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Asymmetric Synthesis of C_2-Symmetric Vicinal Diamines via Reductive Dimerization of *N*-Acylpyridinium and Related Salts

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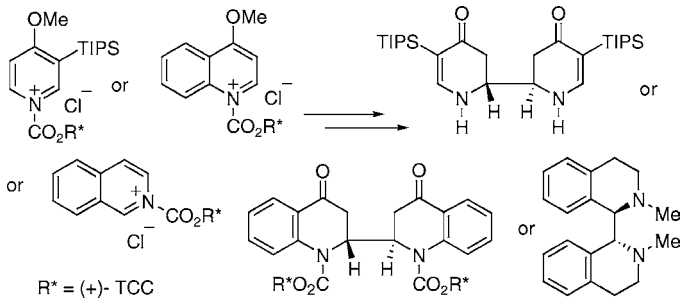
ABSTRACT



A new route to C_2-symmetric diamines via an asymmetric reductive dimerization of 1-acylpyridinium salts and their benzo derivatives is described. This method is practical as the starting heterocycles and chiral auxiliaries are readily available. The titanium reducing agent is inexpensive and easy to prepare. Several novel enantiopure C_2-symmetric diamine derivatives were synthesized using this method.

C_2-Symmetric 1,2-diamines and their derivatives are important in medicinal chemistry, natural products, coordination chemistry, and asymmetric catalysis.[1] They have been extensively used as ligands and catalysts in asymmetric synthesis with impressive results.[2] Because they are so effective as chiral ligands, much work has been reported on the development of methods for their preparation.[3] An attractive approach to vicinal diamines is the reductive coupling of imine species promoted by a metal reducing

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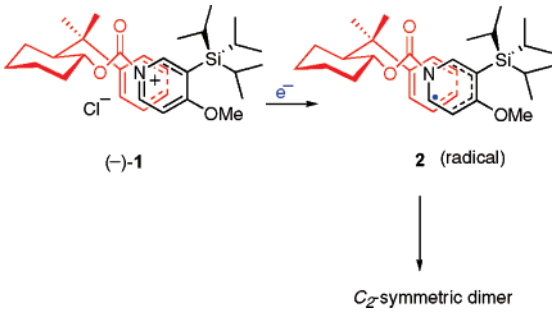
agent. Most of the systems developed to effect this conversion have resulted in low stereoselectivity and produce racemic products.[4] A recent reductive homocoupling of chiral *N*-*tert*-butanesufinyl imines with SmI_2/HMPA generated C_2-symmetric 1,2-diamine derivatives in a highly diastereoselective and enantioselective fashion.[5] A limitation of this method is the destruction of the chiral inducing groups on their removal from the diamine product.

The dimerization of *N*-acylpyridinium salts has the potential for providing unique vicinal diamines. Although some reports of this transformation have appeared, the result is often a mixture of regio- and stereoisomers.[6] If the regioselectivity and facial selectivity can be controlled during the dimerization, then chiral C_2-symmetric 1,2-diamines would result. In this letter we report our successful efforts at dimerizing chiral *N*-acylpyridinium and related salts to afford novel vicinal diamines in an asymmetric fashion.

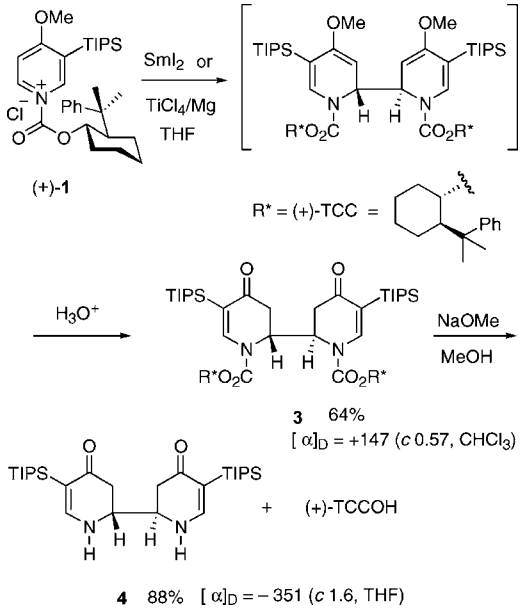
The addition of organometallic nucleophiles to chiral auxiliary-containing *N*-acylpyridinium salt **1** has proven to be a versatile method for the asymmetric synthesis of various heterocycles and natural products.[7,8] We envisaged that addition of an electron to **1** would give delocalized radical **2** which, on dimerization at C6 with auxiliary-directed facial selectivity, would provide a C_2-symmetric dimer. Regioselective reaction at C6 was anticipated due to the methoxy and TIPS groups blocking the C2 and C4 positions (Scheme 1).

Scheme 1



Initially, SmI_2 was used as the one electron reductant. Addition of a THF solution of SmI_2 to chiral salt **1** did afford the C_2-symmetric dimer **3** as the only diastereomer isolated (Scheme 2).

Scheme 2

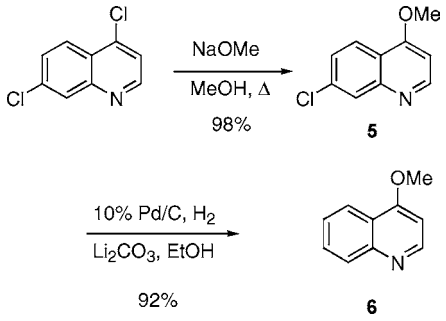


The assigned stereochemistry of **3** was confirmed by single-crystal X-ray analysis. In a search for a less expensive and more convenient reducing agent, it was found that a low-valent titanium species generated from $TiCl_4$/Mg[9] was effective and gave a 64% yield of dihydropyridone dimer **3** on workup with aqueous acid.

As with related *N*-acyldihydropyridones,[7] the chiral auxiliaries could be removed and recovered in high yield by treatment of **3** with NaOMe to give **4** as a white solid that was recrystallized from ether.

To examine other pyridine derivatives in the asymmetric dimerization reaction, our attention turned to 4-methoxyquinoline (**6**). As before, it was anticipated that a 4-methoxy substituent would act as a blocking group to effect regioselective dimerization at the C2 position of the heterocycle. Commercially available 4,7-dichloroquinoline was converted to **6**[10] via **5**[11] on a 10-g scale as shown in Scheme 3.

Scheme 3



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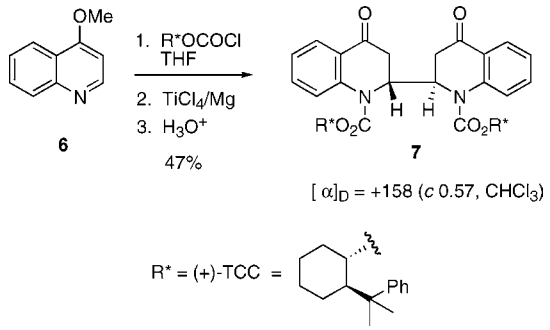
Addition of (+)-TCC chloroformate[12] to 4-methoxyquinoline in toluene formed the *N*-acylquinolinium salt *in situ*. A solution of the low-valent titanium (LVT) was added dropwise, followed by workup with aqueous HCl, to afford the C_2-symmetric dimer **7** in 47% yield (Scheme 4).

Scheme 4

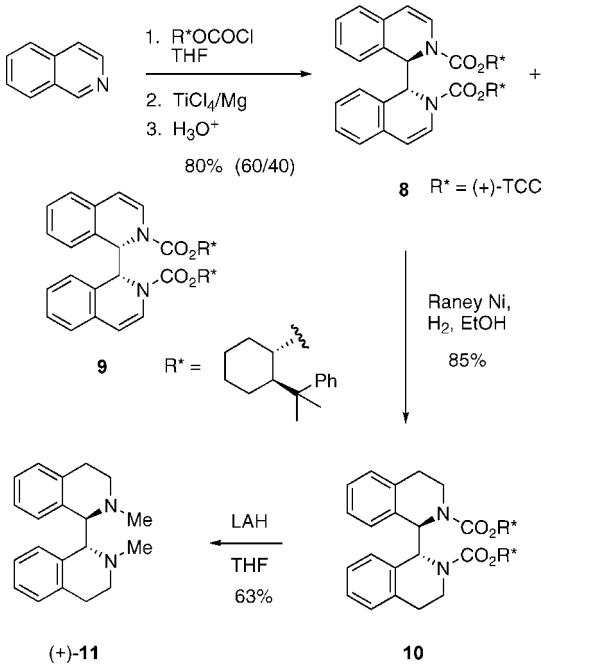


Again, only one diastereomer was observed.[13] Unlike dihydropyridone dimer **3**, the auxiliaries on **7** could not be removed with NaOMe/MeOH.

Since reductive coupling of isoquinoline with Zn/Ac_2O, presumably via an *N*-acylisoquinolinium salt, has been reported,[14] we decided to apply our asymmetric method to this conversion. A solution of LVT in THF was added to the mixture of isoquinoline and (+)-TCC chloroformate in toluene to afford an 80% yield of a mixture (60:40) of the desired dimer **8** and the diastereomer **9** (Scheme 5).

Hydrogenation of **8** over Raney nickel provided derivative **10** which was reduced with LAH to afford the known diamine **11**. The spectral properties of our (−)-**11** are in agreement with reported data for the racemic compound.[14] Elliott and Williams[14b] prepared racemic **11** and found that the basicity of this diamine was unusually high.[14c] In addition to its potential as a chiral base, **11** and derivatives hold obvious value as ligands for catalytic asymmetric reactions.[15,16]

Scheme 5



In conclusion, a new route to C_2-symmetric diamines via an asymmetric reductive dimerization of pyridines and their benzo derivatives has been developed. The method is practical, as the starting heterocycles are readily available and the recoverable chiral auxiliary (TCCOH) can be prepared on multigram scale (>100 g) as either enantiomer. The titanium reducing agent is inexpensive and easy to prepare. Most importantly, numerous variations of C_2-symmetric diamines should be accessible by using readily available substituted heterocycles as starting material, or by modifying the intermediates, i.e., **4**, **7**, **8**, and **10**. The scope of this method and the application of the enantiopure C_2-symmetric diamine derivatives to catalytic asymmetric synthesis are under study in our laboratories.

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Supporting Information Available: Experimental procedures, characterization, and NMR data for **3**−**8** and **11**, and ORTEP plot and X-ray crystal data (cif format) for **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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