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A Preparation of Enantiomerically Enriched Axially Chiral β-Diketimines: Synthesis of (−)- and (+)-IAN Amine

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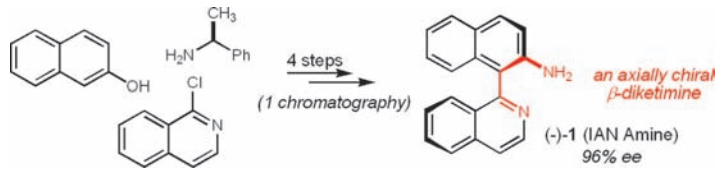
ABSTRACT



The preparation of an enantiomerically enriched β-diketimine composed of isoquinoline and 2-aminonaphthalene (IAN amine) is described, thereby offering new opportunities in the synthesis of nonracemic β-diketimine- and pyridine-based chiral catalysts.

The design of metal-organic complexes is the basis for the discovery of new catalysts that offer unique reactivity and selectivity. Enantioselective reaction development is predicated on the availability of chiral nonracemic ligand variations of the fundamental coordinating unit. One such binding element, the β-diketimine, possesses broad metal-modulating ability[1] but has long lacked a diversity in options for chiral nonracemic variations.[2] Exceptions include semicorrin[3,4] and corrin-like[5] ligands bearing the chiral influence of a secondary amine appended to a planar β-diketimine. These examples have successfully translated to important, even pioneering, enantioselective reactions including cyclopropanation,[3,5] conjugate reduction,[3] and the Michael addition of nonstabilized alkyls.[4] In separate applications, the coordination of two β-diketiminate ligands to a single metal can be highly selective for either homochiral[6] or heterochiral[7] coordination complexes. The resulting complexes have been used subsequently in catalysis and stereoselective synthesis.

Our work has focused on β-diketimines whose design incorporates a chiral element within the coordination sphere of the metal by twisting the β-diketimine binding element (e.g., **1**). This deplanarization provides electronic desymmetrization of the chelating nitrogens, resulting in an unusual example of diastereoselective metal complexation in which a C_2-symmetric homochiral complex is formed selectively from among 13 diastereomers.[6] The barrier to atropisomerization for a series of substituted IAN amines is generally 30 kcal/mol and corresponds to a half-life of >6 days at 70 °C.[8] Until now, our attempts to access enantioenriched IAN

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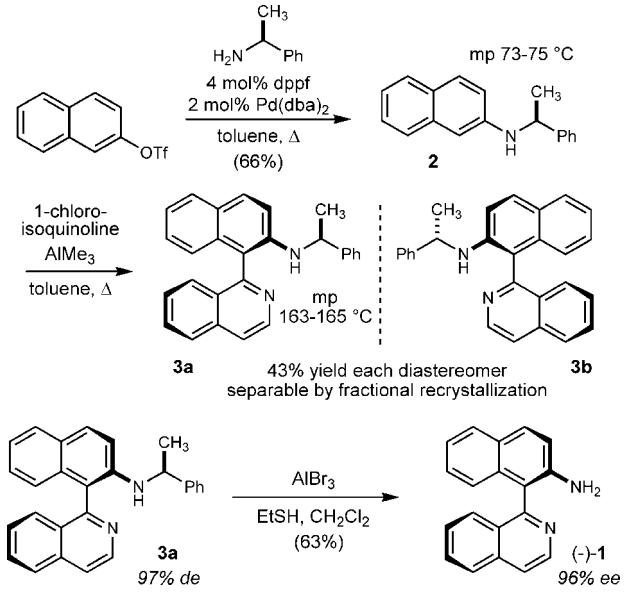
amine derivatives were limited to a single successful separation of Me-IAN enantiomers by preparatory chiral HPLC. We describe here a practical synthesis of IAN amine **1**. As this is a "parent" IAN amine from which numerous others can be synthesized, this development constitutes a general route to N-substituted enantioenriched β-diketimines and considerably extends access to potential chiral β-diketiminate-based complexes.

Extensive efforts to resolve various racemates in this chiral pyridine family were uniformly unsuccessful, including traditional and family[9] approaches to chiral salt formation and fractional recrystallization. These methods used a selection of tartaric and mandelic acids that provided crystalline salts, but without diastereomer enrichment in all fractional recrystallization studies. The synthesis of racemic ligands was readily scaled during this time, and many IAN amine derivatives and their intermediates were routinely crystalline solids. We therefore turned to α-methyl benzylamine IAN **3** and a study of its suitability as a resolving agent without primary recourse to chromatography.

Naphthol 2-triflate[10] was coupled with commercially available (*S*)-α-methylbenzyl amine using palladium catalysis[11] (Scheme 1). The desired aryl amine (**2**)[12] was obtained

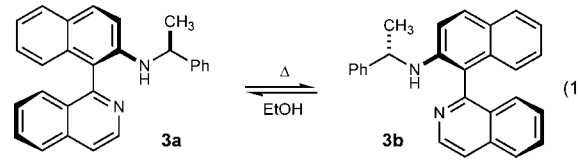
Scheme 1. Preparation of (−)-IAN Amine (**1**)



in 66% yield after direct recrystallization. 1-Chloroisoquinoline is both commercially available and readily prepared.[13] Its coupling with naphthylamine **2** was accomplished using trimethyl aluminum to deliver the desired IAN amine **3** as a 1:1 mixture of diastereomers. This C-arylation was entirely regioselective to the limits of detection (^{1}H NMR) and is attributed to the nature of the intermediate aluminum anilide.[6]

Diastereomers **3a**,**b** provided considerable flexibility to the singular goal to separate them. For example, these diastereomers are readily separated by preparative flash chromatography ($\Delta R_f = 0.09$). The more attractive approach is fractional recrystallization that returns the (*R*)-IAN diastereomer **3a** selectively (>94% purity, HPLC). This diastereomer is consistently a crystalline solid, whereas (*S*)-IAN diastereomer **3b** is routinely a foam (but will occasionally crystallize upon standing when pure and solventless).

Resolutions are normally wasteful in nature as the diastereomer of the chiral auxiliary is often useful only for synthetic access to the enantiomer of the compound of interest. Diastereomer **3b** can be used in this manner to provide (+)-IAN amine. Alternatively, we observed atropisomerization in alcohol solvent that is more rapid than the same isomerization in aromatic hydrocarbons, which require approximately 17 h at 145 °C (xylenes) to reach an equilibrium ratio (1:1) of epimers **3a** and **3b**. Epimerization of **3b** for the purpose of ultimate convergence to one enantiomer (**1**) could be achieved by warming the mother liquor enriched in **3b** in ethanol for 48 h (eq 1).



Subsequent cooling through fractional recrystallization returns (*R*)-IAN **3a** selectively (as a crystalline salt; 25% of theoretical yield for each recycle) and ultimately enantiomerically enriched (−)-**1**.

Removal of the auxiliary was examined using a variety of conditions and strategies. Catalytic hydrogenation using traditional palladium catalysts did not provide the desired IAN amine (**1**) at pressures to 250 psi at room temperature. Transfer hydrogenation required heating in methanol to debenzylate the naphthylamine, but as noted above, atropisomerization under these conditions is favorable. We therefore turned to Lewis acid assisted debenzylation by ethane thiol. Boron tribromide provided IAN amine **1** but was complicated by additional products. By comparison, aluminum tribromide provided a substantially improved outcome, returning IAN amine in 65% yield and 87% ee. This initial result used amounts employed by others, which corresponded to 32 equiv of $AlBr_3$ and ethane thiol solvent (1821 equiv).[14] This protocol was improved by reducing the amount of $AlBr_3$ to 10 equiv while employing an amount of ethane thiol solvent corresponding to 600 equiv. In this manner, the desired IAN amine was obtained in 63% yield and 96% ee reproducibly at the 1 g scale.

It is significant to note that our observations during this optimization indicate that the amounts of Lewis acid and mercaptan can be further lowered, but that the reaction quench must be carefully executed in order to avoid racemization. Specifically, 1 M NaOH must be added *rapidly* to an efficiently cooled reaction flask at 0 °C. Deviation from this protocol resulted in the formation of

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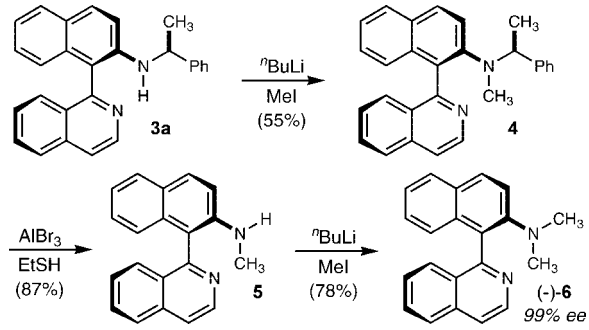
a white gel whose presence typically corresponded to a loss in enantiomeric enrichment (although not complete racemization).

The parent IAN amine is common to many desirable derivatives. For example, alkylation by a deprotonation/electrophile addition procedure provides IAN **4** in 55% yield from **3a** without loss of enantiomeric enrichment. Debenzylation of the tertiary amine using the procedure described above provides Me-IAN (**5**, Scheme 2), which

Scheme 2. Selective Debenzylation of a Tertiary IAN Amine Derivative



can then be alkylated to obtain tertiary amine Me_2-IAN ((−)-**6**). These manipulations are effected without detectable loss of enantiomeric enrichment.

In conclusion, a practical synthesis of the parent IAN amine (−)-**1** in enantiomerically enriched form has been developed. This procedure provides the chiral azabinaphthyl derivative without recourse to preparatory liquid chromatography using a chiral stationary phase. In addition, numerous derivatives can be prepared through either the parent IAN amine or intermediate **3a**. Investigations into the broad application of these axially chiral β-diketimines is now possible as is exploitation of their potential as chiral pyridine derivatives.[15]

Acknowledgment. We are grateful to the NSF for support of this work (CHE-0415811 and REU). Undergraduate research participants were supported by Pfizer (C.M.C.) and NSF-REU (B.R.P.), and we thank Brandon Steele for material contributions.

Supporting Information Available: Procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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