Redox-Tunable Ring Expansion Enabled By A Single-Component Electrophilic Nitrogen Atom Synthon

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ABSTRACT: Controllable installation of a single nitrogen atom is central to many major goals in skeletal editing, with progress often gated by the availability of an appropriate N-atom source. Here we introduce a novel reagent, termed DNIBX, based on dibenzoazabicycloheptadiene (dbabh), which allows the electrophilic installation of dbabh to organic substrates. When indanone β-ketoesters are aminated by DNIBX, the resulting products undergo divergent ring expansions depending on the mode of activation, producing heterocycles in differing oxidation states under thermal and photochemical conditions. The mechanism of each transformation is discussed, and the different reactivity modes of the indanone-dbabh adducts are compared to other nitrogenous precursors.

Skeletal editing requires the concurrent formation or cleavage of multiple new bonds to a single atom.[1–4] Accordingly, central to many of the recent advances in this space are reagents that successfully manage this bond choreography, delivering a single-atom equivalent. An example illustrating this fact can be found in work from Suero, whose single-component reagent has enabled insertion of a carbon atom to olefinic substrates (Fig. 1A).[5–8] An analogous N-atom transfer was demonstrated by Morandi, with nitrogen insertion promoted through in-situ reaction between ammonia and iodine(III) oxidants.[9,10] Though powerful, the lack of a well-defined single-component reagent in this latter case introduces mechanistic ambiguity and limits the potential applications of this reagent system due to competing oxidations.[11,12] Though a range of other reagents have advanced the opportunities for nitrogen atom transfer, including anomeric amides,[13–15] sulphenyl nitrene precursors,[16–18] oxadiazoles,[19] diazirines,[20] and osmium nitrides,[21] many desirable classes of nitrogen atom insertions remain elusive. Continued progress in this area is intimately tied to the further development of novel reagents capable of transferring single nitrogen atoms.

We were inspired by Cummins's use of dibenzoazabicycloheptadiene (dbabh) as a nitrogen atom source in metal nitride synthesis (Fig. 1B).[22,23] While dbabh has served repeatedly as a nitrogen atom synthon in inorganic synthesis, it has largely been ignored in this capacity by organic chemists,[24–28] with the closest precedent in Gribble's synthesis of polyaromatic systems by oxidative deamination, which discards the nitrogen atom.[29–34]

Here we report a single-component nitrogen atom transfer reagent that enables productive skeletal incorporation of the nitrogen atom of dbabh. This hypervalent iodine reagent (Fig. 1C), for which we propose the name DNIBX (**1**, dibenzo-7-azanorbornadiene-benziodoxolone, akin to Waser's EBX reagent[35]), is demonstrated to aminate indanone β-ketoesters; these aminated indanones display divergent subsequent reactivity in which the dbabh functionality allows access to ring-expansion products in multiple redox states.

Hypervalent iodine has traditionally served as a platform for the transfer of *protected* nitrogen species,[36,37] including azide,[38,39] bis-tosylamine,[40] sulfoximine,[41] phthalimide,[42] and diarylimines.[43] A striking recent development in hypervalent iodine chemistry is the realization of stable iodine(III) reagents bearing unprotected amines (primary[44] or secondary[45] alkyl amines, and more recently ammonia[46])

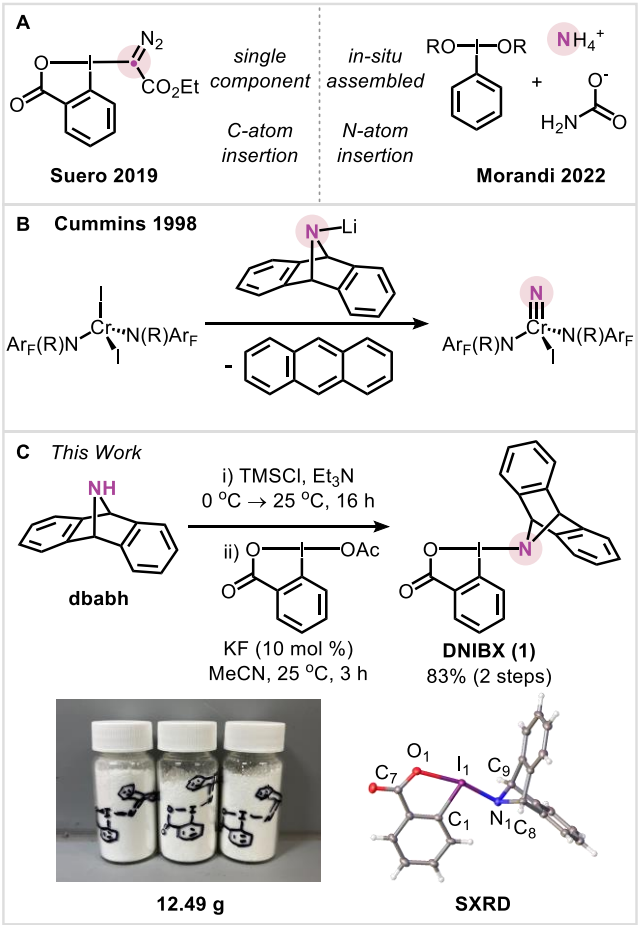

Figure 1. A) Select examples of atom transfer reagents used for skeletal editing. B) Inspiring precedent of N-atom transfer with dbabh. C) Synthesis, scalability, and structure of DNIBX.

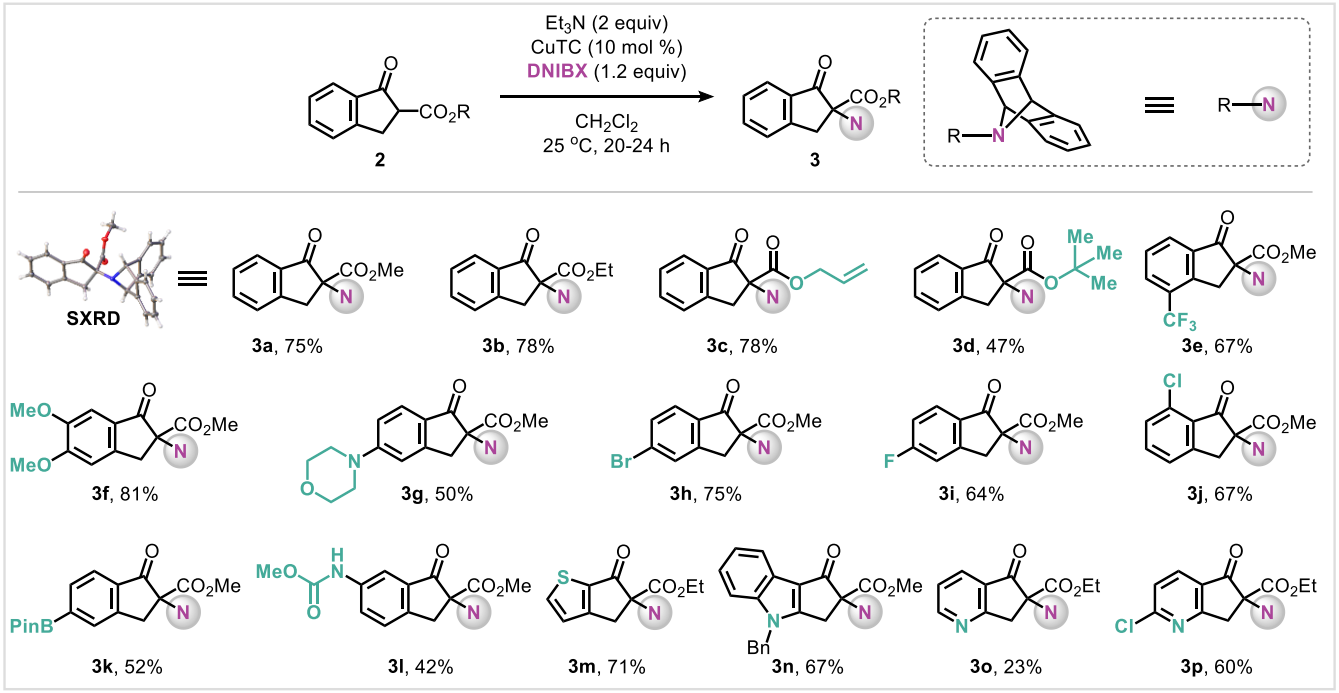

Figure 2. Scope of the amination reaction. Isolated yields on 0.3 mmol scale

for the direct transfer of amino groups. These advances prompted us to synthesize **1** from the corresponding silylamine (Fig. 1C).[25] The synthesis was remarkably scalable, allowing the production of decagrams of **1** in a single batch. Structural data indicates a distorted T-shaped geometry about the iodine, akin to other cyclic amino-iodine(III) species. The N-I-O (165.83°) and endocyclic C-I-O (76.13°) bond angles are comparable to previous reported N-bound cyclic iodine(III).[42–44,47] The I-N bond length (2.087 Å) falls within the range of other I(III)-NR_2 bonds (NR_2 = piperidine, 2.093(11) Å;[45] carbazole, 2.069(4) Å).[47] Differential scanning calorimetry shows a multifaceted exotherm that onsets at temperature of 133 °C and releases 440 kJ/kg (see SI for details). The onset temperature is comparable to azido-hypervalent iodine species, but **1** releases less than one third of the energy per kilogram than Zhdankin's reagent (1770 kJ/kg) and less than half of Waser's ABZ reagent (965 kJ/kg).[39]

With a structurally validated and thermally robust reagent in hand, we chose indanone β-keto-ester enolates (**2**) as model nucleophiles to investigate the reactivity of **1**, envisioning that release of a nitrene through retro-[4+1] electrocyclization of the dbabh functional group[48] would result in ring expansion to the corresponding lactam.[49] Gratifyingly, we found that copper(I)-enolates engaged in productive amination; potassium- or ammonium-enolates reacted only to give oxygenated products (see SI). Routine optimization resulted in a catalytic protocol that uses the commercially available, air-stable copper(I) thiophene-2-carboxylate as a catalyst in combination with stoichiometric triethylamine as a base. This protocol can be adapted for the synthesis of a variety of aminated indanones (Fig. 2). Of note, oxidatively sensitive functional groups (**3f**, **3g**, **3n**) were unaffected by the reaction conditions. Additionally, Chan-Lam coupling of a pinacol boronate ester was not observed, allowing aminated product **3k** to be obtained in good yield. A number of fused heterocycles (**3m, 3n, 3o, 3p**) were also tolerated in the amination reaction. While *tert*-butyl ester **3d** could be formed under these conditions, additional steric hindrance in the form of mono- or dimethyl substitution at the β-position of the indanone resulted in prohibitively sluggish reactivity (see SI). Radical scavenging experiments (TEMPO, BHT) indicate that the copper-catalyzed amination of **2** proceeds via a radical mechanism, in line with previous studies of copper(I) enolates (See SI).[50]

Having synthesized a family of aminated indanones, we sought to engage the newly-installed dbabh functional group as a nitrenoid precursor to generate isoquinolones (**4**) (Fig. 3A).[49] Initially, we tested a variety of conditions to thermolyze **3** in high-boiling solvents and/or in the presence of metal catalysts.[48,51–55] However, we found all of these conditions to be unsuccessful, where the main observed product was often the result of a single C-N bond cleavage.[54] Surprisingly, we found that methanol was a privileged solvent for this transformation; refluxing in methanol afforded **4a** in 21% yield (along with anthracene (**5**) as a byproduct) where heating in other solvents at the same temperature did not yield any product. Further optimization revealed LiCl as an effective promoter (possibly due to an ionic strength effect, *vide infra*), allowing **4a** to be obtained in 70% yield in just 24 h. These conditions proved general, allowing many other isoquinolones to be obtained including those bearing halogen, alkoxy, and boron substituents, as well as unusual, fused heterocycles **4m** and **4o**. However, electron-rich substrates with donors in direct conjugation with the carbonyl (**3g** and **3n**) did not give appreciable yields of **4**. Instead, these substrates typically afforded products of partial solvolysis of the dbabh unit (see SI). It should also be noted that under these conditions, alkyl esters (with the exception of *tert*-butyl) undergo transesterification with the methanol solvent (**4a**, **4m**, **4o**).

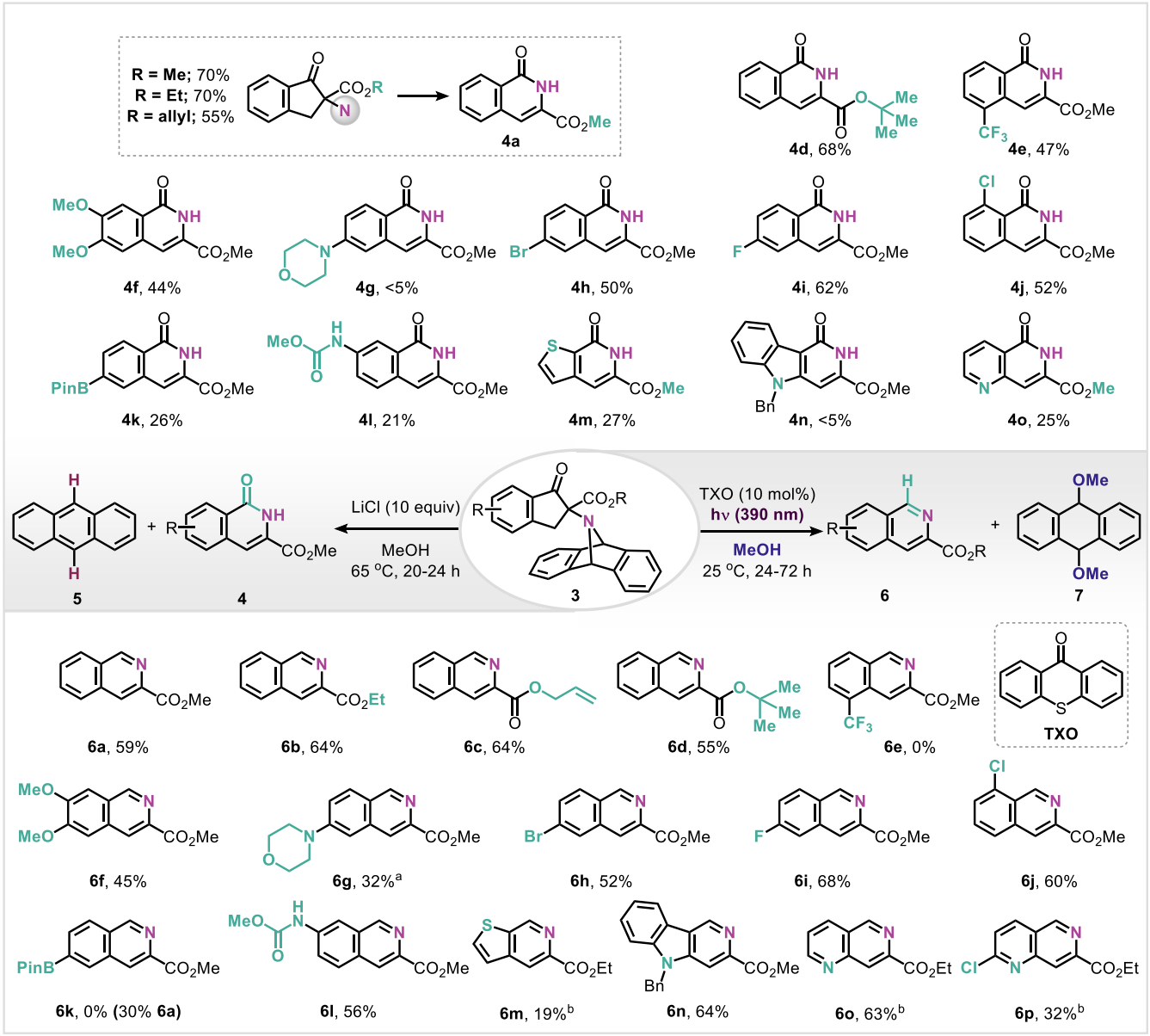

Figure 3. Scope of the ring expansion reactions to form isoquinolones (top) and isoquinolines (bottom). Isolated yields on 0.1 mmol scale. TXO = Thioxanthen-9-one. [a][Ir(dF(CF$_3$)ppy)$_2$(dtbpy)]PF$_6$ and 427 nm Kessil lamp used in place of TXO and 390 nm. [b]Benzoic acid (1 eq) added.

We next sought to explore the photochemistry of the dbabh functional group. In the event, we were surprised to discover that photolysis of **3** in methanol resulted in methyl isoquinol*i*ne-3-carboxylate (**6a**) along with dimethoxydihydroanthracene (**7**, formed as a *cis*/*trans* mixture). This unusual transformation represents a redox transposition of the thermally induced isoquinolone synthesis, formally migrating the oxidation balance from the heterocyclic product to the anthracene-derived leaving group. Again, methanol proved to be unique in its ability to promote this transformation; other solvents arrested at an aldehyde-containing intermediate (*vide infra*).

Our initial investigations into the scope of this reaction revealed highly substrate-dependent reactivity. High throughput experimentation (HTE) was leveraged to remedy this. After exploring a range of photocatalysts and additives (see SI for details), thioxanthen-9-one (TXO) was identified as the optimal photocatalyst, with dilution of the reaction mixture also necessary to enable light penetration due to the generally low solubility of aminated substrates **3** in MeOH. Notably, in contrast to the thermal conditions, transesterificaiton was not observed under photolysis, allowing the synthesis of isoquinolines with varied ester functionality (**6a**, **6b**, **6c**, **6d**, Fig. 3B). Electron rich substrates **6f** and **6g** required extended reaction times, but nonetheless afforded product. While fused pyridine **3o** reacted very sluggishly with poor yield (5% yield after 5 days), an additional round of HTE revealed that a mild acid additive (AcOH or BzOH) rescued its reactivity, allowing napthyridines **6o** and **6p** to be prepared in 63% and 32% yield, respectively.

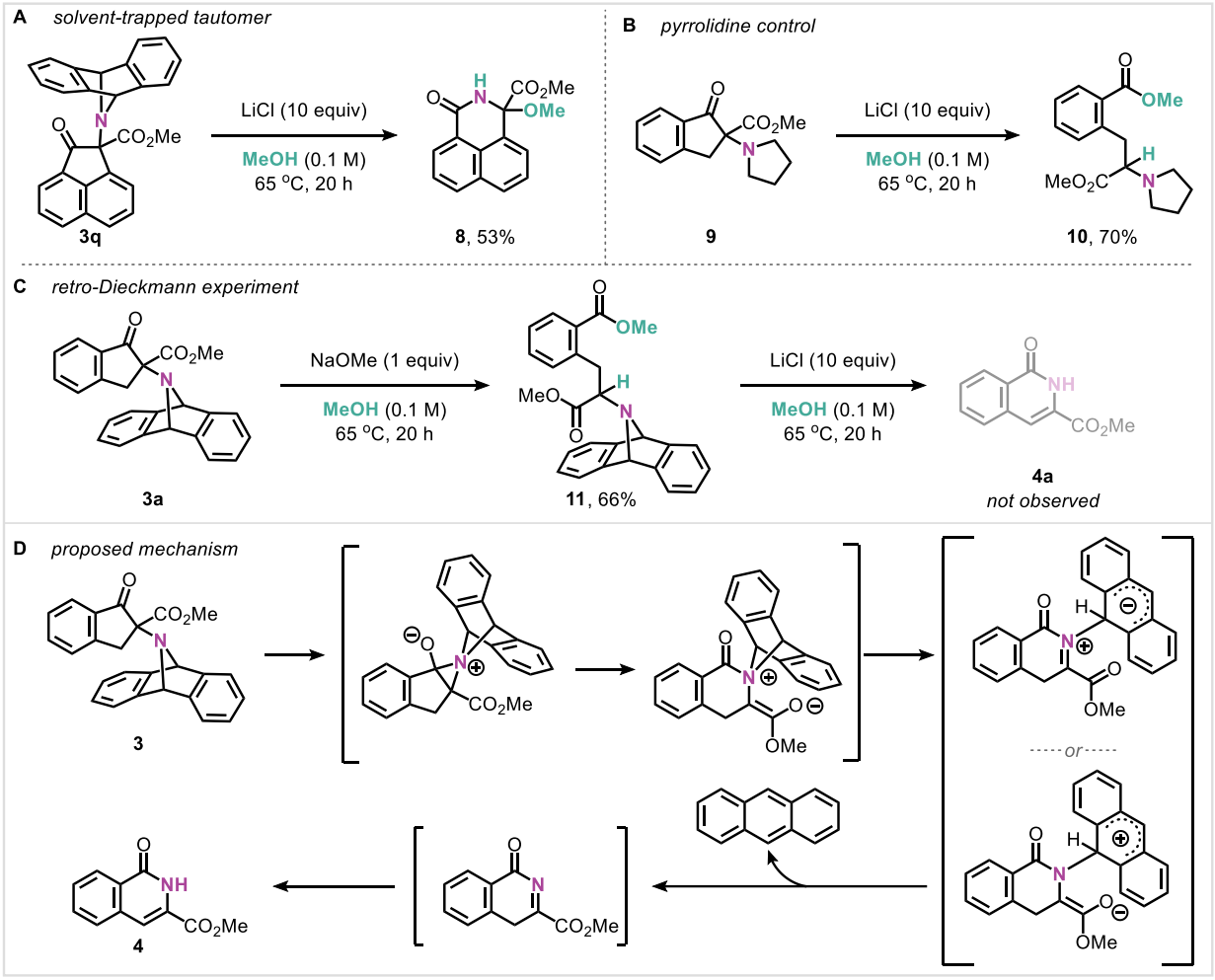

Figure 4. A) Trapping of 4H-isoquinolone. B) Ring opening of α-pyrrolidine indanone. C) Isolation and resubjection of retro-Dieckmann product. D) Proposed mechanism for thermal ring expansion.

Having discovered two new reactions of the dbabh scaffold, we embarked on a mechanistic investigation of each reaction pathway. Despite our initial hypothesis of a pericyclic release of a nitrene from **3**, the stark solvent effect noted in the optimization of the reaction strongly suggests otherwise, as a concerted cheletropic extrusion would be expected to have little-to-no solvent dependence.[56,57] As such, we investigated alternative mechanisms, using related substrates as a guide. First, acenaphthalene derivative **3q** was found to give the methanol-trapped lactam **8** in 53% yield (Fig. 4a); this product represents a solvent-trapped analog of the tautomeric 4*H*-isoquinoline potentially encountered in the parent reaction. Next, pyrrolidine **9** was found to afford the retro-Dieckmann product, diester **10**, in 70% yield (Fig. 4B). To test whether an analogous ring opening is relevant to the formation of **4** we prepared the dbabh-substituted retro-Dieckmann product **11** by reaction with NaOMe. Upon resubjection to the thermal ring expansion reaction conditions, **11** did not yield any **4a**, ruling out such a pathway (Fig. 4C). Instead, we favor a mechanism (Fig. 4D) similar to that proposed by Christoffers for the base-mediated ring expansion of alpha-amino ketones,[58] in which intramolecular alkoxyaziridine formation and Grob-type ring expansion gives a zwitterionic intermediate. This intermediate may extrude anthracene (by either a concerted cheletropic extrusion or stepwise bond cleavage events, as shown) and 4*H*-isoquinolone, which ultimately tautomerizes to **4**.

Under photochemical conditions, our experiments suggest that the dbabh subunit is a spectator in the first stage of the mechanism. Aldehyde **12** is isolated as a mixture of *E*/*Z* isomers as a major product when photolysis is conducted in THF (or other non-protic solvents) in place of methanol (Fig. 5A). Moreover, **12** is observed as an intermediate during the photolysis in methanol, supporting photochemical Norrish cleavage as the first stage of this reaction.[59] Consistent with aryl ketone photochemistry, the consumption of **3** is accelerated by triplet sensitization (e.g., by TXO), indicating a triplet-mediated ring cleavage. A Norrish mechanism is further supported by an intramolecular competition kinetic isotope effect (KIE) experiment; the primary KIE supports a hydrogen atom transfer (HAT) process and the retention of total D incorporation (as well as lack of D incorporation when unlabeled substrate reacts in CD_3OD) suggests solvent is not involved (Fig. 5B).[60,61] As evidence that Norrish cleavage product (**12**) is relevant to the isoquinoline synthesis, it can be resubjected to the reaction conditions to give **6**. However, under otherwise identical conditions, **12** remains unreacted in the dark, indicating that **12** is photoactivated en route to **6**. To determine the nature of this photoactivation, we monitored the photolysis of **(*E*)-12**

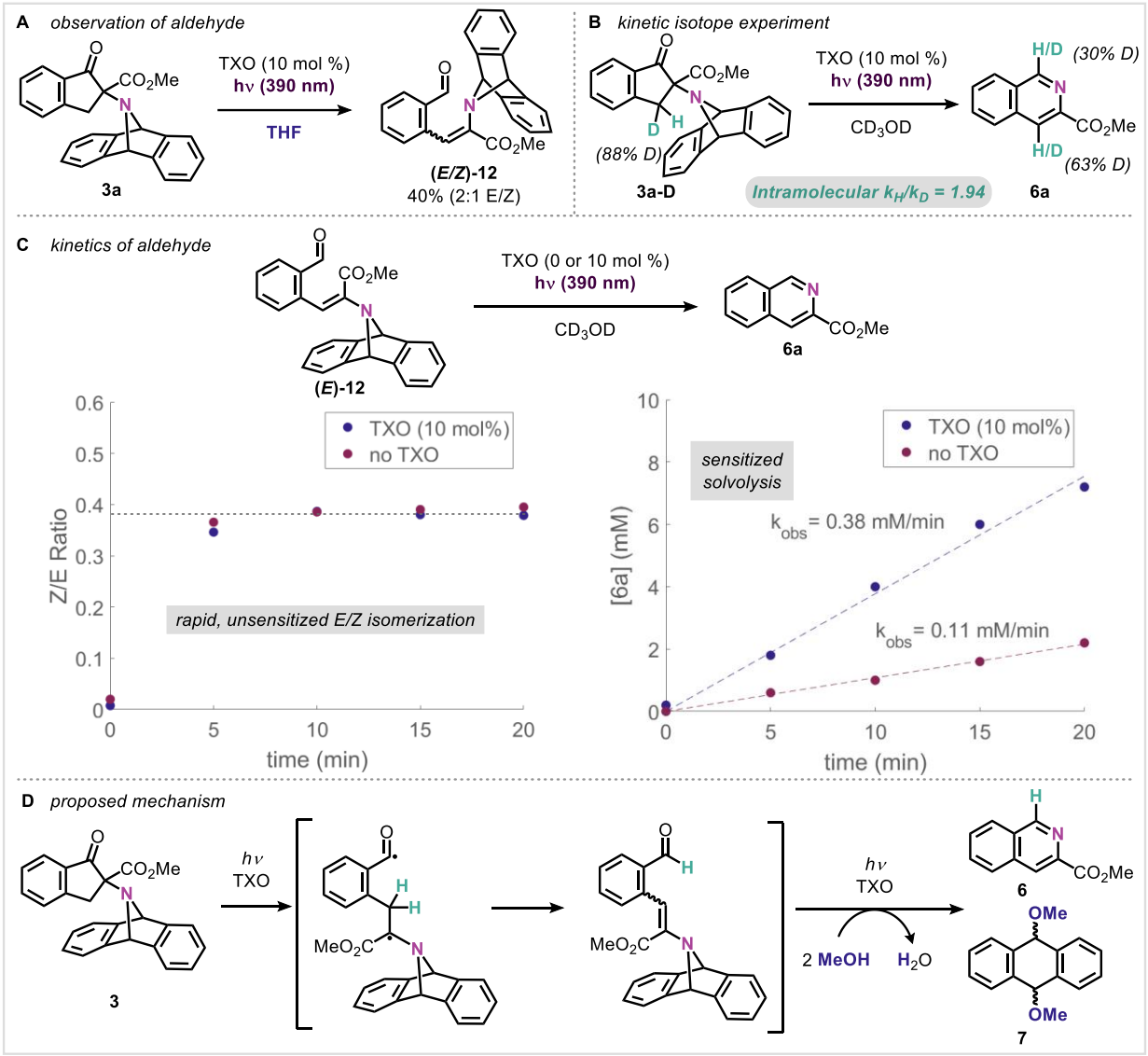

Figure 5. A) Isolation of aldehyde intermediate in aprotic solvent. B) Intramolecular KIE study. C) Aldehyde E/Z ratio and product formation kinetics under sensitized and unsensitized conditions. D) Proposed mechanism for photochemical ring expansion.

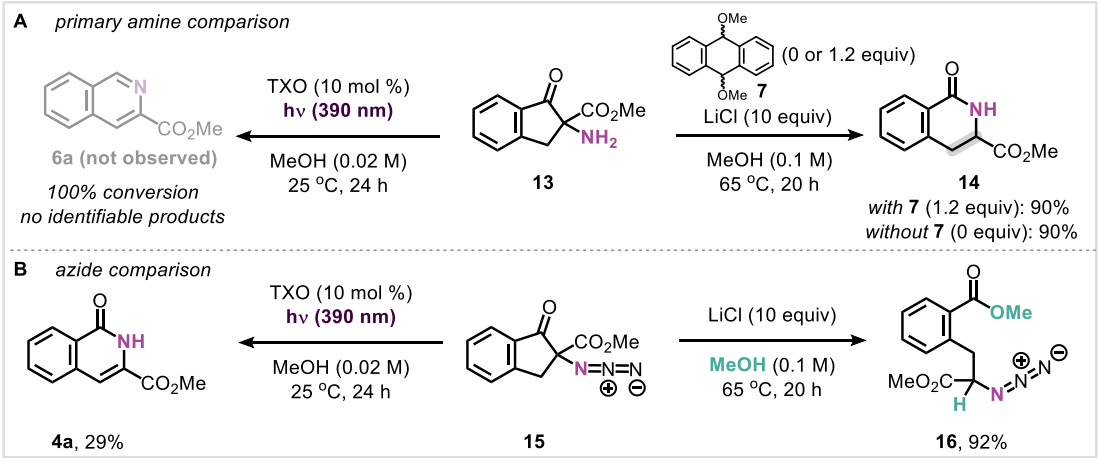

Figure 6. Comparison of primary amine and azide reactivity under thermal and photochemical reaction conditions.

by NMR in the presence and absence of TXO. In each case, the E olefin quickly isomerizes to a mixture of E and Z (~3:1). However, **6** is formed >3x faster in the presence of thioxanthone, indicating that C-N bond cleavage likely proceeds via the triplet excited state of **12** (Fig. 5C). While these studies cannot offer a definitive characterization of the photosolvolysis nor its relative timing with condensation, we suspect an S_N1-like process on the basis of the lack of stereospecificity in the formation of **7**(Fig. 5D).[62,63]

Finally, the reactivity of **3** was compared with other nitrogen atom sources (Fig. 6). Under thermal conditions, primary amine **13** reacts to give 3,4-dihydroisoquinolone **14**.[58] Notably, neither oxygen nor dimethoxydihydroanthrancene **7** were sufficient to oxidize **14**, discrediting a mechanism by which **3** is first solvolyzed to give **14** and is then re-oxidized to form **4**. Under photochemical conditions, **13** reacts to give an unidentified mixture of products, again discrediting its intermediacy in the photochemical ring expansion of **3**. Azide **15** reacts under photochemical conditions as expected to give the nitrenoid ring expansion product **4a**. Surprisingly, **15** underwent thermal retro-Dieckmann ring cleavage with maintenance of the azide to afford **16**. The divergent reactivity of **13** and **15** relative to **3** underscores the complementarity of DNIBX as a nitrogen atom synthon.

In conclusion, we have demonstrated the synthesis and application of DNIBX as a reagent for the preparation of valuable heterocycles under multiple reactivity regimes. In reactions with indanones, the transferred dbabh moiety serves as a unique nitrogen-atom surrogate, resulting in thermally induced ring expansion reactivity to give isoquinolones. Moreover, it allows photochemical ring expansion of indanones to give isoquinolines – reactivity that is only observed with dbabh-functionalized indanones. We anticipate that DNIBX's distinctive nitrogen-atom transfer properties will serve to enable a wide range of skeletal editing transformations.

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All authors have given approval to the final version of the manuscript.

Funding Sources

M.D.L. thanks National Institutes of Health (R35 GM142768) for research support. P.Q.K. thanks the Seymour Goodman fund for fellowship support. The University of Chicago Research Computing Center is thanked for computational resources.

ACKNOWLEDGMENT

Dr. Alexander Filatov and Sophie Whitmeyer are thanked for assistance with X-Ray crystallography. Alex Crolais is thanked for assistance with thermogravimetric analysis and differential scanning calorimetry. Dr. Mikus Purins is thanked for helpful discussions.

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