# <u>Cramic</u> LETTERS

## Nickel-Catalyzed Reductive Cyclization of Alkyl Dihalides

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**Supporting Information** 

**ABSTRACT:** The reductive coupling protocol to intramolecular cyclization of dihaloalkanes is presented. It leads to five- and six-membered rings, with the former being more efficient. The incorporation of secondary alkyl halides generally promotes coupling efficiency. To the best of our knowledge,



M = N, C R<sup>1</sup>, R<sup>2</sup> = H, alkyl, aryl X = I, Br, Cl

this is the first catalytic ring-closure reaction arising from dihaloalkanes under chemical reductive conditions.

Reductive homocoupling of alkyl halides, namely, Wurtztype reactions, usually employ alkali metals such as Na, Mg, etc.<sup>1</sup> The strong reductants generally lead to poor functional group tolerance and poor yields. More importantly, the intrinsically similar reactivity between the two coupling alkyl halides renders the cross-Wurtz reaction extremely challenging.

Recently, transition-metal-catalyzed coupling reactions on alkyl electrophiles have advanced rapidly.<sup>2,3</sup> In particular, a variety of elegant Ni-catalyzed catalytic methods have been developed for the formation of  $C(sp^3)-C(sp^3)$  bonds using alkyl nucleophiles with alkyl electrophiles.<sup>4–7</sup> On the other hand, direct coupling of two alkyl electrophiles under reductive conditions has also received increasing attention;<sup>8-11</sup> this strategy differs from the concurrent oxidative coupling method using two alkyl nucleophiles, e.g., C(sp<sup>3</sup>)-H, which is more economically efficiently but limited to special directing groups.<sup>12</sup> For example, Leigh, Peng, and Weix independently developed Ni-catalyzed reductive homocoupling of alkyl halides using Zn or Mn as the reductant.<sup>9</sup> The cross-coupling of two different alkyl halides remains challenging due to highly competitive homo coupling of the two alkyl coupling partners. We have first disclosed a Ni/Cl-Pybox (3a)/Zn catalytic system that could inhibit the homocoupling of the two coupling alkyl halides to some extent.<sup>10</sup> However, 3 equiv of one of the alkyl halides is necessary, suggesting that the catalytic system is not able to effectively bias the two coupling alkyl halides. Our recent efforts to this challenging issue led to the reductive coupling of secondary with primary alkyl bromides using  $(Bpin)_2$  as the terminal reductant, which utilizes only 1.5 equiv of excess primary alkyl bromides.<sup>1</sup>

In the meantime, although reductive intramolecular cyclization of dihaloalkanes can be achieved using metals such as Zn (heat), Cr(II), Co, Cu, and Li and alkali naphthalenes, etc. (Figure 1), only simple alkyl dihalides (e.g., 1,3-dibromopropane) are studied, which generally require harsh conditions and are unsuited for five-membered and larger rings.<sup>13,14</sup> For example, reaction of *t*-Bu-Li with  $\alpha,\omega$ -dihaloalkanes under -23 °C provides the cyclized products;<sup>13e</sup> activated Cu powder mediated conditions are only competent for 1,3-dibromobutane



Figure 1. Approaches to cyclization of dihaloalkanes.

by in situ formation of alkyl-Cu, which cyclizes to generate methylcyclopropane under -70 °C.<sup>14</sup> Apparently, these existing methods suffer from issues of poor functional group tolerance and limited substrate scope. In addition, both stoichiometric Ni(I)(tmc) complex and catalytic Ni(I)(Salen)/electrochemical protocols have been revealed for the cyclization of dihaloalkanes. However, these conditions again suffer from inconvenient operations and limited substrate scope and low cyclization efficiency.<sup>15</sup>

Herein, we present our studies on Ni-catalyzed reductive cyclization of dihaloalkanes with Zn powder (Figure 1). To the best of our knowledge, this work represents the first catalytic intramolecular cyclization of dihaloalkanes under chemical reductive conditions, which may be useful for the construction of more complex organic skeletons.

Extension of the reductive method for cross-coupling of two alkyl halides to intramolecular cyclization of dihaloalkanes is of interest as closed-ring structures can be obtained, which are generally useful for the construction of more complex organic architectures. However, hydrodehalogenation,  $\beta$ -H elimination, and oligomerization of the dihaloalkanes can be problematic. At the outset, we chose *N*-tethered dihaloalkane **1a** as the model substrate. To our surprise, under the Ni(COD)<sub>2</sub>/3a/DMA/Zn and NiI<sub>2</sub>/6/(Bpin)<sub>2</sub>/NMP reductive conditions that have been previously developed for the cross-coupling of alkyl halides, we did not observe the cyclization product **2a**.<sup>10,11</sup>

With significant optimization efforts, we eventually identified that under the  $NiI_2/4b/DMA$  catalytic conditions the reaction

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generated 2a smoothly in 83% yield at ambient temperature (Table 1, entry 1). Other ligands (entries 2–11, Figure 2),

#### Table 1. Optimization for the Cyclization of 1a

| Br N Br | Nil <sub>2</sub> (10 mol %)<br><b>4b</b> (10 mol %) | Cbz |
|---------|---|-----|
|         | Zn (300 mol %)                                      |     |
| 1a      | DMA, 25 °C, 16 h                                    | 2a  |
|         | "standard" conditions                               |     |

| entry <sup>a</sup> | variation from the "standard" conditions  | yield <sup>b</sup><br>(%) |
|--------------------|---|---------------------------|
| 1                  | none  | 83                        |
| 2                  | 3a, instead of 4b   | 20                        |
| 3                  | 3b, instead of 4b   | 37                        |
| 4                  | 3c, instead of 4b   | 33                        |
| 5                  | 4a, instead of 4b   | 76                        |
| 6                  | 4c, instead of 4b   | 72                        |
| 7                  | 5a, instead of 4b   | 71                        |
| 8                  | 5b, instead of 4b   | 66                        |
| 9                  | 5c, instead of 4b   | $ND^{c}$                  |
| 10                 | 6, instead of 4b  | 64                        |
| 11                 | 7, instead of 4b  | 41                        |
| 12                 | Ni(cod) <sub>2</sub> , instead of NiI <sub>2</sub>                                      | 60                        |
| 11                 | NiBr <sub>2</sub> , instead of NiI <sub>2</sub>   | 75                        |
| 14                 | NiCl <sub>2</sub> , instead of NiI <sub>2</sub>   | $ND^{c}$                  |
| 15                 | Ni(acac) <sub>2</sub> , instead of NiI <sub>2</sub>                                     | $ND^{c}$                  |
| 16                 | DMF, instead of DMA   | 40                        |
| 17                 | THF, instead of DMA   | $ND^{c}$                  |
| 18                 | 1,4-dioxane, instead of DMA   | $ND^{c}$                  |
| 19                 | 5 mol % of NiI <sub>2</sub> and 5 mol % of <b>4b</b> , instead of 10 mol % and 10 mol % | 62                        |

<sup>*a*</sup>Reaction conditions: **1a** (0.15 mmol), NiI<sub>2</sub> (10 mol %), Zn (300 mol %), ligand (10 mol %), DMA (1 mL), 25 °C. <sup>*b*</sup>Isolated yields. <sup>*c*</sup>Not detected.



Figure 2. Structures of ligands.

nickel sources (entries 12-15), and solvents (16-18) were inferior. Lowering the catalyst and ligand loading to 5% significantly diminished the yield of the cyclization product to 62% (entry 19). In general, the major side reaction included hydrodehalogenation reduction and intermolecular oligomerization.

With the optimized conditions in hand, a range of alkyl dibromides and diiodides was examined. The phenyl carbomate **1b** proved to be more efficient than the analogous methyl carbomate **1c**, which gave **2b** and **2c** in 92% and 48% yields (entries 1 and 2). The arylamine-tethered alkyl dibromides **1d**,e delivered the cyclization products **2d**,e in moderate yields (entries 3 and 4). The side reactions of these reactions arose from hydrodehalogenation and oligomerization of the starting halides. Interestingly, the tosyl-protected dibromide **1f** generated the five-membered ring product **2f** in low yield (entry 5), wherein a substantial amount of oligomerization was

detected. These results suggest that the electron properties of the central nitrogen play a very important role in tuning the reactivity of the cyclization. The Cbz-protected diiodide 1g gave 2a (2a = 2g) in 93% yield when a mixture of 1,4-dioxane and DMA solvent was used (entry 6). Under similar conditions, the phenyl carbomate-tethered diiodide 1h generated the cyclization product 2b (2b = 2h) in 70% yield (entry 7), whereas the 4-methylphenyl analogue 1i gave 2e (2e = 2i) in 58% yield (entry 8). On the other hand, the carbon-tethered alkyl dibromides as well as diiodides only generated the cyclization products in moderate yields as evident in 2j and 2k (entries 9–11). The coupling of secondary alkyl bromides with primary and secondary bromides also enabled the production of five-membered ring products in moderate to good yields, as in 2m, 2n, and 2o (entries 12-14), where the cyclization of two secondary alkyl bromides was more efficient (71%, cis/trans = 1:1, entry 14). The intramolecular cyclization of benzylic dichloride 1p generated the 1,2-diphenylcylcopentane 2p in 40% yield (entry 15).

The formation of six-membered rings is generally less efficient than the five-membered rings. For instance, the Cbzprotected N-tethered primary alkyl dibromide 1q generated the six-membered ring product 2q in 50% yield (entry 16). In contrast, the incorporation of a secondary alkyl halide was able to generate a methyl-substituted six-membered ring product 2r in 60% yield (entry 17). While the 1,2-bis(2-bromoethyl)benzene gave a low yield of cyclization product 2s, the cyclization of bis(benzylic chloride) provided 2t in 66% yield (entries 18 and 19). The formation of a seven-membered ring product 2u was achieved in a 38% yield (entry 20), indicating the nature of substrates that are kinetically amenable to cyclization is an important factor in achieving high reaction efficiency. Finally, the formation of 3-membered ring product 2v was not successful due to oligomerization of 1v, while 4membered ring product 2w was obtained in 10% yield majorly due to  $\beta$ -H elimination (Table 2, entries 21 and 22).

In our previous studies for cross-coupling of two alkyl halides, we have determined that the reactions do not involve in situ formation of organozinc reagents. Therefore, a Negishi mechanism should not be operative in our method.<sup>10</sup> According to Vicic's studies on the Ni-catalyzed Negishi mechanism, the oxidative addition of  $R_{alkyl}{-}X$  to  $alkyl{-}Ni(I)$ produces an alkyl-Ni(III)-R<sub>alkyl</sub> intermediate which is crucial for  $C(sp^3)-C(sp^3)$  bond formation.<sup>16</sup> Therefore, we propose the following mechanistic pathway (Scheme 1). Oxidative addition of the first C-X bond in  $X-R_{alkyl}-X$  to Ni(0) leads to  $X-R_{alkyl}-Ni(II)$  complex. A single electron reduction gives a X-R<sub>alkyl</sub>-Ni(I) species, which undergoes a second oxidative addition resulting in c-R<sub>alkyl</sub>-Ni(III) intermediate. Subsequent reductive elimination gives the product and regenerates a second Ni(I) species, which could be reduced to Ni(0) by Zn to continue the catalytic cycle. Alternatively, the second C-X bond may undergo halide abstraction by Ni15a or single electron reduction by Zn to give a radical species which adds to the  $R_{alkyl}$ -Ni(II) to give the c- $R_{alkyl}$ -Ni(III) intermediate (Scheme 1).<sup>17</sup> The formation of c- $R_{alkyl}$ -Ni(III) intermediate may be important for the explanation of why 3-membered ring product 2v was not observed from 1v due to substantial ring strains in the formation of 4-membered alkyl–Ni ring (Table 2, entry 21), which consequently favors oligomerization of 1v.

In conclusion, we have described our studies on the intramolecular cyclization of nitrogen- and carbon-tethered dihaloalkanes. The reaction conditions work effectively for the

### Table 2. Intramolecular Cyclization of Dihaloalkanes $^{a,b}$



<sup>*a*</sup>Reaction conditions: **1** (0.15 mmol), NiI<sub>2</sub> (0.015 mmol), **4b** (0.015 mmol), Zn (0.45 mmol), solvent (1 mL), 25 °C. <sup>*b*</sup>Isolated yields. <sup>*c*</sup>Not detected. <sup>*d*</sup>I<sub>4</sub>-Dioxane/DMA = 3/7, instead of DMA. <sup>*e*</sup>Yield was determined by <sup>1</sup>H NMR spectroscopy by comparison to an internal standard (PhMe<sub>3</sub>Si). <sup>*f*</sup>Ligand **4c** instead of **4b**.

#### Scheme 1. Proposed Mechanistic Pathways



formation of five-membered rings and moderately for sixmembered rings. The coupling involving secondary alkyl halides appears to be more efficient than cyclization of primary/primary alkyl dihalides. The construction of a sevenmembered ring is less efficient, suggesting that both catalyst and substrates are pivotal for efficient cyclization over the undesired intermolecular oligomerization and other side reactions such as hydrodehalogenation. Finally, a mechanism involving a *c*-alkyl-Ni(III) intermediate is proposed.

#### ASSOCIATED CONTENT

#### **Supporting Information**

Experimental details and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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#### Notes

The authors declare no competing financial interest.

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