

## Palladium catalysed aryl enol ether synthesis from vinyl triflates†

Michael C. Willis,\*<sup>a</sup> Dawn Taylor<sup>a</sup> and Adam T. Gillmore<sup>b</sup><sup>a</sup> Department of Chemistry, University of Bath, Bath, UK BA2 7AY. E-mail: m.c.willis@bath.ac.uk; Fax: (44) 01225 386231; Tel: (44) 01225 386568<sup>b</sup> Chemical Research and Development Department, Pfizer Global Research and Development, Sandwich, Kent, UK CT13 9NJ

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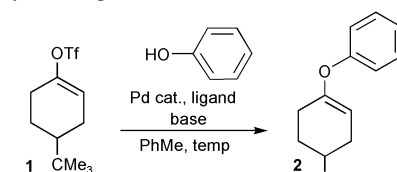
Vinyl triflates can be efficiently converted into the corresponding aryl enol ethers by treatment with a phenol, NaO<sup>t</sup>Bu and a catalyst generated from Pd<sub>2</sub>(dba)<sub>3</sub> and 2-(di-<sup>t</sup>Bu-phosphino)biphenyl.

Enol ethers are useful functional groups for exploitation in synthesis and find use in a range of processes, for example they function as nucleophiles in ene and aldol-type additions,<sup>1</sup> as acyl anion equivalents,<sup>2</sup> Diels–Alder dienophiles<sup>3</sup> and as monomers in the production of oxygen containing vinyl polymers.<sup>4</sup> Traditional methods for their preparation include the *O*-alkylation of enolates,<sup>5</sup> Wittig alkenylation employing *O*-substituted phosphoranes,<sup>6</sup> titanium mediated alkenylation of carboxylic esters,<sup>7</sup> the addition of alcohols to acetylenes<sup>8</sup> and dehydrohalogenation of 2-haloethyl ethers.<sup>9</sup> The synthesis of aryl enol ethers is particularly challenging and the methods for their preparation are more limited, with transvinylation procedures being generally the most useful.<sup>10</sup> Such methods are limited by the availability of suitable vinyl ether donors, with ethyl vinyl ether and acyl vinyl ether being the most commonly employed. A solution to this difficulty that would allow a variety of substituted aryl enol ethers to be prepared would be to employ ketone enolates or their equivalents directly in the aryl ether forming step. Here we describe our studies towards this goal, based on the development of a route employing readily available vinyl triflates as substrates that allows, for the first time, the palladium catalysed synthesis of vinyl C–O bonds, to deliver functionalised aryl enol ethers in good to excellent yields.

The palladium catalysed synthesis of aryl C–N and C–O bonds has emerged as a powerful synthetic tool with catalysed C–N bond formations in particular being employed in a wide variety of processes.<sup>11</sup> Recently, palladium catalysed alkenyl C–N bond formations have also been documented<sup>12</sup> although to the best of our knowledge the corresponding alkenyl C–O syntheses are yet to be reported.<sup>13</sup> Such a bond construction employing alkenyl triflates as substrates in combination with phenols as the coupling partners represents an appealing route to aryl enol ethers (Scheme 1). The ability to selectively prepare the required alkenyl triflates from the corresponding ketones in a predictable and high yielding manner presents these compounds as particularly attractive substrates to study.

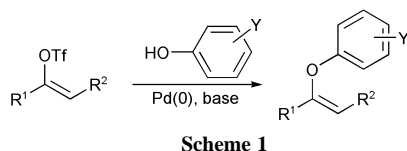
To investigate the proposed synthesis we chose to use 4-*tert*-butylcyclohexanone derived triflate **1** as our initial coupling partner in combination with phenol. Coupling conditions were based on those reported for aryl C–O systems and on those developed for alkenyl C–N bond formation. Palladium catalysts generated from electron rich biphenyl ligands **3** have been

shown to be particularly effective in C–X bond forming reactions and presented an ideal starting point for our investigation.<sup>14</sup> Employing a catalyst generated from Pd(OAc)<sub>2</sub> and ligand **3a** in combination with NaO<sup>t</sup>Bu in toluene at 80 °C delivered 11% of the expected enol ether, while exchanging the base to K<sub>3</sub>PO<sub>4</sub> or Cs<sub>2</sub>CO<sub>3</sub> under the same conditions failed to produce any coupling (entries 1–3, Table 1). Replacing the palladium source with Pd<sub>2</sub>(dba)<sub>3</sub> had a positive effect on the efficiency of the process; used in combination with ligand **3a** and NaO<sup>t</sup>Bu, 64% of the desired enol ether was produced (entry 4). Employing the weaker bases, K<sub>3</sub>PO<sub>4</sub> and Cs<sub>2</sub>CO<sub>3</sub>, was again less effective (entries 5 and 6). Alternative electron rich phosphine ligands **3b**, **3c**, P(<sup>t</sup>Bu)<sub>3</sub> and BINAP were also evaluated using the Pd<sub>2</sub>(dba)<sub>3</sub> and NaO<sup>t</sup>Bu system although all were found to deliver less effective catalysts than that obtained using ligand **3a** (entries 7–10). We had previously found that a complex generated from Pd(OAc)<sub>2</sub> and BINAP was the most effective catalyst for related enamine syntheses *via* C–N bond formation,<sup>12d</sup> however when this catalyst was applied to the present system no product was obtained (entry 11). All of the entries described so far employed 2 mol% palladium and 3 mol% ligand; in entry 12 the ligand loading was increased to 6 mol% with no effect on the amount of enol ether being produced. Increasing the loadings to 3 mol% Pd and 9 mol% of ligand **3a** increased the amount of enol ether to 74% (entry 13). Reducing the temperature to 50 °C had a dramatic effect on the

Table 1 Catalyst/base optimisation<sup>a</sup>


Entry	Catalyst	Ligand	Base	Temp./ °C	Time/h	Conv. <sup>b</sup> (%)
1	Pd(OAc) <sub>2</sub>	<b>3a</b>	NaO <sup>t</sup> Bu	80	20	11
2	Pd(OAc) <sub>2</sub>	<b>3a</b>	K <sub>3</sub> PO <sub>4</sub>	80	24	0
3	Pd(OAc) <sub>2</sub>	<b>3a</b>	Cs <sub>2</sub> CO <sub>3</sub>	80	24	0
4	Pd <sub>2</sub> (dba) <sub>3</sub>	<b>3a</b>	NaO <sup>t</sup> Bu	100	24	64
5	Pd <sub>2</sub> (dba) <sub>3</sub>	<b>3a</b>	K <sub>3</sub> PO <sub>4</sub>	100	24	45
6	Pd <sub>2</sub> (dba) <sub>3</sub>	<b>3a</b>	Cs <sub>2</sub> CO <sub>3</sub>	100	20	2
7	Pd <sub>2</sub> (dba) <sub>3</sub>	<b>3b</b>	NaO <sup>t</sup> Bu	100	24	0
8	Pd <sub>2</sub> (dba) <sub>3</sub>	<b>3c</b>	NaO <sup>t</sup> Bu	100	24	0
9	Pd <sub>2</sub> (dba) <sub>3</sub>	P( <sup>t</sup> Bu) <sub>3</sub>	NaO <sup>t</sup> Bu	100	20	51
10	Pd <sub>2</sub> (dba) <sub>3</sub>	BINAP	NaO <sup>t</sup> Bu	100	20	0
11	Pd(OAc) <sub>2</sub>	BINAP	Cs <sub>2</sub> CO <sub>3</sub>	80	20	0
12 <sup>c</sup>	Pd <sub>2</sub> (dba) <sub>3</sub>	<b>3a</b>	NaO <sup>t</sup> Bu	100	20	64
13 <sup>c</sup>	Pd <sub>2</sub> (dba) <sub>3</sub>	<b>3a</b>	NaO <sup>t</sup> Bu	100	20	74
14 <sup>d</sup>	Pd <sub>2</sub> (dba) <sub>3</sub>	<b>3a</b>	NaO <sup>t</sup> Bu	50	22	11
15 <sup>d,e</sup>	Pd <sub>2</sub> (dba) <sub>3</sub>	<b>3a</b>	NaO <sup>t</sup> Bu	100	20	95
16 <sup>e</sup>	—	—	NaO <sup>t</sup> Bu	100	24	0

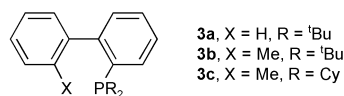
<sup>a</sup> Conditions: triflate (1.0 equiv.), phenol (1.2 equiv.), base (1.4 equiv.), Pd cat. (2 mol%), ligand (3 mol%). <sup>b</sup> Measured by <sup>1</sup>H NMR. <sup>c</sup> 2 mol% cat, 6 mol% ligand. <sup>d</sup> 3.0 mol% cat., 9.0 mol% ligand. <sup>e</sup> Phenol (1.5 equiv.), base (1.75 equiv.).



Scheme 1

† Electronic supplementary information (ESI) available: experimental. See <http://www.rsc.org/suppdata/cc/b3/b307574e/>

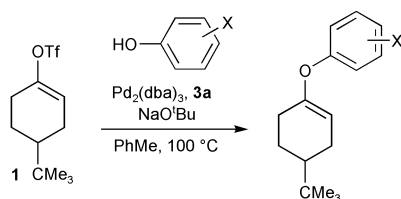
reaction with the conversion being lowered to only 11% (entry 14). Finally, increasing the equivalents of phenol from 1.2 to 1.5 and of the base from 1.5 to 1.75 increased the conversion to enol ether to 95% (entry 15). A blank reaction conducted under these optimised conditions but excluding any catalyst produced no reaction (entry 16).



With optimised conditions in hand we next evaluated the reaction with respect to phenol substitution (Table 2).<sup>15,16</sup> The 95% conversion obtained using phenol as the coupling partner translated to a 85% isolated yield of the pure enol ether (entry 1). *p*-Methyl and <sup>t</sup>Bu substituents are tolerated well (entries 2 and 4) as is a *m*-<sup>t</sup>Bu group (entry 5). The presence of an *o*-methyl group drastically reduced the efficiency of the process with only 34% of the corresponding enol ether being isolated (60% conversion, entry 3). Electron rich phenols participate well with both *p*- and *m*-methoxy substituted phenols providing conversions of 98% and 100% respectively (entries 6 and 7); the low isolated yields obtained for these two substrates reflects the instability of the products to purification. The *o*-substituted isomer of this substrate was again less efficient (entry 8). An acyl group was selected as a typical electron withdrawing substituent; both *p*- and *m*-substituted phenols delivered the predicted enol ethers with good conversions while the *o*-substrate again showed poor reactivity (entries 9–11). The reaction was also shown to tolerate secondary amine, nitro and chloro substituents with the expected products obtained with good conversions and good to moderate yields in all cases (entries 12–14). Finally, an *o*-fluoro substituent could also be included with the corresponding enol ether being obtained in 85% yield (entry 15).

Variation in the structure of the alkenyl triflate was also tolerated well, with triflates derived from acetophenone and tetralone both delivering the desired enol ether adducts in good yields (Table 3). To demonstrate the preparative utility of the developed methodology the coupling of triflate **1** with phenol was conducted on a 1 g (3.5 mmol) scale using 3 mol%

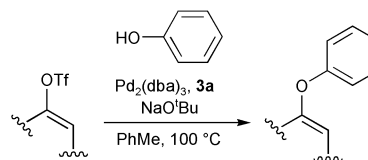
**Table 2** Phenol scope<sup>a</sup>



Entry	Phenol	Time/h	Conv. <sup>b</sup> (%)	Yield <sup>c</sup> (%)
1	phenol	20	95	85
2	4-Me	23	100	83
3	2-Me	23	60	34
4	4- <sup>t</sup> Bu	22	100	98
5	3- <sup>t</sup> Bu	22	100	86
6	4-OMe	22	98	46
7	3-OMe	23	100	37
8	2-OMe	22	30	0
9	4-Ac	22	90	46
10	3-Ac	22	90	60
11	2-Ac	22	0	0
12	3-NMe <sub>2</sub>	23	90	45
13	4-NO <sub>2</sub>	22	95	60
14	4-Cl	23	75	50
15	2-F	23	95	85

<sup>a</sup> Conditions: triflate (1.0 equiv.), phenol (1.5 equiv.), NaO<sup>t</sup>Bu (1.75 equiv.), Pd<sub>2</sub>(dba)<sub>3</sub> (3 mol%), **3a** (9 mol%). <sup>b</sup> Measured by <sup>1</sup>H NMR. <sup>c</sup> Isolated yields of pure material.

**Table 3** Triflate scope<sup>a</sup>



Entry	Substrate	Time/h	Yield (%)
1		22	100
2		48	78

<sup>a</sup> Conditions: substrate (1.0 equiv.), phenol (1.5 equiv.), NaO<sup>t</sup>Bu (1.75 equiv.), Pd<sub>2</sub>(dba)<sub>3</sub> (3 mol%), **3a** (9 mol%).

palladium catalyst. The isolated pure enol ether was obtained in 85% yield (100% conversion).

In summary, a convenient and high yielding route for the preparation of aryl enol ethers has been described. The use of readily available alkenyl triflates in combination with electron rich, electron poor and neutral phenols, allows a variety of substituted enol ethers to be produced. Finally, given the broad utility of enol ethers and the general nature of the described methodology, we anticipate that it should find application in synthesis.

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## Notes and references

- E. Kitazawa, T. Imamura, K. Saigo and T. Mukaiyama, *Chem. Lett.*, 1975, 569.
- J. E. Baldwin, G. A. Höfle and O. W. Lever, Jr., *J. Org. Chem.*, 1974, **96**, 7125.
- D. A. Boger and K. D. Robarge, *J. Org. Chem.*, 1988, **53**, 3373.
- Comprehensive Polymer Science*, ed. G. Allen, Pergamon Press, New York, 1989, vol. 3.
- H. D. Zook and J. A. Miller, *J. Org. Chem.*, 1971, **36**, 1112.
- S. Levine, *J. Am. Chem. Soc.*, 1958, **80**, 6150.
- N. A. Petassis and E. I. Bzowej, *J. Am. Chem. Soc.*, 1990, **112**, 6392.
- H. Christol, H.-J. Cristau and M. Soleiman, *Synthesis*, 1975, 736.
- K. Mizuno, Y. Kimura and Y. Otsuji, *Synthesis*, 1979, 688.
- (a) Y. Okimoto, S. Sakaguchi and Y. Ishii, *J. Am. Chem. Soc.*, 2002, **124**, 1590; (b) W. H. Watannabe and L. E. Conlon, *J. Am. Chem. Soc.*, 1957, **79**, 2828.
- Reviews: (a) J. F. Hartwig, in *Modern Amination Methods*, ed. A. Ricci, Wiley-VCH, Weinheim, 2000; (b) A. R. Muci and S. L. Buchwald, *Top. Curr. Chem.*, 2002, **219**, 131; (c) D. Prim, J.-M. Campagne, D. Joseph and B. Andrioletti, *Tetrahedron*, 2002, **58**, 2041.
- (a) Y. Kozawa and M. Mori, *Tetrahedron Lett.*, 2002, **43**, 111; (b) A. Y. Lebedev, V. V. Izmer, D. N. Kazyul'kin, I. P. Beletskaya and A. Z. Voskoboynikov, *Org. Lett.*, 2002, **4**, 623; (c) J. Barluenga, M. A. Fernández, F. Aznar and C. Valdés, *Chem. Commun.*, 2002, 2362; (d) M. C. Willis and G. N. Brace, *Tetrahedron Lett.*, 2002, **43**, 9085.
- For a recent example of a copper catalysed synthesis of enol ethers from vinyl iodides and alcohols, see: G. Nordmann and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 4978.
- J. P. Wolfe, H. Tomori, J. P. Sadighi, J. Yin and S. L. Buchwald, *J. Org. Chem.*, 2000, **54**, 1158.
- Procedure: Pd<sub>2</sub>(dba)<sub>3</sub> (0.021 mmol, 0.019 g), **3a** (0.063 mmol, 0.018 g) and NaO<sup>t</sup>Bu (1.223 mmol, 0.118 g) were added to a flask containing a phenol (1.049 mmol). The flask was purged with N<sub>2</sub> then dry toluene (5 mL) was added prior to the addition of triflate **1** (0.699 mmol, 0.200 g). After stirring at 100 °C for between 19–24 h the reaction was cooled to rt, diluted with hexane (30 mL), filtered (Celite) and reduced *in vacuo*. The product was purified by flash chromatography (neutral alumina, light petroleum : ethyl acetate) to yield the enol ethers as colourless oils in good to excellent yields.
- See ESI<sup>†</sup> for data for all new compounds.