Asymmetric Addition of Organolithium Reagents to Imines

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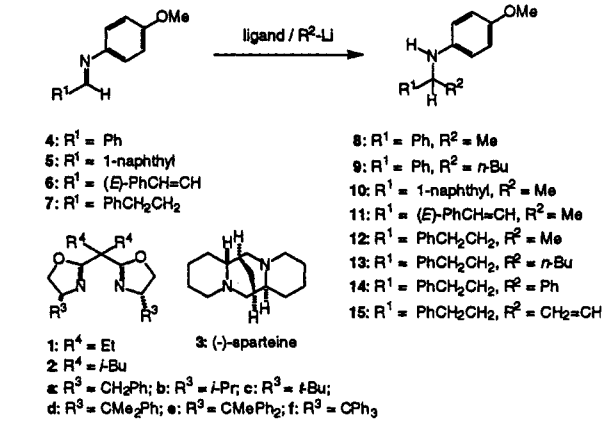
The catalytic, asymmetric construction of carbon–carbon bonds represents one of the major challenges to modern synthetic organic chemistry. For the addition of unstabilized nucleophiles to aldehydes, the catalytic asymmetric addition of organozinc reagents stands as a landmark achievement.[1] By contrast, the catalytic asymmetric addition of carbon nucleophiles to the C=N function has yet to meet with such success. Nevertheless, the lure of a general synthesis of chiral amines by this approach has stimulated much activity.[2,3]

For the external ligand-controlled addition[4] of organometallic reagents to achiral imines, only a handful of reports are extant.[5] Tomioka's[6] method for the asymmetric addition of organolithium reagents to aryl imines using a tridentate ligand, while precedent setting, still suffers from practical limitations. For example, the enantiomeric excesses are variable (47–90%), and the best results are obtained by the use of 2.6 equiv of the ligand at −100 °C. Substoichiometric quantities of the promoter led to significant erosion in enantioselectivity. In addition, the substrates are limited to nonenolizable imines (aromatic and unsaturated), presumably to avoid deprotonation. Thus, to develop a method for the asymmetric addition of organometallic nucleophiles to imines, we set the following boundary conditions: (1) at most, a stoichiometric amount of promoter should be used (ideally, catalytic quantities); (2) the method should be general for nucleophile and imine structure; (3) the ligand should be easily prepared and recoverable; and (4) simple organolithium reagents would serve as the nucleophiles. Herein we report our initial studies on the use of chiral, bidentate, nitrogen-containing ligands to accomplish these objectives (Scheme 1).

After achieving only limited success in the use of chiral promoters with hydrazones,[7] we turned our attention to addition of organolithium reagents to imines in the presence of the bis-oxazolines **1** and **2**. These readily synthesized compounds[8] have found extensive application as chiral ligands for transition metals in many different asymmetric reactions.[9,10] Given the preference

Scheme 1



for aldimines to exist in the *E* configuration, we reasoned that the presumed C_2 symmetry of a bis-oxazoline–RLi complex might provide a complementary match for one enantioface.[9b] Since the organolithium reagents to be used in this study are powerful bases and nucleophiles, the central carbon in **1** and **2** was disubstituted to prevent enolization and addition to the imino ether function.

The optimization of the reaction conditions employed benzaldehyde *N*-anisyl imine (**4**) and MeLi in the presence of the bis-oxazoline ligands **1** or **2c**. Initial studies revealed that at least 2 equiv of MeLi were necessary for complete conversion and that greater amounts could be used without erosion of enantioselectivity. Since the enantiomeric excess of the addition product reflects the weighted average of ligand-catalyzed and non-catalyzed reactions, we first established conditions under which little or no reaction takes place in the absence of **1** or **2c**. To maximize the complexation of the nucleophile with the ligand, a solvent with low coordinating ability for organolithium reagents (toluene) was employed for the initial studies. In the absence of an added ligand, the reaction of MeLi with **4** hardly proceeded at −78 °C, affording **8** in only 6% yield after 4 h (Table 1, entry 1). The influence of the bis-oxazoline ring substituent (**a–f**) was then evaluated in reactions employing a stoichiometric amount of the ligand (i.e., 1 equiv based on **4**). In the presence of **1a–1e**, the addition was accelerated to afford **8** in 75–99% yield after 1 h; only the trityl compound **1f** failed to promote the addition. The reaction selectivity was dependent on the size of the substituents R^3 and R^4, with **1e** and **2c** providing the highest enantioselectivities (entries 6 and 8).[11] Since the *tert*-butyl series is more readily available, **1c** and **2c** were selected for the survey of substrate and nucleophile generality.

The bis-oxazolines **1c** and **2c** were also effective in the MeLi addition to other aromatic (**5**) and conjugated (**6**) imines with high enantioselectivity (Table 2).[12] Most gratifyingly, the aliphatic imine **7** also gave the addition product **12** in high yield and enantioselectivity (entry 8). The additions to conjugated imines were slightly less enantioselective compared to those to aliphatic imines (entries 2, 4, and 5 vs 9). The branched auxiliary **2c** had a beneficial effect on the selectivity of addition to aromatic but not aliphatic imines. This is, in part, due to the higher temperature necessary for complete addition with the more hindered ligand. The balance of yield and selectivity with temperature is seen in the reactions of conjugated imine **6**, which

(1) (a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. (b) Noyori, R.; Kitamura, M. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Verlag: Berlin, 1989; Vol. 5, p 115.

(2) (a) Volkmann, R. A. In *Comprehensive Organic Synthesis, Additions to C–X π Bonds, Part 1*; Schreiber, S. L., Ed.; Pergamon Press: Oxford, 1991; Vol. 1. Chapter 1.12. (b) Kleinman, E. F.; Volkmann, R. A. In *Comprehensive Organic Synthesis, Additions to C–X π Bonds, Part 2*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; Vol. 2., Chapter 4.3. (c) Klein, J. In *The Chemistry of Double-Bonded Functional Groups: Supplement A*; Patai, S., Ed.; Wiley: Chichester, 1989; Vol. 2, Part 1, Chapter 10.

(3) (a) Denmark, S. E.; Weber, T. Piotrowski, D. W. *J. Am. Chem. Soc.* **1987**, *109*, 2224. (b) Weber, T.; Edwards, J. P.; Denmark, S. E. *Synlett* **1989**, 20. (c) Denmark, S. E.; Edwards, J. P.; Nicaise, O. *J. Org. Chem.* **1993**, *58*, 569. (d) Denmark, S. E.; Nicaise, O. *Synlett* **1993**, 359.

(4) Tomioka, K. *Synthesis* **1990**, 541.

(5) (a) Itsuno, S.; Yanaka, H.; Hachisuka, C.; Ito, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1341. (b) Katritzky, A. R.; Harris, P. A. *Tetrahedron: Asymmetry* **1992**, *3*, 437. (c) Soai, K.; Hatanaka, T.; Miyazawa, T. *J. Chem. Soc. Chem. Commun.* **1992**, 1097. (d) Ukaji, Y.; Hatanaka, T.; Ahmed, A.; Inomata, K. *Chem. Lett.* **1993**, 1313.

(6) (a) Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 6681. (b) Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1991**, *32*, 3095. (c) Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1603. (d) Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron* **1994**, *50*, 4429.

(7) Nicaise, O. J.-C. Ph.D. Thesis, University of Illinois at Urbana-Champaign, 1993.

(8) The ligand **1** and **2** were synthesized from L-*tert*-leucinol and corresponding dialkylmalonyl dichloride following a 3-step sequence in 63–65% yield: (1) Et_3N/CH_2Cl_2, (2) $MsCl/Et_3N/CH_2Cl_2$ (3) 0.5M NaOH/MeOH–H_2O(1:1)/100–110 °C.

(9) Reviews: (a) Bolm, C. *Angew. Chem., Int., Ed. Engl.* **1991**, *30*, 542. (b) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339. (c) Reiser, O. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 547.

(10) Corey has employed bis-oxazoline complexes of magnesium ion as catalysts for Diels–Alder and cyanohydrin forming reactions: (a) Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807. (b) Corey, E. J.; Wang, Z. *Tetrahedron Lett.* **1993**, *34*, 4001.

(11) The absolute configurations of the products were established by degradation to the amines (1. *n*-BuLi/$ClCO_2Me$, 2. $Ce(NH_4)_2(NO_3)_6$, 3. TMSI) and comparison of $[\alpha]_D$ with authentic samples.

(12) In all stoichiometric additions of **1c** and **2c**, the ligand was recovered in enantiomerically pure form in 91–100% yield.

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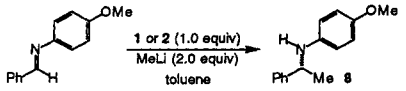
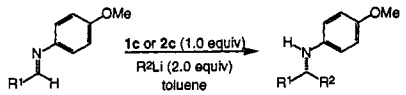
Table 1. Optimization of Ligand Structure: Additions of MeLi[a] to Imine **4**



entry	ligand	R^3	R^4	T, °C	yield,[b] %	ee,[c,d] %
1				−78	6	
2	**1a**	$PhCH_2$	Et	−78	91	34 (*R*)
3	**1b**	*i*-Pr	Et	−78	90	70 (*R*)
4	**1c**	*t*-Bu	Et	−78	95	75 (*R*)
5	**1d**	CMe_2Ph	Et	−78	75	64 (*R*)
6	**1e**	$CMePh_2$	Et	−63	99	81 (*R*)
7	**1f**	CPh_3	Et	−63	0	
8	**2c**	*t*-Bu	*i*-Bu	−63	95	85 (*R*)

[a] MeLi (low halide) in ether. All promoted reactions run for 1 h at the indicated temperature. [b] Yield of analytically pure material. [c] Determined by chiral HPLC analysis. [d] Reference 13.

Table 2. Asymmetric Addition of Organolithium Reagents to Imines with **1c** and **2c** (Stoichiometric)[a]



entry	R^1	ligand	R^2	T, °C	yield,[b] %	ee,[c] %	product[d]
1	Ph	**1c**	Me	−78	95	75	**8** (*R*)
2	Ph	**2c**	Me	−63	95	85	**8** (*R*)
3	1-naphthyl	**1c**	Me	−78	91	71	**10** (*R*)
4	1-naphthyl	**2c**	Me	−41	95	83	**10** (*R*)
5	(*E*)-PhCH=CH	**1c**	Me	−63	79	85	**11** (*R*)
6	(*E*)-PhCH=CH	**1c**	Me	−41	90	79	**11** (*R*)
7	(*E*)-PhCH=CH	**2c**	Me	−41	90	73	**11** (*R*)
8	$PhCH_2CH_2$	**1c**	Me	−63	96	91	**12** (*R*)
9	$PhCH_2CH_2$	**2c**	Me	−63	97	87	**12** (*R*)
10	$PhCH_2CH_2$	**1c**	*n*-Bu	−78	82	57	**13** (*R*)
11[e]	$PhCH_2CH_2$	**1c**	*n*-Bu	−78	86	69	**13** (*R*)
12	$PhCH_2CH_2$	**1c**	Ph	−78	82	30	**14**[f]
13	$PhCH_2CH_2$	**1c**	CH_2=CH	−78	95	89	**15**[f]

[a] MeLi (low halide, ether), *n*-BuLi (hexane), PhLi (ether–cyclohexane), vinyllithium (ether). All reactions run for 1 h at the indicated temperature. [b] Yield of analytically pure material. [c] Determined by chiral HPLC analysis. [d] Reference 13. [e] *i*-Pr_2O solvent. [f] Absolute configuration has not yet been determined.

afforded **11** in 79% yield and 85% ee at −63 °C. Carrying out the reaction at −41 °C increased the yield to 90%, but the selectivity dropped to 79% ee.

To assay the generality of this procedure for the addition of other organolithium nucleophiles,[13] we chose the enolizable imine **7**, which is not compatible with existing methods. It was found that *n*-BuLi, PhLi, and vinyllithium[14] all reacted rapidly in the presence of **1c** at −78 °C to afford high yields of the adducts **13**, **14**, and **15**, respectively (entries 10–13). The reaction selectivities were, however, quite variable (30–89% ee) due to a significant difference of the reaction rate between the ligand-catalyzed and the non-catalyzed reaction.

Since the imines **4**–**7** were shown to be practically unreactive toward MeLi at low temperature in the absence of the ligands, the potential for catalysis was obvious. The results in Table 3 show that additions with substoichiometric amounts of **1c** (0.1–0.2 equiv) proceeded in excellent yield albeit with somewhat reduced enantioselectivity. *For enolizable imine 7, however, the MeLi and vinyllithium additions proceeded with a comparable level of enantioselectivity (82%) (entries 4 and 6).*

The lesser selectivities observed in the additions of *n*-BuLi and PhLi to **7** were suspected to arise from weaker coordination by **1c** and **2c**, and therefore a stronger chelating ligand was sought. The bidentate tertiary amine (−)-sparteine (**3**) was found to serve effectively as the external ligand.[15] The results in Table 4 show

(13) Grignard reagents failed to add to **4** under any conditions.

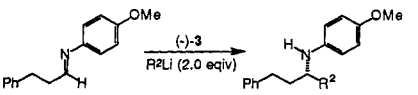
(14) (a) Seyferth, D.; Weiner, M. A. *J. Am. Chem. Soc.* **1961**, *83*, 3583. (b) Soderquist, J. A.; Rivera, I.; Nergron, A. *J. Org. Chem.* **1989**, *54*, 4051.

Table 3. Asymmetric Addition of Organolithium Reagents to Imines with **1c** (Catalytic)[a]

entry	R^1	R^2	**1c**, equiv	T, °C	yield,[b] %	ee,[c] %
1	Ph	Me	0.1	−41	98	68 (*R*)
2	1-naphthyl	Me	0.2	−41	97	60 (*R*)
3	(*E*)-PhCH=CH	Me	0.2	−41	92	68 (*R*)
4	$PhCH_2CH_2$	Me	0.2	−63	81	82 (*R*)
5[d]	$PhCH_2CH_2$	*n*-Bu	0.2	−78	92	51 (*R*)
6	$PhCH_2CH_2$	CH_2=CH	0.2	−78	82	82[e]

[a] See Table 2. [b] Yield of analytically pure material. [c] Determined by chiral HPLC analysis. [d] *i*-Pr_2O solvent. [e] Absolute configuration has not yet been determined.

Table 4. Asymmetric Addition of Organolithium Reagents to **7** with (−)-Sparteine[a]



entry	R^2	**3**, equiv	solvent	T, °C	yield,[b] %	ee,[c] %
1	Me	1.0	toluene	−78	71	72 (*R*)
2	*n*-Bu	1.0	Et_2O	−94	90	91 (*R*)
3	*n*-Bu	1.0	toluene	−94	86	79 (*R*)
4	*n*-Bu	1.0	*i*-Pr_2O	−78	85	83 (*R*)
5	*n*-Bu	0.2	Et_2O	−78	91	79 (*R*)
6	Ph	1.0	toluene	−94	99	82[d]
7	Ph	0.2	toluene	−78	97	39[d]

[a] All reactions run for 1 h at the indicated temperature. [b] Yield of analytically pure material. [c] Determined by chiral HPLC analysis. [d] Absolute configuration has not yet been determined.

that (−)-**3** had a dramatic effect on the rate of reaction, in both stoichiometric and catalytic quantities, allowing complete conversion of **7** with MeLi, *n*-BuLi, and PhLi between −78 and −94 °C. For the addition of MeLi, (−)-**3** was inferior to **1c** under any conditions tested. However, (−)-**3** improved the enantioselectivity in the additions of *n*-BuLi and PhLi significantly. For example, the reaction of **7** with *n*-BuLi in toluene promoted by **1c** afforded **13** in 82% yield and 57% ee (Table 2, entry 10), while the reaction promoted by (−)-**3** afforded **13** in 90% yield and 91% ee (Table 4, entry 2). There is a clear solvent effect in the reaction of *n*-BuLi; both toluene and *i*-Pr_2O gave lower selectivities than Et_2O. The addition of PhLi to **7** was also significantly improved with (−)-**3** compared to **1c** (82% vs 30% ee, entry 6). Even with a catalytic amount of (−)-**3**, the addition of *n*-BuLi to **7** gave amine **13** with useful selectivity.

In summary, we have demonstrated that bis-oxazolines and (−)-sparteine can serve as promoters for the selective addition of organolithium reagents to aromatic, olefinic, and aliphatic aldimines. Current investigations are focused on the structure of the ligand–organolithium complexes.

Acknowledgment. We are grateful to the National Institutes of Health (GM 30938) and the Upjohn Company for generous support of this research. We also thank Dr. B. Kutscher (Asta Medica) for a generous gift of L-*tert*-leucine and Professor Peter Beak for (−)-sparteine.

Supplementary Material Available: Experimental procedures and full spectroscopic characterization of **1c**, **2c**, **8**, and **10**–**15** are provided (15 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(15) (−)-Sparteine is an inexpensive and commercially available chiral diamine that has found applications in asymmetric transformations of organolithium reagents: (a) Nozaki, H.; Aratani, T.; Takaya, T.; Noyori, R. *Tetrahedron* **1971**, *27*, 905. (b) Engelhardt, L. M.; Leung, W.-P.; Raston, C. L. Salem, G.; Twiss, P.; White, A. H. *J. Chem. Soc., Dalton Trans.* **1988**, 2403. (c) Hoppe, D.; Paetow, M.; Hinze, F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 394. (d) Beak, P.; Du, H. *J. Am. Chem. Soc.* **1993**, *115*, 2516.