Three different approaches to C-H bond functionalization in the synthesis of antitumor alkaloids rhazinilam, rhazinal and rhazinicine

Delphine Le Floc'h,[a] Nicolas Gouault,[b] Michèle David,[b] and Pierre van de Weghe[b*]

[a]Département de Chimie Moléculaire, UMR CNRS-UJF 5250, CNRS Université Joseph Fourier-Grenoble I, BP 53, F-38041 Grenoble Cedex 9, France

[b]EA Substances Lichéniques et Photoprotection, Faculté des Sciences Biologiques et Pharmaceutiques, Université de Rennes 1, 2 av. du Prof. Léon Bernard, F-35043 Rennes Cedex, France

E-mail: pierre.van-de-weghe@univ-rennes1.fr

In memory of Prof. Keith Fagnou

Abstract

In the past decade, metal catalyzed or promoted C-H bond activation appears as an attractive alternative to classical cross-coupling reaction. Although the studies of this methodology have grown considerably, applications in total synthesis of natural products remain rare. This short review will focus on the use of the metal catalyzed or promoted C-H bond functionalization for the total synthesis of rhazinilam and congeners and demonstrate the usefulness and the efficiency of this approach.

Keywords: C-H bond activation, total synthesis, antitumor alkaloids

Table of contents

Introduction

(-)-Rhazinilam **1**, an axially chiral phenylpyrrole compound isolated first from *Melodinus australis* and latter from other species, has been shown to interact with tubuline and to mimic the effects of both vinblastine and taxol. Its structure has been established and presents a tetracyclic system comprising a phenyl A-ring, a 9-membered lactam B-ring, a pyrrole C-ring and a piperidine D-ring (Figure 1). Although this alkaloid is now considered to be an artefact of isolation procedure, the unusual anti-mitotic properties and the original structure of **1** inspired several research groups to develop a number of approaches for its total synthesis. More recently, other compounds with closely related structure and similar biological activities were isolated such as (-)-rhazinal **2** and (-)-rhazinicine **3**.[1]

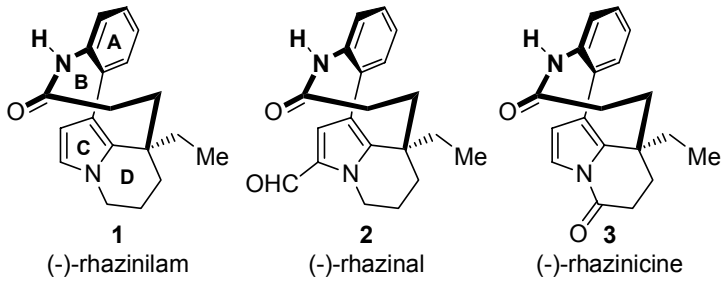
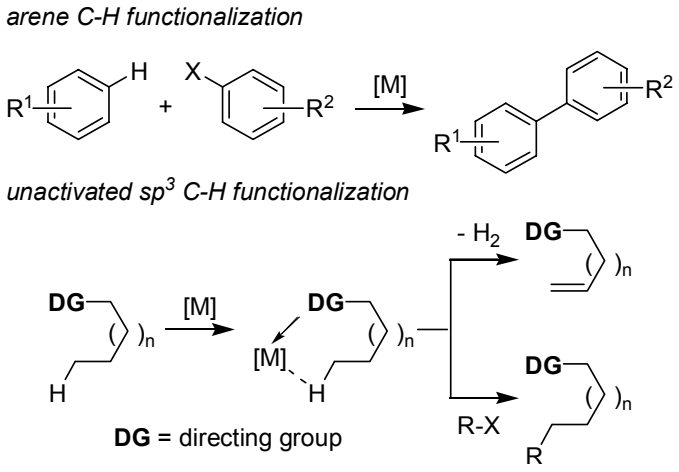


Figure 1. Structure of rhazinilam **1**, rhazinal **2**, rhazinicine **3**.

Transition-metal catalyzed or promoted reactions have totally transformed the organic synthesis. Over the past decades the palladium cross-coupling reactions have emerged as an essential tool for the construction of elaborated molecular structures. Today, it appears that the total synthesis has benefited significantly from these strategies and their uses have become common for the preparation of natural compounds.[2]

In recent years, the development of transition-metal mediated reactions involving C-H bond cleavage/C-C bond formation have emerged as one of the most powerful straightforward methods for synthesis of complex molecules.[3] In the case of arene C-H bond functionalization, this synthetic strategy provides novel approaches as alternative to the Friedel-Crafts reactions or classical electrophilic aromatic substitution. The process of activating the C-H bond replaces also the usual reaction between the transition-metal and an active functional group and allows overcoming of the classic step of transmetallation in the catalytic cycle. This leads to an improvement of the atom economy and reduces the amount of waste in accordance with the principles of green chemistry.[4] On the other hand, the formation of C-C bond from unactivated sp^3 C-H bond is more rare and often the reaction is successful when the substrate has an auxiliary-director group.[5] The reaction is then initiated by chelation-directed cyclometallation before the C-H bond activation (Scheme 1).

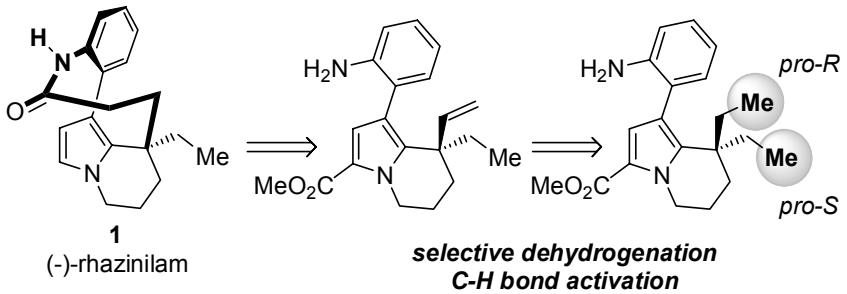


Scheme 1. Transition-metal mediated functionalization of C-H bonds.

To illustrate these class of reactions, this Account will focus on the synthesis of (-)-rhazinilam **1**, (dl)-rhazinal **2** and (dl)-rhazinicine **3** (Fig. 1), three antimitotic compounds belonging to the same family whose the strategy of synthesis is based around one or two steps of C-H bond activation.

2. Selective platinium-mediated sp^3 C-H insertion / β-H elimination; the total synthesis of (-)-rhazinilam

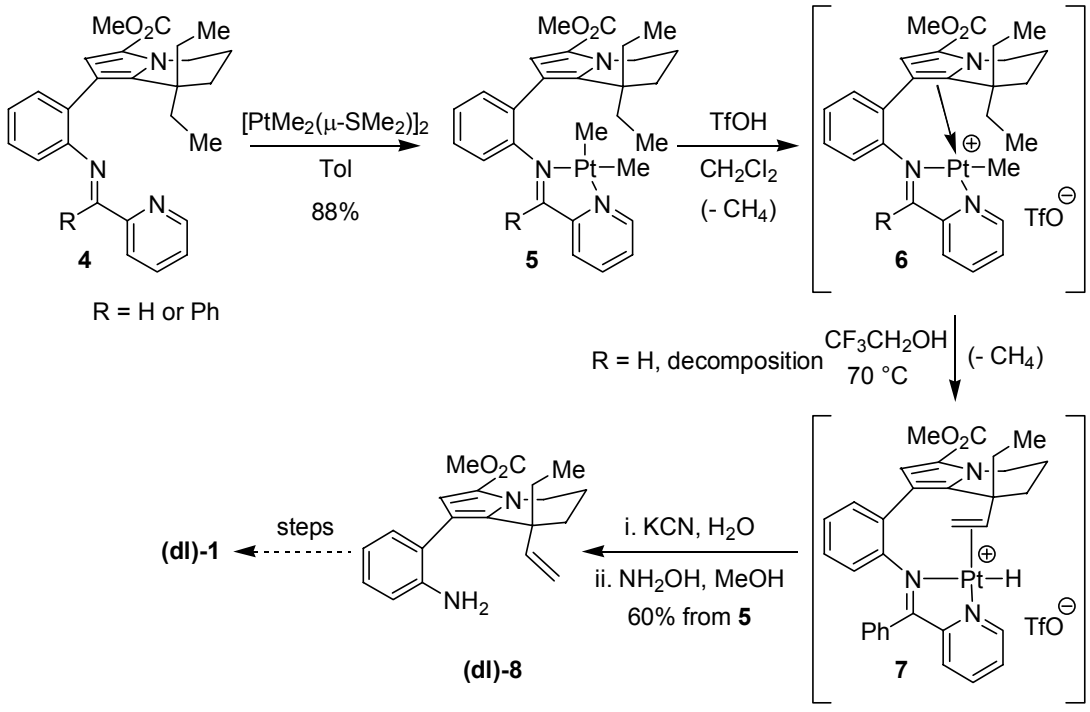
Among the various syntheses reported of (-)-rhazinilam **1**, Sames and co-workers proposed an elegant demonstration of the efficiency of the concept of C-H bond functionalization and its applicability in stereoselective process.[6] This key step involved a selective dehydrogenation of the enantiotopic ethyl groups corresponding to a metal-mediated C-H insertion / β-hydride elimination process (Scheme 2).



Scheme 2. Sames' approach of (-)-rhazinilam **1**.

Because the sp^3 C-H bond activation reactions require harsh reaction conditions, to carry

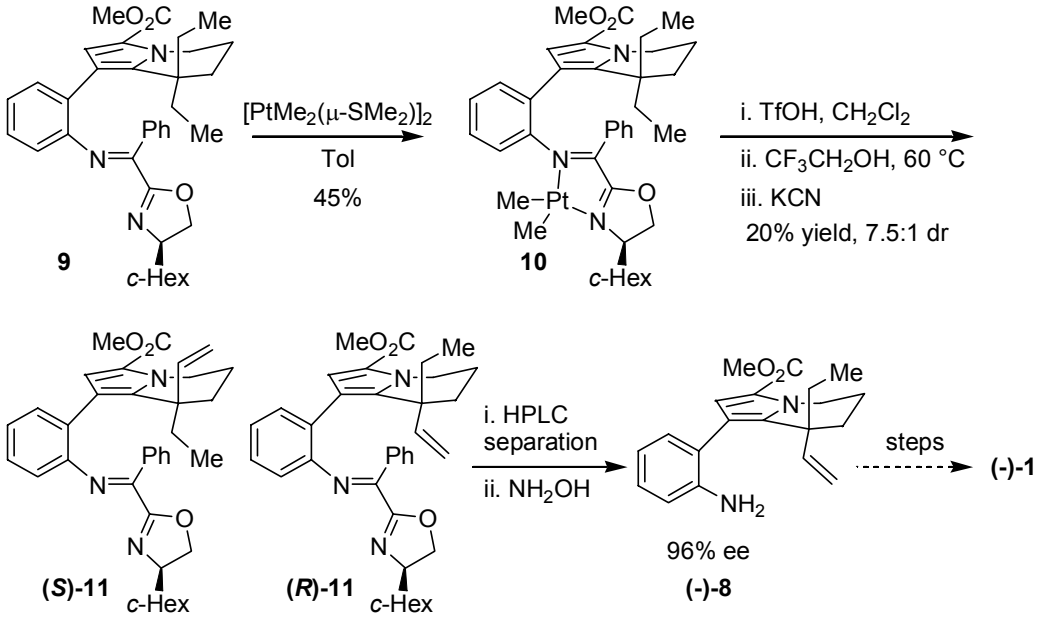
out the C-H bond functionalization Sames and co-workers introduced an auxiliary group containing a pyridine moiety and a Shiff base within the rhazinilam precursor for binding the metal. Reaction of the pyrrole derivative **4** in the presence of the dimethyl platinium reagent $[PtMe_2(\mu\text{-}SMe)_2]_2$ in toluene furnished after chromatography on neutral alumina the isolated platinium complex **5** which after treatment with TfOH formed the cationic complex **6** with concomitant loss of methane. Upon addition of 2,2,2-trifluoroethanol and heating, the complex **6** underwent C-H insertion and subsequent β-H elimination with a second loss of methane to form the cationic hydride platinium complex **7** as a single compound. It is noteworthy that the further transformations of complex **6** led to decomposition under these reaction conditions with R = H; the presence of a bulky substituent such as Ph appeared necessary for the success of this sequence. This was followed by the removal of the platinium metal via treatment with aqueous potassium cyanide and then hydrolysis of the Schiff base with hydroxylamine. The aniline **8** was obtained in 60% yield from **5** and the racemic rhazinilam **1** was isolated after two additional steps (Scheme 3).



Scheme 3. Selective Pt-mediated directed dehydrogenation.

Having demonstrated the efficiency of this strategy to prepare the racemic rhazinilam **1**, Sames and co-workers described a chiral auxiliary-directed diastereoselective C-H functionalization to synthesize **(-)-1** (Scheme 4). For this several oxazoline Schiff base pyrrole compounds were prepared, placed in the presence of $[PtMe_2(\mu\text{-}SMe)_2]_2$ and submitted to the reaction conditions to induce the dehydrogenation. The best compromise

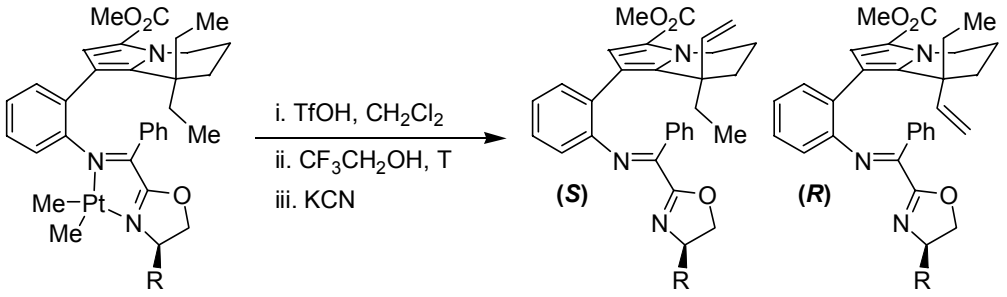
diastereoselectivity / conversion (yield) was obtained when the reaction was carried out with the cyclohexyl oxazoline derivative **9** at 70 °C (Scheme 4). The decomplexation of the platinium metal afforded a mixture of diastereomers **11** with a good ratio in favor of the reaction of the *pro-R* ethyl group as expected (Table 1, entry 9). Using the bulkiest *tert*-butyl oxazoline (entry 10) a better selectivity was observed (dr > 20:1) but with a lowest conversion due to a very low yield of the platinium complexation step (< 10%). The authors showed that the selectivity of the dehydrogenation is also dependent of the temperature. At 60 °C whatever the substituent of the oxazoline, the selectivity is high but at the expense of low conversion.



Scheme 4. Auxiliary-directed diastereoselective dehydrogenation.

After separation of each stereoisomer with preparative HPLC and transamination in the presence of hydroxylamine, the aniline **(-)-8** was isolated in high enantiomeric excess. Direct macrolactam formation via palladium-catalyzed carbonylation reaction followed by deprotection of the methyl ester group gave the (-)-rhazinilam **1** in 8% overall yield.

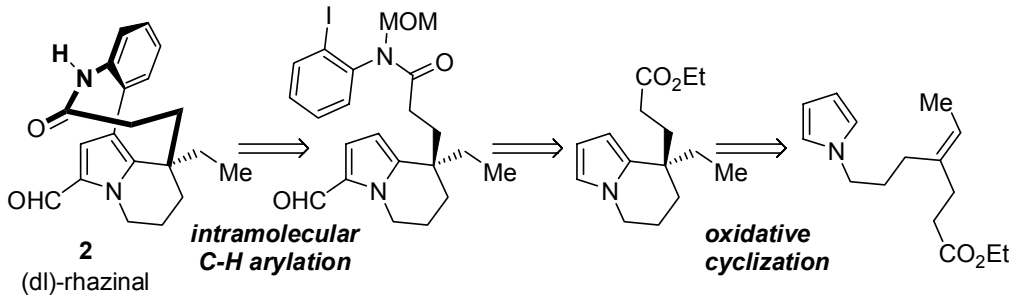
Table 1. Diastereoselective C-H bond functionalization



Entry	R	T (°C)	(*S*) / (*R*)	Conv. (%)	Yield (%)
1	Ph	60	1 : 6	20	15
2		65	1 : 4	60	35
3		70	1 : 3	63	40
4	*i*-Pr	60	1 : 5.5	16	10
5		65	1 : 4	60	36
6	*i*-Pr	70	1 : 3	65	40
7	*c*-Hex	60	1 : 7.5	30	20
8		65	1 : 5.5	58	35
9		70	1 : 4.4	66	42
10	*t*-Bu	70	1 : >20	<10	-

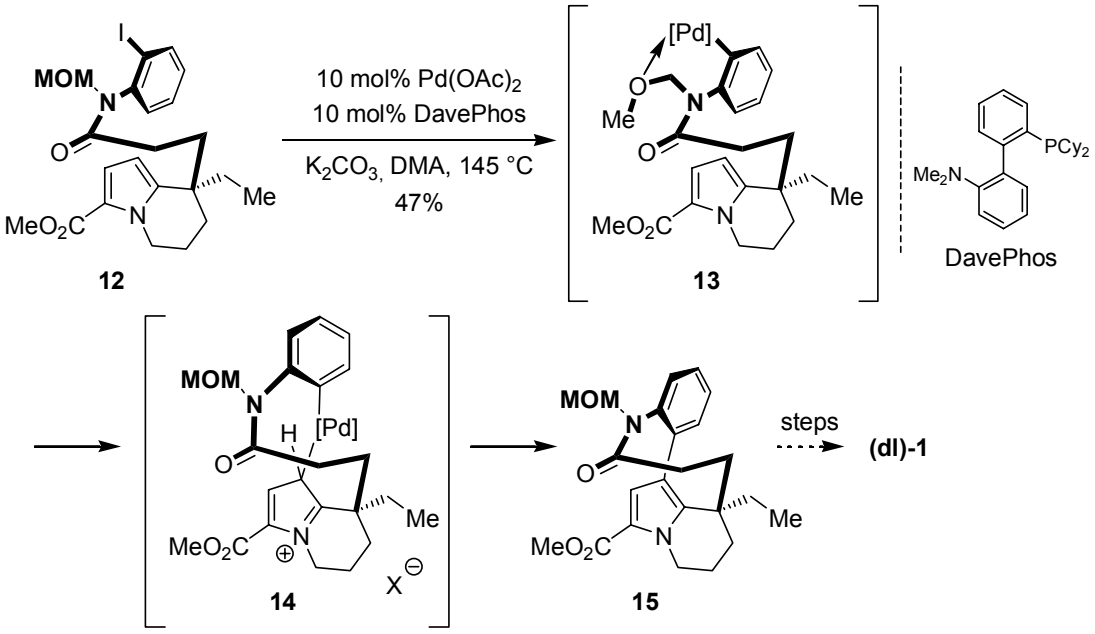
3. Direct cross-coupling reaction; the total synthesis of (±)-rhazinilam and (±)-rhazinal

Relying on their previous work on the direct palladium-catalyzed cross-coupling reaction to obtain the frondosin B a biaryl natural product,[7] Trauner and co-workers reported in 2005 a concise total synthesis of racemic rhazinilam **1** through an aromatic C-H functionalization followed recently by the extension of this approach to prepare (dl)-rhazinal **2**.[8] The retrosynthetic plan of this work consists to form the tetrahydroindolizine intermediate by an oxidative Heck coupling reaction and to construct the lactam ring by the use of the palladium-catalyzed direct cross coupling reaction (Scheme 5).



Scheme 5. Trauner's approach of (dl)-rhazinal G.

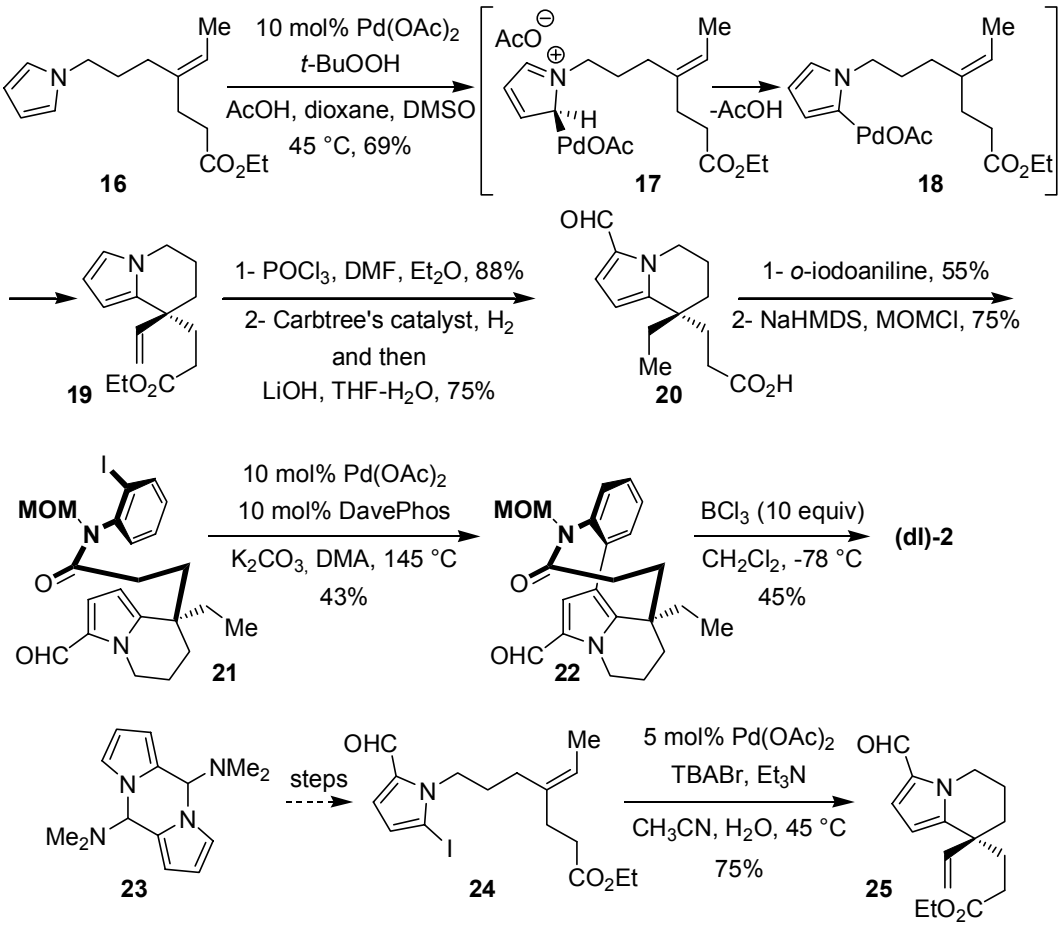
The total synthesis of the racemic rhazinilam **1** proposed by Trauner and co-workers began with the preparation of the iodoaryl **12** in few classical steps. The reaction of **12** in the presence of 10 mol% of palladium acetate, the monophosphine DavePhos and potassium carbonate as base furnished the lactam **15** in moderate yield (47%). The authors suggested the following mechanism. A nucleophilic attack of the pyrrole moiety on the palladium (II) in **13** gives the palladium intermediate **14** which after aromatization of the pyrrolium (loss of proton) undergoes a reductive elimination to afford the 9-membered cycle **15**. The intramolecular C-H arylation occurred when the amide function was protected with a methoxymethyl group. In the absence of this protecting group the deiodination compound was formed. The presence of the MOM prevents probably the protonation of the palladium complex **13**. The final steps of the synthesis of **(dl)-1** were then achieved after carefully removal of the MOM protecting group, saponification of the ester and decarboxylation.



Scheme 6. Trauner's synthesis of (dl)-rhazinilam **1**.

This approach to the formation of the biaryl system by a C-H bond functionalization having shown to be efficient was then employed to prepare the racemic rhazinal **2** (Scheme 7). The tetrahydroindolizine moiety **19** was first prepared by using of an oxidative Heck cyclization from the pyrrole **16**. This palladium (II) oxidation process was carried out in the presence of palladium diacetate and *tert*-butylhydroperoxide as oxidant to give **19** in 69% yield. This method which consists to functionalize a pyrrole catalyzed with palladium (II) under oxidative atmosphere was initially described by Gaunt and co-workers and used for the total synthesis of racemic rhazinicine **3** (see below).[9] A plausible mechanism was proposed. A palladation at C2 occurs via the intermediate **17** followed by the rearomatization to **18**

with loss of acetic acid and a Heck-type reaction yields the tetrahydroindolizine **19**. In parallel to this approach, Trauner and co-workers studied also the preparation of **25** from a classical Heck reaction. The iodopyrrole **24** obtained in few steps from the azafulvene **23** was submitted to modified Jeffery conditions to form **25** with good yield ready to be converted into **20**.

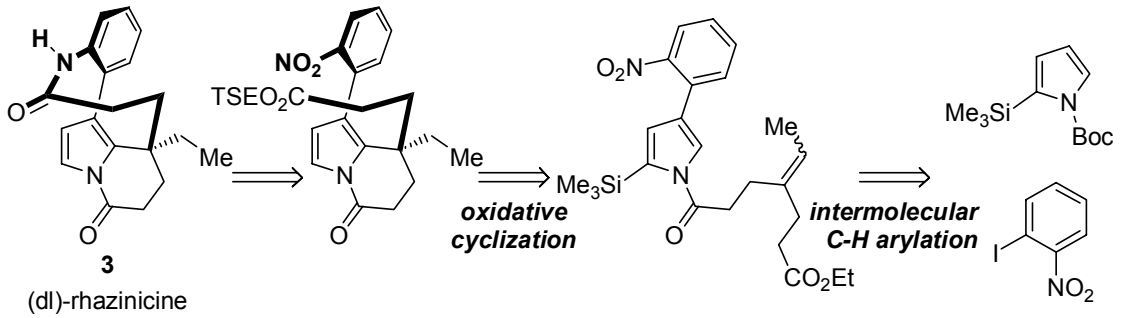


Scheme 7. Trauner's synthesis of (dl)-rhazinal **2**.

After few steps of conversion of **19** to the iodoaryl cylization's precursor **21**, the intramolecular C-H arylation was then engaged to produce the biaryl derivative **22** under the previously established reaction conditions. The racemic rhazinal **2** was obtained after cleavage of the MOM protecting group with 10 equivalents of BCl_3 at low temperature.

4. Metal-catalyzed C-H borylation / Suzuki coupling reaction and oxidative cyclization; the total synthesis of (±)-rhazinicine

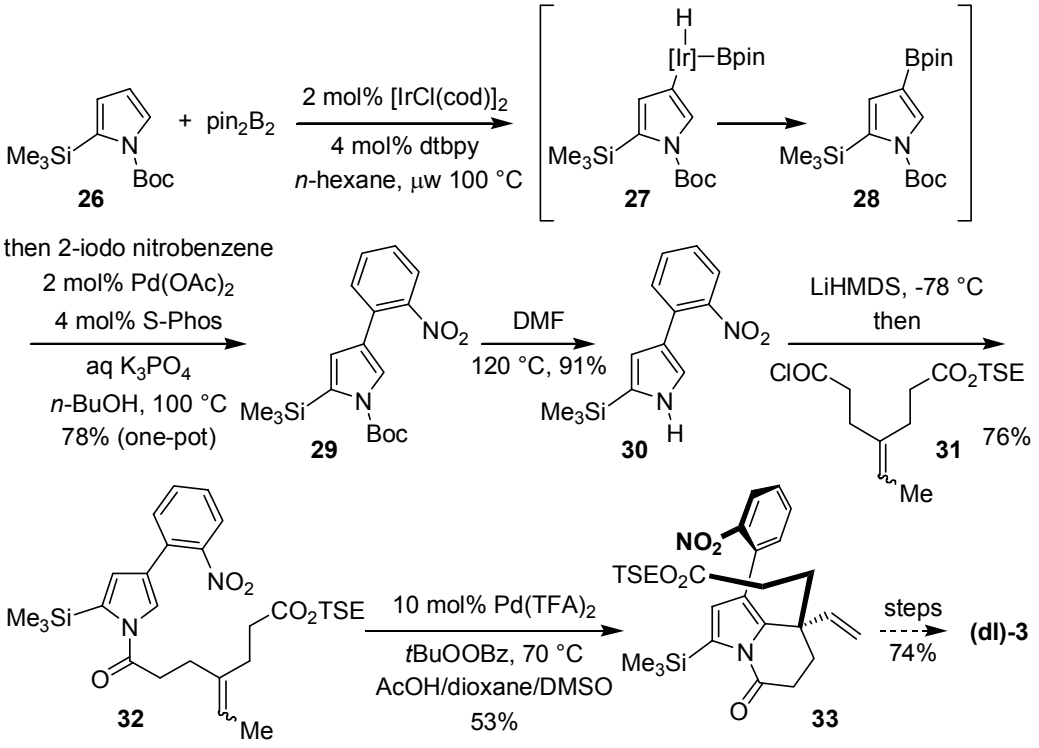
Gaunt and co-workers reported recently the first total synthesis of the rhazinicine **3** a structurally very close compound of rhazinilam **1**.[9] The synthetic plan was based on two key steps using a regioselective intermolecular C-H arylation of pyrrole and an oxidative Heck cyclization. To complete the synthesis a third important step consisted in the formation of the 9-membered lactam (Scheme 8). In previous works, they developed an efficient catalytic system to control the regioselectivity of the alkenylation of indoles[10] and pyrroles.[9] It was shown that the regioselectivity of the functionalization depends strongly on the solvent system and on the N-pyrrole protecting group respectively. In accordance with these observations, the authors focused on the use of their palladium (II)-catalyzed C-H bond activation of pyrroles reaction conditions to form the biaryl system. Despite numerous attempts no satisfactory results were obtained. Therefore they decided to study the Ir-catalyzed C-H borylation[11] followed by a Pd-catalyzed Suzuki coupling reaction. During this work, Gaunt and co-workers have shown that the Ir/Pd-catalytic process works well and the reaction is selective whatever the protecting group (*N*-Boc and *N*-TIPS) yielding only the coupling product at the C3 position of the pyrrole ring.



Scheme 8. Gaunt's approach of (dl)-rhazinicine **3**.

The strategy to functionalize the pyrrole ring has been established, the total synthesis of racemic rhazinicine was engaged as follows. The need to substitute the pyrrole moiety at the position C2 and C3 and to prevent the possible formation of byproducts as noticed by the authors, the installation of a trimethylsilyl group as blocking group at C5 was considered before the Ir-catalyzed C-H bond borylation. Therefore the 2-trimethylsilyl pyrrole *N*-Boc protected **26** was used as starting material and submitted to the sequential one-pot Ir/Pd-catalytic reaction to furnish in good yield the expected cross-coupling product **29** as single isomer. This reaction probably takes place as follows. The aromatic C-H bond cleavage occurs either through an oxidative addition or sigma bond metathesis[12] to form the iridium hydride complex **27** followed by a reductive elimination to form the pyrrol boronic acid **28**. After removal of the Boc group, the pyrrole **30** was converted into the compound **32** ready to

be submitted to the reaction conditions to perform the intramolecular oxidative Heck cyclization. Treatment of **32** with 10 mol% $Pd(TFA)_2$ and *tert*-BuOOBz as oxidant give **33** with a similar mechanism described in Scheme 7. The last steps to obtain the target compound **(±)-3** consist first to reduce the C-C double bond into ethyl group and the NO_2 into aniline under H_2 followed by a cleavage of the TMS and 2-trimethylsilylethyl protecting groups in the presence of $AlCl_3$ and then a macrolactamization using the Mukaiyama's reagent.



Scheme 9. Gaunt's synthesis of (dl)-rhazinicine **3**.

Conclusions

The development of transition-metal mediated reactions involving C-H bond functionalization is among the topical areas of catalytic processes. Although this reaction is now widely studied, few examples have been reported showing its use in total synthesis of natural products. The three applications presented here to synthesize rhazinilam and related derivatives demonstrate the effectiveness of this methodology despite of remaining moderate yields.

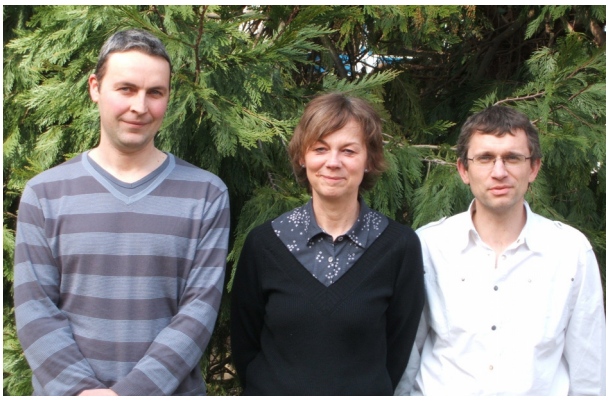
We believe that continuous effort should be devoted to improve the field of use of this methodology, in particulary in respect to the diversity of organic functions in order to extend the C-H bond functionalization for the preparation of elaborated compounds.

References

1. Baudoin, O.; Guénard, D.; Guéritte, F. *Mini Rev. Org. Chem*. **2004**, *1*, 333-341.
2. For selected reviews on the use of transition-metal in total synthesis, see: (a) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4544-4568. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945-2963. (c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442-4489. (d) Chinchilla, R.; Najera, C. *Chem. Rev*. **2007**, *107*, 874-922.
3. For selected recent reviews, see: (a) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35-45. (b) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q *Chem. Soc. Rev.* **2009**, *38*, 3242-3272. (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094-5115. (c) Ackermann, L.; Vicente, R.; Kapli, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792-9826 (d) Thansandote, P.; Lautens, M. *Chem. Eur. J.* **2009**, *15*, 5874-5883. (e) Park, J.-W.; Jun, C.-H. *ChemCatChem* **2009**, *1*, 69-71.
4. (a) Trost, B. M. *Angew. Chem. Int. Ed.* **1995**, *34*, 259-281. (b) Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002**, *35*, 686-694. (c) Sheldon, R. A. *Green Chem.* **2007**, *9*, 1273-1283.
5. (a) Dauglis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074-1086. T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147-1169. (b) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.*, **2010**, *16*, 2654-2672.
6. 6 (a) Johnson, J. A.; Sames, D. *J. Am. Chem. Soc*. **2000**, *122*, 6321-6322. (b) Johnson, J. A.; Li, N.; Sames, D. *J. Am. Chem. Soc*. **2002**, *124*, 6900-6903. (c) see also this review in press, Thirumalairajan, S.; Pearce, B. M.; Thompson, A. *Chem. Commun*., **2010**, *46*, 1797-1812.
7. Huges, C. C.; Trauner, D. *Tetrahedron* **2004**, *60*, 9675-9686.
8. (a) Bowie, A. L.; Hugues, C. C.; Trauner, D. *Org. Lett.* **2005**, *7*, 5207-5209. (b) Bowie, A. L.; Trauner, D. *J. Org. Chem*. **2009**, *74*, 1581-1586.
9. (a) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528-2529. (b) Beck, E. M.; Hatley, R.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 3004-3007.
10. Grimster, N. P.; Godfrey, C. D.; Gaunt, M. J. *Angew. Chem. Int. Ed*. **2005**, *44*, 3125-3129.
11. (a) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc*. **2002**, *124*, 390-391. (b) Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett*. **2002**, *43*, 5649-5651.
12. Lin, Z. *Coord*. *Chem. Rev*. **2007**, *251*, 2280-2291.

Authors' biographies

Delphine Le Floc'h completed a double training at the University of Rennes 1, France, both in pharmacy and in chemistry. She received in 2009 a thesis degree in pharmacy under the guidance of Prof. Pierre van de Weghe. The work was focused on the synthesis of simplified rhazinilam analogues, and analysis of structure-activity relationship. Currently, Delphine is continuing her education with a PhD in organic synthesis in Grenoble, under the supervision of Dr. Jean-Noël Denis. Delphine's current research interests lie in the development of novel methodology for the multi-steps synthesis of biologically active compounds.



Nicolas Gouault (left) studied chemistry at the University of Rennes 1. He received his PhD. from University of Rennes 1 in 2002 under the supervision of Dr. M. David. He was then appointed as Research Assistant Professor in the same group in 2002 and promoted as lecturer in 2004. His research interests include heterocyclic chemistry, fluorous reactions and separations, and gold catalysis.

Michele David (middle) studied at the school of Pharmacy at the University of Rennes 1 where she completed her PhD in 1984 and her habilitation in 1990. She is currently lecturer in therapeutic chemistry. Her main research concerns synthesis, solid-phase synthesis and biological evaluation of various heterocycles. Since 2005 she develops an international collaboration with University Federal of Rio Grande of Sul (Brazil).

Pierre van de Weghe (right) studied chemistry at the University of Paris Sud. In 1995, he completed his PhD in the group of Prof. Henri Kagan under the guidance of Dr Jacqueline Collin on the use of samarium iodides in catalysis. After post-doctoral work in the University of Stuttgart with Prof. V. Jäger as an Alexander von Humboldt fellow, he joined the group of Prof J. Eustache in 1997 as "chargé de recherche CNRS" and obtained his Habilitation in 2004. In 2007, he was appointed Professor at the University of Rennes 1. His main research focuses on the total synthesis of natural products, on gold and palladium catalysis and on the molecular recognition with the help of chiral molecular tweezers. He was the recipient of the CNRS Bronze Medal in 2004.