C–H Bond Formylation Hot Paper

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Photo-induced Substitutive Introduction of the Aldoxime Functional Group to Carbon Chains: A Formal Formylation of Non-Acidic C(sp^3)–H Bonds

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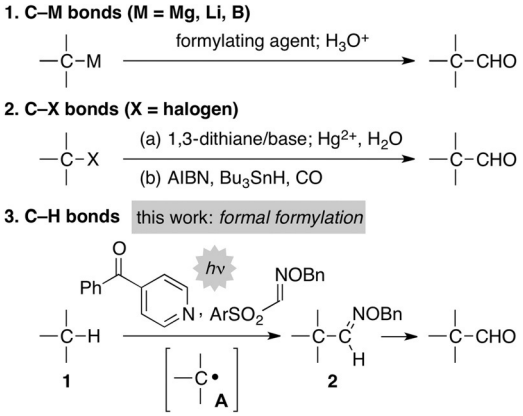
Abstract: *A photo-induced substitutive introduction of an aldoxime functional group to carbon chains was achieved using photo-excited 4-benzoylpyridine as a C(sp^3)–H bond cleaving agent and arylsulfonyl oxime as an aldoxime precursor. The non-acidic C–H bonds in various substances, including cycloalkanes, ethers, azacycles, and cyclic sulfides, were chemoselectively converted at ambient temperature under neutral conditions. The present transformation is a formal formylation of non-acidic C(sp^3)–H bonds in a single step.*

Aldehydes are a critical class of compounds in synthetic organic chemistry because of their dual reactivities as electrophiles and nucleophiles.[1] Among the preparative methods that generate aldehydes, formylation is appealing since attachment of a synthetically versatile carbonyl functionality takes place concomitantly with a one-carbon extension, which is convenient for the rapid increase of structural complexity of organic molecules. Compared to continuing advancements in olefin hydroformylation,[2] strategies for formylation at sp^3-hybridized carbon centers seem to have matured, and representative procedures are shown in Scheme 1. One of the most frequently employed strategies for this purpose is the formylation of organometallic agents (Scheme 1-1). Various electrophilic formylating agents, including *N*-formylpiperidine and CO, have been developed.[3] A two-step sequence, involving alkylation of a nucleophilic 1,3-dithiane anion with alkyl halides and subsequent deprotection, is another option for introducing the formyl functional group (Scheme 1-2a).[4] The treatment of alkyl halides with AIBN/Bu_3SnH/CO gas achieves radical formylation to furnish aldehydes (Scheme 1-2b).[5] Despite the established strategies for formylation at C(sp^3)–M and C(sp^3)–X bonds, there are no general methods for substitutive introduction of a formyl functionality at non-acidic C(sp^3)–H bonds (Scheme 1-3).[6] We therefore initiated an investigation to develop a formal formylation of such unreactive C(sp^3)–H bonds by applying a photochemical C–H functionalization strategy.[7–9] The strategy relies on homolytic cleavage of a C(sp^3)–H bond (**A**) with an oxyl radical species generated by photo-excitation of an aryl ketone. The preparation of aldehydes is not practical under such radical conditions because formyl C(sp^2)–H bonds tend to be preferentially cleaved, over the targeted non-acidic C(sp^3)–H bond of an alkyl chain, as a result of the bonding energies.[10] This energy difference makes it difficult to prevent degradation of the generated aldehyde during the course of the reaction. We thus directed our attention to installing an aldoxime functionality as a masked formyl group. As a result, we achieved the photo-induced substitutive introduction of the aldoxime functionality (**2**) to carbon chains of a variety of compounds (**1**), including cycloalkanes, ethers, azacycles, and cyclic sulfides, by employing the arylsulfonyl oxime as an aldoxime precursor and 4-benzoylpyridine (4-BzPy) as a C–H bond cleaving agent. This is a novel method for formal formylation of non-acidic C(sp^3)–H bonds in a single step that proceeds at room temperature under neutral conditions.



Scheme 1. Representative preparative methods for alkyl aldehydes by formylation at sp^3-hybridized carbon atoms.

We began the optimization of reaction conditions with the design of the aldoxime precursor (Table 1). A sulfonyl oxime was selected as a candidate, based on our previous observations that a sulfonyl unit acts as an excellent leaving group,[7,8b] and in conjunction with the precedent set by radical reactions.[11] Indeed, the photo-irradiation of tetrahydrofuran (THF, **1a**) and toluenesulfonylmethanal *O*-benzyloxime in the presence of benzophenone (Ph_2CO) in acetonitrile (MeCN) resulted in formation of the aldoxime **2a** in 50% yield (entry 1). Employment of electron-donating *p*-methoxy substituted benzenesulfonyl oxime improved the yield of **2a** (75%, entry 2), whereas the electron-withdrawing *p*-CF_3 substituted analogue decreased the product yield (41%,

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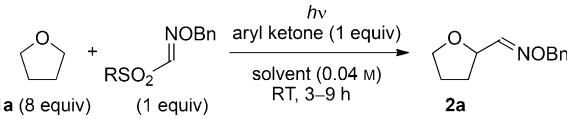
Table 1: Optimization of reaction conditions.[a]



Entry	R	Aryl ketone	Solvent	Yield [%][b]
1	(*p*-Me)C_6H_4	Ph_2CO	MeCN	50
2	(*p*-MeO)C_6H_4	Ph_2CO	MeCN	75
3	(*p*-CF_3)C_6H_4	Ph_2CO	MeCN	41
4	*n*-Bu	Ph_2CO	MeCN	66
5	(*p*-Me)C_6H_4	$(C_6F_5)_2CO$	MeCN	71
6	(*p*-Me)C_6H_4	4-BzPy	MeCN	88
7	(*p*-MeO)C_6H_4	4-BzPy	CH_2Cl_2	90 (85)[c]

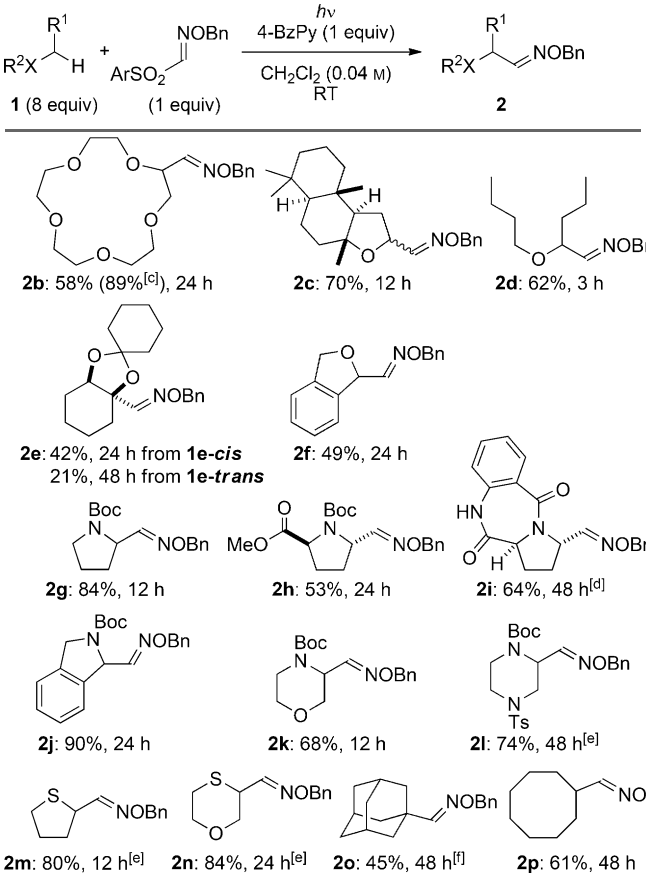
[a] Conditions: THF **1a** (1.78 mmol, 8 equiv), sulfonyl oxime (0.223 mmol, 1 equiv), aryl ketone (0.223 mmol, 1 equiv), solvent (5.6 mL, 0.04 M), photo-irradiation using a medium-pressure Hg lamp at RT for 3–9 h. [b] Combined yield of *E*- and *Z*-aldoximes determined by NMR spectroscopy. [c] Yield of isolated products.

entry 3). The yield of **2a** remained at 66% using the alkylsulfonyl oxime as the aldoxime precursor (entry 4). Screening of aryl ketones revealed that electron-deficient perfluorobenzophenone ($(C_6F_5)_2CO$) and 4-BzPy[7h,12] led to higher yields of **2a** compared to Ph_2CO (71% and 88%, entries 5 and 6). The reaction using (*p*-methoxy)benzenesulfonylmethanal *O*-benzyloxime[13] and 4-BzPy in CH_2Cl_2 gave the highest yield of **2a** (90% yield determined by NMR spectroscopy, 85% yield of isolated products, entry 7) and these conditions were used in subsequent experiments.

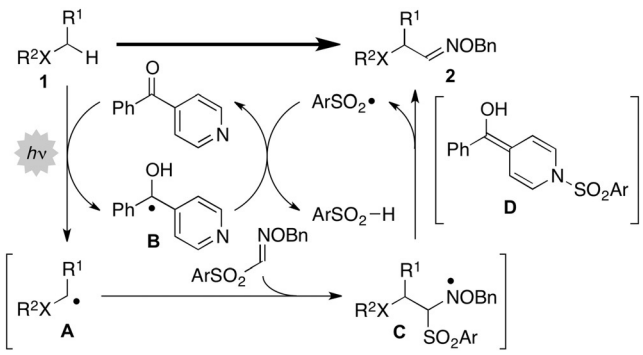
With the optimal reaction conditions in hand, we explored the generality of the photo-induced substitutive introduction of the aldoxime functional group with respect to a variety of substances (Table 2). In spite of the multiple reacting sites in crown ether **1b**, mono-functionalization proceeded selectively to form the aldoxime **2b**.[14] In the case of ambroxide **1c**, chemoselective functionalization of the ethereal C–H bond took place to provide **2c** without affecting potentially reactive methine and methylene C–H bonds. The acyclic dibutyl ether **1d** afforded **2d** as well. The reactions of acetals derived from *cis* and *trans*-cyclohexanediol, **1e-*cis*** and **1e-*trans***, furnished the same product **2e** in 42% (24 h) and 21% (48 h) yields, respectively. These results corroborated that the present transformation proceeds via formation of a common carbon radical intermediate **A** (Scheme 1-3 and Scheme 2), leading to the *cis*-fused adduct **2e** of lower ring strain. The higher reactivity of the *cis*-isomer **1e-*cis*** may be explained by easier access to the less sterically hindered equatorial C–H bond, as well as the higher electron density of the equatorial C–H bond, through hyperconjugation of the geminal oxygen lone pair and the antiperiplanar C–C bond.[15] The aldoxime functionality was also installed at the benzylic position of phthalan **1f**.

Subsequently, introduction of the aldoxime functionality to nitrogen-containing cyclic compounds was investigated. The chemoselective functionalization occurred at the C–H bond proximal to the nitrogen atom of the pyrrolidine core (**1g**), furnishing the aldoxime adduct **2g** in 84% yield. The reaction of the proline derivative **1h** took place at the more

Table 2: Photo-induced substitutive introduction of an aldoxime functionality to non-acidic C(sp^3)–H bonds.[a,b]



[a] Conditions as described in entry 7 of Table 1, unless otherwise noted. Ar = (*p*-MeO)C_6H_4. [b] Isolated yield of all possible isomers such as *E*/*Z*-aldoximes, Boc rotamers, and *syn*/*anti* stereoisomers. [c] Yield estimated by ^{1}H NMR analysis. [d] The major isomers are shown in the Table. [e] Irradiated using an LED lamp at 365 nm. [f] A minute amount of the methylene adduct **2o′** was observed.



Scheme 2. Proposed reaction mechanism for the photo-induced substitutive introduction of an aldoxime functionality to non-acidic C(sp^3)–H bonds.

electron-rich methylene side and the *anti*-adduct **2h** was produced in a stereoselective manner.[16] The same selectivities were observed for benzodiazepine **1i**, affording the adduct **2i**. The aldoxime functionality could be installed at the

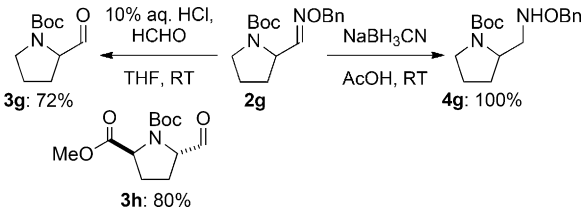
benzylic position of isoquinoline **1j** in 90% yield. The result employing *N*-Boc morpholine **1k** as a starting substance clearly showed that the reactivity of the C–H bond adjacent to the nitrogen atom was higher than that beside an ether functional group (**2k**). Additionally, the reactivities of C–H bonds adjacent to nitrogen atoms were successfully differentiated by judicious selection of protecting groups (**2l**); the aldoxime functionality was selectively introduced to the *N*-Boc side of the molecule, and not to the *N*-Ts side.[17]

We proceeded to examine the introduction of the aldoxime functionality to cyclic sulfides and cycloalkanes. The reactions of tetrahydrothiophene (**1m**) and oxathiane (**1n**) produced the respective aldoximes **2m** and **2n** in yields equivalent to or greater than 80% with irradiation of an LED lamp at 365 nm.[17] The results verified that the reactivity of the C–H bond adjacent to a sulfur atom is higher than that beside an ether oxygen. In the case of adamantane **1o**, monofunctionalization predominantly took place at the methine C–H bond (**2o**)—in preference to the methylene C–H bond (**2o′**)—indicating superior reactivity of the methine C–H bond. The ratio of **2o** and **2o′** (ca. 95:5) was unchanged before and after purification (see the Supporting Information for details). The methylene C–H bond of cyclooctane **1p**[18,19] was smoothly converted and the adduct **2p** was formed in 61% yield.

Having succeeded in the photo-induced substitutive introduction of the aldoxime functionality to a variety of carbon chains under the optimized conditions, we turned our attention to obtaining mechanistic information on the present transformation. Treatment of the sulfonyl oxime (1 equiv) with cyclohexane **1q** (4 equiv) and its deuterated analogue **1q-*d*** (4 equiv) provided the corresponding adducts **2q** and **2q-*d*** in 29% (yield determined by NMR spectroscopy) in a ratio of 83:17.[20] The value of the kinetic isotope effect (KIE) was determined to be 4.9, indicating that C(sp^3)–H bond cleavage is involved in the rate-determining step.

Consequently, we propose a tentative reaction mechanism as illustrated in Scheme 2. The reaction is initiated by hydrogen abstraction of the starting substance **1** with photoexcited 4-BzPy, forming the carbon radical intermediate **A** and the ketyl-type radical **B**. Based on the observed KIE, this hydrogen abstraction step is the rate-determining step. The conformational interconversion during the course of the reaction (**1e-*trans*** to **2e**, in Table 2) supports the involvement of the carbon radical intermediate **A**. Addition of the derived radical **A** to the sulfonyl oxime provides aminyl radical **C**. Expulsion of the sulfonyl radical from **C** affords the aldoxime **2** as a product, completing the substitutive introduction of the aldoxime functionality to the carbon chain of **1**. The released sulfonyl radical accepts a hydrogen atom from the ketyl-type radical **B** to regenerate 4-BzPy,[19,21] most likely through the formation of the sulfonamide **D**, which is generated by coupling of the released sulfonyl radical and **B**.[7h,12,22]

The derived aldoximes are excellent synthetic precursors. We demonstrated several transformations to highlight the utility of the present one-step introduction of the aldoxime functionality to carbon chains (Scheme 3). The acid treatment of the aldoximes **2g** and **2h** with formalin led to selective formation of the respective aldehydes **3g** and **3h**, confirming



Scheme 3. Transformations of aldoximes.

the aldoxime functionality as an excellent mask for the formyl group.[11a] Chemoselective reduction of the aldoxime functionality took place with $NaBH_3CN$ in acetic acid and the benzyloxyamine **4g** was formed quantitatively.[23]

Having obtained a promising result for the conversion of aldoxime **2** into benzyloxyamine **4**, we carried out the reduction of several aldoximes with the intent to unambiguously determine their structures (Figure 1). The reaction of

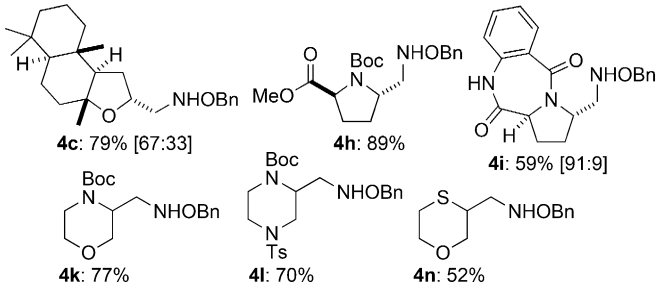
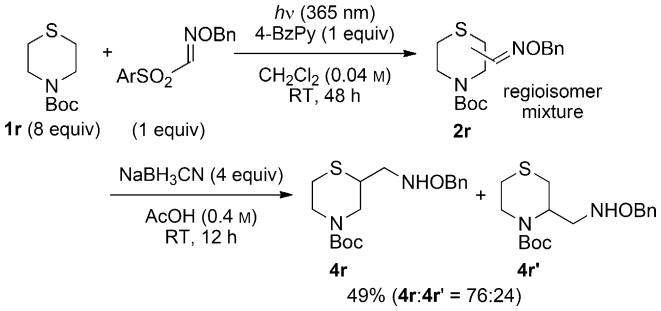


Figure 1. Reduction of aldoximes into benzyloxyamines. Conditions as in Scheme 3. Yield of isolated products. Ratio of stereoisomers in brackets. The major isomer is shown in the Figure.

the aldoxime possessing an ambroxide core (**2c**), which is a mixture of four possible isomers of *E*/*Z* aldoximes as well as *syn/anti* substitutions, provided a mixture of two stereoisomers **4c** in a 79% combined yield in a 67:33 ratio. The reduction of the proline derivative **2h** furnished the *anti*-adduct **4h** as the sole product,[16] and the benzodiazepine derivative **2i** preferentially provided the *anti*-adduct **4i**. Thus, the stereoselective introduction of an aldoxime functionality took place at the five-membered azacycle of the parent substances (**1h** and **1i**). The aldoximes **2k**, **2l**, and **2n**, respectively prepared from morpholine, piperazine, and oxathiane, provided the corresponding benzyloxyamines **4k**, **4l**, and **4n** as single products.

To evaluate the relative reactivity order of C–H bonds adjacent to nitrogen and sulfur atoms, we conducted the photo-induced substitutive introduction of the aldoxime functionality to *N*-Boc thiomorpholine (**1r**, Scheme 4). The formation of multiple isomers hampered a detailed analysis of the products (**2r**). Therefore, the reduction of the aldoxime functionality was subsequently carried out to form two regioisomers (**4r** and **4r′**) in a ratio of 77:23, indicating that the C–H bond proximal to the sulfur atom is more reactive than that next to the *N*-Boc group.

In conclusion, we have developed a chemoselective method involving photo-induced introduction of an aldoxime functionality to carbon chains of various substances, including



Scheme 4. Reaction starting from *N*-Boc thiomorpholine **1r**. Ar = (*p*-MeO)C_6H_4.

cycloalkanes, ethers, azacycles, and cyclic sulfides. The reaction is proposed to proceed through a radical mechanism, in which the homolytic cleavage of non-acidic C(sp^3)–H bonds is effected by photo-excited 4-benzoylpyridine, and the aldoxime functionality is delivered from (*p*-methoxy)benzenesulfonylmethanal *O*-benzyloxime. In this study, we disclosed that: 1) attachment of the electron-donating *p*-MeO substituent to the benzenesulfonyl oxime, and use of 4-BzPy, increased the yield of expected aldoximes **2**; 2) for the first time cyclic sulfides were successfully applied to the photo-induced C–H functionalization, as well as cycloalkanes, ethers, and azacycles; 3) the reactivity order of the C–H bonds in the present transformation is clarified as S-substituted $\geq$ *N*-Boc-substituted > O-substituted > methine > methylene C–H bonds; 4) the reactivity of C–H bonds could be regulated by the nitrogen protecting group, in which the Boc group allows, and the Ts group inhibits, the introduction of the aldoxime functionality at the adjacent C–H bond. The present transformation offers a unique tool for formal formylation of non-acidic C(sp^3)–H bonds in a single step, under neutral reaction conditions, and at ambient temperature, which is otherwise difficult to achieve.

Experimental Section

A CH_2Cl_2 solution (5.6 mL, 0.04 M) of 4-benzoylpyridine (40.8 mg, 0.223 mmol), (4-methoxy)benzenesulfonylmethanal *O*-benzyloxime (68.3 mg, 0.223 mmol), and THF (145 μL, 1.78 mmol) in a Pyrex® test tube was degassed by a freeze-thaw cycle three times and purged with argon. The test tube was placed approximately 5 cm from a UV-lamp and was irradiated at room temperature for 6 h. The mixture was then filtered through a short pad of silica gel (NH silica gel) using ethyl acetate as an eluent, and the filtrate was concentrated. The residue was purified by flash column chromatography (NH silica gel, hexane to hexane/acetone = 30/1) to furnish the adduct **2a** in 85% yield (39.1 mg).

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Keywords: aldoximes · 4-benzoylpyridine · C–H functionalization · photoreactions · radicals

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[13] The arylsulfonyl oxime was selectively prepared in the *Z*-form, according to a reported method.[11f] However it gradually isomerized into the *E*-form, even upon storage in a freezer (< 0 °C). No significant reactivity difference was observed between these *E*- and *Z*-isomers in the present transformation.

[14] Partial deprotection of the oxime functionality of **2b** during isolation using silica gel column chromatography seemed to reduce the yield of isolated products.

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[16] The structure of **2h** was unambiguously confirmed after reduction of the oxime functionality to generate **4h** (in Figure 1) and subsequent removal of the Boc group. See the Supporting Information for details.

[17] Irradiation using an LED lamp at 365 nm was essential to obtain the aldoximes **2l**–**n** in higher yields, whereas irradiation using a Hg lamp decreased the product yields.

[18] The reaction using the aryl oxime as a limiting agent (cyclooctane (**1p**, 1 equiv), arylsulfonyl oxime (1.2 equiv), 4-BzPy (1 equiv)) was detrimental to the yield of **2p** (24% yield determined by NMR spectroscopy).

[19] The reactions applying catalytic amount of aryl ketones (0.2 equiv) gave lower yields of **2p** (yields determined by NMR spectroscopy): 4-BzPy (35%), Ph_2CO (21%), and $(C_6F_5)_2CO$ (50%). These results indicate that the present transformation can potentially be optimized as a catalytic reaction.

[20] The reaction of cyclohexane **1q** gave rise to the aldoxime **2q** in 17% yield (32% yield determined by NMR spectroscopy). See the Supporting Information for details.

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