Catalytic asymmetric synthesis of the alkaloid (+)-myrtine†

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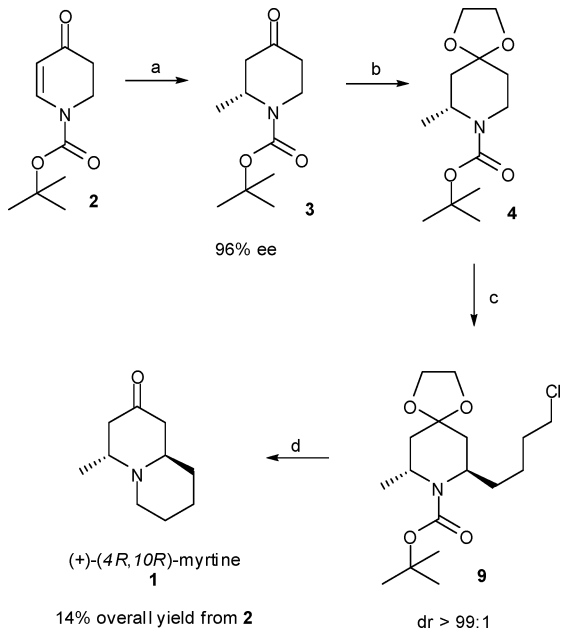
A new protocol for the asymmetric synthesis of *trans*-2,6-disubstituted-4-piperidones has been developed using a catalytic enantioselective conjugate addition reaction in combination with a diastereoselective lithiation–substitution sequence; an efficient synthesis of (+)-myrtine has been achieved *via* this route.

The piperidine ring motif appears ubiquitous in the structure of many alkaloid natural products and drugs. The synthetic importance of substituted piperidines has led to a wide area of research devoted to the preparation of these systems.[1] Simple 2,6-disubstituted piperidine alkaloids have been reported to possess a broad range of biological activities including insecticidal, anti-HIV, antibacterial and antifungal properties.[2] Furthermore, 2,6-disubstituted piperidines can be used as intermediates in the synthesis of more complex indolizidine and quinolizidine ring systems. Recently, we reported the first highly efficient catalytic enantioselective addition of organozinc reagents to *N*-protected-2,3-dehydro-4-piperidones.[3] This method allows for the synthesis of optically active *N*-protected-2-alkyl-4-piperidones, which represent versatile building blocks in the synthesis of piperidine based alkaloids.[4] We described that the addition of Me_2Zn to *N*-protected-2,3-dehydro-4-piperidones allowed the introduction of a methyl substituent with 96% ee.[3] However, the low isolated yield (44%) and the presence of by-products, which made the purification step difficult, prompted us to develop a more efficient route. Here we describe the use of Me_3Al as a useful alternative to Me_2Zn in the enantioselective conjugate addition reaction for the introduction of a methyl group in high yield and with high enantioselectivity.[5] The use of a lithiation–substitution sequence for the further functionalization of the optically active 2-methyl-4-piperidones gives access to *trans*-2,6-disubstituted-piperidones selectively.

The potential of this approach is shown in the total synthesis of the natural occurring alkaloid (+)-myrtine **1**, a quinolizidine alkaloid isolated from *Vaccinium myrtillus* (Ericaceae) whose structure and absolute configuration were determined in 1978 (Scheme 1).[6] Although a number of syntheses of myrtine in racemic form have appeared in the literature,[7] only two syntheses of (+)-myrtine[8,9] and one synthesis of the unnatural isomer (−)-myrtine have been described.[10] The existing procedures, however, are based on the use of chiral auxiliaries[8,10] or the use of optically active precursors obtained *via* enzymatic resolution.[9] In this report, the first catalytic enantioselective synthesis of (+)-myrtine in four steps starting from Boc-protected 2,3-dehydro-4-piperidone **2** is described (Scheme 1).



Scheme 1 (a) Me_3Al (2.0 eq.), $Cu(OTf)_2$ (5 mol%), (*S*,*R*)-**L1** (10 mol%), Et_2O (10 mol%), toluene, −50 °C, 16 h, 73%, (b) PTSA (0.5 eq.), ethylene glycol (6 eq.), MS 3Å, toluene, reflux, 16 h, 60%, (c) *s*-BuLi (2.4 eq), TMEDA (2.4 eq), Et_2O, −78 °C, 3 h then CuCN·2LiCl (2.4 eq), THF, −78 °C/−50 °C, 1 h then $I(CH_2)_4Cl$ (2.4 eq), −78 °C/rt, 16 h, 62%, (d) conc. HCl, acetone, H_2O, reflux, 16 h then $NaHCO_3$, 0 °C, 16 h, 50%.

A catalyst formed from $Cu(OTf)_2$ and chiral phosphoramidite ligand (*S*,*R*)-**L1** (Fig. 1) was used in the addition of Me_3Al to *N*-Boc-2,3-dehydro-4-piperidone **2**,[11] carried out in toluene, at −50 °C. The reaction afforded the methylated product **3** in 73% isolated yield and with an excellent 96% ee. Remarkably, the addition of a small amount of an appropriate co-solvent turned out to be crucial for the reproducibility of the results. Careful optimization showed that adding 1 eq. of dry Et_2O, with respect

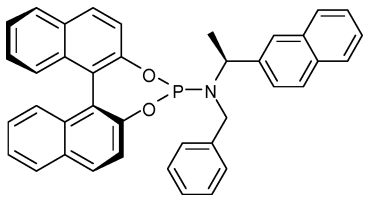


Fig. 1 (*S*,*R*)-**L1**.

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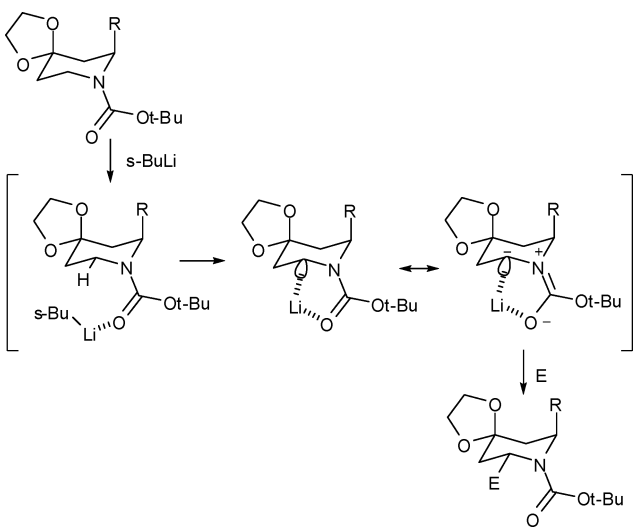
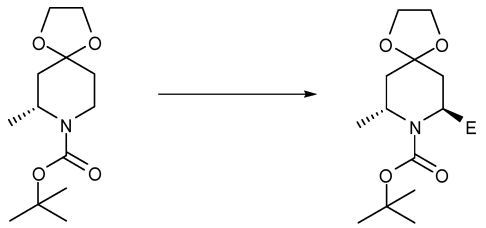
to the ligand, to the reaction mixture guaranteed high conversion and a reproducible high ee. A possible explanation can be found in the formation of a heterogeneous system upon addition of the Me_3Al to the reaction mixture in which the copper complex and the starting material are present already. The formation of insoluble aggregates might inhibit the reaction and makes mixing inefficient. The presence of a coordinating species, such as Et_2O, breaks up, at least partially, the existing aggregates facilitating the reaction. Furthermore, the coordinating properties of the co-solvent might affect the aggregation level of the Me_3Al. In hydrocarbon solvents, such as toluene, coordination of the solvent to Me_3Al is weak and therefore self-association of Me_3Al to a dimeric species occurs.[12] It is possible that when Me_3Al is present in dimeric form, methyl transfer is hampered due to the stability of the dimer. Furthermore, in the addition reaction the aluminium reagent can act as a Lewis acid, activating the enone moiety toward the nucleophilic addition. In the bridged structure the aluminium atom is unavailable for such interaction with the substrate. Interestingly, when the reaction was carried out in Et_2O using (*S*,*R*)-**L1** as chiral ligand, the addition product was obtained in racemic form.

The copper-catalysed addition of Me_3Al to **2** in the presence of the chiral phosphoramidite ligand (*S*,*R*)-**L1** affords compound **3** in good yield and with 96% ee. In this product, the α-methyl substituent will preferentially adopt an axial position in the pseudo chair-like conformation of the piperidone ring, to release the $A^{1,3}$ strain with the nitrogen protecting group.[13] This conformational bias leads, selectively, to the formation of *trans*-2,6-disubstituted-piperidones. When compound **3**, after protection of the carbonyl moiety, is subjected to a lithiation–substitution sequence, an electrophile is introduced equatorial at the less substituted α-position.[14] In this reaction, association of the organolithium reagent with the carbamate group[15] in a preequilibrium complex brings the reactive groups in proximity for directed deprotonation (complex induced proximity effect).[16] Abstraction of the equatorial proton results in a dipole-stabilized carbanion,[17] which reacts with the electrophilic species with retention of configuration.[14a,18] According to these stereochemical requirements, the final product **9** will have *trans* geometry (Scheme 2).



Scheme 2 Lithiation–substitution sequence.

Table 1 Lithiation–substitution of piperidone **4**



4 **5-9**

Entry	Electrophile	Method[a]	Product	Yield (%)	Dr (%)
1	MeI	A	**5**	71	95 : 5
2	TMSCl	A	**6**	74	96 : 4
3	DMF	A	**7**	56	55 : 45
4	CH_2CHCH_2Br	B	**8**	64	>99 : 1
5	$I(CH_2)_4Cl$	B	**9**	62	>99 : 1

[a] Method A: *s*-BuLi (1.2 eq), TMEDA (1.2 eq), Et_2O, −78 °C, 3 h then electrophile (1.2 eq) −78 °C/rt, 16 h. Method B: *s*-BuLi (2.4 eq), TMEDA (2.4 eq), Et_2O, −78 °C, 3 h then CuCN·LiCl (2.4 eq), THF, −78 °C/−50 °C, 1 h then electrophile (2.4 eq) −78 °C/rt, 16 h.

The carbonyl moiety of **3** was protected *via* ketal formation using ethylene glycol. Remarkably, the reaction proceeded slowly to give, after 24 h reaction, the protected product in 60% isolated yield together with the remaining starting material.

According to literature procedures,[14] formation of a stabilized carbanion was accomplished reacting *s*-BuLi with **4** in the presence of TMEDA, at −78 °C. After 3 h the electrophile was added and the temperature allowed to increase to rt slowly. The reactions with MeI and TMSCl as electrophiles gave compounds **5** and **6** in good yield and high diastereomeric ratios (Table 1; entries 1 and 2). The addition of DMF afforded a mixture of the *cis* and *trans* isomers of **7** in a ratio close to 1 : 1 (entry 3). We attribute this lack of diastereoselectivity to epimerization of the aldehyde under the basic conditions. An experimental proof that the lithiation of **4** followed by reaction with the electrophile gives preferably the *trans* diastereomer of the disubstituted product is found by analysis of the stereochemistry of the dimethylated compound **5**. A *cis* relationship of the two α-methyl substituents in **5** would result in an achiral *meso* compound. The presence of optical activity detected for **5** excludes the possibility that the product obtained is an achiral compound, therefore indicating a *trans* relationship of the methyl groups. The use of allyl bromide or 1-chloro-4-iodobutane as electrophile initially did not lead to the desired products. Formation of **8** and **9** was therefore accomplished following the lithiation–transmetallation procedure developed by Dieter *et al.*[19,20] Addition of a THF solution of CuCN·2LiCl to the lithiated species forms a *N*-Boc-piperidyl-cuprate by lithium–copper exchange.[19] Subsequent addition of the electrophile provided the products **8** and **9** in 64% and 62% yield, respectively, with complete diastereoselectivity (entries 4 and 5).

Compound **9** is an immediate precursor of **1**. A one-pot reaction for the deprotection of the ketal and carbamate moieties of **9** followed by *in situ* cyclization led to myrtine in 50% yield (Scheme 1). Comparison of the NMR data recorded for **1** with the spectroscopic data reported in literature[6,7] confirmed that the diastereoisomer obtained has a *trans* configuration, corresponding to the structure of the alkaloid myrtine. Moreover, comparison of

the measured optical rotation, $[\alpha]_D$ +10.2 (*c* 1.8 in $CHCl_3$), with the literature values, lit. $[\alpha]_D^{28}$ +11.3 (*c* 2.7 in $CHCl_3$),[7a] indicates that the isomer obtained corresponds to the natural occurring enantiomer (+)-myrtine in which the absolute configuration of the two stereogenic centers has been established to be (4*R*,10*R*).[6] This finding imposes the *R* configuration to the product **3** of the Me_3Al conjugate addition to **2**, using the chiral phosphoramidite (*S*,*R*)-**L1**.

In conclusion, a new protocol for the synthesis of *trans*-2,6-disubstituted-4-piperidones has been developed.

The copper–phosphoramidite catalyzed asymmetric conjugate addition of organometallic reagents to dehydropiperidones is the key step in which the chirality is introduced in the system. The defined stereochemical outcome of the lithiation–substitution reaction allows one of the diastereoisomers to be obtained selectively during the formation of the second stereogenic center. To demonstrate the versatility of this enantioselective C–C bond formation, this approach was applied in the synthesis of the natural alkaloid (+)-myrtine **1** which was obtained in four steps and 14% overall yield from **2**. This represent the first synthesis of myrtine based on a catalytic enantioselective procedure.

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