Preprint Title	Palladium-catalyzed annulation reactions of quinoline-2-carboxamides via sequential C–H/N–H functionalization
Authors	Shoichi Sugita, Kentaro Okano and Atsunori Mori
Publication Date	30 März 2026
Article Type	Full Research Paper
Supporting Information File 1	Supporting Information File 1.pdf; 14.4 MB
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Palladium-catalyzed annulation reactions of quinoline-2-carboxamides via sequential C–H/N–H functionalization

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Abstract

A novel intermolecular annulation protocol has been developed for the synthesis of quinoline-fused lactams by palladium-catalyzed sequential C–H/N–H functionalization of quinoline-2-carboxamides and 1,2-dihaloarenes. The reaction proceeds at the C–H bond on the quinoline adjacent to the amide group and at the amide N–H bond in the presence of 10 mol% $Pd(OAc)_2$ in *o*-xylene as a solvent to afford the cyclized product in 34% yield. The yield increases to 81% when the reaction is carried out with 80 mol% $P(4\text{-}MeOC_6H_4)_3$ as a ligand and with an increased catalyst loading of 20 mol%. The reaction affords lactams in up to 83% yield using amides containing various functional

groups and substituted 1-bromo-2-iodobenzenes. Furthermore, 1,2-dibromo heteroarenes, such as benzothiophene and pyridine, undergo annulation to give the corresponding heterocycle-fused compounds. The high chemoselectivity of the 1,2-dihaloarene functional groups is confirmed in this reaction, thus enabling divergent synthesis of various multi-fused heterocyclic systems.

Keywords

C–H activation; C–N coupling; sequential reaction; chemodivergent synthesis; fused-ring system

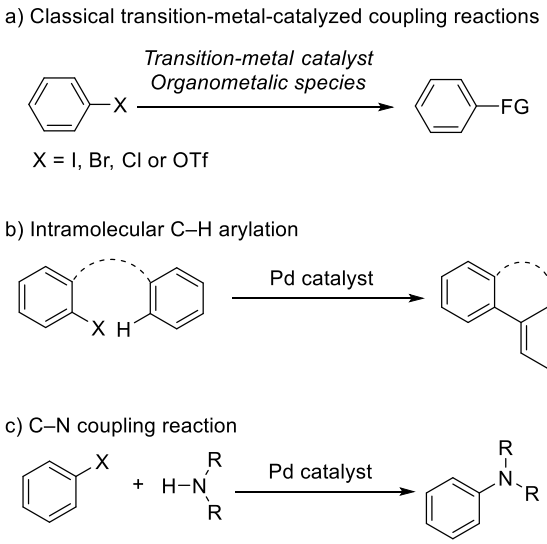
Introduction

Cyclic structures comprising nitrogen-containing multi-fused rings are extremely important because such heterocycle-fused cyclic structures [1,2] are found in various advanced materials [3,4] and biologically essential molecules [5-7]. Quinoline is a particularly intriguing moiety in biologically active compounds (e.g., natural products used for medicines, quinine, and quinidine [5-7]) and synthesized pharmaceutical agents (e.g., quinolone antibiotics [8]). Moreover, quinoline-2-carboxamide derivatives are used as ligands in organic synthesis owing to their high metal affinity [9-13]. It is therefore expected that annulation of the amide moiety in quinoline-2-carboxamides would extend their functionality as biologically active structures, ligands, and extractants.

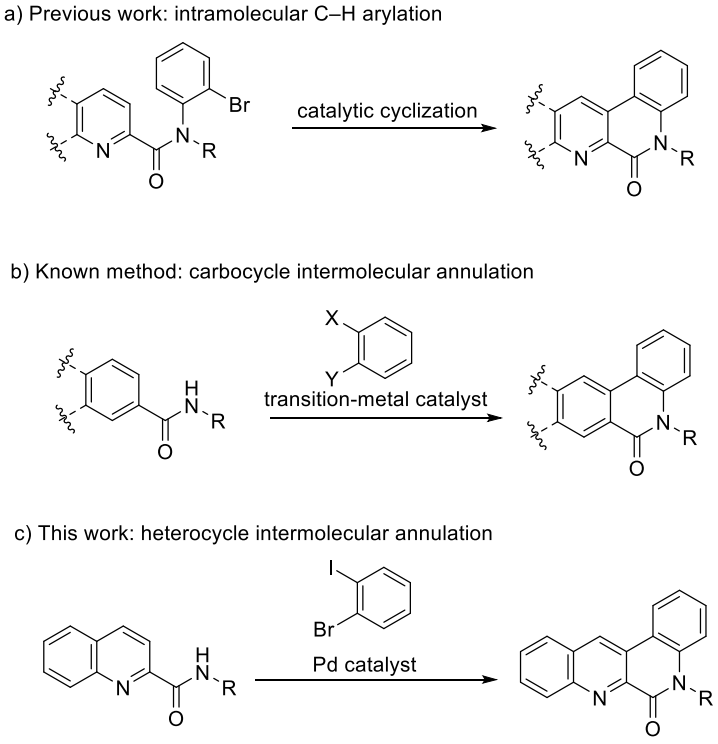
Transition metal-catalyzed coupling reactions are crucial for constructing carbon–carbon and carbon–heteroatom bonds. The classical coupling reactions, such as Kumada–Tamao–Corriu coupling [14-19], Sonogashira coupling [20-25], Negishi coupling [26-31], Migita–Kosugi–Stille coupling [32-37], Suzuki–Miyaura coupling [38-

44], and Hiyama coupling [45-50] involve carbon–halogen and carbon–metal species (Scheme 1a). Fagnou and co-workers reported direct arylation with palladium(II) acetate to synthesize biaryl compounds via concerted metalation-deprotonation (CMD; Scheme 1b) [51-53]. Buchwald, Hartwig, and co-workers explored carbon–nitrogen coupling reactions that allow facile preparation of aromatic amines (Scheme 1c) [54-64]. In general, intramolecular C–H arylation reactions in the presence of a transition-metal catalyst have been reported extensively in recent years. These reactions enable efficient formation of fused-ring systems [65-72]. Additionally, intramolecular C–H arylation reactions with N-heteroaromatics can be used to synthesize various functional molecules that serve as ligands for metal extraction [73-77].

Our group developed a cyclization reaction for intramolecular C–H arylation with N-heterocycles, such as phenanthroline and quinoline, containing amide groups (Scheme 2a) [76,78]. These reactions provide efficient annulation products; however, it remains difficult to selectively obtain a variety of substituent positions following cyclization. Intermolecular annulation reactions of aryl carboxamides offer a method for synthesizing chemodivergent products from a single substrate. Importantly, these reactions are controlled by the different reactivities of the halogen atoms in the reagent structures. Several carbocycle C–H/N–H activated intermolecular annulations have already been reported [79-90], although the reaction mechanism with π-deficient N-heteroaromatics has not been elucidated (Scheme 2b). It is therefore valuable to investigate the differences in reactivity between C–H and N–H for intermolecular arylation in the presence of transition metal catalysts. This can reveal their selectivity in terms of reaction position(s) in chemodivergent synthesis (Scheme 2c). The present report explores intermolecular annulation reactions involving sequential C–H/N–H functionalization by a palladium catalyst.



Scheme 1: Various transition metal-catalyzed coupling reactions involving aryl halides.



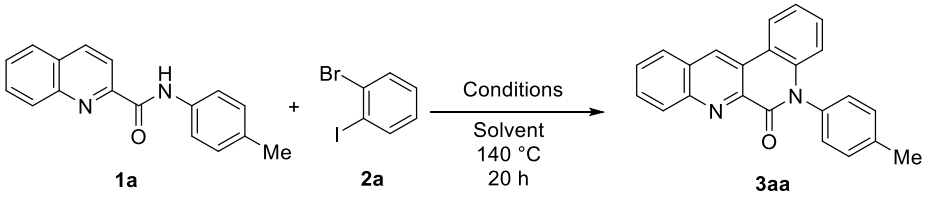
Scheme 2: Synthetic strategy for preparing fused lactams.

Results and Discussion

First, the C–H/N–H annulation reaction between quinoline-2-carboxamide **1a** and 1-bromo-2-iodobenzene (**2a**) was tested. When **1a** was treated with 1.0 equivalent of **2a**, 10 mol% $Pd(OAc)_2$, 40 mol% PPh_3, and 3.0 equivalents of Cs_2CO_3 in dimethylformamide (DMF) at 140 °C, the desired lactam **3aa** was obtained in 19% yield (Table 1, entry 1). This result indicated that the anticipated C–H and N–H intermolecular-intramolecular coupling reactions occurred. When $PdCl_2(PPh_3)_2$ was used instead of $Pd(OAc)_2$ as a catalyst in the absence of PPh_3, **3aa** was afforded in 10% yield (Table 1, entry 2). When $Pd(OCOCF_3)_2$ was used as the catalyst, the desired product was obtained in 39% yield (Table 1, entry 3). Using any base other than Cs_2CO_3 resulted in lower yields, thus confirming that Cs_2CO_3 was the optimal base for this reactivity (Table 1, entries 4-6). Increasing the concentration of **1a** from 0.1 to 1.0 M led to an increased yield, even if $Pd(OAc)_2$ was used as the catalyst (Table 1, entry 7). Using *o*-xylene as the solvent gave results similar to those obtained with DMF (Table 1, entry 8). Notably, the reaction using *o*-xylene as the solvent supported a good mass balance of **1a** and **3aa**. Therefore, the coupling reaction conditions were further optimized using *o*-xylene as the solvent. The ligand effect was examined, and the results indicated that electron-donating ligands were more efficient than electron-withdrawing ligands, particularly in the context of tris(4-methoxyphenyl)phosphine ($P(4\text{-}MeOC_6H_4)_3$) (Table1, entries 9-12). Additionally, the annulation product was detected in less than 1% of the yield in the presence of bulky ligands, such as tri(*o*-tolyl)phosphine (Table 1, entry 13). Next, the relative amounts of reagents were optimized for this annulation reaction (Table 1, entries 14-16). Ultimately, it was determined that the optimal reagents quantities were 20 mol% $Pd(OAc)_2$, 80 mol% P(4-

$MeOC_6H_4)_3$, and 2.0 equivalents of **2a**, which afforded product **3aa** in 81% yield (Table 1, entry 16).

Table 1: Investigation of this C–H/N–H functionalization reaction conditions.



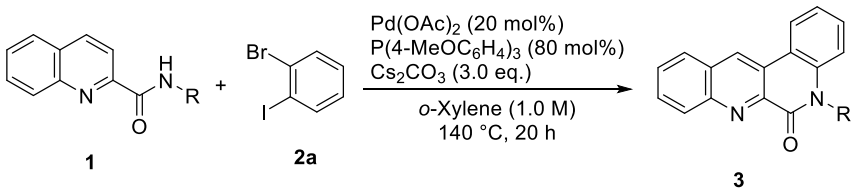
Entry	Catalyst (mol%)	Ligand (mol%)	Base (equiv.)	**2a** (equiv.)	Solvent (M)	Yield (%)[a] **3aa**	**1a**
1	$Pd(OAc)_2$ (10)	PPh_3 (40)	Cs_2CO_3 (3.0)	1.0	DMF (0.1)	19	52
2	$PdCl_2(PPh_3)_2$ (10)	none	Cs_2CO_3 (3.0)	1.0	DMF (0.1)	10	85
3	$Pd(OCOCF_3)_2$ (10)	PPh_3 (40)	Cs_2CO_3 (3.0)	1.0	DMF (0.1)	39	32
4	$Pd(OAc)_2$ (10)	PPh_3 (40)	K_2CO_3 (3.0)	1.0	DMF (0.1)	6	72
5	$Pd(OAc)_2$ (10)	PPh_3 (40)	*t*-BuOK (3.0)	1.0	DMF (0.1)	0	Quant.
6	$Pd(OAc)_2$ (10)	PPh_3 (40)	*t*-BuONa (3.0)	1.0	DMF (0.1)	9	63
7	$Pd(OAc)_2$ (10)	PPh_3 (40)	Cs_2CO_3 (3.0)	1.0	DMF (1.0)	46	28
8	$Pd(OAc)_2$ (10)	PPh_3 (40)	Cs_2CO_3 (3.0)	1.0	*o*-xylene (1.0)	34	58

9	$Pd(OAc)_2$ (10)	PPh_3 (100)	Cs_2CO_3 (3.0)	1.0	*o*-xylene (1.0)	39	30
10	$Pd(OAc)_2$ (10)	P(*p*-tolyl)$_3$ (40)	Cs_2CO_3 (3.0)	1.0	*o*-xylene (1.0)	35	30
11	$Pd(OAc)_2$ (10)	P(4-$MeOC_6H_4)_3$ (40)	Cs_2CO_3 (3.0)	1.0	*o*-xylene (1.0)	44	33
12	$Pd(OAc)_2$ (10)	P(4-$FC_6H_4)_3$ (40)	Cs_2CO_3 (3.0)	1.0	*o*-xylene (1.0)	21	55
13	$Pd(OAc)_2$ (10)	P(*o*-tolyl)$_3$ (40)	Cs_2CO_3 (3.0)	1.0	*o*-xylene (1.0)	<1	Quant.
14[b]	$Pd(OAc)_2$ (10)	P(4-$MeOC_6H_4)_3$ (40)	Cs_2CO_3 (3.0)	1.0 + 1.0	*o*-xylene (1.0)	53	15
15	$Pd(OAc)_2$ (10)	P(4-$MeOC_6H_4)_3$ (80)	Cs_2CO_3 (3.0)	2.0	*o*-xylene (1.0)	45	34
16	$Pd(OAc)_2$ (20)	P(4-$MeOC_6H_4)_3$ (80)	Cs_2CO_3 (3.0)	2.0	*o*-xylene (1.0)	81[c]	N.D.[d]

[a]The yields were determined by ^{1}H-NMR using 1,1,2,2-tetrachloroethane as an internal standard; [b]After stirring for 20 hours at 140 ºC, an additional 1.0 equivalent of **2a** was added to the reaction system, and the reaction was allowed to proceed for another 20 hours at 140 ºC; [c]Isolated yield; [d]Not detected.

The optimized conditions were used to investigate the substrate scope of this C–H/N–H functionalized reaction. First, substituents with the amide group on quinoline-2-carboxamides were examined (Table 2). The C–H/N–H functionalized reactions afforded good to excellent yields, regardless of the presence of a non-substituted phenyl group and with any substituent at the 4-position of the phenyl moiety (Table 2, entries 1-5). In contrast, the quinoline-2-carboxamide containing a 4-nitrophenyl group gave the corresponding product in a low yield (Table 2, entry 6). Similarly, amides bearing mesityl, 2-nitrophenyl, or 2-methoxyphenyl groups afforded the corresponding products in low yields due to steric hindrance (Table 2, entries 7-9). The reaction with the benzyl moiety also resulted in a low yield owing to the lower acidity of the amide proton compared with aromatic amides (Table 2, entry 10).

Table 2: Investigation of the substrate scope and substituent limitations of amide groups for the C–H/N–H functionalization reaction.



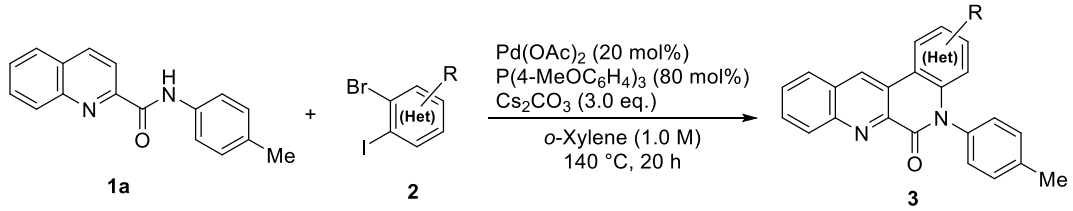
Entry	R	Yield (%)
1	Ph	81 (**3ba**)
2	4-$MeOC_6H_4$	68 (**3ca**)
3	4-^{t}BuC_6H_4	72 (**3da**)
4	4-CNC_6H_4	67 (**3ea**)
5	4-ClC_6H_4	75 (**3fa**)
6	4-$NO_2C_6H_4$	18 (**3ga**)
7	Mesityl	21 (**3ha**)

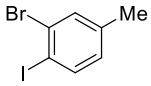
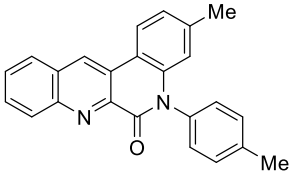
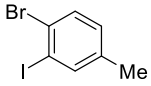
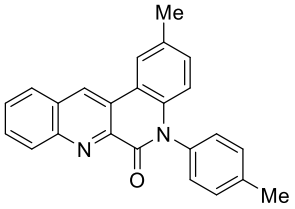
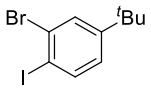
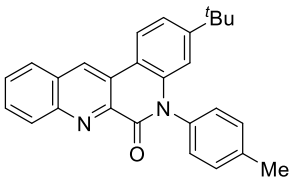
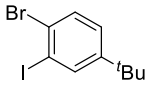
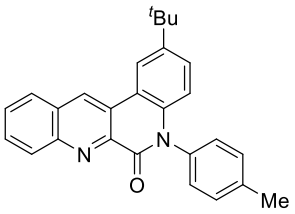
8	2-$NO_2C_6H_4$	14 (**3ia**)
9[a]	2-$MeOC_6H_4$	17 (**3ja**)
10[a]	Bn	21 (**3ka**)

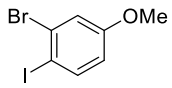
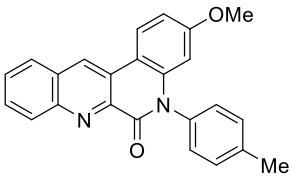
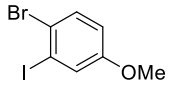
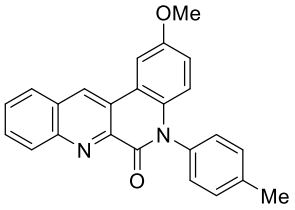
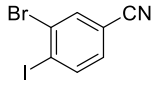
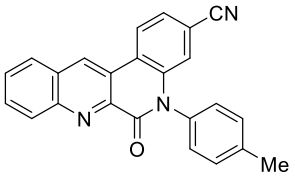
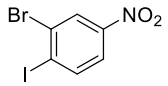
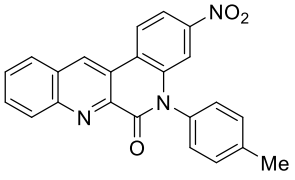
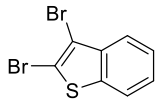
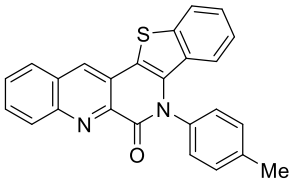
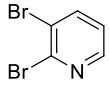
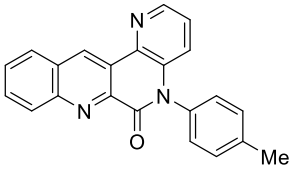
[a]The reaction time was prolonged to 96 h.

Next, the C–H/N–H functionalized reaction was evaluated using various 1,2-dihaloarenes (Table 3). When 1-bromo-2-iodo-5-methylbenzene was used, the corresponding cycloadduct was obtained in good yield (Table 3, entry 1). However, 1-bromo-2-iodo-4-methylbenzene afforded the annulation product in low yield (Table 3, entry 2). The desired products were obtained in excellent yields when the reaction period was prolonged from 20 to 96 h (with dihaloarenes **2b** and **2c**). Although relatively low product yields were obtained when using dihaloarenes **2d** and **2e** (which contain a *tert*-butyl group) after 20 h, the corresponding products were obtained in good to excellent yields when the reaction time was prolonged to 96 h (Table 3, entries 3 and 4). Similar trends were observed in the reactions involving 2-bromo-1-iodo-4-methoxybenzene and 1-bromo-2-iodo-4-methoxybenzene (Table 3, entries 5 and 6). The oxidative addition of the palladium catalyst to the C–I bond of these bromo-iodobenzenes occurred slowly, requiring an extended reaction time to reach completion. Notably, the substrates containing electron-withdrawing groups, such as cyano or nitro groups, resulted in low yields, even after longer reaction times (Table 3, entries 7 and 8). These results were attributed to homo-coupling of 1-bromo-2-iodobenzenes or protonation of activated haloarenes and deactivation of the palladium catalyst. Finally, the coupling reactions with heteroarenes, such as 2,3-dibromobenzothiophene and 2,3-dibromopyridine, afforded the corresponding products in moderate yields with high regioselectivity (Table 3, entries 9 and 10).

Table 3: Investigation of the dihaloarene substrate scope for the C–H/N–H functionalization reaction.

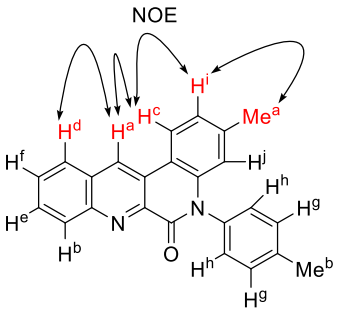


Entry	**2**	Product (yield, %)
1	 **2b**	 **3ab** (63, 79[a])
2	 **2c**	 **3ac** (17, 83[a])
3	 **2d**	 **3ad** (28, 55[a])
4	 **2e**	 **3ae** (18, 81[a])

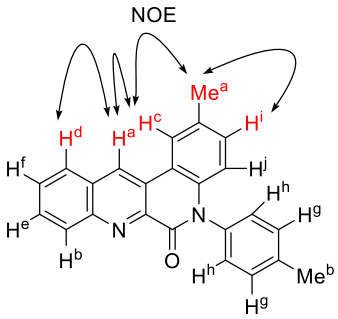
5	 **2f**	 **3af** (32, 51[a])
6	 **2g**	 **3ag** (24, 82[a])
7	 **2h**	 **3ah** (26, 21[a])
8	 **2i**	 **3ai** (7, 7[a])
9	 **2j**	 **3aj** (21)
10	 **2k**	 **3ak** (31)

[a]These yields were obtained when the reaction time was prolonged to 96 h.

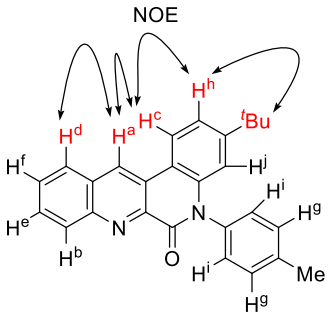
The structures of the isomeric products were confirmed by nuclear Overhauser effect spectroscopy (NOESY, refer to the Supporting Information [SI]). First, the structures of lactams **3ab**, **3ac**, and **3ad** were determined (Figure 1a-c, respectively). The products **3ab** and **3ac**, which were synthesized from **2b** and **2c**, were detected as the corresponding isomers. The methyl group was attached to the C3 or C2 position of products **3ab** and **3ac**, respectively. In the case of 1-bromo-2-iodobenzene, which contains a *tert*-butyl group at the C5 position, product **3ad** (with a similar substitution pattern) was detected as the product derived from 1-bromo-2-iodo-5-methylbenzene. Additionally, when the coupling reaction was carried out with 5-*tert*-butyl-1-bromo-2-iodobenzene, the **Int-1** species was detected as a reaction intermediate, as confirmed by ^{1}H-NMR and mass spectra (Scheme 3; see also the SI). This result indicated that the C–C bond was formed first in the reaction. The structures of other products were inferred from ^{1}H-NMR spectra, while the structures of products **3aj** and **3ak** were also determined by NOESY (Figure 1d,e).



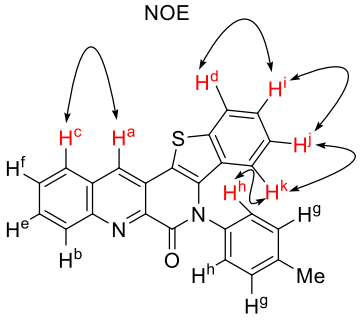
3ab (a)



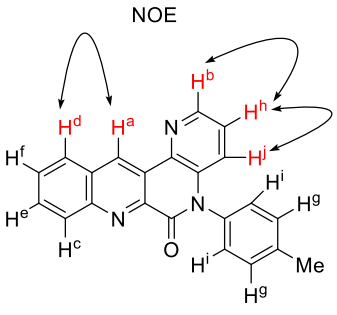
3ac (b)



3ad (c)

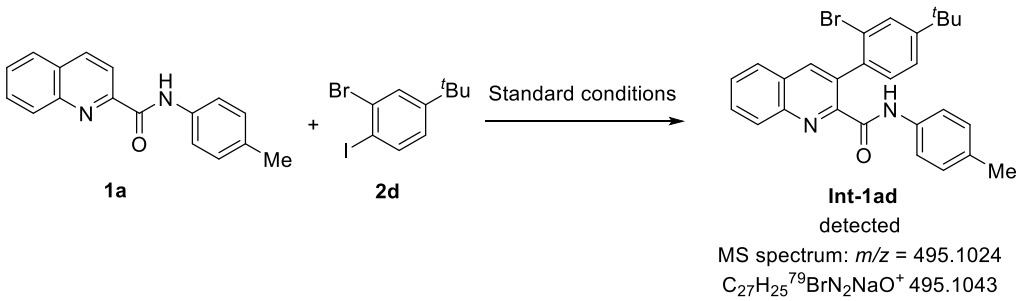


3aj (d)



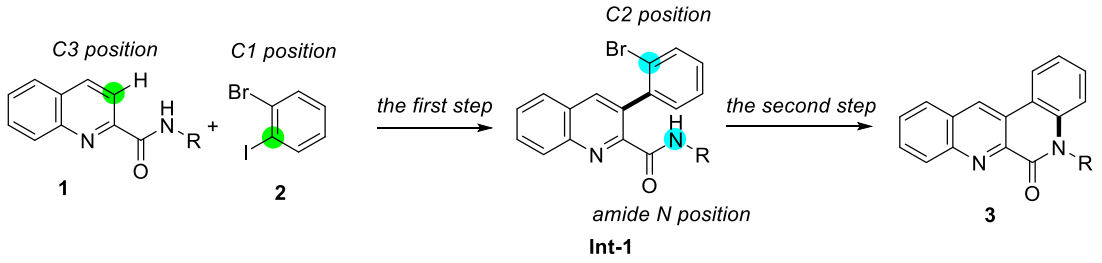
3ak (e)

Figure 1: Nuclear Overhauser effect (NOE) correlations in products (a) **3ab**, (b) **3ac**, (c) **3ad**, (d) **3aj**, and (e) **3ak**.

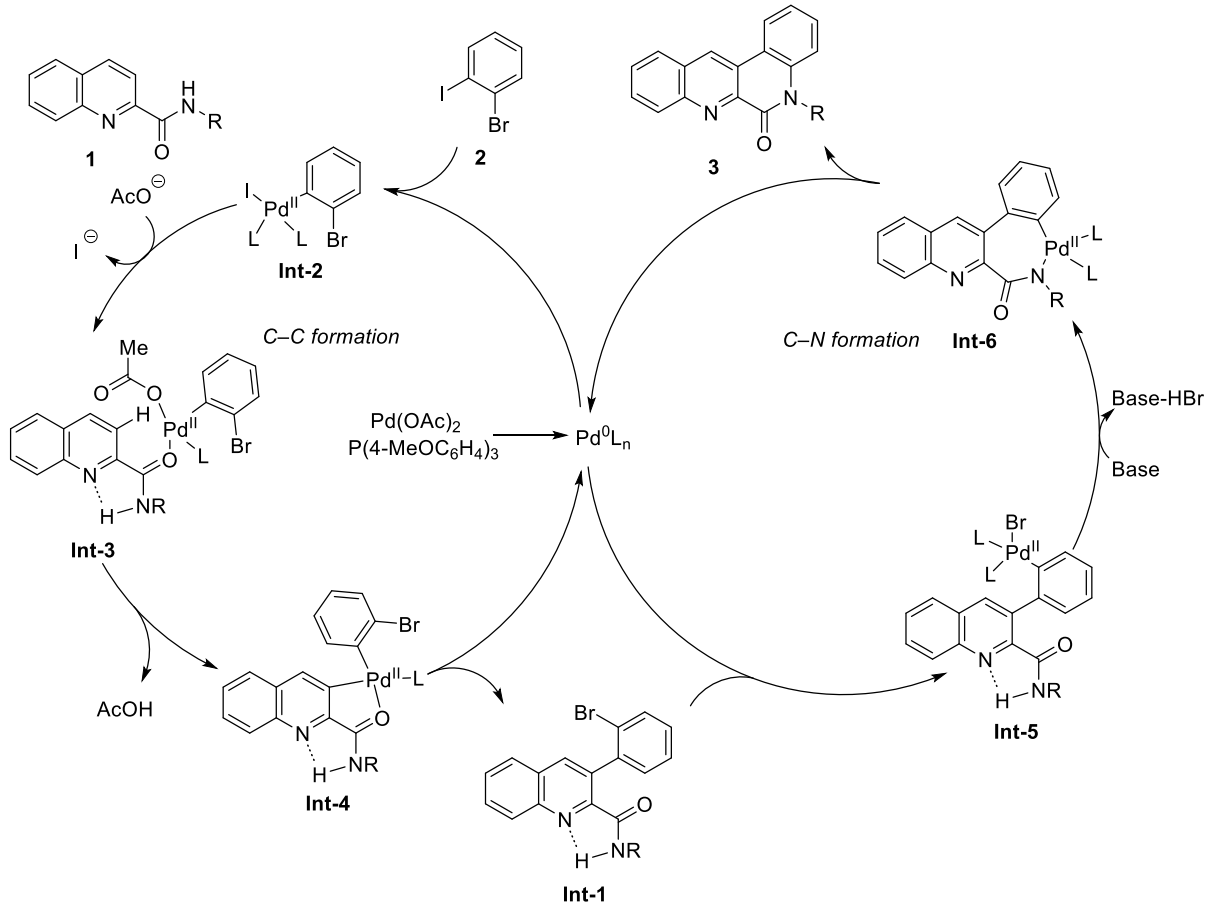


Scheme 3: Detection of the intermediate **Int-1ad** in the annulation reaction of **1a** with 1-bromo-5-*tert*-butyl-2-iodobenzene **2d**.

These results suggested that the carbon–iodine bond in 1-bromo-2-iodobenzene was involved in the formation of the C–C bond, while the carbon–bromine bond was involved in the formation of the C–N bond. (Scheme 4). Accordingly, a plausible reaction mechanism is proposed (Scheme 5). First, the activated palladium(0) catalyst is inserted into the carbon–iodine bond of the 1-bromo-2-iodoarene via oxidative addition. The intermediate **Int-2** undergoes ligand exchange from iodine and phosphine to acetate and quinoline-2-carboxamide to generate intermediate **Int-3**. Then, the palladium catalyst forms a carbon–palladium bond through a CMD process to give the palladacycle intermediate **Int-4**. Next, reductive elimination between quinoline and arene moieties forms the C–C bond to give intermediate **Int-1** and regenerate the palladium(0) catalyst. Oxidative addition to a carbon–bromine bond of **Int-1** generates **Int-5**, and a nitrogen–palladium bond is formed to afford the seven membered palladacycle intermediate **Int-6**. Finally, this intermediate undergoes reductive elimination between nitrogen and carbon atoms to provide the lactam product **3**.



Scheme 4: Step-wise formation of C–C and C–N bonds during the annulation reaction.



Scheme 5: Plausible reaction mechanism of the sequential C–H/N–H functionalization reaction.

Conclusion

This study explored a novel C–H/N–H activated annulation reaction for the synthesis of quinoline-fused lactams. The annulation reaction afforded the desired products in up to 83% yields. The reaction demonstrated broad tolerance for various substituents. Moreover, the reaction demonstrated high chemoselectivity because the reaction proceeded via initial C–C bond formation at C–I, followed by C–N bond formation at C–Br. Thus, the positions of substituents on the products were controlled based on the position of the substituent on 1-bromo-2-iodobenzene derivatives, thus providing facile and efficient access to chemodivergent products. The developed reaction protocol is expected to be applicable to the synthesis of functional materials and bioactive molecules.

Supporting Information

Experimental details and copies of ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra.

Supporting Information File 1:

File Name: Supporting Information File 1

File Format: PDF

Title: Supporting Information

Acknowledgements

This paper is based on results obtained from a project, JPNP23006, commissioned by the New Energy and Industrial Technology Development Organization (NEDO). We thank Suzanne Adam, PhD, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Funding

This work was supported by Kobe University.

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