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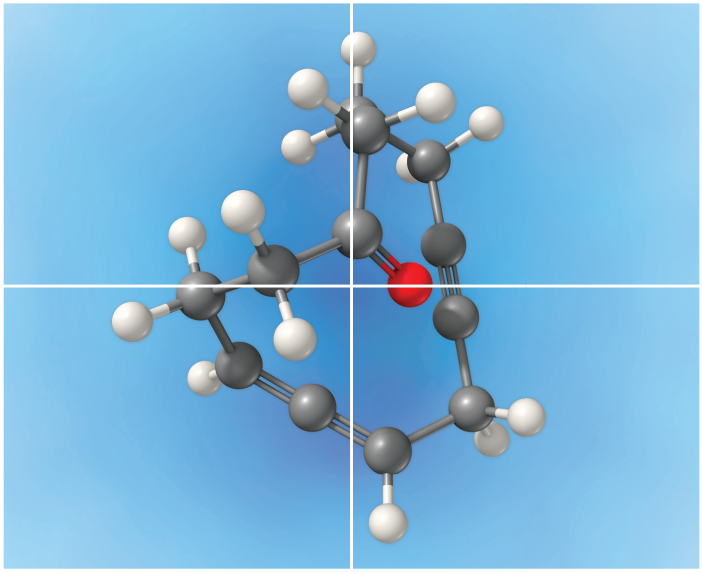

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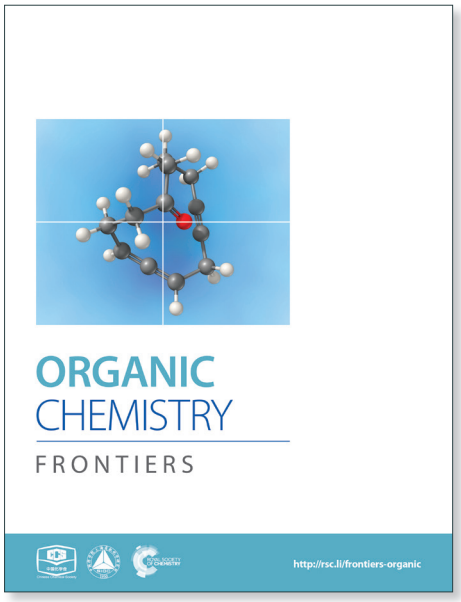

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RESEARCH ARTICLE

Palladium-catalyzed reductive cleavage of tosylated arenes using isopropanol as the mild reducing agent

Cite this: DOI: 10.1039/x0xx00000x

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Received 00th January 2012,
Accepted 00th January 2012

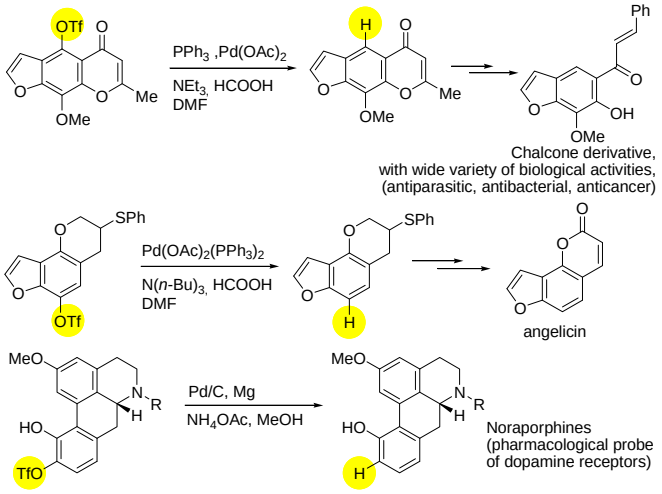
DOI: 10.1039/x0xx00000x

www.rsc.org/

Deoxygenation of tosylated arenes catalyzed by palladium complex is described. This method represents the first general examples of reductive C-O bond cleavage of aryl tosylates *via* palladium catalysis. By simply employing isopropanol as the mild reducing agent, a variety of tosylated arenes can be smoothly reduced. Labelling experiments revealed that the H source originates from isopropanol.

The exploration of catalytic deoxygenation method for alcohols is an important subject for versatile applications to modern chemical syntheses.[1] In particular, the cleavage of $C_{(sp2)}$-O bond from phenolic derivatives remains a challenge due to its intrinsic inertness of the aromatic C-O bond.[2] The robust nature of $C_{(sp2)}$-O bond can be weakened by installing of electron withdrawing group in which it attaches to oxygen. Indeed, one of the most reliable and frequently used protocols for the deoxygenation of phenols is the conversion of phenols to fluorinated sulfonates,[3] such as triflates and nonaflates, followed by nickel- or palladium-catalysed reductive process.[4,5] There have been a number of reported synthetic pharmaceutical intermediates employing this synthetic step (Scheme 1).[6]

New catalyst systems have emerged allowing more difficult aryl sulfonates to be applied in this deoxygenation reaction.[7,8] Aryl tosylates could be deoxygenated mediated by stoichiometric amount of $NiCl_2$-$NaBH_4$ or Raney-Ni/NaOH/H_2(5 atm) systems.[9] Sasaki showed the reduction of aryl mesylate by $NiBr_2(Ph_3P)_2$/dppp as the catalyst, zinc as the reductant and methanol as the hydrogen donor.[10] Lipshutz disclosed that nickel-on-graphite-Ph_3P ($Ni/C_g/Ph_3P$) associated with $Me_2NH{\bullet}BH_3$ could facilitate the catalytic reduction of aryl tosylates and mesylates.[11] The benzthiazole or –CN group-containing substrates were found not compatible under the stated reaction conditions. Sajiki reported that 10 mol% of Pd/C with stoichiometric amount of Mg and NH_4OAc under MeOH promoted the single electron transfer (SET) reductive cleavage of aryl mesylates.[12] Yet, this system indicated that aryl tosylate did not react. To the best of our knowledge, there has been no literature report describing the general palladium-catalysed reductive cleavage of aryl tosylates. Herein, we report a catalytic system, employing isopropanol as the H donor and featuring good functional compatibility, for facile deoxygenation of tosylated arenes.

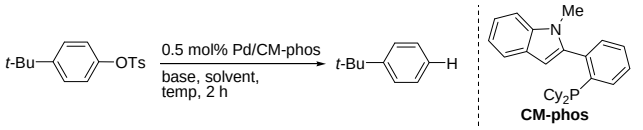


Scheme 1 Selected pharmaceutical examples of using sulfonated precursors in deoxygenation/reduction reaction

We initially tested the feasibility of the reductive cleavage using our developed Pd/CM-Phos system (Table 1).[13] Non-activated 4-*tert*-butylphenyl tosylate was chosen as the prototypical substrate for the deoxygenation reaction. A survey of commonly used inorganic base revealed that K_3PO_4 and K_2CO_3 gave the best results (entries 1-2 and 5). Strong base, e.g. NaO*t*-Bu, led to hydrolysis of aryl tosylate and significant amount of phenolic side products were observed (entry 3). Organic bases such as *i*-Pr_2EtN and Et_3N did not promote the reaction (entries 6-7). Solvent screening indicated that *i*-PrOH

was the solvent of choice (entries 1 *vs* 8-11). In fact, *i*-PrOH serves as both solvent and hydrogen donor in this reaction.

Table 1 Initial screening of the deoxygenation of ArOTs[a]

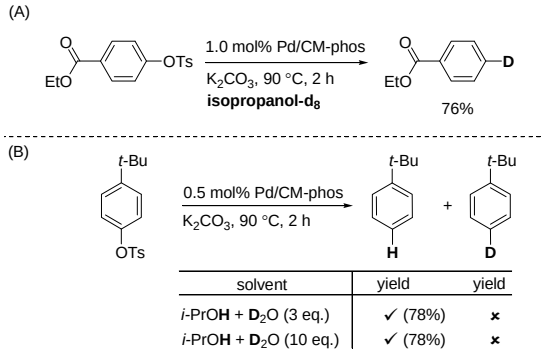


entry	solvent	base	temp. (°C)	yield[b]
1	*i*-PrOH	K_3PO_4	90	88
2	*i*-PrOH	K_2CO_3	90	78
3	*i*-PrOH	NaO*t*-Bu	90	7[c]
4	*i*-PrOH	Na_3PO_4	90	18
5	*i*-PrOH	K_3PO_4•H_2O	90	85
6	*i*-PrOH	*i*-Pr_2EtN	90	trace
7	*i*-PrOH	Et_3N	90	trace
8	MeOH	K_3PO_4	90	4
9	EtOH	K_3PO_4	90	3
10	*t*-BuOH	K_3PO_4	90	trace
11	*t*-AmOH	K_3PO_4	90	12
12	*i*-PrOH	K_3PO_4	70	54
13	*i*-PrOH	K_3PO_4	50	trace
14	*i*-PrOH	K_3PO_4	r.t.	N.R.

[a]Reaction conditions: ArOTs (1.0 mmol), base (3.0 mmol), $Pd(OAc)_2$ (0.005 mmol, 0.5 mol%), CM-phos (0.02 mmol), solvent (3.0 mL) were stirred for 2 hours at indicated temperature under nitrogen. [b]Calibrated GC yields were reported using dodecane as the internal standard. [c]Significant amount of phenolic product was observed.

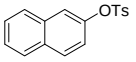
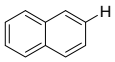
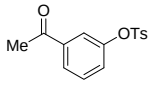
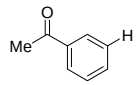
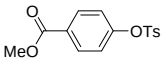
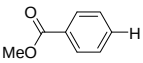
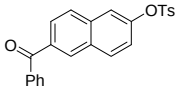
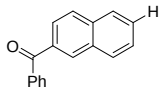
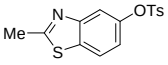
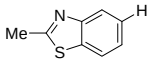
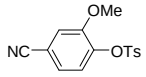
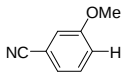
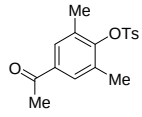
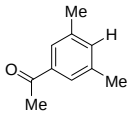
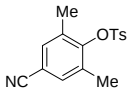
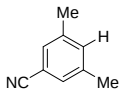
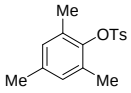
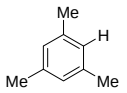
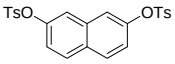
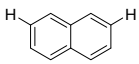
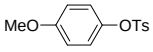
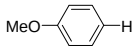
With the optimized reaction conditions in hand,[14] we next investigated the scope of aryl tosylates in deoxygenation reaction (Table 2). In general, this transformation proceeded well at 90 °C in 2 hours. These mild reaction conditions tolerated keto, ester, nitrile and benzothiazolyl groups (entries 3-9), whereas other reducing agents may not fully compatible to them.[15] To expand the substrate scope further, we tested the sterically hindered aryl tosylates (entries 8-10). To our best knowledge, there has been no successful example reported to date using 2,6-disubstituted aryl tosylates in deoxygenation reaction. Electron-rich substrate was reduced smoothly (entry 12).

In order to probe the originality of the H source under this reaction conditions, we performed labelling experiment (Scheme 2). Ethyl 4-tosylbenzoate was deoxygenated under the deuteriated isopropanol medium. The corresponding deuteriated product was obtained in 76% yield (Scheme 2A). Moreover, we attempted to carry out the experiment under the *i*-PrOH/D_2O conditions (Scheme 2B). These results indicated that the hydrogen source was not from the –OH group.



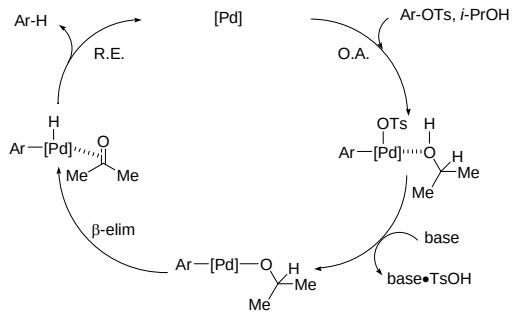
Scheme 2 Labelling experiments of palladium-catalysed deoxygenation of aryl tosylates

Table 2 Palladium-catalyzed deoxygenation of aryl tosylates[a]

entry	ArOTs	ArH	mol% Pd (time)	%yield[b]
1			0.5 (2 h)	82
2			1.0 (2 h)	81
3			0.5 (2 h)	81
4			0.5 (2 h)	82
5			1.0 (2 h)	86
6			1.0 (2 h)	86
7			2.0 (2 h)	86
8[c]			2.0 (24 h)	82
9[c]			2.0 (24 h)	82
10[c]			4.0 (24 h)	72[d]
11			2.0 (2 h)	77
12			1.0 (2 h)	70[d]

[a]Reaction conditions: ArOTs (1.0 mmol), K_2CO_3 (3.0 mmol), $Pd(OAc)_2$ (0.005-0.04 mmol, 0.5-4.0 mol%), CM-phos (Pd:L = 1:4) and *i*-PrOH (3.0 mL) were stirred at 90 °C for indicated period of time under nitrogen. [b]Isolated yields were reported. [c]Reactions were performed at 110 °C. [d]Only determined by GC-FID, yield accorded to GC-FID using authentic sample calibration.

The proposed mechanism is shown in Scheme 3. Aryl tosylate is oxidatively added to the palladium complex.[16] Abstraction of TsOH by inorganic base generates the isopropoxy-palladium species. This intermediate undergoes β-hydride elimination to afford the corresponding aryl-palladium-hydride complex. Reductive elimination gives the deoxygenated product and regenerates the palladium catalyst.



Scheme 3 Proposed mechanism for the deoxygenation of ArOTs under isopropanol

Conclusion

In summary, we have succeeded in showing the first general examples of deoxygenation of aryl tosylates under palladium catalyst system. With the aid of the mild reaction conditions, a number of functional groups are tolerated, including keto, ester, nitrile and benzthiazolyl groups. Particularly noteworthy is that the Pd/CM-phos complex can even promote the difficult deoxygenation of sterically hindered 2,6-disubstituted aryl tosylates smoothly. In fact, there has been no example reported so far for this type of substrate either in Ni or Pd system. The deuterium-labelling experiments show the possibility for incorporating ^{2}H-atom to the aromatic ring, through aryl tosylate pathway at a later stage of the synthetic sequence.[17] Further study of this reaction towards pharmaceutical intermediate synthesis is currently underway.

Acknowledgement

We thank the Research Grants Council of Hong Kong (CRF: PolyU5014/10P). F.Y.K. thanks to the Croucher Foundation for the Croucher Senior Research Fellowship 2013. Grateful to Ms. Pui Ying Choy for her assistance in Supplementary Material preparation.

Notes and references

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†Electronic Supplementary Information (ESI) available: Detailed experimental procedures and spectral data. See DOI: 10.1039/c000000x/

General Procedures: $Pd(OAc)_2$ and CM-phos (Pd:L = 1:4, Pd loading as indicated) were loaded into a Schlenk tube (30 mL) equipped with a Teflon-coated magnetic stir bar (4 × 10 mm). The tube was evacuated and flushed with nitrogen for three times. Precomplexation was applied by adding freshly distilled dichloromethane (~1 mL) and Et_3N (100 μL) into the tube. The solution was stirred and warmed using a hair drier for about 1 to 2 minutes until the solvent started boiling. The solvent was then evaporated under a high vacuum. Aryl tosylates (1.0 mmol), K_2CO_3 (3.0 mmol) were loaded into the tube, and the system was further evacuated and flushed with nitrogen for three times. *iso*-Propanol (3.0 mL) was then added. The tube was stirred at room temperature for several minutes and then placed into a preheated oil bath (90 °C) for the time period as indicated in Tables. After completion of reaction as judged by GC analysis, the reaction tube was allowed to cool to room temperature and quenched with water and diluted with EtOAc. The organic layer was separated and the aqueous layer was washed with EtOAc. The filtrate was concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel (230-400 mesh) to afford the desired product.

1 For a recent review, see: (*a*) J. M. Herrmann and B. Konig, *Eur. J. Org. Chem*. 2013, 7017; for book chapters, see: (*b*) M. Beller and C. Bolm, *Transition metals for organic synthesis: building blocks and fine chemicals*, Wiley-VCH, Weinheim, 2nd Ed., 2004, vol. 1-2; (*c*) A. de Meijere and F. Diederich, Eds., *Metal-catalyzed cross-coupling reactions*, Wiley-VCH, Weinheim, 2nd Ed., 2004, vol. 1-2.

2 (*a*) M. B. Smith, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, John Wiley & Sons: Hoboken, NJ., 7th Ed., 2013. For recent reviews, see: (*b*) B.-J. Li, D.-G. Yu, C.-L. Sun and Z.-J. Shi, *Chem. Eur. J*. 2011, **17**, 1728; (*c*) B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg, V. Percec, *Chem. Rev*. 2011,**111**, 1346; (*d*) C. M. So and F. Y. Kwong, *Chem. Soc. Rev*. 2011, **40**, 4963.

3 For reviews about aryl triflates as synthetic precursors in coupling reactions, see: (*a*) P. J. Stang, M. Hanack and L. R. Subramanian, *Synthesis* 1982, 85; (*b*) K. Ritter, *Synthesis* 1993, 735.

4 For selected nickel catalyst systems, see: (*a*) K. Sasaki, M. Sakai, Y. Sakakibara and K. Takagi, *Chem. Lett*. 1991, 2017; (*b*) L. R. Subramanian, A. G. Martinez, A. H. Fernandez and R. M. Alvarez, *Synthesis* 1984, 481.

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6 For selected examples, see: (*a*) Y.-G. Si, M. P. Gardner, F. I. Tarazi, R. J. Baldessarini and J. L. Neumeyer, *J. Med. Chem*. 2008, **51**, 983; (*b*) J. Cianci, J. B. Baell, B. L. Flynn, R. W. Gable, J. A. Mould, D. Paul and A. J. Harvey, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 2055; (*c*) G. A. Peterson, F.-A.; Kunng, J. S. McCallum and W. D. Wulff, *Tetrahedron Lett.* 1987, **28**, 1381; (*d*) S. Megati, S. E. Ealick, F. N. M. Naguib, M. H. el Kouni, R. S. Klein and B. A. Otter, *Nucleosides Nucleotides* 1994, **13**, 2151.

7 Besides sulfonated phenols, Ar-OR (R = alkyl) substrates were recently found to be deoxygenated by nickel catalyst systems, using $HSiMe(OMe)_2$ or H_2 as the reducing agents, see: (*a*) M. Tobisu, K. Yamakawa, T. Shimasaki and N. Chatani, *Chem. Commun.* 2011, **47**, 2946; (*b*) a) A. G. Sergeev and J. F. Hartwig, *Science* 2011, **332**, 439; (*c*) A. G. Sergeev, J. D. Webb and J. F. Hartwig, *J. Am. Chem. Soc.* 2012, **134**, 20226.

8 Aryl tosylates are far more inexpensive when compared with the corresponding aryl triflates, in terms of attaining the precursors from phenols. The suggested prices of the sulfonating agents are: Tf_2O, approx. USD$1.3/gram; TsCl, approx. USD$0.042/gram from commercial suppliers.

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