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COMMUNICATION

Copper-catalysed addition of α-alkyl azaarenes to ethyl glyoxylate *via* direct C(sp^3)–H activation†

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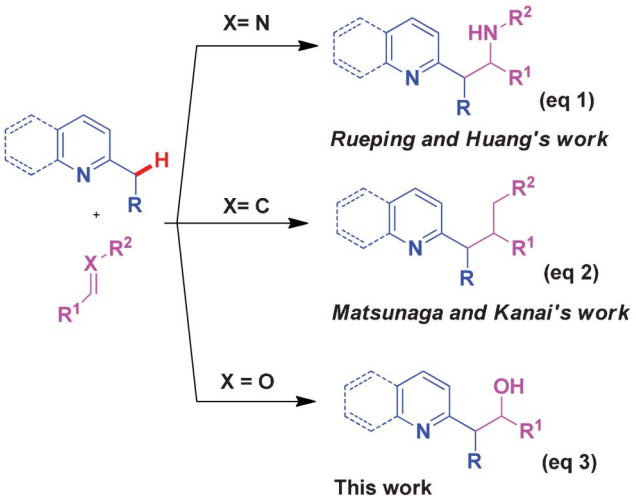
A novel protocol for the copper-catalysed direct C(sp^3)–H bond functionalisation of 2-alkyl azaarenes to C=O double bonds has been developed, which expands the scope of C(sp^3)–H bond activation reactions and provides new access to medicinally important azaarene derivatives.

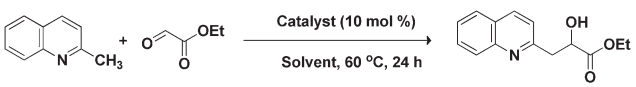
The functionalisation of pyridines and quinolines is a valuable chemical transformation in organic synthesis since derivatives of these aromatic heterocycles can display extremely potent biological, chemical and pharmaceutical properties.[1] The C–H bond functionalisation of pyridines and quinolines[2] is an expedient and atom economical synthetic strategy to access substituted azaarene derivatives. Among them, the direct C(sp^3)–H bond functionalisation of 2-alkyl azaarenes is a challenging synthetic process due to the lower activity of alkyl groups.

Fagnou *et al.* and Charette *et al.* have reported the palladium catalysed C(sp^3)–H activation of 2-alkyl pyridine *N*-oxides[3] and *N*-iminopyridinium ylides[4] through the introduction of an activating group onto the pyridine core to enhance the acidity of the α-H of 2-alkyl pyridine. However, this synthetic strategy requires the modification of substrates and multistep synthetic sequences. Recently, a cluster of reports have appeared on the direct C(sp^3)–H bond functionalisation of 2-alkyl-substituted azaarenes catalysed by palladium and Lewis acid without an activating group.[5–9] For example, Rueping *et al.* and Huang and co-workers reported the addition of α-alkyl azaarenes to the C=N double bond of *N*-sulfonyl aldimines[5a–b,7a](eq 1, Scheme 1). Matsunaga and Kanai and co-workers reported the direct addition of alkyl-substituted azaarenes to the C=C double bonds of enones promoted by Lewis acids[7b] (eq 2, Scheme 1). To the best of our knowledge, the addition of 2-alkyl azaarenes to C=O double bonds catalysed by Lewis acids has not been reported. To address this apparent gap in synthetic capability it was reasoned that the addition of α-alkyl azaarenes to C=O double



Scheme 1 C(sp^3)–H bond functionalisation with different double bond containing electrophiles.

Table 1 Optimisation of the reaction conditions[a]



Entry	Catalyst	Solvent	Ligand	Yield/%[b]
1	CuI	THF	1,10-phenanthroline	68
2	CuBr	THF	1,10-phenanthroline	65
3	CuCl	THF	1,10-phenanthroline	60
4	CuCN	THF	1,10-phenanthroline	72
5	$Cu(OTf)_2$	THF	1,10-phenanthroline	94
6[c]	$Cu(OTf)_2$	THF	1,10-phenanthroline	75
7	$Cu(OTf)_2$	DMF	1,10-phenanthroline	50
8	$Cu(OTf)_2$	dioxane	1,10-phenanthroline	35
9	$Cu(OTf)_2$	toluene	1,10-phenanthroline	43
10	$Cu(OTf)_2$	*i*-PrOH	1,10-phenanthroline	55
11	$Cu(OTf)_2$	CH_2ClCH_2Cl	1,10-phenanthroline	28
12	$Cu(OTf)_2$	THF	none	78
13	$Cu(OTf)_2$	THF	dppp	72

[a] Unless otherwise stated, all reactions were carried out with **1a** (0.6 mmol), **2** (0.2 mmol), ligand (5 mol%), solvent (0.8 mL) in a Schlenk tube at 60 °C for 24 h. [b] Isolated yield. [c] 5 mol% $Cu(OTf)_2$ was used.

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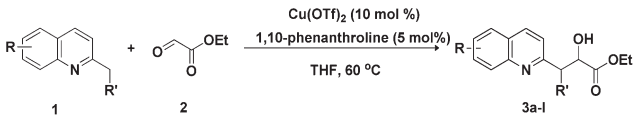
[b]*School of Chemistry and Chemical Engineering, Henan Institute of Science and Technology, Xinxiang, 453003, China*
[c]*School of Chemistry, University of Birmingham, Edgbaston, Birmingham, West Midlands, B15 2TT, UK. E-mail: j.s.fossey@bham.ac.uk*
† Electronic Supplementary Information (ESI) available: Experimental procedures, compound characterizations, and copies of the ^{1}H NMR and ^{13}C NMR spectra. See DOI: 10.1039/c2ra20627g

Table 2 The 2-alkyl quinoline's substituent scope [a]



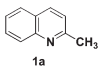
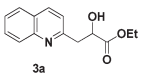
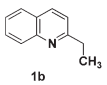
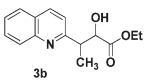
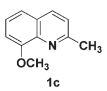
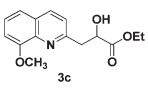
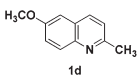
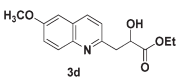
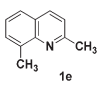
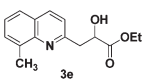
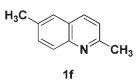
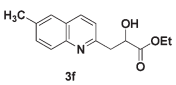
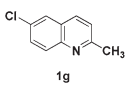
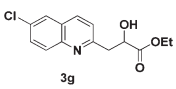
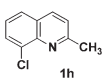
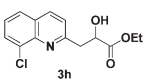
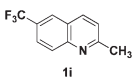
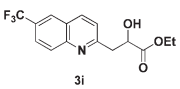
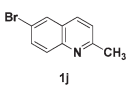
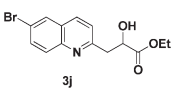
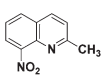
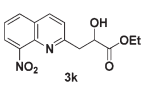
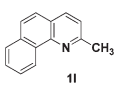
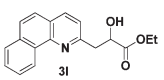
Entry	Substrate	Product	Yield/%[b]
1			94
2			88(7 : 8)[c]
3			78
4			84
5			68
6			73
7			79
8			68
9			80
10			84
11			36
12			54

Table 2 (*Continued*)

[a] Unless otherwise stated, all reactions were carried out with **1a** (0.6 mmol), **2** (0.2 mmol), catalyst (10 mol%), ligand (5 mol%), THF (0.8 mL) in a Schlenk tube at 60 °C for 24 h. [b] Isolated yield. [c] The diastereomeric ratio in parentheses as determined by HPLC.

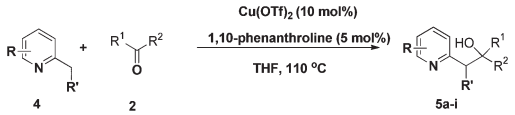
bonds could be achieved when an appropriate Lewis acid[10] was used as a catalyst. After the first draft of this manuscript was submitted, a paper by Li and co-workers appeared online describing the synthesis of azaarene-substituted 3-hydroxy-2-oxindoles catalysed by a Brønsted acid.[11] Our continued interest in C–H bond activation[12] led us to the present report where the copper-catalysed addition of α-alkyl azaarenes to the aldehyde group of ethyl glyoxylate *via* direct C(sp^3)–H activation is detailed.

Initially, 2-methyl quinoline **1a** and ethyl glyoxylate **2** were chosen as model substrates in a reaction designed to deliver product **3a**, optimisation studies are summarised in Table 1. The reactions conducted at 120 °C in line with conditions reported for related reactions proceeded only in very low yields.[5–9] The yield of the product **3a** was satisfactory when the reaction was performed at 60 °C for 24 h. A screening of potential catalysts indicated that copper salts could permit the reaction to proceed smoothly with 10 mol% of $Cu(OTf)_2$ to give product **3a** in higher yields than any of the other copper salts[13] tested (entries 1–5). Reducing the amount of $Cu(OTf)_2$ resulted in diminished yields under otherwise unaltered conditions (entry 6). A survey of solvents revealed tetrahydrofuran (THF) to be an optimal selection (entries 7–11). Although the reaction gave a good yield (78%) in the absence of a ligand (entry 12), product **3a** was obtained in a higher yield (94% after purification) in the presence of 5 mol% of 1,10-phenanthroline (entry 5). The use of 1,3-bis(diphenylphosphino)propane (dppp) as the ligand gave a lower yield than that with 1,10-phenanthroline (entry 13).

The tolerance of this reaction to various 2-alkyl quinolines with electron-neutral, electron-donating or electron-withdrawing groups attached was next examined under the optimised conditions (Table 2). The reaction of ethyl glyoxylate **2** and 2-alkyl quinolines **1a–1j** proceeded smoothly and provided the corresponding products **3a–3j** with yields of 68–94% (entries 1–10). In contrast, the C6-substituted 2-alkyl quinolines gave higher yields than the C8-substituted 2-alkyl quinolines, which might be as a result of steric factors at the C8 position of quinolines. 2-Methyl-8-nitroquinoline **1k** gave a relatively low yield, which might again be due to steric effects compounded by deleterious electronic effects (entry 11). It was remarkable then that halide substituents were tolerated in the quinoline ring (entries 7, 8, and 10). When 2-methyl-7,8-benzoquinoline was used as the substrate, the yield of the corresponding adduct was only 54% (entry 12). Under the described conditions no main ring, C(sp^2)–H, functionalisation was observed in the above reactions.

The use of 2-alkyl pyridines as substrates under the earlier optimised conditions for quinolines is summarised in Table 1. With regards to the different properties of quinoline and pyridine, the reaction temperature for the 2-alkyl pyridines was surveyed and 110 °C emerged as the best. Next, the scope of the 2-alkyl pyridines was also examined. The reaction of ethyl glyoxylate **2** and the 2-alkyl pyridines **4a–4i**, bearing either electron-neutral or electron-withdrawing groups, provided the corresponding products **5a–5i** in

Table 3 Substrate scope of the 2-alkyl pyridines[a]



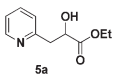
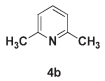
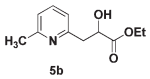
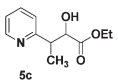
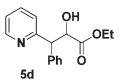
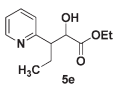
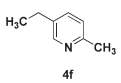
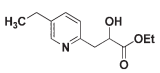
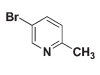
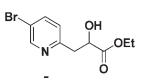
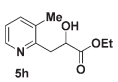
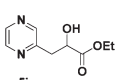
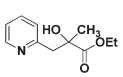
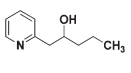
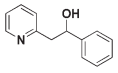
Entry	Substrate	Product	Yield/%[b]
1	 4a	 5a	67[c]
2	 4b	 5b	86
3	 4c	 5c	89(5 : 6)[d]
4	 4d	 5d	64(3 : 1)[d]
5	 4e	 5e	78(1 : 1)[d]
6	 4f	 5f	74
7	 4g	 5g	50
8	 4h	 5h	55
9	 4i	 5i	54
10	 4a		N.R.[e]
11	 4a		N.R.[e]
12	 4a		N.R.[e]

Table 3 (*Continued*)

[a] Unless otherwise stated, reactions were carried out with **1a** (0.6 mmol), **2** (0.2 mmol), catalyst (10 mol%), ligand (5 mol%), THF (0.8 mL) in a Schlenk tube at 60 °C for 24 h. [b] Isolated yield. [c] 4 equiv. of **4a** was used. [d] The diastereomeric ratio in parentheses as determined by HPLC. [e] N.R. is no reaction.

moderate to good yields (entries 1–9, Table 3). The addition of 2,6-lutidine **4b** to ethyl glyoxylate **2** gave a high yield of the mono functionalised product **5b** (entry 2). However, when ethyl glyoxylate **2** was used in excess the double C(sp^3)–H functionalised product increased. Chloride and CF_3 substituents were also tolerated on the ring (entries 7, 8 and 9, Table 2). Unfortunately, the observed ratio was often close to 1 : 1 in reactions with the potential to form mixtures of diastereoisomers (entries 3–5, Table 3). The addition of 2-alkyl azaarenes to ethyl pyruvate, aliphatic aldehydes or aromatic aldehydes failed to deliver the desired addition products under the same reaction conditions (entries 10, 11 and 12, Table 3).

In conclusion, we have developed an efficient copper-catalysed addition of 2-alkyl azaarenes to aldehyde esters through C(sp^3)–H bond functionalisation. This example of the addition of 2-alkyl azaarenes to a C=O double bond catalysed by a Lewis acid expands the scope of C(sp^3)–H bond activation reactions. This protocol provides a simple and rapid approach to access a variety of azaarene derivatives, which are of great interest and importance in medicinal chemistry applications. Further studies to expand the scope of generating new C–C bonds *via* C–H bond activation strategies are ongoing.

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