

# **ORGANIC**CHEMISTRY

FRONTIERS







# **ORGANIC** CHEMISTRY

#### **FRONTIERS**







**View Article Online** View Journal | View Issue

### **RESEARCH ARTICLE**



# Synthesis of oxindoles via reductive CO<sub>2</sub> fixation†‡

Cite this: Org. Chem. Front., 2016, 3,

Toru Amaya,\*a Izumi Kurata and Toshikazu Hirao\*a,b

Received 17th March 2016 Accepted 14th June 2016 DOI: 10.1039/c6qo00107f

rsc.li/frontiers-organic

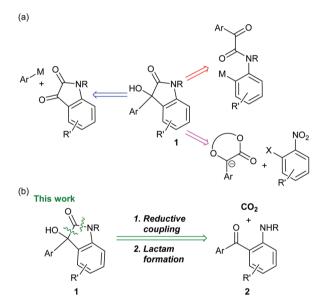
The synthesis of 3-aryl-3-hydroxy-2-oxindoles, which are a structural motif found in various natural products and pharmaceutically active compounds, was conducted via reductive coupling of (2-aminophenyl) (aryl)methanone derivatives and CO2 as a key step. The conditions employing Mg with chlorotrimethylsilane in DMA are the best for the reductive coupling, where the aryl halide moiety is intact. This reaction proceeds well without the protection of the amino group. The reductive coupling and acid-catalyzed lactam formation can be performed in a one-pot reaction to give the oxindoles.

#### Introduction

Carbon dioxide (CO<sub>2</sub>) is considered to be one of the causative agents for global warming. Therefore, the effective utilization of CO<sub>2</sub> collected from plant emissions is important in view of sustainable chemistry. Utilization of CO2 as a C1 synthon for organic synthesis has been developed in this context.<sup>1</sup>

Oxindoles are a structural motif found in various natural products and medicinally relevant molecules.<sup>2</sup> In this study, the synthesis of 3-aryl-3-hydroxy-2-oxindoles 1 is focused on, as the skeleton is included in several pharmaceutical compounds such as SM-130686 3 and ECi8.4 Scheme 1a shows the representative examples of the previously reported retrosynthesis for 1. Most commonly, oxindoles 1 are synthesized via 1,2addition of an aryl anion equivalent to an isatin derivative.<sup>5</sup> Intramolecular arylation to a ketone is also reported. Another approach involves aromatic nucleophilic substitution with an enolate of mandelic acid derivatives as a key step.7 In this context, our retrosynthesis was designed based on reductive CO<sub>2</sub> fixation with (2-aminophenyl)(aryl)methanone derivatives 2, followed by lactam formation (Scheme 1b). So far, an enormous number of synthetic reports for 1 have been published (Scheme 1b). However, to the best of our knowledge, such an approach via CO<sub>2</sub> fixation has not been reported.

Reductive CO2 fixation of diaryl ketones has been studied.8-11 Such a reaction can be roughly classified into four



Scheme 1 (a) Representative examples of the previously reported retrosynthesis for 3-aryl-3-hydroxy-2-oxindoles 1. (b) Our retrosynthesis for 1.

reduction patterns, reduction by (1) electrodes,8 (2) alkali metals, 9 (3) low-valent transition or rare-earth metals 10 and (4) light. 11 Our group also has developed the reductive coupling of aldehydes, especially utilizing early-transition metals such as vanadium and titanium compounds as a catalyst in the presence of chlorotrimethylsilane. 12 Here, we report the synthesis of 3-aryl-3-hydroxy-2-oxindoles 1 via reductive coupling of CO2 and ketoamines 2 as a key step.

#### Results and discussion

Our investigation commences with the screening of the combination of an early-transition metal catalyst and Zn or Mg as a

<sup>&</sup>lt;sup>a</sup>Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Yamada-oka, Suita, Osaka 565-0871, Japan, E-mail: amaya@chem.eng.osaka-u.ac.jp

<sup>&</sup>lt;sup>b</sup>The Institute of Scientific and Industrial Research, Osaka University, Mihoga-oka, Ibaraki, Osaka 567-0047, Japan. E-mail: hirao@chem.eng.osaka-u.ac.jp

<sup>†</sup>This paper is dedicated to Professor Barry M. Trost on the occasion of his 75th birthday.

<sup>‡</sup> Electronic supplementary information (ESI) available: <sup>1</sup>H NMR spectrum for 1a, and <sup>1</sup>H and <sup>13</sup>C NMR spectra for 1d, 1e, 1f, 1h, 1i and 2h. See DOI: 10.1039/c6qo00107f

Table 1 Screening of an early-transition metal catalyst and a solvent for the synthesis of oxindole 1a via reductive coupling of 2a and CO2 in the presence of Zn as a terminal reductant

			Yield <sup>a</sup> /%			
Entry	Catalyst	Solvent	Recovered 2a <sup>b</sup>	Oxindole 1a	Alcohol 3 <sup>b</sup>	
$1^{c,d}$	TiCl <sub>4</sub>	DMF	65	0	n.d. <sup>e</sup>	
$2^c$	$TiCl_4$	THF	Complex mixture			
3 <sup>c</sup>	$TiCl_4$	DME	Complex mixture			
4	Cp <sub>2</sub> TiCl <sub>2</sub>	DMA	20	3	13	
5	$VCl_3$	DMA	23	9	19	
6	$VBr_3$	DMA	22	4	44	
7	$Cp_2VCl_2$	DMA	7	2	27	
8	_	DMA	8	2	43	

<sup>a</sup> Yield was calculated by using the integral ratio of the peaks for each compound and the internal standard (1,3,5-trimethoxybenzene) in the <sup>1</sup>H NMR spectrum of the crude mixture. <sup>b</sup> Starting substrate 2a and the byproducts 3 and 5 were present as a HCl salt in the aqueous layer with a HCl solution after the treatment with an aqueous 3 M HCl solution. To extract them from the aqueous layer, a saturated aqueous  $NaHCO_3$  solution was added, and they were extracted with ethyl acetate.  $^c$  Reaction time was 20 h.  $^d$  The formation of indole 4 and deoxygenated compound 5 was observed as by-products in this entry. e Not determined.

terminal reductant. First, Zn was used as a terminal reductant (Table 1). Ketoamine 2a reacted with CO<sub>2</sub> (balloon) in the presence of TiCl<sub>4</sub> (20 mol%), Zn (5 equivalents) and chlorotrimethylsilane (2 equivalents) in N,N-dimethylformamide (DMF) at room temperature, followed by treatment with an aqueous 3 M HCl solution. But, the desired oxindole 1a was not obtained, instead, indole 4 was formed (Table 1, entry 1). Indole 4 is considered to be formed via intramolecular McMurry coupling after formylation of the amine with DMF. The use of THF or DME gave the complex mixtures (Table 1, entries 2 and 3). When DMA was used as a solvent, the reactions with Cp2TiCl2, VCl3, VBr3 or Cp2VCl2 as a catalyst afforded the desired oxindole 1a in low yields (2-9%) with the alcohol 3 as a main product (Table 1, entries 4-7). The reaction without a catalyst also gave 1a in a low yield (Table 1, entry 8).

The screening was continued using Mg as a terminal reductant in DMA (Table 2). In this case, the desired oxindole 1a was obtained under the conditions with a catalyst shown in entries 1-6 in Table 2. But, the formation of alcohol 3 was observed in the presence of titanium or vanadium catalysts. Finally, the desired oxindole 1a was obtained in the absence of

Table 2 Screening of a catalyst for the synthesis of oxindole 1a via reductive coupling of 2a and CO2 in the presence of Mg as a terminal reductant

		Yield <sup>a</sup> /%			
Entry	Catalyst	Recovered <b>2a</b> <sup>b</sup>	Oxindole 1a	Alcohol 3 <sup>b</sup>	
1	$TiCl_4$	c	44	11	
2	VCl <sub>3</sub>	0	51	5	
3	Cp <sub>2</sub> TiCl <sub>2</sub>	0	68	2	
4	$Cp_2VCl_2$	0	80	16	
5	$Yb(OTf)_3$	7	52	16	
6	VBr <sub>3</sub>	0	52	21	
7	_	0	95	5	
8	— (1 equiv. of Me <sub>3</sub> SiCl)	16	70	7	
9	— (Without Me <sub>3</sub> SiCl)	27	0	48	
10	— (With collidine HCl salt) <sup>d</sup>	51	11	11	
11	— (3 equiv. of Mg)	0	97 (99) <sup>e</sup>	Trace	
12	— (1 equiv. of Mg)	19	74	c	

<sup>a</sup> Yield was calculated by using the integral ratio of the peaks for each compound and internal standard (1,3,5-trimethoxybenzene) in the <sup>1</sup>H NMR spectrum of the crude mixture. <sup>b</sup> Starting substrates 2a and 3 were present as a HCl salt in the aqueous layer with a HCl solution after the treatment with an aqueous 3 M HCl solution. To extract them from the aqueous layer, a saturated aqueous NaHCO3 solution was added, and they were extracted with ethyl acetate. c It was difficult to quantify. <sup>a</sup> Instead of chlorotrimethylsilane. <sup>e</sup> Isolated yield (containing a very small amount of ethyl acetate, see the ESI for the <sup>1</sup>H NMR spectrum).

a catalyst in 95% yield (Table 2, entry 7). Decreasing the amount of chlorotrimethylsilane to 1 equivalent resulted in lowering of the yield of 1a to 70% (Table 2, entry 8). In the absence of both a catalyst and chlorotrimethylsilane, the product 1a was not detected, showing that chlorotrimethylsilane is essential (Table 2, entry 9). This is consistent with the previous results.<sup>12</sup> Instead of chlorotrimethylsilane, the use of collidine HCl salt provided 1a in a low yield (Table 2, entry 10). Keeping the equivalents of Mg at three was not a problem (97%, Table 2, entry 11). But, the further decreasing to one equivalent gave rise to a decrease of the yield of 1a (74%, Table 2, entry 12).

The scope and limitation of the substrates were investigated (Scheme 2). It is important to note that aryl halides such as fluoride, chloride and bromide can be used as a substrate to give oxindoles 1 in good yields in spite of the presence of Mg (96% for 1c, 93% for 1d, 88% for 1e, 76% for 1f and 96% for 1k). The presence of an electron donating group at the para position of the phenyl group was not a problem for this reaction (85% for 1g). The ester moiety was tolerated in this reaction to afford the corresponding product 1h in 83% yield. The product 1i with a furyl group was also synthesized in this reaction. N-Methylated substrates reacted well to give the corresponding products (76% for 1j and 96% for 1k). Instead of the aryl group, the methyl group at R3 did not provide a good result, and the yield of 1i was quite low (2%).

Scheme 2 Scope and limitation of the synthesis of oxindoles 1  $\it via$  reductive coupling of 2 and  $\it CO_2$ .

1k 96%

To gain an insight into the reaction path, aqueous work-up with a basic solution (aqueous saturated NaHCO<sub>3</sub> solution) instead of an aqueous 3 M HCl solution was carried out for the reaction of 2a. The aqueous solution was extracted with ethyl acetate. Both the organic and aqueous layers were separately treated with an aqueous 3 M HCl solution. From the aqueous layer (Scheme 3b), oxindole 1a was obtained in 64% yield, but 11% from the organic layer (Scheme 3a). These results indicate that the lactam formation in entry 7 in Table 2 and Scheme 2 mainly takes place in the process of the treatment with aqueous 3 M HCl solution.

Concerning the reductive coupling with  $CO_2$ , there are two plausible paths (Scheme 4),<sup>13</sup> (1) one-electron reduction of the ketone, addition of the resulting radical anion species to  $CO_2$ , followed by one-electron reduction (path A) and (2) sequential two-electron reduction of the ketone and 1,2-addition of the carbanion (path B). The related papers presenting the mecha-

Scheme 3 Aqueous work-up with a basic solution followed by acid treatment for the synthesis of oxindoles  $1a\ via$  reductive coupling of 2a and  $CO_2$ .

Scheme 4 Plausible paths for the synthesis of oxindoles  $1a\ via$  reductive coupling of 2a and  $CO_2$ .

nisms were also reported for both paths,  ${}^{9a,14,15}$  which cannot be excluded for this reaction at present.

#### Conclusions

We have demonstrated the synthesis of 3-aryl-3-hydroxy-2-oxindoles 1 via reductive coupling of ketoamines 2 and CO<sub>2</sub> as a key step. This synthetic approach is new although the synthesis of oxindoles 1 has been well studied. The conditions employing Mg with chlorotrimethylsilane in DMA are the best for the reductive coupling, where protection of the amino group is not required. In spite of using Mg, an aryl halide moiety such as aryl fluoride, chloride and bromide is intact in this reaction. Further studies including enantioselective synthesis and application to the synthesis of pharmaceutically active compounds are now underway.

## Experimental

#### General

NMR spectra were recorded on a JEOL JNM-ECS 400 spectrometer. Chemical shifts were reported in ppm on the  $\delta$  scale relative to a residual solvent (DMSO- $d_6$ :  $\delta$  = 2.50 for  $^1$ H NMR and 39.52 ppm for  $^{13}$ C NMR) or tetramethylsilane ( $\delta$  = 0 ppm

for <sup>1</sup>H and <sup>13</sup>C NMR) as an internal standard. Infrared spectra were recorded on a JASCO FT/IR-6200. Mass spectra were recorded on a JEOL JMS-700 spectrometer using the fast atom bombardment (FAB) or electron impact (EI) mode. Substrates **2a-f**, **k** are available from commercial sources. Substrates **2g**, <sup>16</sup> **2i**<sup>17</sup> and **2j**<sup>18</sup> were prepared according to the literature. Substrate **2h** was prepared *via* the Suzuki–Miyaura coupling reaction of **2d** with 1.2 equivalents of 4-(ethoxycarbonyl) phenylboronic acid in the presence of 2 mol% Pd(PPh<sub>3</sub>)<sub>4</sub> and aqueous Na<sub>2</sub>CO<sub>3</sub> in toluene and ethanol at 80 °C overnight. Recrystallized **2h** (CH<sub>2</sub>Cl<sub>2</sub>-hexane) after silica-gel column chromatography was used for the reaction.

#### General procedure

To a round-bottomed flask was added Mg (36.5 mg, 1.5 mmol). The atmosphere in the flask was exchanged with argon by repeating evacuation and purge. Then, DMA (4.1 mL, dried with MS4A before use) was added to the flask. The atmosphere in the flask was exchanged with CO2 using a balloon by repeating evacuation and purge. Chlorotrimethylsilane (127 µL, 1.0 mmol, distilled over CaH<sub>2</sub> before use) and the 0.554 M DMA solution of 2 (0.9 mL, 0.5 mmol) were added to the mixture at room temperature. After the reaction mixture was stirred for 4 h, a 3 M aqueous HCl solution (5 mL) was added. The mixture was stirred for at least 30 min. The mixture was transferred to a separatory funnel. The product 1 was extracted with ethyl acetate twice. The organic layer was washed with brine, dried over Na2SO4 and filtered through filter paper. The filtrate was evaporated to give the crude product. To calculate the yield, 1,3,5-trimethoxybenzene (25 mg, 0.15 mmol) was added as an internal standard. The <sup>1</sup>H NMR spectra of the mixture were recorded. The yield was calculated by the integral ratio of the peaks for the product 1 and internal standard. Identification of the products 1 was conducted by comparison with the <sup>1</sup>H NMR data reported previously: 1a,<sup>7</sup> 1b,<sup>5c</sup> 1c,<sup>19</sup> 1g,<sup>20</sup> 1j<sup>6a</sup> and 1k.<sup>5c</sup>

Isolation of 1a. To remove DMA completely, the aqueous work-up was modified. After the treatment with a 3 M aqueous HCl solution,  $\rm H_2O$  (200 mL) and ethyl acetate (50 mL) were added to the mixture in a separatory funnel. The aqueous layer was extracted with a mixed solution of ethyl acetate (20 mL) and hexane (20 mL) twice. The combined organic layer was washed with  $\rm H_2O$  (100 mL  $\times$  2 and 200 mL). The organic layer was concentrated *in vacuo* to give pure 1a (111.4 mg, 0.495 mmol, 99% yield, containing a very small amount of ethyl acetate) without further purification. See the ESI‡ for the  $^1\rm H$  NMR spectrum.

**Isolation of 1d, 1e and 1f.** They were purified to remove the internal standard for the full characterization as below. To their DMSO solution was added  $H_2O$  to give a white precipitate. The precipitation was collected by filtration, and the residue was washed with  $CH_2Cl_2$  to give the corresponding oxindole **1**.

**Isolation of 1h and 1i.** Their crude mixtures were purified by preparative TLC (hexane/ethyl acetate = 1:2 for **1h** and 1:3 for **1i**).

# Characterization data for the compounds whose <sup>1</sup>H NMR data are not reported previously

1d:  $^{1}$ H NMR (400 MHz, DMSO- $^{1}$ 6)  $\delta$  = 10.58 (s, 1 H), 7.44 (dd, J = 8.2, 1.8 Hz, 1 H), 7.38–7.257 (m, 5 H), 7.21 (d, J = 1.8 Hz, 1 H), 6.88 (d, 8.2 Hz, 1 H), 6.79 (s, 1 H) ppm;  $^{13}$ C NMR (100 MHz, DMSO- $^{1}$ 6)  $\delta$  = 177.97, 141.24, 140.82, 136.13, 131.98, 128.28, 127.71, 127.40, 125.30, 113.65, 112.03, 77.33 ppm; IR(ATR)  $\nu$  = 3369, 3199, 2358, 1704, 1473, 1182, 821, 737 cm $^{-1}$ ; HRMS(FAB) m/z:  $[M]^{+}$  calcd for  $C_{14}H_{10}BrNO_{2}$ : 302.9895; found: 302.9889.

1e: <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ )  $\delta$  = 10.67 (s, 1 H), 7.91 (ddd, 7.9, 7.9, 1.8 Hz, 1 H), 7.42–7.25 (m, 3 H), 7.06 (ddd, J = 11.5, 8.1, 1.1 Hz, 1 H), 7.00 (s, 1 H), 6.90 (d, J = 9.9 Hz, 1 H), 6.91 (s, 1 H) ppm; <sup>13</sup>C NMR (100 MHz, DMSO- $d_6$ )  $\delta$  = 177.05, 158.39 (d, J = 245.4 Hz), 141.25, 134.29, 129.88 (d, J = 7.7 Hz), 129.27, 128.16 (d, J = 12.5 Hz), 128.01 (d, J = 3.8 Hz), 125.68, 124.30 (d, J = 2.9 Hz), 124.09, 115.16 (d, J = 21.1 Hz), 111.29, 74.25 ppm; IR(ATR)  $\nu$  = 3410, 3237, 2367, 2328, 1713, 1485, 1049, 823, 755 cm<sup>-1</sup>; HRMS(FAB) m/z: M calcd for M c<sub>14</sub>H<sub>9</sub>ClFNO<sub>2</sub>: 277.0306; found: 277.0308.

1f: <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ )  $\delta$  = 10.70 (s, 1 H), 8.06 (dd, J = 7.8, 1.8 Hz, 1 H), 7.49 (ddd, J = 7.8, 7.8, 1.8 Hz 1 H), 7.41–7.32 (m, 2 H), 7.29 (dd, J = 8.2, 2.3 Hz, 1 H), 7.03 (s, 1 H), 6.89 (d, J = 8.2 Hz, 1 H), 6.76 (d, J = 2.3 Hz, 1 H) ppm; <sup>13</sup>C NMR (100 MHz, DMSO- $d_6$ )  $\delta$  = 176.45, 142.21, 137.89, 133.54, 130.28, 129.72 × 2, 129.29, 129.02, 126.89, 125.51, 123.82, 111.19, 76.07 ppm; IR(ATR)  $\nu$  = 3420, 3237, 2361, 2342, 1711, 1483, 1470, 1437, 1036, 826, 746, 732 cm<sup>-1</sup>; HRMS(FAB) m/z:  $[M]^+$  calcd for  $C_{14}H_9Cl_2NO_2$ : 293.0010; found: 293.0008.

1h: <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ )  $\delta$  = 10.58 (s, 1 H), 7.97 (d, J = 8.7 Hz, 2 H), 7.72 (d, J = 8.7 Hz 2 H), 7.68 (dd, J = 8.2, 2.3 Hz, 1 H), 7.46 (d, J = 1.8 Hz, 1 H), 7.36–7.24 (m, 5 H), 7.04 (d, J = 8.2 Hz, 1 H), 6.75 (s, 1 H), 4.31 (q, J = 7.3 Hz, 2H), 1.32 (t, J = 7.3 Hz, 3H) ppm; <sup>13</sup>C NMR (100 MHz, DMSO- $d_6$ )  $\delta$  = 178.55, 165.63, 144.38, 142.47, 141.27, 134.76, 132.85, 129.87, 128.25, 128.13, 127.61, 126.25, 125.47, 123.18, 110.57, 77.41, 60.73, 14.23 ppm; IR(KBr)  $\nu$  = 3308, 3061, 2980, 2933, 1728, 1713, 1606, 1484, 1278, 1175, 1103, 771 cm<sup>-1</sup>; HRMS(EI) m/z: [M] calcd for C<sub>23</sub>H<sub>19</sub>NO<sub>4</sub>: 373.1314; found: 373.1310.

1i: <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ )  $\delta$  = 10.44 (s, 1 H), 7.59 (brd, J = 1.8 Hz, 1 H), 7.30 (d, J = 7.3 Hz, 1 H), 7.24 (ddd, J = 7.8, 7.8, 0.9 Hz, 1 H), 6.98 (dd, J = 7.3, 7.3 Hz, 1 H), 6.85 (d, J = 7.3, 1 H), 6.73 (s, 1H), 6.40 (dd, J = 3.2, 1.8 Hz, 1 H), 6.30 (d, J = 3.2 Hz, 1 H) ppm; <sup>13</sup>C NMR (100 MHz, DMSO- $d_6$ )  $\delta$  = 176.18, 153.01, 143.19, 141.69, 130.78, 129.56, 124.99, 121.87, 110.27, 109.88, 107.65, 73.48 ppm; IR(KBr)  $\nu$  = 3310, 2822, 2361, 1709, 1684, 1624, 1474, 1311, 1112, 763 cm<sup>-1</sup>; HRMS(EI) m/z:  $[M]^+$  calcd for  $C_{12}H_9NO_3$ : 215.0582; found: 215.0583.

2h:  $^{1}$ H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 8.02 (d, J = 8.7 Hz, 2 H), 7.75 (d, J = 2.3 Hz 1 H), 7.72–7.68 (m, 2 H), 7.62 (dd, J = 8.7, 2.3 Hz, 1 H), 7.56 (tt, J = 7.3, 1.4 Hz, 1 H), 7.51–7.46 (m, 4 H), 6.85 (d, J = 8.7 Hz, 1 H), 6.20 (brs, 2 H) ppm;  $^{13}$ C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 198.89, 166.48, 150.78, 144.54, 139.77, 132.99, 132.88, 131.46, 130.13, 129.24, 128.42, 128.29, 127.25, 125.79, 118.34, 117.67, 60.88, 14.35 ppm; IR(KBr)  $\nu$  = 3487, 3352, 3066,

2986, 2902, 1704, 1639, 1729, 1247, 1107, 775 cm<sup>-1</sup>; HRMS(EI) m/z:  $[M]^+$  calcd for  $C_{22}H_{19}NO_3$ : 345.1365; found: 345.1360.

## Acknowledgements

Financial support from JST (ACT-C) is acknowledged.

#### Notes and references

- (a) T. Sakakura, J.-C. Choi and H. Yasuda, Chem. Rev., 2007,
   107, 2365; (b) Carbon Dioxide as Chemical Feedstock, ed.
   M. Aresta, Wiley-VCH, Weinheim, 2010.
- Reviews: (a) B. M. Trost and M. K. Brennan, Synthesis, 2009, 3003; (b) F. Zhou, Y.-L. Liu and J. Zhou, Adv. Synth. Catal., 2010, 352, 1381; (c) R. Dalpozzo, G. Bartoli and G. Bencivenni, Chem. Soc. Rev., 2012, 41, 7247.
- 3 (a) T. Tokunaga, W. E. Hume, T. Umezome, K. Okazaki, Y. Ueki, K. Kumagai, S. Hourai, J. Nagamine, H. Seki, M. Taiji, H. Noguchi and R. Nagata, J. Med. Chem., 2001, 44, 4641; (b) T. Tokunaga, W. E. Hume, J. Nagamine, T. Kawamura, M. Taiji and R. Nagata, Bioorg. Med. Chem. Lett., 2005, 15, 1789.
- 4 Y. Shen, J. Liu, G. Estiu, B. Isin, Y.-Y. Ahn, D.-S. Lee, A.-L. Barabási, V. Kapatral, O. Wiest and Z. N. Oltvai, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 1082.
- 5 Selected examples: (a) S. J. Angyal, E. Bullock, W. G. Hanger, W. C. Howell and A. W. Johnson, *J. Chem. Soc.*, 1957, 1592; (b) Ref. 3a; (c) R. Shintani, M. Inoue and T. Hayashi, *Angew. Chem., Int. Ed.*, 2006, 45, 3353.
- 6 Selected examples: (a) Y.-X. Jia, D. Katayev and E. P. Kündig, *Chem. Commun.*, 2010, **46**, 130; (b) L. Yin, M. Kanai and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2011, **50**, 7620.
- 7 S. Barroso, G. Blay, L. Cardona, I. Fernández, B. García and J. R. Pedro, *J. Org. Chem.*, 2004, **69**, 6821.
- (a) S. Wawzonek and A. Gundersen, J. Electrochem. Soc., 1960, 107, 537; (b) Y. Ikeda and E. Manda, Bull. Chem. Soc. Jpn., 1985, 58, 1723; (c) S.-F. Zhao, H. Wang, Y.-C. Lan, X. Liu, J.-X. Lu and J. Zhang, J. Electroanal. Chem., 2012, 664, 105; (d) R. Liu, G. Yuan, C. L. Joe, T. E. Lightburn, K. L. Tan and D. Wang, Angew. Chem., Int. Ed., 2012, 51, 6709; (e) S.-F. Zhao, M. Horne, A. M. Bond and J. Zhang, Phys. Chem. Chem. Phys., 2015, 17, 19247.
- (a) Y. V. Kurbatov and A. S. Kurbatova, *Russ. J. Org. Chem.*,
   2001, 37, 1344; (b) A. Häuβermann, F. Rominger and
   B. F. Straub, *Chem. Eur. J.*, 2012, 18, 14174.
- 10 (a) Z. Hou, K. Takamine, O. Aoki, H. Shiraishi, Y. Fujiwara and H. Taniguchi, J. Chem. Soc., Chem. Commun., 1988,

- 668; (b) Z. Hou, K. Takamine, O. Aoki, H. Shiraishi, Y. Fujiwara and H. Taniguchi, J. Org. Chem., 1988, 53, 6077; (c) J. J. Eisch, P. O. Fregene and J. N. Gitua, J. Organomet. Chem., 2007, 692, 4647; (d) J. J. Eisch and P. O. Fregene, Eur. J. Org. Chem., 2008, 4482.
- 11 (a) M. Kanemoto, H. Ankyu, Y. Wada and S. Yanagida, Chem. Lett., 1992, 2113; (b) T. Ogata, K. Hiranaga, S. Matsuoka, Y. Wada and S. Yanagida, Chem. Lett., 1993, 983.
- 12 (a) T. Hirao, T. Hasegawa, Y. Muguruma and I. Ikeda, J. Org. Chem., 1996, 61, 36; (b) For a review: T. Hirao, Chem. Rev., 1997, 97, 2707; (c) T. Hirao, M. Asahara, Y. Muguruma and A. Ogawa, J. Org. Chem., 1998, 63, 2812; (d) T. Hirao, B. Hatano, M. Asahara, Y. Muguruma and A. Ogawa, Tetrahedron Lett., 1998, 39, 5247; (e) B. Hatano, A. Ogawa and T. Hirao, J. Org. Chem., 1998, 63, 9421; (f) T. Hirao, B. Hatano, Y. Imamoto and A. Ogawa, J. Org. Chem., 1999, 64, 7665; (g) T. Hirao, A. Ogawa, M. Asahara, Y. Muguruma and H. Sakurai, Org. Synth., 2005, 81, 26; (h) X. Xu and T. Hirao, J. Org. Chem., 2005, 70, 8594; (i) A. Miyasaka, T. Amaya and T. Hirao, Chem. Eur. J., 2014, 20, 1615.
- 13 To check the possibility of intramolecular reductive coupling of trimethylsilyl arylcarbamate of 2a, an NMR experiment in DMSO- $d_6$  was carried out in the absence of Mg. As a result, the formation of trimethylsilyl arylcarbamate was not observed. Therefore, this path is excluded here.
- 14 Related conditions are reported for the reductive coupling of imines and CO<sub>2</sub>: A. A. Sathe, D. R. Hartline and A. T. Radosevich, *Chem. Commun.*, 2013, 49, 5040.
- (a) I. Nishiguchi, M. Sakai, H. Maekawa, T. Ohno,
   Y. Yamamoto and Y. Ishino, *Tetrahedron Lett.*, 2002, 43,
   635; (b) T. Uchida, Y. Kita, H. Maekawa and I. Nishiguchi,
   Tetrahedron, 2006, 62, 3103.
- 16 (a) Synthesis: S. A. Chandler, P. Hanson, A. B. Taylor,
  P. H. Walton and A. W. Timms, J. Chem. Soc., Perkin Trans.
  2, 2001, 214; (b) Characterization: K. Kobayashi, S. Fujita,
  S. Fukamachi and H. Konishi, Synlett, 2009, 3378.
- 17 V.-H. Nguyen, L. Vendier, M. Etienne, E. Despagnet-Ayoub, P.-A. R. Breuil, L. Magna, D. Proriol, H. Olivier-Bourbigou and C. Lorber, *Eur. J. Inorg. Chem.*, 2012, 97.
- (a) Synthesis: J. Huang, C. Wan, M.-F. Xu and Q. Zhu, Eur. J. Org. Chem., 2013, 1876; (b) Characterization:
   D. Susanti, L. L. R. Ng and P. W. H. Chan, Adv. Synth. Catal., 2014, 356, 353.
- 19 J. Gui, G. Chen, P. Cao and J. Liao, *Tetrahedron: Asymmetry*, 2012, 23, 554.
- 20 Z.-K. Xiao, H.-Y. Yin and L.-X. Shao, Org. Lett., 2013, 15, 1254.