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t-Bu-QuinoxP* Ligand: Applications in Asymmetric Pd-Catalyzed Allylic Substitution and Ru-Catalyzed Hydrogenation

Tsuneo Imamoto,* Miwako Nishimura, Aya Koide, and Kazuhiro Yoshida

Department of Chemistry, Graduate School of Science, Chiba University, Yayoi-cho, Inage-ku, Chiba 263-8522, Japan

imamoto@faculty.chiba-u.jp

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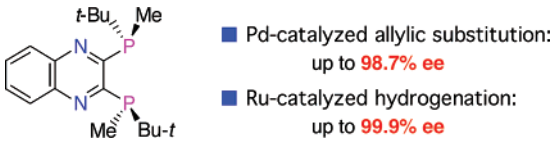
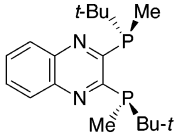


The potential of the *t*-Bu-QuinoxP* ligand (**1**) as a chiral ligand in asymmetric synthesis was examined. The ligand exhibited good to excellent asymmetric induction in Pd-catalyzed asymmetric allylic substitution of 1,3-diphenyl-2-propenyl acetate (up to 98.7% ee) and in Ru-catalyzed asymmetric hydrogenation of ketones (up to 99.9% ee).

The design and synthesis of new and efficient chiral ligands have played a central role in the development of highly enantioselective transition-metal-catalyzed asymmetric reactions.[1,2] In the past decade, we have focused our attention on the development of a series of C_2-symmetric P-chiral phosphine ligands. 1,2-Bis(alkylmethylphosphino)ethanes (BisP*) and 1,2-bis(alkylmethylphosphino)methanes (MiniPHOS), representatives of C_2-symmetric P-chiral phosphine ligands, exhibit very high to almost perfect enantioselectivity in Rh-catalyzed asymmetric hydrogenation.[3−5] However, the sensitivity to air of these ligands, which is derived from the high electron density of the phosphorus atom, has hampered their widespread application in various asymmetric catalyses. In order to overcome this difficulty, we recently developed an air-stable P-chiral phosphine ligand, *t*-Bu-QuinoxP* (**1**), as an alternative.[6,7] This ligand exhibited excellent asymmetric induction not only in Rh-catalyzed hydrogenation[6] but also in Rh-catalyzed 1,4-addition,[6] Pd-catalyzed ring-opening reaction,[6] and Rh-catalyzed hydrosilylation.[8] Herein we report the results of further investigation of **1**, where ligand **1** was successfully applied to asymmetric Pd-catalyzed allylic substitution[9] and Ru-catalyzed hydrogenation.[10]



1: (*R*, *R*)-*t*-Bu-QuinoxP*

In order to determine the crystal structure of a transition-metal catalyst coordinated with **1**, we first prepared $PdCl_2$[(*R*,*R*)-**1**] (**2**) by mixing **1** with $PdCl_2$(cod) in dichloromethane (eq 1). A pure crystal for X-ray diffraction study was obtained by slow diffusion of pentane into the concentrated dichloromethane solution of **2** at room temperature.

$$PdCl_2(cod) + \mathbf{1} \xrightarrow[\text{r.t.}]{CH_2Cl_2} \underset{\mathbf{2}}{PdCl_2(\mathbf{1})} + COD \qquad (1)$$

The crystal structure and the selected bond distances and angles of **2** are shown in Figure 1 and Table 1, respectively.[11] Pd−P distances (2.2327(9) and 2.2326(8) Å) and Pd−Cl distances (2.3656(8) and 2.3671(9) Å) are within the typical range for dichloropalladium complexes bearing diphosphine

* To whom correspondence should be addressed. Tel: +81-43-290-2791. Fax: +81-43-290-2791. E-mail: imamoto@faculty.chiba-u.jp.

(1) For representative reviews, see: (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029−3069. (b) Crépy, K. V. L.; Imamoto, T. *Top. Curr. Chem.* **2003**, *229*, 1−40. (c) Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497−537.

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(7) Both enantiomers of *t*-Bu-QuinoxP* are commercially available from Aldrich Chemical Company. Imamoto, T.; Sugita, K.; Yoshida, K. U.S. Patent 2007021610, 2007; Imamoto, T.; Sugita, K.; Yoshida, K. JP Patent, 2007056007, 2007.

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(11) The unit cell contained two Pd complexes and two dichloromethane molecules. One of the Pd complexes and the dichloromethane molecules are omited in Figure 1 and Table 1; CCDC 649473 for the compounds contains supplementary crystallographic data. The data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 IEZ, UK; fax: (+44) 1223−336-033; e-mail: deposit@ccdc.cam.ac.uk).

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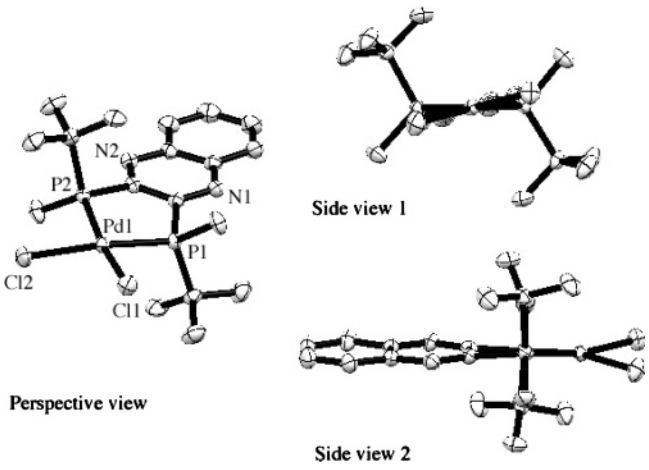

FIGURE 1. Crystal structure of $PdCl_2$[(*R*,*R*)-**1**] (**2**); hydrogen atoms are omitted for clarity.

TABLE 1. Selected Bond Distances and Angles of $PdCl_2$[(*R*,*R*)-1] (2)

Bond Distance (Å)			
Pd(1)−Cl(1)	2.3656(8)	Pd(1)−Cl(2)	2.3671(9)
Pd(1)−P(1)	2.2327(9)	Pd(1)−P(2)	2.2326(8)
Bond Angle (deg)			
Cl(1)−Pd(1)−Cl(2)	93.50(3)	Cl(1)−Pd(1)−P(1)	90.59(3)
Cl(2)−Pd(1)−P(2)	90.01(3)	P(1)−Pd(1)−P(2)	87.57(3)

ligands.[12] The sum of the four angles at palladium involving P(1), P(2), Cl(1), and Cl(2) is 361.7°. The bite angle of the ligand is 87.57(3)°, and the small distortion is balanced by the Cl−Pd−Cl angle of 93.50(3)°. The geometry around the Pd center is described as skewed square planar, which can be ascribed to steric repulsion between the chlorine atom and the bulky *tert*-butyl group: the dihedral angle between the coordination planes of P(1)−Pd−P(2) and Cl(1)−Pd−Cl(2) is 13.8°.

The enantioinduction ability of ligand **1** was examined in Pd-catalyzed asymmetric allylic substitution (Table 2).[13] When the reaction of 1,3-diphenyl-2-propenyl acetate (**3**) with dimethyl malonate was carried out in the presence of 0.5 mol % of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.0 mol % of Pd), 1.1 mol % of **1**, and base [KOAc and *N*,*O*-bis(trimethylsilyl)acetamide (BSA)] at room temperature, the alkylation product was obtained with high enantioselectivity (92% ee) (Table 2, entry 1). The substituted malonates and acetyl acetone as nucleophiles gave comparable enantioselectivities (Table 2, entries 2−7). Lowering the reaction temperature improved enantioselectivity: the highest enantioselectivity (98.7% ee) was observed when the reaction of methyl malonate was performed at a low temperature of −50 °C (Table 2, entry 8).

Asymmetric allylic amination using (*R*,*R*)-*t*-Bu-QuinoxP*−Pd catalyst was also applicable, affording optically active allylic amines. When the reaction was carried out with morpholine as nucleophile, *N*-(1,3-diphenyl-2-propenyl)morpholine (**4h**) was obtained in 69% yield with 78% ee (Table 2, entry 9). Addition of BSA significantly enhanced the reaction rate and the selectivity to 89% ee (Table 2, entry 10).[14] Similar enantioselectivity (90% ee) was observed in the reaction of pyrrolidine with BSA (Table 2, entry 11). Butylamine gave lower enantioselectivity (73% ee), while cyclohexylamine as a primary amine gave high enantioselectivity (89% ee; Table 2, entries 12 and 13).

The potential of *t*-Bu-QuinoxP* (**1**) as a chiral ligand was next explored for the Ru-catalyzed asymmetric hydrogenation of ketones. It was found that a premixed Ru complex generated from $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ and **1** was an excellent catalyst for the reaction. When a solution of 3-oxo-3-phenylpropionic acid ethyl ester in EtOH/CH_2Cl_2 containing the (*R*,*R*)-*t*-Bu-QuinoxP*−Ru complex was stirred under 20 atm H_2 in a stainless steel autoclave at 50 °C for 24 h, corresponding alcohol **6a** was obtained in 89% isolated yield with 99.3% ee (Table 3, entry 1). The enantioselectivity was not strongly affected by substituents (electron-donating or electron-withdrawing) on the aromatic ring, and a series of 3-oxo-3-arylpropionic acid ethyl esters were hydrogenated with almost perfect enantioselectivities (Table 3, entries 2−7).[16] High enantioselectivities were also achieved in the reactions of 3-oxobutyric acid methyl ester and 4-chloro-3-oxobutyric acid ethyl ester, having an alkyl group at the R^1 position (Table 3, entries 8 and 9).[17] When the reaction was carried out with β-keto amide instead of β-keto ester, product **6j** having slightly lower enantioselectivity (97% ee) was obtained (Table 3, entry 10). On the other hand, the hydrogenation of diketone, 5,5-dimethyl-2,4-hexanedione, gave product **6k** with excellent enantioselectivity (99.0% ee; Table 3, entry 11). It should be noted that the enantioselectivities described here are among the best results reported so far.

Finally, the activity of the catalyst was examined. When the reaction of 3-oxo-3-phenylpropionic acid ethyl ester was carried out under 100 atm at 100 °C in the presence of 0.02 mol % of Ru catalyst, TON of 2500 (50% isolated yield) was realized albeit with decreased enantioselectivity to 95% ee (Table 3, entry 12).

In conclusion, we have examined the catalytic potential of the *t*-Bu-QuinoxP* ligand (**1**) in Pd-catalyzed asymmetric allylic substitution and Ru-catalyzed asymmetric hydrogenation and obtained corresponding nonracemic compounds in high yields with good to excellent enantioselectivities. Further modifications of the ligand and studies of its applications in asymmetric catalysis are in progress in our laboratory.

Experimental Section

Synthesis of [(*R*,*R*)-2,3-Bis((*tert*-butyl)methylphosphino)quinoxaline]dichloropalladium (2). A mixture of $PdCl_2$(cod) (29 mg, 0.1 mmol) and (*R*,*R*)-*t*-Bu-QuinoxP* (**1**) (33 mg, 0.1 mmol) in CH_2Cl_2

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(13) It is known that C_2-symmetric ligands are not so effective for Pd-catalyzed asymmetric allylic substitution as expected from their wide range of success in other catalytic asymmetric reactions; see ref 9.

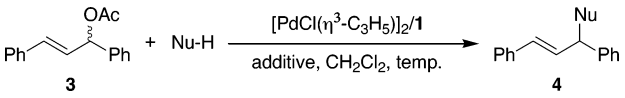
(14) Nemoto, T.; Masuda, T.; Akimoto, Y.; Fukuyama, T.; Hamada, Y. *Org. Lett.* **2005**, *7*, 4447−4450.

(15) Byproducts were observed only in the reaction of 3-oxo-3-arylpropionic acid ethyl esters having an electron-donating group on the aromatic ring. We found that the byproducts were formed by the reaction of produced alcohol **6** with EtOH in the presence of the *t*-Bu-QuinoxP*−Ru complex under the same conditions as those for the hydrogenation. Further, **6c** also reacted with MeOH to give the 3-methoxy-3-(4′-methoxyphenyl)propionic acid ethyl ester. In the absence of hydrogen or Ru complex, no reaction occurred between **6c** and alcohol.

(16) It is noted that hydrogenation product **6g** (99.8% ee) is the key intermediate for epinephrine. See: Singer, R. A.; Carreira, E. M. *Tetrahedron Lett.* **1997**, *38*, 927−930.

(17) It is noted that hydrogenation product **6i** (99.2% ee) is the key intermediate for carnitine. See: Kitamura, M.; Ohkuma, T.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1988**, *29*, 1555−1556.

TABLE 2. Asymmetric Allylic Alkylation and Amination of Racemic 1,3-Diphenyl-2-propenyl Acetate Catalyzed by (*R*,*R*)-*t*-Bu-QuinoxP*−Pd Complex[a]



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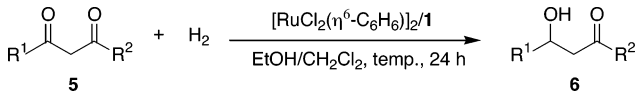
entry	Nu−H	additive	catalyst loading	temp	time (h)	yield[b] (%)	ee[c] (%) (config[d])
1	$H_2C(COOMe)_2$	KOAc + BSA	1 mol % Pd	rt	1	85 (**4a**)	92 (*S*)
2	$HCCH_3(COOMe)_2$	KOAc + BSA	1 mol % Pd	rt	1	97 (**4b**)	95 (*R*)
3	HC(*n*-Bu)$(COOEt)_2$	KOAc + BSA	1 mol % Pd	rt	1	87 (**4c**)	92
4	$HC(CH_2Ph)(COOEt)_2$	KOAc + BSA	1 mol % Pd	rt	48	93 (**4d**)	90
5	$HC(NHCHO)(COOEt)_2$	KOAc + BSA	1 mol % Pd	rt	26	94 (**4e**)	91
6	$HC(NHAc)(COOEt)_2$	KOAc + BSA	1 mol % Pd	rt	27	83 (**4f**)	91 (*R*)
7	$H_2C(COMe)_2$	KOAc + BSA	1 mol % Pd	rt	1	88 (**4g**)	95 (*S*)
8[e]	$HCCH_3(COOMe)_2$	KOAc + BSA	3 mol % Pd	−50 °C	20	92 (**4b**)	98.7 (*R*)
9	morpholine	−	2 mol % Pd	rt	13	69 (**4h**)	78
10	morpholine	BSA	2 mol % Pd	rt	13	94 (**4h**)	89
11	pyrrolidine	BSA	2 mol % Pd	rt	20	81 (**4i**)	90 (*R*)
12	butylamine	BSA	2 mol % Pd	rt	63	>99 (**4j**)	73
13[f]	cyclohexylamine	BSA	4 mol % Pd	rt	48	96 (**4k**)	89

[a] Reaction conditions: (allylic alkylation) 1,3-diphenyl-2-propenyl acetate (**3**)/malonate or acetylacetone/BSA/*t*-Bu-QuinoxP* (**1**)/$[PdCl(\eta^3\text{-}C_3H_5)]_2/CH_2Cl_2$ = 0.50 mmol/1.5 mmol/1.5 mmol/0.0055 mmol/0.0025 mmol/2.0 mL; 1 mol % of Pd; (allylic amination) 1,3-diphenyl-2-propenyl acetate (**3**)/amine/BSA/*t*-Bu-QuinoxP* (**1**)/$[PdCl(\eta^3\text{-}C_3H_5)]_2/CH_2Cl_2$ = 0.50 mmol/1.5 mmol/1.5 mmol/0.011 mmol/0.0050 mmol/2.0 mL; 2 mol % of Pd, unless otherwise stated. [b] Isolated yield. [c] Chiral HPLC analysis. [d] Absolute configuration was determined by comparing chiral HPLC retention times with data in the literature. [e] Reaction conditions: 1,3-diphenyl-2-propenyl acetate (**3**)/methyl malonate/BSA/*t*-Bu-QuinoxP* (**1**)/$[PdCl(\eta^3\text{-}C_3H_5)]_2/CH_2Cl_2$ = 0.50 mmol/1.5 mmol/1.5 mmol/0.016 mmol/0.0075 mmol/2.0 mL; 3 mol % of Pd. [f] Reaction conditions: 1,3-diphenyl-2-propenyl acetate (**3**)/cyclohexylamine/BSA/*t*-Bu-QuinoxP* (**1**)/$[PdCl(\eta^3\text{-}C_3H_5)]_2/CH_2Cl_2$ = 0.50 mmol/1.5 mmol/1.5 mmol/0.021 mmol/0.010 mmol/1.0 mL; 4 mol % of Pd.

TABLE 3. Asymmetric Hydrogenation of Ketones Catalyzed by (*R*,*R*)-*t*-Bu-QuinoxP*−Ru Complex[a]



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entry	R^1	R^2	H_2 (atm)	temp (°C)	yield[b] (%)	ee[c] (%), (config[d])
1	Ph	OEt	20	50	89 (**6a**)	99.3 (*S*)
2	4-MeC_6H_4	OEt	20	70	94 (**6b**)	98.9 (*S*)
3	4-$MeOC_6H_4$	OEt	50	70	73 (**6c**)[e]	99.3 (*S*)
4	4-BrC_6H_4	OEt	20	70	87 (**6d**)	99.5 (*S*)
5	4-ClC_6H_4	OEt	20	70	88 (**6e**)	99.9 (*S*)
6	4-FC_6H_4	OEt	50	70	93 (**6f**)	99.8
7[f]	3,4-dimethoxyphenyl	OEt	100	70	82 (**6g**)[e]	99.8
8	Me	OMe	20	50	>99 (**6h**)[g]	99.7 (*R*)
9	$ClCH_2$	OEt	20	50	96 (**6i**)	99.2
10	Me	NMe_2	20	50	94 (**6j**)[h]	97
11	Me	*t*-Bu	20	50	93 (**6k**)[h]	99.0
12[i]	Ph	OEt	100	100	50 (**6a**)	95 (*S*)

[a] Reaction conditions: ketone/*t*-Bu-QuinoxP* (**1**)/$[RuCl_2(\eta^6\text{-}C_6H_6)]_2$/EtOH/$CH_2Cl_2$ = 0.67 mmol/0.015 mmol/0.0067 mmol/3.0 mL/1.0 mL; 2 mol % of Ru, unless otherwise stated. [b] Isolated yield. [c] Chiral HPLC or GC analysis. [d] Absolute configuration was determined by comparing chiral HPLC or GC retention times with data in the literature. [e] Racemic 3-ethoxy-3-arylpropionic acid ethyl ester was produced as a byproduct. The low yield can be attributed to the byproduct.[15] [f] 16 h. [g] Conversion yield determined by ^1H NMR analysis. [h] NMR yield determined by using 1,4-bis(trimethylsilyl)benzene as an internal standard. [i] Reaction conditions: 3-oxo-3-phenylpropionic acid ethyl ester/*t*-Bu-QuinoxP* (**1**)/$[RuCl_2\ (\eta^6\text{-}C_6H_6)]_2$/EtOH/$CH_2Cl_2$ = 6.0 mmol/0.00132 mmol/0.00060 mmol/3.0 mL/1.0 mL; 0.02 mol % of Ru, 48 h.

(3 mL) was stirred for 30 min at room temperature. All the volatiles were removed under reduced pressure. The yellow residue was dissolved in a minimum amount of CH_2Cl_2 and recrystallized by slow diffusion of pentane into the concentrated dichloromethane solution at room temperature to afford yellow cubic crystals for single-crystal X-ray analysis (88% yield): ^1H NMR (395.75 MHz, $CDCl_3$) δ 1.25 (d, J = 16.8 Hz, 18H), 2.26 (d, J = 11.9 Hz, 6H), 8.09 (dd, J = 6.6, 3.6 Hz, 2H), 8.34 (dd, J = 6.4, 3.7 Hz, 2H); $^{13}C\{^1H\}$ NMR (99.45 MHz, $CDCl_3$) δ 6.23−6.55 (m), 27.89, 36.68−37.04 (m), 130.17, 133.58, 142.54 (t, J = 4.1 Hz), 154.06 (t, J = 56.6 Hz); $^{31}P\{^1H\}$ NMR (202.35 MHz, $CDCl_3$) δ 56.27 (s); $[\alpha]^{20}_D$ = +24.8 (*c* 1.04, $CHCl_3$); HRMS (FAB) calcd for $C_{18}H_{28}ClN_2P_2Pd$ (M^+ − Cl) 475.0455, found 475.0431.

Typical Procedure for Pd-Catalyzed Asymmetric Allylic Alkylation (Table 2, entry 1). A solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 2.5 μmol) and (*R*,*R*)-*t*-Bu-QuinoxP* (**1**) (1.8 mg, 5.5 μmol) in CH_2Cl_2 (0.5 mL) was stirred for 10−30 min at room temperature. Subsequently, to the solution was added a solution of 1,3-diphenyl-2-propenyl acetate (126 mg, 0.50 mmol) in CH_2Cl_2 (1.5 mL), dimethyl malonate (171 μL, 1.50 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (367 μL, 1.50 mmol), and a pinch of AcOK. After being stirred for 1 h at room temperature, the reaction mixture was diluted with Et_2O and quenched by addition of saturated NH_4Cl solution. The mixture was extracted with Et_2O and washed with brine. The organic phase was dried over Na_2SO_4 and concentrated under vacuum. The obtained residue was purified by silica gel column chromatography.

Typical Procedure for Pd-Catalyzed Asymmetric Allylic Amination (Table 2, entry 10). A solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 5.0 μmol) and (*R*,*R*)-*t*-Bu-QuinoxP* (**1**) (3.7 mg, 11 μmol) in CH_2Cl_2 (0.5 mL) was stirred for 10−30 min at room temperature. Subsequently, to the solution was added a solution of 1,3-diphenyl-2-propenyl acetate (126 mg, 0.50 mmol) in CH_2Cl_2 (1.5 mL), morpholine (131 μL, 1.50 mmol), and *N*,*O*-bis(trimethylsilyl)-acetamide (367 μL, 1.50 mmol). After stirring for 13 h at room temperature, the reaction mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography.

Typical Procedure for Ru-Catalyzed Asymmetric Hydrogenation (Table 3, entry 1). (*R*,*R*)-*t*-Bu-QuinoxP* (**1**) (4.9 mg, 15 μmol) and $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ (3.4 mg, 6.7 μmol) were dissolved in anhydrous and degassed DMF (0.5 mL) under nitrogen. The mixture was heated to 100 °C for 10 min. After the mixture was cooled to 50 °C, the solvent was removed under vacuum to give the catalyst as a red-purple solid. The catalyst was taken into a

glovebox and dissolved in degassed ethanol (3 mL). To the solution was added 3-oxo-3-phenylpropionic acid ethyl ester (129 mg, 0.67 mmol) dissolved in CH_2Cl_2 (1 mL), and the mixture was transferred to a stainless steel autoclave. The autoclave was purged with hydrogen four times, and the hydrogen pressure was raised to 20 atm. After being stirred at 50 °C for 24 h, the reaction mixture was cooled to room temperature and the hydrogen was released. The solvents were removed, and the residue was dissolved in Et_2O. The solution was washed with water and brine and dried over Na_2SO_4. After evaporation of all the volatiles, the residue was purified by silica gel column chromatography.

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Supporting Information Available: Characterization of all compounds and X-ray crystal structure files (.cif) for **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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