ORGANIC LETTERS

2011
Vol. 13, No. 5
1206–1209

Nickel-Catalyzed Cycloaddition of Anthranilic Acid Derivatives to Alkynes

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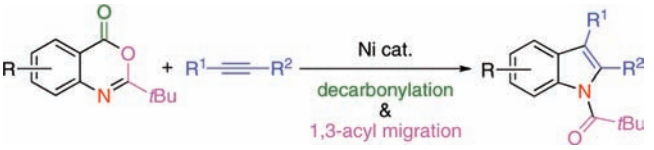
Received January 12, 2011

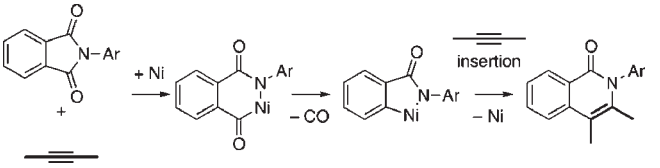
ABSTRACT



A nickel-catalyzed cycloaddition has been developed where readily available anthranilic acid derivatives react with alkynes to afford substituted indoles. The reaction involves oxidative addition of Ni(0) to an ester moiety, which allows intermolecular addition to alkynes via decarbonylation and 1,3-acyl migration.

Indoles are an important class of heterocyclic compounds because they are among the most ubiquitous compounds in both natural products and pharmaceuticals. Although there are a large number of methodologies for synthesis and structural transformation of an indole nucleus, the development of alternative methodologies, which would allow for straightforward access to structurally diverse indoles, remains an important research topic. In the past few decades, transition-metal-catalyzed reactions, such as Larock heteroannulation,[1] have emerged as powerful methodologies for the synthesis of structurally diverse indoles.[2,3] Recently, we demonstrated nickel-catalyzed decarbonylative cycloaddition of alkynes to five-membered heterocyclic compounds via carboamination to give six-membered heterocyclic compounds, namely [5 − 1 + 2] cycloaddition (Scheme 1).[4] Our success in synthesis of a heterocyclic compound from the readily available heterocyclic compound with cycloadditions prompted

Scheme 1. Nickel-Catalyzed [5 − 1 + 2] Cycloaddition



(1) For Larock heteroannulation, see: (a) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652. (b) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689.

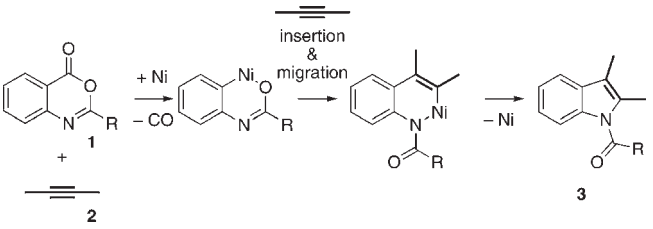
(2) For recent reviews, see: (a) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (b) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (c) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (d) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491. (e) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (f) Joule, J. A. In *Science of Synthesis*, Vol. 10; Thomas, E. J., Ed.; Thieme: Stuttgart, Germany, 2000; p 361. (g) Sundberg, R. J. *Indoles*; Academic Press: San Diego, CA, 1996. (h) Krüger, K.; Tillack, A.; Beller, M. *Adv. Synth. Catal.* **2008**, *350*, 2153.

(3) For some recent transition-metal-catalyzed indole syntheses, see: (a) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474. (b) Shimada, T.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 10546. (c) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024. (d) Bernini, R.; Fabrizi, G.; Sferrazza, A.; Cacchi, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 8078. (e) Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4572. (f) Barluenga, J.; Jiménez-Aquino, A.; Aznar, F.; Valdés, C. *J. Am. Chem. Soc.* **2009**, *131*, 4031. (g) Cao, C.; Shi, Y.; Odom, A. L. *Org. Lett.* **2002**, *4*, 2853. (h) Tillack, A.; Jiao, H.; Garcia Castro, I.; Hartung, C. G.; Beller, M. *Chem.—Eur. J.* **2004**, *10*, 2409. (i) Ackermann, L.; Born, R. *Tetrahedron Lett.* **2004**, *45*, 9541. (j) Zhang, Y.; Donahue, J. P.; Li, C.-J. *Org. Lett.* **2007**, *9*, 627. (k) Siebeneicher, H.; Bytschkov, I.; Doye, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3042. (l) Khedkar, V.; Tillack, A.; Michalik, M.; Beller, M. *Tetrahedron* **2005**, *61*, 7622. (m) Lu, B. Z.; Zhao, W.; Wei, H.-X.; Dufour, M.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2006**, *8*, 3271. (n) Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 11940.

10.1021/ol200090g
Published on Web 02/04/2011

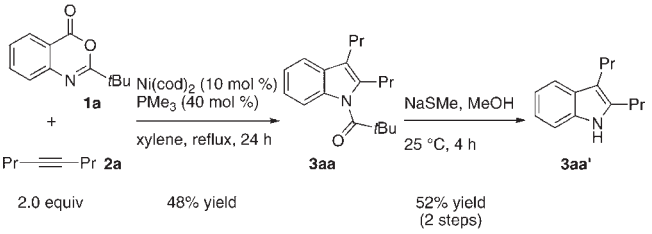
us to investigate a new reaction, which would allow us to prepare indoles from readily available heterocyclic compounds and alkynes.[5−7] Such a process enables the synthesis of indoles with substitution in a five-membered ring; it may find applications in drug discovery and development. Herein, we report our results of nickel-catalyzed [6 − 3 + 2] cycloaddition to provide indoles **3** from readily available anthranilic acid derivative **1** and alkyne **2**,[8] which may proceed via oxidative addition, decarbonylation, alkyne insertion, 1,3-acyl migration, and reductive elimination (Scheme 2).

Scheme 2. Nickel-Catalyzed [6 − 3 + 2] Cycloaddition



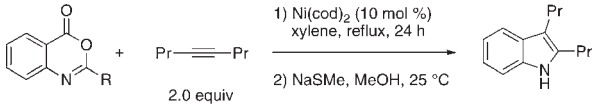
Initially, it was found that **1a** reacted with 4-octyne (**2a**) in the presence of $Ni(cod)_2$ (10 mol %) and PMe_3 (40 mol %) in refluxing xylene to afford *N*-pivaloyl-protected indole **3aa** in 48% yield along with a small amount of deprotected indole **3aa′** (Scheme 3). Deprotected indole **3aa′** was obtained as the sole product in 52% yield when the reaction crude mixture was treated with NaSMe in MeOH as a workup procedure. With the optimized workup procedure in hand, reaction conditions were further examined (Table 1). It was found that anthranilic acid derivative **1** with sterically hindered *tert*-butyl substituent R on the C2-position gave the best yield of indole **3aa′** (entry 1), while **1** with phenyl or methyl substituents gave inferior results (entries 2 and 3). Among the ligands examined, PPr_3 gave the best result and the reaction afforded **3aa′** in 62% yield (entry 7). Trace or lower amounts of **3aa** were obtained in the cases using ligands, such as

Scheme 3. Cycloaddition of **1a** to **2a**



1,2-bis(dimethylphosphino)ethane (dmpe), 1,2-bis(diphenylphosphino)ethane (dpppe), 1,2-bis(dimethylphosphino) ethane (dmpe), 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr), and 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes) (entries 10−13).

Table 1. Nickel-Catalyzed Decarbonylative Cycloadditions[a]



entry	R	ligand	yield (%)[b]
1	*t*Bu	PMe_3	52
2	Ph	PMe_3	11
3	Me	PMe_3	4
4	*t*Bu	PMe_2Ph	47
5	*t*Bu	$PMePh_2$	26
6	*t*Bu	PPh_3	<1
7	*t*Bu	PPr_3	62
8	*t*Bu	PBu_3	47
9	*t*Bu	PCy_3	11
10	*t*Bu	dppe[c]	<1
11	*t*Bu	dmpe[d]	3
12	*t*Bu	IPr[e]	<1
13	*t*Bu	IMes[f]	<1

[a] Reactions were carried out using $Ni(cod)_2$ (10 mol %), ligand (40 mol %), **1** (0.5 mmol), and **2a** (1.0 mmol) in 2 mL of refluxing xylene (160 °C) for 12 h . [b] Isolated yields. [c] 1,2-Bis(diphenylphosphino)ethane. [d] 1,2-Bis(dimethylphosphino)ethane. [e] 1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene. [f] 1,3-Bis(2,4,6-trimethylphenyl)imidazol-2-ylidene.

We next investigated the scope of this cycloaddition with the optimized reaction conditions and workup procedure (Table 2). A range of electron-donating or -withdrawing ring substitutents tolerated the reaction conditions well enough to furnish the corresponding indoles. Deprotection of **3ba** resulted in formation of an unstable indole **3ba′** to purify with silica gel chromatography, and thus the cycloadduct was isolated as *N*-pivaloyl-protected form **3ba** in 68% isolated yield (entry 1). Similarly, **3ca** was obtained by the reaction of **1c** and **2a** (entry 2). While trifluoromethyl-substituted substrate **1d** reacted with **2a** to afford indole **3da′** in 81% yield after the protocol (entry 3). Fluoro-substituted compounds, such as **1e**, **1f**, and **1g** also participated in the reaction to provide correspondingly

(4) (a) Kajita, Y.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2008**, *130*, 6058. (b) Kajita, Y.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2008**, *130*, 17226.

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(6) (a) Miura, T.; Yamauchi, M.; Murakami, M. *Org. Lett.* **2008**, *10*, 3085. (b) Yamauchi, M.; Morimoto, M.; Miura, T.; Murakami, M. *J. Am. Chem. Soc.* **2010**, *132*, 54. (c) Miura, T.; Yamauchi, M.; Kosaka, A.; Murakami, M. *Angew. Chem., Int. Ed.* 2010, *49*, 4955. (4) Miura, T.; Morimoto, M.; Yamauchi, M.; Murakami, M. *J. Org. Chem.* **2010**, *75*, 5359.

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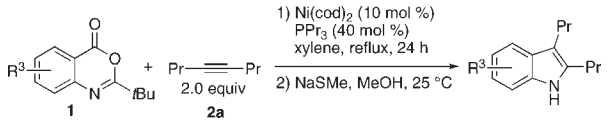
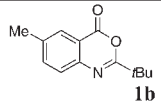
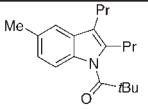
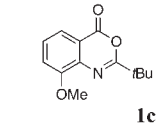
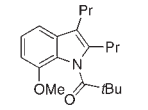
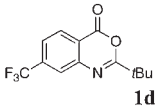
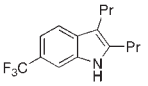
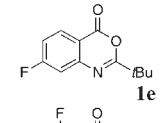
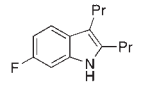
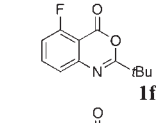
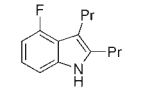
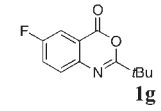
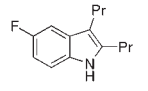
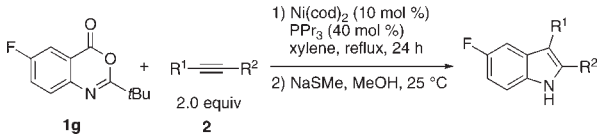
Table 2. Scope of the Cycloaddition[a]

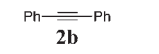
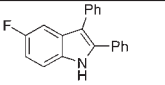
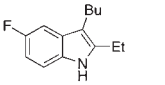
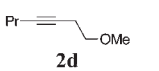
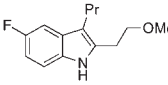
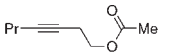
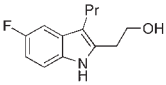
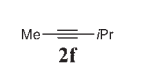
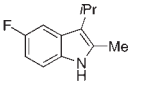
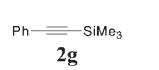
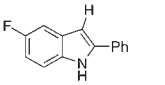
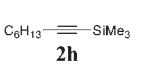
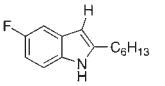
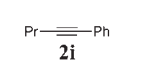
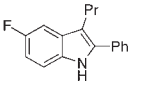


entry	1	product		yield (%)[b]
1	 **1b**		**3ba**	68
2	 **1c**		**3ca**	76
3	 **1d**		**3da'**	81
4	 **1e**		**3ea'**	52
5	 **1f**		**3fa'**	95
6	 **1g**		**3ga'**	95

[a] Reactions were carried out using $Ni(cod)_2$ (10 mol %), ligand (40 mol %), **1** (0.5 mmol), and **2a** (1.0 mmol) in 2 mL of refluxing xylene (160 °C) for 24 h . [b] Isolated yields.

Table 3. Cycloaddition of **1g** to Various Alkynes **2**[a]



entry	2	product		yield (%)[b]
1	 **2b**		**3gb'**	62
2	**2c**		**3gc'**	75 (1/1)[c]
3	 **2d**		**3gd'**	90 (1/1)[c]
4	 **2e**		**3ge'**	56 (1/1)[c]
5	 **2f**		**3gf'**	86 (1/1)[c]
6	 **2g**		**3gg'**	88
7	 **2h**		**3gh'**	94
8	 **2i**		**3gi'**	54

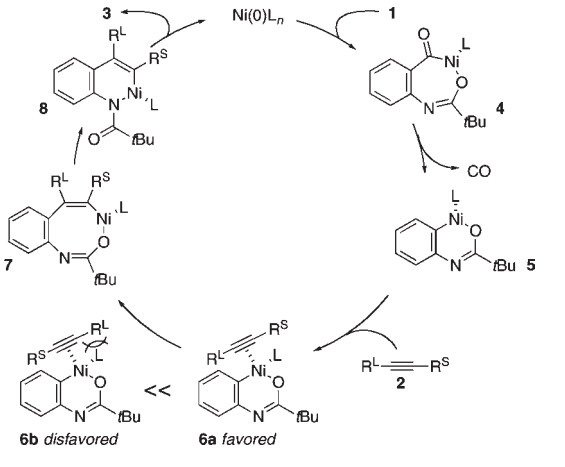
[a] Reactions were carried out using $Ni(cod)_2$ (10 mol %), ligand (40 mol %), **1g** (0.5 mmol), and **2** (1.0 mmol) in 2 mL of refluxing xylene (160 °C) for 12 h . [b] Isolated yields. [c] Ratio of regioisomers.

fluoro-substituted indoles in good to moderate yields (entries 4−6).

To extend the application of this protocol, examination of the alkynes was performed (Table 3). It was found that the reaction is also compatible with diphenylacetylene (**2b**) and afforded **3gb′** in 62% yield (entry 1). The reaction of **1g** with an unsymmetrical alkyne such as **2c**, **2d**, **2e**, or **2f** gave the products consisting of regioisomers with a 1/1 ratio in high yields (entries 2−5). Bulky trimethylsilyl-substituted alkynes such as **2g** and **2h** reacted with **1g** to provide indoles with complete regiocontrol in excellent yields (entries 6 and 7). Monoaryl-substituted internal alkyne **2i** also reacted with **1g** to give **3gi′** regioselectively in 54% yield (entry 8). However, terminal alkynes, such as 1-octyne and phenylacetylene, failed to participate in the reaction, presumably due to rapid oligomerization of alkynes.

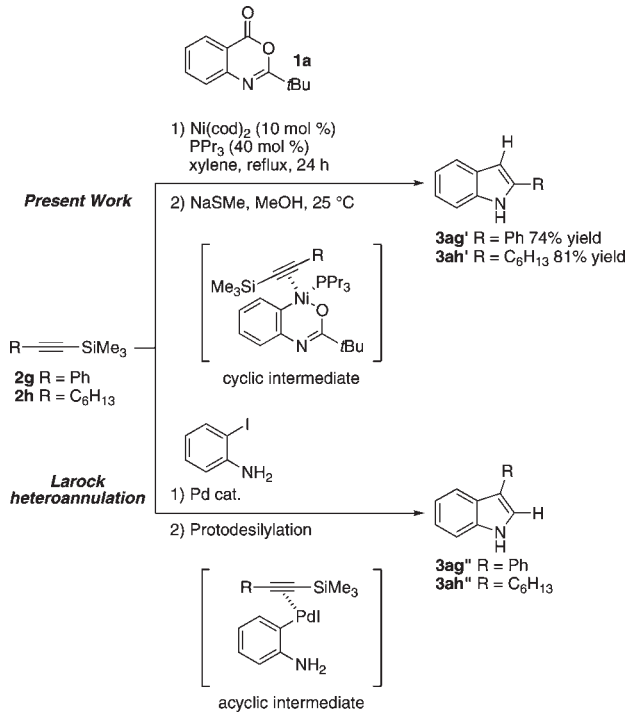
A plausible reaction pathway to account for the formation of indole **3** based on the observed results is outlined in Scheme 4. It is reasonable to consider that the catalytic cycle of the present reaction should consist of the oxidative addition of an ester CO−O bond to a Ni(0) complex.[9,10] Decarbonylation and coordination of alkyne **2** take place, during which the steric repulsive interaction is minimal between the bulkier R^L and the PPr_3 ligand on the nickel, to give nickel(II) intermediate **6a**. The alkyne would then insert into the C−Ni bond to give nickelacycle **7**.[11] With its

Scheme 4. Plausible Pathway



(9) (a) Trost, B. M.; Chen, F. *Tetrahedron Lett.* **1971**, *12*, 2603. (b) Sano, K.; Yamamoto, T.; Yamamoto, A. *Chem. Lett.* **1984**, 941. (c) Sano, K.; Yamamoto, T.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2741. (d) Yamamoto, T.; Sano, K.; Yamamoto, A. *J. Am. Chem. Soc.* **1987**, *109*, 1092. (e) Fischer, R.; Walther, D.; Kempe, R.; Sieler, J.; Schönecker, B. *J. Organomet. Chem.* **1993**, *447*, 131.

Scheme 5. Regioselectivity of the Cycloaddition



eight-membered ring strain, the Ni−O bond can undergo a facile 1,3-acyl migration to give thermodynamically more stable six-membered nickelacycle **8**. Subsequent reductive elimination gives **3** and regenerates the starting Ni(0) complex.

Lastly, it should be noted that the nickel-catalyzed reaction provides an opposite regioisomer to that of the Larock heteroannulation. For example, the palladium-catalyzed reaction of **2g** with 2-iodoaniline gives indole **3ag″** regioselectively after protodesilylation,[1] whereas the nickel-catalyzed reaction of **2g** with **1a** gave regioisomer **3ag′** as a single product after deprotection of the nitrogen group (Scheme 5). The reason is not clear at the moment; however, we assumed that such a difference may be ascribed to differences of intermediate for the carbometalation of alkyne (i.e., cyclic or acyclic).

In conclusion, we have developed a nickel-catalyzed [6 − 3 + 2] cycloaddition and applied the reaction for divergent syntheses of indoles from readily available anthranilic acid derivatives with alkynes. Further efforts to expand the scope of the chemistry and studies of the detailed mechanism are currently underway in our laboratories.

Acknowledgment. This work was supported by Grants-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. T.K. also acknowledges the Asahi Glass Foundation, Kansai Research Foundation, and Mizuho Foundation.

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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(11) For the formation of oxa-nickelacycles, see: (a) Karsch, H. H.; Leithe, A. W.; Reisky, M.; Witt, E. *Organometallics* **1999**, *18*, 90. (b) Ogoshi, S.; Oka, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2004**, *126*, 11802. (c) Ogoshi, S.; Ueta, M.; Arai, T.; Kurosawa, H. *J. Am. Chem. Soc.* **2005**, *127*, 12810. (d) Ogoshi, S.; Nagata, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2006**, *128*, 5350. (e) Ogoshi, S.; Tonomori, K.; Oka, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2006**, *128*, 7077. (f) Ogoshi, S.; Arai, T.; Ohashi, M.; Kurosawa, H. *Chem. Commun.* **2008**, 1347. (g) Hratchian, H. P.; Chowdhury, S. K.; Gutierrez-Garcia, V. M.; Amarasinghe, K. K. D.; Heeg, M. J.; Schlegel, H. B.; Montgomery, J. *Organometallics* **2004**, *23*, 4636. (h) Amarasinghe, K. K. D.; Chowdhury, S. K.; Heeg, M. J.; Montgomery, J. *Organometallics* **2001**, *20*, 370. (i) Montgomery, J.; Amarasinghe, K. K. D.; Chowdhury, S. K.; Oblinger, E.; Seo, J.; Savchenko, A. V. *Pure Appl. Chem.* **2002**, *74*, 129.