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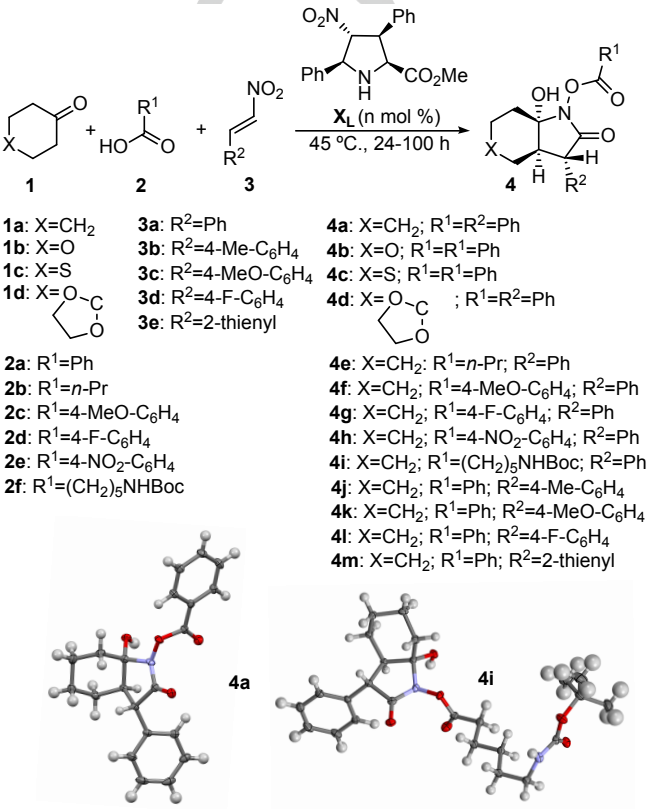
New Three-Component Enantioselective Cyclization Reaction Catalyzed by an Unnatural Amino Acid Derivative

María de Gracia Retamosa,[a] Andrea Ruiz-Olalla, [a] Tamara Bello,[a] Abel de Cózar,[a,b] and Fernando P. Cossío*[a]

Abstract: A new three-component diastereo- and enantioselective cyclization reaction is described. The reaction takes place between a ketone, a carboxylic acid and a nitroalkene to yield a bicyclic octahydro-2*H*-indol-2-one scaffold possessing three chiral centers. This reaction involves a rearrangement of the nitro group under simple thermal conditions. A plausible mechanism is proposed for this new reaction based on DFT calculations and isotope labeling experiments. A new concise enantioselective synthesis of alkaloid (+)-pancracine is presented as an example of the potential of this novel organocatalytic cyclization reaction in the synthesis of natural products.

Natural amino acids and some conveniently functionalized derivatives behave as minimalistic analogues of enzymes. These so-called organocatalysts[1] promote well-known chemical transformations such as aldol and conjugate addition reactions, as well as cycloadditions and domino multicomponent reactions leading to cyclic or polycyclic compounds. However, the question whether small amino acid derivatives can lead to the discovery of novel chemical reactions remains open.

Conjugate (Michael) addition between carbonyl compounds and nitroalkenes takes place efficiently to yield γ-nitrocarbonyl compounds.[2] Previous careful studies[3] have shown that the nitro group participates in the catalytic cycle and in many domino/cascade multicomponent reactions leading to polycyclic systems.[4] However, these domino reactions can be reduced to consecutive known transformations[6].



Scheme 1. Synthesis of γ–lactams **4a-m** via three-component reaction between ketones **1a-d**, carboxylic acids **2a-f** and nitroalkenes **3a-e** catalyzed by densely substituted proline $\mathbf{X_L}$. The structures of **4a** and **4i** (X-ray diffraction analysis, 50% probability ellipsoids) are also given.

Previous work in our group has described the synthesis of unnatural densely substituted proline esters[7] such as $\mathbf{X_L}$ (Scheme 1). We have found that these unnatural amino esters are efficient catalysts for the aldol reaction.[8] Furthermore, their amino derivatives constitute suitable organocatalysts for the conjugate addition between ketones and nitroalkenes.[9] In contrast, nitro derivative $\mathbf{X_L}$ was found to be inefficient in the catalysis of this latter reaction. Analysis of the crude reaction mixtures obtained in the presence of a catalytic amount of acid additive showed the formation of a minor product that incorporated the carboxylic acid used to promote the reaction. Therefore, we repeated the reaction in the presence of an equimolar quantity of the three components, namely cyclohexanone **1a** (X = CH_2, Scheme 1), benzoic acid **2a** (R^1 = phenyl) and (*E*)-nitrostyrene **3a** (R^2 = phenyl). After one day of

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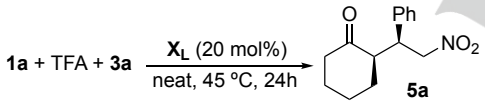
reaction at 45ºC in the presence of 20% catalytic loading we obtained cycloadduct **4a** (Scheme 1, Table 1) with excellent yield and enantiomeric excess. The catalytic loading could be lowered to 10 mol % but the reaction required 60 h to achieve a similar chemical yield. Cycloadduct **4a** was stable under these thermal conditions. However, stronger acidic (TFA, 10 eq., 72h) or basic (TEA, 10 eq. 72h) conditions resulted in decomposition of the reaction product. X-ray diffraction analysis[10] of cycloadduct **4a** showed an unexpected bicyclic structure (Scheme 1) in which three new chiral centers were generated in one single preparative step with virtually complete diastereo- and enantiocontrol. We also tested this protocol in the presence of organocatalysts for which the usual Michael addition reaction has been reported,[9,11] such as L-proline,[11a], a cinchona alkaloid derivative,[11b] an O-silylprolinol derivative[11c] and the amino derivative[9] of $\mathbf{X_L}$. In all these cases, reaction with stoichiometric amounts of acid did not yield **4a**, with the only exception of the latter case, in which a mixture of **4a** and the Michael adduct **5a** (vide infra) was obtained in a 33:67 ratio, with an isolated yield of only 20% for **4a**. Therefore, the steric and electronic features of $\mathbf{X_L}$ are especially adequate for this novel reaction (see the Supporting Information).

The reaction also worked with other ketones such as **1b-d**. Similarly, the new reaction was found to be compatible with aromatic and alkyl acids, although in the case of **2b** another isomer was observed (see the Supporting Information). The structure of the adduct **4i** formed from δ–amino acid **2f** was also confirmed by X-ray diffraction analysis[10]. 4-Nitrobenzoic acid **2e** was satisfactorily incorporated into adduct **4h** (Table 1, entry 9), but a small amount of the Michael product **5a** was observed. However, when TFA was used, no adduct **4** was formed and only **5a** was observed, with a conversion of 43 % after 24 h of reaction:



Therefore, we concluded that, beyond a certain acidity of reactant **2**, the standard conjugate addition competes with the novel reaction.

Table 1. Three-component cyclization reaction between ketones **1a-d**, carboxilic acids **2a-e** and nitroalkenes **3a-d** catalyzed by unnatural amino ester $\mathbf{X_L}$.

Entry[a]	$\mathbf{X_L}$mol %	Time (h)	**1+2+3->4**[b]	Yield[c] (%)	ee[d] (%)
1	20	24	**1a 2a 3a 4a**	91	97
2	10	60	**1a 2a 3a 4a**	88	97
3	20	100	**1b 2a 3a 4b**	56[e]	95
4	20	24	**1c 2a 3a 4c**	71[f]	97
5	20	48	**1d 2a 3a 4d**	62[f]	95
6	20	24	**1a 2b 3a 4e**	38	96
7	20	24	**1a 2c 3a 4f**	86	97
8	20	24	**1a 2d 3a 4g**	81	96
9	20	24	**1a 2e 3a 4h**	78[g]	97
10	20	36	**1a 2e 3a 4i**[d]	58	96
11	20	24	**1a 2a 3b 4j**	65	95
12	20	24	**1a 2a 3c 4k**	76	98
13	20	24	**1a 2a 3d 4l**	86	96
14	20	24	**1a 2a 3e 4m**	67	96

[a] Reactions were monitored by TLC or ^{1}H-NMR until consumption of the starting acid and nitroalkene (conversion $\geq$ 99 %). [b] See Scheme 1 for the substitution patterns of reactants and products. [c] Yields of isolated pure products [d] Enantiomeric excesses (ee, in %) were determined by high-performance liquid chromatography (HPLC) using chiral stationary phases (see the Supporting Information). [e] Only 60 % conversion was observed under these conditions. [f] Reaction carried out in dichloromethane as solvent and with 4 eq. of ketone. [g] A small amount of Michael adduct was detected (See the Supporting Information).

When we repeated the reaction between **1a**, **2a** and **3a** in the absence of visible light or in the presence of radical traps, the reaction proceed normally, thus allowing us to discard photocatalytic processes and the presence of radical or biradical intermediates. In addition, when the previously reported[9] Michael cycloadduct **5a** was allowed to react in the presence of **2a** and $\mathbf{X_L}$, no noticeable formation of **4a** was observed. Likewise, when the *N*-methylated derivative of $\mathbf{X_L}$[9] was tested, no reaction took place, thus demonstrating that the *NH* moiety leading to the enamine intermediate is required for this reaction. In addition, catalyst $\mathbf{X_L}$ was recovered intact after completion of the reaction, thus proving that the nitro group of the catalyst survives along the catalytic cycles.

After analyzing different possible routes, including (2+4) mechanisms, the catalytic cycle shown in Figure 1A emerged as the most plausible proposal. First, ketone **1** forms the enamine intermediate **INT1**, which leads to protonated nitronate **INT2** after reaction with nitroalkene **3**, whose electrophilicity is enhanced by protonation in the presence of acid **2** (see the Supporting Information). Transition structure **TS1** shows an efficient chiral discrimination induced by $\mathbf{X_L}$ and the assistance of the nitro group present in the organocatalyst, thus leading to a quite rigid saddle point, in which the conformation of the enamine moiety is restricted and addition on one of the prochiral faces of the nitroalkene is favored (Figure 1B). This stereocontrol results in a computed enantiomeric ratio of 90:10, in qualitative agreement with the experimentally observed ee value (see entry 3 of Table 1 and the Supporting Information). Acid **2** adds to protonated nitronate **INT2** to form acyl derivative **INT3** via saddle point **TS2** (Figure 1C). The calculated activation barrier associated with this step is *ca.* 23 kcal/mol.[12] Water elimination and subsequent tautomerization lead to intermediates **INT4** and **INT4'**. This latter zwitterionic intermediate generates the amide moiety of **INT5** via transition structure **TS3**, with activation energy of *ca.* 17 kcal/mol. According to this mechanism, the relatively long reaction times

required to complete the catalytic cycle at 45 ºC are associated with **INT2→INT3** and, into a lesser extent, **INT4→INT5** elementary steps, since from this latter intermediate the formation of the γ-lactam ring requires an activation energy of only 8.6 kcal/mol. Finally, from **INT6** the catalyst is released and compound **4** is formed via hydration of cation **INT7** (Figure 1A). Numerical simulations of the kinetic equations resulting from the catalytic cycle gathered in Figure 1A showed that these activation energies result in reaction times of ca. 48 h for ca. 95 % conversion of **1b**, **2a** and **3a** into **INT7b**, in qualitative agreement with the observed reaction time.

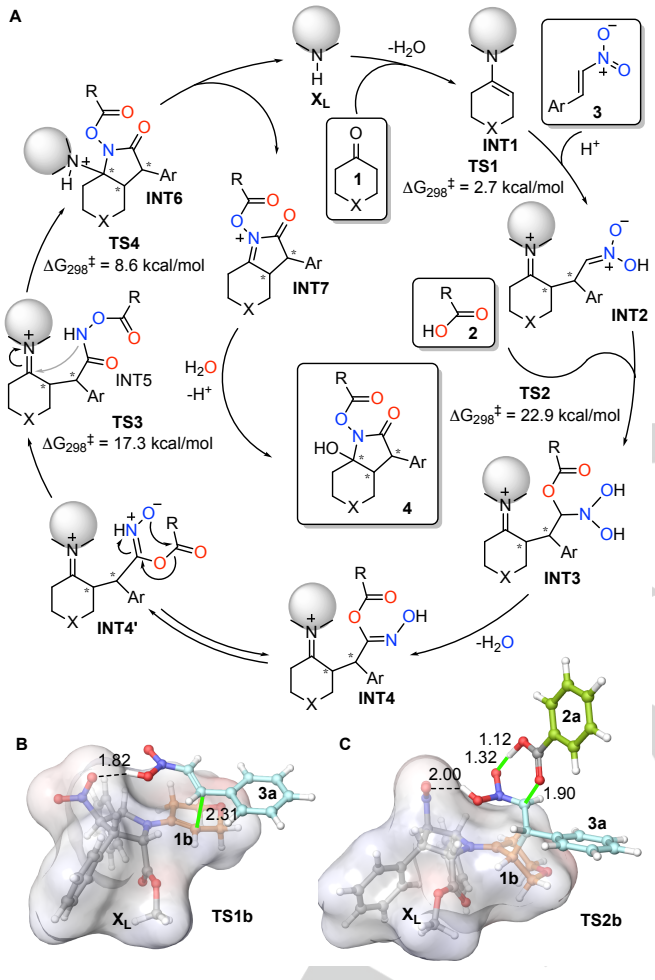
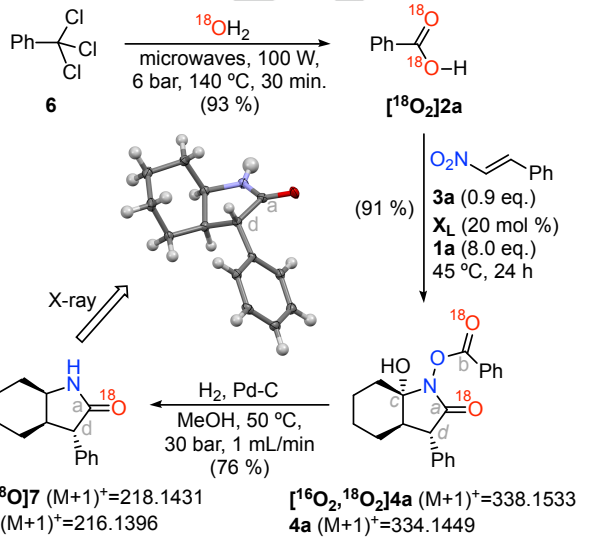


Figure 1. (A) Proposed catalytic cycle for the new reaction described in Scheme 2. Free activation energies calculated for the key steps of the **1b**+**2a**+**3a** ⟶ **4b** reaction, computed at the B3LYP-D3(PCM=cyclohexanone)/6-311+G*//B3LYP-D3/6-31G(d) level of theory, are also given. See the Supporting Information for additional details. (B, C) Optimized structures for **TS1b** (B) and **TS2b** (C). Bond distances are given in Å. Carbon atoms of $\mathbf{X_L}$, **1b**, **3a** and **2a** are highlighted in gray, orange, light blue and green, respectively.

According to this mechanistic proposal, the oxygen atom of the amide bond present in adduct **4** stems from the acid **2** and not from the nitro group of electrophile **3**. To test this prediction we synthesized doubly labeled acid [$^{18}O_2$]**2a** from $^{18}OH_2$ and (trichloromethyl)benzene[13] **6** (Scheme 2). This labeled acid was allowed to react with **1a** and **3a** in the presence of $\mathbf{X_L}$ to yield [$^{16}O_2$,$^{18}O_2$]**4a**. The high-resolution mass spectrum (HR-MS) of this latter compound showed a $(M+1)^+$ signal associated with the presence of two ^{18}O atoms (Scheme 2).



Scheme 2. Synthesis of isotope labelled compounds [$^{16}O_2$,$^{18}O_2$]**4a** and [^{18}O]**7** from acid [$^{18}O_2$]**2a**. The $(M+1)^+$ molecular ion obtained by high-resolution mass spectrometry (HR-MS) for [$^{16}O_2$,$^{18}O_2$]**4a**, **4a**, [$^{16}O_2$,$^{18}O_2$]**7** and **7** are reported. The structure and absolute configuration of **7**, as determined by X-ray diffraction analysis (thermal ellipsoids of non-hydrogen atoms at 50 % probability) are provided.

The ^{13}C-NMR spectrum of mixed **4a** and [$^{16}O_2$,$^{18}O_2$]**4a** showed that the two ^{18}O atoms of [$^{18}O_2$]**2a** were incorporated into the carboxy and the amide groups (Figure 2). In both cases the frequencies of the ^{13}C=^{18}O resonances decrease slightly with respect to the corresponding ^{13}C=^{16}O signals, with an observed $\Delta\delta(^{13}C=^{18}O)$ value of *ca.* –0.03 ppm[14] As a control signal we compared these changes in chemical shifts with the invariance of the signal corresponding to C_c (Scheme 2, Figure 2). Hydrogenolysis of [$^{18}O_2$,$^{16}O_2$]**4a** and **4a** yielded compounds [^{18}O]**7** and **7**, respectively (Scheme 2). The structure of this latter compound was confirmed by X-ray diffraction analysis[10] (Scheme 2). Also in this case, the $(M+1)^+$ MS peak of [^{18}O]**7** was two units higher than that measured for **7**. This result agrees with the ^{13}C-NMR spectra of both compounds, with a similar $\Delta\delta(^{13}C=^{18}O)$ value for the ^{13}C=^{18}O and ^{13}C=^{16}O peaks, whereas the resonance associated with the C_d carbon atom was the same in both compounds (Scheme 2, Figure 2). Therefore, one of the ^{18}O atoms of [$^{18}O_2$]**2a** is present in the carboxamide group of the γ-lactam, thus confirming the prediction made on the basis of the proposed computational mechanism.

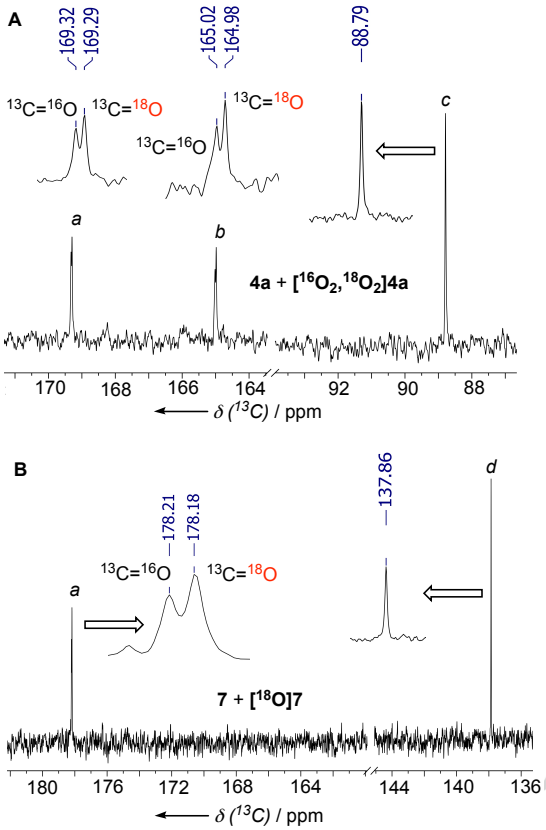
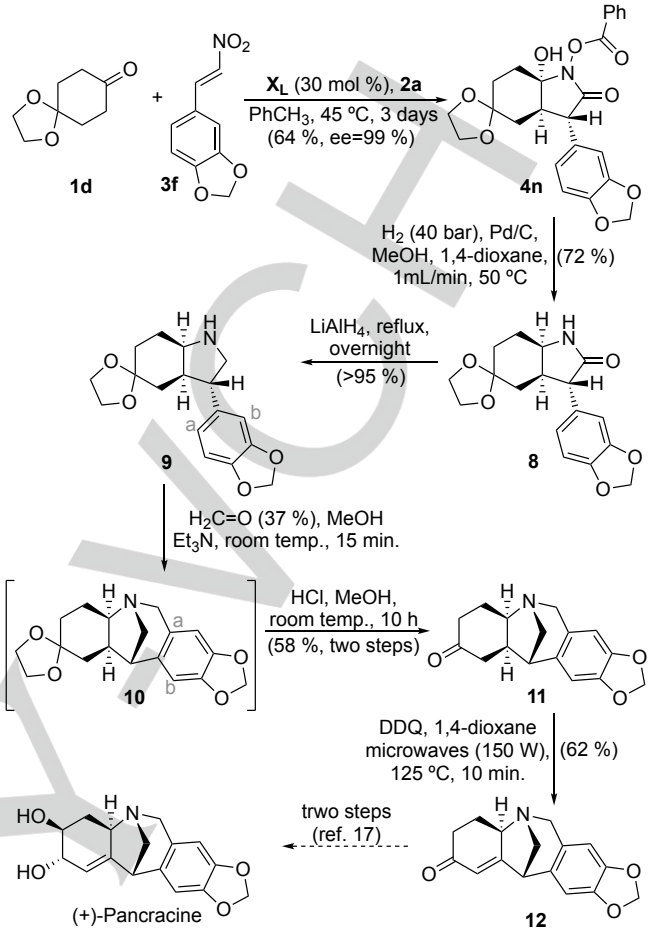


Figure 2. (A)^{13}C NMR spectrum of a mixture of **[$^{16}O_2$,$^{18}O_2$]4a** and **4a**. (B) ^{13}C NMR spectrum of a mixture of **[^{18}O]7** and **7**. Invariant resonances ***c*** and ***d*** are included as internal references.



Scheme 3. Synthesis of (+)-pancracine from three-component reaction catalyzed by unnatural amino ester **X_L**. Numbers in parentheses correspond to chemical yields of isolated pure products.

We selected alkaloid pancracine[15] as a suitable example of the applicability of this novel reaction to the synthesis of polycyclic chiral natural compounds. Our synthesis started with the three-component reaction between ketone **1d**, nitroalkene **3f** (Scheme 3) and benzoic acid **2a**. In the presence of 30 mol% of **X_L**, these reactants yielded chiral γ-lactam **4n** in 64% yield and with complete diastereo- and enatiocontrol (Scheme 3). Hydrogenolysis of this latter compound yielded compound **8** in 72% yield, together with small amounts of two diastereomers **8a,b** (4% and 2%, respectively) and a racemic *α,β*-unsaturated γ-lactam **8c** (4%, see the Supporting Information). The structures of **8a-c** were confirmed by X-ray diffraction analysis[10] . Intermediate **8** was reduced to pyrrolidine **9** in quantitative yield. This latter compound reacted with formaldehyde to form the 1-azabicyclo[3.2.1]octane scaffold of (+)-pancracine. *In situ* deprotection of the dioxolane moiety and oxidation of compound **11** yielded late precursor[16] **12**, from which (+)-pancracine can be obtained according to the procedure described by Overman et al.[17] Thus, our novel reaction reduced the synthetic route to 7 steps and permits a concise synthesis of the unnatural (+)-enantiomer.

In summary, in this work we describe a three-component reaction that yields *N*-acyloxy 7a-hydroxyoctahydro-2*H*-indol-2-ones possessing three chiral centers and we demonstrate the potential of this reaction in synthetic chemistry. We anticipate that unnatural readily available amino acids and their oligomers can lead to the discovery of new catalytic stereocontrolled chemical transformations.

Acknowledgements

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Conflicts of interest

The authors declare no conflict of interest.

Keywords: multicomponent reactions • DFT calculations • asymmetric catalysis • organocatalysis • synthetic methods

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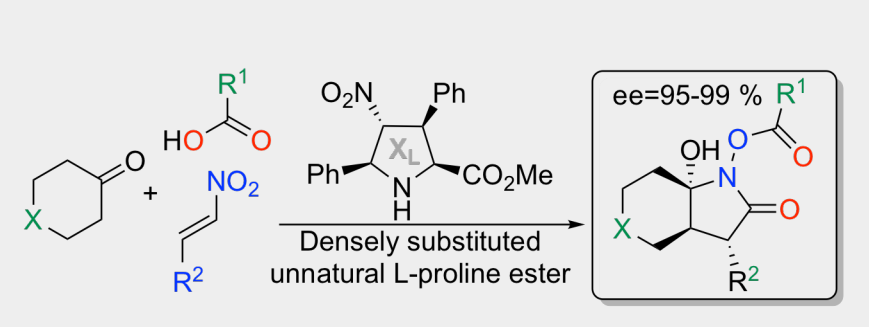

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Brand new cycle. Unnatural densely substituted proline ester $\mathbf{X_L}$ catalyzes the formation of bicyclic γ–lactams possessing three new chiral centers. This new reaction has no equivalent in organocatalytic, enzymatic or organometallic chemistry and can be used in the synthesis of complex natural products.