

**Diastereoselective Addition of Methylcopper- and Dimethylcuprate-
Boron Trifluoride Reagents to (S)-(N-Alkylidene)-1-Phenylethylamines**

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Abstract The reactions of methylcopper- and dimethylcuprate-boron trifluoride reagents with aldimines derived from (S)-1-phenylethylamine afford with good diastereoselectivity (S,S)-amines from aromatic imines, but the (R,S)-amine from an aliphatic imine

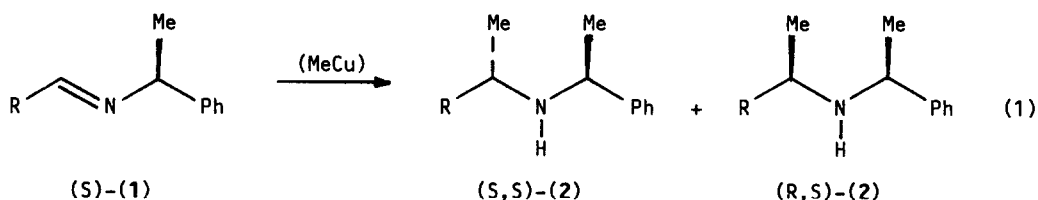
The diastereoselective synthesis of secondary amines by the addition of organometallic reagents to aldimines carrying the stereogenic centre on the nitrogen substituent has been scarcely reported. Benzylic and allylic organometallic compounds successfully react with imines derived from (S)- and (R)-1-phenylethylamine.¹ Similarly, benzylmagnesium chloride and phenyllithium afford only one diastereoisomer upon addition to imines prepared from aromatic aldehydes and homochiral 2-aminoalkanols.² However the reactions of Grignard and organolithium reagents with imines are generally plagued by the poor electrophilicity of the imine, the competing metalation reaction, and the unsatisfactory diastereoselectivity.

Looking for a general method of diastereoselective organometallic addition to homochiral aldimines, we have checked the possibility of using organocopper compounds complexed with boron trifluoride.³

Preliminary experiments were performed on the imines (S)-(1 a-d) using the methylcopper and dimethylcuprate reagents prepared from both methyllithium and methylmagnesium chloride (equation (1) and Table 1).⁴

The analysis of the results obtained allows recognition of the following trends: 1) the copper(I) reagents are more reactive and more selective on respect to the cuprate

reagents (compare entries 1-2, 3-4 and 5-6); 2) the copper reagents prepared from methylmagnesium chloride are more reactive and at the same time only slightly less selective than the analogous reagents prepared from methyllithium, a satisfactory balance between reactivity and selectivity being offered by $\text{MeCu-BF}_3\text{-MgJCl}$ (entry 4); 3) an aliphatic imine such as (1 c) successfully reacts (entry 7), although a lower diastereoselectivity is observed; 4) steric hindrance can inhibit the reactivity of the imine, as shown by the *t*-butyl substituted imine (1 d) (entry 8); 5) the configuration of the newly formed stereogenic center in (2) appears to be dependent on the nature of the R group in the imine: the (S,S) diastereoisomers (2 a,b) are prevalently produced from the aryl-substituted imines (S)-(1 a,b), but the (R,S) diastereoisomer (2 c) is formed from the aliphatic imine (S)-(1 c).



- a: R = Ph
 b: R = *o*-(MeO) C_6H_4
 c: R = *n*- C_5H_{11}
 d: R = *t*-Bu

The configuration of the prevalent diastereoisomers of (2 a,b) was assessed by comparing the optical activities of the pure compounds (isolated by flash-chromatography) with the values reported in the literature for the (S,S)-(-) diastereoisomers.⁵ On the other hand, since (2 c) was previously unknown, the major (-) diastereoisomer, also isolated by flash-chromatography, was submitted to reductive cleavage of the benzylic group, so affording optically active (R)-(-)-2-aminoheptane.⁶

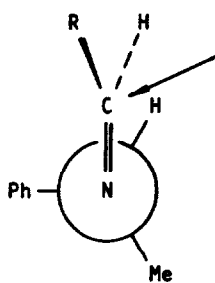
The observed sense of asymmetric induction in this organocopper addition to the aliphatic imine (S)-(1 c) can be explained making use of the conformational model (A) proposed by Yamamoto for the addition of benzylzinc bromide on a chiral imino ester,^{1 b} The model (B), which has been instead proposed to rationalize the asymmetric induction observed in the reaction of allylic organometallic reagents with chiral imines through a cyclic transition state,^{1 a,b} can apparently be used to explain also the preferred formation of (S,S)-(2 a,b) from the aromatic imines (S)-(1 a,b), although we can not

Table 1. Diastereoselective addition of methylcopper- and dimethylcuprate-boron trifluoride reagents to aldimines.^a

Entry	(MeCu) (equivalents)	Imine (Conversion) ^b	Diastereoselectivity (S,S)-(2)·(R,S)-(2) ^b
1	Me ₂ CuLi-BF ₃ -LiJ (5)	(1a) (47 %)	93:7
2	MeCu-BF ₃ -LiJ (2)	" (43 %)	94:6
3	Me ₂ CuMgCl-BF ₃ -MgJCl (2)	" (70 %)	86:14
4	MeCu-BF ₃ -MgCl (2)	" (87 %)	90:10
5	" "	(1b) (80 %)	73:27
6	Me ₂ CuMgCl-BF ₃ -MgJCl (2)	" (70 %)	70:30
7	" (5)	(1c) (80 %)	15:85
8	" (2)	(1d) (0 %)	-

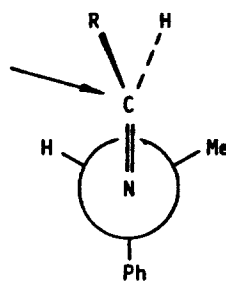
^a The optimized experimental procedure requires the imine to be added to the copper reagent in anhydrous tetrahydrofuran at -78 °C under an argon atmosphere, and the temperature to be allowed to reach -20 °C before quenching with water.

^b Determined by GC-MS analysis.



(A)

(chirality produced: R)



(B)

(chirality produced: S)

actually speculate on the origin of the observed different behaviour of aliphatic and aromatic imines. Work is in progress in order to confirm these results on other aliphatic and aromatic imines, as well as to determine the diastereoselectivity in reactions performed by varying the organocopper reagent and the chiral auxiliaries on the nitrogen atom.

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Notes and References

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- (4) In the absence of boron trifluoride both the copper reagents $\text{Me}_2\text{CuMgCl-BF}_3\text{-MgJCl}$ and $\text{MeCu-BF}_3\text{-MgJCl}$ were unreactive towards (1 a). Methylmagnesium chloride was almost unreactive. On the other hand, upon addition of (1 a) to methyllithium (2 equivalents) in ether at -30°C and allowing the temperature to reach 0°C the amine (2 a) was obtained in 88 % yield as a 70/30 mixture of the (S,S) and (R,S) isomers.
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