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A Novel Chiral Pentamine Ligand for Enantioselective α-Alkylation of Acyclic Lithium Amide Enolates. Optimization of Chiral Ligands for Asymmetric Reactions Using Solid-Phase Organic Synthesis

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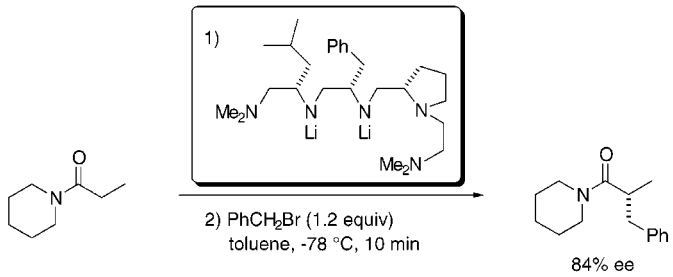
ABSTRACT



A novel pentamine ligand has been developed for enantioselective α-alkylation of simple acyclic lithium amide enolates. It has been demonstrated that solid-phase organic synthesis provides a powerful and rapid method for finding efficient chiral ligands.

Development of asymmetric α-alkylation reactions of carbonyl and related compounds is one of the most important tasks in modern organic synthesis.[1] Although many diastereoselective alkylation reactions have been developed,[1,2] only limited examples of enantioselective reactions are reported.[3−5] Among them, alkylation using lithium enolates is the most promising, and enantioselective α-alkylation of cyclic ketones, lactones, and lactams has been performed using a chiral amine ligand.[5] However, there is no successful example, to the best of our knowledge, of the enantioselective α-alkylation of simple acyclic carbonyl compounds. This is probably because two geometrical isomers of enolates form from acyclic compounds in most cases, and the stereocontrol

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(2) (a) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233−4236. (b) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Appl. Chem.* **1981**, *53*, 1109−1127. (c) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737−1739. (d) Evans, D. A. *Aldrichim. Acta* **1982**, *15*, 23−32. (e) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603−5606.

(3) Phase transfer catalyzed alkylation: Corey, E. J.; Bo, Y.; Busch-Petersen, J. *J. Am. Chem. Soc.* **1998**, *120*, 13000−13001 and references therein.

(4) Palladium-catalyzed reaction: (a) Hayashi, T.; Kanehira, K.; Hagihara, T.; Kumada, M. *J. Org. Chem.* **1988**, *53*, 113−120. (b) Genet, J. P.; Ferroud, D.; Juge, F. S.; Montes, J. R. *Tetrahedron Lett.* **1986**, *27*, 4573−4576. (c) Sawamura, M.; Nagata, H.; Sakamoto, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2586−2592. (d) Trost, B. M.; Radinov, R.; Grenzer, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 7879−7880. (e) Åhman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918−1919.

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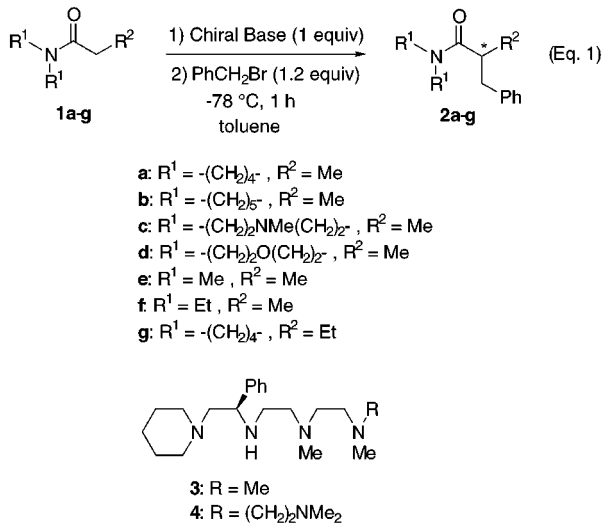
of both enolates is difficult. Accordingly, we undertook the task, and in this paper we report a novel chiral pentamine ligand for the enantioselective alkylation of acyclic lithium amide enolates.

We chose an acyclic amide as a substrate, because it was reported that a (*Z*)-lithium enolate was selectively formed by lithium amide deprotonation,[1a] and that the amide group could be readily converted to other useful functional groups.

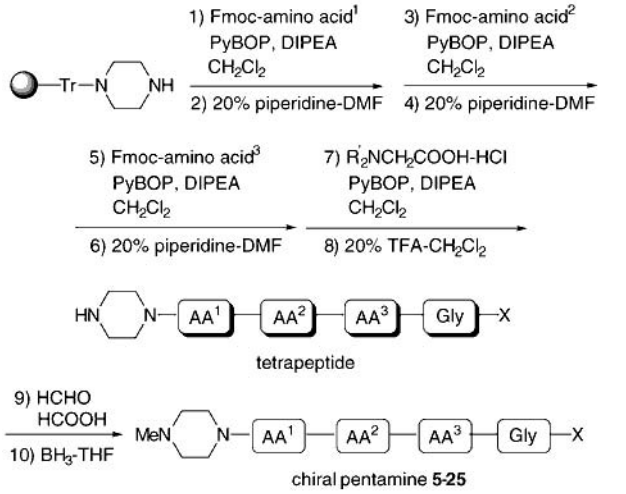
We first used pyrrolidinepropionamide (**1a**, eq 1 in Scheme 1) for a model acyclic amide, and benzylation was performed

Scheme 1



using the chiral induction system consisting of chiral tetradentate amine **3**, LiBr, and a lithium enolate in toluene (nonpolar solvent).[5] While the first trial gave low chemical yield and enantioselectivity (4% yield, 18% ee), both chemical yield and ee were improved (30% yield, 25% ee) when a pentadentate chiral amine (**4**) was used. From these results, it was assumed that pentadentate chiral ligands would be better in this alkylation reaction. To perform more efficient and rapid ligand searching, we decided to use solid-phase synthesis.[6] The ligand syntheses using the solid-phase protocols were performed as shown in Scheme 2. Piperazine was connected to trityl-type resin and this polymer-supported

Scheme 2. Solid-Phase Synthesis of **5**−**25**



amine was used for solid-phase peptide synthesis. After coupling with three amino acids, *N*,*N*-dialkylglycine was added. Cleavage from the solid support was performed at this stage and terminal secondary amine was methylated. Finally, reduction using BH_3·THF gave chiral pentamines.

The chiral ligands synthesized were tested in the benzylation reaction of **1a** (Table 1). First, three ligands having a chiral pyrrolidine structure derived from L-proline were investigated (entries 2−4). Among them, chiral amine **8**, in which L-proline was introduced as the third amino acid (AA^3), was found to be the most effective (36% ee). Thus, L-proline was fixed as the third amine part (AA^3), and then the first and second amino acids (AA^1 and AA^2) and the *N*,*N*-dialkyl groups of glycine were screened. It was revealed that chiral ligand **22**, which was prepared from L-leucine (AA^1), L-phenylalanine (AA^2), L-proline (AA^3), and *N*,*N*-dimethylglycine, gave the best selectivitiy at this stage (47% ee, entry 18). While the second amino acid (AA^2), or the *N*,*N*-dialkyl groups of glycine had little effect on the enantioselectivity, the first amino acid (AA^1) was shown to play an important role in the selectivity.

Although moderate selectivity was obtained at this stage, it was not yet satisfactory. To optimize the chiral ligand structure, we then modified the *N*-methylpiperazine moiety of **22**. When the *N*-methylpiperazine structure was replaced by a piperidine group (**26**), the enantioselectivity was improved to 62% ee (Table 2). Moreover, the ligand complexation conditions of the lithium enolate were found to influence the enantiofacial selectivity dramatically.[7] When

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(8) The absolute configuration of **2a** (46% ee; $[\alpha]_D^{24}$ +31.8 (*c* 1.0, $CHCl_3$)) was determined by acidic hydrolysis to *(S)*-α-benzylpropionic acid (Helmchen, G.; Nill, G.; Flockerzi, D.; Youssef, M. S. K. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 63−65).

(9) **Typical Experimental Procedure.** Under Ar atmosphere, to the solution of **27** (129 mg, 0.30 mmol) in toluene (2.7 mL) was added dropwise *n*-buthyllithium in hexane (1.57 N, 0.36 mL, 0.57 mmol) at −20 °C. After the solution was stirred 30 min, **1b** (38 mg, 0.27 mmol) in toluene (1.5

Table 1. Effect of Chiral Ligands in Benzylation of **1a**[a,b]

Entry	Chiral Amine[c] AA[1]	AA[2]	AA[3]	X		Ee (%)
1	Phe	Phe	Phe	NMe_2	**5**	14
2	Pro	Phe	Phe	NMe_2	**6**	1
3	Phe	Pro	Phe	NMe_2	**7**	—[d]
4	Phe	Phe	Pro	NMe_2	**8**	36
5	Phe	Pro	Pro	NMe_2	**9**	3
6	Pro	Phe	Pro	NMe_2	**10**	—[d]
7	Phe	Gly	Pro	NMe_2	**11**	13
8	Phe	Ala	Pro	NMe_2	**12**	30
9	Phe	Val	Pro	NMe_2	**13**	5
10	Phe	Leu	Pro	NMe_2	**14**	28
11	Phe	D-Phe	Pro	NMe_2	**15**	17
12	Phe	Phe	Pro	$N(CH_2)_4$	**16**	21
13	Phe	Phe	Pro	$N(CH_2)_5$	**17**	23
14	Phe	Phe	Pro	NBn_2	**18**	20
15	Gly	Phe	Pro	NMe_2	**19**	32
16	Ala	Phe	Pro	NMe_2	**20**	46
17	Val	Phe	Pro	NMe_2	**21**	32
18	Leu	Phe	Pro	NMe_2	**22**	47
19	*t*-Leu	Phe	Pro	NMe_2	**23**	4[e]
20	1-Nap-Ala[f]	Phe	Pro	NMe_2	**24**	24
21	D-Phe	Phe	Pro	NMe_2	**25**	16

[a]Benzylation was performed using chiral amine, MeLi, and LiBr in toluene at -78 °C (Cf. Eq. 1). [b]The absolute configuration of the products was *S* unless otherwise noted.[8] [c]L-Amino acids were used unless otherwise noted. [d]No reaction. [e]Reverse enantiofacial selectivity was observed. [f]1-Naphthylalanine.

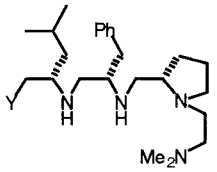
27 and 2 equiv of BuLi were supplied to the lithium amide, the same level of ee was obtained (65%). It is noted that the enantiofacial selectivity was reversed using the new system.

mL) was added and the solution was stirred 30 min. Benzyl bromide (0.04 mL, 0.34 mmol) of toluene (1.0 mL) solution was then added at −78 °C, and the solution was stirred 10 min. The reaction was quenched with 0.1 N aqueous citric acid (5.0 mL), and extracted with AcOEt (10 mL × 3). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, and dried with Na_2SO_4. After filtration, the filtrate was concentrated in vacuo to give a pale yellow oil. This crude product was purified by preparative TLC (hexane/AcOEt) to give **2b** (25 mg, 40% yield). Enantiomeric excess of this product was determined by HPLC under the following conditions: Chiralcel OD-H (hexane/2-propanol = 30/1, 0.5 mL/min, 254 nm) 23.5 min (minor), 28.9 min (major); 84% ee; $[\alpha]^{23}_D$ −39.4 (*c* 0.54, $CHCl_3$); ^1H NMR (400 MHz/$CDCl_3$) δ 1.14 (3H, d, J = 6.3 Hz), 1.3−1.6 (6H, m), 2.6−2.7 (1H, m), 2.9−3.0 (2H, m), 3.26 (2H, brs), 3.41 (2H, brs), 3.60 (1H, brs), 7.1−7.3 (5H, m); ^{13}C NMR (100 MHz/$CDCl_3$) δ 17.86, 24.57, 25.60, 26.38, 37.43, 40.57, 42.86, 46.56, 126.11, 128.28, 129.10, 140.31, 174.09; IR (neat, cm^{-1}) 1637, 1443, 1227, 1010, 701. HRMS Calcd for $C_{15}H_{21}NO$: 231.1623. Found: 231.1605.

Table 2. Effect of Chiral Ligands in Benzylation[a]

Entry	Amide	Chiral Base	Product	Yield (%)	Ee (%)
1	**1a**	**26** + MeLi-LiBr	**2a**[b]	49	62
2	**1a**	**27** + MeLi-LiBr	**2a**[b]	59	3
3	**1a**	**26** + BuLi (2 equiv)	**2a**[c]	72	45
4	**1a**	**27** + BuLi (2 equiv)	**2a**[c]	79	65
5	**1b**	**27** + BuLi (2 equiv)	**2b**	40	84
6	**1c**	**27** + BuLi (2 equiv)	**2c**	50	81
7	**1d**	**27** + BuLi (2 equiv)	**2d**	54	79
8	**1e**	**27** + BuLi (2 equiv)	**2e**	47	78
9	**1f**	**27** + BuLi (2 equiv)	**2f**	66	79
10	**1g**	**27** + BuLi (2 equiv)	**2g**	33	59

[a]Cf. Eq. 1. [b]The absolute configuration was *S*.[8] [c]The absolute configuration was *R*.[8]



26: Y = $N(CH_2)_5$
27: Y = NMe_2

Furthermore, the enantiomeric excess was improved to 84% when piperidinepropionamide (**1b**) was used.[9] The same high selectivity was obtained when using **1c**, **1d**, **1e**, and **1f**.

In conclusion, we have developed pentamine ligand **27** which is effective in enantioselective alkylation of acyclic lithium amide enolates. It has been also demonstrated that solid-phase organic synthesis provides a powerful and rapid method for finding efficient ligands. While the effective chiral ligand was found in this work, the precise structure of the lithium enolate-chiral ligand complex and the transition state of the enantioselective alkylation are still unclear. Further studies to clarify them as well as to show synthetic utility including the scope and limitation of this alkylation are now in progress.

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Supporting Information Available: Experimental procedures and physical data of the products and ligands. This material is available free of charge via the Internet at http://pubs.acs.org.

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