Asymmetric Catalysis, 125[+]

Synthesis of the Stereoisomers of Methohexital by Palladium-Catalyzed Allylation

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Dedicated to Professor Bernt Krebs on the occasion of his 60th birthday

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Allylation of 1-methyl-5-(1′-methylpent-2′-ynyl)barbituric acid (MBS) with allyl acetate using in situ catalysts of palladium(II) acetylacetonate and chiral phosphane imine ligands resulted in the enantioselective formation of 5-allyl-1-methyl-5-(1′-methylpent-2′-ynyl)barbituric acid (Methohexital), an important anesthetic drug. Both, MBS and Methohexital contain two stereogenic carbon atoms. In MBS, the asymmetric centre in the barbiturate system is labile due to enolization. The asymmetric centre in the hexyne side chain is stable and racemic. The two asymmetric centres of Methohexital are stable and give rise to four stereoisomers, two diastereomeric racemates. An analysis of the isomers of MBS and Methohexital was established on the basis of ^{1}H NMR and, in particular, GC including a base-line separation of the four stereoisomers of Methohexital. The stereoselectivity of the allylation is difficult to control, because the new quaternary asymmetric centre in the barbiturate ring of Methohexital is formed within the nucleophile, attacking the η^3-allyl ligand of the catalyst from the side opposite to the palladium atom. Classical optically active ligands, such as diop or norphos, give only 2–6 % ee. Chiral phosphane imine ligands are a successful class of compounds, synthesized by Schiff base condensation of (2-formylphenyl)diphenylphosphane with optically active primary amines. The most efficient ligands have a hydroxymethyl and a bulky alkyl substituent at the asymmetric centre in the imine part, e.g. the L-*iso*-leucinol and the L-*tert*-leucinol derivatives **5** and **7**. In the Pd-catalyzed allylation of MBS a kinetic resolution and the effect of the enantioselective catalyst interplay, the contributions of which are separated. For MBS the best stereoselectivity factor of the kinetic resolution $s = k_R/k_S$ was 2.6 and 83 % "ee" were achieved. The corresponding values for Methohexital were $s = 3.5$ and 80 % ee in the α-*dl* pair. For 10 mixtures of Methohexital stereoisomers the anesthetic doses for rats were determined. With 9.1 mg/kg body weight of the animal the sample obtained from the catalysis with the D-α-phenylglycinol derivative **8** gave a much lower anesthetic dose than the widely used narcotic Brevimytal®Natrium, the sodium salt of the α-*dl* racemate of Methohexital, with 13.0 mg/kg body weight.

Introduction

Recently, we reported on the application of the enantioselective palladium-catalyzed allylic alkylation in the chemistry of barbituric acid derivatives.[2] The starting material 1,5-dimethylbarbituric acid could be converted into the product 5-allyl-1,5-dimethylbarbituric acid in an enantiomeric excess of up to 34% ee by variation of the bases and the optically active ligands.[2–4] In the present paper we transferred the experiences gained in the enantioselective allylation of the model system 1,5-dimethylbarbituric acid to the synthesis of 5-allyl-1-methyl-5-(1′-methylpent-2′-ynyl)-barbituric acid (Methohexital). Methohexital is a pharmaceutically important short-time anesthetic (Eli Lilly).[5–7] For a narcosis on an average 150 mg of substance are needed per person.[8,9] The sodium salt of the α-*dl* racemate of Methohexital is commercially available (trade name Brevimytal®Natrium).[5–11] Besides the allylic group there is a 1′-methylpent-2′-ynyl substituent in 5-position of the barbituric acid skeleton. Therefore, two asymmetric centres result, one in 5-position of the barbiturate system and one in 2′-position of the hexyne side chain. Consequently, there are four stereoisomers, two diastereomeric racemates (*R*,*R*)/(*S*,*S*) and (*R*,*S*)/(*S*,*R*). Gibson and Doran found different narcotic effects for the four stereoisomers.[12,13] The individual enantiomers can be obtained by regiospecific condensation of the enantiomers with respect to the 1′-methylpent-2′-ynyl side chain and subsequent diastereomer separation.[13] The advantage of a synthesis of Methohexital by Pd-catalyzed allylic alkylation is the accessibility of differ-

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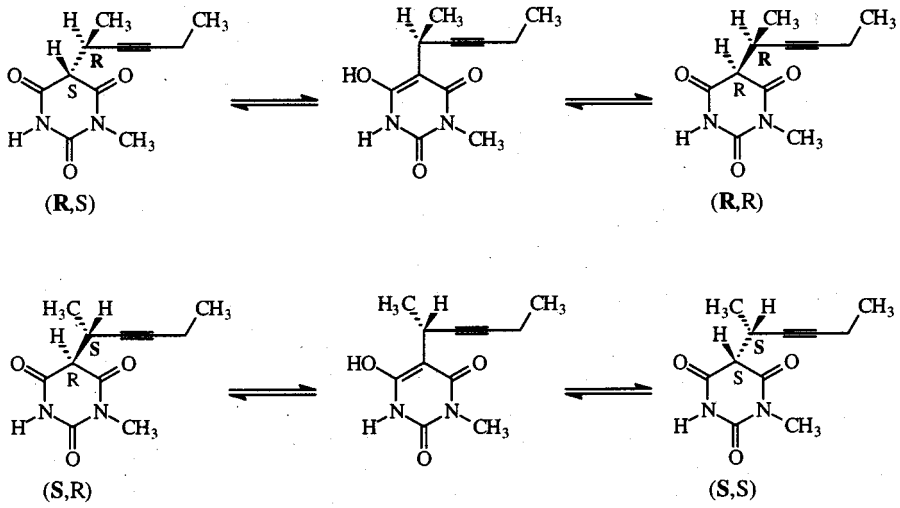


Scheme 1. Keto-enol tautomerism of the labile asymmetric centre of MBS in the barbiturate system

ently enriched diastereomeric and enantiomeric mixtures in one reaction step.

We describe the preparation of the starting material 1-methyl-5-(1′-methylpent-2′-ynyl)barbituric acid (MBS), the analysis of its stereoisomers and its Pd-catalyzed allylation as well as the analysis of the diastereomers and enantiomers of the product Methohexital and the results of the catalytic runs (variation of base and optically active ligand). Then we report on the separation of the contributions of the kinetic resolution and the optically active catalyst, which superpose in the enantioselective Pd-catalyzed allylation of MBS. Finally, the Methohexital mixtures synthesized are tested with regard to their narcotic effect in rats.[3,4]

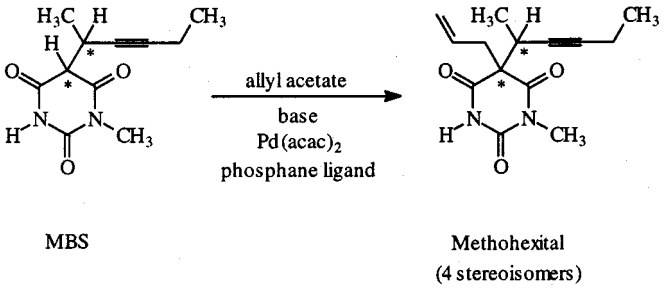
1-Methyl-5-(1′-methylpent-2′-ynyl)barbituric Acid (MBS) and Analysis of Its Stereoisomers

1-Methyl-5-(1′-methylpent-2′-ynyl)barbituric acid (MBS) is synthesized in five steps.[3,4,10−15] MBS contains two asymmetric centres. Therefore, it forms two diastereomeric pairs of enantiomers. The signals of the four stereoisomers of MBS appear in approximately equal intensities in the ^{1}H-NMR spectrum (*N*-methyl groups) after addition of the shift reagent (*S*)-(+)-1-(9′-anthryl)-2,2,2-trifluoroethanol. To follow the accumulation of the stereoisomers of MBS during the catalytic process a GC separation of the stereoisomers on a chiral CP-Chirasil-Dex-CB column (length 25 m), coated with permethylated β-cyclodextrin, was developed. Two peaks of equal areas were obtained, each of which contains the two stereoisomers of MBS, which interconvert by the keto-enol tautomerism of the labile asymmetric centre of the barbiturate system (Scheme 1).

This keto-enol tautomerism is only possible for these two stereoisomers, which have the same configuration in the hexyne side chain (bold configuration symbol), because only the asymmetric centre in the barbiturate system is involved in the tautomerism. Thus, the first peak arises either from the combination (***R***,*S*)/(***R***,*R*) and the second peak from the combination (***S***,*R*)/(***S***,*S*) or vice versa. The absolute configuration is not known. The difference in area between the two peaks is called "combined enantiomeric excess" and abbreviated by "ee". For a racemic MBS sample a "combined enantiomeric excess" of 0% "ee" was measured on the CP-Chirasil-DEX-CB column used for the analysis.

5-Allyl-1-methyl-5-(1′-methylpent-2′-ynyl)barbituric Acid (Methohexital) and Its Stereoisomer Analysis

In the Pd-catalyzed allylation of MBS a configurationally stable second asymmetric centre in 5-position of the barbiturate system of the product Methohexital is formed (Scheme 2).



Scheme 2. Synthesis of Methohexital by Pd-catalyzed allylation of MBS

The four stereoisomers of Methohexital were separated with a GC system consisting of an achiral and a chiral column (Figure 1a). The achiral column was a polar Durabond-DB-225 column (length 30 m) and the chiral column was a Chiraldex-B-DA column (length 30 m). The two enantiomeric pairs are designated α and β and the configuration in the hexyne side chain 1 and 2. Thus, the four stereoisomers of Methohexital are: α1, α2, β1, β2 (Figure 1a). The two α-peaks belong to one pair of enantiomers (α1 and α2) with the literature name α-*dl*[12][13] and the two β-peaks to the other pair of enantiomers (β1 and β2) with the literature name β-*dl*. These two pairs of enantiomers are either

(***R***,*R*)/(***S***,*S*) and (***R***,*S*)/(***S***,*R*) or vice versa. The indices 1 and 2 are choosen such, that stereoisomers with the same index have the same configuration in the hexyne side chain. Thus α1 and β1 have either the configuration (***R***,*R*)/(***R***,*S*) or (***S***,*S*)/(***S***,*R*) (analogously for α2 and β2).

Which of the stereoisomers of Methohexital have the same configuration in the hexyne side chain, was established from a chromatogram of a catalysis with a yield of 94%. As the starting material MBS was racemic with respect to the configuration in the hexyne side chain, the product stereoisomers can be combined to the diastereomeric pairs (***R***,*R*)/(***R***,*S*) or (***S***,*S*)/(***S***,*R*) only in this way, that the pairs do not have more than yields of 50%. Thus, the first and the fourth as well as the second and the third peak must have the same configuration in the hexyne side chain (Figure 1a).

The four stereoisomers of Methohexital could also be separated with a permethylated β-cyclodextrin column Chiraldex-B-PM (length 30 m). In this analysis the second and the fourth peak belong to the α-*dl* pair of Methohexital and the first and the third to the β-*dl* pair (Figure 1b). A Methohexital sample resulting from an achiral catalysis with the ligand triphenylphosphane (Table 1, entry 1) gave an enantiomeric excess, as expected, of 0% ee in the α and β series. The diastereomeric excess of α pair versus β pair was measured to be 8% de with the B-PM column compared to 7% de with the two-column system DB-225 + B-DA (Figure 1a). In the GC investigations of Methohexital samples care had to be taken to separate the starting material MBS completely from the product Methohexital, because both with the DB-225 + B-DA column system as well as with the B-PM column there was overlap[3,4].

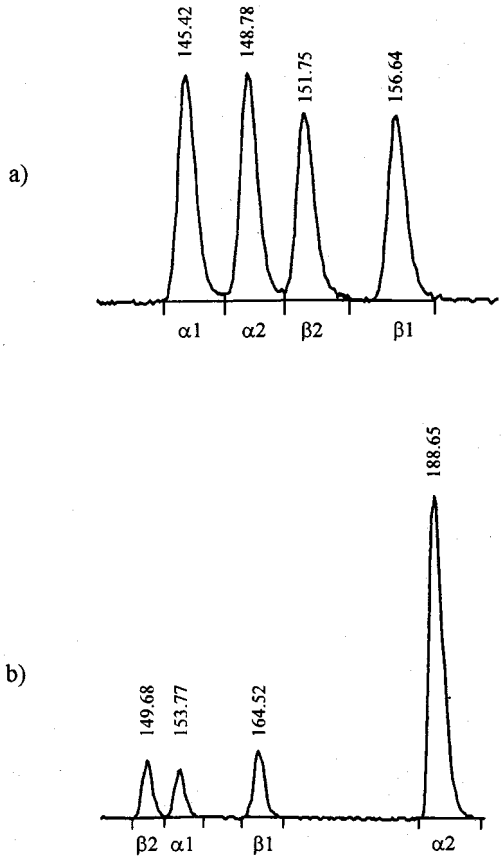


Figure 1. Separation of the four Methohexital isomers: a) on a DB-225 + B-DA column system (catalysis with ligand triphenylphosphane; Table 1, entry 1; 7% de of α pair); b) on a B-PM column (catalysis with ligand **7**; Table 2, entry 3; sample heavily enriched in α2)

Standard Catalytic Allylation of MBS to Methohexital

In the Pd-catalyzed allylation (Scheme 2) MBS is dissolved in dichloromethane/toluene (1:1). To the clear solution a base (NEt_3 or DBU) is added in 5% excess. Then 1 mol-% of palladium(II) acetylacetonate and 4 mol-% of a monodentate or 2 mol-% of a bidentate optically active phosphane are dissolved in the reaction mixture. The reaction is started by addition of allyl acetate in 11% excess. The homogeneous solution containing the "in situ" Pd/ligand complex is stirred for 72 h at 38°C. If the ligands are not soluble in dichloromethane/toluene (1:1), the dichloromethane content is increased.

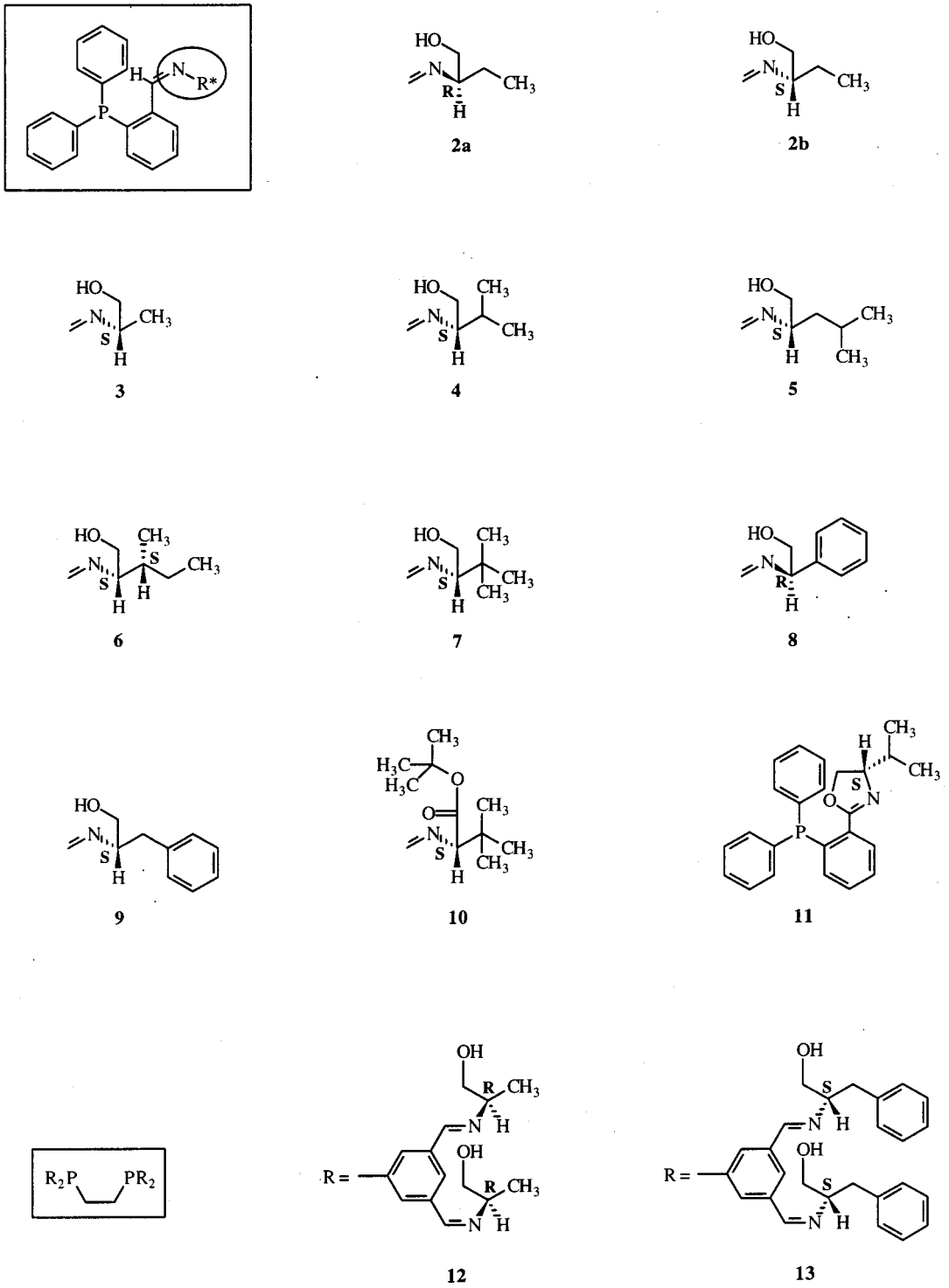
The reaction is stopped by addition of 0.2 M hydrochloric acid. From the organic layer an oily product is obtained, which is chromatographated on silica gel with dichloromethane/acetonitrile (25:1). First, the yellow (2-formylphenyl)diphenylphosphane, the hydrolysis product of the phosphane imine ligands, is eluted, then the excess of allyl acetate and small amounts of the doubly allylated by-product 3,5-diallyl-1-methyl-5-(1′-methylpent-2′-ynyl)barbituric acid (AAMBS), formed in a second allylation (*N*-allylation[2][4]). Then the product Methohexital is eluted. With a qualitative TLC test it is possible to monitor the progress of the chromatography (allyl acetate, AAMBS, Methohexital, and MBS show different yellow spots after dipping into a dilute $KMnO_4$ solution). By changing the eluent to dichloromethane/acetonitrile (3:1) the unreacted starting material MBS can be eluted. After removal of the solvent Methohexital forms a colourless oil, which crystallizes subsequently. The yield is determined by weighing. The analysis of the Methohexital stereoisomers is achieved by GC.

Chiral Ligands in the Palladium-Catalyzed Allylation of MBS

In the Pd-catalyzed allylation of MBS the achiral ligand triphenylphosphane as well as a series of chiral ligands[2] were used. The phosphane imine ligands **2a**, **2b**, **3**−**10** were obtained by Schiff base condensation of (2-formylphenyl)-diphenylphosphane with the following primary amines[2]: (*R*)-(−)-2-amino-1-butanol, (*S*)-(+)-2-amino-1-butanol, L-alaninol, L-valinol, L-leucinol, L-isoleucinol, L-*tert*-leucinol, D-α-phenylglycinol, L-phenylalaninol, L-*tert*-butyl *tert*-leucinate. Further chiral ligands were (−)-(4*S*)-2-[2′-(diphenylphosphanyl)phenyl]-4-isopropyl-1,3-oxazoline (**11**),[16,17]

(+)-1,2-bis{bis[3′,5′-bis(*N*-methyliden-(*R*)-alaninol)phenyl]phosphanyl}ethane (**12**)[2,18] and (−)-1,2-bis{bis[3′,5′-bis(*N*-methylidene-(*S*)-phenylalaninol)phenyl]phosphanyl}-ethane (**13**)[18] (Scheme 3). For a comparison the standard ligands (−)-norphos[19,20] and (−)-diop[21,22] were included. The results of the catalyses are summarized in Table 1.

mate of 7% de was obtained (Table 1, entry 1). Phosphane imine ligands induce a high diastereomeric and enantiomeric excess, if there is a hydroxymethyl substituent at the asymmetric centre near the imine group, which acts as an anchor for the incoming barbiturate anion.[2] The variation of the other side chain at the asymmetric centre leads to



Scheme 3. The phosphane imines **2**−**10**, the phosphane oxazoline **11** and the phosphane octaimines **12** an **13**

With the achiral triphenylphosphane in the Pd-catalyzed allylation of MBS a diastereomeric excess of the α-*dl* race-

distinct differences in the diastereomeric and enantiomeric excess. With the (*R*) ligand **2a** an enantiomeric excess in the

Table 1. Synthesis of Methohexital by palladium-catalyzed allylation of MBS with allyl acetate; procatalyst 1 mol-% [$Pd(acac)_2$], Pd/ligand ratio 1:4, solvent 25 mL of CH_2Cl_2 + 25 mL of toluene, 38°C, 72 h; GC analysis with the DB-225 + B-DA two-column system

Entry	Ligand	Base	Yield [%][c]	ee (α1, α2) [%]	ee (β1, β2) [%]	"ee"[a] (α1+β1, α2+β2) [%]	de (α1, β1) [%]	de (α2, β2) [%]	de (α1+α2, β1+β2) [%]	*s*[b]
1	**1**	DBU	82	0	0	0	7 (α1)	7 (α2)	7 (α1+α2)	1.0
2	**2a**	NEt_3	52	47 (α1)	21 (β2)	27 (α1+β1)	62 (α1)	1 (α2)	40 (α1+α2)	2.3
3	**2b**	NEt_3	52	50 (α2)	14 (β1)	30 (α2+β2)	3 (β1)	60 (α2)	37 (α1+α2)	2.5
4	**3**	NEt_3	66	24 (α2)	8 (β1)	11 (α2+β2)	6 (α1)	36 (α2)	23 (α1+α2)	1.5
5	**3**	DBU	62	15 (α2)	16 (β1)	4 (α2+β2)	8 (α1)	38 (α2)	24 (α1+α2)	1.1
6	**4**	NEt_3	26	62 (α2)	3 (β1)	43 (α2+β2)	3 (β1)	61 (α2)	42 (α1+α2)	2.9
7	**5**	NEt_3	94	33 (α2)	55 (β1)	2 (α2+β2)	12 (β1)	68 (α2)	29 (α1+α2)	1.3
8, 9	**6**	NEt_3	33	62[d] (α2)	8[d] (β1)	42[d] (α2+β2)	6[d] (β1)	64[d] (α2)	44[d] (α1+α2)	3.0
			43	62 (α2)	12 (β1)	42 (α2+β2)	7 (β1)	65 (α2)	44 (α1+α2)	3.3
10	**6**	DBU	63	51 (α2)	38 (β1)	24 (α2+β2)	11 (β1)	69 (α2)	39 (α1+α2)	2.3
11, 12	**7**	NEt_3	89	40 (α2)	59 (β1)	2 (α2+β2)	23 (β1)	71 (α2)	26 (α1+α2)	1.2
			91	40 (α2)	61 (β1)	3 (α2+β2)	22 (β1)	71 (α2)	25 (α1+α2)	1.3
13	**8**	NEt_3	91	26[d] (α1)	32[d] (β2)	5[d] (α2+β2)	55[d] (α1)	3[d] (α2)	30[d] (α1+α2)	1.6
14	**8**	DBU	63	28[d] (α1)	28[d] (β2)	8[d] (α1+β1)	52[d] (α1)	0[d]	28[d] (α1+α2)	1.3
15	**9**	DBU	64	19 (α2)	6 (β1)	8 (α2+β2)	1 (β1)	23 (α2)	12 (α1+α2)	1.3
16	**10**	NEt_3	12	1 (α2)	5 (β1)	2 (α1+β1)	0	5 (α2)	3 (α1+α2)	1.0
17	**10**	DBU	10	1 (α2)	2 (β1)	0	1 (α1)	4 (α2)	3 (α1+α2)	1.0
18	**11**	NEt_3	59	3 (α1)	4 (β1)	3 (α1+β1)	4 (α1)	6 (α2)	5 (α1+α2)	1.1
19	**12**[e,f]	NEt_3	62	8 (α1)	13 (β2)	3 (α2+β2)	5 (α1)	15 (β2)	6 (β1+β2)	1.1
20	**13**[e]	NEt_3	74	12 (α1)	19 (β2)	3 (α2+β2)	18 (α1)	13 (β2)	0	1.1
21	(−)-norphos[e]	NEt_3	93	5[d] (α1)	6[d] (β2)	0[d]	15[d] (α1)	4[d] (α2)	10[d] (α1+α2)	1.0
22	(−)-diop[e]	NEt_3	93	2[d] (α1)	2[d] (β2)	0[d]	11[d] (α1)	7[d] (α2)	9[d] (α1+α2)	1.0

[a] "ee" = "combined enantiomeric excess" (see text). − [b] *s* = stereoselectivity factor. − [c] After chromatography. − [d] GC analysis with the B-PM column. − [e] Pd/ligand ratio 1:2. − [f] 150 mL of CH_2Cl_2 + 25 mL of toluene was used to dissolve ligand **12**.

α-*dl* pair of 47% ee (α1) and in the β-*dl* pair of 21% ee (β1) is achieved, the diastereomeric excess for the α-*dl* pair being 40% de (entry 2). The isomers added in parentheses after the ee and de values are the favoured isomers. The analogous (*S*) ligand **2b** gives a similar enantiomeric excess of the opposite stereoisomers, a similar diastereomeric excess for the α-*dl* pair and the same chemical yield (entry 3). A shortening of the ethyl group at the asymmetric centre in the ligands **2a** and **2b** to a methyl group in the ligand **3** diminishes the diastereomeric and enantiomeric excess considerably, although the chemical yield increases (entries 4, 5).

Branching of the alkyl group as in the ligands **4**−**7** leads to the highest stereoselectivities in the Pd-catalyzed allylation of MBS observed so far similar to the Pd-catalyzed allylation of 1,5-dimethylbarbituric acid[2]. With the ligands **4** and **6**, which contain an isopropyl group and a *sec*-butyl group, respectively, a high enantiomeric excess in the α-*dl* pair of 62% ee (α2) was attained, associated with a low enantiomeric excess of 3−12% ee (β1) in the β-*dl* pair, the diastereomeric excess for the α-*dl* pair being 42 and 43% de. With NEt_3 as a base, the yields are only 26−43% (entries 6, 8, 9). Using DBU leads to an increased yield of 63%. The enantiomeric excess in the α-*dl* pair decreases to 51% ee (α2), whereas the enantiomeric excesses in the β-*dl* pair rises to 38% ee (β1) (entry 10).

The ligands **5** and **7**, which carry an isobutyl group and a *tert*-butyl group at the asymmetric centre, respectively, lead to a lower enantiomeric excess in the α-*dl* pair [33 and 40% ee (α2)] but to a higher enantioselectivity in the β-*dl* pair [55, 59, and 61% ee (β1)] with yields of up to 94% using NEt_3 as a base. The diastereoselectivities are between 25 and 29% de for the α-*dl* pair (entries 7, 11, 12). If the side chain at the asymmetric centre contains a phenyl group (ligands **8** and **9**), the induced enantiomeric excess is higher for ligand **8** than for ligand **3** and distinctly lower for ligand **9** than for ligand **2b** (entries 13−15). A substitution of the hydroxymethyl group at the asymmetric centre by a *tert*-butyl ester group in the ligand **10** reduces the enantiomeric excess appreciably independent of the base used (entry 16).

The phosphane oxazoline ligand **11** gives only a low enantiomeric excess in the product Methohexital similar to the standard ligands (−)-norphos and (−)-diop (entries 17, 20, 21). The ligands **12** and **13** belong to a different group of phosphane imine ligands with two phosphorus atoms. They afford an enantiomeric excess in the various stereoisomers of 8−19% ee using the base NEt_3 (entries 18, 19). Up to now ligand **12** is the only one, which induces a diastereomeric excess in favour of the β-*dl* pair (6% de).

The Interplay of Kinetic Resolution and Catalyst Contribution

In the allylation of 1,5-dimethylbarbituric acid the 1,5-dimethylbarbiturate anion is formed, which no longer contains an asymmetric centre. Thus, there is no kinetic resolution in this reaction and the enantiomeric excess of the product 5-allyl-1,5-dimethylbarbituric acid is only dependent on the enantioselectivity of the chiral catalyst.[2] On the contrary, the starting material 1-methyl-5-(1′-methylpent-2′-ynyl)barbituric acid (MBS) for the synthesis of Me-

Table 2. The interplay of kinetic resolution and catalyst contribution in the Pd-catalyzed allylation of MBS with ligand **7**; procatalyst 1 mol-% of [Pd(acac)$_2$], Pd/ligand ratio 1:4, solvent CH_2Cl_2/toluene (1:1), 38°C, base DBU; GC analysis of MBS with a CP-Chirasil-Dex-CB column and of Methohexital with a B-PM column

		A	B	C	D	E	F	G	H	I	J	K
					Methohexital						MBS	
Entry	Time [h]	Yield [%][c]	ee (α1, α2) [%]	ee (β1, β2) [%]	"ee"[a] (α1+β1, α2+β2) [%]	de (α1, β1) [%]	de (α2, β2) [%]	de (α1+α2, β1+β2) [%]	S[b] (from A, D calcd.)	unreacted MBS [%][c]	"ee"[a] (1., 2.) [%]	s[b] (from A, J calcd.)
1	3	17	77 (α2)	7 (β1)	60 (α2+β2)	11 (β1)	76 (α2)	59 (α1+α2)	4.5	79	5 (1.)	1.7
2	4.5	20	80 (α2)	6 (β1)	62 (α2+β2)	18 (β1)	76 (α2)	58 (α1+α2)	5.0	77	9 (1.)	2.3
3	9	26	80 (α2)	13 (β1)	60 (α2+β2)	20 (β1)	77 (α2)	58 (α1+α2)	4.9	70	14 (1.)	2.7
4	12	32	78 (α2)	17 (β1)	57 (α2+β2)	19 (β1)	77 (α2)	57 (α1+α2)	4.7	65	19 (1.)	2.8
5	72	49	61 (α2)	30 (β1)	36 (α2+β2)	12 (β1)	71 (α2)	45 (α1+α2)	2.9	48	40 (1.)	3.5
6	72	65	42 (α2)	67 (β1)	0	27 (β1)	75 (α2)	24 (α1+α2)	1.0	–	–	–
7	72	91	46 (α2)	72 (β1)	6 (α2+β2)	24 (β1)	82 (α2)	32 (α1+α2)	1.7	7	83 (1.)	2.3

[a] "ee" = "combined enantiomeric excess". – [b] *s* = stereoselectivity factor. – [c] After chromatography.

thohexital contains two asymmetric centres. On addition of base the asymmetric centre in the barbiturate system is removed, but the asymmetric centre in the hexyne side chain is preserved. In the present study the asymmetric centre in the hexyne side chain of the MBS used was racemic. Therefore, two different effects can influence the distribution of the stereoisomers in the Pd-catalyzed allylation of MBS, the kinetic resolution and the enantioselective catalysis, which are both concentration-dependent. The contributions of these two effects can be calculated provided the yields of Methohexital and MBS as well as the diastereomeric and enantiomeric excess of Methohexital and MBS are known. These data were obtained from a standard catalysis with ligand **7** by taking aliquots after 3, 4.5, 9, 12, and 72 h. The yields of Methohexital and MBS were determined and their stereoisomer composition was analysed by GC as described above. In Table 2 the results and calculations are summarized together with those of two other catalytic runs.

The Kinetic Resolution in the Pd-Catalyzed Allylation of MBS with Ligand 7

Due to the kinetic resolution in the reaction with the optically active catalyst there is a chiral discrimination of the MBS anions, which have opposite configurations in the hexyne side chain. One is consumed faster to give the product Methohexital, whereas the other is enriched in the unreacted starting material. This difference in reactivity shows up in the intensity ratio of the first and the second MBS GC peak (Table 2, column J). The "combined enantiomeric excess", calculated as [(|peak1 − peak2|)/(peak1 + peak2)] × 100% reflects the reactivity difference of the MBS stereoisomers, which have opposite configurations in the hexyne side chain.

Addition of the yield of Methohexital (column A) and the amount of unreacted MBS (column I) leads to retrieval rates of 96−98%. The missing 2−4% are lost by the treatment with 0.2 M hydrochloric acid, by the chromatographic purification or by the formation of the doubly allylated byproduct AAMBS. In a reasonable approximation the yield of Methohexital can be used to represent the overall conversion.

After 3 h, the first sample taken gave a yield of 17% of Methohexital and 79% of starting material MBS (Table 2, entry 1). The yield of Methohexital increased from 20% after 4.5 h (77% MBS) via 26% after 9 h (70% MBS) and 32% after 12 h (65% MBS) to 49% after 72 h (48% MBS), as shown in columns A and I of Table 2 (entries 2−5). In comparable reactions Methohexital yields of 65% (MBS not determined) and 91% (7% MBS) were isolated after 72 h (entries 6, 7).

Figure 2 shows the correlation between the yield of Methohexital (column A) and the increase of the "combined enantiomeric excess" of MBS (column J). With the decrease of the amount of unreacted MBS down to 7% after 72 h (entry 7) the enantioselectivities of the remaining MBS rises to an enrichment of 83% "ee" (1.). The designation (1.) means an excess of the first peak of MBS in the GC chromatogram.

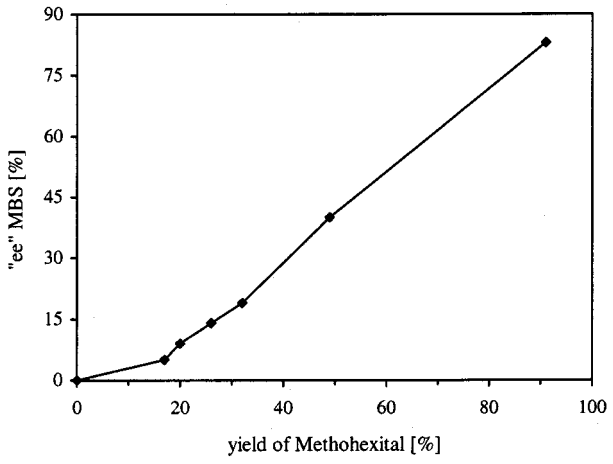


Figure 2. Correlation between the "combined enantiomeric excess" of MBS and the yield of Methohexital

With the rate constants k_R and k_S for the reaction of the two MBS anion enantiomers, the stereoselektivity factor $s = k_R/k_S$ is a measure for the kinetic resolution.[23,24] It can be calculated from the amount and the enantiomeric

excess of the unreacted starting material with Equation 1.[23,24] The values of the stereoselectivity factor *s* of MBS

$$s = \frac{\ln[(1 - C)(1 - ee)]}{\ln[(1 - C)(1 + ee)]}$$

C = conversion: 0 < C < 1 (column A); assumption: retrieval rate of 100%; ee = "ee" = "combined enantiomeric excess" in the unreacted starting material MBS: 0 < "ee" < 1 (column J)

are between 1.7 and 3.5 with an average of 2.6 (column K).

The effect of the kinetic resolution with respect to the product Methohexital can be calculated with the help of the "combined enantiomeric excess" α1 + β1 vs. α2 + β2 (vs. = versus) in column D, obtained from the four GC peaks of the Methohexital stereoisomers. The two components of each sum have the same configuration in the hexyne side chain. It decreases from 60−62% "ee" for a Methohexital yield of 17−26% via 36% "ee" for a yield of 49% to 6% "ee" for a yield of 91% (columns A and D) with increasing conversion (entries 1−5, 7). The value of 0% "ee" for a Methohexital yield of 65% does not fit into this series (entry 6). The stereoselectivity factor *s* (values between 1.7 and 5.0, column H) is calculated with Equation 2.[23,24]

$$s = \frac{\ln[1 - C(1 + ee)]}{\ln[1 - C(1 - ee)]}$$

C = conversion: 0 < C < 1 (column A); assumption: retrieval rate of 100%; ee = "ee" = "combined enantiomeric excess" in the product Methohexital: 0 < "ee" < 1 (column D)

Although the absolute configurations are not known, the starting material MBS and the product Methohexital can be correlated with respect to the configuration in the hexyne side chain. During the reaction the isomers of MBS appearing in the first GC peak are enriched. Thus, they react more slowly to the product Methohexital. The faster reacting MBS isomers lead to a growth of the GC peaks of the Methohexital stereoisomers α2 and β2. Therefore, they must have the same configuration in the hexyne side chain as the isomers of the second MBS peak.

The Contribution of the Optically Active Catalyst in the Pd-Catalyzed Allylation of MBS with Ligand 7

In addition to the kinetic resolution the optically active catalyst contributes to the stereoselectivity of the Pd-catalyzed allylation of MBS. This is reflected in the enantiomeric excess in the α series which decreases from 80% ee (α2) to 42% ee (α2) (Table 2, column B), whereas in the β series it rises from 6% ee (β1) to 72% ee (β1) (column C). Figure 1b shows the highest enantiomeric excess of 80% ee (α2) in the α-*dl* pair of Methohexital obtained up to now (entry 3).

The contribution of the optically active catalyst is concentration-dependent, because the composition of the MBS stereoisomers changes during the reaction due to the kinetic resolution. At the beginning of the reaction MBS is racemic. Thus, the influence of the optically active catalyst can be read off directly from the enantiomeric excess of Methohexital in the beginning of the MBS allylation.

Columns E and F show the diastereomeric excess α1 vs. β1 and α2 vs. β2, which involves the influence of the asymmetric centre in the hexyne side chain and the optically active catalyst on the formation of the new asymmetric centre in the barbiturate ring. For the diastereomeric excess α1 vs. β1 values between 11 and 27% de (β1) were achieved (column E) and for α2 vs. β2 values between 71 and 82% de (α2) (column F). The diastereomeric excess α1 vs. β1 and α2 vs. β2 is relatively independent of the turnover (columns A, E, F). The overall diastereomeric excess α pair vs. β pair decreases from 59 to 24% de (α pair) (column G) depending on the yield of Methohexital (column A).

Kinetic Resolution and Catalyst Contribution for the Other Ligands

The influence of the kinetic resolution in the Pd-catalyzed allylation of MBS is calculated for all the optically active ligands with Equation 2 using enantiomeric excesses α1 vs. α2 and β1 vs. β2 for Methohexital. The results are summarized in Table 1. As expected *s* is 1.0 for the achiral catalysis with triphenylphosphane, as both enantiomeric excesses α1 vs. α2 and β1 vs. β2 are 0% ee. The influence of the kinetic resolution is small for most of the ligands investigated (values for *s* between 1.0 and 1.6) except for the catalyses with the ligands **2a**, **2b**, **4**, and **6** (values for *s* from 2.3 to 3.3).

The contribution of the optically active catalyst in the Pd-catalyzed allylation of MBS for all the ligands is obvious from the enantiomeric excess in the α and β series, although most of the reactions were stopped at higher conversions. It was small for the standard ligands (−)-norphos, (−)-diop, the phosphane oxazoline ligand **11** and the phosphane imine ligand **10** containing a *tert*-butyl ester substituent with an enantiomeric excess between 1 and 6% ee. For the remaining phosphane imine ligands, which carry a hydroxymethyl substituent at the asymmetric centre, the catalyst contribution was much higher with up to 62% ee (Table 1).

Determination of the Anesthetic Doses of Methohexital Stereoisomer Mixtures in Rats

Methohexital is a common anesthetic widely used to initiate narcoses.[5−11] The four stereoisomers of Methohexital exhibit different anesthetic effects in rats, dogs and monkies.[12,13] Injected as a solution of the sodium salt into rats, the β-*l* isomer of Methohexital is the most effective of the stereoisomers with an anesthetic dose of 7 mg/kg body weight of the animal. The α-*d* stereoisomer with 11 mg/kg and the β-*d* stereoisomer with 17 mg/kg follow. For a narcosis with the α-*l* stereoisomer 35 mg/kg are necessary. With 10 mg/kg the β-*dl* racemate is more effective than the α-*dl* racemate with 15 mg/kg. However, because of undesirable stimulating post-anesthetic effects of the β-*dl* racemate caused by the β-*l* stereoisomer the extensively used narcotic is the α-*dl* racemate (Eli Lilly).

Table 3. 10 Methohexital samples and their isomer composition, the reference Brevimytal®Natrium and the anesthetic doses (AD) in Sprague Dawley rats of body weight between 560 and 720 g[25][26]

Sample	Ligand	α1 [%]	α2 [%]	β1 [%]	β2 [%]	AD [mg/kg]	Average AD [mg/kg]
1	**1**	27	27	23	23	10.8, 9.3, 11.1	10.4
2	**2a**	51.5	18.5	12	18	14.6, 13.5, 11.1	13.0
3	**2b**	17	51.5	18	13.5	15.7, 17.7, 14.8	16.1
4	**4**	13.5	58.5	14.5	13.5	17.4, 16.3, 16.4	16.7
5	**5**	22	43	27	8	16.1, 15.3, 15.7	15.7
6	**8**	41	23	13	23	8.9, 9.4, 8.9	9.1
7	**8**	41	24	12	23	17.9, 14.5, 15.6	16.0
8	**3**	26	36	22	16	14.7, 13.7, 14.3	14.2
9	**6**	13.5	58.5	15	13	14.1, 8.9, 9.5	10.9
10	**7**	19	44	29.5	7.5	22.0, 21.0, 20.1	21.0
11	reference[a]	50	50	–	–	16.3, 12.4, 10.3	13.0

[a] Protonated Brevimytal®Natrium (see Experimental Section).

For 10 mixtures of Methohexital stereoisomers, obtained by Pd-catalyzed enantioselective allylation of MBS, the anesthetic dose (AD) in rats was determined using the corneal stimulus technique[25] as described elsewhere.[26] The results were compared with those of a sample of protonated Brevimytal®Natrium (sample 11).

Table 3 summarizes the anesthetic doses obtained by standardising to 1 kg body weight of the rat. The average anesthetic dose of the samples **1**, **6**, and **9** was lower than that of Brevimytal®Natrium with 13.0 mg/kg (Table 3). In particular, sample **6** with 9.1 mg/kg had a distinctly reduced anesthetic dose. Deviations from the average value were small with this sample. However, it is conspicuous, that samples **6** and **7**, which showed marked differences in the anesthetic doses, had a closely related stereoisomer composition (Table 3).[26]

Experimental Section

The instruments used were the same as described in the preceding paper.[2] – All the syntheses and catalytic reactions were carried out with dried solvents under nitrogen. – Palladium(II) acetylacetonate and allyl acetate (Merck) were used without further purification. DBU (Fluka) was dried with $CaCl_2$, NEt_3 (Merck) with CaH_2, and distilled.

1-Methyl-5-(1′-methylpent-2′-ynyl)barbituric Acid (MBS):[3,4,13] 10.9 g (0.474 mol) of sodium was dissolved in 200 mL of refluxing absolute ethanol. After addition of 17.6 g (0.237 mol) of *N*-methylurea and stirring for 15 min, 38.0 g (0.158 mol) of diethyl (1-methylpent-2-ynyl)malonate[4,13,14] was added to the clear boiling solution within 10 min. A solid precipitated after 30 min. After 1.5 h of reflux, the solvent was removed and the product dissolved in about 750 mL of water. With vigorous stirring 80 mL of conc. hydrochloric acid was added to give an oil, which solidified. After 30 min of stirring, the product was filtered off and washed with cold water. Recrystallization from 2-propanol/water (2:1) provided colourless crystals. Yield 20.8 g (59%), m. p. 90–91.5°C. – IR (KBr): $\tilde{\nu}$ = 1754 (m), 1719 (s), 1695 (s) cm^{-1} (C=O). – ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.14/8.09 (2 s, 1 H, N*H*), 3.39–3.31 (m, 2 H, OC–C*H*–C*H*), 3.303/3.298 (2s, 3 H, N–CH_3), 2.102/2.100 (2 dq, 2 H, ^5J = 2.2 Hz, ^3J = 7.5 Hz, C≡C–CH_2–CH_3), 1.444/1.440 (2d, 3 H, ^3J = 7.0 Hz, CH–CH_3), 1.040/1.038 (2 t, 3 H, ^3J = 7.5 Hz, C≡C–CH_2–CH_3). – $^{13}C\{^1H\}$ NMR ($CDCl_3$, 62.9 MHz): δ = 169.3/168.7 (HN–*C*O–CC_3), 167.5/166.8 (H_3C–N–*C*O–CC_3), 151.2/151.1 (HN–*C*O–N–CH_3), 86.6/86.5 (HC–*C*≡C), 76.8 (C≡*C*–CH_2), 54.3 (OC–*C*–CO), 31.8/31.6 (H*C*–C≡C), 27.7/27.4 (N–*C*H_3), 20.0/19.7 (H_3C–CH), 13.8 (CH_2–*C*H_3), 12.1 (C≡C–*C*H_2). – The signals appear doubled because of the two MBS diastereomers. Addition of (*S*)-(+)-1-(9′-anthryl)-2,2,2-trifluoroethanol (Super-Pirkle) to MBS in the molar rate 1:12 results also in a separationof of the enantiomers: δ = 3.059/3.054/3.043/3.035 (4s, N–CH_3), 0.940/0.938/ 0.933/ 0.927 (4 t, ^3J = 7.5 Hz, C≡C–CH_2–CH_3). – MS (EI, 70 eV); *m/z* (%): 222.1 (7) [M^+], 207.1 (45) [M^+ – CH_3], 193.1 (46) [M^+ – C_2H_5], 81.1 (35) [$C_6H_9^+$], 79.1 (100). – $C_{11}H_{14}N_2O_3$ (222.24): calcd. C 59.45, H 6.35, N 12.60; found C 59.52, H 6.34, N 12.63. – GC analysis of MBS: 25-m CP-Chirasil-Dex-CB column (chemically connected with permethylated β-cyclodextrin; 0.25 mm inner diameter, 0.25 µm film thickness; from Chrompack), column temp. 165°C, He pressure 1.2 bar, injector temp. 250°C, detector temp. 230°C (flame ionisation). Retention times: (1.) 23.29 min, (2.) 24.97 min; dead time t_0 (CH_2Cl_2) = 1.21 min. Separation factor: α = 1.07, resolution R = 3.52.

Synthesis of Methohexital by Enantioselective Palladium-Catalyzed Allylation of MBS with Allyl Acetate: 1.07 g (4.81 mmol) of MBS was dissolved in 25 mL of dichloromethane/toluene (1:1) at 38°C under nitrogen. To the clear solution 5.05 mmol of the base was added [DBU (752 µL, 769 mg) or NEt_3 (700 µL, 511 mg), respectively]. After 5 min of stirring, 14.6 mg ($4.81 \cdot 10^{-2}$ mmol) of Pd(acac)$_2$ and $19.2 \cdot 10^{-2}$ mmol of a monodentate or $9.61 \cdot 10^{-2}$ mmol of a bidentate ligand were rinsed into the reaction vessel with another 25 mL of dichloromethane/toluene (1:1). After 2.0 min, 576 µL (5.35 mmol, 536 mg) of allyl acetate was added to the clear yellow solution. Usually, the solution was stirred for 72 h at 38°C. For work-up the solution was diluted with 50 mL of dichloromethane and the reaction was stopped with 50 mL of 0.2 M hydrochloric acid. The organic layer was dried with Na_2SO_4, the Na_2SO_4 was filtered off and washed with 50 mL of dichloromethane. The solvent was removed. The remaining oily product was chromatographed on silica gel with dichlormethane/acetonitrile (25:1). If phosphane imine ligands were used in the catalysis, first the yellow (2-formylphenyl)diphenylphosphane was eluted, followed by the excess of allyl acetate and small amounts of doubly allylated MBS (AAMBS). Then the product Methohexital was eluted. The separation of the products was monitored by a qualitative TLC test (silica 60, Merck; dichloromethane/acetonitrile, 25:1), which showed how much allyl acetate, AAMBS, Methohexital and MBS were present in a specific fraction (yellow spots after dipping into a dilute $KMnO_4$ solution). All the fractions, which contained Methohexital, were combined to prevent an enrichment of the dia-

stereomers during the chromatography. After complete elution of Methohexital, the unreacted starting material MBS was eluted with dichloromethane/acetonitrile (3:1). The yield of Methohexital and unreacted MBS was determined by weighing. After about 1−2 d the colourless oil of Methohexital crystallized to a colourless solid.

Methohexital: Maximum yield 1.19 g (94%, Table 1, entry 7), m. p. 61−65°C. − IR (KBr): $\tilde{\nu}$ = 1717 (s), 1690 (s) cm^{-1} (C=O). − ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.04/8.02 (2 s, 1 H, N*H*), 5.553/5.547 (2 tdd, ^3J = 7.3 Hz, $^3J_{cis}$ = 10.1 Hz, $^3J_{trans}$ = 17.0 Hz, 1 H, $H_2C{=}CH{-}CH_2$), 5.149 (md, ^3J = 17.0 Hz, 1 H, $CH{=}CH_{trans}H$), 5.084 (md, ^3J = 10.1 Hz, 1 H, $CH{=}CH_{cis}H$), 3.293/3.286 (2 s, 3 H, $N{-}CH_3$), 3.087/3.081 (2 tq, ^5J = 2.3 Hz, ^3J = 7.0 Hz, 1 H, $H_3C{-}CH{-}C{\equiv}C{-}CH_2$), 2.864/2.852 (2 dd, ^3J = 7.3 Hz, ^2J = 13.0 Hz, 1 H, $H_2C{=}CH{-}CHH$), 2.657/2.648 (2 dd, ^3J = 7.3 Hz, ^2J = 13.0 Hz, 1 H, $H_2C{=}CH{-}CHH$), 2.102/2.099 (2 dq, ^5J = 2.3 Hz, ^3J = 7.5 Hz, 2 H, $HC{-}C{\equiv}C{-}CH_2{-}CH_3$), 1.301/1.291 (2 d, ^3J = 7.0 Hz, 3 H, $HC{-}CH_3$), 1.038/1.034 (2 t, ^3J = 7.5 Hz, 3 H, $C{\equiv}C{-}CH_2{-}CH_3$). − $^{13}C\{^1H\}$ NMR ($CDCl_3$, 62.9 MHz): δ = 171.6/170.8 ($HN{-}CO{-}CC_3$), 169.9/169.1 ($H_3C{-}N{-}CO{-}CC_3$), 150.4 ($HN{-}CO{-}N{-}CH_3$), 131.2 ($H_2C{=}CH$), 120.6 ($H_2C{=}CH$), 86.4 ($HC{-}C{\equiv}C$), 77.6 ($C{\equiv}C{-}CH_2$), 59.8 ($OC{-}C{-}CO$), 38.0 ($H_2C{=}CH{-}CH_2$), 36.0/35.6 ($HC{-}C{\equiv}C$), 27.6/27.5 ($N{-}CH_3$), 16.0 ($H_3C{-}CH$), 13.8 ($CH_2{-}CH_3$), 12.1 ($C{\equiv}C{-}CH_2$). All the signals appear doubled because of the two Methohexital diastereomers. − MS (EI, 70 eV); *m/z* (%): 262.1 (22) [M^+], 247.1 (30) [$M^+ - CH_3$], 233.1 (32) [$M^+ - C_2H_5$], 221.0 (81) [$M^+ - C_3H_5$], 181.0 (31) [$M^+ - C_6H_9$], 81.0 (100) [$C_6H_9^+$], 79.0 (60), 41.2 (80) [$C_3H_5^+$]. − $C_{14}H_{18}N_2O_3$ (262.31): calcd. C 64.11, H 6.92, N 10.68; found C 63.91, H 6.78, N 10.63.

GC Analysis of Methohexital: 20 mg of Methohexital was dissolved in 1 mL of dichloromethane. − Method a: 30-m Durabond-DB-225 column (25% cyanopropyl-, 25% phenyl-, 50% methylpolysiloxane; 0.25 mm inner diameter, 0.25 μm film thickness; from J & W) linked with an SiO_2 glass connector of Restek to a 30-m Chiraldex B-DA column (dipentylated β-cyclodextrin; 0.25 mm inner diameter, 0.125 μm film thickness; from astec), column temp. 145°C, H_2 pressure 2.07 bar, injector temp. 250°C, detector temp. 250°C (flame ionisation). Retention times: α1 = 145.42 min, α2 = 148.78 min, β1 = 151.75 min, β2 = 156.64 min; dead time t_0 (CH_2Cl_2) = 1.76 min. Separation factors: $\alpha_{\alpha2/\alpha1}$ = 1.02, $\alpha_{\beta2/\alpha2}$ = 1.02, $\alpha_{\beta1/\beta2}$ = 1.03. Resolutions: $R_{\alpha2/\alpha1}$ = 1.66, $R_{\beta2/\alpha2}$ = 1.53, $R_{\beta1/\beta2}$ = 2.52. − Method b: A 30-m Chiraldex B-PM column (coated with permethylated β-cyclodextrin; 0.25 mm inner diameter; from astec), column temp. 125°C, H_2 pressure 1.75 bar, injector temp. 260°C, detector temp. 260°C (flame ionisation). Retention times: β2 = 149.62 min, α1 = 153.62 min, β1 = 164.30 min, α2 = 188.38 min; dead time t_0 (CH_2Cl_2) = 0.64 min. Separation factors: $\alpha_{\alpha1/\beta2}$ = 1.03, $\alpha_{\beta1/\alpha1}$ = 1.07, $\alpha_{\alpha2/\beta1}$ = 1.15, $\alpha_{\alpha2/\alpha1}$ = 1.23, $\alpha_{\beta1/\beta2}$ = 1.10. Resolutions: $R_{\alpha1/\beta2}$ = 1.46, $R_{\beta1/\alpha1}$ = 3.81, $R_{\alpha2/\beta1}$ = 6.88, $R_{\alpha2/\alpha1}$ = 9.93, $R_{\beta1/\beta2}$ = 5.36.

3,5-Diallyl-1-methyl-5-(1′-methylpent-2′-ynyl)barbituric Acid (AAMBS): By-product of the catalysis under standard reaction conditions. AAMBS was separated by chromatography as described above. Yield 0−3%, light yellow liquid. − MS (EI, 70 eV); *m/z* (%): 302.2 (41) [M^+], 287.2 (31) [$M^+ - CH_3$], 273.1 (19) [$M^+ - C_2H_5$], 261.1 (100) [$M^+ - C_3H_5$], 221.0 (41) [$M^+ - C_6H_9$], 81.0 (66) [$C_6H_9^+$], 79.0 (41), 40.9 (84) [$C_3H_5^+$].

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