The Development and Mechanistic Study of an Iron-Catalyzed Intramolecular Nitroso Ene Reaction of Nitroarenes

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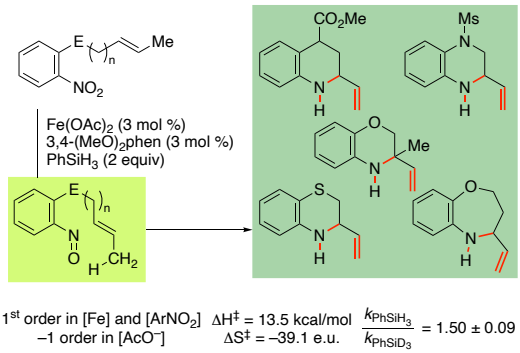
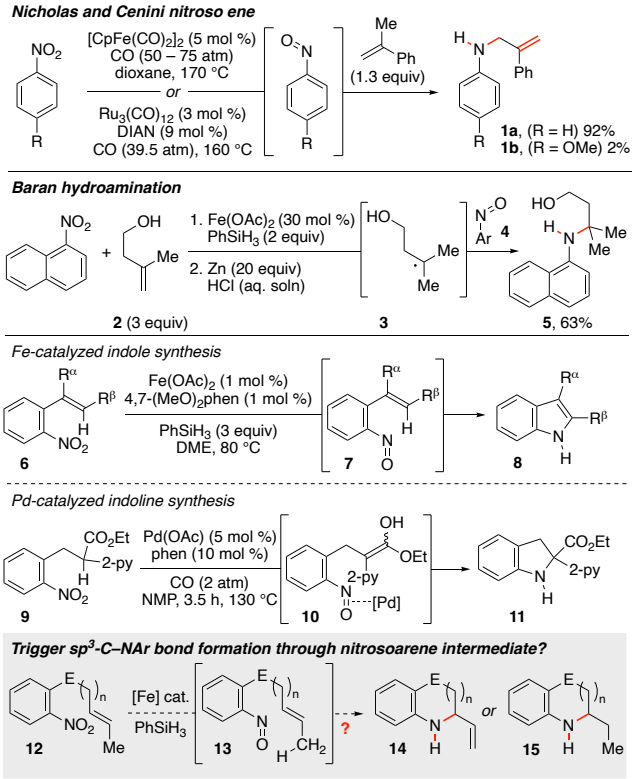


Abstract. An intramolecular iron-catalyzed nitroso ene reaction was developed to afford six- or seven-membered *N*-heterocycles from nitroarenes using an earth abundant iron catalyst and phenylsilane as the terminal reductant. The reaction can be triggered using as little as 3 mol % of iron(II) acetate and 3 mol % of 4,7-dimethoxyphenanthroline as the ligand. The scope of the reaction is broad tolerating a range of electron-releasing or electron-withdrawing substituents on the nitroarene, and the *ortho*-substituent can be modified to diastereoselectively construct benzoxazines, dihydrobenzothiazines, tetrahydroquinolines, tetrahydroquinoxalines, or tetrahydrobenzooxazepines. Mechanistic investigations indicated that the reaction proceeds via a nitrosoarene intermediate, and kinetic analysis of the reaction revealed a first order rate dependence in catalyst- and nitroarene concentration, and an inverse kinetic order in acetate was observed. The difference in rates between $PhSiH_3$ and $PhSiD_3$ was found to be 1.50 ± 0.09, and investigation of the temperature dependence of the reaction rate revealed that the activation parameters to be $\Delta H^{\ddagger} = 13.5$ kcal•mol^{-1} and $\Delta S^{\ddagger} = -39.1$ cal•mol^{-1}•K^{-1}. These data were interpreted to indicate that the turnover-limiting step to be hydride transfer from iron to the coordinated nitroarene, which occurs through an ordered transition state with little Fe–H bond breaking.

The development of C–N bond forming reactions by accessing electrophilic *N*-aryl nitrogen reactive intermediates from nitroarenes has spurred considerable interest from the synthetic community because of the availability and stability of nitroarenes.[1] While the creation of sp^2-C–NAr bonds is legion,[2,3,4] the construction of sp^3-C–N bonds from nitroarenes has developed more slowly.[5] Nitrosoarenes, in contrast, are well established to create sp^3-C–NAr bonds through [4+2] cycloaddition reactions,[6,7] nitroso ene reactions,[8,9] or through nucleophilic addition.[10,11] Consequently, the synthesis of sp^3-C–NAr bonds through the in situ generation of a nitrosoarene intermediate from a nitroarene has emerged as a strategy. Cenini and Nicholas reported that a ruthenium- or iron complex could be used to catalyze the transformation of a nitroarene into an allylic amine **1** through a nitroso ene reaction.[5a, 12] This reaction, however, required high temperatures, high pressures of CO, and its success was dependent on the electronic environment of the nitroarene with those bearing electron-releasing groups affording only trace products. Baran and co-workers reported that sp^3-C–NAr bonds could be formed using 30 mol % of iron acetate and phenyl silane as the terminal reductant by intercepting nitrosoarene intermediate **4** with alkyl radical **3**, which was produced from the insertion of an olefin into an Fe–H bond followed by homolytic cleavage of the resulting Fe–H bond.[5c] Our group showed that as little as 1 mol % $Fe(OAc)_2$ and 1 mol % of 4,7-$(MeO)_2$phenanthroline catalyzed the conversion of 2-nitrostyrenes **6** into indoles **8** using phenylsilane as the terminal reductant.[3o] Subsequently, we reported that intramolecular sp^3-C–NAr bond formation could be achieved by trapping nitrosoarene **10** with a pendant enol.[5g] This reaction, however, required the use of $Pd(OAc)_2$ and

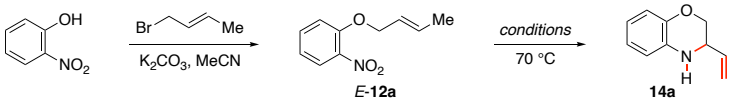
phenanthroline as the catalyst and CO as the terminal reductant and was primarily limited to the formation of five-membered rings. We were curious if larger *N*-heterocycles **14** could be formed through a nitroso ene reaction from nitroarenes, such as **12**, using an earth abundant catalyst and milder silane reductant,[13] or if intramolecular hydroamination would occur instead to afford **15**.



Scheme 1. Formation of sp³-C–N bonds from nitroarenes.

To determine if the nitrosoarene intermediate could be intercepted by the *ortho*-crotyl substituent in an ene reaction, the reactivity of nitroarene **12a** was tested toward reduction conditions (Table 1).[14] The substrate for the optimization study was synthesized in one-step through an S_N2 reaction between 2-nitrophenol and *E*-crotylbromide. To our delight, submitting nitroarene **12a** to the combination of 3 mol % of $Fe(OAc)_2$ and 4,7-$(MeO)_2$phen using 2 equiv of $PhSiH_3$ as the terminal reductant resulted in the formation of 3-vinylbenzoxazine **14a** in 67% with 13% of the nitroarene remaining (entry 1). 3-Ethylbenzoxazine was not observed. Our efforts to improve the yield by changing the identity of the silane reductant resulted in only reduced reaction yields (entries 2 and 3). Modifying the identity of the iron salt also had a detrimental effect on the yield of **14a** (entries 4 and 5). The identities of the ligand also played a critical role in the reaction outcome (entries 6 and 7). Changing the ligand to 2,10-di-*tert*-butylbipyridine resulted in complete consumption of the nitroarene, but only 55% of the 3-vinylbenzoxazine product (entry 6). Reducing the electron-donating nature of the phenanthroline ligand also resulted in diminished yield (entry 7). We posited that the modest solubility of the catalyst might be negatively impacting the reaction outcome. To test this, we screened a variety of solvents and co-solvents (entries 8 – 11). While using DMF as the reaction medium resulted in a homogeneous solution, the yield was reduced. We were able to improve the reaction outcome using the combination of DMF and DME (1:4) to afford 83% of benzoxazine **14a**. The effect of lowering the catalyst loading was examined (entry 12), and we found that $Fe(OAc)_2$ and 4,7-dimethoxyphenanthroline could be reduced to 1 mol % and still afford **14a**, albeit in an attenuated yield. As a result, we chose to explore the scope and limitations of this reaction using 3 mol % of the $Fe(OAc)_2$ and 4,7-$(MeO)_2$phen in a 1:4 mixture of DMF and DME using $PhSiH_3$ as the terminal reductant.

Table 1. Development of the optimal conditions for Fe-catalyzed nitroso ene reaction of nitroarenes.

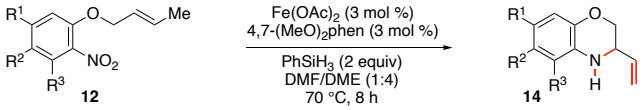


entry	Fe salt (mol %)	ligand (mol %)	reductant (equiv)	solvent	time (h)	**14a** (**12a**) yield, %[a]
1	$Fe(OAc)_2$ (3)	4,7-$(MeO)_2$phen (3)	$PhSiH_3$ (2)	DME	8	67 (13)
2	$Fe(OAc)_2$ (3)	4,7-$(MeO)_2$phen (3)	Ph_2MeSiH (2)	DME	8	11 (70)
3	$Fe(OAc)_2$ (3)	4,7-$(MeO)_2$phen (3)	$(MeO)_2MeSiH$ (2)	DME	8	13 (72)
4	$Fe(OTf)_2$ (3)	4,7-$(MeO)_2$phen (3)	$PhSiH_3$ (2)	DME	8	8 (80)
5	$FeBr_2$ (3)	4,7-$(MeO)_2$phen (3)	$PhSiH_3$ (2)	DME	8	11 (68)
6	$Fe(OAc)_2$ (3)	dtbpy (3)	$PhSiH_3$ (2)	DME	8	55 (trace)
7	$Fe(OAc)_2$ (3)	phen (3)	$PhSiH_3$ (2)	DME	8	50 (33)
8	$Fe(OAc)_2$ (3)	4,7-$(MeO)_2$phen (3)	$PhSiH_3$ (2)	DMF	8	40 (40)
9	$Fe(OAc)_2$ (3)	4,7-$(MeO)_2$phen (3)	$PhSiH_3$ (2)	MeCN/DME (1:4)	5	45 (36)
10	$Fe(OAc)_2$ (3)	4,7-$(MeO)_2$phen (3)	$PhSiH_3$ (2)	DMA/DME (1:4)	5	62 (20)
11	$Fe(OAc)_2$ (3)	4,7-$(MeO)_2$phen (3)	$PhSiH_3$ (2)	DMF/DME (1:4)	8	83 (7)
12	$Fe(OAc)_2$ (1)	4,7-$(MeO)_2$phen (1)	$PhSiH_3$ (2)	DMF/DME (1:4)	5	54 (20)

[a] As determined using ^{1}H NMR spectroscopy using CH_2Br_2 as an internal reference.

Using the optimal conditions, the effect of changing the nitroarene component of **12** was investigated (Table 2). We found that both *E*- and *Z*-isomers were reactive, but a lower yield of benzoxazine **14a** was observed from the *Z*-isomer (entries 1 and 2). After establishing the difference in reactivity between isomers, we applied the reaction conditions to different nitroarenes with *E*-crotyl substituents. Both electron-releasing groups and electron-withdrawing groups at *meta*-R^2-substituent were found to be tolerated (entries 3 – 7). The effect of *para*-R^1-substituents on the reaction outcome was also explored, and benzoxazines **14g** – **14j** were formed (entries 8 – 11). Lastly, we examined the effect of increasing the steric environment around the nitro group on the transformation by adding an R^3-methyl group to the nitroarene (entry 12). While submission of **12k** to reaction conditions produced benzoxazine **14k** the yield was attenuated in comparison to the other substrates examined.

Table 2. Scope and limitations with regards to the nitroarene.

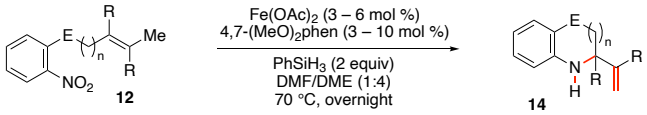


entry[a]	**12**	R^1	R^2	R^3	**14** yield, %[b]
1	*E*-**a**	H	H	H	78
2	*Z*-**a**	H	H	H	52
3	*E*-**b**	H	OMe	H	65
4	*E*-**c**	H	Me	H	71
5	*E*-**d**	H	F	H	70
6	*E*-**e**	H	CF_3	H	67
7	*E*-**f**	H	CN	H	60
8	*E*-**g**	F	H	H	60
9	*E*-**h**	Cl	H	H	60
10	*E*-**i**	CO_2Me	H	H	68
11	*E*-**j**	CF_3	H	H	67
12	*E*-**k**	H	H	Me	45

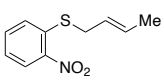
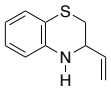
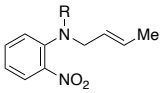
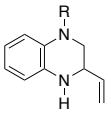
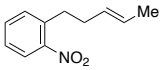
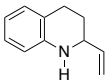
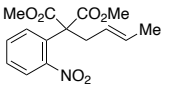
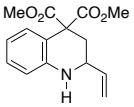
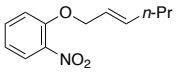
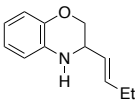
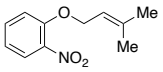
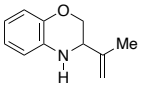
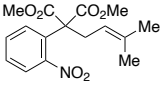
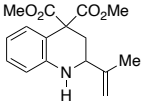
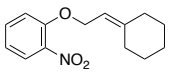
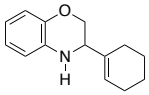
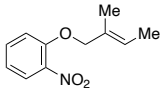
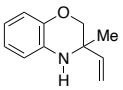
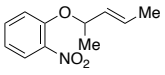
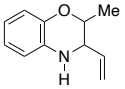
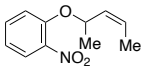
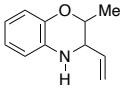
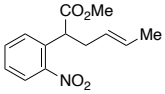
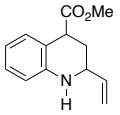
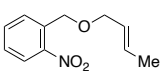
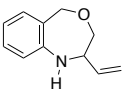
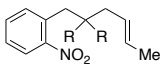
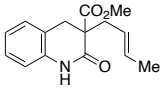
[a] conditions: 0.1 mmol of **12**, 0.03 mmol of $Fe(OAc)_2$, 0.012 mmol of 4,7-$(MeO)_2$phen, 0.2 mmol of $PhSiH_3$, 0.2 mL of DMF, 0.8 mL of DME. [b] Isolated after silica gel chromatography.

We next surveyed the effect of modifying the *ortho*-alkenyl identity on *N*-heterocycle formation (Table 3). The γ-alkenyl substituents were first varied by changing identity of moiety linking the crotyl substituent to the nitroarene (entries 1 – 5). While thioether **12l** was effectively converted to benzothiazine **14l** in 70%, we found that a secondary amine **12n** (entry 2) was not tolerated in the reaction. This result could be rescued by protecting the nitrogen with a Ms-group to afford **14n** in 65% (entry 3). Carbon-linkers were also investigated (entries 4 and 5), and while only a small amount of product was observed using a methylene group (**12o**), submission of malonate **12p** to reaction conditions smoothly converted it to tetrahydroquinoline **14p** (entry 5). The effect of changing the reaction site was probed with substrates **12q** – **12u** (entries 6 – 10). We found that the ene reaction occurred smoothly at a methylene position to afford benzoxazine **14q** as a single isomer (entry 6), and that prenyl substituted substrates could be effectively converted to *N*-heterocycles **14r** and **14s** irrespective if they were connected to the nitroarene via an oxygen-atom or a malonate-group (entries 7 and 8). While a slight drop in the yield was observed for **12u**, we were delighted to see that sterically congested C–N bonds could be constructed in benzoxazine **14u** (entry 10). The diastereoselectivity of the transformation was examined with nitroarenes **12v** and **12x** (entries 11 and 12). We found that nitroarenes bearing an allylic- or homoallylic substituent produced the *N*-heterocyclic product as a 3:1 mixture of diastereomers. The diastereoselectivity was not improved when *Z*-**12v** was submitted to the reaction conditions (entry 13). Finally, the effect of lengthening the tether between the nitro-group and the alkene was examined with **12y** and **12z** (entries 14 and 15). To our delight, increasing the tether length by one methylene did not prevent reaction: exposure of nitroarene to **12y** to reaction conditions produced tetrahydrobenzazepine **14y** albeit in 45%. In contrast, when the oxygen-atom was replaced with a malonate, the reaction outcome changed from seven-membered ring formation to form tetrahydroquinoline **14z** in 84%.

Table 3. Effect of *o*-alkenyl identity on *N*-heterocycle formation.

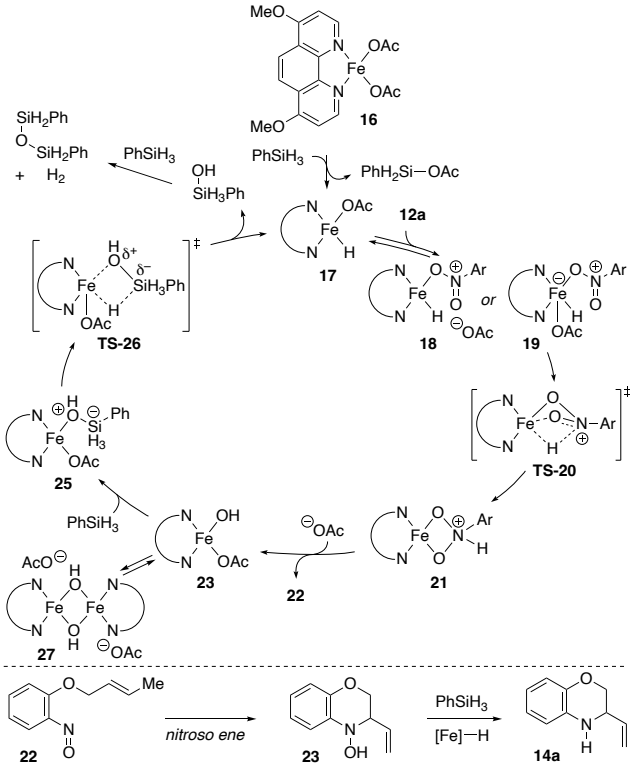


12 → 14

entry[a]	**12**	nitroarene	*N*-heterocycle	**14** yield, %[b]
1	**l**			70
2	**m**			R=H, n.r.
3	**n**			R=Ms, 65
4	**o**			10[c]
5	**p**			71
6	**q**			60 84:16 *E*:*Z*
7	**r**			70
8	**s**			69
9	**t**			56[c]
10	**u**			55
11	*E*-**v**			68 d.r. 71:29
12	*Z*-**v**			18 d.r. 78:22
13	**x**			62[c] d.r. 72:28
14	**y**			45[c]
15	**z**			84

[a] conditions: 0.1 mmol of **12**, 0.03 mmol of $Fe(OAc)_2$, 0.012 mmol of 4,7-$(MeO)_2$phen, 0.2 mmol of $PhSiH_3$, 0.2 mL of DMF, 0.8 mL of DME. [b] Isolated after silica gel chromatography. [c] 100 °C, overnight. [d]70 °C, 8 h.

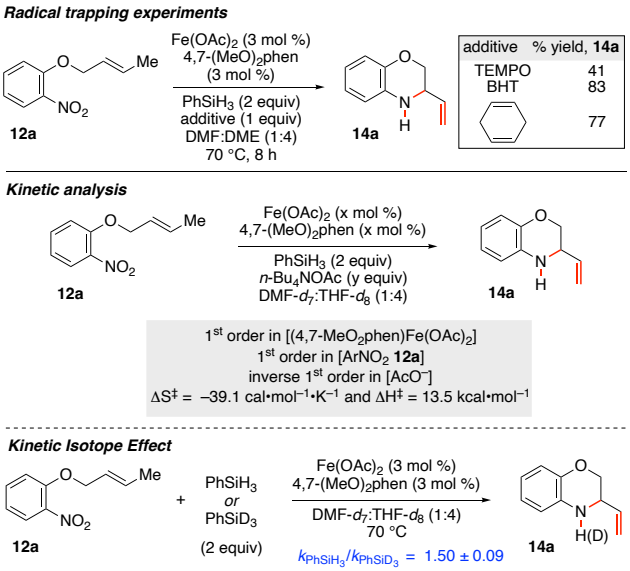
The formation of benzoxazine **14** from nitroarene **12** could occur through a catalytic cycle involving an ene reaction of nitrosoarene **22** (Scheme 2). Reduction of phenanthroline iron acetate **16** with phenylsilane produces iron hydride **17**.[15] Coordination of nitroarene **12** to **17** produces **18** or **19** depending on whether the acetate is directly coordinated to iron.[16] We anticipate that hydride transfer to the nitro-group occurs via transition state **TS-20**, where the iron-hydride bond breaks simultaneously with nitrogen-hydrogen bond formation. The resulting iron species (κ^1- or κ^2-coordinated)[17] fragments to produce nitrosoarene **22** and iron hydroxide **23**.[18] This species could dimerize to produce **24**[19] or react with phenylsilane to produce iron silicate **25**, which transfers a hydride via σ-bond metathesis transition state **TS-26** to regenerate the active catalyst and produce phenylsilanol.[15b, c] This silanol could react with phenylsilane to produce silyl ether and dihydrogen. Nitroso ene reaction of **22** generates *N*-hydroxy-benzoxazine **23**, which is reduced by silane or iron hydride to produce **14a**.



Scheme 2. Potential catalytic cycle.

Several experiments were performed to gain more insight into the mechanism of benzoxazine formation (Scheme 3). To rule out the formation of radical catalytic intermediates, several radical traps (TEMPO, BHT, and cyclohexadiene) were added to the reaction mixture and benzoxazine was still produced. The reaction could be monitored by ^{1}H NMR spectroscopy and neither paramagnetic species nor nitroso- or *N*-hydroxy-compounds were observed. We anticipated that examination of the reaction kinetics might clarify the catalytic cycle. If the resting state of the catalyst was dimer **23**, we anticipated that a kinetic order of less than one would be observed in catalyst. Further if reduction of iron hydroxide **22** was turnover limiting, then a zero order in nitroarene would be expected,[3o] and a significant difference in rates between $PhSiH_3$ and $PhSiD_3$ would be anticipated.[15b, c] To address these questions, the reaction kinetics were examined using ^{1}H NMR spectroscopy in a 1:4 mixture of DMF-d_7 and THF-d_8. The reaction was found to be first order in nitroarene-, first order in catalyst-, and inverse first order in acetate anion concentration. The first order rate dependence on nitroarene concentration differs from the kinetic behavior of our 4,7-dimethoxyphenanthroline iron-catalyzed reductive cyclization of *ortho*-nitrostyrene, which exhibited a zero-order dependence in nitrostyrene,[3o] and suggests that reduction of iron hydroxide **22** is not turnover limiting. The observed first order in catalyst suggests that dimerization of **22** to give **23** is not occurring. Together with the inhibition by increasing acetate formation, these indicate that coordination of nitrosoarene to **16** or reduction to afford **20** is the turnover-limiting step. To distinguish between these possibilities, the

effect of using phenylsilane-d_3 on the rate of the reaction was investigated. Observed rate constants were obtained using ^{1}H NMR spectroscopy, and the difference in rate (k_{PhSiH3}/k_{PhSiD3}) was found to be 1.50 ± 0.09. This kinetic isotope is significantly smaller than the k_H/k_D = 3.0 ± 0.2 observed by Bleith and Gade for the rate-limiting reaction of an iron(II)-alkoxide with silane.[15b, c] While our smaller value could be interpreted that coordination of the nitroarene to **17** is rate-limiting, similar magnitude kinetic isotope effects have been observed previously by Tilley and co-workers and have been assigned to be primary and consistent with σ-bond metathesis reaction mechanism with an early transition state where the hydrogen bond is not significantly broken.[20] The temperature dependence on the reaction rate was also examined using ^{1}H NMR spectroscopy, and the activation parameters were determined to be $\Delta H^{\ddagger}$ = 13.5 kcal•mol^{-1} and $\Delta S^{\ddagger}$ = –39.1 cal•mol^{-1}•K^{-1}. The large negative $\Delta S^{\ddagger}$ is consistent for a highly ordered transition state such as **TS-20**.[21] We interpret our mechanistic experiments suggest that coordination of the nitroarene substrate to an iron hydride is reversible and that the turnover-limiting step is hydride transfer from iron to the coordinated nitroarene that occurs via a highly ordered transition state where the iron hydride bond is not significantly broken.



Scheme 3. Mechanistic experiments.

In conclusion, we have developed an intramolecular iron-catalyzed reductive nitroso ene reaction of 2-substituted nitroarenes to afford six- or seven-membered *N*-heterocycles using phenylsilane as the terminal reductant. This reaction enables diastereoselective access to benzoxazines, dihydrobenzothiazines, tetrahydroquinolines, tetrahydroquinoxalines, or tetrahydrobenzooxazepines. Kinetic studies, kinetic isotope effect measurements, and Eyring analysis provided mechanistic insight to suggest that the reaction proceeds via a nitrosoarene intermediate, and that the turnover-limiting step is the reduction of a κ^1- or κ^2-coordinated nitroarene by an iron hydride that occurs via a highly ordered transition state.

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