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Photoinduced direct 4-pyridination of C(sp^3)–H Bonds†

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Direct substitution of hydrogen in C(sp^3)–H bonds by 4-pyridine was achieved by employing benzophenone and 4-cyanopyridine in aqueous acetonitrile under photo-irradiating conditions. This simple and mild 4-pyridination proceeds in a highly chemoselective manner especially at benzylic C(sp^3)–H bonds without affecting polar functional groups, and enables intermolecular formation of sterically hindered bonds between alkylaromatics and 4-pyridine. The present methodology thus serves as a powerful tool for construction of biologically active and functional molecules with 4-pyridine substructures.

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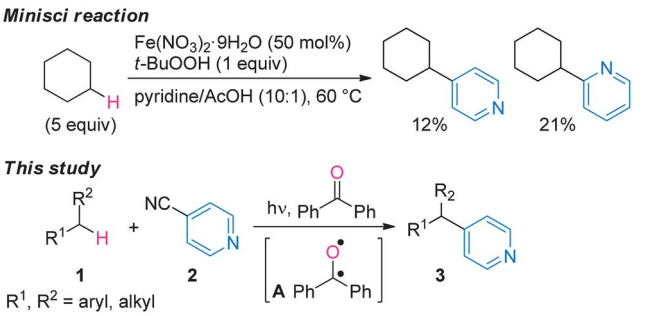
Introduction

Pyridines have a range of applications in many areas of chemistry. They are not only found in the structural cores of numerous agrochemicals, pharmaceuticals and natural products, but are also widely used as building blocks in the preparation of chiral ligands and functional materials with new photo- or electrochemical properties.[1,2] Consequently, chemists have been developing methodologies for pyridine synthesis for over a century and it is unlikely that interest in the field will decrease due to the continued importance of the pyridine substructure in both biological and chemical fields. Among the many methods to generate pyridines,[3] the substitution of hydrogen in C–H bonds by a pyridine fragment is particularly valuable, since such a transformation can eliminate extra steps for the prior activation of substrates and can greatly simplify synthetic schemes. Although a wealth of transition-metal catalyzed methods has recently been developed for this purpose,[4] little work has focused on the pyridination of unreactive C(sp^3)–H bonds of alkanes. Furthermore, the direct introduction of sterically cumbersome tertiary and quaternary carbon centers adjacent to the pyridine ring remains challenging largely due to the general difficulty in activating hindered C(sp^3)–H bonds with transition-metal catalysts.

Radical-based reactions have proven to be suitable for coupling between pyridines and alkanes as exemplified by the Minisci reaction in Scheme 1.[5,6] Nonetheless, low positional selectivity, modest yields and narrow substrate scope have diminished its applicability to architecturally complex substrates. Herein, we report a powerful photochemical protocol for direct 4-pyridination of alkylaromatics by employing benzophenone ($Ph_2C{=}O$) and 4-cyanopyridine **2** under photo-irradiation conditions (**1** → **3**).[7,8] The present metal-free reaction proceeds in a highly chemoselective manner at benzylic C(sp^3)–H bonds without affecting polar functional groups, and realizes intermolecular attachment of congested tertiary or quaternary carbon centers at C4 of pyridine *via ipso*-substitution.[9]



Scheme 1 Photochemically induced coupling reaction of 4-cyanopyridine and C(sp^3)–H Bonds.

Results and discussion

Recently, we developed photoinduced direct cyanation and alkynylation of C(sp^3)–H bonds by using photo-excited $Ph_2C{=}O$ (**A**, Scheme 1) to induce C(sp^3)–H cleavage without transition metal reagents.[10,11] Reflecting the electrophilic nature of oxyl radical **A**, the electron-rich methylene and methine C(sp^3)–H bonds were chemoselectively functionalized to construct tri- and tetra-substituted carbons, respectively.[12] In this context, we selected $Ph_2C{=}O$ as a hydrogen acceptor and cumene **1a** as an electron-rich hydrogen donor in order to establish the direct 4-pyridination reaction (Table 1). After screening pyridine derivatives,[13] it was found that 4-cyanopyridine **2** functioned as an

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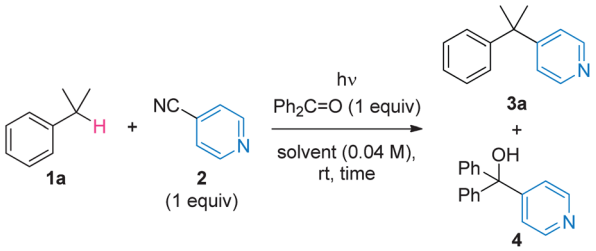
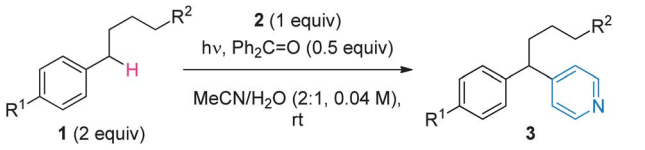
Table 1 Optimization of reaction conditions[ab]



Entry	1a, equiv.	Solvent	*t*, h	Yield 3a, %[c]	Recovery 2, %[d]
1	3	*t*-BuOH	10	69	0
2	3	Benzene	20	(2)	72
3	3	MeCN	20	(55)	22
4	3	MeCN/H_2O (2 : 1)	6	87	0
5	2	MeCN/H_2O (2 : 1)	10	91	0
6[e]	2	MeCN/H_2O (2 : 1)	12	90	0
7[f]	2	MeCN/H_2O (2 : 1)	24	(74)	16
8[g]	2	MeCN/H_2O (2 : 1)	24	(5)	84
9[e]	0	MeCN/H_2O (2 : 1)	12	0	81

[a] *Reaction conditions*: **1a**, **2**, $Ph_2C{=}O$ (1 equiv.), solvent (0.04 M), rt, photo-irradiation using a Riko 100 W medium pressure mercury lamp. [b] The formation of **4** was observed in entries 1–7 in approximately 5% yield. [c] Isolated yield. NMR yield is shown in parentheses. [d] Yield was determined by NMR analysis. [e] $Ph_2C{=}O$ (0.5 equiv.) was employed. [f] $Ph_2C{=}O$ (0.1 equiv.) was employed. [g] The reaction was carried out without $Ph_2C{=}O$.

Table 2 Transformation of butylbenzene derivatives[ab]



Entry	1	R^1	R^2	*t*, h	3	Yield[c], %
1	**1b**	H	H	12	**3b**	72
2	**1c**	OMe	H	10	**3c**	83
3	**1d**	OAc	H	10	**3d**	71
4	**1e**	NHAc	H	12	**3e**	63
5	**1f**	CO_2Me	H	16	**3f**	65
6	**1g**	Br	H	12	**3g**	68
7	**1h**	Cl	H	12	**3h**	70
8	**1i**	H	OBz	14	**3i**	79
9	**1j**	H	CO_2Me	14	**3j**	83
10	**1k**	H	Br	14	**3k**	62

[a] *Reaction conditions*: **1** : **2** : $Ph_2C{=}O$ = 2 : 1 : 0.5, MeCN/H_2O (2 : 1, 0.04 M), rt, photo-irradiation using a Riko 100 W medium pressure mercury lamp. [b] In all entries, the formation of **4** was observed in approximately 15% yield. [c] Isolated yield.

effective coupling agent to produce adduct **3a** (69% yield, entry 1) when treated with **1a** (3 equiv.) and $Ph_2C{=}O$ (1 equiv.) in *t*-BuOH under the photo-irradiation conditions. Importantly, byproduct **4** was formed only in a trace amount, indicating that coupling between **2** and $Ph_2C{=}O$ was the minor pathway.[8a] Formation of **3a** was inhibited when the *t*-BuOH solvent was replaced with benzene (entry 2), and decelerated upon use of MeCN (entry 3). On the other hand, a mixed solvent of MeCN and H_2O significantly accelerated the reaction and increased the yield of **3a** (87% yield, entry 4). Under these conditions, the amount of **1a** could be reduced from 3 equiv. to 2 equiv. without affecting the product yield (entry 5).[14] Moreover, adduct **3a** was produced in 90% and 74% yields, even when the equivalents of $Ph_2C{=}O$ were changed from 1 to 0.5 and 0.1, respectively (entries 6 and 7).[15] Only a trace amount of adduct **3a** was formed without the addition of $Ph_2C{=}O$ (entry 8), and even formation of **4** was inhibited in the absence of hydrogen donor **1a** (entry 9). These two experiments demonstrated the crucial role of both $Ph_2C{=}O$ and **1a** for promotion of the radical reactions (*vide infra*). Because high-yielding construction of **3a** with the quaternary carbon from **1a** and **2** was successfully achieved using the optimal conditions in entry 6, the scope of this transformation was next investigated in detail.

The methylene C–H bonds of the benzylic compounds **1b**–**1k**, having a variety of functional groups on the aromatic rings (R^1) or the side chains (R^2), site-selectively underwent the 4-pyridination (Table 2). The photoirradiation of **2** with butylbenzene **1b** (2 equiv.) in the presence of $Ph_2C{=}O$ (0.5 equiv.) cleanly provided the alkylated pyridine **3b** (entry 1). Further pyridination of product **3b** was not observed, presumably because the pyridine-substituted benzylic C–H bond of **3b** is more electron deficient and thus less reactive than that of **1b** toward the photoactivated $Ph_2C{=}O$ (**A**, Scheme 1). *Para*-substituted electron-donating groups, such as methoxy (**1c**), acetoxy (**1d**) and acetamide (**1e**), and the electron-withdrawing methoxy carbonyl group (**1f**) had little effect on the product yields of **3c**–**3f** (entries 2–5). The reaction worked well in the presence of bromine (**1g**) and chlorine (**1h**) on the aromatic ring, and pyridine derivatives **3g** and **3h** were obtained without the loss of halogen atoms (entries 6 and 7). The substrates with benzoyloxy (**1i**) and methoxy carbonyl (**1j**) groups on the termini of the alkyl chain underwent the transformation to provide **3i** and **3j**, respectively (entries 8 and 9). Even the weak C(sp^3)–Br bond of **1k** was preserved in this radical reaction to produce adduct **3k** (entry 10). Overall, these results demonstrated the mildness and high functional group tolerance of the C(sp^3)–H pyridination.

The broad scope of the methodology was further demonstrated using structurally varied alkylbenzenes (Table 3). In addition to methine (Table 1, entry 6) and methylene C–H bonds (Table 2, entry 1), the primary C–H bond of toluene **1l** was transformed into the pyridine derivative **3l** under the optimized conditions (Table 3, entry 1). The yields of the pyridine derivatives **3a** (90%), **3b** (72%) and **3l** (51%) correlated to the number of alkyl substituents at the reacting carbon, confirming that the hydrogen of the more electron-rich C–H bond was more efficiently abstracted by electron-deficient oxyl radical **A**.[12,16] Remarkably, a quaternary carbon center was introduced at the most hindered C–H bond on the cyclohexane ring of **1m**, leading to **3m** (entry 2). The reaction of *m*-acetoxy (**1n**) and *o*-acetoxy (**1o**) ethylbenzenes with 4-cyanopyridine provided

Table 3 Transformation of various alkylbenzenes[ab]

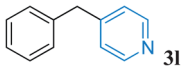
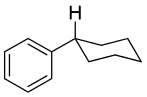
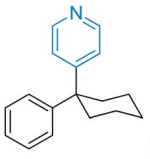
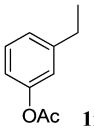
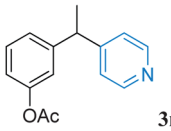
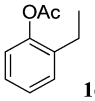
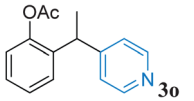
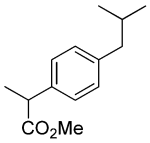
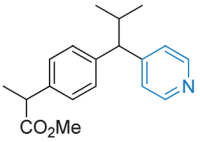
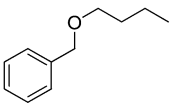
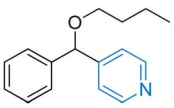
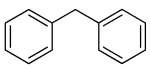
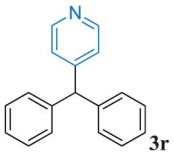
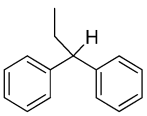
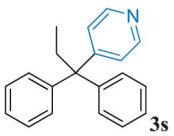
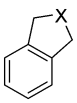
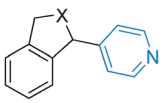
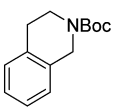
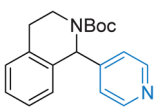
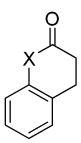
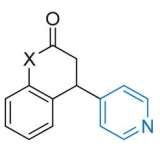
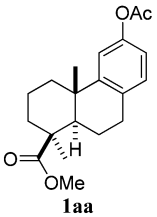
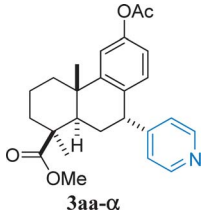
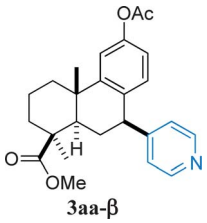
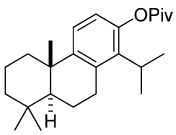
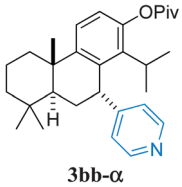
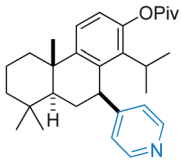
Entry	Starting material	*t*, h	Product	Yield[c], %
1[d]	 **1l**	24	 **3l**	51
2	 **1m**	18	 **3m**	50
3	 **1n**	14	 **3n**	83
4	 **1o**	24	 **3o**	68(80)
5	 **1p**	15	 **3p**	75[e]
6	 **1q**	2	 **3q**	66
7	 **1r**	12	 **3r**	87
8	 **1s**	22	 **3s**	74
9	 **1t**: X = CH_2	8	 **3t**	89
10	**1u**: X = CH_2CH_2	12	**3u**	70
11[d]	**1v**: X = O	1	**3v**	75
12	**1w**: X = NBoc	1	**3w**	77
13	 **1x**	0.5	 **3x**	82
14	 **1y**: X = O	12	 **3y**	84
15	**1z**: X = NH	24	**3z**	84(91)

Table 3 (*Contd.*)

Entry	Starting material	*t*, h	Product	Yield[c], %
16	 **1aa**	10	 **3aa-α**  **3aa-β**	71[f]
17	 **1bb**	12	 **3bb-α**  **3bb-β**	72[g]

[a] *Reaction conditions*: **1** : **2** : $Ph_2C{=}O$ = 2 : 1 : 0.5, MeCN/H_2O (2 : 1, 0.04 M), rt, photo-irradiation using a Riko 100 W medium pressure mercury lamp. [b] In all entries, the formation of **4** was observed in approximately 15% yield. [c] Isolated yield. Yield based on recovered 4-cyanopyridine **2** is shown in parentheses. [d] Starting material **1** (3 equiv.) was employed. [e] Yield was determined by NMR analysis. [f] **3aa-α** : **3aa-β** = 2 : 1. [g] **3bb-α** : **3bb-β** = 2 : 3.

alkylated pyridines **3n** and **3o**, respectively (entries 3 and 4), while the transformation of ibuprofen methyl ester **1p** selectively took place at the more electron-rich benzylic position, affording adduct **3p** (entry 5). The oxygen-substituted benzylic C–H bond of **1q** was transformed to **3q** within only 2 h (entry 6), indicating that the butyl ether functionality enhanced the reactivity of the benzylic position.[17] Diphenyl methane **1r** was smoothly converted into its pyridine derivative **3r** (entry 7),[18] and the hindered quaternary carbon of **3s** was constructed from 1,1-diphenyl propane **1s** (entry 8).[19]

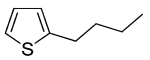
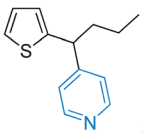
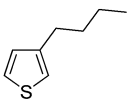
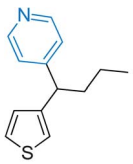
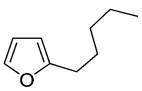
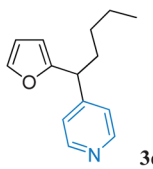
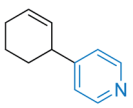
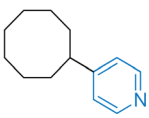
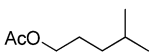
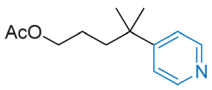
Direct couplings between 4-pyridine and multicyclic compounds were successfully achieved (entries 9–17, Table 3). High-yielding mono-pyridination of the five-membered and six-membered carbocycles **1t** and **1u** was realized to produce **3t** and **3u**, respectively (entries 9 and 10), while phthalane **1v** and *N*-Boc isoindoline **1w** were converted to the corresponding products **3v** and **3w**, respectively (entries 11 and 12). Shorter reaction times for **3v** and **3w** than those for **3t** and **3u** again confirmed that

oxygen and nitrogen atoms increased the reactivity of the proximal C–H bonds. By taking advantage of this feature, the nitrogen-substituted benzylic C–H bond of **1x** was chemoselectively functionalized in the presence of its carbon-substituted counterpart, leading to **3x** as the sole product (entry 13). Lactone **1y** and lactam **1z** were converted to the corresponding products **3y** and **3z**, respectively (entries 14 and 15), showing that the acidic protons [*e.g.* C(O)NH or C(O)CH] in the substrates were inconsequential to the reaction outcomes. Finally, 4-pyridine was directly attached to two architecturally complex tricyclic compounds, both of which were derived from natural products (entries 16 and 17). Pyridination of podocarpic acid derivative **1aa**[20] took place smoothly to provide the corresponding adduct **3aa-α** as the major product along with its epimer **3aa-β** (**3aa-α** : **3aa-β** = 2 : 1). Although the additional isopropyl group on the phenyl ring affected the stereochemical outcome, *O*-pivaloyl totarol **1bb** was converted to pyridine derivative **3bb** (**3bb-α** : **3bb-β** = 2 : 3), and no pyridination occurred at the isopropyl group. The intrinsically more reactive methine C–H bond on the isopropyl substituent of **1bb** was sterically shielded by the Piv group, which explains the site-selective functionalization of the methylene C–H bond to generate **3bb**. Consequently, syntheses of the seventeen diverse molecular frameworks in Table 3 verified the robustness and reliability of the methodology.

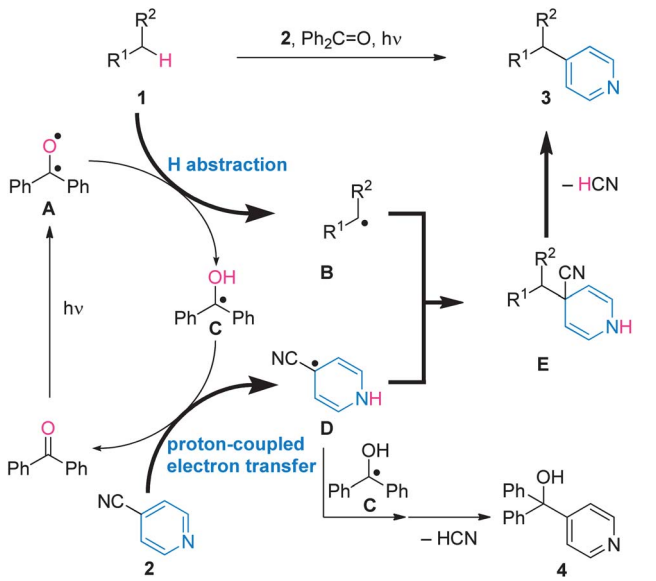
Even broader applicability of the present protocol was proven by successful transformations of heteroaromatics, alkenes and alkanes (Table 4). The reaction of 2-butylthiophene **1cc** and 3-butylthiophene **1dd** with 4-cyanopyridine resulted in the selective transformation of the C(sp^3)–H bond adjacent to the thiophene ring, affording **3cc** and **3dd**, respectively (entries 1 and 2). Even though Paternò-Büchi [2 + 2] cycloaddition[21] between furan **1ee** and $Ph_2C{=}O$ competed, pyridine derivative **3ee** was produced by using an excess amount of the reagents (entry 3). The allylic C–H bond of cyclohexene **1ff** was selectively functionalized to give the corresponding product **3ff**.[8a] Furthermore, the less reactive C(sp^3)–H bonds of alkanes underwent the 4-pyridination when benzylic and allylic C–H bonds were absent. Namely, subjection of cyclooctane **1gg** to the photoirradiating conditions provided **3gg** (entry 5), while the most electron-rich methine C–H bond of linear alkane **1hh** underwent the 4-pyridination, providing product **3hh** with a quaternary carbon (entry 6).

Although the precise reaction mechanism remains to be clarified, a radical-based *ipso*-substitution pathway from **1** to **3** is proposed (Scheme 2). First, the most reactive C–H bond of **1**, such as the benzylic C–H bond, is abstracted by photochemically generated oxyl radical **A**, affording stabilized benzyl radical **B**[22] and α-hydroxy radical **C**. Electron-rich radical **C** and electron-deficient 4-cyanopyridine **2** reorganize through the highly favored proton-coupled electron transfer,[23] resulting in the formation of stable carbon radical **D**[24] and regeneration of $Ph_2C{=}O$ through loss of the electron and proton from **C**. Next, a

Table 4 Transformation of other alkylarenes, alkene, and alkanes[ab]

Entry	Starting material	*t*, h	Product	Yield[c], %
1	 **1cc**	16	 **3cc**	67
2	 **1dd**	24	 **3dd**	47(60)
3[d]	 **1ee**	16	 **3ee**	51(72)
4[e]	 **1ff**	10	 **3ff**	44(51)
5[f]	 **1gg**	22	 **3gg**	35
6[f]	 **1hh**	20	 **3hh**	43

[a] *Reaction conditions*: **1** : **2** : $Ph_2C{=}O$ = 2 : 1 : 0.5, MeCN/H_2O (2 : 1, 0.04 M), rt, photo-irradiation using a Riko 100 W medium pressure mercury lamp. [b] In all entries, the formation of **4** was observed in approximately 15% yield. [c] Isolated yield. Yield based on recovered 4-cyanopyridine **2** is shown in parentheses. [d] The reaction was carried out using $Ph_2C{=}O$ (2 equiv.) and **1ee** (8 equiv.). [e] Cyclohexene **1ff** (3 equiv.) was employed. [f] Alkane **1gg** or **1hh** (5 equiv.) was employed.



Scheme 2 Proposed reaction mechanism.

facile radical–radical coupling reaction between **B** and **D** proceeds to give **E**, which should be rapidly aromatized by expulsion of HCN to give pyridine derivative **3a**. The side reaction to byproduct **4** occurs when radical **D** couples with **C**. Generation of **C** as the key intermediate is supported by the necessity of both hydrogen donor **1** and $Ph_2C{=}O$ to generate adduct **3** or **4** (Table 1). It is noteworthy that the reactive radical species **A**, **B**, **C**, **D** and **E** appear to properly follow the order of these multiple reactions, judging from the high yielding transformations in Tables 1–4.[25]

Conclusions

In summary, a new photochemical metal-free methodology for the one-step preparation of 4-alkylpyridine derivatives has been developed by using the reagent combination of 4-cyanopyridine and $Ph_2C{=}O$ in aqueous MeCN. The C–H pyridination proceeds at ambient temperature under neutral conditions, and is applicable to various alkylaromatics and even to alkenes and alkanes. The obtained 28 compounds in Tables 1–4 possess characteristic 4-pyridine-attached carboskeletons, which are not easily accessible by other known methods. The salient features of the present methodology include the simplicity of the procedure, predictability in terms of chemoselectivity, compatibility with various polar and halogen functionalities, and efficiency in the single-step construction of hindered linkages between carboskeletons and pyridine. Because of these advantages, 4-pyridination of C(sp^3)–H bond introduces a novel and powerful strategy for streamlined synthesis of numerous pyridine-containing compounds, including natural products, agrochemicals, pharmaceuticals, and functional materials.

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15 We also carried out the present reaction on 1 gram scale by using catalytic amount of $Ph_2C{=}O$ (0.1 equiv.) and successfully obtained the product **3aa** in 78% (87% brsm) yield. See ESI† for details.

16 The bond dissociation energy of the C–H bond of toluene decreases upon attachment of Me groups. [*e.g.* H–CH_2Ph (89.7 kcal mol^{-1}), H–CH(Me)Ph (85.4 kcal mol^{-1}), and H–$C(Me)_2$Ph (83.2 kcal mol^{-1})] Y.-R. Luo, BDEs of C–halogen bonds, in *Comprehensive Handbook of Chemical Bond Energies*, CRC Press, Boca Raton, FL, 2007, p. 230.

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