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Parallel Recognition by Virtue of Differentiation between Ketone and Aldehyde

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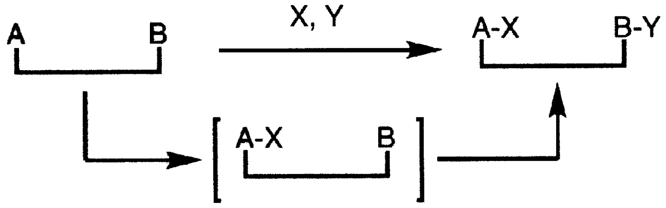
Abstract: The concept of parallel recognition has been applied to differentiate between ketone and aldehyde: $(C_6F_5)_2SnBr_2$-catalyzed Mukaiyama-aldol reaction of a mixture of these two carbonyl substrates with a mixture of enol silyl ethers derived from esters and ketones results in exclusive formation of ketone/ester and aldehyde/ketone aldol adducts, respectively. © 1998 Elsevier Science Ltd. All rights reserved.

Recently, we have advanced a new concept for compaction of multi-step chemical process, "parallel recognition" in which multifold reactions take place simultaneously to incorporate different reagents on the separate reaction sites (Scheme 1).[1] In the conventional stepwise process, A is transformed to A-X initially while B should be protected on many occasions. Then, after being deprotected, B is converted to B-Y. "Parallel recognition" demands no protection-deprotection of functional groups, and the necessary substrates and reagents can be charged altogether at the beginning of the reaction. As a result, highly expeditious and simple chemical processes are feasible. In this protocol, A and B need to be activated under similar conditions but their reactivities towards reagents X and Y should be completely different: A reacts with X but not with Y whereas B reacts with Y but not with X. Such recognition was realized in the $(C_6H_5)_2SnBr_2$-catalyzed Mukaiyama-aldol reaction for the parallel tracks of the ketone/ketene silyl acetal and acetal/ketone-derived enol silyl ether combinations.[1] Since acetal is a protected form of carbonyls, replacement of this component by aldehyde would give rise to a more direct process. This is also of great synthetic significance in terms of differentiation between ketone and aldehyde in naked forms.[2]

Scheme 1



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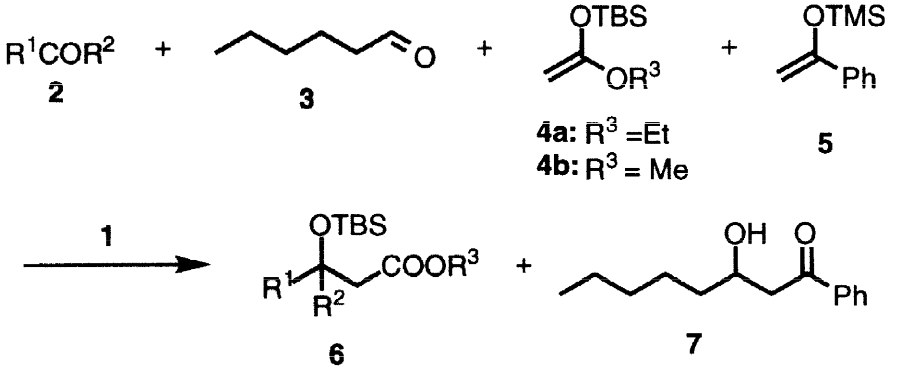
Previously, we disclosed that $(C_6F_5)_2SnBr_2$ (**1**) catalyzed Mukaiyama-aldol reaction of ketene silyl acetal with ketones quite smoothly[1] while only sluggish reaction occurred with aliphatic aldehydes under the same reaction conditions.[3] By contrast, enol silyl ethers derived from ketones reacted with the aldehydes smoothly.[3] These differences in reactivity prompted us to explore the parallel recognition process of naked ketone and aldehyde. For this recognition to be realized, the ketone-derived enol silyl ethers are required to undergo no reaction with ketone. In fact, 1-phenyl-1-(trimethylsiloxy)ethene (**5**) failed to react with acetophenone or 2-hexanone under the normal reaction conditions. With these results in hand, we conducted intermolecular parallel recognition. A mixture of ketone **2** and hexanal **3** (1.0 equiv. each) was exposed to a mixture of ketene silyl acetal **4** (1.3 equiv) and ketone-derived enol silyl ether **5** (2.0 equiv) in the presence of **1** (0.20 equiv) in CH_2Cl_2 at -78 °C for 6 h (Table 1).[4] After aqueous workup, the product distribution was checked by GLC. The clean recognition took place providing the two expected products exclusively among four possible

Table 1. Intermolecular Parallel Recognition.[a]

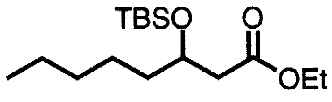


entry	2	4	yield (%) 6	yield (%) 7
1	$C_6H_5COCH_3$	**4a**	79[b,c]	61[b]
2		**4b**	76	66
3	cyclohexanone	**4a**	77	64
4		**4b**	58	65
5	$4\text{-}MeOC_6H_4COCH_3$	**4a**	82	70
6	$2,4\text{-}(MeO)_2C_6H_3COCH_3$	**4a**	73[c]	74
7	$n\text{-}C_4H_9COCH_3$	**4a**	61	55
8		**4a**	59[c]	54

[a] Reaction conditions: **1**:**2**:**3**:**4**:**5** = 0.2:1.0:1.0:1.3:2.0, CH_2Cl_2, -78 °C, 6 h.

[b] Isolated yields after column chromatography: **6**, 72%; **7**, 61%.

[c] A small amount of **8** was formed (1-3% yields).



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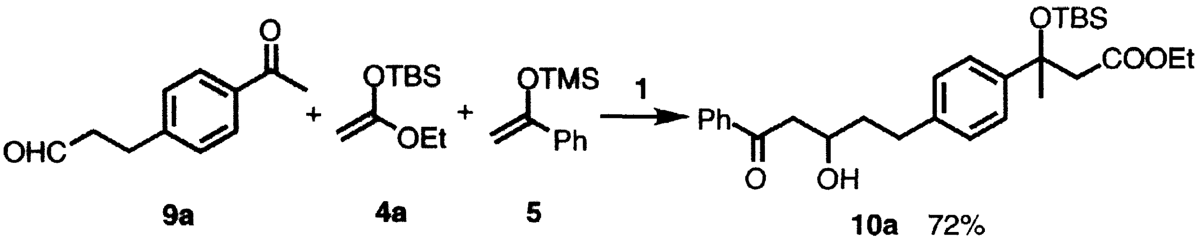
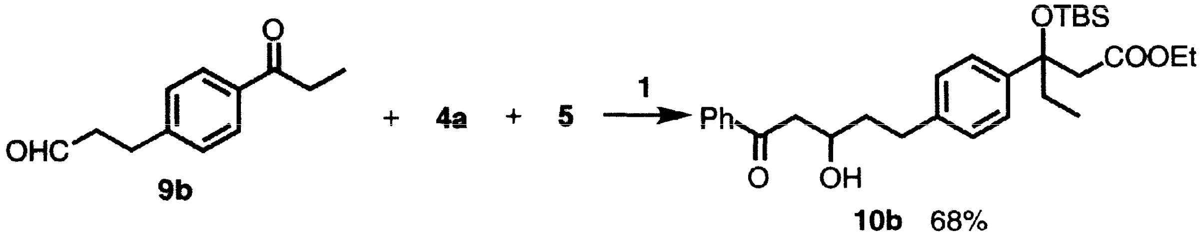
combinations: **6** derived from **2** and **4** while **7** derived from **3** and **5**. No other coupling modes occurred except a few cases in which a very small amount of aldol product **8** was formed from **3** and **4a** (entries 1,6,8). Aromatic ketones (entries 1,2,5,6) and cyclohexanone (entries 3 and 4) afforded better yields of **6** than 2-hexanone (entries 7,8).

Next, we turned our attention to the intramolecular version. Various keto aldehydes were exposed to a mixture of **4a** and **5** (Scheme 2).[5] Notably, the ketene silyl acetal was coupled with the ketone moiety and the other enol silyl ether with aldehyde exclusively. No other products were detected indicative of highly selective recognition. Although **9c** furnished a somewhat lower yield, reasonable outcomes were obtained with both **9a** and **9b** which are intervened by a phenyl ring. This leads us to conclude that the double track reactions proceeded independently to each other. It may be supposed that intramolecular neighboring group participation is responsible for the preference of ketone over aldehyde.[6] This is not the case, however, because the intervention of the planar phenyl ring prevents the intramolecular interaction between the two carbonyls.

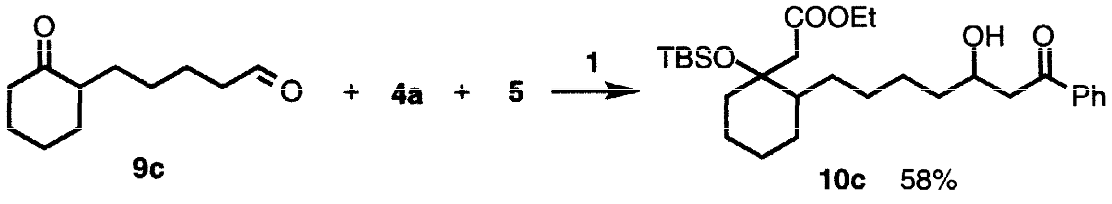
Scheme 2.



Reaction conditions: **9a**:**4a**:**5**:**1** = 1.0:1.3:2.0:0.2, -78°C, 6 h.



Reaction conditions: **9b**:**4a**:**5**:**1** = 1.0:1.3:2.0:0.2, -78°C, 6 h.



Reaction conditions: **9c**:**4a**:**5**:**1** = 1.0:1.3:2.0:0.2, -78°C, 6 h.

In summary, the "parallel recognition" has been successfully applied to differentiate naked ketone and aldehyde. Notably, the subtle differentiation is achievable with the perfluorophenyltin catalyst. Of further synthetic significance is the intramolecular version which enables simultaneous generation of β-hydroxy ester and ketone moieties on the separate reaction sites. This kind of recognition will be of great help in compaction of synthetic processes and find a wide variety of applications.

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References and Notes

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2. (a) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*, Springer-Verlag, Berlin, 1986, Chapter 3. (b) Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.* **1993**, *58*, 4971, and references cited therein. (c) Molander, G. A.; Cameron, K. O. *J. Org. Chem.* **1991**, *56*, 2617; *J. Am. Chem. Soc.* **1993**, *115*, 830.
3. Chen, J.; Sakamoto, K.; Orita, A.; Otera, J. *Synlett* **1996**, 877.
4. A representative procedure is as follows. To a CH_2Cl_2 solution (2 mL) of **1** (122 mg, 0.2 mmol) was added a CH_2Cl_2 solution (2 mL) of acetophenone (106 mg, 1 mmol) and hexanal (100 mg, 1.0 mmol) at -78 °C followed by a CH_2Cl_2 solution (2 mL) of **4a** (263 mg, 1.3 mmol) and **5** (384 mg, 2.0 mmol). The solution was stirred for 6 h. Aqueous workup and evaporation afforded crude products that were analyzed by GLC and NMR by comparing authentic specimen.
5. A representative procedure is as follows. To a CH_2Cl_2 solution (2 mL) of **1** (61 mg, 0.1 mmol) was added a CH_2Cl_2 solution (2 mL) of **9a** (88 mg, 0.5 mmol) at -78 °C followed by a CH_2Cl_2 solution (2 mL) of **4a** (131 mg, 0.65 mmol) and **5** (192 mg, 1.0 mmol). The solution was stirred for 6 h. Aqueous workup and evaporation gave a crude product that was purified by column chromatography on silica gel (80:20 hexane/EtOAc) to afford **10a** (179 mg, 72%). The products obtained in this study were fully confirmed by NMR, mass spectra, and elemental analysis.
6. The intramolecular neighboring group participation was suggested for TMSOTf-catalyzed reaction of enol silyl ethers with 1,4- and 1,5-keto aldehydes: the Lewis acid initially coordinates with the aldehyde moiety and the ketonic oxygen attacks the aldehyde carbon intramolcularly and, accordingly, the ketone function is preferentially activated.[2c]