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Palladium catalysed enamine synthesis from vinyl triflates

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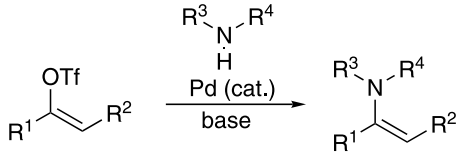
Abstract—Vinyl triflates can be converted into the corresponding enamines by treatment with a secondary amine, Cs_2CO_3 and a catalyst generated from $Pd(OAc)_2$ and *rac*-BINAP.

Enamines are versatile functional groups capable of partaking in a variety of important transformations including regioselective alkylations and acylations, annulation cascades and cycloadditions as well as in a range of heterocycle forming processes.[1] Recently a variety of enamine reactions have been adapted to the solid phase.[2] A further important reaction of enamines is their direct reduction, usually as part of a reductive amination sequence, to provide access to the corresponding amines.[3] Enamines are generally prepared by condensation of a suitable amine and ketone; for less reactive systems acid catalysis is frequently employed.[1] Other notable methods of synthesis include Lewis acid promoted condensations[4] and the use of amine substituted Wadsworth–Emmons reagents.[5] Vinyl and aryl triflates have been shown to be extremely useful coupling partners in a range of palladium catalysed *C–C* bond forming processes, including the well known Stille, Suzuki and Heck reactions.[6] Aryl triflates along with the corresponding aryl halides have recently been exploited in palladium catalysed *C–O* and *C–N* bond forming processes and these new reactions are already proving to be powerful synthetic tools.[7] In an attempt to develop a non acid catalysed route to various enamines we speculated that *vinyl triflates* could function as suitable coupling partners with amines under the action of a palladium catalyst (Scheme 1). Such a route would be complementary to the usual acid promoted enamine syntheses and should find utility when substrate choice necessitates that acid conditions be avoided.[8]



Scheme 1.

To investigate the proposed synthesis we chose to use 4-^{t}butyl cyclohexanone derived triflate **1** as our initial coupling partner in combination with morpholine. Electron rich biphenyl ligands such as **3** have been shown to generate extremely effective catalysts for *C–N* bond formation using aryl substrates.[9] Accordingly we began our investigation using ligand **3a** and a variety of bases (Table 1). Early results indicated that the strong bases KO^{t}Bu and NaO^{t}Bu were optimal, with the weaker Cs_2CO_3 and K_3PO_4 delivering lower amounts of the desired enamine **2** (entries 1–4). Reaction temperature was also shown to be important; the use of ligand **3a** and KO^{t}Bu at 80°C for 24 h resulted in 100% conversion, reducing the temperature to 50°C lowered this to 48% with reaction at room temperature delivering 44% of the enamine (entries 5 and 6). Using KO^{t}Bu for extended reaction times at room temperature was also reasonably effective, providing the required enamine in 77% conversion (entry 7). Variation in ligand structure has been shown to have a significant effect on the efficiency of aryl *C–N* bond formation and we were interested in probing this parameter with respect to our system;[10] a range of alternative electron rich biphenyl ligands, **3b–d**, were investigated with the biphenyldicyclohexylphosphine **3a** still proving optimal (entries 1 and 8–10). In an attempt to uncover as mild conditions as possible these ligand studies were conducted using Cs_2CO_3 as base. Electron rich diphosphines are also known to generate effective catalysts and dppf, BINAP and DPEphos (**4**) were thus investgated.[11] All three diphosphines showed an improvement in conversion over the monophosphines with BINAP being superior, delivering the enamine in 100% conversion after 20 h at 80°C (entries 11–13). Reducing the temperature of the

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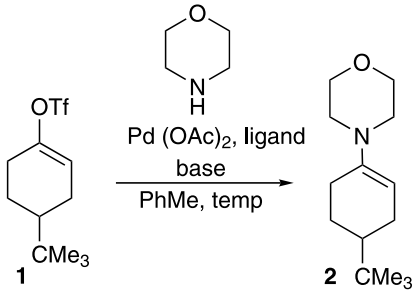
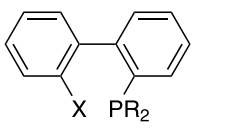
Table 1. Catalyst/base optimisation[a]

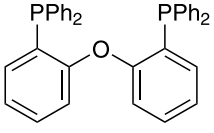


Entry	Ligand	Base	Temp. (°C)	Time (h)	Conv.[b] (%)
1	**3a**	Cs_2CO_3	80	24	28
2	**3a**	K_3PO_4	80	24	14
3	**3a**	KO^{t}Bu	80	24	100
4	**3a**	NaO^{t}Bu	80	24	87
5	**3a**	KO^{t}Bu	50	24	48
6	**3a**	KO^{t}Bu	rt	24	44
7	**3a**	KO^{t}Bu	rt	65	77
8	**3b**	Cs_2CO_3	80	24	20
9	**3c**	Cs_2CO_3	80	24	14
10	**3d**	Cs_2CO_3	80	24	5
11[c,d]	dppf	Cs_2CO_3	80	20	43
12[c,d]	BINAP	Cs_2CO_3	80	20	100
13[c,d]	**4**	Cs_2CO_3	80	20	64
14[c,d]	BINAP	Cs_2CO_3	50	20	7
15[d]	BINAP	KO^{t}Bu	80	20	100
16[d]	BINAP	KO^{t}Bu	rt	20	69
17[e]	-	KO^{t}Bu	80	24	0

[a]Conditions: triflate (1.0 equiv.), amine (2.0 equiv.), base (1.4 equiv.), $Pd(OAc)_2$ (5 mol.%), ligand (10 mol.%); [b]Measured by ^{1}H nmr; [c]2.0 equiv base; [d]7.5 mol% ligand; [e]no $Pd(OAc)_2$.



3a, X = H, R = Cy
3b, X = H, R = ^{t}Bu
3c, X = Me, R = Cy
3d, X = NMe_2, R = Cy



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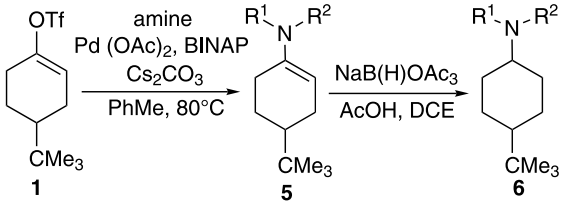
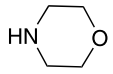
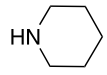
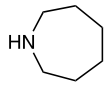
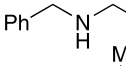
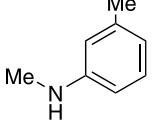
$BINAP/Cs_2CO_3$ system to 50°C lowered the conversion dramatically (7%, entry 14). The effectiveness of BINAP combined with the strong base KO^{t}Bu was also investigated and was found to be efficient at 80°C and at room temperature, providing the enamine in 100% and 69% conversions respectively (entries 15–16). Finally, a control experiment containing all of the reagents, except for the palladium source and ligand, demonstrated the catalyst was crucial to achieve any enamine formation (entry 17).[12]

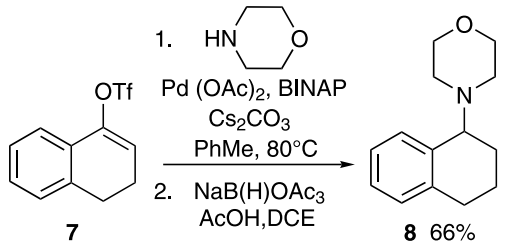
The scope of the process with respect to amine structure was investigated next (Table 2). Optimisation studies (Table 1) had shown that isolation of the enamine products was difficult due to decomposition (hydrolysis), therefore to unequivocally determine that *C–N* bond formation had taken place we elected to reduce the enamines in situ to generate the corresponding amines. Triflate **1** was again employed as our test system and evaluated against a range of secondary amines using the $BINAP/Cs_2CO_3$ conditions developed above.[13] Reaction with morpholine produced the enamine in 100% conversion; direct treatment with $NaB(H)OAc_3$ and acetic acid in DCE produced the corresponding amine in 60% isolated yield (entry 1).[14] Both pyrrolidine and piperidine also performed well, delivering the requisite enamines in 90 and 85% conversions respectively although the reduction products were obtained in moderate yield (entries 2 and 3). Slightly longer reaction times were needed for hexahydroazepine with the amine being isolated in 47% yield after 42 h (entry 4). Increasing the steric bulk of the amine had an adverse effect on the process; reaction with dibenzylamine failed to deliver any enamine product after 48 h at 80°C (entry 5). Pleasingly, reaction with the less nucleophilic *N*-methyl-*m*-toluidine delivered the enamine in 96% conversion and the amine in 49% yield (entry 6).

Table 2. Amine scope[a]

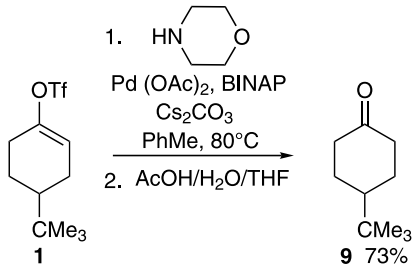


Entry	Amine	Time (h)	conv.[b] to (5) (%)	Yield[c] of (6) (%)
1		20	100	60
2		20	90	34
3		20	85	40
4		42	79	47
5		48	<5	-
6		20	96	49

[a]Conditions: triflate (1.0 equiv.), amine (2.0 equiv.), base (2.0 equiv.), $Pd(OAc)_2$ (5 mol.%), BINAP (7.5 mol.%); [b]Measured by ^{1}H nmr; [c]Isolated yields of pure material.



Scheme 2.



Scheme 3.

The effectiveness of a second vinyl triflate was also examined; reaction of tetralone derived triflate **7** under the standard reaction conditions, followed by direct reduction provided the corresponding enamine in 100% conversion and the isolated amine **8** in 66% yield (Scheme 2).

The direct hydrolysis of enol triflates to the analogous ketones is not a straightforward transformation; direct reaction under either basic or acidic conditions generally results in decomposition.[15] Our observations that the enamines prepared by the palladium catalysed *C–N* bond forming process were prone to hydrolysis presented the possibility of adapting this method to a mild triflate hydrolysis procedure. Triflate **1** was reacted under the standard conditions to provide the corresponding morpholine derived enamine. This was then treated with an acetic acid/water/THF mix to deliver the parent ketone **9** in 73% yield (Scheme 3).

In summary, we have shown that vinyl triflates can undergo palladium catalysed *C–N* bond formation to deliver the corresponding enamines in excellent conversions. Isolation of the enamines proved difficult, however they were successfully reduced in situ to deliver the corresponding amines. Alternatively, the process can be employed as a mild triflate hydrolysis procedure whereby the crude enamines are reacted with aqueous acid to provide the corresponding ketone. These mild methods should find application where acidic conditions must be avoided. Efforts to expand the range of the process and to include vinyl halide substrates are underway and will be reported in due course.

Acknowledgements

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12. Starting triflate recovered in 93% yield.
13. General procedure; To an oven dried flask, $Pd(OAc)_2$ (8 mg, 0.035 mmol) and *rac*-BINAP (33 mg, 0.052 mmol) were added under nitrogen. The flask was flushed with nitrogen, before the triflate (0.70 mmol) and amine (1.40 mmol) were added. The mixture was taken up in dry toluene (1.40 ml) and Cs_2CO_3 (0.45 g, 1.40 mmol) was added. The reaction was stirred at 80°C for 20 h under nitrogen. After cooling, the reaction mixture was diluted with Et_2O (10 ml) and the suspension filtered through a celite pad. The precipitate was washed with Et_2O (20 ml) and the filtrate was reduced in vacuo. The crude product was subjected to ^1H NMR spectroscopy for determination of the percentage conversion to product, or taken immediately into the next reaction.
14. Selected NMR data for isolated amines; Table 2, entry 1: 2:1 mix of diastereomers, major isomer, δ_H ($CDCl_3$, 300 MHz) 0.85 (9H, s), 1.00–1.12 (1H, m), 1.29–1.42 (6H, m), 1.93–2.04 (2H, m), 2.09–2.14 (1H, m), 2.36–2.46 (4H, m),

3.71 (4H, t, *J* 4.5 Hz); minor isomer, δ_H ($CDCl_3$, 300 MHz) 0.84 (9H, s), 0.92–1.09 (3H, m), 1.10–1.26 (2H, m), 1.78–1.88 (2H, m), 1.91–2.02 (2H, m), 2.12 (1H, tt, *J* 11.5 Hz, 3.9 Hz), 2.56 (4H, t, *J* 4.8 Hz), 3.72 (4H, t, *J* 4.8 Hz); entry 2, δ_H ($CDCl_3$, 300 MHz) 0.85 (9H, s), 0.95–1.08 (2H, m), 1.17–1.21 (2H, m), 1.22–1.46 (3H, m), 1.69–1.83 (4H, m), 1.86–1.97 (2H, m), 1.98–2.04 (1H, m), 2.04–2.14 (1H, m), 2.42–2.49 (2H, m), 2.55–2.63 (1H, m); entry 3, δ_H ($CDCl_3$, 300 MHz) 0.85 (9H, s), 1.01–1.12 (1H, m), 1.20–1.31 (2H, m), 1.33–1.45 (4H, m), 1.49–1.62 (4H, m), 1.67–1.77 (2H, m), 1.93–2.04 (2H, m), 2.06–2.12 (1H, m), 2.31–2.42 (3H, m), 2.47–2.56 (1H, m); entry 4, δ_H ($CDCl_3$, 300 MHz) 0.86 (9H, s), 0.91–1.09 (2H, m), 1.26–1.45 (4H, m), 1.51–1.68 (8H, m), 1.74–1.86 (2H, m), 1.86–2.01 (2H, m), 2.57–2.64 (1H, m), 2.66–2.77 (3H, m); entry 6, δ_H ($CDCl_3$, 300 MHz) 0.88 (9H, s), 1.07–1.19 (1H, m), 1.39–1.57 (6H, m), 1.89–1.99 (2H, m), 2.33 (3H, s), 2.82 (3H, s), 3.51–3.59 (1H, m), 6.66 (1H, d, *J* 5.7 Hz), 6.70–6.78 (2H, m), 7.08–7.19 (1H, m). Amine 8; δ_H ($CDCl_3$, 300 MHz) 1.62–1.79 (2H, m), 1.85–2.08 (2H, m), 2.41–2.55 (2H, m), 2.56–2.68 (2H, m), 2.69–2.86 (2H, m), 3.73 (4H, t, *J* 3.9 Hz) 3.75–3.83 (1H, m), 7.00–7.09 (1H, m), 7.09–7.21 (2H, m), 7.70 (1H, d, *J* 6.6 Hz).

15. For a recent example of the indirect conversion of a vinyl triflate to the corresponding ketone, see; Hynes, J., Jr.; Nasser, T.; Overman, L. E.; Watson, D. A. *Org. Lett*. **2002**, *4*, 929.