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# Decarbonylative Cycloaddition of Phthalimides with 1,3-Dienes

**Kyohei Fujiwara, Takuya Kurahashi,* and Seijiro Matsubara***

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

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

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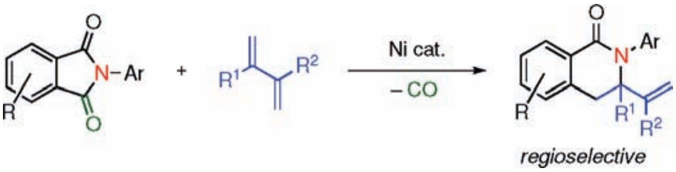
## ABSTRACT



**The decarbonylative cycloadditions of phthalimides with 1,3-dienes were performed by using nickel catalyst. The reactions afford 3-vinyldihydroisoquinolones regioselectively with respect to both 1,3-dienes and phthalimides.**

The transition-metal-catalyzed reactions, which provide structurally diverse heterocyclic compounds by replacing a part of a readily available heterocyclic compound with another molecule in a single step, are rare but represent a straightforward and powerful synthetic methodology.[1−5] Herein, we report our results of decarbonylative cycloadditions of phthalimides with 1,3-dienes, which provide 3-vinyldihydroisoquinolones regioselectively.[6] The reaction represents an unprecedented replacement reaction of a carbon monoxide by a C−C double bond.

Initially, we examined the decarbonylative cycloaddition of *N*-2-pyridylphthalimide (**1a**) with 1,2-dimethylenecyclohexane (**2a**) using Ni(cod)$_2$. After screening of various ligands, PMe$_3$ was found to give the highest yield (78%, Table 1, entries 1−4). Trace amounts of **3aa** were obtained in the cases where N-heterocyclic carbene ligands such as IPr or IMes was used in place of PMe$_3$. In other solvents, such as acetonitrile, tetrahydrofuran, and toluene, yields were even lower (entries 5−7). While the reaction of *N*-phenylphthalimide (**1b**) with **2a** did not give any products (entry 8), electron-deficient *N*-arylphthalimides react with diene efficiently. Indeed, the reaction of **2a** with *N*-perfluorophenylphthalimide (**1c**) successfully provided **3ca** in 59% yield (entry 9). The reactions of **2a** with *N*-diazinephthalimides **1d** and **1e** afford the products in good yields (entries 10 and 11). The highest yield was obtained when *N*-pyrrolylphthalimide **1f** was employed, and the corresponding cycloadduct **3fa** was isolated in 99% yield (entry 12).

With the optimized conditions in hand, we next investigated the use of other 1,3-dienes in this reaction (Scheme

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(1) For Pd-catalyzed cycloadditions via elimination of CO$_2$, see: (a) Shintani, R.; Murakami, M.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12356. (b) Wang, C.; Tunge, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 8118. (c) Shintani, R.; Park, S.; Shirozu, F.; Murakami, M.; Hayashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 16174. (d) Shintani, R.; Park, S.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 14866. (e) Shintani, R.; Tsuji, T.; Park, S.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 7508. (f) Shintani, R.; Murakami, M.; Hayashi, T. *Org. Lett.* **2009**, *11*, 457. (g) Shintani, R.; Hayashi, S.; Murakami, M.; Takeda, M.; Hayashi, T. *Org. Lett.* **2009**, *11*, 3754.

(2) For Ni-catalyzed cycloadditions via elimination of CO, see: (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.

(3) For Ni-catalyzed cycloadditions via elimination of N$_2$, see: (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. (d) Miura, T.; Morimoto, M.; Yamauchi, M.; Murakami, M. *J. Org. Chem.* **2010**, *75*, 5359.

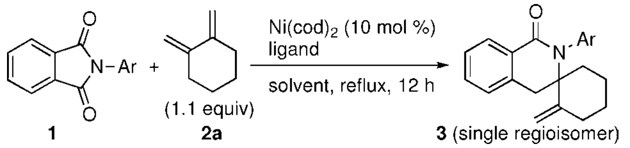
(4) For Ni-catalyzed cycloadditions via elimination of CO$_2$, see: Yoshino, Y.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2009**, *131*, 7494.

(5) For Ni-catalyzed cycloadditions via elimination of isocyanate, see: Yoshino, Y.; Kurahashi, T.; Matsubara, S. *Chem. Lett.* **2010**, *39*, 896.

(6) The isoquinolone skeleton is widely found in various natural products and medicinal drugs that exhibit a broad range of biological properties. For example, see: (a) Le, T. N.; Gang, S. G.; Cho, W.-J. *J. Org. Chem.* **2004**, *69*, 2768. (b) Ruchelman, A. L.; Houghton, P. J.; Zhou, N.; Liu, A.; Liu, L. F.; LaVoie, E. J. *J. Med. Chem.* **2005**, *48*, 792. (c) Asano, A.; Kitamura, S.; Ohra, T.; Aso, K.; Igata, H.; Tamura, T.; Kawamoto, T.; Tanaka, T.; Sogabe, S.; Matsumoto, S.; Yamaguchi, M.; Kimura, H.; Itoh, F. *Bioorg. Med. Chem.* **2008**, *16*, 4715.

10.1021/ol101842y

**Table 1.** Nickel-Catalyzed Decarbonylative Cycloadditions[a]

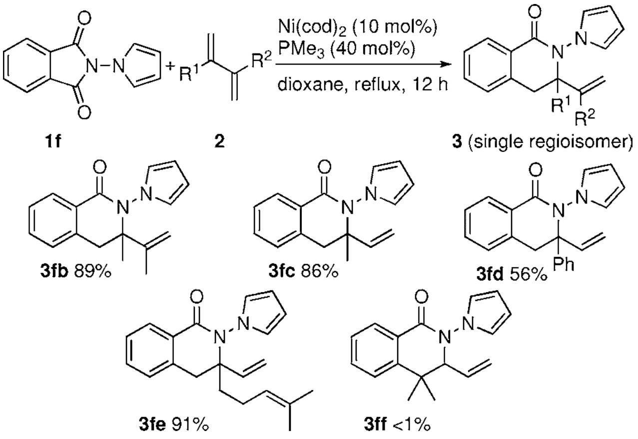


| entry | Ar | ligand | solvent | yield (%)[b] |
|---|---|---|---|---|
| 1 | 2-pyridyl (**1a**) | $PMe_3$ | dioxane | 78 |
| 2 | 2-pyridyl (**1a**) | $PMe_2Ph$ | dioxane | 6 |
| 3 | 2-pyridyl (**1a**) | $PPh_3$ | dioxane | <1 |
| 4 | 2-pyridyl (**1a**) | $PCy_3$ | dioxane | <1 |
| 5 | 2-pyridyl (**1a**) | $PMe_3$ | MeCN | 23 |
| 6 | 2-pyridyl (**1a**) | $PMe_3$ | THF | 21 |
| 7 | 2-pyridyl (**1a**) | $PMe_3$ | toluene | 41 |
| 8 | Ph (**1b**) | $PMe_3$ | dioxane | <1 |
| 9 | $C_6F_5$ (**1c**) | $PMe_3$ | dioxane | 59 |
| 10 | 2-pyrimidinyl (**1d**) | $PMe_3$ | dioxane | 69 |
| 11 | 2-pyrazinyl (**1e**) | $PMe_3$ | dioxane | 82 |
| 12 | *N*-pyrrolyl (**1f**) | $PMe_3$ | dioxane | 99 |

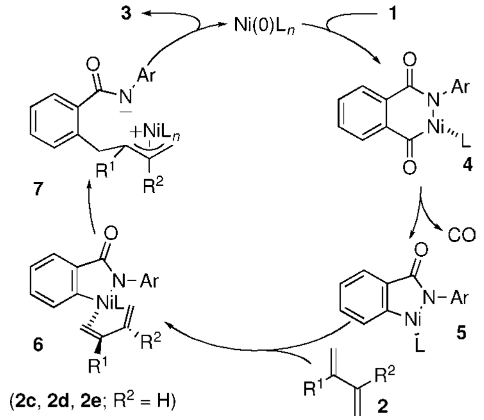
[a] Reactions were carried out using Ni(cod)$_2$ (10 mol %), ligand (40 mol %), **1** (0.5 mmol), and **2** (0.55 mmol) in 20 mL of refluxing solvent for 12 h . [b] Isolated yields.

1). The cycloaddition of **1f** with 2,3-dimethyl-1,3-butadiene (**2b**) gave product **3fb** in 89% yield. The reactions of **1f** with unsymmetrical 1,3-dienes such as isoprene (**2c**) and 2-phenyl-1,3-butadiene (**2d**) gave the products in 86 and 56% yields, respectively. Myrcene (**2e**) also reacted with **1f** as 1,3-diene to afford cycloadduct **3fe** selectively in 91% yield. However, 1,1-disubstituted 1,3-dienes **2f** or nonconjugated olefins, such as 1-octene, norbornene, and methyl acrylate, failed to participate in the reaction.

**Scheme 1.** Scope of the Nickel-Catalyzed Decarbonylative Cycloaddition of **1f** with 1,3-Dienes



**Scheme 2.** Plausible Reaction Pathway for the Nickel-Catalyzed Decarbonylative Cycloaddition of Phthalimides with 1,3-Dienes



A plausible reaction pathway to account for the formation of **3** based on the observed results is outlined in Scheme 2. In view of the mechanism of the previously reported nickel-catalyzed reaction, it is reasonable to consider that the catalytic cycle of the present reaction should consist of the oxidative addition of an amide CO−N bond to a Ni(0) complex.[2a,3,7,8] Subsequent decarbonylation and coordination of bidentate diene **2** took place to give nickel(II) intermediate **6**. The diene would then insert into the C−Ni bond to give more stable acyclic $\pi$-allylnickel intermediate **7**. Nucleophilic addition of nitrogen atom onto $\pi$-allylnickel at the more substituted carbon takes place to afford **3** and regenerate the starting Ni(0) complex.[9,10] Since electron-deficient *N*-arylphthalimides, such as **1c**, **1e**, and **1f**, react with dienes efficiently, oxidative addition of **1** to Ni(0) is most likely the rate-determining step. We thus presumed that the regioselective cycloaddition of unsymmetrically substituted phthalimides with dienes would be accomplished by preferential oxidative addition of a more electrophilic carbonyl moiety to Ni(0). Actually, the reaction of 4-fluorophthalimide **1g** reacted with diene **2a** to afford the correspondingly substituted cycloadduct **3ga** in 68% yield with a regioselectivity ratio of 4/1, while the cycloaddition of 3-fluorophthalimide **1h** with **2a** gave **3ha** in 99% yield with complete regiocontrol (Table 2, entries 1 and 2). The electron-withdrawing $CF_3$ group also performed efficiently with regiocontrol to give a sole cycloadduct **3ia** in excellent yield (entry 3). Furthermore, quinolimide **1j** reacted with **2a** to provide **3ja** regioselectively in 47% isolated yield (entry 4). The effects of electron-donating substituents on phthalimides were also examined. The reaction of 4-methylphthalimide **1k** with **2a** gave cycloadduct **3ka** in 90% yield as a 1/1 mixture of regioisomers, while the reaction of 3-methylphthalimide **1l** with **2a** afforded **3la** with complete regio-

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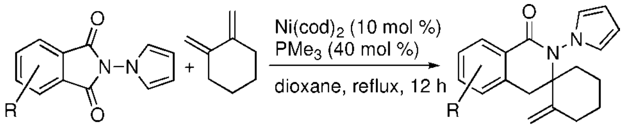
(7) For oxidative addition of the C−N bond to Ni, see: (a) Chan, Y. W.; Renner, M. W.; Balch, A. L. *Organometallics* **1983**, *2*, 1888. (b) Lin, B. L.; Clough, C. R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 2890. (c) Ozerov, O. V.; Guo, C.; Fan, L.; Foxman, B. M. *Organometallics* **2004**, *23*, 5573.

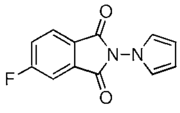
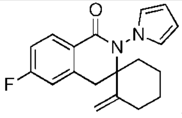
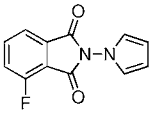
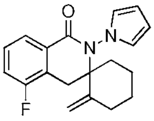
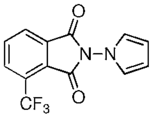
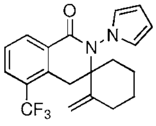
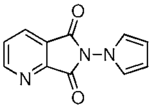
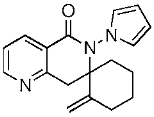
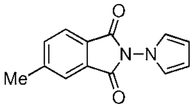
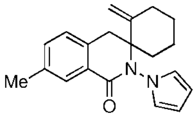
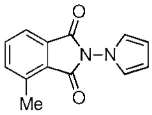
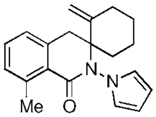
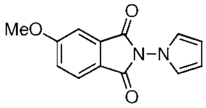
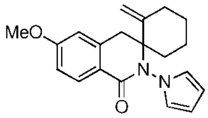
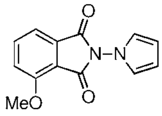
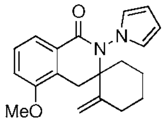
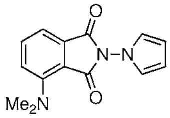
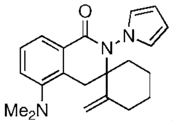
(8) (a) O'Brien, E. M.; Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2003**, *125*, 10498. (b) Johnson, J. B.; Bercot, E. A.; Rowley, J. M.; Coates, G. W.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 2718.

(9) For an example which involves amination of $\pi$-allyl nickel intermediate, see: Pawlas, J.; Nakao, Y.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 3669.

**Table 2.** Effects of Substituents on Regioselectivity[a]



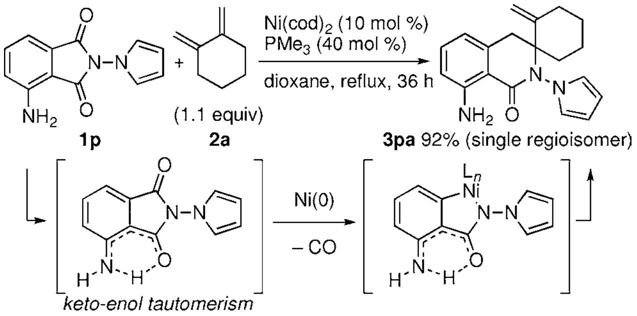
**1** **2a** **3**

| entry | substrate | | product | | yield (%)[b] |
|---|---|---|---|---|---|
| 1 |  | **1g** |  | **3ga** | 68 (4/1)[c] |
| 2 |  | **1h** |  | **3ha** | 99[d] |
| 3 |  | **1i** |  | **3ia** | 99[d,e] |
| 4 |  | **1j** |  | **3ja** | 47[d] |
| 5 |  | **1k** |  | **3ka** | 90 (1/1)[c,e] |
| 6 |  | **1l** |  | **3la** | 69[d,e] |
| 7 |  | **1m** |  | **3ma** | 99 (7/3)[c,e] |
| 8 |  | **1n** |  | **3na** | 99[d,e] |
| 9 |  | **1o** |  | **3oa** | 31[d,f] |

[a] Reactions were carried out using Ni(cod)$_2$ (10 mol %), ligand (40 mol %), **1** (0.5 mmol), and **2** (0.55 mmol) in 20 mL of refluxing solvent for 12 h . [b] Isolated yields. [c] Ratio of regioisomers. [d] Single regioisomer. [e] Reaction time, 36 h. [f] Reaction time, 72 h.

control (entries 5 and 6). The cycloaddition of 4-methoxyphthalimide **1m** with **2a** provided **3ma** as a major product (entry 7). It is noteworthy that 3-methoxyphthalimide **1n** reacted with **2a** to afford **3na** regioselectively in 99% yield (entry 8). The selectivity is thought to arise from coordination of oxygen to the nickel center through oxidative addition and/or stabilization of aza-nickelacycle intermediate **5**. The same regioselectivity was also observed when dimethylamino-substituted phthalimide **1o** reacted with **2a** (entry 9). Moreover, it was found that protons also play an important role in the regiocontrol of the reaction. That is, keto–enol tautomerism may prevent oxidative addition of the corresponding carbonyl moiety to Ni(0), and thus 3-aminophthalimide **1p** reacted with **2a** to provide **1pa** in 92% yield (Scheme 3).

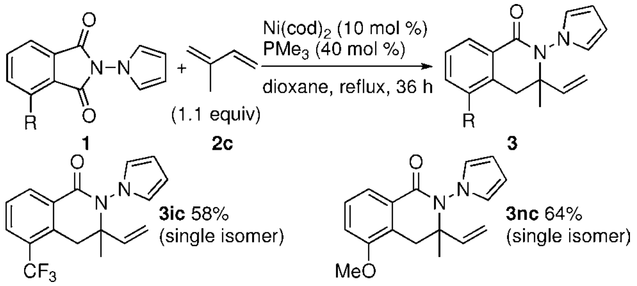
**Scheme 3.** Regioselective Cycloaddition of **1p** with **2a**



**1p** **2a** **3pa** 92% (single regioisomer)

Furthermore, the regioselective cycloaddition of unsymmetrically substituted phthalimides with unsymmetrical 1,3-dienes was successfully demonstrated (Scheme 4). The reaction of 3-trifluoromethylphthalimide **1i** with isoprene (**2c**) afforded cycloadduct **3ic** in 58% yield regioselectively as a sole product out of eight possible regioisomers. The cycloaddition of 3-methoxyphthalimide **1n** with **2c** also provided the correspondingly substituted cycloadduct **3nc** in 64% yield as a sole product.

**Scheme 4.** Regioselective Cycloaddition of **1** with **2c**



**1** **2c** **3**

**3ic** 58% (single isomer) **3nc** 64% (single isomer)

In summary, we have developed a decarbonylative cycloaddition of phthalimides with 1,3-dienes. It was found that the cycloaddition proceeded regioselectively with respect to 1,3-dienes. Moreover, the regioselective cycloadditions of an unsymmetrically functionalized phthalimide with 1,3-dienes were also achieved. The present cycloadditions displayed excellent regio- and chemoselectivity in the presence of functional groups, which may

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(10) For an intensive study on reductive elimination of the C–N bond from Ni(II), see: (a) Koo, K.; Hillhouse, G. L.; Rheingold, A. L. *Organometallics* **1995**, *14*, 456. (b) Koo, K.; Hillhouse, G. L. *Organometallics* **1995**, *14*, 4421.

open the way for a facile divergent synthesis of functionalized isoquinolones.

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**Supporting Information Available:** Experimental procedures including spectroscopic and analytical data of new compounds (PDF), and X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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