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Enantioselective addition of aryllithium reagents to aromatic imines mediated by 1,2-diamine ligands

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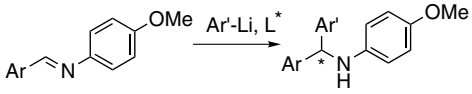
Abstract—A variety of optically enriched amines have been obtained by addition of aryllithium reagents to aromatic imines using *N*,*N*′-tetramethylcyclohexane-1,2-diamine as chiral ligands. Enantiomeric excesses up to 90% could be obtained.

The synthesis of optically enriched amines is an important topic of modern organic chemistry because of their crucial role as chiral auxiliaries, ligands, agents for kinetic resolution and so on.[1] A versatile route for their preparation is the asymmetric addition of organometallic compounds to the azomethine bond of activated imines. Particularly, the addition of dialkylzinc reagents to arylimines promoted by different chiral ligands has been developed by several authors affording arylalkylamines in excellent yields and enantioselectivities.[2] Concerning the synthesis of diarylmethylamines and despite their importance as intermediates in the synthesis of compounds which present biological and therapeutical properties[3] only a few papers appeared[4] since the pioneering work of Tomioka in 1990.[5a] Nowadays the asymmetric chemistry involving organolithium compounds and the imino group in presence of an external chiral ligand remains almost unexplored, except for some isolated, and often unsuccessful, examples.[6] A notable exception is the formation of a phenylarylmethylamine with 92% ee with a stoichiometric amount of a chiral aminodiether and the 4-methoxynaphthyl group on nitrogen.[5b]

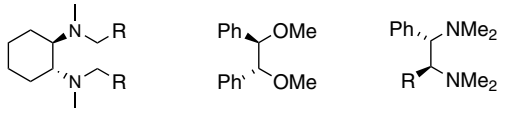


(1)

We wish to present here our first results in the addition of aryllithium reagents to aromatic imines promoted by an external chiral ligand.

In connection with the previous work of our laboratory[7] we tested ligands with a 1,2-diamine structure **1a**–**d** and **2a**,**b** as well as commercially available (−)-sparteine **3** and diether **4**, which gave good enantioselectivities in the addition of PhLi to aliphatic imines (Scheme 1).[8]

To accomplish the synthesis of diarylmethylamines we tested the addition of PhLi to imine **5a** as model substrate (Scheme 2).[9] Two equivalents of the ligand (per imine) were first used, and when the level of enantioselectivity was interesting, a catalytic amount (20%) of ligand was also tested. The reactions were run in toluene solvent, at −78°, the best experimental conditions we had set up previously.[7] We could observe that diamine ligand **1a** gave excellent results, both in stoichiometric



1a: R = H; **1b**: R = $CH_2C(CH_3)_3$ **4** **2a**: R = Me; **2b**: R = Ph
1c: R = Bn; **1d**: R = Et

Scheme 1. Ligands used in this study.

Keywords: Diarylmethylamines; Organolithium; Asymmetry; Diamines; Chiral ligands; Addition to imines.
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5a - 5h **6-15**

5a 2-Thienyl
5b Ph
5c 4-Me-C_6H_4
5d 4-CF_3-C_6H_4
5e 4-MeO-C_6H_4
5f 2,3-(OCH_2O)-C_6H_3
5g 1-Naphth
5h 2-Naphth

6 Ar = 2-Thienyl Ar' = Ph
7 Ar = Ph Ar' = 1-Naphth
8 Ar = 4-Me-C_6H_4 Ar' = Ph
9 Ar = 4-Me-C_6H_4 Ar' = 1-Naphth
10 Ar = 4-CF_3-C_6H_4 Ar' = Ph
11 Ar = 4-MeO-C_6H_4 Ar' = Ph
12 Ar = 3,4-(OCH_2O)-C_6H_3 Ar' = Ph
13 Ar = 3,4-(OCH_2O)-C_6H_3 Ar' = 1-Naphth
14 Ar = 2-Naphth Ar' = Ph
15 Ar = 2-Thienyl Ar' = 1-Naphth

Scheme 2. Imines and products obtained.

Table 1. Addition of PhLi to imine **5a** with various ligands[a]

Entry	Ligand (equiv)	Yield (%)[b]	Ee (%)[c,d]
1	**1a** (2)	69	58 (+)
2	**1a** (0.2)	95	60 (+)
3	**1b** (0.2)	68	3
4	**1c** (0.2)	62	12 (−)
5	**1d** (0.2)	59	7 (+)
6	**2a** (0.2)	82	61 (−)
7	**2b** (0.2)	87	59 (−)
8	**3** (2)	60	44 (−)
9	**3** (0.2)	79	0
10	**4** (2)	62	7 (+)

[a] All reactions were run in toluene, at −78°, for 2 h, with 2 equiv of PhLi and 2 or 0.2 equiv of ligand.
[b] Yields refer to isolated compounds.
[c] Ee's were measured by Supercritical Fluid Chromatography (SFC) with Chiralcel OJ column.
[d] The (+) or (−) signs refer to the optical rotation.

and substoichiometric amounts (compare entries 1 and 2, Table 1). In Et_2O as solvent, the enantioselectivity was similar under stoichiometric conditions, but much lower with 20% ligand (ee 27%). The other two diamines having a *N*,*N*′-tetramethyl substituent, such as **2a** and **2b** gave similar results in catalytic amount (entries 6 and 7). In contrast to our previous findings with alkyllithium reagents, ligands with bulky substituents on the nitrogen atom gave disappointingly low enantioselectivities (entries 3, 4 and 5). The particular behaviour of PhLi, and ArLi in general, is well precedented, and may be due to the aggregation state of aryllithium versus alkyllithium. (−)-Sparteine **3** gave a moderate ee in stoichiometric amount, but a racemic material with 0.2 equiv (entries 8 and 9). Finally, the diether **4** did not seem to be a good ligand for this reaction (entry 10).

One advantage of this procedure, from a practical point of view, is that product **6** is available in both enantiomeric forms. Both enantiomers of diamine **1a** are easily available and very cheap, as well as those of diamine **7a**, starting from either enantiomer of pseudoephedrine. Another way to achieve the same goal is to keep the same ligand and just change the combination of the aryllithium and the imine employed. Thus, the inverse addition of thienyllithium (generated by α-deprotonation of thiophene by *n*-BuLi) to imine **5b** in presence of **1a** afforded the opposite enantiomer of (+)-**6** with a similar degree of enantioselectivity, despite the higher temperature needed to obtain reasonable yields (compare entry 1, Table 1 and entry 1, Table 2).

Having established the optimum conditions for the addition of PhLi, we turned our attention to other imine partners and also other aryllithium reagents (Scheme 2).

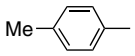
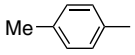
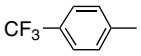
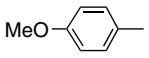
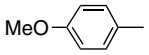
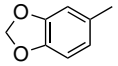
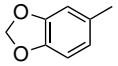
The influence of the imine's substitution partner was evaluated by synthesizing compounds **5a**–**h** by condensation of different aldehydes with *p*-anisidine. The aryllithium reagents tested were 2-thienyllithium, phenyllithium and 1-naphthyllithium. In the case of the least reactive 2-thienyllithium, the reaction had to be run at −20 °C, for 15 h, to afford acceptable yield of amine **6**. Despite such a relatively high temperature, the enantioselectivity remained high with stoichiometric amount of ligand (Table 2, entry 1). The addition of 1-naphthyllithium, generated in situ by metal–halogen exchange with 1-iodonaphthalene and *n*-BuLi, was also slow. The reactions were run at −55 °C with stoichiometric amount of ligand. With 0.2 equiv of ligand **1a**, a slightly lower ee was observed, but the reaction was very slow, and even after 15 h, the yield was very poor. This observation points to a ligand accelerated reaction, but with retention of the ligand to the resulting lithium amide. The addition of phenyllithium was much faster, allowing the reactions to be run at −78 °C. Even more interestingly, the rate of the reaction was not too much affected, allowing the catalytic reactions to be practically useful, without loss of enantioselectivity.

The results shown in Table 2 reflect these trends. All the reactions with phenyllithium gave 60–69% enantioselectivity, whatever the substitution pattern of the aromatic group of the imine. These are the best results so far achieved with a catalytic amount of chiral ligand. The chemical yield and the rate of the reaction were superior when an electron-withdrawing group, such as CF_3–, was present (compare entries 5 with 3, 7 or 8). With both 1- and 2-naphthyl groups on the imine side, the yield was good and the ee remained at the same level (55% and 61%, respectively).

The reactions with 1-naphthyllithium had to be run with stoichiometric amounts of ligand **1a**. However, the enantioselectivities were much higher (entries 2, 4, 9 and 12), reaching 90%, an unprecedented level for such reaction. It should be pointed out that diamine ligand **1a** is not only cheap and easily prepared, but it can also be recovered, in >90% yield, by a simple acid–base treatment.

In conclusion, we have found an excellent chiral ligand **1a** for the addition of aryllithium reagents to aromatic imines. The enantioselectivities are among the best for such an addition and the ligand can be easily recovered. A catalytic use of the ligand is possible with phenyllithium without loss of enantioselectivity. Work is in progress for the determination of the absolute configurations of adducts and for further improvements of the

Table 2. Addition of various Ar′Li to various arylimines, with chiral ligand **1a**[a]

Entry	Imine	Ar′ in Ar′Li	Product	Equiv of **1a**	Time (h)	Yield (%)[b]	Ee (%)[c,d]
1[e]	Ph–	2-Thienyl	**6**	2	2	71	58 (−)
2	Ph–	1-Naphthyl	**7**	2	2	98	90 (−)
3		Ph	**8**	0.2	4	42	63 (−)
4[f]		1-Naphthyl	**9**	2	64	66	88 (−)
5		Ph	**10**	0.2	4	72	60 (+)
6		Ph	**11**	3	4	78	69 (−)
7		Ph	**11**	0.2	3	14	68 (−)
8		Ph	**12**	0.2	4	44	64 (−)
9[g]		1-Naphthyl	**13**	2	67	60	86 (−)
10	1-Naphthyl	Ph	**7**	0.2	4	61	55 (+)
11	2-Naphthyl	Ph	**14**	0.2	2.5	74	61 (+)
12[h]		1-Naphthyl	**15**	2	2	89	88 (−)

[a] Unless otherwise stated, all reactions were conducted with 2 equiv of Ar′Li, in toluene, at −78 °C.
[b] Yields refer to isolated compounds.
[c] Ee's were measured by SFC with Chiralcel OJ column for compounds **6**, **9**, **11** and **13**, Chiralcel OD-H column for compounds **7**, **12**, **14** and **15** and Chiralpak AS-H for compound **10**.
[d] The (+) or (−) signs refer to the optical rotation.
[e] Reaction run at −20 °C.
[f] Reaction run at −55 °C. Not optimized reaction time.
[g] Reaction run at −41 °C. Not optimized reaction time.
[h] Reaction run in Et_2O.

selectivity by screening of other simple diamine ligands. The obtention of the free diarylmethylamines, by removal of the *p*-methoxyphenyl group could be carried out according to a described procedure.[10]

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