ORGANIC LETTERS

2004
Vol. 6, No. 22
4097−4099

A New Class of Substituted Aryl Bis(oxazoline) Ligands for Highly Enantioselective Copper-Catalyzed Asymmetric Aldol Addition of Dienolsilane to Pyruvate and Glyoxylate Esters

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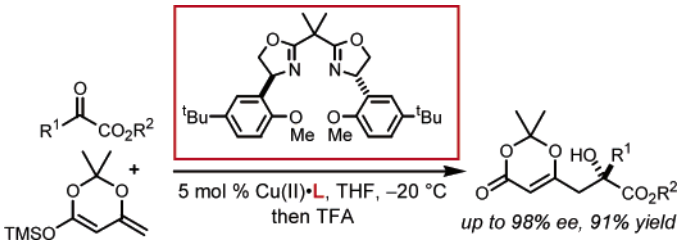
Received September 8, 2004

ABSTRACT



A new class of bis(oxazoline) ligands are introduced that feature *o*-alkoxyaryl substituents and provide the highest enantioselectivities yet reported for the copper-catalyzed asymmetric dienosilane aldol addition to pyruvate and glyoxylate esters. Enantioselectivities up to 98% ee (before recrystallization) and isolated yields up to 91% were observed. Additionally, chloride counterions were found to be superior to triflate for this reaction.

In recent years, the notoriously difficult challenge of executing catalytic, asymmetric nucleophilic additions on prochiral ketone substrates to afford enantiomerically pure tertiary alcohols has inspired a number of ingenious synthetic strategies.[1] In pioneering investigations, Evans described the use of C_2 symmetric bis(oxazoline) ligands (Figure 1, **A**) for the Lewis acid catalyzed aldol addition of trimethylsilyl ketene *S*,*O*-acetals to methyl pyruvate.[2] Recently, we became particularly interested in accessing highly optically enriched tertiary alcohols such as **3** (Scheme 1); however, broadly

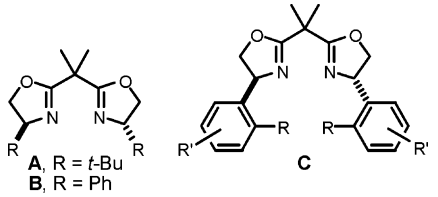
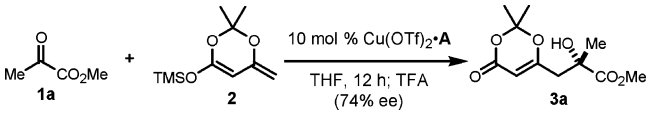


Figure 1.

(1) For recent examples of nonaldol approaches, see: Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 6538−6539. (b) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910−8911. (c) Tian, S.-K.; Hong, R.; Deng, L. *J. Am. Chem. Soc.* **2003**, *125*, 9900−9901. (d) Jeon, S.-J.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 9544−9545. (e) Garcia, C.; LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970−10971. (f) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195−6196. (g) Waltz, K. M.; Gavenonis, J.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3697−3699. (h) Tietze, L. F.; Volkel, L.; Wulff, C.; Weigand, B.; Bittner, C.; McGrath, P.; Johnson, K.; Schafer, M. *Chem. Eur. J.* **2001**, *7*, 1304−1308. (i) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445−446.

10.1021/ol048179w CCC: $27.50
Published on Web 09/30/2004

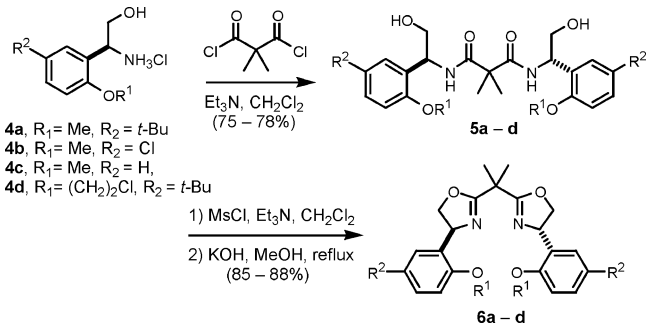
Scheme 1



substrate-tolerant catalysts for aldol additions of dienolsilanes to pyruvate esters have remained elusive.

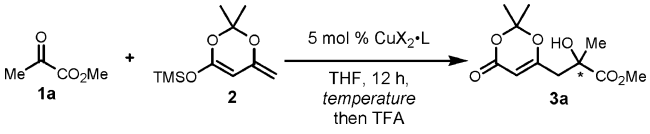
The state-of-the-art in this area provides aldol product **3a** in a modest 74% ee using the commercially available *tert*-butyl box ligand **A** (and 17% ee with ligand **B**).[3] While many structurally diverse bis(oxazoline) architectures have been introduced in recent years,[4−6] there exists a paucity of reported variations in aryl substituents (i.e., **C**) of bis(oxazoline)s.[7] In this regard, the electronic and steric tuning of aryl rings in chiral ligands is a cornerstone of reaction optimization, and given the gearing and high rotational barriers imposed by *ortho* substituents we chose to focus on their influence. However, at the onset of these investigations it became immediately obvious that a lack of suitable aryl glycinol precursors had thwarted advancements in this area. We addressed this deficiency by preparing a family of *o*-alkoxy-substituted aryl glycinols **4**[8] and converting four of these to their corresponding bis(oxazoline)s (Scheme 2).[9,10]

Scheme 2



Herein, we reveal that copper(II) complexes of bis(oxazoline) ligands **6** provide the highest levels of asymmetric induction

Table 1. Ligand Screening and Reaction Optimization[a]



			% ee (% yield)/counterion	
entry	ligand	*T* (°C)	OTf	Cl
1	**A**	−78	74 (77)[b]	91 (31)
2	**B**	−78	11 (70)[b]	40 (35)
3	**6a**	−78	76 (78)	90 (81)
4	**6b**	−78		86 (80)
5	**6c**	−78	39 (80)	20 (75)
6	**6d**	−78	11 (75)	44 (78)
7	**6a**	−40		90 (78)
8	**6a**	−20		94 (81)
9	**6a**	0		92 (85)

[a] Reactions were done in THF (0.25 M), with 1.1 equiv of dienolsilane relative to methyl pyruvate. Isolated yields. Enantiomeric excess was determined by chiral HPLC. [b] These values are similar to those reported in ref 3.

(up to 98% ee) observed to date in the addition of a dienolsilane to pyruvate and glyoxylate esters.

The key results from reaction optimization are summarized in Table 1. Our ideas about ligand design were supported by the substantially better asymmetric induction observed with aryl-substituted ligand **6a** (76% ee, entry 3) than the parent ligand **B** (11% ee, entry 2). The selectivity was further improved to 90% ee by replacing the triflate counterion with chloride.[11,12] Other changes to the ligand, such as decreasing the size of the aryl substituent at C(5) (entries 4 and 5) or increasing the sterics of the alkoxy protecting group (entry 6) resulted in decreased selectivity. The optimized conditions consist of running the reaction at −20 °C (compare entries 7−9) in THF with preformed catalysts.[13]

(2) (a) Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893−7894. (b) Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859−10860. (c) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686−699.

(3) van Lingen, H. L.; van de Mortel J. K. W.; Kekking, K. F. W.; van Delft, F. L.; Songinke, T.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2003**, 317−324. Our results were similar; see Table 1, entries 1 and 2.

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(5) (a) Pfaltz, A. *Acc. Chem. Res.* **1993**, *23*, 339−345. (b) Jørgensen, K. A.; Johannsen, M.; Yao, S.; Audrain, H.; Thorhauge, J. *Acc. Chem. Res.* **1999**, *32*, 605−613. (c) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335.

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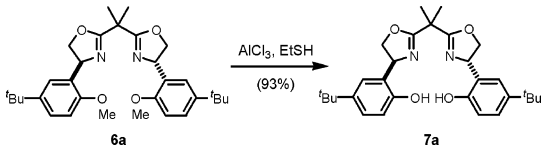
(7) To the best of our knowledge, there is only a single instance of a highly enantioselective (Diels−Alder) reaction catalyzed by a substituted aryl (α-1-naphthyl) bis(oxazoline). Crosignani, S.; Desimoni, G.; Faita, G.; Righetti, P. P. *Tetrahedron* **1998**, *54*, 15721−15730.

(8) Le, J. C−D.; Pagenkopf, B. L. *J. Org. Chem.* **2004**, *69*, 4177−4180.

(9) (a) Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541−4544. (b) Denmark, S. E.; Stavenger, R. A.; Faucher, A.-M.; Edwards, J. P. *J. Org. Chem.* **1997**, *62*, 3375−3389.

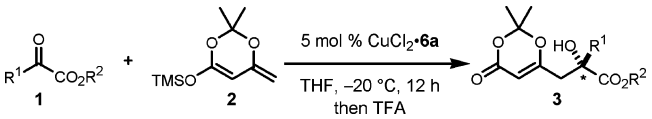
(10) Selection of the *o*-alkoxy substituent was made with the expectation (and realization) that a second ligand architecture **7**, which can be described as a novel *bis(oxazoline) salen hybrid*, is obtained essentially gratis by simple deprotection. Catalytic asymmetric reactions with tetradentate ligands **7**, which we call "oxalens," will be reported elsewhere.



(11) Reaction with **A**·$CuCl_2$ gave **3a** in 92% ee, but only 31% yield. This catalyst system was *inactive* with all the substrates listed in Table 2 except for **1a**.

(12) (a) Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798−800. (b) O'Mahony, D. J. R.; Belanger, D. B.; Livinghouse, T. *Synlett* **1998**, 443−445. (c) For a review, see: Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26−47.

Table 2. Aldol Reaction with Dienolsilane **2**[a]



1 **2** **3**

entry	R^1	R^2	% yield[b]	% ee[c,d]
a	Me	Me	81	94
b	Me	Et	75	94
c	Me	Bn	72	92
d	Me	*t*-Bu	70	79
e[e]	C_6H_5	Me	91	96 (>99)
f	4-$MeOC_6H_4$	Et	82	93
g	4-MeC_6H_4	Et	75	94
h	4-IC_6H_4	Et	90	98
i	4-$CF_3C_6H_4$	Et	74	84
j	4-$NO_2C_6H_4$	Et	77	80 (>99)
k	*n*- C_6H_{13}	Et	85	96
l	*i*-Pr	Et	75	91
m	*E*-PhCH=CH	Et	81	91
n	2-benzothiophene	Et	78	81 (92)

[a] Reactions were done in THF (0.25 M) with 1.1 equiv of dienolsilane relative to substrate. [b] Isolated yield. [c] Enantiomeric excess was determined by chiral HPLC. [d] Value in parentheses: ee after single recrystallization. [e] X-ray data included in the Supporting Information.

Encouraged by the enhanced selectivity, we set out to explore reaction scope. The catalyst system was undeterred by ethyl or benzyl pyruvate esters (Table 2, entries b and c), but increasing the size of the ester substituent to a *tert*-butyl resulted in a drop to 79% ee (entry d). Next, we examined the reaction with aryl glyoxylates, and with electronically neutral or electron rich arenes excellent enantioselectivities were observed, ranging from 93 to 98% ee (entries e−i). The ee of the parent ethyl phenylglyoxylate (entry e) could be fortified to >99% ee by a single recrystallization. Activation of the ketone by electron withdrawing groups on the arene (entries i and j) resulted in a faster aldol reaction, but the rate increase was mitigated by a decrease in enantioselectivity (84 and 80% ee, respectively). Reactions with branched and unbranched alkyl glyoxylates (entries k and l), as well as α,β-unsaturated glyoxylates (entry m) afforded good enantioselectivities (96, 91 and 91% ee, respectively). Entry n demonstrates compatibility with thiophene containing substrates as well.

In summary, a new class of bis(oxazoline) ligands has been introduced that features *o*-alkoxyaryl substituents. These ligands provide the highest enantioselectivities yet reported for the copper-catalyzed asymmetric dienolsilane aldol additions to pyruvate and glyoxylate esters: enantioselectivities up to 98% ee (before recystallization) and isolated yields up to 91%. Bis(oxazoline) ligands have been successfully employed in many contemporary catalytic asymmetric processes,[4−6] including: aldol,[14] aziridination,[15] carbonyl-ene,[16] Diels−Alder,[17] hetero-Diels−Alder,[18] cyclopropanation,[19] and Michael[20] reactions. The ability of the new ligands **6** (and **7**) to positively impact these and other enantioselective transformations will be reported in due course.

Acknowledgment. J.C.-D.L. is grateful to the Gates Millennium Scholars foundation for a graduate fellowship. We thank the Robert A. Welch Foundation, donors of the American Chemical Society Petroleum Research Fund, and the Texas Advanced Research Program for financial support. We thank Vincent Lynch for determination of the X-ray structures.

Supporting Information Available: General experimental procedures, characterization of all new compounds, and X-ray structure data for **3e** and **6a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) With the in situ formed catalyst, conversion decreased by 15% and enantioselectivity dropped by 25−30%. Enantioselectivity dropped by 25% in CH_2Cl_2.

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