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Cobalt-Catalyzed Tandem Radical Cyclization/C−C Coupling Initiated by Directed C−H Activation

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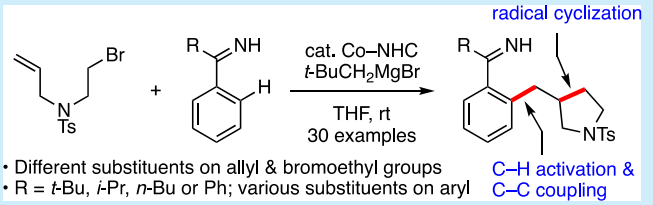
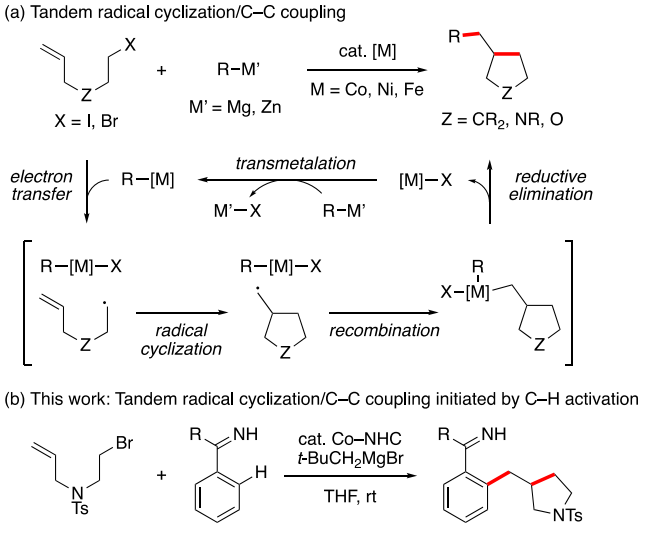
Supporting Information

ABSTRACT: A cobalt−N-heterocyclic carbene catalyst promotes a tandem radical cyclization/C−C coupling reaction between tosylamide-tethered bromo-alkenes and aryl N−H imines initiated by chelation-assisted arene C−H activation, affording 3-(arylmethyl)pyrrolidine derivatives in moderate to good yields. The reaction tolerates a variety of substituents on the aryl imine as well as various modifications on the bromo-alkene substrate.



The transition-metal-catalyzed 1,2-dicarbofunctionalization of unactivated alkenes with organic electrophiles and organometallic reagents represents an attractive transformation to increase molecular complexity in a single operation.[1] The tandem radical addition/transition-metal-mediated cross-coupling has emerged as a powerful approach to achieve such transformations,[2] especially for carbo- and heterocycle synthesis (Scheme 1a). A prototypical mechanistic scenario for

Scheme 1. Transition-Metal-Catalyzed Tandem Radical Cyclization/C−C Coupling



this type of reaction involves single electron transfer (SET; or halide abstraction) between an organotransition metal species and a tethered halo-alkene, radical cyclization, recombination of the resulting radical and the transition metal species, and C−C reductive elimination. This concept was demonstrated by Oshima for cobalt-catalyzed tandem radical cyclization/cross-couplings with various Grignard reagents.[3] The scope of the tandem radical cyclization/C−C coupling has been further extended using nickel[4] or iron[5] catalysts and organozinc or Grignard reagents, allowing access to pharmaceutical- and natural-product-relevant pyrrolidine, tetrahydrofuran, and γ-butyrolactone derivatives.[6] Analogous tandem transformations have also been achieved in a reductive fashion using organic iodides or bromides and zinc in place of preformed organometallic reagents.[7] Herein, we report that an arene bearing a directing group can be used as a viable coupling partner for the tandem radical cyclization/C−C coupling manifold (Scheme 1b). Thus, a cobalt−N-heterocyclic carbene (NHC) catalyst promotes a coupling reaction between a tosylamide-tethered bromo-alkene and an aryl N−H imine, which is initiated by imine-directed C−H activation and affords a 3-benzylated pyrrolidine derivative in moderate to good yield.

Over the past several years, chelation-assisted arene C−H alkylation reactions using alkyl halides and pseudohalides have been developed using various transition metal catalysts including cobalt,[8] nickel,[9] iron,[10] manganese,[11] palladium,[12] and ruthenium,[13] which have allowed regioselective functionalization of arenes with primary and secondary alkyl groups. Among them, the reactions catalyzed by first-row transition metals have been proposed to involve generation of an alkyl radical from the alkyl halide. As a mechanistic probe to support the radical intermediate, 6-bromohex-1-ene was often used to afford a mixture of cyclized and uncyclized C−H alkylation products, albeit in varying ratios depending on the catalytic system and the arene substrate.[8e,9c−f,10b−d,11a] For example, our previously developed cobalt-catalyzed, imine-directed C−H alkylation reactions gave the uncyclized product as the major or even the sole product.[8d−f] We reasoned that this

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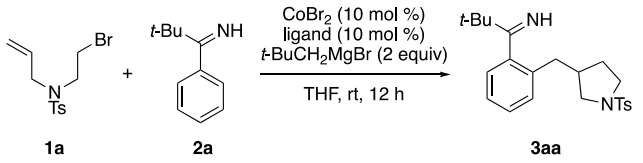
chemoselectivity could be reversed for a bromo-alkene with a bulkier tether group (Z), thus allowing for selective tandem radical cyclization/C−C coupling.

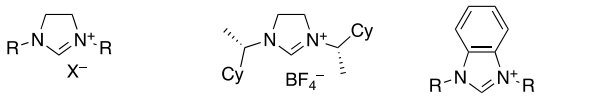
The present study commenced with screening of reaction conditions for the coupling between *N*-allyl-*N*-(2-bromoethyl)-*p*-toluenesulfonamide (**1a**, 0.3 mmol) and pivalophenone N−H imine (**2a**, 0.2 mmol) (Table 1; see Scheme S1 and Table S1 for full details). A catalytic system comprised of $CoBr_2$ (10 mol %), *N*,*N*′-diisopropylimidazolinium tetrafluoroborate (**L1**·HBF_4, 10 mol %), and *t*-BuCH_2MgBr (2 equiv), which was the optimum system for the *ortho*-alkylation of pivalophenone N−H imines,[8f] afforded the desired product **3aa** in 44% yield (entry 1). The reaction was accompanied by several byproducts. Thus, the imine **2a** also underwent *ortho*-alkylation with **1a** without cyclization (6%) and *ortho*-neopentylation with *t*-BuCH_2MgBr (20%). Meanwhile, **1a** underwent dehydrobrominative cyclization and reductive cyclization to afford 3-methylene-1-tosylpyrrolidine and 3-methyl-1-tosylpyrrolidine (22% combined yield). GCMS analysis also indicated the formation of a small amount (2%) of 3-(3,3-dimethylbutyl)-1-tosylpyrrolidine, which likely formed via tandem radical cyclization/cross-coupling with *t*-BuCH_2MgBr. Regardless of the complexity of the side reactions, which were difficult to suppress completely, modification of the NHC ligand allowed us to improve the yield of the desired tandem reaction. Thus, replacement of the *i*-Pr groups of **L1** with bulkier secondary alkyl groups was found to increase the yield of **3aa** (entries 2−5). In particular, NHCs bearing 3-pentyl groups (**L4**) and cyclohexylethyl groups (**L5**) afforded **3aa** in more than 60% yield. Using **L5**, the yield of **3aa** was further improved to 74% by lowering the concentration (entry 6). As expected from the radical cyclization mechanism, **L5** caused no asymmetric induction in the cyclization and afforded **3aa** as a racemic mixture. The use of NHCs bearing either primary alkyl or tertiary alkyl groups led to a diminished yield of **3aa**. Besides the *N*,*N*′-dialkylimidazolinium salts, analogous benzimidazolium salts also displayed comparable performance (entries 7 and 8), whereas common NHCs such as IMes and IPr completely shut down the desired reaction (entries 9 and 10). It should be noted that chloro- and iodo-analogues of **1a** afforded only a trace amount of **3aa**. The C−Cl bond cleavage of the former was rather sluggish, while the latter predominantly underwent cyclization without engaging **2a**.

With the optimized conditions (Table 1, entry 6) in hand, we explored the reaction of **1a** with various N−H imine substrates (Scheme 2). A variety of substituted pivalophenone N−H imines participated in the reaction to afford the desired products **3aa**−**3ao** in moderate to good yields, with tolerance to substituents such as methyl, methoxy, trifluoromethoxy, fluoro, chloro, and trifluoromethyl groups. The reaction of the

Table 1. Effect of Ligands[a]



1a **2a** **3aa**



L1·HBF_4 (R = *i*-Pr)
L2·HCl (R = Cy)
L3·HBF_4 (R = *sec*-Bu)
L4·HBF_4 (R = 3-pentyl)

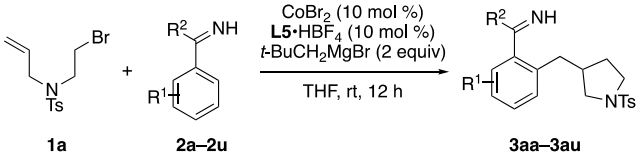
L5·HBF_4

L6·HBr (R = *i*-Pr)
L7·HBr (R = 3-pentyl)

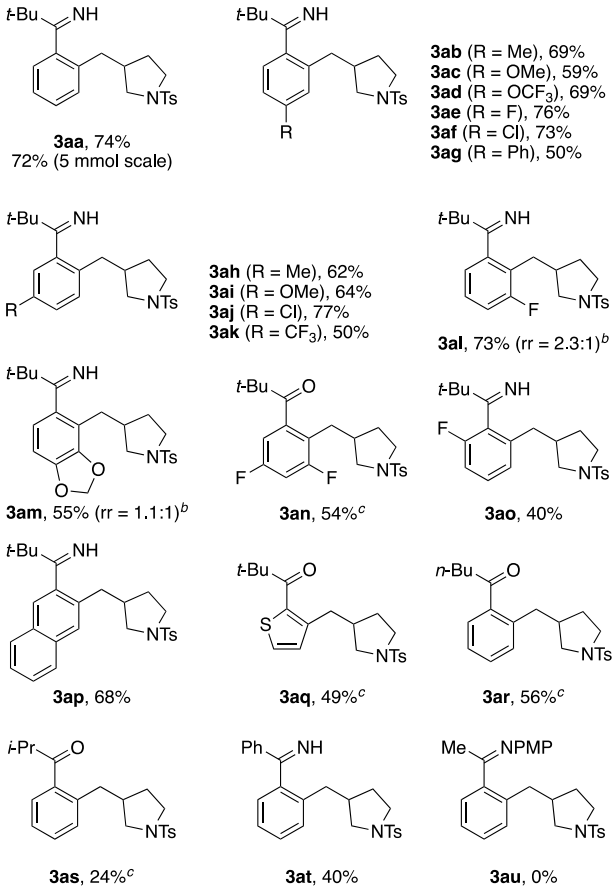
entry	ligand	yield (%)[b]
1	**L1**·HBF_4	44
2	**L2**·HCl	54
3	**L3**·HBF_4	45
4	**L4**·HBF_4	64
5	**L5**·HBF_4	68
6[c]	**L5**·HBF_4	74
7	**L6**·HBr	51
8	**L7**·HBr	62
9	IMes·HCl	0
10	IPr·HCl	0

[a]The reaction was performed using 0.3 mmol of **1a** and 0.2 mmol of **2a** (0.2 M). [b]Determined by GC using *n*-tridecane as an internal standard. [c]The reaction was performed at 0.08 M.

Scheme 2. Reaction of 1a with Various N−H Imines[a]



1a **2a–2u** **3aa–3au**



[a]The reaction was performed on a 0.2 mmol scale under the conditions in Table 1, entry 6. [b]The major regioisomer is shown (rr = regioisomer ratio). [c]The product was obtained after acidic hydrolysis of the crude reaction mixture.

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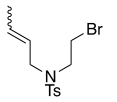
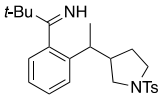
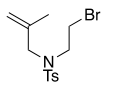
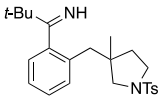
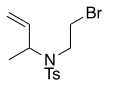
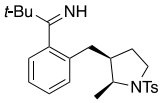
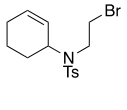
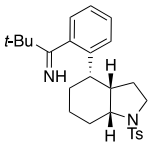
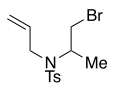
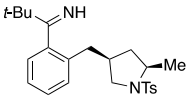
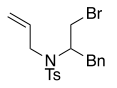
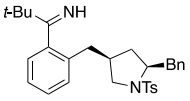
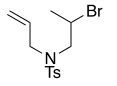
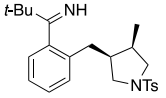
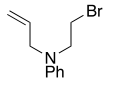
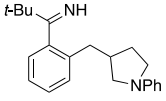
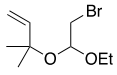
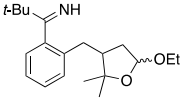
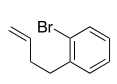
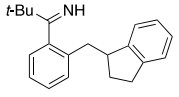
parent pivalophenone imine could be performed on a 5 mmol scale without an apparent decrease in the yield of **3aa**. The C−H activation took place at the less hindered position for the imines bearing a methyl, methoxy, chloro, or trifluoromethyl group at the *meta*-position (see **3ah**−**3ak**). On the other hand, the *meta*-fluoro-substituted imine afforded a mixture of two regioisomers (see **3al**) with preference for the product of proximal C−H activation, presumably due to the secondary directing effect of the fluorine atom. A 3,4-methylenedioxy group also caused competitive formation of two regioisomers (see **3am**). While the imine bearing an *ortho*-methyl group failed to participate in the reaction (data not shown), the one bearing an *ortho*-fluorine atom afforded the desired product **3ao** in moderate yield. 2-Naphthyl imine underwent exclusive C−H activation at the less hindered 3-position (see **3ap**), and 2-thienyl imine was also amenable to the tandem reaction (see **3aq**). Besides *tert*-butyl N−H imine, primary and secondary alkyl N−H imines as well as benzophenone N−H imine also served as directing groups for the present reaction, affording the products **3ar**−**3at** albeit in moderate yields. By contrast, acetophenone N-PMP (*p*-methoxyphenyl) imine failed to participate in the present reaction.

Next, we explored the reaction between **2a** and various bromoalkene substrates (Table 2). NTs-tethered substrates bearing substituted allyl groups such as crotyl, methallyl, 1-buten-3-yl, and cyclohexen-3-yl groups underwent the radical cyclization/arylation to afford the desired products **3ba**−**3ea** in respectable yields (entries 1−4). The diastereoselectivity for the *N*-crotyl substrate, which should be determined in the arylation step, was moderate (1.4:1; entry 1). The *N*-(1-buten-3-yl) substrate afforded the *cis*-isomer as the major product in a 2:1 ratio (entry 3). The *N*-(cyclohexen-3-yl) substrate afforded **3ea** as a single diastereomer as a result of *cis*-fusing cyclization and diastereoselective arylation (entry 4). The present tandem reaction also tolerated modification on the bromoethyl group of the tosylamide substrate, as exemplified by the formation of 2,4-disubstituted or 3,4-disubstituted pyrrolidines **3fa**−**3ha** in 52−66% yields, with the *cis* isomers being the major products (entries 5−7). In general, the diastereoselectivities of these reactions are comparable to that of analogous pyrrolidine-forming radical cyclization reactions,[7c,14] and may be rationalized by the Beckwith−Houk model.[15] The N-Ts group could be replaced by an N-Ph group without significantly affecting the reaction efficiency (entry 8). An acetal oxygen-tethered bromo-alkene underwent efficient tandem cyclization/arylation to afford the tetrahydrofuran derivative **3ja** in high yield (entry 9). 1-Bromo-2-(but-3-en-1-yl)benzene afforded the 1-benzylindane derivative **3ka** in a moderate yield, presumably via the corresponding aryl radical (entry 10). It is worthwhile to comment on byproducts observed in some of the low-yielding examples (see Scheme S2 for detail). The products **3ba** and **3ea** were accompanied by substantial amounts of dehydrobrominative and/or reductive cyclization products, while **3ca** formed together with a nearly equal amount of the uncyclized C−H alkylation product. These problems may be attributed to the sluggishness of the secondary alkylation (for **3ba** and **3ea**) and radical cyclization onto the disubstituted olefinic carbon (for **3ca**). Note that the reaction using 6-bromohex-1-ene under the present conditions predominantly afforded the direct alkylation product, along with a small amount (<10%) of the cyclized product (see Scheme S3 for this and other unsuccessful examples).

Table 2. Reaction of Various Bromo-alkenes with 2a[a]

entry	bromo-alkene	product		yield (%)[b]
1[c]			**3ba**	46 (1.4:1)
2			**3ca**	46
3			**3da**	61 (2.0:1)
4			**3ea**	31
5			**3fa**	66 (5.6:1)
6			**3ga**	62 (5.0:1)
7			**3ha**	52 (3.0:1)
8			**3ia**	62
9			**3ja**	80 (1.7:1)
10			**3ka**	41

[a]The reaction was performed on a 0.2 mmol scale under the conditions in Table 1, entry 6. [b]The diastereomer ratio, determined by ^{1}H NMR, is shown in the parentheses. For entries 3−7, the major diastereomer (shown) was assigned by 2D NMR. [c]The *E*/*Z* ratio of the bromo-alkene was 5.3:1.

The present cyclization products are amenable to radical decomposition of the pivaloyl N−H imine group to a cyano group.[8f] Thus, the *ortho*-iminobenzyl pyrrolidines **3aa**, **3af**, and **3ao** could be readily converted to the corresponding *ortho*-cyanobenzyl derivatives in good yields in the presence of a $Cu(OAc)_2$ catalyst under an oxygen atmosphere (Scheme 3).[16]

Scheme 4 shows a proposed catalytic cycle of the present tandem radical cyclization/arylation via C−H activation. In the presence of excess *t*-$BuCH_2MgBr$, the N−H imine is likely deprotonated to generate magnesium alkylideneamide species **2**·MgBr.[8f] Meanwhile, the Grignard reagent would also transform the cobalt precatalyst and the imidazolinium salt to an NHC-coordinated, low-valent alkylcobalt species **A**. The species **A** would undergo chelation-assisted *ortho*-metalation of

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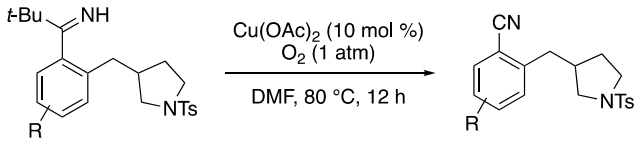
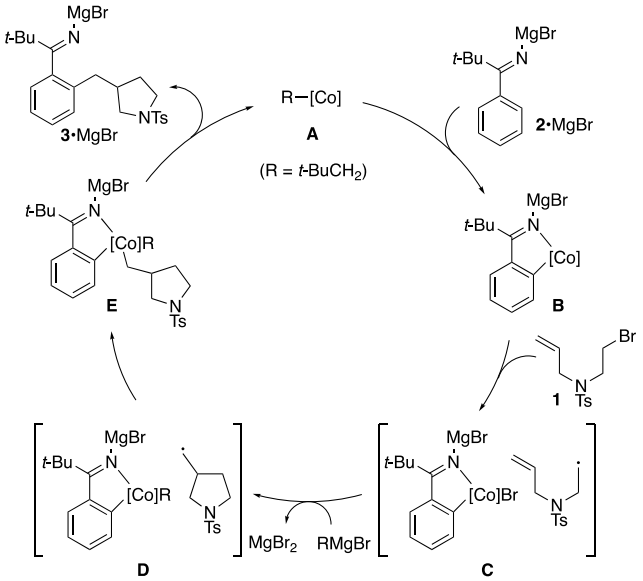
Scheme 3. Imine-to-Nitrile Conversion



3aa (R = H)
3af (R = 4-Cl)
3ao (R = 2-F)

4aa, 84%
4af, 81%
4ao, 64%

Scheme 4. Proposed Catalytic Cycle



2·MgBr to generate a cobaltacycle species **B**. This would be followed by SET from **B** to the bromo-alkene **1**, resulting in a pair of an oxidized cobaltacycle and alkyl radical (**C**). Subsequent radical cyclization would take place in the proximity of the cobalt species, which, in the meantime, would undergo transmetalation with the Grignard reagent to generate the intermediate **D**. Radical recombination of **D** would be followed by C−C reductive elimination of the organocobalt intermediate **E** to afford the product **3**·MgBr and regenerate **A**. The intermediate **E** may alternatively undergo aryl−neopentyl reductive elimination, which would account for the side reactions, i.e., *ortho*-neopentylation as well as dehydrobrominative/reductive cyclizations of **1**. Note that the addition of TEMPO to the model reaction did not significantly retard the formation of **3aa** (50% yield). Also, the reaction in the presence of α-cyclopropylstyrene afforded **3aa** in 51% yield, without forming any detectable byproducts incorporating the radical clock alkene (Scheme S4). These observations would suggest the absence of a free radical and fast recombination of the radical pair.

In summary, we have demonstrated that cobalt-catalyzed directed arene C−H activation and 1,5-radical cyclization could be merged into a single catalytic cycle to achieve dicarbofunctionalization of bromo-alkenes, affording a series of benzylated pyrrolidine and related cyclic products in moderate to good yields.[17] Given the broad scope of conventional radical cyclizations,[18] we expect that the scope of the present tandem process could also be extended to enable access to more complex polycyclic systems.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01846.

Detailed experimental procedures and spectral data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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