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Catalytic Hunsdiecker Reaction and One-Pot Catalytic Hunsdiecker–Heck Strategy: Synthesis of α,β-Unsaturated Aromatic Halides, α-(Dihalomethyl)benzenemethanols, 5-Aryl-2,4-pentadienoic acids, Dienoates and Dienamides☆

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Abstract—The reaction of α,β-unsaturated aromatic (or heteroaromatic) carboxylic acids with *N*-halosuccinimides (1 equiv.) and catalytic tetrabutylammonium trifluoroacetate (0.2 equiv.) in dichloroethane results in facile halodecarboxylation affording the corresponding (*E*)-halides in good to excellent yields. A similar reaction, but with 2 equiv. of *N*-halosuccinimides in acetonitrile-water (1:1 v/v) results in the exclusive formation of the corresponding α-(dihalomethyl)benzenemethanols. Furthermore, a one-pot strategy has been developed combining catalytic Hunsdiecker reaction (using tetrabutylammonium trifluoroacetate in dichloroethane) and Heck coupling (using palladium acetate/triethylamine/triphenylantimony/dichloroethane) for the synthesis of 5-aryl-2,4-pentadienoic acids, esters and amides in moderate to good yields. The natural product piperine and pipergualamine has been synthesized via the above route. Mechanistic and theoretical studies (via AM1 calculations) provide a useful insight into the mechanism of the present halodecarboxylation reaction, suggesting an ionic pathway involving the attack of the halogenium ion across the carbon–carbon double bond, triggering the elimination of carbon dioxide.

Introduction

The halodecarboxylation of Ag(I), Hg(II), Tl(I) or Pb(IV) carboxylates with molecular halogen, trivially known as the Hunsdiecker reaction, is of proven utility for the synthesis of various organic halides notably alkyl (1°, 2°, 3°) and aryl halides.[1] When we viewed this classical reaction from a synthetic organic chemists perspective, the necessity to use stoichiometric metal carboxylate appeared against the dictum of *atom-economy*.[2] Other limitations include: (a) the necessity to use high temperature; (b) the toxicity/hazard related to molecular bromine and salts of Hg, Tl, Pb, Ag; and (c) very poor yields[3] in cases of substrates such as α,β-unsaturated carboxylic acids.

We have recently invoked a novel protocol whereby a catalytic metal–salt pool is utilized in mediating a one-pot Hunsdiecker synthesis from in-situ generated metal carboxylates.[4] The major question that warranted further investigation is: 'What triggers the elimination of carbon dioxide?' In the classical Hunsdiecker reaction, the elimination of carbon dioxide is believed to originate from hard–soft interaction between carboxylate oxygen as hard base and metal such as Ag, Tl, Hg, and Pb as soft acid. Such an interaction leads to homolytic cleavage of the M–O bond, thereby dictating the decarboxylation via a free-radical pathway. In the present study the interaction between carboxylate oxygen and group-1 metal ion is primarily a hard–hard interaction, leading to dominant ionic character. Therefore, it is necessary to find out whether the carboxylate anion of the α,β-unsaturated carboxylic acid is greatly involved in the catalytic Hunsdiecker reaction (CHR). In this direction, generating the carboxylate anion from the reaction of acid with an 'all-organic' catalyst appeared to be an interesting exercise. We delineate herein a study in this direction and our effort in coupling the halodecarboxylation reaction with the Heck reaction in one-pot. Both the strategies resulted in new routes to synthetically important intermediates namely α,β-unsaturated aromatic halides, α-(dihalomethyl)benzenemethanols, 5-aryl-2,4-pentadienoic acids, dienoates and dienamides.

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Keywords: catalytic Hunsdiecker reaction; Heck coupling; unsaturated aromatic halides.

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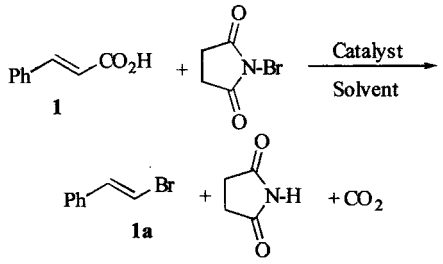
Table 1. Optimization parameters in CHR of cinnamic acid **1** to β-bromostyrene **1a**



#	Solvent	Catalyst	Yield (%)[a]
a	MeCN–H_2O	$Bu_4N^+OAc^-$	29
b		$Bu_4NOC(O)CF_3$	47
c		$Bu_4N^+OH^-$	20
d		$PhCH_2N^+Me_3OAc^-$	20
e		$PhCH_2N^+Me_3^-OC(O)CF_3$	30
f		$PhCH_2N^+Me_3OH^-$	15
g	CH_2Cl_2	$Bu_4NOC(O)CF_3$	31
h	$CHCl_3$	$Bu_4NOC(O)CF_3$	34
i	MeCN	$Bu_4NOC(O)CF_3$	45
j	CH_3NO_2	$Bu_4NOC(O)CF_3$	15
k	$Cl_2CHCHCl_2$	$Bu_4NOC(O)CF_3$	48
l	$ClCH_2CH_2Cl$	$Bu_4NOC(O)CF_3$	73

[a] Reaction time: 16 h (entries a–f); 6 h (entries g–l). Isolated yield with respect to acid.

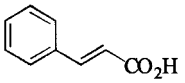
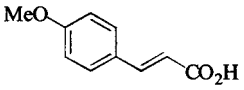
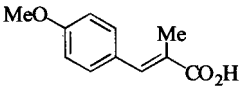
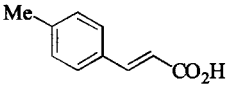
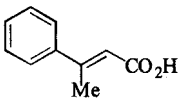
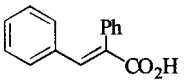
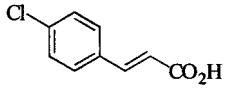
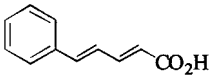
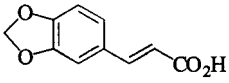
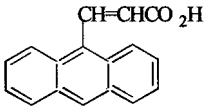
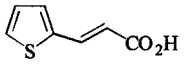
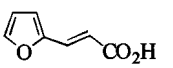
Results and Discussion

CHR of cinnamic acid with tetraalkylammonium salts as catalyst

Initial attempts to react cinnamic acid **1** (1 mmol), with NBS (1.12 mmol), tetrabutylammonium acetate (0.2 mmol) in acetonitrile–water (97:3 v/v) at ambient temperature gave rise to β-bromostyrene in 29% yield (Table 1, entry a). Several variations in the counter cation and anion in the catalyst were made in an attempt to improve the yield of the β-bromostyrene **1a** (entries b–f). Tetrabutylammonium trifluoroacetate (TBATFA) was found to be the best catalyst yielding **1a** in 47% yield (entry b). The influence of trifluoroacetate in the classical Hunsdiecker reaction is well documented.[5] We next looked into the effect of solvents in CHR. To our gratification, dichloroethane (DCE) promotes the halodecarboxylation in remarkable fashion.[6] Thus reaction of cinnamic acid (8 mM) with NBS (11.5 mM) and tetrabutylammonium trifluoroacetate (TBATFA) (1.6 mM) in DCE (16 mL) at ambient temperature after 6 h furnishes β-bromostyrene in 73% isolated yield (entry 1).

Analogous chlorodecarboxylation using NCS affords β-chlorostyrene **1b** in 78% isolated yield (Table 2). Although iododecarboxylation proceeds with equal ease (vide NMR), the product is isolated in low yield due to rapid decomposition during chromatography. It is noteworthy that the present strategy brings the Hunsdiecker synthesis from stoichiometric metal carboxylate protocol to catalytic metal-free version.[7]

Table 2. CHR of α,β-unsaturated acids to haloalkenes (unless otherwise stated, the isomeric purity of the *E* acids and corresponding (*E*)-haloalkenes is >97% (vide ^1H NMR))

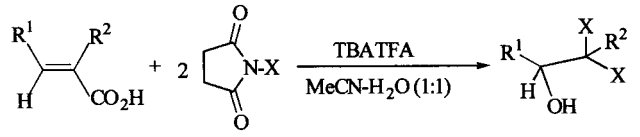
Acid	No.	X	Pdt. no.	Time (h)	Yield (%)[a]
	**1**	Br	**1a**	6	73
		Cl	**1b**	16	78
		I	**1c**	20	18[b]
	**2**	Br	**2a**	2	94
		Cl	**2b**	6	87
		I	**2c**	4	74
	**3**	Br	**3a**	4	96
		Cl	**3b**	7	93[c]
		I	**3c**	4	73[d]
	**4**	Br	**4a**	5	90
	**5**	Br	**5a**	4	93[e]
	**6**	Br	**6a**	27	51
	**7**	Br	**7a**	13	21
	**8**	Br	**8a**	18	91
	**9**	Br	**9a**	8	97
		Cl	**9b**	30	88
		I	**9c**	64	73
	**10**	Br	**10a**	21	71
		Cl	**10b**	70	68
	**11**	I	**11a**	0.5	63
	**12**	Br	**12a**	27	<15

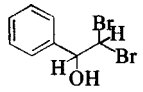
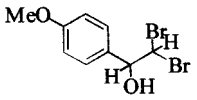
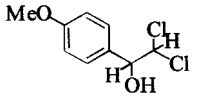
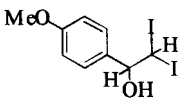
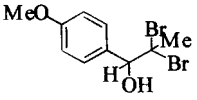
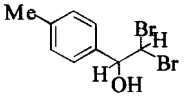
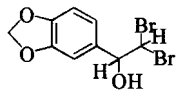
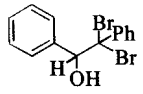
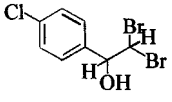
[a] Isolated yields with respect to acid.
[b] Rapid decomposition during chromatography.
[c] *E*:*Z*=1:1.
[d] *E*:*Z*=89:11.
[e] Acid *E*:*Z*=87:13; halide *E*:*Z*=75:25.

CHR of α,β-unsaturated carboxylic acids with tetrabutylammonium trifluoroacetate as catalyst

Encouraged by studies with cinnamic acid, the metal-free

Table 3. Conversion of α,β-unsaturated acids to α-(dibromomethyl)benzenemethanol



#	Acid no.	Product	No.	Yield (%)[a]
a	**1**		**13**	68
b	**2**		**14**	80
c	**2**		**15**	73
d	**2**		**16**	60
e	**3**		**17**	90
f	**4**		**18**	78
g	**9**		**19**	79
h	[b]		**20**	63
i	**6**		**21**	51
j	**7**		**22**	30

[a] Reaction time 16 h in all cases. Isolated yield with respect to acid.
[b] 1-Naphthylacrylic acid.

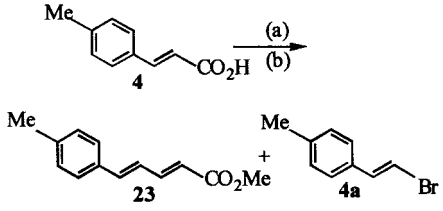
catalytic Hunsdiecker reaction was extended to various substituted cinnamic acids **2**–**7** (Table 2). For example, reaction of 4-methoxycinnamic acid **2** with NBS, TBATFA (0.2 mmol) in DCE (3 mmol) at ambient temperature affords 4-methoxy-β-bromostyrene **2a** in 94% isolated yield. Similar reactions with NCS, NIS furnishes **2b**, **2c**, in 87, 74% isolated yield, respectively. Reduced reaction time and higher yields of products are noteworthy for acids **2**–**5** bearing electron donating substituents either in the aromatic ring or alkene appendage as compared to acids **6** and **7** having electron withdrawing substituents. A futher salient feature of these reactions is the moderate to good degree of stereospecificity, wherein (*E*)-acids give rise to corresponding (*E*)-1-bromoalkenes as the major product.

To further investigate the generality of our protocol, various precursors containing unsaturated carboxylic appendages are chosen. Dienoic acid **8** affords the corresponding bromide **8a** in 91% yield. Piperonal derivative **9**, 9-anthracenyl acrylic acid **10** and 2-thienyl acrylic acid **11** undergo very facile halodecarboxylation giving rise to the corresponding halides **9a**–**9c**, **10a** and **10b**, and **11a**, respectively, as the exclusive *E*-isomer. On the other hand, furylacrylic acid **12** gives rise to the desired Hunsdiecker product **12a** in low yield. Compound **12a** is unstable in solution and characterized by NMR only.

CHR in organic–aqueous phase—a facile route to α-(dihalomethyl)benzenemethanol

A particularly interesting aspect in the present halodecarboxylation reaction is the remarkable role of solvents. Switching from dichloroethane to acetonitrile–water results in the concomitant formation of α-(dibromomethyl)benzenemethanol (Table 3). Thus the reaction of cinnamic acid **1** (1 mmol) with NBS (1.05 mmol), TBATFA (0.2 mmol) in acetonitrile–water (80:20) results in the formation of

Table 4. Optimization parameters in one-pot catalytic Hunsdiecker–Heck (CHH) reaction

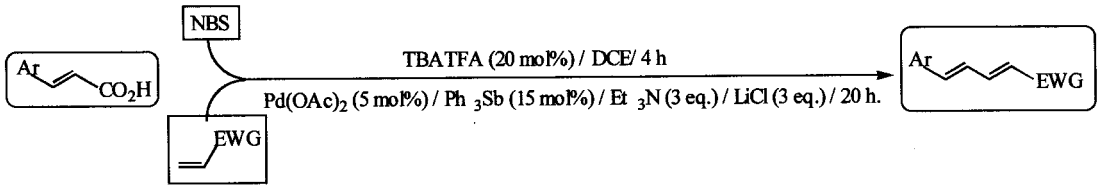


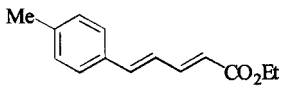
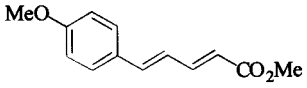
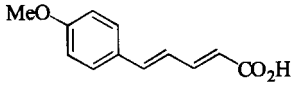
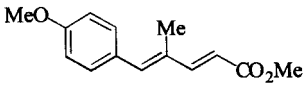
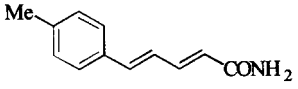
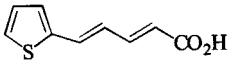
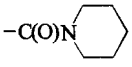
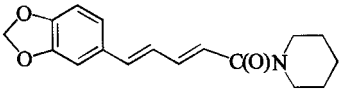
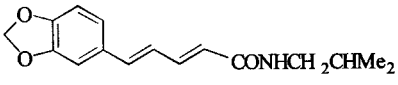
((a) NBS/TBAFTA; (b) CH_2=CH–CO_2Me/Pd(OAc)$_2$/LiCl/Et$_3$/N/L)

#	Solvent	Heck ligand (L)	Yield (%)[a] 23	4a
a	MeCN–H_2O	–	–	90
b	MeCN–H_2O	PPh_3	10	80
c	MeCN–H_2O	Ph_3Sb	49	40
d	MeCN	PPh_3	6	75
e	DCE	PPh_3	15	62
f	MeCN	(*p*-Tolyl)$_3$P	30	58
g	DCE	(*p*-Tolyl)$_3$P	35	60
h	MeCN	(*p*-Tolyl)$_3$As	10	73
i	DCE	(*p*-Tolyl)$_3$As	30	55
j	MeCN	Ph_3Sb	55	20
k	DCE	Ph_3Sb	83	<5

[a] Isolated yield with respect to acid.

Table 5. One-pot catalytic Hunsdiecker–Heck reaction



#	Acid no.	EWG	Product	No.	Yield (%)[a]
a	**4**	$-CO_2Et$		**24**	81
b	**2**	$-CO_2Me$		**25**	45
c	**2**	$-CO_2H$		**26**	50
d	**3**	$-CO_2Me$		**27**	52
e	**4**	$-CONH_2$		**28**	47
f	**11**	$-CO_2H$		**29**	42
g	**9**			**30**	51
h	**9**	$-CONHCH_2CHMe_2$		**31**	34

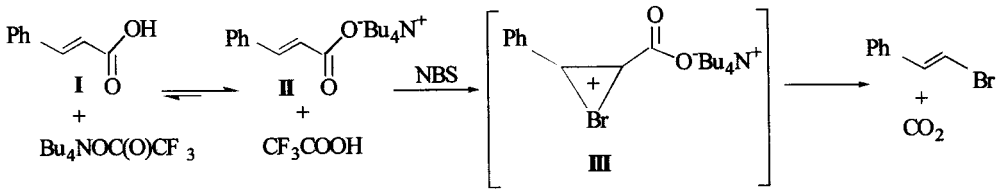
[a] Isolated yield with respect to acid.

β-bromostyrene **1a** and α-(dibromomethyl)benzenemethanol **13** along with unreacted acid in 32, 24 and 25% isolated yields, respectively, after column chromatography. Upon increasing the concentration of water and the concentration of NBS in steps, a simultaneous increase in the yield of **13** is noticed. α-(Dibromomethyl)benzenemethanol **13** is obtained as the exclusive product (vide TLC) when 2 equiv. of NBS and acetonitrile–water (1:1 v/v) is used, the isolated yield being 68% (entry a).

The intermediacy of β-bromostyrene towards the formation of α-(dibromomethyl)benzenemethanol has been confirmed in control experiments with **1**, NBS (1 equiv.) and TBATFA (0.2 equiv.). The reaction has been further extended to various unsaturated acids (Table 3, entries b, e–j). Barring **6** and **7**, all the acids afford the corresponding α-(dibromomethyl)benzenemethanols **14**–**20** in excellent yields. The reaction proceeds with equal ease with *N*-chloro and *N*-iodo succinimides as well (entries c and d).

One-pot catalytic Hunsdiecker–Heck (CHH) strategy for the synthesis of 5-aryl-2,4-penta dienoic acids, dienoates and dienamides

5-Aryl-2,4-pentadienoic acids and their derivatives exhibit a wide array of biological activities.[8] The (2*E*,4*E*)-dienamides



Scheme 1. A plausible mechanism of CHR.

derived from piperidine, pyrrolidine and isobutylamine belong to an important class of alkaloids which are common flavour constituents and also show both physiological and insecticidal activities.[9] Beside the traditional routes[10] like condensation, Reformatsky reaction and Wittig coupling, several new routes[11] have accrued in literature for their synthesis. Enthused by our new-found catalytic Hunsdiecker tool for the conversion of α,β-unsaturated carboxylic acids to the corresponding vinyl halides, we aimed in devising a one-pot strategy for the synthesis of 5-aryl-2,4-pentadienoic acids and derivatives using a halodecarboxylation/C–C coupling protocol. (Tables 4 and 5). We believe that such a protocol will provide an easy access to library synthesis of the title compounds.

Since a one-pot strategy needs to be adaptive to two different reaction conditions, optimization of various parameters is warranted. It is further noteworthy that Heck coupling of β-halostyrenes with acrylic acid and derivatives was not investigated in detail by earlier workers.[12] In view of the above, the Hunsdiecker–Heck route was initially explored under varying conditions for the synthesis of the methyl ester of 5-(4-methylphenyl)-2,4-pentadienoic acid **23** starting from 4-methylcinnamic acid **4**. The results, summarized in Table 4, indicate that changes in solvent and Heck-ligand (L) markedly influence the yield of **23**. A combination of dichloroethane, TBATFA and triphenylantimony is adjudged as best. Under this condition, **23** is isolated in 83% yield and as an all-*E* isomer (entry k).

As a further test of the synthetic adaptability of the present methodology, we have synthesized various 2,4-pentadienoic acids and derivatives **24**–**29**, bearing 5-aryl and heteroaryl substituents, in moderate to excellent yields (Table 5). It is noteworthy that all the compounds show >95% stereoselectivity towards the (2*E*,4*E*)-isomer. Application of our one-pot protocol is further demonstrated in the one-pot synthesis of natural products piperine[13] **30** and pipergualamine[14] **31** (entries g and h). The Heck precursors 1-acryloxypiperidine and 1-acryloxy isobutylamine were synthesized by modification of literature method.[15] To our knowledge, this is shortest route for these important natural products reported so far.

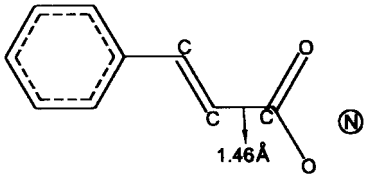


Figure 1. AM1 derived optimized structure of **II**.

Mechanism of CHR

Since no significant change in reaction time and yield of β-bromostyrene is observed for the reaction of cinnamic acid with NBS/TBATFA, in presence of *N*-α-diphenyl nitrone as radical trap, we believe that an ionic pathway is most likely. Unfortunately, from in-situ ^{1}H NMR monitoring at low temperature, no intermediate signal is detected. Our quest for the intermediate in CHR prompted us next to semi-empirical calculations. AM1 calculations were carried out mainly to look into the geometry around $\pi_{C=C}$ in various plausible intermediate species. For simplicity in calculation, ammonium ion was chosen instead of tetraalkyl ammonium ion. As described below, such calculations provide useful mechanistic insight suggesting attack of the bromonium ion at the $\pi_{C=C}$, triggering the elimination of carbon dioxide (Scheme 1).

That the carboxylate anion halodecarboxylates faster than the acid itself, is evidenced by the pronounced catalytic effect of tetraalkylammonium salts. Since experiments are conducted in organic solvent, we believe that the anion is held as tight-ion pair with tetraalkylammonium ion (**II** in Scheme 1). The HOMO of **II**, at an energy of −9.43 eV, shows higher orbital amplitude at the alkene α-carbon (bound to carboxylate), compared to the β-carbon (bound to phenyl ring). The LUMO, at −0.70 eV, is primarily located at the aromatic residue. Interestingly, the charge at the α-carbon is −0.202 compared to a charge of −0.026 at the β-carbon. This suggests the regioselective attack of the bromonium ion at the α-carbon in **II** (Fig. 1). The argument gains further support from the optimized structure of **III** (Fig. 2) where the C_α–Br bond (1.95 Å, close to a Br–C_{sp3} bond) is significantly shorter than the C_β–Br bond (2.74 Å). A weakening of the C_α–COO bond in **III** (1.51 Å) compared to that in **II** (1.46 Å) indicates the elimination of carbon dioxide.

Conclusion

The synthesis of vinyl halides in a stereo-defined fashion continues to be a challenging synthetic task, many new

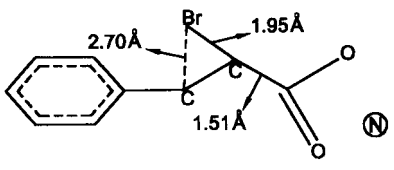


Figure 2. AM1 derived optimized structure of **III**.

routes being accrued in the recent literature. The metal-free catalytic Hunsdiecker reaction described in the present study is a potentially attractive synthetic methodology for the construction of (*E*)-vinyl halides having aromatic and heteroaromatic appendage. The reaction has been scaled up by us in several cases without sacrificing the product yields. The present synthesis of α-(dihalomethyl)benzenemethanols must be viewed with respect to earlier procedures which require stringent low temperature Grignard methodologies. The novel one-pot Hunsdiecker–Heck strategy in constructing aryl substituted (2*E*,4*E*)-dienoic acids, esters and amides provides yet another synthetically amenable route to these potentially useful precursors. Finally, the success of the CHR and CHH stratagem puts forth the Hunsdiecker reaction into yet another frontier that consists of atom economy, mild reaction conditions and reduced environmental hazard thereby enhancing its industrial merit.

Experimental

General experimental procedures are as described previously.[16] *N*-Bromosuccinimide, *N*-Chlorosuccinimide (Loba) were recrystallized from water prior to use. *N*-Iodosuccinimide (Lancaster) was used as received. Dichloroethane was distilled from phosphorus pentoxide. Acetonitrile (analytical grade) was distilled before use. Substituted aromatic unsaturated carboxylic acids were synthesized from the corresponding aldehydes (Lancaster, Ranbaxy).

Semi-empirical calculations (AM1) were performed using the program Hyperchem® 5.0 (Hypercube Inc., Ontario, Canada). The spin pairing mode and electronic state were set to RHF and lowest respectively. During geometry optimization, the convergence limit was set to 0.01 kcal/mol. The algorithm and RMS gradient were Polak–Ribiere (conjugate gradient) and 0.01 kcal/(Å mol), respectively. The convergence limit was changed to 0.0001 kcal/mol for the calculation of orbital energy diagram.

General procedure for synthesis of unsaturated halides using TBATFA

α,β-Unsaturated aromatic carboxylic acid (1 mmol) was added to a solution of TBATFA (0.2 mmol) in 3 mL of dichloroethane. After the mixture was stirred for 5 min at room temperature, *N*-halosuccinimides (1.12 mmol) was added in portions. The progress of the reaction was monitored by TLC (eluent *n*-hexane). After completion of the reaction, solvent was removed under reduced pressure and the mixture was subjected to column chromatography (silica gel 60–120 mesh, eluent *n*-hexane) to afford haloalkenes **1a**–**12a**.

General procedure for synthesis of α-(dihalomethyl)-benzenemethanol

α,β-Unsaturated aromatic carboxylic acid (1 mmol) was added to a solution of TBATFA (0.2 mmol) in 3 mL of MeCN–H_2O (1:1 v/v). After the mixture was stirred for 5 min at room temperature, *N*-halosuccinimide (2 mmol) was added in portions. The progress of the reaction was monitored by TLC (eluent 20% ethyl acetate/hexane). After completion of the reaction, solvent was removed under reduced pressure and the residue was treated with NaCl and extracted with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$ and the crude mixture was subjected to column chromatography (silica gel, eluent 5% ethyl acetate/hexane) to afford α-(dihalomethyl)benzenemethanol **13**–**22**.

General procedure of one-pot catalytic Hunsdiecker–Heck strategy for the synthesis of 5-aryl-2,4-pentadienoic acids, dienoates and dienamide, piperine, pipergualamine

NBS (1.5 mmol) was added in portions to a mixture of acid (1 mmol) and TBATFA (0.2 mmol) in 3 mL DCE. After stirring for 4 h at ambient temperature, LiCl (3 mmol), Et_3N (3 mmol), $Pd(OAc)_2$ (0.05 mmol) and Ph_3Sb (0.15 mmol), were added sequentially under nitrogen. After stirring for 10 min at ambient temperature, Heck precursor (3 mmol) was added and the mixture was heated at 90°C (bath temperature) for 20 h under nitrogen. After solvent removal, the mixture was extracted with ether, washed with water and brine. The organic part was dried over anhydrous $MgSO_4$. After evaporation of solvent, the mixture was subjected to column chromatography (silica gel, eluent 5% ethyl acetate/hexane) to afford the desired product.

Procedure for synthesis of 1-acryloxy piperidine and 1-acryloxy isobutylamine

A mixture of hydroquinone (5 mg), dry triethylamine (9 mmol) and dry piperidine or dry isobutylamine (5 mmol) in 2 mL dry benzene was placed in a 50 mL two-necked flask equipped with addition funnel and $CaCl_2$ guard tube. Then acrylyl chloride (5 mmol) in 2 mL dry benzene was added to the reaction mixture dropwise at cold condition. It was allowed to stir for 5 h at ambient temperature. It was filtered over celite and concentrated under reduced pressure and the mixture was subjected to column chromatography (silica gel 60–120 mesh, eluent ethyl acetate/hexane) to afford 1-acryloxy piperidine or 1-acryloxy isobutylamine.

Spectral characteristics of products

1-Bromo-2-phenylalkene (1a). Lit.[3,4b] (NMR is identical).

1-Chloro-2-phenylalkene (1b). Lit.[3,17] (NMR is identical).

1-Iodo-2-phenylalkene (1c). Lit.[18,19] (NMR is identical).

1-Bromo-2-(4-methoxyphenyl)alkene (2a). Lit.[3,4b] (NMR is identical).

1-Chloro-2-(4-methoxyphenyl)alkene (2b). Lit.[4b] (NMR is identical).

1-Iodo-2-(4-methoxyphenyl)alkene (2c). Lit.[4b,18] (NMR is identical).

1-Bromo-1-methyl-2-(4-methoxyphenyl)alkene (3a). Lit.[4b] (NMR is identical).

1-Chloro-1-methyl-2-(4-methoxyphenyl)alkene (3b). Lit.[4b] (NMR is identical).

1-Iodo-1-methyl-2-(4-methoxyphenyl)alkene (3c). Lit.[4b] (NMR is identical).

1-Bromo-2-(4-methylphenyl)alkene (4a). Lit.[3,4b] (NMR is identical).

1-Bromo-2-methyl-2-phenylalkene (5a). Lit.[3,4b] (NMR is identical).

1-Bromo-1-phenyl-2-phenylalkene (6a). Lit.[3] (NMR is identical).

1-Bromo-2-(4-chlorophenyl)alkene (7a). Lit.[3,4b] (NMR is identical).

1-Bromo-4-phenyl-1,3-butadiene (8a). Lit.[4b] (NMR is identical).

1-Bromo-2-(3,4-methylenedioxyphenyl)alkene (9a). Low melting solid. [Found: C, 47.42; H, 3.33. $C_9H_7O_2Br$ requires C, 47.61, H, 3.11]. δ_H (200 MHz $CDCl_3$) 7.0 (d, 1H, *J*=14 Hz), 6.76 (d, 2H, *J*=9 Hz), 6.72 (s, 1H), 6.58 (d, 1H, *J*=14 Hz), δ 5.98 (s, 2H). EIMS *m/z* (rel intensity): 226 (M^+, 99%), 147 (23%), 117 (15%), 89 (63%), 73 (15%), 63 (40%), 43 (27%). IR (neat) cm^{-1}: 1680 (m), 1504 (s), 1264(vs), 1040 (s).

1-Chloro-2-(3,4-methylenedioxyphenyl)alkene (9b). Oil. [Found: C, 58.97; H, 3.98. $C_9H_7O_2Cl$ requires C, 59.19, H, 3.87]. δ_H (200 MHz $CDCl_3$) 6.78 (d, 1H, *J*=14 Hz), 6.71 (s, 1H), 6.70 (d, 2H, *J*=9 Hz), 6.46 (d, 1H, *J*=14 Hz), 5.98 (s, 2H). EIMS *m/z* (rel intensity): 182 (M^+, 99%), 168 (7%), 126 (7%), 117 (7%), 89 (67%), 73 (18%), 63 (39%), 50 (15%). IR (neat) cm^{-1}: 1676 (m), 1508 (m), 1240 (s), 1035 (w).

1-Iodo-2-(3,4-methylenedioxyphenyl)alkene (9c). Low melting solid. [Found: C, 39.28; H, 2.91. $C_9H_7IO_2$ requires C, 39.44, H, 2.58]. δ_H (200 MHz $CDCl_3$) 7.80 (s, 1H), 7.30 (d, 1H, *J*=14 Hz), 6.68 (d, 2H, *J*=9 Hz), 6.61 (d, 1H, *J*=14 Hz), 5.96 (s, 2H). EIMS *m/z* (rel intensity): 274 (M^+, 94%), 147 (14%), 117 (10%), 89 (60%), 73 (12%), 63 (41%), 50 (16%). IR (neat) cm^{-1}: 1687 (w), 1498 (vs), 1250 (m), 1050 (m).

1-Bromo-2-(9-anthracenyl)alkene (10a). Low melting solid. [Found: C, 67.61; H, 4.14. $C_{16}H_{11}Br$ requires C, 67.86, H, 3.92]. δ_H (200 MHz $CDCl_3$) 8.45 (s, 1H), 8.23 (dd, 2H, *J*=9, 4 Hz), 8.01 (dd, 2H, *J*=9, 4 Hz), 7.91 (d, 1H, *J*=16 Hz), 7.50 (m, 4H), 6.61 (d, 1H, *J*=16 Hz). EIMS *m/z* (rel intensity): 282 (M^+, 11%), 204 (100%), 101 (23%), 88 (7%), 43 (12%). IR (neat) cm^{-1}: 1680 (w), 1600 (m), 1520 (vs), 1264 (s).

1-Chloro-2-(9-anthracenyl)alkene (10b). Low melting solid. [Found: C, 79.98; H, 4.89. $C_{16}H_{11}Cl$ requires C, 80.49, H, 4.65]. δ_H (200 MHz $CDCl_3$) 8.55 (d, 2H, *J*=9 Hz), 8.23 (dd, 2H, *J*=9, 4 Hz), 7.50–7.63 (m, 6H), 6.45 (d, 1H, *J*=15 Hz). EIMS *m/z* (rel intensity): 237 (M^+, 58%), 202 (100%), 118 (19%), 100 (20%), 85 (7%), 71 (15%), 57 (25%), 43 (18%). IR (neat) cm^{-1}: 1676 (w), 1603 (s), 1515 (s), 1265 (m).

1-Bromo-2-(2-thienyl)alkene (11a). Oil. [Found: C, 30.28; H, 2.32. C_6H_5IS requires C, 30.53, H, 2.13]. δ_H (200 MHz $CDCl_3$) 7.40 (d, 1H, *J*=15 Hz), 7.12 (dd, 1H, *J*=8, 4 Hz), 6.89 (d, 1H, *J*=8 Hz), 6.87 (d, 1H, *J*=8 Hz), 6.56 (d, 1H, *J*=15 Hz). EIMS *m/z* (rel intensity): 236 (M^+, 100%), 109 (85%), 65 (36%), 39 (22%). IR (neat) cm^{-1}: 1640 (m), 1610 (w), 1500 (m), 1263 (s).

1-Bromo-2-(2-furyl)alkene (12a). Oil. δ_H (200 MHz $CDCl_3$) 6.89 (d, 1H, *J*=14 Hz), 6.79 (s, 1H), 6.71 (d, 1H, *J*=14 Hz), 6.36 (dd, 1H, *J*=8, 4 Hz), 6.25 (d, 1H, *J*=8 Hz). EIMS *m/z* (rel intensity): 172 (M^+, 37%), 133 (70%), 97 (70%), 69 (69%), 55 (100%). IR (neat) cm^{-1}: 1635 (m), 1608 (s), 1501 (m), 1260 (w).

α-(Dibromomethyl)benzenemethanol (13). Low melting solid. [Found: C, 34.18; H, 2.97. $C_8H_8Br_2O$ requires C, 34.32, H, 2.88]. δ_H (200 MHz $CDCl_3$) 7.31 (s, 5H), 5.71 (d, 1H, *J*=8 Hz), 4.94 (d, 1H, *J*=8 Hz). IR (neat) cm^{-1}: 1591 (w), 1522 (s), 1267 (m).

α-(Dibromomethyl)-4-methoxybenzenemethanol (14). Solid. [Found: C, 34.59; H, 3.39. $C_9H_{10}Br_2O_2$ requires C, 34.87, H, 3.25]. δ_H (200 MHz $CDCl_3$) 7.34 (d, 2H, *J*=9 Hz), 6.91 (d, 2H, *J*=9 Hz), 5.74 (d, 1H, *J*=8 Hz), 4.98 (d, 1H, *J*=8 Hz), 3.81 (s, 3H), 2.85 (br. 1H). EIMS *m/z* (rel intensity): 310 (M^+, 10%), 150 (10%), 137 (100%), 135 (18%), 121 (55%), 109 (21%), 94 (11%), 77 (25%). IR (KBr) cm^{-1}: 1600 (m), 1520 (vs), 1264 (vs).

α-(Dichloromethyl)-4-methoxybenzenemethanol (15). Oil. [Found: C, 48.67; H, 4.72. $C_9H_{10}Cl_2O_2$ requires C, 48.89, H, 4.56]. δ_H (200 MHz $CDCl_3$) 7.34 (d, 2H, *J*=9 Hz), 6.87 (d, 2H, *J*=9 Hz), 5.72 (d, 1H, *J*=8 Hz), 4.87 (d, 1H, *J*=8 Hz), 3.80 (s, 3H), 2.50 (br. 1H). EIMS *m/z* (rel intensity): 220 (M^+, 3%), 137 (100%), 109 (28%), 94 (24%), 77 (33%). IR (neat) cm^{-1}: 1601 (m), 1519 (vs), 1264 (s).

α-(Diiodomethyl)-4-methoxybenzenemethanol (16). Oil. [Found: C, 26.53; H, 2.28. $C_9H_{10}I_2O_2$ requires C, 26.76, H, 2.49]. δ_H (200 MHz $CDCl_3$) 7.31 (d, 2H, *J*=9 Hz), 6.85 (d, 2H, *J*=9 Hz), 5.25 (d, 1H, *J*=8 Hz), 4.60 (s, 1H), 3.81 (s, 3H), 2.78 (br. 1H). EIMS *m/z* (rel intensity): 404 (M^+, 6%), 254 (18%), 128 (51%), 57 (100%). IR (neat) cm^{-1}: 1598 (m), 1522 (vs), 1266 (w).

α-(Dibromomethyl)-α-methyl-4-methoxybenzenemethanol (17). Oil. [Found: C, 36.80; H, 4.01. $C_{10}H_{12}Br_2O_2$ requires C, 37.07.45, H, 3.74]. δ_H (200 MHz $CDCl_3$) 7.38 (d, 2H, *J*=9 Hz), 6.80 (d, 2H, *J*=9 Hz), 4.88 (s, 1H), 3.75 (s, 3H), 2.95 (br. 1H), 2.32 (s, 3H). IR (neat) cm^{-1}: 1601 (w), 1521 (m), 1263 (s).

α-(Dibromomethyl)-4-methylbenzenemethanol (18). Low melting solid. [Found: C, 36.58; H, 3.61. $C_9H_{10}Br_2O$ requires C, 36.77, H, 3.43]. δ_H (200 MHz $CDCl_3$) 7.26 (d, 2H, *J*=9 Hz), 7.11 (d, 2H, *J*=9 Hz), 5.72 (d, 1H, *J*=8 Hz),

4.95 (d, 1H, *J*=8 Hz), 2.85 (br. 1H), 2.35 (s, 3H). EIMS *m/z* (rel intensity): 294 (M^+, 15%), 277 (75%), 198 (51%), 173 (19%), 121 (100%), 115 (8%), 105 (15%), 93 (73%), 91 (55%), 77 (43%), 51 (12%), 43 (14%). IR (neat) cm^{-1}: 1601 (m), 1522 (vs), 1264 (s).

α-(Dibromomethyl)-3,4-methylenedioxybenzenemethanol (19). Low melting solid. [Found: C, 33.24; H, 2.66. $C_9H_8Br_2O$ requires C, 33.37, H, 2.49]. δ_H (200 MHz $CDCl_3$) 6.90 (s, 1H), 6.86 (d, 1H, *J*=9 Hz), 6.79 (d, 1H, *J*=9 Hz), 6.0 (s, 2H), 5.70 (d, 1H, *J*=8 Hz), 4.91 (d, 1H, *J*=8 Hz), 2.80 (br, 1H). EIMS *m/z* (rel intensity): 324 (M^+, 30%), 229 (22%), 151 (100%), 135 (30%), 93 (98%), 65 (81%), 63 (46%). IR (neat) cm^{-1}: 1678 (w), 1503 (s), 1267 (m).

α-(Dibromomethyl)-1-naphthylmethanol (20). Low melting solid. [Found: C, 43.45; H, 3.21. $C_{12}H_{10}Br_2O$ requires C, 43.67, H, 3.05]. δ_H (200 MHz $CDCl_3$) 7.84 (m, 3H), 7.7 (d, 1H, *J*=8 Hz), 7.48–7.56 (m, 3H), 6.08 (d, 1H, *J*=8 Hz), 5.75 (d, 1H, *J*=8 Hz). EIMS *m/z* (rel intensity): 330 (M^+, 9%), 157 (100%), 129 (58%), 115 (9%). IR (neat) cm^{-1}; 1672 (w), 1598 (m), 1265 (vs).

α-(Dibromomethyl)-α-phenyl-benzenemethanol (21). Oil. [Found: C, 47.09; H, 3.21. $C_{14}H_{12}Br_2O$ requires C, 47.22, H, 3.40]. δ_H (200 MHz $CDCl_3$) 7.98 (d, 2H, *J*=8 Hz), 7.26–7.55 (m, 8H), 6.3 (s, 1H). EIMS *m/z* (rel intensity): 356 (M^+, 5%), 258 (6%), 178 (15%), 105 (100%), 77 (91%). IR (neat) cm^{-1}: 1595 (m), 1525 (s), 1265 (m).

α-(Dibromomethyl)-4-chlorobenzenemethanol (22). Low melting solid. [Found: C, 30.08; H, 2.74. $C_8H_7Br_2ClO$ requires C, 30.56, H, 2.25]. δ_H (200 MHz $CDCl_3$) 7.31 (s, 4H), 5.67 (d, 1H, *J*=8 Hz), 4.91 (d, 1H, *J*=8 Hz). IR (neat) cm^{-1}: 1601 (w), 1520 (s), 1263 (m).

Methyl-5-(4-methylphenyl)-2,4-pentadienoate (23). Mp 98–99°C (lit.[10c] 98–99°C).

Ethyl-5-(4-methylphenyl)-2,4-pentadienoate (24). Oil. [Found: C, 77.54; H, 7.61. $C_{14}H_6O_2$ requires C, 77.73, H, 7.47]. δ_H (200 MHz $CDCl_3$) 7.4 (dd, 1H, *J*=11, 15 Hz), 7.3 (d, 2H, *J*=8 Hz), 7.11 (d, 2H, *J*=8 Hz), 6.7-6.9 (m, 2H), 5.9 (d, 1H, *J*=15 Hz), 4.11 (q, 2H, *J*=6 Hz), 2.2 (s, 3H), 1.20 (t, 3H, *J*=6 Hz). EIMS *m/z* (rel intensity): 216 (M^+, 29%), 190 (24%), 171 (18%), 143 (100%), 128 (39%), 115 (27%), 91 (12%). IR (neat) cm^{-1}: 1108 (s), 1154 (s), 1585 (m), 1277 (vs), 2877 (w).

Methyl-5-(4-methoxyphenyl)-2,4-pentadienoate (25). Mp 125–126°C (lit.[10c] 125–126°C).

5-(4-Methoxyphenyl)-2,4-pentadienoic acid (26). Mp 98–100°C. δ_H (200 MHz $CDCl_3$) 7.52 (dd, 1H, *J*=11, 16 Hz), 7.45 (d, 2H, *J*=8 Hz), 7.25 (d, 2H, *J*=8 Hz), 6.7–7.0 (m, 2H), 5.95 (d, 1H, *J*=16 Hz), 3.88 (s, 3H). EIMS *m/z* (rel intensity): 204 (M^+, 39%), 162 (80%) 144 (23%), 115 (100%), 105 (14%), 91 (53%), 65 (32%), 63 (45%), 45 (70%). IR (KBr) cm^{-1}: 1154 (m), 1230 (vs), 1492 (s), 1662 (s), 2877 (w).

Methyl-4-methyl-5-(4-methoxyphenyl)-2,4-pentadienoate (27). Solid. [Found: C, 72.24; H, 7.10. $C_{14}H_{16}O_3$ requires C, 72.38, H, 6.96]. δ_H (200 MHz $CDCl_3$) 7.52 (d, 1H, *J*=16 Hz), 7.32 (d, 2H, *J*=9 Hz), 6.92 (d, 2H, *J*=9 Hz), 6.82 (s, 1H), 5.93 (d, 1H, *J*=16 Hz), 3.88 (s, 3H), 3.80 (s, 3H), 2.1 (s, 3H). EIMS *m/z* (rel intensity): 232 (M^+, 39%), 201 (8%), 173 (100%), 158 (46%), 141 (8%), 129 (12%), 115 (14%). IR (KBr) cm^{-1}: 1154 (vs), 1231 (s), 1492 (m), 1601 (m), 1677 (m), 2876 (w).

5-(4-Methylphenyl)-2,4-pentadienamide (28). Solid. δ_H (200 MHz $CDCl_3$) 7.35 (d, 2H, *J*=9 Hz), 7.13 (d, 2H, *J*=9 Hz), 7.2 (m, 1H), 6.78 (m, 1H), 6.05 (d, 1H, *J*=14 Hz), 2.3 (s, 3H). EIMS *m/z* (rel intensity): 188 (M^+, 5%), 162 (100%), 117 (100%), 101 (81%), 73 (30%). IR (KBr) cm^{-1}: 985 (m), 1369 (s), 1631 (vs), 3108 (w).

5-(2-Thienyl)-2,4-pentadienoic acid (29). Solid. δ_H (200 MHz $CDCl_3$) 7.50 (dd, 1H, *J*=12, 16 Hz), 7.31 (d, 1H, *J*=8 Hz), 7.29 (d, 1H, *J*=16 Hz), 7.15 (dd, 1H, *J*=8, 4 Hz), 7.01 (m, 1H), 6.70 (dd, 1H, *J*=12, 16 Hz), 6.00 (d, 1H, *J*=16 Hz). EIMS *m/z* (rel intensity): 180 (M^+, 6%), 135 (70%) 134 (45%), 108 (14%), 97 (8%), 91 (70%), 65 (15%), 63 (30%), 45 (100%). IR (KBr) cm^{-1}: 1155 (m), 1237 (vs), 1480 (s), 1665 (s), 2875 (w).

Piperine (30). Lit.[13] (NMR is identical).

Pipergualamine (31). Lit.[14] (NMR is identical).

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