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The development of carbon–carbon bond forming reactions of aminal radicals

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ABSTRACT

Aminal radicals were generated and used in synthetic reactions for the first time. Aminal radicals are formed from aminals by radical translocation using AIBN and a stoichiometric hydrogen atom donor, or by SmI_2 reduction of *N*-acyl amidines or amidinium ions in the presence of a proton source. Aminal radicals were found to participate in inter- and intramolecular C–C bond forming reactions with electron deficient alkenes. Chemical yields were as high as 99%.

1. Introduction

Many biologically active molecules, including pharmaceuticals, contain one or more nitrogen atoms. As a result, nitrogen-rich compounds, such as alkaloids and pharmaceuticals, make compelling synthetic targets.[1] However, the complex reactivity of nitrogen can be problematic in synthesis. The ability to quaternize, the Lewis basic lone pair, and the weakly acidic N–H protons found in nitrogen-containing molecules often give rise to undesired reactivity.

In order to mask the complex Lewis acid–base reactivity of nitrogen, synthetic chemists often resort to the use of protective groups.[2] Other strategies, which have proven successful for the synthesis of nitrogen-containing structures include opting to install nitrogen late in the synthesis[3] or in the form of a less reactive functional group (e.g., as a nitro[4] or nitrile[5] group). An alternative means to circumvent the pitfalls of alkaloid synthesis is the use of single electron reactivity (i.e., free radical reactions). Free radicals are known to tolerate heteroatom lone pairs, and N–H bonds are resistive to homolytic cleavage.[6] As a result, free radical reactions have been used successfully for key C–C bond forming reactions in the synthesis of complex alkaloids (e.g., Scheme 1, Eq. 1).[7]

The addition of carbon-centered radicals bearing heteroatoms to C–C multiple bonds has been known for over 50 years.[8] α-Aminoalkyl radicals, such as **1** (Scheme 1), gain stability from the electron lone pair on the adjacent nitrogen atom and react with alkenes to give products of C–C bond formation.[9] This reactivity has proven useful for the synthesis of heterocycles as well as in the total synthesis of alkaloids.[10] Carbon-centered radicals bearing two adjacent heteroatoms, such as acetal radical **2**, are also known to undergo C–C bond forming reactions with alkenes (Scheme 1, Eq. 2). Additionally, *N*,*S*- and *N*,*O*-acetal radicals (**3**) have been presumed as intermediates in C–C bond forming reactions (Scheme 1, Eq. 3).[11]

Carbon-centered radicals bearing two adjacent nitrogen atoms (i.e., aminal radicals) have been implicated as intermediates in the free radical and radiative damage of DNA nucleotide bases,[12] they have been experimentally generated and studied spectroscopically,[13] and long-lived aminal radicals have been isolated.[14] Applications of aminal radicals include their use as photochromic dyes[15] and as tools for mechanistic investigations.[16] Although there are reports of fragmentation,[17] protonation,[18] and dimerization reactions of aminal radicals, there had been no reports of their synthetic utility prior to recent work from our laboratory.[19]

Having considered the known reactivity of acetal and α-aminoalkyl radicals, the creation of a new reaction was envisioned wherein an aminal radical would undergo addition to an alkene to give the product of C–C bond formation. Computational studies indicated that aminal radicals are 1–2 kcal/mol more stable than analogous α-aminoalkyl radicals.[20] This suggested that it would be possible to selectively generate aminal radicals in the presence of carbon atoms bearing a single nitrogen atom. Based on these considerations, we postulated that aminal radical intermediates would be well suited for the construction of the carbon framework in

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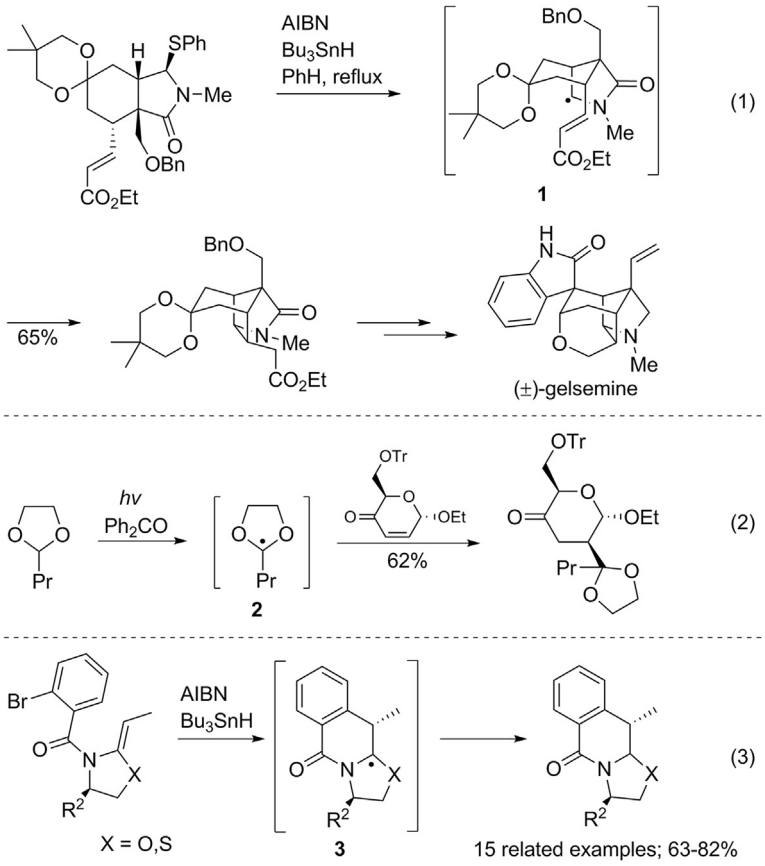
0040-4020/



Scheme 1. Selected transformations involving radical intermediates bearing α-heteroatoms.

nitrogen-rich molecules. For example, Fig. 1 shows a selection of biologically active aminal containing natural products, which have attracted the interest of many synthetic chemists.[21] Furthermore, commercial pharmaceuticals quinethazone and metolazone also possess the aminal functional group.

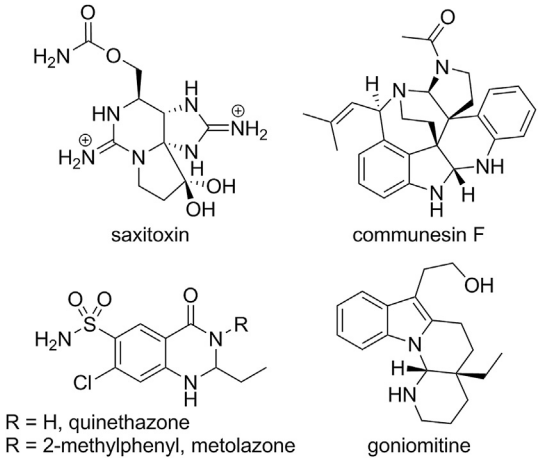


Fig. 1. Selected aminal containing alkaloids and pharmaceuticals.

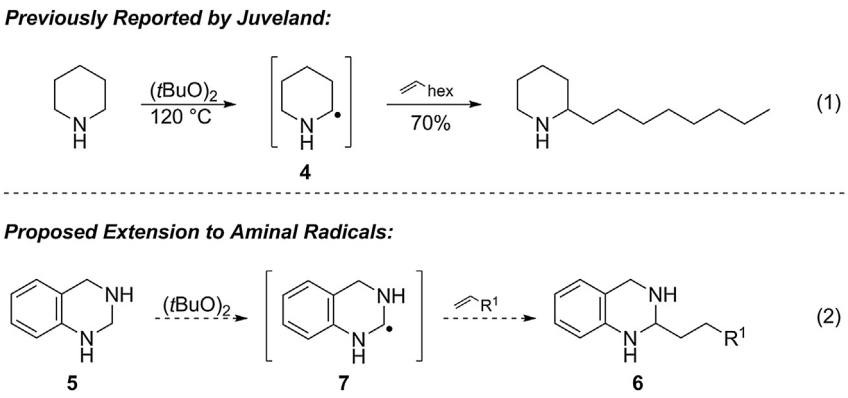
Herein we give a full account of the development of aminal radical reactivity for use in synthesis. In addition to expanded discussions of the results previously reported, we describe our initial efforts to generate aminal radicals under peroxide initiated conditions, the efforts to optimize translocation reactions of aminals, which do not bear an electron-withdrawing group, a deuterium labeling study on the translocation reactions of aminals, which do not bear an electron-withdrawing group, and applications of the translocation method to acyclic aminals relevant to the synthesis of indole alkaloids.

2. Results and discussion

In 1958, Juveland reported the generation of α-aminoalkyl radical intermediate **4** under peroxide initiated conditions (Scheme 2, Eq. 1).[22] Treatment of piperidine with di-*tert*-butylperoxide in the presence of 1-octene yielded 2-octyl piperidine. Extension of this method to the generation of aminal radicals could involve the treatment of an aminal with di-*tert*-butylperoxide in the presence of a suitable radical acceptor (Scheme 2, Eq. 2). Tetrahydroisoquinazoline (**5**) was chosen because it was easy to prepare, it is chromatographically stable, and it contains a chromophore, which allowed for facile monitoring of reaction progress.

Following Juveland's procedure, **5** was heated in the presence of di-*tert*-butylperoxide and 1-octene in a sealed tube. The reaction produced an intractable mixture of products and none of the desired product **6** was observed. In an effort to affect cleaner reactivity, modified reaction conditions were investigated. Lowering the reaction temperature resulted in no reaction. Performing the reaction neat, tethering the radical acceptor to the substrate, or using activated alkenes as radical acceptors all resulted in the formation of a complex mixture of products.[23]

Based on these results, two plausible explanations were formulated. Either the desired aminal radical **7** was generated, and it was reacting in an unselective manner to give the observed decomposition, or aminal radical **7** had not been generated and the



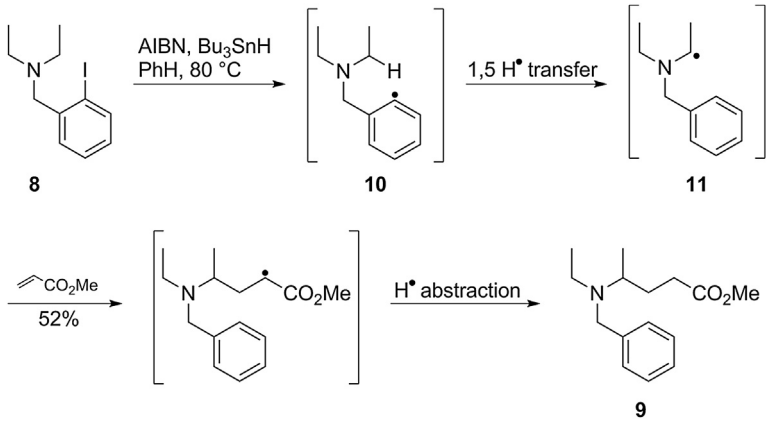
Scheme 2. Extension of Juveland's method.

observed degradation was arising from other reaction pathways. Unable to easily distinguish between these possibilities, an alternative method for the generation of aminal radicals was sought. Ideally, this method would incorporate a functional handle that could be used to determine whether aminal radicals were being generated.

Radical translocation[24] of 2-iodobenzyl (IBn) protected amine **8** with AIBN and Bu_3SnH in the presence of methyl acrylate gives alkylated product **9** (Scheme 3).[25] Reactions of this type proceed through the generation of a phenyl radical (**10**) followed by 1,5-H atom transfer to form an α-aminoalkyl radical intermediate **11**. The α-aminoalkyl radical then adds to the olefin and gives **9** after H atom abstraction from Bu_3SnH.

competent. However, in addition to the desired product **13**, isomeric product **14**,[27] over addition product **15**, and dehalogenated product **16** were observed (Table 1). Formation of the undesired product **14** is competitive with the formation of desired product **13** as a result of the stability of the α-aminobenzylic radical from which it presumably arises. The formation of dehalogenated **16** was not surprising given that similar reaction conditions have been used to perform radical dehalogenation.[28] Although Curran reported the oxidation of 2-iodobenzyl ethers under similar reaction conditions,[29] no amidine formation was observed.

Having successfully demonstrated that aminal radical intermediates could be generated and added to alkenes using the radical translocation method, efforts were turned to reaction op-



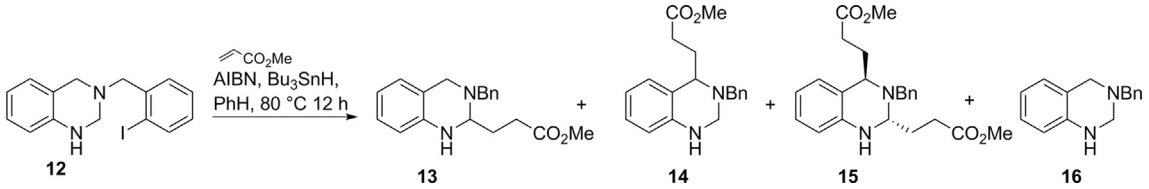
Scheme 3. Protective radical translocation.

The application of radical translocation as a means to generate aminal radicals was particularly attractive because it would provide a functional handle through which problematic reactivity might be diagnosed. Specifically, the loss of iodide is diagnostic for the formation of a phenyl radical. Deuteration experiments could be used to determine whether the desired 1,5-H atom abstraction had occurred if the reaction failed to produce the aminal radical addition product. Additionally, the necessary 2-iodobenzyl substituted starting material **12** (Table 1) could be easily prepared by alkylation of **5**, and the product of the translocation reaction (**13**) would be a benzyl protected aminal.

N-2-Iodobenzyl-tetrahydroquinazoline (**12**) was prepared from **5** and 2-iodobenzyliodide. Treatment of the protected aminal with AIBN and Bu_3SnH in the presence of methyl acrylate yielded some of the desired aminal radical product **13** (Table 1, entry 1).[26] This indicated that the desired aminal radical is synthetically

timization. Variation of the Bu_3SnH equivalents had little effect on the product distribution; however, the yield of **13** decreased when less than 2 equiv were added (Table 1, entries 1–3). Adjustment of the acrylate equivalents showed that only trace amounts of the desired products were formed when less than 2 equiv were used (entry 4). Increasing the stoichiometry of the acrylate up to 5 equiv showed little effect on the product distribution or isolated yield (entries 5, 6). However, using a large excess of the acceptor resulted in a decrease in yield (entry 7). Decreasing the time of addition from 10 h to 1 h was found to partially suppress the formation of the over addition product **15** (entries 8, 9). Systematic variation of the reaction concentration showed that the optimal yield was obtained with a concentration of 0.1 M with respect to the aminal, but the reaction remained unselective (entries 10–12). A solvent screen showed that toluene and cyclohexane were also amenable to the desired reactivity while use of carbon tetrachloride resulted in

Table 1
Attempted optimization of radical translocation



Entry	Bu_3SnH (equiv)	Acrylate (equiv)	Addition time (h)	Concentration (M)	Solvent	**13**+**14**[a] (%)	**16**[a] (%)	**17**[a] (%)
1	*3.9*	3	10	0.1	PhH	32	18	24
2	*2.0*	3	1	0.1	PhH	28	9	37
3	*0.9*	3	1	0.1	PhH	12	8	14
4	2.0	*1*	1	0.1	PhH	4	0	34
5	2.0	*3*	1	0.1	PhH	28	9	37
6	2.0	*5*	1	0.1	PhH	16	8	17
7	2.0	*10*	1	0.1	PhH	6	4	18
8	3.9	3	*10*	0.1	PhH	32	18	24
9	3.9	3	*1*	0.1	PhH	12	0	23
10	3.9	3	10	*0.01*	PhH	16	19	9
11	2.0	3	1	*0.1*	PhH	28	9	37
12	2.0	3	1	*0.5*	PhH	14	5	25
13	2.0	3	1	0.1	*CyH*	6	3	12
14	2.0	3	1	0.1	*PhMe*	12	6	18
15	2.0	3	1	0.1	CCl_4	Decomposition		

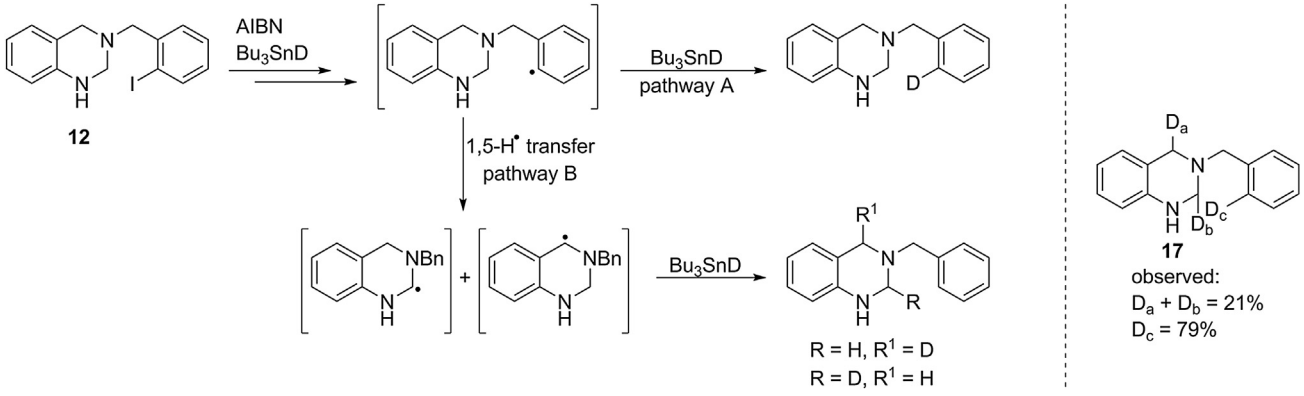
[a] Isolated yields.

decomposition (entries 13–15). Benzene was chosen as the optimal solvent as it was easily removed by rotary evaporation, provided superior yields, and possessed favorable solubility properties. In total, more than one hundred conditions were screened but all failed to cleanly produce **13** in high chemical yield.

Of the undesired side products formed in the reaction of **12**, the dehalogenation product **16** was always the most abundant. Presumably, **16** results from the reaction of a radical intermediate with Bu_3SnH before it has had sufficient opportunity to react with the acrylate. A deuteration experiment was performed in order to probe whether this undesired reduction was occurring before or after the 1,5-H atom transfer event. After homolysis of the C–I bond, a phenyl radical is generated. If the 1,5-H atom transfer is slow and the phenyl radical reacts with Bu_3SnD,[30] then a deuterium atom should be incorporated at the *ortho*-position of the benzyl group (Scheme 4, pathway A). However, if the 1,5-H atom transfer event occurs rapidly, then the deuterium would be incorporated on the aminal containing ring (pathway B).

at the *ortho*-position of the benzyl group while only 21% was incorporated on the tetrahydroquinazoline ring. Assuming that the 1,5-H atom transfer is irreversible, this result suggested that the aminal radical, once formed, reacted smoothly with the acrylate acceptor and proceeded to the desired product. However, the rate of D atom abstraction from Bu_3SnD was competitive with that of 1,5-H atom abstraction from the aminal.

Based on this result, it was reasoned that the use of a terminal reductant, which undergoes H atom abstraction at a slower rate than Bu_3SnH would likely decrease the amount of undesired dehalogenation observed. $(TMS)_3SiH$, a common substitute for tin hydrides in radical processes,[31] is known to undergo H atom abstraction at a rate approximately one fifth than that of Bu_3SnH.[32] Unfortunately, substitution of $(TMS)_3SiH$ for Bu_3SnH in the reaction mixture resulted in no reaction. It was reasoned that the rate of H atom abstraction from $(TMS)_3SiH$ may have been insufficient to sustain the radical chain. Ph_3GeH is known to undergo H atom abstraction at a rate slower than that of Bu_3SnH and faster than that



Scheme 4. Deuterium Incorporation in the dehalogenated side product.

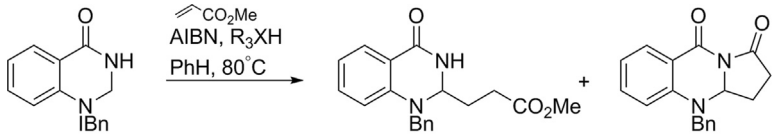
A solution of aminal **12** and methyl acrylate was heated to reflux while a solution of Bu_3SnD and AIBN in benzene was added over a period of 1 h. Deuterium NMR analysis of the dehalogenated product (**17**) revealed that 79% of the deuterium was incorporated

of $(TMS)_3SiH$.[33] However, use of Ph_3GeH as a terminal reductant also failed to give any product formation.

Reasoning that substitution of the benzylic position would eliminate undesired products resulting from reaction of the α-

aminobenzylic radical, dihydroquinizolinone **18** was investigated. Treatment of **18** with the standard reaction conditions resulted in significantly cleaner reactivity than that of aminal **12**. The desired product **19** was obtained in a synthetically useful yield along with a small amount of the imide **20**, which presumably resulted from subsequent intramolecular cyclization of the desired product (Table 2, entry 1). Surprisingly, the reactions of dihydroquinizolinone **18** were found to be substantially more robust than those of tetrahydroquinazoline **12**. While reactions using aminal **12** had required rigorously dried and degassed solvent, aminal **18** reacted smoothly even when wet, non-degassed solvent was used. Encouraged by these results, optimization studies were carried out.

Table 2
Optimization of the translocation method with *N*-acyl aminals



18 **19** **20**

Entry	R_3XH	BnSH (equiv)	AIBN (equiv)	Acrylate (equiv)	**19** (%)	**20** (%)
1	Bu_3SnH	0	0.2	3	49	12
2	Bu_3SnH	0.9	0.2	3	75	0
3	$(TMS)_3SiH$	0.9	0.2	3	72	17
4	Ph_2SiH_2	0.9	0.2	3	No reaction	
5	None	0.9	0.2	3	No reaction	
6	Bu_3SnH	0.1	0.2	5	26	60
7	$(TMS)_3SiH$	0.1	0.2	5	70	21
8	Bu_3SnH	0.9	0	5	18	0

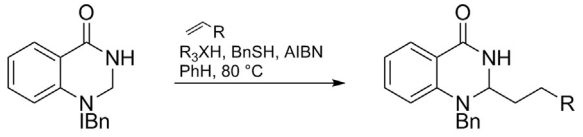
Thiols have been shown to aid in H atom transfer events.[34] It was found that the addition of substoichiometric quantities of benzyl mercaptan provided increased reaction yields (Table 2, entry 2). $(TMS)_3SiH$, which is non-toxic,[35] was found to be an effective H atom donor when BnSH was used (entry 3). No reaction was observed when Ph_2SiH_2 was used (entry 4). When hydrides were omitted and BnSH was used, no reaction was observed (entry 5). The loading of the thiol had no appreciable effect on the reaction yield; however, the formation of **20** decreased in the case when BnSH was used with higher loadings (entries 2 and 3 vs 6 and 7). In the absence of AIBN, only modest product formation was observed (entry 8); it is possible that some C–I bond homolysis occurred thermally.

Having found reaction conditions suitable for the formation of aminal radicals and their addition to alkenes, the substrate scope with respect to the radical acceptor was investigated. It was found that a variety of electron poor alkenes, including acrylates (**21**), acrylonitrile (**22**), and acrolein (**23**) act as suitable radical acceptors (Table 3, entries 1–6). In contrast, unactivated (**24**) and electron-rich alkenes (**25**) did not participate in the reaction (entries 7 and 8). These data suggested that, like their α-aminoalkyl radical analogues, *N*-acyl aminal radicals are nucleophilic in character and react selectively with electrophilic radical acceptors.

A variety of aminal substrates were investigated. The reaction tolerated substitution at either aminal nitrogen, and isomeric aminal **26** participated in the reaction to give products **27**–**29** (Table 4, entries 1–6). The reaction of phenyl substituted aminal **30**, which would give rise to a tertiary benzylic aminal radical, failed to produce any of the desired product **31** (entry 7). It is possible that steric interactions between the phenyl substituent and the radical translocation group disfavored a conformation that would allow the 1,5-H atom abstraction to occur.

It was unclear whether the improved results obtained with these dihydroquinizolinone-derived substrates were simply an effect of blocking the benzylic position, or if there was a stabilizing effect given by the carbonyl. In order to probe this, a side by side comparison of substrates **32** and **33** was performed (Scheme 5). It was found that **32**, which lacks an electron-withdrawing group,

Table 3
Examination of radical acceptor scope for the translocation method



19

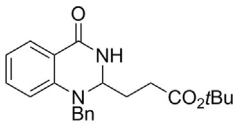
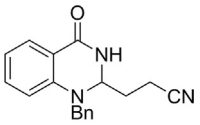
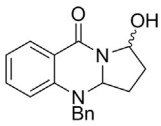
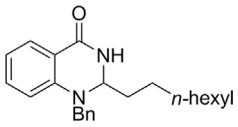
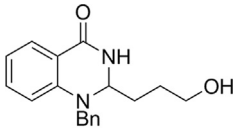
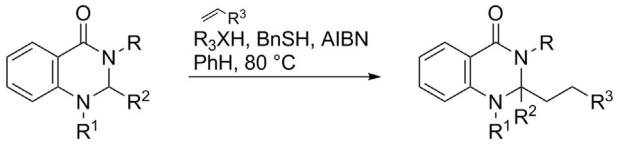
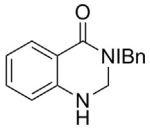
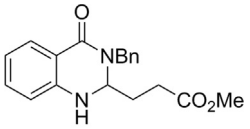
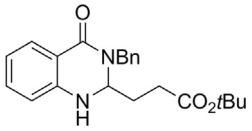
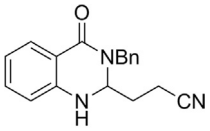
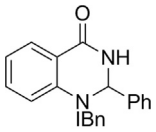
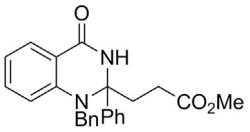
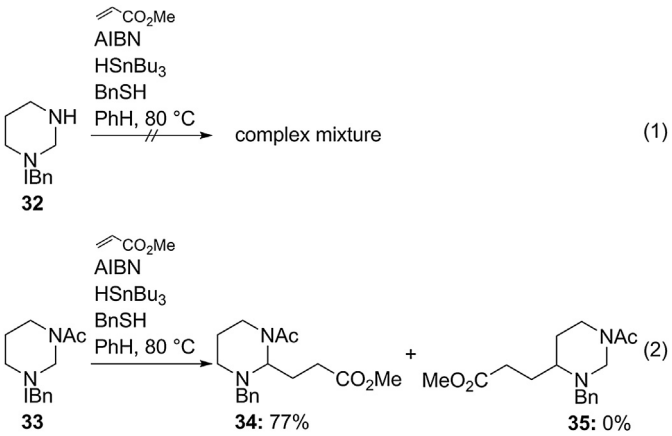
Entry	Product	R_3XH	Yield (%)
1		Bu_3SnH	65
2	**21**	$(TMS)_3SiH$	22
3		Bu_3SnH	79
4	**22**	$(TMS)_3SiH$	56
5		Bu_3SnH	57, 1:1 dr
6	**23**	$(TMS)_3SiH$	20, 1:1 dr
7		Bu_3SnH	0
	24		
8		Bu_3SnH	0
	25		

Table 4
Substrate scope of the translocation method



Entry	Substrate	Product	R_3XH	BnSH (equiv)	Yield (%)
1			Bu_3SnH	0.9	73
2	**26**	**27**	$(TMS)_3SiH$	0.1	75
3	**26**		Bu_3SnH	0.1	67
4		**28**	$(TMS)_3SiH$	0.1	44
5	**26**		Bu_3SnH	0.1	72
6		**29**	$(TMS)_3SiH$	0.1	25
7			Bu_3SnH	0.9	0
	30	**31**			

gave an intractable mixture with no detectable radical addition product (Eq. 1). However, **33**, which bears an *N*-acyl group, gave only product **34** in good yield (Eq. 2). It is also notable that aminal **33** has accessible α-amino C–H bonds but none of the α-aminoalkyl radical addition product **35** was observed. This result suggests that the *N*-acyl aminal radical was selectively generated and reacts without competitive formation of the alternative α-aminoalkyl radical. The electron-withdrawing nature of the carbonyl may stabilize the aminal radical.[36]



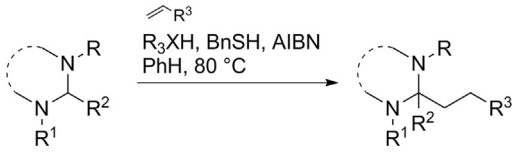
Scheme 5. Selective formation of aminal radicals.

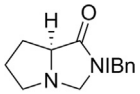
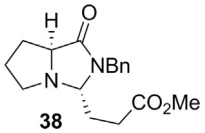
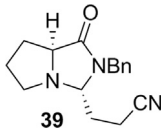
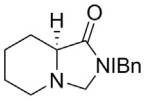
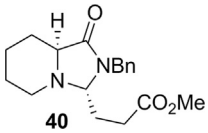
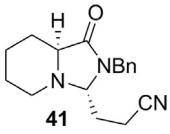
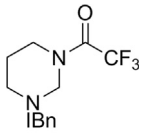
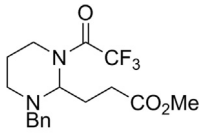
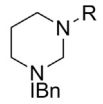
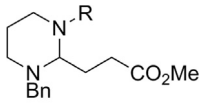
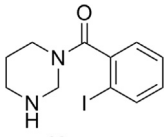
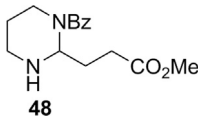
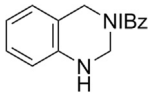
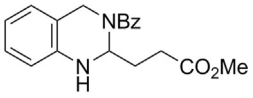
Five-membered aminals were also found to participate in the reaction. Proline and pipecolic acid-derived bicyclic aminals **36** and **37** reacted with methyl acrylate and acrylonitrile to give addition products **38**–**41** (Table 5, entries 1–8). The observed diastereoselectivity likely arises from addition to the convex face of the bicycle. While examining the requirements for the electron-withdrawing substituent, trifluoroacetyl was found to be a suitable activating group as **42** produced the addition product **43**. Attempts to use substrates bearing carbamate (**44a** and **44b**) or sulfone (**44c**) protected aminals failed to produce any of the desired products, instead giving dehalogenation or decomposition, respectively (entry 11).

Hexahydropyrimidine and tetrahydroquinoline derived aminals **46** and **47** bearing a 2-iodobenzoyl group (IBz) were prepared. It was envisioned that the IBz substituent could function as both an electron-withdrawing substituent and the translocation group. The desired products **48** and **49** were not observed upon subjection of **46** and **47** to the standard reaction conditions (entries 12, 13). The absence of the desired reactivity may be attributable to the conformational constraints of the stable amide rotamers, which were clearly observable in the NMR spectra of **46** and **47**. It is possible that the favored amide rotamer may place the IBz group away from the aminal carbon, allowing time for the radical intermediates to react with Bu_3SnH before the substrate can attain a conformation suitable for the 1,5-H atom translocation event.

Substrates bearing a tethered radical acceptor were also investigated and are shown in Table 6. Tetrahydropyrimidinone derivative **50**, which bears a tethered α,β-unsaturated ester, yielded

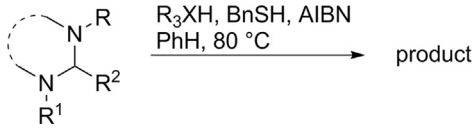
Table 5
Scope of the translocation method

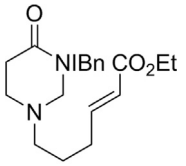
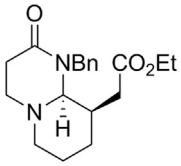
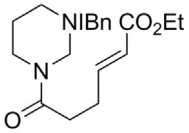
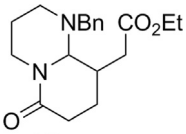
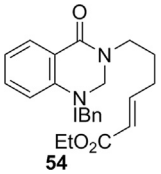
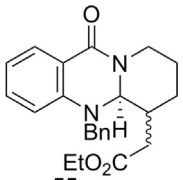
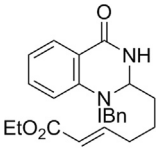
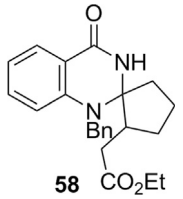
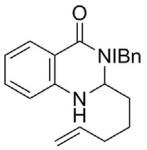
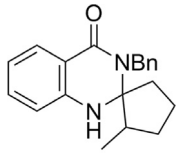


Entry	Substrate	Product	R_3XH	BnSH (equiv)	Yield (%)
1	 **36**	 **38**	Bu_3SnH	0.9	46, dr >20:1
2			$(TMS)_3SiH$	0.9	4, dr not determined
3	**36**	 **39**	Bu_3SnH	0.2	50, dr>20:1
4			$(TMS)_3SiH$	0.1	45, dr 4:1
5	 **37**	 **40**	Bu_3SnH	0.9	68, dr >20:1
6			$(TMS)_3SiH$	0.9	28, dr >20:1
7	**37**	 **41**	Bu_3SnH	0.2	68, dr >20:1
8			$(TMS)_3SiH$	0.1	16, dr not determined
9	 **42**	 **43**	Bu_3SnH	0.1	69
10			$(TMS)_3SiH$	0.1	10
11	 **44a** R = CO_2tBu **44b** R = CO_2Me **44c** R = Ts	 **45a** R = CO_2tBu **45b** R = CO_2Me **45c** R = Ts	Bu_3SnH	0.9	0
12	 **46**	 **48**	$(TMS)_3SiH$	0.9	0
13	 **47**	 **49**	$(TMS)_3SiH$	0.9	0

the bicycle **51** as a single diastereomer. However, isomeric substrate **52**, which bears an exocyclic electron-withdrawing group, produced none of the cyclized product **53**, instead giving only the product of dehalogenation in 82% yield (entries 1–3). The disparity in the observed reactivity of these substrates may again be attributable to the conformational preference of the stable amide rotamers. The quinazolinone-derived aminal **54** cyclized cleanly to produce **55** (entries 4, 5).

Table 6
Scope of the translocation method



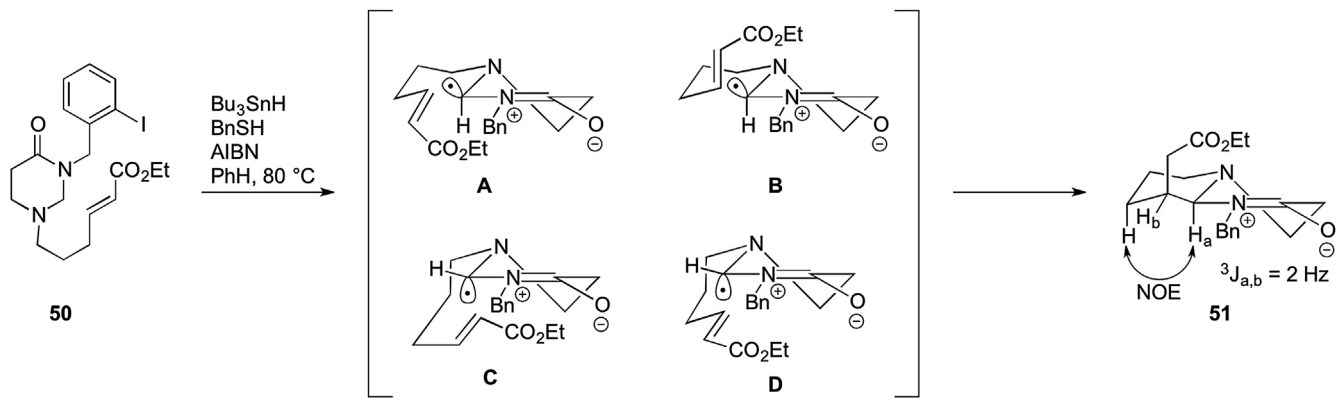
Entry	Substrate	Product	R_3XH	BnSH (equiv)	Yield (%)
1			Bu_3SnH	0.1	55, dr >20:1
2			$(TMS)_3SiH$	0.1	50, dr >20:1
	50	**51**			
3			$(TMS)_3SiH$	0.9	0
	52	**53**			
4			Bu_3SnH	0.1	61, dr 1.5:1
5			$(TMS)_3SiH$	0.9	49, dr 1.5:1
	54	**55**			
6			Bu_3SnH	0.9	0
	56	**58**			
7			$(TMS)_3SiH$	0.9	0
	57	**59**			

Substrates bearing substitution at the aminal carbon, such as **56** and **57**, gave none of the desired spirocyclic aminal containing products **58** and **59** (entries 6, 7). Again, the lack of desired reactivity may be attributed to the steric interactions between the substituent on the aminal carbon and the translocation group, which disfavor the conformation necessary for the 1,5-H atom transfer event.

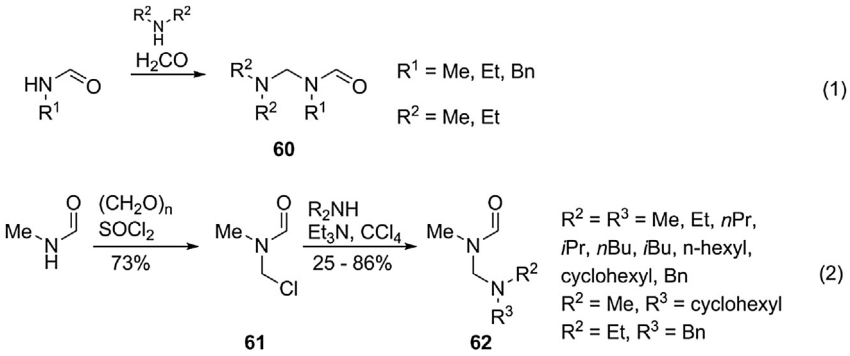
A plausible model explaining the origin of the diastereoselectivity in the formation of aminal **51** is shown in Scheme 6.[37] Four possible diastereomeric transition states were considered for the cyclization (**A**–**D**). Structures **A** and **D** do not lead to the relative stereochemistry observed in the major diastereomer of the product (**51**). The SOMO in structure **C** is aligned with the π system of the amide, and this orientation may lead to stereoelectronic stabilization. However, molecular models indicated that **C** suffers from unfavorable steric interactions between the ester and the six-membered ring. In structure **B**, the SOMO would have less overlap with the amide π system, but it presents the alkene radical acceptor in a more sterically favorable orientation, and we believe this assembly leads to the observed diastereomer. Further experimentation would be necessary to distinguish between these possible models.

Seeking to apply the radical translocation method to the total synthesis of indole alkaloids, we became interested in acyclic *N*-formyl aminals bearing indole. Acyclic *N*-formyl aminals are rare in the literature, possibly because of their propensity to hydrolyze. Scheme 7 depicts the known methods for the preparation of acyclic *N*-formyl aminals. Aminals **60** were prepared by treatment of *N*-substituted formamide derivatives with formaldehyde and a variety of symmetrical secondary amines (Eq. 1).[38] Nucleophilic substitution of alkyl halide **61** with secondary amines gave aminals **62** in 25–86% yield (Eq. 2).[39]

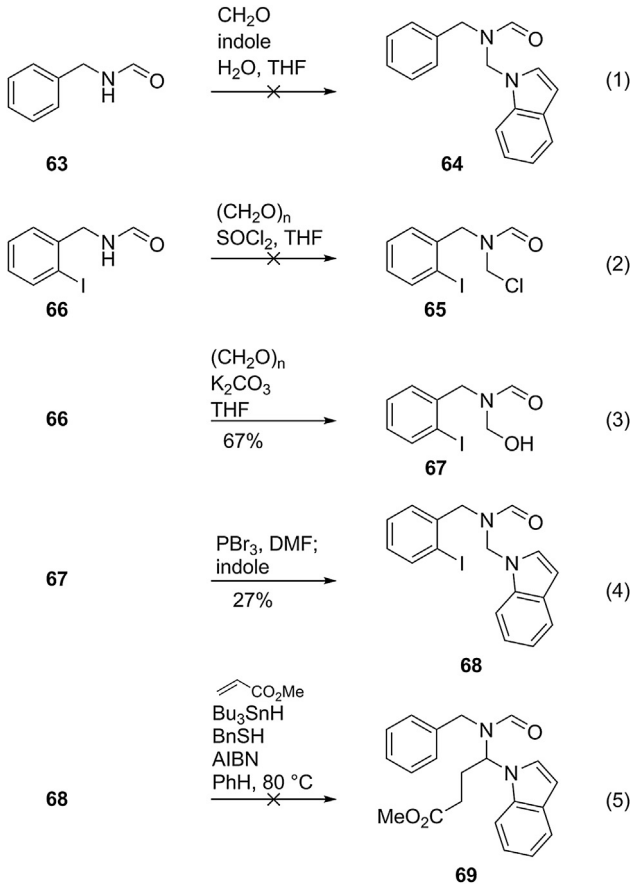
Treatment of *N*-benzylformamide **63** with formaldehyde and indole failed to produce the model aminal **64** (Scheme 8, Eq. 1). It was reasoned that the indole nitrogen was not sufficiently nucleophilic to undergo the necessary condensation with formaldehyde. It was postulated that the reactivity of a pre-formed halide electrophile such as **65** might compensate for the weak nucleophilicity of indole. To that end, **66** was treated with thionyl chloride and formaldehyde but none of **65** was isolated (Eq. 2). Further attempts to form the *N*-chloromethyl formamide **65** under a variety of modified reaction conditions were also unsuccessful. The only isolable product of these reactions was the *N*,*O*-hemiacetal **67**. Formation of **67** likely resulted from the rapid elimination of chloride to give an *N*-acyl iminium ion, which was subsequently trapped by water. The same product was obtained when **66** was exposed to paraformaldehyde under basic conditions (Eq. 3).



Scheme 6. Model for the observed diastereoselectivity.



Scheme 7. Known methods for the preparation of acyclic *N*-formyl aminals.



Scheme 8. Synthesis of indole substituted acyclic *N*-formyl aminal **68**.

Reasoning that exposure of **67** to dehydrating conditions might generate the halide in situ, **67** was treated with PBr_3 followed by subsequent addition of indole (Scheme 8, Eq. 4). Gratifyingly, the desired acyclic aminal **68** was produced in modest yield. However, **68** failed to produce the desired product **69** when subjected to the standard radical translocation conditions (Eq. 5). The aminal **68** was recovered quantitatively.

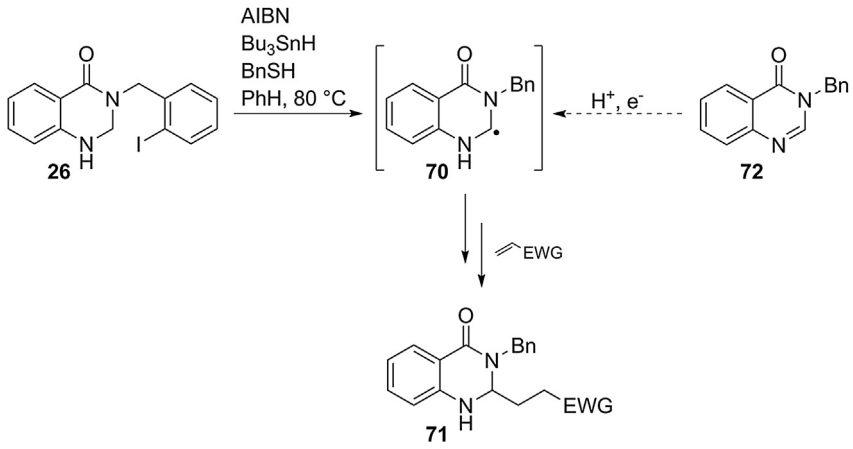
While the radical translocation strategy had served as an effective platform to access aminal radical intermediates, a complimentary method that did not require foul smelling or toxic reagents was desired. Ideally, the starting materials would be easily accessible and would not require a 2-iodobenzyl substituent. Owing to the success of substrate **26** in the radical translocation reaction, should aminal radical **70** be generated in the presence of a suitable radical acceptor by another means, the product **71** would also be obtained (Scheme 9).

It was envisioned that protonation and single electron reduction of the known[40] amidine **72** would give intermediate **70**. Seeking conditions suitable for this transformation, **72** was subjected to reductive conditions in the presence of acrylonitrile (Table 7). Treatment with Zn metal gave no reaction and LiDBB[41] led to decomposition (entries 1–5). However, treatment with SmI_2[42] in the presence of stoichiometric camphorsulfonic acid (CSA) gave the desired product **29** in 31% yield (entry 6). Decreasing the equivalents of SmI_2 and adding the reagent slowly resulted in a dramatic increase in product yield (entry 7). While the reaction proceeded without the addition of a proton source, yields were substantially lower and the starting material was not consumed (entry 8). Ammonium chloride was chosen as the optimal proton source as it is mild, inexpensive, and generally provided high yields (entry 9). The amidine reduction method featured several advantages when compared to the translocation method; it occurred rapidly at room temperature, required no toxic or foul smelling additives, was operationally simple, and provided improved yields.

With the optimized reaction conditions in hand, a variety of substrate combinations were evaluated. Quinazolinones are accessible from the corresponding aminobenzamide derivatives, possess interesting biological activities,[43] and contain the *N*-acyl amidine substructure. Reaction of amidine **72** with methyl and *tert*-butyl acrylates proceeded smoothly to give **73a** and **73b** (Scheme 10). Attempts to use methyl vinyl ketone resulted in reduction of the carbonyl and gave none of the desired radical addition product (**73c**). No addition product was observed when allyl alcohol was used as the radical acceptor (**73d**). The quinazolinone bearing a tethered alkene preferentially underwent bimolecular radical addition with acrylonitrile (**74a**), *tert*-butyl acrylate (**74b**), and methyl acrylate (**74c**) rather than unimolecular 5-*exo*-*trig* radical cyclization with the appended alkene.

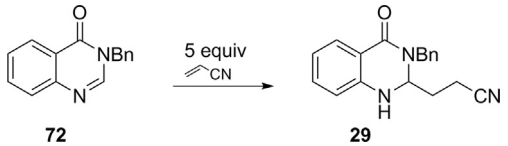
The amidine reduction method does not require a benzyl substituent and substrates bearing *N*-alkyl (**75a**, **b**), *N*-aryl (**76a**–**c**), and unprotected nitrogen (**77a**–**c**) all participated in the reaction. In contrast to the translocation method, fully substituted aminals were prepared in high yield by reductive alkylation of the corresponding amidines (**78a**–**c**, **79a**–**c**). Remarkably, the amidine bearing a sterically demanding *tert*-butyl group also reacted in the desired manner giving an aminal with vicinal fully substituted carbons (**80**). Electron-rich arenes are also compatible with the reaction conditions (**81**), and no reduction of the arene was detected.

Disubstituted acceptors are also reactive in the amidine reduction reaction as ethyl crotonate reacted to produce **82** in good yield, but only modest diastereoselectivity was observed (Table 8, entry 1). In contrast, intramolecular reactions with di- (**83**) and



Scheme 9. Single electron reduction of amidines to generate aminal radicals.

Table 7
Optimization of the amidine reduction method



Entry	Conditons	Result
1	Zn (2.2 equiv), HOAc, rt	No reaction
2	Zn (2.2 equiv), HOAc, 80 °C	No reaction
3	Zn (2.2 equiv), HOAc, reflux	No reaction
4[a]	LiDBB (2.5 equiv), THF, rt	Decomposition
5[a]	LiDBB (2.5 equiv), CSA (1.1 equiv), THF, rt	Decomposition
6	SmI_2 (6.0 equiv), CSA (1.1 equiv), THF, rt	31%
7[a]	SmI_2 (2.5 equiv), CSA (1.1 equiv), THF, rt	90%
8[a]	SmI_2 (2.5 equiv), THF, rt	57%
9[a]	SmI_2 (2.5 equiv), NH_4Cl (1.1 equiv), THF, rt	99%

[a] Slow addition of reductant solution by syringe pump.

trisubstituted (**84**) olefins proceed with high diastereoselectivity giving aminals **85** and **86** (entries 2, 3). Amidines that are not quinazolinones also participate in the reaction. Spirocyclic amidine **87** gave **88** in good yield (entry 4). Norbornene-derived amidine **89** produced **90** as a single diastereomer in nearly quantitative yield (entry 5). Pyrimidinone **91** underwent alkylation to give aliphatic aminal **92** (entry 6). Bicyclic amidine **93** reacted to give the fully substituted aminal **94** in good yield as indicated by ^1H NMR analysis, but could only be isolated in modest yield (entry 7). We speculate that the product may have decomposed during silica gel chromatography. Acylated dihydroquinazole **95a** gave aminal **96a** in modest yield (entry 8).

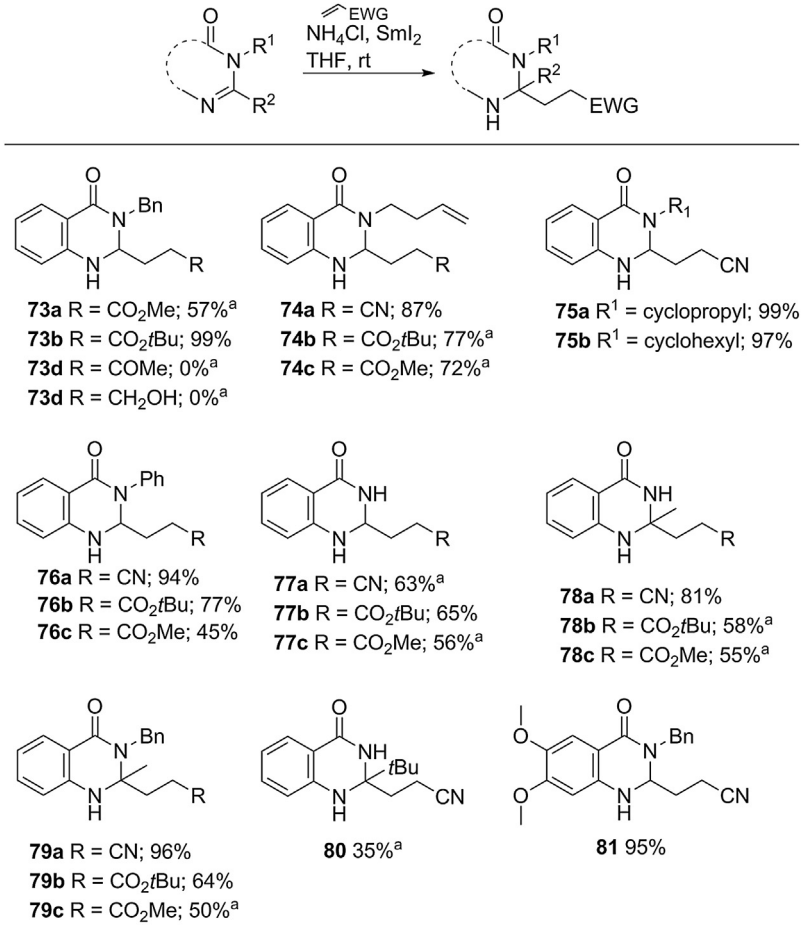
As was observed with the translocation method, an electron-withdrawing group on nitrogen is essential for the desired reactivity. 3,4-Dihydroquinazoline (**95b**), DBU (**97**), and benzimidazole (**99**) gave no reaction under the optimized conditions (entries 8–10). Tosyl protected dihydroquinazole **95c** decomposed under the reaction conditions. This suggested that, as seen with aminal radicals generated using the translocation method, *N*-sulfonyl is not a suitable electron-withdrawing group.

It was postulated that the reaction proceeded through protonation of the amidine followed by reduction of the resulting amidinium ion. If this mechanism was operative, it was reasoned that amidinium ions would also participate in the reaction. Dihydroquinazolinone-derived amidinium ion **101** reacted in excellent yield with methyl acrylate (**102a**), *tert*-butyl acrylate (**102b**), and acrylonitrile (**102c**) (Table 9, entry 1). Amidinium ion **103** reacted to produce fully substituted aminal **104** (entry 2). Pyrimidinone (**105**) and dihydropyrimidinone-derived amidinium ions (**106a**, **b**) also reacted uneventfully to give **107**, **108a**, and **108b**. Dihydroquinazolinium **109**, which does not bear an acyl group on nitrogen, gave no reaction under the optimized conditions and the addition product **110** was not obtained (entry 5).

Based on the observed reactivity, two plausible mechanisms were formulated and are detailed in Scheme 11. In mechanism A, amidine **72** is first protonated and reduced by SmI_2 to give the neutral aminal radical **70**. The aminal radical intermediate then undergoes addition to the alkene, producing free radical intermediate **111**. Finally, single electron reduction and protonation of **111** give the observed product **73b**. Alternatively, the operative mechanism could involve reduction of the alkene by SmI_2 to produce the radical anion **112**, which would then undergo addition to the amidine **72** to give aminyl radical intermediate **113** (Scheme 11, mechanism B). Protonation and single electron reduction of **113** would afford the observed product **73b**. SmI_2 has been shown to reduce α,β-unsaturated esters in some cases and reaction mechanisms similar to mechanism B have been proposed in the literature.[44] Given that the reactions were carried out in the presence of a strong acid, it is unlikely that the reaction proceeds through carbanion intermediates that arise from the reduction of intermediate **70**.

In order to determine whether the amidine reduction method was proceeding through the proposed aminal radical intermediate or by some other pathway, mechanistic investigations were carried out (Scheme 12). If mechanism A was operative, it was reasoned that treatment of amidine **114** with SmI_2 and a proton source would give an α-cyclopropyl aminal radical. Should the radical intermediate be sufficiently long lived, products of cyclopropane fragmentation should be formed.[45] As expected, reduction of amidine **114** in the absence of a radical acceptor produced the cyclopropane ring fragmentation product **115** (Eq. 1). Additionally, treatment of **114** with the standard reaction conditions in the presence of acrylonitrile yielded bicyclic aminal **116**[46] along with addition product **117** (Eq. 2). It should be noted that cyclopropyl substituents that are not on the amidine carbon are tolerated with no observable fragmentation (see Scheme 10, **75a**).

The use of cyclopropyl substituted acrylate **118** in the reaction yielded aminal **119** along with reduction product **120** (Eq. 3). It is possible that the proposed α-ester radical intermediate is short lived and undergoes reduction at a rate greater than that of cyclopropane fragmentation. If mechanism B was the operative pathway, then treatment of the alkene with SmI_2 in the absence of



Scheme 10. Scope of the amidine reduction reaction.

an amidine should give products of reduction. However, no reaction was observed when acrylonitrile, methyl acrylate, *tert*-butyl acrylate, or acrylate **118** were exposed to the standard reaction conditions (Eqs. 4–7). These data indicate that mechanism B is not plausible, and we believe that the reaction proceeds as shown in mechanism A.

3. Conclusion

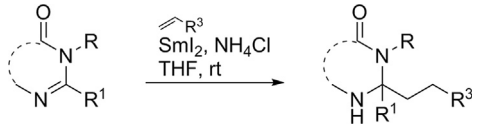
While aminal radicals have been known in the literature for more than 20 years, the synthetic utility of these intermediates had not been reported until recent work from our laboratory. It has been demonstrated that aminal radical intermediates may be generated via radical translocation or by reduction of amidines and amidinium ions. These radicals add to electron poor alkenes to give products of carbon–carbon bond formation in high chemical yield. This reactivity has been shown to be effective in both inter-and intramolecular contexts and can be used to produce fully substituted aminal stereocenters as well as all carbon quaternary stereocenters with good diastereocontrol.

4. Experimental section

4.1. General[47]

All reactions were carried out under an inert Ar atmosphere in oven-dried glassware. Flash column chromatography (FCC) was

Table 8
Substrate scope of the amidine reduction



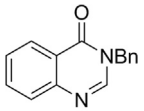
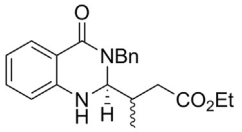
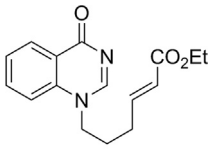
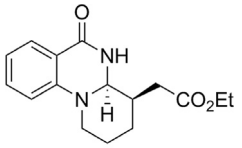
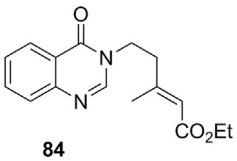
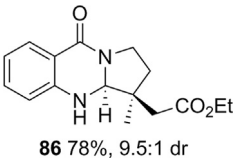
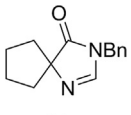
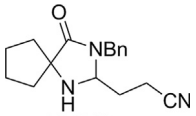
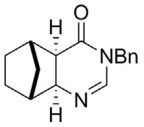
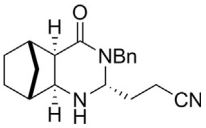
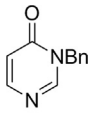
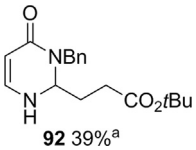
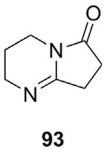
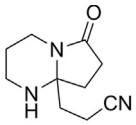
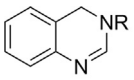
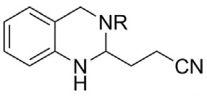
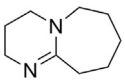
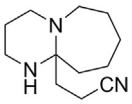
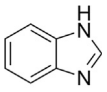
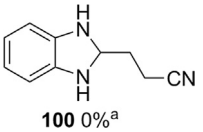
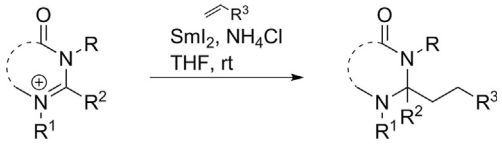
Entry	Substrate	Product
1	 **72**	 **82** 75%, 2:1 dr[a]
2	 **83**	 **85** 75%, dr > 20:1[a]

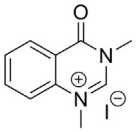
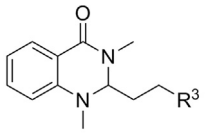
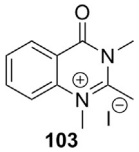
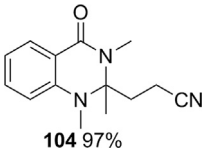
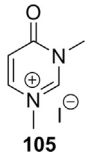
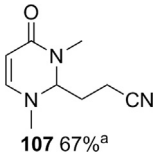
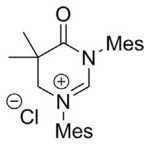
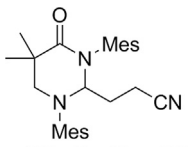
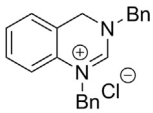
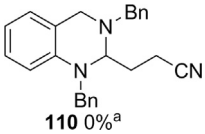
Table 8 (*continued*)

Entry	Substrate	Product
3	 **84**	 **86** 78%, 9.5:1 dr
4	 **87**	 **88** 87%
5	 **89**	 **90** 99%, dr > 20:1
6	 **91**	 **92** 39%[a]
7	 **93**	 **94** 17% (76% by NMR)[a]
8	 **95a** R = Ac **95b** R = H **95c** R = Ts	 **96a** R = Ac; 36%[a] **96b** R = H; 0%[a] **96c** R = Ts; 0%[a]
9	 **97**	 **98** 0%[a]
10	 **99**	 **100** 0%[a]

[a] CSA was used as the acid.

Table 9
Scope of the amidinium reduction



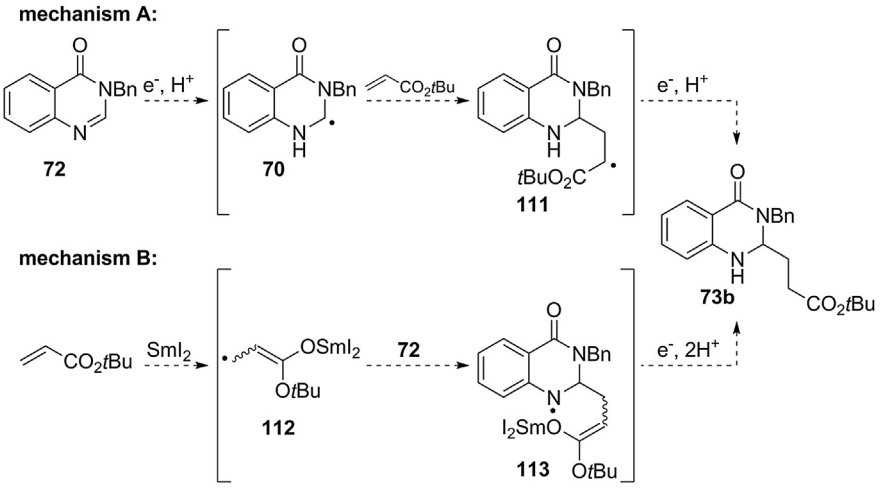
Entry	Starting material	Product
1	 **101**	 **102a** R = CO_2Me; 88% **102b** R = CO_2tBu; 93% **102c** R = CN; 97%
2	 **103**	 **104** 97%
3	 **105**	 **107** 67%[a]
4	 **106a** R = Mes **106b** R = Ph	 **108a** R = Mes; 50% **108b** R = Ph; 56%[a]
5	 **109**	 **110** 0%[a]

[a] CSA was used as the acid.

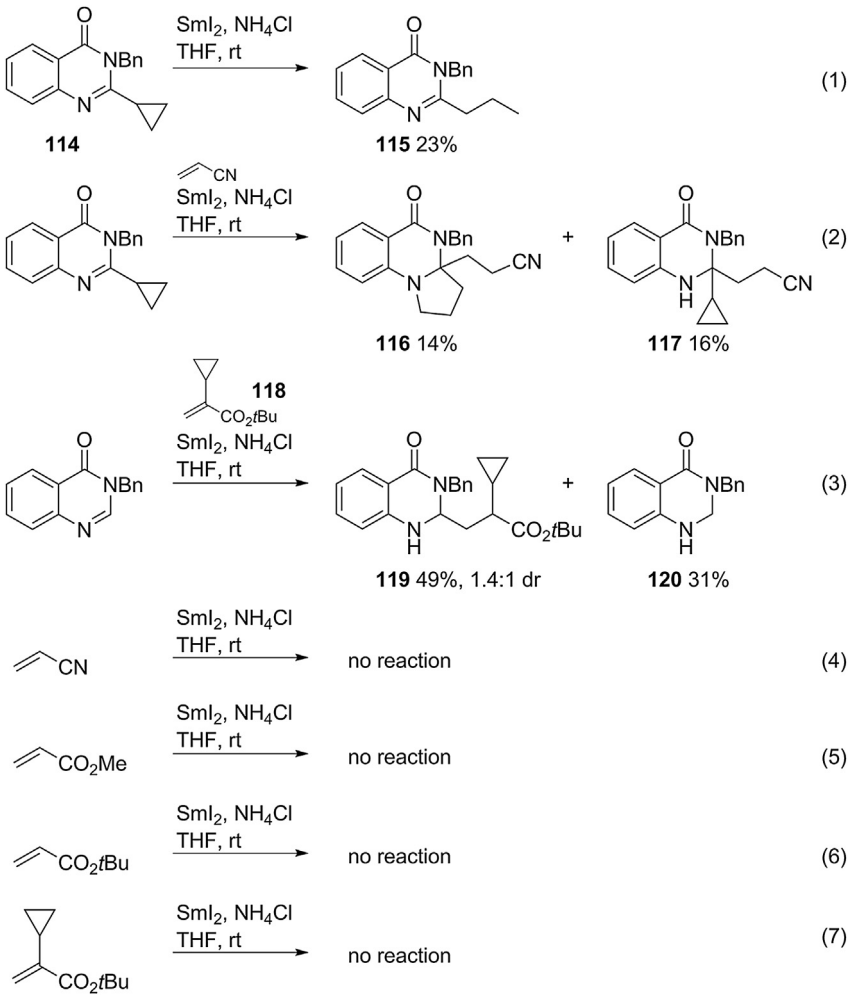
carried out with SiliaFlash P60, 60 Å silica gel. Reactions and column chromatography were monitored with EMD silica gel 60 F_{254} plates and visualized with potassium permanganate, iodine, ninhydrin, or vanillin stains. Tetrahydrofuran (THF) and methylene chloride (DCM) were dried by passage through activated alumina columns. Benzene (PhH) was dried over CaH_2, distilled under an atmosphere of argon, and degassed by three freeze–pump–thaw cycles. Methyl acrylate and *tert*-butyl acrylate were purified by washing with aqueous NaOH, drying over $MgSO_4$, and calcium hydride. These reagents were then distilled under vacuum prior to use. Acrylonitrile was distilled under vacuum prior to use. Bu_3SnH and BnSH were dried over CaH_2 and distilled under vacuum prior to use. Samarium iodide solutions were prepared with THF distilled from sodium and benzophenone and were stored over an atmosphere of argon with vigorous stirring.[48] The concentrations of the samarium iodide solutions were determined by iodometirc titration. All other reagents and solvents were used without further purification from commercial sources. FTIR spectra were measured using NaCl plates. Multiplicities are abbreviated as follows: s=singlet, d=doublet, t=triplet, q=quartet, quin=quintet, br=broad, m=multiplet. Melting points are uncorrected.

4.2. Experimental procedures and data of synthetic intermediates

*4.2.1. 3-(2-Iodobenzyl)-1,2,3,4-tetrahydroquinazoline (**12**).* To a solution of 2-iodobenzyliodide[49] (0.2301 g, 0.690 mmol) and K_2CO_3



Scheme 11. Possible mechanisms of the amidine reduction reaction.



Scheme 12. Mechanistic investigations.

(0.1819 g, 1.32 mmol) in a mixture of water (0.5 mL, 1.4 M) and THF (2 mL, 0.35 M) was added 1,2,3,4-tetrahydroquinazoline[50] (0.1800 g, 1.34 mmol). The mixture was stirred at room temperature for 12 h. At this time, TLC indicated the consumption of 2-iodobenzyliodide. The reaction mixture was concentrated. Flash column chromatography (9:1 hexanes/EtOAc) gave **12** (0.2202 g, 0.629 mmol, 91%) as a yellow oil.

Data for **12**: R_f 0.36 (4:1 hexanes/EtOAc); IR (thin film) 2928, 2847, 1606 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, J=7.6, 0.8 Hz, 1H), 7.47 (dd, J=7.6, 1.6 Hz, 1H), 7.34 (td, J=7.2, 0.8 Hz, 1H),

7.06 (td, *J*=7.6, 1.2 Hz, 1H), 6.98 (td, *J*=7.6, 1.6 Hz, 1H), 6.73 (td, *J*=7.2, 1.2 Hz, 1H), 6.61 (d, *J*=8.0 Hz, 1H), 4.13 (s, 2H), 3.94 (s, 2H), 3.79 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 141.0, 139.6, 130.4, 128.9, 128.2, 127.7, 127.3, 120.1, 118.4, 115.3, 100.7, 63.0, 61.0, 53.2; HRMS (TOF MS ES$^+$) calcd for $C_{15}H_{16}N_2I$ [M+H]: 351.0358, found 351.0347.

*4.2.2. Methyl 3-(3-benzyl-1,2,3,4-tetrahydroquinazolin-2-yl)propanoate (**13**), methyl 3-(3-benzyl-1,2,3,4-tetrahydroquinazolin-4-yl) propanoate (**14**), dimethyl 3,3′-(3-benzyl-1,2,3,4-tetrahydroquinazoline-2,4-diyl)dipropionate (**15**), and 3-benzyl-1,2,3,4-tetrahydroquinazoline (**16**). Representative procedure for the radical translocation reactions of **12***: Compound **12** (0.2030 g, 0.580 mmol) and methyl acrylate (0.16 mL, 1.8 mmol) were dissolved in PhH (4.6 mL, 0.13 M) and the mixture was heated to reflux. A PhH solution (1.2 mL) containing AIBN (0.0198 g, 0.121 mmol) and Bu_3SnH (0.31 mL, 1.2 mmol) was added by syringe pump to the refluxing solution over a period of 1.2 h. After 15 h, the mixture was cooled to room temperature, concentrated, and redissolved in MeCN. The MeCN solution was washed with hexanes, concentrated, and purified by flash column chromatography (8:1 hexanes/EtOAc) to give a 1:1 mixture of **13** and **14** (0.0542 g, 0.1748 mmol, 30%) as a colorless oil, **15** (0.0155 g, 0.0391 mmol, 6.7%) as a colorless oil, and 3-benzyl-1,2,3,4-tetrahydroquinazoline (**16**) (0.0462 g, 0.206 mmol, 36%).

Data for **13**: R_f 0.28 (4:1 hexanes/EtOAc); IR (thin film) 2920, 1732 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.23–7.34 (m, 5H), 7.04 (t, *J*=7.7 Hz, 1H), 6.86 (d, *J*=7.0 Hz, 1H), 6.67 (t, *J*=7.7 Hz, 1H), 6.53 (d, *J*=7.7 Hz, 1H), 4.09 (t, *J*=7.7 Hz, 1H), 4.03 (br s, 1H), 3.97 (d, *J*=16.8 Hz, 1H), 3.60–3.73 (m, 6H), 2.44–2.53 (m, 2H), 2.04–2.09 (m, 1H), 1.89–1.94 (m, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 174.1, 142.2, 139.4, 128.9, 128.4, 127.9, 127.4, 127.1, 118.3, 117.8, 114.4, 69.4, 55.2, 51.8, 48.1, 30.0, 29.7; HRMS (TOF MS ES$^+$) calcd for $C_{19}H_{23}N_2O_2$ [M+H]: 311.1760, found 311.1770.

Data for **14**: R_f 0.28 (4:1 hexanes/EtOAc); IR (thin film) 2950, 1732, 1607 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.03–7.35 (m, 4H), 7.25–7.27 (m, 1H), 7.05 (td, *J*=7.7, 1.4 Hz, 1H), 6.98 (dd, *J*=7.7, 1.4 Hz, 1H), 6.71 (td, *J*=7.0, 1.4 Hz, 1H), 6.57 (dd, *J*=8.4, 1.4 Hz, 1H), 4.33 (d, *J*=11.9 Hz, 1H), 3.90 (br s, 1H), 3.83 (d, *J*=13.3 Hz, 1H), 3.81 (dd, *J*=11.9, 1.4 Hz, 1H), 3.63 (s, 3H), 3.56 (d, *J*=13.3 Hz, 1H), 3.50 (dd, *J*=11.2, 4.9 Hz, 1H), 2.55 (ddd, *J*=16.8, 7.7, 6.3 Hz, 1H), 2.46 (ddd, *J*=14.7, 7.7, 7.7 Hz, 1H), 1.99–2.08 (m, 2H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 174.5, 142.6, 139.3, 129.3, 128.9, 128.3, 127.4, 127.2, 122.9, 117.9, 114.8, 59.0, 57.1, 56.0, 51.6, 33.0, 30.92; HRMS (TOF MS ES$^+$) calcd for $C_{19}H_{23}N_2O_2$ [M+H]: 311.1760, found 311.1750.

Data for **15**: R_f 0.14 (4:1 hexanes/EtOAc); IR (thin film) 2950, 2851, 1735, 1692, 1493 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.34 (m, 5H), 6.99 (td, *J*=8.4, 1.6 Hz, 1H), 6.95 (d, *J*=7.2 Hz, 1H), 6.32 (t, *J*=7.6 Hz, 1H), 5.31 (s, 1H), 4.37 (t, *J*=6.0 Hz, 1H), 3.94 (d, *J*=14.0 Hz, 1H), 3.66 (s, 3H), 3.54 (s, 3H), 3.09 (d, *J*=14.0 Hz, 1H), 2.63 (t, *J*=8.0 Hz, 2H), 2.44 (dt, *J*=16.8, 6.8 Hz, 1H), 2.24–2.32 (m 1H), 2.09 (q, *J*=7.2 Hz, 2H), 2.93 (q, *J*=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 173.7, 143.2, 139.5, 129.1, 128.9, 128.3, 127.1, 126.1, 123.0, 118.4, 114.7, 64.1, 58.0, 51.8, 51.4, 49.1, 32.2, 30.4, 29.4, 27.6; HRMS (CI$^+$) calcd for $C_{23}H_{29}N_2O_4$ [M+H]: 397.2127, found 397.2129.

*4.2.3. 3-(3-Benzyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)propanenitrile (**29**). General reductive alkylation procedure*: To a solution of 3-benzylquinazolin-4(3*H*)-one[51] (0.0327 g, 0.1390 mmol), NH_4Cl (0.0089 g, 0.166 mmol), and acrylonitrile (0.05 mL, 0.76 mmol) in THF (0.46 mL, 0.3 M) was added a THF solution of SmI_2 (3.7 mL, 0.35 mmol) via syringe pump over a period of 1 h. At this time, TLC indicated the consumption of 3-benzylquinazolin-4(3*H*)-one. The reaction mixture was diluted with half-saturated aqueous Rochelle salt. This biphasic mixture was extracted with ethyl acetate. The combined extracts were dried over $MgSO_4$, filtered, and concentrated to give known the adduct **29** (0.0403 g, 0.1383 mmol, 99%) as a colorless oil.

*4.2.4. 2-((2-Iodobenzyl)amino)benzamide (**S1**).* To a solution of 2-aminobenzamide (0.3647 g, 2.68 mmol) and K_2CO_3 (1.1117 g, 8.044 mmol) in DMF (4.5 mL, 0.6 M) was added 2-iodobenzyliodide (1.1087 g, 3.22 mmol). The mixture was stirred at room temperature for 15 h. At this time, TLC indicated the consumption of 2-aminobenzamide. The reaction mixture was diluted with EtOAc, washed with saturated aqueous LiCl, dried over anhydrous $MgSO_4$, filtered, and concentrated. Recrystallization from MeOH gave **S1** (0.9795 g, 2.7 mmol, 100%) as a white solid.

Data for **S1**: R_f 0.38 (1:3 hexanes/EtOAc); mp=160–162 °C; IR (thin film) 3366, 3190, 1649, 1640, 1619, 1511 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.47 (br s, 1H), 7.85 (dd, *J*=7.7, 0.7 Hz, 1H), 7.42 (dd, *J*=7.7, 1.4 Hz, 1H), 7.33 (d, *J*=7.7 Hz, 1H), 7.24–7.28 (m, 2H), 6.95 (td, *J*=7.7, 2.1 Hz, 1H), 6.61 (td, *J*=7.7, 0.7 Hz, 1H), 6.49 (d, *J*=8.4 Hz, 1H), 5.91 (br s, 1H), 5.58 (br s, 1H), 4.39 (s, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 172.2, 150.0, 140.5, 139.5, 133.8, 129.0, 128.6, 128.4, 128.2, 115.3, 113.3, 112.6, 98.3, 52.4; HRMS (TOF MS ES$^+$) calcd for $C_{14}H_{14}N_2OI$ [M+H]: 353.0151, found 353.0144.

*4.2.5. 1-(2-Iodobenzyl)-2-phenyl-2,3-dihydroquinazolin-4(1H)-one (**30**).* To a solution of **S1** (0.483 g, 0.137 mmol) and benzaldehyde (0.02 mL, 0.19 mmol) in DCM (1.4 mL, 0.1 M) was added boron trilfluoride diethyletherate (0.04 mL, 0.32 mmol). The mixture was stirred at room temperature for 24 h. The reaction mixture was then quenched by addition of saturated aqueous $NaHCO_3$, and the biphasic mixture was separated. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. Flash column chromatography (2:1 hexanes/EtOAc) gave **30** (0.0549 g, 0.125 mmol, 91%) as a white solid.

Data for **30**: R_f 0.31 (1:1 hexanes/EtOAc); mp=153–155 °C; IR (thin film) 2918, 1667, 1607, 1489 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.01 (dd, *J*=7.7, 1.4 Hz, 1H), 7.82 (dd, *J*=7.7, 0.7 Hz, 1H), 7.39 (dd, *J*=7.7, 1.4 Hz, 2H), 7.32–7.37 (m, 5H), 7.28 (t, *J*=7.7 Hz, 1H), 6.97 (td, *J*=7.7, 1.4 Hz, 1H), 6.89 (t, *J*=7.7 Hz, 1H), 6.47 (d, *J*=8.4 Hz, 1H), 6.32 (s, 1H), 5.97 (d, *J*=2.1 Hz, 1H), 4.37 (d, *J*=16.8 Hz, 1H), 4.16 (d, *J*=16.8 Hz, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 164.0, 147.3, 139.8, 138.9, 138.0, 134.6, 129.8, 129.3, 129.0, 128.6, 128.3, 127.2, 119.1, 116.5, 113.6, 97.8, 73.4, 57.2; HRMS (TOF MS ES$^+$) calcd for $C_{21}H_{18}IN_2O$ [M+H]: 441.0464, found 441.0455.

*4.2.6. tert-Butyl 3-(2-iodobenzyl)tetrahydropyrimidine-1(2H)-carboxylate (**44a**).* To a solution of 1-(2-iodobenzyl)hexahydropyrimidine (0.4342 g, 1.44 mmol) in a 1:1 mixture of acetone and water (9.6 mL, 0.15 M) was added Boc_2O (0.3763 g, 1.73 mmol). The mixture was stirred at room temperature for 24 h. The acetone was then removed by rotary evaporation and the aqueous mixture was extracted with EtOAc. The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated. Flash column chromatography (8:1 hexanes/EtOAc) gave **44a** (0.5229 g, 1.30 mmol, 90%) as a colorless oil that solidified upon standing.

Data for **44a**: R_f 0.42 (4:1 hexanes/EtOAc); mp=47–49 °C; IR (thin film) 2928, 1695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J*=7.6 Hz, 1H), 7.47 (d, *J*=5.6 Hz, 1H), 7.34 (t, *J*=7.2 Hz, 1H), 6.97 (t, *J*=7.6 Hz, 1H), 4.17 (br s, 2H), 3.64 (s, 2H), 3.53 (t, *J*=5.2 Hz, 2H), 2.85 (br s, 2H), 1.71 (br s, 2H), 1.43 (s, 9H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 154.7, 140.6, 139.6, 130.0, 128.9, 128.2, 100.5, 65.4, 61.2, 52.3, 43.3, 28.5, 22.9; HRMS (TOF MS ES$^+$) calcd for $C_{16}H_{24}IN_2O_2$ [M+H]: 403.0883, found 403.0896.

*4.2.7. Methyl 3-(2-iodobenzyl)tetrahydropyrimidine-1(2H)-carboxylate (**44b**).* To a solution of 1-(2-iodobenzyl)hexahydropyrimidine (0.7488 g, 1.59 mmol) in DCM (10.5 mL, 0.15 M) was added methyl

chloroformate (0.15 mL, 1.94 mmol). The reaction mixture was stirred at room temperature for 15 h. The reaction mixture was then washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Flash column chromatography (5:1 hexanes/EtOAc) gave **44b** (0.5682 g, 1.58 mmol, 64%) as a colorless oil.

Data for **44b**: R_f 0.29 (4:1 hexanes/EtOAc); IR (thin film) 2928, 1695 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.83 (d, J=7.7 Hz, 1H), 7.44 (d, J=37.1 Hz, 1H), 7.32 (t, J=7.7 Hz, 1H), 6.96 (br s, 1H), 4.20 (d, J=27.3 Hz, 2H), 3.70 (d, J=16.8 Hz, 3H), 3.63 (s, 2H), 3.57 (br s, 2H), 2.81 (br s, 2H), 1.74–1.65 (m, 2H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 155.9, 140.4, 139.5, 130.1, 128.9, 128.1, 100.4, 65.2, 61.1, 52.6, 51.8, 43.8, 22.7; HRMS (TOF MS ES$^+$) calcd for $C_{13}H_{18}N_2O_2I$ [M+H]: 361.0413, found 361.0415.

*4.2.8. 1-(2-Iodobenzyl)-3-tosylhexahydropyrimidine (**44c**).* To a solution of 1-(2-iodobenzyl)hexahydropyrimidine (0.1640 g, 0.543 mmol) in a 2:1 mixture of DCM/H_2O (1.65 mL, 0.33 M) were added K_2CO_3 (0.1543 g, 1.12 mmol) and TsCl (0.0932 g, 0.489 mmol). The mixture was stirred at room temperature for 17 h. The reaction mixture was then diluted with brine and the layers were separated. The aqueous mixture was extracted twice with DCM and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. Flash column chromatography (4:1 hexanes/EtOAc) gave **44c** (0.1930 g, 0.423 mmol, 87%) as a colorless oil.

Data for **44c**: R_f 0.57 (3:1 hexanes/EtOAc); IR (thin film) 2860, 1651, 1645 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.84 (dd, J=7.7, 0.7 Hz, 1H), 7.63 (d, J=8.4 Hz, 2H), 7.37 (d, J=7.7 Hz, 1H), 7.33 (td, J=7.0, 0.7 Hz, 1H), 7.30 (d, J=7.7 Hz, 2H), 6.97 (td, J=7.7, 1.4 Hz, 1H), 4.01 (s, 2H), 3.78 (s, 2H), 3.25 (s, 2H), 2.76 (t, J=4.9 Hz, 2H), 2.43 (s, 3H), 1.69 (br s, 2H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 143.5, 140.4, 139.7, 135.0, 130.8, 129.2, 128.3, 127.6, 101.0, 67.2, 60.3, 50.7, 46.1, 21.7, 21.2; HRMS (TOF MS ES$^+$) calcd for $C_{18}H_{21}N_2O_2IS$ [M+H]: 457.0447, found 457.0461.

*4.2.9. tert-Butyl (3-(2-iodobenzamido)propyl)carbamate (**S2**).* To a solution of 2-iodobenzoic acid (0.5464 g, 2.20 mmol) in DCM (11 mL, 0.20 M) were added HOBt (80% in water) (0.4116 g, 2.44 mmol), DCC (0.5063 g, 2.45 mmol), and *tert*-butyl (3-aminopropyl)carbamate[52] (0.4255 g, 2.44 mmol). The mixture was stirred at room temperature for 16 h. The reaction mixture was then filtered through Celite and the solids were rinsed with EtOAc. The filtrate was washed with 1 M aqueous citric acid, saturated aqueous $NaHCO_3$, and brine. The combined organic layers were then dried over anhydrous $MgSO_4$, filtered, and concentrated. Flash column chromatography (2:1 hexanes/EtOAc) gave **S2** (0.6865 g, 1.70 mmol, 77%) as a white solid.

Data for **S2**: R_f 0.19 (1:2 hexanes/EtOAc); mp=112–113 °C; IR (thin film) 3365, 2917, 1649 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.85 (d, J=7.7 Hz, 1H), 7.35–7.39 (m, 2H), 7.09 (ddd, J=7.7, 6.3, 2.8 Hz, 1H), 6.48 (s, 1H), 6.97 (s, 1H), 4.97 (q, J=6.3 Hz, 2H), 3.30 (q, J=6.3 Hz, 2H), 1.76 (quin, J=6.3 Hz, 2H), 1.42 (s, 9H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 170.0, 156.9, 142.5, 140.0, 131.2, 128.3, 128.2, 92.7, 79.6, 37.3, 36.6, 30.3, 28.5; HRMS (TOF MS ES$^+$) calcd for $C_{15}H_{21}N_2O_3NaI$ [M+Na]: 427.0495, found 427.0487.

*4.2.10. 3-(2-Iodobenzamido)propan-1-aminium 2,2,2-trifluoroacetate (**S3**).* To a suspension of **S2** (0.011 g, 0.0272 mmol) in DCM (0.05 mL, 0.50 M) was added trifluoroacetic acid (0.05 mL, 0.653 mmol). The mixture was stirred at room temperature for 1 h. The reaction mixture was then concentrated under vacuum to give **S3** (0.0102 g, 0.0244 mmol, 90%) as a colorless oil.

Data for **S3**: R_f 0.06 (4:1 EtOAc/10% NH_4OH in MeOH); IR (thin film) 2949, 1623 cm^{-1}; ^1H NMR (700 MHz, CD_3OD) δ 7.91 (dd, J=8.4, 0.7 Hz, 1H), 7.45 (td, J=7.7, 1.4 Hz, 1H), 7.37 (dd, J=7.7, 1.4 Hz, 1H), 7.18 (ddd, J=8.4, 7.7, 2.1 Hz, 1H), 3.48 (t, J=7.7 Hz, 2H), 3.12 (t, J=7.7 Hz, 2H), 1.97–2.02 (m, 2H); ^{13}C NMR (176 MHz, CD_3OD) δ 172.0, 160.9 (q, J=35.2 Hz), 142.3, 139.5, 130.9, 128.0, 127.6, 116.5 (q, J=292.2 Hz), 91.9, 37.1, 36.0, 27.3; HRMS (TOF MS ES$^+$) calcd for $C_{10}H_{14}N_2OI$ [M$^+$]: 305.0151, found 305.0163.

*4.2.11. (2-Iodophenyl)(tetrahydropyrimidin-1(2H)-yl)methanone (**46**).* To a solution of **S3** (0.2096 g, 0.501 mmol) in EtOH (1.7 mL, 0.3 M), 0.08 mL (0.6 mmol) of 30% aqueous NaOH and 0.05 mL (0.6 mmol) of 36% aqueous formaldehyde solution were added. The reaction mixture was heated to reflux for 19 h. At this time, the reaction mixture was concentrated. Flash column chromatography (19:1 EtOAc/10% NH_4OH in MeOH) gave **46** (0.1413 g, 0.447 mmol, 89%) as a white foam.

Data for **46**: R_f 0.44 (9:1 EtOAc/10% NH_4OH in MeOH); IR (thin film) 2942, 2859, 1628, 1428 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) as a mixture of amide rotamers δ 7.82 (d, J=7.7 Hz, 1H), 7.37–7.40 (m, 1H), 7.20 (ddd, J=19.6, 7.7, 1.4 Hz, 1H), 7.08 (td, J=7.7, 1.4 Hz, 1H), 4.85 (d, J=12.6 Hz, 0.5H), 4.66 (d, J=12.6 Hz, 0.5H), 4.18 (d, J=13.3 Hz, 0.5H), 4.09–4.13 (m, 0.5H), 4.08 (d, J=13.3 Hz, 0.5H), 3.70 (ddd, J=16.1, 8.4, 3.5 Hz, 0.5H), 3.37–3.41 (m, 0.5H), 3.30–3.33 (m, 0.5H), 3.07–3.15 (m, 1.5H), 3.00–3.04 (m, 0.5H), 1.78–1.84 (m, 0.5H), 1.68–1.74 (m, 1H), 1.58–1.63 (m, 0.5H); ^{13}C NMR (176 MHz, $CDCl_3$) as a mixture of amide rotamers δ 169.2, 168.6, 142.0, 141.7, 139.3, 139.3, 130.6, 130.5, 128.7, 128.6, 127.3, 127.4, 92.5, 92.3, 62.9, 57.1, 64.6, 45.3, 44.8, 41.6, 27.0, 27.0; HRMS (TOF MS ES$^+$) calcd for $C_{11}H_{14}N_2OI$ [M+H]: 317.0151, found 317.0157.

*4.2.12. (1,4-Dihydroquinazolin-3(2H)-yl)(2-iodophenyl)methanone (**47**).* To a solution of 1,2,3,4-tetrahydroquinazoline (0.8921 g, 6.65 mmol) in DCM (22 mL, 0.30 M) were added 2-iodobenzoic acid (1.9783 g, 7.98 mmol), HOBt (80% in water) (1.3430 g, 7.95 mmol), and DCC (1.6464 g, 7.98 mmol). The mixture was stirred at room temperature for 16 h. The reaction mixture was then washed with 1 M aqueous citric acid, saturated aqueous $NaHCO_3$, and brine. The combined organic layers were then dried over anhydrous $MgSO_4$, filtered, and concentrated. Flash column chromatography (2:1 hexanes/EtOAc) gave **47** (2.084 g, 5.72 mmol, 91%) as a white foam.

Data for **47**: R_f 0.52 (1:1 EtOAc/hexanes); IR (thin film) 3006, 2849, 1633 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) as a mixture of rotamers δ 7.86 (ddt, J=10.5, 7.7, 0.7 Hz, 1H), 7.41 (dddd, J=16.1, 7.7, 7.7, 0.7 Hz, 1H), 7.30 (dd, J=7.7, 1.4 Hz, 0.5H), 7.21 (dd, J=7.7 2.1 Hz, 0.5H), 7.08–7.14 (m, 2.5H), 6.89 (td, J=7.7, 0.7 Hz, 0.5H), 6.80 (dt, J=16.8, 7.0 Hz, 1H), 6.74 (d, J=7.7 Hz, 0.5H), 6.70 (d, J=7.7 Hz, 0.5H), 5.17 (dd, J=11.2, 3.5 Hz, 0.5H), 5.10 (d, J=16.8 Hz, 0.5H), 4.88 (dd, J=11.9, 3.5 Hz, 0.5H), 4.83 (d, J=16.8 Hz, 0.5H), 4.48–4.52 (m, 1H), 4.42 (dd, J=11.2, 3.5 Hz, 0.5H), 4.31 (d, J=16.1 Hz, 0.5H), 4.20 (br s, 0.5H), 3.95 (br s, 0.5H); ^{13}C NMR (176 MHz, $CDCl_3$) as a mixture of rotamers δ 169.4, 169.3, 142.7, 141.9, 141.8, 139.4, 130.7, 130.7, 128.6, 128.6, 127.9, 127.6, 127.5, 127.5, 127.3, 126.8, 120.7, 120.5, 120.1, 120.1, 117.8, 117.5, 92.7, 92.3, 58.0, 53.3, 47.8, 43.3; HRMS (TOF MS ES$^+$) calcd for $C_{15}H_{14}N_2OI$ [M+H]: 365.0151, found 365.0155.

*4.2.13. Ethyl (E)-6-(3-(2-iodobenzyl)tetrahydropyrimidin-1(2H)-yl)-6-oxohex-2-enoate (**52**).* To a solution of 1-(2-iodobenzyl)hexahydropyrimidine (0.1168 g, 0.556 mmol) in DCM (2.2 mL, 0.25 M) were added (*E*)-6-ethoxy-6-oxohex-4-enoic acid[53] (0.1059 g, 0.615 mmol), HOBt (80% in water) (0.1078 g, 0.638 mmol), and DCC (0.1279 g, 0.620 mmol). The mixture was stirred at room temperature for 2 h. The reaction mixture was then filtered, diluted with EtOAc, washed with 1 M aqueous citric acid, saturated aqueous $NaHCO_3$, and brine. The combined organic layers were then dried over anhydrous $MgSO_4$, filtered, and concentrated. Flash column chromatography (3:2 hexanes/EtOAc) gave **52** (0.0639 g, 0.140 mmol, 25%) as a colorless oil.

Data for **52**: R_f 0.42 (1:1 EtOAc/hexanes); IR (thin film) 2922, 1716, 1649, 1435 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) as a 2:1 mixture

of amide rotamers δ 7.85 (dd, J=8.0, 1.2 Hz, 0.6H), 7.81 (d, J=8.0 Hz, 0.4H), 7.31–7.46 (m, 2H), 6.84–7.04 (m, 2H), 5.87 (d, J=15.6 Hz, 0.4H), 5.71 (dt, J=15.6, 1.6 Hz, 0.6H), 4.34 (s, 0.8H), 4.18 (q, J=7.2 Hz, 2H), 4.01 (s, 1.2H), 3.16–3.64 (m, 2H), 3.58 (s, 1.2H), 3.35 (t, J=5.6 Hz, 0.8H), 2.84 (t, J=5.2 Hz, 0.8H), 2.79 (t, J=5.6 Hz, 1.2H), 2.25–2.60 (m, 2.8H), 2.22–2.26 (m, 1.2H), 1.66–1.75 (m, 2H), 1.25–1.3 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) as a 2:3 mixture of amide rotamers δ 170.5, 170.0, 166.6, 174.8, 140.0, 139.9, 139.6, 130.5, 129.4, 129.0, 128.4, 122.2, 121.8, 100.7, 66.7, 63.1, 62.3, 61.5, 60.4, 60.3, 53.0, 51.8, 45.4, 42.2, 31.5, 31.1, 27.6, 27.5, 24.0, 23.8, 14.4; HRMS (TOF MS ES$^+$) calcd for $C_{19}H_{26}N_2O_3I$ [M+H]: 457.0988, found 457.0971.

*4.2.14. Ethyl (E)-6-(1-(2-iodobenzyl)-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)hex-2-enoate (**56**).* To a solution of **S1** (1.3201 g, 3.75 mmol) and ethyl (*E*)-7-oxohept-2-enoate[54] (0.7731 g, 4.54 mmol) in DCM (37 mL, 0.1 M) was added boron trifluoride diethyletherate (0.95 mL, 7.56 mmol). The mixture was stirred at room temperature for 21 h. The reaction mixture was then quenched by addition of saturated aqueous $NaHCO_3$, and the biphasic mixture was separated. The aqueous layer was extracted with EtOAc, the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. Flash column chromatography (1:1 hexanes/EtOAc) gave **56** (0.9909 g, 1.96 mmol, 52%) as a white foam.

Data for **56**: R_f 0.15 (1:1 EtOAc/hexanes); IR (thin film) 2937, 1714, 1667, 1607, 1491 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.00 (br s 1H), 7.93 (d, J=7.7 Hz, 1H), 7.86 (d, J=7.7 Hz, 1H), 7.34 (d, J=7.7 Hz, 1H), 7.21–7.31 (m, 2H), 6.99 (t, J=7.0 Hz, 1H), 6.83–6.89 (m, 2H), 6.54 (d, J=7.7 Hz, 1H), 5.77 (d, J=16.1 Hz, 1H), 4.60–4.64 (m, 2H), 4.20 (d, J=16.1 Hz, 1H), 4.14 (q, J=7.0 Hz, 2H), 2.13–2.21 (m, 2H), 1.85–1.91 (m, 1H), 1.71–1.76 (m, 1H), 1.57–1.64 (m, 1H), 1.48–1.54 (m, 1H), 1.25 (t, J=7.0 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 166.6, 164.5, 148.1, 146.2, 139.8, 138.2, 134.3, 129.5, 128.8, 128.7, 122.1, 118.8, 117.1, 114.0, 98.2, 70.0, 60.3, 58.2, 33.7, 31.7, 23.0, 14.4; HRMS (TOF MS ES$^+$) calcd for $C_{23}H_{26}N_2O_3I$ [M+H]: 505.0988, found 505.0979.

*4.2.15. 2-(Pent-4-en-1-yl)-2,3-dihydroquinazolin-4(1H)-one (**S4**).* To a solution of 2-aminobenzamide (0.1111 g, 0.677 mmol) and hex-5-enal (0.4162 g, 4.24 mmol) in EtOH (6.3 mL, 0.6 M) was added 0.10 mL (0.75 mmol) of 30% aqueous NaOH. The mixture was heated at reflux for 24 h. The reaction mixture was then diluted with brine and the biphasic mixture was separated. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. Flash column chromatography (3:2 hexanes/EtOAc) gave **S4** (0.0756 g, 0.350 mmol, 8%) as a white solid.

Data for **S4**: R_f 0.23 (1:1 EtOAc/hexanes); mp=137–139 °C; IR (thin film) 2852, 1634 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.88 (dd, J=7.7, 1.4 Hz, 1H), 7.31 (ddd, J=8.4, 7.7, 2.1 Hz, 1H), 6.59 (ddd, J=7.7, 7.7, 0.7 Hz, 1H), 6.67 (d, J=7.7 Hz, 1H), 6.13 (br s, 1H), 5.79 (ddd, J=9.8, 6.3, 6.3 Hz, 1H), 5.00–5.06 (m, 2H), 4.90 (td, J=5.6, 0.7 Hz, 1H), 4.20 (br s, 1H), 2.14 (q, J=7.0 Hz, 2H), 1.78 (ddd, J=7.7, 7.7, 5.6 Hz, 2H), 1.51–1.61 (m, 2H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 165.4, 147.5, 137.7, 134.0, 128.8, 119.6, 116.0, 115.8, 114.9, 65.4, 35.0, 33.3, 23.3; HRMS (TOF MS ES$^+$) calcd for $C_{13}H_{17}N_2O$ [M+H]: 217.1341, found 217.1342.

*4.2.16. 3-(2-Iodobenzyl)-2-(pent-4-en-1-yl)-2,3-dihydroquinazolin-4(1H)-one (**57**).* To a solution of **S4** (0.2487 g, 1.15 mmol) and NaOH (0.0984 g, 2.46 mmol) in THF (4 mL, 0.3 M) was added 2-iodobenzyliodide (0.4478 g, 1.30 mmol). The mixture was heated to reflux for 15 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc, washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Flash column chromatography (8:1 hexanes/EtOAc) gave **57** (0.1937 g, 0.448 mmol, 39%) as a white foam.

Data for **57**: R_f 0.21 (1:7 EtOAc: hexanes); IR (thin film) 2935, 1629 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.95 (dd, J=8.4, 1.4 Hz, 1H), 7.83 (dd, J=8.4, 1.4 Hz, 1H), 7.42 (dd, J=7.7, 1.4 Hz, 1H), 7.28–7.32 (m, 2H), 6.97 (td, J=7.7, 0.7 Hz, 1H), 6.86 (td, J=7.7, 0.7 Hz, 1H), 6.65 (dd, J=7.7, 0.7 Hz, 1H), 5.71 (ddd, J=10.5, 7.0, 7.0 Hz, 1H), 5.46 (d, J=15.4 Hz, 1H), 4.30–4.97 (m, 2H), 4.51 (dd, J=9.1, 3.5 Hz, 2H), 4.10 (d, J=15.4 Hz, 1H), 2.00–2.04 (m, 2H), 1.89–1.95 (m, 1H), 1.71 (dddd, J=23.1, 10.5, 5.6, 3.5 Hz, 1H), 1.41–1.47 (m, 1H), 1.32–1.38 (m, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 162.4, 145.2, 139.6, 139.2, 137.8, 133.7, 129.3, 128.9, 128.9, 128.7, 119.3, 116.7, 115.5, 115.2, 98.8, 68.8, 52.4, 33.2, 32.4, 24.1; HRMS (TOF MS ES$^+$) calcd for $C_{20}H_{22}N_2OI$ [M+H]: 433.0777, found 433.0789.

*4.2.17. N-(Hydroxymethyl)-N-(2-iodobenzyl)formamide (**67**).* To a solution of known *N*-(2-iodobenzyl)formamide[55] (224 mg, 0.857 mmol) in THF (4.3 mL) were added paraformaldehyde (31 mg, 1.03 mmol) and K_2CO_3 (142 mg, 1.03 mmol) at room temperature and the reaction was monitored by TLC. After 12 h, the reaction mixture was diluted with Et_2O, washed with brine, and dried over $NaSO_4$. Purification by flash column chromatography (2:1 EtOAc/hexanes) afforded **67** (168 mg, 67%) as a colorless oil.

Data for **67**: R_f 0.25 (2:1 EtOAc/hexanes); IR (thin film) 3356, 2921, 1667, 1438, 1403, 1013 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.38 (d, J=21.2 Hz, 1H), 7.89 (ddd, J=14, 8, 1.2 Hz, 1H), 7.38 (dtd, J=20, 7.6, 1.2 Hz, 1H), 7.29 (td, J=5.6, 2 Hz, 1H), 7.04 (dtd, J=18.8, 7.6, 1.6 Hz, 1H), 4.82 (d, J=3.6 Hz, 2H), 4.75 (s, 1H), 4.59 (s, 1H), 1.68 (br s, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 164.9, 163.2, 140.1, 139.7, 138.5, 137.8, 129.9, 129.6, 129.4, 129.2, 128.9, 128.8, 99.2, 98.6, 71.8, 67.6, 55.1, 49.3; HRMS (TOF MS ES$^+$) calcd for [M+H]: $C_9H_{10}INO_2$ 291.9836, found 291.9835.

*4.2.18. N-((1H-Indol-1-yl)methyl)-N-(2-iodobenzyl)formamide (**68**).* To a solution of *N*,*O*-acetal **67** (38 mg, 0.131 mmol) in DMF (0.53 mL) at 0 °C was added dropwise PBr_3 (0.01 mL, 0.053 mmol). After 2.5 h at 0 °C, another portion of PBr_3 (0.01 mL, 0.053 mmol) was added and allowed to slowly warm to room temperature. After 4.5 h, indole (15 mg, 0.131 mmol) was added and was stirred overnight at room temperature. The reaction mixture was diluted with Et_2O and washed with water. The aqueous layer was extracted with Et_2O and the combined organic layers were dried over Na_2SO_4. Purification by flash column chromatography (2:1 hexanes/EtOAc) afforded **68** (13.6 mg, 27%) as a colorless oil.

Data for **68**: R_f (3:2 hexanes/EtOAc); IR (thin film) 2918, 2850, 1659, 1437, 1014 cm^{-1}; ^{1}H (700 MHz, $CDCl_3$), δ 8.55 (d, J=194 Hz, 1H), 8.15 (d, J=29 Hz, 1H), 7.89 (dd, J=36, 1.4 Hz, 1H), 7.62 (dd, J=140, 7.4 Hz, 1H), 7.41 (m, 2H), 7.31 (m, 1H), 7.27 (m, 1H), 7.19 (m, 3H), 7.13 (m, 1H), 7.03 (dtd, J=49, 15.3, 7.4 Hz, 1H), 4.68 (s, 1H), 4.57 (d, J=6.7 Hz, 2H), 4.34 (s, 1H); ^{13}C (176 MHz, $CDCl_3$) δ 163.6, 163.0, 140.1, 139.6, 138.2, 138.0, 136.6, 136.4, 129.6, 129.1, 128.6, 128.5, 128.5, 128.4, 126.7, 126.3, 124.6, 124.1, 122.8, 122.6, 120.3, 120.1, 119.6, 118.6, 111.5, 111.1, 110.6, 110.1, 98.7, 98.5, 54.6, 49.8, 43.0, 36.4; HRMS (TOF MS ES$^+$) calcd for [M+H]: $C_{17}H_{15}IN_2O$ 391.0290, found 391.0307.

*4.2.19. 3-Tosyl-3,4-dihydroquinazoline (**95c**).* To a solution of 3,4-dihydroquinazoline (0.0748 g, 0.556 mmol) and NEt_3 (0.12 mL, 0.86 mmol) in THF (1.4 mL, 0.4 M) was added TsCl (0.1201 g, 0.630 mmol). The mixture was stirred at room temperature for 23 h. The reaction mixture was then diluted with EtOAc, washed with saturated brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Flash column chromatography (4:1 hexanes/EtOAc) gave **95c** (0.0968 g, 0.338 mmol, 60%) as a white solid.

Data for **95c**: R_f 0.58 (2:1 EtOAc/hexanes); IR (thin film) 2917, 2849, 1620, 1597, 1350 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.88 (s,

1H), 7.79 (d, J=9.1 Hz, 1H), 7.38 (d, J=7.7 Hz, 1H), 7.19–7.23 (m, 2H), 7.12 (td, J=7.7, 2.1 Hz, 1H), 6.92 (dd, J=7.0, 0.7 Hz, 1H), 4.62 (s, 2H), 2.45 (s, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 145.6, 141.1, 138.6, 133.4, 130.5, 129.1, 127.8, 127.5, 126.3, 126.0, 120.4, 43.7, 21.8; HRMS (TOF MS ES$^+$) calcd for $C_{15}H_{15}N_2O_2S$ [M+H]: 287.0854, found 287.0840.

*4.2.20. 2-(Pent-4-en-1-yl)-1,2,3,4-tetrahydroquinazoline (**S11**).* To a solution of hex-5-enal[56] (0.2041 g, 2.08 mmol) and NH_4Cl (0.0185 g, 0.346 mmol) in EtOAc (10 mL, 0.1 M) was added 2-aminobenzylamine (0.2109 g, 1.7262 mmol). The mixture was stirred at room temperature for 0.5 h. At this time, TLC indicated the consumption of 2-aminobenzylamine. The reaction mixture was filtered through Celite and was then concentrated. A light yellow oil resulted. Flash column chromatography (3:1 hexanes/EtOAc) gave **S11** (0.2501 g, 1.236 mmol, 72%) as a colorless oil.

Data for **S11**: R_f 0.16 (1:1 hexanes/EtOAc); IR (thin film) 2928, 2849, 1607 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (td, J=8.0, 0.4 Hz, 1H), 6.89 (d, J=7.2 Hz, 1H), 6.68 (td, J=7.2, 0.8 Hz, 1H), 6.51 (d, J=8.0 Hz, 1H), 5.83 (dddd, J=23.6, 10.0, 6.4, 6.4 Hz, 1H), 4.97–5.07 (m, 2H), 4.11–4.16 (m, 2H), 3.95 (d, J=16.8 Hz, 1H), 3.88 (br s, 1H), 2.13 (q, J=6.8 Hz, 2H), 1.54–1.66 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 138.4, 127.3, 126.3, 121.7, 118.1, 115.1, 66.9, 46.7, 46.7, 36.1, 33.7, 24.3; HRMS (EI$^+$) calcd for $C_{13}H_{18}N_2$ [M$^+$]: 202.14700, found 202.14632.

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Supplementary data

Depiction of ^{1}H and ^{13}C NMR spectra of all new compounds. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.12.067.

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