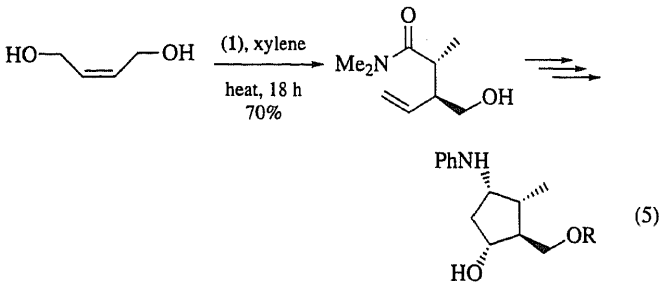
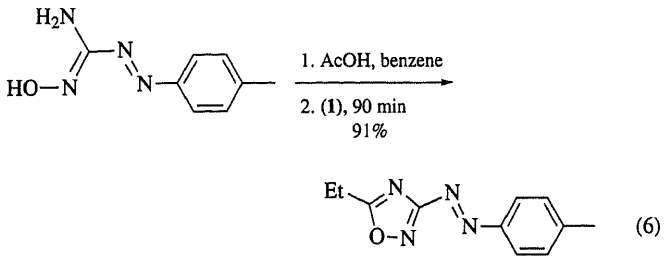
The propionamide acetal rearrangement was used to establish the *threo* stereochemistry in intermediates for prostaglandin H analog synthesis (eq 5).[7]



(5)

Other Applications. The reaction of the reagent with an amide oxime gives 5-ethyl-1,2,4-oxadiazoles (eq 6).[8]



(6)

Related Reagents. 1,1-Dimethoxypropene, *N,N*-Dimethylacetamide Dimethyl Acetal; *N,N*-Dimethylformamide Diethyl Acetal; Dimethyl Sulfate; Methylketene Dimethyl Acetal; Triethyl Orthoacetate.

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2. For recent reviews on Claisen rearrangements, see: (a) Wipf, P. *COS* **1991**, *5*, Chapter 7.2. (b) Kallmarten, J.; Wittman, M. D. *Stud. Nat. Prod. Chem.* **1989**, *3*, 233. (c) Blechert, S. *S* **1989**, 71. (d) Ziegler, F. E. *CRV* **1988**, *88*, 1423. (e) Moody, C. J. *Adv. Heterocycl. Chem.* **1987**, *42*, 203.
3. (a) Bredereck, H.; Effenberger, F.; Beyerlin, H. P. *CB* **1964**, *97*, 3081. (b) Meerwein, H.; Florian, W.; Schon, N; Stopp, G. *LA* **1961**, *641*, 1.
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5. Kumin, A; Maverick, E; Seiler, P; Vanier, N; Damm, L; Hobi, R.; Dunitz, J. D.; Eschenmoser, A. *HCA* **1980**, *63*, 1158.
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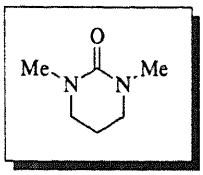
N,N'-Dimethylpropyleneurea[1,2]



[7226-23-5] $C_6H_{12}N_2O$ (MW 128.18)

(dipolar aprotic solvent and cosolvent with properties very similar to those of HMPA; usually a somewhat larger amount is required in order to observe the same cosolvent effect as with HMPA; unlike HMPA, it was found to be nonmutagenic in a comparative investigation[1])

Alternate Names: DMPU; 1,3-dimethyltetrahydro-2(1*H*)-pyrimidone.

Physical Data: bp 110 °C/10 mmHg; mp ca. –20 °C; *d* 1.064 g cm^{-3}; $\varepsilon_r = 36$.

Solubility: miscible with most organic solvents, and with water; a ca. 25% solution in THF can be cooled to dry-ice temperature without crystallization or phase separation.[3]

Form Supplied in: colorless, hygroscopic liquid; commercially available.

Purification: predry over KOH (only necessary with rather wet material), and distill from CaH_2 in vacuo.

Handling, Storage, and Precautions: store at rt in a bottle with a three-way stop cock and a serum cap, over freshly activated molecular sieve (4 Å) and under an inert atmosphere; if stored as indicated, DMPU is stable and ready for use for many months; samples should be withdrawn by syringe technique.

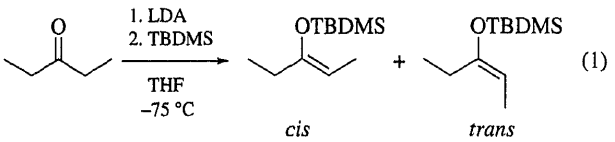
Like HMPA,[4] the cyclic urea DMPU is the prototype of a dipolar aprotic solvent (cf. DMSO, DMF, NMP). As a solvent and cosolvent, DMPU causes increased basicity and nucleophilicity of reagents. It was found to be especially useful for reactions of polyanionic species. Surprisingly, it may have a stabilizing effect on anionic systems that have a tendency to undergo fragmentation. A crystal structure of a Li enolate solvated by DMPU has been described.[5] The lower homolog ***1,3-Dimethyl-2-imidazolidinone*** (DMI) has also been recommended, but it is less useful for low-temperature work due to its greater tendency to crystallize.[6] Although DMPU is a carbonyl compound, it may be used as a cosolvent under the most vigorous metallating conditions (BuLi), at least at low temperatures. The similarity of effects observed with DMPU and the mutagenic HMPA is striking in many cases. (The effects of HMPA on the structure of Li compounds and Li enolates have been thoroughly investigated.[7]) For a detailed discussion of the many uses of HMPA in organic

synthesis see ***Hexamethylphosphoric Triamide***. For safety reasons it is recommended that DMPU is tested as a substitute for HMPA in each case, even in research laboratories; large-scale industrial applications of HMPA have been banned.

The reactions discussed in the following paragraphs are taken from work in which HMPA and DMPU have been compared. In an increasing number of publications on DMPU applications, no comparison is mentioned; some of these are included in the list of references.

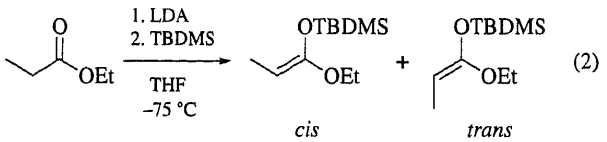
Chiral DMPU derivatives have been synthesized; the best induction with one of them gave an aldol of 15% ee.[8]

Generation and Stereoselective Reactions of Lithium Enolates. Bulky Li amide bases deprotonate ketones and esters to *trans* Li enolates (the trivial *cis/trans* nomenclature is used in order to avoid unnecessarily cumbersome language). This has been proved by the X-ray crystal structure analysis of several ester Li enolate derivatives[9] and by numerous NMR investigations of the silyl enol ethers, the trapping products of Li enolates with chlorosilanes. In connection with studies on the Ireland–Claisen rearrangement it was discovered[10] that the *cis* Li enolates are formed when the reaction is carried out in the presence of HMPA, under otherwise identical conditions. As can be seen from eq 1[3] and eq 2,[11] this cosolvent effect can be fully reproduced with DMPU; a review about the careful optimization of this enolate formation includes all details.[11] The diastereoselectivity of most enolate reactions is determined by the geometry of the enolate double bond, and therefore the DMPU effect outlined in eqs 1 and 2 is most important in organic synthesis.[12]



(1)

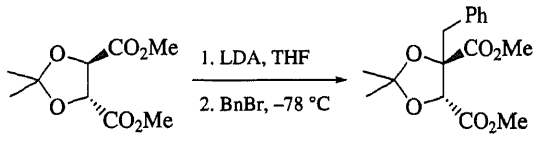
Cosolvent	
–	30:70
HMPA	95: 5
DMPU	94: 6



(2)

Cosolvent	
–	6:94
HMPA (23%)	85:15
DMPU (30%)	98: 2

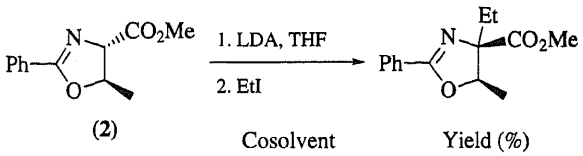
Another useful application of the dipolar cosolvent is shown in eq 3[3] and eq 4.[13] The Li enolates from dimethyl tartrate acetonide (**1**) and from the threonine-derived oxazoline (**2**) have a tendency to undergo destructive β-elimination which can be suppressed to some extent by the presence of DMPU, allowing these enolates to be alkylated in reasonable to excellent yields. It is remarkable that a cosolvent which most chemists would expect to remove cations from their counterions (i.e. to generate 'naked' anions) stabilizes species in which a migration of negative charge (i.e. elimination/fragmentation) leads to decomposition (cf. the use of the novel phosphazene bases (see ***Phosphazene Base P_4-t-Bu***)[14,15] for the same purpose[14a]); notice that the alkylation of the tartrate derivative (**1**) occurs from the face *cis* to the CO_2Me group.[13]



(3)

(**1**)

Cosolvent	Yield (%)
–	<5
HMPA (17%)	54
DMPU (33%)	52

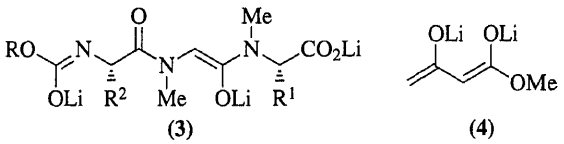


(4)

(**2**)

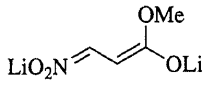
Cosolvent	Yield (%)
–	66
HMPA (17%)	94
DMPU (25%)	91

Generation and Reactions of Polylithiated Derivatives. The reactivity of strong bases as necessary for double and polylithiations is often enhanced in the presence of DMPU, and at the same time the resulting species become more reactive. Some examples of such species are the peptide Li_3 enolate (**3**),[16] ***Methyl Dilithioacetoacetate*** (**4**),[17] the Li_2 nitronate-enolate (**5**)[3] (see ***Methyl 3-Nitropropanoate***), the lithio lithium nitronate (**6**)[3,18] (see ***O,O-Dilithio-1-nitropropene***), and the doubly lithiated iminonitrocyclohexane (**7**)[19] and ergolinylurea (**8**).[20] (We are aware of only one case in which HMPA could not be replaced at all by DMPU: the double lithiation of 1,1,1-trifluoro-2-nitropropane.[18])

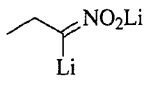


(**3**)

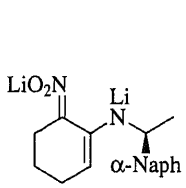
(**4**)



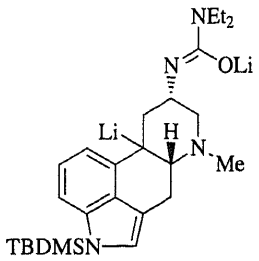
(**5**)



(**6**)



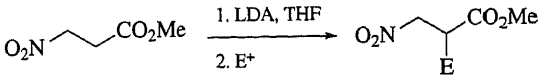
(**7**)



(**8**)

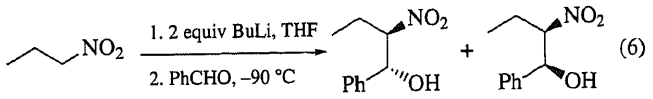
For four of these intermediates the corresponding DMPU effects are specified in eqs 5–8. Thus the nitropropionate is not doubly lithiated at all in the absence of cosolvent, and HMPA and DMPU have the same effect on the yields of products (**9**) formed with various electrophiles (eq 5).[3] The addition of dou-

bly lithiated nitropropane to benzaldehyde is not diastereoselective in THF alone, and gives the nitroaldol of (*l*) configuration preferentially in the presence of DMPU (eq 6);[3] this means that the intermediate nitronate-alkoxide is protonated diastereoselectively upon quenching the reaction mixture in the presence of cosolvent.[21] (see ***Trimethylsilyl Methanenitronate***). The chiral imine of 2-nitrocyclohexanone shown in eq 7 is doubly lithiated to a solution containing (**7**) and ***Lithium Diisopropylamide*** (since ***Diisopropylamine*** forms complexes with lithiated species, which are responsible for poor yields, the amine is converted to LDA for better results),[22] and allylation gives best yields of product (**10**) and highest diastereoselectivity in the presence of DMPU.[19] Finally, the conversion delineated in eq 8 shows a reversal of the stereochemical course of a benzylic lithiation/methylation in THF as compared to THF/DMPU (see epimers (**11a**) and (**11b**) in eq 8).[20] This case also exemplifies the compatibility of DMPU with a large excess of ***t-Butyllithium*** at –75 °C.

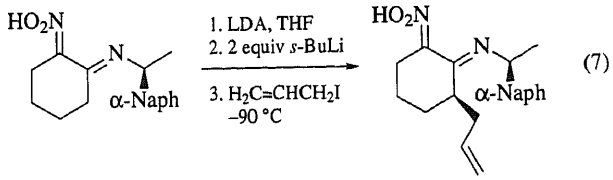


(**9**)

Cosolvent	Yield (%)
–	<5
HMPA	50–85
DMPU	50–85



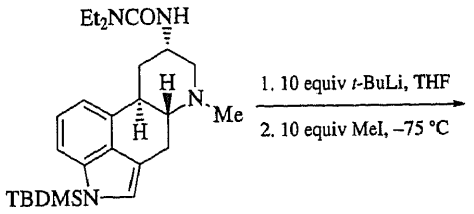
Cosolvent	(*l*):(*u*)
–	1:1
HMPA (20%)	9:1
DMPU (25%)	9:1

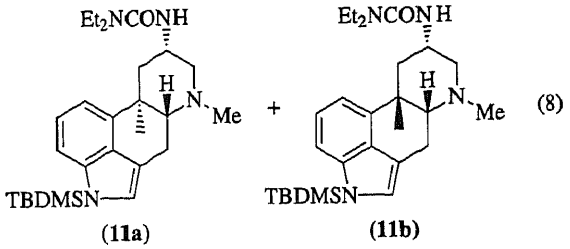


(**10**)

Cosolvent	dr	Yield (%)
–	4:1	34
HMPA	6.5:1	73
DMPU	9:1	74

Nucleophilicity Enhancement in the Presence of DMPU. Very often, nucleophilic substitutions of the S_N2 type are greatly accelerated by HMPA.[4] Again this effect is fully reproduced by DMPU. Thus sluggish alkylations of Li dithianes can be accelerated as shown in eq 9 for a reaction which is part of a ca. 50-step total syntheses[23] of myxovirescine A_1 and M_2.[24] Epoxide ring opening by acetylides is a classical case of a reaction which requires a boost, and this may be supplied by DMPU, being not quite as effective as HMPA (eq 10);[3] alkylations of acetylides by alkyl bromides and iodides have also been shown to give better yields in the presence of DMPU.[25,26] An interesting solvent effect is shown in eq 11: the ***Tetra-n-butylammonium Fluoride***-

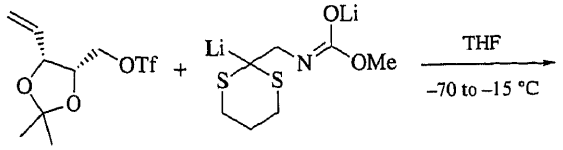




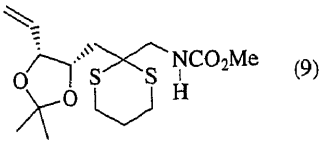
(**11a**) (**11b**)

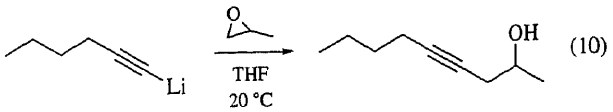
Cosolvent	Yield (%) (**11a**)	(**11b**)
–	6	73
DMPU	82	10

mediated addition of a silane to an aldehyde at room temperature occurs only at a reasonable rate in a dipolar aprotic solvent, and HMPA or DMPU win![27]

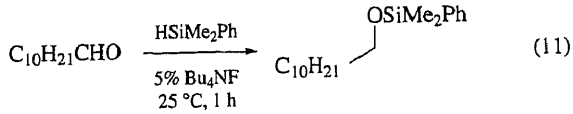


Cosolvent	Yield (%)
–	25
HMPA (1 equiv)	55
DMPU (2 equiv)	73





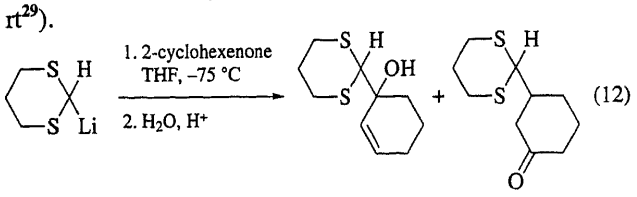
Cosolvent	Yield (%)
–	<5
HMPA (17%)	70
DMPU (50%)	59



Solvent	CH_2Cl_2	THF	DMF	HMPA	DMPU
Yield (%)	1	9	56	91	89

A different type of effect on the nucleophilicity of a reagent is exhibited in the addition of ***2-Lithio-1,3-dithiane*** to cyclohexenone. Under standard conditions (THF, dry-ice temperature), 1,2-addition occurs almost exclusively;[28] in the presence of HMPA[29] or DMPU,[3] 1,4-addition takes place (eq 12). Again, this is a remarkable effect, because hard nucleophilic centers should prefer attack at the harder center of the enone, which is the carbonyl carbon ('charge control'), and soft centers should combine with the softer β-carbon (in fact, lithiated thioacetals bearing Si or Sn on the carbanionoid center add to enones in a 1,4-fashion[30]); thus the polar cosolvent renders the lithio

dithiane C(2) carbon softer! (It was shown that the Li alkoxide of (**12**) does not rearrange to the Li enolate of (**13**) even after 24 h at rt[29]).

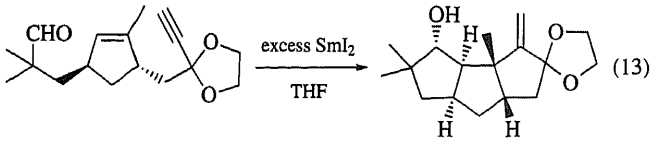


(12)

(**12**) (**13**)

Cosolvent	
–	98: 2
HMPA (2 equiv)	5:95
DMPU (4 equiv)	8:92

Transition Metal and Lanthanide Chemistry. In an increasing number of publications, DMPU is described as a solvent or cosolvent in redox and radical reactions. Two examples are presented here. The spectacular, highly diastereoselective radical cyclization of the cyclopentene (**14**) to the tricyclic compound (**15**) in eq 13 is very slow in THF even at reflux temperature, while the addition of a tiny amount of DMPU accelerates it to such an extent that a respectable yield of 60% of the desired product is obtained at 0 °C (the authors call it a titration).[31] Other ***Samarium(II) Iodide*** reductive coupling reactions (for instance, of α,β-unsaturated esters to 3,4-disubstituted adipic esters)[32] and reductions (of ketones to alcohols and of enones to ketones)[33] are also improved in the presence of DMPU cosolvent.

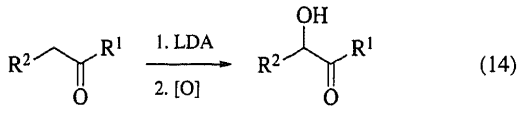


(13)

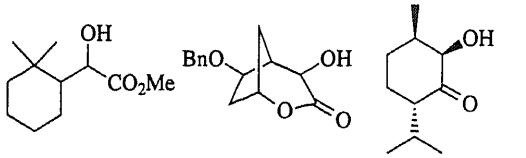
(**14**) (**15**)

Cosolvent	°C	Yield (%)
–	64	<11
HMPA (5%)	0	67 (as free ketone)
DMPU (5%)	0	69 (as free ketone)

Finally, a complex of MoO_5 with pyridine and DMPU can be used instead of the corresponding HMPA complex ***Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)*** for hydroxylations of Li enolates (eq 14).[34] Even the crystal structures of the two complexes are similar.[35] In this case, switching from HMPA to DMPU does not remove all hazards: MoO_5·py·DMPU has been reported to be explosive, so must be handled behind appropriate safety equipment.[36]



(14)



MoO_5•py•HMPA	63%	72%	74%
MoO_5•py•DMPU	72%	72%	43%

Related Reagents. Dimethyl Sulfoxide; Hexamethylphosphoric Triamide; 1-Methyl-2-pyrrolidinone; *N,N,N',N'',N''*-Pentamethyldiethylenetriamine; *N,N,N',N'*-Tetramethylethylenediamine.

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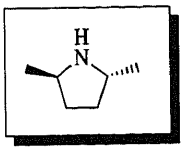
trans-2,5-Dimethylpyrrolidine



(racemate)
[62617-69-0; 39713-72-9] $C_6H_{13}N$ (MW 99.18)
(2*S*,5*S*)
[117968-50-0]
(2*R*,5*R*)
[62617-70-3]
(·HCl, racemate) $C_6H_{14}ClN$ (MW 135.64)
[114143-75-8; 4832-49-9]
(·HCl, 2*S*,5*S*)
[138133-34-3]
(·HCl, 2*R*,5*R*)
[70144-18-2]

(C_2 symmetric chiral pyrrolidine,[1] useful in optically active form as a chiral auxiliary in a variety of asymmetric reactions)

Physical Data: free amine: bp 102–103 °C; (2*S*,5*S*) $[\alpha]_D^{25}$ +10.6° (*c* 1.0, EtOH);[2] (2*R*,5*R*) $[\alpha]_D^{25}$ −11.5° (*c* 1.0, EtOH).[2] Hydrochloride: racemate mp 187–189 °C;[3] (2*S*,5*S*) mp 200–201 °C,[4] $[\alpha]_D^{25}$ −5.63° (*c* 0.67, CH_2Cl_2);[4] (2*R*,5*R*) mp 200–203 °C,[5] $[\alpha]_D^{25}$ +5.57° (*c* 1.18, CH_2Cl_2).[5]

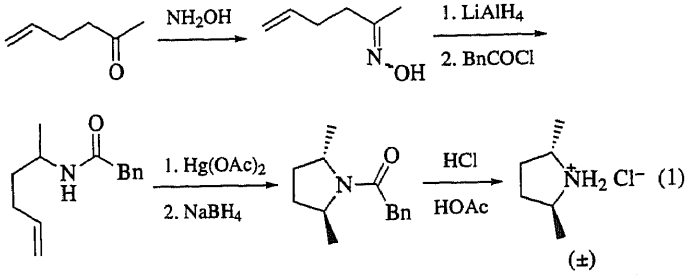
Form Supplied in: colorless oil; commercially available as a mixture of (±)-*trans* and *cis* isomers (the mixture is not easily separated).[6]

Purification: the free amine can be purified by fractional distillation; the hydrochloride salt can be recrystallized from absolute ethanol and diethyl ether.

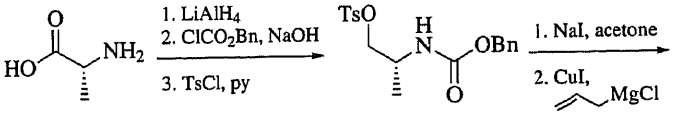
Handling, Storage, and Precautions: irritant; flammable. Use in a fume hood.

Synthesis. Several routes are available for the synthesis of *trans*-2,5-dimethylpyrrolidine.[2-9,22] Discussed below are preparative scale procedures for the synthesis of the pure *trans* compound in racemic and enantiomerically pure form.

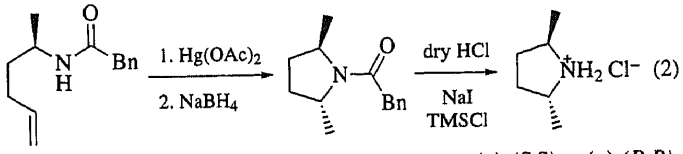
The racemic hydrochloride salt can be prepared in four steps and 70% overall yield (eq 1).[3] The synthesis is carried out on 2 mmol scale and starts with commercially available 5-hexen-2-one. The key step involves a mercury-catalyzed intramolecular amidomercuration to form the pyrrolidine ring. If desired, the racemate can be resolved via the salts of ***Mandelic Acid***.[2]



Alternatively, an efficient synthesis of either antipode starting from D- or L-alanine has been reported (eq 2).[9] The asymmetric synthesis conducted on 10 mmol scale involves a six-step sequence which incorporates the amidomercuration method.[3] The enantiomerically pure product is isolated as its hydrochloride salt in 44% overall yield. Furthermore, an optimization of the capricious cuprate reaction which improves both the yield and reproducibility has been described.[4]



D- or L-alanine



(−)-(*S*,*S*) or (+)-(*R*,*R*)
44% overall

More recently, a four-step synthetic sequence which provides expedient access to the (−)-(*R*,*R*)-enantiomer in 42% overall yield has been reported.[5] This route is convenient for large-scale preparation (0.2 mol scale), and is highlighted by an asymmetric ***Baker's Yeast*** reduction of 2,5-hexanedione. Subsequent mesylation, *N*,*N*-dialkylation, and deprotection provides the enantiomerically pure free pyrrolidine (eq 3). Alternatively, either enantiomer of the chiral pyrrolidine can be obtained in 15% overall yield from an isomeric mixture of 2,5-hexanediol, via a similar sequence in which (*S*)-α-methylbenzylamine is used as a chiral auxiliary.[22] Also, an enantioselective route to either (2*S*,5*S*)- or (2*R*,5*R*)-hexanediol has been reported.[23]

Asymmetric Alkylations and Michael Additions. Asymmetric alkylation of the cyclohexanone enamine derived from (+)-*trans*-2,5-dimethylpyrrolidine has been studied (eq 4).[2] Alkylation with ***Iodomethane***, *n*-propyl bromide, and ***Allyl Bromide*** afforded the corresponding 2-*n*-alkylcyclohexanones in yields of 50–80% and with enantiomeric purities of 66, 86, and 64%, respectively.