Efficient and convenient preparation of 3-aryl-2,2-dimethylpropanoates *via* Negishi coupling†

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An efficient and convenient Negishi coupling protocol was developed for the preparation of 3-aryl-2,2-dimethylpropanoates providing easy access to key pharmaceutical intermediates that often require multi-step synthesis using conventional enolate chemistry.

2,2-Dimethylpropanoic acids are common structural motifs in small molecule drug discovery, particularly in targeting nuclear hormone receptors.[1] Their prevalence may be attributed to the ability of the geminal methyl groups to shield or add steric bulk to carboxylic acids. Two examples[2] of 3-aryl-2,2-dimethylpropanoates in late stage drug development are shown in Fig. 1.

Conventional syntheses of 2,2-dimethyl-3-arylpropanoates involve ester enolate alkylation approaches as depicted in Fig. 2, *i.e.*, an exhaustive alkylation approach (Method A)[3] or a C2–C3 bond formation strategy (Method B).[4] Each method has inherent limitations. For instance, the exhaustive alkylation of unsubstituted enolates (Method A) can rarely be driven to completion and the remaining mono-alkylation adducts are often very difficult to separate during purification. Alkylation of tetrasubstituted enolates (Method B), meanwhile, depends upon the accessibility of the benzylic halides. Diverse heteroarylmethyl halides, in particular, are not readily available from commercial sources.

Prompted by the need to develop an alternative synthesis of 2,2-dimethyl-3-arylpropanoates that would address the shortcomings described above, we envisioned a direct C–C coupling[5] of two commercially or readily available alkyl halides (Method C in Fig. 3). The zinc-homoenolate **2**,[6] readily derived from **1**,[7] is known as an air-stable white crystalline material but few examples report the functionalization of its hindered neopentyl position despite an abundance of known examples using zinc-homoenolates for Negishi coupling reactions.[8] Herein we report our studies on a Negishi coupling reaction using **2** as the key reaction intermediate for preparation of 3-aryl-2,2-dimethylpropanoates.

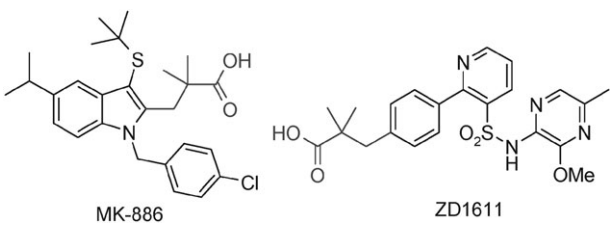

Fig. 1 Drug development candidates bearing 3-aryl-2,2-dimethylpropanoates.

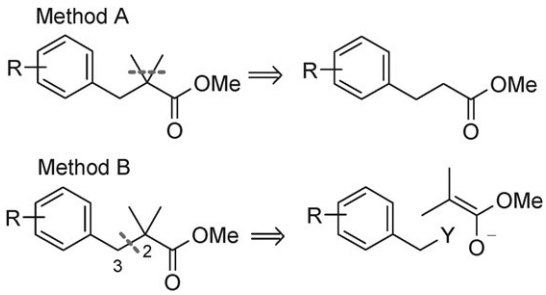

Fig. 2 Conventional syntheses of 3-aryl-2,2-dimethylpropanoates.

To develop a viable one-step protocol, the zinc-homoenolate **2** was generated *in situ* by treating **1** with excess Zn–Cu couple following Yamamoto's procedure.[9] Formation of **2** was monitored by TLC observing the consumption of **1**. **1** was not detectable by TLC after heating at 110 °C for 3 h and the heating was continued for an additional 3 h to ensure complete formation of **2**. The reaction mixture was then treated with 2-bromo-4-methylpyridine and 3 mol% $Pd(PPh_3)_4$ at 70 °C to provide the desired Negishi coupling product **3** in 93% yield (Scheme 1).‡ We discovered that formation of the zinc-homoenolate intermediate is more efficient with the iodide **1**

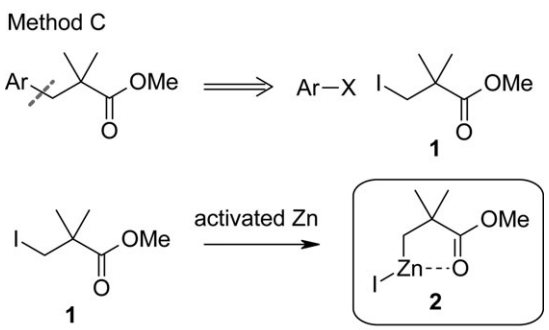

Fig. 3 The envisioned direct C–C coupling method and the zinc-homoenolate **2**.

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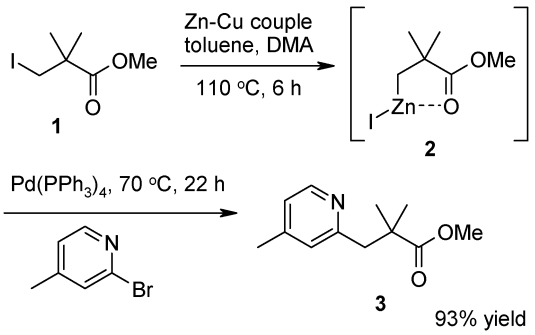
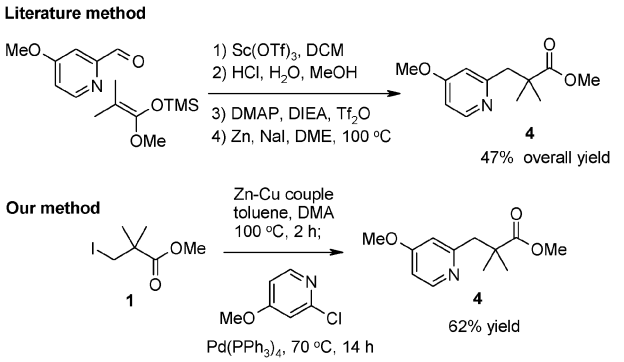
† Electronic supplementary information (ESI) available: Characterization spectral data for all compounds described. See DOI: 10.1039/b902779c

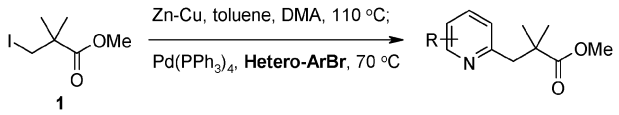


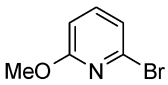
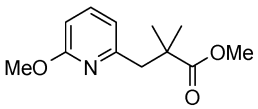
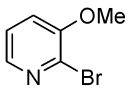
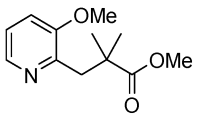
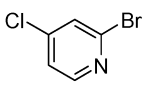
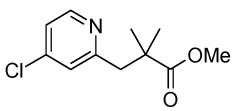
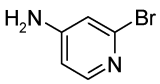
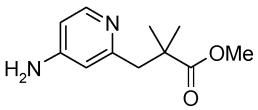
Scheme 1



Scheme 2

Table 1 Preparation of 2,2-dimethyl-3-pyridinylpropionic acid methyl esters *via* Negishi coupling



Entry	Hetero-ArBr[a]	Product	Yield (%)[b]
1			92
2			93
3			72
4			(20)[c]

[a] 0.74 equiv. of the aryl halides were used relative to iodide. [b] Yields are isolated yields. [c] Not isolated. Reaction failed to proceed after *ca.* 20% conversion detected by LC-MS.

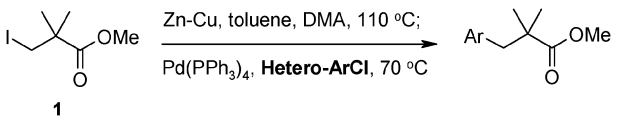
than the bromide **6** which required two days under the same reaction conditions.[10]

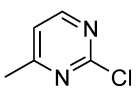
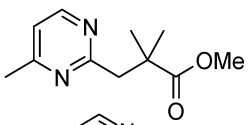
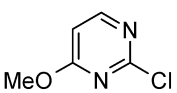
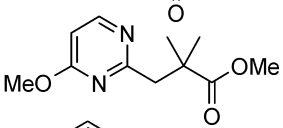
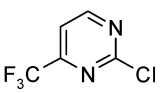
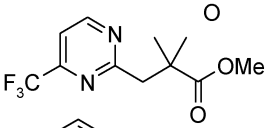
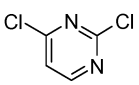
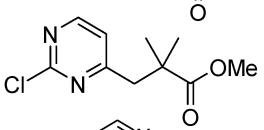
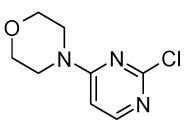
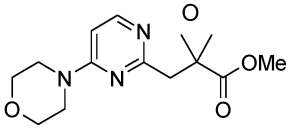
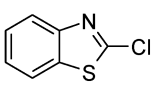
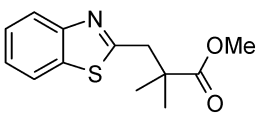
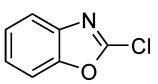
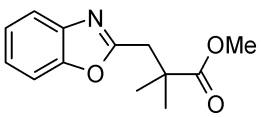
Encouraged by this result, we further examined the Negishi coupling reaction with 2-halopyridines and the results are summarized in Table 1. The Negishi coupling was efficient for most substrates examined thus far, suggesting that their steric or electronic nature was of minimal influence on the outcome of the reaction. In the case of 4-amino-2-bromopyridine (entry 4), despite several additions of the Pd catalyst, the reaction stalled at 20% conversion, presumably due to unproductive binding of amino group to the Pd catalyst.

To illustrate the efficiency of our system, we recognized the utility of **4** to prepare a set of imidazopyridine derivatives for the treatment of ulcers.[11] This intermediate is prepared in *ca.* 47% overall yield *via* a multi-step synthesis featuring a Mukayama aldol reaction followed by a reductive deoxygenation. Negishi coupling with 2-chloro-4-methoxypyridine and **1** afforded **4** in one step in 62% yield (Scheme 2), which demonstrates the convenience of our coupling strategy.

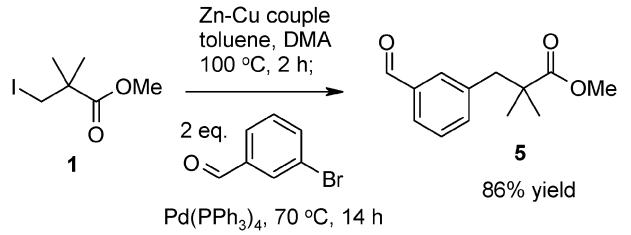
Investigation of other coupling partners revealed that this coupling method appears quite general with diverse

Table 2 Preparation of 2,2-dimethyl-3-heteroarylpropionic acid methyl esters *via* Negishi coupling



Entry	Hetero-ArCl[a]	Products	Yield (%)[b]
5			98
6			73
7			78
8			61
9			49
10			73
11			75

[a] 0.74 equiv. of aryl halide was used with respect to the starting iodide. [b] All the yields are isolated yields.



Scheme 3

heterocyclic electrophiles (Table 2). The coupling tolerated a wide range of substituents including electron withdrawing trifluoromethyl group and electron donating morpholine group in good yields (49–98%). We observed a regioselective (97% by ^{1}H-NMR) alkylation on C-4 with 2,4-dichloropyrimidine (entry 8). Finally, the Negishi coupling of **1** and 3-bromobenzaldehyde occurred smoothly to provide **5** in 86% yield as shown in Scheme 3. This example attests to the utility of the coupling protocol in synthesizing 2,2-dimethylpropanoates that are not readily accessible *via* enolate chemistry.

In summary, we have developed a convenient Negishi coupling method using the zinc-homoenolate **2**. We anticipate that this new protocol will provide a very useful synthetic strategy in medicinal chemistry for synthesis of 2,2-dimethyl-3-arylpropanoates. Negishi coupling reactions with amides or diversely substituted analogues of **1** are being investigated and will be reported in due course.

Notes and references

‡ **General procedure for the Negishi coupling.** Preparation of **3**: A suspension of Zn–Cu couple (3.45 g) in toluene–DMA (13 : 1, 30 mL) was degassed by bubbling N_2 into the system for 15 min. Iodide **1** (2.21 g, 9.14 mmol) was added to the suspension, and the resulting mixture heated at 110 °C for 6 h. The reaction mixture was allowed to cool to 70 °C and 2-bromo-4-methylpyridine (751 uL, 6.77 mmol) and $Pd(PPh_3)_4$ (235 mg, 0.203 mmol) were added. The reaction mixture was maintained at 70 °C for 22 h. Upon cooling, the mixture was filtered, and the filter cake rinsed with Et_2O. The filtrate was extracted with 1 M HCl (2 × 75 mL). The acidic extracts were basified by addition of $NaHCO_3$, and the resulting solution extracted with Et_2O (2 × 75 mL). The combined organics were dried over Na_2SO_4 and the solvent evaporated to yield **3** (1.31 g, 6.32 mmol, 93%) as an oil which was pure by NMR and HPLC. ^{1}H NMR (400 MHz, CD_2Cl_2): δ ppm 1.19 (s, 6 H), 2.32 (s, 3 H), 3.00 (s, 2 H), 3.63 (s, 3 H), 6.94 (s, 1 H), 6.99 (d, J = 4.93 Hz, 1 H), 8.32 (d, J = 5.05 Hz, 1 H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ ppm 21.23, 25.51, 43.46, 48.54, 51.99, 122.84, 125.46, 147.51, 149.13, 158.86, 178.17; FT-IR (CH_2Cl_2): 1728, 1605 cm^{-1}; HRMS calcd for $C_{12}H_{18}NO_2$ $[M + H]^+$: 208.1337, found 208.1336.

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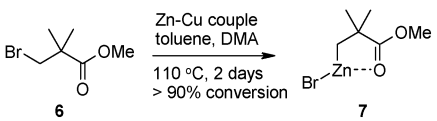
10 Bromozinc-homoenolate formation with Zn–Cu couple:



11 R. Boer, W. R. Ulrich, M. Eltze, D. Marx, U. Graedler and T. Fuchss, *PCT Int. Appl.*, 2005, WO 2005030768. An example is shown below: