Cyclopentenone Formation by Regioselective Intermolecular Coupling of Trisubstituted Alkenes, Alkynes, and Isocyanates

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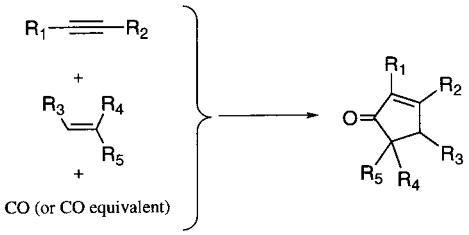
Summary: Zirconocenediethyl reacted with an alkyne, an isocyanate, and a trisubstituted alkene with two electron-withdrawing groups in this order to give cyclopentenone derivatives in good yields after hydrolysis.

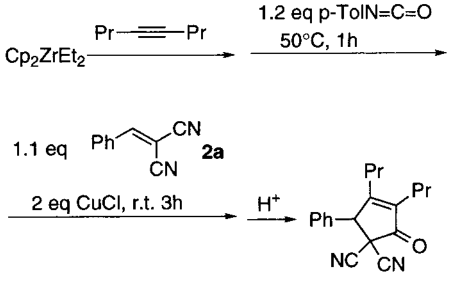
Cyclopentenone formation from three components, alkenes, alkynes, and carbon monoxide (or its equivalent), using transition metal complexes is very useful and has been extensively studied.[1−5] However, the use of trisubstituted alkenes has been critically limited for intermolecular coupling reactions. One reason is the low reactivity of trisubstituted olefins toward intermolecular coupling reactions. Another reason is the difficulty of the control of its regioselectivity. Therefore, there are only several examples using strained olefins such as five-membered cyclic olefins, norbornenes, and similar bicyclic olefins,[6,7] but there is no successful example for nonstrained trisubstituted alkenes (eq 1).



(1)

Herein we would like to report a new strategy for the synthesis of polysubstituted cyclopentenones using a trisubstituted functionalized nonstrained alkene, an alkyne, and an isocyanate.

A typical procedure is as follows. Zirconacyclopentene **1b** was prepared in situ by the reaction of 4-octyne with Cp_2ZrEt_2 at 0 °C.[8] To a solution of **1b** in THF was added 1.2 equiv of tolylisocyanate, and the reaction mixture was stirred for 1 h at 50 °C. Then 1.1 equiv of benzylidenemalononitrile **2a** and 2.0 equiv of CuCl were added at room temperature, and the reaction mixture was stirred for 3 h. GC analysis of the reaction mixture by quenching with 3 N HCl showed the cyclopentenone derivative **3b** was formed in 90% yield. After separation and purification by column chromatography, **3b** was obtained in 75% yield. Tolylamine was isolated in 92% yield as a byproduct from the aqueous phase. X-ray analysis verified the structure of **3b**.



(2)

3b

The results are presented in Table 1. In the presence of CuCl, the cyclization reaction with ylidenemalono-

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[1] For reviews, see: (a) Pauson, P. L. In *Organometallics in Organic Synthesis. Aspects of Morden Interdisciplinary Field;* de Meijere, A., tom Dieck, H., Eds.; Springer-Verlag: Berlin, 1987; p 233. (b) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081. (c) Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 1037. (d) Schore, N. E. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Elsevier: New York, 1995; Vol. 12, p 703. (e) Negishi, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 5, pp 1163, and references therein. (f) Geis, O.; Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 911, and references therein.

[2] For recent examples by intermolecular coupling reactions, see Zr: (a) Takahashi, T.; Kageyama, M.; Denisov, V.; Hara, R.; Negishi, E. *Tetrahedron Lett.* **1993**, *34*, 687−690. (b) Takahashi, T.; Kasai, K.; Xi, Z.; Denisov, V. *Chem. Lett.* **1995**, 347−351. (c) Takahashi, T.; Xi, Z.; Nishihara, Y. Huo, S.; Kasai, K.; Aoyagi, K. Denisov, V.; Negishi, E. *Tetrahedron*, **1997**, *53*, 9123−9134. Co: (a) Sugihara, T.; Yamaguchi, M. *Synlett* **1998**, 1384. (b) Sugihara, T.; Yamaguchi, M. *J. Am. Chem. Soc.* **1998**, *120*, 10782. (c) Kim, J. W.; Chung, Y. K. *Synthesis* **1998**, 142. (f) Hayashi, M.; Hashimoto, Y.; Yamamoto, Y.; Usuki, J.; Saigo, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 631. (h) Castro, J.; Moyano, A.; Pericas, M. A.; Riera, A.; Maestro, M. A.; Mahia, J. *Organometallics* **2000**, *19*, 1704. Rh: (i) Koga, Y.; Kobayashi, T.; Narasaka, K. *Chem. Lett.* **1998**, 249.

[3] For the reaction of Fischer carbenes with alkynes, see: (a) Challener, C. A.; Wulff, W. D.; Anderson, B. A.; Chamberlin, S.; Faron, K. L.; Kim, O. K.; Murray, C. K.; Xu, Y.-C.; Yang, D. C.; Darlin, S. D. *J. Am. Chem. Soc.* **1993**, *115*, 1359. (b) Wulff, W. D.; Bax, B. M.; Brandvold, T. A.; Chan, K. S.; Gilbert, A. M.; Hsung, R. P. *Organometallics* **1994**, *13*, 102.

[4] For the use of isocyanide as a CO equivalent, see: (a) Tamao, K.; Kobayashi, K. Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 1286. (b) Grossman, R. B.; Buchwald, S. L. *J. Org. Chem.* **1992**, *57*, 5803. (c) Zhang, M.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 4498.

[5] For the use of bis(trichloromethyl)carbonate as a CO equivalent, see: Zhao, Z.; Ding, Y.; Zhao, G. *J. Org. Chem.* **1998**, *63*, 9285.

[6] For intramolecular reactions using strained trisubstituted cyclic olefins, see: (a) Knudsen, M. J.; Schore, N. E. *J. Org. Chem.* **1984**, *49*, 5025. (b) Schore, N. E.; Knudsen, M. J. *J. Org. Chem.* **1987**, *52*, 569. (c) Schore, N. E.; Rowley, E. G. *J. Am. Chem. Soc.* **1988**, *110*, 5224. (d) Billington, D. C.; Kerr, W. J.; Pauson, P. L.; Farnocchi, C. F. *J. Organomet. Chem.* **1988**, *356*, 213.

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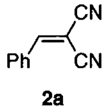
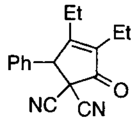
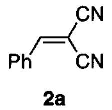
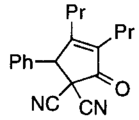
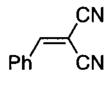
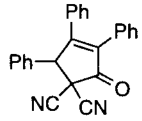
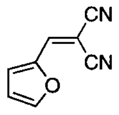
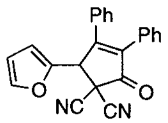
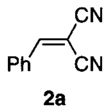
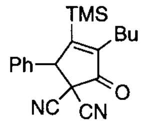
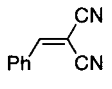
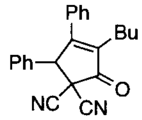
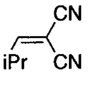
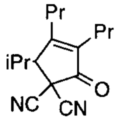
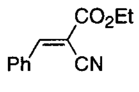
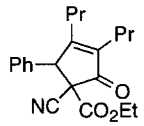
Table 1. Formation of Cyclopentenone Derivatives[a]

Entry	Alkyne	Isocyanate	Alkene	Cyclopentenone	Yield / %[c]
1	Et—≡—Et	PhN=C=O	 **2a**	 **3a**	87 (63)
2	Pr—≡—Pr	*p*-Tol-N=C=O	 **2a**	 **3b**	90 (75)
3	Ph—≡—Ph	BuN=C=O	 **2a**	 **3c**	- (53)
4	Ph—≡—Ph	BuN=C=O	 **2b**	 **3d**	76 (51)
5	TMS—≡—Bu	BuN=C=O	 **2a**	 **3e**	56 (42)
6	Ph—≡—Bu	*p*-Tol-N=C=O	 **2a**	 **3f**	73 (60)
7	Pr—≡—Pr	*p*-Tol-N=C=O	 **2c**	 **3g**	65 (51)
8	Pr—≡—Pr	*p*-Tol-N=C=O	 **2d**	 **3h**	80 (58)

[a] All coupling reactions of alkynes and isocyanates were carried out at 50 °C for 1−3 h. [c] GC yields; isolated yields are given in parentheses.

nitriles including aryl or alkyl substituents occurred smoothly to afford the corresponding cyclopentenones in good to high yields (entries 1−4). It is noteworthy that two cyano groups were exclusively at the 5-position of cyclopentenones. Alkenes conjugated with electron-withdrawing groups are generally not suitable for the intermolecular Pauson−Khand reaction, since reactions of such olefins with an alkyne coordinated on cobalt complexes gives conjugated dienes.[9,10] In our reaction, cyano groups are introduced to cyclopentenones successfully by the intermolecular reaction. When unsymmetrical alkynes such as 1-trimethylsilyl-1-hexyne and 1-phenyl-1-hexyne were employed, cyclopentenones **3e** and **3f** were obtained in 56% and 73% yields, respec-

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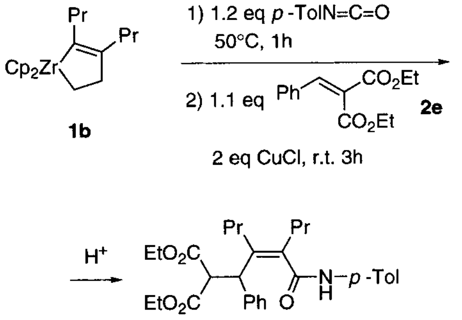
(7) For intermolecular coupling of strained trisubstituted cyclic olefins, see: (a) Khand, I. U.; Pauson, P. L. *J. Chem. Soc., Perkin Trans.* **1976**, *1*, 30. (b) Montana, A.-M.; Moyano, A.; Pericas, M. A.; Serratosa, F. *Tetrahedron* **1985**, *41*, 5995. (c) La Belle, B. E.; Knudsen, M. J.; Olmstead, M. M.; Hope, H.; Yanuck, M. D.; Schore, N. E. *J. Org. Chem.* **1985**, *50*, 5215. (d) Rowley, E. G.; Schore, N. E. *J. Organomet. Chem.* **1991**, *413*, C5.

(8) For the first report on zirconacyclopentene formation from Cp_2ZrEt_2 and an alkyne, see: (a) Takahashi, T.; Rousset, C. J.; Kageyama, K.; Aoyagi, K.; Hara, R.; Denisov, V.; Suzuki, N. *The 39th Symposium on Organometallic Chemistry, Japan*, A111 **1992**, 31−33. See also: (b) Takahashi, T.; Xi, Z.; Rousset, C. J.; Suzuki, N. *Chem. Lett.* **1993**, 1001−1004. (c) Reference 2a.

(9) (a) Khand, I. U.; Pauson, P. L. *J. Chem. Soc., Chem. Commun.* **1974**, 379. (b) Khand, I. U.; Pauson, P. L. *Heterocycles* **1978**, *11*, 59.

(10) For intramolecular reactions with an olefin moiety with an electron-withdrawing group, see: (a) Vereteonv, A. L.; Smit. W. A.; Vorontsova, L. G.; Kurella, M. G.; Caple, R.; Gybin, A. S. *Tetrahedron Lett.* **1991**, *32*, 2109. (b) Hoye, T. R.; Suriano, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 1154.

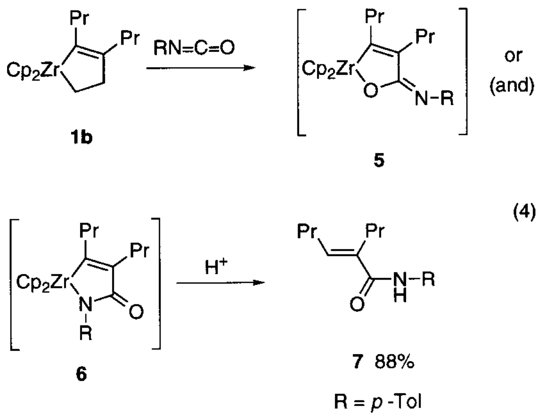
tively, with high regioselectivity (entries 5 and 6). Surprisingly, the use of **2d** instead of **2a** gave only one diastereoisomer, **3h**, in 80% yield (entry 8). In the case of diethyl benzylidenemalonate **2e**, however, only linear product **4** was obtained in 59% isolated yield even when the reaction mixture was treated at 50 °C (eq 3).



4 59%

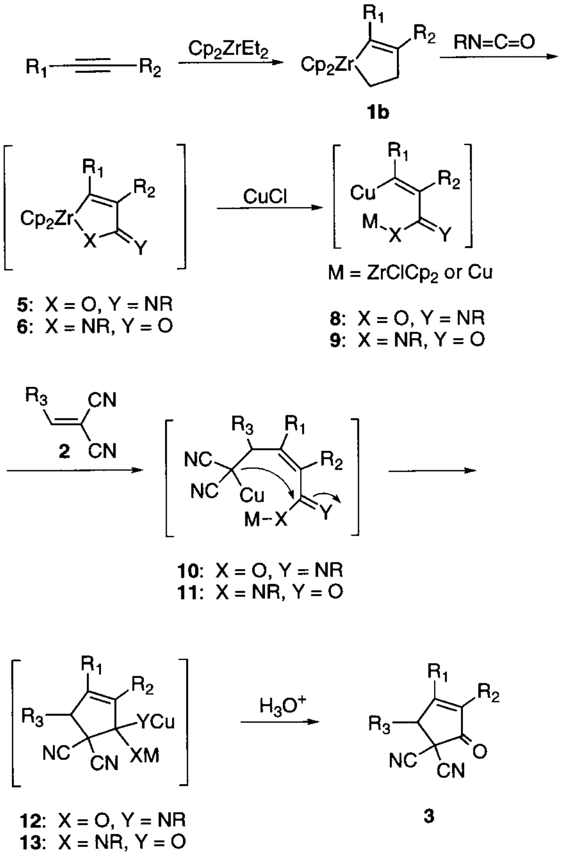
(3)

We have already reported that Cp_2ZrEt_2 reacted with an alkyne to give zirconacyclopentenes.[8] The zirconacyclopentenes **1** reacted with isocyanates to afford α,β-unsaturated amide **7** in 88% yield after hydrolysis (eq 4). Monitoring the reaction mixture by NMR indicated that there were several zirconium species in the solution. The formation of either oxa- or azazirconacyclopentenes, **5** or **6**, via the β,β′ carbon−carbon bond cleavage of **1** is reasonable.[8c,11] There are several reports on a coupling reaction of an alkyne and an isocyanate on early transition metals affording α,β-unsaturated amides after hydrolysis, although the intermediates of these reactions have not been characterized.[12]



(4)

Scheme 1



On the basis of the results obtained above, a plausible reaction mechanism is shown in Scheme 1. Transmetalation of zirconacycles **5** or **6** to CuCl gives **8** or **9**, which reacts with ylidenemalononitriles with excellent regioselectivity to give **10** or **11**.[13] The intramolecular addition of a Cu−C bond to the imino group in **10** or the carbonyl group in **11** affords **12** or **13**, which produces **3** after hydrolysis.

Supporting Information Available: Experimental details and spectroscopic characterization of compounds, and structure, tables of crystallographic data, atomic coordinates, thermal parameters, and bond lengths and angles for **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) For a review of the carbon−carbon bond cleavage of zirconacycles, see: (a) Takahashi, T.; Kotora, M.; Hara, R.; Xi, Z. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2591−2602. See also: (b) Xi, Z.; Hara, R.; Takahashi, T. *J. Org. Chem.* **1995**, *60*, 4444. (c) Takahashi, T.; Xi, Z.; Obora, Y.; Suzuki, N. *J. Am. Chem. Soc.* **1995**, *111*, 1672. (d) Z. Xi, Fischer, R.; Hara, R.; Sun, W.-H.; Obora, Y.; Suzuki, N.; Nakajima, K.; Takahashi, T. *J. Am. Chem. Soc.* **1997**, *119*, 12842. (e) Takahashi, T.; Kondakov, D. Y.; Xi, Z.; Suzuki, N. *J. Am. Chem. Soc.* **1995**, *117*, 5871. (f) Takahashi, T.; Suzuki, N.; Kageyama, M.; Kondakov, D. Y.; Hara, R. *Tetrahedron Lett.*, **1993**, *34*, 4811. (g) Takahashi, T.; Kondakov, D. Y.; Suzuki, N. *Chem. Lett.* **1994**, 259. (h) Suzuki, N. Kondakov, D. Y.; Kageyama, M.; Kotora, M.; Hara, R.; Takahashi, T. *Tetrahedron* **1995**, *51*, 4519. (i) Takahashi, T.; Xi, C.; Xi, Z.; Kageyama, M.; Fischer, R.; Nakajima, K.; Negishi, E. *J. Org. Chem.* **1998**, *63*, 6802.

(12) For Zr: (a) van Wagenen, B. C.; Livinghouse, T. *Tetrahedron Lett.* **1989**, *30*, 3495. For Nb: (b) Williams, A. C.; Sheffels, P.; Sheehan, D.; Livinghouse, T. *Organometallics* **1989**, *8*, 1566. For Ta: (c) Takai, K.; Kataoka, Y.; Yoshizumi, K.; Oguchi, Y. *Chem. Lett.* **1991**, 1479.

(13) The first C−C bond formation of zirconacycles via transmetalation to CuCl, see: (a) Takahashi, T.; Kotora, M.; Kasai, K.; Suzuki, N. *Organometallics* **1994**, *13*, 4183−4185.