# Palladium-catalyzed amidation–hydrolysis reaction of *gem*-dihaloolefins: efficient synthesis of homologated carboxamides from ketones†

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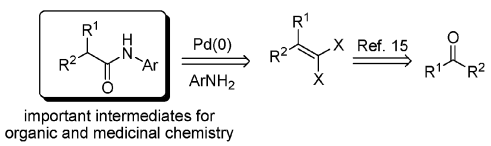
**A simple and efficient palladium-catalyzed amidation–hydrolysis reaction has been developed to afford *N*-aryl monosubstituted carboxamides in good to excellent yields from easily accessible ketone-derived *gem*-dihaloolefins and aryl amines.**

Amides are playing critical roles as building blocks, functional linkages, and pharmacophores in chemistry, biochemistry, and materials science.[1,2] The prevalence of monosubstituted carboxamides as scaffolds for biologically active molecules[3] has promoted the development of many useful methods for their preparation, including amidation of amines with carboxylic acids,[4] carboxylic anhydrides,[5] or carboxyl chlorides,[6] carbene catalyzed amide bond formation of α-reducible aldehydes and amines,[7] nickel-catalyzed arylation of α-halocarbonyl compounds,[8] palladium-catalyzed aminocarbonylation reaction,[9] and one-carbon homologation of aldehydes.[10] Some of these methods, however, either have limited substrate scope, use additives,[4c,d,g,5,7] or are inapplicable for aryl amines[10a,b] or ketones.[10a,d]

*gem*-Dihaloolefins have been extensively studied in recent years as important and versatile building blocks in synthetic chemistry.[11] Recently, Lautens[12] and Urabe[13] have developed several novel and elegant methods allowing the conversion of *gem*-dihaloolefins to nitrogen-containing heterocycles *via* palladium- or copper-catalyzed reactions. In a program aimed at developing *gem*-dihaloolefins as useful synthons,[14,15] we found that 2,2-disubstituted-1,1-dihaloalkenes could be efficiently converted into the target carboxamides in combination with aryl amines as a successful extension based on Shen's work.[10a] In this study, we report a palladium-catalyzed amidation–hydrolysis reaction for the efficient synthesis of *N*-aryl monosubstituted carboxamides from easily accessible *gem*-dihaloolefins and aryl amines (Scheme 1). To the best of our knowledge, the given approach provides the shortest and most convenient route to prepare homologated *N*-aryl monosubstituted carboxamides from ketones.

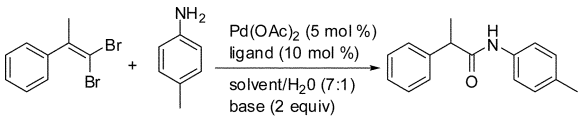
Initial study was performed by examining the reaction of **1a** with *p*-toluidine in the presence of $Pd(PPh_3)_4$ (5 mol%) in aqueous dioxane using $Cs_2CO_3$ as a base. However, this reaction gave monosubstituted carboxamide **3aa** in only 29% yield (Table 1, entry 1). When $Pd(OAc)_2/PPh_3$ was used, the yield could be improved to 44% (entry 2). Other ligands in combination with $Pd(OAc)_2$ led to good yields of **3aa** (entries 3 and 4), while Xantphos afforded the best result in 91% yield (entry 5, Condition A). In comparison with $Cs_2CO_3$, other bases such as $K_2CO_3$, $K_3PO_4$, NaOH and *t*-BuOK failed to give better yields (entries 6–9). When the solvent was switched to DMF, toluene or $CH_3CN$, the yield of **3aa** decreased (entries 10–12). Lower reaction temperature led to lower yield (entry 13) and no product was detected in the absence of palladium and ligand (entry 14). No di-amidation side-product was detected in the reaction.




**Scheme 1** Formation of amides *via* homologation of ketones.

Encouraged by the results above, we then extended the reaction to a range of commercially available arylamines. As illustrated in Table 2, **1a** was readily reacted with functionalized arylamines bearing *ortho*, *meta* and *para* substitutions on the aryl ring to give the carboxamides **3** in moderate to good yields (entries 1–11). The homologation reaction worked better with arylamines containing electron-donating groups (entries 1 and 2 *vs.* entry 7; entry 8 *vs.* entry 9) and with those that are less

**Table 1** Optimization for synthesis of monosubstituted carboxamides[ab]




1a 2a 3aa

| entry | ligand | solvent | base | *T*/°C | *t*/h | yield[c] (%) |
|---|---|---|---|---|---|---|
| 1 | $Pd(PPh_3)_4$[d] | Dioxane | $Cs_2CO_3$ | Reflux | 7 | 29 |
| 2 | $PPh_3$ | Dioxane | $Cs_2CO_3$ | Reflux | 7 | 44 |
| 3 | DPPP | Dioxane | $Cs_2CO_3$ | Reflux | 12 | 61 |
| 4 | s-BINAP | Dioxane | $Cs_2CO_3$ | Reflux | 12 | 83 |
| 5 | **Xantphos** | **Dioxane** | **$Cs_2CO_3$** | **Reflux** | **7** | **91** |
| 6 | Xantphos | Dioxane | $K_2CO_3$ | Reflux | 12 | 54 |
| 7 | Xantphos | Dioxane | $K_3PO_4$ | Reflux | 12 | 58 |
| 8 | Xantphos | Dioxane | NaOH | Reflux | 4 | 85 |
| 9 | Xantphos | Dioxane | *t*-BuOK | Reflux | 7 | 63 |
| 10 | Xantphos | DMF | $Cs_2CO_3$ | 120 | 4 | 43 |
| 11 | Xantphos | Toluene | $Cs_2CO_3$ | Reflux | 12 | 54 |
| 12 | Xantphos | $CH_3CN$ | $Cs_2CO_3$ | Reflux | 7 | 57 |
| 13 | Xantphos | Dioxane | $Cs_2CO_3$ | 80 | 12 | 78 |
| 14 | — | Dioxane | $Cs_2CO_3$ | Reflux | 12 | 0 |

[a] *Reaction conditions*: under nitrogen atmosphere, **1a** (0.5 mmol), **2a** (1.0 mmol), $Pd(OAc)_2$ (5 mol%), ligand (10 mol%), base (1.0 mmol), and solvent : $H_2O$ = 7 : 1 (1.2 mL); BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene, DPPP = 1,3-bis(diphenylphosphino)propane, Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene. [b] For effect of amount of water, see ESI.† [c] Isolated yield. [d] $Pd(PPh_3)_4$ used alone instead of $Pd(OAc)_2$/ligand combination

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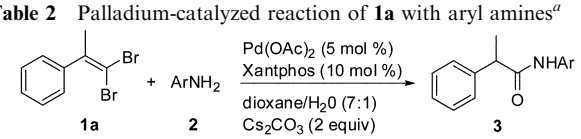
† Electronic Supplementary Information (ESI) available: General experimental procedures, spectral data for all compounds, $^1H$ and $^{13}C$ NMR spectra for all compounds.

**Table 2** Palladium-catalyzed reaction of **1a** with aryl amines[a]




1a 2 3

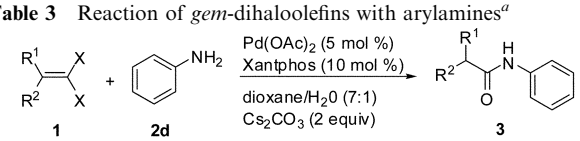
| entry | amine | R | product | | *t*/h | yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | | *p*-Me | | **3aa** | 7 | 91 |
| 2 | | *p*-OMe | | **3ab** | 7 | 90 |
| 3 | | *p*-$NH_2$ | | **3ac** | 12 | 78 |
| 4 | | *p*-H | | **3ad** | 3 | 77 |
| 5 | NH2 | *p*-Cl | | **3ae** | 7 | 70 |
| 6 | | *p*-Br | | **3af** | 7 | 61[c] |
| 7 | R **2a-k** | *p*-$CO_2Et$ | R | **3ag** | 12 | 47 |
| 8 | | *m*-Me | | **3ah** | 18 | 85 |
| 9 | | *m*-Ac | | **3ai** | 7 | 73 |
| 10 | | *o*-Me | | **3aj** | 20 | 76 |
| 11 | | *o*-OMe | | **3ak** | 20 | 71 |
| 12 | NH2 **2l** | | | **3al** | 7 | 72 |
| 13 | N NH2 N **2m** | | N | **3am** | 24 | 52 |

[a] All reactions were performed under $N_2$ on a 0.5 mmol scale, using arylamine (2 equiv), $Pd(OAc)_2$ (5 mol%), Xantphos (10 mol%) and $Cs_2CO_3$ (2 equiv) in 1.2 mL of dioxane–$H_2O$ (7 : 1) under reflux. [b] Isolated yield. [c] 3 equiv. of 4-bromoaniline was used.

sterically demanding (entry 1 *vs*. entry 10; entry 2 *vs*. entry 11). This reaction was not limited to simple benzene-containing aromatics, the naphthalene- and pyrimidine-containing substrates **2l** and **2m** also afforded **3al** and **3am** in good yields, respectively (entries 12–13). However, aliphatic amines such as butylamine, benzylamine and diisopropylamine failed to react under the same conditions.

To further explore the scope of this reaction, a variety of *gem*-dibromoolefins **1b–l**[15] were investigated. As shown in Table 3, this method was compatible with different types of vinyl dibromides, which were attached with methyl and aryl groups (entries 1–6), cycloalkyl groups (entries 7–8), diphenyl groups (entry 9), and alkyl and heteroaryl groups (entry 10). *gem*-Dibromoolefins containing electron-donating groups afforded products in good yields (entries 1 and 2), whereas the substrates with electron-withdrawing groups such as nitro group gave slightly lower yields (entry 3). For substrates having bromo substituents, the yields turned out to be lower (entries 5 and 6), possibly due to the competitive reactions at the different reactive bromines. Cycloalkyl substrates **1h** and **1i** showed better reactivities and yields toward carboxamides than the aryl ones (entries 7 and 8). Diphenyl substituted **1j** showed lower reactivity and afforded **3jd** in 54% yield (entry 9), while the replacement from aryl ring to furan gave **3kd** in 51% yield (entry 10). It is noteworthy that under the employed conditions the styrenyl derivative **1l** could be easily converted to (*E*)-2-methyl-*N*,4-diphenylbut-3-enamide **3ld**, an analogue of alkene dipeptide isosteres, which are usually difficult to access (entry 11).[16] In particular, the employment of *gem*-dichloroolefin **1m**[17] could also afford **3aa** and **3ab** in moderate yields when reacted with **2a** and **2b**, respectively (entries 12 and 13). Benzaldehyde derived *gem*-dibromoolefin gave no desired carboxamide.

**Table 3** Reaction of *gem*-dihaloolefins with arylamines[a]



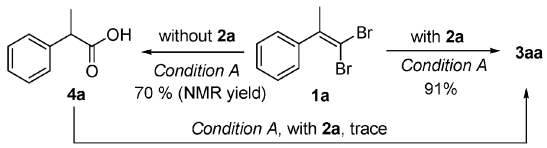

1 2d 3

| entry | reactant | R | product | | *t*/h | yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | | *p*-Me | | **3bd** | 24 | 71 |
| 2 | | *p*-OMe | | **3cd** | 7 | 80 |
| 3 | | *p*-$NO_2$ | | **3dd** | 24 | 64 |
| 4 | | *p*-Cl | | **3ed** | 24 | 72 |
| 5 | R Br Br **1b-g** | *p*-Br | R | **3fd** | 24 | 55 |
| 6 | | *m*-Br | | **3gd** | 24 | 54 |
| 7 | Br Br **1h** | | | **3hd** | 4 | 82 |
| 8 | Br Br **1i** | | | **3id** | 4 | 92 |
| 9 | Ph Br Br **1j** | | Ph | **3jd** | 24 | 54 |
| 10 | O Br Br **1k** | | O | **3kd** | 24 | 51 |
| 11 | Br Br **1l** | | | **3ld** | 5 | 74 |
| 12 | Cl Cl **1m** | | | **3aa** | 7 | 55[c] |
| 13 | Cl Cl **1m** | | OMe | **3ab** | 7 | 52[d] |

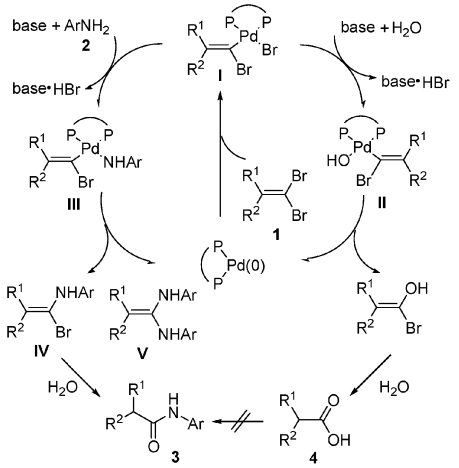
[a] All reactions were performed under $N_2$ on a 0.5 mmol scale, using aniline (2 equiv), $Pd(OAc)_2$ (5 mol%), Xantphos (10 mol%) and $Cs_2CO_3$ (2 equiv.) in 1.2 mL of dioxane–$H_2O$ (7 : 1) under reflux. [b] Isolated yield. [c] **2a** was used. [d] **2b** was used.

It was well reported that *gem*-dihaloolefins could be exploited as substrates for the preparation of carbonyl derivatives.[18] Li and Alper found that 2-phenylpropanoic acid **4a** could be obtained in 23% yield when a mixture of **1a**, KOH, $Pd(OAc)_2$ and DPPE was heated to 65 °C for 17 h.[19] For comparison, **4a** was produced in 70% NMR yield from **1a** after reaction for 20 h under Condition A (Table 1, entry 5) in the absence of arylamine (Scheme 2). However, only a trace amount of **3aa** could be observed from NMR when a mixture of **4a**[4d] and **2a** was heated for 10 h under Condition A (Scheme 2), indicating that the carboxamide **3aa** might not be achieved through carboxylic acid **4**, which could be generated *via* intermediate **II** (Scheme 3, right circle).[19] From the results in Scheme 2, the formation of a C–N bond appears to be faster than that of the C–O bond in the presence of arylamine under palladium catalysis.

A possible mechanism for the conversion of *gem*-dibromoolefin **1** to carboxamide **3** is demonstrated in Scheme 3. The palladium complex **I** is obtained when one of two C–Br bonds in **1** is oxidatively added to the Pd(0) complex[14b] and the palladium(II) arylamide **III**[20] was formed subsequently to afford the target carboxamide **3** by direct hydrolysis of **IV**. Currently, we cannot rule out the




**Scheme 2** The formation of **3aa** *via* **4a** under Condition A.




**Scheme 3** Plausible mechanism for homologation of arylamines with *gem*-dibromoolefins.

possibility of the existence of compound **V** during the reaction (Scheme 3).

In summary, we have developed a general and efficient method for the one-pot synthesis of carboxamides from easily available *gem*-dihaloolefins by using $Pd(OAc)_2$/Xantphos in aqueous dioxane. The given approach provides the most convenient pathway for accessing *N*-aryl monosubstituted carboxamides from ketones by one-carbon homologation. The scope and limitations of the reaction itself and the synthetic applications for bioactive compounds are under investigation.

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