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SYNTHESIS OF 3-(2-PYRIDYL)-2-PYRAZOLINE DERIVATIVES AS CANDIDATES FOR HETEROCYCLIC CHIRAL LIGANDS OF THE CHIRALITY RELAY TYPES

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Abstract – The synthetic work of 3-(2-pyridyl)-2-pyrazolines bearing a chiral center at the 5-position is presented. Three synthetic routes have been examined, including (1) intramolecular cyclization of the hydrazones of α,β-unsaturated ketones, (2) synthesis of *N*-unsubstituted pyrazolines followed by the optical resolution of diastereomers of sulfonamide derivatives, and (3) asymmetric pyrazoline synthesis between enones and arylhydrazines catalyzed by a chiral metal acetate complex catalyst.

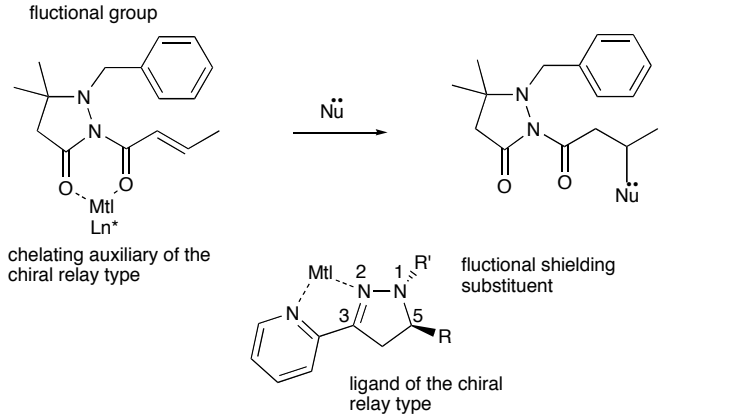
INTRODUCTION

Catalytic chirality induction of reactions by use of chiral metal complex catalysts provides one of the most direct and effective synthetic methods leading to enantiomers of product molecules.[1] Therefore, the rational structural design of chiral ligands is needed for the success of catalytic activity as well as enantioselectivity of particular reactions.

The concept of "chirality relay system" has recently been introduced in the field of asymmetric synthesis.[1] When the chirality can be relayed from a chiral center of either chelating auxiliary or chiral ligand to the reaction site, more effective chiral induction is expected. Sibi and coworkers have recently reported some pioneering works on this basis.[2] They have applied 5,5-dialkyl-3-pyrazolidinones as achiral chelating auxiliary bearing a fluctional substituent (Figure 1). When the α,β-unsaturated amide derivatives of 3-pyrazolidinone auxiliary are employed in the reactions catalyzed by a chiral catalyst, chirality of the catalyst is relayed effectively to a shielding substituent, fluctional benzyl group at the 1-position in this case. Therefore, this provides an example for the "chirality relay system" installed in the

chelating auxiliary. Although efficiency was not high enough, other chiral relay type ligands are also known.[3]

Figure 1. The pyrrazolidinone chelating auxiliary and the 3-(2-pyridyl)-2-pyrrazoline chiral ligand of the chiral relay types



The authors expected to develop a new chiral ligand in which a chirality relay system is incorporated. Our structural design for the new chiral ligand includes the skeleton of 2-pyrazoline bearing a 2-pyridyl substituent at 3-position and a chiral center at 5-position. A metal salt would coordinate between the 2-nitrogen of the pyrazoline ring and the nitrogen atom of the pyridine ring producing the chiral complex catalyst, in which the fluctional shielding substituent on the 1-nitrogen would stay trans to the adjacent substituent R at the chiral 5-position.

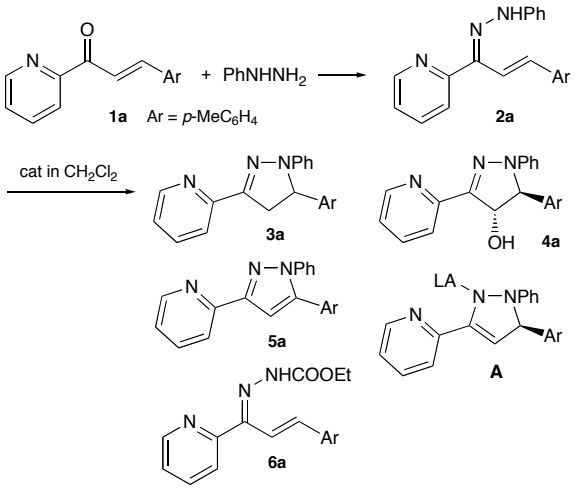
In this communication, we would like to report the synthetic work of 3-(2-pyridyl)-2-pyrazolines bearing a chiral center at the 5-position. Three synthetic routes have been examined in the present work, including (1) intramolecular cyclization of the hydrazones of α,β-unsaturated ketones, (2) synthesis of *N*-unsubstituted pyrazolines followed by optical resolution of the diastereomers of sulfonamide derivatives, and (3) the asymmetric pyrazoline synthesis between enones and arylhydrazines catalyzed by a chiral metal acetate catalyst.[3]

RESULTS AND DISCUSSION

3-(*p*-Methylphenyl)-1-(2-pyridyl)-1-propenone (**1a**, Ar = *p*-MeC_6H_4) was readily prepared by condensation of the commercially available 2-acetylpyridine with *p*-methylbenzaldehyde under basic conditions at rt in ethanol (Scheme 1). The resulting enone **1a** was readily converted to phenylhydrazone **2a** in acetic acid at rt (64%, in 22 h). The intramolecular cyclization of hydrazone **2a** was effectively promoted by an equimolar amount of $TiCl_4$, and the reaction was complete in 10 min at rt in CH_2Cl_2 to give pyrazoline **3a** in 67% yield. However, use of the $TiCl_4$ complex of 1,1'-bi(2-naphtol) led to the racemic derivative of **3a** in 68% yield after 18 h at rt.

Although a variety of Lewis acids were examined, we could not find the catalysts better than $TiCl_4$ in terms of reaction rate enhancement. Reactions catalyzed with $Ni(ClO_4)_2$•$6H_2O$, $Zn(OTf)_2$, and $Mg(ClO_4)_2$, either with or without DBFOX/Ph, indaBox, Box/Ph chiral ligands, gave only other cyclization product **4a** in moderate yields (31-48%). This product was characterized to be the 4-hydroxypyrazoline **4a** on the basis of the X-ray structural analysis (Figure 2).

Scheme 1. The intramolecular cyclization of hydrazone **2** of enones **1a** giving pyrazolines **3**.



Conditions	Yield / % 3a	4a	5a
under Ar	23	38	31
degassed solvent	37	27	33
under air	14	36	47

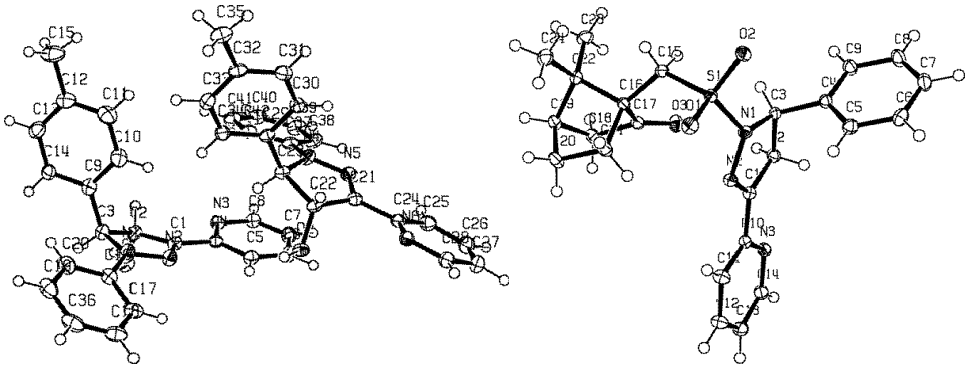


Figure 2. X-Ray determined structures for 4-hydroxy-2-pyrazoline **4a** (left hand) and *N*-sulfonyl-2-pyrazoline **8** (right hand).

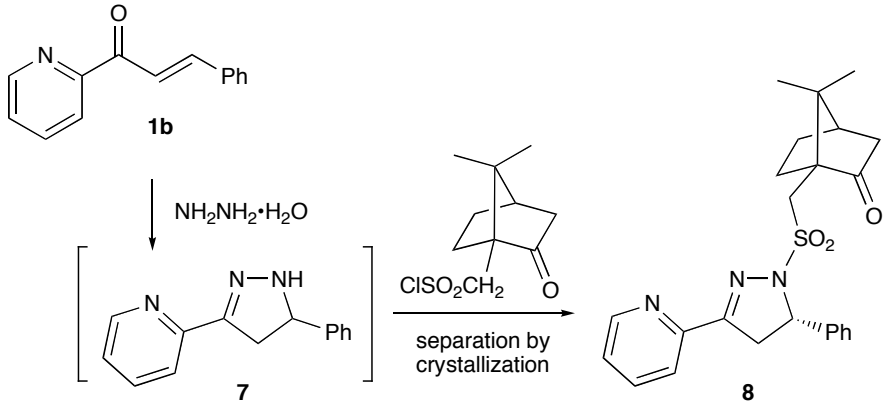
Other catalysts such as $Co(ClO_4)_2$•$6H_2O$, $Cu(OTf)_2$, $Sc(TfO)_3$, AgOTf, $Ni(OAc)_2$•$4H_2O$, $AlCl_3$, $MgBr_2$, $Pd(OAc)_2$ produced mixtures of **3a**, **4a**, and/or pyrazole derivative **5a** (see Table 1 in Experimental section). No cyclization product was produced from the hydrazone **6a** of ethyl carbazate under similar catalytic conditions.

It was found that pyrazoline **3a** was slowly dehydrogenated into pyrazole **5a** even in the absence of Lewis acid catalysts, but faster in the presence of the catalysts, indicating that pyrazole **5a** as dehydrogenated product was the secondary product of **3a**; the yield of **5a** was increased especially when the reaction time became long. On the other hand, 4-hydroxypyrazoline **4a** was not produced on treatment of pyrazoline **3a** under the reaction conditions using Lewis acid catalysts. Presumably, **4a** was produced from the *N*-metalated enamine intermediate **A** (LA: Lewis acid) through the air oxidation.

When the cyclization reaction of **2a** was performed, with a catalytic amount of titanium dibromide diisopropoxide in CH_2Cl_2 at rt, even under argon atmosphere and in the degassed CH_2Cl_2, 4-hydroxypyrazoline **4a** and pyrazole **5a** were again produced together with the desired pyrazoline **3a**, the product ratios being almost comparable. Under open air conditions, the combined yield of **4a** and **5a** was increased to 83% yield.

The second aproach to prepare the enantiomers of 2-pyrazolines includes the synthesis of *N*-unsubstituted pyrazoline **7** and substitution at the 1-nitrogen atom, followed by the optical resolution (Scheme 2). Although it was easy to prepare 5-phenyl-3-(2-pyridyl)-2-pyrazoline (**7**) by treatment of 3-phenyl-1-(2-pyridyl)-2-propen-1-one (**1b**) with hydrazine hydrate (2 equiv) in ethanol,[4] **7** was too unstable to be purified through silica gel column chromatography to give a mixture of **7** and dehydrogenated product. Pyrazoline **7** could be stored at rt only for a few hours.[5,6] Accordingly, the crude **7** separated from the reaction mixture was immediately converted to *N*-sulfonyl derivative **8** in 71% yield on treatement with (1*S*)-(+)-10-camphorsulfonyl chloride and triethylamine (2 equiv) at 0 °C for 24 h in CH_2Cl_2. It was our delight that a pure diastereomer of **8** (dr = 100:1 by ^{1}H NMR) could be obtained when the 1:1 diastereomer mixture of **8** was purified by crystallization from ethyl acetate/diethyl ether, while purification only with ethyl acetate failed (dr = 3:2). The enantiomer isolated by crystallization of **8** was the *S*-enantiomer.

Scheme 2. The chiral resolution of *N*-unsubstituted pyrazoline **8**.

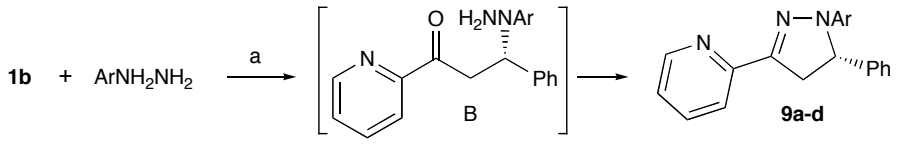


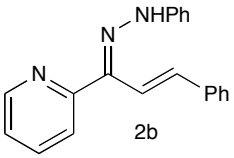
The pure enantiomer of **7** was expected to obtain by removal of the *N*-sulfonyl group from the pure diastereomer of **8** separated. However, this was not the case observed. Due to the unusually low stability of **7**,[6] it was totally unsuccessful to obtain the pure enantiomer of **7** and further transformation into *N*-alkylated derivatives failed.

The last approach includes the Lewis acid catalyzed enantioselective reactions of enone **1b** with a variety of arylhydrazines (Scheme 3). The reaction of **1b** with *p*-methylphenylhydrazine in the presence of a catalytic amount (10 mol%) of the 3a*S*,8a*R*-indaBox complex[7] of $Ni(OAc)_2•4H_2O$ in *i*-PrOH was complete in 1 h at rt to give pyrazoline **9b** in 70% yield. Although the enantioselectivity was only moderate (54% ee), a pure enantiomer (99% ee) of **9b** was obtained by single crystallization from isopropyl alcohol. Other indaBox metal complexes derived from $Zn(OAc)_2•2H_2O$ (33% after 24 h, 58% ee) and $Co(OAc)_2•4H_2O$ (20% after 24 h, 46% ee) were also found to be active catalysts in the reactions of **1b** with *p*-methylphenylhydrazine, but both the reactivity and selectivity remained unsatisfactory enough. $Mg(OAc)_2•4H_2O$ gave the racemic product of **9b** (58% after 24 h).

Similar reactions of phenylhydrazine, *p*-chlorophenylhydrazine, and p-bromophenylhydrazine with 3-phenyl-1-(2-pyridyl)-1-propenone (**1b**) were performed in the presence of the indaBox complex of $Ni(OAc)_2•4H_2O$ in *i*-PrOH at rt gave the corresponding pyrazoline derivatives **9a,c,d** in moderate to excellent yields with moderate enantioselectivities, respectively.

Scheme 3. Catalyzed enantioselective conjugate addition reactions of arylhydrazines to enone **1b** giving pyrazolines **9a-d**.

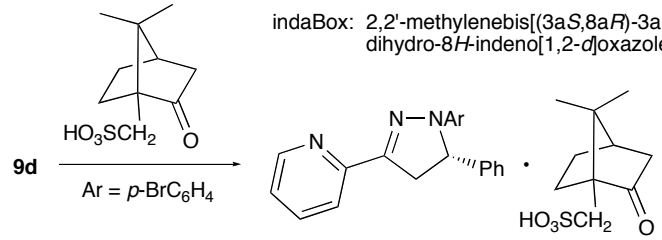




$ArNHNH_2$	Time / h	Products	Yield / %	ee/%
$PhNHNH_2$	3	**9a**	94	58
	24		94	60
p-$MeC_6H_4NHNH_2$	1	**9b**	70	54 (99)[b]
p-$ClC_6H_4NHNH_2$	1	**9c**	62	53
p-$BrC_6H_4NHNH_2$	1	**9d**	54	31

[a]indaBox / $Ni(OAc)_2•4H_2O$ (10 mol% each) in *i*-PrOH, rt.
[b]After crystallization from *i*-PrOH.

indaBox: 2,2'-methylenebis[(3a*S*,8a*R*)-3a,8a-dihydro-8*H*-indeno[1,2-*d*]oxazole]



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Intramolecular cyclization of 3-phenyl-1-(2-pyridyl)-1-propenone phenylhydrazone (**2b**) with $Ni(OAc)_2$•$4H_2O$, in a few days at rt, resulted in either no reaction or only low yield formation of **9a**, indicating that the phenylhydrazone **2b** was not the intermediate for the transformation of **1a** with phenylhydrazine into **9a** (Scheme 3). Accordingly, we concluded that the initial bond formation took place, in the reaction catalyzed with $Ni(OAc)_2$•$4H_2O$, at the α-nitrogen of phenylhydrazine to give intermediate **B** and the intramolecular condensation was quickly followed. This reaction provides the first example of chiral pyrazoline synthesis through the enantioselective hydrazine conjugate addition reactions, albeit both the yields and selectivities are far from the satisfactory levels.[8]

Absolute configuration of the major enantiomer of **9** was determined to be the (5*S*)-enantiomers on the basis of X-ray analysis of the 1:1 salt **10** produced from pyrazoline **9d** and (1*S*)-(+)-10-camphorsulfonic acid as shown in Figure 3.

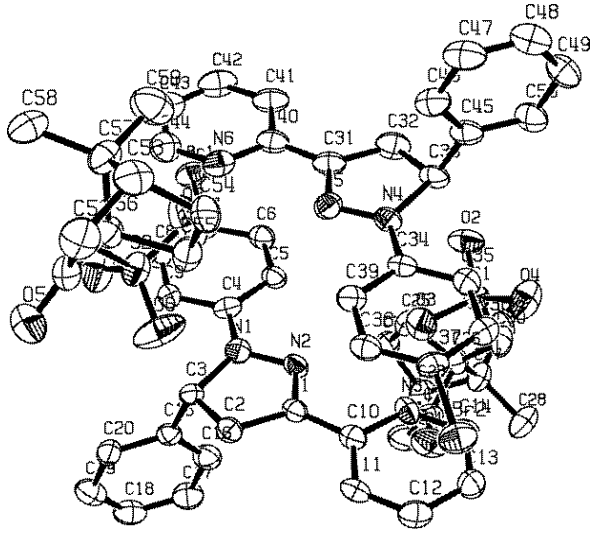

Figure 3. X-Ray determined structures for the salt **10** derived from **9d** and (1*S*)-(+)-10-camphorsulfonic acid, in which each two molecules are included in a unit cell. Hydrogens are all omitted for clarity.

EXPERIMENTAL

Cyclization of the phenylhydrazones 2a in the presence of Lewis acid giving pyrazoline 3a:

As a typical example, the reaction of **2a** with an equimolar amount of of $TiCl_4$ is described below: To the orange colored solution of 3-(*p*-methylphenyl)-1-(2-pyridyl)-1-propenone phenylhydrazone (**2a**, 313 mg, 1 mmol) in dry CH_2Cl_2 (10 mL, 0.1 M) was slowly added at 0 °C $TiCl_4$ (190 mg, 1 mmol), and the mixture was stirred at rt for 10 min. The mixture was poured into saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (15 mL x 3). The combined extracts were dried over magnesium sulfate and evaporated in vacuo. The residue was purified through column chromatography over silica gel with hexane/ethyl acetate (5/1 v/v) to give 5-(*p*-methylphenyl)-1-phenyl-3-(2-pyridyl)-2-pyrazoline (**3a**, 210 mg, 67% yield).

3a: Yellow needles from EtOH; mp 127-128 °C; ^{1}H NMR ($CDCl_3$): δ = 2.31 (3H, s, *p*-Me), 3.30 (1H, dd, J = 18.0 and 7.2 Hz, one of H4), 3.96 (1H, dd, J = 18.0 and 12.8 Hz, the other of H4), 5.33 (1H, dd, J = 12.8 and 7.2 Hz, H5), 6.80 (1H, dd, J = 7.6 and 5.2 Hz, H5'), 7.09-7.21 (9H, *p*-MeC_6H_4 and Ph), 7.69 (1H, t, J = 7.6 Hz, H4'), 8.13 (1H, d, J = 7.6 Hz, H3'), and 8.53 (1H, d, J = 5.2 Hz, H6'); ^{13}C NMR ($CDCl_3$): δ = 21.10, 43.17, 64.39, 113.54, 119.46, 120.60, 122.58, 125.71, 128.93, 129.74, 135.87, 137.13, 139.32, 144.31, 148.00, 149.11, and 152.21; MS (rel. intensity, %) m/z = 313 (M^+, 91), 312 (28), 223 (17), 222 (base peak), 195 (29), and 194 (23); HRMS Found: m/z = 313.1576. Calcd for $C_{21}H_{19}N_3$: m/z = 313.1579. EA. Anal. Calcd for $C_{21}H_{19}N_3$: C, 80.48; H, 6.11; N, 13.41. Found: C, 80.35; H, 6.03; N, 13.36.

Results of the cyclization reactions using other catalysts are summarized in Table 1.

Table 1. Cyclization of the phenylhydrazones **2a** in the presence of Lewis acid.

				Yield/%		
Catalyst	mol%	Solvent	Time/h	**3a**	**4a**	**5a**
$Ni(ClO_4)_2$•$6H_2O$	10	CH_2Cl_2	48	0	37	0
$Zn(OTf)_2$	10	CH_2Cl_2	48	0	39	0
$Mg(ClO_4)_2$	10	CH_2Cl_2	48	0	48	0
$Co(ClO_4)_2$•$6H_2O$	10	CH_2Cl_2	36	2	31	43
$Cu(OTf)_2$	10	CH_2Cl_2	136	0	13	55
$Yb(OTf)_3$	10	CH_2Cl_2	120	11	17	0
$Sc(OTf)_3$	10	CH_2Cl_2	72	2	35	34
AgOTf	10	CH_2Cl_2	72	0	49	34
$Ni(OAc)_2$•$4H_2O$	10	THF	120	0	40	42
$AlCl_3$	10	CH_2Cl_2	72	0	38	47
$MgBr_2$	10	CH_2Cl_2	72	0	35	43
$TiCl_4$	10	CH_2Cl_2	48	22	22	36
$TiCl_4$	100	CH_2Cl_2	10 min	67	0	0

A Sequence of cyclization and air oxidation of phenylhydrazones 2a in the presence of Lewis acid giving 4-hydroxypyrazoline 4a:

As a typical example, the reaction of hydrazone **2a** with a catalytic amount of $Mg(ClO_4)_2$ is described: An orange colored suspension of 3-(*p*-methylphenyl)-1-(2-pyridyl)-1-propenone phenylhydrazone (**2a**, 313 mg, 1 mmol) and a catalytic amount (10 mol%) of $Mg(ClO_4)_2$ (22 mg, 0.1 mmol) in dry CH_2Cl_2 (10 mL, 0.1 M) was stirred for 48 h at rt. After the reaction is over (checked by tlc), this solution was poured into saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (15 mL x 3). The combined extracts were dried over magnesium sulfate and evaporated in vacuo. The residue was purified through column chromatography over silica gel with hexane/EtOAc (5/1 v/v) to give 4-hydroxy-5-(*p*-methylphenyl)-1-phenyl-3-(2-pyridyl)-2-pyrazoline (**4a**, 163 mg, 48% yield).

4a: Yellow needles from EtOH; mp 156-157 °C; ^{1}H NMR ($CDCl_3$): δ = 2.24 (3H, s, *p*-Me), 5.13 (1H, d, J = 3.2 Hz,H4), 5.36 (1H, d, J = 3.2 Hz, H5), 6.84 (1H, dd, J = 5.2 and 4.0 Hz, H5'), 7.12-7.26 (9H, m,

p-MeC_6H_4 and Ph), 7.72 (1H, ddd, J = 5.6, 5.2, and 1.2 Hz, H4'), 8.08 (1H, d, J = 5.6 Hz, H3'), and 8.45 (1H, d, J = 4.0 Hz, H6'); ^{13}C NMR ($CDCl_3$): δ = 21.12, 72.11, 83.81, 113.92, 120.28, 120.48, 122.76, 125.83, 128.96, 129.86, 136.24, 136.61, 137.56, 143.78, 147.16, 148.70, and 152.01; MS (rel. intensity, %) m/z = 329 (22, M+), 312 (23), 311 (base peak), 310 (66), 196 (24), 195 (29), and 105 (19). EA. Anal. Calcd for $C_{21}H_{19}N_3O$: C, 76.57; H, 5.81; N, 12.76. Found: C, 76.43; H, 5.85; N, 12.79.

Pyrazoline synthesis from 3-phenyl-1-(2-pyridyl)-2-propen-1-one (1b) and hydrazine, followed by *N*-sulfonylation with a chiral sulfonyl chloride giving 8: To a solution of 3-phenyl-1-(2-pyridyl)-2-propen-1-one (**1b**, 0.2 g, 1 mmol) in EtOH (1 mL) was added hydrazine monohydrate (0.05 g, 1 mmol). After the resulting solution was sirred at rt for 2 h, saturated aqueous NH_4Cl was added and extracted with CH_2Cl_2 (30 mL x 3). The combined extracts were dried with Na_2SO_4 and evaporated in vacuo. The residue was dissolved in a new portion of CH_2Cl_2 (10 mL) and this was cooled to –78 °C. (1S)-(+)-10-camphorsulfonyl chloride (0.38 g, 1.5 mmol) was slowly added. Stirring was continued at –78 °C for 24 h and poured into saturated aqueous NH_4Cl. The resulting mixture was extracted with with CH_2Cl_2 (30 mL x 3). The combined extracts were dried with Na_2SO_4 and evaporated in vacuo. The reside was chromatographed on silica gel with hexane/ethyl acetate (1:1 v/v) to give **8** (311 mg, 71%) as a 1:1 mixture of diastereomers, which was then crystallized from EtOAc /Et_2O to give S-enantiomer of **8**.

8: Colorless needles from EtOAc/hexane; mp 194-196 °C; ^1H NMR ($CDCl_3$): d = 0.90, 1.14 (each 3H, s, Me), 1.37 (1H, ddd, *J* = 8.8, 6.4, and 2.8 Hz, one of H5'), 1.59 (1H, ddd, *J* = 8.8, 5.6, and 2.8 Hz, one of H6'), 1.85 (1H, d, *J* = 11.6 Hz, one of H3'), 2.02 (1H, m, the other of H5'), 2.07 (1H, t, *J* = 2.8, H4'), 2.34 (1H, dt, *J* = 11.6, and 2.8 Hz, the other of H3'), 2.51 (1H, ddd, *J* = 7.6 and 2.8 Hz, the other of H6'), 3.15 (1H, d, *J* = 10.0 Hz, one of CH_2SO_2), 3.43 (1H, dd, *J* = 12.4 and 5.6 Hz, one of H4 of Pyz), 3.49 (1H, d, *J* = 10.0 Hz, the other of CH_2SO_2), 4.05 (1H, dd, *J* = 12.4 and 8.0 Hz, the other of H4 of Pyz), 5.46 (1H, *J* = 8.0 and 5.6 Hz, H5 of Pyz), 7.31 (1H, dd, *J* = 6.0 and 3,6, H5 of 2-Py), 7.35-7.42 (5H, m, Ph), 7.75 (1H, dd, *J* = 6.0 and 5.2 Hz, H4 of 2-Py), 8.16 (1H, d, *J* = 5.2, H3 of 2-Py), and 8.59 (1H, d, *J* = 3.6 Hz, H6 of 2-Py); ^{13}C NMR ($CDCl_3$): δ = 19.80, 20.13, 25.28, 26.84, 42.52, 43.01, 43.64, 47.63, 47.82, 58.63, 64.34, 121.81, 124.57, 126.79, 128.09, 128.80, 136.30, 141,20, 149.32, 150.22, 157.62, and 214.87; MS (rel. intensity, %) m/z = 437 (M^+, 6), 265 (17), 223 (base peak), 222 (65), 215 (13), 195 (10), 194 (59), 193 (24), 192 (11), 151 (21), 146 (56), 123 (26), and 109 (25); HRMS Found: m/z = 437.1769. Calcd for $C_{24}H_{27}N_3O_3S$: m/z = 437.1773. EA. Anal. Calcd for $C_{24}H_{27}N_3O_3S$: C, 65.88; H, 6.22; N, 9.60. Found: C, 65.88; H, 6.24; N, 9.61.

Enantioselective conjugate addition reactions of 3-phenyl-1-(2-pyridyl)-1-propenone (1b) with arylhydrazines giving 3-pyrazolines 9a-d:

As a typical example, reaction between 3-phenyl-1-(2-pyridyl)-1-propenone (**1b**) and phenylhydrazine is given as follows: A solution of *i*-PrOH (2 mL, 0.1 M) of nickel(II) acetate tetrahydrate (5 mg, 0.02 mmol) and 2,2'-methylenebis[(3a*S*,8a*R*)-3a,8a-dihydro-8*H*-indeno[1,2-*d*]oxazole] (6.6 mg, 0.02 mmol) was stirred at rt for 3 h. To the resulting solution were added in this order Molecular Sieves 4A (100 mg, 500 mg/mmol), phenylhydrazine (0.2 μL, 0.2 mmol), and 3-phenyl-1-(2-pyridyl)-1-propenone (**1b**, 42 mg, 0.2 mmol). The stirring was continued at rt for additional 3 h, while the reaction was monitored by tlc. After the completion of reaction (checked by tlc), the mixture was filtered through a short silica gel column with hexane/EtOAc (1:1 v/v) as eluent, followed by purification through column chromatography over silica gel with hexane/EtOAc (6:1 v/v) to give 1,5-diphenyl-3-(2-pyridyl)-2-pyrazoline[9] (**9a**, 56 mg, 94%) with the enantioselectivity of 54% ee. The pure enantiomer of **9a** was provided through crystallization from *i*-PrOH.

9a: Enantioselectivity of this compound was determined to be 54% ee through the chiral hplc analysis using a Daicel OD-H chiral column with hexane/*i*-PrOH 9:1 v/v (flow rate: 1 mL/min).

Other derivatives **9b-d** were similarly produced and their spectral data are given below.

1-(*p*-Methylphenyl)-5-phenyl-3-(2-pyridyl)-2-pyrazoline (9b): Yellow solid from EtOAc / hexane; mp 144-145 °C; ^{1}H NMR ($CDCl_3$): δ = 2.24 (3H, s, *p*-Me), 3.30 (1H, dd, *J* = 18.0 and 7.6 Hz, one of H-4), 3.97 (1H, dd, *J* = 18.0 and 12.4 Hz, the other of H-4), 5.32 (1H, dd, *J* = 12.4 and 7.6 Hz, H-5), 7.17 (1H, dd, *J* = 6.8 and 4.8 Hz, H-5'), 7.26-7.32 (9H, m, Ar), 7.68 (1H, *J* = 8.2 and 6.8 Hz, H-4'), 8.13 (1H, d, *J* = 8.2 Hz, H-3'), and 8.53 (1H, d, *J* = 4.8 Hz, H-6'); ^{13}C NMR ($CDCl_3$): δ = 20.40, 42.88, 64.54, 113.06, 119.98, 121.90, 125.23, 126.85, 128.23, 128.44, 128.86, 135.22, 141.47, 141.74, 146.76, 148.39, and 151.53; MS (rel. intensity, %) m/z = 314 (M^++1, 16), 313 (M^+, 66), 312 (19), 279 (22), 237 (17), 236 (93), 167 (34), 150 (12), 149 (base peak), 134 (16), 121 (13), 120 (11), 113 (15), 112 (13), 111 (15), 109 (14), 105 (25), 104 (14), 97 (23), 96 (10), 95 (20), 91 (37), 85 (19), 84 (10), 83 (27), 82 (12), 81 (20), 78 (11), and 77 (16). HRMS Found: m/z = 313.1578. Calcd for $C_{21}H_{19}N_3$: m/z = 313.1579.

1-(*p*-Chlorophenyl)-5-phenyl-3-(2-pyridyl)-2-pyrazoline (9c): Yellow solid from EtOAc / hexane; mp 160-161 °C; ^{1}H NMR ($CDCl_3$): δ = 3.34 (1H, dd, *J* = 17.9 and 6.8 Hz, one of H-4), 3.99 (1H, dd, *J* = 17.9 and 12.5 Hz, the other of H-4), 5.32 (1H, dd, *J* = 12.5 and 6.8 Hz, H-5), 7.05, 7.13 (each 2H, d, *J* = 9.2 Hz, *p*-BrC_6H_4), 7.20 (1H, dd, *J* = 6.8 and 5.8 Hz, H-5'), 7.26-7.35 (5H, m, Ph), 7.71 (1H, dd, *J* = 8.2 and 6.8 Hz, H-4'), 8.12 (1H, d, *J* = 8.2 Hz, H-H-3'), and 8.54 (1H, d, *J* = 5.8, H-6'); ^{13}C NMR ($CDCl_3$): δ = 43.07, 64.25, 114.10, 120.10, 122.29, 123.74, 125.14, 127.11, 128.24, 128.58, 135.33, 141.09, 142.12, 147.94, 148.49, and 151.15; MS (rel. intensity, %) m/z = 335 (M^++2, 22), 334 (M^++1, 21), 333 (M^+, 65), 332 (21), 258 (33), 257 (17), 256 (base peak), 149 (21), and 125 (13). HRMS Found: m/z = 333.1038. Calcd for $C_{20}H_{16}N_3Cl$: m/z = 333.1033. EA. Anal. Calcd for $C_{20}H_{16}N_3Cl$: C, 71.96; H, 4.83; N, 12.59. Found: C,

71.47; H, 4.83; N, 12.48.

1-(*p*-Bromophenyl)-5-phenyl-3-(2-pyridyl)-2-pyrazoline (9c): Yellow solid from EtOAc / hexane; mp 167-169 °C; ^{1}H NMR ($CDCl_3$): δ = 3.34 (1H, dd, *J* = 17.9 and 6.8 Hz, one of H-4), 3.99 (1H, dd, *J* = 17.9 and 12.6 Hz, the other of H-4), 5.32 (1H, dd, *J* = 12.6 and 6.8 Hz, H-5), 6.91, 7.32 (each 2H, d, *J* = 8.7 Hz, *p*-BrC_6H_4), 7.20 (1H, dd, *J* = 7.7 and 4.9 Hz, H-5'), 7.25-7.27 (5H, m, Ph), 7.71 (1H, dd, *J* = 8.2 and 6.7 Hz, H-4'), 8.12 (1H, d, *J* = 8.2 Hz, H-3'), and 8.54 (1H, d, *J* = 4.9, H-6'); ^{13}C NMR ($CDCl_3$): δ = 43.07, 64.15, 111.11, 114.55, 120.12, 122.31, 125.12, 127.13, 128.59, 135.34, 141.02, 142.51, 148.03, 148.50, and 151.12; MS (rel. intensity, %) m/z = 379 (M^++2, 15), 377 (M^+, 16), 302 (22), 300 (22), 279 (23), 167 (37), 150 (12), 149 (base peak), 121 (20), 120 (12), 113 (14), 112 (11), 97 (12), 95 (11), 91 (13), 85 (10), 83 (17), and 81 (12). HRMS Found: m/z = 377.0526. Calcd for $C_{20}H_{16}N_3Br$: m/z = 377.0528. EA. Anal. Calcd for $C_{20}H_{16}N_3Br$: C, 63.50; H, 4.26; N, 11.11. Found: C, 62.43; H, 4.32; N, 10.78.

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5. Heating or treatment through silica gel column chromatography gives a mixture of many products including the corresponding pyrazole derivative made by dehydrogenation of **7**.
6. Instability of 2-pyrazoline derivatives without substituent at 1-position is due to either the ready

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