Organic LETTERS

Letter

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Catalytic Asymmetric Nazarov Cyclization of Heteroaryl Vinyl Ketones through a Crystallographically Defined Chiral Dinuclear Nickel Complex

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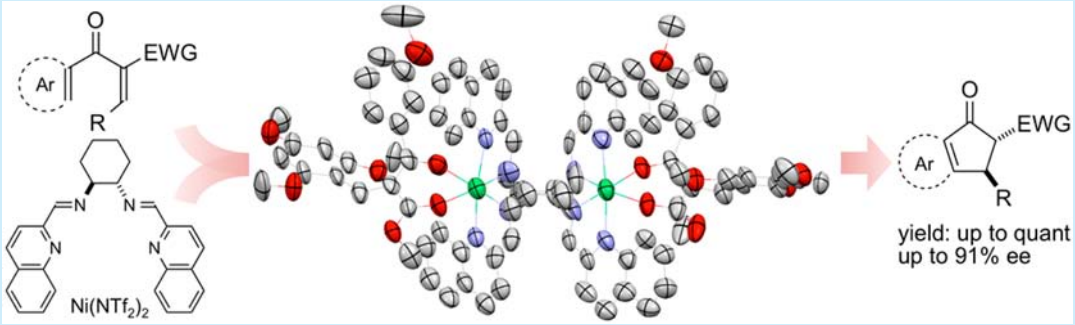
Supporting Information

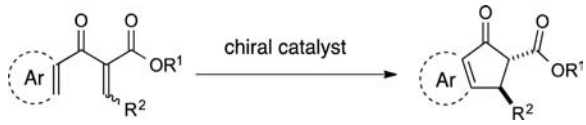


ABSTRACT: A $Ni(NTf_2)_2$ and tetradentate bisimino-bisquinoline ligand complex catalyzed the enantioselective Nazarov cyclization of heteroaryl vinyl ketones. An X-ray-quality crystal was obtained from a mixture of the Ni complex and the substrate, which was the dinuclear chiral Ni complex. From information regarding the structure of the complex, the substrate was distorted to form a helical shape, and the carbon atoms involved in bond formation were close to each other. In addition, mechanistic studies revealed that the configuration of the olefin moiety was isomerized before bond formation.

Nazarov cyclization is a ring-closing reaction of divinyl ketones via a pentadienyl cation intermediate in the presence of a Brønsted acid or Lewis acid, which gives a multisubstituted five-membered ring.[1] The resulting five-membered ring accepts various chemoselective transformations, and several synthetic applications to biologically active compounds have been demonstrated.[2] After Frontier's great contribution to the use of polarized substrates,[3] various catalysts, including asymmetric catalysts, have been developed to promote Nazarov cyclization under mild conditions. Thus, this area of research has recently been in the spotlight.[4] Meanwhile, the mechanism of Nazarov cyclization, especially the stereoselectivity, has mainly been discussed through the use of computational studies.[5] The lack of information about the transition state supported by experimental evidence[6] might limit the type of chiral catalyst in this area of research. Here, we report the Nazarov cyclization of heteroaryl vinyl ketones catalyzed by $Ni(NTf_2)_2$ and bisimino-bisquinoline (ImQ)[7] complex and discuss the mechanism based on an X-ray crystallographic analysis of the Ni–ImQ–substrate complex.

Aryl vinyl ketone is a subtype of Nazarov substrates (Scheme 1). However, there have been only two reports on catalytic and enantioselective variants. Ma reported the fluorinative cyclization reaction using Cu-BOX catalyst.[8] Recently, Rueping introduced an indolyl substrate to this type of reaction, also using Cu–BOX catalyst.[9] We set compound **1** as a substrate for

Scheme 1. Enantioselective Nazarov Cyclization of Aryl Vinyl Ketones



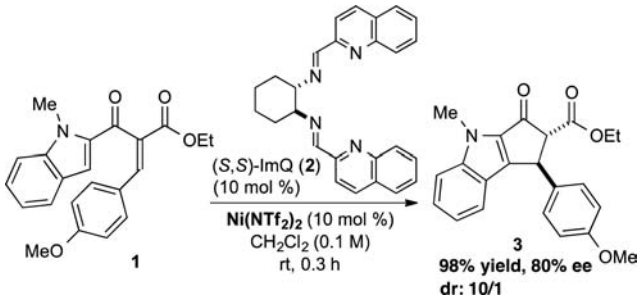
Nazarov cyclization and screened catalysts using various metal triflic imidates, since we have been focusing on the development of reactions to construct heteroaromatic ring-fused multicyclic chiral synthetic intermediates[10] and on demonstrating the synthetic utility of metal triflic imidates ($M_m(NTf_2)_n$) as a Lewis acid.[10a] When we used ImQ (**2**) as a chiral ligand, a promising degree of enantioinduction was observed in combination with various metal triflic imidates.[11] Optimization of the reaction conditions revealed that the conditions in Scheme 2 gave the best result.

When we mixed the catalyst and compound **4**[12] with cyclopentyl methyl ether,[13] we could isolate a red crystal. X-ray crystallographic analysis of this crystal revealed that it was dinuclear nickel complex $[Ni_2(imq)_2(\mathbf{4})_2]^{4+}\cdot 4(NTf_2)^-$ (**5**) (Figure 1B,C).[14,15] Remarkably, the isolated complex **5** acted

Received: August 31, 2015
Published: October 14, 2015

DOI: 10.1021/acs.orglett.5b02497
Org. Lett. 2015, 17, 5184–5187

Scheme 2. Enantioselective Nazarov Cyclization of 1 Catalyzed by Nickel Complex



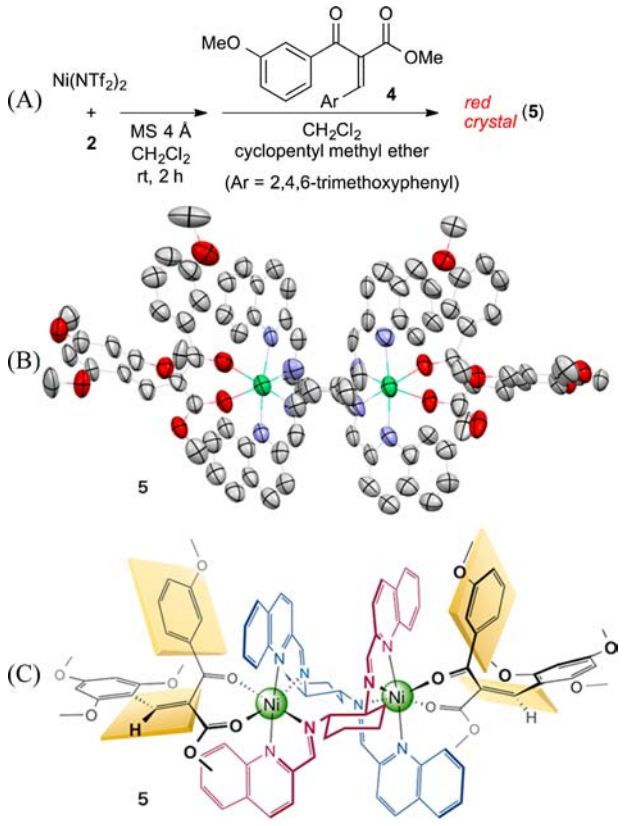
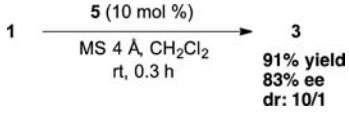


Figure 1. Procedure to obtain the crystal (A) and its crystallographic characterization. ORTEP figure (B) and ChemDraw drawing (C) of complex **5**. Hydrogen atoms, water molecules, disordered atoms, and counteranions have been omitted for clarity. Ellipsoids are drawn at the 30% probability level.

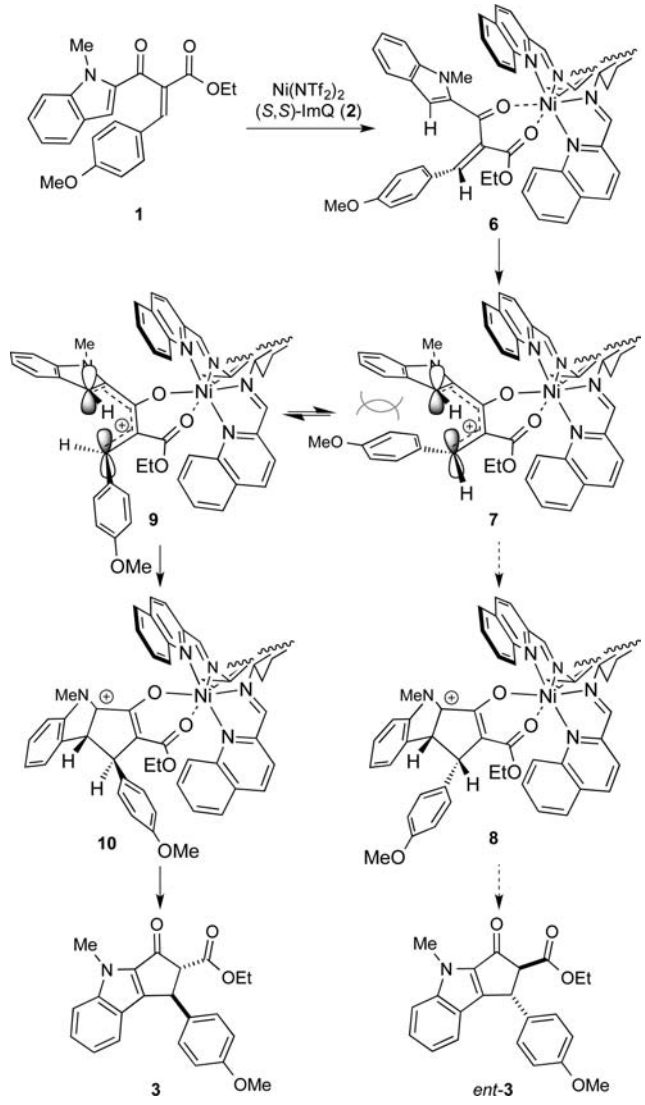
as a catalyst (Scheme 3) with a similar reactivity and stereoselectivity as the in situ catalyst system shown in Scheme 2.[11] This result shows that the substrate **4** in the complex should be exchanged with a new molecule of the substrate. Therefore, we speculated that a dinuclear nickel complex $[Ni_2(imq)_2]^{4+}\cdot 4(NTf_2)^-$ would be the active catalyst.[16]

Scheme 3. Asymmetric Nazarov Cyclization Using 5 as a Catalyst



Interestingly, substrate **4** in the crystal structure was distorted to make a helical shape.[17] This *P*-helical configuration was controlled by the chiral catalyst. Consequently, the two sp^2 carbons, where the new bond would be formed, were placed close to each other. Based on this observation, we proposed the reaction mechanism shown in Scheme 4. The representative

Scheme 4. Proposed Reaction Mechanism[a]



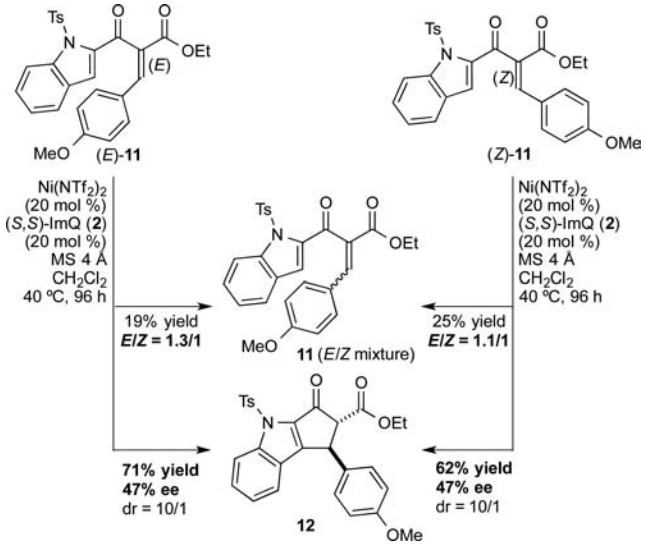
[a]The remaining half of the complex has been omitted for clarity.

substrate **1** would coordinate to the nickel catalyst to assemble a complex **6** similar to the crystal structure. Activated substrate formed the five-centered cationic intermediate **7** with a *P*-helical topology, where the terminal molecular orbitals easily overlapped. The resulting cyclized intermediate **8** could afford the Nazarov adduct; however, the absolute stereochemistry of the product should be opposite that of the actual product. Therefore, we supposed that the configuration of the olefin moiety would be isomerized while an equilibrium was being achieved between **7** and **9**.[18] The isomerization to **9** could avoid the steric hindrance between two aromatic rings of the substrate, and this intermediate would afford **10** to give the actual product **3**.

DOI: 10.1021/acs.orglett.5b02497
Org. Lett. 2015, 17, 5184−5187

To elucidate the equilibrium between **7** and **9**, both (*E*)- and (*Z*)-isomers of **11** were independently treated with the catalyst and quenched before the reaction was complete. In both cases, the recovered substrates became a mixture of (*E*)- and (*Z*)-isomers (Scheme 5), and the *E*/*Z* ratios were similar. The

Scheme 5. Asymmetric Nazarov Cyclization Using (*E*)- and (*Z*)-Isomers of 11

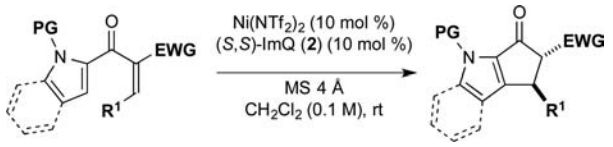


products **12** also had an identical ee value: 47% ee. The absolute configuration of the product was independent of the configuration of the substrate. This experiment in Scheme 5 strongly supported the existence of an equilibrium.

Our nickel catalyst promoted Nazarov cyclization of various heteroaryl vinyl ketones with good enantioselectivity (Table 1). The substituent on the olefin moiety could be an aromatic, heteroaromatic, or alkenyl group to give the Nazarov adduct in good yields with moderate to good ee's (entries 1−5). The electron-withdrawing group could be an ester, amide, ketone, or phosphoric ester (entries 6−11). Substrates that contained amides were less reactive, while substrates that contained ketones were more reactive than those that contained esters. For the protective group on the nitrogen of the indole ring, a tosyl group was suitable (entry 12), although both the reactivity and enantioselectivity were decreased. Benzyl protection slightly affected the enantioselectivity (entry 13). We performed reactions with two substrates with methoxy or fluorine substituents on the indole ring (entries 14 and 15). Both substrates gave good results. Nonprotected indoles were less reactive, but high enantioselectivity was achieved in all cases (entries 16−18). A pyrrole derivative could be used instead of indole in our catalytic system (entry 19).[19]

In conclusion, we have developed a novel nickel catalyst for the catalytic and enantioselective Nazarov cyclization of heteroaryl vinyl ketones. We also successfully isolated the chiral active catalyst and the substrate complex, $[Ni_2(imq)_2(\mathbf{4})_2]^{4+}\cdot 4(NTf_2)^-$ (**5**). From its structure, we proposed that carbon−carbon bond formation occurred as a result of distortion of the substrate. We also confirmed that the olefin moiety of the substrate was isomerized under the reaction conditions. Information on the structure of **5** should contribute to both the design of chiral ligands and mechanistic studies of the general reaction using Lewis acid activated β-ketoesters.

Table 1. Substrate Scope



entry	product	time (h)	yield (%)	% ee	dr
	R¹ =				
1	*p*-MeO-C_6H_4- (**3**)	0.3	98	80	10/1
2	*o*-MeO-C_6H_4- (**13**)	0.3	91	66	14/1
3	ph (**14**)	0.3	86	69	>20/1
4	2-furyl (**15**)	0.5	94	73	14/1
5	cinnamyl (**16**)	48	83	66	8/1
	EWG =				
6	CO_2t-Bu (**17**)	0.3	99	72	8/1
7[a]	$CONMe_2$ (**18**)	14	96	91	>20/1
8[a]	$CONBn_2$ (**19**)	36	90	80	3/1
9[a]	CO(4-morpholinyl) (**20**)	24	99	75	>20/1
10	Ac (**21**)[b]	0.2	89	80	>20/1
11	$PO(OEt)_2$ (**22**)	24	quant	73	>20/1
12[c]	**PG** = Ts, **R²** = H (**12**)	48	82	53	13/1
13	**PG** = Bn, **R²** = H (**23**)	1	95	66	10/1
14	**PG** = Me, **R²** = OMe (**24**)	0.3	95	77	12/1
15	**PG** = Me, **R²** = F (**25**)	0.3	95	80	13/1
	R³ =				
16	H (**26**)	37	93	84	20/1
17	OMe (**27**)	13	93	80	20/1
18	Cl (**28**)	67	84	82	>20/1
19[d]	(**29**)[b]	17	80	72	>20/1

[a]The reaction was carried out at 40 °C. [b]Obtained as a mixture of the keto form and enol form.[11] [c]The reaction was carried out at 40 °C with 20 mol % of the catalyst. [d]The reaction was carried out with 20 mol % of the catalyst.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02497.

DOI: 10.1021/acs.orglett.5b02497
Org. Lett. 2015, 17, 5184−5187

Experimental details, substrate supply, NMR and HPLC spectra for obtained compounds, and supporting figures (PDF)
X-ray data for compound **5** (CIF)

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Author Contributions

All authors contributed equally to the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by JSPS KAKENHI (Grant Nos. 25460006 (S.H.) and 25293001 (A.N.)). We thank Dr. Hiroyasu Sato (RIGAKU Co., Japan) for his generous help with the X-ray crystallographic analysis of the nickel complex.

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(11) For details, see the Supporting Information.

(12) Compound **4** with 10 mol % of $Ni(NTf_2)_2$ gave Nazarov adduct in 43% yield. For details, see the Supporting Information. Compound **4** was also used for Nazarov cyclization by Luo's group. Xi, Z.-G.; Zhu, L.; Luo, S.; Cheng, J.-P. *J. Org. Chem.* **2013**, *78*, 606. The substrates used in Table 1 were not appropriate for crystallization because the reaction proceeded.

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(14) CCDC 1058249 contains the supplementary crystallographic data. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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(18) A similar proposal was also discussed in Rueping's report. See ref 9.

(19) The absolute configuration of **27** was unambiguously assigned by X-ray crystallographic analysis after conversion. For details, see the Supporting Information and CCDC 1058248. This result, together with NMR analyses, was used to establish the relative and absolute configuration of our compounds.

DOI: 10.1021/acs.orglett.5b02497
Org. Lett. 2015, 17, 5184−5187