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Formation of Carbocycles by Intramolecular Conjugate Displacement: Scope and Mechanistic Insights

Lihong Wang, Bodhuri Prabhudas, and Derrick L. J. Clive*

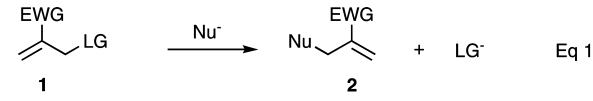
Chemistry Department, University of Alberta, Edmonton, Alberta T6G 2G2, Canada

Received February 3, 2009; E-mail: derrick.clive@ualberta.ca

Abstract: A detailed study has been made of a method of ring closure categorized as an all-carbon intramolecular conjugate displacement (ICD). This reaction involves intramolecular addition of a carbanion, which is stabilized by at least one electron-withdrawing group, to a Michael acceptor which has a leaving group in an allylic position. The process formally resembles a combination of Michael addition and S_N2' displacement. The overall result is formation of a ring with loss of the allylic leaving group and shift of the original double bond to a new location spanning the positions of the electron-withdrawing substituent of the Michael acceptor subunit and the original allylic leaving group. The starting materials are easily prepared by a selenium-based version of the Morita−Baylis−Hillman reaction. The cyclizations are transition metal free and occur under mild conditions, using DBU or Cs_2CO_3 in MeCN or THF. Acetate is a suitable leaving group and the electron-withdrawing substituent of the Michael acceptor unit can be CO_2R, SO_2Ph, or CN. Six- and seven-membered rings are formed efficiently, and complex structures, such as those resembling the core of CP-225,917, are easily assembled. The products of these ICD reactions are themselves classical Michael acceptors. A range of mechanisms probably operates, depending on the structure of the starting material and the reaction conditions, but conclusive evidence for a stepwise mechanism was obtained in a suitably biased case, while other observations are compatible with a concerted process or a stepwise path involving a short-lived carbanion that evades capture by a proton source.

Introduction

The generic intermolecular process summarized in eq 1 (EWG = electron-withdrawing group, LG = leaving group) formally represents a hybrid of classical Michael addition and S_N2' displacement. In the particular cases represented by eq 2, the reactivity was shown to be greater than in the absence of the leaving group,[1] so that reaction could easily be stopped with the formation of **4**, which was isolated and then subjected to classical Michael addition. This enhanced reactivity is evidently general,[2] and examples conforming to the intermolecular



formulation of eq 1 for various electron-withdrawing groups are known—generally using acetates derived from Morita−Baylis−Hillman (MBH) alcohols.[2] However, the synthetic opportunities available by using such reactions in an *intramolecular* manner do not appear to have been appreciated, apart from occasional use to make azamacrocycles[2e,f] (nitrogen as the nucleophile) or for cross-linking of proteins,[3] and the many examples[4,5] studied in this laboratory (nitrogen as the nucleophile). In previous work on the synthesis of halichlorine,[4,5] the amine **6**, generated in situ, was found to undergo spontaneous ring closure to **7** (>70% yield, Scheme 1).[6] This method for making nitrogen-containing rings is general and was studied extensively.[4,5] Such processes have been classified as intramolecular conjugate displacement (ICD) reactions.[5] The corre-

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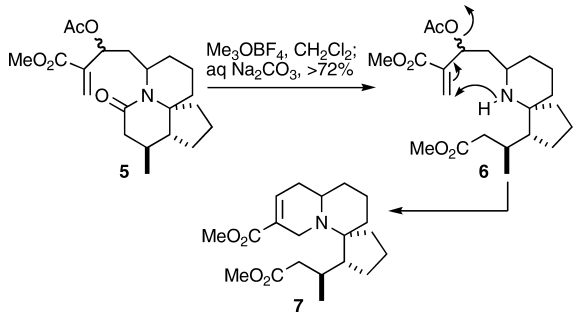
(3) Mitra, S.; Lawton, R. G. *J. Am. Chem. Soc.* **1979**, *101*, 3097–3110.

(4) Clive, D. L. J.; Yu, M.; Li, Z. *Chem. Commun.* **2005**, 906–908.

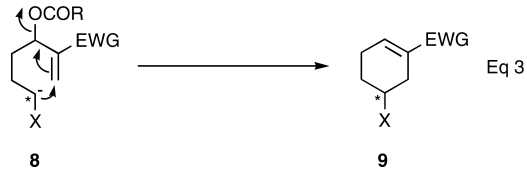
(5) Clive, D. L. J.; Li, Z.; Yu, M. *J. Org. Chem.* **2007**, *72*, 5608–5617.

(6) For a mechanistically related (and earlier) approach to the halichlorine system, see: (a) Christie, H. S.; Heathcock, C. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12079–12084. (b) A variant of this approach has been used in a formal synthesis of (±)-halichlorine: Andrade, R. B.; Martin, S. F. *Org. Lett.* **2005**, *7*, 5733–5735.

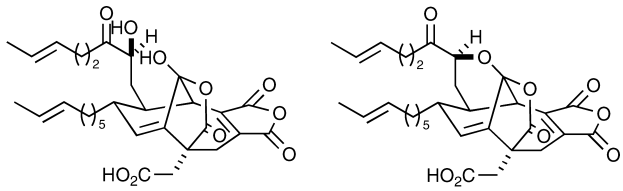
Scheme 1. Initial Development of Intramolecular Conjugate Displacement



sponding all-carbon ICD reaction (eq 3) is also general,[7] and we describe here the scope of this method for making carbocycles, as well as insights into its mechanism. In eq 3 the starred carbon carries a group X that makes that carbon potentially or actually nucleophilic.

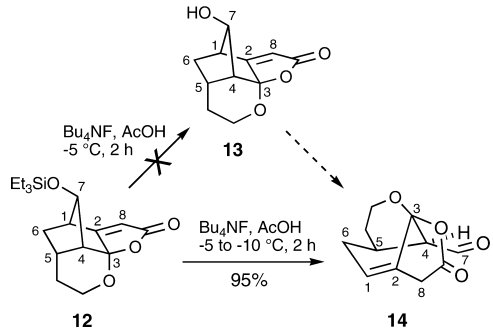


Development of the All-Carbon ICD Reaction. In the course of studies aimed at the synthesis of CP-225,917 (**10**) and the related CP-263,114 (**11**), the silyl ether **12** was treated with Bu_4NF in the hope of liberating the parent alcohol **13** (Scheme 2). In the event, none of this material was obtained and only the fragmentation product **14** was isolated. Although not the desired product, we quickly recognized that aldehyde **14** might

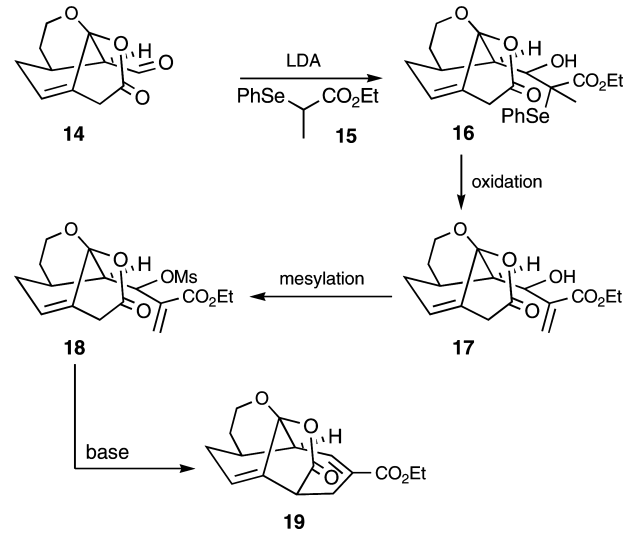


be far more useful than the compound we had originally wanted because it provided an opportunity to try the ICD process in an all-carbon system, along the lines summarized in Scheme 3. Moreover, this scheme represents a sufficiently demanding case, that its successful implementation would imply appreciable synthetic value for the all-carbon ICD process. A critical step of the proposed sequence of Scheme 3 was the requirement that

Scheme 2. Fragmentation of Tetracyclic Alcohol **13**



Scheme 3. First Application of All-Carbon ICD Reaction



the selenium-based method[4,5,8] for generating MBH alcohols (see **14**→**16**→**17**) could be effected without epimerization of the starting aldehyde. In prior work in this laboratory,[4,5] which involved the formation of nitrogen-containing heterocycles (cf. Scheme 1), none of the aldehydes used possessed an epimerizable center α to the aldehyde carbonyl, but in the event, aldehyde **14** was converted easily into the desired adduct **16** and that, in turn, afforded the MBH alcohol **17** on oxidation of the PhSe group. Mesylation proceeded without incident and, crucially, treatment with base (DBU) gave the cyclized product **19** in excellent yield (96%). This result made it obvious that a detailed study of the scope of the ICD route to carbocycles was appropriate, and we have now examined a large number of substrates and also probed some of the mechanistic possibilities.

Preparation of Substrates for the All-Carbon ICD Reaction. Most of the aldehydes we have used in our studies are listed in Table 1. They were prepared by conventional means, and full details are given in the Supporting Information. Initially, we were interested in identifying what types of carbon nucleophile and electron-withdrawing groups are suitable for the ICD reaction and, to a lesser extent, also the range of ring sizes that would be available. These considerations guided our choice of substrates.

In order to convert our aldehydes into MBH alcohols or the corresponding acetates, we almost always used a selenium-based method[5,8] that operates along the lines expressed in Scheme 4. In all cases, oxidation of the selenium produced an allylic alcohol[9] or the corresponding acetate (if the hydroxyl was first acetylated). This approach to MBH alcohols has now been tested with many examples[5] and is both efficient and general. In the single case where a comparison was made (formation of **20d**) the standard Baylis-Hillman conditions (DABCO, room temperature, 2 days) gave a complex mixture.

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Table 1. Preparation of ICD Substrates

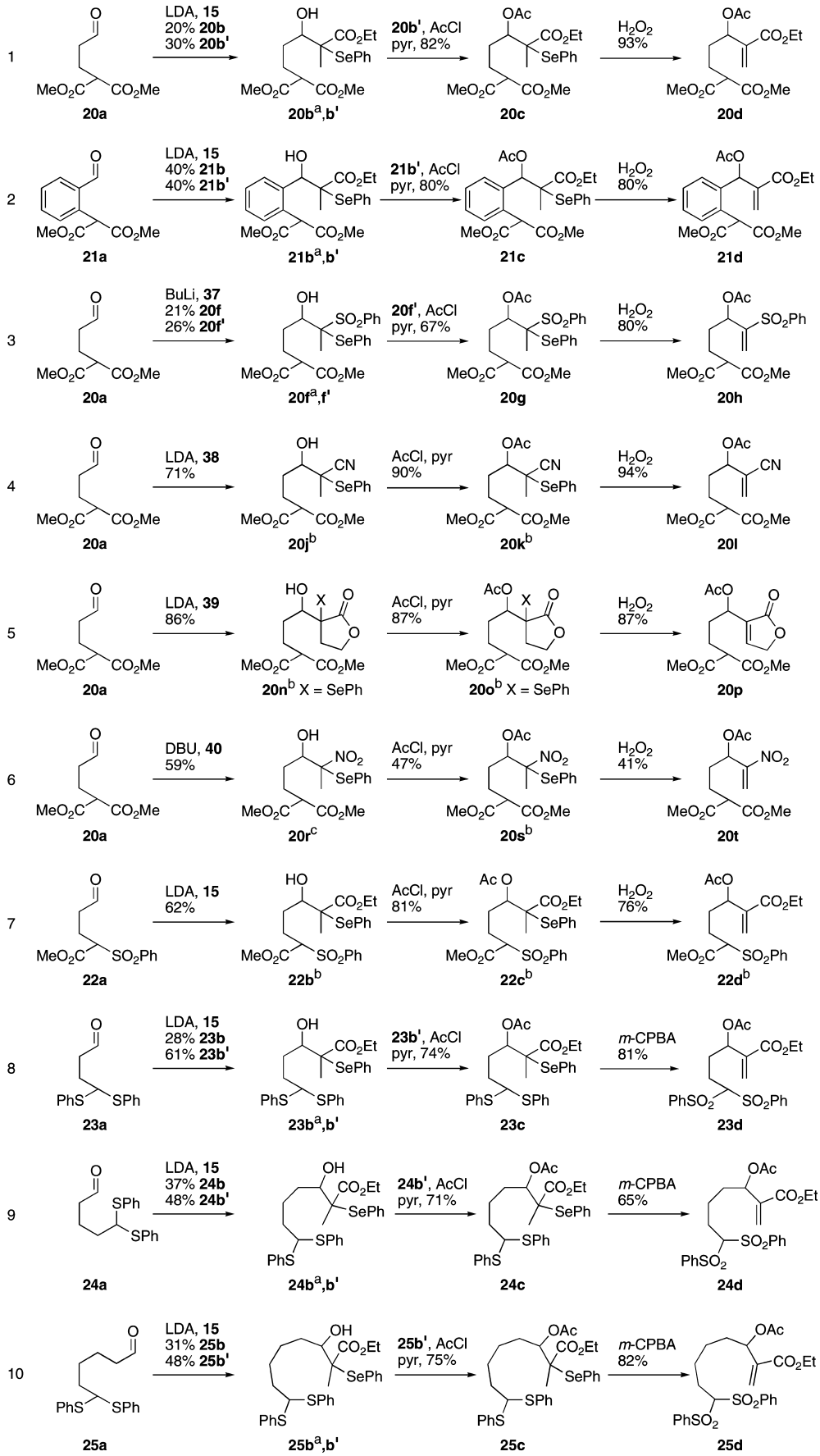
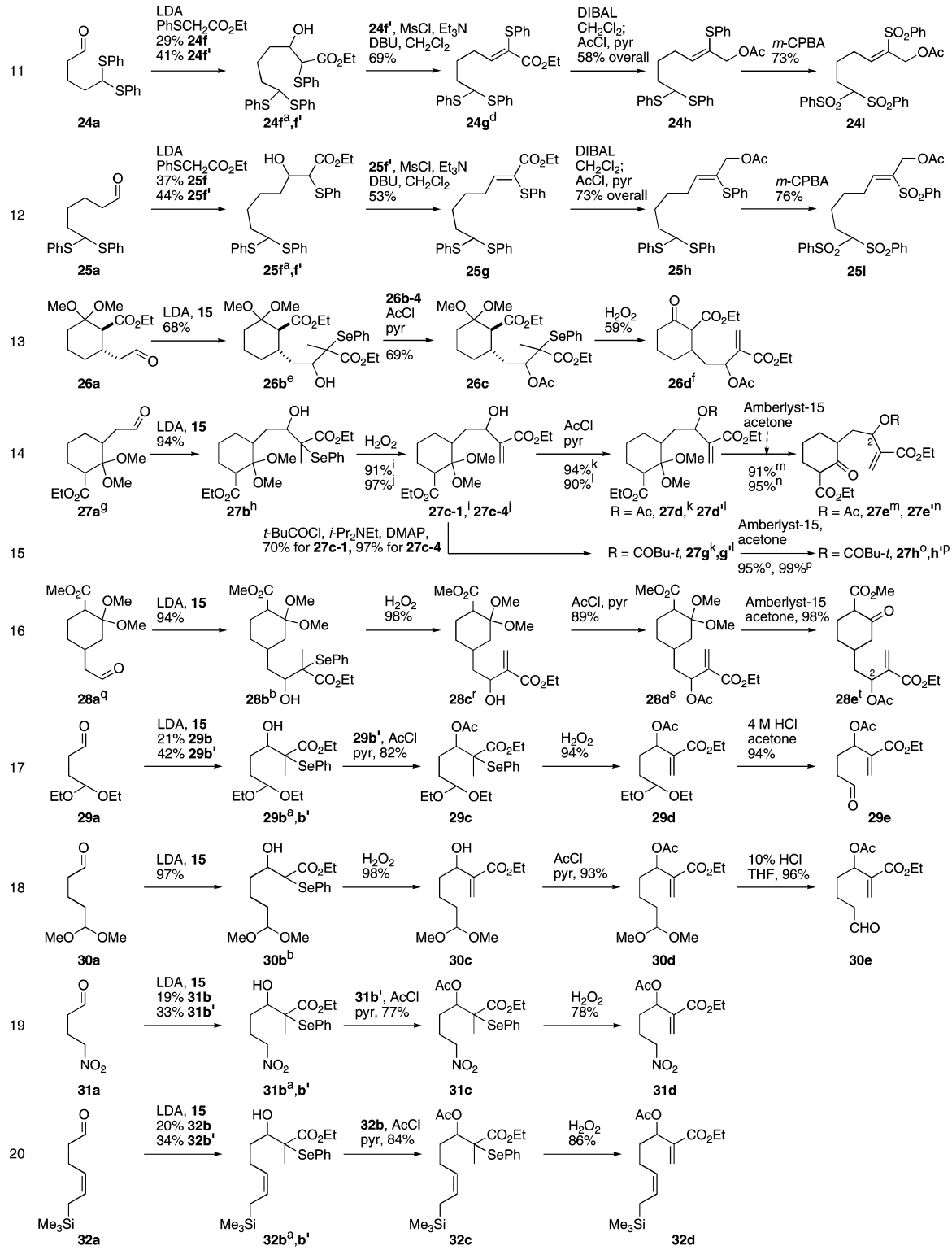
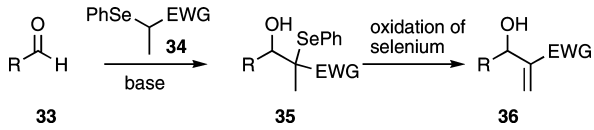


Table 1. Continued



[a] Less polar isomer. [b] Mixture of diastereoisomers. [c] Two inseparable isomers contaminated by starting aldehyde. [d] Assignment of double bond geometry tentative. [e] This product was separated into three fractions: **26b-1** (least polar, a single isomer, 15%); a mixture of two isomers, **26b-2** and **26b-3**, 35%; and **26b-4** (most polar, a single isomer, 18%). Only **26b-4** was taken forward. [f] An equilibrium mixture of keto−enol tautomers. [g] Compound **27a** is a single isomer of unestablished stereochemistry. [h] This product was separated into three fractions: **27b-1** (least polar, a single isomer, 19%); a mixture of two isomers, **27b-2** and **27b-3**, 46%; and **27b-4** (most polar, a single isomer, 29%). The stereochemical configuration at the carbinol carbon is the same in **27b-1** and **27b-2**, while the opposite configuration at the carbinol center applies to **27b-3** and **27b-4**. Only the least polar isomer (**27b-1**) and the most polar isomer (**27b-4**) were taken further. [i] From least polar isomer (**27b-1**). [j] From most polar isomer (**27b-4**). [k] From **27c-1**. [l] From **27c-4**. [m] From **27d**. [n] From **27d′**. [o] From **27g**. [p] From **27g′**. [q] Single isomer. [r] Inseparable mixture of two isomers that differ in stereochemistry at the hydroxyl-bearing carbon. [s] Inseparable mixture of two isomers that differ in stereochemistry at the acetoxy-bearing carbon. [t] Mixture of isomers including keto−enol tautomers.

Scheme 4. Selenium-Based Route to MBH Alcohols[a]



[a] EWG = electron-withdrawing group.

The selenides we have used are **15**[10] (see Scheme 3), **37**,[11] **38**,[12] **39**,[13] and **40** (Figure 1).[8e] They are all known compounds and were easily prepared by quenching the appropriate carbanion with PhSeCl, except for **15**, which was made by displacing bromide from ethyl 2-bromopropionate with PhSeNa.

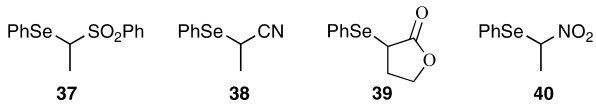


Figure 1. Selenides for making MBH alcohols and acetates.

In each case the selenide (**15** or **37**−**40**) was deprotonated, usually with LDA, and a solution of the aldehyde was added to the resulting carbanion. In one case (Table 1, entry 3), BuLi was used for the deprotonation (the yield was higher), and in another (entry 6) DBU was used since stronger bases (LDA or BuLi) caused loss of the PhSe group. The expected alcohols were always obtained as a mixture of diastereoisomers; sometimes these could be separated, but further processing as a mixture is perfectly satisfactory. In most cases where the diastereoisomers were separated, only one of them was taken further. The yields of the alcohols ranged from just below 50% to above 80%. Acetylation with AcCl in the presence of pyridine and DMAP proceeded without incident, and the required double bond was then generated in satisfactory yield (71−94%) by oxidation of the PhSe group with 30% H_2O_2 or *m*-CPBA. In the preparation of **27d,d′**, **27g,g′**, **28e**, and **30e**, the normal sequence was altered, the selenoxide elimination being done before acetylation.

The examples shown in entries 11 and 12 of Table 1 are different from all the others in that the key double bond was generated not by selenoxide elimination, but by dehydration via a mesylate. In these two cases the starting aldehyde was treated with the carbanion generated from $PhSCH_2CO_2Et$.[14]

The condensation, acetylation, oxidation sequence for examples 1−10 of Table 1 directly generated the substrates needed for the ICD reaction, but the examples of entries 11−16 required a few extra steps to reach the ICD substrates. Both **24g** and **25g** were reduced with DIBAL and the resulting alcohols were acetylated; treatment with *m*-CPBA then generated the sulfone groups. It should be noted that when the selenium-based method for making MBH alcohols is used, oxidation to form the double bond is accompanied by conversion of PhS groups to $PhSO_2$ groups; this is a particularly convenient feature, as illustrated by the preparation of **23d**, **24d**, and **25d**; it is also an essential feature, as earlier oxidation of the sulfur to the sulfone level would acidify the adjacent C−H bond to an extent that would likely interfere with some of the subsequent steps.

Most of our ICD substrates were designed to examine endo cyclization modes of the type shown in eq 3, but **24i** and **25i** (entries 11 and 12 of Table 1) were prepared in order to explore the possibility of exocyclic closure. Entries 14 and 15 of Tables 1 and 2 represent cases where cyclization through both carbon and oxygen is possible—and was indeed observed.

Cyclization by ICD Reaction. As indicated above, our studies on the all-carbon ICD reaction were initiated[7] during synthetic work on CP-compounds. When we first tried to cyclize **18** to **19**, we used $(Me_3Si)_2NLi$, but obtained a complex mixture. Accordingly, we then tried a weaker base and arbitrarily used DBU in MeCN at room temperature. This experiment gave the desired product very efficiently (96%) after a short reaction time. Consequently, this base−solvent combination became our usual first choice, and we explored other bases and solvents only when the DBU−MeCN system failed to perform well. The entries of Tables 1 and 2 are not in chronological order, and the first time the DBU−MeCN system proved unsatisfactory was with compound **27e**; in this case, we examined Cs_2CO_3 as the base but retained MeCN as solvent. Since the result of that experiment was a very high yield (99%) of the desired ICD product, we now had two useful base−solvent combinations. When we came to the cyanide **20l**, we were disappointed to find that both of these bases in MeCN gave a low yield, and so we were forced to carry out a more extensive survey, which is summarized in Table 3. The data collected in this table showed that Et_3N−MeCN is satisfactory and that the addition of Me_3SiCl is of no benefit. When we applied the Et_3N method to lactone **20p**, a complex mixture was obtained, and even DBU or Cs_2CO_3 in MeCN also gave little, if any, of the desired product. In an attempt to run the reaction at −78 °C, we turned to THF as the solvent (with Cs_2CO_3 as base). Compound **20p** did not react under these conditions, but on raising the temperature in ∼10 °C increments we established that smooth reaction occurs at room temperature to give the expected product in 97% yield. Because of the superior performance of Cs_2CO_3 in dry THF, we subsequently made these conditions our first choice, and we also reinvestigated the nitrile **20l**, with the result shown in Table 3 (entry 9).

While no obvious trend is apparent from the data in Table 3, the empirical findings are that DBU or Cs_2CO_3 in MeCN, or Cs_2CO_3 in THF are preferred conditions for the ICD reactions. Probably, THF is best and, once we had identified it as an appropriate solvent, it was used for most of our subsequent experiments. With this solvent, workup is also straightforward, as simple filtration and evaporation of the THF often gave products in which we could not detect impurities by ^1H NMR measurements, and chromatography was unnecessary.

In a few of our screening experiments to find an appropriate base, we identified a minor problem in that elimination of the leaving group occurred instead of the desired ICD closure when we used DABCO with **20l** or Hünig's base with **20p**. This pathway was not observed with Cs_2CO_3, however.

In the case of entries 1−16 and 19 of Table 2, the nucleophilic carbon was generated by deprotonation, but entries 17, 18, and 20 represent other ways of forming a nucleophilic carbon.

In general, ring closure by the ICD process occurs under mild conditions and usually proceeds in high yield, often above 90%. Most reactions are over within no more than a few hours at room temperature, but a few required heating (Table 2, entries 14, 15, 17, and 18). Six- and seven-membered rings are formed

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(11) Simpkins, N. S. *Tetrahedron* **1991**, *47*, 323–332.
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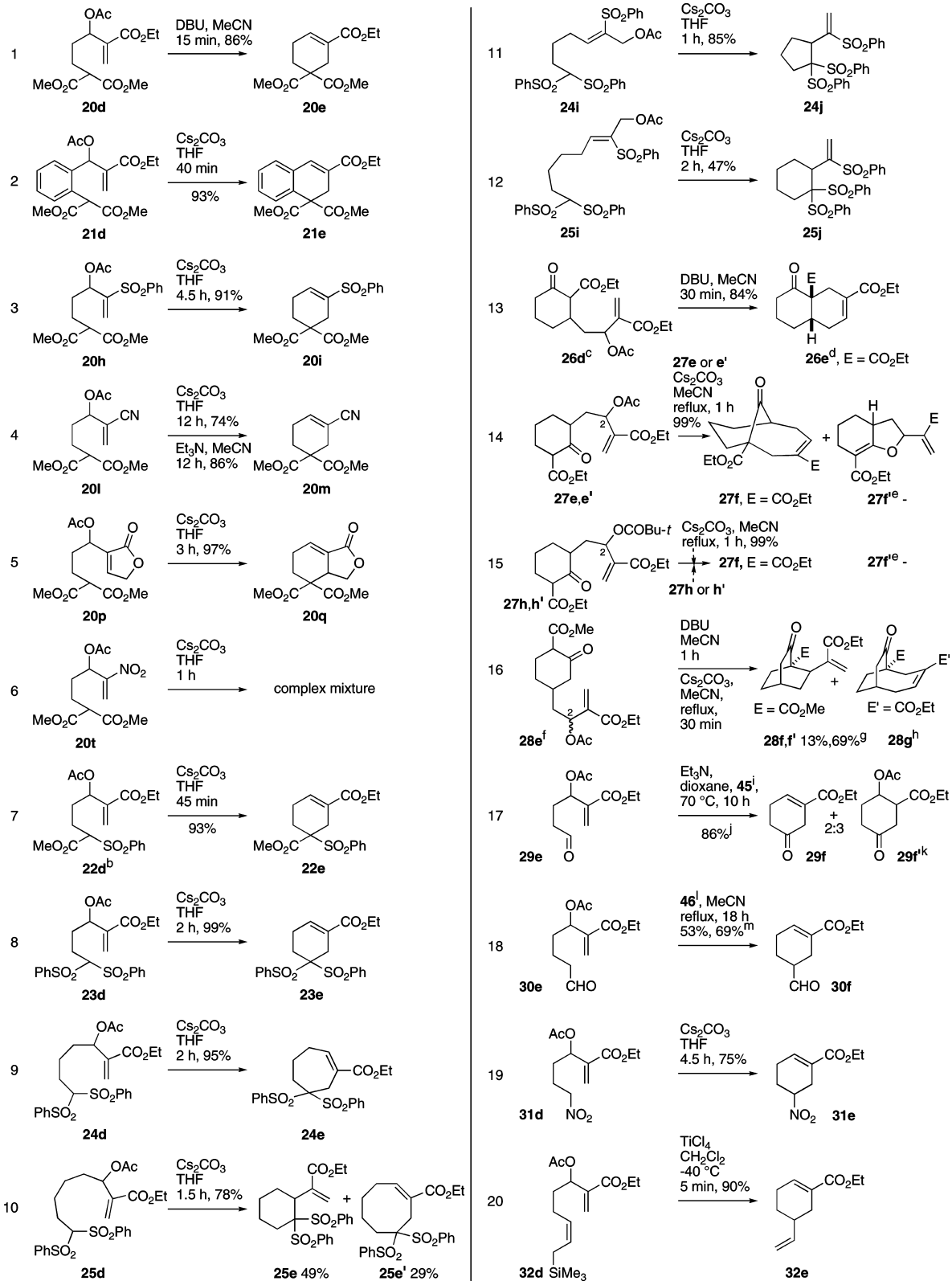
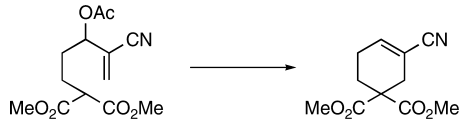
(14) Yoon, N. M.; Choi, J.; Ahn, J. H. *J. Org. Chem.* **1994**, *59*, 3490–3493.

Table 2. ICD Reactions[a]



[a] All reactions at room temperature, unless otherwise indicated. [b] Compound **22d** is a mixture of diastereoisomers. [c] Compound **26d** is a mixture of keto−enol tautomers. [d] The stereochemical assignment to **26e** is tentative. [e] Compound **27f'** was isolated only when DBU was used. [f] Mixture of isomers including keto−enol tautomers. Both stereochemistries at acetoxy-bearing carbon. [g] Minor and major isomers, respectively, from reaction with DBU. [h] Only a trace of **28g** is detected with DBU; with Cs_2CO_3 the yield of **28g** is 11%, but **28f,f'** are not formed. [i] 3-Benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (structure shown later in the text). [j] Combined yield of both products. [k] Single isomer of unestablished stereochemistry. [l] (2*S*)-2-[Diphenyl[(trimethylsilyl)oxy]methyl]pyrrolidine (structure shown later in the text). [m] Yield 69% after correction for recovered starting material.

Table 3. ICD Optimization with **20l**



20l **20m**

1	DBU	MeCN	rt	10 min	47%
2	DBU	CH_2Cl_2	rt	25 min	52%
3	DBU	DMSO	rt	25 min	40%
4	DBU	PhMe	rt	15 min	16%
5	DBU	MeCN	−10 °C	6 min	33%
6	DBU	MeCN	reflux	5 min	38%
7	Cs_2CO_3	MeCN	reflux	50 min	55%
8	Cs_2CO_3	CH_2Cl_2	rt	several h	CM[b]
9	Cs_2CO_3	THF	rt	12 h[c]	74%
10	Et_3N	MeCN	rt	12 h	86%
11	Et_3N	MeCN	reflux	4.5 h	78%
12	Et_3N, Me_3SiCl	MeCN	rt	15 min	74%
13	*i*-Pr_2NEt	MeCN	reflux	24 h	40%
14	DABCO	MeCN	rt	15 min	−[d]
15	pyridine, Me_3SiCl	MeCN	reflux	12 h	CM

[a] Reactions were monitored by TLC and, except for overnight runs, were stopped when all starting material had been consumed. [b] CM = complex mixture. [c] Reaction appeared to be half-over after 80 min. [d] Elimination of acetate from **20l** occurred (^{1}H NMR).

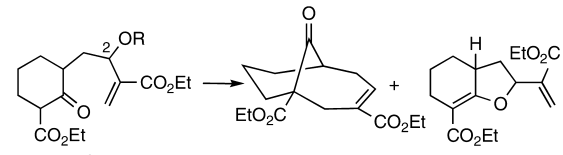
readily, except in the case of the nitro compound **20t**, which gave a complex mixture (Table 2, entry 6). In the case of **25d** (Table 2, entry 10) the expected eight-membered ring was the minor product, the major pathway being one that led to **25e**. We did not establish the mechanism leading to this product; possibly, it is the result of direct S_N2 displacement (6-*exo-tet*) of the allylic acetate.

The β-ketoester **26d** was smoothly converted into the cis-fused[15] decalin system **26e**, but the β-ketoesters **27e**,**e′** and **27h**,**h′** behaved in a more complicated manner. When using DBU in MeCN, short reaction times (30−50 min) led to **27f** and **27f′** for both the acetates (**27e**,**e′**) and the pivaloates (**27h**,**h′**). The heterocyclic product **27f′** was obtained as a 7:3 mixture of epimers, irrespective of the stereochemistry at C(2) in the starting material. The formation of **27f′** is reversible and with a much longer reaction time (150 min) complete conversion of **27f′** to **27f** was achieved (we did not test the acetate series with a long reaction time). Compound **27f′** was, of course, itself converted into **27f** by the action of DBU in MeCN at room temperature (75%). In contrast to this complicated behavior, the use of Cs_2CO_3 as base in refluxing MeCN led only to isolation of **27f** with both isomeric acetates and pivaloates. As the yield of **27f** was almost quantitative under these conditions, we did not attempt to detect intermediates such as **27f′** in these reactions mediated by Cs_2CO_3, beyond routine TLC analysis (which showed only **27f**). Our experiments with **27e**,**e′** and **27h**,**h′** are summarized in Table 4.

In the case of DBU as the base. there are several potential pathways available that would give **27f′**: direct S_N2 displacement (5-*exo-tet*) of acetate (or pivaloate) by the ketone oxygen of **27e**,**e′** (or **27h**,**h′**), followed by equilibration involving ring-opening to a species of type **41**, would account for the constant ratio of isomers of **27f′** irrespective of the initial stereochemistry of the starting material. Alternatively, an intermediate of type **42** (or **41**) might be generated directly from **27e**,**e′**; this could

(15) (a) Cf. Berthiaume, G.; Lavallée, J.-F.; Deslongchamps, P. *Tetrahedron Lett.* **1986**, *45*, 5451–5454. (b) Liu, H.-J.; Ngooi, T. K. *Can. J. Chem.* **1984**, *62*, 2676–2681.

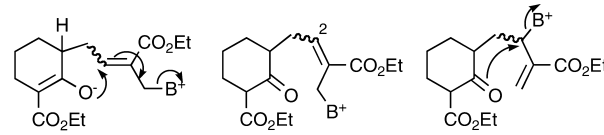
Table 4. Cyclization of **27e**,**e′** and **27h**,**h′**



27e,**e′** (R = Ac) or **27h**,**h′** (R = *t*-BuCO) **27f** **27f′**

R = Ac, less polar		
DBU, MeCN, room temp, 30 min	5%	79%[a]
Cs_2CO_3, MeCN, reflux, 60 min	100%	-%[b]
R = Ac, more polar		
DBU, MeCN, room temp, 50 min	53%	38%[a]
Cs_2CO_3, MeCN, reflux, 45 min	99%	-%[b]
R = *t*-BuCO, less polar		
DBU, MeCN, room temp, 30 min	5%	80%[a]
Cs_2CO_3, MeCN, reflux, 60 min	100%	−
R = *t*-BuCO, more polar		
DBU, MeCN, room temp, 20 min	23%	51%[a]
DBU, MeCN, room temp, 150 min	73%	−
Cs_2CO_3, MeCN, reflux, 60 min	99%	-%

[a] Diastereoisomeric mixture (7:3). [b] Compound **27f′** not isolated.

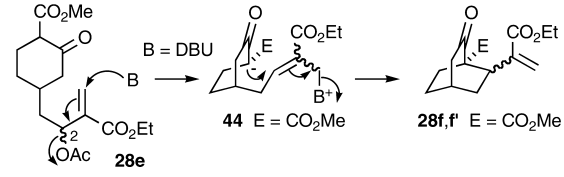


41 B = DBU **42** B = DBU **43** B = DBU

then give **27f′** by intramolecular conjugate displacement. An alternative pathway could involve reaction of DBU with **42** (or **41**) in a second intermolecular conjugate displacement at C(2), followed by 5-*exo-tet* alkylation of oxygen (see **43**). Similarly, **27f** itself might arise by 7-*exo-tet* cyclization of the *E*-isomer of **42**, and other DBU-mediated cyclizations may also involve related *exo-tet* pathways. When **27f′** was treated with Cs_2CO_3 in MeCN at room temperature (12 h) slight decomposition occurred but no **27f** was formed (^{1}H NMR). At reflux temperature (2 h), **27f′** simply decomposed and again **27f** was not formed. These observations are consistent with the mechanisms suggested for the reactions mediated by DBU, as Cs_2CO_3 would not be expected to be capable of the (reversible) nucleophilic processes proposed for DBU.

We had expected compound **28e** to give the bridged cyclooctenone **28g**, but the major products were the bridged cyclohexanones **28f**,**f′**, isolated in a combined yield of ca. 82%. The minor isomer (**28f**) was not obtained pure and its ^{1}H NMR spectrum showed a small signal at 6.95 ppm, characteristic of **28g**. Integration of the spectrum suggested that the yield of **28g** was only ca. 3%. Possibly, the formation of **28f**,**f′** with DBU is the result of both intermolecular[16] and intramolecular conjugate displacements (Scheme 5). Such a pathway accounts for the fact that **28e**, which is a 1:1 mixture of C(2) epimers, gives **28f**,**f′** as a 1:5 epimeric mixture. When we later came to treat **28e** with Cs_2CO_3 (MeCN, reflux, 30

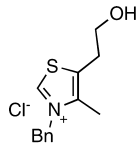
Scheme 5. Suggested Mechanism for Formation of **28f**,**f′**



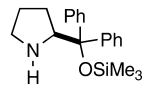
min), it was possible to isolate pure **28g** (11%). In that experiment, only a trace (<1%) of **28f** and/or **28f′** was formed, as judged by the ^{1}H NMR spectrum of the reaction mixture. With Cs_2CO_3 in THF (room temperature, 12 h) a complex mixture was formed and again the ^{1}H NMR spectrum of the crude material suggested the presence of a trace of **28g**. These observations are compatible with an essential role for DBU, along the lines shown in Scheme 5.

Two exocyclic closures were examined (Table 2, entries 11 and 12); the one leading to a five-membered ring proceeding in good yield (85%), but the one giving a six-membered ring was much less efficient (47%).

The examples of Table 2, entries 17, 18, and 20 represent very different ways from all the other cases of generating the nucleophilic carbon. We treated aldehyde **29e** with the thiazolium salt **45** in the presence of Et_3N and obtained a 2:3 mixture of the expected ICD product **29f** and the simple Michael addition product **29f′**. Formation of **29f** is related to a known[17] intramolecular Stetter reaction, while **29f′** was the only case where an acetate leaving group is retained, and we discuss below the mechanistic implications of this outcome.



45

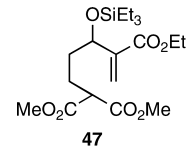


46

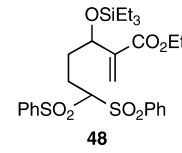
Aldehyde **30e** (Table 2, entry 18) did not give an ICD product with DBU in MeCN; it appeared to suffer elimination of acetate to yield a diene that underwent further reaction(s), but we briefly examined two organocatalysts, proline and the proline derivative **46**.[18] Proline itself performed poorly, giving **30f** in 29% yield (53% after correction for recovered starting material) after a 24-h reflux period in MeCN. The catalyst **46** (18 mol %, refluxing MeCN, 15 h) provided some improvement, and **30f** could be isolated in 53% yield (69% after correction for recovered starting material). The performance of the organocatalysts was clearly inferior to the standard procedure used with our other examples, and we did not explore this method further; in particular, we did not establish the ee of aldehyde **30f**.

The allylic silane **32d**[19] cyclized to **32e** in the presence of $TiCl_4$. Single experiments with **32d** using $BF_3 \cdot OEt_2$ or Bu_4NF were unsuccessful and were not examined further because of the high efficiency (90%) with which the desired closure occurred using $TiCl_4$.

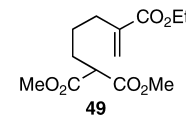
Mechanistic Considerations. Some of the experiments used to define the scope of the all-carbon ICD reaction are relevant to a discussion of the possible mechanisms, but further experiments were done specifically to address mechanistic questions. Compounds **47**−**50** served as the starting materials for the additional experiments; of these **47**, **48**, and **50** were made by protection (silylation or acylation) of the alcohols **20b′** (see Table 1, entry 1) and **23b′** (see Table 1, entry 8), followed in each case by oxidation. The preparation of **49** was more involved, and the route is summarized in Scheme 6. As indicated in the scheme, the selenide **52** was readily obtained, but selenoxide elimination occurred with poor regioselectivity, and a 3:1 mixture of the desired olefin **49** and the regioisomer **53** was generated. We were unable to separate the compounds, and so we used the material as a mixture.



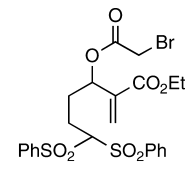
47



48

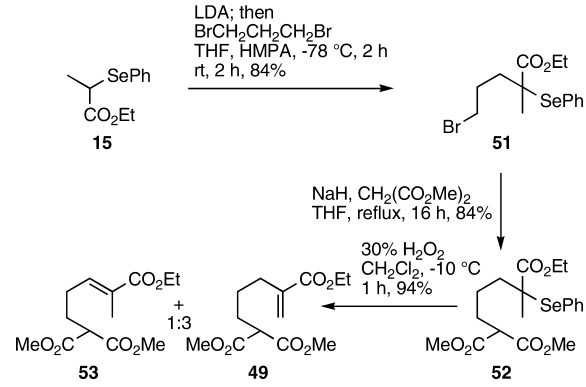


49



50

Scheme 6. Preparation of **49**



When we carried out ICD reactions with **20d**, **47**, and **49** (mixed with **53**), we observed a clear trend in reactivity: the better the leaving group, the faster the reaction. With DBU in MeCN, **20d** cyclized in 86% yield within 15 min at room temperature, **47** cyclized more slowly and required a period of 90 min to give the product (96%), while **49** failed to undergo any change on exposure to DBU in MeCN (room temperature, 32 h), as judged by NMR examination of the crude reaction product. Compound **49** did react, however, when the mixture with **53** was treated with DBU in MeOH (41 h), but only simple Michael addition of MeOH occurred, as well as ester exchange (replacement of OEt by OMe).

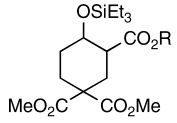
Observations made in the case of *intermolecular* conjugate displacements (eq 2) establish that the presence of the allylic leaving group renders the system more reactive than it would otherwise be[1,2] and, as mentioned earlier, reactions of the type shown in eq 2 are easily stopped at the stage of the Michael acceptor **4**, which can then be subjected to standard conjugate addition in a separate step. The enhanced reactivity may be due to the presence of the leaving group, whose departure acts as an irreversible trap for an initial carbanionic Michael adduct or it could be the result of an inherent greater reactivity resulting from a lowering of the LUMO of the acceptor double bond by

(16) Cf. Chung, Y. M.; Gong, J. H.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2001**, *42*, 9023–9026.
(17) Wasnaire, P.; de Merode, T.; Markó, I. E. *Chem. Commun.* **2007**, 4755–4757.
(18) (a) Hayashi, Y.; Gotoh, H.; Tamura, T.; Yamaguchi, H.; Masui, R.; Shoji, M. *J. Am. Chem. Soc.* **2005**, *127*, 16028–16029. (b) Review on diarylprolinol ethers as organocatalysts: Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876–7880. (c) Preparation of **46**: Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212–4215.
(19) We are aware of a single reaction related to the cyclization of **32d**: Majetich, G.; Zhang, Y.; Nishide, I.; Hull, K. *Bull. Soc. Chim. Fr.* **1995**, *132*, 575–584.

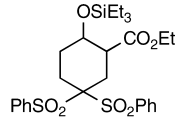
the electron-withdrawing leaving group. Both factors could be involved, but it is not clear for the case of eq 2 or for the intramolecular reactions of the present work, whether the process of nucleophilic attack and leaving group departure are stepwise or concerted.[20] If the latter, the extent of bond formation between the attacking nucleophile and the double bond terminus and the extent of C−O bond breaking for the departing acetate may be synchronous or asynchronous. In the case of a stepwise pathway, the buildup of negative charge on the carbon bearing the electron-withdrawing group of the acceptor subunit (and delocalized into that subunit) may be of sufficiently small magnitude and/or short lifetime that it evades capture by an external or internal electrophile.

We have probed the stepwise or concerted nature of the cyclization by experiments that would trap cyclized species with significant carbanionic character at the carbon bearing the electron-withdrawing group. To this end, the sulfone acetate **23d** was treated with Cs_2CO_3 in THF−*t*-BuOH, pure *t*-BuOH, or pure MeOH in the hope of isolating material resulting from simple Michael addition, i.e., still retaining the original acetoxy group or the parent hydroxy that would result from subsequent hydrolysis. However, the ^{1}H NMR spectrum of the total reaction product (no chromatography) showed only the presence of the normal ICD product **23e**. Evidently, if there is significant buildup of negative charge on the carbon carrying the electron-withdrawing group (CO_2Et), protonation is not competitive with expulsion of acetate. Attempts to trap such carbanionic species intramolecularly were then made by subjecting bromoacetate **50** to the action of Cs_2CO_3 in THF; the reaction was quenched before completion, but ^{1}H NMR measurements showed only starting material and **23e**.

Since **47** cyclized slowly (DBU, MeCN), we wondered if the presence of the poor leaving group ($OSiEt_3$), as opposed to a relatively good leaving group (OAc), would make the compound a better candidate for experiments designed to trap a carbanionic intermediate. When we treated **47** with DBU in MeOH (34 h), we obtained the normal ICD product in which some ester exchange had occurred (OEt replaced by OMe), but we were also able to intercept the putative carbanion as **54** (ca. 28%), also with some ester exchange. The stereochemistry of **54** was not established.



54 R = Me, Et

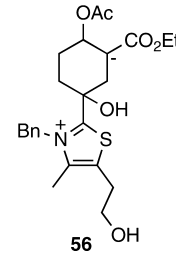


55a,a′

We also treated **48** with DBU in MeCN (40 min) and obtained the normal ICD product (27%), as well as the two isomers (cis and trans) of the simple Michael adducts **55a**,**a′** (44% and 5%). When the major adduct (**55a**, trans) was resubjected to the action of DBU in CD_3CN it was unchanged (^{1}H NMR, 45 min), and the other isomer **55a′** was likewise stable under these conditions. Our observations with **47** and **48** show that in suitable cases, even in the absence of a protic solvent, a carbanionic intermediate can be trapped.

Our inability to trap the putative carbanion using *aprotic* solvents when acetate is the leaving group is consistent with a concerted mechanism or the involvement of a carbanionic species with a sufficiently short lifetime (i.e., expulsion of the leaving group is much faster than protonation) and/or sufficiently small (i.e., partial) negative charge that it evades capture by the low concentration of the proton source (protonated DBU). We appreciate that a range of mechanisms may apply, depending on the structure and conformation of the substrate, as well as the reaction conditions, but we have at least defined one end of the range by the successful trapping experiments.

As stated earlier, when we used the thiazolium salt **45** with aldehyde **29e** the major product was **29f′**, still retaining the original acetoxy group. In this case, an intermediate carbanion (**56**) would likely be stabilized by Coulombic interactions, allowing inter- or intramolecular protonation to yield **29f′**. The ICD product **29f** may be formed from carbanion **56** or it may be the product of a concerted process that is also occurring. Our ICD cyclizations mediated by DBU are over within a few hours at room temperature, but when we treated **29f′** with DBU in MeCN (50 °C, 12 h) some **29f′** still remained in the resulting complex mixture, suggesting, as is expected on the basis of pK_a values, that none of the ICD products are formed by way of a simple protonated Michael adduct that then undergoes elimination of acetate.



56

The mechanistic situation with the allyl silane **32d** is very different as it is initiated by Lewis acid complexation with either or both of the ester groups (CO_2Et and OAc), rather than by generation of a carbanion.

Conclusions

The all-carbon ICD reaction is a general method for making a wide range of usefully functionalized carbocycles under mild conditions. Formation of five-, six-, and seven-membered rings occurs readily in the presence of Cs_2CO_3 or DBU. Palladium-mediated cyclizations of a carbanion in a formally S_N2' manner are well-known,[21] but cases in which the internal sp^2-hybridized carbon of the allylic subunit carries an electron-withdrawing group must be very rare and are perhaps unknown; we have not been able to locate any examples, and could find only one analogous reaction in which the nucleophile is nitrogen.[22] Unlike the palladium-mediated closures of carbanions, the present method[23] does not require a transition metal and must therefore be tolerant of palladium-sensitive groups. Additionally, the method is appropriate for situations where the presence of heavy metals must be avoided.

The substrates for the ICD process are usually easy to prepare by the selenium-based equivalent of the MBH reaction (Scheme 4), and the use of bis-sulfones is particularly convenient since the sulfone groups can be generated from the corresponding

(20) Reviews on the mechanism of S_N2' displacements: (a) Paquette, L. A.; Stirling, C. J. M. *Tetrahedron* **1992**, *48*, 7383–7423. (b) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901–1930.

(21) (a) Trost, B. M. *Angew. Chem., Int. Ed.* **1989**, *28*, 1173–1192. (b) Heumann, A.; Réglier, M. *Tetrahedron* **1995**, *51*, 975–1015. (c) Trost, B. M.; Brickner, S. J. *J. Am. Chem. Soc.* **1983**, *105*, 568–575.

(22) Trost, B. M.; Oslob, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 3057–3064.

(23) For the rare radical analog of an ICD reaction, see: Harvey, I. W.; Whitham, G. H. *J. Chem. Soc., Perkin Trans 1* **1993**, 191–196.

sulfides at the same time as the acceptor double bond is formed (Table 1, entries 8−10). This feature greatly facilitates the preparation of the starting materials for the ICD process. The simultaneous presence of an allylic leaving group and a Michael acceptor confers an enhanced degree of reactivity on the Michael acceptor subunit. The products of the cyclizations are themselves Michael acceptors, but of lower reactivity than the starting materials, and they offer many opportunities for further manipulation.[24]

The utility of the all-carbon ICD process is illustrated by the successful application[7] to the specific case of several complex models representing the core of CP-225,917 and CP-263,114 (Scheme 3).[25]

(24) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992.
(25) For a recent example (in a natural product synthesis) of a process we would classify as an ICD reaction: Watanabe, H.; Nakada, M. *J. Am. Chem. Soc.* **2008**, *130*, 1150–1151.

The mechanism of these ICD reactions can involve a stepwise pathway, at least in cases that are deliberately biased by incorporating a poor leaving group. However, with good leaving groups, if carbanionic species are involved they are not trappable by the protic solvents we tested, and so the processes may then be concerted.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for financial support, and Professor W. R. Roush for helpful comments. L.W. holds a Marie Arnold Cancer Research Graduate Scholarship and an Alberta Heritage Foundation for Medical Research Graduate Studentship. We thank E. J. L. Stoffman for assistance.

Supporting Information Available: Experimental procedures and copies of NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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