

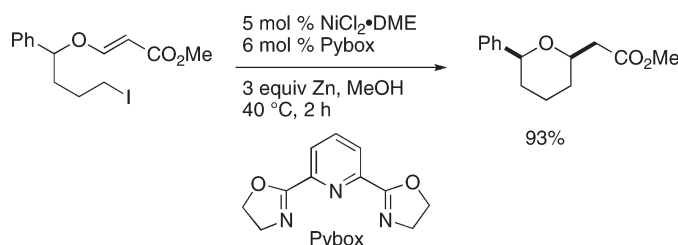
Nickel-Catalyzed Reductive Cyclization of Organohalides

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ABSTRACT

A mild and convenient nickel-catalyzed method for free-radical cyclization of organohalides is described. The use of a $\text{NiCl}_2 \cdot \text{DME}$ /Pybox complex as the catalyst and zinc powder in methanol efficiently promotes the reductive cyclization of various unsaturated alkyl halides to give carbo-, oxa-, and azacycles as products in high yields.

Free radical cyclization of unsaturated organohalides is a powerful method for ring construction that has found widespread use in various domains of organic synthesis.¹ This process may be performed with a variety of radical mediators, among which stannane reagents have been most popular despite the toxicity and purification issues associated

with certain organotin species. Among the nonstannane-based protocols,² transition-metal-promoted radical reactions represent an attractive approach due to the capability of effecting catalysis,³ as exemplified by an array of atom transfer radical addition (ATRA) reactions.⁴ However, these processes, making use of the Kharasch mechanism,⁵ typically proceed with substrates activated by polyhalogen substitution or an adjacent π -bond. Potentially more useful catalyst systems applicable to simple alkyl halides are far less common, and examples have been limited largely to electrochemical settings⁶ or practiced in a narrow structural context in the presence of a rather strong reductant.⁷ Given the broadly established utility of the radical cyclization, the development of an efficient catalyst that encompasses simple halide substrates would be of high synthetic value, significantly expanding the scope of the reaction. Herein, we report a mild and convenient nickel-catalyzed method that effects reductive radical cyclization of various alkyl halides to give rise to carbo- and heterocyclic products in high yield.

Our initial investigations were focused on examining the feasibility of metal catalysis for the cyclization of

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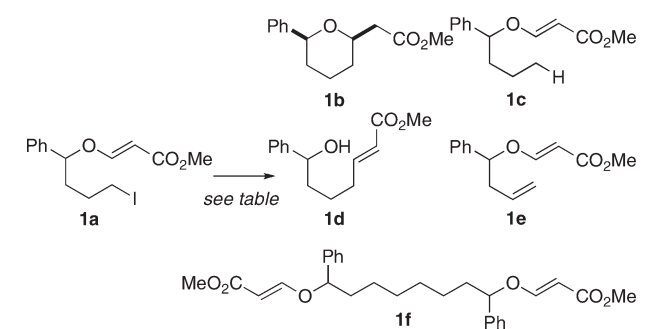
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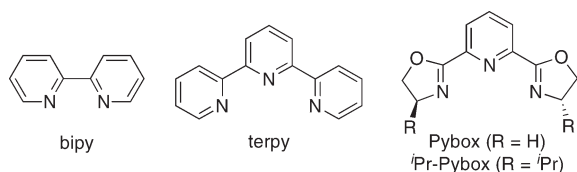
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Table 1. Transition-Metal-Catalyzed Reductive Cyclization of β -Alkoxyacrylate **1a**^a



entry	conditions	conversion ^b 1b:1c:1d:1e:1f
1	3 mol % Pd(PPh ₃) ₄ 3 equiv Zn, DMA, 40 °C, 4 h	95% 20:27:27:26:0
2	15 mol % NiCl ₂ •6H ₂ O, 140 mol % pyridine 2.3 equiv Zn, THF, 60 °C, 24 h	99% 19:31:36:14:0
3	20 mol % NiCl ₂ •DME, 25 mol % bipy 6 equiv Zn, DMA, 25 °C, 30 h	99% 43:11:25:0:21
4	20 mol % NiCl ₂ •DME, 25 mol % terpy 6 equiv Zn, DMA, 25 °C, 22 h	99% 33:8:22:0:37
5	20 mol % NiCl ₂ •DME, 25 mol % ⁱ Pr-Pybox 6 equiv Zn, DMA, 25 °C, 46 h	99% 53:23:10:0:14
6	5 mol % NiCl ₂ •DME, 6 mol % ⁱ Pr-Pybox 3 equiv Zn, DMA, 25 °C, 24 h	91% 33:30:37:0:0
7	5 mol % NiCl ₂ •DME, 6 mol % ⁱ Pr-Pybox 3 equiv Zn, THF, 25 °C, 12 h	99% 54:18:27:0:0
8	5 mol % NiCl ₂ •DME, 6 mol % ⁱ Pr-Pybox 3 equiv Zn, H ₂ O, 25 °C, 35 h	70% 87:13:0:0:0
9	5 mol % NiCl ₂ •DME, 6 mol % ⁱ Pr-Pybox 3 equiv Zn, CH ₃ OH, 25 °C, 4 h	99% 91:9:0:0:0
10	5 mol % NiCl ₂ •DME, 6 mol % Pybox 3 equiv Zn, CH ₃ OH, 25 °C, 20 h	99% 93:6:0:0:0

^a All reactions were carried out in 0.2 M concentration. ^b Conversion and product ratios were determined by ¹H NMR analysis of the crude reaction mixtures.



β -alkoxyacrylate **1a**, a transformation demonstrated for its exceptional utility in the syntheses of numerous oxacyclic natural products (Table 1).⁸ Thus, a series of catalysts were tested for the reaction of **1a** under reductive conditions. While Pd(PPh₃)₄ did induce the cyclization of **1a** to give oxacycle **1b**, there were generated substantial amounts of byproducts presumably through simple reduction (**1c**), ring-opening (**1d**), and β -hydrogen elimination (**1e**) (entry 1). Similar mixtures of products were formed under the nickel catalysis known to be capable of activating alkyl halides

(entry 2).⁹ Interestingly, the use of a multidentate nitrogen ligand in lieu of pyridine completely suppressed β -hydrogen elimination but led to significant dimerization to form **1f** (entries 3–5). While lowering catalyst loadings prevented dimer formation (entries 6–9), promising results came from solvent screening experiments in which a marked increase in the yield of **1b** was achieved using protic solvents (entries 6 and 7 vs entries 8 and 9). With methanol as the solvent and the prototypal Pybox (R = H) as the ligand, the reaction afforded the desired oxacycle **1b** as a single diastereomer in greater than 90% isolated yield (entry 10). It was also noteworthy that the reaction could be completed in 2 h at 40 °C and rigorous exclusion of oxygen was unnecessary.

Table 2 illustrates the impact of additional reaction parameters on the course of the reductive cyclization of **1a**. Control experiments revealed all components of the catalyst system (Ni/Pybox and Zn) to be indispensable to the reaction (entries 2–4). Replacement of NiCl₂•DME with other nickel or palladium salts led to no or negligible reaction (entries 5–7). Similarly, the use of zinc as the reductant was also found to be critical; the reaction was ineffective with Mn or Et₂Zn (entries 8 and 9). Finally, subjecting **1a** to the Ni-catalyzed conditions^{7a} known to promote a radical cyclization resulted in the formation of a complex mixture of products, from which **1b** was obtained only in 12% yield along with **1c** and **1d** in 30% and 45% yield, respectively (entry 10).

Table 2. Effects of Reaction Parameters on the Efficiency of the Reductive Cyclization of **1a**

entry	variation from "standard" conditions	yield (%) ^a
1	none	>90
2	no NiCl ₂ •DME	<2
3	no Pybox	<2
4	no Zn	nr
5	NiCl ₂ instead of NiCl ₂ •DME	nr
6	Ni(acac) ₂ instead of NiCl ₂ •DME	nr
7	PdCl ₂ (MeCN) ₂ instead of NiCl ₂ •DME	<1
8	Mn instead of Zn	nr
9 ^b	Et ₂ Zn instead of Zn	<2
10 ^c	Ni(acac) ₂ /Et ₂ Zn instead of NiCl ₂ •DME/Zn	12

^a Determined by ¹H NMR. ^b THF solvent. ^c The reaction was carried out in THF with 2 mol % Ni(acac)₂ and 2 equiv of Et₂Zn at –78 °C as described in ref 7a.

With the established standard conditions, the scope of the reaction was probed with an assortment of substrates. As summarized in Table 3, a variety of unsaturated alkyl halides underwent reductive cyclization under the nickel-catalyzed conditions furnishing five- and six-membered oxa- (entries 1–7), carbo- (entries 8–10), and azacyclic (entries 11–13) products in excellent yields. In most cases, simple reduction products were formed in less than 5% yields. The reaction

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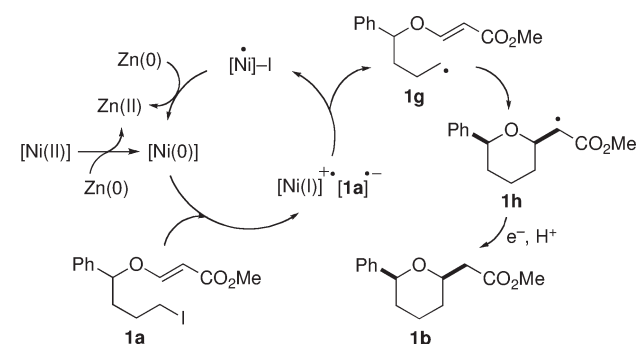
Table 3. Ni-Catalyzed Reductive Cyclization of Organohalides^a

entry	reactant	product	time (h)	yield (%) ^b
1			2	93
2			60	88
3			2	87
4			48	81
5 ^c			0.8	91 ^d
6			2	90
7 ^c			0.8	87 ^e
8			1	99
9			6	98
10			1	93
11			0.5	85
12			4	85 ^f
13			2	87

^a All reactions were carried out in methanol (0.2 M) at 40 °C in the presence of 5 mol % NiCl₂•DME, 6 mol % Pybox, and 3 equiv of Zn powder. ^b Isolated yields. ^c A 1:1 diastereomeric mixture was employed as the reactant. ^d dr = 58:42. ^e dr = 52:48. ^f The simple deiodination product was obtained in 10% yield.

conditions were compatible with a broad range of functional groups such as esters, ethers, sulfones, acetals, amides, and sulfonamides. In general, iodo substrates were cyclized more efficiently than bromides providing higher yields in shorter reaction times (entries 1, 3, and 8 vs entries 2, 4, and 9), whereas the corresponding chloride, tosylate, and mesylate substrates did not react. Interestingly, secondary iodide **5a** reacted more rapidly than the primary iodide **1a** (entry 5). With respect to the unsaturation, both alkenes and alkynes of varying electronic nature participated well in the reaction.

On the basis of the findings thus far garnered from our studies, a free radical mechanism is proposed for the Ni-catalyzed cyclization (Scheme 1). After reduction from the Ni(II) precatalyst salt, the resulting Ni(0) complex brings about homolysis of the C–I bond of **1a** to give the carbon-centered radical **1g** through a single electron transfer or direct iodine abstraction process.¹⁰ While **1g** enters on the course of 6-exo-trig addition and subsequent reduction to yield **1b**, the active Ni(0) species may be regenerated through reduction mediated by zinc. This free radical mechanism, rather than a two-electron pathway involving a carbon–metal σ -complex, is more consistent with the enhanced reactivity of the secondary halide substrate and the 2,5- and 2,6-*cis*-diastereoselectivity in the formation of **1b** and **3b**.¹¹

Scheme 1. Proposed Mechanism for Ni-Catalyzed Cyclization

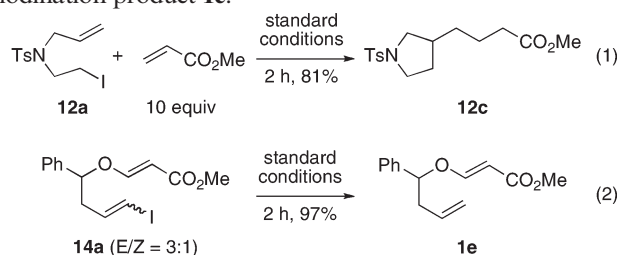
The radical mechanism operative in the present nickel catalysis permits the cyclization reaction to be conducted in combination with additional C–C bond formation (eq 1). Under the standard conditions in the presence of 10 equiv of methyl acrylate, **12a** was transformed into **12c** in 81% yield via tandem intra- and intermolecular addition, a result mirroring that from the protocol using an organotin hydride.¹² In sharp contrast to alkyl halides, alkenyl substrates, however, displayed a differential mode of reactivity. As shown in eq 2, only clean reduction took place in the reaction of a 3:1 (*E/Z*) mixture of iodide **14a** under the same conditions,¹³ suggesting

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(11) For discussion on the exclusive *cis*-stereoselectivity observed in the radical cyclization of **1a**–**4a**, see ref 8b.

(12) For a similar tandem radical addition reaction using tributyltin hydride, see: Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303.

the existence of a mechanistic crossover. It is surmised that the low valent nickel complex in this case did not prompt homolytic cleavage of the C–I bond, but instead formed a C–Ni σ -bond via oxidative addition, possibly due to the instability of the alkenyl radical in comparison with alkyl radicals. Then, protonation of the C–Ni bond would generate the reductive deiodination product **1e**.¹⁴



In summary, we have developed a mild and convenient nickel-catalyzed method for radical cyclization. Using zinc as the reductant in methanol, the Ni/Pybox catalyst efficiently promotes reductive cyclization of various alkyl

(13) The same reaction with a 1:14 (E/Z) mixture of **14a** took 7 h to give **1e** in 92% yield.

halides with an effectiveness comparable or superior to that of organotin hydride conditions without the necessity of slow addition. In addition to the remarkable operational simplicity, the high functional group tolerance is also a noteworthy feature of the present method. Current efforts are aimed at exploring the full potential of the reaction, including the expansion of the scope of both substrates and reductants and applications in complex molecule synthesis.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(14) The reduction in an aprotic solvent required a longer reaction time; the reaction of **14a** (3:1 = E/Z) in DMA for 40 h resulted in the formation of **1e** in 67% yield with a 29% recovery of **14a** as a 1:3 (E/Z) mixture. No reaction occurred with (Z)-**14a**.