Nickel-Catalyzed Decarbonylative Alkylidenation of Phthalimides with Trimethylsilyl-Substituted Alkynes

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Ⓢ *Supporting Information*

ABSTRACT: We have developed a nickel-catalyzed transformation, in which phthalimides react with trimethylsilyl-substituted alkynes in the presence of Ni(0)/PMe₃/MAD catalyst to provide isoindolinones. The reaction process displays an unusual mechanistic feature—decarbonylation and alkylidenation. The use of both trimethylsilyl-substitued alkynes and MAD was found to be essential for the transformation with high selectivities.

The transition-metal-catalyzed reaction of alkynes, which involves isomerizations of the π bond for constructing two more thermodynamically stable σ bonds, is widely used to form cyclic and acyclic molecular frameworks as precursors for complex organic compounds. A representative example would be transition-metal-catalyzed vicinal difunctionalization of internal alkynes, wherein various chemical bonds are cleaved and alkynes are inserted to provide tetrasubstituted alkenes in a single step.[1] The related alkylidenation, i.e., geminal difunctionalization of alkynes, has also been a research topic of great interest. Herein, we wish to report that the reaction of phthalimides with trimethylsilyl-substituted alkynes in the presence of a Ni(0) catalyst to provide isoindolinones through decarbonylation and alkylidenation.[2]

We previously demonstrated that the decarbonylative addition of phthalimides to alkynes provided isoquinolones in the presence of a Ni(0)/PMe₃ catalyst (Scheme 1a).[3] During the course of our study, we found that on addition of a catalytic amount of Lewis acid, the reaction afforded isoindolinones selectively via decarbonylation and alkylidenation of phthalimides with alkynes (Scheme 1b). The effects of Lewis acid and detailed reaction conditions were also examined.[4] These effects are summarized in Table 1. When phthalimide **1a** and alkyne

Scheme 1. Nickel-Catalyzed Decarbonylative Addition of Phthalimides to Alkynes
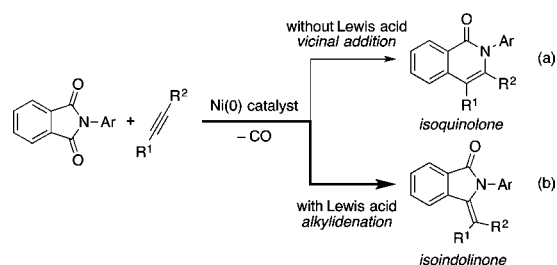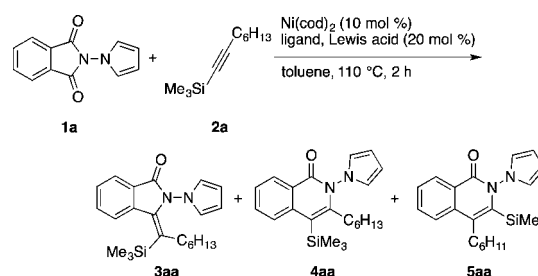

Table 1. Effects of Lewis Acid on the Nickel-Catalyzed Decarbonylative Alkylidenation[a]

entry	ligand (mol %)	Lewis acid	yield[b] (%)		
			3aa	4aa	5aa
1	PMe₃ (40)	–	<1	12	3
2	PMe₃ (40)	AlMe₃	20	22	18
3	PMe₃ (40)	MAD[c]	56	22	5
4	PMe₃ (40)	AlMe₂Cl	11	20	24
5	PMe₃ (40)	Al(OPh)₃	13	20	21
6	PMe₃ (40)	B(C₆F₅)₃	2	7	22
7	PMe₂Ph (40)	MAD[c]	38	40	7
8	PMePh₂ (40)	MAD[c]	3	24	<1
9	IPr[e] (20)	MAD[c]	<1	44	8
10	PMe₃ (20)	MAD[c]	82[d]	7[d]	3[d]
11	PMe₃ (10)	MAD[c]	35	3	8

[a]Reactions were carried out using Ni(cod)₂ (10 mol %), ligand, Lewis acid (20 mol %), **1a** (0.2 mmol), and **2a** (0.3 mmol) in 2 mL of toluene (110 °C) for 2 h. [b]Determined by ¹H NMR analysis using CHBr₃ as internal standard. [c]MAD: methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide). [d]Isolated yields are given. [e]IPr: 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

2a were treated in the presence of Ni(cod)₂ (10 mol %) and PMe₃ (40 mol %) in toluene at 110 °C for 2 h, isoquinolones **4aa** and **5aa** were obtained in 12% and 3% yields, respectively (entry 1). Isoindolinone **3aa** was obtained in 20% yield as a minor product when the same reaction was performed after adding trimethylaluminium (20 mol %) (entry 2). Methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) is a sterically bulky and monomeric homogeneous Lewis acid in organic solvent and consequently shows high Lewis acidity. The use of MAD was found to be effective in affording **3aa** in 56% yield (entry 3).[5] The use of Lewis acids, such as AlMe₂Cl, Al(OPh)₃ and B(C₆F₅)₃, was found to be less effective in

affording **3aa** (entries 4−6). When ligands, such as PMe$_2$Ph, PMePh$_2$ and 1,3-bis(2,6-diisopropylphenyl) imidazol-2-ylidene (IPr), were used in place of PMe$_3$, only trace or lower amounts of **3aa** were obtained (entries 7−9). Among the reaction solvents examined, toluene gave the best results in affording **3aa**. When optimizing the molecular ratio of Ni(cod)$_2$ and PMe$_3$ for the reaction, a ratio of 1:2 was found to provide **3aa** stereoselectively in 82% yield (entries 3, 10, 11).

After obtaining these optimized conditions, we next investigated the reaction of phthalimides **1** with 1-trimethylsilyl-substituted alkynes **2** having different functional groups (Table 2). Under the optimized reaction conditions, phthalimide **1a** also reacted with **2b** to afford **3ab** in 77% isolated yield (entry 2). A range of substituents tolerated the reaction conditions sufficiently to afford the correspondingly substituted isoindolinone **3** in good yields stereoselectively (entries 3−7). We also found that *N*-phenyl phthalimide (**1b**) can participate in the reaction with **2a** to afford **3ba** in 44% yield with prolonged reaction time (4 h) and increased amount of MAD (60 mol %); almost the rest of **1b** was recovered unchanged. The reaction of **1c** with **2a** under the same reaction conditions provided **3ca** in 73% yield as a sole isomer. However, *N*-aryl phthalimides, which had pyridine and diazine moiety as the substituent on the phthalimide nitrogen, did not afford any products.
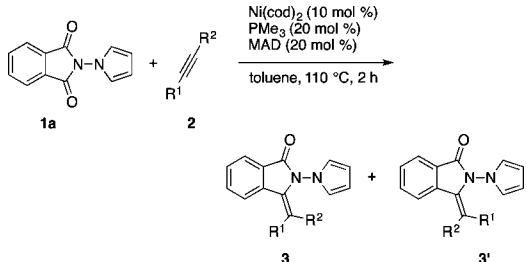
We next investigated the effects of substituents on alkynes **2**. As summarized in Table 3, the alkyne **2a** possessing the trimethylsilyl group exhibited better results in terms of providing isoindolinone **3aa** than dimethylphenylsilyl- or *tert*-butyldimethylsilyl-substituted alkynes **2h** and **2i** (entries 1−3). The reaction of **1a** with sterically hindered *tert*-butyl-substituted alkyne **2j** or 2-nonyne (**2k**) did not furnish isoindolinones (entries 4 and 5). It was found that aryl-substituted trimethylsilylacetylenes also participated in the decarbonylative 1,1-addition with phthalimide **1a** to afford the corresponding substituted isoindolinones (entries 6−8). The reaction of 1-phenyl-2-trimethylsilylacetylene (**2l**) with **1a** provided **3al** as a major product in 72% isolated yield and **3al′** as a minor product in 7% yield (entry 6). Although 1-aryl-2-trimethylsilylacetylene **2m**, which possesses the electron-withdrawing trifluoromethyl substituent on the phenyl group, reacted with **1a** to afford **3am** as a sole product (entry 7), electron-donating methoxy-substituted 1-aryl-2-trimethylsilylacetylene **2n** reacted with **1a** to afford **3an** and its isomer **3an′** in 53% and 21% yields, respectively. The molecular structures of the major product **3an** and minor product **3an′** were determined using X-ray crystal structure analysis (for details, see Supporting Information), and the configurations of all other examples were assigned analogously. The reaction of **1a** with other carbon−carbon unsaturated compounds, such as alkenes, 1,3-dienes, and allenes, in place of alkynes did not afford any 1,1-addition type products.

Although the mechanism of this reaction is not completely elucidated, we proposed the following reaction mechanism based on our observed results, to account for the unprecedented decarbonylative alkylidenation and stereochemical outcome of the reaction (Scheme 2). In view of the reaction mechanism of the previously reported nickel-catalyzed reaction of phthalimides with alkynes, the catalytic cycle of the present reaction could be considered to consist of the oxidative addition of an imide CO−N bond to a Ni(0) complex in association with MAD.[6] The subsequent decarbonylation and coordination of alkyne **2** takes place to afford a five-membered

Table 2. Scope of Nickel-Catalyzed Decarbonylative Alkylidenation[a]

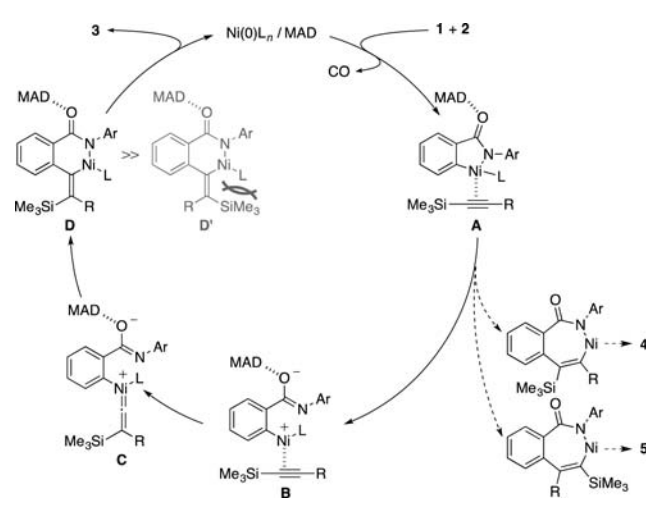| entry	1	2	3	yield[b] (%)
1	**1a**	**2a**	**3aa**	82
2	**1a**	**2b**	**3ab**	77
3	**1a**	**2c**	**3ac**	77
4	**1a**	**2d**	**3ad**	83
5	**1a**	**2e**	**3ae**	90
6	**1a**	**2f**	**3af**	69
7	**1a**	**2g**	**3ag**	64
8[c]	**1b**	**2a**	**3ba**	44
9[c]	**1c**	**2a**	**3ca**	73

[a]Reactions were carried out using Ni(cod)$_2$ (10 mol %), PMe$_3$ (20 mol %), MAD (20 mol %), **1** (0.2 mmol), and **2** (0.3 mmol) in 2 mL of toluene 110 °C for 2 h. [b]Isolated yields are given. [c]MAD (60 mol %) and reaction time was 4 h.

Table 3. Effects of Substituents on Alkynes in Decarbonylative Alkylidenation[a]

Scheme 2. Plausible Reaction Mechanism

nickelacycle **A**. MAD, which is coordinated to carbonyl oxygen, would then promote the formation of acyclic cationic nickel **B**; electron-rich phosphine ligand PMe_3 may also promote the formation of **B** by stabilizing the cationic nature of the nickel center. The nucleophilic addition of alkyne takes place to afford cationic nickel vinylidene complex **C** via a [1,2]-shift of the silyl group on alkyne **2**.[7−9] The insertion of vinylidene moiety to the carbon−nickel bond affords a six-membered nickelacycle **D**, which undergoes reductive elimination to furnish isoindolinone **3** and regenerates the starting Ni(0). The stereoselectivity of the reaction can be attributed to the direction of insertion of vinylidene moiety, in which the steric repulsive interaction is minimal between the sterically bulkier trimethylsilyl group and the phosphine ligand on the nickel to afford intermediate **D** in preference to **D′**.[10]

In summary, we have developed an unprecedented reaction pattern that provides isoindolinone with a nickel-catalyst and MAD-cocatalyst from phthalimides and trimethylsilyl-substituted alkynes. This reaction represents the first example of alkylidenation with alkynes involving decarbonylation. Efforts to expand the scope of the reaction as well as detailed studies to elucidate its underlying mechanism are underway.

■ ASSOCIATED CONTENT

ⓈSupporting Information

Experimental procedures, spectroscopic and analytical data for new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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[a]Reactions were carried out using Ni(cod)$_2$ (10 mol %), PMe$_3$ (20 mol %), MAD (20 mol %), **1** (0.2 mmol), and **2** (0.3 mmol) in 2 mL of toluene 110 °C for 2 h. [b]Isolated yields are given.

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■ REFERENCES

(1) For some selected reviews on vicinal difunctionalization of internal alkynes, see: (a) Beletskaya, I.; Moberg, C. *Chem. Rev.* **1999**, *99*, 3435. (b) Suginome, M.; Ito, Y. *Chem. Rev.* **2000**, *100*, 3221. (c) Oestreich, M.; Hartmann, E.; Mewald, M. *Chem. Rev.* **2013**, *113*, 402.

(2) The isoindolinone framework is widely found in various natural product and medicinal drug that exhibits a broad range of biological properties, e.g.: (a) Ren, J.; Esnouf, R. M.; Hopkins, A. L.; Stuart, D. I.; Stammers, D. K. *J. Med. Chem.* **1999**, *42*, 3845. (b) Belliotti, T. R.; Brink, W. A.; Kesten, S. R.; Rubin, J. R.; Wustrow, D. J.; Zoski, K. T.; Whetzel, S. Z.; Corbin, A. E.; Pugsley, T. A.; Heffner, T. G.; Wise, L. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1499. (c) Kawanishi, N.; Sugimoto, T.; Shibata, J.; Nakamura, K.; Masutani, K.; Ikuta, M.; Hirai, H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5122.

(3) (a) Kajita, Y.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2008**, *130*, 6058. (b) Miura, T.; Yamauchi, M.; Murakami, M. *Org. Lett.* **2008**, *10*, 3085.

(4) (a) Ikeda, S.; Mori, N.; Sato, Y. *J. Am. Chem. Soc.* **1997**, *119*, 4779. (b) Mahadevan, V.; Getzler, Y. D. Y. L.; Coates, G. W. *Angew. Chem., Int. Ed.* **2002**, *41*, 2781. (c) Kamijo, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 3230. (d) Getzler, Y. D. Y. L.; Mahadevan, V.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2002**, *124*, 1174. (e) Fontaine, F.-G.; Zargarian, D. *J. Am. Chem. Soc.* **2004**, *126*, 8786. (f) Ogoshi, S.; Ueta, M.; Arai, T.; Kurosawa, H. *J. Am. Chem. Soc.* **2005**, *127*, 12810. (g) Rubina, M.; Conley, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 5818. (h) Nakao, Y.; Yada, A.; Ebata, S.; Hiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 2428. (i) Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7734. (j) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 2448. (k) Baxter, R. D.; Montgomery, J. *J. Am. Chem. Soc.* **2008**, *130*, 9662. (l) Koester, D. C.; Kobayashi, M.; Werz, D. B.; Nakao, Y. *J. Am. Chem. Soc.* **2012**, *134*, 6544. (m) Nakai, K.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2011**, *133*, 11066.

(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) (a) Kajita, Y.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2008**, *130*, 17226. (b) Fujiwara, K.; Kurahashi, T.; Matsubara, S. *Org. Lett.* **2010**, *12*, 4548. (c) Ochi, Y.; Kurahashi, T.; Matsubara, S. *Org. Lett.* **2011**, *13*, 1374.

(7) (a) Yamazaki, S.; Katoh, S.; Yamabe, S. *J. Org. Chem.* **1992**, *57*, 4. (b) Crabtree, R. H. *New J. Chem.* **2003**, *27*, 771. (c) Pezacki, J. P.; Loncke, P. G.; Ross, J. P.; Warkentin, J.; Gadosy, T. A. *Org. Lett.* **2000**, *2*, 2733. (d) Barton, T. J.; Lin, J.; Ijadi-Maghsoodi, S.; Power, M. D.; Zhang, X.; Ma, Z.; Shimizu, H.; Gordon, M. S. *J. Am. Chem. Soc.* **1995**, *117*, 11695.

(8) For some recent examples of the use of unique reactivity of silyl substituted carbon–carbon unsaturated compounds in nickel-catalyzed reaction, see: (a) Ho, C.-Y.; He, L. *Chem, Commun.* **2012**, *48*, 1481. (b) Ogata, K.; Atsuumi, Y.; Fukuzawa, S. *Org. Lett.* **2011**, *13*, 122. (c) Shirakura, M.; Suginome, M. *J. Am. Chem. Soc.* **2009**, *131*, 5060. (d) Shirakura, M.; Suginome, M. *J. Am. Chem. Soc.* **2008**, *130*, 5410.

(9) For some examples of formation of vinylidene complexes from internal alkynes, see: (a) Ikeda, Y.; Yamaguchi, T.; Kanao, K.; Kimura, K.; Kamimura, S.; Mutoh, Y.; Tanabe, Y.; Ishii, Y. *J. Am. Chem. Soc.* **2008**, *130*, 16856. (b) Shaw, M. J.; Bryant, S. W.; Rath, N. *Eur. J. Inorg. Chem.* **2007**, 3943. (c) King, P. J.; Knox, S. A. R.; Legge, M. S.; Orpen, A. G.; Wilkinson, J. N.; Hill, E. A. *J. Chem. Soc., Dalton Trans.* **2000**, 1547.

(10) To gain insight into the reaction mechanism, partially ^{13}C-enriched alkynes were prepared and subjected to the reaction conditions for the nickel-catalyzed decarbonylative 1,1-addition (for details, see SI).