Chiral Aminal Templates: Diastereoselective Addition to Hydrazones; An Asymmetric Synthesis of α-Amino Aldehydes

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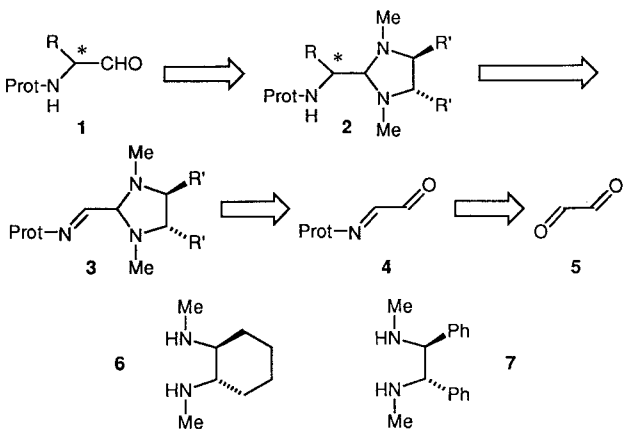
The monohydrazone of glyoxal may be derivatized into a chiral aminal with diamine **7**. The resulting chiral reagent **13** reacts with complete diastereocontrol with organolithium reagents in THF. This sterically controlled reaction may be altered to chelation control by using Grignard reagents in toluene, affording the opposite diastereomer in excellent de. The N–N bond of the hydrazine functionality is then cleaved with Raney nickel, assisted by ultrasound. After protection of the resulting primary amino functionality, the aminal is hydrolyzed to afford the desired α-amino aldehydes without epimerization. The same reaction sequence, without cleavage of the N–N bond, affords an α-hydrazino aldehyde.

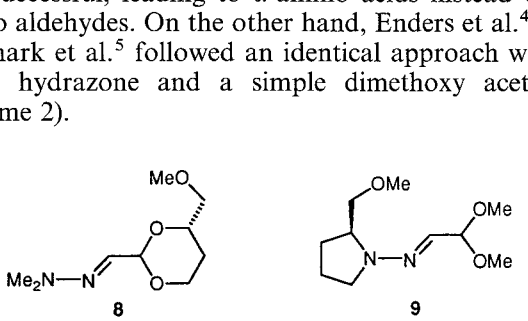
α-Amino aldehydes are particularly useful chiral synthetic intermediates and they have been the starting point of numerous total syntheses of biologically active natural products.[1,2] Indeed, the intermediate oxidation state of the aldehyde functionality makes them useful precursors to both α-amino acids and α-amino alcohols. Their preparation usually starts from an α-amino acid, through a partial reduction step, or through a total reduction and partial reoxidation step, and therefore their availability relies on the availability of the α-amino acid. Although many synthetic methods are known for chiral α-amino acids,[3] there are very few examples for α-amino aldehydes.[1,4–6] Moreover, some methods, in which a protected aldehyde functionality exists, are directed towards acids through an oxidative deprotection step, owing to the difficulties in deprotecting the aldehyde without α-epimerization.[7,8] These problems point to the crucial importance of the protecting group of the aldehyde functionality. A synthetic method which would allow direct access to chiral α-amino aldehydes, bypassing the need for an α-amino acid, would be welcome.



Scheme 1

Recently, our group has been involved in the use of *C2* symmetrical diamines as chiral auxiliaries.[9–11] These diamines form aminals (*N,N*-acetals) very easily, which can be hydrolyzed back to the aldehyde under very mild conditions, avoiding α-epimerization.[12] Thus, the chiral aminal group would serve a double purpose: (a), as a protecting group for the aldehyde functionality; and (b), as an efficient stereodirecting group. Therefore, our retrosynthetic route (see Scheme 1) to protected α-amino aldehydes **1** involves an α-amino aminal **2**, prepared from either of the diamines **6** or **7**. The stereogenic center in **2** could be created by an organometallic addition to the C=N double bond in **3**, in turn prepared from glyoxal **5**.

Thus, our efforts towards this goal started with glyoxal **5**, a useful, inexpensive two carbon reagent.[13] This strategy to chiral α-amino aldehydes was also explored by three other groups. Chastrette et al.[7] used a chiral acetal, instead of an aminal, and a simple achiral hydrazone functionality (see **8**). However, the final hydrolysis of the chiral acetal was difficult and only an oxidative cleavage was successful, leading to α-amino acids instead of α-amino aldehydes. On the other hand, Enders et al.[4] and Denmark et al.[5] followed an identical approach with a chiral hydrazone and a simple dimethoxy acetal **9** (Scheme 2).



Scheme 2

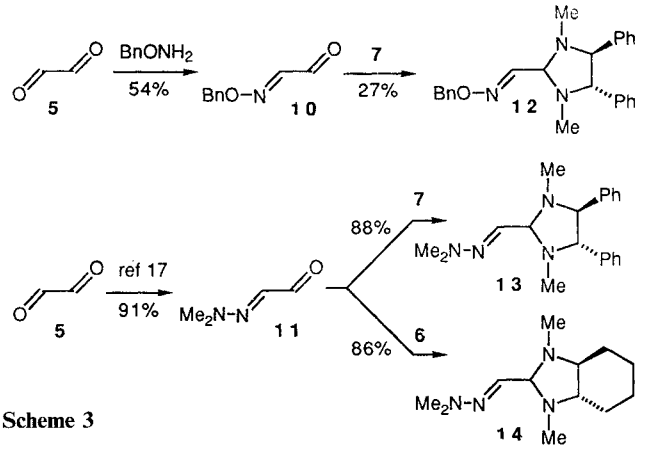
We report herein our full results[14] using chiral aminals as auxiliaries and protecting groups for the aldehyde functionality which allow the preparation of a variety of optically pure α-amino aldehydes.

Preparation of the Chiral Synthons

Our approach (Scheme 1) is based on the transformation of one of the two aldehyde funtionalities of glyoxal into imine **4**, and then aminal **3**, able to react with various organometallic reagents. This monoderivatization of glyoxal is not an easy process.[13,15] The formation of an imine could not be stopped at the monoimine stage; only the bisimine or polymers were obtained. By analogy to the work of Fujioka et al.,[16] the reaction with *O*-benzyl hydroxylamine was attempted, but gave, in quantitative

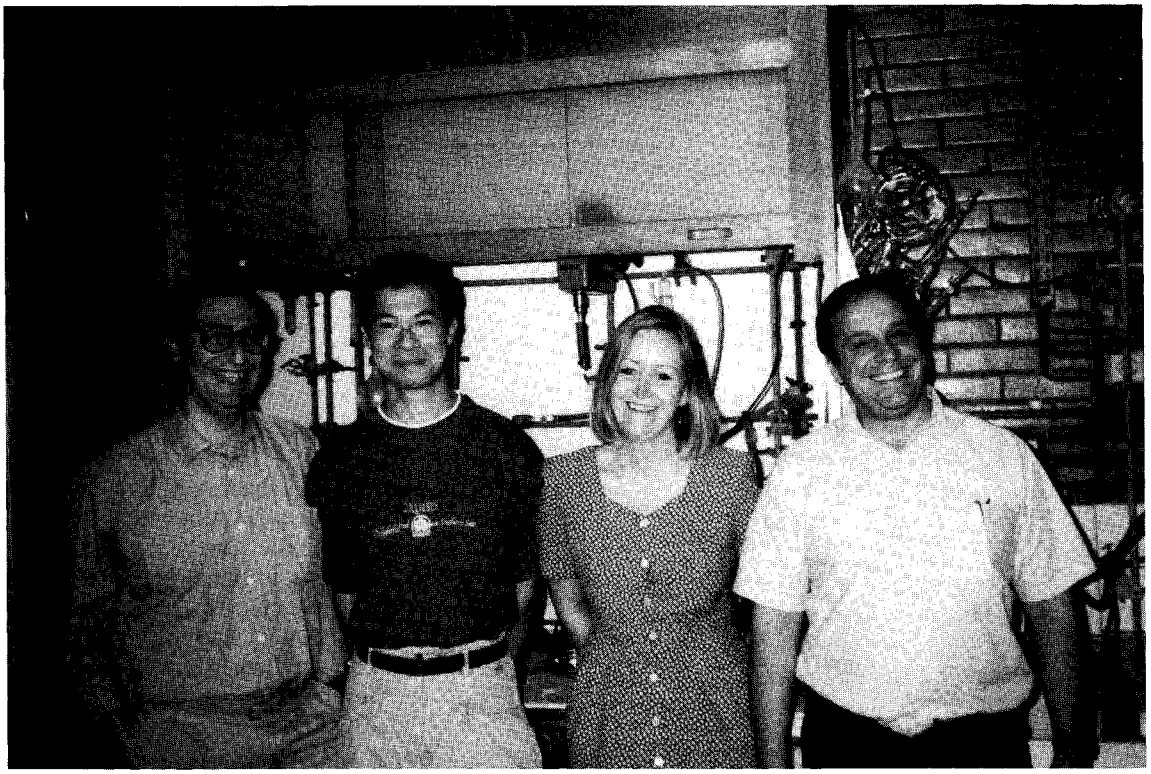
yield, a mixture of mono- and bisoxime (60:40). Monooxime **10** could be isolated in 54% yield after preparative thin layer chromatography. By contrast, the desymmetrization of glyoxal by formation of the monohydrazone is a straightforward process[17] and, by reaction with dimethyl hydrazine, we obtained monohydrazone **11**, in 91% yield, after distillation (Scheme 3).

The formation of aminals of the remaining aldehyde functionality on **11** was easily and smoothly achieved with chiral diamines having a *C2* axis of symmetry,[11,18] such as **6** and **7**. Thus, the preparation of the starting materials **13** and **14** was simple and very efficient because no new stereogenic center is formed in the aminalization process. By contrast, the isolated yield of aminal oxime **12** was



Scheme 3

Biographical Sketches



From left to right: A. Alexakis, J.-P. Tranchier, N. Lensen, P. Mangeney

Alex Alexakis, was born in Alexandria in 1949. He graduated from Paris VI University in 1970 and received his PhD in 1975. After a postdoctoral stay at Johns Hopkins University, he joined the CNRS at Pierre et Marie Curie University in 1977, being appointed Directeur de Recherche in 1985. In 1994 he was awarded the Silver Medal of the CNRS. His research focusses on organometallic synthesis, particularly copper reagents, and is presently directed towards asymmetric synthesis.

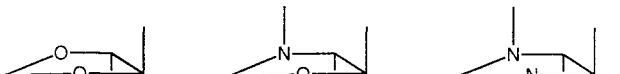
Pierre Mangeney was born in 1947, graduated from Paris VI University in 1970 and received his PhD 1979. He joined the CNRS in 1978 and discovered in 1979 the anticancer "Navelbine" while working in P. Potier's group. Starting in 1985, he led, in collaboration with A.A., the asymmetric synthesis team.

Nathalie Lensen was born in 1964 in Lille and obtained her PhD in 1992. After a post doctoral stay at University of California, Los Angeles, she was appointed Maître de Conférence at Cergy-Pontoise University.

Jean-Philippe Tranchier was born in 1969 in Vientiane and received his PhD in 1994. He is presently doing his military duties.

rather low (27%) owing to the transformation of monooxime **10** into a mixture of bisoxime and **12**.

Aminal **13** is a crystalline compound and it was possible to perform an X-ray analysis[19] in order to have a picture of its conformation in the solid state. Indeed, our main hypothesis for the higher efficiency of chiral aminals (as an imidazolidine ring) as compared to acetals (as dioxolanes) lies in the conformation of the *N*-substituent. By analogy to oxazolidines,[20] we hypothesized that the substituent on the nitrogen should be located *trans* to the substituent on the next carbon (Scheme 4). Therefore, the stereogenic center which controls the diastereoselectivity becomes the nitrogen atom, and this control may be exerted in different ways: (a), a steric control by the bulk of the *N*-substituent; and (b), a chelation control by the lone pair of one of the two nitrogen atoms. The PLUTO view[21] of aminal **13** (Figure 1) completely fulfilled our expectations, showing clearly the *trans* relationship between the *N*-substituent and the phenyl group on the next carbon.

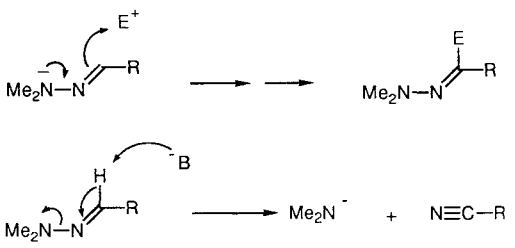


Scheme 4

Figure 1. PLUTO view of aminal **13**[21]

Reactivity of the Chiral Reagents

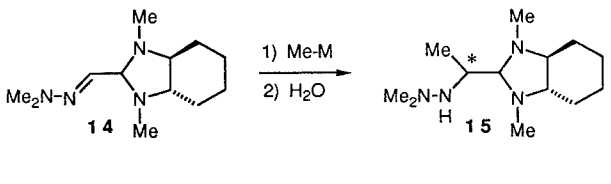
The electrophilic reactivity of hydrazones is rather poor.[22] They may even be regarded as nucleophilic reagents[23] (Scheme 5). On the other hand, the hydrazonic proton is quite acidic and may be easily removed by a base, resulting in the formation of a nitrile[24] (Scheme 5).



Scheme 5

Nevertheless, hydrazones and oximes are known to react with organolithium,[25,26] Grignard[25a,27] and even cuprate reagents.[26] More recently, organocerium reagents were described to be the most effective.[28] As far as stereoselectivity is concerned, there are reports on α-heterosubstituted hydrazones and oximes where a good level of diastereocontrol may be achieved. Thus, Fujioka et al.[16] reacted *O*-benzyl oximes bearing a chiral ketal moiety with organocerium reagents (de 50–100%). Chiral acetal **8** was also used by Chastrette et al.[7] with organolithium reagents (de 50–100%). Claremon et al.[26] reacted protected α-hydroxy hydrazones with various reagents (mainly organolithium reagents) and obtained, through chelation stereocontrol, good de (50–96%).

Although **12** was the least easily prepared, we tried to react it with various organometallic reagents (RMgX, RLi or $RCeCl_2$ in Et_2O or THF). All reactions failed, with recovery of the starting material. Therefore, all the further work was done on hydrazones **13** and **14**. The preliminary study was done with methyl organometallics (see Scheme 6) and the results are shown in Table 1.



Scheme 6

The determination of the diastereomeric excess was easily and accurately done by ^1H and/or ^{13}CNMR. Chiral aminals are known to be excellent derivatives for the determination of the enantiomeric composition of chiral aldehydes.[29] Although aminal **14** was more reactive than aminal **13**, the observed diastereoselectivity with MeLi was rather poor and no further studies were done on this compound (entries 1, 2 and 3). In contrast, aminal **13** reacted with very high stereoselectivity with MeLi (entry 5), giving a single diastereomer **16a** in THF. Indeed, THF was a superior solvent as far as the diastereoselectivity was concerned (compare entries 4 and 5) and this point was even more pronounced with other organolithium reagents. With organocerium derivatives, in our hands, only the trimethylcerium reagent[30] reacted to afford **16a** alone (compare entries 9 and 10). Cuprate reagents were unreactive under a variety of reaction conditions (entries 6, 7 and 8). The reactivity of Grignard reagents was strongly dependent on the solvent. In THF no reaction occured, even at reflux (entry 11). In Et_2O, the reaction required 24 h at reflux for completion (entry 12), whereas in toluene (entry 13), the reaction was over at room temperature in less than 2 h! Such increase of reactivity of Grignard reagents has some precedent with nitriles[31] but not with hydrazones;[32] it may be ascribed to the Lewis acidity of the magnesium salts which increases the

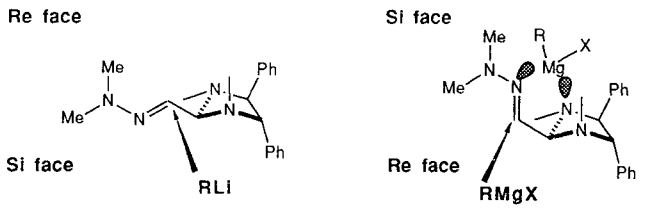
Table 1. Reaction of Hydrazones **13** and **14** with Methyl Organometallic Reagents (Scheme 6).

Entry	Organometallic Reagent	Chiral Hydrazone	Solvent	React. Conditions temp. (°C)/time (h)	Yield[a] (%)	de[b] (%) (configuration)
1	MeLi, LiBr	**14**	Et_2O	−70−+20/0.5	76	20
2	MeLi, LiBr	**14**	THF	−70−+20/0.5	80	40
3	MeLi, LiBr	**14**	THF + 4TMEDA	−70−+20/0.5	83	40
4	MeLi, LiBr	**13**	Et_2O	−70−+20/0.5	72	96 (*S*)
5	MeLi, LiBr	**13**	THF	−70−+20/0.5	74	>99 (*S*)
6	Me_2CuLi	**13**	Et_2O	−50−+20/2	0	–
7	Me_2CuLi, BF_3	**13**	Et_2O	−50−+0/5	0	–
8	Me_2CuLi	**13**	Et_2O + $2ClCO_2Me$	−50−−20/5	0	–
9	$MeCeCl_2$	**13**	THF	−70−+20/0.5	0	–
10	Me_3Ce, 3 LiCl	**13**	THF	−70−+20/0.5	76	>99 (*S*)
11	MeMgBr	**13**	THF	+20−+65/5	0	–
12	MeMgBr	**13**	Et_2O	+20−+35/24	87	60 (*R*)
13	MeMgBr	**13**	toluene + Et_2O	+20/2	85	88 (*R*)
14	MeMgBr	**13**	toluene	+20/2	83	88 (*R*)

[a] Yield of isolated material.
[b] Determined by ^1H NMR.

electrophilicity of the C=N double bond.[33] The most striking aspect of the reaction of **13** with Grignard reagents concerns the diastereoselectivity, which is opposite to that observed with organolithium or organocerium derivatives.[34] The de of **16b** was 60% in Et_2O, increasing to 88% in toluene. Efforts to obtain **16b** as a single isomer were unsuccessful either by removing the ethereal content of the Grignard solution (entry 14) or by using MeMgI or MeMgCl instead of MeMgBr.

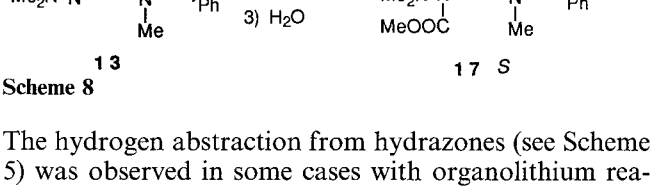
In view of the conformation of chiral reagent **13**, as seen in Figure 1, and assuming that this conformation in the crystal is not very different from that in solution, we may ascribe the observed diastereoselectivity to a steric control or to a chelation control. Thus, in the case of organolithium reagents in a strongly coordinating solvent such as THF, steric control will be exerted by the pseudoequatorial N–Me group impeding a Bürgi–Dunitz approach (110°)[35] of the nucleophile from the *Re* face (for an *S,S* diamine) (see Scheme 7). With the Lewis acidic Grignard reagents, in a non-coordinating solvent such as toluene, a tight chelate could be formed with the lone pair of one of the two nitrogens of the imidazolidine ring and the hydrazone nitrogen. In such a rigid conformation, the pseudoequatorial N–Me group this time masks the *Si* face of the hydrazone functionality leading to the opposite diastereomer.



Scheme 7

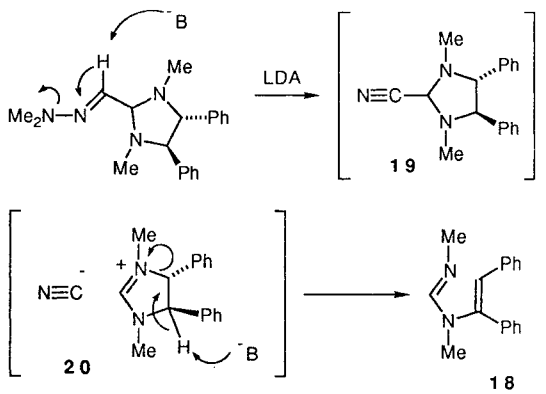
Scope and Limitations

Hydrazines, such as **16**, are usually considered as quite sensitive compounds being prone to air oxidation and unstable upon storage or handling on silica gel.[28a] We did not observe any such degradation with our hydrazines, perhaps due to the bulkiness of the imidazolidine ring. They could be stored in the refrigerator for months without any problem. Nevertheless, in one case, we quenched the lithium hydrazide with methyl chloroformate to obtain the corresponding carbamate **17** (compounds which are considered as more stable[28a]) in 74% yield. However, the NMR spectra were complicated by the presence of conformers (duplication and widening of all signals) and this way of quenching was abandoned (Scheme 8).



Scheme 8

The hydrogen abstraction from hydrazones (see Scheme 5) was observed in some cases with organolithium reagents when the reaction temperature was raised too quickly. The basicity of RLi competed with its nucleophilicity. Indeed, when **14** was treated with lithium diisopropylamide[24a] a fast decomposition occurred (at around 0 °C) giving formamidine **18** in high yield. It was impossible to observe the intermediate nitrile **19** indicating that this compound might exist in its dissociated form **20** (Scheme 9).



Scheme 9

Table 2. Reaction of Hydrazone **13** with Various Organolithium Reagents (Scheme 10).

Entry	Organometallic Reagent	Solvent	React. Conditions temp. (°C)/time (h)	Product	Yield[a] (%)	de[b] (%) (config.)
1	MeLi, LiBr	Et_2O	−70→+20/0.5	**16a**	72	96 (*S*)
2	MeLi, LiBr	THF	−70→+20/0.5	**16a**	74	>99 (*S*)
3	PrLi, LiBr	THF	−70→+20/0.5	**21a**	77	>99 (*S*)
4	BuLi	Et_2O	−70→+20/0.5	**22a**	65	>99 (*S*)
5	BuLi	THF	−70→+20/0.5	**22a**	68	>99 (*S*)
6	*i*-BuLi, LiBr	Et_2O	−70→+20/0.5	**23a**	52	74 (*S*)
7	*i*-BuLi, LiBr	THF	−70→+20/0.5	**23a**	65	>99 (*S*)
8	*s*-BuLi	Et_2O	−70→−30/0.5	**24a**	75	>99 (*S*) and 28[c]
9	*t*-BuLi	Et_2O	−70→−60/0.5	**25a**	91	>99 (*S*)
10	PhLi, LiBr	Et_2O	−70→+20/1	**26a**	55	53 (*R*)
11	PhLi, LiBr	THF	−70→+20/1	**26a**	78	>99 (*S*)
12	$Me_2C{=}CHLi$, LiBr	Et_2O	−70→+20/1	**27a**	74	60 (*S*)
13	$Me_2C{=}CHLi$, LiBr	THF	−70→+20/1	**27a**	62	>99 (*S*)
14	2-FurylLi	THF or Et_2O	−70→+20/24	–	0	–
15	Pent-C≡CLi	THF	−70→+20/24	–	0	–
16	$Cl(CH_2)_4Li$	Et_2O/pentane	−70→−30/0.5	**31**[d]	92	>99 (*S*)

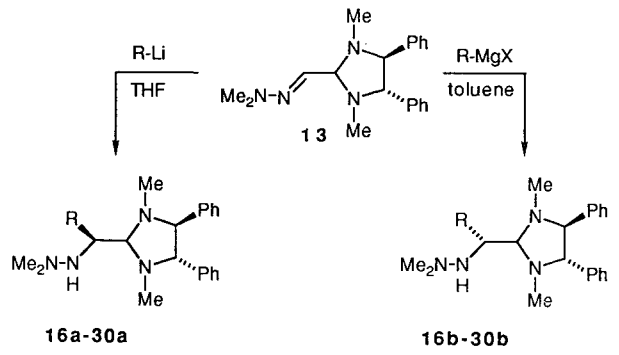
[a] Yield of isolated material.
[b] Determined by ^1H NMR.
[c] Value for the second stereocenter. See text.
[d] See Scheme 11.

Table 3. Reaction of Hydrazone **13** with Various Grignard Reagents (Scheme 10).

Entry	Organometallic Reagent	Solvent	React. Conditions Temp. (°C)/time (h)	Product	Yield[b] (%)	de[c] (%) (config.)
16	MeMgBr	toluene + Et_2O[a]	+20/2	**16b**	83	88 (*R*)
17	PrMgCl	toluene + Et_2O[a]	+20/2	**21b**	89	>99 (*R*)
18	BuMgBr	toluene + Et_2O[a]	+20/2	**22b**	94	>99 (*R*)
19	*i*-BuMgCl	toluene + Et_2O[a]	+20/2	**23b**	92	>99 (*R*)
20	*c*-HexMgCl	toluene + Et_2O[a]	+20/2	**28b**	91	>99 (*R*)
21	*t*-BuMgCl	toluene + Et_2O[a]	+80/2	**25b**	67	>99 (*R*)
22	PhMgBr	toluene + Et_2O[a]	+80/2	**26b**	82	>99 (*R*)
23	$CH_2{=}CHCH_2MgBr$	toluene + Et_2O[a]	+20/10 min	**29b**	88	54 (*R*)
24	$CH_2{=}CHCH_2MgBr$	toluene + Et_2O[a]	−50/1	**29b**	83	64 (*R*)
25	$CH_2{=}CHCH_2MgBr$	CH_2Cl_2 + 1 $TiCl_4$	−70/0.5	**29b**	78	92 (*R*)
26	$MeCH{=}CHCH_2MgBr$	toluene + Et_2O	−70/0.5	**30b**	90	85 (*R*)
27	$MeCH{=}CHCH_2MgBr$	CH_2Cl_2 + 1 $TiCl_4$	−70/0.5	**30b**	87	84 (*R*)

[a] The Et_2O of the Grignard solution was not removed.
[b] Yield of isolated material.
[c] Determined by ^1H NMR.

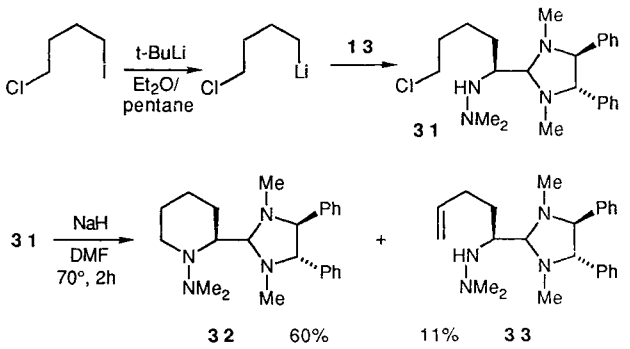
The generalization of these results to other organolithium and Grignard reagents according to Scheme 10 is shown in Tables 2 and 3.



Scheme 10

Primary, secondary and tertiary alkyllithium as well as phenyl- and alkenyllithium derivatives all gave a single detectable diastereomer in THF. The use of *sec*-BuLi created a second stereocenter which was hardly controlled (de 28%). It is interesting to note that phenyllithium, in Et_2O instead of THF, gave the opposite diastereomer albeit in moderate de (53%). A single diastereomer **26a** was obtained only when a large excess of THF was added to the ethereal PhLi solution. Finally, furyl- and an alkynyllithium were not reactive enough to afford any adduct. An interesting example is the use of an ω-functionalized organolithium reagent such as δ-chlorobutyllithium (Scheme 11). This organolithium reagent has to be reacted at low temperature in Et_2O and generated from 1-iodo-4-chlorobutane with only one equivalent of *t*-BuLi (instead of the usual two equiv).[36] The intermediate lithium hydrazide could be protonated at low tem-

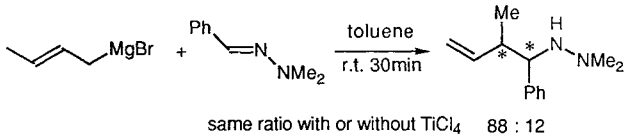
perature but could not be cyclized intramolecularly in situ. The diastereomerically pure adduct **31** was then treated with NaH in DMF at 70 °C for 2 h to afford in 60 % yield the cyclized product **32** along with the elimination product **33** in 11 % yield.



Scheme 11

Grignard reagents all gave systematically the opposite diastereomer in toluene. Apart from MeMgX (de 88 %), the diastereoselectivity was excellent, a single diastereomer being detected. Primary and secondary alkyl, as well as phenyl, Grignard reagents reacted at room temperature in excellent yields. The introduction of the *tert*-butyl group was more troublesome. No reaction occured at + 20 °C whereas at refluxing temperature (110 °C) extensive reduction product was obtained.[37] Moderate heating (80 °C) gave the optimum result with 67 % yield of the desired *tert*-butylated adduct, and only 22 % yield for the reduction product.

Allyl Grignard reagent was a special case because it reacted even in THF. The de was low (in THF) to moderate (in toluene); by decreasing the reaction temperature, a slight improvement was observed (compare entries 23 and 24). In order to increase the rigidity of the chelation transition state (see Scheme 7) we used a stronger bidentate Lewis acid, such as $TiCl_4$, and the de jumped to 92 % (entry 25). With crotyl Grignard reagent (entry 26), a second stereocenter is created. Of the four possible diastereomers, only two were detected in a 93:7 ratio. Since a double diastereoselection is usually more efficient than a single one, we believe that a perfect control is achieved for the usual α-stereocenter whereas the second one is partially controlled (de 86 %). That this de corresponds to the *syn*/*anti* ratio (or vice versa) is supported by the facts that $TiCl_4$ does not improve the de, and that the reaction of crotyl Grignard with a simple hydrazone gives a *syn*/*anti* ratio of 88:12 (or the reverse)[38] (Scheme 12).



Scheme 12

Synthesis of α-Amino Aldehydes

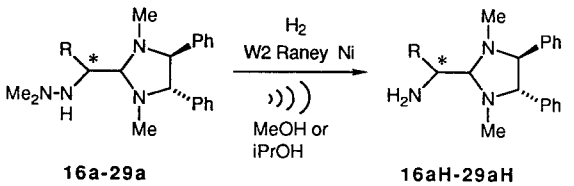
To complete our synthesis of α-amino aldehydes, it was necessary to cleave the N–N bond of the above hydrazines. The cleavage method should be compatible with the aminal group and therefore non-acidic conditions were required. The Raney nickel method[39] seemed the most appropriate for this task and has been extensively used in the literature. When hydrazine **16a** was treated with commercial W2 Raney nickel under 50 atm H_2 pressure at 40 °C, the cleavage was completed in 72 h, giving the α-amino aminal **16aH** in 72 % isolated yield. No epimerization was detected at this stage as judged by ^1H and ^{13}C NMR where a single set of signals was observed. However, these harsh conditions were not successful with the other more hindered hydrazines. We next turned our attention to ultrasonic assistance, postulating that the cavitation effects in the solvent could recreate locally these conditions of high pressure and high temperature.[40] Indeed, the use of ultrasound (in a simple cleaning bath) had a dramatic influence; **16a** could be hydrogenolyzed

Table 4. Further Transformations of Hydrazines **16–29** (Schemes 13–15).

Entry	Hydrazine (R)	N–N cleavage Yield[a] (%)	*t*-Boc Protection Yield[a] (%)	α-Amino Aldehyde Yield[a] (%)/$[\alpha]_D^{20}$[b]
1	**16a**, R = Me	**16aH** 74	**16aBoc** 73	**16c** (*S*) 72/+ 31 (*c* = 0.055)
2	**16b**, R = Me	**16bH** 57	**16bBoc** 72	**16c** (*R*) 71/− 33 (*c* = 0.024)
3	**21a**, R = Pr	**21aH** 75	**21aBoc** 85	**21c** (*S*), 78/+ 29 (*c* = 0.012)
4	**21b**, R = Pr	**21bH** 76	**21bBoc** 78	**21c** (*R*), 84/− 31 (*c* = 0.01)
5	**22a**, R = Bu	**22aH** 60		
6	**22b**, R = Bu	**22bH** 62		
7	**23a**, R = *i*-Bu	**23aH** 85		
8	**23b**, R = *i*-Bu	**23bH** 86	**23bBoc** 74	**22c** (*R*) 67/− 3 (*c* = 0.016)
9	**28b**, R = cHex	**28bH** 85	**28bBoc** 81	**28c** (*R*) 71/− 27 (*c* = 0.008)
10	**25a**, R = *t*-Bu	**25aH** 66		
11	**26a**, R = Ph	**26aH** 70		
12	**29b**, R = Allyl	**21bH** 60		
13	**16a**, R = Me	see text	**16d**[c] 92	**16e** (*S*) 65/+ 66 (*c* = 0.056)

[a] Yield of isolated material.
[b] All rotations are measured in $CHCl_3$.
[c] Scheme 15.

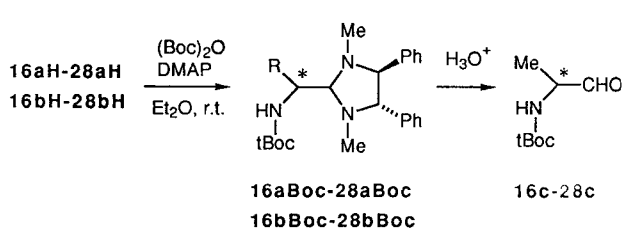
with Raney nickel in only 2 h at room temperature and at atmospheric pressure. The other examples follow the same trend (see Scheme 13 and Table 4) and all hydrazones were cleaved without epimerization.[14b,41] The most hindered case **25** (R = *t*-Bu) required 24 h for completion. It should be pointed out that in no case did we observe any epimerization during this cleavage procedure even when R = Ph. This could be due to the large steric bulk of the aminal group, since in less hindered cases we[42] and others[4] have observed such partial epimerizations.



Scheme 13

The limitation of the method is that unsaturated bonds in the substrate are hydrogenated. Aminal **27a** was partially saturated whereas aminal **29b** (entry 12) having a terminal vinyl group was totally hydrogenated to give **21bH**. This observation allowed the determination of the relative configuration of the material obtained by reaction of allyl Grignard reagent in THF or toluene. Comparison with the compounds obtained by reaction of PrLi/THF **(21aH)** or PrMgBr/toluene **(21bH)** clearly showed that the allyl Grignard reagent reacted under chelation control even in THF.

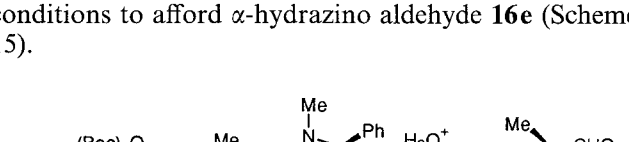
Before hydrolyzing the aminal protecting group, it was necessary to protect the primary amino functionality. Only some of the above aminals were chosen for this study. From the methods of protecting primary amines,[43] we selected the simple *t*-Boc group which was effected under usual conditions (Scheme 14). The ^{1}H NMR signals of these *t*-Boc protected amines (**16aBoc–28aBoc** and **16bBoc–28bBoc**) were not sharp due to the presence of conformers and rotamers. However, a single spot was detected by TLC. It should be pointed out that the two diastereomeric aminals were well separated by TLC, as is usually the case with chiral aminals.[29] These aminals were perfectly stable compounds; they did not decompose or racemize when stored in the refrigerator for months. This is in striking contrast with *t*-Boc α-amino aldehydes which racemize rather quickly at room temperature, or below,[1] and even during purification or drying procedures.[44] Thus, it may be considered that these aminals are a convenient way of storing this sensitive class of aldehydes.



Scheme 14

In contrast to acetals, and particularly to chiral acetals,[45,46] the hydrolysis of aminals occurs under very mild acidic conditions, avoiding α-epimerization. To illustrate this fact, we hydrolyzed some of the above aminals (**16aBoc–28aBoc** and **16bBoc–28bBoc**) with 2% aq HCl or using Conia's method[47] giving the corresponding *t*-Boc-protected α-amino aldehydes **16c–28c** in good yields. Comparison of the rotation of alaninal **16c** with an authentic sample prepared by DIBAL-reduction of L-ethyl alaninate[44b] allowed the determination of the absolute configuration. That no epimerization occured during the hydrolysis step was checked by formation of the diastereomeric aminal formed either with the *R,R* or *S,S* diamine **7**; a single spot of different R_f could be seen in both cases. It should be recalled that the chiral lability of these aldehydes precludes any confidence in the absolute optical rotation value.[44,48]

An additional feature of this methodology should be pointed out: α-hydrazino aldehydes, being precursors of the corresponding acids, are interesting compounds in themselves.[49] Indeed, α-hydrazino aminal **16a** was easily protected as *t*-Boc **16d** and hydrolyzed under the above conditions to afford α-hydrazino aldehyde **16e** (Scheme 15).



Scheme 15

Conclusion

The synthetic methodology disclosed above seems to be of general applicability and use. It allows the easy preparation of unusual α-amino aldehydes of either absolute configuration in excellent enantiomeric purities. This study also shows that chiral aminals are an effective controlling group either by steric effects or by chelation effects. In addition, the chiral auxiliary, being an amine, is very easily recovered at the final hydrolysis step by a simple basification of the aqueous phase.

All mps are uncorrected. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. NMR spectra were recorded on a JEOL GSX 400 or Bruker AC 200 spectrometer. IR spectra (neat) were recorded on a Perkin-Elmer 1420 spectrophotometer. Compounds **13, 16a, b, 16aBoc, 21a, b, 21aBoc, 21bBoc, 22b, 23b, 25a, b, 26b, 28b, 29b, 30b** and **31–33** gave C,H,N analysis ±0.17%.

(4*S*,5*S*)-2-[*N*,*N*-Dimethylhydrazonomethyl]-1,3-dimethyl-4,5-diphenylimidazolidine (13):

To a solution of (1*S*,2*S*)-*N*,*N*'-dimethyl-1,2-diphenylethane-1,2-diamine (**7**)[50] (3.78 g, 15.75 mmol) in CH_2Cl_2 (100 mL) was added the monohydrazone **11**[17] (1.57 g, 15.75 mmol). The mixture was stirred for 48 h at r.t. in the presence of molecular sieves 4 Å (1 g). After filtration and evaporation of the solvent, the resulting oil was dissolved in the minimum of Et_2O and crystallized in the refrigerator. The crystals were filtered off and washed with pentane. The mother liquor was evaporated and the residue treated with Et_2O as above, yielding compound **13** (4.47 g, 88%); mp 127°C. $[\alpha]_D^{20}$ −17 (*c* = 0.02, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.3–7.1 (m, 10H), 6.67 (d, J = 7.4 Hz, 1H), 4.25 (d, J = 7.4 Hz, 1H), 3.84 (d, J = 8.1 Hz, 1H), 3.56 (d, J = 8.1 Hz, 1H), 2.88 (s, 6H), 2.28 (s, 3H), 2.21 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.7, 139.4, 136.6, 128.4, 128.1, 127.9, 127.4, 86.1, 78.0, 76.4, 43.1, 37.8, 34.7.

IR: ν = 2920, 2850, 1458, 1375 cm^{-1}.

The crystallographic data were as follows: $C_{20}H_{26}N_4$, M_r = 322.46, orthorhombic, $P2_12_12_1$, a = 5.624(2), b = 14.334(9), c = 23.569(10) Å, V = 1900.0(15) Å^3, D_x = 1.13 g.cm^{-3} for Z = 4. The intensities of 1672 independent reflexions were collected on a Huber four circle diffractometer using MoKα graphite monochromatized radiation (λ = 0.71069 Å). 1349 reflexions with $I \geq 2.5\sigma(I)$ were used in the refinement. The structure was solved by direct method using SHELXS86[51] and refined by anisotropic least squares on f values using SHELX76.[52] All H atoms were located from a difference Fourier synthesis and included in the refinement with a common isotropic temperature factor (B = 6.8 Å^2). $w = 1/(\sigma^2 + 0.00009F^2)$, R = 0.041, R_w = 0.043, S = 2.3 for 1349 observed reflections. The list of atomic coordinates and molecular dimensions has been deposited with the Cambridge Crystallographic Data Centre.

(1*S*,6*S*)-8-[*N*,*N*-Dimethylhydrazonomethyl]-7,9-dimethyl-7,9-diazabicyclo[4.3.0]nonane (14):

Same procedure as above with (1*S*,2*S*)-*N*,*N*'-dimethyl-1,2-diaminocyclohexane. The resulting oil was distilled using a Kugelrohr oven at 120°C (0.2 Torr). Yield 86%, oil, $[\alpha]_D^{20}$ −0.9 (c = 0.5, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.56 (d, J = 7.57 Hz, 1H), 4.08 (d, J = 7.57 Hz, 1H), 2.58 (s, 6H), 2.35 (s, 3H), 2.30 (s, 3H), 2.1–1.7 (m, 6H), 1.04–1.45 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 135.9, 88.0, 69.8, 68.7, 42.9, 37.7, 34.9, 29.6, 29.2, 24.9, 24.8.

IR: ν = 2920, 2845, 2770, 1590, 1450, 1355 cm^{-1}.

Addition of RLi (Table 2); General Procedure:

To a cold solution (−70°C) of imidazolidine **13** (100 mg, 0.31 mmol) in THF (or Et_2O if stated in Table 2) (50 mL) was added the organolithium solution (in hexane or Et_2O, 1.55 mmol). The cooling bath was removed and the homogeneous solution was stirred while slowly warming. After 30 min at room temperature, the mixture was hydrolyzed by addition of sat. aq NH_4Cl (20 mL). The organic phase was washed with sat. aq NH_4Cl, and the aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic phase was dried (K_2CO_3), then concentrated in vacuo. The residue was purified by chromatography (basic alumina; cyclohexane/EtOAc, 90–95/10–5).

(4S,5S)-2-[(S)-1-(N,N-Dimethylhydrazino)ethyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(16a)** *(R = Me):*

Yield 74%, oil, $[\alpha]_D^{20}$ −39 (c = 0.052, CH_2Cl_2).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.1 (m, 10H), 4.05 (d, J = 9 Hz, 1H), 3.82 (d, J = 3.4 Hz, 1H), 3.65 (d, J = 9 Hz, 1H), 3.25 (dq, J = 3.4 Hz, 1H), 2.5 (s, 6H), 2.45 (s, 3H), 2.33 (s, 3H), 1.34 (d, J = 6.4 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.6, 139.1, 129.2, 128.3, 128.0, 127.6, 127.4, 87.9, 77.7, 75.3, 56.3, 49.0, 42.0, 35.4, 17.6.

IR: ν = 3055, 3020, 2940, 2840, 2795, 1450, 1355 cm^{-1}.

(4S,5S)-2-[(S)-1-(N,N-Dimethylhydrazino)butyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(21a)** *(R = Pr):*

Yield 77%, oil, $[\alpha]_D^{20}$ = +12 (c = 0.023, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.12 (m, 10H), 4.08 (d, J = 8.7 Hz, 1H), 3.95 (d, J = 2.2 Hz, 1H), 3.65 (d, J = 8.7 Hz, 1H), 3.03 (m, 1H), 2.47 (s, 6H), 2.39 (s, 3H), 2.30 (s, 3H), 1.87–0.90 (m, 7H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.7, 139.2, 129.4, 129.1, 128.6, 128.0, 127.7, 127.3, 127.1, 85.6, 77.0, 75.1, 60.5, 48.5, 40.8, 35.7, 32.5, 20.5, 14.6.

IR: ν = 3055, 3020, 2940, 2840, 2795, 1450, 1355 cm^{-1}.

(4S,5S)-2-[(S)-1-(N,N-Dimethylhydrazino)pentyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(22a)** *(R = Bu):*

Yield 68%, oil, $[\alpha]_D^{20}$ −49 (c = 0.053, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.09 (m, 10H), 4.12 (d, J = 8.7 Hz, 1H), 3.97 (d, J = 2 Hz, 1H), 3.67 (d, J = 8.7 Hz, 1H), 3.02 (dt, J = 2, 6 Hz, 1H), 2.5 (s, 6H), 2.43 (s, 3H), 2.32 (s, 3H), 1.7–0.8 (m, 9H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.8, 139.5, 129.2, 128.1, 127.8, 127.4, 127.2, 85.6, 77.6, 75.5, 60.8, 48.6, 40.9, 35.8, 30.2, 29.9, 23.3, 14.3.

IR: ν = 3055, 3020, 2940, 2840, 2795, 1450, 1355 cm^{-1}.

(4S,5S)-2-[(S)-1-(N,N-Dimethylhydrazino)-3-methylbutyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(23a)** *(R = i-Bu):*

Yield 65%, oil, $[\alpha]_D^{20}$ −47 (c = 0.064, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.1 (m, 10H), 4.1 (d, J = 8.6 Hz, 1H), 3.9 (d, J = 1.84 Hz, 1H), 3.65 (d, J = 8.6 Hz, 1H), 3.15 (m, 1H), 2.49 (s, 6H), 2.38 (s, 3H), 2.31 (s, 3H), 1.76 (m, 2H), 1.45 (m, 1H), 1.02 (d, J = 6.3 Hz, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 141.0, 139.9, 129.4, 128.2, 128.0, 127.5, 127.3, 85.7, 77.5, 75.6, 58.6, 48.6, 39.7, 35.9, 26.1, 23.8, 23.1, 18.9.

IR: ν = 3055, 3020, 2940, 2840, 2795, 1450, 1355 cm^{-1}.

(4S,5S)-2-[(S)-1-(N,N-Dimethylhydrazino)-2-methylbutyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(24a)** *(R = s-Bu):*

Reaction run in Et_2O. Yield 75%, oil. The signals corresponding to the minor isomer are in italics.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.27–7.1 (m, 10H), 4.18 (*4.15*) (d, J = 9 Hz, 1H), 3.89 (*3.87*) (d, J = 9 Hz, 1H), 3.7 (*3.67*) (d, J = 4.5 Hz, 1H), 2.89 (*2.91*) (m, 1H), 2.50 (*2.48*) (s, 6H), 2.46 (*2.45*) (s, 3H), 2.2 (*2.22*) (s, 3H), 1.85 (*1.70*) (m, 1H), 1.18 (*1.20*) (d, J = 7.5 Hz, 3H), 0.98 (m, 2H), 0.95 (t, J = 8.6 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 141.1, 138.3, 128.7, 128.6, 127.9, 127.7, 127.4, 127.0, 87.1 (*88.2*), 75.1, 74.3, 63.4 (*62.1*), 48.2, 42.0, 37.6.

IR: ν = 3055, 3020, 2940, 2840, 2795, 1450, 1355 cm^{-1}.

(4S,5S)-2-[(S)-1-(N,N-Dimethylhydrazino)-2,2-dimethylpropyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(25a)** *(R = t-Bu):*

Reaction run in Et_2O. Yield 91%, mp 90°C (Et_2O), $[\alpha]_D^{20}$ +42 (c = 0.11, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.36–7.1 (m, 10H), 4.0 (d, J = 8.4 Hz, 1H), 3.87 (d, J = 1.2 Hz, 1H), 3.68 (d, J = 8.4 Hz, 1H), 2.56 (s, 6H), 2.29 (s, 3H), 2.25 (s, 3H), 1.09 (s, 9H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.4, 139.8, 129.1, 128.3, 128.2, 127.9, 127.5, 127.4, 84.7, 78.1, 75.1, 65.7, 48.5, 39.9, 35.3, 27.8.

IR: ν = 3055, 3020, 2940, 2840, 2795, 1450, 1335 cm^{-1}.

(4S,5S)-2-[(S)-α-(N,N-Dimethylhydrazino)benzyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(26a)** *(R = Ph):*

Yield 78%, oil, $[\alpha]_D^{20}$ +97 (c = 0.07, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.65–7.1 (m, 15H), 4.31 (d, J = 3.8 Hz, 1H), 4.08 (d, J = 9 Hz, 1H), 3.95 (d, J = 3.8 Hz, 1H), 3.76 (d, J = 9 Hz, 1H), 2.58 (s, 6H), 2.3 (s, 3H), 2.06 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 142.0, 140.5, 138.2, 129.4, 128.9, 128.6, 128.3, 128.2, 128.1, 127.9, 127.7, 127.5, 127.4, 126.9, 126.7, 90.2, 75.2, 74.8, 65.1, 48.1, 40.1, 37.1.

(4S,5S)-2-[(S)-1-(N,N-Dimethylhydrazino-3-methylbut-2-enyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(27a)** *(R = $Me_2C{=}CH{-}$):*

Yield 62%, oil, $[\alpha]_D^{20}$ +19 (c = 0.12, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.24–7.1 (m, 10H), 5.35 (dq, J = 8.8, 1.2 Hz, J = 1.1 Hz, 1H), 4.12 (d, J = 8.9 Hz, 1H), 4.02 (dd, J = 8.8, 2.7 Hz, 1H), 3.88 (d, J = 2.7 Hz, 1H), 3.54 (d, J = 8.9 Hz, 1H), 2.5 (s, 6H), 2.4 (s, 3H), 2.37 (s, 3H), 1.80 (d, J = 1.1 Hz, 3H), 1.78 (d, J = 1.2 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.4, 139.4, 132.6, 128.6, 128.5, 128.1, 127.9, 127.7, 127.6, 127.3, 127.0, 126.9, 87.0, 78.0, 75.3, 59.5, 49.2, 42.0, 33.9, 29.6, 26.0.

(4*S*,5*S*)-2-[(S)-1-(*N*,*N*-Dimethylhydrazino)-5-chloropentyl]-1,3-dimethyl-4,5-diphenylimidazolidine (31) (Scheme 11):

To a solution of 1-iodo-4-chlorobutane (400 mg, 1.86 mmol) in Et_2O (7 mL) and pentane (10 mL) was added, at −78 °C, a solution of *t*-BuLi in pentane (1.6 M, 1.16 mL, 1.86 mmol). After 30 min at −78 °C, Et_2O (20 mL) was added, followed by an ethereal solution (10 mL) of the imidazolidine **13** (200 mg, 0.62 mmol). The mixture was stirred for 2 h at −35 °C, then hydrolyzed and worked up as above to afford 237 mg (yield 92 %) of purified **31** (chromatography on basic alumina). Oil, $[\alpha]_D^{20}$ −32 (c = 0.036, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.26–7.15 (m, 10 H), 4.07 (d, J = 8.7 Hz, 1 H), 3.89 (d, J = 2.5 Hz, 1 H), 3.67 (d, J = 8.7 Hz, 1 H), 3.61 (t, J = 6.6 Hz, 2 H), 3.05 (m, 1 H), 2.46 (s, 6 H), 2.39 (s, 3 H), 2.28 (s, 3 H), 2.40–1.50 (m, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.7, 139.0, 129.3, 127.3, 86.1, 77.0, 75.2, 60.5, 48.6, 45.2, 41.1, 36.1, 33.2, 29.7, 24.6.

IR: ν = 3055, 3020, 2940, 2840, 2795, 1450 cm^{-1}.

(4*S*,5*S*)-2-[(2*S*)-1-Dimethylamino-2-piperidyl]-1,3-dimethyl-4,5-diphenylimidazolidine (32):

To a solution of the above hydrazine **31** in anhydr. DMF (10 mL) was added NaH (2.9 mmol, 115 mg, 60 % in mineral oil). The mixture was stirred under nitrogen and heated to 70 °C for 2 h, whereupon all of the starting material disappeared. After cooling to r.t., sat. aq NH_4Cl (40 mL) and Et_2O (50 mL) were added. Usual work up gave an oil which was purified by column chromatography (silica gel; cyclohexane/EtOAc, 70:30). The first fraction (180 mg, 60 % yield) was the title compound. $[\alpha]_D^{20}$ −45 (c = 0.02, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.23–7.13 (m, 10 H), 4.60 (d, J = 1.4 Hz, 1 H), 3.97 (d, J = 8.6 Hz, 1 H), 3.60 (d, J = 8.6 Hz, 1 H), 3.10–3.0 (m, 1 H), 2.38 (s, 3 H), 2.34 (s, 6 H), 2.30 (s, 3 H), 2.20–0.80 (m, 8 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.7, 139.1, 129.4, 127.2, 82.3, 75.5, 64.9, 43.5, 40.0, 35.9, 29.8, 26.7, 26.3, 25.4, 18.9.

IR: ν = 3055, 3020, 2940, 2840, 2795, 1450 cm^{-1}.

(4*S*,5*S*)-2-[(*S*)-1-(*N*,*N*-Dimethylhydrazino)pent-4-enyl]-1,3-dimethyl-4,5-diphenylimidazolidine (33):

Isolated from the second fraction from the preceding reaction. $[\alpha]_D^{20}$ −56 (c = 0.011, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.31–7.15 (m, 10 H), 6.02–5.82 (m, 1 H), 5.15–4.98 (m, 1 H), 4.05 (d, J = 8.7 Hz, 1 H), 3.90 (d, J = 2.4 Hz, 1 H), 3.63 (d, J = 8.7 Hz, 1 H), 3.04 (m, 1 H), 2.46 (s, 6 H), 2.39 (s, 3 H), 2.29 (s, 3 H), 2.40–1.60 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.6, 139.08, 139.07, 129.1, 127.1, 114.6, 85.7, 77.6, 75.1, 59.8, 48.5, 40.7, 35.9, 31.5, 29.4.

IR: ν = 3055, 3020, 2940, 2840, 2795, 1450 cm^{-1}.

Addition of RMgX (Table 3); General Procedure:

To a solution of imidazolidine **13** (100 mg, 0.31 mmol) in toluene (50 mL) was added, at r.t. (−50 °C for allyl and crotyl), the Grignard solution (in Et_2O, 0.93 mmol). The mixture was stirred for 1–2 h, then hydrolyzed by addition of sat. aq NH_4Cl (20 mL). The organic phase was washed with sat. aq NH_4Cl, and the aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic phase was dried (K_2CO_3), then concentrated in vacuo. The residue was purified by chromatography (basic alumina; cyclohexane/EtOAc, 90–95:10–5).

(4S,5S)-2-[(R)-1-(N,N-Dimethylhydrazino)ethyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(16b)** *(R = Me):*

Yield 83 %, oil, $[\alpha]_D^{20}$ −15 (c = 0.057, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.30–7.10 (m, 10 H), 3.95 (d, J = 8.9 Hz, 1 H), 3.84 (d, J = 3.3 Hz, 1 H), 3.70 (d, J = 8.9 Hz, 1 H), 3.32–3.17 (m, 1 H), 2.51 (s, 6 H), 2.50 (s, 3 H), 2.27 (s, 3 H), 1.30 (d, J = 6.5 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.5, 138.6, 129.0, 125.3, 86.8, 77.6, 75.2, 57.8, 48.1, 41.3, 35.7, 16.5.

IR: ν = 3055, 3020, 2940, 2840, 2795, 1450, 1355 cm^{-1}.

(4S,5S)-2-[(R)-1-(N,N-Dimethylhydrazino)butyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(21b)** *(R = Pr):*

Yield 89 %, oil, $[\alpha]_D^{20}$ −10 (c = 0.02, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.27–7.14 (m, 10 H), 3.93 (d, J = 8.8 Hz, 1 H), 3.91 (d, 1 H), 3.59 (d, J = 8.8 Hz, 1 H), 3.03 (m, 1 H), 2.49 (s, 6 H), 2.44 (s, 3 H), 2.24 (s, 3 H), 1.70–1.0 (m, 7 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.3, 129.0, 128.0, 127.97, 127.8, 127.3, 127.1, 85.6, 77.2, 75.6, 60.1, 47.9, 40.6, 35.5, 32.7, 20.1, 14.62.

IR: ν = 3055, 3020, 2940, 2840, 2795, 1450, 1355 cm^{-1}.

(4S,5S)-2-[(R)-1-(N,N-Dimethylhydrazino)pentyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(22b)** *(R = Bu):*

Yield 94 %, oil, $[\alpha]_D^{20}$ +4.5 (c = 0.08, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.30–7.10 (m, 10 H), 3.95 (d, J = 2.1 Hz, 1 H), 3.93 (d, J = 8.7 Hz, 1 H), 3.61 (d, J = 8.7 Hz, 1 H), 3.01 (td, J = 6.1, 2.1 Hz, 1 H), 2.49 (s, 6 H), 2.44 (s, 3 H), 2.24 (s, 3 H), 1.73–1.65 (m, 2 H), 1.50–1.30 (m, 4 H), 0.97 (t, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.5, 139.1, 130.0, 129.0, 128.0, 127.6, 127.4, 127.1, 85.4, 77.0, 75.6, 60.4, 47.9, 40.7, 35.7, 30.3, 29.7, 23.3, 14.2.

IR: ν = 3055, 3020, 2940, 2840, 2795, 1450, 1355 cm^{-1}.

(4S,5S)-2-[(R)-1-(N,N-Dimethylhydrazino)-3-methylbutyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(23b)** *(R = i-Bu):*

Yield 92 %, oil, $[\alpha]_D^{20}$ +13 (c = 0.15, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.3–7.1 (m, 10 H), 4.01 (d, J = 1.1 Hz, 1 H), 3.89 (d, J = 8.5 Hz, 1 H), 3.54 (d, J = 8.5 Hz, 1 H), 3.17 (m, 1 H), 2.48 (s, 6 H), 2.45 (s, 3 H), 2.26 (s, 3 H), 1.85–1.40 (m, 3 H), 1.01 (d, J = 6.4 Hz, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 141.4, 140.2, 129.6–127.9, 85.9, 78.5, 76.5, 58.3, 48.7, 41.6, 40.6, 35.9, 26.2, 24.9, 23.4.

(4S,5S)-2-[(R)-(N,N-Dimethylhydrazino)(cyclohexyl)methyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(28b)** *(R = cyclohexyl):*

Yield 91 %, oil, $[\alpha]_D^{20}$ −63 (c = 0.14, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.34–7.11 (m, 10 H), 4.07 (d, J = 8.6 Hz, 1 H), 3.76 (d, J = 2.0 Hz, 1 H), 3.67 (d, J = 8.6 Hz, 1 H), 2.71 (m, 1 H), 2.50 (s, 6 H), 2.39 (s, 3 H), 2.18 (s, 3 H), 1.92–1.0 (m, 11 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.7, 139.1, 129.3, 128.2, 128.1, 127.8, 127.7, 127.4, 127.2, 86.5, 76.6, 75.3, 64.3, 47.8, 40.1, 39.8, 36.6, 32.3, 30.3, 29.7, 27.1, 27.0.

IR: ν = 3055, 3020, 2940, 2840, 2795, 1450 cm^{-1}.

(4S,5S)-2-[(R)-1-(N,N-Dimethylhydrazino)-2,2-dimethylpropyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(25b)** *(R = t-Bu):*

Yield 67 %, oil, $[\alpha]_D^{20}$ −68 (c = 0.04, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.36–7.17 (m, 10 H), 4.17 (d, J = 8.9 Hz, 1 H), 3.66 (d, J = 8.9 Hz, 1 H), 3.55 (s, 1 H), 2.70 (d, 1 H), 2.61 (s, 6 H), 2.33 (s, 3 H), 2.07 (s, 3 H), 1.05 (s, 9 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 130.0, 128.2, 128.0, 127.7, 127.4, 127.2, 87.3, 76.0, 74.1, 68.4, 48.3, 38.7, 37.6, 34.9, 29.0.

(4S,5S)-2-[(R)-α-(N,N-Dimethylhydrazino)benzyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(26b)** *(R = Ph):*

Yield 82 %, oil, $[\alpha]_D^{20}$ −85 (c = 0.1, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.65–7.05 (m, 15 H), 4.29 (d, J = 3.8 Hz, 1 H), 4.01 (d, J = 8.9 Hz, 1 H), 3.98 (d, J = 3.8 Hz, 1 H), 3.77 (d, J = 8.9 Hz, 1 H), 3.10 (s, 1 H), 2.58 (s, 6 H), 2.32 (s, 3 H), 2.09 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 142.0, 140.4, 138.1, 130.0–126.6, 90.1, 75.1, 74.8, 65.1, 48.0, 40.0, 37.0.

IR: ν = 3055, 3020, 2940, 2840, 2795, 1450, 1355 cm^{-1}.

Special Procedure with $TiCl_4$:

To a solution of imidazolidine **13** in dry CH_2Cl_2 was added, at −70 °C, $TiCl_4$ (0.12 mL, 1.1 mmol). The solution turned orange. After 5 min, the allyl or crotyl Grignard solution (in Et_2O; 3 mmol)

was added. When no starting material was left (30 min), the reaction was quenched by addition of Et_3N (3 mL) and MeOH (5 mL), the temperature was raised to 0 °C and the solution was hydrolyzed with sat. aq NH_4F (40 mL). The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 40 mL). The combined organic phases were dried (K_2CO_3) and the solvents removed in vacuo. The residue was purified by column chromatography (basic alumina).

(4S,5S)-2-[(R)-1-(N,N-Dimethylhydrazino)but-3-enyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(29b)** *(R = Allyl):*

Yield 78% (entry 25, Table 3), oil, $[\alpha]_D^{20}$ +16 (*c* = 0.047, $CHCl_3$). The signals corresponding to the minor isomer are given in italics.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.28–7.11 (m, 10 H), 6.04–5.83 (m, 1 H), 5.26–5.10 (m, 2 H), 4.03 (*3.98*) (d, *J* = 2.0 Hz, 1 H), 3.91 (*4.08*) (d, *J* = 8.6 Hz, 1 H), 3.59 (*3.69*) (d, 1 H), 3.11 (m, 1 H), 2.50 (*2.41*) (s, 3 H), 2.45 (s, 6 H), 2.44 (m, 2 H), 2.26 (*2.31*) (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.4, 139.0, (*141.6, 138.5*), 136.8 (*137.1*), 129.2–127.1, 117.2 (*117.1*), 84.6 (*85.4*), 77.6, 75.4 (*77.3, 74.9*), 59.2 (*59.8*), 47.7 (*48.2*), 41.0, 34.6 (*40.6, 34.1*), 35.2 (*36.3*).

(4S,5S)-2-[(R)-1-(N,N-Dimethylhydrazino)pent-3-enyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(30b)** *(R = crotyl):*

Yield 87% (entry 27, Table 3), oil, a large fraction of pure major diastereomer could be isolated. $[\alpha]_D^{20}$ −94 (*c* = 0.019, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.31–7.11 (m, 10 H), 6.05–5.88 (m, 1 H), 5.12–5.0 (m, 2 H), 4.11 (d, *J* = 8.8 Hz, 1 H), 3.73 (d, 1 H), 3.71 (d, *J* = 2.6 Hz, 1 H), 2.86 (dd, *J* = 2.6, 6.5 Hz, 1 H), 2.68 (m, 1 H), 2.51 (s, 6 H), 2.39 (s, 3 H), 2.18 (s, 3 H), 1.28 (d, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 144.1, 140.6, 138.2, 129.5, 128.1, 128.0, 127.7, 127.6, 127.4, 127.2, 113.5, 86.8, 75.7, 74.8, 63.4, 47.7, 40.4, 39.8, 37.2, 16.9.

IR: ν = 3055, 3020, 2940, 2840, 2795, 1450, 1355 cm^{-1}.

Cleavage of the N–N Bond of Hydrazines; General Procedure:

In a flat flask, such as an Erlenmeyer, were placed the hydrazine derivative to be cleaved (2 mmol), MeOH or *i*-PrOH (10 mL), and recently bought W-2 Raney nickel (two small spatulas; commercial grade from Aldrich or Fluka). The flask was flushed with hydrogen and then maintained under hydrogen atmosphere. This flask was immersed in an ultrasound cleaning bath filled with water, and sonicated until disappearance of the starting material. The content of the flask was then filtered through Celite under nitrogen, the Raney nickel was washed three times with MeOH or *i*-PrOH, and the solvents were removed with a rotatory evaporator. The residue was dissolved in Et_2O (50 mL), dried (Na_2CO_3), and concentrated in vacuo. The crude product may be quickly purified by column chromatography (silica gel; cyclohexane/EtOAc, 70:30, containing 1% NEt_3, or more conveniently on alumina). Most often the crude product is directly protected as a Boc derivative.

(4S,5S)-2-[(S)-1-Aminoethyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(16aH)** *(R = Me):*

Yield 74%, oil, $[\alpha]_D^{20}$ +23 (*c* = 0.02, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.1 (m, 10 H), 4.02 (d, *J* = 8.7 Hz, 1 H), 3.78 (d, *J* = 1.9 Hz, 1 H), 3.64 (d, *J* = 8.7 Hz, 1 H), 3.34 (dq, *J* = 6.8, 1.9 Hz, 1 H), 2.5 (s, 3 H), 2.3 (s, 3 H), 1.25 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.9, 140.1, 128.8, 128.3, 127.8, 127.7, 127.4, 88.5, 78.7, 75.5, 49.8, 43.1, 34.0, 22.2.

IR: ν = 3500–3200, 3020, 2950, 2850, 1600, 1500, 1450, 750, 700 cm^{-1}.

(4S,5S)-2-[(S)-1-Aminobutyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(21aH)** *(R = Pr):*

Yield 75%, oil, $[\alpha]_D^{20}$ +11 (*c* = 0.014, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.40–7.11 (m, 10 H), 4.01 (d, *J* = 8.7 Hz, 1 H), 3.83 (d, *J* = 1.5 Hz, 1 H), 3.61 (d, *J* = 8.7 Hz, 1 H), 3.0 (m, 1 H), 2.43 (s, 3 H), 2.26 (s, 3 H), 1.92–0.89 (m, 7 H).

(4S,5S)-2-[(S)-1-Aminopentyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(22aH)** *(R = Bu):*

Yield 60%, oil, $[\alpha]_D^{20}$ −4 (*c* = 0.04, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.4–7.1 (m, 10 H), 4.0 (d, *J* = 8.8 Hz, 1 H), 3.89 (d, *J* = 1.7 Hz, 1 H), 3.62 (d, *J* = 8.8 Hz, 1 H), 3.05 (m, 1 H), 2.45 (s, 3 H), 2.28 (s, 3 H), 1.78–1.3 (m, 6 H), 0.98 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.1, 139.6, 128.8, 128.6, 128.1, 127.7, 127.4, 127.3, 87.2, 78.7, 70.3, 54.4, 42.6, 36.1, 33.6, 29.5, 23.0, 14.1

IR: ν = 3500–3200, 3020, 2950, 2850, 1600, 1500, 1450 cm^{-1}.

(4S,5S)-2-[(S)-1-Amino-3-methylbutyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(23aH)** *(R = i-Bu):*

Yield 85%, oil, $[\alpha]_D^{20}$ −13 (*c* = 0.03, CH_2Cl_2).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.3–7.1 (m, 10 H), 4.05 (d, *J* = 8.7 Hz, 1 H), 3.85 (d, *J* = 1.74, 1 H), 3.62 (d, *J* = 8.7 Hz, 1 H), 3.18 (dt, *J* = 1.7, 6.9 Hz, 1 H), 2.45 (s, 3 H), 2.32 (s, 3 H), 1.85 (m, *J* = 6.6 Hz, 1 H), 1.4 (m, 2 H), 1.03 (d, *J* = 6.6 Hz, 3 H), 0.96 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.05, 140.0, 128.7, 128.3, 127.9, 127.6, 127.4, 87.7, 78.9, 75.6, 52.0, 45.8 42.7, 33.8, 25.2, 24.0, 22.2.

IR: ν = 3500–3200, 3060, 3020, 2930, 2920, 2845, 2790 cm^{-1}.

(4S,5S)-2-[(S)-1-Amino-2,2-dimethylpropyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(25aH)** *(R = t-Bu):*

Yield 66%, oil, $[\alpha]_D^{20}$ +8 (*c* = 0.14, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.26–7.20 (m, 10 H), 4.2 (d, *J* = 8.8 Hz, 1 H), 4.11 (s, 1 H), 3.83 (d, *J* = 8.8 Hz, 1 H), 3.20 (s, 3 H), 2.79 (s, 1 H), 2.58 (s, 3 H), 1.06 (s, 9 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.9, 139.6, 129.7, 129.1, 128.9, 128.4, 128.2, 127.6, 85.4, 78.2, 74.5, 60.9, 43.7, 34.8, 34.5, 27.7.

(4S,5S)-2-[(S)-α-Aminobenzyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(26aH)** *(R = Ph):*

Yield 70%, oil, $[\alpha]_D^{20}$ +63 (*c* = 0.17, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.5–7.1 (m, 15 H), 4.39 (s, 1 H), 4.18 (s, 1 H), 4.07 (d, *J* = 9.4 Hz, 1 H), 3.55 (d, *J* = 9.4 Hz, 1 H), 2.4 (s, 3 H), 1.84 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 144.7, 139.7, 139.5, 128.5, 128.2, 128.12, 128.08, 127.6, 127.5, 127.2, 126.7, 126.5, 88.7, 78.5, 75.1, 57.3, 42.1, 33.5.

(4S,5S)-2-[(R)-1-Aminoethyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(16bH)** *(R = Me):*

Yield 57%, oil, de = 88%.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.40–7.10 (m, 10 H), 4.02 (d, *J* = 8.7 Hz, 1 H), 3.75 (d, *J* = 8.7 Hz, 1 H), 3.54 (d, 1 H), 3.17 (m, 1 H), 2.42 (s, 3 H), 2.23 (s, 3 H), 1.29 (d, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.0, 137.5, 129.6, 127.2, 90.8, 75.2, 75.0, 54.3, 40.1, 37.2, 35.9.

IR: ν = 3500–3200, 3020, 2940, 2850, 1600, 1500, 1450 cm^{-1}.

(4S,5S)-2-[(R)-1-Aminobutyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(21bH)** *(R = Pr):*

Yield 76%, oil, $[\alpha]_D^{20}$ −18 (*c* = 0.014, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.31–7.13 (m, 10 H), 4.08 (d, *J* = 9.3 Hz, 1 H), 3.76 (d, *J* = 9.3 Hz, 1 H), 3.50 (d, *J* = 2.7 Hz, 1 H), 2.96 (m, 1 H), 2.39 (s, 3 H), 2.22 (s, 3 H), 1.90–0.95 (m, 7 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.2, 137.7, 129.4, 128.2, 128.1, 128.0, 127.7, 127.5, 127.2, 91.0, 75.3, 75.1, 54.4, 40.5, 37.3, 36.1, 20.3, 14.3.

IR: ν = 3500–3200, 3020, 2940, 2850, 1600, 1500, 1450 cm^{-1}.

(4S,5S)-2-[(R)-1-Aminopentyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(22bH)** *(R = Bu):*

Yield 62%, oil, $[\alpha]_D^{20}$ −13 (*c* = 0.02, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.30–7.10 (m, 10 H), 4.08 (d, *J* = 8.5 Hz, 1 H), 3.78 (d, 1 H), 3.55 (d, *J* = 1.5 Hz, 1 H), 2.96 (m, 1 H), 2.40 (s, 3 H), 2.23 (s, 3 H), 2.80–0.90 (m, 9 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.1, 137.4, 129.5, 127.3, 91.0, 75.3, 74.9, 55.0, 40.9, 37.4, 36.1, 21.0, 14.9, 14.1.

IR: ν = 3500–3200, 3020, 2940, 2850, 1600, 1500, 1450, 750, 700 cm^{-1}.

(4S,5S)-2-[(R)-1-Amino-3-methylbutyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(23bH)** *(R = i-Bu):*

Yield 86%, oil, $[\alpha]_D^{20}$ −20 (c = 0.025, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.3–7.05 (m, 10H), 4.08 (d, J = 9.4 Hz, 1H), 3.77 (d, J = 9.4 Hz, 1H), 3.47 (d, J = 2.4 Hz, 1H), 3.04 (m, 1H), 2.38 (s, 3H), 2.20 (s, 3H), 1.88 (m, 1H), 1.40 (m, 2H), 0.97 (d, J = 6 Hz, 3H), 0.96 (d, J = 6 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.3, 137.7, 129.5, 128.2, 128.1, 127.8, 127.6, 127.3, 91.5, 77.7, 75.2, 52.5, 43.3, 40.6, 37.5, 25.4, 24.1, 21.9.

(4S,5S)-2-[(R)-(Amino)(cyclohexyl)methyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(28bH)** *(R = cyclohexyl):*

Yield 85%, oil, $[\alpha]_D^{20}$ −13 (c = 0.035, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.1 (m, 10H), 4.12 (d, J = 9.4 Hz, 1H), 3.81 (d, J = 9.4 Hz, 1H), 3.62 (d, J = 3.2 Hz, 1H), 2.70 (m, 1H), 2.35 (s, 3H), 2.28 (s, 3H), 1.90–0.82 (m, 10H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.2, 137.5, 129.5, 129.0, 128.3, 128.1, 128.0, 127.8, 127.5, 127.3, 88.2, 75.3, 74.3, 43.5, 39.6, 38.5, 31.1, 30.2, 26.7, 26.5.

Boc Protection:

To a solution of α-aminoimidazolidine (1 mmol) in Et_2O (20 mL) were added, at r.t., di-*tert*-butyl carbonate (1.5 mmol) and 4-dimethylaminopyridine (1.5 mmol). The mixture was stirred until disappearance of the starting material (1–5 h), then hydrolyzed with aq NH_4Cl (50 mL). The aqueous phase was extracted with Et_2O (2 × 50 mL) and the organic phase dried (K_2CO_3). The salts were filtered off and the solvents evaporated in vacuo. The residue was purified by column chromatography (basic alumina).

(4S,5S)-2-[(S)-1-(1,2-Dimethylethoxycarbonylamino)ethyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(16aBoc)** *(R = Me):*

Yield 73%, oil, $[\alpha]_D^{20}$ −81 (c = 0.068, CH_2Cl_2).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.1–7.35 (m, 10H), 5.48 (d, J = 9.5 Hz, 1H), 4.16 (dq, J = 6.9, 9.5 Hz, 1H), 3.90 (d, J = 8.9 Hz, 1H), 3.59 (d, J = 8.9 Hz, 1H), 2.5 (s, 3H), 2.25 (s, 3H), 1.5 (s, 9H), 1.29 (d, J = 6.9 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 154.9, 139.6, 128.5, 128.4, 128.0, 127.8, 127.7, 87.0, 79.2, 75.0, 47.8, 42.7, 33.4, 28.8, 19.6.

IR: ν = 3420, 3050, 3020, 2965, 2840, 2795, 1710, 1600, 1490, 1445, 1360 cm^{-1}.

(4S,5S)-2-[(R)-1-(1,1-Dimethylethoxycarbonylamino)ethyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(16bBoc)** *(R = Me):*

Yield 72%, oil, $[\alpha]_D^{20}$ +22 (c = 0.051, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.28–7.12 (m, 10H), 4.11 (m, 1H), 3.87 (d, J = 8.7 Hz, 1H), 3.61 (d, J = 8.7 Hz, 1H), 3.61 (d, J = 8.7 Hz, 1H), 2.49 (s, 3H), 2.24 (s, 3H), 1.49 (s, 9H), 1.31 (d, 3H).

IR: ν = 3500–3300, 2960, 1700, 1600, 1500, 1450, 1360, 1170 cm^{-1}.

(4S,5S)-2-[(S)-1-(1,1-Dimethylethoxycarbonylamino)butyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(21aBoc)** *(R = Pr):*

Yield 85%, oil, $[\alpha]_D^{20}$ −23 (c = 0.023, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.11 (m, 10H), 4.02 (d, 1H), 3.98 (t, 1H), 3.93 (d, J = 8.9 Hz, 1H), 3.60 (d, J = 8.9 Hz, 1H), 2.49 (s, 3H), 2.27 (s, 3H), 1.51 (s, 9H), 1.58–0.91 (m, 7H).

IR: ν = 3500–3300, 2960, 1700, 1600, 1500, 1450, 1360, 1170 cm^{-1}.

(4S,5S)-2-[(R)-1-(1,1-Dimethylethoxycarbonylamino)butyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(21bBoc)** *(R = Pr):*

Yield 78%, oil, $[\alpha]_D^{20}$ +32 (c = 0.045, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.27–7.14 (m, 10H), 3.95 (m, 1H), 3.92 (d, J = 8.6 Hz, 1H), 3.61 (d, J = 8.6 Hz, 1H), 2.40 (s, 3H), 2.22 (s, 3H), 1.49 (s, 9H), 1.80–0.90 (m, 7H).

IR: ν = 3500–3300, 2960, 1700, 1600, 1500, 1450, 1360, 1170 cm^{-1}.

(4S,5S)-2-[(R)-1-(1,1-Dimethylethoxycarbonylamino)-3-methylbutyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(23bBoc)** *(R = i-Bu):*

Yield 74%, oil, $[\alpha]_D^{20}$ +48 (c = 0.008, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.11 (m, 10H), 4.75 (d, J = 10 Hz, 1H), 4.04 (m, 1H), 3.9 (d, J = 8.6 Hz, 1H), 3.83 (d, J = 2 Hz, 1H), 3.6 (d, J = 8.6 Hz, 1H), 2.38 (s, 3H), 2.21 (s, 3H), 1.9–1.2 (m, including s at δ = 1.47, 12H), 1.00 (d, J = 6.4 Hz, 3H), 0.96 (d, J = 6.4 Hz, 3H).

(4S,5S)-2-[(R)-(1,1-Dimethylethoxycarbonylamino)(cyclohexyl)methyl]-1,3-dimethyl-4,5-diphenylimidazolidine **(28bBoc)** *(R = cyclohexyl):*

Yield 81%, oil, $[\alpha]_D^{20}$ −7 (c = 0.014, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.11 (m, 10H), 5.20 (d, J = 9.4 Hz, 1H), 4.07 (d, J = 8.9 Hz, 1H), 3.78 (d, J = 8.9 Hz, 1H), 3.68 (d, J = 1.6 Hz, 1H), 3.60 (m, 1H), 2.32 (s, 3H), 2.14 (s, 3H), 2.08–1.02 (m, including s at δ = 1.52, 19H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 160.1, 140.5, 137.8, 130.1, 128.7, 128.4, 128.0, 127.5, 88.0, 75.6, 75.1, 56.1, 40.8, 39.2, 38.3, 31.5, 30.3, 28.6, 27.1, 26.7.

(4S,5S)-2-{(S)-1-[N-(1,1-Dimethylethoxycarbonyl)-N',N'-dimethylhydrazino]ethyl}-1,3-dimethyl-4,5-diphenylimidazolidine **(16d)** *(R = Me) (Scheme 15):*

Yield 92%, mp 108°C (Et_2O), $[\alpha]_D^{20}$ −22 (c = 0.04, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.4–7.13 (m, 10H), 4.18 (d, J = 9.3 Hz, 1H), 4.09 (m, 1H), 3.88 (d, J = 9.3 Hz, 1H), 3.78 (d, J = 4.7 Hz, 1H), 2.8 (s, 3H), 2.75 (s, 3H), 2.46 (s, 3H), 2.38 (s, 3H), 1.5 (s, 9H), 1.45 (d, J = 7 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 146.9, 141.1, 138.0, 129.8, 129.2, 128.6, 128.2, 127.9, 127.5, 90.3, 87.8, 80.1. 79.4, 61.8, 45.1, 40.9, 38.4, 29.0, 15.9.

IR: ν = 3060, 3020, 2980, 2940, 2880, 2790, 1690, 1450, 1365 cm^{-1}.

Hydrolysis of the Aminal to the Aldehyde:

To a solution of Boc-aminal (1 mmol) in Et_2O (100 mL) was added 2% aq HCl (50 mL) at r.t. The biphasic system was vigorously stirred for 20–60 min until disappearance of the starting material [an aliquot of the aqueous phase was neutralized ($NaHCO_3$), a few drops of Et_2O were added and the organic phase was spoted on TLC]. The two layers were separated, the aqueous phase was extracted with Et_2O (2 × 50 mL) and the combined organic phase was dried ($MgSO_4$). After removal of the salts by filtration, the solvent was evaporated and the residue quickly purified by flash chromatography (silica gel).

Alternatively, Conia's method[47] may be used. Sat. aq oxalic acid (5 mL) was added dropwise to a stirred suspension of silica gel (5 g) in CH_2Cl_2 (7 mL). After 5 min, a solution of Boc-aminal (1 mmol) in CH_2Cl_2 (0.5 mL) was added, and the suspension stirred for 5–15 h. The mixture was then filtered and the precipitate washed twice with CH_2Cl_2. The filtrate was evaporated and the residue quickly purified by flash chromatography (silica gel).

(2S)-2-(1,1-Dimethylethoxycarbonylamino)propanal **(16c)** *(R = Me):*

From **16aBoc**:

Yield 72%, oil, $[\alpha]_D^{20}$ +31 (c = 0.055, $CHCl_3$).

From **16bBoc**:

Yield 71%, oil, $[\alpha]_D^{20}$ −33 (c = 0.024, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.55 (s, 1H), 4.25 (m, 1H), 1.45 (s, 9H), 1.37 (d, J = 7.4 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 199.9, 155.2, 80.0, 55.8, 28.5, 15.0.

IR: ν = 3350, 2970, 2925, 1740, 1700 cm^{-1}.

(2S)-2-(1,1-Dimethylethoxycarbonylamino)pentanal **(21c)** *(R = Pr):*

From **21aBoc**:

Yield 78%, oil, $[\alpha]_D^{20}$ +29 (c = 0.012, $CHCl_3$).

From **21bBoc**:

Yield 84%, oil, $[\alpha]_D^{20}$ −31 ($c = 0.01$, $CHCl_3$).

^1H NMR (200 MHz, $CDCl_3$): $\delta = 9.58$ (s, 1H), 4.26 (m, 1H), 1.43 (s, 9H), 2.0–0.90 (m, 7H).

^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 201.2$, 156.5, 81.0, 60.8, 32.4, 30.7, 19.5, 15.0.

IR: $\nu = 3350$, 2970, 2925, 1740, 1700 cm^{-1}.

(2R)-2-(1,1-Dimethylethoxycarbonylamino)-4-methylpentanal **(23c)** *(R = i-Bu):*

From **23bBoc**. Yield 67%, oil, $[\alpha]_D^{20}$ −3 ($c = 0.016$, $CHCl_3$).

^1H NMR (200 MHz, $CDCl_3$): $\delta = 9.61$ (s, 1H), 4.93 (m, 1H), 4.27 (m, 1H), 1.83–1.33 (m, including s at $\delta = 1.49$, 12H), 1.0 (d, $J = 6.6$ Hz).

(2R)-2-(1,1-Dimethylethoxycarbonylamino)-2-cyclohexylethanal **(28c)** *(R = cyclohexyl):*

From **28bBoc**. Yield 71%, oil, $[\alpha]_D^{20}$ −27 ($c = 0.008$, $CHCl_3$).

^1H NMR (200 MHz, $CDCl_3$): $\delta = 9.72$ (s, 1H), 5.15 (m, 1H), 4.28 (m, 1H), 2.05–0.75 (m, including s at $\delta = 1.49$, 20H).

(2S)-2-[N-(1,1-Dimethylethoxycarbonyl)-N',N'-dimethylhydrazino]-propanal **(16e)**:

From **16d**. Yield 65%, oil, $[\alpha]_D^{20}$ +66 ($c = 0.056$, $CHCl_3$).

^1H NMR (200 MHz, $CDCl_3$): $\delta = 9.61$ (s, 1H), 4.3 (m, 1H), 2.74 (s, 6H), 1.6 (s, 9H), 1.35 (d, $J = 6$ Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 199.5$, 166.2, 81.3, 64.2, 45.3, 28.5, 12.6.

IR: $\nu = 2981$, 2940, 2880, 1740, 1710, 1695 cm^{-1}.

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