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Ru(III)-catalyzed oxidation of homopropargyl alcohols in ionic liquid: an efficient and green route to 1,2-allenic ketones

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ABSTRACT

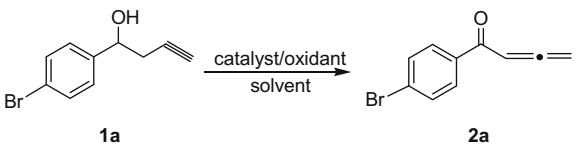
An efficient and environmentally benign synthesis of 1,2-allenic ketones via $RuCl_3$-catalyzed oxidation of homopropargyl alcohols in ionic liquid with *tert*-butyl hydroperoxide (TBHP) as the oxidant was reported for the first time. With its reasonable efficiency and green nature, this oxidation provides a novel alternative route to 1,2-allenic ketones.

Allenic ketones have shown interesting reactivity[1,2] by acting as Michael acceptors,[3] Diels–Alder dienophiles,[2] building blocks in furan,[4] and 1,3-dipoles in unusual [8+2] annulation.[5] Due to their importance, various synthetic routes to allenic ketones have been reported.[6–8] In particular, one often used approach involves the reaction of allenyl or homopropargylmetals with carbonyl compounds, followed by oxidation of the resulting allenic or homopropargylic alcohols.[9] The oxidant used in the above-mentioned method is usually DMP (Dess–Martin Periodinane) and the reaction is called Dess–Martin oxidation. Though Dess–Martin oxidation is an efficient procedure, the formation of the corresponding 1,2-allenic ketones is in many cases along with side products resulting from either the addition of acetic acid (from DMP) to the allenes with electron-rich substituents or the isomerization of the 1,2-allenic ketones with electron-withdrawing substituents.[10] Moreover, Dess–Martin oxidation and other traditional methods usually involve the use of stoichiometric or excessive metal reagents, toxic organic solvents, or require harsh reaction conditions. Therefore, the development of methods with less environmentally adverse impact still remains a challenge.

On the other hand, transition metal-catalyzed reactions are among the most powerful tools in modern organic synthesis. In this regard, organic transformations catalyzed by ruthenium(III) species have been a focus of attention in the recent years due to their high efficiency and excellent chemoselectivity. The use of catalytic amount of ruthenium(III) together with oxidants such as H_2O_2,[11] CH_3CO_3H,[12] $NaIO_4$,[13] oxygen,[14] (diacetoxyiodo)benzene (DIB),[15] bromamine-T,[16] $CeCl_3/NaIO_4$,[17] and oxygen/sodium cyanide,[18] have been used in an array of oxidative transformations, such as oxidation of phenols, alcohols, and unactivated C–H bond; oxidative cleavage of olefins to aldehydes; oxidation of Hantzsch 1,4-dihydropyridine to the corresponding pyridines, and dihydroxylation of unreactive olefins and oxidative cyanation of tertiary amines.

In a recent research program, we needed some 1,2-allenic ketones for the preparation of substituted furans. Considering that $RuCl_3$ as well as other ruthenium salts and complexes has been successfully used to catalyze the oxidation of a number of substrates with various stoichiometric oxidants as mentioned previously, we envisioned a new route to 1,2-allenic ketone through $RuCl_3$-catalyzed oxidation of homopropargyl alcohols[19] by using *tert*-butyl hydroperoxide (TBHP) or hydrogen peroxide (H_2O_2) as the oxidant. Herein, we report that $RuCl_3$/TBHP is able to transform a variety of homopropargyl alcohols to 1,2-allenic ketones with a reasonable efficiency.

The study was initiated by using 1-(4-bromophenyl)but-3-yn-1-ol (**1a**, Scheme 1) as the substrate and the reaction was firstly run in CH_2Cl_2. It turned out that when **1a** was treated with $RuCl_3$ (0.01 equiv) and TBHP (3 equiv) at rt, **2a** could be obtained, but in low yield (Table 1, entry 1). With higher amount of $RuCl_3$ and higher reaction temperature, the yields of **2a** increased remarkably (entries 2–6). With 0.04 equiv of $RuCl_3$ and 4 equiv of TBHP, **2a** could be obtained in a yield of 80% after the reaction mixture being stirred under reflux for 2 h (entry 6). The oxidation was also studied in other solvents such as CH_3CN and THF, but the yields of **2a** were lower than that in CH_2Cl_2 (entries 8 and 9). Remarkably, this reaction could be carried out efficiently in two readily available



1a **2a**

Scheme 1.

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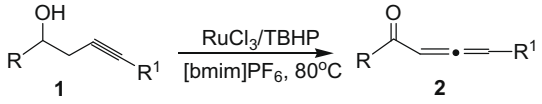
Table 1
Oxidation of homopropargyl alcohol (**1a**) under different reaction conditions[a]

Entry	Solvent	Amount of $RuCl_3$ (equiv)	Amount of TBHP (equiv)	Amount of H_2O_2 (equiv)	Reaction time (h)	Temperature (°C)	Yield[b] (%)
1	CH_2Cl_2	0.01	3	—	5	rt	25
2	CH_2Cl_2	0.02	3	—	5	rt	33
3	CH_2Cl_2	0.03	3	—	5	rt	40
4	CH_2Cl_2	0.04	3	—	5	rt	51
5	CH_2Cl_2	0.03	3	—	2	Reflux	73
6	CH_2Cl_2	0.04	4	—	2	Reflux	80
7	CH_2Cl_2	0.04	5	—	2	Reflux	81
8	CH_3CN	0.04	4	—	2	Reflux	65
9	THF	0.04	4	—	2	Reflux	55
10	$[bmim]BF_4$	0.04	3	—	3	80	60
11	$[bmim]PF_6$	0.04	3	—	4	80	70
12	$[bmim]PF_6$	0.04	4	—	4	80	75
13	$[bmim]PF_6$	0.04	5	—	4	80	74
14	H_2O	0.04	4	—	4	80	22
15	$[bmim]PF_6$	0.04	—	5	4	80	25
16	H_2O	0.04	—	5	4	80	20

[a] Reaction conditions: **1a** (1 mmol).
[b] Isolated yields.



Scheme 2.

ionic liquids, $[bmim]BF_4$ and $[bmim]PF_6$ (entries 10–13). It turned out that **2a** was obtained in a yield of 75% with 0.04 equiv of $RuCl_3$ and 4 equiv of TBHP by treating the mixture in $[bmim]PF_6$ at 80 °C (entry 12). Though the yield was lower than that with CH_2Cl_2, we prefer $[bmim]PF_6$ as the oxidation medium due to the fact that those 1-alkyl-3-methylimidazolium-based ionic liquids have emerged as promising alternative green solvents for chemical synthesis because of their negligible vapor pressure, easy recyclability, and reusability.[20] The reaction was also tried in H_2O, but the yield was unfortunately low (entry 14). In addition, when H_2O_2 was used as an oxidant, **2a** was obtained in much lower yields compared with that of TBHP (entries 15 and 16).

With the optimized reaction conditions, the oxidation of a range of substrates was then investigated (Scheme 2) and the examples

Table 2
Oxidation of homopropargyl alcohols with $RuCl_3$/TBHP in $[bmim]PF_6$[a]

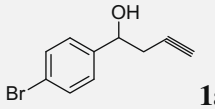
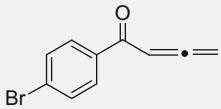
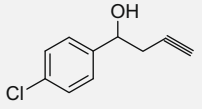
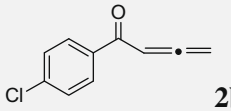
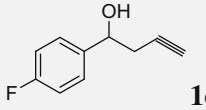
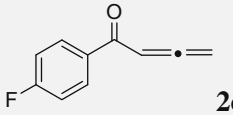
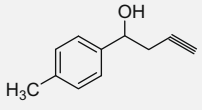
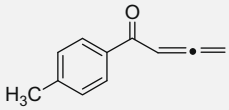
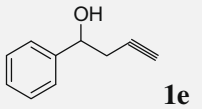
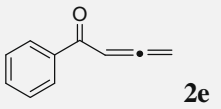
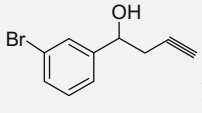
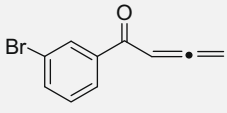
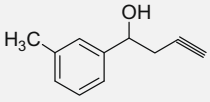
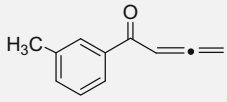
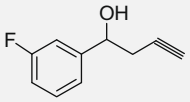
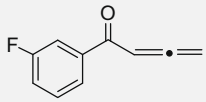
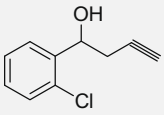
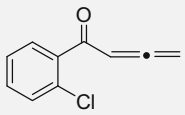
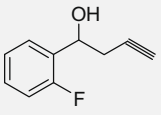
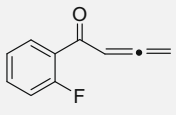
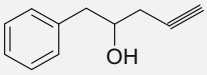
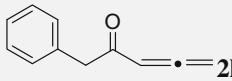
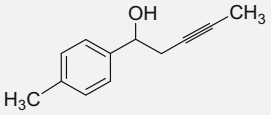
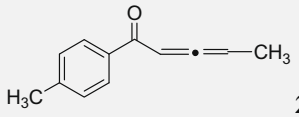
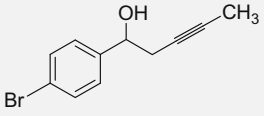
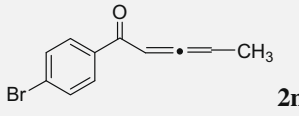
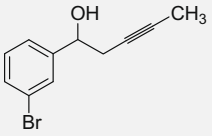
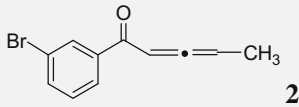
Entry	Homopropargyl alcohol	Product	Reaction time (h)	Yield[b] (%)
1	 **1a**	 **2a**	4	75
2	 **1b**	 **2b**	4	73
3	 **1c**	 **2c**	4	72
4	 **1d**	 **2d**	4	73
5	 **1e**	 **2e**	4	76
6	 **1f**	 **2f**	4	70

Table 2 (*continued*)

Entry	Homopropargyl alcohol	Product	Reaction time (h)	Yield[b] (%)
7	 **1g**	 **2g**	4	72
8	 **1h**	 **2h**	4	70
9	 **1i**	 **2i**	6	55
10	 **1j**	 **2j**	6	58
11	 **1k**	 **2k**	8	21[c]
12	 **1l**	 **2l**	4	72
13	 **1m**	 **2m**	4	70
14	 **1n**	 **2n**	5	66

[a] Reaction conditions: **1** (1 mmol), $RuCl_3$ (0.04 mmol), TBHP (4 mmol), [bmim]PF_6 (1 mL), 80 °C.
[b] Isolated yields.
[c] H NMR yield.

are summarized in Table 2. It was observed that with aryl-substituted homopropargyl alcohols (Table 2, entries 1–10), the reactions underwent smoothly, and the corresponding products were produced in moderate yields. With either electron-withdrawing or electron-donating groups at the *para* position of the phenyl ring, the oxidation proceeded efficiently (Table 2, entries 1–4). The reactions were slowed with substrates bearing substituted groups at the *ortho* position of the phenyl ring (Table 2, entries 9 and 10). These results indicated that the electronic effect on the phenyl ring in these propargyl alcohols did not play a significant role in affecting the oxidation, probably due to their high reactivity. In contrast, steric hindrance seemed to be an important factor in affecting the oxidation. Moreover, various functional groups such as alkyl and halide on the phenyl ring were well tolerated under these conditions. It is worth to be noted that the oxidation of aliphatic substrate was much more difficult and the corresponding product was only formed in low yield (Table 2, entry 11). Encouragingly, with internal alkyne substrates (**1l**, **1m**, and **1n**), the reaction underwent smoothly to afford the corresponding 1,2-allenic ketones in moderate yields (Table 2, entries 12–14).[21]

Next, the recyclability of the oxidation system was studied by using **1a** as the model substrate. It followed that $RuCl_3$ together with [bmim]PF_6 could be reused for a new cycle after being fully extracted with diethyl ether (10 mL × 3), dried in vacuo and added with certain amount of TBHP. [21]The results shown in Table 3 demonstrate that it was readily recyclable for at least three times, with only slight drop in its catalytic activity over each cycle.

In conclusion, a novel and green method for the preparation of 1,2-allenic ketones through the oxidization of propargyl alcohols with $RuCl_3$ as a catalyst and TBHP as an oxidant was developed. This oxidation proceeds under mild conditions and a series of functional groups can be tolerated. Due to its environmentally benign nature and reasonable efficiency, this method provides a novel alternative to 1,2-allenic ketones and may stimulate further research efforts on reactions catalyzed by $RuCl_3$ species in ionic liquids. Studies to probe the mechanism and to broaden the scope of these reactions are currently underway in our laboratory and the results will be reported in due course.

Table 3
Reusability study of the catalytic system in the preparation of **2a**

Run	Temperature (°C)	Time (h)	Yield[a] (%)
1	80	4	75
2	80	4	71
3	80	4	68
4	80	5	61

[a] Isolated yield.

Acknowledgments

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21. *General procedure for the preparation of 1,2-allenic ketones*: To 1 mL of $[bmim]PF_6$ in a round-bottomed flask were added propargyl alcohol (1 mmol) and $RuCl_3$ (0.04 mmol) at rt. The flask was then put into an oil bath. Over rigorous stirring, TBHP (4 mmol) was added dropwise, during which time, the oil bath was gradually heated to 80 °C. Upon completion of addition, the mixture was stirred at 80 °C and the reaction was monitored by TLC. Upon completion, H_2O (5 mL) was added and the mixture was extracted with diethyl ether (10 mL × 3). The combined organic phases were washed with H_2O and dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by column chromatography eluting with hexane/ethyl acetate (0–5%) to give the corresponding 1,2-allenic ketone products. The ionic liquid phase was concentrated and dried in vacuo overnight for reuse. **2a**: liquid; IR (neat): 2930, 2858, 1960, 1935, 1670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.27 (d, 2H, J = 6.4 Hz, CH_2), 6.39 (t, 1H, J = 6.4 Hz, CH), 7.59 (d, 2H, J = 8.4 Hz, ArH), 7.76 (d, 2H, J = 8.4 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 79.5, 93.2, 127.9, 130.2, 131.7, 136.1, 190.0, 217.2. MS: m/z 245 $[M+Na]^+$. HRMS (FAB) Calcd for $C_{10}H_8BrO$: 222.9758 $(MH)^+$, found: 222.9755. Compound **2b**: liquid; IR (neat): 2931, 2858, 1961, 1938, 1668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.27 (d, 2H, J = 6.4 Hz, CH_2), 6.39 (t, 1H, J = 6.4 Hz, CH), 7.42 (d, 2H, J = 8.4 Hz, ArH), 7.84 (d, 2H, J = 8.4 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 79.5, 93.2, 128.7, 130.1, 135.7, 139.2, 189.8, 217.2. MS: m/z 201 $[M+Na]^+$. HRMS (FAB) Calcd for $C_{10}H_8ClO$: 179.0263 $(MH)^+$, found: 179.0263. Compound **2d**: liquid; IR (neat): 2925, 2860, 1961, 1932, 1670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.41 (s, 3H, CH_3), 5.25 (d, 2H, J = 6.4 Hz, CH_2), 6.45 (t, 1H, J = 6.4 Hz, CH), 7.25 (d, 2H, J = 8.0 Hz, ArH), 7.82 (d, 2H, J = 8.0 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6, 79.1, 93.1, 128.8, 129.1, 134.9, 143.7, 190.5, 216.8. MS: m/z 181 $[M+Na]^+$. HRMS (FAB) Calcd for $C_{11}H_{11}O$: 159.081 $(MH)^+$, found: 159.0819. Compound **2e**: liquid; IR (neat): 2926, 2856, 1961, 1932, 1670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.27 (d, 2H, J = 6.4 Hz, CH_2), 6.46 (t, 1H, J = 6.4 Hz, CH), 7.44–7.48 (m, 2H, ArH), 7.55–7.59 (m, 1H, ArH), 7.90–7.92 (m, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 79.2, 93.2, 128.3, 128.7, 132.8, 137.4, 191.0, 217.1. MS: m/z 167 $[M+Na]^+$. HRMS (FAB) Calcd for $C_{10}H_9O$: 145.0653 $(MH)^+$, found: 145.0658. Compound **2g**: liquid; IR (neat): 2922, 2864, 1960, 1934, 1665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.42 (s, 3H, CH_3), 5.26 (d, 2H, J = 6.4 Hz, CH_2), 6.46 (t, 1H, J = 6.4 Hz, CH), 7.34–7.39 (m, 2H, ArH), 7.70–7.72 (m, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.3, 79.2, 93.2, 125.9, 128.2, 129.1, 133.6, 137.4, 138.2, 191.1, 217.0. MS: m/z 181 $[M+Na]^+$. HRMS (FAB) Calcd for $C_{11}H_{11}O$: 159.081 $(MH)^+$, found: 159.0815. Compound **2m**: liquid; IR (neat): 2928, 1960, 1934, 1651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.99–2.02 (m, 3H, CH_3), 5.04–5.07 (m, 2H, 2 × CH), 7.53 (d, 2H, ArH, J = 8.4 Hz), 7.63 (d, 2H, ArH, J = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.6, 78.7, 102.0, 126.7, 130.5, 131.1, 136.8, 193.9, 217.5. MS: m/z 259 $[M+Na]^+$. HRMS (FAB) Calcd for $C_{11}H_{10}BrO$: 236.9915 $(MH)^+$, found: 236.9909. Compound **2n**: liquid; IR (neat): 2927, 2864, 1934, 1654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.99–2.02 (m, 3H, CH_3), 5.06–5.09 (m, 2H, 2 × CH), 7.28 (t, 1H, ArH, J = 8.0 Hz), 7.62–7.69 (m, 2H, ArH), 7.88–7.89 (m, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.5, 78.9, 102.1, 121.9, 127.5, 129.4, 131.9, 134.7, 139.8, 193.8, 217.8. MS: m/z 259 $[M+Na]^+$. HRMS (FAB) Calcd for $C_{11}H_{10}BrO$: 236.9915 $(MH)^+$, found: 236.9910.