Base Promoted Tandem Synthesis of 2-Azaaryl Tetrahydroquinolines

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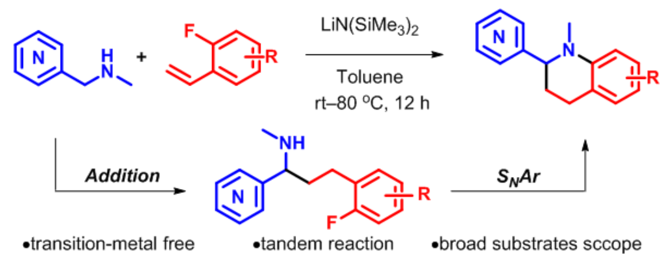
Supporting Information Placeholder



ABSTRACT: A novel method to synthesize 2-azaaryltetrahydroquinolines by tandem reaction of azaaryl methyl amines and styrene derivatives promoted by base is reported (over 30 examples, yields up to 95%). Mechanistic probe experiments demonstrate that deprotonation of the benzylic C–H and addition to the styrene vinyl group proceeds the S_NAr.

Tetrahydroquinolines are an important and common class of nitrogen containing heterocycles in the pharmaceutical and agrochemical industries.[1-3] Their diverse biological activity in natural products and therapeutic agents include antifungal agents,[4] Na^+ channel antagonists,[5] anticancer agents[6] and hormone receptor antagonists (Figure 1).[7,8] Among tetrahydroquinolines, 2-azaaryl tetrahydroquinolines have attracted significant attention. In general, approaches for the synthesis of 2-azaaryl tetrahydroquinolines can be divided into transition metal catalyzed hydrogenations (Scheme 1a),[9-16] Diels−Alder reactions of imines with alkenes in the presence of strong acids (Scheme 1b)[17,18] and rhodium-catalyzed tandem conjugate addition-Mannich cyclization reactions (Scheme 1c).[16] These methods, while quite useful, do have their drawbacks, including use of expensive catalysts or strong acids. Thus, new methods to prepare 2-azaaryl tetrahydroquinolines that circumvent these shortcomings would be welcome by medicinal chemists.

Our team has been interested in the deprotonation of weakly acidic benzylic C–H's and the use of the resulting carbanions to form C–C bonds. We recently developed a one-pot aminobenzylation of aldehydes to prepare functionalized amines from toluene derivatives (Scheme 2a).[19,20] We introduced a convergent one-pot synthesis of indoles from 2-fluorotoluenes and benzonitriles that proceeds via an S_NAr on an unactivated aryl fluoride (Scheme 2b).[21] The combination of benzylic carbanions with S_NAr reactions is a powerful method for building complexity from relatively simple and readily available precursors. Of note, S_NAr reactions are

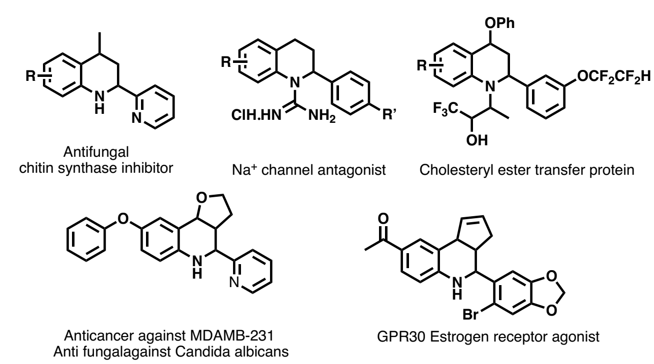
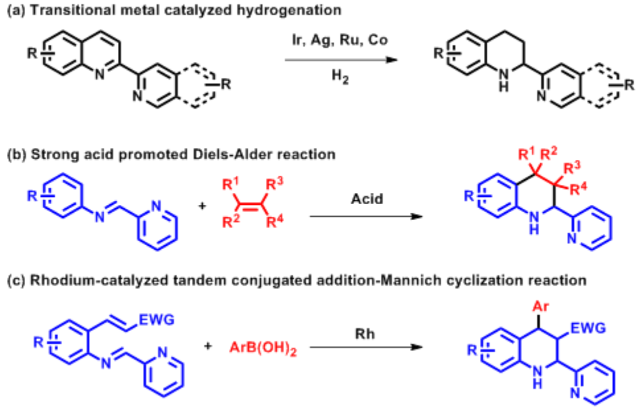


Figure 1. Selected examples of biologically relevant 2-substituted tetrahydroquinolines.

among the most commonly employed by medicinal chemists.[22]

With this in mind, we wondered if it would be possible to construct 2-azaaryl tetrahydroquinolines from azaaryl methylamines and 2-fluorostyrenes. To do so would require sequential deprotonation of both the benzylic C–H and the amino N–H of the substrate. Although the pK_a values of these positions have not been measured, we used the pK_a of 2-methyl pyridine (pK_a = 34 in THF) as a proxy for the benzylic methylene group of the azaaryl methylamines and LDA (pK_a = 36 in THF) as a stand-in for the NH of azaaryl methylamines.[23,24] Based on these pK_a values, we anticipated that deprotonation of the benzylic C–H's would be slightly more favorable than deprotonation of the N–H. We also realized that the addition of both benzylic carbanions and amides to styrene were both known,[25-30]

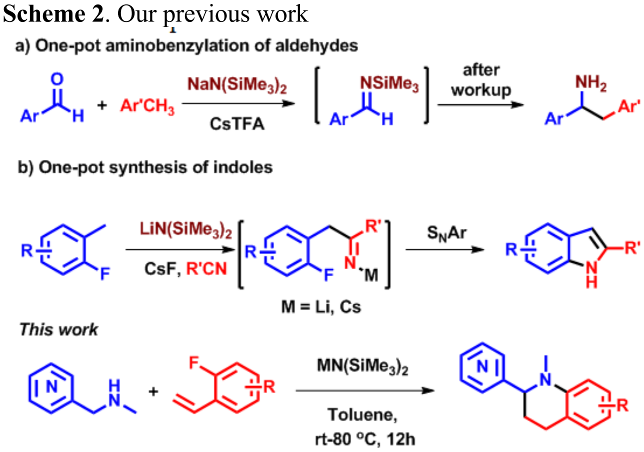
Scheme 1. Routes to 2-azaaryl tetrahydroquinolines



including beautiful work by Guan on additions of alkyl pyridines to styrenes[26,29] and Kobayashi's additions of toluene derivatives to styrene-based substrates.[30] Thus, selectivity in the addition to styrene could be problematic.

In our system, we envisioned that the more prevalent benzylic carbanion would add to styrene more rapidly to generate a new benzylic carbanion. Protonation at carbon followed by deprotonation of the amine would form an intermediate amide that was anticipated to cyclize on the aryl fluoride via S_NAr. Herein we report the realization of this strategy for the one-pot synthesis of 2-azaaryl tetrahydroquinolines from 2-fluorostyrenes and azaarylmethyl amines.[31]

Scheme 2. Our previous work

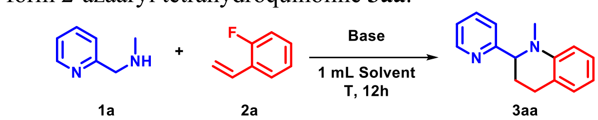


At the outset of our study, we were concerned about the selectivity, as discussed above. If C-selectivity could be obtained in the addition to styrene, the next hurtle would be the S_NAr. S_NAr reactions generally employ electron-deficient arenes.[32-34] In our case, we anticipated that the intramolecular cyclization to form a 6-membered ring would override the need for electron withdrawing substituents.

To initiate our studies we used 2-pyridylmethyl amine (**1a**) as pronucleophile to react with 2-fluoro styrene (**2a**) in the presence of various bases. Initially, the ratio of 2-pyridylmethyl amine : styrene : base was set at 1 : 1 : 1 with reactions conducted in THF at 80 °C. Examination of the reaction with various bases [*t*-BuOLi, *t*-BuONa, *t*-BuOK, $LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$ and $KN(SiMe_3)_2$] was performed (Table 1, entries 1–6). Alkoxide bases did not afford the desired products and starting materials remained. In contrast, we were encouraged to find that $MN(SiMe_3)_2$ bases (M = Li, Na, K) generated the target product **3aa** in 44–46% AY (entries 4–6, AY = assay yield, determined by ^{1}H NMR spectroscopy by integrating the crude reaction mixture against an internal standard).[23] Because lithium bases are generally milder than their Na and K counterparts, due to increased aggregation, we decided to focus on $LiN(SiMe_3)_2$. Several solvents were, therefore, screened with $LiN(SiMe_3)_2$. The reaction performed better in toluene (76% AY) than dioxane (60% AY) or CPME (cyclopentyl methyl ether, 60% AY) as shown in entries 7–9. Lowering the temperature (70 °C) led to decreased AY (56%, entry 10).

We next examined the ratio of pronucleophile : styrene : base. We rationalized that trace water, dioxygen, or other impurities in the reaction mixture might consume some of the base or nucleophile, diminishing the reaction yield. We, therefore, increased the base and pronucleophile to 1.2 equiv each, which resulted in little change (72% AY, entry 11). Further increasing the base to 1.4 and 1.5 equiv resulted in 92 and 78% AY (entries 12 and 13, respectively). The sensitivity of this reaction to the amount of base is revisited below. Based on the data in Table 1, the optimized conditions for this tandem reaction involve **1a** (1.2 equiv), **2a** (1 equiv), $LiN(SiMe_3)_2$ (1.4 equiv) in toluene.

Table 1. Optimization of the base promoted tandem reaction to form 2-azaaryl tetrahydroquinoline **3aa**.[a]



Entry	Base	**1a**:**2a**:Base	Solvent	T (°C)	AY[b] (%)
1	*t*-BuOLi	1 : 1 : 1	THF	80	-
2	*t*-BuONa	1 : 1 : 1	THF	80	-
3	*t*-BuOK	1 : 1 : 1	THF	80	-
4	$LiN(SiMe_3)_2$	1 : 1 : 1	THF	80	44%
5	$NaN(SiMe_3)_2$	1 : 1 : 1	THF	80	46%
6	$KN(SiMe_3)_2$	1 : 1 : 1	THF	80	44%
7	$LiN(SiMe_3)_2$	1 : 1 : 1	Dioxane	80	60%
8	$LiN(SiMe_3)_2$	1 : 1 : 1	CPME	80	60%
9	$LiN(SiMe_3)_2$	1 : 1 : 1	Toluene	80	76%
10	$LiN(SiMe_3)_2$	1 : 1 : 1	Toluene	70	56%
11	$LiN(SiMe_3)_2$	1.2 : 1 : 1.2	Toluene	80	72%
12	$LiN(SiMe_3)_2$	1.2 : 1 : 1.4	Toluene	80	92%
13	$LiN(SiMe_3)_2$	1.2 : 1 : 1.5	Toluene	80	78%

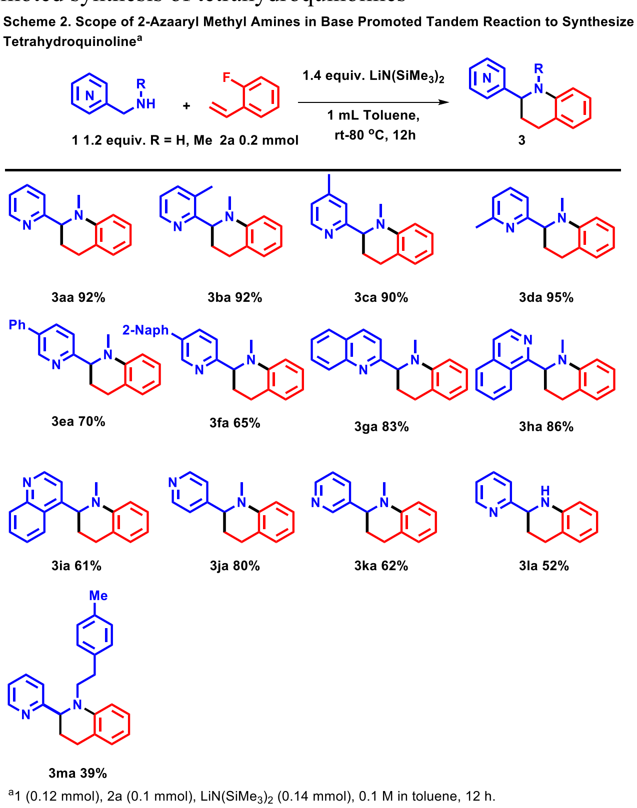
[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), base (0.1 mmol), 0.1 M, 12 h. [b] AY = Assay yield, determined by ^{1}H NMR integration with CH_2Br_2 as internal standard. THF = tetrahydrofuran, CPME = cyclopentyl methyl ether.

With the optimized conditions in hand, we set out to define the scope of azaaryl pronucleophiles (Scheme 3). In general, the reaction was tolerant of azaarylmethylamine pronucleophiles. The more sterically hindered 2-pyridylmethyl amine derivative bearing a 3-methyl group on the pyridyl ring (**1b**) was a suitable nucleophile and resulted in the target product **3ba** in 92% yield. The 4-methyl (**1c**) and 6-methyl (**1d**) derivatives were also compatible with the process, providing **3ca** and **3da** with 90% and 95% yields, respectively. Nucleophiles incorporating phenyl and 2-naphthyl groups in the 5-position of the pyridine ring **1e** and **1f** afforded the corresponding tetrahydroquinolines **3ea** and **3fa** with 70% and 65% yield, respectively. Switching to quinoline (**1g**), product **3ga** was generated in 83% yield. An isoquinoline derivative also proved to be a competent nucleophile, resulting in **3ha** with 86% yield. These pronucleophiles all contain 2-azaaryl groups that can potentially coordinate to the Li^{+} of the $LiN(SiMe_3)_2$ and facilitate deprotonation. We next investigated derivatives that did not possess groups capable of such chelation.

We first examined the 4-quinoline and 4-pyridyl derivatives, because these are known to be more acidic than the 2-pyridyl derivatives.[23,24] We were please to find that both these substrates were viable, affording the quinoline- and 4-pyridine-substituted tetrahydroquinolines in 61% (**3ia**) and 80% (**3ja**) yields, respectively. The 3-pyridylmethylamine, which has the highest pK_a of the pyridylmethylamines examined, also reacted under our standard conditions, providing the corresponding tetrahydroquinoline in 62% yield (**3ka**).

The pyridylmethyl amines examined contained an *N*-methyl group. We were curious if pyridyl methyl amines lacking the *N*-methyl would take part in the tandem reaction. We, therefore, examined the parent 2-pyridylmethylamine, which provided the secondary amine product **3la** in 52% yield. Secondary amine **1m** also afforded the cyclic product **3ma** with 39% yield. Finally, substituten of 2-chlorostyrene for the fluorine analogue **2a** gave only 11% yield of the cyclized product **3aa**. This result is consistent with the greater utility of fluoride in most S_NAr reactions.

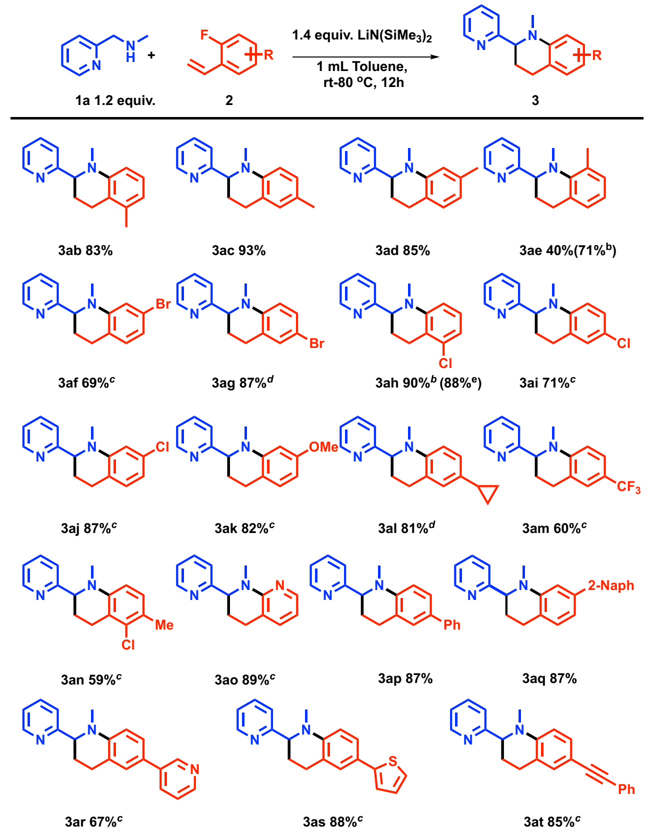
Scheme 3. Scope of azaaryl methyl amines in the base promoted synthesis of tetrahydroquinolines[a]



[a]**1** (0.12 mmol), **2a** (0.1 mmol), $LiN(SiMe_3)_2$ (0.14 mmol), 0.1 M in toluene, 12 h.

We next focused our investigations on styrene electrophiles (Scheme 4). Fluoro styrenes with methyl groups at the 3, 4 or 5 positions (**2b**, **2c** and **2d**) readily participated in the tandem reaction, supplying the target products **3ab**, **3ac** and **3ad** in 83%, 93% and 85% yield, respectively. The sterically hindered 6-methyl derivative **2e** furnished the corresponding tetrahydroquinoline **3ae** in 40% yield at 80 °C and 71% yield at 90 °C. Tetrahydroisoquinolines bearing halides are attractive targets, because they can be readily elaborated using standard cross-coupling methods. Thus, 2-fluoro styrenes bearing bromo and chloro substituents (**2f–2j**) were investigated. The tandem reaction was successful with halides at the 5, 6, and 7 positions, affording **3af**–**3aj** in 69–90% yields. A one gram scale reaction to generate **3ah** provided product in 88% yield. We were curious if an electron donating methoxy group would impact either the addition to the styrene or the S_NAr. Thus, **2k** with a methoxy group located para to the styrene vinyl was examined. In the event, **2k** underwent smooth conversion to the desired product **3ak** in 82% yield. Cyclopropyl substrate **2l** was next examined under the standard conditions, leading to **3al** in 87% yield. A substrate bearing a trifluoromethyl group (**2m**) underwent the reaction to provide the product **3am** with 60% yield. The 5,6 – disubstituted tetrahydroqunoline **3an** was also obtained with 59% yield. A substrate containing a vinyl pyridine (**2o**) underwent the tandem reaction to give product **3ao** with multiple heterocycles in 89% yield. Next, aryl rings such as phenyl (**2p**), 2-naphthyl (**2q**), 3-pyridyl (**2r**) and 2-thienyl (**2s**) were introduced, affording the corresponding tetrahydroquinolines **3ap**, **3aq**, **3ar** and **3rs** in 67 – 88% yields. Alkynyl substrate **2t** was also suitable under the standard conditions and supplied the target product **3rt** in 85% yield.

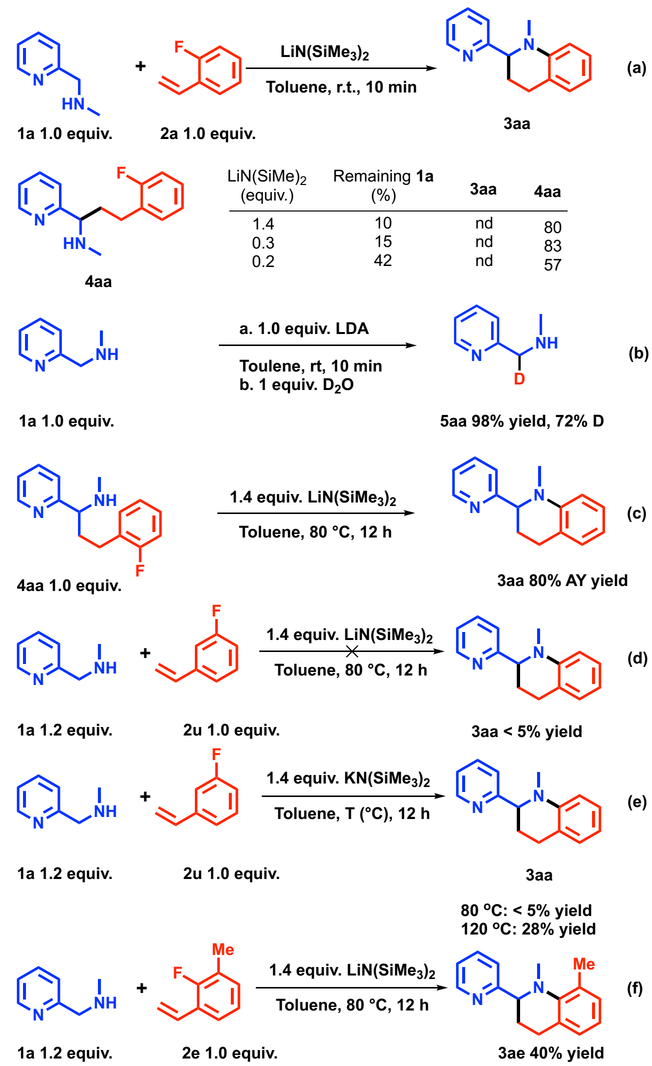
Scheme 4. Scope of 2-Fluoro Styrenes in Base Promoted Tandem Reactions for the Synthesis of Tetrahydroquinolines[a]



[a]**1a** (0.12 mmol), **2** (0.1 mmol), $LiN(SiMe_3)_2$ (0.14 mmol), 0.1 M in toluene, 12 h. [b]90 °c [c]THF instead of toluene as solvent. [d]A solution of $LiN(SiMe_3)_2$ in THF was slowly added and the reaction with stirred at 50 °C in THF for 12 h. [e]1.0 gram scale reaction

In order to gain insight into the mechanism of this tandem reaction, several experiments were performed. Pyridyl methyl amine **1a** was employed with 2-fluorostyrene **2a** and 1.4 equiv. $LiN(SiMe_3)_2$ at room temperature (Scheme 5a). The reaction was quenched with water after 10 min in the hopes of observing reaction intermediates. Under these conditions, we detected the uncyclized intermediate **4aa**, which was isolated in 80% yield (Scheme 5a). When the amount of base was reduced to 30 and 20 mol%, intermediate **4aa** was isolated in 83% and 57% yields, respectively. Using 1 equiv of the stronger base LDA to deprotonate the amine **1a** at room temperature followed by quenching with ~ 1 equiv. D_2O after 10 min, we recovered near quantitative **5aa** with 72% D in the benzylic position (Scheme 5b). Upon heating **4aa** with 1.4 equiv. $LiN(SiMe_3)_2$ at 80 ºC, **3aa** was obtained in 80% AY (Scheme 5c, as determined by ^{1}H NMR integration against CH_2Br_2 internal standard). These results are consistent with the benzylic deprotonation and addition of the α carbanion to styrene proceeding the S_NAr of the *N*-centered anion.

Although we favor an S_NAr pathway for cyclization/formation of the C–N bond, another feasible pathway involves a benzyne intermediate. To address the benzyne pathway, *meta*-fluoro styrene **2u** was employed with **1a** under otherwise standard conditions (Scheme 5d). In the event, only trace product was observed. Using $KN(SiMe_3)_2$ in place of $LiN(SiMe_3)_2$ at 80 ºC also afforded trace product. When the temperature was raised to 120 ºC, the target product was generated in 28% yield (Scheme 5e). The low yield may result from poor regioselectivity in formation of the benzyne intermediate. Further evidence against the intermediacy of the benzyne is gained from use of 2-fluoro-1-methyl-3-vinylbenzene (**2e**), which is not able to form a benzyne intermediate, but did undergo the tandem reaction to provide **3ae** in 40% yield (Scheme 5f). These reactions demonstrate that the major pathway for ring closure is S_NAr.



Scheme 5. Mechanistic probes.

In conclusion, we have developed a novel tandem reaction promoted by $LiN(SiMe_3)_2$ without transition metals. Experiments to probe the mechanism are consistent with a pathway that is initiated by deprotonation of the azaaryl methyl amine at the benzylic C–H. The resulting carbanion adds to the terminal position of styrene to form a new C–C bond and a benzylic carbanion. Net proton transfer between the carbanion and amine generated the amide, which cyclizes via S_NAr to afford the corresponding tetrahydroquinoline. This method provides a straightforward strategy for the synthesis of 2-azaaryl tetrahydroquinolines. We anticipate that it will be easily adopted by medicinal chemists to prepare these valuable heterocycles.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: .

Experimental procedures, characterization data, and NMR spectra (PDF)

FAIR Data is available as Supporting Information for Publication and includes the primary NMR FID files for compounds: **1b-1i**, **2b-2e**, **2f-H**, **2g**, **2h-H**, **2i-2q**, **2q-Pre**, **2r**, **2r-Pre**, **2s**, **2t**, **2t-Pre**, **3aa-3at**, **3ba-3la**, **4aa**, **4au**

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Notes
The authors declare no competing financial interest.

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