Asymmetric Synthesis of Axially Chiral *cis*-Arylmethylenebicyclo[3.3.0]octanes Using α-Thio- and α-Selenoorganolithium Compounds

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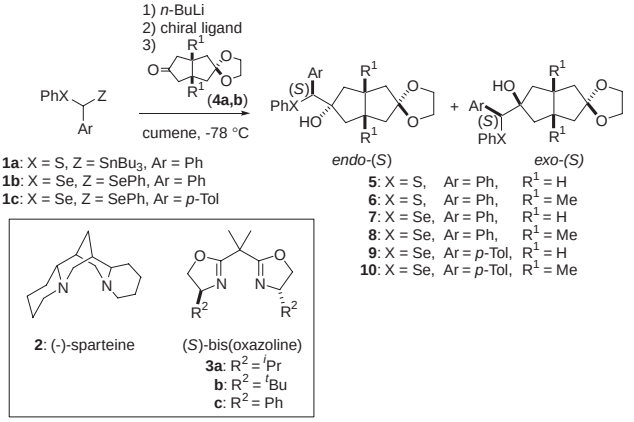
Enantioselective reaction of α-thio carbanion derived from 1-phenyl-1-(phenylthio)-1-(tributylstannyl)methane with *cis*-bicyclo[3.3.0]octane-3,7-dione monoethylene ketals in the presence of bis(oxazoline)s gave products with high diastereoselectivity and with high enantioselectivity. The reaction of α-seleno carbanions derived from bis(phenylseleno)arylmethanes also showed high diastereoselectivity and enantioselectivity. Deprotection and subsequent stereospecific elimination afforded axially chiral *cis*-arylmethylenebicyclo[3.3.0]octanes with high enantioselectivity (up to 99% ee).

It is of keen interest to develop an efficient preparative method for axially chiral olefins, especially, axially chiral bicyclic olefins. The unique chiroptical property of axially chiral bicyclic olefins has been noticed in the development of materials that can be switched by light.[1] Furthermore, the *cis*-bicyclo[3.3.0]octylidene structure is involved in carbacyclin,[2] chemically stable and biologically potent prostacyclin[3] analogue, and hence its axially chiral version can be a key intermediate for the synthesis of carbacyclin and its congeners.[4] Although diastereoselective syntheses of axially chiral bicyclic olefins using chiral reagents have been reported,[5] there are no reports on their enantioselective preparation.[6] Recently, we have reported a convenient synthetic method for optically pure, axially chiral benzylidenecyclohexanes by the enantioselective reaction of 4-substituted cyclohexanones with the α-phenylthio and α-phenylseleno carbanions and subsequent stereospecific β-elimination.[7] We herein report an efficient synthesis of axially chiral *cis*-arylmethylenebicyclo[3.3.0]octanes with excellent diastereo- and with high enantioselectivity.

Reaction of the sulfide **1a** with 1.2 equiv of *n*-BuLi and 1.25 equiv of a chiral ligand in cumene at −78 °C formed Li-**1a**, which was then reacted with 1.3 equiv of *cis*-bicyclo[3.3.0]octane-3,7-dione monoethylene ketal **4a** to give the product **5**. The yields and the enantioselectivities obtained in the reaction are shown in Table 1. The reaction of Li-**1a** with **4a** using (−)-sparteine as a chiral ligand gave *endo*-**5** as a single diastereomer but with low enantioselectivity (Entry 1), where the carbanion attacked the carbonyl group from the exo direction exclusively. On the other hand, the reaction using (*S*)-bis(oxazoline)-^{i}Pr **3a** afforded *endo*-(*S*)-**5** with excellent diastereoselectivity as well as with high enantioselectivity (Entry 2). The enantioselectivity depended on the bis(oxazoline) used; **3a** showed higher enantioselectivity than other (*S*)-bis(oxazoline)s **3b** and **3c** (Entries 3 and 4). The reaction of Li-**1a** with *cis*-1,5-dimethylbicyclo[3.3.0]octane-3,7-dione monoethylene ketal **4b** in the presence of **3a** afforded *endo*-(*S*)-**6** as a major product with slightly lower diastereoselectivity but both *endo*-(*S*)- and *exo*-(*S*)-isomers were obtained with high enantioselectivities (Entry 5).

Table 1. Enantioselective reaction of lithiated **1a**–**1c** with bicyclo[3.3.0]octane-3,7-dione monoethylene ketals **4**



Entry	1	Ligand	R^1	Product	Yield /%	Ratio[a]	ee *endo*/%[b]	ee *exo*/%[b]
1	**1a**	**2**	H	**5**	60	>98:2	7	—
2	**1a**	**3a**	H	**5**	77	>98:2	99	—
3	**1a**	**3b**	H	**5**	80	>98:2	95	—
4	**1a**	**3c**	H	**5**	35	>98:2	72	—
5	**1a**	**3a**	Me	**6**	98	88:12	98	99
6	**1a**	**3b**	Me	**6**	97	86:14	92	90
7	**1b**	**3a**	H	**7**	70	>98:2	56	—
8	**1b**	**3b**	H	**7**	80	>98:2	92	—
9[c]	**1b**	**3b**	H	**7**	15	>98:2	81	—
10	**1b**	**3a**	Me	**8**	93	73:27	64	57
11	**1b**	**3b**	Me	**8**	92	82:18	91	86
12	**1c**	**3b**	H	**9**	79	>98:2	92	—
13	**1c**	**3b**	Me	**10**	60	>98:2	91	—

[a] *endo*-(*S*):*exo*-(*S*) [b] Determined by the HPLC analysis using Chiralpak AD–H, Chiralcel OJ–H or Chiralcel OD–H. [c] A deficient amount (0.2 equiv) of **4a** was used.

The diastereomers *endo*-(*S*)-**6** and *exo*-(*S*)-**6** were easily separated by column chromatography. The enantioselective reaction of the α-seleno carbanion Li-**1b** derived from bis(phenylseleno)-phenylmethane **1b** was also examined. In the reaction of Li-**1b** with **4a**, bis(oxazoline)-^{t}Bu **3b** showed higher enantioselectivity than **3a** (Entries 7 and 8). We have previously clarified that the reaction of the α-phenylthio carbanion proceeds through a dynamic kinetic resolution pathway, whereas that of the α-phenylseleno carbanion proceeds through a dynamic thermodynamic resolution pathway.[8] The difference in the resolution pathway can be ascribed to the fact that the α-phenylseleno carbanion is configurationally more stable than the α-phenylthio carbanion.[9] We also confirmed that the reaction of Li-**1b** proceeded

through a dynamic thermodynamic resolution pathway by the reaction with a deficient amount (0.2 equiv) of **4a** showing lower enantioselectivity than that under normal conditions (Entry 8 vs Entry 9). The reaction of Li-**1b** with **4b** gave a mixture of diastereomers and enantioselectivities were better for the both diastereomers when ligand **3b** was used (Entries 10 and 11). The reaction of Li-**1c** derived from bis(phenylseleno)-*p*-tolylmethane **1c** with **4a** afforded **9** as a single diastereomer with high enantioselectivity (Entry 12). It should be noted that **4b** gave **10** as a single diastereomer with high enantioselectivity (Entry 13). The stereochemistry of the major isomer of **7** was assigned to be *endo* by the X-ray crystallographic analysis. We have previously confirmed that the α-phenylthio and α-phenylseleno carbanions give, without exception, (*S*)-products in the reaction with carbonyl compounds in the presence of (*S*)-bis(oxazoline)-^{i}Pr or -^{t}Bu. These results enabled us to assign the configuration of the major isomer of **7** to be *endo*-(*S*). The configuration of other products was assigned as such.

Next, compounds *endo*-(*S*)-**5**–**10** and *exo*-(*S*)-**6**, **8** were separately treated with 1 M HCl in acetone to give *cis*-bicyclo[3.3.0]octanones, which, without purification, were reacted with methanesulfonyl chloride in the presence of Et_3N at 0 °C to afford axially chiral *cis*-arylmethylenebicyclo[3.3.0]octanes **11**–**14** without substantial racemization (Table 2). Thus, optically active *endo*-(*S*)-sulfides *endo*-(*S*)-**5**, **6** and -selenides *endo*-(*S*)-**7**–**10** gave (a*R*)-**11**–**14**, and *exo*-(*S*)-sulfide *exo*-(*S*)-**6** and -selenide *exo*-(*S*)-**8** afforded (a*S*)-**12** by the stereospecific β-elimination in an anti fashion.[10,11]

In summary, we have demonstrated the first convenient, enantioselective preparation of axially chiral *cis*-arylmethylenebicyclo[3.3.0]octanes by the reaction of α-thio- and α-seleno carbanions with *cis*-bicyclo[3.3.0]octane-3,7-dione ethylene ketals in the presence of (*S*)-bis(oxazoline)s and subsequent stereospecific β-elimination.

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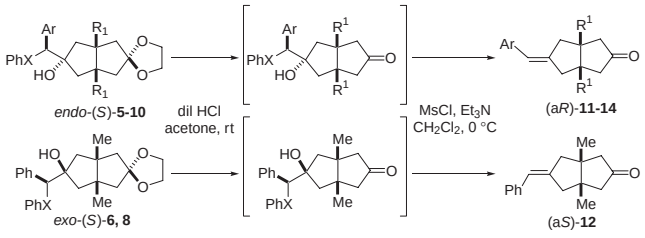
Table 2. Preparation of axially chiral arylmethylenebicyclo-[3.3.0]octanes from *endo*-(*S*)-**5**–**10** and *exo*-(*S*)-**6**, **8**



Entry	Substrate	ee /%	Product	Yield /%	ee /%	Config.
1	*endo*-(*S*)-**5**	99	**11**	61	98	a*R*
2	*endo*-(*S*)-**6**	98	**12**	43	98	a*R*
3	*exo*-(*S*)-**6**	99	**12**	53	99	a*S*
4	*endo*-(*S*)-**7**	92	**11**	92	90	a*R*
5	*endo*-(*S*)-**8**	89	**12**	91	89	a*R*
6	*exo*-(*S*)-**8**	86	**12**	88	84	a*S*
7	*endo*-(*S*)-**9**	92	**13**	93	92	a*R*
8	*endo*-(*S*)-**10**	91	**14**	88	91	a*R*

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