CHEMISTRY
A EUROPEAN JOURNAL

COMMUNICATION

DOI: 10.1002/chem.201201639

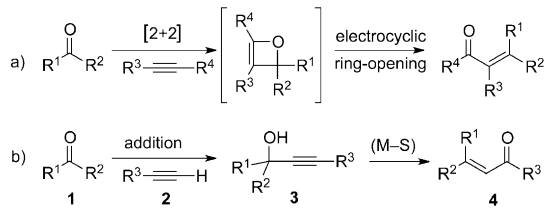
One-Pot Consecutive Reactions Based on the Synthesis of Conjugated Enones by the Re-Catalysed Meyer–Schuster Rearrangement

Elio Mattia, Alessio Porta, Valentina Merlini, Giuseppe Zanoni, and Giovanni Vidari*[a]

Conjugated enones are one of the most used building blocks in synthetic organic chemistry[1] and are an important moiety in natural products and biologically active compounds. Given its high synthetic versatility, the enone system is involved in several carbon–carbon bond-forming reactions, such as cyclopropanation, Michael addition, Diels–Alder and 1,3-dipolar cycloaddition reactions, and in the conversion to other functional groups, such as allylic alcohols, epoxides and amines.[2]

Traditional preparations by well-known protocols, such as aldol-like condensations and Wittig, Horner–Wadsworth–Emmons, Julia and Peterson olefinations, usually require basic conditions, which may be incompatible with different functional groups and/or the preservation of the original stereochemistry.[3] Moreover, these procedures are multistage sequences and exhibit an overall low atom economy.[4] They may also generate noxious byproducts and are usually highly sensitive to steric congestion around the carbonyl group.

In contrast to the aforementioned addition/elimination protocols, the addition of an alkyne to a carbonyl derivative followed by a rearrangement process offers the prospect of an efficient and completely atom-economical strategy. In this regard, several inter- and intramolecular alkyne–carbonyl metatheses, involving either a highly electron-rich alkyne, or an alkyne and a Lewis or Brönsted acid catalyst, have been extensively investigated (Scheme 1a).[5] Alternatively,



Scheme 1. Addition/rearrangement olefination strategies: a) alkyne–carbonyl metathesis; and b) nucleophilic 1,2 addition/Meyer–Schuster rearrangement.

propargylic alcohols **3**, produced by the smooth nucleophilic 1,2 addition of terminal alkynes **2** to carbonyl compounds **1**, may be subjected to isomerisation to the enones **4** by protic or, more frequently, Lewis acid catalysed Meyer–Schuster (M–S) rearrangements (Scheme 1b).[6]

In all procedures based on the M–S rearrangement that have been developed so far, homologation of aldehydes and ketones has been executed in two distinct stages: by first preparing the alkynol, and then subjecting it to the M–S reaction in a separate flask.[6] We deemed it highly desirable to develop a new, one-pot procedure for the olefination of carbonyl compounds; the consecutive preparation and isomerization of the alkynol in the same flask would effectively improve the efficiency and atom economy of the entire pathway. In this way, the entire addition/M–S rearrangement sequence would correspond more closely to the Wittig and other traditional olefination protocols, which involve reaction intermediates that collapse directly into the enone moiety. However, by avoiding most of the drawbacks that plague the classical procedures, the new protocol would represent a significant advancement in synthetic organic chemistry.

To increase the appeal of the method, we also explored the possibility of using the resulting enone in additional reactions that could take place immediately after the M–S rearrangement, without it first being isolated. The reduction of the carbonyl group to the corresponding allylic alcohol and the use of the enone moiety in a carbon–carbon bond-forming reaction, such as a Diels–Alder cycloaddition, appeared feasible. Herein, we describe the achievement of these goals.

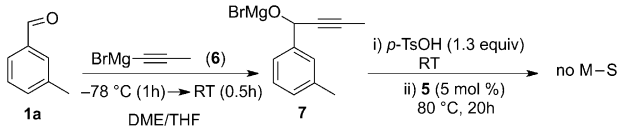
We have recently developed a new general catalytic procedure for the rapid and efficient M–S rearrangement of free secondary and tertiary propargylic alcohols to the corresponding α,β-unsaturated carbonyl compounds[6b] by using the readily available rhenium complex $[ReOCl_3(OPPh_3)(SMe_2)]$ (**5**).[7] The reaction proceeded under neutral conditions, showing virtually complete *E* stereoselectivity and preserving the configurational integrity of potentially enolisable stereocenters.[6b] Moreover, in striking contrast to the majority of M–S reactions, which occur in protic solvents,[6] the Re-promoted rearrangement proceeded smoothly in either THF or dimethoxyethane (DME). Thus the Re catalysis in an ethereal medium was, in principle, compatible with the classical conditions for preparing propargylic alcohols by a lithium or magnesium acetylide addition to a car-

[a] E. Mattia, Dr. A. Porta, Dr. V. Merlini, Dr. G. Zanoni, Prof. G. Vidari
Dipartimento di Chimica, Università di Pavia
Via Taramelli 12, 27100 Pavia (Italy)
E-mail: vidari@unipv.it

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201201639.

bonyl compound. However, we anticipated the need to develop an efficient means of quenching the intermediate salt that would arise from the acetylide addition. In fact, in accordance with our proposed mechanism for the M–S rearrangement, the catalytic cycle is initiated by the addition of the propargylic free hydroxyl group across the Re=O bond of the catalyst **5**.[6b] Therefore, at the onset of our efforts, we aimed to develop an effective in situ method for quenching the lithium or magnesium alkoxide that would not be harmful to the rhenium catalyst.

In an exploratory experiment, the addition/rearrangement of propynyl magnesium bromide (**6**) to *meta*-tolualdehyde (**1a**) was investigated (Scheme 2). As expected, the addition

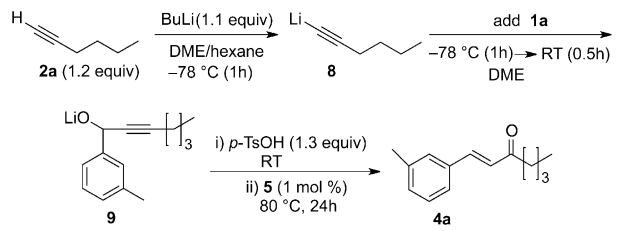


Scheme 2. Attempted one-pot olefination of aldehyde **1a** with the Grignard acetylide **6**.

of the commercially available Grignard reagent **6** (1.1 equiv) to aldehyde **1a** proceeded readily in DME/THF to produce the presumed alkoxide **7** (indicated by TLC analysis). Subsequently, the salt was protonated by the addition of solid *p*-TsOH·H_2O. Freshly prepared complex **5**[7] was then added to the mixture, which was heated at 80 °C for several hours. However, rather unexpectedly, no M–S rearrangement product was observed, and a workup returned the unaltered 1-(*meta*-tolyl)but-2-yn-1-ol intermediate product.

Assuming that bromide or magnesium ions might inhibit the catalytic activity of complex **5**, lithium acetylide **8**, generated by deprotonation of alkyne **2a** with BuLi, was added to aldehyde **1a**. After protonation of the intermediate alkoxyde **9** with *p*-TsOH·H_2O, the corresponding alkynol was subjected to the in situ Re-catalysed M–S rearrangement (Scheme 3). Under these conditions the reaction proceeded uneventfully, producing the expected enone **4a** as only the (*E*)-isomer (determined by NMR spectroscopy) in 66% overall yield.

We noticed that the reaction required slightly acidic conditions to proceed; the M–S rearrangement occurred only when the pH of the medium was about 5–6. On the other hand, *p*-TsOH·H_2O was required mainly for the protonation



Scheme 3. One-pot olefination of aldehyde **1a** with the lithium acetylide **8**.

of salt **9**, and its catalytic effect on the M–S rearrangement was assumed to be very modest. In fact, in the presence of excess *p*-TsOH·H_2O alone, excluding the catalytically active complex **5**, the M–S rearrangement of 1-(*meta*-tolyl)hept-2-yn-1-ol to enone **4a** proceeded very slowly with the formation of several byproducts.[8]

To explore the general applicability of this protocol, different carbonyl compounds **1** were subjected to the one-pot olefination process with alkyl- and aryl-substituted terminal alkynes **2** (Table 1). Aromatic substrates gave the corresponding isolated enones **4** with reasonable to excellent overall yields and, for most reactions, with almost complete *E* stereoselectivity. Furthermore, it was notable that the Re catalyst loading could be reduced to only 1 mol%. In sharp contrast, the aliphatic aldehyde **1f** gave a modest yield of enone **4f** (Table 1, entry 6), even in the presence of 5 mol% of catalyst **5**.[9]

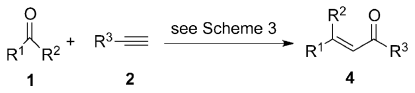
In later experiments (Table 2), the overall yields of the (*E*)-enones **4** were significantly improved by substituting *p*-TsOH·H_2O with the sulfonic resin Amberlite IR120 H (compare Table 1, entries 2–4 and 10 with Table 2, entries 1–4). This improvement in yield was attributed to the absence of H_2O in the reaction medium, the presence of which considerably reduces the catalytic activity of the Re complex **5**.[6b]

In conclusion, we have developed a new atom-economical procedure for the olefination of carbonyl compounds that demonstrates, for the first time, the feasibility of a one-pot procedure based on an alkynyl lithium addition followed by a Meyer–Schuster rearrangement of the intermediate alkynol.

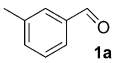
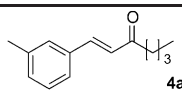
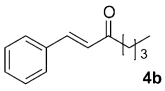
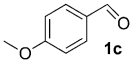
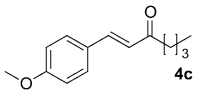
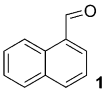
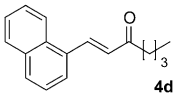
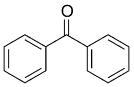
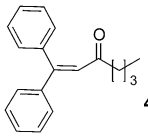
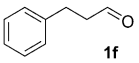
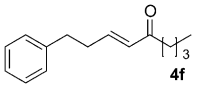
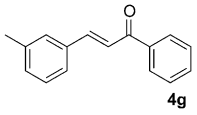
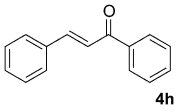
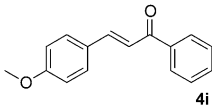
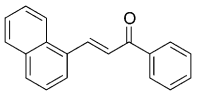
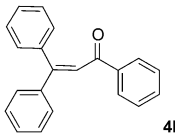
To increase the attractiveness of our protocol, we envisaged that an enone **4**, obtained from compounds **1** and **2**, could be submitted directly, without isolation, to a variety of additional reactions that are typically carried out in an ethereal solvent, such as DME. In the first set of experiments, enones **4**, obtained from aldehydes **1**, were reduced in situ to the allylic alcohols **10** by exposure to $LiAlH_4$. Parallel experiments showed that product yields were significantly improved by using *p*-TsOH, instead of the sulfonic resin Amberlite, in the aldehyde olefination sequence and by quenching excess $LiAlH_4$ with a base (see the Supporting Information for details). Under optimised reaction conditions, the entire one-pot sequence from **1** to **10** was executed in gratifying yields (Table 3). Given the ability of rhenium complexes to catalyse the 1,2 hydrosilylation of enones,[10] we also examined the possibility of substituting $LiAlH_4$ with Me_2PhSiH as the reducing agent in the reaction sequence shown in Table 3. However, we observed no reduction of the intermediate enones **4**.

To further increase the molecular complexity of the products by a consecutive carbon–carbon bond-forming reaction, enones **4** were submitted to an in situ Diels–Alder cycloaddition. To this end, enones **4** were formed by the M–S rearrangement of alkynols **3** and immediately exposed to cyclopentadiene (2 equiv), based on the assumption that the rhenium–oxo catalyst **5** could also be a reasonable Lewis acid

Table 1. One-pot olefination of carbonyl compounds.[a]



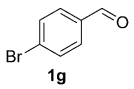
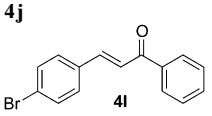
1 2 4

	1	2	4	Yield [%][b]
1				66
2		**2a**		77[c]
3		**2a**		75
4		**2a**		55[d]
5		**2a**		72
6		**2a**		30
7	**1a**			77
8	**1b**	**2b**		74
9	**1c**	**2b**		96
10	**1d**	**2b**		69
11	**1e**	**2b**		96

[a] See the Supporting Information for details. [b] Yield of the isolated *E* isomer. [c] Mixture of *E* and *Z* isomers (75:25). [d] Mixture of *Z* and *E* isomers (61:39).

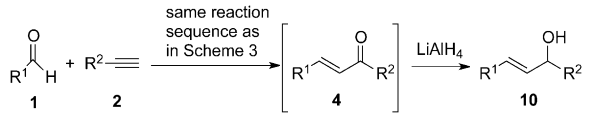
and thus be capable of catalysing the Diels–Alder reaction. However, no cycloadduct was formed upon heating the mixtures containing an enone **4** and cyclopentadiene, in the presence of only the rhenium catalyst **5**, in DME at reflux for several hours. Instead, the reactions proceeded smoothly at RT after the addition of $BF_3{\cdot}Et_2O$ (1.1 equiv) to the mixture, providing the expected *endo* cycloadducts **11** (Table 4).[11] The overall yields of the two consecutive reactions, that is, the M–S rearrangement of alkynol **3** followed

Table 2. Amberlite variant of the one-pot olefination of carbonyl compounds.[a]

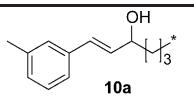
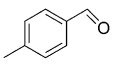
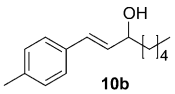
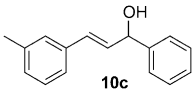
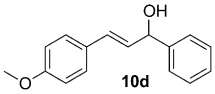
	1	2	4	Yield [%][b]
1	**1b**	**2a**	**4b**	88
2	**1c**	**2a**	**4c**	95
3	**1d**	**2a**	**4d**	82
4	**1d**	**2b**	**4j**	97
5		**2b**		93

[a] See the Supporting Information for details. [b] Yield of the isolated *E* isomer.

Table 3. One-pot olefination of aldehydes **1**, followed by the in situ reduction of intermediate enones **4**.[a]



1 2 4 10

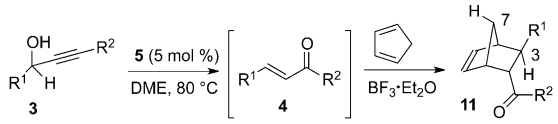
	1	2	10	Yield [%][b]
1	**1a**	**2a**		60
2				76
3	**1a**	**2b**		60
4	**1c**	**2b**		80

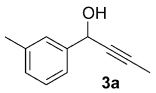
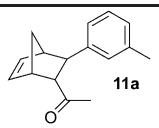
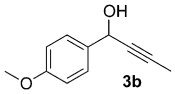
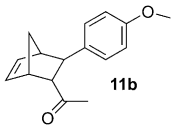
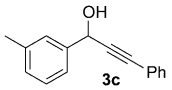
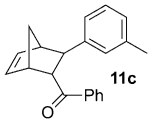
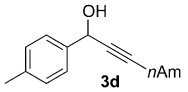
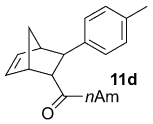
[a] See the Supporting Information for details. [b] Yield of the isolated *E* isomer.

by a Diels–Alder reaction, ranged from reasonable to good. More interestingly, the combined yields of the two reactions performed separately were comparable to that of the corresponding one-pot process, demonstrating that the cycloaddition reaction was not inhibited by the presence of the catalyst **5**.

In summary, we have developed an unprecedented, atom-economical, one-pot procedure for the olefination of carbonyl compounds to form conjugated enones that is based on the rhenium(V)-catalysed Meyer–Schuster rearrangement of intermediate alkynols. This procedure compares favourably with other traditional protocols in terms of efficiency, stereoselectivity, simplicity of execution and ready accessibility of starting materials. Moreover, we have shown that the rhenium(V) complex **5** is a robust catalyst that is compatible with a variety of other reagents and can thus be used in different one-pot operations to quickly assemble a number of products while generating a minimal amount of waste. We believe that these new procedures add to other

Table 4. One-pot Meyer–Schuster rearrangement of alkynols **3**, followed by the in situ Diels–Alder reaction of intermediate enones **4**.[a]



Entry	3	11	Yield [%]
1			55
2			30
3			73
4			75

[a] See the Supporting Information for details. The *endo* stereochemistries of adducts **11** were established on the basis of NOESY and ^{1}H–^{1}H-COSY NMR spectroscopy experiments. Am = C_5H_{11}.

protocols of modern organic chemistry by illustrating the brevity and the efficiency of one-pot, consecutive reaction processes.[12] Our current work includes efforts to couple the Re-catalysed M–S rearrangement with different carbon–carbon bond-forming reactions, and to apply this olefination strategy in total synthesis.

Experimental Section

General procedure for the one-pot olefination of carbonyl compounds: BuLi (1.6 M in hexane, 1.1 equiv) was added dropwise to a solution of alkyne **2** (1.2 equiv) in DME that was cooled at −78 °C. After stirring for 1 h at −78 °C, carbonyl compound **1** (1 equiv) was added in a single portion and the reaction mixture was stirred for 1.5–3 h, depending on the substrate (Table 1), until the complete disappearance of starting material **1** was indicated by TLC. Only in the case of the reaction between ketone **1e** and alkyne **2b** was the reaction mixture allowed to warm to RT. After completion of the reaction, the mixture was warmed to RT and a solution of *p*-TsOH (1.43 equiv) in DME was added. After checking the acidity of the medium, the complex $[ReOCl_3(OPPh_3)(SMe_2)]$ (**5**; 1 mol %) was added and the solution was warmed to 80 °C for a time that varied between 4 h and 7 days, depending on the substrate (Table 1), until complete disappearance of the intermediate alkynol was indicated by TLC. The reaction mixture was quenched by the addition of a saturated solution of aqueous NH_4Cl, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated at reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc gradient, from 98:2 to 95:5) to give enone **4**. The overall yields (from NMR data) of chromatographically pure (*E*)-enones **4** based on carbonyl compounds **1**, and the individual times for the coupling reactions of **1** and **2** and the subsequent in situ Meyer–Schuster rearrangement are reported in Table 1. Enones **4b** and **4d** were inseparable mixtures of *E* and *Z* isomers: 75:25 and 31:69, respectively (determined by ^{1}H NMR spectroscopy data).

General procedure for the one-pot Meyer–Schuster rearrangement of alkynols 3, followed by the in situ Diels–Alder reaction of intermediate enones 4: Complex **5** ($[ReOCl_3(OPPh_3)(SMe_2)]$; 5 mol %) was added to a solution of alkynol **3** in DME and the mixture was heated to 80 °C and stirred for 1–3 h (Table 4) until the disappearance of starting material **3**. Subsequently, the reaction mixture was cooled to room temperature and freshly distilled cyclopentadiene (4.0 equiv) was added. The mixture was then further cooled to −78 °C and BF_3·Et_2O (46.5 % solution in Et_2O, 1.16 equiv) was added. The reaction was stirred for 4 h at −78 °C, then at RT for an additional 8 h. The reaction mixture was quenched with a saturated solution of aqueous $NaHCO_3$ and extracted with Et_2O. The aqueous phase was washed with Et_2O (3 × 30 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated at reduced pressure. The residue was separated by column chromatography; elution with hexane/EtOAc (95:5) gave the chromatographically pure *endo*-norbornene cycloadduct **11**. The overall yields of cycloadducts **11** based on alkynols **3** are reported in Table 4, and the individual times for the Meyer–Schuster rearrangement and the Diels–Alder reaction are provided in the Supporting Information. The *endo* stereochemistry of each cycloadduct **11** was established by using NOESY and COSY experiments.

Acknowledgements

Financial support from the Italian MIUR (funds PRIN 2008 and 2009) is acknowledged.

Keywords: carbonyl compounds · isomerization · Meyer–Schuster reactions · olefination · rhenium · synthetic methods

[1] a) S. Patai, Z. Rappoport, *The Chemistry of Enones*, Wiley, New York, **1989**; b) C. E. Foster, P. R. Mackie in *Comprehensive Organic Functional Group Transformations II, Vol. 3* (Eds.: A. R. Katritzky, R. J. K. Taylor), Elsevier, Oxford, **2005**, pp. 215–266; c) J. Otera, *Modern Carbonyl Chemistry*, Wiley–VCH, Weinheim, **2000**.

[2] For reviews, see: a) M. E. Jung in *Comprehensive Organic Synthesis, Vol. 4* (Eds.: B. M. Trost, I. Fleming, M. F. Semmelhack), Pergamon, Oxford, **1991**, pp. 1–67; b) V. J. Lee in *Comprehensive Organic Synthesis, Vol. 4* (Eds.: B. M. Trost, I. Fleming, M. F. Semmelhack), Pergamon, Oxford, **1991**, pp. 69–137, 139–168; c) J. A. Kozlowski in *Comprehensive Organic Synthesis, Vol. 4* (Eds.: B. M. Trost, I. Fleming, M. F. Semmelhack), Pergamon, Oxford, **1991**, pp. 169–198.

[3] J. Clayden, N. Greeves, S. Warren, P. Wothers, *Organic Chemistry*, Oxford University Press, Oxford, **2001**.

[4] B. M. Trost, *Science* **1991**, *254*, 1471–1477.

[5] a) L. Liu, B. Xu, G. B. Hammond, *Beilstein J. Org. Chem.* **2011**, *7*, 606–614; b) D. A. Engel, G. B. Dudley, *Org. Biomol. Chem.* **2009**, *7*, 4149–4158, and references therein.

[6] For examples, see: a) R. S. Ramón, N. Marion, S. P. Nolan, *Tetrahedron* **2009**, *65*, 1767–1773; b) M. Stefanoni, M. Luparia, A. Porta, G. Zanoni, G. Vidari, *Chem. Eur. J.* **2009**, *15*, 3940–3944; c) see Ref. [5b]; d) H. Zheng, M. Lejkowski, D. G. Hall, *Chem. Sci.* **2011**, *2*, 1305–1310.

[7] a) B. D. Sherry, R. N. Loy, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 4510–4511; b) M. M. Abu-Omar, S. I. Khan, *Inorg. Chem.* **1998**, *37*, 4979–4985.

[8] D. A. Engel, G. B. Dudley, *Org. Lett.* **2006**, *8*, 4027–4029.

[9] For comparison, the M–S rearrangement of isolated 1-phenylnon-4-yn-3-ol, catalysed by **5** (1 mol %) in DME, gave the enone **4f** in 41 % yield.

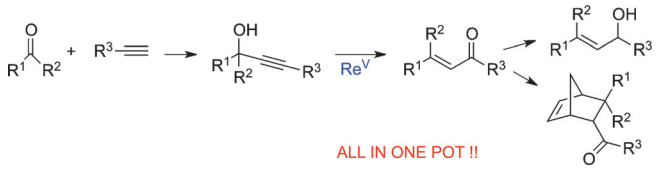
[10] During the course of this work, the one-pot Re-catalysed Meyer–Schuster rearrangement of propargyl alcohols followed by 1,2 hydrosilylation of the enone with Me_2PhSiH was reported: K. A. Nolin, R. W. Ahn, Y. Kobayashi, J. J. Kennedy-Smith, F. D. Toste, *Chem. Eur. J.* **2010**, *16*, 9555–9562.
[11] At this stage, it is premature to speculate whether $BF_3{\cdot}Et_2O$ promotes the Diels–Alder reaction by coordination to the carbonyl group of the enone **4** and/or by coordination to the complex **5**, which is likely to enhance its catalytic activity.
[12] T. Hudlicky, J. W. Reed, *The Way of Synthesis*, Wiley–VCH, Weinheim, **2007**.

Received: May 9, 2012
Revised: June 17, 2012
Published online: ■■ ▮▮, 0000

Domino Reactions

*E. Mattia, A. Porta, V. Merlini, G. Zanoni, G. Vidari** ..... ▮▮▮▮–▮▮▮▮

One-Pot Consecutive Reactions Based on the Synthesis of Conjugated Enones by the Re-Catalysed Meyer–Schuster Rearrangement



Re catalysis in one-pot reactions: An atom-economical, one-pot strategy that involves alkyne deprotonation and a subsequent rhenium(V)-catalysed Meyer–Schuster rearrangement of the alkynol to provide α,ß-unsaturated enones in high yield has been developed (see scheme). Subsequent in situ a hydride reduction or Diels–Alder reaction of the enones provided products in good-to-high overall yields.

These are not the final page numbers!