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Lewis Acid-Promoted Asymmetric Conjugate Allylation of *N*-Acyl-2,3-dihydro-4-pyridones Induced by Intramolecular π Interactions

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Abstract: Lewis acid-promoted conjugate addition reaction of an allylsilane to a series of the chiral 8-arylmenthol-derived *N*-acyl-2,3-dihydro-4-pyridones leads to the 2-allyl-4-piperidones with moderate to high levels of asymmetric induction, indicating π-stacking contribution to chirality control. This methodology was applied to the asymmetric synthesis of (–)-*N*-methylconiine. Copyright © 1996 Elsevier Science Ltd

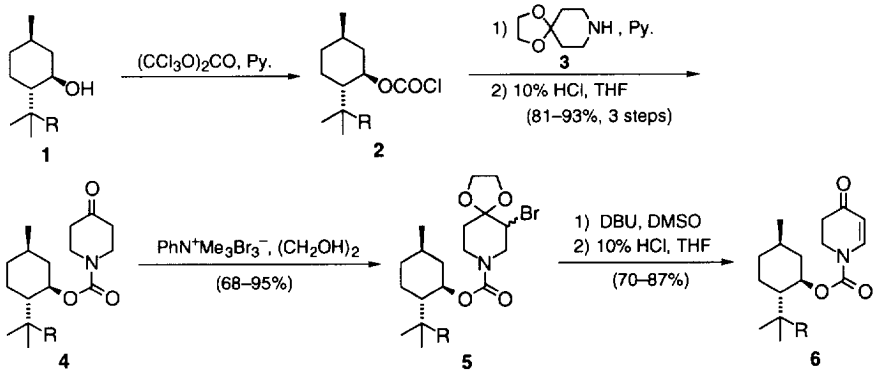
Although the exact nature of the π-stacking effect (either charge transfer or simple van der Waals forces) is still a subject of some debate, such a phenomenon is generally proposed to be the origin of diastereoselective selection attributed to a through-space attractive interaction between π electronic systems.[1] Since introduction of 8-phenylmenthol by Corey in 1975,[2] cyclohexyl-based chiral auxiliaries of the 8-phenylmenthol type[3] have proved to behave as effective chiral inductors in a variety of different types of asymmetric reactions, including Diels–Alder reaction, ene reaction, and conjugate addition to enoates, which are suggested to lie in π-stacking interactions between the aromatic ring and the π system.[1] Our interest in this area focused on the use of 8-arylmenthols for the development of new methodology for asymmetric C–C bond formation and substantiating the intramolecular π-stacking interaction involved. Herein we report our observations on a $TiCl_4$-promoted enantioselective conjugate addition of an allylsilane to 8-arylmenthol-derived 2,3-dihydro-4-pyridones.

The auxiliaries levorotatory 8-substituted menthols **1**, prepared from (+)-pulegone in analogy with Corey's procedure,[2] and commercial (–)-menthol (**1**, R = H) were converted to the corresponding the *N*-acyl-2,3-dihydro-4-pyridones **6** by a sequence involving coupling with 4-piperidone ethylene ketal (**3**), bromoketalization, and elimination according to a modified Kozikowski method[4] (Scheme 1).

Although dihydropyridones have been recognized as versatile building blocks for alkaloid synthesis, they have been used sparingly in asymmetric synthesis.[5] In view of the enone moiety present within the dihydropyridone, we envisioned that, on application of Lewis acid-mediated conjugate addition of allylsilanes (Sakurai allylation),[6] the chiral menthol-derived dihydropyridones **6** would undergo asymmetric conjugate allyl addition. Thus, as illustrated in eq 1, **6a–i** were allowed exposure to 3 equiv of $TiCl_4$ in CH_2Cl_2 (–30 °C, 10 min) and then the mixtures were treated with allyltrimethylsilane (10 equiv) at –30 °C. Workup and purification by column chromatography on silica gel afforded the allylated products as chromatographically separable mixtures of the diastereomers **7a–i** and **8a–i**, and the results are presented in Table 1.

In entry 1, the 2,3-dihydro-4-pyridone **6a** bearing (–)-menthol as the auxiliary shows almost no selectivity in the conjugate allyl addition. On the other hand, the reaction is markedly affected by the presence of the 8-phenyl substituent in the menthol auxiliary (entry 2), showing the high diastereoselectivity of 11.7:1 in the

Scheme 1



formation of the (2*R*)-allyl adduct **7b** (for the assignment to the newly created stereogenic center, see below). Enhanced electron density on the aromatic ring in position 8 of the menthyl group induced by an electron donating group such as *m*- or *p*-methoxyl groups as in **6c** and **6d** appreciably increases the selectivities to 17.4:1 and 17.1:1, respectively (entries 3, 4). In contrast to this, decreased electron density on the aromatic ring induced by an electron withdrawing group such as a *p*-bromine as in **6e** (entry 5) serves to decrease the diastereoselectivity (8.1:1). In the case of the *p*-nitro group as in **6f**, however, such a decrease in the selectivity was not observed despite its strong electron-withdrawing character, but rather higher selectivity (12.6:1) occurred (entry 6) compared with that observed for the phenyl derivative **6b**. The reason for this unexpectedly increasing result in the selectivity of **6f** is rationalized in the discussion in the following paragraph. The highest diastereoselectivity was observed for **6g** with 8-(2-naphthyl)menthol which gave a 30.0:1 ratio of the (*R*)-allylated isomer **7g** (entry 7). In sharp contrast to these results obtained for the aromatic menthyl substrates, the levels of diastereoselectivity with **6h** and **6i** which correspond to the aliphatic menthyl derivatives of **6b** and **6f**, respectively, definitely decrease to 1.2:1 and 1.4:1, respectively (entries 8, 9).

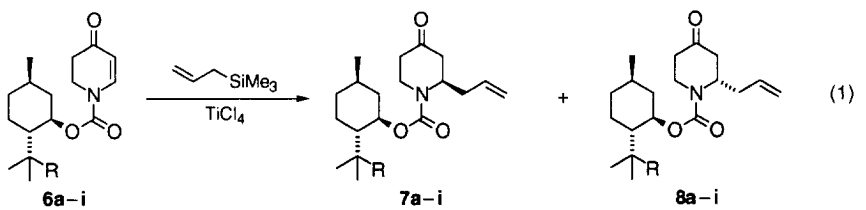
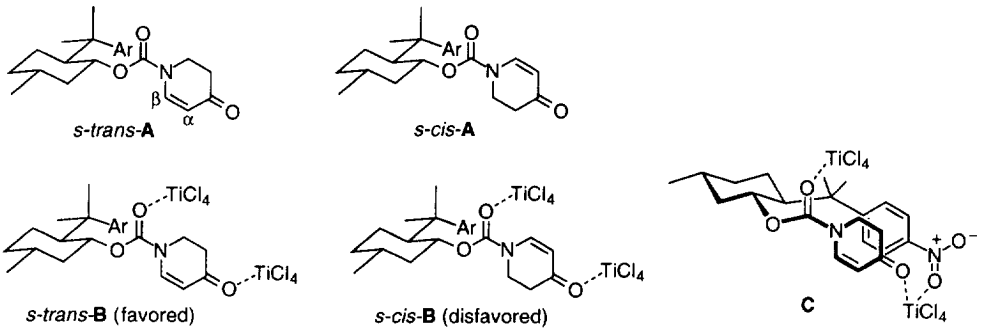


Table 1. $TiCl_4$-promoted conjugate allylation of the cyclic *N*-acyl enaminones **6a–i**.

Entry	Compound	R	Products	Ratio[a]	Yield, %[b]
1	**6a**	H	**7a/8a**	1.1 : 1	96
2	**6b**	Ph	**7b/8b**	11.7 : 1	97
3	**6c**	*m*-$MeOC_6H_4$	**7c/8c**	17.4 : 1	90
4	**6d**	*p*-$MeOC_6H_4$	**7d/8d**	17.1 : 1	92
5	**6e**	*p*-BrC_6H_4	**7e/8e**	8.1 : 1	90
6	**6f**	*p*-$NO_2C_6H_4$	**7f/8f**	12.6 : 1	86
7	**6g**	2-naphthyl	**7g/8g**	30.0 : 1	89
8	**6h**	cyclohexyl	**7h/8h**	1.2 : 1	76
9	**6i**	*trans*-4-nitrocyclohexyl	**7i/8i**	1.4 : 1	65

[a] Determined by HPLC analysis. [b] Isolated yield of the diastereomeric mixture.

These experiments obviously demonstrate that the presence of the 8-aryl substituent in the menthol auxiliary is a critically important factor in the efficiency of these inductors. This outcome may be understood in terms of a π-stacking interaction between the aryl ring and the $TiCl_4$ complexed enamide portion preferably lying in the *s-trans* conformation (with respect to the amide C–N bond) as depicted by *s-trans*-**B**, in which the aryl group might block the *si* face of the enaminone system to induce the *R* configuration at the β position.



^{1}H NMR spectral analysis of the olefinic protons of the enaminone moiety of the dihydropyridones **6a–h** shows pronounced differences in the chemical shifts between the aromatic and nonaromatic menthyl dihydropyridones (Table 2). Each olefinic proton at α and β positions in the aromatic menthyl dihydropyridones **6b–g** gives rise to two sets of broad signals, of which one attributed to β-H suffers a marked downfield shift to δ 7.74–7.77 presumably due to the deshielding effect of the proximal carbonyl group in the enamide unit with the synplanar conformation *s-cis*-**A**. These spectroscopic outcomes are in agreement with the aryl stacked conformers where the aromatic rings exert steric influence which restricts rotation about the amide C–N bond sufficiently to enable conformational interconversion between *s-trans*-**A** and *s-cis*-**A** on the NMR time scale at ambient temperature. However, in the case of the nonaromatic menthyl dihydropyridones **6a** and **6h**, both α-H and β-H appear as a single set of broad signals considerably downfield from those observed for the aromatic menthyl dihydropyridones, which can be explained considering the non-stacked conformation (probably a trans conformation)[7] in which the fast conformational exchange of the *s-trans* and *s-cis* rotamers at ambient temperature is allowed to show average spectra.

Table 2. ^{1}H NMR chemical shift data for olefinic protons of the cyclic *N*-acyl enaminones **6a–h**.

			After complexation with $TiCl_4$	
Compound	Hα[a]	Hβ[b]	Hα	Hβ
6a	5.33	7.84	6.17	8.60
6b	4.95, 5.25	6.23, 7.74	5.83	7.29
6c	4.91, 5.23	6.32, 7.76	5.75	ur[c]
6d	4.85, 5.25	6.40, 7.77	5.79	7.27
6e	5.08, 5.27	6.48, 7.75	5.96	7.52
6f	5.12, 5.29	6.45, 7.76	5.70	ur
6g	4.26, 5.01	5.99[d]	5.20	7.04
6h	5.34	7.85	6.05	8.47

[a]Appeared in 2–1.5:1 ratio for **6b–g**. [b]Appeared in 2–1.5:1 ratio for **6b–f**. [c]Unresolved. [d]Accompanied by an unresolved signal at lower field than 5.99 ppm.

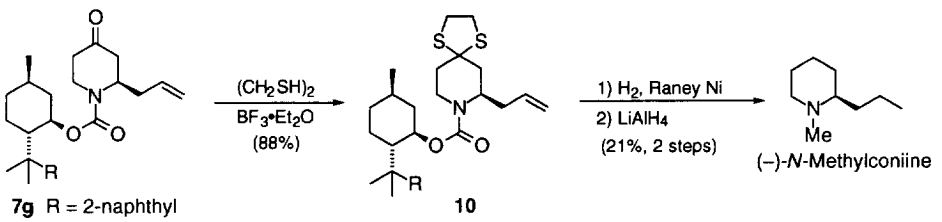
When run in the presence of $TiCl_4$, the spectra of the aromatic menthyl dihydropyridones **6b–g** show only a single set of rather sharp signals for both α-H and β-H, so indicating that coordination to the amide carbonyl group with $TiCl_4$ precludes the rotamer *s-cis*-**B** based on a steric destabilizing interaction between the coordinated amide carbonyl group and the β hydrogen of the enone, and hence the rotamer equilibrium is shifted heavily toward *s-trans*-**B** in which the back face of the enamide moiety is blocked by an aryl group.

As mentioned above, the conjugate allylation of **6f** was found to provide unexpectedly increasing selectivity (Table 1, entry 6) despite the decreasing π-stacking effect due to the presence of the arylic nitro group with a strong electron-withdrawing character. This can be rationalized by invoking the initial formation of a bidentate chelate of titanium with the enone carbonyl and nitro oxygens[8] as depicted by **C**, which leads to conformational rigidity in the reactive complex, permitting the aromatic ring to be held in the stacked position.

As evidenced by this set of results, consistent with previous observations,[9] the more upfield the shift of the olefinic protons of the enamide moiety, the higher the observed diastereoselectivity in the $TiCl_4$-mediated conjugate allylation. Moreover, $TiCl_4$ coordination to the *N*-acyl enaminones in this reaction would be responsible for the enhancement of the selectivity attributed to the reactive complex *s-trans*-**B**, in which it plays significant roles not only in fixing the *s-trans* geometry of the rotamer but also in increasing π attractive interactions between the π systems of the aromatic ring with donor ability and the enamide portion which becomes electron deficient by biscomplexation with the two carbonyl oxygens.

The developed methodology of asymmetric induction, in which 8-(2-naphthyl)menthol has been proved to be the most powerful auxiliary, was next applied to an alkaloid synthesis. Thus, the 2-allyl-4-piperidone **7g** obtained by allylation of **6g** in excellent selectivity (Table 1, entry 7) was chosen and converted to (–)-*N*-methylconiine as outlined in Scheme 2. The ^1H NMR spectrum of the synthetic material was identical with that reported,[10] and its HCl salt had physical properties [mp 187–189 °C; $[\alpha]^{26}_D$ –30.0 (*c* 0.2, MeOH)] in good agreement with those reported for the HCl salt of the unnatural (–)-enantiomer [lit.[11] mp 192–194 °C; lit.[11] $[\alpha]_D$ –27.2 (H_2O)], establishing the *R* absolute configuration at the allyl substituted center of the allyl adducts **7** and demonstrating the benefits of the π-stacking effect in this asymmetric C–C bond forming strategy.

Scheme 2



7g R = 2-naphthyl **10**

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