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Dichlorination of olefins with NCS/Ph_3P†

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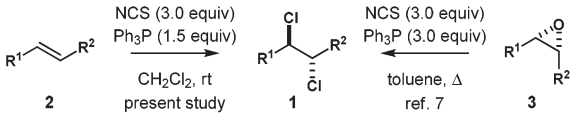
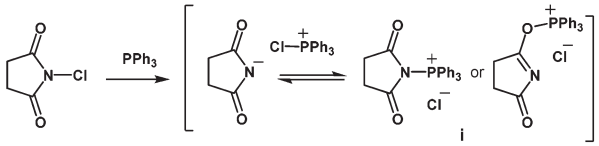
A 2 : 1 mixture of NCS and Ph_3P successfully promoted the *anti*-dichlorination of olefins to provide corresponding dichlorides, serving as a molecular chlorine surrogate generated *in situ*.

The increasing interest in bioactive organochlorines widely distributed in the natural environment has spearheaded efforts to devise synthetic methodologies for the formation of carbon–chlorine bonds.[1–3] Of particular interest is the class of organochlorines bearing an sp^3C–Cl (sp^3carbon–chlorine) bond as their stereoselective construction still poses a significant challenge. Olefin dichlorination with molecular chlorine (Cl_2) is one of the most straightforward approaches for elaborating such a functionality. However, molecular chlorine is often difficult to handle due to its gaseous state as well as potential safety problems. Fortunately, those drawbacks are circumvented by using molecular chlorine surrogates. Examples of such surrogates include Et_4NCl_3 (Mioskowski reagent)[4] and $BnEt_3NCl$–$KMnO_4$–TMSCl (Markó–Maguire reagent),[5] which have found successful applications in the preparation of a variety of organochlorines.[6] The stereochemical outcome in the olefin dichlorinations with those surrogates generally agrees well with that obtained with molecular chlorine that installs vicinal chlorine atoms to the double bond in an *anti* fashion. In the present study, we demonstrated that the combination of NCS and Ph_3P in a 2 : 1 stoichiometry promoted the *anti*-dichlorination of olefins to furnish corresponding dichlorides (**2**→**1**), allowing us to expand the versatility of this readily available chlorination reagent (Scheme 1).

Previous studies in this and other laboratories found that a 1 : 1 mixture of NCS/Ph_3P and a combination of cat. Ph_3PO/$(COCl)_2$ were suited for the stereospecific nucleophilic replacement of the oxygen atom of an epoxide with chlorine atoms to furnish the corresponding dichloride (**3**→**1**).[7,8] In that



Scheme 1 Dichlorination of olefin **2** with NCS/Ph_3P in 2 : 1 stoichiometry.



Scheme 2 Chlorophosphonium complexes generated from NCS/Ph_3P.

transformation, the chlorophosphonium complex generated *in situ* served as a Lewis acidic activator of the epoxide as well as a chloride source (Scheme 2). It occurred to us that an additional 'chloronium source,' *i.e.*, NCS, would reasonably activate the double bond of an olefin to form a chloronium intermediate, and that intermediate would further undergo ring opening with a chloride ion generated from the chlorophosphonium complex, forming a dichloride.

Our hypothesis was tested by applying 2 : 1 NCS/Ph_3P to various olefins (Table 1). Protected olefin **4** was treated with 2 : 1 NCS/Ph_3P to afford corresponding dichloride **10** in 89% yield (entry 1). Cyclooctene (**5**) was converted into dichloride **11** in high yield (93%) (entry 2).[9] Dichlorination of ethyl sorbate (**6**) with 2 : 1 NCS/Ph_3P provided regioisomeric dichlorides **12** and **13** in a 3.6 : 1 ratio, favoring the 1,2-adduct (entry 3).[10] *trans*- and *cis*-Stilbenes **7** and **8** gave a diastereomeric mixture of dichloride **14** in almost the same ratio (*ca.* 1 : 1) (entries 4 and 5).[11] In those cases, the *anti* stereospecificity was lost probably due to the propensity of the S_N1-like substitution *via* a benzylic cation. Functionalized substrate **9** was also dichlorinated with 2 : 1 NCS/Ph_3P to furnish *trans*-dichloride **15** in 96% yield (entry 6).[12] The stereochemistry of the above-mentioned dichlorides **11**, **12**, and **15** indicated that the reaction took place *via* an anti-addition mechanism.

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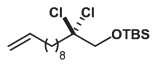
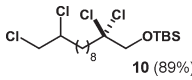
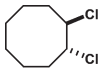
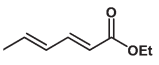
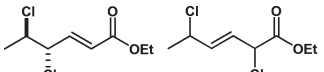
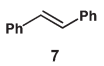
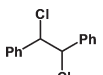
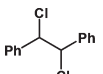
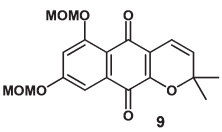
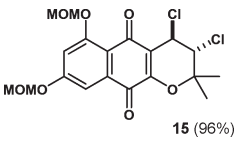
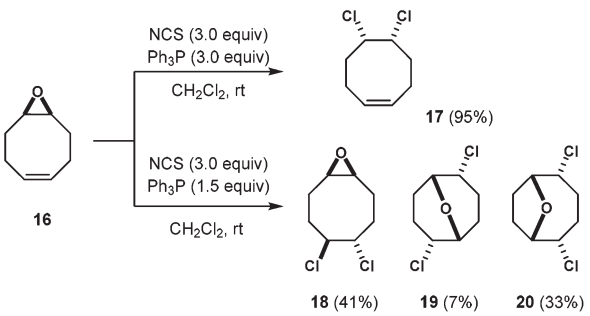
†Electronic supplementary information (ESI) available: Experimental protocols, spectroscopic and analytical data, and copies of ^{1}H and ^{13}C NMR. See DOI: 10.1039/c3ob27345h

Table 1 Dichlorination of olefins with NCS/Ph_3P in 2 : 1 stoichiometry[a]

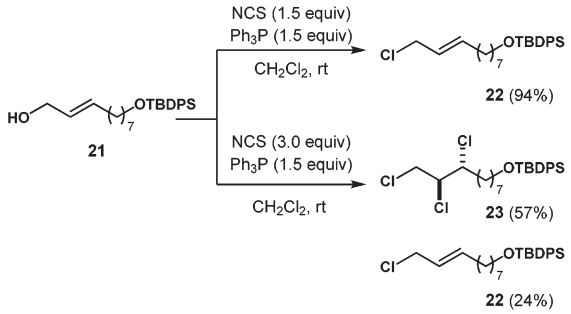
Entry	Substrate	Dichloride[b] (%)
1[c]	 **4**	 **10** (89%)
2	 **5**	 **11** (93%)
3	 **6**	 **12** (76%) **13** (21%)[d]
4[e]	 **7**	 **14** (77%)[f]
5[g]	 **8**	 **14** (81%)[h]
6	 **9**	 **15** (96%)

[a] All reactions were carried out in CH_2Cl_2 at room temperature using olefin (1 equiv.), Ph_3P (1.5 equiv.) and NCS (3.0 equiv.). [b] Isolated yield after chromatographic purification. [c] Regioisomeric chlorohydrins (*ca.* 1 : 1) were produced as a minor product (7%). [d] Stereochemistry has yet to be determined. [e] Chlorohydrin (7%) was produced. [f] 1 : 1 *syn* : *anti* dichloride was obtained. [g] Chlorohydrin (6%) was produced. [h] 1 : 1 *syn* : *anti* dichloride was obtained.

Further application of the present dichlorination system to bifunctional substrate **16** provided insights into its unique reaction scope (Scheme 3). With the addition of a 1 : 1 mixture of NCS/Ph_3P, epoxy cyclooctene **16** was cleanly and smoothly converted into dichloride **17** with the double bond remaining intact. This outcome indicated that the chlorophosphonium reagent was rapidly generated *in situ* to preferentially undergo deoxydichlorination over double bond activation. In contrast, the 2 : 1 combination of NCS/Ph_3P afforded epoxy dichloride **18** (41%) and ring-opened isomeric products **19** (7%) and **20** (33%). The production of such chlorides in the latter case by



Scheme 3 Dichlorination of cyclooctene **16** with NCS/Ph_3P in either 2 : 1 or 1 : 1 stoichiometry.



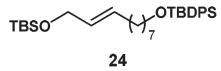
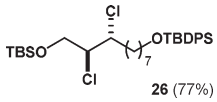
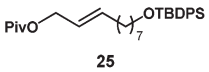
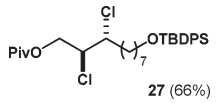
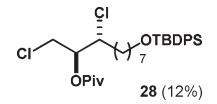
Scheme 4 Chlorination of allylic alcohol derivative **21** with NCS/Ph_3P in either 2 : 1 or 1 : 1 stoichiometry.

modifying the stoichiometry of the reagent suggested that in the presence of additional NCS, the double bond was preferentially activated and dichlorinated. Compounds **19** and **20** obtained by 2 : 1 NCS/Ph_3P addition were likely to be produced by anchimeric assistance of the epoxide onto the chloronium intermediate, followed by ring opening of the resultant oxonium intermediate[13] with a chloride, although the intramolecular chloroetherification of a chlorohydrin generated from the epoxide might also be operative.

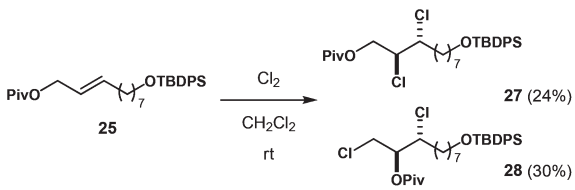
The preferential activation of a hydroxy group over a double bond was generally observed irrespective of the reagent stoichiometry (Scheme 4). Thus, a 1 : 1 mixture of NCS/Ph_3P efficiently promoted the Appel-type allylic chlorination to afford chloride **22** in 94% yield. In contrast, the 2 : 1 combination afforded trichloride **23** as the major product (57%) along with allylic chloride **22** (24%). Trichloride **23** was likely produced *via* dichlorination of allylic chloride **22** because, in another experiment, treatment of **22** with the 2 : 1 reagent system promptly gave **23** in 92% yield. It should be noted that trichloride **23** was predominantly produced when more reagents were used, *i.e.*, 6 equiv. of NCS and 3 equiv. of Ph_3P. The trichlorination of the allylic alcohol represented a unique property of the 2 : 1 reagent; neither the 1 : 1 NCS/Ph_3P reagent nor molecular chlorine facilitated such a transformation.

Under the present conditions, TBS-protected olefin **24** was cleanly transformed into *anti*-dichloride **26** in 77% yield (Table 2, entry 1). In contrast, treatment of pivalate **25** with 2 : 1 NCS/Ph_3P afforded the expected dichloride **27** (66%) along with ester-migrated product **28** (12%) (entry 2). The migration strongly suggested the intermediacy of a chloronium ion, which likely suffered from anchimeric assistance by the neighboring ester functionality. This was further supported by the observation that the dichlorination of olefin **25** with molecular chlorine (Cl_2) afforded **28** (30%), **27** (24%), and recovered olefin **25** (27%) (Scheme 5). The distinct product ratio observed for the 2 : 1 NCS/Ph_3P system and molecular chlorine reflected the concentration of chloride ions in the reaction media, *i.e.*, the higher the chloride ion concentration was, the less often the migration took place: the 2 : 1 system promptly produced a high concentration of chloride ions necessary for intermolecular nucleophilic chlorination, whereas molecular chlorine concomitantly generated a limited number of chloride ions

Table 2 Dichlorination of olefins **24** and **25** with NCS/Ph_3P in 2 : 1 stoichiometry[a]

Entry	Substrate	Dichloride[b] (%)
1	 **24**	 **26** (77%)
2	 **25**	 **27** (66%)
		 **28** (12%)

[a] All reactions were carried out in CH_2Cl_2 at room temperature using olefin (1 equiv.), Ph_3P (1.5 equiv.) and NCS (3.0 equiv.). [b] Isolated yield after chromatographic purification.



Scheme 5 Dichlorination of olefin **25** with molecular chlorine (Cl_2).

via chloronium intermediate formation. Therefore, with the 2 : 1 reagent that had a high concentration of nucleophilic chloride ions, the migration was relatively suppressed. It should be noted that such neighboring participation was not observed in the deoxydichlorination of epoxides bearing a pivalic ester functionality.[14]

In conclusion, we have demonstrated that the NCS/Ph_3P system, a well-known source of the chlorophosphonium ion, is a readily available dichlorination reagent for olefins by modifying the reagent stoichiometry. This simple combination is expected to expand its scope in further chlorination reactions of organic molecules.

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