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A Robust First-Pass Protocol for the Heck–Mizoroki Reaction

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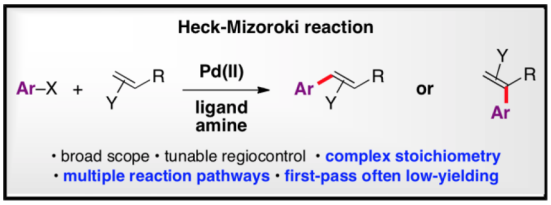
Supporting Information

ABSTRACT: The Heck–Mizoroki (HM) reaction is one of the most widely used C–C bond-forming methods of contemporary synthesis. Notwithstanding this, these reactions frequently require significant optimization before efficient transformations can be obtained. We describe here the results of a study that aimed to establish a generic experimental protocol for HM reactions which enables acceptable yields from first-pass experiments. The methodology utilizes readily available stable catalysts and can be applied to a broad range of coupling partners.

INTRODUCTION

The use of transition metal-catalyzed coupling reactions has revolutionized organic synthesis, and the goal of achieving a fuller understanding of these processes means the area continues to provide a fertile ground for researchers. Although groundbreaking advances in metal-catalysed amination, amidation, etherification, alcohol activation, hydroamination, and hydroacylation reactions have been reported in the past two decades, even "mature" metal-catalyzed C–C bond-forming reactions, such as alkene-aryl halide/pseudohalide cross-couplings [the Heck–Mizoroki (HM) reaction],[1] continue to provide challenges. This is particularly true from the perspective of predictive catalysis, which aims to establish a reliable methodology for a broad range of metal-catalyzed bond-forming processes. In the latter arena, the continuing disclosure of modifications to HM reactions[2,3] is a telling comment upon the unmet need for optimization and genericization. Thus, despite the enormous effort expended in the area, and the ubiquity of HM reactions in academic and industrial[4] contexts, many class-leading studies have been tightly focused, for instance, on the use of particular substrates (such as aryl chlorides) or catalyst/ligand permutations, rather than aimed at delivering general, robust, and efficient protocols. The pursuit of a ubiquitous HM protocol which consistently delivers good yields of coupled product is, therefore, a challenging target; this is due to the complexity typical of metal-catalyzed reactions, where a remarkable diversity of ingredients (ligand, cocatalyst, solvent, base, additives, etc.) can be (and often are) needed for satisfactory performance. It remains the case that there is no single experimental protocol for HM reactions which has been clearly demonstrated to give acceptable first-pass yields when reacting a broad range of coupling partners. Indeed, to the nonexpert practitioner there is a daunting diversity of reported procedures for every type of transition metal-catalyzed reaction, often resulting in the need for significant optimization. This became clear to us when, as part of a program of research directed toward the production of Crestor (rosuvastatin calcium),[5] we anticipated that an HM process would facilitate a key C–C bond-forming event but were disappointed to find that a range of "standard" conditions were ineffective; a time-consuming lengthy optimization process was required to provide acceptable yields in the key cross-coupling. Given the extensive literature reports and commercial use of HM reactions, a reliable and robust procedure for Heck reactions would be of considerable value. Challenged by the limitations imposed upon our chemistry by probably the best-known and most widely used Pd-catalyzed cross-coupling method, we sought to design a set of generic conditions[6] for HM reactions, and we report here the results of our studies in the area.



RESULTS AND DISCUSSION

As mentioned, a great deal of effort has been expended in designing ligands which tune the key steps of HM reactions; however, there is still no single protocol which is reported to work "off the shelf", and delivering such a flexible method was our primary goal. For the purposes of our study, we defined a "successful reaction" as one which delivered an at least 70% yield of cross-coupled product in a first-pass reaction. To tailor a generic method for HM reaction, one must take account of the eclectic cocktail of catalyst, cocatalyst(s), reagents, base, solvent, and additive(s) which are often required, so we planned our study to proceed in several phases. In the first phase, we analyzed catalyst variation,[7] using a representative set of aryl bromides (still the most widely used oxidative addition substrates), with the members of the bromide set chosen to map the spectrum of electronic (bromides **3**–**6** and **8**–**10**) and steric factors (bromides **6**–**10**); the initial alkene coupling partner sets were

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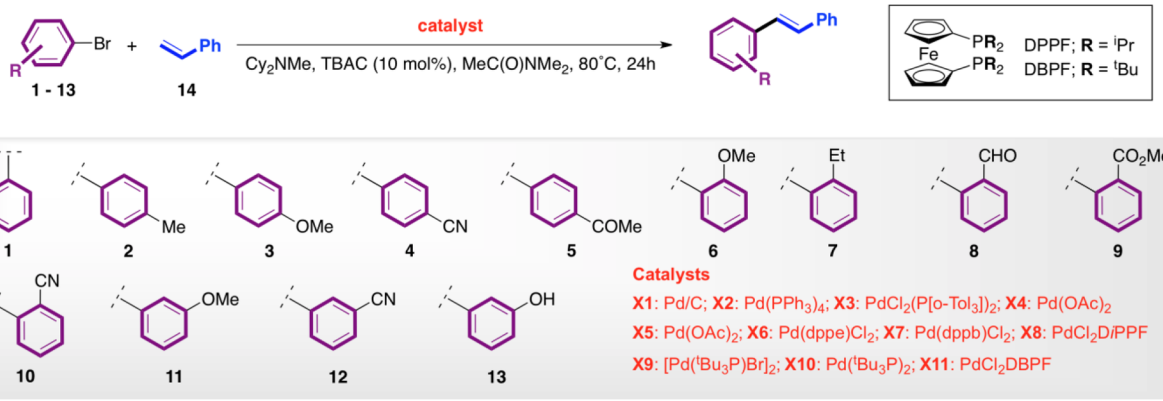
Table 1. A Generic Heck–Mizoroki Protocol for Styrene



		conversion[a] (%)												
entry	catalyst	1	2	3	4	5	6	7	8	9	10	11	12	13
A	**X1**	NE[b]	14	NE[b]	**100**	**100**	NE[b]	0	0	0	NE[b]	50	95	0
B	**X2**	60	26	15	11	34	0	0	0	0	0	6	0	**80**
C	**X3**	0	NE[b]	15	**99**	**99**	3	**99**	**99**	**99**	**99**	**99**	**99**	**75**
D	**X4**[c]	0	NE[b]	0	30	0	3	0	0	0	15	15	30	4
E	**X5**	0	67	0	**100**	**100**	0	12	0	**100**	0	**100**	**100**	4
F	**X6**	0	**88**	0	**100**	**100**	0	13	0	0	0	66	14	0
G	**X7**	0	0	30	0	0	3	0	0	0	0	**72**	0	0
H	**X8**	30	NE[b]	0	0	**99**	3	0	0	0	0	30	15	0
I	**X9**	**99**	**100**	**99**	**100**	**100**	**99**	63	**100**	**100**	**99**	**100**	**100**	**100**
J	**X10**	**99**	**100**	**99**	**100**	**100**	**99**	**81**	**73**	**100**	**99**	**100**	**100**	**100**
K	**X11**	**99**	**90**	**99**		**90**	15	**80**	**80**	**76**	**30**	**70**	**79**	**99**

[a]Assessed using GC/GCMS, using internal standards to ensure reproducibility. [b]Reaction not examined. [c]"Homeopathic" palladium.

comprised of styrene (**14**) and acrylates **15** and **16** (these two alkene classes significantly outnumber every other HM substrate class reported in the contemporary literature). With regard to catalysts, given the plethora of reported complex–ligand combinations, the selection process was more daunting; to simplify the primary analysis, we chose to analyze palladium catalysts **X1**–**X11** based primarily on the criteria of ready availability, stability, and cost. The reactions were conducted using a hindered amine base (methyldicyclohexylamine) to accelerate reductive elimination, in a polar solvent [dimethylacetamide (DMAC)] in the presence of substoichiometric tetrabutylammonium chloride (TBAC).[a] Thus, we commenced with a study of HM reactions of styrene (Table 1).[8] This process quickly identified catalysts **X9**–**X11** as privileged mediators of the HM reaction, with electronic factors seemingly nonsignificant, and only the sterically encumbered 2-ethyl bromobenzene **7** proving to be a demanding coupling partner (entries I7–K7). Because transition metal-catalyzed couplings of ortho-substituted partners are usually sensitive to steric effects, this was not surprising. Another noteworthy observation was the efficient cross-coupling of 3-hydroxybromobenzene (entries B13 and C13 and I13–K13), because the literature is sparsely populated by reports of successful HM reactions of unprotected phenols.[9]

When the screening process was extrapolated to acrylates (Table 2), catalysts **X9**–**X11** again proved to be the most effective mediators, but with less efficient conversions; encouragingly, the cross-coupling of demanding substrate **7** proceeded with acceptable conversions (entries Q7, S7, and U7), with methacrylate proving to be a more challenging substrate partner (entries R7, T7, and V7). The reactions of the acrylate subset indicated that electronics were now a significant factor (entries R4/5 and T4/5).

Somewhat less explicably, reactions of both electron-rich and electron-deficient meta-substituted bromides were often inefficient with the first-generation privileged catalyst set (entries Q11–Q13 to V11–V13), with the full data set indicating that only catalysts **X10** [$Pd(^tBu_3P)_2$] and **X11** [$PdCl_2(DBPF)_2$] were consistently successful in providing acceptable conversions to the cross-coupled product. It should be pointed out here that in these screening processes (Tables 1 and 2), no trace of biaryl side products was observed and GC analysis indicated high yields of cross-coupled products.

To assess the impact of intimate substitution in the alkene coupling partner, we next examined methyl crotonate as a substrate (Table 3). With a subset of the aryl bromide pool, yields were generally acceptable with the exception of that of 2-bromobenzoate (Table 3, entry E).

In the next phase of our study, we validated the yields of the HM reactions of styrene and acrylates and examined the scope of cross-coupling reactions using privileged catalyst **X11** (the most stable and easiest- handled of the triad of privileged catalysts identified); Scheme 1 summarizes the results obtained from single, unoptimized reactions, the majority of which proceeded in high yield. In addition to the good yields for first-time reactions, of particular note were the generally efficient reactions with notoriously hindered substrates, such as 2,6-diethylbromobenzene, which delivered coupled product **17k** in 77% yield (at 90% conversion). It is also reassuring that variations in the electron density of the oxidative addition substrates seem to have little effect, with both electron-deficient and electron-rich aryl bromides reacting efficiently. As mentioned above, it was especially satisfying to witness the successful and generally

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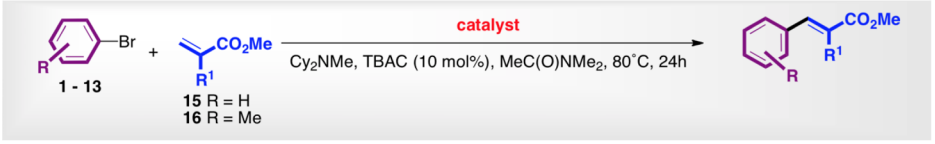
Table 2. A Generic Heck−Mizoroki Protocol for Acrylates



		conversion[a] (%)													
entry	catalyst	1	2	3	4	5	6	7	8	9	10	11	12	13	acrylate
A	**X1**	NE[b]	42	NE[b]	**81**	**99**	NE[b]	24	0	30	NE[b]	**76**	**92**	0	**15**
B		NE[b]	8	NE[b]	26	62	NE[b]	0	0	0	NE[b]	17	29	0	**16**
C	**X2**	**99**	67	45	0	0	0	0	0	0	0	32	0	52	**15**
D		30	0	0	0	0	0	0	0	0	0	0	0	64	**16**
E	**X3**	0	NE[b]	60	**99**	**99**	3	0	15	**99**	**99**	**99**	**99**	**75**	**15**
F		0	NE[b]	15	**75**	**99**	0	0	0	0	**99**	30	**99**	**75**	**16**
G	**X4**	0	NE[b]	15	**99**	30	3	0	15	0	60	45	**99**	0	**15**
H		0	NE[b]	0	15	0	0	0	0	0	15	0	15	0	**16**
I	**X5**	0	**100**	0	**100**	**100**	0	57	0	**100**	0	**100**	**100**	9	**15**
J		0	24	0	48	53	0	57	0	0	0	34	25	0	**16**
K	**X6**	15	**100**	30	67	**100**	3	**93**	0	0	0	**100**	60	0	**15**
L		0	28	0	29	37	0	77	0	0	0	25	6	0	**16**
M	**X7**	30	0	99	0	44	3	0	0	0	0	100	0	0	**15**
N		0	0	0	0	10	0	0	0	0	0	18	0	0	**16**
O	**X8**	**99**	NE[b]	15	30	**99**	3	0	15	15	0	45	45	15	**15**
P		15	NE[b]	0	0	60	0	0	0	0	0	0	0	0	**16**
Q	**X9**	**99**	**100**	**99**	**78**	77	**99**	**96**	**92**	**76**	**99**	**88**	**78**	47	**15**
R		**99**	41	**99**	35	55	**99**	45	59	53	**99**	48	40	57	**16**
S	**X10**	**99**	**96**	**99**	**80**	**90**	**99**	**80**	14	57	**99**	53	77	60	**15**
T		**99**	51	**99**	39	46	**99**	45	12	**83**	**99**	0	35	56	**16**
U	**X11**	**99**	**88**	**99**	**94**	**93**	62	**88**	82	**94**	**99**	**85**	**90**	**92**	**15**
V		**99**	**100**	**99**		**100**	0	**70**	**70**	**80**	15	**70**	**80**	60	**16**

[a]Assessed using GC/GCMS, using internal standards to ensure reproducibility. [b]Reaction not examined.

efficient cross-couplings of 3-bromophenol (to give products **17o−r**). Hetarene cross-coupling reactions using bromides containing σ-donors (such as pyridines), known to be sluggish substrates[10] in HM reactions, proceed smoothly (to give compounds **17s−aa**). It is important to reiterate that these data were obtained from first-pass, single reactions; to the best of our knowledge, this is the first general HM protocol to be identified as such a robust method.

To complete the study, having demonstrated the broad applicability of our method in electron-neutral and electron-deficient alkenes, we conducted a scoping analysis for electron-rich and unpolarized alkene coupling partners. Thus, butyl vinyl ether **18** reacted in good yield, but with variable regiocontrol (Table 4).

Dimethylpentene **21** reacted in good yield with a subset of the bromide coupling pool (Table 5), but with variable regioselectivity (here the use of Cy_2NMe as a base is crucial, because it minimises the lifetime of transient Pd-H species, ensuring selectivity likely results from β-hydride elimination rather than isomerisation of the initial product[7]). In most cases, the major product was styrene **22**, which was always accompanied by substantial (in the case of 3-bromopyridine, dominating) amounts of isomerised linear product **23**.

CONCLUSION

This project was established to define an experimental protocol for Heck−Mizoroki reactions which would be predictable and robust using a range of substrates, in an industrial environment. Our studies have probed the catalyst map for HM reactions and successfully identified the first general "first-pass" protocol which provides good yields in cross-coupling, giving a broad range of molecules of interest and utility to a diverse range of chemists. The protocol has been used by a large number of industry chemists and shown to be reliable and efficient, and also applicable to compounds for which rigorous purification is not possible. We are currently engaged in a more complete analysis of Heck−Mizoroki reactions (especially with a view of reducing catalyst loading) and the details of the mechanism in play (we currently favor a process involving ligated mononuclear Pd complexes as the catalytically competent species) and will disclose our results in due course.

EXPERIMENTAL SECTION

Chemicals and Methods. All palladium catalysts were purchased from Johnson Matthey. Dimethylacetamide (DMAC) was purchased (>99% pure) from Acros as spectrophotometric grade with <0.05% water and used without further purification or drying. Dicyclohexylamaine (Cy_2NMe) and tetrabutylammonium chloride (TBAC) were purchased (>97% pure) from Fluka and used as received. All alkenes and aryl bromides were purchased from Aldrich and used as received. Catalysts were stored and used in an MBraun glovebox.[b] Solid reagents were dispensed using a Mettler Toledo Flexiweigh. Liquid reagents, base, and solvents were dispensed using a Mettler Toledo MiniMapper. The removal of solvents in vacuo was achieved using a Büchi rotary evaporator. Commercially available Merck Kieselgel $60F_{254}$ aluminium-backed plates were used for TLC analysis. Visualisation was achieved by either UV fluorescence or

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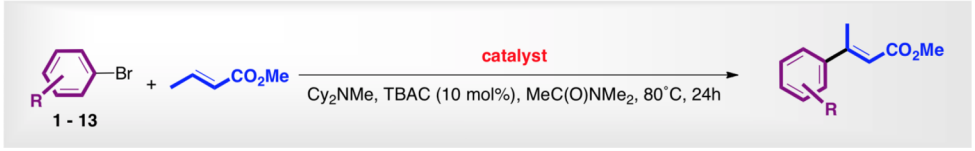
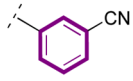
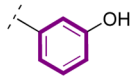
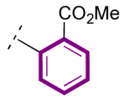
Table 3. A Generic Heck−Mizoroki Protocol for Crotonate



Entry	Catalyst	Ar	Yield % (BORSM)	*E* : *Z*[a]
A	X10		51 (90)	100 : 00
B	X10		86 (100)	100 : 00
C	X11		87 (100)	100 : 00
D	X11		59 (100)	100 : 00
E	X10 or X11		0	100 : 00
F	X11		53 (100)	100 : 00

[a]Determined by ^{1}H NMR.

a basic $KMnO_4$ solution and heat. Flash column chromatography (FCC) was performed using Radley's prepacked Silica SPE cartridges (10.0 g); the crude material was applied to the column by preadsorption onto silica. Melting points were determined using a Stuart Scientific melting point apparatus (aluminium block) and are uncorrected. NMR spectra were recorded on a Varian Inova 400 MHz spectrometer. Chemical shifts are quoted in parts per million; ^{1}H NMR and ^{13}C NMR spectra are referenced to TMS as an internal standard. Coupling constants (J) are quoted to the nearest 0.5 Hz. Other abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Assignments of ^{1}H NMR and ^{13}C NMR signals were made, where possible, using COSY, HMQC, and HMBC experiments. Mass spectra were determined by either electron impact (EI) or chemical ionisation (CI) using a Varian Saturn 2000 msms instrument. Reactions were monitored by GC using a Varian CP 3800 GC system. Analytical conditions: injector, 300 °C; column, 10 m × 0.53 mm fused silica coating UF 5 ms MS DF 0.25 mm; GC, 1.5 mL/min constant flow, 100 °C, 0.5 min hold, 60 °C/min to 300 °C, hold 2.17 min (total run time of 6 min); MS, 0 to 0.4 min; filament delay, 0.4 to 6 min, 50 to 450 m/z EI auto.

General Experimental Procedure for the Heck Reaction. In a glovebox (vide supra), $PdCl_2$(DBPF) or $Pd(^tBu_3P)_2$ (2 mol % relative to aryl bromide), TBAC (45.8 mg, 0.17 mmol), 4,4′-di-*tert*-butylbiphenyl (44 mg, 0.17 mmol, internal standard), Cy_2NMe (530 μL, 2.47 mmol), aryl bromide (1.65 mmol), and alkene (1.2 or 2 equiv relative to aryl bromide) were dissolved in *N*,*N*-dimethylacetamide (3.00 mL), and the resulting mixture was heated to 80 °C for 24 h unless otherwise stated. The mixture was then cooled to rt, diluted with methyl *tert*-butyl ether (25 mL), washed with water (2 × 25 mL), dried (Na_2SO_4 or $MgSO_4$), and concentrated in vacuo to afford the crude product, which was purified by FCC.

(*E*)-3-*p*-Tolylacrylic Acid Methyl Ester 17a.[11] FCC (9:1 to 4:1 *i*-hexane/EtOAc) afforded the title compound (256 mg, 88%) as a colourless, crystalline solid: mp 51−52.5 °C (CH_2Cl_2/*i*-hexane); δ_H (400 MHz, $CDCl_3$) 2.36 (s, 3H), 3.79 (s, 3H), 6.39 (d, J = 16.0, 1H), 7.18 (d, J = 8.0, 2H), 7.41 (d, J = 8.0, 2H), 7.67 (d, J = 16.0, 1H); δ_C (100 MHz, $CDCl_3$) 21.4, 51.6, 116.7, 128.0, 129.6, 131.6, 140.7, 144.8, 167.6. The spectroscopic properties of this compound were consistent with reported data.

(*E*)-3-(4-Cyanophenyl)acrylic Acid Methyl Ester 17b.[12] FCC (9:1 to 4:1 *i*-hexane/EtOAc) afforded the title compound (290 mg, 94%) as a cream-coloured, crystalline solid: mp 110−112 °C (CH_2Cl_2/*i*-hexane); δ_H (400 MHz, $CDCl_3$) 3.83 (s, 3H), 6.52 (d, J = 16.0, 1H), 7.59−7.71 (m, 5H); δ_C (100 MHz, $CDCl_3$) 52.0, 113.4, 118.3, 121.3, 128.4, 132.6, 138.6, 142.4, 166.5. The spectroscopic properties of this compound were consistent with reported data.

(*E*)-3-(4-Acetylphenyl)acrylic Acid Methyl Ester 17c.[13] FCC (9:1 to 4:1 *i*-hexane/EtOAc) afforded the title compound (316 mg, 94%) as a cream-coloured, crystalline solid: mp 95−97 °C (CH_2Cl_2/*i*-hexane); δ_H (400 MHz, $CDCl_3$) 2.62 (s, 3H), 3.83 (s, 3H), 6.53 (d, J = 16.0, 1H), 7.58−7.63 (m, 2H), 7.71 (d, J = 16.0, 1H), 7.95−8.00 (m, 2H); δ_C (100 MHz, $CDCl_3$) 26.6, 51.9, 120.3, 128.1, 128.8, 138.0, 138.7, 143.3, 166.9, 197.2. The spectroscopic properties of this compound were consistent with reported data.

(*E*)-3-(2-Ethyl)phenylacrylic Acid Methyl Ester 17d.[14] FCC (9:1 to 4:1 *i*-hexane/EtOAc) afforded the title compound (276 mg, 88%) as a colourless oil: δ_H (400 MHz, $CDCl_3$) 1.21 (t, J = 7.5, 3H), 2.78 (q, J = 7.5, 2H), 3.81 (s, 3H), 6.37 (d, J = 16.0, 1H), 7.18−7.24 (m, 2H), 7.28−7.33 (m, 1H), 7.52−7.57 (m,

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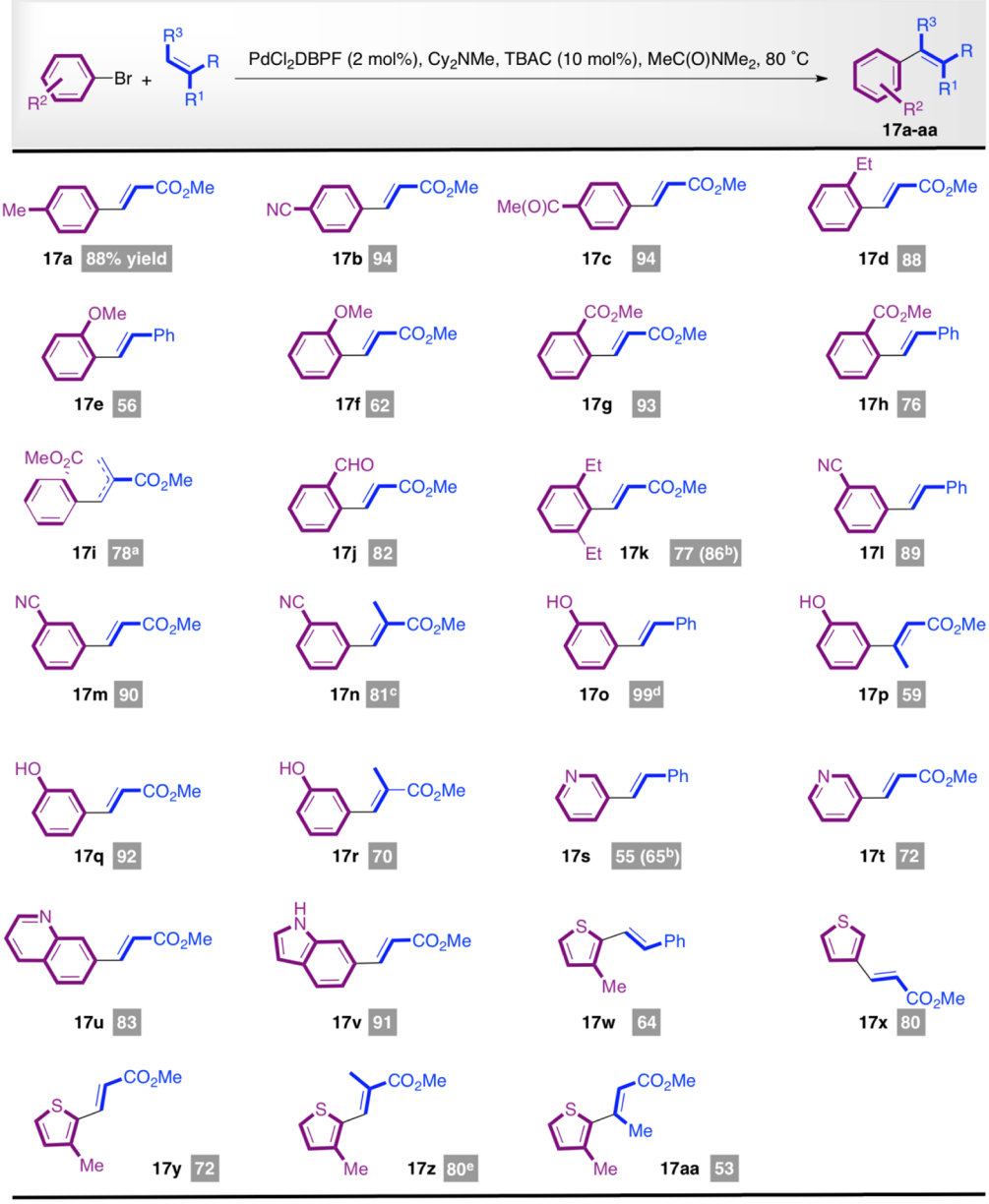
Scheme 1. A Generic Heck−Mizorocki Protocol for Validation



[a]A 50:50 ratio of alkenes.

[b]Yield based on recovered SM.

[c]A 80:20 ratio of alkenes.

[d]A 1,2:1,1-prodict = 92:8.

[e]A 92:8 ratio of alkenes.

1H), 8.02 (d, J = 16.0, 1H); δ_C (100 MHz, $CDCl_3$) 15.8, 26.3, 51.6, 119.0, 126.3, 126.5, 129.2, 130.2, 132.7, 142.3, 143.8, 167.4. The spectroscopic properties of this compound were consistent with reported data.

1-Methoxy-2-[(*E*)-styryl]benzene 17e.[15] FCC (1:0 to 19:1 *i*-hexane/EtOAc) afforded the title compound (196 mg, 56%) as a colourless oil: δ_H (400 MHz, $CDCl_3$) 3.86 (s, 3H), 6.81 (td, J = 7.5, 1.5, 1H), 6.85−6.90 (m, 2H), 6.96 (t, J = 7.5, 1H), 7.10 (d, J = 16.5, 1H), 7.20−7.27 (m, 2H), 7.30−7.36 (m, 1H), 7.49 (d, J = 16.5, 1H), 7.51−7.54 (m, 1H), 7.57−7.60 (m, 1H); m/z (EI$^+$) 210 ([M]$^+$, 100%). The spectroscopic properties of this compound were consistent with reported data.

(*E*)-3-(2-Methoxyphenyl)acrylic Acid Methyl Ester 17f.[16] FCC (1:0 to 19:1 *i*-hexane/EtOAc) afforded the title compound (196 mg, 62%) as a colourless oil: δ_H (400 MHz, $CDCl_3$) 3.79 (s, 3H), 3.87 (s, 3H), 6.53 (d, J = 16.0, 1H), 6.90 (d, J = 8.0, 1H), 6.95 (t, J = 7.5, 1H), 7.31−7.36 (m, 1H), 7.50 (dd, J = 7.5, 1.5, 1H), 8.00 (d, J = 16.0, 1H); δ_C (100 MHz, $CDCl_3$) 51.6, 55.4, 111.1, 118.2, 118.2, 123.3, 128.9, 131.5, 140.2, 158.3, 167.9. The spectroscopic properties of this compound were consistent with reported data.

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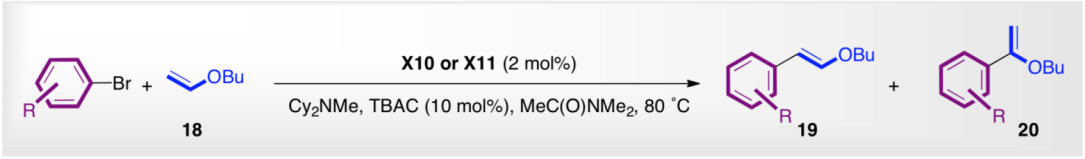
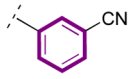
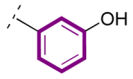
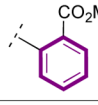
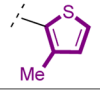
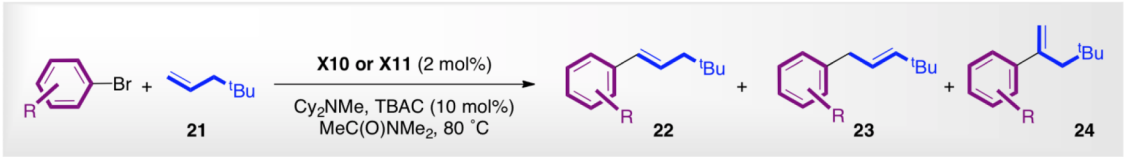
Table 4. A Generic Heck–Mizoroki Protocol for Vinyl Ethers

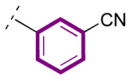
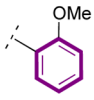
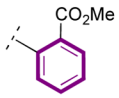


Entry	Catalyst	Ar	19 : 20	Yield % (BORSM)	*E* : *Z*
A	X10		**19a** : **20a** = 45 : 55[a]	57 (100[b])	80 : 20[a]
B	X10		**19b** : **20b** = 75 : 25	91 (100)	67 : 33
C	X11		**19c** : **20c** = 67 : 33	51 (80)	83 : 17
D	X11		**19d** : **20d** = 100 : 0	61 (100)	60 : 40
E	X11		**19e** : **20e** = 38 : 62	69 (100)	80 : 20
F	X11		**19f** : **20f** = <10 : 90	91[c] (100)	50 : 50

[a]Estimated from ^{1}H NMR spectra of crude products. [b]Yield based on recovered SM. [c]Yield of the corresponding carbonyl compound.

Table 5. A Generic Heck–Mizoroki Protocol for Dimethylpentene



Entry	Catalyst	Ar	22 : 23 : 24	Yield % (BORSM)	*E* : *Z*
A	X10		**22a** : **23a** : **24a** = 29 : 70 : 1	94 (100[a])	100 : 0[b]
B	X11		**22b** : **23b** : **24b** = 54 : 41 : 5	76 (90)	100 : 0
C	X10		**22c** : **23c** : **24c** = 80 : 13 : 7	92 (80)	100 : 0
D	X11		**22d** : **23d** : **24d** = 54 : 41 : 5	82 (90)	100 : 0

[a]Yield based on recovered SM. [b]Estimated from ^{1}H NMR spectra of crude products.

2-[(*E*)-2-Methoxycarbonyl]phenyl Acrylic Acid Methyl Ester 17g[3]. FCC (9:1 to 7:3 *i*-hexane/EtOAc) afforded the title compound (338 mg, 93%) as a pale yellow oil: δ_H (400 MHz, $CDCl_3$) 3.81 (s, 3H), 3.93 (s, 3H), 6.31 (d, *J* = 16.0, 1H), 7.43 (td, *J* = 7.5, 1.5, 1H), 7.51–7.55 (m, 1H), 7.59 (dd, *J* = 7.5, 1.0, 1H), 7.96 (dd, *J* = 7.0, 1.0, 1H), 8.45 (d, *J* = 16.0, 1H); δ_C (100 MHz, $CDCl_3$) 51.7, 52.3, 120.6, 127.9, 129.3, 129.7, 130.7, 132.3, 136.3, 143.9, 166.9, 167.1. The spectroscopic properties of this compound were consistent with reported data.

2-[(*E*)-Styryl]benzoic Acid Methyl Ester 17h.[17] FCC (1:0 to 19:1 *i*-hexane/EtOAc) afforded the title compound (300 mg, 76%) as a colourless oil: δ_H (400 MHz, $CDCl_3$) 3.91–3.92 (m,

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3H), 7.00 (d, J = 15.5, 1H), 7.21−7.39 (m, 4H), 7.49 (td, J = 7.5, 1.5, 1H), 7.52−7.56 (m, 2H), 7.71 (d, J = 7.5, 1H), 7.92 (dd, J = 8.0, 1.5, 1H), 7.99 (d, J = 16.0, 1H); m/z (EI^+) 238 ($[M]^+$, 100%). The spectroscopic properties of this compound were consistent with reported data.

2-[(*E*)-2-Methoxycarbonylpropenyl]benzoic Acid Methyl Ester and 2-(2-Methoxycarbonylallyl)benzoic Acid Methyl Ester 17i. FCC (1:0 to 4:1 *i*-hexane/EtOAc) afforded the title compound (302 mg, 78%, 1:1 *endo*:*exo*) as a pale yellow oil and as an inseparable mixture of isomers: δ_H (400 MHz, $CDCl_3$) 1.90 (d, J = 1.5, 3H, *endo*), 3.76 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 3.89 (s, 3H), 4.02−4.03 (m, 2H, *exo*), 5.21 (dt, J = 1.5, 1.0, 1H, *exo*), 6.18−6.20 (m, 1H, *exo*), 7.15−7.56 (m, 6H), 7.89−8.06 (m, 2H), 8.10 (s, 1H, *endo*); δ_C (400 MHz, $CDCl_3$) 13.8, 35.9, 51.9, 51.9, 52.0, 52.1, 125.6, 126.5, 127.8, 127.9, 130.0, 130.2, 130.7, 130.8, 131.5, 131.9, 132.0, 137.8, 139.7, 140.0, 140.1, 142.4, 166.9, 167.4, 167.7, 168.8. The spectroscopic properties of 2-[(*E*)-2-methoxycarbonylpropenyl)benzoic acid methyl ester[18] were consistent with the data available in the literature.

(*E*)-3-(2-Formylphenyl)acrylic Acid Methyl Ester 17j.[19] FCC (9:1 to 7:3 *i*-hexane/EtOAc) afforded the title compound (257 mg, 82%) as a yellow, crystalline solid: mp 48−49 °C (CH_2Cl_2/*i*-hexane); δ_H (400 MHz, $CDCl_3$) 3.84 (s, 3H), 6.38 (d, J = 16.0, 1H), 7.53−7.66 (m, 3H), 7.86−7.90 (m, 1H), 8.54 (d, J = 16.0, 1H), 10.29 (s, 1H); δ_C (100 MHz, $CDCl_3$) 51.9, 122.7, 127.9, 129.9, 132.4, 133.8, 133.9, 136.5, 141.2, 166.6, 191.8. The spectroscopic properties of this compound were consistent with reported data.

(*E*)-3-(2,6-Diethylphenyl)acrylic Acid Methyl Ester 17k. FCC (1:0 to 19:1 *i*-hexane/EtOAc) afforded the title compound (260 mg, 72%) as a yellow oil: ν_{max} (film) 1721 (s), 1639 (m), 1454 (m), 1307 (m), 1269 (m), 1192 (m) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.18 (t, J = 7.5, 6H), 2.65 (q, J = 7.5, 4H), 3.82 (s, 3H), 6.04 (d, J = 16.5, 1H), 7.09 (d, J = 7.5, 2H), 7.21 (t, J = 7.5, 1H), 7.90 (d, J = 16.0, 1H); δ_C (100 MHz, $CDCl_3$) 15.4, 26.8, 51.7, 123.8, 126.2, 128.5, 133.4, 142.3, 143.9, 166.9; m/z (CI^+) 219 ($[M + H]^+$, 100%); HRMS-GCT m/z [M^+] calcd for $C_{14}H_{18}O_2$ 218.1307, found 218.1297.

3-[(*E*)-Styryl]benzonitrile 17l.[20] FCC (1:0 to 4:1 *i*-hexane/EtOAc) afforded the title compound (302 mg, 89%) as a colourless solid: mp 61−62 °C (CH_2Cl_2/*i*-hexane); δ_H (400 MHz, $CDCl_3$) 7.03 (d, J = 16.5, 1H), 7.13 (d, J = 16.5, 1H), 7.26−7.46 (m, 6H), 7.47−7.54 (m, 2H), 7.66−7.72 (m, 1H), 7.72−7.77 (m, 1H); δ_C (100 MHz, $CDCl_3$) 112.9, 118.8, 126.2, 126.8, 128.4, 128.8, 129.5, 129.8, 130.5, 130.7, 131.3, 136.3, 138.6. The spectroscopic properties of this compound were consistent with reported data.

(*E*)-3-(3-Cyanophenyl)acrylic Acid Methyl Ester 17m.[21] FCC (9:1 to 4:1 *i*-hexane/EtOAc) afforded the title compound (290 mg, 94%) as a cream-coloured, crystalline solid: mp 120−121 °C (CH_2Cl_2/*i*-hexane); δ_H (400 MHz, $CDCl_3$) 3.83 (s, 3H), 6.49 (d, J = 16.0, 1H), 7.52 (t, J = 8.0, 1H), 7.63−7.69 (m, 2H), 7.72−7.76 (m, 1H), 7.78−7.80 (m, 1H); δ_C (100 MHz, $CDCl_3$) 51.9, 113.4, 118.1, 120.5, 129.8, 131.3, 131.9, 133.2, 135.6, 142.0, 166.6. The spectroscopic properties of this compound were consistent with reported data.

(*E*)-3-(3-Cyanophenyl)-2-methylacrylic Acid Methyl Ester 17n. FCC (1:0 to 7:3 *i*-hexane/EtOAc) afforded the title compound (264 mg, 80%, 4:1 *endo*:*exo*) as a pale pink oil: ν_{max} (film) 2230 (m), 1710 (s), 1482 (m), 1435 (s), 1263 (s), 1179 (m) cm^{-1}; δ_H (400 MHz, $CDCl_3$) *endo* 2.10 (d, J = 1.5, 3H), 3.84 (s, 3H), 7.52 (dd, J = 7.50, 7.5, 1H), 7.62 (m, 4H), *exo* (characteristic signals only) 3.66 (d, J = 1.5, 2H), 3.74 (s, 3H), 5.57 (dt, J = 1.5, 1.0, 1H), 6.29−6.30 (m, 1H); δ_C (100 MHz, $CDCl_3$) (signals for *exo* only) 14.0, 52.3, 112.8, 118.4, 129.3, 130.9, 131.5, 132.7, 133.6, 136.2, 137.1, 168.3; m/z (EI^+) 201 ($[M]^+$, 40%), 141 (100); HRMS-GCT m/z [M^+] calcd for $C_{12}H_{11}NO_2$ 201.0790, found 201.0786.

3-[(*E*)-Styryl]phenol 17o.[22] FCC (1:0 to 4:1 *i*-hexane/EtOAc) afforded the title compound (320 mg, 99%, ∼12:1 β:α) as a cream-coloured solid: mp 109−109 °C (CH_2Cl_2/*i*-hexane); δ_H (400 MHz, $CDCl_3$) (data for β-**17o** only) 6.73 (ddd, J = 8.0, 2.0, 0.5, 1H), 7.05 (d, J = 4.5, 1H), 7.06−7.10 (m, 2H), 7.19−7.28 (m, 2H), 7.32−7.37 (m, 2H), 7.47−7.51 (m, 2H); δ_C (100 MHz, $CDCl_3$) (data for β-**17o** only) 113.0, 114.7, 119.5, 126.6, 127.7, 128.2, 128.7, 129.2, 129.9, 137.1, 139.1, 155.7. The spectroscopic properties of this compound were consistent with reported data.

(*E*)-3-(3-Hydroxyphenyl)-2-methylacrylic Acid Methyl Ester 17p. FCC (1:0 to 4:1 *i*-hexane/EtOAc) afforded the title compound (220 mg, 70%) as a pale yellow solid: mp 58−60 °C (CH_2Cl_2/*i*-hexane); ν_{max} (film) 3372 (br m), 1682 (s), 1579 (m), 1435 (s), 1241 (s), 1115 (s) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.11 (d, J = 1.5, 3H), 3.83 (s, 3H), 6.14 (br s, 1H) 6.84 (dd, J = 8.0, 2.0, 1H), 6.89−6.92 (m, 1H), 6.94 (dd, J = 7.5, 0.5, 1H), 7.25 (t, J = 8.0, 1H), 7.65 (s, 1H); δ_C (100 MHz, $CDCl_3$) 14.1, 52.3, 115.6, 116.4, 122.0, 128.3, 129.6, 137.2, 139.2, 155.8, 169.7; m/z (CI^+) 193 ($[M + H]^+$, 100%); HRMS-GCT m/z [M^+] calcd for $C_{11}H_{12}O_3$ 192.0786, found 192.0745.

(*E*)-3-(3-Hydroxyphenyl)acrylic Acid Methyl Ester 17q.[23] FCC (9:1 to 3:2 *i*-hexane/EtOAc) afforded the title compound (270 mg, 92%) as a a pale yellow, crystalline solid: mp 78−79 °C (CH_2Cl_2/*i*-hexane); δ_H (400 MHz, $CDCl_3$) 3.82 (s, 3H), 6.40 (d, J = 16.0, 1H), 6.91 (ddd, J = 8.0, 2.5, 1.0, 1H), 7.02−7.09 (m, 2H), 7.21−7.27 (m, 1H), 7.65 (d, J = 16.0, 1H); δ_C (100 MHz, $CDCl_3$) 52.0, 114.6, 117.7, 117.8, 120.7, 130.1, 135.7, 145.2, 156.3, 168.1. The spectroscopic properties of this compound were consistent with reported data.

(*E*)-3-(3-Hydroxyphenyl)but-2-enoic Acid Methyl Ester 17r. FCC (1:0 to 9:1 *i*-hexane/EtOAc) afforded the title compound (188 mg, 59%) as a pale yellow solid: mp 50−51 °C (CH_2Cl_2/*i*-hexane); ν_{max} (film) 3381 (br m), 1687 (s), 1622 (s), 1579 (m), 1435 (s), 1351 (m), 1294 (m), 1171 (s) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.55 (s, 3H), 3.76 (s, 3H), 6.13 (s, 1H), 6.85 (dd, J = 8.0, 2.5, 1H), 6.93−6.96 (m, 1H), 7.03 (d, J = 7.5, 1H), 7.20−7.27 (m, 1H); δ_C (100 MHz, $CDCl_3$) 18.0, 51.2, 113.3, 116.0, 116.8, 118.7, 129.7, 143.8, 155.7, 155.7, 167.5; m/z (EI^+) 192 ($[M]^+$, 10%), 160 (100); HRMS-GCT m/z [M^+] calcd for $C_{11}H_{12}O_3$ 192.0786, found 192.0780.

3-[(*E*)-Styryl]pyridine 17s.[24] FCC (1:0 to 2:1 *i*-hexane/EtOAc) afforded the title compound (165 mg, 55%) as a pale yellow, crystalline solid: mp 68−70 °C (CH_2Cl_2/*i*-hexane); δ_H (400 MHz, $CDCl_3$) 7.06 (d, J = 16.5, 1H), 7.16 (d, J = 16.5, 1H), 7.24−7.32 (m, 2H), 7.34−7.40 (m, 2H), 7.50−7.54 (m, 2H), 7.81 (ddd, J = 8.0, 2.0, 2.0, 1H), 8.48 (dd, J = 5.0, 1.5, 1H), 8.72 (d, J = 2.0, 1H); δ_C (100 MHz, $CDCl_3$) 123.5, 124.9, 126.6, 128.2, 128.8, 130.8, 132.6, 133.0, 136.6, 148.5 (only 10 signals observed). The spectroscopic properties of this compound were consistent with reported data.

(*E*)-3-Pyridin-3-ylacrylic Acid Methyl Ester 17t.[25] FCC (1:0 to 2:1 *i*-hexane/EtOAc) afforded the title compound (195 mg, 72%) as a yellow, crystalline solid: mp 38−40 °C (CH_2Cl_2/*i*-hexane); δ_H (400 MHz, $CDCl_3$) 3.83 (s, 3H), 6.52 (d, J = 16.0, 1H), 7.33 (dd, J = 8.0, 5.0, 1H), 7.69 (d, J = 16.0, 1H), 7.84 (ddd, J = 8.0, 2.0, 1.5, 1H), 8.61 (dd, J = 5.0, 1.5, 1H), 8.75 (d, J = 2.0,

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1H); δ_C (100 MHz, $CDCl_3$) 51.8, 120.0, 123.7, 130.1, 134.1, 141.1, 149.7, 151.0, 166.7. The spectroscopic properties of this compound were consistent with reported data.

(*E*)-3-Quinolin-7-ylacrylic Acid Methyl Ester 17u. FCC (1:0 to 2:1 *i*-hexane/EtOAc) afforded the title compound (293 mg, 83%) as a yellow solid: mp 86−87 °C (CH_2Cl_2/*i*-hexane); ν_{max} (film) 1704 (s), 1635 (s), 1500 (m), 1432 (m), 1280 (s) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.84 (s, 3H), 6.57 (d, J = 16.0, 1H), 7.42 (dd, J = 8.0, 4.5, 1H), 7.85 (d, J = 16.0, 1H), 7.87−7.91 (m, 2H), 8.08−8.12 (m, 1H), 8.16 (dd, J = 8.5, 1.0, 1H), 8.92 (dd, J = 4.0, 2.0, 1H); δ_C (100 MHz, $CDCl_3$) 51.8, 119.1, 121.8, 127.2, 128.2, 129.2, 130.3, 132.6, 136.4, 143.8, 149.0, 151.3, 167.1; m/z (CI^+) 214 ($[M + H]^+$, 100%); HRMS-GCT m/z [M^+] calcd for $C_{13}H_{11}NO_2$ 213.0790, found 213.0778.

(*E*)-3-(1*H*-Indol-6-yl)acrylic Acid Methyl Ester 17v.[26] FCC (1:0 to 2:1 *i*-hexane/EtOAc) afforded the title compound (304 mg, 91%) as a yellow solid: mp 91−92 °C (CH_2Cl_2/*i*-hexane); δ_H (400 MHz, $CDCl_3$) 3.81 (s, 3H), 6.45 (d, J = 16.0, 1H), 6.50−6.53 (m, 1H), 7.26 (t, J = 3.0, 1H), 7.33 (dd, J = 8.5, 1.5, 1H), 7.50 (s, 1H), 7.61 (d, J = 8.5, 1H), 7.82 (d, J = 16.0, 1H), 8.56 (br s, 1H); δ_C (100 MHz, $CDCl_3$) 51.6, 103.0, 112.3, 115.2, 119.4, 121.1, 126.6, 128.3, 129.9, 135.9, 146.6, 168.2. The spectroscopic properties of this compound were consistent with reported data.

3-Methyl-2-[(*E*)-styryl]thiophene 17w.[27] FCC (*i*-hexane) afforded the title compound (211 mg, 64%) as a colourless solid: mp 48−49 °C (CH_2Cl_2/*i*-hexane); δ_H (400 MHz, $CDCl_3$) 2.31 (s, 3H), 6.82 (d, J = 5.0, 1H), 6.86 (d, J = 16.0, 1H), 7.08 (d, J = 5.0, 1H), 7.20−7.26 (m, 2H), 7.31−7.36 (m, 2H), 7.45−7.49 (m, 2H); δ_C (100 MHz, $CDCl_3$) 14.0, 120.3, 122.8, 126.2, 127.4, 127.7, 128.7, 130.8, 135.6, 136.4, 137.3. The spectroscopic properties of this compound were consistent with reported data.

(*E*)-3-Thiophen-3-ylacrylic Acid Methyl Ester 17x.[28] FCC (1:0 to 19:1 *i*-hexane/EtOAc) afforded the title compound (223 mg, 80%) as a colourless, crystalline solid: mp 44−46 °C (CH_2Cl_2/*i*-hexane); δ_H (400 MHz, $CDCl_3$) 3.79 (s, 3H), 6.26 (d, J = 16.0, 1H), 7.29 (dd, J = 5.0, 1.0, 1H), 7.33 (ddd, J = 5.0, 3.0, 0.5, 1H), 7.49 (dd, J = 3.0, 1.0, 1H), 7.68 (d, J = 16.0, 1H); δ_C (100 MHz, $CDCl_3$) 51.6, 117.4, 125.1, 126.9, 128.1, 137.5, 138.3, 167.6. The spectroscopic properties of this compound were consistent with reported data.

(*E*)-3-(3-Methylthiophen-2-yl)acrylic Acid Methyl Ester 17y.[29] FCC (1:0 to 19:1 *i*-hexane/EtOAc) afforded the title compound (232 mg, 77%) as a colourless oil: δ_H (400 MHz, $CDCl_3$) 2.33 (s, 3H), 3.78 (s, 3H), 6.17 (d, J = 15.5, 1H), 6.86 (d, J = 5.0, 1H), 7.24 (d, J = 5.0, 1H), 7.85 (dd, J = 15.5, 1.0, 1H); δ_C (100 MHz, $CDCl_3$) 14.1, 51.6, 115.5, 126.9, 131.1, 133.5, 135.6, 141.3, 167.5. The spectroscopic properties of this compound were consistent with reported data.

(*E*)-2-Methyl-3-(3-methylthiophen-2-yl)acrylic Acid Methyl Ester 17z. FCC (1:0 to 19:1 *i*-hexane/EtOAc) afforded the title compound (257 mg, 80%, 12:1 *endo*:*exo*) as a pale yellow oil: ν_{max} (film) 1699 (s), 1613 (m), 1433 (m), 1259 (s), 1120 (s) cm^{-1}; δ_H (400 MHz, $CDCl_3$) (for **30** only) 2.21 (d, J = 1.5, 3H), 2.36 (s, 3H), 3.81 (s, 3H), 6.93 (q, J = 5.5, 1H), 7.39 (d, J = 5.0, 1H), 7.90−7.92 (m, 1H); δ_C (100 MHz, $CDCl_3$) (data for **30** only) 14.2, 14.5, 52.2, 123.5, 127.6, 130.0, 130.2, 132.8, 140.7, 169.2; m/z (EI^+) 196 ($[M]^+$, 12%), 165 (100); HRMS-GCT m/z [M^+] calcd for $C_{10}H_{12}O_2S$ 196.0558, found 196.0529.

(*E*)-3-(3-Methylthiophen-2-yl)but-2-enoic Acid Methyl Ester 17aa. FCC (1:0 to 9:1 *i*-hexane/EtOAc) afforded the title compound (173 mg, 53%) as a yellow oil: ν_{max} (film) 1710 (s), 1612 (s), 1433 (m), 1339 (m), 1258 (m), 1170 (s) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.35 (s, 3H), 2.58 (d, J = 1.0, 3H), 3.74 (s, 3H), 5.98−6.00 (m, 1H), 6.86 (d, J = 5.0, 1H), 7.22 (d, J = 5.0, 1H); δ_C (100 MHz, $CDCl_3$) 16.2, 20.5, 51.1, 117.4, 124.6, 131.8, 135.5, 139.7, 149.7, 167.0; m/z (EI^+) 196 ($[M]^+$, 40%), 137 (100); HRMS-GCT m/z [M^+] calcd for $C_{10}H_{12}O_2S$ 196.0558, found 196.0543.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR data for products **17a**−**aa**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ADDITIONAL NOTES

[a]The addition of TBAC increases catalyst activity and conversions. We thank Prof. G. C. Fu (Massachusetts Institute of Technology, Cambridge, MA) for this recommendation.

[b]The glovebox was used only to facilitate the automated dispensing of reagents. The protocol is perfectly applicable under "normal" (i.e., without O_2 exclusion) laboratory conditions; indeed, this was a key criterion of the project.

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