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Efficient access to chiral *trans*-2,6-dialkyl-1,2,5,6-tetrahydropyridines via allylation of chiral imines and ring-closing metathesis

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Dedicated to the memory of our colleague Dr. Alain Reliquet who died in September 2002

Abstract—Enantiomerically pure *trans*-2,6-dialkyl-1,2,5,6-tetrahydropyridines are synthesized in five steps from Garner's aldehyde in 37–44% overall yield. This strategy is based on the allylation of chiral iminoalcohols formed in situ followed by a ring-closing metathesis. © 2002 Elsevier Science Ltd. All rights reserved.

The piperidine ring system is a common structure unit found in natural products and synthetic compounds that exhibit a wide range of biological activity.[1] It was recently noted in the literature that during the last 10 years, over 12000 piperidine derivatives have been mentioned in clinical or preclinical studies.[2] For this reason, there has been considerable interest in the development of practical access to piperidinic compounds, particularly in their asymmetric version.[3] Nevertheless, to our knowledge the synthesis of chiral *trans*-2,6-dialkyl-1,2,5,6-tetrahydropyridines is a more difficult task and consequently have attracted much less attention[4] although this moiety also occurs in many natural products.[5] In addition, the double bond of the ring may be of great interest for an easy access of highly functionalized piperidines. In the course of our studies of the synthesis of piperidine alkaloids with biological activity,[6] we wish to report here an efficient access to *trans*-2,6-dialkyl-1,2,5,6-tetrahydropyridines. Our approach involves the allylation of chiral iminoalcohols, followed by a ring-closing metathesis (RCM) (Fig. 1).

Our methodology started from the commercially available (*S*)-Garner's aldehyde[7] (Scheme 1). A Wittig olefination of **1** without racemization, according to the procedure described by Horikawa et al.[8] led to **2** in 7/3 *E*/*Z* mixture in 82% yield and with an enantiomeric excess of 96% for (*E*)-**2**.[9] Isomers were easily separated after flash chromatography and recrystallization in petroleum ether. For a large scale preparation, **2** can easily be obtained by a straightforward protocol at high enantiomeric purity (98% ee) from the D- or L-Serine.[10] Acidic cleavage of the dimethyloxazolidine and the Boc groups afforded the key chiral (*R*)-aminoalcohol **3** in good yield (82%). The (*S*)-enantiomer could easily be obtained by starting from the (*R*)-Garner's aldehyde.

In a one-pot two-step procedure, the condensation of various aldehydes with **3** afforded the corresponding imines, which was directly reacted with an excess of allylmagnesium bromide leading, after work-up, to

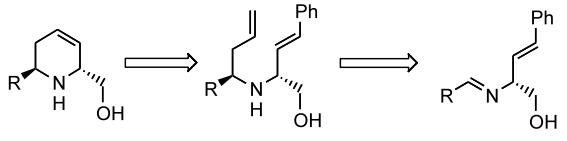
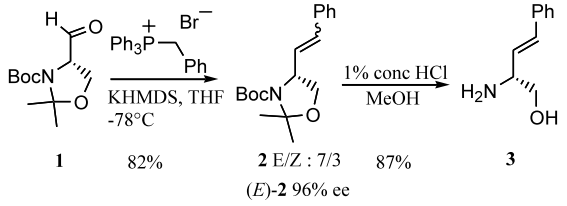


Figure 1.



Scheme 1.

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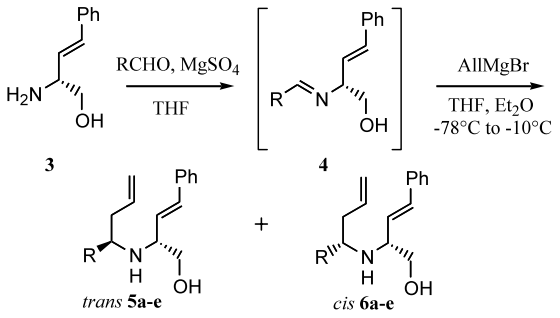


Scheme 2.

Table 1.

Entry	R	*trans*/*cis*[a]	Product	Yield (%), *trans*/*cis*[b]
1	Ph	86/14	**5a**/**6a**	73/12
2	$PhCH_2CH_2$	89/11	**5b**/**6b**	62/8
3	C_6H_{13}	90/10	**5c**/**6c**	62/8
4	Cyclohexyl	90/10	**5d**/**6d**	66/7
5	*i*Propyl	90/10	**5e**/**6e**	68/8

[a] Ratios of diastereoisomers measured by ^{1}H NMR.
[b] Yield of isolated product.

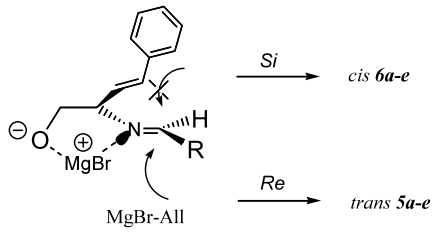
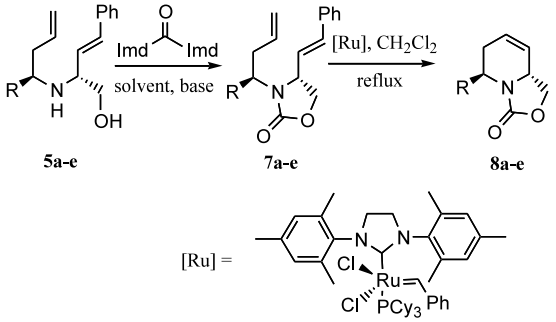


Figure 2.



Scheme 3.

diethylenic amines *trans* **5a**–**e** and *cis* **6a**–**e** with good yields and diastereoselectivities (Scheme 2 and Table 1).[11] Diastereoisomers were separated by flash chromatography.[12] It should be noted that the addition of organometallic reagents over chiral iminoalcohols derived from valinol or phenylglycinol have been widely described in the literature to provide optically active amines, after the removal of the auxiliary.[13] An obvious advantage of introducing a phenyl group in **2** is that this substituent is sufficiently bulkier to induce a good diasteroselectivity in the addition step to give *trans* **5a**–**e**. Also, the styryl substrates are good candidate for RCM.

Stereoselectivity was slightly higher with aliphatic substituents than with aromatic ones, probably due to the lower reactivity of the imine. The *trans* addition, the most common in all cases (vide supra), was in accordance with the generally accepted transition state.[14] This high stereoselectivity may be attributed by an internal chelation of the magnesium atom of the Grignard reagent with the hydroxyl group and the imino nitrogen. Thus, the Grignard reagent attacks the less hindered face of the imine, the *Re* face for the *trans* addition (Fig. 2).

It is well known that olefin metathesis is incompatible with free amine owing to catalyst inhibition by the basic nitrogen.[15] Consequently, aminoalcohols were protected as internal carbamates by treatment with carbonyldiimidazole (Scheme 3 and Table 2). The use of additional bases was necessary for the success of this reaction. Without bases, the intramolecular cyclization did not occur and only the *O*-(1-imidazolyl)-carbonyl derivatives were isolated. We found that Et_3N was sufficient in the case of compounds **5a** to **5c** but with the more hindered amines, **5d** and **5e**, a strong base like DBU was required. Having a good access to diethylenic substrates, we turned our attention to the RCM. Thus, RCM[16] using 5% mol of [Ru] proceeded in 1 h with high yields to give *trans*-2,6-dialkyl-1,2,5,6-tetrahydropyridines **8a**–**e**.

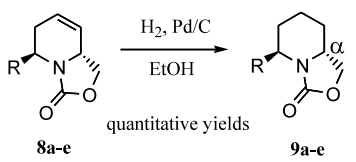
The configuration was definitively established on the hydrogenated product after treatment with H_2 and Pd/C. Displacement by chemical shift of Cα in ^{13}C NMR was characteristic of the relative configuration of the piperidines (Scheme 4). As previously reported for similar systems, the *trans* isomer showed a displacement by chemical shift in the range of 50.6–51.2 ppm, whereas the *cis* isomer appeared 7 ppm upfield.[17] Moreover, for unambiguous assignment of the *trans* configuration the compounds **8a** and **8c** were converted to known derivatives.[18] This difference of Cα chemical shift between *trans* and *cis* isomers can be attributed to the *gauche* 1,4-interaction[19] (also called the γ-effect) between R and Cα only in the *trans* isomer. Thus, it should be noted that, whatever the nature of the R substituent, the Cα chemical shift of the *trans* isomer was in the range of 50.6–51.2 ppm.

In conclusion, the present method provides a new useful way for the stereoselective preparation of *trans*-2,6-dialkyl-1,2,5,6-tetrahydropyridines. The versatility of the strategy was demonstrated by the ease with which the chiral aminoalcohol **3** was obtained in its *R* or *S* form. Furthermore, applications of the approach to the synthesis of alkaloids is in progress and will be reported in due course.

Table 2.

Entry	Substrate	Base/solvent/yield (%)[a]	Product	RCM yield (%)[a]	Product
1	**5a**	Et_3N/CH_2Cl_2/89	**7a**	88	**8a**
2	**5b**	Et_3N/CH_2Cl_2/97	**7b**	92	**8b**
3	**5c**	Et_3N/CH_2Cl_2/81	**7c**	89	**8c**
4	**5d**	DBU/THF/80	**7d**	99	**8d**
5	**5e**	DBU/CH_2Cl_2/93	**7e**	98	**8e**

[a] Yield of isolated product.



Product	$^{13}C\alpha$ (ppm)
9a	51.2
9b	50.6
9c	50.7
9d	51.0
9e	50.8

Scheme 4.

Acknowledgements

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12. Preparation of **5a** (typical procedure for all diethylenic aminoalcohols): To the aminoalcohol **3** (300 mg, 1.84 mmol) in THF (5 mL) was added benzaldehyde (195 mg, 1.84 mmol) and $MgSO_4$. The mixture was stirred overnight and then filtered. The clear solution was slowly added over 20 min to a solution of AllMgBr (5.52 mL, 1 M in Et_2O) in THF (4 mL) cooled to −78°C. The resulting mixture was stirred 1 h at −78°C and then slowly allowed to warm up to −10°C over 4 h. The reaction was quenched with NH_4Cl and extracted with Et_2O (4×). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography (30% EtOAc–petroleum ether) to furnish two diastereoisomers **5a** (394 mg, 73%) and **6a** (65 mg, 12%) as a colorless solid. *trans*-**5a**: mp 62–63°C. $[\alpha]_D^{20}=-90.8$ (*c* 1.166, $CHCl_3$). IR (KBr) *v* 1639, 2925, 3061, 3323. ^1H NMR δ (ppm) 2.14 (s, 2H), 2.45–2.53 (m, 2H), 3.39–3.49 (m, 2H), 3.65–3.75 (m, 1H), 3.82 (t, 1H, $J=6.7$ Hz), 5.02–5.12 (m, 2H), 5.60–5.81 (m, 1H), 5.99 (dd, 1H, $J=7.3$ Hz, $J=16$ Hz), 6.45 (d, 1H, $J=16$ Hz), 7.24–7.33 (m, 10H); ^{13}C NMR δ (ppm) 42.1, 59.9, 60.0, 64.2, 117.7, 126.5, 127.3, 127.8, 128.6, 129.5, 132.1, 135.1, 136.8, 144.0. Anal. calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.80; H, 7.95; N, 4.75. *cis*-**6a**: mp 102–103°C. $[\alpha]_D^{20}=-228.2$ (*c* 0.953, $CHCl_3$). IR (KBr) *v* 1642, 2911, 3031, 3198. ^1H NMR δ (ppm) 2.30 (sl, 2H), 2.36–2.53 (m, 2H), 3.11–3.21 (m, 1H), 3.38–3.62 (m, 2H), 3.87 (dd, 1H, $J=5.8$ Hz, $J=7.9$ Hz), 5.10–5.20 (m, 2H), 5.64–5.85 (m, 1H), 5.96 (dd, 1H, $J=8.4$ Hz, $J=16$ Hz), 6.40 (d, 1H, $J=16$ Hz), 7.27–7.44 (m, 10H); ^{13}C NMR δ (ppm) 43.5, 58.8, 59.2, 65.4, 118.1, 126.5, 127.4, 127.5, 127.9, 128.6, 128.7, 128.7, 133.1, 135.4, 136.7, 143.6. HRMS (EI) calcd for $C_{19}H_{20}N$ ($M-CH_2OH^+$) 262.1596, found 262.1593.
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