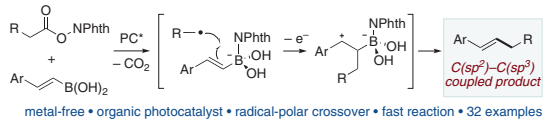
Organophotocatalytic Radical–Polar Cross-Coupling of Styrylboronic Acids and Redox-Active Esters

Jeremy Brals[a]
Nicholas D'Arcy-Evans[a]
Thomas M. McGuire[b]
Allan J. B. Watson*[a]

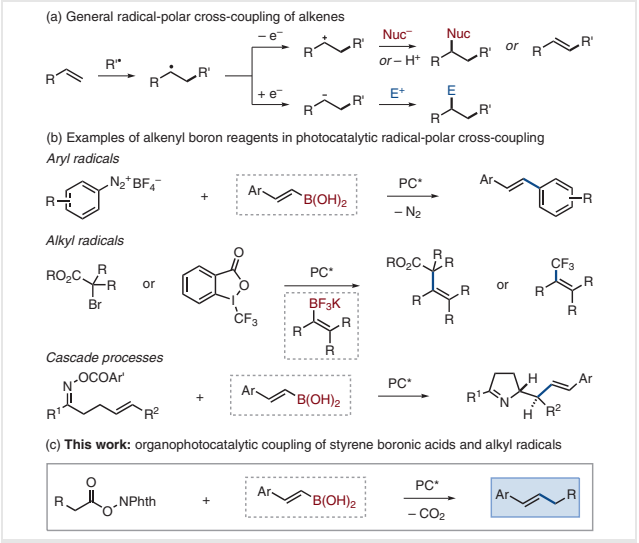
[a] EaStCHEM, School of Chemistry, University of St Andrews, Purdie Building, North Haugh, St Andrews, KY16 9ST, UK
aw260@st-andrews.ac.uk
[b] AstraZeneca, Darwin Building, Unit 310, Cambridge Science Park, Milton Road, Cambridge, CB4 0WG, UK



Received: 01.09.2023
Accepted: 21.09.2023
Published online: 21.09.2023 (Accepted Manuscript), 23.10.2023 (Version of Record)
DOI: 10.1055/a-2179-6570; Art ID: ST-2023-09-0376-L

Abstract We report the development of a radical–polar cross-coupling reaction using styrylboronic acids and redox-active esters under organophotoredox catalysis. The reaction proceeds through a formal polarity-mismatched radical addition. The use of an organic photocatalyst permitted very low loadings of the electron-shuttle additive and accelerated reaction times compared with established processes. The scope of the reaction was explored, and the utility of the products is demonstrated.

Key words esters, styrylboronic acids, photocatalysis, radical–polar cross-coupling



Scheme 1 Radical–polar cross-coupling and selected examples of radical–polar cross-couplings using styrylboronic acid derivatives

Radical–polar cross-coupling reactions are broadly useful methods for synthesis.[1] The addition of a radical species to an alkene forges an initial C–C or C–X bond and produces an intermediate radical that can, in turn, be used to access several different products, depending on the reaction conditions (Scheme 1a). For example, oxidation of the intermediate radical delivers a carbocation that can be intercepted by a nucleophile or can lose a proton to forge an alkene. Alternatively, reduction of the intermediate radical generates an anion that can undergo reaction with an electrophile. Extensions to this chemistry where the intermediate radical reacts with another substrate (e.g., a second alkene or hydrogen donor) or a transition metal to promote further bond formations have also been developed.[2] The functionalization of the alkene starting material can be critical to the downstream reactivity of the intermediate radical.

Borylated alkenes have been used in radical–polar cross-coupling in three main approaches: (i) as π-nucleophiles to intercept an intermediate carbocation,[3] (ii) to generate α-boryl radicals for addition to alkenes or as SOMOphiles,[4,5] and (iii) as SOMOphiles where the boryl unit acts as a leaving group to facilitate formation of alkene products.[5]

The third approach has seen several applications, selected examples of which are shown in Scheme 1b. For example, Wu and co-workers developed a method for photocatalytic coupling of aryl radicals, generated from diazonium salts, with styrylboronic acids.[5a] The groups of Leonori and Akita have developed photocatalytic couplings of potassi-

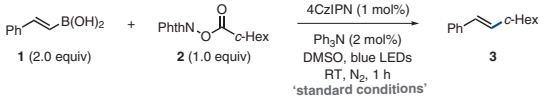
um alkenyl(trifluoro)borates with radicals generated from α-halocarbonyls or the Togni reagent, respectively.[5b,c] Yu and co-workers have shown how styrylboronic acids can react with C-centered radicals generated from cascade processes.[5d,e]

We recently reported a method for coupling styrylboronic acids with redox-active *N*-hydroxyphthalimide (NHPI) esters using Ru photocatalysis.[5f] Here, we report an improved process based on organophotoredox catalysis that is metal-free and permits a faster reaction using lower loadings of the electron-shuttle additive (Scheme 1c).

The motivation for this work was to move away from noble-metal-based photocatalysts to improve the sustainability of coupling processes.[6] Accordingly, we focused on the use of organic photocatalysts. The benchmark reaction between styrylboronic acid (**1**) and cyclohexyl (*c*-Hex) NHPI ester (**2**) to give the desired C(sp^2)–C(sp^3) coupled product is shown in Table 1. The optimized reaction conditions required 1 mol% of 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN)[7] as a photocatalyst and 2 mol% of Ph_3N as an electron shuttle (see below), with the reaction complete in one hour (Table 1, entry 1). This represented an improvement on previous conditions, which used 1 mol% of an Ru-based photocatalyst, 10 mol% of an electron-shuttle additive ($PhNMe_2$), and required three hours for a similar yield.[8] Selected optimization data are provided. First, the reaction did not proceed with eosin Y[9] and $PhNMe_2$ under irradiation from blue LEDs (entry 2), but required green LEDs and an extended reaction time to give a low yield (entry 3). Using 4CzIPN with $PhNMe_2$ for an extended reaction time gave a good yield, but resulted in erosion of stereochemical integrity (entry 4). This extended reaction time resulted in photocatalytic alkene isomerization.[10] Solvent variation was not tolerated (entries 6 and 7). Control reactions confirmed the requirement for blue LEDs (entries 8 and 9). Other additives were assessed, such as catechol (entry 10), but none offered an improvement on Ph_3N. An increased loading of Ph_3N offered no advantage compared with 1 mol% (entry 11). Finally, the reaction was more effective with the boronic acid: the equivalent Bpin, Bcat (cat = 1,2-$O_2C_6H_4$), and BF_3K compounds were less effective or were unreactive (entries 12–14).

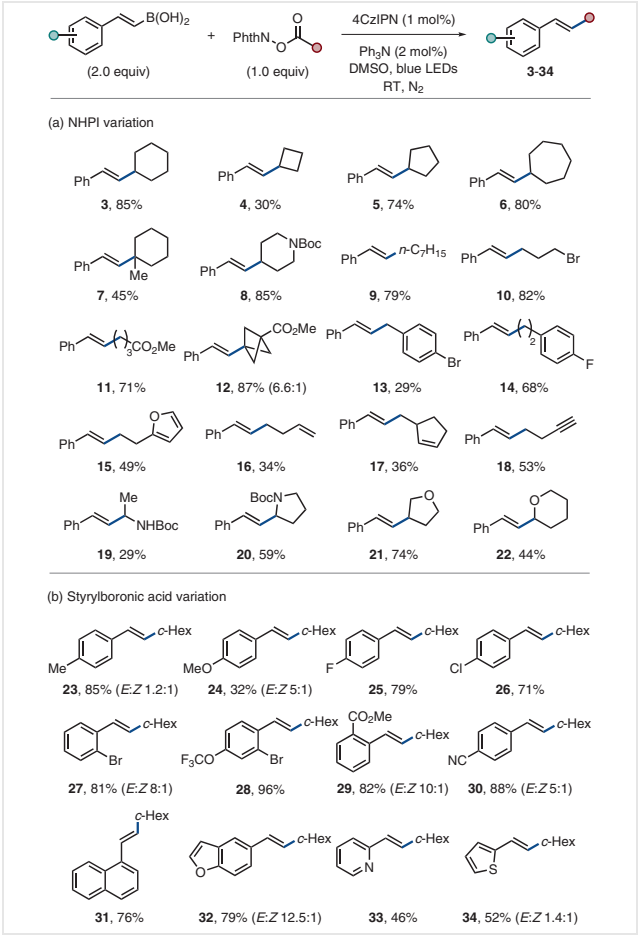
The generality of the benchmark reaction conditions was assessed by application to a range of NHPI esters and styrylboronic acids (Scheme 2). Variation of the NHPI component was generally well tolerated, with some fluctuations in the isolated yield (Scheme 2a). Cycloalkyl NHPI es-

Table 1 Reaction Development.



Entry	Deviation from standard conditions	Yield[a] (%) (*E*/*Z*)[a,b]
1	–	93, 85[c]
2	eosin Y (10 mol%), $PhNMe_2$ (10 mol%), 3 h	–
3	eosin Y (10 mol%), $PhNMe_2$ (10 mol%), green LEDs, 24 h	33
4	$PhNMe_2$ (10 mol%), 18 h	91 (3.3:1)
5	**1** (1.0 equiv), $PhNMe_2$ (10 mol%)	50
6	MeCN as solvent	47
7	acetone as solvent	46
8	darkness, 20 h	–
9	ambient light, 20 h	–
10	catechol (10 mol%)	82
11	Ph_3N (10 mol%)	90
12	**1** Bpin ester	37
13	**1** Bcat ester	51
14	**1** BF_3K salt	14

[a] Determined by ^1H NMR analysis using an internal standard.
[b] *E*/*Z* > 20:1 unless noted.
[c] Isolated yield.



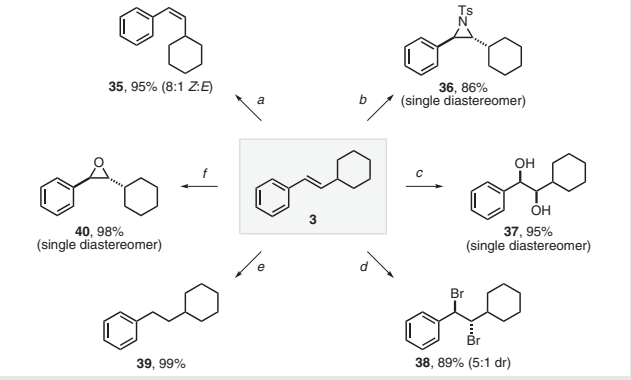
Scheme 2 Example scope. Isolated yields are reported. *E*/*Z* > 20:1 unless noted (determined by ^1H NMR).

ters were typically well tolerated (**3**–**8**, **12**, **20**–**22**), except for the cyclobutyl example (**4**). Linear alkyl NHPI esters bearing a range of functionalities were similarly well accommodated (**9**–**11**, **13**–**19**), including those bearing alkyl bromide (**10**), ester (**11**), or (het)arene groups (**14**, **15**). Compounds with side chains containing alkene, alkyne (**16**–**18**), or benzyl units (**13**) underwent coupling but in lower yields in general. Finally, NHPI esters with α-heteroatoms, including nitrogen or oxygen, could be employed (**19**, **20**, **22**).

A range of styrylboronic acids with various electronic and steric parameters were generally effective reactants (Scheme 2b). There was no clear electronic trend, with some electron-rich (**24**) or electron-deficient (**33**) examples providing diminished yields.

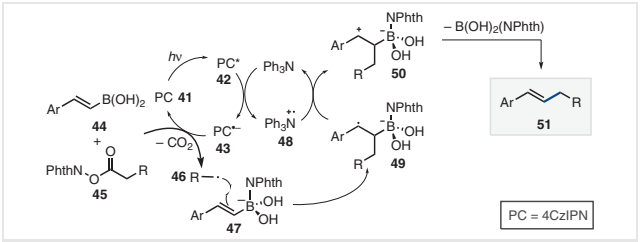
Lastly, the majority of products were isolated with >20:1 *E*/*Z* ratios; however, several examples notably displayed an erosion of stereochemical integrity through uncontrolled photocatalytic isomerization (noted in Scheme 2).[10]

To showcase the synthetic utility of this photocatalytic coupling method, we used product **3** in a range of downstream derivatization processes (Scheme 3). Photocatalytic *E*→*Z* isomerization was achieved under the conditions reported by Gilmour and co-workers to give **35**.[10d] Ru-catalyzed aziridination delivered **36**.[11] Catalytic dihydroxylation smoothly delivered diol **37**,[12] whereas dibromination was also straightforward, giving **38**.[13] Hydrogenation using a Pt catalyst gave the linear alkane **39** in a good yield.[14] Finally, Prilezhaev epoxidation gave **40**.[15]



Scheme 3 Examples of diversification of products. *Reaction conditions*: (a) $Ir(ppy)_3$ (1 mol%), MeCN (0.1 M), blue LEDs, RT, 16 h. (b) $TsNH_2$ (2.0 equiv), PhIO (2.0 equiv), $Ru(bpy)_3PF_6$ (2 mol%), CH_2Cl_2 (0.1 M), 3 Å MS, blue LEDs, N_2, RT, 4 h. (c) OsO_4 (1.5 mol%), NMO (1.5 equiv), $MeSO_2NH_2$ (1.0 equiv), acetone–H_2O (0.1 M), RT, 1 h. (d) Br_2 (1.5 equiv), $CHCl_3$ (0.1 M), RT, 2 h. (e) PtO_2 (5 mol%), EtOH (0.1 M), H_2, RT, 2 h. (f) *m*CPBA (1.5 equiv), CH_2Cl_2 (0.1 M), N_2, RT, 16 h.

Based on our previous work,[5f] a proposed mechanism for the reaction is shown in Scheme 4. Irradiation of the 4CzIPN (PC; **41**) gives the excited photocatalyst **42** [$E_{1/2}$ (**42**/**43**) = 1.35 V vs SCE].[8b] This is capable of one-electron oxidation of Ph_3N ($E_{1/2}$ = 0.98 V vs SCE) to give the reduced photocatalyst **43** and the aminium radical **48**.[16] Radical anion **43** [$E_{1/2}$ (**41**/**43**) = –1.21 V vs SCE][8b] facilitates single-electron transfer to **45** ($E_{1/2}$ = –1.26 V vs SCE),[17] resulting in decarboxylation and loss of a phthalimide anion ($NPhth^-$) to give alkyl radical **46**. Concomitant boronate formation from **44** and $NPhth^-$ gives **47**. Radical **46** can then undergo addition to alkene **47** to give radical intermediate **49**. Oxidation of **49** [$E_{1/2}$ (**50**/**49**) = 0.37 V][18] by **48** ($E_{1/2}$ = –0.98 vs SCE)[16] gives carbocation **50**, which is primed for elimination of the boron unit to give the product **51**.



Scheme 4 Proposed mechanism

In summary, a metal-free approach to radical-polar cross-coupling of styrylboronic and NHPI esters has been developed. The reaction conditions offer several advantages over established methods, including the avoidance of noble metals, lower loadings of catalytic additives, and shorter reaction times. This $C(sp^3)$–$C(sp^2)$ coupling is general and affords the desired products in typically good yields.[19]

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

Engineering and Physical Sciences Research Council (EP/W007517); Leverhulme Trust (RF-2022-014)

Acknowledgment

J.B. thanks AstraZeneca and the Engineering and Physical Sciences Research Council (EPSRC) for a Ph.D. studentship. A.J.B.W. thanks the Leverhulme Trust for a research fellowship, and the EPSRC Programme Grant 'Boron: Beyond the Reagent' for support.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-2179-6570.

References and Notes

(1) (a) Pitzer, L.; Schwarz, J. L.; Glorius, F. *Chem. Sci.* **2019**, *10*, 8285. (b) Wiles, R. J.; Molander, G. A. *Isr. J. Chem.* **2020**, *60*, 281. (c) Sharma, S.; Singh, J.; Sharma, A. *Adv. Synth. Catal.* **2021**, *363*, 3146.

(2) For HAT examples, see: (a) Capaldo, L.; Ravelli, D. *Eur. J. Org. Chem.* **2017**, 2056. (b) Capaldo, L.; Lafayette Quadri, L.; Ravelli, D. *Green Chem.* **2020**, *22*, 3376. For cascade reactions, see: (c) Xu, G.-Q.; Xu, P.-F. *Chem. Commun.* **2021**, *57*, 12914. For multicomponent reactions, see: (d) Coppola, G. A.; Pillitteri, S.; Van der Eycken, E. V.; You, S.-L.; Sharma, U. K. *Chem. Soc. Rev.* **2022**, *51*, 2313. For dual photocatalysis examples, see: (e) Skubi, K. L.; Blum, T. R.; Yoon, T. R. *Chem. Rev.* **2016**, *116*, 10035. (f) Mastandrea, M. M.; Pericàs, M. A. *Eur. J. Inorg. Chem.* **2021**, 3421. (g) Chan, A. Y.; Perry, I. B.; Bissonnette, N. B.; Buksh, B. F.; Edwards, G. A.; Frye, L. I.; Garry, O. L.; Lavagnino, M. N.; Li, B. W.; Liang, Y.; Mao, E.; Millet, A.; Oakley, J. V.; Reed, N. L.; Sakai, H. A.; Seath, C. P.; MacMillan, D. W. C. *Chem. Rev.* **2022**, *122*, 1485.

(3) For examples, see: (a) Li, J.; Luo, Y.; Cheo, H. W.; Lan, Y.; Wu, J. *Chem* **2019**, *5*, 192. (b) Badir, S. O.; Molander, G. A. *Chem* **2020**, *6*, 1327. (c) Zhu, C.; Yue, H.; Chu, L.; Rueping, M. *Chem. Sci.* **2020**, *11*, 4051. (d) Cabrera-Afonso, M. J.; Sookezian, A.; Badir, S. O.; El Khatib, M.; Molander, G. A. *Chem. Sci.* **2021**, *12*, 9189.

(4) For examples, see: (a) Marotta, A.; Adams, C. E.; Molloy, J. J. *Angew. Chem. Int. Ed.* **2022**, *61*, e202207067. (b) Marotta, A.; Fang, H.; Adams, C. E.; Marcus, K. S.; Daniliuc, G. C.; Molloy, J. J. *Angew. Chem. Int. Ed.* **2023**, *62*, e202307540.

(5) (a) Yasu, Y.; Koike, T.; Akita, M. *Chem. Commun.* **2013**, *49*, 2037. (b) Reina, D. F.; Ruffoni, A.; Al-Faiyz, Y. S. S.; Douglas, J. J.; Sheikh, N. S.; Leonori, D. *ACS Catal.* **2017**, *7*, 4126. (c) Shen, X.; Huang, C.; Yuan, X.-A.; Yu, S. *Angew. Chem. Int. Ed.* **2021**, *60*, 9672. (d) Chen, H.; Guo, L.; Yu, S. *Org. Lett.* **2018**, *20*, 6255. (e) Qu, C.-H.; Yan, X.; Li, S.-T.; Liu, J.-B.; Xu, Z.-G.; Chen, Z.-Z.; Tang, D.-Y.; Liu, H.-X.; Song, G.-T. *Green Chem.* **2023**, *25*, 3453. (f) Brals, J.; McGuire, T. M.; Watson, A. J. B. *Angew. Chem. Int. Ed.* **2023**, *62*, e202310462.

(6) (a) Joshi-Pangu, A.; Lévesque, F.; Roth, H. G.; Oliver, S. F.; Campeau, L.-C.; Nicewicz, D.; DiRocco, D. A. *J. Org. Chem.* **2016**, *81*, 7244. (b) Crisenza, G. E. M.; Melchiorre, P. *Nat. Commun.* **2020**, *11*, 803.

(7) (a) Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075. (b) Shang, T.-Y.; Lu, L.-H.; Cao, Z.; Liu, Y.; He, W.-M.; Yu, B. *Chem. Commun.* **2019**, *55*, 5408. (c) Bell, J. D.; Murphy, J. A. *Chem. Soc. Rev.* **2021**, *50*, 9540.

(8) (a) Murarka, S. *Adv. Synth. Catal.* **2018**, *360*, 1735. (b) Parida, S. K.; Mandal, T.; Das, S.; Hota, S. K.; Sarkar, S. D.; Murarka, S. *ACS Catal.* **2021**, *11*, 1640. (c) Zhu, X.; Fu, H. *Chem. Commun.* **2021**, *57*, 9656.

(9) (a) Hari, D. P.; König, B. *Chem. Commun.* **2014**, *50*, 6688. (b) Srivastava, V.; Singh, P. P. *RSC Adv.* **2017**, *7*, 31377.

(10) (a) Metternich, J. B.; Artiukhin, D. G.; Holland, M. C.; von Bremen-Kühne, M.; Neugebauer, J.; Gilmour, R. *J. Org. Chem.* **2017**, *82*, 9955. (b) Molloy, J. J.; Schäfer, M.; Wienhold, M.; Morack, T.; Daniliuc, C. G.; Gilmour, R. *Science* **2020**, *369*, 302. (c) Neveselý, T.; Wienhold, M.; Molloy, J. J.; Gilmour, R. *Chem. Rev.* **2022**, *122*, 2650. (d) Molloy, J. J.; Metternich, J. B.; Daniliuc, C. G.; Watson, A. J. B.; Gilmour, R. *Angew. Chem. Int. Ed.* **2018**, *57*, 3168.

(11) Guo, Y.; Pei, C.; Koenigs, R. M. *Nat. Commun.* **2022**, *13*, 86.

(12) Iida, T.; Itaya, T. *Tetrahedron* **1993**, *49*, 10511.

(13) Cain, D. L.; McLaughlin, C.; Molloy, J. J.; Carpenter-Warren, C.; Anderson, N. A.; Watson, A. J. B. *Synlett* **2019**, *30*, 787.

(14) Onodera, S.; Togashi, R.; Ishikawa, S.; Kochi, T.; Kakiuchi, F. *J. Am. Chem. Soc.* **2020**, *142*, 7345.

(15) Vedejs, E.; Fleck, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 5861.

(16) Seo, E. T.; Nelson, R. F.; Fritsch, J. M.; Marcoux, L. S.; Leedy, D. W.; Adams, R. N. *J. Am. Chem. Soc.* **1966**, *88*, 3498.

(17) Lackner, G. L.; Quasdorf, K. W.; Pratsch, G.; Overman, L. E. *J. Org. Chem.* **2015**, *80*, 6012.

(18) Wayner, D. D. M.; McPhee, D. J.; Griller, D. *J. Am. Chem. Soc.* **1988**, *110*, 132.

(19) **Alkenes 3–34; General Procedure**

An oven-dried photoreactor vial equipped with a Teflon-coated stirrer bar was charged with the appropriate NHPI ester (200 µmol, 1.0 equiv) and styrylboronic acid (400 µmol, 2.0 equiv), together with 4CzIPN (1.6 mg, 2.0 µmol, 1 mol%) and Ph_3N (1.0 mg, 4.0 µmol, 2 mol%). The vial was then sealed, purged by using N_2–vacuum cycles (×3), and backfilled with N_2. Degassed dry DMSO-d_6 (2.0 mL, 0.1 M) was then added from a syringe. The cap was wrapped with Parafilm, and the mixture was stirred under blue LEDs at RT (~20 °C) for 1 h. The mixture was then partitioned between Et_2O (5 mL) and brine (5 mL), and the organics were extracted with Et_2O (2 × 10 mL). The organic phases were combined, washed with brine (15 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude residue was purified by flash chromatography (silica gel; hexane, hexane–EtOAc, or hexane–Et_2O).

[(*E*)-2-Cyclohexylvinyl]benzene (3)

Prepared according to the general procedure from 1,3-dioxoisoindolin-2-yl cyclohexanecarboxylate (**2**; 54.7 mg, 200 µmol, 1.0 equiv), [(*E*)-2-phenylvinyl]boronic acid (**1**; 59.2 mg, 400 µmol, 2.0 equiv), 4CzIPN (1.6 mg, 2.0 µmol, 1 mol%), and Ph_2N (1.0 mg, 4.0 µmol, 2 mol%) in DMSO-d_6 (2 mL, 0.1 M). The crude residue (95% ^{1}H NMR yield) was purified by flash chromatography (silica gel, hexane) to give a colorless oil; yield: 31.8 mg (85%, *E*/*Z* > 20:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.33 (m, 2 H), 7.31–7.27 (m, 2 H), 7.21–7.16 (m, 1 H), 6.35 (d, *J* = 16.01 Hz, 1 H), 6.18 (dd, *J* = 15.98, 6.96 Hz, 1 H), 2.18–2.08 (m, 1 H), 1.86–1.74 (m, 4 H), 1.72–1.65 (m, 1 H), 1.39–1.25 (m, 2 H), 1.25–1.14 (m, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 138.2, 137.0, 128.6, 127.3, 126.9, 126.1, 41.3, 33.1, 26.3, 26.2.