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Reductive Synthesis of Aminal Radicals for Carbon–Carbon Bond Formation

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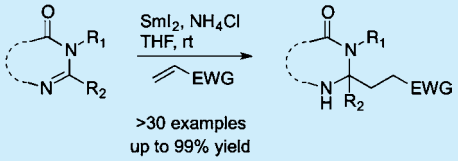
Supporting Information

ABSTRACT: Aminal radicals were generated by reduction of the corresponding amidine or amidinium ion. The intermediate radicals participate in C–C bond-forming reactions to produce fully substituted aminal stereocenters. No toxic additives or reagents are required. More than 30 substrate combinations are reported, and chemical yields are as high as 99%.



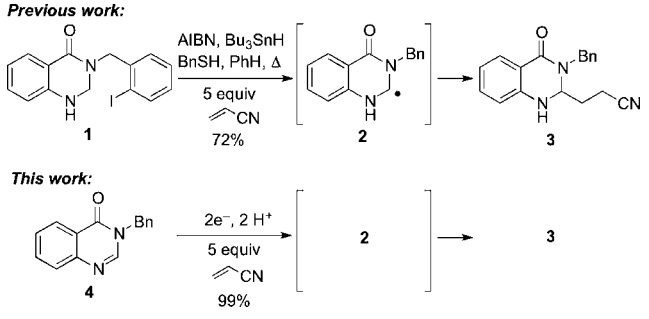
Biologically active molecules commonly contain one or more nitrogen atoms. As a result, nitrogenous molecules, such as alkaloids, make compelling targets for synthesis.[1] However, synthesis of molecules containing Lewis basic nitrogen atoms or Bronsted acidic nitrogenous functional groups is not trivial. For example, the Lewis basic reactivity of amines, the weakly acidic N–H hydrogens, and the ability of amines to quaternize represent considerable challenges for the synthetic chemist.

Single-electron processes (i.e., radical reactions) can be used to circumvent the acid–base reactivity of nitrogen.[2] Carbon-centered radicals are generally tolerant of heteroatom lone pairs and N–H bonds. Thus, chemoselective reactions of nitrogen-rich functional groups would enjoy useful application in synthesis. The aminal functional group was identified as a particularly attractive substrate for radical-based bond-forming reactions.

Aminals are conveniently prepared from condensation reactions of readily available starting materials. Furthermore, calculations suggested that carbon-centered aminal radicals could be prepared in the presence of other nitrogen-containing carbon atoms.[3]

We recently reported the first use of aminal radical intermediates in synthetic reactions (Scheme 1).[4] Iodobenzyl-substituted aminals (**1**) undergo radical translocation[5] (i.e., hydrogen atom abstraction) to give aminal radical intermediates such as **2**. The aminal radicals add to electron-poor alkenes to give products of carbon–carbon bond formation (**3**). Radical translocation selectively activates the aminal position in the presence of carbons bearing only one nitrogen atom. Intermolecular and intramolecular reactions are possible, and diastereoselectivities can be quite high.

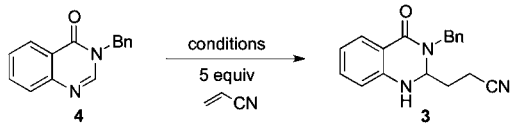
Scheme 1. Formation of C–C Bonds with Aminal Radicals



Despite the potential of the aminal radical reaction in synthesis, a complementary approach for the formation of the aminal radical intermediates was desired. Such a reaction would avoid the use of toxic or foul-smelling reagents. Starting materials that are convenient to prepare and do not require an iodobenzyl group would be particularly useful. An amidine reduction reaction (Scheme 1; **4** → **3**) satisfies these criteria and was selected for further study.

The success of substrate **1** in the translocation reaction indicated that if presumptive intermediate radical **2** was produced under different conditions then the desired product **3** could be formed. Amidine **4** was prepared and subjected to reductive conditions in the presence of acrylonitrile (Scheme 2). Reductions with Zn and LiDBB[6] did not give the desired product (entries 1–4). Gratifyingly, treatment of **4** with the

Scheme 2. Development of the Amidine Reduction Reaction



entry	conditions	result
1	Zn (2.2 equiv), HOAc (0.1 M), rt	no reaction
2	Zn (2.2 equiv), HOAc (0.1 M), 118 °C	no reaction
3	LiDBB (2.5 equiv), CSA (1.1 equiv), THF (0.3 M), rt	decomposition
4	LiDBB (2.5 equiv), THF (0.3 M), rt	decomposition
5	SmI_2 (2.5 equiv), CSA (1.1 equiv), THF (0.3 M), rt	90%
6	SmI_2 (2.5 equiv), THF (0.3 M), rt	57%
7	SmI_2 (2.5 equiv), NH_4Cl (1.1 equiv), THF (0.3 M), rt	99%

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single-electron reducing agent SmI_2,[7] camphorsulfonic acid (CSA), and acrylonitrile as a radical acceptor gave product **3** (entry 5). The reaction is operationally easy, requires no noxious reagents, is high yielding, and occurs rapidly at rt. The reaction yield decreased if an acid was not present (entry 6). After a screen of several acids, ammonium chloride was identified as a convenient and effective proton source that generally gives higher yields than CSA (entry 7).[8]

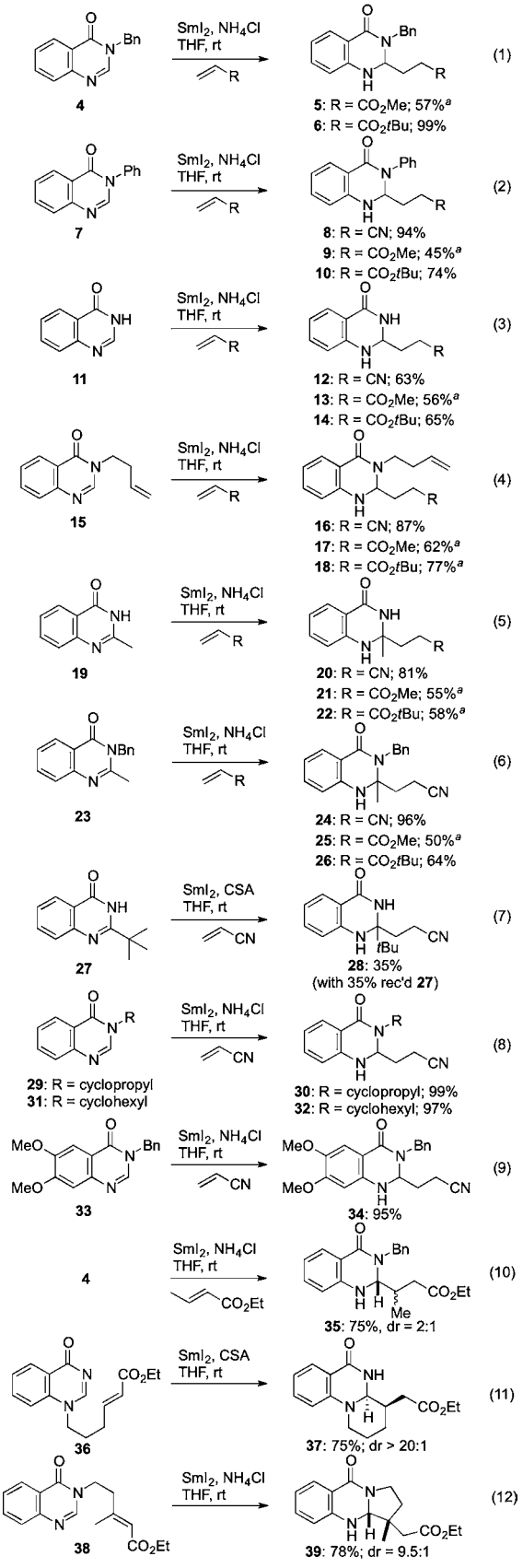
The amidine reduction reaction was examined with various substrates and acceptors (Scheme 3). Quinazolinones have important medicinal properties,[9] are easy to prepare,[10] and have an acylamidine substructure. Substrate **4** reacted with acrylates to form products **5** and **6**, respectively. In the amidine reduction reaction, a benzyl group is not required. Thus, phenyl substitution is tolerated, and **7** reacts with acrylonitrile, methyl acrylate, and *tert*-butyl acrylate to give **8**, **9**, and **10**, respectively. Unsubstituted quinazolinone **11** reacted to give **12**−**14** in good yield. The presumptive aminal radical intermediate does not add to unactivated alkenes. Thus, substrate **15** preferentially undergoes bimolecular addition to acrylonitrile and acrylates giving **16**−**18** rather than unimolecular 5-*exo*-*trig* cyclizations of the pendent alkene. Gratifyingly, substituted amidines also participate in the reaction in good yields. Substrate **19** gave products **20**−**22** which contain fully substituted carbon stereocenters. Benzyl-substituted amidine **23** reacted to give fully substituted aminals **24**−**26**. Even the *tert*-butyl-substituted amidine **27** reacts to give product **28**, which contains vicinal fully substituted carbon atoms. Cyclopropyl groups are tolerated in the substrate (**29**), provided they are distant from the carbon-centered radicals, to give product **30**. A sterically hindered amidine appended with a cyclohexyl group (**31**) participated giving product **32**. Electron-rich arenes are tolerated in the reaction, and **33** reacts to form **34** in high yield. Disubstituted alkenes are reactive acceptors, and **4** added to ethyl crotonate to give **35** in good yield, but the diastereoselectivity was modest.[11] However, intramolecular reactions proceeded in good yield and high diastereocontrol. Substrate **36** reacted to form a six-membered ring product **37**. This reaction also demonstrates that the amidine can be substituted at either nitrogen atom. Compound **38** contains a trisubstituted alkene acceptor, and it reacts smoothly in high yield and high diastereoselectivity to give **39**, which contains a quaternary carbon stereocenter. The relative stereochemistry was confirmed by NOE methods.

Acyl amidines that are not quinazolinones are suprisingly rare in the literature. Nevertheless, we found that they also participate in the reaction (Scheme 4). Spiro-fused amidine **40** reacted to produce **41**. Substituted amidine substrate **42** reacted under the conditions to give **43**. Bicyclic amidine **44** gave **45**, which contains a fully substituted stereocenter. The acyl substiutent may be present as an acetyl group on the amidine, and substrate **46** reacted with acrylonitrile to give **47**. Pyrimidinone **48** underwent dearomatizative reductive bond formation to give substituted product **49**.

The mechanism of the amidine reduction reaction may involve initial protonation of the amidine to form an amidinium ion, followed by single-electron reduction to give the aminal radical. If this is the case, then amidinium ions should participate in the reaction.

Various amidinium ions were formed using standard transformations of the corresponding amidine.[10] Subjection of the amidinium ions to SmI_2, acid, and a radical acceptor led to carbon−carbon bond formation in good yields (Scheme 5).[12]

Scheme 3. Scope of the Amidine Reduction Reaction



[a]Reaction was performed with CSA.

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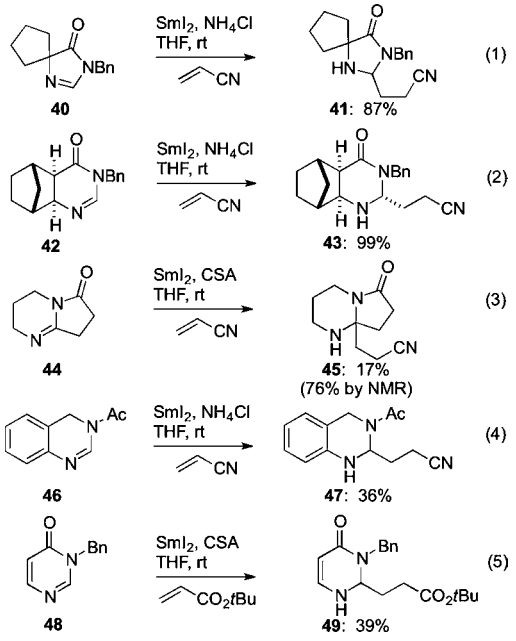
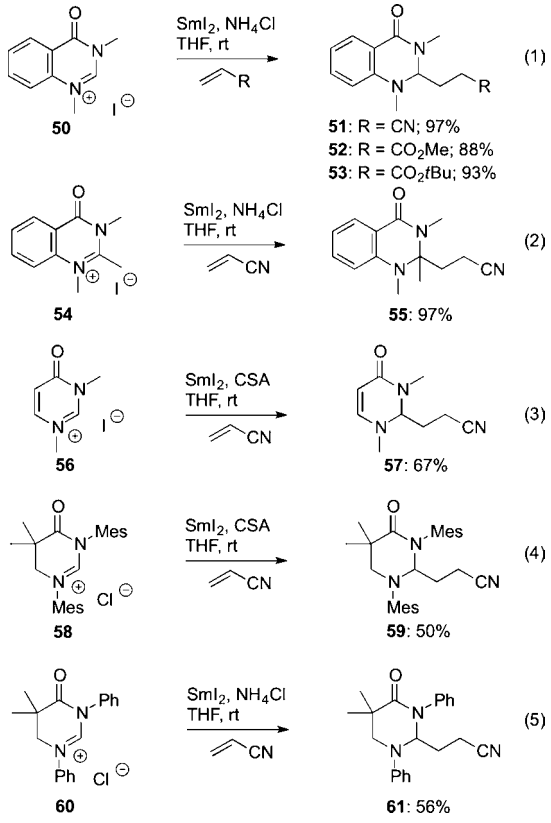
Scheme 4. Scope of Amidine Substrates



Scheme 5. Amidinium Reduction

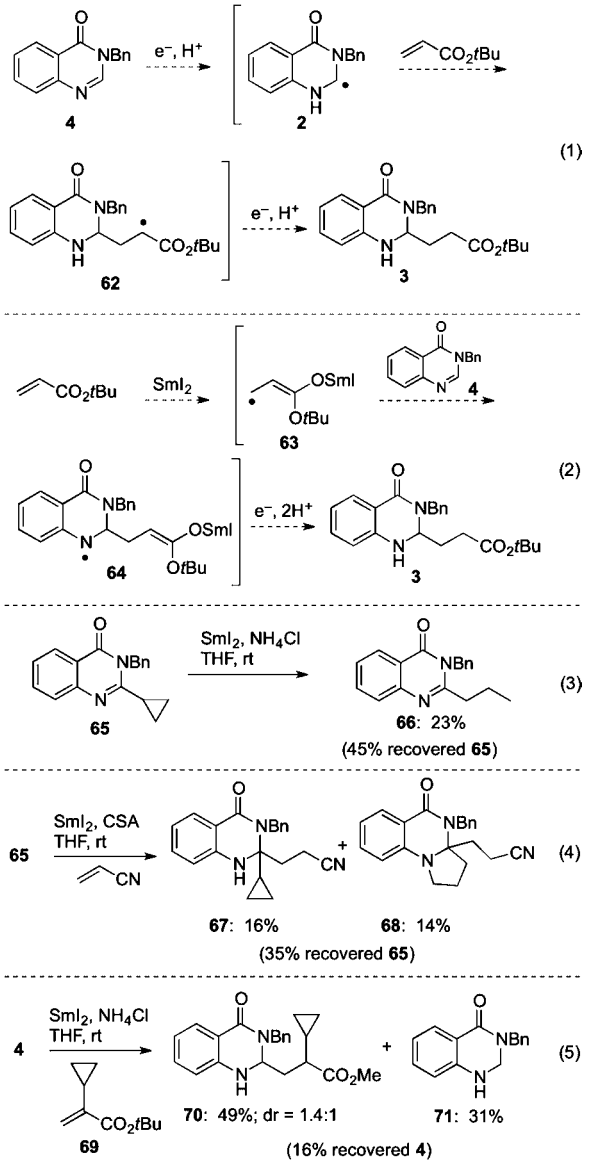


Quinazolinone-derived amidinium ion **50** participated in the reaction with standard radical acceptors to give **51**−**53**. Substituted amidinium ion **54** also particpated in the reduction, giving a product (**55**) with a fully substituted carbon stereocenter. The monocyclic amidinium substrate **56** also participated in the reaction giving good yield of the desired product (**57**).

Aliphatic amidinium ions also participated in the reduction. Known amidinium **58** underwent reductive bond formation with acryonitrile to form product **59**. Phenyl-substituted amidinium **60** reacted to form **61**.

Mechanistically, amidine **4** may receive a proton and an electron to form neutral aminal radical **2** (Scheme 6, eq 1). The

Scheme 6. Mechanistic Investigations



aminal radical could react with the electron-poor acceptor to give radical **62**. This radical would be further reduced and protonated to give the product **3**. Alternatively, the acrylate may be reduced to radical **63** (Scheme 6, eq 2). Addition to the amidine would give intermediate **64**. This intermediate could be reduced and protonated to give the product **3**. Related radical mechanisms have been proposed in the literature.[13]

To distinguish between these mechanistic possibilities, amidine substrate **65** was prepared, which contains a cyclopropyl group attached directly to the amidine. Reduction of **65** by SmI_2 in the absence of a radical acceptor leads to fragmentation of the cyclopropane and formation of **66** (Scheme 6, eq 3). Reduction of **65** in the presence of an

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acceptor gave addition product **67** and formation of ring-fragmentation product **68** (Scheme 6, eq 4).[14]

Cyclopropyl-containing radical acceptors were also investigated. Amidine **4** reacted with cyclopropyl acrylate **69** to form addition product **70** (Scheme 6, eq 5). The balance of the material was the reduction product **71** and unreacted starting material. Control experiments indicated the acrylate acceptors (acrylonitrile, methyl acyrlate, *tert*-butyl acrylate, and **69**) did not react under the reaction conditions in the absence of the amidine. This suggests that the amidine is reduced prior to reactions with the alkene acceptor. Reduction of the aminal radical such as **2** to carbanion intermediates is unlikely in the presence of strong acids (CSA and NH_4Cl). On the basis of these experiments, we believe the first mechanism is operative (i.e., **4** → **2** → **62** → **3**, Scheme 6, eq 1).

In conclusion, aminal radicals are formed via reduction of the corresponding amidine and amidinium ions in the presence of a proton source. The putative radical intermediates react with radical acceptors in C−C bond-forming reactions in good yields without the use of heavy metal hydrides or thiols. The reaction can be performed in inter- and intramolecular contexts in high yield. Furthermore, fully substituted aminal stereocenters are formed in good yields with this chemistry. We believe this reactivity will be useful in the synthesis of nitrogen-rich alkaloids, and efforts to apply this chemistry in synthesis are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data, and depiction of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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(8) The reaction stoichiometry requires 2 equiv of acid, but our optimized conditions use 1.1 equiv of H^+. We speculate that upon aqueous workup an anionic intermediate (e.g., an enolate) is protonated.

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(10) See the Supporting Information.

(11) The configuration of the major diastereomer was not determined.

(12) The amidinium reduction stoichiometry requires 1 equiv of acid, and the reaction yield drops substantially if acid is omitted.

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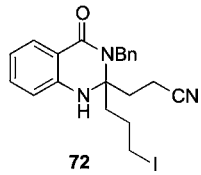

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