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CATALYTIC ASYMMETRIC SYNTHESIS OF CHIRAL 4-PYRAZOLYLALKANOLS BY THE ENANTIOSELECTIVE ALKYLATION OF PYRAZOLE-4-CARBALDEHYDES WITH DIALKYLZINCS

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Abstract - (1S,2R)-N,N-Dialkylnorephedrines catalyze the enantioselective alkylation of various pyrazole-4-carbaldehydes with dialkylzincs. Enantiomerically enriched secondary-4-pyrazolylalkanols with up to 95% e.e. were obtained.

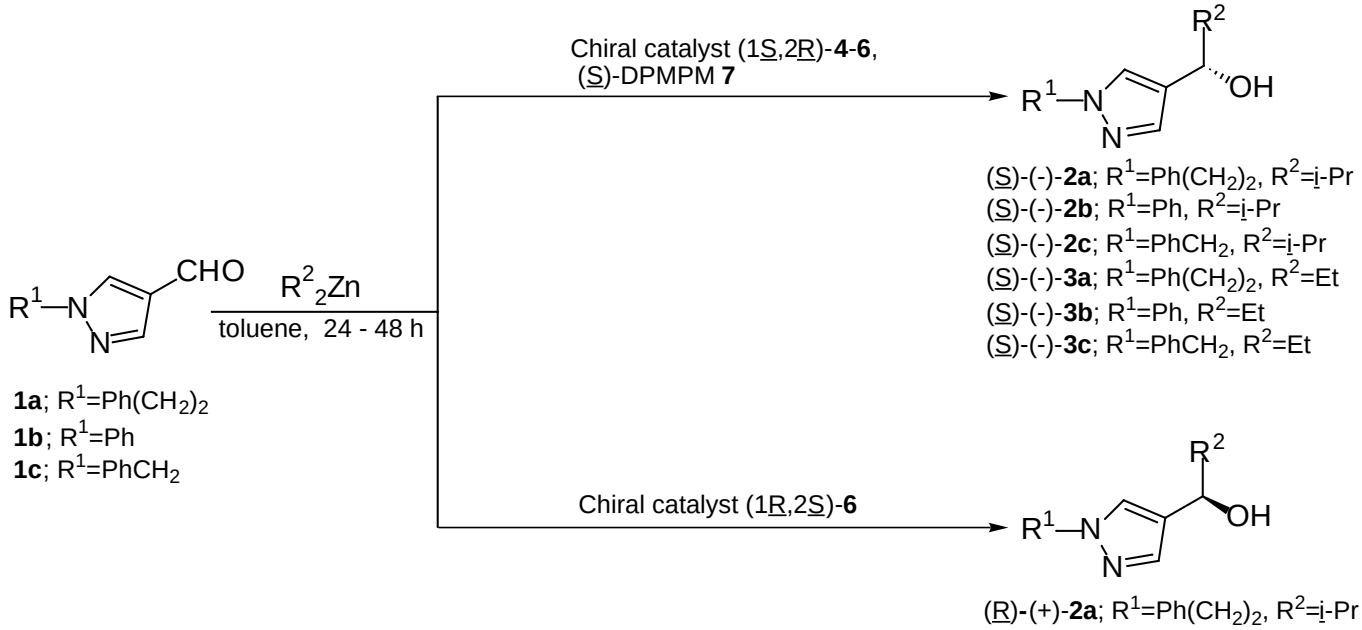
Chiral compounds possessing a pyrazole ring[1] have been utilized as chiral ligands in asymmetric synthesis.[2] Meanwhile, pyrazole ring is a fundamental skeleton of potential bioisosters of thromboxane–synthetase inhibitor possessing a physiological activity.[3] To our knowledge, however, there have been very few reports on an efficient asymmetric synthesis of chiral compounds possessing a pyrazole ring. On the other hand, we previously reported enantioselective alkylation of aldehydes possessing heterocyclic rings in the presence of chiral amino alcohols as asymmetric catalysts.[4]

In this paper, we report a highly enantioselective alkylation of 1-substituted pyrazole-4-carbaldehydes with dialkylzincs for the preparation of enantiomerically enriched 4-pyrazolylalkanols (Scheme 1).

Firstly, we examined an enantioselective isopropylation of 1-(2-phenylethyl)pyrazole-4-carbaldehyde (**1a**) using diisopropylzinc (i-Pr_2Zn) in the presence of chiral amino alcohols (**4**-**7**). The results are summarized in Table 1. When (1S,2R)-N,N-dipropylnorephedrine (**4**) (DPNE)[4] (20 mol%) was employed as an asymmetric catalyst, the reaction proceeded smoothly to give the corresponding chiral pyrazolylalkanol ((S)-(-)-**2a**) with 94% e.e. in 81% yield (Entry 1). The reaction using (1S,2R)-N,N-dibutylnorephedrine (**5**) (DBNE)[5] (20 mol%) gave (S)-(-)-**2a** with 92% e.e. in 76% yield (Entry 2). The e.e. of (S)-(-)-**2a** reached 95% when 50 mol% of **5** was used (Entry 3). The reaction using (1S,2R)-2-pyrrolidinyl-1-phenylpropanol (**6**) (PPP)[5b,6] as a chiral catalyst also gave optically active (S)-(-)-**2a** with high enantiomeric enrichment (89% e.e., Entry 4). When the reaction was run at room temperature, the yield of **2a** increased up to 85% without a decrease in the enantioselectivity (88% e.e.) (Entry 5). Furthermore, by using an asymmetric catalyst with the opposite configuration, i.e., (1R,2S)-**6**, it was possible to synthesize optically active (R)-(+)-**2a** with 89% e.e. (Entry 6). The reaction using (S)-diphenyl(1-methylpyrrolidin-2-yl)methanol (**7**) (DPMPM)[7] at 0 ˚C gave (S)-(-)-**2a** with 87% e.e. in a moderate yield (Entry 7).

Next, various 1-substituted pyrazole-4-carbaldehydes (**1a**-**c**) were subjected to the enantioselective

Scheme 1.



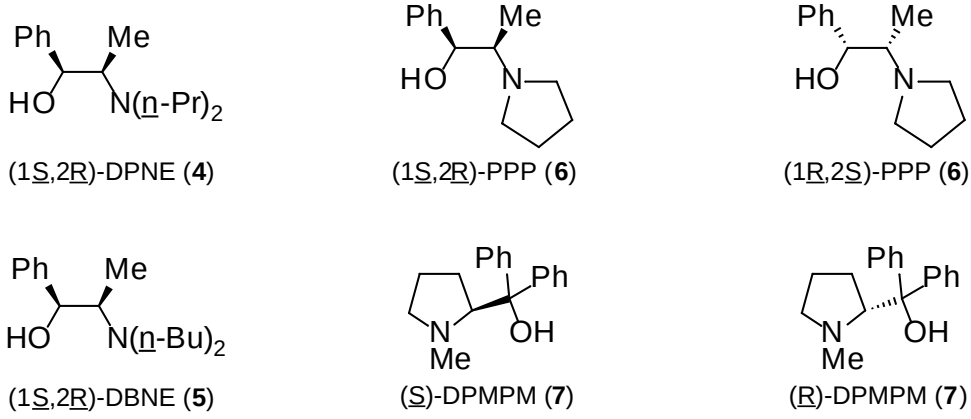
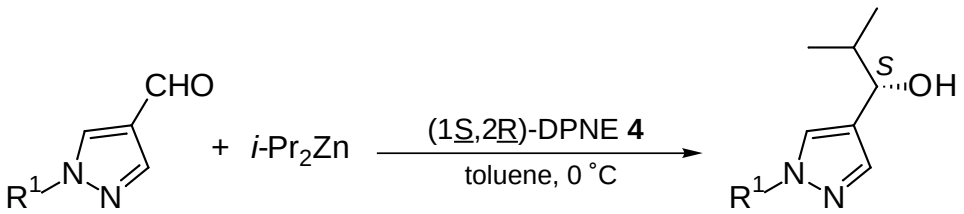


Table 1. Enantioselective synthesis of **2a** using chiral amino alcohols (**4**-**7**)

Entry	Chiral catalyst		Temp. (˚C)	Pyrazolylalkanol (**2a**)		
				Yield (%)	E.e.[a] (%)	Configuration[b]
1[c]	(1S,2R)-DPNE	**4**	0	81	94	S
2[c]	(1S,2R)-DBNE	**5**	0	76	92	S
3[d]	(1S,2R)-DBNE	**5**	0	87	95	S
4[c]	(1S,2R)-PPP	**6**	0	59	89	S
5[e]	(1S,2R)-PPP	**6**	rt	85	88	S
6[e]	(1R,2S)-PPP	**6**	rt	92	89	R
7[c]	(S)-DPMPM	**7**	0	47	87	S
8[f]	(S)-DPMPM	**7**	rt	87	62	S

[a] Determined by HPLC analyses using a chiral column (Chiralcel OD-H). [b] Absolute configuration was estimated by the modified Mosher's method (ref. 8). [c] Molar ratio. Chiral catalyst : **1a** : i-Pr_2Zn = 0.2 : 1.0 : 2.2. [d] Molar ratio. Chiral catalyst : **1a** : i-Pr_2Zn = 0.5 : 1.0 : 3.5. [e] Molar ratio. Chiral catalyst : **1a** : i-Pr_2Zn = 0.2 : 1.0 : 6.2. [f] Molar ratio. Chiral catalyst : **1a** : i-Pr_2Zn = 0.2 : 1.0 : 3.2.

isopropylation (Table 2). When **1a-c** were treated with i-Pr_2Zn using (1S,2R)-**4** (20 mol%) as a chiral catalyst, chiral pyrazolylalkanols ((S)-(-)-**2a-c**) with high e.e.s of 94-95% were obtained in good to high yields (73-81%) (Entries 1-3).



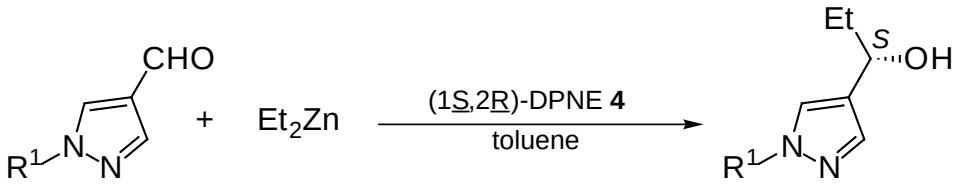
1a-c **2a-c**

Table 2. Enantioselective isopropylation of **1a-c** using (1S,2R)-DPNE (**4**) as a chiral catalyst

Entry	R^1		**2a-c**			
				Yield (%)	E.e. (%)	
1[a]	Ph $(CH_2)_2$	**1a**	**2a**	81	94[b]	S
2[a]	Ph	**1b**	**2b**	80	95[b]	S[c]
3[d]	Ph CH_2	**1c**	**2c**	73	95[e]	S[c]

[a] Molar ratio. Chiral catalyst **4** : **1a-c** : i-Pr_2Zn = 0.2 : 1.0 : 2.2. [b] Determined by HPLC analysis using a chiral column (Chiralcel OD-H). [c] Absolute configuration was estimated by the analogy with **2a**. [d] Molar ratio. Chiral catalyst **4** : **1a-c** : i-Pr_2Zn = 0.2 : 1.0 : 3.0. [e] Determined by HPLC analysis using a chiral column (Chiralcel OD).

We also examined the ethylation of aldehydes (**1a-c**) with diethylzinc in the presence of (1S,2R)-DPNE (**4**) as an asymmetric catalyst. As shown in Table 3, the enantioselective ethylation proceeded to give chiral pyrazolylalkanols ((S)-(-)-**3a-c**) with 71-89% e.e.



1a-c **3a-c**

Table 3. Enantioselective ethylation of **1a-c** using (1S,2R)-DPNE (**4**) as a chiral catalyst

Entry[a]	R^1		Temp. (˚C)	**3a-c**		
				Yield (%)	E.e.[b] (%)	
1	Ph $(CH_2)_2$	**1a**	0	**3a**	41	85
2	Ph $(CH_2)_2$	**1a**	rt	**3a**	79	71
3	Ph	**1b**	rt	**3b**	86	89
4	Ph CH_2	**1c**	rt	**3c**	93	71

[a] Molar ratio. Chiral catalyst **4** : **1a-c** : Et_2Zn = 0.2 : 1.0 : 2.2. [b] Determined by HPLC analyses using a chiral column (Chiralcel OD-H). Absolute configuration were estimated by the analogy with **2a**.

The treatment of **1a** with Et_2Zn using (1S,2R)-**4** at 0 ˚C gave optically active (S)-(-)-**3a** in a moderate yield with a high e.e. of 85% (Entry 1). The yield of **3a** increased up to 79% at room temperature with a decrease in e.e. (71%, Entry 2). Especially, enantioselective ethylation of 1-phenylpyrazole-4-carbaldehyde (**1b**) gave the corresponding chiral (S)-(-)-**3b** with a high e.e. of 89% in a high yield of 86% (Entry 3).

In summary, optically active pyrazolylalkanols (**2a-c**) and (**3a-c**) with up to 95% e.e. were prepared by the enantioselective addition of dialkylzincs to pyrazole-4-carbaldehydes in the presence of catalytic amounts of chiral amino alcohols (**4-7**).

EXPERIMENTAL

General. Optical rotations were measured by Jasco DIP-1000 polarimeter. IR spectra were recorded with Horiba FT-210 spectrophotometer. ^1H and ^{13}C NMR spectra were measured with Bruker DPX300 spectrometer using tetramethylsilane as an internal standard and $CDCl_3$ was used as a solvent. High resolution mass spectra (HRMS) were obtained with Hitachi M-80B or JEOL JMS-AX505HA mass spectrometer. Toluene was distilled from calcium hydride and dried over molecular sieves 4A. All reactions were carried out under an argon atmosphere. Pyrazole-4-carbaldehydes (**1b**)[9] and (**1c**)[10] were prepared according to the literature procedures.

Preparation of 1-(2-phenylethyl)pyrazole-4-carbaldehyde (1a). To a solution of 4-bromo-1-(2-phenylethyl)pyrazole (170 mg, 0.68 mmol) in THF (5 mL) was added dropwise at -100 ˚C a 1.53 M solution of n-BuLi in hexane (0.44 mL, 0.68 mmol) and ethyl formate (0.16 mL, 2.0 mmol) successively. After stirring for 30 min, the reaction was quenched by the addition of a mixed solvent (10 mL) of water and THF (1/1, *v*/*v*) at -100 ˚C. The temperature was raised up to rt, and the mixture was extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressures. Purification of the residue by TLC on silica gel (developing solvent. hexane : acetone = 1 : 1) afforded pyrazole-4-carbaldehyde (**1a**). Colorless plate (recrystallized from hexane– ethyl acetate). 50.7 mg. Yield 37%. mp 68.5-70.0 ˚C; IR (KBr) 1668 cm^{-1}; ^1H NMR δ= 3.18 (t, J= 7.0 Hz, 2H), 4.38 (t, J= 7.0 Hz, 2H), 7.03-7.30 (m, 5H), 7.63 (s, 1H), 7.98 (s, 1H), 9.76 (s, 1H); ^{13}C NMR δ= 36.2, 54.1, 123.8, 126.9, 128.5, 128.7, 133.0, 137.1, 140.8, 183.9; HRMS found m/z 200.0952, calcd for $C_{12}H_{12}N_2O$: 200.0952.

General procedure for the enantioselective alkylation of pyrazole-4-carbaldehydes (1a-c) using amino alcohols (4-7) as chiral catalysts. To a solution of chiral amino alcohols (**4-7**) (0.1 mmol) in toluene (7.2 mL), 1 M toluene solution of dialkylzincs (1.1 mL, 1.1 mmol) were added at 0 ˚C and the mixture was stirred for 20 min. After addition of pyrazole-4-carbaldehyde (**1a-c**) (0.5 mmol) in toluene (3 mL) and the mixture was stirred for 24-48 h at 0 ˚C, the reaction was quenched at 0 ˚C by the addition of 1 M HCl (5 mL) followed by sat. aq. sodium bicarbonate (15 mL). The resultant mixture was filtered through celite and the filtrate was extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressures. Purification of the crude mixture on silica gel TLC gave pyrazolylalkanols (**2a-c**) and (**3a-c**).

(S)-(-)-2-Methyl-1-[1-(2-phenylethyl)-4-pyrazolyl]-1-propanol (2a). Colorless oil. 99.2 mg. Yield 81%. Enantiomeric enrichment of **2a** was determined to be 94% e.e. by HPLC analysis using a chiral

column (Daicel Chiralcel OD-H: 4 x 250 mm, 220 nm UV detector, rt, eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 31.4 min for the minor isomer and 40.4 min for the major isomer). $[\alpha]^{29}_{D}$ –13.1° (c 1.1, MeOH) [prepared in the presence of (1S, 2R)- DPNE (**4**)]; IR (neat) 3332 cm^{-1}; ^{1}H NMR δ= 0.79 (d, J= 6.7 Hz, 3H), 0.90 (d, J= 6.7 Hz, 3H), 1.84 (dqq, J= 6.3, 6.7, 6.7 Hz, 1H), 2.90 (brs, 1H), 3.08 (t, J= 7.2 Hz, 2H), 4.23 (t, J= 7.2 Hz, 2H), 4.32 (d, J= 6.3 Hz, 1H), 7.00-7.27 (m, 1H+5H), 7.38 (s, 1H); ^{13}C NMR δ= 18.0, 18.1, 34.5, 36.6, 53.3, 71.6, 123.7, 126.3, 127.4, 128.2, 128.4, 137.4, 137.8; HRMS found m/z 244.1583, calcd for $C_{15}H_{20}N_2O$: 244.1577. Anal. Calcd for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.47. Found: C, 73.57; H, 8.18; N, 11.46.

(S)-(-)-2-Methyl-1-(1-phenyl-4-pyrazolyl)-1-propanol (2b). Colorless oil. 86.0 mg. Yield 80%. Enantiomeric enrichment of **2b** was determined to be 95% e.e. by HPLC analysis using a chiral column (Daicel Chiralcel OD-H: 4 x 250 mm, 254 nm UV detector, rt, eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 17.0 min for the minor isomer and 24.1 min for the major isomer). $[\alpha]^{25}_{D}$ –16.9° (c 2.9, MeOH); IR (neat) 3396 cm^{-1}; ^{1}H NMR δ= 0.89 (d, J= 6.7 Hz, 3H), 0.93 (d, J= 6.7 Hz, 3H), 1.96 (dqq, J= 6.2, 6.7, 6.7 Hz, 1H), 2.48 (brs, 1H), 4.48 (d, J= 6.2 Hz, 1H), 7.23-7.65 (m, 1H+5H), 7.83(s, 1H); ^{13}C NMR δ= 18.0, 18.4, 34.7, 72.0, 118.8, 124.7, 126.25, 126.29, 129.3, 139.4, 139.9; HRMS found m/z 216.1263, calcd for $C_{13}H_{16}N_2O$: 216.1264.

(S)-(-)-1-(1-Benzyl-4-pyrazolyl)-2-methyl-1-propanol (2c). Colorless oil. 169 mg. Yield 73%. Aldehyde (**1c**) (187mg. 1.0 mmol) was used as a starting material. Enantiomeric enrichment of **2c** was determined to be 95% e.e. by HPLC analysis using a chiral column (Daicel Chiralcel OD: 4 x 250 mm, 220 nm UV detector, rt, eluent: 5% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 37.4 min for the minor isomer and 44.8 min for the major isomer). $[\alpha]^{22}_{D}$ –9.5° (c 1.2, MeOH); IR (neat) 3334 cm^{-1}; ^{1}H NMR δ= 0.85 (d, J= 6.7 Hz, 3H), 0.95 (d, J= 6.7 Hz, 3H), 1.86 (br s, 1H), 1.90 (dqq, J= 6.4, 6.7, 6.7 Hz, 1H), 4.41 (d, J= 6.4 Hz, 1H), 5.27 (s, 2H), 7.18-7.37 (m, 1H+5H), 7.46 (s, 1H); ^{13}C NMR δ= 18.1, 18.5, 34.8, 56.0, 72.3, 124.8, 127.3, 127.6, 128.0, 128.8, 136.5, 137.7; HRMS found m/z 230.1415, calcd for $C_{14}H_{18}N_2O$: 230.1420.

(S)-(-)-1-[1-(2-Phenylethyl)-4-pyrazolyl]-1-propanol (3a). Colorless oil. 47.1 mg. Yield 41%. Enantiomeric enrichment of **3a** was determined to be 85% e.e. by HPLC analysis using a chiral column (Daicel Chiralcel OD-H: 4 x 250 mm, 220 nm UV detector, rt, eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 30.0 min for the minor isomer and 36.2 min for the major isomer). $[\alpha]^{22}_{D}$ –7.8° (c 2.2, MeOH); IR (neat) 3332 cm^{-1}; ^{1}H NMR δ= 0.89 (t, J= 7.3 Hz, 3H), 1.73 (dq, J= 6.6, 7.3 Hz, 2H), 2.22 (brs, 1H), 3.12 (t, J= 7.3 Hz, 2H), 4.27 (t, J= 7.3 Hz, 2H), 4.54 (t, J= 6.6 Hz, 1H), 7.04-7.43 (m, 1H+5H), 7.46 (s, 1H); ^{13}C NMR δ= 10.0, 31.3, 36.9, 53.6, 67.9, 125.2, 126.6, 127.3, 128.5, 128.6, 137.3, 138.0; HRMS found m/z 230.1423, calcd for $C_{14}H_{18}N_2O$: 230.1420.

(S)-(-)-1-(1-Phenyl-4-pyrazolyl)-1-propanol (3b). Colorless oil. 81.3 mg. Yield 86%. Enantiomeric enrichment of **3b** was determined to be 89% e.e. by HPLC analysis using a chiral column (Daicel Chiralcel OD-H: 4 x 250 mm, 254 nm UV detector, rt, eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 95.9 min for the minor isomer and 66.3 min for the major isomer). $[\alpha]^{25}_{D}$ –15.2° (c 1.0, $CHCl_3$); IR (neat) 3369 cm^{-1}; ^{1}H NMR δ= 1.00 (t, J= 7.3 Hz, 3H), 1.88 (dq, J= 7.3, 6.6 Hz, 2H), 2.07 (brs, 1H), 4.71 (t, J= 6.6 Hz, 1H), 7.24-7.66 (m, 1H+5H), 7.87 (s, 1H); ^{13}C NMR δ= 10.5, 31.8,

68.5, 119.4, 124.9, 126.9, 128.1, 129.8, 139.5, 140.5; HRMS found m/z 202.1107, calcd for $C_{12}H_{14}N_2O$: M, 202.1107.

(S)-(-)-1-(1-Benzyl-4-pyrazolyl)-1-propanol (3c). Colorless oil. 101 mg. Yield 93%. Enantiomeric enrichment of **3c** was determined to be 71% e.e. by HPLC analysis using a chiral column (Daicel Chiralcel OD-H: 4 x 250 mm, 220 nm UV detector, rt, eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 20.6 min for the minor isomer and 26.4 min for the major isomer). $[\alpha]^{26}_{D}$ –6.7° (c 1.9, $CHCl_3$); IR (neat) 3338 cm^{-1}; ^1H NMR δ= 0.90 (t, J= 7.4 Hz, 3H), 1.74 (dq, J= 6.6, 7.4 Hz, 2H), 2.64 (br s, 1H), 4.54 (t, J= 6.6 Hz, 1H), 5.21 (s, 2H), 7.16-7.35 (m, 1H+5H), 7.43 (s, 1H); ^{13}C NMR δ= 10.0, 31.3, 55.8, 67.8, 126.2, 127.0, 127.6, 127.9, 128.7, 136.3, 137.3; HRMS found m/z 216.1267, calcd for $C_{13}H_{16}N_2O$: 216.1264. Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.35; H, 7.57; N, 12.70.

ACKNOWLEDGMENT

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REFERENCES

1. J. Elguero, 'Comprehensive Heterocyclic Chemistry II: Pyrazole,' Vol. 3, ed. by A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Pergamon, Oxford, 1996, pp. 1-76.
2. (a) U. Burckhardt, L. Hintermann, A. Schnyder, and A. Togni, *Organometallics*, 1995, **14**, 5415; (b) D. L. Christenson, C. J. Tokar, and W. B. Tolman, *Organometallics*, 1995, **14**, 2148; (c) H. Brunner and T. Scheck, *Chem. Ber.*, 1992, **125**, 701; (d) H. Kotsuki, H. Hayakawa, M. Wakao, T. Shimanouchi, and M. Ochi, *Tetrahedron: Asymmetry*, 1995, **6**, 2665.
3. E. J. Barreiro and A. C. C. Freitas, *J. Heterocycl. Chem.*, 1992, **29**, 407.
4. (a) T. Shibata, K. Choji, H. Morioka, T. Hayase, and K. Soai, *Chem. Commun.*, 1996, 751; Reviews: (b) K. Soai and S. Niwa, *Chem. Rev.*, 1992, **92**, 833; (c) K. Soai and T. Hayase, *Yuki Gosei Kagaku Kyokaishi* (*J. Synth. Org. Chem., Jpn.*), 1995, **53**, 138; (d) R. Noyori and M. Kitamura, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 49.
5. (a) K. Soai, S. Yokoyama, K. Ebihara, and T. Hayasaka, *J. Chem. Soc., Chem. Commun.*, 1987, 1690; (b) K. Soai, S. Yokoyama, and T. Hayasaka, *J. Org. Chem.*, 1991, **56**, 4264.
6. (a) K. Soai, T. Konishi, and T. Shibata, *Heterocycles*, 1999, **51**, 1421; (b) I. Sato, T. Saito, D. Omiya, Y. Takizawa, and K. Soai, *Heterocycles*, in press.
7. K. Soai, A. Ookawa, T. Kaba, and K. Ogawa, *J. Am. Chem. Soc.*, 1987, **109**, 7111.
8. I. Ohtani, T. Kusumi, Y. Kashman, and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092.
9. I. L. Finar and G. H. Lord, *J. Chem. Soc.*, 1957, 3314.
10. A. Werner, A. Sánchez-Migallón, A. Fruchier, J. Elguero, C. Fernández-Castaño, and C. Foces-Foces, *Tetrahedron*, 1995, **51**, 4779.