Nanocatalysts

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Enantiospecific C–H Activation Using Ruthenium Nanocatalysts

*Céline Taglang, Luis Miguel Martínez-Prieto, Iker del Rosal, Laurent Maron, Romuald Poteau, Karine Philippot, Bruno Chaudret, Serge Perato, Anaïs Sam Lone, Céline Puente, Christophe Dugave, Bernard Rousseau, and Grégory Pieters**

Abstract: *The activation of C–H bonds has revolutionized modern synthetic chemistry. However, no general strategy for enantiospecific C–H activation has been developed to date. We herein report an enantiospecific C–H activation reaction followed by deuterium incorporation at stereogenic centers. Mechanistic studies suggest that the selectivity for the α-position of the directing heteroatom results from a four-membered dimetallacycle as the key intermediate. This work paves the way to novel molecular chemistry on nanoparticles.*

Syntheses and modifications of functional molecules are critical steps in many areas of research and industry, including drug discovery and development, biochemistry, imaging techniques, material science, and nanobiotechnology. This is classically achieved through step-by-step functional-group modification, which is a time-consuming and environmentally detrimental process. Over the last decade, the revolutionary emergence of C–H bond activation and functionalization has opened the way to the rapid construction and atom-economic and late-stage diversification of functional molecules.[1–7] Historically, numerous works have been dedicated to $C(sp^2)$–H activation and more recently to $C(sp^3)$–H activation.[8–18] Among these studies, only few reported enantioselective C–H activation, and these examples all involved chiral metal complexes. Moreover, no general enantiospecific method has been developed to date, and only sporadic examples have been reported.[19–21] In this active field of research, the control over the stereochemistry of C–H activation and the discovery of novel key mechanisms that enable the development of new reactions remain two major breakthroughs to be realized. Herein, we report the development of a catalytic enantiospecific C–H activation reaction of several classes of compounds (amines, amino acids, peptides) using ruthenium nanoparticles under mild conditions.[22,23] To rationalize the chemoselectivity, the enantiospecificity, and the low activation energy of this intriguing reaction, DFT calculations were performed and revealed a four-membered dimetallacycle as the key intermediate.

Recently, we developed a smooth and selective $C(sp^3)$–H activation/deuteration process in the α-position of the nitrogen atom of amines using ruthenium nanoparticles dispersed in a polyvinylpyrrolidone matrix (RuNP@PVP).[24] However, in all cases studied, the C–H activation took place on methyl or methylene groups and never at a chiral center. To study the stereochemical outcome of such transformations, three different chiral amines, compounds **1** to **3**, were subjected to RuNP@PVP catalyzed C–H activation followed by deuteration (Figure 1). In all cases, the corresponding deuterated

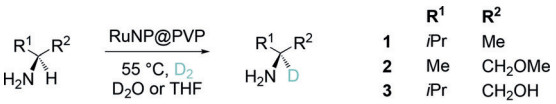

Figure 1. Enantiospecific C–H activation/deuteration using RuNP@PVP nanoparticles (3%) under an atmosphere of D_2 gas (2 bar) at 55 °C for 36 h in THF (compounds **1** and **2**) or D_2O (compound **3**).

compounds were isolated in 70–80% yield. The C–H deuteration at the chiral center occurred efficiently to give highly isotopically enriched compounds (99%) with full retention of configuration.

We then generalized this method to the deuteration of amino acids because they play a central role in the chemistry of life. Furthermore, deuterated amino acids have repeatedly been shown to have important applications.[25,26] Gratifyingly, this reaction occurred enantiospecifically at the $C_\alpha(sp^3)$ position with full retention of configuration. Efficient deuterium incorporation (77–99% isotopic enrichment) was observed for amino acids with aliphatic (**4** to **8**), amide (**9** and **10**), and nitrogen-containing (**11** and **12**) side chains (Figure 2), highlighting the general scope of this enantiospecific C–H activation process. For serine (**13**) and threonine (**14**), together with the expected enantiospecific labeling at the C_α position, an additional C–H activation process occurred at the C_β position. Remarkably, the latter also proceeded with full retention of configuration for both chiral centers of threonine (**14**). For histidine (**15**), the expected enantiospecific labeling at the C_α position was observed. Interestingly, full labeling of the imidazole ring occurred owing to the high affinity of this coordinating group for the nanocatalyst surface. For the water-soluble compounds **16** and

[*] C. Taglang, Dr. S. Perato, A. Sam Lone, C. Puente, Dr. C. Dugave, Dr. B. Rousseau, Dr. G. Pieters
CEA Saclay, SCBM, iBiTec-S, Building 547, PC # 108
91191 Gif sur Yvette (France)
E-mail: gregory.pieters@cea.fr
L. M. Martínez-Prieto, Dr. I. del Rosal, Prof. L. Maron, Prof. R. Poteau, Dr. B. Chaudret
LPCNO; Laboratoire de Physique et Chimie de Nano-Objets
UMR 5215 INSA-CNRS-UPS, Institut National des Sciences Appliquées, 135, Avenue de Rangueil, 31077 Toulouse (France)
L. M. Martínez-Prieto, Dr. K. Philippot
CNRS; LCC (Laboratoire de Chimie de Coordination)
205, Route de Narbonne, 31077 Toulouse (France)

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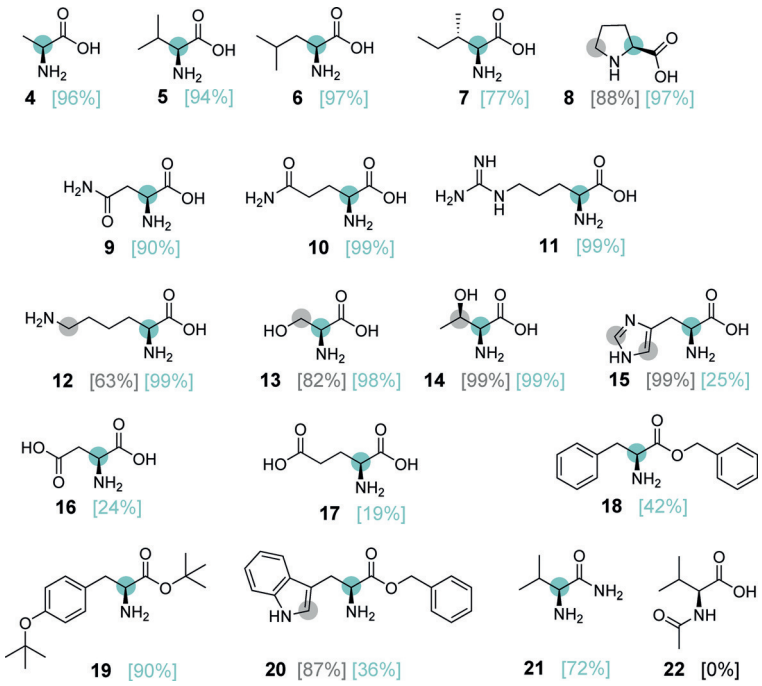

Figure 2. Enantiospecific C–H activation/deuteration of amino acids and derivatives. Isotope enrichments are given in brackets. The sites of deuterium incorporation are indicated in green for the C_α position and gray for additional sites.

17 and the hydrophobic molecules **18** to **20** (which were treated in THF or DMF), C–H activation still occurred enantiospecifically at the C_α position. For compounds **15** to **18** and **20**, which possess three good ruthenium coordination units (amines, carboxylic acids, aromatic rings), lower deuterium incorporation was observed. Multiple sites of coordination may decrease the flexibility of the molecule interacting with the nanoparticle surface. As a consequence, the accessibility of the C_α–H bond to the catalyst could be reduced, which might explain the lower deuterium incorporation.

The reaction proceeded with high regioselectivity and full enantiospecificity in different solvents (water, THF, DMF), thus demonstrating the broad potential of the C–H activation process catalyzed by this ruthenium nanocatalyst. When necessary, the C–H deuteration can be substantially improved by increasing the amount of catalyst (e.g., from 3 to 9%, see the Supporting Information).

We then applied our method to the late-stage C–H deuteration of more complex, biologically relevant structures. The selective modification of peptides, which are of growing interest in medicinal chemistry,[27–29] is challenging because of the coexistence of multiple racemizable chiral centers and manifold functional groups (Figure 3). We tested the peptide amide His-Phe (**23**), a common sequence found in many peptides, including ACTH and melanotropins,[30] the nanotube-forming dipeptide Val-Ala (**24**),[31] the integrin recognition sequence Arg-Gly-Asp (**25**),[32] and tuftsin (**26**), an Ig-associated tetrapeptide that triggers the immunogenic function of macrophages.[33] In all four cases, the expected C–H activation/deuteration occurred at the C_α carbon atom of the N-terminal amino acid without detectable epimerization of the substrate, leading to substantial deuterium incorporation. Additional labeling was observed on the imidazole moiety of compound **23** and both the threonine and lysine side chains of tuftsin (**26**), as previously observed with isolated amino acids (see Figure 2).

The mechanism of this reaction was investigated first by an experimental approach and then by theoretical calculations. One important aspect of this mechanistic study was the determination of the source of the incorporated deuterium. A set of experiments demonstrated that the D_2 gas was the isotope source in this reaction (see the Supporting Information). Moreover, no reaction was observed with *N*-acetyl valine (**22**; Figure 2) whereas valine (**5**) and valine amide (**21**; Figure 2) were efficiently deuterated. These observations strongly suggest that C–H deuteration requires a coordinating nitrogen atom acting as a directing group. Nitrogen coordination to ruthenium nanoparticles has previously been established in the case of hexadecylamine, where some deuteration was also observed.[34]

DFT calculations were then used to quantitatively delineate the elementary steps of several possible mechanisms on a 13 atom scale model with 1.6 D atoms per Ru surface atom. The most relevant pathways were then validated with

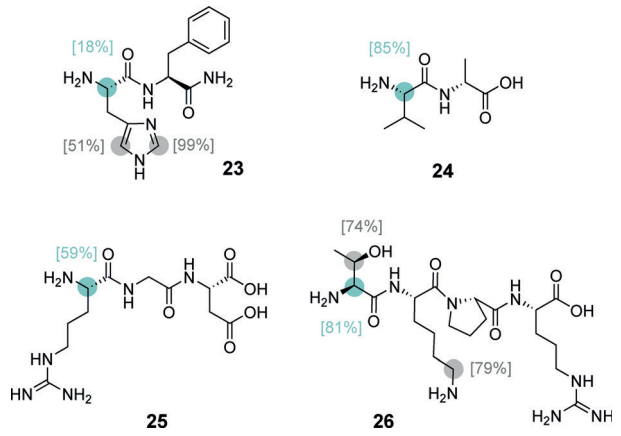

Figure 3. Enantiospecific C–H activation/deuteration of biologically active peptides. Isotope enrichments are given in brackets. The sites of deuterium incorporation are indicated in green for the C_α position and gray for additional sites.

a fully deuterated 1.0 nm Ru_{55} nanocluster, again with 1.6 D atoms per Ru surface atom (Figure 4). All postulated reaction mechanisms start with the exothermic N grafting of the amine (ca. −20 to −31 kcal mol^{-1} depending on the adsorption site). As a model amine, we chose achiral isopropylamine to facilitate the computations, but this change does not prevent the stereochemical outcome of the reaction from being identified.

This first step may follow either an Eley–Rideal mechanism ($amine_{ads} + D_{2,gas} \rightarrow$ deuterated $amine_{ads} + HD_{gas}$) or a Langmuir–Hinshelwood mechanism ($amine_{ads} + D_{ads} \rightarrow$ deuterated $amine_{ads} + H_{ads}$). Despite several attempts, a transition

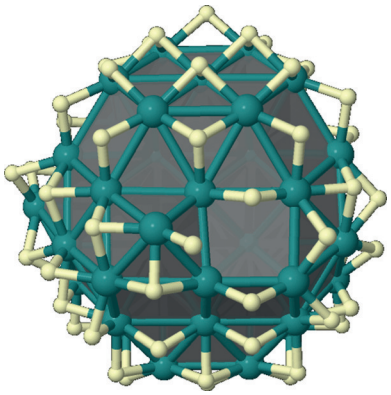

Figure 4. Deuterated Ru_{55} nanoparticle (1 nm) as a model for RuNP@PVP, with 1.6 D atoms per Ru surface atom; deuterium yellow, ruthenium green.

state corresponding to the first mechanism was not found. Considering the second mechanism (Langmuir–Hinshelwood), two competitive pathways were found, which both proceed by activation of the C_α–H bond by a ruthenium atom vicinal to the nitrogen adsorption site (Figure 5): a mechanism based on oxidative addition (pathway a) and a less favorable mechanism involving σ-bond metathesis (pathway b, see the Supporting Information). Our calculations show that C–H activation occurs on the surface of the ruthenium nanoparticles, although the calculated activation barrier (ca. 30 kcal mol^{-1}) is higher than the usual C–H bond breaking energies on bare Ru(0001) surfaces. This is due to the saturation of the surface by deuterides, which stabilize the d-band center[35] of the nanoparticle and consequently render the surface less active. The C–H bond breaking is therefore the rate-limiting step. Given the preliminary grafting of the amine group and the C–H bond breaking, both pathways proceed through the formation of a four-membered dimetallacycle, which explains the experimentally observed regioselectivity. It is noteworthy that molecular metal complexes such as $Pd(X)_2$ lead to the formation of a four- or five-membered metallacycle containing only one metal atom and furnish a functionalization in the β- or γ-position of the directing heteroatom.[36] In other terms, this finding clearly paves the way for the development of a new type of C–H functionalization. This novel key intermediate (**2a**) also permits the rationalization of the enantiospecificity of this reaction. Indeed, the joint grafting of the N and C atoms onto two vicinal Ru atoms of the surface proceeds with retention of configuration because of the rigidity of the dimetallacycle. We identified a very interesting feature of the oxidative addition to the deuterated Ru_{13} cluster (see the Supporting Information) and confirmed it at the nanometer scale with the deuterated Ru_{55} nanocluster. Intermediate species that have ruthenium atoms with low D coordination in close vicinity to the amine grafting site seem to favor C–H activation by significantly lowering the activation energy to approximately 19 to 23 kcal mol^{-1} according to our model (compared to 32.1 kcal mol^{-1} for Ru sites with high D coordination). In other words, owing to the facile diffusion of surface deuterides, the active metal center can keep its formal oxidation state during oxidative addition.

This is in line with the qualitative concept of Paul Sabatier, as the catalytic efficiency will be reduced if the reactants adsorb too strongly, whereas no reaction will occur if the interactions are too weak.[37] Nevertheless, deuterated ruthenium nanoparticles are intrinsically able to fulfill the Sabatier principle by finding an optimal local arrangement of deuterides around the active ruthenium plateau. This feature finally leads to a lowering of the energy barrier of the rate-limiting step, promoting oxidative addition as the most favorable mechanism.

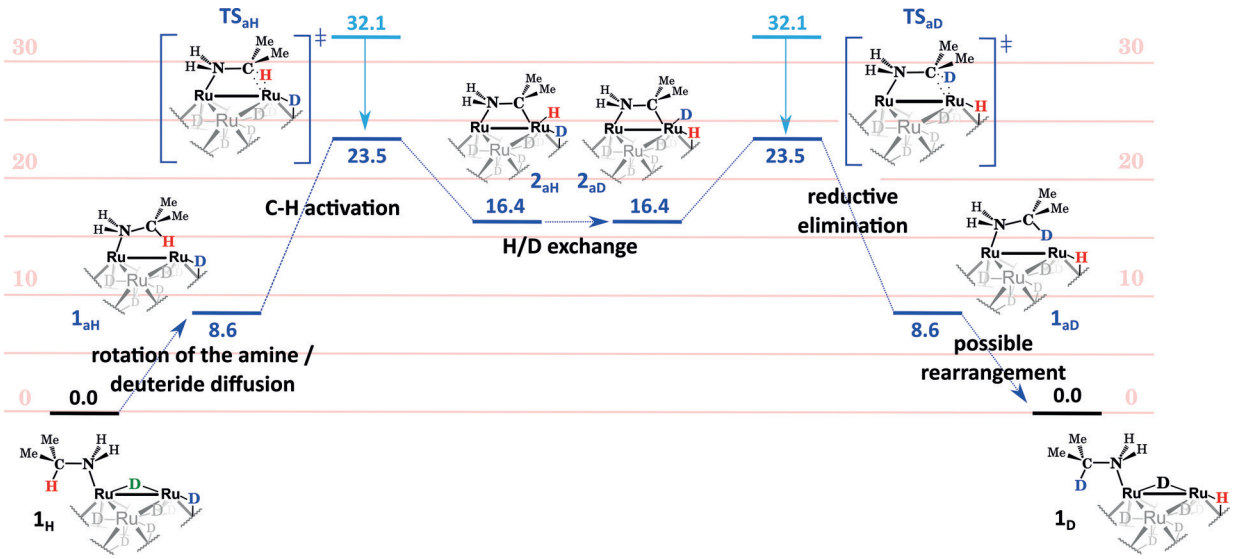

Figure 5. Energy diagram for the Langmuir–Hinshelwood-type H/D exchange mechanism as investigated with 1 nm $Ru_{55}D_n$ clusters; energies are given in kcal mol^{-1}. The rate-limiting step is an oxidative addition (mechanism a; a comparison with the σ-bond metathesis pathway, mechanism b, is given in the Supporting Information). The dark blue pathway was obtained after lowering the number of deuterides directly bound to the ruthenium atom that activates the C_α–H bond by two, in order to simulate a ruthenium surface with low deuteride coordination.

In conclusion, we have reported the first general method for enantiospecific C–H activation, which could be applied to a wide range of synthetically and biologically useful compounds. This reaction is a rare example of C–H activation in the α-position of a heteroatom, which is difficult to achieve using other catalytic systems. This reaction enables the unprecedented deuteration of complex molecules of biological interest under mild conditions in water or organic solvents. A theoretical study revealed a four-membered dimetallacycle as the key intermediate and suggested that a collective motion of surface species can optimize the C–H activation step by modulating the local electronic structure. These findings clearly demonstrate the great potential of nanoparticles for the catalysis of C–H bond activation and pave the way for the rational development of new enantiospecific C–H functionalization reactions.

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