Organocatalysis through Halogen-Bond Activation

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Abstract: Haloperfluoroalkanes have been used as catalysts for the reduction of 2-phenylquinoline to its corresponding 1,2,3,4-tetrahydro derivative using a Hantzsch ester as reductand. The results suggest a substrate activation by halogen bonding.

Key words: amine synthesis, halogen bonding, imine reduction, organocatalysis, quinoline reduction

In the emerging field of organocatalysis, hydrogen bonding is one of the most important noncovalent interactions that allows the activation of an electrophile towards a nucleophilic attack.[1,2] Much less attention has been paid to activations by other atoms, which can also act as electron acceptors. For example, attractive interactions between halogen atoms and electron donors have been known for more than one century,[3] and for their characterization the term 'halogen bond' was introduced a few years ago. Thus, halogen bonding describes any noncovalent interaction between a halogen atom acting as a Lewis acid and an electron donor (Lewis base).[4]

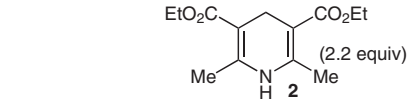
Since halogen bonds are strong, specific, and directional interactions, they can give rise to well-defined supramolecular structures.[5] Thus, halogen bonding has gained importance in crystal engineering as well as in the interpretation of biological systems and processes.[6] Although this type of interaction shows many similarities to hydrogen bonding, to the best of our knowledge it has not yet been applied to organocatalysis. An additional attraction of this approach is the potential of rendering the process asymmetric using enantiopure haloalkanes.[7]

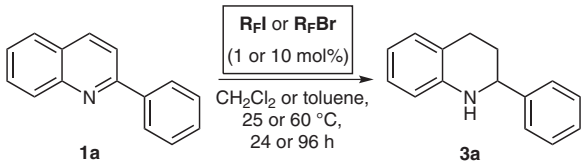
Inspired by the examples of molecular aggregations based on attractive interactions between organic halides (X = Br, I) and nitrogen-containing compounds,[5a,b] we initiated our exploratory study by focusing on the activation of C=N bonds by haloalkanes towards electrophilic hydride additions. In particular, the effect of highly fluorinated iodoalkanes was of interest, since those were known to form the strongest halogen bonds to sp^2-type nitrogens. As specific test reaction, the transfer hydrogenation of 2-phenylquinoline (**1a**) by Hantzsch ester **2** was selected. This type of heteroaryl reduction is well-established,[8] and even organocatalytic asymmetric versions involving chiral Brønstedt acid catalysts have recently been developed.[9,10] The results of our study are presented in Table 1.

First it was confirmed that under the chosen reaction conditions (dichloromethane or toluene solutions at 25 °C or 60 °C, respectively) no uncatalyzed (background) reduction of **1a** by **2** occurred (Table 1, entries 1 and 2).

Then, the effect of the presence of various perfluorinated haloalkanes was studied. Under standard conditions, 10 mol% of the haloalkane and 2.2 equivalents of Hantzsch ester **2** were used.[11] Except in one case (entry 3), the for-

Table 1 Reduction of 2-Phenylquinoline (**1a**) in the Presence of Haloperfluoroalkanes[a]





Entry	R_FX	Amount (mol%) of R_FX	Solvent	Temp (°C)	Yield of **3a** (%)[a]
1	–	–	CH_2Cl_2	25	–
2	–	–	toluene	60	–
3	$BrCF_2CBrFCF_3$	10	CH_2Cl_2	25	–
4	$BrCF_2CBrFCF_3$	10	toluene	60	39 (67)[b]
5	$CF_3CF_2CFICF_3$	10	CH_2Cl_2	25	72[b]
6	$CF_3(CF_2)_5I$	10	CH_2Cl_2	25	35[b]
7	$CF_3(CF_2)_5I$	10	toluene	60	63[b]
8	$CF_3(CF_2)_5Br$	10	CH_2Cl_2	25	20[b]
9	$CF_3(CF_2)_5Br$	10	toluene	60	12[b]
10	$CF_3(CF_2)_6I$	10	CH_2Cl_2	25	90
11	$CF_3(CF_2)_7I$	10	CH_2Cl_2	25	98
12	$CF_3(CF_2)_7I$	1	CH_2Cl_2	25	69[b]
13	$CF_3(CF_2)_7Br$	10	CH_2Cl_2	25	38[b]
14	$CF_3(CF_2)_9I$	10	CH_2Cl_2	25	88

[a] Isolated by column chromatography.
[b] The reaction time was 96 h.

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mation of the expected tetrahydroquinoline **3a** was observed confirming our initial hypothesis. As indicated by the comparison of entries 6, 10, and 11 of Table 1, the activity enhancement of the perfluorinated iodoalkanes increased with the length of the carbon chain. Only perfluorodecyliodide (entry 14) was an exception, which could be due to the low solubility of this compound. Perfluorinated iodoalkanes were more active than their bromo counterparts (compare entries 6 vs. 8 and 12 vs. 13). Use of perfluorohexyliodide in dichloromethane at 25 °C even allowed a reduction of the catalyst loading from 10 mol% to 1 mol% (entries 11 and 12) leading to **3a** in remarkable 69% yield (after 96 h).

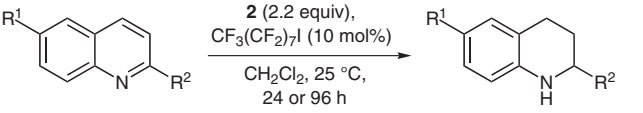
In order to detect the proposed N–halo interaction various NMR experiments were performed (using CD_2Cl_2 solutions of substrate **1a**, Hantzsch ester **2**, and perfluorooctyliodide as activator). After 3 hours product **3a** was identified in the reaction mixture, and full conversion was achieved after 24 hours. No signal shifts were found in the ^1H NMR spectra. This contrasted the ^{13}C NMR behavior, where in the reaction mixture the quinoline signals were slightly shifted to lower field (by 0.01–0.06 ppm). We interpret this difference in chemical shift as indication for a weak interaction between the quinoline nitrogen and the iodide of the perfluoro compound. This suggestion was supported by the ^{19}F NMR spectra, in which the signal for the CF_2I group resonated at lower magnetic field ($\Delta\delta = 0.1$ ppm). For the CF_2 and CF_3 signals a downfield shift of ca. 0.06 ppm was observed. Analogous shifts have been reported with respect to other interactions between haloperfluoroalkanes and nitrogen-containing hydrocarbons.[5d,12] As expected, all chemical shifts were strongly concentration dependant.

The ^{13}C and ^{19}F NMR studies in the absence of reductant **2**, using a 1:1 mixture of the 1-iodoperfluorooctane and quinoline **1a** in CD_2Cl_2 (ca. 0.07 M) showed a similar shift behavior, supporting the suggested N···I interaction also in this case. At higher concentrations (e.g., 1 M) a larger chemical-shift variation $\Delta\delta$ (1.1 ppm for CF_2I and 0.15–0.44 ppm for CF_3 and CF_2) was observed. However, since under those conditions the haloperfluroalkane was not completely soluble leading to a two-phase system, the latter data should be noted with caution.

To our surprise, attempts to perform NMR studies of mixtures of Hantzsch ester **2** and 1-iodoperfluorooctane in the absence of substrate **1a** led to decomposition of the haloperfluroalkane within a few hours. Thus, the presence of the quinoline appeared to 'protect' the perfluoroalkylhalide from being destructed by the reductant.

In order to further analyze the hypothesized reductive reaction path and to determine if alternative reaction mechanisms were operating, the reaction shown in Table 1 was performed in the presence of additives. Both 4-acetamino-TEMPO and 1,8-bis(dimethylamino)naphthalene hampered the conversion of **1a** and **2** into product **3a**. These observations can be explained on the basis of the known formation of halogen-bonded complexes between of TEMPO and perfluoroalkylhalides[13] and an assumed interaction between the latter compounds and the naphthalene derivative leading to a catalyst inhibition. In contrast, in the presence of AIBN the reduction of **1a** to give **3a** proceeded well. Presumably, under those conditions an alternative mechanism operates affording the product in an exceptional >90% yield on a radical pathway.

Table 2 Substrate Scope of the Reduction of 2-Substituted Quinolines in the Presence of Haloperfluoroalkanes



1b–g **3b–h**

Entry	R^1	R^2	Product	Yield of **3** (%)[a]
1	H	Me	**3b**	82[b]
2	Me	Me	**3c**	75
3	F	Me	**3d**	98
4	H	Et	**3e**	83
5	H	*i*-Bu	**3f**	70
6	H	2-tolyl	**3g**	74
7	H	2-furyl	**3h**	88

[a] Isolated by column chromatography.
[b] The reaction time was 24 h (instead of the common 96 h).

Finally, the substrate scope was investigated. Table 2 shows the respective results. Using perfluorooctyliodide (10 mol%) as activator a range of 2-substituted quinolines could efficiently be reduced at room temperature using Hantzsch ester **2** as reductant. The highest yield (98%) was observed in the reduction of 6-fluoro-substituted 2-methylquinoline **1d** (entry 3). A comparison of that result with the ones achieved in the conversions of the corresponding 6-methyl- and 6-unsubstituted quinolines **1c** and **1b**, respectively, indicated that electron-poor quinolines were better substrates than electron-rich ones. Steric modifications at the 2-position had only a minor effect on the reaction process.

In summary, we have shown that the quinoline reduction of **1** with Hantzsch ester **2** leading to the corresponding 1,2,3,4-tetrahydroquinoline derivative **3** can be catalyzed by haloperfluroalkanes. It is suggested that the reaction mechanism involves an activation of the heterocycle by halogen bonding arising from a Hal–N interactions. Further studies are ongoing trying to demonstrate this new and potentially useful concept in other organocatalyses.

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(11) **General Procedure for the Hantzsch Ester Reduction of 1**

A high-vacuum-dried Schlenk flask was charged with quinoline **1** (1.0 mmol), Hantzsch ester **2** (2.2 mmol), the perfluorohalogenated compound (0.1 mmol), and anhyd CH_2Cl_2 (14 mL). The mixture was stirred under inert atmosphere at the appropriate temperature for the indicated period of time. The solvent was removed under reduced pressure and the remaining product was purified by flash column chromatography on silica gel (3% EtOAc–pentane) to afford the corresponding 1,2,3,4-tetrahydroquinoline **3**.

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