

Ni(II)-Catalyzed Conia-Ene Reaction of  
1,3-Dicarbonyl Compounds with Alkynes

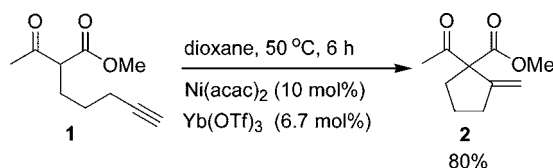
Qiang Gao, Bao-Fu Zheng, Jin-Heng Li, and Dan Yang\*

Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong,  
P. R. China

yangdan@hku.hk

Received March 11, 2005

## ABSTRACT



We have discovered a Ni(II)-catalyzed Conia-ene reaction of 1,3-dicarbonyl compounds with alkynes. In the presence of Ni(acac)<sub>2</sub> and Yb(OTf)<sub>3</sub>, various acetylenic 1,3-dicarbonyl compounds underwent Conia-ene reaction to give mono- and bicyclic olefinic cyclopentanes. A mechanism involving the enol-yne-Ni complex formation is proposed and supported by deuterium-labeling experiments.

The  $\alpha$ -alkylation of 1,3-dicarbonyl compounds is one of the most common methodologies for the formation of carbon–carbon bonds.<sup>1</sup> Direct  $\alpha$ -alkylation of 1,3-dicarbonyl compounds without prior enolate formation represents a more efficient approach.<sup>2–5</sup> One example is Conia-ene reaction: ketones undergo thermal cyclization onto alkynes to yield cyclic  $\alpha$ -vinylated ketones.<sup>6</sup> However, the high temperature required for this reaction limits its application in organic synthesis. The use of transition-metal catalysts allows the reaction to proceed at lower temperatures, but strong base,<sup>7</sup>

strong acid,<sup>8</sup> or UV irradiation is still required.<sup>3</sup> Recently, Toste and co-workers reported an elegant gold(I)-catalyzed Conia-ene reaction of  $\beta$ -ketoesters with alkynes under mild and neutral conditions.<sup>5a</sup> In the presence of catalytic amounts of (PPh<sub>3</sub>)AuCl and AgOTf, a series of alkynic  $\beta$ -ketoesters gave the cycloisomerization products in high yield. Here we report the utilization of Ni(acac)<sub>2</sub>–Yb(OTf)<sub>3</sub> as the catalyst in the Conia-ene reaction of 1,3-dicarbonyl compounds with alkynes.

Intramolecular cyclizations mediated by nickel complexes have been extensively explored in recently years for substrates such as dienes, enynes, dienynes, and bis-dienes.<sup>9</sup> To the best of our knowledge, nickel-catalyzed hydroalkylation

(1) Caine, D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 3, pp 1–63.

(2) (a) Pei, T.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 11290–11291. (b) Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 2056–2057. (c) Wang, X.; Pei, T.; Han, X.; Widenhoefer, R. A. *Org. Lett.* **2003**, *5*, 2699–2701. (d) Yang, D.; Li, J. H.; Gao, Q.; Yan, Y. L. *Org. Lett.* **2003**, *5*, 2869–2871. (e) Wang, X.; Widenhoefer, R. A. *Chem. Commun.* **2004**, 660–661. (f) Han, X.; Wang, X.; Pei, T.; Widenhoefer, R. A. *Chem. Eur. J.* **2004**, *10*, 6333–6342.

(3) (a) Cruciani, P.; Stammer, R.; Aubert, C.; Malacria, M. *J. Org. Chem.* **1996**, *61*, 2699–2708. (b) Cruciani, P.; Aubert, C.; Malacria, M. *Tetrahedron Lett.* **1994**, *35*, 6677–6680. (c) Renaud, J.-L.; Petit, M.; Aubert, C.; Malacria, M. *Synlett* **1997**, 55, 931–932. (d) Renaud, J.-L.; Aubert, C.; Malacria, M. *Tetrahedron* **1999**, *55*, 5113–5128.

(4) (a) Yao, X.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 6884–6885. (b) Nguyen, R.-V.; Yao, X.-Q.; Bohle, D. S.; Li, C.-J. *Org. Lett.* **2005**, *7*, 673–675.

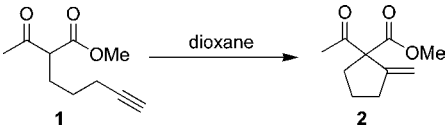
(5) (a) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526–4527. (b) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 5350–5352.

(6) For a review see: Conia, J. M.; Le Perche, P. *Synthesis* **1975**, 1–19.

(7) (a) Pd-catalyzed: Balme, G.; Bouyssi, D.; Faure, R.; Gore, J.; Van Hemelryck, B. *Tetrahedron* **1992**, *48*, 3891–3902. (b) Mo-catalyzed: McDonald, F. E.; Olson, T. C. *Tetrahedron Lett.* **1997**, *38*, 7691–7692. (c) Cu-catalyzed: Bouyssi, D.; Monteiro, N.; Balme, G. *Tetrahedron Lett.* **1999**, *40*, 1297–1300. (d) Ti-mediated: Kitagawa, O.; Suzuki, T.; Inoue, T.; Watanabe, Y.; Taguchi, T. *J. Org. Chem.* **1998**, *63*, 9470–9475.

(8) Boaventura, M. A.; Drouin, J.; Conia, J. M. *Synthesis* **1983**, 801–804.

(9) For reviews see: (a) Wilke, G. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 185–206. (b) Tamao, K.; Kobayashi, K.; Ito, Y. *Synlett* **1992**, 539–546. (c) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1–16. (d) Mortreux, A. In *Transition Metal Catalysed Reactions*; Murahashi, S.-I., Davies, S. G., Eds.; Blackwell Science Ltd.: London, 1999; pp 159–167. (e) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467–473. (f) Montgomery, J.; Amarasinghe, K. K. D.; Chowdhury, S. K.; Oblinger, E.; Seo, J.; Savchenko, A. V. *Pure Appl. Chem.* **2002**, *74*, 129–133. (g) Ikeda, S.-I. *Angew. Chem., Int. Ed.* **2003**, *42*, 5120–5122.

**Table 1.** Screening of the Reaction Conditions<sup>a</sup>


entry	Ni (equiv)	Yb(OTf) <sub>3</sub> (equiv)	T (°C)	time (h)	yield <sup>b</sup> (%)
1	Ni(PPh <sub>3</sub> ) <sub>4</sub> (0.2)	0.5	50	15	<i>c</i>
2	Ni(COD) <sub>2</sub> (0.1)	0.1	50	4	<i>d</i>
3	NiCl <sub>2</sub> (dppe) <sub>2</sub> (0.2)	0.5	rt	4.5	<i>d</i>
4	Ni(acac) <sub>2</sub> (0.2)	0.5	rt	4.5	<i>c</i>
5	Ni(acac) <sub>2</sub> (0.2)	0.5	50	15	68
6	Ni(acac) <sub>2</sub> (0.1)	0.2	50	12	83
7	Ni(acac) <sub>2</sub> (0.05)	0.1	50	30	80
8	Ni(acac) <sub>2</sub> (0.1)	0	50	30	77

<sup>a</sup> Reaction conditions: **1** (0.33 mmol), dioxane (15 mL), air atmosphere.<sup>b</sup> Isolated yield. <sup>c</sup> No reaction. <sup>d</sup> Complex mixture but no **2** was formed.

of unactivated alkynes by sp<sup>3</sup>-hybridized C–H bonds has not been reported.<sup>10</sup> In our initial study, we examined the catalytic efficiency of various nickel reagents in the cyclization of β-keto ester **1** (Table 1).<sup>11</sup> To increase the enol content of the β-keto esters, we added Lewis acid Yb(OTf)<sub>3</sub> as a cocatalyst.<sup>12</sup> Treatment of **1** with 20% Ni(PPh<sub>3</sub>)<sub>4</sub> in dioxane failed to give any reaction even at 50 °C (entry 1). On the other hand, **1** was rapidly consumed by Ni(COD)<sub>2</sub> or NiCl<sub>2</sub>-(dppe)<sub>2</sub>, but a mixture of unidentified compounds were produced with no desired cyclization product (entries 2 and 3). While no reaction was observed using 20% Ni(acac)<sub>2</sub> and 50% Yb(OTf)<sub>3</sub> at room temperature (entry 4), we obtained desired product **2** in 68% yield by raising the reaction temperature to 50 °C for 15 h (entry 5). When we reduced the catalyst loading to 10% Ni(acac)<sub>2</sub> and 20% Yb(OTf)<sub>3</sub>, a higher yield of **2** (83%) was observed (entry 6). Further reducing the catalyst loading to 5% Ni(acac)<sub>2</sub> and 10% Yb(OTf)<sub>3</sub> did not obviously compromise the yield, although a longer reaction time was needed (entry 7). We found that a similar yield of **2** could be achieved even in the absence of Yb(OTf)<sub>3</sub>; however, a much longer reaction time was required for completion (entry 8 vs entry 6). It should be pointed out that all our Ni(acac)<sub>2</sub>-catalyzed reactions were carried out in open air without exclusion of oxygen from the reaction flask.<sup>13</sup> In contrast, when the cyclization was conducted in argon atmosphere, i.e., Ni(acac)<sub>2</sub> (0.1 equiv)/Yb(OTf)<sub>3</sub> (0.2 equiv)/Ar/dioxane/50 °C/6 h, substrate **1**

(10) A Ni(acac)<sub>2</sub>-catalyzed addition of β-dicarbonyl derivatives to α,β-unsaturated nitriles has been reported. See: Veronese, A. C.; Callegari, R.; Morelli, C. F.; Basato, M. T. *J. Mol. Catal. A: Chem.* **1999**, *142*, 373–376.

(11) Other transition-metal complexes, such as Pd(PPh<sub>3</sub>)<sub>4</sub>, Pd(OAc)<sub>2</sub>, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, PdCl<sub>2</sub>(MeCN)<sub>2</sub>, CpCo(CO)<sub>2</sub>, Fe(acac)<sub>2</sub>, and Fe(acac)<sub>3</sub> gave either a complex mixture or no reaction.

(12) (a) Yang, D.; Ye, X.-Y.; Gu, S.; Xu, M. *J. Am. Chem. Soc.* **1999**, *121*, 5579–5580. (b) Yang, D.; Gu, S.; Yan, Y.-L.; Zhu, N.-Y.; Cheung, K.-K. *J. Am. Chem. Soc.* **2001**, *123*, 8612–8613. (c) Yang, D.; Gu, G.; Yan, Y.-L.; Zhao, H.-W.; Zhu, N.-Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 3014–3017. (d) Yang, D.; Gao, Q.; Lee, O.-Y.; *Org. Lett.* **2002**, *4*, 1239–1241.

**Table 2.** Ni(acac)<sub>2</sub>-Catalyzed Conia-Ene Reaction of Various 1,3-Dicarbonyl Compounds with Alkynes<sup>a</sup>

entry	substrates	time (h)	products	yield <sup>c</sup>
1		3 <sup>b</sup> 18	4 <sup>b</sup>	79%
2		5 <sup>b</sup> 18	6 <sup>b</sup>	82%
3		7 <sup>b</sup> 19	8 <sup>b</sup>	80%
4		9 <sup>b</sup> 19	10 <sup>b</sup>	78%
5 <sup>d</sup>		11 <sup>b</sup> 20	12 <sup>b</sup>	73%
6		13 20		14 71%
7 <sup>e</sup>		15 21		16 69%
8		17 15		18 42%
9		19 17		20 83%
10		21 10		22 88%
11		23 16		24 86%
12		25 18		26 80%

<sup>a</sup> Reaction conditions: Yb(OTf)<sub>3</sub> (0.2 equiv), Ni(acac)<sub>2</sub> (0.1 equiv), 0.03 M substrate in dioxane, 50 °C, air atmosphere. <sup>b</sup> **3** and **4**, R = Me, R' = 'Bu; **5** and **6**, R = 'Pr, R' = Me; **7** and **8**, R = Me, R' = allyl; **9** and **10**, R = CH<sub>2</sub>CH<sub>2</sub>CH=CH<sub>2</sub>, R' = Me; **11** and **12**, R = Ph, R' = Et. <sup>c</sup> Isolated yield. <sup>d</sup> Yb(OTf)<sub>3</sub> (0.5 equiv) and Ni(acac)<sub>2</sub> (0.2 equiv) were used. <sup>e</sup> Yb(OTf)<sub>3</sub> (0.067 equiv) and Ni(acac)<sub>2</sub> (0.1 equiv) were used.

decomposed quickly and only 20% of **2** was isolated. This observation suggests that the presence of oxygen is beneficial to the cyclization reaction, probably because it can reoxidize any adventitiously reduced Ni(0) species that are generated as the reaction proceeds.

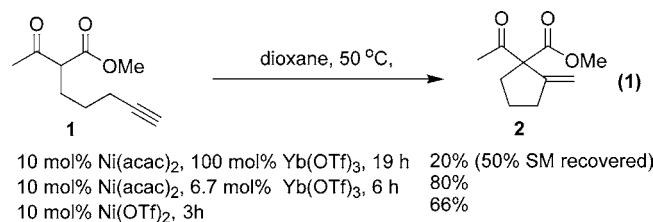
Having established the suitable reaction conditions, we then examined this Ni(II)-catalyzed cycloisomerization on a wide range of ε-acetylenic 1,3-dicarbonyl substrates (Table 2). Compared with the reaction of **1**, a longer reaction time

(13) We also screened the effects of other solvents on this reaction. Under the same reaction condition, the reaction conducted in THF produced **2** in poor yield (25%), whereas the reaction failed to proceed in MeCN. Although **2** was obtained in 40% yield in DCE, the conversion was relative low compared with that in dioxane; even lower conversion (<5%) was observed in toluene.

was needed when the size of substituents increased either on the ester or the ketone moiety (substrates **3** and **5**; entries 1 and 2). For substrates **7** and **9**, which contain olefinic groups, the cyclizations were completely chemoselective, and the olefinic groups did not participate in the reaction (entries 3 and 4).  $\beta$ -Ketoester **11**, in which the presence of a phenyl group might cause 1,3-allylic strain for its enol form, was also cyclized successfully in 73% yield (entry 5). Besides  $\beta$ -ketoesters, the Ni(II)-catalyzed cyclization is also applicable for 1,3-diketones: the cyclization of **13** provided diketone **14** in 71% yield (entry 6). Interestingly, even the cyclization of  $\beta$ -ketoamide **15** was achieved in moderate yield (69%) (entry 7). However, the corresponding *N,N*-dimethyl substituted  $\beta$ -keto amide failed to react due to severe 1,3-allylic strain.<sup>5a</sup>

The Ni(II)-catalyzed cyclization reactions are applicable to the preparation of bicyclic compounds. While bicyclo-[3.2.1]octanone **18** was obtained in moderate yield from the cyclization of  $\beta$ -ketoester **17** under the standard conditions (entry 8), *cis*-fused 6,5-bicyclic compound **20** was synthesized from cyclohexanone **19** in good yield (entry 9). Similarly, ene reaction of cyclopentanone **21** afforded *cis*-fused 5,5-bicyclic keto **22** in 88% yield (entry 10). The synthetic utility of this reaction is further demonstrated by the preparation of bicyclic ring systems containing heterocyclic units. For example, the cyclization of lactone **23** provided *cis*-fused 5,5-heterocyclic compound **24** in 86% yield (entry 11), and the procedure was also employed in the construction of a bicyclic lactam **26** (entry 12).

It is surprising that, as described above (Table 1, entries 4 and 5), longer reaction time and lower yield were obtained when the amount of Yb(OTf)<sub>3</sub> increased. To determine the role that Yb(OTf)<sub>3</sub> plays in the reaction, we repeated the cyclization of **1** under the same reaction condition but increased the loading of Yb(OTf)<sub>3</sub> to 1 equiv. After 19 h, only half of **1** was consumed and **2** was isolated in only 20% yield (eq 1). In contrast, when 0.067 equiv of Yb(OTf)<sub>3</sub>

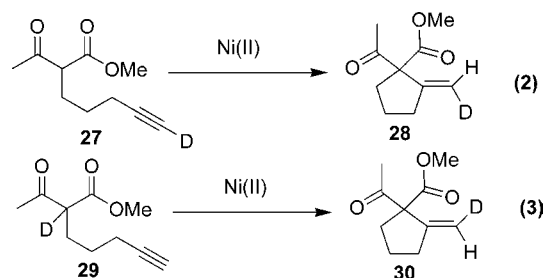


was used, the reaction time was shortened dramatically to 6 h while the yield remained good. The 3:2 ratio of Ni(acac)<sub>2</sub> and Yb(OTf)<sub>3</sub> indicates the more active catalyst may be the in situ formed Ni(OTf)<sub>2</sub> in the reaction system. Indeed, the reaction can be catalyzed by Ni(OTf)<sub>2</sub><sup>14</sup> with a higher reaction rate but slightly lower yield. The excess amount of Yb(OTf)<sub>3</sub> may decrease the reaction rate by competing complexation with the carbonyl groups of substrates.

To further probe the mechanism of our Ni(II)-catalyzed Conia-ene reactions, we synthesized deuterated  $\beta$ -ketoesters

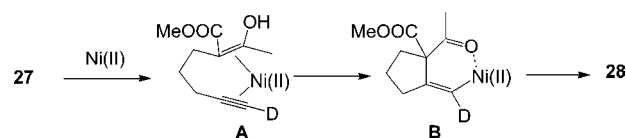
(14) Ni(OTf)<sub>2</sub> was prepared according to the literature procedure: Byington, A. R.; Bull, W. E. *Inorg. Chim. Acta* **1977**, 21, 239–244.

**27** and **29**.<sup>5a</sup> Cyclization of **27** gave product **28**, in which the deuterium predominately (77%:1% = *anti*/*syn*) locates *anti* to the  $\beta$ -ketoesters group (eq 2). In contrast, the Ni(acac)<sub>2</sub>-catalyzed cyclization of **29** afforded cyclopentanone **30** selectively (22%:5% = *syn*/*anti*), with deuterium *syn* to the  $\beta$ -ketoester moiety (eq 3).



These deuterium labeling results are in contrast with those obtained by Toste et al. in the Au(I)-catalyzed Conia-ene reactions,<sup>15</sup> suggesting that a completely different mechanism might be involved in our Ni(II)-catalyzed reactions. A plausible mechanism is depicted in Scheme 1, which involves

**Scheme 1.** Proposed Mechanism for the Ni(II)-Catalyzed Conia-ene Reaction



the formation of the enol–yne–Ni complex **A**. The insertion of Ni enolate to the alkyne generates a Ni(II) vinyl species **B** and then protonation of the C–Ni bond to give the cyclization product **28**.

In conclusion, we have developed a new Ni(II)-catalyzed Conia-ene reaction of 1,3-dicarbonyl compounds with alkynes. This represents the first example of nickel-catalyzed hydroalkylation of unactivated alkynes by sp<sup>3</sup> hybridized C–H bonds. The simple catalyst system provides various mono- and bicyclic olefinic cyclopentanes in a highly regioselective manner. A mechanism involving the enol–yne–Ni complex formation is proposed and supported by deuterium labeling experiments. The neutral and mild reaction condition should make the Conia-ene reaction a valuable method to synthesize quaternary carbon centers.<sup>16</sup>

(15) Toste and co-workers have studied the mechanism of Au(I)-catalyzed Conia-ene reaction and proved the pathway which involves the formation of enyne–Au complex, followed by the nucleophilic attack of the enol on the alkyne to give cyclic intermediate, and finally **2** after protonation. See ref 5.

(16) For reviews, see: (a) Fuji, K. *Chem. Rev.* **1993**, 93, 2037–2066. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, 110, 388–401. (c) Christoffers, J.; Mann, A.; *Angew. Chem., Int. Ed.* **2001**, 40, 4591–4597. (d) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, 42, 1688–1690. (e) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, 59, 10105–10146.

**Acknowledgment.** This work was supported by The University of Hong Kong and the Hong Kong Research Grants Council (Project No. HKU 7121/02P). D.Y. acknowledges the Bristol-Myers Squibb Foundation for an Unrestricted Grant in Synthetic Organic Chemistry.

**Supporting Information Available:** Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL050532Q