

annulation of 1,2-dienes. Our results are summarized in Table I.

A variety of reaction conditions have been examined, and some variations in our earlier procedures have proven desirable. In the annulation of 1,2-dienes, best results have been obtained with use of carbonate bases and catalytic amounts of PPh₃. Heteroannulation can usually best be effected by running the reactions at 100 °C, while carbonyl annulation is best carried out at the lowest temperature at which reaction occurs in a convenient period of time. Functionally substituted aryl halides with substituents as diverse as phenols, alcohols, tosyl amides, malonates, and nitro groups can effect annulation in high yield. Acyclic, cyclic, terminal, and internal 1,2-dienes have all been successfully employed in this annulation process with little variation in yield.

The regioselectivity of this annulation process is generally very high. Indeed, with most unsymmetrically substituted 1,2-dienes, only one regioisomer is observed. Several factors appear to play an important role in determining the regioselectivity. The formation of five-membered rings involves exclusive annulation across the more highly substituted carbon-carbon double bond (entries 1, 4, and 7). Even carbanions, which generally undergo intermolecular π-allylpalladium attack at the less substituted termini, afford exclusively the products of

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 (5) Larock, R. C.; Yum, E. K. *Synlett* 1990, 529.

attack at the more substituted end of the 1,2-diene when a five-membered ring is formed. On the other hand, six-membered rings are generally formed by annulation primarily across the less substituted carbon-carbon double bond (entries 5, 8, and 9), although exceptions have been observed (entry 2). Clearly, the nature of the functional group plays an important role as well. Only six-membered ring formation using monosubstituted 1,2-dienes (entries 5 and 8) leads to mixtures of regioisomers. This annulation process offers an exciting new way to generate quaternary carbon centers, even adjacent quaternary centers (entry 7).⁶

These reactions most likely proceed as illustrated in Scheme I. The addition of arylpalladium compounds to 1,2-dienes is known to produce π-allylpalladium compounds.⁷ Subsequent intermolecular nucleophilic substitution has been reported.^{7a-f} Related intramolecular processes employing aryl or vinylic halides and allenic malonates,^{7g,h} or ortho-thallated benzoic acids plus simple allenes⁷ⁱ are known. The occasional formation (entries 5 and 8) of mixtures of stereoisomers is presumably due to the generation of both syn and anti π-allylpalladium intermediates.

Acknowledgment. We gratefully acknowledge the National Institutes of Health for their generous financial support and Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. for the palladium acetate.

Supplementary Material Available: General procedures for the annulation reactions and experimental data (¹H and ¹³C NMR, IR, elemental analyses, and exact mass spectra) for all products shown in Table I (7 pages). Ordering information is given on any current masthead page.

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A Novel Concept for Regiochemical and Stereochemical Control in Lewis Acid Promoted [3 + 4] Annulation Reactions

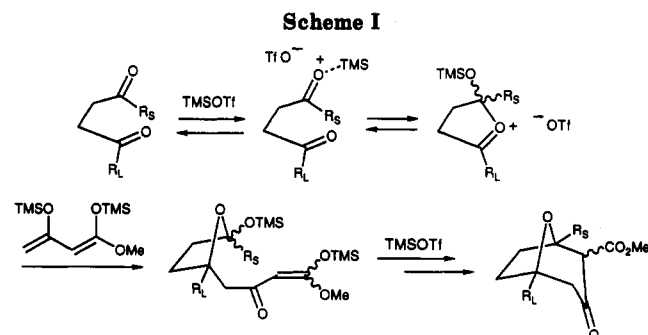
Gary A. Molander*¹ and Kimberly O. Cameron

Department of Chemistry and Biochemistry, University of Colorado, Boulder, Colorado 80309-0215

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Summary: Studies on the regioselective and stereoselective formation of a variety of 2-carbalkoxy-8-oxabicyclo-[3.2.1]octan-3-ones by means of a Lewis acid promoted [3 + 4] annulation process leads to a novel concept for selectivity in Lewis acid promoted carbonyl addition reactions.

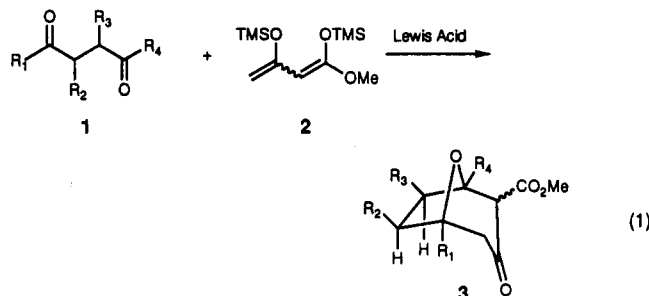
Development of general annulation strategies for the construction of stereodefined medium-sized carbocycles possessing variable substitution patterns remains a considerable challenge in organic synthesis.² Recently, we



reported a [3 + 4] annulation process that allowed access to functionalized, unsymmetrical seven- and eight-mem-

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bered carbocycles.³ The strategy involved the use of the bis(trimethylsilyl) enol ether of methyl acetoacetate **2** as a 1,3-dianionic synthon for annulation with dicarbonyl electrophiles.⁴ The discrete reactivity of the two nucleophilic centers in these dianionic synthons is well-documented, with the terminal carbon center reacting preferentially to the internal carbon center in reactions with a variety of electrophiles and Lewis acid promoters.⁵ Lewis acid promoted cyclization of **2** with 1,4-dicarbonyl substrates of differential reactivity was thus expected to generate [3 + 4] annulation products with high regioselectivity (eq 1). In initial studies, TiCl₄ was utilized as



the Lewis acid promoter in the annulation reaction of 1,4-keto aldehydes with **2**. Subsequent studies demonstrated that these reactions were capricious because complete regiocontrol in the cyclization was often lacking. The use of TiCl₄ offered other difficulties as well. For example, the bis(trimethylsilyl) enol ether itself reacted under the reaction conditions.⁶ In addition, 1 full equiv of the Lewis acid "catalyst" was required, causing subsequent workup problems. Finally, the relative asymmetric induction in annulation reactions with chiral dicarbonyl substrates was suspect. In order to overcome these difficulties, a survey of diverse Lewis acid catalysts was carried out. Among the many Lewis acids tried, trimethylsilyl trifluoromethanesulfonate (TMSOTf) showed surprising results that not only provided a solution to the problems delineated pre-

Table I. TMSOTf-Promoted Annulation of 1,4-Dicarbonyl Substrates **1** with **2**

entry	product	R ₁	R ₂	R ₃	R ₄	% isold yield (3) ^a	diastereo-selectivity ^b (regio-selectivity)
1	3a	Me	H	H	Me	56	
2	3b	Me	H	H	H	53	(>200:1)
3	3c	<i>n</i> -Pr	H	H	H	78–90	(>200:1)
4	3d	Ph	H	H	H	87	(>200:1)
5	3e	<i>t</i> -Bu	H	H	H	88	(>200:1)
6	3f	<i>t</i> -Bu	H	H	Me	74	(28:1)
7	3g	<i>i</i> -Pr	H	H	Me	67	(6:1)
8	3h	<i>n</i> -Pr	H	H	Me	73	(7:1)
9	3i	Et	Me	H	H	77	5.4:1 ^c
10	3j	Me	Ph	H	H	68	15:1 ^c
11	3k	<i>i</i> -Bu	<i>i</i> -Pr	H	H	77	15.6:1 ^c
12	3l	Me	H	Me	H	75	13.5:1 ^c
13	3m	Me	H	<i>i</i> -Pr	H	87	27.3:1 ^c
14	3n	Ph	H	<i>i</i> -Pr	H	68	>160:1 ^c

^a Refers to yields of purified products. All of these compounds have been fully characterized spectroscopically (¹H NMR, ¹³C NMR, IR), and elemental composition has been established by combustion analysis and/or exact mass. ^b Diastereoselectivities and regioselectivities were determined by fused silica capillary GLC analysis. ^c The crude bicyclic keto ester **3** was first derivatized to the corresponding enol acetate for determination of yield and diastereoselectivity.

viously, but also led us to propose a novel concept for regio- and stereochemical control in Lewis acid promoted carbonyl addition reactions of bifunctional substrates.

It had been previously demonstrated that TMSOTf was an effective catalyst for aldol-type condensations of trimethylsilyl enol ethers with acetal electrophiles. However, simple ketone and aldehyde electrophiles do not readily undergo TMSOTf-promoted condensations with silyl enol ethers.⁷ We were therefore quite surprised to find that 2,5-hexanedione reacted smoothly with **2** at -78 °C in the presence of catalytic (15–30%) TMSOTf, providing the annulated product **3** (Table I, entry 1).⁸ Having established that efficient annulation could be effected under these conditions, the next concern was chemoselectivity utilizing unsymmetrical dicarbonyl substrates. As a test, the bis(trimethylsilyl) enol ether **2** was reacted with a 1:1 mixture of 2-heptanone and octanal. *Surprisingly, only the ketone reacted!*⁹ As demonstrated in Table I, this same chemoselectivity was evident when various 1,4-keto aldehydes were reacted with **2** in the presence of catalytic TMSOTf. The bicyclic ethers **3** were obtained regioisomerically pure (with initial attack of the dinucleophilic synthon at the ketone) in 53–90% isolated yields (entries 2–5).

Unsymmetrical 1,4-diketones (entries 6–8) gave even more surprising results: the major regioisomer obtained was that due to initial attack of the terminal carbon of **2** at the *more hindered carbonyl center!*¹⁰ These surprising

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(4) Precedent for [3 + 4] annulations using bis(trimethylsilyl) enol ethers had previously been established. (a) Brownbridge, P.; Chan, T. H. *Tetrahedron Lett.* 1979, 4437. (b) Lee, S. D.; Chan, T. H. *Tetrahedron* 1984, 40, 3611.

(5) Hagiwara, H.; Kimura, K.; Uda, H. *J. Chem. Soc., Chem. Commun.* 1986, 860. (b) Yokoyama, Y. S.; Inoue, T.; Kuwajima, I. *Bull. Chem. Soc. Jpn.* 1984, 57, 553. (c) Attrill, R. P.; Barrett, A. G. M.; Quayle, P.; Van der Westhuizen, J.; Betts, M. J. *J. Org. Chem.* 1984, 49, 1679. (d) Hirai, K.; Ojima, I. *Tetrahedron Lett.* 1983, 24, 785. (e) Yokoyama, Y. S.; Elmoghayar, M. R. H.; Kuwajima, I. *Tetrahedron Lett.* 1982, 23, 2673. This reactivity pattern was confirmed in our laboratories by treating 2-heptanone with the bis(trimethylsilyl) enol ether of methyl acetoacetate in the presence of TMSOTf. Reaction occurred exclusively at the terminal carbon of the dinucleophilic synthon as expected.

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(7) (a) Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* 1988, 44, 4259.

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(8) Interestingly, in a competitive reaction of **2** with a 1:1 mixture of 2-heptanone and 4-oxoheptanal in the presence of TMSOTf, **3c** is isolated as the sole product in 57% yield. There is no trace of the product resulting from simple addition of the bis(trimethylsilyl) enol ether to 2-heptanone.

(9) Reaction of **2** with a 1:1 mixture of 2-heptanone and octanal in the presence of 10 mol % TMSOTf produced methyl 5-hydroxy-5-methyl-3-oxodecanoate in 52% isolated yield. None of the product resulting from addition to octanal could be detected.

(10) Regiochemistry was determined by NOE spectroscopy. When **2** was reacted with a 1:1 mixture of 2-heptanone and pinacolone in the presence of catalytic TMSOTf, a 20:1 mixture of alcohols was obtained. As expected, the major product was methyl 5-hydroxy-5-methyl-3-oxodecanoate, isolated in 66% yield.

Table II. TMSOTf-Promoted Annulation of 4-Oxoheptanal with 4

entry	product	R ₁	R ₂	% isold yield (5 + 6) ^a	diastereo-selectivity (5:6) ^b
1	5a + 6a	Me	Me	73	>40:1
2	5b + 6b	Me	<i>t</i> -Bu	80	1.3:1
3	5c + 6c	Me	OEt	76	1:>35
4	5d + 6d	<i>i</i> -Pr	OEt	73	1:25
5	5e + 6e	-CH ₂ CH ₂ O-		75	1:1.3

^a Refers to yields of purified products. All of these compounds have been fully characterized spectroscopically (¹H NMR, ¹³C NMR, IR), and elemental composition has been established by combustion analysis and/or exact mass. ^b Diastereoselectivities and regioselectivities were determined by fused silica capillary GLC analysis.

results suggested that the origin of unusual chemoselectivity was much more complex in nature than we had originally anticipated.

Stereoselectivity in the process was next examined by utilizing chiral, racemic 1,4-keto aldehydes in conjunction with **2** and TMSOTf.¹¹ The observed stereoselectivities of the annulation products (5.4:1 to >160:1, Table I, entries 9–14) were much higher than that obtained in the intermolecular reaction of **2** with a simple acyclic ketone like 3-methyl-2-pentanone (1.8:1, 56% yield). Another interesting feature of the annulation process is that the relative 1,3-asymmetric induction (Table I, entries 12–14) appears to be as good as, if not better than, 1,2-asymmetric induction (Table I, entries 9–11).¹²

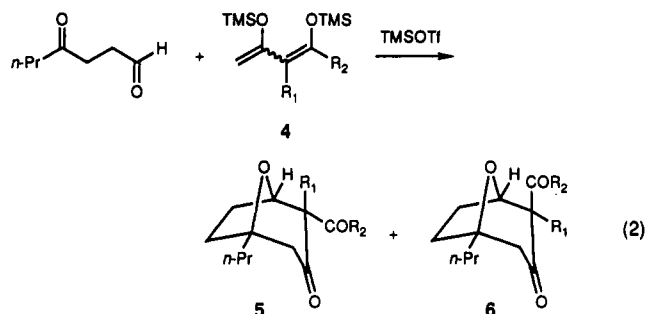
On the basis of the remarkable trends in chemoselectivity and stereoselectivity delineated previously, a plausible mechanism invoking a unique neighboring group participation is outlined in Scheme I. Activation of the *less hindered* carbonyl by TMSOTf¹³ followed by intramolecular participation by the remaining, *more hindered* carbonyl forms an electrophilic oxonium ion. Nucleophilic attack of the terminal carbon of **2** at the electron-deficient, more hindered carbon center followed by cyclization explains the remarkable regiochemistries observed for unsymmetrical 1,4-diketones. The unusual sense and relative magnitudes of the diastereoselectivities obtained in this reaction is also rationalized by initial formation of a cyclic intermediate.¹⁴

(11) Diastereoselectivities were determined by first derivatizing the resulting bicyclic keto ester (**3**) to the enol acetate, thereby eliminating the methoxycarbonyl stereocenter.

(12) Stereochemistry at C-7 was determined from ¹H NMR coupling constants. The bridgehead proton (H-1) couples only to the *exo* substituent at C-7. H-1 in the major diastereomer (R³ *exo*) appeared as a singlet (**3l–n**), but in the minor diastereomer (R³ *endo*) it appeared as a doublet ($J = 5.9$ Hz, **3l**). An X-ray crystal structure of **3j** allowed stereochemical determination of that compound.

(13) (a) Maruoka, K.; Araki, Y.; Yamamoto, H. *Tetrahedron Lett.* 1988, 29, 3101. (b) Maruoka, K.; Araki, Y.; Yamamoto, H. *J. Am. Chem. Soc.* 1988, 110, 2650. (c) Maruoka, K.; Nagahara, S.; Yamamoto, H. *J. Am. Chem. Soc.* 1990, 112, 6115. (d) Maruoka, K.; Nagahara, S.; Yamamoto, H. *Tetrahedron Lett.* 1990, 31, 5475.

Stereoselectivity engendered in the [3 + 4] annulation reaction of α -substituted β -dicarbonyl dianionic synthons **4** with 4-oxoheptanal in the presence of TMSOTf was also studied (eq 2). One unusual feature of these reactions is



that the product derived from the reaction of 3-substituted bis(trimethylsilyl) enol ethers of β -keto esters (entries 3 and 4, Table II) has the opposite relative stereochemistry as that obtained by reaction of 3-substituted bis(trimethylsilyl) enol ethers of β -diketones (entry 1, Table II).¹⁵ While the origin of this phenomenon is as yet unknown, the ability to access both stereoisomeric product manifolds with functionalized quaternary stereogenic centers is impressive.¹⁶

In summary, TMSOTf promotes the [3 + 4] annulation of bis(trimethylsilyl) enol ethers with a variety of 1,4-dielectrophiles. Unusual chemoselectivities and diastereoselectivities are observed in these transformations. A mechanism involving neighboring group participation has been invoked to account for these remarkable results. Further mechanistic and synthetic studies are underway to elucidate the scope and nature of these reactions.

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Supplementary Material Available: Complete experimental details and spectral data for all of the annulations described herein. Details of the X-ray crystallographic structural determination and NMR assignments pertaining to the determination of product regio- and diastereoselectivities (26 pages). Ordering information is given on any current masthead page.

(14) A similar trend of 1,2- and 1,3-relative asymmetric induction was observed for nucleophilic addition of allylsilanes to substituted 2-hydroxytetrahydrofurans. Schmitt, A.; Reissig, H. *Synlett* 1990, 1, 40.

(15) An example of the method utilized for stereochemical determination is given. The bicyclic compound derived from annulation of the bis(trimethylsilyl) enol ether of 2,4-pentanedione with 4-oxoheptanal was prepared. Alkylation (NaH, MeI, THF, 0 °C to rt) provided the 2-*exo*-methyl-substituted bicyclic compound, which had physical and spectral characteristics identical with **5a**.

(16) Isolated products resubjected to the reaction conditions shown no sign of epimerization. Consequently, the reaction appears to be kinetically controlled.

Metabolic Transformation of the Phytoalexin Brassinin by the "Blackleg" Fungus

M. Soledade C. Pedras* and Janet L. Taylor

Plant Biotechnology Institute, National Research Council of Canada, Saskatoon, Saskatchewan, S7N 0W9 Canada

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Summary: The metabolism of a phytoalexin from *Brassica* species, brassinin (**1**), by the phytopathogenic fungus *Phoma lingam* was investigated and the unusual structure

of the first metabolic intermediate was assigned as methyl (3-indolylmethyl)dithiocarbamate *S*-oxide (**2**) based on spectroscopic data and synthesis of a methyl derivative.