Ni-catalysed reductive arylalkylation of unactivated alkenes†

Youxiang Jin and Chuan Wang
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In this protocol Ni-catalysed reductive arylalkylation of unactivated alkenes tethered to aryl bromides with primary alkyl bromides has been accomplished, providing a new path to construct diverse benzene-fused carbocyclic and heterocyclic cores including indanes, tetrahydroisoquinolines, indolines and isochromanes. Notably, this new method circumvents the pregeneration of organometallics and demonstrates high tolerance to a wide range of functional groups. The preliminary mechanistic investigations suggest a reaction pathway with an intermediate reduction.

Results and discussion

For the optimization of reaction conditions, we used bromo-phenyl (1a) tethering a terminal olefinic unit and 4-bromo-butyl acetate (2a) as the standard substrate (Table 1). Systematic screening of the reaction parameters provided the optimum conditions using NiBr₂ as a catalyst, L₁ as a ligand, DMA as a solvent and Zn as a reducing agent at 55 °C (entry 1). Generally, all the reactions delivered a dimer compound 3a-1 in a 1 : 1 diastereomeric ratio as the major by-product and its yields are also shown in the table (entries 2–23). Furthermore, the formation of a low amount of reductive Heck product 3a-2, debromination product 3a-3 and cross-coupling product 3a-4 was also observed. In comparison, replacing either or both of these bromide precursors with their iodo-analogues gave rise to increasing amounts of the reductive Heck product 3a-2 in the product mixtures (entries 2–4). The use of other pyridine-based ligands L₂–L₆ resulted in lower reaction efficiency (entries 5–9).

Table 1

| Entry | Ligand | Solvent | Reductant | Product |
|-------|--------|---------|-----------|---------|
| 1     | L₁     | DMA     | Zn         | 3a-1    |
| 2     | L₁     | DMA     | Zn         | 3a-2    |
| 3     | L₁     | DMA     | Zn         | 3a-3    |
| 4     | L₁     | DMA     | Zn         | 3a-4    |
| 5     | L₂     | DMA     | Zn         | 3a-5    |
| 6     | L₃     | DMA     | Zn         | 3a-6    |
| 7     | L₄     | DMA     | Zn         | 3a-7    |
| 8     | L₅     | DMA     | Zn         | 3a-8    |
| 9     | L₆     | DMA     | Zn         | 3a-9    |

† Electronic supplementary information (ESI) available: Experimental procedure, spectral data, NMR-data, and HPLC-data. See DOI: 10.1039/c8sc04279a

Scheme 1

Redox-neutral (A) and reductive (B) arylalkylation of tethered alkenes for the synthesis of benzene-fused cyclic compounds.
Table 1  Variation of the reaction parameters for the Ni-catalysed reductive arylalkylation reaction

| Entry | Variation from the optimum conditions | Yield 3a<sup>a</sup> (%) | Yield: 3a-1<sup>b</sup> (%) |
|-------|--------------------------------------|--------------------------|-----------------------------|
| 1     | None                                 | 69 (67<sup>c</sup>)      | 9                           |
| 2     | Iodo-analogue of 1a used             | 32                       | 19 (8<sup>d</sup>)          |
| 3     | Iodo-analogue of 2a used             | 10                       | 18 (31<sup>d</sup>)         |
| 4     | Both iodo-analogues of 1a and 2a used| 17                       | 10 (30<sup>d</sup>)         |
| 5     | L2 instead of L1                     | 30                       | 49                          |
| 6     | L3 instead of L1                     | 45                       | 2                           |
| 7     | L4 instead of L1                     | 54                       | 13                          |
| 8     | L5 instead of L1                     | 32                       | 50                          |
| 9     | L6 instead of L1                     | 0                        | 0                           |
| 10    | NiI<sub>2</sub> instead of NiBr<sub>2</sub> | 61                       | 8                           |
| 11    | Ni(OTf)<sub>2</sub> instead of NiBr<sub>2</sub> | 32                       | 4                           |
| 12    | NiBr<sub>2</sub>·glyme instead of NiBr<sub>2</sub> | 63                       | 8                           |
| 13    | Ni(COD)<sub>2</sub> instead of NiBr<sub>2</sub> | 63                       | 7                           |
| 14    | DMF instead of DMA                   | 43                       | 3                           |
| 15    | NMP                                   | 68                       | 8                           |
| 16    | THF instead of DMA                   | 0                        | 0                           |
| 17    | MeCN instead of DMA                  | 0                        | 0                           |
| 18    | Mn instead of Zn                      | 51                       | 17                          |
| 19    | 75 °C instead of 55 °C                | 62                       | 8                           |
| 20    | 35 °C instead of 55 °C                | 27                       | 2                           |
| 21    | 1.2 equiv. 2a used                   | 50                       | 13                          |
| 22    | 10 mol% NiBr<sub>2</sub> used        | 63                       | 13                          |
| 23    | 2 equiv. Zn used                     | 50                       | 7                           |

<sup>a</sup> Unless otherwise specified, reactions were performed on a 0.2 mmol scale of aryl bromide 1a with 2 equiv. bromobutyl acetate (2a), 15 mol% NiBr<sub>2</sub>, 15 mol% ligand L1 and 4 equiv. Zn as the reductant in 0.5 mL DMA at 55 °C for 10 h. <sup>b</sup> GC yields using n-dodecane as an internal standard. <sup>c</sup> Yield of the isolated product. <sup>d</sup> Yield of 3a-2.
Ni-salt screening indicated that the studied reactions could be promoted by both Ni(II)- and Ni(0)-catalysts (entries 10–13). Performing the reaction in other polar solvents including DMF and NMP led to decreased yields (entries 14 and 15), whereas the reaction was completely shut down when using THF or MeCN as the solvent (entries 16 and 17). The reaction employing Mn instead of Zn as a reducing agent yielded the product in a reduced yield (entry 18). In addition, the temperature impact on this reaction was also investigated and both raising and lowering the reaction temperature had a detrimental effect on the reaction efficiency (entries 19 and 20). Moreover, reducing the amount of alkyl bromide 4, NiBr₂ or Zn-powder all resulted in lower yields (entries 21–23).

After establishing the best reaction conditions, we started to evaluate the substrate spectrum of this Ni-catalyzed reductive alkylalkylation reaction by varying the structure of both pendant alkenes 1 and alkyl bromides 2 (Table 2). First, we studied the influence of the alkene substitution pattern on the outcome of this reaction. In the case of disubstituted terminal olefins, the reactions provided the products 3a–e in moderately good yields.

**Table 2** Evaluation of the substrate scope of the Ni-catalysed reductive alkylalkylation reaction$^{a,b}$

| R¹ | R² | R³ | R⁻ | Yield (%) | dr (%) |
|-----|-----|-----|-----|-----------|--------|
| Me  | Me  | Me  | 3a  | 67% (60%) |        |
| Et  | Me  | Me  | 3b  | 61%       |        |
| n-Pr| Me  | Me  | 3c  | 55%       |        |
| i-Pr| Me  | Me  | 3d  | 46%       |        |
| c-Hex| Me  | Me  | 3e  | 58%       |        |
| Cl  | Me  | Me  | 3h  | 65%       |        |
| 5-MeO| Et  | Me  | 3i  | 52%       |        |
| 5-F  | Et  | Me  | 3j  | 53%       |        |
| 5-Cl | Et  | Me  | 3k  | 61%       |        |
| 6-F  | Et  | Me  | 3l  | 58%       |        |
| Me  | 2-Methyl allyl | 3m  | 61% |          |
| Br  | Me  | Me  | 3n  | 57%       |        |
| R  | Me  | Me  | 3o  | 50%       |        |
| R  | 2-Methyl allyl | 3p  | 57% |          |
| R  | Br  | Me  | 3q  | 51%       |        |
| R  | Ts  | Me  | 3r  | 61%       |        |
| R  | OH  | Me  | 3s  | 51%       |        |
| R  | BPin | 3t  | 42% |          |

$^{a}$ Unless otherwise specified, reactions were performed on a 0.4 mmol scale of aryl bromides 1 with 2 equiv. alkyl bromides 2, 15 mol% NiBr₂, 15 mol% ligand L1 and 4 equiv. Zn as the reductant in 1.0 mL DMA at 55 °C for 10 h. $^b$ Yields of the isolated products. $^c$ Reaction was performed on a 1 g scale using 5 mol% NiBr₂ and 5 mol% ligand L1 at 65 °C for 12 h. $^d$ Determined by $^{13}$C-NMR-spectroscopy. $^e$ Reactions were performed at 70 °C. $^f$ Determined by HPLC-analysis.
Remarkably, the reactions employing 1,1,2-trisubstituted alkenes also proceeded smoothly under the optimum reaction conditions yielding the products 3f and 3g in excellent diastereoselectivities, although the E/Z ratios of the alkenes precursors are nearly 1:1. The high diastereocntrol indicates that this Ni-catalyzed reaction is probably not initiated by the radical addition of the alkyl group to the C–C double bond. When 1,2-disubstituted and monosubstituted alkenes were used as substrates, no desired products were obtained due to the high tendency to undergo the Heck reaction. Next, the examination of the substituent effect on the phenyl ring was undertaken. To our delight, all the substrates bearing electron-withdrawing or donating groups turned out to be suitable substrates providing the corresponding products 3h–m, 3w and 3ae in moderate to good yields. Furthermore, our method is not limited to the synthesis of indane derivatives. A series of indolines 3n–p and 3ah and tetrahydroisoquinolines 3q–t and an isochroman 3u were also successfully prepared through this Ni-catalysed reaction. Subsequently, diverse primary alkyl bromides were reacted with various pendant olefins. Of note is that this Ni-catalysed reaction demonstrates the high compatibility of a wide range of functional moieties including alcohol (3y), boronate (3z), acetal (3aa), imide (3ac and 3ae), nitrile (3ad), ester (3af and 3ah), aldehyde (3ag) and ketone (3ai). Moreover, the reaction using 1a and 2a was performed on a one-gram scale still furnishing the product 3a in a 65% yield with 5 mol% catalyst loading. A limitation of this method was observed in the case of secondary and tertiary bromides, which failed to yield the aryalkylation products.

A series of control experiments were carried out to explore the mechanism of this Ni-catalyzed ring opening reaction. First, we reacted Zn-powder with both bromide precursors under the standard reaction conditions and the results indicated that no organozincs were formed in the reaction mixture (Scheme 2). Consequently, the Negishi coupling reaction pathway is less likely for the studied reaction.

Next, we carried out a stoichiometric reaction between Ni(COD)₂ and the aryl bromide 1a. After 10 h the reaction was quenched with water and it turned out that nearly half of the starting material was recovered and the major product was the dimer 3a-1 (Scheme 3A). If the alkyl bromide 2a was added to the reaction mixture instead of water, only traces of the desired product 3a were formed in this case (Scheme 3B). In contrast, the sequential stoichiometric reactions of Ni(COD)₂ with 1a and 2a in the presence of Zn furnished the product 3a in a 30% yield (Scheme 3C). These results suggest that Zn is required in a step of an intermediate reduction instead of serving as a terminal reductant in this Ni-catalysed reaction, which is likely initiated by the oxidative addition of aryl bromide to a Ni(0)-species followed by an intramolecular migratory insertion. A similar process was reported very recently by Kong et al. in Ni-catalysed reductive diarylation of activated olefins.⁵

Subsequently, we conducted the reaction using TEMPO as a radical scavenger and in this case the reaction was completely shut down revealing that a radical species might be involved in the key step of this reaction. This is not surprising since alkyl bromide can easily form radicals in Ni-catalyzed reductive arylation.⁶ However, it is unknown whether the migratory insertion of Ni–Ar into the C–C double bond proceeds through a radical pathway or not under reductive conditions. In order to gain more insights into the mechanism of this reaction, a radical clock experiment employing a cyclopropyl-substituted alkene as a substrate was conducted (Scheme 4). In this case a ring opening product 3aj was obtained in 32% yield, whereas the formation of unrearranged product 3aj’ was not observed. This result could be rationalized by cyclisation involving an aryl radical, which is generated through the interaction of aryl bromide with the Ni-catalyst. Alternatively, the initial migratory insertion could be non-radical, but the resultant Ni-alkyl species after cyclisation might undergo homolytic Ni–alkyl bond exchange.

Scheme 2 Stoichiometric reactions of bromides 1a and 2a with Zn-powder.

Scheme 3 Stoichiometric control experiments for the Ni-catalyzed reductive aryalkylation.

![Scheme 3](image-url)
cleavage, affording the same C-centered radical as the one generated in the aryl-radical-mediated ring closure. Moreover, the high diastereoselectivities of 3f and 3g also support the formation of this alkyl radical; otherwise similar diastereomeric ratios would be obtained to their trisubstituted alkene-precurors. To differentiate the two possible pathways mentioned above we conducted Ni-catalysed reductive arylalkylation employing a chiral oxazoline ligand (Scheme 5). In this case the product 3a was obtained with a moderate enantioselectivity. This report clearly excludes the possibility of radical-mediated cyclisation, which is supposed to provide the product as a racemic mixture.

Based on the aforementioned experimental results we proposed the following plausible mechanism for this Ni-catalyzed reaction (Scheme 6). Initially, under the reductive reaction conditions a Ni(0)-species I is generated, which undergoes oxidative addition with aryl bromides 1 to afford a Ni(II) complex II. Next, the ring closure is accomplished via an intramolecular non-radical migratory insertion. The generated Ni(II) species III stays in equilibrium with an alkyl radical IV and Ni(i)LnBr before Zn-mediated reduction to the Ni(i) species V. The subsequent oxidative addition of alkyl bromides 2 involves the formation of a cage VI and the following recombination provides a Ni(III) intermediate VII. Finally, the reductive elimination of the Ni(iii) complex VII furnishes the products 3 and the Ni(i) species VIII, which is subsequently reduced to the Ni(0)-species I for the next catalytic cycle.

Conclusions

In conclusion, we have developed Ni-catalysed reductive arylalkylation of unactivated alkenes tethered to aryl bromides with an array of primary alkyl bromides, providing a new path to synthesize benzene-fused cyclic compounds such as indanes, tetrahydroisoquinolines, indolines and isochromanes with an all-carbon-stereogenic center. This new method is distinguished by avoidance of the use of pregenerated organometallics, high tolerance of a broad range of functional moieties and base-free reaction conditions. The preliminary mechanistic studies indicate that this Ni-catalysed reaction proceeds in a reaction pathway with an intermediate reduction. Further investigations into the asymmetric version of this reaction are in progress and will be published in due course.

Conflicts of interest

There is no conflict to declare.

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