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Ni-Catalyzed Two-Component Reductive Dicarbofunctionalization of Alkenes via Radical Cyclization

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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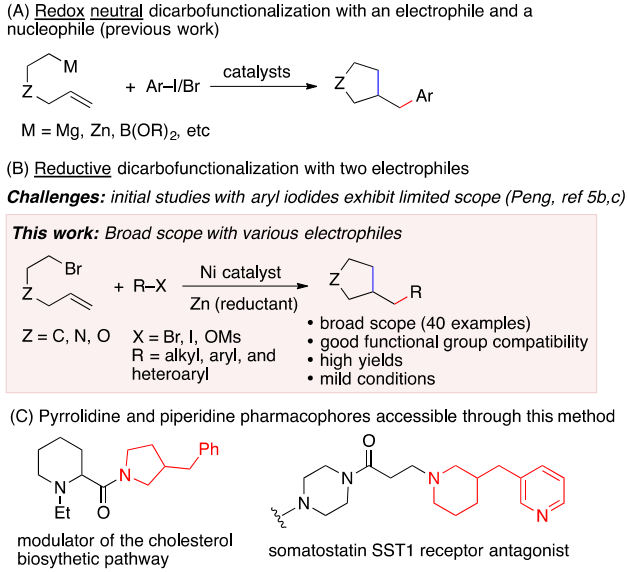
Published on 15 February 2018. Downloaded by University of Windsor on 15/02/2018 15:49:15.

A reductive dicarbofunctionalization of alkenes has been developed and applied to the preparation of substituted carbo- and heterocycles. The reaction conditions avoid the use of air-sensitive organometallic reagents, and are compatible with a broad range of bromo-electrophiles and a wide variety of substituents to give cyclic products in excellent yields.

An appealing method to rapidly increase molecular complexity is the 1,2-dicarbofunctionalization of alkenes, which can enable new disconnections in organic synthesis.[1,2] Previous research on dicarbofunctionalization of alkenes focused on the use of a nucleophile and an electrophile to generate tri- and tetra-substituted patterns (Scheme 1A).[1,2] Stoichiometric organometallic nucleophiles often require glovebox manipulations and are typically incompatible with electrophilic functional groups, such as aldehydes and ketones. An alternative strategy that bears a broad range of substrates with excellent functional group tolerance would expand the synthetic utility of olefin difunctionalization.

Reductive dicarbofunctionalization of alkenes with two electrophiles would bypass the need for pre-generation of organometallic nucleophiles, thus broadening the scope, increasing functional group tolerance, and avoiding handling air-sensitive organometallic reagents (Scheme 1B).[3,4] Despite recent examples of reductive dicarbofunctionalization using aryl iodides as the electrophiles,[5] a variant compatible with aryl and alkyl bromides remains an unmet challenge (Scheme 1B). Commercially available bromo-electrophiles are 10 times more abundant than iodo-electrophiles. Moreover, tolerance of functional groups, such as heterocycles, would largely expand the utility of this strategy, which has not been demonstrated in previous reductive methods. We hypothesize that such a reaction could be used to prepare substituted pyrrolidine and piperidine derivatives that are common pharmacophores (Scheme 1C).[6,7] The results presented below validate this hypothesis and show that a wide range of bromo-alkene substrates undergo difunctionalization with a variety of aryl, heteroaryl, and alkyl bromo-electrophiles to afford cyclopentane, pyrrolidine, piperidine, and tetrahydrofuran derivatives. The broad scope and good functional group tolerance makes this reaction an appealing method for synthetic applications.



Scheme 1. Synopsis of 1,2-Dicarbofunctionalization of Alkenes and Potential Applications in Synthesis

Radical cyclizations have been applied extensively to the preparation of carbo- and heterocycles.[8] Previous radical cyclization often completes with the oxidation or reduction of the radical (Scheme 2, dashed arrow).[8,9] Nickel catalysts have been recently characterized to generate alkyl radicals upon

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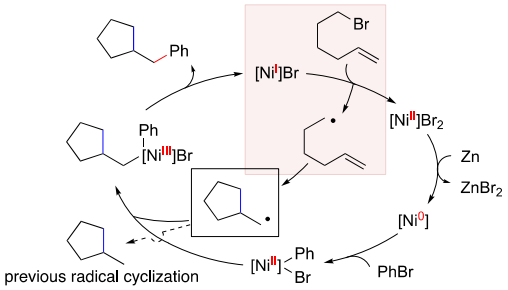
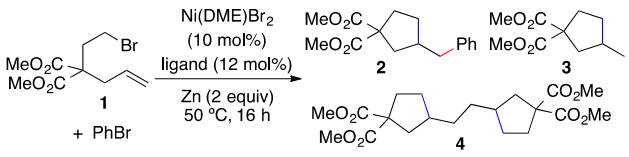
halogen abstraction.[10,11] We speculate that the radical generated from an alkyl bromide with a Ni catalyst could cyclize with a tethered alkene (Scheme 2). The resulting radical is then trapped by a Ni(II) aryl intermediate, which is formed from the oxidative addition of PhBr to Ni(0). Reductive elimination from the Ni(III) intermediate would give the difunctionalization product.[1,2]



Scheme 2. Adaptation of Radical Cyclization to Ni-Catalyzed Alkene Dicarbofunctionalization

We set out to test our design by evaluating Ni catalysts under reductive conditions. The coupling of 6-bromoalkene **1** with PhBr was chosen as the model reaction (Table 1). Three products were observed in a series of experiments: **2** from the desired reductive difunctionalization, **3** from reductive cyclization, and **4** from radical dimerization. Recent advances in Ni-catalyzed reductive coupling reveal the beneficial effect of bidentate nitrogen ligands.[4,12] The use of di-^{t}Bu-bpy (4,4'-di-*tert*-butyl-2,2'-bipyridine) formed **2** in 76% yield (Table 1, entry 1). The yield of **2** was optimized to 91% by replacing di-^{t}Bu-bpy with phenanthroline (entry 2), while the use of more hindered neocuproine resulted in a lower yield (entry 3). It is noteworthy that in the absence of PhBr, the reaction formed **4** in quantitative yield with di-^{t}Bu-bpy as the ligand (entry 8).

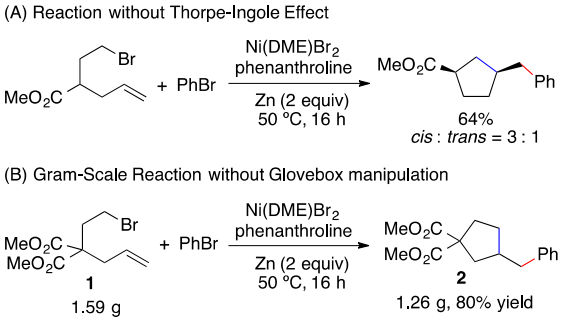
Table 1. Optimization of Reaction Conditions[a]



	Ligand	Solvent	**2** (%yield)[b]	**3** (%yield)[b]	**4** (%yield)[b]
1	di-^{t}Bu-bpy	DMA	76	0	7
2	**1,10-phenanthroline**	**DMA**	**91 (94)**	**0**	**8**
3	neocuproine	DMA	19	6	30
4	1,10- phenanthroline	DMF	33	6	45
5	1,10- phenanthroline	HMPA	53	0	6
6	1,10- phenanthroline	THF	0	8	0
7[c]	1,10- phenanthroline	DMA	0	0	0
8[c]	di-^{t}Bu-bpy	DMA	0	0	99 (99)

[a] 0.1 mmol scale, 2 equiv of PhBr, 2 equiv. of Zn. DMA = *N,N*-dimethylacetamide, DMF = *N,N*-dimethylformamide, HMPA = hexamethylphosphoramide. [b] Calibrated NMR yields using CH_3NO_2 as an internal standard. Isolated yields in parentheses. [c] No PhBr.

Mono-substituted substrates without the Thorpe-Ingold effect underwent reductive cyclization in good yields (Scheme 3A). The unsubstituted carbochain, however, favors direct coupling with PhBr prior to cyclization. In order to explore the practicality of the method, we carried out a gram-scale reaction of **1** using standard Schlenk techniques without the use of gloveboxes (Scheme 3B). The reaction proceeded to high conversion to **2**.



Scheme 3. Substituents Effect and Reaction on Scale.

With optimized conditions in hand, the substrate scope of this reaction, with respect to the coupling partner, was then investigated (Table 2). The reaction appears to be relatively insensitive to the electronic properties of the aryl bromide: both electron-rich (entry 2) and electron-deficient (entries 3-8) *para*-substituted aryl bromides undergo effective coupling in excellent yields. The optimized conditions also showed high compatibility with electrophiles with varying steric effects, and tolerated *meta*- and *ortho*-substituents well (entries 9-12). Reactive functional groups, including chloride (entry 4), ketone (entry 6), aldehyde (entry 7), alkene (entry 8), and ester groups (entry 10) are conserved. Pyridines, which are conventionally problematic in transition metal catalysis, due to their strong coordination capability, did not inhibit the reactions (entries 13-15). Similarly high yields were observed with indole and thiophene derivatives (entries 16-18).

In addition to sp^2 hybridized electrophiles, the reaction conditions are compatible with alkyl bromides (Table 2, entries 19-23). The yields for alkyl electrophiles were generally lower than those with aryl electrophiles, with a substantial amount of **4** observed as the byproduct. We attribute the reduced yields to slower activation of alkyl bromides relative to aryl bromides,[13] which causes the cyclized radical intermediate to accumulate and dimerize. In the presence of an alkyl chloride substituent, the coupling is selective for the bromide, and the chloride substituent survives the conditions (entry 20).

After assessing the scope of aryl and alkyl bromides, we examined the use of other electrophiles (Table 2, entries 24-27). Given the versatile reactivity of Ni with aryl iodides and pseudo-halides,[14] we investigated PhI as the coupling partner. PhI gave slightly lower yield of **2** compared to that of PhBr (entry 24), with concomitant formation of biphenyl as the major by-product, resulting from reductive coupling of PhI. Mesylates are anticipated to be harder to activate, and 2-naphthyl mesylate undergoes coupling with **1** to give 37% yield (entry 25). PhCl is

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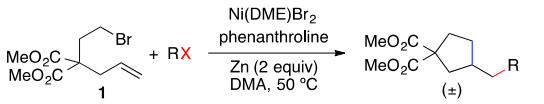
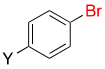
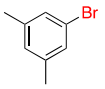
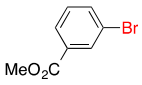
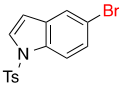
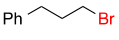
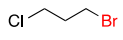
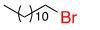
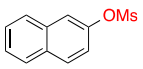
inert (entry 26), whereas BnCl can be activated to give a modest yield of the product (entry 27).

Table 2. Scope of Electrophiles[a]

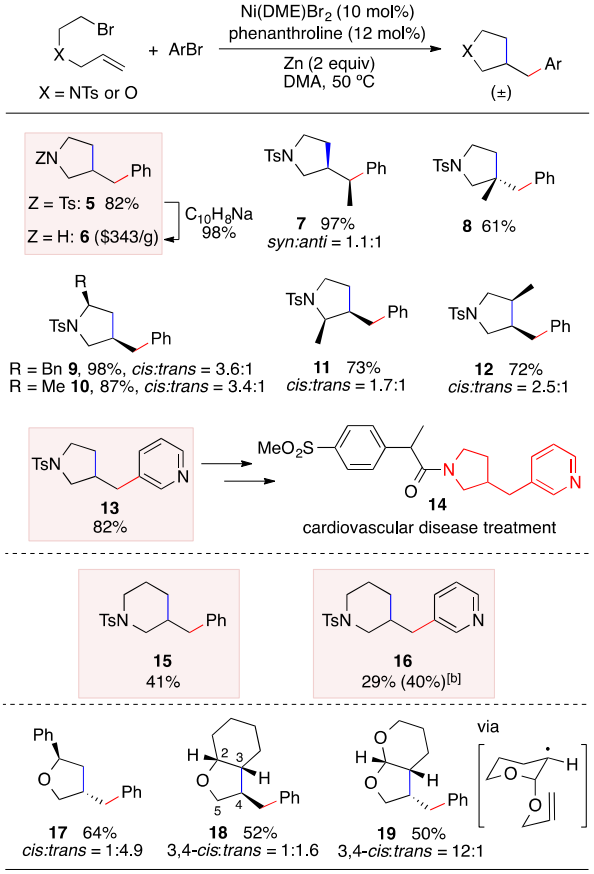


Entry	RX	%yield[b]	Entry	RX	%yield[b]
1	 Y = H	94	13		92
2	Y = Me	99			
3	Y = CF_3	95			
4	Y = Cl	80			
5	Y = Ph	99			
6	Y = COPh	74	14		99
7	Y = CHO	85			
8	Y = $CHCH_2$	86			
9		86	15		98
10		70	16		99
11		83	17		85
12		81	18		71
19		54	22		45
20		61	23		48
21		34			
24	PhI	77	26	PhCl	0
25		37	27	BnCl	31

[a] 0.1 mmol scale, 2 equiv of ArBr, 2 equiv of Zn, 10 mol% Ni, 12 mol% phenanthroline. Entries 19-23: 0.2 mmol scale, 4 equiv of RBr, 5 mol% Ni, 6 mol% phenanthroline. [b] Isolated yields.

The optimized difunctionalization reaction is readily applicable to synthesizing heterocycles (Table 3). Many pharmacophores share the 3-benzyl pyrrolidine **6** motif, including a modulator of the cholesterol biosynthetic pathway[6] (Scheme 1C) and a calcium-sensing receptor antagonist.[15] The present reaction offers a more efficient route to **6** compared to previous preparation.[16] The reductive difunctionalization is particularly useful when various substituents on the olefins exhibit little influence on the yields (**7**-**12**). The diastereoselectivity is consistent with previous observations in radical cyclization[8a,17] and follows the Beckwith-Houk model.[18] 3-Bromopyridine proved to be a competent coupling partner under the standard conditions to give **13** in 82% yield, a key intermediate en route to an anti-soluble epoxide hydrolase (sEH) inhibitor **14**, which is a potential cardiovascular disease treatment.[19]

Table 3. Scope of Alkenes and Synthesis of *N*- and *O*-Heterocycles[a]



[a] 0.1 mmol scale, 2 equiv of ArBr, 2 equiv of Zn, 10 mol% Ni, 12 mol% phenanthroline. Isolated yields. The assignment of the diastereomers is facilitated by NOESY experiments. [b] NMR yield in parenthesis.

Previous 2-component difunctionalization of alkenes are restricted to the formation of 5-membered rings.[1] Under our conditions, piperidine derivative **15** is obtained in 41% yield. The desired pathway competes against the direct reductive coupling of the alkyl bromide with PhBr without cyclization, which is consistent with the anticipated slow 6-*exo*-*trig* cyclization.[8a] The use of 3-bromopyridine as a coupling partner formed piperidine **16**. The importance of these results is apparent in the context of synthesizing biologically active molecules. For example, **15** is an epigenetic polycomb repressive complex 2 (PRC2) inhibitor,[20] while **16** is an intermediate to a somatostatin SST1 receptor antagonist (Scheme 1C).[7]

In addition to *N*-heterocycles, tetrahydrofuran derivatives are accessible by the difunctionalization of allyl bromoethyl ethers. For this class of substrates, at least one substituent is needed to promote the cyclization, while unsubstituted allyl bromoethyl ether undergoes direct coupling without cyclization. The high diastereoselectivity of *cis*-**19** is attributed to stabilization of the chair conformation by the anomeric effect.[17]

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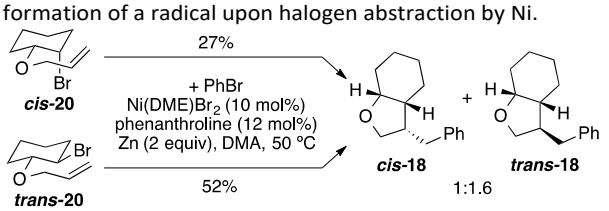
Preliminary mechanistic studies are carried out to probe the radical pathway. Both *cis*- and *trans*-**20** proceeded to give a mixture of *cis*- and *trans*-**18** in the same ratio (Scheme 4). The poor diastereoselectivity reflects the small energy difference in the chair and boat conformations and is consistent with previous radical cyclization initiated by tin hydride.[21] Moreover, the lack of influence of the starting stereocenter supports the formation of a radical upon halogen abstraction by Ni.



Scheme 4. Effect of the Stereocenter in the Substrate

In summary, the Ni-catalyzed reductive dicarbofunctionalization of alkenes provides efficient access to substituted pyrrolidine, piperidine, and tetrahydrofuran derivatives, many of which are of pharmaceutical importance. This new method features a broad substrate scope and good functional group tolerance, and represents an important alternative to the redox neutral dicarbofunctionalization reactions.

This work was supported by the National Science Foundation under award number CHE-1654483.

Conflicts of interest

The authors declare no conflict of interest.

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