Highly Efficient Direct Allylation of Oxindoles with Simple Allylic Alcohols Enabled by Palladium/Brønsted Acid Catalysis

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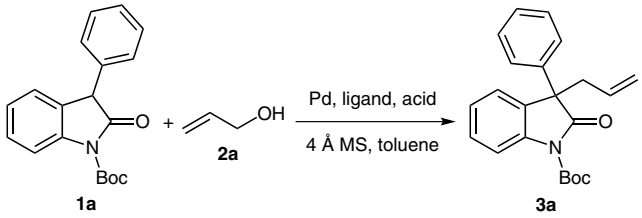
Abstract: A highly efficient and practical direct allylic alkylation of oxindoles with simple allylic alcohols cocatalyzed by $Pd(OAc)_2/Ph_3P$ and $PhCO_2H$ under mild conditions has been developed, which streamlines the installation of an all-carbon quaternary allylic center at the oxindole 3-position. Enantioselective allylic alkylation has also been realized with the product in almost quantitative yield and 17% enantiomeric excess. Mechanistically, ESI analysis indicates that a palladium(0) species and π-allyl-$Pd(PPh_3)_2$ cation were involved.

Key words: oxindole, allylic alkylation, Brønsted acids, allylic alcohol, palladium

Since pioneering examples reported in 1960s, palladium-catalyzed Tsuji–Trost-type allylic alkylation reaction has been witnessed tremendous advances for constructing C–C bonds in synthetic organic chemistry.[1] Traditionally, such reactions took place between nucleophiles and activated allylic alcohol derivatives, such as carbonates, halides, acetates, and amine, which always generates stoichiometric waste.[2] Nowadays, the development of highly atom-/step-economic and sustainable chemical transformation is becoming more and more desirable.[3] Undoubtedly, the direct use of allylic alcohol itself instead of its derivatives as precursor of the π-allyl fragment for the allylation reaction is much more attractive and practical since only water is formed as byproduct. Significant efforts have been made for this purpose;[4–8] notable examples include strong acid-catalyzed α-allylation of aldehyde via Claisen rearrangement under harsh conditions[4] and palladium-catalyzed allylic alkylation reaction with As_2O_3,[5] $SnCl_2$,[6] $Ti(O\textit{i}\text{-}Pr)_4$,[7] and BEt_3[8] as extra activators to enable leaving of the hydroxyl group. Remarkably, Yamamoto et al.,[9] Kobayashi et al.,[10] List et al.,[11] Beller et al.,[12] and Gong et al.[13] developed independently elegant approaches for the allylic alkylation processes by using simple Brønsted acids as activators. On the other hand, for such direct allylation reactions with allylic alcohols, the nucleophiles were extensively confined to ketones, imidates, malonates, and aromatic aldehydes.[1,2] Nevertheless, the exploration of the direct allylic alkylation reaction to other nucleophiles, especially to valuable nitrogen-containing compounds, is very sparse, although which is of particular interest and significance.[1,14]

Table 1 Optimization of Reaction Conditions for the Direct Allylation of **1a** with **2a**[a]



Entry	[Pd] (mol%)	Ligand (mol%)	Acid (mol%)	Yield (%)
1	$Pd(PPh_3)_4$ (5.0)	–	–	69
2	$Pd(PPh_3)_4$ (5.0)	–	$PhCO_2H$ (5.0)	>99
3	$Pd(OAc)_2$ (5.0)	Ph_3P (20)	$PhCO_2H$ (5.0)	>99
4	$Pd(OAc)_2$ (5.0)	Ph_3P (5.0)	$PhCO_2H$ (5.0)	>99
5	$Pd(OAc)_2$ (3.0)	Ph_3P (3.0)	$PhCO_2H$ (3.0)	>99 (98)
6	$PdCl_2$ (3.0)	Ph_3P (3.0)	$PhCO_2H$ (3.0)	>99 (98)
7	$Pd(OAc)_2$ (2.0)	Ph_3P (2.0)	$PhCO_2H$ (2.0)	46
8	$Pd(OAc)_2$ (1.5)	Ph_3P (3.0)	$PhCO_2H$ (3.0)	50
9	$Pd(OAc)_2$ (5.0)	Ph_3P (5.0)		41
10	$Pd(OAc)_2$ (5.0)	–	$PhCO_2H$ (5.0)	n.r.
11	–	Ph_3P (5.0)	$PhCO_2H$ (5.0)	n.r.
12	$Pd(OAc)_2$ (3.0)	Ph_3P (3.0)	$MeCO_2H$ (3.0)	88
13	$Pd(OAc)_2$ (3.0)	Ph_3P (3.0)	F_3CCO_2H (3.0)	80

[a] Reactions performed on 0.2 mmol scale (**1a**) using 2.0 equiv of **2a** and 100 mg of 4 Å MS in 1.0 mL of toluene at 60 °C for 12 h. Yields were determined by ^1H NMR. Isolated yield in the parenthesis; n.r. means no reaction.

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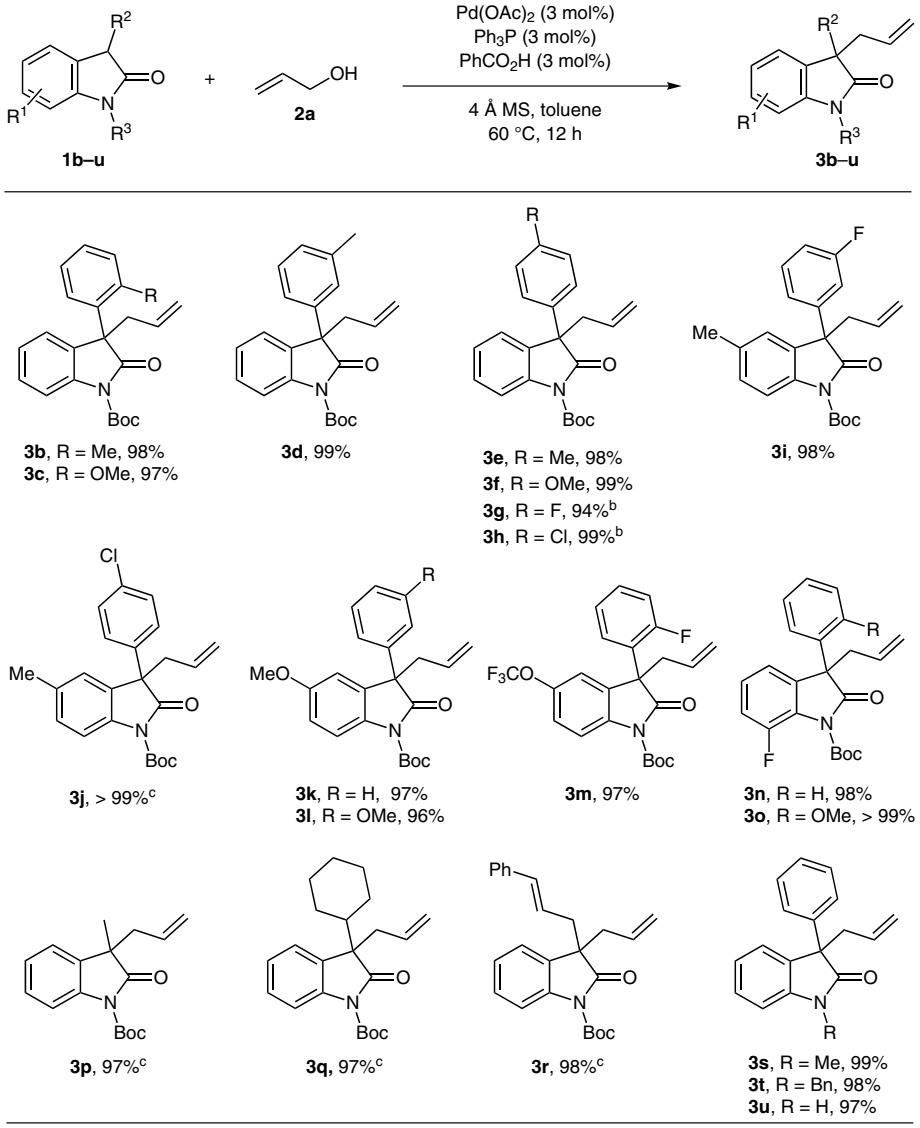
The 3-alkyl-3-aryl oxindoles comprise a prominent structural motif in a number of pharmaceuticals and biologically active natural products, as well as important building blocks for alkaloid synthesis.[15] Therefore, the development of practical synthetic methods for these kinds of compounds is extremely anticipated in organic chemistry.[16,17] Among these well-documented strategies to access the unique structure, Trost's allylic alkylation of oxindoles with allyl acetates is one of meritorious approaches.[17] Obviously, the direct allylic alkylation of oxindole with allylic alcohol itself represents a straightforward and atom-/step-economic method. Herein, we report our preliminary results on the direct allylic alkylation of oxindoles with allylic alcohols instead of allyl acetates that is cocatalyzed by the combination of $Pd(OAc)_2/Ph_3P$ and $PhCO_2H$ under mild reaction conditions, which provides a highly practical method to construct 3-allyl-3-aryl/alkyl oxindoles.

Initially, the treatment of *tert*-butyl 2-oxo-3-phenylindoline-1-carboxylate (**1a**) with 2.0 equivalents of allylic alcohol **2a** in the presence of 5.0 mol% of $Pd(PPh_3)_4$ and 4 Å molecular sieves in toluene at 60 °C for 12 hours afforded the desired allylated product **3a** in 69% yield (Table 1, entry 1).

Extra addition of 5.0 mol% $PhCO_2H$ improved the yield to >99% (Table 1, entry 2), which confirmed that the simple Brønsted acid $PhCO_2H$ could accelerate the direct allylic alkylation reaction.[9,10] $Pd(OAc)_2/Ph_3P$ was also efficient for the reaction (Table 1, entry 3). Surprisingly, decreasing the loading of Ph_3P to 5.0 mol%, one equivalence to $Pd(OAc)_2$ that is dramatically different from the traditional ratio of palladium catalysis,[1] even lowering the amount of $Pd(OAc)_2$, Ph_3P, and $PhCO_2H$ to 3.0 mol%,

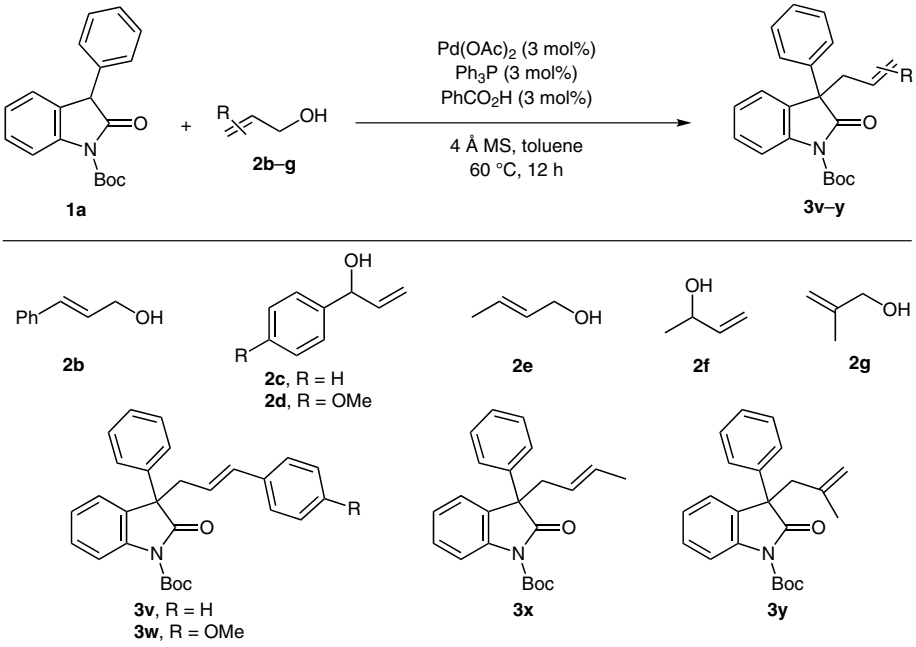


Scheme 1 Direct allylation of diverse oxindoles with **2a**.[a a] *Reagents and conditions* (unless indicated otherwise): **1** (0.2 mmol), **2a** (0.4 mmol), $Pd(OAc)_2$ (3.0 mol%), Ph_3P (3.0 mol%), $PhCO_2H$ (3.0 mol%), 4 Å MS (100 mg), toluene (1.0 mL), 60 °C, 12 h. Yield of the isolated product after silica gel chromatography. [b] $Pd(OAc)_2$ (5.0 mol%), Ph_3P (5.0 mol%), $PhCO_2H$ (10 mol%). [c] $Pd(OAc)_2$ (5.0 mol%), Ph_3P (20.0 mol%), $PhCO_2H$ (10 mol%).

also gave **3a** in quantitative yield (Table 1, entries 4 and 5). Using $PdCl_2$ instead of $Pd(OAc)_2$ also facilitated full conversion (Table 1, entry 6). Further reducing the catalysts to 2.0 mol% or just reducing the loading of $Pd(OAc)_2$ to 1.5 mol% lowered the conversion of **1a** into **3a** in 46% and 50%, respectively (Table 1, entries 7 and 8). As a contrast to entry 4 (Table 1), only using 5.0 mol% of $Pd(OAc)_2/Ph_3P$ without addition of $PhCO_2H$, the conversion of **1a** decreased to 41% which verified that $PhCO_2H$ played a positive role in such direct allylic alkylation process again (Table 1, entry 9). Control experiments revealed that both combinations of $Pd(OAc)_2/PhCO_2H$ and $Ph_3P/PhCO_2H$ could not trigger this reaction (Table 1, entries 10 and 11). Using $MeCO_2H$ and F_3CCO_2H instead of $PhCO_2H$ gave **3a** in 80% and 88% yields, respectively (Table 1, entries 12 and 13).Upon the optimized reaction conditions, the substrate scope was investigated with respect to the oxindoles and allylic alcohols. Firstly, a number of oxindoles and allylic alcohol **2a** were subjected to the standard reaction conditions (Scheme 1). Remarkably, in nearly all cases, almost quantitative yields were obtained for 3-aryl oxindoles regardless of the nature of the substituent and the oxindole ring.

For example, bearing the electron-donating substituent, such as *ortho*/*meta*/*para*-methyl, methoxyl, **1b**–**f** and **1k**,**l** led to the corresponding adducts **3b**–**f**[21] and **3k**,**l** in 96–99% yields smoothly. For oxindoles **1g**,**h** and **1j** with a halogen substituent, such as F and Cl at the *para* position, the allylation reaction also took place readily, which furnished **3g**–**h** and **3j** in 94% to >99% yield, although a slightly higher catalyst loading was required for complete substrate conversions. Oxindoles **1i** and **1m**, with a fluorine atom at the *ortho* and *meta* position, are very applicable to the direct allylation process as well, and the reactions afforded **3i** and **3m** in 98% and 97% yield, respectively. Compounds **1n** and **1o** with a fluoride at the 7-position underwent the alkylation reaction and gave **3n** and **3o** in excellent 98% and >99% yields, respectively. Interestingly, substrates can be extended to 3-alkyl-3-aryl oxindoles. Accordingly, allylated products **3p**–**r** containing 3-methyl, 3-cyclohexyl, and even 3-cinnamyl group could be isolated in almost quantitative yields despite the

Table 2 Direct Allylic Alkylation of Oxindole **1a** with Diverse Allylic Alcohols



Entry[a]	Allylic alcohol	Product	Yield (%)
1	**2b**	**3v**	>99
2	**2c**	**3v**	>99
3	**2d**	**3w**	>99
4[b]	**2e**	**3x**	96
5[b]	**2f**	**3x**	97
6[b]	**2g**	**3y**	98

[a] Reaction conditions: **1a** (0.2 mmol), **2b**–**d** (0.24 mmol), $Pd(OAc)_2$ (3.0 mol%), Ph_3P (3.0 mol%), $PhCO_2H$ (3.0 mol%), 4 Å MS (100 mg), toluene (1.0 mL), 60 °C, 12 h, isolated yield.
[b] Reactions conditions: **2** (0.4 mmol), $Pd(OAc)_2$ (5.0 mol%), Ph_3P (20 mol%), $PhCO_2H$ (10 mol%).

fact that an increased catalyst loading was necessary. Significantly, different N-protecting groups can be accommodated to the direct allylation approach, for instance, both methyl and benzyl groups can be used. The treatment of **1s**,**t** with **2a** to the standard reaction conditions provided readily the desired allylic alkylated products **3s**,**t** in 98–99% yields. Strikingly, the challenging oxindole **1u** with an unprotected N–H group, which was restricted in Trost's palladium- and molybdenum-catalyzed allylic alkylation processes,[15a,b] was surprisingly well tolerated, and the reaction gave **3u** in 97% yield smoothly.

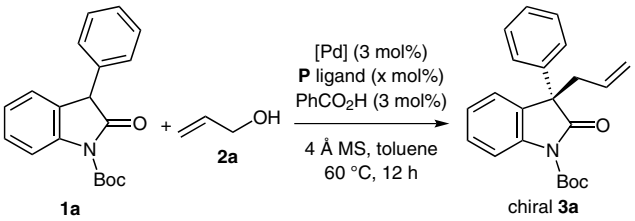
Importantly, besides allylic alcohol **2a**, a series of substituted allylic alcohols proved to be applicable to the practical allylation process.

As shown in Table 2, treating oxindole **1a** with allylic alcohols **2b**–**g** readily furnished the desired product **3v**–**y** in excellent yield. It is noteworthy that the reactions of **1a** with both **2b** and **2c** afforded exclusively **3v** (Table 2, entries 1 and 2), which indicate dramatically that both reactions proceeded via the same π-allyl-palladium intermediate. Unprecedentedly, excellent regioselectivity was observed when less sterically unsymmetrical allylic alcohols **2e** and **2f** were employed that resulted in nearly quantitative **3x** alone (Table 2, entries 4 and 5).[18]

Next, we carried out a preliminary attempt for the palladium-catalyzed direct asymmetric allylic alkylation of **1a** with **2a**. Several typical mono- and diphosphine ligands **P1**–**P6** were employed (Table 3). Monophosphines **P1**–**P3** (Figure 1) led to racemic **3a** in low yields (Table 3, entries 1–3). Use of diphosphine ligands **P4**, **P5**, and **P6**[19] furnished **3a** in excellent yield smoothly, yet 5–15% enantiomeric excess (Table 3, entries 3–5). Using $Pd_2(dba)_3$ instead of $Pd(OAc)_2$ with **P4** as catalyst formed **3a** in 95% yield and 17% enantiomeric excess.

Mechanistically, the reaction of oxindole **1a** with allylic alcohol **2a** under the standard reaction conditions for 15 minutes was investigated by ESI-MS (on microTOF-Q II). Besides **1a** (*m/z* = 332, with Na) and allylic product **3a** (*m/z* = 371, with Na), $Pd(PPh_3)_2$ (*m/z* = 631), π-allyl-$Pd(PPh_3)_2$ cation (*m/z* = 671), and oxindole-palladium cation (*m/z* = 413) were detected clearly (Figure 2).

Table 3 Preliminary Attempt for the Palladium-Catalyzed Direct Asymmetric Allylation of **1a** with **2a**



Entry[a]	[Pd]	**P** ligand (mol%)	Yield (%)	ee (%)
1	$Pd(OAc)_2$	**P1** (7)	<5	–
2	$Pd(OAc)_2$	**P2** (7)	22	5
3	$Pd(OAc)_2$	**P3** (7)	19	rac.
4	$Pd(OAc)_2$	**P4** (4)	96	15
5	$Pd(OAc)_2$	**P5** (4)	90	5
6	$Pd(OAc)_2$	**P6** (4)	97	7
7[b]	$Pd_2(dba)_3$	**P4** (7)	95	17

[a] Reactions performed on 0.2 mmol scale (**1a**) using 2.0 equiv of **2a** and 100 mg of 4 Å MS in 1.0 mL of toluene at 60 °C for 12 h; isolated yield; ee was determined by chiral HPLC analysis.
[b] 1.5 mol% of $Pd_2(dba)_3$ was used instead of $Pd(OAc)_2$.

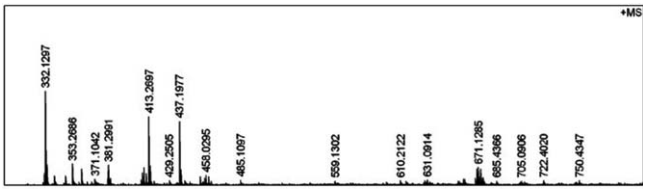


Figure 2 ESI-MS for the reaction of **1a** with **2a**

The observations indicate that a palladium(0) intermediate was formed, followed by π-allylic insertion to $PhCO_2H$-activated allylic alcohol,[9–11,20] which led to the allylation of oxindole.

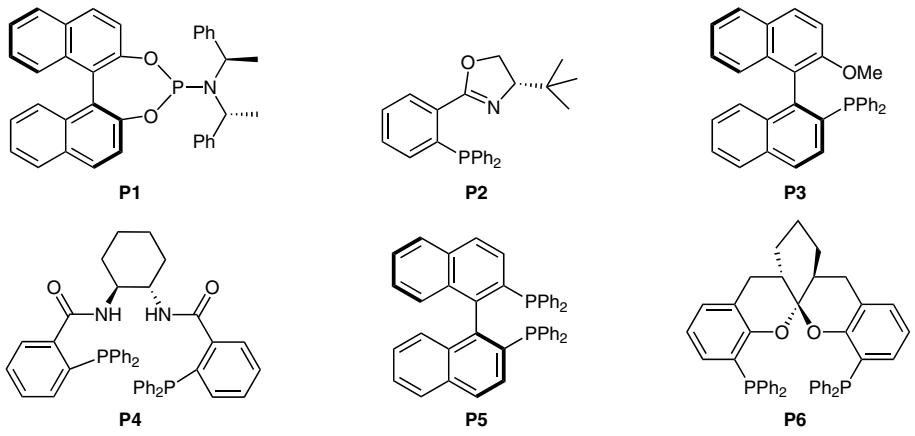


Figure 1

In summary, we have demonstrated an efficient and practical direct allylic alkylation of oxindoles with simple allylic alcohols catalyzed by the combination of palladium catalyst and benzoic acid for the generation of an all-carbon quaternary allylic center at the oxindole 3-position.[20] This protocol tolerates a diverse scope of functional groups in both oxindoles and allylic alcohols. Significantly, excellent regioselectivities were observed when unsymmetrical substituted allylic alcohols were used as allylic species. Enantioselective allylic alkylation has also been realized with the product in almost quantitative yield and 17% enantiomeric excess. ESI-MS analysis indicates that a palladium(0) species was involved and might function as the real active catalyst. Further applications of the practical method and the investigation for clear mechanism are ongoing in our laboratory and will be reported in due course.

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(21) **Typical Procedure**

To a flame-dried Schlenk tube charged with 4 Å MS (50 mg/0.1 mmol) and a magnetic stir bar was added 3-aryloxindoles **1** (0.1 mmol), allylic alcohol **2** (0.2 mmol), $Pd(OAc)_2$ (3.0–10 mol%), Ph_3P (3.0–10 mol%), and PhCOOH (3.0–10 mol%) in dry toluene (0.5 mL). The resulting suspension was stirred at the specified temperature under argon for 12 h. Upon completion of the reaction (monitored by TLC), the reaction mixture was diluted with EtOAc and then quenched with sat. aq NH_4Cl. The aqueous layer was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, concentrated in vacuo, and purified by flash chromatography to afford pure products **3**.

***tert*-Butyl 3-Allyl-2-oxo-3-*o*-tolylindoline-1-carboxylate (3b)**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.61 (s, 9 H), 2.31 (s, 3 H), 3.02 (m, 2 H), 4.97 (m, 2 H), 5.42 (m, 1 H), 7.12 (m, 2 H), 7.22 (m, 3 H), 7.36 (m, 1 H), 7.91 (d, *J* = 8.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.31, 28.25, 28.84, 42.59, 55.92, 88.26, 115.04, 119.79, 125.71, 127.68, 128.71, 129.09, 130.58, 134.12, 137.66, 139.64, 149.46, 176.55. HRMS (EI): *m/z* calcd for $C_{23}H_{25}NNaO_3$ $[M + Na]^+$: 386.1729; found: 386.1727.

***tert*-Butyl 3-Allyl-3-(2-methoxyphenyl)-2-oxoindoline-1-carboxylate (3c)**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65 (s, 9 H), 3.01 (m, 2 H), 3.46 (s, 3 H), 4.97 (m, 2 H), 5.40 (m, 1 H), 6.78 (m, 2 H), 7.04 (m, 3 H), 7.23 (m, 1 H), 7.51 (m, 1 H), 7.81 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.31, 28.25, 28.84, 42.59, 55.92, 88.26, 115.04, 119.79, 125.71, 127.68, 128.71, 129.09, 130.58, 134.12, 137.66, 139.64, 149.46, 176.55. HRMS (EI): *m/z* calcd for $C_{23}H_{25}NNaO_4$ $[M + Na]^+$: 402.1667; found: 402.1676.

***tert*-Butyl 3-Allyl-2-oxo-3-m-tolylindoline-1-carboxylate (3d)**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.61 (s, 9 H), 2.31, (s, 3 H), 3.01 (m, 1 H), 3.11 (m, 1 H), 5.02 (m, 2 H), 5.40 (m, 1 H), 7.06 (m, 2 H), 7.21 (m, 4 H), 7.34 (m, 1 H), 7.93 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.56, 21.61, 27.96, 28.09, 28.16, 42.55, 56.61, 84.27, 115.09, 119.70, 124.25, 124.32, 125.16, 127.86, 128.39, 130.53, 131.95, 138.24, 139.18, 139.83, 149.28, 176.33. HRMS (EI): *m/z* calcd for $C_{20}H_{21}NNaO_3$ $[M + Na]^+$: 346.1408; found: 346.1414.

