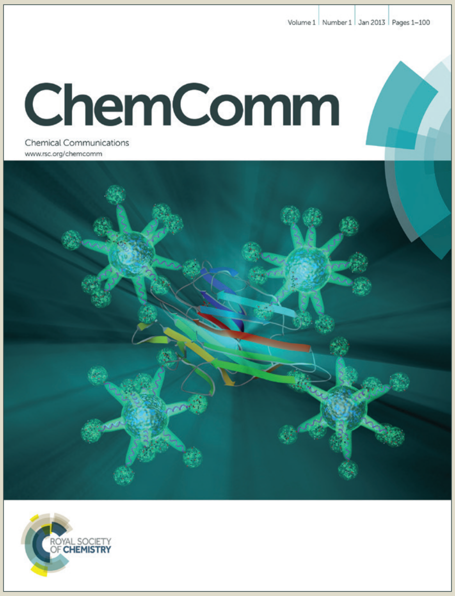
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Manganese-Catalyzed Intermolecular C–H/C–H Coupling of Carbonyls and Heteroarenes

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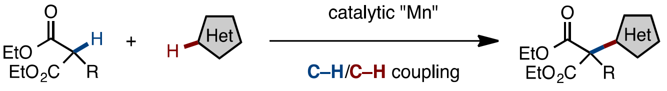
Manganese-catalyzed intermolecular C–H/C–H coupling of carbonyls and heteroarenes has been developed. The presence of $NaIO_4$ as an oxidant is crucial for the catalytic reaction. These new, inexpensive reaction conditions allow the gram-scale synthesis of α-heteroaryl carboxylic acids.

α-Heteroaryl carbonyl structure has stimulated interested in organic synthesis because it is a highly prevalent motif in pharmaceuticals and natural products.[1] To date, metal-catalyzed α-arylation of carbonyls with aryl halides has been extensively studied with mainly Pd-based catalysts.[2] Although the introduction of six-membered aromatic rings in this manner is possible, the use of five-membered heteroaryl halides as arylating agents presents issues in terms of substrate stability, difficulty of preparing (pseudo)halo heteroarene starting materials, and sluggish reactivity when compared to six-membered systems. In an alternative synthesis pathway, the coupling between functionalized carbonyls and heteroarenes (including its halide and organometallic derivatives) have been reported by several research groups, but the carbonyl starting materials in such reactions must be synthesized using several steps.[3] Thus, a catalytic C–H/C–H coupling of carbonyls and heteroarenes without pre-functionalization has attracted attention as a more concise and greener process for the synthesis of α-heteroaryl carbonyl compounds.

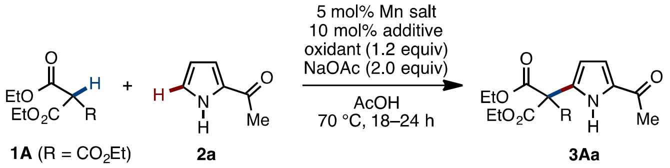
Recently, Pd-catalyzed intramolecular C–H/C–H coupling between carbonyls and heteroarenes (specifically pyridines) has been reported.[4] Furthermore, an intermolecular coupling of carbonyls and indoles/pyrroles using stoichiometric copper salts and excess amounts of strong bases was successfully demonstrated by Baran and co-workers.[5] However, the satisfaction of both criteria, i.e., catalytic *and* intermolecular, has not been achieved for the coupling of carbonyls and heteroarenes without functional group handles. To approach this challenge, we hypothesized that the key lies in manganese-catalyzed coupling reactions.[6] It is known that Mn(III) species can mediate intramolecular oxidative cyclization reactions[7,8] and biaryl couplings[9] using stoichiometric amounts or catalytic amounts of $Cu(OAc)_2$ as a co-oxidant. Two decades ago, Mn-mediated intermolecular C–H/C–H coupling of carbonyls and (hetero)arenes was reported by Muchowski,[10] which required 2.5 equivalents of $Mn(OAc)_3$[11] (US$9.0 per gram).[12] Based on these pioneering studies, we envisioned that the amount of Mn can be reduced to catalytic amounts, thereby rendering the synthesis of α-heteroaryl carbonyl compounds more practical. Herein, we describe the development of a practical method for an intermolecular C–H/C–H coupling of carbonyls and heteroarenes using a manganese catalyst (Scheme 1).



Scheme 1 Mn-catalyzed C–H/C–H coupling of carbonyls and heteroarenes

Our investigation commenced with the coupling reaction of tri(ethoxycarbonyl)methane (**1A**: 1.0 equiv) and 2-acetylpyrrole (**2a**: 2.0 equiv) in the presence of a catalytic Mn complex (5 mol%), various oxidants (1.2 equiv) and NaOAc (2.0 equiv) as shown in Table 1 (see also electronic supplementary information (ESI)). Primarily, we investigated the effect of oxidants. Disappointingly, representative oxidants such as Ag_2CO_3, $Cu(OAc)_2$, $K_2S_2O_8$, and benzoquinone (BQ) interfered with the coupling reaction and completely shut it down (entries 1–4). When *t*-butyl hydroperoxide (TBHP) or $CeSO_4$•$4H_2O$ was used, the corresponding coupling product **3Aa** was obtained, albeit in very low yields (entries 5 and 6). To our great delight, the coupling reaction proceeded smoothly to afford the desired product in 32% yield when sodium periodate ($NaIO_4$) was used as an oxidant. When Mn complexes were systematically changed, the reactions gave **3Aa** in yields ranging from 24% to 64% (entries 7–10). Although MnI_2 (US$78.90 per gram)[12] gave the best yield (64%, entry 9), $Mn(OAc)_2$•$4H_2O$ is a significantly less expensive catalyst (US$0.06 per gram)[11] and was therefore selected as the catalyst of choice despite the slightly lower yield (57%, entry 10). The addition of sodium acetate is crucial to give **3Aa** in good yield (entry 11). Consequently, various additives were tested (entries 12–18) and, from these studies, it appeared that trisubstituted phosphines such as PPh_3 (72%, entry 14) and X-Phos (77%, entry 15) were effective in increasing the yield of **3Aa**, whereas sulfoxide (e.g., DMSO, entry 12), pyridine (entry 13), and trialkylphosphine (e.g., Cy_3P, entry 16) were not. Surprisingly, bidentate phosphine (e.g., dppe, entry 17) completely shut down the reactivity. We then assumed that trisubstituted phosphines are being oxidized to phosphine oxides under the reaction conditions, and thus added triphenylphosphine oxide. However, the yield was the same as the reaction without additive (compare entry 18 to entry 10), showing that unoxidized trisubstituted phosphines are necessary to improve the yield of **3Aa**.[13] PPh_3 is the least expensive, and therefore, we selected it as the additive of choice for this reaction.

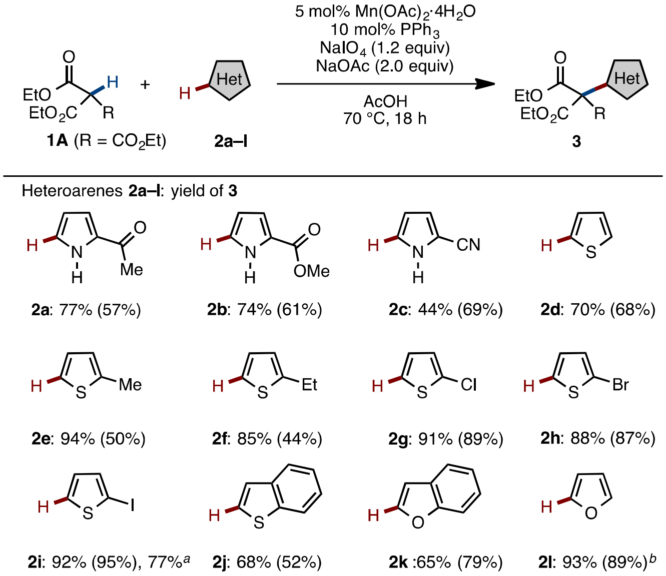
Table 1. Screening of the Mn-catalyzed C–H/C–H coupling of **1A** and **2a**[a]



Entry	Mn salt	Oxidant	Additive	Yield of **3Aa** /%[b]
1	$Mn(OAc)_3•2H_2O$	Ag_2CO_3	–	0
2	$Mn(OAc)_3•2H_2O$	$Cu(OAc)_2•H_2O$	–	0
3	$Mn(OAc)_3•2H_2O$	BQ	–	0
4	$Mn(OAc)_3•2H_2O$	$K_2S_2O_8$	–	1
5	$Mn(OAc)_3•2H_2O$	TBHP	–	9
6	$Mn(OAc)_3•2H_2O$	$CeSO_4•4H_2O$	–	10
7	$Mn(OAc)_3•2H_2O$	$NaIO_4$	–	32
8	$MnCl_2$	$NaIO_4$	–	24
9	MnI_2	$NaIO_4$	–	64
10	$Mn(OAc)_2•4H_2O$	$NaIO_4$	–	57
11[c]	$Mn(OAc)_2•4H_2O$	$NaIO_4$	–	9
12	$Mn(OAc)_2•4H_2O$	$NaIO_4$	DMSO	33
13	$Mn(OAc)_2•4H_2O$	$NaIO_4$	pyridine	36
14	$Mn(OAc)_2•4H_2O$	$NaIO_4$	PPh_3	72(77)[d]
15	$Mn(OAc)_2•4H_2O$	$NaIO_4$	X-Phos	77
16	$Mn(OAc)_2•4H_2O$	$NaIO_4$	Cy_3P	37
17	$Mn(OAc)_2•4H_2O$	$NaIO_4$	dppe	2
18	$Mn(OAc)_2•4H_2O$	$NaIO_4$	$O{=}PPh_3$	55

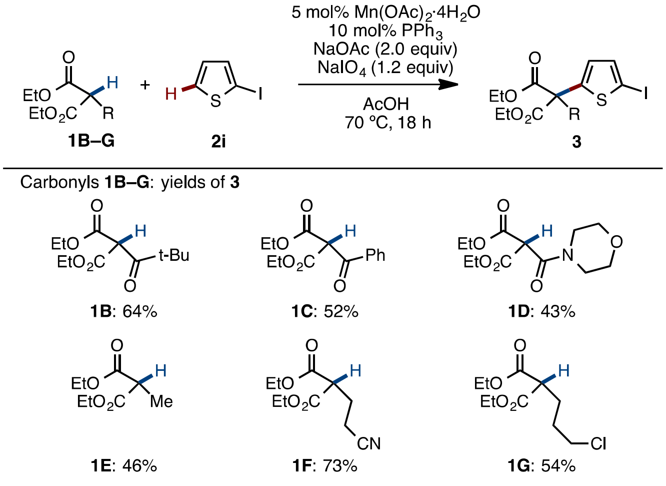
[a] Conditions: **1A** (1.0 mmol), **2a** (2.0 mmol), Mn salt (0.05 mmol), oxidant (1.2 mmol), NaOAc (2.0 mmol), additive (0.1 mmol), AcOH (2.0 mL), 70 °C, 18 h. [b] GC yield. [c] The reaction was performed without NaOAc. [d] Isolated yield.

With the optimal conditions in hand, we investigated the scope of C–H/C–H coupling of tri(ethoxycarbonyl)methane (**1A**) with various five-membered heteroarenes (Scheme 2). When the C2-substituent of the pyrrole was changed from acetyl (**2a**) to methoxycarbonyl (**2b**) and cyano (**2c**), the coupling proceeded well to give the corresponding products in good yields. Unsubstituted thiophene (**2d**) performed well (68% yield), and C2-alkylated thiophenes such as methyl (**2e**) and ethyl (**2f**) thiophenes also gave the products in excellent yields. In the case of C2-halogenated thiophenes such as chloro (**2g**), bromo (**2h**), and iodo (**2i**) thiophenes, these reactions worked very well without loss of the halogen atom. To our delight, the coupling reaction of **1A** with **2i** was conducted in the presence of only 1 mol% $Mn(OAc)_2•4H_2O$, giving the corresponding product in 77% yield. Benzothiophene (**2j**), benzofuran (**2k**), and furan (**2l**) were applicable for this coupling reaction to afford the products in good yields. It is of note that PPh_3 was not needed for heteroarenes **2d**, **2g**, **2h**, and **2i**, and actually decreased the yields slightly when **2c** and **2k** were used. Unfortunately, using indole as a heteroarene gave the corresponding product in 20% yield. Additionally, electron-rich aromatics such as dimethoxybenzene did not react under the present conditions.



Scheme 2. Substrate scope of heteroarene coupling partners. The yields of coupling products without PPh_3 are shown in parentheses. [a] 1 mol% of $Mn(OAc)_2•4H_2O$ was used. [b] 10 equiv of furan was employed.

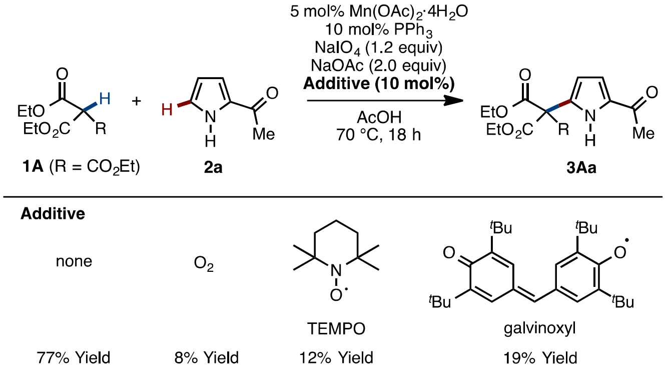
Next, the scope of carbonyl coupling partner was investigated with 2-iodothiophene (**2i**) under the optimal conditions (Scheme 3). It was found that the carbonyl partner always required the diester moiety, and otherwise the reactions did not proceed at all. Substrates wherein the ethyl ester of **1A** was changed to *t*-butylketone (**1B**), phenylketone (**1C**), or morpholine amide (**1D**) were tolerated albeit in moderate yields. Using diethyl 2-methylmalonate (**1E**) as the carbonyl partner, the coupling reaction proceeded to give the product in 46% yield. This was extended to other malonate derivatives, including a cyano-containing (**1F**: 73%) and chloro-containing alkyl chain (**1G**: 54%).



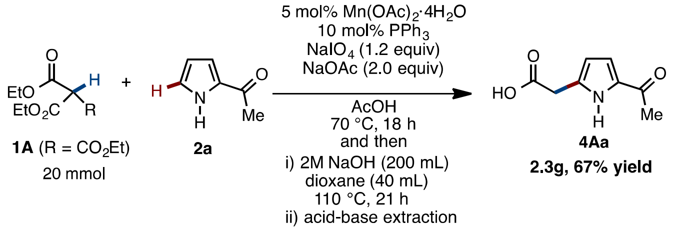
Scheme 3 Substrate scope of carbonyls

As the presence of a radical scavenger suppressed the Mn-catalyzed C–H/C–H coupling of **1A** and **2a** (Scheme 4), we assume that the reaction proceeds via a radical mechanism.[14] For example, when this reaction was performed under oxygen, the yield of **3Aa** was only 8% yield; similar effects were observed when adding TEMPO (12% yield) and galvinoxyl (19% yield). The reaction mechanism remains unclear, but these experiments support a radical pathway for this coupling reaction.

Finally, a gram-scale synthesis of α-heteroaryl carbonyls was performed (Scheme 5). 20 mmol of **1A** was coupled with **2a** under our optimized conditions, followed by hydrolysis and decarboxylation of **3Aa**. Thereafter, acid-base extraction of the crude product afforded 2.3 g of pure α-heteroaryl carboxylic acid **4Aa** without column chromatography (67% yield overall).



Scheme 4. Addition of radical scavengers



Scheme 5. Gram-scale synthesis of α-hetero carboxylic acid **4Aa**

In summary, we have developed a practical intermolecular C–H/C–H coupling of carbonyls and heteroarenes catalyzed by manganese.[15] The oxidant, sodium periodate, is a readily available, inexpensive oxidant. This method tolerates a wide range of heteroarenes to furnish the α-heteroaryl carbonyl products (18 examples, including various carbonyl partners). A gram-scale C–H/C–H coupling demonstrated that the reaction could be applied to the practical synthesis of □-heteroaryl carboxylic acids. Further modifications of the Mn catalyst to achieve a broad scope for the carbonyl partner are ongoing in our laboratory.

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Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for products. See DOI: 10.1039/c000000x/

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12 Based on current prices from Sigma-Aldrich, Inc.

13 Almost immediately after starting the reaction (5 min), it was determined that Ph_3P was completely oxidized to $Ph_3P{=}O$. Therefore, we assume that the role of Ph_3P might be to quench some peroxides such as peracetic acid that is slightly produced from AcOH and $NaIO_4$.

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