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The Heck–Matsuda arylation of 2-hetero-substituted acrylates

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ABSTRACT

The Heck–Matsuda arylation of 2-aza and 2-oxo-substituted acrylates is described. Several reaction conditions were evaluated including the influence of solvents, temperature, catalysts, and stoichiometry. While the oxygenated system was successfully arylated in benzonitrile with $Pd_2(dba)_3$ as catalyst, the aza-acrylate furnished methoxylated products. The methoxylated products were subjected to an elimination/reduction protocol to obtain the corresponding *N*,*O*-protected phenylalanine derivatives. A one-pot procedure for the preparation of phenylalanine derivatives from 2-aza-substituted acrylates is presented.

The α-amino and α-hydroxy acid structural motifs are central to a large number of biologically important compounds found in nature.[1] α-Amino acids, for example, display valuable characteristics such as conformational restrictions, which are cleverly exploited in peptidomimetics research.[2] Aromatic amino acids having luminescent properties[3] are important probes in protein structural studies. On the other hand, α-hydroxy acids are present in several natural products bearing promising biological activities. Several of such compounds are used in pharmaceutical and medicinal research, namely pulvinic acids and their derivatives,[4] thyroid hormone analogs,[5] and other natural products such as leprapinic acid and calycine.[6]

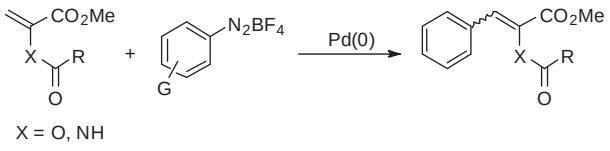
Among the several syntheses of amino acids described in the literature,[1] α-amino acids bearing aromatic rings were extensively prepared through the Heck arylation, a powerful C–C coupling reaction mediated by Pd(0),[7] often followed by asymmetric hydrogenation.[8,9] In spite of the efficiency of the traditional Heck protocols, these reactions usually require phosphine ligands, additives such as quaternary ammonium salts, inert atmosphere, high temperatures, and long reaction times.

To the best of our knowledge, the Heck–Matsuda protocol,[10] which replaces aryl halides with the more reactive arenediazonium salts, has not been evaluated for the synthesis of aromatic amino acids. The Heck–Matsuda reaction offers several advantages over the traditional Heck reaction, such as shorter reaction times, phosphine-free conditions, easy handling of the process, and quite often, lower reaction temperatures. In the last few years, we[11] and others[12] have demonstrated the synthetic potential of the arenediazonium salts in several cases, and herein we wish to disclose our results for the Heck–Matsuda arylation of methyl 2-hetero-substituted acrylates as presented in Scheme 1.

We began this study with the oxygenated system **1** and *p*-methoxyphenyldiazonium tetrafluoroborate **2**. For our initial studies, we used equimolar amounts of olefin and diazonium salts and evaluated the base, the sources of palladium, the temperature, and the reaction medium (Table 1).

Product **3** was isolated in low to modest yields under the reaction condition tested (Table 1, entries 2–8). Other solvents different from those presented in Table 1 were also tested (toluene, THF, methylene chloride, acetone, ethyl acetate, and water) with $Pd_2(dba)_3$ and sodium acetate at room temperature, providing lower yields of the desired product. Essentially, a base and heating were necessary, as demonstrated in Table 1 (entries 1–6). Excess of the olefin or the diazonium salt was also evaluated but no further improvements were observed.

A moderate 59% yield was obtained in benzonitrile (entry 7) and this result is comparable to that described in the literature for the Heck reaction employing aryl halides.[4a,c] The conditions reported herein avoided phosphine ligands, required shorter reaction times, and used equal amounts of the olefin and the arylating agent. Even shorter reaction times were achieved under microwave irradiation albeit with a slight decrease in yields. Remarkably, only the *Z* isomer was obtained with its configuration assigned by comparison with the literature data.[4a] Other arenediazonium salts such as *p*-iodo and *m*-nitrophenyldiazonium tetrafluoroborates were also evaluated, but gave poor yields (typically <10%).



Scheme 1. Heck–Matsuda arylation of 2-hetero-substituted acrylates.

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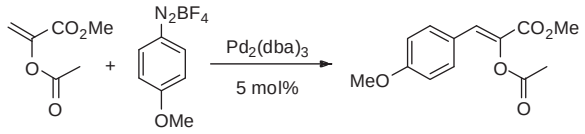
Table 1
Representative results for the arylation of methyl 2-acetoxyacrylate **1**[a]



1 **2** **3**

Entry	Solvent	Base (equiv)	T (°C)[e]	t (h)	Yield (%)
1	MeCN	None	25	2	0
2	MeCN	NaOAc (3)	25	2	14
3	MeOH	NaOAc (3)	Reflux	2	16
4	MeCN	NaOAc (3)	Reflux	27	18
5[b]	MeCN	DTBMP (3)	Reflux	3	36
6	PhCN	DTBMP (1)	80	6	46
7	PhCN	DTBMP (1)	110	3	59
8[c]	PhCN	DTBMP (1)	110	0.5	53
9[d]	PhCN	DTBMP (1)	110	3	6

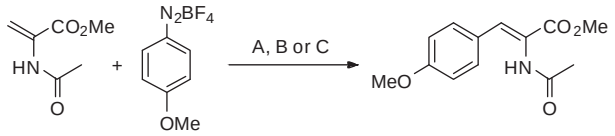
[a] Reaction conditions: 0.42 mmol of acrylate, 0.42 mmol of diazonium salt, 1–3 equiv of base, $Pd_2(dba)_3$ 5 mol %, 1.6 mL of solvent.
[b] DTBMP: 2,6-di-*t*-butyl-4-methylpyridine.
[c] Microwave heating.
[d] Catalyst: $Pd(OAc)_2$.
[e] Oil bath temperature.

As the oxygenated system **1** presented itself rather resistant to the Heck–Matsuda arylation, we turned our attention to the nitrogenated acrylate **4**. To our surprise, reaction conditions previously employed for the oxygenated acrylate **1** resulted in low yields or in no Heck product (Scheme 2).

Nitrilic solvents did not provide the desired Heck adduct **5** in spite of changes in solvent composition (including mixtures with water) and temperature (from room temperature to 110 °C). However, the Heck product **5** could be obtained in 37% yield in *t*-butanol ($Pd(OAc)_2$ as catalyst). Other solvents such as THF, water, and mixtures of THF/water proved less efficient than *t*-butanol (lower yield and longer reaction time).

A completely new scenario was observed when methanol was applied as solvent (Table 2). Instead of the expected acrylate type Heck adduct **5**, the 2-methoxy-phenylalanines **8–10** were obtained in good to excellent yields. We also tested isopropanol as solvent, sodium acetate or silver carbonate as base, $Pd_2(dba)_3$ or Pd/C as catalyst, as well as microwave heating. None of these changes led to any improvement over the conditions described in Table 2 employing methanol, palladium acetate, and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as base. In the absence of a base, a sharp decrease in yield was observed (12% yield) with lower conversion (91%).

The scope of the methodology was evaluated with acrylate **4**. In general, the efficiency of the arylation dropped as the electron withdrawing capacity of the substituent groups on the diazonium aromatic ring increased (entries 1–3, Table 2). Different nitrogen protecting groups were also evaluated.

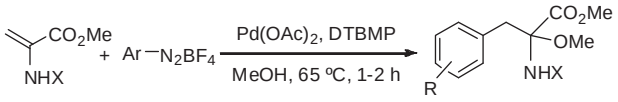


4 **2** **5**

A: $Pd_2(dba)_3$, NaOAc, MeCN, 25 ºC (no product detected)
B: $Pd_2(dba)_3$, DTBMP, PhCN, 110 ºC (no product detected)
C: *t*-BuOH, $Pd(OAc)_2$, DTBMP, 65 ºC, 2 h, 37 %

Scheme 2. Initial studies for the Heck–Matsuda arylation of **4**.

Table 2
Scope of 2-aza-acrylates arylation with diazonium salts[a]



4,6 or 7 **8-16**

Entry	X	Ar	Product	Yield (%)
1	C(O)CH_3 [**4**]	*p*-$OMeC_6H_5$	**8**	73
2	C(O)CH_3 [**4**]	*p*-FC_6H_5	**9**	68
3	C(O)CH_3 [**4**]	*p*-IC_6H_5	**10**	46
7	C(O)CF_3 [**6**]	*p*-$OMeC_6H_5$	**11**	75
9	C(O)CF_3 [**6**]	*p*-IC_6H_5	**12**	86
6	C(O)CF_3 [**6**]	*p*-FC_6H_5	**13**	81
7	C(O)CF_3 [**6**]	2-Naphthyl	**14**	77
8	C(O)CF_3 [**6**]	*m*-$NO_2C_6H_5$	**15**	65
9	C(O)CF_3 [**6**]	C_6H_5	**16**	67
10	Ts [**7**]	*p*-$OMeC_6H_5$		—

[a] Reaction conditions: 0.42 mmol of acrylate, 0.42 mmol of diazonium salt, 0.42 mmol of DTBMP, $Pd(OAc)_2$ 10 mol %, 1.6 mL of methanol, 65 °C, 1–2 h.

Trifluoroacetyl group proved to be the best protecting group (acrylate **6**), providing better yields for all diazonium salts tested. Examples shown in Table 2 are representative of the type of substituents evaluated.[13] Surprisingly, the tosyl protecting group (acrylate **7,** entry 10) was not effective.

A rationale for the formation of the 2-methoxylated Heck products follows our previous proposal for the Heck–Matsuda mechanism (Fig. 1).[14] Formation of 2-methoxylated Heck products is proposed to proceed through the iminium ion **17**, which could be formed in situ by the protonation of the enamine portion of the primary Heck adduct or by a β-elimination with the amide hydrogen leading to imine **18**. These routes involving an iminium ion look plausible due to the fact that the acid originating from the Heck catalytic cycle remains complexed with the pyridine base. The 2-methoxylated product is probably formed by the addition of methanol to the iminium ion **17**.

The Heck adducts obtained are highly functionalized small molecules, and to demonstrate their synthetic usefulness, we envisioned the synthesis of some phenylalanine derivatives from them. These phenylalanine analogs were obtained from the corresponding 2-methoxylated Heck adducts by an elimination/reduction protocol using Lewis acids and alkyl/arylsilane.[15,16]

Methoxylated Heck adducts **8** and **9** gave good yields of the reduced products **19** and **20** when reacted with boron trifluoride diethyl etherate as a Lewis acid and triethylsilane as the reductant (entries 1 and 2, Table 3). On the other hand, the trifluoromethyl adducts **11** and **12** gave lower yields of the reduced products. Attempts to increase the yields by changing temperature, solvent, Lewis acid, or reductant proved to be fruitless (Table 3).

Another possible explanation for the lower yields with trifluoromethyl adducts might be the instability of the iminium ion intermediate. Therefore, silane attack must be a fast process or the system undergoes disproportion to the Heck primary adduct **23**. Other reductants (Et_3SiH, Ph_3SiH, $PhSiH_3$, H_2/AcOH, H_2/Et_3SiH) gave low yields of the desired phenylalanine products. The best protocol was achieved with TMSOTf and Et_3SiH in 1,2-dichloroethane at 83 °C (36% yield). Alternatively, the demethoxylated phenylalanine **22** was obtained after catalytic hydrogenation of the mixture obtained from the elimination/reduction protocol in good overall yield (71%, Scheme 3).[17]

Finally, since silanes are compatible with the presence of arenediazonium salts,[18] we imagined a one-pot strategy for the preparation of phenylalanine derivatives (Table 4). Thus, a balance between diazonium salt, silicon reductant, and methanol

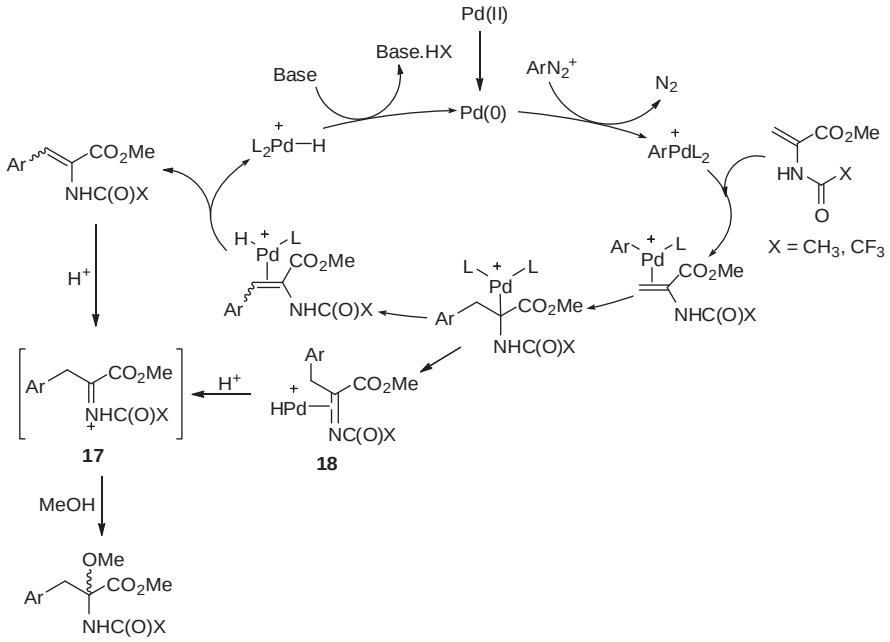
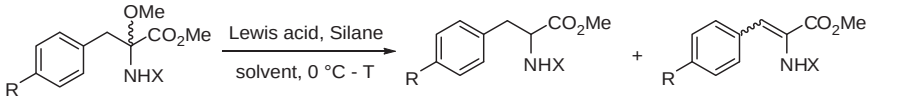


Figure 1. Rationale for the formation of 2-methoxy-adducts.

Table 3
Preparation of the phenylalanine derivatives[a]



8,9, 11 or 12

19 X = $C(O)CH_3$, R = OMe
20 X = $C(O)CH_3$, R = F
21 X = $C(O)CF_3$, R = I
22 X = $C(O)CF_3$, R = OMe

23 X = $C(O)CF_3$, R = OMe

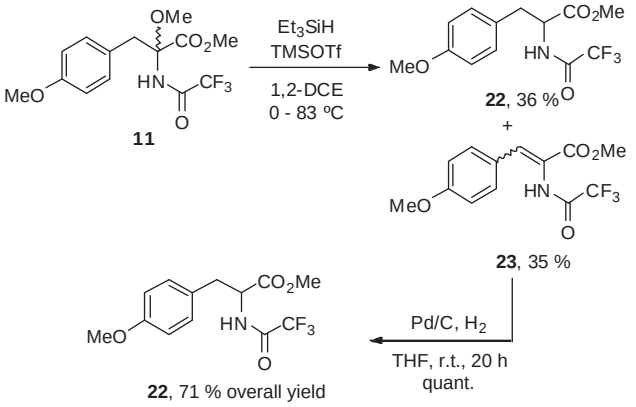
Entry	S.M.	R	X	Solvent[b]	Lewis acid	Silane	*T* (°C)	Time (h)	Yield (%)[d]
1	**8**	OMe	$C(O)CH_3$	CH_2Cl_2	$BF_3{\cdot}OEt_2$	Et_3SiH	25	18	78 [**19**]
2	**9**	F	$C(O)CH_3$	CH_2Cl_2	$BF_3{\cdot}OEt_2$	Et_3SiH	25	20	75 [**20**]
3	**12**	I	$C(O)CF_3$	CH_2Cl_2	$BF_3{\cdot}OEt_2$	Et_3SiH	25	18	—
4	**12**	I	$C(O)CF_3$	CH_2Cl_2	$BF_3{\cdot}OEt_2$	Et_3SiH	40	18	43 [**21**]
5	**12**	I	$C(O)CF_3$	THF	$BF_3{\cdot}OEt_2$	Et_3SiH	65	27	—
6	**12**	I	$C(O)CF_3$	CH_2Cl_2	TMSOTf	Et_3SiH	25	36	—
7[c]	**12**	I	$C(O)CF_3$	1,2-DCE	$BF_3{\cdot}OEt_2$	Et_3SiH	83	28	28 [**21**]
8[c]	**11**	OMe	$C(O)CF_3$	1,2-DCE	$BF_3{\cdot}OEt_2$	Et_3SiH	83	120	32 [**22**]
9	**11**	OMe	$C(O)CF_3$	1,2-DCE	TMSOTf	Et_3SiH	83	17	36 [**22**], 35 [**23**]
10	**11**	OMe	$C(O)CF_3$	1,2-DCE	TMSOTf	$PhSiH_3$	83	17	31 [**22**], 54 [**23**]
11	**11**	OMe	$C(O)CF_3$	1,2-DCE	TMSOTf	Ph_3SiH	83	20	22 [**22**], 5 [**23**]

[a] Reaction conditions: starting material (1 equiv), Lewis acid (4 equiv), silane (10 equiv), concentration (0.06 mol L^{-1}).
[b] 1,2-DCE: 1,2-dichloroethane.
[c] 8 equiv of Lewis acid and 20 equiv of silane were used.
[d] Product numbers are in brackets.

amounts was screened to find the best condition to provide the phenylalanine derivative **19**. As shown in Table 4, the best yield was 54%, using a mixture of THF:MeOH = 3:2 as the solvent and a lower temperature compared to the original Heck process (Table 2). Although not fully optimized, the overall yield is comparable to that observed for the two-step process (Scheme 4).

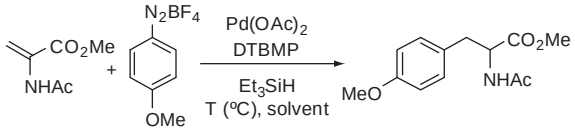
In summary, the Heck–Matsuda arylation of 2-aza and 2-oxo-substituted acrylates was investigated. Several reaction conditions were evaluated including solvents, temperature, catalysts, and stoichiometry. A more vigorous protocol was needed for the arylation of the oxygenated system **1**, while the 2-aza-substituted acrylates **4** and **6** were arylated in methanol in lower temperature furnishing the corresponding methoxylated adducts **8–16**.

As a demonstration of the synthetic potential of this Heck–Matsuda protocol, the functionalized products were submitted to an elimination/reduction protocol to obtain the phenylalanine derivatives. A one-pot procedure for the preparation of phenylalanine derivatives starting from 2-aza-substituted acrylates was also demonstrated. Further developments of the Heck–Matsuda arylation of 2-hetero-substituted acrylates are under investigation in our laboratories.



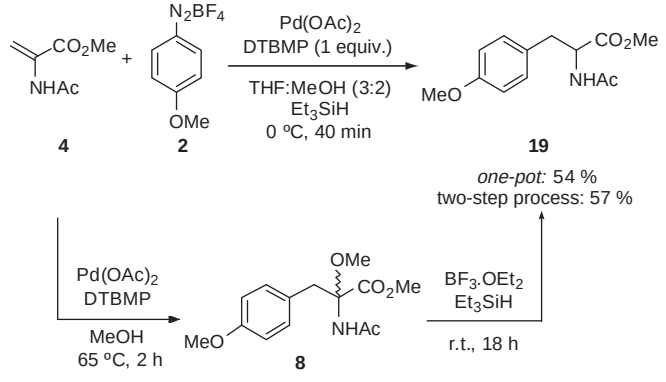
Scheme 3. Route to the phenylalanine derivatives.

Table 4
One-pot approach to the phenylalanine derivatives



Entry	Equiv 4:2:silane	*T* (°C)	Solvent	Yield (%)
1	1:1:2	65	MeOH	21
2	1:1:10	65	MeOH	35
3	1:1:10	65	THF:MeOH (3:2)	42
4	1:1:10	65	THF:MeOH (6:1)	34
6	1:2:5	0	THF:MeOH (3:2)	54
7[a]	1:2:2	0	THF:MeOH (3:2)	43

[a] Silane: Ph_3SiH.



Scheme 4. Comparison between one- and two-step processes.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.132.

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13. Application of the reaction conditions reported by Felpin (Ref. 12a). to the reaction of acrylate **4** with diazonium salt **2** (methanol, room temperature, 2 mol % of $Pd(OAc)_2$) furnished the methoxylated product **8** in only 4% yield after four days (10% conversion of the starting material). However, reaction of acrylate **6** with diazonium salt **2** under the same conditions furnished the methoxylated product **8** in 92% yield after 18 h. On the other hand, reaction of acrylate **6** with *m*-nitrodiazonium tetrafluoroborate salt furnished the methoxylated product **15** in <10% yield, after 18 h.
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