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Catechol-Based Phosphoramidites: A New Class of Chiral Ligands for Rhodium-Catalyzed Asymmetric Hydrogenations

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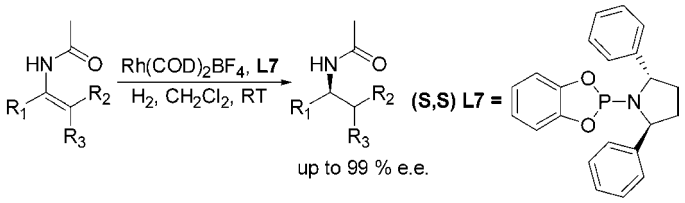
ABSTRACT



The synthesis and application of a new class of catechol-based phosphoramidites is described. Ees up to 99% were obtained in the rhodium-catalyzed asymmetric hydrogenation of dehydroamino acids and enamides.

Rhodium-catalyzed asymmetric hydrogenation of enamides is a key method for synthesizing enantiomerically pure amino acids and amines.[1] The majority of successful ligands used in this reaction are bidentate in nature,[2] e.g., DUPHOS (1,2-Bis(-2,5-dimethylphospholano)benzene),[3] DiPAMP (1,2-ethanediylbis[(*o*-methoxyphenyl)-phenyl-phosphine]),[4] DIOP (2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane),[5] BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl),[6] PennPhos (*P*,*P*′-1,2-phenylenebis(*endo*-2,5-dialkyl-7-phosphabicyclo-[2.2.1]heptane),[7] and ferrocenyl-based ligands.[8] With the exception of CAMP (*o*-anisyl-methylcyclohexylphosphine),[9] limited success was obtained with monodentate ligands.[1c] These ligands were considered not particularly effective since they lack the possibility to form chelating complexes with the metal. After nearly 30 years of asymmetric hydrogenation, it was unequivocally demonstrated in 2000 that bidentate chiral ligands are not a conditio sine qua non to reach high enantioselectivities. Three groups showed that monodentate phosphonites,[10a] phosphites,[10b] and phosphoramidites[10c] can be applied successfully as chiral ligands in rhodium-catalyzed asymmetric hydrogenation providing excellent enantioselectivities (Figure 1). A major advantage of these monodentate ligands is that they can be

(1) For reviews see: (a) Chaloner, P. A.; Esteruelas, M. A.; Joó, F.; Oro, L. A. *Homogeneous Hydrogenation*; Kluwer: Dordrecht, 1994. (b) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, Chapter 5.1. (c) Lagasse, F.; Kagan, H. B. *Chem. Pharm. Bull.* **2000**, *48*, 315.

(2) For a review, see: Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.

(3) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8515.

(4) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946.

(5) (a) Dang, T.-P.; Kagan, H. B. *Chem. Commun.* **1971**, 481. (b) Kagan, H. B.; Dang, T.-P. *J. Am. Chem. Soc.* **1972**, *94*, 6429.

(6) (a) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932. (b) Takaya, H.; Akutagawa, S.; Noyori, R. *Org. Synth.* **1988**, *67*, 20.

(7) (a) Jiang, Q.; Jiang, Y.; Xiao, D.; Cao, P.; Zhang, X. *Angew. Chem., Int. Ed.* **1998**, *37*, 1100. (b) Zhang, Z.; Zhy, G.; Jiang, Q.; Xiao, D.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 1774.

(8) JosiPhos: Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062. FerroPhos: Kang, J.; Lee, J. H.; Ahn, S. H.; Choi, J. S. *Tetrahedron Lett.* **1998**, *39*, 5523.

(9) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D. *Chem. Commun.* **1972**, 10.

(10) (a) Claver, C.; Fernandez, E.; Gillon, A.; Heslop, K.; Hyett, D. J.; Martorell, A.; Orpen, A. G.; Pringle, P. G. *Chem. Commun.* **2000**, 961 (b) Reetz, M. T.; Mehler, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 3889 (c) Van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; Van Esch, J.; De Vries, A. H. M.; De Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 11539.

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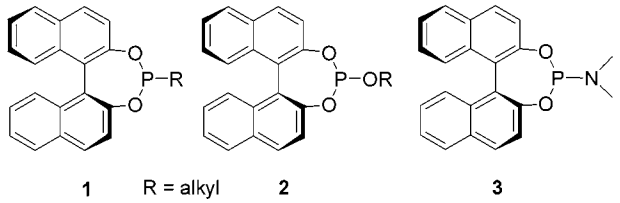


Figure 1. Monodentate phosphonites, phosphites, and phosphoramidites.

prepared in one or two steps at low costs, which makes variations very easy.

All successful monodentate ligands recently introduced consist of a chiral diol backbone, with another chiral or achiral moiety attached to phosphorus.[11] The chirality of the backbone dictates, in nearly all cases, the chirality of the product.[10b] The chirality of the other moiety at phosphorus is found to be less important. It is illustrative that one of the most effective monodentate ligands for hydrogenation reactions, the commercially available[12] phosphoramidite MonoPhos (**3**), has, besides the chiral BINOL part, an achiral *N*,*N*-dimethylamine moiety. A few reports on alternative ligands using chiral backbones such as biphenyls or spiro compounds have appeared.[13]

We now describe a new class of monodentate phosphoramidites for the rhodium-catalyzed asymmetric hydrogenation of enamides, based on an *achiral* catechol backbone. In this case, the chirality of the products must be dictated solely by the chirality of the amine moiety. Not only is the chiral moiety the amine instead of the diol but also the bulkiness

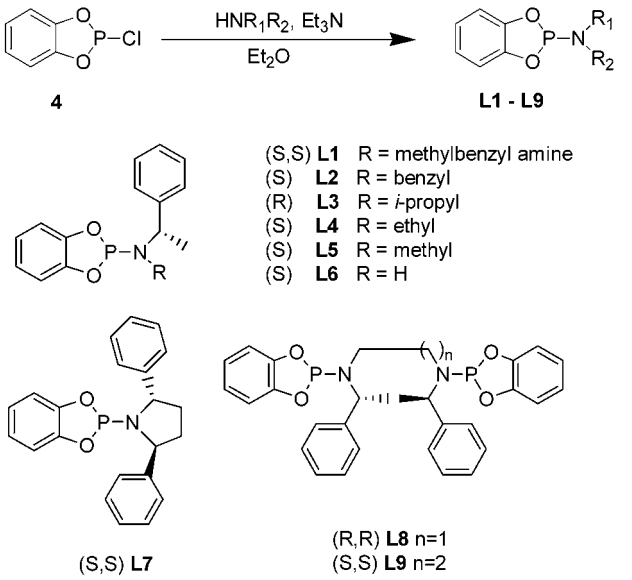


Figure 2. Catechol-based phosphoramidites.

of the diol backbone is reduced, as a planar catechol is present whereas the size of the amine moiety is increased compared to MonoPhos (**3**). From earlier results it was evident that, in the case of BINOL-derived phosphoramidites, a small amine moiety is favored for the hydrogenation of dehydroamino acids.[10c,11c]

The synthesis of the ligands is straightforward, starting with the commercially available *o*-phenylene phosphorochloridite (**4**) and an appropriate amine. A variety of easily accessible chiral amines, based on 1-phenyl ethylamine, were used in the preparation of ligands **L1**−**6** (Figure 2). The cyclic analogue **L7** of ligand **L1** was obtained from the corresponding chiral amine.[14] For comparison, bidentate ligands **L8** and **L9** were also examined.

As a benchmark reaction, the ligands were tested in the rhodium-catalyzed asymmetric hydrogenation of *N*-acyl dehydrophenylalanine methyl ester (**5**) under standard conditions.[15] The results are depicted in Table 1.

The catalysts based on ligands **L2**−**6** gave modest to full conversions, while the ligand **L1**, based on a sterically demanding amine, surprisingly gave no conversion at all. The enantiomeric excesses are disappointing in all cases (entries 1−6). In sharp contrast, however, is the excellent yield and enantioselectivity of >92% reached with ligand **L7** (entry 7). Although **L1** and **L7** have a similar kind of structure, a remarkable difference in activity was observed by introduction of a ring structure in the ligand. The bidentate ligands **L8** and **L9** gave full conversion but rather poor ees, although a longer spacer in the ligand resulted in a slightly higher ee (entries 8 and 9, Table 1).

To expand the scope of the catalytic hydrogenation employing **L7**, several substrates were tested. As shown in

(11) (a) Komarov, I. V.; Börner, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 1197. (b) Reetz, M. T.; Mehler, G.; Meiswinkel, A.; Sell, T. *Tetrahedron Lett.* **2002**, *43*, 7941. (c) Jia, X.; Li, X.; Xu, L.; Shi, Q.; Yao, X.; Chan, A. S. C. *J. Org. Chem.* **2003**, *68*, 4539. (d) Reetz, M. T.; Sell, T.; Meiswinkel, A.; Mehler, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 790. (e) van den Berg, M.; Minnaard, A. J.; Haak, R. M.; Leeman, M.; Schudde, E. P.; Meetsma, A.; Feringa, B. L.; de Vries, A. H. M.; Maljaars, C. E. P.; Willans, C. E.; Hyett, D.; Boogers, J. A. F.; Henderickx, H. J. W.; de Vries, J. G. *Adv. Synth. Catal.* **2003**, *345*, 308. (f) Li, X.; Jia, X.; Lu, G.; Au-Yeung, T. T.-L.; Lam, K.-H.; Lo, T. W. H.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2003**, *14*, 2687. (g) Jia, X.; Guo, R.; Li, X.; Yao, X.; Chan, A. S. C. *Tetrahedron Lett.* **2002**, *43*, 5541. (h) Chen, W.; Xiao, J. *Tetrahedron Lett.* **2001**, *42*, 2897. (i) Junge, K.; Oehme, G.; Monsees, A.; Riermeier, T.; Dingerdissen, U.; Beller, M. *Tetrahedron Lett.* **2002**, *43*, 4977. (j) Peña, D.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 14552. (k) Peña, D.; Minnaard, A. J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 475. (l) Doherty, S.; Robins, E. G.; Pál, I.; Newman, C. R.; Hardacre, C.; Rooney, D.; Mooney, D. A. *Tetrahedron: Asymmetry* **2003**, *14*, 1517. (m) Junge, K.; Oehme, G.; Monsees, A.; Riermeier, T.; Dingerdissen, U.; Beller, M. *J. Organomet. Chem.* **2003**, *675*, 91. (n) Reetz, M. T.; Mehler, G. *Tetrahedron Lett.* **2003**, *44*, 4593. (o) Reetz, M. T.; Goossen, L. J.; Meiswinkel, A.; Paetzold, J.; Jensen, J. F. *Org. Lett.* **2003**, *5*, 3099. (p) Peña, D.; Minnaard, A. J.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Org. Biomol. Chem.* **2003**, *1*, 1087. (q) Ostermeier, M.; Brunner, B.; Korff, C.; Helmchen, G. *Eur. J. Org. Chem.* **2003**, 3453. (r) Van den Berg, M.; Haak, R. M.; Minnaard, A. J.; De Vries, A. H. M.; De Vries, J. G.; Feringa, B. L. *Adv. Synth. Catal.* **2002**, *344*, 1003.

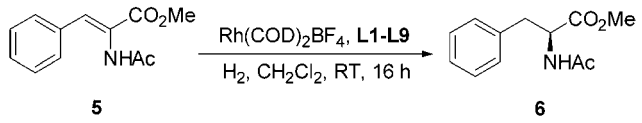
(12) MonoPhos (**3**) is commercially available from Strem chemicals.

(13) (a) Chen, W.; Xiao, J. *Tetrahedron Lett.* **2001**, *42*, 8737. (b) Fu, Y.; Xie, J.-H.; Hu, A.-G.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Chem. Commun.* **2002**, 480. (c) Hu, A.-G.; Fu Y.; Xie, J.-H.; Zhou, H. Wang, L−X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2002**, *41*, 2348. (d) Hannen, P.; Militzer, H.-C.; Vogl, E. M.; Rampf, F. A. *Chem. Commun.* **2003**, 2210. (e) Hua, Z.; Vassar, V. C.; Ojima, I. *Org. Lett.* **2003**, *5*, 3831.

(14) Aldous, D. J.; Dutton, W. M.; Steel, P. G. *Tetrahedron: Asymmetry* **2000**, *11*, 2455.

(15) Standard conditions are 0.2 mmol of substrate, 1 mol % catalyst (**L**:Rh = 2:1) in 4 mL of CH_2Cl_2 at rt and 5 bar of H_2 pressure.

Table 1. Asymmetric Hydrogenation of *N*-Acyl Dehydrophenylalanine Methyl Ester (**5**) Catalyzed by Rh−Phosphoramidite Ligand Systems Derived from Catechol



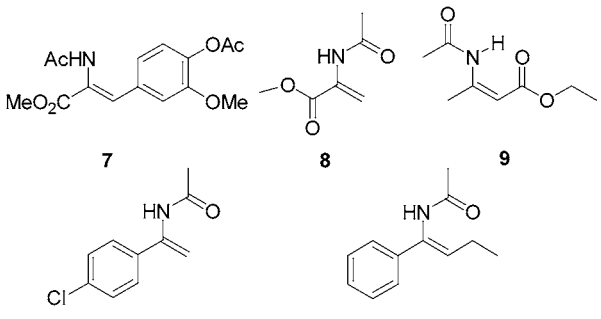
5 **6**

entry	ligand	conversion[a,b]	ee[c]
1	**L1**	0	
2	**L2**	60	<3
3	**L3**	45	<3
4	**L4**	100	<3
5	**L5**	60	<3
6	**L6**	90	<3
7	**L7**	100	**92**[d]
8	**L8**	100	5[d]
9	**L9**	100	32[d]

[a] Reactions performed under standard conditions.[15] [b] Conversions determined by ^{1}H NMR; besides product and/or starting material, no side products were observed. [c] Ee determined by CSP GC (CP Chiralsil-L-Val). [d] Product has the (*R*)-configuration, except when **L8** is used.

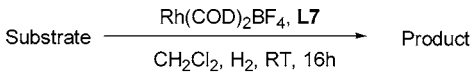
Table 2, other α-amino acid precursors gave full conversions with modest ees (entries 1 and 2). With full conversions, isolated yields (Tables 2 and 3) are 99% after filtration. In contrast, *β*-amino acid precursor **9** gave no conversion at all

Table 2. Asymmetric Hydrogenation of a Variety of Alkenes Catalyzed by Rh−Phosphoramidite (**L7**) Catalyst



7 **8** **9**

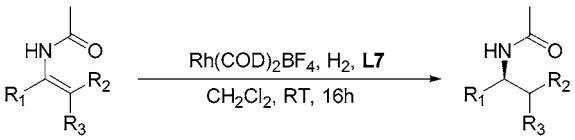
10 **11**



entry	substrate	product	conversion[a,b]	ee[c,d]
1	**7**	**12**	100	89
2	**8**	**13**	100 (>99)	66
3	**9**	**14**	0	
4[e]	**9**	**14**	40	80
5	**10**	**15**	100 (>98)	89
6	**11**	**16**	100 (>99)	**99**

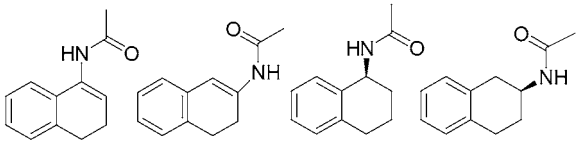
[a] Reactions performed under standard conditions.[15] [b] Conversions determined by ^{1}H NMR. Besides product and/or starting material, no side products were observed; isolated yields are given in parentheses. [c] Ees determined by CSP GC or HPLC (CP Chiralsil-L-Val, CP Chiralsil-Dex CB, Chiralcel OD). [d] All products had the (*R*)-configuration. [e] Reaction was performed in *i*-PrOH.

Table 3. Asymmetric Hydrogenation of Enamides by Rh−Phosphoramidite **L7** Catalyst[a]



10 : R_1 = *p*-ClPh, R_2 = H, R_3 = H
11 : R_1 = Ph, R_2 = Et, R_3 = H
17: R_1 = *t*-Bu, R_2 = H, R_3 = H
18: R_1 = Ph, R_2 = H, R_3 = H
19 : R_1 = *p*-MePh, R_2 = H, R_3 = H
20 : R_1 = *p*-MeOPh, R_2 = H, R_3 = H
21 : R_1 = Ph, R_2 = H, R_3 = Et
22 : R_1 = Ph, R_2 = Et/H, R_3 = H/Et
23 : R_1 = Ph, R_2 = Me, R_3 = Me

15: R_1 = *p*-ClPh, R_2 = H, R_3 = H
16 : R_1 = Ph, R_2 = Et, R_3 = H
26: R_1 = *t*-Bu, R_2 = H, R_3 = H
27 : R_1 = Ph, R_2 = H, R_3 = H
28 : R_1 = *p*-MePh, R_2 = H, R_3 = H
29 : R_1 = *p*-MeOPh, R_2 = H, R_3 = H
30 : R_1 = Ph, R_2 = Me, R_3 = Me



24 **25** **31** **32**

entry	substrate	product	ee[b−e] CH_2Cl_2 5 bar	ee[b−e] CH_2Cl_2 25 bar	ee[b−e] EtOAc 25 bar
1	**17**	**26**	63	70	26
2	**18**	**27**[f]	92	93	**96.5**
3	**19**	**28**	95	94	**97**
4	**20**	**29**	97	97	**97**
5	**10**	**15**	89	89	94
6	**11**	**16**	**99**	>**99**	>**99**
7	**21**	**16**	90	88	80
8	**22**[g]	**16**	92	93	84
9	**23**	**30**	9 (3.5)	20 (6)	<3 (14)
10	**24**	**31**	35 (48)	35 (95)	27
11	**25**	**32**	4 (14)	9 (38)	35 (40)

[a] Reactions performed in 4 mL of solvent with 0.2 mmol of substrate and 1 mol % catalyst at rt under a H_2 atmosphere for 16 h. [b] Conversions determined by ^{1}H NMR; besides product and/or starting material, no side products were observed. [c] Ees determined by CSP GC (CP Chiralsil-Dex CB). [d] Conversions are given in parentheses if reactions were not run to completion. [e] In all cases, the (*R*)-enantiomer was obtained, except for products **30** and **31**. [f] Isolated yield for **27** was >99%. [g] Mixture with a 3:2 ratio of (*E*)- and (*Z*)-alkene was used.

in CH_2Cl_2 (entry 3). When the reaction was performed in *i*-PrOH, 80% ee was obtained at 40% conversion (entry 4). In earlier studies,[11j] it was shown that *i*-PrOH is the best solvent for the Rh−phosphoramidite catalyst system in the hydrogenation of *β*-amino acid precursors with a *Z*-configuration. Elimination of the internal hydrogen bond by *i*-PrOH has been postulated as the origin of this change in reactivity.[16] Enamides **10** and **11** gave full conversion, and the ees were good to excellent (entries 5 and 6).

This initial study revealed that **L7** is comparable to MonoPhos (**3**) with respect to selectivity in the hydrogenation of α-amino acid precursors. In the hydrogenation of enamides, however, higher enantioselectivities are observed with a remarkable 99% ee for the hydrogenation of **11**.[10c,11r]

(16) (a) Lee, S.-g.; Zhang, Y. J. *Org. Lett.* **2002**, *4*, 2429 (b) Lubell, W. D.; Kitamura, M.; Noyori, R. *Tetrahedron: Asymmetry* **1991**, *2*, 543.

With these results in hand we decided to screen a series of enamides in two solvents at 5 and 25 bar of H_2 pressure to examine the scope of the asymmetric hydrogenation. The substrates were synthesized using the methods of Zhang[7b] and Burk.[17]

With the exception of **23**, containing a tetrasubstituted alkene, and the bicyclic systems **24** and **25** (Table 3, entries 9−11, column 4), all substrates gave full conversion. The enantioselectivity is lower when R_1 is an alkyl group instead of an aryl group (compare entries 1 and 2, column 4). This can be due to an increase of steric hindrance, although this seems to be a common feature of this catalytic system, since similar results were also observed in the hydrogenation of the α-amino acid precursors (compare entry 7, Table 1, and entry 2, Table 2). Favorable $\pi-\pi$ interactions between the aromatic moiety of the substrate and the ligand might be another reason for this observation. Different substituents on the aromatic ring seem to have hardly any influence on the enantioselectivity (entries 2−5, column 4). Trisubstituted alkenes gave good to excellent enantioselectivities. The best results were obtained with enamides with a *Z*-configuration (entries 6 and 7, column 4), while an *E*/*Z* mixture gave the calculated average of the enantioselectivities for both isomers (entry 8, column 4). Tetrasubstituted alkenes and bicyclic systems are not suitable substrates for this new catalytic system. Low conversions and moderate enantioselectivities were obtained (entries 9−11, column 4). High enantioselectivities for these substrates have been obtained with a variety of bidentate phosphines.[18] Reasonable enantioselectivities for alkene **24** were obtained using MonoPhos (**3**) at −20 °C.[11g]

An increase in the pressure to 25 bar had no influence on the enantioselectivity, although the conversion did increase.[19] Only in the case of the tetrasubstituted alkene and the bicyclic systems derived from β-tetralone did the ee increase (entries 9 and 11).

The use of EtOAc as solvent resulted in higher enantioselectivities for most of the substrates (Table 3, column 6). Surprisingly, the only exceptions are those with R_1 is a *t*-Bu group (entry 1) or when R_3 is not a hydrogen (entries 7−10).

In conclusion, a new class of monodentate phosphoramidites has been developed on the basis of an achiral catechol backbone. Notable features are the excellent levels of enantioselectivity and high conversions obtained in the rhodium-catalyzed hydrogenation of enamides. These enantioselectivities are the highest reached so far for monodentate ligands with this class of substrates and are comparable to those achieved using bidentate ligands.

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Supporting Information Available: Experimental details and chromatographic and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084.

(18) Gridnev, I. D.; Yasutake, M.; Higashi, N.; Imamoto, T. *J. Am. Chem. Soc.* **2001**, *123*, 5268.

(19) Reactions were run overnight, although in most cases reactions were completed in 4 h at 5 bar and in 2 h at 25 bar of hydrogen pressure.