Indium-Catalyzed Friedel–Crafts Alkylation of Monosubstituted Benzenes by 1-Bromoadamantane

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Abstract: Indium salts such as $InCl_3$ and $InBr_3$ (ca. 1–5 mol%) efficiently catalyzed the Friedel–Crafts reaction of 1-bromoadamantane with benzene and monosubstituted benzenes to give 1-adamantyl benzenes. Indium bromide enabled faster reactions than indium chloride but the latter was more suitable in the case of halobenzenes.

Key words: adamantanes, alkylation, catalysis, indium, Lewis acids

Although the first steps in Friedel–Crafts (FC) chemistry were taken more than a century ago,[1] the topic still receives much attention and is a frequently studied area for catalytic C–C bond formation.[2] In recent years, due to the high demand for environmentally benign ('green') processes, the use of conventional, effective but harmful and corrosive catalysts and promoters ($AlCl_3$, BF_3, H_2SO_4, etc.) is being discouraged for large-scale industrial applications. Furthermore, although great strides have been made in catalytic FC reactions, there remain several challenges, such as utilizing electron-deficient arenes and avoiding side-reactions such as polyalkylation and isomerization. In recent years, indium(III) salts have emerged as excellent catalysts with a Lewis acid character for many reactions.[3] They have received a great deal of interest due to their relatively low toxicity, stability in air and water, and recyclability. However, reports of their use for FC reactions are scant, being limited to reaction of allylic[4] and benzylic[5] halides as well as to some acylation reactions[5b,6] and in fluorine chemistry.[7] An interesting variant was the $InCl_3$-catalyzed reductive FC reaction using ketones and chlorodimethylsilane both as a hydride source and as a cocatalyst.[8]

Whereas the FC reaction with short-chain alkyl halides has been well studied, this is not the case for adamantylation of aromatics, in spite of the potential importance of such chemistry. The adamantyl group increases lipophilicity and has therefore been incorporated into biologically active molecules.[9] Due to its steric bulk, it has also been incorporated into some catalysts[10,11] including asymmetric compounds.[12] The adamantane framework has also been used as a scaffold.[13]

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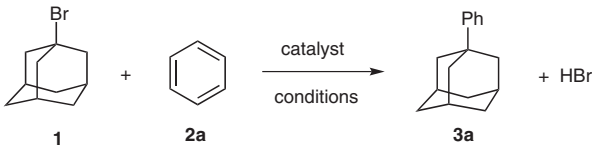
The reaction of 1-bromoadamantane with benzene and toluene has been reported with a few catalysts. Initially, catalysis by $AlCl_3$ was investigated by Newman,[14] but mixtures of mono, di, and triphenyladamantanes were formed, suggesting that the reaction conditions were rather harsh. Subsequently, $FeCl_3$ in large excess at ca. 100 °C was reported for the successful monoadamantylation of monosubstituted benzenes with formation of only the *para* isomer.[15,16] Subsequently, a more systematic study of the reaction was described by Olah et al. using boron tris(triflate) as a very efficient, although unselective, catalyst.[17] Olah, Török et al. subsequently showed that substituted benzenes could be adamantylated with high regioselectivity for the *para* isomer by using various supported acid catalysts at 111 °C.[18] The reaction was further studied using weaker acids, which appeared to favor kinetic control with a high selectivity for formation of the *para* isomer, whereas strong acids initiated a secondary isomerization reaction resulting in a thermodynamic mixture of *meta* and *para* isomers.[19] In the course of our program on the design of new asymmetric catalysts, we were interested in introducing adamantyl substituents in aromatic systems.

We first investigated the reaction of 1-bromoadamantane with benzene in the presence of group III_A and III_B metallic salts with Lewis acid character (Table 1).

Yttrium chloride and ytterbium triflate proved to be ineffective at 50 °C (Table 1, entries 1 and 2). This result may appear surprising because of the good Lewis character of YCl_3 and $Yb(OTf)_3$, but it may be explained by the insolubility of these salts in the reaction medium. As indium salts are known to be mild Lewis acids, which efficiently catalyze miscellaneous reactions,[3] we tested them for this reaction. We were pleased to find that both indium chloride and bromide efficiently catalyzed the formation of 1-phenyladamantane (**3a**) at room temperature. $InBr_3$ was found to give faster reactions and by using 0.05 equiv catalyst, $InCl_3$ and $InBr_3$ both afforded excellent yields of **3a** in respectively 40 and 2.5 hours (entries 5 and 6). Using more $InCl_3$ was not beneficial because *p*-di(1-adamantyl)benzene (**3j**) was formed as a by-product (entry 4) except when the reaction temperature was lowered (entry 3). $InBr_3$ could even be used in a very low amount (less than 0.01 equiv, entry 7) albeit at the expense of yield and increased reaction time as well as formation of **3j**.[20] The use of indium triflate gave a very slow reaction at room temperature due to insufficient solubility. At 55 °C, a 65%

Table 1 Influence of the Catalyst on the Adamantylation of Benzene

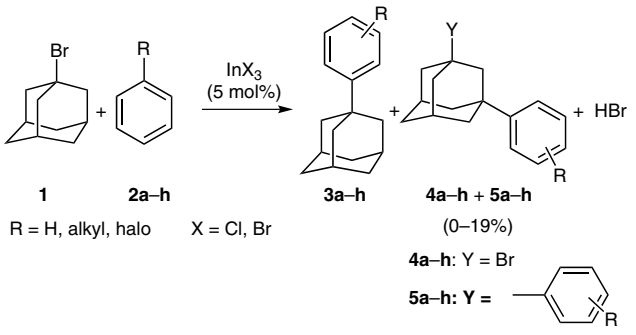


Entry	Catalyst	Equiv	Temp (°C)	Time (h)	Yield (%)[a]
1	YCl_3	0.106	50	47	nr
2	$Yb(OTf)_3$	0.08	50	31	nr
3	$InCl_3$	0.15	8	15	95
4	$InCl_3$	0.08	25	40	75[b]
5	$InCl_3$	0.05	25	40	94
6	$InBr_3$	0.05	23	2.5	93
7	$InBr_3$	0.0083	35	166	57[c]
8	$In(OTf)_3$	0.02	55	7	65[d]
9	$In(OMs)_3$	0.08	50	22	nr
10	$In(OTs)_3$	0.10	20	24	nr
11	$In(OTs)_3$	0.10	50	20	76[e]

[a] nr: no reaction.
[b] *p*-Di(1-adamantyl)benzene (**3j**; 7%) was also formed.
[c] Unreacted **1** (3%) remained and **3j** (9%) was also formed.
[d] Compound **3j** (3%), 1,3-diphenyladamantane (4%) and adamantane (3%) were also formed; almost no reaction was observed at r.t.
[e] 1,3-Diphenyladamantane (9%) was also formed.

yield was obtained (entry 8). Indium mesylate[21] did not catalyze any reaction at 50 °C, probably also due to its insolubility in the reaction medium (entry 9). On the other hand, indium tosylate[21] catalyzed the reaction at 50 °C (entry 11) but not at room temperature (entry 10).

A study of the reaction of 1-bromoadamantane (**1**) with a range of monosubstituted benzenes **2b**–**h** under $InCl_3$-catalysis was then initiated (Scheme 1, X = Cl; Table 2).[22]



Scheme 1 $InCl_3$- and $InBr_3$-catalyzed adamantylation of benzene(s)

The catalyst loading was reduced to 5 mol%, an amount that proved to be sufficient for all studied substrates. The aromatic component was used as both substrate and solvent for the reaction and was therefore used in large excess. As expected, substitution of the benzene nucleus with an alkyl group enhanced the reactivity for the formation of **3b**–**d** but this effect diminished when the size of the alkyl group increased (from methyl to isopropyl; Table 2, entries 2–4). The reaction was highly selective since the *para* isomer was mainly formed with only 5–7% *meta* isomer.

Not surprisingly, halogenated benzenes were found to be less reactive (Table 2, entries 5–7). The yield was still reasonable for fluorobenzene (65%) but dropped to 33% for chlorobenzene and bromobenzene. For these less reactive substrates, more polar inseparable 1-bromo-3-aryladamantane **4f**–**h** and 1,3-diaryladamantane **5f**–**h** were also formed in minor amounts (11–18%). However, the reaction was found to be completely *para*-selective because no trace of the *meta* isomer was detected for **3f**–**h**, **4f**–**h** or **5f**–**h**.

Table 2 $InCl_3$-Catalyzed Adamantylation of Benzene(s)[a]

Entry	R	Temp (°C)	Time (h)	Products: isolated yield (%)[b]	*para*/*meta* for **3**
1	H	25	40	**3a**: 94	–
2	Me	30	15	**3b**: 90; **4**,**5b**: nd	93:7
3	Et	30	96	**3c**: 92; **4**,**5c**: nd	94:6
4	*i*-Pr	30	43	**3d**: 53; **4**,**5d**: nd	95:5
5	F	45	64	**3f**: 65; **4f**+**5f**: 12	100:0
6	Cl[c]	30	30	**3g**: 33; **4g**+**5g**: 19	100:0
7	Br[d]	35	24	**3h**: 33; **4h**+**5h**: 12	100:0

[a] Reaction conditions: $InCl_3$ (ca. 5 mol%) and 2.5 mL aromatic/mmol of **1** were used except when otherwise stated.
[b] nd: not detected.
[c] Chlorobenzene (4 equiv) was used.
[d] $InCl_3$ (4.5 mol%) and bromobenzene (6.5 equiv) were used.

As in the case of benzene, it was initially observed that $InBr_3$ was a more efficient catalyst than $InCl_3$; the reaction of **1** with monosubstituted benzenes **2b**–**h** was also studied in the presence of 5 mol% $InBr_3$ (Scheme 1, X = Br; Table 3). Monoalkylated benzenes reacted fairly well and gave good yields of **3b**–**e** (77–91%). However, increasing the size of the alkyl group decreased the reactivity. Whereas the *para*-selectivity was good for toluene, ethylbenzene and cumene (92–94%, entries 2–5), it dropped sharply to 65% (entry 6) with isobutylbenzene. In the case of halogenated benzenes, $InBr_3$ proved to be a less suitable catalyst than $InCl_3$ (entries 7–9). Fluorobenzene (entry 7) afforded a good yield of **3f** (75%) but the product contained a small amount of the *meta*-isomer (1.5%), and **5f** (17%) was also formed. Chlorobenzene (entry 8) afforded a complex mixture, and bromobenzene (entry 9) afforded the expected product **3h** but in a low yield (14%), accompanied by 10% of the *meta* isomer as well as **4h** and inseparable impurities.

Table 3 $InBr_3$-Catalyzed Adamantylation of Benzene(s)[a]

Entry	R	Temp (°C)	Time (h)	Products: isolated yield (%)[b]	*para*/*meta* for **3**
1	H	23	2.5	**3a**: 93; **5a**: trace	–
2	Me	30	17	**3b**: 91; **4**,**5b**: nd	92:8
3	Et	30	22	**3c**: 77; **4**,**5c**: nd	94:6
4	*i*-Pr	30	17	**3d**: 60; **4**,**5d**: nd	92:8
5	*i*-Pr	30	41	**3d**: 77; **4**,**5d**: nd	94:6
6	*i*-Bu	45	17	**3e**: 77; **5e**: 15	65:35
7	F	45	27	**3f**: 75; **5f**: 17	98.5:1.5
8	Cl	30	23	**3g**: –[c]	–
9	Br	20	40	**3h**: 14; **4h**: 8	90:10

[a] Reaction conditions: $InCl_3$ (ca. 5 mol%) and 2 or 2.5 mL aromatic/mmol of **1** were used except 5 equiv for isobutylbenzene and 3 equiv for bromobenzene.
[b] nd: not detected
[c] A complex mixture was obtained.

Although, in the foregoing work, the aromatic substrate was used in large excess, as in all previously described studies of the adamantylation of aromatics, that is not convenient when the aromatic substrate is expensive or difficult to separate from product(s), or a solid. Therefore, we focused on using a limited amount of aromatic substrate with an additional solvent. Among several solvents tried, dichloromethane proved to be the best choice.[23] For four type-**2** aromatics,[24] a satisfactory yield of monoadamantylated compound **3** was obtained (Table 4).[25] For the three less reactive substrates, a minor amount of a more polar mixture of **4** and **5** was also formed. The *para* isomer of **3** was formed as the major product (in the case of ethylbenzene and isobutylbenzene, respectively, 12 and 5% *meta* isomer) or the exclusive product when R was bulky (in the case of *tert*-butylbenzene and 1-phenyladamantane).

Table 4 $InBr_3$-Catalyzed Adamantylation of Aromatics **2** by **1** in CH_2Cl_2[a]

R in **2**	Equiv of **2**	$InBr_3$ (equiv)	Temp (°C)	Time (h)	Products: isolated yield (%)	*para*/*meta* for **3**
Et	3	0.049	20	96	**3c**: 65; **4c**+**5c**: 9	88:12
i-Bu	1.55	0.049	25	64	**3e**:61; **4e**+**5e**: 6	95:5
t-Bu	1.74	0.038	25	121	**3i**: 68; **4i**+**5i**: 6	100:0
1-Ad[b]	0.833	0.05	16	16	**3j**: 84	100:0

[a] 1 mL CH_2Cl_2/mmol of **1**.
[b] 1-Ad: 1-adamantyl; 0.67 mL CH_2Cl_2/mmol **1** was used.

In summary, $InCl_3$ and $InBr_3$ efficiently catalyze FC-type alkylation of benzenes by 1-bromoadamantane under mild conditions. $InBr_3$ was found to be more efficient for alkylbenzenes, while $InCl_3$ was better suited for halobenzenes. $In(OTf)_3$ also showed some efficiency. Dichloromethane was an excellent solvent that enabled the reaction to be performed with a limited amount of aromatic substrate, selectively for the *para* isomer.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(20) Using more $InBr_3$ than 0.05 equiv favored the formation of a small amount of the more polar 1,3-diphenyladamantane.

(21) Indium mesylate and tosylate were prepared by dissolving metallic indium powder in aqueous methanesulfonic acid (3.2 equiv) or *p*-toluenesulfonic acid (3.0 equiv) at 70 °C (respectively 0.3 and 0.8 mL H_2O/mmol In was used) for respectively 2 and 20 h, followed by removal of water under vacuum at 70 °C. Remarkably, in contrast to indium mesylate and halides, indium tosylate did not exhibit appreciable hygroscopicity, a fact that made it far more convenient to handle.

(22) **Representative Procedure**: $InBr_3$ (7.1 mg, 0.02 mmol) was introduced in an oven- or flame-dried 10 mL round-bottomed flask followed by an olive-shaped magnetic stirring bar. The apparatus was dried by heating for 1–2 min with a heat gun under vacuum. 1-Bromoadamantane (**1**; 86 mg, 0.4 mmol) and the monosubstituted benzene **2a**–**h** (or benzene itself, 1 mL) were added. The flask was flushed under nitrogen and well stoppered.[26] The reaction was left under gentle stirring in a water or oil bath at the specified temperature (see Tables) with protection against light by aluminum foil. After reaction for the specified time (see Tables), abundant evolution of hydrogen bromide (white smoke, caution!) occurred on opening. The reaction mixture was taken up with pentane and washed with water until neutral. After drying (Na_2SO_4) and concentration, chromatography on silica gel (ca. 3 g), eluting with pentane, afforded monoadamantylated benzene **3a**–**h** followed in some cases by more polar 1-bromo-3-aryladamantane (**4**) and 1,3-diaryladamantane (**5**).

1-Phenyladamantane (3a): Mp 82 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (dm, *J* ~ 8 Hz, 2 H), 7.31 (ddm, *J* = 8.2, 6.8 Hz, 2 H), 7.17 (ddt, *J* = 7.6, 6.7, 1.4 Hz, 1 H), 2.12–2.07 (m, 3 H), 1.92 (d, *J* = 2.8 Hz, 6 H), 1.83–1.72 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.34 ($1C_q$), 128.10 (2CH), 125.50 (1CH), 124.84 (2CH), 43.23 ($3CH_2$), 36.88 ($3CH_2$), 36.22 ($1C_q$), 29.04 (3CH).

1-(4-Methylphenyl)adamantane (3b): Mp 97–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (half of an A_2X_2 system, 2 H), 7.13 (half of an A_2X_2 system coupled with CH_3, $J_{\text{with Me}}$ = 0.7 Hz, 2 H), 2.32 (t, *J* = 0.7 Hz, 3 H, C*H*$_3$), 2.12–2.05 (m, 3 H), 1.90 (broad d, *J* = 2.8 Hz, 6 H), 1.82–1.71 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.48 ($1C_q$), 134.90 ($1C_q$), 128.81 (2CH), 124.72 (2CH), 43.30 ($3CH_2$), 36.87 ($3CH_2$), 35.85 ($1C_q$), 29.03 (3CH), 20.87 ($1CH_3$).

1-(4-Ethylphenyl)adamantane (3c): Mp 58 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (half of an A_2X_2 system, 2 H), 7.15 (half of an A_2X_2 system coupled with CH_2, $J_{\text{with CH2}}$ = 0.6 Hz, 2 H), 2.62 (q, *J* = 7.6 Hz, 2 H, C*H*$_2$CH$_3$), 2.12–2.05 (m, 3 H), 1.91 (broad d, *J* = 2.8 Hz, 6 H), 1.82–1.71 (m, 6 H), 1.23 (t, *J* = 7.6 Hz, 3 H, CH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.68 ($1C_q$), 141.23 ($1C_q$), 127.55 (2CH), 124.75 (2CH), 43.29 ($3CH_2$), 36.87 ($3CH_2$), 35.88 ($1C_q$), 29.03 (3CH), 28.29 ($1CH_2$), 15.45 ($1CH_3$).

1-(4-Isopropylphenyl)adamantane (3d): Mp 87 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (half of an A_2X_2 system, 2 H), 7.18 (half of an A_2X_2 system coupled with CH, $J_{\text{with CH}}$ = 0.6 Hz, 2 H), 2.88 [qq, *J* = 6.9, 6.9 Hz, 1 H, C*H*$(CH_3)_2$], 2.12–2.05 (m, 3 H), 1.91 (broad d, *J* = 2.8 Hz, 6 H), 1.82–1.70 (m, 6 H), 1.24 [d, *J* = 6.9 Hz, 6 H, CH$(CH_3)_2$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.74 ($1C_q$), 145.81 ($1C_q$), 126.09 (2CH), 124.69 (2CH), 43.29 ($3CH_2$), 36.88 ($3CH_2$), 35.87 ($1C_q$), 33.55 (1CH), 29.03 (3CH), 24.02 ($2CH_3$).

1-(4-Isobutylphenyl)adamantane (3e): Mp 34.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (half of an A_2X_2 system, 2 H), 7.08 (half of an A_2X_2 system coupled with CH_2, $J_{\text{with CH2}}$ = 0.6 Hz, 2 H), 2.44 (d, *J* = 7.2 Hz, 2 H, CH_2 of *i*-Bu), 2.12–2.05 (m, 3 H), 1.91 (broad d, *J* = 2.8 Hz, 6 H), 1.85 [tqq, *J* = 7.2, 6.6, 6.6 Hz, 1 H, C*H*$(CH_3)_2$], 1.82–1.70 (m, 6 H), 0.90 (d, *J* = 6.6 Hz, 6 H, CH$(CH_3)_2$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.67 ($1C_q$), 138.70 ($1C_q$), 128.80 (2CH), 124.49 (2CH), 45.00 (CH_2), 43.30 ($3CH_2$), 36.89 ($3CH_2$), 35.88 ($1C_q$), 30.19 (1CH), 29.04 (3CH), 22.48 ($2CH_3$). Anal.

Calcd for $C_{20}H_{28}$ (268.44): C, 89.49; H, 10.51. Found: C, 89.57; H, 10.46.

1-(4-*tert*-Butylphenyl)adamantane (3i): Mp 127.5 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.34 (half of an A_2X_2 system, 2 H), 7.29 (half of an A_2X_2 system, 2 H), 2.12–2.05 (m, 3 H), 1.91 (d, *J* = 2.8 Hz, 6 H), 1.83–1.70 (m, 6 H), 1.31 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.30 ($1C_q$), 148.06 ($1C_q$), 124.92 (2CH), 124.42 (2CH), 43.22 ($3CH_2$), 36.85 ($3CH_2$), 35.76 ($1C_q$), 34.25 ($1C_q$), 31.40 ($3CH_3$), 28.99 (3CH).

1,4-Di-1-adamantylbenzene (3j)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (s, 4 H), 2.12–2.05 (m, 6 H), 1.91 (d, *J* = 2.8 Hz, 12 H), 1.82–1.71 (m, 12 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.35 ($2C_q$), 124.45 (4CH), 43.21 ($6CH_2$), 36.86 ($6CH_2$), 35.79 ($2C_q$), 28.99 (6CH).

For data of other compounds, see the Supporting Information.

(23) For instance, no reaction was observed with **1** and isobutylbenzene at 40 °C in CCl_4. In 1,2-dichloroethane and 1-chlorobutane at 35–40 °C, the reactions of **1** with isobutylbenzene and *tert*-butylbenzene afforded complex mixtures.

(24) Halobenzenes were not studied in CH_2Cl_2 as solvent because of their reduced reactivity and also due to the fact that $InBr_3$ was not a good catalyst in their case.

(25) The same procedure as previously described was used, except that a reduced amount of aromatic substrate was used (see Table 3) and dichloromethane was added (its amount was adjusted by weight after flushing with nitrogen and stoppering).

(26) Based on two experiments that were performed with toluene and ethylbenzene with HBr vented through a bubbler, no change was observed in reaction rate or selectivity (same *para*/*meta* ratios). Yields of 99% were obtained compared with 90 and 92% ($InCl_3$ as a catalyst).

