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Facile *β*-Alkyl and *β*-Hydride Elimination in the Nickel-Catalyzed Annulation of *o*-Iodophenyl Ketones and Aldehydes with Bicyclic Alkenes

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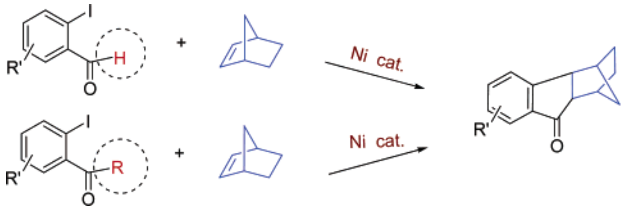
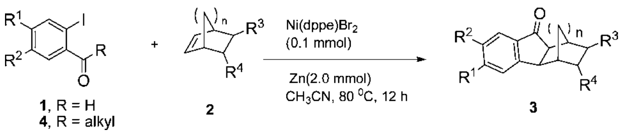
ABSTRACT



o-Iodoaryl aldehydes react with bicyclic alkenes in the presence of NiBr$_2$(dppe) and Zn powder in acetonitrile at 80 °C undergoing annulation to give polycyclic ketone derivatives. Surprisingly, *o*-iodoaryl alkyl ketones also react with bicyclic alkenes to form polycyclic ketones with structures the same as those from the corresponding *o*-iodoaryl aldehydes.

Selective C−C bond formation employing transition-metal complexes as catalysts is at the core of modern synthetic chemistry.[1] Carbocyclization being an excellent method to accomplish desired C−C bond formation, reports abound in this field.[2] Conversely, reports pertaining to transition-metal-catalyzed C−C bond cleavage leading to *β*-alkyl elimination are few.[3] However, some reports regarding catalytic *β*-alkyl eliminations in strained[4] and other[5] systems are worth noting. Our long interest in nickel-promoted cyclizations[6] prompted us to investigate the reaction of *ortho*-iodophenyl carbonyl compounds with norbornene derivatives. Recently, Larock and co-workers reported a palladium-catalyzed annulation of *o*-iodobenzonitriles with norbornene to give polycyclic ketones.[7] While extending our reaction of aldehydes to ketones, we discovered an unprecedented *β*-alkyl elimination. Amazingly, the products of reaction of aldehydes or ketones with the same bicyclic alkene were the same, i.e., ketones (Scheme 1). To the best of our knowledge, such *β*-alkyl eliminations are unknown in the case of nickel-catalyzed reactions.

Scheme 1



We first set out to examine the products obtained from the nickel-catalyzed reaction of various *o*-iodobenzaldehydes with a variety of bicyclic alkenes; the results are summarized in Table 1. Thus, treatment of 2-iodobenzaldehyde (**1a**) with

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[1] Hegedus, L. S. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, U.K., 1995; Vol. 12. Davies, S. G. In *Organotransition Metal Chemistry−Application to Organic Synthesis*; Pergamon: Oxford, U.K., 1982.

[2] (a) Tsuji, J. In *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; John Wiley & Sons: New York, 1995. (b) Heck, R. F. In *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985. (c) Negishi, E.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365−393. (d) Li, J. J.; Gribble, G. W. In *Palladium in Heterocyclic Chemistry*; Pergamon: Oxford, 2000. (e) Bäckvall, J.-E. *Pure Appl. Chem.* **1992**, *64*, 429−437.

[3] For a recent review on catalytic cleavage of a C−C bond including *β*-alkyl eliminations, see: Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610−618 and references therein.

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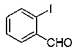
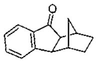
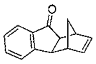
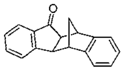
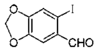
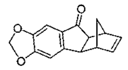
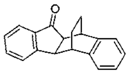
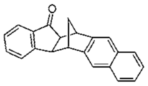
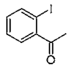
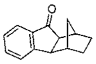
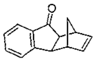
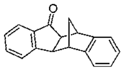
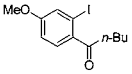
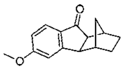
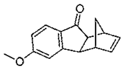
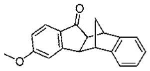
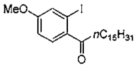
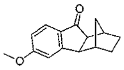
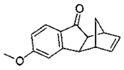
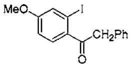
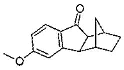
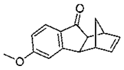
norbornene (**2a**) in the presence of Ni(dppe)Br$_2$ catalyst and Zn powder, in acetonitrile at 80 °C, gave annulated product **3a** in 80% isolated yield. Norbornadiene (**2b**) also reacted similarly with **1a** to furnish **3b** in 77% yield. When benzonorbornadiene (**2c**) was treated with **1a**, polycyclic ketone **3c** was obtained in 75% yield. Electron-donating 6-iodopiperonal **1b** also underwent annulation with bicyclic alkene **2b** to furnish the expected ketone product **3d** in 70% yield. The reaction of **1a** with bicyclic alkene **2d**, where *n* = 2 (Scheme 1), also proceeded smoothly resulting in the formation of product **3e** in 68% yield. Likewise, treatment of **1a** with naphthonorbornadiene **2e** resulted in the formation of **3f** in 74% isolated yield.

Encouraged by these results, we extended the present catalytic annulation to include *o*-iodophenyl alkyl ketones as substrates. To our surprise, the reaction of these ketones with norbornene derivatives under similar catalytic conditions gave the same keto products as those from the corresponding *o*-iodobenzaldehydes. Thus, 2-iodoacetophenone (**4a**) reacted with norbornene (**2a**) in the presence of Ni(dppe)Br$_2$ and Zn powder in acetonitrile at 80 °C to form keto product **3a** (entry 1, Table 2), which is the same as that from the reaction of *o*-iodobenzaldehyde (**1a**) with norbornene, in 70% yield. The expected annulated indenol derivative[8] was not observed. Similarly, the reaction of **4a** with norbornadiene (**2b**) afforded keto product **3b** in 61% yield. In the same vein, benzonorbornadiene **2c** underwent annulation with **4a** to provide multicyclic keto product **3c** in 52% yield. In all of these cyclization reactions, a dealkylation step presumably occurred during the process of catalysis prior to the formation of the final product (Table 2, entries 1−3).

To further understand the nature and scope of the above annulation reactions, we prepared several different alkyl *o*-iodo-*p*-anisyl ketones, **4b−d**, for the cyclization with norbornene derivatives. The reaction of *n*-butyl *o*-iodo-*p*-anisyl ketone (**4b**) with **2a−c** proceeded smoothly under similar catalytic conditions to give the corresponding ketones **3h−j** in 71~63% yields (entries 10−12), respectively. Clearly, the butyl group bonded to the carbonyl in **4b** was cleaved during these catalytic reactions. In a similar manner,

Table 1. Results of Nickel-Catalyzed Annulation of *o*-Iodobenzaldehydes and *o*-Iodophenyl Alkyl Ketones with Bicyclic Alkenes[a]

entry	1	bicyclic alkene 2	product 3	yield[b] (%)
1	 **1a**	**2a**		**3a** 80
2	**1a**	**2b**		**3b** 77
3	**1a**	**2c**		**3c** 75
4	 **1b**	**2b**		**3d** 70
5	**1a**	**2d**		**3e** 68
6	**1a**	**2e**		**3f** 74
7	 **4a**	**2a**		**3a** 70
8	**4a**	**2b**		**3b** 61
9	**4a**	**2c**		**3c** 52
10	 **4b**	**2a**		**3h** 63
11	**4b**	**2b**		**3i** 67
12	**4b**	**2c**		**3j** 71
13	 **4c**	**2a**		**3h** 55
14	**4c**	**2b**		**3i** 74
15	 **4d**	**2a**		**3h** 50
16	**4d**	**2b**		**3i** 58

[a] Unless stated otherwise, all reactions were conducted using iodo compound **1** or **4** (1.0 mmol), alkene **2** (3.0 mmol), NiBr$_2$(dppe) (0.10 mmol), and zinc powder (2.0 mmol), in CH$_3$CN at 80 °C for 12 h. [b] Isolated yields.

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(4) (a) Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **2000**, *122*, 12049−12050. (b) Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 11010−11011. (c) Nishimura, T.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **2000**, *122*, 12049−12050. (d) Murakami, M.; Takahashi, K.; Amii, H.; Ito, Y. *J. Am. Chem. Soc.* **1997**, *119*, 9307−9308 and references therein. (e) Matsuda, T.; Makino, M.; Murakami, M. *Org. Lett.* **2004**, *6*, 1257−1259. (f) Murakami, M.; Ashida, S.; Matsuda, T. *J. Am. Chem. Soc.* **2006**, *128*, 6932−6933.

(5) (a) Kondo, T.; Kodoi, K.; Nishinaga, E.; Okada, T.; Morisaki, Y.; Watanabe, Y.; Mitsudo, T. *J. Am. Chem. Soc.* **1998**, *120*, 5587−5588. (b) Terao, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2001**, *123*, 10407−10408. (c) Nishimura, T.; Araki, H.; Maeda, Y.; Uemura, S. *Org. Lett.* **2003**, *5*, 2997−2999. (d) Jun, C.-H.; Lee, H.; Lim, S. G. *J. Am. Chem. Soc.* **2001**, *123*, 751−752. (e) Terao, Y.; Wakui, H.; Kawasaki, S.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2004**, *126*, 8658−8659. (f) Harayama, H.; Kuroki, T.; Kimura, M.; Tanaka, S.; Tamaru, Y. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2352 and references therein.

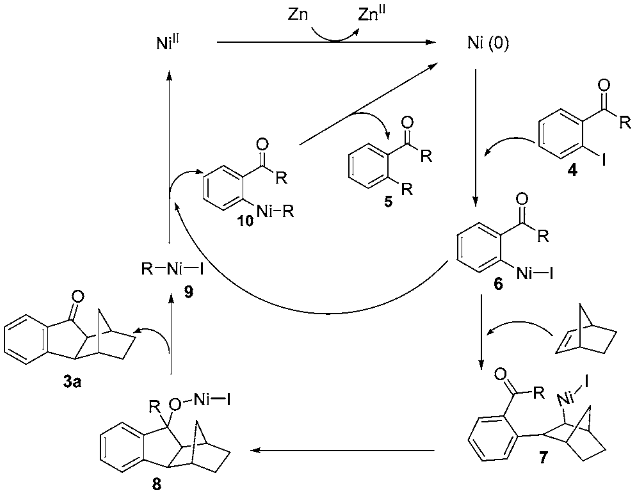
(6) (a) Rayabarapu, D. K.; Cheng, C.-H. *J. Am. Chem. Soc.* **2002**, *124*, 5630−5631. (b) Rayabarapu, D. K.; Shukla, P.; Cheng, C. H. *Org. Lett.* **2003**, *5*, 4903−4906. (c) Jeevanandam, A.; Korivi, R. P.; Huang, I.-W.; Cheng, C.-H. *Org. Lett.* **2002**, *4*, 807−810. (d) Shanmugasundaram, M.; Wu, M.-S.; Cheng, C.-H. *Org. Lett.* **2001**, *3*, 4233−4236. (e) Hsiao, T.-Y.; Santhosh, K. C.; Liou, K.-F.; Cheng, C.-H. *J. Am. Chem. Soc.* **1998**, *120*, 12232−12236. (f) Rayabarapu, D. K.; Cheng, C.-H. *Chem.−Eur. J.* **2003**, *9*, 3164. (g) Rayabarapu, D. K.; Chiou, C.-F.; Cheng, C.-H. *Org. Lett.* **2002**, *4*, 1679−1682. (h) Huang, D.-J.; Rayabarapu, D. K.; Li, L.-P.; Sambaiah, T.; Cheng, C.-H. *Chem.−Eur. J.* **2000**, *6*, 3706−3713.

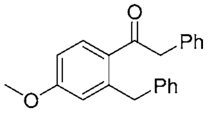
(7) (a) Larock, R. C.; Tian, Q.; Pletnev, A. A. *J. Am. Chem. Soc.* **1999**, *121*, 3238−3239. (b) Pletnev, A. A.; Tian, Q.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9276−9287.

(8) (a) Rayabarapu, D. K.; Cheng, C. H. *Chem. Commun.* **2002**, 942−944. (b) Rayabarapu, D. K.; Yang, C.-H.; Cheng, C.-H. *J. Org. Chem.* **2003**, *68*, 6726−6731.

the very long-chain ketone, 1-(*o*-iodo-*p*-anisyl)hexadecan-1-one (**4c**), underwent dealkylative annulation with **2a** and **2b** successfully, giving rise to cyclic ketones **3h** and **3i**, respectively (entries 13 and 14), in decent yields. Finally, the reaction of *o*-iodoanisyl ketone **4d** consisting of a benzyl moiety, with **2a** and **2b**, also furnished the same annulated ketones **3h** and **3i**, respectively (entries 15 and 16), in moderate yields. To see the fate of the benzyl group in **4d** after reaction, the reaction mixture of **4d** with **2a** was carefully analyzed leading to the isolation of product **5d** in 37% yield, in addition to product **3h**. It should be noted that the catalytic reaction does not work for the reaction of *o*-iodobenzophenone and *o*-iodophenyl 2-thienyl ketone with **2a**, indicating that the annulation is limited to alkyl *o*-iodoaryl ketones.

Scheme 2





5d

Figure 1. Structure of compound **5d**.

On the basis of the foregoing observations and the established nickel chemistry, we propose the mechanistic pathway shown in Scheme 2 to account for the present dealkylative annulation reaction. The catalytic reaction is likely initiated by the reduction of Ni(II) to Ni(0). Oxidative addition of the *o*-iodoaryl ketone to Ni(0) to give intermediate **6**, coordination, and insertion of a norbornene molecule lead to the formation of **7**. Intramolecular addition of the norbornenyl group to the keto moiety gives a cyclized alkoxy intermediate **8**.[6] After this step, *β*-alkyl elimination occurs to yield the observed ketone product **3** and a Ni^{II} alkyl species **9**. The details of the fate of the alkyl group in the Ni^{II} alkyl species are not entirely clear. For the alkyl species without a *β*-hydrogen, a possible route is the transfer of the alkyl group in **9** to another molecule of intermediate **6** to afford **10**. Reductive elimination of **10** leads to product **5**. Similar pathways were proposed previously for the palladium-catalyzed arylation of *t*-butylcyclobutanols by aryl bromide that involved a *β*-alkyl elimination as the key step.[4b] Strong evidence of the formation of **5** is the isolation of **5d** (Figure 1) in 37% yield from the reaction of **4d** with **2a**. The formation of **5** explains at least in part the low yields of products **3** from **4**. For the dealkylative annulation reaction of long-chain alkyl ketones **4b** or **4c** with norbornene derivative **2**, we did not observe the corresponding product **5**. In these reactions, the Ni^{II} alkyl species **9** likely undergoes the facile *β*-hydrogen elimination to give the corresponding olefin. However, attempts to isolate the expected olefin failed.

The present dealkylative annulation is interesting in view of the fact that most *β*-alkyl eliminations occur with cyclobutanols leading to a C−C bond cleavage in the butanol rings. In the present nickel-catalyzed reactions, 1-alkylcyclopentenol is involved as a key intermediate and the C−C bond between the alkyl and the α-carbon is cleaved in the catalytic reaction. To the best of our knowledge, this is the first time that such alkyl elimination was observed. A possible driving force for the present alkyl elimination is the large repulsion of the three bulky substituents on the tertiary alkoxide **8**. A *β*-alkyl elimination of this intermediate to give the final ketone product can greatly reduce the repulsion.

Scheme 2 can also be used to account for the reaction of *o*-iodoaryl aldehydes with norbornene derivatives catalyzed by nickel complexes. The major difference is that intermediate **8** undergoes *β*-hydride elimination to give ketone **3** instead of the *β*-alkyl elimination for the reaction of *o*-iodoaryl ketones with norbornene derivatives.

We have demonstrated a novel nickel-mediated carbocyclization involving *o*-iodoaryl ketones and aldehydes with a variety of bicyclic alkene derivatives to yield the same annulated ketone products. The reaction exhibits unique C−C bond cleavage such that the alkyl group attached to the starting ketone compound undergoes *β*-alkyl elimination. Further studies to pinpoint the mechanistic aberrations and to broaden the scope of this interesting reaction are currently underway.

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Supporting Information Available: General experimental procedures, spectral data, and spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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