CHEMISTRY

Direct N-alkylation of unprotected amino acids with alcohols

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***N*-alkyl amino acids find widespread application as highly valuable, renewable building blocks. However, traditional synthesis methodologies to obtain these suffer from serious limitations, providing a major challenge to develop sustainable alternatives. We report the first powerful catalytic strategy for the direct N-alkylation of unprotected α-amino acids with alcohols. This method is highly selective, produces water as the only side product leading to a simple purification procedure, and a variety of α-amino acids are mono- or di-N-alkylated, in most cases with excellent retention of optical purity. The hydrophobicity of the products is tunable, and even simple peptides are selectively alkylated. An iron-catalyzed route to mono-*N*-alkyl amino acids using renewable fatty alcohols is also described that represents an ideal green transformation for obtaining fully bio-based surfactants.**

INTRODUCTION

α-Amino acids are a prominent class of naturally occurring chiral compounds (*1*) that may serve as renewable alternatives to amines derived from fossil resources (Fig. 1A) (*2*, *3*). In particular, *N*-alkyl amino acids are highly valuable as chiral building blocks for the synthesis of pharmaceutically active compounds (*4*), biodegradable polymers (*5*), ligands for asymmetric catalysis (*6*), or in other specialized applications (Fig. 1B) (*7*–*9*). *N*-alkyl amino acids have shown promise as amphoteric surfactants (*10*). Being commodities, surfactants are produced on a large scale, and there is a pressing need to develop direct sustainable catalytic methods to obtain environmentally friendly (*11*) and fully bio-based alternatives (*12*), especially in the context of the bio-based economy (*13*). Despite the obvious potential of *N*-alkyl amino acids, there is a complete lack of selective catalytic methods to obtain these compounds via direct functionalization of unprotected α-amino acids. In general, N-alkylation of α-amino acids is performed using stoichiometric methods, such as reductive alkylation with aldehydes, which use inorganic reductants or nucleophilic substitution with alkyl halides (*14*). These conventional strategies usually suffer from limited availability, versatility, or stability of the starting materials and, in particular, the formation of stoichiometric amounts of by-products and tedious purification procedures (Fig. 2A). Herein, we demonstrate the catalytic direct N-alkylation of amino acids with alcohols as inexpensive and renewable reaction partners in a fully atom-economic process avoiding racemization and producing only water as by-product (Fig. 2B). Setting our design criteria, the ultimate method should be applicable to the exclusive use of biorenewable feedstock amino acids and alcohols, be based on abundant Fe-based catalysts, produce only innocuous water as side product, and directly lead to a common product, that is, a surfactant.

Alcohols can be derived from renewable resources through the fermentation of carbohydrates (*13*), catalytic depolymerization of lignocellulose (*13*, *15*), as well as the reduction of fatty acids contained in plant triglycerides (Fig. 1A) (*16*). Thus, alcohols are widely abundant, ideal starting materials to accomplish the direct N-alkylation of α-amino acids.

A desired catalytic approach to carry out such a privileged N-alkylation protocol is based on the borrowing hydrogen strategy (*17*, *18*) that proceeds via a sequence of reaction steps (Fig. 2C) involving dehydrogenation of the alcohol substrate to yield the corresponding carbonyl compound followed by imine formation and subsequent imine hydrogenation, using an appropriate catalyst. Although a number of transition metal complexes (*17*) are known to catalyze the coupling of a variety of amines and alcohols using this method, the direct alkylation of amino acids as substrates using homogeneous hydrogen borrowing catalysis is unprecedented.

There are several reasons why the selective N-alkylation of unprotected amino acids, compared to simple amines, is expected to be highly challenging. First, most amino acids have limited solubility in nonpolar organic solvents, and their zwitterionic character renders these substrates sensitive to changes of pH and basic or acidic reagents. Furthermore, competing esterification of the amino acid instead of N-alkylation could take place. Moreover, racemization of the substrate or the formed products under the reaction conditions may be a serious problem, because many hydrogen borrowing methods require the addition of a strong base (*17*, *18*). To the best of our knowledge, only very few examples of N-alkylation or N-allylation of free amino acids are known to mainly use heterogeneous catalysts (*19*–*21*).

RESULTS AND DISSCUSION

To accomplish the novel N-alkylation of amino acids with alcohols according to the reaction sequence shown in Fig. 2C, we have initially selected a well-defined, homogeneous ruthenium complex, the Shvo catalyst (**Cat 1**) (*22*), which has already demonstrated potential in transfer hydrogenation of polar double bonds (*23*) and trialkylation of ammonia salts with alcohols (*24*). Because of its unique structure, this complex is capable of bifunctional activation of the alcohol substrate without the need for any additional base, an important requirement for preserving enantiopurity of the amino acid substrate and derived products.

In preliminary experiments, to establish proof of principle for the desired hydrogen borrowing sequence involving **Cat 1** (Fig. 2C), we chose the cyclic unprotected amino acid proline (**1a**) and the simple N-alkylation reagent ethanol (**2a**) as substrates, whereby ethanol served both as reagent and solvent. The reaction temperature was kept at 90°C to minimize possible competing esterification reactions. Gratifyingly, full conversion of **1a** was observed using a catalyst loading as low as 1 mole percent (mol %) **Cat 1**, and upon simply removing the excess of ethanol, *N*-ethyl-proline **3aa** was obtained in quantitative yield and excellent purity [as evidenced by ^{1}H nuclear magnetic resonance (NMR) measurement; see p. S36 in the Supplementary Materials],

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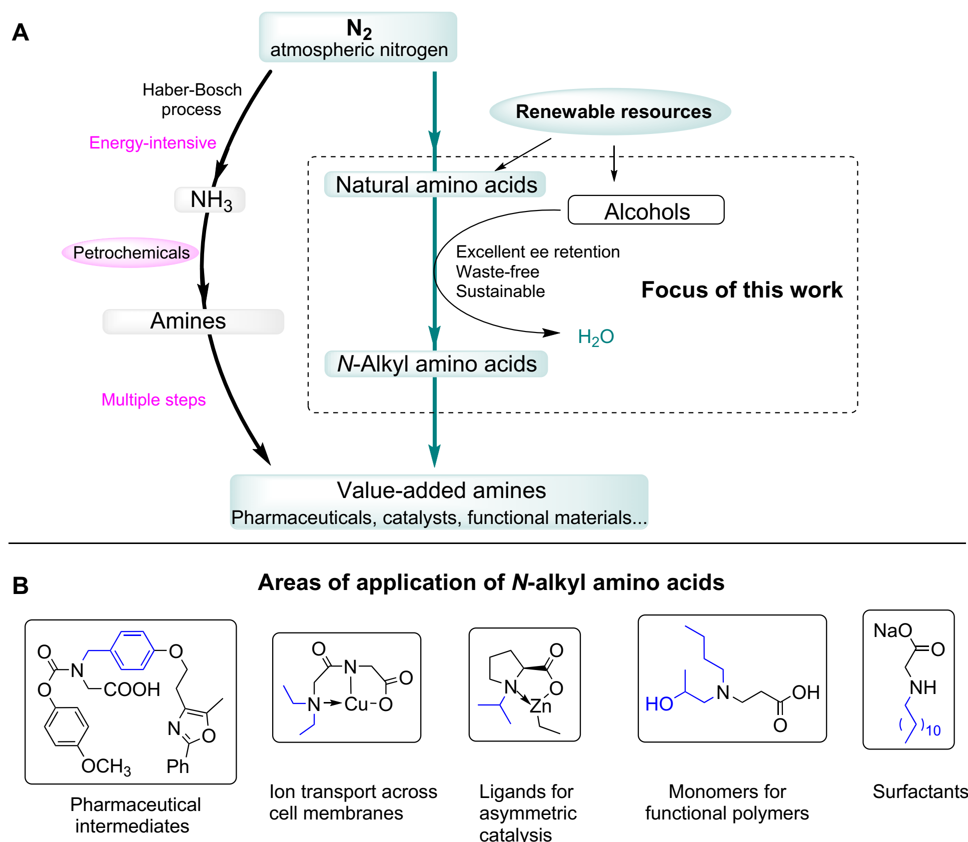

Fig. 1. Sustainable catalytic methods for the synthesis of *N*-alkyl amino acids and areas of application. (**A**) Fossil versus renewable pathways to value-added amines. The nonrenewable path proceeds via the Haber-Bosch process and uses petrochemicals as reaction partners to obtain simple amines, which are further functionalized. The alternative pathway uses natural amino acids, which are directly coupled with alcohols derived from renewable resources to obtain fully bio-based *N*-alkyl amino acids. The fundamental challenge is the development of efficient and sustainable catalytic methods to enable this step. ee, enantiomeric excess. (**B**) Various areas of application of *N*-alkyl amino acids.

not requiring any purification steps. To demonstrate the power of this highly selective N-alkylation methodology, we fully converted a variety of amino acids such as glycine (**1b**), alanine (**1c**), valine (**1d**), leucine (**1e**), and phenylalanine (**1f**) to the corresponding *N*,*N*-di-alkylated analogs with perfect selectivity (Fig. 3). Even serine (**1g**), bearing a free hydroxyl functionality at the side chain, provided the desired *N*,*N*-diethyl-serine (**3ga**) in quantitative yield. No product was observed with lysine (**1h**); however, N^6-Ac-lysine (**1i**) provided the desired product in 74% isolated yield. A crucial requirement for a method for selective modification of amino acids is that the valuable chiral information contained in the starting material should be retained upon functionalization. Excellent ee values (93 to 99%) were measured for products **3aa**, **3da**, **3ea**, and **3fa.** Racemization occurred to a small extent in the case of *N*,*N*-diethyl-serine (86% ee) and *N*,*N*-diethyl-alanine (84% ee), which is very likely due to the dehydrogenation of the amine functionality in alanine and serine or their monoalkylated analogs. The activity of the Shvo catalyst in amine dehydrogenation was previously described by Casey and Johnson (*25*) and Beller and co-workers (*26*).

Next, a simple secondary alcohol, isopropanol (**2b**), was applied in the N-alkylation of α-amino acids. Whereas *N*-isopropyl-proline (**3ab**) was readily obtained upon functionalization of proline (**1a**) in neat isopropanol, other amino acids had limited solubility. This prompted us to investigate methanol (**2c**) and CF_3CH_2OH (**2d**) as solvents. CF_3CH_2OH was found to be an excellent solvent for the isopropyl functionalization of amino acids **1c** to **1g** to provide products **3cb** to **3gb**, respectively, in quantitative yield. In all cases, selective monoalkylation was observed, likely due to the steric hindrance created after the insertion of the first isopropyl moiety. This general method allows easy access to mono-N-alkylated amino acids for the synthesis of modified proteins with higher lipophilicity.

Excellent scope was achieved in the functionalization of proline (**1a**) with diverse aliphatic and aromatic alcohols **2e** to **2i** (Fig. 3). Notably, the chloro-substituted amino acid derivatives **3ag** and **3ai** would allow for further functionalization of these building blocks. Subsequently, the functionalization of phenylalanine (**1f**) with 1-butanol (**2e**), 1-nonanol (**2j**), and 1,5-pentane-diol (**2k**) was readily achieved, yielding the corresponding di-N-alkylated products **3fe**, **3fj**, and **3fk**, respectively. This represents a convenient strategy for modulating the hydrophilicity/lipophilicity of the obtained products (**3fk** versus **3fj**). The modular functionalization of the simplest amino acid, glycine **1b**, was further explored. With 2-butanol (**2l**), selective monoalkylation while using benzylalcohol (**3h**) dialkylation was observed. Interestingly, with 1-pentanol (**2m**), selectivity toward the corresponding mono-N-alkylated (**3bm′**) or di-N-alkylated (**3bm**) product could be achieved simply by adjusting the glycine–to–1-pentanol ratio. Long-chain N-alkylated amino acids have surfactant properties; however, their synthesis

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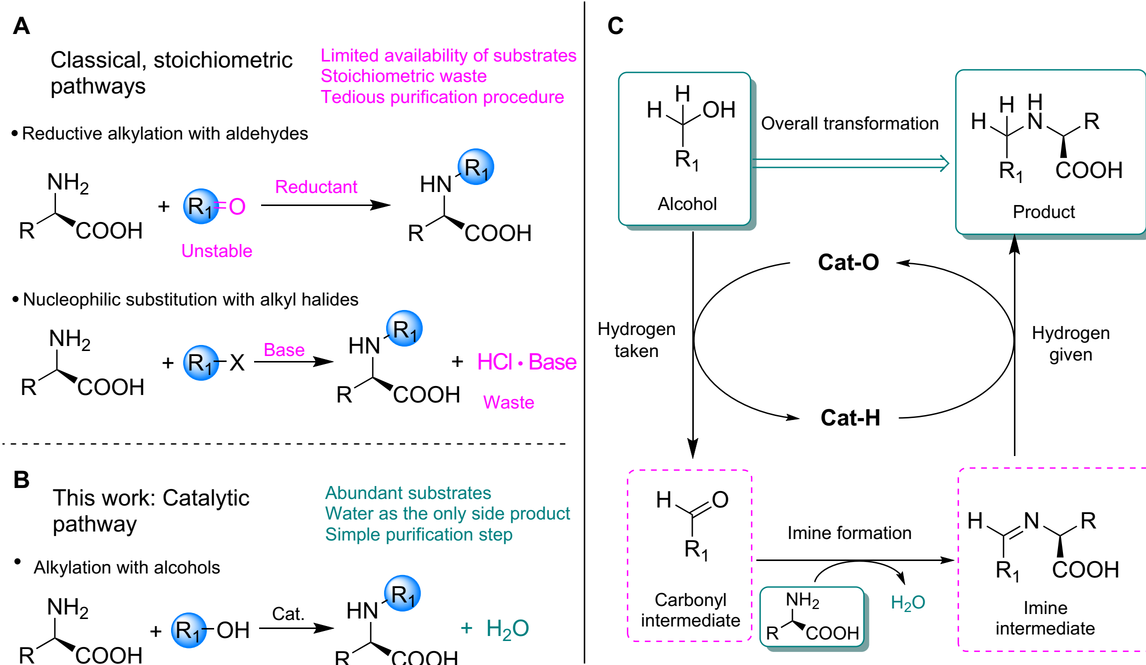

Fig. 2. Classical strategies versus sustainable pathways for N-alkylation of unprotected amino acids. (**A**) Classical methods for the N-alkylation of α-amino acids. (**B**) Sustainable, waste-free direct coupling of α-amino acids with alcohols. (**C**) Proposed mechanism of the direct N-alkylation of α-amino acids with alcohols via the "borrowing hydrogen" strategy.

and purification have thus far been proven challenging. Using our methodology, long-chain N-alkylated amino acids are easily synthesized by direct coupling of glycine with 1-nonanol (**2j**) and 1-dodecanol (**2n**) to yield **3bj** and **3bn**, respectively, in excellent yields (>90%).

Encouraged by the generality of the method for the functionalization of amino acids, we envisioned the selective N-terminal modification of simple peptides. On the basis of this new protocol, the hydrophobicity or hydrophilicity of peptides could be easily tuned by introducing either longer-chain alkyl groups or polar moieties such as hydroxyl groups through simple variation of the alcohol reaction partner. First, it was shown that dipeptide glycylalanine (**4a**) can be quantitatively diethylated (**5aa**) in neat ethanol using **Cat 1**, and even the tripeptide leucylglycylglycine (**4b**) underwent dialkylation on the N terminus, yielding product **5ba.** Furthermore, when dipeptide **4a** was reacted with 1-dodecanol (**2n**), the corresponding dialkylated product **5an**, a lipophilic dipeptide, was obtained, which can be used for transporting metal ions across cell membranes (*8*). On the other hand, the reaction of **4a** with diol **2k** afforded a dipeptide **5ak** with increased hydrophilicity. These reactions represent the first examples of the selective and high-yielding dialkylation of peptide substrates on their N terminus with simple alcohols, allowing for extremely easy purification procedures (*27*). This methodology also has potential for simple N-terminal modification of proteins to affect protein activation and degradation, thereby further diversifying biological functions (*28*).

The waste-free synthesis of environmentally benign and renewable surfactants is a high-impact and, from an industrial perspective, a particularly relevant area of application for our novel methodology (*11*, *12*, *16*). Amino acids serve as versatile building blocks for the preparation of nontoxic and biodegradable surface-active materials, either through functionalization of the carboxylic acid moiety or via N-acylation or N-alkylation of the amino group using acyl or alkyl halogenides (Fig. 4A) (*29*). The latter strategy involves the release of stoichiometric amounts of waste (Fig. 2A) and challenging purification procedures. To overcome these bottlenecks, we set to develop an alternative, highly modular catalytic strategy that provides convenient access to a broad variety of existing and novel surfactant structures solely derived from renewable resources. Such a fully sustainable approach directly couples α-amino acids with long-chain aliphatic alcohols, which can be produced from natural fats and oils (*16*) to obtain *N*-alkyl amino acids, preferably using an Earth-abundant metal catalyst. Recently, our group reported the direct and selective N-alkylation of simpler amines with alcohols using well-defined iron complexes (*30*). On the basis of the results presented here, we attempted the direct N-alkylation of glycine (**1b**) with 1-dodecanol (**2n**) using an Fe-based catalyst that is a structural analog of the Ru complex (**Cat 1**) used above. Gratifyingly, ideal reaction conditions were found at 110°C with 5 mol % **Cat 2**, and mono-*N*-dodecylglycine (**3bn′**) was isolated in 54% yield, besides a smaller amount 8% of *N*,*N*-didodecylglycine (**3bn**). The monoalkylation product (**3bn′**) has already been identified as a surfactant (*10*). After adding KOH and H_2O to **3bn′**, a rich foam formation was observed (Fig. 4B). Next, a variety of fatty alcohols including 1-nonanol (**2j**), 1-decanol (**2o**), 1-tetradecanol (**2p**), 1-hexadecanol (**2q**), and 1-octadecanol (**2n**) were reacted with **1b**, and the corresponding mono-*N*-alkyl glycine derivatives were isolated (Fig. 4B). Furthermore, alanine (**1c**) and proline (**1a**) were successfully N-alkylated with 1-dodecanol (**2n**) and 1-nonanol (**2j**), respectively. These examples demonstrate a novel, straightforward and fully sustainable route to completely biobased surfactants because both unprotected amino acids and alcohols can be derived from renewable resources.

This study shows the direct N-alkylation of unprotected α-amino acids and simple peptides with a variety of alcohols using 1 mol % homogeneous Ru catalyst representing a high-yield and atom-economic

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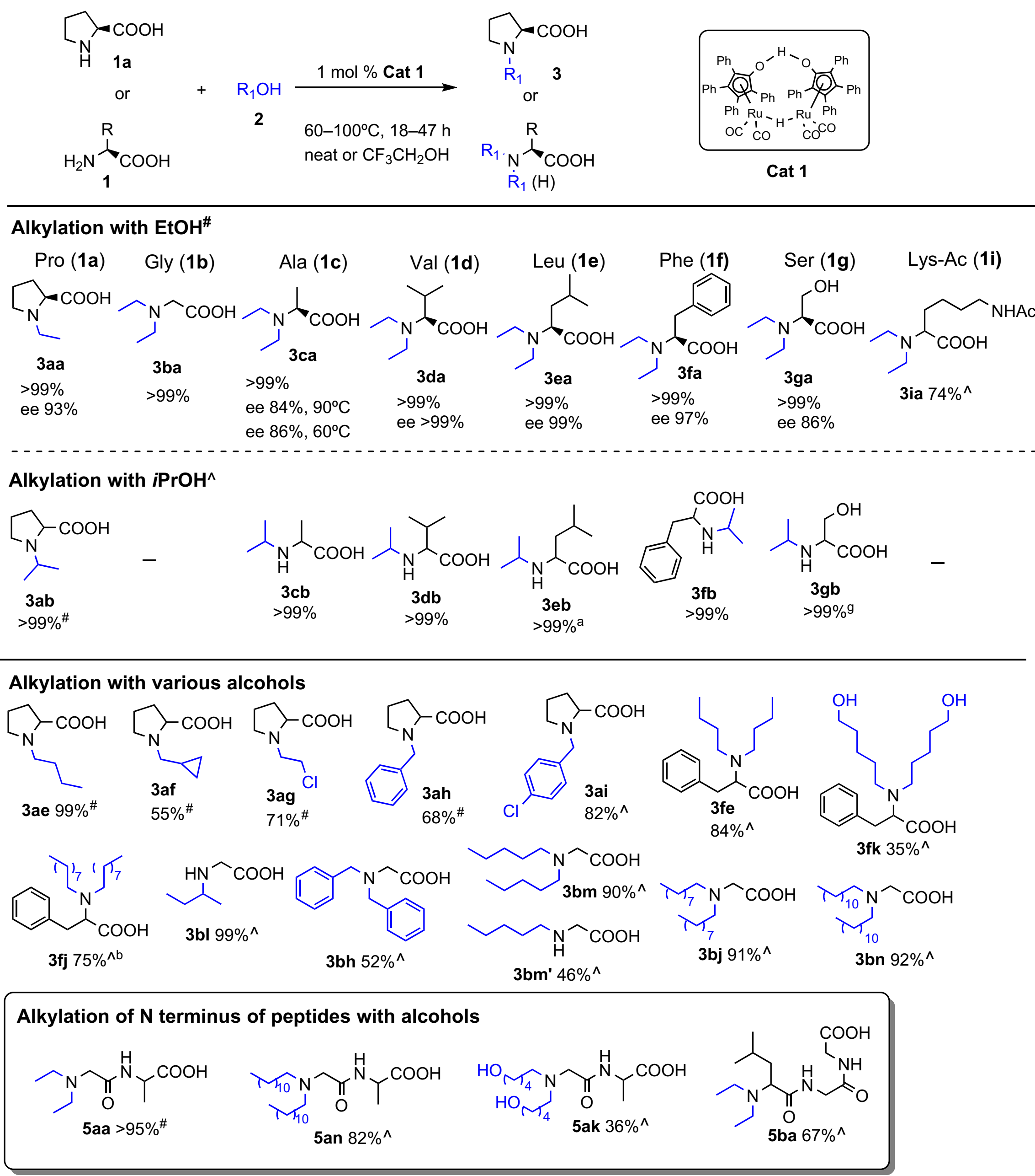

Fig. 3. N-alkylation of amino acids and N-terminal modification of peptides with various alcohols. See the General procedure in Materials and Methods for the description of the experimental procedure and tables S2 to S5 for further details on these experiments. General reaction conditions: 0.2 mmol of **1**, 1 to 5 ml or 0.6 to 2 mmol of **2**, 1 mol % **Cat 1**, neat when using ethanol (**2a**), 1 ml of CF_3CH_2OH (**2d**) when using *i*PrOH (**2b**), 18 to 47 hours, and 90°C unless otherwise specified. Isolated yields are shown, and the ee of the product was measured by high-performance liquid chromatography (HPLC) upon established derivatization procedures (see Determination of the optical purity of products in the Supplementary Materials). #Neat; ^CF_3CH_2OH was used as solvent; [a]2 mol % **Cat 1** was used; [b]100°C.

transformation with excellent selectivities and only water as by-product. The method allows the use of a range of alcohols of various lengths as reaction partners, leading to functionalized amino acids with modular properties such as low or high hydrophilicity. Finally, the demonstration that long-chain alcohols and amino acids can be used as only reaction partners to provide directly mono-*N*-alkyl amino acid surfactants, applying a nonprecious iron catalyst with water as the only waste, represents a nearly ideal transformation, illustrating the great potential for future fully sustainable production of completely bio-based products.

MATERIALS AND METHODS

General methods

Merck silica gel type 9385 (230 to 400) mesh or Merck Al_2O_3, 90 active neutral, was used for chromatography, whereas Merck silica gel 60 (0.25 mm) was used for thin-layer chromatography (TLC). Components were visualized by ultraviolet, ninhydrin, or I_2 staining. Progress of the reactions was determined by ^1H NMR spectroscopy. Mass spectra were recorded on an AEI MS-902 mass spectrometer [EI^+ (positive electron ionization)] or an LTQ Orbitrap XL [ESI^+ (positive

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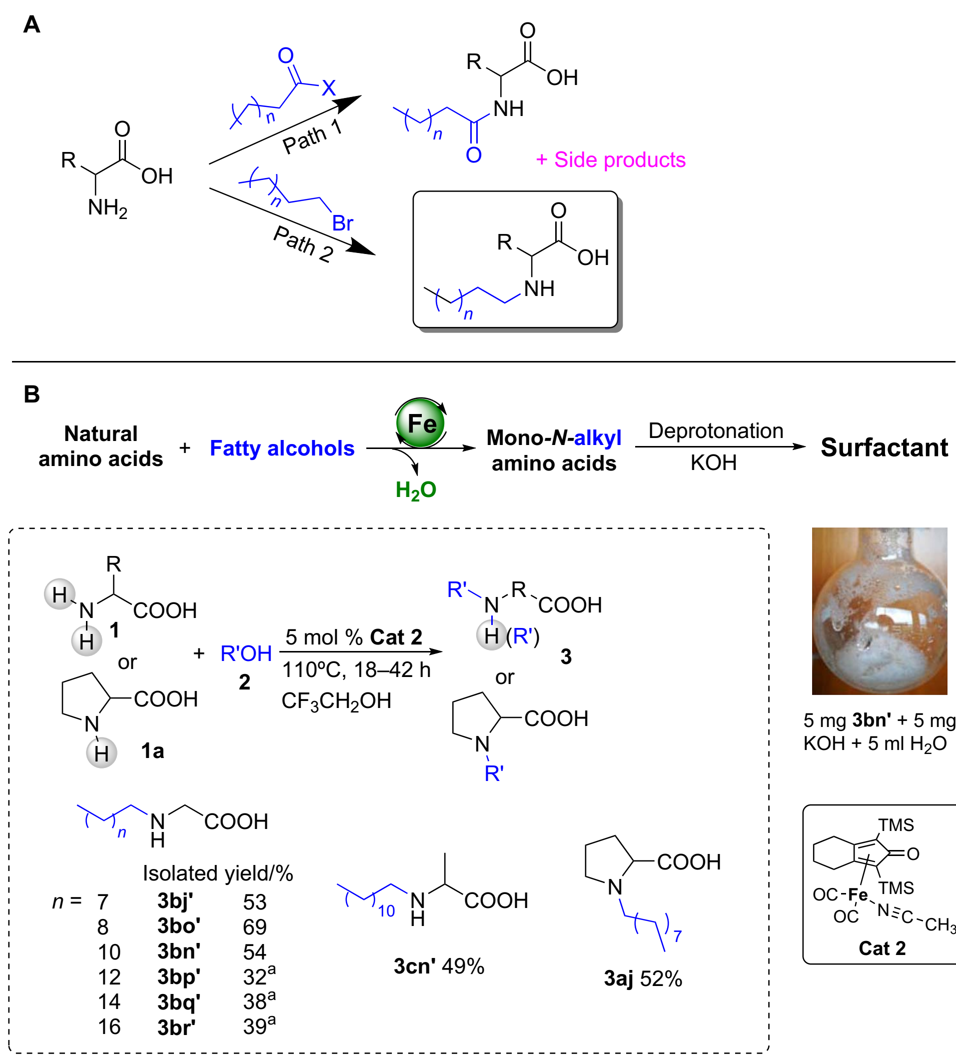

Fig. 4. Synthesis of bio-derived surfactant. (**A**) Conventional stoichiometric pathways for synthesizing amino acid–based surfactants. (**B**) Novel, catalytic method for the direct N-alkylation of amino acids with fatty alcohols with a well-defined iron catalyst, using alcohols of various lengths and cyclic and acyclic amino acids, to provide amino acid–based surfactants after the addition of aqueous KOH. See General procedure in Materials and Methods for the description of the experimental procedure and table S6 for further details on these experiments. General reaction conditions: 0.5 mmol of **1**, 1 ml or 2 mmol of **2**, neat or CF_3CH_2OH (**2d**) as solvent, 5 mol % **Cat 2**, 18 to 42 hours, and 110°C. Isolated yields are shown. [a]The corresponding methyl esters were isolated. TMS, tetramethylsilane.

electrospray ionization)]. ^1H and ^{13}C NMR spectra were recorded on a Varian AMX400 (400 and 100 MHz, respectively) using $CDCl_3$, CD_3OD, D_2O, or dimethyl sulfoxide-d_6 (DMSO-d_6) as solvents. Chemical shift values are reported in parts per million with the solvent resonance as the internal standard ($CDCl_3$, 7.26 for ^1H and 77.00 for ^{13}C; CD_3OD, 3.31 for ^1H and 49.00 for ^{13}C; D_2O, 4.79 for ^1H; and DMSO-d_6, 2.50 for ^1H and 39.52 for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; br., broad; m, multiplet), coupling constants (in hertz), and integration.

All reactions were carried out under an argon atmosphere using oven-dried (110°C) glassware and using standard Schlenk techniques. Toluene was collected from a MBRAUN solvent purification system (MB SPS-800). CF_3CH_2OH (>99.0%) was purchased from TCI without further purification. Complex **Cat 2a** (see table S5) was synthesized according to a previously reported procedure (*31*). **Cat 1** was purchased from Strem. All other reagents were purchased from Sigma, TCI, or Acros in reagent or higher grade and were used without further purification.

Representative procedures

General procedure for the N-alkylation of amino acids with alcohols

An oven-dried 20-ml Schlenk tube equipped with stirring bar was charged with an amino acid (or peptide; given amount), **Cat 1**, **Cat 2a** + 2 equiv. of Me_3NO or **Cat 2** (given amount), and alcohol (given amount); solvent was added when indicated, otherwise the reactions were performed under neat conditions. Amino acid (or peptide) and catalyst were added into the Schlenk tube under air, the Schlenk tube was subsequently connected to an argon line, and a vacuum-backfill cycle was performed three times. Alcohol and solvent were charged under an argon stream. The Schlenk tube was sealed with a screw cap, and the mixture was rapidly stirred at room temperature for 1 min and then was placed into a preheated oil bath at the appropriate temperature and stirred for a given time. The reaction mixture was cooled down to room temperature and concentrated in vacuo. The crude product was characterized by ^1H NMR to determine conversion. In several cases, no additional

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purification was required. As specified, where needed, further purification was conducted through flash column chromatography or crystallization to provide the pure *N*-alkyl amino acid (or peptide) product.

Esterification procedure (for the preparation of methyl ester of alky amino acids 3bp′, 3bq′, and 3br′)

Continuing the General procedure, until the reaction mixture was cooled down to room temperature, 3 ml of benzene was added, and under stirring, $TMSCHN_2$ (2 M in toluene) was added. The reaction was monitored by TLC [SiO_2, mono-*N*-alkyl amino acid, retention factor (R_f) = 0.3 in ethylacetate/MeOH (1:1); methyl mono-*N*-alkyl amino acid ester, R_f = 0.3 in Et_2O]. Finally, the corresponding methyl ester was purified by flash column chromatography [toluene/Et_2O (50:50 to 0:100)].

Preparation of Cat 2

An oven-dried 250-ml Schlenk tube was charged with 100 ml of dry acetone and 2 ml of dry CH_3CN, and the solution was degassed with N_2 for 20 min. Then, 1 g of **Cat 2a** (2.38 mmol) was added under N_2 and stirred for 1 min until it fully solubilized, after which 216 mg of Me_3NO (1.2 equiv.) was added under N_2. A direct color change from yellow to orange was observed within 5 s. The conversion of **Cat 2a** can be monitored by TLC [pentane/ethyl acetate (1:1), on silica gel, R_{fCat2a} = 0.95, R_{fCat2} = 0.35). After 1 hour, the solvent was removed by vacuum; **Cat 2** was purified by flash column chromatography and obtained as a brown solid (0.91 g, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05 to 2.48 (m, 4H), 2.21 (s, 3H), 1.38 to 1.73 (m, 4H), and 0.22 (s, 18 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.80, 180.12, 126.00, 106.58, 69.91, 24.83, 22.31, 4.43, and −0.12. The physical data were identical in all respects to those previously reported (*32*). **Cat 2a** and **Cat 2** are slightly light-sensitive but air-stable.

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/3/12/eaao6494/DC1

table S1. Optimization of reaction conditions for the direct N-ethylation of unprotected amino acids (**1a** to **1i**) with ethanol (**2a**).

table S2. Direct mono-N-isopropylation of an amino acid (**1**) with isopropanol (**2b**).

table S3. Direct N-alkylation of a free amino acid (**1**) with various alcohols (**2**).

table S4. Direct N-alkylation of di- and tripeptides (**4a** to **4b**) with alcohols (**2**).

table S5. Iron-catalyzed N-ethylation of amino acids with ethanol (**2a**).

table S6. Iron-catalyzed N-alkylation of unprotected amino acids (**1a** to **1c**) with long-chain aliphatic alcohols (**2**) to produce surfactants.

Spectral data of isolated compounds

Determination of the optical purity of products

HPLC traces

^{1}H and ^{13}C NMR spectra

References (*33–45*)

REFERENCES AND NOTES

1. T. J. Osberger, D. C. Rogness, J. T. Kohrt, A. F. Stepan, M. C. White, Oxidative diversification of amino acids and peptides by small-molecule iron catalysis. *Nature* **537**, 214–219 (2016).
2. C. O. Tuck, E. Pérez, I. T. Horváth, R. A. Sheldon, M. Poliakoff, Valorization of biomass: Deriving more value from waste. *Science* **337**, 695–699 (2012).
3. T. M. Lammens, M. C. R. Franssen, E. L. Scott, J. P. M. Sanders, Availability of protein-derived amino acids as feedstock for the production of bio-based chemicals. *Biomass Bioenergy* **44**, 168–181 (2012).
4. C. R. Waites, M. A. Dominick, T. P. Sanderson, B. E. Schilling, Nonclinical safety evaluation of muraglitazar, a novel PPARα/γ agonist. *Toxicol. Sci.* **100**, 248–258 (2007).
5. S. Santra, J. M. Perez, Selective *N*-alkylation of β-alanine facilitates the synthesis of a poly(amino acid)-based theranostic nanoagent. *Biomacromolecules* **12**, 3917–3927 (2011).
6. D. R. Fandrick, J. T. Reeves, J. M. Bakonyi, P. R. Nyalapatla, Z. Tan, O. Niemeier, D. Akalay, K. R. Fandrick, W. Wohlleben, S. Ollenberger, J. J. Song, X. Sun, B. Qu, N. Haddad, S. Sanyal, S. Shen, S. Ma, D. Byrne, A. Chitroda, V. Fuchs, B. A. Narayanan, N. Grinberg, H. Lee, N. Yee, M. Brenner, C. H. Senanayake, Zinc catalyzed and mediated asymmetric propargylation of trifluoromethyl ketones with a propargyl boronate. *J. Org. Chem.* **78**, 3592–3615 (2013).
7. M. Y. Pavlov, R. E. Watts, Z. Tan, V. W. Cornish, M. Ehrenberg, A. C. Forster, Slow peptide bond formation by proline and other *N*-alkylamino acids in translation. *Proc. Natl. Acad. Sci. U.S.A.* **106**, 50–54 (2009).
8. M. C. Cleij, P. Scrimin, P. Tecilla, U. Tonellato, Efficient and highly selective copper(II) transport across a bulk liquid chloroform membrane mediated by lipophilic dipeptides. *J. Org. Chem.* **62**, 5592–5599 (1997).
9. P. K. Sasmal, C. N. Streu, E. Meggers, Metal complex catalysis in living biological systems. *Chem. Commun.* **49**, 1581–1587 (2013).
10. Y. Li, K. Holmberg, R. Bordes, Micellization of true amphoteric surfactants. *J. Colloid Interface Sci.* **411**, 47–52 (2013).
11. M. C. Morán, A. Pinazo, L. Pérez, P. Clapés, M. Angelet, M. T. García, M. P. Vinardell, M. R. Infante, "Green" amino acid-based surfactants. *Green Chem.* **6**, 233–240 (2004).
12. M. Kjellin, I. Johansson, *Surfactants from Renewable Resources* (Wiley, 2010).
13. A. J. Ragauskas, C. K. Williams, B. H. Davison, G. Britovsek, J. Cairney, C. A. Eckert, W. J. Frederick Jr., J. P. Hallett, D. J. Leak, C. L. Liotta, J. R. Mielenz, R. Murphy, R. Templer, T. Tschaplinski, The path forward for biofuels and biomaterials. *Science* **311**, 484–489 (2006).
14. A. B. Hughes, Ed. *Amino Acids, Peptides and Proteins in Organic Chemistry: Origins and Synthesis of Amino Acids* (Wiley, 2009), vol. 1.
15. K. Barta, P. C. Ford, Catalytic conversion of nonfood woody biomass solids to organic liquids. *Acc. Chem. Res.* **47**, 1503–1512 (2014).
16. U. Biermann, U. Bornscheuer, M. A. R. Meier, J. O. Metzger, H. J. Schäfer, Oils and fats as renewable raw materials in chemistry. *Angew. Chem. Int. Ed.* **50**, 3854–3871 (2011).
17. S. Bähn, S. Imm, L. Neubert, M. Zhang, H. Neumann, M. Beller, The catalytic amination of alcohols. *ChemCatChem* **3**, 1853–1864 (2011).
18. C. Gunanathan, D. Milstein, Applications of acceptorless dehydrogenation and related transformations in chemical synthesis. *Science* **341**, 1229712 (2013).
19. V. N. Tsarev, Y. Morioka, J. Caner, Q. Wang, R. Ushimaru, A. Kudo, H. Naka, S. Saito, *N*-methylation of amines with methanol at room temperature. *Org. Lett.* **17**, 2530–2533 (2015).
20. C.-P. Xu, Z.-H. Xiao, B.-Q. Zhuo, Y.-H. Wang, P.-Q. Huang, Efficient and chemoselective alkylation of amines/amino acids using alcohols as alkylating reagents under mild conditions. *Chem. Commun.* **46**, 7834–7836 (2010).
21. H. Hikawa, Y. Yokoyama, Palladium-catalyzed mono-*N*-allylation of unprotected amino acids with 1,1-dimethylallyl alcohol in water. *Org. Biomol. Chem.* **9**, 4044–4050 (2011).
22. Y. Shvo, D. Czarkie, Y. Rahamim, D. F. Chodosh, A new group of ruthenium complexes: Structure and catalysis. *J. Am. Chem. Soc.* **108**, 7400–7402 (1986).
23. B. L. Conley, M. K. Pennington-Boggio, E. Boz, T. J. Williams, Discovery, applications, and catalytic mechanisms of Shvo's catalyst. *Chem. Rev.* **110**, 2294–2312 (2010).
24. C. Segarra, E. Mas-Marzá, J. A. Mata, E. Peris, Shvo's catalyst and [IrCp*Cl_2(amidine)] effectively catalyze the formation of tertiary amines from the reaction of primary alcohols and ammonium salts. *Adv. Synth. Catal.* **353**, 2078–2084 (2011).
25. C. P. Casey, J. B. Johnson, Isomerization and deuterium scrambling evidence for a change in the rate-limiting step during imine hydrogenation by Shvo's hydroxycyclopentadienyl ruthenium hydride. *J. Am. Chem. Soc.* **127**, 1883–1894 (2005).
26. D. Hollmann, S. Bähn, A. Tillack, M. Beller, A general ruthenium-catalyzed synthesis of aromatic amines. *Angew. Chem. Int. Ed.* **46**, 8291–8294 (2007).
27. C. D. Spicer, B. G. Davis, Selective chemical protein modification. *Nat. Commun.* **5**, 4740 (2014).
28. Z. W. Lai, A. Petrera, O. Schilling, Protein amino-terminal modifications and proteomic approaches for *N*-terminal profiling. *Curr. Opin. Chem. Biol.* **24**, 71–79 (2015).
29. R. Bordes, K. Holmberg, Amino acid-based surfactants—Do they deserve more attention? *Adv. Colloid Interface Sci.* **222**, 79–91 (2015).
30. T. Yan, B. L. Feringa, K. Barta, Iron catalysed direct alkylation of amines with alcohols. *Nat. Commun.* **5**, 5602 (2014).
31. T. Yan, B. L. Feringa, K. Barta, Benzylamines via iron-catalyzed direct amination of benzyl alcohols. *ACS Catal.* **6**, 381–388 (2016).
32. T. N. Plank, J. L. Drake, D. K. Kim, T. W. Funk, Air-stable, nitrile-ligated (cyclopentadienone) iron dicarbonyl compounds as transfer reduction and oxidation catalysts. *Adv. Synth. Catal.* **354**, 597–601 (2012).
33. G. Verardo, P. Geatti, E. Pol, A. G. Giumanini, Sodium borohydride: A versatile reagent in the reductive *N*-monoalkylation of α-amino acids and α-amino methyl esters. *Can. J. Chem.* **80**, 779–788 (2002).
34. Y. Song, A. D. Sercel, D. R. Johnson, N. L. Colbry, K.-L. Sun, B. D. Roth, A simple method for preparation of *N*-mono- and *N*,*N*-di-alkylated α-amino acids. *Tetrahedron Lett.* **41**, 8225–8230 (2000).

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35. A.-H. Liu, R. Ma, C. Song, Z.-Z. Yang, A. Yu, Y. Cai, L.-N. He, Y.-N. Zhao, B. Yu, Q.-W. Song, Equimolar CO_2 capture by *N*-substituted amino acid salts and subsequent conversion. *Angew. Chem. Int. Ed.* **51**, 11306–11310 (2012).
36. T. Wein, M. Petrera, L. Allmendinger, G. Höfner, J. Pabel, K. T. Wanner, Different binding modes of small and large binders of GAT1. *ChemMedChem* **11**, 509–518 (2016).
37. M. Jörres, X. Chen, J. L. Aceña, C. Merkens, C. Bolm, H. Liu, V. A. Soloshonok, Asymmetric synthesis of α-amino acids under operationally convenient conditions. *Adv. Synth. Catal.* **356**, 2203–2208 (2014).
38. S. J. Barraza, P. C. Delekta, J. A. Sindac, C. J. Dobry, J. Xiang, R. F. Keep, D. J. Miller, S. D. Larsen, Discovery of anthranilamides as a novel class of inhibitors of neurotropic alphavirus replication. *Bioorg. Med. Chem.* **23**, 1569–1587 (2015).
39. R. A. Breitenmoser, H. Heimgartner, Scope and limitation of the acid-catalyzed isomerization of Aib-containing thiopeptides. *Helv. Chim. Acta* **84**, 786–796 (2001).
40. M. Ferrer-Casal, C. Li, M. Galizzi, C. A. Stortz, S. H. Szajnman, R. Docampo, S. N. J. Moreno, J. B. Rodriguez, New insights into molecular recognition of 1,1-bisphosphonic acids by farnesyl diphosphate synthase. *Bioorg. Med. Chem.* **22**, 398–405 (2014).
41. F. Wessendorf, B. Grimm, D. M. Guldi, A. Hirsch, Pairing fullerenes and porphyrins: Supramolecular wires that exhibit charge transfer activity. *J. Am. Chem. Soc.* **132**, 10786–10795 (2010).
42. V. H. Thorat, T. S. Ingole, K. N. Vijayadas, R. V. Nair, S. S. Kale, V. V. E. Ramesh, H. C. Davis, P. Prabhakaran, R. G. Gonnade, R. L. Gawade, V. G. Puranik, P. R. Rajamohanan, G. J. Sanjayan, The Ant-Pro reverse-turn motif. Structural features and conformational characteristics. *Eur. J. Org. Chem.* **2013**, 3529–3542 (2013).
43. A. El-Faham, R. S. Funosas, R. Prohens, F. Albericio, COMU: A safer and more effective replacement for benzotriazole-based uronium coupling reagents. *Chemistry* **15**, 9404–9416 (2009).
44. A. Presser, A. Hüfner, Trimethylsilyldiazomethane—A mild and efficient reagent for the methylation of carboxylic acids and alcohols in natural products. *Monatsh. Chem.* **135**, 1015–1022 (2004).
45. N. Matsuda, K. Hirano, T. Satoh, M. Miura, Copper-catalyzed amination of ketene silyl acetals with hydroxylamines: Electrophilic amination approach to α-amino acids. *Angew. Chem. Int. Ed.* **51**, 11827–11831 (2012).

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