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# Iron-Catalyzed Carboamination of Olefins: Synthesis of Amines and Disubstituted β-Amino Acids

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**ABSTRACT:** Intermolecular carboamination of olefins with general alkyl groups is an unsolved problem. Diastereoselective carboamination of acyclic olefins represents an additional challenge in intermolecular carboaminations. We have developed a general alkylamination of vinylarenes and the unprecedented diastereoselective *anti*-carboamination of unsaturated esters generating amines and unnatural β-amino acids. This alkylamination is enabled by difunctional alkylating reagents and the iron catalyst. Alkyl diacyl peroxides, readily synthesized from aliphatic acids, serve as both alkylating reagents and internal oxidizing agents. A computational study suggests that addition of a nitrile to the carbocation is the diastereoselectivity-determining step and hyperconjugation is proposed to account for the highly diastereoselective *anti*-carboamination.

## INTRODUCTION

C-C and C-N bonds are two of the most ubiquitous chemical bonds in nature and carboamination of olefins is an effective strategy to create these bonds simultaneously. This process directly converts simple olefins into various compounds including amines[1] and amino acids,[2] and has therefore attracted much attention. Despite the great synthetic potential of this approach,[3-5] general strategies for the carboamination of olefins with both intermolecular carbon and nitrogen sources have been less explored.[6] Among the successful carboamination examples with intermolecular carbon and nitrogen sources, classic arylamination, aminocyanation, trifluoromethylamination and alkylcyanoamination reactions producing diverse amines have been developed by Greaney,[6a] Akita,[6b] Zhang,[6c] Liu,[6d,j,l] König,[6e] Tambar,[6f] Wang,[6g] Masson,[6h] Heinrich,[6i] and Li.[6k] Liu[7a], Rovis[7b] and Glorius[7c] have reported elegant carboamination reactions of olefins, generating amino acids (Figure 1a). Notwithstanding these significant breakthroughs, carboamination with general alkyl groups remains an unsolved problem. This challenge can perhaps be attributed to the difficulty of initiating the reaction when using general alkylating reagents, such as alkyl halides. To achieve aminoalkylation with general alkyl groups, oxidative alkylating reagents that are more active than alkyl halides are required.

Diastereoisomeric control in intermolecular carboamination of acyclic olefins is a further significant challenge in the carboamination of olefins. So far only Rovis et al.[7b] have accomplished diastereoselective intermolecular carboamination of acyclic alkenes *via* a concerted *syn*-addition of both carbon and nitrogen functionalities. Stepwise intermolecular diastereoselective carboamination remains an unsolved problem.

β-Amino acids have seen increasing use as building blocks for molecular design and synthesis of pharmaceutically important chemicals. Consequently, the synthesis of β-amino acids has been studied extensively[2c] and many strategies including homologation of α-amino acids,[8] the Mannich reaction,[9] conjugate addition of α,β-unsaturated carbonyl compounds[10] and hydrogenation of β-amino- acrylic acid derivatives[11] have been developed. Recent work by Liu et al.[7a] has revealed that the carboamination of olefins offers a new strategy with which to generate monosubstituted β-amino acids. Despite all the progress that has been made to date however, the diastereoselective construction of α,β-disubstituted β-amino acids from readily available chemicals remains a difficult task.

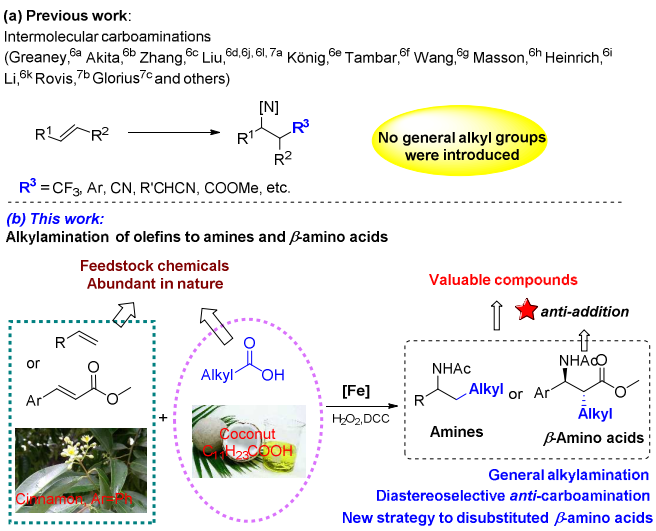



**Figure 1**. Carboamination of olefins

Carboxylic acids are inexpensive, stable and non-toxic feedstock chemicals and are widely used in numerous reac-

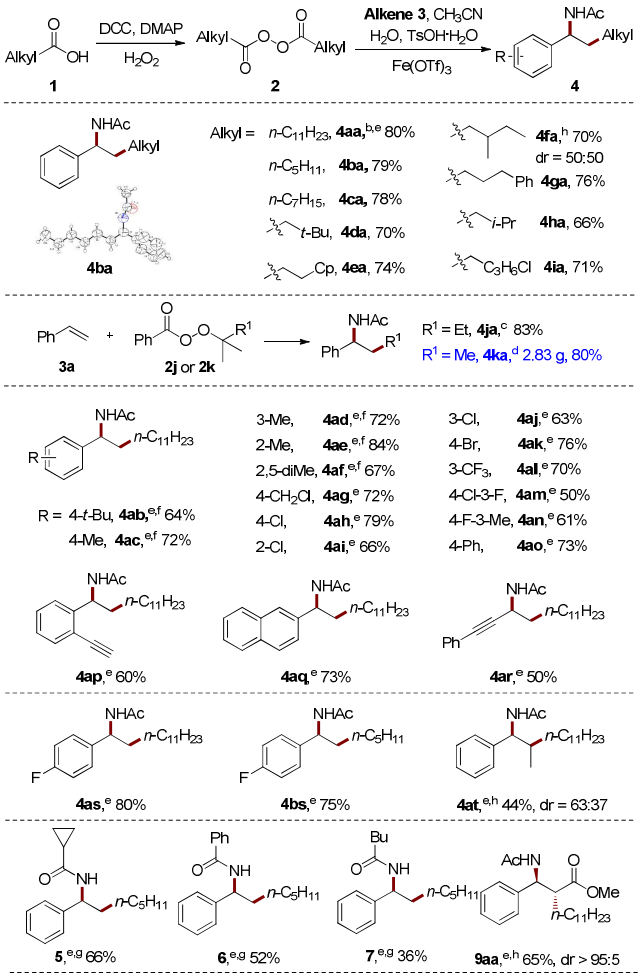
tions.[12] The activation of carboxylic acids through the formation of redox-active esters is emerging as a powerful strategy for decarboxylative coupling reactions.[13] Diacyl peroxides, readily prepared from carboxylic acids, are another type of activated carboxylic acid. One significant advantage of alkyl peroxides as alkylating reagents is their ability to serve simultaneously as alkylating and oxidizing agents. We have established an alkyl etherification reaction of vinylarenes using alkyl peroxides as alkylating reagents.[14] To develop a general intermolecular alkylamination process and address the challenge of diastereoselective intermolecular carboamination in acyclic systems, we studied intermolecular alkylamination using aliphatic acids as an alkyl source and nitriles as a nitrogen source.[15] Here, we report the first general alkylamination and diastereoselective alkylamination with *trans*-addition of carbon and nitrogen sources to double bonds (Figure 1b). This method enables the direct synthesis of benzylic amines from vinylarenes and rapid construction of $\alpha$-alkyl-$\beta$-aryl-$\beta$-amino acids, which are not readily accessible by classical methods of amino acid synthesis.

## RESULTS AND DISCUSSION

**General alkylamination of vinylarenes to amines.** Based on our hypothesis that oxidative alkylating reagents are required in carboamination reactions, the bench-stable, commercially available chemical feedstock dilauroyl peroxide (LPO, **2a**) was used to initiate the carboamination reaction of styrene in the presence of metal catalysts. It was found that use of $Fe(OTf)_3$ as catalyst and dioxane/acetonitrile as solvent leads to the corresponding product (**4aa**) in 35% yield (see details in SI). After investigating solvents and additives, the yield of product **4aa** was increased to 80% with acetonitrile as solvent and $TsOH{\cdot}H_2O$ as an additive. Other metal catalysts, such as $Mn(OAc)_2$, AgOTf, and $Pd(TFA)_2$, delivered only a small amount of product but the reaction fails completely in the absence of a metal catalyst. These results imply that diacyl peroxide and $Fe(OTf)_3$ are both essential for this reaction. Furthermore, diacyl peroxides simultaneously act as alkylating reagents and internal oxidants, while the iron catalyst possibly promotes the generation of the alkyl radical. The scope of diacyl peroxides as alkylating reagents was studied under the optimized reaction conditions and the results are shown in Table 1. Diacyl peroxides (**2b-2h**) afford the desired products (**4ba-4ha**) in good yields (66-79%). The chlorine-substituted diacyl peroxide is compatible with the reaction conditions, providing the product (**4ia**) in 71% yield. Interestingly, peresters **2j** and **2k** deliver the ethylamination (**4ja**) and methylamination products (**4ka**) in 83% and 80% yield respectively. The perester **2k** was employed to conduct a gram scale reaction, demonstrating the practicability of this method.

This alkylamination reaction was successfully extended to a broad scope of vinylarenes and enynes (Table 1). Reactions of *o*-, *m*-, *p*-alkyl substituted vinylarenes afford products **4ab-4ag** in good yields (64-84%). Vinylarenes featuring electron-withdrawing groups such as chlorine, bromine and trifluoromethyl groups lead to **4ah-4al** in good (63-79%) yields. Vinylarenes with two substituents on the aryl ring can also be used in the reaction, generating the desired products **4am** and **4an** with 50% and 61% yields, respectively. 4-vinyl-1,1'-biphenyl affords the corresponding product (**4ao**) in 73% yield. The ethynyl group of 2-ethynyl styrene is unchanged under the standard reaction conditions, and the product (**4ap**) is obtained

**Table 1.** Decarboxylative alkylamination of alkenes with alkyl diacyl peroxides.[a]

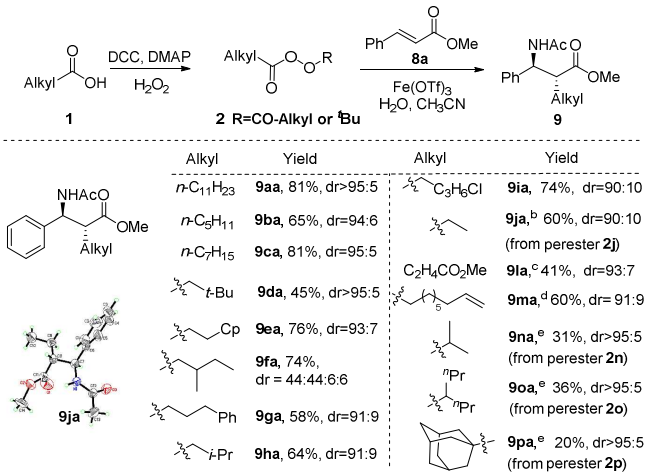



Reaction conditions: [a] Aliphatic acids **1** (3 mmol, 3 equiv.), DCC (3.4 mmol, 3.4 equiv.), DMAP (0.3 mmol, 0.3 equiv.), $H_2O_2$ (3.75 mmol, 3.75 equiv. 30%, v/v), DCM (7.5 mL), styrene **3** (1 mmol, 1 equiv.), $Fe(OTf)_3$ (10 mol%), $CH_3CN$ (0.25 M), $TsOH{\cdot}H_2O$ (2 mmol, 2 equiv.), $H_2O$ (2 mmol, 2 equiv.), 70 °C, 5 h, isolated yield. [b] LPO **2a** (1.5 mmol). [c] Styrene **3a** (1 mmol), perester **2j** (3 mmol). [d] Styrene **3a** (20 mmol), perester **2k** (60 mmol). [e] Peroxide **2** (1 mmol, 1 equiv.), alkene **3** (1.5 mmol, 1.5 equiv.). [f] at 50 °C. [g] Cyclopropanecarbonitrile, benzonitrile and pentanenitrile were applied as the solvent respectively. [h] dr value was determined by $^1$HNMR.

in 60% yield. 2-Vinylnaphthalene delivers the aminoalkylated product (**4aq**) in 73% yield. An enyne was also tolerated in this transformation, delivering the corresponding terminal-cross-coupled product (**4ar**) in 50% yield. 4-Fluoro-styrene (**3s**) reacts with diacyl peroxides **2a** and **2b**, generating products **4as** and **4bs**, analogues of an anti-inflammatory agent[16] in 80% and 75% yield respectively. The reaction of $\beta$-methyl styrene delivers product **4at** in 44% yield. Cyclopropanecarbonitrile, benzonitrile and pentanenitrile can be applied to the aminoalkylation reaction, giving the carboamination products **5-7** in good to moderate yields (66%-36%). When a 1,2-disubstituted alkene, methyl cinnamate (**8a**) is subjected to the standard conditions, 65% yield of the $\beta$-amino acid derivative (**9aa**) is obtained in one step and surprisingly, a single diastereomer of **9aa** is formed (diastereoisomer ratio, dr > 95:5).

**Diastereoselective alkylamination of unsaturated esters to amino acids. The acid effect.** In view of the challenges of diastereoselective intermolecular carboamination in acyclic systems and the broad application potential of *β*-amino acids, we further explored the iron-catalyzed carboamination in the diastereoselective synthesis of *β*-amino acid derivatives. On the basis of our initial results, the conditions were re-optimized for the reaction of methyl cinnamate (**8a**) with dilauroyl peroxide (**2a**) (see details in SI). The amino acid derivative **9aa** was obtained in 81% yield and with as high as >95:5 dr, by using 15 mol% $Fe(OTf)_3$ as a catalyst without other additives. Using the optimal conditions in hand, we converted a variety of aliphatic acids into alkyl diacyl peroxides or alkyl peresters and examined the subsequent diastereoselective carboamination (Table 2). From simple primary alkyl peroxides, amino acids are obtained in up to 81% yield. Primary aliphatic acids with additional functionality such as chloro, alkenyl and ester groups are well tolerated in this reaction, delivering the corresponding products (**9ia, 9la** and **9ma**) in moderate (41-74%) yields (Table 2,). Ethylamination of methyl cinnamate with *tert*-pentyl peroxybenzoate provides the product (**9ja**) in 60% yield. Products **9na**, **9oa** and **9pa** containing secondary and tertiary alkyl groups are obtained in relatively low yields from aliphatic acids *via* alkyl peresters. The overall diastereoselectivity of this reaction is satisfactory and the products are potentially useful. Compound **9ma** for example, could serve as the key monomer in a stapled peptide synthesis.[17]

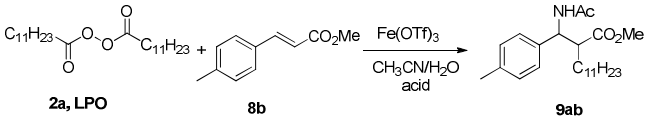
**Table 2.** Diastereoselective alkylamination of **8a** with alkyl diacyl peroxides.[a]

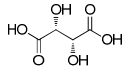
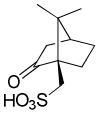
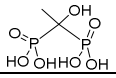



[a] Reaction conditions: **2** (1 mmol, 1 equiv.), **8a** (1.5 mmol, 1.5 equiv.), $Fe(OTf)_3$ (15 mol%), $CH_3CN$ (0.25M), $H_2O$ (2 mmol, 2 equiv.), 80 °C, 5 h, isolated yield, dr value was determined by $^1$HNMR. [b] Perester **2j** (1.5 mmol, 1.5 equiv.), **8a** (1 mmol, 1 equiv.). [c] Peroxide **2k** (0.5 mmol, 1 equiv.), **8a** (0.75 mmol, 1.5 equiv.), $H_2SO_4$ (0.5 mmol, 1 equiv.). [d] Peroxide **2l** (5 mmol, 1 equiv.). [e] Perester **2** (1.5 mmol, 3 equiv.), **8a** (0.5 mmol, 1 equiv.).

Subsequently, we investigated the scope of the unsaturated esters (**8**) in the carboamination with LPO. Interestingly, the reaction of 4-methylcinnamate (**8b**) affords the product (**9ab**) in 80% yield, with a dr of 85:15 (Table 3, entry 1). We speculated that acids might affect the dr for this reaction and studied the effect of acids. Monoacids (entries 2-5), failed to assist the reaction in terms of the diastereoselectivity. D-Tartaric acid fails to improve the dr (entry 6), but addition of $H_2SO_4$ increases the dr to 92:8 (entry 7). Camphor sulfonic acid was assessed as an additive but no improvement in the dr was observed (entry 8). $H_3PO_4$ was checked in the reaction and the product is obtained with high dr but in low yield. Etidronic acid was examined in the reaction and a slightly better dr was observed. We speculate that binary acids or ternary acids improve dr while monoacids fail to do so.

**Table 3.** Acid effect in diastereoselective alkyamination of 4-methylcinnamate. [a]

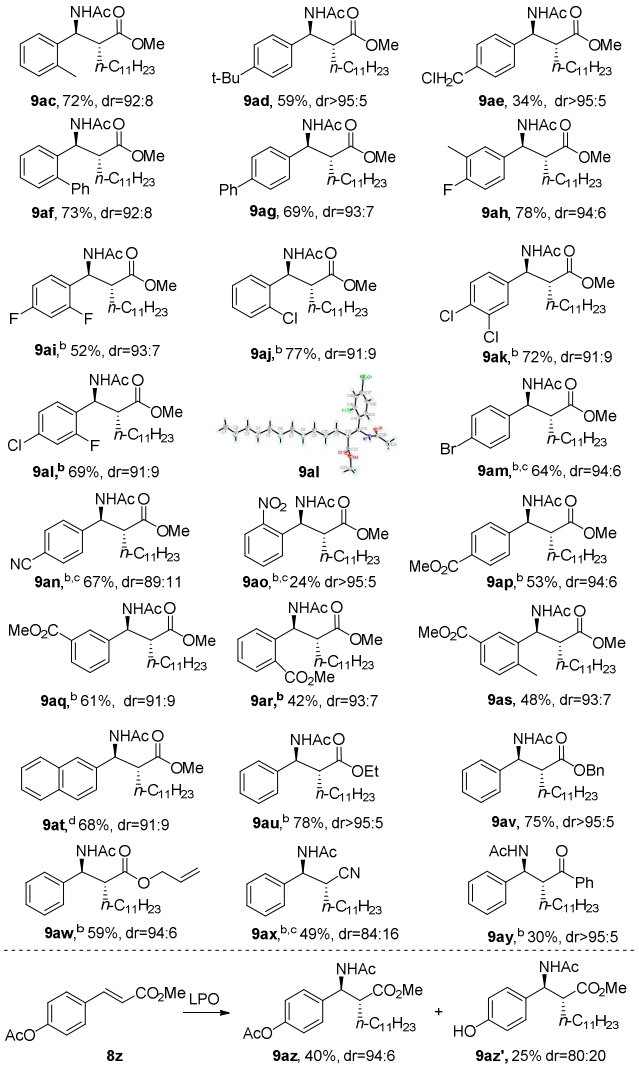



| Entry | Acid | dr[b] | Yield[c] |
|---|---|---|---|
| 1 | / | 85:15 | 80 |
| 2 | HOTf | 81:19 | 57 |
| 3 | HOMes | 85:15 | 78 |
| 4 | HOTs | 80:20 | 68 |
| 5 | $HPF_6$ | 76:24 | 77 |
| 6 |  | 82:18 | 66 |
| 7 | $H_2SO_4$ | 92:8 | 77 |
| 8 |  | 85:15 | 70 |
| 9 | $H_3PO_4$ | 93:7 | 24 |
| 10 |  | 89:11 | 58 |

[a] Reaction conditions: **8b** (0.75 mmol), LPO **2a** (0.5 mmol), $Fe(OTf)_3$ (15 mol%), acid (0.5 mmol), $CH_3CN$ (2 mL), $H_2O$ (1 mmol), 80 °C, 5 h. [b] Determined by $^1$H NMR. [c] Yield of isolated product.

Other substrates were examined using these additional optimal conditions (Table 4). Substrates containing alkyl or phenyl substituents afford the corresponding products (**9ac-9ah**) in 34-78% yield. Methyl cinnamates substituted with Cl, F, and Br afford the products (**9ai-9am**) in 52-77% yield. Methyl cinnamates substituted with *p*-cyano, *o*-nitro, *o*-, *m*-, and *p*-ester groups provide the corresponding *β*-amino acid derivatives (**9an-9as**) in 24-67% yields with no added acid. (*E*)-methyl 3-(naphthalen-2-yl)acrylate is compatible in the transformation, furnishing a 68% yield of **9at**. Ethyl cinnamate, benzyl cinnamate and allylcinnamate all exhibit good reactivity, affording the corresponding products (**9au, 9av** and **9aw**) in 59%-78% yields. Reaction of *β*-cyano styrene (cinnamonitrile) delivers product **9ax** in 49% yield. Reactions of chalcone afford the corresponding product (**9ay**) in 30% yield. (*E*)-methyl 3-(4-acetoxyphenyl)acrylate is transformed to *β*-tyrosine (**9az**), an analogue of a natural product, in 40% yield with dr 94:6 and the deprotected product (**9az'**) in 25% yield, with dr 80:20. Dimethyl fumarate fails to participate in the carboamination under the optimized reaction conditions.

**Table 4.** Diastereoselective general alkylamination of unsaturated esters, ketone and nitrile with LPO.[a]




[a] Reaction conditions: **2a** (0.5 mmol, 1 equiv.), **8** (0.75 mmol, 1.5 equiv.), $Fe(OTf)_3$ (15 mol%), $CH_3CN$ (0.25M), $H_2O$ (1 mmol, 2 equiv.), $H_2SO_4$ (0.5 mmol, 1 equiv.), 80 °C, 5 h, isolated yield, dr value was determined by $^1$HNMR. [b] Acid free. [c] dr value was determined by GC. [d] $Fe(OTf)_3$ (25 mol%).

**Origin of diastereoselectivity and a proposed mechanism.** The absolute configurations of *anti-β*-amino acid derivatives (**9**) determined by X-ray crystallography suggest that *anti*-addition is a major pathway. Density functional theory (DFT) studies were conducted in an effort to understand the origin of diastereoselectivity in this Fe-catalyzed alkylamination.[18] The overall potential energy surface is depicted in Figure S1. The addition of acetonitrile to the benzylic carbocation (**INT4**) is the diastereoselectivity-determining step and a conformational search was performed to explore all possible conformations in this critical step. Twenty-four conformations of transition-state **TS3** for each *SS* and *RS*-configuration were optimized (See Table S6) and the most stable conformers leading to *SS* and *RS* products are presented in Figure 2. The activation free energy *via* ***RS*-TS3** is 2.0 kcal mol$^{-1}$ lower than that of ***SS*-TS3** (Figure 2a), corresponding to a product ratio (dr) of 96:4, which is in good agreement with the experimental finding that *anti-β*-amino acid derivatives are the major products. Because the addition of acetonitrile enjoys an unhindered approach, steric factors were felt to be unlikely to dictate the selectivity. Natural Bond Orbital (NBO) analysis of the two transition states revealed the origin of the diastereoselective preference.[19] The stabilizing interactions between the C-C bond (highlighted in green) and the unoccupied carbon cation orbital in ***SS*-TS3** and ***RS*-TS3** are 7.0 and 8.2 kcal/mol, respectively. This hyperconjugation may account for the diastereoselectivity.

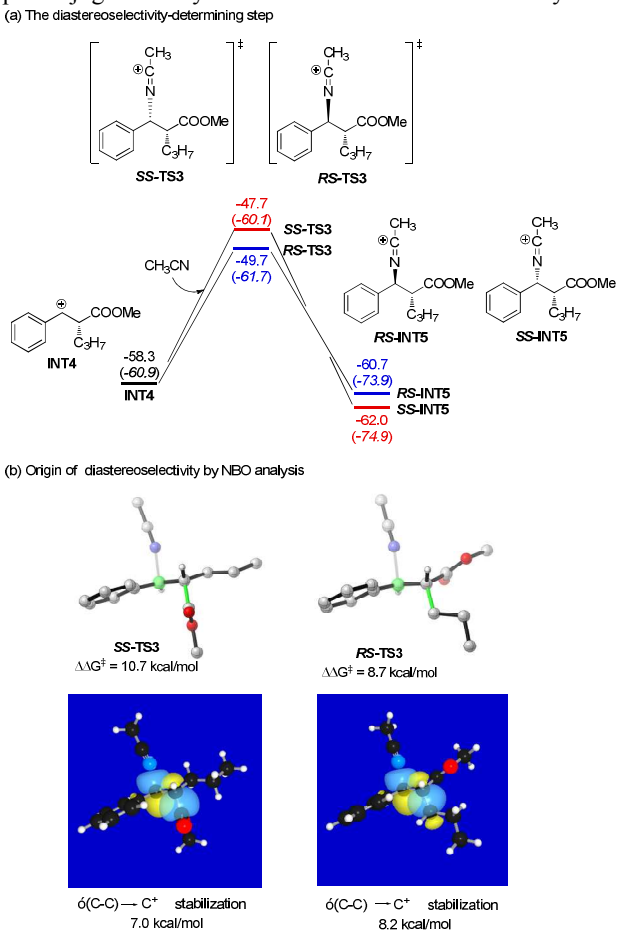



**Figure 2** (a) The free energy profile for the addition of acetonitrile to the benzylic carbocation (**INT4**) derived from Density Functional Theory (DFT) calculation. Relative free energies (energies) are in kcal/mol. (b) The most stable conformers and the hyperconjugation orbitals of ***SS*-TS3** and ***RS*-TS3** (irrelevant hydrogen atoms are omitted for clarity).

The barrier to the addition of acetonitrile is not high and the relative free energy of **INT4** and **INT5** are comparable, implying that the addition step could be reversible and equilibration could potentially lead to an opposite stereoselectivity. Consequently, the barrier for the subsequent step becomes critical. As illustrated in Figure 3, when this subsequent barrier is sufficiently low, the addition of acetonitrile is subject to kinetic control and leads to the observed selectivity. The theoretical calculations reveal that the barrier to the hydrolysis process in the Ritter reaction can be lowered through an intramolecular $HSO_4^-$ assisted transition state (**TS4**) compared to the acid free condition (**TS4a**). This result may account for improved dr value in the presence of $H_2SO_4$.

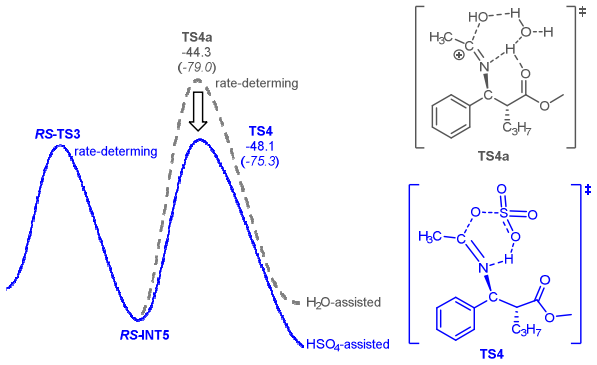



**Figure 3.** Change in the rate-determining step between the sulfuric acid-assisted and double water-assisted pathways. Relative free energies (energies) are in kcal/mol.

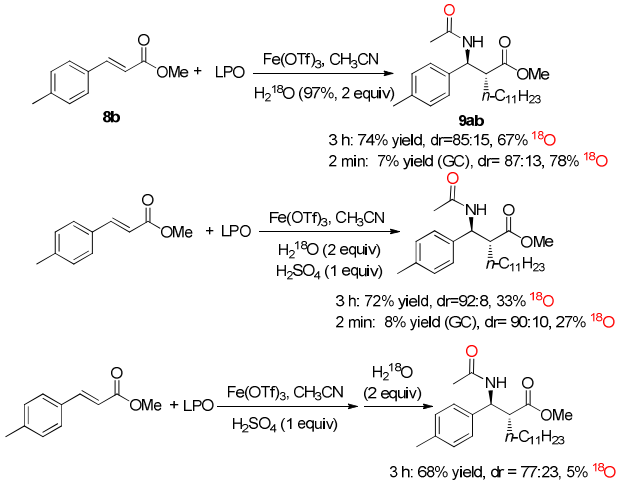



**Figure 4.** Isotope labeling experiments for the alkylamination of alkenes with alkyl diacyl peroxides.

In view of the possible error in such a calculation, the comparison between two steps might not be conclusive[20] and further experiments were conducted seeking conformation. In the transition states of **TS4a** and **TS4**, the oxygen atoms originate from $H_2O$ and $HSO_4^-$, respectively and consequently, isotope-labeling experiments may distinguish between these two models. As shown in Figure 4, the presence of $H_2SO_4$ dramatically changes the incorporation ratio of $^{18}O$ from $H_2{}^{18}O$ in the product. In the absence of $H_2SO_4$, 67% of the amide species contains $^{18}O$. In the presence of both $H_2SO_4$ and $H_2{}^{18}O$, 33% of the product contains $^{18}O$. It is possible that $H_2{}^{18}O$ exchanges $^{18}O$ with $H_2SO_4$ under the reaction conditions,[21] and therefore we examined the content of $^{18}O$ in the product at the beginning of the reactions (after 2 minutes). A larger difference (78% vs. 27%) of $^{18}O$ labeled product between two control experiments is observed by GC-MS, indicating that $H_2O$, in competition with $H_2SO_4$, is unlikely to be the major O source. When $H_2{}^{18}O$ is added to quench the reaction, only 5% $^{18}O$ is observed in the product. These labeling experiments suggest that $H_2SO_4$ indeed participates in the hydrolysis process *via* **TS4** and delivers oxygen to the final product.

A possible radical-polar crossover[22] mechanism for the reaction is shown in Figure 5. The Fe(II) compound transfers an electron to LPO, generating the Fe(III) complex and an alkyl-acyloxy radical. Subsequently, an alkyl radical is formed by a decarboxylation process. This alkyl radical reacts with the methyl cinnamate to generate a benzylic radical containing a stereogenic center. The benzylic radical is then oxidized by Fe(III) to a carbocation species which adds to the nitrile nitrogen to give a nitrilium ion intermediate. This is followed by a hydrolysis assisted by $H_2O$ or $H_2SO_4$ producing the corresponding product.[23] The two essential ingredients for this successful catalytic cycle are the alkylating reagents and metal catalyst.

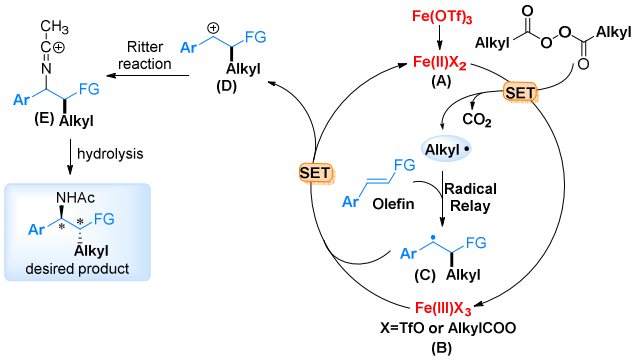



**Figure 5.** The proposed catalytic cycle for the iron-catalyzed carboamination of olefins.

**Synthetic applications.** To exemplify a synthetic application of this method, **14** and **18**, analogues of a peptide opioid agonist (Tyr-Gly-Leu-Phe, Figure 6a),[24] were synthesized with the carboamination products (**12** and **16**) replacing tyrosine. In addition, an analogue of the antiviral compound (**20**) was prepared from styrene in two steps *via* alkylamination and Friedel-Crafts alkylation reaction sequence with adamantyl bromide **19** (Figure 6b).[25]

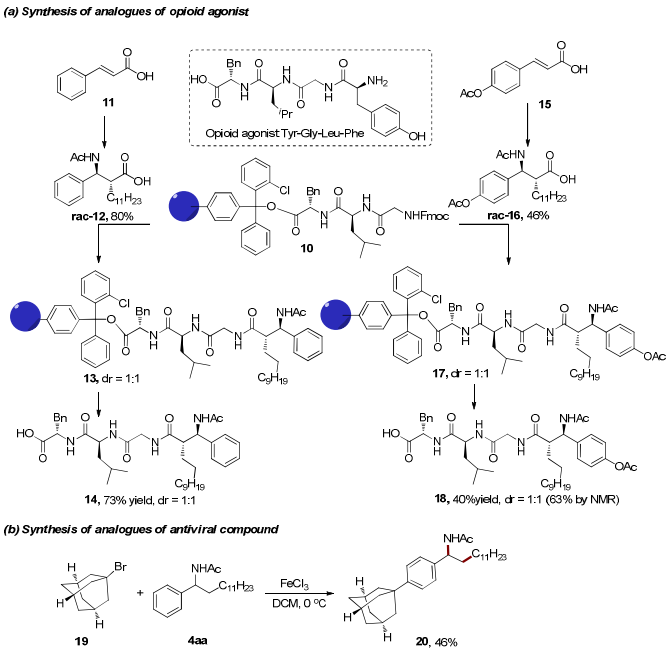



**Figure 6.** Alkylamination of olefins and synthetic applications.

## CONCLUSION

We have established the intermolecular alkylamination of vinylarenes and the diastereoselective *anti*-alkylamination of $\alpha,\beta$-unsaturated esters through a sequence of radical addition, oxidation and a Ritter reaction. Various useful amines and unnatural disubstituted $\beta$-amino acid derivatives can be

formed from simple olefins with moderate to good efficiency. In particular, the $\beta$–amino acids are obtained with high diastereoselectivity and this will support their further use in other fields. This radical-polar crossover reaction is enabled by an iron catalyst and the difunctional alkyl peroxides. On the basis of a computational study, addition of nitriles to the carbocation was found to be the diastereoselectivity-determining and hyperconjugation was proposed to account for the high diastereoselective *anti*-carboamination.

## ASSOCIATED CONTENT

### Supporting Information

Supplementary information and chemical compound information are available free of charge on the ACS Publications website. Correspondence and requests for materials should be addressed to H. B. Accession codes: the x-ray crystal data and structure refinements of **4ba, 9ja** and **9al** have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition number 1541218 for **4ba,** 1541217 for **9ja,** and 1541192 for **9al**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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### Author Contributions

‡B. Qian and S. Chen contributed equally.

### Notes

The authors declare no competing financial interests.

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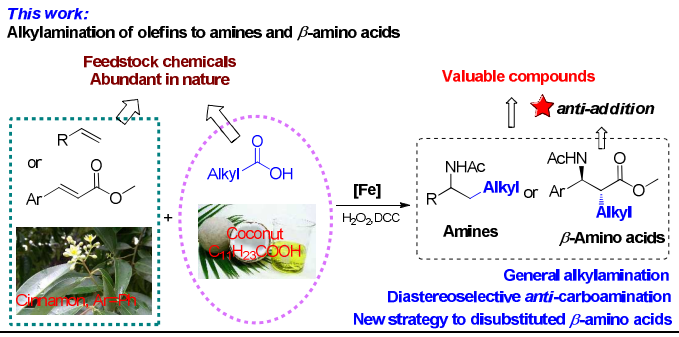
This work:
Alkylamination of olefins to amines and β-amino acids
Feedstock chemicals
Abundant in nature
Valuable compounds
anti-addition
R
or
Ar
O
Alkyl
OH
Coconut
C11H23COOH
Cinnamon, Ar=Ph
[Fe]
H2O2,DCC
NHAc
Alkyl
or
AcHN
Amines
β-Amino acids
General alkylamination
Diastereoselective anti-carboamination
New strategy to disubstituted β-amino acids