



Title	Boron-Catalyzed alpha-Amination of Carboxylic Acids
Author(s)	Morisawa, Takuto; Sawamura, Masaya; Shimizu, Yohei
Citation	Organic letters, 21(18), 7466-7469 https://doi.org/10.1021/acs.orglett.9b02769
Issue Date	2019-09-20
Doc URL	https://hdl.handle.net/2115/79227
Rights	This document is the Accepted Manuscript version of a Published Work that appeared in final form in Organic Letters, copyright c American Chemical Society after peer review and technical editing by the publisher. To access the final edited and published work see https://doi.org/10.1021/acs.orglett.9b02769 .
Type	journal article
File Information	Morisawa_OL_revise_final.pdf



Boron-Catalyzed α -Amination of Carboxylic Acids

Takuto Morisawa,[‡] Masaya Sawamura,^{*,†,‡} and Yohei Shimizu^{*,†,‡}

[†]) Institute for Chemical Reaction Design and Discovery (WPI-ICReDD), Hokkaido University, Kita 21 Nishi 10, Kita-ku, Sapporo, Hokkaido 001-0021, Japan

[‡]) Department of Chemistry, Faculty of Science, Hokkaido University, Kita 10 Nishi 8, Kita-ku, Sapporo, Hokkaido 060-0810, Japan

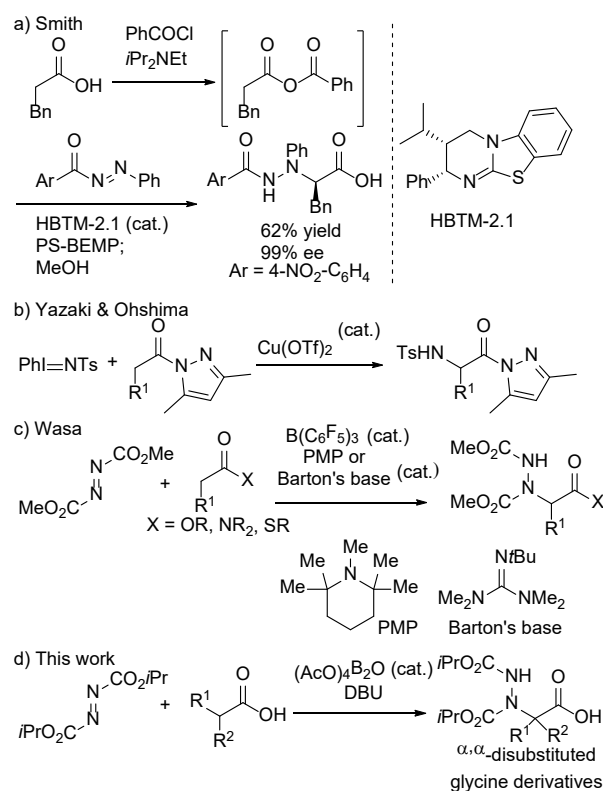
Supporting Information Placeholder



ABSTRACT: A boron-catalyzed α -amination of simple carboxylic acids was developed. Catalytically generated boron enolates of carboxylic acids reacted with an electrophilic aminating reagent, diisopropylazodicarboxylate, to provide amino acid derivatives. The catalysis afforded not only α -mono-substituted glycine derivatives but also α,α -disubstituted derivatives. The resulting α -aminocarboxylic acid was easily converted to carboxylic acid derivatives. Extension to a catalytic asymmetric variant was possible by introducing a chiral ligand on the boron catalyst.

α -Amino acids are attractive synthetic targets due to their versatile applicability as building blocks of biologically active molecules and functional molecules. One of the most efficient and straightforward synthetic methods to construct α -amino acids is the catalytic α -amination¹ of readily available carboxylic acids. However, this method is less developed compared to those with other carbonyl congeners, e.g., aldehydes,² ketones,³ 1,3-dicarbonyl compounds,⁴ and oxyindoles.⁵ The high pK_a value of the α -proton of carboxylic acid derivatives causes the major hurdle to realize the catalytic reaction. Pre-formation of active surrogates, such as ketenesilylacetals⁶ or α -bromoesters,⁷ is an alternative approach toward the α -amination of carboxylic acid derivatives. However, the direct catalytic α -amination via deprotonation of the α -proton has been limited to α -arylacetic acid derivatives,⁸ in which the enolate formation is relatively easy due to anion stabilization by conjugation. Hence the utilization of α -alkylsubstituted acetic acid derivatives has been challenging. Smith reported one entry of a catalytic enantioselective α -amination of 3-phenylpropionic acid through *in situ* pre-formation of an acid anhydride intermediate (Scheme 1a).⁹ The acid anhydride is further activated by a chiral isothiourea catalyst for α -amination *via* a C1-ammonium enolate. Yazaki and Ohshima recently reported a copper-catalyzed α -amination of acylpyrazoles (Scheme 1b).¹⁰ Wasa employed a frustrated Lewis pair (FLP) system comprised of $B(C_6F_5)_3$ and a bulky base (pentamethyl piperidine or Barton's

Scheme 1. Catalytic α -Amination of Carboxylic Acid Derivatives.

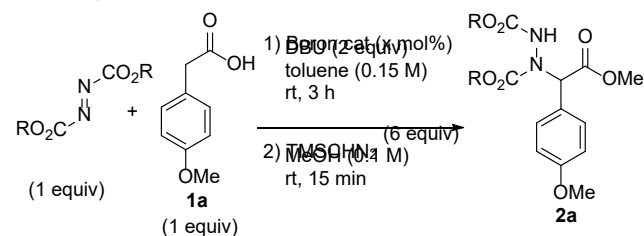


base) for α -amination of simple esters (Scheme 1c).¹¹ Despite these reports, construction of tetra-substituted carbon centers α to the carboxy group remains elusive.

We previously reported the chemoselective enolate formation of carboxylic acids using a boron activator.¹² The reversible covalent bond formation between the carboxylic acid and the Lewis acidic boron activator increases the acidity of the α -proton, thus enabling enolate formation of the carboxylic acid under mild basic conditions. We envisaged that this method could be extended to the direct α -amination of carboxylic acids leading to α,α -disubstituted glycine derivatives (Scheme 1d). Herein, we report a boron-catalyzed direct α -amination of carboxylic acids, which is applicable to the synthesis of α,α -disubstituted glycine derivatives.

To assess the feasibility of the proposed reaction, *p*-methoxyphenylacetic acid (**1a**) was selected as a substrate. Based on the results from previous studies of the boron-catalyzed Mannich-type reaction, conditions with $\text{BH}_3\cdot\text{SMe}_2$ (20 mol%), 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) (2 equiv), and toluene as a solvent were applied for the carboxylic acid enolate formation, and diethylazodicarboxylate (DEAD) was used as the electrophilic aminating reagent (Table 1, entry 1). The isolated yield was determined after converting the product to the corresponding methyl ester by treating the crude mixture with TMSCHN_2 . The initial conditions gave the α -amination product **2a** in 40% yield. Changing the boron catalyst to BBr_3 , which has a better leaving group (Br^-) on the boron atom, significantly increased the reactivity (entry 2, 79% yield). Further improvement was made with $(\text{AcO})_4\text{B}_2\text{O}$, giving **2a** in 89% yield (entry 3). On the other hand, $\text{B}(\text{OEt})_3$ was not effective at all. Next, we surveyed electro-

Table 1. Boron-Catalyzed α -Amination of α -Monoarylacetic Acid.^a



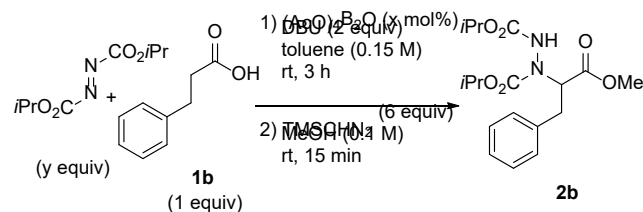
Entry	Boron source (x mol%)	R	Yield (%)
1	$\text{BH}_3\cdot\text{SMe}_2$ (20 mol%)	Et	40
2	BBr_3 (20 mol%)	Et	79
3	$(\text{AcO})_4\text{B}_2\text{O}$ (10 mol%)	Et	89
4	$\text{B}(\text{OEt})_3$ (20 mol%)	Et	0
5	$(\text{AcO})_4\text{B}_2\text{O}$ (10 mol%)	<i>i</i> Pr	96
6	$(\text{AcO})_4\text{B}_2\text{O}$ (10 mol%)	<i>t</i> Bu	86
7 ^b	$(\text{AcO})_4\text{B}_2\text{O}$ (2.5 mol%)	<i>i</i> Pr	91

^a**1a** (0.1 mmol), azodicarboxylate (0.1 mmol), boron catalyst, DBU (0.2 mmol), toluene (0.15 M), room temperature, 3 h. Crude mixture was treated with TMSCHN_2 (0.6 mmol) in MeOH (0.1 M). Isolated yield. ^bThe reaction was conducted in 0.2 mmol scale.

philic aminating reagents to avoid the formation of DEAD-derived hydrazine as a byproduct.¹³ Increasing the steric bulk of the aminating reagent by changing DEAD to diisopropylazodicarboxylate (DIAD) was effective to suppress undesired hydrazine formation, promoting the α -amination reaction to produce **2a** in excellent yield (entry 5, 96% yield). Bulkier di-*tert*-butylazodicarboxylate did not improve the product yield (entry 6, 86% yield). The catalyst loading could be reduced to 2.5 mol% without significant loss of catalytic activity (entry 7, 91% yield). Nitrosobenzene was not reactive as an electrophile.

The conditions optimized for the reaction of **1a** did not give satisfactory results for the reaction of α -monoalkylacetic acid **1b** (Table 2, entry 1). The product **2b** was obtained in only 27% yield under the same conditions as Table 1, entry 7. This was likely due to the lower acidity of **1b** at the α -methylene group compared to that of **1a**. The yield could be improved to 66% by increasing the boron catalyst loading to 10 mol% (entry 2). Since a significant amount of hydrazine was observed as a side product even with DIAD, the amount of DIAD was increased to two equivalents. This resulted in a marked increase in the yield to 84% (entry 3).

Table 2. Boron-Catalyzed α -Amination of α -Monoalkylacetic Acid.^a



Entry	$(\text{AcO})_4\text{B}_2\text{O}$ (x mol%)	DIAD (y equiv)	Yield (%)
1 ^b	2.5	1	27
2	10	1	66
3	10	2	84

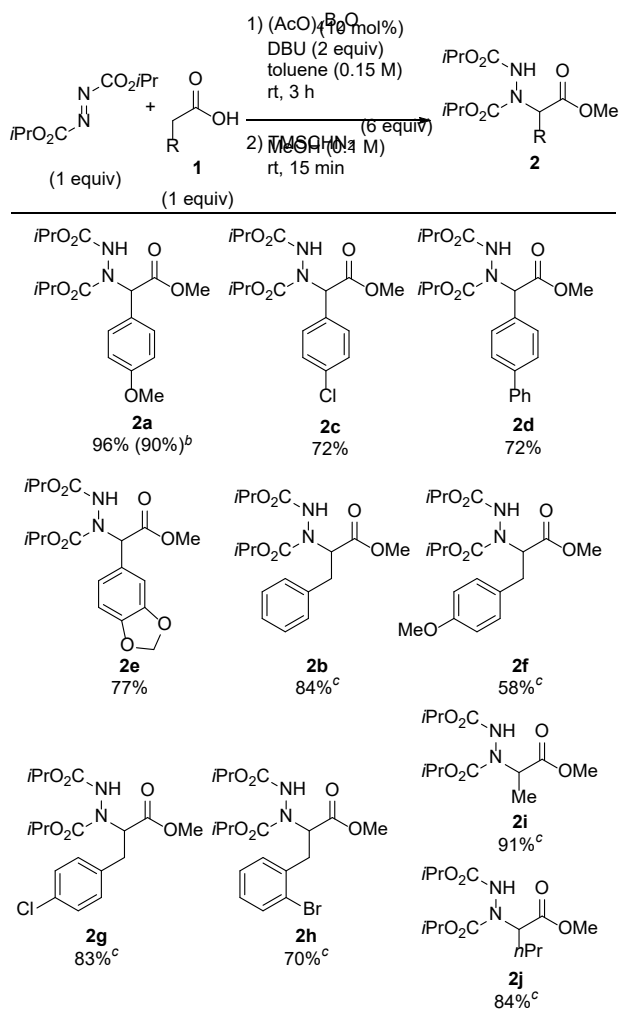
^a**1a** (0.1 mmol), DIAD (0.1–0.2 mmol), $(\text{AcO})_4\text{B}_2\text{O}$ (0.0025–0.01 mmol), DBU (0.2 mmol), toluene (0.15 M), room temperature, 3 h. Crude mixture was treated with TMSCHN_2 (0.6 mmol) in MeOH (0.1 M). Isolated yield. ^bThe reaction was conducted in 0.2 mmol scale.

The scope of the carboxylic acids was examined using 10 mol% $(\text{AcO})_4\text{B}_2\text{O}$. One equivalent of DIAD was used for the reaction of phenylacetic acid derivatives (Scheme 2). Both electron-withdrawing and -donating substituents on the α -aryl group afforded the corresponding amino acid derivatives in good yields (**2a**: 96%; **2c**: 72%; **2d**: 72%; **2e**: 77%). 1 mmol scale reaction using **1a** afforded **2a** in 90% yield. On the other hand, 2 equiv of DIAD were used for hydrocinnamic acid derivatives. Although an electron-donating methoxy substituent at the *para*-position of the aryl group decreased the yield (**2f**: 58%), the electron-withdrawing *p*-chloro substituent did not affect the reactivity (**2g**: 83%). *o*-Bromo substitution slightly decreased the yield probably due to increased steric bulk (**2h**: 70%). α -Monoalkylacetic acids other than hydrocinnamic acid derivatives, propionic

acid (**1i**) and valeric acid (**1j**), were also competent to afford **2i** (91% yield) and **2j** (84% yield).

Next, we attempted to use the catalyst for the synthesis of α,α -disubstituted glycine derivatives. Gratifyingly, α -methylhydrocinnamic acid (**1k**) was converted to the product **2k** in 88% yield with 10 mol% $(\text{AcO})_4\text{B}_2\text{O}$ and 2 equiv DIAD (Scheme 3). The yield was low with 1 equiv of DIAD (28% yield). Both electron-donating and electron-withdrawing substituents were tolerated on the aryl group of α -methylhydrocinnamic acid (**2l**: 57%; **2m**: 67%). The sterically demanding *o*-bromo substituent on the aryl group of α -methylhydrocinnamic acid was also tolerated albeit with a lower yield (**2n**: 47%). Since there is a member of non-steroidal anti-inflammatory drugs (NSAIDs)

Scheme 2. Substrate Scope for α -Monosubstituted Acetic Acids.^a

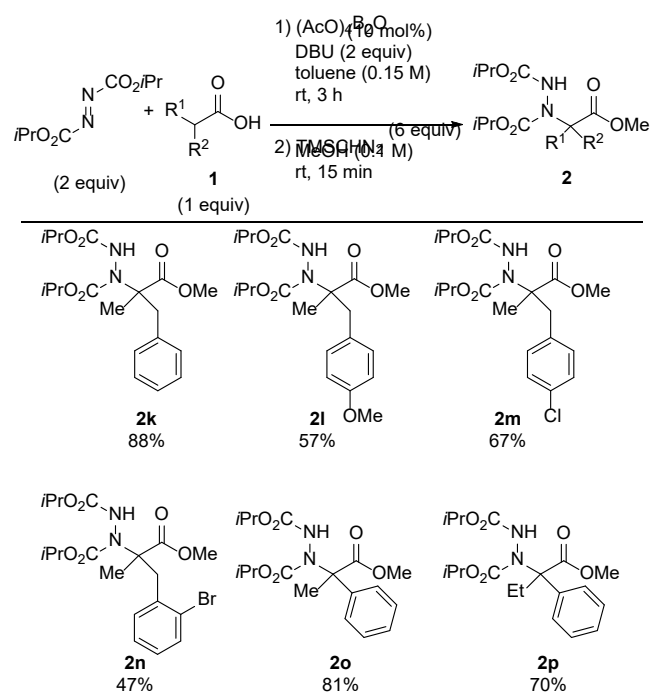


^a**1a** (0.1 mmol), DIAD (0.1 mmol), $(\text{AcO})_4\text{B}_2\text{O}$ (0.01 mmol), DBU (0.2 mmol), toluene (0.15 M), room temperature, 3 h. Crude mixture was treated with TMSCHN_2 (0.6 mmol) in MeOH (0.1 M). Isolated yield. ^bThe reaction was conducted on a 1 mmol scale. The yield is shown in parentheses. ^cDIAD (0.2 mmol) was used.

which possess α -methyl- α -aryl carboxylic acid core structure, such as ibuprofen and naproxen, we examined 2-phenylpropionic acid (**1o**) as a simple model. The reaction proceeded well and the product **2o** was obtained in 81% yield, indicating that the present reaction would be applicable to α -amination of NSAIDs. Slightly bulkier 2-phenylbutyric acid (**1p**) was also competent to provide **2p** in 70% yield.

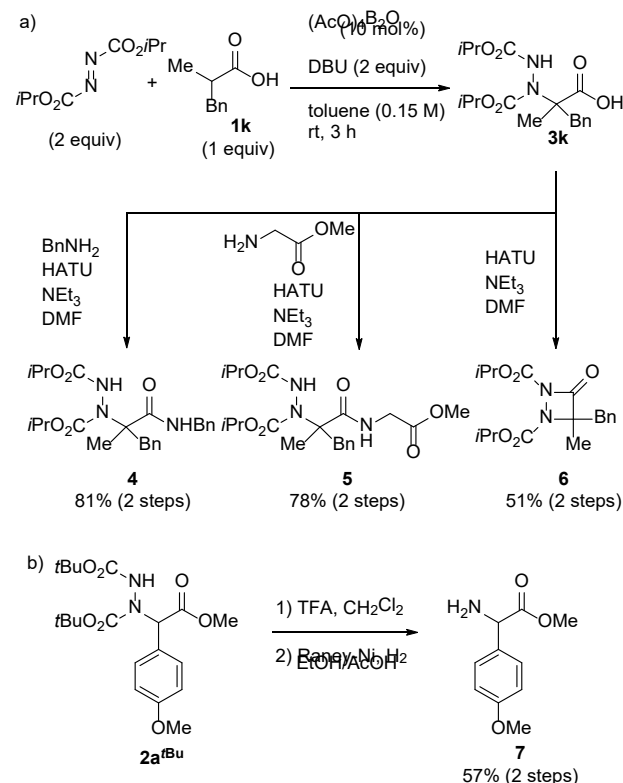
Transformation of the carboxy group was examined next (Scheme 4). After the catalytic amination of **1k**, the crude material was purified by silica gel column chromatography and subjected to condensation reactions (Scheme 4a). Condensation with benzylamine using hexafluorophosphate azabenzotriazole tetramethyl uronium (HATU) gave amide **4** in 81% yield over two steps. When glycine was used as a coupling partner, dipeptide analogue **5** was obtained in 78% yield. Intramolecular self-condensation provided diazetidinone **6** in 51% yield. Although several attempts to cleave the N-N bond of **2a** resulted in failure,¹⁴ a *N*-*tert*-butoxy carbonyl analogue **2a^{tBu}** was successfully transformed to α -amino acid methyl ester **7** in two steps: TFA-mediated cleavage of *tert*-butoxy carbonyl groups followed by N-N bond scission by hydrogenolysis using Raney-Ni (Scheme 4b).

Scheme 3. Substrate Scope for α,α -Disubstituted Acetic Acids.^a

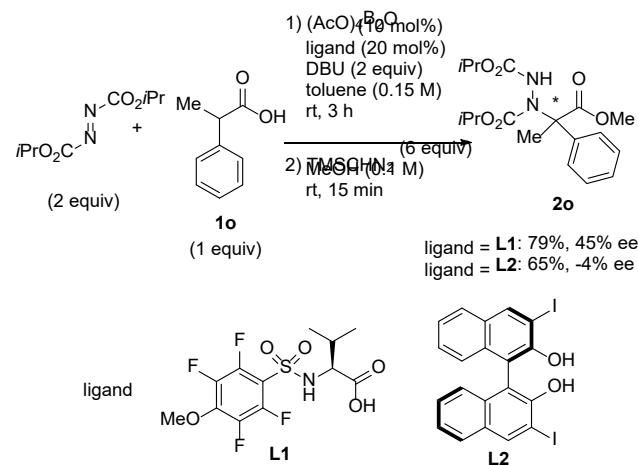


^a**1a** (0.1 mmol), DIAD (0.2 mmol), $(\text{AcO})_4\text{B}_2\text{O}$ (0.01 mmol), DBU (0.2 mmol), toluene (0.15 M), room temperature, 3 h. Crude mixture was treated with TMSCHN_2 (0.6 mmol) in MeOH (0.1 M). Isolated yield.

Scheme 4. Transformation of the α,α -Disubstituted Glycine Derivative.



Scheme 5. Catalytic Enantioselective α -Amination of a Carboxylic Acid.



Preliminary results of our investigation on the catalytic enantioselective α -amination of **10** by introducing a chiral ligand on the boron catalyst are shown in Scheme 5. Valine derived **L1** and 3,3'-I₂-BINOL **L2**, which were effective chiral ligands for the previous study of the boron-catalyzed asymmetric C–C bond forming reactions of carboxylic acids,^{12a,12d} were selected for initial investigations. Although **L2** did not induce meaningful stereoselectivity, **L1** provided **20** in decent enantioselectivity, 45% ee. This result suggests that the boron-catalyzed α -amination of carboxylic acids may provide a useful method for the asymmetric synthesis of α,α -disubstituted glycine derivatives through proper chiral modification of the boron catalyst.

In summary, we have developed the first boron-catalyzed direct α -amination of carboxylic acids. The reaction provided a variety of α -amino acid derivatives including α,α -disubstituted glycine derivatives. Preliminary investigations revealed that the present method can be extended to an asymmetric variant by introducing a chiral ligand on the boron catalyst. Modification of the chiral ligand and to improve the enantioselectivity is ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures, characterization data, NMR spectra, HPLC chart.

AUTHOR INFORMATION

Corresponding Author

*E-mail: sawamura@sci.hokudai.ac.jp
shimizu-y@sci.hokudai.ac.jp

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

Institute for Chemical Reaction Design and Discovery (ICReDD) was established by World Premier International Research Initiative (WPI), MEXT, Japan. This work was supported by JSPS KAKENHI Grant-in-Aid for Scientific Research (A) to M.S. (No. JP18H03906), JSPS KAKENHI Grant-in-Aid for Early-Career Scientists (No. 18K14207), and grants-in-aid from the Fugaku Trust for Medicinal Research to Y.S.

REFERENCES

- (1) (a) Fleming, A. *Br. J. Exp. Pathol.* **1929**, *10*, 226-236. For reviews on catalytic asymmetric α -amination of carbonyl compounds, see: (b) Zhou, F.; Liao, F.-M.; Yu, J.-S.; Zhou, J. *Synthesis* **2014**, *46*, 2983. (c) Janey, J. M. *Angew. Chem. Int. Ed. Engl.* **2005**, *44*, 4292. (d) Smith, A. M. R.; Hii, K. K. *Chem. Rev.* **2011**, *111*, 1637. (e) Maji, B.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **2015**, *88*, 753. (f) de la Torre, A.; Tona, V.; Maulide, N. *Angew. Chem. Int. Ed.* **2017**, *56*, 12416.
- (2) For selected examples of catalytic α -amination of aldehydes, see: (a) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254. (b) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656. (c) Cecere, G.; König, C. M.; Alleva, J. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 11521. N-heterocyclic carbene-catalyzed redox α -amination of aldehydes afforded products with carboxylic acid oxidation state: (d) Taylor, J. E.; Daniels, D. W.; Smith, A. D. *Org. Lett.* **2013**, *15*, 6058-6061. (e) Yang, L.; Wang, F.; Lee, R.; Lv, Y.; Huang, K.-W.; Zhong, G. *Org. Lett.* **2014**, *16*, 3872-3875. (f) Huang, R.; Chen, X.; Mou, C.; Luo, G. Li, Y.; Li, X.; Xue, W.; Jin, Z.; Chi, Y. R. *Org. Lett.* **2019**, *21*, 4340-4344.
- (3) For selected examples of catalytic α -amination of ketones, see: (a) Momiya, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5360. (b) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254. (c) Han, Y.; Corey, E. J. *Org. Lett.* **2019**, *21*, 283. (d) Yang, X.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3205.
- (4) For selected examples of catalytic α -amination of 1,3-dicarbonyl compounds, see: (a) Saaby, S.; Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120. (b) Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* **2006**, *128*, 16044. (c) Sandoval, D.; Frazier, C.

- P.; Bugarin, A.; Read de Alaniz, J. *J. Am. Chem. Soc.* **2012**, *134*, 18948. (d) Deng, Q.-H.; Bleith, T.; Wadepohl, H.; Gade, L. H. *J. Am. Chem. Soc.* **2013**, *135*, 5356. (e) Nelson, H. M.; Patel, J. S.; Shunatona, H. P.; Toste, F. D. *Chem. Sci.* **2015**, *6*, 170. (f) Hasegawa, Y.; Watanabe, M.; Gridnev, I. D.; Ikariya, T. *J. Am. Chem. Soc.* **2008**, *130*, 2158.
- (5) For selected examples of catalytic α -amination of oxindoles, see: (a) Shen, K.; Liu, X.; Wang, G.; Lin, L.; Feng, X. *Angew. Chem. Int. Ed. Engl.* **2011**, *50*, 4684. (b) Bui, T.; Hernández-Torres, G.; Milite, C.; Barbas III, C. F. *Org. Lett.* **2010**, *12*, 5696. (c) Mouri, S.; Chen, Z.; Mitsunuma, H.; Furutachi, M.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 1255. (d) Ohmatsu, K.; Ando, Y.; Nakashima, T.; Ooi, T. *Chem* **2016**, *1*, 802. (e) Yang, Z.; Wang, Z.; Bai, S.; Shen, K.; Chen, D.; Liu, X.; Lin, L.; Feng, X. *Chem. Eur. J.* **2010**, *16*, 6632. (f) Shen, K.; Liu, X.; Wang, G.; Lin, L.; Feng, X. *Angew. Chem. Int. Ed.* **2011**, *50*, 4684.
- (6) (a) Sandoval, D.; Samoshin, A. V.; Read de Alaniz, J. *Org. Lett.* **2015**, *17*, 4514. (b) Miura, T.; Morimoto, M.; Murakami, M. *Org. Lett.* **2012**, *14*, 5214. (c) Tanaka, M.; Kurosaki, Y.; Washio, T.; Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **2007**, *48*, 8799. (d) Evans, D. A.; Bilodeau, M. T.; Faul, M. M. *J. Am. Chem. Soc.* **1994**, *116*, 2742. (e) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed. Engl.* **2012**, *51*, 11827. (f) Kiyokawa, K.; Okumatsu, D.; Minakata, S. *Angew. Chem. Int. Ed.* **2019**, DOI: 10.1002/anie.201904971. (g) Miura, T.; Morimoto, M.; Murakami, M. *Org. Lett.* **2012**, *14*, 5214.
- (7) (a) Fisher, D. J.; Burnett, G. L.; Velasco, R.; Read de Alaniz, J. *J. Am. Chem. Soc.* **2015**, *137*, 11614. (b) Ishida, S.; Takeuchi, K.; Taniyama, N.; Sunada, Y.; Nishikata, T. *Angew. Chem. Int. Ed.* **2017**, *56*, 11610.
- (8) (a) Zhao, B.; Du, H.; Shi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 7220. (b) Evans, R. W.; Zbieg, J. R.; Zhu, S.; Li, W.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 16074. (c) Evans, D. A.; Nelson, S. G. *J. Am. Chem. Soc.* **1997**, *119*, 6452. (d) Smulik, J. A.; Vedejs, E. *Org. Lett.* **2003**, *5*, 4187.
- (9) Morrill, L. C.; Lebl, T.; Slawin, A. M. Z.; Smith, A. D. *Chem. Sci.* **2012**, *3*, 2088.
- (10) Tokumasu, K.; Yazaki, R.; Ohshima, T. *J. Am. Chem. Soc.* **2016**, *138*, 2664.
- (11) Shang, M.; Wang, X.; Koo, S. M.; Youn, J.; Chan, J. Z.; Yao, W.; Hastings, B. T.; Wasa, M. *J. Am. Chem. Soc.* **2017**, *139*, 95.
- (12) (a) Morita, Y.; Yamamoto, T.; Nagai, H.; Shimizu, Y.; Kanai, M. *J. Am. Chem. Soc.* **2015**, *137*, 7075. (b) Nagai, H.; Morita, Y.; Shimizu, Y.; Kanai, M. *Org. Lett.* **2016**, *18*, 2276. (c) Ishizawa, K.; Nagai, H.; Shimizu, Y.; Kanai, M. *Chem. Pharm. Bull.* **2018**, *66*, 231. (d) Fujita, T.; Yamamoto, T.; Morita, Y.; Chen, H.; Shimizu, Y.; Kanai, M. *J. Am. Chem. Soc.* **2018**, *140*, 5899.
- (13) Treatment of DEAD with DBU (2 equiv), (AcO)₄B₂O (10 mol%) in toluene (0.15 M) produced diethyl hydrazine-1,2-dicarboxylate.
- (14) See supporting information for details.
-