High-Pressure Asymmetric Michael Additions of Thiols, Nitromethane, and Methyl Oxoindancarboxylate to Enones

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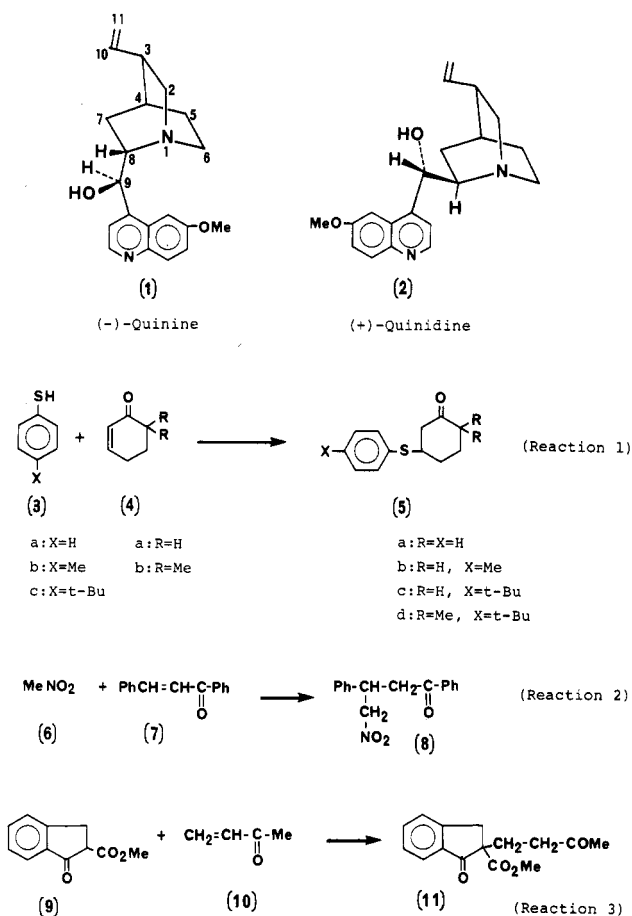
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Quinine- and quinidine-catalyzed asymmetric Michael additions of benzenethiols **3** to cyclohexenones **4** (reaction 1, Scheme I), of nitromethane (**6**) to chalcone (**7**) (reaction 2), and of methyl oxoindancarboxylate **9** to methyl vinyl ketone (**10**) (reaction 3) are investigated under high pressure (400 MPa–1.5 GPa). A quinine- or quinidine–acrylonitrile copolymer is also employed as a catalyst in the reaction 3. Pressure decreases the enantiomeric excess (ee) in the reactions 1 and 3. Pressure dependence of the ee's is discussed in terms of tightness of transition states of the reactions. Although the reaction 2 does not take place at atmospheric pressure, it proceeds well under high pressure. The ee of the quinine-catalyzed reaction 2 also decreases under high pressure; however, that of quinidine-catalyzed reaction 2 is not affected so much by pressure.

The Michael-type conjugate additions to α,β-unsaturated carbonyl systems have been recognized as one of versatile functionalization methods in organic synthesis. The use of chiral catalysts may transform prochiral carbon atoms of Michael acceptors into chiral ones to yield optical active compounds with reasonable chemical and optical yields. During the past decade attention has been paid to the possibility of asymmetric Michael additions by the use of chiral amine catalysts. Intriguing examples of alkaloid-catalyzed Michael additions are those of thiols to cyclohexenones[1–3] or nitrostyrenes,[4] of keto esters to acrolein[5] or methyl vinyl ketone,[4–7] of nitrosulfone to methyl vinyl ketone,[6] of thioglycollic acid to nitrostyrenes,[8] and of nitromethane to chalcone.[3,9] Synthetic poly(amino acid)s[10–13] and alkaloid–acrylonitrile copolymers[14–16] or a polymer-linked alkaloid[17] have also been reported to be effective for asymmetric Michael-type additions as well.

On the other hand, application of hydrostatic pressure is known to accelerate chemical reactions which take place with net contraction of the molar volume of reactants (reactions characterized by negative values of activation volume). From a volume profile of the Michael reaction, it is anticipated that the reaction will be highly accelerated by pressure.[18] Indeed many Michael-type additions, which were unsuccessful under conventional reaction conditions,

Scheme I

(1) (−)-Quinine

(2) (+)-Quinidine

(Reaction 1)

(3)   (4)   (5)

a: X=H   a: R=H   a: R=X=H
b: X=Me   b: R=Me   b: R=H, X=Me
c: X=t-Bu   c: R=H, X=t-Bu
                      d: R=Me, X=t-Bu

(Reaction 2)

MeNO₂ + PhCH=CH-C-Ph → Ph-CH-CH₂-C-Ph
(6)   (7)   (8)

(Reaction 3)

(9)   (10)   (11)

proceeded smoothly on application of high pressure of a 1–1.5 GPa region to give adducts in good yields.[19–21] In addition, asymmetric induction under high pressure has become an interesting and profitable methodology in organic synthesis. For example, Jurczak and his co-workers[22,23] showed that [4 + 2] cycloaddition of butadiene with

(1) Helder, R.; Arends, R.; Bolt, W.; Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, 2181.

(2) Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417.

(3) Colonna, S.; Re, R.; Wynberg, H. *J. Chem. Soc., Perkin Trans. 1* **1981**, 547.

(4) Kobayashi, N.; Iwai, K. *J. Polym. Sci., Polym. Lett. Ed.* **1982**, *20*, 85.

(5) Langstrom, B.; Bergson, G. *Acta Chem. Scand.* **1973**, *27*, 3118.

(6) Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, 4057.

(7) Hermann, K.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2238.

(8) Kobayashi, N.; Iwai, K. *J. Org. Chem.* **1981**, *46*, 1823.

(9) Colonna, S.; Hiemstra, H.; Wynberg, H. *J. Chem. Soc., Chem. Commun.* **1978**, 238.

(10) Fukushima, H.; Ohashi, S.; Inoue, S. *Makromol. Chem.* **1975**, *176*, 2751.

(11) Fukushima, H.; Inoue, S. *Makromol. Chem.* **1975**, *176*, 3609.

(12) Ueyanagi, K.; Inoue, S. *Makromol. Chem.* **1976**, *177*, 2807.

(13) Inoue, S.; Kawano, Y. *Makromol. Chem.* **1979**, *180*, 1405.

(14) Kobayashi, N.; Iwai, K. *J. Am. Chem. Soc.* **1978**, *100*, 7071.

(15) Kobayashi, N.; Iwai, K. *J. Polym. Sci., Polym. Chem. Ed.* **1980**, *18*, 923.

(16) Kobayashi, N.; Iwai, K. *Makromol.* **1980**, *13*, 31; *Tetrahedron Lett.* **1980**, *21*, 2167; *Polym. J.* **1981**, *13*, 263.

(17) Hodge, P.; Khoshdel, E.; Waterhouse, J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2327.

(18) Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* **1985**, 1.

(19) Matsumoto, K. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1013; **1981**, *20*, 770.

(20) Daubene, W. G.; Bunce, R. A. *J. Org. Chem.* **1983**, *48*, 4642.

(21) Hashimoto, S.; Matsumoto, K.; Otani, S. *J. Org. Chem.* **1984**, *49*, 4543.

(22) Jurczak, J. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3438.

Table I. Addition of Benzenethiols to Cyclohexenones (Reaction 1)

entry	catal	thiol	enone	press, MPa	ee %[a]	product config[b]	ee% at 900 MPa/ ee % at 0.1 MPa
1	QN (1)	3a	4a	0.1	39[c]	(R)-5a	
				900	26[d]	(R)-5a	0.67
2	QN (1)	3b	4a	0.1	37[c]	(R)-5b	
				900	20[d]	(R)-5b	0.54
3	QN (1)	3c	4a	0.1	50.4	(R)-5c	
				900	40.5	(R)-5c	0.80
4	QN (1)	3c	4b	0.1	19.7	(R)-5d	
				900	18.3	(R)-5d	0.93
5	QD (2)	3a	4a	0.1	49[c]	(S)-5a	
				900	24[d]	(S)-5a	0.49
6	QD (2)	3c	4a	0.1	60.8	(S)-5c	
				900	52.3	(S)-5c	0.86
7	QD (2)	3c	4b	0.1	30.9	(S)-5d	
				900	28.8[c]	(S)-5d	0.93

[a] Data are averages from three or more experiments and reproducible within 0.3%. [b] Absolute configuration of the product produced in excess. [c] Reproducible within 2%. [d] Reproducible within 5%.

Table II. Addition of Nitromethane to Chalcone (Reaction 2)

entry	catal, mmol	nitromethane, mmol	solvent[a]	press., MPa	chem yield, %	ee %[b]
	QN (1)					
1	0.1	15	toluene	0.1	0	
2	0.3	15	toluene	400	33	35
3	0.3	15	toluene	600	51	31
4	0.3	15	toluene	900	100	27
5	0.3	15	toluene	1500	100	23
6	0.3	30	toluene	900	100	23
7	0.3	15	CH₂Cl₂	900	100	1
	QD (2)					
8	0.3	15	toluene	400	36	58
9	0.3	15	toluene	600	81	59
10	0.3	15	toluene	900	100	60
11	0.3	15	toluene	1500	100	53
12	0.3	30	toluene	900	100	56
13	0.3	15	CH₂Cl₂	900	100	20

[a] A total volume of the reaction mixture was 10 mL. [b] Data are averages from two or more experiments and reproducible within 2%.

di-(–)-menthyl fumarate or (–)-menthyl glyoxalate took place under high pressure to give the corresponding Diels–Alder adducts in moderate optical yields. One of the authors also reported preliminarily a high-pressure Michael addition of nitromethane to chalcone in the presence of alkaloid catalysts.[24] The present paper concerns pressure effect on the alkaloid and alkaloid–acrylonitrile copolymer catalyzed additions of thiols, nitromethane, and methyl oxoindancarboxylate to enones. Transition-state models of the additions, which account for observed enantiomeric excess under high pressure, will be discussed in terms of conformation and geometry change of the Michael donor or acceptor as well as the catalysts.

Results

Pressure dependence of the degree of asymmetric induction of the Michael additions were investigated. The chiral catalysts employed were (–)-quinine (QN, 1), (+)-quinidine (QD, 2), and their copolymers with acrylonitrile (AN–QN and AN–QD). The following reactions were examined under high pressure (Scheme I): reaction 1, the QN- and QD-catalyzed additions of benzenethiols 3 to cyclohexen-3-ones 4; reaction 2, the QN- and QD-catalyzed additions of nitromethane (6) to chalcone (7); reaction 3, the AN–QN- and AN–QD-catalyzed additions of methyl 1-oxoindan-2-carboxylate (9) to methyl vinyl ketone (10). The high-pressure reactions were carried out at ambient temperature in a Teflon tube placed in a high-pressure

reactor. Representative results are summarized in Tables I–III.

Additions of Benzenethiols to Cyclohexen-3-ones (Reaction 1, Table I). Although benzenethiols 3 can react with cyclohexenones 4 in the presence of QN or QD even at atmospheric pressure, the reactions under high pressure were also carried out in toluene to compare with those under atmospheric pressure. A period of 4–5 min was required for pressurizing operation (from a preparation of a reaction mixture to a finish of pressurization). All reactions gave the corresponding adducts 5 in nearly quantitative yields. Values of enantiomeric excess percent (ee %) of the isolated products were determined polarimetrically based on the reported values of the optical rotation of the products.[2] In all reactions QD gave higher ee's than QN did. High pressure decreased the value of ee's, but the degree of decrease in the ee's under higher pressure (compare ee % at 900 MPa/ee % at 0.1 MPa) was found to be small where sterically congested thiol 3c and/or enone 4b were employed.

Additions of Nitromethane to Chalcone (Reaction 2, Table II). The alkaloid-catalyzed addition of nitromethane (6) to chalcone (7) in toluene did not take place at atmospheric pressure.[9] However, the addition proceeded smoothly under high pressure to give the adduct 8 in good yields. Both QN and QD catalyzed well the reactions under high pressure; QD being more effective in asymmetric induction. Higher pressure resulted in higher chemical yields. However, the ee's determined by polarimetry[9] decreased monotonously at higher pressure when QN was employed as the catalyst, while in the QD-catalyzed additions the ee's did not decrease so much by

(23) Jurczak, J.; Tkacz, M. *J. Org. Chem.* **1979**, *44*, 3347.
(24) Matsumoto, K.; Uchida, T. *Chem. Lett.* **1981**, 1673.

Table III. Addition of Methyl Oxoindancarboxylate to Methyl Vinyl Ketone (Reaction 3)

entry	catal	press., MPa	ee %[a]	config[b]	ee % at 900 MPa/ ee % at 0.1 MPa
1	QN (1)	0.1	51	S	
		900	44	S	0.86
2	AN–QN (20:1)[c]	0.1	33	S	
		900	17	S	0.49
3	AN–QN (13:1)[c]	0.1	22	S	
		900	3	S	0.14
4	QD (2)	0.1	40	R	
		900	34	R	0.85
5	AN–QD (23:1)[c]	0.1	31	R	
		900	19	R	0.61
6	AN–QD (14:1)[c]	0.1	29	R	
		900	7	R	0.24

[a] Data are averages from two or more experiments and reproducible within 3.7%. [b] Absolute configuration of the product produced in excess. [c] Figures in parentheses represent the molar ratio of AN to QN or AN to QD in the copolymers. An amount of the catalyst equivalent to 0.05 mmol as QN or QD was employed.

pressure. The degree of asymmetric induction was much higher in toluene than in dichloromethane.

Additions of Methyl 1-Oxoindan-2-carboxylate to Methyl Vinyl Ketone (Reaction 3, Table III). Copolymer catalysts AN–QN (20:1 and 13:1) and AN–QD (23:1 and 14:1) were prepared. Figures in parentheses represent the molar ratios of AN to QN or to QD in the copolymers. The AN–QN- and AN–QD-catalyzed additions (under heterogeneous conditions) of methyl 1-oxo-indan-2-carboxylate (9) to methyl vinyl ketone (10) were reported to give the adduct 11 at atmospheric pressure;[14,15] however, the observed ee's were somewhat depressed as compared with those of QN- and QD-catalyzed additions (under homogeneous conditions). These reactions were reexamined in toluene at atmospheric pressure. The adduct 11 was isolated, and the ee's were determined by polarimetry. The recently reported optical rotation of enantiomerically pure (−)-11 of $[\alpha]_D$ −80.5°[14,15] was used for calculation instead of $[\alpha]_D$ −77°.[7] The stereoselectivity of the QN catalyst was higher than that of the QD catalyst. The pressure dependence of the ee's was almost the same for the QN- and QD-catalyzed reactions.

In the copolymer-catalyzed additions, the AN-QN catalysts yielded (S)-11 in excess as in the case of the monomeric QN-catalyzed additions, whereas the AN–QD catalysts did (R)-11 in excess. The ee's were higher when the copolymer catalysts of low alkaloid content [AN–QN (20:1) and AN–QD (23:1)] were employed. Pressure depressed the ee's in the all copolymer-catalyzed additions. The depression of the ee's was remarkable for the copolymers of high alkaloid content.

Discussion

Additions of Benzenethiols to Cyclohexenones. Wynberg and his co-workers[1–3] have thoroughly investigated the cinchona alkaloid catalyzed additions of benzenethiols 3 to cyclohexen-3-ones 4. The transition-state characteristic was fully discussed in connection with the observed degree of enantiomeric excess and absolute configuration of the products. Steric requirement was pointed out as the most important stereodifferentiating factor which caused a free energy difference between two possible orientations of 4 in the transition states leading to the R or S product. The following features are deduced: (a) the alkaloid catalyst abstracts a proton from 3 to give an ion pair, whereas the hydroxyl group of the alkaloid catalyst holds 4 by a hydrogen bond to give a termolecular
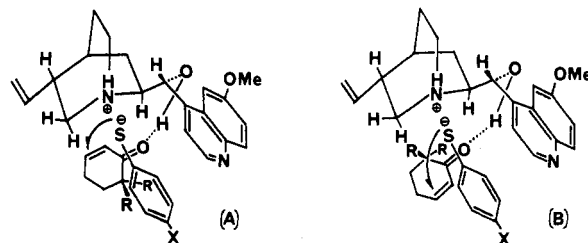
Figure 1. Two possible orientations of cyclohexenone in the transition states of the quinine-catalyzed addition of a thiol: A, leading to R enantiomer; B, leading to S enantiomer.[2]

complex, (b) the rate-controlling addition of the thiolate ion to the double bond of 4 occurs in two ways according to the two possible orientations of 4 in the termolecular complex—an addition to the re face of 4 to give (R)-5 (Figure 1; A, in the case of QN catalyst) or that to the si face of 4 to give (S)-5 (Figure 1; B, in the case of QN catalyst), (c) in the case of Figure 1, A, steric interaction between the C_2 methylene group of the catalyst and the substituents (or the methylene group) of cyclohexenones makes the thiol addition to the re face of 4 predominant, so that the R enantiomer is produced in excess.

Thus the termolecular complex B is the sterically more congested, unfavored transition state irrespective of the kind of the substituent R and/or X. In other words, the transition state B is said to be looser than the A. The free energy difference between the complexes A and B is responsible for the observed ee at atmospheric pressure. Pressure is anticipated to favor the formation of an enantiomer which is produced through a sterically more congested transition state.[25,26] That is, pressure is expected to reduce, in general, the ee of asymmetric reactions. The observed decrease in the ee's by pressure is explained by this difference in pressure effect on the two transition states. A similar explanation rationalizes also the pressure induced decreases in the ee's of the QD-catalyzed additions taking into account conformations of similar termolecular transition-state complexes. However, as is seen in entries 4 and 7, introduction of methyl substituents on the C_6 of cyclohexen-3-one makes the decrease in the ee's by pressure less pronounced. In the cases of enone **4b**, both transition states A and B suffer steric hindrance caused by the methyl groups, and then the somewhat looser transition states resulted in the lower ee's at atmospheric pressure. By the same token, decrease in the ee's by pressure become small. That is, inherent steric hindrance in the transition states A and B is overcome almost evenly by high pressure. This observation may promise a possibility to achieve some sterically hindered, alkaloid-catalyzed Michael additions without fatal decrease in ee's under pressure, which do not proceed at all or are very sluggish at atmospheric pressure as described in the next section.

Additions of Nitromethane to Chalcone. At atmospheric pressure the Michael addition of nitromethane (6) to chalcone (7) did not take place at all with the QN catalyst in aprotic solvents. The free alkaloids are of moderate basic strength. Therefore they are of limited use as bases in asymmetric Michael additions. Although the reaction 2 proceeded well in methanol to give the corresponding nitro ketone 8, the asymmetric induction was quite low (<1%).[9] By the use of N-substituted quininium fluoride the extent of ee increased to 10% in toluene.[3,9] We had reported briefly that the addition of 6 to 7 could be

(25) Asano, T.; le Noble, W. J. *Chem. Rev.* **1978**, *78*, 407.
(26) Jenner, G. *J. Chem. Soc., Faraday Trans. 1* **1985**, *81*, 2437.
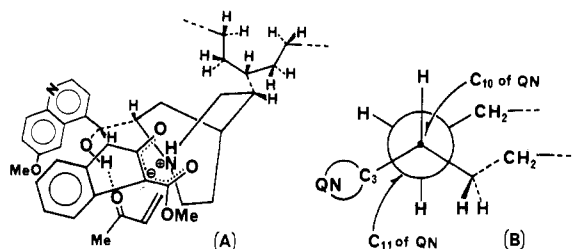
Figure 2. A: One of the two possible orientations of the anion of methyl 1-oxoindan-2-carboxylate in the transition state of the AN–QN-catalyzed addition to methyl vinyl ketone. B: Conformation of AN–QN around C_{10}–C_{11}.

catalyzed by free QN or QD under high pressure to give 8 quantitatively. The asymmetric induction had reached up to 51% ee in toluene.[24] The high pressure reactions were reexamined, and the results (Table II) shows that high pressure is actually a profitable means to perform sluggish asymmetric reactions being composed of rather inert reactants and/or a catalyst. For such inert reactants–catalyst pairs, employment of polar solvents or quaternarized chiral catalysts makes the additions to take place. However, in these circumstances, construction of structured transition states like those depicted in Figure 1 cannot be attained, and one can not expect high degree of asymmetric induction. High pressure is an expedient means for acceleration of asymmetric reactions by holding the structuredness of the transition states. In the QN-catalyzed reaction, the ee's decrease monotonously under high pressure, while in the QD-catalyzed reaction the ee's are kept almost unchanged under high pressures (entries 8–10). Although examination was made on the transition-state conformation and geometry constructed by a space-filling molecular model (imitated those of Figure 1), it did not allow a reasonable mechanistic interpretation which rationalized the pressure-insensibility of the ee's of the QD-catalyzed reaction.

Unexpectedly the ee of the QD-catalyzed reaction dropped sharply at 1.5 GPa (entry 11). The reason for this anomaly has not been clarified yet. However, we assume, at the present time, that partial solidification of toluene[27] or partial crystallization of the catalyst[28] may be responsible for this decrease in the ee of the reaction.

As expected, the ee's decreased considerably in dichloromethane which is more polar than toluene.[3] The decrease in the ee was also found in the cases where an excess amount of 6 was employed (entries 6 and 12). This will be due to an increased polarity of the mixed solvent.[29] Since nitro ketones are versatile intermediates in amino alcohol synthesis, the present high-pressure asymmetric synthesis is of value for the synthesis of such chiral building blocks.

Additions of Methyl 1-Oxoindan-2-carboxylate to Methyl Vinyl Ketone. The QN- and QD-catalyzed additions of methyl 1-oxoindan-2-carboxylate (9) to methyl vinyl ketone (10) afforded (S)- and (R)-11 in excess, respectively. A most plausible transition-state model is depicted in Figure 2 for the QN-catalyzed reaction. The QN catalyst abstracts a proton from 9 to give a planar

resonance stabilized anion of 9 in which the two faces are enantiotopic. Thus the reaction is considered to be a stereodifferentiating addition. In the Figure 2, A, a more favored of two possible termolecular transition-state models is given; the *pro-S* center of the anion faces to the protonated QN catalyst which also holds 10 below the anion by a hydrogen bond. The other transition state, in which the *pro-R* center of the anion faces to the protonated QN, suffers severe steric interaction between the methylene group of the anion and the hydrogen atoms on C_8 and C_9 of QN. Thus the (S)-11 is produced in excess over the R enantiomer.

The addition of 9 to 10 is also catalyzed by AN–QN and AN–QD catalysts. The same stereochemical outcome is observed as in the cases of QN and QD. A pendent QN moiety of the AN–QN (20:1) catalyst is apart from the neighboring QN by 42 methylene groups in the polymer chain. An inspection of stereo models reveals that a pendant point is so much crowded that the conformation around C_{10}–C_{11} (originally the vinyl carbon atoms) of QN is forced to be as depicted in Figure 2, B. Hence, the polymer chain keeps no longer a favored zig-zag conformation, but it bends sharply at this point. In this instance, the polymer chain may interfere an approach of the *pro-S* anion center to the protonated QN to give low ee's of the reaction. Application of high pressure in these cases results in depression of enantioselectivity as described above.

There will be another possibility that high pressure causes a total volume contraction including conformational change of the polymer chain. This may result in a new but unexpected steric requirement, but we have no sound evidence to claim this type of pressure effect at the present time.

The above-mentioned interference of the ion pair formation is more reinforced in the cases of AN–QN (13:1) catalyst, and hence the ee's decrease considerably at atmospheric pressure as well as under high pressure. Results obtained with QD and AN–QD catalysts are rationalized in a similar manner.

Experimental Section

Melting points were obtained on a micro-hot plate melting point apparatus and are uncorrected. NMR spectra were recorded on JEOL PS-100 and PMX-60 spectrometers. Chemical shifts are given in ppm downfield from internal tetramethylsilane. IR spectra were recorded on a JASCO IRA-1 spectrometer. Optical rotations were determined by JASCO ORD/UV-5 and DIP-181 polarimeters.

(–)-Quinine (1) and (+)-quinidine (2) were recrystallized repeatedly from benzene. Benzenethiols **3a–c**, cyclohexen-3-one (**4a**), nitromethane (6), and methyl vinyl ketone (10) were commercially available and distilled prior to use. Chalcone (7) was recrystallized from hexane. 4,4-Dimethylcyclohexen-3-one (**4b**)[30] and methyl 1-oxoindan-2-carboxylate (**9**)[31] were synthesized according to the literature procedures.

Preparation of AN–QN (13:1).[32] A solution of 2.16 g (6.6 mmol) of 1, 3.18 g (60 mmol) of acrylonitrile, and 0.08 g of azobisisobutyronitrile in 20 mL of DMF was degassed, and the solution was placed in a sealed ampule. The ampule was heated at 90 °C for 44 h. The reaction mixture was worked up as usual to give 1.67 g of a raw copolymer. The air-dried copolymer was extracted with methanol by using a Soxhlet extractor until no yellow color retained in the extract. The purified copolymer was pale light yellow solid, $[\alpha]_D$ –22.8° (DMF, *c* 2). Anal. Found: C, 67.20; H, 6.54; N, 5.60. The AN:QN ratio of the copolymer was

(27) Toluene is known to solidify at 960 MPa at 30 °C.[18]

(28) The pressure dependence of solubility of alkaloids in solvents is not known. In general, the solubilities of solids in liquids at high pressure are lower than the values at atmospheric pressure, as might be guessed from the effect of pressure on melting points of solids. le Noble, W. J. *Progr. Phys. Org. Chem.* **1967**, *5*, 207.

(29) A 10-mL solution containing 30 mmol of nitromethane consists of approximately 2.0 mL of nitromethane (*D* 38.6) and 8.0 mL of toluene (*D* 2.38).

(30) King, F. E.; King, T. J.; Topliss, T. G. *J. Chem. Soc.* **1957**, 919; Johnson, W. S.; Posvic, H. *J. Am. Chem. Soc.* **1947**, *69*, 1361; Holysz, R. P. *J. Am. Chem. Soc.* **1953**, *75*, 4432.

(31) House, H. O.; Hadson, C. B. *J. Org. Chem.* **1970**, *23*, 647.

(32) Kobayashi, N.; Iwai, K. *J. Polym. Sci., Polym. Chem. Ed.* **1980**, *18*, 223.

calculated from the analytical data[32] to be 13:1.

The other copolymer were prepared and characterized in a similar manner. AN–QN (20:1), $[\alpha]_D$ −19.7° (DMF, *c* 1); AN–QD (14:1), $[\alpha]_D$ +30.1° (DMF, *c* 1); AN–QD (23:1), $[\alpha]_D$ +25.6° (DMF, *c* 1).

Typical Procedures of Asymmetric Michael Reactions. Reaction 1 at Atmospheric Pressure. Quinine (1, 0.032 mmol), benzenethiol (3a, 4 mmol), and cyclohexen-3-one (4a, 5 mmol) were dissolved in 7 mL of toluene, and the solution was allowed to stand at ambient temperature. The reaction was almost complete after 5 h. The reaction mixture was extracted, successively, twice with 2 N hydrochloric acid and twice with water and dried over magnesium sulfate. Benzene was added to the solution, if necessary, during the washing procedure. The solvent and the reactants were evaporated completely under reduced pressure to give the addition product 5a in a almost quantitative yield. For purification of 5a, a short silica gel column was employed; benzene being an eluent. The optical rotation of 5a was determined in benzene (*c* 0.5–1), and compared with the rotation of enantiomerically pure 5a, $[\alpha]_{365}$ 651°[1] to determine ee %.

Reaction 1 at High Pressure. The reaction solution was prepared in a similar manner as described above and placed in a Teflon tube plugged at the both ends with Teflon stoppers. The tube was placed in a high-pressure reactor and pressurized. Generally it was 4–5 min from a preparation of the reaction mixture to a finish of pressurization operation. After 5 h, the pressure was released and the reaction mixture was worked up as described above.

Products of Reaction 1. 3-(Phenylthio)cyclohexanone (5a):[2] colorless oil, IR 1720 cm⁻¹; ¹H NMR (CCl₄) 1.2–2.7 (m, 8 H), 3.0–3.5 (m, 1 H), 6.7–7.3 (m, 5 H). 3-((*p*-Methylphenyl)thio)cyclohexanone (5b):[2] colorless oil; IR 1720 cm⁻¹; ¹H NMR (CCl₄) 1.4–2.8 (m, 8 H), 2.24 (s, 3 H), 6.8–7.3 (m, 4 H). 3-((*p*-*tert*-Butylphenyl)thio)cyclohexanone (5c):[2] colorless oil; IR 1710 cm⁻¹; ¹H NMR (CCl₄) 1.32 (s, 9 H), 1.8–2.8 (m, 8 H), 3.3 (m, 1 H), 7.15 (s, 4 H). 3-((*p*-*tert*-Butylphenyl)thio)-6,6-dimethylcyclohexanone (5d):[2] colorless oil; ¹H NMR (CCl₄) 1.00 (s, 1 H), 1.08 (s, 1 H), 1.5–2.1

(m, 4 H), 1.29 (s, 9 H), 3.2 (m, 1 H), 7.10 (s, 4 H).

Reaction 2. The reaction 2 at atmospheric or high pressure was performed in a similar manner as described for reaction 1. Chromatographic separation of 8 from 6 was achieved by a short silica gel column (diethyl ether–hexane, 1/9 to 3/7). 1,3-Diphenyl-4-nitrobutan-1-one (8):[3] 33–100% yield, depending on pressure; mp 87–89 °C; IR (KBr) 1370, 1550, 1690 cm⁻¹; ¹H NMR (CDCl₃) 3.38 (d, 2 H), 3.9 (m, 1 H), 4.46 (q, 2 H), 7.0–7.9 (m, 10 H). The ee % was determined polarimetrically. The optical rotation of an enantiomerically pure (−)-8, $[\alpha]_D$ −41° was used for calculation.

Reaction 3. The AN–QN- or AN–QD-catalyzed reaction 3 at atmospheric or high pressure was performed in a similar manner as described for reaction 1. For example, methyl 1-oxoindan-2-carboxylate (9, 2 mmol) and methyl vinyl ketone (10, 2 mmol) were dissolved in toluene (10 mL), and to this solution was added an AN–QN (13:1) catalyst (42 mg, 0.05 mmol as QN). The reaction mixture was allowed to stand without stirring for 2 days or pressurized as described for reaction 1 for 2 days. The mixture was filtered, and the catalyst was washed with a small amount of benzene. The combined filtrate and washings were evaporated to dryness, and the residue was chromatographed on a short silica gel column eluted by dichloromethane to give the adduct 11 in a yield of 72–76%. Methyl 2-(3-oxobutyl)-1-oxoindan-2-carboxylate (11):[15] mp 104.5–107 °C; IR (KBr) 1715, 1730 cm⁻¹; ¹H NMR (CDCl₃) 2.15 (s, 3 H), 2.1–2.8 (m, 4 H), 3.06 and 3.78 (2 d, 2 H), 7.4–8.1 (m, 4 H). The ee was determined polarimetrically by using $[\alpha]_D$ −80.5° for the enantiomerically pure (−)-11.[14,15]

N-Dienyl Lactams: Preparation and Selectivity in the Diels–Alder Reaction[1a]

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We have shown that *N*-dienyl lactams are prepared in good yield by reaction of a lactam with an α,β-unsaturated aldehyde. The *N*-dienyl lactam is obtained with good selectivity for the *E,E*-isomer. The *N*-dienyl lactams are excellent enophiles and react with electron-deficient olefins to give exclusively the ortho regioisomer with good selectivity for the endo (*Z*) adduct, similar to results observed for dienyl amides. In addition, the yield of the Diels–Alder adduct can be significantly enhanced by the use of aqueous solvents when compared to traditional aprotic solvents.

In recent years the synthesis of heteroatom-substituted dienes and their use in the Diels–Alder reaction has become an area of major interest. There are a few examples of 1-(dialkylamino)-1,3-butadienes[2] as well as other 1- and 2-amino dienes which were shown to give primarily the *Z* and endo adduct in Diels–Alder reactions.[3–5] There are

also several examples of *N*-dienyl amides and carbamates which are excellent enophiles in the Diels–Alder reaction.[6,7] Oppolzer prepared *N*-dienyl amides via treatment of the imine derived from reaction of amines with α,β-unsaturated aldehydes with dimsylsodium and an acid chloride.[6] Overman reported that pyrolysis of acetylenic imino ethers gave the dienyl amide.[7] Overman also prepared *N*-dienyl carbamates from the corresponding dienyl acid and ethyl

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(2) Mannich, C.; Handke, K.; Roth, K. *Chem. Ber.* **1942**, *69*, 2112.

(3) Langenbeck, W.; Gödde, O.; Weschky, L.; Schaller, R. *Chem. Ber.* **1942**, *75*, 232.

(4) Hünig, S.; Kahanek, H. *Chem. Ber.* **1957**, *90*, 238.

(5) Farmer, M. L.; Billups, W. E.; Greenlee, R. E.; Kurtz, A. N. *J. Org. Chem.* **1966**, *31*, 2885.

(6) Oppolzer, W.; Fröstl, W. *Helv. Chim. Acta* **1975**, *58*, 587

(7) (a) Overman, L. E.; Clizbe, L. A. *J. Am. Chem. Soc.* **1976**, *98*, 2352, 8295. (b) Overman, L. E.; Taylor, G. F.; Jessup, P. J. *Tetrahedron Lett.* **1976**, 3086.