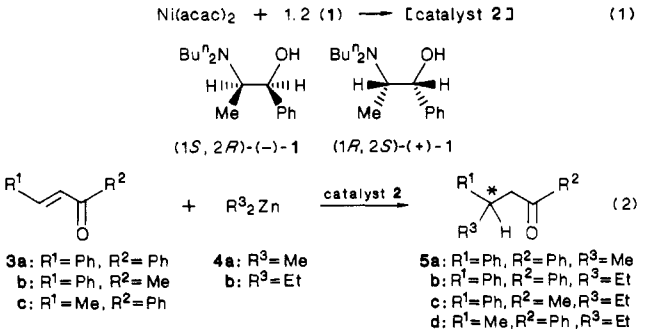
Table I. Catalytic Asymmetric Addition of Dialkylzincs to Enones 3 Using 2

entry	3	4, R^3	molar ratio 2:3	5	[α] (c, solvent)	yield, %	% ee[a]	config[b]
1	a	Me	0.60[c]	a	$[\alpha]^{24}_{546}$ −6.78° (1.80, CCl_4)	72	40	R
2	a	Et	0.50[c]	b	$[\alpha]^{22}_{365}$ −58.09° (2.50, EtOH)	75	45	R
3	a	Et	0.06[c]	b	$[\alpha]^{22}_{D}$ −1.92° (2.50, EtOH)	94	20	R
4	a	Et	0.06[d]	b	$[\alpha]^{25}_{D}$ +1.32° (2.50, EtOH)	89	22	S
5	b	Et	0.60[c]	c	$[\alpha]^{23}_{D}$ −3.48° (2.30, EtOH)	63	12	R
6	c	Et	0.50[c]	d	$[\alpha]^{22}_{D}$ −4.26° (1.01, Et_2O)	78	44	R

[a] Determined by HPLC analysis using a chiral column (Daicel Chiralcel OD, 250 mm). Flow rate, 0.5 mL/min; eluant, 0.25% 2-propanol in hexane; UV detector (254 nm). Retention time for **5a**, *S* isomer (minor), 33.8 min, *R* isomer (major), 37.3 min. For **5b**, *S* isomer (minor), 28.9 min, *R* isomer (major), 32.7 min. For **5d**, eluant, 0.20% 2-propanol in hexane, *S* isomer (minor), 36.8 min, *R* isomer (major), 40.2 min. [b] Based on the reported values of optical rotations. For (*R*)-(−)-**5a**, $[\alpha]^{25}_{546}$ −18.9° (*c* 1.8, CCl_4): Leitereg, T. J.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 4011. For (*S*)-(+)-**5b**, $[\alpha]^{23}_{D}$ +10.5° (*c* 2.5, EtOH), cf. $[\alpha]^{23}_{364}$ +75° (*c* 2.5, EtOH): Brienne, M. J.; Ouannes, C.; Jacques, J. *Bull. Soc. Chim. Fr.* **1967**, 613. For (*S*)-(+)-**5c**, $[\alpha]^{22}_{D}$ +30° (*c* 2.3, EtOH), see the literature for **5b**. For (*S*)-(+)-**5d**, $[\alpha]_{D}$ +19.6° (*c* 5, Et_2O): Seebach, D.; Steinmuller, D. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 619. [c] (1*S*, 2*R*)-(−)-1 was used. [d] (1*R*, 2*S*)-(+)-1 was used.



5b was formed.[5] Conjugate addition of dimethylzinc (**4a**) to **3a** also afforded (*R*)-**5a** in 40% ee (entry 1). The both enantiomers of norephedrine are readily available. Thus either enantiomers of **5b** were synthesized by employing an appropriate enantiomer of **1** (entries 3 and 4). Conjugate addition of **4b** to 1-phenyl-2-buten-1-one (**3c**) (without a phenyl substituent in the olefinic part) afforded (*R*)-**5d** in 44% ee (entry 6).

Ee's of **5** were depend upon the molar ratio of **2** to **3**. Ee's increased according to the increase of the molar ratio. Although further investigation should be necessary, we tentatively assume two possibilities to account for the above result. One is that catalyst **2** is unstable under the reaction conditions and decomposes to yield some other nickel species which will also catalyze the reaction. The other is that the aggregation(s) of the complex between catalyst **2** and dialkylzinc may be reactive species. In this case, the concentration of the catalyst may affect ee's.

In a typical experiment (Table I, entry 2), a mixture of $Ni(acac)_2$ (0.50 mmol) and (1*S*,2*R*)-(−)-**1** (0.60 mmol) in toluene (1 mL) was stirred at 80 °C for 1 h and then cooled to room temperature.[6] Chalcone (**3a**) (1.00 mmol) in toluene (2 mL) was added, and the mixture was stirred for 20 min and then cooled to −30 °C. Diethylzinc (**4b**) (1 M solution in hexane, 2.20 mmol) was added dropwise, and then the resulting mixture was stirred at −30 °C for 2 h. The reaction was quenched with 1 M hydrochloric acid (7 mL), the organic layer was separated, and the aqueous layer was extracted with dichloromethane (8 mL × 4). The combined organic layer was dried (Na_2SO_4) and then evaporated under reduced pressure. The residue was purified by preparative TLC over silica gel (eluent, hexane/chloroform, 1:1, v/v) to afford (*R*)-(−)-**5b** (0.75 mmol) in 75% (45% ee).

Although the degrees of the asymmetric induction are moderate, the present results may open the way to the catalytic enantioselective conjugate addition of organometallic reagents to enones.

(1) Bosnich, B. *Asymmetric Catalysis* Martinus Nijhoff: Dordrecht, 1986; Chapter 3.

(2) Imamoto, T.; Mukaiyama, T. *Chem. Lett.* **1980**, 45. Mukaiyama, T.; Iwasawa, N. *Ibid.* **1981**, 913. Soai, K.; Ookawa, A. *J. Chem. Soc., Perkin Trans. 1* **1986**, 759. Soai, K.; Machida, H.; Yokota, N. *Ibid.* **1987**, 1909. Soai, K.; Machida, H.; Ookawa, A. *J. Chem. Soc., Chem. Commun.* **1985**, 469. Davis, S. G.; Walker, J. C. *Ibid.* **1985**, 209. Fleming, I.; Kindon, N. D. *Ibid.* **1987**, 1177. Oppolzer, W.; Moretti, R.; Godel, T.; Meunier, A.; Loeher, H. *Tetrahedron Lett.* **1983**, *24*, 4971. Leyendecker, F.; Jesser, F.; Laucher, D. *Ibid.* **1983**, *24*, 3513. Mangeney, P.; Alexakis, A.; Nomant, J. F. *Ibid.* **1983**, *24*, 373. Fukutani, Y.; Maruoka, K.; Yamamoto, H. *Ibid.* **1984**, *25*, 5911. Helmchen, G.; Weger, G. *Ibid.* **1985**, *26*, 6051. Liebeskind, L. S.; Welker, M. E. *Ibid.* **1985**, *26*, 3079. Tomioka, K.; Suenaga, T.; Koga, K. *Ibid.* **1986**, *27*, 369. Somfai, P.; Tanner, D.; Olsson, T. *Tetrahedron* **1985**, *41*, 5973. Berlan, J.; Besace, Y.; Prat, D.; Pourcelot, G. *J. Organomet. Chem.* **1984**, *264*, 399. Corey, E. J.; Naef, R.; Hannon, F. J. *J. Am. Chem. Soc.* **1986**, *108*, 7114. Hua, D. H.; C-Y-King, R.; Mckie, J. A.; Myer, L. *Ibid.* **1987**, *109*, 5026.

(3) (a) Soai, K.; Ookawa, A.; Ogawa, K.; Kaba, T. *J. Chem. Soc., Chem. Commun.* **1987**, 467; *J. Am. Chem. Soc.* **1987**, *109*, 7111. (b) Soai, K.; Niwa, S.; Yamada, Y.; Inoue, H. *Tetrahedron Lett.* **1987**, *28*, 4841. (c) Soai, K.; Yokoyama, S.; Ebihara, K.; Hayasaka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1690. (d) Soai, K.; Nishi, M.; Ito, Y. *Chem. Lett.* **1987**, 2405.

(4) Greene, A. E.; Lansard, J. P.; Luche, J. L.; Petrier, C. *J. Org. Chem.* **1984**, *49*, 931. Petrier, C.; S-Barbosa, J. C.; Dupuy, C.; Luche, J. L. *Ibid.* **1985**, *50*, 5761.

(5) In addition, no reaction occurred between **3a** and **4b** in the presence of (−)-**1**.

(6) When the eliminated acac was evaporated in vacuo at this stage, catalyst **2** afforded (*R*)-(−)-**5b** of 37% ee in 80% yield.

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Intramolecular Arylations of Soft Enolates Catalyzed by Zerovalent Palladium

Summary: A new method of ring formation involving palladium-catalyzed displacement of halide from aromatic substrates by stabilized enolates is described. The new reaction permits creation of benzo-fused, five- or six-membered rings, in the homocyclic or in the heterocyclic mode.

Sir: The direct arylation of carbonyl enolates is an unusual mode of C–C connectivity. Such transformation normally requires activation of the aromatic component, as a result of the reluctance of ordinary aromatic substrates to function as electrophiles.[1] Several methods for arylation

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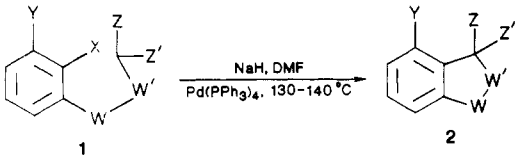
Table I



entry	W	W′	X	Y	Z	Z′	yield, %
a	CH_2	CH_2	I	H	CN	CN	54
b	CH_2	CH_2	I	H	CN	COOEt	38
c	CH_2	CH_2	I	H	COOMe	COMe	53
d	CH_2	CH_2	I	H	COOEt	COOEt	62
e	CH_2	CH_2	Br	H	COOEt	COOEt	48
f	CH_2	$(CH_2)_2$	I	H	COOEt	CN	49
g	CH_2	$(CH_2)_2$	I	H	COOEt	COOEt	41
h	CH_2	CH_2	I	Me	COOEt	COOEt	75
i	CH_2	SO_2	I	H	H	$COOCH(CH_3)CH_2CH{=}CH_2$	37
j	NMe	CO	I	H	Me	COOEt	31
k	CH_2	CO	I	H	H	COOMe	0

of *hard* ($pK_a > 19$) enolates exist.[2] An *intramolecular* variant of that reaction may often be recognized as a means to significantly simplify the multistep synthesis of a polycyclic goal. We encountered such occurrence in the course of studies on Fredericamycin synthesis,[3] wherein the need to arylate *soft* ($pK_a < 15$) enolates materialized. Existing techniques for arylation of such nucleophiles[4] proved to be inadequate for our needs. Thus, a mild new method was developed, which relies on palladium catalysis to induce cyclization by intramolecular displacement of aromatic halide. Herein, we disclose results of studies that suggest generality for the new cyclization procedure.

Substrates 1[5] were deprotonated (dry DMF, NaH, 0 °C), and the resulting solution of enolate was filtered through Celite,[6] under argon, directly into a flask containing 5 mol % $Pd(PPh_3)_4$. The mixture was degassed (argon) and heated at 130–135 °C, whereupon cyclization occurred. Completion of the reaction typically required 1–6 h.

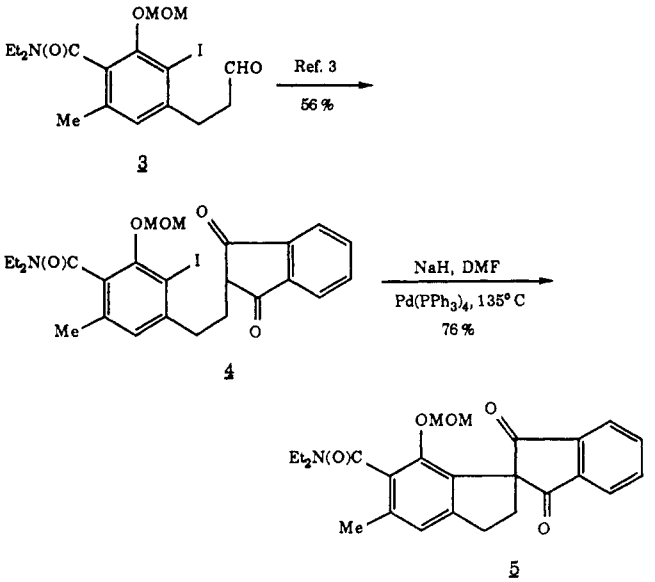


Figure 1.

Unoptimized yields of chromatographed products were normally between 45 and 65% (Table I).[7]

Table I shows results relating to a representative number of systems examined. Successful nucleophiles include anions of β-keto esters, β-diketones, cyanoacetates, malonates, malononitriles, α-sulfonyl ester, etc. Interestingly, with the exception of malononitriles and cyanoacetates,[8] these nucleophiles were completely ineffective in bimolecular reactions.[9] Aryl bromides and iodides may be used as "electrophiles," though the latter afford yields 10–15% higher. Formation of five- or six-membered rings is permissible, either in the homocyclic or in the heterocyclic mode. Four-membered ring formation was attempted with several substrats of the type 1, in which (W + W′) = CH_2, but this mode of reactivity proved to be quite elusive. The formation of larger rings by the new method is currently under investigation.

(1) Well-known exceptions are aromatic structures substituted with strongly electron-withdrawing groups. See: (a) Zoltewicz, J. A. *Top. Curr. Chem.* **1975**, *59*, 33. (b) Bernasconi, C. F. *Chimia* **1980**, *34*, 11.

(2) Aryltion of hard enolates or of derivatives thereof: (a) Semmelhack, M. F.; Stauffer, R. D.; Rogerson, T. D. *Tetrahedron Lett.* **1973**, 4519. (b) Clark, R. D.; Caroon, J. M. *J. Org. Chem.* **1982**, *47*, 2804. (c) Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* **1975** *97*, 2507. (d) Semmelhack, M. F.; Bargar, T. *J. Am. Chem. Soc.* **1980**, *102*, 7765. (e) Beaugelmans, R.; Bois-Choussy, M. *Synthesis* **1981**, 729. (f) Millard, A. A.; Rathke, M. W. *J. Am. Chem. Soc.* **1977**, *99*, 4833. (g) Kuwajima, I.; Urabe, H. *J. Am. Chem. Soc.* **1982**, *104*, 6830. (h) Urabe, H.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 1355. (i) RajanBabu, T. V.; Fukunaga, T. *J. Org. Chem.* **1984**, *49*, 4571. (j) Geoffroy, P.; Mouaddib, A.; Carre, M. C.; Caubere, P. *Tetrahedron Lett.* **1988**, *29*, 1385. The arylations described in parts a–j illustrate several methods for activation of the aromatic substrate, and all require a nucleophilic carbonyl component. For an interesting case in which carbonyl polarity reversal is employed, see: (k) Sacks, C. E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1975**, *97*, 7372. Reactions that seemingly to not require any type of activation of the aryl component have been reported: (l) Kochhar, K. S.; Pinnick, H. *Tetrahedron Lett.* **1983**, *24*, 4785. Presumably these reactions proceed either via arynes, or through some type of $S_{RN}1$ mechanism.

(3) Ciufolini, M. A.; Browne, M. E. *Tetrahedron Lett.* **1987**, *28*, 171.

(4) For arylation of soft enolates, enols, or derivatives thereof, see, e.g.: (a) Bruggink, A.; McKillop, A. *Tetrahedron* **1975**, *31*, 2607. (b) Barton, D. H. R.; Lester, D. J.; Motherwell, W. B.; Barros-Papoula, M. T. *J. Chem. Soc., Chem. Commun.* **1980**, 246. (c) Bell, H. C.; Pinhey, J. T.; Sternhell, S. *Aust. J. Chem.* **1982**, *35*, 2237. (d) Kozyrod, R. P.; Pinhey, J. T. *Org. Synth.* **1984**, *62*, 24. (e) Kende, A. S.; Koch, K.; Smith, C. A. *J. Am. Chem. Soc.* **1988**, *110*, 2210 and references cited therein.

(5) Flowcharts for the preparation of the various substrates are furnished as supplementary material.

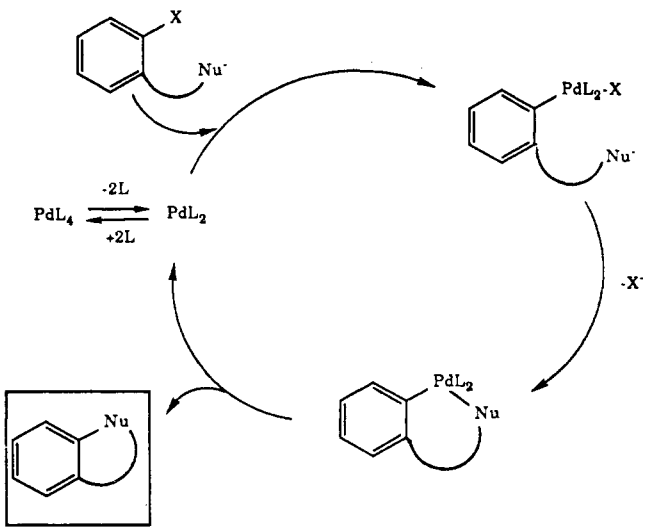
(6) Filtration served to remove excess NaH, the presence of which during the cyclization step is damaging. This operation is easily conducted by forcing (gentle argon pressure, double-tipped needle) a preformed solution of enolate through a filter bed of oven-dried Celite, deposited inside a septum-capped syringe barrel, which is connected directly to the flask containing the catalyst with a short needle.

(7) Blank runs in which solutions of enolates, prepared as described above, were heated in the absence of the palladium catalyst gave no cyclized products.

(8) (a) Uno, M; Seto, K.; Takahashi, S. *J. Chem. Soc., Chem. Commun.* **1984**, 932. (b) Uno, M; Seto, K.; Masuda, M.; Ueda, W.; Takahashi, S. *Tetrahedron Lett.* **1985**, *26*, 1553. (c) Uno, M; Seto, K.; Ueda, W.; Masuda, M.; Takahashi, S. *Synthesis* **1985**, 506.

(9) Procedures by Takahashi et al. (ref 8) were entirely reproducible in our hands. However, we were unable to perform such bimolecular reactions with nucleophiles other than cyanoacetates and malononitriles.

Scheme I



Cyclization of **1i** to the Cava–Nicolaou-type sulfone[10] **2i**, a precursor to an orthoquinodimethane, suggests that one of the carbanion-stabilizing groups may be located at the endocyclic position of the incipient ring. This theme is underscored in the conversion of **1i** to indolone **2i**. Interestingly, in the course of the latter reaction, decarbethoxylation took place.[11] However, yields of such endo-type arylations are 30–40%. Moreover, cyclization of substrates of the type **1k** was unsuccessful under a number of conditions. Thus, although one of the carbanion-stabilizing groups may be tolerated at an endocyclic position, the reaction appears to prefer a regime in which both such groups emerge exocyclic relative to the new ring.

An additional alkyl group ortho to the halogen appears to facilitate the reaction. For instance, cyclization of **1h** was complete in 40 min, and it afforded the expected **2h** in 75% chromatographed yield. The effect of an ortho oxygenated substituent was addressed by using substrate **4**, which was synthesized from aldehyde **3** (Figure 1).[5] Examination of the chemistry of **4** constituted a crucial test, since similar system would be used in our planned Fredericamycin synthesis. We were delighted to discover that compound **4** cyclized smoothly in just 30 min and in 76% chromatographed yield. The major byproducts obtained from most of these reactions were the dehalogenated substrates (10–15% yield). Significantly, no products derived from *bimolecular* arylations were detected.

Modification of experimental parameters (solvents, temperatures, mode of addition, nature of the catalyst, etc.) did not seem to have significant effects on the course of the reaction, provided that a good donor solvent is used (DMF, *N*-methyl-2-pyrrolidinone) and that the catalyst is introduced as a Pd(0) complex. The course of the reaction may be understood based on the catalytic cycle in Scheme I.

It is recognized that the new chemistry permits relatively facile arylation of tertiary centers, leading to quaternary carbons. The creation of such highly substituted carbons is often a major problem in many synthetic endeavors.[12] One limitation of our method is apparent at this point. The relatively high temperature required for the reaction *in its current format* precludes the use of hard enolates, which would probably not survive elevated temperatures. However, excellent methods for intramolecular arylations of those structures are known.[13] Therefore, our chemistry serves as a useful complement to existing techniques in that it offers unique advantages for the arylation of soft enolates. A number of applications of the new technology are under investigation, and progress in these areas will be the subject of future reports.

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Supplementary Material Available: Flowcharts for the preparation of the various substrates and detailed experimental procedure for the cyclization reaction (4 pages). Ordering information is given on any current masthead page.

(10) Nicolaou, K. C.; Barnette, W. E.; Ma, P. *J. Org. Chem.* **1980**, *45*, 1463 and references cited therein.

(11) We presume that a Krapcho-type decarbethoxylation occurred, since iodide ion is generated in the course of the reaction and since the enolate of the resulting indolone is strongly stabilized by its aromatic character. Krapcho, A. P. *Synthesis* **1982**, 805 and 893.

(12) Cf. Martin, S. F. *Tetrahedron* **1980**, *36*, 419.

(13) It may be argued that the best method for intramolecular arylation of hard enolates is the Semmelhack photochemical reaction (ref 1 d,e). Regrettably, we could only confirm Semmelhack's observation that soft enolates do not participate in this reaction. The reasons for this failure are not clear. Perhaps soft enolates act as internal filters, thus blocking the main photochemical pathway.

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Preferred Conformation of *C*-Glycosides. 4. Importance of 1,3-Diaxial-like Interactions around the Nonglycosidic Bond: Prediction and Experimental Proof

Summary: A simple but effective approach has been developed to predict the conformational preference of *C*-disaccharides and related compounds, recognizing the importance of 1,3-diaxial-like interactions. Three sets of *C*-disaccharides have been studied to demonstrate the usefulness of this approach.

Sir: Recent interest in this laboratory has focused on the preparation and conformational analysis of *C*-glycosides.[1] We have shown that (1) the conformational preference of both α(axial)- and β(equatorial)-*C*-glycosidic bonds is such that the C1′–C2′ bond is antiperiplanar to the nonglycosidic Cα–C*n* bond and (2) the conformational preference around the glycosidic bond is so overwhelming that a structural deviation from the ideal staggered conformation to avoid steric interactions takes place in rotating primarily the nonglycosidic bond over the glycosidic bond. Thus, it is possible to predict the conformational behavior around the glycosidic bond of given *C*-saccharides by placing the C1′–C2′ bond antiperiplanar to the nonglycosidic Cα–C*n* bond and then focusing principally on the steric interactions around the nonglycosidic bond, which can conveniently be performed by use of a diamond

(1) (a) Babirad, S. A.; Wang, Y.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 1370. (b) Wu, T.-C.; Goekjian, P. G.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 4819. (c) Goekjian, P. G.; Wu, T.-C.; Kang, H.-Y.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 4823. (d) Babirad, S. A.; Wang, Y.; Goekjian, P. G.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 4825.

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