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Nickel-Catalyzed Decarboxylative Carboamination of Alkynes with Isatoic Anhydrides

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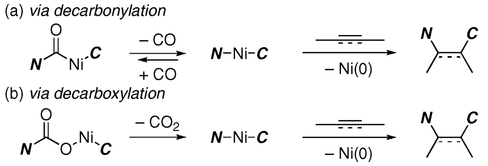
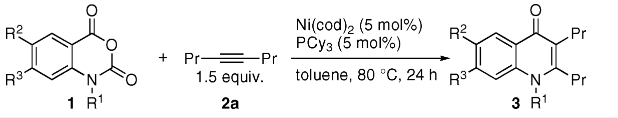
Addition of C and N fragments across unsaturated C−C bonds to form C−C and C−N bonds simultaneously (i.e., carboamination) would be a potentially useful and straightforward method for introducing a nitrogen atom function into organic molecules.[1−4] Recently, we demonstrated that oxidative addition of an amide to a Ni(0) complex and subsequent decarbonylation afford C−Ni−N species,[5,6] which lead to the carboamination of alkynes (Scheme 1a).[7] A key step in the reaction is migratory extrusion of CO. The extruded CO should be removed from the reaction system for an efficient catalytic cycle, since it interacts very strongly with Ni and saturates the coordination sites, thus interfering with regeneration of an active catalyst or causing the reverse. We postulated that an active species (C−Ni−N) might be generated alternatively via oxidative addition of a carbamate to Ni(0) followed by decarboxylation (Scheme 1b). This would allow for robust carboamination of alkynes, since CO_2 coordinates to Ni much less strongly than CO does.[8,9] Thus, we attempted the addition of isatoic anhydride **1** to alkyne **2** to form quinolone **3** using a Ni(0) catalyst.[7,10]

Scheme 1. Nickel-Catalyzed Carboamination via Decarbonylation and Decarboxylation



Initially, *N*-phenylisatoic anhydride (**1a**) was treated with 4-octyne (**2a**), 5 mol % $Ni(cod)_2$, and 5 mol % PCy_3 in toluene at 80 °C for 24 h. This led to formation of quinolone **3aa** in 97% isolated yield (Table 1, entry 1). Under the same conditions, the decarboxylative carboaminations of **2a** with *N*-arylisatoic anhydrides possessing electron-donating and -withdrawing groups also provided quinolones in 95 and 96% yield, respectively (entries 2 and 3). The reaction of *N*-methylisatoic anhydride (**1d**) with **2a** also gave the product **3da** in 93% yield (entry 4). The reactions of *N*-cyclopropyl-substituted and *N*-Boc-protected isatoic anhydrides with **2a** also afforded the correspondingly substituted quinolones in 69 and 99% yield, respectively (entries 5 and 6). Ring-substituted *N*-phenylisatoic anhydrides possessing electron-donating and -withdrawing groups also provided the corresponding quinolones in excellent yields (entries 7 and 8).

Table 1. Nickel-Catalyzed Decarboxylative Carboamination of 4-Octyne with Isatoic Anhydrides[a]

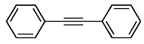
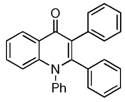
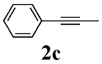
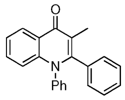
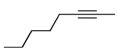
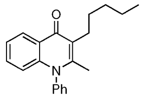
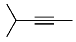
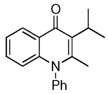
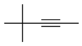
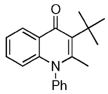
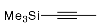
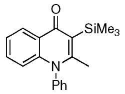
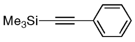
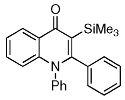
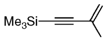
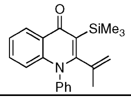


entry	R^1	R^2	R^3	1	3	yield (%)[b]
1	Ph	H	H	**1a**	**3aa**	97
2	4-MeO-C_6H_4	H	H	**1b**	**3ba**	95
3	4-CF_3−C_6H_4	H	H	**1c**	**3ca**	96
4	Me	H	H	**1d**	**3da**	93
5	cyclopropyl	H	H	**1e**	**3ea**	69[c]
6	Boc	H	H	**1f**	**3fa**	99[c]
7	Ph	MeO	H	**1g**	**3ga**	95
8	Ph	H	CF_3	**1h**	**3ha**	92

[a] Reactions were carried out using $Ni(cod)_2$ (5 mol %), PCy_3 (5 mol %), isatoic anhydride (0.5 mmol), and **2a** (0.75 mmol) in 2 mL of toluene at 80 °C for 24 h. [b] Isolated yields. [c] The reaction was carried out at 60 °C to prevent decomposition of the substrate.

We next investigated the scope of the reaction using various alkynes. The carboamination was also compatible with an aryl-substituted alkyne (Table 2, entry 1), affording the corresponding quinolone **3ab** in 66% yield. The reaction of **1a** with the

Table 2. Nickel-Catalyzed Decarboxylative Carboamination of Alkynes with **1a**[a]

entry	2	3		yield (%)[b]
1	 **2b**		**3ab**	66[c]
2	 **2c**		**3ac**	69[c] (3/1)[d,e]
3	 **2d**		**3ad**	86 (2/1)[d,e]
4	 **2e**		**3ae**	94 (6/1)[d,f]
5	 **2f**		**3af**	90[e]
6	 **2g**		**3ag**	90[e]
7	 **2h**		**3ah**	94[e]
8	 **2i**		**3ai**	69[e]

[a] Reactions were carried out using $Ni(cod)_2$ (5 mol %), PCy_3 (5 mol %), **1a** (0.5 mmol), and alkyne (0.75 mmol) in 2 mL of toluene at 80 °C for 24 h. [b] Isolated yields. [c] Pyridine was used as the solvent instead of toluene. [d] Ratio of regioisomers. [e] The structure of the major product was determined by single-crystal X-ray structure analysis. [f] The structure of the major product was determined by NOE analysis.

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unsymmetrical alkynes **2c**−**e** gave the quinolones consisting of regioisomers in a range of ratios from 2/1 to 6/1 (entries 2−4), whereas reaction with **2f** gave quinolone **3af** with high selectivity (entry 5). Bulky trimethylsilyl-substituted alkynes **2g** and **2h** also reacted with **1a** to provide adducts with complete regiocontrol in 90 and 94% yield, respectively (entries 6 and 7). Trimethylsilyl-substituted enyne **2i** also reacted with **1a** to furnish **3ai** regioselectively in 69% yield.

A reaction pathway based on the observed results that accounts for the formation of quinolones **3** is outlined in Scheme 2. In view of the mechanism of the previously reported nickel-catalyzed cross-coupling reaction of anhydrides with organometallic reagents, it is reasonable to consider that the catalytic cycle of the present reaction should consist of oxidative addition of an anhydride O−CO bond to nickel.[11] Subsequent decarboxylation and coordination of alkyne affords Ni(II) intermediate **6**. The alkyne then inserts into the acyl−nickel bond to give nickelacycle **7**, which undergoes reductive elimination to give **3** and regenerate the starting Ni(0). The regioselectivity of the reaction can be rationalized in terms of the direction of alkyne insertion, in which the repulsive steric interaction is minimal between the bulkier R^L and the PCy_3 ligand on the nickel to give nickel(II) intermediate **6a**. Thus, the reaction of **1a** with **2e** using less sterically hindered ligands, such as PPh_3 and PMe_3, affords **3ae** with lower regioselectivity (Table 3, entries 2 and 3), while the reaction using a more sterically hindered N-heterocarbene ligand shows higher regioselectivity (entry 4).[12]

Scheme 2. Plausible Pathway for Decarboxylative Carboamination of Alkynes with Isatoic Anhydrides

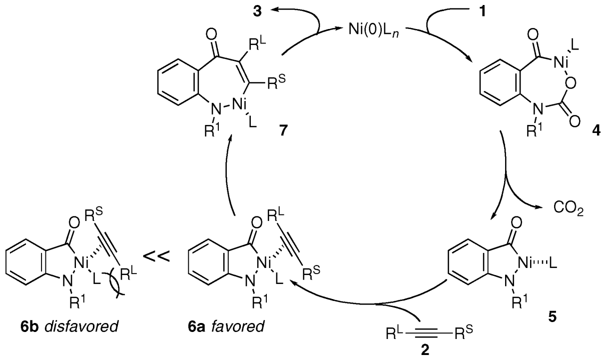
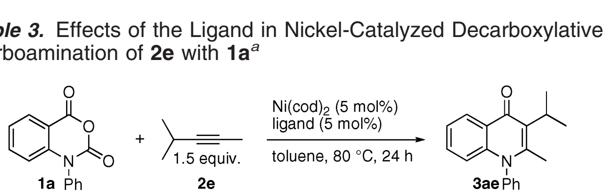


Table 3. Effects of the Ligand in Nickel-Catalyzed Decarboxylative Carboamination of **2e** with **1a**[a]



entry	ligand	ratio of regioisomers	yield (%)[b]
1	PCy_3	6/1	94
2	PPh_3	3/1	94
3	PMe_3	3/2	85
4	NHC[c]	10/1	50
5	P^tBu_3	3/1	94
6	$Cy_2PCH_2CH_2PCy_2$	5/1	74

[a] Reactions were carried out using Ni(cod)$_2$ (5 mol %), ligand (5 mol %), **1a** (0.5 mmol), and **2a** (0.75 mmol) in 2 mL of toluene at 80 °C for 24 h. [b] Isolated yields. [c] 1,3-Bis(2,6-diisopropyl)imidazol-2-ylidene.

In summary, we have demonstrated a new nickel-catalyzed reaction of alkynes with isatoic anhydrides to provide quinolones. We have shown that carbamates are susceptible to oxidative addition of a Ni(0) complex, which allows intermolecular addition to alkynes via decarboxylation. Further efforts to expand the scope of the chemistry and studies of the detailed mechanism are currently underway in our laboratories.

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Supporting Information Available: Experimental procedures, spectroscopic and analytical data for new compounds, and CIF files for **3ac**, **3ad**, and **3af**−**ai**. This material is available free of charge via the Internet at http://pubs.acs.org.

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