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A simple and scalable procedure for $TiCl_4$-promoted aldol reaction

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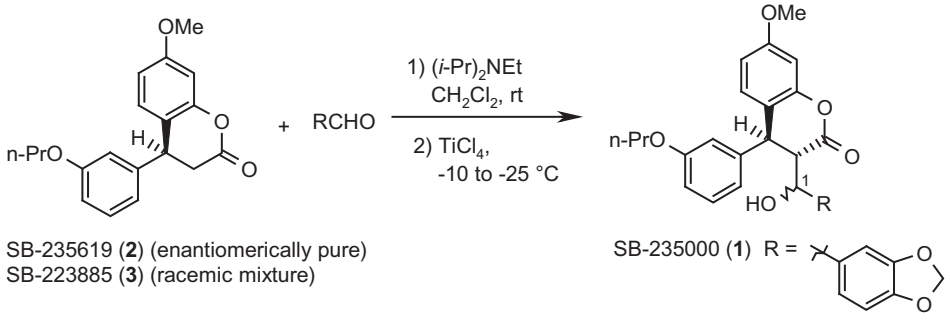
ABSTRACT

$TiCl_4$-promoted aldol reaction was carried out by adding $TiCl_4$ to a solution of the aldol reaction substrates and $(i\text{-Pr})_2NEt$ (DIPEA) in CH_2Cl_2. Compared to the conventional order of addition (sequentially adding $TiCl_4$, DIPEA, and piperonal to the lactone **2** in CH_2Cl_2), this simplified procedure, gave a much cleaner reaction that could be executed on large scale and without cryogenic cooling. However this procedure provided no stereoselectivity.

Since Evans reported the procedure for the direct generation of Ti-enolates,[1] the $TiCl_4$-promoted aldol reaction has emerged as an extremely powerful method for the formation of carbon–carbon bonds, and has been applied widely in natural product and pharmaceutical synthesis because of its high stereoselectivity.[2] SB-235000 (**1**), a key intermediate in a concise total synthesis of endothelin receptor antagonists,[3] was prepared from the aldol reaction of lactone SB-235619 (**2**)[4] with piperonal. Our initial study revealed that when the reaction was performed via Li-enolate, transmetalation with zirconocene dichloride (Cp_2ZrCl_2) or magnesium chloride ($MgCl_2$) was required to stabilize the aldol product **1**. Alternatively, the aldol reaction could be carried out via the Ti-enolate according to the conventional Evans' procedure (sequentially adding $TiCl_4$, DIPEA, and piperonal to the lactone **2** in CH_2Cl_2), but we found the reaction needed to be kept below −72 °C to give a clean reaction (96% HPLC solution yield) on a gram-scale. However, as the reaction was scaled up it became less clean and the yield suffered even at −72 °C or lower, the solution yield for 30 g and 100 g dropped to 92% and 82%, respectively, which was not acceptable from a process chemistry view. The drop in yield may be attributed to problems mixing the thick slurry of the Ti-enolate with the aldehyde. Enolate stability was also problematic: decomposition was observed especially at temperatures above −72 °C and worsened upon scale up. After a series of experiments we were pleased to find that by changing the order of addition, adding $TiCl_4$ last to a solution of **2**, piperonal, and DIPEA in CH_2Cl_2, the reaction proceeded cleanly at temperatures as high as −10 °C (Eq. 1). Presumably, in situ generation of the Ti-enolate and immediate reaction with pre-charged aldehyde avoided the thick enolate slurry and prevented its decomposition. This simplified addition sequence produced a much cleaner reaction than the conventional order of addition at higher temperature, and most importantly, was reproducible on large scale. For example (Table 1, entry 1), when the reaction was carried out at −10 to −25 °C, the new procedure (B) provided 97% HPLC solution yield of **1** on a 280 g scale. For comparison, the conventional order of addition was also performed at −10 to −25 °C (procedure A),[5] but only gave 36% yield even on a 1.0 g small scale.



(1)

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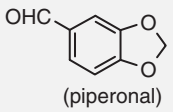
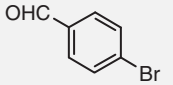
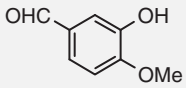
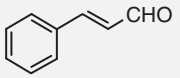
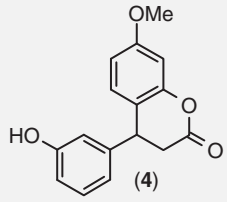
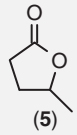
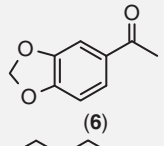
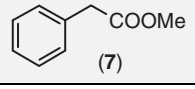
Table 1
Aldol reaction of aldehydes with **2** or **3**

Entry	RCHO	Procedure[a]	Yield (%)
1	 (piperonal)	A	36[b]
		B	97[c]
2		A	20[b]
		B	92[b]
3		A[e]	26[b]
		B[e]	87[b], 94[d]
4		A	37[b]
		B	100[b]
5	$(CH_3)_3CCHO$	A	22[b]
		B	84[b], 94[d]
6	$(CH_3)_2CHCHO$	A	<20
		B	<20

[a] Procedure A: Sequentially adding $TiCl_4$, DIPEA and a solution of aldehyde in CH_2Cl_2 to **2** (or **3**) in CH_2Cl_2 at −10 to −25 °C. Procedure B: Adding $TiCl_4$ to the CH_2Cl_2 solution of **2** (or **3**), aldehyde and DIPEA at −10 to −25 °C.
[b] Isolated yield after chromatography.
[c] Solution yield for a 280 g scale reaction of **2** by HPLC.
[d] Conversion yield based on recovered lactone.
[e] 2 equiv of $TiCl_4$ and 2 equiv of DIPEA were used.

Table 2
Aldol reaction of piperonal with carbonyl compounds

Entry	Carbonyl compounds	Procedure[a]	Yield (%)
1	 (**4**)	A[c]	32[b]
		B[c]	81[b]
2	 (**5**)	A	0[d]
		B	34[b]
3	 (**6**)	A	0[d]
		B	58[e]
4	 (**7**)	A	0[d]
		B	90[b]

[a] Same as footnote **a** in Table 1.
[b] Isolated yield after chromatography.
[c] 2 equiv of $TiCl_4$ and 2 equiv of DIPEA were used.
[d] Messy reaction with self-condensation products detected by LC–MS. Piperonal was unreacted.
[e] Plus 19% yield of the dehydration product from the aldol adduct.

The results were surprising since initially we were concerned about formation of $TiCl_4$ and DIPEA complex in view of the literature report on the order of reagent addition: that it is critical for substrate-$TiCl_4$ complexation to precede the introduction of base because the uncomplexed $TiCl_4$ would otherwise irreversibly complex with DIPEA resulting in no enolization.[1a] It is important to point out that, procedure B gave no stereoselectivity at −10 to −25 °C and produced 1:1 ratio of two diastereomers at C1 of SB-235000, while the conventional order of addition performed below −72 °C provided a diastereomer ratio of 2:1. Fortunately, the diastereoselectivity was not a concern for our synthesis because the stereo center at C1 was destroyed in the following step and both isomers led to the desired product.[3]

To study the advantages of this new order of addition, we compared the aldol reactions of racemic lactone SB-223885 (**3**) with a series of aromatic, α,β-unsaturated, and aliphatic aldehydes at −10 to −25 °C using both procedures (Table 1). We found that the new procedure B gave dramatically (>60%) higher yields of the aldol products than procedure A (entries 2–5), except when the aldehyde contained an enolizable α-H (entry 6). In this case, both procedures gave low yields (<20%) of the aldol products.

We also compared the two procedures on the aldol reactions of piperonal with several other carbonyl compounds (Table 2). Phenol **4**, another potential precursor used in our total synthesis, produced 81% yield of the aldol product using procedure B, while only 32% yield was obtained when employing procedure A (entry 1). We then compared the two procedures using compounds **5**, **6** and **7**, chosen as representatives for five-membered-ring lactones, ketones, and esters, respectively (entries 2–4). While because of decomposition of the Ti-enolate along with self-condensation of the carbonyl substrates, no aldol products were detected by LC–MS when applying procedure A, procedure B produced 34%, 58%, and 90%, respectively, of aldol products (plus 19% yield of the dehydration product in the case of ketone **6**). It is worth noting that, ^1H NMR analysis of the crude reaction mixture of methyl phenylacetate (**7**, entry 4) with piperonal under the new procedure (B) gave 57:43 ratio, almost no stereoselectivity between the *syn* and *anti* isomers.[6]

In conclusion, we have developed a simple and scalable process for the $TiCl_4$-promoted aldol reaction by changing the order of reagent addition. This new procedure gives clean reaction at temperatures as high as −10 °C (vs −72 °C), needs only one temperature-sensitive addition (vs three temperature-sensitive additions), and is reproducible on large scale comparing to the conventional order of addition. However this new procedure provided no stereoselectivity.

References and notes

1. (a) Evans, D. A.; Urpí, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215–8216; (b) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpí, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047–1049; (c) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866–868.
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3. Wood, J. L.; McGuire, M. A.; Mills, R. J.; Pridgen, L. N.; Yu, M. S.; Su, Q. U. S. Patent 6,114,549, 2000; U.S. Patent 6,441,173, 2002.
4. McGuire, M. A.; Shilcrat, S. C.; Sorenson, E. *Tetrahedron Lett.* **1999**, *40*, 3293–3296.
5. See Refs. 1c and 2b for performing the aldol reactions by the conventional order of addition at temperatures as high as 0 °C.
6. Examples of typical procedures for $TiCl_4$-promoted aldol reactions:
   Procedure A. $TiCl_4$ (0.39 mL, 1.2 equiv) was added dropwise to a solution of methyl phenylacetate (**7**) (0.47 g, 1.05 equiv) in CH_2Cl_2 (2.5 mL) at −10 to −25 °C under N_2. After 2 min, DIPEA (0.63 mL, 1.2 equiv) was added dropwise. The resulting dark slurry was stirred at −10 to −25 °C for 15 min. After the dropwise addition of a CH_2Cl_2 (2 mL) solution of piperonal (0.45 g, 3.0 mmol, 1.0 equiv), stirring was continued at −10 to −25 °C for 15 min. The reaction was quenched with H_2O (8 mL) and stirred to 15 °C. The aqueous layer was extracted with CH_2Cl_2 (2 mL). LC–MS analysis of the CH_2Cl_2 layer indicated no desired aldol products, some self-condensation products were detected.
   Procedure B. A mixture of methyl phenylacetate **7** (0.47 g, 1.05 equiv), piperonal (0.45 g, 3.0 mmol, 1.0 equiv) and DIPEA (0.63 mL, 1.2 equiv) in CH_2Cl_2 (4.5 mL) was stirred at rt under N_2 for 5 min and then cooled to −25 °C. $TiCl_4$ (0.39 mL, 1.2 equiv) was then added dropwise. The reaction was kept at −10 to −25 °C during the addition and stirred at this temperature for another 15 min after the addition. The reaction was quenched with H_2O (8 mL) and

stirred to 15 °C. The aqueous layer was extracted with CH_2Cl_2 (2 mL). The combined CH_2Cl_2 layer was washed with H_2O (2 mL) and concentrated. Purification by silica gel column chromatography (10–50% EtOAc in Hexanes) provided totally 0.79 g (90% yield) of the *syn* and *anti* aldol products. Isomer 1: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.56 (s, 3H), 3.85 (d, J = 9.0 Hz, 1H), 5.21 (d, J = 9.0 Hz, 1H), 5.95 (s, 2H), 6.73–6.86 (m, 3H), 7.31–7.42 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.5, 60.2, 75.2, 101.4, 107.5, 108.3, 120.7, 128.4, 129.1, 129.5, 135.2, 135.4, 147.6, 148.0, 173.1; MS (*m/z*): 283.3 $[M+H-H_2O]^+$, 323.3 $[M+Na]^+$. Isomer 2: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.86 (d, J = 9.0 Hz, 1H), 5.13 (d, J = 9.0 Hz, 1H), 5.90 (dd, J = 6.0, 3.0 Hz, 2H), 6.47–6.50 (m, 1H), 6.59 (d, J = 9.0 Hz, 1H), 6.72 (d, J = 3.0 Hz, 1H), 7.10–7.13 (m, 2H), 7.20–7.22 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.7, 60.3, 76.8, 101.3, 107.3, 108.1, 120.8, 128.0, 128.9 (2C), 135.1, 135.6, 147.4, 147.9, 174.3; MS (*m/z*): 283.3 $[M+H-H_2O]^+$, 323.3 $[M+Na]^+$.