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Diastereoselective synthesis of (2*S**)-2-[(*R**)-1*H*-indol-3-yl(phenyl)methyl]-2,3-dihydro-1*H*-inden-1-one

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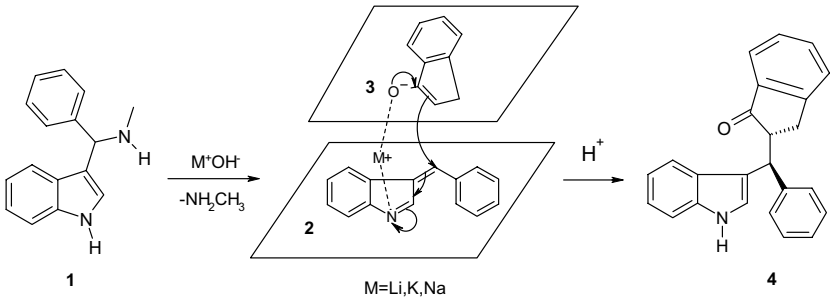
The article is dedicated to the 70th birthday of Professor Yurii I. Smushkevich, Chair of Organic Chemistry, D. I. Mendeleev University of Chemical Technology

Abstract—Double asymmetric induction in Michael reactions has been studied. Enantioselective alkylation of a cyclic ketone (1-indanone) with α-phenyl-*nor*-gramine was carried out. The relative configuration of (2*S**)-2-[(*R**)-1*H*-indol-3-yl(phenyl)-methyl]-2,3-dihydro-1*H*-inden-1-one was established by X-ray diffraction. The relative configuration of (*R**,*R**,*S**)- and (*S**,*R**,*S**)-2-1*H*-indol-3-yl(phenyl)methyl]-2,3-dihydro-1*H*-inden-1-ols was established by ^{1}H NMR studies.

Attempts have been made to forecast qualitatively[1] and quantitatively[2] the course of diastereoselective reactions. We observed high diastereoselectivity in the Michael reaction of α-phenyl-*nor*-gramine **1**[3] with ethyl acetoacetate, giving mainly ethyl (2*R**)-2-[(*S**)-1*H*-indol-3-yl (phenyl)methyl]-3-oxobutanoate (de 90%).[4] In continuation of this work, we speculated that if **1** and cyclic ketones were to be employed as starting materials, the reaction would occur diastereoselectively and diastereospecifically, and we have proposed a mechanism for this process, according to which, if both reactants had a planar structure, only one diastereomer would be formed, namely, the *Z*/*Z*-*R***R**; *Z*/*E*-*R***S** isomer.[5]

To test this hypothesis, we reacted **1** and 1-indanone. We assumed that the reaction would occur via an intermediate **2** followed by Michael addition of enolate **3**. The confirmation of the *Z*-configuration of intermediate



1 **2** **3** **4**

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2, by means of MNDO, was reported earlier.[6–8] We further speculated that coordination between the metal cation, anion **3** and the p-orbital of nitrogen atom of intermediate **2** would bring the Re and Si sides together, which is an '*unlike attack*',[9–12] and would produce diastereomer **4**.

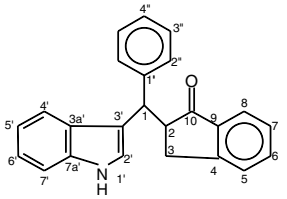
We used NaOAc, Et_3N, K_2CO_3, Cs_2CO_3, LiOH, NaOH and KOH as bases in this reaction. In all cases except for KOH, we obtained a single diastereomer (R^*,S^*) **4**,[13] the relative configuration of which was determined by an X-ray diffraction study and is shown in Figure 1.[14] In the case of KOH, we obtained a mixture of R^*S^*/R^*R^* diastereomers, mainly the R^*,S^* diastereomer (de 80%). This stereochemical result can be explained by enolisation of compound **4** leading to the formation of the R^*,R^* diastereomer.

Using cinchonine, quinine and anabasine, we also obtained a single (R^*,S^*) diastereomer. The chemical shifts for the R^*,S^* and R^*,R^* diastereomers are shown in Table 1. In order to determine the enantioselectivity in the synthesis of **4**, we introduced a third chiral centre by reduction of the carbonyl group with $NaBH_4$ to give compounds **5**[15] and **8**,[15] the ^1H NMR data for which revealed the presence of four diastereomers.

This stereochemical result can be explained by proposing that several reactions occur in parallel: reduction of (R^*,S^*) diastereomer **4** to (R^*,S^*,R^*)/(R^*,S^*,S^*) diastereomers **5** *and* conversion of **4** into enolate **6** with the formation of (R^*,R^*) diastereomer **7** followed by its reduction into (R^*,R^*,R^*)/(R^*,R^*,S^*) diastereomers **8**.

These diastereomeric pairs were identified based on the integral intensity of characteristic C*H*OH protons. Table 2 lists the relative intensities of these characteristic signals and the diastereoselectivity of the synthesis of isomers of 2-[1*H*-indol-3-yl(phenyl)methyl]-1-indanol, **5** and **8**, by the reduction of compound **4**, which was prepared using potassium carbonate, quinine, cinchonine and anabasine as catalysts.

Table 1. ^1H and ^{13}C chemical shifts for 2-[1*H*-indol-3-yl(phenyl)-methyl]-1-indanone



	R^*S^*		R^*R^*	
	^{13}C	^1H	^{13}C	^1H
1	42.0	5.05	46.7	4.90
2	51.2	3.65	45.4	5.18
3	29.5	3.50, 3.00	32.9	4.20, 3.92
4	153.9	—	148.7	—
5	126.6	7.43	125.5	7.60
6	134.6	7.54	133.9	7.67
7	127.2	7.33	127.2	7.45
8	122.9	7.63	123.1	7.74
9	136.5	—	138.9	—
10	206.6	—	193.5	—
1′	—	10.97	—	10.93
2′	122.9	7.48	122.9	7.54
3′	116.2	—	116.8	—
3a′	126.6	—	127.0	—
4′	118.8	7.06	119.3	6.95
5′	118.2	6.83	117.9	6.77
6′	121.0	7.03	120.8	6.97
7′	111.3	7.37	111.2	7.30
7a′	136.5	—	136.5	—
1″	141.3	—	140.7	—
2″	128.8	7.13	128.9	6.95
3″	127.7	7.07	127.7	7.04
4″	126.1	7.03	126.8	6.85

The structure of the predominant enantiomer was determined as follows. Previously, it has been shown that the highly enantioselective reduction of a carbonyl group in the presence of (*S*)-BINAL-H results in a predomi-

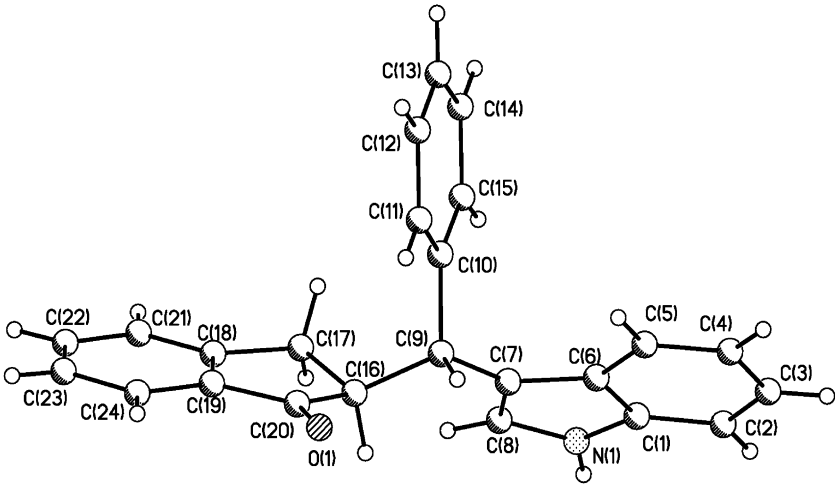


Figure 1.

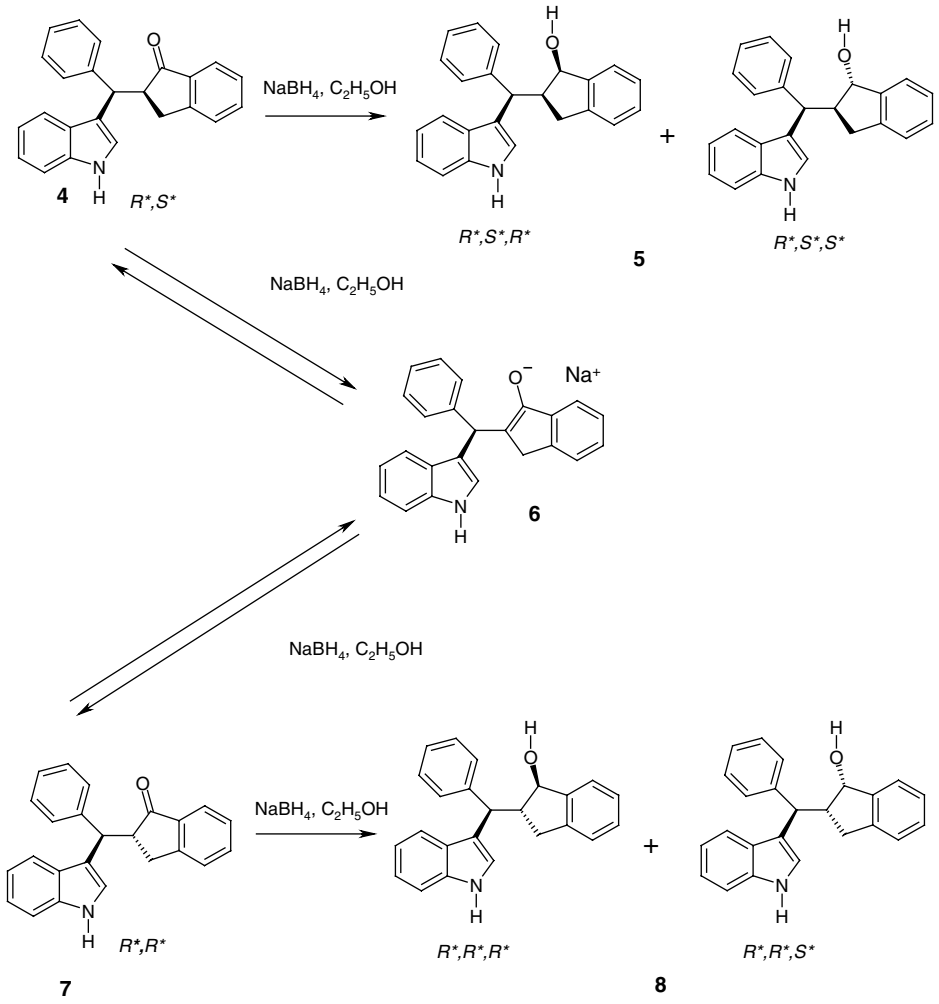


Table 2. Relative intensities of characteristic signals and the diastereoselectivity of the synthesis of (*R**,*R**,*S**), (*R**,*S**,*R**), (*R**,*R**,*R**), (*S**,*R**,*R**) 2-1*H*-indol-3-yl(phenyl)methyl]-2,3-dihydro-1*H*-inden-1-ols (**5** and **8**)

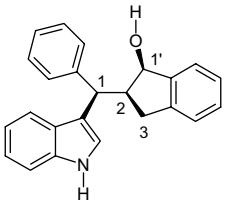
Catalyst	Compounds **5**		Diastereoselectivity	Compounds **8**		Diastereoselectivity
	*R***S***S**	*R***S***R**	de %	*R***R***S**/*R***R***R**		de %
Potassium carbonate	1.00	2.50	42	1.00	0.73	15
Quinine	1.00	2.60	44	0.65	0.62	2
Cinchonine	1.00	3.49	55	0.55	0.58	2
Anabasine	1.00	1.81	28	0.04	0.09	38
(*S*)–BINAL-H	1.00	0.67	20	—	—	—

nance of the *S*-enantiomer.[16] Based on this, we assumed that the centre introduced in compounds **5** using this reductant[17] would have the *S** configuration.

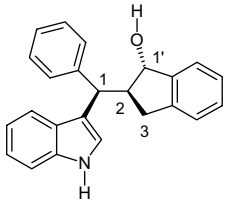
One can see from Table 2 that the enantioselectivity induced by tertiary chiral amines was within 2–13% (in the case of quinine and cinchonine) with a predominance of the *SR* enantiomer and was 14% in the case of anabasine, with a predominance of the *RS* enantiomer. Characteristic ^{1}H and ^{13}C chemical shifts for the compounds are presented in Table 3. The relative configurations were established by 2D NMR spectroscopic data. The COSY technique was used to assign all the aliphatic protons in compounds **5** and **8**, and the NOESY technique allowed us to determine the protons, which were located close to each other. These data enabled a conclusion about the configuration of these compounds, taking into account that the carbon that bears the hydroxyl group has an *S* configuration in compounds obtained by (*S*)-BINAL-H reduction.

Thus, we have demonstrated the possibility of creating double asymmetric induction in Michael reactions with achiral reagents using chiral catalysts.

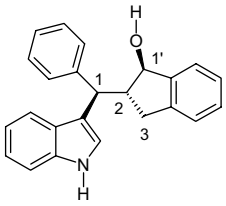
Table 3. Characteristic ^{1}H and ^{13}C NMR chemical shifts for (*R**,*S**,*S**), (*R**,*S**,*R**), (*R**,*R**,*R**), (*R**,*R**,*S**) 2-1*H*-indol-3-yl(phenyl)methyl]-2,3-dihydro-1*H*-inden-1-ols (**5** and **8**)



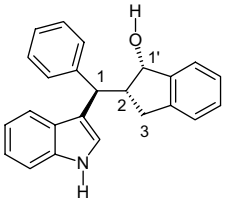
*R**,*S**,*R**



*R**,*S**,*S**



*R**,*R**,*R**



*R**,*R**,*S**

Atom no.	*R***S***S**		*R***S***R**	
	^{1}H	^{13}C	^{1}H	^{13}C
1	4.14	45.4	4.52	42.2
1′	4.80	78.8	4.44	73.9
1′(OH)	5.15	—	4.63	—
2	3.16	52.9	3.22	50.0
3	3.02, 2.45	34.9	2.70, 2.24	36.4
NH	10.86	—	10.80	—

Atom no.	*R***R***R**/*R***R***S**		*R***R***S**/*R***R***R**	
	^{1}H	^{13}C	^{1}H	^{13}C
1	4.45	42.2	4.14	46.1
1′	4.85	74.1	4.74	78.4
1′(OH)	4.56	—	4.87	—
2	3.15	49.8	3.14	53.0
3	2.71, 2.24	36.4	3.15, 2.60	35.9
NH	10.77	—	10.86	—

References and notes

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3. A 33% solution of methylamine (150 g, 1.59 mol) was added over 20 min to a solution of benzaldehyde (106 g, 1 mol). Mixing was accompanied by considerable heat evolution. In order to complete the reaction, the mixture was kept for 12 h at ~20 °C. The mixture was saturated with sodium chloride and extracted with ether. The ethereal extract was dried ($MgSO_4$) and then the ether distilled off. The residue was distilled to give benzalmethylamine (83 g, 70%). Bp 183–185 °C. (Literature data: bp 92–93 °C at 34 mm).[18] A solution of indole (30 g, 0.26 mol) in benzalmethylamine (36 g, 0.30 mol) was heated for 40 h at 70 °C. The mixture was then kept at room temperature until complete crystallisation occurred. The resulting precipitate was filtered off and recrystallised from benzene giving white crystals that turned pink in air (49 g, 65%). Mp 139–141 °C. (Literature data: mp 139–141 °C).[19]
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13. A solution of a base (0.1 g) in H_2O (1 ml) and 1-indanone (0.625 mmol) was added to a boiling solution of α-phenyl-*nor*-gramine **1** (1.0 g, 0.42 mmol) in ethanol (90%, 10 ml); the mixture was refluxed under a stream of an argon until the starting material was consumed (TLC ethyl acetate–CCl_4, 1:4). The reaction mixture was cooled to room temperature and the resulting precipitate filtered off. Yield 45%, mp 247 °C. In the case of chiral catalysts, $[\alpha]_D^{21}$ +0.5 (*c* 2, DMSO).
14. X-ray diffraction analysis: at 120 K, the crystals of **4** ($C_{24}H_{19}NO$) are monoclinic, space group *C2/c*, $a = 24.044(3)$, $b = 6.3355(8)$, $c = 25.451(3)$ Å, $\beta = 115.060(3)°$, $V = 3512.0(8)$ Å^3, $Z = 8$ ($Z' = 1$), $M = 337.40$, $d_{calc} = 1.276$ g cm^{-3}, $\mu(MoK\alpha) = 0.77$ cm^{-1}, $F(000) = 1424$. Intensities of 7420 reflections were measured at 120 K with a Smart 1000 CCD diffractometer ($\lambda(MoK\alpha) = 0.71072$ A, $2\theta < 52°$), and 3423 independent reflections ($R_{int} = 0.0701$) were used in the further refinement. The structure was solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. The hydrogen atoms were located from the Fourier density synthesis. The refinement converged to $wR_2 = 0.1532$ and GOF = 0.938 for all independent reflections ($R1 = 0.0581$ was calculated against F for 1393 observed reflections with $I > 2\sigma(I)$). All calculations were performed using SHELXTL PLUS 5.0. Crystallographic data (excluding structure factors) for the structures reported in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary no. 291553. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ UK (Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk).

15. 2-[1*H*-Indol-3-yl(phenyl)methyl]-2,3-dihydro-1*H*-inden-1-one (0.089 g, 0.026 mmol) was added to a suspension of sodium borohydride (0.01 g, 0.026 mmol) in ethanol (10 ml) and the mixture was kept for two weeks at room temperature. The reaction mixture was poured into water and the resulting precipitate filtered off. Yield 80%. Mp 190 °C.
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17. A solution of ethanol (0.04 g, 0.087 mmol) in anhydrous THF (0.44 ml) was added to lithium aluminohydride (0.033 g, 0.086 mmol) in 0.53 ml of anhydrous THF. The mixture was cooled to 0 °C, and a solution of (*S*)-BINAL-H (0.25 g, 0.087 mmol) in anhydrous THF (1.35 ml) was added. The resulting mixture was stirred for 1 h at room temperature, then 0.088 g (0.026 mmol) of (2*R**)-2-[(*S**)-1*H*-indol-3-yl(phenyl)methyl]-2,3-dihydro-1*H*-inden-1-one was added. The mixture was stirred for 12 h at rt and poured into water; the resulting precipitate was filtered off. Yield 83%. Mp 210 °C.
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