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Allylic and benzylic sp³ C–H oxidation in water†

Wei Jie Ang and Yulin Lam*

A copper-catalyzed method for the oxidation of allylic and benzylic sp³ C–H by aqueous tert-butyl hydroperoxide (T-Hydro) in water using a recyclable fluorous ligand has been developed. The reaction procedure is tolerant to additional functional groups and the fluorous ligand could be reused with little loss of catalytic activity.

Introduction

Allylic and benzylic oxidations via the direct sp³ C–H bond activation of alkenes and alkylarenes to the corresponding α,β-unsaturated enones and carbonyl compounds are important transformations with a wide variety of industrial applications including the synthesis of drug precursors and building blocks in many organic syntheses. Although several organocatalysts have been developed for these oxidations, the efficiency of metal-catalyzed allylic and benzylic oxidations remains remarkable. To-date several protocols for sp³ C–H oxidation catalysed by metal complexes in combination with tert-butyl hydroperoxide (TBHP) have been reported. However, amongst the different metals, fewer oxidations have been done using Cu as the catalyst, even though copper proteins found in nature are catalysts, especially for oxidation reactions.

Previously, we have reported a recyclable, fluorous catalyst that efficiently promoted carbon–carbon bond formation reactions in water. Since the development of aqueous-phase reaction is an active field in organic synthesis due to demands for realization of green chemical processes and many classic reactions that are commonly used in organic synthesis are currently being re-examined in order to develop cleaner chemical processes and to reduce or eliminate existing drawbacks and inefficiencies, we herein report a protocol for room temperature, copper-catalyzed allylic and benzylic oxidation by T-Hydro in water using a recyclable fluorous ligand L1 (Fig. 1). To the best of our knowledge, there are no earlier publications on metal-catalyzed allylic oxidation in water.

Results and discussion

In the initial assessment of the allylic oxidation reaction, 1-phenyl-1-cyclohexene 1a was chosen as the model substrate. We investigated the optimization reaction conditions by varying the solvent, catalyst, base and oxidants (Table 1). When the allylic oxidation was conducted using 1a, 5 mol% CuI, 5 mol% L1 as the ligand, TBHP (6 M in decane), K2CO3 and water as the solvent at room temperature, the desired 3-phenylcyclohex-2-enone 2a was obtained after 12 h in 29% yield (Table 1, entry 1). When water was replaced with acetonitrile, compound 2a was obtained in similar yield (Table 1, entry 2). To optimize the reaction, we varied the metal catalyst and found that the reaction in aqueous medium was most efficient with CuI (Table 1, entries 3–10). Next we varied the base and established that the reaction was most efficient in the absence of a base (Table 1, entries 11–14). Subsequently, we screened different oxidants on the reaction which indicated that TBHP was a more effective oxidant than H2O2, DTBP or m-CPBA. In addition, both T-Hydro and TBHP provided compound 2a in similar yields (Table 1, entries 15–21). Hence we decided to use T-Hydro as the oxidant since the absence of decane would increase the environmental friendliness of the reaction. We also examined the effect of varying the ratio of CuI and L1 but this provided compound 2a in lower yield (Table 2, entries 2–4). The minimum time for the reaction to reach completion was also determined to be 2 h (Table 2, entry 5). The amount of oxidant employed was also examined. Lowering the amount of oxidant to 4 equivalents increased the yield of 2a to 62% but further decreasing the amount of
It was previously reported that surfactant molecules could aid in reaction rates. Thus the effect of additives was investigated and the reaction was most effective when 5 mol% of sodium dodecyl sulfate (SDS) was added. The addition of 5 mol% SDS not only halved the reaction time but also provided compound 2a in a higher yield (Table 2, entries 9–12). Besides L1, we also tested two other fluororous ligands, L2 and L3 (Fig. 1), but found L1 to be the most effective ligand for facilitating the allylic oxidation reaction (Table 2, entries 13 and 14). Finally, in a control experiment in the absence of L1, only a trace amount of 2a was obtained (Table 2, entry 15).

Having established the optimal reaction conditions, different alkenes were tested to explore the generality of this oxidation transformation. As shown in Table 3, the reaction conditions were compatible with both the electron-withdrawing and -donating substituents as well as the reactive functional group (entries 3–5). The oxidation reaction was also regioselective at the least hindered allylic carbon which is consistent with the previously published results. It is worth noting that the allylic oxidation of substrate 1c did not occur at the methyl substituent (entry 3). Attempts to extend the substrate scope to linear allylic alkenes (1-hexene, 1-octene, 1-decene, and 3-pentenenitrile) were unsuccessful under the optimized conditions.

tert-Butyl peroxy ether of the allylic substrates was observed as the by-product in the allylic oxidation reaction (Table 3, entries 1–5). 3-t-Butylperoxy-1-phenylcyclohexene 1a′ was isolated from the allylic oxidation of 1a in 10% yield (Table 3, entry 1). When the isolated 1a′ was subjected to the allylic oxidation conditions, 2a was obtained in 75% yield (Scheme 1). Purification and isolation of tert-butyl peroxy ether of 1b–1e was unsuccessful but 1H NMR of the by-product fraction shows the t-Bu signal in the 1.2 ppm region.

Encouraged by the promising results, we extended the optimized conditions to benzylic oxidation (Table 3, entries 6–13). We found that diphenylmethane type substrates gave the corresponding products in good yields (Table 3, entries 6, 7 and 11) although the reaction required a longer time to complete. This could be attributed to these substrates being solids at room temperature and have poor solubilities in water. When the temperature was increased to 50 °C, the reaction time was considerably shortened and the products were obtained in comparable yields. Substrates bearing a heteroatom were also compatible with the reaction conditions and provided the benzylic oxidation products in moderate yields (Table 3, entries 9 and 10). Alkylarenes bearing an electron-withdrawing group on the alkyl moiety are difficult substrates for direct oxidation due to the inert benzylic C–H bond. Gratifyingly, we were able to apply our conditions to the oxidation of substrate 1m to obtain compound 2m in 73% yield (Table 3, entry 13). The methyl ester functionality of substrate 1m was tolerated under the mild conditions with no hydrolyzed product observed. Long chain aryl alkane 1n was also successfully ox-
dized to the corresponding ketone albeit in lower (51%) yield (Table 3, entry 14).

Next we investigated the possibility of recycling and reusing L1. 1-Phenyl-1-cyclohexene 1a was used for the model study under the optimized reaction conditions. The recycling experiments were carried out over 5 cycles and the time taken for the reaction to complete was 1–2 h to provide 2a in 81–95% yields (Table 4). The recovered L1 showed a slow decline in catalytic activity after several recoveries. In addition, the recovery of L1 via F-SPE was good except in the 5th cycle. The fluorous silica gel used in F-SPE could be reused10 which minimized waste thus making the recovery of L1 a greener procedure.

Finally to apply this reaction in gram-scale reaction, 10.8 mmol (1.71 g) of 1a was used for the allylic oxidation reaction under the optimized reaction conditions. The reaction proceeded smoothly, gave the corresponding product 2a in similar (70%) yield with 9% of 1a′ and the recovery of L1 was also high (94%) (Scheme 2).

A proposed catalytic cycle of the L1/CuI catalyzed allylic oxidation is depicted in Scheme 3. The copper complex I was formed in situ from L1 and CuI. The formation of tert-butyl peroxy radical IV abstracts a hydrogen atom from the alkene to give the radical V which forms the tert-butyl peroxy intermediate VI. This is supported by the reaction of 1a′ in Scheme 1.

### Table 3 Copper-catalyzed allylic and benzylic oxidation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2a</td>
<td>1</td>
<td>71 (10°)</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>2b</td>
<td>2</td>
<td>58 (10°)</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>2c</td>
<td>1</td>
<td>62 (5°)</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>2d</td>
<td>1</td>
<td>58 (8°)</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>2e</td>
<td>1</td>
<td>74 (8°)</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>2f</td>
<td>6 (2d)</td>
<td>88 (90°)</td>
</tr>
<tr>
<td>7</td>
<td>1g</td>
<td>2g</td>
<td>6 (2d)</td>
<td>81 (84°)</td>
</tr>
<tr>
<td>8</td>
<td>1h</td>
<td>2h</td>
<td>1</td>
<td>70</td>
</tr>
<tr>
<td>9</td>
<td>1i</td>
<td>2i</td>
<td>3°</td>
<td>51°</td>
</tr>
<tr>
<td>10</td>
<td>1k</td>
<td>2k</td>
<td>1</td>
<td>68</td>
</tr>
<tr>
<td>11</td>
<td>1l</td>
<td>2l</td>
<td>6 (2d)</td>
<td>85 (86°)</td>
</tr>
<tr>
<td>12</td>
<td>1m</td>
<td>2m</td>
<td>1</td>
<td>68</td>
</tr>
<tr>
<td>13</td>
<td>1n</td>
<td>2n</td>
<td>1</td>
<td>73</td>
</tr>
<tr>
<td>14</td>
<td>11</td>
<td>21</td>
<td>1</td>
<td>51</td>
</tr>
</tbody>
</table>

**Reaction conditions:** substrate (0.5 mmol), CuI (5 mol%), L1 (5 mol%), T-Hydro (4.0 equiv.), SDS (5 mol%), H2O (1.0 mL), r.t.

### Table 4 Recycling of L1

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Time (h)</th>
<th>Yieldb (%)</th>
<th>Recovered L1c (wt%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>71</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>69</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>66</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>64</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>60</td>
<td>81</td>
</tr>
</tbody>
</table>

**Reaction conditions:** 1a (2.5 mmol), CuI (5 mol%), L1 (5 mol%), T-Hydro (4.0 equiv.), SDS (5 mol%), H2O (5.0 mL), r.t. "Isolated yields.

**Scheme 1** Reaction of 1a′ under optimized reaction conditions.

**Scheme 2** Gram-scale synthesis of 2a.
Experimental

General

All chemicals purchased were used without further purification. Compound 6\textsuperscript{11} and 7\textsuperscript{12} were synthesized according to the previously reported procedure. Moisture-sensitive reactions were carried out under nitrogen with commercially obtained anhydrous solvents. Analytical thin-layer chromatography (TLC) was carried out on precoated F254 silica plates and visualized with UV light. Column chromatography was performed with silica (Merck, 230–400 mesh). F-SPE was performed with FluoroFlash\textsuperscript{®} silica gel (40 micron). \(^1\)H and \(^13\)C NMR spectra were recorded at 298 K. Chemical shifts are expressed in terms of \(\delta\) (ppm) relative to the internal standard tetramethylsilane (TMS). Mass spectra were performed under EI and ESI mode (Scheme 4).

Synthesis of fluorous ligands L1–L3

Synthesis of 4-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11-heptadeca fluorous decyloxy)benzaldehyde (5). To a solution of 4-hydroxybenzaldehyde (0.61 g, 5.0 mmol) in DMF (10 mL) was added \(\text{K}_2\text{CO}_3\) (1.38 g, 10 mmol) and \(\text{C}_8\text{F}_{17}(\text{CH}_2)_4\text{I}\) (1.96 g, 3.33 mmol). The reaction mixture was stirred at room temperature for 12 h, quenched with \(\text{H}_2\text{O}\) (5 mL) and consecutively washed with EtOAc (20 mL \(\times\) 3). The combined organic layer was washed with brine (10 mL \(\times\) 3), dried over anhydrous \(\text{MgSO}_4\), filtered and concentrated. The desired product 5 (2.90 g, 99%) was obtained as a white solid after purification by F-SPE.

Synthesis of \(\text{N}-(4-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11-heptadeca fluorous decyloxy)benzyl)-1-(pyridin-2-yl)-\text{N}-(pyridin-2-ylmethyl)methanamine (L1).\) To a solution of compound 5 (0.58 g, 1.0 mmol) in dichloroethane (15 mL) was added di-(2-picoly)amine (0.22 mL, 1.2 mmol). The reaction mixture was stirred at room temperature for 1 h. Thereafter \(\text{NaBH(OAc)}_3\) (305 mg, 1.44 mmol) was added and the reaction mixture was further stirred for 24 h. After which, the reaction mixture was quenched with \(\text{H}_2\text{O}\) (2 mL) and the organic layer was separated. The aqueous layer was further extracted with dichloromethane (15 mL) and the combined organic layer was dried over anhydrous \(\text{MgSO}_4\) and filtered. The desired product L1 (377 mg, 62%) was obtained as a yellow oil after purification by F-SPE.

Synthesis of 4-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11-heptadecafluorous decyloxy)-2,6-di(2-pyridyl)pyridine (L2). To a solution of [2,2′:6,2″-terpyridin]-4′-ol 6 (125 mg, 0.5 mmol) in DMF (5.7 mL) was added \(\text{K}_2\text{CO}_3\) (104 mg, 0.75 mmol). The reaction mixture was stirred at 80 °C for 30 min. Thereafter \(\text{C}_8\text{F}_{17}(\text{CH}_2)_4\text{I}\) (441 mg, 0.75 mmol) was added and the reaction mixture was further stirred for 24 h, quenched with \(\text{H}_2\text{O}\) (2 mL) and filtered. The desired product L2 (345 mg, 97%) was obtained as a white solid after washing with hexane (5 mL \(\times\) 2) to remove residual \(\text{C}_8\text{F}_{17}(\text{CH}_2)_4\text{I}\).

Synthesis of \(\text{2,2′-(4-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11-heptadecafluorous decyloxy)pyridine-2,6-diyl)bis(1H-benzo[d]imidazole)} (L3).\) To a solution of 2,6-bis(1H-benzo[d]imidazol-2-yl)pyridin-4-ol 7 (164 mg, 0.5 mmol) in DMF (5.7 mL) was added \(\text{K}_2\text{CO}_3\) (104 mg, 0.75 mmol). The reaction mixture was stirred at 80 °C for 30 min. After which, \(\text{C}_8\text{F}_{17}(\text{CH}_2)_4\text{I}\) (441 mg, 0.75 mmol) was added and the reaction mixture was further stirred for 24 h, then quenched with \(\text{H}_2\text{O}\) (2 mL) and filtered. The desired product L3 (352 mg, 89%) was obtained as an off-white solid after washing with hexane (5 mL \(\times\) 2) to remove residual \(\text{C}_8\text{F}_{17}(\text{CH}_2)_4\text{I}\).

General procedure for the copper-catalyzed allylic and benzylic oxidation

A mixture of the substrate (0.5 mmol), L1 (5 mol%), CuI (5 mol%), SDS (5 mol%) and water (1.0 mL) was added K\(_2\)CO\(_3\) (3 mL) and \(\text{C}_8\text{F}_{17}(\text{CH}_2)_4\text{I}\) (1.96 g, 3.33 mmol). The reaction mixture was stirred at room temperature for 12 h, quenched with \(\text{H}_2\text{O}\) (5 mL) and consecutively washed with EtOAc (20 mL \(\times\) 3). The combined organic layer was washed with brine (10 mL \(\times\) 3), dried over anhydrous \(\text{MgSO}_4\), filtered and concentrated. The desired product 5 (2.90 g, 99%) was obtained as a white solid after purification by F-SPE.
General procedure for the recycling experiment using F-SPE

Recycling experiments were carried out on a 2.50 mmol scale using the general procedure described above. The crude product was first diluted with THF–H2O = 7:3 (1 mL) and loaded into a F-SPE fluorous silica column (column diameter: 2.20 cm; amount of fluorous silica required: 10% of crude product by weight). The crude product was then eluted using THF–H2O = 7:3 (30 mL) as the eluent and L1 was subsequently eluted with THF (20 mL). The fluorous silica was regenerated and reused (5 times) after washing with acetone (10 mL). To determine the amount of product formed after each recycling experiment, the solution of crude product was concentrated, diluted with EtOAc (20 mL) and washed with water (10 mL). The organic layer was dried over anhydrous MgSO4, filtered, concentrated and then purified accordingly.

Conclusion

An environmentally benign procedure for the room temperature, copper-catalyzed allylic and benzyllic oxidation by aqueous TBHP in water using a recyclable fluorous ligand has been developed. Pre-generation of the organometallic reagent was not required. This increases the green aspect of the reaction. Fluorous ligand L1 was recycled and reused with little loss of catalytic activity. The oxidation procedure would also be applied to the gram-scale reaction.

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Notes and references


