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Desymmetrization of Metallated Cyclohexadienes with Chiral *N-tert*-Butanesulfinyl Imines

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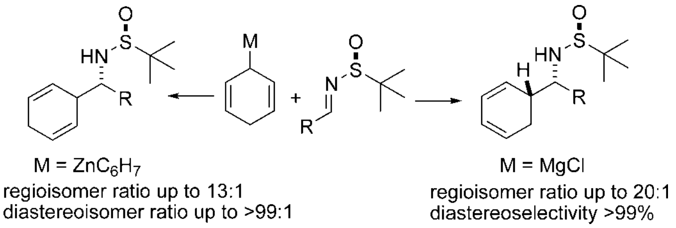
ABSTRACT



This communication describes the desymmetrization of various achiral metallated cyclohexadienes with a series of chiral *N-tert*-butanesulfinyl imines. Depending on the metal used, either the symmetrical diene (dicyclohexadienyl-zinc) or the desymmetrized diene (cyclohexadienyl-MgCl) is obtained in a good regioselectivity with excellent diastereoselectivity. The products formed should be useful building blocks for natural product synthesis. The symmetrical 1,4-dienes are readily oxidized to the corresponding diarylmethylamine derivatives.

The desymmetrization of 1,4-cyclohexadienes is a highly useful route to interesting chiral building blocks for natural product synthesis. Ionic and radical C−C bond forming reactions, cycloadditions, and transition-metal mediated processes have been successfully used to achieve that goal.[1]

We have recently shown that the chiral cyclohexadienyl-Ti complex **1**reacts highly stereoselectively with various aldehydes to the desymmetrized cyclohexadienes **2**.[2] More recently, a catalytic variant was developed using silylated cyclohexadiene **3**[3] in combination with a chiral Cu-catalyst.[4] So far, our research in this area focused on the study of chiral cyclohexadienyl nucleophiles. In the present communication, we describe the desymmetrization of achiral metallated cyclohexadienes with the aid of a chiral electrophile. As promising electrophiles, we decided to study chiral *N-tert*-butanesulfinyl imines **4**, which have often been used in stereoselective synthesis[5,6] to give dienes of type **5** (Scheme 1).

The influence of the metal M on the desymmetrization reaction was studied first. To this end, various cyclohexadienyl metal compounds, which were readily prepared from the corresponding Li-derivative via transmetalation, were reacted with chiral sulfonyl imine **4a** (R = Ph). Along with the desired desymmetrization product **5a**, the symmetrical

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(1) Reviews: (a) Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765. (b) Rahman, A. N.; Landais, Y. *Curr. Org. Chem.* **2002**, *6*, 1369. (c) Hoffmann, R. W. *Synthesis* **2004**, 2075. (d) Schleth, F.; Studer, A. *Synlett* **2005**, 3033.

(2) (a) Schleth, F.; Studer, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 313. (b) Schleth, F.; Vogler, T.; Harms, K.; Studer, A. *Chem.−Eur. J.* **2004**, *10*, 4171.

(3) For the use of silylated cyclohexadienes in radical chemistry, see: (a) Studer, A.; Amrein, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3080. (b) Studer, A.; Amrein, S.; Schleth, F.; Schulte, T.; Walton, J. C. *J. Am. Chem. Soc.* **2003**, *125*, 5726. (c) Walton, J. C.; Studer, A. *Acc. Chem. Res.* **2005**, *38*, 794.

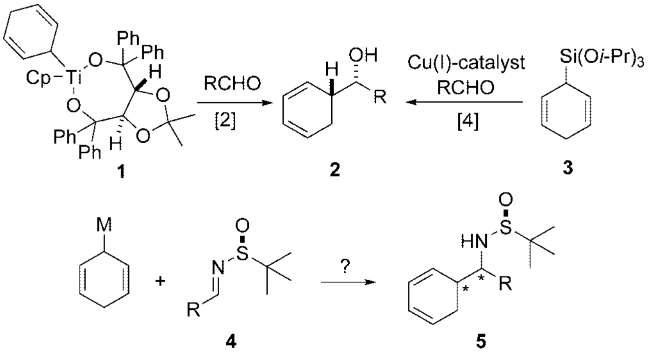
(4) Umeda, R.; Studer, A. *Org. Lett.* **2007**, *9*, 2175.

(5) Reviews: (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (b) Ellman, J. A. *Pure Appl. Chem.* **2003**, *75*, 39. (c) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003. (d) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869.

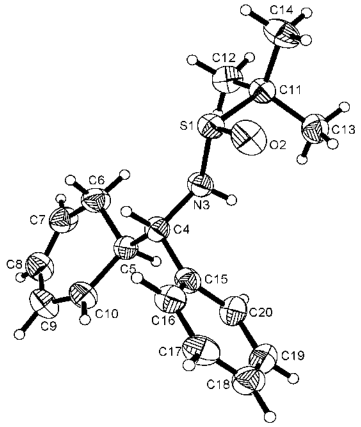
(6) Some recent examples on allyl metal additions:(a) Li, S.-W.; Batey, R. A. *Chem. Commun.* **2004**, 1382. (b) Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3823. (c) Kolodney, G.; Sklute, G.; Perrone, S.; Knochel, P.; Marek, I. *Angew. Chem., Int. Ed.* **2007**, *46*, 9291.

10.1021/ol800478q CCC: $40.75

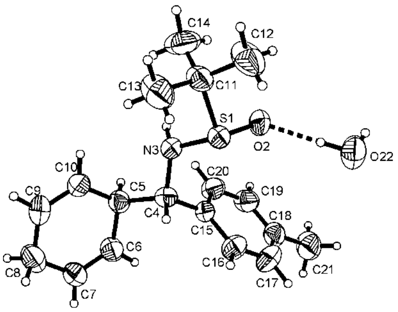
Scheme 1. Desymmetrization of Cyclohexadienes



diene **6a** was formed in larger amounts depending on the metal used. The relative configuration of the major isomer **5a** was unambiguously assigned by X-ray analysis (see Figure 1). For the symmetrical diene **6a** the relative configuration was assigned in analogy to the X-ray structure of its derivative **6b**.



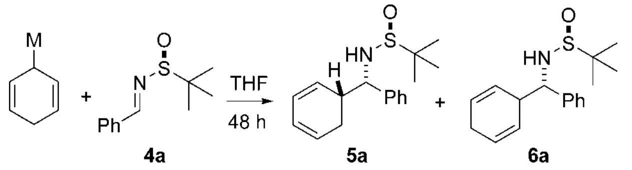
5a



6b

Figure 1. X-ray structures of compounds **5a** and **6b**.

Table 1. Reaction of Various Metallated Cyclohexadienes with **4a**



entry	M	temp [°C]	**5a** [%]	**6a** [%]
1	Li	−50	50	11[a]
2	ZnC_6H_7	−50	14[a]	62
3	ZnC_6H_7	−30[b]	24[a]	50
4	ZnC_6H_7	−78[c]	18[a]	29[a]
5	ZnC_6H_7	−50[d]	58	9
6	ZnCl	−50	13[a]	55
7	MgCl[e]	−78	69	6
8	MgCl[f]	−78	77	8

[a] Isolated as an inseparable mixture with other isomers. [b] Reaction was run for 18 h. [c] Reaction was run for 64 h. [d] Reaction was conducted in Et_2O. [e] Transmetalation with 0.55 equiv $MgCl_2$. [f] Transmetalation with 1.0 equiv $MgCl_2$.

The reactive cyclohexadienyl-Li compound provided the desired desymmetrization product **5a** (50%) along with an inseparable mixture of an unidentified isomer and the symmetrical diene **6a** (Table 1, entry 1). A reversal of the regioselectivity was achieved with the dicyclohexadienyl zinc derivative.[7] The symmetrical isomer **6a** was isolated as major compound in 62% yield with a high diastereoselectivity (entry 2).[8] The diene **5a** was isolated as an inseparable mixture containing the diastereoisomer of **6a** and another unidentified isomer in 14% combined yield. The same reaction at −30 °C afforded a similar result (entry 3). At −78 °C, reaction with **4a** was far slower and a lower selectivity resulted (entry 4). Interestingly, the selectivity was reversed upon switching to Et_2O as a solvent (entry 5). We assume that transmetalation to zinc did not occur under these conditions since the selectivity was similar to the selectivity obtained for the Li-experiment. Reaction of the more Lewis-acidic cyclohexadienyl-ZnCl-derivative with **4a** gave a slightly lower selectivity as compared with the result obtained using the dicyclohexadienyl zinc derivative (entry 6). The addition of cyclohexadienyl-triisopropoxy titanate (M = Ti(O*i*-Pr)$_3$) to **4a** at −78 °C occurred with low selectivity (6 isomers were identified by GC analysis) and with a low combined yield (32%, not shown in Table 1). At higher temperature, the Ti-cyclohexadienyl derivative was not stable.[9] Pleasingly, with the cyclohexadienyl-MgCl compound the desired desymmetrized product **5a** was obtained with excellent diastereoselectivity (69% yield, ds > 99%, entry 7). The diene **6a** was isolated in 6% yield as the only detectable side product. The other possible three isomers of the product 1,3-diene were not identified. A slightly lower regioselectivity but higher yield was obtained upon using 1.0 equiv of $MgCl_2$ in the transmetalation step (entry 8). To

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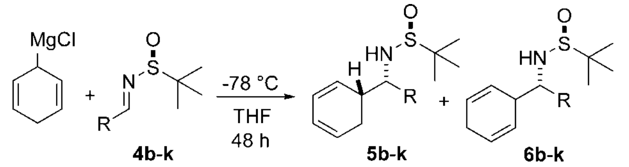
(7) Allyl-zinc compounds have successfully been used in stereoselective allylations: (a) Ren, H.; Dunet, G.; Mayer, P.; Knochel, P *J. Am. Chem. Soc.* **2007**, *129*, 5376. (b) Dunet, G.; Mayer, P.; Knochel, P *Org. Lett.* **2008**, *10*, 117. See also ref. 6c.

(8) An authentic sample of the diastereoisomer of symmetrical diene **6a** was prepared for comparison. In the fraction of the inseparable isomers (14% combined yield), the diastereoisomer of **6a** was identified and the diastereoselectivity was calculated to be 50:1.

(9) Knoop, C. A.; Studer, A. *Adv. Synth. Catal.* **2005**, *347*, 1542.

summarize the screening studies we can state that depending on the metal used, either the symmetrical diene **6a** (cyclohexadienyl-ZnC$_6$H$_7$) or the diene **5a** (cyclohexadienyl-MgCl) could be obtained in a good yield with good regioselectivity and excellent diastereoselectivity.

Table 2. Reaction of Cyclohexadienyl-MgCl with Various Imines[a]



entry	R	compd	**5** [%]	ds (**5**) [%][b]	**6** [%]
1	4-MeC$_6$H$_4$	**b**	74	>99	4
2	2-MeC$_6$H$_4$	**c**	69[c]	>99	13
3	4-MeOC$_6$H$_4$	**d**	86	>99	5
4	2-MeOC$_6$H$_4$	**e**	72	>99	8
5	2-furyl	**f**	77	>99	5
6	*trans*-PhCH=CH	**g**	75	>99	5
7	*i*-Pr	**h**	79[d]	>99	4
8	C$_6$H$_{11}$	**i**	74[d]	>99	9
9	*t*-Bu	**j**	58[d,e]	>99	1
10	PhCH$_2$	**k**	48[c,d]	>99	3

[a] Conditions: 1,4-cyclohexadiene (1.0 mmol), *s*-BuLi (1.1 mmol), TMEDA (1.1 mmol) in THF at −78 °C for 1.5 h, then MgCl$_2$ (0.55 mmol) at −78 °C for 3 h, imines **4** for 30 min at −78 °C. [b] Diastereoselectivity with respect to the other three possible 1,3-diene isomers. [c] Containing 2% of the diastereoisomer of **6**. [d] The symmetrical diene **6** could not be separated from **5**. Yield was calculated based on the ratio **5** to **6** measured by GC-analysis. [e] The diastereoisomer of **6j** was detected by GC analysis (<1%).

To study the scope and limitations of our new method, various imines were reacted under the optimized conditions with cyclohexadienyl-MgCl (Table 2) and with the dicyclohexadienyl zinc derivative (Table 3). The relative configuration of the products **5b**−**k** was assigned in analogy to compound **5a**, and the assignment of the relative configuration of products **6a** and **6c**−**i** is based on the X-ray structure of **6b**.

Table 3. Reaction of Cyclohexadienyl-ZnC$_6$H$_7$ with Various Imines[a]

entry	R	compd	**6** [%]	dr (**6**)	other isomers [%][b]
1	4-MeC$_6$H$_4$	**b**	64	30:1	16
2	2-MeC$_6$H$_4$	**c**	49	9:1	24
3	4-MeOC$_6$H$_4$	**d**	59[c]	11:1	10
4	2-MeOC$_6$H$_4$	**e**	49[c]	n.d.	18
5	2-furyl	**f**	32	n.d.	22
6	*i*-Pr	**h**	57[c]	>99:1	9
7	C$_6$H$_{11}$	**i**	58[c]	>99:1	4

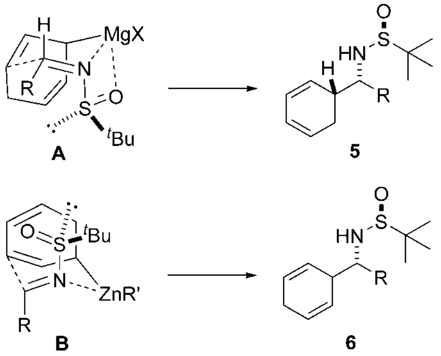
[a] Conditions: 1,4-cyclohexadiene (2.0 mmol), *s*-BuLi (2.2 mmol), TMEDA (2.2 mmol) in THF at −78 °C for 1.5 h, then ZnCl$_2$ (1.1 mmol) at −78 °C for 3 h, then imines **4**, at −50 °C for 18 h to 2d. [b] Combined yield of other isomers formed. [c] The other isomer(s) could not be separted. Yield calculated based on the ratio determined by GC- or ^{1}H NMR analysis.

Excellent diastereoselectivities were obtained for the reaction with the *p*-substituted sulfinyl aryl amines **4b** and **4d** to give **5b** and **5d** as major compounds with good yields and high regioselectivities (entries 1,3). The ortho-substituted congeners delivered similar results (entries 2,4). A high regioselectivity was also achieved with the furyl derivative **4f** (entry 5). Nonaromatic sulfinyl imines **4g**−**k** reacted with cyclohexadienyl-MgCl with excellent diastereoselectivities and good to excellent regioselectivities (entries 6−10).

Compared to the Mg-dienyl complex, the dicyclohexadienyl zinc derivative provided slightly lower selectivities favoring the symmetrical dienes **6** (Table 3). Aromatic *N-tert*-butanesulfinyl imines **4b**−**e** provided the dienes **6b-e** in moderate to good yields with high diastereoselectivities (49−64%, entries 1−4).[10] The 1,3-dienes were formed as a mixture of isomers in 10−24% combined yield. A lower regioselectivity was obtained with the furyl derivative **4f** (entry 5). High regioselectivities, excellent diastereoselectivities and good yields were achieved with the alkylsulfinyl imines **4h** and **4i** (entries 6,7).

As a mechanism to explain the regiodivergent outcome and the stereoselectivities of the reactions, we suggest the following two models. The Grignard reagent probably reacts from its symmetrical cyclohexadienyl-MgCl isomer via a six-membered chair transition state according to model **A** (Scheme 2). The Mg-metal acts as Lewis acid to complex the nitrogen lone pair and the oxygen atom of the sulfinyl group.[11] The sulfinyl imine reacts via its cis isomer[12] to **5**. Reaction of the dicyclohexadienyl-zinc compound probably occurs via the non symmetrical dienyl metal structure as depicted in **B** to provide **6**. A similar transition state model was recently suggested by Marek for diastereoselective allylations of allyl zinc derivatives to chiral *N-tert*-butanesulfinyl imines.[6c]

Scheme 2. Models to Explain the Selectivity



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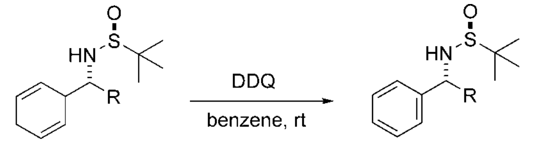
[10] An authentic sample of the diastereoisomer of symmetrical diene **6a** was prepared for comparison. The ^{1}H NMR showed characteristic signals which were used to identify the presence of the diastereoisomers of **6b**−**d**. Due to signal overlap, the diastereosiomer ratio could not be determined for **6e** and **f**. By GC analysis, the diastereoisomer of **6i** was not identified. Selectivity of **6h** was assigned in analogy.

[11] Tang, T. P; Ellman, J. A *J. Org. Chem.* **1999**, *64*, 12.

[12] Stereoselective additions onto *cis*-imines: (a) Corey, E. J.; Decicco, C. P.; Newbold, R. C *Tetrahedron Lett.* **1991**, *32*, 5287. (b) Roy, U. K.; Roy, S. *Tetrahedron Lett.* **2007**, *48*, 7177.

Scheme 3. DDQ Mediated Oxidation



6b (R = 4-MeC_6H_4)
6c (R = 2-MeC_6H_4)

7b (77%, R = 4-MeC_6H_4)
7c (85%, R = 2-MeC_6H_4)

Finally, we decided to oxidize the product dienes to the corresponding chiral diarylmethylamine derivatives. This important structural unit can be found in biologically active compounds.[13] In agreement with our previous studies,[14] the 1,3-dienes **5** could not be cleanly oxidized. However, smooth oxidation of the symmetrical 1,4-dienes could be achieved. Hence, treatment of **6b** or **6c** with DDQ in benzene at room temperature afforded the corresponding protected diarylmethylamines **7b** and **7c** in good yields as diastereoisomerically pure compounds (Scheme 3).

In summary, we present a novel approach for the desymmetrization of achiral metallated cyclohexadienes with chiral *N*-*tert*-butanesulfinyl imines. The reaction of readily generated cyclohexadienyl-MgCl with various *N*-*tert*-butanesulfinyl imines provided the corresponding desymmetrized 1,3-dienes with excellent diastereoselectivities and high regioselectivities. The regioselectivity could be reversed by using dicyclohexadienyl-Zn. The 1,4-dienes obtained with the Zn-chemistry were readily oxidized to the corresponding diarylmethylamine derivatives.

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

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(13) Stereoselective syntheses: (a) Hayashi, T.; Ishigedani; M, *J. Am. Chem. Soc.* **2000**, *122*, 976. (b) Plobeck, N.; Powell, D. *Tetrahedron: Assymetry* **2002**, *13*, 303. (c) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584. (d) Castagnolo, D.; Giorgi, G.; Spinosa, R.; Corelli, F.; Botta, M. *Eur. J. Org. Chem.* **2007**, 3676.

(14) Umeda, R.; Studer, A. *Org. Lett.* **2008**, *10*, 993.