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$B(C_6F_5)_3$-Catalyzed Hydroarylation of Terminal Alkynes with Phenols

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Abstract: We developed a $B(C_6F_5)_3$ catalyzed hydroarylation of terminal alkynes with various phenols at room temperature without adding any additives, leading to the synthesis of 2-*gem*-vinylphenols with good regio-selectivity. Those transformations featured a broad substrate scope with moderate yields. Mechanism studies indicated that those transformations proceeded through the activation of phenol by $B(C_6F_5)_3$ with subsequent protonation of alkyne/Friedel-Crafts-type reaction.

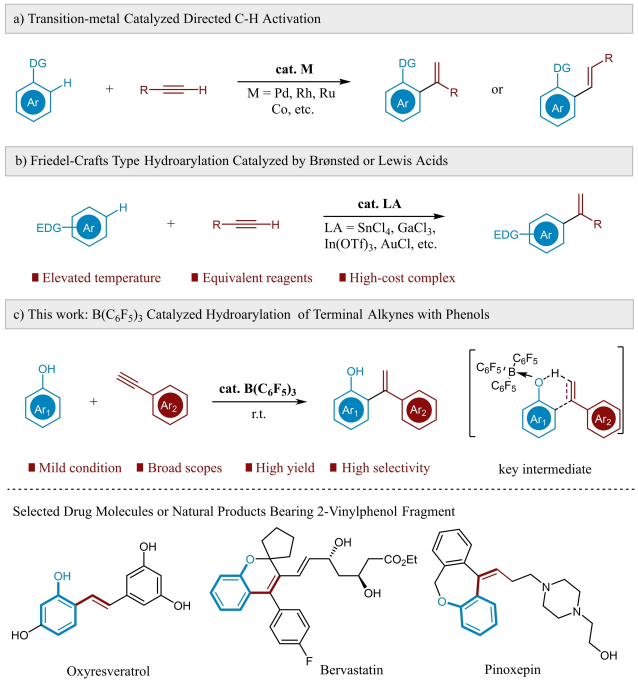
Keywords: $B(C_6F_5)_3$; 2-*gem*-vinylphenols; alkynes; phenols

The C–H hydroarylation of alkynes was a straightforward and atom-economical method for the synthesis of substituted styrenes,[1a–b] which were valuable building blocks and common structural motifs in natural products, pharmaceuticals, materials science.[2] In most transition-metal catalyzed C–H hydroarylation of alkynes, symmetrical internal alkynes or electronically biased alkynes were utilized as substrates to avoid the problematic regioselectivity issue or obtain the sole regioselectivity due to the biased electronic property of alkyne.[1c–k] Generally, terminal alkynes were less compatible with C–H activation conditions, therefore, the direct hydroarylation of terminal alkynes was underdeveloped.[3] Recently, some elegant works were reported to achieve the controllable 1,2-insertion[3a–c] and 2,1-insertion[3c–g] of terminal alkynes based on the radius of metal catalyst (Scheme 1a). The second route was Friedel-Crafts type hydroarylation of alkyne with electron-rich aromatic compounds *via* the electrophilic activation of alkynes by Brønsted or Lewis acids (Scheme 1b).[3h–j] For the direct hydroarylation of terminal alkynes with phenols, the seminal work was reported by Yamaguchi and colleagues using stoichiometric amount of $SnCl_4$–NBu_3 adduct.[4] Later, homogeneous Lewis acid such as $SnCl_4$, $GaCl_3$, $In(OTf)_3$, gold catalyst and some heterogeneous catalysts were found to be active catalyst for those transformations.[5] Though a series of 2-vinyl phenol derivatives were obtained in good yields through those methods, it still exhibited several disadvantages including using strong inorganic acid, or expensive gold catalyst, high reaction temperature, poor regioselectivity and narrow substrate scopes.

2-Vinylphenol moiety was an important synthetic intermediate and widely existed in bioactive compounds, such as oxyresveratrol, bervastatin, pinoxepin (Scheme 1c).[6] Therefore, the development of efficient and robust methods to construct 2-vinylphenol under mild conditions from commercially available phenols and alkynes were highly desirable.

In recent years, electron-deficient boron-based catalyst systems, especially for $B(C_6F_5)_3$ catalyst, had exhibited great potential for direct C–H bond transformations.[7–8] Zhang and co-workers reported a $B(C_6F_5)_3$ catalyzed chemoselective and *ortho*-selective alkylation of phenol derivatives with α-aryl diazoesters.[8a] In 2019, Li group achieved the $B(C_6F_5)_3$ catalyzed *ortho*-selective hydroarylation of 1,3-dienes with various phenols.[8b] Interesting, Bentley and Caputo reported the $B(C_6F_5)_3$-catalyzed hydroarylation of alkenes and phenols with *para*-selectivity.[8c] Inspired by those works, we developed a $B(C_6F_5)_3$-catalyzed hydroarylation of terminal alkyne with phenols to selectively give 2-*gem*-vinylphenols under mild conditions (Scheme 1c).

We started our investigations using 4-methoxyphenol **1a** and phenylacetylene **2a** as substrates. After extensive condition screening, we defined the optimal conditions as the use of $B(C_6F_5)_3$ (5 mol%) as



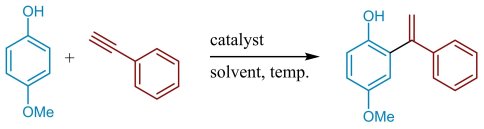
Scheme 1. Direct C–H hydroarylation of terminal alkyne.

catalyst, chlorobenzene as solvent at 25 °C for 36 h, which could afford the *ortho*-selective product **3 a** in 94% yield (Table 1, entry 1). An array of other solvents was less effective, especially high polarity solvent such as DMSO, DMF or CH_3CN giving no desired product even at elevated 90 °C (Table 1, entry 2–4). Slightly increasing or decreasing temperature lead to a similar outcome. However, further increasing the temperature to 60 °C resulted in the yield decreased to 71% (Table 1, entries 5–7). When the reaction was performed under air or with a lower catalyst loading, the yield respectively dropped to 63% or 75% (Table 1, entries 8–9). Other Lewis or Brønsted acid catalysts, such as $Sn(OTf)_2$, $In(OTf)_3$, BF_3-Et_2O, BCl_3 or PTSA failed to afford the desired product (Table 1, entries 10–14).

With the optimized conditions in hand, we investigated the scope of phenylacetylene derivatives (Scheme 2). A variety of *para*-substituted phenylacetylenes were suitable substrates for those transformations (Scheme 2, **3 a–3 i**). It was worth mentioning that methoxy, fluoride, chloride, bromide were tolerated, (Scheme 2, **3 e–3 h**) which could be further transferred into other functional groups *via*

transition-metal catalyzed cross-coupling reactions.[9] When 1,4-diethynylbenzene was utilized as substrates, the *mono*-hydroarylation product was afforded in 46% yield (Scheme 2, **3 i**). Those transformations appeared insensitively to the steric hindrance of the phenylacetylene derivatives. *ortho*-,

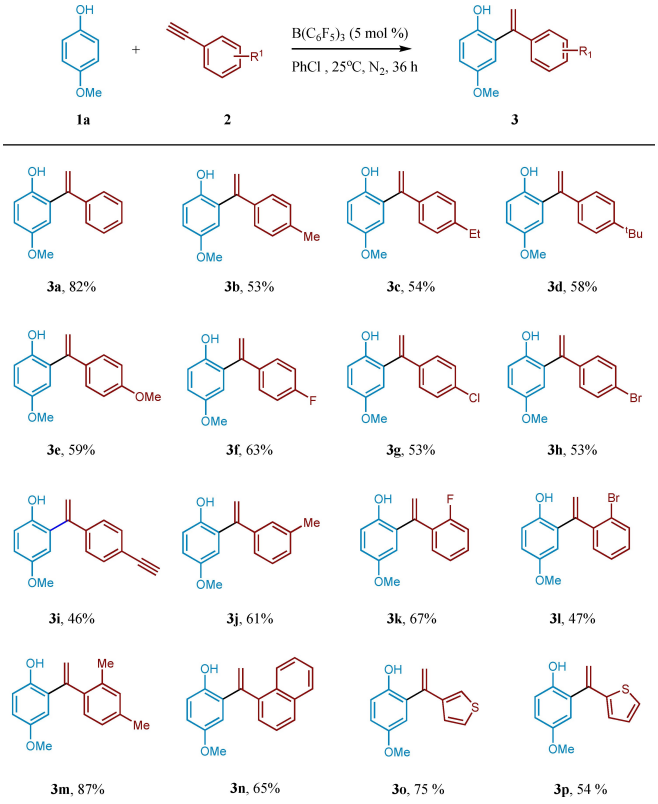
Table 1. Optimization of reaction conditions.[a]



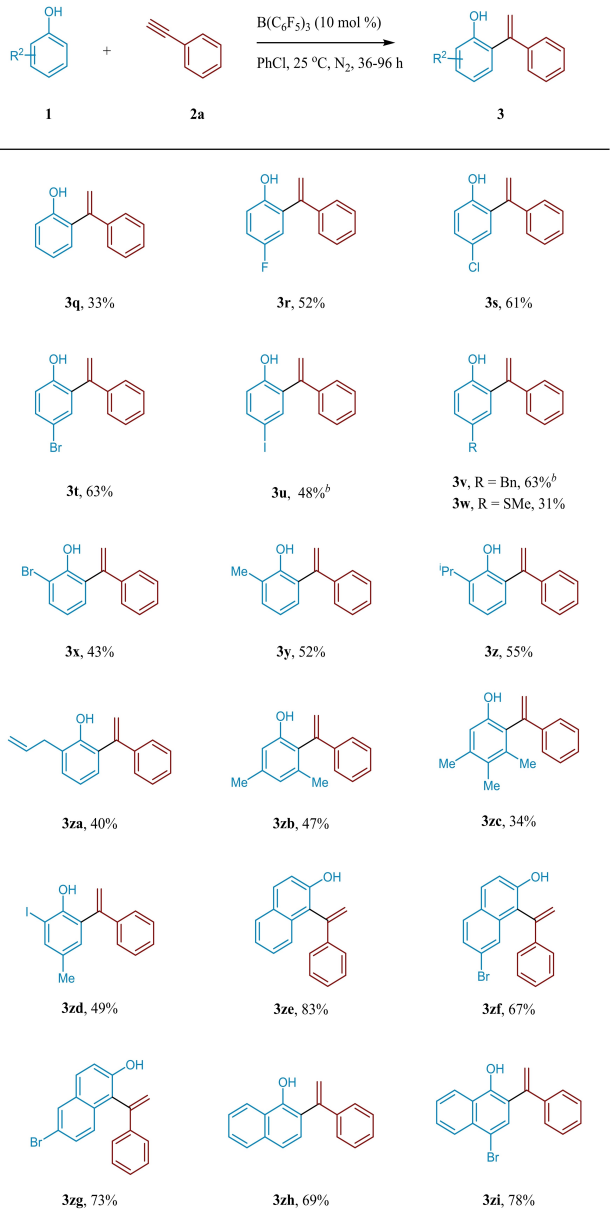
1a **2a** **3a**

Entry	Catalyst	Solvent	Temp (°C)	Yield(%)[b]
1	$B(C_6F_5)_3$	PhCl	25	94(82)[c]
2	$B(C_6F_5)_3$	toluene	25	16
3	$B(C_6F_5)_3$	DCM	25	88
4	$B(C_6F_5)_3$	DMSO, DMF or MeCN	25 or 90	n.d.
5	$B(C_6F_5)_3$	PhCl	0	89
6	$B(C_6F_5)_3$	PhCl	40	92
7	$B(C_6F_5)_3$	PhCl	60	71
8[d]	$B(C_6F_5)_3$	PhCl	25	63
9[e]	$B(C_6F_5)_3$	PhCl	25	75
10	$Sn(OTf)_2$	PhCl	25	n.d.
11	$In(OTf)_3$	PhCl	25	n.d.
12	BF_3-Et_2O	PhCl	25	n.d.
13	BCl_3	PhCl	25	n.d.
14	PTSA	PhCl	25	n.d.

[a] Reaction conditions: **1 a** (0.1 mmol), **2 a** (0.2 mmol), catalyst (5 mol%), solvent (1 mL), under N_2 for 36 h.
[b] Yields were determined by GC using dodecane as internal standard.
[c] Isolated yield in the parentheses.
[d] under air.
[e] 2 mol% catalyst was used.



Scheme 2. Substrate scope of phenylacetylenes. reaction conditions: **1a** (0.5 mmol), **2** (1.0 mmol), $B(C_6F_5)_3$ (5 mol%), dry PhCl (5 mL), under N_2, 25 °C for 36 h. Isolated yield.

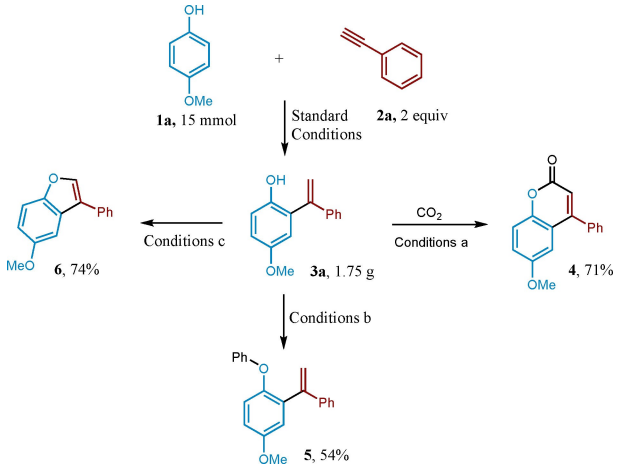


Scheme 3. Substrate scope of phenols.

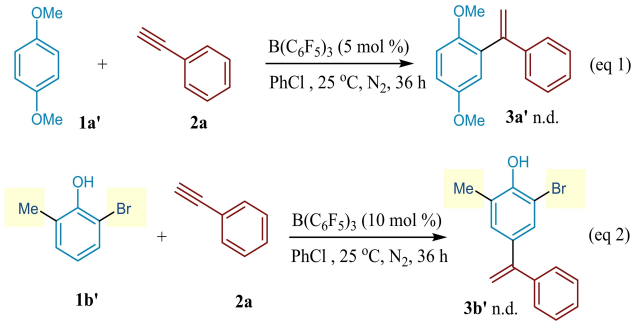
meta-, and multi-substituted phenylacetylenes were converted into the desired products in moderate yields (Scheme 2, **3j–3m**). The naphthalene and thiophene derivatives were compatible during those transformations (Scheme 2, **3n–3p**). The aliphatic substituted terminal alkynes and internal alkynes were nonreactive under the standard conditions. Subsequently, we continued to evaluate the substrate scope with regard to the phenols. For less electron-rich phenol substrates, 10 mol% $B(C_6F_5)_3$ and longer reaction time was needed to assurance a good yield (see supporting information for details). Simple phenol was *ortho*-alkenylated in 33% yield (Scheme 3, **3q**). Halide (Scheme 3, **3r–3u**), benzyl (Scheme 3, **3v**), thioether (Scheme 3, **3w**), allyl group (Scheme 3, **3za**) were well compatible in those transformations. It was glad to obtain the selective *ortho*-substituted products and no *para*-substituted by-products were detectable (Scheme 3, **3x--3za**). Multi-substituted phenols, 1-naphthol, 2-naphtholderivatives were all transferred into desired products in good yields (Scheme 3, **3zb–3zi**).

The robustness and potential applications of the $B(C_6F_5)_3$-catalyzed hydroarylation of phenols with terminal alkynes was demonstrated by the gram-scale reaction and several follow-up transformations (Scheme 4). 2-*gem*-Vinylphenol **3a** was obtained with 1.75 g in a 15 mmol scale reaction without further optimization. The synthetic utilities of 2-*gem*-vinylphenol moiety were demonstrated by one-step conversions of **3a** into versatile functional molecules such as coumarin derivative in 71% yield,[10] diaryl ether in 54% yield,[11] benzofuran in 74% yield.[12]

Finally, several control experiments were conducted to explore the mechanism (Scheme 5 eq 1–2). The hydroarylation did not occur at all when 1,4-dimethoxybenzene **1a'** was utilized to displace 4-methoxyphenol as the substrate. It clearly supported the critical role of hydroxyl group of phenol in those transformations.[8b] Subsequently, when 2,6-disubsti-



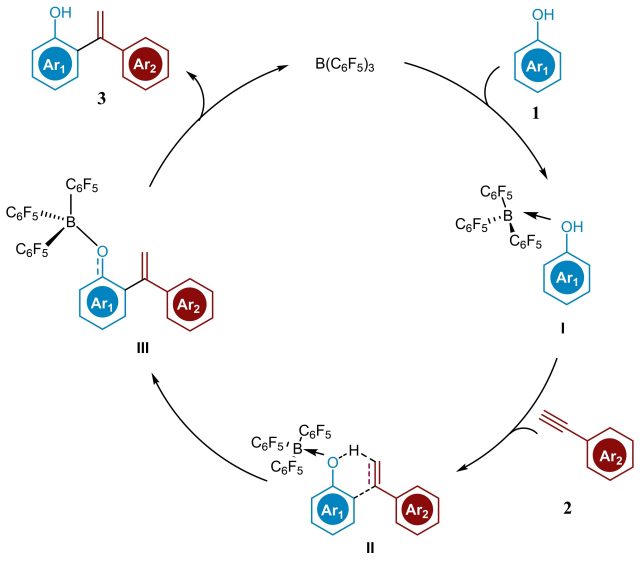
Scheme 4. Applications of $B(C_6F_5)_3$ catalyzed hydroarylation. Conditions a: **3 a** (0.5 mmol), $Pd(OAc)_2$ (7.5 mol%), Cs_2CO_3 (1.5 mmol), diglyme (5.0 ml), 100 °C for 18 h, under CO_2. Conditions b: **3 a** (0.5 mmol), KO^{t}Bu (1.1 equiv.), Ph_2IOTf (1.2 equiv.), THF (2.0 ml), 25 °C for 24 h, under N_2. Conditions c: **3 a** (0.4 mmol), $Ni(acac)_2$ (5 mol%), PPh_3 (10 mol%), TEMPO (10 mol%), DMA (1 mL), 140 °C for 36 h, under 1 atm of O_2.



Scheme 5. Control experiments.

tuted phenol **1b'** was applied as substrate, no *para*-hydroarylation product was formed, which further supported the high ortho-selectivity of those transformations. The hydroxyl peak of **1 a** shifted from 4.83 ppm to 5.81 ppm after adding equivalent amount of $B(C_6F_5)_3$ to the system (see supporting information for details). $B(C_6F_5)_3$ acted as Lewis acid to activate the hydroxyl group and increased the acidity of phenol,[8b] which was beneficial to the protonation of terminal alkyne and followed by the *ortho* Friedel-Crafts-type addition of phenol.

On the basis of previous work[7–8] and our control experiment results, we tentatively proposed a plausible mechanism (Scheme 6). Coordination of the phenol to $B(C_6F_5)_3$ generated the Lewis adduct **I**. Then proton transferred from the phenolic O–H group to the alkyne formed an ion-pair intermediate **II**, which were followed by the electrophilic attack of the carbocation



Scheme 6. Plausible mechanism.

to the phenol anion to afford the dearomatized intermediate **III**. Rearomatization of **III** followed by the dissociation of $B(C_6F_5)_3$ provided the desired product and regenerated the catalyst.

In summary, we presented a $B(C_6F_5)_3$-catalyzed intermolecular hydroarylation of terminal alkynes with phenols to construct 2- vinylphenols. Those transformations exhibited mild reaction conditions, high yields, and a broad substrate scope. Moreover, this protocol offered practical access to diverse *ortho*-alkenyl phenols, which were versatile building blocks for subsequent chemical transformations.

Experimental Section

In a nitrogen glovebox, the mixture of 4-methoxyphenol **1 a** (0.5 mmol, 62 mg), $B(C_6F_5)_3$ (5 mol%, 12.5 mg) and ethynylbenzene **2 a** (1 mmol, 102 mg) were dissolved in 5 mL anhydrous chlorobenzene in a 20-mL Schlenk tube with a magnetic stir bar. The Schlenk tube was taken out of the glovebox and the reaction mixture was stirred at 25°C for 36 h to complete the reaction (monitoring the reaction by TLC). Then, 5 mL of brine was added to the reaction mixture and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layer was dried over Na_2SO_4 and then concentrated in vacuo to afford the crude product. This crude material was purified by chromatography to afford the desired product **3 a**.

For further details (NMR spectra, optimization and substrate isolation) please see the supporting information.

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References

[1] a) T. Kitamura, *Eur. J. Org. Chem.* **2009**, 1111–1125; b) V. P. Boyarskiy, D. S. Ryabukhin, N. A. Bokach, A. V. Vasilyev, *Chem. Rev.* **2016**, *116*, 5894–5986; c) C. Jia, D. Piao, J. Oyamada, W. Lu, T. Kitamura, Y. Fujiwara, *Science* **2000**, *287*, 1992–1995; d) C. Jia, W. Lu, J. Oyamada, T. Kitamura, K. Matsuda, M. Irie, Y. Fujiwara, *J. Am. Chem. Soc.* **2000**, *122*, 7252–7263; e) B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **1996**, *118*, 6305–6306; f) D. J. Schipper, M. Hutchinson, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 6910–6911; g) K. Gao, P. S. Lee, T. Fujita, N. Yoshikai, *J. Am. Chem. Soc.* **2010**, *132*, 12249–12251; h) Y. Nakao, K. S. Kanyiva, T. A. Hiyama, *J. Am. Chem. Soc.* **2008**, *130*, 2448–2449; i) M. Simonetti, I. Larrosa, *Nat. Chem.* **2016**, *8*, 1086–1088; j) D. G. Johnson, J. M. Lynam, N. S. Mistry, J. M. Slattery, R. J. Thatcher, R. J. Thatcher, A. C. Whitwood, *J. Am. Chem. Soc.* **2013**, *135*, 2222–2234; k) M. T. Reetz, K. Sommer, *Eur. J. Org. Chem.* **2003**, 3485–3496.

[2] a) T. Adak, J. Schulmeister, C. D. Martin, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Eur. J. Org. Chem.* **2019**, 3867–3876; b) S. Kumar, H. Y. Lee, J. P. Liou, *J. Nat. Prod.* **2017**, *80*, 1294–1301; c) E. Díez-Barra, J. C. García-Martínez, R. D. Rey, J. Rodríguez-López, F. Giacalone, L. José, J. L. Segura, N. Martín, *J. Org. Chem.* **2003**, *68*, 3178–3183.

[3] a) R. Gao, C. S. Yi, *J. Org. Chem.* **2010**, *75*, 3144–3146; b) X. K. Zhou, Y. X. Luo, L. H. Kong, Y. W. Xu, G. F. Zheng, Y. Lan, X. W. Li, *ACS Catal.* **2017**, *7*, 7296–7304; c) X. K. Zhou, Y. P. Pan, X. W. Li, *Angew. Chem. Int. Ed.* **2017**, *56*, 8163–8167; *Angew. Chem.* **2017**, *129*, 8275–8279; d) B. Sun, T. Yoshino, M. Kanai, S. Matsunaga, *Angew. Chem. Int. Ed.* **2015**, *54*, 12968–12972; *Angew. Chem.* **2015**, *127*, 13160–13164; e) B. W. Zhou, H. Chen, C. Y. Wang, *J. Am. Chem. Soc.* **2013**, *135*, 1264–1267; f) Z. X. Zhang, H. Jiang, Y. Huang, *Org. Lett.* **2014**, *16*, 5976–5979; g) J. L. Jia, J. J. Shi, J. Zhou, X. L. Liu, Y. L. Song, H. E. Xu, W. Yi, *Chem. Commun.* **2015**, *51*, 2925–2928; h) M. T. Reetz, K. Sommer, *Eur. J. Org. Chem.* **2003**, 3485–3496; i) A. Kumar, Z. Li, S. K. Sharma, V. S. Parmar, E. V. Van der Eycken, *Chem. Commun.* **2013**, *49*, 6803–6805; j) D. Eom, S. Park, Y. Park, K. Lee, G. Hong, P. H. Lee, *Eur. J. Org. Chem.* **2013**, 2672–2682.

[4] a) M. Yamaguchi, A. Hayashi, M. Hirama, *J. Am. Chem. Soc.* **1995**, *117*, 1151–1152; b) M. Yamaguchi, M. Arisawa, Y. Kidoa, M. Hirama, *Chem. Commun.* **1997**, 1663–1664; c) M. Yamaguchi, M. Arisawa, K. Omata, K. Kabuto, M. Hirama, T. Uchimaru, *J. Org. Chem.* **1998**, *63*, 7298–7305; d) K. Kobayashi, M. Yamaguchi, *Org. Lett.* **2001**, *3*, 241–242.

[5] a) J. S. Yadav, B. V. S. Reddy, S. Sengupta, S. K. Biswas, *Synthesis* **2009**, *8*, 1301–1304; b) V. K. Rao, G. M. Shelke, R. Tiwari, K. Parang, A. Kumar, *Org. Lett.* **2013**, *15*, 2190–2193; c) C. Sreenivasulu, A. G. K. Reddy, G. Satyanarayana, *Org. Chem. Front.* **2017**, *4*, 972–977; d) M. Murai, M. Yamamoto, K. Takai, *Org. Lett.* **2019**, *21*, 3441–3445; e) T. Li, Y. H. Yang, B. M. Luo, B. Li, L. Y. Zong, W. G. Kong, H. Yang, X. P. Cheng, L. M. Zhang, *Org. Lett.* **2020**, *22*, 6045–6049; f) T. Adak, J. Schulmeister, M. C. Dietl, M. Rudolph, F. Romiger, A. S. K. Hashmi, *Eur. J. Org. Chem.* **2019**, 3867–3876; g) S. Haldar, S. Koner, *Beilstein J. Org. Chem.* **2013**, *9*, 49–55.

[6] a) K. M. Gligorich, M. J. Schultz, M. S. Sigman, *J. Am. Chem. Soc.* **2006**, *128*, 2794–2795; b) K. Sasano, J. Takaya, N. Iwasawa, *J. Am. Chem. Soc.* **2013**, *135*, 10954–10957; c) A. Seoane, N. Casanova, N. Quinones, J. Mascareñas, M. Gulías, *J. Am. Chem. Soc.* **2014**, *136*, 834–837; d) A. Seoane, N. Casanova, N. Quinones, J. L. Mascareñas, M. Gulías, *J. Am. Chem. Soc.* **2014**, *136*, 7607–7610; e) N. Casanova, A. Seoane, J. L. Mascareças, M. Gulías, *Angew. Chem. Int. Ed.* **2015**, *54*, 2374–2377; *Angew. Chem.* **2015**, *127*, 2404–2407; f) N. Casanova, K. P. Del Rio, R. García-Fandiño, J. L. Mascareñas, M. Gulías, *ACS Catal.* **2016**, *6*, 3349–3353; g) P. Finkbeiner, U. Kloeckner, B. J. Nachtsheim, *Angew. Chem. Int. Ed.* **2015**, *54*, 4949–4952; *Angew. Chem.* **2015**, *127*, 5033–5036; h) Y. Wang, J. C. A. Oliveira, Z. Lin, L. Ackermann, *Angew. Chem. Int. Ed.* **2021**, *60*, 6419–6424; *Angew. Chem.* **2021**, *133*, 6490–6495.

[7] Selected reviews about $B(C_6F_5)_3$ catalyzed reactions: a) M. Oestreich, J. Hermeke, J. Mohr, *Chem. Soc. Rev.* **2015**, *44*, 2202–2220; b) D. W. Stephan, *J. Am. Chem. Soc.* **2015**, *137*, 10018–10032; c) S. Bähr, M. Oestreich, *Angew. Chem. Int. Ed.* **2017**, *56*, 52–59; *Angew. Chem.* **2017**, *129*, 52–59; d) Y. Hoshimoto, S. Ogoshi, *ACS Catal.* **2019**, *9*, 5439–5444; e) S. Y. Liu, D. W. Stephan, *Chem. Soc. Rev.* **2019**, *48*, 3434–3435; f) S. Basak, L. Winfrey, B. A. Kustiana, R. L. Melen, L. C. Morrill, A. P. Pulis, *Chem. Soc. Rev.* **2021**, *50*, 3720–3737; g) Y. Ma, S. J. Lou, Z. M. Hou, *Chem. Soc. Rev.* **2021**, *50*, 1945–1967.

[8] Selected examples about $B(C_6F_5)_3$ catalyzed C–H transformations: a) Z. Z. Yu, Y. F. Li, J. M. Shi, B. Ma, L. Liu, J. L. Zhang, *Angew. Chem. Int. Ed.* **2016**, *55*, 14807–14811; *Angew. Chem.* **2016**, *128*, 15027–15031; b) G. Q. Wang, L. Z. Gao, H. Chen, X. T. Liu, J. Cao, S. D. Chen, X. Cheng, S. H. Li, *Angew. Chem. Int. Ed.* **2019**, *58*, 1694–1699; *Angew. Chem.* **2019**, *131*, 1708–1713; c) J. N. Bentley, C. B. Caputo, *Organometallics* **2018**, *37*, 3654–3658; d) S. S. Meng, X. W. Tang, X. Luo, R. B. Wu, J. L. Zhao, A. S. C. Chan, *ACS Catal.* **2019**, *9*, 8397–8403; e) S. Basak, A. A. Montoya, L. Winfrey, R. L. Melen, L. C. Morrill, A. P. Pulis, *ACS Catal.* **2020**, *10*, 4835–4840; f) W. Li, T. Werner, *Org. Lett.* **2017**, *19*, 2568–2571; g) Q. Yin, H. F. T. Klare, M. Oestreich, *Angew. Chem. Int. Ed.* **2017**, *56*, 3712–3717; *Angew. Chem.* **2017**, *129*, 3766–3771; h) N. Gandham-

setty, S. Joung, S. W. Park, S. Park, S. Chang, *J. Am. Chem. Soc.* **2014**, *136*, 16780–16783; i) Y. X. Han, S. T. Zhang, J. H. He, Y. T. Zhang, *J. Am. Chem. Soc.* **2017**, *139*, 7399–7407; j) Y. T. Ma, B. L. Wang, L. Zhang, Z. M. Hou, *J. Am. Chem. Soc.* **2016**, *138*, 3663–3666; k) J. B. Zhang, S. Park, S. Chang, *J. Am. Chem. Soc.* **2018**, *140*, 13209–13213; l) Y. H. Ma, L. Zhang, Y. Luo, M. Nishiura, Z. M. Hou, *J. Am. Chem. Soc.* **2017**, *139*, 12434–12437.

[9] a) A. Biffis, P. Centomo, A. D. Zotto, M. Zecca, *Chem. Rev.* **2018**, *118*, 2249–2295; b) T. Stahl, H. F. T. Klare, M. Oestreich, *ACS Catal.* **2013**, *3*, 1578–1587; c) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417–1492.

[10] K. Sasano, J. Takaya, N. Iwasawa, *J. Am. Chem. Soc.* **2013**, *135*, 10954–10957.

[11] N. Jalalian, T. B. Petersen, B. Olofsson, *Chem. Eur. J.* **2012**, *18*, 14140–14149.

[12] S. Aggarwal, D. Srinivas, C. Sreenivasulu, G. Satyanarayana, *RSC Adv.* **2020**, *10*, 22264–22272.

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