Pd-catalyzed cross-coupling of carboxylic acids with nitroethane *via* combination of decarboxylation and dehydrogenation†

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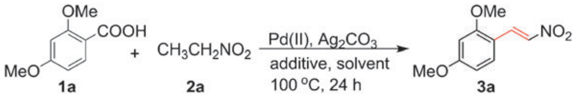
An unexpected coupling reaction of arene carboxylic acid with nitroethane *via* a combination of decarboxylation and dehydrogenation is described. The method provides exclusively (*E*)-β-nitrostyrenes.

The development of catalytic methods for decarboxylative coupling of carboxylic acids has received much attention recently since such transformations provide new opportunities to use readily available carboxylic acids as starting materials for organic synthesis.[1–8] As a consequence, a series of efficient catalyst systems have been established for the achievement of decarboxylative cross-coupling of a wide range of carboxylic acids with aryl halides, triflates[2,3] and others.[4] Advances have also been reported in the development of Pd-catalyzed decarboxylative Heck-type coupling of benzoic acids with olefins.[5] Very recently, the decarboxylative coupling reactions of α-amino acids with an array of nucleophiles have appeared.[6] These studies demonstrated that depending on the nature of the metal catalysts, the organometallic intermediates generated from metal-promoted decarboxylation of carboxylic acids served as either electrophiles or nucleophiles, which indicates the potential of carboxylic acids as versatile coupling components. Moreover, Pd-catalyzed carboxyl-directed *ortho*-C–H functionalization,[9] in conjunction with decarboxylative cross-coupling, would offer a rapid entry into complex molecules from readily available materials through concise steps.[7]

The development of the metal-catalyzed direct C–H functionalization reactions provides the most atom-efficient synthetic methods, and currently represents a very active area of research.[10,11] However, the reactions involving decarboxylative cross-coupling of benzoic acids with C–H bonds are still scarce,[6a,12] although this class of reactions combines the advantages of the high efficiency of C–H functionalization and the ready availability of carboxylic acids. The primary obstacles to realize this process arise from the difference in reaction rate between the two independent processes, decarboxylation and C–H cleavage, which often leads to homocoupling or protodecarboxylation. Thus, the key to achieving this cross-coupling is the identification of the critical factors whose modification enables decarboxylation and C–H cleavage to match each other. Herein, we report the first example of the reactions of *ortho*-substituted benzoic acids with nitroethane that produce exclusively (*E*)-β-nitrostyrenes *via* a combination of decarboxylation and dehydrogenation.

To achieve a decarboxylative α-arylation product of nitroethane, we initially examined the reaction of 2,4-dimethoxybenzoic acid (**1a**) with 2.0 equiv. of nitroethane (**2a**) under various conditions using bases such as Cs_2CO_3, K_2CO_3, K_3PO_4 as additives, but did not obtain any product from this reaction. Surprisingly, upon removal of base from the reaction system, in presence of 10 mol% $Pd(TFA)_2$ as catalyst, 2.5 equiv. of Ag_2CO_3 as oxidant in 5% DMSO–DMF, the reaction gave an unexpected decarboxylative vinylation product (**3a**) in 11% yield (entry 2, Table 1). We speculated that introduction of additional acids to the reaction system would increase the electrophilicity of the catalyst, thus promoting decarboxylation of carboxylic acid. As expected, addition of 1.0 equiv. of pivalic acid led to an increase in the yield of **3a** (entry 3). Replacing 5% DMSO–DMF with 10% DMSO–DME (DME = 1,2-dimethoxyethane) further improved the yield. Screening analogs of pivalic acid as an additive and their amounts revealed that 2.5 equiv. of pivalic acid maximized the beneficial effect of the additional acid as an

Table 1 Optimization of reaction conditions[a]



Entry	Equiv. of **2a**	Additive (equiv.)	Solvent	Yield of **3a** (%)[b]
1	2	Cs_2CO_3 (1.0)	5% DMSO–DMF	0
2	2	—	5% DMSO–DMF	11
3	2	PivOH (1.0)	5% DMSO–DMF	19
4	2	PivOH (1.0)	10% DMSO–DME	28
5	2	PivOH (2.5)	10% DMSO–DME	44
6	2	PivOH (4.0)	10% DMSO–DME	33
7	2	AcOH (2.5)	10% DMSO–DME	21
8	2	EtCOOH (2.5)	10% DMSO–DME	22
9	2	1-AdCOOH (2.5)	10% DMSO–DME	38
10	2	CF_3COOH (2.5)	10% DMSO–DME	10
11	2	*p*-TsOH (2.5)	10% DMSO–DME	4
12[c]	2	PivOH (2.5)	10% DMSO–DME	45
13[c]	5	PivOH (2.5)	10% DMSO–DME	58
14[c]	7	PivOH (2.5)	10% DMSO–DME	64
15[c]	7	PivOH (2.5)	10% DMSO–dioxane	73
16[c,d]	7	PivOH (2.5)	10% DMSO–dioxane	66
17[c,e]	7	PivOH (2.5)	10% DMSO–dioxane	38

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), $Pd(TFA)_2$ (10 mol%), Ag_2CO_3 (2.5 equiv.), solvent (2.0 mL), 100 °C, 24 h. [b] GC yield. [c] Ag_2CO_3 (2.0 equiv.). [d] Under air. [e] $Pd(MeCN)_2Cl_2$ (20 mol%).

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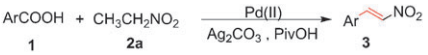
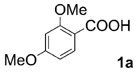
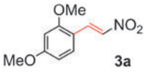
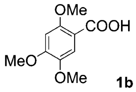
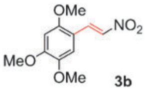
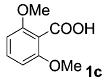
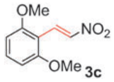
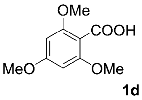
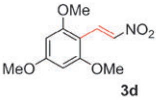
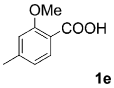
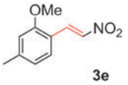
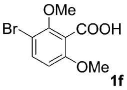
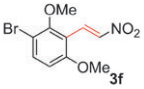
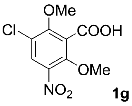
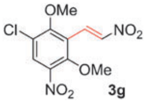
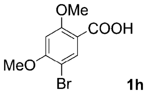
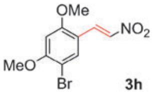
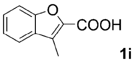
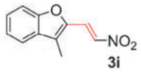
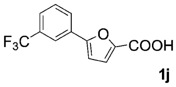
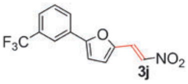
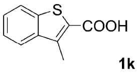
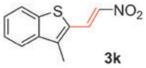
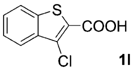
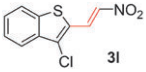
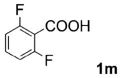
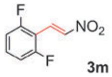
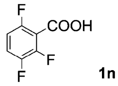
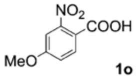
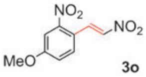
additive (entry 5 *vs.* entries 6–11). We also observed that reducing the amount of Ag_2CO_3 to 2.0 equiv. gave the same result as obtained using 2.5 equiv. of Ag_2CO_3 (entry 12). Increasing the amount of **2a** relative to **1a** resulted in a significant increase in yield as a result of suppressing protodecarboxylation of benzoic acid (entry 12 *vs.* entries 13 and 14). Gratifyingly, 73% yield was obtained when the reaction of **1a** with 7.0 equiv. of **2a** was conducted in 10% DMSO–dioxane at 100 °C (entry 15). Interestingly, the reaction can be carried out under air with yield slightly reduced (entry 16).

Notably, when the optimized procedure (entry 15, Table 1) was applied to a range of benzoic acids, small adjustments were required to the reaction conditions in some cases due to the variations in reactivity towards decarboxylation of benzoic acids (Table 2). Since DMSO functions as a ligand for the catalyst, we speculated that the amount of DMSO must be an important parameter that influences the rate of decarboxylation. As expected, in the cases of electron-rich benzoic acids, more DMSO was required to slow the decarboxylation of more electron-rich ones compared with the standard conditions whereas a decreasing amount of DMSO and increasing temperature were required for less electron-rich ones (**3c–3e**). In the reaction of electron-deficient benzoic acids, pivalic acid led to protodecarboxylation, therefore was removed from the reaction system, and $Pd(MeCN)_2Cl_2$ was observed to perform better than $Pd(TFA)_2$ (**3m–3o**). Thus, both electron-rich and -deficient benzoic acids underwent smoothly the reaction with nitroethane to produce exclusively (*E*)-β-nitrostyrenes. In most cases, synthetically useful yields were obtained. The reaction conditions are compatible with halide substituents (**3f**, **3h**, **3l**), providing an opportunity for further elaboration of products. The heterocyclic carboxylic acids also served as suitable substrates to participate in this reaction (**3i–3l**), in which substituents *ortho* to carboxyl were required to afford good yields. Because of the difficulty in slowing the rate of decarboxylation, 2,4,6-trimethoxybenzoic acid yielded the desired product in poor yield (**3d**). Unfortunately, when 1-nitropropane **3** was induced to react with 2,4-dimethoxybenzoic acid (**1a**), the reaction provided a mixture of *E*/*Z* isomers in the ratio of 3 : 2, and the yield is quite low (Scheme 1). Further investigation indicated that although nitroethane and 1-nitropropane worked under the established reaction conditions, more sterically demanding nitro compounds such as 2-nitropropane, nitrocyclohexane, α- and β-nitroethylbenzene were ineffective.

This method is not limited to the small-scale reaction as described above (*e.g.*, 0.2 mmol). The reaction of 2,4-dimethoxybenzoic acid with nitroethane on a gram scale provided 70% yield (entry 1 in Table 2).

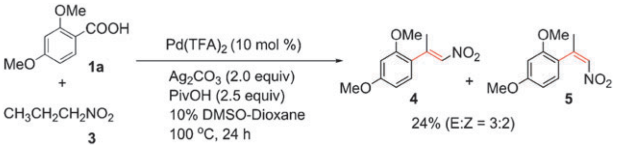
Table 2 Decarboxylative coupling of benzoic acids with nitroethane[a]



Entry	Substrate	Product	Yield (%)[b]
1	 **1a**	 **3a**	71% (70%)
2	 **1b**	 **3b**	70%
3	 **1c**	 **3c**	74%^{c}
4	 **1d**	 **3d**	28%^{d}
5	 **1e**	 **3e**	65%^{e}
6	 **1f**	 **3f**	52%^{e,f}
7	 **1g**	 **3g**	40%^{f,g}
8	 **1h**	 **3h**	73%^{e}
9	 **1i**	 **3i**	68%
10	 **1j**	 **3j**	25%
11	 **1k**	 **3k**	67%^{e}
12	 **1l**	 **3l**	64%^{e,f}
13	 **1m**	 **3m**	63%^{f,g}
14	 **1n**	 **3n**	60%^{f,g}
15	 **1o**	 **3o**	53%^{f,g}

[a] Reactions were run under the conditions of entry 15 in Table 1. See Supporting Information for details. [b] Isolated yields (Value in parentheses refers to the yield from reaction on a 10 mmol scale). [c] 15% DMSO. [d] 40% DMSO. [e] 5% DMSO. [f] In the absence of PivOH. [g] $Pd(MeCN)_2Cl_2$ (20 mol%), 2% DMSO.

The difference in reaction conditions between electron-rich and -deficient benzoic acids led us to consider whether there were two different reaction pathways in the decarboxylative coupling of benzoic acids with nitroethane. We observed that stoichiometric $Pd(TFA)_2$ enabled the reaction of electron-rich benzoic acids with nitroethane in the absence of Ag_2CO_3 whereas the use of Ag_2CO_3 alone, in the absence of $Pd(TFA)_2$ under otherwise identical conditions, was ineffective for the decarboxylation of electron-rich benzoic acids, clearly indicating that decarboxylation of electron-rich benzoic acids resulted from the contribution of $Pd(TFA)_2$ rather than Ag_2CO_3. In contrast, the reactions of electron-deficient benzoic acids were observed to mainly arise from Ag-promoted decarboxylation.[13]



Scheme 1 Reaction of 2,4-dimethoxybenzoic acid (**1a**) with 1-nitropropane **3**.

On the other hand, the detailed reaction behavior of nitroethane in the reaction of benzoic acids with nitroethane is still unclear; the formation of vinylation products from this system implies that this reaction may involve *in situ* generation of nitroethylene followed by decarboxylative Heck coupling, although nitroethylene was reported to be unstable because of its facile polymerization.[14] Thus, (*E*)-β-nitrostyrenes were dominantly formed as observed in most decarboxylative Heck coupling reactions.[5]

In summary, we have described the first metal-catalyzed method for the cross-coupling of a broad range of benzoic acids with nitroethane that produces (*E*)-β-nitrostyrenes with high selectivity. Current efforts are directed towards the detailed investigation on the mechanism of this process, and the improvement of substrate scope.

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