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Nickel-catalyzed Cycloadditions of Benzoxazinones with Alkynes: Synthesis of Quinolines and Quinolones

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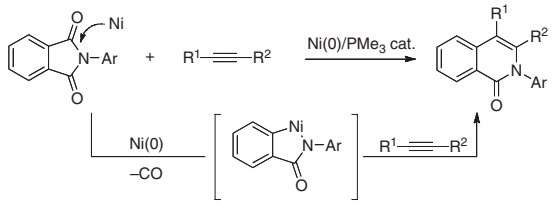
A nickel-catalyzed cycloaddition has been developed where readily available benzoxazinones react with alkynes to afford substituted quinolines or quinolones. The specific cycloaddition can be achieved by tuning a substituent on C2 of benzoxazinone in favor of the formation of quinolines or quinolones selectively.

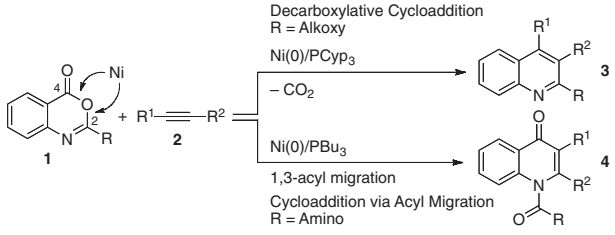
Transition-metal-catalyzed reactions have emerged as powerful methodologies for the syntheses of structurally diverse heterocycles.[1,2] Recently, we demonstrated nickel-catalyzed decarbonylative cycloaddition of *N*-arylphthalimides with alkynes via carboamination to give isoquinolones (Scheme 1).[3–5] The reaction proceeded via oxidative addition of an amide to Ni(0), subsequent decarbonylation and alkyne insertion. This prompted us to investigate such reactions that would allow us to prepare heterocyclic compound from readily available benzoxazinone.[6,7] Considering the structure of benzoxazinone derivatives **1**, two carbonyl moieties (C2 and C4) are potentially reactive toward nucleophilic attack (Scheme 2). That is, they possess two different reaction sites toward oxidative addition that may lead to different types of heterocyclic compound via cycloaddition with alkynes. Herein we wish to report our success in controlling the relative reactivity of two carbonyl moieties by tuning substituent R on the C2-position of benzoxazinone, which leads to specific cycloaddition of benzoxazinones **1** to alkynes **2** in favor of the formation of quinolines **3**[8] or quinolones **4**.[9]

Our working hypothesis is the following. If oxidative addition occurs at the C2 carbonyl triggered by the proximate effect by coordination of the substituent R to Ni(0), we presume that it would give quinoline **3** via decarboxylation and alkyne insertion (Scheme 3). To our delight, we found that 2-ethoxybenzoxazinone (**1a**) reacted with 4-octyne in the presence of Ni(0)/PMe_3 catalyst in refluxing xylene leading to quinoline **3a** in 23% yield (Table 1, Entry 1).[10,11] Among phosphine ligands examined, $PCyp_3$, tricyclopentylphosphine gave the best yield and the reaction afforded **3a** in 90% isolated yield (Entries 2–5). Trace amounts of **3a** were obtained in the cases where *N*-heterocyclic carbene ligands, such as IPr: 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene and IMes: 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene, were used in place of phosphine ligand. In other reaction solvent, such as toluene and THF, yields were even lower (Entries 6 and 7).

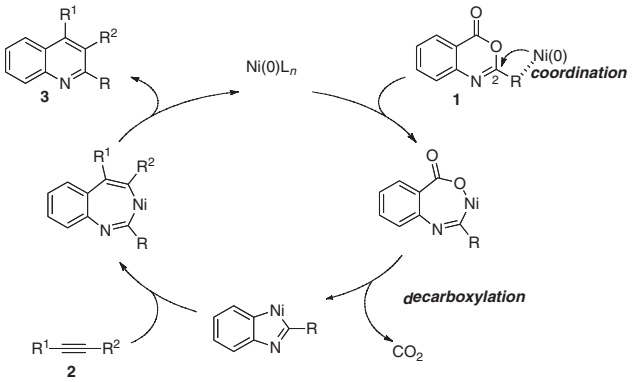
Under the optimized conditions, the decarboxylative cycloaddition of 4-octyne with 2-ethoxybenzoxazinone possessing an electron-donating or -withdrawing group affords the correspondingly substituted quinolines in moderate to excellent yields (Table 2). The decarboxylative cycloaddition of **1a** with 3-



Scheme 1. Cycloaddition of *N*-arylphthalimides with alkynes.

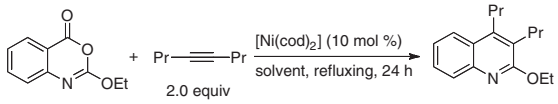


Scheme 2. Cycloaddition of benzoxazinones with alkynes.



Scheme 3. Working hypothesis.

Table 1. Nickel-catalyzed decarboxylative cycloaddition[a]

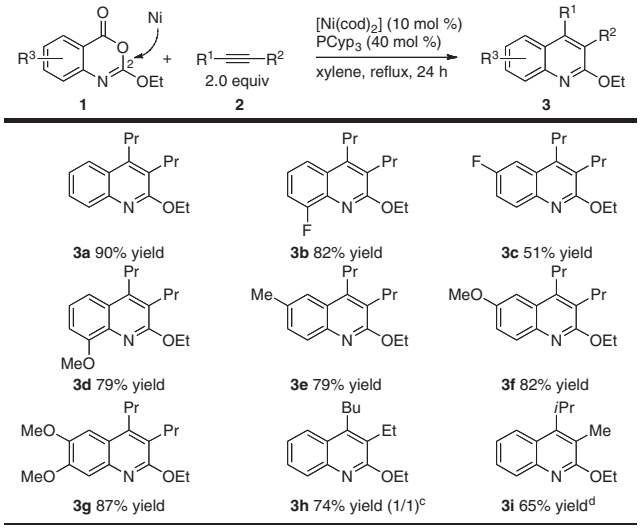


1a 2a 3a

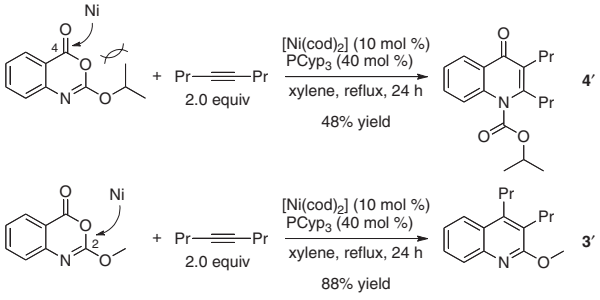
Entry	Ligand	Solvent	Yield/%
1	PMe_3	xylene	23
2	PBu_3	xylene	34
3	PPh_3	xylene	12
4	PCy_3	xylene	89
5	$PCyp_3$	xylene	90
6	$PCyp_3$	toluene	86
7	$PCyp_3$	THF	54

[a]All reactions were carried out using $[Ni(cod)_2]$ (10 mol %), ligand (40 mol %), **1a** (0.5 mmol), and **2a** (1.0 mmol) for 24 h.

Table 2. Decarboxylative cycloaddition of benzoxazinones **1** with alkynes **2**[a,b]



[a]All reactions were carried out using $[Ni(cod)_2]$ (10 mol %), $PCyp_3$ (20 mol %), **1** (0.5 mmol), and **2** (1.0 mmol) in 2 mL of refluxing xylene for 24 h. [b]Isolated yields. [c]Ratio of regioisomers. [d]Only a single regioisomer was formed.



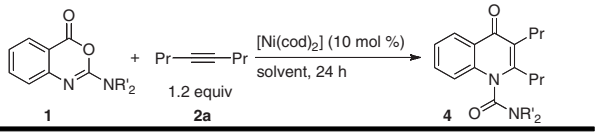
Scheme 4. Effects of substituent.

octyne gave the quinoline **3h** consisting of regioisomers in 1/1 ratio, whereas reaction with 4-methyl-2-pentyne gave the quinoline **3i** with high selectivity.

During the course of our study, we found that the reaction of 2-isopropoxybenzoxazinone with an alkyne gave a quinolone **4′** exclusively in 48% yield instead of a quinoline **3**, while the reaction of 2-methoxybenzoxazinone with an alkyne furnished quinoline **3′** (Scheme 4). Taking these results into account, we suspected that, with bulky heteroatom substituent on C2-position of benzoxazinone, we could control the oxidative addition to Ni(0) in favor of the formation of quinolones **4**. After thorough screening, it was found that an amino group is the most effective for that purpose (Table 3). The cycloaddition of 2-dimethylaminobenzoxazinone and 4-octyne with Ni(0) (10 mol %) and PBu_3 (40 mol %) in xylene (80 °C) led to quinolone **4** in 82% yield (Entry 1). Among dialkyl amines examined, morpholino afforded the highest yield of product **4** (90% yield, Entry 4). The reaction of 2-morpholinobenzoxazinone with 4-octyne (**2a**) did not gave any cycloadduct **4** in the case of using ligands, such as PPh_3, PCy_3, $PCyp_3$, instead of PBu_3 (Entries 6–8).

With the optimized conditions in hand, we next investigated the scope of this reaction (Table 4). Methoxy or trifluoromethyl

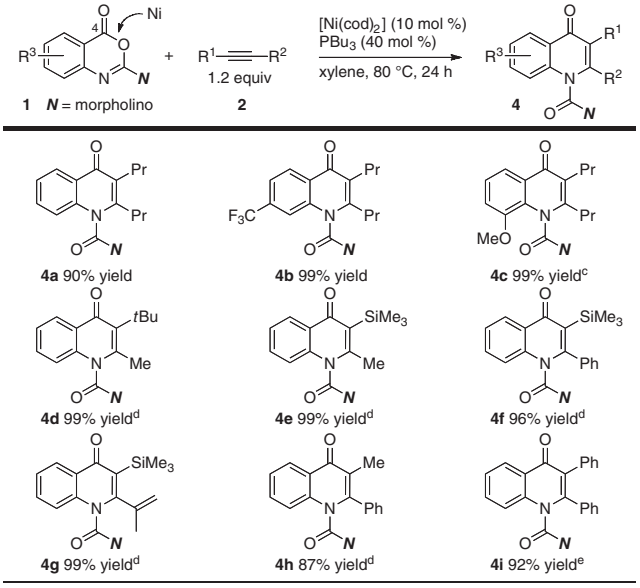
Table 3. Nickel-catalyzed cycloaddition via acyl migration[a]



Entry	NR'_2	Ligand	Yield/%
1	NMe_2	PBu_3	82
2	pyrrolidinyl	PBu_3	93
3	piperidino	PBu_3	96
4	morpholino	PBu_3	90
5	morpholino	PMe_3	62
6	morpholino	PPh_3	<1
7	morpholino	PCy_3	<1
8	morpholino	$PCyp_3$	<1

[a]All reactions were carried out using $[Ni(cod)_2]$ (10 mol %), ligand (40 mol %), **1** (0.5 mmol), and **2a** (1.0 mmol) in xylene (80 °C) for 24 h.

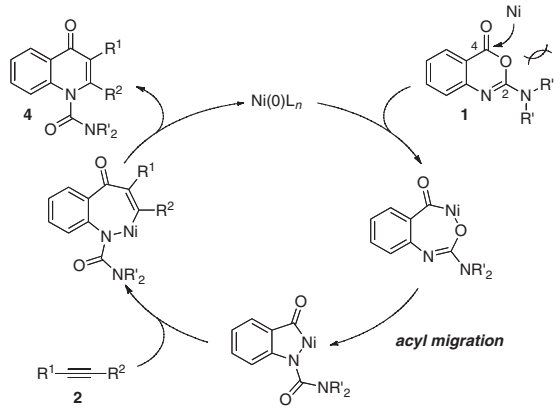
Table 4. Cycloaddition of benzoxazinones **1** with alkynes **2** via acyl migration[a,b]



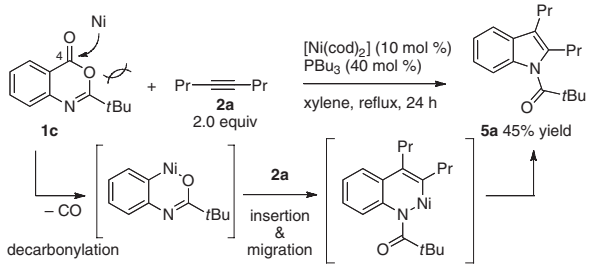
[a]All reactions were carried out using $[Ni(cod)_2]$ (10 mol %), PBu_3 (40 mol %), **1** (0.5 mmol), and **2** (0.6 mmol) in 2 mL of xylene (80 °C) for 24 h. [b]Isolated yields. [c]120 °C. [d]Only a single regioisomer was formed. [e]3 equivalents of alkyne was employed.

ring-substituents tolerated the reaction conditions well enough to furnish the corresponding quinolones **4b** and **4c** in excellent yields. Bulky *tert*-butyl- or trimethylsilyl-substituted alkynes reacted with **1** to provide adducts with complete regiocontrol in excellent yields. Monoaryl-substituted alkyne also reacted with **1** to give **4h** in 87% yield. The reaction is also compatible with diphenylacetylene and afforded **4i** in 92% yield.

A plausible reaction pathway to account for the formation of quinolones **4** based on the observed results is outlined in Scheme 5. The catalytic cycle of the present reaction may consist of the oxidative addition of an ester CO–O bond on the C4 carbonyl to a Ni(0) complex.[12] Subsequent acyl migration prior to decarbonylation and coordination of alkyne **2** take place. The alkyne would then insert into the C–Ni bond to give 7-



Scheme 5. Plausible reaction mechanism.



Scheme 6. Cycloaddition via decarbonylation and acyl migration.

membered nickelacycle, which undergoes reductive elimination to give **4**,[13] and regenerates the starting Ni(0) complex.

It should be noted that the reaction of 2-*tert*-butylbenzoxazinone (**1c**) reacted with 4-octyne (**2a**) in the presence of Ni/PBu_3 catalyst to give indole **5a** in 45% yield as a sole product via decarbonylation and acyl migration (Scheme 6). Thus, all the results described above may suggest the effects of substituents on the C2-position of benzoxazinone as follows; (1) sterically hindered substituents led to the oxidative addition of less sterically hindered C4 carbonyl to Ni(0), and (2) dialkyl amino substituents accelerate acyl migration in preference to decarbonylation.

In conclusion, we developed a nickel-catalyzed cycloaddition of benzoxazinones and alkynes. It was demonstrated that specific cycloaddition can be achieved by tuning substituents in favor of the formation of quinolines or quinolones. Further efforts to expand the scope of the chemistry and studies of the detailed mechanism are currently underway in our laboratories.[14]

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