nature chemistry

ARTICLES

PUBLISHED ONLINE: 12 JANUARY 2015 | DOI: 10.1038/NCHEM.2141

Catalytic, stereospecific *syn*-dichlorination of alkenes

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As some of the oldest organic chemical reactions known, the ionic additions of elemental halogens such as bromine and chlorine to alkenes are prototypical examples of stereospecific reactions, typically delivering vicinal dihalides resulting from *anti*-addition. Although the invention of enantioselective variants is an ongoing challenge, the ability to overturn the intrinsic *anti*-diastereospecificity of these transformations is also a largely unsolved problem. Here, we describe the first catalytic, *syn*-stereospecific dichlorination of alkenes, employing a group transfer catalyst based on a redox-active main group element (selenium). With diphenyl diselenide (PhSeSePh) (5 mol%) as the pre-catalyst, benzyltriethylammonium chloride ($BnEt_3NCl$) as the chloride source and an *N*-fluoropyridinium salt as the oxidant, a wide variety of functionalized cyclic and acyclic 1,2-disubstituted alkenes, including simple allylic alcohols, deliver *syn*-dichlorides with exquisite stereocontrol. This methodology is expected to find applications in streamlining the synthesis of polychlorinated natural products such as the chlorosulfolipids.

Since the seminal report of the 1,2-addition of molecular chlorine to carbon–carbon double bonds in 1877 (that is, the dearomatizing addition of 2 equiv. Cl_2 to 1,5-dichloronaphthalene)[1], the vicinal dichlorination of alkenes has continued to challenge the ingenuity of synthetic organic chemists in providing creative solutions to fundamental problems of selectivity. Owing largely to the high reactivity of Cl_2 and the difficulties associated with controlling the stoichiometry of a gaseous reactant, the reactions of alkenes with elemental chlorine are frequently plagued by side reactions (ionic and/or radical)[2], and the extremely toxic and corrosive nature of Cl_2 gas renders it experimentally unappealing. Accordingly, somewhat milder and more practical electrophilic chlorinating agents for alkene dichlorination have been developed, including SO_2Cl_2 (ref. 3), $PhICl_2$ (ref. 4), Et_4NCl_3 (ref. 5; Mioskowski's reagent) and 2:1 NCS-PPh_3 (ref. 6; Yoshimitsu's reagent). Alternatively, Cl_2 (or its formal equivalent) may be generated *in situ* from the oxidation of chloride sources with strong oxidants and reagent systems such as H_2O_2–HCl (ref. 7), $KMnO_4$–Me_3SiCl–$BnEt_3NCl$ (ref. 8; Markó–Maguire reagent) and Oxone-NaCl (ref. 9) have been tailored for this purpose.

However, whereas the advent of new reagents for alkene dichlorination has largely solved the practicality and reactivity issues surrounding the use of Cl_2, solutions have been less forthcoming to the problems of control over the relative and absolute configurations of the dichloride products. In recent years, state-of-the-art stereoselective chlorination methods have been showcased in synthetic efforts toward the chlorosulfolipids (for example, **1**–**5**)[10–14], a class of stereochemically complex, polychlorinated natural products isolated from marine sources (Fig. 1, left). The daunting synthetic challenge of constructing such densely functionalized arrays of chlorinated stereogenic centres has provided impetus for the study of (external) diastereocontrol in the dichlorination of chiral alkene substrates[12], as well as more recent efforts to effect enantioselective dichlorinations of allylic alcohols[15].

However, almost invariably, all of the aforementioned reagents or reagent combinations that react via ionic reaction pathways afford vicinal dichloride products resulting from stereospecific *anti*-addition to alkenes—an inescapable stereoelectronic consequence of the nucleophilic attack of chloride ion on chloriranium ion[16] or alkene-Cl_2 π-complex[17] intermediates. A complementary, direct *syn*-dichlorination is notably lacking from the synthetic chemist's repertoire (Fig. 1, right). Although several examples of direct, *syn*-stereospecific dichlorinations involving the treatment of unfunctionalized alkenes (often in excess) with stoichiometric amounts of high-valent metal chlorides based on antimony[18] and molybdenum[19–21] are on record, the harsh Lewis acidity, high oxidation potential and toxicity of these reagents detract significantly from their utility. Consequently, the only current solution to the *syn*-dichlorination problem with functionalized alkene substrates is to orchestrate indirect, two-step oxidation–deoxochlorination sequences via the intermediacy of epoxides[22,23] or chlorohydrins[24].

In this Article, we describe the first catalytic, *syn*-stereospecific dichlorination of alkenes, employing a group transfer catalyst based on a redox-active main group element (selenium). On the basis of the known ability of $PhSeCl_3$ to chloroselenylate alkenes in an *anti*-stereospecific fashion[25,26] and the invertive nucleophilic displacement of the high-valent selenium(IV) moiety[27] by chloride ions in such adducts to afford *syn*-dichlorides[28,29], we surmised that a direct alkene *syn*-dichlorination that is catalytic in selenium may be possible. However, a key challenge in formulating such a catalytic cycle is the identification of a suitable stoichiometric oxidant to regenerate Se(IV) from Se(II). Although electrophilic chlorine sources may seem obvious candidates, both Sharpless[30] and Tunge[31] have reported that the selenium-catalysed reaction of alkenes with *N*-chlorosuccinimide generates allylic chlorides as the major products. Alternatively, a non-chlorine-based oxidant could be used in the presence of an exogenous chloride source. Specifically, the oxidant selected must fulfil the following criteria: (1) it must not react (or must react only very slowly) with the alkene substrate, (2) it must not oxidize chloride ions to molecular Cl_2 or any other active 'Cl^+' equivalent over the timescale of the reaction, (3) it must not contain or release nucleophiles that might outcompete chloride in the reaction, and (4) it must not lead to the formation of selenoxide intermediates that are capable of rapid

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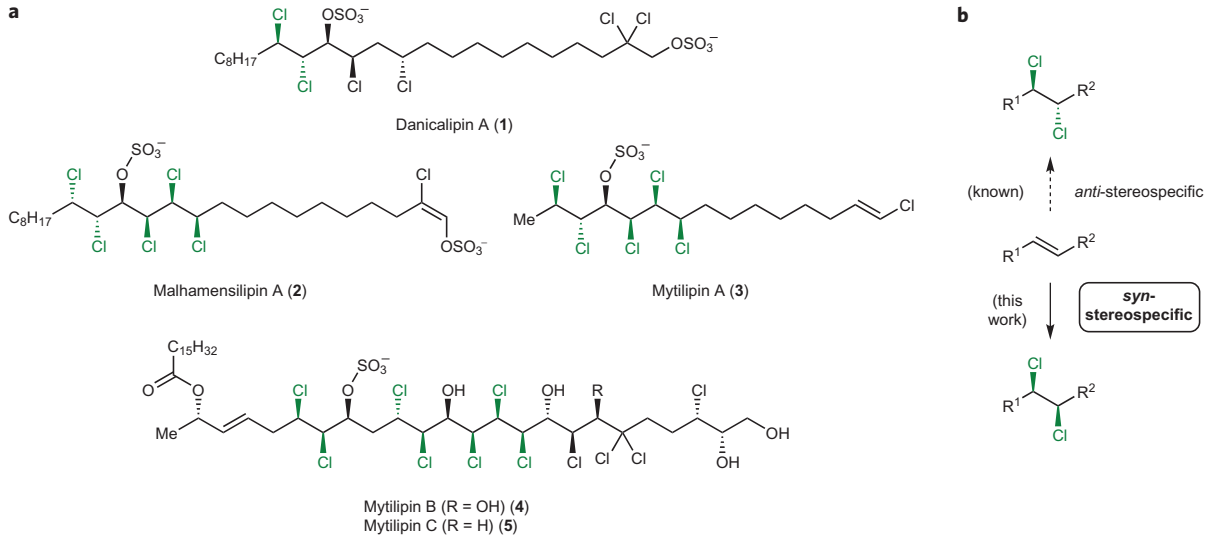


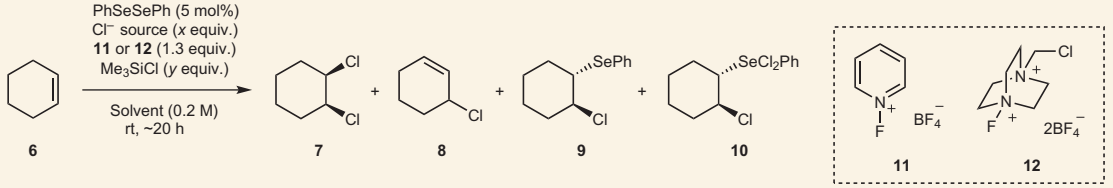
Figure 1 | The vicinal dichloride motif in natural products. a, Selected chlorosulfolipids (with vicinal dichloride motifs highlighted). **b**, Most dichlorinations of alkenes (and all of those that are catalytic) exhibit *anti*-stereospecificity, and no generally applicable, direct *syn*-stereospecific alkene dichlorination has been reported. Such a method would complement current chlorination strategies employed in the synthesis of polychlorinated natural products such as the chlorosulfolipids.

syn-elimination[32]. With these restrictions in mind, cationic N–F reagents were considered as possible candidates, a choice that was inspired by the use of 'F^+' reagents as oxidants in transition metal-catalysed processes[33] and, more significantly, in a PhSeSePh-catalysed allylic amination of alkenes[34].

Results

Reaction development. To probe the feasibility of a *syn*-dichlorination process that is catalytic in selenium, orienting experiments were carried out with cyclohexene **6** (1.0 equiv.) as the substrate, 5 mol% of PhSeSePh as the pre-catalyst, *n*-Bu_4NCl as the chloride source (3.0 equiv.) and *N*-fluoropyridinium tetrafluoroborate **11** (CAS# 107264-09-5) as the oxidant, with MeCN-d_3 as the solvent (Table 1). 1,1,2,2-Tetrachloroethane (1.0 equiv.) was added as an internal standard, and ^{1}H NMR peaks for species **6**–**10** were compared against authentic samples in MeCN-d_3. Under these conditions at ambient temperature for ~20 h, an encouraging 19% yield of the desired *syn*-dichloride **7** was observed, although 50% of starting material **6** remained (Table 1, entry 1). It was surmised that fluoride ions generated as a by-product from oxidant **11** may be interfering with catalytic turnover and that the addition of a fluoride scavenger may be advantageous. Chlorotrimethylsilane (Me_3SiCl) was selected for this purpose on the basis that silicon has a high affinity for fluoride[35] and that the by-products of such scavenging would simply be additional chloride ion and unreactive fluorotrimethylsilane (Me_3SiF). Gratifyingly, the addition of 1.0 equiv. Me_3SiCl gave a substantial improvement in catalytic turnover (61% yield of **7** by ^{1}H NMR spectroscopic analysis; entry 2) and complete consumption of alkene **6** occurred when 2.0 equiv. Me_3SiCl was added, affording **7** in 81% yield (entry 3). However, increasing the amount of Me_3SiCl to 3.0 equiv. led to no further enhancement (entry 4). The reaction also proved sensitive to the quantity of *n*-Bu_4NCl; an attempt to lower the

Table 1 | Reaction development with cyclohexene.



Entry	Cl^- source (equiv.)	Oxidant	Me_3SiCl (equiv.)	Solvent	NMR yield (%)*				
					6	7	8	9	10
1	*n*-Bu_4NCl (3.0)	11	0.0	MeCN-d_3	50	19	3	9	0
2	*n*-Bu_4NCl (3.0)	11	1.0	MeCN-d_3	12	61	10	10	0
3	*n*-Bu_4NCl (3.0)	11	2.0	MeCN-d_3	0	81	10	0	0
4	*n*-Bu_4NCl (3.0)	11	3.0	MeCN-d_3	0	81	8	0	0
5	*n*-Bu_4NCl (2.5)	11	2.0	MeCN-d_3	0	74	10	0	0
6†	*n*-Bu_4NCl (0.0)	11	2.0	MeCN-d_3	54	0	2	0	8
7	*n*-Bu_4NCl (3.0)	11	2.0	CD_2Cl_2	0	73	12	4	0
8	*n*-Bu_4NCl (3.0)	11	2.0	THF-d_8	55	17	2	0	0
9	*n*-Bu_4NCl (3.0)	12	2.0	MeCN-d_3	0	71	10	0	0
10	$BnEt_3NCl$ (3.0)	11	2.0	MeCN-d_3	0	83	10	0	0

*Measured by ^{1}H NMR spectroscopy with 1,1,2,2-tetrachloroethane (1.0 equiv.) as an internal standard; †11% of an unidentified species was also observed by ^{1}H NMR spectroscopy.

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amount to 2.5 equiv. led to an erosion in the yield of **7** (entry 5) and no **7** was produced when the *n*-Bu_4NCl was omitted altogether (entry 6). The effect of solvent was also briefly investigated, with both CD_2Cl_2 and THF-d_8 giving inferior results (entries 7 and 8). Pleasingly, the reaction could also be carried out with Selectfluor **12** as an alternative stoichiometric oxidant, albeit with a slightly diminished yield of **7** (71%) (entry 9). Finally, *n*-Bu_4NCl was replaced with $BnEt_3NCl$, which is far less expensive, and the results were essentially identical (entry 10). Notably, in no case was any of the diastereomeric *anti*-dichloride product detected; an observation that is particularly surprising given that Selectfluor **12** is known to oxidize chloride ions to a 'Cl^+' equivalent (possibly Cl_2) in MeCN[36]. In fact, a control experiment with cyclohexene **6** in which PhSeSePh was omitted from the reaction gave ~35% yield of the *anti*-dichloride after 20 h, implying that a background *anti*-dichlorination process is possibly operative but is significantly slower than the catalysed reaction.

Before further optimization efforts aimed at minimizing the formation of allylic chloride **8**, it was first necessary to establish the mechanistic provenance of this particular species. Although **8** is a known by-product in the reaction of **6** with Cl_2 under both ionic and radical reaction manifolds[2], the absence of any *anti*-dichloride under our conditions argues against the involvement of molecular Cl_2. Another possibility is synperiplanar elimination of a selenoxide intermediate[32] derived from the hydrolysis of **10** with adventitious water, although both rigorously dry conditions and the addition of trace water had no effect on the **7**/**8** ratio. Lastly, antiperiplanar E2 elimination of the Se(IV) moiety in intermediate **10** could also furnish **8**. To unambiguously determine which elimination pathway is in operation, an acyclic alkene substrate capable of generating (*E*)- or (*Z*)-configured *vinylic* chloride by-products was considered (note, for cyclohexene **6**, antiperiplanar elimination to give a vinylic chloride is geometrically impossible from **10**). Dichlorination of (*E*)-*tert*-butyl(hex-4-en-1-yloxy)diphenylsilane **13** under the optimized conditions gave a 68:23:9 mixture of *syn*-dichloride **14**, vinylic chlorides **15** + **16**, and two (tentatively assigned) allylic chlorides, respectively, with **14** being isolated in 63% yield (>99:1 d.r.) and **15** + **16** in 14% combined yield (Fig. 2). Crucially, the configurations within **15** and **16**, as deduced via 1D nuclear Overhauser enhancement spectroscopy (NOESY) experiments (reciprocal enhancements indicated with double-headed arrows), were found to be consistent with their formation via an antiperiplanar E2 elimination process (Fig. 2b). Similar conclusions were drawn from an analogous experiment with the (*Z*)-isomer of alkene **13**, which also gave vinylic chloride by-products consistent with antiperiplanar E2 elimination (Supplementary Information, p. 117).

With this information in hand, additional optimization experiments to minimize the competitive elimination process were conducted on (*E*)-1-benzyloxy-4-hexene **17** as the substrate (Table 2). Interestingly, a threefold rate acceleration was noted when sulfolane was used as a co-solvent (1:3 vol/vol) with MeCN-d_3, although the extent of E2 elimination was unperturbed (compare entries 1 and 2). Based on this observation, we elected to screen a variety of Lewis basic additives (1.0 equiv.) to search for similar acceleration effects (entries 3–8). Although the amount of elimination consistently proved insensitive to the presence of these additives, the rate enhancement effect appeared to be general and 2,6-lutidine *N*-oxide **23** was identified as the optimal additive in this respect (entry 8).

The effect of tuning the electronic nature of the aryl group on the selenium pre-catalyst was also examined (entries 9–12). Interestingly, electron-deficient pre-catalysts **24** and **25** gave longer reaction times, favoured E2 elimination processes, and significantly eroded the *syn*:*anti* dichlorination ratio (entries 9 and 10). On the other hand, the electron-rich 4-methoxyphenyl

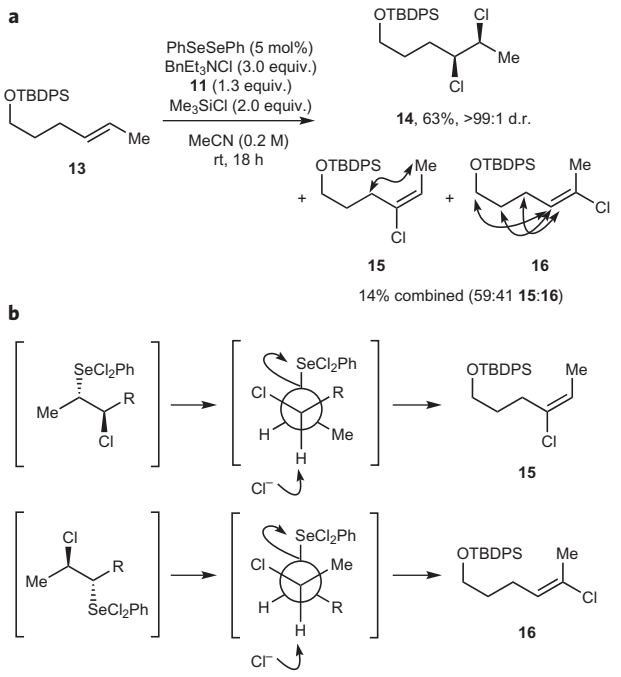

Figure 2 | Identification of E2 elimination by-products. a, Formation of vinylic chloride by-products **15** and **16** from the dichlorination of alkene **13** and determination of their configurations via 1D NOESY experiments (reciprocal enhancements indicated with double-headed arrows). **b**, Mechanistic rationale for the formation of vinyl chlorides **15** and **16** from constitutionally isomeric *anti*-chloroselenylated intermediates via antiperiplanar elimination. TBDPS, *tert*-butyldiphenylsilyl.

pre-catalyst **26** behaved in precisely the opposite sense, giving reduced reaction times, less E2 elimination and near complete *syn*-diastereoselectivity (entry 11). In contrast, the 2-methoxyphenyl pre-catalyst **27** behaved similarly to PhSeSePh, albeit with a slightly extended reaction time (entry 12).

Reaction generality. The generality of the catalytic *syn*-dichlorination with a range of alkene substrates was next surveyed (Table 3). Despite the fact that our optimization studies had identified **26** as the optimal pre-catalyst, its ability to reduce elimination by-products (relative to PhSeSePh) did not prove to be general with other substrates (see Supplementary Information, page 48). Consequently, PhSeSePh was used in all preparative-scale reactions. To take advantage of the rate enhancement imparted by **23**, this additive was included in all preparative reactions, with the exception of allylic alcohols **28t–x**, for which reduced conversions and the formation of unidentified by-products were observed in the presence of **23**. However, the inclusion of **23** is not mandatory for the success of the reactions and it can generally be omitted without detriment to yields or diastereoselectivities, albeit at the expense of reaction rates (for comparison, the yields and diastereoselectivities for reactions conducted for 18 h without **23** are given in square brackets for several substrates).

As representative cyclic alkenes, both cyclohexene **6** and cycloheptene **28a** underwent efficient *syn*-dichlorination with >99:1 and 99:1 d.r., respectively, with the disparity between the isolated yields and those calculated by ^1H NMR spectroscopy being attributed to difficulties in product isolation. Cyclopentene derivatives **28b** and **28c** also participated and the sense of diastereofacial selectivity in both cases was consistent with preferential attack of the selenium electrophile on the sterically more accessible alkene faces, culminating in net, contrasteric *syn*-

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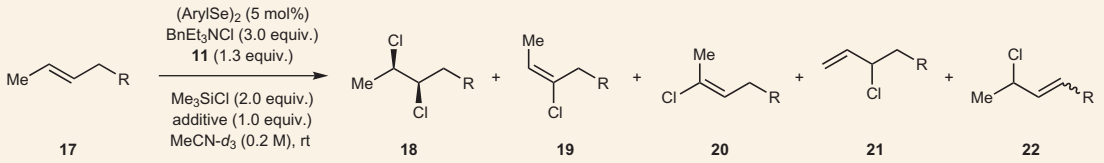
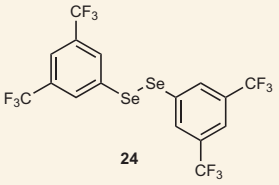
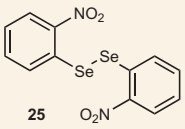
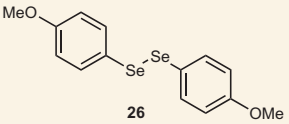
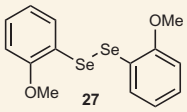
Table 2 | Reaction development with (*E*)-1-benzyloxy-4-hexene.



Entry	$(ArylSe)_2$	Additive	Time (h)	18:(19 + 20 + 21 + 22)*	18 d.r.*
1	PhSeSePh	–	6	80:20	99:1
2	PhSeSePh	Sulfolane†	2	80:20	99:1
3	PhSeSePh	HMPA	3	82:18	98:2
4	PhSeSePh	DMPU	3.5	80:20	98:2
5	PhSeSePh	DMI	2.5	80:20	99:1
6	PhSeSePh	$Ph_3P{=}O$	3.5	80:20	98:2
7	PhSeSePh	Pyridine *N*-oxide	2.5	80:20	98:2
8	PhSeSePh	2,6-Lutidine *N*-oxide **23**	2	80:20	99:1
9	 **24**	–	10	58:42	88:18
10	 **25**	–	18	59:41	55:45
11	 **26**	–	3.5	90:10	99:1
12	 **27**	–	8	83:17	98:2

*Measured by ^{1}H NMR spectroscopy; †sulfolane was used as a co-solvent with MeCN-d_3 in 1:3 vol/vol. HMPA, hexamethylphosphoramide; DMPU, *N,N′*-dimethylpropyleneurea; DMI, *N,N′*-dimethyl-2-imidazolidinone.

dichlorinations. The relative configurations within both **29b** and **29c** were secured by chemical correlation to an epoxy alcohol of known configuration.

For acyclic alkenes, the reaction proved generally applicable to both terminal and 1,2-disubstituted olefins, although 1,1-disubstituted, trisubstituted and aryl-conjugated alkenes afforded complex mixtures of products. Similarly, alkenes bearing pendant nucleophiles able to engage in cyclizations also formed complex mixtures (see Supplementary Information, p. 122, for a table of problematic substrates). Crucially, the stereospecific nature of the *syn*-dichlorination reaction was confirmed by reaction of various pairs of (*E*)- and (*Z*)-configured alkenes, in which both isomers could be dichlorinated with exceptional *syn*-diastereoselectivity (that is, **17**/**28h**, **13**/**28i**, **28q**/**r**, **28u**/**v**). The relative configurations in each case were typically assigned by comparison to known (or analogous) dichlorides, or to authentic samples of the diastereomeric dichlorides prepared by an *anti*-selective dichlorination method. For acyclic vicinal dichlorides, the $^3J_{HH}$ coupling constant was diagnostic, with *syn*-configured dichlorides **14**, **18**, **29j–n** and *anti*-configured dichlorides **29h**,**i**,**o**,**p** giving $^3J_{HH}$ values of 3.0–3.3 and 6.5–6.6 Hz, respectively. A similar trend was noted for dichlorides such as **29q** and **29r** derived from allylic alcohol derivatives, for which the *syn*-configured isomer (**29q**) gave a $^3J_{HH}$ value of 2.2 Hz, whereas the *anti*-configured isomer (**29r**) gave a value of 6.3 Hz.

In terms of functional group compatibility, the reaction is tolerant of free hydroxyl groups (**28t–x**), benzyl ethers (**17**, **28h**,**w**,**x**), *tert*-butyldiphenylsilyl (TBDPS) ethers (**13**, **28c**,**d**,**i**,**q**,**r**), esters (**28b**,**k**,**l**,**n**), acetals (**28e**,**m**), simple or electron-rich arenes (for example, **28f**,**j**,**s**,**u**,**v**), cyclopropanes (**28l**), electron-poor alkenes (**28n**), *tert*-butoxy carbamates (**28o**) and imides (**28p**). However, silicon-based protecting groups other than TBDPS, including triisopropylsilyl (TIPS, **28j**) and *tert*-butyldimethylsilyl (TBS, **28s**), are partially cleaved under the reaction conditions. Although this methodology can accommodate silyl ether functionality at the allylic position (for example, **28q–s**), free allylic (primary) alcohols are also perfectly competent substrates (**28t–x**), providing a convenient functional handle for further elaboration. However, allylic secondary alcohols, as well as their silyl ether or *O*-acyl derivatives, afforded complex mixtures of products for reasons that are currently unclear (see Supplementary Information, page 122). Curiously, subjection of the (*E*)-configured 1,4-dioxygenated alkene **28w** to the dichlorination conditions returned a 56:44 diastereomeric mixture of *syn*- and *anti*-dichlorides **29w**, respectively, whereas the analogous (*Z*)-configured alkene **28x** underwent *syn*-dichlorination with 93:7 diastereoselectivity.

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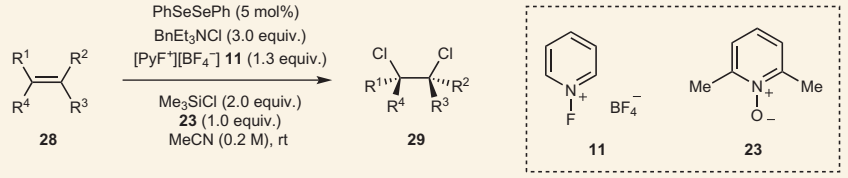
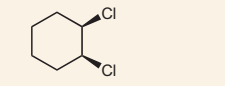
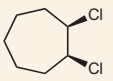
Table 3 | Reaction generality.

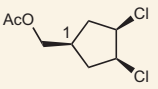




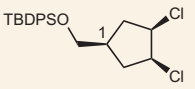
7, 51% (80%*), >99:1 d.r. (10 h) [83%*, >99:1 d.r.]



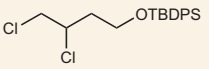
29a, 77% (96%*) d.r. 99:1 d.r. (4 h)



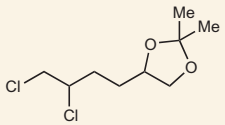
29b, 73%, >99:1 d.r., 89:11 d.r. at C(1)† (24 h), [76%, >99:1 d.r., 90:10 d.r. at C(1)†]



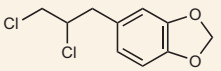
29c, 71%, >99:1 d.r., 91:9 d.r. at C(1) (16 h)



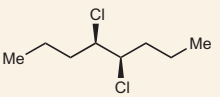
29d, 91% (6 h) [91%]



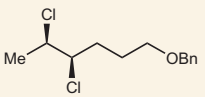
29e, 85% (4.5 h)



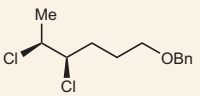
29f, 77% (3.5 h)



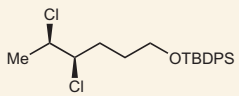
29g, 40% (66%*) d.r. 99:1 d.r. (4 h)



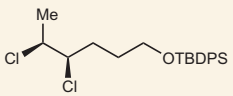
18, 71%, 99:1 d.r. (3.5 h) [64%, >99:1 d.r.]



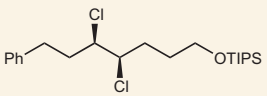
29h, 67%, >99:1 d.r. (4 h) [67%, >99:1 d.r.]



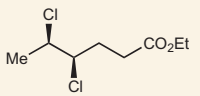
14, 64%, >99:1 d.r. (4 h) [63%, >99:1 d.r.]



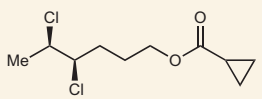
29i, 67%, >99:1 d.r. (6 h) [63%, >99:1 d.r.]



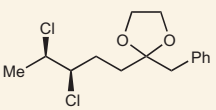
29j, 37%‡, 97:3 d.r. (5 h)



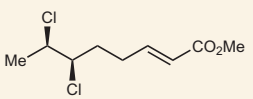
29k, 70%, >99:1 d.r. (3.5 h)



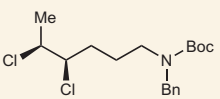
29l, 69%, >99:1 d.r. (3.5 h)



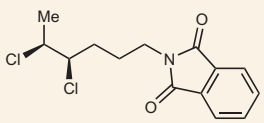
29m, 73%, >99:1 d.r. (3.5 h)



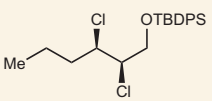
29n, 70%, 99:1 d.r. (4.5 h)



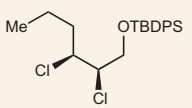
29o, 72%, 99:1 d.r. (5 h)



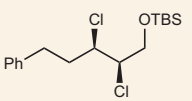
29p, 72%, 97:3 d.r. (3.5 h)



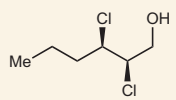
29q, 71%, >99:1 d.r. (7 h)



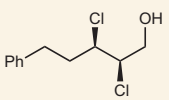
29r, 67%, 99:1 d.r. (9 h)



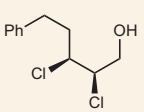
29s, 47%§, >98:2 d.r.‖ (6 h)



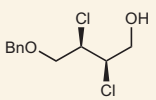
29t, 66%¶, 99:1 d.r. (14 h)



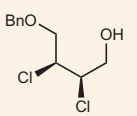
29u, 76%¶, 98:2 d.r. (9 h)



29v, 71%¶, 98:2 d.r. (9 h)



29w, 67%¶, 56:44 d.r. (47 h)



29x, 73%¶, 93:7 d.r.# (15 h)

For comparison, yields and diastereoselectivities for selected reactions conducted for 18 h without additive **23** are given in square brackets. Each diastereomeric ratio (d.r.) was determined on the crude mixture after passing through a short plug of silica gel.
*Yield was determined by ^{1}H NMR spectroscopy with 1,1,2,2-tetrachloroethane (1.0 equiv.) as an internal standard; †91:9 d.r. at C(1) after isolation; ‡24% of the free alcohol *syn*-dichloride was also isolated and tentatively assigned cyclized products were also observed in the crude product mixture; §21% of the free alcohol *syn*-dichloride was also isolated; ‖the d.r. corresponds to the sum of the dichlorides; ¶additive **23** was omitted; #97:3 d.r. after isolation.

Certain alkene substates unexpectedly returned dichloride products resulting from *anti*-addition upon exposure to the standard reaction conditions. Similarly, the presence of branching at the allylic position of acyclic (*E*)-alkenes led to incomplete conversion and ≥80:20 selectivity in favour of *anti*-addition (Supplementary Information, p. 122). The preference for *anti*-dichlorination in these cases is difficult to rationalize at present, and may be substrate-dependent. A better understanding of this phenomenon will form part of a broader mechanistic investigation of the catalytic *syn*-dichlorination, to be reported in due course.

Discussion

A proposed catalytic cycle for the selenium-catalysed *syn*-dichlorination process is outlined in Fig. 3, albeit with omission of the 2,6-lutidine *N*-oxide additive **23**. Initial oxidation of the PhSeSePh pre-catalyst with oxidant **11** in the presence of chloride ion could generate $PhSeCl_3$ as the active catalyst, with Me_3SiCl presumably serving to trap the 0.3 equiv. (w.r.t. alkene) of fluoride ion by-product as Me_3SiF. Addition of $PhSeCl_3$ to the alkene may then ensue, possibly via loss of chloride to generate $PhSeCl_2^+$ **30** as the active electrophile, which can then intercept the alkene to form

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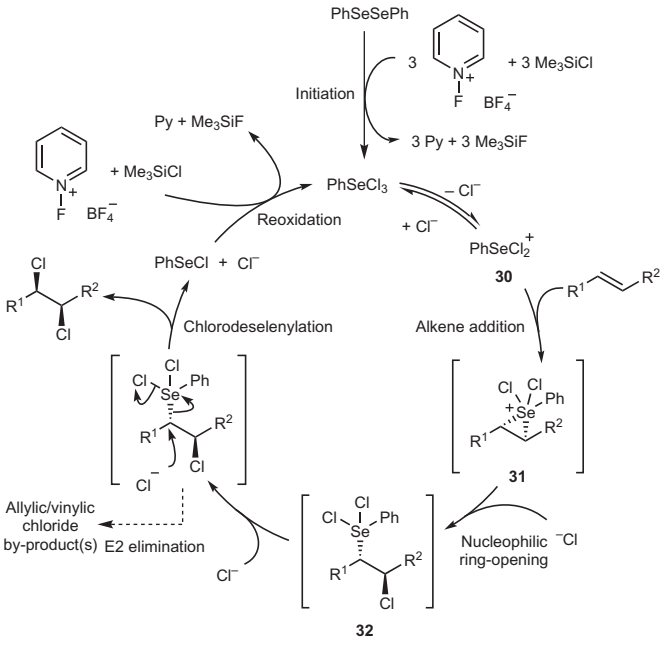

Figure 3 | Proposed catalytic cycle for the selenium-catalysed *syn*-dichlorination of alkenes. Following oxidation of the PhSeSePh pre-catalyst, the catalytic cycle commences with *anti*-chloroselenylation of the alkene to give **32**. Invertive displacement of the selenium moiety with chloride ion furnishes the *syn*-dichloride product. Finally, reoxidation of Se(II) to Se(IV) closes the cycle. Py, pyridine.

seleniranium ion intermediate **31**. Nucleophilic ring-opening of **31** with chloride ion would then furnish the (β-chloroalkyl)phenylselenium dichloride species **32**[25,26] and subsequent invertive displacement of the Se(IV) nucleofuge with chloride ion[28,29] would deliver the *syn*-dichloride product, releasing the selenium as PhSeCl. The dissociation of a chloride ligand from the selenium atom within **32** before nucleophilic displacement is a possibility, as this would enhance the nucleofugality of the selenium by rendering it cationic. The stereochemical outcome in the chlorodeselenylation step hinges on the fact that neighbouring chloro substituents are comparatively reluctant to engage in anchimeric assistance[37].

To complete the cycle, oxidation of PhSeCl by **11** in the presence of chloride ions could regenerate the $PhSeCl_3$ catalyst, although it is possible that addition of PhSeCl to the alkene could precede the oxidation of Se(II) to Se(IV). In any case, the mechanism of the reoxidation process requires further scrutiny and the possibility that trace amounts of Cl_2 (generated from the oxidation of Cl^- by **11**) may serve as the active oxidant cannot be ruled out at this stage.

The crucial role of Me_3SiCl in the reaction also requires further investigation, but an initial hypothesis is that it may serve to trap fluoride ions (from the reduction of oxidant **11**) that would otherwise interfere with catalytic turnover (note that Me_3SiF was observed in reaction mixtures by ^1H and ^{19}F NMR spectroscopy). Specifically, it may be that halide dissociation (Cl^- or F^-) from $PhSeX_3$ to generate the active $PhSeX_2^+$ electrophile (where X = Cl or F) is slower when the selenium centre carries one or more fluoride ligands. In support of this assertion, it is known that the stoichiometric reaction of cyclohexene with $PhSeF_3$ is slow, requiring 2–3 h to reach completion[38], whereas the analogous addition of $PhSeCl_3$ requires only a few minutes[26].

The observation of allylic or vinylic chloride by-products can be accounted for by a competitive E2 elimination between **32** and chloride ion, which is a weak but competent base in acetonitrile (pK_a of HCl = 10.3 in MeCN[39]). The possibility that pyridine (generated from the reduction of oxidant **11**) may serve as the base in this process cannot be excluded (pK_a of pyridinium ion = 12.3 in MeCN[40]) although its concentration (particularly early in the reaction) will be much lower than chloride ion.

The role of the 2,6-lutidine *N*-oxide additive **23** is not clear, but a control experiment with alkene **17** in which the *N*-fluoropyridinium salt **11** was omitted (leaving **23** as the only potential oxidant for selenium) gave no reaction, indicating that **23** is not functioning as an oxidant. Similarly, omission of the PhSeSePh pre-catalyst gave no *syn*-dichloride and only a slow background *anti*-dichlorination was observed (40% conversion after 20 h), verifying that the combination of $BnEt_3NCl$, **11** and **23** alone is not capable of effecting *syn*-dichlorination via some other mechanistic pathway. As the turnover-limiting step of the catalytic cycle is yet to be elucidated, it would be premature to speculate on the origin of the rate enhancement imparted by **23**.

In summary, we have developed the first catalytic, *syn*-stereospecific dichlorination of alkenes, employing a group transfer catalyst based on a redox-active main group element (selenium). The method is applicable to a wide variety of functionalized cyclic and acyclic 1,2-disubstituted alkenes, including simple (primary) allylic alcohols, and is operationally simple to perform. As well as providing a convenient solution to the problem of direct alkene *syn*-dichlorination, this process could also form the basis of a conceptually new strategy for catalytic, enantioselective alkene dichlorination. Importantly, the absence of chloriranium ion intermediates can circumvent the site selectivity issue inherent in the nucleophilic trapping of such species with chloride ion—a recognized, and as yet unsolved, problem in controlling the enantioselectivity of dichlorinations of electronically unbiased, (*E*)- or (*Z*)-configured alkenes[15].

Methods

Full experimental details and characterization of compounds can be found in the Supplementary Information.

General procedure for catalytic *syn*-dichlorination of alkenes. The general procedure for the catalytic, *syn*-dichlorination of alkenes with 2,6-lutidine *N*-oxide as additive is as follows. In a typical experiment, an oven-dried, 10 ml Schlenk flask equipped with a magnetic stirrer bar was taken into the glovebox and charged sequentially with diphenyl diselenide (15.8 mg, 0.05 mmol, 5 mol%), benzyltriethylammonium chloride (690 mg, 3.03 mmol, 3.0 equiv.) and *N*-fluoropyridinium tetrafluoroborate (240 mg, 1.30 mmol, 1.3 equiv.) and was then sealed with a rubber septum, removed from the box and placed under argon. MeCN (5.0 ml), 2,6-lutidine *N*-oxide (126 mg, 115 µl, 1.02 mmol, 1.0 equiv.) and chlorotrimethylsilane (218 mg, 255 µl, 2.01 mmol, 2.0 equiv.) were then added sequentially and stirring was commenced. After ~10 min, an off-white suspension was observed. At this point, the requisite alkene (1.00 mmol, 1.0 equiv.) was transferred via syringe to the reaction mixture (for alkenes of unknown density, only 3.0 ml MeCN was added initially and the remaining 2.0 ml (in two 1.0 ml portions) was used to transfer the alkene across from an oven-dried, 4 ml dram vial under argon, via syringe). The resultant suspension was stirred at room temperature and was monitored by thin layer chromatography (TLC) until no alkene substrate was detected. Once the reaction had reached completion, sat. aq. $NaHCO_3$ (1.0 ml) was added to quench any unreacted chlorotrimethylsilane and stirred for ~10 min. The mixture was then transferred to a separatory funnel and diluted with H_2O (15 ml). The aqueous layer was extracted with Et_2O (3 × 15 ml) and the combined organic extracts were washed with brine (15 ml), then dried ($MgSO_4$), filtered and concentrated *in vacuo* (20–23 °C at ~20 mmHg for non-volatile products or 5–8 °C, ~20 mmHg for volatile products). The resultant residue was re-dissolved in Et_2O (5.0 ml) and eluted through a short plug of silica gel (~0.55 g SiO_2 packed into a Pasteur pipet to a height of ~40 mm) to partially remove 2,6-lutidine *N*-oxide and any ammonium salts, and the plug was then rinsed through with further portions of Et_2O (3 × 5 ml). The solvent was removed *in vacuo* (20–23 °C, ~20 mmHg for non-volatile products or 5–8 °C, ~20 mmHg for volatile products) and an aliquot of the crude mixture was dissolved in $CDCl_3$ to measure the *syn*/*anti* diastereoisomeric ratio (d.r.) by ^1H NMR spectroscopy. The *syn*-dichloride product was then isolated by flash column chromatography on silica gel and/or Kugelrohr distillation at reduced pressure. The procedure for the catalytic, *syn*-dichlorination of allylic alcohols and the preparations of the alkene substrates are presented in the Supplementary Information.

Received 18 September 2014; accepted 18 November 2014; published online 12 January 2015

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Acknowledgements

The authors acknowledge the National Institutes of Health (GM R01-085235) for financial support. S.T-C.E. thanks the Agency for Science, Technology and Research of Singapore (A*STAR) for a postdoctoral fellowship.

Author contributions

A.J.C. planned and carried out the experimental work and initial optimization. S.T-C.E. completed the experimental work and final characterizations. S.E.D. directed and coordinated the project. A.J.C. wrote the manuscript with the assistance of the other authors.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to S.E.D.

Competing financial interests

The authors declare no competing financial interests.

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