Nickel-Catalyzed Cycloaddition of *o*-Arylcarboxybenzonitriles and Alkynes via Cleavage of Two Carbon−Carbon σ Bonds

Kenichiro Nakai, Takuya Kurahashi,* and Seijiro Matsubara*

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 615-8510, Japan

S *Supporting Information*

ABSTRACT: An intermolecular cycloaddition reaction has been developed, where *o*-arylcarboxybenzonitriles react with alkynes to afford coumarins in the presence of Ni-(0)/P(CH$_2$Ph)$_3$/MAD as a catalyst. The reaction process displays an unusual mechanistic feature—the cleavage of two independent C−CN and C−CO bonds.

The development of chemical transformations involving activation of the carbon−carbon σ bond is an ongoing challenge in organometallic chemistry, because it allows novel transformations that are difficult to achieve by conventional synthetic methods.[1] Herein, we report that *o*-arylcarboxybenzonitriles **1** react with alkynes **2** in the presence of a nickel catalyst to afford coumarins **3**; the reaction proceeds with the cleavage of two carbon−carbon σ bonds and the insertion of alkynes to form two carbon−carbon σ bonds (Scheme 1).[2−4]

Scheme 1. Cycloaddition via C−C σ Bond Cleavage
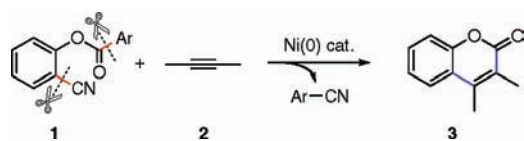
Initially, when *o*-arylcarboxybenzonitrile **1a** and 4-octyne (**2a**) were treated in the presence of a nickel catalyst, which was prepared in situ from Ni(cod)$_2$ (10 mol %) and PMe$_3$ (20 mol %) with methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) as a cocatalyst (30 mol %) in toluene at 120 °C for 12 h,[5] coumarin **3aa** was obtained in 38% yield (Table 1, entry 1). Upon optimization of the nickel catalyst, the cycloadduct **3aa** was obtained in excellent yield; a combination of Ni(cod)$_2$ and P(CH$_2$Ph)$_3$ was found to be effective in affording **3aa** in 80% yield (entry 6). The use of other phosphine ligands or 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes) gave inferior results (entries 2−5). In optimizing the molecular ratio of Ni(cod)$_2$ and P(CH$_2$Ph)$_3$ to employ for the reaction, it was found that a ratio of 1:1 provided **3aa** in 81% yield (entry 7). In the absence of the MAD cocatalyst, the formation of **3aa** was not observed at all (entry 8). The use of Lewis acids such as AlMe$_3$ and BPh$_3$ along with Ni(cod)$_2$/P(CH$_2$Ph)$_3$ as a catalyst completely retarded the reaction (entries 9 and 10), whereas the use of B(C$_6$F$_5$)$_3$ as a cocatalyst afforded the desired cycloadduct **3aa** in 39% yield (entry 11).[3b] The amount of **3aa**

Table 1. Cycloaddition of 1 and 2a by Nickel Catalyst[a]
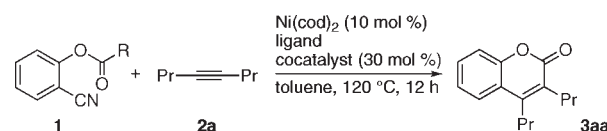
| entry	ligand (mol %)	cocatalyst	R	1	yield (%)[b]
1	PMe$_3$ (20)	MAD[c]	4-Me$_2$N-C$_6$H$_4$-	1a	38
2	PPh$_3$ (20)	MAD	4-Me$_2$N-C$_6$H$_4$-	1a	45
3	PCy$_3$ (20)	MAD	4-Me$_2$N-C$_6$H$_4$-	1a	68
4	P*t*Bu$_3$ (20)	MAD	4-Me$_2$N-C$_6$H$_4$-	1a	14
5	IMes (20)	MAD	4-Me$_2$N-C$_6$H$_4$-	1a	11
6	P(CH$_2$Ph)$_3$ (20)	MAD	4-Me$_2$N-C$_6$H$_4$-	1a	80
7	P(CH$_2$Ph)$_3$ (10)	MAD	4-Me$_2$N-C$_6$H$_4$-	1a	81
8	P(CH$_2$Ph)$_3$ (10)	—	4-Me$_2$N-C$_6$H$_4$-	1a	<1
9	P(CH$_2$Ph)$_3$ (10)	AlMe$_3$	4-Me$_2$N-C$_6$H$_4$-	1a	<1
10	P(CH$_2$Ph)$_3$ (10)	BPh$_3$	4-Me$_2$N-C$_6$H$_4$-	1a	<1
11	P(CH$_2$Ph)$_3$ (10)	B(C$_6$F$_5$)$_3$	4-Me$_2$N-C$_6$H$_4$-	1a	39
12	P(CH$_2$Ph)$_3$ (10)	MAD[d]	4-Me$_2$N-C$_6$H$_4$-	1a	99
13	P(CH$_2$Ph)$_3$ (10)	MAD	4-MeO-C$_6$H$_4$-	1b	80
14	P(CH$_2$Ph)$_3$ (10)	MAD	4-Me-C$_6$H$_4$-	1c	81
15	P(CH$_2$Ph)$_3$ (10)	MAD	C$_6$H$_5$-	1d	65
16	P(CH$_2$Ph)$_3$ (10)	MAD	4-CF$_3$-C$_6$H$_4$-	1e	49
17	P(CH$_2$Ph)$_3$ (10)	MAD	Mesityl-	1f	30
18	P(CH$_2$Ph)$_3$ (10)	MAD	Me-	1g	<1
19	P(CH$_2$Ph)$_3$ (10)	MAD	Me$_2$N-	1h	9

[a] Reactions were carried out using Ni(cod)$_2$ (10 mol %), ligand, cocatalyst (30 mol %), **1a** (0.5 mmol), and **2a** (1.5 mmol) in 3 mL of toluene at 120 °C for 12 h in a sealed tube. [b] Isolated yields are given. [c] MAD: methylaluminum bis(2,6-di-*tert*-butyl-4-methyl-phenoxide). [d] MAD (60 mol %).

attained quantitative yields on increasing the amount of MAD to 60 mol % (entry 12). With the optimized reaction conditions in hand, we next evaluated the effects of the *o*-arylcarboxy group on **1**. Benzonitriles consisting of the *o*-phenylcarboxy moiety with electron-donating substituents, such as dimethylamino, methoxy, and methyl groups, afforded **3aa** in good yields (entries 7, 13, and 14, respectively). Whereas benzonitrile **1d** possessing the *o*-phenylcarboxy moiety reacted with **2a** to afford **3aa** in 65% yield (entry 15), electron-withdrawing trifluoromethyl substituted *o*-phenylcarboxybenzonitrile **1e** and *o*-mesitylcarboxybenzonitrile

Scheme 2. Elimination of Ar—CN through Cycloaddition
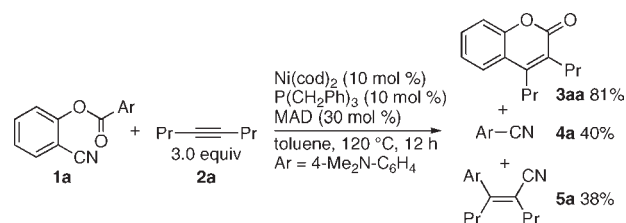
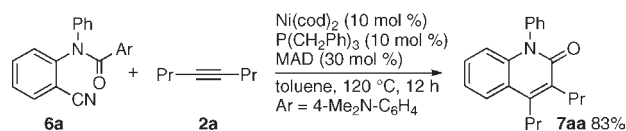1f reacted with 2a to afford 3aa in lower yields of 49% and 30%, respectively (entries 16 and 17). Neither o-acetoxybenzonitrile 1g nor o-carbamoyloxy benzonitrile 1h reacted with 2a to afford 3aa in sufficient yields (entries 18 and 19).

Detailed observations revealed that the present catalytic reaction proceeded together with the elimination of aryl cyanide 4 (Scheme 2). It was found that the reaction of 1a with 2a afforded 3aa in 81% yield and 4a in 40% yield. Furthermore, 3-aryl-2-cyano-4-octene 5a, which can be produced by the nickel-catalyzed addition reaction of 4a with 2a, was observed in 38% yield.[6]

In order to demonstrate the scope of this cycloaddition, we next examined the reaction of 4-octyne (2a) with various o-aryl-carboxybenzonitriles 1 having different functional groups (Table 2). Under the optimized reaction conditions, naphthonitrile 1i also reacted with 2a to afford 3ia in 99% isolated yield (entry 1). A range of electron-donating or -withdrawing ring substituents tolerated the reaction conditions well enough to furnish the corresponding cycloadducts 3 in good to excellent yields (entries 2−6). The reaction of 1a with unsymmetrical alkynes such as 1-methoxy-3-heptyne (2b) and 2-octyne (2c) afforded products consisting of regioisomers in ratios of 1/1 and 3/2 in 71% and 70% yields, respectively (entries 7 and 8).The regioselectivity of the cycloaddition with unsymmetrical alkynes may originate from the steric bulkiness of the substitution on an alkyne; the reaction of 1a with 4-methyl-2-pentyne (2d) afforded 3ad in 75% yield with a higher regioselectivity (entry 9). The molecular structure of the major cycloadduct 3ad was determined through X-ray crystal structure analysis. Moreover, bulky trimethylsilyl-substituted alkyne 2e reacted with 1c to provide the adduct 3ce with complete regiocontrol (entry 10). Mono-aryl-substituted internal alkyne 2f also reacted with 1c to afford 3cf in 90% yield (entry 11). Diphenylacetylene 2g participated in the reaction with 1c to afford the desired product, 3cg, in 59% yield (entry 12). However, terminal alkynes such as 1-octyne and phenylacetylene failed to participate in the reaction, presumably because of the rapid oligomerization of alkynes. As shown in Scheme 3, the present nickel-catalyzed cycloaddition can be applied not only to the synthesis of coumarin 3 but also to that of quinolone 7. The nickel-catalyzed reaction of alkyne 2a with o-arylamide-substituted benzonitrile 6a afforded quinolone 7aa in 83% yield.[8]

Scheme 3. Nickel-Catalyzed Cycloaddition To Form Quinolone

Table 2. Scope of Nickel-Catalyzed Cycloaddition[a]

entry	1	2	3 (yield[b])
1	1i	Pr≡Pr 2a	3ia (99%)
2	1j	Pr≡Pr 2a	3ja (95%)
3	1k	Pr≡Pr 2a	3ka (99%)
4	1l	Pr≡Pr 2a	3la (93%[c])
5	1m	Pr≡Pr 2a	3ma (95%[c])
6	1n	Pr≡Pr 2a	3na (75%[c])
7	1a	Pr≡—OMe 2b	3ab (71%, 1/1[d])
8	1a	Me≡C5H11 2c	3ac (70%, 3/2[d])
9	1a	Me≡iPr 2d	3ad (75%, 3/1[c,d])
10	1c	Me≡SiMe3 2e	3ce (36%[c])
11	1c	Pr≡Ph 2f	3cf (90%, 2/1[c,d])
12	1c	Ph≡Ph 2g	3cg (59%[c])

[a] Reactions were carried out using Ni(cod)₂ (10 mol %), P(CH₂Ph)₃ (10 mol %), MAD (30 mol %), 1 (0.5 mmol), and 2 (1.5 mmol) in 3 mL of toluene at 120 °C for 12 h in a sealed tube. [b] Isolated yields are given. [c] MAD (60 mol %). [d] Ratio of regioisomers.

In summary, we have developed an unprecedented type of cycloaddition; *o*-arylcarboxybenzonitrile reacted with alkynes to afford coumarins over a nickel catalyst. The reaction represents the first example of intermolecular cycloaddition involving the cleavage of two carbon−carbon σ bonds of two independent C−CN and C−CO bonds. Efforts to expand the scope of the reaction and detailed studies to elucidate its underlying mechanism are underway.[9]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Experimental procedures including spectroscopic and analytical data of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

tkuraha@orgrxn.mbox.media.kyoto-u.ac.jp; matsubar@orgrxn.mbox.media.kyoto-u.ac.jp

■ ACKNOWLEDGMENT

■ REFERENCES

(1) For reviews on carbon−carbon bond activation with a transition metal, see: (a) Bonesi, S. M.; Fagnoni, M. *Chem.—Eur. J.* **2010**, *16*, 13572. (b) Nečas, D.; Kotora, M. *Curr. Org. Chem.* **2007**, *11*, 1566. (c) Satoh, T.; Miura, M. *Top. Organomet. Chem.* **2005**, *14*, 1. (d) Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610. (e) van der Boom, M. E.; Milstein, D. *Chem. Rev.* **2003**, *103*, 1759. (f) Murakami, M.; Ito, Y. *Top. Organomet. Chem.* **1999**, *3*, 97. (g) Rybtchinski, B.; Milstein, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 870.

(2) For pioneering examples of nickel-catalyzed cycloaddition involving C−CO bond activation, see: (a) Murakami, M.; Ashida, S.; Matsuda, T. *J. Am. Chem. Soc.* **2005**, *127*, 6932. (b) Murakami, M.; Ashida, S. *Chem. Commun.* **2006**, 4599. (c) Ashida, S.; Murakami, M. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 885. (d) Murakami, M.; Makino, M.; Ashida, S.; Matsuda, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1315. (e) Murakami, M.; Ashida, S.; Matsuda, T. *Tetrahedron* **2006**, *62*, 7540.

(3) For examples of nickel-catalyzed C−CN bond activation in insertion reactions with carbon−carbon unsaturated compounds, see: (a) Nakao, Y.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 13904. (b) Nakao, Y.; Yada, A.; Ebata, S.; Hiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 2428. (c) Nakao, Y.; Yukawa, T.; Hirata, Y.; Oda, S.; Satoh, J.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 7116. (d) Hirata, Y.; Yukawa, T.; Kashihara, N.; Nakao, Y.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131*, 10964. For studies on an oxidative addition of a C−CN bond to nickel(0), see: (e) Brunkan, N. M.; Brestensky, D. M.; Jones, W. D. *J. Am. Chem. Soc.* **2004**, *126*, 3627. (f) García, J. J.; Arévalo, A.; Brunkan, N. M.; Jones, W. D. *Organometallics* **2004**, *23*, 3997. (g) García, J. J.; Brunkan, N. M.; Jones, W. D. *J. Am. Chem. Soc.* **2002**, *124*, 9547. (h) Favero, G.; Morvillo, A.; Turco, A. *J. Organomet. Chem.* **1983**, *241*, 251. (i) Abla, M.; Yamamoto, T. *J. Organomet. Chem.* **1997**, *532*, 267. (j) Parshall, G. W. *J. Am. Chem. Soc.* **1974**, *96*, 2360. (k) Morvillo, A.; Turco, A. *J. Organomet. Chem.* **1981**, *208*, 103.

(4) For examples of transition-metal-catalyzed reactions for synthesis of coumarins, see: (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.*

1996, *118*, 6305. (b) Kadnikov, D. V.; Larock, R. C. *Org. Lett.* **2000**, *2*, 3643. (c) Kadnikov, D. V.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 9423.

(5) (a) Maruoka, K.; Itoh, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 4573. (b) Maruoka, K.; Araki, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 2650.

(6) The nickel-catalyzed reaction of **1d** with **2a** also afforded **3aa** in 65% yield along with 3-phenyl-2-cyano-4-octene in 63% yield. This result may suggest that the electron-donating dimethylamino substituent on **1a** slows down the side reaction; the nickel-catalyzed insertion reaction of the resulting 4-dimethylaminobenzonitrile **4a** to **2a** proceeds at a slower rate than that of benzonitrile. For effects of an electron-donating substituent on benzonitrile in the nickel-catalyzed insertion reaction to alkynes, see ref 3a.

(7) The reactions of 4-octyne with *o*-arylcarboxybromobenzene or *o*-arylcarboxyanisole in place of *o*-arylcarboxybenzonitrile did not afford any cycloadduct.

(8) For examples of transition-metal-catalyzed reactions for synthesis of quinolones, see: (a) Kadnikov, D. V.; Larock, R. C. *J. Org. Chem.* **2004**, *69*, 6772. (b) Iwai, T.; Fujihara, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* **2010**, *132*, 9602.

(9) To probe the nature of the reaction mechanism, the reaction of **8** was performed in the presence of a nickel catalyst. In this case, both cycloadduct **3aa** and aryl cyanide **4a** were not obtained at all, and **8** was recovered quantitatively. This result may indicate that the present cycloaddition proceeds with the initial elimination of aryl cyanide **4** followed by the reaction with alkyne **2**.