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Asymmetric Deprotonation of *N,N*-Dihexyl-1-Naphthamides to Provide Atropisomers of *N,N*-Dihexyl-2-Alkyl-1-Naphthamides

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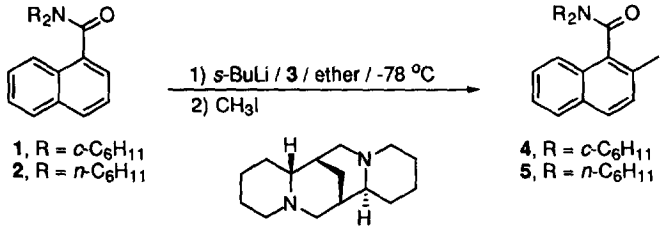
Abstract: Asymmetric deprotonation of *N,N*-dihexyl-1-naphthamide using *sec*-butyllithium / (-)-sparteine followed by reactions with methyl or ethyl alkylation reagents give the atropisomers of *N,N*-dihexyl-2-alkyl-1-naphthamide with 50% and 55% ee, respectively.

The combination of butyllithium/(-)-sparteine has proven effective for the induction of asymmetry in lithiations/substitutions of benzylic, α-heteroatom, and ortho aromatic hydrogens.[1] We now report an extension of the methodology to atropisomers by the enantioselective replacement of the ortho hydrogen of *N,N*-dihexyl-1-naphthamide. There are relatively few reports on stereoselective synthesis of non-biaryl atropisomeric molecules.[2] To the best of our knowledge, there is no previous report on the enantioselective synthesis of non-biaryl atropisomers using external chiral auxiliaries. Clayden and co-workers recently have reported a synthesis of diastereomeric atropisomers from the addition of *N,N*-dialkyl-2-lithio-1-naphthamides to aldehydes.[3,4]



1, R = *c*-C_6H_{11}
2, R = *n*-C_6H_{11}

(-)-sparteine (**3**)

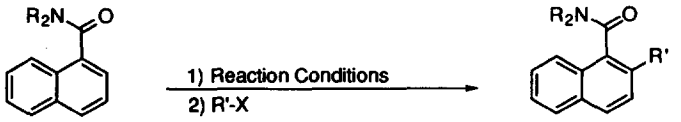
4, R = *c*-C_6H_{11}
5, R = *n*-C_6H_{11}

Atropisomers due to the barrier for interconversion of *N,N*-dialkyl-2-substituted aromatic carboxamides are well known and their chiral chromatographic separations have been reported.[5-11] We have found that the treatment of (*S*)-*N,N*-dicyclohexyl-1-naphthamide (**1**) with *sec*-butyllithium / (-)-sparteine (**3**) followed by reaction with methyl iodide provides (*S*)-*N,N*-dicyclohexyl-2-methyl-1-naphthamide (**4**) in 35% yield (92% conversion) in 30% ee. Treatment of *N,N*-dihexyl-1-naphthamide (**2**) with *sec*-butyllithium/**3** at -78 °C in diethyl ether followed by reaction with methyl iodide provided (*R*)-*N,N*-dihexyl-2-methyl-1-naphthamide (**5**) in 30% yield (53% conversion) with 50% ee.[12] Mixtures of diastereomers resulting from the addition of *sec*-butyllithium to the naphthalene nucleus are observed as the major side products for **5**.[13] The

different absolute configurations of **4** and **5** are provisionally assigned by analogy to Pirkle's assignment for the corresponding *N,N*-dimethylamide using his chromatographic separation models.[11a,14]

Although significantly lower amounts of side products are obtained when the reaction is carried out in THF, the product **5** is obtained as a racemic mixture in 62% yield. When the reaction is carried out in pentane, the product (*R*)-**5** is obtained with 63% ee in approximately 5% yield. The major products in this reaction appear to result from the addition of *sec*-butyllithium to the naphthalene nucleus, and the amide group.[15] Use of *n*-butyllithium in the place of *sec*-butyllithium in diethyl ether resulted in *n*-butyl naphthyl ketone as the major product.

Treatment of *N,N*-dihexyl-1-naphthamide with *sec*-butyllithium/**3** in diethyl ether followed by reaction with methyl triflate afforded (*R*)-**5** with 55% ee in 25% yield. With ethyl iodide as electrophile, the product *N,N*-dihexyl-2-ethyl-1-naphthamide (**6**) is obtained with 55% ee in only 8% yield. With trimethyl silyl chloride as the electrophile, the product *N,N*-dihexyl-2-(trimethylsilyl)-1-naphthamide (**7**) is obtained as a racemic mixture in 10% yield. The yield improves to 35% when trimethylsilyl triflate is used as the electrophile, but the product **7** is still racemic.[16]



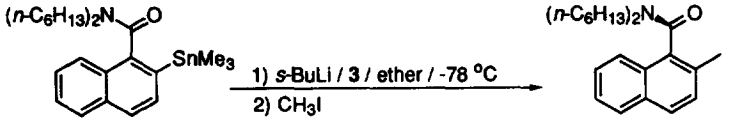
Substrate	Reaction Conditions	Electrophile (R'-X)	Product	Yield (%)	ee (%)
1 (R=*c*-C_6H_{11})	*s*-BuLi / **3** / Et_2O / -78 °C	CH_3-I	(*S*)-**4**	35	30
2 (R=*n*-C_6H_{13})	*s*-BuLi / **3** / Et_2O / -78 °C	CH_3-I	(*R*)-**5**	30	50
	s-BuLi / **3** / THF / -78 °C	CH_3-I	**5**	62	0
	s-BuLi / **3** / pentane / -78 °C	CH_3-I	(*R*)-**5**	5	63
	n-BuLi / **3** / Et_2O / -78 °C	CH_3-I	**5**	<5	NA
	s-BuLi / **3** / Et_2O / -78 °C	CH_3-OTf	(*R*)-**5**	25	55
	s-BuLi / **3** / Et_2O / -78 °C	C_2H_5-I	(*R*)-**6**	8	55
	s-BuLi / **3** / Et_2O / -78 °C	Me_3Si-Cl	**7**	10	0
	s-BuLi / **3** / Et_2O / -78 °C	Me_3Si-OTf	**7**	35	0

We observe that (*R*)-*N,N*-dihexyl-2-methyl-1-naphthamide (**5**) of 52% ee racemizes to 5% ee over 8 days at room temperature.[17] When (*R*)-**5** (50% ee) is heated to 65 °C over a period of one hour, the compound racemizes completely. The racemization of *N,N*-dihexyl-2-ethyl-1-naphthamide (**6**) occurs more slowly. The rates of racemization of **4** and **5** are similar.

Two limiting mechanistic possibilities can be proposed to explain this enantioselective replacement of hydrogen. (*i*) The substrate *N,N*-dihexyl-1-naphthamides exist as a mixture of non-equilibrating atropisomers at -78 °C, and *s*-BuLi/**3** deprotonates the one atropomer selectively. In this mechanism, the enantioselectivity is determined in the deprotonation step.[18] (*ii*) The lithiated intermediates, *N,N*-dihexyl-2-lithio-1-naphthamide

exists as a rapidly equilibrating atropisomeric mixture and which react stereoselectively with the alkylating agent in the presence of **3**. In this mechanism, the enantioselectivity is determined in the substitution step.

These two mechanisms were differentiated by generating *N,N*-dihexyl-2-lithio-1-naphthamide from a racemic mixture of *N,N*-dihexyl-2-(trimethylstannyl)-1-naphthamide (*rac*-**8**). Treatment of the stannyl compound **8** with *s*-BuLi/**3** followed by reaction with methyl iodide provides **5** in 60% yield and 14% ee. Under this protocol, the *S*-atropomer which is different from the selectivity obtained in the deprotonation-substitution sequence for **2**, is obtained. If it is presumed that tin-lithium exchange provides a racemic *ortho*-lithiated intermediate, this result suggests that the enantioselectivity is not determined in the substitution step.[17] Therefore, the enantioselection in this case is considered to arise from an asymmetric deprotonation.



rac-**8** (*S*)-**5**
60% yield; 14% ee

Optimizing the reaction conditions to improve the yields and enantioselectivities, extending the methodology to other substrates, and understanding further the mechanism of the reaction will be the focus of future work.

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4) Fuji reported that atropisomerism is responsible in the 'memory of chirality' in the reaction of naphthylketone enolates, see: Kawabata, T.; Yahiro, K.; Fuji, K. *J. Am. Chem. Soc.* **1991**, *113*, 9694.

5) Atropisomerism, caused by the high energy barrier to interconversion between the conformational isomers, is an important property found in several organic molecules.[6] The phenomena is a key motifs in asymmetric organic synthesis,[7] molecular recognition,[8] and for biologically important molecules.[9] Among the molecules which possess axial chirality and high barriers to conformational interconversion, 2,2'-disubstituted binaphthyls and biphenyls are the class of chiral molecules which has received most attention in asymmetric organic synthesis.[10]

6) For a review on axially chiral heteroaromatics, see: Gallo, R.; Roussel, C.; Berg, U. *Adv. Heterocyclic Chem.* **1988**, *46*, 173.

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12) The enantiomeric excess of the axially twisted naphthamides were determined using commercially available (*S,S*)-Whelk-o-1 HPLC columns.[11a]

13) Meyers observed similar additions to the naphthalene nucleus in the reaction of alkyllithiums with 1-naphthyloxazolines, see: Rawson, D.J.; Meyers, A.I. *J. Org. Chem.* **1991**, *56*, 2292.

14) The provisional assignments of different absolute configurations assume that the dicyclohexyl and the di-*n*-hexyl isomers behave in analogous fashion on chromatography.

15) These products were identified by GC-mass spectrometry.

16) The conversion of **1** to **5** is higher than 10% and 35% with trimethylsilyl chloride and trimethyl silyl triflate respectively. However, difficulties with separation of **5** from the side products resulted in lower isolated yield.

17) The mechanism of racemization of these naphthamides are assumed to be similar to that proposed for the naphthyl ketones. Casarini, D.; Lunazzi, L.; Pasquali, F.; Gasparrini, F.; Villani, C. *J. Am. Chem. Soc.* **1992**, *114*, 6521.

18) An alternative possibility is that substrate **2** is resolved by the selective addition of butyllithium to the naphthalene nucleus of the (*S*)-enantiomer of **2**. Deprotonation of this resolved atropomer of **2** followed by trapping with methyl iodide could provide (*R*)-**5**. This would require **1** and **2** to follow different pathways for enantioselective substitution, since in the former case, there was little addition.

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