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Macrolide Synthesis through Intramolecular Oxidative Cross-Coupling of Alkenes

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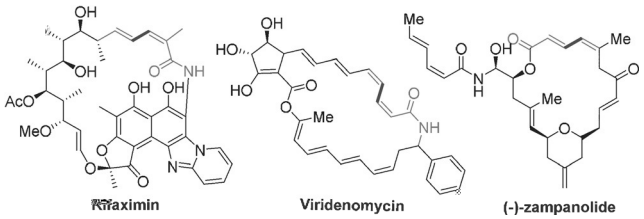
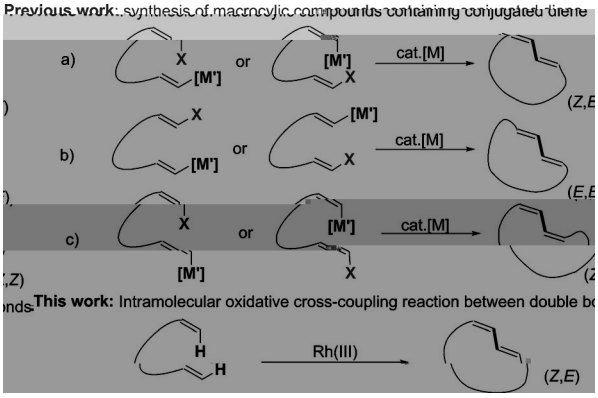
Abstract: A Rh^{III}-catalyzed intramolecular oxidative cross-coupling between double bonds for the synthesis of macrolides is described. Under the optimized reaction conditions, macrocycles containing a diene moiety can be formed in reasonable yields and with excellent chemo- and stereoselectivity. 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 1a 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 (1l) 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 2l 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) (0.01m) at 100 °C upon stirring for 24 h under argon atmos-

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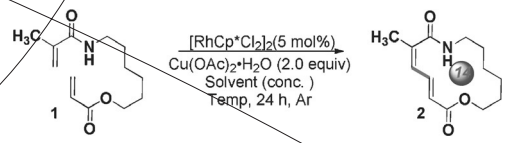
Table 1: [RhCp*Cl$_2$]$_2$-catalyzed macrocyclization of **1l**.



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)$_2$·H$_2$O 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 determined by ^{1}H NMR using mesitylene as an internal standard. [c] 2 mL acetone (2.0 equiv) was used. [d] 2.5 mol% [RhCp*Cl$_2$]$_2$. [e] Under air atmosphere. [f] Under oxygen atmosphere. [g] 5 mol% [RhCp*Cl$_2$]$_2$. [h] 5 mol% Rh(CH$_3$CN)$_3$Cp*(SbF$_6$)$_2$. [i] 1 mL acetone (2.5 equiv) was used.

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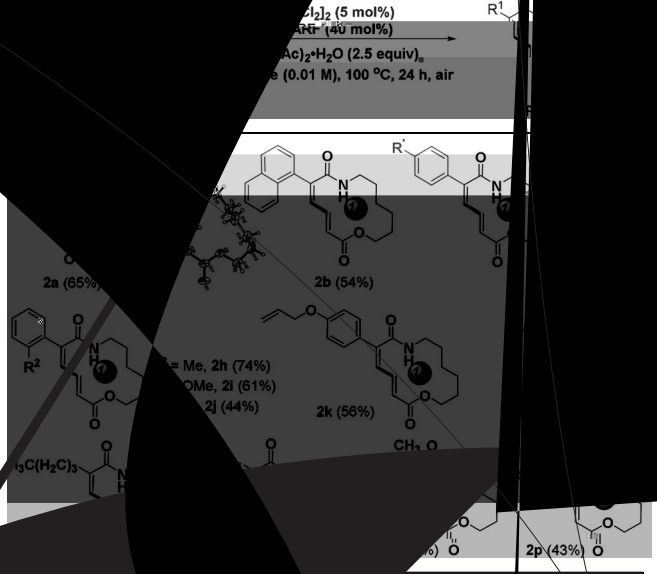
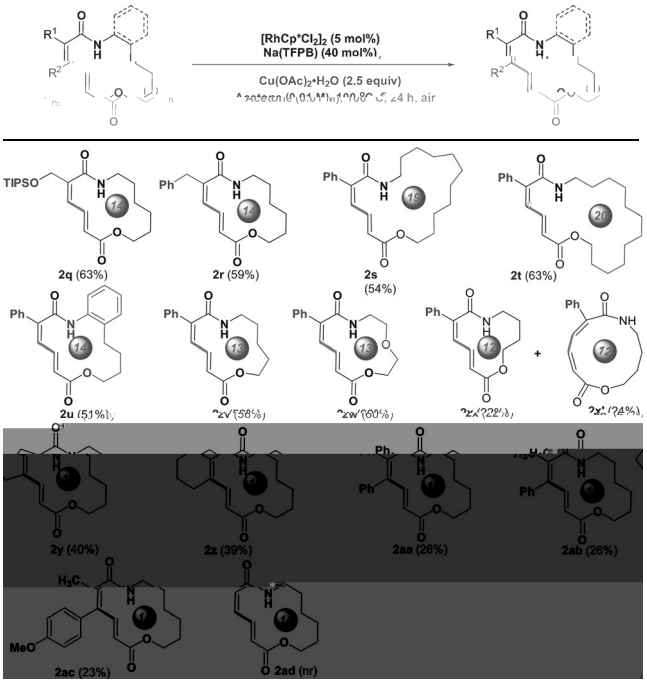


...ol% [RhCp*Cl$_2$]$_2$, 0.375 mmol ... in 15 mL acetone at 100 °C for ... parentheses are yields of isolated

...esired 14-membered macrocycles were ...rate to high yields ...ates with an ... at the a-position. Bot... ...drawing functional grou... ...enyl ring. The corresponding ... ...74% yields. The structure of 2... ...figured diene moiety, was determin... ...lography diffraction analysis.[16] Further... ...aliphatic substituents at the a-position ... tested (2l–2o). It was found that substrate... ...on chain, ethoxymethyl, (triisopropylsilyl)oxy... ...nzyl group all reacted well and furnished t... ...ding products in moderate to good yields (2p–... ...urrent annulation method allowed to access even ... ...maller rings upon tethering a longer or shorter ... ...etween acrylate and acrylamide fragments (2s–2x/2... ...3). It is worth noting that apart from the formation ... ...uct 2x in 22% yield with a Z,E configuration, anoth... ...membered macrocyclic product 2x' with a Z,Z configu... ...was also isolated in 24% yield when the acrylamide ...te 1x was applied in this reaction. Moreover, in contrast ...e previous result,[10b] substrate 1u, which has an N-phen... 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 a-

pher... ...ur... ...OS... ...lide... ...C(sr... ...pera... ...fou... ...ield i... ...to ...ng di... ...mem- ...was a... ...ith the ...-memb... ...ic product ...d (Tabl... ...concentration ...en teste... ...d other rhodium ...but they pr... ...nt improvement on this product yield (... ...5). A cationic rhodium species was expe... ...reactive to catalyze this coupling reacti... ...5 mol% sodium tetrakis[3,5-bis(trifluorom... ...rate (NaBARF) was introduced as an... ...the desired product was obtained in 52% yi... ...ntry 18). Finally, the desired product 2l was i... ...% yield upon increasing the loading of NaBA... ...1%) and Cu(OAc)$_2$·H$_2$O (2.5 equivalents; Tabl... ...19–20). Control experiments indicated that all

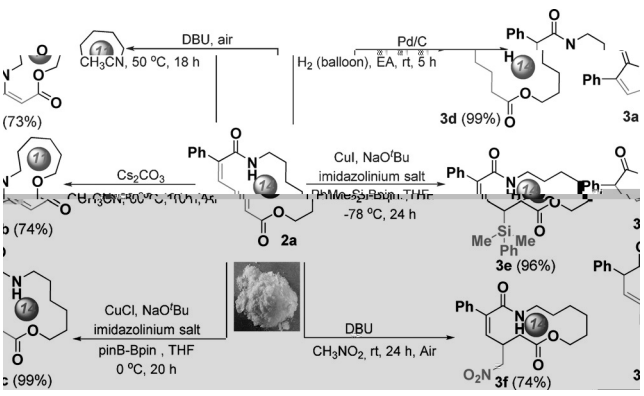
Table 3: Substrate scope for the intramolecular cross-coupling reaction



[a] Reaction was run under the following reaction conditions: 0.15 mmol **1**, 5 mol% $[RhCp^*Cl_2]_2$, 0.375 mmol $Cu(OAc)_2{\cdot}H_2O$ 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.

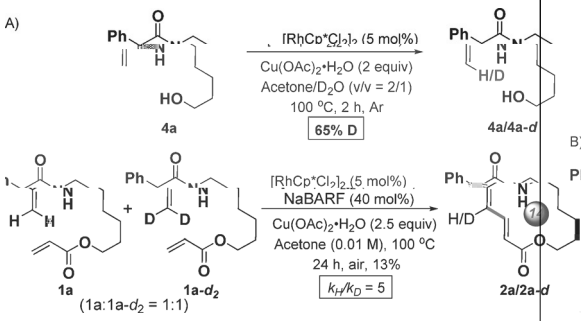
substituted substrates, but was also compatible with a,b-disubstituted acrylamide derivatives. However, these substrates only exhibited low reactivity along with low conversion. Acrylamides with a cyclopentenyl and a cyclohexenyl moiety afforded the desired bicyclic compounds in 40% and 39% yields, respectively (2y–2z). Low yields of the products 2aa and 2ab were observed when a-phenyl-b-phenyl- and a-methyl-b-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.



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

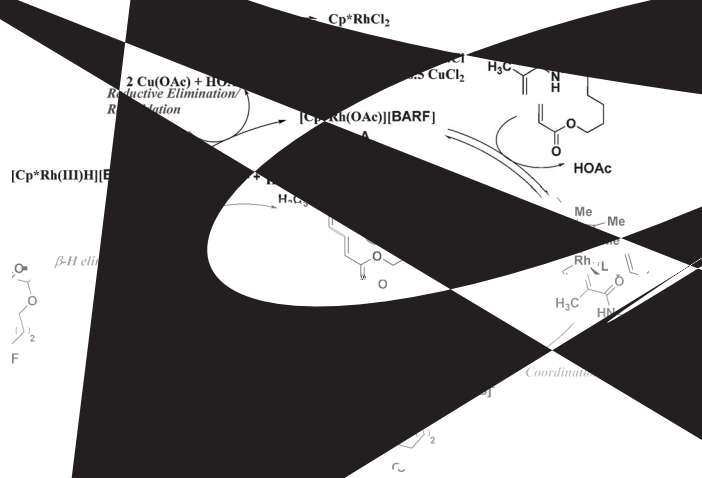
Finally, to gain some preliminary understanding of the mechanism, an isotope-labeling experiment with acrylamide 4a was carried out. A remarkable Z-selective olefinic H/D exchange was detected with addition of D_2O, which implies a reversible cyclometalation process [Scheme 3 A]. Furthermore, a kinetic 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 3 B].



Scheme 3. Isotope-labeling experiments for KIE studies.

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 b-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 … echanism.

featu… hemoselectivity and stereoselectivity, good func… group compatibility, and versatile utility of the dien… fragment in further derivation reactions. In-depth application studies of this intramolecular oxidative cross-coupling reaction in organic synthesis are underway in our laboratory.

Acknowledgements

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