Highly Stereoselective Dimerization of 3-Alkoxyimino-2-aryl-alkylnitriles via Oxidative Carbon–Carbon Bond Formation

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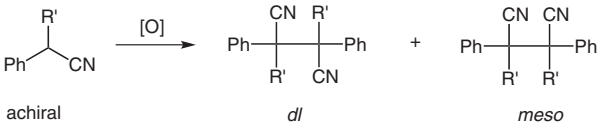
Received 16 March 2009

Abstract: The MnO_2-mediated oxidative dimerization of a series of 3-alkoxyimino-2-aryl-alkylnitriles was investigated. The developed method stereospecifically afforded solely the corresponding C_2-symmetric *dl*-dimers, with the *trans*-configuration of the C=N double bonds, in good to excellent yields under mild conditions. The alkoxyimino substituents in the substrates and a thermodynamically controlled mechanism are proposed to be essential for the stereoselectivity of this radical dimerization process.

Key words: MnO_2, oxidative dimerization, 3-alkoxyimino-2-aryl-alkylnitriles, *dl*-dimers, stereoselectivity

Oxidative homocoupling of α-substituted benzylcyanides can result in carbon–carbon bond formation between the two identical sp^3-hybridized benzylic carbon atoms, which would provide the most straightforward and expedient approach to the synthesis of the substituted 2,3-diarylsuccinonitriles. A large variety of oxidants, for example *tert*-butyl peroxide,[1] iodine,[2] sodium nitrite,[3] oxygen,[1b] H_2O_2,[1b,4] $K_3Fe(CN)_6$,[3,5] HNO_3,[6] NiO_2,[7] $KMnO_4$,[3,8] Ag_2O,[3] PbO_2,[3] and di-*tert*-butylhyponitrite[9] have been reported for such homocoupling reactions. Generally, these transformations undergo non-diastereoselective radical dimerization processes and mixtures of both *dl*- and *meso*-isomers are obtained (Scheme 1). Due to the fact that a great deal of effort has been devoted to achieving high diastereoselectivity in many other homocoupling reactions,[10] we thought it desirable to realize the stereoselective oxidative dimerization of α-substituted benzylcyanide derivatives. Herein, we report the stereospecific homocoupling of 3-alkoxyimino-2-aryl-alkylnitriles, a class of highly α-functionalized benzylcyanides, which affords exclusively the *dl*-dimers with no formation of the *meso*-isomers (Scheme 1).

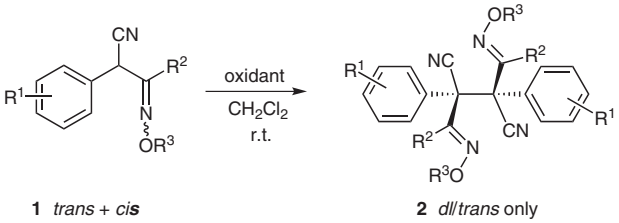
We recently reported an efficient and practical $FeCl_3$-mediated intramolecular cyclization of 3-alkoxyimino-2-aryl-alkylnitriles that allows the facile preparation of a series of *N*-alkoxyindole-3-carbonitriles.[11] In an attempt to elucidate the reaction mechanism, we also applied $K_3Fe(CN)_6$, which is a less potent single-electron oxidant than $FeCl_3$, to treat substrate **1a**, and it was found that the homodimer of **1a** was obtained without any detection of the cyclized indole products. This oxidative coupling



Scheme 1

reaction intrigued us enough to further explore its oxidative condition and stereoselectivity as well as its scope and generality.

We began our investigation with **1a**, a mixture of *trans* and *cis*-isomers (*trans*/*cis* = 4.7:1), as the model substrate with which to screen various readily available oxidants (Scheme 2). It was found that, in addition to $K_3Fe(CN)_6$, MnO_2 and Ag_2O could also efficiently convert **1a** into its homodimer, while the other oxidants were either unreactive or inefficient for this transformation (see Table 1). Based on the experimental results, compound **1a** in all cases was found to give solely the *dl*-isomer rather than a mixture of *dl*- and *meso*-isomers; a distinct feature always observed for such homocoupling reactions. We finally selected the convenient oxidant MnO_2 to transform a series of 3-alkoximino-2-aryl-alkylnitriles into their corresponding homocoupled dimers.



Scheme 2

After optimization,[12] the oxidative coupling reaction under study was finally conducted in the presence of four equivalents of MnO_2 in dried CH_2Cl_2 with stirring at room temperature. The results shown in Table 2 show that substrates with both electron-withdrawing and electron-donating groups on the benzene ring could conveniently furnish the corresponding homodimers in good to excellent yields (84–97%). When the electron-withdrawing groups were substituted on the benzene ring (entries 4, 5 and 13 in Table 2), the reaction proceeded smoothly to furnish the coupling dimer in high yields (93–96%) within shorter periods of time (0.5 h). It is noteworthy that when

SYNLETT 2009, No. 11, pp 1835–1841
Advanced online publication: 12.06.2009
DOI: 10.1055/s-0029-1217369; Art ID: W03609ST

Table 1 Oxidants Screened for the Homocoupling of **1a**[a]

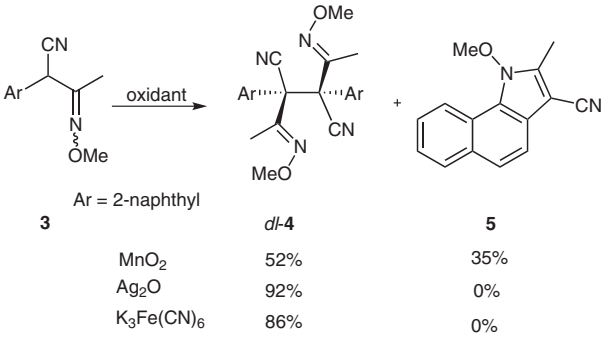
Entry	Oxidant (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%)[b,c]
1	DDQ (1.5)	CH_2Cl_2	r.t.	2	NR
2	I_2 (2.0)	CH_2Cl_2	r.t.	2	NR
3	CAN (2.5)	MeCN	r.t.	2	NR
4[d]	$K_3Fe(CN)_6$ (2.0)	MeOH	r.t.	0.5	89
5	$KMnO_4$ (1.5)	Acetone	r.t.	0.5	–[e]
6	$Cu(OAc)_2{\cdot}H_2O$ (2.0)	AcOH	100	1	30
7	$Mn(OAc)_3{\cdot}3H_2O$ (1.5)	AcOH	100	1	20
8	$NaNO_2$ (3.0)	AcOH	r.t.	2	NR
9	PbO_2 (2.0)	AcOH	r.t.	1	–[e]
10	Ag_2O (2.0)	CH_2Cl_2	r.t.	3	94
11	MnO_2 (2.0)	CH_2Cl_2	r.t.	4	89
12	MnO_2 (3.0)	CH_2Cl_2	r.t.	2.5	92
12	MnO_2 (4.0)	CH_2Cl_2	r.t.	1	97
13	MnO_2 (5.0)	CH_2Cl_2	r.t.	1	93

[a] Reaction conditions: **1a** (2.0 mmol), oxidant, solvent (30 mL).
[b] Isolated yield after silica gel chromatography. [c] NR: no reaction occurred.
[d] 10% aq NaOH (7 equiv) was added as additive. [e] Complex mixture, no desired product detected.

R^2 or R^3 were bulkier benzyl, phenyl, or long-chained alkyl groups (entries 3, 7, 8, 11 and 14 in Table 2), the reaction also furnished the desired product in good yields (84–92%), at the expense of requiring relatively longer reaction times (2–3 h).

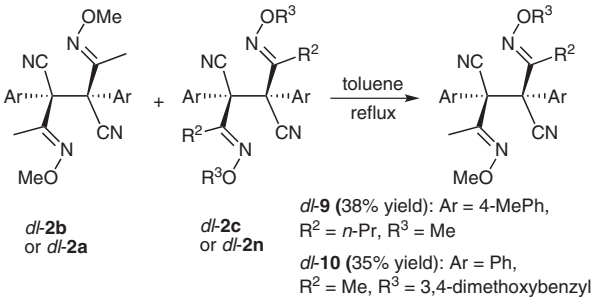
The products were stable solids whose structures were determined by detailed studies of the spectroscopic data. In all cases, only one single isomer was observed and the number of signals in the ^1H and ^{13}C NMR spectra clearly established the symmetry of the molecules. The C_2-symmetry was further established by the X-ray crystal structure of the coupling product *dl*-**2n** (Figure 1).[13] The C=N double bonds in the dimerized products were assigned the *trans*-configuration, regardless of the stereochemistry (*trans* or *cis*) of the substrates employed (for the ratios of the *trans* and *cis* isomers, see Table 2).

When a similar substrate **3**, structurally differing from substrate **1** by the naphthalene ring, was treated with MnO_2 under the same reaction conditions, an intramolecular cyclized product **5** was also obtained in a yield of 35%, in addition to the expected coupling dimer *dl*-**4**. However, if either Ag_2O or $K_3Fe(CN)_6$ was applied as the oxidant, only the dimerized *dl*-**4** was obtained in yields of 92% and 86%, respectively, with no formation of the cyclized **5** in either case (Scheme 3).



Scheme 3

We finally turned our attention to a possible explanation for the stereoselectivity of this radical dimerization process. Firstly, we wanted to know whether *dl*-**2** could be converted into a thermodynamic mixture of both *dl*- and *meso*-isomers. The previous report showed that similar dimerized products of some benzylcyanides α-substituted with an ester, could display thermal equilibration of the *dl*- and *meso*-diastereoisomers via a radical dissociation–recombination process.[3,14] Surprisingly, it was found that no new product was generated when each dimerized *dl*-**2** was heated at reflux temperature in toluene over two hours. However, heating a mixture of equimolar equivalents of *dl*-**2b** and *dl*-**2c** in toluene at reflux temperature over 30 min did afford the cross-dimerized *dl*-**9** as the only heterocoupling product in 38% yield, in addition to the recovered *dl*-**2b** (60%) and *dl*-**2c** (59%). Similarly, the single cross-heterodimer *dl*-**10** was obtained in 35% yield from *dl*-**2a** and *dl*-**2n** under identical conditions, with 61% of *dl*-**2a** and 63% of *dl*-**2n** recovered (Scheme 4).



Scheme 4

Unfortunately, all attempts to separate the other expected cross-dimers, for example, the heterocoupling dimers from *dl*-**2a** and *dl*-**2b**, *dl*-**2e** and *dl*-**2k**, *dl*-**2h** and *dl*-**2k**, or *dl*-**2h** and *dl*-**2j** as pure products failed, since the three dimers, i.e., the two starting homodimers and the expected heterodimer, always coexisted as a mixture in each case.

Secondly, treating the unsubstituted α-phenyl ketonitrile **11** with MnO_2 under the described conditions led to a mixture of *dl*- and *meso*-**12** in a ratio of 1.2:1, determined by ^1H NMR analysis (Scheme 5). This result is in general agreement with previous observations reported in the literature on the dimerization of substrate **11** with PbO_2.[3]

Table 2 Oxidative Dimerization of 3-Alkoxyimino-2-aryl-alkylnitriles Mediated by MnO_2[a]

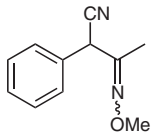
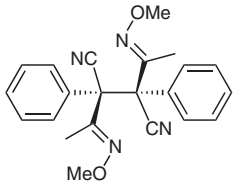
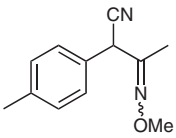
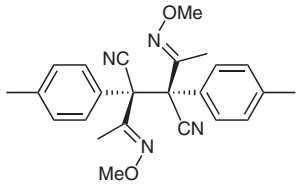
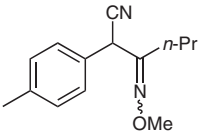
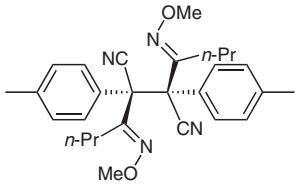
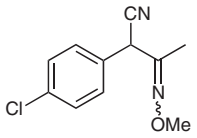
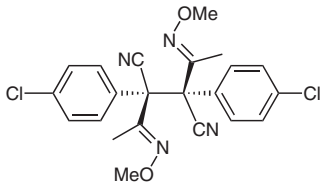
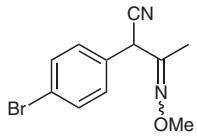
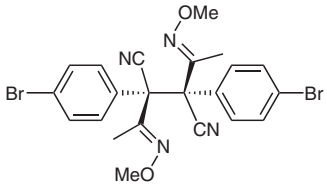
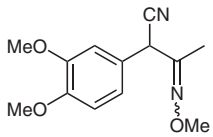
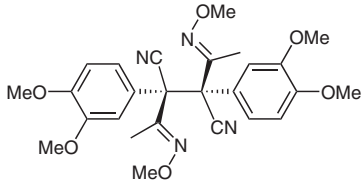
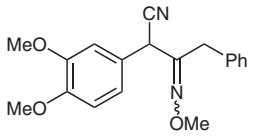
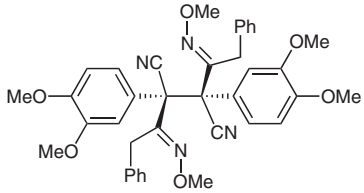
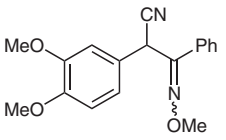
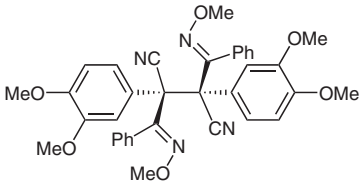
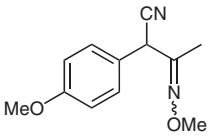
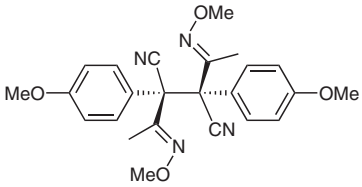
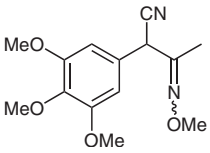
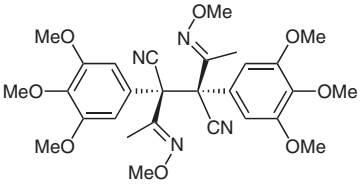
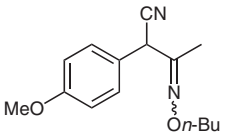
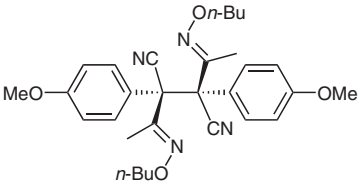
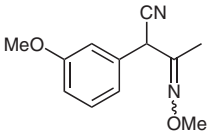
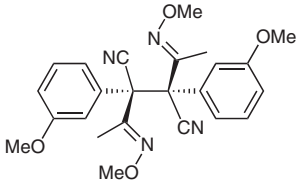
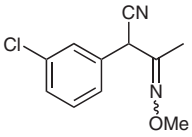
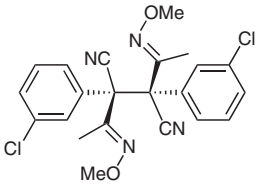
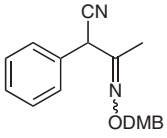
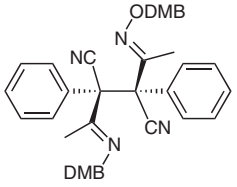
Entry	Substrate (*trans*/*cis*)	Dimer	Yield (%)[b]	Time (h)
1	 (4.7:1) **1a**	 *dl*-**2a**	97	1
2	 (3.9:1) **1b**	 *dl*-**2b**	93	1
3	 (1.1:1) **1c**	 *dl*-**2c**	92	1
4	 (25:1) **1d**	 *dl*-**2d**	96	0.5
5	 (4.8:1) **1e**	 *dl*-**2e**	93	0.5
6	 (5.2:1) **1f**	 *dl*-**2f**	94	1.5
7	 (6.3:1) **1g**	 *dl*-**2g**	92	2

Table 2 Oxidative Dimerization of 3-Alkoxyimino-2-aryl-alkylnitriles Mediated by MnO_2[a] (continued)

Entry	Substrate (*trans*/*cis*)	Dimer	Yield (%)[b]	Time (h)
8	 (7.2:1) **1h**	 *dl*-**2h**	84	3
9	 (5:1) **1i**	 *dl*-**2i**	96	1.5
10	 (5.5:1) **1j**	 *dl*-**2j**	87	1.5
11	 (4.1:1) **1k**	 *dl*-**2k**	91	2
12	 (5.6:1) **1l**	 *dl*-**2l**	90	2
13	 (19:1) **1m**	 *dl*-**2m**	94	0.5
14	 (4:1) **1n**	 *dl*-**2n**[c]	91	2

[a] Reaction conditions: MnO_2 (4.0 equiv), r.t., CH_2Cl_2.
[b] Isolated yield after silica gel chromatography.
[c] DMB refers to 3,4-dimethoxybenzyl group.

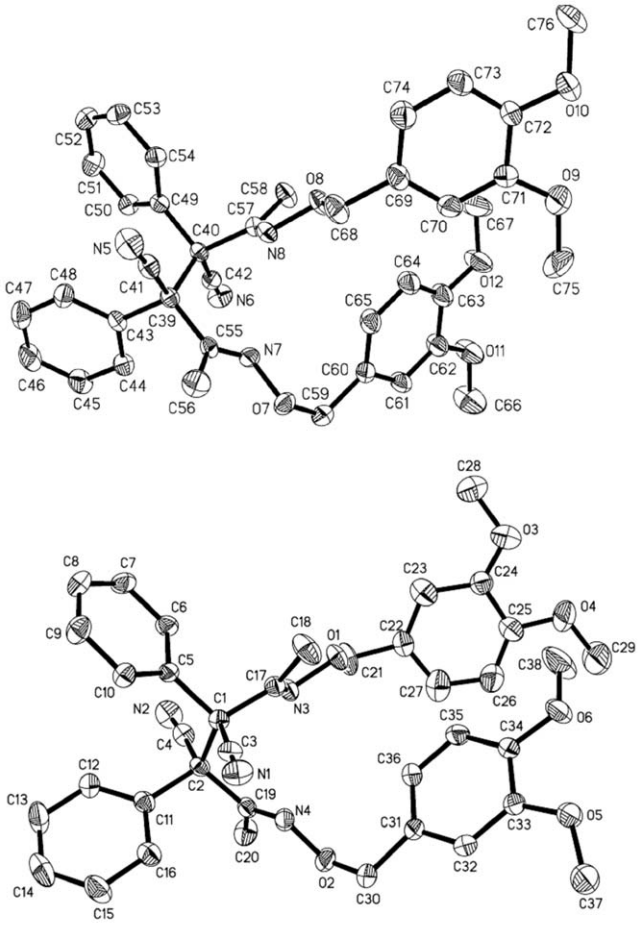
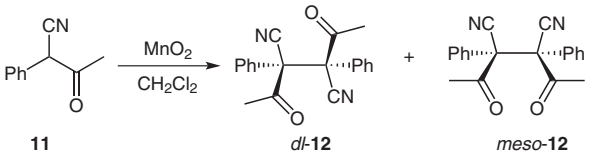


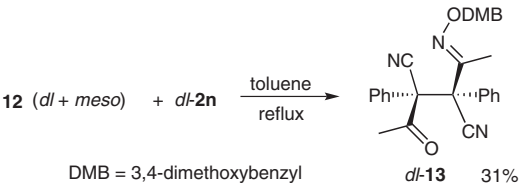
Figure 1 X-ray crystal structure of *dl*-**2n**



85% (*dl*/*meso* = 1.2:1, determined by ^{1}H NMR)

Scheme 5

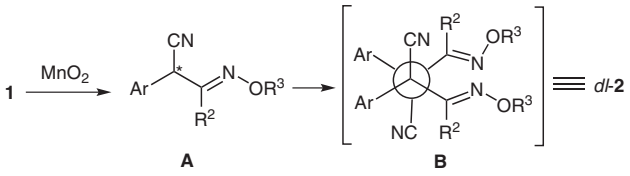
Furthermore, a mixture of equimolar amounts of **12** (*dl* + *meso*) and *dl*-**2n**, upon being refluxed in toluene for 30 min, afforded the cross-dimerized product *dl*-**13** as a sole heterodimer in 25% yield, together with 68% of **12** (*dl* + *meso*) and 72% of recovered *dl*-**2n** (Scheme 6).



Scheme 6

These experimental observations prompted us to conclude that the alkoxyimino substituent in substrate **1** should play an important role in the stereoselective formation of single *dl*-dimers and that the stereospecific dimerization should follow a thermodynamically controlled, rather than an oxidant-mediated dynamically controlled pathway.

Alternatively, we tentatively propose that the presence of the alkoxyimino substituent in substrate **1** might be partially responsible for the stereochemistry of this radical coupling reaction. Moreover, the weak π–π stacking interaction (concluded from the X-ray data) between the two aryl groups could direct the predominant *Re*-face (or *Si*-face) approach of the radical intermediate **A**. The formation of the most preferable transition-state **B** should then be responsible for this highly substrate-controlled diastereoselective dimerization process (Scheme 7).



Scheme 7

In conclusion, a class of highly α-substituted benzylcyanides that could undergo oxidative dimerization to generate the 2,3-diarylsuccinonitriles with complete diastereoselectivity under mild and efficient conditions has been discovered.[15–21] Further studies on the application of the obtained *dl*-dimers in organic synthesis are currently under investigation in our lab.

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

Acknowledgment

We acknowledge the National Natural Science Foundation of China (#20802048) and Cultivation Foundation (B) for New Faculty of Tianjin University (#5110109) for financial support. We also thank Miss Xiling Zhao, University of California, San Diego, for revising our English text.

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(12) (a) CaH_2-dried EtOAc, THF and MeCN were also tested as solvents, but were not superior to CH_2Cl_2. (b) An excess of MnO_2 (4 equiv) was used for a complete conversion of **1a** into dimerized *dl*-**2a** within a shorter period of time (1 h) although two equivalents of MnO_2 was enough for the total consumption of **1a**.
(13) Compound *dl*-**2n**: Crystallized in the monoclinic space group P2 (1) with cell dimensions: a = 8.0723 (11) Å, b = 26.531 (4) Å, c = 16.356 (2) Å, α = 90°, β = 92.325 (2)°, γ = 90°, V = 3499.9 (8) Å^3, Dc = 1.227 g/cm^3, Z = 2. CCDC: 712678.
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(15) **General Procedure for the Synthesis of the Homocoupling Dimers *dl*-2:** To a solution of 3-alkoxyimino-2-aryl-alkylnitriles **1** (4 mmol) in CH_2Cl_2 (30 mL) was added, in one portion, the dried MnO_2 (16 mmol) powder with stirring at room temperature. TLC was used to monitor the reaction process until the total consumption of **1** was observed. The insoluble materials were removed via filtration and the filtrate was evaporated in vacuum to remove the solvent. The residue was then purified by flash silica gel chromatography, using a mixture of petroleum ether (PE) and EtOAc as eluent, to afford the desired homodimers **2**. The synthesis of **12** (*dl* + *meso*) from **11** was conducted under similar reaction conditions.
(16) **Procedures for the Synthesis of *dl*-4 and 5:** Case 1: When either MnO_2 or Ag_2O was used as the oxidant, the reactions were conducted following the procedure described for the synthesis of dimers *dl*-**2**. Case 2: When $K_3Fe(CN)_6$ was used as the oxidant: A mixture of **3** (5 mmol), $K_3Fe(CN)_6$ (20 mmol), and aq 10% NaOH (35 mmol) in MeOH (20 mL) was stirred at r.t. for 0.5 h. The reaction mixture was then extracted with EtOAc (3 × 20 mL) and the combined organic layer, after drying over anhydrous Na_2SO_4, was evaporated to remove the solvent. The residue was purified by silica gel column to give the homodimerized *dl*-**4** in 86% yield, with no separation of **5**.
(17) **General Procedure for the Synthesis of Heterodimerized *dl*-Dimers:** A mixture of *dl*-**2b** (0.30 mmol) and *dl*-**2c** (0.30 mmol) in toluene (20 mL) was stirred at reflux for 30 min. After cooling to room temperature, the mixture was evaporated to remove the solvent. The residue was passed through silica gel column using a mixture of PE and EtOAc as eluent, to give the heterodimerized *dl*-**9**. Unreacted *dl*-**2b** and *dl*-**2c** were also recovered.
(18) Substrates **1a**, **1c**, **1d**, **1f** and **1m** were synthesized and characterized in our previous work (see reference 11). The others substrates were characterized as follows: (**1b**) White solid; mp 55–57 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ(*trans*) = 7.29–7.18 (m, 4 H), 4.70 (s, 1 H), 3.93 (s, 3 H), 2.36 (s, 3 H), 1.77 (s, 3 H); δ(*cis*) = 7.29–7.18 (m, 4 H), 5.78 (s, 1 H), 3.93 (s, 3 H), 2.36 (s, 3 H), 1.91 (s, 3 H); HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{12}H_{15}N_2O$: 203.1179; found: 203.1180. (**1e**) White solid; mp 74–75 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ(*trans*) = 7.55–7.52 (m, 2 H), 7.30–7.26 (m, 2 H), 4.70 (s, 1 H), 3.93 (s, 3 H), 1.78 (s, 3 H); δ(*cis*) = 7.55–7.52 (m, 2 H), 7.30–7.26 (m, 2 H), 5.77 (s, 1 H), 3.94 (s, 3 H), 1.92 (s, 3 H); HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{11}H_{12}BrN_2O$: 267.0128; found: 267.0112. (**1g**) White solid; mp 86–87 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ(*trans*) = 7.25–6.54 (m, 8 H), 4.51 (s, 1 H), 4.04 (s, 3 H), 4.00 (d, J = 14.5 Hz, 1 H), 3.87 (s, 3 H), 3.82 (s, 3 H), 3.19 (d, J = 15 Hz, 1 H); δ(*cis*) = 7.25–6.54 (m, 8 H), 5.54 (s, 1 H), 4.01 (s, 3 H), 3.85 (s, 3 H), 3.71 (s, 3 H), 3.58 (d, J = 6 Hz, 2 H); HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{19}H_{21}N_2O_3$: 325.1547; found: 325.1555. (**1h**) White solid; mp 101–102 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ(*trans*) = 7.52–6.76 (m, 8 H), 6.10 (s, 1 H), 4.11 (s, 3 H), 3.87 (s, 3 H), 3.84 (s, 3 H); δ(*cis*) = 7.52–6.76 (m, 8 H), 4.98 (s, 1 H), 3.95 (s, 3 H), 3.87 (s, 3 H), 3.80 (s, 3 H); HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{18}H_{19}N_2O_3$: 311.1390; found: 311.1397. (**1i**) White solid: mp 80–81 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ(*trans*) = 7.32–7.28 (m, 2 H), 6.93–6.90 (m, 2 H), 4.68 (s, 1 H), 3.93 (s, 3 H), 3.81 (s, 3 H), 1.77 (s, 3 H); δ(*cis*) = 7.32–7.28 (m, 2 H), 6.93–6.90 (m, 2 H), 5.75 (s, 1 H), 3.94 (s, 3 H), 3.81 (s, 3 H), 1.92 (s, 3 H). HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{12}H_{15}N_2O_2$: 219.1128; found: 219.1135. (**1j**) White solid; mp 89–90 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ(*trans*) = 6.59 (s, 2 H), 4.67 (s, 1 H), 3.96 (s, 3 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 1.82 (s, 3 H); δ(*cis*) = 6.59 (s, 2 H), 5.77 (s, 1 H), 3.97 (s, 3 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 1.94 (s, 3 H); HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{14}H_{19}N_2O_4$: 279.1339; found: 279.1345. (**1k**) Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ(*trans*) = 7.31–7.29 (d, 2 H), 6.93–6.89 (m, 2 H), 4.68 (s, 1 H), 4.13 (t, J = 8.0 Hz, 2 H), 3.80 (s, 3 H), 1.78 (s, 3 H), 1.70–1.63 (m, 2 H), 1.44–1.26 (m 2 H), 0.95 (t, J = 9.0, 3 H); δ(*cis*) = 7.31–7.29 (d, 2 H), 6.93–6.89 (m, 2 H), 5.77 (s, 1 H), 4.13 (t, J = 8.0 Hz, 2 H), 3.80 (s, 3 H), 1.91 (s, 3 H), 1.70–1.63 (m, 2 H), 1.44–1.26 (m, 2 H), 0.95 (t, J = 9.0 Hz, 3 H); HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{15}H_{21}N_2O_2$: 261.1598; found: 261.1610. (**1n**) White solid: mp 54–56 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ(*trans*) = 7.38–7.34 (m, 5 H), 6.95–6.85 (m, 3 H), 5.11 (s, 2 H), 4.73 (s, 1 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 1.81 (s, 3 H); δ(*cis*) = 7.38–7.34 (m 5 H), 6.95–6.85 (m, 3 H), 5.83 (s, 1 H), 5.10 (s, 2 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 1.93 (s, 3 H); HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{19}H_{21}N_2O_3$: 325.1547; found: 325.1553.
(19) (*dl*-**2a**) White solid; mp 185–186 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.33 (m, 1 H), 7.23 (d, J = 7.5 Hz, 2 H), 7.13 (d, J = 7.5 Hz, 2 H), 4.06 (s, 3 H), 1.91 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.1, 131.8, 129.8, 129.7, 128.3, 118.0, 62.8, 59.8, 14.1; HRMS (ESI): *m*/*z* [M + Na$^+$] calcd for $C_{22}H_{22}N_4NaO_2$: 397.1635; found: 397.1639. (*dl*-**2b**) White solid; mp 144–146 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.06–7.00 (m, 4 H), 4.04 (s, 3 H), 2.33 (s, 3 H), 1.90 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.4, 139.7, 129.8, 129.0, 128.8, 118.2, 62.7, 59.6, 21.3, 14.1; HRMS

(ESI): *m/z* [M + Na^+] calcd for $C_{24}H_{26}N_4NaO_2$: 425.1948; found: 425.1953. (*dl*-**2c**) White solid; mp 176–177 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.05–7.01 (t, 4 H), 4.04 (s, 3 H), 2.54–2.48 (m, 1 H), 2.34 (s, 3 H), 1.83–1.74 (m, 2 H), 1.69–1.61 (m, 1 H), 0.88 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.4, 139.6, 130.0, 129.1, 128.9, 118.1, 62.6, 59.0, 31.9, 21.3, 19.6, 14.8; HRMS (ESI): *m/z* [M + Na^+] calcd for $C_{28}H_{34}N_4NaO_2$: 481.2574; found: 481.2577. (*dl*-**2d**) White solid; mp 143–144 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 11.5 Hz, 2 H), 7.09 (d, *J* = 11.5 Hz, 2 H), 4.05 (s, 3 H), 1.90 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.8, 136.4, 131.2, 130.1, 128.7, 117.5, 62.9, 59.2, 14.1; HRMS (ESI): *m/z* [M + Na^+] calcd for $C_{22}H_{20}Cl_2N_4NaO_2$: 465.0856; found: 465.0861. (*dl*-**2e**) White solid; mp 160–161 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8.5 Hz, 2 H), 7.03 (d, *J* = 8.5Hz, 2 H), 4.05 (s, 3 H), 1.90 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.7, 131.7, 131.4, 130.6, 124.7, 117.4, 62.9, 59.3, 14.1; HRMS (ESI): *m/z* [M + Na^+] calcd for $C_{22}H_{20}Br_2N_4NaO_2$: 552.9845; found: 552.9850. (*dl*-**2f**) White solid; mp 186–187 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 6.77 (s, 2 H), 6.61 (s, 1 H), 4.05 (s, 3 H), 3.88 (s, 3 H), 3.67 (s, 3 H), 1.94 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.2, 149.7, 148.1, 123.8, 122.3, 118.0, 112.8, 110.2, 62.5, 59.5, 55.9, 55.7, 13.9; HRMS (ESI): *m/z* [M + Na^+] calcd for $C_{26}H_{30}N_4NaO_6$: 517.2058; found: 517.2065. (*dl*-**2g**) White solid; mp 189–190 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 7.5 Hz, 2 H), 7.19–7.11 (m, 3 H), 6.70–6.60 (m, 3 H), 3.94 (s, 3 H), 3.93 (d, *J* = 14.0 Hz, 1 H), 3.85 (s, 3 H), 3.62 (s, 3 H), 3.47 (d, *J* = 14.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.6, 149.9, 148.1, 135.7, 129.6, 128.2, 126.5, 124.0, 122.8, 118.1, 113.2, 110.3, 62.7, 59.7, 56.1, 55.9, 35.2; HRMS (ESI): *m/z* [M + Na^+] calcd for $C_{38}H_{38}N_4NaO_6$: 669.2684; found: 669.2689. (*dl*-**2h**) White solid; mp 198–199 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.29 (m, 3 H), 6.84–6.82 (m, 5 H), 4.14 (s, 3 H), 3.90 (s, 3 H), 3.69 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.0, 150.2, 148.2, 131.9, 129.8, 128.4, 128.3, 123.5, 118.0, 113.7, 110.5, 63.4, 61.4, 56.2, 55.9; HRMS (ESI): *m/z* [M + Na^+] calcd for $C_{36}H_{34}N_4NaO_6$: 641.2371; found: 641.2377. (*dl*-**2i**) White solid; mp 146–147 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.05 (d, *J* = 8.5 Hz, 2 H), 6.78 (d, *J* = 9.0 Hz, 2 H), 4.04 (s, 3 H), 3.80 (s, 3 H), 1.91 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.5, 150.4, 131.2, 123.5, 118.3, 113.6, 62.7, 59.5, 55.5, 14.1; HRMS (ESI): *m/z* [M + Na^+] calcd for $C_{24}H_{26}N_4NaO_4$: 457.1852; found: 457.1854. (*dl*-**2j**) White solid; mp 180–182 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 6.42 (s, 1 H), 4.05 (s, 3 H), 3.84 (s, 3 H), 3.71 (s, 6 H), 1.97 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.7, 150.2, 138.9, 127.1, 118.1, 107.1, 62.8, 61.1, 60.1, 56.3, 14.2; HRMS (ESI): *m/z* [M + Na^+] calcd for $C_{28}H_{34}N_4NaO_8$: 577.2269; found: 577.2273. (*dl*-**2k**) White solid; mp 67–70 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.04 (d, *J* = 8.0 Hz, 2 H), 6.77 (d, *J* = 9.0 Hz, 2 H), 4.27–4.19 (m, 2 H), 3.79 (s, 3 H), 1.91 (s, 3 H), 1.76 (quin, *J* = 7.0 Hz, 2 H), 1.45 (sext, *J* = 7.5 Hz, 2 H), 1.00 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.5, 149.9, 131.2, 123.8, 118.4, 113.6, 74.6, 59.6, 55.5, 31.8, 19.2, 14.2, 14.1; HRMS (ESI): *m/z* [M + Na^+] calcd for $C_{30}H_{38}N_4NaO_4$: 541.2785; found: 541.2792. (*dl*-**2l**) White solid; mp 101–102 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 9.18 (t, *J* = 8.0 Hz, 1 H), 6.89 (dd, *J* = 8.0, 2.5 Hz, 1 H), 6.80 (d, *J* = 7.5 Hz, 1 H), 6.65 (s, 1 H), 4.05 (s, 3 H), 3.64 (s, 3 H), 1.93 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.3, 150.1, 133.3, 129.3, 121.9, 118.0, 115.9, 115.1, 62.8, 59.7, 55.4, 14.1; HRMS (ESI): *m/z* [M + Na^+] calcd for $C_{24}H_{26}N_4NaO_4$: 457.1846; found: 457.1852. (*dl*-**2l**) White solid; mp 142–143 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.30 (t, 1 H), 7.19–7.16 (t, 2 H), 7.05–6.99 (m, 4 H), 6.88 (d, *J* = 8.0 Hz, 1 H), 5.79 (d, *J* = 12 Hz), 5.10 (d, *J* = 12.5 Hz), 3.93 (s, 3 H), 3.89 (s, 3 H), 1.85 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.8, 148.9, 131.3, 130.5, 129.6, 129.5, 128.0, 121.4, 117.9, 112.0, 111.0, 59.8, 56.0, 55.9, 14.3; HRMS (ESI): *m/z* [M + Na^+] calcd for $C_{38}H_{38}N_4NaO_6$: 669.2684; found: 669.2689. (*dl*-**2m**) White solid; mp 163–164 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 7.5 Hz, 1 H), 7.27 (d, *J* = 8.0 Hz, 1 H), 7.11 (d, *J* = 4.5 Hz, 1 H), 4.06 (s, 3 H), 1.93 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.4, 134.7, 133.6, 130.3, 130.0, 129.7, 127.7, 117.2, 62.9, 59.4, 14.2; HRMS (ESI): *m/z* [M + Na^+] calcd for $C_{22}H_{20}Cl_2N_4NaO_2$: 465.0856; found: 465.0862. (*dl*-**2n**) White solid; mp 142–143 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.30 (t, 1 H), 7.19–7.16 (t, 2 H), 7.05–6.99 (m, 4 H), 6.88 (d, *J* = 8.0 Hz, 1 H), 5.79 (d, *J* = 12 Hz), 5.10 (d, *J* = 12.5 Hz, 1 H), 3.93 (s, 3 H), 3.89 (s, 3 H), 1.85 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.8, 148.9, 131.3, 130.5, 129.6, 129.5, 128.0, 121.4, 117.9, 112.0, 111.0, 76.7, 59.8, 56.0, 55.9, 14.3; HRMS (ESI): *m/z* [M + Na^+] calcd for $C_{38}H_{38}N_4NaO_6$: 669.2684; found: 669.2689.

(20) (*dl*-**4**) White solid; mp 202–204 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.0 Hz, 1 H), 7.65 (d, *J* = 8.5 Hz, 1 H), 7.59–7.50 (m, 3 H), 7.44–7.41 (m, 1 H), 7.20–7.18 (t, 1 H), 4.14 (s, 3 H), 1.98 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.3, 133.5, 132.5, 130.3, 129.1, 128.9, 128.0, 127.6, 127.6, 126.8, 126.3, 118.1, 62.9, 60.0, 14.3; HRMS (ESI): *m/z* [M + Na^+] calcd for $C_{30}H_{26}N_4NaO_2$: 497.1948; found: 497.1949.(**5**) White solid; mp 100–101 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 8.5 Hz, 1 H), 7.95 (d, *J* = 8.0 Hz, 1 H), 7.70–7.61 (m, 3 H), 7.54–7.50 (m, 1 H), 4.14 (s, 3 H), 2.70 (s, 3 H). This compound was well characterized in our previous report (see reference 11).

(21) (*dl*-**9**) White solid; mp 166–168 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.06–6.99 (m, 8 H), 4.05 (s, 3 H), 4.03 (s, 3 H), 2.54–2.46 (m, 1 H), 2.34 (s, 6 H), 1.90 (s, 3 H), 1.84–1.78 (m, 1 H), 1.76–1.62 (m, 2 H), 0.88 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.4, 150.4, 139.7, 139.6, 130.0, 129.9, 129.8, 129.0, 128.9, 128.9, 128.8, 118.3, 118.0, 62.7, 62.6, 59.5, 59.1, 31.9, 21.3, 19.6, 19.5, 14.8, 14.1; HRMS (ESI): *m/z* [M + Na^+] calcd for $C_{26}H_{30}N_4NaO_2$: 453.2261; found: 453.2268. (*dl*-**10**) White solid; mp 126–129 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.31 (m, 2 H), 7.24–7.17 (m, 4 H), 7.07–7.03 (m, 5 H), 6.90 (d, *J* = 8.0 Hz, 1 H), 5.21 (q, 2 H), 3.93–3.92 (t, 9 H, 3 × OMe), 1.95 (s, 3 H), 1.78 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.1, 149.7, 149.1, 131.9, 131.5, 131.0, 129.8, 129.7, 129.6, 128.3, 128.2, 121.7, 118.1, 118.0, 112.4, 111.3, 77.0, 62.6, 59.9, 59.8, 56.2, 56.2, 14.6, 13.0; HRMS (ESI): *m/z* [M + Na^+] calcd for $C_{30}H_{30}N_4NaO_4$: 533.2159; found: 533.2165.(**12**) White solid; mp 161–162 °C; ^1H NMR (500 MHz, $CDCl_3$): δ(*dl*) = 7.46–7.33 (m, 3 H), 7.03–7.01 (q, 2 H), 2.47 (s, 3 H); δ(*meso*) = 7.46–7.33 (m, 5 H), 2.31 (s, 3 H). For previous characterization of this compound, see reference 3. (*dl*-**13**) White solid; mp 139–141 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.23 (m, 7 H), 7.10 (d, *J* = 7.5 Hz, 2 H), 6.70–6.96 (t, 4 H), 6.91 (d, *J* = 7.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.3, 151.4, 149.3, 149.2, 130.9, 130.3, 130.1, 129.9, 129.5, 129.4, 128.9, 128.5, 128.2, 120.9, 118.1, 117.3, 111.5, 111.2, 77.0, 64.4, 60.0, 56.2, 56.2, 28.4 (CH_3), 14.5 (CH_3); HRMS (ESI): *m/z* [M + Na^+] calcd for $C_{29}H_{27}N_3NaO_4$: 504.1894; found: 504.1899.