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Synthesis of Arylglycines from CO_2 through α-Amino Organomanganese Species

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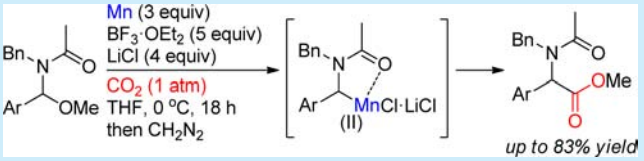
Supporting Information

ABSTRACT: In the presence of three readily available chemicals, Mn powder, $BF_3{\cdot}OEt_2$, and LiCl, *N*-acyl-*N*,*O*-acetals were successfully converted into the corresponding α-amino acids (arylglycine derivatives) under 1 atm of a CO_2 atmosphere in high yields. The LiCl additive is necessary in order to increase the solubility and the nucleophilicity of an organomanganese intermediate. The products thus obtained were transformed into free α-amino acids in two steps.



Carbon dioxide is an ideal carbon feedstock for organic synthesis due to its abundance, low cost, and low toxicity. The reaction of carbon nucleophiles with CO_2 is one of the most efficient approaches to afford carboxylic acids and their derivatives.[1] Among the various approaches, α-amino acid synthesis through CO_2 incorporation under mild conditions is especially attractive since α-amino acids have broad applications in both biochemistry and organic chemistry.[2] Early examples of the synthesis of α-amino acids using CO_2 were mostly represented by the carboxylation of α-amino organolithium compounds[2g,3,4] and electrochemically promoted insertion of CO_2 into the C═N bond.[5] In 2011, we reported a one-pot synthesis of *N*-Boc-α-amino acids from *N*-Boc-α-amido sulfones by using a combination of TMS−$SnBu_3$ and CsF under CO_2 pressure (Scheme 1, eq 1).[6] It was an alternative method for Strecker amino acid synthesis from imine equivalents, but a toxic tin reagent was utilized.[7,8] Further investigation revealed that the use of less toxic $PhMe_2Si$−Bpin in combination with a catalytic amount of *p*-TsOH·H_2O could mediate the one-pot carboxylation more efficiently (Scheme 1, eq 1).[9] These processes avoided the use of strongly basic organolithium reagents, which are often incompatible for many functional groups; however, bismetal reagents, which are relatively expensive and not so easily prepared, are necessary. Recently, SmI_2 was reported to promote the reductive coupling of nitrones with CO_2 to afford α-amino acids.[10] In addition, direct reductive carboxylation of aromatic imines with CO_2 could also be realized by using Mg turnings.[11] These two transformations utilized commercially available and relatively inexpensive reagents; however, high CO_2 pressure (45−50 atm) is necessary, thus limiting their applicability to organic synthesis.

With these precedents in mind, we envisioned a new strategy for α-amino acid synthesis using *N*-acyl-*N*,*O*-acetals,[12] which are easily prepared from the corresponding aldehydes or acetals (Scheme 1, eq 2).[12e,13] These *N*,*O*-acetals would be converted into iminium species in the presence of a Lewis acid. The following reduction of the resulting iminium species by a zerovalent metal would occur to produce α-amino metals,[12b−e] which would undergo carboxylation with CO_2 followed by protonation to afford the target amino acids. We report herein a new protocol to synthesize α-amino acids based on the above strategy using commercially available and inexpensive reagents under mild reaction conditions (1 atm of CO_2).

Scheme 1. α-Amino Acid Synthesis from CO_2

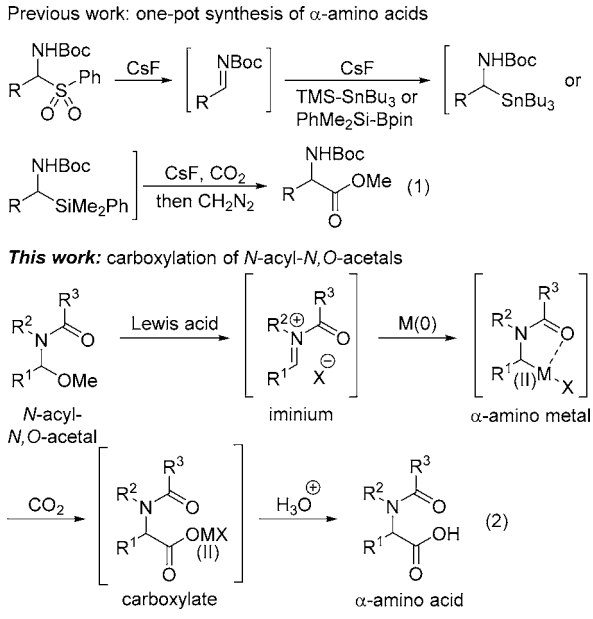


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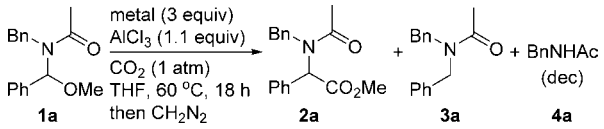
Table 1. Investigation of Several Zero-Valent Metals



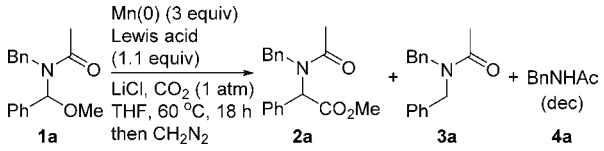
		yield (%)[a]		
entry	metal	2a	3a	4a
1	Mg	<1	9	44
2	Mn	24	19	16
3	Zn	2	22	22
4	Fe	–	–	35
5	Cu	–	–	45

[a]Yields were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

(for the determination of yields by ^{1}H NMR analysis and the ease of further purification), the desired methyl carboxylate **2a** was obtained together with the protonated compound **3a** and a decomposed product **4a**. Several basic metals including Mg, Mn, Zn, Fe, and Cu were examined under these conditions (entries 1−5). As a result, **2a** was reasonably produced in 24% yield only when Mn[14] was used (entry 2).

We next tested Lewis acids, including $AlCl_3$, $AlEtCl_2$, $Al(O^iPr)_3$, $Ti(O^iPr)_4$, $Sc(OTf)_3$, and $BF_3{\cdot}OEt_2$, in the presence of Mn metal (Table 2), and we found that only the use of $AlCl_3$

Table 2. Screening of Lewis Acids with/without LiCl



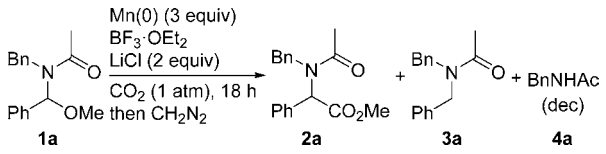
			yield (%)[a]		
entry	Lewis acid	LiCl (equiv)	2a	3a	4a
1	$AlCl_3$	–	24	19	16
2	$AlEtCl_2$	–	2	8	23
3	$Al(O^iPr)_3$	–	–	–	83
4	$Ti(O^iPr)_4$	–	–	–	73
5	$Sc(OTf)_3$	–	–	–	45
6	$BF_3{\cdot}OEt_2$	–	–	–	46
7	$AlCl_3$	2	13	15	51
8	$Ti(O^iPr)_4$	2	–	–	72
9	$BF_3{\cdot}OEt_2$	2	31	6	27

[a]Yields were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

and $AlEtCl_2$ afforded the desired product **2a** (entries 1 and 2). In order to improve the yield, we employed LiCl as an additive since it plays a crucial role in several transformations mediated by Mg, Mn, Zn, and In (vide infra).[15,16] The use of $AlCl_3$ together with LiCl decreased the yield to 13% probably because $AlCl_3$ reacted with LiCl to generate an aluminum ate complex, leading to a decrease in the Lewis acidity of $AlCl_3$ (entry 7). Although the combined use of $Ti(O^iPr)_4$ and LiCl did not afford the desired product (entry 8), a combination of $BF_3{\cdot}OEt_2$ and LiCl actually promoted the reaction moderately and the desired product **2a** was obtained in 31% yield (entry 9), whereas **2a** was not obtained at all without LiCl (entry 6).

Next, several solvents were investigated in the presence of Mn, $BF_3{\cdot}OEt_2$, and LiCl (Table 3, entries 1−5), and the highest

Table 3. Investigation of Solvents, Temperatures, and Reagent Stoichiometry



				yield (%)[a]		
entry	$BF_3{\cdot}OEt_2$ (equiv)	solvent	temp (°C)	2a	3a	4a
1	1.1	DMF	60	26	–	58
2	1.1	CH_3CN	60	2	7	16
3	1.1	1,4-dioxane	60	3	12	28
4	1.1	DME	60	26	10	19
5	1.1	THF	60	31	6	27
6	3	THF	60	48	10	4
7	3	THF	rt	58	10	–
8	3	THF	0	67	8	7
9	3	THF	−10	45	7	22
10[b]	5	THF	0	82 (80)	16	–

[a]Yields were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. The value in parentheses represents the yield of the isolated product. [b]4 equiv of LiCl were added.

yield was observed in THF (entry 5). The yield of **2a** slightly increased to 48% by using 3 equiv of $BF_3{\cdot}OEt_2$ (entry 6). A screening of reaction temperatures (entries 6−9) revealed that **2a** was obtained in 67% yield when the reaction was carried out at 0 °C (entry 8). Eventually, by using 5 equiv of $BF_3{\cdot}OEt_2$ and 4 equiv of LiCl, the highest yield (82%) was achieved (entry 10). It should be noted that this carboxylation requires Mn, $BF_3{\cdot}OEt_2$, and LiCl. Without any one of those, **2a** was not obtained at all.

With the optimal conditions in hand, we explored the scope of this carboxylation (Figure 1). Several *N*-acyl-*N*,*O*-acetals possessing electron-rich arenes (**1a**−**1d**) underwent carboxylation smoothly to afford the corresponding arylglycine derivatives in up to 80% yield. Among them, moderate reactivity was observed for **1d**, probably because the relatively strong electron-donating effect of the methyl group on the *para*-position impeded reduction of iminium species by Mn(0). As for the electron-deficient arenes, regardless of the location of the substituents at the *para*- (**1e**−**1g**) or *meta*-position (**1h**−**1j**), the products were obtained in moderate to good yields. The tolerance of the halides offered an opportunity for further transformations, such as a transition-metal-catalyzed cross-coupling reaction. Naphthalene substrates (**1k**−**1l**) could also be carboxylated efficiently. Furthermore, substrates with different protecting groups on the nitrogen atom, including propionyl (**1m**), *para*-methoxybenzyl (PMB) (**1n**), allyl (**1o**), and propyl groups (**1p**), were examined. Gratifyingly, regardless of the structure of the protecting group, the reactions proceeded smoothly, showing a high compatibility of *N*-substitutions of *N*-acyl-*N*,*O*-acetals. Unfortunately, *α*-alkenyl and *α*-alkyl *N*-acyl-*N*,*O*-acetals were not active in this carboxylation.

Considering the synthetic utility of the products, removal of the protecting groups on the nitrogen atom of **2n** was performed (Scheme 2). The *N*-PMB group was oxidatively removed by cerium ammonium nitrate to give **5n** in 73% yield.[17] The resulting monoprotected **5n** was heated at 100 °C

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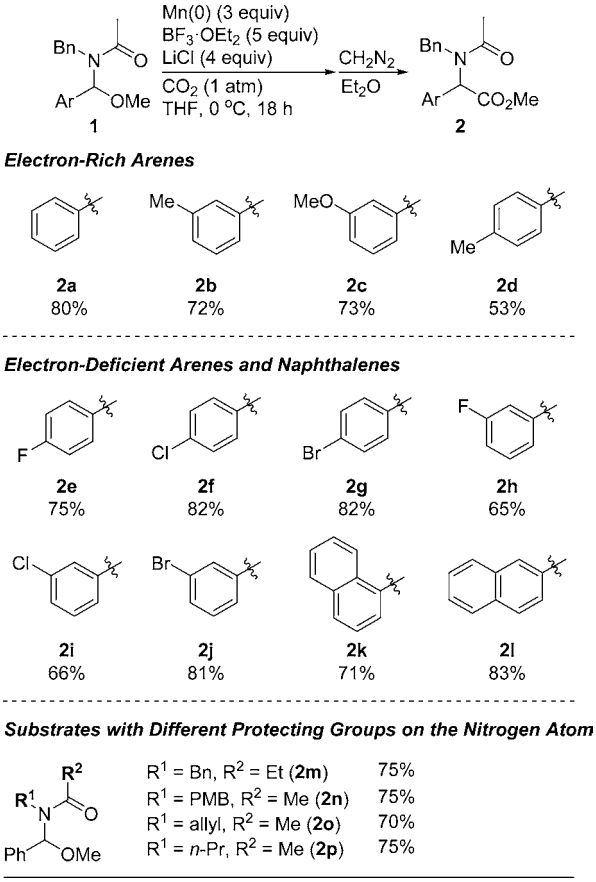
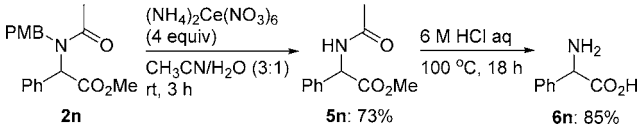


Figure 1. Substrate scope and limitations. Isolated yields are shown. PMB = *para*-methoxybenzyl.

Scheme 2. Removal of the Protecting Group



in 6 M HCl aqueous solution for 18 h.[18] After ion-exchange column chromatography, phenylglycine (**6n**) was obtained in 85% yield as white solids.[19]

A preliminary reaction mechanism of this carboxylation is proposed (Figure 2). Iminium formation from *N*-acyl-*N*,*O*-acetal is initiated by BF_3.[12a,b,f] The resulting iminium species is then reduced by way of single-electron transfer, which is analogous to Mg-mediated reductive carboxyaltion.[11] The first electron transfer would occur to generate an α-aminobenzyl radical, followed by the second electron transfer to afford an RMnCl·LiCl compelx[15f] in the presence of an excess amount of LiCl. It is thought that LiCl can rapidly remove the formed α-amino organomanganese species from the metal surface by generating a highly soluble RMnCl·LiCl complex,[15] thus allowing further carboxylation to proceed immediately and thereby avoiding competitive deactivation of the active metal sites. Furthermore, by forming this RMnCl·LiCl complex, the nucleophilicity of the organomanganese intermediate might be enhanced.[16] As a result, carboxylation with CO_2 would proceed smoothly to give manganese carboxylate.[20] Finally, the acid workup affords the desired α-amino acid.

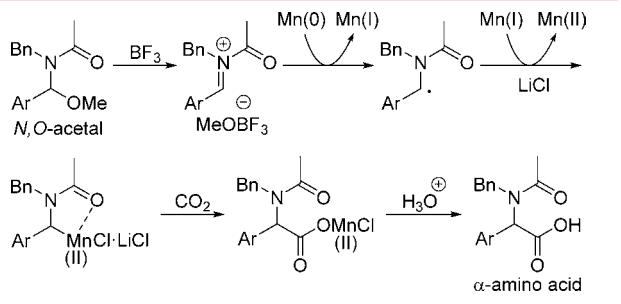


Figure 2. Proposed reaction mechanism.

In summary, we have developed an efficient protocol for the conversion of *N*-acyl-*N*,*O*-acetals to arylglycine derivatives through CO_2 incorporation. The reagents used, Mn powder, BF_3·OEt_2, and LiCl, are commercially available and inexpensive. LiCl is thought to promote generation of the organomanganese intermediate and enhance its nucleophilicity toward CO_2 by forming an RMnCl·LiCl complex. Compared to the previous examples, 1 atm of a CO_2 atmosphere is sufficient in this carboxylation. Studies toward an enantioselective variant of this transformation are now ongoing.

■ ASSOCIATED CONTENT

Supporting Information

Details of experimental procedures and physical properties of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) Mn powder (99.99%) was purchased from Sigma-Aldrich and used directly without preactivation. The use of Mn powder (98%) purchased from Wako Pure Chemical Industries gave a similar yield of **2a** under the optimal conditions (84% NMR yield). For the use of Mn power for carboxylation, see: (a) Fujihara, T.; Nogi, K.; Xu, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* **2012**, *134*, 9106. (b) Correa, A.; León, T.; Martin, R. *J. Am. Chem. Soc.* **2014**, *136*, 1062.

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