Palladium-Catalyzed Asymmetric Allylic Alkylation of Barbituric Acid Derivatives: Enantioselective Syntheses of Cyclopentobarbital and Pentobarbital

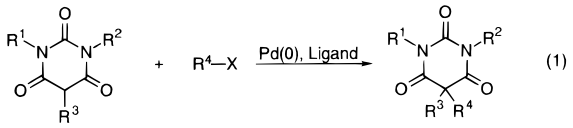
Barry M. Trost* and Gretchen M. Schroeder

Department of Chemistry, Stanford University, Stanford, California 94305-5080

Received September 22, 1999

Introduction

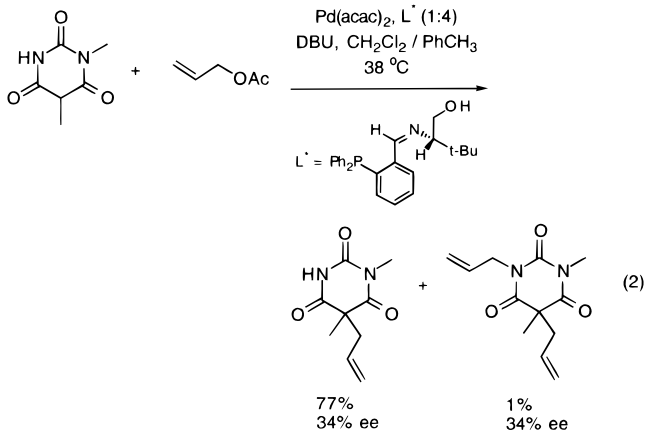
Barbituric acids[1] have attracted the attention of the pharmaceutical community for over 100 years due to their therapeutic value. It has been shown that enantiomers of chiral barbituric acids can exhibit different biological effects. Chiral barbituric acids can be classified in one of two categories. In one, the chirality is associated with the heterocyclic ring (eq 1, $R^1 \neq R^2$), while in the other the chirality is outside of the ring as part of R^3 or R.[4] Optically active barbituric acids have been synthesized by the resolution of enantiomers or by the use of chiral starting materials.



(1)

A more attractive and economical approach to the synthesis of chiral barbituric acids would be to develop a general catalytic asymmetric route. The palladium-catalyzed asymmetric allylic alkylation reaction[2] (AAA reaction) is one such way by which enantioenriched barbituric acids could potentially be generated. The use of barbituric acids as nucleophiles in the AAA reaction raises several issues (eq 1). One, when $R^1 = R^2$, the AAA reaction results in the creation of a stereocenter at a prochiral electrophile. On the other hand, when $R^1 \neq R^2$ a stereocenter may also be formed at the nucleophile. A further complication arises when R^1 or R^2 is hydrogen, since N as well as C alkylation can occur.

In 1998, Brunner reported the first and, to the best of our knowledge, only catalytic asymmetric synthesis of a barbituric acid derivative.[3] The AAA reaction of 1,5-dimethylbarbituric acid with allyl acetate was found to give 5-allyl-1,5-dimethylbarbituric acid as the main product in up to 34% ee (eq 2). In this reaction, alkylation generates a stereocenter at the nucleophile, a formidable task as the nucleophile is segregated from the palladium and chiral ligand by the π-allyl moiety.[3,4] Also, the nucleophilic character of the secondary amide nitrogen is evident by the formation of some bis-alkylated product.

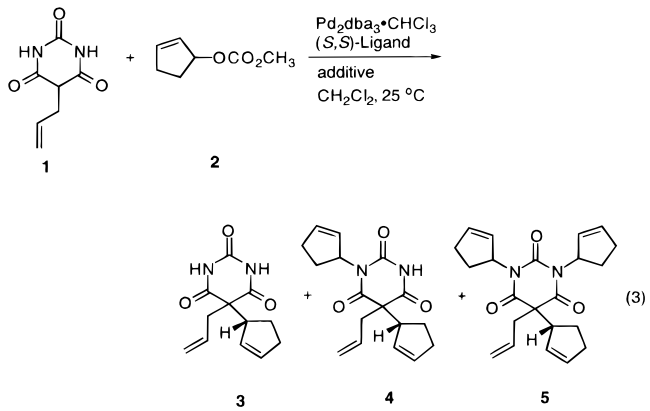


(2)

In this paper, we share our efforts in this area. We describe the enantioselective synthesis of cyclopentobarbital (**3**) and pentobarbital (**9**) in which the AAA reaction generates a stereocenter at the electrophile. We also describe our attempts to achieve the asymmetric allylic alkylation of prochiral nucleophiles.

Results and Discussion

Cyclopentobarbital (5-allyl-5-cyclopent-2-enylbarbituric acid, **3**) is a pharmaceutical known for its sedative and hypnotic properties.[5] To the best of our knowledge, it has not been synthesized in enantiopure form; thus, the biological effects of each enantiomer have yet to be determined. We envisioned synthesizing **3** from barbiturate **1**[6] and carbonate **2** by the AAA reaction depicted in eq 3. The initial results with cyclohexyldiamine ligand



(3)

L1 (Figure 1) and a tertiary amine base showed that

(1) For some reviews, see: Bojarski, J. T.; Mokrosz, J. L.; Barton, H. J.; Paluchowska, M. H. *Adv. Heterocycl. Chem.* **1985**, *38*, 229. Doran, W. J. *J. Med. Chem.* **1959**, *4*, 1.

(2) For recent reviews, see: Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. Heumann, A.; Reglier, M. *Tetrahedron* **1995**, *51*, 975. Hayashi, T. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers Inc.; New York, 1993. Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857. Fiaud, J. C. In *Metal-Promoted Selectivity in Organic Synthesis*; Graziani, M., Hubert, A. J., Noels, A. F., Eds.; Kluwer Academic Publishers: Dordrecht, 1991. Consiglio, G.; Waymouth, R. M. *Chem. Rev.* **1989**, *89*, 257.

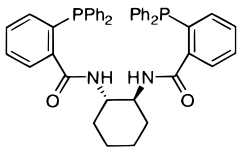
(3) Brunner, H.; Deml, I.; Dirnberger, W.; Nuber, B.; Reisser, W. *Eur. J. Inorg. Chem.* **1998**, 43. Brunner, H.; Ruckert, T. *Monatsh. Chem.* **1998**, *129*, 339. Brunner, H.; Furst, J. *Inorg. Chim. Acta* **1994**, *220*, 63.

(4) For examples of chiral induction at the nucleophile in the AAA reaction, see: Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759. Trost, B. M.; Radinov, R.; Grenzer, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 7879. Hayashi, T.; Kanehira, K.; Hagihara, T.; Kumada, M. *J. Org. Chem.* **1988**, *53*, 113.

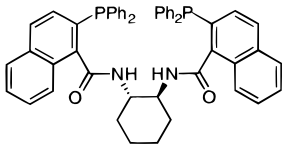
(5) Centolella, A. P.; Nelson, J. W.; Kolloff, H. G *J. Am. Chem. Soc.* **1943**, *65*, 2091.

(6) Ishikawa, I.; Khachatrian, V. E.; Melik-Ohanjanian, R. G.; Kawahara, N.; Mizuno, Y.; Ogura, H. *Chem. Pharm. Bull.* **1992**, *40*, 846.

10.1021/jo991491c CCC: $19.00
Published on Web 02/11/2000



(*S,S*)-L1



(*S,S*)-L2

Figure 1. Ligands.

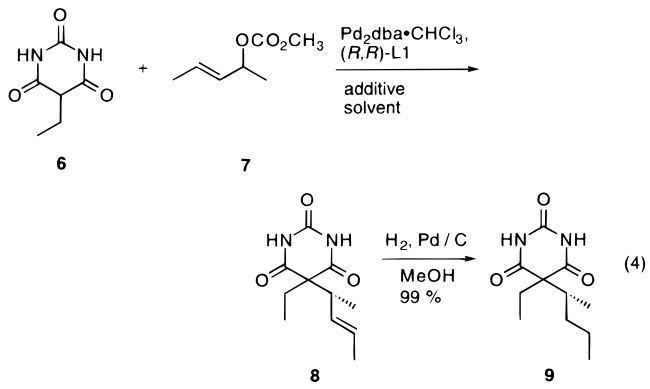
Table 1. Synthesis of Cyclopentobarbital 3[a]

entry	base (1 equiv)	ligand	additive (10 mol %)	mono/di/tri-alkylation[b]	% yield[c]	% ee[d]
1	Et_3N	L1		4.3:1:1	39	84
2	Et_2N-*i*-Pr	L1		1:1:0.3	24	93
3	NaH	L1		2.3:1:0.9	20	87
4		L1		2.8:1:0	39	74
5		L1	Hex_4NBr	3.6:1:0	80	94
6[e]		L1	Hex_4NBr	2.1:1:0	59	96
7		L2		11.4:1:0	86	85
8		L2	Hex_4NBr	100:0:0	85	91

[a] All reactions were performed using 2.5 mol % of tris(dibenzylideneacetone)dipalladium(0) chloroform complex and 5 mol % ligand in CH_2Cl_2 at room temperature unless otherwise noted. [b] Determined by GC. [c] Isolated yield. [d] Determined by chiral HPLC. [e] The reaction was performed at 0 °C.

polyalkylation was a significant problem, resulting in low yields of **3** (entry 1, Table 1). Gratifyingly, however, **3** was formed in excellent ee. A contributing factor to the polyalkylation is no doubt the higher solubility of the monoalkylation product **3** compared to the starting material **1** in methylene chloride. In fact, the reaction could conveniently be monitored by following the disappearance of **1** to ultimately give a homogeneous solution at the end of the reaction. Switching to a stronger base (sodium hydride) resulted in even more overalkylation. Remarkably, the reaction proceeded without any added base; however, it still gave significant amounts of polyalkylation and diminished ee (entry 4). We thought that the addition of a tetraalkylammonium salt might prove beneficial as the salt could associate with **1**, creating a more sterically demanding nucleophile. The creation of a more sterically encumbered nucleophile should make a second alkylation event more difficult. Also, the greater steric demand should augment the interactions between the nucleophile and ligand, thereby leading to enhanced ee. Indeed, the addition of tetra-*n*-hexylammonium bromide (THAB) gave **3** in dramatically improved yield and ee (entry 5). Attempts to improve the yield further by lowering the reaction temperature proved fruitless (entry 6). The solution to the problem proved to be ligand choice. In other work, we designed ligand L2, bearing a naphtho linker, to create more rigid and confined chiral space. In this environment, steric accessibility of the π-allylpalladium intermediate to attack by the monoalkylation product **3** would be considerably reduced compared to the starting material **1**. Indeed, a catalyst using ligand L2 generated **3** in 85% yield and 91% ee with no detectable amounts of **4** or **5** in the presence of THAB (entry 8). The absolute configuration shown in eq 3 was assigned by applying the mnemonic developed for the AAA reaction with ligands L1 and L2.[7] The validity of the mnemonic for this class of nucleophile is established in the synthesis of pentobarbital (vide infra).

Pentobarbital (5-ethyl-5-(1-methyl-1-butyl)barbituric acid, **9**) is also a sedative/hypnotic. The (*R*)-enantiomer has been synthesized from a chiral starting material, (*R*)-pulegone;[8] however, the (*S*)-enantiomer has proven much more difficult to make in high optical purity.[9] We began our studies by applying the reaction conditions developed for cyclopentobarbital to the reaction of barbiturate **6**[10] with allylic carbonate **7** using ligand L1 to give barbituric acid derivative **8**[11] (eq 4). The reaction was found to be



6 **7** **8** **9**

much slower than the previous case, and gentle heating was required to achieve complete conversion (Table 2, entry 2). Like **1**, **6** was only partially soluble in methylene chloride; however, polyalkylation was much less common. In an attempt to increase the rate of the reaction, various bases were tried. With 1 equiv of triethylamine, the reaction proceeded at room temperature, but, like with cyclopentobarbital, significant amounts of polyalkylation were observed. Since the nucleophile is involved in the enantiodiscriminating event, factors such as nature of the counterion and solvent might influence the structure of the ion pair and thereby the ee. Surprisingly, the addition of 1 equiv of 1,1,3,3-tetramethylguanidine (TMG) or 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) gave no reaction. Apparently, the amine base forms an aggregate with **6**, which is even less soluble in methylene chloride than the nucleophile alone. Catalytic quantities of base, however, gave the desired product **8** but with the same modest ee. Solvent variation had no beneficial effect. While 1,2-dichloroethane (DCE) gave results similar to methylene chloride, a methylene chloride/DMSO mixture, THF, and DME gave inferior results. The additive was also varied with some interesting results. Switching from THAB to tetra-*n*-butylammonium chloride led to a slow reaction and low yield. On the other hand, the addition of tetra-*n*-butylammonium triphenyldifluorosilicate (TBAT) dramatically accelerated the rate of the reaction. While reactions at room temperature typically required 12 or more hours, the addition of TBAT gave complete conversion within 1 h. Decreasing the catalyst loading from 5 to 2 mol % still provided the alkylated product **8** in 96% yield (72% ee) in just 3 h. Attempts to increase the ee further by recrystallization of **8** were unsuccessful. However, after hydrogenation of the olefin, one recrystallization did increase the ee of pentobarbital (**9**) to 81%.[12] The absolute configuration predicted by the

(7) See Trost and Van Vranken in ref 2.

(8) Cook, C. E.; Tallent, C. R. *J. Heterocycl. Chem.* **1969**, *6*, 203.

(9) Carroll, F. I.; Meck, R. *J. Org. Chem.* **1969**, *34*, 2676. Knabe, J.; Philipson, K. *Arch. Pharm.* (*Weinheim*) **1966**, *299*, 232. Kleiderer, E. C.; Shonle, H. A. *J. Am. Chem. Soc.* **1934**, *56*, 1772.

(10) Hurd, C. D.; McAuley, M. L. *J. Am. Chem. Soc.* **1948**, *70*, 1650.

(11) Shonle, H. A.; Waldo, J. H. *J. Am. Chem. Soc.* **1933**, *55*, 4649.

(12) The absolute configuration was determined by comparison of the rotation to that reported in the literature (ref 9). Thus, using the (*R,R*)-L1, (*R*)-**9** was obtained.

Table 2. Synthesis of Pentobarbital[a]

entry	solvent	base (equiv)	additive (10 mol %)	*T*, °C	mono/dialkylation[b]	% yield[c]	% ee[d]
1	CH_2Cl_2		Hex_4NBr	25	100:0	55	71
2	CH_2Cl_2		Hex_4NBr	40	100:0	83	64
3	CH_2Cl_2	Et_3N (1)	Hex_4NBr	25	1.7:1	67	73
4	CH_2Cl_2	TMG (1)	Hex_4NBr	40	NR		
5	CH_2Cl_2	DBU (1)	Hex_4NBr	40	NR		
6	CH_2Cl_2	Et_3N (0.2)	Hex_4NBr	25	100:0	44	74
7	CH_2Cl_2	TMG (0.2)	Hex_4NBr	25	100:0	32	72
8	CH_2Cl_2	DBU (0.2)	Hex_4NBr	25	100:0	89	69
9	CH_2Cl_2/DMSO		Hex_4NBr	25	2.9:1	69	69
10	THF		Hex_4NBr	25	100:0	10	32
11	DME		Hex_4NBr	40	100:0	22	65
12	DCE		Hex_4NBr	25	100:0	81	70
13[e]	CH_2Cl_2		Bu_4NCl	25	100:0	9	71
14	CH_2Cl_2		TBAT	25	100:0	98	69
15[f]	CH_2Cl_2		TBAT	25	100:0	96	72

[a] All reactions were performed using 2.5 mol % of tris(dibenzylideneacetone)dipalladium(0) chloroform complex and 5 mol % ligand unless otherwise noted. [b] Determined by GC. [c] Isolated yield. [d] Determined by chiral HPLC. [e] 30 mol % Bu_4NCl was used. [f] 1 mol % of tris(dibenzylideneacetone)dipalladium(0) chloroform complex and 2 mol % ligand were used. TMG = 1,1,3,3-tetramethylguanidine. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. DCE = 1,2-dichloroethane. TBAT = tetra-*n*-butylammonium triphenyldifluorosilicate.

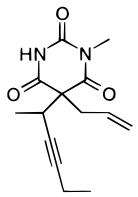
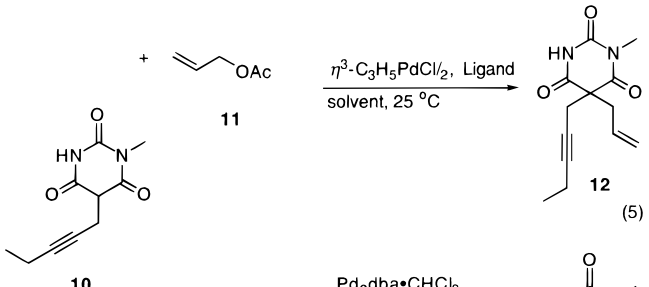


Figure 2. Methohexital.

mnemonic for the AAA reaction using (*R,R*)-L1 is *R* (as depicted). This assignment is confirmed after hydrogenation to **9** by comparison of its sign of rotation to that of the known product.

Methohexital,[13] an anesthetic, contains two chiral centers: one at C-5 of the pyrimidinetrione ring and the other at C-1 of the alkynyl side chain (Figure 2). The two diastereomeric forms of methohexital have different biological effects. The AAA reaction of barbiturate **10** and allyl acetate **11** to give barbituric acid derivative **12**[14] could serve as a model system for the synthesis of methohexital (eq 5). Furthermore, it allows one to



examine the use of prochiral nucleophiles in the AAA reaction of barbituric acid derivatives. In this reaction, the chiral ligand must differentiate between the amide hydrogen and the amide methyl group. Initial efforts gave the allylated product in good yield, but with no enantioselectivity (Table 3). It was thought that performing the reaction in a solvent capable of forming hydrogen bonds with the secondary amide nitrogen might prove beneficial. In such a solvent, the difference between the two facial approaches of the nucleophile would be greater and the ligand might therefore be able to distinguish between them more readily. Indeed, performing the reaction in DMSO gave **12** in good yield and with some ee (19%, entry 2). When the more sterically demanding ligand L2 was used, the enantioselectivity could be further increased to 37%. When the reaction was performed with L2 in a CH_2Cl_2/DMSO mixture, inferior results were obtained (entry 4). Also, in situ protection of the secondary amide with bis(trimethylsilyl)acetamide (BSA) followed by palladium-catalyzed allylic alkylation gave the product in 69% yield and low ee (7%) (entry 5).

Table 3. Synthesis of 12[a]

entry	ligand	solvent	% yield[b]	% ee[c]
1	L1	CH_2Cl_2	72	0
2	L1	DMSO	62	19
3	L2	DMSO	72	37
4	L2	CH_2Cl_2/DMSO[d]	69	7
5[e]	L1	CH_2Cl_2	42	7

[a] All reactions were performed using 2.5 mol % of π-allyl palladium chloride dimer and 5 mol % ligand at room temperature unless otherwise noted. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Two equivalents of DMSO was added. [e] One equivalent of BSA was added.

Due to the disappointing results obtained using allyl acetate, the reaction of barbiturate **10** was reexamined with cyclopentenyl carbonate **2** (eq 6) with the hope that formation of diastereomers instead of enantiomers would lead to greater selectivity (Table 4). It was found that use of just 1 mol % of the standard cyclohexyl diamine ligand gave the alkylated product **13** in excellent yield and ee; however, the diastereomeric ratio was low (entry 1). Switching to solvents capable of forming hydrogen bonds with the substrate (DMSO, ethanol) resulted in decreased ee and de (entries 2,3). Also, the addition of base gave inferior results (entry 4). The more sterically demanding naphthyl ligand L2 gave the product in slightly better de, but in lower ee (entry 6). Decreasing

(13) Doran, W. J. *J. Org. Chem.* **1960**, *25*, 1737. Gibson, W. R.; Doran, W. J.; Wood, W. C.; Swanson, E. C. *J. Pharmocol. Exp. Ther.* **1959**, *125*, 23. Krieglstein, J.; Mwasekaga, S. *Arzeim. Forsch.* **1987**, *37*, 291.

(14) E. Lilly & Co. US 2872448, 1956. Doran, W. J. *Chem. Abstr.* **1959**, *53*, 13185.

Table 4. Synthesis of 13[a]

entry	ligand	solvent	*T*,° C	dr[b]	% yield[c]	% ee[d]
1[e]	L1	CH_2Cl_2	25	2:1	78	93, 86
2	L1	DMSO	25	1.1:1	61	78, 71
3	L1	C_2H_5OH	25	2.1:1	86	68, 38
4[f]	L1	CH_2Cl_2	25	1.9:1	92	85, 62
5	L2	DMSO	25	1.6:1	76	43, 70
6	L2	CH_2Cl_2	25	2.5:1	54	77, 89
7	L1	CH_2Cl_2	0	2.5:1	82	92, 82
8	L1	CH_2Cl_2	−20	2.4:1	93	90, 78
9	L2	CH_2Cl_2	−20	2.2:1	63	75, 90

[a] All reactions were performed using 2.5 mol % of tris(dibenzylideneacetone)dipalladium(0) chloroform complex and 5 mol % ligand unless otherwise noted. [b] Determined by GC. [c] Isolated yield. [d] Determined by chiral HPLC. The ee of the major enantiomer is given first. [e] 0.5 mol % of tris(dibenzylideneacetone)−dipalladium(0) chloroform complex and 1 mol % ligand was used. [f] One equivalent of DBU was added.

the reaction temperature did not improve the results. Efforts to improve the diastereomeric ratio by recrystallization were not successful. To conclude, discrimination of the amide hydrogen and methyl groups of **10** remains a challenge in the AAA reaction of barbituric acid derivatives.

In summary, the AAA reaction has been applied to the synthesis of barbituric acid derivatives. Cyclopentobarbital (**3**) and pentobarbital (**9**) were synthesized in 91% and 81% ee, respectively. To the best of our knowledge, this is the first report of a catalytic asymmetric synthesis of barbituric acids with high ee. The generation of enantioselectivity at the nucleophile has proven difficult with the best conditions giving the alkylated product in 37% ee. While this selectivity is modest, the extent of the chiral recognition is still remarkable considering the nearly symmetrical nature of the nucleophile. It should be pointed out that no base is required in these reactions. The acidity of the barbituric acids makes the use of a base unnecessary and the basicity of the leaving group of the electrophile is apparently strong enough to promote the reaction. The promising results obtained to date in the AAA reaction of barbituric acid derivatives suggest that this reaction may serve as a useful strategy for asymmetric synthesis of these biologically highly active molecules and that additional work may further enhance the enantioselectivity.

Experimental Section

General Experimental Conditions. All reactions were performed under an atmosphere of dry nitrogen. Solvents were distilled under an atmosphere of nitrogen before use. THF and DME were distilled from sodium benzophenone ketal. Dichloromethane, Hunig's base, and triethylamine were distilled from calcium hydride. 1,1,3,3-Tetramethylguanidine (TMG) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were purchased from Aldrich and distilled prior to use. Methanol was distilled from magnesium methoxide. Anhydrous solvents were transferred via oven-dried syringes.

HPLC was performed on a Thermo Separation Products Spectraseries P100 and UV100 or P200 and UV200 ($\lambda = 254$) using Chiralcel columns (OD, AD, or AS).

Representative Procedure for the Synthesis of 3: Cyclopentobarbital (5-Allyl-5-(2-cyclopenten-1-yl)barbituric Acid, 3).[5] A test tube was charged with barbiturate **1**[6] (25 mg, 0.16 mmol) and then flushed with nitrogen. CH_2Cl_2 (0.3 mL) was added, and the heterogeneous mixture was sonicated for approximately 1 min. A prestirred solution (15 min) of tetrahexylammonium bromide (7.0 mg, 0.016 mmol), tris(dibenzylidineacetone)dipalladium(0) chloroform complex (4.1 mg, 0.004 mmol), (*S,S*)-L2 (6.3 mg, 0.008 mmol), and carbonate **2** (25 mg, 0.18 mmol) in CH_2Cl_2 (0.6 mL) was added, and the mixture was stirred under nitrogen at room temperature for 1 h at which time the reaction became homogeneous. The product was isolated by flash chromatography on silica gel (50% ether/petroleum ether) to give 31.7 mg (85%) of (*R*)-**3** as a white solid: $R_f = 0.54$ (40% ethyl acetate/petroleum ether); mp = 140−141 °C (lit.[5] mp 139−140 °C); $[\alpha]^{23}_D = 158.9°$ (*c* 1.3, dichloromethane); HPLC (Chiralcel AD column, 90:10 heptane/2-propanol, flow = 0.80 mL/min, $\lambda = 254$) t_R (major) = 22.33 min, t_R(minor) = 24.73 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.12 (s, 1H), 8.06 (s, 1H), 5.90−5.93 (m, 1H), 5.51−5.67 (m, 2H), 5.07−5.18 (m, 2H), 3.34−3.35 (m, 1H), 2.80 (t, $J = 6.0$ Hz, 2H), 2.27−2.33 (m, 2H), 1.95−2.06 (m, 2H).

Representative Procedure for the Synthesis of 8. 5-Ethyl-5-(1-methyl-2-butenyl)barbituric Acid (8).[11] A test tube was charged with barbiturate **6**[10] (15 mg, 0.096 mmol), flushed with nitrogen, and then charged with CH_2Cl_2 (0.3 mL). The resulting mixture was sonicated for 1 min. A prestirred solution (15 min) of tris(dibenzylidineacetone)dipalladium(0) chloroform complex (1.0 mg, 0.96 μmol), (*R,R*)- L1 (1.3 mg, 0.0019 mmol), pent-2-enyl methyl carbonate **7** (15 mg, 0.11 mmol), and TBAT (5.2 mg, 0.0096 mmol) in CH_2Cl_2 (0.6 mL) was added. The heterogeneous reaction was stirred under nitrogen at room temperature for 3 h. The resulting homogeneous solution was purified by flash chromatography on silica gel (40% ether/petroleum ether) to give 20.7 mg of **8** (96%) as a white solid: $R_f = 0.20$ (20% ethyl acetate/petroleum ether); mp = 108−110 °C (lit.[11] mp 114.5−116 °C); $[\alpha]^{23}_D = 2.4°$ (*c* 2.8, dichloromethane); HPLC (Chiralcel AS column, 90:10 heptane/2-propanol, flow = 1.00 mL/min, $\lambda = 254$) t_R (major) = 10.42 min, t_R (minor) = 13.41 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.76 (s, 1H), 8.68 (s, 1H), 5.47−5.59 (m, 1H), 5.31 (ddd, $J = 15.2$, 9.3, 1.5 Hz, 1H), 2.70−2.80 (m, 1H), 1.97−2.07 (m, 2H), 1.64 (dd, $J = 6.3$, 1.2 Hz, 3H), 1.07 (d, $J = 6.9$ Hz, 3H), 0.82 (t, $J = 7.5$ Hz, 3H).

Pentobarbital (5-Ethyl-5-(1-methylbutyl)barbituric Acid, 9).[8,9] Barbiturate **8** (110 mg, 0.49 mmol), 10% palladium on charcoal (52 mg, 0.049 mmol), and methanol (5 mL) were placed in a 15 mL round-bottom flask. The flask was flushed with hydrogen and then stirred under hydrogen for 1 h. The mixture was filtered through silica gel with ether and then concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (50% ether/petroleum ether) to give 110 mg of (*R*)-**9** (99%) as a white solid. Recrystallization from ether/petroleum ether gave **9** (50% yield) in 81% ee: $R_f = 0.19$ (20% ethyl acetate/petroleum ether); chiral GC (cyclosil B, isotherm 190 °C) t_R (major) = 28.023 min, t_R (minor) = 27.208 min; mp = 120 °C (lit.[8] mp 122−122.5 °C); $[\alpha]^{23}_D = 10.9$ (*c* 1.7, ethanol) [lit.[8] (*R*), 99% ee: $[\alpha]^{22}_D = 13.1$ (*c* 2.0, ethanol)]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.84 (s, 2H), 2.04−2.16 (m, 3H), 1.41−1.45 (m, 2H), 1.12−1.16 (m, 2H), 1.02 (d, $J = 6.9$ Hz, 3H), 0.83 (t, $J = 6.6$ Hz, 6H).

1-Methyl-5-(2-pentynyl)barbituric Acid (10). A solution of sodium (0.56 g, 24 mmol) and ethanol (25 mL) was charged with diethyl-2-(2-pentynyl)malonate[15] (2.5 g, 12 mmol). The solution was transferred to a 50 mL round-bottom flask containing methylurea (0.89 g, 12 mmol). The resulting mixture was stirred at reflux for 1 h. The solution was concentrated to remove ethanol. The residue was dissolved in 20 mL of water and acidified to pH 2−3 by the dropwise addition of concentrated HCl. An oil separated from the aqueous solution. The aqueous layer was extracted with ethyl acetate (3 × 25 mL). The extracts were pooled and then concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (50% ethyl acetate/petroleum ether) to give 1.0 g (38%) of **10** as a white crystalline solid: mp 83−84 °C; IR (neat) ν 3408, 3208, 1710, 1448 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.75 (bs, 1H), 3.50 (t, $J = 4.5$ Hz, 1H), 3.30 (s, 3H), 2.99 (d, $J = 1.2$ Hz, 2H), 2.01−2.09 (m, 2H), 1.00 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 168.4, 167.5, 150.4, 86.2, 72.3, 48.3, 27.8, 21.6, 13.8, 12.2. Anal. Calcd for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.59; H, 5.91; N, 13.00.

Representative Procedure for the Synthesis of 12. 5-Allyl-1-methyl-5-(2-pentynyl)barbituric Acid (12).[14] A test

(15) Bergman, R.; Nilsson, B.; Wickberg, B. *Tetrahedron Lett.* **1990**, *31*, 2783.

tube was charged with π-allyl palladium chloride dimer (1.1 mg, 0.003 mmol), (*R*,*R*)-L2 (4.8 mg, 0.006 mmol), and barbiturate **10** (25 mg, 0.12 mmol). The test tube was flushed with nitrogen, and then 1.0 mL of DMSO was added. The solution was stirred at 60 °C for 15 min, cooled to room temperature, and then charged with allyl acetate (**11**, 13 μL, 0.12 mmol). The reaction was stirred under nitrogen at room temperature for 1.5 h. The product was isolated by flash chromatography on silica gel (30% ethyl acetate/petroleum ether) to give 21 mg (72%) of **12** as a clear oil: R_f = 0.36 (20% ethyl acetate/petroleum ether); HPLC (Chiralcel AD column, 90:10 heptane/2-propanol, flow = 0.80 mL/min, λ = 220) t_R(major) = 11.54 min, t_R(minor) = 14.14 min; IR (neat) ν 3574, 3242, 1715, 1682, 1446 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85 (bs, 1H), 5.49−5.61 (m, 1H), 5.09−5.17 (m, 2H), 3.31 (s, 3H), 2.77 (s, 2H), 2.68 (d, J = 7.2 Hz, 2H), 2.06 (q, J = 7.2 Hz, 2H), 1.02 (t, J = 7.2 Hz, 3H).

Representative Procedure for the Synthesis of 13. 5-(2-Cyclopenten-1-yl)-1-methyl-5-(2-pentynyl)barbituric Acid (13). A test tube was charged with tris(dibenzylidineacetone)-dipalladium(0) chloroform complex (0.95 mg, 0.92 μmol) and (*R*,*R*)-L1 (1.3 mg, 0.0018 mmol). The test tube was flushed with nitrogen, charged with CH_2Cl_2 (0.1 mL), and then charged with carbonate **2** (29 mg, 0.20 mmol). The solution was stirred at room temperature for 15 min and was then charged with a solution of barbiturate **10** (40 mg, 0.092 mmol) in CH_2Cl_2 (0.2 mL). The reaction was stirred under nitrogen at room temperature for 3 h. The product was isolated by flash chromatography on silica gel (20% ethyl acetate/petroleum ether) to give 41 mg (78%) of **13** as a white crystalline solid: R_f = 0.36 (15% ethyl acetate/petroleum ether); HPLC (Chiralcel OD column, 95:5 heptane/2-propanol, flow = 0.30 mL/min, λ = 220) t_R(major diastereomer) = 35.91, 39.14 min, t_R(minor diastereomer) = 53.51, 55.78 min; IR (neat) ν 3238, 1718, 1677, 1448 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) major diastereomer δ 7.89 (s, 1H), 5.87−5.88 (m, 1H), 5.52−5.54 (m, 1H), 3.31 (s, 3H), 3.28−3.31 (m, 1H), 2.87 (s, 2H), 2.27 (m, 2H), 1.91−2.07 (m, 4H), 0.99 (dt, J = 7.5, 1.5 Hz, 3H); minor diastereomer δ 8.00 (s, 1H), 5.59−5.61 (m, 1H), 3.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) (mixture of diastereomers) δ 171.0, 169.8, 149.9, 135.2, 127.8, 85.1, 73.4, 59.7, 54.9, 31.9, 27.9, 25.3, 24.9, 14.0, 12.2. Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.45; H, 6.57; N, 10.41.

Acknowledgment. We thank the National Institutes of Health, General Medical Sciences, and the National Science Foundation for their generous support of our programs. We thank ChiroTech and NSC Technologies for the generous gifts of ligands.

JO991491C