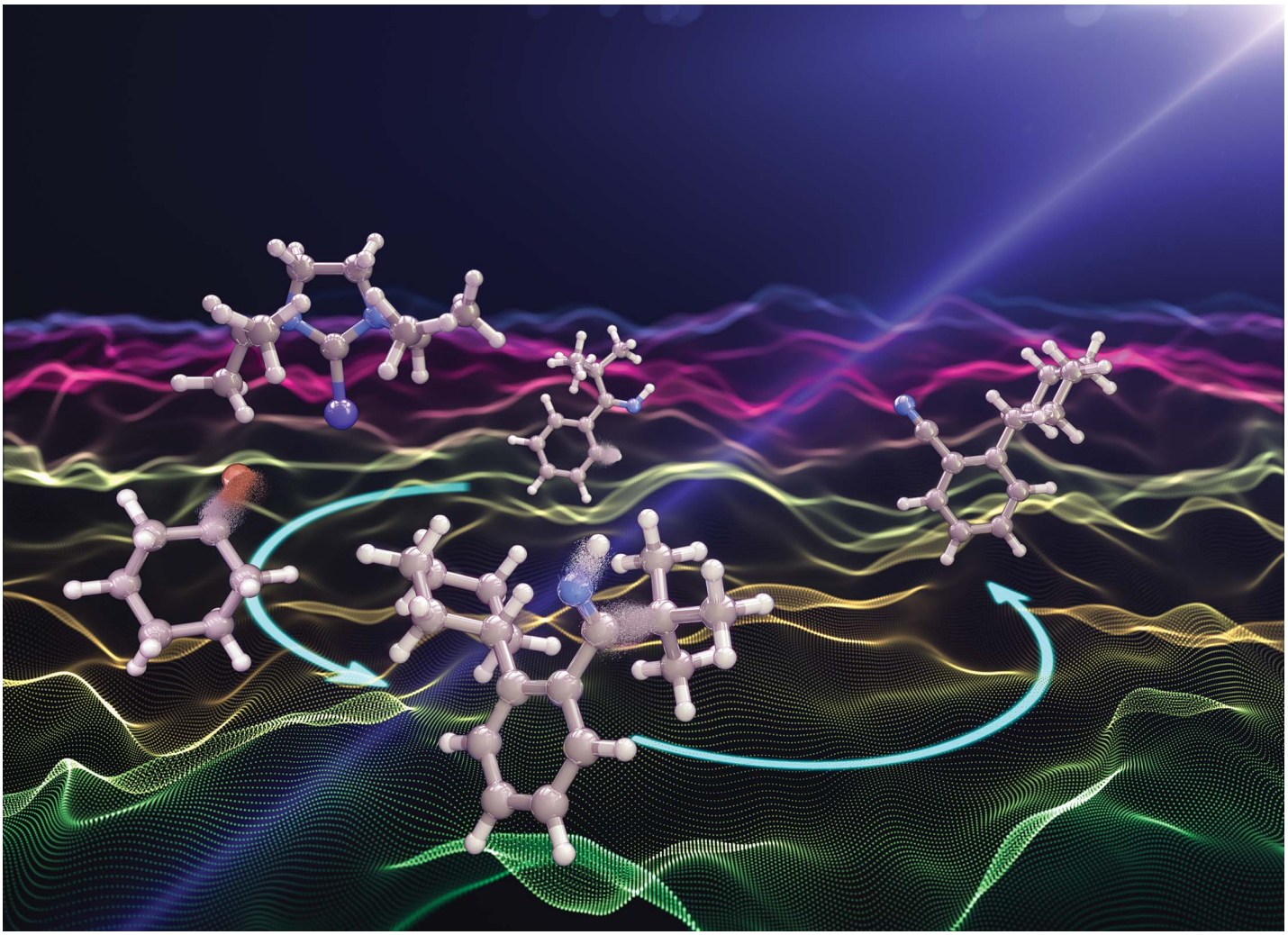

Showcasing research from Dr Naohiko Yoshikai's laboratory, Nanyang Technological University, Singapore.

Pivalophenone imine as a benzonitrile surrogate for directed C–H bond functionalization

Pivalophenone N–H imine was found to be an excellent substrate for ortho C–H alkylation and arylation reactions using the corresponding organic halides in the presence of cobalt–N-heterocyclic carbene catalysts. Owing to the increased steric crowding, the tert-butyl group and the hydrogen atom of the resulting ortho-substituted imine can be ripped off *via* a radical mechanism, enabling clean imine-to-nitrile conversion. Overall, the dual role of the pivaloyl imine as a directing and transformable group allows efficient access to ortho-substituted benzonitriles, for many of which no direct preparative method from benzonitrile exists.

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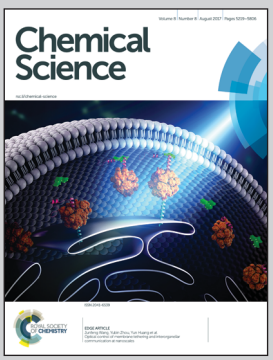

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Cite this: *Chem. Sci.*, 2017, **8**, 5299

Pivalophenone imine as a benzonitrile surrogate for directed C–H bond functionalization†

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Received 19th April 2017
Accepted 29th May 2017

DOI: 10.1039/c7sc01732d

rsc.li/chemical-science

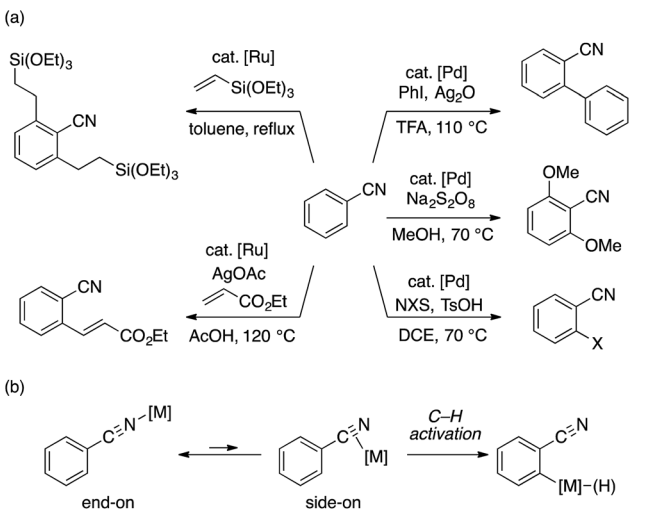
Pivalophenone N–H imine has been found to serve as a prominent substrate for directed C–H alkylation and arylation reactions with alkyl bromides and aryl chlorides, respectively, under cobalt–N-heterocyclic carbene (NHC) catalysis. Unlike the case of the parent pivalophenone imine, the increased steric bulk of the resulting *ortho*-substituted pivalophenone imines allows them to undergo clean imine-to-nitrile conversion under peroxide photolysis or aerobic copper catalysis conditions. Overall, these two-step transformations offer convenient synthetic methods for *ortho*-functionalized benzonitriles.

Introduction

Transition metal-catalyzed, directing group-assisted C–H bond activation represents a powerful means to transform C–H bonds into C–C and C–heteroatom bonds with predictable regioselectivity.[1] The utility of such transformations should largely depend on the availability and the versatility of the directing group. In this context, a cyano group can potentially be a very useful directing group, owing to its presence in a large number of commercial chemicals as well as to its applicability to various synthetic transformations. Following the seminal report of Murai and coworkers on the Ru-catalyzed addition of benzonitrile to vinylsilane,[2] several examples of *ortho*-functionalization of benzonitriles, such as Pd-catalyzed arylation,[3] alkoxylation,[4] halogenation,[5] and Ru-catalyzed olefination,[6] have been reported to date (Scheme 1a). However, expansion of the scope of such transformations appears nontrivial because of intrinsic competition between π- (side-on) and σ- (end-on) coordination modes of the cyano group, only the former being suitable for *ortho* C–H activation (Scheme 1b).[7] As such, the development of a readily accessible and transformable directing group that functions as a cyano group equivalent would be attractive.[8] This would be particularly the case for arene C–H alkylation using alkyl electrophiles, because, when compared to C–H arylation and olefination,[9] directing groups for this reaction manifold are still limited regardless of the recent progress made by palladium,[10] ruthenium,[11] nickel,[12] cobalt,[13] and iron[14] catalysts.[15]

Recently, we demonstrated that aryl N–H imines, typically derived from the corresponding aryl nitriles and organolithium or Grignard reagents, smoothly participate in the cobalt-catalyzed directed hydroarylation of alkenes (Scheme 2a),[16] which represents a rare example of N–H imine-directed C–H functionalization that results in the retention of the imine directing group.[17] On our way to extend the utility of the N–H imine as a directing group for C–H functionalization, we became interested in the potential utility of the N–H imine functional group as a nitrile surrogate. In particular, our attention was attracted to the seminal work of Ingold on the reaction of N–H imines under peroxide photolysis conditions (Scheme 2b).[18] Their study revealed that di-*tert*-butyl imine ((*t*-Bu)$_2$C = NH) undergoes facile fragmentation into pivalonitrile (*t*-BuCN) and *tert*-butyl radical, while sterically less hindered N–H imines undergo dimerization of the corresponding iminyl radicals to form azine derivatives.

Building on the above background, we have found that pivalophenone N–H imine serves as a benzonitrile surrogate for directed C–H functionalization reactions under cobalt



Scheme 1 Cyano group-directed arene C–H bond functionalizations: examples and intrinsic difficulty.

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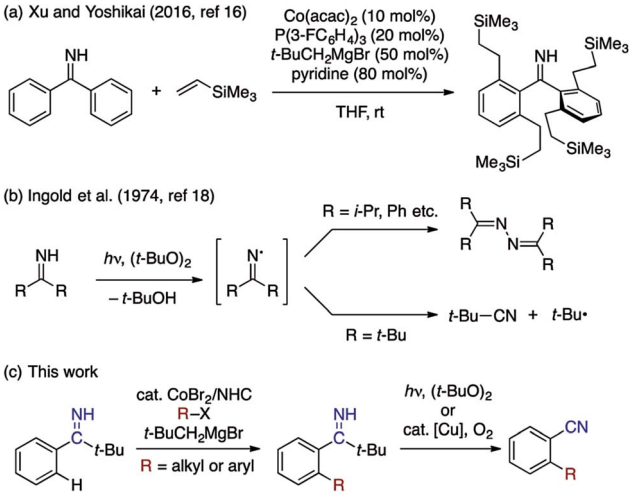
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7sc01732d



Scheme 2 N–H imine as directing and transformable functional group for cobalt-catalyzed C–H activation.

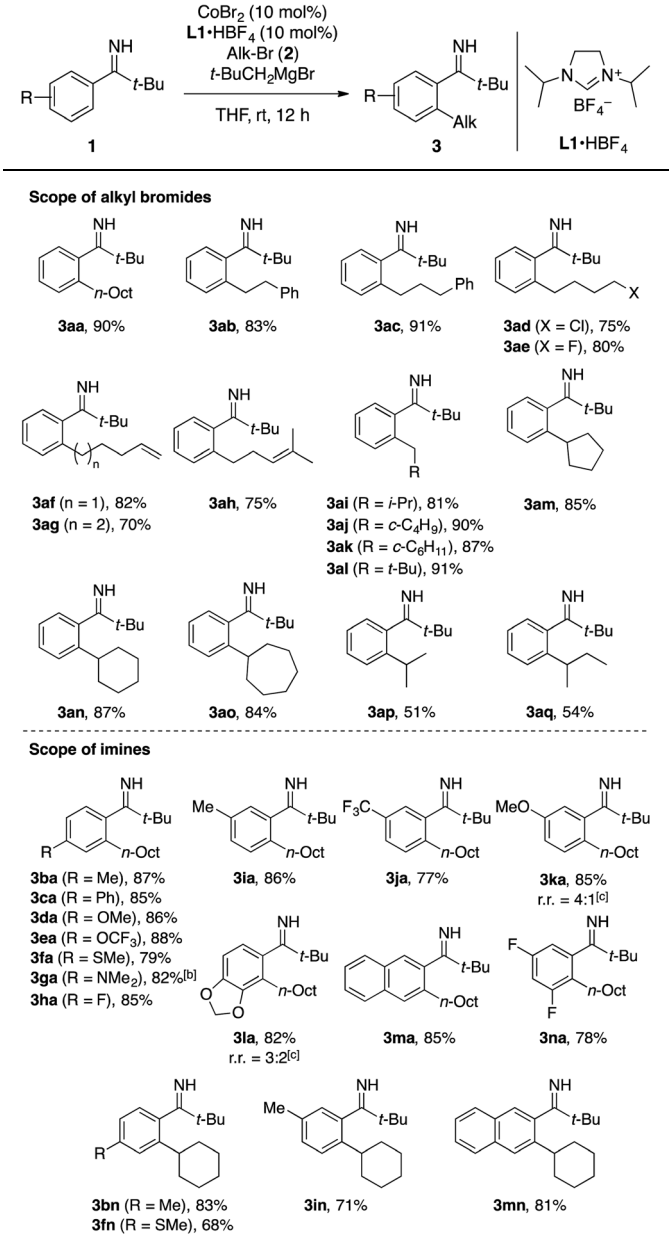
catalysis,[19] which is reported herein. Thus, the *tert*-butyl N–H imine group smoothly directs cobalt-catalyzed C–H alkylation[13] and arylation[20] with the corresponding organic halides, and then readily undergoes fragmentation into a cyano group under peroxide photolysis or aerobic copper catalysis (Scheme 2c). Interestingly, the fragmentation step has proved to become feasible only after the installation of the *ortho*-substituent, which prevents the undesirable iminyl radical dimerization. The overall process offers a complementary and convenient route to a variety of *ortho*-substituted aryl nitriles, especially *ortho*-alkylated aryl nitriles, for which no direct preparative method from the corresponding aryl nitriles exists.

Results and discussion

The feasibility of the C–H alkylation of pivalophenone N–H imine (**1a**) was initially explored using *n*-octyl bromide (**2a**, 1.5 equiv.) as an alkylating agent. As a result of screening experiments (Table S1†), a catalytic system comprising $CoBr_2$ (10 mol%), *N*,*N*′-diisopropylimidazolinium tetrafluoroborate (**L1**·HBF_4, 10 mol%), and *t*-$BuCH_2MgBr$ (2 equiv.) was found to promote the desired reaction at room temperature, exclusively affording the monoalkylation product **3aa** in 90% yield (Table 1). As was the case with previously reported cobalt-catalyzed C–H alkylation reactions,[13b–e] the choice of the imidazol(in)ium salt as an N-heterocyclic carbene (NHC) precursor was crucial. The reaction using *n*-octyl chloride instead of **2a** also afforded **3aa** albeit in a modest yield.

Table 1 summarizes the scope of the present C–H alkylation. The reaction of **1a** with various primary alkyl bromides afforded the corresponding monoalkylation products **3aa–3al** in good yields, tolerating alkyl chloride (**3ad**), alkyl fluoride (**3ae**), olefin moieties (**3af–3ah**), and bulky substituents at the α-position (**3ai–3al**). Note that the reaction of 6-bromo-1-hexene exclusively afforded the simple alkylation product **3ag**, while the analogous reaction using acetophenone *N*-aryl imine was accompanied by a ring-closing alkylation (cyclopentylmethylation) product.[13d]

Table 1 *ortho*-Alkylation of pivalophenone N–H imines[a]



[a] Reaction conditions: imine **1** (0.2 mmol), alkyl bromide **2** (1.5 equiv.), $CoBr_2$ (10 mol%), **L1**·HBF_4 (10 mol%), *t*-$BuCH_2MgBr$ (2 equiv.), THF, rt, 12 h. [b] The product was isolated in the form of ketone after acidic hydrolysis. [c] The major regioisomer is shown (r.r. = regioisomer ratio). The yield refers to the overall yield.

Cyclic and acyclic secondary alkyl bromides also reacted with **1a** to afford the corresponding products **3am–3aq** in moderate to good yields.

A variety of substituted pivalophenone imines participated in the C–H alkylation using *n*-octyl bromide, tolerating substituents such as methoxy, trifluoromethoxy, methylthio, dimethylamino, fluoro, and trifluoromethyl groups (see **3da–3ha** and **3ja**). Imines bearing methyl, trifluoromethyl, or methoxy group at the *meta* position and 2-naphthyl imine

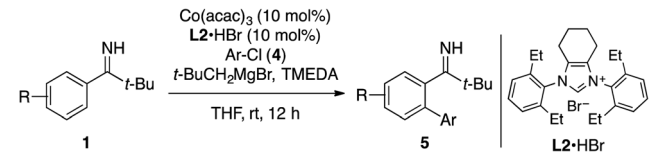
underwent exclusive or selective alkylation at the less hindered position (see **3ia–3ka** and **3ma**), whereas a 3,4-methylenedioxy group directed the reaction to take place preferentially at its proximity, albeit with modest regioselectivity (see **3la**). Unfortunately, *ortho*-substituted pivalophenone imine failed to participate in the reaction. Cyclohexylation reactions were also successfully performed using several substituted imines (see **3bn**, **3fn**, **3in**, and **3mn**). Note that, under the present conditions, the *n*-octylation reaction using valerophenone N–H imine instead of **1a** took place rather sluggishly (<30% yield).

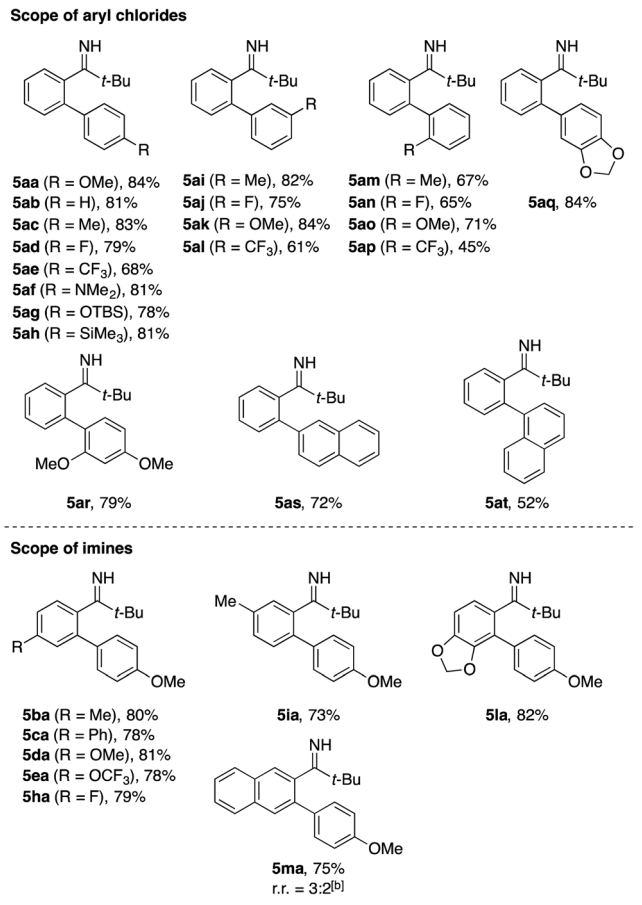
Next, we examined the feasibility of cobalt-catalyzed directed C–H arylation.[13c,e,20] Upon screening conditions for the coupling of imine **1a** with 4-chloroanisole (**4a**), imidazolium salt **L2**·HBr featuring 2,6-diethylphenyl groups and cyclohexyl backbone emerged as an effective NHC precursor among others such as commercially available IMes and IPr derivatives (see Table S2† for detail). Furthermore, the use of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) as an additive proved beneficial. Thus, a catalytic system comprised of these key components, $Co(acac)_3$, and *t*-$BuCH_2MgBr$ promoted the arylation reaction at room temperature, affording the desired biaryl **5aa** in 84% yield (Table 2). Note that the use of 4-bromoanisole instead of **4a** failed to produce **5aa** but resulted in the direct cross-coupling between 4-bromoanisole and *t*-$BuCH_2MgBr$.

Under the optimized conditions, **1a** reacted with various aryl chlorides to afford the corresponding biaryls **5ab–5at** in moderate to good yields, tolerating substituents including methoxy, dimethylamino, siloxy, fluoro, and trifluoromethyl groups. A series of substituted pivalophenone imines could also be arylated with 4-chloroanisole in good yields (see **5ba–5ma**). Note that the imine bearing a 3,4-methylenedioxy group underwent exclusive arylation at the proximal *ortho* position (see **5la**), in contrast to the modest regioselectivity observed for the alkylation of the same imine (see **3la** in Table 1). Also notable was the behavior of 2-naphthyl imine, which produced the arylation product **5ma** as a regioisomeric mixture while undergoing exclusive alkylation at the less hindered position (see **3ma** and **3mn**). As was the case with the C–H alkylation, *ortho*-substituted pivalophenone imine was reluctant to undergo the C–H arylation.

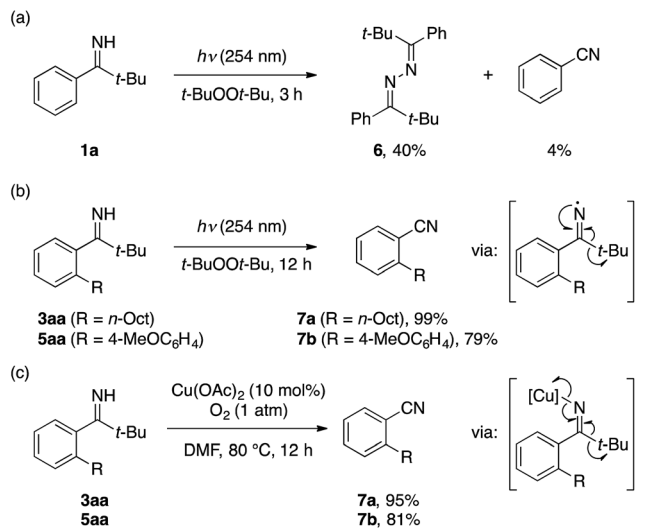
To probe the feasibility of the imine-to-nitrile conversion, we initially subjected **1a** to UV irradiation (254 nm) in di-*tert*-butyl peroxide. Not unexpectedly, the reaction mainly afforded azine **6** *via* dimerization of the iminyl radical, accompanied by only a trace amount of benzonitrile (Scheme 3a). In contrast, the *ortho*-alkylated imine **3aa** quantitatively furnished 2-alkylbenzonitrile **7a** under the same conditions (Scheme 3b). The *ortho*-arylated imine **5aa** also afforded 2-cyanobiaryl **7b**, albeit in somewhat lower yield (79%) due to the formation of 6-(*tert*-butyl)-3-methoxyphenanthridine as a byproduct *via* intramolecular cyclization of the iminyl radical.[21] Furthermore, alternative conditions employing catalytic $Cu(OAc)_2$ under O_2

Table 2 *ortho*-Arylation of pivalophenone N–H imines[a]





[a] Reaction conditions: imine **1** (0.2 mmol), aryl chloride **4** (1.5 equiv.), $CoBr_2$ (10 mol%), **L2**·HBr (10 mol%), *t*-$BuCH_2MgBr$ (2.5 equiv.), TMEDA (80 mol%), THF, rt, 12 h. [b] The major regioisomer is shown (r.r. = regioisomer ratio). The yield refers to the overall yield.

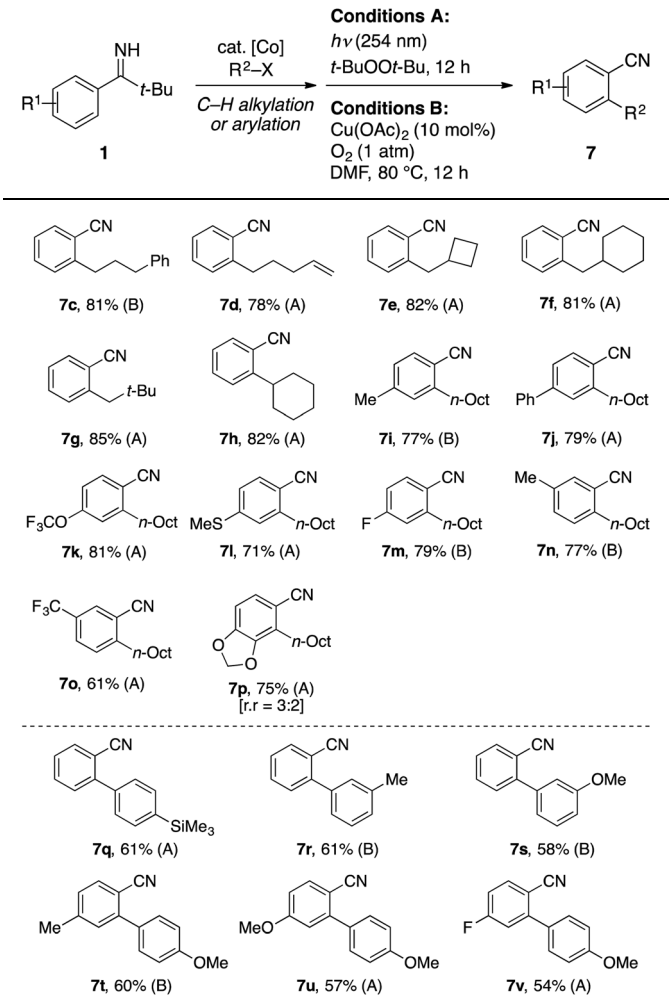


Scheme 3 Decomposition reactions of pivalophenone imines.

atmosphere, originally developed by Chiba for the conversion of 2-biaryl N–H imines to phenanthridines,[22] proved equally effective for the conversion of **3aa** and **5aa** to **7a** and **7b**, respectively, presumably *via* fragmentation of a putative iminylcopper species (Scheme 3c).

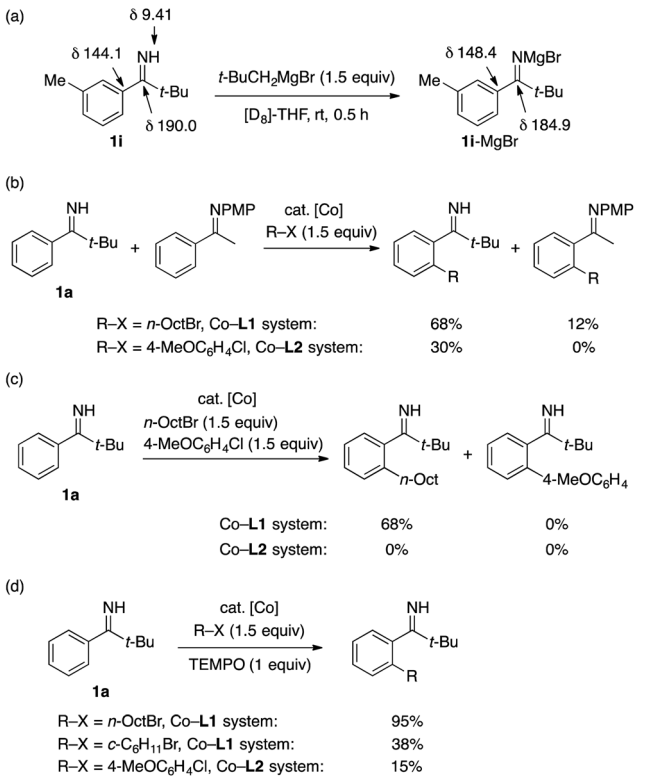
With the imine-to-nitrile conversion methods in hand, we explored two-step synthesis of *ortho*-alkylated or -arylated benzonitriles (Table 3). Thus, alkylation or arylation reactions of pivalophenone N–H imines were followed by submission of the crude products to the peroxide photolysis (A) or the aerobic copper catalysis (B). To our satisfaction, these protocols worked particularly well for the preparation of *ortho*-alkylbenzonitriles **7c–7p**, many of which were obtained in yields close to the yields of the corresponding C–H alkylation products (Table 1). On the other hand, the yields of the *ortho*-arylbenzonitriles **7q–7v** (*ca.* 60%) were apparently lower than that of the corresponding C–H arylation products (*ca.* 80%; Table 2), reflecting the lower efficiency of the second step.

Table 3 Two-step synthesis of *ortho*-substituted benzonitriles[a]



[a] See the ESI for the detailed procedure. The yields refer to overall yields based on **1**.

Several experiments were performed to gain mechanistic insight into the present reactions (Scheme 4). A treatment of imine **1i** in [D_8]-THF with excess *t*-BuCH_2MgBr caused a near complete disappearance of the N–H proton signal and a sizable chemical shift change of the C=N carbon in the ^{1}H and ^{13}C NMR spectra (Fig. S1†), indicating formation of a magnesium alkylideneamide species (Scheme 4a). This suggests that the alkylideneamide anion, rather than the parent N–H imine,[16,23] serves as the actual directing group for cobalt-mediated C–H activation, as is also the case for cobalt-catalyzed, secondary amide-directed C–H alkylation and arylation.[13a,20c] The superiority of this anionic directing group to an *N*-aryl imine directing group[13b,20a] was demonstrated for both the alkylation and arylation reactions by competition experiments (Scheme 4b). The reaction of **1a** with a mixture of *n*-octyl bromide and 4-chloroanisole exclusively afforded the alkylation product under the Co–**L1** system (Scheme 4c), which is consistent with the inability of **L1** to promote the C–H arylation reaction (Table S2†). By contrast, the same reaction under the Co–**L2** system produced none of the C–H functionalization products, presumably due to the interference of the C–H activation step by *n*-octyl bromide. The addition of TEMPO caused no apparent interference with the C–H alkylation using *n*-octyl bromide but substantially inhibited the reactions of cyclohexyl bromide and 4-chloroanisole (Scheme 4d). These observations suggest that, at least for the latter two cases, single electron transfer is involved in the carbon–halogen bond cleavage.[13,19a–d]



Scheme 4 Mechanistic experiments (PMP = *p*-methoxyphenyl). The yields in Scheme **4b–d** were determined by GC using *n*-tridecane as an internal standard.

Conclusions

In summary, we have demonstrated that pivalophenone N–H imine serves as an excellent substrate for the cobalt-catalyzed directed C–H alkylation and arylation reactions with alkyl bromides and aryl chlorides, respectively. Owing to the added steric bulk in the *ortho* position, the resulting unpurified *ortho*-alkylated or -arylated pivalophenone imines undergo clean fragmentation of the imine functionality to afford the corresponding *ortho*-functionalized aryl nitriles. The present two-step protocol would be particularly attractive for the preparation of *ortho*-alkylated aryl nitriles, which have not been directly accessed from the corresponding aryl nitriles *via* C–H activation. We anticipate that pivalophenone N–H imine could be exploited as a benzonitrile surrogate not only for cobalt catalysis but also for other transition metal-catalyzed C–H functionalization reactions under mild conditions.[24] Studies in this direction are ongoing in our laboratory.

Acknowledgements

This work was supported by the Singapore Ministry of Education, Nanyang Technological University (RG 5/14, RG 114/15), and JST, CREST. We thank Dr Pin-Sheng Lee for the preparation of NHC precursors including **L2**·HBr.

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