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Origin of the Difference in Reactivity between Ir Catalysts for the Borylation of C–H Bonds

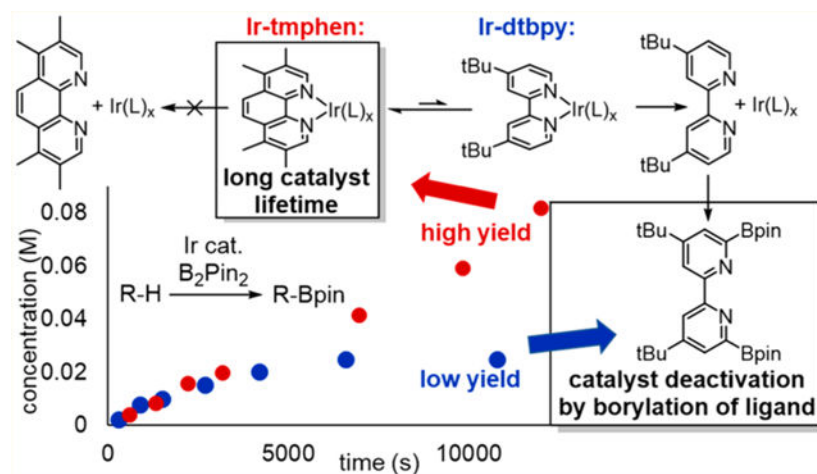
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Abstract

A mechanistic study on the origin of the difference in reactivity between Ir catalysts for C–H borylation reactions is reported. Catalytic reactions of B_2pin_2 with a series of substrates that require high temperatures and long reaction times were conducted. These reactions catalyzed by the combination of $[Ir(COD)(OMe)]_2$ and 3,4,7,8-tetramethylphenanthroline (tmphen) occur in yields that are substantially higher than those of reactions catalyzed by $[Ir(COD)(OMe)]_2$ and 4,4'-di-*tert*-butylbipyridine (dtbpy). The electronic properties of Ir catalysts ligated by dtbpy or tmphen and their stoichiometric reactivity were investigated. It was found that a longer lifetime rather than higher reactivity of the catalyst leads to higher yields of reactions catalyzed by Ir-tmphen. The catalyst ligated by dtbpy decomposes principally by dissociation of the ligand and rapid borylation at the positions alpha to nitrogen. Thus, the greater stability of the catalyst containing tmphen results from its greater binding constant.

Graphical Abstract



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The authors declare no competing financial interest.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b08920.

Experimental procedures, characterization of new compounds, and crystallographic information (PDF)

X-ray crystallographic data for **13** (CIF)

INTRODUCTION

The borylation of C–H bonds has become a widely used and researched method for the functionalization of C–H bonds (Scheme 1).^{1,2} These reactions occur without directing groups with regioselectivities that result from steric hindrance and, in some cases, the acidity of the C–H bond. This selectivity complements that of other catalytic and classical functionalizations of aryl C–H bonds.³ The reaction forms organoboronate esters that can be transformed to a variety of C–C and C–heteroatom bonds.⁴

The ligands used for these iridium-catalyzed functionalizations are typically based on nitrogen Lewis bases, and the catalyst is often generated from the combination of [Ir(COD)OMe]₂ and 4,4'-di-*tert*-butylbipyridine (dtbpy).^{5–11} Some of these reactions occur with turnover numbers approaching 20 000^{11,12} and have been used to produce kilograms of active pharmaceutical ingredients (APIs).^{13,14} However, the borylation of many types of arenes and heteroarenes catalyzed by [Ir(COD)OMe]₂ and dtbpy occur in low yields or require high catalyst loadings (Scheme 2a,b). In these cases, higher yields of the aryl or heteroaryl boronic esters have been achieved by generating the catalyst from [Ir(COD)OMe]₂ and 3,4,7,8-tetramethylphenanthroline (tmphen).^{9,15} This system even catalyzes the borylation of aliphatic C–H bonds (Scheme 2c), including primary and secondary alkyl C–H bonds of amines, ethers,^{16,17} and silanes¹⁸ (Scheme 2d).

Many catalysts for reactions involving organometallic intermediates of noble metals contain phosphines as dative ligands,^{19–21} and many studies have revealed the effects of the properties of phosphines on such catalytic reactions.^{22–24} Far fewer catalysts of such metals contain dative ligands bearing only Lewis-basic nitrogen donors.^{25–29} Few studies on the origins of the activity of such metal–ligand complexes have been published, and most of these studies focus on the polymerization of alkenes.^{30–32} Thus, the origins of the differences in reactivity of complexes of bipyridine and phenanthroline ligands on the borylation of C–H bonds are difficult to glean from prior published literature.

To reveal the origin of the difference in reactivity between the combination of [Ir(COD)OMe]₂ and dtbpy or tmphen as ligand for the borylation of C–H bonds, we studied the relative rates for reaction of the boryl intermediates with various substrates, the relative rates for catalyst decomposition, and the origin of catalyst decomposition. We show that the rates of the reactions catalyzed by the two types of complexes are similar to each other, but the lifetime of the catalyst containing tmphen is much longer than that containing dtbpy, and this longer lifetime, rather than higher reactivity of the catalytic boryl intermediate, leads to the higher yields of reactions catalyzed by tmphen than of those catalyzed by dtbpy. The catalyst lifetime is limited by the borylation of the free nitrogen-based ligand; the higher binding constant of phenanthroline ligands and thereby lower concentration of free ligand, not slower modification of free, phenanthrolines, accounts for the difference in lifetime.

RESULTS AND DISCUSSION

To determine the origins of the difference in reactivity between catalysts containing 4,4'-di-*tert*-butylbipyridine (dtbpy) and 3,4,7,8-tetramethylphenanthroline (tmphen), we first

monitored the rates of reactions of a series of substrates of varying reactivity with the iridium-trisboryl complexes $[\text{Ir}(\text{Bpin})_3(\text{L}_2)\text{-(alkene)}]$ (**1** and **2**) in which L_2 is dtbpy or tmphen and the alkene is derived from the catalyst precursor. Such tris-boryl complexes are known to be the resting state of the catalyst during the borylation of arenes,³³ and the reaction of such complexes with the C–H bond of the substrate is known to be rate limiting for reactions of arenes catalyzed by complexes of both ligands. These complexes react with the substrate after dissociation of the alkene.³³

The rates of the stoichiometric reactions of tris-boryl complexes **1** and **2** with 1,3-dimethoxybenzene (**3**), an arene that forms the product of borylation in high yield with both catalysts, was studied first to assess differences in the rate of reaction of aryl C–H bonds with the two complexes containing the different ligands. These data are provided in Figure 1 and show that the rate of the reaction with dtbpy complex **1** is similar to that with tmphen complex **2**. Thus, an inherently higher reactivity of the complex ligated by tmphen with aryl C–H bonds than of the complex ligated by dtbpy does not explain the difference in yields of reactions catalyzed by complexes of the two ligands. Analogous reactions of **1** and **2** with benzene and 2-methoxy-1,3-dimethylbenzene also showed that the rates of the reactions of complex **1** are similar to those of complex **2** with the same arene (see Supporting Information).

Consistent with the similar rates for reactions of complexes of the two ligands, the degree of electron density at iridium in the trisboryl complex containing dtbpy was similar to that containing tmphen. The infrared stretching frequencies of the Ir-bound carbonyl²³ ligands in trisboryl complexes $[\text{Ir}(\text{Bpin})_3(\text{L}_2)(\text{CO})]$ ($\text{L}_2 = \text{dtbpy}$, **4**;³⁴ and $\text{L}_2 = \text{tmphen}$, **5**) ligated by CO in place of the alkene (Scheme 3) were 1971 and 1972 cm^{-1} , respectively. These data, together with the kinetic data for stoichiometric reactions, show that the origin of the difference in yields of reactions catalyzed by the two iridium-ligand combinations is more likely due to factors besides a difference in reactivity resulting from variations in the electronic properties of the two trisboryl complexes.

To point toward alternative origins of the differences in yields of reactions catalyzed by complexes of the two ligands, we conducted catalytic reactions of B_2pin_2 with THF and with two aromatic compounds that react in higher yield with the catalyst ligated by tmphen than with that ligated by dtbpy. $(\text{Mes})\text{Ir}(\text{Bpin})_3$ was used as catalyst precursor instead of $[\text{Ir}(\text{COD})(\text{OMe})_2]$, which is more typically used for synthetic purposes, to eliminate the induction period sometimes observed with $[\text{Ir}(\text{COD})(\text{OMe})_2]$.³³ The profiles of the borylation of with the two catalysts are shown in Figure 2. The reactions of these arenes with the trisboryl complex ligated by tmphen formed the products in high yield (**7**, 103%; **9**, 91%; **11**, 88%), whereas the reactions with the trisboryl complex ligated by dtbpy formed the product in much lower yield (**7**, 5%; **9**, 31%; **11**, 30%; Table 1).

The formation of product over time began to reveal the origin of these differences in yields. These plots showed that the initial rates (Figure 2 and Table 1) of the reactions catalyzed by Ir-tmphen are similar to those catalyzed by Ir-dtbpy. However, the reactions catalyzed by Ir-tmphen occurred to high conversion and high yield, whereas the reactions catalyzed by Ir-dtbpy stopped after partial conversion. The plots show that the remaining material

in these reactions was starting substrate, and no significant accumulation of side products was observed (see Supporting Information). These results show that the lower yields from the borylations of alkanes, electron-rich arenes, and heteroarenes catalyzed by Ir-dtbpy than those from the borylations catalyzed by Ir-tmphen is due to catalyst lifetime, not due to a difference in inherent reactivity of the trisboryl intermediate with the substrate or formation of side products from reactions of the catalyst bearing dtbpy.

To reveal the origin of the difference in catalyst lifetime, the borylation of THF catalyzed by Ir-dtbpy was analyzed by ^1H NMR spectroscopy after 12 h at 100 °C. We observed the formation of a new species corresponding to signals at 8.70 and 7.82 ppm. A comparison of the ^1H NMR spectra of independently synthesized 2,2'-(pinB)₂-4,4'-(tBu)₂ bpy (**13**) matched that of the new species observed during the reaction (see Supporting Information for solid-state structure by X-ray diffraction).³⁵ To gauge the rate of the borylation of dtbpy versus that of the borylation of the substrate, the reactions of equal concentrations of dtbpy and *o*-xylene side by side were monitored. The plot in Figure 3a shows that the rate of the borylation of dtbpy is comparable to that of the borylation of *o*-xylene. To determine if the borylation of dtbpy is competitive with the borylation of *o*-xylene in the same reaction solution, we conducted the reaction of B₂pin₂ with 1 equiv of *o*-xylene and 1 equiv of dtbpy catalyzed by the Ir-dtbpy system (Scheme 3b). Monoborylated dtbpy (46%), diborylated dtbpy (8%), and monoborylated *o*-xylene (58%) all formed. These experiments show that the rate of the borylation of dtbpy is similar to that of the borylation of arenes and that it is plausible that dtbpy undergoes borylation during the catalytic processes, particularly during catalytic reactions of substrates, such as THF, containing less reactive C–H bonds.

To assess whether dtbpy underwent borylation during reactions of substrates that form borylated products in higher yields when catalyzed by Ir-tmphen than when catalyzed by Ir-dtbpy, we obtained ^1H NMR spectra of crude reactions of THF, aminoarene **8**, and heteroarene **10** after 12 h of reaction time at 80 °C. These spectra showed that 80%, 60%, and 45% of the dtbpy ligand had converted to the borylated dtbpy **13** for the reactions of THF, aminoarene **8** and heteroarene **10**, respectively (Table 1). These data are consistent with the conclusion that the ligand undergoes borylation in competition with the substrate and that this borylation leads to catalyst deactivation.

To investigate whether the borylation of the ligand inactivates the catalyst, we tested the activity of Ir catalysts containing diborylated ligand **13** for the borylation of Julolidine (**8**) and 2,4-dimethylbenzimidazole (**10**). Consistent with the borylation of dtbpy leading to catalyst deactivation, the borylation of **8** and **10** catalyzed by the combination of (Mes)Ir(Bpin)₃ and modified ligand **13** (Scheme 4) gave only traces of product (<5%).

To test whether the longer lifetime of the catalyst containing tmphen is due simply to a difference in rate of the borylation of the ligand, which could be retarded by the presence of methyl groups in the 3 and 8 positions of the phenanthroline, we conducted the reaction of 1 equiv of tmphen with 2 equiv of B₂pin₂ under the same conditions that led to the borylation of dtbpy. In contrast to the slower rate of decomposition of the catalyst containing tmphen than of that containing dtbpy, the reaction of free tmphen with B₂pin₂ was *faster* than that of dtbpy (Figure 4). This reaction of tmphen formed a complex mixture of products. After

oxidation of the borylation products with H₂O₂ and NaOH, the mixture was analyzed by HPLC/MS. Several species corresponding to mono and dihydroxy-lated phenanthrolines were detected, suggesting that tmphen is borylated at both aromatic and benzylic positions (see Supporting Information).

Because the faster catalytic borylation of free tmphen than of free dtbpy runs counter to the relative catalyst lifetimes, we considered that the differences in binding of the ligand to iridium and effect of binding on the borylation process could account for the difference in catalyst stability. To determine the relative binding of dtbpy and tmphen to the trisboryl-iridium fragment and qualitative rate of ligand exchange, we conducted ligand substitution reactions (Scheme 5). The reaction of 1 equiv of (dtbpy)Ir(Bpin)₃(COE) (**1**) with 1 equiv of tmphen in THF-*d*₈ was monitored by ¹H NMR spectroscopy. Free tmphen fully replaced bound dtbpy within 5 min, showing that tmphen binds substantially more strongly to Ir than does dtbpy.³⁶ The higher binding constants of phenanthroline ligands than of bipyridine ligands are due to the more favorable orientation of the nitrogen atoms for binding the metal in free phenanthrolines than in free bipyridines. In contrast to the orientation of the nitrogen atoms in free phenanthroline, the two nitrogen atoms in the most stable conformation of free dtbpy are distal from each other, and the dipoles are aligned more favorably than they are in the required orientation of the nitrogen atoms for binding of bpy ligands.^{37,38}

After this solution was allowed to sit for 5 h at room temperature, borylated dtbpy was observed by ¹H NMR spectroscopy (ca. 40%), but no signals corresponding to borylated tmphen were observed. On the other hand, a solution of 1 equiv of (tmphen)Ir(Bpin)₃(COE) (**2**) and 1 equiv of dtbpy was unchanged after 5 min, and only borylated dtbpy was observed after 5 h. These results, together with the faster borylation of free tmphen than of free dtbpy, imply that dtbpy and tmphen are borylated when they are unbound from the metal. Thus, the stronger binding of tmphen than of dtbpy leads to a lower concentration of free ligand in reactions catalyzed by Ir-tmphen than in those catalyzed by Ir-dtbpy. This lower concentration of free ligand leads to slower borylation of tmphen and accompanying slower catalyst decomposition.

The borylation of free bipyridine-based structures has been observed previously but has not been connected to the lifetime of the catalyst. For example, the diborylation of dtbpy catalyzed by Ir-dtbpy was reported by Marder et al. in a study on C–H borylations of pyridines.³⁵ In related work, the borylation of a pincer ligand on cobalt was reported by Chirik et al., and, in this case, the borylation of ligand was shown to decrease activity of cobalt catalysts for the borylation of arenes.³⁹ However, the ligand on cobalt is a strongly bound pincer. Thus, borylation of the pincer ligand presumably occurs directly on the bound ligand, and borylation process likely imparts unfavorable changes to the electronic properties of the catalyst that decreases its reactivity.

CONCLUSIONS

A series of experiments on reaction rates, catalyst lifetime and pathways to catalyst decomposition shows that the activity of the iridium catalysts ligated by tmphen and dtbpy are similar but the yields for reactions catalyzed by Ir-dtbpy are lower than those catalyzed

by Ir-tmphen in many cases because of catalyst deactivation. Table 1 summarizes our data on reaction yields, initial rates, and amount of borylated dtbpy formed in reactions of an aliphatic compound, an electron-rich arene, and a heteroarene: THF (**6**), Julolidine (**8**), and 2,4-dimethylbenzimidazole (**10**). The electronic properties of the two catalysts are similar to each other, and the rates of the stoichiometric reactions of arenes with the trisboryl complexes ligated by the two ligands are similar to each other. However, the catalyst containing dtbpy decomposes during borylations that require higher temperatures and longer reaction times, such as the borylation of C_{sp3}-H bonds, electron-rich arenes, and heteroarenes, and this catalyst decomposition limits reaction yields.

The major decomposition pathway occurs by borylation of the nitrogen-based ligand when it is unbound from the metal. Counterintuitively, tmphen, which leads to the more stable catalyst, reacts in its free form with B₂pin₂ faster than free dtbpy reacts with B₂pin₂. Thus, the longer lifetime of the Ir-tmphen catalyst than of the Ir-dtbpy catalyst is due to stronger binding of tmphen to the metal than of dtbpy, as a result of its more rigid structure. Stronger binding leads to a lower concentration of free ligand and, thereby, slower borylation of the ligand and catalyst decomposition. These data predict that catalysts containing other rigid bidentate ligands should resist catalyst deactivation during the borylation of C-H bonds, and these findings will guide our future studies on the development of new catalysts for the borylation of C-H bonds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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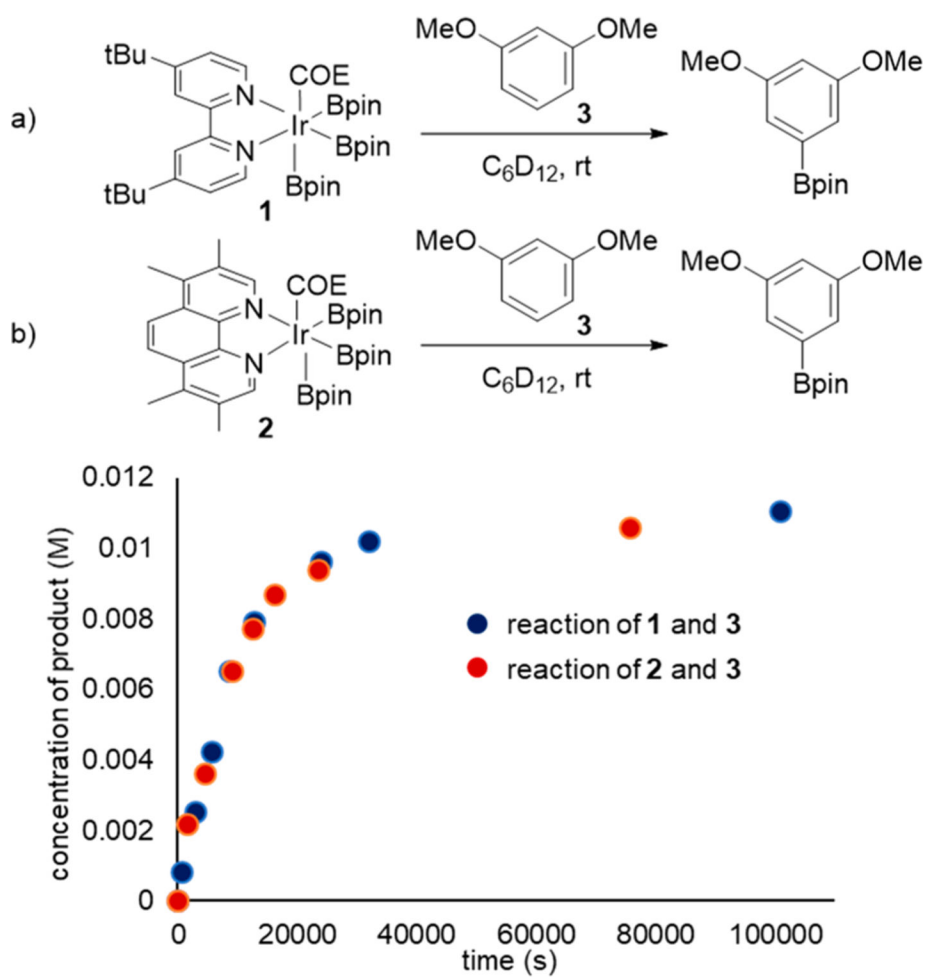
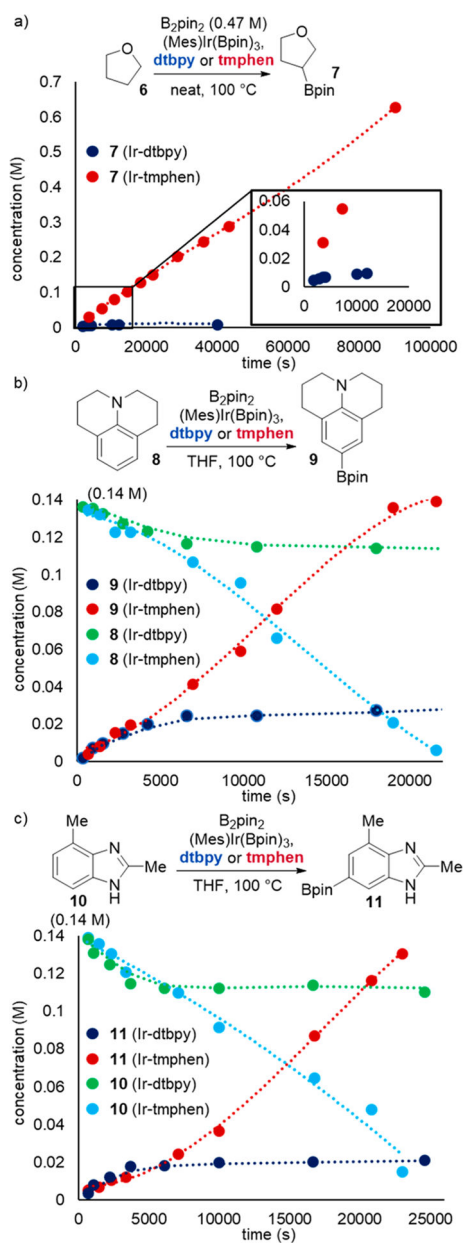
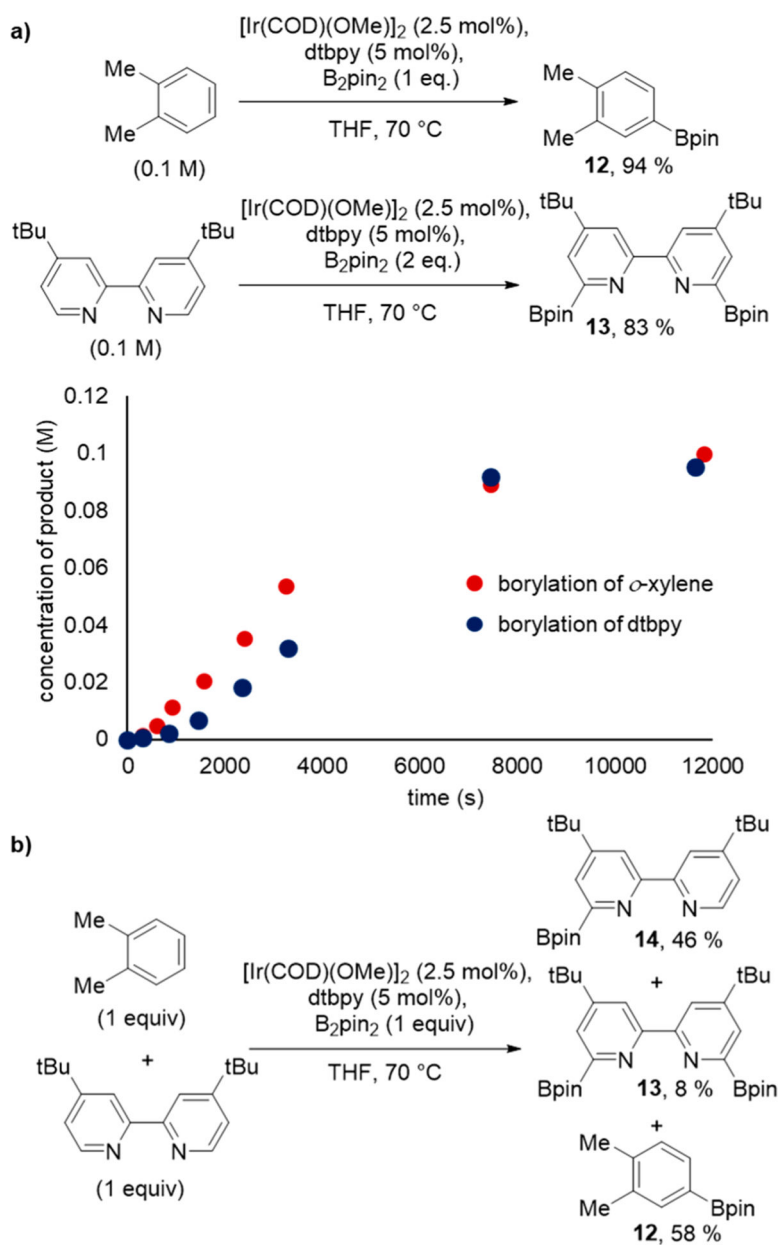


Figure 1. Reaction profile of stoichiometric borylation of *m*-dimethoxybenzene (**3**) with Ir complexes (10.5 μ M) **1** (blue) and **2** (red).

**Figure 2.**

Catalytic borylation of (a) THF (**6**), (b) Julolidine (**8**), and (c) 2,4-dimethylbenzimidazole (**10**) with $(Mes)Ir(Bpin)_3$ (5 mol%). Initial rates: **6**, $5.7 \times 10^{-6} \text{ M s}^{-1}$ (Ir-*tmphen*) and $2.7 \times 10^{-6} \text{ M s}^{-1}$ (Ir-*dtbpy*); **8**, $7.1 \times 10^{-6} \text{ M s}^{-1}$ (Ir-*tmphen*) and $6.6 \times 10^{-6} \text{ M s}^{-1}$ (Ir-*dtbpy*); **10**, $3.7 \times 10^{-6} \text{ M s}^{-1}$ (Ir-*tmphen*) and $4.9 \times 10^{-4} \text{ M s}^{-1}$ (Ir-*dtbpy*).

**Figure 3.**

(a) Catalytic borylation of *o*-xylene and *tert*-butylbipyridine with $[\text{Ir}(\text{COD})(\text{OMe})_2]$ (2.5 mol%). (b) Reaction of 1 equiv *o*-xylene, 1 equiv *tert*-butylbipyridine, and 1 equiv B_2pin_2 .

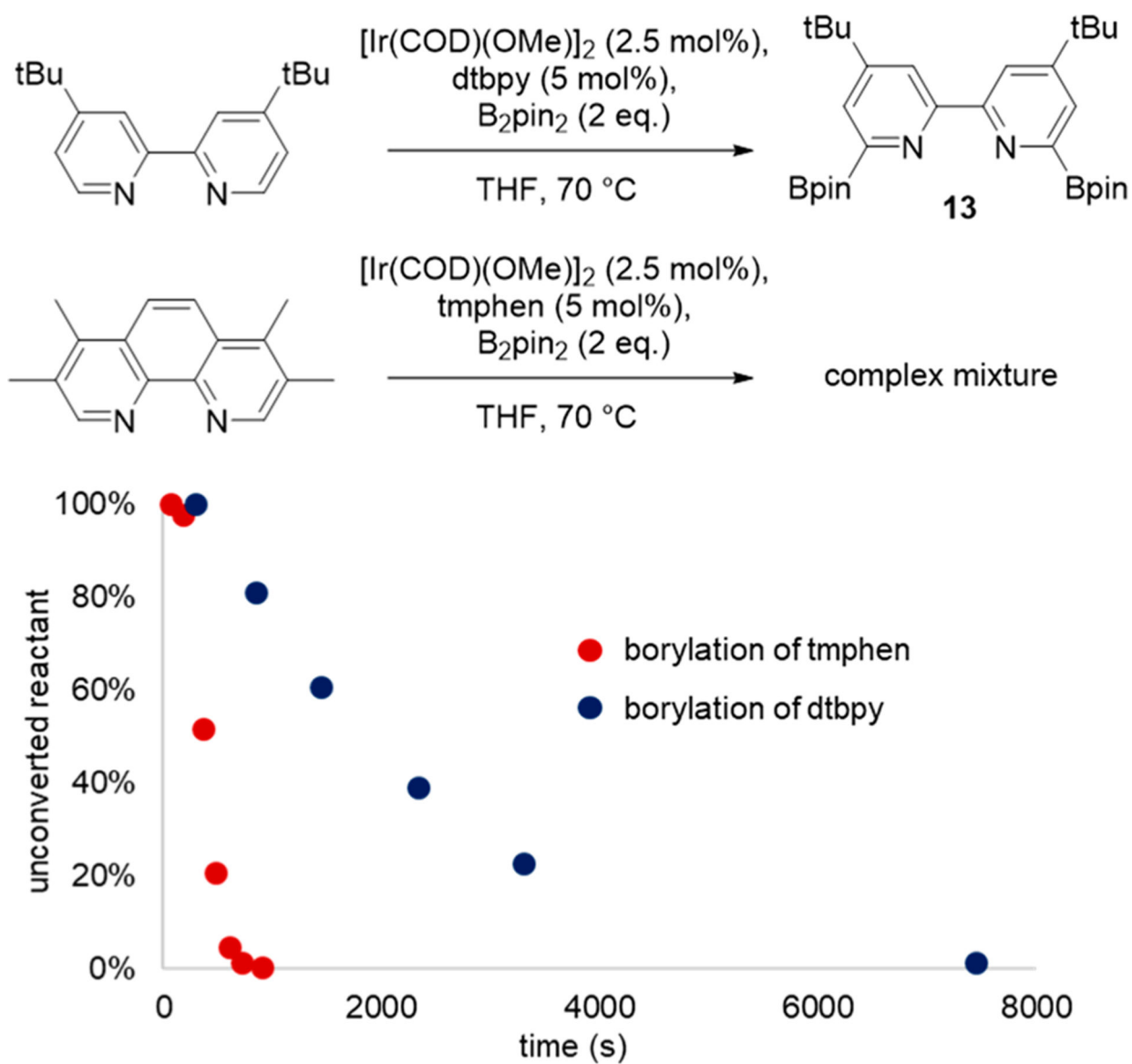
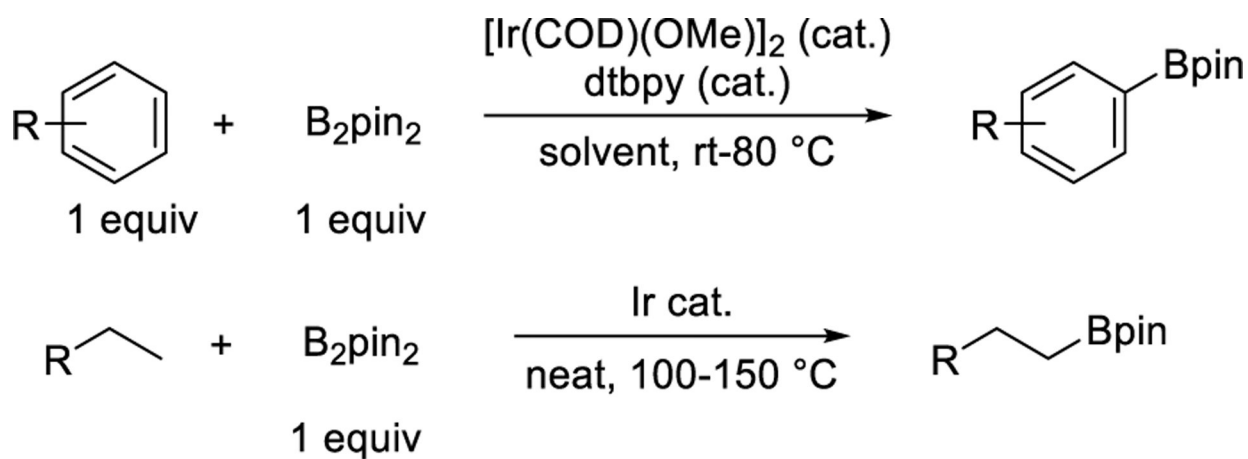
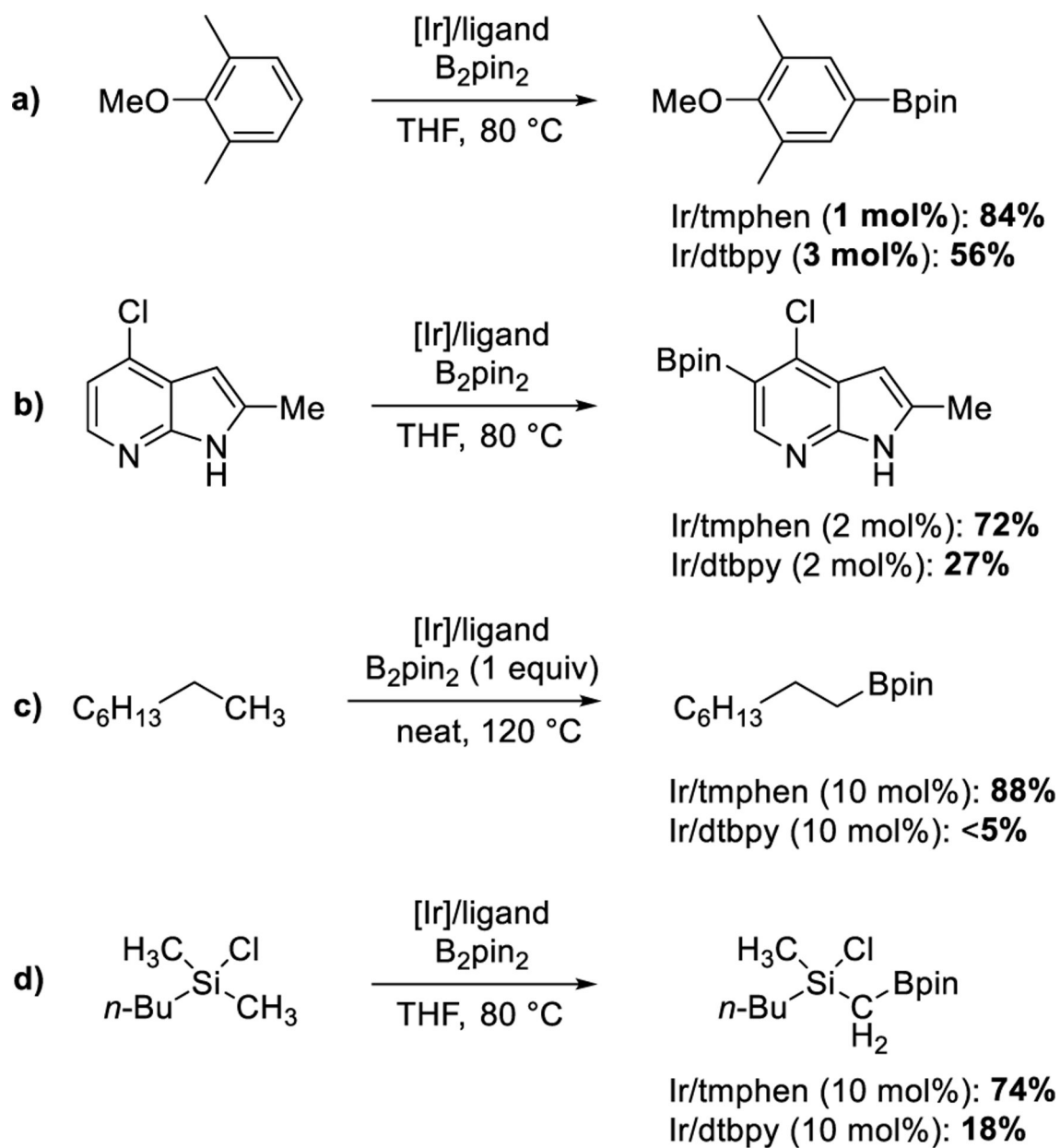


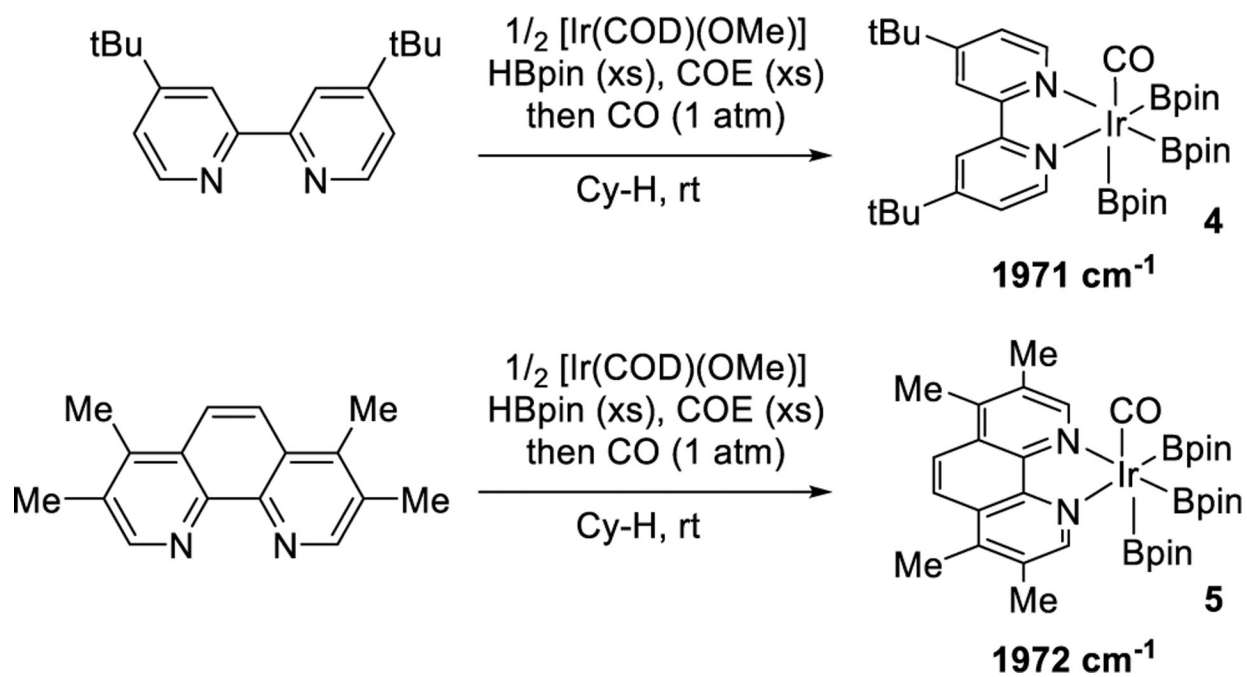
Figure 4.
Consumption of dtbpy (blue) and tmphen (red) over time.



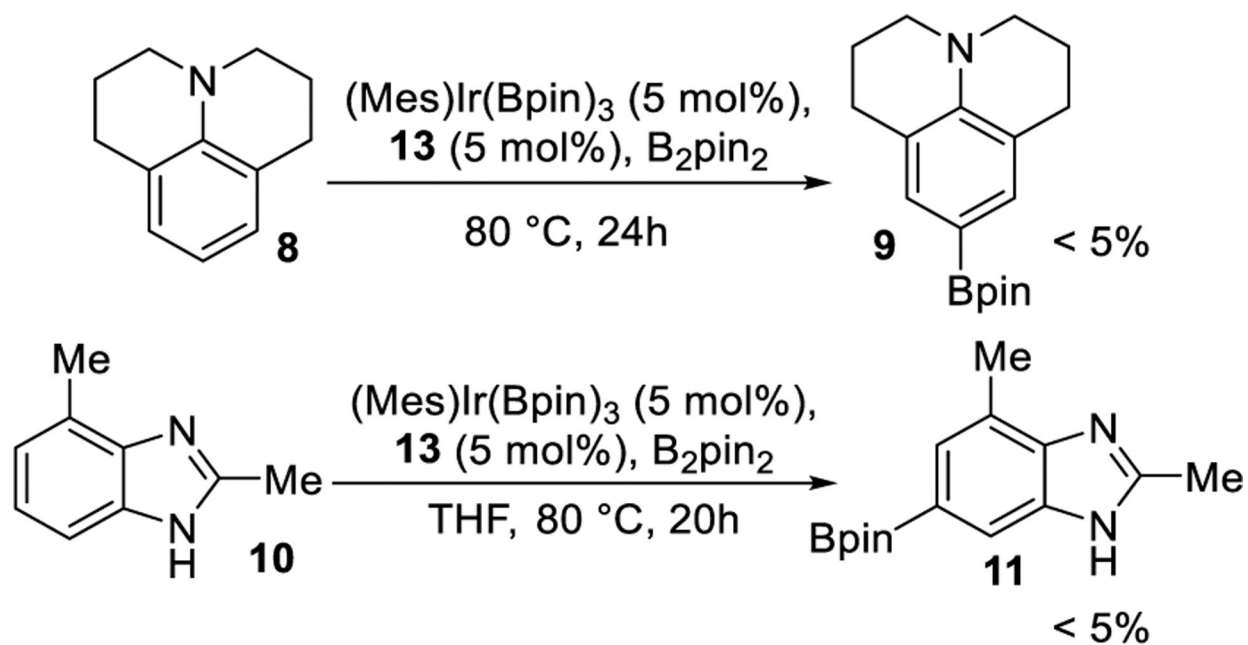
Scheme 1.
Typical Reaction Conditions for Ir-Catalyzed Borylation of Arenes

**Scheme 2.**

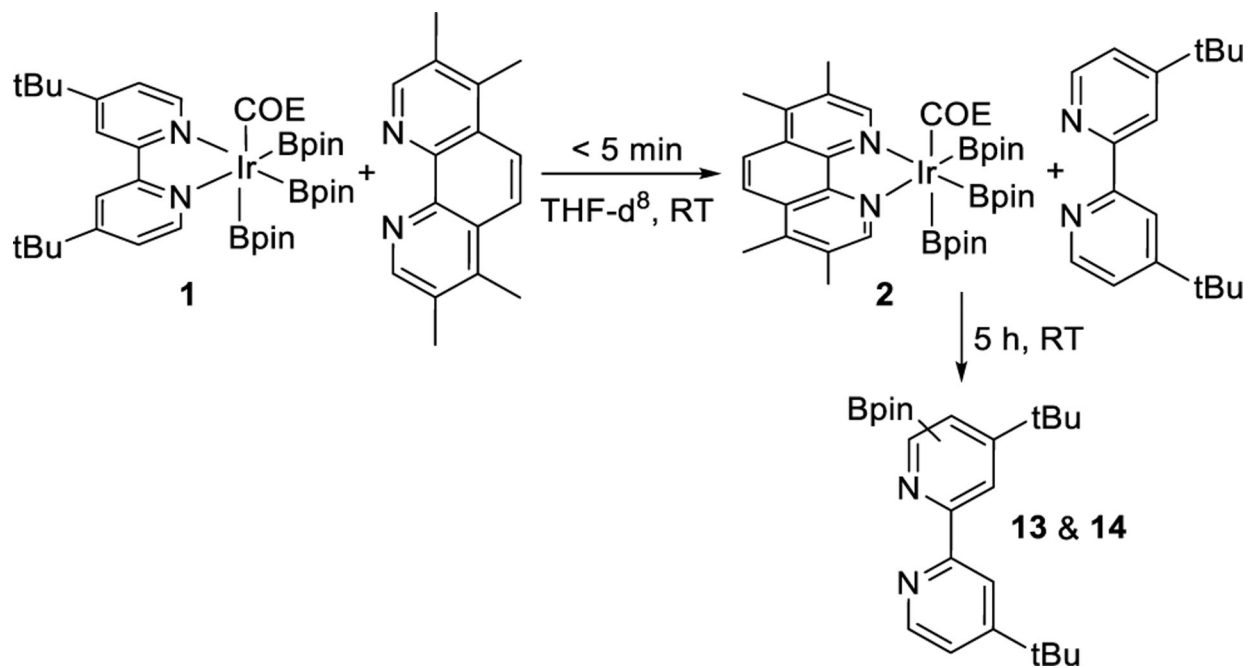
Published Examples of the Borylations of C–H Bonds Showing the Different Yields for Reactions Catalyzed by Ir-tmphphen and Ir-dtbpy

**Scheme 3.**

C–O Stretching Frequencies of Iridium-Trisboryl Carbonyl Complexes 4 and 5



Scheme 4.
Reactions with Bpin₂-tbpy **13** as Ligand



Scheme 5.
Ligand Exchange Followed by Borylation of dtbpy

Table 1.

Yields of Borylated Product after 24 h, Initial Rates of the Borylation Reactions, and Percentage of Borylated Dtbpy Ligand for the Catalytic Reactions of THF (6), Julolidine (8), and 2,4-Dimethylbenzimidazole (10)

	product		
	7	9	11
yield with 5 mol% Ir-dtbpy (%)	5	31	30
yield with 5 mol% Ir-tmphen (%)	103	91	88
initial rates with 5 mol% Ir-dtbpy ($M s^{-1}$)	2.7×10^{-6}	6.6×10^{-6}	4.9×10^{-6}
initial rates with 5 mol% Ir-tmphen ($M s^{-1}$)	5.7×10^{-6}	7.1×10^{-6}	3.7×10^{-6}
percentage of dtbpy ligand borylated after 24 h	80	60	45

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