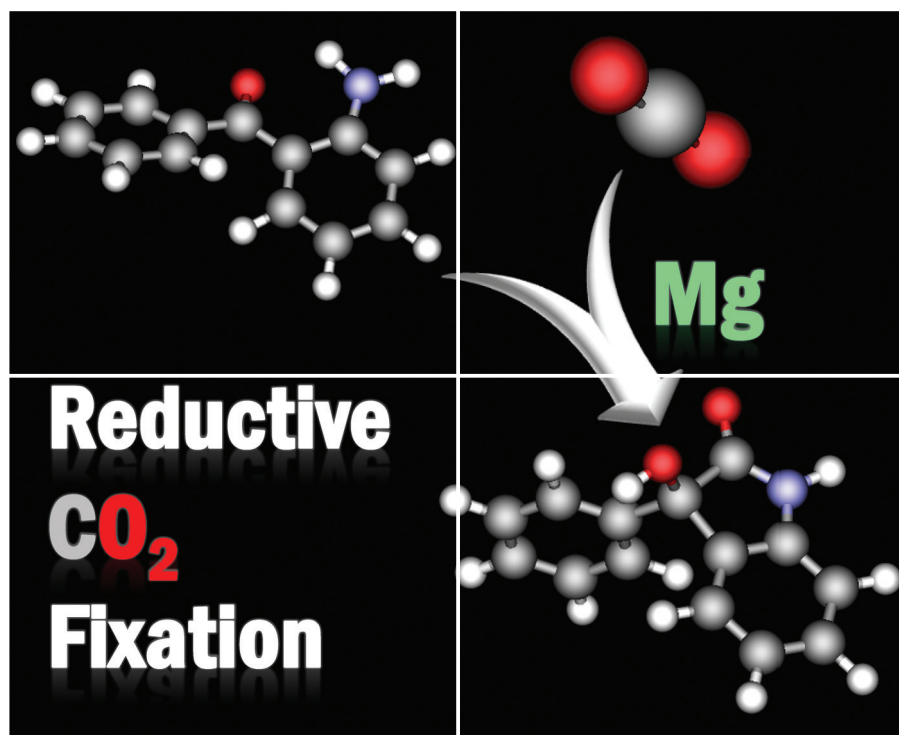




ORGANIC CHEMISTRY

FRONTIERS

RESEARCH ARTICLE

View Article Online

View Journal | View Issue



Cite this: *Org. Chem. Front.*, 2016, **3**, 929

Received 17th March 2016,

Accepted 14th June 2016

DOI: 10.1039/c6qo00107f

rsc.li/frontiers-organic

Synthesis of oxindoles *via* reductive CO₂ fixation†‡

Toru Amaya,*^a Izumi Kurata^a and Toshikazu Hirao*^{a,b}

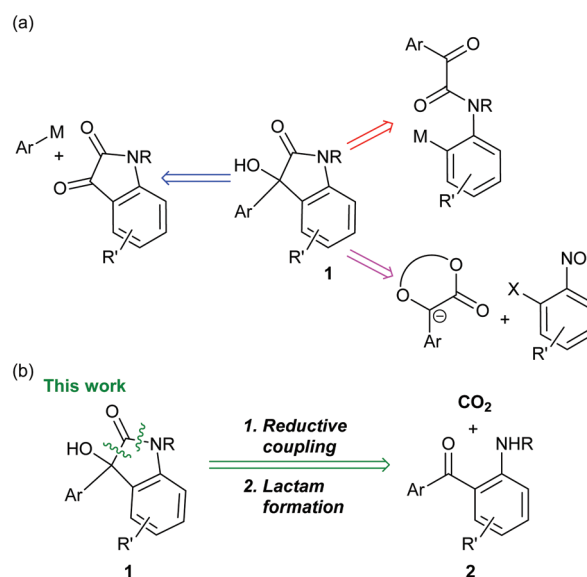
The synthesis of 3-aryl-3-hydroxy-2-oxindoles, which are a structural motif found in various natural products and pharmaceutically active compounds, was conducted *via* reductive coupling of (2-aminophenyl)(aryl)methanone derivatives and CO₂ as a key step. The conditions employing Mg with chlorotrimethylsilane 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 (CO₂) is considered to be one of the causative agents for global warming. Therefore, the effective utilization of CO₂ 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.¹

Oxindoles are a structural motif found in various natural products and medicinally relevant molecules.² 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-130686³ and ECi8.⁴ Scheme 1a shows the representative examples of the previously reported retrosynthesis for **1**. Most commonly, oxindoles **1** are synthesized *via* 1,2-addition of an aryl anion equivalent to an isatin derivative.⁵ Intramolecular arylation to a ketone is also reported.⁶ 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 CO₂ 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* CO₂ 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 metals¹⁰ 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

^aDepartment 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

^bThe Institute of Scientific and Industrial Research, Osaka University, Mihoga-oka, Ibaraki, Osaka 567-0047, Japan. E-mail: hirao@chem.eng.osaka-u.ac.jp

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

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

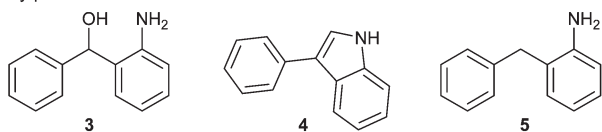


Table 1 Screening of an early-transition metal catalyst and a solvent for the synthesis of oxindole **1a** via reductive coupling of **2a** and CO₂ in the presence of Zn as a terminal reductant

Entry	Catalyst	Solvent	Yield ^a /%		
			Recovered 2a ^b	Oxindole 1a	Alcohol 3 ^b
1 ^{c,d}	TiCl ₄	DMF	65	0	n.d. ^e
2 ^c	TiCl ₄	THF	Complex mixture		
3 ^c	TiCl ₄	DME	Complex mixture		
4	Cp ₂ TiCl ₂	DMA	20	3	13
5	VCl ₃	DMA	23	9	19
6	VBr ₃	DMA	22	4	44
7	Cp ₂ VCl ₂	DMA	7	2	27
8	—	DMA	8	2	43

^a Yield was calculated by using the integral ratio of the peaks for each compound and the internal standard (1,3,5-trimethoxybenzene) in the ¹H NMR spectrum of the crude mixture. ^b 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 NaHCO₃ 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.

By-products



terminal reductant. First, Zn was used as a terminal reductant (Table 1). Ketoamine **2a** reacted with CO₂ (balloon) in the presence of TiCl₄ (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

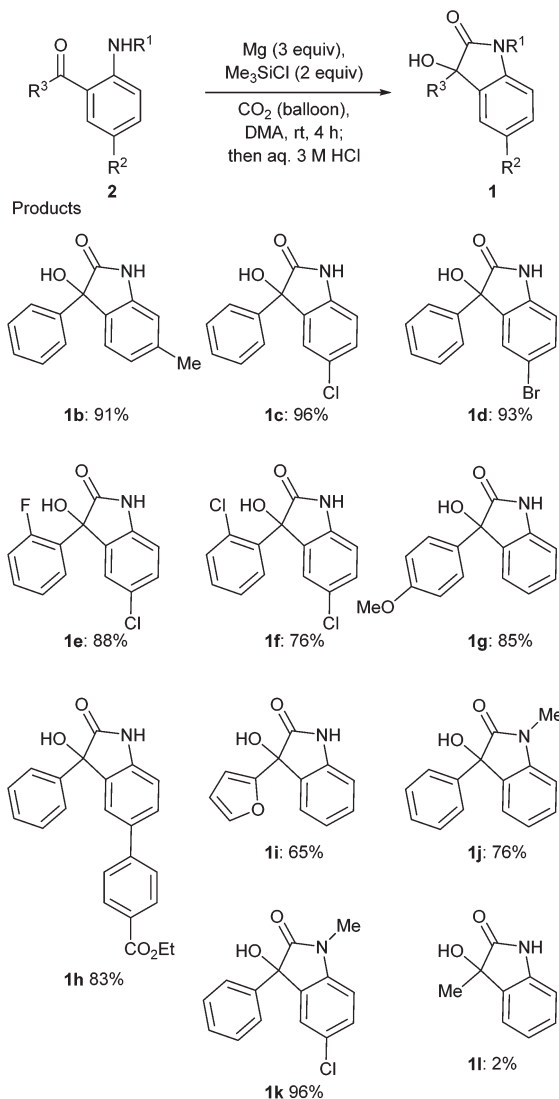
Catalyst (20 mol%), Mg (7 equiv), Me₃SiCl (2 equiv) 2a $\xrightarrow{\text{CO}_2 \text{ (balloon), DMA, rt, 4 h; then aq. 3 M HCl}}$ 1a + 3				
		Yield ^a /%		
Entry	Catalyst	Recovered 2a ^b	Oxindole 1a	Alcohol 3 ^b
1	TiCl ₄	— ^c	44	11
2	VCl ₃	0	51	5
3	Cp ₂ TiCl ₂	0	68	2
4	Cp ₂ VCl ₂	0	80	16
5	Yb(OTf) ₃	7	52	16
6	VBr ₃	0	52	21
7	—	0	95	5
8	— (1 equiv. of Me ₃ SiCl)	16	70	7
9	— (Without Me ₃ SiCl)	27	0	48
10	— (With collidine HCl salt) ^d	51	11	11
11	— (3 equiv. of Mg)	0	97 (99) ^e	Trace
12	— (1 equiv. of Mg)	19	74	— ^c

^a Yield was calculated by using the integral ratio of the peaks for each compound and internal standard (1,3,5-trimethoxybenzene) in the ¹H NMR spectrum of the crude mixture. ^b 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. ^d Instead of chlorotrimethylsilane. ^e Isolated yield (containing a very small amount of ethyl acetate, see the ESI for the ¹H NMR spectrum).

a catalyst in 95% yield (Table 2, entry 7).¹³ 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.¹² 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%).

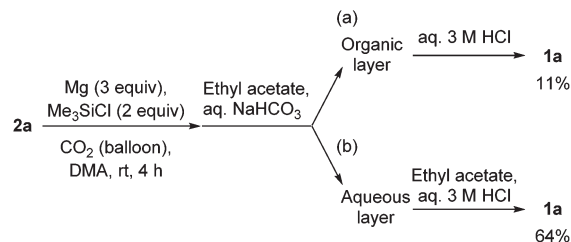




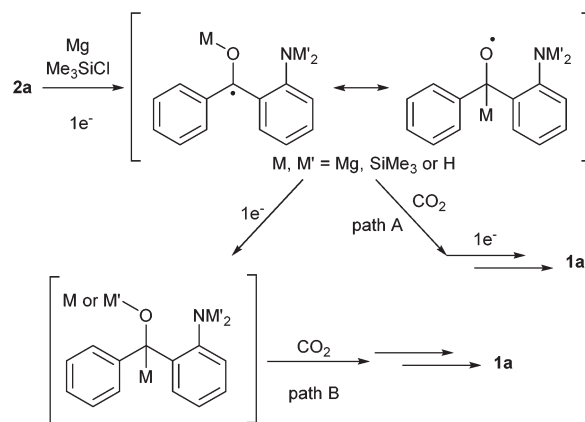
Scheme 2 Scope and limitation of the synthesis of oxindoles **1** via reductive coupling of **2** and CO₂.

To gain an insight into the reaction path, aqueous work-up with a basic solution (aqueous saturated NaHCO₃ 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 CO₂, there are two plausible paths (Scheme 4),¹³ (1) one-electron reduction of the ketone, addition of the resulting radical anion species to CO₂, 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 CO₂.



Scheme 4 Plausible paths for the synthesis of oxindoles **1a** via reductive coupling of **2a** and CO₂.

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 CO₂ 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 δ scale relative to a residual solvent (DMSO-*d*₆: δ = 2.50 for ¹H NMR and 39.52 ppm for ¹³C NMR) or tetramethylsilane (δ = 0 ppm).



for ^1H and ^{13}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**,¹⁶ **2i**¹⁷ and **2j**¹⁸ 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% $\text{Pd}(\text{PPh}_3)_4$ and aqueous Na_2CO_3 in toluene and ethanol at 80 °C overnight. Recrystallized **2h** (CH_2Cl_2 –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 CO_2 using a balloon by repeating evacuation and purge. Chlorotrimethylsilane (127 μL , 1.0 mmol, distilled over CaH_2 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 Na_2SO_4 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 ^1H 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 ^1H NMR data reported previously: **1a**,⁷ **1b**,^{5c} **1c**,¹⁹ **1g**,²⁰ **1j**^{6a} and **1k**.^{5c}

Isolation of 1a. To remove DMA completely, the aqueous work-up was modified. After the treatment with a 3 M aqueous HCl solution, 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 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 ^1H 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 ^1H NMR data are not reported previously

1d: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 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, $\text{DMSO}-d_6$) δ = 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) ν = 3369, 3199, 2358, 1704, 1473, 1182, 821, 737 cm^{-1} ; HRMS(FAB) m/z : $[M]^+$ calcd for $\text{C}_{14}\text{H}_{10}\text{BrNO}_2$: 302.9895; found: 302.9889.

1e: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 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; ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ = 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) ν = 3410, 3237, 2367, 2328, 1713, 1485, 1049, 823, 755 cm^{-1} ; HRMS(FAB) m/z : $[M]^+$ calcd for $\text{C}_{14}\text{H}_9\text{ClFNO}_2$: 277.0306; found: 277.0308.

1f: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 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; ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ = 176.45, 142.21, 137.89, 133.54, 130.28, 129.72 $\times$ 2, 129.29, 129.02, 126.89, 125.51, 123.82, 111.19, 76.07 ppm; IR(ATR) ν = 3420, 3237, 2361, 2342, 1711, 1483, 1470, 1437, 1036, 826, 746, 732 cm^{-1} ; HRMS(FAB) m/z : $[M]^+$ calcd for $\text{C}_{14}\text{H}_9\text{Cl}_2\text{NO}_2$: 293.0010; found: 293.0008.

1h: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 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; ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ = 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) ν = 3308, 3061, 2980, 2933, 1728, 1713, 1606, 1484, 1278, 1175, 1103, 771 cm^{-1} ; HRMS(EI) m/z : $[M]^+$ calcd for $\text{C}_{23}\text{H}_{19}\text{NO}_4$: 373.1314; found: 373.1310.

1i: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 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; ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ = 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) ν = 3310, 2822, 2361, 1709, 1684, 1624, 1474, 1311, 1112, 763 cm^{-1} ; HRMS(EI) m/z : $[M]^+$ calcd for $\text{C}_{12}\text{H}_9\text{NO}_3$: 215.0582; found: 215.0583.

2h: ^1H NMR (400 MHz, CDCl_3) δ = 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_3) δ = 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) ν = 3487, 3352, 3066,



2986, 2902, 1704, 1639, 1729, 1247, 1107, 775 cm^{-1} ; HRMS(EI) m/z : $[M]^+$ calcd for $\text{C}_{22}\text{H}_{19}\text{NO}_3$: 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.
- (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.
- 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.
- 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.
- 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.
- 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. Häußermann, F. Rominger and B. F. Straub, *Chem. – Eur. J.*, 2012, **18**, 14174.
- (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.
- (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.
- (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.
- To check the possibility of intramolecular reductive coupling of trimethylsilyl arylcarbamate of **2a**, an NMR experiment in $\text{DMSO}-d_6$ 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.
- Related conditions are reported for the reductive coupling of imines and CO_2 : 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.
- (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.
- V.-H. Nguyen, L. Vendier, M. Etienne, E. Despagne-Ayoub, P.-A. R. Breuil, L. Magna, D. Proriot, 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.
- J. Gui, G. Chen, P. Cao and J. Liao, *Tetrahedron: Asymmetry*, 2012, **23**, 554.
- Z.-K. Xiao, H.-Y. Yin and L.-X. Shao, *Org. Lett.*, 2013, **15**, 1254.

