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COMMUNICATION

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Silver sequestration of halides for the activation of $Pd(OAc)_2$ catalyzed Mizoroki-Heck reaction of 1,1 and 1,2 - Disubstituted alkenes

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A ligand free catalytic system consisting of $Pd(OAc)_2$ (cat) and stoichiometric quantities of silver salts, AgOAc or $AgBF_4$, exhibit high efficiency in the Mizoroki-Heck arylation, transforming aryl iodides and 1,1 as well as 1,2 disubstituted alkenes into 1,1,2 – trisubstituted aryl alkenes in excellent yields in very short reaction times.

KEYWORDS
1,1-disubstituted alkenes, 1,2-disubstituted alkenes, $AgBF_4$, AgOAc, Mizoroki-Heck reaction

1 | INTRODUCTION

The Mizoroki-Heck arylation of monosubstituted alkenes is a fast and well studied reaction while that of 1,1 and 1,2-disubstituted alkenes is relatively less explored. 1,1,2 –Trisubstituted and 1,1,2,2,-tetrasubstituted aryl alkenes are an important structural motif in several bioactive molecules, functional materials, OLED and various organic electroluminiscent devices.[1–7] Several methodologies are available for the synthesis of these 1,1,2- and 1,1,2,2- aryl alkenes but they give mixtures of E-Z stereoisomers and isomeric purity is essential for bioactivity.[8–16] Here, the Mizoroki-Heck reaction could be preferred for its E-stereoselectivity. A few known synthesis of 1,1,2-trisubstituted aryl alkenes from the Mizoroki-Heck reaction of 1,1 and 1,2-disubstituted alkenes[17–24] are sluggish reactions, and/or require special reagents, bases, ligands and other reaction conditions.[25–30] The Mizoroki-Heck reaction of stilbenes has been applied to the synthesis of Tamoxifen.[31] Other bioactive molecules have been derived from the similar reaction of aryl halides with dimethyl itaconate ester and various disubstituted alkenes.[32–35]

The halide sequestration property of stoichiometric silver salts has been put to advantage in the asymmetric Mizoroki-Heck reaction.[36–47] AgOAc has been used in

the Mizoroki-Heck reaction of allyl alcohols and vinyl iodides.[48] One of the recent reports is the Ag_2CO_3 mediated arylation of fluoroacrylates.[49] So we experimented on the use of stoichiometric AgOAc for the Mizoroki-Heck reaction.[50]

2 | RESULTS AND DISCUSSION

The addition of stoichiometric AgOAc to the reaction mixture of 4-iodo anisole and diphenyl ethene in refluxing acetic acid as solvent, to our delight gave very high, 84% isolated yield of the desired product in short reaction time. No reaction was observed with the use of K_2CO_3 or NaOAc instead of AgOAc. The results of the reaction of several aryl iodides with 1,1 –disubstituted alkenes to give the 1,1,2-trisubstituted aryl alkenes is shown in Table 1. The reaction with diphenyl ethene was normally completed in 2 - 3 h. The reaction of ethyl atropate took 24 h for completion, while dimethylitaconate ester took 1.5-6 h (Table 1), all giving high isolated yields (Scheme 1).

An inseparable mixture of E-Z isomers was obtained in the reaction with ethyl atropate, observed by ^{1}H NMR (ratios ranging from 1:0.43 to 6: 1). Here the E- isomer was the major product, resulting in the desired Z- stilbene structural motif, confirmed by 2D NOESY NMR. No reaction was observed in the absence of AgOAc. Aryl bromides were unreactive under these conditions.

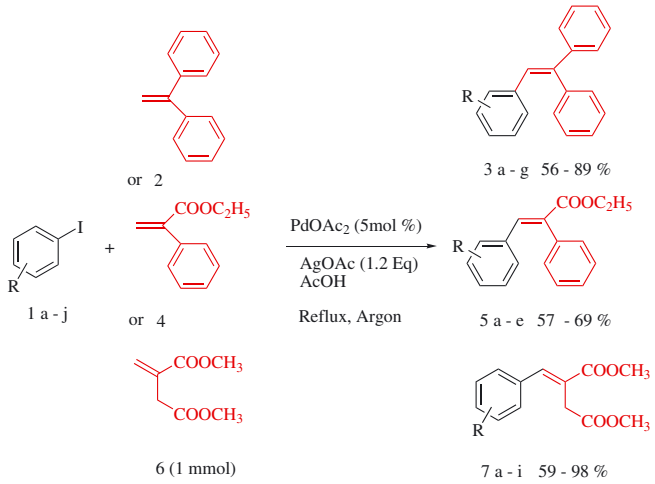
The Mizoroki - Heck reaction of itaconate ester with aryl halides and triflates has been shown to give the 2-(E)-benzylidene succinates.[34,35] These are excellent precursors of chiral benzyl succinates which can be obtained by asymmetric hydrogenation. The AgOAc protocol gave very high yields of the E - isomer (also confirmed by 2D NOESY NMR) in very short reaction times (Table 1).

The AgOAc sequestration with 1,2 –disubstituted alkenes and aryl iodides gave high isolated yields of the desired 1,1,2-trisubstituted aryl alkenes in 1- 6 h (Scheme 2, Table 2). A cationic mechanism is probably playing a role in the high yielding reaction, with AgOAc abstraction of the aryl iodide and also a Pd iodide intermediate. Various solvents like ethylene glycol, PEG-200, PEG-400 were also suitable for the reaction. $AgBF_4$, which is a stronger sequestrating agent, with greater affinity for halides, was also studied (Scheme 3). Reactions were

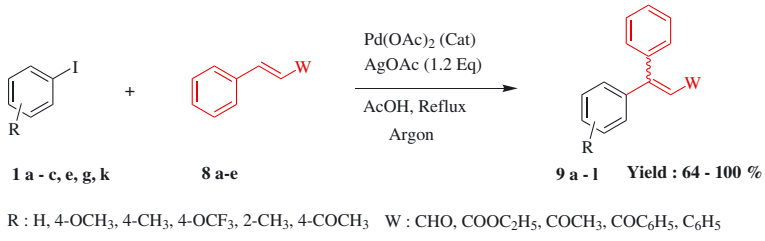
TABLE 1 $Pd(OAc)_2$ (cat)/AgOAc mediated Mizoroki-Heck reaction with 1, 1 –disubstituted alkenes[a]

S.No	Aryl iodide	Alkene	Time, h	Yield, %	Product
1	C_6H_5I (1a)	2 (DPE)	2	74	3a
2	4-$CH_3OC_6H_4I$ (1b)	2	2.5	77	3b
3	4-$CH_3C_6H_4I$(1c)	2	3	56	3c
4	4-ClC_6H_4I(1d)	2	3	60	3d
5	4-$OCF_3C_6H_4I$ (1e)	2	2.5	64	3e
6	2,4-FC_6H_3I(1f)	2	3	89	3f
7	2-$CH_3C_6H_4I$(1 g)	2	2	76	3g
8	C_6H_5I (1a)	4 (ethyl atropate)	22	58	5a(2.4: 1)
9	4-$CH_3C_6H_4I$ (1c)	4	24	69	5b (6:1)
10	4-ClC_6H_4I (1d)	4	24	61	5c (1:0.43)
11	4-FC_6H_4I(1 h)	4	21	60	5d (3: 1)
12	2,4-FC_6H_3I(1f)	4	22	57	5e (3: 1)
13	C_6H_5I (1a)	6 (Itaconate)	5	74	7a(E)
14	4-$CH_3OC_6H_4I$ (1b)	6	1.5	69	7b(E)
15	4-$CH_3C_6H_4I$ (1c)	6	3.5	89	7c(E)
16	4-ClC_6H_4I (1d)	6	3	87	7d(E)
17	4-FC_6H_4I (1 h)	6	2.5	93	7e(E)
18	4-$NO_2C_6H_4I$ (1i)	6	6	74	7f(E)
19	2-$CH_3C_6H_4I$ (1 g)	6	6	63	7g(E)
20	4-$OCF_3C_6H_4I$ (1e)	6	2	77	7h(E)
21	4-$CF_3C_6H_4I$ (1j)	6	2	98	7i(E)

[a]Reaction conditions: DPE (1 mmol), ArI (1 mmol), AgOAc (1.2 Eq), $Pd(OAc)_2$ (5 mol %), AcOH, Argon, Reflux



SCHEME 1 $Pd(OAc)_2$ (cat)/AgOAc mediated Mizoroki-Heck reaction with 1, 1 –disubstituted alkenes[a]

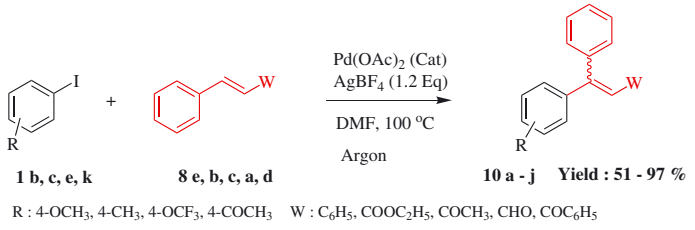


SCHEME 2 $Pd(OAc)_2$ (Cat)/AgOAc mediated Mizoroki-Heck reaction of 1,2-disubstituted alkenes[a]

TABLE 2 $Pd(OAc)_2$ (Cat)/AgOAc mediated Mizoroki-Heck reaction of 1,2-disubstituted alkenes[a]

S. No	Aryl halide	Alkene	Time, h	Yield, %	Product (E: Z)
1	C_6H_5I (1a)	8a	1	89	(9a) -
2	4-$CH_3OC_6H_4I$ (1b)	8b	1	74	(9b)-3: 1
3	4-$CH_3C_6H_4I$ (1c)	8c	1	89	(9c)-3: 1
4	4-$CF_3OC_6H_4I$ (1e)	8c	1	88	(9d)-2: 1
5	4-$CH_3COC_6H_4I$ (1 k)	8b	2	95	(9e)-8: 1
6	4-$CH_3OC_6H_4I$ (1b)	8c	5	94	(9f)-1: 1
7	4-$CH_3OC_6H_4I$ (1b)	8a	6	100	(9 g)-2: 1
8	2-$CH_3C_6H_4I$ (1 g)	8a	7	64	(9 h)-3: 1
9	4-$CH_3OC_6H_4I$ (1b)	8e	40 mins	99	(9i)-3: 1
10	2-$CH_3C_6H_4I$ (1 g)	8e	6	100	(9j)-3: 1
11	4-$CH_3C_6H_4I$ (1c)	8a	40 mins	80	(9 k)-4: 1
12	4-$CH_3OC_6H_4I$ (1b)	8d	1	97	(9 l)-2: 1

[a]Reaction conditions: ArI (1.2 mmol), 1,2-Disubstituted alkene (1 mmol), AgOAc (1.2 Eq), $Pd(OAc)_2$ (5 mol %), AcOH, Argon, Reflux



SCHEME 3 $AgBF_4$ mediated $Pd(OAc)_2$ catalyzed Mizoroki-Heck reaction[a]

complete in 2 – 7 h, in DMF as solvent, at 100 °C giving 51–97% yield (Table 3). The use of aryl bromides or even aryl chlorides is desirable in these reactions but were unreactive even with $Pd[(PPh)_3]_4$ as catalyst.

3 | EXPERIMENTAL SECTION

3.1 | General Procedure for AgOAc mediated monoarylation of 1,1-disubstituted or 1,2-disubstituted alkenes

To a solution of silver acetate (0.2 g, 1.2 mmol) and palladium acetate (0.011 g, 5 mol %) in acetic acid was added aryl iodide (1 mmol) and 1,1-diphenyl ethene (1 mmol) or cinnamaldehyde (1 mmol). The resulting mixture was heated to 110 °C for 3 h under argon. After completion of reaction (monitored by TLC), a saturated solution of $NaHCO_3$ was added to the reaction mixture to neutralize the acetic acid. The aqueous solution was extracted with ethyl acetate (3 x 20 ml) and the combined extract was washed with brine and dried over Na_2SO_4. The organic layer was concentrated under vacuum and the crude product purified by column chromatography on silica gel (100–200 mesh, Petroleum ether or Petroleum ether: 2 – 5 % Ethyl acetate) to give the pure product.

Ethene-1,1,2-triyltribenzene (**3a**) (2 h, 0.190 g, 0.74 mmol, 74 %) CAS Registry Number 58-72-0 ^{1}H NMR (200 MHz, $CDCl_3$, δ)- 7.39-7.23 (m, 10H), 7.19-7.05 (m, 5H), 7.02 (s, 1H), ^{13}C NMR (200 MHz, $CDCl_3$, δ)- 143.4, 142.6, 140.3, 137.4, 130.4, 129.5, 128.6, 128.2, 127.9, 127.6, 127.5, 127.4, 126.7, 116.5, 87.5, 83.1, 68.8, 65.1, 64.6 IR (cm^{-1}) – 3023, 2402, 1597, 1522, 1428, 1216, 1028, 928, 768, 671 HRMS-ESI: $[M^+ + H]^+$ calculated for $C_{20}H_{17}$ $[M^+ + H]^+$ 257.1325 Found: 257.1326

3,3-Diphenylacrylaldehyde (**9a**) (1 h, 0.185 g, 0.89 mmol, 89 %), CAS Registry Number 1210-39-5 ^{1}H NMR (200 MHz, $CDCl_3$, δ) – 9.56-9.54 (d, 1H), 7.52-7.28 (m, 10H), 6.64-6.62 (d, 1H), ^{13}C NMR (200 MHz, $CDCl_3$, δ)- 193.18, 161.92, 139.34, 136.31, 133.37, 128.35, 128.26, 127.98, 126.91 (IR (cm^{-1}) – 3305, 3019, 2852, 2400, 1660, 1593, 1572, 1492, 1445, 1422, 1389, 1343, 1215, 1156, 1127, 1075, 1046, 768, 701, 668 HRMS-ESI: $[M^+ + H]^+$ calculated for $C_{15}H_{13}O$ $[M^+ + H]^+$, found: 209.096

3.2 | General Procedure for $AgBF_4$ mediated monoarylation of 1,2-disubstituted alkenes

To a solution of $AgBF_4$ (0.234 g, 1.2 mmol) and palladium acetate (0.011 g, 5 mol %) in DMF under argon, was added aryl iodide (1.5 mmol) and 1,2-disubstituted alkene (1 mmol). The resulting mixture was heated to 100 °C under argon. After completion of reaction (monitored by TLC), water was added to quench the reaction. The aqueous solution was extracted with ethyl acetate (3 x 20 ml) and the combined extract was washed with brine and dried over Na_2SO_4. The organic layer was concentrated under vacuum and the crude product purified by column chromatography on silica gel (100–200 mesh, Petroleum ether or Petroleum ether: 2 – 5 % Ethyl acetate) to give the pure product.

4-Phenyl-4-(p-tolyl)but-3-en-2-one (**10a**) (2 h, 0.200 g, 0.85 mmol, 85 %) CAS Registry Number 39092-21-2 ^{1}H NMR (200 MHz, $CDCl_3$, δ)- 7.44-7.13 (m, 9H), 6.61(s, 1H, E isomer), 6.57 (s, 1H, Z isomer), 2.44 (s, 3H, Z isomer), 2.39 (s, 3H, E isomer), 1.92 (s, 3H, Z isomer), 1.89 (s, 3H, E isomer) ^{13}C NMR (200 MHz, $CDCl_3$, δ)- 200.45, 200.18, 154.19, 154.07, 141.04, 139.76, 139.12,

TABLE 3 $AgBF_4$ mediated $Pd(OAc)_2$ catalyzed Mizoroki-Heck reaction[a]

S. No	Aryl halide	Alkene	Time, h	Yield %	Product (E: Z ratio)
1	4-$CH_3OC_6H_4I$ (1b)	8e	2	76	(10 a)- 2: 1
2	4-$CH_3C_6H_5I$ (1c)	8c	2	85	(10 b)- 1: 1
3	4-$CH_3COC_6H_4I$ (1 k)	8b	2	83	(10 c)- 2: 1
4	4-$CF_3OC_6H_4I$ (1e)	8b	5	91	(10 d)- 14: 1
5	4-$CH_3OC_6H_4I$ (1b)	8b	7	91	(10 e)- 3: 1
6	4-$CH_3OC_6H_4I$ (1b)	8d	3	67	(10 f)- 2: 1
7	4-$CH_3COC_6H_4I$ (1 k)	8d	3	83	(10 g)- 2: 1
8	4-$CH_3COC_6H_4I$ (1 k)	8e	4	51	(10 h)- 1: 0.07
9	4-$CH_3OC_6H_4I$ (1b)	8a	3	84	(10 i)- 2: 1
10	4-$CH_3COC_6H_4I$ (1 k)	8a	3	97	(10 j)- 1: 1

[a]Reaction conditions: ArI (1.5 mmol), 1,2-Disubstituted alkene (1 mmol), $AgBF_4$ (1.2 Eq), $Pd(OAc)_2$ (5 mol %), DMF, Argon, 100 °C.

138.84, 137.88, 135.95, 129.57, 129.14, 128.33, 127.55, 126.88, 30.27, 21.21 IR (cm^{-1}) - 3681, 3374, 3019, 2400, 1644, 1590, 1513, 1422, 1357, 1216, 1117, 1043, 928, 851, 772, 669 HRMS-ESI: $[M^+ + H]^+$ calcd for $C_{17}H_{17}O$ $[M^+ + H]^+$ 257.1325 Found: 237.127

4 | CONCLUSIONS

In summary, the Mizoroki-Heck arylation of various 1,1- and 1,2-disubstituted alkenes to give 1,1,2-trisubstituted aryl alkenes with the bioactive Z-stilbene and benzylidene succinate motif has been described using AgOAc and $AgBF_4$ as sequestrating agents, in very high yields and short reaction times. The non Ag mediated reactions are also being investigated.

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