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Conference paper

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Cobalt-catalyzed directed alkylation of arenes with primary and secondary alkyl halides[1]

Abstract: A cobalt–*N*-heterocyclic carbene catalyst allows ortho-alkylation of aromatic imines with unactivated primary and secondary alkyl chlorides and bromides under room-temperature conditions. The scope of the reaction encompasses or complements that of cobalt-catalyzed ortho-alkylation reactions with olefins as alkylating agents that we developed previously. Stereochemical outcomes of secondary alkylation reactions suggest that the reaction involves single-electron transfer from a cobalt species to the alkyl halide to generate the corresponding alkyl radical. A cycloalkylated product obtained by this method can be transformed into unique spirocycles through manipulation of the directing group and the cycloalkyl groups.

Keywords: alkylation; C–H functionalization; cobalt; imines.

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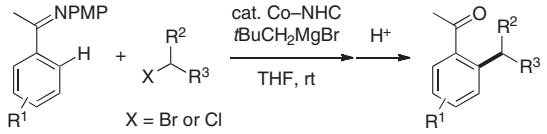
Introduction

It has been two decades since the group of Murai, Kakiuchi, and Chatani reported their groundbreaking work on ruthenium-catalyzed ortho-alkylation of aromatic ketones with olefins [1]. This olefin hydroarylation reaction features ketone-directed oxidative addition of the ortho C–H bond to ruthenium as one of key elementary steps, and has opened a new opportunity for regioselective aromatic alkylation that goes beyond the conventional Friedel–Crafts chemistry. The scope of the directing group-assisted olefin hydroarylation has been significantly expanded by further development of not only ruthenium catalysts but also rhodium and other transition-metal catalysts [2]. Over the past several years, our group has demonstrated competence of cobalt catalysts for such transformations through the development of a series of pyridine- or imine-directed olefin hydroarylation reactions [3, 4], which often feature mild reaction conditions and/or unique regioselectivity. However, regardless of the two decades of development, there exists a common limitation in this type of aromatic alkylation. Except for some limited cases [5, 6], secondary alkylation is not feasible for several reasons, such as anti-Markovnikov selectivity for terminal olefins, rapid isomerization of olefins containing allylic hydrogens, and intrinsically low reactivity of multisubstituted olefins. In addition, some olefins such as cyclobutene are not readily available from commercial sources.

In the past several years, an alternative ortho-alkylation strategy using alkyl halides as alkylating agents has emerged [7]. However, even with this strategy, secondary alkylation has not been trivial, presumably because of poor reactivity of secondary alkyl halides toward oxidative addition. Indeed, only limited examples of secondary alkylation have been reported for representative catalytic systems, including ruthenium catalysis of 2-arylpyridines and aryl imines, cobalt catalysis of benzamides, and palladium catalysis of arenes bearing a bidentate nitrogen-directing group [8]. Herein, we report on a significant expansion of the scope of this alkylation strategy achieved with a cobalt–*N*-heterocyclic carbene (NHC) catalytic system, which allows ortho-alkylation of aromatic imines using a variety of unactivated primary and secondary alkyl chlorides and bromides under mild conditions (Scheme 1) [9].



Scheme 1 Cobalt–NHC-catalyzed ortho-alkylation of aryl imine with alkyl chloride or bromide.

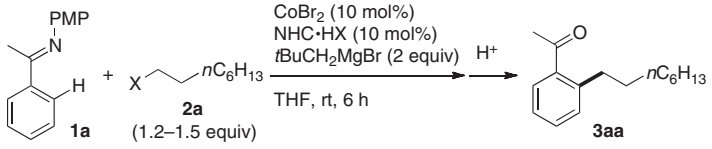
Optimization of cobalt–NHC catalyst

With the above background and our previous studies on cobalt–NHC-catalyzed ortho C–H functionalization using electrophiles such as aryl aldimines and aryl chlorides [10–12], we initiated the present study with optimization of the alkylation reaction using acetophenone imine **1a** and *n*-octyl chloride **2a** under a catalytic system consisting of $CoBr_2$ (10 mol%), NHC preligand (10 mol%), and neopentylmagnesium bromide (2 equiv) (Table 1). While popular NHC derivatives such as IMes·HCl (1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride) and IPr·HCl (1,3-bis(2,6-diisopropylphenyl)imidazolium chloride) performed only modestly (entries 1–3), simple diisopropylimidazolinium salt **L1** and its benzo-fused analogue **L4** significantly improved the yield of the alkylation product **3aa** (entries 4 and 7). Diisopropylimidazolium salt **L2** and di(*tert*-butyl)imidazolinium salt **L3** gave rise to much reduced catalytic activities (entries 5 and 6). The catalytic systems with **L1** and **L4** also efficiently promoted the reaction using *n*-octyl bromide instead of *n*-octyl chloride (entries 8 and 9). In contrast, the yield became significantly lower with *n*-octyl iodide because it largely decomposed through dehydrohalogenation (entries 10 and 11).

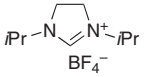
Primary and secondary alkylations

With the optimized catalytic systems in hand, we first explored alkylation of acetophenone imine **1a** using primary alkyl chlorides and bromides (Scheme 2). The reaction using *n*-hexyl bromide **2b** proceeded efficiently on a 10 mmol scale, affording the corresponding alkylation product in 77 % yield. Alkyl halides with

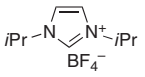
Table 1 Cobalt-catalyzed ortho-alkylation of acetophenone imine **1a** with *n*-octyl halide.



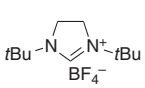
Entry	X	NHC·HX	Yield (%)[a]
1	Cl	IMes·HCl	38
2	Cl	SIMes·HCl	20
3	Cl	IPr·HCl	13
4	Cl	**L1**	64
5	Cl	**L2**	38
6	Cl	**L3**	14
7	Cl	**L4**	82[b]
8	Br	**L1**	79[b]
9	Br	**L4**	57
10	I	**L1**	14
11	I	**L4**	6



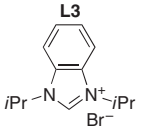
L1



L2

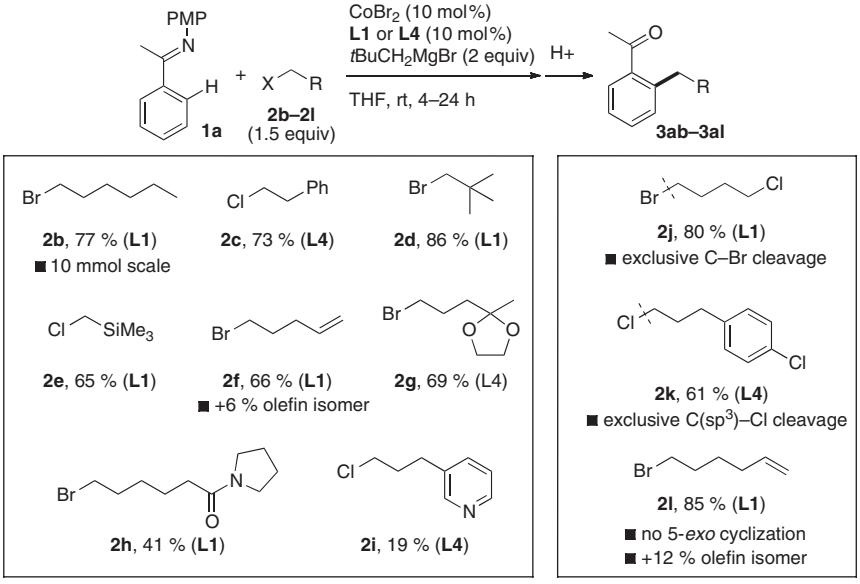


L3



L4

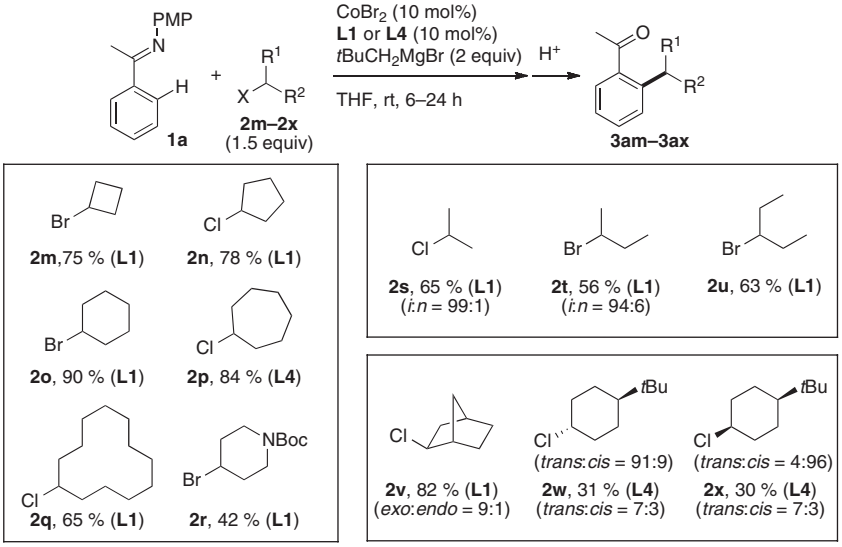
[a]Determined by GC using n-tridecane as an internal standard. [b]Isolated yield.



Scheme 2 Scope of primary alkyl chlorides and bromides.

steric hindrance around the β-position (**2d** and **2e**) or functional groups such as olefin (**2f**), acetal (**2g**), and secondary amide (**2h**) could be tolerated, while the reaction becomes sluggish in the presence of a coordinating pyridyl moiety in the alkyl chloride (**2i**). Reactions using dihalogenated reactants showed notable chemoselectivities. Thus, 1-bromo-4-chlorobutane **2j** reacted exclusively at the C–Br bond in good yield, the C–Cl bond being entirely intact. Exclusive cleavage of an alkyl chloride moiety was also achieved in the presence of an aryl chloride moiety (**2k**). In addition, 6-bromohexene **2l**, a potential source of 5-hexenyl radical, afforded a simple alkylation product and its internal olefin isomer as the major and minor products, respectively, but did not produce any products arising from 5-exo cyclization.

The present catalytic systems also allowed ortho-alkylation with a variety of secondary alkyl chlorides and bromides (Scheme 3). Cycloalkyl halides of various ring sizes (**2m–2q**) participated in the reaction to afford the corresponding alkylation products in moderate to good yields. The reaction tolerated



Scheme 3 Scope of secondary alkyl chlorides and bromides.

4-bromo-*N*-Boc-piperidine **2r** albeit in a modest yield. The reaction of acyclic alkyl halides **2s–2u** also produced the desired secondary alkylation products in moderate yields along with minor amount of primary isomers. *Exo*-chloronorbornane **2v** afforded the *exo*-arylation product as the major product with the exo/endo ratio of 9:1. *Trans*- and *cis*-isomers of 1-chloro-4-*tert*-butylcyclohexane (**2w** and **2x**) both afforded a mixture of *trans*- and *cis*-arylation products with the same *trans*/*cis* ratio of 7:3. Thus, these stereochemical probes demonstrate that the reaction is not stereospecific and suggest involvement of a radical intermediate (vide infra).

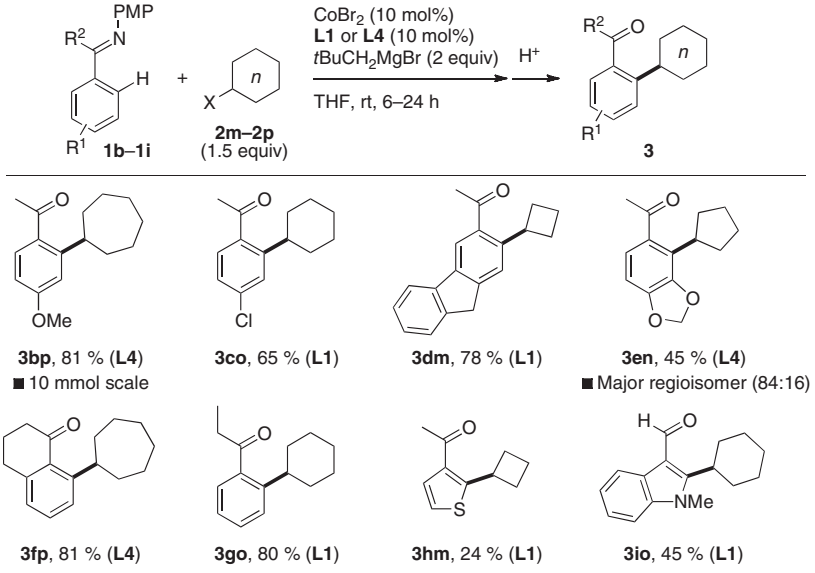
Next, the scope of aryl imines was explored using cycloalkyl halides as the reaction partners (Scheme 4). The reaction of imine derived from 4-methoxyacetophenone with cycloheptyl chloride was achieved on a 10 mmol scale to afford the product **3bp** in 81 % yield. The regioselectivity of C–H functionalization of unsymmetrically substituted imines appears to be governed by a steric factor for the case of imine derived from 3-acetylfluorene (see **3dm**) and by secondary coordination of the oxygen atom for the case of imine bearing a methylenedioxy group at the 3,4-position (see **3en**). Heteroaromatic C–H bonds of thiophene and indole could also be alkylated albeit in modest yields (see **3hm** and **3io**).

Derivatization of alkylation product

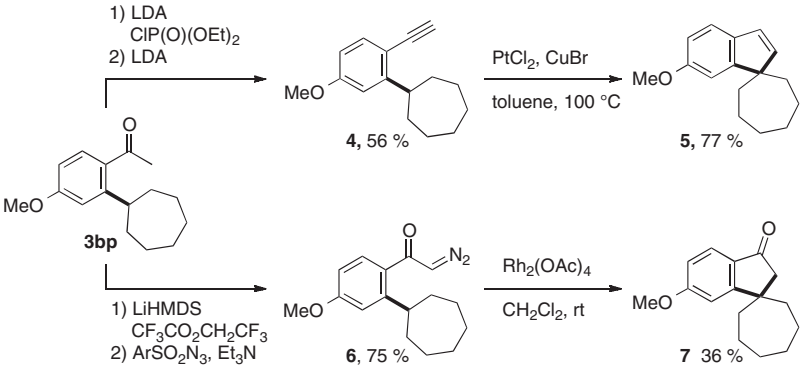
The product of the cycloalkylation reaction, **3bp**, could be transformed into unique spirocycles by making use of both the acetyl and the cycloalkyl groups (Scheme 5). Conversion of the acetyl group into an ethynyl group via an enol phosphate was followed by platinum-catalyzed carbocyclization, affording a spirocyclic indene **5** in a moderate overall yield of 43 % [13]. A sequence of diazo transfer to the acetyl group and rhodium-catalyzed intramolecular C–H insertion allowed preparation of a spirocyclic indanone **7** albeit in a low overall yield.

Mechanistic consideration

On the basis of our experimental observations as well as previous studies of Yorimitsu and Oshima on cobalt-catalyzed C–C bond formation involving alkyl halides and Grignard reagents [14], we propose a mechanistic framework involving radical processes (Scheme 6). The reaction of the cobalt precatalyst and the Grignard



Scheme 4 Ortho-alkylation of various aryl imines with cycloalkyl halides.

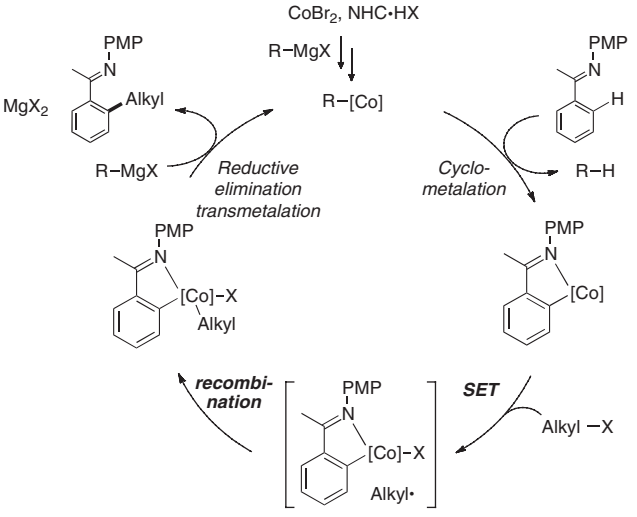


Scheme 5 Transformation of cycloalkylation product **3bp** into spirocyclic compounds.

reagent initially generates a low-valent organocobalt species, which undergoes cyclometalation of the aryl imine to afford a cobaltacycle species while liberating an alkane (R–H) [15]. The cobaltacycle species then undergoes single-electron transfer to the alkyl halide, which results in one-electron oxidation of the cobalt center and generation of an alkyl radical. Recombination of this radical pair is followed by reductive elimination and transmetalation with the Grignard reagent, affording the ortho-alkylation product and regenerating the initial cobalt species. The radical-based mechanism is consistent with the reaction outcomes of the stereochemical probes (Scheme 3) [16]. For the reaction of 6-bromohexene that afforded the simple alkylation product (Scheme 2), we speculate that the radical recombination took place at a faster rate than the 5-exo cyclization [17].

Summary

In summary, we have developed cobalt–NHC catalytic systems for ortho-alkylation of aromatic imines with alkyl halides. The reaction is applicable to a variety of primary and secondary alkyl chlorides and bromides, and features notable chemoselectivity, mild room-temperature conditions, and reasonable scalability for laboratory-scale synthesis [18]. The proposed mechanism features the combination of cyclometalation and electron-transfer processes, which may hold promise for further development of stereoselective alkylation reactions with racemic alkyl halides.



Scheme 6 Proposed catalytic cycle for the cobalt-catalyzed ortho-alkylation.

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