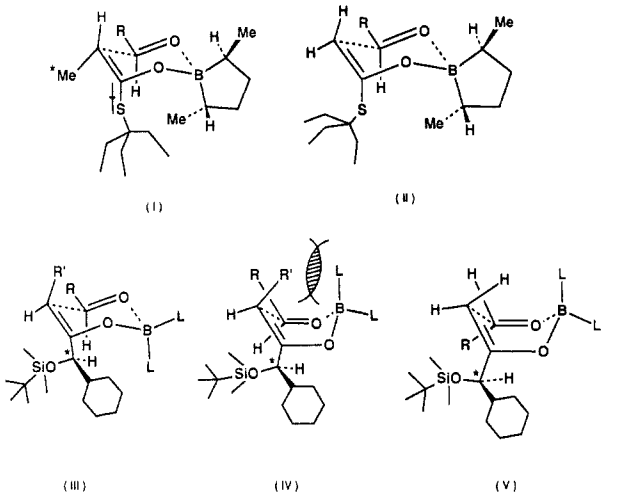
We have also examined whether reagent **5b**, prepared from *S*-3-(3-ethyl)pentyl ethanethioate (**7b**) in a similar manner as that for **5a**, achieves equally high enantioselection in the aldol reaction with achiral aldehydes.[6] As outlined in Table II, the ee's of the aldol products obtained from primary and secondary alkylcarboxaldehydes and aromatic aldehydes are found in a narrow region of 89–93% (entries 1, 2, and 4–7), and thus there is still room for further improvement. It is noted, however, that the selectivity increases with pivalaldehyde.

As has been the case for many aldol reactions,[3] a Zimmerman–Traxler model is again most conveniently used to rationalize the higher enantioselectivity exhibited by **5a** than by **5b**. In the transition state I for reaction of an aldehyde with reagent **5a**, the asterisked methyl group steers the 3-ethyl-3-pentanethiol group toward the borolane moiety, the chirality of which is thus transferred effectively. In the absence of this "steering effect",



as may be the case in transition state II for the reaction with reagent **5b**, the enantioselection of the reaction decreases. This supposition that both reactions proceed through a chair-form transition state is of great interest in that both **5a** and **5b** have no *Z*(*O*)-methyl substituent (see below). It has been known for some time that the reaction with **3a** proceeds with near-perfect enantioselection but that with **3b** provides a roughly 1/1 mixture of two diastereomeric aldols,[3] a puzzling fact for which no reasonable explanation has been offered. While the preferred transition state of the reaction with **3a** is III[2a] (rather than IV where the steric hindrance between the *Z*(*O*)-methyl group (R′ = Me) and the ligand (L) attached to the borane atom is prohibitively severe[11]), the reaction with **3b** may in all likelihood proceed through the boat-form transition state IV (R′ = H) or V. Both transition states would then be expected to be of approximately equal energy, differing only in the orientation of the reacting aldehyde with respect to **3b** as shown. The reaction thus proceeds stereorandomly. In contrast, the triethylcarbinyl group in I and II, despite its large steric bulk, apparently can be accommodated within the chair-form framework as the conformation of the group is flexible due to its rotation along the axis of the sulfur and carbon atoms indicated by the dagger.

Acknowledgment. We thank the National Institutes of Health (GM 33039 and GM 35879) for financial support. T.A.W. is a recipient of a Deutschen Forschungsgemeinshaft postdoctoral fellowship.

Supplementary Material Available: Tables containing survey of the recent literature on the enantioselective aldol reaction and allylboration and experimental methods and spectral data (27 pages). Ordering information is given on any current masthead page.

(11) Thus the presence of the methyl group (R′) is essential for reagent **3a** to be enantioselective, and for that matter, all other known reagents of the same or a similar type having a group other than hydrogen for R′ exhibit excellent selection.

Tandem Michael–Carbene Insertion Reactions of Alkynyliodonium Salts. Extremely Efficient Cyclopentene Annulations

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Intramolecular carbon–hydrogen insertion reactions of carbenes have proven to be powerful and invaluable tools in the synthesis of highly functionalized, five-membered ring systems.[2] We report herein a novel and potentially highly versatile cyclopentene annulation utilizing hypervalent organoiodine(III) compounds, alkynyliodonium salts, via the tandem Michael–carbene insertion (MCI) reaction (Scheme I).

Michael-type addition of "soft" carbanions generated from 1,3-diketones or 1,3-diesters by base abstraction of a methine hydrogen to the carbon–carbon triple bond of alkynyliodonium tetrafluoroborates **1** ($X^- = BF_4^-$)[3,4] constitutes a key step of the facile cyclopetene annulation reaction. On the other hand, reaction of alkynyliodonium tosylate **1** (R = *t*-Bu, $X^- = OTs^-$) with "hard" carbanions like 2-lithiofuran has been shown to occur at the hypervalent iodine atom of **1** to give diaryliodonium tosylates with a concomitant loss of the *tert*-butylethynyl group.[5] Thus, the reaction described here is the first to show the effectiveness of alkynyliodonium salts **1** as a good Michael acceptor toward carbanions.[4a,6]

When 1-decynyl(phenyl)iodonium tetrafluoroborate (**1a**) dissolved in *tert*-butyl alcohol or THF was treated with stable enolate anions generated from 1,3-diketones or 1,3-diesters, 3-pentylcyclopentenes **6–9** were obtained directly in reasonable yields (Table I, entries 1–4). Similarly, [1-(3-cyclopentyl)propynyl]-phenyl- and [1-(4-cyclohexyl)butynyl]phenyliodonium tetrafluoroborates (**1b** and **1c**) afforded fused bicyclic and spiro products, respectively (entries 5–7). (4-Methylhexynyl)iodonium salt **1d** showed some 1,2-diastereoselection in the annulation and produced trans-3,4 diastereomer **13** as the major product (entry 8). The reaction process, shown in Scheme I, may account for the formation of these cyclopentenes. Michael addition of an enolate anion (Nu^-) to **1** produces unstable iodonium ylide **2**,[8,9]

(1) (a) Kyoto University. (b) Shionogi & Co. Ltd. (c) Osaka University of Pharmaceutical Sciences.

(2) For reviews, see: (a) Stang, P. J. *Chem. Rev.* **1978**, *78*, 383. (b) Kirmse, W. *Carbene Chemistry*, 2nd ed.; Academic Press: New York, 1971. (c) Jones, M., Jr.; Moss, R. A., Eds. *Carbenes*; Wiley-Interscience: New York, 1973; Vol. I, II.

(3) For general synthesis of alkynyliodonium salts **1**, see: (a) Rebrovic, L.; Koser, G. F. *J. Org. Chem.* **1984**, *49*, 4700. (b) Ochiai, M.; Kunishima, M.; Sumi, K.; Nagao, Y.; Fujita, E. *Tetrahedron Lett.* **1985**, *26*, 4501.

(4) (a) Beringer, F. M.; Galton, S. A. *J. Org. Chem.* **1965**, *30*, 1930. (b) Merkushev, E. B.; Karpitskaya, L. G.; Novosel'tseva, G. I. *Dokl. Akad. Nauk SSSR* **1979**, *245*, 607. (c) Koser, G. F.; Rebrovic, L.; Wettach, R. H. *J. Org. Chem.* **1981**, *46*, 4324.

(5) Margida, A. J.; Koser, G. F. *J. Org. Chem.* **1984**, *49*, 4703.

(6) In the reaction of alkenyliodonium salts with nucleophiles, only the substitution reaction was observed; Michael type addition did not occur at all.[7]

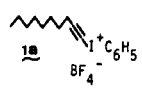
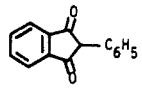
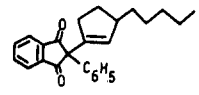
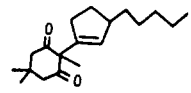
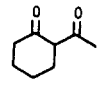
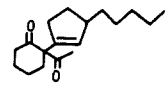
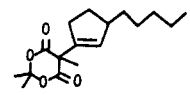
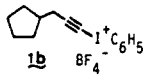
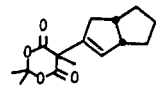
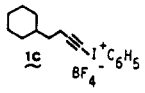
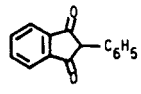
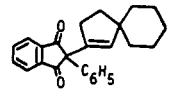
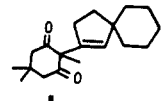
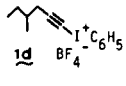
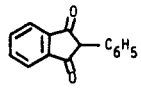
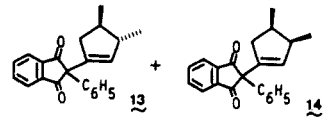
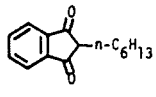
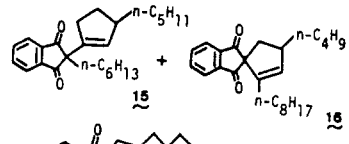
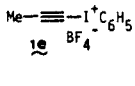
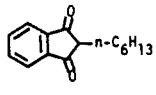
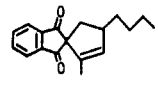
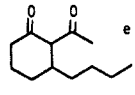
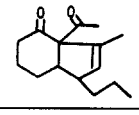
(7) Ochiai, M.; Sumi, K.; Nagao, Y.; Fujita, E. *Tetrahedron Lett.* **1985**, *26*, 2351 and references cited therein.

(8) For an excellent review of aryliodonium ylides, see: Koser, G. F. *The Chemistry of Functional Groups, Supplement D*; Wiley: New York, 1983; Chapter 18.

(9) For a few recent examples, see: (a) Moriarty, R. M.; Bailey, B. R., III; Prakash, O.; Prakash, I. *J. Am. Chem. Soc.* **1985**, *107*, 1375. (b) Olah, G. A.; Doggweiler, H.; Felberg, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 4975. (c) Svastits, E. W.; Dawson, J. H.; Breslow, R.; Gellman, S. H. *J. Am. Chem. Soc.* **1985**, *107*, 6427. (d) Hadjiarapoglou, L.; Spyroudis, S.; Varvoglis, A. *J. Am. Chem. Soc.* **1985**, *107*, 7178. (e) Moriarty, R. M.; Prakash, I.; Prakash, O.; Freeman, W. A. *J. Am. Chem. Soc.* **1984**, *106*, 6082. (f) Breslow, R.; Gellman, S. H. *J. Am. Chem. Soc.* **1983**, *105*, 6728.

0002-7863/86/1508-8281$01.50/0

Table I. Cyclopentene Annulation via Sequencial Michael–Carbene Insertion Reaction

entry	alkynyliodonium salt **1**	nucleophile	reactn condtns[a]	annulation prod(s)	% yield[b] (ratio)	annulation type
1	 **1a**		A,RT,20 min	 **6**	84	[5+0]
2	**1a**		A,40°,10 min	 **7**	50	[5+0]
3	**1a**		B,RT,10 min	 **8**	47 (1:1)	[5+0]
4	**1a**		A,RT,10 min	 **9**	62	[5+0]
5	 **1b**		C,RT,10 min	 **10**	93	[5+0]
6	 **1c**		A,RT,10 min	 **11**	67	[5+0]
7	**1c**		A,83°,10 min	 **12**[c]	52	[5+0]
8	 **1d**		C,RT,10 min	 **13** **14**	75 (76:24)[d]	[5+0]
9	**1a**		C,67°,10 min	 **15** **16**	86 (79:21)	[5+0] [2+3]
10	 **1e**		C,67°,10 min	 **17**	73	[2+3]
11	**1e**		D,RT,10 min	 **18**	74 (64:36)	[2+3]

[a] Base used for the generation of enolate anion–solvent: A, *t*-BuONa–*t*-BuOH; B, KH–THF; C, *tert*-BuOK-THF; D, *tert*-BuOK-dioxane. RT: room temperature. [b] Isolated yields of products purified by chromatography on SiO_2. IR, ^1H NMR, ^{13}C NMR, and mass spectral data were fully consistent with the assigned structures. High-resolution mass spectra and/or elemental analyses were obtained for all new compounds. [c] Structure of **12** was established by X-ray analysis. [d] The major isomer was tentatively assigned as **13** by ^1H NMR analysis. Hanselaer, R.; Samson, M.; Vandewalle, M. *Tetrahedron* **1978**, *34*, 2393. [e] Tanaka, T.; Kurozumi, S.; Toru, T.; Kobayashi, M.; Miura, S.; Ishimoto, S. *Tetrahedron* **1977**, *33*, 1105.

which has an alternative resonance structure, "iodo-allene" **3**. Reductive elimination of **2** may produce the highly reactive alkylidene carbene **4a** (or carbenoid), which regioselectively undergoes the intramolecular 1,5-carbon–hydrogen insertion reaction to yield the cyclopentene **5a**.[10] Since all carbon atoms of the cyclopentene ring of **5a** come from the substituted ethynyl group of **1**, the reaction is termed a [5 + 0] cyclopentene annulation.

By appropriate design of the structure of **1** and nucleophiles, the MCI reaction also becomes valuable as a [2 + 3] cyclopentene annulation, in which two sp^2 and three sp^3 carbon atoms of the cyclopentene ring of product **5b** originate from acetylenic carbons of **1** and carbon nucleophiles, respectively. In this annulation, 1,5-C–H insertion of carbene **4b** takes place on the methylene group of nucleophiles (entries 10 and 11).

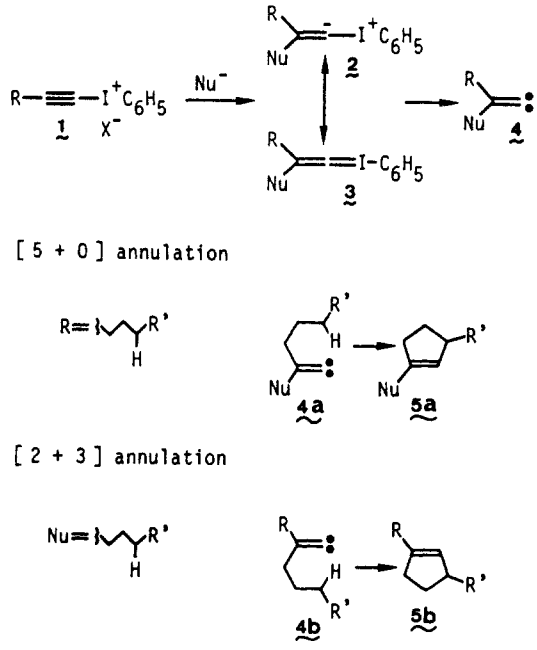
Competition between [5 + 0] and [2 + 3] annulations occurred in the sequential MCI reaction using **1a** and a potassium enolate of 2-hexyl-1,3-indandione. The reaction afforded a mixture of cyclopentene **15**, a [5 + 0] annulation product, and spirocyclopentene **16**, a [2 + 3] product, in a 79:21 ratio in 86% yield (entry 9).[11]

The tandem MCI reaction can be used to directly synthesize polysubstituted furans. Exposure of iodonium salt **1a** to sodium enolate of β-keto sulfone possessing an active methylene group gave rise to 2,3,4-trisubstituted furan **19** in 67% yield. Similarly, 3-cyanofuran **20** was obtained in 46% yield. Intramolecular 1,5 insertion of enolized alkylidene carbenes into the enolic O–H bond

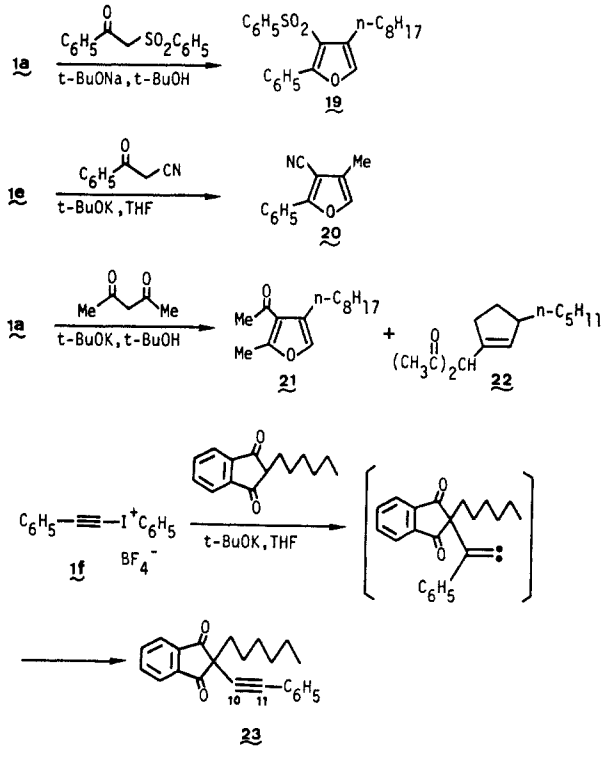
(10) (a) Gilbert, J. C.; Giamalva, D. H.; Weerasooriya, U. *J. Org. Chem.* **1983**, *48*, 5251. (b) Walsh, R. A.; Bottini, A. T. *J. Org. Chem.* **1970**, *35*, 1086. (c) Wolinsky, J.; Clark, G. W.; Thorstenson, P. C. *J. Org. Chem.* **1976**, *41*, 745. (d) Gilbert, J. C.; Giamalva, D. H.; Baze, M. E. *J. Org. Chem.* **1985**, *50*, 2557. (e) Karpf, M.; Huguet, J.; Dreiding, A. S. *Helv. Chim. Acta* **1982**, *65*, 13. (f) Erickson, K. L.; Wolinsky, J. *J. Am. Chem. Soc.* **1965**, *87*, 1143.

(11) Mass spectra of **15** and **16** showed relatively abundant fragments corresponding to $M^+ - C_5H_{11}$ and $M^+ - C_4H_9$, respectively. Such a cleavage of allylic carbon–carbon bonds has been shown to be an extremely efficient process in the mass spectra of 3-alkylcyclopentene derivatives.[10a,c]

Scheme I



Scheme II



may reasonably explain the formation of these furans.[12] Exclusive formation of the furan **19** clearly shows that the intramolecular 1,5 insertion into C–H bonds of methylene groups cannot compete with that into O–H bonds of enols. However, the stereochemistry of enolized carbene intermediates plays an important role in the furan synthesis. Thus the tandem MCI reaction of **1a** with acetylacetone afforded a mixture of furan **21** and cyclopentene **22** in a 64:36 ratio in 61% yield (Scheme II).

The new MCI reaction has some limitation. The attempted [2 + 3] annulation using (phenylethynyl)iodonium salt **1f** and 2-hexyl-1,3-indandione gave no cyclopentene derivative but alkyne **23** in 74% yield. Beringer and co-workers reported similar results and concluded that the substitution reaction occurs on the α-acetylenic carbon atom of alkynyliodonium salts.[4a] However, we found on the basis of a ^{13}C NMR experiment that the formal substitution reaction proceeds via Michael addition of nucleophiles toward iodonium salts followed by 1,2-phenyl migration of the resulting alkylidene carbenes (or carbenoids).[13,14]

The tandem MCI reaction not only offers many advantages including high efficiency and mildness of the reaction conditions but also provides general and simple access to a diverse spectrum of complex cyclopentenes and substituted furans.

Supplementary Material Available: Tables of the X-ray diffraction analysis of **12** including atomic coordinates, bond lengths and angles, and thermal parameters and the molecular structure of **12** (6 pages). Ordering information is given on any current masthead page.

(12) (a) Stang, P. J.; Mangum, M. G.; Fox, D. P.; Haak, P. *J. Am. Chem. Soc.* **1974**, *96*, 4562. (b) Newman, M. S.; Okorodudu, A. O. M. *J. Org. Chem.* **1969**, *34*, 1220.

(13) When phenyl(phenylethynyl-2-^{13}C)iodonium tetrafluoroborate (99% enriched) was used, the enrichment at the acetylenic carbons of **23** obtained was determined as 94% (C-10) and 6% (C-11) from the ^{13}C NMR spectrum.

(14) The facile 1,2-aryl migration of unsaturated carbenoids has been reported.[2a]

Novel Fluorescent 1,4-Dihydropyridines[1]

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Received August 13, 1986

Malondialdehyde (MDA) is produced in mammalian tissues as a side product of prostaglandin and thromboxane biosynthesis and, along with other aldehydes, as an end product of unsaturated lipid peroxidation.[2,3] Aldehydes have been implicated in degenerative processes in vivo,[4] and MDA particularly may be of considerable importance physiologically because of its ability to modify and cross-link biological macromolecules.[5-8] Although vinylogous amidine linkages have been suggested as being formed in lipofuscins, a seemingly ubiquitous group of fluorescent pigments which have been linked to aging,[9] the chromophoric component responsible for the fluorescence of lipofuscins or other cross-linked biomolecules[10,11] remains unknown. UV–visible and fluorescence data[12,13] appear to be consistent with the formation of vinylogous amidines as well as highly fluorescent heterocyclic systems of unknown structure. This paper reports on model studies with MDA that involve the isolation and structural characterization of novel heterocyclic adducts of similar UV and fluorescence data as those reported in the aforementioned biological studies.

We have discovered that when MDA (**1**) was allowed to react with amino acids (e.g., glycine methyl ester) under aqueous acidic conditions for prolonged periods (72 h), the UV spectrum shifted gradually from a single absorption at about 250 nm to absorptions

(1) Dedicated to Professor Nelson J. Leonard on the occasion of his 70th birthday.

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