Letter

Catalytic *Vicinal* Dichlorination of Unactivated Alkenes

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ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.9b02313 • Publication Date (Web): 08 Jul 2019

Catalytic *Vicinal* Dichlorination of Unactivated Alkenes

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ABSTRACT: Organocatalytic strategies for the programmed, catalytic oxidation of π-bonds through regioselective halogenation remain comparatively underdeveloped. The *vicinal* dichlorination of unactivated alkenes is a pertinent example, where stoichiometric reagents and pre-functionalisation steps are often employed. This is surprising given the prominence of the 1,2-dichloro moiety in an array of bioactive natural products of both terrestrial and marine origin. Inspired by Willgerodt's seminal discovery in 1886 that $PhICl_2$ can be generated by passing $Cl_{2(g)}$ through iodobenzene, a catalytic *vicinal* dichlorination of unactivated alkenes has been designed based on an I(I)/I(III) manifold. *In situ* generation of *p*-$TolICl_2$ is achieved using Selectfluor® and CsCl. Substrate scope, mechanistic delineation and preliminary validation of an enantiomeric variant are established. Over a century after the initial discovery of the Willgerodt reagent ($PhICl_2$), an operationally simple, catalytic alternative has been validated.

KEYWORDS. 1,2-chlorination • halogenation • iodine • organocatalysis • selectivity • stereospecificity

Organocatalysis-based strategies to enable the *vicinal* dihalogenation of unactivated alkenes are conspicuously under represented.[1] The exigency is particularly prominent in the 1,2-dichlorination of unactivated alkenes using low molecular weight catalysts and simple chloride salts.[2] This is surprising, given the diversity of marine and terrestrial poly-chlorinated, secondary metabolites bearing the 1,2-dichloro motif (Figure 1), and the well-delineated biosynthesis pathways that generate formal electrophilic "Cl^+" sources from abundant salts.[3] Prominent synthesis campaigns directed towards the chlorosulfolipids by Vanderwal,[4] Carreira,[5] and Yoshimitsu,[6] have been instrumental in triggering a renaissance in organo-chlorine chemistry: This is a consequence of the unique conformational[7] and physicochemical properties of the *vicinal* dichloro unit, and the wider biological and environmental impacts of complex, polychlorinated systems.[8] Logically, this has led to a rapid expansion in strategies to enable this fundamental transformation. In addition to reliable, multi-step processes that involve alkene pre-activation, such as epoxide functionalisation under Appel conditions,[9] a number of reagent-based processes remain indispensable: The venerable Mioskowski reagent (Et_4NCl_3) remains popular although caution must be exercised during preparation due to the corrosive nature of $Cl_{2(g)}$.[10] These strategies are complemented by a series of elegant transition metal-mediated protocols using manganese,[11] molybdenum,[12] ruthenium[13] and vanadium.[14] Stereospecificity is frequently observed in many scenarios due to the involvement of transient chloronium ions;[15] an aspect of reagent-based chlorination that has been beautifully harnessed in the aforementioned total syntheses.[4-8] More recently, an organo-catalytic strategy to access the elusive *vicinal syn*-configured adducts has been achieved by Denmark and co-workers via a key seleniranium intermediate.[16] It is important to highlight that there have been rapid advances in the catalytic, diastereo- and enantioselective *vicinal* dichlorination of allylic alcohol derivatives.[17,18,19] Recently, Hennecke and co-workers reported a catalytic, enantioselective dichlorination of *Z*-configured, alkyl substituted styrenes using 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) and TESCl as the electrophilic and nucleophilic chlorinating reagents, respectively, in the presence of a cinchona alkaloid-based catalyst.[20] Whilst these conditions are effective for alkyl substituted styrenes, simple alkenes remain challenging.

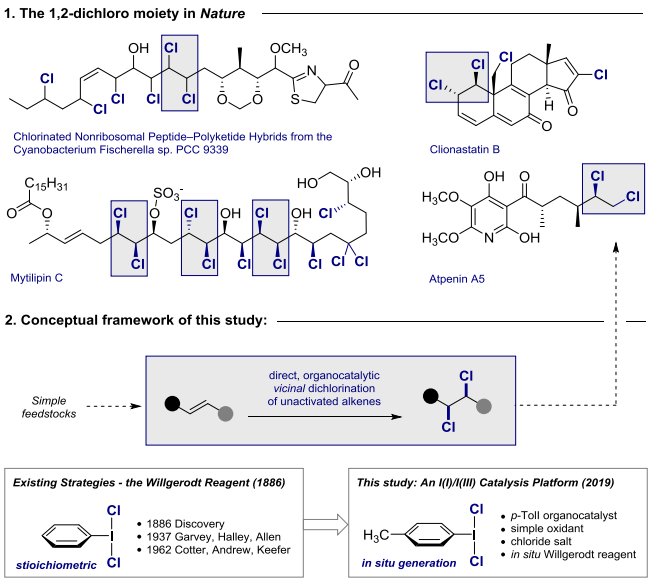
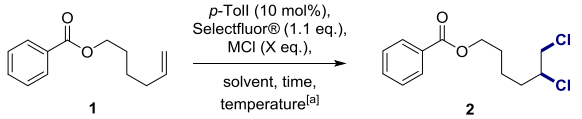


Figure 1. Top: Selected examples of marine and terrestrial natural products containing the *vicinal* dichloro motif. Bottom: The conceptual framework of this study.

Emulating the formal *Umpolung* process enabled by haloperoxidases in biology ($Cl^- \rightarrow Cl^+$) has proven to be a valuable and expansive blueprint for the design of synthetic chlorination processes.[3] Inspired by this, and based on our interest in the I(I)/I(III) manifold,[21] we sought to generate Willgerodt-type reagents ($ArICl_2$)[22] *in situ* from a simple aryl iodide organocatalyst, oxidant and chloride source. First isolated in 1886, this reagent has a distinguished history in stoichiometric chlorination,[17,23] yet there is a conspicuous absence of catalytic variants.[24,25] Motivation stemmed from previous work on the catalytic *vicinal* difluorination of alkenes, and mitigating the current safety and sustainability shortcomings of stoichiometric reagent preparation.

It was envisaged that inexpensive, commercially available *p*-TolI would serve as an excellent small molecule organocatalyst upon which to base an I(I)/I(III) catalysis cycle.[26,27] Inspired by the seminal studies by Cotter and co-workers who explored the role of trifluoroacetic acid in the stoichiometric reaction of iodobenzene dichloride with alkenes,[28] the effect of various additives on reaction efficiency were also investigated (Table 1). To that end, a process of design was initiated by exploring the *vicinal* dichlorination of model substrate **1** in the presence of 10 mol% catalyst loading. Initially, the title reaction was attempted with *p*-TolI as the catalyst and KCl in dichloromethane. A screen of common oxidants, including NaOCl, $NaIO_4$, CAN, AcO_3H, *t*-BuO_2H, H_2O_2, $K_2S_2O_8$, proved ineffective. Switching to *m*-CPBA furnished the corresponding epoxide in 68%, whereas reactions using Oxone® resulted in a competing background reaction in the absence of catalyst: This latter scenario would render translation to an enantioselective paradigm futile. Finally, Selectfluor® was investigated. An early study by Lal and co-workers disclosed its ability to oxidise iodide and bromide ions but not chlorides, rendering it ideal for this study.[29] Changing solvent to TFE boosted reaction efficiency, yielding the product in 51% yield (Table 1, entries 1-4). Further improvement resulted from performing the reaction in hexafluoroisopropanol (HFIP) and utilising CsCl as a chloride source (entries 5-10). As illustrated in entry 11, the control reaction without *p*-TolI did not furnish the expected product **2**. Cognisant of the critical role of HFIP in Gulder and co-workers recent study on haliranium-ion cyclisation cascades, a co-solvent system was explored using HFIP.[30]

Table 1. Optimization of the I(I)/I(III)-mediated *vicinal* dichlorination of alkenes.



1 2

entry	MCl (X eq.)	solvent	additive (X eq.)	time (h)	T (°C)	yield[a]
1	KCl (5.0)	CH_2Cl_2	-	15	r.t.	<5%
2	KCl (5.0)	MeCN	-	15	r.t.	<5%
3	KCl (5.0)	CF_3CO_2Et	-	15	r.t.	<5%
4	KCl (5.0)	TFE	-	3	r.t.	51% (42%)
5	KCl (5.0)	HFIP	-	3	r.t.	59%
6[b]	KCl (5.0)	HFIP	-	3	r.t.	60%
7	NaCl (5.0)	HFIP	-	3	r.t.	<5%
8	CsCl (5.0)	HFIP	-	3	r.t.	70%
9	CsCl (3.0)	HFIP	-	3	r.t.	76%
10[c]	CsCl (3.0)	HFIP	-	3	r.t.	71%
11[d]	CsCl (3.0)	HFIP	-	3	r.t.	<5%[e]
12	CsCl (3.0)	CH_2Cl_2	HFIP (9.0)	3	r.t.	88% (73%)
13[d]	CsCl (3.0)	CH_2Cl_2	HFIP (9.0)	3	r.t.	12%
14[d]	CsCl (3.0)	CH_2Cl_2	HFIP (9.0)	8	0	<5%
15	CsCl (3.0)	CH_2Cl_2	HFIP (9.0)	8	0	78% (65%)
16[f]	CsCl (3.0)	CH_2Cl_2	HFIP (9.0)	8	0	84% (75%)

[a] ^{1}H NMR yield using DMF as internal standard (yield after column chromatography). [b] Reaction performed in the dark. [c] 5 mol% of *p*-TolI. [d] Control experiment without catalyst. [e] Complete consumption of the starting material by ^{1}H NMR. [f] 20 mol% of *p*-TolI. N.B. A screening of common oxidants is provided in the SI.

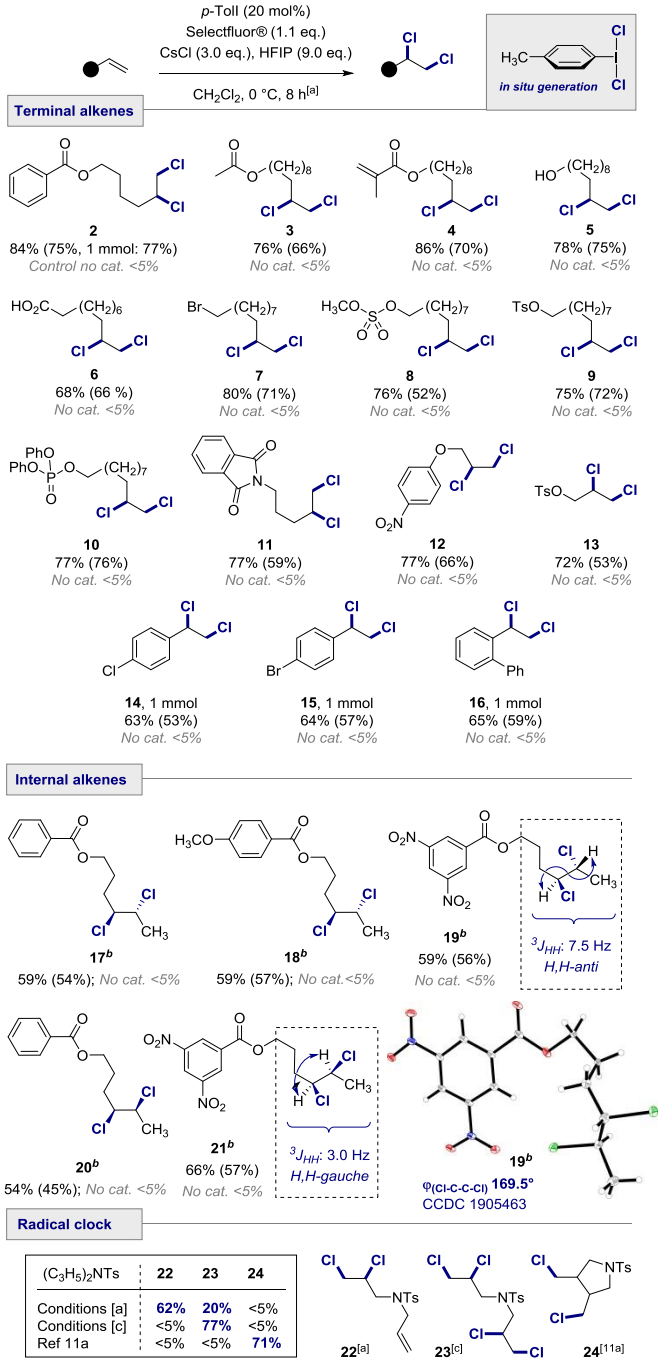


Figure 2. Establishing the scope of the catalytic, *vicinal* dichlorination of alkenes and a demonstration of stereospecificity. [1]H NMR yield using DMF as internal standard (yield after column chromatography). [a] *p*-TolI (20 mol%), Selectfluor® (1.1 eq.), CsCl (3.0 eq.), HFIP (9.0 eq.), CH_2Cl_2, 8 h, 0 °C. [b] *p*-TolI (20 mol%), Selectfluor® (1.1 eq.), CsCl (3.0 eq.), HFIP (9.0 eq.), CH_2Cl_2, 8 h, r.t. [c] *p*-TolI (40 mol%), Selectfluor® (2.2 eq.), CsCl (6.0 eq.), HFIP (18.0 eq.), CH_2Cl_2, 8 h, 0 °C.

The addition of 9.0 eq. of HFIP had a notable effect on reaction efficiency, furnishing **2** in 88% yield (entry 12). However, the control reaction without catalyst at ambient temperature revealed a competing background reaction which had to be suppressed with a future view to developing an enantioselective process (entry 13). This was achievable at 0 °C (entry 14) and so the reaction scope was established at this temperature (entry 15, 78%). Increasing the catalyst loading to 20 mol% further increased the yield to 84% (entry 16). The scope of the transformation was then explored under the standard conditions (Figure 2). Substrates containing spacers were employed to mitigate complications arising from anchimeric participation. The general catalysis conditions proved to be compatible with an array of functional groups. Esters **2**, **3** and **4** were formed in synthetically useful yields (up to 86%): Product **4** demonstrates the chemoselectivity of the process for electron rich alkenes in the presence of an electron deficient system. Gratifyingly, unprotected alcohols were compatible with the *vicinal* dichlorination conditions (**5**, 78%) as were free acids (**6**, 68%). The primary bromide was not susceptible to Finkelstein chemistry, allowing the desired *vicinal* dichloride to be formed cleanly (**7**, 80%), and the corresponding sulfate and tosylate were compatible with the general conditions (**8**, 76%; **9**, 75%). In view of the importance of phosphate groups in bioactive lipids, compound **10** was prepared (77%). Examples with reduced spacer lengths proved unproblematic.

The masked amine **11** was generated in 77% yield, and the protected C3 building blocks **12** and **13** could also be accessed via this method (up to 77%). Styrenes also proved to be competent substrates as evidenced by dichloride **14**, **15** and **16** (up to 59%). Simultaneous scope expansion and mechanistic interrogation was achieved by moving to internal alkenes. Consistent with Denmark's mechanistic description of the stoichiometric reaction,[1a] the reactions were found to be highly stereospecific (Figure 2, lower). The *anti*-configured *vicinal* dichlorides **17**-**19** were generated from the corresponding *E*-alkene ($^3J_{HH}$ = 7.5 Hz for **19**). Conversely, the *syn*-adducts **20** and **21** derived from the starting *Z*-alkene ($^3J_{HH}$ = 3.0 Hz for **21**).

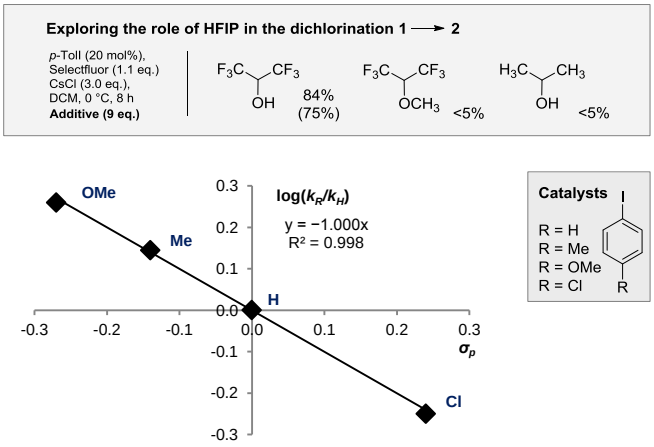


Figure 3. Exploring the effects of the additive and the catalyst on the dichlorination **1** → **2**. Upper: Control experiments to demonstrate the role of HFIP. Lower: Hammett plot with *para*-substituted iodoarenes ($\rho < 0$).

X-ray crystallographic analysis of **19** unequivocally established the relative configuration of the *vicinal* dichloro motif, and revealed a dihedral angle ϕ = 169.5° (Figure 2, lower, CCDC 1905463). This contrasts sharply with the *gauche* conformation inherent to *vicinal* difluorides.[31] A radical clock experiment also proved instructive favouring formation of the di- (**22**) and tetra-chlorinated (**23**) products with 20 or 40 mol% catalyst loading respectively. This is in contrast to the electrochemical conditions reported by Lin and co-workers[11e] that generate the cyclic adduct **24**.

The importance of HFIP as an additive in the title transformation was established by unproductive control experiments using the methylated and non-fluorinated analogues (<5% in both scenarios) (Figure 3, top). A Hammett plot of electronically distinct, *para*-substituted iodoarenes (R = OMe, Me, Cl, H) established $\rho < 0$ indicating a build-up of positive charge in the transition state, and a manifest rate acceleration as a result of electron-donating groups (Figure 3).[32]

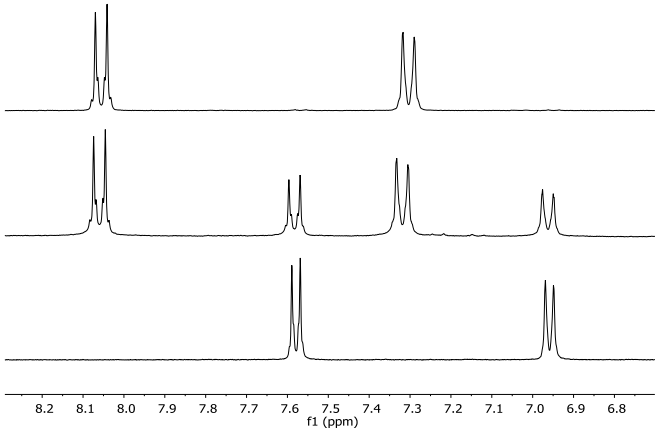
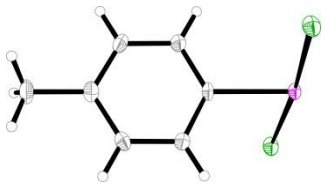


Figure 4. Top: Reference spectrum of *p*-TolICl$_2$ in CD_2Cl_2. Middle: Reaction mixture after 20 min. Standard reaction conditions at 0.2 mmol: *p*-TolI (40 μmol, 20 mol%), CsCl (0.6 mmol, 3.0 eq.), Selectfluor® (0.22 mmol, 1.1 eq.), HFIP (1.8 mmol, 9.0 eq.), CD_2Cl_2 (0.9 mL). Bottom: Reference spectrum of *p*-TolI in CD_2Cl_2. Inset: X-ray structure of *p*-TolICl$_2$. CCDC 1555066.



Finally, it was possible to demonstrate *in situ* formation of the Willgerodt-type reagent by comparing the reaction mixture with *p*-TolI and a sample of *p*-TolICl$_2$ prepared independently (Figure 4, inset, CCDC 1555066). Collectively, these data suggest a catalytic process in which the C-Cl bond forming stages are mechanistically consistent with Denmark's reaction classifications.[1a] With a view to rendering this process enantioselective, preliminary studies with a chiral aryl iodide catalyst[33] were conducted. The expected dichloride **14** was generated with 64:36 *e.r.* thus providing preliminary validation (Figure 5).

More than a century after the discovery of the Willgerodt reagent, a protocol to generate *p*-TolICl$_2$ *in situ* is disclosed and applied to the organocatalytic, *vicinal* dichlorination of unactivated alkenes. The general catalysis conditions demonstrate broad functional group tolerance and allow single regioisomers to be generated in a highly stereospecific manner. Importantly, preliminary validation of enantioselectivity is described on a challenging mono-substituted system,[34] and is the subject of ongoing research in this laboratory.

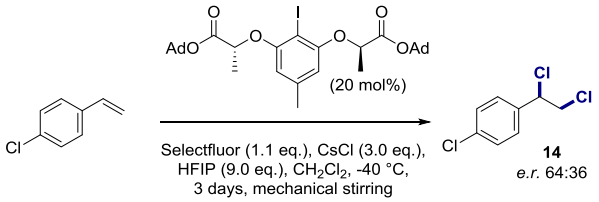


Figure 5. Preliminary validation of an enantioselective variant.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website. Full experimental details and NMR spectra (PDF).

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We acknowledge financial support from the WWU Münster, and the Deutsche Forschungsgemeinschaft (Excellence Cluster *EXC 1003*, and SFB 858). This manuscript is dedicated to Prof. Dr. Erick M. Carreira.

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