Asymmetric Catalysis

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Asymmetric Synthesis of Chiral 1,3-Diaminopropanols: Bisoxazolidine-Catalyzed C–C Bond Formation with α-Keto Amides**

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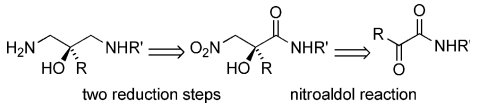
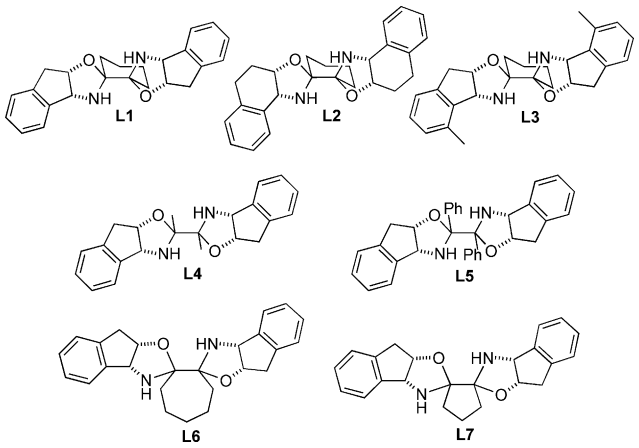
The ever-increasing demand for enantiopure drugs and agrochemicals, and the use of chiral building blocks in polymers, liquid crystals, and other materials has generated a strong stimulus for the development of asymmetric methods that utilize previously unexplored starting materials to generate efficient access to new and emerging target compounds.[1] New drug candidates that bear a chiral 1,3-diaminopropanol moiety or a corresponding oxazolidinone derivative have recently been introduced for the treatment of tuberculosis, Alzheimer's disease, and nosocomial infections caused by bacteria that are resistant to common antibiotics.[2] The formation of these challenging structures relies on multistep syntheses from chiral epoxy alcohols or esters and typically involves laborious protection/deprotection protocols. We envisioned that the enantioselective synthesis of N-substituted 1,3-diaminopropanols could be accomplished in three steps by nitroaldol reaction of α-keto amides, which are unexplored starting materials in asymmetric catalysis, and subsequent reduction of the nitro and amide groups (Scheme 1). The first catalytic asymmetric nitroaldol reaction



Scheme 1. Retrosynthetic analysis of N-monosubstituted 1,3-diaminopropanols.

was developed in 1992 by Shibasaki and coworkers, who used a BINOL-derived rare-earth-metal complex.[3] This reaction has since received considerable attention and its value for the synthesis of important chiral building blocks and complex target compounds has been demonstrated by many research groups.[4] Relatively few examples of asymmetric nitroaldol reactions with ketones[5] are known compared to the wealth of reactions with aldehydes. The use of α-keto amides has not been reported to date, in fact, catalytic asymmetric intermolecular C–C bond formations with α-keto amides have so far been elusive.[6] We expected that careful reduction of the nitro group in α-hydroxy β-nitro propanamides would avoid problems with the facile retro-aldol reaction[7] and thus lead to a practical route to a series of chiral 1,3-diaminopropanols.[8]

In recent years, chiral 1,3-oxazolidines have found increasing use as ligands and auxiliaries in asymmetric synthesis, which may be attributed to the intriguing ring topology and the possibility of modular synthesis from amino alcohols.[9] We have previously introduced bisoxazolidine **L1** and showed several applications of this C_2-symmetric N,O-diketal in asymmetric catalysis (Scheme 2).[10] Despite the ease of preparation of **L1**, which can be obtained in a single step from inexpensive *cis*-1-amino-2-indanol and 1,2-cyclo-



Scheme 2. Structures of bisoxazolidines **L1**–**L7**.

hexanedione, the synthesis of other diketone-derived bisoxazolidines is not straightforward and requires careful selection of starting materials and reaction conditions.[11] Accordingly, we chose to prepare a series of new ligands **L2**–**L7** derived from (1*R*,2*S*)-aminoindanol analogues and several diketones to vary the rigidity of the N,O-diketal backbone and to explore the catalytic performance of fluxional bisoxazolidines in the nitroaldol reaction with keto amides.

The synthesis of **L2** started with the bromination of 1,2-dihydronaphthalene (**1**) and mild hydrolysis of dibromide **2** to give racemic *trans*-2-bromo-1-hydroxytetrahydronaphthalene (**3**) in a high yield (Scheme 3).[12] The Ritter reaction of **3** then produced racemic *cis*-1-amino-2-hydroxytetrahydronaphthalene (**4**) in 79% yield. Resolution of the enantiomers of **4** by crystallization with mandelic acid furnished (1*R*,2*S*)-**4** in more than 99.5% *ee* according to HPLC analysis of the *tert*-butoxycarbonyl (*t*Boc) protected analogue (see the Support-

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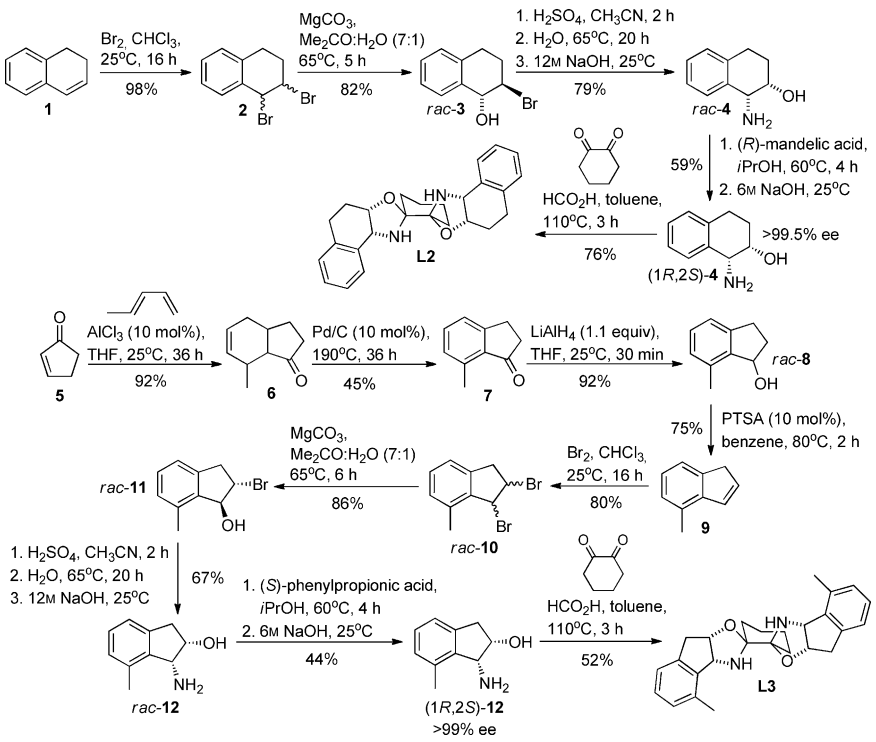
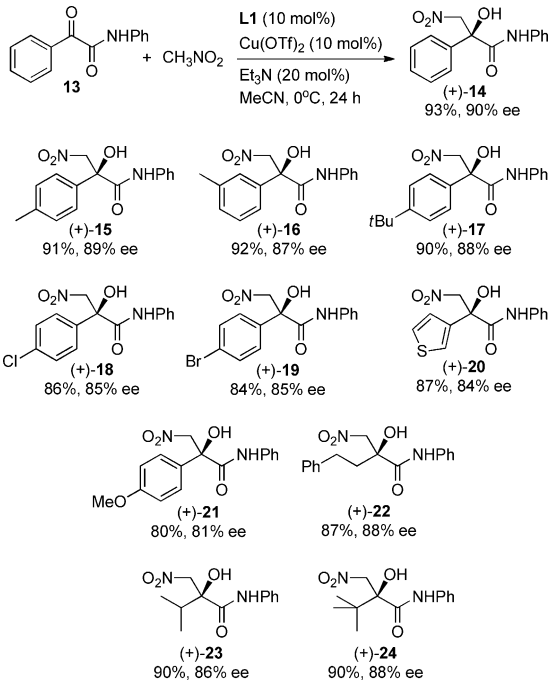


Scheme 3. Synthesis of ligands **L2** and **L3**. THF = tetrahydrofuran, PTSA = *p*-toluenesulfonic acid.

ing Information for details). Finally, **L2** was isolated in 76% yield after condensation of (1*R*,2*S*)-**4** with cyclohexanedione. We chose a similar route toward ligand **L3**. We first prepared 7-methyl-2,3-dihydro-1*H*-inden-1-one (**7**) in two steps by a Diels–Alder reaction between cyclopentenone (**5**) and 1,3-pentadiene to give **6** in 92% yield, and subsequent dehydrogenation at high temperature.[13] Reduction and elimination of alcohol **8** then provided 4-methyl-1*H*-indene (**9**), which was employed in the previously established bromination, hydrolysis, and Ritter reaction protocols to afford *cis*-7-methylaminoindanol (**12**). The enantiomers of **12** were separated by crystallization with phenylpropionic acid and we obtained the (1*R*,2*S*)-enantiomer in more than 99% *ee* based on HPLC analysis of its *t*Boc-protected derivative. The condensation with cyclohexanedione finally provided **L3** in 52% yield. Bisoxazolidines **L4**–**L7** were prepared accordingly from two equivalents of (1*R*,2*S*)-aminoindanol and the corresponding diketones in the presence of formic acid (see the Supporting Information for details).

With ligands **L1**–**L7** synthesized, we investigated the nitroaldol reaction with α-keto amides. We first employed 10 mol% of copper(II) triflate and the bisoxazolidine ligands in the reaction between *N*-phenyl 2-oxo-2-phenylacetamide (**13**) and nitromethane in THF as solvent. We were pleased to find that the desired *N*-phenyl 2-hydroxy-3-nitro-2-phenylpropanamide (**14**) was formed in high yield and 57–60% *ee* when **L1**, **L4**, and **L6** were used at 0 °C for 24 h (see Table 1 in the Supporting Information). The other bisoxazolidine ligands generated **14** in similar yields but low *ee* values, whereas the sense of asymmetric induction was reversed when ligand **L3** was used. A decrease in temperature improved the enantioselectivity but proved detrimental to the yield. This trend was also observed when the reaction was performed without solvent. Screening of different solvents showed that the yields and *ee* values of the nitroaldol reaction vary significantly. Most importantly, we found that (*S*)-**14** is produced in 89% yield and 86% *ee* when acetonitrile is used as solvent.[14]

A thorough evaluation of the effect of a wide range of base additives in both THF and acetonitrile did not improve yields and *ee* values (see Table 2 in the Supporting Information). However, we were surprised to find that the enantioselectivity of the nitroaldol reaction with keto amide **13** is very sensitive to the order of addition of reagents. Compound **14** was obtained in essentially the same yield but in only 9% *ee* when the base was introduced to a solution of ligand **L1** and $Cu(OTf)_2$ prior to the addition of nitromethane and the substrate. Further fine-tuning of the procedure showed that (*S*)-**14** can be produced in 93% yield and 90% *ee* when nitromethane is added first and the reaction mixture is stirred at room temperature for 30 min before addition of Et_3N and **13** at 0 °C. With this optimized reaction protocol established, we evaluated the substrate scope with a range of aromatic and aliphatic keto amides



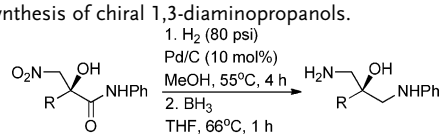
Scheme 4. Enantioselective synthesis of 2-substitued 2-hydroxy-3-nitropropanamides by using 10 mol% of $Cu(OTf)_2$ and ligand **L1**. Tf = trifluoromethanesulfonyl.

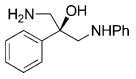
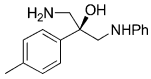
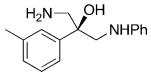
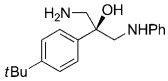
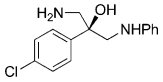
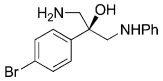
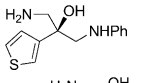
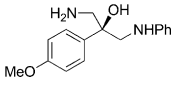
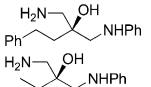
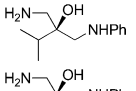
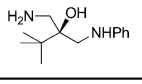
(Scheme 4). The **L1**-catalyzed nitroaldol reaction produced several aromatic analogues, including thiophene **20**, with excellent results. Importantly, the high yields and *ee* values were not compromised when aliphatic substrates were employed, and 2-hydroxy-3-nitroalkanamides **22–24** were isolated in 87–90% yield and 86–88% *ee*.[15]

With a general approach to chiral (*S*)-2-alkyl- and 2-aryl-2-hydroxy-3-nitropropanamides established, we evaluated methods for the careful transformation of the nitro and the amide group to the corresponding primary and secondary amino functions. As expected, all attempts to reduce **14** under slightly basic or acidic conditions gave **13** because of the facile retro-nitroaldol reaction. However, this complication could essentially be avoided by palladium-catalyzed hydrogenation in methanol at 55 °C, and we isolated the desired primary amine in 94% yield (Table 1, entry 1). We then tested several reported protocols for the amide reduction, including the use of metal hydrides, ruthenium-catalyzed hydrogenation at high temperatures, and the use of triethoxysilane in the presence of catalytic amounts of zinc acetate, all of which were unsuccessful.[16] Finally, we discovered that 1-amino-2-phenyl-3-(phenylamino)propan-2-ol (**25**) can be obtained in 88% yield when borane is used in THF at reflux for one hour.[17] This two-step reduction sequence was then used to form the desired series of chiral 1,3-diaminopropan-2-ols **25–35** in excellent overall yields (Table 1, entries 1–11).

In summary, we have developed the first example of catalytic intermolecular enantioselective C–C bond formations with α-keto amides. The bisoxazolidine-catalyzed nitroaldol reaction of these unexplored bifunctional building blocks provides a practical approach to a wide range of chiral 1,3-diaminopropanols that bear a central, tertiary alcohol group. The screening of seven C_2-symmetric bisoxazolidine ligands and several reaction parameters showed that both aliphatic and aromatic keto amides are converted to 2-alkyl- and 2-aryl-2-hydroxy-3-nitropropanamides in up to 93% yield and 90% *ee* in the presence of 10 mol% of **L1** and copper(II) triflate in acetonitrile. Selective hydrogenation and borane reduction of the nitro and amide groups were found to generate chiral 1,3-diaminopropanols in high overall yields and without the need for functional-group protection. We expect that the results from this study will direct increasing attention to the use of keto amides as readily available, versatile starting materials for asymmetric synthesis.

Table 1: Synthesis of chiral 1,3-diaminopropanols.



Entry	R	1,3-Diaminopropanol		Yield [%][a] Step 1	Step 2
1	Ph	(+)-**25**		94	88
2	4-MeC_6H_4	(+)-**26**		95	88
3	3-MeC_6H_4	(+)-**27**		90	87
4	4-*t*BuC_6H_4	(+)-**28**		90	78
5	4-Cl	(+)-**29**		93	86
6	4-Br	(+)-**30**		87	82
7	3-C_4H_3S	(+)-**31**		82	85
8	4-$MeOC_6H_4$	(+)-**32**		86	80
9	PhC_2H_4	(+)-**33**		84	85
10	*i*Pr	(+)-**34**		89	83
11	*t*Bu	(+)-**35**		89	85

[a] Yields of isolated products.

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[11] We found that in most cases double condensation to generate a bisoxazolidine structure does not occur with a wide range of amino alcohols and diketones. In contrast, only one carbonyl group reacts even under harsh conditions to give a monooxazolidine, or other by-products are formed.

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[14] The absolute configuration of the nitroaldol products was confirmed by NMR analysis with a chiral solvating agent (see the Supporting Information).

[15] The nitroaldol reaction with *N*-propyl and *N*-benzyl 2-oxo-2-phenylacetamide gave the product in 92–95% yield and 26–30% *ee*.

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[17] Formation of the *t*Boc derivative of **25** and HPLC analysis on a chiral stationary phase (Chiralpak AD) showed that the *ee* value was slightly reduced from 90% to 86% after the two reduction steps (see the Supporting Information).

