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Nickel-Catalyzed Cycloaddition of Salicylic Acid Ketals to Alkynes via Elimination of Ketones

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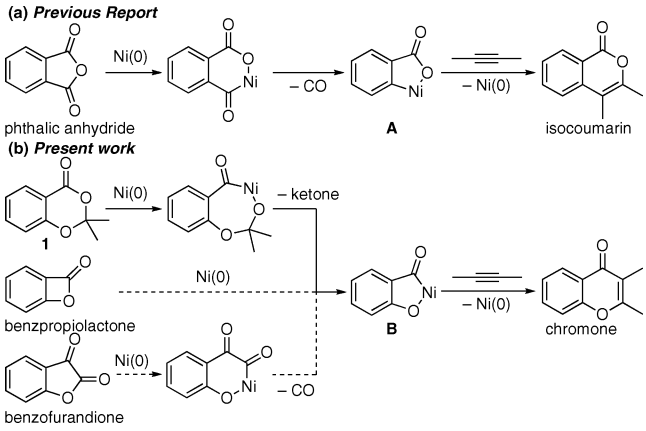
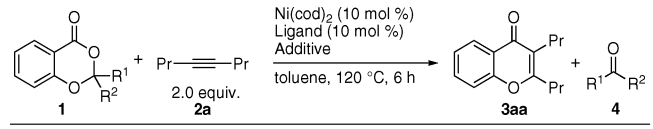
New methodology for rapid transformation from readily available starting materials into a complex molecule is in constant demand in modern organic synthesis. The transition metal catalyzed insertion reaction of an unsaturated carbon−carbon bond into a carbon−oxygen bond of an oxacyclic compound is a useful transformation to prepare more complicated oxacyclic compounds in a single step. Recently, we demonstrated that an oxidative addition of phthalic anhydrides to a Ni(0) complex and subsequent decarbonylation afford oxa-nickelacycle **A**, which allows insertion of alkynes to provide isocoumarins (Scheme 1a).[1] The result encouraged us to investigate the formation of an isomeric oxa-nickelacycle **B**, which leads to an isomeric compound of isocoumarins (e.g., chromones) by insertion of alkynes.[2] Although a direct oxidative addition of a Ni(0) complex to benzpropiolactone or a decarbonylative oxidative addition of a Ni(0) complex to benzofurandione would provide access to the oxa-nickelacycle **B** (Scheme 1b), such starting oxacyclic compounds are rather unstable and/or not readily available.[3] We postulated that an oxidative addition of a six-membered salicylic acid ketal **1**,[4] which can be readily prepared from salicylic acids and ketone, to a Ni(0) complex would give a seven-membered oxa-nickelacycle;[5] the advantage of seven-membered ring strain relief would enhance the β-elimination of a ketone to furnish the oxa-nickelacycle **B**.[6] Thus, we attempted the cycloaddition of salicylic acid ketal **1** to alkyne **2** using Ni(0) catalyst to form chromones **3**; this is an unprecedented substitution reaction of a ketone by an alkyne. That is, we can prepare heterocyclic compounds from readily available heterocyclic compounds.

Scheme 1. Nickel-Catalyzed Cycloaddition via Oxa-Nickelacycle Intermediates



Our initial experiments began with finding a ketone that is capable of β-elimination. We discovered that an addition of salicylic acid derivative **1a**, which eliminates benzophenone through the reaction, to 4-octyne (**2a**) with 10 mol % of Ni(0)/PCy_3 catalyst led to chromone **3aa** in 38% yield (Table 1, entry 1), while the reaction with salicylic acid acetal **1b** gave **3aa** in 24% yield via elimination of acetone (entry 2). Among the ligands examined, PCy_3 gave the best result. Trace or lower amounts of **3aa** were obtained in the cases using PMe_3, PPh_3, and IPr in place of PCy_3 (entries 3−5). Further examination of the reaction conditions revealed that an addition of 20 mol % of pyridine improved the yield of **3aa** to 56% (entry 6). On addition of 100 mol % of pyridine, the reaction proceeds to furnish the product in 99% and benzophenone **4** in 99% yield, respectively (entry 7). More basic or bulky amines, such as DMAP and DABCO, were not as efficient as pyridine (entries 8 and 9). Addition of a Lewis acid inhibits the reaction completely (entry 10).

Table 1. Optimization of the Reaction Conditions[a]



entry	R^1	R^2	**1**	ligand	additive (mol %)	conversion **1** (%)	yield **3aa** (%)
1	Ph	Ph	**1a**	PCy_3	—	42	38
2	Me	Me	**1b**	PCy_3	—	29	24
3	Ph	Ph	**1a**	PMe_3	—	12	9
4	Ph	Ph	**1a**	PPh_3	—	19	10
5	Ph	Ph	**1a**	IPr[b]	—	15	13
6	Ph	Ph	**1a**	PCy_3	pyridine (20)	60	56
7	Ph	Ph	**1a**	PCy_3	pyridine (100)	>99	99
8	Ph	Ph	**1a**	PCy_3	DMAP[c] (100)	48	43
9	Ph	Ph	**1a**	PCy_3	DABCO[d] (100)	21	13
10	Ph	Ph	**1a**	PCy_3	$ZnCl_2$ (20)	<1	<1

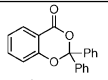
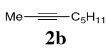
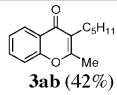
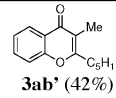
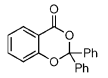
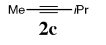
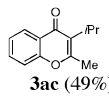
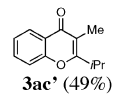
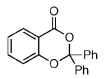
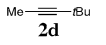
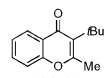
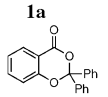
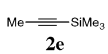
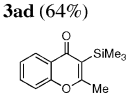
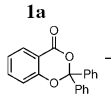
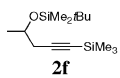
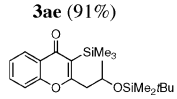
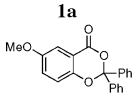
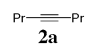
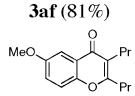
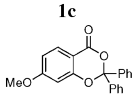
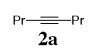
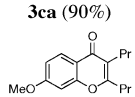
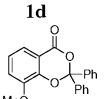
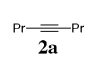
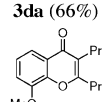
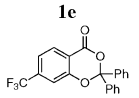
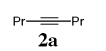
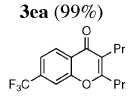
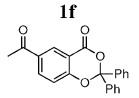
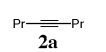
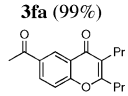
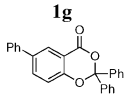
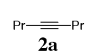
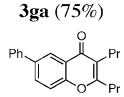
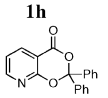
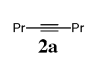
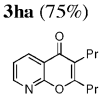
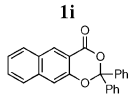
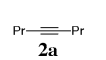
[a] Reactions were carried out using $Ni(cod)_2$ (10 mol %), ligand (10 mol %), **1** (0.5 mmol), and **2** (1.0 mmol) in 2 mL of toluene at 120 °C for 6 h in sealed tube. [b] 1,3-Bis(2,6-diisopropyl)imidazol-2-ylidene. [c] *N*,*N*-Dimethyl-4-aminopyridine. [d] 1,4-Dizabicyclo[2,2,2]octane.

With the optimized conditions in hand, we next investigated the use of other alkynes in this reaction. The reaction of **1a** with unsymmetrical alkynes such as 2-octyne (**2b**) and 4-methyl-2-pentyne (**2c**) gave the products consisting of regioisomers in a 1/1 ratio in 84 and 98% yields (Table 2, entries 1 and 2). Bulky *tert*-butyl- or trimethylsilyl-substituted alkynes such as **2d**, **2e**, and **2f** reacted with **1a** to provide adducts with complete regiocontrol in good yields (entries 3−5). However, terminal alkynes, such as 1-octyne and phenylacetylene, failed to participate in the reaction, presumably due to rapid oligomerization of alkynes. A range of electron-donating or -withdrawing ring substitutents tolerated the reaction conditions well enough to furnish the corresponding adducts in good to excellent yields (entries 5−11). The addition of **1i** to **2a** gave the product in 38% yield even with prolonged reaction time (entry 12). The reaction with **1j** with **2a** provided the corresponding adducts **3jk** in 99% yield (entry 13).

A plausible reaction pathway to account for the formation of chromone **3** based on the observed results is outlined in Scheme 2.

10.1021/ja904068p CCC: $40.75

Table 2. Nickel-Catalyzed Cycloaddition of **1** to **2** via Elimination of Benzophenone[a]

entry	1	2	3 (yield[b])	
1	 **1a**	 **2b**	 **3ab** (42%)	 **3ab'** (42%)
2	 **1a**	 **2c**	 **3ac** (49%)	 **3ac'** (49%)
3	 **1a**	 **2d**	 **3ad** (64%)	
4	 **1a**	 **2e**	 **3ae** (91%)	
5	 **1a**	 **2f**	 **3af** (81%)	
6	 **1c**	 **2a**	 **3ca** (90%)	
7	 **1d**	 **2a**	 **3da** (66%)	
8	 **1e**	 **2a**	 **3ea** (99%)	
9	 **1f**	 **2a**	 **3fa** (99%)	
10	 **1g**	 **2a**	 **3ga** (75%)	
11	 **1h**	 **2a**	 **3ha** (75%)	
12[c]	 **1i**	 **2a**	 **3ia** (38%)	
13	 **1j**	 **2a**	**3ja** (99%)	

[a] All reactions were carried out using $Ni(cod)_2$ (10 mol %), PCy_3 (10 mol %), pyridine (100 mol %), **1** (0.5 mmol), and **2** (1.0 mmol) in 2 mL of toluene at 120 °C for 24 h in sealed tube. [b] Isolated yields. [c] Reaction time: 72 h.

In view of the mechanism of the previously reported nickel-catalyzed addition reaction of phthalic anhydrides with alkynes,[2] it is reasonable to consider that the catalytic cycle of the present reaction should consist of the oxidative addition of an ester CO−O bond to a Ni(0) complex. Subsequent elimination of benzophenone (**4a**) and coordination of alkyne **2** take place, in which the steric repulsive interaction is minimal between the bulkier R^1 and the PCy_3 ligand on the nickel, to give nickel(II) intermediate **7a**. The alkyne would then insert into the C−Ni bond to give nickelacycle

Scheme 2. Plausible Reaction Mechanism

8, which undergoes reductive elimination to give **3** and regenerates the starting Ni(0) complex.

In conclusion, we have developed a new nickel-catalyzed cycloaddition of salicylic acid ketals to alkynes, which opens the way for divergent synthesis of chromones. We also demonstrated that ketones are capable of β-elimination, which allows formation of the key oxa-nickelacycle intermediate. 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 including spectroscopic and analytical data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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