Serial [5+2]/[4+2] Cycloadditions: Facile, Preparative, Multi-Component Syntheses of Polycyclic Compounds from Simple, Readily Available Starting Materials**

Paul A. Wender,* Gabriel G. Gamber, and Marc J. C. Scanio

The frontiers of organic synthesis are most clearly defined by the level of molecular complexity that can be achieved with efficiency. Ideally, the synthesis of complex targets would be based on readily available starting materials and proceed quickly and quantitatively in one simple, safe, environmentally acceptable, and resource-effective operation.[1] However, most reactions do not provide sufficient increases in complexity to achieve such synthetic brevity. As a result, efforts to achieve complexity *and* brevity must rely on coupling multiple individual transformations into one synthetic operation.[2–5]

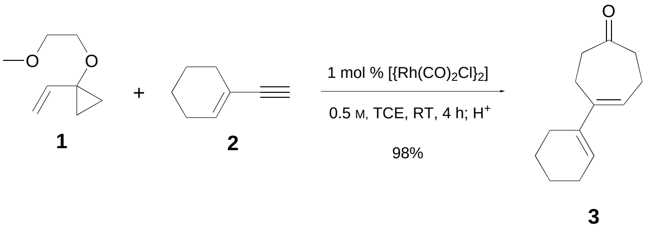
Cycloaddition reactions are among the synthetically most useful individual processes for increasing molecular complexity.[6, 7] The synergistic effects of linking multiple cycloaddition reactions in series can lead to highly desirable increases in molecular complexity.[3, 4] We recently introduced a fundamentally new and remarkably general cycloaddition for seven-membered ring synthesis based on transition metal catalyzed [5+2] cycloadditions.[8, 9] We now report our studies on a novel, serial [5+2]/[4+2] cycloaddition process, and the finding that the serial process proceeds more efficiently than the uncoupled individual steps.

We have reported that [{Rh(CO)$_2$Cl}$_2$] catalyzes intermolecular [5+2] cycloadditions with complete chemoselectivity for alkynes.[8b,c] Based on this selectivity, we envisioned that an intermolecular [5+2] cycloaddition with a conjugated enyne would yield a diene that could react in a [4+2] cycloaddition, affording a polycyclic compound from three simple starting materials in a single operation.

1,1,2,2-Tetrachloroethane (TCE) was selected as our initial solvent because it was found to work superbly in the [5+2] cycloaddition (Scheme 1). Furthermore, because of its relatively high boiling point (147 °C), TCE enables thermally demanding [4+2] cycloadditions without the need for sealed tubes.

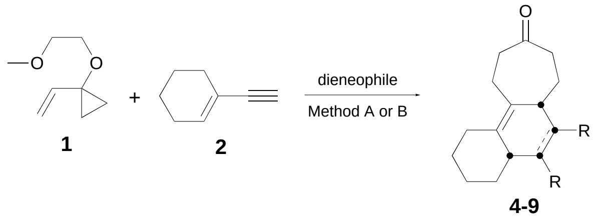
Our initial study of the [5+2]/[4+2] cycloadditions used a sequential addition protocol (Method A). The [5+2] cycloaddition was run to completion, the dienophile added and the reaction heated. Hydrolysis of the resultant enol gave good to excellent yields of a single diastereomeric product (Table 1, Method A). X-ray analysis indicates that the stereoselectivity is derived from the *endo* transition state of the Diels–Alder reaction.[10] Tricycle **8**, a dihydroarene, is obtained smoothly under the reaction conditions but is easily aromatized with DDQ to the arene in 87 %.

Sequential addition, while operationally easy, would be further simplified by addition of all three reactants at the outset of the reaction (Method B). Gratifyingly, this procedure afforded the target polycycles in better yields than the initial procedure (Table 1, Method B). Since diene **3** decomposes at elevated temperatures,[11] the higher yields obtained by Method B are a consequence of the diene being trapped as



Scheme 1. [5+2] cycloaddition of **1** and **2** is chemoselective and efficient at room temperature.

Table 1. Serial [5+2]/[4+2] cycloadditions with 1-ethynylcyclohexene (**2**).



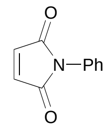
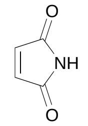
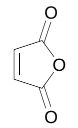
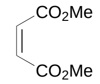
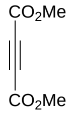
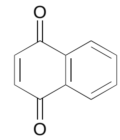
Entry	Dienophile	Method	T [°C]	t [h]	Product	Yield [%]
1		A	100	1	**4**	87
2		B	60	5	**4**	91
3		A	100	1	**5**	86
4		B	60	3	**5**	92
5		A	100	2	**6**	79
6		B	80	5	**6**	89
7		A	140	9	**7**	77
8		B	140	21.5	**7**	84
9		A	130	24	**8**	77
10		B	60	2	**9**	87

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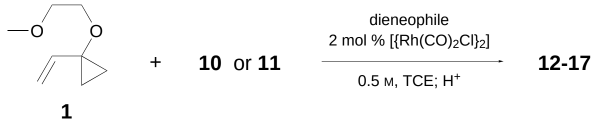
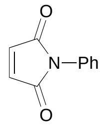
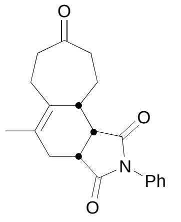
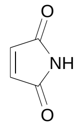
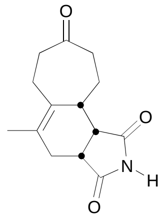
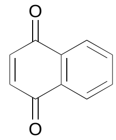
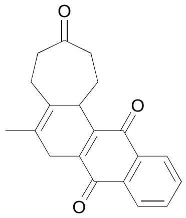
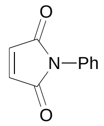
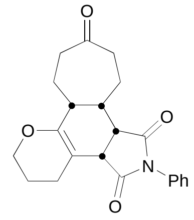
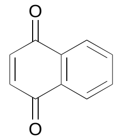
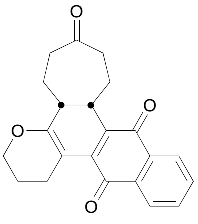
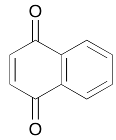
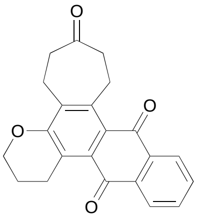
Table 2. [5+2]/[4+2] Cycloadditions with enyne **10** or **11**.



Entry	Dieneophile	Enyne	T [°C]	t [h]	Product	Yield [%]
1		**10**	40	24	 **12**	89
2		**10**	60	3	 **13**	83
3		**10**	60	10	 **14**	91
4		**11**	50	36	 **15**	89
5		**11**	50	36	 **16**	93
6		**11**	50	36	 **17**	81[a]

[a] During hydrolysis the reaction was stirred open to the air overnight, affording **17** from **16**. Yield refers to the transformation from **16** to **17**.

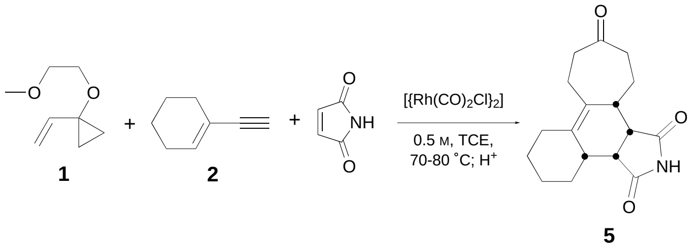
it forms in a [4+2] cycloaddition, avoiding deleterious side reactions. Thus, in a single, operationally simple step, two rings, four carbon–carbon bonds, and four stereocenters are formed in a predictable and specific manner. The enyne, dienophile and catalyst are commercially available and used without further purification. The vinylcyclopropane is easily and inexpensively prepared on multigram scale.[8c]

The generality of this three-component process with other enynes was also explored (Table 2). Good yields were obtained with enynes 2-methyl-1-buten-3-yne (**10**) and 6-ethynyl-3,4-dihydro-2*H*-pyran (**11**), and various dienophiles,[12] which demonstrates that a variety of enynes and dienophiles are tolerated.

The [5+2]/[4+2] addition product of naphthoquinone and **10** is oxidized during workup to give compound **14**, the result of a three-component, three-reaction process (Table 2, entry 3). The products initially formed from enyne **11** isomerized predictably and stereospecifically to the thermodynamically more stable enol ether (Table 2, entries 4, 5). As observed in the formation of **14**, the product of the [5+2]/[4+2] addition of naphthoquinone and **11** gave **16**. Moreover, stirring **16** overnight in solution exposed to air during the hydrolysis step afforded the aromatized product **17**, the result of five different steps in one operation (Table 2, entry 6).

This serial cycloaddition process is also readily scaled up. Increasing the reaction scale by 10- and 100-fold gave comparable yields of isolated products (Table 3). For example, 14.42 g (100 mmol) of **1** was converted to 26.32 g (91.6 mmol, 91%) of **5** in just 200 mL of solvent with only 1 mol% of catalyst.

Table 3. Scale-up study of the [5+2]/[4+2] cycloadditions.



Entry	Mol% Catalyst	t [h]	Scale	Yield [%][a]
1	2 mol%	1 h	1 mmol	92
2	1 mol%	4 h	1 mmol	90
3	1 mol%	6 h	10 mmol	92
4	1 mol%	6 h	100 mmol	91

[a] Yields of isolated products.

In summary, a novel, serial [5+2]/[4+2] cycloaddition is described. Complex polycyclic compounds are quickly and efficiently generated from simple, readily available starting materials. This reaction has been demonstrated with a variety of enynes and dienophiles and can be conducted on a preparative scale. The highly functionalized polycyclic products could serve as flexible building blocks for complex molecule syntheses, combinatorial libraries and medicinal targets. Further studies are in progress.

Experimental Section

Full procedures and characterization data are given in Supporting Information.

Method A: To an oven-dried, septum-capped test tube was added $[\{Rh(CO)_2Cl\}_2]$ (3.8 mg, 0.01 mmol) and anhydrous TCE (2 mL) under a positive argon pressure vented to a bubbler. To this was added **1** (142.2 mg, 1 mmol) and **2** (127.4 mg, 1.2 mmol). The reaction was stirred at room temperature for 6 h, the dienophile (1.2 – 1.5 mmol) was then added and the reaction heated to the temperature indicated in Table 1.

Method B: To an oven-dried, septum-capped test tube was added $[\{Rh(CO)_2Cl\}_2]$ (7.6 mg, 0.02 mmol) and anhydrous TCE (2 mL) under a positive argon pressure vented to a bubbler. To this was added **1** (142.2 mg, 1 mmol), **2** (127.4 mg, 1.2 mmol), and the dienophile (1.5 mmol). The reaction was heated to the temperature indicated in Table 1.

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[2] For reviews and lead references see: a) P. A. Wender, B. L. Miller in *Organic Synthesis: Theory and Applications*, *Vol. 2* (Ed.: T. Hudlicky), JAI, Greenwich, **1993**, pp. 27 – 66; b) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115 – 136; c) T. L. Ho, *Tandem Organic Reactions*, Wiley, New York **1992**; d) G. H. Posner, *Chem. Rev.* **1986**, *86*, 831 – 844; e) L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137 – 170; *Angew. Chem. Int. Ed. Engl.* **1993**, *23*, 131 – 163; f) R. A. Bunce, *Tetrahedron* **1995**, 13 103 – 13 159; g) H. M. L. Davies, *Tetrahedron* **1993**, *49*, 5203 – 5223.

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[4] For other [5+2]/[4+2] cycloadditions see: a) J. R. Rodríguez, A. Rumbo, L. Castedo, J. L. Mascareñas, *J. Org. Chem.* **1999**, *64*, 966 – 970; b) J. R. Rodríguez, L. Castedo, J. L. Mascareñas, *J. Org. Chem.* **2000**, *65*, 2528 – 2531.

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[6] a) *Advances in Cycloaddition*, *Vol. 1 – 3*, JAI, Greenwich, **1994**; b) C. P. Dell, *Contemp. Org. Synth.* **1997**, *4*, 87 – 117; c) C. P. Dell, *J. Chem. Soc. Perkin Trans. 1* **1998**, 3873 – 3905.

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[9] For recent studies from other laboratories see: a) S. R. Gilbertson, G. S. Hoge, *Tetrahedron Lett.* **1998**, *39*, 2075 – 2078; b) P. Binger, P. Wedemann, S. I. Kozhushkov, A. de Meijere, *Eur. J. Org. Chem.* **1998**, 113 – 119; c) B. M. Trost, F. D. Toste, H. Shen, *J. Am. Chem. Soc.* **2000**, *122*, 2379 – 2380.

[10] Crystallographic data (excluding structure factors) for the structures reported in this paper (**4**, **12**, **14**, **15**, **16**, and **17**) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-162748 – CCDC-162754. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[11] **3** was found to decompose with a half life of 30 h at 100 °C, 0.5 M in TCE. $[\{Rh(CO)_2Cl\}_2]$ accelerated the decomposition. See Supporting Information for additional detail.

[12] **11** was synthesized according to L. Brandsma, *Preparative Acetylenic Chemistry*, Elsevier, New York, **1988**, pp. 206 – 207.

Synthesis of Isotopically Labeled (*E*)-β,γ-Unsaturated Esters with Total or High Diastereoselectivity by Using Samarium Diiodide[**]

José M. Concellón,[*] Pablo L. Bernad, and
Humberto Rodríguez-Solla

β,γ-Unsaturated esters are generally synthesized by isomerization of α,β-unsaturated esters,[1] either by selective, conjugate reduction of alkyl alka-2,4-dienoates,[2] or by carbonylation of allylic compounds,[3] or from α-bromo-α,β-unsaturated esters.[4] However, no simple, general, highly diastereoselective preparation of β,γ-unsaturated esters has been described.

Recently, we reported a highly diastereoselective synthesis of (*E*)-α,β-unsaturated esters[5] and amides[6] from 2-halo-3-hydroxyesters and amides, respectively, by using SmI_2. Subsequently, we described a sequential elimination – reduction reaction promoted by SmI_2, which gave 2,3-dideuterioesters and amides from 2-halo-3-hydroxyesters and amides, respectively, by using D_2O as the deuteration reagent.[7] Here we report a new method to obtain β,γ-unsaturated esters **2**, with total or high diastereoselectivity by a sequenced elimination – reduction process of the readily available α-halo-β-hydroxy-γ,δ-unsaturated esters **1** by using SmI_2 and H_2O (see Table 1). Taking into account the usefulness of isotopically labeled compounds for establishing the mechanism of organic reactions and the biosynthetic pathways of many natural compounds,[8] we have also applied this method to obtain α,δ-

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