ORGANIC LETTERS
2002
Vol. 4, No. 13
2277−2280

Cobalt Cluster-Containing Carbonyl Ylides for Catalytic, Three-Component Assembly of Oxygen Heterocycles

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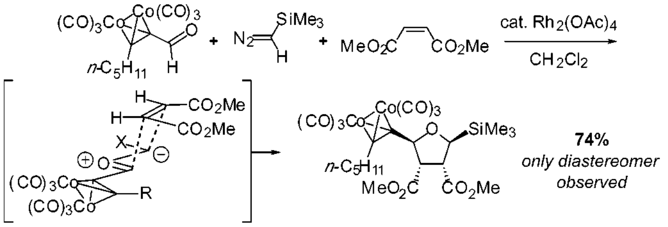
Received May 7, 2002

ABSTRACT



A dicobalt hexacarbonyl ($Co_2(CO)_6$) cluster is essential for the unusually broad dipolarophile scope and for the sense and degree of diastereoselection in a catalytic, three-component synthesis of tetrahydrofurans and dihydrofurans. Likely involving a new class of carbonyl ylide, these cycloadditions are stereospecific with respect to the dipolarophile and exhibit high diastereoselectivity and regioselectivity in most cases. Differentiation of all four positions of the tetrahydrofuran can thus be accomplished in a triply convergent manner.

Tetrahydrofurans[1] are found in a number of natural products,[2] and efficient construction of this family of heterocycles has received much attention.[1−3] A highly convergent, three-component coupling method of tetrahydrofuran synthesis involves 1,3-dipolar cycloaddition between an alkene and a carbonyl ylide generated in situ, thus creating two C−C bonds and one C−O bond in a single operation.[4]

The pioneering work of Huisgen demonstrated that carbonyl ylides derived from a diazo compound and an aromatic aldehyde underwent cycloaddition with either another aldehyde molecule (to give a dioxolane) or an electron-deficient alkene (to give a tetrahydrofuran).[5] Maas[6] and Doyle[7] later discovered more active catalysts for the latter process and expanded its scope to include two examples of carbonyl ylides generated from nonaromatic aldehydes. With certain aldehydes and dipolarophiles, however, dioxolane formation was a significant competing pathway, limiting the range of tetrahydrofurans that could be prepared in this fashion.[8]

In this work we report a catalytic, three-component assembly of tetrahydrofurans that features a novel, cobalt cluster-modified carbonyl ylide[9] (**A**, Scheme 1). Relative to existing methods, the putative 1,3-dipole possesses an

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(1) Reviews: (a) Elliot, M. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4175−4200. (b) Greve, S.; Reck, S.; Friedrichsen, W. *Prog. Hetercycl. Chem.* **1998**, *10*, 129−152. (c) Elliot, M. C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1291−1318.

(2) (a) Monensin: Haney, M. E., Jr.; Hoehn, M. M. *Antimicrob. Agents Chemother.* **1968**, 349−52. (b) Lonomycin: Otake, N.; Keonuma, M.; Miyamae, H.; Sato, S.; Saito, Y. *Tetrahedron Lett.* **1975**, *16*, 4147−4150. (c) Amphidinolides (review): Ishibashi, M.; Kobayashi, J. *Heterocycles* **1997**, *44*, 543−572. (d) Acetogenins (review): Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504−540.

(3) Reviews: (a) Semple, J. E.; Joullie, M. M. *Heterocycles* **1980**, *14*, 1825−1870. (b) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 1−72. (c) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309−3362. (d) Harmange, J. C.; Figadere, B. *Tetrahedron: Asymmetry* **1993**, 1711−1754. (e) Friedrichsen, W.; Pagel, K. *Prog. Heterocycl. Chem.* **1995**, *7*, 130−147.

(4) Reviews: (a) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919−940. (b) Doyle, M. P. *Acc. Chem. Res.* **1986**, *19*, 348−356. (c) Padwa, A. *Acc. Chem. Res.* **1991**, *24*, 22−28. (d) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263−309. (e) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223−269. (f) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911−935. (g) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley & Sons: New York, 1998.

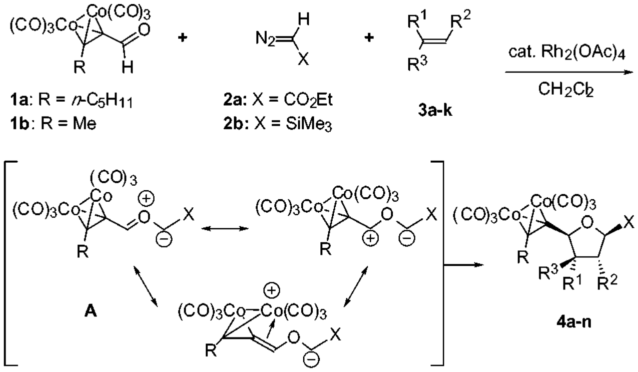
(5) (a) de March, P.; Huisgen, R. *J. Am. Chem. Soc.* **1982**, *104*, 4952. (b) Huisgen, R.; de March, P. *J. Am. Chem. Soc.* **1982**, *104*, 4953−4954.

(6) Alt, M.; Maas, G. *Tetrahedron* **1994**, *50*, 7435−7444.

(7) Doyle, M. P.; Forbes, D. C.; Protopopova, M. N.; Stanley, S. A.; Vasbinder, M. M.; Xavier, K. R.; *J. Org. Chem.* **1997**, *62*, 7210−7215.

10.1021/ol026149s CCC: $22.00

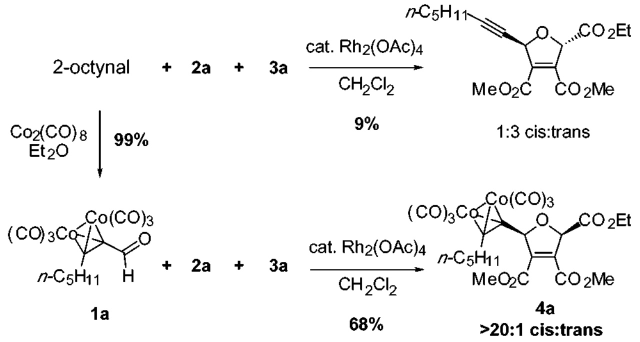
Scheme 1. Catalytic, Three-Component Assembly of Oxygen Heterocycles via a Novel Carbonyl Ylide



unusually broad range of reactivity, undergoing cycloaddition with not only highly electron-deficient alkynes and alkenes but also styrene, vinyl(trimethylsilane), and even simple olefins (e.g., 1-heptene). The cobalt cluster is also essential for the high stereoselectivity observed in these reactions. Taken together, differentiation of all four positions of the tetrahydrofuran is accomplished with 3-fold convergence.

In our initial investigations, we observed that slow addition of ethyl diazoacetate (EDA, **2a**) to a solution of 2-octynal, dimethyl acetylene dicarboxylate (DMAD, **3a**), and a catalytic amount of $Rh_2(OAc)_4$ afforded a dihydrofuran in 9% yield, favoring the trans diastereomer (Scheme 2).

Scheme 2. Reversal and Enhancement of Diastereoselectivity by a $Co_2(CO)_6$ Cluster in Catalytic, Three-Component Couplings

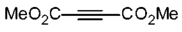
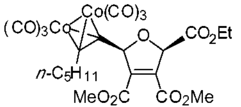
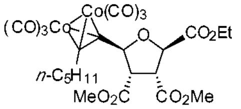
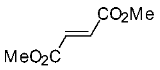
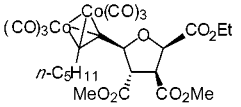


We suspected that protection of the triple bond as its $Co_2(CO)_6$ complex would prevent interference of the ynal as a dipolarophile and might also strongly affect the steric and electronic properties of the aldehyde and the 1,3-dipole.

Under otherwise identical conditions, $Co_2(CO)_6$ complex **1a** underwent efficient three-component coupling, affording dihydrofuran **4a** in 68% yield (Scheme 2). Most notably, the cluster remained intact and provided a complete *reversal* of diastereoselectivity, giving the heterocycle *exclusively as its 2,5-cis diastereomer (>20:1)*.[10]

Encouraged by these initial results, we examined the scope of this process with respect to the dipolarophile (Table 1).

Table 1. Catalytic, Three-Component Coupling of Cobalt Cluster **1a**, EDA (**2a**), and Three Dipolarophiles (Scheme 1)[a]

entry	dipolarophile	product	yield	d.r.[b]
1[c]	 **3a**	 **4a**	68%	>20:1
2	 **3b**	 **4b**	50%	>20:1
3[d]	 **3c**	 **4c**	50%	6:1

[a] Standard reaction conditions: a solution of EDA (**2a**, 3 mmol) in CH_2Cl_2 (5 mL) was added over 6 h to a solution of **1a** (1 mmol), dipolarophile (1 mmol), and $Rh_2(OAc)_4$ (0.025 mmol) in CH_2Cl_2 (5 mL). Purification on SiO_2 (1:3 CH_2Cl_2/hexanes) afforded the products as thick red-brown oils. Structural assignment of **4c** was based on NOE measurements. Assignments of **4a** and **4b** were based on analogy to **4c** and the crystal structure of **6** (see Figure 1). [b] Diastereomeric ratios were determined by ^{1}H NMR analysis of unpurified product mixtures. [c] DMAD (1 mmol) in 2.5 mL of CH_2Cl_2 and EDA (3 mmol) in 2.5 mL of CH_2Cl_2 were added via separate syringes over 6 h. [d] Reaction was conducted at reflux.

Reactions involving dimethyl maleate or dimethyl fumarate yielded the desired cycloadduct along with approximately 20% of the dipolar cycloaddition products of diethyl fuma-

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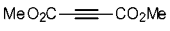
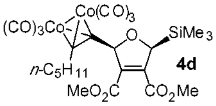
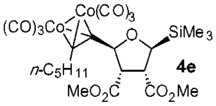
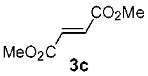
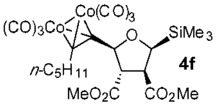
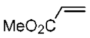
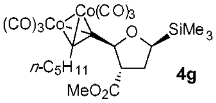
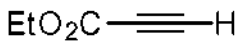
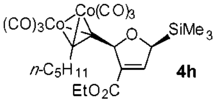
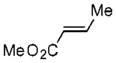
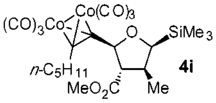
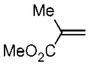
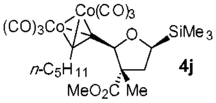
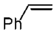
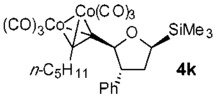
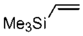
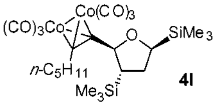
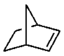
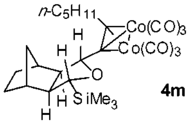
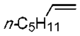
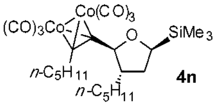
(8) Other methods of tetrahydrofuran synthesis involving carbonyl ylide cycloaddition: (a) Kagan, J.; Firth, B. E. *J. Org. Chem.* **1974**, *39*, 3145–3147. (b) Markowski, V.; Huisgen, R. *Tetrahedron Lett.* **1976**, *17*, 4643–4646. (c) Gill, H. S.; Landgrebe, J. A. *J. Org. Chem.* **1983**, *48*, 1051–1055. (d) Hojo, M.; Ohkuma, M.; Ishibashi, N.; Hosomi, A. *Tetrahedron Lett.* **1993**, *34*, 5943–5946. (e) Hojo, M.; Aihara, H.; Hosomi, A. *J. Am. Chem. Soc.* **1996**, *118*, 3533–3534. (f) Hojo, M.; Ishibashi, N.; Hosomi, A. *Synlett* **1996**, 234–237. (g) Hojo, M.; Aihara, H.; Ito, H.; Hosomi, A. *Tetrahedron Lett.* **1996**, *37*, 9241–9244. (h) Hojo, M.; Aihara, H.; Suginohara, Y.; Sakata, K.; Nakamura, S.; Murakami, C.; Hosomi, A. *J. Org. Chem.* **1997**, *62*, 8610–8611. (i) Takai, K.; Kaihara, H.; Higashiura, K.-i.; Ikeda, N. *J. Org. Chem.* **1997**, *62*, 8612–8613. (j) Hamaguchi, M.; Matsubara, H.; Nagai, T. *J. Org. Chem.* **2001**, *66*, 5395–5404.

(9) Tungsten-containing carbonyl ylide: Iwasawa, N.; Shido, M.; Kusama, H. *J. Am. Chem. Soc.* **2001**, *123*, 5814–5815.

(10) Reactions of ynals and ynones in which a $Co_2(CO)_6$ cluster provides increased stereoselectivity. *Aldol reactions:* (a) Ju, J.; Reddy, B. R.; Khan, M.; Nicholas, K. M. *J. Org. Chem.* **1989**, *54*, 5426–5428. (b) Mukai, C.; Nagami, K.; Hanaoka, M. *Tetrahedron Lett.* **1989**, *30*, 5623–5626. (c) Mukai, C.; Nagami, K.; Hanaoka, M. *Tetrahedron Lett.* **1989**, *30*, 5627–5630. (d) Mukai, C.; Suzuki, K.; Nagami, K.; Hanaoka, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 141–145. (e) Mukai, C.; Kataoka, C.; Hanaoka, M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 563–571. *Allylmetal and crotylmetal addition reactions:* (f) Roush, W. R.; Park, J. C. *J. Org. Chem.* **1990**, *55*, 1143–1144. (g) Ganesh, P.; Nicholas, K. M. *J. Org. Chem.* **1993**, *58*, 5587–5588. (h) Ganesh, P.; Nicholas, K. M. *J. Org. Chem.* **1997**, *62*, 1737–1747. *Lewis acid-mediated Nicholas reactions:* (i) Schreiber, S. L.; Sammakia, T.; Crowe, W. E. *J. Am. Chem. Soc.* **1986**, *108*, 3128–3130. (j) Schreiber, S. L.; Klimas, M. T.; Sammakia, T. *J. Am. Chem. Soc.* **1987**, *109*, 5749–5759. (k) Sui, M.; Panek, J. S. *Org. Lett.* **2001**, *3*, 2439–2442. *Catalytic asymmetric reductions of α,β-ynones ($Co_2(CO)_6$ complex):* (l) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153–9156. (m) Bach, J.; Berenguer, R.; Garcia, J.; Loscertales, T.; Vilarrasa, J. *J. Org. Chem.* **1996**, *61*, 9021–9025. (n) Corey subsequently described catalytic asymmetric reductions of uncomplexed ynones: Helal, C. J.; Magriotis, P. A.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 10938–10939.

Table 2. Catalytic, Three-Component Coupling of Cobalt Cluster **1a**, TMSD (**2b**), and 11 Dipolarophiles (Scheme 1)[a]

entry	dipolarophile	major product	yield[b]	d.r.[c]
1[d]	 **3a**	 **4d**	32%	>20:1
2	 **3b**	 **4e**	74%	>20:1
3[e]	 **3c**	 **4f**	66%	6:1
4	 **3d**	 **4g**	73% (53:47)	>20:1[f]
5	 **3e**	 **4h**	60% (75:25)	>20:1[g]
6	 **3f**	 **4i**	55% (50:50)	>20:1[h]
7[e]	 **3g**	 **4j**	64% (71:29)	>20:1[h]
8	 **3h**	 **4k**	46% (82:18)	>20:1[g]
9	 **3i**	 **4l**	37% (70:30)	>20:1[g]
10	 **3j**	 **4m**	29%	>20:1
11	 **3k**	 **4n**	11% (60:40)	>20:1[g]

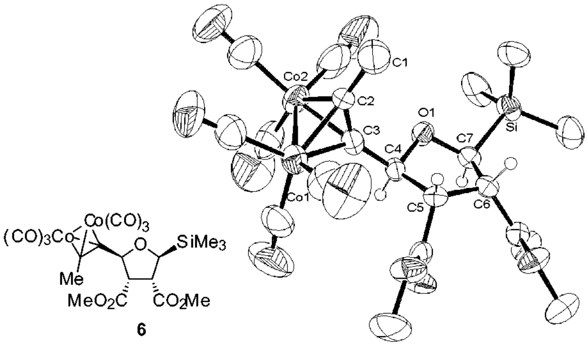
[a] Standard reaction conditions: a solution of TMSD (**2b**, 2 mmol) in CH_2Cl_2/hexanes (5 mL/1 mL) was added over 6 h to a solution of **1a** (1 mmol), dipolarophile (2 mmol), and $Rh_2(OAc)_4$ (0.025 mmol) in CH_2Cl_2 (5 mL). Purification on SiO_2 (1:3 CH_2Cl_2/hexanes) afforded the products as thick red-brown oils. Structural assignments of **4f** and **4k** were based on NOE measurements. Assignment of **4e** was based on analogy to the X-ray structure of **6** (Figure 1). Structural assignments of other products were based on analogy. [b] Major product is shown; regioselectivity is given in parentheses. [c] Diastereomeric ratios (d.r.) were determined by ^1H NMR analysis of unpurified product mixtures and are given for the major regioisomer. [d] DMAD (1 mmol) in 2.5 mL of CH_2Cl_2 and TMSD (3 mmol) in 2.5 mL of CH_2Cl_2 were added via separate syringes over 6 h. [e] Reaction was conducted at reflux. [f] For the minor regioisomer, d.r. = 3:1. [g] For the minor regioisomer, d.r. > 20:1. [h] For the minor regioisomer, d.r. = 1:1.

rate. Presumably, interception of the Rh-carbenoid by another molecule of ethyl diazoacetate generated diethyl fumarate, which underwent competitive dipolar cycloaddition with the cobalt complex-containing carbonyl ylide.

We then turned to (trimethylsilyl)diazomethane[11] (TMSD, **2b**) to avoid this competing "dimerization" reaction.[12] Under optimum conditions[13] (100 mol % cobalt cluster **1a**, 200 mol % dipolarophile, 200 mol % TMSD (addition over 6 h), 2.5 mol % $Rh_2(OAc)_4$), a wide range of tetrahydrofurans could be prepared with good to high stereoselectivity (Table 2).

As shown in Table 2, dipolarophiles containing at least one electron-withdrawing group, styrene, or vinyltrimethylsilane gave the desired heterocycles. Even norbornylene and 1-heptene (entries 10 and 11) underwent cycloaddition, albeit in low yield. These results highlight the unusually broad dipolarophile scope that the $Co_2(CO)_6$ cluster provides in these cycloadditions. Furthermore, that dioxolane byproducts were isolated in less than 10% yield in all cases studied was surprising since dioxolane formation often is the major reaction pathway in related cycloadditions when less electron-deficient dipolarophiles are used.[5−7] The steric demand of the metal cluster may play a role in the diminished rate of cycloaddition of the carbonyl ylide with a second molecule of aldehyde.

When the same reaction sequence was performed using the cobalt complex of 2-butynal (**1b**), TMSD (**2b**), and dimethyl maleate (**3b**), a single solid product was obtained in 73% isolated yield, and crystals suitable for X-ray crystallographic analysis were obtained from hexanes (Figure 1).[14]



6

Figure 1. Molecular structure of tetrahydrofuran **6** (crystallization from hexanes; some hydrogen atoms are omitted for clarity). Thermal ellipsoids are drawn at 40% probability.

This structure encapsulates the three factors that govern the high degree of configurational control in these reactions

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(11) Seyferth, D.; Menzel, H.; Dow, A. W.; Flood, T. C. *J. Organomet. Chem.* **1972**, *44*, 279−290.

(12) It has been proposed that the Rh-carbenoid derived from TMSD is less electrophilic and imparts a greater steric demand than that derived from ethyl diazoacetate: Carter, D. S.; Van Vranken, D. L. *Org. Lett.* **2000**, *2*, 1303−1305.

(13) See Supporting Information for details.

(14) Crystallographic data deposited with the Cambridge Crystallographic Data Centre (CCDC-177866).

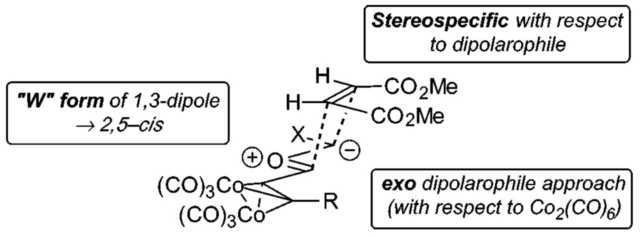
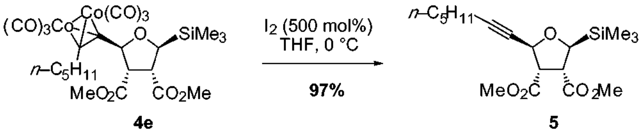


Figure 2. Proposed model of three factors that govern stereoinduction.

(Figure 2). (1) The cycloadditions are stereospecific with respect to the dipolarophile. (2) The relationship of the substituents at the 2- and 5-positions is exclusively cis (>20:1). This observation is consistent with cycloaddition of the "W" form of the 1,3-dipole and is in contrast to related methods that favor the 2,5-trans diastereomer or display low stereoselectivity.[5−8] (3) Finally, the cycloaddition itself is highly exo selective (with respect to the cobalt cluster), whereas related carbonyl ylide cycloadditions favor an endo product or proceed with low exo/endo selectivity.[5−7]

The cobalt cluster enables elaboration of the heterocycle via Pauson−Khand[15] or Nicholas[10i−k,16] reactions. Alternatively, liberation of the alkyne occurs in excellent yield upon exposure to I_2[17] (Scheme 3), affording 2-alkynyl tetrahydrofurans and, after suitable functionalization, stereodefined alkenes and alkyl chains.

Scheme 3



In summary, incorporation of a (μ-η^2-alkyne)-$Co_2(CO)_6$ cluster adjacent to a carbonyl ylide confers increased reactivity, selectivity, and scope in cycloadditions with unsaturated carbon−carbon bonds, rapidly constructing highly substituted heterocycles in moderate to good yields with high stereoselectivity. This transformation may proceed via a novel 1,3-dipole (**A**, Scheme 1) that resembles dicobalt hexacarbonyl-stabilized propargylic cations.[10i−k,16] To the best of our knowledge, these are the first dipolar cycloadditions of any type in the presence of alkyne−cobalt complexes[18] and the first application of (trimethylsilyl)diazomethane as the carbene source in cycloaddition reactions of carbonyl ylides.[4]

Our ongoing studies in this area are directed toward the development of analogous asymmetric catalytic[19−21] three-component couplings and the use of these methods in the synthesis of complex natural products.

Acknowledgment. We thank The Donors of The Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work (ACS-PRF #36189-G1). We thank MIT, the NSF (Graduate Fellowship to A.J.S.; CAREER Award to T.F.J. (CHE-0134704)), Pfizer (Summer Undergraduate Research Fellowship to E.Y.L.), 3M, Merck, and Boehringer-Ingelheim for their generous support of our work.

Supporting Information Available: Experimental and characterization data for new compounds and X-ray crystallographic data for **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026149S

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