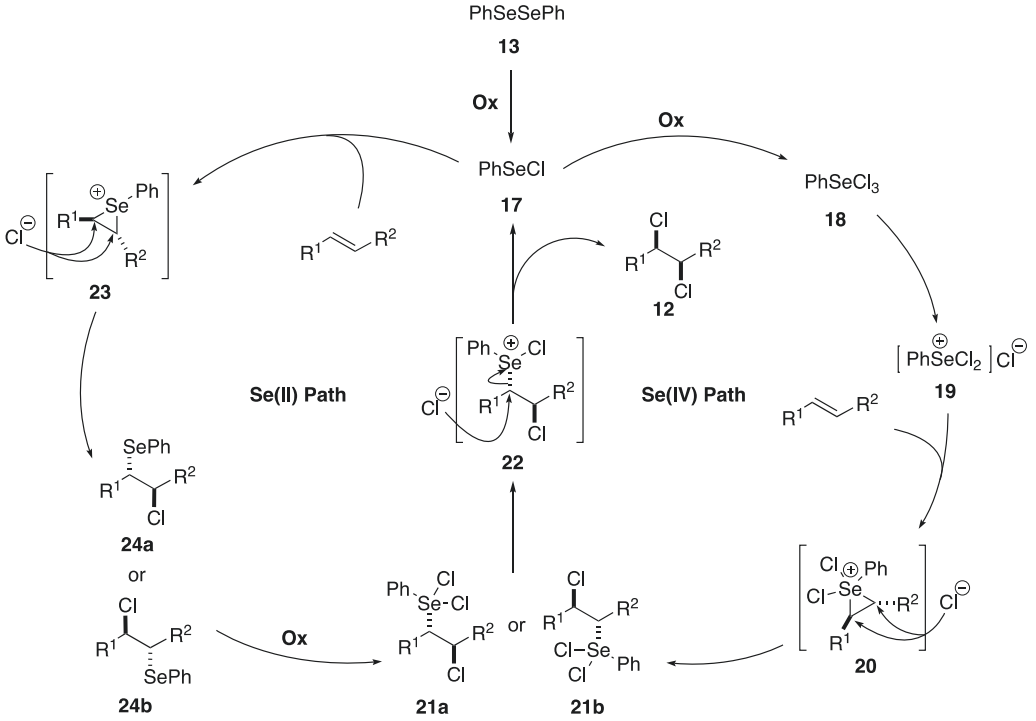
The mechanistic hypothesis for the catalytic cycle is founded on previous knowledge of the elementary steps [36–40]. Namely, that diphenyl diselenide is oxidized to phenylselenyl trichloride with three equivalents of chlorine (or other electrophilic chlorine source), that areneselenenyl trichlorides react with olefins to give chloroselenylated adducts, and that chloroalkyl areneseleniniu-m(IV) dichlorides can be displaced by chloride to afford *syn*-vicinal dichlorides (Scheme 6).

At reaction onset, diphenyl diselenide is oxidized by two equivalents of phenylselenium(II) chloride **17** with one equivalent each of chloride source **14**, oxidant **15**, and fluoride scavenger **16**. Typically, alkene is not added until the other reaction components have been stirred for 10 min at room temperature, so this oxidation presumably occurs once more to afford phenylselenium(IV) trichloride **18**. Subsequent ionization is assumed necessary to afford the charge-separated complex **19**, which has the requisite open valence available for alkene coordination. Reaction with alkene produces the Se(IV) seleniranium ion **20**, which can be opened antarafacially by chloride at either of the constitutionally heterotopic carbons, affording a mixture of isomers **21a** and **21b**. Ionization to **22** followed by stereospecific, S_N2 displacement of the cationic phenylselenium(IV) chloride by chloride anion results in a convergence of these constitutional isomers to a single vicinal *syn*-dichloride product **12** and regenerates phenylselenium(II) chloride **17**.

The β-chloroalkyl phenylselenium(IV) dichlorides **21** are postulated to be the catalytic resting state based on their presence in the ^{1}H NMR spectra of incomplete reaction mixtures. Thus, the turnover-limiting step is likely the ionization of **21** to **22** and nucleophilic displacement by chloride to afford the product *syn*-dichloride **12**.

Further catalytic turnover need not, however, proceed again through oxidation to **18**, but could instead result from reaction of **17** with alkene to form Se(II) seleniranium ion **23**. Antarafacial nucleophilic ring opening at the constitutionally heterotopic carbons by chloride affords β-chloroalkyl phenyl selenides **24a** and **24b**. This mixture of aryl-alkyl selenides is then further oxidized by **14/15/16** to return to the previous cycle at **21a** and **21b**. These two paths are indistinguishable by NMR analysis of an incomplete reaction mixture, as the resting state of either pathway could be at their point of convergence, i.e. **21**. Indeed, the relative rates of oxidation of **17** versus its reaction with alkene may vary with the concentration of alkene or oxidant, both of which decrease as the reaction progresses.

Nevertheless, phenylselenyl chloride **17** was demonstrated to be an effective catalyst for the stereospecific vicinal *syn*-dichlorination of alkenes, allowing for the opportunity to develop an enantioselective method using a chiral, enantioenriched arylselenium catalyst. Diastereoselective selenofunctionalizations have been performed with a variety of chiral, enantioenriched electrophilic



Scheme 6. Stereospecific *syn*-dichlorination of olefins: mechanistic hypothesis. **Ox** = $[BnNEt_3]^+[Cl]^-$ (**14**) + $[PyF]^+[BF_4]^-$ (**15**) + Me_3SiCl (**16**).

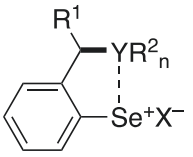
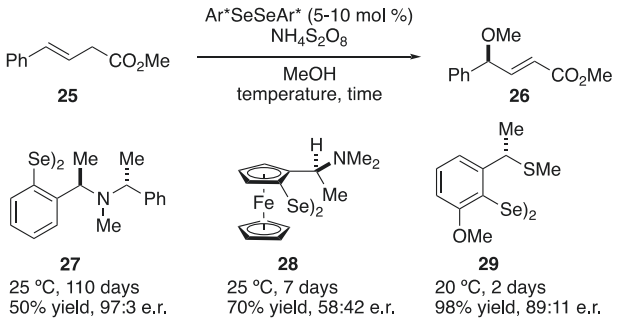


Fig. 3. General structure for a chiral, enantioenriched organoselenium reagent. Y = O, N, S; $R^1 = R^2$ = alkyl, aryl; X = Cl, Br, OTf, HSO_4, PF_6, etc.



Scheme 7. Catalytic, enantioselective allylic etherification with chiral, enantioenriched electrophilic selenium catalysts.

selenium reagents in the last several decades [41]. It was thus hypothesized that application of one of these reagents to *syn*-dichlorination could potentially result in good enantioselectivity, provided that the initial seleniranium ion formation proceeded with high enantiotopic face selectivity. Moreover, the structural features that lead to high selectivity in diastereoselective selenofunctionalizations have been identified, allowing for the formulation of selectivity models that can be used to improve the performance of these reagents [41,42]. Such chiral, enantioenriched organoselenium reagents typically feature an aryl selenide substituted at the 2-position by a stereogenic substituent bearing a coordinating heteroatom (O, N, S) (Fig. 3).

The coordination of the heteroatom to the electrophilic selenium atom (i.e. chalcogen bonding, Lewis base activation of Lewis acid) [43,44], rigidifies the structure and enhances electrophilicity. In addition to the use of these chiral, enantioenriched organoselenium reagents to stoichiometric, diastereoselective processes, several applications to catalytic enantioselective transformations have also been reported, namely in inter- and intramolecular selenofunctionalization-eliminations (Scheme 7) [45–50].

Previous studies in organoselenium catalyzed suprafacial dichlorination show that *anti*-dichlorination can be observed, likely owing to chloride oxidation to chlorine, when catalyst turnover becomes sluggish. Thus, the catalyst design was guided by the optimization of two key parameters: sufficient room-temperature turnover to avoid *anti*-dichloride formation, and excellent enantiotopic face selectivity.

3. Results and discussion

3.1. Synthesis and evaluation of chiral, enantioenriched diselenides

3.1.1. Diselenides bearing ether coordinating groups

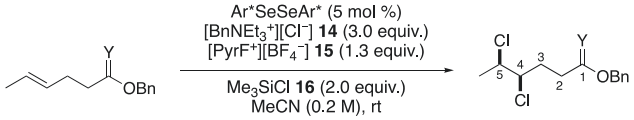
Orienting experiments for enantioselective dichlorination began with the most synthetically accessible chiral diselenides that also displayed optimal diastereoselectivity in selenofunctionalization reactions. Thus, diether **34** was selected as the first target as it was accessible by well-described synthetic transformations in six steps from 2-bromoisophthalic acid [51,52]. These *syn*-dichlorination reactions were performed with conditions identical to those used in the racemic reaction catalyzed by diphenyl diselenide (Scheme 5). *E*-4-Hexen-1-yl benzyl ether **30** and benzyl *E*-4-hexenoate **31** were selected as substrates for their synthetic accessibility and lack of any strong electronic bias. Although the diselenide precatalyst effected dichlorination much more slowly than diphenyl diselenide, and a significant portion of *anti*-dichloride was obtained from background oxidation of chloride, the enantiomeric ratio of 61:39 for the *syn*-dichloride was an encouraging first result suggesting that enantioselection was achievable with chiral diselenides (Table 1, entry 1).

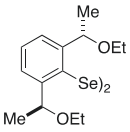
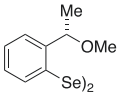
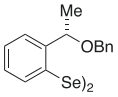
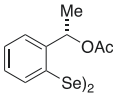
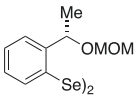
This initial result suggested that the steric crowding about the selenium atom was contributing to the significant attenuation of the rate of the catalytic process and motivated the investigation of singly 2-substituted catalyst structures. Thus, the methyl ether **35** [53,54], (entry 2) gave substantially improved reactivity, but with a decrease in enantioselectivity. Exchanging the methyl ether for the benzyl ether in **36** (entry 3) resulted in similar selectivity, while the acetate **37** [55] (entry 4) improved enantioselectivity with concomitant decrease in diastereoselectivity. Exchange for a methoxymethyl acetal in **38** [56] (entry 5) gave nearly racemic product.

3.1.2. Diselenides bearing carbonyl coordinating groups

It was readily apparent that the oxygen substituent imparted

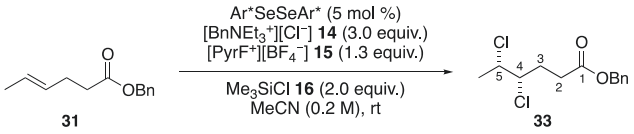
Table 1
Syn-dichlorination selectivities of catalysts bearing ether coordinating Groups.

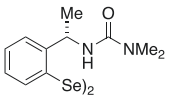
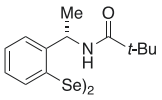
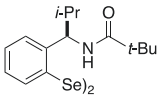
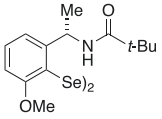
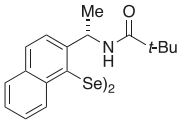
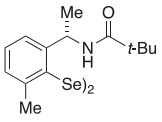


entry	catalyst		product; d.r. (*syn*/*anti*)[a]	e.r.[c]	configuration[b]
1		**34**	**32**; 30:70	61:39	*R,R*
2		**35**	**32**; >95:5 **33**; >95:5	54:46 54:46	*S,S* *S,S*
3		**36**	**32**; 90:10	55:45	*S,S*
4		**37**	**32**; 70:30	58:42	*R,R*
5		**38**	**32**; 90:10	50:50	–

[a] The d.r. was determined by ^{1}H NMR integration of diagnostic signals at HC(4) and HC(5) (see Experimental).
[b] The absolute configuration of the major enantiomer was determined by elution order compared to dichloride of known configuration (for Y = O) or by analogy to the ester (for Y = H_2) (see Supporting Information).
[c] The e.r. was determined by chiral stationary phase HPLC (see Supporting Information).

Table 2
Syn-dichlorination selectivities of catalysts bearing carbonyl coordinating Groups.



entry	catalyst		33 d.r. (*syn/anti*)[a]	e.r.[c]	e.s.	configuration[b]
1		**39**	70:30	65:35	65:35	*R,R*
2		**40**	90:10	65:35	65:35	*R,R*
3		**41**	83:17	62:38	62:38	*S,S*
4		**42**[d]	95:5	58:42	59:41	*R,R*
5		**43**[e]	80:20	61:39	64:36	*R,R*
6		**44**[f,g]	80:20	73:27	74:26	*R,R*

[a] The d.r. was determined by ^{1}H NMR integration of diagnostic signals at HC(4) and HC(5) (see Experimental).
[b] The absolute configuration of the major enantiomer was determined by elution order compared to dichloride of known configuration (see Supporting Information).
[c] The e.r. was determined by chiral stationary phase HPLC (see Supporting Information).
[d] The e.r. of the catalyst was 95:5.
[e] The e.r. of the catalyst was 90:10.
[f] The e.r. of the catalyst was 97:3.
[g] Reaction with (*Z*)-**31** afforded predominately the *anti*-dichloride with a d.r. of 70:30 and an e.r. of 55:45.

relatively little influence on enantioselectivity. Finding a more selective catalyst would require examining different coordinating groups and catalyst geometries. Urea **39** [57] was therefore selected for its alternative binding mode in which the carbonyl oxygen serves as an alternative coordinating group, forming what is expected to be a 7-membered ring. The dichloride products obtained with urea **39** and with the novel pivalamide **40** (Table 2, entries 1 and 2) had enantiomeric ratios exceeding any previously obtained with absolute configuration matching what was obtained with acetate **37**.

Further examination involved structural modifications to the pivalamide catalyst **40**. Exchange of the methyl group adjacent to the stereocenter for an isopropyl group on **41** resulted in a decrease in both enantioselectivity and diastereoselectivity (entry 3). Substitution of the aromatic ring at the 6-position with a methoxy group or a benzene ring fusion (**42** and **43**) also resulted in a decrease in enantioselectivity (entries 4 and 5). Only placement of a methyl group at the 6-position in **44** resulted in an increase in enantioselectivity, albeit with an attendant decrease in diastereoselectivity (entry 6), likely due to increased steric crowding about the reactive center, thus attenuating the catalytic rate.

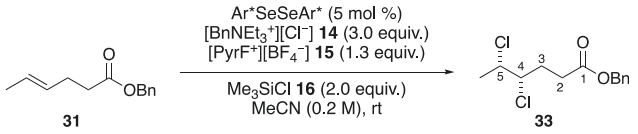
3.1.3. Diselenides bearing oxazoline coordinating groups

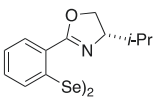
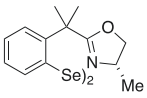
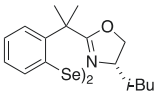
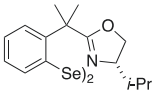
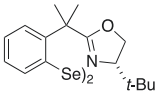
A reasonable hypothesis posited that the relatively weak binding of the ether and carbonyl coordinating groups were contributing to the low selectivities. Under this premise stronger Lewis basic donors beginning with readily accessible oxazolines were tested. Although oxazoline coordinating groups had previously been employed in diastereoselective selenofunctionalizations [58], diselenide **45** did not impart any appreciable selectivity in dichlorination (Table 3, entry 1). Catalysts **46**–**49** were prepared to examine the effect of 6-membered ring coordination structures. Systematic variation of the substituent adjacent to the coordinating nitrogen atom had very little effect on enantioselectivity (entries 2–5). The most significant effect of the stronger coordinating group can be observed in the decreased diastereoselectivity across all oxazoline catalysts, that is, the stronger coordinating group resulted in slower catalytic dichlorination and greater predominance of the background *anti*-dichlorination. Introduction of an adjacent, bulky group led to further deterioration of the diastereomeric ratio.

3.1.4. Bicyclic diselenides

At this stage greater variation in catalyst backbone was sought,

Table 3
Syn-dichlorination selectivities of catalysts bearing oxazoline coordinating Groups.



entry	catalyst		33 d.r. (*syn*/*anti*)[a]	e.r.[c]	configuration[b]
1		**45**	60:40	50:50	–
2		**46**	90:10	54:46	*R,R*
3		**47**	90:10	53:47	*S,S*
4		**48**	83:17	52:48	*S,S*
5		**49**	70:30	50:50	–

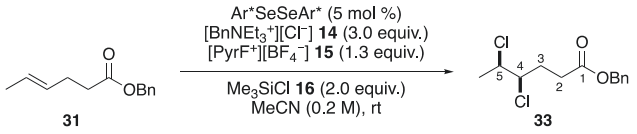
[a] The d.r. was determined by ^{1}H NMR integration of diagnostic signals at HC(4) and HC(5) (see Experimental).
[b] The absolute configuration of the major enantiomer was determined by elution order compared to dichloride of known configuration (see Supporting Information).
[c] The e.r. was determined by chiral stationary phase HPLC (see Supporting Information).

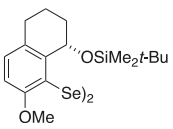
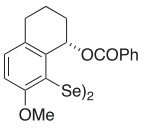
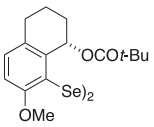
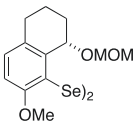
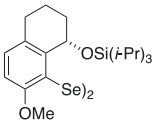
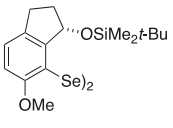
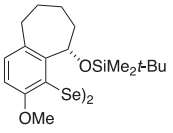
with a return to more weakly coordinating neighboring heteroatoms to improve diastereoselectivity. Rigid tetralin-derived organoselenium reagents had been previously described and appeared to be suitable candidates [54,56]. Additionally, related electrophilic selenium reagents had recently been employed catalytically to afford excellent enantioselectivities in oxidative lactonization [59]. Silyl ether **50** provided the dichloride in a d.r. of >95:5 and an e.r. of 74:26 (Table 4, entry 1). Exchanging the silyl ether for a benzoate, pivalate, or methoxymethyl acetal (**51**–**53**) resulted in a decrease in enantioselectivity (entries 2–4), whereas replacing the *tert*-butyldimethylsilyl ether with a triisopropylsilyl ether **54** resulted in only a slight improvement in enantioselectivity (entry 5). The ring-contracted indane catalyst **55** gave poorer selectivity, as did the ring-expanded benzosuberan catalyst **56** (entries 6 and 7). Notably, all of the catalysts derived from tetralin **50** led to substantially faster reactions than the more flexible enantioenriched diselenides employed above. For example, the dichlorination catalyzed by **50** was complete in 5 h – faster even than diphenyl diselenide.

3.2. Mechanistic investigations

Despite a wide variety of diselenide structures surveyed, many of which afforded excellent enantioselectivities in other transformations, the enantioselectivity had plateaued at 75:25. To better understand the mechanistic features that could be leading to reduced enantioselectivity, three potential sources were identified for consideration and evaluation: (1) low intrinsic selectivity in formation of the seleniranium ion; (2) competing pathways of Se(II) and Se(IV) addition to the olefin, each pathway imparting different

Table 4
Syn-dichlorination selectivities of rigid bicyclic Catalysts.



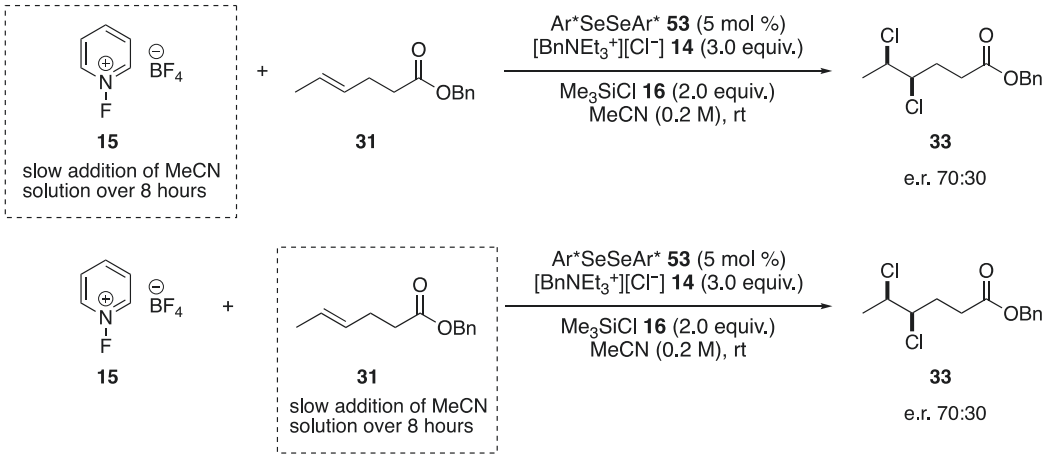
entry	catalyst		33 d.r. (*syn*/*anti*)[a]	e.r.[c]	configuration[b]
1		**50**	>95:5	74:26	*R,R*
2		**51**	>95:5	65:35	*R,R*
3		**52**	>95:5	66:34	*R,R*
4		**53**	>95:5	70:30	*R,R*
5		**54**	>95:5	76:24	*R,R*
6		**55**	>95:5	63:37	*R,R*
7		**56**	>95:5	55:45	*R,R*

[a] The d.r. was determined by ^{1}H NMR integration of diagnostic signals at HC(4) and HC(5) (see Experimental).
[b] The absolute configuration of the major enantiomer was determined by elution order compared to dichloride of known configuration (see Supporting Information).
[c] The e.r. was determined by chiral stationary phase HPLC (see Supporting Information).

selectivity; and (3) epimerization of catalytic intermediates owing to reversible addition prior to catalyst turnover.

3.2.1. Determination of selenium oxidation state at seleniranium ion formation

Before intrinsic selectivity could be considered, it was necessary to establish whether the transformation was proceeding through Se(II) or Se(IV) addition to the alkene. On the basis of X-ray crystal structural data [60] for intramolecularly coordinated arylseleniu-m(II) and (IV) chlorides, the two have very different geometries. Coordinated arylselenium(II) chlorides assume a T-shape geometry, with chlorine atom opposite the coordinating group, whereas arylselenium(IV) trichlorides are pseudo-pyramidal. It follows that alkene approach to the electrophilic selenium atom at either



Scheme 8. Syringe pump addition experiments limiting selenium oxidation state.

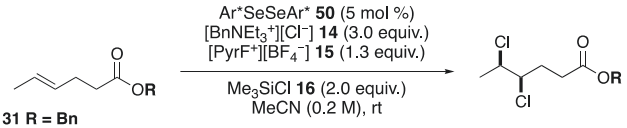
oxidation state could be subject to entirely different steric environments. Furthermore, both pathways could potentially be operative over the course of the reaction, as relative rates of oxidation and seleniranium ion formation could be differentially dependent on oxidant and olefin concentrations, respectively.

It was hypothesized that with a low concentration of oxidant relative to olefin, seleniranium ion formation would proceed (at least predominately) at the Se(II) oxidation state. To maintain low oxidant concentration for the duration of the dichlorination, a solution of oxidant **15** was added by syringe pump over 8 h (the typical time to full conversion) to a solution of precatalyst **53**, chloride source **14**, fluoride scavenger **16**, and alkene **31** (Scheme 8). The dichloride product obtained had the same e.r. (70:30) as when all reagents were combined at the start of the reaction. Likewise, it was hypothesized that with a low concentration of alkene relative to the oxidant, seleniranium ion formation would proceed at the Se(IV) oxidation state. Thus, slow addition of a solution **31** to a solution of **14, 15, 16** and **53** also afforded the same e.r. (70:30). Therefore, either the same pathway was operative in all three circumstances, or the Se(II) and Se(IV) seleniranium ion formation pathways impart nearly identical selectivities on the overall transformation.

A more informative experiment was then performed by measurement of the enantiomeric ratio of aliquots at 10% and 100% conversion. In a typical dichlorination reaction, all of the reagents save for the alkene substrate were combined for 10 min [24] to allow for oxidation of the diselenide precatalyst to the arylselenium trichloride species. Therefore, at 10% conversion (i.e. one catalytic turnover), the vast majority of dichloride product should arise from Se(IV) seleniranium ion formation. At a 1 mmol scale, the amount of *syn*-dichloride product obtained at 10% conversion was insufficient to achieve UV detection on HPLC. Thus, new olefin substrates were prepared to allow for detection at lower concentrations, while the reaction with alkene **31** was run on 5 mmol scale. For all three ester substrates there appeared to be no significant change (Table 5). Thus, the reaction most likely proceeds through Se(IV) seleniranium ion formation from initiation through to full conversion or both oxidations states afford similar selectivity.

Unfortunately little is known about the enantiotopic face selectivity of Se(IV) addition to olefins, as the vast majority of stoichiometric reactions have been performed using reagents at the Se(II) oxidation state. Attempts to measure diastereomeric ratio of the Se(IV) chloroalkyl adduct by combination of stoichiometric amounts of precatalyst **50** with either sulfuryl chloride or N-F oxidant/chloride and olefin led to ^{1}H NMR spectra too complex to

Table 5
Measurement of Dichloride e.r. at 10% and 100% Conversion.



entry	Alkene	e.r. at 10% conversion[a]	e.r. at 100% conversion
1	**31**	76:24	75:25
2	**57**	79:21	76:24
3	**58**	77:23	75:25

[a] e.r. was determined by chiral stationary phase HPLC (see experimental).

make any conclusions about the d.r. It was therefore difficult to rule out low facial selectivity as a contributor to the overall low selectivity. There was, however, one especially compelling piece of evidence that pointed to a mechanistic origin for low enantioselectivity.

3.2.2. *Reversibility of ArSe(IV)Cl$_2^+$ addition to alkene*

Early ^{1}H NMR studies wherein the combination of the β-chloroalkylarylselenium(IV) dichloride prepared from *E*-octene **60** (formed in situ by treatment of a trifluoroacetate precursor **59** with ethereal HCl) [61] and *E*-1,4-diphenyl-2-butene **61** led to exchange between the olefins to afford mixture of alkenes and chloroselenylated adducts (Fig. 4). At t = 0 before the addition of hydrochloric acid, trifluoroacetate **59** and diphenylbutene are visible. However, 20 h after the addition of hydrochloric acid, there was a clear increase in spectral complexity as multiple chloroselenylated species began to appear. These new signals changed over the subsequent 45 h until equilibrium was reached. Comparison of the new component, **63**, to an independently prepared chloroselenylated 1,4-diphenylbutene adduct confirmed its identity. The reverse reaction in which *E*-octene **62** was introduced to the β-chloroalkylarylselenium(IV) dichloride prepared from *E*-1,4-diphenyl-2-butene **63** likewise led to a similar mixture in the same amount of time, ruling out any thermodynamic bias.

The reversibility of seleniranium ion formation and opening indicated that, although the initial seleniranium ion formation may have been selective, it was not likely to be the enantiodetermining step. The mechanism of the transformation may be far more

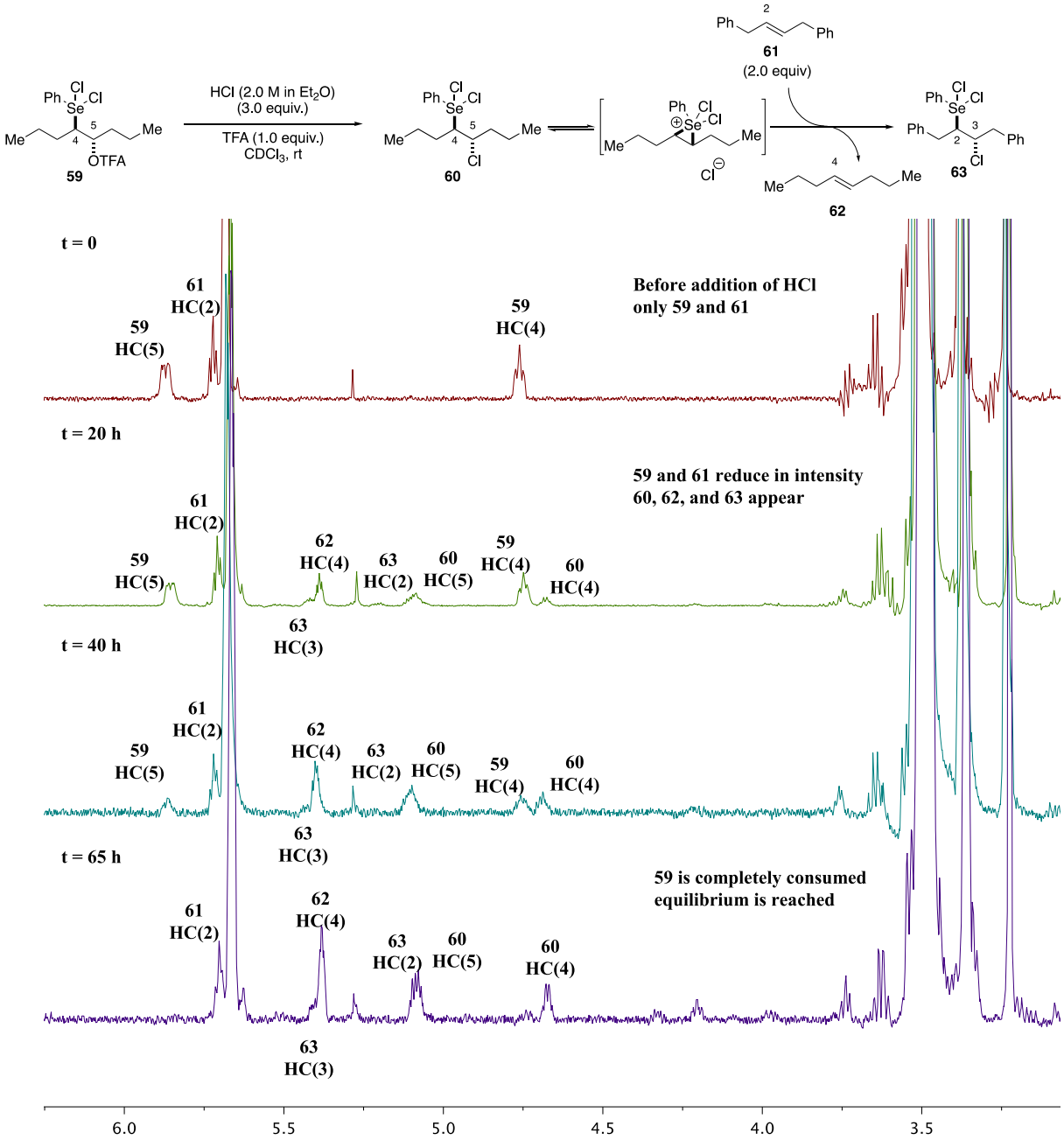
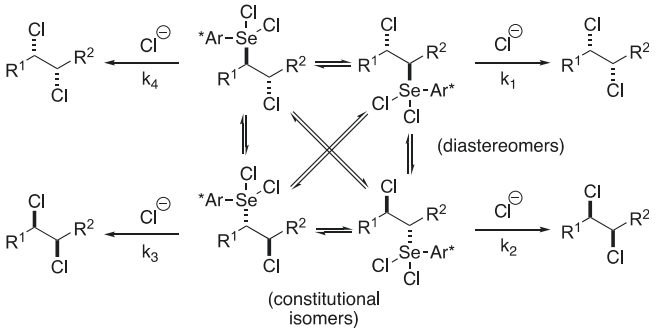


Fig. 4. Scrambling of arylselenium(IV) chloride adduct with external olefin.

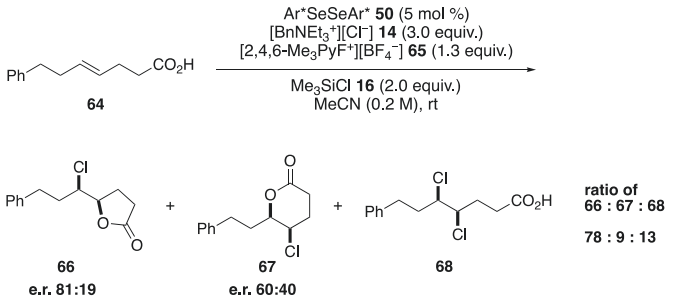
complicated, as diastereomeric ring-opened chloroalkylarylselenium(IV) dichloride adducts could now equilibrate prior to irreversible chloride displacement. Furthermore, the diastereomeric and constitutionally isomeric chloroselenylated adducts comprising this mixture have the potential to undergo S_N2 displacement by chloride at different rates, funneling the equilibrium to the intermediate that undergoes fastest displacement by chloride, leading to a dynamic kinetic asymmetric transformation (DyKAT) (Scheme 9) [62].

3.2.3. *Intramolecular trapping of the seleniranium intermediate*

To provide support for this new mechanistic hypothesis and to make seleniranium ion formation the enantiodetermining step, we sought to preclude reversibility by rapid capture using a tethered



Scheme 9. Dynamic kinetic asymmetric transformation of equilibrating chloroselenylated adducts.



Scheme 10. Chlorolactonization of *E*-7-phenylhept-4-enoic acid **64.**

nucleophile. Adapting the method to chlorolactonization indeed proved simple. Exchanging benzyl *E*-hexenoate for 7-phenyl-4-heptenoic acid **64** under identical reaction conditions afforded a mixture of *syn*-γ-lactone **66**, *syn*-δ-lactone **67**, *syn*-dichlorinated carboxylic acid **68** [63], and various elimination products (Scheme 10). When catalyst **50** was employed with similar conditions, substituting **15** for 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate **65** to improve reaction homogeneity, γ-lactone **66** was formed in a 78:9:13 ratio with **67** and **68**, respectively, and with an e.r. of 81:19, marginally higher than the e.r. of *syn*-dichloride obtained from benzyl hexenoate with the same catalyst (*vide supra*). The constitutional isomer **67** was obtained with a lower e.r. of 60:40.

Modifying oxidant stoichiometry, chloride stoichiometry, and solvent all resulted in small changes to both the product ratio and, to a lesser degree, enantioselectivity. Unfortunately, the presence of the *syn*-dichloride regardless of the modified conditions indicated that reversibility was still operative owing to the unexpected intermolecular chloride capture outcompeting an intramolecular capture by carboxylate. It is possible that the equivalent of acid produced as a reaction byproduct was capable of activating the lactone towards displacement by the adjacent selenium to reform the seleniranium ion (Scheme 11).

4. Conclusions

In this study we have demonstrated that chiral, enantioenriched arylselenium(IV) chlorides can be employed as redox catalysts for the suprafacial dichlorination of alkenes to provide vicinal, *syn*-dichloride products with modest enantioselectivity. Twenty-three diaryl diselenides across four general classes were evaluated for their selectivity in the dichlorination, with a maximum e.r. of 76:24 obtained with triisopropylsilyl ether **54**.

Higher product enantioenrichment may not be attainable through improvement of catalyst enantiofacial selectivity toward the alkene alone, as the free alkene and the catalytic resting state β-chloroalkylarylselenium(IV) dichloride appear to be in equilibrium. Furthermore, it does not appear that acceleration of the seleniranium ion opening by a tethered carboxylate results in any appreciable reduction in the reversibility of the overall transformation. There is, however, potential to improve selectivity by accelerating the second displacement to outcompete any reversibility by change of substrate to allow for intramolecular capture of the resting state intermediate. Likewise, there is potential to leverage the equilibrium for a DyKAT process with a second chiral catalyst to deliver chloride selectively to one isomer of the resting state intermediate.

Research employing chiral, enantioenriched diselenides as redox catalysts for suprafacial alkene difunctionalization, wherein the second displacement is accelerated, is ongoing.

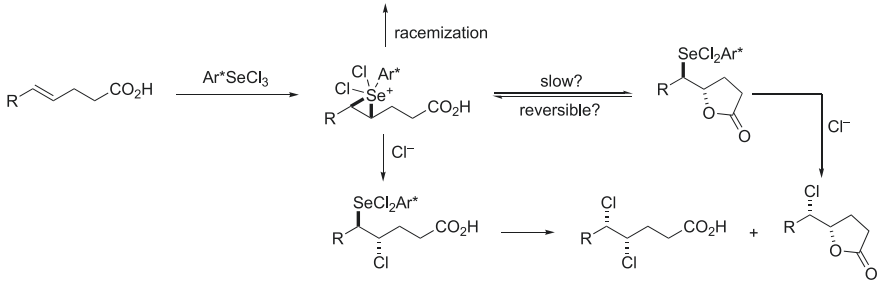
5. Experimental

5.1. General experimental

All reactions were performed in 120 °C oven- or flame-dried glassware equipped with a Teflon-coated magnetic stir bar under inert nitrogen atmosphere unless otherwise noted. Catalytic chlorination reactions were performed in flame-dried dram vials equipped with magnetic stir bars and septa under nitrogen atmosphere.

Benzyltriethylammonium chloride was purchased from Oakwood Chemical and moved into the glove box without purification. *N*-fluoropyridinium tetrafluoroborate and *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate were purchased from TCI America and moved into the glove box without purification. Trimethylsilyl chloride (Aldrich, 97+%) was distilled from calcium hydride at atmospheric pressure. Reaction solvent acetonitrile (Fisher, HPLC grade) was distilled from calcium hydride. Reaction solvents hexane, tetrahydrofuran, diethyl ether, toluene, *N,N*-dimethylformamide and dichloromethane were dried by percolation through two columns packed with neutral alumina under a positive pressure of argon. Reaction solvent ethyl acetate was degassed by sparging with argon for 2 h and stored over molecular sieves. Reaction solvent pentane was distilled from sodium. Sodium hydride suspension in mineral oil was washed several times with hexanes and stored in the glove box. Solvents for chromatography were: hexanes (Fisher, ACS Grade), ethyl acetate (Fisher, ACS Grade), diethyl ether (Fisher, ACS Grade), pentane (J. T. Baker, reagent grade), petroleum ether (J. T. Baker, reagent grade), dichloromethane (Aldrich, ACS Grade), and *tert*-butyl methyl ether (Acros, reagent grade). Brine refers to a saturated solution of sodium chloride in water.

^{1}H NMR, and ^{13}C NMR were recorded on Varian Unity-400 (400 MHz, ^{1}H; 100 MHz, ^{13}C) and Varian Inova-500 (500 MHz, ^{1}H; 126 MHz, ^{13}C) spectrometers. Spectra were referenced to residual chloroform (7.26 ppm, ^{1}H; 77.00 ppm, ^{13}C). Chemical shifts are reported in parts per million (ppm), multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m



Scheme 11. Chlorolactonization of *E*-7-phenylhept-4-enoic acid: mechanistic hypothesis for reversibility.

(multiplet) and br (broad). Coupling constants, J, are reported in Hertz with integration provided and assignments indicated. Electron Impact (EI) mass spectra were performed on a 70-VSE spectrometer with methane reagent gas. Electrospray Ionization (ESI) mass spectra were performed on a Micromass Quattro spectrometer. Data are reported in the form of (M/Z) (intensity relative to the base peak = 100 where applicable).

Analytical thin-layer chromatography was performed on Merck silica gel plates with QF-254 indicator. Visualization was accomplished with UV (254 nm), and ceric ammonium molybdate staining solution or *p*-anisaldehyde solution. Flash column chromatography was performed using Silacycle silica gel P60 230–400 mesh (60–63 μm) or Woelm high porosity silica gel. Preparative, radial, centrifugally accelerated thin-layer chromatography was performed on a chromatotron using glass-backed, circular TLC plates prepared with silica gel (high-purity grade, pore size 60 Å, 2–25 μm particle size, without binder, with fluorescent indicator, pore volume 0.75 cm^3/g) and calcium sulfate hemihydrate (≥99%). Analytical supercritical fluid chromatography (SFC) was performed with supercritical CO_2 adapter for supercritical fluid chromatography and a UV detector (220 nm or 254 nm) using Daicel Chiralcel OD, OJ, and OB, Daicel Chiralpak AD and AS, and Regis (*R,R*)-Whelk-O1 columns.

5.2. Representative procedure for catalytic syn-dichlorination of alkenes

To a 15 × 45 mm dram vial was added the diselenide catalyst **50** (7.42 mg, 0.010 mmol, 0.050 equiv) The vial was then transferred into the glove box and $[BnNEt_3]^+[Cl]^-$ (**14**) (131 mg, 0.6 mmol, 3.0 equiv) and $[PyrF]^+[BF_4]^-$ (**15**) (48 mg, 0.26 mmol, 1.3 equiv) were added. The vial was capped with a rubber septum and removed from the glove box. Acetonitrile (1 mL) and TMSCl (**16**) (51 μL, 0.4 mmol, 2.0 equiv) were added and the reaction was stirred for 10 min at room temperature. Benzyl hex-4-enoate (41 mg, 0.2 mmol) was added dropwise and the mixture was stirred at room temperature. The reaction was allowed to proceed until the olefin was completely consumed, with periodic monitoring by TLC (pentane/Et_2O, 19:1; **31** R_f = 0.42, **33**. R_f = 0.25). Once complete, the reaction was quenched by the slow addition of saturated sodium bicarbonate solution (1 mL). After dilution with deionized water (2 mL), the organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over Na_2SO_4 (2 g), filtered, and concentrated under reduced pressure by rotary evaporation (25 °C, 4 mm Hg). The crude mixture was re-dissolved in Et_2O (3 mL) and filtered through a short silica plug. The crude product was characterized qualitatively by ^1H NMR spectroscopy to determine the diastereomeric ratio of 95:5. Diagnostic peaks were: ***syn*-33**: 4.25 (qd; *J* 6.7, 2.9 Hz, HC(10)); 4.10 (dt; *J* = 10.8, 3.0 Hz, HC(9)); ***anti*-33**: 4.10 (quint; *J* = 6.6 Hz, HC(10)); 4.01 (ddd; *J* = 10.2, 6.5, 2.6 Hz, HC(9)). Purification by silica gel column chromatography (1.5 cm ø x 20 cm column) eluting with hexanes/TBME, 95:5 gave ***syn*-33** (39 mg, 71%) as a clear, colorless oil and *anti*-**33** (1.5 mg, 3%) as a colorless residue.

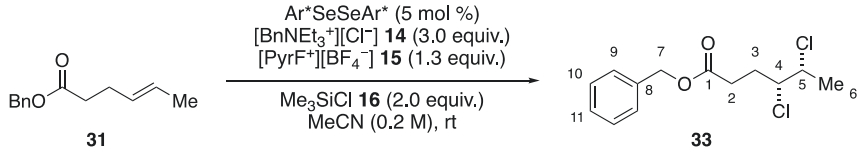
Data for ***syn*-33**:

An authentic sample of ***anti*-33** was obtained from an identical reaction without diphenyl diselenide catalyst.

^1H NMR:	(500 MHz, $CDCl_3$) δ 7.41–7.31 (m, 5 H, HC(aryl)), 5.14 (d, *J* = 3.1 Hz, 2 H, HC(7)), 4.25 (qd, *J* = 6.7, 2.9 Hz, 1 H, HC(5)), 4.10 (dt, *J* = 10.8, 3.0 Hz, 1 H, HC(4)), 2.67 (ddd, *J* = 16.9, 7.8, 5.6 Hz, 1 H, HC(2)), 2.57 (dt, *J* = 16.8, 7.7 Hz, 1 H, HC(2)), 2.30 (dtd, *J* = 14.4, 7.8, 2.9 Hz, 1 H, HC(3)), 2.06 (dddd, *J* = 14.4, 10.8, 7.7, 5.5 Hz, 1 H, HC(3)), 1.59 (d, *J* = 6.6 Hz, 3 H, HC(6)).
^{13}C NMR:	(126 MHz, $CDCl_3$) δ 172.6 (C(1)), 135.9 (C(8)), 128.8 (C(10)), 128.5 (C(11)), 128.4 (C(9)), 66.7 (C(7)), 65.2 (C(4)), 59.9 (C(5)), 31.3 (C(2)), 29.4 (C(3)), 21.0 (C(6)).
HRMS:	(ES+) Found: 297.0427; Calc. for $C_{13}H_{16}O_2NaCl_2$: 297.0425
HPLC:	***(S,S)*-33**, t_R 14.9 min (26.2%), ***(R,R)*-33**, t_R 18.6 min (73.7%) (Daicel Chiralpak OJ-H; hexanes/*i*-PrOH, 9:1; 0.5 mL/min, 210 nm).

Data for ***anti*-33**:

^1H NMR:	(500 MHz, $CDCl_3$) 7.45–7.30 (m, 5 H, HC(aryl)), 5.14 (d, *J* = 2.6 Hz, 2 H, HC(7)), 4.10 (p, *J* = 6.6 Hz, 1 H, HC(5)), 4.01 (ddd, *J* = 10.2, 6.5, 2.6 Hz, 1 H, HC(4)), 2.68 (ddd, *J* = 16.8, 8.4, 5.3 Hz, 1 H, HC(2)), 2.58 (ddd, *J* = 16.8, 8.1, 7.4 Hz, 1 H, HC(2)), 2.43 (dddd, *J* = 14.5, 8.4, 7.4, 2.6 Hz, 1 H, HC(3)), 2.01 (dddd, *J* = 14.6, 10.2, 8.1, 5.3 Hz, 1 H, HC(3)), 1.63 (d, *J* = 6.5 Hz, 3 H, HC(6)).
HRMS:	(ES+) Found: 297.0427; Calc. for $C_{13}H_{16}O_2NaCl_2$: 297.0425
HPLC:	t_R1 34.5 min (50%), t_R2 37.0 min (50%) (Daicel Chiralpak OJ-H; hexanes/*i*-PrOH, 19:1; 0.5 mL/min; 210 nm)



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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2019.05.054.

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