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STANNOUS TRIFLATE: A FACILE CROSS-ALDOL REACTION BETWEEN TWO KETONES VIA DIVALENT TIN ENOLATES

Rodney W. STEVENS, Nobuharu IWASAWA, and Teruaki MUKAIYAMA*

Department of Chemistry, Faculty of Science,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

Divalent tin enolates, formed from stannous triflate and ketones, react with a second ketone under mild conditions to afford the corresponding cross-aldol products in good to excellent yields. In the case of the cross-coupling with aromatic ketone, enhanced threo-selectivity was observed.

Recently we have demonstrated that divalent tin enolates, generated from stannous trifluoromethanesulfonate (stannous triflate) and ketones in the presence of tertiary amine, react smoothly with carbonyl compounds to afford aldol products in good yields, and that in the case of the cross-aldol reaction with aldehydes, with good to excellent erythro-selectivity.[1] We also reported that when N-methylmorpholine was employed as base, self-coupling of ketones was noted as the main reaction. On the basis of these preliminary investigations which both indicated that by proper choice of base (that is, use of N-ethylpiperidine) cross-aldol reaction was achievable and that the present divalent tin enolate also displays enhanced reactivity toward ketones, we next examined the directed aldol reaction between two different ketones and now wish to disclose our initial findings. We also report here elucidation to the diastereoselectivity attainable by this reaction and have noted that enhanced threo-selectivity is observed for the cross-aldol reaction with aromatic ketone.

Although much fruitful progress has been made in the cross-aldol reaction between various metal enolates and aldehydes,[2] the analogous aldol reaction between two different ketones has proved to be less successful.[3] For example, though boron enolates have clearly been demonstrated to be powerful synthetic tools in aldol reaction with aldehydes, they display poor reactivity toward ketones. Furthermore, the more nucleophilic lithium enolates react with less hindered ketones in moderate yield only,[4] retro-aldol and/or cross-enolization being preferred to 1,2-addition. Recently Kowalski[5] has in part solved this problem by utilizing considerably more nucleophilic α-keto dianions which undergo irreversible aldol-type reaction. However, generation of the α-keto dianion necessitates use of strongly basic conditions and thus this reaction has limited synthetic application. On the other hand, we have found that by employing

divalent tin enolates, directed aldol reaction between ketones is easily achievable.

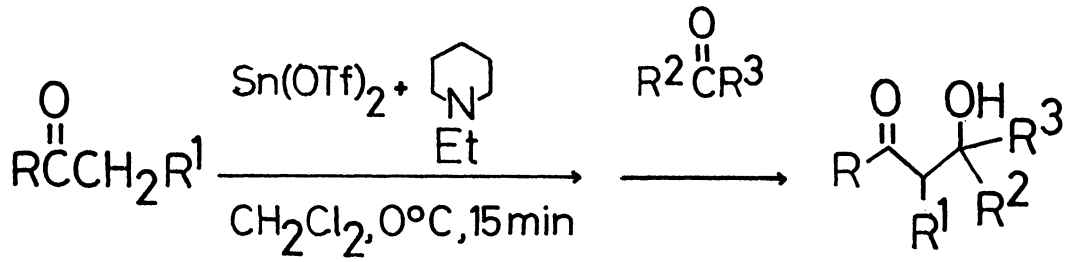


TABLE Cross-Aldol Reaction Between Ketones

Entry	Enolized Ketone R	R^1	Acceptor Ketone R^2	R^3	Reaction Time(min)	Yield(%)[a]	Erythro:Threo[b]
1	Ph	CH_3	$-(CH_2)_5-$		10	83	–
2	"		$-(CH_2)_4-$		10	75	–
3	"		Et	Et	60	80	–
4	"		Ph	CH_3	40	60	0 : 100[c]
5	"		i-Pr	CH_3	80	69	50 : 50 [d]
6	"		i-Bu	CH_3	80	69	50 : 50 [d]
7	"		$Ph(CH_2)_2$	CH_3	80	78	50 : 50 [c]
8	Ph	Et	$-(CH_2)_5-$		20	87	–
9	"		$-(CH_2)_4-$		15	76	–
10	"		Ph	CH_3	35	41	0 : 100[c]
11	Ph	Cl	$-(CH_2)_5-$		15	87	–
12	Ph	i-Pr	$-(CH_2)_5-$		2.5 h	48	–
13	Et	Et	Ph	CH_3	60	45	13 : 87 [c,d]
14	Ph	OC(O)Ph	$-(CH_2)_5-$		3	96	–
15	"		$-(CH_2)_4-$		40	78	–
16	"		Ph	CH_3	55	85	30 : 70 [d,e]
17	"		" (-78°C)		5 h	48	> 95 :< 5 [d,e]

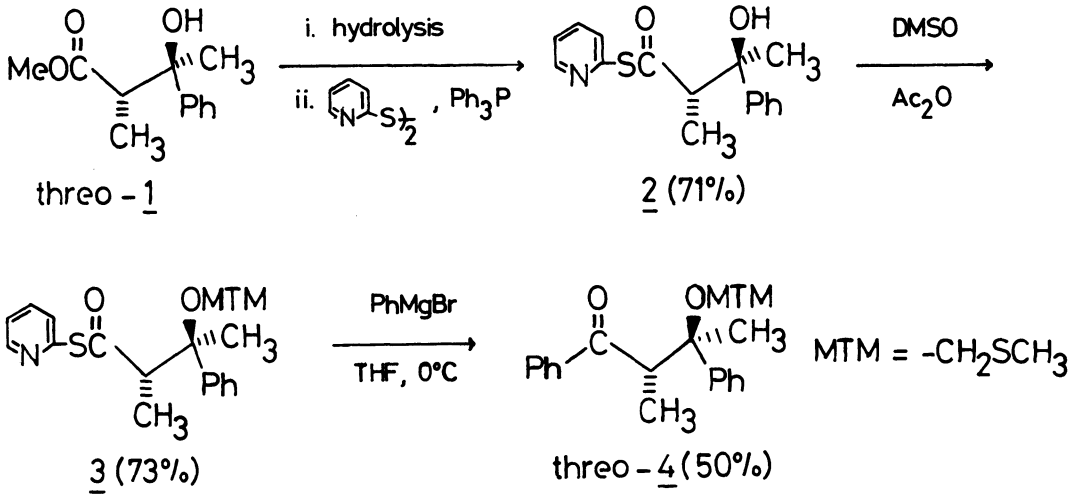
a) Isolated yield. All samples gave satisfactory ^1H NMR and IR spectra.
b) Relative configuration assigned by comparison of MTM ether of aldol with that of authentic sample prepared according to scheme.
c) Diastereomeric ratio determined by ^{13}C NMR.
d) Diastereomeric ratio determined by 90 MHz ^1H NMR.
e) Relative configuration assignment was not made.

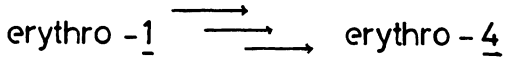
In the first place, the divalent tin enolate of propiophenone was treated with cyclohexanone according to the previously described reaction procedure.[1] Usual work-up of the reaction mixture gave cross-aldol product in only 25% isolated yield even after prolonged reaction time. On the other hand, by conducting the reaction at 0°C for 10 minutes, desired aldol was afforded in 83% yield. It should be noted that analogous attempts to react cyclohexanone with

the simple lithium enolate of propiophenone under a variety of conditions gave only 13% of adduct at best. Other examples are illustrated in the Table.

Having clearly established that facile cross-coupling of ketones is readily achievable employing divalent tin enolates, we next examined the diastereoselectivity attainable in this reaction. And, as can be seen from the results summarized in the Table, although coupling with aliphatic ketones (entries 5-7) gave essentially equal mixture of diastereomers, when aromatic ketone (entries 4, 10, 13 and 14) was employed enhanced threo-selectivity was observed in all cases. These results are interpreted to reflect product stability under the thermodynamic conditions employed. This is further supported by the reaction of the highly reactive divalent tin enolate of α-benzoyloxy acetophenone with acetophenone (entry 16). Under the above thermodynamic reaction conditions, a diastereomeric mixture of 70:30 of aldol was obtained. On the contrary, when kinetic reaction conditions were employed, exclusive formation of one aldol isomer was observed. (entry 17).

To our knowledge only one example of a diastereoselective cross-aldol reaction between two ketones has been reported in the literature.[6] Thus, rigorous assignment of relative configuration was undertaken. For example, the relative configuration of the single aldol isomer from the reaction of the divalent tin enolate of propiophenone with acetophenone (entry 4) was unambiguously established as illustrated in the Scheme. Thus, pure threo-β-hydroxy methyl ester 1, prepared by the Reformatsky reaction of α-bromopropionic acid methyl ester and acetophenone[7], was hydrolyzed to the corresponding acid and then transformed to the S-(α-pyridyl)thioate 2.[8] Next, tertiary alcohol was protected as the methylthiomethyl (MTM) ether 3[9] and subsequently treated with phenylmagnesium bromide to afford authentic threo-phenyl ketone MTM ether 4. Comparison of





SCHEME

spectral data with that of the MTM ether of the β-hydroxy ketone prepared from stannous triflate mediated aldol reaction was identical in all respects. (NMR ($CDCl_3$) δ 8.2-8.0 (m, 2 H), 7.6-7.2 (m, 8 H), 4.3-3.95 (m, 3 H), 1.7 (s, 6 H), 0.85 (d, J=7 Hz, 3 H)). Similarly, preparation of the erythro-MTM ether 4 from pure erythro-β-hydroxy methyl ester 1 by analogous procedure gave product with differing nmr signals (NMR ($CDCl_3$) δ 7.6-6.9 (m, 10 H), 4.35 (d, J=11 Hz, 1 H), 4.12 (d, J=11 Hz, 1 H), 4.03 (q, J=7 Hz, 1 H), 2.15 (s, 3 H), 1.82 (s, 3 H), 1.28 (d, J=7 Hz, 3 H)).

A typical reaction procedure is described for the reaction of propiophenone with acetophenone (entry 4); to a suspension of stannous triflate (1.458 g, 1.1 mmol) and N-ethylpiperidine (0.138 g, 1.2 mmol) in 2 ml of dichloromethane was added dropwise propiophenone (0.134 g, 1.0 mmol) in 2 ml of dichloromethane at 0°C under argon with stirring. After the mixture had been stirred for 15 min, acetophenone (0.156 g, 1.3 mmol) in 1 ml of dichloromethane was added dropwise at this temperature. The reaction mixture was allowed to stand for 1 h, then pH 7 phosphate buffer added. After separation of the organic layer, the aqueous layer was extracted with dichloromethane, three times, then the combined organic extracts dried over Na_2SO_4. After evaporation under reduced pressure, the resultant oil was purified by preparative thin layer chromatography (hexane:Et_2O = 9:1) to yield crystalline threo-3-hydroxy-2-methyl-1,3-diphenyl-1-butanone (0.151 g, 60%).

Thus it is noted that for the first time a facile method for the directed aldol reaction between two different ketones is realized by using divalent tin enolates prepared from stannous triflate and ketones. Examination of the diastereoselectivity achievable in this reaction revealed that when aromatic ketone was chosen as acceptor carbonyl compound enhanced threo-selectivity was observed in all cases. Further studies related to the application of this reaction in synthesis of natural products are currently under way.

References.

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