Organic LETTERS

Letter

pubs.acs.org/OrgLett

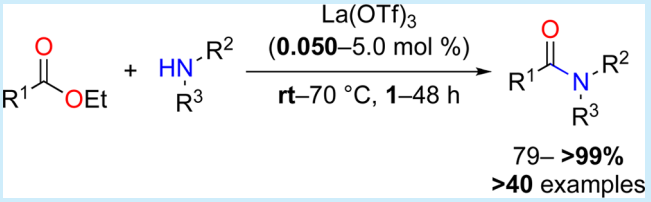
Lanthanum(III) Triflate Catalyzed Direct Amidation of Esters

Hiroyuki Morimoto,* Risa Fujiwara, Yuhei Shimizu, Kazuhiro Morisaki, and Takashi Ohshima*

Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka, 812-8582, Japan

Supporting Information

ABSTRACT: Lanthanum trifluoromethanesulfonate is an effective single-component catalyst for synthesizing a variety of amides directly from esters and amines under mild conditions. Highly selective amidation of esters and amines, as well as catalyst-controlled amidation of esters, demonstrated the effectiveness of the catalyst system.

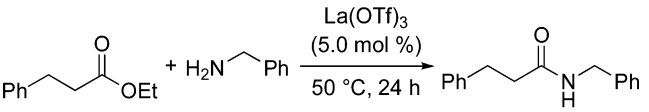


Amides are ubiquitous in many organic molecules, such as peptides, natural products, and pharmaceutical agents, as well as ligands and catalysts in organic synthesis. Efficient synthesis of amides is thus an important topic in synthetic organic chemistry.[1] Amides are generally prepared from the corresponding carboxylic acids and amines using stoichiometric amounts of condensing agents, which generates stoichiometric amounts of unwanted coproducts. Recent efforts to circumvent this problem have provided effective means of synthesizing amides in a catalytic manner,[2] but further improvement of these reactions is required to improve the substrate scope, reduce the need for a high temperature and the use of large amounts of desiccating agents, such as molecular sieves, to maintain catalyst activity.

Direct amidation of esters with amines without the formation of carboxylic acids is another method of synthesizing amides. This is a desirable approach for amide synthesis because esters are common synthetic intermediates of the target compounds.[3] Although conventional direct amidation of esters requires stoichiometric amounts of reagents,[4] efficient catalytic protocols that generate the targeted amides together with only alcohols as the sole coproduct were recently developed.[5,6] There are several drawbacks to these catalytic protocols, however, including (1) high catalyst loading (10 mol % in general), (2) limited substrate scope, and (3) requirement of additives to modulate or attenuate catalyst activity, which increases the complexity of the optimization of reaction conditions for particular substrates. Thus, the development of simple but effective catalysts that can promote direct amidation of esters under mild conditions is in high demand.

This work stems from our recent interest in the transformation of amide bonds. During our investigation of amide bond cleavage reactions,[7] we envisaged that acidic catalysts would promote the direct amidation of esters under mild conditions. After screening of various acidic catalysts using ethyl 3-phenylpropionate (**1a**) and benzylamine (**2a**) as model substrates,[8] we finally found that lanthanum trifluoromethanesulfonate possessed high catalytic activity to provide amide **3a** in 98% isolated yield after 24 h at 50 °C (Scheme 1).[9−11] The use of **1a** and **2a** in a 1:1 stoichiometry also produced **3a** in 92% yield.

Scheme 1. La(OTf)$_3$-Catalyzed Direct Amidation of Esters



1a (1.0 mmol) **2a** (1.2/1.0 mmol) **3a** 98%/92%

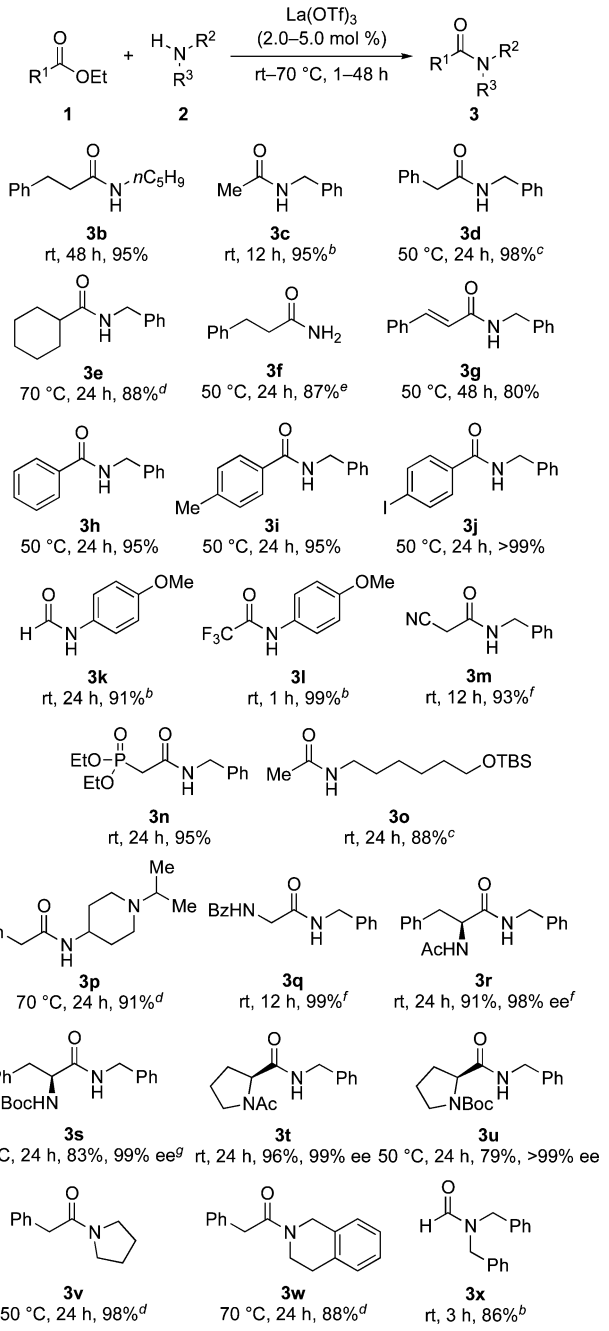
With these promising results in hand, we examined the substrate scope (Scheme 2). These reaction conditions were applied to both various esters **1** and amines **2** to give the corresponding amide **3** in yields ranging from 79% to more than 99% yields at room temperature to 70 °C. Aliphatic, α,β-unsaturated, and aromatic esters gave amides **3** in good yields, and less nucleophilic ammonia and anilines were also good amine components.[12] Functionalities, such as iodo, cyano, phosphonate, *tert*-butyldimethylsilyloxy, tertiary amine, carbamate, and amide groups, were tolerated under the reaction conditions. It is noteworthy that no significant epimerization at the α-position occurred for *N*-acetyl-α-amino acid esters, which readily racemize under conventional amidation conditions of the corresponding carboxylic acids using condensing reagents.[13] Secondary amines also reacted to afford amides **3** in good yields. In all cases, the background reactions were quite slow in the absence of the catalyst.[8]

This catalytic system can also be adapted to the synthesis of 2-pyridinecarboxamide derivatives **4**, a class of substrates for potential C−H functionalization reactions (Scheme 3).[14] Catalyst loading was reduced to as low as 0.050 mol % for the synthesis of **4a** on a multigram scale, which is, to the best of our knowledge, the lowest catalyst loading for direct catalytic amidation of esters. Because of the high activity of the catalyst system, reaction with propylamine **2j** (boiling point 48 °C) also gave **4b** at room temperature for 1 h in >99% yield.

Received: February 24, 2014

   dx.doi.org/10.1021/ol500593v | *Org. Lett.* XXXX, XXX, XXX−XXX

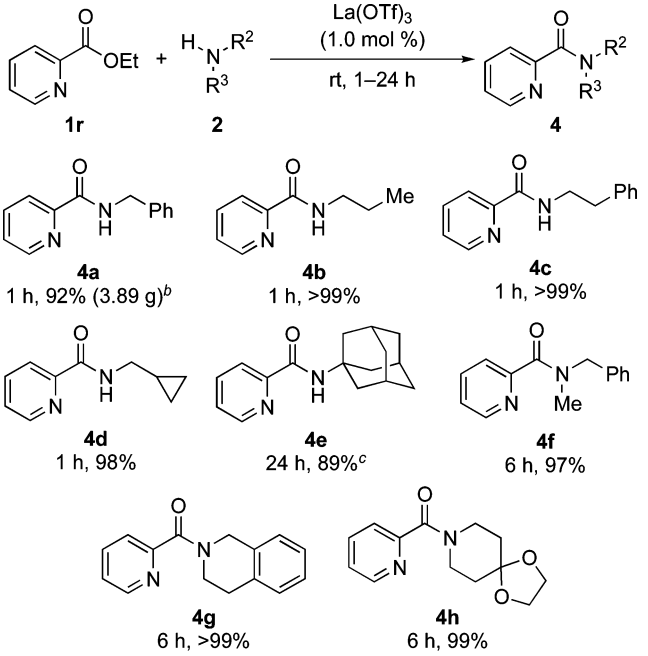
Scheme 2. Scope of $La(OTf)_3$-Catalyzed Direct Amidation[a]



[a]Reaction conditions: ester **1** (1.0 mmol), amine **2** (1.2 mmol), $La(OTf)_3$ (5.0 mol %), rt−70 °C, 1−48 h, isolated yields, unless otherwise noted. [b]1.2 mmol of **1** and 1.0 mmol of **2** were used. [c]2.0 mol % of $La(OTf)_3$ was used. [d]1.5 mmol of **2** was used. [e]Reaction was performed with saturated NH_3 solution in EtOH. [f]Reaction was performed in toluene (1.0 M). [g]Reaction was performed in toluene (2.0 M).

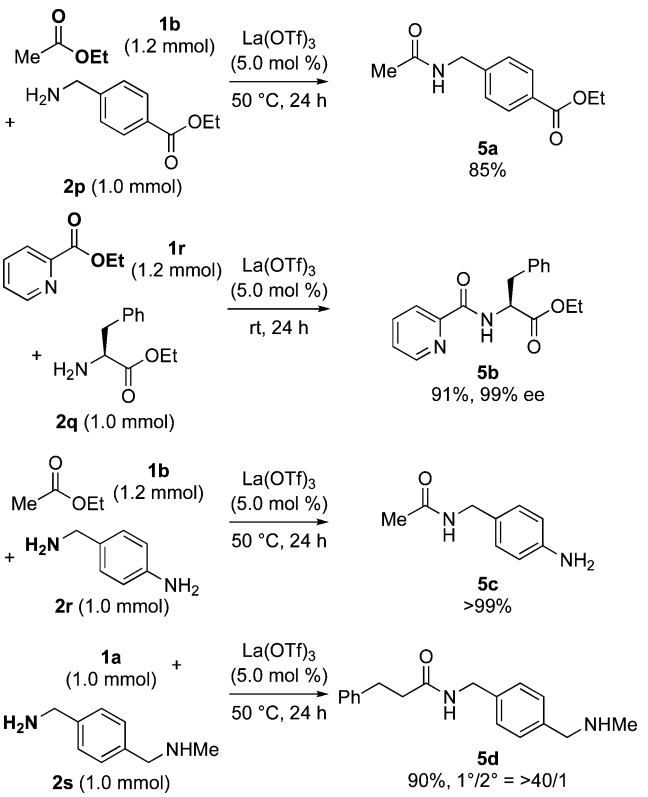
We also showed highly selective amidation of esters and amines in the presence of similar functionalities (Scheme 4). Amidation of ethyl acetate (**1b**) selectively proceeded with **2p** to give **5a** in 85% yield, while the ethyl ester moiety of **2p** was not affected. Selective amidation of esters was also possible in the reaction of **1r** and **2q** at room temperature to give **5b** in 91% yield without significant epimerization at the chiral center of **2q**, and ester moiety of **2q** was not affected. Selective

Scheme 3. $La(OTf)_3$-Catalyzed Direct Amidation of Ethyl 2-Pyridinecarboxylate[a]



[a]Reaction conditions: ester **1r** (1.0 mmol), amine **2** (1.2 mmol), $La(OTf)_3$ (1.0 mol %), rt, 1−24 h, isolated yields, unless otherwise noted. [b]Reaction was performed using **1r** (20 mmol), **2a** (20 mmol), and 0.050 mol % of $La(OTf)_3$. [c]Reaction was performed using 5.0 mol % of $La(OTf)_3$ at 70 °C.

Scheme 4. Selective Amidation of Esters and Amines



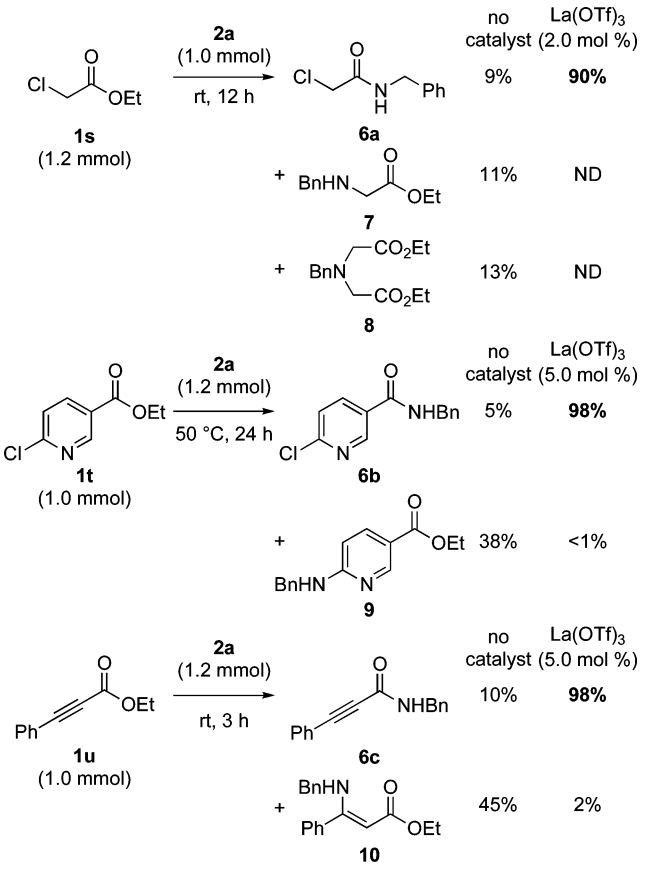
amidation of aliphatic amine over aromatic amine was also realized with **1b** and **2r** to give **5c** in >99% yield. Notably, the

dx.doi.org/10.1021/ol500593v | Org. Lett. XXXX, XXX, XXX−XXX

reaction of **1a** with one equivalent of amine **2s** having both primary and secondary amine moieties reacted selectively at the primary amine site to give **5d** in 90% yield with better than 40/1 selectivity.

As part of our studies of the catalyst control of chemoselectivity,[15] we examined the following examples (Scheme 5)

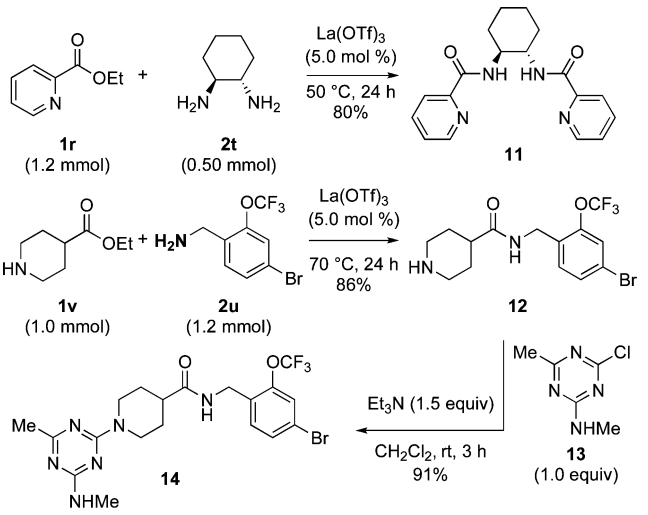
Scheme 5. Catalyst-Controlled Amidation of Esters



to test whether $La(OTf)_3$ could alter the inherent reactivity of esters. Ethyl chloroacetate (**1s**) reacts with amines in a S_N2 manner at the α-position to produce amino esters such as **7** and **8**.[16] On the other hand, reaction in the presence of 2 mol % of $La(OTf)_3$ preferentially provided amide **6a**, thus overriding the intrinsic reactivity of **1s**. The same trend was observed in the case of ethyl 6-chloropyridine-3-carboxylate (**1t**), for which an S_NAr reaction is preferable in the absence of a catalyst.[16] In the presence of a catalyst, however, direct amidation of the ester proceeded cleanly to give **6b** with negligible formation of the S_NAr side-product **9**. Furthermore, ethyl phenylpropiolate (**1u**) gave amidation product **6c** in 98% yield at room temperature in 3 h in the presence of 5 mol % of $La(OTf)_3$, while 1,4-addition product **10** was predominant in the absence of a catalyst. These results clearly demonstrate the effectiveness of the catalyst system, and suggest that activation of an ester moiety with $La(OTf)_3$ is key for accelerating the amidation reaction.

Finally, this method was applied to the synthesis of important molecules (Scheme 6). Bis(amide) **11**, an effective ligand for asymmetric transformations,[17] was synthesized in 80% yield without the use of stoichiometric amounts of condensing agents. We also demonstrated the synthesis of a soluble epoxide hydrolase inhibitor **14**.[18] The reaction of aminoester **1v** with amine **2u** proceeded to give amide **12** in

Scheme 6. Synthetic Applications



86% yield without self-condensation of **1v**. Amide **12** was further treated with triazine derivative **13** to give the final product **14** overall without protection/deprotection of the amino group of **1v**.

In summary, we developed a lanthanum trifluoromethanesulfonate-catalyzed direct amidation of esters. The reactions proceeded efficiently using as little as 0.050 mol % of commercially available and single-component catalyst at room temperature to 70 °C for 1−48 h to give amides in yields of 79% to more than 99%. A variety of esters and amines (22 esters and 21 amines; total 41 examples) can be used under the catalytic conditions and significant racemization was not observed even for *N*-acetyl-α-amino acid esters. We also demonstrated highly selective amidation of esters and amines while other esters and amines were present. Catalyst-controlled amidation of esters that override the inherent substrate reactivity and application to the synthesis of important molecules further proved the effectiveness of the catalyst system. Further studies to evaluate the application of the catalyst system are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: hmorimot@phar.kyushu-u.ac.jp.
*E-mail: ohshima@phar.kyushu-u.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Scientific Research (B) (No. 24390004), a Grant-in-Aid for Young Scientists (B) (No. 23790014), Scientific Research on Innovative Areas (No. 24106733), and Platform for Drug Discovery, Informatics, and Structural Life Science from MEXT, CREST from JST, Uehara Memorial Foundation, and the Naito Foundation. H.M. thanks Takasago Award in

dx.doi.org/10.1021/ol500593v | *Org. Lett.* XXXX, XXX, XXX−XXX

Synthetic Organic Chemistry, Japan and Y.S. thanks JSPS Research Fellowships for Young Scientists. We thank the research group of Prof. Hiroshi Suemune at Kyushu University for the use of a polarimeter.

REFERENCES

(1) Recent reviews on the synthesis of amides: (a) Stolze, S. C.; Kaiser, M. *Synthesis* **2012**, *44*, 1755. (b) El-Faham, A.; Albericio, F. *Chem. Rev.* **2011**, *111*, 6557. (c) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471. (d) Allen, C. L.; Williams, J. M. J. *Chem. Soc. Rev.* **2011**, *40*, 3405. For the importance of amidation reactions, see: (e) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411.

(2) For a review, see: (a) Lanigan, R. M.; Sheppard, T. D. *Eur. J. Org. Chem.* **2013**, 7453. For selected recent examples of catalytic direct amidation of carboxylic acids, see: (b) Yamashita, R.; Sakakura, A.; Ishihara, K. *Org. Lett.* **2013**, *15*, 3654. (c) Gernigon, N.; Al-Zoubi, R. M.; Hall, D. G. *J. Org. Chem.* **2012**, *77*, 8386. (d) Lundberg, H.; Tinnis, F.; Adolfsson, H. *Chem.—Eur. J.* **2012**, *18*, 3822. (e) Allen, C. L.; Chhatwal, A. R.; Williams, J. M. J. *Chem. Commun.* **2012**, *48*, 666. (f) Arnold, K.; Batsanov, A. S.; Davies, B.; Whiting, A. *Green Chem.* **2008**, *10*, 124.

(3) For recent analysis, see: (a) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451. (b) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337.

(4) For example, see: (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171. (b) Lipton, M. F.; Basha, A.; Weinreb, S. M. *Org. Synth.* **1979**, *59*, 49. (c) Ishihara, K.; Kuroki, Y.; Hanaki, N.; Ohara, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 1569.

(5) For selected recent examples of catalytic direct amidation of esters, see: (a) Caldwell, N.; Jamieson, C.; Simpson, I.; Watson, A. J. B. *ACS Sustainable Chem. Eng.* **2013**, *1*, 1339. (b) Caldwell, N.; Jamieson, C.; Simpson, I.; Tuttle, T. *Org. Lett.* **2013**, *15*, 2506. (c) Ohshima, T.; Hayashi, Y.; Agura, K.; Fujii, Y.; Yoshiyama, A.; Mashima, K. *Chem. Commun.* **2012**, *48*, 5434. (d) Whitten, K. M.; Makriyannis, A.; Vadivel, S. K. *Tetrahedron Lett.* **2012**, *53*, 5753. (e) Price, K. E.; Larriveée-Aboussafy, C.; Lillie, B. M.; McLaughlin, R. W.; Mustakis, J.; Hettenbach, K. W.; Hawkins, J. M.; Vaidyanathan, R. *Org. Lett.* **2009**, *11*, 2003. (f) Yang, X.; Birman, V. B. *Org. Lett.* **2009**, *11*, 1499. (g) Sabot, C.; Kumar, K. A.; Meunier, S.; Mioskowski, C. *Tetrahedron Lett.* **2007**, *48*, 3863. (h) Han, C.; Lee, J. P.; Lobkovsky, E.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 10039. (i) Movassaghi, M.; Schmidt, M. A. *Org. Lett.* **2005**, *7*, 2453.

(6) For selected other approaches toward environmentally benign amide formation reactions, see: (a) Gunanathan, C.; Ben-David, Y.; Milstein, D. *Science* **2007**, *317*, 790. (b) Gnanaprakasam, B.; Milstein, D. *J. Am. Chem. Soc.* **2011**, *133*, 1682. (c) Soulé, J.-F.; Miyamura, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2011**, *133*, 18550. (d) Kang, B.; Fu, Z.; Hong, S. H. *J. Am. Chem. Soc.* **2013**, *135*, 11704.

(7) Shimizu, Y.; Morimoto, H.; Zhang, M.; Ohshima, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 8564.

(8) See the Supporting Information for details.

(9) For reviews of rare-earth metal catalysts, see: (a) Shibasaki, M.; Matsunaga, S.; Kumagai, N. In *Acid Catalysis in Modern Organic Synthesis*; Yamamoto, H., Ishihara, K., Eds.; Wiley-VCH: Weinheim, 2008; Vol. 2, Chapter 13. (b) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227. For recent examples of the use of lanthanum and other rare-earth metal salts as catalyst in related transformations, see: (c) Hatano, M.; Ishihara, K. *Chem. Commun.* **2013**, *49*, 1983 and references therein. (d) Hatano, M.; Furuya, Y.; Shimmura, T.; Moriyama, K.; Kamiya, S.; Maki, T.; Ishihara, K. *Org. Lett.* **2011**, *13*, 426. (e) Distaso, M.; Quaranta, E. *Tetrahedron* **2004**, *60*, 1531. (f) Distaso, M.; Quaranta, E. *J. Catal.* **2004**, *228*, 36. (g) Brown, R. S.; Neverov, A. A.; Tsang, J. S. W.; Gibson, G. T. T.; Montoya-Pelaez, P. J. *Can. J. Chem.* **2004**, *82*, 1791. (h) Neverov, A. A.; McDonald, T.; Gibson, G.; Brown, R. S. *Can. J. Chem.* **2001**, *79*, 1704. See also ref 5h.

(10) Although several rare-earth metal triflates were briefly examined for direct catalytic amidation of esters,[5h] those catalysts were less effective than zirconium-based catalysts and not fully examined in detail.

(11) The reaction did not proceed well in the presence of catalytic amounts of TfOH (4% after 24 h).[8]

(12) *p*-$TsNH_2$ and $H_2NOH{\cdot}HCl$ with Et_3N did not provide amidation products under our catalytic conditions.

(13) For related examples with α-amino acids using $B(OCH_2CF_3)_3$ as a stoichiometric reagent, see: Lanigan, R. M.; Starkov, P.; Sheppard, T. D. *J. Org. Chem.* **2013**, *78*, 4512.

(14) For example, see: (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Gou, F.-R.; Wang, X.-C.; Huo, P.-F.; Bi, H.-P.; Guan, Z.-H.; Liang, Y.-M. *Org. Lett.* **2009**, *11*, 5726. (c) Zhao, Y.; Chen, G. *Org. Lett.* **2011**, *13*, 4850. (d) He, G.; Chen, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 5192. (e) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3. (f) Nadres, E. T.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 7. (g) Zhang, S.-Y.; He, G.; Zhao, Y.; Wright, K.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 7313. (h) He, G.; Lu, C.; Zhao, Y.; Nack, W. A.; Chen, G. *Org. Lett.* **2012**, *14*, 2944. (i) Zhao, Y.; He, G.; Nack, W. A.; Chen, G. *Org. Lett.* **2012**, *14*, 2948. (j) Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 2124. (k) Hack, W. A.; He, G.; Zhang, S.-Y.; Lu, C.; Chen, G. *Org. Lett.* **2013**, *15*, 3440. (l) Sustac Roman, D.; Charette, A. B. *Org. Lett.* **2013**, *15*, 4394. (m) Nadres, E. T.; Franco Santos, G. I.; Shabashov, D.; Daugulis, O. *J. Org. Chem.* **2013**, *78*, 9689.

(15) For example, see: (a) Hayashi, Y.; Santoro, S.; Azuma, Y.; Himo, F.; Ohshima, T.; Mashima, K. *J. Am. Chem. Soc.* **2013**, *135*, 6192. (b) Ohshima, T.; Iwasaki, T.; Maegawa, Y.; Yoshiyama, A.; Mashima, K. *J. Am. Chem. Soc.* **2008**, *130*, 2944. (c) Uesugi, S.; Li, Z.; Yazaki, R.; Ohshima, T. *Angew. Chem., Int. Ed.* **2014**, *53*, 1611.

(16) Limited conversion for **1s** and **1t** in the absence of the catalyst would be due to the formation of HCl during the reaction that reduces the nucleophilicity of amine **2a**.

(17) (a) Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104. (b) Barnes, D. J.; Chapman, R. L.; Vagg, R. S.; Watton, E. C. *J. Chem. Eng. Data* **1978**, *23*, 349. (c) Conlon, D. A.; Yasuda, N. *Adv. Synth. Catal.* **2001**, *343*, 137.

(18) Thalji, R. K.; McAtee, J. J.; Belyanskaya, S.; Brandt, M.; Brown, G. D.; Costell, M. H.; Ding, Y.; Dodson, J. W.; Eisennagel, S. H.; Fries, R. E.; Gross, J. W.; Harpel, M. R.; Holt, D. A.; Israel, D. I.; Jolivette, L. J.; Krosky, D.; Li, H.; Lu, Q.; Mandichak, T.; Roethke, T.; Schnackenberg, C. G.; Schwartz, B.; Shewchuk, L. M.; Xie, W.; Behm, D. J.; Douglas, S. A.; Shaw, A. L.; Marino, J. P., Jr. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3584.