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A new reactivity pattern for vinyl bromides: *cine*-substitution *via* palladium catalysed C–N coupling/Michael addition reactions†

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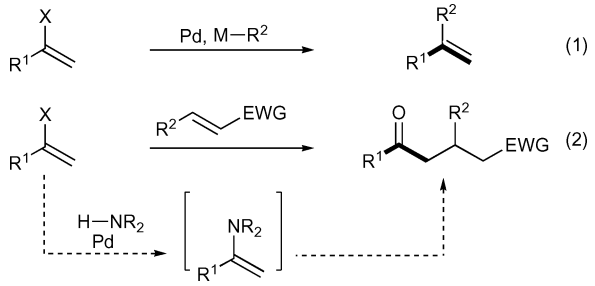
Palladium catalysed C–N bond formation can be used to convert vinyl bromides to the corresponding enamines, which are reacted *in situ* with alkylidene malonates to provide Michael adducts. The overall transformation results in *cine*-substitution of the starting vinyl bromide.

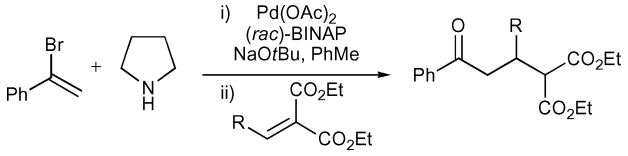
Vinyl halides are versatile functional groups used extensively in a range of transition metal catalysed coupling reactions.[1] In particular a range of palladium catalysed cross-coupling processes such as Stille, Suzuki and Heck reactions all regularly employ vinyl halides (or pseudo halides) as substrates.[2] All of these transformations result in *ipso*-substitution of the original C–X bond to deliver the required cross-coupled products (reaction 1, Scheme 1). Recently, the palladium catalysed C–O and C–N bond forming processes developed by Buchwald and Hartwig for aryl systems[3] are beginning to be transferred to vinyl substrates.[4] The ability to convert vinyl halides to the corresponding enamines and enol ethers has the potential to deliver a new mode of reactivity for these functional groups, resulting from transformations delivering substitution *cine* to the original C–X bond (reaction 2, Scheme 1). In this communication we document how this new reactivity pattern can be achieved using the palladium catalysed conversion of vinyl bromides to the corresponding enamines, which are then reacted *in situ* with alkylidene malonates to deliver Michael addition products (Scheme 1).



Scheme 1 Vinyl bromides as nucleophiles in Michael addition reactions; *ipso*- and *cine*-substitution of vinyl bromides.

The use of enamines in Michael-type additions is well established,[5] and methods to convert vinyl halides[6] and pseudo halides[7] to enamines have also been recently developed; the initial challenge was therefore to identify reaction conditions compatible with both steps of the overall process. We chose to study the reaction of α-bromostyrene with simple alkylidene malonates as our test system.[8] In the event, literature conditions for enamine formation proved optimal; reaction of α-bromostyrene with pyrrolidine and NaO*t*Bu using a catalyst generated from $Pd(OAc)_2$ (1 mol%) and (*rac*)-BINAP in toluene solution at 80 °C resulted in complete conversion to the required enamine. Addition of diethyl ethylidene malonate resulted in the formation of the required Michael adduct in a moderate 31% yield (Table 1, entry 1). The yield of the Michael adduct could be significantly increased (92%) if the reaction temperature was reduced to ambient, concurrent with the addition of the alkylidene malonate (entry 2). This lowering of temperature was needed to limit polymerisation. A variety of alternative catalyst and base combinations were investigated, however all proved to be inferior.[9] The scope of the process with respect to the substitution of the alkylidene malonate was found to be good, with simple alkyl and α- and β-branched substituents delivering adducts in good to excellent yields (entries 3–6). An aryl substituent was also tolerated well (entry 8), however a *tert*-butyl substituent was sufficient to suppress the reaction (entry 7).‡

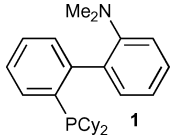
Table 1 The palladium mediated addition of α-bromostyrene to alkylidene malonates[a]



Entry	R	Yield (%)[b]
1[c]	Me	31
2	Me	92
3	*n*Bu	87
4	*i*Bu	83
5	*i*Pr	78
6[d]	Cy	73
7	*t*Bu	0
8	Ph	89

[a] Conditions: α-bromostyrene (1.0 equiv.), pyrrolidine (1.0 equiv.), $Pd(OAc)_2$, (1 mol%), (*rac*)-BINAP (3 mol%), NaO*t*Bu (1.1 equiv.), toluene, 80 °C, 3 h; then alkylidene malonate (1.2 equiv.), rt, 20 h. [b] Isolated yields. [c] Alkylidene malonate added at 80 °C. [d] 2.0 Equiv. of alkylidene malonate used.

Variation of the vinyl bromide component was also tolerated well. Phenyl-, methyl- and *tert*-butyl-substituted styrenes all provided Michael adducts in good yields (entries 1–3, Table 2). Simple alkyl and cyclic-alkyl systems were also shown to be competent substrates (entries 4–6). Finally, we demonstrated that the transformation is not restricted to vinyl bromide substrates and is applicable to alternative halides and pseudohalides: α-chloro- and α-iodosytrene together with the corresponding vinyl triflate all performed well, delivering the required adducts in good yields (Entries 7–10). Although the catalyst generated



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† Electronic supplementary information (ESI) available: characterisation of new compounds. See http://dx.doi.org/10.1039/b508464d

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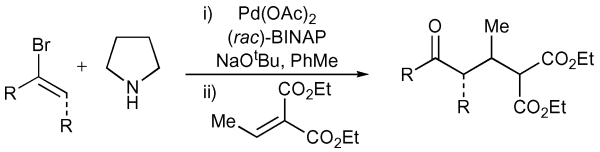
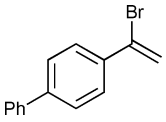
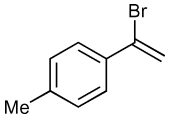
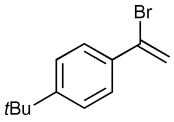
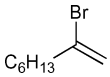
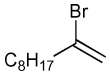
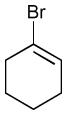
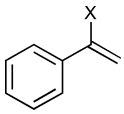
Table 2 Variation of the vinyl bromide component[a]



Entry	Vinyl halide	Yield (%)[b]
1		76
2		81
3		89
4		76
5		80
6		73[c]
7 X = Cl 8[d] X = Cl 9 X = I 10 X = OTf		58 87 77 84

[a] Conditions: vinyl halide (1.0 equiv.), pyrrolidine (1.0 equiv.), $Pd(OAc)_2$, (1 mol%), (*rac*)-BINAP (3 mol%), NaO*t*Bu (1.1 equiv.), toluene, 80 °C; then diethyl ethylidene malonate (1.2 equiv.), rt, 20 h. [b] Isolated yields. [c] Product obtained as a 4 : 1 mixture of diastereoisomers, as determined by ^{1}H NMR spectroscopy. [d] Pd_2dba_3 (1 mol%) and ligand **1** employed (3 mol%).

using (*rac*)-BINAP could be employed with the vinyl chloride example, the amination was considerably slower, resulting in only a 58% yield of the final product (entry 7). A more efficient reaction, producing a 87% yield, could be achieved by the use of biphenyl ligand **1** in combination with Pd_2dba_3 (entry 8).[10]

In summary, we have demonstrated that by using palladium catalysis to convert vinyl halides to enamines, they can be employed as nucleophilic components in a series of Michael addition reactions. A range of alkyl and aryl substituents are tolerated on both the vinyl bromide and alkylidene malonate substrates, to provide substituted Michael adducts in high yield. The ability to unveil a reactive functional group using mild and selective reagents is attractive in both combinatorial[11] and diversity-oriented synthesis.[12] This new reactivity pattern described for vinyl halides, delivering products substituted *cine* to the original C–X bond, should complement the traditional C–C based coupling processes resulting in *ipso*-substitution. This new process has the potential to find application in diversity-oriented synthesis where it is advantageous if a functional group can be transformed into structurally and topologically distinct products using related reactions. Efforts to expand the general process to alternative reactions and to develop asymmetric variants are underway and will be reported in due course.

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Notes and references

‡ General procedure for the addition of α-bromostyrene to alkylidene malonates: A flask was charged with $Pd(OAc)_2$ (3 mg, 0.01 mmol, 1 mol%), (*rac*)-BINAP (19 mg, 0.03 mmol, 3 mol%), toluene (4 mL) under a nitrogen atmosphere and heated to 80 °C until the solution became homogeneous (5 min). The reaction was cooled to rt, α-bromostyrene (130 μL, 1.0 mmol), pyrrolidine (85 μL, 1.02 mmol) and sodium *tert*-butoxide (106 mg, 1.1 mmol) were added and the reaction heated to 80 °C for 3 h. The reaction was cooled to rt, and the alkylidine malonate (1.2–2.0 mmol) in toluene (1 mL) was added, and the reaction was allowed to stir for 20 h at rt. The reaction was quenched with sat. NH_4Cl (1 mL) and partitioned between EtOAc (20 mL) and H_2O (10 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL) and the organic portions combined, washed with H_2O (10 mL), sat. NaCl (10 mL), dried ($MgSO_4$) and reduced *in vacuo*. The residue was purified by column chromatography (SiO_2) to produce the desired compound. See the electronic supplementary information for characterisation of all new compounds.

1 A. De Meijere and F. Diederich, *Metal-catalyzed Cross-coupling Reactions, 2nd edn.*, Wiley-VCH, New York, 2004.
2 *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*, ed. J. Tsuji, Wiley, Chichester, 2004.
3 For recent reviews on Pd catalysed C–O and C–N bond formation, see: (*a*) A. R. Muci and S. L. Buchwald, *Top. Curr. Chem.*, 2002, **219**, 131; (*b*) J. F. Hartwig, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E. Negishi, Wiley, New York, 2002; (*c*) D. Prim, J.-M. Campagne, D. Joseph and B. Andrioletti, *Tetrahedron*, 2002, **58**, 2041–2075.
4 For a recent review on the synthesis of enamines and enol ether using metal mediated coupling reactions, see: J. R. Dehli, J. Legros and C. Bolm, *Chem. Commun.*, 2005, 973–986.
5 (*a*) J. K. Whitesell, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991; (*b*) *Enamines: Synthesis, Structure and Reactions, 2nd edn.*, ed. A. G. Cook, Marcel Decker, New York, 1987; (*c*) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz and R. Terrell, *J. Am. Chem. Soc.*, 1963, **85**, 207–222.
6 (*a*) J. Barluenga, M. A. Fernández, F. Aznar and C. Valdés, *Chem. Commun.*, 2002, 2362–2363; (*b*) J. Barluenga, M. A. Fernández, F. Aznar and C. Valdés, *Chem. Eur. J.*, 2004, **10**, 494–507; (*c*) J. Barluenga, M. A. Fernández, F. Aznar and C. Valdés, *Chem. Commun.*, 2004, 1400–1401; (*d*) J. Barluenga, F. Aznar, P. Moriel and C. Valdés, *Adv. Synth. Catal.*, 2004, **346**, 1697–1701.
7 M. C. Willis and G. N. Brace, *Tetrahedron Lett.*, 2002, **43**, 9085–9088.
8 S. J. Blarer and D. Seebach, *Chem. Ber.*, 1983, **116**, 2250.
9 Weaker bases such as Cs_2CO_3 or K_3PO_4 were not effective. Similarly, the ligands DPEphos and Xantphos delivered no enamine product.
10 D. W. Old, J. P. Wolfe and S. L. Buchwald, *J. Am. Chem. Soc.*, 1998, **120**, 9722–9723.
11 *Molecular Diversity and Combinatorial Chemistry: Principles and Applications*, ed. M. C. Pirrung, Elsevier, 2004.
12 M. D. Burke and S. L. Schreiber, *Angew. Chem., Int. Ed.*, 2004, **43**, 46–58.