Directed C–H Alkenylation of Aryl Imines with Alkenyl Phosphates Promoted by a Cobalt–N-Heterocyclic Carbene Catalyst

Pin-Sheng Lee,[a†] Wengang Xu,[a†] and Naohiko Yoshikai[a]*

[a] Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore
Fax: +(65)-6791-1961; e-mail: nyoshikai@ntu.edu.sg

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Abstract. We report herein an *ortho*-C–H alkenylation reaction of aryl imines with alkenyl phosphates promoted by a cobalt–N-heterocyclic carbene (NHC) catalytic system. While commercially available bulky NHC ligands exhibited only modest catalytic activity, elaboration of the N-substituents and the backbone of NHC enabled the desired transformation in high yield at a mild temperature. The new Co–NHC system proved applicable to a variety of aryl imines and alkenyl phosphates to afford *ortho*-alkenylated aryl imines, which serve as precursors to benzofulvene derivatives.

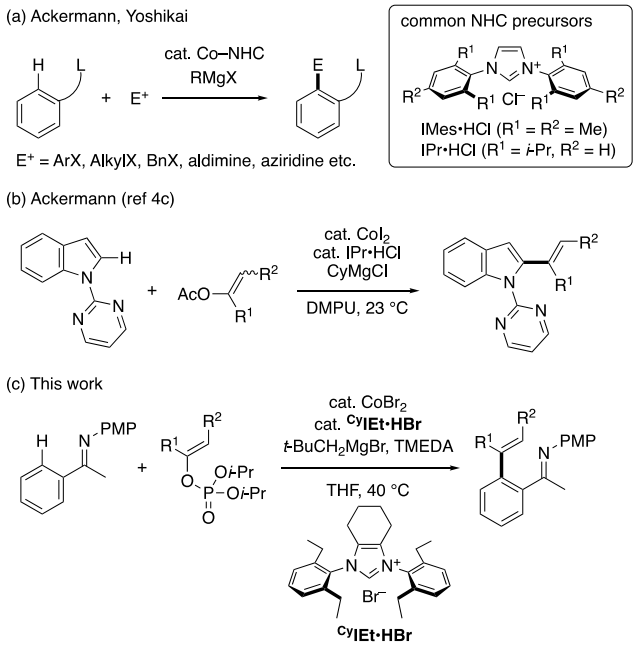
Keywords: C–H functionalization; C–C bond formation; homogeneous catalysis; cobalt; N-heterocyclic carbenes

Introduction

Transition metal-catalyzed, directing group-assisted arene C–H bond activation has evolved as an atom- and step-economical approach to the synthesis of functionalized arenes.[1] This approach is not just useful for the high efficiency and predictable regioselectivity of C–H activation. The product of the directed C–H activation reaction would serve as an intermediate for the synthesis of carbo- and heterocycles through simultaneous utilization of the directing group and the newly introduced functional group. In this context, the introduction of alkenyl groups into the *ortho* position of functionalized arenes, which has been most commonly achieved by way of dehydrogenative Heck-type process,[2] is particularly attractive because of the versatility of alkenyl groups.

Over the last years, low-valent cobalt-catalyzed directed *ortho*-C–H functionalization of arenes using organic electrophiles have been achieved by Nakamura,[3] Ackermann,[4] and our group[5] using a catalyst generated from a cobalt(II) or cobalt(III) precatalyst, a supporting ligand, and a Grignard reagent, where the Grignard reagent serves as a reductant for the cobalt precatalyst and also as a base to remove the *ortho* C–H proton.[6,7] In particular, the Ackermann group and our group have independently demonstrated the utility of N-heterocyclic carbenes (NHCs) as supporting ligands for such transformations (Scheme 1a). Like many transition metal–NHC complex-catalyzed reactions,[8] readily available bulky NHCs such as IMes (1,3-bis(2,4,6-trimethylphenyl)imidazole-2-ylidene) and IPr (1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene) have often showed optimal performance for various electrophiles including aryl carbamates/sulfamates/chlorides,[4a,b,5b] alkyl halides,[4b] aldimines,[5a] and aziridines.[5d] Along this line, Ackermann recently achieved mild and efficient cobalt-catalyzed C–H alkenylation of N-pyrimidyl indoles and pyrroles with alkenyl acetates using IPr as the supporting ligand (Scheme 1b).[4c] The same catalytic system also allowed the use of alkenyl carbamates, carbonates, and phosphates as alkenylating agents. The reaction is particularly attractive as it complements other types of C–H alkenylation such as dehydrogenative Heck reaction[9] and hydroarylation of alkynes,[10-12] while the scope of the aromatic substrates remains to be extended.[13]

As a part of our exploration of cobalt-catalyzed arene C–H functionalization with versatile imine directing groups,[5,11b,14] we have developed an *ortho* C–H alkenylation reaction of aryl imines with alkenyl phosphates, which is described herein (Scheme 1c). The key to the success of this reaction was an NHC ligand ^{Cy}IEt,[15] which evolved through elaboration of the N-substituents and the backbone of NHC. The present Co–NHC system was applicable to a variety of aryl imines and alkenyl phosphates, and proved to be complementary to Ackermann's alkenylation system.



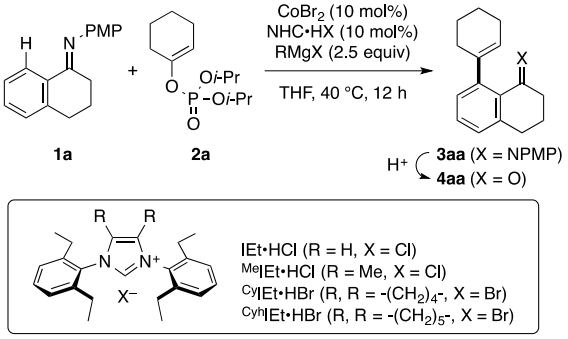
Scheme 1. Cobalt–NHC catalysis for directed C–H functionalization with electrophiles (PMP = *p*-methoxyphenyl).

Results and Discussion

The present study commenced with a screening of conditions for the reaction of imine **1a** derived from tetralone and *p*-anisidine with cyclohexenyl phosphate **2a** (Table 1). We initially tested catalytic systems comprising $CoBr_2$ (10 mol%), IMes•HCl or IPr•HCl (10 mol%), and *t*-$BuCH_2MgBr$ (2.5 equiv), which were previously developed for the *ortho* C–H functionalization of aryl imines with aryl chlorides, aldimines, and aziridines.[5a,b,d] However, these systems afforded, upon acidic hydrolysis, the desired *ortho*-cyclohexenylated ketone **4aa** only in modest yields (entries 1 and 2). In addition, Ackermann's catalytic system for the alkenylation of *N*-pyrimidylindole (Scheme 1b)[4c] failed to promote the present reaction (entry 3).

Given these unsatisfactory preliminary results, we turned to modification of the NHC ligand and search for additives to improve the reaction. Throughout this effort, we noted substantial effects of the *N*-substituent and backbone of NHC on the catalytic activity, and also beneficial influence of *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA, 7 equiv) as an additive (entries 4–10). The use of an imidazolium salt bearing 2,6-diethylphenyl groups (IEt•HCl) as the NHC precursor and TMEDA as the additive improved the yield of **4aa** to 62% (entry 5). The reaction was further improved by installation of methyl groups on the 4,5-positions of the NHC precursor (^{Me}IEt•HCl; entry 6). Finally, NHC precursors ^{Cy}IEt•HBr and ^{Cyh}IEt•HBr featuring *N*,*N*'-bis(2,6-diethylphenyl) groups and cyclohexane- or cycloheptane-fused backbone promoted the alkenylation to afford **4aa** in more than 90% yield (entries 7 and 8). Using ^{Cy}IEt•HBr, the amount of the Grignard reagent could be reduced to 2 equiv without notable decrease in the product yield (entry 9). While TMEDA did not improve the reaction using IMes (entries 1 and 4), it clearly exhibited a beneficial effect when combined with the modified NHC (entries 9 and 10). While the origin of this effect is not clear, we suspect that TMEDA acts as a Lewis base to magnesium rather than as a ligand to cobalt, thus affecting the aggregation state of the Grignard reagent and its transmetalation with cobalt species. As was the case with other C–H/electrophile coupling reactions developed by our group,[5] the use of *t*-$BuCH_2MgBr$ was crucial, as other Grignard reagents such as *i*-PrMgBr and CyMgCl shut down the desired alkenylation (entries 11 and 12). Note that attempts to use cyclohexenyl acetate or carbamate in place of **2a** did not afford **4aa** under any of the examined conditions.

Table 1. Screening of reaction conditions.[a]



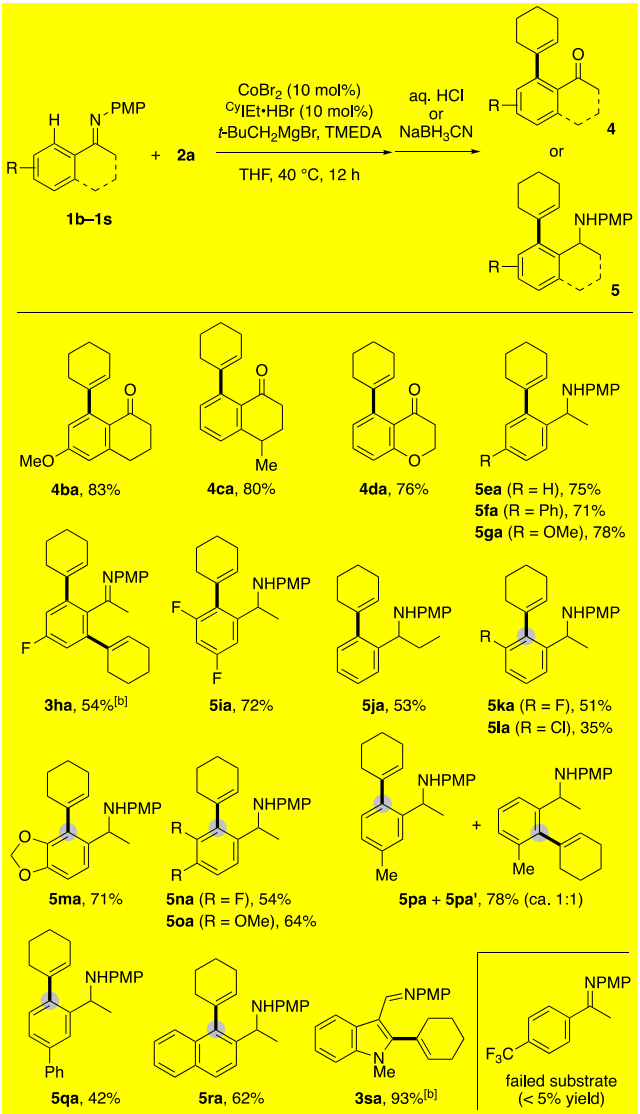
Entry	NHC	RMgX	Additive	Yield [%][b]
1	IMes	*t*-$BuCH_2MgBr$	None	39
2	IPr	*t*-$BuCH_2MgBr$	None	28
3[c]	IPr	CyMgCl	None	< 1
4	IMes	*t*-$BuCH_2MgBr$	TMEDA	24
5	IEt	*t*-$BuCH_2MgBr$	TMEDA	62
6	^{Me}IEt	*t*-$BuCH_2MgBr$	TMEDA	69
7	^{Cy}IEt	*t*-$BuCH_2MgBr$	TMEDA	94 (90)
8	^{Cyh}IEt	*t*-$BuCH_2MgBr$	TMEDA	96 (90)
9[d]	^{Cy}IEt	*t*-$BuCH_2MgBr$	TMEDA	(90)
10	^{Cy}IEt	*t*-$BuCH_2MgBr$	None	65
11	^{Cy}IEt	*i*-PrMgBr	TMEDA	2
12	^{Cy}IEt	CyMgCl	TMEDA	4

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), $CoBr_2$ (10 mol%), NHC•HX (10 mol%), *t*-$BuCH_2MgBr$ (0.75 mmol), TMEDA (0 or 2 mmol) in THF, 40 °C, 12 h. [b] Determined by GC using *n*-tridecane as an internal standard. Isolated yield is shown in parentheses. [c] Ackermann's system (CoI_2, IPr•HCl, DMPU) was used. [d] 0.6 mmol of the Grignard reagent was used.

With the Co–^{Cy}IEt catalytic system in hand, we explored the scope of the *ortho* C–H alkenylation reaction. First, various aryl ketimines were subjected to the reaction with cyclohexenyl phosphate **2a** (Table 2). As expected, the imines derived from substituted tetralones or chromanone smoothly participated in the reaction to afford, upon acidic

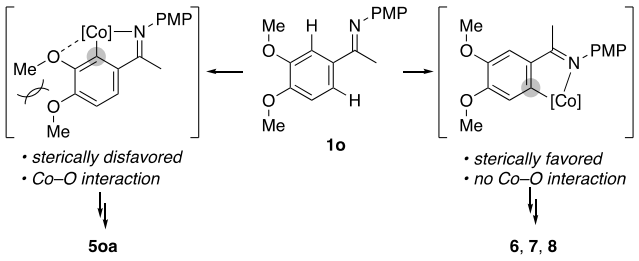
hydrolysis, the desired alkenylated ketones **4ba**–**4da** in good yields. The imines derived from acetophenone and propiophenone derivatives were also amenable to the present C–H alkenylation. For such imines, the alkenylation products were subjected to reduction with $NaBH_3CN$ and then isolated in the form of benzylic amine **5**, while their treatment under acidic hydrolysis conditions caused intramolecular cyclization (vide infra). The imines bearing two equivalent *ortho* C–H bonds exclusively afforded monoalkenylation products **5ea**–**5ga**, **5ia**, and **5ja** in moderate to good yields, except for the one derived from 4-fluoroacetophenone, which underwent twofold alkenylation to afford the dialkenylated imine **3ha** in 54% yield. The reaction proved to be sensitive to a highly electron-withdrawing substituent, as acetophenone imine bearing a *para*-CF_3 group failed to produce the desired alkenylation product in an appreciable yield.

Table 2. Reaction of various aryl imines with cyclohexenyl phosphate **2a**.[a]



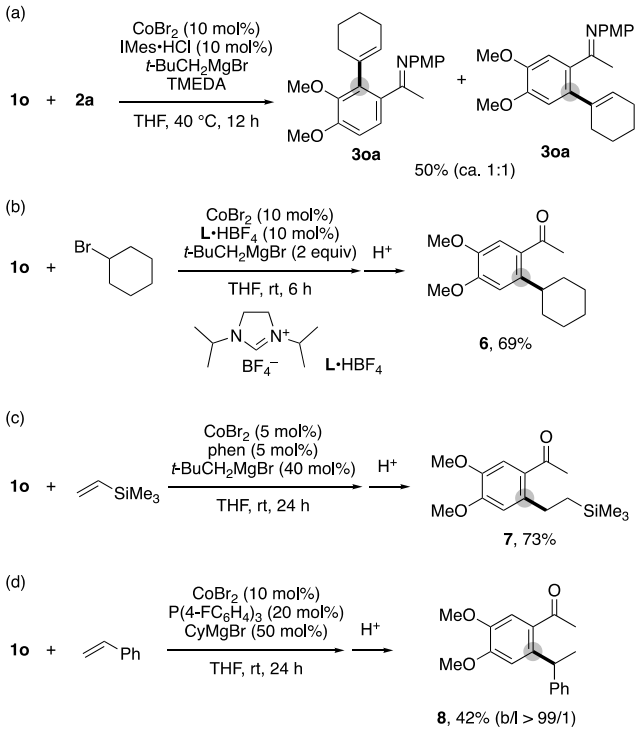
[a] The reaction was performed on a 0.3 mmol scale according to the standard conditions in Table 1, entry 7. [b] Isolated in the form of imine without hydrolysis and reduction.

In light of our previous studies on cobalt-catalyzed C–H functionalization,[6] it was not surprising that the unsymmetrical imines bearing 3-fluoro, 3-chloro, 3,4-methylenedioxy, and 3,4-difluoro groups underwent regioselective C–H activation at the more hindered *ortho* position (see **5ka**–**5na**), which could be ascribed to the secondary directing effect of the lone pair of these substituents. On the other hand, it was unusual that the imine bearing 3,4-dimethoxy groups also exhibited the same regioselectivity (see **5na**), because the buttressing effect of the adjacent methoxy groups is expected to make the 3-methoxy group act as a steric bulk rather than a secondary directing group (Scheme 2).[16] Another peculiar observation was that the imine bearing a 3-methyl group afforded a ca. 1:1 mixture of two regioisomers **5pa** and **5pa'**, while the one bearing a 3-phenyl group underwent exclusive alkenylation at the less hindered position (see **5qa**). Imine derived from 2-acetylnaphthalene was alkenylated at the 1-position (see **5ra**). C2-alkenylation of 3-iminoindole was also achieved in high yield (see **3sa**).



Scheme 2. Expected effect of 3,4-dimethoxy groups.

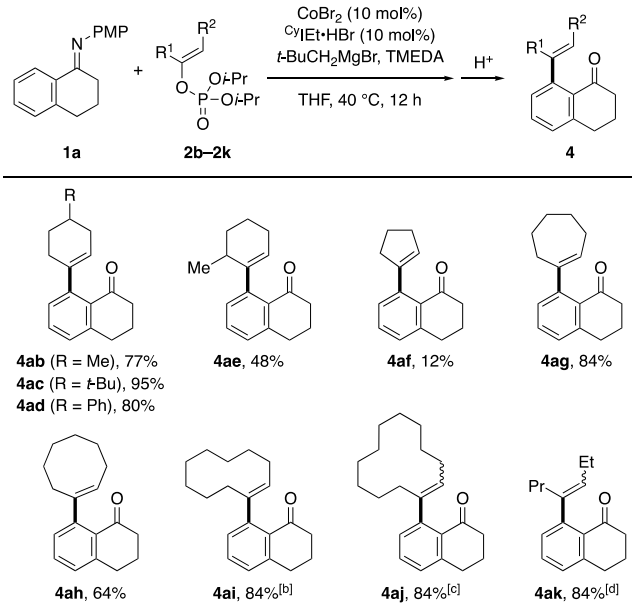
We performed several reference experiments to gain insight into the origin of the counterintuitive regioselectivity observed for the 3,4-dimethoxy-substituted imine **1o** (Scheme 3). First, the use of IMes instead of ^{Cy}IEt in the alkenylation reaction of **1o** with **2a** resulted in a near equimolar mixture of two regioisomeric products (Scheme 3a). Second, cobalt-catalyzed *ortho* C–H functionalization of **1o** with cyclohexyl bromide,[5c] vinyltrimethylsilane,[14a] or styrene[14b] under previously developed catalytic systems uniformly resulted in the exclusive functionalization of the less hindered *ortho* C–H bond to afford the respective products **6**–**8** (Scheme 3b–3d), regardless of the secondary directing effect of substituents such as 3-fluoro and 3,4-methylenedioxy groups observed in these catalytic systems. On the basis of these results, we suspect that the steric and electronic nature of the ^{Cy}IEt ligand is primarily responsible for the unique regioselectivity, where the interaction between the cobalt center and the 3-methoxy group would override the unfavorable repulsion between the methoxy groups (Scheme 2).



Scheme 3. Reference experiments using 3,4-dimethoxy-substituted imine **1o**.

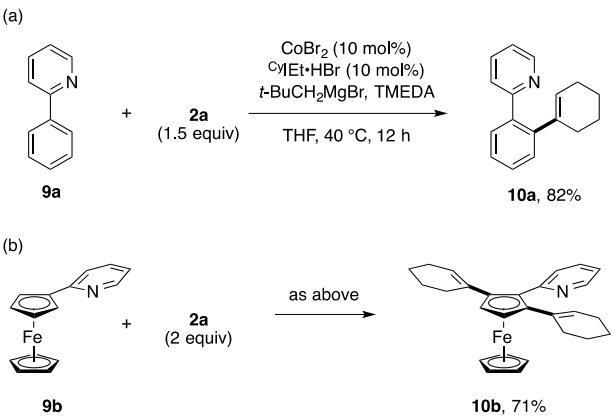
We next examined C–H alkenylation of tetralone imine **1a** with a series of alkenyl phosphates (Table 3). As expected, 4-substituted cyclohexenyl phosphates smoothly participated in the reaction, affording the desired products **4ab**–**4ad** in good yields. The reaction of a cyclohexenyl phosphate having a 6-methyl substituent was less efficient (see **4ae**), presumably because of the steric hindrance. While cyclopentenyl phosphate reacted rather sluggishly (see **4af**), other cycloalkenyl phosphates with larger ring sizes afforded the desired products **4ag**–**4ai** in good yields. Notable among these examples are the reactions of cyclodecenyl- and cyclododecenyl phosphates. The former reaction involved conversion of an *E*/*Z* mixture of the alkenyl phosphate into the single *E*-product **4ai**. On the other hand, in the latter reaction, *Z*-rich alkenyl phosphate (*Z*/*E* = ca. 9:1) ended up in the alkenylated product **4aj** as a ca. 2:1 mixture of the *E*- and *Z*-isomers. Likewise, the reaction of *E*-rich alkenyl phosphate (*E*/*Z* = ca. 3:1) derived from 4-heptanone resulted in the product **4ak** as a mixture of the *E*- and *Z*-isomers with a moderate ratio (ca. 2:1).

Table 3. Reaction of imine **1a** with various alkenyl phosphates.[a]



[a] The reaction was performed on a 0.3 mmol scale according to the standard conditions described in Table 1, entry 7. Unless otherwise noted, the configuration of the alkenyl phosphate was *E*. [b] A mixture of *E* -and *Z*-alkenyl phosphate (ratio = ca. 1:1) was used. [c] *Z*-rich alkenyl phosphate (*Z*/*E* = ca. 9:1) was converted to a ca. 2:1 mixture of *E*- and *Z*-isomers. [d] *E*-rich alkenyl phosphate (*E*/*Z* = ca. 3:1) was converted to a mixture of *E*- and *Z*-isomers (ratio = ca. 2:1).

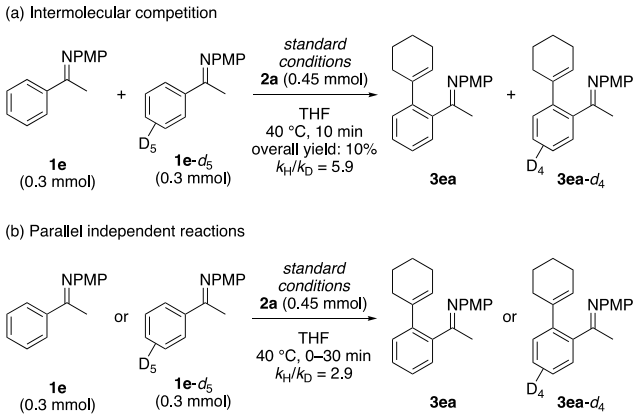
Besides the aryl imines, substrates bearing a pyridyl directing group were also amenable to the present alkenylation reaction. Thus, the reaction of 2-phenylpyridine (**9a**) with **2a** exclusively afforded the monoalkenylation product **10a** in 82% yield (Scheme 4a). By contrast, 2-ferrocenylpyridine (**9b**) afforded a mixture of mono- and di-alkenylation products under the standard conditions using 1.5 equiv of **2a**, indicating high reactivity of the ferrocenyl C–H bonds. Indeed, the reaction of **9b** with 2 equiv of **2a** furnished the dialkenylation product **10b** in good yield (Scheme 4b). This observation is notable because Ackermann's catalytic system promoted exclusive mono-alkenylation of the same ferrocene substrate.[4c]



Scheme 4. C–H alkenylations directed by a 2-pyridyl group.

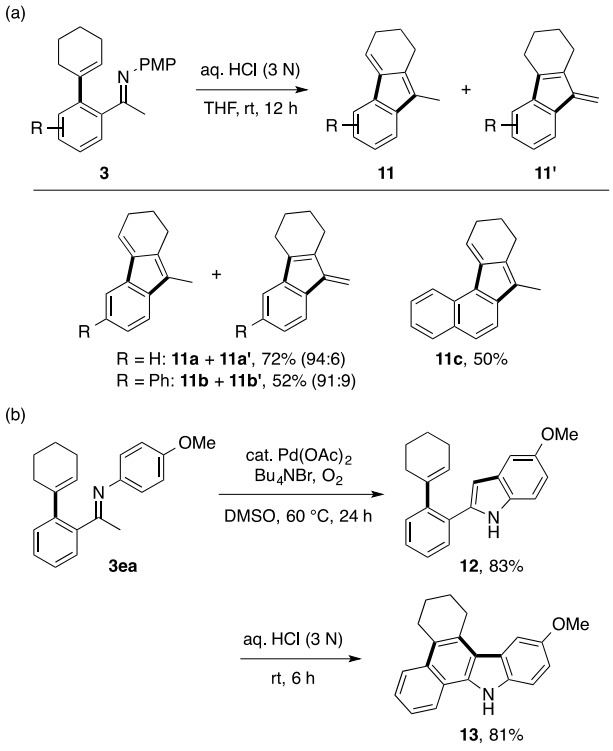
In order to gain insight into the nature of the C–H activation step in the present reaction, we performed kinetic isotope effect (KIE) experiments using a pentadeuterated imine **1e**-d_5 (Scheme 5). Prior to the KIE experiments, we confirmed that the reaction of **1e**-d_5 with **2a** under the standard conditions afforded the alkenylation product **3ea**-d_4 in a moderate yield (68%), without any loss of the remaining deuterium atoms on the aromatic ring. An intermolecular competition reaction of **1e** and **1e**-d_5 quenched at a reaction time of 10 min resulted in predominant alkenylation of the former, corresponding to a KIE value of 5.9 (Scheme 5a). Comparison of parallel independent reactions of **1e** and **1e**-d_5 also gave a smaller but substantial KIE value of 2.9 (Scheme 5b). While the KIE observed in the intermolecular competition would directly reflect the nature of C–H activation as the first irreversible step, the KIE determined by the parallel reactions would indicate that C–H activation is a major rate-controlling step of the present reaction.[17]

We assume that the present C–H alkenylation reaction shares some of key mechanistic features with other previously developed C–H/electrophile coupling reactions. First, an alkylcobalt species generated from the precatalyst and the Grignard reagent would undergo C–H metalation (cyclometalation) of the imine.[18] The resulting cobaltacycle intermediate would be intercepted by the alkenyl phosphate to afford the alkenylation product and a cobalt phosphate species. Transmetalation of the cobalt phosphate with the Grignard reagent would regenerate the alkylcobalt species. In Ackermann's alkenylation system, alkenyl acetate, which has higher C–O dissociation energy than alkenyl phosphate, behaved as a more reactive alkenylating agent.[4c] With this reactivity order and other observations, they proposed that the alkenylation would take place through migratory insertion of the alkenyl C=C bond to a cobaltacycle species followed by β-acetoxy elimination. Because our catalytic system was not effective for alkenyl acetates, we consider that the cobaltacycle intermediate in the present reaction would behave differently. Given the lack of stereochemical integrity with respect to the alkenyl phosphate (cf. **4ai**–**4ak** in Table 3), we suspect that the reaction may involve an electron transfer from the cobaltacycle intermediate to the alkenyl phosphate to form a radical species.



Scheme 5. Kinetic isotope effect experiments.

The C–H alkenylation products obtained from acetophenone-derived imines serve as unique precursors to benzofulvene derivatives, which have attracted much interest as synthetic intermediates for indene derivatives, precursors to metallocene complexes, and organic materials.[19] Thus, treatment of the *ortho*-cyclohexenylated imines **3** with aqueous HCl at room temperature caused intramolecular deaminative cyclization, thus affording tricyclic benzofulvenes **11a**–**11c** in respectable yields (Scheme 6a). Besides the acid-mediated intramolecular cyclization, one can also utilize the alkenyl and the imine groups of the alkenylation products in a different manner. To illustrate this point, two-step conversion of the alkenylated imine **3ea** to a fused carbazole derivative **13** was achieved through Pd-catalyzed aerobic dehydrogenative cyclization of the imine moiety to the indole **12**[20] followed by acid-mediated intramolecular Friedel–Crafts cyclization and subsequent aromatization (Scheme 6b).



Scheme 6. Transformation of the alkenylated products.

Conclusion

In conclusion, we have developed a cobalt–NHC-catalyzed *ortho* C–H alkenylation reaction of an aryl imine using an alkenyl phosphate as the alkenylating agent. The reaction was achieved by the elaboration of both the *N*-substituents and the backbone of 1,3-diarylimidazolium salt; the NHC precursors ^{Cy}IEt•HBr and ^{Cyh}IEt•HBr exhibited much higher catalytic efficiency than commercially available IMes and IPr derivatives. The present reaction not only tolerated a variety of aryl imines and alkenyl phosphates but also displayed unique regioselectivity for *meta*-substituted aryl imines, which would warrant further investigation. We anticipate that, as has been amply demonstrated for Pd–NHC catalysis,[8,21] elaboration of the NHC architecture would also lead to improvement of other C–H activation and related transformations promoted by low-valent cobalt catalysts.[22,23]

Experimental Section

Typical Procedure for *ortho*-Alkenylation of Aryl Imine

In a Schlenk tube were placed (*E*)-*N*-(3,4-dihydronaphthalen-1(2*H*)-ylidene)-4-methoxyaniline (**1a**, 75 mg, 0.30 mmol), ^{Cy}IEt•HBr (13.8 mg, 0.030 mmol), a freshly prepared THF solution of $CoBr_2$ (0.30 M, 0.10 mL, 0.030 mmol), and THF (0.25 mL). The resulting solution was cooled in an ice bath, followed by the addition of *t*-BuCH_2MgBr (1.5 M in THF, 0.40 mL, 0.60 mmol) and TMEDA (0.30 mL, 2.0 mmol). After stirring for 30 min, cyclohex-1-en-1-yl diisopropyl phosphate (**2a**, 108 µL, 0.45 mmol) was added. The resulting mixture was stirred at 40 °C for 12 h. The reaction was then quenched by the addition of HCl (3 N, 1.0 mL), and stirred for 1 h. The resulting mixture was extracted with EtOAc (5 mL x 3). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded 8-(cyclohex-1-en-1-yl)-3,4-dihydronaphthalen-1(2*H*)-one (**4aa**) as a light yellow oil (61 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 5.43–5.41 (m, 1H), 2.95 (t, *J* = 6.1 Hz, 2H), 2.62 (t, *J* = 6.8 Hz, 2H), 2.19–2.14 (m, 2H), 2.12–2.06 (m, 4H), 1.84–1.78 (m, 2H), 1.73–1.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.7, 147.2, 145.5, 142.1, 132.5, 130.7, 129.4, 127.7, 122.0, 40.8, 31.0, 30.4, 25.7, 23.4, 23.2, 22.4; HRMS (ESI) Calcd for $C_{16}H_{19}O$ $[M + H]^+$ 227.1436, found 227.1441.

Acknowledgements

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