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ARTICLE

Formal nitrogen-to-carbon replacement in isoindolines to form indenes via N-alkyl tetrahydroisoquinolines

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Ryan T. Steele, Julius Domack and Richmond Sarpong*

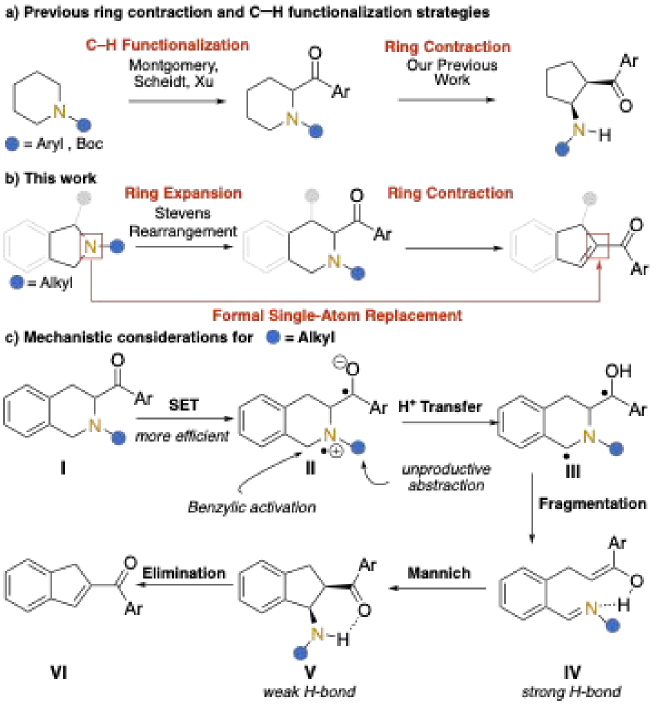
Herein, we report a Stevens rearrangement ring expansion of isoindolines to N-alkyl-2-aroyl-tetrahydroisoquinolines, followed by a photochemical nitrogen atom extruding ring contraction and elimination to give indene derivatives. By combining the ring expansion and ring contraction in a one-pot procedure, a net single-atom nitrogen-to-carbon replacement was realized. Factors that guide the stability of the immediate amino-indane products that are formed through photochemical ring contraction were studied. Reaction of the amino-indane intermediates with anhydrides yielded stable and isolable functionalized amino indane derivatives in some cases.

Introduction

Saturated nitrogen heterocycles are increasingly common motifs in natural products and FDA-approved pharmaceuticals.[1–4] Recently, there has been dedicated effort in the synthetic community to achieve single-atom “skeletal editing” of nitrogen-containing heterocycles to enable facile “scaffold hopping” in medicinal chemistry campaigns.[5–8] Skeletal editing methods that enable scaffold hopping may enable the exploration of novel chemical space and accelerate medicinal chemistry campaigns.[9] Thus, many novel synthetic strategies have been developed to interconvert closely related core structures through ring expansion [10–14] or contraction.[15–20] Specifically, there has been recent interest in single-atom replacement strategies in cyclic scaffolds (atom transmutations) given that such transformations could modify, for example, a hydrogen-bonding vector without changing ring size. This type of change could facilitate interrogations of ligand-receptor interactions.[6,21] However, the majority of reports for atom transmutation use aromatic heterocycles as substrates.[22–40] Fewer examples exist for single-atom transmutation in saturated (hetero)cycles.[41–45]

Recently, our laboratory reported a photochemical ring contraction of piperidines bearing an α-aryl ketone (aroyl group) to a corresponding amino-cyclopentane (Scheme 1a).[46–48] This reaction was previously explored with electron-withdrawing and aryl substituents on nitrogen. Our expansion of this photochemical ring contraction methodology to N-alkyl heterocycles has now set the stage of a formal N→C transmutation of isoindolines (Scheme 1b).

One challenge that has limited the applicability of the previously reported ring contraction chemistry is the direct installation of the requisite aryl ketone photochemical handle. While C–H functionalization strategies have been reported for the installation of α-aroyl groups for both N-Boc[49,50] and N-Aryl[51] piperidines (Scheme 1a), no reports exist for the corresponding *N-alkyl* heterocycles. We recognized that α-aroyl bearing N-alkyl piperidines (and related derivatives, e.g., tetrahydroisoquinolines) could be accessed through a skeletal transformation. By using a Stevens rearrangement, ring expansion of cyclic tertiary amines to install an α-aroyl group could be achieved.[52,53] In general, because the Stevens rearrangement requires a radical-stabilized benzylic position (i.e., an aryl substituent or ring fusion), we chose to focus our initial studies on α-aryl pyrrolidines and isoindolines. Overall, the two-step ring expansion/ring contraction strategy that we have now achieved allows for a formal single-atom nitrogen-to-carbon replacement in isoindolines.



Scheme 1 Photochemical ring contraction of six-membered nitrogen heterocycles and strategies for the installation of an aryl ketone.

Department of Chemistry, University of California, Berkeley, CA 94720, USA
**Corresponding author. Email: rsarpong@berkeley.edu*

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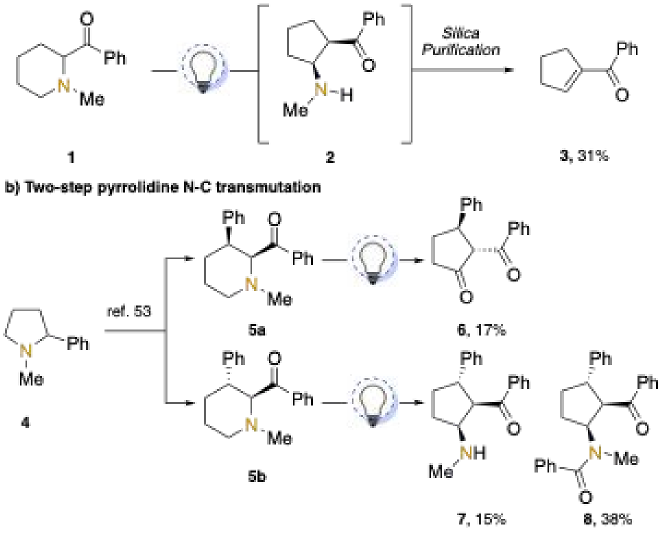
The photochemical ring contraction of N-alkyl heterocycles raises several mechanistic considerations (Scheme 1c).[47] First, the more electron-rich nitrogen atom in this case should enhance the efficiency of single-electron transfer (SET) from the tertiary amine to the excited state aryl ketone (see **I→II**). A potential issue is unproductive H-transfer from the exocyclic N-alkyl substituent (see **II**). This issue is partially circumvented with tetrahydroisoquinoline substrates, which feature increased reactivity at the desired benzylic methylene position (see **II**). Furthermore, we envisioned that the more electron-rich N-alkyl group would result in a stronger hydrogen bond in the imine intermediate (see **IV**) to facilitate the Mannich ring closure.

Finally, it was anticipated that the amino-indane ring contraction product would feature a weaker hydrogen bond, which could decrease product stability and promote an elimination of the amine to give an indene (see **V→VI**). Previously, Boswell *et al.* demonstrated that replacing an endocyclic nitrogen atom with a carbon atom bearing an exocyclic H-bonding carbonyl group can be used to extend hydrogen-bonding interactions.[54] Similarly, in this work, the introduction of an exocyclic carbonyl extends H-bonding interactions.

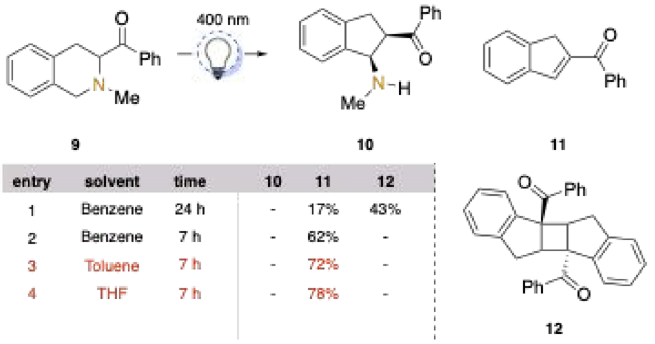
Results and Discussion

We began our studies by testing the viability of the photochemical ring contraction of N-methyl piperidine **1** (Scheme 2a). The ring contraction of **1** at 400 nm proved to be low-yielding. The immediate amino-cyclopentane ring contraction product (**2**) spontaneously converted to cyclopentene **3**, which was obtained in 17% yield upon purification on silica gel.

Our proposed ring expansion/ring contraction strategy was then tested with N-methyl pyrrolidine **4** (Scheme 2b). The known ring expansion of **4** to a mixture of separable diastereomers of N-methyl piperidine (**5a,b**) set the stage for the nitrogen extrusion reaction.[53] The ring contraction of *cis* diastereomer **5a** proceeded successfully to give cyclopentanone **6** in low yield. The ring contraction of *trans* diastereomer **5b** proceeded sucessfully to give amino cyclopentane **7** as a single diastereomer, albeit in low yield, and benzoyl amide **8**. We posit that **6** and **8** result from irradiation and photo-fragmentation of ring contraction product **7**, and that the differing reactivity between diastereomers **5a,b** arises from differences in the relative rates of the ring contraction arising from conformational differences in the starting materials (see the Supplementary Information, Section 10, for a proposed mechanism and further discussion). Unlike amino cyclopentane **2**, ring contraction product **7** was stable to purification on silica gel. The low yield of the products resulting from ring contraction of **5a** and **5b**, as well as photo-fragmentation leading to **6** and **8** suggests that ring contraction product **7** does not persist upon continued irradiation.



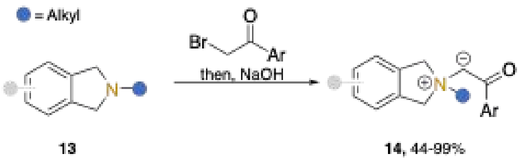
Scheme 2. Photochemical ring contraction of six-membered nitrogen heterocycles and strategies for the installation of an aryl ketone. Ring contraction conditions: 0.10 mmol starting material, 0.05M toluene, 400 nm, 24 h.



entry	solvent	time	10	11	12
1	Benzene	24 h	-	17%	43%
2	Benzene	7 h	-	62%	-
3	Toluene	7 h	-	72%	-
4	THF	7 h	-	78%	-

Table 1. Optimization of photochemical ring contraction of N-methyl tetrahydroisoquinoline.

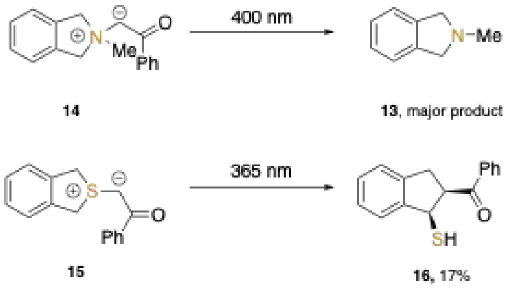
Given the low yields and challenges associated with **1** and **5a/b** as substrates, N-methyl tetrahydroisoquinoline (**9**) was selected for further exploration (Table 1). Initial studies with this substrate proved more promising (entry 1). While the expected amino-indane product (**10**) was not observed in the crude reaction mixture or following purification, indene **11** and dimer **12** were observed in high combined yield. The presence of these products indicated that the photochemical ring contraction had occurred as expected and a subsequent elimination of the extruded nitrogen group led to indene **11**. Dimer **12** presumably forms from continued irradiation of the indene, which forms spontaneously during the reaction rather than upon workup or purification. Further irradiation of a dilute solution of dimer **12** did not lead to reversion to the monomer, indicating that the photochemical dimerization is irreversible under the reaction conditions. The spontaneous elimination of the extruded nitrogen group appears to be unique to N-alkyl tetrahydroisoquinoline substrates on the basis of our studies.



Scheme 3. General method for the preparation of isoindoline ylides.

Decreasing the irradiation time to 7 h primarily gave the ring contracted monomer (i.e., indene **11**) with full consumption of the starting material (entry 2). Additional screening of solvents identified THF and toluene as optimal, leading to the highest yields (entries 3,4).

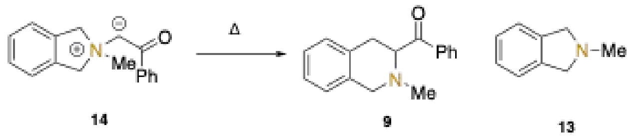
With conditions that lead to good yields of the ring contraction product identified, we focused on accomplishing a one-pot, sequential, Stevens rearrangement ring expansion/photochemical ring contraction to effect the envisioned single-pot formal N→C replacement in isoindolines. Isoindoline ylides (see **14**, Scheme 3) can be prepared directly from the parent isoindoline (see **13**) in good yields by adding α-bromo acetophenones, followed by the addition of base. Purification of the resulting ylides, which are generally stable at ambient temperatures,[52] is not required.



Scheme 4. Ylide irradiation studies. 0.10 mmol scale, 0.2M Toluene, 7 h.

We also investigated potential photochemical Stevens rearrangements of the ylides that would have enabled a single-step ring expansion/ring contraction cascade (Scheme 4). However, all attempts to effect a photochemical Stevens rearrangement of ylide **14** yielded only isoindoline **13** as the major product through a net heterolytic photochemical cleavage of the C–N bond.[55,56] While ammonium ylides did not undergo successful photochemical Stevens rearrangements, the analogous rearrangement of sulfonium ylide **15** is precedented.[57] Thus, we were able to accomplish a single-pot atom exchange of 1,3-dihydrobenzo[c]thiophene via photochemical Stevens rearrangement of the corresponding ylide (**15**)**,** followed by ring contraction to thiol **16**, using 365 nm light for both photochemical processes. However, the overall cascade in this case is low yielding. Unlike amino-indane **10**, thiol **16** was stable to purification on silica.

Given the limitation of a single-step photochemical cascade to sulfur-based substrates, we focused on optimizing the thermal Stevens rearrangement followed by photochemical ring contraction to accomplish a two-step, single-pot, protocol for isoindolines (Table 2). The Stevens rearrangement proceeds in quantitative yields in toluene at 90 °C — a higher yield and a significantly lower temperature than has been reported for the solid phase rearrangement, which occurs at 155 °C (entries 1,2).[52] Interestingly, in THF, significant amounts of the parent isoindoline (**13**) were recovered upon heating ylide **14** (entry 3). Thus, the Stevens rearrangement was performed thermally at 90 °C in toluene, followed by irradiation at room temperature to effect the ring contraction without a need to change solvent.



entry	solvent	temperature	time	9	13
1	Neat	155 °C	5 min	72%	-
2	Toluene	90 °C	30 min	quant.	-
3	THF	reflux	2 h	34%	63%

Table 2. Optimization of Stevens rearrangement. 0.05 mmol scale.

The scope for the two-step, one-pot, transformation is illustrated in Scheme 5. Multiple isoindoline ylides with varying N-alkyl substituents (**14a–c**) underwent the two-step protocol to yield indene **11a**. The two-step process is tolerant of electronically diverse aryl ketones (**11d–g**), heteroaryl ketones (**11h,i**), as well as various substituents on the arene portion (**11j–l**).

Non-symmetric isoindoline ylides lead to two constitutional isomers of the indene product that differ with respect to the position of the double bond (**11m–r**). Poor position selectivity was observed for the alkene group in all cases except for **11m**. Double-bond isomerization of indenes through sequential 1,5-hydrogen atom shifts is well precedented.[58] Therefore, the possibility that the observed product ratio reflects indene isomerization to a thermodynamic equilibrium (Table 3) was investigated. The ratios of two possible tetrahydroisoquinoline intermediates following Stevens rearrangement (**9 I:9 II**; Table 3) should reflect the ratio of indene products (i.e., **11 I:11 II**) if double bond isomerization does not occur. For the case of methoxy substituted ylide **14m**, a 50:50 ratio of tetrahydroisoquinoline isomers **9m I** and **9m II** was observed, which did not match the 70:30 mixture of indene isomers (i.e., **11m I :11m II**) in the crude reaction mixture. This observation is consistent with indenes **11m I** and **11m II** interconverting under the reaction conditions. In all other cases, the ratio of tetrahydroisoquinolines (determined by ^{1}H NMR) matched the ratio of indenes in the crude reaction mixture. This result indicates that the indene isomers do not interconvert under the reaction conditions, and that the Stevens rearrangement is the selectivity-determining step in these cases.

Some indenes were observed to isomerize upon purification on silica, so this possibility was also investigated.[59] Upon purification, the ratio remained the same in all cases, providing no evidence that isomerization of the indene double bond occurs on silica.

A formal nitrogen-to-carbon exchange of C_1-substituted isoindolines was also explored (Scheme 5e). For this purpose, C_1 phenyl-substituted isoindoline **13s** was used. Attempted formation of the corresponding isoindoline ylide led directly to the Stevens rearrangement product (tetrahydroisoquinoline **9s**) at room temperature. The mixture of diastereomers of **9s** was subjected to irradiation, which resulted in a crude mixture of diastereomers of

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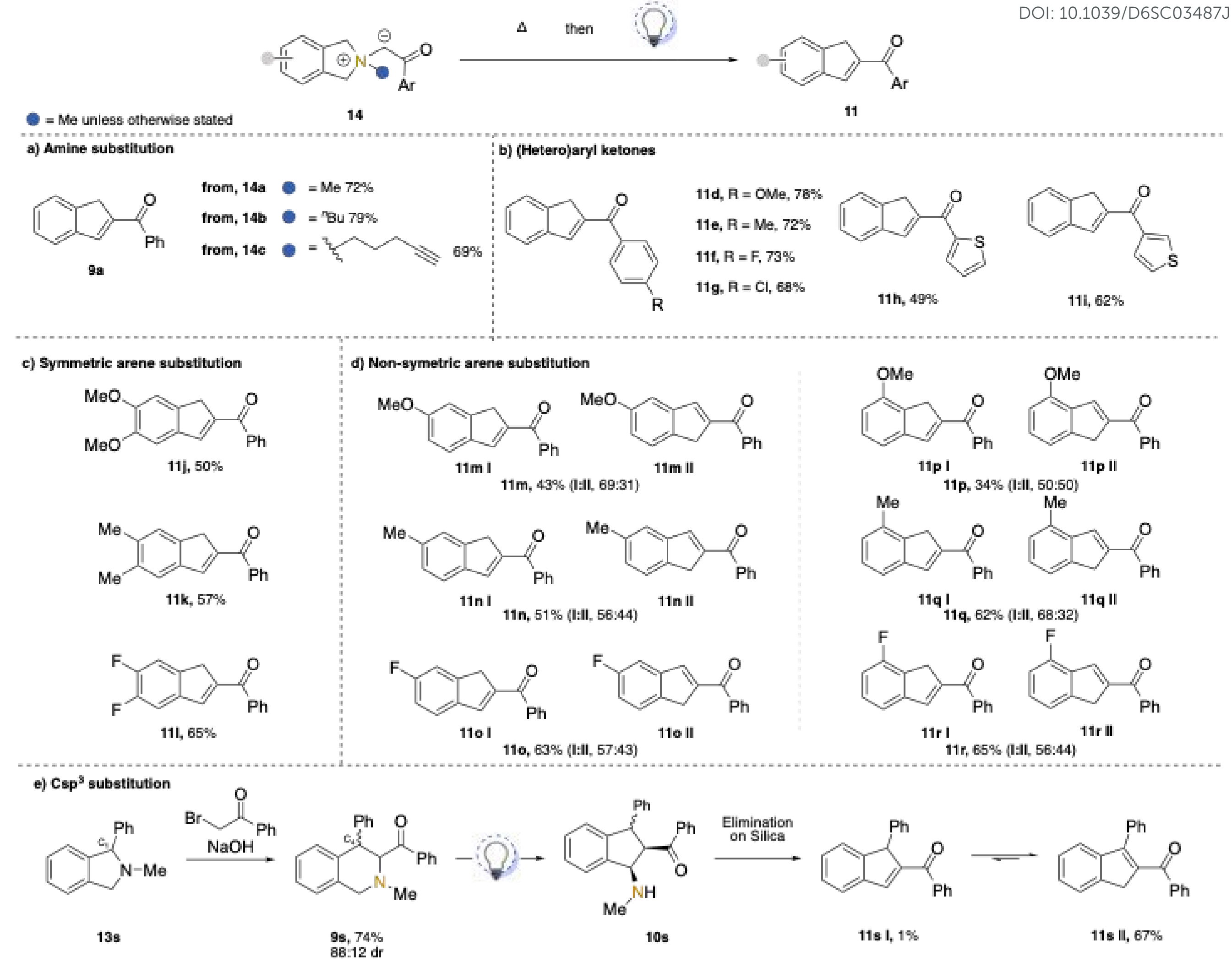

Scheme 5. Scope for single-pot isoindoline to indene conversion. Reaction conditions: 0.10 mmol starting material, 0.05M toluene, 90 °C, 30 min, then 400 nm, 24 h.

the amino indanes (see **10s**), which cleanly converged to indene **11s II** upon purification on silica with only trace amounts of isomer **11s I** observed.

In some other cases, we observed that the amino-indane product (**10**) was stable under the reaction conditions and only underwent elimination to **11** in the presence of silica gel (Table 4). In general, this was true for tetrahydroisoquinolines bearing strained rings or electron-withdrawing groups on nitrogen. As the ring strain of the cycloalkane increases (see **14v** relative to **14t,u**), more of amino-indane **10** relative to indene **11** is observed in the crude reaction mixture. This trend likely reflects the increasing electron-withdrawing nature of the attached carbon of the cyclopropane (i.e., greater s-character).

To further investigate this observed trend, an array of N-ethyl substrates was prepared with increasing fluorine substitution (see **14w→14x→14y**). From these substrates, we again observed that as the electron-withdrawing nature of the substituent increases, more of amino indane **10** can be observed in the crude reaction mixture.

The trends in elimination of the strained ring and fluorinated substituents are contrary to typical trends in elimination as one would expect an electron-withdrawing group to enhance the ability of the amine to act as a leaving group and more easily facilitate elimination. Instead, we observe that as the electron-withdrawing nature of the N-substituent is increased, the amino indane (**10**) becomes more persistent.

On the basis of this observation, we hypothesized that by trapping the immediate amino indane products with electrophilic reagents, stability could be achieved for a range of N-alkyl amino indanes that would otherwise spontaneously eliminate to afford the corresponding indene (Scheme 6a). This strategy was effective using acetic anhydride to form N-acetyl indane **17** and Boc amino indane **18**. We were unable to further stabilize less nucleophilic amino-indanes (e.g., **10v**, Table 4 entry 3**)** using this strategy.

The persistence of **10v,x,y** under continued irradiation could arise from the relatively strong intramolecular hydrogen bond in these cases due to the electron-withdrawing N-substituent, increasing the barrier to elimination. However, the persistence of compounds **17** and **18** cannot be rationalized by hydrogen-bonding interactions, suggesting the existence of another more significant stabilizing interaction.

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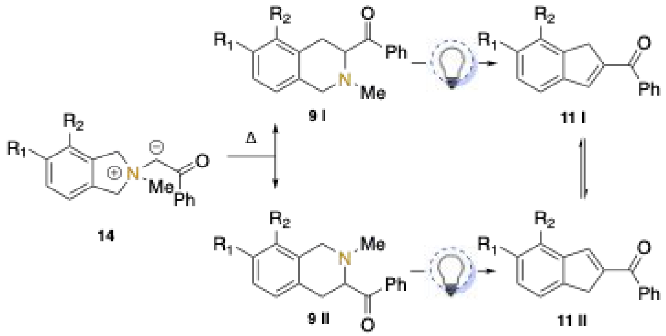


entry	14	R_1	R_2	9 I:II	11 I:II (Crude)	11 I:II (Purified)
1	**14m**	OMe	H	50:50	71:29	69:31*
2	**14n**	Me	H	56:44	56:44	56:44
3	**14o**	F	H	57:43	59:41	57:43
4	**14p**	H	OMe	56:43	50:50	50:50
5	**14q**	H	Me	65:35	66:34	68:32
6	**14r**	H	F	53:47	Not Determined	56:44

Table 3. Ratios of constitutional isomers of tetrahydroisoquinolines and indenes following Stevens rearrangement and ring contraction. Isomers were not assigned unambiguously unless otherwise stated. Crude ratio of **11r** isomers could not be determined due to overlapping signals. *Isomers of **11m I:II** were separated and assigned unambiguously.

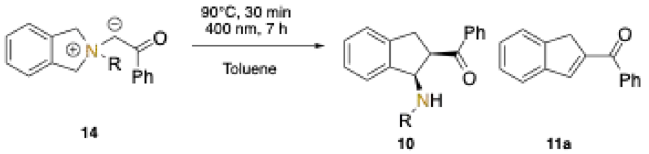
The isolation of **17** and **18** from **9a** supports high-selectivity for the *cis* diastereomer, consistent with our previous observations with N-phenyl and N-sulfonyl tetrahydroisoquinoline ring contractions.[46,47] N-Boc **18** is formed and isolated as a single diastereomer. However, we noted that over time and without additional irradiation, *cis*-configured **17** converts to the *trans* diastereomer (see Section 13.4 of the Supplementary Information). Therefore, the exact diastereomeric ratio for the ring contraction of **9a** to **17** cannot be unambiguously determined.

Similarly, N-acetyl cyclopentane **19** was isolated in good yield from piperidine **1** following addition of acetic anhydride to the reaction mixture (Scheme 6b). In this case as well, the *cis* diastereomer of **19** converts to the *trans* isomer over time, and upon purification. Nonetheless, the *cis* diastereomer was isolated as the major isomer.

In the absence of acetic anhydride, only low yields of cyclopentene **3** were obtained from **1** (Scheme 6b). The significantly higher yield of **19** relative to **3** suggests that the acetic anhydride additive leads to an increase in the yield of the ring contraction. Likely, N-acetyl **19** is more stable under the irradiation conditions than the corresponding secondary amine (i.e., **2**). We had initially hypothesized that the low yield observed in the ring contraction of **1→3** could be due to unproductive reactivity of the exocyclic N-methyl group. However, the high-yield obtained for ring-contraction product **19** indicates that the exocyclic N-methyl substituent does not significantly compete as a H-atom source with the endocyclic methylene group that leads to productive reactivity (Scheme 1c). More likely is that ring contraction product **2** undergoes photo-fragmentation and decomposition under continued irradiation. In contrast, ring contraction of benzene-fused substrates (**9**) leads to indenes (**11**) that are presumably more persistent under continued irradiation, resulting in a significant increase in yield compared to the piperidine case (i.e., **1**) where elimination of the amine (**2→3**) only occurs upon purification.

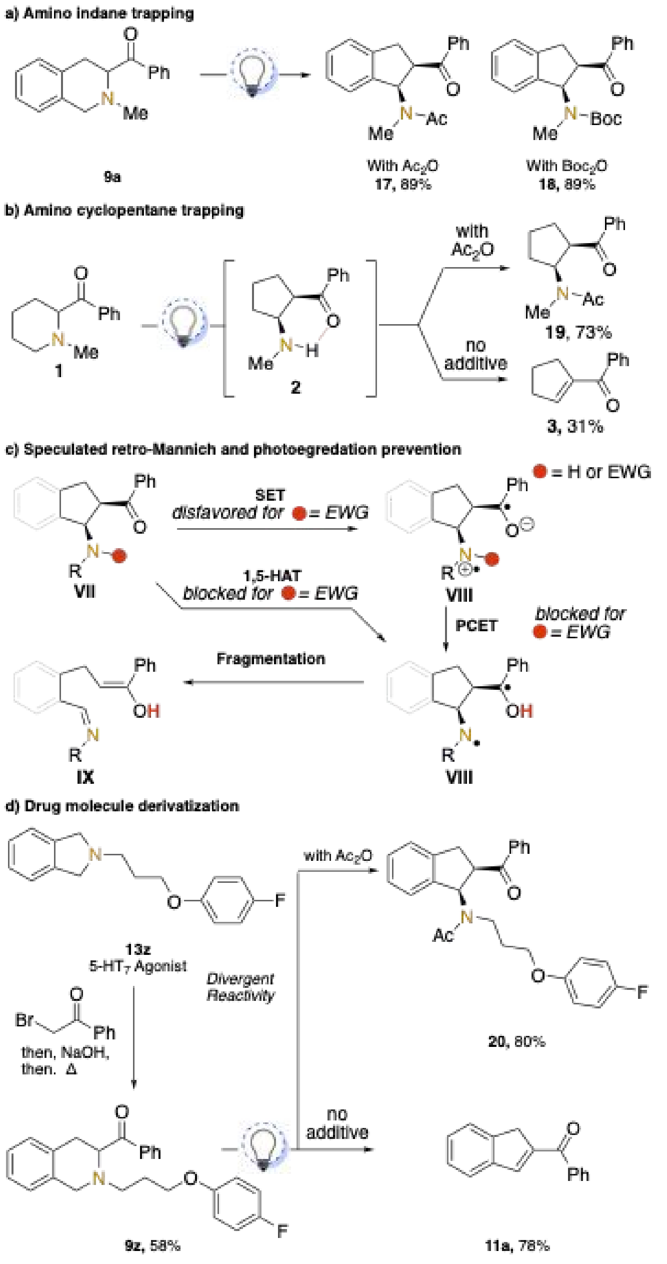
In Scheme 6c, we illustrate a proposal for the role of the acetyl group in preventing photodegradation. Previously, we reported that the ring-closing Mannich step is reversible for N-sulfonyl substrates under continued irradiation (see **VII→IX**).[48] This reversibility could arise through a SET and PCET pathway (see **VI→VII→VIII**) or 1,5-HAT pathway (**VI→VIII**) followed by fragmentation to the Mannich precursor. Any aspect of the retro-Mannich pathway could ultimately lead to decomposition of the N-alkyl ring contraction products upon continued irradiation. The introduction of an electron-withdrawing group on the nitrogen group could prevent the retro-Mannich by either disfavoring electron transfer or by blocking the HAT process — stabilizing. **17** and **18** to continued irradiation.

The anhydride additive protocol now enables access to products bearing functionalized N-alkyl fragments. For example, isoindoline **13z**, a pharmacologically active small molecule 5-HT_7 receptor antagonist, is converted to the corresponding N-acetyl indane derivative (**20**) in good yield (Scheme 6d)[59] via tetrahydroisoquinoline **9z**, which is related to other biologically active tetrahydroisoquinolines.[60] N-Acetyl indane **20** is obtained as the *cis* diastereomer, and does not appear to epimerize over time unlike **17**. Alternatively, irradiation of **9z** in the absence of acetic anhydride yields indene **11a**.



entry	14	R	10:11a	yield 11a (following purification)
1	**14t**	Cyclopentyl	0:100	77%
2	**14u**	Cyclobutyl	0:100	72%
3	**14v**	Cyclopropyl	92:8	73%
4	**14w**	CH_2CH_3	0:100	72%
5	**14x**	CH_2CH_2F	40:60	55%
6	**14y**	CH_2CHF_2	83:17	65%

Table 4. Ratios of amino-indane to indene of crude reaction mixtures. *Isolated yield following purification. Compound **9** converts to **10a** upon purification. 0.10 mmol, 0.05 M.



Scheme 6. Anhydride trapping strategy. Ring contraction conditions: 0.10 mmol starting material, 0.05M THF, 400 nm, 7 h. If listed, 1.5 equiv anhydride, 2.0 equiv triethylamine were used.

Conclusions

We have developed a photochemical ring contraction of N-alkyl tetrahydroisoquinolines, which expands the scope of this class of reactions. When combined with an initial thermal Stevens rearrangement ring expansion of isoindolines, a formal nitrogen-to-carbon replacement and scaffold hop to indenes from isoindolines proceeding through the intermediacy of isoindoline ylides is achieved.

Unique trends pertaining to the persistence of the immediate amino-indane products resulting from the ring contraction of N-alkyl tetrahydroisoquinolines were observed. From these trends, we concluded that increased electron-withdrawing character of the alkyl substituent on nitrogen increases the persistence of the amino indane products. For substrates where elimination of the amino indane nitrogen group occurs spontaneously, acylation with anhydrides stabilizes the molecule and reduces the propensity for elimination of the N-group.

Overall, this study highlights the power of combined ring-expansion and ring-contraction methodologies to convert between related core structures, providing a complementary approach to accessing novel chemical space that may facilitate interrogation of structure-activity relationships in medicinal chemistry campaigns.

Author contributions

R.T.S and R.S made the initial discovery and conceived the project. R.T.S optimized the reaction conditions. R.T.S. and J.D. performed the experiments. J.D. discovered the reaction of **15** to **16**. R.T.S. wrote the original manuscript, with input from R.S. and J.D. R.S. directed the research.

Conflicts of interest

There are no conflicts to declare.

Data availability

All the primary data for this article is included in the Supplementary Information. References 61-77 are cited in the Supplementary information (SI)

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Data availability

All the primary data for this article is included in the Supplementary Information. References 61-77 are cited in the Supplementary information (SI)