Letter

A Dual Catalytic Platform for Enabling sp3 a C–H Arylation & Alkylation of Benzamides

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A Dual Catalytic Platform for Enabling *sp³* α C–H Arylation & Alkylation of Benzamides

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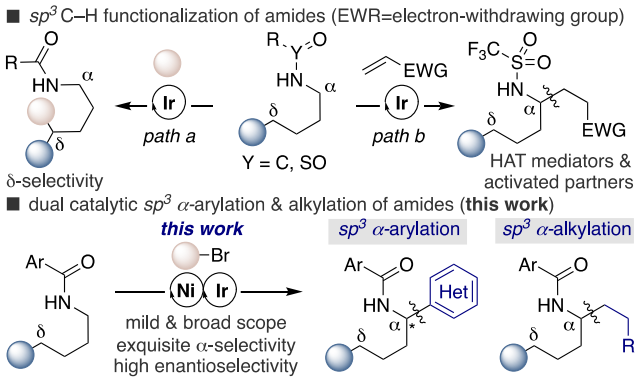
Supporting Information Placeholder

ABSTRACT: A dual catalytic *sp³* α C–H arylation & alkylation of benzamides with organic halides is described. This protocol exhibits an exquisite site-, chemo- and enantioselectivity pattern, offering a complementary reactivity mode to existing *sp³* arylation or alkylation events via transition metal catalysis or photoredox events.

Keywords: sp³ C–H activation, Photocatalysis, Nickel, enantioselectivity, metallaphotoredox.

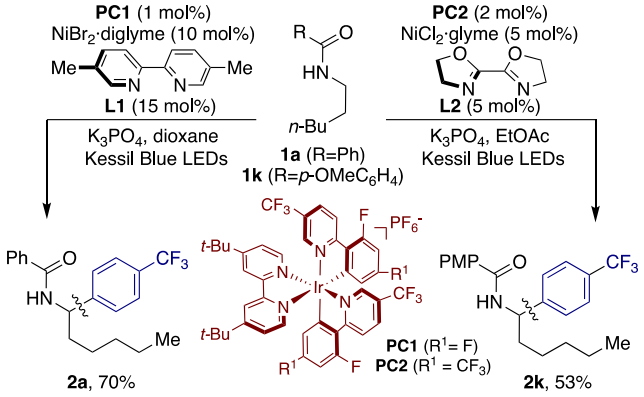
Catalytic C–H functionalization reactions have streamlined the synthesis of valuable molecules by avoiding functional group manipulations while offering a reliable solution to forge C–C bonds from simple precursors.[1] However, the ability to rationally and predictably switch the site-selectivity pattern in these endeavors still remains a problematic, yet highly rewarding, scenario.[2]

Scheme 1. Site-Selective *sp³* Functionalization of Amides.



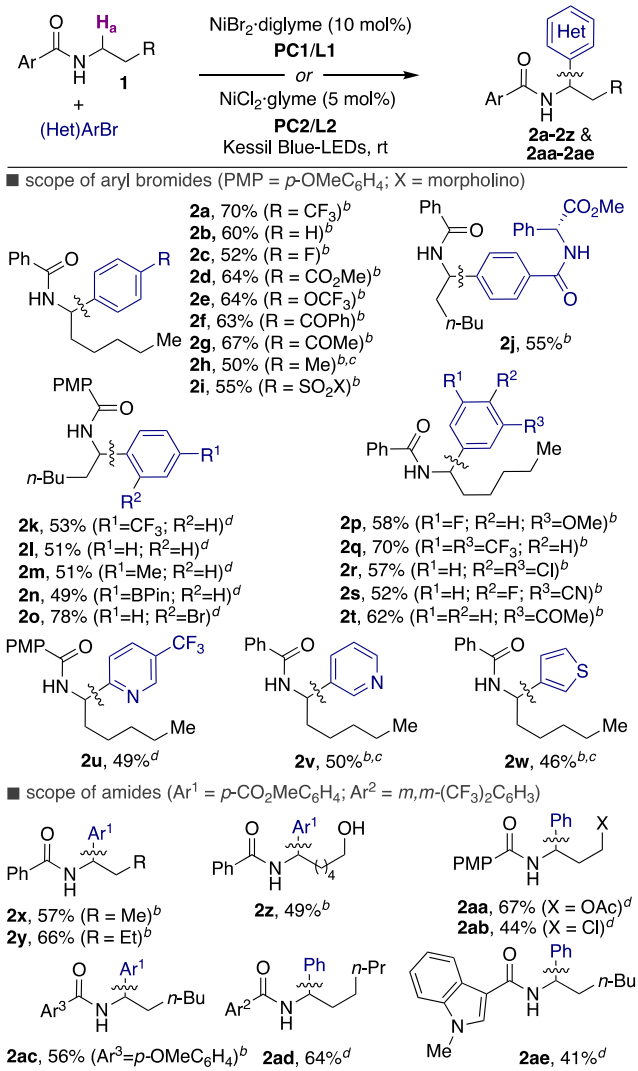
The prevalence of aliphatic amines in a myriad of molecules displaying biological activities[3] has prompted chemists to develop mild, non-invasive site-selective *sp³* C–H functionalizations as a platform for structural diversity.[4] In this vein, photoredox catalysis has recently offered new tactics for the α *sp³* C–H functionalization of aliphatic tertiary amines via single-electron transfer (SET) or hydrogen-atom transfer (HAT) pathways due to their favorable redox profile.[4,5]Although the higher reduction potential of tertiary amide congeners makes the functionalization of this substrate class more difficult, elegant solutions have been described with more oxidizing catalysts or conditions.[6] In contrast, the *sp³* C–H functionalization of aliphatic *secondary* amides have received much less attention. Independent work developed by Rovis[7] and Knowles[8] established a new rationale for enabling δ *sp³* C–H alkylation with activated Michael acceptors through [1,5]-HAT processes via amidyl radical species (Scheme 1, *path a*).[9] Although a site-selectivity switch has recently been obtained with specific amide patterns (*path b*),[10] this technology remains confined to activated electron-deficient olefins and stoichiometric HAT-mediators.[6,11] In view of the foregoing, the design of a catalytic protocol aimed at expanding the boundaries of *sp³* α-functionalization of aliphatic *secondary* amides with broadly applicable counterparts might provide an opportunity to explore inaccessible chemical space while offering new strategic bond-forming reactions. Herein, we describe the successful realization of this goal via dual catalysis (Scheme 1, *bottom*).[12,13] Our protocol is distinguished by its mild reaction conditions, broad substrate scope and exquisite site-, chemo- and enantioselective pattern.

Scheme 2. *sp³* α C–H Arylation of Aliphatic Benzamides.



We started our investigations by studying the *sp*³ α-arylation of **1a** and **1k** with 4-trifluoromethyl bromobenzene (Scheme 2). After systematic evaluation of all reaction parameters,[14] we found that a protocol based on **PC1**/**L1** or **PC2**/**L2** provided the best results under Blue-LED irradiation, affording **2a** and **2k** in 70% and 53% yield. As expected, the nature of the ligand, nickel precatalyst and photocatalyst had a non-negligible impact on reactivity. Equally important was the nature of the base and solvent; indeed, inferior results were found for K_2HPO_4 and Cs_2CO_3 or solvents other than dioxane and EtOAc, thus showing the subtleties of our protocol.[15,16]

Table 1. *sp*³ α-Arylation of Benzamides.[a]

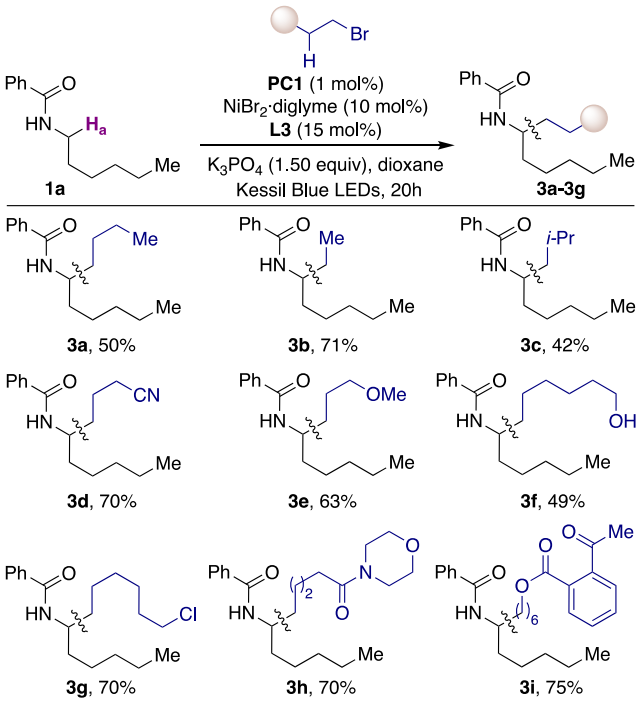


[a] Isolated yields, average of two independent runs. [b] **1** (0.40 mmol), (Het)ArBr (0.20 mmol), $NiBr_2$·diglyme (10 mol%), **L1** (15 mol%), **PC1** (1 mol%), K_3PO_4 (0.30 mmol), dioxane (1.0 mL) at rt for 20 h. [c] **1** (3 equiv) were used. [d] **1** (0.20 mmol), (Het)ArBr (1.50 mmol), $NiCl_2$·glyme (5 mol%), **L2** (5 mol%), **PC2** (2 mol%), K_3PO_4 (0.4 mmol), EtOAc (1.0 mL) at rt for 20 h.

Next, we turned our attention to investigating the generality of our dual catalytic *sp*³ α-arylation. As shown in Table 1, compounds bearing esters (**2d, 2j**), nitriles (**2s**), sulfonamides (**2i**), ketones (**2f**, **2g, 2t**) or amides (**2j**) could all be well-accommodated. Similar results were found independently whether substituents were located at the *ortho, meta* or *para* position. Importantly, however, electron-deficient arenes generally provided better yields of the targeted *sp*³ α-arylated products. The method shows a strong preference for aryl bromides, as the corresponding aryl chlorides (**2r**), aryl fluorides (**2c**, **2p, 2s**) or boronic esters (**2n**) remained inert, thus providing ample room for further derivatization via conventional cross-coupling reactions. Albeit in slightly lower yields, the method was shown to be compatible with heteroaryl

bromides (**2u-2w**). The exclusive formation of **2j** bearing two seemingly similar benzamides is particularly noteworthy; no traces of sp^3 C–H functionalization adjacent to the ester motif were found in the crude mixtures. Although tentative, this result is consistent with C–C bond-formation occurring at the more hydridic sp^3 C–H bond that is more susceptible to HAT by electrophilic radical species.[4,5] Notably, similar results were found for benzamides possessing different electronic environments (**2ac, 2ad**) or with heteroaryl-substituted motifs (**2ae**) regardless of the length of the alkyl side-chain (**2x, 2y**), even in the presence of free alcohols (**2z**), acetates (**2aa**) or alkyl chlorides (**2ab**).

Table 2. sp^3 **α-Alkylation of Benzamides.**[a,b]

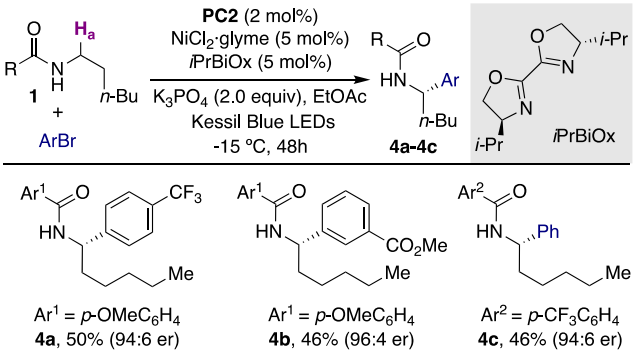


[a] **1** (0.60 mmol), (Het)ArBr (0.20 mmol), $NiBr_2$·diglyme (10 mol%), **L3** (bipyridine; 15 mol%), **PC1** (1 mol%), K_3PO_4 (0.30 mmol), dioxane (1.0 mL) at rt. [b] Isolated yields, average of at least two independent runs.

Encouraged by these results, we wondered whether our method would be robust enough to forge related sp^3–sp^3 linkages by using *unactivated* alkyl halides as counterparts. The successful implementation of such a protocol, however, might not be particularly straightforward. Indeed, the available sp^3 α-alkylation portfolio of aliphatic *secondary* amides largely remains confined to the use of particularly activated α,β-unsaturated carbonyls as coupling partners,[9a] although some developments from MacMillan have described alkylations on substrate classes other than secondary aliphatic amides.[9b] In addition, β-hydride elimination and the low propensity for sp^3–sp^3 C–C reductive elimination represent important drawbacks to be overcome.[17]

Therefore, at the outset of our investigations it was unclear whether it would be possible to promote a sp^3–sp^3 bond-formation adjacent to the amide function with *unactivated* alkyl halides. Gratifyingly, we found that the sp^3 α-alkylation was within reach by using a Ni/**L3** regime under otherwise identical reaction conditions to those shown in the sp^3 α-arylation event (Table 2). As shown in Table 3, a host of unactivated alkyl halides possessing β-hydrogens promoted the targeted transformation with similar ease. In addition, the presence of nitriles (**3d**), free alcohols (**3f**), alkyl chlorides (**3g**), amides (**3h**), ketones or esters (**3i**) did not hinder the reaction.

Table 3. Enantioselective sp^3 **α-Arylation of Benzamides.**[a,b]



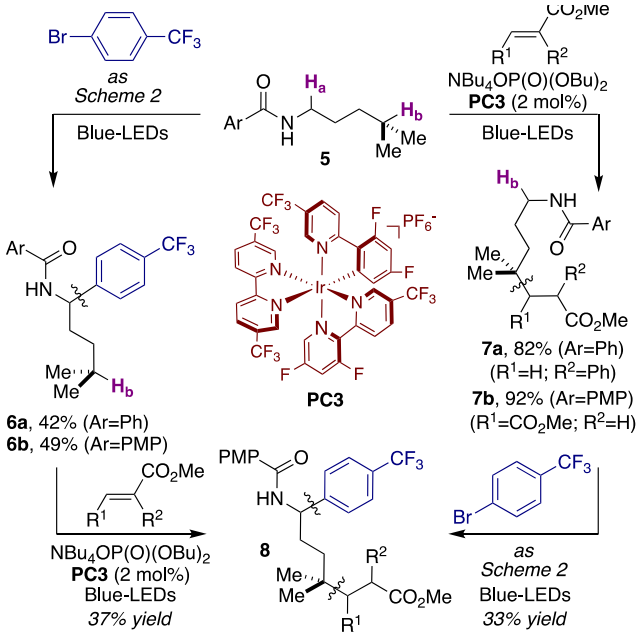
[a] **1** (0.20 mmol), ArBr (1.50 mmol), $NiCl_2$·glyme (5 mol%), ^{i}PrBiOx (5 mol%), **PC1** (2 mol%), K_3PO_4 (0.40 mmol), EtOAc (1.0 mL) at –15 ºC. [b] Isolated yields.

A close inspection into the literature data reveals that an asymmetric sp^3 C–H arylation initiated via photoinduced HAT processes remains an elusive endeavour within the metallaphotoredox arena.[13,18] To address this gap, we focused on developing an enantioselective sp^3 α C–H functionalization of aliphatic secondary amides with aryl halides. Gratifyingly, we found that a protocol based on *i*PrBiOx (**L3**) was particularly suited for our purposes (Table 3). Although preliminary, the corresponding α-arylated products could be obtained in high levels of enantioselectivity with comparable yields to those shown in Table 2 regardless of the substitution pattern at both the aryl halide and the aliphatic amide backbone (**4a-4c**), thus constituting a complementary, yet powerful, platform to elegant protocols recently described by Doyle and Yu.[18,19]

Prompted by the PCET work of Rovis[6,8] and Knowles[7] on the δ sp^3 C–H alkylation of aliphatic *secondary* amides with electron-deficient olefins,[20] we anticipated that our protocol might serve as an orthogonal gateway to forge sp^3 C–C bonds in aliphatic amides at either α- or δ-positions. As shown in Scheme 3, this turned out to be the case and regiodivergent C–C bond-formation could be accessed by using **5** as substrate. As expected, δ-alkylation with an activated α,β-unsaturated compound

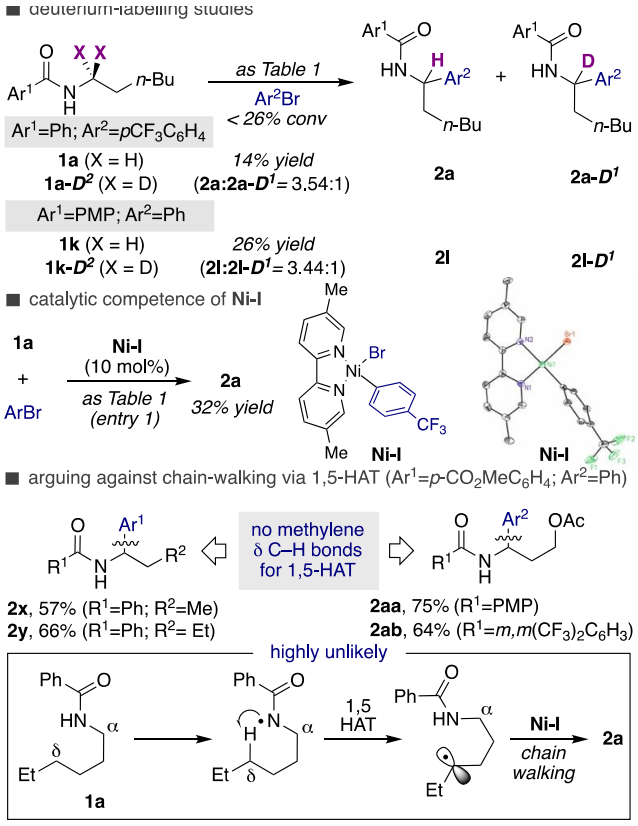
was obtained by subjecting **5** to **PC-3** and $NBu_4OP(O)(OBu)_2$ under Blue-LED irradiation,[7] whereas exclusive *sp³* α-arylation (**7a**, **7b**) was obtained under the Ni(**L1**)/**PC1** or Ni(**L2**)/**PC2** couple. Notably, **8** could be prepared from **6b** and **7b** following the same rationale, demonstrating the orthogonality of our *sp³* C–H functionalization approach for forging C–C bonds at either α or δ-positions. At present, we don´t have an explanation for the low yields obtained. Taken together, the results in Tables 1-3 and Scheme 3 illustrate the prospective impact of our dual catalytic platform for forging *sp³* C–C linkages adjacent to benzamide motifs in a site-selective manner.

Scheme 3. Orthogonality with 1,5-HAT processes.



Next, we decided to gather indirect evidence about the mechanism by deuterium-labelling (Scheme 4, *top*). As shown, a primary kinetic isotope effect (KIE) was observed by exposing a 1:1 mixture of **1a** and **1a-*D²*** under a **PC1/L1** regime, suggesting that *sp³* C–H bond-cleavage might be involved in the rate-determining step of the reaction. Similar results were found using a 1:1 ratio of **1k:1k-*D²*** with **PC2/L2**. Aimed at shedding light on the subsequent C–C bond-forming event, we turned our attention to study the reactivity of the putative oxidative addition species **Ni-I**, readily obtained by reacting 4-trifluoromethyl bromobenzene to $Ni(COD)_2$ and **L1** in THF (*middle*).[14] As expected, **Ni-I** was found to be catalytically competent, affording **2a** in 32% yield.[21] Although speculative, the lower yields of **2a** employing **Ni-I** when compared to an in situ protocol based on $NiBr_2$·diglyme/**L1** can tentatively be ascribed to its inherent instability in the absence of aryl bromide and its strong absorption in the visible light region.[22] In addition, the preparation of **2x**, **2y**, **2aa** and **2ab** is particularly illustrative, arguing against a scenario based on 1,5-HAT followed by recombination with **Ni-I** and a chain-walking manifold prior to C–C bond-formation at the α-position (*bottom*).[23] Whether the key transient radical species adjacent to the amide function are obtained via intermolecular HAT processes or invoke other mechanistic considerations is the subject of ongoing studies.[24]

Scheme 4. Preliminary Mechanistic Experiments.



In summary, we have documented a dual catalytic strategy that enables an *sp³* α-arylation and *sp³* α-alkylation of benzamides, offering a complementary activation mode to existing metal-catalyzed or photoinduced processes. The protocol is characterized by its mild conditions, wide scope and exquisite site-, chemo- and enantioselectivity. Further studies to unravel the mechanistic intricacies of the reaction and the extension to other C–C bond-forming scenarios are currently ongoing.

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Author contributions

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Funding Sources

No competing financial interests have been declared.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, crystallographic data and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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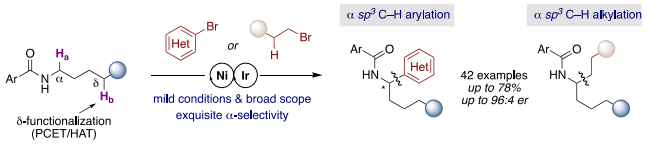
(21) An otherwise similar result was obtained with PhBr.

(22) Unfortunately, the inherent instability of **Ni-I** prevented fluorescence quenching studies to be performed.

(23) For selected reviews on chain-walking reactions: (a) Janssen-Müller, D.; Sahoo, B.; Sun, S.-Z.; Martin, R. Tackling remote sp^3 C−H functionalization via Ni-catalyzed "chain-walking" reactions. *Isr. J. Chem*. **2019**, *59*, 1-13. (b) Sommer, H.; Julia-Hernandez, F.; Martin, R.; Marek, I. Walking metals for remote functionalization. *ACS Cent. Sci.* **2018**, *4*, 153-165. (c) Vasseur, A.; Bruffaerts, J.; Marek, I. Remote functionalization through alkene isomerization. *Nat. Chem.* **2016**, *8*, 209-219. (d) Larionov, E.; Li, H.; Mazet, C. Well-defined transition metal hydrides in catalytic isomerizations. *Chem. Commun*. **2014**, *50*, 9816-9826.

(24) Based on our available data, several possibilities might come into play for the generation of the key α-carbon radical intermediates. If we take **PC1** into consideration, we could consider the following: (a) triplet-triplet energy transfer occurring from **PC1*** to **Ni-I** (see ref. 21) followed by arylNi(II)–Br homolysis, generating bromine radicals that enable an intermolecular HAT at the α sp^3 C–H bond (a close look at the triplet energies of **PC-1** (61.8 kcal/mol) *vs fac*-$Ir(ppy)_3PF_6$ (58.1 kcal/mol) or $Ir(ppy)_2(dtbpy)PF_6$ (49.2 kcal/mol) is particularly illustrative (see Supporting information for details). For a leading reference, see: Shields, B.; Doyle, A. G. Direct C(sp^3)–H cross coupling enabled by catalytic generation of chlorine radicals. *J. Am. Chem. Soc.* **2016**, *138*, 12719-12722; (b) PCET followed by [1,2]-HAT assisted by the K_3PO_4 (see Morton, C. M.; Zhu, Q.; Ripberger, H.; Troian-Gautier, Z. S.; Toa, D.; Knowles, R. R.; Alexanian, E. J. C–H Alkylation via Multisite-Proton-Coupled Electron Transfer of an Aliphatic C–H Bond. *J. Am. Chem. Soc.* **2019**, *141*, 13253-13260 and Wakaki, T.; Sakai, K.; Enomoto, T.; Kondo, M.; Masaoka, S.; Oisaki, K.; Kanai, M. C(sp3)−H Cyanation Promoted by Visible - Light Photoredox/Phosphate Hybrid Catalysis. *Chem. –Eur. J.* **2018**, *24*, 8051-8055 or (c) SET oxidation of **PC1*** to K_3PO_4 followed by intermolecular HAT (see Margrey, K. A.; Czaplyski, W. L.; Nicewicz, D. A.; Alexanian, E. J. A General Strategy for Aliphatic C–H Functionalization Enabled by Organic Photoredox Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 4213-4217).


δ-functionalization
(PCET/HAT)
Het
Br
or
Br
H
Ni
Ir
mild conditions & broad scope
exquisite α-selectivity
α sp³ C–H arylation
α sp³ C–H alkylation
42 examples
up to 78%
up to 96:4 er