C–H Activation

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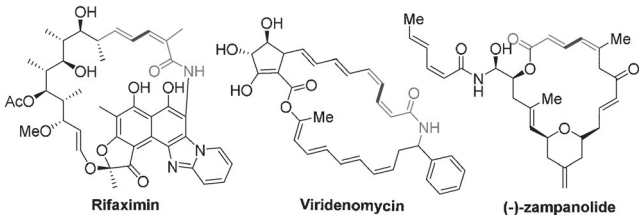
Macrolide Synthesis through Intramolecular Oxidative Cross-Coupling of Alkenes

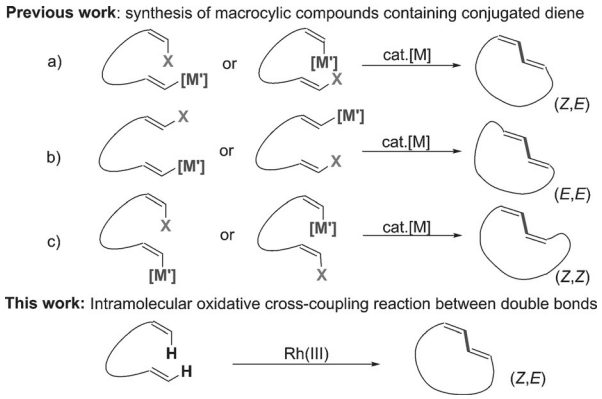
Bing Jiang, Meng Zhao, Shu-Sen Li, Yun-He Xu, and Teck-Peng Loh**

Abstract: *A Rh^{III}-catalyzed intramolecular oxidative cross-coupling between double bonds for the synthesis of macrolides is described. Under the optimized reaction conditions, macrocycles containing a diene moiety can be formed in reasonable yields and with excellent chemo- and stereoselectivity. This method provides an efficient approach to synthesize macrocyclic compounds containing a 1,3-conjugated diene structure.*

Macrocycles are an important class of compounds since they feature widely in many natural products and pharmaceuticals.[1] Common strategies utilized to construct these macrocyclic compounds are macrolactonizations,[2] macroaldolizations,[3] and macrolactamizations.[4] In recent decades, transition-metal-catalyzed cross-coupling reactions to forge new C–C or C–X (X = heteroatom) bonds for the construction of large rings have also emerged as powerful tools.[5] In recent years, the strategy of ring-closing metathesis (RCM) has also become a popular way to construct large rings containing double bonds, albeit with difficulty in controlling the *E*/*Z* stereoselectivity.[6] There are also numerous macrocyclic natural products, such as rifaximin, viridenomycin, and (−)-zampanclide, that contain a conjugated diene moiety.[7]

However, methods to construct this type of macrocycles are rare. In addition to the traditional strategies involving step-by-step synthesis of the conjugated double bonds, a few examples involving the synthesis of such compounds through transition-metal-catalyzed coupling reactions using organometallic reagents to connect different double bonds have also recently been reported (Scheme 1 a and b).[8] Inspired by the recent advances on direct transition-metal-catalyzed C–H bond functionalization,[9] especially the pioneering work reported by Glorious and co-workers on Rh-catalyzed oxidative cross-coupling reactions between electron-deficient alkenes,[9a,b] and as part of our long-standing interest in the alkene-alkene coupling reactions,[10] we envisage that an intramolecular cross-coupling between two different double bonds will provide an efficient method to access this class of compounds. Herein, we report a Rh^{III}-catalyzed macrocyclization reaction through intramolecular oxidative cross-coupling between double bonds. Macrocyclic products with large ring sizes can be obtained in reasonable yields through this strategy. This method is atom-economical and the products obtained can be converted into other useful functional compounds. In addition, this is the first example of intramolecular oxidative cross-coupling between double bonds.



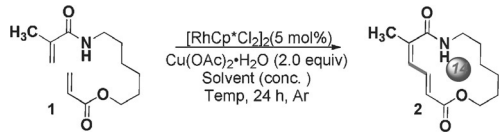


Scheme 1. Synthesis of macrocyclic compounds containing a 1,3-conjugated diene moiety.

To evaluate the feasibility of the rhodium-catalyzed intramolecular cross-coupling reaction between alkenes, we chose the easily available 6-methacrylamidohexyl acrylate (**11**) for the model reaction. Optimization of the reaction conditions was carried out by employing $[RhCp^*Cl_2]_2$ as the catalyst, and the results were summarized in Table 1. Pleasingly, the 14-membered-ring product **21** could be obtained in 8% yield and with a single *Z*,*E* configuration in the presence of 5 mol% $[RhCp^*Cl_2]_2$ catalyst and $Cu(OAc)_2{\cdot}H_2O$ (2.0 equiv) as an oxidant in 1,2-dichloroethane (DCE) (0.01 M) at 100 °C upon stirring for 24 h under argon atmos-

[*] B. Jiang, M. Zhao, S.-S. Li, Prof. Dr. Y. H. Xu, Prof. Dr. T. P. Loh
Hefei National Laboratory for Physical Sciences at the Microscale
iChEM (Collaborative Innovation Center of Chemistry for Energy Materials), University of Science and Technology of China
Hefei, Anhui 230026 (China)
E-mail: xyh0709@ustc.edu.cn
teckpeng@ustc.edu.cn
Prof. Dr. T. P. Loh
Institute of Advanced Synthesis, Jiangsu National Synergetic Innovation Center for Advanced Materials, Nanjing Tech University
Nanjing, Jiangsu, 210009 (China)
and
Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University
Singapore 637616 (Singapore)
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201710601.

Table 1: $[RhCp^*Cl_2]_2$-catalyzed macrocyclization of **1l**.



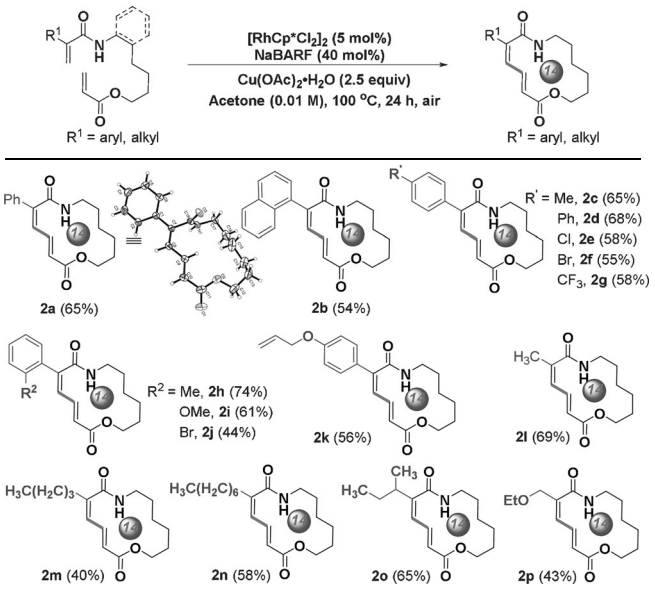
Entry	Additive	Solvent	Conc. [mol L^{-1}]	T [°C]	Yield[b] [%]
1	–	DCE	0.01	100	8
2	–	Toluene	0.01	100	19
3	–	THF	0.01	100	26
4	–	Acetone	0.01	100	42
5[c]	–	Acetone	0.01	100	38
6	–	Acetone	0.01	80	34
7	–	Acetone	0.01	120	29
8	–	Acetone	0.20	100	25
9	NaOAc (1.5 equiv)	Acetone	0.01	100	32
10	HOAc (15 equiv)	Acetone	0.01	100	39
11	$AgPF_6$ (20 mol%)	Acetone	0.01	100	21
12	$AgSbF_6$ (20 mol%)	Acetone	0.01	100	11
13[d]	–	Acetone	0.01	100	28
14[e]	–	Acetone	0.01	100	46
15[f]	–	Acetone	0.01	100	24
16[g]	–	Acetone	0.01	100	42
17[e,h]	–	Acetone	0.01	100	nr
18[e]	NaBARF (20 mol%)	Acetone	0.01	100	52
19[e]	NaBARF (40 mol%)	Acetone	0.01	100	55
20[e,i]	**NaBARF (40 mol%)**	**Acetone**	**0.01**	**100**	**65 (69)**

[a] Reaction was run under the following reaction conditions: 0.15 mmol **1**, 5 mol% $[RhCp^*Cl_2]_2$, 0.375 mmol $Cu(OAc)_2{\cdot}H_2O$ and 0.06 mmol NaBARF in 15 mL acetone at 100°C for 24 h under air atmosphere. Yields in parentheses are yields of isolated product. NaBARF = sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate. [b] Yield was determined by ^1H NMR using mesitylene as an internal standard. [c] Ag_2CO_3 (2.0 equiv) was used. [d] 2.5 mol% $[RhCp^*Cl_2]_2$ was used. [e] Under air atmosphere. [f] Under oxygen atmosphere. [g] Reaction was run for 48 h. [h] 5 mol% $Rh(CH_3CN)_3Cp^*(SbF_6)_2$ was used. [i] $Cu(OAc)_2{\cdot}H_2O$ (2.5 equiv) was used.

phere (Table 1, entry 1). The *Z*,*E*-configuration of the product **2l** was determined by ^1H-^1H COSY NMR spectrum analysis, which indicated that the amide group possibly acted as a directing group in the $C(sp^2)$–$C(sp^2)$ bond formation step. Different solvents, reaction temperatures, and oxidants were examined in sequence. It was found that the desired product could be obtained in 42% yield in acetone. It is worthwhile to note that a cross-coupling dimer product with a 28-membered-ring structure was also generated, along with the formation of the 14-membered normal macrocyclic product **2l** in 25% yield (Table 1, entry 8) at high concentration (0.2 M). We then tested some additives and other rhodium catalysts but they produced no significant improvement on the product yield (Table 1, entries 9–13). A cationic rhodium species was expected to be more reactive to catalyze this coupling reaction. Therefore, 20 mol% sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) was introduced as an additive, and the desired product was obtained in 52% yield (Table 1, entry 18). Finally, the desired product **2l** was isolated in 69% yield upon increasing the loading of NaBARF (40 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (2.5 equivalents; Table 1, entry 19–20). Control experiments indicated that all the components in the catalytic system were necessary in this reaction to afford the desired product **2l** in a good yield.

After determining the optimized reaction conditions, further investigation of the substrate scope and limitations of this intramolecular oxidative cross-coupling was performed. First, we turned our attention to examining the substituents tolerated on the acrylamide part (Table 2). It was

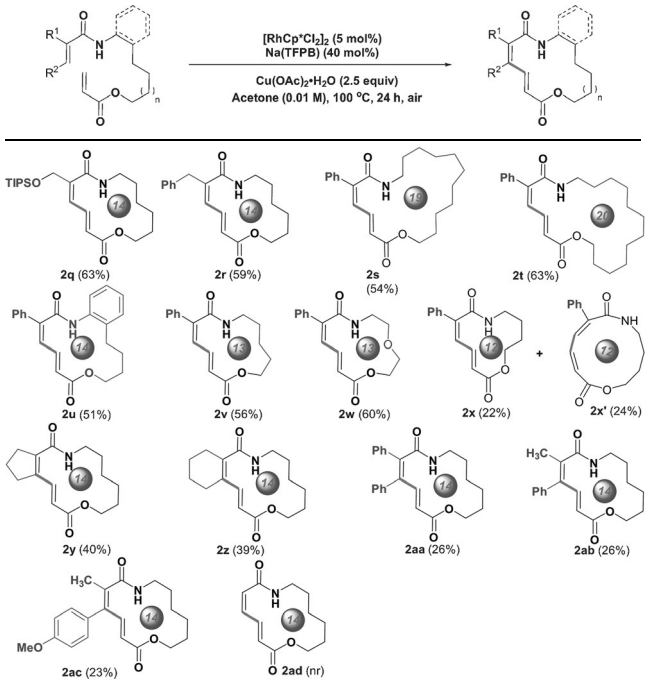
Table 2: Substrate scope for the intramolecular cross-coupling reaction



[a] Reaction conditions: 0.15 mmol **1**, 5 mol% $[RhCp^*Cl_2]_2$, 0.375 mmol $Cu(OAc)_2{\cdot}H_2O$ and 0.06 mmol NaBARF in 15 mL acetone at 100°C for 24 h under air atmosphere. Yields in parentheses are yields of isolated product.

observed that the desired 14-membered macrocycles were obtained in moderate to high yields with substrates with an aryl substituent at the α-position. Both electron-donating and electron-withdrawing functional groups were well tolerated on the phenyl ring. The corresponding products were isolated in 44–74% yields. The structure of **2a**, which has a *Z*,*E*-configured diene moiety, was determined by X-ray crystallography diffraction analysis.[16] Furthermore, substrates with aliphatic substituents at the α-position of acrylamide were tested (**2l**–**2o**). It was found that substrates bearing a carbon chain, ethoxymethyl, (triisopropylsilyl)oxy)methyl, or benzyl group all reacted well and furnished the corresponding products in moderate to good yields (**2p**–**2r**). The current annulation method allowed to access even larger or smaller rings upon tethering a longer or shorter linker between acrylate and acrylamide fragments (**2s**–**2x/2x′**; Table 3). It is worth noting that apart from the formation of product **2x** in 22% yield with a *Z*,*E* configuration, another 12-memberd macrocyclic product **2x′** with a *Z*,*Z* configuration was also isolated in 24% yield when the acrylamide enoate **1x** was applied in this reaction. Moreover, in contrast to the previous result,[10b] substrate **1u**, which has an *N*-phenyl acrylamide moiety, also showed good reactivity, and the desired 14-membered ring product **2u** was obtained in 51% yield. Further studies showed that this method was not limited to α-

Table 3: Substrate scope for the intramolecular cross-coupling reaction

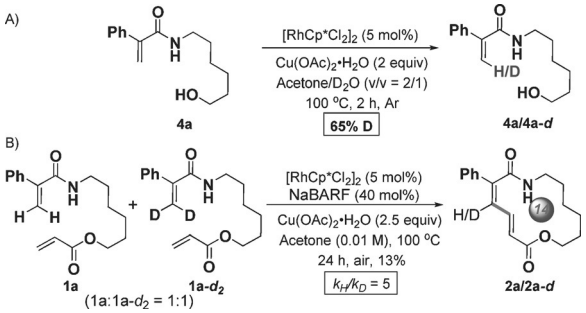


[a] Reaction was run under the following reaction conditions: 0.15 mmol **1**, 5 mol% $[RhCp^*Cl_2]_2$, 0.375 mmol $Cu(OAc)_2.H_2O$ and 0.06 mmol NaBARF in 15 mL acetone at 100 °C for 24 h under air atmosphere. Yields in parentheses are yields of isolated product.

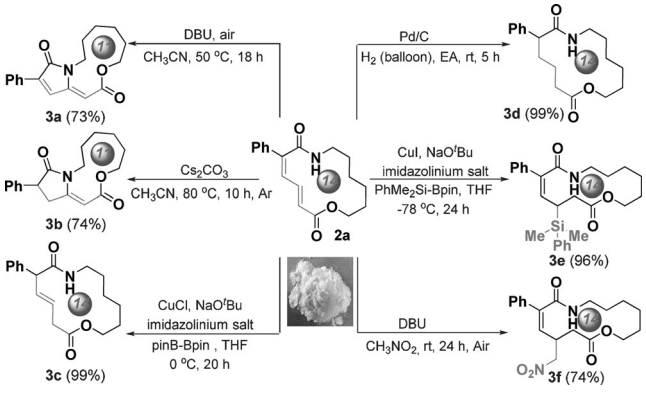
substituted substrates, but was also compatible with α,β-disubstituted acrylamide derivatives. However, these substrates only exhibited low reactivity along with low conversion. Acrylamides with a cyclopentenyl and a cyclohexenyl moiety afforded the desired bicyclic compounds in 40% and 39% yields, respectively (**2y**–**2z**). Low yields of the products **2aa** and **2ab** were observed when α-phenyl-β-phenyl- and α-methyl-β-aryl-substituted acrylamides were subjected to this reaction. Unfortunately, the unsubstituted substrate **1ad** did not give any desired product under the optimized reaction conditions, even with a prolonged the reaction time.

To explore the synthetic utility of this method, derivatization reactions of macrocycle **2a** were investigated (Scheme 2). Treatment of **2a** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile afforded the bicyclic compound **3a** in 73% yield through intramolecular Michael addition and dehydrogenation processes.[11] In contrast to this result, if **2a** was treated with Cs_2CO_3, the more stable Michael addition product **3b** could be obtained in 74% yield.[12] In addition, the 1,4-hydrosilylation of acrylate fragment product **3e** was obtained in 96% yield under the NHC-Cu-O^{t}Bu catalytic system.[13] A similar chemoselective 1,4-Michael addition reaction happened when nitromethane was used as a nucleophile under basic conditions,[14] and the desired product **3f** was isolated in 74% yield. In addition, a highly stereoselective reductive product **3c** with *E* configuration was obtained in excellent yield when using a bis(pinacolato)diboron reagent and a copper catalyst. This result is attributed to a 1,6-conjugated boryl addition and a sequential allylic boronate reduction. Furthermore, hydrogenation reaction of **2a** catalyzed by Pd/C led to the product **3d** in a high yield.

Finally, to gain some preliminary understanding of the mechanism, an isotope-labeling experiment with acrylamide **4a** was carried out. A remarkable *Z*-selective olefinic H/D exchange was detected with addition of D_2O, which implies a reversible cyclometalation process [Scheme 3A]. Furthermore, a kinetic isotope effect (KIE) value ($k_H/k_D = 5$) was observed in the competitive cross-coupling reactions of **1a** and **1a**-d_2, thus suggesting that the alkenyl C–H bond activation might be rate-determining step [Scheme 3B].



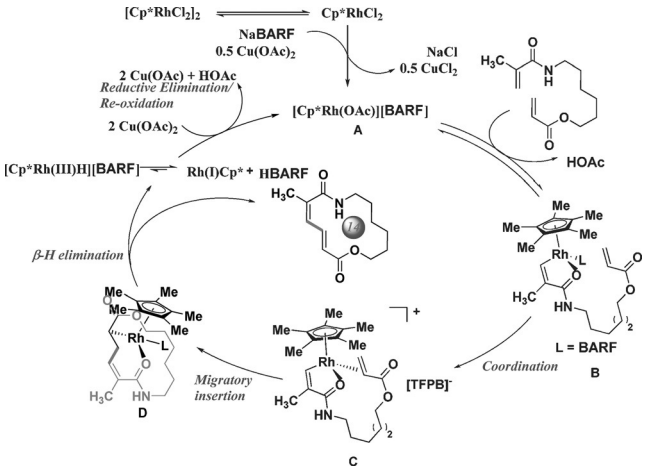
Scheme 3. Isotope-labeling experiments for KIE studies.



Scheme 2. Derivatization of the cross-coupling macrocycle product.

Therefore, a plausible mechanism to account for the Rh^{III}-catalyzed macrocyclization was proposed on the basis of our experimental results and literature precedent (Scheme 4).[15] Anion exchange of $[RhCp^*Cl_2]_2$ with NaBARF and $Cu(OAc)_2{\cdot}H_2O$ afforded the reactive species **A**, which selectively activates the *Z*-olefinic C–H bond of acrylamide derivative **1** to form an vinylrhodium(III) species **B**. Subsequent intramolecular coordination and migratory insertion of acrylate form intermediates **C** and then **D**, which undergoes β-hydride elimination to provide the macrocycle with concomitantly release a Rh^{III} hydride species. Reductive elimination followed by reoxidation of $[Rh^I]$ to $[Rh^{III}]$ by $Cu(OAc)_2{\cdot}H_2O$ would release the active catalyst for the next catalytic cycle.

In summary, we have accomplished the first intramolecular Rh^{III}-catalyzed oxidative cross-coupling reaction between double bonds. This work provides a rapid and atom-economical synthetic pathway to form macrolide compounds with a *Z*,*E*-configured diene moiety. This work also



Scheme 4. Proposed reaction mechanism.

features high chemoselectivity and stereoselectivity, good functional-group compatibility, and versatile utility of the diene fragment in further derivation reactions. In-depth application studies of this intramolecular oxidative cross-coupling reaction in organic synthesis are underway in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

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[16] CCDC 1574636 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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