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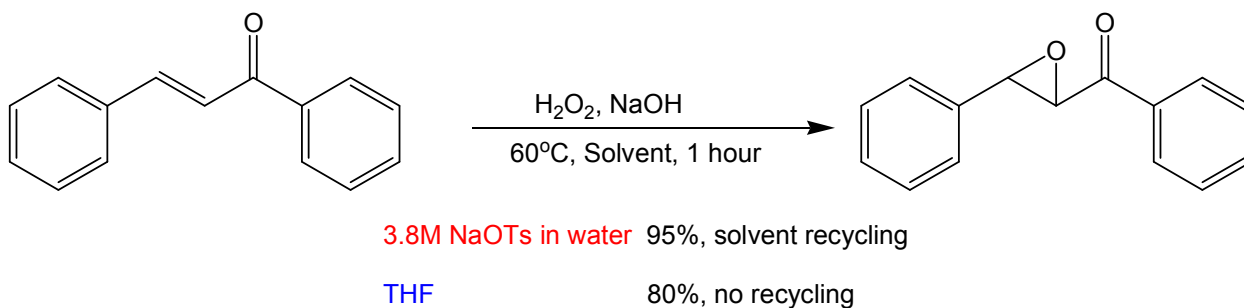
Concentrated Aqueous Sodium Tosylate as Green Medium for Alkene Oxidation and Nucleophilic Substitution Reactions

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ABSTRACT Hydrotropic solution of highly-concentrated sodium tosylate (NaOTs) can be used as a recyclable medium for the environmentally-benign oxidation of conjugated alkenes with

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3 H₂O₂. Both un-catalyzed and metal-catalyzed reactions provided the corresponding oxidation
4 products in higher yields than in pure water or many common organic solvents.
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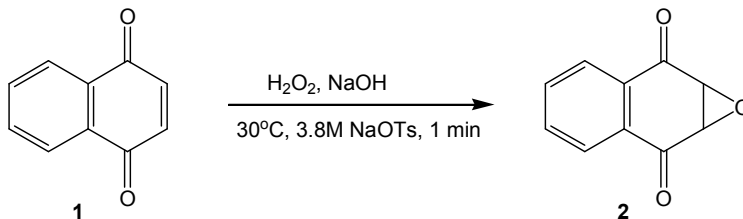
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10 Although organic solvents are the major source of chemical waste in multi-step processes, such
11 as the pharmaceuticals production, their replacement by environmentally benign solvents,
12 particularly with water, represents a significant challenge.¹ In addition to very low solubility of
13 many organic compounds one needs to consider the difficulties associated with the product
14 isolation and water recycling.²
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21 Low solubility represents an intrinsic problem of organic reactions in water and is generally
22 addressed by utilizing micelle-forming surfactants.³ Interestingly, non-micellar solutions of
23 hydrotropes received considerably less attention in organic synthesis. Unlike common
24 surfactants, hydrotropic compounds do not possess distinct amphiphilic features, such as
25 hydrophilic “head” and hydrophobic “tail”, and require higher concentration to significantly
26 increase the solubility of organic compounds in the aqueous phase.⁴ In particular, the minimum
27 hydrotrope concentration (an approximate analogue of the critical micellar concentration of
28 surfactants) of sodium tosylate (NaOTs) is ca. 0.32-0.35 M.⁵ There are scattered literature
29 examples of successful organic reactions performed in hydrotropic solutions that usually lack
30 generality and comparison with pure water and/or organic solvents.⁶ In addition, aqueous media
31 recycling is rarely addressed.⁷
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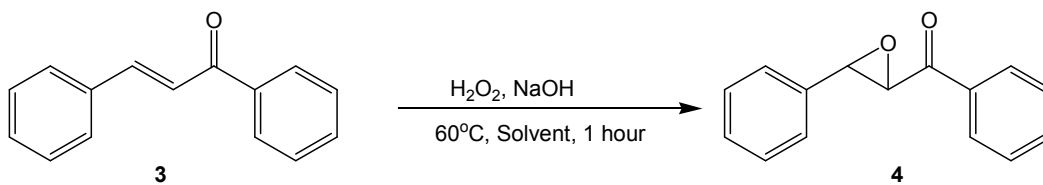
47 Our group has a long-term interest in green oxidation reactions using water or aqueous
48 solutions as the media.⁸ In line with this interest, we decided to explore hydrotropic solutions as
49 potential media for new oxidation methods. In particular, we intended to study the selective
50 alkene oxidation to epoxides using hydrotropes to increase the solubility alkenes in the aqueous
51 phase where they would react with water-soluble environmentally benign oxidants, such as
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H_2O_2 .⁹ In our early work, we showed that in a saturated (3.8M at 25^oC) solution of sodium tosylate (NaOTs), an inexpensive and readily available salt, highly hydrophobic organic intermediates readily react with aqueous nucleophiles.¹⁰ Interestingly, treating a heterogeneous mixture of solid 1,4-naphthaquinone **1** with 2 equiv. of H_2O_2 in sat. NaOTs gave quantitatively the corresponding epoxide **2** within 1 min at RT. After 30 sec, more than 90% conversion was observed (Scheme 1). For comparison, when pure water was used, similar conversion was observed only after 1.5 hrs. The product could be isolated by filtration and aqueous phase recycled without need for addition purification (98 % conversion after 1 min). ¹H NMR solubility studies using an external reference showed that in saturated NaOTs, 1,4-naphthaquinone is ca 10 times more soluble than in pure water.



Scheme 1. 1,4-Naphthaquinone epoxidation in a hydrotropic solution



Scheme 2. Chalcone epoxidation with H_2O_2

With this result at hand, we moved to explore the epoxidation of chalcone **3**, a difficult substrate for epoxidation in aqueous media.¹¹ While the conversion was low at RT, performing the reaction at 60^o C for 1 hr led to 95% conversion to the corresponding epoxide **4** (Scheme 2, Table 1). Importantly, only about 10% of the product was observed with pure water as the reaction medium after 1 hour, the yield slowly reaching 40% after 16 hrs.

Using concentrated solution of NaClO₄ (4M), a known “salting-in” reagent,¹² under similar pH (11-12) did not improve the yield compared with pure water, testifying for the uniqueness of the hydrotropic NaOTs solution. More surprisingly, the NaOTs solution was on a par with DMSO and better than THF or CH₃CN which formed homogeneous solutions under the reaction conditions (Table 1).¹³ Using aqueous NaOTs offers significant advantage over above solvents considering the ease of the product isolation after the reaction. As **4** precipitates during the reaction, it could be simply collected by filtration and aqueous phase successfully recycled. On a small scale, additional extraction with diethyl ether further increased the isolated yield without affecting the recycling. Both initial oxidation reactions and subsequent oxidation reactions performed with recycled NaOTs/H₂O₂ showed similar levels of conversion at the less than 1-hour time-points, indicating no noticeable loss of activity after recycling. While the reactions could be performed in conc. NaOTs dissolved in the local tap, distilled or de-ionized water trace amounts of EDTA (200-400 ppm) were added prior to each cycle to prevent the non-productive decomposition of H₂O₂.

Table 1. Chalcone epoxidation with H₂O₂ in various solvents

Entry	Solvent	Yield of 4 (%) ^a	pH
1	H ₂ O	10 (40) ^b	9
2	NaOTs 3.8M	95 ^c	11-12
3	NaClO ₄ 4M	7	11-12
4	DMSO	100	
5	THF	80	
6	CH ₃ CN	44	

7 Benzene 0

^a 100 mg (0.51 mmol) of **3** in 2 ml of solvent, 100 μ l of H₂O₂ (1 mmol), 10 μ l of NaOH (10M) stirred at 1100 rpm for 1 hr at 60°C. See the Experimental for more detail. ^b After 16 hrs. ^c This yield remained unchanged for at least three consecutive recycling experiments

While hydrogen peroxide is clearly the preferred oxidation reagent, other inexpensive oxidants could also be used. For example, stirring **3** with 2 equivalents of commercial bleach purchased in a local store at 30°C for 24 hours gave **4** in a 90% isolated yield, while only 13% of the product was obtained in pure water. Similar results were obtained when a reagent-grade NaOCl (Aldrich) was used.

The hydrotrope concentration effect on the reaction rate remains a topic of debate.^{4,14} There were several reports on the maximum hydrotrope concentration above which no increase in the reaction rate was observed.^{6b,c,7} To address this point, the oxidation of **3** was performed at different concentration of NaOTs and the reaction was stopped after 15 min (Table 2). Under typical conditions, the yield of **4** increased monotonously with the increase of concentration of NaOTs even above the estimated maximum hydrotrope concentration ($C_{\max} \sim 2\text{-}2.2$ M) determined for this salt.¹⁵ The higher yields correlated well with the solubility of **3** in water, which also increased with the increased concentration of NaOTs (Table 2).

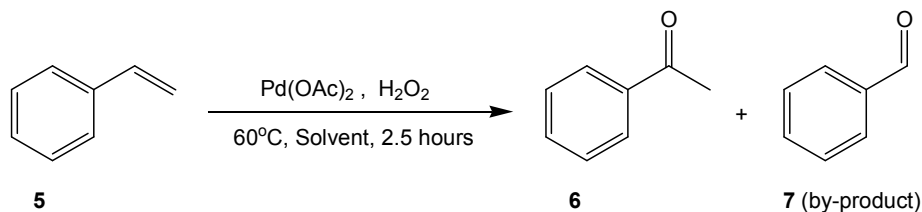
Table 2. Chalcone epoxidation at different NaOTs concentrations

Entry	Liquid	Yield of 4 (%) ^{a, b}	Solubility of 3 (mM) ^c
1	H ₂ O	2	<0.1
2	NaOTs 1M	7	

3	NaOTs 2M	21	5
4	NaOTs 3M	35	
5	NaOTs 3.8M	69	12

^a Same conditions as in Table 1, after 15 min at 60°C, see the Experimental for more detail. ^b Distilled water with 400ppm EDTA. ^c Determined by ¹H NMR spectroscopy

Uncatalyzed epoxidation of alkenes is not the only oxidation reaction that can be performed in the hydrotropic NaOTs. We also found that hydrotropic solutions of NaOTs are compatible with the green *metal-catalyzed* oxidation chemistry.¹⁶ As a test reaction, oxidation of styrene (**5**) by H₂O₂ under the Pd-catalyzed conditions was explored.¹⁷ Thus, while the reaction in water with 0.4% of Pd(OAc)₂ as the catalyst gave 30% of acetophenone (**6**) after 2.5 hrs at 60°C, using the 3.8 NaOTs led to 98% yield with only 2% of benzaldehyde (**7**) as the byproduct (Scheme 3, Table 3). No activity loss took place when the reaction mixture was recycled.¹⁸ Importantly, lower yields and larger amounts of the by-product were obtained when the reactions were performed in THF or acetone (Table 3). Therefore, oxidation in hydrotropic solution can be successfully applied to the oxidation of commodity chemicals, such as terminal α-olefins.



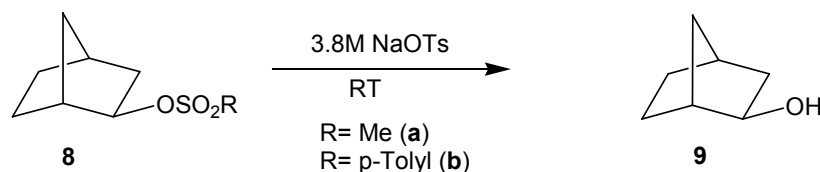
Scheme 3. Pd-catalyzed styrene oxidation in various solvents

Table 3. Pd-catalyzed styrene oxidation

Entry	Liquid	Yield of 6 (%) ^a
1	H ₂ O	30
2	NaOTs 3.8M	98 (2) ^b
3	THF	64 (5) ^b
4	Acetone-d ₆	47 (10) ^b

^a 52 mg (0.5 mmol) of **5**, 0.5 mg (0.002 mmol) of Pd(OAc)₂, 60 μl of H₂O₂ and 0.8 mg (0.0027 mmol) of EDTA in 2 ml of solvent stirred at 1100 rpm for 2.5 hrs at 60°C. See the Experimental for more detail. ^b Yield of by-product **7** is shown in parentheses.

Although our interests are mainly in the green oxidation chemistry, we also ran a short scope survey of several common organic transformations that can be successfully performed in the hydrotropic NaOTs. For example, well-established nucleophilic substitution reactions were found to run extremely well in this medium (Scheme 4, Table 4). Thus, the S_N1 hydrolysis of *exo*-2-norbornyl sulfonates proceeded rapidly at room temperature or slightly above it while the same reactions in pure water took significantly longer times and/or were incomplete. Again, NaOTs was essential for this high reactivity, as concentrated solutions of other salts did not show significant advantage over pure water. Interestingly, the hydrolysis of *exo*-2-norbornyl tosylate **8b** is considerably faster in 3.8M NaOTs than in water despite the presence of a common ion (OTs⁻) at very high concentrations.



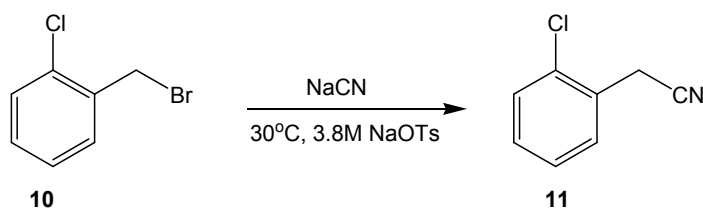
Scheme 4. S_N1 hydrolysis of *exo*-2-norbornyl sulfonates

Table 4. S_N1 hydrolysis of *exo*-2-norbornyl sulfonates

Entry	Compound	Liquid (pH)	Yield of 9 (%) ^a
1	8a	H ₂ O (7)	3 (100) ^b
2	8a	NaOTs 3.8M (3.2)	93
3	8a	NaClO ₄ 4M (5.3)	5
4	8a	NaPF ₄ 4M (2.4)	15
5	8b	H ₂ O	5 ^c (45) ^d
6	8b	NaOTs 3.8M	95 ^c

^a Determined by ¹H NMR analysis after 3 min at 25°C. ^b After 2.5 hrs. ^c Determined by ¹H NMR analysis after 1 hr at 30°C. ^d After 7 hrs. See the Experimental for more detail.

Similarly, S_N2 reactions can also be run in concentrated aqueous NaOTs. For example, cyanation of the benzylic bromide **10** in this solution gave the cyanide **11** in 95% yield after 48 hrs at 30°C, while the same reaction in water proceeded only to 40% conversion (Scheme 5). It is noteworthy that the benzylic cyanation is performed in an industrial scale in organic media and high temperatures (80-100°C), often using phase-transfer catalysts.¹⁹



Scheme 5. S_N2 cyanation of a benzylic bromide **10**.

In conclusion, we have demonstrated the utility of highly concentrated (hydrotropic) solutions of NaOTs in alkene oxidation with H₂O₂. Both, un-catalyzed and metal-catalyzed reactions can be performed under mild conditions giving the corresponding products in higher

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3 yields than reactions performed in pure water or common organic solvents. Importantly, the
4 hydrotropic phase can be easily recycled, further contributing to the process being
5 environmentally benign. Furthermore, we demonstrated application of the NaOTs hydrotropic
6 solution in other common organic transformations, such as S_N1 and S_N2 reactions. Overall, we
7 believe that the reactions reported herein will lead to broader applications of hydrotropic media
8 in synthetic organic chemistry.
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20 Experimental Section

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22 Commercially available reagents (Aldrich, Strem, Alfa and Acros) were used as received.
23 Hydrogen peroxide was used as a 30% solution in water. Chalcone (Benzalacetophenone, **3**) was
24 recrystallized from ethanol before use. 2-*exo*-norbornyl mesylate (**8a**)²⁰ and 2-*exo*-norbornyl
25 tosylate (**8b**)²¹ were prepared from commercial 2-*exo*-norborneol **9** by literature protocols.
26 Commercial H₂O₂ was titrated with KI prior to use to determine the oxidant content. The crude
27 reaction mixtures were analyzed by ¹H-NMR. pH was measured with HI98103 Checker pH
28 meter by Hanna instruments. The reactions were performed in test tubes with the Radleys
29 Carousel Workstation. ¹H and ¹³C NMR spectra were recorded at ambient temperature in CDCl₃
30 or D₂O on a Bruker Avance-400 spectrometer. The chemical shifts are reported in δ relative to
31 the solvent residual peaks as internal reference (7.26 or 4.79 ppm, and 77.16 ppm for ¹H and ¹³C
32 NMR spectra, respectively). HRMS measurements were recorded on a VG-Autospec M-250
33 instrument using TOF analyzer.
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53 Epoxidation of **1**
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3 In a typical experiment, a mixture 80 mg (0.5 mmol) of **1** in 2 ml of liquid (water or NaOTs
4 solution) was vigorously stirred at 1100 rpm with an octagonal stirring bar at 30°C.²² After the
5 addition of 100µl of H₂O₂ (1 mmol) and 10µl of NaOH (10M) the stirring continued for the
6 reported time and the mixture was directly extracted with CDCl₃ and analyzed by ¹H NMR
7 spectroscopy. For 3.8M NaOTs, most of the conversion was achieved already after 30 sec (ca.
8 90%), while 1 min of reaction resulted in a complete conversion. The compound was isolated as
9 a white solid 85 mg (98%).

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11 Naphthoquinone oxide (**2**): ¹H NMR (CDCl₃): 4.01 (2H, s, COCH₃), 7.75 (2H, dd, J=3.2Hz,
12 5.8Hz, Ar), 7.96 (2H, dd, J=3.2Hz, 5.8Hz, Ar). ¹³C{¹H} NMR: 55.4, 127.3, 131.8, 134.8, 190.8.
13 HRMS (ESI - TOF) m/z: [M + H]⁺ Calcd for C₁₀H₇O₃ 175.0395; Found 175.0391.
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20 Epoxidation of **3**

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22 In a typical experiment, a mixture 100 mg (0.51 mmol) of **3** in 2 ml of liquid (water or NaOTs
23 solution) was vigorously stirred at 1100 rpm with an octagonal stirring bar at 60°C. After the
24 addition of 100µl of H₂O₂ (1 mmol) and 10µl of NaOH (10M) the stirring continued for 1 hr and
25 the mixture was directly extracted with CDCl₃ and analyzed by ¹H NMR spectroscopy.
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29 For recycling experiments, after 1 hr the mixture was filtered through a glass sinter and the
30 liquid was directly used as the medium for the next reaction. The solid was washed with water
31 and dried under vacuum giving ca. 104 mg (93%) of pure **4**. Additional 3 mg of **4** could be
32 obtained by extraction with 2x2 ml of Et₂O (overall 107 mg, 95% yield).
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41 For reactions in DMSO and THF, the reaction mixture was diluted with water and organic
42 products were extracted 3 times with CH₂Cl₂, the combined organic phase dried on MgSO₄ and
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3 evaporated. For CH₃CN and benzene, the solvent was evaporated and products ratio analyzed by
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5 ¹H NMR spectroscopy.
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8 Benzalacetophenone oxide (**4**): ¹H NMR (CDCl₃): 4.08 (1H, d, J=2.0Hz, COCH), 2.30 (1H, d,
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10 J=2.0Hz, OCH), 7.39 (5H, m, Ar), 7.49 (2H, t, J=7.6Hz, Ar), 7.61 (1H, m, Ar), 8.02 (2H, m, Ar).
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12 ¹³C{¹H} NMR: 59.5, 61.2, 125.9, 128.5, 128.9, 129.0, 129.2, 134.1, 135.6, 193.2. HRMS (APPI
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14 - TOF) m/z: [M - H]⁻ Calcd for C₁₅H₁₁O₂ 223.0759; Found 223.0767.
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20 Palladium-catalyzed oxidation of **5**:

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22 In a typical experiment, a mixture 52 mg (0.5 mmol) of styrene **5** and 0.5 mg (0.002 mmol) of
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24 Pd(OAc)₂ in 2 ml of liquid (water or NaOTs solution) was vigorously stirred at 1100 rpm with an
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26 octagonal stirring bar at 60°C. After the addition of 60 μl of H₂O₂ and 0.8 mg (0.0027 mmol) of
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28 EDTA the stirring continued for 2.5 hrs and the mixture was directly extracted with CDCl₃,
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30 filtered through a cotton pad to remove Pd black and analyzed by ¹H NMR spectroscopy with
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32 anisole as an internal reference. For the reaction in THF, the solvent was evaporated and residue
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34 dissolved in CDCl₃. No work-up was performed for the reaction in acetone-d₆ as the reaction
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36 mixture was analyzed directly.
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43 Hydrolysis of 2-norbornyl sulfonates:

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45 In a typical experiment, 0.5 mmol of either **8a** or **8b** was added to a 2 ml of liquid (water or
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47 aqueous salt solution) and stirred at 1100 rpm for the indicated time at the indicated temperature.
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49 The organic mixture was extracted with CDCl₃ and analyzed by ¹H NMR spectroscopy using
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51 mesitylene as an internal reference.
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Cyanation of **10**:

To the stirring solution of 54 mg (1.1 mmol) of NaCN in 2 ml of liquid (water or NaOTs solution) was added 130 μ l (1 mmol) of 2-chlorobenzyl bromide (**10**) and the mixture was stirred at 1100 rpm at 30^oC for 48 hrs. The mixture was extracted with CDCl₃ and analyzed by ¹H NMR spectroscopy. The compound was isolated as a white solid 72 mg (95%).

2-chlorobenzyl cyanide (**11**): ¹H NMR 3.84 (2H, s, CH₂CN), 7.30 (2H, m, Ar), 7.42 (1H, m, Ar), 7.50 (1H, m, Ar). ¹³C{¹H} NMR: 22.2, 116.9, 127.6, 128.2, 129.7, 129.8, 129.9, 133.6. HRMS (APCI - TOF) m/z: [M]⁺ Calcd for C₈H₆NCl 151.0189; Found 151.0191.

Solubility determination:

In a typical experiment, an excess of **1** or **3** was vigorously stirred with 3 ml of liquid (water or NaOTs solution) for overnight to prepare the saturated solution. One ml of the solution was withdrawn with a syringe and extracted with copious amounts of CH₂Cl₂. The organic solvent was evaporated and the residue was dissolved in CDCl₃ and analyzed by ¹H NMR spectroscopy vs. added mesitylene as a reference.

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Supporting Information

Supporting information is available free of charge on the ACS publications website:
NMR spectra of reaction products (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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