

Enantioselective Molybdenum-Catalyzed Allylic Alkylation Using Chiral Bisoxazoline Ligands

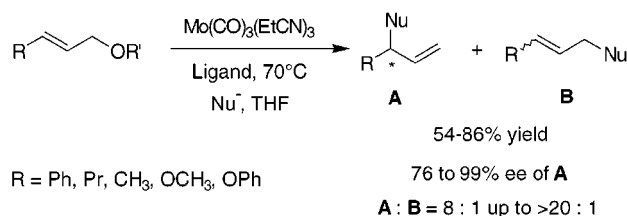
Frank Glorius and Andreas Pfaltz*

Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1,
D-45470 Mülheim an der Ruhr, Germany[§]

pfaltz@ubaclu.unibas.ch

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ABSTRACT



A series of chiral C_2 -symmetric bisoxazolines with *trans*-1,2-diaminocyclohexane backbones was synthesized. In view of the promising results obtained by Trost with analogous bispyridine ligands, we tested our new ligands in the enantioselective molybdenum-catalyzed allylic alkylation of 1- and 3-monosubstituted allylic substrates. Enantiomeric excesses of up to 98% and branched/linear ratios of up to 11:1 were obtained with (*E*)-3-(*n*-alkyl)allyl carbonates. (*E*)-3-Phenoxyallyl acetate gave a branched/linear ratio of >20:1 and an ee of 98%.

Enantioselective transition metal-catalyzed allylic alkylation has become an important tool for asymmetric synthesis.¹ During the past few years, substantial progress has been made, and as a result, excellent enantiomeric excesses can now be obtained with many prochiral or racemic substrates. Nevertheless, the search for new chiral ligands and catalysts continues, since there are still classes of substrates which give unsatisfactory results with the known catalysts.

Unsymmetrically substituted allyl derivatives are particularly demanding substrates, because, in addition to the requirement of enantiocontrol, the problem of regioselectivity has to be solved. With most palladium catalysts, monosubstituted allyl systems such as 1- or 3-aryllallyl derivatives react with carbon nucleophiles preferentially at the unsubstituted terminus, giving rise to an achiral linear product. It is only recently that catalysts have been discovered that allow

the preparation of chiral, branched regioisomers from 1- or 3-aryllallyl esters, with good enantio- and regioselectivity. Such a reversal of regioselectivity has been achieved using palladium complexes with certain chiral ligands such as **1**,² tungsten complexes derived from ligand **2**,³ related iridium catalysts,⁴ and, most recently, with a molybdenum complex⁵ derived from ligand **3**.⁶ In terms of regio- and enantioselectivity, the chiral molybdenum catalyst developed by Trost⁵ is clearly the most effective catalyst available today, giving a branched-to-linear ratio of 49:1 and an ee of 99% in the reaction of methyl (*E*)-1-phenylallyl carbonate with dimethyl malonate.

(2) Pretot, R.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 323. See, also: Hayashi, T.; Kawatsura, M.; Uozumi, Y. *J. Chem. Soc., Chem. Commun.* **1997**, 561.

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(5) Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104.

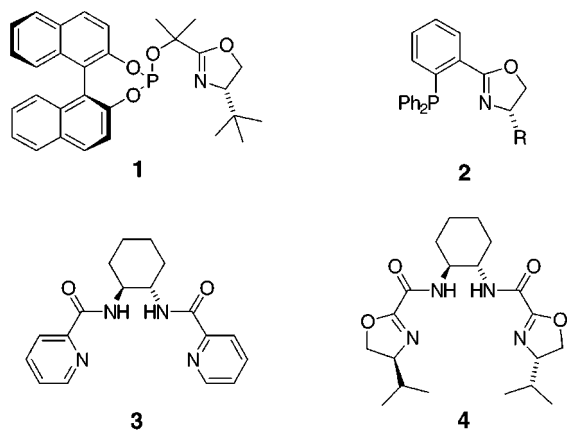
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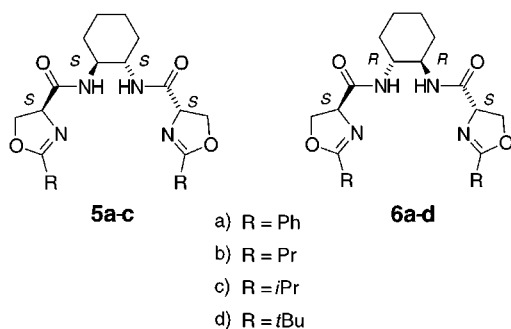
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[§] New address: Department of Chemistry, University of Basel, St. Johans-Ring 19, CH-4056 Basel, Switzerland.

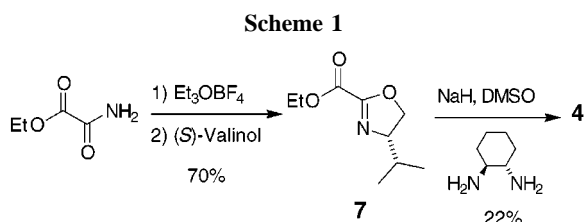
(1) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. Hayashi, T. In *Catalytic Asymmetric Synthesis*; Ojima, Ed.; VCH Publishers: New York, 1993; pp 325–365. Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089. Consiglio, G.; Waymouth, R. M. *Chem. Rev.* **1989**, *89*, 257.



In the course of our work on chiral oxazoline ligands,⁷ we have prepared a series of bisoxazolines with a *trans*-1,2-diaminocyclohexane backbone. Although these ligands were originally designed for other applications,⁸ Trost's promising results with ligand **3** prompted us to test the bisoxazolines **4–6** in the molybdenum-catalyzed allylic alkylation of monosubstituted allyl derivatives.



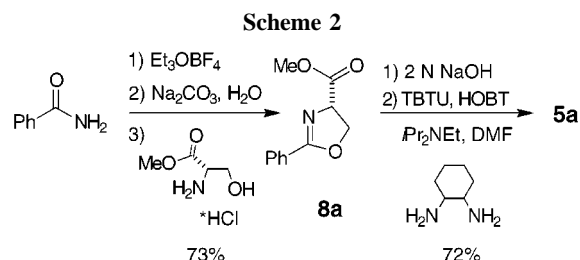
Ligands **4–6** can be readily synthesized using chiral amino alcohols and *trans*-1,2-diaminocyclohexane as commercially available enantiopure components. For example, ligand **4** was obtained in just two steps from ethyl oxamate; initial reaction with (*S*)-valinol afforded the oxazoline **7** which was coupled to (*S,S*)-1,2-diaminocyclohexane as shown in Scheme 1.



Although the yield of the latter reaction was low, the procedure is attractive because it is simple and avoids additional steps for the activation of the carboxyl group of **7**.

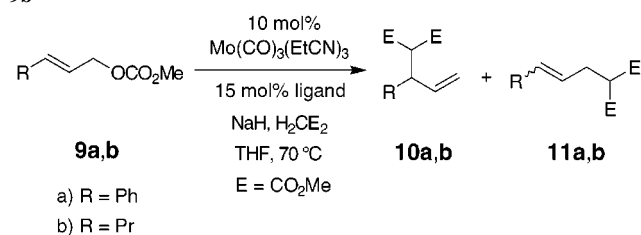
Similarly, the diastereomeric ligands **5** and **6** were prepared from the corresponding amides as exemplified in Scheme

2. In the synthesis of **5a**, the imidate derived from benzamide was coupled with *L*-serine methyl ester hydrochloride to give the oxazoline ester **8a** in 73% overall yield. The corresponding carboxylic acid was obtained in 76% yield by hydrolysis with 2 N aqueous sodium hydroxide solution at room temperature. Finally, coupling with (*S,S*)-1,2-diaminocyclohexane, using standard procedures, gave the desired ligand **5a** in 95% yield from the carboxylic acid.



For our initial allylic alkylation experiments, methyl (*E*)-3-phenyl-2-propenyl carbonate **9a** was used as a test substrate to compare the performance of our ligands with ligand **3**. The bisoxazolines **4** and **5b** were found to induce similar levels of enantioselectivity as the bispyridine ligand **3**; however, the branched/linear ratios were lower and the reactions somewhat slower (Table 1, entries 1–3). Further-

Table 1. Enantioselective Allylic Alkylation Using Substrates **9a** and **9b**^a

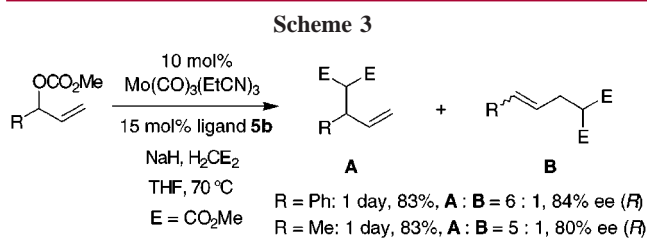


entry	R	ligand	time, days	% yield ^b	10:11	% ee of 10 ^c
1 ^d	Ph	3	3 h	70	49:1	99 (<i>R</i>)
2	Ph	4	0.5	86	14:1	99 (<i>R</i>)
3	Ph	5b	1	83	6:1	98 (<i>R</i>)
4	Pr	3	1.5	80	8:1	98 (–)
5	Pr	5b	2	69	2:1	96 (+)
6	Pr	6b	1.5	84	8:1	98 (–)
7	Pr	5c	2.5	54	2:1	86 (+)
8	Pr	6c	1.5	83	8:1	97 (–)

^a All reactions were carried out under argon. ^b Isolated combined yields. ^c Determined by HPLC using Daicel Chiralcel OJ and GC using Chiraldex γ -CD-TA columns. ^d Entry taken from ref 5 (reaction at room temperature).

more, in line with observations by Trost,⁵ the corresponding branched substrate reacted with significantly lower ee (with **5b** 84% vs 98% ee; Scheme 3).

Next we turned our attention toward the analogous alkyl-substituted substrates. Recently, achiral iridium⁹ and rhod-

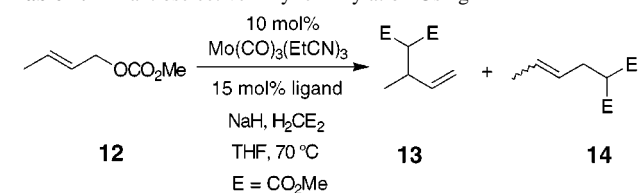


ium¹⁰ catalysts have been described, which give high branched/linear ratios with such allylic systems. However, highly enantioselective allylic substitutions with carbon nucleophiles have not been achieved so far with this class of substrate.

As expected, (*E*)-2-hexenyl methyl carbonate **9b** was less reactive than the corresponding 3-phenylallyl derivative and required reaction times of 1.5–2.5 days at 70 °C. Ligands **3**, **6b**, and **6c** all gave an 8:1 ratio of **10**:**11** with ee's of 97–98% (entries 4, 6, and 8). The corresponding diastereomers **5b** and **5c**, which are derived from the opposite enantiomer of 1,2-diaminocyclohexane, gave lower branched/linear ratios and, in the case of **5c**, a distinctly lower ee (entries 5 and 7). Ligands **5b,c** also induced the opposite absolute configuration to **6b,c**, implying that the enantioselectivity is largely controlled by the *trans*-diaminocyclohexane unit.

Our results for (*E*)-2-butenyl methyl carbonate **12** are summarized in Table 2.¹¹ When ligand **4** was used, a 1.5:1 mixture of **13**:**14** was obtained in 88% yield with 94% ee after 1 day at 70 °C (entry 2). Reducing the amount of Mo(CO)₃(EtCN)₃ to 2.5% led to an increase in reaction time but left the regio- and enantioselectivity virtually unchanged (entry 3).

Table 2. Enantioselective Allylic Alkylation Using **12**^a



entry	ligand	time, days	% yield ^b	13 : 14	% ee of 13 ^c
1	3	1	85	5:1	94 (<i>R</i>)
2	4	1	88	1.5:1	94 (<i>R</i>)
3	4 ^d	5	80	1.5:1	93 (<i>R</i>)
4	5a	5	73	5:1	74 (<i>R</i>)
5	6a	3	76	7:1	85 (<i>S</i>)
6	5b	1	81	9:1	97 (<i>R</i>)
7	6b	2	80	11:1	96 (<i>S</i>)
8	5c	1.5	81	9:1	95 (<i>R</i>)
9	6c	1	86	7:1	92 (<i>S</i>)
10	6d	2	85	1.5:1	0

^a All reactions were carried out under argon. ^b Isolated combined yields. ^c Determined by GC (Chiraldex γ -CD-TA). ^d The reaction was performed with 2.5 mol % Mo(CO)₃(EtCN)₃ and 3.8 mol % **4**.

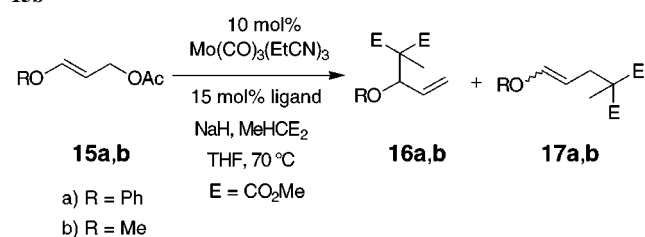
The phenyl-substituted ligands **5a** and **6a** gave higher branched/linear ratios, although at the expense of lower ee's (entries 4 and 5). The best results with the bisoxazoline ligands were obtained with the *n*-propyl-substituted derivatives **5b** and **6b**, comparing favorably with the bispyridine ligand **3**. Specifically, by employing ligand **5b**, a 9:1 mixture of **13** and **14** was obtained in 81% yield with an ee of 97% (entry 6), whereas ligand **6b** gave an 11:1 mixture of **13** and **14** in 80% yield and an ee of 96% (entry 7). The isopropyl-substituted ligands **5c** and **6c** gave slightly lower selectivities (entries 8 and 9) and the *tert*-butyl-substituted ligand **6d** afforded only racemic product with a low branched/linear ratio. These results show that by systematic variation of the substituents in the oxazoline ring, the regio- as well as the enantioselectivity can be optimized.

Once again, the corresponding branched substrate reacted with considerably lower enantioselectivity (80% vs 97% ee with ligand **5b**; Scheme 3).

Finally, the phenoxy- and methoxy-substituted allylic acetates **15a** and **15b** were studied as substrates. The Pd(PPh₃)₄-catalyzed reaction of **15b** with diethyl methylmalonate has been reported by Cazes and co-workers to yield only the branched product.¹²

Consistent with Cazes' result, the phenoxy derivative **15a** gave branched/linear ratios of greater than 20:1 in all cases (Table 3). The best enantioselectivity (98% ee) was achieved with ligand **5b**, whereas the other ligands afforded ee's of 93–96% ee. However, the methoxy derivative **15b** reacted with distinctly lower regio- and enantioselectivity. In contrast to the analogous Pd-catalyzed reaction,¹² the linear product

Table 3. Enantioselective Allylic Alkylation Using Substrates **15a** and **15b**^a



entry	R	ligand	time, days	% yield ^b	16 : 17	% ee of 16 ^c
1	Ph	3	2	79	>20:1	93 (–)
2	Ph	5b	2	79	>20:1	98 (–)
3	Ph	6b	1.5	81	>20:1	93 (+)
4	Ph	5c	2	78	>20:1	95 (–)
5	Ph	6c	2	75	>20:1	96 (+)
6	Me	3	1	60	>20:1	74 (+)
7	Me	5b	1	52	6:1	62 (+)
8	Me	6b	1	38	5:1	63 (–)
9	Me	5c	1	72	5:1	66 (+)
10	Me	6c	1	54	13:1	76 (–)
11	Me	6d	1	35	3:1	21 (–)

^a All reactions were carried out under argon. ^b Isolated combined yields. ^c Determined by HPLC using Daicel Chiralcel OJ and GC using Chiraldex γ -CD-TA.

17b was formed in varying amounts. High branched/linear ratios of 13:1 to >20:1 could be obtained with ligands **3** and **6c**, although the ee's were only moderate (74–76%; entries 6 and 10).

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(11) **Representative experimental procedure:** A solution of ligand **5b** (0.025 mmol) and Mo(CO)₃(EtCN)₃ (0.017 mmol) in 0.7 mL of freshly distilled THF was degassed and then stirred at 70 °C in an ampule with a Teflon-sealed (Young) valve under an argon atmosphere for 1 h. A solution of dimethyl sodiomalonate (prepared from dimethyl malonate (0.3 mmol) and NaH (0.22 mmol) in 1.0 mL of THF at room temperature) and (*E*)-2-butenyl methyl carbonate (0.17 mmol) were added. The solution was again degassed, and then stirred at 70 °C for 24 h. After the solution was cooled to room temperature, water was added. The mixture was extracted with ether, and the combined extracts were washed with brine and dried over MgSO₄. The solvents were evaporated in vacuo, and the resulting oil was purified by column chromatography on silica gel (pentane/*tert*-butyl methyl ether 10:1) to give 25.7 mg (0.138 mmol; 81% yield) of a 9:1 mixture of (*R*)-**13** and **14**. The enantiomeric excess of **13** and the regioselectivity were determined by GC. Chiraldex γ -CD-TA, 30 m, 50–100 °C, 1°/min, 90 kPa H₂, *t*_R = 33.4 min ((*R*)-(+)-**13**), 34.7 min ((*S*)-(–)-**13**), 41.7 min ((*E*)-**14**), 44.2 min ((*Z*)-**14**). Restek Rtx-1701, 30 m, 60–120 °C, 2°/min, 60 kPa H₂, *t*_R = 23.2 min (**13**), 27.4 min ((*E*)-**14**), 28.1 min ((*Z*)-**14**).

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In summary, we have shown that high enantio- and regioselectivities can be obtained in molybdenum-catalyzed allylic substitutions with monosubstituted 3-alkyl- and 3-phenoxyallyl esters, using the bispyridine ligand **3** or analogous chiral bisoxazolines **5–6**. In general, **3**, which is structurally simpler, is the ligand of choice. However, with certain substrates, the analogous bisoxazolines can give improved regio- and enantioselectivity. An attractive feature of the bisoxazoline ligands is the option to fine-tune their structure by variation of the substituents in the oxazoline rings.

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Supporting Information Available: General experimental procedures and analytical data for compounds **4–17**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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