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An expedient synthesis of poly-substituted 1-arylisoquinolines from δ-ketonitriles via indium-mediated Barbier reaction protocol

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ABSTRACT

We developed an efficient synthetic strategy of poly-substituted 1-arylisoquinolines via an indium-mediated Barbier type allylation from δ-ketonitriles. Initial attack of allylindium species occurred at the nitrile group selectively to form the enamine intermediate, which reacted with the ketone group intramolecularly to furnish the isoquinolines.

Allylindium reagents have been used extensively for the introduction of allyl group in a Barbier type manner.[1–3] Although allylindium reagents can be added to many reactive functional groups including aldehyde, ketone, and activated imine with acyl or tosyl group,[1,2] the reaction with nitrile has not been reported much except recent Yamamoto's Letter[3] and ours.[4] According to the results introduction of allylindium can be carried out with only nitrile compounds having both an α-hydrogen atom and an α-EWG group.[3,4]

Isoquinoline and related compounds play an important role in organic chemistry as key structural units in many biologically interesting substances including illudinine, berberine, coptisine, noscapine and PK11195,[5] and there have been reported numerous approaches for the synthesis of this framework.[6] Recently we reported an efficient synthesis of diallylated δ-valerolactam[4a] and poly-substituted pyrroles[4b] via an indium-mediated Barbier type allylation, as summarized in Scheme 1. During the synthesis of pyrroles[4b] we found that benzoyl group was less reactive than nitrile to allylindium. Thus, we imagined that δ-ketonitrile such as **3a** could be converted to 1-phenylisoquinoline **4a** via the chemoselective allylation at the nitrile and the following cyclization of the enamine intermediate, as shown in Scheme 2. As expected the reaction of **3a** and allyl bromide (2.0 equiv) in the presence of indium powder (1.0 equiv) in THF afforded **4a** in 74% in short reaction time (reflux, 30 min).[7]

Encouraged by the results, we prepared various δ-ketonitriles **3b–f** and examined the reaction with allyl bromide, methallyl bromide and crotyl bromide as shown in Table 1. Compounds **3a–c**, **3e** and **3f** were prepared in moderate yields (51–63%) from 2-fluorobenzophenone derivatives **1a–c** and active methylene compounds **2a–c** under the influence of Cs_2CO_3 in DMSO (130–140 °C, 5 h).[7] Compound **3d** ($R^1 = R^3 = H$, Ar = Ph) was prepared from 2-methylbenzophenone.[8]

The reaction of **3b–f** and allyl bromide in the presence of indium powder showed the formation of desired 3-allylisoquinoline derivatives **4b–f** in good to moderate yields (65–76%) in a one-pot in short time (30–60 min),[7] as summarized in Table 1. The reaction was also effective when we used methallyl bromide (entry 7) or crotyl bromide (entry 8) instead of allyl bromide. In these cases, however, excess amounts of indium (2.0 equiv) and the corresponding bromides (4.0 equiv) were required for the reasonable yields of compounds **4g** and **4h**.

As a next trial, we examined the reaction of **3g**[9] and **3h**[9] which have ester group instead of benzoyl moiety, as shown in Scheme 3. As expected, the reaction of **3g** and allylindium provided isoquinoline derivative **5a**[7] in moderate yield (51%). Diallyl dihydroisoquinolinone **6a** (19%) was formed as a minor product via the double allylation reaction.[4a] In the case of compound **3h**, the yields of mono-allyl and di-allyl compounds were relatively low. Instead enamine **8** was isolated in appreciable amounts (45%). This enamine was easily converted into mono-allyl compound **5b**[7] under the influence of acid catalyst (AcOH, toluene, reflux, 10 h, 83%). The nucleophilicity of the amino group in **8** might be low due to the presence of conjugated ester moiety. Thus the next cyclization of **8** to **5b** was not effective under the Barbier reaction conditions.

In order to check the relative reactivity between aromatic and aliphatic nitriles, we prepared compound **3i**[9] and carried out the reaction as shown in Scheme 4. Compound **9a** was isolated in 52% and we could not isolate the other compounds in appreciable

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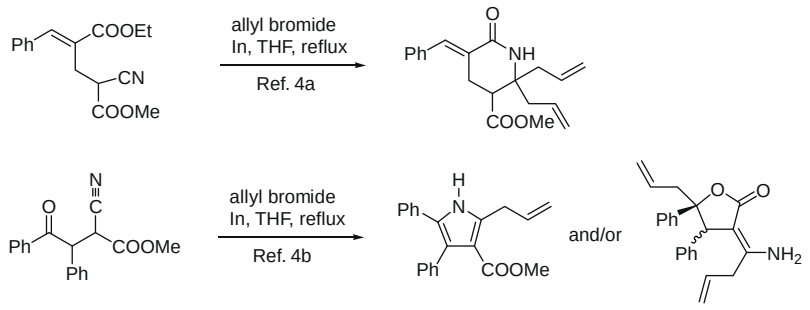
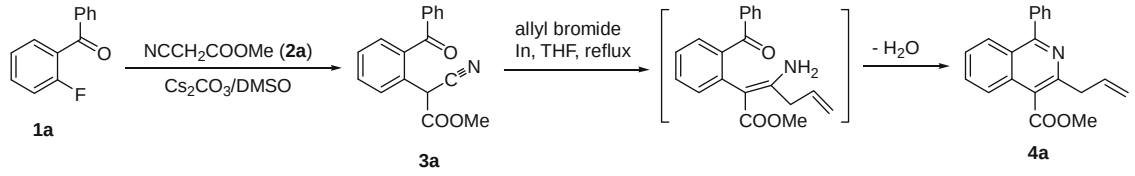
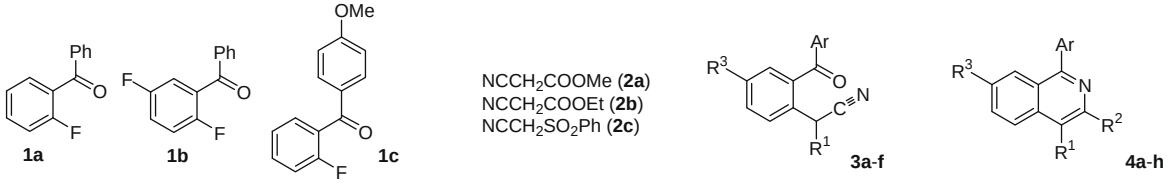


Scheme 1.



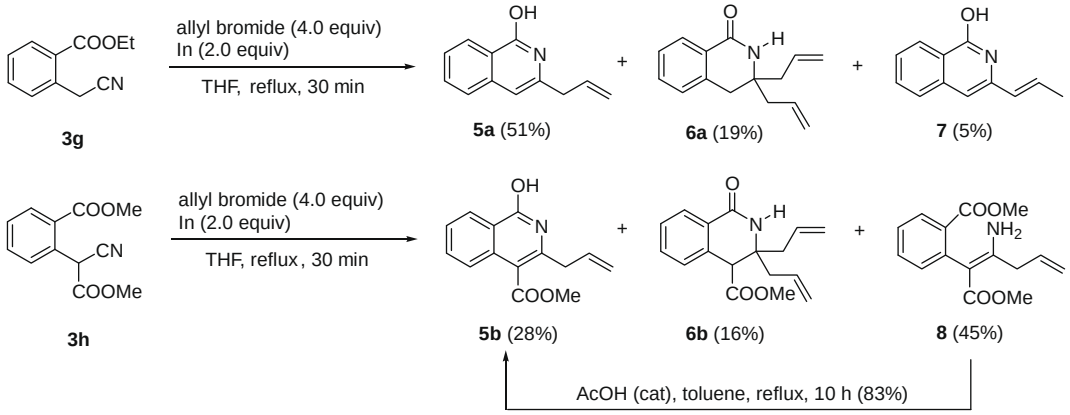
Scheme 2.

Table 1
Synthesis of starting materials **3a–f** and 1-arylisoquinolines **4a–h**

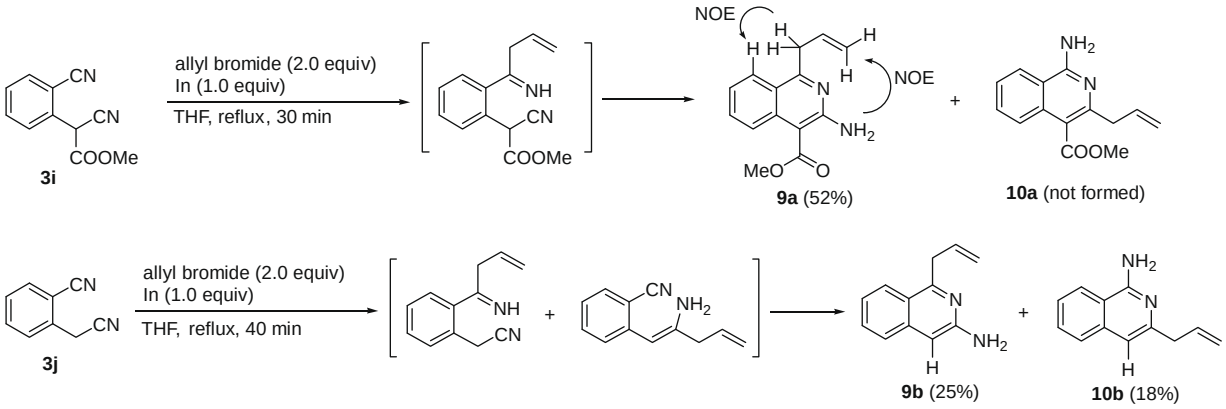


Entry	**1** + **2**	**3**[a] (%)	Conditions	Isoquinoline **4** (%)
1	**1a** + **2a**	**3a** (63)	Allyl bromide (2.0 equiv), In (1.0 equiv) THF, reflux, 30 min	**4a** (R^1 = COOMe, R^2 = allyl, R^3 = H, Ar = Ph) (74)
2	**1a** + **2b**	**3b** (61)	Allyl bromide (2.0 equiv), In (1.0 equiv) THF, reflux, 30 min	**4b** (R^1 = COOEt, R^2 = allyl, R^3 = H, Ar = Ph) (71)
3	**1a** + **2c**	**3c** (51)	Allyl bromide (2.0 equiv), In (1.0 equiv) THF, reflux, 50 min	**4c** (R^1 = SO_2Ph, R^2 = allyl, R^3 = H, Ar = Ph) (72)
4	[b]	**3d**[b]	Allyl bromide (2.0 equiv), In (1.0 equiv) THF, reflux, 30 min	**4d** (R^1 = H, R^2 = allyl, R^3 = H, Ar = Ph) (65)
5	**1b** + **2a**	**3e** (62)	Allyl bromide (2.0 equiv), In (1.0 equiv) THF, reflux, 60 min	**4e** (R^1 = COOMe, R^2 = allyl, R^3 = F, Ar = Ph) (76)
6	**1c** + **2b**	**3f** (59)	Allyl bromide (2.0 equiv), In (1.0 equiv) THF, reflux, 60 min	**4f** (R^1 = COOMe, R^2 = allyl, R^3 = H, Ar = 4-OMePh) (71)
7	—	**3a**	Methallyl bromide (4.0 equiv), In (2.0 equiv) THF, reflux, 7 h	**4g** (R^1 = COOMe, R^2 = $CH_2C(CH_3)=CH_2$, R^3 = H, Ar = Ph) (66)
8	—	**3a**	Crotyl bromide (4.0 equiv), In (2.0 equiv) THF, reflux, 7 h	**4h** (R^1 = COOMe, R^2 = $CH(CH_3)CH=CH_2$, R^3 = H, Ar = Ph) (56)

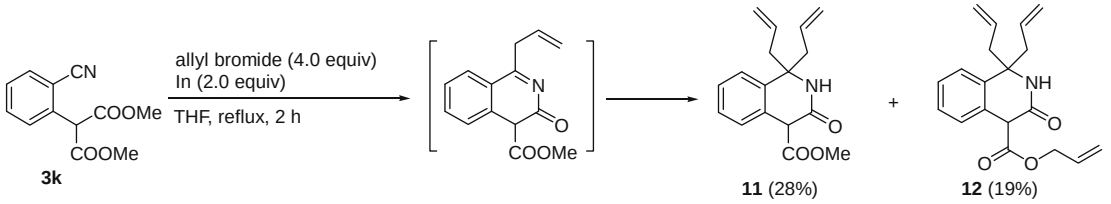
[a] Conditions: compound **1** (1.0 mmol), compound **2** (2.0 equiv), Cs_2CO_3 (2.0 equiv), DMSO, 130–140 °C, 5 h.
[b] See text.[8]



Scheme 3.



Scheme 4.



Scheme 5.

amounts. The structure of **9a**[7] was confirmed by NOE experiments. The results clearly stated that first attack of allylindium occurred at the aromatic nitrile instead of the nitrile of methyl cyanoacetate moiety. In the case of compound **3j**,[9] two compounds **9b** and **10b** were obtained although the combined yields were moderate (43%). Similarly, we isolated compounds **11** and **12**[10] from the reaction of compound **3k**[9] under the similar conditions (Scheme 5), albeit in low yields. From the results we could conclude that the intrinsic reactivity of nitrile toward allylindium species is sufficient to form the imine or enamine intermediates to cause subsequent reaction to form a cyclic compound when a suitable electrophile (benzoyl, ester and nitrile) is present at the δ-position of the same molecule.

In summary, we developed an efficient synthetic strategy of poly-substituted 1-arylisoquinolines via an indium-mediated allylation of δ-ketonitriles. In addition, we found that various allylated cyclic compounds can be synthesized via the initial indium-mediated allylation of nitrile and the following cyclization of the imine or enamine intermediate with a suitable electrophile in the same molecule such as benzoyl, ester and nitrile.

Acknowledgments

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7. *Typical procedure for the synthesis of compounds* **3a** and **4a**: A stirred mixture of 2-fluorobenzophenone (**1a**, 200 mg, 1.0 mmol), methyl cyanoacetate (**2a**, 198 mg, 2.0 mmol), Cs_2CO_3 (751 mg, 2.0 mmol) in DMSO (2 mL) was heated to 130–140 °C for 5 h. After the usual aqueous workup and column chromatographic purification process (hexanes/EtOAc/CH_2Cl_2, 16:2:1) compound **3a** was isolated as a pale yellow solid, 176 mg (63%). A stirred mixture of compound **3a** (140 mg, 0.50 mmol), allyl bromide (121 mg, 1.0 mmol) and indium powder (57 mg, 0.5 mmol) in THF (1 mL) was heated to reflux for 30 min. After the usual aqueous workup and column chromatographic purification process (hexanes/CH_2Cl_2/EtOAc, 16:1:1)

compound **4a** was isolated as pale yellow oil, 113 mg (74%). Other compounds were synthesized similarly and the selected spectroscopic data of **3a**, **4a**, **4e**, **4g**, **5a**, **5b**, **9a** and **11** are as follows.*Compound* **3a**: 63%; pale yellow solid, mp 91–92 °C; IR (KBr) 2252, 1752, 1658, 1448, 1272 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.72 (s, 3H), 5.71 (s, 1H), 7.44–7.52 (m, 4H), 7.59–7.66 (m, 2H), 7.77–7.81 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.92, 53.78, 115.64, 128.42 (2C), 129.96, 129.99, 130.35, 131.27, 131.96, 133.33, 136.66, 137.18, 165.26, 197.31; ESIMS *m*/*z* 280 (M^++1).*Compound* **4a**: 74%; pale yellow oil; IR (film) 2950, 1726, 1553, 1254, 1214 cm^{-1}; ^1H NM ($CDCl_3$, 300 MHz) δ 3.85 (dt, *J* = 6.6 and 1.5 Hz, 2H), 4.05 (s, 3H), 5.08–5.21 (m, 2H), 6.08–6.22 (m, 1H), 7.46–7.55 (m, 4H), 7.65–7.72 (m, 3H), 7.89–7.92 (m, 1H), 8.05–8.08 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.19, 52.39, 116.29, 122.33, 124.08, 124.71, 126.81, 127.77, 128.32, 128.84, 129.95, 130.84, 134.32, 135.70, 139.07, 150.02, 161.93, 168.94; ESIMS *m*/*z* 304 (M^++1). Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 79.44; H, 5.89; N, 4.37.*Compound* **4e**: 76%; white solid, mp 87–88 °C; IR (KBr) 2951, 1726, 1556, 1250, 1214 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.84 (dt, *J* = 6.6 and 1.5 Hz, 2H), 4.06 (s, 3H), 5.08–5.20 (m, 2H), 6.07–6.20 (m, 1H), 7.45–7.57 (m, 4H), 7.63–7.72 (m, 3H), 7.95 (dd, *J* = 9.3 and 5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.07, 52.50, 111.16 (J_{C-F} = 22.1 Hz), 116.40, 121.29 (J_{C-F} = 25.2 Hz), 122.12, 125.65 (J_{C-F} = 8.0 Hz), 127.01 (J_{C-F} = 8.3 Hz), 128.52, 129.10, 129.75, 131.43, 135.59, 138.64, 149.80 (J_{C-F} = 2.6 Hz), 160.54 (J_{C-F} = 247.3 Hz), 161.31 (J_{C-F} = 5.5 Hz), 168.65; ESIMS *m*/*z* 322 (M^++1). Anal. Calcd for $C_{20}H_{16}FNO_2$: C, 74.75; H, 5.02; N, 4.36. Found: C, 74.91; H, 4.96; N, 4.22.*Compound* **4g**: 66%; pale yellow oil; IR (film) 2949, 1727, 1552, 1252, 1214 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.79 (s, 3H), 3.84 (s, 2H), 4.03 (s, 3H), 4.70–4.71 (m, 1H), 4.85–4.86 (m, 1H), 7.45–7.55 (m, 4H), 7.65–7.72 (m, 3H), 7.89–7.92 (m, 1H), 8.06–8.10 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.62, 44.69, 52.37, 112.37, 122.86, 124.14, 124.70, 126.81, 127.72, 128.32, 128.81, 129.97, 130.77, 134.30, 139.10, 143.36, 149.86, 161.59, 169.00; ESIMS *m*/*z* 318 (M^++1). Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.64; H, 6.24; N, 4.35.*Compound* **5a**: 51%; white solid, mp 132–133 °C; IR (KBr) 3170, 1681, 1647 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.43 (dd, *J* = 6.9 and 0.9 Hz, 2H), 5.20–5.38 (m, 2H), 5.95–6.08 (m, 1H), 6.33 (s, 1H), 7.39–7.48 (m, 2H), 7.58–7.63 (m, 1H), 8.39 (dt, *J* = 8.1 and 0.6 Hz, 1H), 11.68 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.45, 104.15, 118.71, 124.42, 125.68, 125.81, 127.16, 132.45, 133.14, 138.52, 139.85, 164.76; ESIMS *m*/*z* 186 (M^++1). Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 78.03; H, 6.12; N, 7.52.*Compound* **5b**: 28%; pale yellow solid, mp 182–183 °C; IR (KBr) 3179, 1719, 1675, 1620, 1206 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.61 (dt, *J* = 6.9 and 1.5 Hz, 2H), 3.97 (s, 3H), 5.19–5.24 (m, 1H), 5.37–5.44 (m, 1H), 5.94–6.07 (m, 1H), 7.47–7.53 (m, 1H), 7.70 (ddd, *J* = 8.7, 7.2 and 1.5 Hz, 1H), 7.87–7.90 (m, 1H), 8.43 (ddd, *J* = 8.1, 1.5 and 0.6 Hz, 1H), 11.46 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.79, 52.12, 109.24, 119.11, 124.21, 124.59, 126.66, 127.33, 132.94, 133.17, 135.52, 142.20, 163.91, 167.23; ESIMS *m*/*z* 244 (M^++1). Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.18; H, 5.63; N, 5.45.*Compound* **9a**: 52%; pale yellow oil; IR (film) 3436, 3317, 1669, 1612, 1526, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.67–2.85 (m, 2H), 3.60 (s, 3H), 5.09–5.22 (m, 3H, two vinyls and one NH), 5.66–5.80 (m, 1H), 7.27–7.30 (m, 1H), 7.35 (td, *J* = 7.5 and 1.5 Hz, 1H), 7.53 (td, *J* = 7.5 and 1.5 Hz, 1H), 7.64–7.67 (m, 1H), 8.85 (br s, 1H, one NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.99, 50.88, 94.62, 115.97, 118.42, 120.00, 127.04, 132.19 (2C), 132.46, 133.15, 141.80, 159.83, 168.94; ESIMS *m*/*z* 243 (M^++1). Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.69; H, 5.98; N, 11.28.*Compound* **11**: 28%; pale yellow oil; IR (film) 3206, 1752, 1674, 1435, 1247 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.57–2.82 (m, 4H), 3.71 (s, 3H), 4.59 (s, 1H), 5.01–5.19 (m, 4H), 5.35–5.49 (m, 1H), 5.70–5.84 (m, 1H), 6.81 (br s, 1H), 7.26–7.30 (m, 1H), 7.33–7.45 (m, 2H), 7.52–7.55 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 42.16, 47.50, 53.44, 61.82, 73.55, 120.31, 120.40, 124.98, 127.17, 128.17, 129.05, 131.31, 131.85, 132.22, 135.68, 168.34, 171.31; ESIMS *m*/*z* 286 (M^++1). Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.77; H, 6.88; N, 4.67.

8. Starting material **3d** (R^1 = R^3 = H, Ar = Ph) was prepared from 2-methylbenzophenone by successive bromination (NBS, AIBN, CCl_4, reflux, 2 h, 80%) and displacement reaction with cyanide (KCN, DMF, rt, 1 h, 61%).
9. Compound **3g** was prepared from *o*-toluic acid via three steps: (i) H_2SO_4 (cat)/EtOH (reflux, 7 h, 96%), (ii) NBS/AIBN (cat)/CCl_4 (reflux, 4 h, 81%), and (iii) KCN/H_2O/EtOH (reflux, 4 h, 74%). Compound **3h** was prepared from homophthalic acid via three steps: (i) H_2SO_4 (cat)/MeOH (reflux, 7 h, 94%), (ii) NBS/AIBN (cat)/CCl_4 (reflux, 4 h, 79%), and (iii) KCN/DMF (rt, 1 h, 69%). Compounds **3i** and **3k** were prepared from 2-fluorobenzonitrile via a S_NAr reaction with methyl cyanoacetate and dimethyl malonate under the influence of Cs_2CO_3/DMSO (100–110 °C, 5 h) in 61% and 63%, respectively. Compound **3j** was purchased from commercial source.
10. The compound **11** must be formed via a double Barbier type allylation as in our previous Letter,[4a] however, the reactivity of **3k** was sluggish than other examples in this Letter. Interestingly, we observed the formation of allyl ester **12** in low yield (19%) together. For the similar In-catalyzed transesterification, see: Ranu, B. C.; Dutta, P.; Sarkar, A. *J. Org. Chem.* **1998**, *63*, 6027–6028.