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Regiocontrolled Benzannulation of Diaryl(*gem*-dichlorocyclopropyl)methanols for the Synthesis of "Unsymmetrically" Substituted α-Arylnaphthalenes

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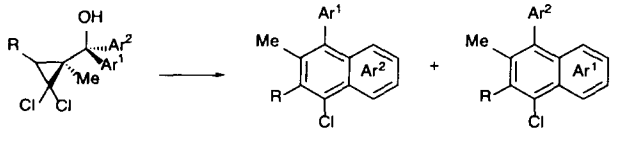
Abstract: Aryl[1](aryl[2])(*gem*-dichlorocyclopropyl)methanols **1** underwent alternative benzannulation to give "unsymmetrically" substituted 1-(aryl[1])-4-chloronaphthalenes **2/A** catalyzed by $SnCl_4$ or $TiCl_4$ and to give 1-(aryl[2])-4-chloronaphthalenes **2/B** catalyzed by silyl triflates with good to excellent selectivities. © 1997 Elsevier Science Ltd.

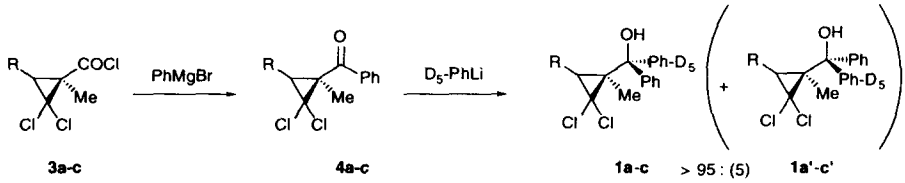
Much attention has recently been focused on the regioselective synthesis of substituted naphthalene analogs.[1] Benzannulations utilizing *gem*-dihalocyclopropane derivatives provide unique and useful synthetic methods for synthesizing various α-arylnaphthalenes and α-arylnaphthols,[2] some of which are attracting considerable interest because of their biological activities.[3] Regarding the regioselectivity (orientation of the cyclization), the reaction using both the *erythro* and the *threo* diastereomers of 2,2-dichloro-1-methylcyclopropyl(phenyl)methanols gave 1-chloro-3-methylnaphthalene in almost the same yields (ca. 60%).[2a] This result indicates that both reactions certainly proceeded through the same S_N1'-like cationic intermediate, consequently being non-regioselective. Taking this fact into consideration, on the reaction of aryl[1](aryl[2])(*gem*-dichlorocyclopropyl)methanols (aryl[1] ≠ aryl[2]; abbreviated AACMs **1**) it would be naturally hard to differentiate the two aryl groups during the benzannulation which proceeds through a similar S_N1'-type pathway.

However, provided that the conformations of the AACMs **1** are suitably fixed during the ring-opening step, the cyclization-orientation would be rationally controlled. We report here the regiocontrolled benzannulation of AACMs **1** to alternatively give "unsymmetrically" substituted α-arylnaphthalenes **2/A** and **2/B**.



AACM 1 **2/A** **2/B**

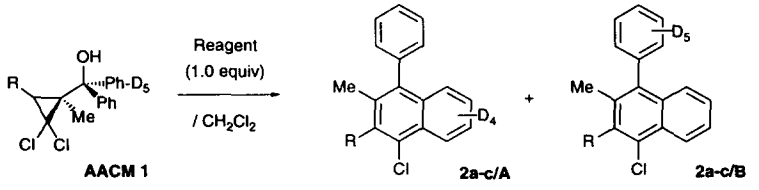
To investigate the regioselectivity of the benzannulation, we prepared the C_6D_5-substituted diastereomers of AACMs (**1a-c**) from *gem*-dichlorocyclopropanecarbonyl chlorides **3a-c** *via* highly stereoselective addition of D_5-PhLi to ketones **4a-c**.[4] Table 1 lists the results of the benzannulations using **1a-c**.

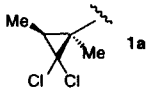
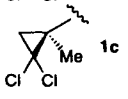


3a-c **4a-c** **1a-c** > 95 : (5) **1a'-c'**

Although CF_3CO_2H and $BF_3{\cdot}OEt_2$ reagents were not effective for enhancement of the regioselectivity, $SnCl_4$ and $TiCl_4$ were found to allow the regioselective benzannulations to give α-C_6H_5-5,6,7,8-tetradeuterionaphthalenes **2a-c/A**.[5] In clear contrast, silyl triflate catalysts predominantly gave the other isomer, α-C_6D_5-naphthalenes **2a-c/B**.[6] These facts eliminated the speculation that the present benzannulation proceeds *via* the same cationic intermediate and/or the same transition state. Thus, we propose a chelation mechanism in the case of MCl_4 (M=Sn, Ti) and a non-chelation mechanism for that of silyl triflates as illustrated in scheme 1.

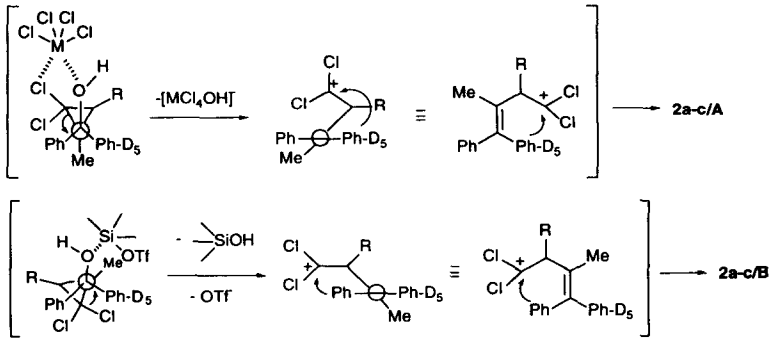
Table 1



AACM	Reagent	Temp. / °C	Product	A:B[a]	Yield /%
 **1a**	CF_3CO_2H[b]	0-5	**2a**	1:1.5	83
	$BF_3{\cdot}OEt_2$	0-5		1:1	94
	$SnCl_4$	-60		3:1	90
	$TiCl_4$	0-5		5:1	38[c]
	$TiCl_4$	-60		9:1	91
	TMSOTf	-60		1:2	35[d]
	TBDMSOTf	-60		1:6	43[d]
	TBDMSOTf	-60		1:5	84[e]
 **1b**	$TiCl_4$	-60	**2b** (≈**2a**)	10:1	46[c]
	TBDMSOTf	-60		1:4	49[d]
 **1c**	$TiCl_4$	-60	**2c**	9:1	81
	TBDMSOTf	-60		1:8	51[e,f]

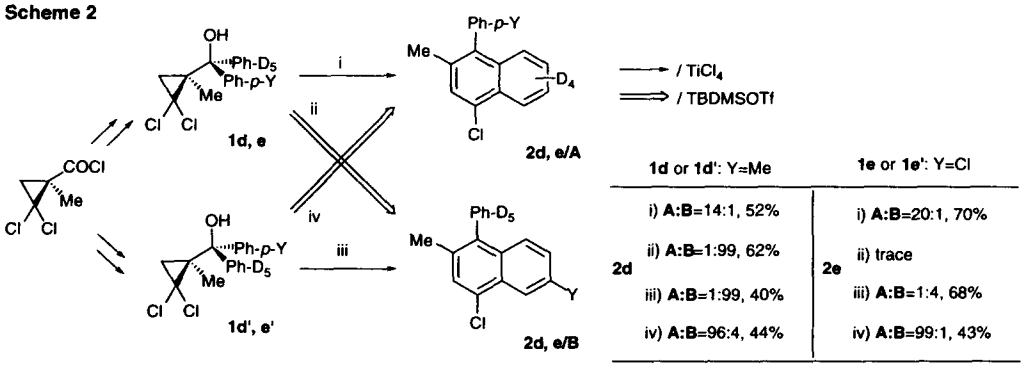
a) These ratios were determined by ^1H NMR (400 MHz) integration values of the aromatic protons. b) CF_3CO_2H was used as solvent. c) Complex mixtures were given as by-products. d) See Ref. 7 e) The reaction was carried out in toluene solvent. The reason for an improvement of the yield is not clear at present. f) See Ref. 8.

Scheme 1



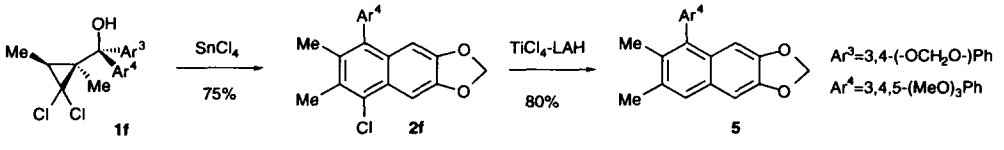
Next, the regiocontrolled benzannulation of AACMs **1d**, **1d'**, **1e**, and **1e'** were examined. These AACMs were prepared in good yield with high stereoselectivity *via* two alternative steps.[9] As scheme 2 illustrates, eight crossover experiments reveal the usefulness of this method,[10] although only one case failed.[11] It should be noted that the reactivity of 3,4,5-trimethoxyphenyl is higher than 3,4-methylenedioxyphenyl for the aromatic electrophilic reaction,[12] none the less, AACM **1f** was also found to undergo the benzannulation to give α-arylnaphthalene **2f**,[13] which seems to be a good candidate of the "unsymmetrically" substituted lignan lactone analog[2a] (scheme 3). All these results obviously support the proposed mechanism. The chlorine in **2f** could be readily removed by $TiCl_4$-LAH to give the naphthalene **5**.

Scheme 2



	1d or 1d': Y=Me	1e or 1e': Y=Cl
2d / 2e	i) A:B=14:1, 52%	i) A:B=20:1, 70%
	ii) A:B=1:99, 62%	ii) trace
	iii) A:B=1:99, 40%	iii) A:B=1:4, 68%
	iv) A:B=96:4, 44%	iv) A:B=99:1, 43%

Scheme 3



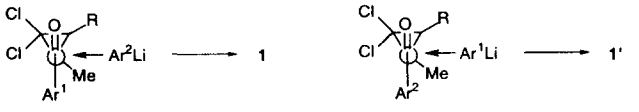
In conclusion, we achieved the regiocontrolled benzannulation of AACMs **1** to give "unsymmetrically" substituted α-arylnaphthalenes, wherein the α-aryl moiety could be alternatively introduced by choosing either the order of the reaction sequences or the catalysts. Application of this method to the synthesis for "unsymmetrically" substituted lignan lactone analog is now under way.

Acknowledgment: We appreciate Professors Mitsuo Komatsu and Ilyoug Ryu of Osaka University for helpful discussions about the reaction mechanism. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture (Japan). One of the authors (Y. N.) acknowledges the JSPS fellowship for Japanese Junior Scientists.

References and Notes

1. For recent representative studies: (a) Katritzky, A. R.; Zhang, G.; Xie, L. *J. Org. Chem.* **1997**, *62*, 721. (b) Kobayashi, K.; Uneda, T.; Takada, K.; Tanaka, H.; Kitamura, T.; Morikawa, O.; Konishi, H. *J. Org. Chem.* **1997**, *62*, 664. (c) Cotelle, P.; Catteau, J-P. *Tetrahedron Lett.* **1997**, *38*, 2969. (d) Charlton, J. L.; Oleschuk, C. J.; Chee, G-L. *J. Org. Chem.* **1996**, *61*, 3452.
2. (a) Tanabe, Y.; Seko, S.; Nishii, Y.; Yoshida, T.; Utsumi, N.; Suzukamo, G. *J. Chem. Soc., Perkin Trans. 1*, **1996**, 2157. (b) Nishii, Y.; Tanabe, Y. *J. Chem. Soc., Perkin Trans. 1*, **1997**, 477.
3. For reviews: (a) Ward, R. S. *Chem. Soc. Rev.*, **1982**, *11*, 75. (b) Ward, R. S. *Natural Product Report*, **1995**, *12*, 183. (c) Ohmizu, H.; Iwasaki, T. *J. Synth. Org. Chem. Jpn.*, **1995**, *53*, 593.

4. Ketones **4a** (86%), **4b** (84%), and **4c** (73%) were prepared by the reported procedure.[2b] The reaction of these ketones **4a-c** with D_5-PhLi at -60 °C for 1 h and then rt for 5 h produced **1a** (95%), **1b** (74%), and **1c** (92%), (**1**:**1'** = >95:5) respectively. By switching these reaction sequences, **1**'s were similarly prepared. The relative configuration of **1** or **1'** was determined based on the previous report[2a]; ArLi attacks the less hindered side of the preferential *s-cis* conformer of **4** or **4'**. AACM (**1a**): colorless crystals; mp 93-95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (3H, s), 1.52 (1H, q, *J* = 6.8 Hz), 1.78 (3H, d, *J* = 6.8 Hz), 2.80 (1H, brs, OH), 7.35-7.46 (3H, m), 7.49-7.54 (2H, m). AACM (**1a'**): colorless crystals; mp 91-94 °C; selected data of ^{1}H NMR δ 7.20-7.24 (2H, m), 7.26-7.34 (3H, m).



4 *s-cis* **4'** *s-cis*

5. A typical procedure: $TiCl_4$ (95 mg, 0.5 mmol) was added to a stirred solution of AACM (**1a**; 163 mg, 0.5 mmol) in CH_2Cl_2 at -60 °C and the mixture was stirred for 1 h. A usual work up gave 4-phenylnaphthalene **2a/A** (123 mg, 91%; **A**:**B** = 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (3H, s), 2.62 (3H, s), 7.29-7.32 (2H, m), 7.51-7.52 (1H, m), 8.34 (1H, d, *J* = 8.5 Hz).
6. Use of TBDMSOTf in the place of $TiCl_4$ (Ref. 5) in toluene solvent gave **2a/B** (84%; **A**:**B**=1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (3H, s), 2.62 (3H, s), 7.21-7.22 (1H, m), 7.42-7.46 (1H, m), 7.47-7.51 (2H, m).
7. 4,4-Dichloro-1-(pentadueteriophenyl)-2,3-dimethyl-1-phenyl-1,3-butadiene was produced as the isolated by-product (15-20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85 (3H, s), 1.89 (3H, s), 7.10-7.30 (2H, m), 7.40-7.60 (3H, m).
8. 4,4-Dichloro-1-(pentadueteriophenyl)-2-methyl-1-phenyl-1,3-butadiene was produced as the isolated by-product (30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (3H, s), 6.65 (1H, s), 7.10-7.20 (2H, m), 7.23-7.60 (3H, m).
9. Stereoselectivities of the addition are >95:5. **1d**: colorless crystals; mp 63-66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (3H, s), 1.27 (1H, d, *J* = 7.3 Hz), 2.41 (3H, s), 2.52 (1H, d, *J* = 7.3 Hz), 2.60-2.85 (1H, br, OH), 7.25 (2H, d, *J* = 8.0 Hz), 7.42 (2H, d, *J* = 8.0 Hz). **1d'**: colorless crystals; mp 44-49 °C; δ 1.19 (3H, s), 1.28 (1H, d, *J* = 7.3 Hz), 2.34 (3H, s), 2.52 (1H, d, *J* = 7.3 Hz), 2.72-2.84 (1H, br, OH), 7.05 (2H, d, *J* = 8.4 Hz), 7.09 (2H, d, *J* = 8.4 Hz). **1e**: colorless crystals; mp 71-75 °C; δ 1.16 (3H, s), 1.30 (1H, d, *J* = 7.3 Hz), 2.51 (1H, d, *J* = 7.3 Hz), 2.70-3.00 (1H, br, OH), 7.41 (2H, d, *J* = 8.5 Hz), 7.47 (2H, d, *J* = 8.5 Hz). **1e'**: colorless crystals; mp 98-102 °C; δ 1.19 (3H, s), 1.28 (1H, d, *J* = 7.3 Hz), 2.49 (1H, d, *J* = 7.3 Hz), 2.78-2.86 (1H, br, OH), 7.11 (2H, d, *J* = 9.0 Hz), 7.24 (2H, d, *J* = 9.0 Hz).
10. **2d/A**: a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.21 (3H, s), 2.46 (3H, s), 7.13 (2H, d, *J* = 7.5 Hz), 7.31 (2H, d, *J* = 7.5 Hz), 7.54 (1H, s). **2d/B**: a colorless oil; δ 2.16 (3H, s), 2.36 (3H, s), 7.15 (1H, s), 7.34 (1H, d, *J* = 8.9 Hz), 7.45 (1H, s), 8.15 (1H, d, *J* = 8.9 Hz). On the reaction using **1d** and **1d'**, following by-products were detected: i) 1,1-dichloro-2,2-dihydro-3-methyl-4-(*p*-tolyl)-5,6,7,8-tetradeuterionaphthalene (48%), δ 2.04 (3H, s), 2.31 (3H, s), 3.69 (2H, s), 7.08-7.15 (4H, m); iii) 1,1-dichloro-2,2-dihydro-3,7-dimethyl-4-(pentadeuteriophenyl)naphthalene (20%), δ 2.02 (3H, s), 2.32 (3H, s), 3.73 (2H, s), 7.00-7.12 (3H, m); and iv) 4,4-dichloro-2-methyl-1-(pentadeuteriophenyl)-1-(*p*-tolyl)-1,3-butadiene (42%), δ 2.08 (3H, s), 2.36 (3H, s), 6.55 (1H, s), 7.03-7.14 (4H, m).
2e/A: a colorless oil; δ 2.20 (3H, s), 7.18 (2H, d, *J* = 8.5 Hz), 7.48 (2H, d, *J* = 8.5 Hz), 7.53 (1H, s). **2e/B**: a colorless oil; δ 2.19 (3H, s), 7.37 (1H, d, *J* = 2.0 Hz), 7.45 (1H, dd, *J* = 2.0 Hz, *J* = 9.5 Hz), 7.52 (1H, s), 8.20 (1H, d, *J* = 9.5 Hz). On the reaction using **1e** and **1e'**, following by-products were detected: ii) See Ref. 11; and iv) 4,4-dichloro-1-(4-chlorophenyl)-2-methyl-1-(pentadeuteriophenyl)-1,3-butadiene (42%), δ 2.01 (3H, s), 6.48 (1H, s), 7.03 (2H, d, *J* = 8.3 Hz), 7.24 (2H, d, *J* = 8.3 Hz).
11. 4,4-Dichloro-1-(4-chlorophenyl)-2-methyl-1-(pentadeuteriophenyl)-1,3-butadiene was produced as the main product (60%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (3H, s), 6.48 (1H, s), 7.04 (2H, d, *J* = 8.6 Hz), 7.24 (2H, d, *J* = 8.6 Hz). We suppose that the formation of this product is due to the inherent low reactivity of 4-chlorophenyl.
12. Even 3,4-dimethoxyphenyl group is considerably more reactive than 3,4-methylenedioxyphenyl group: Sha, C-K.; Young, J-J.; Yeh, C-P.; Chang, S-C.; Wang, S-L. *J. Org. Chem.* **1991**, *56*, 2694.
13. The reaction was carried out using 1.0 equiv of $SnCl_4$ in high diluted (*ca.* 0.001 M) refluxing 1,2-dichloroethane. The other regioisomer was given in >10% yield. The use of $TiCl_4$ resulted in the present benzannulation in ca. 50% total yields . **2f**: A colorless solid, mp 224-227 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (3H, s), 2.55 (3H, s), 3.82 (6H, s), 3.94 (3H, s), 6.01 (2H, s), 6.42 (2H, s), 6.68 (1H, s), 7.64 (1H, s); IR (KBr) 3424, 1464, 1238, 1121 cm^{-1}.
14. All these experimental results show that the regiochemistry of the bond cleavage of *gem*-dichlorocyclopropanes is consistent as shown in scheme 1. This tendency clearly accord with those of previous reports.[2]

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