Carbonyl Reactivity

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Reversing the Reactivity of Carbonyl Functions with Phosphonium Salts: Enantioselective Total Synthesis of (+)-Centrolobine**

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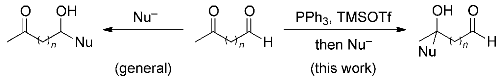
The control of chemoselective transformations irrespective of the individual reactivity of functional groups still remains a largely unanswered challenge. Carbonyl groups, such as aldehydes and ketones, are without doubt the most important functional groups in organic chemistry and their reactions are well known. The order of the reactivity of carbonyl groups toward nucleophiles is generally aldehyde > ketone > ester. Therefore, it is easy to react an aldehyde in the presence of ketones and esters. In contrast, it is difficult to react a ketone prior to an aldehyde. Therefore, protective groups have to be employed for such transformations, which thus become intrusive three-step operations that involve the protection of the aldehyde, transformation of the ketone, and deprotection of the aldehyde. The reversal of the reactivity of functional groups is a challenging theme in chemistry and there are few reports on such transformations.[1,4b] Luche and Gemal reported pioneering and representative work, in which a ketone was selectively reduced in the presence of an aliphatic aldehyde.[1a] The conversion of the aldehyde into an acetal, the subsequent reduction of the ketone with $NaBH_4$, and the deacetalization were carried out in one pot by using the $CeCl_3$–MeOH–$NaBH_4$ system. However, this reaction was limited to reductions and is difficult to apply to other reactions. Other methods, such as the use of metal amides,[1b–g] a bulky Lewis acid,[1i] and a copper catalyst with a bulky phosphine ligand,[1j] were reported. However, these methods have drawbacks, such as lower generality, the need to prepare special reagents, and strict control of stoichiometry because of the use of highly reactive reagents. Therefore, more practical and facile methods for the selective transformation of carbonyl groups are required.

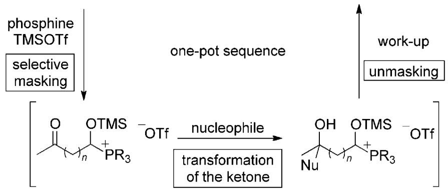
Herein we report the convenient and versatile selective one-pot transformation of less-reactive carbonyl groups in the presence of aldehydes (or ketones) by using the combination of PPh_3 (or PEt_3) and TMSOTf to selectively mask the aldehyde prior to the addition of the nucleophile (Scheme 1). The asymmetric transformation of a less-reactive carbonyl group in the presence of a more-reactive carbonyl group was also accomplished, and was applied to the short asymmetric total synthesis of (+)-centrolobine.



Scheme 1. Reversal of the reactivity of ketone and aldehyde. Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

We previously developed the unprecedented chemoselective deprotection of acetals in the presence of ketals with TESOTf–2,4,6-collidine.[2] This is the only method reported to date with which the reactivity of acetals and ketals can be switched. The key aspect of the reaction is the selective formation of collidinium salt intermediates from acetals by distinguishing their steric environment using TESOTf. In addition, the reactivity of the salt could be changed by changing the structure of the base. We have also recently reported the reactivity of O,P acetals, which were generated from O,O acetals and various phosphines and have a similar reactivity to pyridinium salts.[3] We then presumed that if the salt of an aldehyde in a keto aldehyde could be formed selectively and would be less reactive than the ketone, the selective transformation of the ketone should be possible (Scheme 2).[4]

We investigated several Lewis acid/pyridine and Lewis acid/phosphine combinations and reducing reagents. As a result, the selective transformation of a ketone to an alcohol in the presence of an aldehyde was achieved by the combination of PPh_3–silyltriflate and $BH_3{\cdot}THF$ (Table 1). When TMSOTf was used, the aldehyde was recovered from the phosphonium salt by hydrolysis with a weak base (aqueous $NaHCO_3$; Table 1, entry 1). On the other hand,



Scheme 2. Strategy for the reversal of the reactivity.

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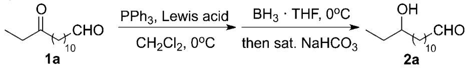
Table 1: Optimization of the reaction conditions.[a]

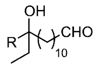
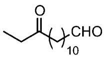
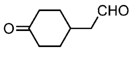
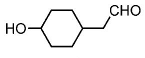
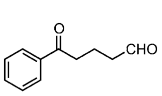
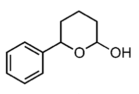
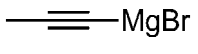
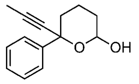
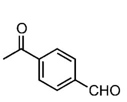
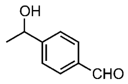
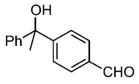
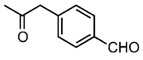
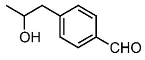
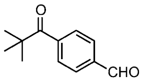
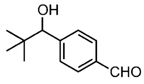
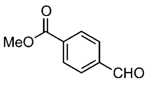
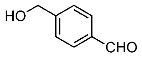
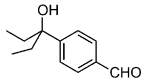


Entry	Lewis acid (equiv)	Equiv PPh_3	Equiv $BH_3{\cdot}THF$	Yield [%][b]
1	TMSOTf (2.0)	3.0	4.0	90
2[c]	TESOTf (2.0)	3.0	4.0	86
3[c]	TBSOTf (2.0)	3.0	4.0	94
4	$BF_3{\cdot}Et_2O$ (2.0)	3.0	4.0	trace
5[d]	TMSOTf (1.2)	1.2	1.5	88
6[d,e]	TMSOTf (1.2)	1.2	1.5	96
7[f]	–	–	1.2	0

[a] Reaction conditions: **1a** was treated with PPh_3 and Lewis acid in CH_2Cl_2 (0.1 M) at 0 °C for 1 h. Then, $BH_3{\cdot}THF$ was added at 0 °C. After the reaction was completed, the mixture was treated with sat. $NaHCO_3$ (unless stated otherwise). [b] Yield of isolated product **2a**. [c] TBAF (3.0 equiv) was used for the work-up. [d] PPh_3 and TMSOTf were added at RT. [e] Reduction was performed at −40 °C. [f] Reaction was performed in the absence of Lewis acid and PPh_3. TBAF = tetra-*n*-butylammonium fluoride, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, THF = tetrahydrofuran.

Table 2: Selective one-pot transformation of carbonyl groups in the presence of aldehydes.[a]

$$\mathbf{1} \xrightarrow[\text{2. } BH_3THF\ (-40^{\circ}C) \text{ or Grignard reagent (RT) then sat. } NaHCO_3\text{, MeOH, } 40^{\circ}C]{\text{1. } PPh_3 \text{ (1.2 equiv), TMSOTf (1.2 equiv), RT}} \mathbf{2}$$

Entry	Substrate	Reagent (equiv)	Product	Yield [%][b]
				
1	**1a** 	$BH_3{\cdot}THF$ (1.5)	**2a** R = H	96
2		PhMgBr (3.0)	**2b** R = Ph	93
3		EtMgCl (1.5)	**2c** R = Et	87
4		allylMgBr (1.5)	**2d** R = allyl	75
5	**1b** 	$BH_3{\cdot}THF$ (1.5)	**2e** 	87
6	**1c** 	$BH_3{\cdot}THF$ (1.5)	**2f** 	89
7		 (3.0)	**2g** 	93
8	**1d** 	$BH_3{\cdot}THF$ (1.5)	**2h** 	96
9		PhMgBr (3.0)	**2i** 	85
10[c]	**1e** 	$BH_3{\cdot}THF$ (1.5)	**2j** 	87
11[d]	**1f** 	$BH_3{\cdot}THF$ (2.0)	**2k** 	74
12[e]	**1g** 	DIBAL-H (2.2)	**2l** 	80
13		EtMgCl (3.0)	**2m** 	76

[a] Reaction conditions: Substrate **1** was treated with PPh_3 (1.2 equiv) and TMSOTf (1.2 equiv) in CH_2Cl_2 (0.1 M) at RT for 1 h. Then, the reagent was added at the given temperature. After the reaction was completed, the mixture was treated with aq sat. $NaHCO_3$/MeOH at 40 °C for 2 h. [b] Yield of isolated product **2**. [c] Reduction was performed at −40 °C → −20 °C. [d] Reduction was performed with $BH_3{\cdot}THF$ (2.0 equiv) at −40 °C → RT. [e] DIBAL-H (2.2 equiv) was used as a reductant at 0 °C. DIBAL-H = diisobutylaluminium hydride.

when other silyltriflates, such as TESOTf and TBSOTf, were used, treatment with TBAF was necessary to recover the aldehyde (Table 1, entries 2 and 3). The use of $BF_3{\cdot}Et_2O$ was not effective in this reaction (Table 1, entry 4). Reducing the amount of PPh_3 and TMSOTf did not lead to a significantly lower yield, however, the reduction at −40 °C gave the best results (Table 1, entries 5 and 6). The nonselective reduction proceeded in the absence of the silyltriflate and PPh_3, and diol and aldehyde-reduced keto alcohol were obtained in 20 % and 74 % yield, respectively (Table 1, entry 7).

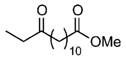
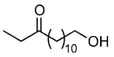
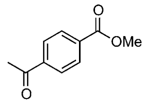
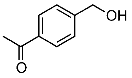
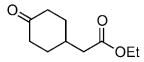
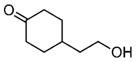
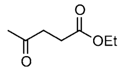
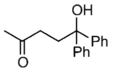
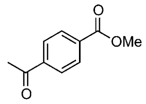
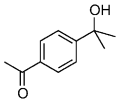
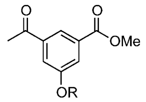
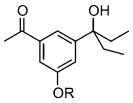
We explored the generality of the reaction by using various keto aldehydes under the optimized conditions (Table 2). Our method could be applied to both the reduction of ketones and their alkylation with various Grignard reagents. Aliphatic aldehydes were effectively masked in situ, and the selective transformation of aliphatic, aromatic, and cyclic ketones proceeded selectively (Table 2, entries 1–7). The selective transformation of the 5-oxoaldehyde derivative **1c** gave lactols **2f** and **2g** in good yields (Table 2, entries 6 and 7), thus providing an efficient route for the construction of lactol derivatives in one pot. The aromatic aldehydes were also protected without difficulty (Table 2, entries 8–13).[5] The easily enolizable ketone **1e** could be converted into the corresponding alcohol **2j** in good yield (Table 2, entry 10). A bulky ketone **1f** was selectively reduced with 2 equivalents of reductant (Table 2, entry 11). The selective reduction as well as the selective alkylation of an ester in the presence of an aldehyde were also successful; when DIBAL-H and the Grignard reagent were used, the benzyl alcohols **2l** and **2m** were obtained in 80 % and 76 % yields, respectively (Table 2, entries 12 and 13).

It is notable that this method can also be applied to the selective transformation of ketones by changing PPh_3 to PEt_3. The ketone did not react with PPh_3–TMSOTf even when an excess of reagents was used, because of the low nucleophilicity of PPh_3. Therefore, we attempted to employ PEt_3 instead of PPh_3, because the former has a high reactivity and is commercially available. As we anticipated, after pretreatment with PEt_3–TMSOTf, the keto esters were selectively reduced with DIBAL-H to give the keto alcohols in high yields (Table 3, entries 1–3). The selective alkylation of the ester group of keto esters was also successful and left the ketone intact (Table 3, entries 4–7). In addition, MOM and TBS groups were able to endure the reaction conditions to give the desired products in high yields (Table 3, entries 6 and 7).

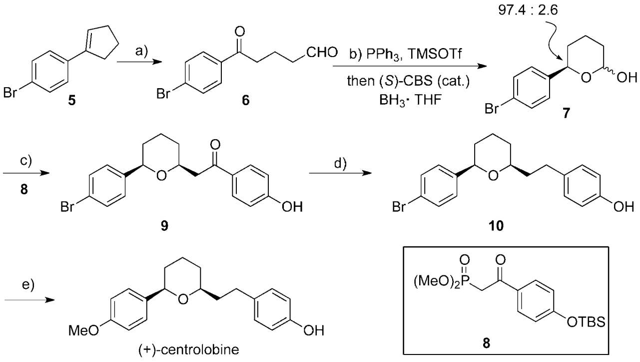
To demonstrate the synthetic utility of this methodology, we carried out the total synthesis of centrolobine, which is isolated from the heartwood of *Centrolobium robustum* and exhibits anti-inflammatory and antibacterial as well as anti-

Table 3: Selective one-pot transformation of esters in the presence of ketones.[a]

$$\mathbf{3} \xrightarrow[\substack{\text{2. DIBAL-H (0}^{\circ}\text{C) or Grignard reagent (RT)} \\ \text{then sat. NaHCO}_3\text{, MeOH, 40}^{\circ}\text{C}}]{\text{1. PEt}_3\text{ (1.2 equiv), TMSOTf (1.2 equiv), RT}} \mathbf{4}$$

Entry	Substrate	Reagent (equiv)	Product	Yield [%][b]
1	**3a** 	DIBAL-H (3.0)	**4a** 	82
2	**3b** 	DIBAL-H (3.0)	**4b** 	93
3	**3c** 	DIBAL-H (3.0)	**4c** 	76
4	**3d** 	PhMgBr (4.0)	**4d** 	76
5	**3b** 	MeMgBr (3.0)	**4e** 	83
6	 **3e** R=MOM	EtMgCl (3.0)	 **4f** R=MOM	80
7	**3f** R=TBS	EtMgCl (3.0)	**4g** R=TBS	74

[a] Reaction conditions: Substrate **3** was treated with PEt_3 (1.2 equiv) and TMSOTf (1.2 equiv) in CH_2Cl_2 (0.4 M) at RT for 1 h. Then, the reagent was added at the given temperature. After the reaction was completed, the mixture was treated with aq sat. $NaHCO_3$/MeOH at 40 °C for 2 h. [b] Yield of isolated product **4**. MOM = methoxymethyl.



Scheme 3. Asymmetric synthesis of (+)-centrolobine. a) O_3, CH_2Cl_2, −78 °C; PPh_3, 99 %; b) PPh_3, TMSOTf, CH_2Cl_2, RT; (*S*)-CBS (30 mol %), BH_3·THF, −40 °C, then aq sat. $NaHCO_3$/MeOH, 40 °C, 81 %; c) **8**, LiOMe, MeOH, 0 °C→RT, 99 %; d) $LiBH_4$, Et_2O, 0 °C; Et_3SiH, TFA, 0 °C→RT, 96 %; e) CuI, NaOMe, DMF, 100 °C, 99 %. DMF = *N*,*N*-dimethylformamide, TFA = trifluoroacetic acid.

leishmanial activities.[6] Although the asymmetric synthesis of centrolobine has been reported by several groups, these routes consist of multiple steps and/or have low yields.[7] Centrolobine has a chiral tetrahydropyranyl (THP) ring skeleton that can be constructed by the ketone-selective asymmetric reduction of 5-oxoaldehyde (see Table 2, entry 6).

The ozonolysis of commercially available cyclopentene **5** quantitatively afforded the key intermediate keto aldehyde **6** (Scheme 3). As we expected, the asymmetric reduction of the ketone efficiently proceeded with the Corey–Bakshi–Shibata (CBS) reagent[8] to give lactol **7** with high selectivity (97.4:2.6)[9] without reducing the aldehyde. To the best of our knowledge, this result is the first reported asymmetric transformation of a ketone in the presence of an aldehyde.

The Horner–Wadsworth–Emmons (HWE) reaction of **7** using phosphonate **8** was followed by the decarbonylation of **9** and furnished the desired 2,6-*cis*-THP **10** with a phenethyl group. Finally, an Ullmann coupling with CuI–NaOMe completed the synthesis. The spectral data of the synthetic (+)-centrolobine were identical in all respects to those reported for the natural product. This enantioselective synthesis was accomplished in five steps from commercially available cyclopentene **5**, and with an overall yield of 75 %, which is the highest total yield reported for the asymmetric synthesis of centrolobine.

In conclusion, we have developed a novel and facile selective transformation method of ketones in the presence of aldehydes by using the commercially available reagents PPh_3 and TMSOTf. A variety of reagents can be used in this reaction, such as BH_3, DIBAL-H, the CBS catalyst, and Grignard reagents. In addition, the selective transformation of esters in the presence of ketones was achieved by replacing PPh_3 with PEt_3. Furthermore, we accomplished the asymmetric synthesis of (+)-centrolobine in five steps with the highest reported overall yield. Further investigations of the applicability of other reagents and the reversal of the selectivity of other functional groups are currently under way.

Experimental Section

General procedure for the selective reduction of a ketone in the presence of an aldehyde: TMSOTf (0.238 mmol) was added dropwise to a solution of keto aldehyde (0.200 mmol) and PPh_3 (0.240 mmol) in CH_2Cl_2 (2.0 mL) at RT. The reaction mixture was stirred for 1 h at RT, then cooled to −40 °C, and BH_3·THF (0.302 mmol) was added slowly by syringe. Stirring at −40 °C was continued until the starting material was consumed (TLC analysis was conducted after quenching a small amount of the reaction mixture with a drop of TBAF (1.0 M in THF)). A saturated aqueous solution of $NaHCO_3$ (2.0 mL) and MeOH (1.0 mL) were added to the solution, and the resulting mixture was stirred for 2 h at 40 °C. The mixture was cooled to RT and extracted several times with EtOAc (total amount 50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. Purification was accomplished by flash column chromatography to afford the desired product (see the Supporting Information for details).

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[5] The selective formation of the phosphonium salt was confirmed by an NMR study on substrate **1d**. See the Supporting Information for details.

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[9] After the transformation, the selectivity was determined by HPLC analysis on a chiral stationary phase. See the Supporting Information for details.