C–H Activation Hot Paper

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Ligand-Controlled Regiodivergent Nickel-Catalyzed Annulation of Pyridones**

*Pavel A. Donets and Nicolai Cramer**

Abstract: *The 1,6-annulated 2-pyridone motif is found in many biologically active compounds and its close relation to the indolizidine and quinolizidine alkaloid core makes it an attractive building block. A nickel-catalyzed C–H functionalization of 2-pyridones and subsequent cyclization affords 1,6-annulated 2-pyridones by selective intramolecular olefin hydroarylation. The switch between the exo- and endo-cyclization modes is controlled by two complementary sets of ligands. Irrespective of the ring size, the regioselectivity during the cyclization is under full catalyst control. Simple cyclooctadiene promotes an exo-selective cyclization, whereas a bulky N-heterocyclic carbene ligand results in an endo-selective mode. The method was further applied in the synthesis of the lupin alkaloid cytisine.*

The 2-pyridone structural motif is common[1] in natural products and pharmacologically potent compounds displaying a diversity of properties such as anti-tumor,[2a] antimicrobial,[2b] anti-inflammatory,[2c] cardiotonic,[2d] and antiviral[2e] activity. An important subclass of 2-pyridone derivatives, including several biologically active natural products,[3] contains a 1,6-carboannulated 2-pyridone ring (Figure 1). Besides their high significance for medicinal chemistry, annulated 2-pyridones can serve as valuable intermediates for the synthesis of bioactive indolizidine and quinolizidine alkaloids.[4]

Camptothecine-like annulation patterns of an aromatic ring linked to the pyridone core are accessible by intramolecular Heck reactions.[5] In contrast, annulations with saturated cycles have been accomplished by radical cyclization methods[6] or nucleophilic 1,6-addition[7] followed by rearomatization. However, both methods require additional steps for a separate installation of the reacting functional group (an iodide or an amide correspondingly) for the initiation of the cyclization. Moreover, they lack flexibility since the ring size of the appended cycle strictly depends on the position of the functional group in the side-chain of the substrate. A powerful C6-selective method for alkenylation[8a] and alkylation[8b] of pyridones by C–H activation/olefin hydroarylation,[9] employing cooperative nickel(0)/Lewis acid catalysis,[10] has been developed by Nakao, Hiyama, and co-workers. The two reported examples of an intramolecular alkylation afforded mostly the *exo*-cyclization products and showed ring-size-dependent differences in selectivity (Scheme 1). Principally, both ends of the double bond could react, thus resulting in the formation of either *exo*- or *endo*-cyclization products. Whereas often one pathway is preferred,[11] control and switch of the cyclization modes is desirable, but often very challenging.[12] For instance, hydro-

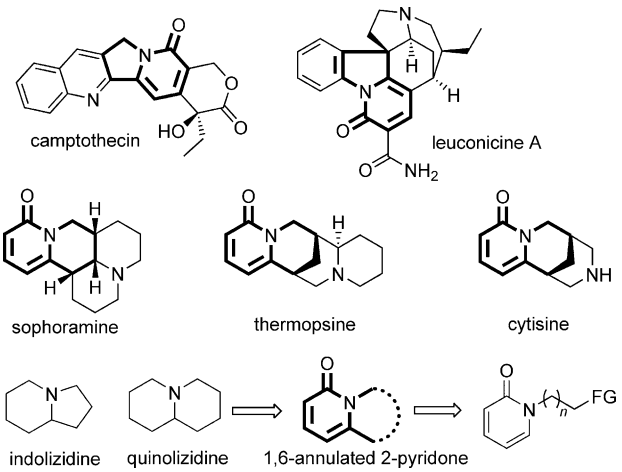
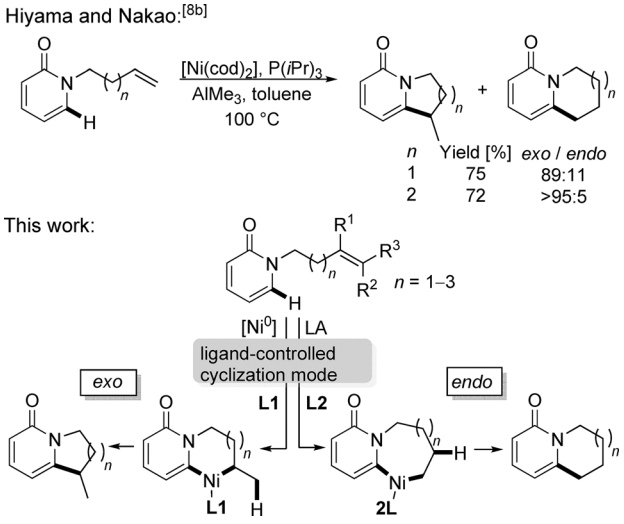


Figure 1. Bioactive 1,6-annulated 2-pyridone natural products.



Scheme 1. Intramolecular 2-pyridone hydroarylation. cod = 1,5-cyclooctadiene.

[*] Dr. P. A. Donets, Prof. Dr. N. Cramer
Laboratory of Asymmetric Catalysis and Synthesis
EPFL SB ISIC LCSA
BCH 4305, 1015 Lausanne (Switzerland)
E-mail: Nicolai.cramer@epfl.ch
Homepage: http://isic.epfl.ch/lcsa

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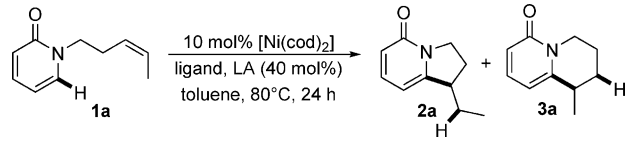
metalations proceed generally in a Markovnikov fashion[13] and preferentially place the metal at the least substituted carbon atom. Thus, besides the ring size formed, the regioselectivity of the cyclization should be expected to depend strongly on the olefin substitution pattern. Ideally, suitable steering ligands would be able to override both of these intrinsic substrate controls and allow predictable switching between *endo*- and *exo*-cyclization modes (Scheme 1). Intrigued by the perspective of an efficient and versatile access to 1,6-annulated 2-pyridones suitable for concise assembly of pyridone natural products, we decided to investigate the nickel(0)-catalyzed intramolecular hydroarylation in greater detail. Herein, we report our findings using different ligand sets to fully control and to effect selectively either *exo* or *endo* cyclization during the olefin hydrometalation step.

We initiated our studies with the cyclization of the pyridone **1a** bearing an unbiased 1,2-disubstituted double bond (Table 1). Monodentate phosphine ligands provided

Table 1: Optimization of the regiodivergent cyclization.[a]



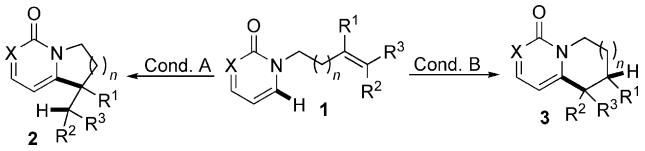
Entry	Ligand[b]	Lewis acid	Yield [%][c]	**2a**/**3a**[c]
1	$(i\text{Pr})_3\text{P}$	$AlMe_3$	70	>95:5
2	$(t\text{Bu})_3\text{P}$	$AlMe_3$	68	>95:5
3	Cy_3P	$AlMe_3$	70	>95:5
4	$(Cy_2PCH_2)_2$	$AlMe_3$	0	–
5	–	$AlMe_3$	83 (80)	>95:5
6	–	$AlEt_3$	0	–
7	–	MAD	0	–
8	$(Cy_3P)_2Ni(C_2H_4)$	$AlMe_3$	68	>95:5
9	IMes	$AlMe_3$	70	>5:95
10	$IMes_2Ni$	$AlMe_3$	63	>5:95
11	IPr	$AlMe_3$	77 (70)	6:94
12	IPr	MAD	81 (74)	>5:95
13	SIPr	$AlMe_3$	55	15:85

[a] 0.10 mmol of **1a**, 10 mol% $[Ni(cod)_2]$, 40 mol% LA, toluene (0.4 mL), 80°C for 24 h. [b] 25 mol% monodentate phosphine, 15 mol% bidentate phosphine or NHC, 10 mol% nickel complex. [c] Determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. Yield of isolated product given within parentheses. LA = Lewis acid, MAD = see Ref. [15].

excellent *exo* selectivity in the reaction of **1a** (entries 1–3) with $[Ni(cod)_2]$ as a metal source and $AlMe_3$ as Lewis acid.[8] Surprisingly, the yield of **2a** was almost independent of the phosphine structure. Moreover, the bidentate ligand $[(Cy_2PCH_2)_2]$ completely inhibited the reaction (entry 4). This observation prompted us to investigate whether $[Ni(cod)_2]$ might be solely responsible for the reactivity. The Lewis acid present in the reaction might potentially bind the free phosphine resulting from dissociation[14] of the initially formed nickel(0) complex, thus shifting the equilibrium to $[Ni(cod)_2]$. Indeed, omitting the phosphine ligand in the reaction exclusively delivered the *exo* product **2a** with very good yield, thus surpassing the efficiency of the reaction with a phosphine (entry 5). Other aluminum-based Lewis acids like $AlEt_3$ or MAD[15] were inefficient as cocatalysts (entries 6 and 7). Although $[Ni(cod)_2]$ is an efficient cyclization catalyst, phosphine/nickel(0) complexes also deliver competent catalytic species, as $[(Cy_3P)_2Ni(C_2H_4)]$[16] displayed similar reactivity to that of the $[Ni(cod)_2]$/phosphine combinations (entry 8). Importantly, the selectivity mode of the cyclization completely switched when using an N-heterocyclic carbene (NHC) ligand (IMes) under otherwise identical reaction conditions (entry 9). The preformed complex $[IMes_2Ni]$[17] performed similarly to the in situ $[Ni(cod)_2]$/IMes combination, thus indicating little contribution of cod ligand to the catalytic activity in this case (entry 10). The bulkier IPr ligand afforded a higher overall reaction yield albeit with a marginally lower selectivity (entry 11). Both parameters could be improved in the presence of MAD (entry 12). Interestingly, the usage of saturated analogue SIPr led to a significant erosion of the selectivity and drop in the yield (entry 13).

With the two sets of reaction conditions for a powerful switch between *endo*/*exo* cyclization modes, the scope of the cyclization was evaluated (Table 2). Notably, exclusive formation of either product **2** or **3** could be attained for all the substrates **1** independent of their structure. For some instances, slight fine-tuning of the reaction conditions was required to enhance the selectivity. The deuterated 6-D-pyridone **1b** underwent complete deuterium transfer to the methyl group of **2b** in the *exo*-cyclization mode and to the methylene group of **3b** in the *endo*-cyclization mode. These findings strongly support the C6–H nickel(0) insertion/hydroarylation mechanism suggested by Nakao, Hiyama, and co-workers.[8] Moreover, the absence of any deuterium scrambling indicates an irreversible hydroarylation step. The *exo* cyclization of **1c**, bearing an existing stereogenic center in the tether, provided the more stable *trans*-product **2c** with a 4:1 selectivity. Most substrates bearing 1,2-disubstitited double bonds were efficiently transformed through both cyclization modes, thus affording the corresponding pyridones **2d–f** and **3d–f**. Interestingly, *trans*-**1d** showed a higher reactivity than the corresponding *cis*-**1d** (entries 3 and 4), despite the presumed higher affinity of the latter to the metal center.[18] The pyridone **1f** underwent smooth cyclizations in both modes to give the *cis*-fused tricycle **2f** as well as the bridged tricycle **3f** (entry 6). The related *N*-Boc-containing substrate **1g** worked efficiently in the *exo* mode, but failed to give the *endo*-cyclization product, probably because of the bulk of the N-Boc moiety (entry 7). The substrate **1h**, containing a 1,1-dialkyl-substituted olefin, smoothly delivered the *endo*-product **3h**. In this case, the *exo* cyclization was not possible, and is likely to be the result of the congested nickelacycle with the metal at the tertiary carbon atom.[19] Along the same lines, trialkyl-substituted olefins (**1i** and **1j**) are competent as long as it does not involve a nickel/tertiary carbon organometallic intermediate (entries 8 and 9). In contrast, the formation of quaternary carbon centers is possible with aryl-substituted olefins (entries 11–14), thus indicating a stabilization via a η^3-benzylic-nickel intermediate.[8,20] The *endo* cyclization of **1n** produced the *trans*-product **3n** in moderate diastereoselectivity (entry 14). The minor *cis* isomer is probably formed

Table 2: Scope of regioselective cyclization.[a]



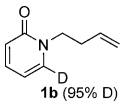
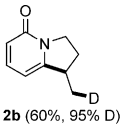
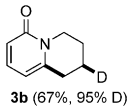
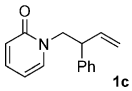
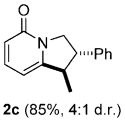
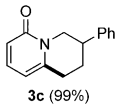
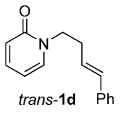
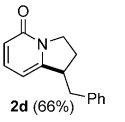
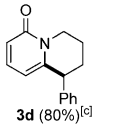
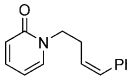
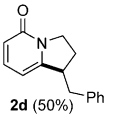
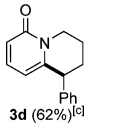
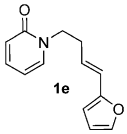
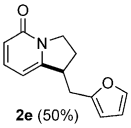
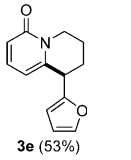
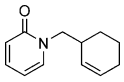
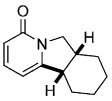
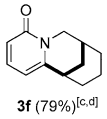
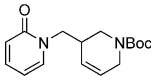
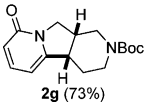
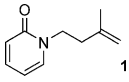
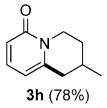
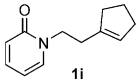
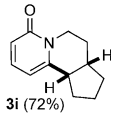
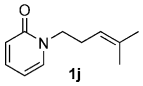
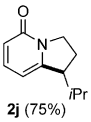
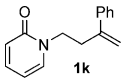
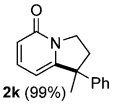
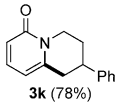
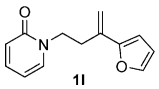
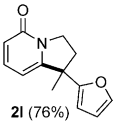
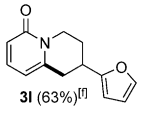
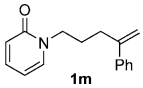
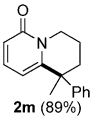
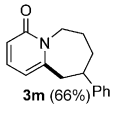
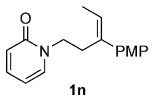
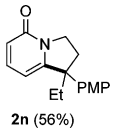
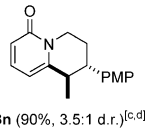
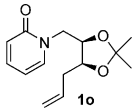
Entry	Substrate **1**	**2**[b]	**3**[b]
1	 **1b** (95% D)	 **2b** (60%, 95% D)	 **3b** (67%, 95% D)
2	 **1c**	 **2c** (85%, 4:1 d.r.)	 **3c** (99%)
3	 *trans*-**1d**	 **2d** (66%)	 **3d** (80%)[c]
4	 *cis*-**1d**	 **2d** (50%)	 **3d** (62%)[c]
5	 **1e**	 **2e** (50%)	 **3e** (53%)
6	 **1f**	 **2f** (80%)	 **3f** (79%)[c,d]
7	 **1g**	 **2g** (73%)	n.r.[e]
8	 **1h**	n.r.[e]	 **3h** (78%)
9	 **1i**	n.r.[e]	 **3i** (72%)
10	 **1j**	 **2j** (75%)	n.r.[f]
11	 **1k**	 **2k** (99%)	 **3k** (78%)
12	 **1l**	 **2l** (76%)	 **3l** (63%)[f]
13	 **1m**	 **2m** (89%)	 **3m** (66%)

Table 2: (Continued)

Entry	Substrate **1**	**2**[b]	**3**[b]
14	 **1n**	 **2n** (56%)	 **3n** (90%, 3.5:1 d.r.)[c,d]
15	 **1o**	n.r.[e]	**3o** (71%)
16	**1p**	**2p** (85%)	**3p** (88%)
17	**1q**	n.r.[e]	**3q** (87%)

[a] Conditions A: 0.10 mmol of **1**, 10 mol% $[Ni(cod)_2]$, 40 mol% $AlMe_3$, toluene (0.4 mL), 80 °C for 24 h; Conditions B: 0.10 mmol of **1**, 10 mol% $[Ni(cod)_2]$, 15 mol% IPr, 40 mol% $AlMe_3$, toluene (0.4 mL), 80 °C for 24 h. [b] Yield of isolated product. [c] MAD instead of $AlMe_3$. [d] IMes instead of IPr. [e] No conversion. [f] 100 °C. Boc = *tert*-butoxycarbonyl, PMP = *para*-methoxyphenyl.

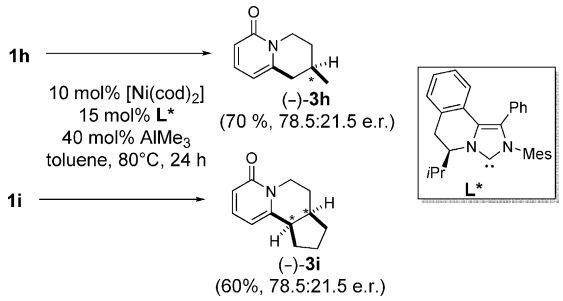
because of the concomitant double bond isomerization of **1n** promoted by the Ni–H species.[21,22] The medium-sized rings **3m**,**o** could be selectively obtained by *endo* cyclization (entries 13 and 15). Besides pyridones, the uracil **1p** is a competent substrate (entry 16). The benzopyridone **1q** gave *endo*-cyclization product **3q** in excellent yield, however failed in the *exo* mode as a result of rapid catalyst degradation (entry 16).

To showcase the viability of the developed cyclization for the synthesis of naturally occurring compounds, we turned our attention to the lupin alkaloid cytisine occurring in many *leguminosae* (Scheme 2).[23] (−)-Cytisine was identified as a potent and selective partial agonist for the α4β2 neuronal nicotinic acetylcholine receptor.[24] While smoothly reacting in the *exo* mode, the Boc-protected substrate **1g** previously failed for the *endo*-cyclization mode (Table 2, entry 7). Pleasingly, switching the Boc group for a benzoyl group (**1r**) enabled successful *endo* cyclization (Scheme 2). Higher

Scheme 2. Application of the *endo*-cyclization mode for the synthesis of the lupin alkaloid (±)-cytisine. brsm = based on recovered starting material, Bz = benzoyl.

amounts of Lewis acid were necessary to drive the cyclization to a better conversion, thus giving **3r** in acceptable yield. Acidic cleavage of the benzoyl group proceeded smoothly, thus affording (±)-cytisine in high yield.

We next explored the possibility to conduct the *endo*-cyclization mode[25] in enantioselective fashion using a chiral N-heterocyclic carbene[26] as a steering ligand. For instance, reaction of **1h** and **1i** in the presence of $[Ni(cod)_2]$, $AlMe_3$, and a chiral N-heterocyclic carbene (**L***) based on the isoquinoline framework developed by Hong et al.[27] delivered the corresponding enantioenriched pyridones (−)-**3h** and (−)-**3i** in 78.5:21.5 e.r. (Scheme 3).



Scheme 3. Preliminary results towards a catalytic asymmetric version of the *endo* cyclization with a chiral NHC ligand.

In summary, we report a regiodivergent and highly selective synthesis of 1,6-annulated 2-pyridones by intramolecular nickel(0)-catalyzed cyclization. The regioselectivity of the cyclization is fully controlled by the ligand and virtually independent of the ring size and olefin substitution pattern. Reaction in the presence of cyclooctadiene exclusively delivers *exo*-cyclization products, whereas bulky NHC ligands selectively promote the *endo*-cyclization mode. Notably, the method enables facile construction of quaternary carbon centers, medium-sized rings, and bicyclo[3.3.1]nonane skeletons. Relatively labile functional groups such as an acetonide and a Boc group are well tolerated. Moreover, the utility of transformation was exemplified by a concise synthesis of lupin alkaloid (±)-cytisine. Further work is directed towards the development of a more efficient asymmetric process and its application to the synthesis of 2-pyridone natural products.

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