Chiral auxiliary-based aldol bond constructions remain the strategy of choice for accessing single isomers of β-hydroxy acid derivatives as chiral building blocks for bioactive compounds. Chiral N-acyloxazolidinones, derived from enantiopure amino alcohols, serve as ester surrogates with excellent control of enolate geometry and versatility in auxiliary cleavage.\(^1\) Previous reports have illustrated the use of these substrates for syn-diastereoselective aldol reactions with chlorotitanium and dialkylboron enolates with high yields and selectivities (eq 1).\(^2\) The corresponding anti-aldol process has not been fully realized with these chiral auxiliaries;\(^3\) however, independent strategies for anti-selective enolate-based aldol reactions have been reported for (Z)-boryl enolates by Yan and Heathcock\(^4\) and for (E)-boryl enolates by Masamune.\(^5\) We now wish to report a highly diastereoselective direct anti-aldol reaction\(^6\) with chiral acyloxazolidinones promoted by catalytic amounts of MgCl\(_2\) in the presence of triethylamine and chlorotrimethylsilane (eq 2). This procedure has important implications in the eventual design of catalytic enantioselective aldol reactions using chiral metal complexes.

![Diagram of aldol reaction]

Our initial design of an aldol reaction, catalytic in metal salt, with imide enolates rested on finding a suitable metal salt capable of facilitating enolization of N-propionyl imide 1a with an amine base, yet able to form a reversible complex with the amine base. Magnesium salts were chosen as candidate Lewis acids for this process due to their precedented use in carbonyl-based enolization with tertiary amines.\(^7\) It was envisioned that the turnover step in the catalytic process would involve ammonium ion protonation of the metal aldolate, thus returning both the metal halide and the acid base to the reaction pool. However, protonation of the metal aldolate proved not to be a practical solution for metal halide turnover. We then focused on metal aldolate silylation\(^8\)–\(^10\) as a strategy for turning over the metal center while improving the prospects for kinetic aldol diastereoselection.

Choice of a silylation agent was contingent upon finding the proper level of reagent reactivity such that reaction with the metal aldolate product, but not with other reaction constituents (e.g. the metal enolate), might be achieved. Chlorotrimethylsilane (TMSCl) was fortuitously found to meet these criteria affording silylated anti-aldol products with high diastereoselectivity and yield.\(^11\) \(^12\) Initial experiments demonstrated that 0.1–0.2 equiv of MgCl\(_2\), MgBr\(_2\), or MgBr\(_2\)-OTf\(_2\) are preferred over magnesium salts with more dissociating counterions such as Mg(OTf)\(_2\) and Mg(NTf\(_2\))\(_2\). Tetrahydrofuran and ethyl acetate are the most effective solvents in promoting the reaction of 1a with benzaldehyde to >90% conversion with >20:1 diastereoselectivity after 20 h at room temperature. Ethyl acetate proved to be optimal for a range of substrates due to faster reaction rates and was selected as the solvent of choice.

Table 1 documents the scope and limitations of representative N-acyloxazolidinones in reactions with benzaldehyde. A current limitation to this aldol procedure includes β-branching on the acyl substituent (entry 6). In addition, α-heteroatom-substituted acyloxazolidinones provide low diastereoselectivity with these conditions. Reactions of 1a with benzaldehyde are effected using 10 mol % of MgCl\(_2\) with 2.0 equiv of triethylamine and 1.5 equiv of TMSCl. Less reactive aldehydes require increasing the magnesium chloride ion byproduct increases the level of conversion. We have found that the addition of 30 mol % of NaSbF\(_6\) is adequate to achieve full turnover for the substrates examined (Procedure B). These two procedures were screened with each aldehyde to maximize yield and diastereoselectivity.

Variation of the aldehyde reaction component resulted in larger changes in diastereoselectivity in the reactions with N-propionyl-oxazolidinone 1a. As summarized in Table 2, the MgCl\(_2\)-catalyzed aldol reaction performs well with a number of aromatic and unsaturated aldehydes, providing moderate-to-high selectivities of anti-aldol products.\(^13\) Even sensitive aldehydes such as methacrolein provide a 16:1 diastereoselectivity and a 77% yield of the isolated anti-aldol adduct.

The following control experiments have provided some insight into the overall mechanism of this transformation. This process does not proceed through a Mukaiyama aldol pathway, as the enolide of 1a is not formed under these reaction conditions. Furthermore, the independently prepared enolsilane of 1a does not react with benzaldehyde under MgCl\(_2\) catalysis in ethyl acetate.\(^14\) Metal
of product silylation and retro-aldolization (eq 5). In conjunction with this trapping experiment it was determined that p-tolualsemialdehyde reacts under the indicated conditions twice as fast as p-methoxybenzaldehyde in a direct competition experiment. In the illustrated reaction, the diastereomerically pure aldol adduct (Table 2) is combined with an equivalent amount of p-tolualsemialdehyde and subjected to the standard reaction conditions (Procedure A). The silylated aldol adduct 6 was isolated as the principal product (83%) while the crossover silylated aldol adduct 7 was isolated in 17% yield. The diastereomer ratios within each family of aldol adducts are noted. It is evident from these results that there exists a delicate balance between metal aldolate silylation and fragmentation (retro-aldolization). Analogous experiments with the silylated aldol adduct 6 show that, once silylated, the aldol products do not interconvert through product epimerization.

Chiral acylthiazolidinethiones have also been reported as useful ester surrogates in diastereoselective reactions, often providing a major diastereomer different from the corresponding oxazolidinone case. Magnesium-catalyzed aldol reaction of chiral acylthiazolidinethione 8 with cinnamaldehyde and subsequent desilylation workup afforded 9 in 87% isolated yield of the major diastereomer (eq 6). Optimized conditions for this family of substrates include the use of MgBr₂·OEt₂. Chemical correlation with known material showed that 9 is the opposite anti-aldol diastereomer to that seen in the oxazolidinone series (eq 4). Propiophenone readily undergoes the magnesium-catalyzed aldol reaction with benzaldehyde, affording 90% yield and 95:5 syn:anti diastereomeric ratio (eq 7). Further investigations into the mechanism and catalytic enantioselective variants of this process are currently underway and results will be reported in due course.

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Supporting Information Available: Experimental procedures, spectral data for all compounds, crystallographic data, and stereochemical proofs (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References