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# Chemoselective reductive alkylation of tertiary amides by Ir and Cu(I) bis-metal sequential catalysis†

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We report herein a convenient and versatile method for the direct reductive alkylation of tertiary amides to give propargylic amines through sequential Ir-catalysed hydrosilylation–Cu(I)-catalysed alkylation. The reactions proceed chemoselectively at the amide group in the presence of several sensitive functional groups including the very reactive aldehyde group on either the amide or the alkyne coupling partner. The method is general for *tert*-amides with or without  $\alpha$ -hydrogen.

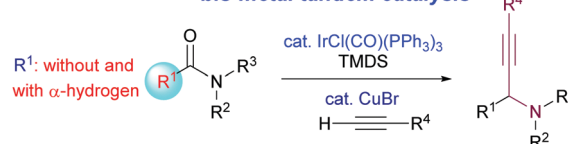
Reductive alkylation of amides is an essential transformation in the synthesis of alkaloids and nitrogen-containing medicinal agents.<sup>1,2a,b</sup> However, due to the poor electrophilicity of the amide carbonyl group, those transformations frequently require the use of highly reactive organometallic reagents (*e.g.* RLi and RMgX) and harsh conditions, which lead to low chemoselectivity and poor functional group tolerance. Consequently, multi-step methods are being routinely employed instead.<sup>1b,fg</sup>

Within the context of developing efficient synthetic methods, the step-economical direct transformation of amides has attracted considerable attention in recent years, leading to the accumulation of a host of synthetically useful methods.<sup>2,3</sup> Despite the advances, catalytic C–C bond forming reactions that employ common amides as substrates remain rare and challenging. Recently, based on Nagashima's iridium-catalysed transformation of amides into enamines (Scheme 1a),<sup>4</sup> Dixon and Chida/Sato have independently developed a catalytic intramolecular reductive nitro-Mannich-type reaction,<sup>5</sup> and a chemoselective reductive nucleophilic addition to *N*-methoxyamides.<sup>6</sup> Very recently, Chida and Sata have reported an iridium-catalysed reductive transformation of *N*-hydroxyamides into nitrones.<sup>7</sup> However, only *tert*-amides with  $\alpha$ -hydrogens have been employed as substrates in all these methods.<sup>4–7</sup>

a. Catalytic reduction of *tert*-amides to enamines (Nagashima)



b. This work: Reductive alkylation of *tert*-amides by bis-metal tandem catalysis



Scheme 1 (a) Nagashima's catalytic reduction of amides to enamines and (b) bis-metal sequential catalytic transformation of amides with C–C bond formation.

Propargylic amines are a class of versatile building blocks in organic synthesis and medicinal chemistry.<sup>1f,g,8</sup> The catalytic synthesis of these important structures has been extensively investigated in the last 15 years.<sup>8,10</sup> These efforts have resulted in several highly efficient and powerful methodologies.<sup>8–11</sup> However, to the best of our knowledge, the access to propargylic amines through the direct catalytic reductive alkylation of amides and lactams has hitherto been unknown. Considering the widespread use of amides as versatile synthetic intermediates in the synthesis of alkaloids and medicinal agents,<sup>1,2a</sup> and the fact that amides are products of numerous powerful synthetic methodologies,<sup>12</sup> the catalytic transformation of amides leading to C–C bond formation is highly desirable. Except for one report,<sup>13</sup> the known methods for the reductive alkylation of amides are stepwise and require additional steps to convert amides/lactams to more reactive thioamides/lactams,<sup>1f,g,14</sup> and selenoamides.<sup>15</sup> As a continuation of our research program on the direct transformation of amides,<sup>3b,e,g-i</sup> we report herein a bis-metallic Ir- and Cu(I)-catalysed reductive alkylation of common tertiary amides with or without an  $\alpha$ -hydrogen to give propargylic amines (Scheme 1b).

On the basis of the abovementioned literature precedents, our goal was to develop a direct, sequential catalytic hydrosilylation–alkynylation of common *tert*-amides. Although Nagashima's

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method (Scheme 1a)<sup>4</sup> has been developed and applied only for *tert*-amides containing  $\alpha$ -hydrogens,<sup>5–7</sup> we wondered if this method could be extended to include common *tert*-amides without an  $\alpha$ -hydrogen as substrates. Thus, a toluene solution of *N,N*-dimethylbenzamide (**1a**) was treated with a catalytic amount of Vaska's complex [IrCl(CO)(PPh<sub>3</sub>)<sub>2</sub>, 1 mol%], 1.2 equiv. of TMDS, 1.2 equiv. of phenylacetylene, and 5 mol% of CuBr (Table 1).<sup>9b</sup> To our delight, the desired propargylamine **3a** was obtained in 89% yield after being stirred at room temperature for 12 h. Similarly, subjecting of amide **1b** (the structures of all amides and alkynes used are listed in the ESI†) to the two-step, one-pot reductive alkynylation reaction afforded propargylic amine **3b** in 90% yield. Reactions of aliphatic amides **1c** and **1d** produced the corresponding propargylic amines **3c** and **3d** in 60% and 80% yield, respectively. The relatively low yield of **3c** could be attributed to the steric hindrance of the amide substrate. The reaction of sterically hindered *N,N*-diisopropylbenzamide **1e** also provided the corresponding amine (**3e**) in a moderate yield (67%), much lower than those of sterically unencumbered *N,N*-dimethylbenzamide (**1a**) and *N,N*-diallylbenzamide (**1f**). Functionalized alkyne **2b** participated in the reaction to afford amine **3g** in an excellent yield (91%). On the other hand, amides bearing either electron-rich groups such as furan-2-yl (**1h**) and benzo[*b*]thiophen-2-yl (**1i**) or electron-poor groups such as *para*-nitrophenyl (**1j**) all reacted similarly to give the corresponding amines **3h**, **3i**, and **3j** in 80%, 81%, and 77% yield, respectively.

After examining the steric and electronic effects, we explored the chemoselectivity and functional group tolerance.<sup>4,6,9e</sup> The mild reductive alkynylation reaction showed remarkable functional group tolerance and chemoselectivity as demonstrated by the formation of products **3j–3p**. The reaction tolerated redox-sensitive functional groups such as nitro (**3j**), cyano (**3k**), and aldehyde (**3l**), and common nitrogen protecting groups such as Boc (**3m**) and Cbz (**3n**). It is well known that amides are far less reactive than aldehydes. However, under the current conditions, the reaction of an aldehyde-containing substrate took place chemoselectively at the carbonyl of the amide instead of that of the aldehyde, leading to the isolation of amino aldehyde **3l** in 64% yield, along with the (aldehyde group) concomitantly reduced product **3l'** in 8% yield. Moreover, the reductive alkynylation reaction is fully compatible with a Boc-protected amine that contains an acidic proton (NHBoc, **1o**), affording the desired product **3o** in excellent yield (89%). Interestingly, the reaction of an amide bearing a free hydroxyl group (**1p**) yielded the *O*-silylated product **3p** in 52% yield when 2.0 equiv. of TMDS was used. It is worth mentioning that *o*-cyanobenzamide **1k** is a product of metal-catalysed C–H cyanation.<sup>12e</sup>

We next investigated the stereoselectivity of the reductive alkynylation reaction. For this purpose, benzamide derivatives derived from methyl (*S*)-proline **1q–1s** were selected as substrates. These functionalized substrates also provided opportunities for the further examination of the functional group tolerance and chemoselectivity of the reaction. The reductive phenylacetylenation of amido ester **1q** proceeded chemoselectively at the amido group to give a 20:1 diastereomeric mixture from which the major diastereomer **3q** was isolated in 78% yield (Table 1).

Table 1 Direct reductive alkynylation of common *tert*-amides without  $\alpha$ -hydrogen by sequential catalysis



<sup>a</sup> Isolated yield. <sup>b</sup> 2.0 equiv. of TMDS used. <sup>c</sup> Yield for the major diastereomer. <sup>d</sup> Ratio determined by <sup>1</sup>H NMR of the crude reaction mixture.

Similarly, excellent chemoselectivities and diastereoselectivities (dr = 17:1, 15:1, and 17:1) were also observed for the reactions of



trimethylsilylacetylene with **1q**, and phenylacetylene with the bromo-, cyano-substituted prolinates **1r** and **1s**, which afforded the major diastereomers **3r**, **3s** and **3t** in 78%, 79%, and 85% yield, respectively. Note that in the latter two reactions, the bromo, cyano, and ester groups remained intact during the reductive alkylation process. The relative stereochemistry of the major diastereomer **3q** was assigned to *S,S* by comparing the NMR data with those reported by Tu,<sup>9d</sup> and Che<sup>9e</sup> (two diastereomers of ethyl ester of **3q**, cf. ESI<sup>†</sup>), and those of **3r–3t** were assigned accordingly.

After the successful development of catalytic reductive alkylation of amides without  $\alpha$ -hydrogen, we turned our attention to extend the reaction to amides bearing  $\alpha$ -hydrogen atoms. Moreover, to further examine the scope of the alkynes, functionalized ones were employed. Thus, the reductive alkylation of amide **1t** with propiolaldehyde diethylketal **2b** furnished the propargylic amine **3u** in 94% yield (Scheme 2). This gram-scale reaction used 2 equiv. of TMDS instead of the usual 1.2 equiv. Subsequent reduction of **3u** with H<sub>2</sub> and Pd/C could be combined with the reductive alkylation in one-pot to give the alkaloid ( $\pm$ )-bgugaine (**4**)<sup>16</sup> (Scheme 2). Bgugaine is an alkaloid isolated from the tubers of *Arisarum vulgare* and has been shown to be a strong hepatotoxin with antibacterial and antimycotic activities.<sup>16</sup> Methyl propiolate could also be used for the direct reductive alkylation to afford propargylic amine **3v** in 88% yield even on a 5 mmol scale. Remarkably, the direct reductive alkylation with an acetylene bearing an unprotected aldehyde group underwent smooth reaction to afford the desired amino aldehyde **3w** in 67% yield.

We next undertook a preliminary mechanistic study. For this purpose, <sup>1</sup>H NMR spectra of starting amide **1v** (spectrum A, cf. ESI<sup>†</sup>), its mixture with TMDS (spectrum B, cf. ESI<sup>†</sup>), and the mixture formed 10 min after addition of the Ir catalyst



Scheme 2 Direct catalytic reductive alkylation of *tert*-amides containing  $\alpha$ -hydrogens.



Scheme 3 Plausible mechanism for the bis-metallic Ir- and Cu(I)-catalysed reductive alkylation of *tert*-amides.

(spectrum C, Fig. S1, ESI<sup>†</sup>) were recorded. Spectrum C showed that the starting amide was completely consumed ( $\delta_{\alpha\text{-H}} = 2.06$ , q) with the clean formation of enamine **A-v** ( $\delta_{\text{enamine-H}} = 6.07$ , d). On the other hand, the <sup>1</sup>H NMR spectra of starting benzamide **1b** (spectrum A', cf. ESI<sup>†</sup>), an amide without an  $\alpha$ -hydrogen, its mixture with TMDS (spectrum B', cf. ESI<sup>†</sup>), and the mixture formed 30 min after the addition of the Ir-catalyst (spectrum C', Fig. S2, ESI<sup>†</sup>) indicated that the amide ( $\delta_{\text{NMe-H}} = 2.64$ , s) was transformed cleanly to give hemiaminal silyl ether **B-b** ( $\delta_{\text{NCHO}} = 5.61$ , s). On the basis of the above-mentioned information, a plausible mechanism for the reaction is depicted in Scheme 3. Upon coordination with CuBr, terminal hydrogen in alkyne **C** became more acidic and was deprotonated with either enamine **A** or hemiaminal silyl ether intermediate **B** to generate an alkynylidene ion **D** and an iminium intermediate **E** or **E'**. The scenario of the reaction between **C** and **A** is in analogy with that proposed by Knochel.<sup>10a,c</sup> The addition of the alkynylidene ion **D** to the iminium ions **E/E'** then gives **F/F'**, which, after work-up, affords the propargylic amines **3**.

In summary, we have demonstrated that the Ir-catalysed hydrosilylation of *tert*-amides is compatible with the Cu(I)-catalysed alkylation reaction. On the basis of this finding, we have developed a mild, sequential catalysis method for the direct reductive alkylation of *tert*-amides to give propargylic amines.

The method is broad in scope, allowing the employment of aromatic as well as aliphatic *tert*-amides with or without  $\alpha$ -hydrogen and bearing functional groups with diverse electronic and steric properties. The method also shows excellent 1,3-asymmetric induction. The reaction exhibits remarkable chemoselectivity at the least reactive amide group and is



compatible with several sensitive functional groups such as aldehyde, cyano, ester, and nitro groups on either the amide or alkyne partners.

*General procedure for the reductive alkynylation of amides.*

To a dried 10 mL round-bottom flask containing  $\text{IrCl}(\text{CO})(\text{PPh}_3)_2$  (1 mol%, weighted in a glove box) were added a toluene (5 mL) solution, a *tert*-amide (1.0 mmol) and TMDS (1.2 mmol) or TMDS (2.0 mmol) (for amides with  $\alpha$ -hydrogen) at rt. After being stirred for 30 min (for amides without  $\alpha$ -hydrogen) or 10 min (for amides with  $\alpha$ -hydrogen), the resulting solution and an alkyne (1.2 mmol) were added to a suspension of  $\text{CuBr}$  (5 mol%) in toluene (3 mL). The mixture was stirred for 12 h at rt and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the corresponding propargylic amine **3**.

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