Asymmetric Catalysis

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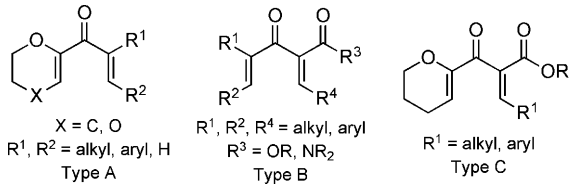
Asymmetric Nazarov Reaction Catalyzed by Chiral Tris(oxazoline)/Copper(II)**

*Peng Cao, Chao Deng, You-Yun Zhou, Xiu-Li Sun, Jun-Cheng Zheng, Zuowei Xie, and Yong Tang**

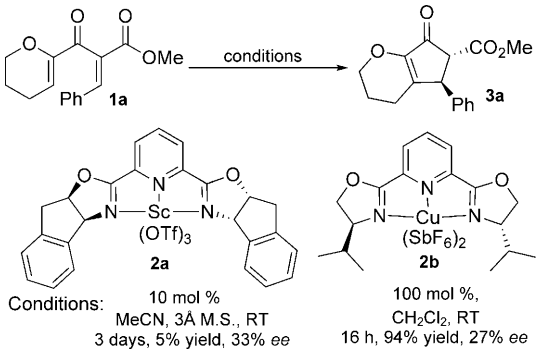
The frequent occurrence of five-membered carbocycles in natural products and other biologically active compounds has provided a major impetus for the development of efficient methods for their construction.[1] Towards this end, the Nazarov cyclization, a stereospecific 4π electrocyclization that converts divinyl ketones into cyclopentenones through a conrotatory cyclization, has distinguished itself as a powerful tool for the synthesis of such compounds.[2] Over several decades, great efforts have been devoted to the exploitation of the Nazarov reaction,[3] further highlighting its synthetic utility, as demonstrated by its increasing use in total syntheses.[4] However, the asymmetric Nazarov reaction with a catalytic amount of chiral source was not reported until the end of 2003, probably because of the complex mechanism of the reaction.[5] Of those catalytic asymmetric reactions developed,[5] few examples have been reported that give good to excellent enantiocontrol in good yields, except for divinyl ketones that belong to type A or B (Scheme 1).



Scheme 1. Representative divinyl ketones used in the Nazarov reaction.

Trauner and Liang reported the asymmetric Nazarov reactions of type A divinyl ketones, catalyzed by 10 mol% of indane-pybox/$Sc(OTf)_3$ **2a** (pybox = 2,6-bis(2-oxazolin-2-yl)pyridine) with *ee* values of 72–97% in good yields.[5f] Aggarwal and Belfield developed the first asymmetric Nazarov cyclization of type B ketones, promoted by a stoichiometric amount of pybox/Cu^{2+} complex **2b**, with enantioselectivities of 44–88%.[5h] Recently, Rueping et al. reported the first example of organocatalytic asymmetric Narazov reactions with high enantioselectivities and moderate diastereoselectivities[5a,d] using polarized alkoxy divinyl β-ketoesters (type C) that were elegant substrates in this transformation.[3f,m,n] To date, no highly enantioselective version has been reported.

We found that both pybox-derived complexes **2a** and **2b**, which were excellent catalysts or promoters in the enantioselective Nazarov reaction of type A and B substrates,[5f,h] were not efficient for type C substrates. For example, when alkoxy divinyl β-ketoester **1a** underwent cyclization in the presence of indane-pybox/$Sc(OTf)_3$ **2a** or *i*Pr-Pybox/$CuBr_2$/$AgSbF_6$ **2b**, the desired product **3a** was formed as the sole product with 33% *ee* in 5% yield and 27% *ee* in 94% yield,



Scheme 2. Nazarov reaction of **1a** catalyzed by indane-Pybox/$Sc(OTf)_3$ and *i*Pr-Pybox/Cu^{II} complexes.

respectively (Scheme 2). Compared with the planar pybox, we envisioned that a pendant group on the box ligand[6] may be better able to tune the three-dimensional conformation of the catalyst–substrate complex, and subsequently improve the enantiocontrol at the newly generated stereogenic centers (Figure 1). Therefore, several tris(oxazoline)s[7] were synthesized and were found to be excellent catalysts for the asymmetric Nazarov cyclization of alkoxy divinyl β-ketoesters, affording *ee* values of up to 98%. Herein, we report our preliminary results with this catalyst system.

Tris(oxazoline)s (toxs) **4a**, **4b**, and **5c–d** (Figure 2) are readily available from alkylation of their corresponding bis(oxazoline)s.[7h] As isopropyltris(oxazoline) (*i*Pr-tox) **4a** is an efficient ligand in the asymmetric reactions of bidentate

[*] Dr. P. Cao, C. Deng, Y.-Y. Zhou, Dr. X.-L. Sun, Dr. J.-C. Zheng, Prof. Dr. Y. Tang
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
345 Lingling Lu, Shanghai 200032 (P. R. China)
Fax: (+86) 21-5492-5078
E-mail: tangy@mail.sioc.ac.cn
Prof. Dr. Z. Xie
Department of Chemistry, The Chinese University of Hong Kong
Shatin, New Territories, Hong Kong (China)

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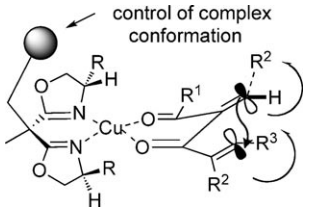


Figure 1. Catalyst design for the asymmetric Nazarov reaction.

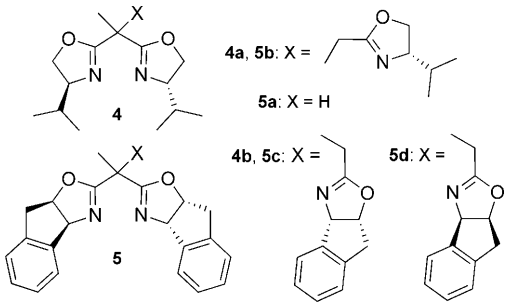
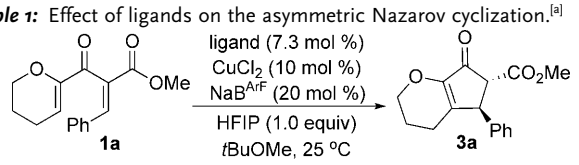


Figure 2. Ligands used in this investigation.

malonate derivatives,[7g,i] we decided to employ **4a** to optimize the reaction conditions of model substrate divinyl β-ketoester **1a**. The combination of $CuCl_2$ and sodium tetrakis[3,5-bis(trifluoromethyl)phenyl] borate (NaB^{ArF})[8] in *t*BuOMe with hexafluoro-2-propanol (HFIP) as an additive was found to be the most successful among various metals, additives, and solvents that were screened,[9] furnishing product **3a** in 85% yield and 78% *ee* as a single diastereomer (Table 1, entry 1).

Table 1: Effect of ligands on the asymmetric Nazarov cyclization.[a]



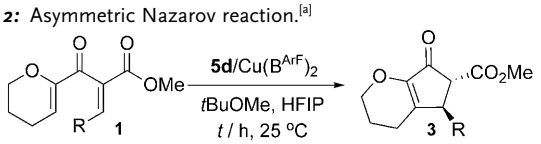
Entry	Ligand	d.r.[b]	Yield [%][c]	*ee* [%][d]
1	**4a**	>99:1	85	78
2	**4b**	>99:1	85	80
3	**5a**	>99:1	69	86
4	**5b**	>99:1	74	88
5	**5c**	>99:1	73	85
6	**5d**	>99:1	90	92

[a] Reaction conditions: $CuCl_2$ (2.7 mg, 0.02 mmol), ligand (0.0146 mmol), NaB^{ArF} (36.0 mg, 0.04 mmol), HFIP (20 μL, 0.20 mmol), **1a** (54 mg, 0.20 mmol), *t*BuOMe (2.0 mL), 20 hours. [b] Determined by 300 MHz ^{1}H NMR. [c] Yield of isolated product. [d] Determined by chiral HPLC.

Encouraged by these preliminary results with **4a**, we further investigated the effect of several tris(oxazoline)s (Figure 2) on the enantioselectivity of the reaction. As shown in Table 1, ligands **4b** and **5a–d** all provided good enantioselectivities and yields under the optimized conditions. Substitution of the isopropyloxazoline group in **4a** for an indane-oxazoline pendant group did not affect the Nazarov process too much (Table 1, entries 1 vs. 2). However, significant influence was observed when the modular box scaffold was altered. Simply replacing *i*Pr-box with the more rigid indane-box led to an increase in the *ee* by 10%, albeit at the cost of an 11% decline in yield (Table 1, entries 1 vs. 4). Further studies revealed that the configuration of the chiral pendant sidearm also had an effect on the outcome (Table 1, entries 5 vs. 6). Fortunately, when 10 mol% of ligand **5d** was employed as the chiral source, the desired optically active product was formed in 90% yield and 92% *ee* (Table 1, entry 6).

With the optimal combination of ligand, Lewis acid, additive, and solvent in hand, we turned our attention to survey the scope and limitation of the Nazarov cyclization. As summarized in Table 2, a variety of alkoxy divinyl β-ketoesters that contained R groups with different electronic and steric properties were examined. The nature of the β-aryl substituents (R = aryl) had a limited influence on the stereoselectivities. Excellent d.r. (>99:1) and *ee* values (92–98%) were consistently afforded (Table 2, entries 1–11), whereas the reaction rate and yield varied according to the nature of the aryl substituents. Electron-rich aromatic substituents improved the reaction rate and good to excellent yields were obtained with excellent enantioselectivity, even with 5 mol% of catalyst in some cases (Table 2, entries 2–6). When R = 2-methylphenyl, the cyclization proceeded with moderate conversion (Table 2, entry 7), probably owing to steric encumbrance. The electron-poor aromatic substituents were less reactive and moderate yields with high *ee* values were obtained in the presence of 10 mol% catalyst at 40°C (Table 2, entries 8–11). Fortunately, those substrates success-

Table 2: Asymmetric Nazarov reaction.[a]

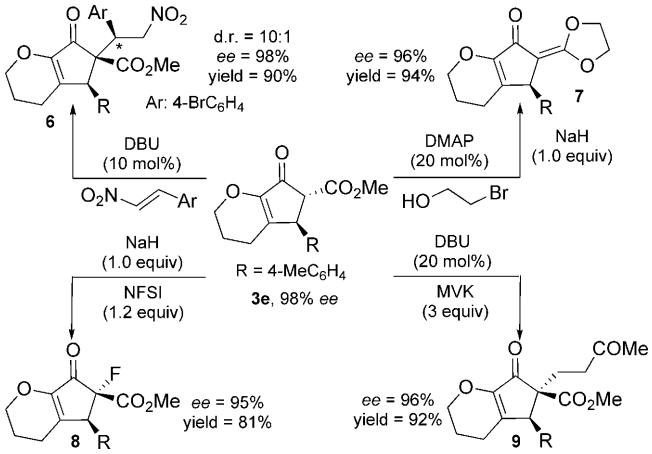


Entry	1	R	Cu^{II} [mol%]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**1a**	phenyl	10	26	90	92
2[d]	**1b**	4-hydroxy-3,5-dimethoxyphenyl	5	66	77	96
3[e]	**1c**	3,4,5-trimethoxyphenyl	5	4 days	96	98
4	**1d**	4-methoxyphenyl	10	18	80	96
5	**1e**	4-methylphenyl	10	26	84	95
6	**1f**	3-methylphenyl	10	26	87	93
7[f]	**1g**	2-methylphenyl	10	47	58	94
8[g]	**1h**	4-fluorophenyl	10 (20)	50 (30)	53 (69)	93 (96)
9[g]	**1i**	4-chlorophenyl	10 (20)	58 (38)	46 (75)	93 (96)
10[g]	**1j**	3-chlorophenyl	10 (20)	70 (50)	45 (63)	91 (93)
11[g]	**1k**	4-bromophenyl	10 (20)	64 (57)	77 (76)	94 (96)
12[h]	**1l**	cyclohexyl	10	5 days	88	78

[a] Reaction conditions: **5d**/$CuCl_2$/NaB^{ArF} (molar ratio) = 0.73:1.0:2.0 (entries 1–7, 12) or 1.1:1.0:2.0 (entries 8–11), HFIP (20 μL, 0.20 mmol), **1** (0.20 mmol), *t*BuOMe (2.0 mL). [b] Yield of isolated product. [c] Determined by chiral HPLC. [d] At 15°C. [e] At 15°C, without HFIP. [f] 65% conversion. [g] 40°C; the data in brackets are results when 20 mol% catalyst was used. [h] DCE as solvent, 50% conversion.

fully underwent Nazarov cyclization in the presence of 20 mol% catalyst (Table 2, entries 8–11, data in brackets). The β-alkyl substituent was also tested and the reaction occurred smoothly, affording the desired product in 88% yield, albeit with 78% *ee* (Table 2, entry 12). In all cases, β-keto esters **3** were isolated as single regio- and *trans* isomers.

To demonstrate the synthetic potential of this asymmetric Nazarov reaction, several transformations were carried out. As shown in Scheme 3, reactions of cyclopentenone **3e** through Michael additions, electrophilic fluorination,[5e] and esterification/cyclization proceeded successfully in high yields without loss of optical purity. These transformations provide a facile method for the construction of functional cyclopentenone derivatives. The absolute configuration of compound **6** was determined by X-ray analysis as 5*S*,6*R*.[9,10] Accordingly, **3e** was assigned as having a 5*S*,6*R* configuration.



Scheme 3. Chemical transformations of cyclopentenone **3e**. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP = 4-(dimethylamino)pyridine, NFSI = *N*-fluorodibenzenesulfonimide, MVK = methyl vinyl ketone.

A stereochemical model, shown in Figure 3, was developed to account for the observed enantioselectivity. In the presence of **5d**/Cu^{II}, (*E*)-**1** is firstly isomerized to the corresponding *Z* isomer as proposed by Frontier and coworkers,[3f] followed by conrotatory annulation by either a clockwise or an anticlockwise pathway. Using DFT calculations,[9] we found that intermediate **I**, formed by an anticlockwise conrotatory cyclization, is favored by 3.94 kJ mol^{-1} over intermediate **II**, which was formed by a clockwise conrotatory cyclization, owing to steric effects (Figure 3). This result is consistent with the absolute stereochemistry of the product observed. To understand the role of the pendant group, DFT calculations were performed using **5c**/Cu^{II} and **5d**/Cu^{II} as models. Based on the results calculated, the sidearm might influence the conformation of the catalytic species through steric hindrance, leading to a discrimination between the transition states and different enantioselectivities.[9] The exact role of the sidearm is not clear and requires further investigation.

In conclusion, we have developed a highly regio-, diastereo-, and enantioselective asymmetric Nazarov reaction that is catalyzed by the combination of tris(oxazoline)/Cu^{II}.

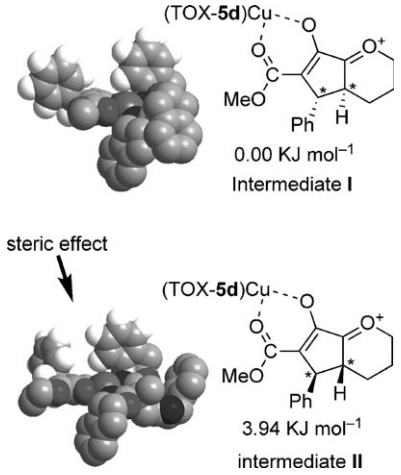


Figure 3. Energies for the intermediates in the asymmetric Nazarov reaction. Some hydrogen atoms are omitted for clarity.

Using DFT calculations, a stereochemical model was proposed to understand the high enantiocontrol exerted by the catalyst. The mild reaction conditions, high enantioselectivity, reasonable yields, and their utility in the construction of quaternary stereogenic carbon centers make the present reaction potentially highly useful in organic synthesis.

Experimental Section

Typical procedure for the asymmetric Nazarov reaction, (**3a** as an example): $CuCl_2$ (2.7 mg, 0.02 mmol), NaB^{ArF} (36.0 mg, 0.04 mmol), and ligand **5d** (7.5 mg, 0.015 mmol) were stirred in anhydrous *t*BuOMe (1.0 mL) at 25 °C for 2 hours. HFIP (21 μL, 0.2 mmol) was added, followed by **1a** (54.5 mg, 0.2 mmol), and *t*BuOMe (1.0 mL). After the reaction was complete (monitored by TLC), the mixture was rapidly filtered through a short pad of silica gel and eluted with EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 8:1) to afford the desired product **3a** as liquid. Yield: 49 mg (90%). *ee*: 92% (determined by HPLC: Chiralcel AD column; eluent: hexane/*i*PrOH (70:30); 0.8 mL min^{-1}; 238 nm; t_{R1}(minor) = 10 min, t_{R2}(major) = 12 min. $[\alpha]_D^{20} = +176.1°$ ($c = 0.5$, $CHCl_3$, 92% *ee*). ^{1}H NMR (300 MHz, $CDCl_3$/TMS) $\delta = 7.29$–7.37 (m, 3H), 7.14 (d, $J = 6.6$ Hz, 2H), 4.24 (d, $J = 1.2$ Hz, 1H), 4.15–4.20 (m, 2H), 3.78 (s, 3H), 3.33 (d, $J = 1.2$ Hz, 1 H), 2.13–2.21 (m, 2H), 1.93–1.98 ppm (m, 2H).

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[9] For details, please see the Supporting Information.

[10] The structure was determined by X-ray analysis. CCDC 738787 (**3e**), 738788 (**6**), and 738789 (**7**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

