Asymmetric N-Heterocyclic Carbene Catalyzed Annulation of 2-Alkenylbenzothiazoles with α-Chloro Aldehydes

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Dedicated to Professor Martin Jansen on the occasion of his 70th birthday

Abstract  Diastereo- and enantioselective N-heterocyclic carbene catalyzed 1-azadiene Diels–Alder reactions of (E)-2-styrylbenzothiazoles with α-chloro aldehydes are reported. This annulation strategy provides an efficient access to medicinally important dihydrobenzothiazolopyridin-1-ones in good to excellent yields (44–97%) with very good to excellent stereoselectivities (up to 9:1 dr, 98% ee) and tolerates quite a range of substituents.

Key words  N-heterocyclic carbenes, organocatalysis, asymmetric synthesis, aza-Diels–Alder reaction, annulation

The aza-Diels–Alder (aza-DA) reaction is one of the most powerful and elegant synthetic approaches to form C–C and C–N bonds, resulting in nitrogen-containing six-membered heterocycles.1 Since Ghosez’s pioneering work introducing the reaction of 1-azadienes with electron-deficient dienophiles,2 followed by Danishefsky’s report on the formation of piperidine rings from imines and electron-rich dienes,3 a great variety of aza-DA reactions under thermal conditions or catalyzed by Lewis acids4 have been reported. With the renaissance of organocatalysis, enantioselective aza-DA reactions catalyzed by amines;5 thioureas,6 or chiral phosphoric acids,7 were intensively investigated.

Over the past few decades, N-heterocyclic carbenes (NHCs), as an outstanding class of organocatalysts, have provided efficient access to various structural scaffolds through the Umpolung of aldehydes.8 In 2004, the groups of Glorius and Bode reported the generation of homoenoates via NHC catalysis.9 This provided an elegant way to activate the β-position of enals (conjugated Umpolung). Later, as an extended activation mode, azolium enolates were developed and acted as reactive nucleophiles in various NHC-catalyzed reactions.10 Notably, the in situ generated azolium enolates paved the way to numerous important heterocyclic manifolds via [2+2]11 and [2+3] cycloadditions,12 as well as [2+4] inverse-electron-demand Diels–Alder reactions.13 In 2006, Bode and co-workers were the first to report a highly enantioselective aza-DA reaction of 1-azadienes with the enolate species generated in situ from enals.14 Afterwards, Ye and co-workers employed ketenes15 and α-chloro aldehydes16 as substrates, which reacted with 1-azadienes in the presence of NHC catalysts. Then, Rovis and co-workers accessed the azolium enolate equivalents via oxidation of the Breslow intermediates, and constructed the corresponding lactams with azadienes.17 Recently, Chi and co-workers have reported an NHC-catalyzed reaction of α-aryl esters with azadienes.18 However, these reported studies all utilized acyclic 1-azadienes as reaction partners (Scheme 1, eq 1). To the best of our knowledge, little attention has been given to aza-DA reactions of cyclic 1-azadienes with in situ generated azolium enolate species.

Scheme 1  NHC-catalyzed aza-Diels–Alder reactions
Herein, we describe an enantioselective NHC-catalyzed cycloaddition of (E)-2-styrylbenzothiazoles with α-chloro aldehydes (Scheme 1, eq 2). The resulting dihydro-1H-benzothiazolopyridine core is an important structural motif existing in various biologically active products and numerous pharmaceuticals, such as antitumor and antibacterial drugs.

Initially, we investigated the reaction of (E)-2-(benzothiazol-2-yl)-3-phenylacrylonitrile (1a) with 2-chloro-3-phenylpropanal (2a) at room temperature in toluene in the presence of triethylamine and triazolium precatalyst A. The reaction was finished within 16 hours and gave theaza-DA adduct 3a in a good cis/trans diastereoselectivity (dr = 6:1) and an excellent ee value (95%) of the major cis-diastereomer, albeit in a low yield (29%) (Table 1, entry 1). Other triazolium precatalysts B–D were also tested, but only traces (Table 1, entries 2 and 3) or even no product at all (Table 1, entry 4) was obtained under the same conditions. In an attempt to increase the yield of the desired 3a, we elevated the reaction temperature to 40 °C, leading to no improvement (Table 1, entry 5). Next, base screening showed that organic bases (such as TMEDA, DIPEA, or DABCO) gave better or similar yields as well as excellent stereoselectivities (Table 1, entries 6–8); however, inorganic bases (such as NaOAc or K$_2$CO$_3$) furnished only traces or no product at all (Table 1, entries 6–8). Notably, this protocol could also be extended to (E)-2-(benzoxazol-2-yl)-3-phenylacrylonitrile (1j), which produced product 3j in 97% yield, 4:1 dr, and 95% ee. With regard to the α-chloro aldehydes 2, aliphatic linear aldehydes are also tolerated, leading to the corresponding products 3k and 3l in moderate yields. The relative configuration of the major diastereomer of 3 was assigned by NOE measurements on 3d (see Supporting Information). It was clear that H$^a$ and H$^b$ are in a cis-relationship, which is in accordance with the absolute configuration of compound 3d determined by X-ray crystal structure analysis (Figure 1).

A possible mechanism explaining the cis configuration of the major diastereomer is shown in Scheme 2. Initially, nucleophilic addition of the free carbene A$^*$ to the α-chloro aldehyde 2 affords the adduct I, followed by the removal of hydrogen chloride to form the enolate species II. Since the Re face of the azolium enolate is blocked by the indane backbone of the NHC, the enolate undergoes an aza-DA reaction on the Si face with the (E)-2-styrylbenzothiazole 1, via the favored endo transition state endo-TS. Subsequent α-elimination leads to the final product 3 and liberates the NHC catalyst for further cycles. In a more asynchronous manner, the annulation can be seen as a Michael–lactamization sequence. The rather low ee values of the minor trans-diastereomer may be explained by the presence of an E/Z-azolium enolate mixture (see Supporting Information).

In summary, we have developed an efficient NHC-catalyzed asymmetric reverse-electron-demand 1-azadiene Diels–Alder reaction of (E)-2-styrylbenzothiazoles with α-chloro aldehydes, resulting in the desired cis-dihydrobenzothiazolopyridin-1-ones in good to excellent yields, good diastereomeric ratios and excellent ee values. This annulation protocol tolerates quite a range of substrates, leading to medicinally interesting tricyclic dihydrobenzothiazolopyridines bearing a synthetically useful cyano group at the 4-position.
Synthesis

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All reactions were carried out under argon. THF and toluene were distilled over Solvona®. CH2Cl2 was distilled over CaH2. All other chemicals were used without further purification. Triazolium salts, chiral triazolium-derived carbene catalysts A–D and the achiral triazolium-derived carbene catalyst 2-phenyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (which was used to synthesize the racemic products) were prepared according to known literature procedures.23 (E)-2-(Benzoazol-2-yl)-3-phenylacrylonitriles were prepared from benzothiazol-2-ylacetonitriles.24 α-Chloro aldehydes were prepared from aldehydes.25 Chromatographic purification of the products was performed on Merck silica gel 60, particle size 0.040–0.063 mm (230–240 mesh, flash). Analytical TLC was performed on Sil G–25 UV254 plates (MACHEREY-NAGEL). The developed TLC plates were visualized with ultraviolet irradiation (254 nm). Optical rotation values were measured on a Perkin-Elmer 241 polarimeter. Microanalyses were performed with a Vario EL elemental analyzer. Mass spectra and high-resolution mass spectra were acquired on a Finnigan MAT 95 (EI/CI) or on a Thermo Fisher Scientific LTQ Orbitrap XL (ESI) mass spectrometer. IR spectra were recorded on a Perkin-Elmer FT-IR Spectrum 100 spectrometer using a Diamant/KRS5 ATR attachment. Evaluation was undertaken using the supplementary software. The absorption bands are given in wavenumbers.

### Table 1 Optimization of the Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Precatalyst</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>dr (cis/trans)</th>
<th>ee (%) (cis)</th>
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<td>1</td>
<td>A</td>
<td>Et3N</td>
<td>toluene</td>
<td>29</td>
<td>6:1</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>Et3N</td>
<td>toluene</td>
<td>trace</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>C</td>
<td>Et3N</td>
<td>toluene</td>
<td>trace</td>
<td>–</td>
<td>–</td>
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<tr>
<td>4</td>
<td>D</td>
<td>Et3N</td>
<td>toluene</td>
<td>n.r.</td>
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<td>–</td>
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<tr>
<td>5a</td>
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<td>Et3N</td>
<td>toluene</td>
<td>29</td>
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<td>93</td>
</tr>
<tr>
<td>6</td>
<td>A</td>
<td>TMEDA</td>
<td>toluene</td>
<td>40</td>
<td>5:1</td>
<td>95</td>
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<tr>
<td>7</td>
<td>A</td>
<td>DIPEA</td>
<td>toluene</td>
<td>37</td>
<td>7:1</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>A</td>
<td>DABCO</td>
<td>toluene</td>
<td>30</td>
<td>3:1</td>
<td>94</td>
</tr>
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<td>9</td>
<td>A</td>
<td>NaOAc</td>
<td>toluene</td>
<td>trace</td>
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<td>A</td>
<td>K2CO3</td>
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<td>n.r.</td>
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<tr>
<td>12</td>
<td>A</td>
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<td>mesitylene</td>
<td>29</td>
<td>3.5:1</td>
<td>94</td>
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<tr>
<td>13</td>
<td>A</td>
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<td>46</td>
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<td>14</td>
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<td>TMEDA</td>
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<td>96</td>
<td>1:2.5</td>
<td>96</td>
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<td>58</td>
<td>1:13</td>
<td>87</td>
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<tr>
<td>16</td>
<td>A</td>
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<td>99</td>
<td>3.5:1</td>
<td>97</td>
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<td>A</td>
<td>DIPEA</td>
<td>toluene–MeCN, 4:1</td>
<td>76</td>
<td>7:5:1</td>
<td>97</td>
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<td>97</td>
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<td>97</td>
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<td>19</td>
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<td>DIPEA</td>
<td>toluene–MeCN, 2:1</td>
<td>94</td>
<td>7:1</td>
<td>97</td>
</tr>
<tr>
<td>20</td>
<td>A</td>
<td>DIPEA</td>
<td>toluene–MeCN, 1:2</td>
<td>95</td>
<td>7:1</td>
<td>98</td>
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</tbody>
</table>

a Reaction conditions: 1a (0.2 mmol), 2a (0.3 mmol), precatalyst (0.02 mmol), base (0.4 mmol), solvent (v/v, 2 mL in total), r.t., under argon, 16 h.
b Yield of isolated product 3a after column chromatography; n.r. = no reaction.
c Determined by 1H NMR spectroscopy.
d Determined by HPLC on a chiral stationary phase.
e Performed at 40 °C.
### Table 2  Asymmetric Synthesis of Dihydrobenzothiazolopyridin-1-ones 3a

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>Yield (a) (%)</th>
<th>dr (b)</th>
<th>ee (c) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Bn</td>
<td>a</td>
<td>93</td>
<td>7:1</td>
<td>96</td>
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<tr>
<td>4-Tol</td>
<td>Bn</td>
<td>b</td>
<td>74</td>
<td>9:1</td>
<td>96</td>
</tr>
<tr>
<td>4-MeOC6H4</td>
<td>Bn</td>
<td>c</td>
<td>72</td>
<td>8:1</td>
<td>94</td>
</tr>
<tr>
<td>3-MeOC6H4</td>
<td>Bn</td>
<td>d</td>
<td>94</td>
<td>6:1</td>
<td>98</td>
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<tr>
<td>4-CIC6H4</td>
<td>Bn</td>
<td>e</td>
<td>84</td>
<td>6:1</td>
<td>97</td>
</tr>
<tr>
<td>3-CIC6H4</td>
<td>Bn</td>
<td>f</td>
<td>97</td>
<td>4:1</td>
<td>98</td>
</tr>
<tr>
<td>4-FC6H4</td>
<td>Bn</td>
<td>g</td>
<td>97</td>
<td>4:1</td>
<td>97</td>
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<tr>
<td>2-furyl</td>
<td>Bn</td>
<td>h</td>
<td>68</td>
<td>6:1</td>
<td>92</td>
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<tr>
<td>Ph</td>
<td>Bn</td>
<td>i</td>
<td>97</td>
<td>9:1</td>
<td>98</td>
</tr>
<tr>
<td>Ph</td>
<td>n-Bu</td>
<td>j</td>
<td>71</td>
<td>8:1</td>
<td>98</td>
</tr>
<tr>
<td>Ph</td>
<td>n-Hex</td>
<td>l</td>
<td>44</td>
<td>5:1</td>
<td>96</td>
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</tbody>
</table>

**a** Reaction conditions: 1 (0.5 mmol), 2 (0.75 mmol), precatalyst A (0.05 mmol), DIPEA·HBF4 (1.0 mmol), toluene–MeCN (1:2, v/v; 5 mL in total), r.t., under argon, 16 h; R1 = Cl, X = S, unless otherwise noted.

**b** Yield of isolated product 3 as a mixture of diastereomers after column chromatography.

**c** Determined by 1H NMR spectroscopy.

**d** Determined by HPLC on a chiral stationary phase.

**e** Reaction time was 43 h.

**f** Reaction time was 40 h.

**g** Reaction time was 18 h.

**h** X = O.

**Scheme 2  Proposed reaction mechanism**

(2R,3R)-2-Benzyl-1-oxo-3-phenyl-2,3-dihydro-1H-benzo[4,5]thiazolo[3,2-a]pyridine-4-carbonitrile (3a)

The ee (96%) was determined by HPLC using a chiral stationary phase [Daicel IC; n-heptane–EtOH, 9:1, 0.5 mL/min; tR = 11.01 min (minor), 13.47 min (major)].

Yield: 183.2 mg (93%); colorless solid; mp 140–142 °C.

(2R,3R)-2-Benzyl-1-oxo-3-(p-toly)-2,3-dihydro-1H-benzo[4,5]thiazolo[3,2-a]pyridine-4-carbonitrile (3b)

The ee (96%) was measured by HPLC using a chiral stationary phase [Daicel IC; n-heptane–i-ProOH, 97:3, 1.0 mL/min; tR = 16.05 min (minor), 27.22 min (major)].

Yield: 151.8 mg (74%); colorless solid; mp 133–135 °C.
(2R,3R)-2-Benzyl-3-(4-methoxyphenyl)-1-oxo-2,3-dihydro-1H-benz-[d][3]-pyridazine-3,4-carbonitrile (3c)

The ee (94%) was measured by HPLC using a chiral stationary phase [Chiralpak AD; n-heptane–EtOH, 7:3, 0.5 mL/min; \( t_f = 18.94 \) min (minor), 25.78 min (major)].

Yield: 152.0 mg (72%); colorless solid; mp 96–98 °C.

[\( \delta \)] = 500.9 (c 2.89, CHCl₃).

IR (ATR): 3455, 3017, 2956, 2841, 2631, 2321, 2195, 2102, 2063, 2008, 1908, 1727, 1605, 1455, 1366, 1224, 1132, 1029, 930, 826, 747, 701 cm⁻¹.

1H NMR (600 MHz, CDCl₃): \( \delta = 8.43 \) (d, \( J = 8.4 \) Hz, 1 H), 7.41–7.22 (m, 6 H), 7.08 (d, \( J = 7.2 \) Hz, 2 H), 6.98 (d, \( J = 8.4 \) Hz, 2 H), 6.86 (d, \( J = 8.4 \) Hz, 2 H), 3.80 (s, 3 H), 3.59 (d, \( J = 7.2 \) Hz, 1 H), 3.52–3.49 (m, 1 H), 3.44 (dd, \( J_1 = 14.4 \) Hz, \( J_2 = 4.8 \) Hz, 1 H), 2.49 (dd, \( J_1 = 15.0 \) Hz, \( J_2 = 9.6 \) Hz, 1 H).

13C NMR (150 MHz, CDCl₃): \( \delta = 169.4, 159.6, 151.8, 138.1, 137.4, 128.9 (2 C), 128.8 (2 C), 128.7 (2 C), 127.5 (2 C), 127.1, 126.8, 125.9, 123.8, 121.8, 117.9, 117.3, 83.7, 48.1, 42.7, 31.5, 21.1.

MS (ESI): m/z = 409.1373 [M + H]⁺.


(2R,3R)-2-Benzyl-3-(3-chlorophenyl)-1-oxo-2,3-dihydro-1H-benz-[d][4]thiazolo[3,2-a]pyridazine-3,4-carbonitrile (3f)

The ee (98%) was measured by HPLC using a chiral stationary phase [Daicel IC; n-heptane–EtOH, 97:3, 1.0 mL/min; \( t_f = 9.42 \) min (minor), 13.16 min (major)].

Yield: 208.5 mg (97%); colorless solid; mp 85–86 °C.

[\( \delta \)] = 506.3 (c 1.0, CHCl₃).

IR (ATR): 3441, 3025, 2929, 2640, 2322, 2195, 2101, 1979, 1718, 1601, 1458, 1362, 1315, 1221, 1135, 1081, 870, 747, 698 cm⁻¹.

1H NMR (600 MHz, CDCl₃): \( \delta = 8.43 \) (d, \( J = 7.8 \) Hz, 1 H), 7.43–7.22 (m, 8 H), 7.05 (d, \( J = 7.2 \) Hz, 2 H), 6.98 (d, \( J = 8.4 \) Hz, 2 H), 3.61 (d, \( J = 7.2 \) Hz, 1 H), 3.56–3.52 (m, 1 H), 3.46 (dd, \( J_1 = 14.4 \) Hz, \( J_2 = 4.8 \) Hz, 1 H), 2.44 (dd, \( J_1 = 15.0 \) Hz, \( J_2 = 9.6 \) Hz, 1 H).

13C NMR (150 MHz, CDCl₃): \( \delta = 168.9, 152.9, 138.4, 137.6, 137.3, 134.9, 130.6, 129.1, 125.1, 128.8 (2 C), 128.8 (2 C), 128.7, 128.1, 127.2, 127.0, 126.1, 125.6, 121.9, 117.3, 82.8, 47.7, 42.4, 31.5.

MS (ESI): m/z = 429.0825 [M + H]⁺.

Yield: 208.3 mg (97%); colorless solid; mp 240–242 °C.

Yield: 129.8 mg (68%); colorless solid; mp 76–78 °C.

13C NMR (150 MHz, CDCl 3): δ = 168.8, 153.7, 149.7, 143.1, 138.0, 137.7, 129.0 (2 C), 128.8 (2 C), 127.1, 126.9, 125.8, 123.7, 121.8, 117.8, 117.4, 110.4, 109.0, 79.9, 47.4, 36.2, 31.7.

MS (ESI): m/z = 383.0845 [M – H]–.

(2R,3R)-2-Benzyl-8-chloro-1-oxo-3-phenyl-2,3-dihydro-1H-benzo[4,5][thiazolo][3,2-a]pyridine-4-carbonitrile (3i)
The ee (98%) was measured by HPLC using a chiral stationary phase [Daicel IC; n-heptane–EtOH, 97:3, 0.5 ml/min; tf = 15.99 min (minor), 19.09 min (major)].

Yield: 128.1 mg (71%); colorless solid; mp 100–102 °C.

[a]D 21 = +111.7 (c 0.96, CHCl3).


1H NMR (600 MHz, CDCl 3): δ = 8.40 (d, J = 7.8 Hz, 1 H), 7.40–7.23 (m, 6 H), 7.12 (dd, J1 = 7.8 Hz, J2 = 2.4 Hz, 2 H), 3.84 (dd, J1 = 7.2 Hz, J2 = 1.0 Hz), 3.09 (dd, J1 = 3.0 Hz, J2 = 0.9 Hz, 1 H), 1.94–1.88 (m, 1 H) 1.42–1.21 (m, 5 Hz), 0.88 (t, J = 7.2 Hz, 3 H).

13C NMR (150 MHz, CDCl 3): δ = 169.8, 152.5, 137.6, 136.5, 129.2 (2 C), 128.3, 127.4 (2 C), 127.1, 125.9, 123.8, 121.8, 118.1, 117.2, 83.0, 46.5, 43.9, 29.5, 25.4, 22.5, 13.9.

MS (ESI): m/z = 359.1202 [M – H]–.


(2R,3R)-2-Heptyl-1-oxo-3-phenyl-2,3-dihydro-1H-benzo[4,5][thiazolo][3,2-a]pyridine-4-carbonitrile (3j)
The ee (96%) was measured by HPLC using a chiral stationary phase [Daicel IC; n-heptane–EtOH, 97:3, 0.7 ml/min; tf = 12.62 min (minor), 14.81 min (major)].

Yield: 85.5 mg (44%); colorless solid; mp 123–125 °C.

[a]D 21 = –448.6 (c 1.0, CHCl3).

IR (ATR): 3427, 3029, 2927, 2858, 2645, 2321, 2196, 2104, 1993, 1804, 1717, 1607, 1457, 1305, 1225, 1135, 1062, 1028, 908, 850, 744 cm–1.

1H NMR (600 MHz, CDCl 3): δ = 8.40 (d, J = 8.4 Hz, 1 H), 7.38 (d, J = 7.8 Hz, 1 H), 7.32–7.23 (m, 5 H), 7.12 (dd, J1 = 7.8 Hz, J2 = 2.4 Hz, 2 H), 3.84 (dd, J1 = 7.2 Hz, J2 = 1.0 Hz), 3.09 (dd, J1 = 3.0 Hz, J2 = 0.9 Hz, 1 H), 1.93–1.87 (m, 1 H), 1.43–1.38 (m, 2 H), 1.31–1.20 (m, 7 H), 0.86 (t, J = 7.2 Hz, 3 H).

13C NMR (150 MHz, CDCl 3): δ = 169.8, 152.5, 137.6, 136.5, 129.2 (2 C), 128.3, 127.4 (2 C), 127.1, 125.9, 123.8, 121.8, 118.1, 117.2, 83.0, 46.5, 43.9, 31.5, 29.1, 27.3, 25.7, 22.5, 14.0.

MS (ESI): m/z = 387.1536 [M + H]–.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379369. Included are copies of the $^1$H and $^13$C NMR spectra of products 3a–l, HPLC measurements of products 3a–l, and the NOESY spectrum of 3d.

References


