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Catalytic, asymmetric synthesis of α-phenoxy-β-aryl-β-lactams

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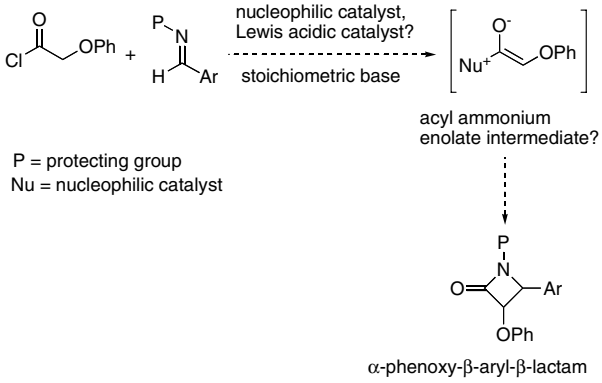
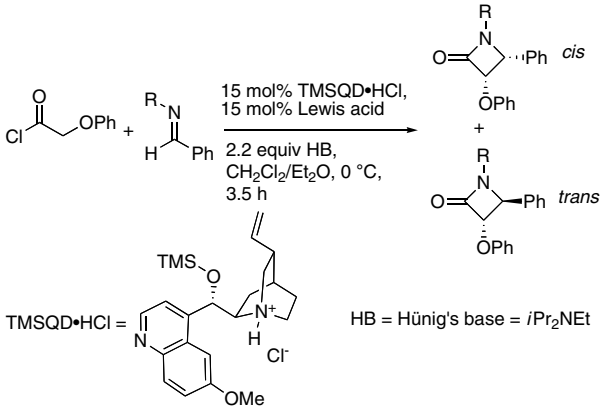
Abstract—The reactions of phenoxyacetyl chloride with aryl imines in the presence of catalytic quantities of a silyl cinchona alkaloid and an achiral Lewis acid affords α-phenoxy-β-aryl-β-lactams. These reactions presumably proceed by way of ketene or acyl ammonium enolate intermediates. These reactions occur in a high enantioselectivity regardless of the nature of the Lewis acid, however, a high diastereoselectivity depended on the use of a hindered lanthanide complex as the Lewis acidic co-catalyst.

We desired an asymmetric synthesis of α-phenoxy-β-aryl-β-lactams. These compounds have potential antibiotic activity in their own right,[1] and also could serve as precursors to the α-hydroxy-β-arylalanine moiety found in biologically active natural products such as the taxoids.[2] We postulated that the Staudinger reaction of a phenoxyketene and an aryl imine would afford the appropriately substituted β-lactam (Scheme 1). Lectka and co-workers have developed an efficient equivalent to the Staudinger reaction that most likely passes through an acyl ammonium enolate intermediate.[3] This reaction and the one reported by Hodous and Fu proceed in a high enantioselectivity,[4] yet neither have been applied to the synthesis of α-phenoxy-β-aryl-β-lactams. We therefore sought to develop an acyl ammonium enolate-based reaction for the coupling of a glycolate equivalent with an aryl imine. Based on the precedents mentioned above, we began with the reactions of acid chlorides and imines in the presence of stoichiometric tertiary amine base and under catalysis from a nucleophilic cinchona alkaloid and perhaps a Lewis acid.



Scheme 1.

Our initial investigations focused on determining the optimal substrate and conditions for a maximum conversion (Scheme 2, Table 1).[5] We first determined that the reaction did not proceed to a useful extent in the absence of a Lewis acid. We next discovered that $Sc(OTf)_3$ effectively catalyzed the reaction of sulfonyl imines, and



Scheme 2.

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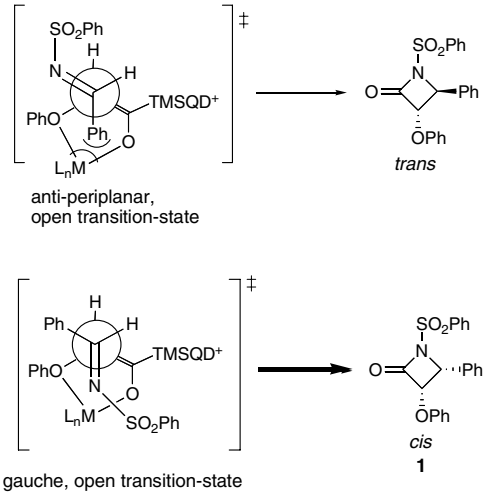
Table 1. Results for optimization of substrate and conditions

R	Lewis acid	Overall % yield	cis:trans[a]	% ee cis[b]
OMe	None	<5	nd[c]	nd
OBz	None	<5	nd	nd
OBz	$Sc(OTf)_3$	<5	nd	nd
$PhSO_2$	None	<5	nd	nd
$PhSO_2$	$Sc(OTf)_3$	65	2:1	93
$PhSO_2$	$Yb(OTf)_3$	61	6:1	92

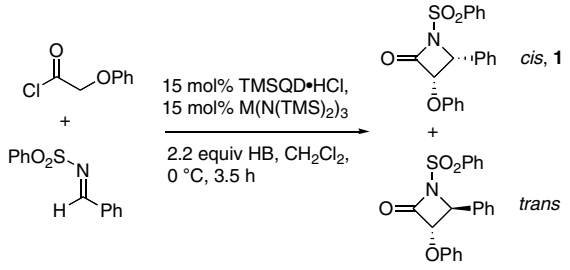
[a] Determined by reverse phase HPLC analysis of the unpurified reaction mixture.
[b] Determined by HPLC analysis of the purified isomer.
[c] nd—not determined.

that various oximes did not react, even in the presence of Lewis acid.[6] These results mirror those reported by Lectka and co-workers in the reactions of glyoxal-derived imines. Finally, the initial results showed that lanthanide triflates also catalyzed the reactions of sulfonyl imines. However, the diastereoselectivities for all the Lewis acid-catalyzed reactions were too low for synthetic utility.

The results with metal triflate catalysts led us to consider the mechanism for the reaction, with a particular focus on issues of diastereoselectivity (Scheme 3). Based on the precedent for the β-lactone-forming reactions, we assumed that the acyl ammonium enolate (formed from the reaction of the acid chloride, the Hünig's base and the TMSQN) coordinated to the Lewis acid prior to reaction with the imine.[7] The lack of a difference in diastereoselectivity between the reactions with and without Lewis acid led us to believe that the Lewis acid was not coordinating to the imine nitrogen in the transition state. The size and electron-withdrawing ability of the sulfonyl group also would lead one to believe that coordination of the imine nitrogen would be unlikely. A further analysis of the proposed transition state suggested that increasing the size of the ligands on the metal would lead to a greater selectivity for the formation of cis-product **1**.



Scheme 3.



Scheme 4.

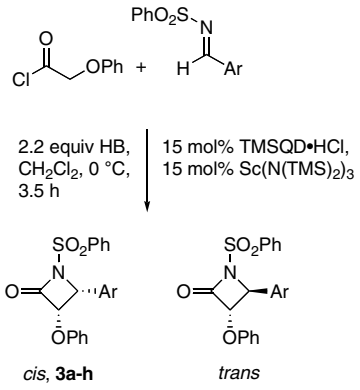
Table 2. Results for optimization of reaction diastereoselectivity

M	Overall % yield	cis:trans[a]	% ee cis[b]
Sc	68	18:1	92
Y	59	22:1	94
Nd	72	12:1	94
Yb	83	25:1	94

[a] Determined by reverse phase HPLC analysis of the unpurified reaction mixture.
[b] Determined by HPLC analysis of the purified isomer.

The use of the tris(hexamethyldisylazide)metal complexes led to a striking increase in the diastereoselectivity of the reaction (Scheme 4, Table 2).[8] Gratifyingly, despite the presumably increased steric bulk and decreased Lewis acidity, the hexamethyldisylazide complexes afforded equivalent conversions and yields to the triflate co-catalysts.[9] We observed a modestly higher diastereoselectivity with the ytterbium complex (Yb ionic radius = 0.858) relative to the scandium complex (Sc ionic radius = 0.732), a fact that further implicates steric bulk around the metal as the factor leading to an increase in diastereoselectivity. The enantioselectivities were again excellent.

We next tested the scope of the reaction. Imines bearing electron-withdrawing aryl substituents uniformly reacted in moderate yields to give the *cis*-β-lactams in high diastereo and enantioselectivities (Scheme 5, Table 3). The reaction proceeded well with substrates bearing both strongly and weakly electron-withdrawing substit-



Scheme 5.

Table 3. Results for determination of reaction scope

Ar	Product	cis:trans[a]	% Yield **3**	% ee **3**[b]
4-Fluorophenyl	**3a**	19:1	47	97
4-Chlorophenyl	**3b**	28:1	57	97
4-Bromophenyl	**3c**	14:1	70	97
4-Cyanophenyl	**3d**	12:1	52	94
4-Methylphenyl	**3e**	19:1	69	95
4-Nitrophenyl	**3f**	16:1	55	94
4-Trifluoromethyl-phenyl	**3g**	18:1	67	95
3,5-Dichlorophenyl	**3h**	14:1	66	96

[a] Determined by reverse phase HPLC analysis of the unpurified reaction mixture.
[b] Determined by HPLC analysis of the purified isomer.

uents, and was also effective with a substrate containing a mildly electron-donating group (**3e**). Interestingly, the 4-halophenyl products, **3a**–**c**, could potentially serve as precursors to highly active taxoid derivatives.[10]

In summary, we have developed conditions for the catalytic, asymmetric preparation of *cis*-α-phenoxy-β-aryl-β-lactams. Sulfonyl imines of aromatic aldehydes bearing electron-withdrawing substituents function as optimal substrates for this reaction, and a high diastereoselectivity requires the use of lanthanide and pseudolanthanide Lewis acids with bulky ligands. An investigation into the conditions and protecting groups necessary for conversion of the α-phenoxy-β-aryl-β-lactams into α-hydroxy-β-arylalanine derivatives continues.

Acknowledgments

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Supplementary data

General experimental procedures and characterization data for compounds **1** and **3a**–**h** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.12.091.

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