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Catalytic Oxidative 1,2-Shift in 1,1′-Disubstituted Olefins Using Arene(iodo)sulfonic Acid as the Precatalyst and Oxone as the Oxidant

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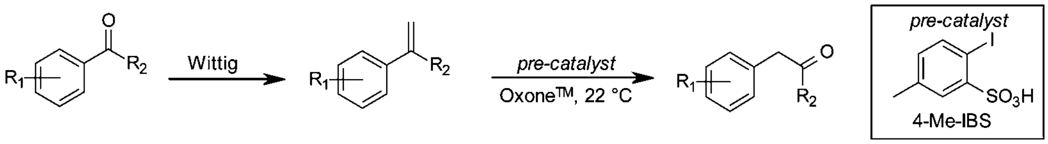
ABSTRACT



An efficient, catalytic hypervalent iodine-mediated oxidative 1,2-shift of 1,1′-disubstituted olefins is described. This methodology provides concise access to homobenzylic ketones with electron-donating substituents. In the case of cyclic systems, this transformation results in ring-expanded β-benzocycloalkanones, which are useful for further elaboration.

Catalytic application of hypervalent iodine reagents[1] has become an engaging area of research in the field of organocatalysis.[2] The seminal work by Koser et al.[3] toward the application of stoichiometric hydroxytosyloxy iodobenzene (HTIB) in promoting oxidative 1,2-shifts of 1,1-disubstituted olefins for the preparation of homobenzylic ketones stands as a benchmark for seeking environmentally benign conditions (Scheme 1). Historically, this transformation employed stoichiometric $Tl(NO_3)_3$.[4] Although the efficiency for a thallium-mediated transformation is typically high, the cost,[5] toxic nature, and resulting byproducts limit its use in the pharmaceutical industry.[6] In the case of cyclic systems and depending on the desired ring size, the homo-β-benzocycloalkanone motif provides a useful functionality for further elaboration to pharmacologically significant intermediates. Herein we report a catalytic reaction design that provides a practical synthesis of homobenzylic ketones while circumventing the use of stoichiometric oxidative reagents.

1-Methoxy-5,7,8,9-tetrahydrobenzocyclohepten-6-one (**1c**) is an intermediate in the synthesis of a preclinical candidate (Scheme 1). Initially, this intermediate was prepared through a two-step procedure that utilized a Wittig olefination of corresponding tetralone **1a**, followed by an oxidative ring expansion of **1b** using stoichiometric thallium

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(1) (a) Uyanik, M.; Yasui, T.; Ishihara, K. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3848. (b) Yakura, T.; Omoto, M. *Chem. Pharm. Bull.* **2009**, *57*, 643. (c) Zhou, Z-S; He, X.-H. *Tetrahedron. Lett.* **2010**, *51*, 2480. (d) Uyanik, M.; Yasui, T.; Ishihara, K. *Tetrahedron* **2010**, *66*, 5841. (e) Yusubov, M. S.; Zhdankin, V. V. *Mendeleev Commun.* **2010**, *20*, 185. (f) Dohi, T.; Takenaga, N.; Fukushima, K.; Uchiyama, T.; Kato, D.; Motoo, S.; Fujioka, H.; Kita, Y. *Chem. Commun.* **2010**, *46*, 7697. (g) Uyanik, M.; Ishihara, K. *Aldrichimica Acta* **2010**, *43*, 83. (h) Zhou, Z.; He, X. *Synthesis* **2011**, *2*, 207. (i) Rodriguez, A.; Moran, W. J. *Org. Lett.* **2011**, *13*, 2220. (j) Xu, Y.; Hu, J.; Yan, J. T. *Chin. Chem. Lett.* **2012**, *23*, 891. (k) Uyanik, M.; Mutsuga, T.; Ishihara, K. *Molecules* **2012**, *17*, 8604. (l) Hamamoto, H. *Chem. Pharm. Bull.* **2012**, *60*, 799. (m) List, B. *Topics in Current Chemistry: Asymmetric Organocatalysis*; Springer: Heidelberg, 2010: Vol. 290. (n) Richardson, R. D.; Wirth, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4402. (o) For asymmetric application, see: Uyanik, M.; Okamoto, H.; Yasui, T.; Ishihara, K. *Science* **2010**, *328*, 1376. (p) Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2175.

(2) For reviews, see: (a) Kita, Y.; Dohi, T. *Chem. Commun.* **2009**, 2073. (b) Varvoglis, A. *Tetrahedron* **2010**, *66*, 5739. (c) Dohi, T. *Chem. Pharm. Bull.* **2010**, *58*, 135. (d) Merritt, E. A.; Olofsson, B. *Synthesis* **2011**, *4*, 517. (e) Yusubov, M. S.; Zhdankin, V. V. *Curr. Org. Syn.* **2012**, *9*, 247. (f) Zhdankin, V. V. *J. Org. Chem.* **2011**, *76*, 1185.

(3) Justik, M. W.; Koser, G. *Tetrahedron. Lett.* **2004**, *45*, 6159.

(4) (a) Taylor, E. C.; Conley, R.. A.; Katz, A. H.; McKillop, A. J. *J. Org. Chem.* **1984**, *49*, 3840. (b) McKillop, A.; Swann, B. P.; Taylor, E. C. . *J. Am. Chem. Soc.* **1973**, *95*, 3340. (c) Taylor, E.; McKillop, A. J.; Swann, B. P. *J. Am. Chem. Soc.* **1971**, *93*, 4919. (d) Yamauchi, T.; Nakao, K.; Fuji, K. *J. Chem. Soc., Perkin Trans. 1* **1987**, *6*, 1255.

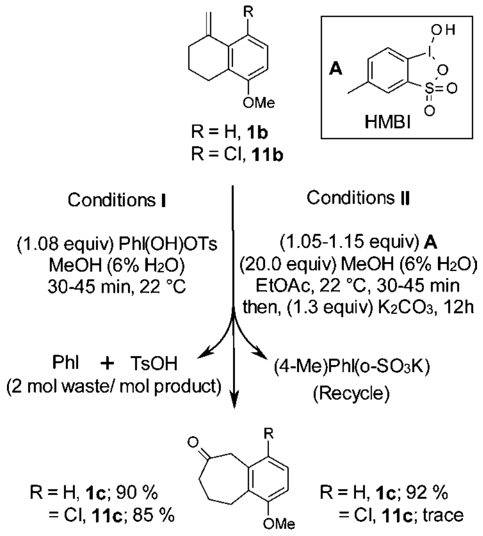
(5) $Tl(NO_3)_3$ is commercially available from Sigma-Aldrich: \$4/g.

(6) *Green Chemistry: Theory and Practice*; Anastas, P. T., Warner, J. C., Eds.; Oxford University Press: New York, 2000; pp 1−129.

10.1021/ol400432x

nitrate to give **1c**. As this program advanced, an alternative to thallium was required. Application of Koser's stoichiometric conditions[3] using hydroxytosyloxy iodobenzene and MeOH (95%) provided the initial entry into the oxidative shift of exocyclic olefin **1b** to the *β*-aryl ketone **1c**. Introducing a para-chloro substituent also resulted in corresponding ring-expanded **11c** in good yields.[7]

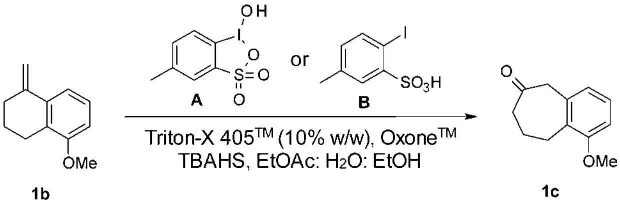
Scheme 1. Stoichiometric Conditions for **1b** and **11b**



Silica gel chromatographic purification of the reaction byproducts PhI and TsOH was difficult (Scheme 1, conditions I). Therefore, attempts were made using a water-soluble analogue of HTIB. We recognized that the application of 1*H*-1-5-methyl-1,2,3-benziodoxathiole-3,3-dioxide (HMBI, **A**)[8] in this transformation could allow for the direct removal of the reduced iodosulfonic acid by precipitation or pH adjustment of the reaction mixture (Scheme 1, conditions II). Gratifyingly, upon consumption of **1b** followed by the introduction of K_2CO_3, **1c** was isolated in high yields (>95% HPLC purity).[9] Interestingly, attempts to convert **11b**→**11c** using stoichiometric **A** failed under a variety of conditions (e.g., various proton sources, temperatures, and solvents). Although HMBI was a suitable reagent for the conversion of **1b**→**1c**, drawbacks associated with constraints on stoichiometry and availibility for large-scale applications prompted us to probe the catalytic manifold on olefin **1b**. Presumably, both substoichiometric HMBI (**A**) or precatalyst 4-Me-IBS (**B**) should facilitate the transformation.

At the outset, Oxone[10] was chosen as a terminal oxidant in a EtOAc/water biphasic system using tetrabutylammonium hydrogensulfate (TBAHS, 15 mol %) and Triton X-405[11] as phase transfer promoters at 35 °C.[12] Gratifyingly, substoichiometric quantities of **A** and **B** gave promising results. The early result using 20 mol % of **A** gave an 84% assay yield and 76% isolated yield of **1c** after column chromatography (Table 1, entry 3).

Table 1. Screening for Catalytic Conditions



entry[a]	reagent (equiv)	Oxone (equiv)	time (h)	% conversion[k]	% yields **1c**[l]
	A				
1	1.05[b]		17	85	65
2	0.2	0.85	24	75	71
3	0.2	0.95	22	ND	84 (76)[c]
	B				
4		1.05	4	1.5	ND
5	0.2	1.1	40	83	54
6	0.4	1.05	18	95	72
7	0.4[d]	1.05	4	18	18
8	0.4[e]	1.05	4	67	67
9	0.4[e,f]	1.1	1	89	73
10	0.10[e,g]	1.1	1	65	55
11	0.10[e,h]	1.1	2	20	20
12	0.125[e,i]	0.6	1	72	64
13	0.125[e,j]	0.65	17	74	71

[a] Unless indicated, all reactions were performed with 15 mol % of TBAHS, at 35 °C in EtOAc/H_2O (1:1). [b] 100 mol % of TBAHS, 22 °C. [c] Isolated by column chromatography. [d] No Triton-X added. [e] No TBAHS. [f] 10.0 equiv of EtOH, 70 °C. [g] 5.0 equiv of EtOH, *c* 0.125 w/v, 70 °C. [h] No H_2O, 10.0 equiv of EtOH, 50 °C. [i] 0.125 w/v, 10.0 equiv of EtOH, 50 °C. [j] 0.125 w/v, 10.0 equiv EtOH, 22 °C. [k] HPLC area percent conversion. [l] Numbers in parentheses indicate weight-based solution yields. See Supporting Information for details.

We studied the catalytic conditions in the absence of **B** and confirmed that no appreciable background reaction occurred with Oxone (entry 4). However, in the presence of 20 mol % of **B**, nearly complete conversion to the product could be obtained after 40 h (entry 5). A similar conversion profile was observed with almost twice the rate with slightly higher yields using 40 mol % of **B** (entry 6). Control experiments indicated that the role of surfactant Triton-X

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(7) Ring expansion of substrates **1b** and **11b** with HTIB was performed on a 2 and 10 g scale, respectively.

(8) (a) Koser, G. F.; Sun, G.; Porter, C. W.; Youngs, W. J. *J. Org. Chem.* **1993**, *58*, 7310. (b) Justik, M. W. *Tetrahedron Lett.* **2007**, *48*, 3003.

(9) Control experiments indicated that MeOH was essential and only trace turnover could be obtained in H_2O as the solvent even at 50 °C.

(10) For use of Oxone in phase transfer catalysis, see: (a) Denmark, S. E.; Forbes, D. C.; Hays, D. S.; DePue, J. S.; Wilde, R. G. *J. Org. Chem.* **1995**, *60*, 1391. (b) Aggarwal, V. K.; Lopin, C.; Sandrinelli, F. *J. Am. Chem. Soc.* **2003**, *125*, 4229. (c) Trost, B.; Braslau, R. *J. Org. Chem.* **1988**, *53*, 532. (d) Travis, B. R.; Ciaramitaro, B. P.; Borhan, B. *Eur. J. Org. Chem.* **2002**, 3429.

(11) (a) Bhattacharya, A.; Purohit, V. C.; Rinaldi, F. *Org. Process Res. Dev.* **2003**, *7*, 254. (b) Bhattacharya, A.; Purohit, V. C.; Suarez, V.; Tichkule, R.; Parmer, G.; Rinaldi, F. *Tetrahedron Lett.* **2006**, *47*, 1861.

(12) Typical exotherm for the stoichiometric conditions was 10 °C using HTIB, and therefore, entries 4–9 were conducted at this temperature.

was significant for acceptable rate of reaction; however, TBAHS was not required (entries 7 and 8). Introducing slightly higher amounts of ethanol (up to 10 equiv) as an additive at 70 °C gave significant consumption of **1b**, but with higher level of impurities (entry 9 vs 10). Interestingly, 12.5 mol % of **B** at ambient temperatures proved to be optimal in achieving balance between reaction rate and stoichiometry of the precatalyst (entry 13 vs 12).

Next, a survey of cosolvent systems including MTBE, acetonitrile, and *i*-PrOAc along with ethanol or isopropyl alcohol as additives was performed (Table 2). MTBE and isopropyl alcohol (7.5 equiv, > 98% conversion) gave the best results, controlling the total amount of low level impurities to less than 10% after workup (entry 4). With optimized reaction conditions, a chromatography-free procedure to isolate pure, homobenzylic ketone was developed through the direct isolation of the corrresponding crystalline bisulfite salt **1c′** (Scheme 2).[13] Subsequent hydrolysis then gave pure **1c** in consistent yields with no additional purification required.

Table 2. Catalytic Conditions: Solvent and Additive Effects

entry[a]	solvent	time (h)	% conversion (% yields) **1c**[b]
1	IPAc/H_2O/EtOH	16	75 (72)
2	CH_3CN/H_2O/EtOH	16	27 (ND)[c]
3	MTBE/H_2O/EtOH	4	88 (79)
4	MTBE/H_2O/*i*-PrOH	3	88 (78)

[a] Unless indicated, all reactions were performed with 12.5 mol % of precatalyst **B**. See Supporting Information for details. [b] HPLC area percent conversion, and numbers in parentheses indicate weight-based solution yields. [c] Not determined.

Scheme 2. Optimized Conditions for Conversion of **1b** to **1c**

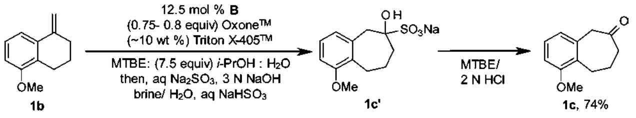
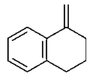
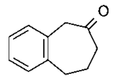
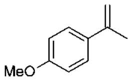
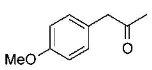
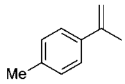
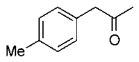
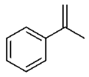
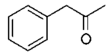
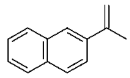
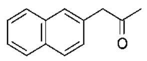
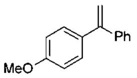
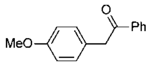
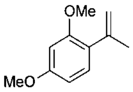
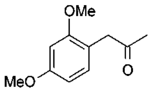
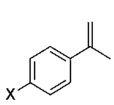
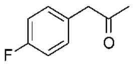
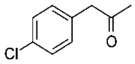
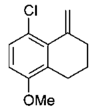
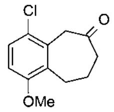
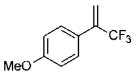
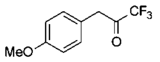
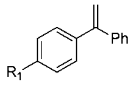
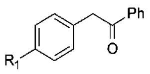
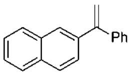
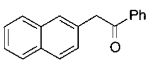
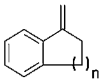
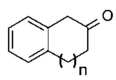


Table 3. Scope of the Oxidative 1,2-Shift

olefin **b**		product **c**		% yields[a]
	**2b**		**2c**	66
	**3b**		**3c**	68
	**4b**		**4c**	67
	**5b**		**5c**	64
	**6b**		**6c**	66
	**7b**		**7c**	81
	**8b**		**8c**	73
	X = F, **9b**		**9c**	47
	X = Cl, **10b**		**10c**	70[b]
	**11b**		**11c**	trace
	**12b**		**12c**	trace
	R_1 = H, **13b**		**13c**	-
	R_1 = Me, **14b**		**14c**	-
	**15b**		**15c**	-
	n = 1, **16b**		**16c**	trace
	n = 3, **17b**		**17c**	trace

[a] Isolated two-step yields using the optimized conditions used for conversion of **1b** to **1c**. [b] Isolated by column chromatography.

While **1b** was used to optimize this novel transformation, various cyclic and acyclic olefins were also used to further define the scope of the reaction.[14] Owing to their similarity with **1b**, olefins containing higher electron density in the ortho or para position of the aromatic ring were initially investigated (**2b**, **3b**, **4b**, **6b**, and **8b**; Table 3). Comparable reaction rates were observed with **3b**, **4b**, and **8b**. Gratifyingly, moderate to good yields of the corresponding ketone products could be obtained from their electron-rich olefinic precursors. Ring expansion of the six-membered ring **2b** worked well by changing the additive to a more acidic and polar CF_3CH_2OH (TFE). This resulted in nearly complete consumption of **2b** after 22 h. Finally, substitutions R = H, Cl, and F on the benzylic olefins

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(13) For large-scale applications. see: (a) Ragan, J. A.; Ende, D. J.; Brenek, S. J.; Eisenbeis, S. A; Singer, R. A.; Tickner, D. L.; Teixeira, J. J.; Vanderplas, B. C.; Weston, N. *Org. Process Res. Dev.* **2003**, *7*, 155. (b) Hirayama, Y.; Ikunaka, M.; Matsumoto, J. *Org. Process Res. Dev.* **2005**, *9*, 30.

(14) Olefins (**1**, **2**, **3**, **7**, **8**, **11**, **16**, **17**)**b** were prepared by Wittig olefination, and all other substrates were obtained commercially. Also see: Ainge, D.; Ennis, D.; Gidlund, M.; Stefinovic, M.; Vaz, L.-M. *Org. Process Res. Dev.* **2003**, *7*, 198and Supporting Information for typical procedure.

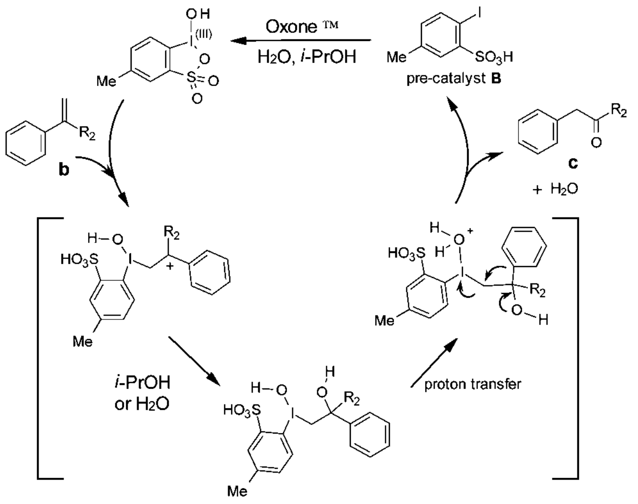
could also be tolerated (**5b**,[15] **9b**, and **10b**). Importantly, the role of the electron-donating methoxy group is clearly seen with **7b** giving complete regioselective 1,2-shift to **7c** in high yields.[16] Isolations of all products were performed by conversion to the bisulfite adduct followed by hydrolysis, negating the need for chromatographic purification.[17] The purity of the homobenzylic ketones isolated via the corresponding bisulfite adducts was >95% by ^{1}H NMR and HPLC.[18]

The scope and limitations for the 1,2-shift were further defined with additional substrates in the study (Table 3, **11b**−**17b**). Interestingly, when electron-donating groups were coupled with the electron-withdrawing substitution, either on the ring (**11b**) or directly substituted on the olefin (−CF_3 group, **12b**), only trace amounts of the product were generated. Note that this result is in contradiction to substrates **9b** and **10b** showing that the location of the electron-withdrawing group plays an important role. Moreover, the failure of olefins **13b**,[19] **14b**, or **15b** also suggests that the regioselective bias for 1,2-shift could depend on steric and electronic factors. Finally, five- and seven-membered ring sized olefins (**16b** and **17b**) provided only trace quantities of the ring expansion products, unlike the six-membered example (**2b**).[20]

Mechanistically, the oxidative 1,2-shift could proceed via either catalytic I(III) or I(V) oxidation states generated in situ by Oxone (Scheme 3). Subsequently, the addition of a hypervalent iodine species[21] across the alkene and the capture of benzylic carbocation with either isopropyl alcohol or water would allow an oxocarbenium-assisted 1,2-phenyl migration under acidic conditions to regenerate the precatalyst.

In summary, the discovery and development of an unprecendented, novel catalytic reaction toward synthesis of homobenzylic ketones was achieved via oxidative 1,2-shift. For cyclic precursors, the oxidative shift results in a formal ketone ring expansion when coupled with a Wittig olefination. This process avoids use of thallium trinitrate salts that are highly toxic with dangerous cumulative effects. This process has been demonstrated on a 20 kg scale for olefin **1b**, providing >97% purity of ketone **1c** after its isolation as the bisulfite adduct. Efforts to expand the application of this catalytic reaction design to other classes of reactions, as well as further mechanistic studies, continue in our laboratory.

Scheme 3. Plausible Mechanism



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Supporting Information Available. General procedures and optimization studies with characterization data for all compounds (^{1}H and ^{13}C NMR spectra). This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] In the case of **5b**, the reaction stalled after 12 h under optimized conditions.

[16] Determined by g-COSY ^{1}H NMR.

[17] Ketone **10c** was isolated using column chromatography.

[18] Bisulfite adducts were hydrolyzed with 2 N HCl/MTBE. See Supporting Information for details.

[19] Only trace reaction was observed with **13b** and **11b** with TFE as an additive. Also, under otherwise catalytic conditions with **13b**, iodobenzoic acid, *p*-iodoanisole, or iodobenzenesulfonic acid as the catalysts, TFE instead of IPA as an additive was ineffective.

[20] For instance, with benzosuberone-derived olefin **17b**, only trace amounts of desired product were detected after 18 h at room temperature or 4 h at 45 °C. On the other hand, indanone-derived olefin **16b** resulted in very fast consumption of the starting material with indiscernible product distribution. Also, iodobenzene as the catalyst or TFE as an additive was also ineffective.

[21] An electron transfer mechanism cannot be ruled out. See: (a) Dohi, T.; Ito, M.; Yamaoka, N.; Morimoto, K.; Fujioka, H.; Kita, Y. *Tetrahedron* **2009**, *65*, 10797. (b) Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684and references cited therein.

The authors declare no competing financial interest.