C_2-Symmetric Bissulfoximines in Palladium-catalyzed Allylic Alkylations

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Abstract: C_2-Symmetric bissulfoximines **2** have been used as chiral ligands in palladium-catalyzed asymmetric allylic alkylations. With **2c** enantioselectivities of up to 98% ee have been achieved in the reaction of 1,3-diphenylpropenyl acetate with malonates as nucleophiles.

Key words: asymmetric catalysis, allylic alkylation, enantioselectivity, palladium, sulfoximines

Since their discovery by Bentley and Whitehead,[1] sulfoximines have emerged as versatile reagents in organic synthesis.[2] Their application ranges from the use as chiral auxiliaries[3] and ligands[4] in catalysis to incorporations as modules in pseudopeptidic structures.[5] Recently, we introduced a new aryl-bridged C_2-symmetric bissulfoximine **1** and demonstrated its potential as ligand in highly enantioselective copper(II)-catalyzed hetero Diels–Alder reactions.[6] As part of the ongoing study we now found that structurally related bissulfoximines **2** having an alkyl backbone can be applied in palladium-catalyzed allylic alkylations[7] furnishing products with very high enantiomeric excesses (Figure 1).

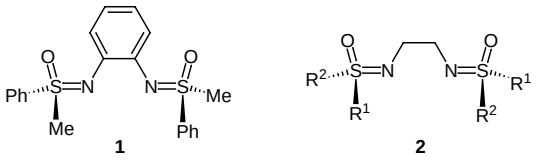
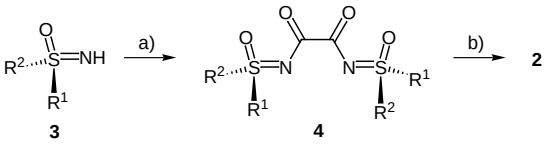


Figure 1

The syntheses of the new alkyl-bridged C_2-symmetric bissulfoximines **2** followed a synthetic strategy described earlier.[8] Thus, treatment of the corresponding sulfoximine **3**[9] with oxalyl chloride followed by borane reduction of the carbonyl groups of the resulting bridged compounds **4** gave the desired bissulfoximines **2** in good yields (Table 1).

The potential of the new bissulfoximines to serve as ligands in Pd-catalyzed nucleophilic substitution reactions was first investigated with 1,3-diphenylpropenyl acetate (**5**) and dimethylmalonate (**6**) as substrates. In all catalyses the yield of **7** was good (72%) and the enantioselectivities ranged from 8 to 93% ee (Table 2).[10,11]

Table 1 Synthesis of Ethylene-bridged Bissulfoximines **2a**–**d** via an Acylation Reduction Sequence



a) $(COCl)_2$ (0.5 equiv), DMAP (cat.), CH_2Cl_2, 0 °C. b) BH_3•THF, CH_2Cl_2.

Entry	R^1	R^2	Yields of **3** → **4** [%]	Yields of **4** → **2** [%]	Bissulfoximine
1	Me	Ph	90	68	**2a**
2	*i*-Pr	Ph	88	66	**2b**
3	*c*-Pen	Ph	85	65	**2c**
4	2-MeO-Ph	Me	93	69	**2d**

The best results (93% ee at 0 °C) were obtained with bissulfoximine **2c** having a cyclopentyl group as aliphatic substituent at sulfur (entries 3 and 7). Using the *S*,*S*-enantiomer of **2c** led to *R*-configurated **7** predominately. Lowering the reaction temperature had a positive effect on the ee of **7**. To our surprise use of **2d** gave **7** only with 8% ee. This result was unexpected, because in the previously studied HDA reaction, catalyses with **2d** gave products with > 90% ee. Along with the low ee in the reaction with **2d** a remarkable high reactivity was observed. Thus in this case the conversion was complete after 2 hours, whereas in catalyses with **2a**–**c** reaction times of several days were required to afford **7** in high yield. Raising the reaction temperature to 50 °C effected an increase in yield at significantly shorter reaction times, but lowered the ee of **7** (entries 8 and 9).

With the notion that an increased steric bulk at the sulfur atoms of **2** would be beneficial for the enantioselectivity of the catalysis, we attempted to prepare bis(*tert*-butyl)-substituted bissulfoximine **2e** according to the synthetic strategy described above (coupling of two sulfoximines with oxalyl chloride followed by borane reduction). Whereas the first step starting from (*S*)-*S*-*tert*-butyl-*S*-phenyl sulfoximine (**3e**)[9] proceeded well to give **4e**, the subsequent selective reduction of the two carbonyl groups failed. Instead of the desired bissulfoximine **2e** compound **8** was obtained in 60% yield.[12,13] Finally, **2e** became accessable on another route involving a double deprotonation of **2b** followed by alkylation of the intermediate dianion with iodomethane (50% yield) (Figure 2).

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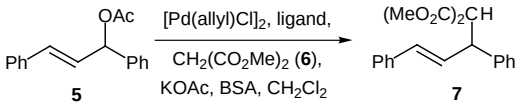
Table 2 Enantioselective allylic Alkylation of 1,3-Diphenylpropenyl Acetate using Bissulfoximines **2a**–**d**[a]



Entry	Ligand	Yield [%]	Temp [°C]	Time	ee of **7** [%]
1	**2a**	73	r.t.	5 d	72
2	**2b**	78	r.t.	5 d	76
3	**2c**	78	r.t.	5 d	90
4	**2d**	99	r.t.	2 h	8
5	**2a**	70	0	11 d	76
6	**2b**	72	0	11 d	81
7	**2c**	75	0	11 d	93
8[c]	**2c**	99	+50	1.5 h	84
9[d]	**2c**	99	+50	2 h	82

[a] Conditions: $[Pd(allyl)Cl]_2$ (5 mol%), ligand (10 mol%), 3 equiv BSA, 3 equiv malonate, cat. KOAc.
[b] Determined by HPLC using a chiral column (Chiralcel AD; heptane:*i*-PrOH = 95:5).
[c] 7.5 mol% of $[Pd(allyl)Cl]_2$.
[d] 5 mol% of **2c** and 2.5 mol% of $[Pd(allyl)Cl]_2$ was used.

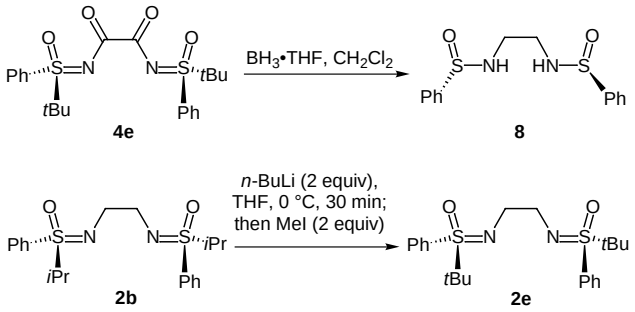
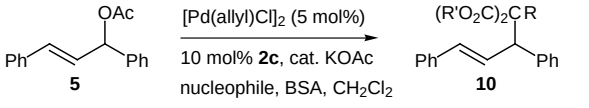


Figure 2

Contrary to our expectations, use of **2e** as ligand in the described allylic alkylation with **5** and **6** did not improve the catalysis at all. Thus, even after one week reaction time only 15% conversion of **5** was observed and finally **7** was isolated as a racemate. Most likely, the attack of the intermediate Pd-allyl complex by the nucleophile is sterically too hindered due to the presence of the bulky *tert*-butyl groups in **2e**, which in consequence causes the low conversion compared to the catalyses with the other bissulfoximines.

Since bissulfoximine **2c** gave the best results in the catalysis, we also studied its use in the reaction of 1,3-diphenylpropenyl acetate (**5**) with other malonates. Table 3 summarizes the most significant results.

Table 3 Use of substituted Malonates in the enantioselective allylic Alkylation of 1,3-Diphenylpropenyl Acetate (**5**)



a: R = R' = Me
b: R = NHAc, R' = Et

Entry	Nucleophile	Yield [%]	Temp [°C]	Time [h]	ee of **10** [%]
1	$MeCH(CO_2Me)_2$, (**9a**)	79	45	30	94[a]
2	$AcNHCH(CO_2Et)_2$, (**9b**)	89	45	96	98[b]

[a] Determined by ^1H NMR using 15 mol% $Eu(hfc)_3$.
[b] Determined by HPLC using a chiral column (Chiralcel OJ; heptane:*i*-PrOH = 3:1).

To our delight we found that with methyl malonic acid dimethylester (**9a**) the corresponding substitution product (*S*)-**10a** had 94% ee. Use of the acetamido derivative **9b** afforded (*S*)-**10b** with 98% ee.[14,15]

In summary, we demonstrated the use of C_2-symmetric bissulfoximines as ligands in the palladium-catalyzed asymmetric alkylations and achieved enantioselectivities of up to 98% ee.

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References

(1) Whitehead, J. K.; Bentley, H. R. *J. Chem. Soc.* **1952**, 1572.
(2) Reviews: (a) Johnson, C. R. *Aldrichimica Acta* **1985**, *18*, 3. (b) Johnson, C. R. *Acc. Chem. Res.* **1973**, *6*, 341. (c) Pyne, S. G. *Sulfur Rep.* **1992**, *12*, 57. (d) Reggelin, M.; Zur, C. *Synthesis* **2000**, 1.
(3) Selected examples: (a) Pyne, S. G.; Dong, Z.; Skelton, B. W.; White, A. W. *J. Org. Chem.* **1997**, *62*, 2337. (b) Reggelin, M.; Heinrich, T.; *Angew. Chem. Int. Ed.* **1998**, *37*, 2883; *Angew. Chem.* **1998**, *110*, 3005. (c) Bosshammer, S.; Gais, H.-J. *Synthesis* **1998**, 919. (d) Paquette, L. A.; Gao, Z.; Ni, Z.; Smith, G. F. *J. Am. Chem. Soc.* **1998**, *120*, 2543. (e) Harmata, M.; Kahraman, M.; Jones, D. E.; Pavri, N.; Weatherwax, S. E. *Tetrahedron* **1998**, *54*, 9995.
(4) (a) Bolm, C.; Felder, M.; Müller, J. *Synlett* **1992**, 439. (b) Bolm, C.; Felder, M. *Tetrahedron Lett.* **1993**, *34*, 6041. (c) Bolm, C.; Müller, J.; Schlingloff, G.; Zehnder, M.; Neuburger, M. *J. Chem. Soc., Chem. Commun.* **1993**, 182. (d) Bolm, C.; Seger, A.; Felder, M. *Tetrahedron Lett.* **1993**, *34*, 8079. (e) Bolm, C.; Felder, M. *Synlett* **1994**, 655. (f) Bolm, C.; Müller, P. *Tetrahedron Lett.* **1995**, *36*, 1625. (g) Bolm, C.; Müller, P. *Acta Chem. Scand.* **1996**, *50*, 305.
(5) (a) Bolm, C.; Kahmann, J. D.; Moll, G. *Tetrahedron Lett.* **1997**, *38*, 1169. (b) Bolm, C.; Moll, G.; Kahmann, J. D. *Chem.– Eur. J.* **2001**, *7*, 1118.
(6) Bolm, C.; Simic, O. *J. Am. Chem. Soc.* **2001**, *123*, 3830.

(7) Reviews: (a) Hayashi, T. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, **1993**, 325. (b) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (c) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, **1999**, 833. (d) Helmchen, G. *J. Organomet. Chem.* **1999**, *576*, 203. (e) Trost, M. B.; Lee, C. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, **2000**.

(8) Bolm, C.; Bienewald, F.; Harms, K. *Synlett* **1996**, 775.

(9) Both enantiomers of *S*-methyl-*S*-phenyl-sulfoximine (**3a**) are commercially available (Lancaster). To prepare **3a** in enantiopure form on a large scale, we recommend the improved protocol described in: Brandt, J.; Gais, H.-J. *Tetrahedron: Asymmetry* **1997**, *6*, 909. Sulfoximines **3b**, **3c**, and **3e** were prepared from TMS-protected (*S*)-*S*-methyl-*S*-phenyl-sulfoximine via a metalation/alkylation sequence. The synthesis of **3d** followed the procedure described in ref.[4g] (MSH imination of the corresponding enantiopure sulfoxide).

(10) In a typical experiment $[Pd(C_3H_5)Cl]_2$ (4.0 mg, 0.011 mmol) and **2c** (10.0 mg, 0.023 mmol) were dissolved in 2 mL of CH_2Cl_2 under an argon atmosphere and the resulting pale yellow solution was stirred for 30 min at r.t. To this solution was added 1,3-diphenylpropenyl acetate (57 mg, 0.23 mmol) and stirring was continued for further 10 min. After cooling to 0 °C bistrimethylsilylamide (BSA) (165 μL, 137 mg, 0.68 mmol), dimethylmalonate (77 μL, 89 mg, 0.68 mmol) and a catalytic amount of potassium acetate were added and the reaction monitored by TLC. After consumption of the starting material (Table 2, entry 7) the product was directly purified by column chromatography, (silica, petroleum ether–Et_2O, 3:1, R_f = 0.35) furnishing **7** (56 mg, 0.17 mmol, 75%) as a colorless solid.

(11) For the use of a C_1-symmetric sulfoximine-containing ligand in this reaction, see: Bolm, C.; Kaufmann, D.; Zehnder, M.; Neuburger, M. *Tetrahedron Lett.* **1996**, *37*, 3985.

(12) Similar compounds have recently been used in asymmetric Cu-catalyzed [4+2] cycloadditions: Owens, T. D.; Hollander, F. J.; Oliver, A. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 1539.

(13) The absolute configuration of **8** has not been determined, but we assume that the reduction of **4e** proceeds with retention of configuration at sulfur as shown.

(14) For the assignment of the absolute configurations of **10a** and **10b**, see: (a) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566; *Angew. Chem.;* **1993**, *105*: 614. (b) Vyskočil, Š.; Smrčina, M.; Hanuš, V.; Polášek, M.; Kočovský, P. *J. Org. Chem.* **1998**, *63*, 7738.

(15) Attempts to employ cyclohexenyl acetate as substrate (together with **6**) resulted in the formation of corresponding product with only 20% ee.