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Regioselective Synthesis of 1,3,5-Substituted Benzenes via the $InCl_3$/2-Iodophenol-Catalyzed Cyclotrimerization of Alkynes

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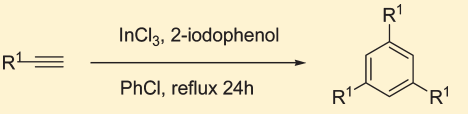
Supporting Information

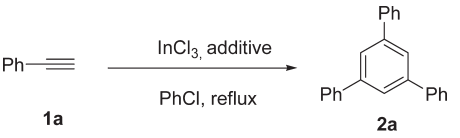
ABSTRACT: A novel indium(III)-catalyzed cyclotrimerization of alkynes in the presence of 2-iodophenol gave 1,3,5-substituted benzenes in excellent yields with complete regioselectivity. The reaction condition is tolerant to air, and atom economical, in accordance with the concept of modern green chemistry. This method provides a rapid and efficient access to 1,3,5-substituted benzenes.



The importance of the chemistry of the carbon−carbon triple bond has been well recognized since this functional group has shown to be one of the main building blocks of organic and material chemistry.[1] The transition-metal-catalyzed cyclotrimerization of alkynes continues attract considerable attention by virtue of its intrinsic atom economy and convergent nature, as well as the importance of substituted benzenes as synthetic intermediates.[2] Since it was first discovered by Reppe and coworkers,[3] complexes of many transition metals involving palladium, ruthenium, cobalt, nickel, rhodium, or other transition metals have been developed as effective catalysts or precursors for the transformation.[4] However, a mixture of 1,3,5- and 1,2,4-trisubstituted benzenes is obtained in general. This drawback limits the application of transition-metal-based methods. Therefore, a cheaper, more general and efficient catalyst with a high regioselectivity has been in great demand. Herein, we describe the highly regioselective synthesis of 1,3,5-trisubstituted benzenes via the $InCl_3$-catalyzed[5] trimerization of alkynes.[6]

Initially, phenylacetylene (**1a**) (0.9 mmol) was treated with 2-iodophenol (0.3 mmol) in the presence of 10 mol % of $InCl_3$ in chlorobenzene at reflux for 24 h, and the desired 1,3,5-triphenyl benzene (**2a**) was isolated in 91% yield (Table 1, entry 1).[7] In an attempt to better understand the structure−activity relationship of an additive, we decided to screen the indium(III)-catalyzed cyclotrimerization using a variety of phenol, thiophenol, aniline, and nitrobenzene derivatives.[8] As a result, we found that the use of different monohydroxyl- and/or monoiodo-based additives in combination with $InCl_3$ afforded the cyclotrimerization product 1,3,5-triphenylbenzene (Table 1, entries 1−8). When additives with no hydroxyl or iodo substituents were used, such as 2-aminobenzenethiol and 1,2-diaminobenzene, the reaction failed to afford the desired products (Table 1, entries 10 and 11). Surprisingly, 1,2-benzenediol did not work as an additive in this cyclotrimerization (Table 1, entry 9). Control experiments confirmed that in the absence of either 2-iodophenol or $InCl_3$ the reaction led to recovery of starting materials,[9] which illustrated the necessity of both phenol and iodo derivatives and indium(III) catalyst in this transformation.

Table 1. Screening of Additives for the Synthesis of 1,3,5-Substituted Benzene[a]



1a **2a**

entry	additive	yield[b] (%)
1	2-iodophenol	91
2	phenol	10
3	2-chlorophenol	8
4	2-aminophenol	30
5	4-*tert*-butylphenol	65
6	4-nitrophenol	5
7	2-iodobenzenamine	50
8	1-iodo-3-nitrobenzene	8
9	1,2-benzenediol	0
10	2-aminobenzenethiol	0
11	1,2-diaminobenzene	0

[a] Reaction conditions: all reactions were carried out in sealed tubes using **1a** (0.9 mmol), additive (0.3 mmol), and $InCl_3$ (10 mol %) in PhCl (2 mL) at reflux 24 h. [b] Isolated yield of pure product based on phenylacetylene **1a**.

As 2-iodophenol proved to be the most effective additive, further experiments were focused on its use with other metal cations. A variety of Lewis acid catalysts and solvents were screened using phenylacetylene (**1a**, 0.9 mmol, Table 2) as a model substrate. First, $Fe(OTf)_3$ exhibited activity similar to that of $InCl_3$, affording the cyclized product **2a** in 85% yield (Table 2, entry 2), while $FeCl_3$ (anhydrous) failed to afford the desired product (Table 2, entry 3). Zn(II) catalysts afforded the

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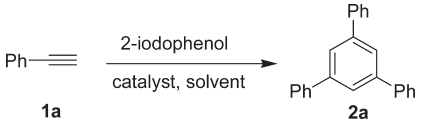
Table 2. Optimization of Formation of Substituted Benzene[a]



entry	catalyst	solvent	yield[b] (%)
1	$InCl_3$	PhCl	91
2	$Fe(OTf)_3$	PhCl	85
3	$FeCl_3$	PhCl	0
4	$ZnCl_2$	PhCl	10
5	$Zn(OTf)_2$	PhCl	15
6	$Cu(OTf)_2$	PhCl	70
7	$Bi(OTf)_3$	PhCl	60
8	AgOTf	PhCl	50
9	$Sc(OTf)_3$	PhCl	10
10	CuCl	PhCl	0
11	$BiCl_3$	PhCl	0
12	$InCl_3$	$PhCH_3$	40
13	$InCl_3$	CH_3NO_2	10
14	$InCl_3$	DCE	5
15	$InCl_3$	THF	0
16	$InCl_3$	CH_3COCH_3	0
17	$InCl_3$	CH_3CN	0
18	$InCl_3$	DCM	0

[a] Reaction conditions: all reactions were carried out in sealed tubes using **1a** (0.9 mmol), 2-iodophenol (0.3 mmol), and catalyst (10 mol %) in solvent (2 mL) at reflux 24 h. [b] Isolated yield of pure product based on phenylacetylene **1a**.

cycloadduct **2a** in 10−15% yields (Table 2, entries 4 and 5). The trimerization of alkyne **1a** using $Cu(OTf)_2$, $Bi(OTf)_3$, AgOTf, and $Sc(OTf)_3$ produced **2a** in 70%, 60%, 50%, and 10% yields, respectively (Table 2, entries 6−9). CuCl- and $BiCl_3$-catalyzed trimerization of **1a** failed (Table 2, entries 10 and 11). $InCl_3$ was found to be the most effective catalyst to promote the cyclotrimerization efficiently. In addition, it was found that the solvent played a crucial role in this reaction (Table 2, entries 1 and 12−18). The $InCl_3$/2-iodophenol-catalyzed cyclotrimerization of **1a** was performed using several solvents at refluxing temperature. Chlorobenzene was found to be the most suitable solvent to afford the product **2a** in 91% yield (Table 2, entry 1). When the reaction was carried out in toluene, the yield of product **2a** dramatically decreased to 40% (Table 2, entry 12). The reaction in nitromethane or 1,2-dichloroethane yielded only 10 and 5% of **2a**, respectively (Table 2, entries 13 and 14). In other solvents, such as THF, CH_3COCH_3, CH_3CN, and DCM, starting material **1a** was recovered (Table 2, entries 15−18). The above investigations revealed that the $InCl_3$/2-iodophenol/chlorobenzene system is the best combination for promoting the cyclotrimerization of alkyne **1a**.

With these optimal conditions in hand, we examined the scope of this cyclotrimerization reaction. The alkyl- and aryl-substituted alkynes gave the corresponding symmetrical product **2** in complete regioselectivities (Table 3).[10] Initially, we carried out the cyclotrimerization of 1-phenyl-2-trimethylsilylacetylene under prolonged reaction time (72 h); however, the product **2a** obtained was only in 15% yield instead of tris(trimetylsilyl)-triphenylbenzene (**2ab**) (Table 3, entry 1). 2-Butyne reacted smoothly affording the desired product **2b** in 88% yield (Table 3, entry 2). However, diphenylethyne did not form the benzene derivative **2c** under the same conditions (Table 3, entry 3). The terminal aryl alkyne **1d** possessing an electron-donating group at the aryl ring (R_1 = 4-$MeOC_6H_4$) reacted smoothly and afforded the desired product **2d** in 96% yield (Table 3, entry 4). Substrates **1e** and **1f** possessing electron-withdrawing groups (R_1 = 4-FC_6H_4, 4-BrC_6H_4) at the aryl ring were also successfully employed in the cyclotrimerization and gave the benzene derivatives **2e** and **2f** in 41% and 60% yields, respectively (Table 3, entries 5 and 6). Remarkably, electron-rich terminal alkynes provided the desired products in higher yields than electron-poor terminal alkynes did. Moreover, the cyclotrimerizations of alkynes **1g**−**j** (R_1 = 4-MeC_6H_4, 4-EtC_6H_4, 4-$^nPrC_6H_4$, and 3-MeC_6H_4) also proceeded smoothly to afford benzene derivative **2g**−**j** in excellent yields with complete regioselectivity (Table 3, entries 7−10). However, the cyclotrimerizations **1k** did not form the desired benzene derivative **2k** (Table 3, entry 11), presumably due to the steric effect of the substituent in the *ortho*-position of **1k**.[11] Additionally, alkynes bearing a heterocyclic aromatic substituent such as 2-ethynylthiophene **1l** were found to afford the desired product **2l** in 60% yield (Table 3, entry 12). The terminal alkyl alkynes **1m** and **1n** in the presence of $InCl_3$/2-iodophenol also underwent a smooth cyclotrimerization to give the products **2m** and **2n** in 90% and 95% yields, respectively (Table 3, entries 13 and 14). However, 3,3-dimethyl-1-butyne and cyclopropylacetylene failed to afford the desired products and led to recovery of starting materials (Table 3, entries 16 and 17). In addition, the reaction of 5-chloropentyne under the same conditions resulted in the formation of a complex mixture of unidentified compounds (Table 3, entry 15). These results indicated the limitations of the $InCl_3$/2-iodophenol catalytic system.

We proposed a possible mechanism of the indium(III) chloride catalyzed cyclotrimerization of alkynes, shown in Scheme 1. Our hypothesis is that the *cis*-addition of alkynes and $InCl_3$ may form *cis*-chloroindium intermediate **3**, followed by consecutive *cis*-addition of alkynes, and the chloroindiumation intermediate may give the new chloroindiumation intermediate **5** which then undergoes cyclization to generate intermediate **6**.[12] Upon the assistance of 2-iodophenol, the reaction affords benzene derivatives and regenerates the active $InCl_3$ quickly (Scheme 1).[13] When R^1 = alkyl, *p*-BrPh, *p*-MeOPh, or *p*-MePh, R^2 = H, and R^1 = alkyl, R^2 = alkyl, there is less steric hindrance in **5** during the ring-closure process, and the products of the cyclotrimerization are symmetrical benzene derivatives. When R^1 = Ph, R^2 = Ph, and R^1 = alkyl (*tert*-Butyl and cyclopropyl) or *o*-MeOPh, R^2 = H, **5** is more sterically hindered, and no desired product was obtained.

In summary, we have developed a novel cyclotrimerization of alkynes catalyzed by $InCl_3$ in conjunction with 2-iodophenol to give a variety of 1,3,5-trisubstituted benzenes in excellent yields with complete regioselectivity. This operationally simple method gives a rapid access to the 1,3,5-trisubstituted benzenes. Air-tolerant and atom-economical characteristics of the method accord with the concept of modern green chemistry and will be appealing for industries.

EXPERIMENTAL SECTION

A general experimental procedure for the reaction of alkynes (**1**) catalyzed by $InCl_3$/2-iodophenol is described below: The reaction

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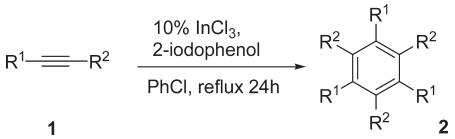
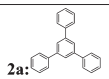
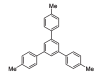
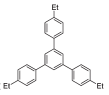
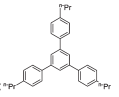
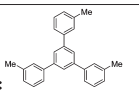
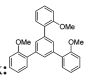
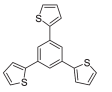
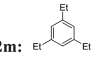
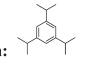
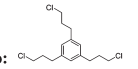
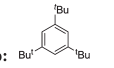
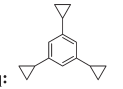
Table 3. Synthesis of Substituted Benzenes 2 Catalyzed by $InCl_3$/2-Iodophenol[a]



1 2

Entry	Alkyne	Product	Yield (%)[b]
1[c]	**1ab:** R^1 = Ph; R^2 = TMS	**2a:** 	15
2	**1b:** R^1 = Me; R^2 = Me	**2b:** 	88
3	**1c:** R^1 = Ph; R^2 = Ph	**2c:** 	0
4	**1d:** R^1 = 4-$MeOC_6H_4$; R^2 = H	**2d:** 	96
5	**1e:** R^1 = 4-FC_6H_4; R^2 = H	**2e:** 	41
6	**1f:** R^1 = 4-BrC_6H_4; R^2 = H	**2f:** 	60
7	**1g:** R^1 = 4- MeC_6H_4; R^2 = H	**2g:** 	88
8	**1h:** R^1 = 4-EtC_6H_4; R^2 = H	**2h:** 	84
9	**1i:** R^1 = 4-^{n}PrC_6H_4; R^2 = H	**2i:** 	90
10	**1j:** R^1 = 3-MeC_6H_4; R^2 = H	**2j:** 	85
11	**1k:** R^1 = 2-$OMeC_6H_4$; R^2 = H	**2k:** 	0
12	**1l:** R^1 = Thienyl; R^2 = H	**2l:** 	60
13	**1m:** R^1 = Et; R^2 = H	**2m:** 	90
14	**1n:** R^1 = *i*-pr; R^2 = H	**2n:** 	95
15	**1o**: R^1 = 3-Cl-propyl; R^2 = H	**2o:** 	0
16	**1p**: R^1 = *t*-Bu; R^2 = H	**2p:** 	0
17	**1q**: R^1 = Cyclopropyl; R^2 = H	**2q:** 	0

[a] Reaction conditions: all reactions were carried out in sealed tubes using **1a** (0.9 mmol), 2-iodophenol (0.3 mmol), and $InCl_3$ (10 mol %) in chlorobenzene (2 mL) at reflux 24 h. [b] Yield of the isolated product after flash chromatography. [c] Reaction time is 72 h.

mixture of alkyne **1** (0.9 mmol), 2-iodophenol (0.3 mmol), chlorobenzene (2.0 mL), and indium trichloride (0.09 mmol) in a 10 mL sealed tube was stirred at reflux and monitored periodically by TLC. Upon completion, chlorobenzene was removed under reduced pressure using an aspirator, and then the residue was purified by flash chromatography (hexane/ethyl acetate) on silica gel to afford the 1,3,5-trisubstituted benzenes.

1,3,5-Triphenylbenzene (2a). This product was purified via flash column chromatography with hexane, yielding 91% as a white solid: mp 172−174 °C (lit.[14] mp 170−172 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.42 (m, 3H), 7.49−7.51 (m, 6H), 7.72−7.73 (m, 6H), 7.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 125.2, 127.4, 127.5, 128.8, 141.2, 142.4; MS [M + H^+] 307.

Hexamethylbenzene (2b). This product was purified via flash column chromatography with hexane, yielding 88% as a white solid: mp 162−164 °C (lit.[15] mp 162−163 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.0, 16.8; MS [M + H^+] 163.

1,3,5-Tris(4-methoxyphenyl)benzene (2d). Purified via flash column chromatography with 10% ethyl acetate/hexane, yielding 96% as a white solid: mp 142−143 °C (lit.[16] mp 140−142 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88 (s, 9H), 7.02 (d, J = 8.6 Hz, 6H), 7.63 (d, J = 8.6 Hz, 6H), 7.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.4, 114.3,123.8, 128.3, 133.9, 141.8, 159.3; MS: [M + H^+] 397.

1,3,5-Tris(4-fluorophenyl)benzene (2e). Purified via flash column chromatography with hexane, yielding 41% as a yellow solid: mp 238−239 °C (lit.[14] mp 238−240 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (s, 3H), 7.63−7.65 (m, 6H), 7.15−7.19 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 141.6, 137.1, 128.9, 124.9, 115.8; MS [M + H^+] 361.

1,3,5-Tris(4-bromophenyl)benzene (2f). Purified via flash column chromatography with hexane, yielding 60% as a yellow solid: mp 261−263 °C (lit.[14] mp 260−261 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J = 8.4 Hz, 6H), 7.61 (d, J = 8.4 Hz, 6H), 7.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 120.3, 124.9, 129.1, 132.3, 133.8, 141.7; MS [M + H^+] 544.

1,3,5-Tris(4-methylphenyl)benzene (2g). Purified via flash column chromatography with 1% ethyl acetate/hexane, yielding 88% as a pale yellow solid: mp 175−176 °C (lit.[15] mp 177−178 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.42 (s, 9H), 7.29 (d, J = 7.8 Hz, 6H), 7.60

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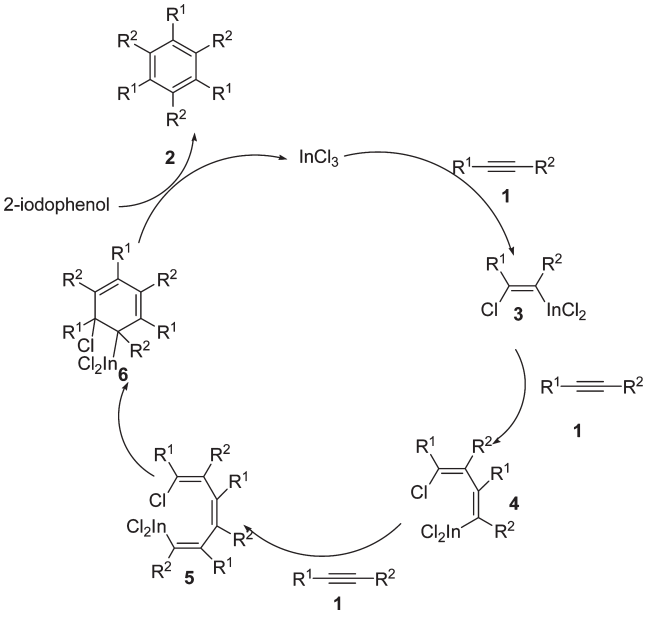
Scheme 1. Proposed Mechanism



(d, J = 8.0 Hz, 6H), 7.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1. 124.6, 127.2, 129.5, 137.3, 138.4, 142.2; MS: [M + H$^+$] 349.

1,3,5-Tris(4-ethylphenyl)benzene (2h). Purified via flash column chromatography with 1% ethyl acetate/hexane, yielding 84% as a pale yellow solid: mp 111−113 °C (lit.[17] mp 112−114 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (t, J = 7.6 Hz, 9H), 2.74 (q, J = 7.6 Hz, 6H), 7.33 (d, J = 7.8 Hz, 6H), 7.63 (d, J = 7.9 Hz, 6H), 7.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.6, 28.5, 124.6, 127.3, 128.3, 138.7, 142.2, 143.6; MS [M + H$^+$] 391.

1,3,5-Tris(4-propylphenyl)benzene (2i). Purified via flash column chromatography with 1% ethyl acetate/hexane, yielding 90% as a pale yellow solid: mp 142−143 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (t, J = 7.3 Hz, 9H), 1.76−1.66 (m, 6H), 2.69−2.64 (m, 6H), 7.30 (d, J = 8.0 Hz, 6H), 7.63 (d, J = 8.1 Hz, 6H), 7.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9, 24.6, 37.7, 124.6, 127.2, 128.9, 138.6, 142.0, 142.1; MS [M + H$^+$] 433. Anal. Calcd for $C_{33}H_{36}$: C, 91.61; H, 8.39. Found: C,91.84; H, 8.24.

1,3,5-Tris(3-methylphenyl)benzene (2j). Purified via flash column chromatography with 1% ethyl acetate/hexane, yielding 85% as a white solid: mp 117−118 °C (lit.[18] mp 116.8−118.1 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.46 (s, 9H), 7.22 (d, J = 7.5 Hz, 3H), 7.38 (t, J = 7.6 Hz, 3H), 7.51 (d, J = 7.6 Hz, 6H), 7.76 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 21.5, 124.5, 125.1, 128.2, 128.3, 128.7, 138.4, 141.3, 142.4; MS [M + H$^+$] 349.

1,3,5-Tris(2-thienyl)benzene (2l). Purified via flash column chromatography with hexane, yielding 60% as a pale yellow solid: mp 157−158 °C (lit.[19] mp 156−158 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (dd, J = 5.0, 3.6 Hz, 3H), 7.32−7.36 (m, 3H), 7.42 (dd, J = 3.5, 1.0 Hz, 3H), 7.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 122.8, 123.9, 125.4, 128.1, 135.7, 143.6; MS [M + H$^+$] 325.

1,3,5-Triethylbenzene (2m). Purified via flash column chromatography with hexane, yielding 90% as yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (t, J = 7.6 Hz, 9H), 2.71 (q, J = 7.6 Hz, 6H), 6.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.6, 28.9, 124.8, 144.2; MS [M + H$^+$] 163. Anal. Calcd for $C_{12}H_{18}$: C, 88.82; H, 11.18. Found: C, 88.59; H, 11.41.

1,3,5-Triisopropylbenzene (2n). Purified via flash column chromatography with hexane, yielding 95% as pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (d, J = 7.0 Hz, 18H), 2.96−3.00 (m, 3H), 7.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.1, 34.3, 122.1, 148.7; MS [M + H$^+$] 205. Anal. Calcd for $C_{153}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.32; H, 11.58.

■ ASSOCIATED CONTENT

Supporting Information. Spectra data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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