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Synthesis of alkylidene pyrrolo[3,4-*b*]pyridin-7-one derivatives *via* Rh^{III}-catalyzed cascade oxidative alkenylation/annulation of picolinamides†

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A practical Rh^{III}-catalyzed cascade olefination/annulation of picolinamides leading to pyrrolo[3,4-*b*]pyridines has been developed. The reaction shows wide scope, complete regiocontrol and excellent stereoselectivity.

The direct C–H functionalization of nitrogen heteroarenes has attracted wide interest as they are key structural units found in drugs and functional materials.[1] Compared to the significant progress made with electron-rich heteroarenes,[2,3] general strategies for the functionalization of privileged electron-deficient azaheterocycles such as pyridine remain underdeveloped.[4] Due to the binding ability of the sp^2-hybridized nitrogen to the metal catalyst, most reactions are C2-selective.[4] However, the use of directing groups has enabled functionalization at C3 and C4.[5] Recent work has shown the application of this strategy to arylation and alkylation reactions, whereas comparatively little has been reported on direct alkenylation reactions.[6,7]

From a synthetic practicality standpoint, removable directing groups that provide an additional handle to introduce diversity and structural complexity in the final product are highly valuable.[8] For example, Glorius *et al.* described the Rh^{III}-catalyzed oxidative olefination/annulation of primary benzamides to afford isoindolin-1-ones.[9] Subsequently, Li and co-workers applied this reaction to the synthesis of pyrrolo[3,4-*c*]pyridines from isonicotinamides.[10] However, the application of this strategy to the more challenging picolinamide substrates remained undocumented. A point of concern of using picolinamide substrates is that the amide group at C2 might strengthen the interaction between the pyridinic nitrogen and the metal through a bidentate coordination, thereby preventing the catalyst from interacting with the target pyridinic C–H bond.[11] In fact, the picolinamide group (COPy) has proven to be highly efficient in promoting a variety of $C(sp^2)$–H and $C(sp^3)$–H bond functionalization reactions,[5e,12] whereas derivatization at the pyridine ring has been seldom reported.[13] This gap stimulated us to develop a practical method for the Rh^{III}-catalyzed olefination/annulation of picolinamides. Remarkably, the resulting pyrrolo[3,4-*b*]pyridines can be considered as conformationally constrained nicotinoids, thereby becoming attractive candidates for selective nicotinic acetylcholine receptor ligands, or dipeptide mimics.[14] While our current studies were in the final stage of development, a report by Shi and co-workers on the Rh-catalyzed *ortho*-olefination of tertiary picolinamides with ethyl acrylate appeared[15] which prompted us to communicate our results. In Shi's work, two single examples of tandem olefination/annulation of secondary picolinamides to give pyrrolo[3,4-*b*]-pyridines were described.[15] Herein we report a practical synthesis of variously functionalized pyrrolo[3,4-*b*]pyridines *via* a Rh-catalyzed cascade olefination–cyclization of picolinamides. The benzylic nature of the *N*-substituent allows for an easy deprotection of the final products.

At the outset, solvents, ligands, and counter anions that could significantly influence this reaction were screened in the model reaction of the picolinamide **1a** with methyl acrylate (Table 1). Initial experiments were performed with $[RhCp^*Cl_2]_2$ (2.5 mol%) and $AgSbF_6$ (10 mol%) in *tert*-amyl alcohol at 120 °C. To our delight, the desired product **2** was obtained with a promising 64% GC yield after 3 hours, yet accompanied by a 6% of the reduced product **3** (entry 1).[16] Prolonging the reaction time to 5 hours led to complete conversion with similar **2**/**3** selectivity, allowing the isolation of the product **2**[17] in 78% yield (entry 2). Control experiments revealed the importance of the silver salt, presumably for generating active cationic Rh^{III} species (entry 3), and the $Cu(OAc)_2$ as oxidant (entries 4–6). Acetate was also found to be crucial for efficient catalyst turnover, possibly by facilitating cyclometalation[18] and regeneration of the Rh catalyst (see ESI† for details). Among the solvents tested, *p*-xylene appeared to be equally effective (entries 10 and 11), whereas other solvents such as DMF, NMP or dioxane provided lower conversion or an increased ratio of the reduced product **3** (entries 7–9). Under the

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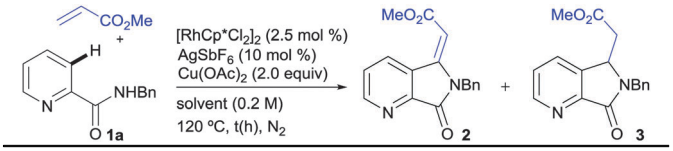
Table 1 Evaluation of the reaction conditions

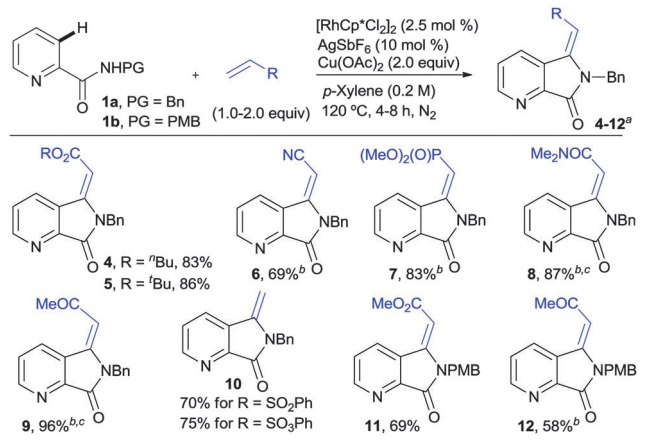


Entry	Time (h)	Solvent	Conv.[a] (%)	2[b] (%)	3[b] (%)
1	3	*t*-AmylOH	70	64	6
2	5	*t*-AmylOH	98	82 (78)[c]	8
3[d]	3	*t*-AmylOH	12	11	Traces
4[e]	3	*t*-AmylOH	0	—	—
5[f]	3	*t*-AmylOH	90	60	37
6[f,g]	3	*t*-AmylOH	18	16	—
7	3	DMF	57	53	4
8	3	NMP	40	38	2
9	3	Dioxane	99	84	15
10	3	*p*-Xylene	73	69	4
11	5	*p*-Xylene	98	85 (83)[c] (84)[h]	Traces
12[i]	3	*p*-Xylene	30	23	11

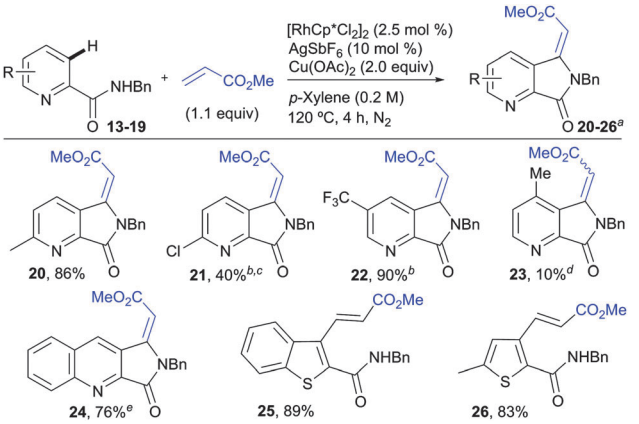
Conditions: **1a** (0.15 mmol), methyl acrylate (0.15 mmol), $[RhCl_2Cp^*]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), $Cu(OAc)_2$ (2.0 equiv.), 0.2 M, 3 h, N_2. [a] By GC on the crude mixture with respect to **1a**. [b] GC yields (n-$C_{16}H_{34}$ as internal standard). [c] Isolated yield. [d] Without $AgSbF_6$. [e] Without $Cu(OAc)_2$. [f] With 1 equiv. of $Cu(OAc)_2$. [g] Under O_2. [h] Isolated yield at the 0.5 gram scale. [i] 100 °C.

optimized conditions (in *p*-xylene) the desired product **2** was isolated in 84% yield. Moreover, the reaction can be scaled up to 10 times (0.5 gram scale) without the need for an inert atmosphere for maintaining the high efficiency (84% yield), thus emphasizing the robustness of this method (entry 11 and ESI†).

Investigation of the reaction of **1a** with alternative electron-deficient alkenes revealed that not only acrylates (**4** and **5**) but also a variety of Michael acceptor-type olefins including acrylonitrile (**6**), vinyl phosphonate (**7**), acrylamide (**8**) or methyl vinyl ketone (**9**) were effective, affording the corresponding alkylidene pyrrolo[3,4-*b*]pyridinone derivatives in good yields (69–96%) and excellent *E*-stereoselectivity (Scheme 1). Interestingly, the use of phenyl vinyl sulfone (or its sulfonate derivative) led to the formation of the methylene-substituted product **10** in good yield (70–75%). The *p*-methoxybenzyl (PMB)-protected picolinamide **1b** was also amenable to the reaction, although with slightly lower yields (**11** and **12**, 58–69%). This issue is important because it offers varied possibilities for subsequent *N*-deprotection. Unfortunately, styrene and (*E*)-methyl crotonate were found to be unreactive olefins (starting material recovered).[19]



Scheme 1 Scope with regard to the olefin. For experimental details, see ESI.† [a] Isolated yields for products **4–12**. [b] Using olefin (2.0 equiv.), $[RhCl_2Cp^*]_2$ (5.0 mol%), $AgSbF_6$ (20 mol%) and $Cu(OAc)_2$ (2.0 equiv.). [c] Using $Cu(OAc)_2$ (4.0 equiv.).



Scheme 2 Scope of the heteroaromatic counterpart. [a] Isolated yields. [b] Using $[RhCl_2Cp^*]_2$ (5.0 mol%), $AgSbF_6$ (20 mol%) and $Cu(OAc)_2$ (2.0 equiv.), at 140 °C, 16 h. [c] 15% of the protodehalogenated **2** also isolated. [d] GC-yield ($nC_{16}H_{34}$); stereochemistry not determined. [e] 10% of the double bond reduced product also isolated.

This method was next applied to various picolinamide derivatives (Scheme 2). Pyridines substituted at C6 with electron-donating groups reacted with methyl acrylate more rapidly than pyridines holding electron-withdrawing groups, the latter requiring higher temperature (140 °C) and longer reaction times (16 h), to afford typically 80–90% yield of the coupling products (**20**, **22**). The presence of a Cl atom was tolerated only to some extent (**21**, 40%), with the yield compromised by competitive dechlorination. Nonetheless, it is worth mentioning that besides the versatility of this functional handle, the chloropyridine unit is found in many biologically active compounds.[14b] The C4-methyl substituted picolinamide **16** suffered from reduced reactivity (**23**, 10% GC yield), presumably because of its increased steric requirements.

Likewise, the successful C–H functionalization of other heterocyclic systems holding the benzamide directing group at Cα such as quinolone, benzothiophene and thiophene turned out to be viable (Scheme 2). However, whereas the quinolone substrate reacted smoothly to give the expected pyrrolo[3,4-*b*]quinolinone product **24** in good yield (76%), in the case of the thiophene-containing substrates the reaction stopped cleanly at the *ortho*-olefination stage without traces of cyclization products (**25** and **26**, 83–89%). This result suggests that the cascade olefination/annulation process is unfavorable for the construction of two fused five-membered heterocyclic ring arrangements.

The nature of the *N*-substituent was also investigated and showed a remarkable influence on the reactivity (Table 2). Linear aliphatic groups (R = Et) provided decreased reactivity (**31**, 57% yield, incomplete conversion, entry 1), whereas an aromatic group (R = Ph) was totally ineffective (**32**, entry 2). The presence of a

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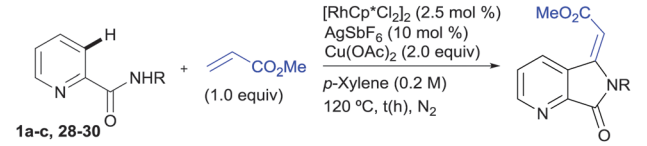
Table 2 Evaluation of different *N*-substituents



Entry	R	Substrate	*t* (h)	Prod.	Yield[a] (%)	*E*/*Z*[b]
1	Et	**28**	4	**31**	57	>98 : <2
2	C_6H_5	**29**	16	**32**	0	—
3	$CH_2CH_2C_6H_5$	**30**	4	**33**	89	90 : 10
4	$CH_2C_6H_5$	**1a**	1	**2**	35[c] (86)[d]	>98 : <2
5	$CH_2(p\text{-}MeOC_6H_4)$	**1b**	1	**11**	22[c] (69)[d]	>98 : <2
6	$CH_2(p\text{-}CF_3C_6H_4)$	**1c**	1	**34**	44[c] (79)[d]	>98 : <2

[a] Isolated yields. [b] Determined by ^{1}H NMR. [c] GC yields after 1 h (n-$C_{16}H_{34}$ as internal standard). [d] Isolated yield after 4 h.

Scheme 3 Selective deprotection and catalytic hydrogenation of **2**.

phenethyl group (benzyl homolog) restored the reactivity, albeit with loss of stereocontrol (89% yield, *E*/*Z*-**33** = 9 : 1, entry 3). Understanding that the benzyl group has an active role in the catalytic cycle, a kinetic study was performed to probe its electronic sensitivity. Three electronically different *N*-benzyl-type derivatives [benzyl, *p*-methoxybenzyl and *p*-(CF_3)benzyl] were subjected to the model reaction with methyl acrylate for 1 h (Table 2, entries 4–6). It was apparent that electron poor substrates reacted slightly faster than electron-rich one, but in all cases useful yields were obtained in 4 h (69–86%).

Scheme 3 illustrates the chemoselective *N*-deprotection of **2** to give product **35** (70% yield), and the selective hydrogenation of the exocyclic double bond of **2** to afford **3** (74%).

In summary, we have developed a Rh^{III}-catalyzed tandem oxidative olefination/annulation of picolinamides enabling rapid access to pyrrolo[3,4-*b*]pyridines. Good structural versatility in both alkene and heteroarene coupling components, high functional group tolerance and excellent regio- and stereocontrol were achieved.

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