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Cobalt(III)-Catalysed C-H Alkylation with Vinylaziridines

Lingyu Kong,^a Bohdan Biletskyi,^a Didier Nuel^a and Hervé Clavier^{a*}

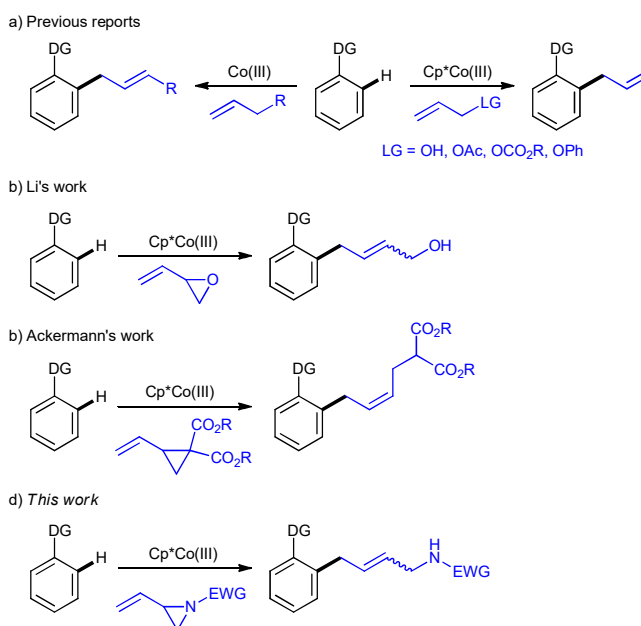
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Lingyu Kong ORCID [0000-0002-7125-680X](#)Bohdan Biletskyi ORCID [0000-0003-3132-2566](#)Didier Nuel ORCID [0000-0002-5055-0583](#)Hervé Clavier ORCID [0000-0002-2458-3015](#)

A cobalt-catalysed C-H alkylation of aromatic and heteroaromatic compounds with vinylaziridines is described. This transformation occurring under mild reaction conditions proceeds through C-H activation, carbon-carbon double insertion and β -nitrogen elimination. Its scope and limitations have been investigated and a synthetic application of products has been achieved.

The development of direct functionalization of aromatic C-H bonds catalysed by transition metal complexes has increased tremendously over the past decade¹ to reach now a status of powerful synthetic methodology for the preparation of natural compounds, pharmaceuticals, agrochemical products, polymers and commodity and specialty chemicals.² Among the various functionalizations, C-H alkylation is of interest since allyl moieties can be straightforwardly manipulated to afford a wide range of useful functionalities.³ Various transition metal-based catalytic systems enable direct C-H alkylation such as 3d (iron, cobalt, nickel), 4d (ruthenium, palladium, rhodium) or 5d (iridium) metals. For quite some time Rh was considered to be superior to other metals regarding its reactivity. Recently, research has demonstrated cobalt complexes, in particular high-valent species,^{4,5} represent efficient catalysts for C-H functionalization⁶ including C-H alkylation. For example, a Co-catalysed C-H alkylation using unactivated olefin partners was recently developed (Scheme 1a).⁷ A major catalytic breakthrough was accomplished in this field with the development of Cp*Co(III)-type complexes.^{8,9} With this catalyst, Glorius and Matsunaga and Kanai reported independently C-H alkylation processes with allylic derivatives involving carbon-carbon double bond insertion and subsequent β -oxygen elimination.¹⁰ From an atom economy point of view, the release of a leaving group is not desirable. Therefore, Li and coworkers



Scheme 1 Co-catalysed C-H alkylation.

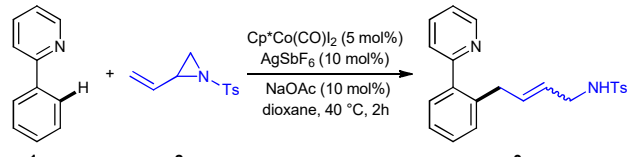
explored successfully the possibility to perform C-H alkylation with vinylloxirane (Scheme 2b).¹¹ Importantly, allylated products were obtained as mixture of *E*- and *Z*-isomers with ratios spanning from 3.2 to 1.7 to 1. Prior to this work, Ackermann had described that activated vinylcyclopropanes could be used as allylating partners.¹² The β -carbon elimination being highly selective, mainly *Z*-isomers were isolated. Of note, these two reactions were successfully performed with enamides substrates.¹³ As a part of our interest for the metal-catalysed activation of small rings,^{14,15} we report now herein the use of vinylaziridines to carry out the Cp*Co(III)-cobalt catalysed direct C-H alkylation involving a β -nitrogen elimination step.¹⁶ We have optimized the cobalt-catalysed C-H alkylation using the benchmark substrates 2-phenylpyridine **1a** and tosyl-containing vinylaziridine **2a** and determined that, through the appropriate choice of conditions, the reaction can be achieved with good

^a Aix Marseille Université, Centrale Marseille, CNRS, iSm2 UMR 7313, 13397, Marseille, France.

E-mail: herve.clavier@univ-amu.fr

† Footnotes relating to the title and/or authors should appear here.

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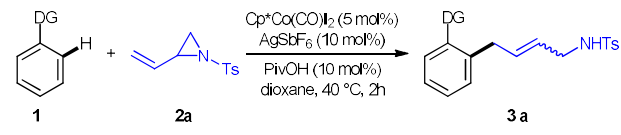
Table 1 Optimization of the reaction conditions^a


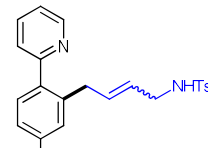
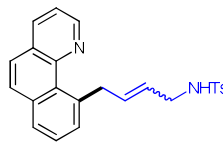
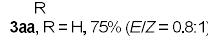
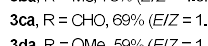
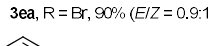

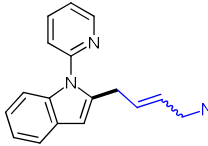
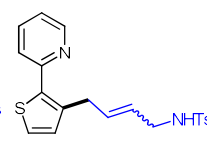
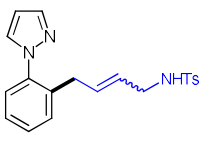
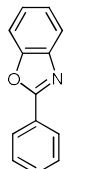
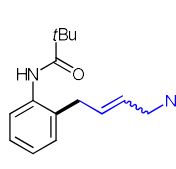
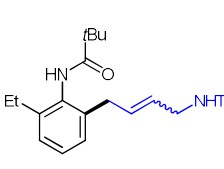
Entry	Change from "the standard conditions"	Isolated yield (%)	<i>E/Z</i> ^b
1	None	63	0.8:1
2	AgBF ₄ instead of AgSbF ₆	11	1.0:1
3	AgPF ₆ instead of AgSbF ₆	-	-
4	AgOTf instead of AgSbF ₆	5	2.3:1
5	toluene instead of dioxane	42	1.1:1
6	DCE instead of dioxane	58	1.3:1
7	CF ₃ CH ₂ OH instead of dioxane	43	0.9:1
8	DMF instead of dioxane	-	-
9	No NaOAc	13	0.8:1
10	LiOAc instead of NaOAc	42	0.8:1
11	KOAc instead of NaOAc	57	0.8:1
12	CsOAc instead of NaOAc	18	0.8:1
13	NaOBz instead of NaOAc	33	0.8:1
14	NaOPiv instead of NaOAc	35	0.8:1
15	AcOH instead of NaOAc	58	1.0:1
16	BzOH instead of NaOAc	54	0.8:1
17	PivOH instead of NaOAc	75	0.8:1
18	PivOH (20 mol%) instead of NaOAc	32	0.8:1
19	PivOH (5 mol%) instead of NaOAc	53	0.8:1

^a Reaction conditions: **1a** (36 μ L, 0.25 mmol), vinylaziridine **2a** (56 mg, 0.25 mmol, 1 equiv.), Cp*Co(CO)₂ (6.0 mg, 5 mol%), silver salt (10 mol%), additive (10 mol%), solvent (0.5 mL). ^b Determined by ¹H NMR.

efficiency but unfortunately low *E/Z* selectivity (Table 1). Thus, during all the experiments of this optimization study, only inseparable mixtures of *E*- and *Z*-isomers of allylation products in the range of 0.8 to 1.3:1 **3aa** were observed. AgSbF₆ was found competent to generate the cationic active species from the well-defined Cp*Co(CO)₂.¹⁷ With NaOAc as additive, the catalytic system allowed for the formation of 63% of the expected allylation product **3aa** in only 2 h at 40 °C in 1,4-dioxane (entry 1). With other silver salt such as AgBF₄, AgPF₆ or AgOTf only small quantities of **3aa** were isolated (entries 2-4). The Co-catalyzed C-H allylation can be carried out in other solvents than 1,4-dioxane, but in slightly lower yields (entries 5-7). Without carboxylate additive, only tiny amount of **3aa** were isolated (entry 10). Among the various carboxylate salts we have tested, NaOAc was the most effective (entries 1 and 10-14). Instead of carboxylate salts, carboxylic acids have been evaluated as additive (entries 15-17). The use of pivalic acid - 10 mol% being the optimum quantity - allowed to reach 75% of **3aa** (entries 17-19).

Having established the optimal reaction conditions, we investigated further the scope of the catalytic system with a range of arenes bearing various directing groups (DG) (Table 2). The Co-catalyzed C-H allylation was successfully applied to several para-functionalized 2-phenylpyridines and the expected products were obtained in good to excellent yields but again contained almost equal quantities of *E*- and *Z*-isomers. Importantly, with these substrates no traces of diallylation

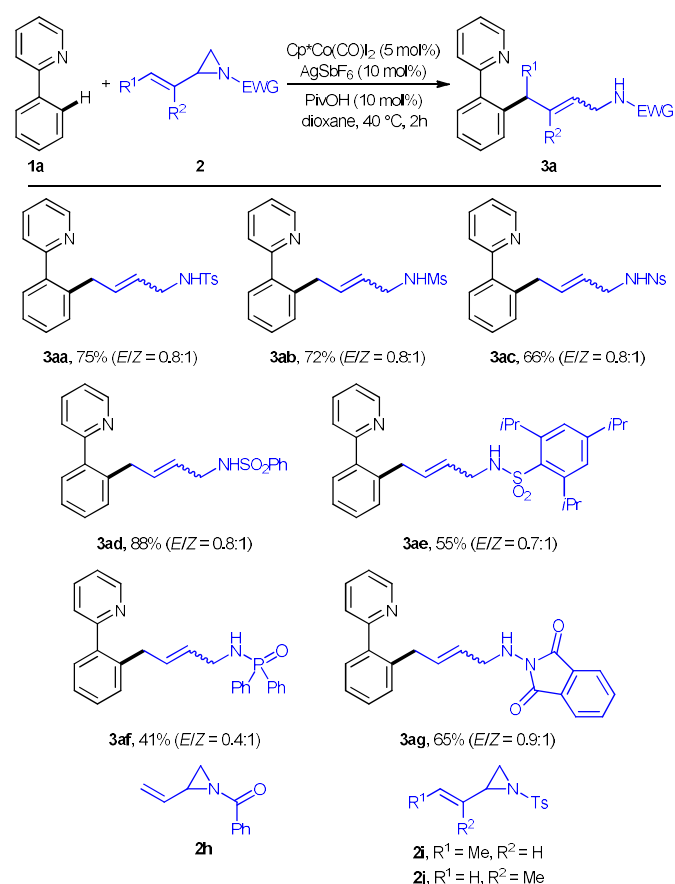
Table 2 Substrate scope and limitation of various arenes^a


 3aa , R = H, 75% (<i>E/Z</i> = 0.8:1)	 3fa , 52% (<i>E/Z</i> = 1.0:1)
 3ba , R = Me, 73% (<i>E/Z</i> = 1.0:1)	
 3ca , R = CHO, 69% (<i>E/Z</i> = 1.0:1)	
 3da , R = OMe, 59% (<i>E/Z</i> = 1.0:1)	
 3ea , R = Br, 90% (<i>E/Z</i> = 0.9:1)	
 3ga , 58% (<i>E/Z</i> = 2.7:1)	 3ha , 52% (<i>E/Z</i> = 0.7:1)
 3ia , 58% (<i>E/Z</i> = 1.6:1)	
 1j , unreactive substrate	 3ka , 38% (<i>E/Z</i> = 0.8:1)
	 3la , 38% (<i>E/Z</i> = 0.5:1)

^a Reaction conditions: Arene **1** (0.25 mmol), vinylaziridine **2a** (56 mg, 0.25 mmol, 1 equiv.), Cp*Co(CO)₂ (6.0 mg, 5 mol%), AgSbF₆ (8.6 mg, 10 mol%), PivOH (2.4 mg, 10 mol%), 1,4-dioxane (0.5 mL). *E/Z* ratio determined by ¹H NMR.

products were detected, highlighting a high mono/di selectivity. With the same conditions, benzo[*h*]quinolone **1f** reacted to afford **3fa** in moderate yield (52%). Furthermore, the scope of arene substrates was broadened to heterocycles such as indole **1g** and thiophene **1h**. Noticeably, product **3ga** was obtained with a significantly higher ratio in favour of the *E*-isomer. Not only the pyridine moiety could be used as directing group since pyrazole-containing product **3ia** and acetanilides **3ka** and **3la** were isolated albeit in moderate yields. Despite repeated attempts with increase of the reaction temperature, 2-phenylbenzoxazole **1j** was found unreactive.

Whereas the works of Ackermann¹² and Li¹¹ on vinylcyclopropanes and 2-vinylloxirane respectively were limited to 1 or 2 examples, we were wondering if this cobalt-catalyzed allylation could be extended to other vinylaziridines **2**. The scope and limitations of vinylaziridines are depicted in Table 3. Overall, sulfonyls as electron-withdrawing groups are well tolerated with yields spanning from 55% for the bulky (2,4,6-triisopropylphenyl) sulfonamide derivative **3ae** to 88% for **3ad** bearing a (phenyl)sulphonamide group. To our delight, vinylaziridines with diphenylphosphinyl and phthalimide groups **1f** and **1g** reacted well to afford the expected products in 41 and 65% respectively. The use of these different electron-withdrawing groups seems to have no significant influence of the *E/Z* ratio of the allylated compounds. No C-H allylation

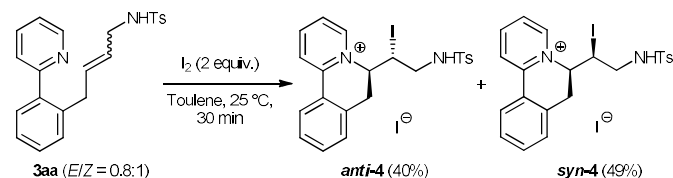
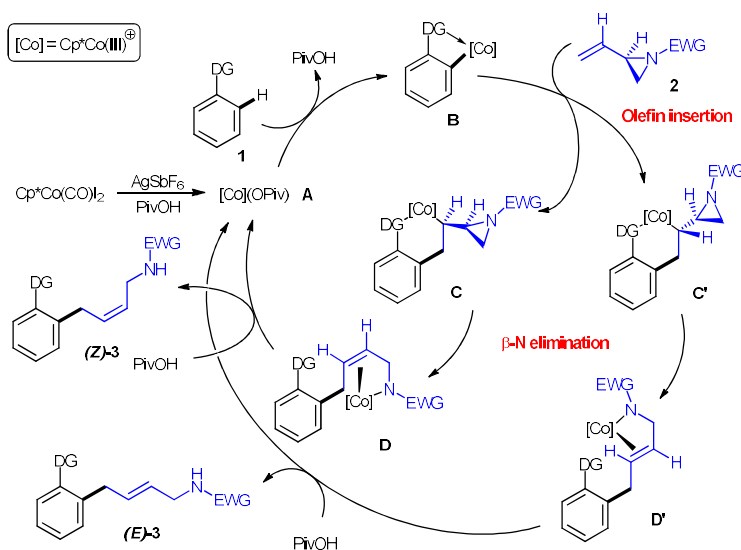
Table 3 Substrate scope and limitations of various vinylaziridines^a

^a Reaction conditions: **1a** (36 μL , 0.25 mmol), vinylaziridine **2** (0.25 mmol, 1 equiv.), $\text{Cp}^*\text{Co(CO)}_2\text{I}_2$ (6.0 mg, 5 mol%), AgSbF_6 (8.6 mg, 10 mol%), PivOH (2.4 mg, 10 mol%), 1,4-dioxane (0.5 mL). *E/Z* ratio determined by $^1\text{H NMR}$. Ns = 4-nitrobenzenesulfonyl.

occurred with vinylaziridine **2h**; since under the reaction conditions used, **2h** was converted into the more stable vinyloxazoline. Unfortunately and despite harsher reaction

conditions, when the carbon-carbon double bond of the vinylaziridine was substituted by a methyl, either in terminal or internal position, **2i** and **2j** respectively, no formation of the expected allylation products was observed. In the case of allylating reagents bearing a leaving group, this type of substitution did not shut down the reaction;^{10b-d} but this point was not discussed for vinylcyclopropane and vinyloxirane.^{11,12} Considering recent related mechanistic studies,^{10b,12,18} a plausible mechanism is shown in Scheme 2. Formation of catalytically active species **A** is followed by C-H activation process giving rise to cobaltacycle **B**. Olefin insertion leads to intermediates **C** and **C'** (only one enantiomer depicted) and subsequent *syn* β -N eliminations afford **D** and **D'** respectively. Of note, β -H elimination process seems to be disfavoured since the formation of alkylideneaziridine was never detected. A protonolysis step releases products **3** and regenerates active species **A**. The low or no selectivity in the formation of *E*- and *Z*-isomers seems to indicate that the selective-determining step, olefin insertion, cannot be selectively achieved. Thus, intermediates **C** and **C'** are formed in almost equal amounts.

To illustrate the synthetic usefulness of allylated compounds **3**, **3aa** was treated with iodine in toluene at 25 $^\circ\text{C}$ (Scheme 3). After only 30 min, the starting material was completely consumed and pyridinium salt **4** was obtained as a separable mixture of diastereomers with a ratio *anti/syn* (0.8:1) corresponding to the *E/Z* ratio of **3aa**.¹⁹ This of note that the 6,7-dihydro-benzo[*a*]quinolizinium moiety of compounds **4** is present in the skeleton of various natural products such as Berberine and related alkaloids.²⁰

**Scheme 3** Iodocyclisation of C-H allylation product **3aa**.**Scheme 2** Proposed mechanism.

Conclusions

In summary, we have developed a Co-catalysed direct C-H allylation of arenes using vinylaziridines to prepare various allylated aromatic and heteroaromatic compounds overall in good yields. Despite a low *E/Z* selectivity, this reaction occurring under mild reactions conditions was found relatively broad in scope for both arenes and vinylaziridines. The reaction pathway probably involves a C-H activation step carried out by the versatile cationic cobalt(III) complex, olefin insertion that determines the formation of either *E*- or *Z*-isomer, and subsequent β -nitrogen elimination that triggers the aziridine ring-opening. A synthetic application of the allylation products has been achieved. Further developments are currently underway in our laboratory and will be reported in due course.

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Conflicts of interest

There are no conflicts to declare.

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