

An Anionic Nucleophilic Catalyst System for the Diastereoselective Synthesis of *trans*- β -Lactams

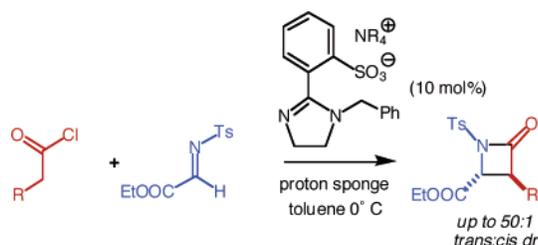
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ABSTRACT



Trans-disubstituted β -lactams show increasing utility and prominence in numerous pharmaceutical applications, making their asymmetric synthesis an attractive goal for chemists. We introduce an anionic, nucleophilic catalyst system that provides an efficient, diastereoselective route to *trans*-disubstituted β -lactams, a complement to our previously described catalytic methodology for generating the corresponding *cis* diastereomers. This catalytic, “switch mechanism” process allows for flexibility in the stereoselective synthesis of β -lactams, producing either *cis* or *trans* products as desired from the same substrates.

Long at the forefront of antibiotic development,¹ β -lactam chemistry has begun to branch out forcefully into new areas of research. Many of the new uses of β -lactams, most notably as serine protease inhibitors,² particularly of thrombin,³ chymase,⁴ and tryptase,⁵ as well as β -lactamase inhibitors,⁶ have one common requirement: they all necessitate a *trans*

relationship between the ring substituents of an α,β -disubstituted β -lactam core. While we have previously developed catalytic methodology to produce disubstituted *cis*- β -lactams in excellent yields and high enantio- and diastereoselectivity,⁷ the disubstituted *trans*- β -lactams have remained a more elusive target, with only a few catalyst-mediated routes known.⁸ A hallmark of these published works is the careful choice of substrates to obtain the desired selectivities.

In this letter, we report the development of an anionic, nucleophilic catalyst system based on a 2-aryl-2-imidazoline scaffold that has allowed us to obtain *trans*- β -lactams in good to excellent diastereoselectivity. We employ acid chlorides (as ketene precursors),⁹ imino esters, and proton sponge (as

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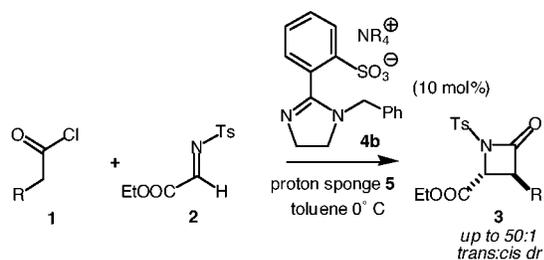
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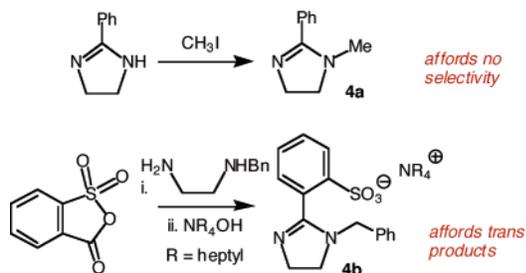
Scheme 1. Catalytic Formation of *trans*- β -Lactams



the stoichiometric “thermodynamic” base) in a Staudinger-type reaction whose selectivity is catalyst mediated but substrate independent (Scheme 1). This methodology allows us to obtain either a *cis* or a *trans* product, as desired, from the same starting materials solely on the basis of catalyst choice.¹⁰

As is the case with our complementary, *cis*-directing cinchona alkaloid-based systems, the catalyst in this reaction presumably acts as a “shuttle” base for ketene (enolate) formation as well. Surprisingly, the effect of a remotely positioned negative charge on the reactivity of a nucleophile has not been well investigated in organic chemistry.¹¹ We hypothesized that in some cases, its reactivity should be enhanced, and in the presence of a bulky, weakly coordinating counterion, its selectivity may be altered as well. We began by testing a number of anionic nucleophiles, ultimately settling on catalysts based on readily available 2-aryl-2-imidazolines (Scheme 2). Such compounds have the advantage of being easily synthesized from commercially available starting materials. In the case of **4a**, the desired product was obtained in one step through methylation of 2-phenyl-2-imidazoline (obtained from Aldrich) with CH_3I . Compound **4b** was synthesized in two steps through condensation of sulfobenzoic anhydride with *N*-benzylethylenediamine followed by ion exchange with tetraheptylammonium chloride (all reagents are commercially available).

Scheme 2. Synthesis and Performance of 2-Aryl-2-imidazoline Catalysts



The prototype neutral catalyst **4a**, while active in the reaction of phenylacetyl chloride (**1a**, R = Ph) with *N*-tosyl imino ester (**2**) in the presence of proton sponge (PS, **5**), gave no selectivity, producing the β -lactam product with a 1:1 diastereomeric ratio (dr). However, when tested under

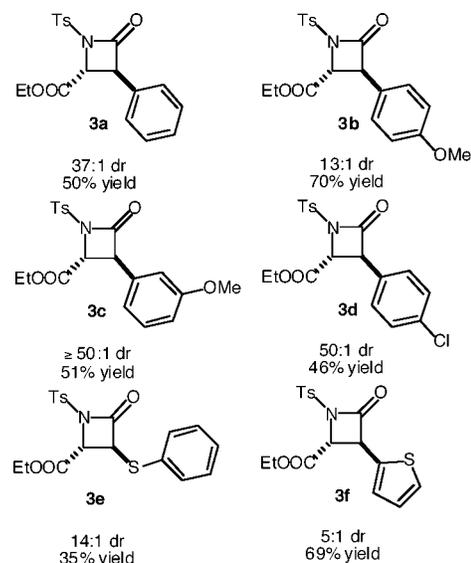


Figure 1. *trans*- β -Lactams synthesized. All compounds shown were synthesized using catalyst **4b**. All dr's were determined by ^1H NMR data obtained from crude reaction mixtures and are displayed in a *trans*:*cis* format. Yields given are for products purified by column chromatography.

the same conditions, **4b** produced the β -lactam product in approximately 50% yield and with a 37:1 dr (*trans*:*cis*). *The significant difference between the charged catalyst and the neutral control is the presence of the anionic sulfonate group.* These promising initial tests prompted us to screen a series of acid chlorides to investigate the scope of this new reaction (Figure 1).

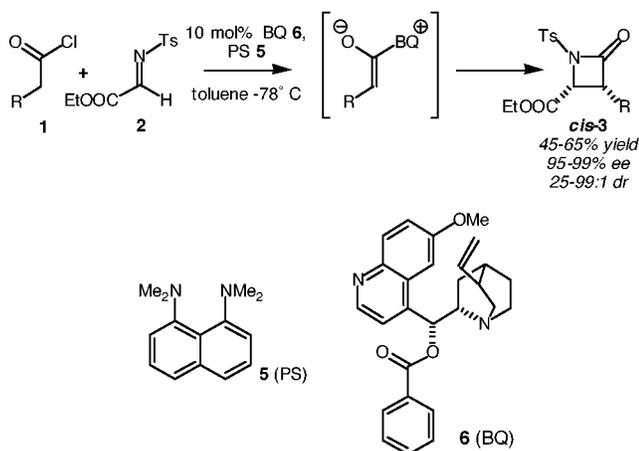
We discovered that, for a variety of acid halide precursors, the *trans* diastereomers predominate (dr's ranging from 5:1 to 50:1). For example, phenylacetyl chloride (**1a**) affords largely the *trans* product (50% yield, 37:1 *trans*:*cis*). Additionally, (*p*-methoxyphenyl)acetyl chloride (**1b**) leads to product in 13:1 dr and 70% yield, whereas (*p*-chlorophenyl)acetyl chloride (**1d**) leads to product in 46% yield and 50:1 dr. Other substituted phenylacetyl halides work similarly to produce the desired products in good dr and moderate to good yield. To date, aliphatic acid chlorides work poorly in the reaction, affording little, if any, β -lactam products at all. Efforts to optimize reaction conditions for these aliphatic substrates are ongoing.

An important question concerns how the catalyst produces the *trans* diastereomers preferentially. In our earlier work with benzoylquinine (BQ) and other cinchona alkaloid-derived catalysts, we proposed that the β -lactam-forming reaction proceeded through the zwitterionic enolate inter-

(10) Change in diastereoselectivity can be termed a “switch mechanism” (wherein a change in the nature of the catalyst affords a dramatically different reaction outcome for the same reacting partners), a long-standing interest of ours. For example, see: Ferraris, D.; Drury, W. J., III; Cox, C.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 4568–4569.

(11) Such a system appears to be unique, the closest analogy evident in the literature, although not strictly applicable, can be seen in: Ritchie, C. D.; Hofelich, T. C. *J. Am. Chem. Soc.* **1980**, *102*, 7039–7044.

Scheme 3. Enantioselective *cis*- β -Lactam Formation

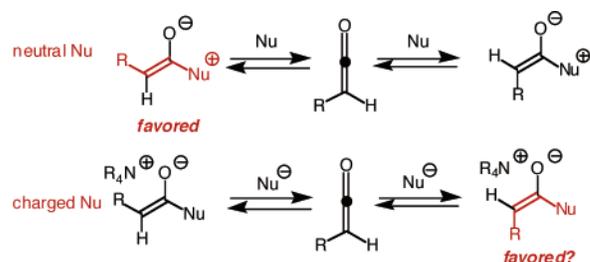


mediate shown in Scheme 3.⁷ We believe that it is through attack on the imine by this enolate species that the stereochemistry of the product is determined. Thus, if the enolate geometry is altered or the reactive imine diastereoface is flipped, the selectivity of the reaction can change from *cis* to *trans*.

This reasoning led to our working hypothesis that the (*Z*)-enolate (which is generally believed to be thermodynamically more stable than the (*E*)-enolate) could lead preferentially to the *cis*- β -lactam diastereomer, whereas the reaction leading to the *trans* isomer may prefer an (*E*)-enolate geometry in some cases. In one possible scenario, an anionic nucleophile may overcome the putative thermodynamic preference for the (*Z*)-enolate, especially when countered by a bulky tetraalkylammonium cation. We theorize that reaction of such a nucleophile would produce an intermediate in which much of the negative charge resides on the enolate oxygen; we expect that this would then bring the oxygen into close proximity with the bulky counterion, which may result in an (*E*)-enolate conformation (Scheme 4).¹² In another possibility, the (*Z*)-enolate geometry would be retained; however, the negative charge on the intermediate enolate could serve to alter the approach of the imino ester (such that the other diastereoface presents itself), again leading to the *trans* product.

(12) This mechanistic hypothesis can be thought of as a specific example of the more general phenomenon of ion aggregation and the role that it may be playing in the diastereoselectivity of the reaction.

Scheme 4. Flipping Enolate Geometry with a Bulky Cation



A third scenario would involve product epimerization by the basic catalyst, converting the original product from *cis* to *trans* during the course of the reaction. Although we have not observed substantial epimerization employing BQ as a catalyst and proton sponge as a stoichiometric base, the new anionic catalysts may be better thermodynamic bases than BQ and/or better kinetic bases than proton sponge. To examine this possibility, we performed control experiments that showed that catalyst **4b** could indeed epimerize the *cis* diastereomer (*cis*-**3a**, made via the BQ-catalyzed reaction) to the *trans* diastereomer over the course of the reaction time; however, this resulted in only an approximate 1:1 mixture of diastereomers.¹³ This experiment, when considered with other controls, indicates that epimerization may play only a minor role in determining the dr of the reaction and that equilibrium mixtures of *cis* and *trans* products brought about by the action of an appropriate base are significantly higher in *cis* content than is observed in our *trans*-selective reaction.

Further work on this new anionic catalyst system, including reaction optimization, mechanistic studies, extension of scope to include aliphatic and other classes of acid chlorides, and development of asymmetric variants, will be reported in due course.

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Supporting Information Available: General experimental procedures and compound characterization. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(13) Epimerization can conceivably occur through proton abstraction on the formed β -lactam product, either at the α - or β -positions. However, another plausible mechanism involves the epimerization of the acidified α -proton on a ring-opened acylammonium intermediate. Further study should differentiate between these possibilities.