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Darzens Reaction of Acyl Phosphonates with α-Bromo Ketones: Selective Synthesis of *cis*- and *trans*-Epoxyphosphonates

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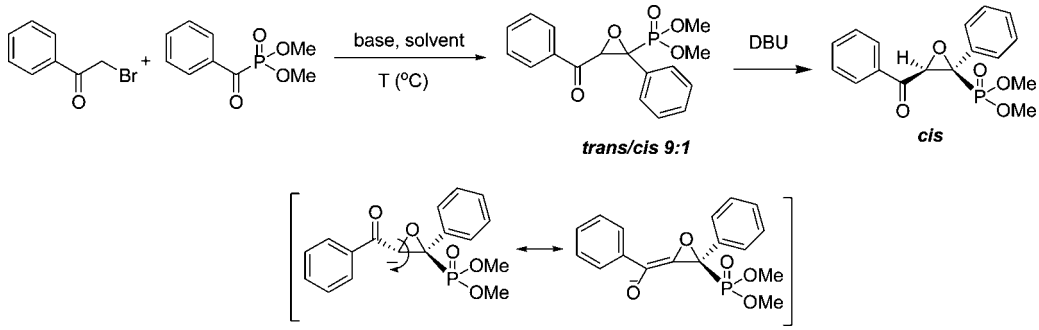

Acyl phosphonates with α-halo ketones in the presence of bases at room temperature afford *cis*- and *trans*-epoxyphosphonates in good chemical yields and high selectivities using different bases. The diastereoselectivity of this reaction is easily controlled by changing the base. Changing the base from Cs_2CO_3 to DBU changed the diastereomeric ratio (*trans*/*cis*) from 3/2 to 9/1. Moreover, the treatment of the *trans* isomer with DBU showed a complete conversion to the corresponding *cis* isomer.

Introduction

Epoxides rank among the most versatile synthetic intermediates, constituting convenient building blocks for the synthesis of many products of biological interest. Among them, 1,2-epoxyphosphonates have attracted considerable interest since the first discovery of the antibiotic fosfomycin.[1] (1*R*,2*S*)-(−)-(1,2)-Epoxypropyl phosphonic acid is a clinically important drug with wide-spectrum antibiotic activity. A vast number of fosfomycin derivatives have been synthesized over the years with biological activities, of which many have included the synthesis of epoxyphosphonates as intermediates.[2]

A straightforward method for the preparation of epoxyphosphonates is the direct epoxidation of the corresponding alkenyl phosphorus compound;[3] however, several other methods also are available.[4−6] These methods include the reaction of α-halo ketones and α-tosyl ketones with metal dialkyl phosphites,[2−4] the cyclization of halohydrins in the presence of a base,[2,5] the Darzens-type reaction of chloromethyl phosphonates with carbonyl compounds,[2,6] and a rather recently published work, including a rhodium acetate-mediated reaction of diazobenzylphosphonates with carbonyl compounds.[7] Although there are many methods for the preparation of these important intermediates, many of these methods lack stereoselectivity, efficiency, and ease of preparation of the starting materials, so there is still a need for alternative synthetic approaches.

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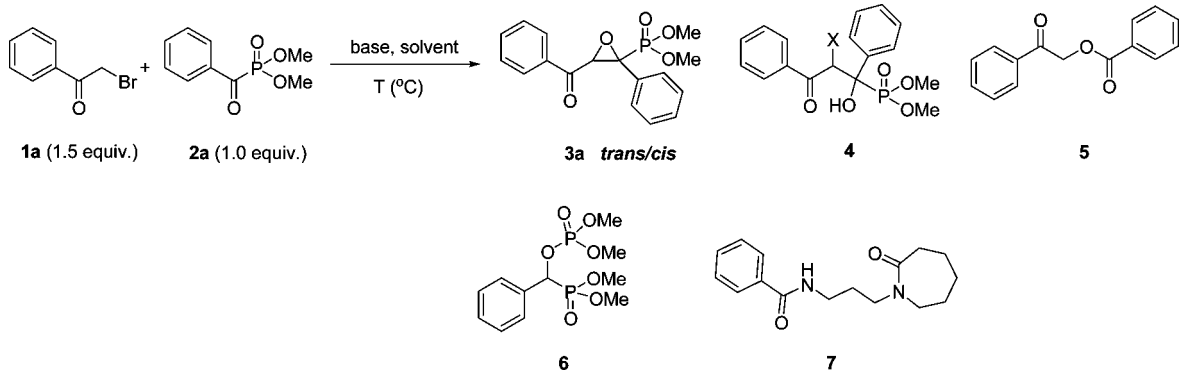
SCHEME 1. Darzens Reaction of Benzoylphosphonates with α-Bromoacetophenone



The Darzens reaction is one of the most powerful methodologies for the synthesis of α,β-epoxy carbonyl and related compounds and, therefore, has been recognized as one of the most significant C−C, C−O bond-forming processes in synthetic organic chemistry.[8] It employs the base-induced condensation of α-halo carbonyl compounds with aldehydes for the construction of highly functionalized oxiranes.

In light of this reaction, and on the basis of our previous studies carried out with acyl phosphonates,[9ae] we report an approach for the diastereoselective synthesis of highly functionalized epoxyphosphonates by applying a Darzens-type reaction of α-halo ketones with acyl phosphonates.[f]

Results and Discussion

To the best of our knowledge, a Darzens-type reaction including the use of acyl phosphonates has not been reported so far. Moreover, there are a vast number of methods for the synthesis of epoxyphosphonates,[1−7] in which there are no examples affording this type of highly functionalized epoxyphosphonates that could be useful intermediates in several reactions.

In the present study, we examined the reactions of a broad range of acyl phosphonates, containing electron-withdrawing and electron-donating substituents with α-halo ketones under various conditions. Although the classical Darzens condensation is still performed in the presence of strong bases such as RONa, ROK, and $NaNH_2$ and is carried out under anhydrous conditions and at low temperatures,[8] the sensitivity of acyl phosphonates to such bases prompted us to use comparably milder bases such as carbonates or organic bases to prevent the hydrolysis of acyl phosphonates.

TABLE 1. Darzens Reaction of Benzoylphosphonate with α-Bromoacetophenone under Different Reaction Conditions

entry	base	solvent	*T* (°C)	*trans*-**3a** (%)	*cis*-**3a** (%)	**4** (%)	**5** (%)	**6** (%)	**7** (%)
1	K_2CO_3	CH_3CN	0	5	−	−	−	20	−
2	K_2CO_3	CH_3CN	25	29	5	5	10	15	−
3	K_2CO_3	CH_3CN	60	35	10	−	15	25	−
4	KOH	THF	25	15	10	5	15	10	−
5	^{t}BuOK	THF	25	12	10	−	12	20	−
6	Cs_2CO_3	CH_3CN	25	35	20	−	15	20	−
7	DMAP	CH_3CN	25	−	−	−	−	−	−
8	DBU	CH_3CN	25	45	5	_	10	5	20
9	DBU	THF	25	_	_	_	15	20	_
10	Et_3N	CH_3CN	25	_	_	_	−	80	_

At first, the reaction of benzoylphosphonate, **2a**, with α-bromoacetophenone, **1a**, is initially carried out at room temperature in the presence of K_2CO_3, and the formation of the products is monitored by TLC. At the end of the reaction (10 h), two diastereomeric epoxyphosphonates, **3a** (*trans*/*cis*) (34%), are isolated as major products together with minor products, **4** (5%), **5** (10%), and **6** (15%), as shown in Scheme 1. The reaction is carried out by using different bases and solvents at room temperature. The use of bases such as KOH, NaOH, and ^{t}BuOK is avoided in order to prevent the hydrolysis of the acyl phosphonate, which would cause acyl phosphonates to easily decompose. The desired product is formed in low yield together with side products (Table 1, entries 4−5). The reaction time decreases at higher temperatures (6 h, 45%), whereas the conversion is very slow at low temperatures (Table 1, entry 1, 24 h, 5%).

By screening the bases, K_2CO_3 is replaced with the more active base, Cs_2CO_3. The reaction is carried out at room temperature in CH_3CN. In this way, not only is the reaction time decreased (6 h), but the reaction yield is increased, and **3a** was obtained in a 55% yield together with side products **5** and **6** (Table 1, entry 6). The diastereomeric ratio was found to be 35/20 (*trans*/*cis*), which was determined by using NMR spectroscopy. The diastereomers are easily separated by flash column chromatography.

To illustrate the generality of this reaction, a range of acyl phosphonates, **2a**−**h**, are treated with variously substituted α-bromo ketones, **1a**−**c**, under optimized reaction conditions (Cs_2CO_3, CH_3CN, rt; or DBU, CH_3CN, rt). The results are shown in Table 2. The use of electron-donating and electron-withdrawing groups furnished a comparable yield.

For the epoxidation reactions, organic bases also were screened. Among the bases DMAP, DABCO, DBU, and triethylamine, the use of DBU in CH_3CN gives **3a** in a 50%

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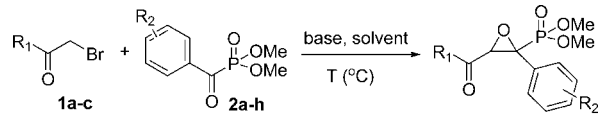
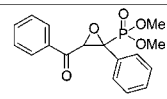
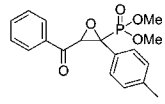
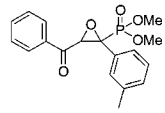
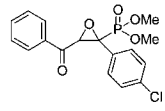
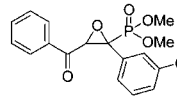
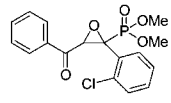
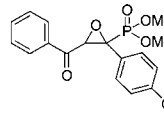
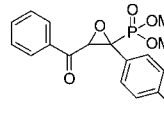
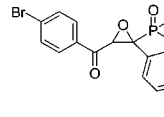
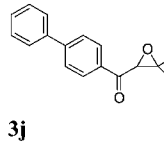
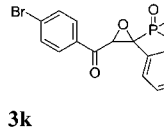
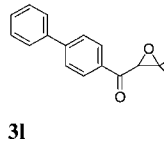
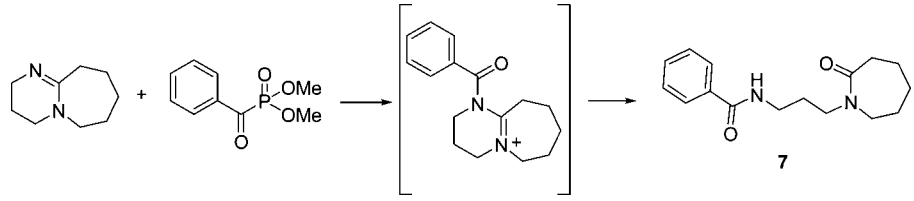
TABLE 2. Reaction of Acyl Phosphonates, 2a−h, with α-Halo Ketones, 1a−c, in the Presence of Bases in Acetonitrile

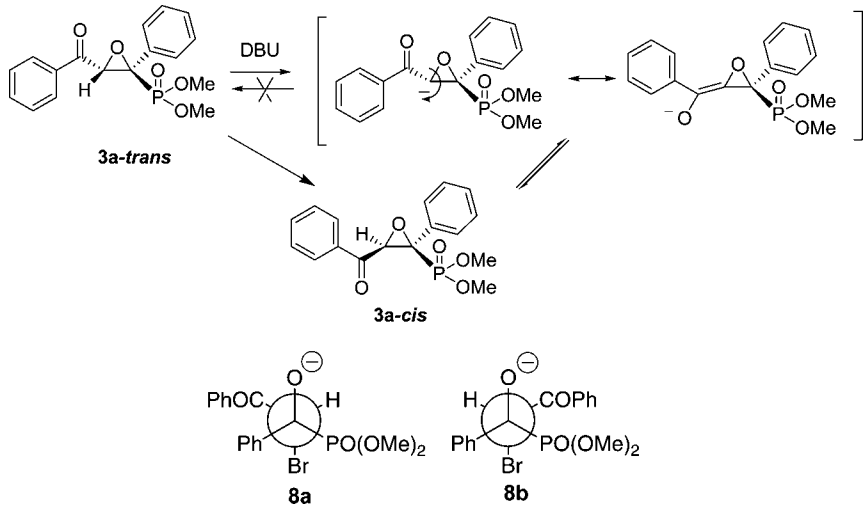


entry	ketone 1	phosphonate 2	epoxyphosphonate 3	Cs_2CO_3			DBU		
	R_1	R_2		time (h)	yield (%)	*trans*/*cis*	time (h)	yield (%)	*trans*/*cis*
1	C_6H_5	H	 **3a**	4	49	3/2	3	50	8/1
	1a	**2a**							
2	C_6H_5	4-CH_3	 **3b**	5	54	3/2	5	56	7/1
	1a	**2b**							
3	C_6H_5	3-CH_3	 **3c**	5	44	2/1	5	45	7/1
	1a	**2c**							
4	C_6H_5	4-Cl	 **3d**	6	48	2/1	4	45	8/1
	1a	**2d**							
5	C_6H_5	3-Cl	 **3e**	8	41	2/1	6	42	6/1
	1a	**2e**							
6	C_6H_5	2-Cl	 **3f**	12	37	2/1	9	30	5/1
	1a	**2f**							
7	C_6H_5	4-OCH_3	 **3g**	5	63	2/1	5	60	7/1
	1a	**2g**							
8	C_6H_5	4-F	 **3h**	3	69	3/2	2	68	9/1
	1a	**2h**							
9	4-Br-C_6H_5	4-F	 **3i**	7	51	3/2	6	48	8/1
	1b	**2h**							
10	4-C_6H_5-C_6H_5	4-F	 **3j**	8	52	5/3	8	49	8/1
	1c	**2h**							
11	4-Br-C_6H_5	4-OCH_3	 **3k**	7	46	5/3	6	43	7/1
	1b	**2g**							
12	4-C_6H_5-C_6H_5	4-OCH_3	 **3l**	8	42	5/3	8	45	7/1
	1c	**2g**							

SCHEME 2. Reaction of DBU with Acyl Phosphonate



SCHEME 3. Formation of a *cis* Isomer from a *trans* Isomer



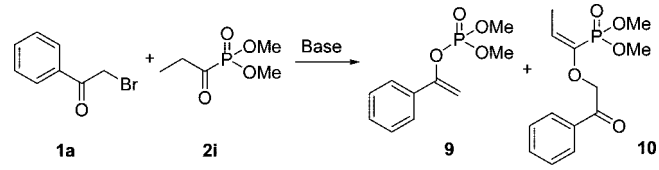
yield (Table 1, entry 8). No product formation was observed with DBU by using THF as a solvent (Table 1, entry 9). Other bases such as DMAP and DABCO showed no product formation. The use of triethylamine as a base (Table 1, entry 10) in the reaction proceeded to give compound **6**, which is the main characteristic behavior of acyl phosphonates in the presence of amines.[10] Dry conditions are crucial in order to prevent the formation of halohydrin, **4**, which is formed by proton abstraction of the corresponding intermediate.

The promising results prompted us to carry out the experiments with DBU. The reaction of acyl phosphonates with α-bromo ketones in the presence of DBU in CH_3CN at room temperature was carried out for maximum conversion with monitoring by TLC. After the workup, the desired products were obtained in 30−68% yields. The isomeric ratios of the products are determined by NMR to be 5/1−9/1 *trans*/*cis*. Both isomers were easily separated by flash column chromatography.

The diasteromeric epoxides are easily characterized by ^{1}H NMR spectra. In the ^{1}H NMR spectra, the single-bridge proton appears as a doublet at 4.68 ppm for the *cis* epoxide and at 3.91 ppm for the *trans* isomer.[11] In addition to these products, three side products also were isolated. Two of them are characterized as **5** and **6**, and the last one is identified as a seven-membered ring amide, **7**. For the formation of **7**, DBU reacted with phosphonates, in which further hydrolysis afforded the corresponding seven-membered ring amide. Similar reactions of DBU with alkyl halides have been reported in the literature (Scheme 2).[12]

As seen from the results, changing the base surprisingly changed the stereoselectivity of this reaction. In general, the

SCHEME 4. Darzens Reaction of Acyl Phosphonate, 2i, with α-Bromoacetophenone



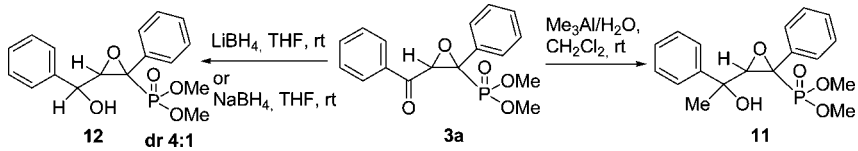
experiments performed in the presence of Cs_2CO_3 gave a product distribution of approximately 3/2 (*trans*/*cis*), whereas the use of DBU significantly increased the selectivity to 9/1 (*trans*/*cis*).

Close inspection of the reaction with DBU afforded interesting results. With the careful monitoring of the reaction by TLC, the distribution for both diastereomers in the presence of DBU is easily controlled. Initially the *trans* isomer is formed in relative excess to *cis* isomer (9/1). However, at a prolonged reaction time, the *trans* isomer isomerizes to afford the *cis* isomer. To support this observation, both of the isolated diastereomeric epoxides are treated under the same reaction conditions (1 equiv of DBU, CH_3CN, rt). As a result of this experiment, the *trans* epoxide isomerizes to afford the *cis* epoxide, whereas the reverse is not the case.

With the Darzens condensation, the formation of the epoxide is the favored course of the reaction. The carbanion of α-halo ketones can attack the carbonyl carbon of phosphonate to form the intermediate halohydrins, **8a** and **8b**. The positioning of the halide *trans* to the oxygen, which is involved in the nucleophilic attack, forms the epoxide. According to published works,[8b,13] the Darzens intermediate (Scheme 3) is commonly formed in the rate-determining step, in which the exclusive formation of the *trans* product may be attributed to the steric inhibition in the formation of the *cis* isomer.

(10) Sekine, M.; Satoh, M.; Yamagata, H.; Hata, T. *J. Org. Chem.* **1980**, *45*, 4162–416.
(11) Rahman, M. M.; Matano, Y.; Suzuki, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1533–1541.

SCHEME 5



Clearly, a *cis* halohydrin anion, **8b**, is not the intermediate in the formation of the *cis* product in the Darzens reaction;[14] rather, the only possible way in which *cis* can be obtained in the Darzens reaction is through the formation of the *trans* product, followed by base-catalyzed isomerization (Scheme 3). The existence of a very large effect, in both the rates and equilibrium of the ring-forming reactions, opposing the formation of *cis* substituents on small rings, constitutes a further basis for assigning greater thermodynamic stability to a *trans* versus a *cis* oxide.

In the case of DBU-mediated *trans*−*cis* conversion, it is rather possible that the carbanion−enolate intermediate of the epoxide is responsible for the formation of the *cis* isomer, were the formation of *trans* isomers from *cis* not possible. As shown in Scheme 3, the carbanion−enolate structure, which gives the *cis* isomer, should be more stable.[14b] This conclusion is only tentative and is currently undergoing further investigation in our laboratory.

Substituted benzoylphosphonates proceed efficiently to give epoxides; however, the treatment of alkyl phosphonate, **2i**, under the same reaction conditions is not very efficient and never yields the corresponding epoxides. This result revealed that the alkyl phosphonates are comparably much more reactive to the bases than benzoylphosphonates, and they hydrolyze more easily. A great amount of work has been conducted in order to find the conditions, but unfortunately, in all cases, the product that is isolated is only compound **9**[15] and **10** (Scheme 4).

Two representative reactions are carried out with *cis*-**3a**. The methylation of *cis*-**3a** with Me_3Al yielded the corresponding epoxy alcohol, **11**, with high selectivity (Scheme 5). The same selectivity is obtained by the reduction of *cis*-**3a** with $LiBH_4$ or $NaBH_4$ (2 equiv of $NaBH_4$, THF, rt; or 2 equiv of $LiBH_4$, THF, rt), which furnished a mixture of diastereomeric epoxy alcohol, **12** (4/1). In both of the reactions, the epoxide ring is preserved. These types of reactions open an entry for the selective synthesis of new fosfomycin analogs.[1]

In summary, we described for the first time a synthesis of epoxyphosphonates applying a Darzens-type reaction to acyl phosphonates with α-bromo ketones in the presence of different bases. The diastereoselectivity of this reaction is easily controlled by changing the base. Accordingly, changing the base from Cs_2CO_3 to DBU changed the diastereomeric ratio (*trans/cis*) from 3/2 to 9/1. Moreover, the treatment of the *trans* isomer with DBU showed a complete conversion to the corresponding *cis* isomer. These products with multifunctionality can be further converted to various interesting compounds. As a representative example, selective reduction of the carbonyl group and the methylation reaction is carried out by keeping the epoxide ring. We are currently investigating the precise origin of the diasterocontrol, in which further applications of these epoxides are currently under way.

Experimental Section

General Procedure for the Preparation of Epoxyphosphonates, 3a−l. (i) Method 1. DBU (2 mmol) is added slowly (addition completed over 1−2 h, controlled by TLC) to a stirred solution of **2a−i** (1 mmol) and the α-bromo ketone, **1a−c**, (2 mmol) in anhydrous acetonitrile at room temperature under an argon atmosphere. The reaction mixture is stirred for several hours (2−12 h). The reaction is monitored by TLC. Water is added, and the mixture is extracted with ethyl acetate; the combined organic layers are dried over $MgSO_4$. After the evaporation of the solvent under reduced pressure, the crude product is purified on silica gel to afford **3a−l** (ether/petroleum ether, 5/1).

(ii) Method 2. Benzoylphosphonate, **2a−i** (1 mmol), is added to a mixture of α-bromo ketone, **1a−c** (1.2 mmol), and Cs_2CO_3 (1.5 mmol) in anhydrous acetonitrile at room temperature under an argon atmosphere. The reaction mixture is stirred for several hours (2−12 h). The reaction is monitored by TLC. Water is added, and the mixture is extracted with ethyl acetate; the combined organic layers are dried over $MgSO_4$. After the evaporation of the solvent under reduced pressure, the crude product is purified on silica gel to afford **3a−l** (ether/petroleum ether, 5/1).

(iii) Dimethyl 3-Benzoyl-2-phenyloxiran-2-ylphosphonate (*trans*-3a). Yield: 100 mg (30%), white solid (mp = 125 °C). IR (KBr): 3007, 2352, 1650, 1220, 1059 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.51 (3H, s), 3.53 (3H, s), 3.91 (1H, d, J = 4.16 Hz), 7.28−8.05 (10H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 53.6 (d, J_{C-P} = 7.4 Hz), 54.3 (d, J_{C-P} = 6.9 Hz), 61.8 (d, J_{C-P} = 202 Hz), 66.0, 126.7 (d, J_{C-P} = 2.7 Hz), 128.6, 128.7, 129.0, 134.0 (d, J_{C-P} = 14.5 Hz), 134.4, 134.9, 190.6. ^{31}P NMR: δ 16.121. Anal. Calcd for $C_{17}H_{17}O_5P$: C, 61.45; H, 5.16. Found: C, 61.32; H, 5.17.

(iv) Dimethyl 3-Benzoyl-2-phenyloxiran-2-ylphosphonate (*cis*-3a). Yield: 64 mg (19%), white solid (mp = 120−122 °C). IR (KBr): 2968, 2360, 1688, 1258, 1059 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.71 (3H, d, J = 10.7 Hz), 3.81 (3H, d, J = 10.5 Hz), 4.68 (1H, d, J = 5.6 Hz), 7.13−7.81 (10H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 54.4 (d, J_{C-P} = 7.2 Hz), 54.5 (d, J_{C-P} = 6.5 Hz), 61.2 (d, J_{C-P} = 198 Hz), 61.7, 127.6 (d, J_{C-P} = 2.7 Hz), 128.1, 128.2, 128.8, 128.9, 129.6, 129.7, 133.9, 135.0, 189.7. ^{31}P NMR: δ 16.638. Anal. Calcd for $C_{17}H_{17}O_5P$: C, 61.45; H, 5.16. Found: C, 61.42; H, 5.20.

Isomerization of *trans*-3a to *cis*-3a. DBU (1 mmol) is added to a solution of *trans*-**3a** (1 mmol) in anhydrous acetonitrile at room temperature. The reaction mixture is stirred for 3 h. The reaction is monitored by TLC. Water is added, and the mixture is extracted

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with ethyl acetate; the combined organic layers are dried over $MgSO_4$. After the evaporation of the solvent under reduced pressure, the crude product is purified on silica gel to afford *cis*-**3a** (ether).

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

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