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Letter

Methyltrimethoxysilane (MTM) as a Reagent for Direct Amidation of Carboxylic Acids

D. Christopher Braddock,* Joshua J. Davies, and Paul D. Lickiss*

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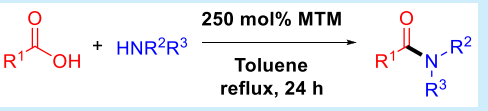
ABSTRACT: Methyltrimethoxysilane [MTM, $CH_3Si(OMe)_3$] has been demonstrated to be an effective, inexpensive, and safe reagent for the direct amidation of carboxylic acids with amines. Two simple workup procedures that provide the pure amide product without the need for further purification have been developed. The first employs an aqueous base-mediated annihilation of MTM. The second involves simple product crystallization from the reaction mixture providing a low process mass intensity direct amidation protocol.



The direct amidation of carboxylic acids with amines is a topic of much ongoing interest,[1] due to the importance of the amide bond in medicinal chemistry[2] and in the pharmaceutical industry.[3] State-of-the-art protocols include thermal amidations,[4] boron-based catalysts[5] and reagents,[6] oxophilic transition metal catalysts,[7] silicon-based reagents,[8] and others.[9] However, the search for a sustainable direct amidation reagent that is nontoxic, inexpensive, and widely available affording amide products in high yields with all acid−amine combinations and proceeds with an overall low process mass intensity (PMI) that avoids chromatography continues.[10] Toward that end, we have recently reported the use of tetramethylorthosilicate [TMOS, $Si(OMe)_4$] (**1**) as a reagent for direct amidation.[11] TMOS is inexpensive and widely available, successfully mediates direct amidation of aromatic and aliphatic carboxylic acids with primary amines, secondary amines, and anilines in an ideal 1:1 stoichiometry, and is annihilated to silica in a simple aqueous workup procedure that delivers the amide product in pure form without the need for chromatographic purification. However, because hydrolysis of

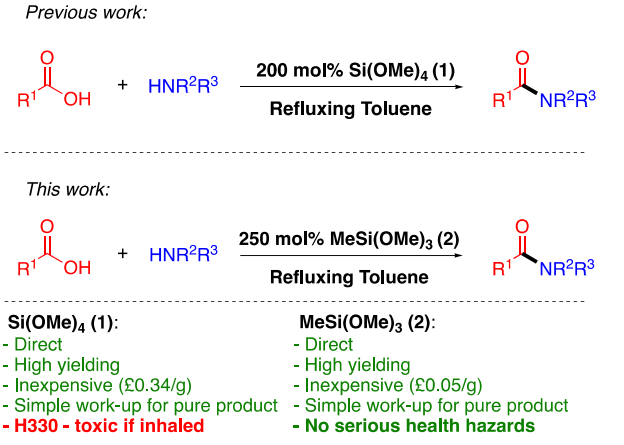


Figure 1. Previous work developed by Braddock et al. utilizing $Si(OMe)_4$ (**1**) as a reagent for direct amidation. This work utilizes $MeSi(OMe)_3$ (**2**).

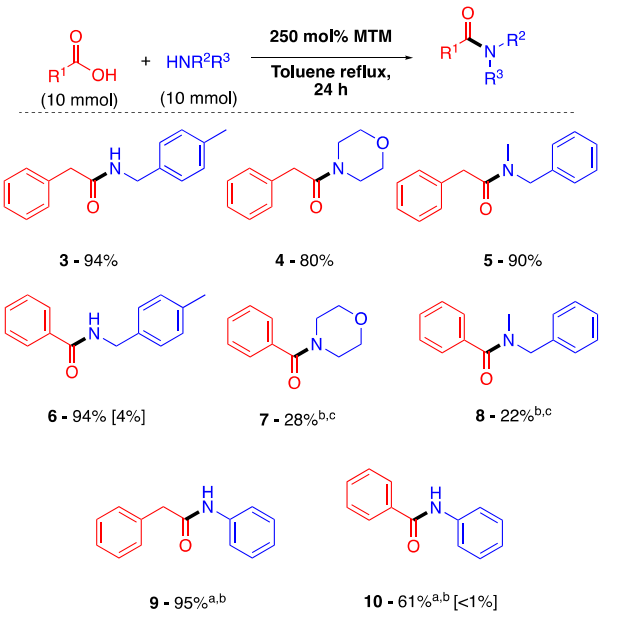


Figure 2. $MeSi(OMe)_3$ (**2**)-mediated direct amidation of representative carboxylic acids and amines with 1 M acid and 1 M amine. [a]With 2 equiv of acid. [b]With 2 M amine. The isolated yield from a background reaction (i.e., without MTM) is given in brackets. [c]With fractional distillation of MeOH.

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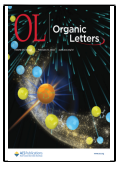

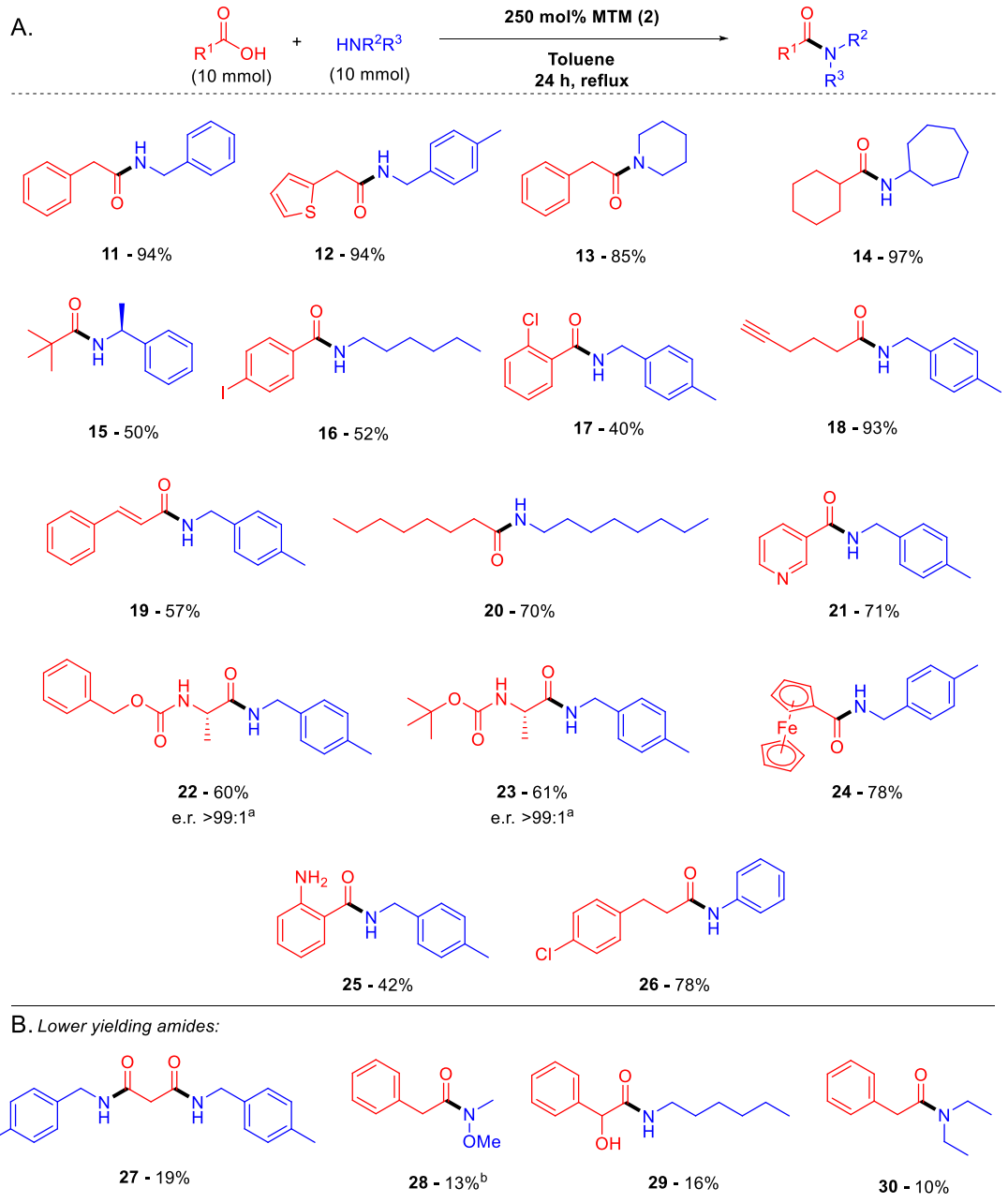

Figure 3. (A) Expanded scope of $MeSi(OMe)_3$ (**2**)-mediated amidation of carboxylic acids and amines with 1 M acid and 1 M amine. (B) Amides formed in lower yields. [a]The er was determined by HPLC analysis on a chiral stationary phase by reference to an authentic racemic sample. [b]One equivalent of NEt_3 was added to liberate amine from HCl salt.

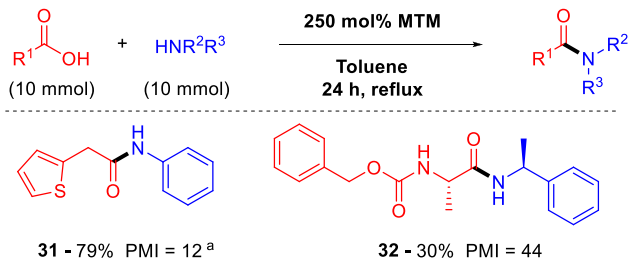

Figure 4. Low-PMI $MeSi(OMe)_3$ (**2**)-mediated direct amidation of carboxylic acids and amines with 1 M acid and 1 M amine. [a]On a 45 mmol scale with fractional distillation of MeOH.

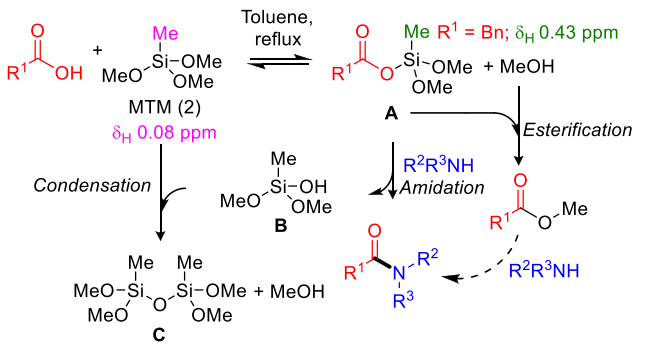

Figure 5. Postulated mechanism for MTM direct amidations.

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TMOS to silica in the lung induces silicosis, TMOS is considered fatal if inhaled (GHS H330), thereby reducing its attractiveness. Accordingly, we envisioned employing an alternative silicon-based reagent that retains the inherent reactivity of TMOS but cannot undergo hydrolysis to silica and is still amenable to removal in a workup procedure. Herein, we present methyltrimethoxysilane [MTM, $MeSi(OMe)_3$] (**2**) as a safer (and, in fact, cheaper) alternative to TMOS for the sustainable direct amidation of carboxylic acids with amines (Figure 1).

Phenylacetic acid and benzoic acid were chosen as representative acids to be amidated using MTM (**2**) with a representative primary amine, a secondary cyclic amine, a secondary acyclic amine, and an aniline to enable a direct comparison with the use of TMOS (**1**).[11] While we were hopeful that this single "methoxy-to-methyl" switch would not be too deleterious to reactivity, we anticipated that the workup procedure would require significant modification to deal with the complex mixture of linear and cyclic polysiloxanes known to result in hydrolysis of MTM (**2**).[12] In the event, the use of 250 mol % MTM (for optimization of MTM loading, see the Supporting Information) in refluxing toluene provided pure amide products **3**−**10** directly after a suitably modified workup (for development of the workup procedure, see the Supporting Information). Specifically, evaporation of the reaction mixture postreaction removes the solvent as well as siloxane $(MeO)_2MeSi\text{-}O\text{-}SiMe(OMe)_2$ and methanol as the expected stoichiometric byproducts of the amidation process.[13] Non-volatile oligomeric polysiloxanes were found to be completely removed after subsequent stirring of the residue in a homogeneous THF/aqueous NaOH solution for 1 h, where any unwanted methyl ester side product also undergoes hydrolysis. Any unreacted carboxylic acid is also removed in this step, and any unreacted amine is removed in a subsequent aqueous acid wash. This workup procedure thereby provides the amide products in pure form without the need for any further purification regardless of the extent of amidation reaction conversion.

Inspection of the isolated yields for amides **3**−**10** shows that MTM is as effective as TMOS (**1**) as a reagent for amidation of the representative aliphatic carboxylic acid with all of the main amine classes (Figure 2). The use of benzoic acid as a representative, less reactive, aromatic carboxylic acid was a high yield with a primary amine but less successful with secondary amines, and in contrast to the case of TMOS,[11] the attempted use of 4 Å molecular sieves for these amidations in the reaction mixture or suspended in the headspace proved to be detrimental. Pleasingly, the use of both aliphatic and aromatic carboxylic acids with aniline provided the amide products in good yields.[14]

Further exemplification of the MTM direct amidation method gave amides **11**−**26** (Figure 3A). These include examples of amide formation using branched carboxylic acids and amines, heteroaromatic and ferrocenyl-containing entities, halogenated substrates, and unsaturated carboxylic acids. Notably, both *N*-Cbz- and *N*-Boc-protected amino acids underwent successful amidation[15] to give amides **22** and **23**, respectively, without racemization. It is important to emphasize that all of these amidations were conducted on a gram scale, where the devised workup procedure gave the pure amide product without the requirement for chromatography. However, attempts to (doubly) amidate malonic acid, or an α-hydroxy acid,[16] to form a Weinreb amide[17] or to use a low-boiling point amine[18] under these conditions gave amides **27**−**30** (Figure 3B) in only low yield, albeit pure directly after workup, and these experiments show the current limits of the method.

As part of these investigations, we discovered that several secondary amide products crystallized from their reaction mixtures on cooling where residual MTM and its byproducts remained in solution. This allowed isolation of the pure amide product directly by filtration (and a hexane wash) without the need for any further workup, thereby resulting in low PMI values as exemplified for amides **31** and **32** (Figure 4).[19] To the best of our knowledge, this is the first demonstration of insolubility of secondary amides in toluene being utilized for product isolation in an amidation protocol, and we anticipate that it would be widely applicable to other secondary amide products.

Mechanistically, it has been proposed that amidations promoted by stoichiometric silicon reagents form silyl esters as activated intermediates.[8] We therefore propose that these amidations take place by reversible reaction of the carboxylic acid with MTM to produce a silyl ester of type **A** with loss of methanol, followed by subsequent irreversible attack by amine to form the amide product (Figure 5). The liberated silanol **B** evidently must undergo favorable condensation with a second equivalent of MTM to form siloxane **C** and a second equivalent of methanol. The observation of small quantities of methyl esters (which may themselves undergo amidation) in crude reaction mixtures implicates some competitive direct attack of silyl ester **A** by methanol. In support of this mechanistic proposal, reaction of phenylacetic acid with MTM (**2**) showed the formation of an intermediate with a ^1H NMR shift at 0.42 ppm, which is consistent with assignment to the $Si\text{-}CH_3$ of a silyl ester. The silyl ester was found to be completely consumed upon addition of amine with concomitant amide formation.[20]

In conclusion, we have reported the use of MTM (**2**) as an effective, inexpensive reagent for the direct amidation of carboxylic acids with amines, providing a safe alternative to the previously published protocol using TMOS (**1**). The amide products can be isolated in pure form either via a workup procedure that removes residual MTM and any linear and cyclic polysiloxane reaction byproducts or (in the case of secondary amides) by simple crystallization from the reaction mixture. We expect that the latter finding will be generally applicable to provide secondary amides by this method with low process mass intensities.[21]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c04265.

General experimental section, optimization of MTM loading, optimization of the workup procedure, experimental details and characterization data for compounds, copies of ^1H and ^{13}C spectra for all compounds, and chiral HPLC analysis of amides **22** and **23** (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

D. Christopher Braddock − *Department of Chemistry, Molecular Sciences Research Hub, Imperial College London, London W12 0BZ, U.K.*; orcid.org/0000-0002-4161-7256; Email: c.braddock@imperial.ac.uk

Paul D. Lickiss − *Department of Chemistry, Molecular Sciences Research Hub, Imperial College London, London W12 0BZ,*

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U.K.; orcid.org/0000-0002-8507-9867;
Email: p.lickiss@imperial.ac.uk

Author

Joshua J. Davies − *Department of Chemistry, Molecular Sciences Research Hub, Imperial College London, London W12 0BZ, U.K.;* orcid.org/0000-0001-7665-982X

Complete contact information is available at:
https://pubs.acs.org/10.1021/acs.orglett.1c04265

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For recent representative reviews, see: (a) Muramatsu, W.; Hattori, T.; Yamamoto, H. Amide bond formation: beyond the dilemma between activation and racemization. *Chem. Commun.* **2021**, *57*, 6346−6359. (b) Pedrood, K.; Bahadorikhalili, S.; Lotfi, V.; Larijani, B.; Mahdavi, M. Catalytic and non-catalytic amidation of carboxylic acid substrates. *Mol. Diversity* **2021**, DOI: 10.1007/s11030-021-10252-0. (c) Massolo, E.; Pirola, M.; Benaglia, M. Amide bond formation strategies: latest advances on a dateless transformation. *Eur. J. Org. Chem.* **2020**, *2020*, 4641−4651. (d) Wang, X. Challenges and outlook for catalytic direct amidation reactions. *Nat. Catal.* **2019**, *2*, 98−102. (e) Sabatini, M. T.; Boulton, L. T.; Sneddon, H. F.; Sheppard, T. D. A green chemistry perspective on catalytic amide bond formation. *Nat. Catal.* **2019**, *2*, 10−17.

(2) Boström, J.; Brown, D. G.; Young, R. J.; Keserü, G. M. Expanding the medicinal chemistry synthetic toolbox. *Nat. Rev. Drug Discovery* **2018**, *17*, 709−727.

(3) Dunetz, J. R.; Magano, J.; Weisenburger, G. A. Large-scale applications of amide coupling reagents for the synthesis of pharmaceuticals. *Org. Process Res. Dev.* **2016**, *20*, 140−177.

(4) (a) Gooßen, L. J.; Ohlmann, D. M.; Lange, P. P. The thermal amidation of carboxylic acids revisited. *Synthesis* **2009**, *2009*, 160−164. (b) Charville, H.; Jackson, D. A.; Hodges, G.; Whiting, A.; Wilson, M. R. The Uncatalysed Direct Amide Formation Reaction-Mechanism Studies and the Key Role of Carboxylic Acid H-Bonding. *Eur. J. Org. Chem.* **2011**, *2011*, 5981−5990.

(5) Representative examples: (a) Ishihara, K.; Ohara, S.; Yamamoto, H. 3,4,5-Trifluorobenzeneboronic acid as an extremely active amidation catalyst. *J. Org. Chem.* **1996**, *61*, 4196−4197. (b) Tang, P. Boric acid catalyzed amide formation from carboxylic acids and amines: *n*-benzyl-4-phenylbutyramide. *Org. Synth* **2005**, *81*, 262−272. (c) Arnold, K.; Batsanov, A. S.; Davies, B.; Whiting, A. Synthesis, evalution and application of novel bifunctional *N,N*-di-isopropylbenzylamineboronic acid catalysts for direct amide formation between carboxylic acids and amines. *Green Chem.* **2008**, *10*, 124−13. (d) Al-Zoubi, R. M.; Marion, O.; Hall, D. G. Direct and waste-free amidations and cycloadditions by organocatalytic activation of carboxylic acids at room temperature. *Angew. Chem., Int. Ed.* **2008**, *47*, 2876−2879. (e) Gernigon, N.; Al-Zoubi, R. M.; Hall, D. G. Direct Amidation of Carboxylic Acids Catalysed by *ortho*-Iodo Arylboronic Acids: Catalyst Optimization, Scope, and Preliminary Mechanistic Study Supporting a Peculiar Halogen Acceleration Effect. *J. Org. Chem.* **2012**, *77*, 8386−8400. (f) Yamashita, R.; Sakakura, A.; Ishihara, K. Primary alkylboronic acids as highly active catalysts for the dehydrative amide condensation of α-hydroxycarboxylic acids. *Org. Lett.* **2013**, *15*, 3654−3657. (g) Mohy El Dine, T.; Erb, W.; Berhault, Y.; Rouden, J.; Blanchet, J. Catalytic chemical amide synthesis at room temperature: one more step toward peptide synthesis. *J. Org. Chem.* **2015**, *80*, 4532−4544. (h) Ishihara, K.; Lu, Y. Boronic acid−DMAPO cooperative catalysis for dehydrative condensation between carboxylic acids and amines. *Chem. Sci.* **2016**, *7*, 1276−1280. (i) Sabatini, M. T.; Boulton, L. T.; Sheppard, T. D. Borate esters: Simple catalysts for the sustainable synthesis of complex amides. *Sci. Adv.* **2017**, *3*, No. e1701028. (j) Noda, H.; Furutachi, M.; Asada, Y.; Shibasaki, M.; Kumagai, N. Unique physiochemical and catalytic properties dictated by the B_3NO_2 ring system. *Nat. Chem.* **2017**, *9*, 571−577. (k) Liu, Z.; Noda, H.; Shibasaki, M.; Kumagai, N. Catalytic Oligopeptide Synthesis. *Org. Lett.* **2018**, *20*, 612−615. (l) Arkhipenko, S.; Sabatini, M. T.; Batsanov, A. S.; Karaluka, V.; Sheppard, T. D.; Rzepa, H. S.; Whiting, A. Mechanistic insights into boron-catalysed direct amidation reactions. *Chem. Sci.* **2018**, *9*, 1058−1072. (m) Sawant, D. N.; Bagal, D. B.; Ogawa, S.; Selvam, K.; Saito, S. Diboron-Catalyzed Dehydrative Amidation of Aromatic Carboxylic Acids with Amines. *Org. Lett.* **2018**, *20*, 4397−4400. (n) Opie, C. R.; Noda, H.; Shibasaki, M.; Kumagai, N. All Non-Carbon B_3NO_2 Exotic Heterocycles: Synthesis, Dynamics, and Catalysis. *Chem. - Eur. J.* **2019**, *25*, 4648−4653. (o) Noda, H.; Asada, Y.; Shibasaki, M.; Kumagai, N. Neighboring Protonation Unveils Lewis Acidity in the B_3NO_2 Heterocycle. *J. Am. Chem. Soc.* **2019**, *141*, 1546−1554. (p) Shimada, N.; Hirata, M.; Koshizuka, M.; Ohse, N.; Kaito, R.; Makino, K. Diboronic Acid Anhydrides as Effective Catalysts for the Hydroxy-Directed Dehydrative Amidation of Carboxylic Acids. *Org. Lett.* **2019**, *21*, 4303−4308. (q) Coomber, C. E.; Laserna, V.; Martin, L. T.; Smith, P. D.; Hailes, H. C.; Porter, M. J.; Sheppard, T. D. Catalytic direct amidations in tert-butyl acetate using $B(OCH_2CF_3)_3$. *Org. Biomol. Chem.* **2019**, *17*, 6465−6469. (r) Michigami, K.; Sakaguchi, T.; Takemoto, Y. Catalytic dehydrative peptide synthesis with gem-diboronic acids. *ACS Catal.* **2020**, *10*, 683−688. (s) Koshizuka, M.; Makino, K.; Shimada, N. Diboronic Acid Anhydride-Catalyzed Direct Peptide Bond Formation Enabled by Hydroxy-Directed Dehydrative Condensation. *Org. Lett.* **2020**, *22*, 8658−8664.

(6) Representative examples: (a) Starkov, P.; Sheppard, T. D. Borate esters as convenient reagents for direct amidation of carboxylic acids and transamidation of primary amides. *Org. Biomol. Chem.* **2011**, *9*, 1320−1323. (b) Lanigan, R. M.; Starkov, P.; Sheppard, T. D. Direct Synthesis of Amides from Carboxylic Acids and Amines Using $B(OCH_2CF_3)_3$. *J. Org. Chem.* **2013**, *78*, 4512−4523. (c) Karaluka, V.; Lanigan, R. M.; Murray, P. M.; Badland, M.; Sheppard, T. D. $B(OCH_2CF_3)_3$-mediated direct amidation of pharmaceutically relevant building blocks in cyclopentyl methyl ester. *Org. Biomol. Chem.* **2015**, *13*, 10888−10894. (d) Lanigan, R. M.; Karaluka, V.; Sabatini, M. T.; Starkov, P.; Badland, M.; Boulton, L.; Sheppard, T. D. Direct amidation of unprotected amino acids using $B(OCH_2CF_3)_3$. *Chem. Commun.* **2016**, *52*, 8846−8849.

(7) Recent representative examples: (a) Lundberg, H.; Tinnis, F.; Zhang, J.; Algarra, A. G.; Himo, F.; Adolfsson, H. Mechanistic elucidation of zirconium-catalyzed direct amidation. *J. Am. Chem. Soc.* **2017**, *139*, 2286−2295. (b) Lundberg, H.; Tinnis, F.; Adolfsson, H. Zirconium catalyzed amide formation without water scavenging. *Appl. Organomet. Chem.* **2019**, *33*, No. e5062. (c) Muramatsu, W.; Yamamoto, H. Tantalum-Catalyzed Amidation of Amino Acid Homologues. *J. Am. Chem. Soc.* **2019**, *141*, 18926−18931. (d) Muramatsu, W.; Hattori, T.; Yamamoto, H. Substrate-Directed Lewis-Acid Catalysis for Peptide Synthesis. *J. Am. Chem. Soc.* **2019**, *141*, 12288−12295. (e) Wang, H.; Dong, W.; Hou, Z.; Cheng, L.; Li, X.; Huang, L. Direct amidation of non-activated carboxylic acid and amine derivatives catalyzed by $TiCp_2Cl_2$. *Appl. Organomet. Chem.* **2020**, *34*, No. e5568.

(8) For a review of stoichiometric silicon reagents for direct amidation, see: (a) Davies, J. J.; Braddock, D. C.; Lickiss, P. D. Silicon compounds as stoichiometric coupling reagents for direct amidation. *Org. Biomol. Chem.* **2021**, *19*, 6746−6760. For the use of a catalytic silicon entity in conjunction with a stoichiometric silicon reagent, see: (b) Muramatsu, W.; Manthena, C.; Nakashima, E.; Yamamoto, H. Peptide Bond-Forming Reaction via Amino Acid Silyl Esters: New Catalytic Reactivity of an Aminosilane. *ACS Catal.* **2020**, *10*, 9594−9603.

(9) Recent representative examples: (a) Krause, T.; Baader, S.; Erb, B.; Gooßen, L. J. Atom-economic catalytic amide synthesis from amines and carboxylic acids activated *in situ* with acetylenes. *Nat. Commun.* **2016**, *7*, 11732. (b) Potadar, S. M.; Mali, A. S.; Waghmode, K. T.; Chaturbhuj, G. U. Repurposing *n*-butyl stannoic acid as highly efficient catalyst for direct amidation of carboxylic acids with amines. *Tetrahedron Lett.* **2018**, *59*, 4582−4586. (c) Srivastava, V.; Singh, P. K.; Singh, P. P. Visible light photoredox catalyzed amidation of carboxylic acids with amines. *Tetrahedron Lett.* **2019**, *60*, 40−43. (d) Handoko; Satishkumar, S.; Panigrahi, N. R.; Arora, P. S. Rational design of an organocatalyst for peptide bond formation. *J. Am. Chem. Soc.* **2019**, *141*, 15977−15985. (e) Li, Z.; Liu, L.; Xu, K.; Huang, T.; Li, X.; Song, B.; Chen, T. Palladium-Catalyzed N-Acylation of Tertiary Amines by Carboxylic Acids: A Method for the Synthesis of Amides. *Org. Lett.* **2020**, *22*, 5517−5521. (f) Wang, J.; Hou, H.; Hu, Y.; Lin, J.; Wu, M.; Zheng, Z.; Xu, X. Visible-light-induced direct construction of amide bond from carboxylic acids with amines in aqueous solution. *Tetrahedron Lett.* **2021**, *65*, 152801.

(10) (a) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L., Jr.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. Key green chemistry research areas—a perspective from pharmaceutical manufacturers. *Green Chem.* **2007**, *9*, 411−420. (b) Bryan, M. C.; Dunn, P. J.; Entwistle, D.; Gallou, F.; Koenig, S. G.; Hayler, J. D.; Hickey, M. R.; Hughes, S.; Kopach, M. E.; Moine, G.; Richardson, P.; Roschangar, F.; Steven, A.; Weiberth, F. J. Key Green Chemistry research areas from a pharmaceutical manufacturers' perspective revisited. *Green Chem.* **2018**, *20*, 5082−5103. (c) Santos, A. S.; Silva, A. M.; Marques, M. M. B. Sustainable Amidation Reactions−Recent Advances. *Eur. J. Org. Chem.* **2020**, *2020*, 2501−2516.

(11) Braddock, D. C.; Lickiss, P. D.; Rowley, B. C.; Pugh, D.; Purnomo, T.; Santhakumar, G.; Fussell, S. J. Tetramethyl Orthosilicate (TMOS) as a Reagent for Direct Amidation of Carboxylic Acids. *Org. Lett.* **2018**, *20*, 950−953.

(12) Sprung, M. M.; Guenther, F. O. The partial hydrolysis of methyltrimethoxysilane. *J. Am. Chem. Soc.* **1955**, *77*, 4173−4175.

(13) Inspection of the distillate (2.4 mbar, 80 °C) by ^{1}H NMR found a single silicon component corresponding to disiloxane $(MeO)_2MeSi\text{-}O\text{-}SiMe(OMe)_2$: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.2 (s, 6H), 3.6 (s, 12H). The isolation of this siloxane implicates the loss of methanol in the amidation process corresponding to the following stoichiometric equation: $RCO_2H + R'NH_2 + 2MeSi(OMe)_3 \rightarrow RCONHR' + (MeO)_2MeSi\text{-}O\text{-}SiMe(OMe)_2 + 2MeOH$. Inspection of this stoichiometric equation reveals that 2 equiv of MTM is required. The expected 2 equiv of methanol could be collected in a Dean−Stark trap by fractional distillation in an amidation experiment under standard conditions for amide **31** on a 45 mmol scale (cf. Figure 4).

(14) An acid wash could not remove aniline during the workup; however, final trituration with petroleum ether was found to provide pure amide products.

(15) Fmoc-protected amino acids were shown to undergo deprotection.

(16) (a) Meng, Z.; Butcher, W. E. Development of One-Pot Synthesis of α-Hydroxy α-Trifluoromethyl Amides. *Tetrahedron Lett.* **2013**, *54*, 5133−5136. (b) Huang, M.; Zhong, S.; Xu, M.; Liu, Y. Synthesis of α-Hydroxyl Amides via Direct Amidation of Lactic Acid at Solvent- and Catalyst-Free Conditions. *J. Chem. Res.* **2015**, *39* (5), 274−276.

(17) For the original report, see: (a) Nahm, S.; Weinreb, S. M. *N*-Methoxy *N*-methylamides as effective acylating agents. *Tetrahedron Lett.* **1981**, *22*, 3815−3818. For representative recent examples, see: (b) Prakoso, N. I.; Matsuda, F.; Umezawa, T. Efficient Synthesis of α,β-Dichlorinated Ketones from α,β-Dichlorinated Weinreb Amides through a Simple Work-up Procedure. *Org. Biomol. Chem.* **2021**, *19*, 7822−7826. (c) Senatore, R.; Ielo, L.; Monticelli, S.; Castoldi, L.; Pace, V. Weinreb Amides as Privileged Acylating Agents for Accessing α-Substituted Ketones. *Synthesis* **2019**, *51*, 2792−2808.

(18) For representative recent examples, see: (a) Ramachandran, P. V.; Hamann, H. J. Ammonia-Borane as a Catalyst for the Direct Amidation of Carboxylic Acids. *Org. Lett.* **2021**, *23*, 2938−2942. (b) Ramachandran, P. V.; Hamann, H. J.; Choudhary, S. Amine-Boranes as Dual-Purpose Reagents for Direct Amidation of Carboxylic Acids. *Org. Lett.* **2020**, *22*, 8593−8597.

(19) Amide **3** (96%, PMI = 11), **11** (96%, PMI = 11), and **26** (78%, PMI = 14) were also isolated in pure form after crystallization.

(20) Phenylacetic acid (2.45 g, 18 mmol) in refluxing toluene was stirred with MTM (5.16 mL, 36 mmol). Aliquots of the reaction mixture were analyzed by ^{1}H NMR spectrocopy using durene as an internal standard. *N*-Benzylmethylamine was added after 3 h.

(21) ^{1}H NMR, ^{13}C NMR, IR, and MS data are available via a data repository: Davies, J. J. Methyltrimethoxysilane (MTM) as a Reagent for Direct Amidation of Carboxylic Acids. *Imperial College HPC Data Repository*, 2020 DOI: 10.14469/hpc/9991.

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