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Catalytic asymmetric hydrogenation of heterocyclic ketone-derived hydrazones, pronounced solvent effect on the inversion of configuration

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ABSTRACT

An enantioselective hydrogenation of hydrazones derived from heterocyclic ketones was developed with up to 85% ee. The enantiomeric purity was enriched to >99% ee by crystallization from EtOAc in >80% yield. Optimization studies have revealed a notable solvent effect that resulted in inversion of enantioselectivity from 85% ee in MeOH to −27% ee in DCE. The hydrazone geometry and possible hydrogenation via endocyclic alkene were examined as possible factors for the inversion of enantioselectivity.

1. Introduction

Chiral hydrazines are integral substructures of many clinically relevant pharmaceutical compounds.[1] Despite the advances in asymmetric hydrogenation of imines,[2] limited attention was given to asymmetric hydrogenation of hydrazones. Several publications were reported since the detailed study by Burk et al.[3] in 1994 on the asymmetric hydrogenation of *N*-benzoyl hydrazones of acetophenone derivatives. While high enantioselectivity was obtained in the case of these substrates, low selectivity (43% ee) has been reported for alkyl hydrazones derived from 2-butanone. Yoshikawa et al.[3e] reported recent studies focused on the asymmetric hydrogenation of *N*-alkoxycarbonyl hydrazones of acetophenone derivatives, ligand screening was required to obtain high enantioselectivity. The optimized conditions provided 64% ee in the hydrogenation of bis-alkylhydrazone derived from benzylacetone.

Herein, we describe our studies on the enantioselective hydrogenation of hydrazones of heterocyclic ketones A (Scheme 1), where an unexpected solvent effect resulted in the inversion of enantioselectivity. To the best of our knowledge, hydrogenations of hydrazones derived from cyclic ketones of the current work and inversion of enantioselectivity in the asymmetric hydrogenation of hydrazones have not been previously reported.

2. Results and discussion

The asymmetric hydrogenations of *N*-benzoylhydrazones and Boc-hydrazones were expected to provide different enantioselectivities,[3e] therefore, hydrazones **1a** and **1b** were prepared[4] and studied.

Variety of chiral ligands (Fig. 1) were examined for substrates **1a** and **1b**, using 3% $Rh(NBD)_2BF_4$ in MeOH under 300 psi of H_2 at 30 °C. Representative results (Table 1) identified Mandyphos ligand **4** as optimal; it provided complete conversion of the Boc protected substrate **1a** with 85% ee. Interestingly, under the same conditions, the hydrogenation of benzoyl protected substrate **1b**, gave poor reactivity and low enantioselectivity (entry 2). Conversely, the use of Et-Duphos as ligand provided higher enantioselectivity (60% ee) with the benzoyl protected hydrazone **1b** and poor selectivity with substrate **1a**. In general, high conversions were obtained in most cases of alkylphosphine as well as arylphosphine ligands.

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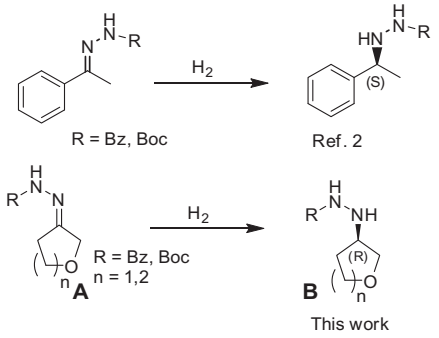


Scheme 1. Substrates A (R = Bz, Boc) pose a challenge for asymmetric hydrogenation.

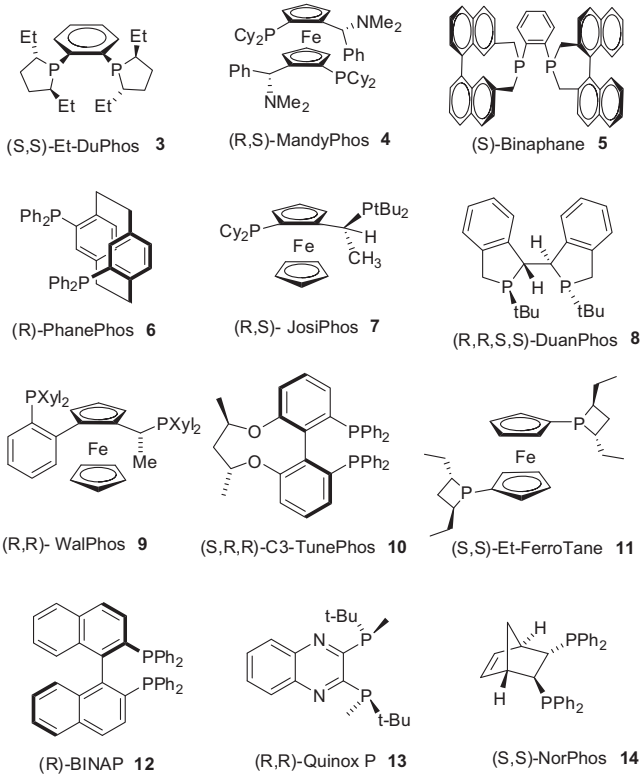


Figure 1. Selected ligands tested in this study.

The hydrogenation of substrate **1a** with ligand **4** was examined at 0 °C when a minor increase of enantioselectivity was observed. Additional testing with ligand kits of MandyPhos, JosiPhos and WallPhos series of ferrocene based ligands[5] with substrate **1a**, did not provide us with a more effective catalyst than Mandyphos ligand **4**.

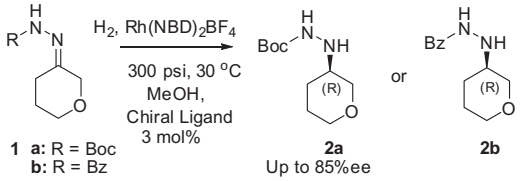
In an attempt for further optimization on *N*-Boc-hydrazone **1a**, different solvents were examined with Mandyphos ligand **4**. Methanol emerged as the solvent of choice with this ligand. As described in Table 2, the tested alcohols indicated a large effect on the conversion and enantioselectivity of the reaction, the bulkier alcohols yielding a diminished enantioselectivity and lower conversion (MeOH > EtOH > *n*-pentanol > 3-pentanol),[6] presumably due to increased steric constraints at the metal center via solvent ligation. Water was found to play a detrimental role on the enantioselectivity, 5% water in methanol reduced the enantioselectivity from 85% ee to 26% ee. More notable is the inverted configuration of the major product when the hydrogenation was carried out in the nonco-ordinating solvents dichloromethane or 1,2-dichloroethane[7] (enries 6–9). While unexpected inversions in asymmetric reactions are documented,[8,9] inversion of chirality under homogeneous Rh catalyzed hydrogenation of hydrazones or imines as a result of solvent effect is unprecedented.

Similar inversion of enantioselectivity as a factor of solvent was obtained with substrate **1b** (Table 2, entry 14). This result suggests minor or no effect of the nature of the hydrazone protecting group. The inversion of configuration in nonco-ordinating solvents could indicate co-ordination effect of the oxygen heteroatom.

Hydrazone **15** was prepared and tested for similar inversion. Hydrogenation under the optimized conditions, using (*R*,*S*)-MandyPhos **4** as ligand in MeOH, provided **16** in high enantioselectivity (Table 3).

Hydrogenation of **15** in dichloromethane provided lower enantioselectivity compared to methanol or 1,2-dichloroethane. Interestingly, no inversion of the configuration of the major product was obtained with this substrate. In order to adequately address the possibility that other factors such as hydrazone geometry or hydrogenation via possible endocyclic eneamine

Table 1
Selected ligand screening experiments for substrates **1a** and **1b**



1 **a:** R = Boc
b: R = Bz

2a Up to 85%ee

2b

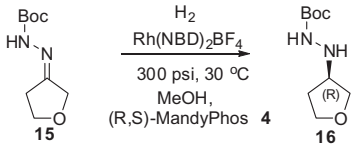
Entry	Ligand	2a		2b	
		% Conv.[a]	% ee[b]	% Conv.	% ee[c]
1	(*S*,*S*)-Et-DuPhos **3**	100	2	100	60
2	(R,S)-MandyPhos **4**	100	85	60	14
3	(*S*)-Binaphane **5**	100	36	0	n/a
4	(*R*)-PhanePhos **6**	100	44	100	14
5	(*R*,*S*)-JosiPhos **7**	100	44	70	34
6	(*R*,*R*,*S*,*S*) DuanPhos **8**	100	28	100	54
7	(*R*,*R*)-WalPhos **9**	100	63	100	10
8	(*S*,*R*,*R*)-TunePhos **10**	45	28	100	20
9	(*S*,*S*)-Et-FerroTane **11**	<5	N/A	100	35
10	(*R*)-BINAP **12**	30	8	40	21
11	(*R*,*R*)-Quinox P **13**	42	12	—	—
12	(*S*,*S*)-NorPhos **14**	28	9	—	—

[a] Conversions were determined by NMR and HPLC.
[b] ee was determined by GC.
[c] ee was determined by HPLC.

Table 2
Solvent screening using (*R*,*S*)-MandyPhos **4** (3 mol %) under 300 psi H_2, 30 °C for 20 h

Entry	Substrate	Solvent	Conversion	% ee
1	**1a**	MeOH	100	85
2	**1a**	EtOH	80	54
3	**1a**	1-Pentanol	100	26
4	**1a**	3-pentanol	20	4
5	**1a**	THF	100	32
6	**1a**	DCM	50	−24
7	**1a**	DCM	90	−14
8	**1a**	1,2-DCE	50	−27
9	**1a**	1,2-DCE	100	−12
10	**1a**	CF_3CH_2OH	100	26
11	**1a**	Toluene	5	8
12	**1a**	MeOH/H_2O	100	26
13	**1b**	MeOH	60	14
14	**1b**	1,2-DCE	100	−14

Table 3
Solvent effect using (*R,S*)-Mandyphos **4** under 300 psi H_2, rt for 20 h



Entry	Solvent	Conversion	% ee
1	MeOH	100	72
2	DCM	30	12
3	1,2-Dichloroethane	100	71

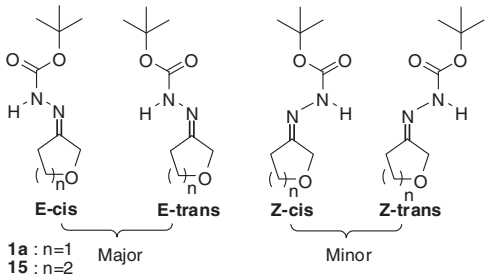


Figure 2. Possible geometrical isomers of hydrazones **1a** and **15**.

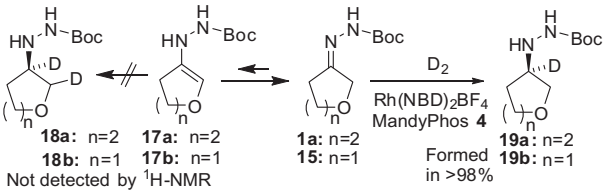
intermediate contribute to this difference between five- and six-membered ring heterocycles, we compared the geometry of hydrazones **1a** and **15** in different solvents by NMR and tested their possible hydrogenation via endocyclic isomer.

The geometry of hydrazones, namely the ratio of *cis*/*trans* amide conformers, is known to be affected by the nature of the solvent.[10] The effect of solvents on *Z*/*E* geometrical isomerization was reported on *N*-acyl and *N*-aroylhydrazones compounds with preferred *Z* configuration stabilized by intramolecular hydrogen bonding.[11] We examined the geometry and isomeric ratios of substrates **1** and **15** in CD_3OD and CD_2Cl_2 by NMR. NOE experiments confirmed *E*-geometry of the major isomers of **1a** and **15** at 0 °C and 25 °C. Four isomers were detected for compound **15** in CD_2Cl_2 at 0 °C (Fig. 2). NOESY data show two sets of NOE between the NH protons and the C4-methylene protons, consistent with *E-cis*, *E-trans*, *Z-cis* and *Z-trans* possible conformers.

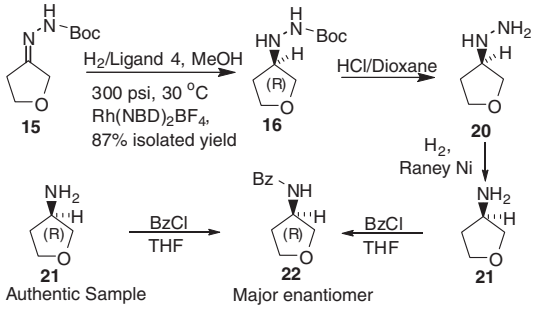
One set of geometrical isomers was detected at 25 °C with *E*/*Z* ratio of 1/0.15. A similar ratio of 1/0.18 was obtained in CD_3OD. Similar *E*/*Z* ratio for substrate **15**, 1/0.25 in CD_2Cl_2 and 1/0.18 in CD_3OD was determined. These results indicate that the initial configurations of hydrazones **1a** and **15** in both solvents (MeOH, CH_2Cl_2) do not play a key role in reversing the enantioselectivity (Table 2).

Hydrogenation via isomerization of the hydrazone double bond to the endocyclic ene-hydrazone **17a** is another possible factor that might contribute to reversed enantioselectivity in **1a**. This was examined for the five- and six-membered ring systems in methanol and for **1a** in CH_2Cl_2 as described in Scheme 2.

Hydrogenation of hydrazones **1** and **15** with deuterium under the optimized conditions, revealed single deuterium incorporation at the tertiary carbon in both compounds **19a** and **19b** as confirmed by LCMS and NMR data. The results consequently are consistent with hydrogenation of the exocyclic C=N bond in both substrates with no effective hydrogenation via isomerization to the corresponding endocyclic double bond **17**. To this end, neither the initial hydrazone configuration nor endocyclic double bond



Scheme 2. Deuterium labeling did not result in the formation of **18a** or **18b** at a detectable limit.



Scheme 3. Assignment of absolute configuration of **16**.

isomerization contributes to the reversed enantioselectivity detected in substrates **1**.

The enantiomeric purity of **1a** was enriched from 85% ee to >99% ee by crystallization from EtOAc in >80% yield. The absolute configuration of hydrazine **16** was determined by comparison to an authentic sample of **22** with known (*R*)-configuration (Scheme 3). A 300 mg sample of **15** was reduced under the optimized conditions, using 0.5 mol % catalyst. Sample of hydrazine **16** (67% ee) was deprotected with 4 N HCl/Dioxane followed by reductive cleavage of the N–N bond of **20** under 300 psi of H_2 with Raney Ni[3b,12] to the corresponding amine **21** which then was treated with benzoyl chloride to give the known compound[13] **22** with 67% ee. Chiral GC comparison of this sample with an authentic sample of (*R*)-**22**, prepared from (*R*)-(+)-3-aminotetrahydrofuran, indicated an overlap with the major enantiomer of the reaction mixture, confirming (*R*)-configuration in compound **16**. The (*R*)-configuration of hydrazene **2a** was assigned based on optical rotation sign and order of GC elution in comparison with **16**.

3. Conclusion

We have developed practical enantioselective hydrogenation of hydrazones of five- and six-membered ring heterocyclic ketones with up to 85% ee that was enriched to >99% ee after crystallization in good yield. Optimization studies revealed an unexpected solvent effect on the inversion of enantioselectivity in the six-membered ring compounds **1**, while retention of configuration was found in the five-membered ring compound **15**. Detailed studies ruled out the hydrazone geometry or hydrogenation via endocyclic alkene as possible factors for the inversion of configuration.

4. Experimentals

^1H and ^{13}C chemical shifts were calibrated versus TMS. ^1H and ^{13}C spectra observe frequencies were ^1H: 600 or 400 MHz; ^{13}C: 150 or 100 MHz; HRMS were performed on a Time of Flight mass spectrometer (LC/MSD TOF). Enantiomeric excess was determined by GC (Chiralsil-L-Val, 25 m, 0.25 mm) or HPLC (Chiralcel OD-H, 4.6 × 250 mm column) with detection at 220 nm, isocratic 92/8 Heptane/IPA with 1.5 mL/min flow rate for 20 min. (*R*)-(+)-3-amin-

otetrahydrofuran-4-toluene sulfonate was purchased from Fluka. All reagents were used as received unless stated otherwise.

4.1. Typical procedure for the hydrazones synthesis

4.1.1. *Tert*-butyl-2-(2H-pyran-3(4H,5H,6H)-ylidene)hydrazine-carboxylate (1a)

A 100 mL 3-neck flask with inert gas valve and septum was charged with (6.50 g, 49.04 mmol) *tert*-butylhydrazinecarboxylate and 30 mL MeOH. (4.91 g, 49.04 mmol) dihydro-2*H*-pyran-3(4*H*)-one was syringed into the flask. The mixture was stirred at rt for 2 h to observe the disappearance of *tert*-butylhydrazinecarboxylate monitored by LC–MS. The mixture was then dried over Na_2SO_4 and the solution was filtered and the solvent removed under reduced pressure to yield 10.4 g of white solid (99% yield). The compound was further purified by passing through a short silica pad using 50% EtOAc in hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77 (br s, 1H), 4.20 (s, 2H), 3.78 (t, J = 5.38 Hz, 2H), 2.43 (t, J = 6.60 Hz, 2H), 1.85 (m, 2H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.08, 149.49, 81.31, 71.51, 67.30, 28.24, 24.83, 23.19; HRMS for [2 $C_{10}H_{18}N_2O_3$+H^+]: observed 429.2706, calculated 429.2707.

4.1.2. *N′*-(2*H*-pyran-3(4*H*,5*H*,6*H*)-ylidene)benzohydrazide (1b)

Following the typical procedure for **1a**, the mixture was heated to 60 °C for 7 h until benzohydrazide detected at <2% by LC-MS. The product was isolated as white solid in 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$ δ: 7.56 (br s, 1H), 7.80–7.82 (m, 2H), 7.52–7.56 (m, 1H), 7.44–7.48 (m, 2H), 4.31 (br s, 2H), 3.79–3.85 (t, J = 5.2 Hz, 2H), 2.54–2.57 (t, J = 6.6 Hz, 2H), 1.89–1.95 (quint, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.24, 156.49, 133.33, 131.92, 128.68, 127.26, 71.40, 67.14, 24.96, 24.22; HRMS for [$C_{12}H_{14}N_2O_2$+H^+]: observed 219.1142, calculated 219.1128.

4.1.3. *Tert-butyl-2-(dihydrofuran-3(2H)*-ylidene)hydrazine-carboxylate (15)

Following the typical procedure for**1a**, hydrazone **15** was prepared in 85% yield as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (br s, 1H), 4.22 (s, 2H), 4.01 (t, J = 6.96 Hz, 2H), 2.45 (t, J = 6.92 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.30, 152.78, 81.54, 69.41, 67.78, 28.24, 27.43; HRMS for [2 $C_9H_{16}N_2O_3$+H] $^+$: observed 401.2407, calculated 401.2394.

4.2. Typical procedure for asymmetric hydrogenations

4.2.1. *(R)-tert*-butyl-2-(tetrahydro-2*H*-pyran-3-yl)hydrazine-carboxylate (2a)

The catalyst solution was prepared in a 10 mL flask in the glove box by addition of ligand **4** (25.35 mg, 0.03 mmol) to $Rh(NBD)_2BF_4$ (11.25 mg, 0.03 mmol) in degassed methanol (1 mL). The mixture was stirred for 20 min at rt. Hydrazone **1a** (320 mg, 1.5 mmol) was placed in a 10 mL autoclave under N_2 followed by addition of 3 mL methanol. The catalyst solution was transferred to the hydrazone solution then the mixture purged three times with N_2 followed by two times with H_2. The reaction was stirred under 300 psi H_2 at 30 °C for 20 h. LCMS and ^{1}H-NMR confirmed complete conversion. The product was purified by column chromatography to provide 556 mg product of 85% ee in 87% isolated yield as a white solid. Crystallization from ethylacetate provided 80% of the product in 99.4% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.10 (bs, 1H), 3.90 (bs, 1H), 3.87 (dd, J_1 = 2.4, J_2 = 11.2 Hz, 1H), 3.75 (dt, J_1 = 5.3, J_2 = 11.2 Hz, 1H), 3.46 (dt, J_1 = 2.8, J_2 = 11.9 Hz, 1H), 3.3 (dd, J_1 = 7.9, J_2 = 11.3 Hz, 1H), 3.9 (m, 1H), 1.89 (m, 1H), 1.75 (m, 1H), 1.59 (m, 1H), 1.47 (s, 9H), 1.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.3, 84.2, 68.1, 66.43, 57.3, 28.1, 23.8, 22.5; HRMS for [2. $C_{10}H_{20}N_2O_3$+H^+]: observed 433.3015, calculated 433.3020; 99.4% ee; $[\alpha]_D^{20}$ = +33.7° (c 0.78, $CHCl_3$).

4.2.2. (*R*)-*tert*-butyl-2-(3-deuteriotetrahydro-2*H*-pyran-3-yl) hydrazinecarboxylate (19a)

Hydrazone **1a** (100 mg, 0.45 mmol) was hydrogenated following the typical procedure described above, under 300 psi of D_2. The compound was isolated in 93% yield as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.18 (bs, 1H), 3.89 (bs, 1H), 3.60 (d, J =11.2 Hz, 1H), 3.75 (dt, J_1 = 4.4, J_2 = 11.2 Hz, 1H), 3.45 (dt, J_1 = 2.8, J_2 = 10.6 Hz, 1H), 3.28 (d, J =11.2 Hz, 1H), 1.85 (m, 1H), 1.75 (m, 1H), 1.55 (m, 1H), 1.44 (s, 9H), 1.40 (m, 1H);

4.2.3. (*R*)-*N′*-(2*H*-pyran-3(4*H*,5*H*,6*H*)-ylidene)benzohydrazide (2b)

Hydrazene **2b** was prepared and isolated in 91% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.86 (dd, J_1 = 2.4, J_2 = 11.3 Hz, 1H), 3.66 (m, 1H), 3.57 (m, 2H), 3.25 (b s, 1H), 1.95 (m, 1H), 1.82 (m, 1H), 1.69 (m, 1H), 1.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.4, 132.3, 131.7, 128.7, 127.4, 69.5, 68.2, 56.1, 26.6, 23.3; HRMS for [$C_{12}H_{16}N_2O_2$+H^+]: observed 221.1302, calculated 221.1284; 60% ee; $[\alpha]_D^{20}$ = −6.2° (c 1.11, $CHCl_3$).

4.2.4. *(R)-tert*-butyl-2-(dihydrofuran-3-(2*H*)-ylidene)hydrazine carboxylate (16)

Hydrazene **16** was prepared and isolated in 87% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.41 (br s, 1H), 3.98 (br s, 1H), 3.92 (m, 2H), 3.80–3.68 (m, 4H), 2.00 (m, 1H), 1.76 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.0, 80.7, 71.8, 67.1, 60.3, 31.0, 28.3; HRMS for [2 $C_9H_{18}N_2O_3$+H^+]: observed 405.2716, calculated 405.2707; 72% ee; $[\alpha]_D^{20}$ = +10.5° (c 1.14, $CHCl_3$).

4.2.5. (*R*)-*tert*-butyl-2-(3-deuteriotetrahydrofuran-3-yl) hydrazine carboxylate (19b)

Hydrazene **19b** was prepared under 300 psi of D_2. The compound was isolated in 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.20 (br s, 1H), 3.92 (dd, J_1 = 7.6, J_2 = 15.7 Hz, 1H), 3.78 (six, J_1 = 4.8, J_2 = 8.3, J_3=13.2 Hz, 1H), 3.73 (d, J = 9.6 Hz, 1H), 3.69 (d, J = 9.6 Hz, 1H), 2.00 (m, 1H), 1.75 (m, 1H), 1.45 (s, 9H).

Procedures related to the assignment of absolute configuration described at the Supplementary data.

Supplementary data

Supplementary data (experimental procedures, characterization data; ^{1}H and ^{13}C spectra for new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.017.

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4. Hydrazones were prepared with minor modification of literature procedure (Ref. 3e).
5. Ligands kit available from Solvias.
6. In contrast to low solubility of substrate **1b** in IPA (Ref. 3e), hydrazone **1a** is highly soluble in the tested alcohols.

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13. Desai, L. V.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5737. compound **2b**′ in Supplementary data of this reference.