One-Pot Synthesis of Alpha-Diimines from Alkylammonium Salts†

Emily K. Burke[a], Shay Heans Moreyra[a,c], Erin N. Welsh[a,d], Izabella O. Krug[a,e], Katherine N. Robertson[b], Alexander W. H. Speed*[a]

[a]Department of Chemistry, Dalhousie University, Halifax, Nova Scotia, Canada B3H 4R2
[b]Department of Chemistry, Saint Mary's University, Halifax, Nova Scotia, Canada B3H 3C3
[c]Present Address: McGill University, Montreal, Québec
[d]Present Address: Nova Scotia Health, Halifax, Nova Scotia
[e]Present Address: University of British Columbia, Vancouver, British Columbia

*e-mail address: aspeed@dal.ca

†Dedicated to the memory of Professor Steve Westcott (Mount Allison University), in admiration of his legacy of education and undergraduate-centred research.

Abstract: A one-pot synthesis of alkyl-containing diazabutadienes from primary alkylamine-HCl salts is presented. This synthesis avoids halogenated solvents, and the need for a separate free-basing step for commercially available or synthesized amine-HCl salts. Since amine HCl salts are conveniently handled, and diazabutadienes are commonly used as either ligands, or precursors for heterocycles including N-heterocyclic carbenes and diazaphospholenes, this route will be of convenience to many researchers in multiple areas of catalysis.

Introduction: Diazabutadienes (DADs), also known as alpha-diimines, are condensation products between amines and glyoxal. While the preparation of DADs from anilines and glyoxal is readily accomplished by mixing the aniline and glyoxal in alcoholic solvent, resulting in precipitation of the product,[1] the synthesis of DADs derived from alkyl amines can be less straightforward. In some cases, when water-soluble alkyl amines are used, the amine can be mixed with glyoxal in water, with the product precipitating out.[2] However, this procedure does not usually extend to bulkier and less water-soluble amines. In addition, if subsequent applications require anhydrous DADs, *in vacuo* drying of DADs prepared in water is challenging if the DADs are volatile.[3] Chiral amines are a common example of bulkier, water-insoluble

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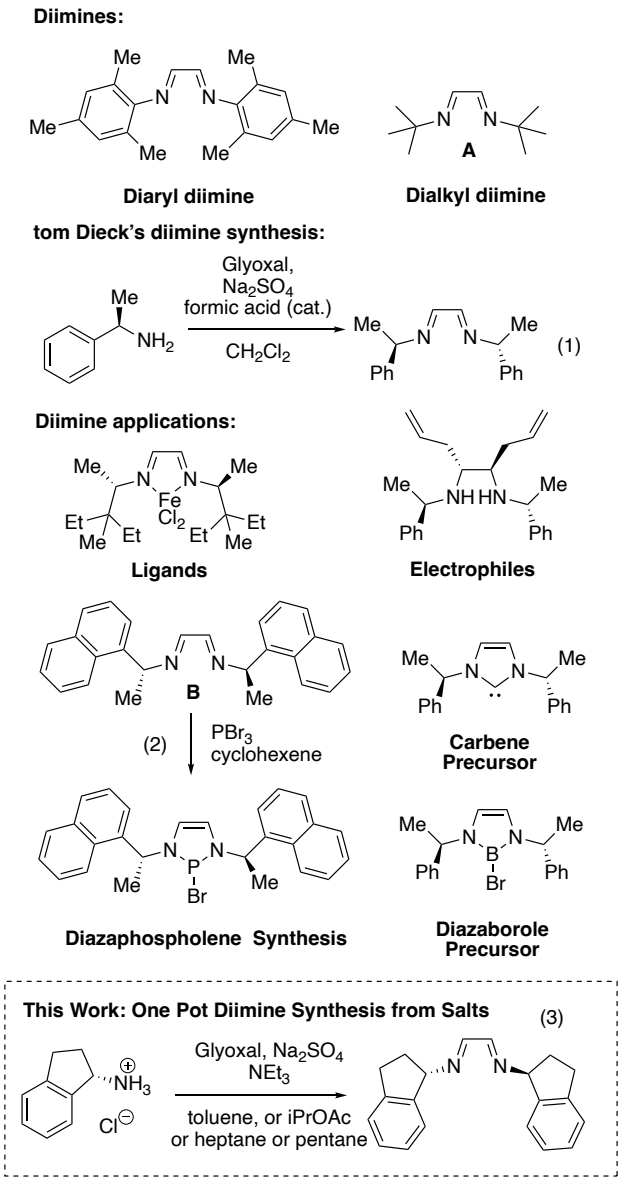
substrates for DAD synthesis. For these amines, condensation with glyoxal in an organic solvent with a drying agent is typically preferred. In 1985, tom Dieck disclosed a procedure to minimize the formation of impurities in chiral DAD synthesis from alkylamines using dichloromethane or chloroform as solvent, sodium sulfate or magnesium sulfate as drying agents, and catalytic formic acid (Equation 1, Scheme 1).[4] The formic acid proved crucial to tom Dieck's procedure, accelerating the reaction and minimize the formation of strongly coloured and difficult to separate impurities.



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Scheme 1. Synthesis and Applications of Diimines

Dialkyldiazabutadienes are versatile and sought-after compounds, and have been used as electrophiles,[5] ligands for metals,[6] precursors to N-heterocyclic carbenes,[7] precursors to diazaboroles,[8] and precursors to diazaphospholenes (Equation 2, Scheme 1).[9,10] Given the many and common uses, a robust route to these diimines is crucial in catalysis. Tom Dieck's procedure remains the most common approach to the formation of chiral DADs from chiral amines and glyoxal described above. In the course of our investigation of diazaphospholenes, we have frequently employed tom Dieck's conditions in dichloromethane, which works very well for certain bulky substrates, including preparation of diimine **A** on a 27 gram scale with 84% yield, and diimine **B** on a 71 g scale with 68% yield (Scheme 1).[11,12] However, we encountered several limitations or concerns with tom Dieck's method, which may be addressed by a complementary method described here. Limitations we have observed are as follows: while the formic acid conditions minimizes the formation of impurities, we have found extended reaction times, or condensation of amines with relatively low steric demand such as 1-phenethylamine frequently results in the formation of impure products, and inconsistent product cleanliness from batch to batch.[13] Another potential downside to existing diimine condensation protocols is that dichloromethane, the optimal solvent for the formic acid procedure, is facing increasing regulatory burden.[14] Finally, some primary amines are commercially available or best prepared as their HCl salts. HCl salts are an attractive way to store primary amines, as they are resistant to reaction with atmospheric CO_2, unlike the parent amines.[15] Use in tom Dieck's method requires freebasing the salts, and this sometimes requires experimentation, as the solubility of the free amines in common organic solvents such as dichloromethane or diethyl ether varies. In addition,

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freebasing a volatile amine, then removing the solvent can result in poor recovery. In this work, we describe an alternate procedure for DAD synthesis that proceeds directly in one pot from amine HCl salts, avoiding a separate freebasing step. Halogenated solvents are avoided, and addition of formic acid is unnecessary.

Results and Discussion: Because amine HCl salts are readily stored and are also common intermediates in the synthesis of chiral primary amines, we became interested in preparing diimines directly from HCl salts. We reasoned that addition of a tertiary amine base to the diimine formation would liberate the free-base primary amine in situ.[16] For our initial studies, we started with amine **1a** as our model. Amine **1a** is one of the most inexpensive primary chiral amines. While **1a** is commercially available as the freebase, we prepared the protonated form **2a** for our studies, by treating a solution of **1a** in ethyl acetate with HCl, and collecting the resulting solid. Storing amines as the HCl salts has some advantages. Amine **1a** rapidly forms an adduct with CO_2 within minutes upon exposure to air (images of the adduct formation are in the Supporting Information), while samples of salt **2a** have been stable for over 5 years in our lab, stored at room temperature with no protection from the air other than a loose-fitting lid.

In the initial experiment, a mixture of salt **2a**, glyoxal aqueous solution, sodium sulfate, and triethylamine was stirred in CH_2Cl_2. Diimine **3a** was observed to form in an aliquot analyzed by NMR spectroscopy after 24 hours. Formic acid was not added, with the anticipation that triethylamine hydrochloride would be a suitable acid to promote diimine formation. Filtration to remove drying agent, and evaporation showed diimine **3a**, mixed with triethylammonium hydrochloride. Adding toluene to the resulting residue and filtering the insoluble

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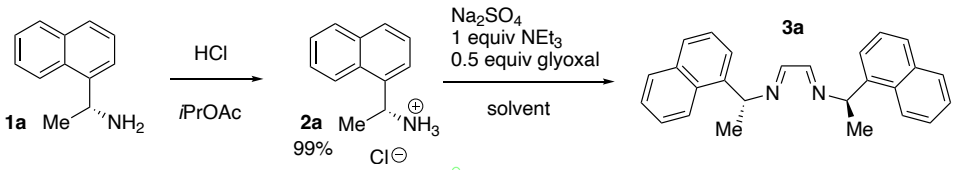
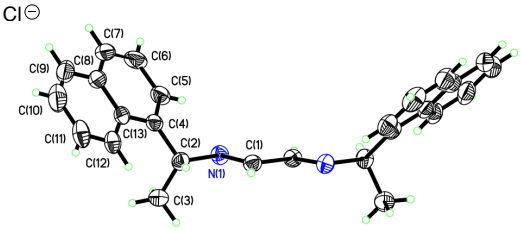
triethylammonium hydrochloride off, then removing the toluene was used to purify the diimine, which was obtained in x% yield (Table 1, Entry 1).



Entry	Solvent	yield **3a**
1	CH_2Cl_2	%[a]
2	toluene	96%
3	iPrOAc	95%
4	heptane	94%



X-Ray Structure of 3a[b]

Scheme 2. Development of One-Pot Diimine Synthesis

a) yield after extraction with toluene and filtration b) Hydrogen atoms are included but not labelled. Drawn with 50% probability ellipsoids.

We investigated if the diimine formation could be directly conducted in toluene to avoid the solvent change step for purification. Gratifyingly, a similar yield was obtained after 24 h of reaction time with toluene as solvent. Direct filtration and concentration of the product gave diimine **3a**, without contamination with triethylamine hydrochloride (Table 1, Entry 2). The purity of the material from this reaction as assessed by ^{1}H NMR was comparable to the best material we previously used in diazaphospholene synthesis.[11A] Slow evaporation of toluene provided crystals that were subject to X-ray diffraction studies, confirming the structure of the product.

We studied two other solvents, that are known to form azeotropes with water, do not dissolve triethylamine hydrochloride, and are frequently preferred for environmental and safety reasons.[17]

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With isopropyl acetate, a comparable yield and product purity was obtained after 24 h reaction time (Table 1, Entry 3). With heptane, good results were also obtained, with a slight diminishment of yield. (Table 1, Entry 4).

In past experiences with the formic acid method, we corroborated tom Dieck's observations that extended reaction times for diimine formation in halogenated solvents led to complex product mixtures. The reaction in toluene appeared robust. Part of this research was conducted during the acute phase of the COVID-19 pandemic, when researchers were under significant time restrictions in our lab. Accordingly, some reactions were conducted over periods as long as 72 hours, yet final product purity was essentially equivalent to the 24-hour reaction periods. The cleanliness of the products is of significance, since there are a relatively limited number of ways to purify diimines derived from alkylamines. Due to the hydrolytic sensitivity of diimines, column chromatography is not usually successful. We have found crystallization attempts of dialkyl diimines typically results in low product recovery, potentially due to high solubility in various solvents. Our preferred purification method to remove minor impurities from solid diimines is trituration with cold ethanol or diethyl ether. For trituration to be successful, the initial purity of the diimine typically needs to be relatively high, and this procedure provides diimines of suitably high quality. For liquid diimines, we have not identified any satisfactory purification methods, so high initial product purity is desirable. While we do not have a concrete explanation for the divergence in outcome with solvent, it is possible that the mild electrophilicity of dichloromethane may result in slow side reactions from nucleophilic attack by amine or diimine.[18]

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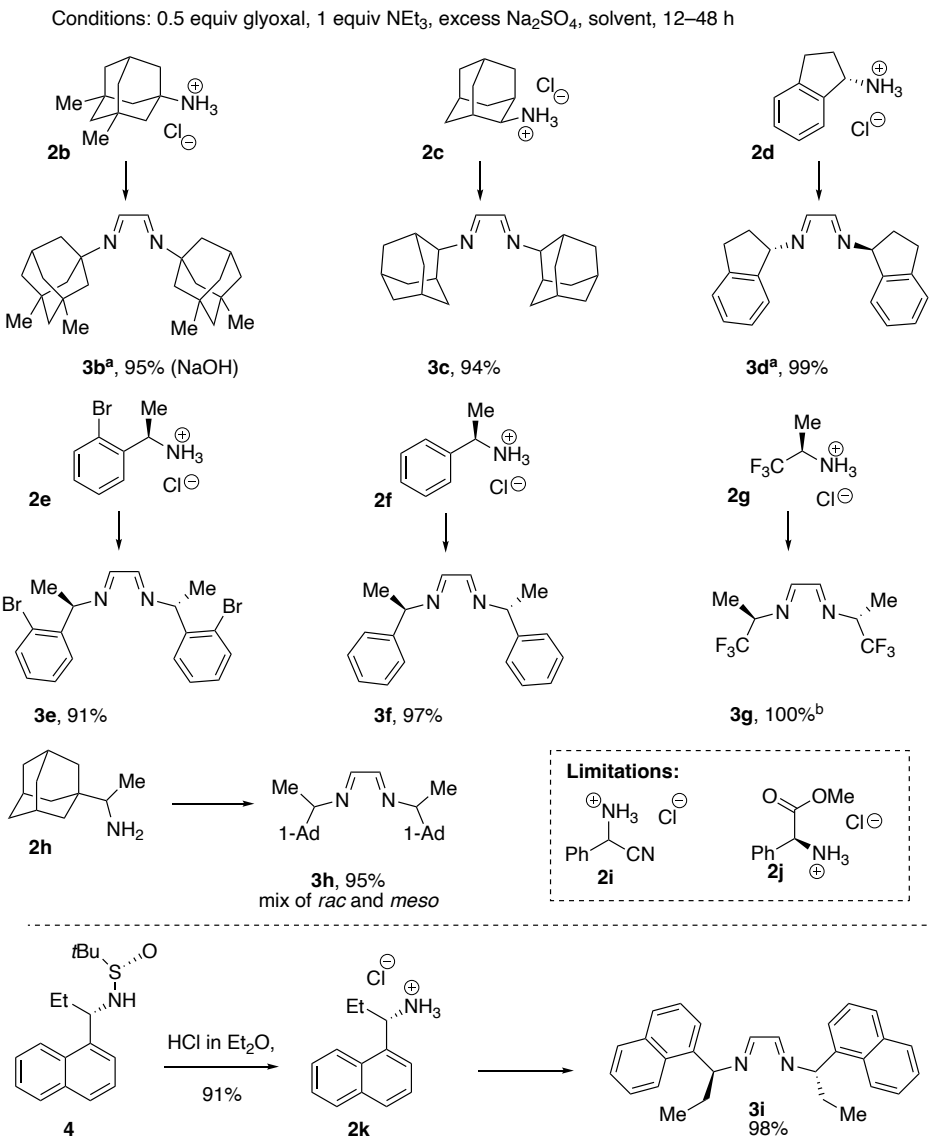

Scheme 3: Examination of Scope a) 6 M NaOH used as base, b) yield before purification

We conducted an examination of scope, using commercially available amine HCl salts. (Scheme 2) The pharmaceutical memantine hydrochloride **2b** was converted to diimine **3b** by the general procedure in 95% yield. The secondary adamantyl diimine **3c** could be prepared from 2-adamantylamine hydrochloride **2c** in 94% yield.

(*S*)-indan-1-amine hydrochloride **2d**, and (*R*)-2-bromophenyl ethanamine hydrochloride **2e** were likewise converted to chiral diimines **3d** and **3e** in 99 and 91% yields respectively. (*R*)-phenyl

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ethanamine hydrochloride **2f** was converted into the diimine **3f** in 97% yield. In this case, the product of the reaction was cleaner than samples prepared with tom Dieck's method in dichloromethane.

An electron-deficient DAD **3g** could be prepared from (*R)*-2-amino-1,1,1-trifluoropropane hydrochloride. **2g** In this case, DAD **3g** was extremely volatile, so pentane was used as the reaction solvent. A crude yield of 100% was obtained. The product could be purified by sublimation, however an accurate yield for the sublimation could not be determined due to difficulty in recovering all the material, which made extremely feathery deposits, and tended to fall back down into the sublimation chamber upon any disturbance, including the repressurization of the sublimation apparatus. It should be noted that volatile diimines are lachrymators and irritants, so caution should be taken in handling an obviously volatile compound such as **3g**.[19,20]

Rimantdine hydrochloride **2h**, a racemic chiral amine, was subject to the conditions to form a mixture of diimines **3h** in a 95% mass recovery. In toluene, a 50:50 mixture of the diastereomers were formed, while in isopropyl acetate, it was noted the mixture was enriched in one diastereomer, now with a 10:1 ratio. Unfortunately, we were not able to completely purify or crystalize this material to determine a relative configuration of the dominant product.

Attempts to prepare other electron-deficient DADs revealed some limitations. Attempted condensation of either (*rac*)-2-amino-2-phenylacetonitrile hydrochloride **2i** or phenylglycinol

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methyl ester HCl salt **2j** under the standard conditions resulted in no diimine formation. The freebase of **2i** likewise did not undergo condensation.

A multi-step sequence further illustrates the practicality of this method, and potential to reduce the number of steps in a synthetic sequence. Ellman auxiliary chemistry represents a powerful way to prepare chiral non-racemic amines.[21] Our group previously used Ellman's auxiliary chemistry to prepare diimine **3i**, a ethyl-containing analogue of **3a**.[11] The immediate cleavage of the sulfinamide produces a HCl salt **2k**, which is collected by filtration. In our prior procedure this was converted to the free amine before diimine synthesis. We prepared **4** via Ellman chemistry,[22] and removed the auxiliary with ethereal HCl to afford salt **2k** after filtration. Salt **2k** was directly converted to diimine **3i** by the standard procedure in 98% yield. Chiral amines prepared on relatively small scale such as **2k** are particularly conveniently isolated and stored as their HCl salts, to avoid decomposition, and now these amine salts can be directly used in condensations.

Two final variations of the condensation procedure were explored (Scheme 4). Many chiral amines are available not as HCl salts, but as salts of chiral acids that are used for their resolution. (1*R*, 2*S*)-2-(3,4-difluorophenyl)cyclopropaminium *R*-mandelate **2l** was subject to the standard conditions. While the product **3j** was observed with toluene solvent, significant quantities of triethylammonium mandelate were observed, presumably due to the high solubility of the ion pair in toluene. The salt was soluble in other solvents such as ether, so could not be removed by filtration. In a modification of the conditions, 6.0 M aqueous NaOH was used as base. Product **3j** of satisfactory cleanliness was obtained in 75% yield after filtration and concentration, though

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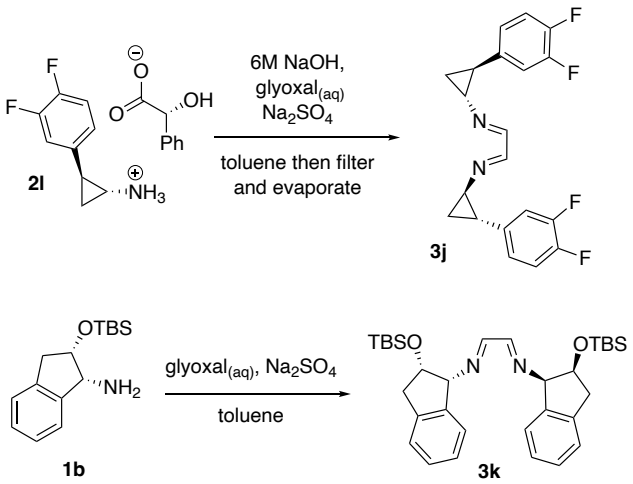
trituration was not possible as the product was an oil. We noted this diimine had limited stability, so characterization was conducted with toluene present.



Scheme 4. Procedural Variants

We also examined the condensation reaction in toluene with free amine **1b** derived from silylated (1*R*,2*S*)-aminoindanol,[23] without formic acid present. While formic acid was essential to avoid impurities in halogenated solvents in tom Dieck's work, condensation of amine **1b** proceeded with 81% yield with just sodium sulfate and toluene. The qualitative cleanliness of product **3k** was again higher than attempts to make this compound under the formic acid conditions, potentially due to a propensity for silyl migration or cleavage under acidic conditions.[4]

Conclusion: We document that chiral diimines can conveniently be prepared from primary amine salts and glyoxal, with an appropriate base in non-halogenated solvents. The product purity is often superior to the most popular method of preparing chiral amines, formic acid catalysis in dichloromethane. Given the importance of chiral diimines, the difficulty in purifying

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chiral diimines when they are formed in an impure manner, and convenience of this method, we anticipate this will be a useful addition to the toolbox of chemists working with chiral diimines.

Corresponding Author:
*E-mail: aspeed@dal.ca

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