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N-Iminopyridinium ylide-directed, cobalt-catalysed coupling of sp^2 C–H bonds with alkynes†

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Abstract

N-Iminopyridinium ylides are competent monodentate directing groups for cobalt-catalysed annulation of sp^2 C–H bonds with internal alkynes. The pyridine moiety in the ylide serves as an internal oxidant and is cleaved during the reaction. The annulation reactions possess excellent compatibility with heterocyclic substrates, tolerating furan, thiophene, pyridine, pyrrole, pyrazole, and indole functionalities.

First-row transition-metal, and more specifically, cobalt-catalysed carbon–hydrogen bond functionalization has received substantial attention in recent years.¹ Compared to their 4d and 5d analogues, non-noble transition metals are abundant and cheap. Additionally, the reaction manifolds accessible by 3d transition metals sometimes differ from those of their 4d and 5d counterparts.

We have recently reported palladium-catalysed, N-iminopyridinium ylide-directed sp^3 C–H arylation and alkylation reactions.^{2a} Furthermore, copper-promoted sp^2 C–H/N–H couplings were also disclosed.^{2b} Monodentate N-iminopyridinium ylide directing groups appear to be nearly as efficient as the widely used bidentate auxiliaries in palladium-catalysed C–H functionalization.^{2,3} Their performance in copper-promoted sp^2 C–H amination is superior to those of other monodentate directing groups.^{2b} Thus, we were interested in exploring the reactivity of N-iminopyridinium ylides in cobalt-catalysed C–H functionalization.

A pioneering report by Matsunaga and Kanai in 2014 described $Cp^*Co(III)$ -catalysed coupling of alkynes with aromatic C–H bonds.^{4a,b} Our group reported a method for cobalt-catalysed, aminoquinoline- and picolinamide-directed coupling of alkynes with $C(sp^2)$ –H bonds. The reaction employs a simple $Co(OAc)_2$ hydrate catalyst, and oxygen from the air as a terminal oxidant.^{4c} Subsequently, many similar high-valent cobalt catalysed transformations have been reported.^{5,6} Simple cobalt salt promoted transformations typically possess high regioselectivity for reactions with unsymmetrical alkynes and require a bidentate directing group.⁵ Only on rare cases, monodentate directing groups can be used.⁵ⁱ Reactions that are catalysed by various cyclopentadienylcobalt(III) complexes can be

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Conflicts of interest

The authors declare no conflict of interest.

performed by employing simpler, monodentate, directing groups, but the regioselectivity observed for unsymmetric alkynes may be lower.⁶ Other metals and low-valent cobalt catalysis have been employed as well.⁷ Among cobalt-catalysed transformations that result in the formation of isoquinolones, few papers report the use of monodentate directing groups.^{6e,m} The compatibility of these methodologies with heterocyclic substrates is underexplored. We report here N-iminopyridinium ylide-directed, cobalt-catalysed coupling of sp^2 C–H bonds with alkynes that uses the N–N bond as an internal oxidant forming isoquinolones. These transformations are highly compatible with heterocyclic substrates.

The reaction optimization studies are presented in Table 1. The use of simple cobalt salts such as $\text{Co}(\text{OAc})_2$ and $\text{Co}(\text{acac})_2$ did not afford any product, and thus cyclopentadienylcobalt(III) complexes were employed. After screening a number of solvents, cobalt complexes, and additives, we found that the best results were obtained by using a $[\text{Cp}^*\text{Co}(\text{MeCN})_3][\text{SbF}_6]_2$ catalyst in HFIP solvent with added pivalic acid. Subsequently, modification of the ylide moiety was undertaken (entries 1–3). Relatively low yield was obtained by employing a ylide derived from commercially available 1-aminopyridinium iodide and *p*-toluoyl chloride (entry 1). Switching to 4-methoxypyridinium derivative **2** and 4-*tert*-butylpyridinium ylide **3**, previously utilized for copper promoted C–H amination,^{2b} allowed the yields to be increased to 81–82% (entries 2 and 3). Pivalic acid additive was found to be optimal for the reaction (entries 4 and 5).

Best catalytic performance was observed for $[\text{Cp}^*\text{Co}(\text{MeCN})_3][\text{SbF}_6]_2$, while *in situ* generated active species (entry 6) and $[\text{CpCo}(\text{MeCN})_3][\text{SbF}_6]_2$ (entry 7) gave lower yields.

After identification of the optimal reaction conditions, we evaluated the generality of the directed C–H annulation of aryl ylides with symmetric alkynes such as diphenylacetylene and 3-hexyne (Scheme 1). Various functional groups such as alkoxy (**5**), halides (**6**, **7**, **13**, **14**, and **17**), esters (**10** and **15**), nitrile (**12**), trifluoromethyl (**9**), and sulfone (**11**) on the aryl rings are well tolerated furnishing good to excellent yields of isoquinolones regardless of the substituent electronic properties and positions on the arene. The annulation of substrates with substituents at the meta position of an aryl group occurred regioselectively at the less hindered site (**13–15**). Compared to meta and para substituted compounds, ortho substituted substrates gave products in somewhat lower yields (**16** and **17**). The annulation is not limited to aromatic substrates. Acrylic acid derivatives are reactive as well (**18** and **19**). In addition to diphenylacetylene, 3-hexyne can be employed as a substrate for the annulation to generate the corresponding products (**20–22**). Comparison of *t*-butyl pyridinium ylides with the corresponding methoxy pyridinium derivatives is instructive. In some cases, performance is nearly identical (**4**). For most other substrates, the methoxy derivative performs substantially better (**14**, **16**, and **17**) even with shorter reaction times.

The annulation protocol was investigated with respect to heteroaryl substrates (Scheme 2). Thiophene derivatives gave the expected products in good yields, irrespective of the substitution pattern (**23–25**). The best results were obtained with 3-substituted thiophene which afforded the cyclized product **25** regioselectively and reacted faster than other substrates. Furan derivatives are competent substrates (**26–28**) but if a ylide derived from furan-2-carboxylic acid was employed, the product was isolated in a low yield (**26**). Notably,

a brominated furan derivative is reactive (**28**). Furthermore, nitrogen-containing heteroarene substrates participate in the transformation. Pyridine (**29** and **30**), pyrrole (**31**), pyrazole (**32**), and indole moieties (**33**) are all compatible with the reaction conditions, irrespective of the potentially strong coordinating ability of the heteroatom which may interfere with the C–H functionalization step of the annulation reaction.⁸ In all cases except that for the 6-methoxypyridinium substrate (**30**), formation of only one product isomer was observed. For **30**, two isomers (C2 : C4 = 5.9 : 1) were obtained. Next, the annulation of heterocycles with 3-hexyne was investigated. Thiophenes and benzo[*b*]thiophene gave products in good yields (**34–37**). However, the furan-containing substrate afforded **38** in a modest yield. In most cases the methoxy-substituted pyridine ylide derivative performs substantially better compared with the ylide derived from *t*-butylpyridine.

Regioselectivity of the reactions with unsymmetrical alkynes was investigated next (Scheme 3). The annulation with ethyl hept-2-ynoate exhibited good selectivity (**39** and **40**). The use of ethyl 3-phenylpropiolate resulted in about 2 : 1 ratio of isomeric products **41** and **42**. Poor selectivity was observed in the reaction with 4-phenylbut-3-yn-2-one (**43** and **44**). The selectivities are consistent with those observed for cyclopentadienylcobalt(III)-catalysed annulation reactions with alkynes.⁶

We carried out preliminary mechanistic experiments to delineate the annulation mechanism. The C–H bond cleavage step is reversible as determined by D/H scrambling (Scheme 4). Two deuterium atoms at the *ortho* positions of the ylide were completely replaced with hydrogens in the absence of alkyne (**45** to **45-d3**). The reaction of deuterated ylide with 3-hexyne gave the isoquinoline product with 52% hydrogen incorporation (**45** to **46-h**). When the reaction was stopped before completion, H/D scrambling in both the recovered ylide starting material and product was observed (**45** to **45-h** and **46-h**, eqn (3)). These results suggest that the C–H bond cleavage step is not the rate determining step.

In a competitive annulation using a 1 : 1 molar mixture of *tert*-butyl pyridinium ylide **3** and methoxy pyridinium ylide **47**, a 1 : 1.35 mixture of 6-methyl-isoquinoline **4** and 6-ethylisoquinoline **48** was obtained (Scheme 5). Somewhat higher reaction rate for the methoxy pyridinium ylide may reflect the higher coordinating ability of a more electron-rich ylide.

We attempted to prepare the cyclometalated complex *via* C–H activation of the pyridinium ylide with a stoichiometric amount of [Cp*Co(MeCN)₃][SbF₆]₂, but the desired cobaltacycle could not be isolated. Reversible C–H cobaltation may have contributed to the failure to isolate the complex. However, the Cp*Co(III)-pyridinium ylide complex **50** was prepared by chelation-assisted oxidative addition of the pyridinium ylide Ar–I bond to Cp*Co(CO)₂, generated *in situ* from cobalt carbonyl (Scheme 6, eqn (1)).⁹ Complex **50** was characterized by single crystal X-ray diffraction and NMR spectroscopy. Iodide abstraction by treatment of AgSbF₆ in acetonitrile afforded cationic cobalt complex **51**, which is a competent annulation catalyst, affording isoquinolone **4** in 68% yield (Scheme 6, eqn (2)).

Based on the mechanistic studies and the reported mechanism for high valent cobalt catalysed annulations with alkynes in the literature, we propose the catalytic cycle in

Scheme 7.^{6e,i,k,m,10} The reaction starts with ligand exchange followed by subsequent chelation assisted C–H activation to give the cobaltacycle **A**. Ligand exchange between the alkyne and nitrile, followed by migratory insertion forms the seven-membered cobaltacycle **B**. Next, intramolecular C–N bond formation furnishes the isoquinoline and releases the pyridine and Co(III) catalyst closing the catalytic cycle.

In conclusion, we have shown that N-iminopyridinium ylides act as competent monodentate directing groups for cobalt-catalysed annulation of sp^2 C–H bonds with internal alkynes. Coupling reactions proceed in hexafluoroisopropanol solvent at increased temperatures and are catalysed by the $[Cp^*Co(MeCN)_3][SbF_6]_2$ complex. The pyridine moiety in the ylide is cleaved during the reaction, serving as an internal oxidant. The annulation reactions possess excellent compatibility with heterocyclic substrates, tolerating furan, thiophene, pyridine, pyrrole, pyrazole, and indole functionalities.

Supplementary Material

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Scheme 1.

Reaction scope with respect to ylides.^{a a} Reaction scale: 0.2 mmol, HFIP 1 mL. ^b Time: 20 h. ^c Time: 48 h. ^d Catalyst: [Cp*Co(MeCN)₃][SbF₆]₂ (20 mol%), PivOH (30 mol%), 48 h. ^e Time: 72 h. ^f Catalyst: [Cp*Co(MeCN)₃][SbF₆]₂ (20 mol%), PivOH (30 mol%), 72 h. Isolated yields reported. Please see the ESI† for details.

†Electronic supplementary information (ESI) available. CCDC 1991068 and 2014034. For ESI and crystallographic data in CIF or other electronic format see DOI: [10.1039/d0cc05294a](https://doi.org/10.1039/d0cc05294a)

Scheme 2.

Reaction scope with respect to heteroaryl ylides.^{a a} Reaction scale: 0.2 mmol, HFIP 1 mL. ^b Time: 48 h. ^c Time: 20 h. ^d Catalyst: $[\text{Cp}^*\text{Co}(\text{MeCN})_3][\text{SbF}_6]_2$ (20 mol%), PivOH additive (30 mol%), 48 h. ^e Catalyst: $[\text{Cp}^*\text{Co}(\text{MeCN})_3][\text{SbF}_6]_2$ (20 mol%), PivOH additive (30 mol%), 72 h. ^f Product major isomer is shown (5.9 : 1). Isolated yields are reported. Please see the ESI† for details.

Scheme 3.

Reactions with unsymmetrical alkynes.^a ^aReaction scale: 0.2 mmol, HFIP 1 mL. ^b

$[\text{Cp}^*\text{Co}(\text{MeCN})_3][\text{SbF}_6]_2$ (20 mol%), PivOH (30 mol%), 48 h. ^c $[\text{Cp}^*\text{Co}(\text{MeCN})_3][\text{SbF}_6]_2$ (15 mol%), PivOH (20 mol%), 48 h.

Scheme 4.
Scrambling experiments.

Scheme 5.
Competition reaction.

Scheme 6.

Cp*Co(III)-pyridinium ylide complex.

Scheme 7.
Proposed catalytic cycle.

Table 1Optimization of the reaction conditions^a

Entry	Deviation from standard conditions	Yield ^b (%)
1	R ¹ = H, 1	24
2	R ¹ = OMe, 2	82
3	R ¹ = tBu, 3	81
4	1-AdCO ₂ H instead of PivOH	77
5	Without PivOH	55
6	Cp*CoI ₂ (CO) (20 mol%) AgSbF ₆ (40 mol%) 1-AdCO ₂ H (50 mol%)	60
7	[CpCo(MeCN) ₃][SbF ₆] ₂	7

^aReaction conditions: ylide (0.2 mmol), HFIP (1 mL).^bIsolated yields. Abbreviations: HFIP = 1,1,1,3,3,3-hexafluoroisopropanol, 1-AdCO₂H = 1-adamantanecarboxylic acid, PivOH = pivalic acid.