Kinetic Diastereoselection of Homoallylic Indium Alkoxides: *Syn* Crotylation of Arylaldehydes

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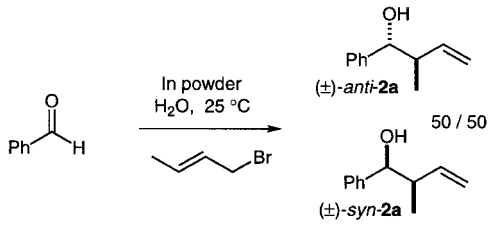
Abstract: Reaction of crotylindium sesquibromide with benzaldehyde in DMF at 20 °C affords *syn*-1-phenyl-2-methylbut-3-enol (ca. 40 % de) after aqueous acidic work-up. At 22 °C in DMF, prior to work-up a greater relative proportion of the *anti* intermediate is decomposed as compared to its *syn* diastereomer. The resultant kinetic diastereoselection upgrades, the *syn* / *anti* ratio to 99 / 1 with a concomitant drop in overall yield.

Recently, indium-mediated aqueous "Barbier-type allylation"[1] of ketones and aldehydes has received much attention.[2] The reaction is often high yielding and convenient. When crotylbromide is employed, the reaction is highly regioselective: for example, benzaldehyde affords 2-methyl-1-phenylbut-3-en-1-ol **2a** exclusively,[3] Scheme 1. Isaac and Chan[3a] have examined a range of aldehyde / allylic bromide combinations and of these, crotyl bromide / benzaldehyde was the only non-diastereoselective pair - indeed all other combinations afforded the *anti* diastereomer in 36 - 92 % de. These reactions have been proposed to proceed by formation of crotylindium species which then react with the aldehyde *via* Zimmermann-Traxler type transition states.[3a] Whilst this conveniently explains the regioselectivity, it is somewhat surprising that there is no diastereoselectivity with benzaldehyde (1 / 1 *syn* / *anti*).



Scheme 1

$InCl_3$-promoted Sn-mediated conditions[4] also fail to induce diastereoselectivity as does use of In(I) iodide in THF.[5] Indeed, the only example of diastereoselectivity for the indium-mediated reaction of crotyl bromide with benzaldehyde is reported by Butsugan *et al.*[6] who also employed Barbier-type conditions but employed anhydrous DMF instead of water and obtained **2a** with low selectivity for the *syn* isomer (16-32 % de). We were thus intrigued as to whether this moderate *syn* selectivity could be improved upon.

Herein we report on the effect of reaction conditions on the *syn* - selective addition of crotylindium sesquibromide to benzaldehyde, Table 1. First we repeated the aqueous In-mediated Barbier type crotylation reported by Isaac and Chan[3a] (entry 1, conditions **A**) and then compared this with the use of pre-formed crotylindium sesquibromide reagents in DMF (entries 2, 3 and 4).

The crotylation reactions in DMF afforded **2a** with moderate *syn*-selectivity (73 - 78 %, entries 2 and 3, conditions **B**) Notably, with preformed reagent, the *syn* selectivity is higher than when "Barbier" type conditions are employed (58 - 66 % *syn*).[6] Recently, we[7] and others[8] have reported that addition of alkoxide or halide to allylindium species (to form "ate" complexes) can usefully modify allylindium reagents and we thus examined the crotylindium "ate" complex generated by addition of LiBr to crotylindium sesquibromide in DMF

Table 1. Diastereoselectivity of the In-mediated reactions of crotylbromide with benzaldehyde. Entry 1 (an aqueous Barbier type reaction) has previously been reported - see references 3a-e

Entry	Conditions[a,b]	*syn* / *anti* [d]	Yield / %[c]
1[e]	**A** H_2O, 22 °C, 2 h	50 / 50[e]	78 (>95)
2	**B** DMF, 22 °C, 20 min	73 / 27	68 (>95)
3	**B** DMF, 0 °C, 20 min	78 / 22	94 (>95)
4	**C** DMF / LiBr, 22 °C, 20 min	65 / 35	-- [f] (>95)

a) Crotylbromide ("CB"). ca. 80 % *E*, 15% *Z*, 5 % 1-methylallybromide. Indium as powder (100 mesh). b) Conditions: **A**: Barbier type reaction: In (2 mmol), CB (2 mmol) and benzaldehyde ("BA") (1 mmol) added to H_2O (2 ml); **B**: In (4 mmol) reacted with CB (6 mmol) in DMF (2.5 ml) then BA (2 mmol) added. Reaction mixture stirred at 25 °C for time given before being quenched with 1M HCl and stirred for 12h. Extraction with ether afforded the crude products.; **C** as for **B** but LiBr (4 mmol) added before addition of BA. c) Yield is isolated yield of analytically pure material; figure in brackets is "NMR yield". d) Ratio of *anti* and *syn* product measured by integration of ^{1}H NMR spectrum of crude product. e) See references 3a-c. f) not determined

(entry 4, conditions **C**). However, this reduced the selectivity somewhat (65 % *syn*) and we therefore returned to employing the crotylindium sesquibromide reagent and sought methods to improve the *syn*-selectivity.

The reaction between crotylindium sesquibromide and benzaldehyde in DMF occurs rapidly - indeed no benzaldehyde could be detected by TLC immediately after addition of the aldehyde to a 0 °C DMF solution of the crotylindium sesquibromide. Reactions quenched at this point by addition of 1M HCl (aq) gave excellent isolated yields of **2a** (entry 3). However, it became evident that if the reaction mixture was not quenched immediately, some decomposition products could be detected in the ^{1}H NMR of the crude reaction product.

The ratio of *syn* / *anti* **2a** was also variable and furthermore, the extent of decomposition was dependent upon both the ratio of indium / crotylbromide employed to prepare the crotylindium reagent and the time that the reaction mixture was left before quenching. When an excess of reagent was employed and then the reaction mixture left for 96 h at RT, the *syn* / *anti* ratio of **2a** was dramatically increased from the initial (73 / 27) to > 99 / 1.

The variations in diastereoselectivity / final diastereomeric excess could occur by a number of processes - Figure 1. For example, the formation of the intermediates - assumed to be indium homoallylic alkoxide species (**1a**) - could be reversible (Mode **I**). Alternatively, the addition could be irreversible but species (**1a**) could epimerise e.g. by deprotonation-reprotonation at the benzylic or allylic positions (Mode **II**). In either case the initial 73 / 27 ratio of *syn* to *anti* is the result of a kinetic allylation whilst the final ratio would be the thermodynamic product mixture. Other possibilities include selective decomposition of the intermediate indium homoallylic alkoxide species (**1a**). If this effected a kinetic diastereoselection of *anti* **1a** then a higher proportion of the *syn* alcohol **2a** would be obtained on quenching (Mode **III**).

To investigate the possibilities shown in Fig. 1, we added benzaldehyde to crotylindium sesquibromide in DMF at 20 °C and then took samples at various time intervals. The samples were quenched by addition to a large volume of 1M HCl, extracted with ether, concentrated and then analysed by ^{1}H NMR. The percentage yield of **2a** and diastereomeric

excess are presented graphically in Fig 2. Interestingly, the rate of decomposition of the *syn* intermediate parallels that of the *anti* intermediate and thus as the concentration of *anti* -**1a** nears zero, the ratio of decomposition of *syn*-**1a** slows dramatically - although not completely.[9] These results are most consistent with Mode **III** - but do not completely rule out Modes **I** or **II** or other possibilities. Nonetheless, since the upgrading of the diastereomeric excess occurs by near-complete decomposition of the *anti*- versus the *syn* intermediate the initial ratio of *syn* to *anti* **1a** limits the ultimate yield of diastereomerically pure *syn* **2a**. Having noticed a small increase in the *syn / anti* ratio when the benzaldehyde was added at 0 °C (78 / 22 versus 73 / 27 at 22 °C. Table 1, entries 2,3) we tried to improve the procedure by adding the benzaldehyde at -78 °C and then, after 1h, heated the reaction mixture to 60 °C for 2 h. Under these conditions, the isolated yield of *syn* crotylation product was low (24 %) but with a de in excess of 99 %. A control experiment indicated the initial *syn / anti* selectivity at -78 °C was lower (60 / 30) than at 22 °C (73 / 27). We thus returned to addition at 0 °C and ageing at 22 °C (Scheme 2; Table 2, entry 1). Under these conditions two other aryl aldehydes gave analogous products (**2b** and **2c**)[11] in moderately high de (*syn*), Table 2, entries 2 and 4, albeit with lower final yields. For comparison, we also performed these reactions under aqueous In-mediated Barbier type conditions (entries 3 and 5). In conclusion, we have shown how the conditions employed for the reaction of simple aromatic aldehydes with crotylindium sesquibromide complex in DMF can dramatically affect both the final yield and diastereomeric excess. These reactions afford products with high *syn* / *anti* ratios through an initial moderately *syn*-selective addition[10] and a subsequent decomposition that upgrades the de substantially. Further studies are in progress and will be reported in due course.

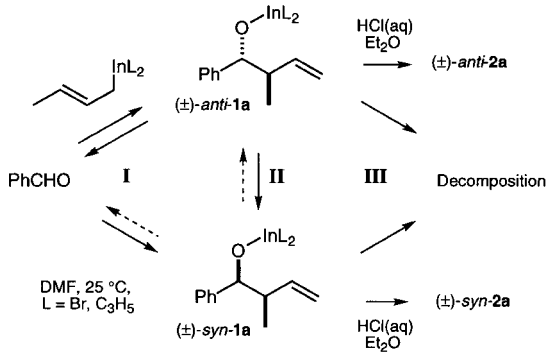
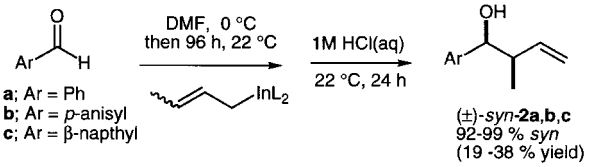


Figure 1. Three possible modes for the variable diastereoselectivity observed in the crotylation of benzaldehyde with crotylindium sesquibromide in DMF when the reaction mixture is left at 20 °C prior to quenching with aqueous HCl. Mode **I**: reversible reaction (i.e. retrocrotylation) resulting in the generation of a fully equilibrated mixture of intermediates **1**. Mode **II**: interconversion (epimerisation) of *syn* and *anti* intermediates **1** e.g. by benzylic deprotonation. Mode **III**: Diastereoselective decomposition of the *anti* indium homoallylic alkoxide intermediate **1** resulting in a kinetic resolution



Scheme 2

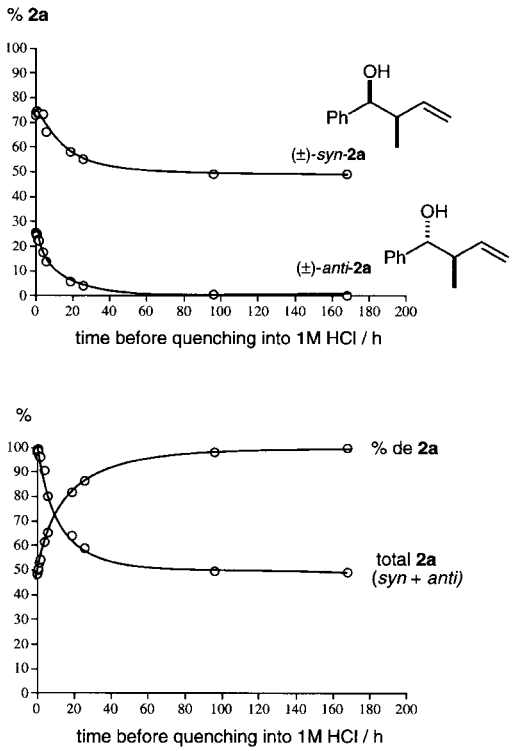


Figure 2. Time dependence of the % yield of crotylation products *syn*-**2a** and *anti*-**2a** (top graph) and total yield and diastereomeric excess of crotylation product **2a** (lower graph) obtained after quenching samples from crotylation of benzaldehyde with crotylindium sesquibromide in DMF at 20 °C (% yields estimated by ^{1}H NMR)

Table 2. Kinetic diastereoselection (under conditions **B**) of indium homoallylic alkoxide intermediates **1a**, **1b**, and **1c** - as scheme 2

Entry	Ar	Conditions[a]	Yield **2** (%)[b]	*syn* / *anti* [c]
1	Ph	**B** (DMF, 96 h)	38	99 / 1
2	*p*-anisyl	**B**	19	93 / 7
3	*p*-anisyl	**A** (H_2O, 24 h)	56	55 / 45
4	β-napthyl	**B**	20	92 / 8
5	β-napthyl	**A**	40	56 / 44

a) see footnotes a and b Table 1. b) Isolated yield of analytically pure product after chromatography on silica-gel. c) Ratio of *syn* and *anti* product estimated by integration of benzylic resonances in ^{1}H NMR of purified material

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References and Notes

(1) Barbier type allylation refers to reactions in which the carbonyl, metal and allylic halide are reacted simultaneously. This may proceed *via* formation of radical ion pairs rather than *via* genuine allylmetal species. T. H. Chan, C. J. Li, M. C. Lee, Z. Y. Wei, *Can. J. Chem.*, **1994**, *72*, 1181-1192.

(2) For leading recent references see: M. B. Isaac, L. A. Paquette, *J. Org. Chem.*, **1997**, *62*, 5333-5338; see also X.-H. Yi, Y. Meng, C.-J. Li, *Tetrahedron Lett.*, **1997**, *38*, 4731-4734; T.-P. Loh, X. R. Li, *Angew. Chem., Int. Ed. Engl.*, **1997**, *36*, 980-982. For reviews see: C.-J. Li, *Tetrahedron*, **1996**, *52*, 5643-68; *idem*, *Chem. Rev.*, **1993**, *93*, 2023-35; P. Cintas, *Synlett*, **1995**, 1087-1096.

(3) a) M. B. Isaac, T. H. Chan, *Tetrahedron Lett.*, **1995**, *36*, 8957-8960; b) S.-C. H. Diana, K.-Y. Sim, T.-P. Loh, *Synlett*, **1996**, 263-264; c) T. H. Chan, M. B. Isaac, *Pure & Appl. Chem.*, **1996**, *68*, 919-924.

(4) X.-R. Li, T.-P. Loh, *Tetrahedron: Asymmetry*, **1996**, *7*, 1535-1538.

(5) S. Araki, H. Ito, N. Katsumara, Y. Butsugan, *J. Organometal. Chem.*, **1989**, *369*, 291-296.

(6) S. Araki, H. Ito, Y. Butsugan, *J. Org. Chem.*, **1988**, *53*, 1831-33.

(7) S. M. Capps, G. C. Lloyd-Jones, M. Murray, T. M. Peakman, K. E. Walsh; *Tetrahedron Lett.*, **1998** *39*, 2853-2856; H. A. F. Höppe, G. C. Lloyd-Jones, M. Murray, T. M. Peakman, K. E. Walsh; *Angew. Chem., Int. Ed.* **1998**, *110*, 1545.

(8) M. T. Reetz, H. Haning, *J. Organometal. Chem.*, **1998**, *541*, 117-120. For tetraorganoindates see: S. Araki, S.-J. Jin, Y. Butsugan, *J. Chem. Soc., Perkin Trans. 1*, **1995**, 549-552.

(9) We are currently trying to ascertain what the decomposition products are. We note that the major rotamer of the benzyl-allylic C-C bond in the *anti* intermediate is likely to be that in which the internal alkenyl carbon is antiperiplanar to the C-OIn bond - decomposition may involve cyclopropyl type intermediates - see ref 7. Also excess crotyl bromide and indium is necessary. As noted, the rate of decomposition of *syn*-**1a** may be kinetically linked to *anti*-**1a**. A much more detailed kinetic investigation is in progress and will be reported in full in due course.

(10) The *Z*-crotyl anion is thermodynamically favoured over the *E*-form ($\Delta G_{Z/E}$ = 4 kcal mol^{-1}, M. Schlosser, J. Hartmann, *J. Am. Chem. Soc.*, **1976**, *98*, 4674-4676). However, due to low polarisation of the C-In bond *E*-crotylindium is expected to be favoured and would afford *anti*-crotylation products on reaction with arylaldehydes *via* Zimmermann-Traxler type transition states. We suggest that the crotylations discussed here occur through open transition states for which the *syn* product is expected.

(11) Diastereomeric identities of **2a**, **b** and **c** were assigned by analysis of the $^3J_{HH}$ benzylic-allylic coupling constants in $CDCl_3$ solution (*syn*, 5.5, 5.7 and 5.4 Hz; *anti*, 7.9, 8.1 and 7.7 Hz respectively). 2-Methyl-1-phenylbut-3-en-1-ol **2a** and 2-methyl-1-(*p*-methoxyphenyl)but-3-en-1-ol **2b** are known compounds (**2a**, U. Schöllkopf, K. Fellenberger, M. Rizk, *Liebigs Ann. Chem.*, **1970**, *734*, 106-115; **2b**, J. P. Takahara, Y. Masuyama, Y. Kurusu, *J. Am. Chem. Soc.*, **1992**, *114*, 2577-2586). 2-Methyl-1-(β-naphthyl)but-3-en-1-ol **2c**: ^{1}H NMR (300 MHz) *syn*-**2c**: 7.68-7.82 (*m*, 4H, arom. H); 7.35-7.47 (*m*, 4H, H arom.); 5.75 (*ddd*, ^3J = 17.7, 10.7, 7.2, 1H, CH=); 5.02 (*ddd*, ^2J = 1.1, ^3J = 17.7, ^4J = 1.1, 1H, $=CH_2$ *trans*), 5.01 (*ddd*, ^2J = 1.1, ^3J = 10.7, ^4J = 1.1, 1H, $=CH_2$ *cis*); 4.69 (*d*, ^3J = 5.4, 1H, C<u>H</u>(OH)), 2.63 (*ddddq*, ^3J = 7.2, 6.8, 5.4, ^4J = 1.1, 1.1, 1H, C<u>H</u>(Me)), 2.27 (*bs*, 1H, OH), 1.00 (*d*, ^3J = 6.8, 3H, CH_3); *anti*-**2c**: 7.68-7.82 (*m*, 4H, arom. H); 7.35-7.47 (*m*, 4H, H arom.); 5.77 (*ddd*, ^3J = 17.1, 11.7, 8.1, 1H, CH=); 5.19 (*ddd*, ^2J = 1.1, ^3J = 17.1, ^4J = 1.9, 1H, $=CH_2$ *trans*), 5.16 (*ddd*, ^2J = 1.1, ^3J = 11.7, ^4J = 1.1, 1H, $=CH_2$ *cis*); 4.47 (*d*, ^3J = 7.7, 1H, C<u>H</u>(OH)), 2.55 (*ddddq*, ^3J = 8.1, 7.7, 6.8, ^4J = 1.9, 1.1, 1H, C<u>H</u>(Me)), 2.40 (*bs*, 1H, OH), 0.86 (*d*, ^3J = 6.8, 3H, CH_3); ^{13}C NMR (75 MHz) *syn*-**2c** 140.5 (CH=); 140.0 (C(2)arom.); 133.0, 132.8 (2 x C-arom.) ; 127.9, 127.7, 127.6, 125.9, 125.2, 124.6 (7 x CH-arom.); 115.5 ($=CH_2$); 77.4 (C(OH); 44.5 (<u>C</u>H(Me)); 14.0 (CH_3); *anti*-**2c**; 140.5 (CH=); 139.8 (C(2)-arom.), 133.1, 133.0 (2 x C-arom.) ; 128.0, 127.8, 127.6, 126.0, 125.8, 125.7, 124.6 (7 x CH-arom.); 116.8 ($=CH_2$); 77.9 (C(OH); 46.0 (<u>C</u>H(Me)); 16.5 (CH_3); IR(NaCl) 3415 (ν_{OH}); 1270 (ν_{C-O}) cm^{-1}; MS(EI) 212 (M^+,1); 194 (2); 179 (11); 157 (90); 129 (100); $C_{15}H_{16}O$, 212.29, requires C, 84.87; H, 7.60 %; found C, 84.50; H 7.94 %.