

Organic Synthesis

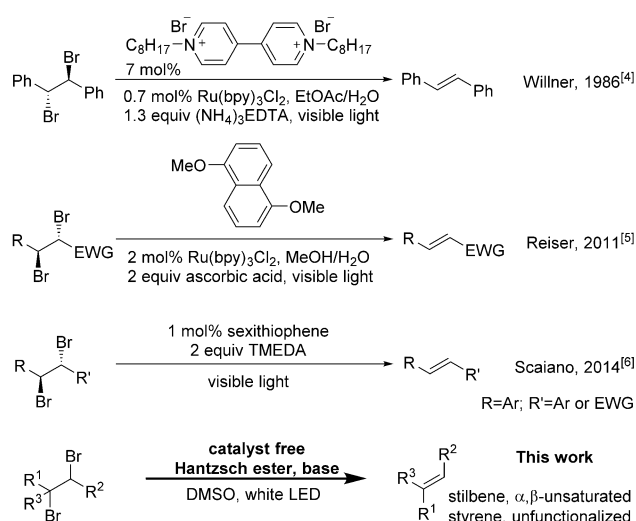
Hantzsch Ester as a Photosensitizer for the Visible-Light-Induced Debromination of Vicinal Dibromo Compounds

Wenxin Chen,^[a] Huachen Tao,^[a] Wenhao Huang,^[a] Guoqiang Wang,^[b] Shuhua Li,^{*,[b]}
Xu Cheng,^{*,[a]} and Guigen Li^[a, c]

Abstract: The debromination of vicinal dibromo compounds to generate alkenes usually requires harsh reaction conditions and the addition of catalysts. Just recently the visible-light-induced debromination of vicinal dibromo compounds emerged as a possible alternative to commonly used methods, but the substrate scope of this reaction is limited and a photocatalyst is necessary for the successful conversion of the starting compounds. A catalyst-free visible-light-induced debromination of vicinal dibromo compounds with a base-activated Hantzsch ester as photosensitizer is reported. The method has a wide substrate scope and a broad functional-group compatibility.

Vicinal dibromination has been established as an efficient method for the protection of C–C double bonds in organic synthesis, and the corresponding deprotection can be carried out with metal reductants, however, harsh reaction conditions are required; for example, the zinc-mediated reduction typically requires an acidic medium at elevated temperatures.^[1] Furthermore, the use of strongly reductive metal species limits the functional-group compatibility.^[2] Recently, the visible-light-induced mesolysis emerged as a powerful strategy for cleaving C–Br bonds.^[3] Because the functional groups commonly found in organic molecules do not absorb visible light, this reaction requires a photocatalyst that acts as an electron shuttle (Scheme 1).

In 1986, Willner et al reported the Ru(bpy)₃⁺-catalyzed deprotection of 1,2-dibromostilbene under visible-light irradiation with NADH as the terminal reductant.^[4] In 2011, Reiser et al



Scheme 1. Visible-light-induced debromination to form alkenes.

demonstrated the Ru(bpy)₃⁺-catalyzed debromination of vicinal dibromocarbonyl compounds to yield α,β -unsaturated molecules.^[5] Both of these methods require a costly transition-metal catalyst. In 2014, the photoreductive debromination using sexithiophene as photocatalyst was demonstrated by Scaiano and co-workers, who focused on stilbene and α -carbonyl dibromo compounds.^[6] Despite these reports, a general strategy for unmasking alkenes, especially unfunctionalized ones, from dibromo precursors has not been reported. In this study, we investigated the catalyst-free visible-light-induced deprotection of a wide range of substrates by a method that uses the Hantzsch ester as light harvester, electron donor, and hydrogen donor. Beyond its passive role as a reductant in closed-shell^[7] and open-shell chemistry,^[8] the Hantzsch ester can be self-activating with the help of an inorganic base to directly achieve an electron transfer.

We chose *p*-bromophenyl-1,2-dibromoethane (**1a**), a styrene precursor, as a typical substrate for the optimization of the debromination reaction to form the alkene **3a** (Table 1). The deprotection of 0.2 mmol **1a** was carried out with 1.1 equiv of the Hantzsch ester **2** and 1.1 equiv of a base under irradiation with a 12 W white LED at room temperature. DMSO was found to be the optimal solvent (Table 1, entry 6), but DMF also gave good yields (Table 1, entry 1). In acetonitrile, DCM, THF, or toluene, the reaction did not run to completion (Table 1, entries 2–

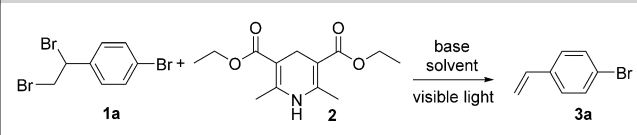
[a] W. Chen, H. Tao, W. Huang, Prof. Dr. X. Cheng, Prof. Dr. G. Li
Institute of Chemistry and Biomedical Sciences
School of Chemistry and Chemical Engineering
Nanjing University, Xianlin Road, 163, Nanjing, (China)
E-mail: chengxu@nju.edu.cn

[b] G. Wang, Prof. Dr. S. Li
Key Laboratory of Mesoscopic Chemistry of Ministry of Education
Institute of Theoretical and Computational Chemistry
School of Chemistry and Chemical Engineering
Nanjing University, Hankou Road, 22, Nanjing (China)
E-mail: shuhua@nju.edu.cn

[c] Prof. Dr. G. Li
Department of Chemistry and Biochemistry, Texas Tech University
Memorial Circle & Boston, TX 79409–1061 Lubbock(United States)

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Table 1. Optimization of the debromination conditions.^[a]



Entry	Base	Solvent	Yield [%] ^[b]
1	Na ₂ CO ₃	DMF	84
2	Na ₂ CO ₃	CH ₃ CN	55
3	Na ₂ CO ₃	CH ₂ Cl ₂	18 ^[c]
4	Na ₂ CO ₃	THF	31 ^[c]
5	Na ₂ CO ₃	toluene	9 ^[c]
6	Na ₂ CO ₃	DMSO	98
7	K ₂ CO ₃	DMSO	88
8	CsF	DMSO	51
9	NaHCO ₃	DMSO	84
10	NaOH	DMSO	79
11	KOtBu	DMSO	28
12	Na ₂ CO ₃	DMSO	0 ^[d]
13	Na ₂ CO ₃	DMSO	0 ^[e]
14	— ^[f]	DMSO	0

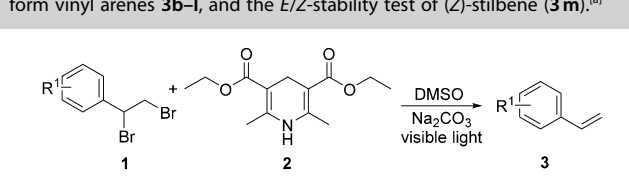
[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.22 mmol), base (0.22 mmol), solvent (1.5 mL), 12 W white LED, rt, 1.5 h. [b] Isolated yield. [c] Yield estimated by GC-MS. [d] No visible-light irradiation. [e] No addition of Hantzsch ester **2**. [f] No addition of base.

5). Sodium carbonate, as well as KOtBu (potassium *tert*-butoxide), outperformed the other inorganic bases tested (Table 1, entries 7–11). A 98% yield of **3a** was achieved within 1.5 h with sodium carbonate in DMSO. The reaction did not proceed in the absence of the Hantzsch ester, light-irradiation, or base (Table 1, entries 12–14).

With the optimized reaction conditions in hand (Table 1, entry 6), we explored the substrate scope of the reaction (Table 2). First, we screened a series of bromine adducts. To our delight, the corresponding styrenes were obtained in good to excellent yields from a variety of substrates (Table 2, entries 1–9). Furthermore, phenyl boronic acid, a valuable synthetic module, also underwent the transformation to **3g** in 91% yield (Table 2, entry 6). Other vinyl arenes, such as 2-vinylnaphthalene **3h** and 9-vinylnanthracene **3i**, were obtained in almost quantitative yields (Table 2, entries 7 and 8). Stilbene was obtained from its dibromo precursor in 95% yield (Table 2, entry 10), and the alcohol **11** underwent the debromination reaction to afford cinnamyl alcohol (**3l**) in 83% yield (Table 2, entry 11). (*Z*)-stilbene **3m** was used as a substrate with the same debromination reaction conditions and recovered without any *E/Z* isomerization.

Next we evaluated the use of the method for deprotection reactions to form α,β -unsaturated products (Table 3). When we irradiated the ester **1n** and the lactone **1o** under a 12 W white LED in the presence of the Hantzsch ester **2** and Na₂CO₃, the corresponding conjugated products were obtained in excellent yields (Table 3, entries 1,2). Terminal alkenes **3p** and **3q** could also be prepared (Table 3, entries 3,4), and the alkyne **3r** could be obtained similarly from the unsaturated ester **1r** (Table 3, entry 5). The amide **1s** gave cinnamide (**3s**) smoothly in 96% yield, and the trisubstituted *E*-cinnamide **3t** could also be ob-

Table 2. Debromination reactions of **1b–l** with the Hantzsch ester **2** to form vinyl arenes **3b–l**, and the *E/Z*-stability test of (*Z*)-stilbene (**3m**).^[a]



Entry	Substrate	Product	Yield [%] ^[b]
1	1b	3b	95
2	1c	3c	86
3	1d	3d	80
4	1e	3e	99
5	1f	3f	91
6	1g	3g	91
7	1h	3h	99
8	1i	3i	99
9	1j	3j	99
10	1k	3k	95 ^[c]
11	1l	3l	83 ^[c]
12	3m	—	100 ^[d]

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.22 mmol), Na₂CO₃ (0.22 mmol), DMSO (1.5 mL), 12 W white LED, rt, 1.5 h. [b] Isolated yield. [c] Only the *E*-product was detected by GC-MS and ¹H NMR spectroscopy. [d] No *E/Z* isomerization.

tained (Table 3, entries 6,7). Ketones, such as **1u** and **1v**, are also suitable substrates; the desired α,β -unsaturated ketones were isolated in 80% and 97% yields, respectively (Table 3, entries 8,9). Substrates **1w** and **1x**, which bear metal-reductant-sensitive functional groups, are also suitable candidates for the described reaction (Table 3, entries 10,11). Several dibromo trisubstituted alkenes were prepared and subjected to the debromination reaction (Table 3, entries 12–14). Compound **1y**, with a *syn/anti* ratio of 54:46, gave the (*E*)- β -methyl cinnamate as predominant product in 86% yield. This trend was also ob-

Table 3. Debromination reactions of **1 n–z** and **1 aa** with **2** to the form α,β -unsaturated compounds **3 n–z** and **3 aa**.^[a]

Entry	Substrate	Product	Yield [%] ^[b]
1			98 ^[c]
2			96
3			95
4			98 ^[d]
5			98
6			96 ^[c]
7			98 ^[c]
8			80 ^[c]
9			97 ^[c]
10			98 ^[c]
11			81 ^[c,e]
12			86 E
13			80 E
14			92 ^[c]

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.22 mmol), Na₂CO₃ (0.22 mmol), DMSO (1.5 mL), 12 W white LED, rt, 1.5 h. [b] Isolated yield. [c] Only the *E*-product was detected by GC-MS and ¹H NMR spectroscopy. [d] 2.5 h. [e] In DMF, 50 min.

served when substrate **1 z** was irradiated with visible light. The *syn*-configured compound **1 aa** gave the (*E*)- α -methyl cinnamate as the only detected product.

After successful debromination of substrates with at least one activated C–Br bond, we extended the scope to dibromo compounds derived from unfunctionalized alkenes (Table 4), deprotection of which has not been achieved by means of visible-light-induced methods so far. The terminal alkene **1 ab** was deprotected in 82% yield after 12 h (Table 4, entry 1). The steroid **1 ac** was more reactive and was converted to 3 β -chloro-5-cholestene (**3 ac**) in only 1.5 h (Table 4, entry 2). The long-chain alkene **3 ad** was isolated in 65% yield (Table 4, entry 3), and the allyl ester **1 ae** was also successfully debrominated in almost quantitative yield after 24 h (Table 4, entry 4).

To investigate the compatibility of the deprotection with an extensive list of functionalities, we carried out a robustness screening. In the presence of various spectator molecules, carrying the different functional groups, **1 a** was deprotected under the standard conditions (Table 5). All tested molecules (besides artemisin), such as piene, caryophyllene, taicros, nerolidol, phenol, nitrobenzene, phenylacetylene, phenyl cyclopropyl ketone, glycidol ether, 2-thiopheneethanol, and pyridine, remained intact throughout the visible-light-induced reaction, and had no influence on the product formation; the alkene **3 a** was isolated in nearly quantitative yields. Even in the presence of the structurally complex spectator molecule artemisinin, the reaction gave a 54% yield of **3 a**, and the natural product survived the reaction. The lowered yield of **3 a** was caused by elimination of HBr from **1 a**.^[9]

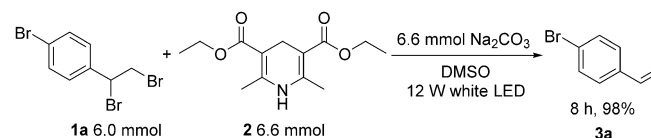
To investigate the mechanism of this transformation, we performed several experiments. Initially, we examined the possibility of a charge–transfer complex formation, by means of NMR and UV/Vis spectroscopy. No significant interaction between the Hantzsch ester and the dibromo species was observed, suggesting that an intermolecular process was occurring. A Stern–Volmer experiment showed that the substrate **1 a** did not quench the fluorescence generated by the Hantzsch ester **2** in DMSO (Scheme 2a, ■).^[10] Thus, the base not only scavenged HBr but also participated in the electron-transfer process. When Na₂CO₃ was added to a solution of **1 a** and **2** in DMSO, a weak but reproducible quenching of the fluorescence was observed (Scheme 2a, ●). This quenching was also observed when **2** and Na₂CO₃ were mixed. Therefore, we propose that the base plays a pivotal role in the reactivity of the Hantzsch ester. The quenching was weak because the interactions between **2** and Na₂CO₃ were limited by the poor solubility of the latter in DMSO.^[11] On the basis of these results, we propose the mechanism outlined in Scheme 2b. First, the Hantzsch ester **2** harvests light with the help of the base. Subsequently, the electron transfer (ET) from activated **2** to the dibromo substrate results in the mesolysis of one of the C–Br bonds, and then cleavage of the other C–Br bond affords the alkene and pyridine products. Because the Hantzsch ester was excited by visible light almost identically in all the reactions, the significantly different reactivities, for example **1 a** is 16 times faster than **1 ae**, suggest that the rate determining step is downstream; the ET process from the Hantzsch ester to the

Entry	Substrate	Product	t [h]	Yield [%] ^[b]
1			12	82
2			1.5	90
3			72	65
4			24	99

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.22 mmol), Na₂CO₃ (0.22 mmol), DMSO (1.5 mL), 12 W white LED, rt. [b] Isolated yield.

substrate or the radical fragmentation of the alkene. First, to elucidate the factors behind the varied reactivity, cyclic voltammetry experiments for different dibromo substrates were carried out (Scheme 2c); a large difference of the reduction potential between **1a** ($E_{1/2}^{\text{red}} = -0.80$ V vs. SCE) and **1ae** ($E_{1/2}^{\text{red}} = -1.87$ V vs. SCE) was observed. Therefore, **1a** will gain electrons more easily and react faster than **1ae** in the ET step. Second, because the proposed radical intermediates **A** (**1a** and **1ae**) are too transient for any chemical analysis, computational studies were carried out for the step from **A** to the final alkenes (**3a** and **3ae**, respectively) at the UB3LYP/6-311G(d,p) level to optimize the geometries of all stationary points.^[12] (Scheme 2d). The optimized structure of **A-1ae** shows that its C–Br bond (2.51 Å) is longer than that of **A-1a** (2.08 Å) and a “conventional” C–Br bond (1.90 Å).^[13] Meanwhile, the overall ΔG for these reactions were -55.0 and -60.7 kcal mol⁻¹ for **A-1a** and **A-1ae**, respectively, indicating that the second cleavage of C–Br is quite smooth and **A-1ae** will be even closer to the product than **A-1a**. These results support that the first ET transfer from the Hantzsch ester to dibromo compounds is the rate determining step.

To demonstrate the potential of the described procedure, the debromination reaction employing the Hantzsch ester **2** and substrate **1a** was scaled up to several grams. The reaction reached full conversion after 8 h with an isolated yield of 98% also using the standard 12 W LED irradiation (Scheme 3).

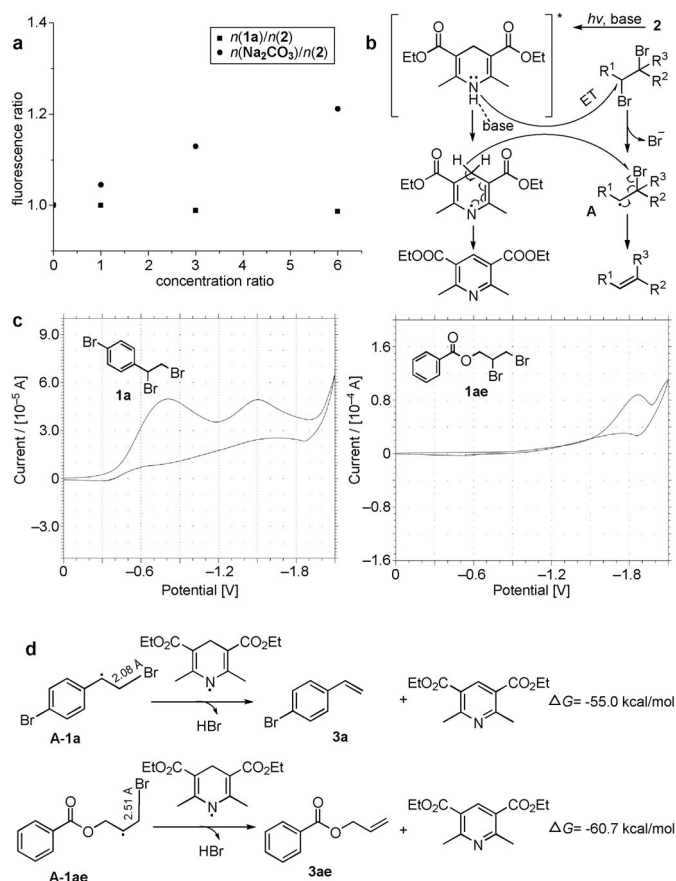


Scheme 3. Gram scale debromination reaction of **1a** and **2**.

In conclusion, we developed an efficient method for the deprotection of vicinal dibromo compounds to afford alkenes. With the help of an inorganic base, a Hantzsch ester acts as a self-activating reductant under visible-light irradiation. The tolerated substrates include styrene, α,β -unsaturated compounds, and unfunctionalized alkenes. Robustness screening demonstrated that this method is compatible with a great variety of functional groups. Mechanistic experiments revealed that the base is critical for the activation of the Hantzsch ester.

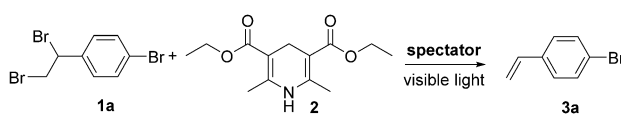

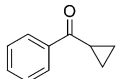

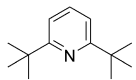

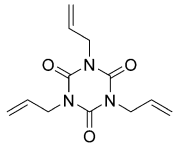

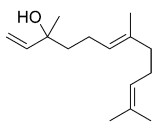
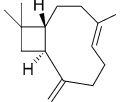
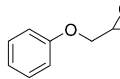
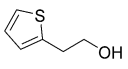
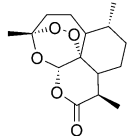
Experimental Section

A flask equipped with a rubber septum and a magnetic stirrer was charged with the dibromo substrate **1a** (0.2 mmol), the Hantzsch ester **2** (0.22 mmol), Na₂CO₃ (0.22 mmol), and DMSO (1.5 mL) under nitrogen. The mixture was irradiated with a 12 W white LED at ambient temperature for 1.5 h and then concentrated by under reduced pressure on rotavapor. The residue was purified by silica gel



Scheme 2. Plausible mechanism for the debromination reaction. a) Proposed reaction mechanism (ET = electron transfer). b) Fluorescence-intensity-ratio measurements of **1a** (*p*-bromophenyl-1,2-dibromoethane) and the Hantzsch ester **2** at varying concentrations. c) CV measurements with **1a** and **1ae**. d) Computational studies with transient reaction intermediates **A-1a** and **A-1ae**.

Table 5. Robustness screening with different spectator molecules in the reaction of **1a** with **2**.^[a]

			
Spectator molecule	Yield [%] ^[b]	Spectator molecule	Yield [%] ^[b]
	99		99
	99		98
	99		99
	99		98
	98		99
	95		54

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.22 mmol), Na₂CO₃ (0.22 mmol), DMSO (1.5 mL), 12 W white LED, rt. [b] Isolated yield of **3a**; the intactness of the spectator molecules was detected by GC-MS and NMR spectroscopy.

column chromatography with petroleum ether/AcOEt = 1:1, v/v as the eluent to give **3a**.

Acknowledgements

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Keywords: alkenes · catalyst-free reactions · debromination · Hantzsch ester · visible light

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- [10] For a recent report showing that an α -carbonyl bromide can quench the fluorescence of the Hantzsch ester, see: J. Jung, J. Kim, G. Park, Y. You, E. J. Cho, *Adv. Synth. Catal.* **2016**, *358*, 74–80.
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Organic Synthesis

W. Chen, H. Tao, W. Huang, G. Wang,
S. Li,* X. Cheng,* G. Li

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 **Hantzsch Ester as a Photosensitizer
for the Visible-Light-Induced
Debromination of Vicinal Dibromo
Compounds**

