NMR ($CDCl_3$): $\delta = 143.94$, 143.66, 143.48, 143.20, 131.05, 131.00, 130.93, 126.33, 46.24, 46.20, 46.17, 46.13, 45.92, 45.69, 45.61, 45.38, 40.17, 40.05, 39.89, 39.73, 39.61, 39.52, 39.33, 39.29, 39.26, 34.76, 34.61. 34.51, 34.41, 34.26, 22.69, 22.65, 22.61, 20.82; ^{31}P NMR ($CDCl_3$): $\delta = -7.3$; $[\alpha]_D = +221.8^\circ$ ($c = 1.01$, $CHCl_3$); HR-MS calcd for $C_{22}H_{32}P_2$: 358.1975; found: 358.1982.

6: ^1H NMR ($CDCl_3$): $\delta = 7.20-7.10$ (m, 2H, aromatic), 7.05–6.90 (m, 2H, aromatic), 3.38 (br d, 2H, $^2J(P,H) = 14.2$ Hz, PCH), 2.85 (br d, 2H, $^2J(P,H) = 13.5$ Hz, PCH), 1.85–1.45 (m, 12H), 1.30–1.08 (m, 4H), 1.03 (d, 6H, $^3J(H,H) = 6.4$ Hz, CH_3), 0.96 (d, 6H, $^3J(H,H) = 5.6$ Hz, CH_3), 0.86 (d, 6H, $^3J(H,H) = 6.5$ Hz, CH_3), 0.47 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$): $\delta = 143.97$, 143.62, 143.56, 143.50, 143.45, 143.09, 130.96, 130.90, 130.86, 126.11, 54.10, 54.06, 54.03, 48.65, 48.56, 48.46, 42.02, 41.96, 41.24, 41.20, 41.18, 41.14, 37.94, 37.77, 37.60, 37.46, 33.29, 33.27, 33.24, 31.69, 23,45, 23.40, 23.35, 22.22. 20.97, 20.54; ^{31}P NMR ($CDCl_3$): $\delta = -8.7$; $[\alpha]_D = +226.7$ ($c = 1.03$, $CHCl_3$); HR-MS calcd for $C_{30}H_{48}P_2$: 470.3231; found: 470.3229.

General procedure for asymmetric hydrogenation: To a solution of $[Rh(cod)Cl]_2$ (2.5 mg, 0.005 mmol) in MeOH (10 mL) was added **5** (3.7 mg, 0.01 mmol). After the reaction mixture was stirred at room temperature for 10 min, acetophenone (1.0 mmol) was added. The orange-yellow solution was stirred for 2 min, and the desired amount of the additive (as a solution in MeOH) was then added. This mixture was stirred for about 5 min, and hydrogen was introduced. The hydrogenation was performed in a Parr autoclave at room temperature under 30 atm of hydrogen for 24 h. The residue was passed through a short silica gel column to remove the catalyst, and eluted with diethyl ether. The enantiomeric excesses and reaction conversion were measured by gas chromatography on a Supelco β-DEX 120 column. The absolute configuration of the product was determined by comparing the observed rotation with the reported value.[5c,8d]

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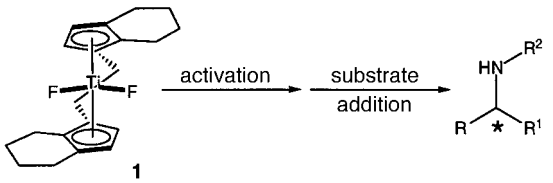
[13] ^{31}P NMR data for [Rh(cod)**5**]Cl (prepared in situ, CD_3OD): ABX system, $\delta = 50.7$ (dd, $^1J(Rh,P) = 140.6$ Hz), $^2J(P,P) = 23.6$ Hz), 37.1 (dd, $^1J(Rh,P) = 141.6$ Hz, $^2J(P,P) = 23.6$ Hz)). It is noteworthy that the ligand **5** in [Rh(cod)(**5**)]Cl does not have C_2 symmetry. A possible explanation is that the phosphabicyclo[2.2.1]heptane is too bulkly to allow the PennPhos to exist in a C_2-symmetrical fashion.

Amine Additives Greatly Expand the Scope of Asymmetric Hydrosilylation of Imines**

Xavier Verdaguer, Udo E. W. Lange, and Stephen L. Buchwald*

Dedicated to Professor Satoru Masamune

The demand for enantiomerically pure secondary amines has prompted considerable effort[1] in the development of catalytic processes for asymmetric hydrogenation[2] and hydrosilylation[3] of imines. We recently reported a highly enantioselective titanium-catalyzed hydrosilylation of imines.[4] This method involves treatment of (*S,S*)-ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)titanium difluoride[5] (**1**) with phenylsilane,[4, 6] which yields a very active catalytic system for the hydrosilylation of *N*-methyl and cyclic imines [Eq. (1)]. For example, *N*-methylimine **2** undergoes complete hydrosilylation within 12 h at room temperature (Table 1, entry 1). Although high turnover numbers (up to 5000) and



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[*] Prof. Dr. S. L. Buchwald, Dr. X. Verdaguer, Dr. U. E. W. Lange
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, MA 02139 (USA)
Fax: (+1) 617-253-3297
E-mail: sbuchwal@mit.edu

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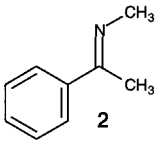

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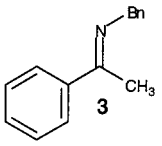

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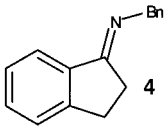

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Table 1. Catalytic reduction of imines with and without the addition of primary amine.[a]

Entry	Silane	Amine additive[b]	Imine	t [h]	Conversion [%]	ee [%]
1	$PhSiH_3$	–	**2**	12[c]	100	97
2	$PhSiH_3$	–	**3**	96[d]	55	47
3	PMHS	–	**2**	48[d]	50	–
4	PMHS	–	**4**	24	5	–
5	PMHS	nHexNH$_2$	**4**	2	100	85
6	PMHS	tBuNH$_2$	**4**	24	39	–
7	PMHS	pyrrolidine	**4**	24	4	–
8	PMHS	iBuNH$_2$	**4**	2	100	92
9	PMHS	(±)-sBuNH$_2$	**4**	2	75	78

[a] The reactions were conducted with 5 mol% of **1** at 60 °C unless otherwise noted. [b] The amines were introduced with a syringe pump over a period of 80 min. [c] 1 mol% catalyst, room temperature. [d] 10 mol% catalyst.

excellent enantioselectivity (93–99% *ee*) were achieved, the reaction is extremely sensitive to steric bulk in the nitrogen substituent. When the analogous *N*-benzylimine **3** was subjected to the standard hydrosilylation conditions[4] the reaction failed to go to completion, and a precipitous drop was observed in enantioselectivity (entry 2). A change in the nature of the silane had a similar effect: When polymethylhydrosiloxane (PMHS) was used instead of $PhSiH_3$, reduction of **2** reached only 50% conversion after 2 d at 60 °C (entry 3).

The rate-determining step in the titanium-catalyzed hydrogenation of imines has been proposed to be cleavage of the Ti–N bond in the intermediate amido complex through a σ-bond metathesis pathway;[7] we presume that the same applies to the hydrosilylation reaction.[8] Our previous work implies that this metathesis, which takes place in the crowded wedge of the bis(tetrahydroindenyl) scaffold, is quite sensitive to steric effects.[7] Specifically, the rate of Ti–N cleavage for imine substrates with moderate to large nitrogen substituents is very low.

It is common practice in organic chemistry to utilize a nucleophilic catalyst (e.g., 4-dimethylaminopyridine) to transform an intermediate into a more reactive species.[9a, b] By analogy, we felt that introduction of a nucleophilic additive into the reaction mixture might convert the titanium–amido intermediate into a more reactive complex and thereby lead to a procedure applicable to a wider range of substrates. Several amines, alcohols, and thiols were tested as additives. Among these, primary amines had the most pronounced effect on the reaction. For example, use of our standard reaction protocol (see Table 2) with *N*-benzyl-1-indanimine (**4**) was ineffective, and only 5% conversion into product was observed after 24 h at 60 °C (Table 1, entry 4). However, slow addition of four equivalents of *n*-hexylamine to the hydrosilylation reaction mixture at 60 °C resulted in complete reduction of **4** within 2 h (entry 5). With **4** as the test substrate, we then studied the influence of the added amine on the outcome of the reaction. Bulky primary amines such as *tert*-butylamine and secondary amines such as pyrrolidine proved to be ineffective (entries 6 and 7). Isobutylamine generally gave the best results: high reaction rate and the greatest enantioselectivity (entry 8).[9c, d] (±)-2-Butylamine (entry 9) was also found to be useful, although it produced a somewhat smaller enantiomeric excess in the reduction of **4**.

Results for the reduction of a series of acyclic imines and details of the experimental protocol are summarized in Table 2. An important feature of this catalytic system is that, in comparison to analogous hydrogenations with a Brintzinger-type catalyst, acyclic amines are reduced with significantly higher levels of enantioselectivity.[10] Generally, amine products are obtained with 91–99% *ee*. It is significant that the enantiomeric excess of the product does not correspond to the *E*:*Z* ratio of the starting imine, in contrast to the earlier hydrogenation.[11] The most dramatic examples of this behavior are represented by entries 8 and 9 in Table 2. Whereas the imines exist as 2.5:1 and 1.8:1 mixtures of *E* and *Z* isomers, titanocene-catalyzed reduction produces amines with 93 and 97% *ee*, respectively. At present we have no explanation for these results, although labeling studies rule out the involvement of enamine intermediates.

An additional practical aspect of the amine-promoted protocol is that it allows use of PMHS, an inexpensive and convenient silylation reagent,[12] as the stoichiometric reductant.[13] Typical catalyst loadings range from 0.5–1 mol%. A reduction in the amount of catalyst to 0.05 mol% compromises neither the yield nor the enantioselectivity of the reaction (entry 5). However, slow addition (syringe pump) of the primary amine (1.5–4 equiv) to the reaction mixture is essential to ensure complete reduction of the starting imine. After all the imine has been consumed, acidic workup provides the desired chiral amine in high yield and a purity greater than 95% (GC and ^{1}H NMR).

Although a detailed mechanistic study has not yet been undertaken, one possible pathway is the catalytic cycle shown in Scheme 1a. Amines are obtained with the same absolute configuration as in the case of titanium-catalyzed hydrogenation, which suggests a chirality-transfer step in which the imine is inserted into the Ti—H bond of the titanocene hydride **5** in analogy to the hydrogenation case.[7] The additive would then react with the sterically encumbered titanium–amido complex **6** to release a chiral amine and to generate the new amido complex **7**. Finally, reaction of the less hindered complex **7** with silane regenerates **5**. When PMHS is used as a hydride source the ^{1}H NMR spectrum of the crude product shows the presence of free amine, whereas the isobutylamine additive is attached to the siloxane polymer.

The proposed catalytic cycle also explains why slow addition of the additive is required. Thus, the promoter can also react with titanocene hydride **5**, in a process that competes with imine reduction, to generate complex **7** with concomitant loss of hydrogen (Scheme 1b). Further reaction of **7** with silane affords a silylated primary amine. When the primary amine is present in high concentration, this reaction pathway becomes an important side reaction.[14]

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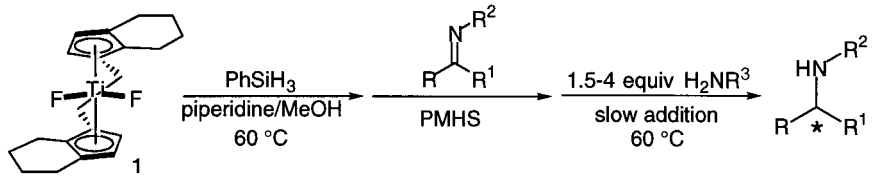
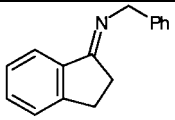
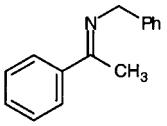
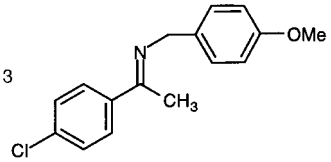
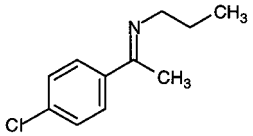
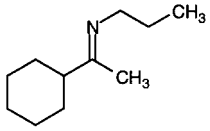
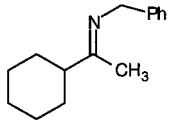
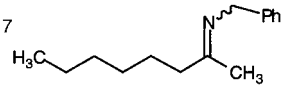
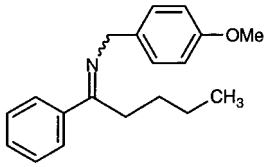
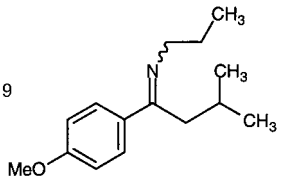


Table 2. Amine-promoted catalytic assymetric reduction of acyclic imines.

Entry	Imine	*E*:*Z*[a]	Cat. [mol %]	Silane	Amine	Yield [%][b]	*ee* [%]
1		> 50:1	1	PMHS	*i*BuNH$_2$	96	92[c]
2		15:1	0.5	PMHS	*i*BuNH$_2$	95	98[c, d]
3		15:1	0.5	PMHS	*i*BuNH$_2$	92	99[c]
4		18:1 18:1	2 1	PhSiH$_3$ PMHS	*s*BuNH$_2$ *i*BuNH$_2$	88 97	96[e] 98
5		20:1 20:1	2 0.05	PhSiH$_3$ PMHS	*s*BuNH$_2$ *i*BuNH$_2$	73 95	93[e] 98
6		23:1	0.5	PMHS	*i*BuNH$_2$	96	91[c, d]
7		3.5:1	1	PMHS	*i*BuNH$_2$	96	69[e]
8		2.5:1	5	PMHS	*i*BuNH$_2$	86	93[d, f]
9		1.8:1	1	PhSiH$_3$	*i*BuNH$_2$	90	97[f]

[a] Established by ^{1}H NMR spectroscopy. [b] Yields are based on isolated compounds with greater than 95 % purity (determined by GC and ^{1}H NMR spectroscopy). [c] The enantiomeric excess (*ee*) was established by HPLC (Chiralcel-OD column). [d] The absolute configuration of the *S* product was determined by polarimetry. [e] The enantiomeric excess (*ee*) was determined by GC (Chiraldex-B-PH and Chiraldex-G-TA columns). [f] The enantiomeric excess (*ee*) was determined by ^{1}H NMR analysis of the diastereomeric salts formed upon addition of (*R*)- or (*S*)-*O*-acetylmandelic acid.

An alternative explanation for the effect of added amine is shown in Scheme 1c. As mentioned above, the primary amine can be silylated to an *N*-silylamine. This species might facilitate cleavage through silylation of the Ti–N bond by coordination to the titanium center followed by σ-bond metathesis. Such an amine exchange process would be intramolecular, which may make it particularly facile. The product of amine exchange is **7**, which can then be rapidly

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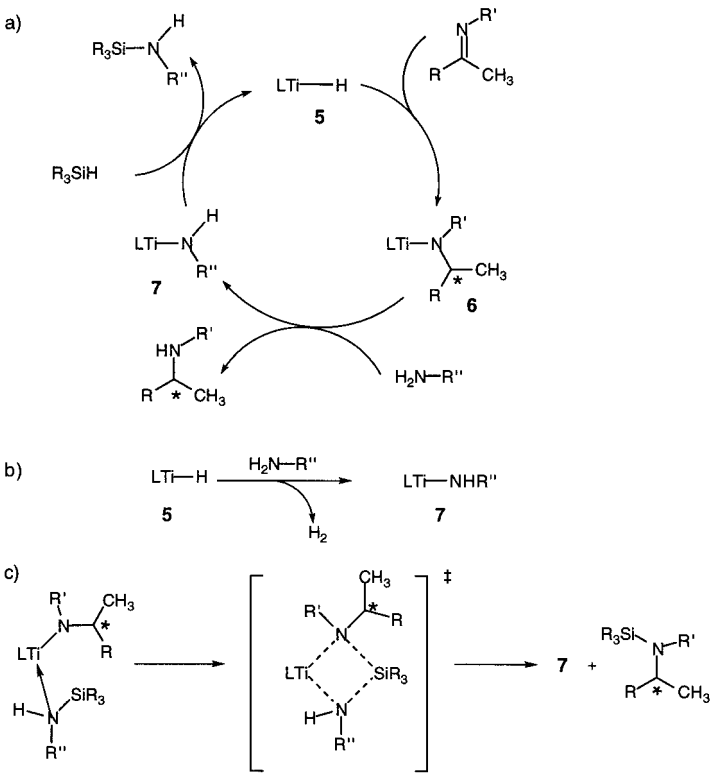

Scheme 1. a) Postulated catalytic cycle. b, c) See text. L = (*S*,*S*)-ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl).

converted into **5** and the silylated amine.[15] Experiments are currently underway to probe the viability of these possible mechanisms.

Thus, use of primary amines as additives in titanium-catalyzed asymmetric hydrosilylation of imines greatly expands the scope of the reaction. This new protocol utilizes PMHS, a convenient and inexpensive hydride source, and encourages the preparation of a wide array of almost enantiomerically pure secondary amines. It is significant that the enantioselectivity achieved is not limited by the *E*:*Z* ratio of the starting imine.[8] Further work is in progress to clarify the mechanism of the transformation and its application to other asymmetric processes.[16]

Experimental Section

Typical experimental procedure: A dry resealable Schlenk flask was charged with **1** (9 mg, 0.025 mmol) and dry THF (1 mL) under argon. The resulting yellow solution was heated to 60 °C, and $PhSiH_3$ (12 μL, 0.1 mmol), piperidine (9 μL, 0.1 mmol), and methanol (4 μL, 0.1 mmol) were added by syringe. The mixture was stirred at 60 °C for 15 – 20 min, which produced a color change from yellow to green. THF (1 mL) and PMHS (1.65 mL, 27 mmol) were then added by syringe. The sealed Schlenk flask was removed from the oil bath, cooled to room temperature, and introduced into an argon-filled glovebox. *N*-Benzyl-1-indanimine (0.64 g, 2.9 mmol) was added, and the reaction mixture was heated to 65 °C; the color of the reaction mixture changed to brown. Isobutylamine (0.6 mL, 6 mmol) was added to this solution over a period of 2.5 h (0.25 mL h^{-1} flow rate) with a syringe pump. After addition of the amine the color of the reaction mixture had changed from brown to green, and GC analysis showed complete consumption of the starting material. The reaction mixture was cooled to room temperature, removed from the glovebox, diluted with Et_2O (30 mL), and stirred with 1 M HCl (15 mL) for 30 min (**caution**: vigorous bubbling). The aqueous layer was separated, made basic with 3 M NaOH, and extracted with Et_2O. The combined Et_2O layers were dried ($MgSO_4$) and concentrated in vacuo to afford 611 mg of (+)-*N*-benzylindan-1-amine (95 % yield, 92 % *ee*). In the case of more reactive substrates or with use of a higher catalyst loading it proved feasible to add the amine promoter portionwise by syringe. For reactions with 1 mol % or more of catalyst, amine addition was conducted in a hood under argon in a septum-capped Schlenk flask.

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[14] Although a decrease in the concentration of amine additive was observed, we have not quantified the extent of its conversion into a silylamine.
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Facile *meso* Functionalization of Porphyrins by Nucleophilic Substitution with Organolithium Reagents**

Werner W. Kalisch and Mathias O. Senge*

Dedicated to Professor Emanuel Vogel on the occasion of his 70th birthday

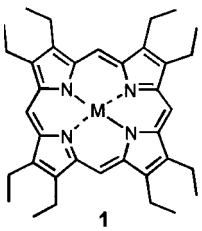
It is generally accepted that the *meso* positions of porphyrins are the most reactive both for electrophilic and nucleophilic substitutions.[1] While several examples have been described for S_E reactions on porphyrins[1, 2] only scattered attempts have been made to use S_N reactions for the modification of porphyrins. Published examples of the latter all utilized some form of activated porphyrin, for example π-radical cations or dications,[3] high-valent metal derivatives,[4] or activated porphyrins with electron-withdrawing substituents.[5] Some of these reactions are suitable only for the preparation of 5,5′-disubstituted dihydroporphyrins (phlorins).[4b, 6] At best two substituents could be introduced with electrophilic or nucleophilic reagents, and the methods were limited with regard to the starting porphyrin or the introduction of different substituents.[7] To date, no general method exists for the direct *meso* substitution of unactivated porphyrins with alkyl or aryl residues or for the introduction of more than two substituents.

During a systematic study on the use of organometallic reagents for C–C coupling reactions, we found that octaethylporphyrin (H_2(oep); oep = dianion of octaethylporphyrin) undergoes facile substitution reactions with organolithium reagents; this allows the synthesis of a variety of porphyrins with alkyl or aryl substituents at the *meso* positions. Treatment of [Ni(oep)] (**1a**) with butyllithium (3 – 4 equiv) between − 80 and − 100 °C in THF followed by hydrolysis of the intermediate (a Meisenheimer-type complex) provided the corresponding 5-butyl-15-hydroporphodimethene. Subsequent oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave the *meso*-butylporphyrin **2a** in quantitative yield. The reaction sequence formally proceeds as shown in Equation (a).

$$[M(oep)] \xrightarrow{LiR} [M(oepLiR)] \xrightarrow{H_2O} [M(oepHR)] \xrightarrow[-H_2]{DDQ} [M(oepR)] \quad (a)$$

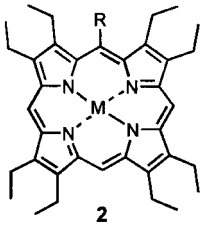
The reaction is easily extended to a variety of different alkyl and aryl reagents, including those that allow further chemical modifications and coupling reactions. For example, reaction of **1a** with 2-(1,3-dioxane-2-yl)ethyllithium gave **2e** in 70% yield. The reaction is not limited to alkyllithium reagents, but can also be used for the convenient introduction of aryl groups. Reaction of phenyllithium with **1a** gave **2f** in 65% yield. Again, aryl substituents could be introduced which will allow further chemical transformations. Compound **2h**, whose 4-bromophenyl group is useful for other organometallic coupling reactions, could be prepared from **1a** with *p*-bromophenyllithium in 40% yield. Introduction of the 2,5-dimethoxyphenyl group in **2i**, which proceeded in 65% yield, is an example of the synthesis of donor – acceptor systems (by formation of the benzoquinone). The free base porphyrins substituted in the 5-position are available by demetalation of the nickel(II) complexes. For example, treatment of **2a** with concentrated sulfuric acid gave **2b** in 75% yield.

Next, we turned out attention to the reactivity of different metals in the same porphyrin. Treatment of **1b** with butyllithium under standard conditions gave the respective free base **2b** in 40% yield, while **1c** and **1d** could be converted into the monobutylmetalloporphyrins **2c** and **2d** in 75 and 40% yield, respectively. Even more surprising was the result that free base porphyrins such as **1e** could be treated directly with butyllithium to give **2b** in 50% yield or with phenyllithium to give **2g** in 90% yield. Presumably, this reaction proceeds by initial formation of a dilithioporphyrin [Li_2(oep)] of the type

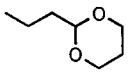
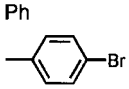
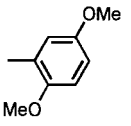


1

	M
1a	Ni
1b	Zn
1c	Cu
1d	Co
1e	2H



2

	M	R
2a	Ni	Bu
2b	2H	Bu
2c	Cu	Bu
2d	Co	Bu
2e	Ni	
2f	Ni	Ph
2g	2H	Ph
2h	Ni	
2i	Ni	

[*] Priv.-Doz. Dr. M. O. Senge, Dipl.-Chem. W. W. Kalisch
Institut für Organische Chemie (WE02)
Fachbereich Chemie der Freien Universität
Takustrasse 3, D-14195 Berlin (Germany)
Fax: (+49) 30-838-4248
E-mail: mosenge@chemie.fu-berlin.de.

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