



## Nickel-catalyzed decarboxylative cycloaddition of isatoic anhydrides with alkenes



Meng Sun, Yan-Na Ma, Ya-Min Li, Qiu-Ping Tian, Shang-Dong Yang\*

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, PR China

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### ABSTRACT

A new method for the synthesis of tricyclic 2,3-dihydro-4-quinolones by the  $\text{NiCl}_2(\text{PMe}_3)_2$ -catalyzed carboamination of alkenes by intermolecular decarboxylative cycloaddition reaction is reported here. Isatoic anhydrides were reacted with various norbornenes to afford the novel structure of quinolones. This protocol is simple and easy to handle.

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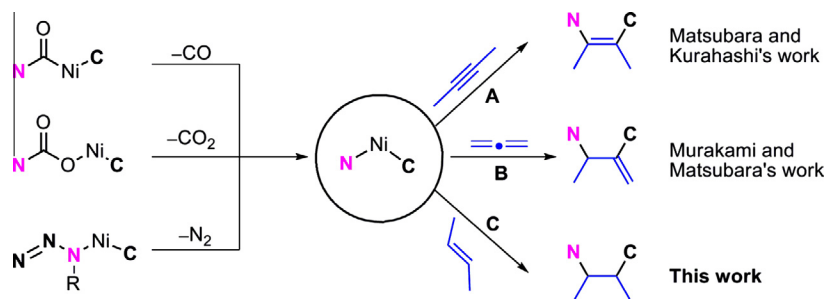
Tricyclic 2,3-dihydro-4-quinolones are found in a number of bioactive small molecules, including the acronycine family of alkaloids that possess potent anticancer properties.<sup>1</sup> As a result, strategies have been developed in order to synthesize this framework. The [4+2] cycloaddition reaction is one of the most straightforward methods of synthesis.<sup>2</sup> Another popular synthetic route is the intermolecular Diels–Alder reaction.<sup>3</sup> Moreover, decarboxylative reactions are also considered to be a powerful method.<sup>4</sup> Other methods also involve palladium-catalyzed enolate arylation.<sup>5</sup> However, despite a number of innovative synthetic approaches to such *N,O*-polyheterocycles have been reported, existing compound collections occupy only a small fraction of biogenic chemical space. Thus, in order to enable the discovery of bioactive chemotypes, the development of new and more efficient methods for the synthesis of novel heterocyclic molecules is crucial. Recently, a nickel(0)-catalyzed direct insertion of an unsaturated carbon–carbon bond into a carbon–nitrogen bond has offered a useful transformation. This process takes into account an atom and step economy which undertakes to prepare more complicated azacyclic compounds in a single step, namely the addition of C and N fragments to form C–C and C–N bonds simultaneously (Scheme 1).<sup>6–10</sup> It has been shown that heterocyclic compounds such as triazoles, phthalimides, phthalic anhydride, and isatoic anhydrides can work with Ni(0) through oxidative addition and then extrusion of gaseous molecules such as CO, CO<sub>2</sub>, and N<sub>2</sub> to generate an active species (C–Ni–N). This process leads to the carboamination of alkenes or

allenes and can be applied to the synthesis of different new heterocyclic compounds (Scheme 1, **A** and **B**).<sup>11–13</sup> However, only two precedents exist for such a potentially valuable methodology with alkenes;<sup>11f,13c</sup> the easy elimination of  $\beta$ -hydride elimination when alkenes are added or a process of rapid self-oligomerization may be the reason. Herein, we disclose a Ni(0), generated in situ, catalyzed cycloaddition of isatoic anhydrides with norbornenes by carboamination to synthesize quinolone derivatives (Scheme 1, **C**).

Our initial experiment began with *N*-methylisatoic anhydride (**1a**), which was treated with norbornene (**1b**),<sup>14</sup> 5 mol % Ni(cod)<sub>2</sub>, and 10 mol % PCy<sub>3</sub> in toluene at 100 °C for 24 h. Although only a trace of the desired product of **2a** was obtained, this result hinted to us that the reaction was practical. Therefore, we screened different trialkylphosphine ligands such as PMe<sub>3</sub>, P<sup>t</sup>-Bu<sub>3</sub>, PPh<sub>3</sub>, or *N*-heterocyclic carbene ligands, but no good result was found (Table 1, entries 2–5). Generally, some pioneering reports have shown that the addition of appropriate Lewis acid (LA) will effectively improve the conversion and yield of reactions.<sup>15</sup> Results of investigating diverse Lewis acids served to correct our tactics: the addition of Zn(OTf)<sub>2</sub> or Zn promoted the reaction, thus improving the yield 20% or 51% (Table 1, entries 6–14). This unsatisfying result prompted us to consider other accounts. We all know that the nickel(0) species is very active and prone to oxidation if stored improperly or imposed on an ill-defined operation. With this in mind, we subsequently concentrated our screening on the nickel(0) catalyst generated in situ and guaranteed its genuine and high activity. To our delight, when we selected NiCl<sub>2</sub>(PMe<sub>3</sub>)<sub>2</sub> and activated Zn powder as an additive in the reaction, the quinolone **2a** was obtained in 90% isolated yield (Table 1, entry 16). In addition,

\* Corresponding author. Tel./fax: +86 931 891 2859.

E-mail address: [yangshd@lzu.edu.cn](mailto:yangshd@lzu.edu.cn) (S.-D. Yang).



**Scheme 1.** Different pathways of nickel-catalyzed carboamination.

**Table 1**  
Reaction condition screening<sup>a,b,c</sup>

Entry	Cat. [mol %]	Ligand [mol %]	Additive [equiv]	Solvent	Yield [%] <sup>b</sup>
1	Ni(cod) <sub>2</sub> 5%	PCy <sub>3</sub>		toluene	<5%
2	Ni(cod) <sub>2</sub> 5%	PPh <sub>3</sub>		toluene	trace
3	Ni(cod) <sub>2</sub> 5%	Pt-Bu <sub>3</sub>		toluene	trace
4	Ni(cod) <sub>2</sub> 5%	Me <sub>3</sub> P		toluene	n. r.
5	Ni(cod) <sub>2</sub> 5%	IMes		toluene	n. r.
6	Ni(cod) <sub>2</sub> 5%	HOAc	AlMe <sub>2</sub> Cl (0.2)	toluene	n. r.
7	Ni(cod) <sub>2</sub> 5%	PCy <sub>3</sub>	BPh <sub>3</sub> (0.2)	toluene	n. r.
8	Ni(cod) <sub>2</sub> 5%	PCy <sub>3</sub>	Cu(OTf) <sub>2</sub> (0.2)	toluene	12%
9	Ni(cod) <sub>2</sub> 5%	PCy <sub>3</sub>	Mg(OTf) <sub>2</sub> (0.2)	toluene	9%
10	Ni(cod) <sub>2</sub> 5%	PCy <sub>3</sub>	Yb(OTf) <sub>3</sub> (0.2)	toluene	17%
11	Ni(cod) <sub>2</sub> 5%	PCy <sub>3</sub>	Zn(OTf) <sub>2</sub> (0.2)	toluene	20%
12	Ni(cod) <sub>2</sub> 5%	PCy <sub>3</sub>	ZnCl <sub>2</sub> (0.2)	toluene	n. r.
13	Ni(cod) <sub>2</sub> 5%	PCy <sub>3</sub>	FeCl <sub>3</sub> (0.2)	toluene	n. r.
14	Ni(cod) <sub>2</sub> 5%	PCy <sub>3</sub>	Zn (5.0)	toluene	51%
15	NiCl <sub>2</sub> (PMe <sub>3</sub> ) <sub>2</sub> 5%		Zn (5.0)	toluene	49% <sup>c</sup>
16	NiCl <sub>2</sub> (PMe <sub>3</sub> ) <sub>2</sub> 5%		Zn (5.0)	toluene	90%
17	NiCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub> 5%		Zn (5.0)	toluene	n. r.
18	NiCl <sub>2</sub> (dppf) 5%		Zn (5.0)	toluene	n. r.
19	NiCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> 5%		Zn (5.0q)	toluene	n. r.
20	NiCl <sub>2</sub> (PMe <sub>3</sub> ) <sub>2</sub> 5%		Zn (5.0)	dioxane	82%
21	NiCl <sub>2</sub> (PMe <sub>3</sub> ) <sub>2</sub> 5%		Zn (5.0)	THF	74%
22	NiCl <sub>2</sub> (PMe <sub>3</sub> ) <sub>2</sub> 5%		Zn (5%)	toluene	n. r.
23	NiCl <sub>2</sub> (PMe <sub>3</sub> ) <sub>2</sub> 5%		Zn (10%)	toluene	n. r.
24	NiCl <sub>2</sub> (PMe <sub>3</sub> ) <sub>2</sub> 5%		Zn (1.0)	toluene	trace
25	NiCl <sub>2</sub> (PMe <sub>3</sub> ) <sub>2</sub> 5%		Zn (2.0)	toluene	21%

<sup>a</sup>All the reactions were carried out in the presence of 0.5 mmol of **1a** and 0.75 mmol of **1b** in 5.0 mL toluene at 100 °C.

<sup>b</sup>Isolated yields.

<sup>c</sup>80 °C.

the product was also obtained in moderate yield under the condition of Ni(cod)<sub>2</sub> with PMe<sub>3</sub> and Zn. Lastly, the solvent screening showed that toluene is the best choice.

With the optimized conditions in hand, we next investigated the scope of various isatoic anhydrides in the reactions. Initially, a variety of N-protected isatoic anhydrides **1b–d** were surveyed, which were readily prepared from isatoic anhydride **1e**.<sup>16</sup> Reaction of the isatoic anhydrides **1b–d** with norbornene resulted in the corresponding N-substituted derivatives **2b–d** with good-to-excellent yields (Table 2). The results demonstrated that steric hindrance is not crucial to the cycloaddition reaction, although the corresponding yields were depressed with the increasing size of the N-substituted groups. It was encouraging that isatoic anhydrides **1e** also took part in this reaction, although the quinolone product was only isolated in a 29% yield. In order to study the impact of varying isatoic anhydride aromatic substituents in the

reaction of decarboxylative annulation, a wide variety of N-methyl benzo-substituted isatoic anhydrides **1f–o** were subjected to optimized conditions. The isatoic anhydrides, which possess electron-donating groups at the aromatic ring, proceeded to completion. High yields of quinolone compounds were therefore obtained. In particular, **1g** and **1i**, which had methyl substituents at the *para*-position or *ortho*-position of amides, provided quinolones **2g** and **2i** in 81% and 82% yields, respectively. However, lower amounts of **2j** and **2l** were obtained because of the high steric hindrance of **1j** and the decomposition of **1l** in reaction conditions. On the other hand, the quinolones were also isolated in good yields. The quinolones were originally isatoic anhydrides, which we substituted with electron-withdrawing groups as fluoro, trifluoromethyl, and methoxycarbonyl groups. The addition of norbornene across **1m** and **1n** afforded organofluorine quinolones in 74% and 70% yields. Moreover, we attributed the moderate yield obtained for

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