Palladium-catalyzed decarboxylative 1,2-addition of carboxylic acids to aldehydes or imines[†]

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The first example of palladium-catalyzed decarboxylative 1,2-addition of carboxylic acids to aldehydes or imines under mild conditions is described.

Since Miyaura and co-workers reported the rhodium-catalyzed 1,2-addition in 1998,¹ using transition metal complexes of rhodium, palladium, nickel, copper and platinum as catalysts for 1,2-addition reactions of organoboronic acids to aldehydes or imines has become established as a universal tool for C-C bond formation.²⁻⁵ Typically, stoichiometric amounts of costly organoboron compounds had to be utilized in such transformation. Meanwhile, recently increasing interest has been paid to the palladium-catalyzed decarboxylative cross-coupling reactions,⁶⁻¹⁰ since it provides an important alternative route for carbon-carbon bond formation. Compared to the conventional transition metal-catalyzed cross-coupling reactions and the direct arylation through C-H activation, this method has several advantages as highlighted by Baudoin⁶ concerning the regioselectivity with atom and step economy issues. And currently, it is well-recognized that this approach combines the key benefit of regiospecificity as well as broad availability, low cost, and easy handling of carboxylate substrates. In the last two years, breakthroughs have been achieved in the development of palladium-catalyzed decarboxylative cross-coupling reactions.

It is well known that the synthesis of diarylmethyl amines or diaryl methanols is of great importance because they are present in a variety of pharmacologically active structures.¹¹ Prompted by the advancement of 1,2-addition reactions of organoboronic acids to aldehydes or imines and the palladiumcatalyzed decarboxylative cross-coupling reactions, we conceived that carboxylic acids might be a good substrate as a replacement for organoboron compound in the transition-metal catalyzed 1,2-addition reactions (Scheme 1), due to their easy availability and low cost. In addition, employing carboxylic acids in such transformations would greatly contribute to the creation of environmentally benign processes. As mentioned above for the decarboxylative cross couplings, the carboxylic acid would convert into a carbon nucleophile by extrusion of CO₂ and directly couple with carbon electrophiles. Moreover, stoichiometric amounts of costly organometallic reagents would be avoided.



Scheme 1 Proposed route for palladium-catalyzed decarboxylative 1,2-addition of carboxylic acids to aldehydes or imines.

With these considerations in mind and to verify the practicability of the projected route as shown in Scheme 1, we approached the search for an effective catalyst system using as a model reaction, the decarboxylative 1,2-addition of carboxylic acid 1a to aldehyde 2a. A few key experiments selected from our investigation of various palladium catalysts, additives, and conditions are displayed in Table 1. Initially, the reaction was performed in the presence of PdCl₂ (10 mol%) as catalyst in toluene at 80 °C. However, no reaction occurred. The result could not be improved when the reaction temperature was increased to 120 or 160 °C. Subsequently, we shifted our focus on other palladium catalysts. After screening different palladium catalysts and solvents, we identified that Pd(OTf)₂ was the most effective catalyst in DMSO-DMF (1 : 20 v/v)and the desired product 3a was isolated in 73% yield (Table 1, entry 6). This result was similar to the previous report, 7^c in which the rate of decarboxylation in an mixture of DMF and DMSO was much faster. Based on this result, we conceived that Pd(OTf)₂ might be generated in situ by combination of

OMe 1a	COOH + `OMe O ₂ N´	CHO - 2a	[Pd] catalyst (10 mol %) solvent → [OMe OH ON 3a	Me NO ₂		
Entry	[Pd]	Additive	Solvent	$T/^{\circ}\mathrm{C}$	Yield ^a (%)		
1	PdCl ₂	_	Toluene	80	NR		
2	$PdCl_2$	_	Toluene	120	NR		
3	PdCl ₂		Toluene	160	NR		
4	$Pd(OTf)_2$		Toluene	80	Trace		
5	$Pd(OTf)_2$		DMF	80	Trace		
6	$Pd(OTf)_2$		DMSO-DMF	80	73		
7	PdCl ₂	AgOTf	DMSO	80	58		
8	PdCl ₂	AgOTf	DMF	80	Trace		
9	$PdCl_2$	AgOTf	DMSO-DMF	80	87		
^a Isolated yield based on 4-nitrobenzaldehyde 2a.							

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PdCl₂ and AgOTf. Thus, the reaction was tested in the presence of PdCl₂ (10 mol%) and AgOTf (20 mol%). To our delight, the corresponding product 3a was obtained in 87% yield in DMSO–DMF (1 : 20 v/v) at 80 °C (Table 1, entry 9). Lower yield was observed when the catalyst amount was reduced to 5 mol%. Inferior results were also observed when the reaction was conducted at 50 °C.

Using the optimized palladium-catalyzed conditions [PdCl₂ (10 mol%), AgOTf (20 mol%), DMSO-DMF (1 : 20 v/v), 80 °C], the scope of this reaction was then investigated (Table 2). For the decarboxylative 1,2-addition reactions of 2,6-dimethoxybenzoic acid 1a, various aldehydes were examined.[‡] From Table 2, it was found that reactions of aldehydes with electron-withdrawing groups attached to the aromatic backbone proceeded smoothly to afford the desired products in moderate to good yields. Moreover, different functional groups such as nitro, trifluoromethyl and ester groups could be tolerated under the conditions. However, no reaction occurred when benzaldehydes with electron-donating groups attached on the aromatic ring were utilized as substrates (data not shown in Table 2), which might be due to their lower electrophilicity. Aliphatic aldehydes and ketones were also examined as substrates. However, no reactions occurred under the standard conditions (data not shown in Table 2). This decarboxylative 1,2-addition reaction was also extended to imines. As expected, the benzoic acids reacted with aldimines leading to the desired amines in good yields (Table 2, entries 9-19).

Other carboxylic acids were also tested in the decarboxylative 1,2-addition reactions of aldehydes. Interestingly, when 2,4,6trimethoxybenzoic acid 1b was employed in the reactions with aldehydes under the standard conditions, triarylmethanes 4 were produced in the transformation (Scheme 2). However,

 Table 2
 Palladium-catalyzed decarboxylative 1,2-addition of carboxylic
acids to aldehydes or imines

R ^{1_1}	$+ R^2 \frac{H}{U}$	PdCl ₂ (10 mol %) AgOTf (20 mol %) DMSO:DMF = 1:20 80 °C	R ¹	XH R ²
Entry	R ¹	R ²	Х	Yield ^a (%)
1	2,6-(OMe) ₂ (1a)	4-NO ₂	0	87 (3a)
2	2,6-(OMe) ₂ (1a)	2,4-Cl ₂	0	68 (3b)
3	2,6-(OMe) ₂ (1a)	2-C1	0	57 (3c)
4	2,6-(OMe) ₂ (1a)	2-Br-4-F	0	53 (3d)
5	2,6-(OMe) ₂ (1a)	$4-CF_3$	0	57 (3e)
6	2,6-(OMe) ₂ (1a)	$2-NO_2$	0	41 (3f)
7	2,6-(OMe) ₂ (1a)	4-CO ₂ Me	0	50 (3g)
8	2,6-(OMe) ₂ (1a)	2-Br-5-F	0	60 (3h)
9	2,6-(OMe) ₂ (1a)	$4-NO_2$	NTs	62 (3i)
10	2,4,6-(OMe) ₃ (1b)	$4-NO_2$	NTs	77 (3 j)
11	2,6-(OMe) ₂ (1a)	2,4-Cl ₂	NTs	60 (3k)
12	2,4,6-(OMe) ₃ (1b)	2,4-Cl ₂	NTs	60 (3l)
13	2,6-(OMe) ₂ (1a)	2-Br-4-F	NTs	70 (3m)
14	2,4,6-(OMe) ₃ (1b)	2-Br-4-F	NTs	65 (3n)
15	2,4,6-(OMe) ₃ (1b)	2-C1	NTs	68 (3o)
16	$2,6-(OMe)_2$ (1a)	$2-NO_2$	NTs	62 (3 p)
17	$2,6-(OMe)_2$ (1a)	2-Br-5-F	NTs	51 (3q)
18	$2,6-(OMe)_2$ (1a)	$4-CF_3$	NTs	57 (3r)
19	$2,4,6-(OMe)_3$ (1b)	$4-CF_3$	NTs	73 (3s)
^a Isolated	yield based on aldeh	yde or imine 2.		

other benzoic acids are not effective in the reactions. It seems that the scope of the process is presently clearly limited to electron-rich aryl carboxylic acids and electron-poor aryl aldehydes/imines.



Scheme 2 Palladium-catalyzed decarboxylative reaction of carboxylic acid 1b with benzaldehydes.

In conclusion, the method disclosed herein clearly demonstrates the concept of decarboxylative 1,2-addition of carboxylic acids to aldehydes or imines, which opens a new avenue for carboncarbon bond formation. Although this reaction currently has scope limitations we believe that this environmentally benign process combined with the mild conditions would be attractive and beneficial for its further development.

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Notes and references

General procedure for palladium-catalyzed decarboxylative 1,2addition of carboxylic acids to aldehydes or imines: Carboxylic acid 1 (0.24 mmol) and aldehyde or imine 2 (0.20 mmol) were added to a mixture of PdCl₂ (10 mol%, 3.6 mg) and AgOTf (20 mol%, 10.3 mg) in DMF (2.0 mL) and DMSO (0.1 mL). The reaction was stirred at 80 °C. After completion of reaction as indicated in TLC, the mixture was diluted by EtOAc (20 mL), washed with saturated brine $(2 \times 20 \text{ mL})$, and dried by Na₂SO₄. Evaporation the solvent followed by purification on silica gel provided the product 3. Data of selected examples: (2,6-Dimethoxyphenyl)(4-nitrophenyl)methanol 3a. White solid, mp 136–137 °C. ¹H NMR (400 MHz, CDCl₃): δ 8.12 (d, J = 7.8 Hz, 2H), 7.50 (d, J = 8.7 Hz, 2H), 7.26 (m, 1H), 6.60 (d, J =8.3 Hz, 2H), 6.38 (s, 1H), 4.31 (br, 1H), 3.80 (s, 6H). ¹³C NMR (100 MHz): *δ* 157.5, 152.6, 146.6, 129.6, 126.2, 123.1, 118.3, 104.5, 67.8, 55.8. IR (thin film): ν/cm^{-1} 3536, 1597, 1518, 1476. HRMS (ESI) calc. for $C_{15}H_{15}NO_5 [M + Na]^+$ requires 312.0848, found 312.0848. 4-Methyl-N-((4-nitrophenyl)(2,4,6-trimethoxyphenyl)methyl)benzenesulfonamide 3j. White solid, mp 138-139 °C. ¹H NMR (400 MHz, CDCl₃): δ 8.03 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.7 Hz, 2H), 7.04 (d, J = 8.2 Hz, 2H), 6.37 (d, J = 10.5 Hz, 1H), 6.15 (d, J = 10.5 Hz, 1H), 5.9 (s, 2H), 3.74 (s, 3H), 3.62 (s, 6H), 2.31 (s, 3H). ¹³C NMR (100 MHz): δ 161.3, 157.6, 149.4, 146.6, 142.8, 137.2, 128.8, 127.1, 126.8, 123.1, 107.7, 90.4, 55.5, 55.3, 51.0, 21.3. IR (thin film): ν/cm^{-1} 3317, 1597, 1518, 1495. HRMS (ESI) calc. for $C_{23}H_{24}N_2O_7S [M + Na]^+$ requires 495.1202, found 495.1209. Anal. Cale. for $C_{23}H_{24}N_2O_7S$: C, 58.46; H, 5.12; N, 5.93; Found: C, 58.76; H, 4.96; N, 5.88 (for details see ESI[†]).

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