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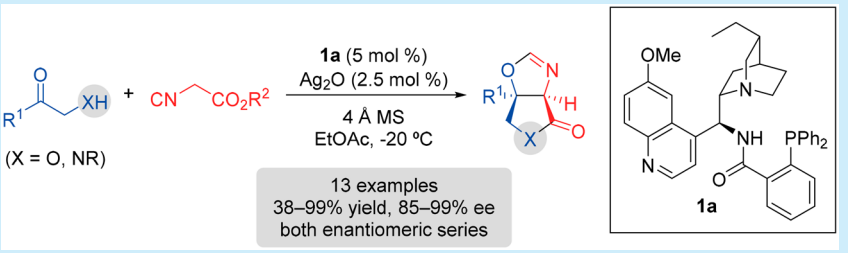
Enantioselective Silver-Catalyzed Cascade Synthesis of Fused Lactone and Lactam Oxazolines

Raquel de la Campa, Rubén Manzano,[†] Paul Calleja, Sam R. Ellis, and Darren J. Dixon*

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford OX1 3TA, U.K.

Supporting Information



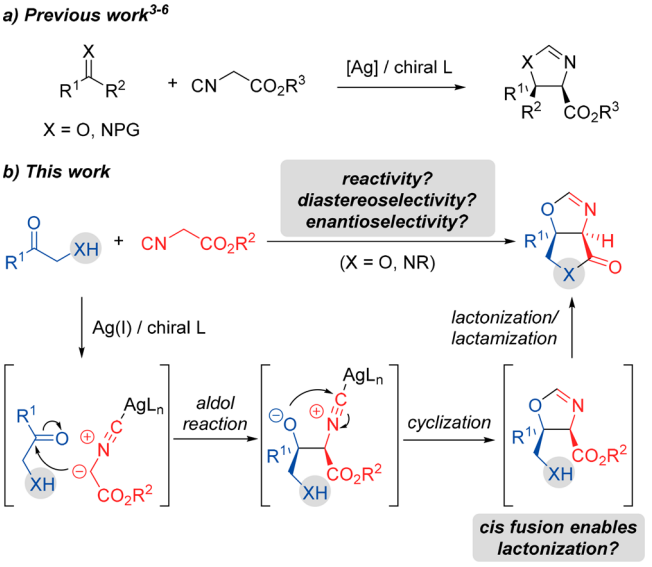
ABSTRACT: A new and highly stereoselective cascade reaction between isocyanoacetate esters and α-hydroxy and α-amino ketones has been developed. A cinchona alkaloid derived aminophosphine/silver(I) catalyst complex promoted the reaction and enabled the ready synthesis of fused bicyclic γ-lactone and γ-lactam oxazolines with high enantiocontrol (up to 99% ee).

Cascade reactions constitute an important resource efficient tool to rapidly build complex molecular architectures from simple starting materials while reducing processing times and avoiding the need for isolation of intermediate compounds.[1,2] In particular, the enantioselective synthesis of heterocycles via cascade processes has attracted considerable interest from the synthetic community. In this context, inspired by the seminal works of Hayashi, Ito, and Sawamura,[3] our group has developed enantioselective silver-catalyzed reactions of isocyanoacetates with aldehydes, ketones, and ketimines to afford enantioenriched oxazolines[4] and imidazolines (Scheme 1a).[5] The catalyst system, formed from a quinine-derived aminophosphine ligand and a silver(I) salt, is able to coordinate the isocyanoacetate and electrophile simultaneously to promote cyclization to the corresponding heterocycle in a highly enantiocontrolled fashion.[5a] Analogous enantioselective transformations have been reported using Ag and other metals such as Cu and Ni.[6]

As part of our research program into the development of new enantioselective complexity-generating reactions, we considered a multistage, one-pot cascade process between isocyanoacetates and ketones possessing pendant nucleophilic moieties, such as a hydroxy or an amino group. We envisaged that a chiral silver/ligand complex might initially catalyze an enantioselective aldol-type reaction which, following cyclization, would result in oxazoline formation.

At this stage, the pendant nucleophilic group would then be positioned to react with the adjacent ester functionality to afford fused bicyclic γ-lactone or γ-lactam oxazolines possessing a fully substituted β-carbon atom (Scheme 1b). Such cascade products would have the potential to be readily converted into α-amino-β-hydroxy-γ-lactones or -γ-lactams and, therefore, could be considered as masked polyhydroxylated α-amino acids, which can be found in many biologically active antibacterial[7] and antifungal[8] drugs. Although several stereoselective syntheses of polyhydroxylated α-amino acids and derivatives have been reported,[9,10] a general enantioselective synthesis of β,γ-dihydroxy-α-amino acid precursors to date has not been realized, and herein we wish to report our findings.

Scheme 1. Proposed Cascade Reaction of Isocyanoacetates and α-Hydroxy or α-Amino Ketones



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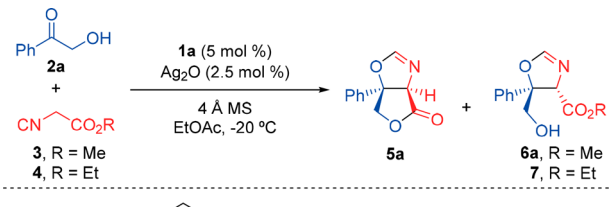
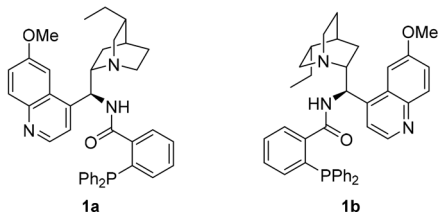
Preliminary studies to assess the feasibility of this cascade concept were performed employing 2-hydroxyacetophenone **2a** and methyl isocyanoacetate **3** as the model system. Building on our previous work,[4,5] a range of silver salts, aminophosphine ligands, and other reaction parameters were investigated. Pleasingly, under previously reported conditions (Table 1, entry 1) employing Ag_2O and the quinine-derived aminophosphine ligand **1a**, the *cis*-fused bicyclic γ-lactone oxazoline (3a*R*,6a*S*)-**5a** was formed as the major product in good yield with excellent enantioselectivity (99% ee). In addition, monocyclic oxazoline **6a** was isolated as a minor reaction side product.[11] EtOAc proved to be optimal as the solvent, with lower yields and enantioselectivities being obtained in other solvents (entries 2 and 3), while changing the temperature (entries 4 and 5) or silver salt (entries 6 and 7) offered no improvement. Importantly, use of the pseudoenantiomeric aminophosphine ligand **1b** led to formation of the enantiomeric product (3a*S*,6a*R*)-**5a** with excellent enantioselectivity (96% ee, entry 8). Control reactions demonstrated that both Ag_2O and the aminophosphine ligand were required, as no reaction occurred in their absence (entries 9 and 10 respectively). The reaction performed similarly well using ethyl isocyanoacetate **4**, with the product being formed in comparable yield and enantioselectivity (99% ee, entry 11) to the reaction with **3**.

Table 1. Optimization of the Cascade Synthesis of Fused Bicyclic γ-Lactone Oxazolines[a]



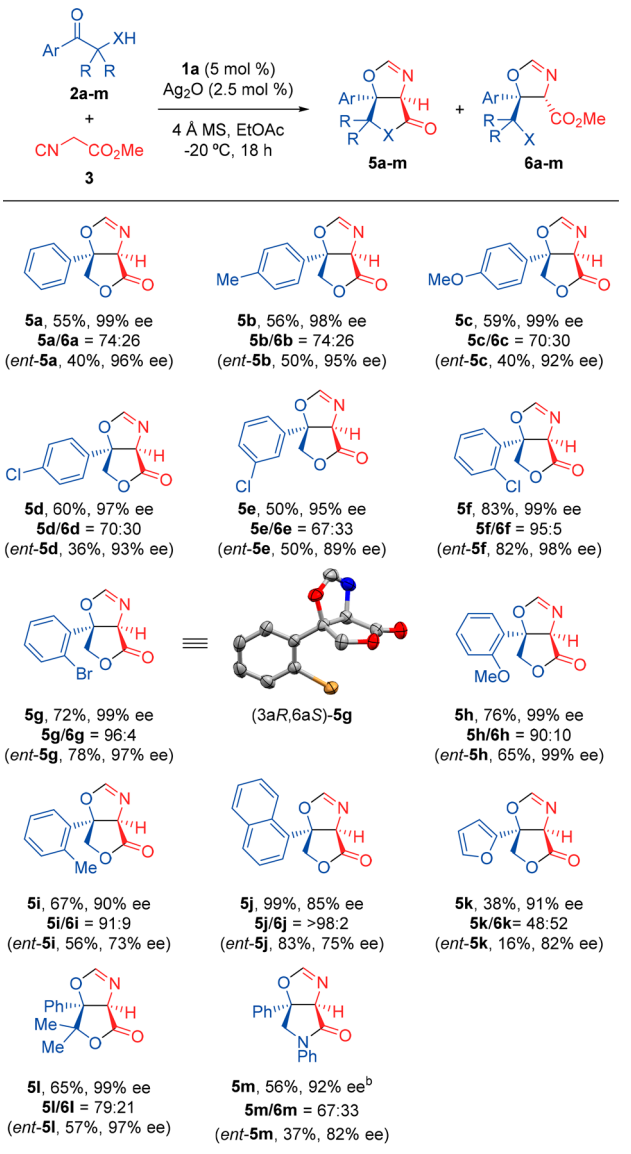


entry	change in conditions	5a (%)[b]	6a (%)[b]	5a/6a ratio[c]	ee of 5a[d] (%)
1	none	55	25	74:26	99
2	CH_2Cl_2	36	46	52:48	91
3	MeOH	50	43	54:46	14
4	−40 °C	46	24	72:28	94
5	0 °C	50	36	69:31	95
6	Ag_2CO_3	52	16	73:27	96
7	AgOAc (5 mol %)	54	23	67:33	92
8	**1b**	40	20	66:34	96[e]
9[f]	no Ag_2O				
10[f]	no **1a**				
11	R = Et (**4**)	53	35 (7)	63:37	99

[a]Conditions: isocyanoacetate **3** (0.35 mmol), α-hydroxy ketone **2a** (1.1 equiv), Ag_2O (2.5 mol %), and ligand **1a** (5 mol %) in EtOAc (2 mL) at −20 °C for 16 h. [b]Yield of isolated product after flash column chromatography. [c]Ratio of **5a** and **6a** was determined by ^1H analysis of the crude reaction mixture [d]Enantiomeric excess of **5a** was determined by HPLC analysis on a chiral stationary phase. [e]Enantiomeric product (3a*S*,6a*R*)-**5a** was formed. [f]No reaction.

With the optimized conditions established, the scope of the cascade reaction was explored using methyl isocyanoacetate **3** and a variety of 2-hydroxy ketones **2** (Scheme 2). The reaction proceeded with several *para*-substituted 2-hydroxyacetophenones possessing either electron-withdrawing or -donating groups, **2b**−**d**, and the corresponding fused γ-lactone oxazolines (**5b**−**d**) were obtained as the major products with good product selectivity (**5**/**6** ratio) and excellent enantioselectivities (97−99% ee). The use of *meta*-substituted 2-hydroxyacetophenone **2e** afforded the bicyclic product **5e** with similar

Scheme 2. Scope of the Enantioselective Cascade Synthesis of Fused Bicyclic γ-Lactone and γ-Lactam Oxazolines[a]



[a]Conditions: methyl isocyanoacetate **3** (0.35 mmol), α-hydroxy ketone **2** (1.1 equiv), Ag_2O (2.5 mol %), and ligand **1a** (5 mol %) in EtOAc (2 mL) at −20 °C. Yields given are of isolated product after flash column chromatography. **5**/**6** ratios were determined by ^1H NMR analysis of the crude reaction mixture. Enantiomeric excess of **5** was determined by HPLC analysis on a chiral stationary phase. Values in parentheses represent the reaction with ligand **1b** generating the enantiomeric product. [b]AgOAc (5 mol %) and **1a** (10 mol %) were used.

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levels of enantiocontrol as compared to **5d**. Importantly, the use of *ortho*-substituted 2-hydroxyacetophenones **2f–i** was well-tolerated, and bicyclic oxazolines **5f–i** were obtained with higher product selectivity (90:10 to 96:4) and yield compared to their corresponding *meta* or *para* equivalents. The products were also obtained with excellent enantioselectivity (90–99% ee).

1-Acetonaphthone derivative **2j** was an excellent substrate and afforded the *cis*-fused γ-lactone oxazoline **5j** with excellent product selectivity (>98:2) and with good enantioselectivity.

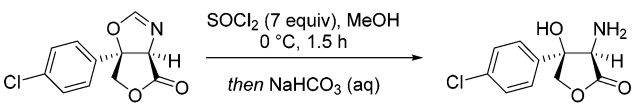
Heteroaromatic ketone **2k** also engaged in this reaction, affording oxazoline **5k** with good enantioselectivity, albeit with minimal diastereocontrol in the initial aldol reaction. Interestingly, sterically hindered alcohols such as the tertiary alcohol **2l** performed well, with **5l** being obtained with excellent enantioselectivity. The reaction could be readily extended to obtain bicyclic lactams, with the corresponding *cis*-fused γ-lactam oxazoline product (**5m**) being obtained from the aniline-derived acetophenone **2m** with good enantiocontrol. In addition, enantiomeric products of **5a–m** could be prepared by employing pseudoenantiomeric aminophosphine ligand **1b** with similar (albeit reduced) yields and enantioselectivities in most cases.

The absolute configuration of product **5g** (obtained using ligand **1a**) was established by single-crystal X-ray diffraction analysis[12] and was in agreement with previous observations;[5a] other products were assigned by analogy.

The absolute configuration of monocyclic oxazolines **6** was assigned by chemical correlation; treatment of **6e** and *ent*-**6e** with DBU afforded bicyclic oxazolines **5e** and *ent*-**5e** in 10% and 6% ee, respectively, presumably through epimerization adjacent to the ester and concomitant cyclization. See the Supporting Information for further details.

The versatility of the fused γ-lactone oxazoline bicyclic products was demonstrated by subjecting **5d** to acidic methanolic conditions, which afforded functionally dense and stereochemically defined α-amino-β-hydroxy-γ-lactone **8** without erosion of enantiopurity (Scheme 3).

Scheme 3. Application to the Synthesis of α-Amino-β-Hydroxy-γ-Lactones



5d, 97% ee — **8**, 65% yield, 98% ee

In summary, we have developed a highly enantioselective synthesis of fused γ-lactone and γ-lactam oxazolines from isocyanoacetate pronucleophiles and α-hydroxy or α-amino ketones, respectively. One carbon–carbon bond, two carbon–heteroatom bonds, and two stereogenic centers of the bicyclic product were created through a cascade reaction employing a silver(I)/aminophosphine catalyst system. Application to the synthesis of α-amino-β-hydroxy-γ-lactones was also demonstrated. Work to apply these findings to other enantioselective cascade reactions is ongoing in our laboratory, and the results will be disclosed in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02383.

All experimental details, copies of NMR spectra, and HPLC data (PDF)

Accession Codes

CCDC 1542388 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: darren.dixon@chem.ox.ac.uk.

ORCID

Rubén Manzano: 0000-0001-7290-3979
Sam R. Ellis: 0000-0003-1412-113X
Darren J. Dixon: 0000-0003-2456-5236

Present Address

†(R.M.) Department of Organic Chemistry II, University of the Basque Country (UPV/EHU), P.O. Box 644, 48080 Bilbao, Spain.

Notes

The authors declare no competing financial interest.

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