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Communication

# Ni-Catalyzed Carboxylation of Aziridines en Route to β-Amino Acids

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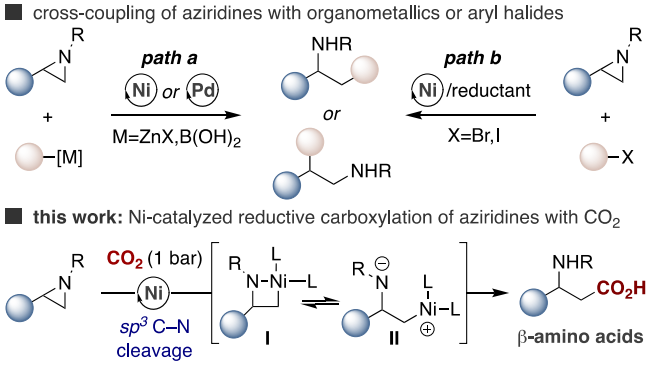
**ABSTRACT:** A Ni-catalyzed reductive carboxylation of *N*-substituted aziridines with $CO_2$ at atmospheric pressure is disclosed. The protocol is characterized by its mild conditions, experimental ease, and exquisite chemo- and regioselectivity pattern, thus unlocking a new catalytic blueprint to access β-amino acids, important building blocks with considerable potential as peptidomimetics.



Catalytic reductive carboxylation techniques of organic (pseudo)halides with carbon dioxide ($CO_2$) have become a valuable tool for our synthetic arsenal in the construction of carboxylic acids,[1] privileged motifs in a myriad of biologically relevant molecules.[2] Despite the advances realized,[1] chemists are still challenged to design alternative catalytic carboxylation techniques that might offer improved versatility and flexibility in synthetic design while streamlining the preparation of valuable, yet *a priori* inaccessible building blocks.

Prompted by the seminal studies of Hillhouse and Wolfe,[3] chemists have recently exploited the ability of enabling catalytic arylation/alkylation reactions of readily accessible aziridines with stoichiometric organometallics,[4] *ortho*-directed C−H functionalizations,[5] or reductive pathways[6] via $sp^3$ C−N cleavage (Scheme 1, *top*).[7] Unfortunately, the utilization of

**Scheme 1. Catalytic Cross-Coupling of Aziridines**




counterparts other than aryl moieties remains an elusive endeavor in reductive coupling events, yet has potential to open up a broad range of novel transformations while streamlining the synthesis of valuable β-functionalized amines. As part of our interest in carboxylation reactions,[8] we wondered whether we could design a new catalytic protocol for incorporating $CO_2$ into aziridines in a site-selective manner via **I**/**II** (Scheme 1, *bottom*). If successful, we anticipated that such a scenario would be a worthwhile endeavor for chemical invention, as it might offer (a) a conceptually new entry to β-amino acids—molecules displaying important biological activities with potential as peptidomimetics[9]—without requiring hazardous diazo compounds,[10] cyanide sources,[11] or carbon monoxide[7,12] and (b) an unrecognized opportunity to expand the catalytic carboxylation portfolio of C−N electrophiles beyond activated benzyl quaternary ammonium salts.[13] Herein, we report the successful realization of this goal. This protocol is characterized by its mild conditions, broad scope, and excellent chemo- and regioselectivity for a wide number of aziridines without recourse to organometallic reagents.

We began our studies by employing **1a** as the model substrate (Table 1). Interestingly, not even traces of **2a** were observed under conditions previously developed for other catalytic carboxylation reactions of organic (pseudo)halides,[1,8] thus contributing to the perception that the catalytic carboxylation of aziridines might not be particularly straightforward. We hypothesized that (a) hindered ligands might favor ring-opening of **I** to zwitterionic **II** and (b) the stability of **II** might be improved by interaction with a suitable additive. After extensive optimization,[14] we found that the purity of **1a**,[15] the inclusion of MeOH, and a subtle balance of electronic/steric effects at the ligand backbone was critical for suppressing undesirable side reactions while improving the efficiency of the process. Finally, we found that the combination of $NiCl_2$·glyme (10 mol %), **L1** (20 mol %), and MeOH (5 equiv) in DMPU (0.40 M) with Mn powder (3 equiv) as reductant under 1 bar $CO_2$ delivered **2a** in 73% yield (Table 1, entry 1). Under the limits of detection, no cyclic carbamates arising from $CO_2$ incorporation at the *N*-tosyl amide[16] were found in the crude mixtures. As shown in entries 2−7, subtle differences on the Ni/**L1** ratio or the employment of ligands or precatalysts other than $NiCl_2$·glyme/**L1** resulted in lower yields of **2a**. Likewise, the nature of the solvent,

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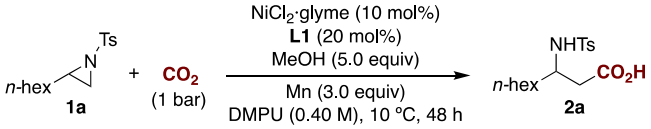
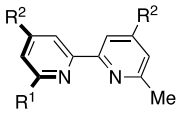
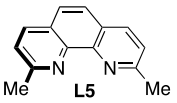
**Table 1. Optimization of the Reaction Conditions**[a]




| entry | deviation standard conditions | 2a (%)[b] |
|---|---|---|
| 1 | none | 73 |
| 2 | using $NiCl_2$**L1** as precatalyst | 50 |
| 3 | using **L1** (15 mol%) | 61 |
| 4 | using **L2** instead of **L1** | 47 |
| 5 | using **L3** instead of **L1** | 0 |
| 6 | using **L4** instead of **L1** | trace |
| 7 | using **L5** instead of **L1** | 56 |
| 8 | DMA as solvent | 62 |
| 9 | NMP as solvent | 67 |
| 10 | reaction conducted at rt | 53 |
| 11 | reaction time 72h | 76 (71)[c] |
| 12 | 72h, $CO_2$ (2.5 bar) | 65 |
| 13 | no $NiCl_2$·glyme, **L1** or MeOH | 0 |




$R^1$=Me; $R^2$=OMe (**L1**)
$R^1$=Me; $R^2$=*t*-Bu (**L2**)
$R^1$=Me; $R^2$=Me (**L3**)
$R^1$=H; $R^2$=OMe (**L4**)

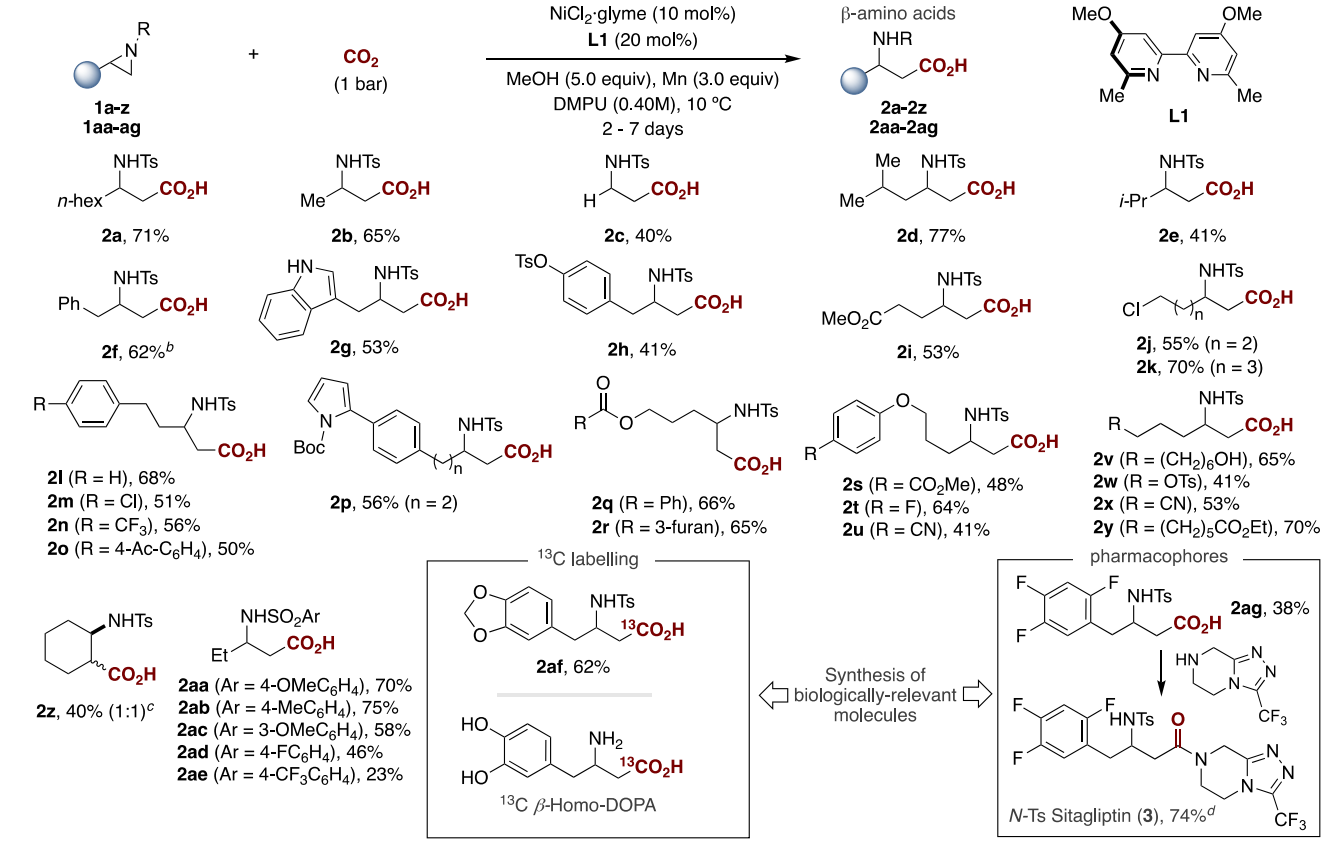



[a]**1a** (0.20 mmol), $NiCl_2$·glyme (10 mol %), **L1** (20 mol %), Mn (0.60 mmol). MeOH (1 mmol), $CO_2$ (1 bar), DMPU (0.50 mL) at 10 °C for 48 h. [b]$^1$H NMR yields using trimethoxybenzene as internal standard. [c]Isolated yield.

temperature, and $CO_2$ pressure had a non-negligible impact on reactivity (entries 8−10 and 12) whereas a slight improvement in yield was found after a 72 h reaction time (entry 11). Rigorous control experiments confirmed that all of the reaction parameters were critical for success (entry 13).

With the optimized reaction conditions in hand, we proceeded to investigate the generality of our protocol. A particular focus was the ability to generate *β*-derivatives of naturally occurring amino acids (Table 2). Although some compounds were obtained in moderate yields, these results should be interpreted against the challenge that is addressed, providing a complementary approach to an elegant solution recently disclosed by Skrydstrup using stoichiometric Ni-metallacycles and CO.[12] As shown, *β*-alanine derivative **2c** was obtained in moderate yields whereas the inclusion of substituents at the aziridine backbone delivered the corresponding *β*-homoalanine (**2b**), *β*-homoleucine (**2d**), *β*-homophenylalanine (**2f**), *β*-homotryptophan (**2g**), *β*-homoglutamate methyl ester (**2i**), or *β*-homotyrosine (**2h**) derivatives in good yields. Note, however, that more hindered substrate combinations proved challenging, with *β*-leucine being obtained in moderate yield (**2e**). As evident from the results illustrated in Table 2, our protocol tolerated the presence of a variety of functional groups, including esters (**2i**, **2q**, **2r**, **2s**, **2y**), ketones (**2o**), and nitriles (**2u**, **2x**). Notably, the presence of nitrogen- or oxygen-containing heterocycles did not interfere with productive carboxylation of the aziridine backbone (**2g**, **2p**, **2r**). Even primary alcohols did not compete with the efficacy of the reaction (**2v**). While aryl tosylates (**2h**), chlorides (**2m**), and alkyl halides (**2j**, **2k**) or sulfonates (**2w**) are inherently disposed to Ni-catalyzed carboxylation reac-

**Table 2. Ni-Catalyzed Carboxylation of Aziridines**[a]




[a]As Table 1 (entry 1); isolated yields, average of at least two independent runs. [b]1 mmol scale. [c]10 day reaction time. [d]**2ag** (0.07 mmol), tetrahydropyrazine (1.10 equiv), EDC·HCl (2 equiv), DMAP (4 equiv), $CH_2Cl_2$, rt.



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tions,[17] $CO_2$ insertion occurred exclusively at the aziridine backbone, thus providing a handle for further functionalization via conventional cross-coupling reactions.[18] Interestingly, our protocol could be implemented with 2,3-disubstituted aziridines, albeit in low yields and diastereoselectivities (**2z**). As shown for **2aa**−**2ae**, sulfonyl groups other than the tosyl moiety could be utilized, with electron-rich aromatics providing the best results. Unfortunately, 2-aryl aziridines were not compatible reaction partners.[19] Importantly, our protocol could be easily implemented with $^{13}CO_2$ (**2af**), thus providing a useful entry point to $^{13}$C-labeled $\beta$-homo-DOPA after a single deprotection step. Moreover, **2ag** was easily within reach, representing a useful strategy en route to Sitagliptin. Figure 1 further illustrates the potential applicability

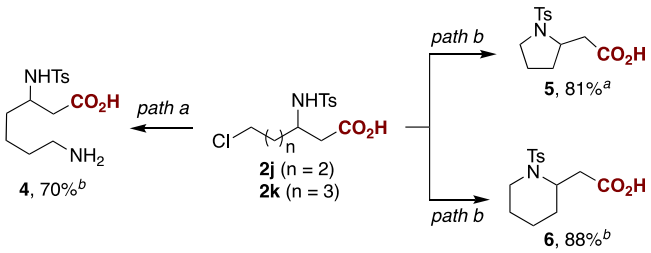
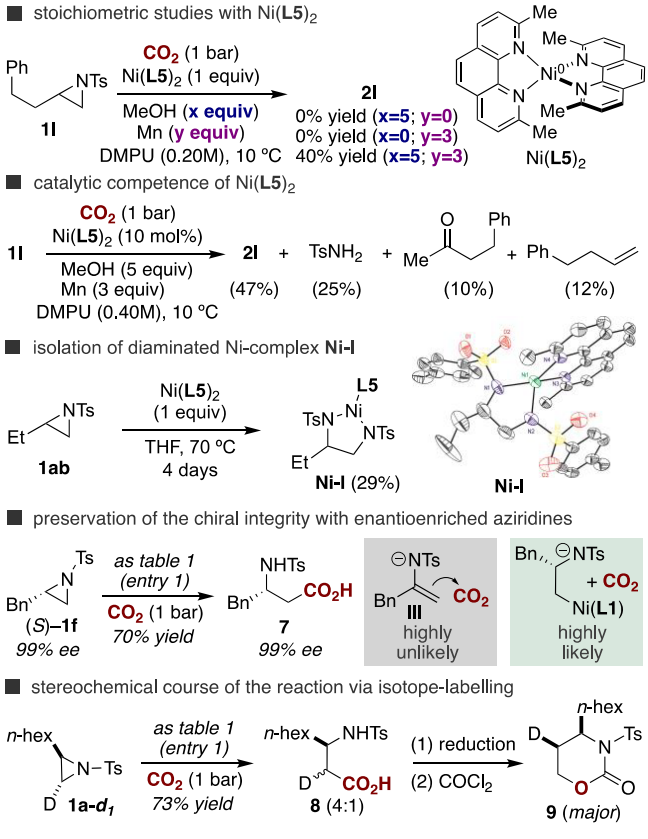



**Figure 1.** Derivatization en route to other $\beta$-amino acids. Conditions: (*path a*) $NH_4OH$ (20 equiv), reflux; (*path b*) NaH (2.2 equiv), DMF, rt. [a] Using **2j**. [b] Using **2k**.

of our Ni-catalyzed carboxylation of aziridines. Specifically, **2j** and **2k** could be used as formal linchpins en route to $\beta$-homolysine (**4**), $\beta$-homoproline (**5**) and piperidin-2-yl-acetic acid (**6**) in a single-step operation.

Next, we turned our attention to studying the mechanistic intricacies of our reaction. While azanickelacyclobutanes of type **I** (Scheme 1) can *a priori* be prepared by exposing low valent Ni complexes to aziridines,[3a,12] this unfortunately was not the case with sterically encumbered **L5** possessing substituents adjacent to the nitrogen motif.[20] Prompted by this observation, experiments were undertaken with Ni(**L5**)$_2$, as this complex was found to be catalytically competent as an intermediate en route to **2l** (Scheme 2).[21] Interestingly, carboxylation of **1l** with Ni(**L5**)$_2$ (1 equiv) could only be conducted in the presence of both MeOH and Mn,[22] thus suggesting the intervention of Ni(I) species within the catalytic cycle (Scheme 2, *top*).[23] While the enigmatic role of MeOH still remains to be elucidated, we tentatively believe that it might promote and/or stabilize intermediates of type **II**. Careful examination of the crude mixtures en route to **2l** revealed the formation of $TsNH_2$, 4-phenylbutan-2-one, and 4-phenyl-1-butene, thus suggesting $\beta$-hydride and/or deamination pathways of alkyl nickel complexes. The latter was indirectly corroborated by the isolation of rather intriguing diazanickelacyclopentene (**Ni-I**) upon subjecting **1ab** to Ni(**L5**)$_2$ (Scheme 2, *middle*),[14,24] the identity of which could be univocally assigned by X-ray diffraction.[14] While one might argue that these results suggest that our carboxylation event might occur via nucleophilic addition of in situ generated metalla-enamines **III** onto $CO_2$ (Scheme 2), the ability to convert enantiopure (*S*)-**1f** into **7** with preservation of the chiral integrity at the $sp^3$ C−N site argues against such a scenario.[25] This result is particularly interesting, as it offers an opportunity to exploit the applicability of enantioenriched aziridines that can be easily accessed from readily available

**Scheme 2. Preliminary Mechanistic Studies**




precursors[26] and an alternative to the classical Arndt−Eistert homologation.[10]

Next, we turned our attention to studying the stereochemical course of the reaction. As shown in Scheme 2 (*bottom*), we found that the carboxylation of *trans* **1a**-$d_1$ followed by reduction and a cyclization event resulted in **9** with a 4:1 *cis*/*trans* ratio. While the identity of the major product might be explained via an $S_N2$ type insertion of Ni(0) into the aziridine backbone, the presence of the *trans* isomer, together with the lack of diastereocontrol in **2z** (Table 2), suggests that other conceivable pathways might come into play. Whether these results indicate the participation of single-electron transfer processes or recombination events via radical intermediates is the subject of ongoing investigations.[27−29]

In summary, we have developed a mild and selective catalytic protocol to access valuable $\beta$-amino acid building blocks from readily accessible aziridines. The salient features of this technique are the experimental ease and wide substrate scope, thus broadening the generality of Ni-catalyzed carboxylations beyond activated $sp^3$ nitrogen electrophiles. Notably, the addition of MeOH, Mn as reductant, and the ligand backbone were critical for success.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c01916.

Experimental procedures, spectral and crystallographic data (PDF)



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### Accession Codes

CCDC 2049249−2049250 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Author Contributions

‖D.J.M. and D.P.Z. contributed equally to this work.


### Notes

The authors declare no competing financial interest.

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(19) The utilization of these coupling partners resulted in competing β-hydride elimination products. This outcome has already been observed in related carboxylations at activated positions: (a) Correa, A.; Leon, T.; Martin, R. Ni-Catalyzed Carboxylation of $C(sp^2)$− and $C(sp^3)$−O Bonds with $CO_2$. *J. Am. Chem. Soc.* **2014**, *136*, 1062. (b) Leon, T.; Correa, A.; Martin, R. Ni-Catalyzed Direct Carboxylation of Benzyl Halides with $CO_2$. *J. Am. Chem. Soc.* **2013**, *135*, 1221. (c) Ishida, N.; Masuda, Y.; Imamura, Y.; Yamazaki, K.; Murakami, M. Carboxylation of Benzylic and Aliphatic C−H Bonds with $CO_2$ Induced by Light/Ketone/Nickel. *J. Am. Chem. Soc.* **2019**, *141*, 19611.

(20) All our attempts to prepare azanickelacyclobutanes by exposure of $(\mathbf{L5})_2Ni(0)$ to aziridines were unsuccessful. However, qualitative data could be gathered by MALDI-MS, allowing identification of the presence of **I** with **L5**. For more details, see Supporting Information.

(21) We chose **L5** for our stoichiometric studies due to its catalytic competence (Table 1, entry 7) and the ease at which $(\mathbf{L5})_2Ni(0)$ can be accessed in large quantities. For direct comparison, aziridine **1l** gave **2l** (48%) after a 3 day reaction with **L5** (20 mol%) instead of **L1**.

(22) While **2l** was not observed with Mn in the presence of MeOH, substantial amounts of an aliphatic carbonate were formed instead. Its formation likely arises from a nucleophilic attack of MeOH to a cyclic carbamate intermediate; see: Tascedda, P.; Duñach, E. Electrosynthesis of cyclic carbamates from aziridines and carbon dioxide. *Chem. Commun.* **2000**, 449. For more details, see Supporting information.

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(24) Intriguingly, a second nickel complex was isolated from stoichiometric reactions between **1ab** and $Ni(\mathbf{L5})_2$ in which C−H functionalization onto **L5** took place (**Ni-II**). Although tentative, this complex might arise via β-hydride elimination pathways. See Supporting Information for details.

(25) The preservation of chiral integrity in enantioenriched aziridines is not particularly common in Ni-catalyzed reactions. For a remarkable exception, see ref 6b.

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(27) The high reduction potential of **1ab** ($E_p^{red}$ = − 2.4 V vs Ag/AgCl in MeCN) argues against the possibility of an outer sphere type single-electron transfer from $Ni(0)\mathbf{L}_n$ to the aziridine backbone.

(28) Intriguingly, the utilization of homogeneous reductants such as DMAP-OED or $Cp^*_2Co$ resulted in no conversion of **1l** to **2l**. See: (a) Murphy, J. A.; Garnier, J.; Park, S. R.; Schoenebeck, F.; Zhou, S.-z.; Turner, A. T. Super-Electron Donors: Bis-pyridinylidene Formation by Base Treatment of Pyridinium Salts. *Org. Lett.* **2008**, *10*, 1227. (b) Charboneau, D. J.; Brudvig, G. B.; Hazari, N.; Lant, H. M. C.; Saydjari, A. K. Development of an Improved System for the Carboxylation of Aryl Halides through Mechanistic Studies. *ACS Catal.* **2019**, *9*, 3228. Instead, we obtained substantial amounts of an



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aliphatic carbonate that likely arises from a nucleophilic attack of MeOH to a cyclic carbamate intermediate. See Supporting Information for details.

(29) For a mechanistic hypothesis, see the Supporting Information.



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