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Organocatalytic Asymmetric Conjugate Addition of 3-Monosubstituted Oxindoles to (*E*)-1,4-Diaryl-2-buten-1,4-diones: A Strategy for the Indirect Enantioselective Furanylation and Pyrrolylation of 3-Alkyloxindoles

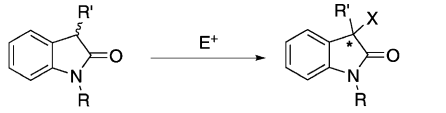
Yu-Hua Liao,[a, d] Xiong-Li Liu,[a, d] Zhi-Jun Wu,[b] Xi-Lin Du,[c] Xiao-Mei Zhang,[a] and Wei-Cheng Yuan*[a]

Abstract: An asymmetric conjugate addition of 3-monosubstituted oxindoles to a range of (*E*)-1,4-diaryl-2-buten-1,4-diones, catalyzed by commercially available cinchonine, is described. This organocatalytic asymmetric reaction affords a broad range of 3,3′-disubstituted oxindoles that contain a 1,4-dicarbonyl moiety and vicinal quaternary and tertiary stereogenic centers in high-to-excellent yields (up to 98%), with excellent diastereomeric and moderate-to-high enantiomeric ratios (up to 99:1 and 95:5, respectively). Subsequently, cyclization of the 1,4-dicarbonyl moiety in the resultant Michael adducts under different Paal–Knorr conditions results in two new kinds of 3,3′-disubstituted oxindoles—3-furanyl- and 3-pyrrolyl-3-alkyl-oxindoles—in high yields and good enantioselectivities. Notably, the studies presented here sufficiently confirm that this two-step strategy of sequential conjugate addition/Paal–Knorr cyclization is not only an attractive method for the indirect enantioselective heteroarylation of 3-alkyloxindoles, but also opens up new avenues toward asymmetric synthesis of structurally diverse 3,3′-disubstituted oxindole derivatives.

Keywords: butendiones · conjugate addition · organocatalysis · oxindoles · Paal–Knorr cyclization

Introduction

The efficient and highly stereoselective construction of complex heterocycles is an ongoing challenge for synthetic chemistry. In particular, oxindoles with a chiral tetrasubstituted carbon atom at the C3 position have emerged as attractive synthetic targets because of their "privileged structure" status in synthetic and medicinal chemistry.[1] Accordingly, considerable effort has been devoted to the construction of diverse 3,3′-disubstituted oxindole cores.[2] However, among the various established strategies for preparation of optically active 3,3′-disubstituted oxindoles, the direct asymmetric functionalization (alkylation,[3] hydroxylation,[4] amination,[5] amino-oxygenation[6a] or hydroxyamination,[6b] chlorination,[7] arylation,[8] fluorination,[9] aldol reaction,[10] Mannich reaction,[11] and Michael addition reaction)[12] of 3-monosubstituted oxindoles with various electrophiles should be the most straightforward approach (Scheme 1). Indeed,



3-monosubstituted oxindoles 3,3'-disubstituted oxindoles

Scheme 1. Direct asymmetric functionalization of 3-monosubstituted oxindoles with electrophiles.

each of these methods can lead to a different class of 3,3′-disubstituted oxindoles that may show promise as biologically active compounds or serve as extremely versatile building blocks for synthetically useful transformations. Asymmetric Michael addition[13] is one of the most powerful strategies used to obtain chiral compounds in organic synthesis and the 3-monosubstituted oxindoles have emerged as valuable synthons for the synthesis of natural products and biologically active compounds.[2] As a result, the synthetic and medicinal chemistry communities have paid much attention to the reaction between 3-monosubstituted oxindole donor substrates and various Michael acceptors. However, the Mi-

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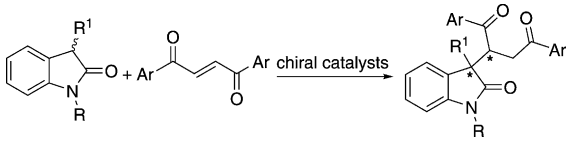
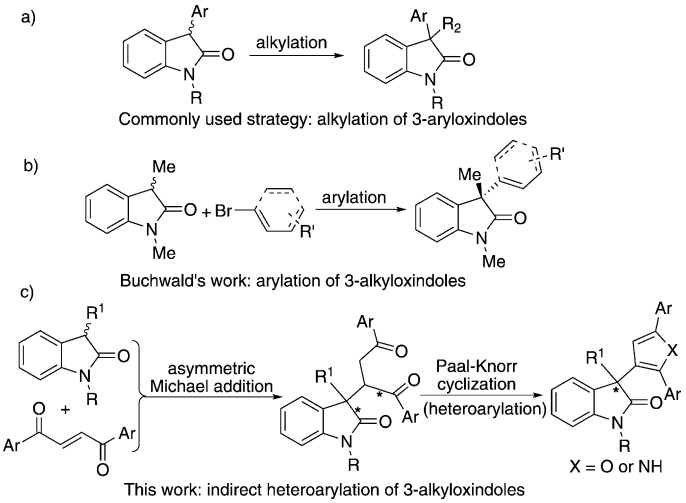
chael acceptors have generally been limited to nitro-olefins,[12c–e,14] enals,[12a,f] enones,[7,11c,12b,15] vinyl sulfones,[12b,16] vinyl selenones,[17] 2-chloroacrylonitrile,[18] maleimides,[19] and ethyl 2-phthalimidoacrylate.[20] To the best of our knowledge, there is no current precedent for the catalytic asymmetric conjugate addition of 3-monosubstituted oxindoles to (*E*)-1,4-diaryl-2-buten-1,4-diones (Scheme 2).[21]



Scheme 2. Asymmetric conjugate addition of 3-monosubstituted oxindoles to (*E*)-1,4-diaryl-2-buten-1,4-diones.

In accordance with our recent research into the development of new methods for the catalytic asymmetric construction of structurally diverse 3,3′-disubstituted oxindoles,[14c,19,22] we devised a research program to investigate the asymmetric conjugate addition of 3-monosubstituted oxindoles to (*E*)-1,4-diaryl-2-buten-1,4-diones (Scheme 2). This reaction possesses some significant merits: 1) delivery of a new series of chiral 3,3′-disubstituted oxindoles that contain a 1,4-dicarbonyl moiety, 2) creation of two sterically hindered contiguous quaternary and tertiary stereogenic centers in one step, and, more importantly, 3) the 1,4-dicarbonyl moieties in the resultant adducts may be further transformed into a heteroaryl unit by Paal–Knorr cyclization, to deliver a series of 3,3′-disubstituted oxindoles that bear a substituted heteroaryl group.[23] The 3-aryl-3-alkyl-oxindole structural motif is a prominent feature in a number of biologically active natural products and pharmaceutically important molecules.[24] Either installing an aryl group on a to 3-alkyloxindole, or installing an alkyl group onto a 3-aryloxindole is the most straightforward approach to the 3-aryl-3-alkyl-oxindole scaffold. However, to the best of our knowledge, the most commonly used method in this research field is alkylation of 3-aryloxindoles, which utilizes the high nucleophilicity of the oxindole C3 position (Scheme 3a).[2] In contrast, only a single report describes the asymmetric arylation of 3-alkyloxindoles (Scheme 3b).[8] Accordingly, more efficient and general methods for the enantioselective arylation of 3-alkyloxindoles are anticipated. We envisioned that a sequential asymmetric conjugate addition of 3-monosubstituted oxindoles to (*E*)-1,4-diaryl-2-buten-1,4-diones and subsequent Paal–Knorr cyclization of the 1,4-dicarbonyl moiety contained in the adducts might provide an alternative approach to optically active 3-aryl-3-alkyl-oxindoles (Scheme 3c). Certainly, if successful, this process would present another method for the arylation of 3-alkyloxindoles further to Buchwald's report.[8]

Additionally, because asymmetric organocatalysis is maturing into a powerful tool in organic synthesis,[25] we have recently investigated the diastereo- and enantioselective conjugate addition of 3-monosubstituted oxindoles to (*E*)-1,4-diaryl-2-buten-1,4-diones with commercially available cinchonine as a catalyst. A range of 3,3′-disubstituted oxindoles that bore a 1,4-dicarbonyl moiety were afforded in high yields (up to 98%) with good-to-excellent diastereoselectivities (diastereomeric ratio (d.r.) up to 99:1) and moderate-to-high enantioselectivities (enantiomeric ratio (e.r.) up to 95:5). In addition, two sterically hindered contiguous quaternary and tertiary stereogenic centers were created in one reaction step (Scheme 3c). Moreover, we have investigated the cyclization of the related 1,4-dicarbonyl moiety contained in the resultant adducts under different Paal–Knorr conditions and achieved the synthesis of 3-furanyl or 3-pyrrolyl chiral 3,3′-disubstituted oxindoles with good results (Scheme 3c). Herein, we report our results on this subject.

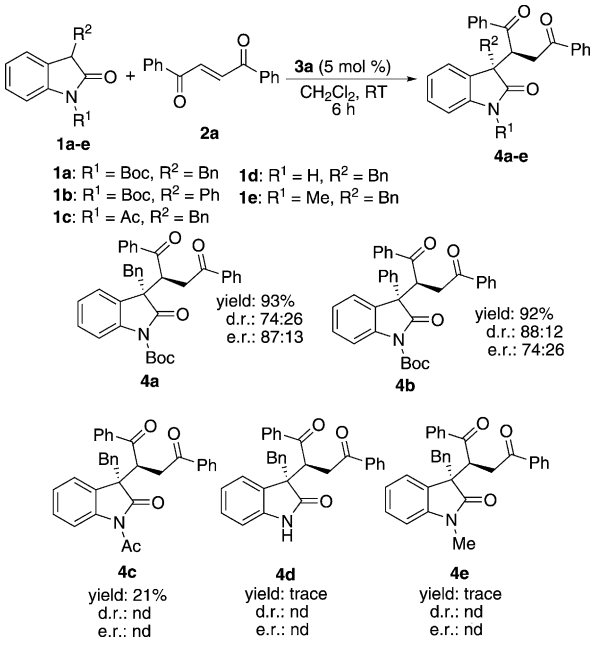


Scheme 3. 3-Monosubstituted oxindoles as starting materials for the construction of 3-aryl-3-alkyl-oxindole scaffolds.

Results and Discussion

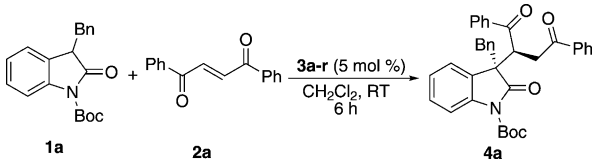
Reaction optimization: Initially, the conjugate addition of oxindoles **1a–e** to (*E*)-1,4-diphenyl-2-buten-1,4-dione (**2a**) were carried out in CH_2Cl_2 at room temperature to examine compatibility with the substituent at the C3 position and the N-protecting group of the oxindoles (Scheme 4). With Takemoto's thiourea catalyst **3a** as the promoter, both 3-benzyloxindole **1a** and 3-phenyloxindole **1b** reacted well to afford the adducts **4a** and **4b**, respectively, in similar yield, but **1a** gave better enantioselectivity than **1b**, although with a slightly inferior diastereoselectivity. Significantly, the reaction activity was very sensitive to the N-protecting group. Very poor reactivity was observed with *N*-acetyloxindole **1c** and there was almost no reaction with either NH oxindole **1d** or *N*-methyloxindole **1e** as the substrate. Based on these results, we chose to use *N*-Boc-3-benzyl oxindole (**1a**) for further optimization of the reaction conditions.

Subsequent studies were focused on the optimization of various chiral organocatalysts **3a–q** (Scheme 5) for the con-



Scheme 4. Screening of the substituents at the C3 position and the N-protecting groups of oxindoles **1**. The reaction was performed with **1** (0.12 mmol), **2a** (0.1 mmol) and **3a** (5 mol %) in CH_2Cl_2 (1.0 mL) at RT for 6 h. The isolated yields are reported; d.r. values were determined by ^1H NMR spectroscopy; e.r. values were determined by chiral HPLC analysis for the major diastereomer; nd = not determined. Boc = *tert*-butoxycarbonyl; Bn = benzyl; Ac = acetyl.

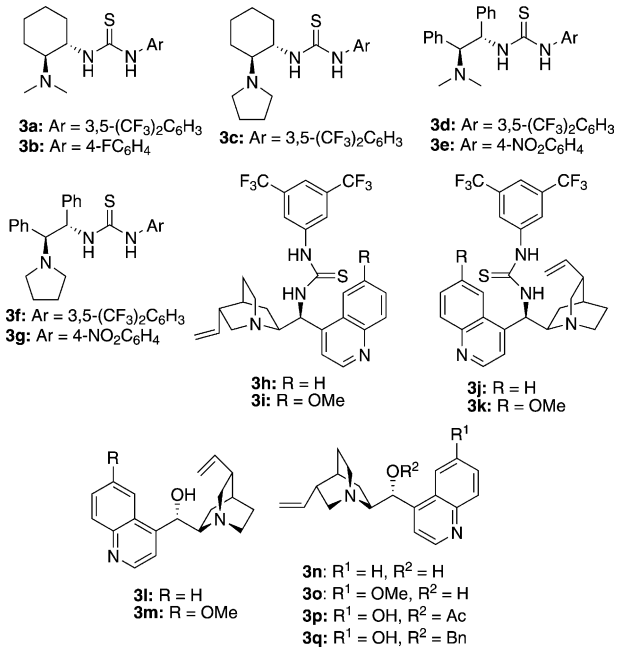
Table 1. Screening of various chiral organocatalysts for the reaction of **1a** with **2a**.[a]



Entry	3	Yield [%][b]	d.r.[c]	e.r. [%][d]
1	**3a**	93	76:24	87:13 (−)
2	**3b**	86	77:23	74:26 (−)
3	**3c**	93	75:25	84:16 (−)
4	**3d**	80	95:5	60:40 (−)
5	**3e**	56	92:8	73:27 (−)
6	**3f**	71	96:4	66:34 (−)
7	**3g**	73	95:5	81:19 (−)
8	**3h**	89	84:16	67:33 (−)
9	**3i**	89	82:18	65:35 (−)
10	**3j**	69	82:18	63:37 (−)
11	**3k**	86	79:21	55:45 (−)
12	**3l**	96	90:10	87:13 (−)
13	**3m**	95	81:19	60:40 (−)
14	**3n**	89	85:15	85:15 (+)
15	**3o**	89	70:30	62:38 (+)
16	**3p**	71	91:9	63:37 (−)
17	**3q**	98	93:7	75:25 (−)

[a] The reaction was performed with **1a** (0.12 mmol), **2a** (0.1 mmol), and **3** (5 mol %) in CH_2Cl_2 (1.0 mL) at RT for 6 h. [b] Isolated product yield. [c] Determined by ^1H NMR spectroscopy. [d] Determined by chiral HPLC analysis for the major diastereomer (the major isomer is indicated in parentheses).

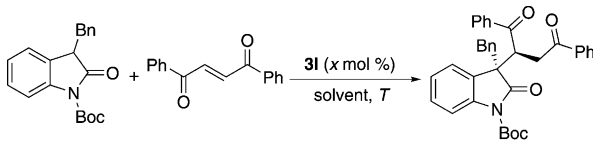
jugate addition of **2a** to **1a** (Table 1). To our delight, the model reaction generally exhibited high efficiency in the presence of organocatalysts **3a–q** at room temperature in CH_2Cl_2. We found that the reactions with chiral bifunctional thiourea tertiary amines **3a–k** as catalysts (Table 1, entries 1–11) could deliver the corresponding adduct **4a** in up to 93 % yield (Table 1, entries 1 and 3) with a d.r. of up to 96:4 (Table 1, entry 6) and an e.r. of up to 87:13 (Table 1, entry 1) for the major diastereomer. We also investigated organocatalysts **3l–q**, the *Cinchona* alkaloids and their derivatives, with the same model reaction (Table 1, entries 12–17). It was found that reaction with **3q** as the catalyst proceeded smoothly and afforded the product in 98 % yield with a 93:7 d.r. but only a 75:25 e.r. (Table 1, entry 17). In addition, commercially available cinchonine **3l** promoted the reaction to give **4a** in 96 % yield with a 90:10 d.r. and up to an 87:13 e.r. (Table 1, entry 12). Therefore, we selected **3l** as the optimal catalyst for further optimization of the reaction conditions.



Scheme 5. The chiral organocatalysts evaluated in this study.

We turned our attention to the further optimization of the **3l** catalyzed reaction to improve the conjugate addition reaction efficiency (Table 2). A solvent screen revealed that the product **4a** could be obtained from the reaction catalyzed by **3l** (5 mol %) in high yields after 6 h in all cases, but variation of the solvent did have an effect on the stereoselectivity (Table 2, entries 1–13). Very poor asymmetric induction was obtained when the reaction was conducted in DMF (Table 2. entry 1). Good diastereoselectivity (d.r. = 92:8) but low enantioselectivity (e.r. = 57:43) was observed with CH_3CN as the solvent (Table 2, entry 2). Among several other solvents surveyed (Table 2, entries 3–13), the best results could be achieved in trichloroethane (yield = 95 %, d.r. = 95:5, e.r. = 88:12; Table 2, entry 13). When the reaction temperature was lowered from room temperature to −30 °C there was an improvement of diastereoselectivity (d.r. =

Table 2. Further screening of various reaction conditions.[a]



1a 2a 4a

Entry	Solvent	x [mol%]	T [°C]	Yield [%][b]	d.r.[c]	e.r. [%][d]
1	DMF	5	RT	84	51:49	52:48
2	CH_3CN	5	RT	89	92:8	57:43
3	EtOAc	5	RT	93	91:9	80:20
4	THF	5	RT	88	91:9	69:31
5	Et_2O	5	RT	90	96:4	67:33
6	PhOMe	5	RT	93	90:10	86:14
7	$(CH_3OCH_2)_2$	5	RT	89	92:8	83:17
8	toluene	5	RT	93	92:8	85:15
9	CH_2Cl_2	5	RT	96	90:10	87:13
10	$CHCl_3$	5	RT	89	90:10	80:20
11	$ClCH_2CH_2Cl$	5	RT	93	91:9	86:14
12	$Cl_2CHCHCl_2$	5	RT	95	93:7	83:17
13	Cl_3CCH_3	5	RT	95	95:5	88:12
14	Cl_3CCH_3	5	−30	92	99:1	89:11[e]
15	Cl_3CCH_3	10	−30	92	99:1	92:8[e]
16	Cl_3CCH_3	20	−30	94	98:2	93:7[e]
17	Cl_3CCH_3	20	−30	94	98:2	94:6[e,f]

[a] Unless specified, the reaction was performed with **1a** (0.12 mmol), **2a** (0.1 mmol), and **3l** (5 mol%) in specified solvent (1.0 mL) for 6 h. [b] Isolated product yield. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by chiral HPLC analysis for the major diastereomer (the major isomer is indicated in parentheses). [e] Run for 36 h. [f] c = 0.2 mol L^{-1}.

99:1) and a similar enantioselectivity without sacrifice to the yield, although an extended reaction time was required (Table 2, entry 14 versus 13). Next, a survey of the catalyst loading revealed that the enantioselectivity improved slightly with an increase of catalyst loading (Table 2, entries 15 and 16). Finally, up to a 98:2 d.r. and a 94:6 e.r. could be reached at higher concentration (Table 2, entry 17). To summarize, the optimized reaction conditions for the asymmetric conjugate addition of 3-monosubstituted oxindoles **1** to (*E*)-1,4-diaryl-2-buten-1,4-diones **2** were: **1a** (0.24 mmol), **2a** (0.2 mmol), and **3l** (20 mol%) at −30°C in trichloroethane (1.0 mL).

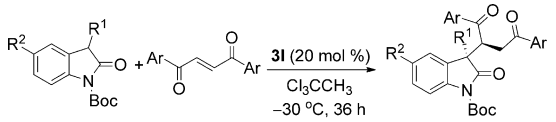
Substrate scope of the asymmetric conjugate addition of oxindoles 1 to dienones 2: With the optimized reaction conditions in hand, we next examined a variety of 3-substituted oxindoles (**1a** and **1f–s**) and (*E*)-1,4-diaryl-2-buten-1,4-diones (**2a–j**) to establish the general utility of this asymmetric transformation (Table 3). First, we focused our studies on addition of **1a** to **2b–i** to investigate the scope and limitations of the electrophile. As shown in Table 3, the reaction tolerated different electron-withdrawing groups on the aryl moieties of **2**; compounds **4f–h** were obtained in high yields, with high d.r. and good e.r. values (Table 3, entries 1–3). We also found that electrophilic substrates **2c**, **2f**, and **2g**, which contain the same electron-withdrawing group but in different positions on the phenyl ring, smoothly delivered the corresponding adducts **4g**, **4j**, and **4k** in high yield and with good d.r. and e.r. values (Table 3, entries 2, 5, and 6). In addition, the reaction with **2e**, which bears an electron-donating group on each phenyl ring, also proceeded well and furnished the desired product **4i** in 95% yield, 97:3 d.r. and 91:9 e.r. (Table 3, entry 4). The reaction also took place with the heteroaromatic substituent thiophene on the dienone (**2h**) to give **4l** in good yield and diastereoselectivity, but moderate enantioselectivity (Table 3, entry 7). The bulkier naphthyl group could be present (**2i**) without impeding the course of the reaction and **4m** was obtained with acceptable results (Table 3, entry 8).

On the other hand, we prepared a library of 3-benzyl oxindoles **1** that bore different substituents and employed them in the reaction with **2a** under the standard conditions (Table 3, entries 9–17). Gratifyingly, these cinchonine-catalyzed conjugate addition reactions proceeded well to provide Michael adducts **4n–v** in very high yields, with excellent d.r. and good e.r. values. These results revealed that the reactivity and the selectivity of these asymmetric Michael addition reactions were not sensitive to the electronic and steric properties of the substituents incorporated into the benzene ring of the oxindole C3-benzyl group (Table 3, entries 9–15). The bulkier oxindole **1m** could also be smoothly converted into **4u** with very good results (Table 3, entry 16). Meanwhile, installation of a thienylmethyl group at the oxindole C3 position allowed the conjugate addition between **1n** and **2a** to proceed smoothly to give **4v** (Table 3, entry 17). We also found that electron-donating and electron-withdrawing substituents could be tolerated on the oxindole aromatic ring (Table 3, entries 18 and 19). Notably, an aliphatic group (a methyl group in **1q**) at the C3 position of the oxindole was tolerated and the desired product **4y** was obtained with good selectivity (d.r. = 93:7 and e.r. = 88:12), albeit in only 37% yield (Table 3, entry 20). Similarly, substrate **1r** could smoothly deliver the expected adduct **4z** with acceptable results (Table 3, entry 21). Reaction with ester-substituted oxindole **1s** was also successful and afforded **4a′** with pleasing results (Table 3, entry 22). Unfortunately, the reaction with (*E*)-hex-3-ene-2,5-dione (**2j**) as the acceptor did not proceed (Table 3, entry 23). However, it was gratifying to find that (*E*)-ethyl-4-oxo-4-phenylbut-2-enoate (**2k**) was able to give **4c′** in a reasonable yield with moderate d.r. and e.r. values under the optimized reaction conditions (Table 3, entry 24).

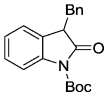
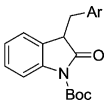
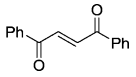
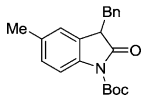
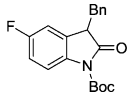
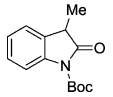
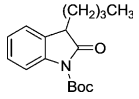
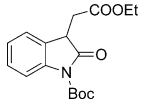
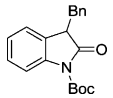
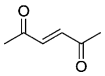
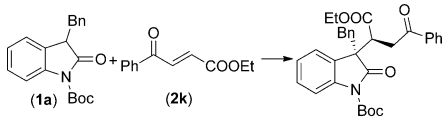
Determination of the absolute configuration of the product and proposed working model for the reaction: To determine the absolute and relative configuration of the asymmetric conjugate addition products, single crystals suitable for X-ray crystallographic analysis were fortunately obtained from enantiopure **4k**, which bears a chlorine atom.[26] As shown in Figure 1, **4k** contains a (C7*R*, C21*S*) configuration. The configuration of the other adducts in this work were tentatively assigned by analogy.

Based on the experimental results discussed above and the observed absolute configuration of **4k**, a possible working model to account for the stereoselectivity of the reaction is shown in Scheme 6. One double hydrogen-bonding inter-

Table 3. Asymmetric conjugate addition of 3-monosubstituted oxindoles **1** to (*E*)-1,4-diaryl-2-buten-1,4-diones **2**.[a]



1 **2** **4**

Entry	**1**		**2**		**4**	Yield [%][b]	d.r.[c]	e.r.[d]
1			Ar = *p*-F–Ph (**2b**)		**4f**	96	95:5	90:10
2			Ar = *p*-Cl–Ph (**2c**)		**4g**	93	97:3	94:6
3			Ar = *p*-Br–Ph (**2d**)		**4h**	88	92:8	89:11
4		(**1a**)	Ar = *m*-MeO–Ph (**2e**)		**4i**	95	97:3	91:9
5			Ar = *m*-Cl–Ph (**2f**)		**4j**	88	95:5	87:13
6			Ar = *o*-Cl–Ph (**2g**)		**4k**	92	97:3	87:13[e]
7			Ar = 2-thienyl (**2h**)		**4l**	93	93:7	78:22[f]
8			Ar = 2-naphthyl (**2i**)		**4m**	61	91:9	76:24[f]
9		Ar = *p*-MeO–Ph (**1f**)		(**2a**)	**4n**	94	98:2	92:8
10		Ar = *p*-F–Ph (**1g**)			**4o**	95	98:2	93:7
11		Ar = *m*-Me–Ph (**1h**)			**4p**	95	97:3	87:13
12		Ar = *m*-F–Ph (**1i**)			**4q**	93	98:2	93:7
13		Ar = *o*-MeO–Ph (**1j**)			**4r**	88	96:4	84:16
14		Ar = *o*-F–Ph (**1k**)			**4s**	90	96:4	90:10
15		Ar = 3,4-(MeO)$_2$–Ph (**1l**)			**4t**	96	98:2	92:8
16		Ar = 1-naphthyl (**1m**)			**4u**	95	98:2	93:7
17		Ar = 2-thienyl (**1n**)			**4v**	95	98:2	95:5
18		(**1o**)			**4w**	82	96:4	89:11
19		(**1p**)			**4x**	93	98:2	94:6
20		(**1q**)			**4y**	37	93:7	88:12[f]
21		(**1r**)			**4z**	70	98:2	89:11[f]
22		(**1s**)			**4a′**	97	93:7	92:8
23		(**1a**)		(**2j**)	**4b′**	NR[f,g]	–	–
24					**4c′**	81	75:25	87:13

[a] Unless specified, the reaction was performed with **1** (0.24 mmol), **2** (0.2 mmol), and **3l** (20 mol %) in trichloroethane (1.0 mL) at −30 °C for 36 h. [b] Isolated product yield. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by chiral HPLC analysis for the major diastereomer (the major isomer is indicated in parentheses). [e] Single crystals suitable for X-ray crystallographic analysis were obtained, see ref. [26]. [f] Run at RT for 24 h. [g] NR = no reaction.

action might be formed between the protonated tertiary amine group of the catalyst and the two carbonyl units of the protected oxindole. Meanwhile, another hydrogen-bonding interaction would be generated between the C9 hydroxyl group of the catalyst and one carbonyl group of **2g**. Consequently, the nucleophilic oxindole **1a** and the electrophilic dienone **2g** are simultaneously activated by bifunctional organocatalyst **3l** through multiple hydrogen-bonding interactions. Here, there are two possible transition states, **A** and **B**. Of them, transition state **A** is formed predominately; transition state **B** is disfavored, likely due to the unfavorable hydrogen-bonding interaction between the C9 hydroxyl

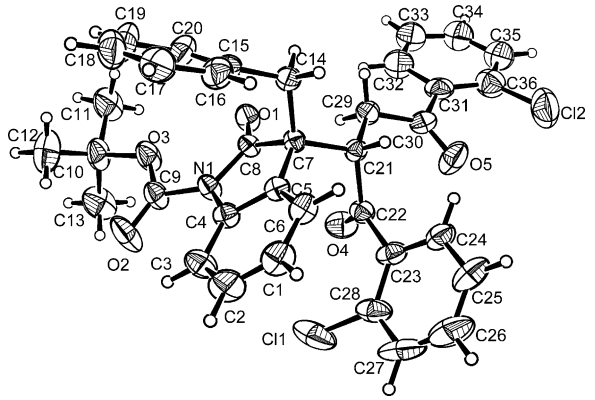
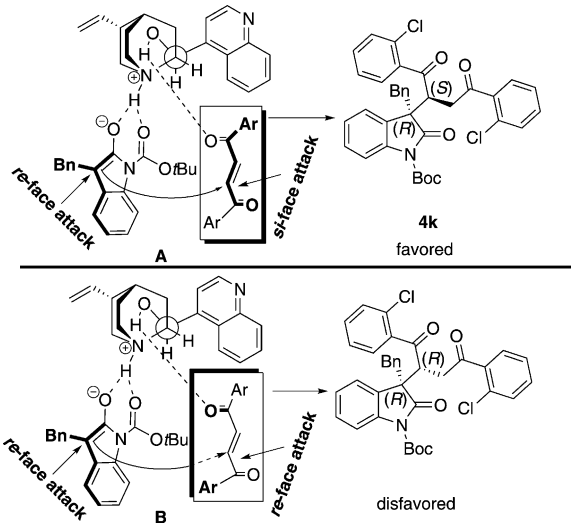


Figure 1. X-ray structure of **4k**.



Scheme 6. Proposed working model for the asymmetric conjugate addition of 3-monosubstituted oxindoles to (*E*)-1,4-diaryl-2-buten-1,4-diones.

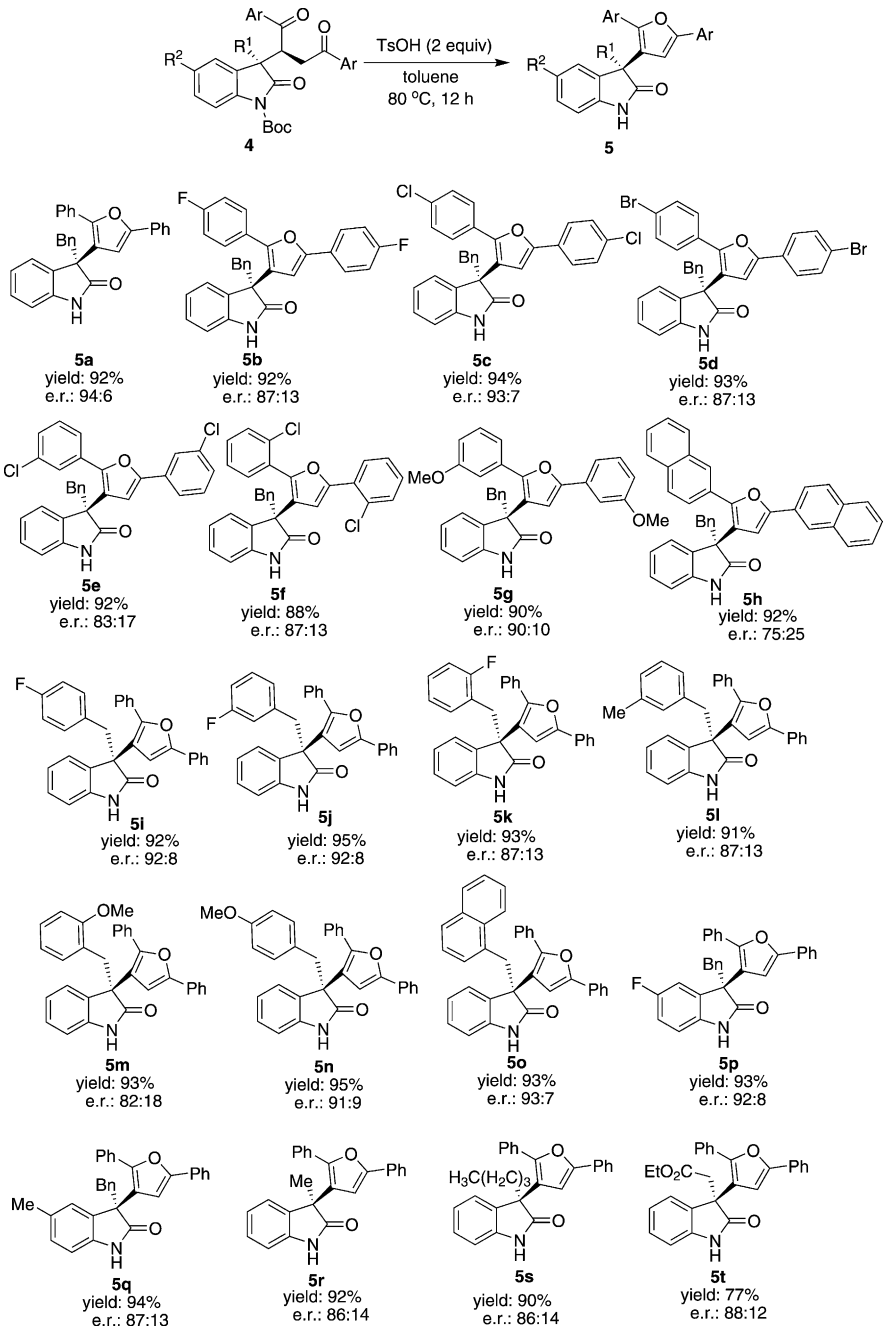
group of the catalyst and one carbonyl group of the dienone. In light of the X-ray crystallographic analysis of product **4k**, it is likely deduced that the *Si* face of dienone **2g** was preferentially attacked by the *Re* face of the enolate of **1a** to afford the Michael adduct **4k** with a (C7*R*,C21*S*) configuration.

Cyclization of the 1,4-dicarbonyl moiety of Michael adducts 4 for the synthesis of 3-furanyl-3-alkyl-oxindoles 5: The 3-aryl-3-alkyl-oxindole structural motif is the ubiquitous core of some bioactive natural products and pharmaceutically active compounds.[24] With the successful construction of a wide range of 3,3′-disubstituted oxindoles substituted at the C3 position with a 1,4-dicarbonyl moiety realized, we decided to further transform these resultant Michael adducts **4** into 3-tetrasubstituted oxindoles which possess a heteroaryl group at the C3 position by treatment with different Paal–Knorr conditions.[23] First, we tried to convert the 1,4-dicarbonyl moiety into furanyl ring. To our delight, treatment of the Michael adducts **4** with TsOH (2 equiv) in toluene at 80 °C for 12 h, resulted in the formation of a wide scope of 3-furanyl-3-alkyl-oxindoles **5a–s** with good e.r. values (up to 94:6) and yields from 88–95 % (Scheme 7).[27] Electron-donating (**5g**) and electron-withdrawing groups (**5b–f**) on the aryl ring of the 1,4-dicarbonyl moiety were compatible with the Paal–Knorr furanylation conditions. Similarly, a variety of functional groups on the benzyl moiety (**5i–n**) and the oxindole aromatic ring (**5p–q**) were also tolerated. Additionally, reversal of the steric properties of the substituents on the 1,4-dicarbonyl and C3-benzyl moieties (**5h** versus **5o**) showed almost no influence on the cyclization. Replacement of the benzyl group with a methyl (**5r**) or *n*-butyl group (**5s**) at the C3 position had no effect on the reaction. The Michael adduct **4a′** also could be smoothly transformed to give product **5t** (Scheme 7). Notably, in all cases, the *N*-Boc group of compounds **4** was cleanly removed during the Paal–Knorr furanylation reaction and, thus, afforded a class of unprotected 3-furanyl-3-alkyl-oxindoles **5** that are difficult to access by other methods.

Cyclization of the 1,4-dicarbonyl moiety of Michael adducts 4 for the synthesis of 3-pyrrolyl-3-alkyl-oxindoles 6: Inspired by the success of the Paal–Knorr furanylation described above, we attempted to convert the diverse 1,4-dicarbonyl moieties of the Michael adducts **4** into pyrrolyl rings. As shown in Scheme 8, various Michael adducts **4** were subjected to Paal–Knorr pyrrolylation conditions with ammonium acetate (10 equiv) in acetic acid at 100 °C for 3.5 h.[27] Similar to the preceding Paal–Knorr furanylation studies, the 1,4-dicarbonyl group cyclized smoothly to give the pyrrole ring. As a result, an array of 3-pyrrolyl-3-alkyl-oxindoles **6a–s** with various steric and electronic parameters were constructed in high yields (up to 94 %) with moderate-to-good e.r. values that ranged from 75:25 to 94:6 (Scheme 8). Interestingly, the *N*-Boc group of compounds **4** was also deprotected under these Paal–Knorr pyrrolylation conditions. Overall, two kinds of unprotected chiral 3,3′-disubstituted oxindole derivative, namely, 3-furanyl-3-alkyl-oxindoles **5** and 3-furanyl-3-alkyl-oxindoles **6**, were obtained smoothly under different Paal–Knorr conditions by the indirect strategies described above.

Conclusion

We have developed an efficient method for the catalytic asymmetric conjugate addition reaction of 3-monosubstituted oxindoles **1** to various (*E*)-1,4-diaryl-2-buten-1,4-diones **2** with cinchonine (**3l**) as a catalyst. This new organocatalytic reaction proceeds with excellent diastereo- and moderate-to-high enantioselectivity to deliver a broad range of 3,3′-disubstituted oxindole derivatives **4** in high-to-excellent yields. The resultant 3-tetrasubstituted oxindole adducts **4** are characterized by the presence of a 1,4-dicarbonyl moiety and two adjacent quaternary and tertiary stereocenters that are difficult to access by other methods. A plausible working model that involves concerted activation has been proposed. Furthermore, the cyclization of the 1,4-dicarbonyl moiety



Scheme 7. Transformation of Michael adducts **4** (0.2 mmol) to 3-furanyl-3-alkyl-oxindole derivatives **5**. The yield given is the isolated yield and e.r. values were determined by chiral HPLC analysis.

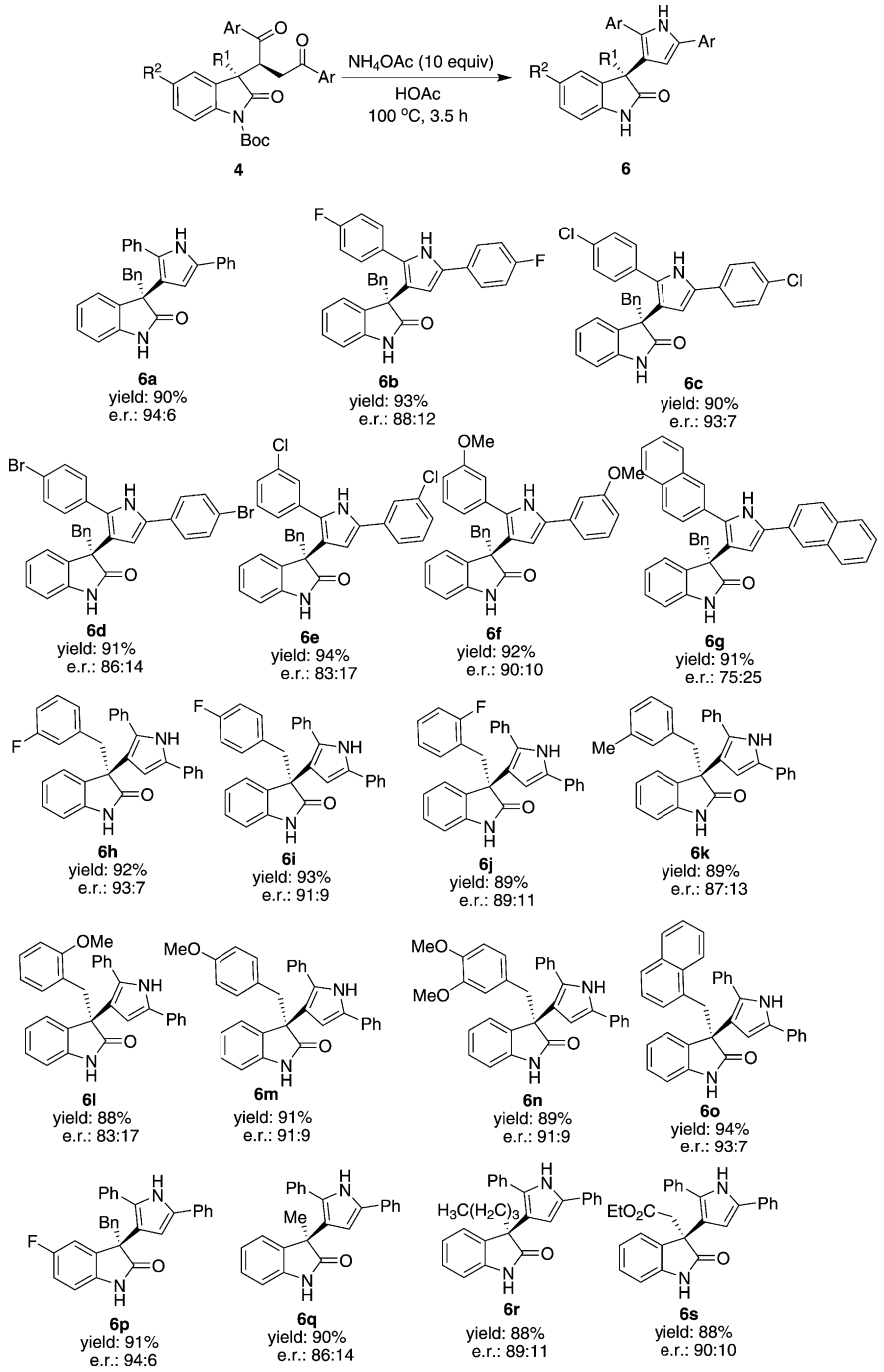
contained in the Michael adducts **4** under different Paal–Knorr conditions results in unprotected 3-furanyl- or 3-pyrrolyl-3-alkyl-oxindoles (**5** and **6**, respectively). These two classes of chiral 3-heteroaryl-3-alkyl-oxindoles have been obtained smoothly, with wide substrate scope, in high yields, and with good enantioselectivities. In addition, the reactivity and selectivity of the Paal–Knorr furanylation and pyrrolylation reactions are not sensitive towards the steric and electronic variation of the Michael adducts. Notably, the realization of this two-step strategy of sequential conjugate addition/Paal–Knorr cyclization not only furnishes an efficient method for the indirect enantioselective heteroarylation of 3-alkyl-oxindole derivatives, but also provides a new route towards the synthesis of structurally diverse 3,3′-disubstituted oxindole derivatives.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz spectrometer in $CDCl_3$ or [D_6]DMSO with tetramethylsilane (TMS) as an internal standard. Optical rotations were measured on a PerkinElmer 241 polarimeter. Melting points were recorded on a Büchi melting point B-545 apparatus. HPLC was performed with a Shimadzu instrument. 1,1,1-Trichloroethane was distilled over CaH_2 prior to use; toluene was distilled from sodium benzophenone. Unless noted, commercial reagents were used without further purification. All reactions were conducted in a closed system under an atmosphere of air and were monitored by TLC, except when noted. 3-Monosubstituted oxindoles **1**[28] and (*E*)-1,4-diaryl-2-buten-1,4-diones **2**[29] were prepared by literature procedures.

General procedure for cinchonine-catalyzed asymmetric conjugate addition of oxindoles 1 to dienones 2 (4a): A solution of **1a** (0.24 mmol), **2a** (0.2 mmol), and cinchonine **3l** (0.04 mmol) in 1,1,1-trichloroethane (1 mL) was stirred for 36 h at −30 °C. The reaction mixture was directly subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate) to furnish **4a** as a white solid (94 %, d.r. = 98:2, e.r. = 94:6). HPLC (performed after the *N*-Boc group was deprotected by treatment with CF_3COOH in CH_2Cl_2 at RT, Chiralcel AD-H column, *i*PrOH/hexane 50:50, flow rate = 1.0 mL min^{-1}, UV detection at λ = 254 nm): $t_{R(major)}$ = 84.80 min, $t_{R(minor)}$ = 17.30 min; m.p. 84.6–87.3 °C; $[\alpha]_D^{20} = -2.4$ (c = 1.37 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56 (s, 9H), 2.86 (d, J = 12.6 Hz, 1H), 3.14 (d, J = 12.6 Hz, 1H), 3.46 (dd, J = 7.5, 18.6 Hz, 1H), 3.85 (dd, J = 4.5, 18.6 Hz, 1H), 5.18 (dd, J = 4.5, 7.5 Hz, 1H), 6.63 (d, J = 7.5 Hz, 2H), 6.92–7.01 (m, 3H), 7.06–7.15 (m, 2H), 7.41–7.54 (m, 8H), 7.93 (d, J = 7.5 Hz, 2H), 8.11 ppm (d, J = 12.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.9, 38.1, 43.9, 46.7, 54.6, 83.8, 114.6, 123.9, 124.0, 126.7, 127.4, 128.2, 128.3, 128.4, 128.6, 128.7, 129.7, 133.2, 133.5, 133.9, 135.9, 137.4, 139.9, 148.5, 177.2, 197.6, 200.7 ppm; IR (KBr): $\tilde{\nu}$ = 1757, 1730, 1677, 1597, 1482, 1294, 1150, 750, 698 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{36}H_{33}NNaO_5$: 582.2251 [M+Na]$^+$; found: 582.2244.

General procedure for the synthesis of 3-furanyl-3-alkyl-oxindoles (5a): A solution of **4a** (0.2 mmol) and TsOH (0.4 mmol) in toluene (5 mL) was heated at 80 °C for 12 h. After cooling to RT, the reaction mixture



Scheme 8. Transformation of Michael adducts **4** (0.2 mmol) to 3-pyrrolyl-3-alkyl-oxindole derivatives **6**. The yield given is the isolated yield and e.r. values were determined by chiral HPLC analysis.

was purified by flash chromatography (petroleum ether/ethyl acetate) on silica gel to afford **5a** as a white solid (92%, e.r. = 94:6). HPLC (Chiralcel AD-H column, *i*PrOH/hexane 30:70, flow rate = 1.0 mL min^{-1}, UV detection at $\lambda = 254$ nm): $t_{R(major)} = 16.06$ min, $t_{R(minor)} = 11.24$ min; m.p. 59.4–61.9 °C; $[\alpha]_D^{20} = +40.4$ ($c = 2.50$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.39$ (d, $J = 12.6$ Hz, 1H), 3.71 (d, $J = 12.6$ Hz, 1H), 6.52 (d, $J = 7.8$ Hz, 1H), 6.81–6.85 (m, 3H), 6.98–7.07 (m, 5H), 7.16–7.20 (m, 5H), 7.25–7.26 (m, 1H), 7.36–7.42 (m, 3H), 7.73 ppm (d, $J = 7.5$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 44.0$, 53.3, 107.2, 109.7, 121.8, 122.0, 123.7, 124.8, 126.6, 127.4, 127.5, 127.9, 128.5, 128.7, 130.0, 130.3, 131.3, 131.5, 134.8, 140.7, 150.1, 152.3, 180.0 ppm; IR (KBr) $\tilde{\nu} = 1709$, 1619, 1492, 1472, 1219, 698 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{31}H_{23}NNaO_2$: 464.1621 $[M+Na]^+$; found: 464.1632.

General procedure for the synthesis of 3-pyrrolyl-3-alkyl-oxindoles (6a): A mixture of **4a** (0.2 mmol) and NH_4OAc (2 mmol) in AcOH (2 mL) was heated at 100 °C for 3.5 h. After cooling to RT, the reaction mixture was diluted with CH_2Cl_2 and washed with H_2O. The aqueous phase was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, then the combined organic phase was concentrated in vacuo and purified by flash chromatography (petroleum ether/ethyl acetate) on silica gel to afford **6a** as a white solid (90%; e.r. = 94:6). HPLC (Chiralcel AD-H column, *i*PrOH/hexane 30:70, flow rate = 1.0 mL min^{-1}, UV detection at $\lambda = 254$ nm): $t_{R(major)} = 43.76$ min, $t_{R(minor)} = 10.70$ min; m.p. 80.1–82.6 °C; $[\alpha]_D^{20} = +26.7$ ($c = 3.12$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.50$ (d, $J = 12.6$ Hz, 1H), 3.74 = (d, $J = 12.6$ Hz, 1H), 6.36 (d, $J = 7.8$ Hz, 1H), 6.81–6.87 (m, 4H), 6.90–7.04 (m, 6H), 7.09–7.12 (m, 5H), 7.15–7.20 (m, 1H), 7.35–7.38 (m, 2H), 7.52 (d, $J = 7.8$ Hz, 2H), 8.38 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 44.0$, 54.2, 106.5, 109.2, 120.7, 121.7, 123.6, 124.7, 126.0, 126.3, 127.2, 127.3, 127.4, 128.7, 129.4, 129.9, 130.5, 130.8, 132.2, 133.3, 135.3, 140.5, 180.8 ppm; IR (KBr): $\tilde{\nu} = 1707$, 1619, 1584, 1490, 1471, 1219, 699 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{31}H_{24}N_2NaO$: 463.1781 $[M+Na]^+$; found: 463.1784.

Acknowledgements

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[26] CCDC-844296 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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