Synthesis of 2-Aryl-Substituted Chromans by Intramolecular C–O Bond Formation

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Abstract: A synthetic route for the preparation of 2-aryl-substituted chromans from commercially available starting materials and utilizing either a palladium- or copper-catalyzed intramolecular cyclization of aryl bromides is described. Chromans with stereocontrol at C-2 can thus be obtained via a palladium-catalyzed asymmetric allylic etherification procedure utilizing a chiral indolephosphine oxazoline (IndPHOX) ligand.

Key words: intramolecular cyclization, chromans, chalcones, palladium, copper

Synthetic approaches towards 2-substituted chromans (tetrahydrobenzopyrans) have attracted considerable attention continuously due to the formation of a core that exhibits biological activities in numerous natural products.[1] A well-known example is α-tocopherol (**1**), a member of the vitamin E family that serves as a radical scavenger and lipophilic antioxidant. Moreover, the compound 4′,6-dichloroflavan (BW683C; **2**) is a potent inhibitor of rhinovirus replication in vitro,[2] and 2-(2-piperidyl)chroman **3** and 2-(2-pyrrolidyl)chroman **4** have shown to be promising new types of nicotine agonists (Figure 1).[3]

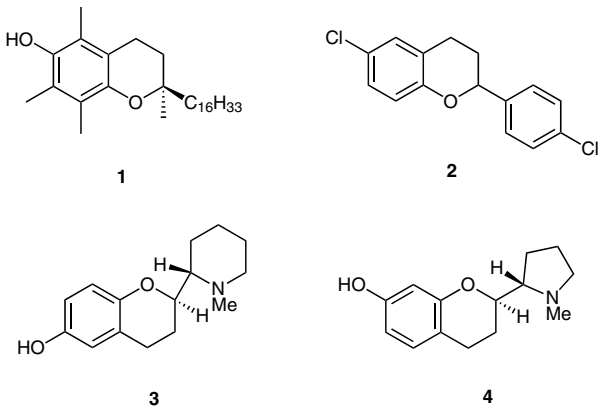
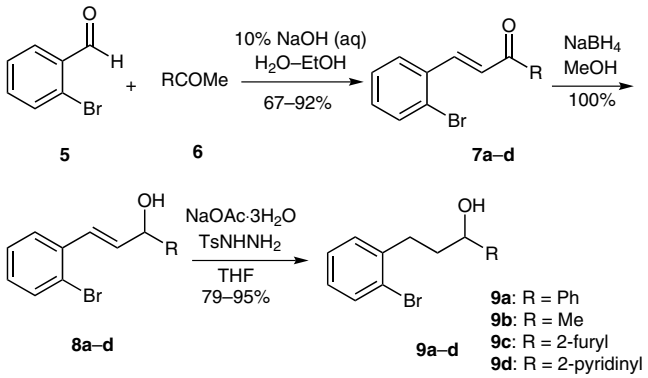


Figure 1 Examples of biologically active chroman compounds

There are several synthetic studies on the construction of the chroman core utilizing many strategies.[4–6] The process of Pd-[7] or Cu-catalyzed[8] intramolecular C–O bond formation using aryl halides has been successfully established for the preparation of diverse oxygen-containing heterocyclic compounds. On the other hand, there are only a few examples to synthesize 2-alkyl chromans,[7b,d,9] and especially 2-aryl chromans[9a] via this approach. In this paper we report a new synthetic route for 2-aryl-substituted chromans with the intramolecular cyclization of aryl bromides as the key step (Scheme 1), which also enables access to enantiomerically enriched chromans.

Chalcones **7a–d**, prepared from commercially available 2-bromoaldehyde (**5**) and ketones **6a–d**, were readily converted to the corresponding alcohols **8a–d** in quantitative yields using sodium borohydride (Scheme 1). The following reduction of the allylic double bond with *para*-toluenesulfonyl hydrazide and sodium acetate trihydrate led to the desired *ortho*-bromophenylpropanols **9a–d** in high yields without notable cleavage of the aryl–bromide bond.[10]

With compounds **9a–d** in hand, the intramolecular C–O bond formation was studied. We first studied the palladium-catalyzed cyclization procedure reported by Buchwald,[7b] employing the biaryl ligand **11** (Table 1).[11] The reactions with phenyl- and methyl-substituted aryl propanols **9a** and **9b** proceeded smoothly to provide chromans **10a** and **10b** in good yields (71% and 79%, respectively; entry 1 and entry 2), whereas the results for 2-heteroaryl-substituted chromans (**10c** and **10d**) were poor. Due to the formation of the β-hydride elimination by-product,[12] the 2-furylchroman (**10c**) was obtained in moderate yield (43%, entry3). After 96 hours at 90 °C we noticed that substrate **9d** reacted poorly and gave a very low yield (16%, entry 4) of the product probably because



Scheme 1 Synthesis of 3-(2-bromophenyl)propan-1-ol derivatives **9a–d**

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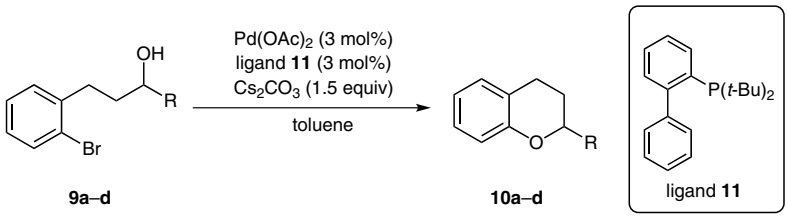
Table 1 Palladium-Catalyzed Intramolecular Cyclization[a]

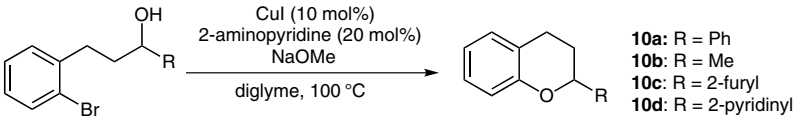


9a–d **10a–d**

Entry	Temp (°C)	Time (h)	Product	Isolated yield (%)
1	90	24	**10a**	71
2[b]	65	24	**10b**	79
3	90	24	**10c**	43
4	90	96	**10d**	16

[a] See Supporting Information for details.
[b] See reference 7b.

Table 2 Copper-Catalyzed Intramolecular Cyclization of Compounds **9a–d**[a]



9a–d **10a–d**

Entry	NaOMe (equiv)	Time (h)	Product	Isolated yield (%)
1	1.5	24	**10a**	78
2	2.1[b]	24	**10b**	44
3	1.5	48	**10c**	74
4	1.5	24	**10d**	88

[a] See Supporting Information for details.
[b] No reaction was observed using NaOMe (1.5 equiv).

of the palladium catalyst deactivation caused by the pyridinyl group.

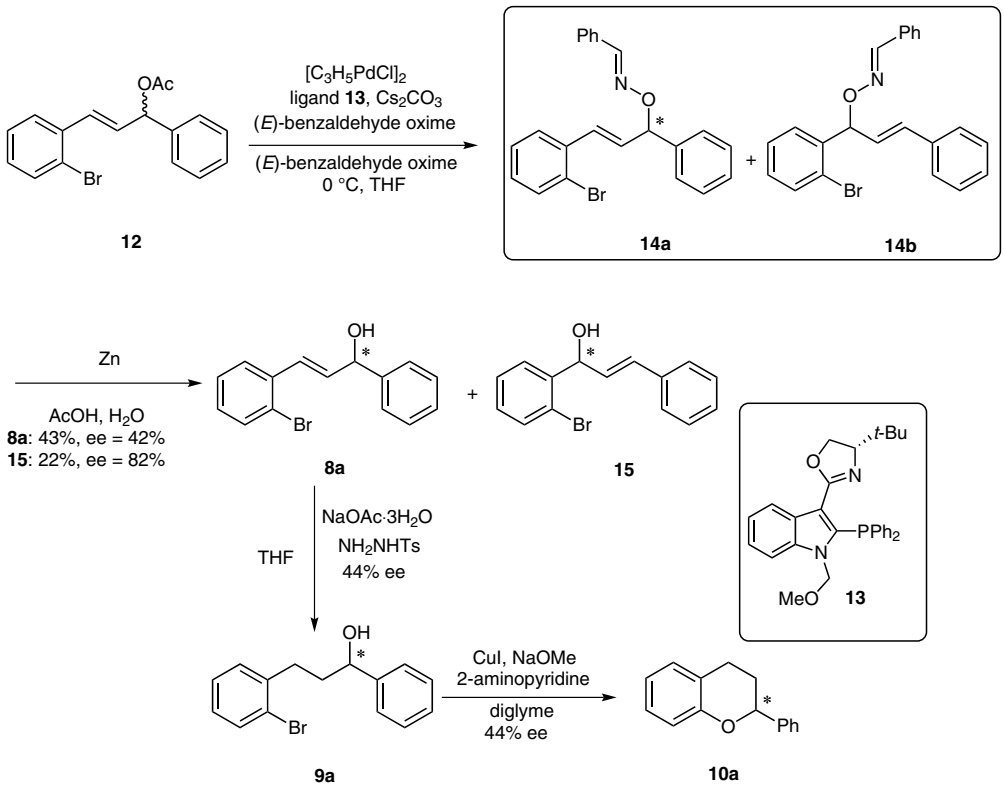
Because of the limitation of the palladium-catalyzed method for the cyclization, we started to investigate the possibility to use an intramolecular Ullmann alkoxylation reaction for the cyclization of **9** instead.

After a preliminary screening, we noticed that a previously reported approach using CuI and 2-aminopyridine with sodium methoxide as base in diglyme was suitable for our purposes (Table 2).[13] Although 2-alkyl chroman **10b** was only obtained in moderate yield (44%, entry 2), the method worked well to afford 2-aryl chromans **10a**, **10c** and **10d** in high yields (78%, 74% and 88%, respectively, entries 1, 3 and 4).[14]

After establishing the synthetic route for racemic 2-monosubstituted chromans, we next turned our attention to the asymmetric synthesis of chiral chromans. Based on our previous work with the Pd-catalyzed asymmetric allylic substitutions using indole-phosphine oxazoline (IndPHOX) ligands,[15] we designed a new route for the synthesis of chromans with stereocontrol at C-2 via the preparation of a chiral alcohol **8** obtained by an asymmetric allylic etherification procedure.

Preliminary experiments were carried out for the synthesis of chiral 2-phenylchroman (**10a**; Scheme 2). Starting from acetate **12**, the catalytic reaction was performed utilizing our IndPHOX ligand **13** with (*E*)-benzaldehyde oxime and cesium carbonate as base in THF at 0 °C, yielding a mixture of oximes **14a** and **14b**. After treatment with zinc powder in AcOH–H_2O,[16] the linear alcohol **8a** was isolated in 43% yield with moderate enantioselectivity (41%);[17] while the branched product **15**, derived from the attack of the nucleophile to the more sterically hindered position by S_N2' mechanism, was obtained in good ee value (82%).[17] After reduction of the double bond of alcohol **8a**, followed by cyclization using CuI, the chiral chroman **10a** was obtained with 44% enantioselectivity (Scheme 2).

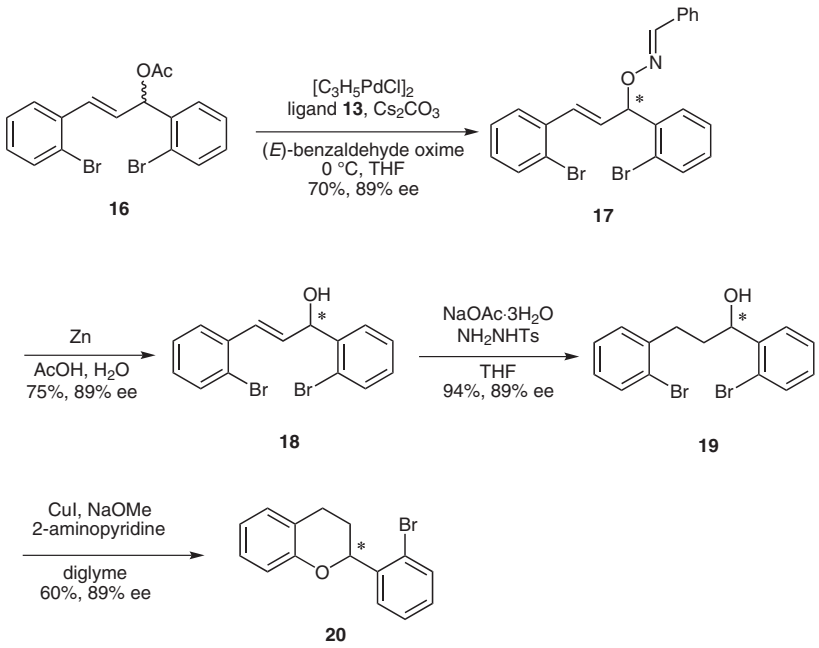
Encouraged by these promising results, we continued the investigation with (*E*)-1,3-bis(2-bromophenyl)allyl ace-



Scheme 2 Synthesis of chiral chroman **10a**

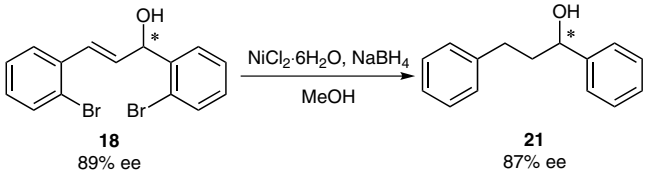
tate (**16**), which was chosen based on the following aspects: (i) to suppress regioselectivity issue in Pd-catalyzed allylic substitution; (ii) to enhance the enantioselectivity; and to (iii) afford diversity to further chroman derivatives. When starting material **16** was reacted with (*E*)-benzaldehyde oxime using IndPHOX ligand **13** and cesium carbonate as base in THF at 0 °C for 24 hours, oxime **17** was obtained with good enantioselectivity (89%)[17] and 70% yield (Scheme 3). The subsequent cleavage of the N–O bond, the reduction of the double bond and the intramolecular cyclization proceeded smoothly to afford chroman **20**,[18] maintaining original enantiopurity.

The absolute configuration of compound **18** was determined by transforming it into known chiral compound **21**



Scheme 3 Synthesis of chiral chroman **20**

(Scheme 4). The reduction of **18** was performed in methanol using $NaBH_4$ in the presence of nickel(II) chloride hexahydrate, providing chiral **21** without remarkable racemization. Comparison of the optical rotation value[19] of **21** with the literature data[20] revealed that the absolute stereochemistry of **18** was *R*.



Scheme 4 Determination of the absolute configuration of compound **18**

The adjacent 2-bromophenyl group in the structure of chroman **20** offered various possibilities for further applications via catalytic transformations.[21] As an example, we carried out a Suzuki coupling reaction.[21c–e] Chroman **20** with 89% ee was reacted with phenylboronic acid (**22**) using $Pd(PPh_3)_4$ with sodium carbonate as base in toluene–H_2O–EtOH for 20 hours at 80 °C.

The Suzuki reaction proceeded well to afford product **22**[22] in high yield (88%) and without loss of ee (Scheme 5).

In conclusion, we have developed a preparation route to 2-aryl-substituted chromans from readily available starting materials. The route gives access to enantiomerically enriched chromans as well. Chiral 2-phenylchroman (**10a**) and 2-(2-bromophenyl)chroman (**20**) were obtained in moderate and high ee values when utilizing IndPHOX ligand **13**. The further modification of **20** was investigated by Suzuki cross-coupling affording 2-([1,1′-biphenyl]-2-yl)chroman (**23**) with preserved enantioselectivity.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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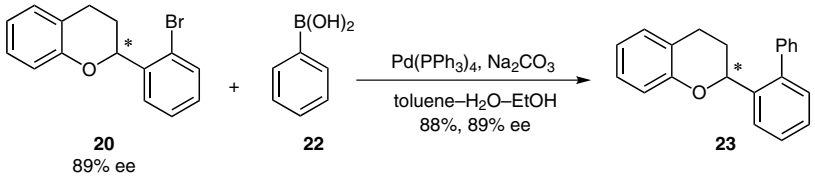
References and Notes

(1) (a) *Chemistry of Heterocyclic Compounds: Chromans and Tocopherols*, Vol. 36; Ellis, G. P.; Lockhart, I. M., Eds.; Wiley: New York, **1981**. (b) Saengchantara, S. T.; Wallace, T. W. *Nat. Prod. Rep.* **1986**, *3*, 465.
(2) Bauer, D. J.; Selway, J. W. T.; Batchelor, J. F.; Tisdale, M.; Caldwell, I. C.; Young, D. A. *Nature (London)* **1981**, *292*, 369.
(3) Efange, S. M. N.; Tu, Z.; von Hohenberg, K.; Francesconi, L.; Howell, R. C.; Rampersad, M. V.; Todaro, L. J.; Papke, R. L.; Kung, M. P. *J. Med. Chem.* **2001**, *44*, 4704.
(4) For some recent examples of the racemic synthesis of chromans, see: (a) Sugimoto, H.; Nakamura, S.; Ohwada, T. *Adv. Synth. Catal.* **2007**, *349*, 669. (b) Yamamoto, Y.; Itonaga, K. *Org. Lett.* **2009**, *11*, 717. (c) Batsomboon, P.; Phakhodee, W.; Ruchirawat, S.; Ploypradith, P. *J. Org. Chem.* **2009**, *74*, 4009. (d) Radomkit, S.; Sarnpitak, P.; Tummatorn, J.; Batsomboon, P.; Ruchirawat, S.; Ploypradith, P. *Tetrahedron* **2011**, *67*, 3904.
(5) For some recent examples of the asymmetric synthesis of chromans, see: (a) Hernandez-Torres, G.; Carreno, M. C.; Urbano, A.; Colobert, F. *Eur. J. Org. Chem.* **2011**, *20-21*, 3864. (b) Valla, C.; Baeza, A.; Menges, F.; Pfaltz, A. *Synlett* **2008**, 3167. (c) Chandrasekhar, S.; Reddy, M. V. *Tetrahedron* **2000**, *56*, 6339. (d) Hodgetts, K. J. *Tetrahedron* **2005**, *61*, 6860.
(6) For a recent review on the asymmetric synthesis of chromans, see: Shen, H. C. *Tetrahedron* **2009**, *65*, 3931.
(7) For some selected examples, see: (a) Neogi, A.; Majhi, T. P.; Achari, B.; Chattopadhyay, P. *Eur. J. Org. Chem.* **2008**, *2*, 330. (b) Kuwabe, S.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202. (c) Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. *J. Am. Chem. Soc.* **2000**, *122*, 10718. (d) Torraca, K. E.; Kuwabe, S. I.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12907.
(8) For some recent examples, see: (a) Zhao, J.; Zhao, Y. F.; Fu, H. *Angew. Chem. Int. Ed.* **2011**, *50*, 3769. (b) Niu, J. J.; Guo, P. R.; Kang, J. T.; Li, Z. G.; Xu, J. W.; Hu, S. J. *J. Org. Chem.* **2009**, *74*, 5075. (c) Adams, H.; Gilmore, N. J.; Jones, S.; Muldowney, M. P.; von Reuss, S. H.; Vemula, R. *Org. Lett.* **2008**, *10*, 1457. (d) Fang, Y.; Li, C. *J. Org. Chem.* **2006**, *71*, 6427.
(9) (a) Xu, B.; Xue, J.; Zhu, J.; Li, Y. *Chem. Lett.* **2008**, *37*, 202. (b) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553. (c) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333.
(10) Gan, Y.; Spencer, T. A. *J. Org. Chem.* **2006**, *71*, 5870.
(11) **General Procedure for Palladium-Catalyzed Intramolecular Cyclization**: To a mixture of $Pd(OAc)_2$ (2.4 mg, 0.0105 mmol), ligand **11** (3.1 mg, 0.0105 mmol) and Cs_2CO_3 (0.17 g, 0.525 mmol), compound **9** (0.35 mmol) in toluene (1.2 mL) was added. After stirring under 90 °C for reported time, the reaction mixture was cooled to r.t., diluted with Et_2O, and filtered through a pad of celite. The resulting solution was purified by silica gel chromatography (*n*-hexane–EtOAc, 30:1).



Scheme 5 Suzuki coupling reaction with chroman **20** and phenylboronic acid **22**

(12) The by-product was 1-(furan-2-yl)-3-phenylpropan-1-one, isolated in 22% yield. For the reaction mechanism, see reference 7b.
(13) Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuvo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043.
(14) **General Procedure for Copper-Catalyzed Intramolecular Cyclization**: To a mixture of CuI (2.8 mg, 0.015 mmol), 2-aminopyridine (2.8 mg, 0.03 mmol) and NaOMe (12 mg, 0.225 mmol), compound **9** (0.15 mmol) in diglyme (0.7 mL) was added. After stirring under 100 °C for reported time, the reaction mixture was cooled to r.t., quenched with H_2O, and extracted with Et_2O. The extracts were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (*n*-hexane–EtOAc, 30:1).
(15) (a) Wang, Y.; Hämäläinen, A.; Tois, J.; Franzén, R. *Tetrahedron: Asymmetry* **2010**, *21*, 2376. (b) Wang, Y.; Vaismaa, M.; Hämäläinen, A.; Tois, J.; Franzén, R. *Tetrahedron: Asymmetry* **2011**, *22*, 524.
(16) Miyabe, H.; Matsumura, A.; Moriyama, K.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 4631.
(17) The reported ee is the average value of three entries.
(18) **2-(2-Bromophenyl)chroman** (**20**): $[\alpha]_D^{20}$ +71.2 (*c* = 0.95, $CHCl_3$, 89% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54–7.61 (m, 2 H), 7.36 (td, *J* = 7.7, 1.2 Hz, 1 H), 7.10–7.19 (m, 3 H), 6.86–6.93 (m, 2 H), 5.38 (td, *J* = 10.2, 2.2 Hz, 1 H), 3.00–3.10 (m, 1 H), 2.75–2.83 (m, 1 H), 2.31–2.39 (m, 1 H), 1.85–1.94 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.4, 141.3, 133.0, 130.0, 129.4, 128.1, 127.8, 127.7, 122.3, 121.8, 120.8, 117.2, 77.3, 29.1, 25.5. HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{13}ONaBr$: 311.0047; found: 311.0015.
(19) $[\alpha]_D^{20}$ +27.7 (*c* = 0.5, CH_2Cl_2, 87% ee).
(20) Yasunori, Y.; Tomohiko, S.; Momoko, W.; Kazunori, K.; Norio, M. *Molecules* **2011**, *16*, 5020.
(21) For some reviews of reactions for aromatic halides, see: (a) Sadig, J. E. R.; Willis, M. C. *Synthesis* **2011**, 1. (b) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338. (c) Bubnov, Y. N. *Heterocycles* **2010**, *80*, 1. (d) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2008**, *64*, 3047. (e) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461. (f) Bras, J. L.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170. (g) Felpin, F. X.; Nassar-Hardy, L.; Callonnec, F. L.; Fouquet, E. *Tetrahedron* **2011**, *67*, 2815.
(22) **2-([1,1′-Biphenyl]-2-yl)chroman** (**22**): $[\alpha]_D^{20}$ –36.5 (*c* = 0.40, $CHCl_3$, 89% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64–7.67 (m, 1 H), 7.25–7.46 (m, 8 H), 7.00–7.11 (m, 2 H), 6.80–6.88 (m, 2 H), 5.05–5.10 (m, 1 H), 2.71–2.78 (m, 2 H), 2.01–2.09 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.8, 141.2, 141.0, 139.3, 130.4, 129.8, 129.6, 128.5, 128.2, 128.0, 127.5, 127.4, 126.7, 122.2, 120.5, 117.3, 75.2, 30.1, 25.9. HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{18}ONa$: 309.1255; found: 309.1263.