Asymmetric Catalysis

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Highly Diastereo- and Enantioselective Silver-Catalyzed Double [3+2] Cyclization of α-Imino Esters with Isocyanoacetate**

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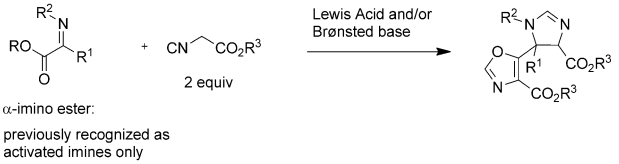
Dedicated to Professor Amir H. Hoveyda on the occasion of his 55th birthday

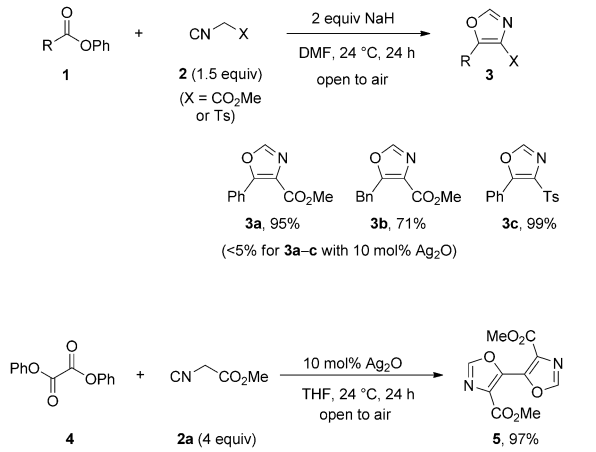
Abstract: *Presented herein is a new complexity-generating method in which both functionalities of α-imino esters undergo stereoselective cyclization with isocyanoacetates to produce directly linked oxazole-imidazolines, which can be transformed into highly functionalized α,β-diamino esters and imidazolinium salts in high diastereo- and enantiopurity.*

The generation of complexity and diversity in molecular structures in an efficient and economical fashion is an important goal in organic synthesis and chemical biology,[1] for which multicomponent reactions (MCRs)[2] and cascade reactions[3] have proven to be the most useful strategies. Along these lines, isocyanoacetates (as functionalized isocyanides)[4] have found wide application not only in classical Passerini- and Ugi-type MCRs, but they have also proven to be a versatile functionality to react with carbonyls,[5] imines,[6] α,β-unsaturated carbonyls,[7] activated alkenes/alkynes,[8] etc. to produce a wide range of heterocyclic compounds. The combination of these reactions with further functionalization of the products in a tandem fashion has also been extensively studied, in particular by the group of Zhu, to produce more complex structures.[9] We present here a conceptually different complexity-generating method, that is, both functionalities in α-imino esters (previously recognized as activated imines only) undergo cyclization with isocyanoacetate to yield directly linked oxazole-imidazolines catalyzed by a silver salt (Scheme 1).[10] An asymmetric variant has also been developed with the Dixon-type catalyst[5e] to produce these compounds in high diastereo- and enantiopurity, and these products can be further transformed into other valuable and highly functionalized entities.

Our attention was drawn to this possibility of a double cyclization during our initial attempts of oxazole formation from the reaction between isocyanoacetates and esters, as they should be more functional-group tolerant and easier to handle than using of strong acylating reagents such as acid chlorides (Scheme 2).[4a] Such a combination, however, was known to fail to react even under harsh reaction conditions because of the low reactivity of the enolate, derived from the isocyanoacetate, towards an ester.[11] We argued that the use of aryl esters could be beneficial, as the better leaving group, aryloxide (compared with simple alkoxide from alkyl esters), should facilitate the addition of the enolate to the ester. This indeed led to efficient oxazole formation from different aryl esters (**1**) and isocyanoacetates (**2**; or toluenesulfonylmethyl isocyanide) by the use of a stoichiometric amount of a strong base (71–99% yield for **3a–c** with the use of NaH). For the oxalate **4**, interestingly, the formation of the bis(oxazole) **5** in excellent yield was realized by using a much milder silver-catalyzed procedure, which failed to yield **3a–c** at all. Clearly there is a synergetic effect between the ester functionalities in **4**, and thus led us to consider substrates bearing different functionalities which could mutually activate each other for the reaction with isocyanoacetate to produce complex molecules.



Scheme 1. Double cyclization with both the imine and ester functionalities in α-imino esters.



Scheme 2. Oxazole formation from aryl esters. Yields are those of the isolated products. DMF = *N*,*N*′-dimethylformamide, Ts = 4-toluenesulfonyl. THF = tetrahydrofuran.

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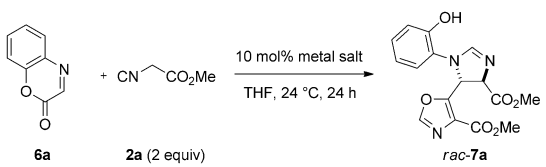
The cyclic α-imino ester **6a** (for structure see Table 1) was chosen as the model substrate because of its unique α-imino aryl ester structure, as well as its easy synthesis.[12] The proposed double cyclization with both imine and aryl ester moieties with isocyanoacetate will also be entirely atom economical as the product incorporates all portions of the starting materials. It is also noteworthy that the reaction of isocyanoacetates (or isocyanoacetamides) with imines is known to follow divergent pathways to produce either imidazolines[6a,e–g] or oxazoles (initiated by isocyanide addition to activated imines).[6b–d] These factors, combined with the reaction at the aryl ester moiety, could in principle lead to a complex mixture.

As shown in Table 1, various metal salts having different levels of basicity or Lewis acidity were screened for the reaction of **6a** and **2a** at ambient temperature. Gratifyingly,

Table 1: Metal-salt screening for double [3+2] cyclization of **6a** and **2a**.[a,b]



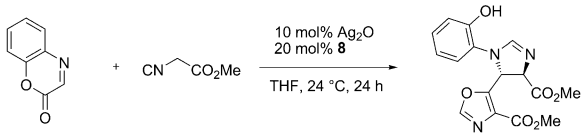
Entry	Metal salt	Yield [%][b]	Entry	Metal salt	Yield [%][b]
1	Cu_2O	72	7	Ag_2O	99
2	$Cu(OAc)_2$	40	8	Ag_2CO_3	99
3	$CuCl_2$	<2	9	$AgBF_4$	<2
4	$ZnCl_2$	<2	10	AgOTf	<2
5	$AuCl_3$	<2	11	$BF_3{\cdot}OEt_2$	<2
6	AgOAc	90	12	$Sc(OTf)_3$	<2

[a] Carried out in air for 24 h. See the Supporting Information for details. [b] Yield of isolated product. Tf = trifluoromethanesulfonyl.

the desired double [3+2] cyclization product **7a** was obtained cleanly (>20:1 d.r.) when copper and silver salts, which are strongly basic, were used with Ag_2O and Ag_2CO_3 as the optimal choices (99% yield). In contrast, zinc or gold salts, and even strong Lewis acids such as $BF_3{\cdot}OEt_2$ or $Sc(OTf)_3$, failed to promote the reaction. This result led us to speculate that this may be a base-catalyzed process in which the Mannich reactivity of **2a** predominates and yields imidazoline with concomitant oxazole formation from reaction with the aryl ester moiety.

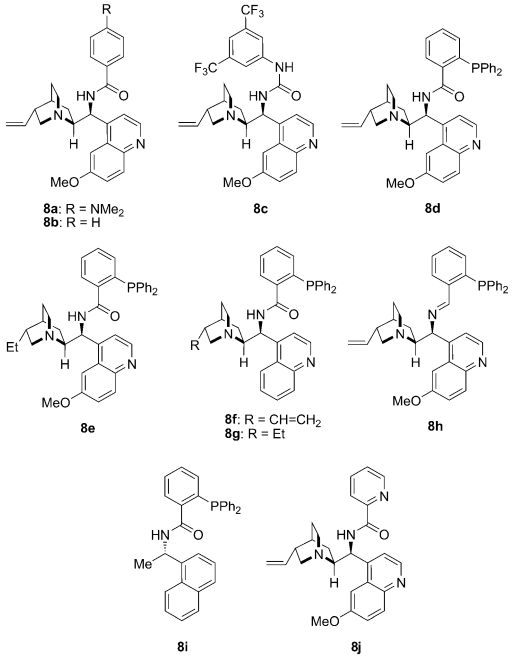
With an efficient reaction in hand, we turned our attention to the development of an asymmetric variant by evaluating copper or silver complexes supported by various chiral ligands. After extensive experimentation, Ag_2O turned out to be the most promising choice for the metal salt, and the screening data for different chiral ligands is summarized in Table 2. Initially we focused on simple quinine amides, which we recently disclosed for silicon activation and copper catalysis,[13] and to our disappointment, they did not lead to asymmetric induction (entries 1–3). Inspired by the recent report from the group of Dixon on enantioselective isocyanoacetate aldol reaction catalyzed by a silver complex with a new family of cinchona-derived amino phosphine precatalysts,[5e,14] we tested the related **8d–g** for our reaction. The use of the quinine-derived phosphine **8d** with Ag_2O gratifyingly yielded **7a** with a good *ee* value of 81% (entry 4). Modification on the structure of **8d**, as reported by the group of Dixon (reduction to **8e** or use of cinchonidine-derived **8f,g**),[5e] unfortunately led to lower *ee* values (entries 5–7). The structurally related imine **8h** was also tested, and proved to be much less selective (entry 8). The simple chiral-phosphine-containing amide **8i** did not result in any enatioselectivity, thus implying the importance of quinuclidine moiety for the asymmetric induction in addition to the phosphine amide moiety (entry 9). Finally, the use of the pyridyl-containing **8j**[15] yielded a racemic product. With the optimal ligand identified, we re-tested the use of Ag_2CO_3, which again proved less selective than Ag_2O (entry 11 versus entry 4). Further optimization of the reaction conditions with the use of the Ag_2O/**8d** system was carried out (see the Supporting Information for details). While solvent screening showed

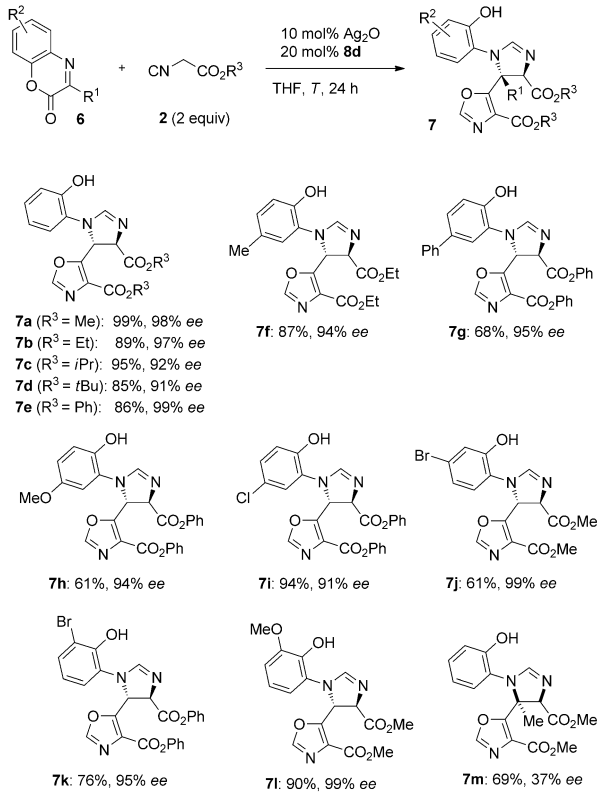
Table 2: Catalyst screening for enantioselective double [3+2] cyclization.[a–d]



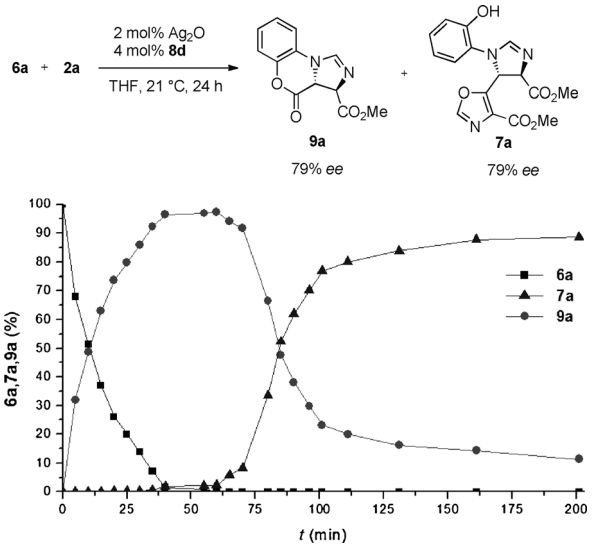
Entry	8	Yield [%][b]	*ee* [%][c]	Entry	8	Yield [%][b]	*ee* [%][c]
1	**8a**	95	<2	7	**8g**	99	58
2	**8b**	98	<2	8	**8h**	95	14
3	**8c**	67	<2	9	**8i**	95	−3
4	**8d**	99	81	10	**8j**	99	<2
5	**8e**	99	79	11[d]	**8d**	96	67
6	**8f**	99	72	12[e]	**8d**	**99**	**98**

[a, b] See Table 1. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Ag_2CO_3 was used instead of Ag_2O. [e] The reaction was carried out at −20°C.





Scheme 3. Scope for enantioselective double [3+2] cyclization of **6** and **2**. Yields are those of the isolated products. With a few exceptions, the reactions were carried out at −20 °C for 24 h. See the Supporting Information for details.



Scheme 4. NMR studies revealed a stepwise reaction profile.

THF was still the optimal solvent, lowering the reaction temperature led to a dramatic increase in the enantioselectivity. When the reaction was carried out at −20 °C, **7a** was obtained in excellent yield (99 %) with 98 % *ee* (entry 12).[16]

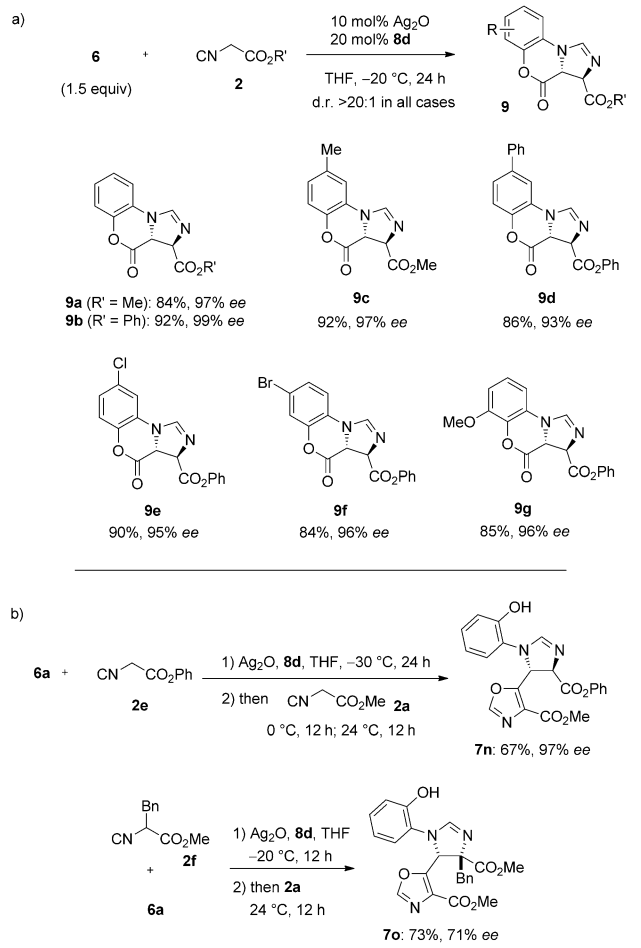
The substrate scope of this system was studied next (Scheme 3). It is noteworthy that in almost all cases perfect diastereoselectivity was obtained for the product **7** with an *anti*-diamine moiety. Isocyanoacetates bearing different ester groups were all suitable substrates, thus producing the products **7a–e** in uniformly high yields with excellent *ee* values (91–99 %). Different substitution patterns on the aryl ring (*para*, *meta*, and *ortho*) were well tolerated and formed highly functionalized imidazolines with different phenol units in excellent enantioselectivity (**7f–l**). Ketimines turned out to be difficult substrates for the double cyclization. A mixture of the mono-[3+2] cycloaddition product (with imine) and the desired product **7m** was obtained for the methyl-substituted ketimine. Surprisingly a different *syn* diastereomer was formed, with a lower *ee* value of 37 %.

It is worth noting that the current reaction is simple to perform with catalysts which can be easily prepared from inexpensive starting materials. The reactions are set up open to air with no need for exclusion of air or moisture. The level of diastereo- and enantioselectivity compares favorably with previously reported Mannich reaction of isocyanoacetate with imines,[6e–g] with the additional advantage of generating complexity from concomitant imidazoline and oxazole formation.

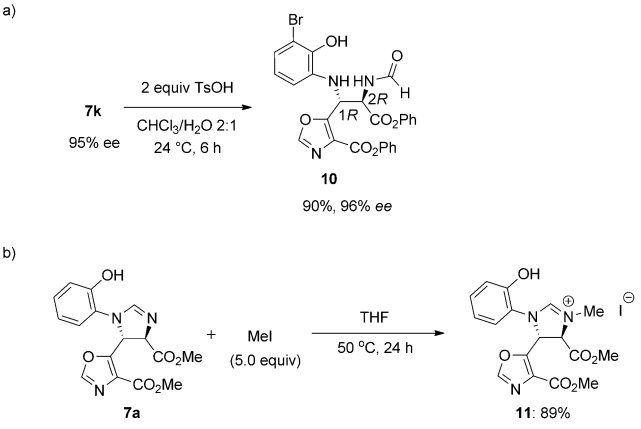
In an effort to better understand the mechanism of the system, the kinetics of the reaction between **6a** and **2a** were monitored by NMR spectroscopy (Scheme 4). With a lower catalyst loading and, in turn, decreased reaction rate, the two cyclization reactions were identified to be stepwise. Strikingly, an essentially full conversion of **6a** into the monocyclization product **9a** was observed within 60 minutes at 21 °C before the formation of **7a** began. As expected, the enantioselectivity was determined in the first step; **9a** and **7a** were obtained with the same 79 % *ee*.

While the nature of this stepwise reaction profile necessitates further investigation, it provided more possibilities for our methodology to produce structurally different compounds. As shown in Scheme 5a, the mono-[3+2] cyclization products **9a–g** could be isolated in high yield with good to excellent *ee* values when the reaction was carried out at −20 °C with **2** as the limiting reagent (see the Supporting Information for details). Alternatively, a three-component reaction of two different isocyanoacetates with **6a** was also realized (Scheme 5b). The compounds **2e** and **2a** were added sequentially to yield **7n** in 67 % yield with 97 % *ee*. In addition, the use of substituted isocyanoacetates such as **2f** led to a smooth [3+2] cycloaddition with **6a**, and subsequent cyclization of **2a** with the ester unit in the intermediate, to yield **7o** in 73 % yield and a slightly lower *ee* value of 71 %. X-ray analysis of **7o**[19] further confirmed the directly linked oxazole-imidazoline structure of the products.

The products of this reaction can be easily converted into useful entities in asymmetric catalysis. The imidazoline moiety could be readily hydrolyzed under acidic conditions to yield highly functionalized α,β-diamino esters, such as **10**, in high yield (Scheme 6a), the X-ray analysis of which[19] confirmed the relative and absolute configuration of the products **7**. The formamide **10** has been identified to be a highly efficient Lewis base catalyst for the addition of allyltrichlorosilane to aliphatic aldehydes, a process which



Scheme 5. Isolation of intermediates (a) and three-component reactions



Scheme 6. Derivatization of **7** to give a) an α,β-diamino ester and b) imidazolinium salt.

was seriously hampered in most previous systems because of chloride addition to the aldehyde.[17] Systematic optimization is ongoing with the compounds **7a**–**m** and related analogues, and the results will be reported in due course.

Alternatively, **7a** was transformed into the imidazolinium salt **11** in high yield upon treatment with an alkylating reagent such as methyl iodide (Scheme 6b). The application of related compounds as bidentate N-heterocyclic carbine/phenoxide ligand in enantioselective catalysis has been beautifully demonstrated by the group of Hoveyda.[18] The unique structure of our products, bearing multiple functionalities, may provide new opportunities in asymmetric catalysis.

Experimental Section

Anhydrous THF (1 mL) was added to a 10 mL vial charged with **8d** (12 mg, 0.020 mmol) and Ag_2O (2.3 mg, 0.010 mmol). The mixture was stirred at ambient temperature for 5 min and then cooled to −20 °C. The cyclic α-imino ester **6a** (0.10 mmol) was added, followed by isocyanoacetate **2a** (0.20 mmol) using a micropipette. The reaction mixture was stirred at −20 °C for 24 h, and then concentrated and purified by flash chromatography (hexanes/ethyl acetate) to afford the product **7a** (99 %).

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[16] Decreased catalyst loading of 5 mol% Ag_2O with 10 mol% **8e** yielded **7a** in high 97% yield but with a lower *ee* value of 90%.

[17] For more details, see Ref. [13a] and references therein.

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[19] CCDC 996233 (**7o**) and CCDC 996234 (**10**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Selected data is also included in the Supporting Information.

