Organic LETTERS

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Catalytically Asymmetric Pd/Norbornene Catalysis: Enantioselective Synthesis of (+)-Rhazinal, (+)-Rhazinilam, and (+)-Kopsiyunnanine C1−3

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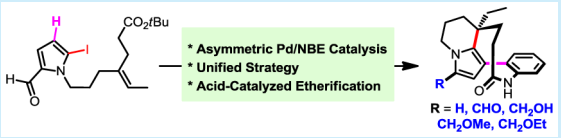
Supporting Information

ABSTRACT: A catalytically asymmetric palladium/norbornene-catalyzed reaction is reported, where α-aryl tetrahydroquinoline derived phosphoramidite **L15** is found to be the optimum ligand. Taking advantage of this transformation, the concise and unified enantioselective syntheses of (+)-rhazinal, (+)-rhazinilam, and (+)-kopsiyunnanine C1, C2, and C3 are realized.

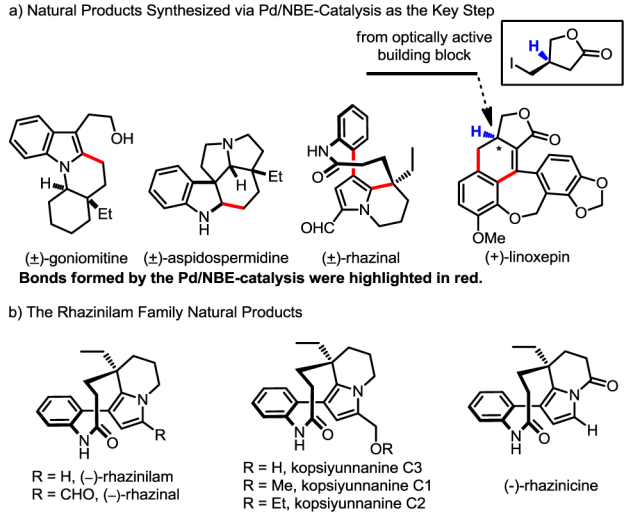


Palladium-catalyzed cross-coupling reactions have been widely applied in organic synthesis, notably the synthesis of complex natural products, due to its great capacity for the selective construction of C−C and C−heteroatom bonds.[1] Among them, Pd/norbornene (NBE)-catalyzed reaction is a particularly powerful method for the synthesis of arenes with 1,2,3-trisubsitution via *ortho* C−H functionalization followed by *ipso* coupling. Since discovery in 1997 by Catellani,[2] Lautens was the first who realized the synthetic potential of this reaction in 2000.[3] Subsequently, a series of useful transformations and a number of molecules with versatile structures were synthesized by a number of groups.[4,5]

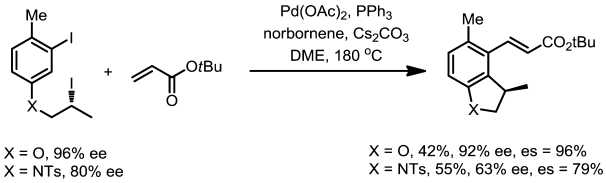
The utility of Pd/NBE-catalyzed domino reaction was further demonstrated by the concise synthesis of complex natural products. Lautens and co-workers reported an elegant synthesis of (+)-Linoxepin by the use of a chiral alkyl iodide (Scheme 1a).[6] (±)-Goniomitine and (±)-aspidospermidine were efficiently synthesized by the Bach group via Pd/NBE-catalyzed α-alkylation of indoles.[7] We also disclosed a concise synthesis of (±)-rhazinal via Pd/NBE catalysis of chemoselective *ortho*-arylation of 2-iodopyrroles followed by intramolecular Heck cyclization.[8] The high efficiency of these total syntheses unambiguously demonstrated the powerful bond formation ability of Pd/NBE catalysis. However, it is easy to recognize that these molecules were synthesized either in racemic forms or by the use of a building block with preinstalled stereogenic atoms, and yet no catalytically asymmetric Pd/NBE-catalyzed reaction was reported.

Catalytically asymmetric transformation of palladium catalysis is a powerful method for the preparation of chiral molecules or building blocks. However, the catalytically asymmetric Catellani-type reaction is unexpectedly ignored in comparison with other related Pd-catalyzed transformations. Seminal results for the asymmetric Pd/NBE catalysis were reported by Lautens and co-workers in 2007, who studied the intra- and intermolecular chirality transfer reactions of aryl halide with enantio-enriched secondary alkyl iodides.[9] In intramolecular reactions, the tether is important to keep the stereochemical information (Scheme 2). With oxygen atom as the tether atom, high enantiospecificity (es = 96%) was observed, while with NTs as the tether the ee value dropped from 80% to 63% (es = 79%). Recently

Scheme 1. Natural Products Synthesized by Pd/NBE-Catalysis as the Key Step and the Rhazinilam Family Natural Products



Scheme 2. Chirality Transfer Studies



Received: June 20, 2016

DOI: 10.1021/acs.orglett.6b01790
Org. Lett. XXXX, XXX, XXX−XXX

the same group developed an expedient reaction condition for the intermolecular alkylation with secondary optically active iodides, and the solvents played a pivotal role.[10] In view of these facts, continuing research on catalytically asymmetric Catellani reactions is necessary and important, yet still challenging.

Rhazinilam,[11] rhazinal,[12] and rhazinicine[13] have drawn significant attention from many synthetic chemists because of their unique bioactivities toward various cancer cell lines and the interesting diversely substituted pyrrole skeleton (Scheme 1b).[14,15] Kopsiyunnanine C1−3 were isolated in 2009,[16] and there is no report regarding their total synthesis to date. Kopsiyunnanine C1−2 contain methoxymethyl or ethoxymethyl functionality, which was rarely found in natural products. Herein we report a catalytically asymmetric version of Pd/norbornene catalysis and its application in the unified synthesis five members of rhazinilam family natural products.[17]

Studies began with the asymmetric version of the key domino reaction of our previous racemic synthesis of rhazinal.[8] Poor conversion was observed when bidentated ligands, such as (*R*)-BINAP and (*R*)-DIOP, were used. The reactions with a TADDOL-based monodentated ligand, such as **L1** and **L2**, gave very poor enantioselectivity (Scheme 3). The screening of a [2′-methoxy-(1,1′-binaphthalen)-2-yl]-diphenylphosphine[MOP]-type ligand indicated that **L3** was superior over its analogues; however the reaction did not give satisfactory yields and ee's in various conditions.[18] The reaction with SIPNOL-based phosphoramidite **L4** afforded a 40% yield of **3** with decent enantioselectivity. Ligands **L5** and **L6** with an acyclic amino group had very low chiral induction. Phosphoramidites bearing cyclic amine moieties, such as **L7**−**L9**, were screened, and inferior to moderate ee values were observed. It was found that the substituent at the α-position of tetrahydroquinoline greatly affected the stereoselectivity of this reaction. The α-methyl tetrahydroquinoline derived **L10**, which was synthesized by You and co-workers in 2009, gave an improved enantioselectivity (72% ee).[19] Further investigation on the solvent effect by the use of **L10** as the ligand did not find a better solvent than fluorobenzene, which was used in the later screenings. Changing the configuration of the amino moiety or replacing the α-methyl group to the ethyl group in the tetrahydroquinoline structure (**L11**, **L12**) only led to a drop in both the yield and enantioselectivity.

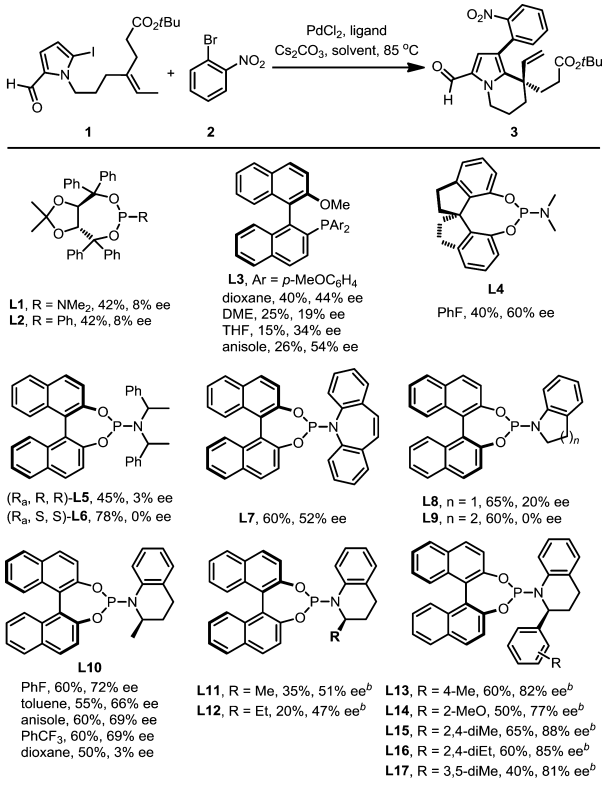
Further optimization focused on the α-aryl tetrahydroquinoline derived phosphoramidites, whose syntheses were detailed in Scheme 4. The semireduction of 2-arylquinolines[20] gave the desired tetrahydroquinoline by following Rueping's procedure via 9-phenanthrenyl chiral phosphoric acid (CPA) catalysis in the presence of Hantzsch ester.[21] The tetrahydroquinoline with PCl_3 in toluene followed by the addition of (*S*)-BINOL gave the enantiopure phosphoramidites in moderate yields.

Pleasingly, the reaction with α-(*p*-tolyl) tetrahydroquinoline based ligand **L13** delivered the product in 82% ee, and the ligand **L14** gave marginally lower enantioselectivity. 2,4-Dimethylphenyl tetrahydroquinoline derived ligand **L15** showed good stereoselectivity and afforded **3** in 88% ee. However, the bulkier ligand **L16** and 2-(3′,5′-dimethylphenyl) 1,2,3,4-tetrahydroquinoline based ligand **L17** did not show better asymmetric induction.

With optically active key intermediate **3** in hand, we continued our efforts for the synthesis of rhazinilam and the related natural products (Scheme 5). One step transformation of **3** could reduce both the nitro group and C−C double bond under Pd/C and H_2 to deliver **4** in high yield (Scheme 5a). Removal of the *tert*-butyl group in **4** with TFA, followed by intramolecular amide bond formation, gave (+)-rhazinal (**5**) in 80% yield. The reduction of the aldehyde group by $NaBH_4$/EtOH and quenching with aqueous NaOH gave (+)-kopsiyunnanine C3 (**6**) in excellent yield.[22] The removal of the aldehyde functionality of **3** via decarbonylation with stoichiometric Wilkinson catalyst afforded **7**, which was readily converted to (+)-rhazinilam in good overall yield via hydrogenation, basic hydrolysis, and macrolactam formation (Scheme 5b).

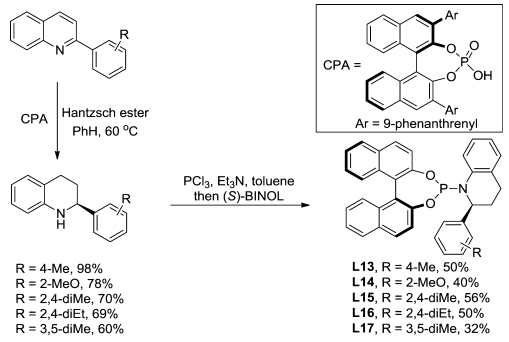
The attempt to synthesize (+)-kopsiyunnanine C1 and C2 by the etherification of (+)-kopsiyunnanine C3 was

Scheme 3. Reaction Conditions Optimization[a]



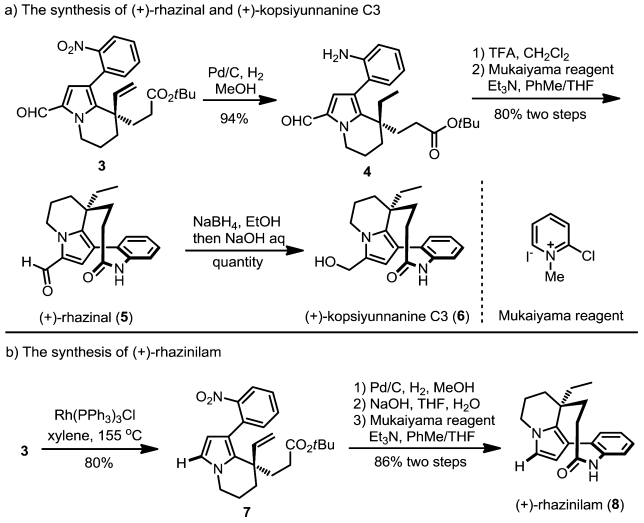
[a]Unless stated otherwise, the reaction was conducted with **1** (0.10 mmol, 1.0 equiv), **2a** (0.60 mmol), $Pd(OAc)_2$ (10 mol %), ligand (20 mol %), and Cs_2CO_3 (0.25 mmol) in dioxane (0.10 M). [b]PhF was used as the solvent.

Scheme 4. Synthesis of Phosphoramidites

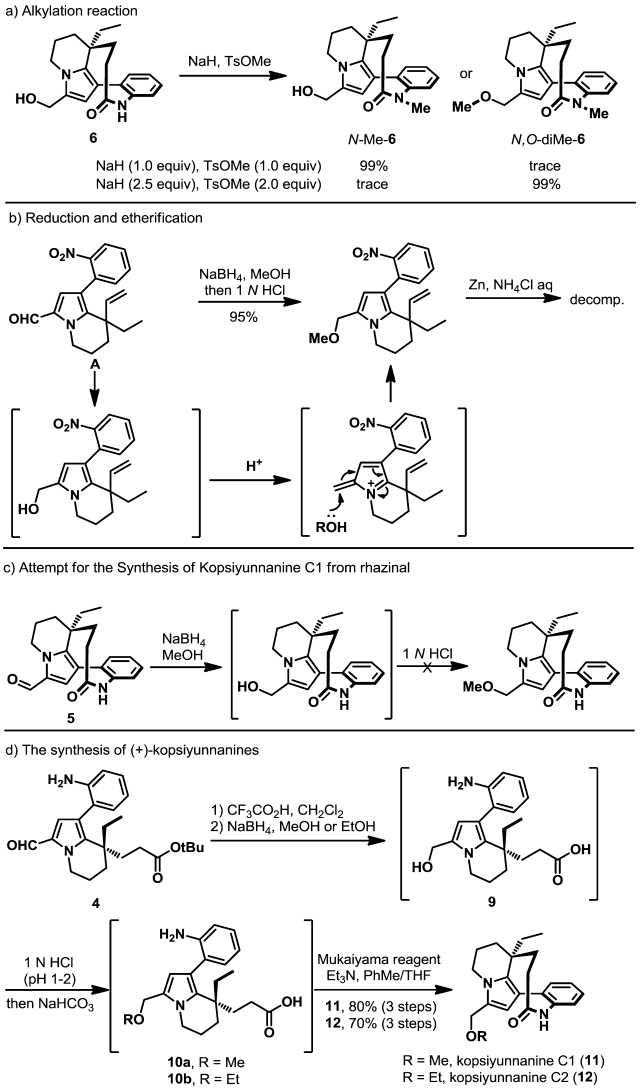


DOI: 10.1021/acs.orglett.6b01790
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 5. Synthesis of (+)-Rhazinal, (+)-Kopsiyunnanine C3, and (+)-Rhazinilam



Scheme 6. Synthesis of (+)-Kopsiyunnanine C1 and C2



unsuccessful in our hands. The *N*-alkylation of the amide functionality was superior over etherification. Thus, by treatment of **6** with 1.0 equiv of NaH and 1.0 equiv of TsOMe, *N*-Me-**6** was obtained in quantitative yield, while *N,O*-diMe-**6** was formed as the sole product when excess NaH and 2.0 equiv of TsOMe were used (Scheme 6a). It is interesting to observe that the reduction of our model compound **A** by $NaBH_4$ in MeOH, followed by acidic workup (1 N HCl), gave the ether derivative in high yields (Scheme 6b). The ethers were possibly formed by acid-catalyzed iminium ion formation and nucleophilic addition of the alcohols. Unfortunately, the ether decomposed after the reduction of the nitro group to an amine or other related further transformation. The reduction of (+)-rhazinal (**5**) in MeOH,[23] followed by the treatment of 1 N HCl, resulted in the decomposition of the material (Scheme 6c). Alternatively, hydrolysis of the *tert*-butyl ester of **4** by trifluoroacetic acid, followed by the treatment of $NaBH_4$ to give the alcohol **10**, which was carefully acidified to pH 1−2 with aqueous HCl to form the ethers **10a** or **10b**. The sensitive crude amino acids should be kept in the solution all the time, and they were used directly for the macrolactam formation without purification to deliver (+)-kopsiyunnanine C1 (**11**) and C2 (**12**) in satisfactory overall yields (Scheme 6d). The analytic data of these synthetic samples well matched those reported for natural products.

In conclusion, we present here a catalytically asymmetric palladium/norbornene-catalyzed domino *ortho*-arylation and Heck cyclization reaction. It demonstrates the first example of catalytically asymmetric Catellani-type reaction. The α-aryl tetrahydroquinoline derived phosphoramidite was superior over other ligands, and excellent enantioselectivity was achieved. Taking advantage of this method, five members of the rhazinilam family natural products were enantioselectively synthesized in a concise and unified manner. The newly discovered acid-catalyzed ether formation of (pyrrol-2-yl) methanol provided a convenient approach for the synthesis of kopsiyunnanine C1−2.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01790.

Analytical data, experimental procedures, and NMR spectra for all compounds reported (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the '973' project from the MOST of China (2015CB856600), NSFC (21272221, 21472179), and Strategic Priority Research Program of the Chinese Academy of Sciences (XDB20000000). X.S. thanks the Grant from China Postdoctoral Science Foundation (2015M581995). We thank Professor L. Gong and Professor

DOI: 10.1021/acs.orglett.6b01790
Org. Lett. XXXX, XXX, XXX−XXX

Z. Han (USTC) for providing (*S*)-2-phenyl-1,2,3,4-tetrahydroquinoline.

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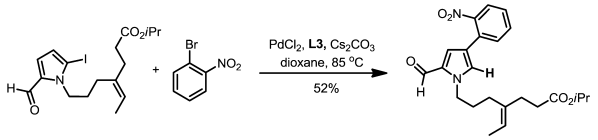
(18) Changing the geometry of C═C double bond resulted in the formation of an uncyclized product.



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(22) Kopsiyunnanine C3 was quite acid sensitive. The reaction should be quenched under basic conditions.

(23) The process of reduction could be well monitored by TLC. However, the addition of HCl led to the decomposition of the corresponding alcohol.

DOI: 10.1021/acs.orglett.6b01790
Org. Lett. XXXX, XXX, XXX−XXX