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Stereochemical Diversity in Chiral Ligand Design: Discovery and Optimization of Catalysts for the Enantioselective Addition of Allylic Halides to Aldehydes

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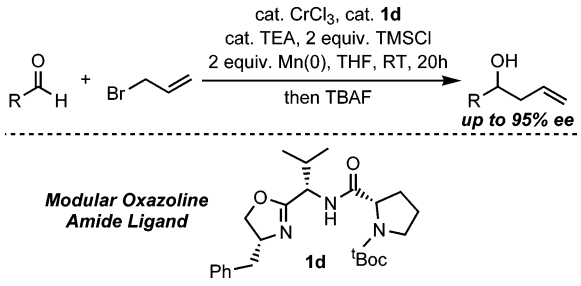
ABSTRACT



We have identified a new set of stereochemically diverse oxazoline ligands derived from simple amino acids that promote the Cr-catalyzed enantioselective addition of allylic halides to aldehydes in up to 95% ee. The Cr-catalyzed allylation using ligand 1d is rather insensitive to the nature of the allylic bromide (crotyl, allyl, and methallyl) in that >90% ee is observed for all three bromides evaluated in the addition to benzaldehyde.

The versatility of Cr(II)-mediated carbon−carbon bond formation in target-oriented and diverse chiral building block synthesis provides for a compelling target in asymmetric catalysis.[1] The foundation for the development of such catalytic systems was provided by Fürstner and Shi when they reported a method to render Cr(II)-mediated processes catalytic in Cr with Mn(0) as the reductant and trimethylsilyl chloride as the turnover agent.[2] Since then, several enantioselective Cr(II)-catalyzed reactions have been reported with variable success.[3,4] Herein, we report a set of new catalysts for the chromium-catalyzed enantioselective addition of allyl fragments to aldehydes[5] (Nozaki−Hiyama reaction) in which ligand stereochemical diversity plays a vital role in catalyst optimization.

(1) For reviews, see: (a) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991−1045. (b) Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1−36. (c) Nozaki, H.; Takai, K. *Proc. Jpn. Acad.* **2000**, *76*, 123−131.

(2) (a) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 2533−2534. (b) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349−12357.

(3) For salen-based systems, see: (a) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3357−3359. (b) Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Chem. Commun.* **2002**, 919−927 and references therein. (c) For an application, see: Lombardo, M.; Licciulli, S.; Morganti, S.; Trombini, C. *Chem. Commun.* **2003**, 1762−1763. (d) Berkessel, A.; Menche, D.; Sklorz, C. A.; Schröder, M.; Paterson, I. *Angew. Chem., Int. Ed.* **2003**, *42*, 1032−1035. (e) Berkessel, A.; Schröder, M.; Sklorz, C. A.; Tabanella, S.; Vogl, N.; Lex, J.; Neudörfl, J. M. *J. Org. Chem.* **2004**, *69*, 3050−3056. For an application, see: Paterson, I.; Bergmann, H.; Menche, D.; Berkessel, A. *Org. Lett.* **2004**, *6*, 1293−1295.

(4) For oxazoline-based systems, see: (a) Choi, H.-W.; Nakajima, K.; Demeke, D.; Kang, F.-A.; Jun, H.-S.; Wan, Z.-K.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4435−4438. (b) Inoue, M.; Suzuki, T.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 1140−1141. (c) Using modified catalytic conditions ($Zr(Cp)_2Cl_2$ instead of TMSCl), see: Namba, K.; Kishi, Y. *Org. Lett.* **2004**, *6*, 5031−5033. (d) For propargylation, see: Inoue, M.; Nakada, M. *Org. Lett.* **2004**, *6*, 2977−2980.

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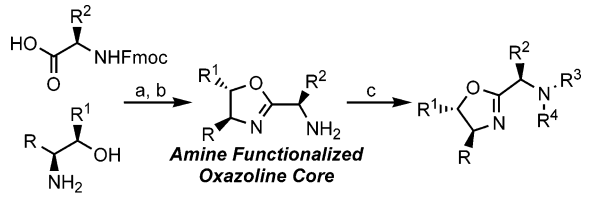
Recently, we disclosed the synthesis of a modular amine-functionalized oxazoline core that incorporates stereochemical diversity from naturally available chiral sources (Figure 1).[6,7] The diversity is controlled by the introduction of up to

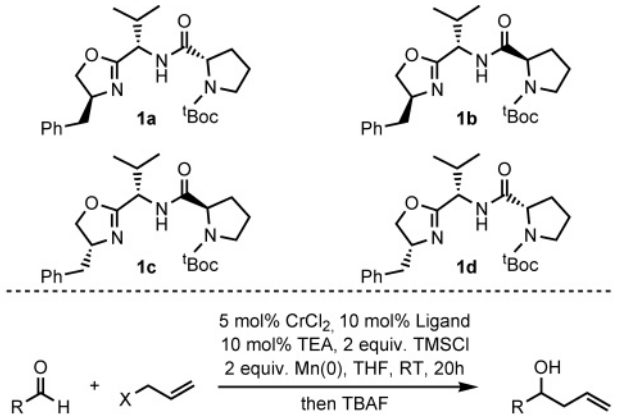


(a) PPh_3, CCl_4, $(iPr)_2NEt$; (b) piperidine, MeOH; (c) capping.

Figure 1. Modular approach to new oxazoline-based ligands.

three chiral centers on the core as well as derivatives off the free amine group. Initial evaluation of ligands incorporating a variety of capping groups for the Cr(II)-catalyzed addition of allyl bromide to benzaldehyde revealed that proline amides lead to excellent reactivity and measurable enantioselectivity. After initial optimization of ligand substituents,[8] ligand **1**, which is derived from phenylalanine, valine, and proline, was found to be the most promising (Figure 2). Previous studies on C_1-symmetric ligands have shown that the relative stereochemical orientations of the chiral elements play an important role in enantioselection.[9] Therefore, a complete set of diastereomers of ligand **1** were synthesized and evaluated for the allylation of benzaldehyde (Figure 2, entries 1−4). Ligand diastereomer **1d** led to the best catalytic system for the Cr(II)-catalyzed addition of allyl bromide to benzaldehyde, giving a 92% ee in 95% isolated yield (Figure 2, entry 4). Other allylic halides led to poorer results in allylation (entries 5 and 6). It is important to note that changing the catalyst diastereomer has a profound effect on the reaction outcome and is showcased in the evaluation of ligand **1c** where the facial selection is completely reversed to give the product in 89% ee and a diminished yield (entry 3).

To probe the initial scope of the allylation reaction, two optimized procedures were established: (A) using catalytic $CrCl_2$ or (B) using catalytic $CrCl_3$, a much easier to handle and considerably cheaper source of Cr. Both cases led to consistent reaction outcomes with little variation in observed enantioselectivity. Aryl aldehydes prove to be excellent substrates highlighted by a 92% ee for furylaldehyde (Table



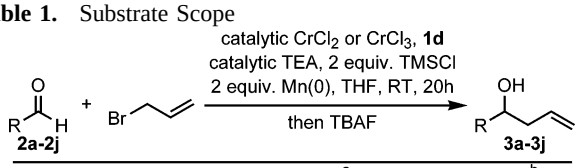
entry	ligand	R	X	yield(%)	%ee[a]	configuration[b]
1	**1a**	Ph	Br	75	76	*S*
2	**1b**	Ph	Br	88	36	*R*
3	**1c**	Ph	Br	22	89	*S*
4	**1d**	Ph	Br	95	92	*R*
5	**1d**	Ph	I	85	84	*R*
6	**1d**	Ph	Cl	15	83	*R*

(a) ee determined by HPLC equipped with a chiral stationary phase (b) see supporting information for details.

Figure 2. Identification and optimization of oxazoline-amide ligands.

1, entries 7 and 8) and a 94% ee for 2-naphthaldehyde (entry 9). Additionally, an α,β-unsaturated aldehyde also proves to be a good substrate for allylation with cinnamaldehyde

Table 1. Substrate Scope



entry	R	method[a]	yield(%)	%ee[b]
1	C_6H_5 (**2a**)	A	95	92
2		B	89	94
3	4-BrC_6H_5 (**2b**)	A	87	91
4		B	73	90
5	4-$MeOC_6H_5$ (**2c**)	A	95	89
6		B	98	89
7	2-Furyl (**2d**)	A	73	92
8		B	61	92
9	2-Napthyl (**2e**)	B	93	94
10	PhCH=CH (**2f**)	A	79	89
11		B	79	87
12	$PhCH_2CH_2$ (**2g**)	A	94	46
13		B	98	48
14	C_6H_{11} (**2h**)	A	81	89
15		B	64	87
16	$BnOCH_2$ (**2i**)	A	67	53
17	2-Napthyl, **2j**	B	60	77

[a] Method A: 5 mol% $CrCl_2$, 10% **1d**, 10 mol% TEA. Method B: 10 mol% $CrCl_3$, 10 mol% **1d**, 15 mol% TEA. [b] See Supporting Information for enantiomeric excess and absolute configuration determination.

(5) For reviews on asymmetric allylation, see: (a) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763−2793. (b) Yanagisawa, A. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999; Vol. 2, pp 965−979.

(6) Rajaram, S.; Sigman, M. S. *Org. Lett.* **2002**, *4*, 3399−3401.

(7) For examples of the use of oxazoline amine cores in asymmetric catalysis, see: (a) Pastor, I. M.; Adolfsson, H. *Tetrahedron Lett.* **2002**, *43*, 1743−1746. (b) Wipf, P.; Wang, X. *Org. Lett.* **2002**, *4*, 1197−1200. (c) McManus, H. A.; Barry, S. M.; Andersson, P. G.; Guiry, P. J. *Tetrahedron* **2004**, *60*, 3405−3416.

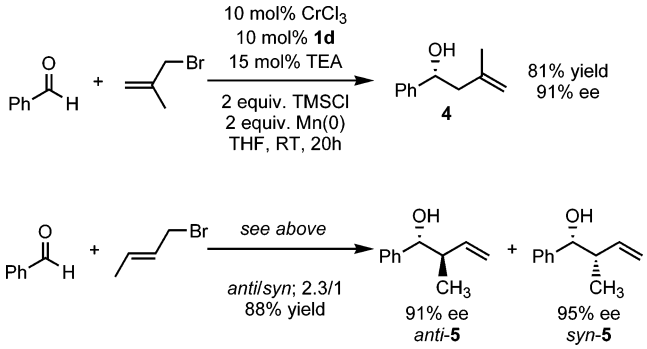
(8) See Supporting Information for details.

(9) For an example, see: Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901−4902.

leading to a 89% ee (entry 10). Mixed results are observed for allylation of aliphatic aldehydes, with **2g** and **2i** leading to poorer ee's (entries 12, 13, and 16). To test if this is related to the ligand structure, all ligand diastereomers were tested for the allylation of **2g**, with the results mimicking the allylation results observed for benzaldehyde.[10] However, α-substitution on the aliphatic aldehyde leads to a significant enhancement of enantioselectivity, with substrate **2h** giving 89% ee (entries 14 and 15) and substrate **2j** giving 77% ee (entry 17). Of additional note, a reversal of facial selectivity occurs for the aliphatic substrates **2i** and **2j**. In most cases, good to excellent yields of the homoallylic alcohol are observed.

To further explore the substrate scope, methallyl bromide and *trans*-crotyl bromide were evaluated as substrates in the allylation of benzaldehyde (Scheme 1). The addition of

Scheme 1. Cr-Catalyzed Addition of Other Allylic Halides to Benzaldehyde



methallyl bromide proceeded smoothly leading to **4** in 91% ee and 81% isolated yield. When using *trans*-crotyl bromide for the crotylation of benzaldehyde, the observed diastereoselectivity of the crotylation is relatively low with a 2.3:1 ratio favoring the *anti*-product. This low diastereoselectivity is similar to all reported asymmetric crotylations using Fürstner/Nozaki−Hiyama conditions.[11] In contrast to these reports, this crotylation leads to high enantiomeric excess for both diastereomers with 95% ee for the *syn* and 91% ee for the *anti* diastereomer.[8] To the best of our knowledge, the observed enantiomeric excesses for each diastereomer are the highest to date in an asymmetric crotylation using a Cr(II)-based system. The same sense of aldehyde facial selection is observed in both products. The relatively low diastereoselection points toward an open transition state[12] leading to a variety of intriguing mechanistic scenarios, including bimetallic processes where both Cr and Mn may play a role.[13,14]

In summary, we have identified a new set of stereochemically diverse oxazoline ligands derived from simple amino acids that promote the Cr-catalyzed enantioselective addition of allylic halides to aldehydes in up to 95% ee. The ligand stereochemistry plays a vital role in the identification of the optimal catalyst. Both aromatic and α-substituted aliphatic aldehydes are excellent substrates for the enantioselective addition. Crotylation of benzaldehyde leads to an *anti* to *syn* ratio of 2.3 to 1 and >90% ee for both diastereomers. Of additional note, the Cr-catalyzed allylation using ligand **1d** is rather insensitive to the nature of the allylic bromide (crotyl, allyl, and methallyl) in that >90% ee is observed for all three bromides evaluated. Elucidating the mechanistic details of this complicated reaction, enhancing the diastereoselection of aldehyde crotylation, and application of this new, modular ligand class to other catalytic asymmetric transformations are subjects of current and future research.

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Supporting Information Available: Catalyst optimization, ligand synthesis, catalytic procedures, and enantiomeric excess determination. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) **1a**, 24% ee (*S*); **1b**, 4% ee (*R*); **1c**, 1% ee (*S*); **1d**, 48% ee (*R*).

(11) Enantiomeric excess was determined by GC analysis of the methyl ether. Absolute configuration was determined by Mosher ester analysis.

(12) When ligand-less conditions are utilized, Nakada[4b] and Fürstner[2a] see significantly higher *anti*:*syn* ratios consistent with a closed-transition state.

(13) Cozzi and co-workers propose a bimetallic mechanism where Cr and Mn salen derivatives are involved. See ref 3b for details.

(14) Use of (*E*)-crotyl bromide with Mn-graphite in the addition to benzyaldehyde has been reported. The diastereoselectivity is 64:36 *anti*:*syn*. See: Fürstner, A.; Brunner, H. *Tetrahedron Lett.* **1996**, *37*, 7009−7012.