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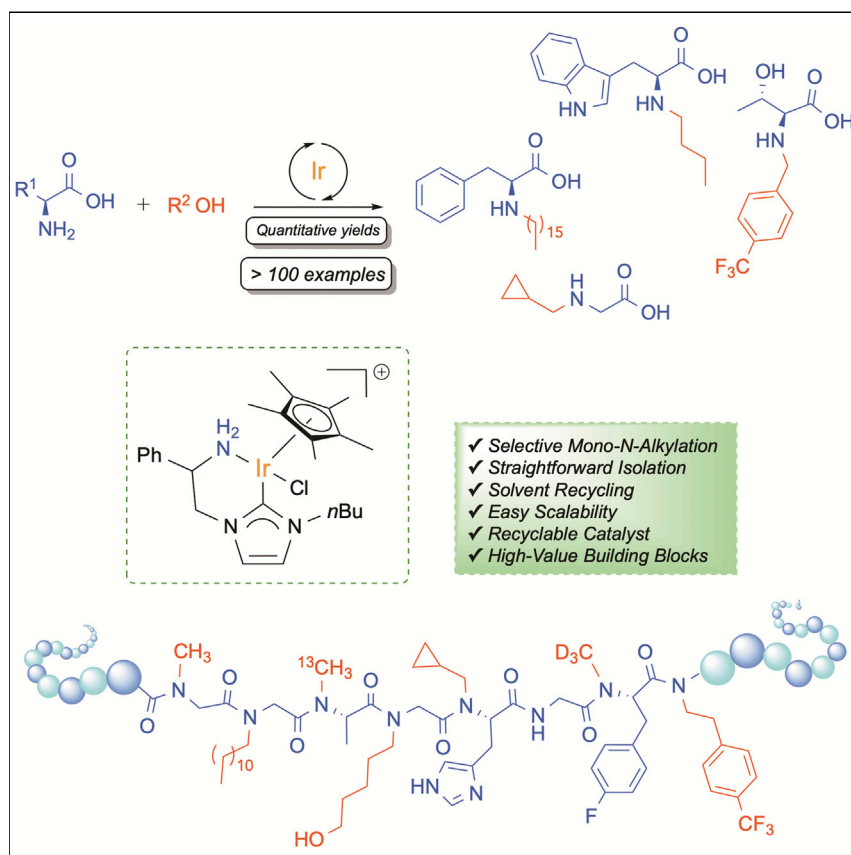**Article**

Selective and quantitative functionalization of unprotected α-amino acids using a recyclable homogeneous catalyst

Aitor Bermejo-López, Majken Raeder, Elisa Martínez-Castro, Belén Martín-Matute

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Highlights

Newly designed, robust Ir-NHC complex

Straightforward synthesis of *N*-modified unprotected amino acids

Convenient access to monomethylated amino acids and biodegradable surfactants

Easy scale-up and recyclable methodology

A recyclable homogeneous Ir(III)-NHC complex that enables the direct modification of unprotected α-amino acids is presented. In particular, the complex catalyzes the selective mono-*N*-alkylation of the amino functional group of these zwitterionic intermediates using alcohols as alkylating agents. The only by-product produced is water. The reactions are quantitative and the catalyst, as well as the solvent, could be reused for several runs.

Article

Selective and quantitative functionalization of unprotected α-amino acids using a recyclable homogeneous catalyst

Aitor Bermejo-López,[1] Majken Raeder,[1] Elisa Martínez-Castro,[1] and Belén Martín-Matute[1,2,*]

SUMMARY

A new Ir(III)-NHC catalyst is reported that shows remarkable activity in the *N*-alkylation of unprotected amino acids. The catalytic system gives excellent selectivity toward monoalkylated α-amino acids and a high degree of retention of stereochemistry. A wide range of unprotected nonnatural amino acids have been prepared. These compounds represent an array of building blocks that could be used for the direct synthesis of peptidomimetics. The synthesis of amino-acid-based surfactants is also reported. This catalytic method gives the amino acid products in quantitative yield; hence, tedious purifications by derivatization are therefore avoided. Furthermore, although the catalyst is a homogeneous metal complex, it can be recycled and reused for several runs. This also contributes to the efficiency and sustainability of the method.

INTRODUCTION

α-Amino acids are the building blocks that make up peptides and proteins, which are vital for all living organisms. The nature of the side chains of the amino acids is very important, as the order and type of amino acids dictate the folding and function of peptides and proteins.[1,2] Peptides can have applications as antibiotic drugs in the diagnosis and treatment of cancer and in the development of vaccines.[3]

The properties of peptides and proteins can be altered by introducing substituents on the nitrogen atom of the α-amino acid components or by introducing nonnatural α-amino acids. The former modification affects the hydrogen-bonding ability of the α-amino acid components and, as a result, affects the conformations of the proteins and peptides.[4] These modifications also affect their proteolytic stability,[5] lipophilicity, and thus membrane permeability,[6] as well as their half-lives.[7] These are all important properties for peptide-based drugs formed from nonnatural amino acids, a class of peptidomimetic pharmaceuticals.[5,8–10]

Alkylated α-amino acids are also found in small-molecule pharmaceuticals. Examples include ropivacaine and levobupivacaine, which are both used as local anesthetics. Furthermore, *N*-alkylated amino acids with long aliphatic side chains are used as biodegradable surfactants.[11] Chiral amino acids are used as organocatalysts or as additives in catalytic reactions (Figure 1).[12–16]

α-Amino acids exist in their zwitterionic form under neutral conditions, as ammonium salts at low pH, and as carboxylate salts at high pH. Therefore, the solubility of α-amino acids in organic solvents is poor, and as a result, the derivatization of these compounds is challenging.[17–19] The purification of derivatives of α-amino acids is

THE BIGGER PICTURE

Nonnatural α-amino acids are important organic molecules with outstanding applications in drug discovery, as small-molecule drugs or as components in peptide therapeutics. A simple, atom-economical, and versatile method to prepare a wide range of these compounds would also enable the construction of new proteins with modified biochemical properties. However, the synthesis of nonnatural α-amino acids by modifying available precursors is cumbersome due to their zwitterionic nature and involves a great number of additional protection/deprotection steps. In this study, we present a method in which an iridium catalyst is employed to achieve the selective mono-*N*-alkylation of unprotected α-amino acids in a single step by using alcohols as alkylating agents. The targeted modified α-amino acids are obtained in quantitative yields after a simple filtration and do not require further purification. Furthermore, the new NHC-Ir(III) catalyst developed for this homogeneous system is recyclable.
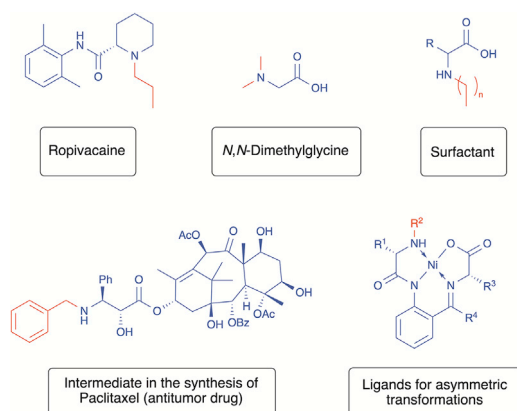
Figure 1. Selected examples of amino acid derivatives with various different applications

also challenging. Their high polarity and zwitterionic character mean that separation from remaining starting materials or by-products is essentially not viable. The purification problem has been tackled by introducing a further derivatization step. Typically, α-amino acid derivatives may be purified after the formation of an ester derivative. The protecting group then needs to be removed in a second additional step; hence, the overall process has a rather poor sustainability. To overcome these issues, amino acid modifications should be based on transformations that give quantitative yields. This would contribute to a high atom economy and also a high step economy.[20]

Traditionally, the alkylation of amines is achieved through classic nucleophilic substitution reactions with alkyl halides (Hofmann alkylations),[21,22] reductive aminations,[23] imine reductions,[24] or metal-assisted couplings.[25,26] These are very efficient methods, but they cannot usually be used for the alkylation of α-amino acids. The need for basic additives or the formation of salts as by-products contributes to difficult purifications. When it comes to selectivity, overalkylation is a commonly encountered problem in Hofmann alkylations and in metal-catalyzed cross couplings.

An alternative method for the formation of higher-order amines involves replacing the alkyl halides by aliphatic alcohols as the alkylating reagents. The atom economy is increased, as water is produced as a by-product instead of a halide salt.[27,28] Alcohols are abundant in nature and can be derived from renewable sources, such as from cellulose fermentation or waste biomass.[29] Furthermore, they can be handled more safely than the corresponding alkyl halides, as the latter may cause respiratory irritation.[30] In this field, since the pioneering works published by Grigg[27] and Watanabe[28] in 1981 using homogeneous metal complexes, the number of reports using different metal catalysts (e.g., palladium,[31] ruthenium,[32] manganese,[33] iron,[34] and iridium),[35–43] has dramatically increased.[44] The reaction occurs by a hydrogen-transfer process consisting of three key steps (Figure 2). First, oxidation of the alcohol forms a metal-hydride species. The resulting carbonyl compound reacts in an off-cycle manner with the amine substrate to give the corresponding imine. This intermediate is reduced by the metal-hydride species to give the final substituted amine.[31]

There are only a handful of examples where this approach has been applied to highly functionalized molecules, including carbohydrates,[45] nitrogen-containing heterocycles,[46] and acylhydrazines.[47] A seminal work by Barta and Feringa[48] is applicable to unprotected α-amino acids and represents an important milestone in the synthesis

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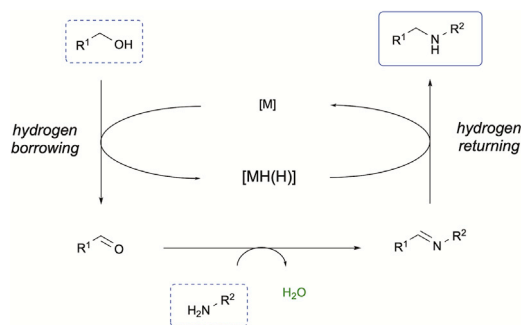
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Figure 2. General mechanistic scheme for the *N*-alkylation of amines with alcohols by hydrogen transfer

of functionalized chiral molecules through this strategy (Scheme 1). With a low loading of Shvo ruthenium catalyst, α-amino acids can be doubly *N*-alkylated in good yields with a variety of alcohols through hydrogen borrowing, whereas monoalkylation was observed only with bulky alcohols. Moreover, earth-abundant iron catalyst can be employed with fatty alcohols to allow modular synthesis of zwitterionic surfactants. Owing to the chemical nature of amino acids, however, selective mono-*N*-alkylation, efficient purification-free synthesis, and more sustainable use of precious metal catalysts remain challenging.

We have previously reported on a bifunctional Ir(III)-NHC (*N*-heterocyclic-carbene) catalyst bearing an alkoxy functionality on the NHC ligand (**Ir-1-BF₄**, Figure 3).[38] This complex catalyzed the alkylation of anilines with benzylic alcohols at 110°C for 2 h in excellent yields. Importantly, and similarly to the Shvo catalyst, the bifunctionality of the complexes allowed us to run the reaction in the absence of a base.[38]

Later, extensive mechanistic studies were carried out, which led to a better understanding of the reaction mechanism.[40] The alkoxy moiety was shown to play a role in proton-transfer steps, and an off-cycle resting state consisting of the amine substrate coordinated to an iridium-hydride intermediate was identified (Figure 3, right). The rate-limiting step therefore comprised a number of elementary steps from resting state **I**, including decoordination of the amine substrate from **I** and coordination of the imine formed *in situ*. With the aim of inhibiting the formation of off-cycle resting state **I**, and therefore enhancing the rate of the reaction and thus making it more widely applicable, we embarked on the design and synthesis of a new Ir(III)-NHC complex.

In this paper, we report the design and synthesis of a new Ir(III)-NHC catalyst that allows the selective mono-*N*-alkylation of unprotected amino acids using alcohols as alkylating reagents. It is presented as a sustainable and very efficient approach to gain direct access to a wide variety of chiral *N*-modified amino acid products in a single synthetic step (Scheme 2).

RESULTS AND DISCUSSION

Catalyst design

We started by designing a new Ir(III)-NHC catalyst based on the knowledge gained from our previous work.[40] A major limitation with alkoxy-functionalized catalyst **Ir-1-BF₄** is that it only gave good results with relatively simple alcohols and electron-poor amines, i.e., anilines. With electron-rich aliphatic amines, substrate inhibition
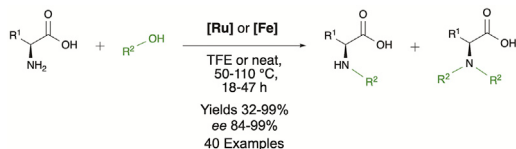
Scheme 1. Previous state of the art in N-alkylation of unprotected amino acid with alcohols

occurred, probably through coordination of the amines to the iridium center. The activity of **Ir-1-BF$_4$** in the alkylation of unprotected α-amino acid **1a** with benzyl alcohol **2a** was tested under the optimized conditions for this catalyst (i.e., toluene, 110°C), and only traces of the alkylated amino acid **3aa** were obtained (Figure 4). To improve the solubility of **1a**, toluene was replaced by 2,2,2-trifluoroethanol (TFE), but in this case, a yield of only 15% was obtained after a reaction time of 8 h.

We therefore started to look into modifying the structure of the bifunctional NHC ligand. To try to avoid the formation of an off-cycle resting state similar to **I**, observed when using **Ir-1-BF$_4$**,[40] the oxygen functional group on the wingtip of the NHC ligand was replaced by a nitrogen-containing functionality. We expected that the stronger σ-donating character of nitrogen versus oxygen would promote coordination of the nitrogen functionality on the wingtip to the Ir center and therefore inhibit off-cycle species formed upon coordination of the amine substrates. We therefore synthesized complexes **Ir-2-BF$_4$** and **Ir-3-BF$_4$**. The former complex contains an NHC ligand analogous to that of **Ir-1-BF$_4$**, but with the alkoxy functionality replaced by an amino group (NH$_2$). The second complex, **Ir-3-BF$_4$**, contains a benzylic amino substituent. Complex **Ir-2-BF$_4$** was synthesized according to our previous procedure (see Scheme S1).[49]

The synthesis of the new Ir(III)-NHC complex **Ir-3-BF$_4$** is shown in Scheme 3. From imidazole, (**4**) two consecutive alkylations, first with 2-bromoacetophenone (**6**) and then with *n*-butyl chloride, gave imidazolium **7** in a good yield over two steps. Oxime **8** was obtained in nearly quantitative yield from **7** and was then hydrogenated using H$_2$ in the presence of Pd/C. A silver carbene was formed upon reaction with Ag$_2$O, which then underwent transmetallation with commercially available [Cp*IrCl$_2$]$_2$ to give the thermally and air stable precatalyst species **11**. The structure of complex **11** was confirmed by ^{1}H and ^{13}C NMR (nuclear magnetic resonance) spectroscopy, and by single crystal X-ray diffraction analysis,[50] which showed that the NH$_2$ group was coordinated to the metal center. This species is stable in air and can be stored for months. A final step consisting of the activation of precatalyst **11** with a silver salt is needed to obtain the catalytically active species **Ir-3-BF$_4$** (Scheme 3).

Optimization of the reaction conditions

With complexes **Ir-2-BF$_4$** and **Ir-3-BF$_4$** in hand, we tested the alkylation of L-phenylalanine (**1a**) with benzyl alcohol (**2a**) in the absence of base. In toluene, the preferred solvent for **Ir-1-BF$_4$**, very low yields were obtained with all three iridium catalysts (Figure 4; Table 1, entries 1–3). As α-amino acids are poorly soluble in this solvent, we investigated the reaction in more polar solvents. In 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and in 2,2,2-trifluoroethanol (TFE), all three iridium complexes gave improved yields of **3aa** (Figure 4; Table 1, entries 4–9). Quantitative yields were observed only with **Ir-3-BF$_4$** in both of these solvents (Table 1, entries 6 and 9). **Ir-3-BF$_4$** was also tested in dichloromethane and in water (Table 1, entries 10 and 11), but the yields were not comparable with those obtained in the polar
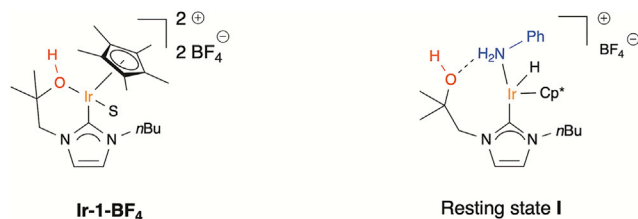
Figure 3. Previous Ir-NHC complex developed in the Martín-Matute group
Left: bifunctional Ir(III)-NHC catalyst (S = solvent). Right: off-cycle identified resting state.

fluorinated solvents.[51,52] We can conclude that the structure of the iridium catalyst and also the reaction medium are both important for obtaining excellent yields.

We went on to examine the ee of the alkylated product (**3aa**) for the reactions run in HFIP and TFE. We found out that the ee was only maintained in TFE (Table 1, entry 9 versus entry 6). Further optimization was therefore carried out for catalyst **Ir-3-BF₄** in TFE. Lowering the catalyst loading to 2 mol% and increasing the reaction time to 20 h gave **3aa** in quantitative yield, and a high degree of retention of stereochemistry was maintained (Table 1, entry 12 versus 9). Decreasing the number of equivalents of alcohol **2a** did not affect the outcome of the reaction (Table 1, entry 13 versus entry 12). We found that when we changed the concentration of the reaction mixture, either by slow addition of the alcohol substrate or by dilution, the yield decreased (Table 1, entries 14 and 15, respectively).

The effect of the counterions X⁻ on the catalytic activity of **Ir-3-X** was also investigated. These counterions are introduced in the final step of the synthesis of the catalyst (*vide supra*, Scheme 3). Only moderate yields were obtained with tetrakis[3,5-bis(trifluoro-methyl)phenyl]borate (BArF⁻) and with OTs⁻ after 20 h (Table 1, entries 16 and 17). However, PF₆⁻, OTf⁻, SbF₆⁻, and bis(trifluoromethanesulfonyl)imide (NTf₂⁻) gave good yields, analogous to those obtained with BF₄⁻ (entries 18, 19, 20, and 21, respectively). Importantly, a high degree of retention of stereochemistry was only achieved with NTf₂⁻ (98%, as determined by derivatization, see the supplemental information), while keeping an excellent catalytic activity (Table 1, entry 21 versus entries 18–20). Even when forcing the reaction conditions using 4 equiv of benzyl alcohol substrate, only monoalkylated product was formed (see Table S2 for the full optimization studies).

Next, we investigated the effects of the reaction conditions on this transformation (Figure 5).[53] We found that the reaction is highly sensitive to the temperature and the catalyst loading. Furthermore, not removing the dichloromethane used in the activation of the catalyst (last step in Scheme 3) resulted in a dramatic decrease in yield. The reaction was not significantly affected by the presence of water (2 equiv), or when a significant excess of the silver salt (AgNTf₂) was used for the activation of the catalyst (see radar diagram in Figure 5), or when the concentration was increased or decreased by a factor of two. Complex **Ir-3-NTf₂** could be kept in the fridge for one week under air, maintaining excellent activity. With sustainability in mind, we investigated the recyclability of the solvent. We found that TFE could be reused after distillation for several consecutive runs without affecting the outcome of the reactions; hence, the amount of waste generated was kept to a minimum.

When using the optimized conditions (Table 1, entry 21), a simple rinse with diethyl ether to remove the excess alcohol and the catalyst is sufficient to give benzylated amino acid **3aa** in >98% isolated yield with outstanding purity.
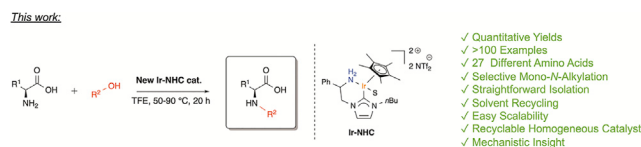
Scheme 2. Selective and quantitative mono-*N*-alkylation of unprotected amino acids with alcohols by hydrogen transfer with a recyclable bifunctional Ir(III) catalyst (S = solvent)

N-Alkylation of unprotected amino acids with alcohols

The scope of the reaction was first investigated with benzyl alcohols as alkylating agents using catalyst **Ir-3-NTf$_2$**, (*vide supra*, Table 1, entry 21). Aromatic amino acid L-phenylalanine gave quantitative yields of **3aa** (98% *ee*), **3ad**, and **3ae** when alkylated with benzyl alcohol, 4-methylbenzyl alcohol, and 3-methylbenzyl alcohol, respectively. Fluorinated moieties are of interest in drug discovery as diagnostic tools,[54,55] and fluorine-substituted amino acids are important in the field of peptidomimetics.[56] To our delight, 4-fluorobenzyl alcohol gave **3aj** also in quantitative yield.

We then evaluated the *N*-alkylation of L-proline (**1b**). Quantitative yields of **3ba**–**3bi** were obtained, and a high degree of retention of the stereochemistry was observed in most instances. However, slight racemization was observed when *ortho*-methyl-benzyl alcohol was used. The product **3bf** was obtained quantitatively, but with 83% *ee*. Interestingly, even the highly electron-poor 4-(trifluoromethyl)benzyl alcohol reacted at room temperature to give a quantitative yield of **3bi** with 90% *ee*.

Next, we varied the structure of the unprotected α-amino acid substrate (Scheme 4). Selective monoalkylation was also obtained in the reaction between glycine and benzyl alcohol (**3ca**). *N*-Alkylation of aliphatic amino acids L-alanine and L-leucine also worked well, with 90% *ee* after derivatization (**3da** and **3ea**, respectively). A quantitative isolated yield was also obtained with the more sterically hindered amino acid L-valine (**3fa**). Nitrogen-containing L-tryptophan and L-histidine were monoalkylated upon reaction with various benzylic alcohols, in all instances with full selectivity toward monoalkylation and in quantitative yields (**3ga**–**3gf**, **3ha**, and **3hd**). The presence of an alcohol moiety in the amino acid substrate was perfectly tolerated and did not affect the outcome of the reaction, as seen in the alkylation reactions of L-hydroxyproline, L-serine, and L-threonine with benzyl alcohol, yielding **3ia**, **3ja**, and **3ka**, respectively. Unfortunately, when L-cysteine was used as a substrate, no formation of the alkylated product was observed. This might be due catalyst inhibition through coordination of the thiol functional group to the iridium center. This limitation did not apply to thioether derivatives L-ethylcysteine and L-methionine, which were converted quantitatively into **3la**, **3ld**, and **3ma**. Basic amino acids L-asparagine and L-arginine were not tolerated in this catalytic system (see the supplemental information, Figure S1). The catalytic system was extended to β-amino acid substrates; β-alanine and homo-alanine gave the desired selective monoalkylated amino acid products upon reaction with benzyl alcohol (Scheme 4, **3na** and **3oa**, respectively). These reactions also took place in quantitative yields, which confirms the broad applicability of the method.

Non-proteinogenic amino acids were also evaluated. Thus, fluorinated L-phenylalanine gave **3pa** in quantitative yield. Excellent results were also obtained using the *p*-chloro, *p*-bromo, *m*-cyano, and *o*-fluoro analogs (**3qa**, **3ra**, **3sa**, and **3ta**, respectively). Sterically hindered L-*tert*-leucine and benzylated L-serine also gave quantitatively mono-*N*-alkylated products **3ua** and **3va**, respectively.
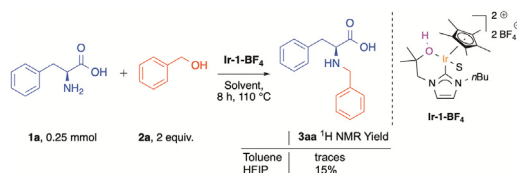
**Figure 4. Initial results obtained using previously reported catalyst Ir-1 (S = solvent)**

L-Pipecolic acid, a precursor of ropivacaine[57] and levobupivicaine,[9] was transformed into N-benzyl pipecoloxylidine derivative **3wa**. Amino acid **1x**, which lacks α protons, gave the desired benzylated amino acid **3xa**, and thiophene-functionalized thienylglycine also reacted to give **3ya**.

All compounds were obtained in quantitative isolated yields following the isolation procedure and did not require any further purification. Remarkably, no dialkylation was observed in any case.

Encouraged by the excellent results obtained using benzylic alcohols, we went on to test the method with aliphatic alcohols (Scheme 5). First, 3-phenylpropanol was tested as the alkylating agent, and phenylalanine derivative **3bk** was obtained in quantitative yield. Cyclopropanemethanol also gave N-alkylated amino acids **3al**, **3bl**, **3gl**, **3hl**, and **3ll** quantitatively. Proline and tryptophan gave **3bm** and **3hm** upon alkylation with 1-butanol. In recent years, the use of amino-acid-based polymers for medical and biotechnological purposes has been investigated.[58] An example of this is mono-N-butylated β-alanine (**3nm**), which is used as monomer in the synthesis of theranostic nanoagents.[59] This compound was also obtained quantitatively under the conditions reported here. It is important to note that in contrast to the results reported here, alcohols like 1-butanol tend to give dialkylated compounds when they are used as alkylating agents in metal-catalyzed borrowing-hydrogen methods.[45] The very high selectivity toward mono-alkylation under the conditions described here was also observed when 1,5-pentadiol was used to alkylate proline and tryptophan (**3an** and **3bn**). In all three instances, the second hydroxy group remained intact, and the potential intramolecular second alkylation did not take place. Remarkably, furfuryl alcohol and 2-thiophenemethanol could also be used as alkylating agents, which once again demonstrates the high functional-group tolerance of this catalytic system (**3ao** and **3ap**). Even ethanol, when used in excess as a cosolvent, TFE/EtOH (10:1, v/v), gave ethylated proline in quantitative isolated yield (**3bq**). The dipeptide Gly–Gly was also alkylated with ethanol, with alkylation taking place selectively at the primary amine functionality (Scheme 5, **3zq**).

We went on to examine the use of long-chain aliphatic alcohols as alkylating agents (Scheme 6). These alcohols are naturally occurring compounds that can be found in fats and oils.[60] Thus, proline, tryptophan, and methionine underwent alkylation reactions under the standard conditions with alcohols of up to sixteen carbons as alkylating agents to give **14as**, **14at**, **14br–14bw**, **14gt**, and **14lt–14lv**. These derivatives could have applications as amino-acid-based surfactants. The a direct, quantitative, and selective formation of these compounds highlights the efficiency of this method compared with existing approaches.[61–63]

We then turned our attention to the use of methanol as alkylating agent. Methylation is very important in medicinal chemistry due to the magic methyl effect,[64,65] namely the profound effect that a CH_3 group can have on the biological activity
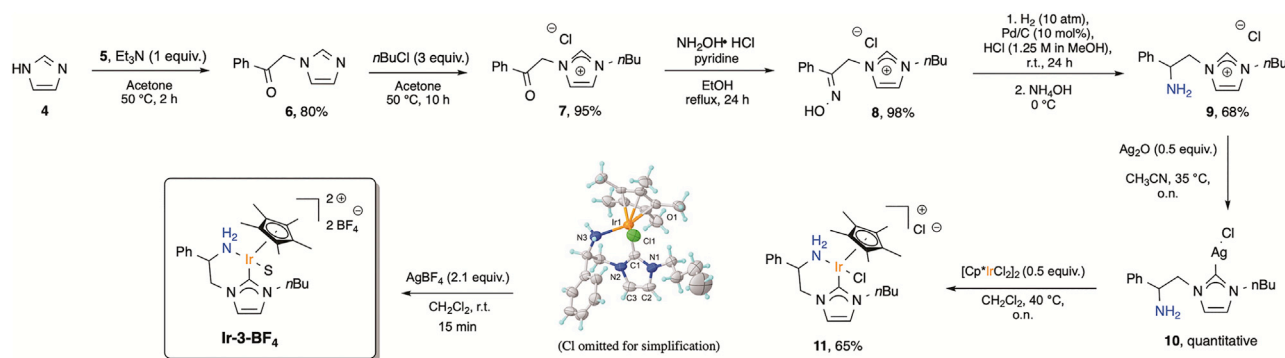
Scheme 3. Synthesis of Ir(III)-NHC complex Ir-3-BF4 (S = solvent)
Isolated yields are shown.

or selectivity of a molecule.[2] Indeed, some approaches to access *N*-methylated amines using methanol as alkylating agent can be found in the literature.[66–68] In this regard, a very recent work by the Naka's group reports for the first time a photocatalytic system that allows for the synthesis of *N*-dimethylated amino acids.[69]

With this new aim set in mind, a variety of amino acids with different functionalities were subjected to the alkylation reaction conditions with methanol as cosolvent at temperatures as low as 50°C. In contrast to all the alcohol substrates used above, methanol gave *tertiary* amines as a result of two consecutive alkylations. Glycine underwent methylation to give dimethylglycine (**15c**), also known as vitamin B$_{16}$ (Scheme 7). Complete methylation of the amino group was achieved in quantitative isolated yields with a high degree of retention of configuration after derivatization, as measured for methylproline (**15b**, 90% *ee*).

Since methanol is a good reagent for the alkylation of secondary amines, we then explored the possibility of alkylating amino acids with two different alcohols, using methanol as the second alkylating agent. The optimized reaction conditions using benzyl alcohol or ethanol were applied to a variety of unprotected amino acids. Subsequently, the mixture was cooled to 50°C, and methanol was added. When the reaction was complete, the mixture was rinsed with diethyl ether to give dialkylated products **16a–d'**, in a two-step, one-pot synthesis, in quantitative isolated yields (Schemes 8 and 21).

Obtaining monomethylated α-amino acids still remained a challenge. To try to achieve this goal, we explored a three-step, one-pot pathway. This involved benzylation with benzyl alcohol, methylation with methanol, and finally, hydrogenolysis of the benzyl group using Pd/C. The hydrogenolysis proceeded well under one atmosphere of H$_2$ using 1 mol% of Pd. This one-pot three-step procedure gave monomethylated α-amino acids **17a**, **17c**, **17e**, and **17u** in quantitative yields (Scheme 8).

The use of methanol to alkylate these substrates opens up the possibility of efficient deuterium- and ^{13}C-labeling of amino acid building blocks. We tested our method with both deuterated methanol and ^{13}C-labeled methanol and found it to be highly effective. Deuterated L-phenylalanine, L-proline, and L-valine derivatives were obtained in quantitative yields with outstanding retention of configuration (Figure 6, **18a** with 95% deuterium incorporation, **18b** with 98% deuterium incorporation,

Table 1. Optimization of the reaction conditions

1a, 0.25 mmol   2a, Z equiv.   [Ir] (Y mol%), Solv., time, 90 °C   3aa

Ir-1-X   Ir-2-X   Ir-3-X
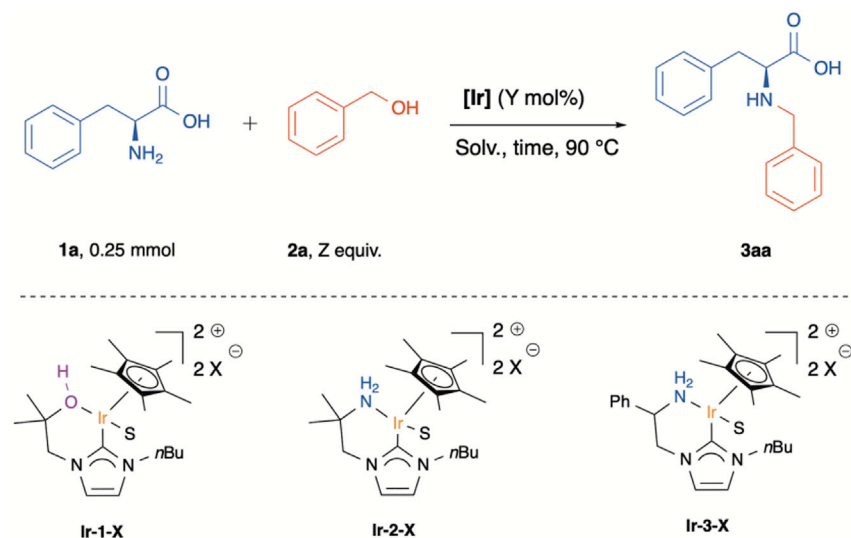
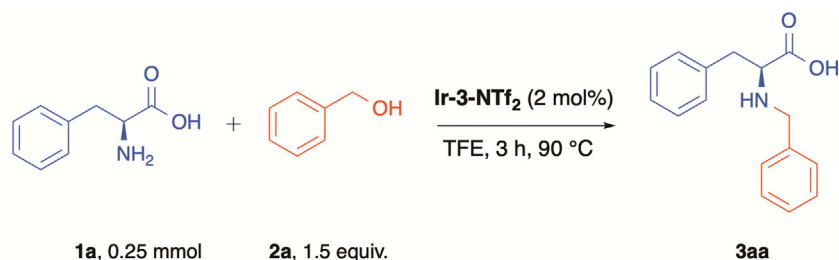| Entry	Solvent	Z	Y	Time (h)	[Ir]	X⁻	Yield 3aa[a]	Ee[b]
1	Toluene	2	4	8	Ir-1-X	BF$_4^-$	traces	n.d.
2	Toluene	2	4	8	Ir-2-X	BF$_4^-$	5%	n.d.
3	Toluene	2	4	8	Ir-3-X	BF$_4^-$	10%	n.d.
4	HFIP	2	4	8	Ir-1-X	BF$_4^-$	15%	n.d.
5	HFIP	2	4	8	Ir-2-X	BF$_4^-$	26%	n.d.
6	HFIP	2	4	8	Ir-3-X	BF$_4^-$	>98%	60%
7	TFE	2	4	8	Ir-1-X	BF$_4^-$	15%	n.d.
8	TFE	2	4	8	Ir-2-X	BF$_4^-$	25%	n.d.
9	TFE	2	4	8	Ir-3-X	BF$_4^-$	>98%	82%
10	CH$_2$Cl$_2$	2	4	8	Ir-3-X	BF$_4^-$	<5%	n.d.
11	H$_2$O	2	4	8	Ir-3-X	BF$_4^-$	30%	n.d.
12	TFE	2	2	20	Ir-3-X	BF$_4^-$	>98%	82%
13	TFE	1.5	2	20	Ir-3-X	BF$_4^-$	>98%	82%
14[c]	TFE	1.5	2	20	Ir-3-X	BF$_4^-$	40%	n.d.
15[d]	TFE	1.5	2	20	Ir-3-X	BF$_4^-$	72%	n.d.
16	TFE	1.5	2	20	Ir-3-X	BArF⁻	40%	n.d.
17	TFE	1.5	2	20	Ir-3-X	OTs⁻	45%	n.d.
18	TFE	1.5	2	20	Ir-3-X	PF$_6^-$	89%	78%
19	TFE	1.5	2	20	Ir-3-X	OTf⁻	91%	90%
20	TFE	1.5	2	20	Ir-3-X	SbF$_6^-$	85%	90%
21	TFE	1.5	2	20	Ir-3-X	NTf$_2^-$	>98%	98%

[a]Yield determined by ^{1}H NMR spectroscopic analysis using an internal standard.
[b]Enantiomeric excess measured upon esterification. n.d., not determined.
[c]Slow addition.
[d]TFE (2 mL).

and **18c** with 99% deuterium incorporation and 93% *ee*). Benzyl alcohol-*d$_2$* was also used as an alkylating agent to give monoalkylated product **18d** with 91% deuterium incorporation. Using the two-step procedure described above, a variety of amino acids were dialkylated using different alcohols along with deuterated methanol to give the products with high deuterium content (**18e**, **18f**, **18g**, and **18h**). Monomethylated amino acids **18i** and **18j** were also formed, maintaining a very high deuterium content after the three-step procedure (*vide supra*, Scheme 8). The method was extended to ^{13}C-labeled methanol with complete ^{13}C incorporation and excellent yields (Figure 6, **18k** and **18l**).
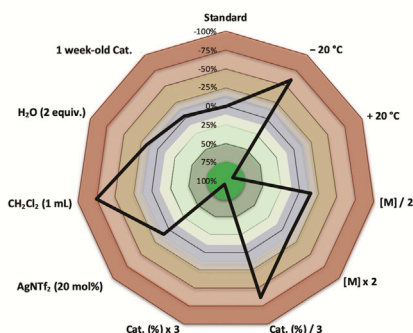
Figure 5. Sensitivity assessment for the N-monobenzylation of L-phenylalanine (1a)
[a]Yields determined by ^{1}H NMR spectroscopic analysis using an internal standard.

We also investigated an alternative approach to monoalkylated amino acids based on the use of Boc-protected α-amino acids. Interestingly, under our standard alkylation reaction conditions, mono-N-alkylation and Boc-deprotection were observed. Control experiments showed that TFE was responsible for the Boc-deprotection step at 90°C. Thus, commercially available Boc-protected α-amino acids were transformed into monoalkylated α-amino acids in quantitative yields in a single synthetic step (Scheme 9).

Chemically modified peptides are of interest in drug discovery.[70] Such modifications generally have an impact on the pharmacokinetics and stability of the peptide derivatives.[1] Commonly, peptides are synthesized either by solid-phase peptide synthesis (SPPS)[71] or liquid-phase peptide synthesis (LPPS).[72] These methods involve coupling an α-amino ester and a Boc-protected α-amino acid. Employing this method for the synthesis of peptides composed of alkylated amino acids would be cumbersome due to the need of protecting groups in the amino moiety to avoid side reactions. Here, we present an alternative protocol that relies on the use of N-benzyl-N-alkyl amino acids, such as **16a**. The benzyl group can then be removed under palladium catalysis. Thus, applying the coupling procedure used for LPPS[72] to N-benzyl-N-methyl-phenylalanine (16a) and L-phenylalanine methyl ester hydrochloride (**20**), dipeptide **21** was obtained in 87% isolated yield (Scheme 10, step 2). The corresponding monomethylated modified peptide **22** was obtained in quantitative yield after a Pd-catalyzed hydrogenolysis (Scheme 10, step 3).

We tested the performance of the catalyst on a larger scale of 3 mmol of L-phenylalanine, using benzyl alcohol as the alkylating agent. The activity and selectivity were maintained, and **3aa** was obtained with 95% ee (Scheme 11).

In the field of homogeneous catalysis, catalyst recycling remains a major challenge. Common purification methods used to separate reagents or products are unsuitable
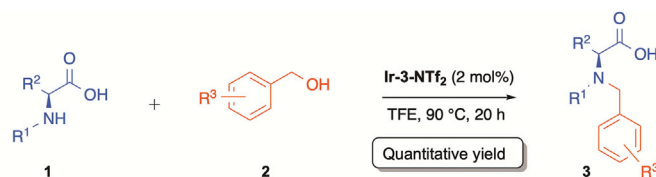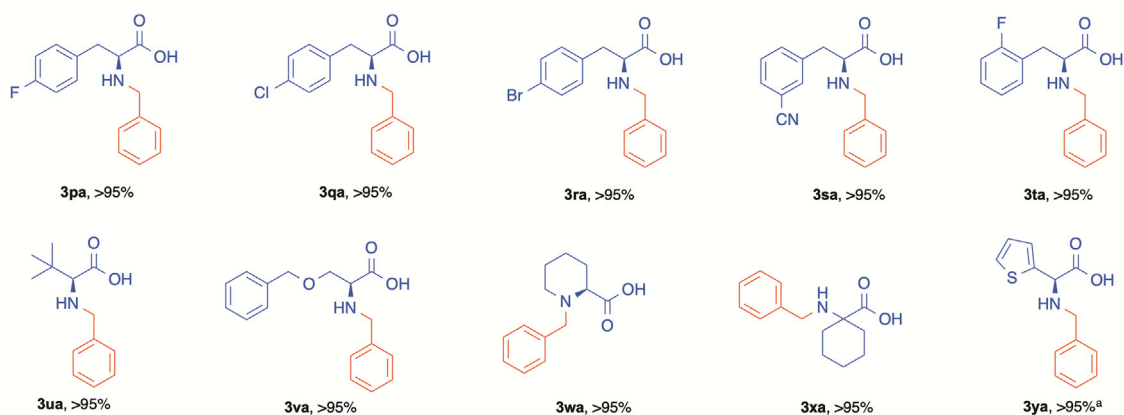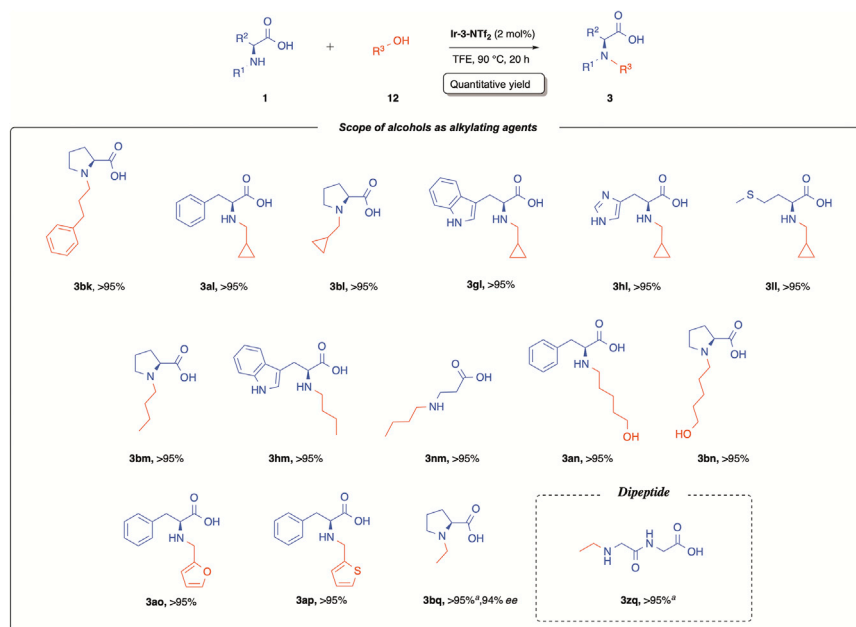
Scheme 4. N-Monoalkylation of amino acids with benzyl alcohols

α-Amino acid (0.25 mmol), benzyl alcohol (0.37 mmol), TFE (1 mL). Quantitative isolated yields.

[a] >98% ^{1}H NMR conversion. Co-crystallizes with solvent. Estimated yield of 86%.

**Scheme 5. N-Monoalkylation of amino acids with a variety of alcohols**

α-Amino acid (0.25 mmol), benzyl alcohol (0.37 mmol), TFE (1 mL). Quantitative isolated yields.
[a]EtOH (0.1 mL).

for the reisolation of homogeneous catalysts as they are present in such low concentrations. Thus, more elaborate strategies are required.[73–76]

The approach described in this paper allows not only the solvent but also the catalyst to be recovered fairly simply as the reaction products precipitate from the reaction media (see the supplemental information, Figures S3 and S4). The solution containing the catalyst can then be reused in a consecutive run. The excellent catalytic activity remained for up to six runs. This represents a turnover number of at least 300. The robustness of the process was shown when different amino acids were used in the recycling experiment. All products were obtained in quantitative yields (Figure 7).

Kinetic experiments with deuterium-labeled benzylic alcohol were carried out to investigate the relative rates of the alcohol-oxidation step. The reaction profiles constructed for the independent reactions of L-phenylalanine, and each of the benzyl alcohols (**2a** or **2a-d_2**) showed a significant difference in the reaction rate. Based on the initial rates of these transformations, we calculated a KIE (kinetic isotope effect) value of 1.98 ± 0.18 (supplemental information, Figure S5). This result suggests that the alcohol-dehydrogenation step contributes to the overall rate of the reaction.

A crossover experiment was carried out to examine whether the oxygen atom from the alcohol substrate remains coordinated to the iridium center throughout the catalytic cycle until the final product is released. Hence, L-phenylalanine was treated with a 1:1 mixture of benzyl alcohols **2a** and **2a-d_2**. Interestingly, monodeuterated product **3aa-d_1** was formed in this reaction in up to 28% yield by NMR spectroscopy (after 8 h). This compound was successfully identified by ^{1}H NMR spectroscopy, quantitative ^{13}C NMR spectroscopy, and HRMS (high-resolution mass spectrometry). This result suggests that the oxidized alcohol substrate decoordinates from
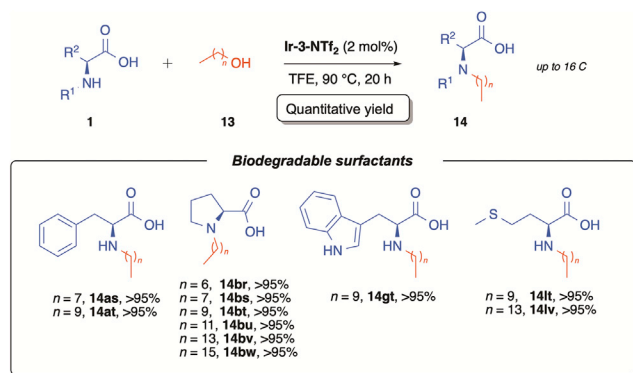
Scheme 6. Synthesis of surfactants
α-Amino acid (0.25 mmol), benzyl alcohol (0.37 mmol), and TFE (1 mL). Quantitative isolated yields.

the iridium-hydride/deuteride complex to condense with the amino acid substrate (Figure 8). The resulting imine intermediate can then be hydrogenated by an iridium-hydride species containing a different isotope of hydrogen.[77,78]

The crossover experiment also showed that product **3aa** was formed at a considerably faster rate than its deuterated analogs (Figure S6). These results, and the fact that the formation of monodeuterated benzyl alcohol **2a-d_1** was not detected, support the hypothesis that the alcohol dehydrogenation is irreversible.

Suggested mechanism

We therefore suggest the following mechanism (Figure 9). The amine group of the functionalized side arm is deprotonated by one molecule of the amino acid substrate. Subsequent decoordination of a solvent molecule results in the formation of iridium complex **Ir-3-NTF$_2$''**. This complex offers two active sites that are responsible for the alcohol-oxidation step (Figure 9, step i). Then, the oxidized carbonyl compound condenses with the amino acid substrate to form the imine intermediate **23**. This unsaturated intermediate is then reduced in a final step by the metal-hydride species formed previously to give the desired N-alkylated amino acid product and regenerate the active catalyst species (Figure 9, step ii). Formation of the imine (alternatively iminium) intermediate could not be detected by ^{1}H NMR spectroscopy, which suggests that the hydrogenation step occurs quickly. During this transformation, the only by-product generated is H_2O, which highlights the high atom economy and environmentally friendly nature of this method.

Conclusions

We have developed a very efficient method for the selective mono-N-alkylation of unprotected amino acids with alcohols, catalyzed by a highly active newly designed Ir(III)-NHC complex. This procedure is base free, has very good functional-group tolerance, and maintains a high enantiomeric excess. Valuable building blocks are synthesized in quantitative yields, independently of the structure of the reactants. This outstanding reactivity enables their straightforward isolation, with no need for further derivatization and purification; hence, this approach represents a green alternative with minimized waste production. A three-step, one-pot procedure to give monomethylated unprotected amino acids is also described. We also report the formation of monomethylated amino acids from commercially available Boc-protected precursors.
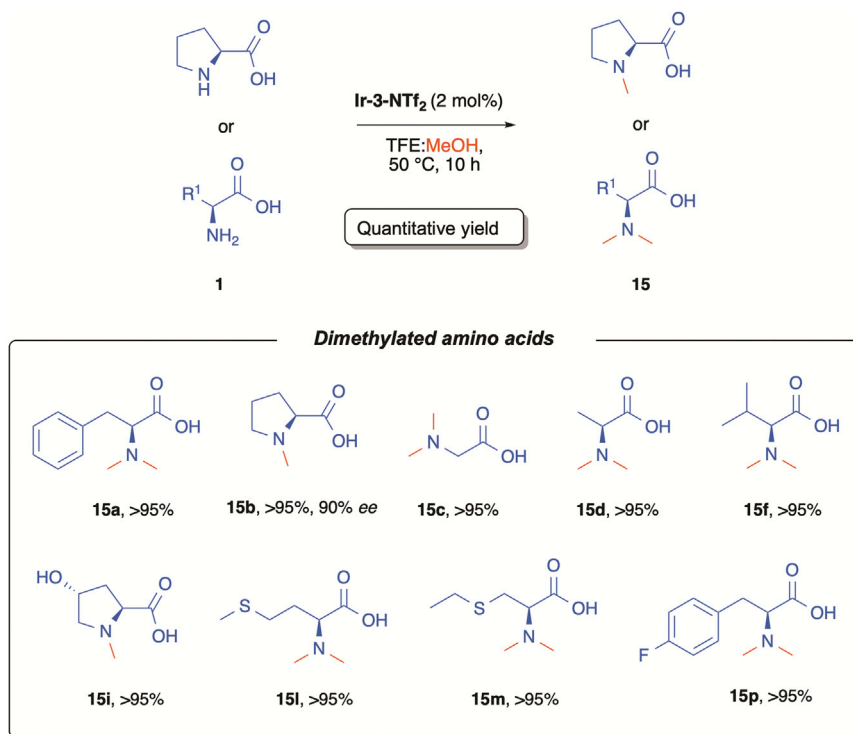
Scheme 7. N-Methylation of α-amino acids
α-Amino acid (0.25 mmol), TFE (1 mL), and methanol (0.1 mL). Quantitative isolated yields.

We have reported an outstanding efficiency for this atom-economical transformation. Furthermore, as isolation is achieved by simple crystallization and derivatizations for isolations are avoided, the environmental factor to give such a wide range of products from both proteinogenic and non-proteinogenic amino acids using alcohols as alkylating agents is favorably low. We have successfully obtained valuable compounds that can be used in the synthesis of pharmaceuticals, in peptide synthesis, and as surfactants, among other areas of application. In addition, the very low solubility of the products formed in the reaction media allowed us to recover the catalyst, which could be used for several further runs. This highlights the efficiency and sustainability of the process.

EXPERIMENTAL PROCEDURES

### Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Belén Martín-Matute (belen.martin.matute@su.se).

Materials availability

All compounds synthesized in this project are available upon request from the lead contact. Full experimental procedures can be found in the supplemental information.

Data and code availability

All data supporting this report are available in the supplemental information. All original code has been deposited at Zenodo: https://doi.org/10.5281/zenodo.7002830 and is publicly available as of the date of publication. The accession
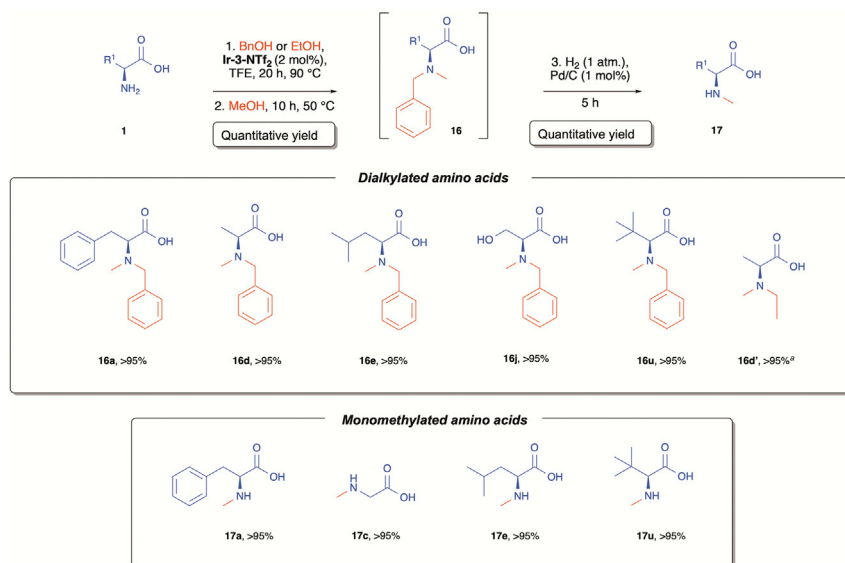
Scheme 8. N-Alkylation with two different alcohols, and monomethylation of unprotected α-amino acids

α-Amino acid (0.25 mmol), benzyl alcohol (0.37 mmol), and TFE (1 mL). Then methanol (0.1 mL). Quantitative isolated yields.

[a]Ethanol (0.1 mL), then methanol (0.1 mL).

number for the single crystal X-ray structure reported in this paper, and deposited in the Cambridge Structural Database is CCDC 2196047. Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

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

Iridium complex 11 (3.2 mg, 0.005 mmol, 1 equiv) and silver salt AgNTf$_2$ (4.2 mg, 0.011 mmol, 2.1 equiv) were suspended in anhydrous dichloromethane (1 mL) in a vial covered with aluminum foil. The reaction mixture was stirred at RT for 15 min. The mixture was filtered through a pad of Celite to remove the AgCl precipitate, and the filtrate was transferred to an oven-dried pressure tube. The solvent was evaporated under vacuum, and the active catalyst species was used *in situ*.

Dry TFE (1 mL) was added to the pressure tube containing the active iridium species Ir-3-NTf$_2$ (0.005 mmol, 2 mol%). The amino acid (0.25 mmol, 1 equiv) and alcohol (0.37 mmol, 1.5 equiv) were added, and the mixture was stirred at 90°C for 20 h. The mixture was then cooled to RT, and the solvent was removed under vacuum. Diethyl ether (3 mL) was added, and the flask containing the reaction mixture introduced in an ultrasonic bath for 5 min. The ethereal phase containing any remaining alcohol and the catalyst was removed. This process was repeated 3 times. After drying, 1 mL of methanol to remove remaining diethyl ether was added, and the crude was dried under vacuum. Quantitative isolated yields were obtained for all substrates without the need for any further work-up or purification.

General procedure for the N-methylation of unprotected amino acids with methanol

Iridium complex 11 (3.2 mg, 0.005 mmol, 1 equiv) and silver salt AgNTf$_2$ (4.2 mg, 0.011 mmol, 2.1 equiv) were suspended in anhydrous dichloromethane (1 mL) in a
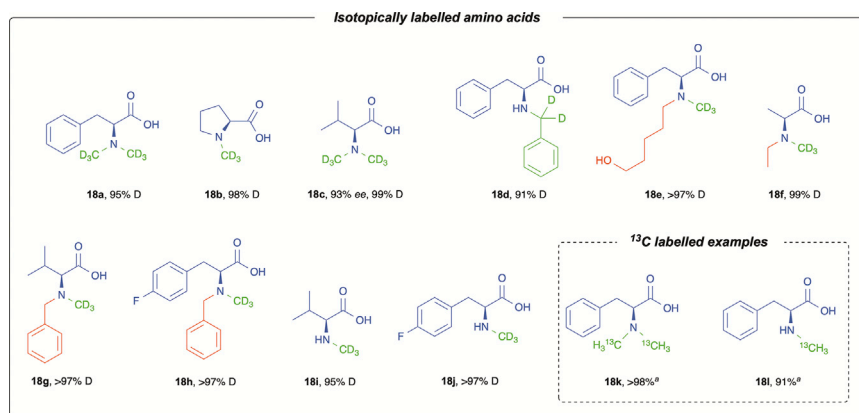
Figure 6. Isotopically labeled N-alkylated amino acids
Quantitative isolated yields. [a]Yield determined by NMR spectroscopy.

vial covered with aluminum foil. The reaction mixture was stirred at RT for 15 min. The mixture was filtered through a pad of Celite to remove the AgCl precipitate, and the filtrate was transferred to an oven-dried pressure tube. The solvent was evaporated under vacuum, and the active catalyst species was used *in situ*.

Dry TFE (1 mL) was added to the pressure tube containing the active iridium species **Ir-3-NTf$_2$** (0.005 mmol, 2 mol%). The amino acid (0.25 mmol, 1 equiv) and methanol (0.1 mL) were added, and the mixture was stirred at 50°C overnight. The mixture was then cooled to RT, and the solvent was removed under vacuum. The residue was washed with diethyl ether (3 × 3 mL) to remove any remaining methanol and the catalyst. Quantitative isolated yields were obtained for all substrates without the need for any further work-up or purification.

General procedure for the *N*-dialkylation of unprotected amino acids with alcohols
Iridium complex 11 (3.2 mg, 0.005 mmol, 1 equiv) and silver salt **AgNTf$_2$** (4.2 mg, 0.011 mmol, 2.1 equiv) were suspended in anhydrous dichloromethane (1 mL) in a vial covered with aluminum foil. The reaction mixture was stirred at RT for 15 min. The mixture was filtered through a pad of Celite to remove the AgCl precipitate, and the filtrate was transferred to an oven-dried pressure tube. The solvent was evaporated under vacuum, and the active catalyst species was used *in situ*.

Dry TFE (1 mL) was added to pressure tube containing the active iridium species **Ir-3-NTf$_2$** (0.005 mmol, 2 mol%). The amino acid (0.25 mmol, 1 equiv) and alcohol (0.37 mmol, 1.5 equiv) were added, and the mixture was stirred at 90°C for 20 h. The mixture was then cooled to 50°C, and methanol (0.1 mL) was added. The resulting mixture was stirred overnight. After this time, the mixture was cooled to RT, and the solvent was removed under vacuum. The residue was rinsed with diethyl ether (3 × 3 mL) to remove any remaining alcohol and the catalyst. Quantitative isolated yields were obtained for all substrates without the need of any further work-up or purification.

General procedure for the *N*-monomethylation of unprotected amino acids with alcohols
Iridium complex 11 (3.2 mg, 0.005 mmol, 1 equiv) and silver salt **AgNTf$_2$** (4.2 mg, 0.011 mmol, 2.1 equiv) were suspended in anhydrous dichloromethane (1 mL) in a
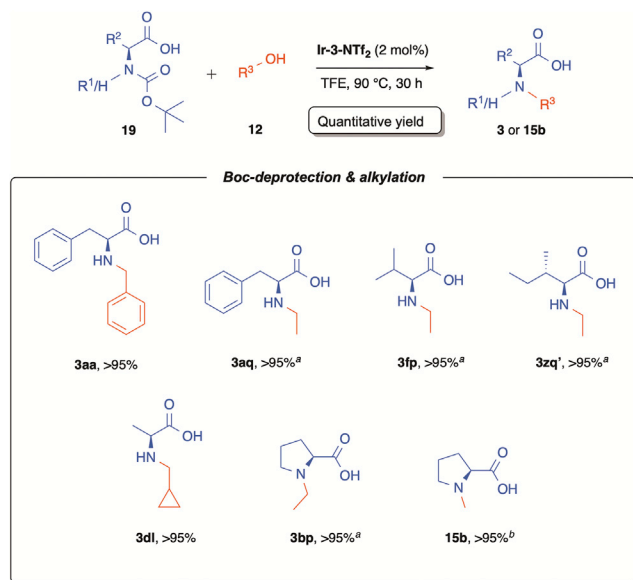
Scheme 9. Boc-deprotection and subsequent N-alkylation of unprotected α-amino acids
Amino acid (0.25 mmol), alcohol (0.37 mmol), and TFE (1 mL). Quantitative isolated yields.
[a]EtOH (0.1 mL).
[b]MeOH (0.1 mL).

vial covered with aluminum foil. The reaction mixture was stirred at RT for 15 min. The mixture was then filtered through a pad of Celite to remove the AgCl precipitate, and the filtrate was transferred to an oven-dried pressure tube. The solvent was evaporated under vacuum, and the active catalyst species was used *in situ*.

Dry TFE (1 mL) was added to the pressure tube containing the active iridium species **Ir-3-NTf₂** (0.005 mmol, 2 mol%). The corresponding amino acid (0.25 mmol, 1 equiv) and alcohol (0.37 mmol, 1.5 equiv) were added, and the mixture was stirred at 90°C for 20 h. Then, the mixture was cooled to 50°C, and methanol (0.1 mL) was added. The mixture was stirred overnight. After this time, the mixture was cooled to RT, and palladium (10 wt. % on carbon, 1 mol%) was added. The mixture was stirred under a hydrogen atmosphere. After 5 h, the mixture was filtered through a pad of Celite. The filtrate was dried under vacuum, and the resulting residue was rinsed with diethyl ether (3 × 3 mL) to remove any remaining alcohol and the catalyst. Excellent isolated yields were obtained for all substrates without the need for any further work-up or purification.
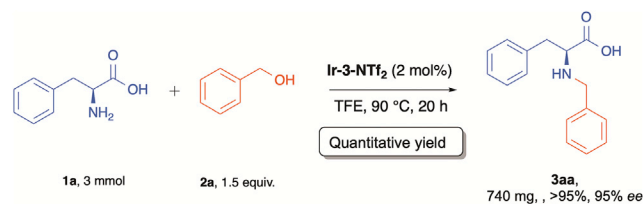
General procedure for the synthesis of N-modified peptides
Et₃N (2 equiv) was added dropwise to a suspension of the amino acid methyl ester HCl (0.5 mmol, 2 equiv) in THF (10 ml). The mixture was stirred for
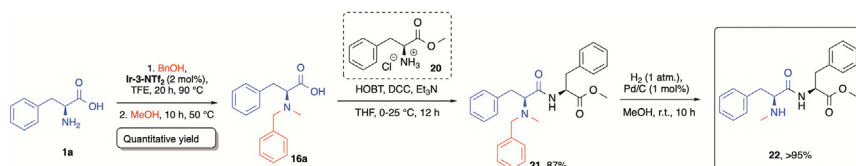
Scheme 10. Synthesis of N-dialkylated dipeptide 21 and N-monomethylated dipeptide 22
Isolated yields.

Scheme 11. Scale-up N-monoalkylation of L-phenylalanine with benzyl alcohol
L-phenylalanine (496 mg, 3 mmol), benzyl alcohol (0.47 mL, 4.5 mmol, 1.5 equiv), and TFE (12 mL).
Quantitative isolated yield.

15 min. After this time, HOBt (1 equiv) and di-*N*-alkylated amino acid (1 equiv) were added. The mixture was cooled to 0°C, and a solution of DCC (1 equiv) in THF (5 mL) was added. After 5 min, the mixture was removed from the ice bath, and it was stirred at RT overnight. The precipitate (DCU) was removed by filtration, and the solvent was removed from the filtrate under vacuum. The resulting crude oil was dissolved in EtOAc (50 mL), and the solution was placed in the freezer to allow any unreacted DCC to precipitate. The resulting precipitate was then removed by filtration. The solvent was removed from the filtrate under vacuum, and the resulting residue was purified by column chromatography to give the final product.
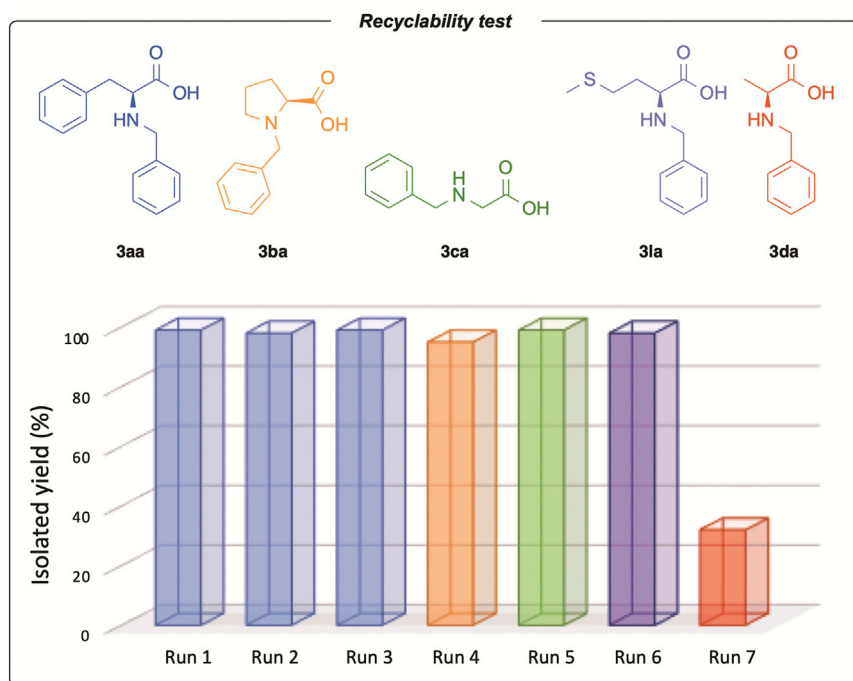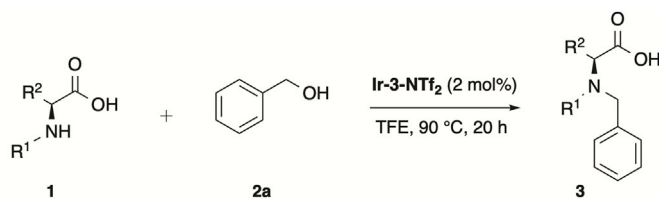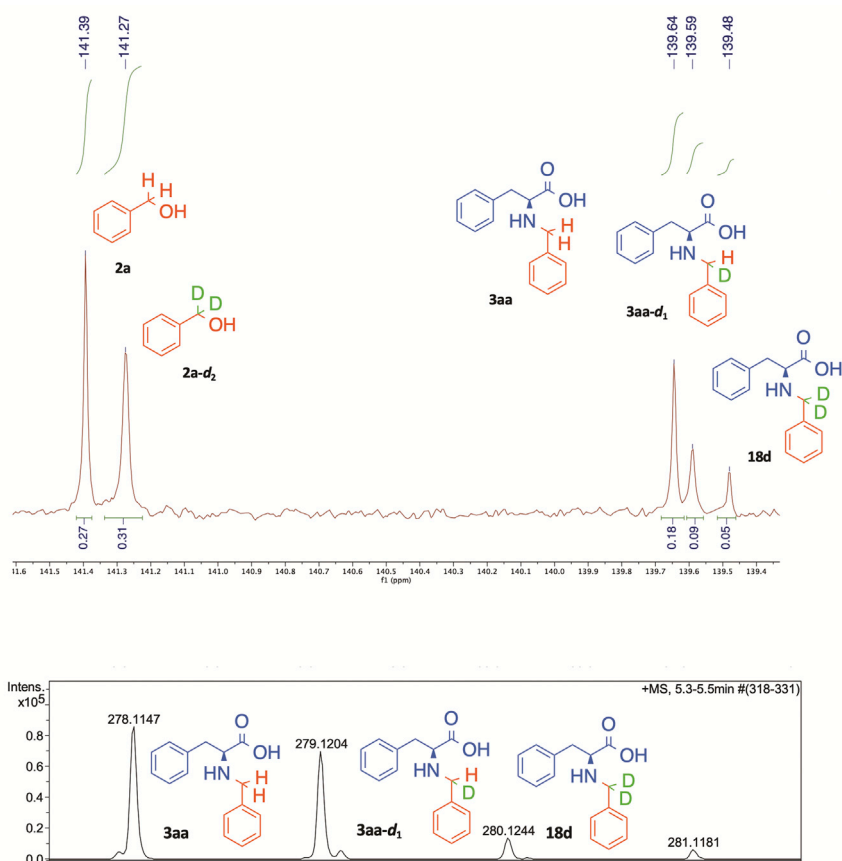

Figure 7. Recyclability studies

Figure 8. Crossover experiment. Formation of product 3aa-d_1, as observed by ^{13}C NMR spectroscopy (top) and HRMS (bottom)

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.chempr.2022.08.017.

AUTHOR CONTRIBUTIONS

A.B.-L. carried out the synthesis of the catalyst, optimization of the reaction conditions, and the majority of the investigation of the substrate scope. He also wrote the manuscript and the supplemental information. M.R. synthesized the catalyst and contributed to the investigation of the substrate scope and the writing of the manuscript. M.R. and A.B.-L. synthesized the modified peptides. E.M.-C. contributed to the design and initial synthesis of the catalyst and to the optimization of the reaction conditions. B.M.-M. supervised the project and wrote the paper with contributions from all authors.
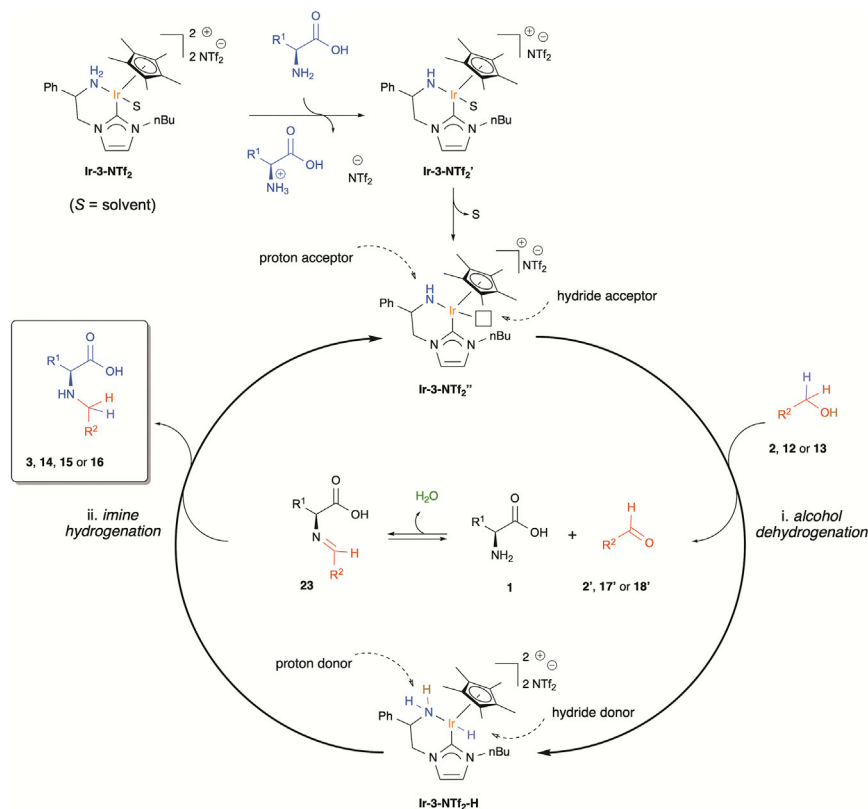
Figure 9. Suggested mechanism for the mono-*N*-alkylation of unprotected amino acids with alcohols catalyzed by an amine-functionalized NHC-Ir(III) complex (S = solvent)

DECLARATION OF INTERESTS

The authors declare no competing interests.

INCLUSION AND DIVERSITY

One or more authors of this paper self-identifies as living with a disability. One or more authors of this paper received support from a program designed to increase minority representation in science. While citing references scientifically relevant for this work, we also actively worked to promote the gender balance in our reference list.

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