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Selective Transformations of Carbonyl Functions in the Presence of α,β-Unsaturated Ketones: Concise Asymmetric Total Synthesis of Decytospolides A and B

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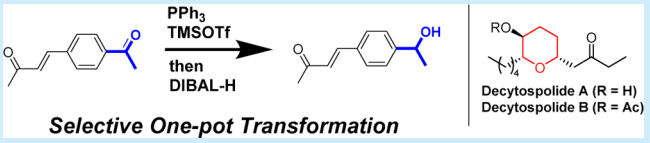
Supporting Information

ABSTRACT: Enones selectively react with a combination of PPh_3 and TMSOTf to produce phosphonium silyl enol ethers, which work as protective groups of enones during the reduction of other carbonyl functions and can be easily deprotected to regenerate parent enones at workup. Furthermore, the first ketone selective alkylations in the presence of enones were also accomplished. This in situ protection method was applied to concise asymmetric total syntheses of decytospolides A and B.



Control of the reactivity of individual functional groups in organic compounds is a very important issue in organic synthesis. For example, it is well-known that the order of 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. For the achievement of such transformation, in some cases in situ protection methods have been developed to alleviate this problem,[1] although intrusive multistep operations involving the introduction and removal of protective groups are usually required. However, in situ protection methods do not exist for discriminating between two functions that have similar reactivity, and then it is difficult to design selective reaction for one of these two.

Ketones and α,β-unsaturated ketones display nearly identical reactivity, although ketones generally have slightly higher reactivity toward nucleophiles than enones. In the past, only three different methods have been reported to describe selective reductions of ketones in the presence of enones.[2] Ward et al. described a ketone-selective reduction in the presence of enones using $NaBH_4$ in $MeOH/CH_2Cl_2$.[2a] Ranu et al. realized that $Zn(BH_4)_2$ in DME can also be employed to perform selective reductions of ketones.[2b] Although these methods are applicable to selective reductions of aliphatic ketones, they cannot be used to differenciate aromatic ketones from enones owing to their highly similar reactivities. Maruoka et al. described a procedure for chemoselective reductions of saturated aldehydes and a ketone in the presence of unsaturated carbonyls that employs a bulky tin hydride and Lewis acid.[2c] Although this method was effective in the discrimination of aldehydes, the yield of the ketone reduction was moderate. In addition, the key organotin reagent needs to be prepared using a multistep sequence.

As described above, although there are a few methodologies succeeding in the selective transformation between closely related carbonyl functions, ketones, and enones, there is no general method for selective reduction of carbonyl functions in the presence of α,β-unsaturated enones, let alone the method for selective alkylation.

In our previous studies, we have developed procedures for reversing the reactivity of carbonyl functions that relies on the use of a combination of TMSOTf and phosphines to temporarily protect aldehydes and ketones (Scheme 1 a).[3] In these processes, aldehydes and ketones are temporarily protected by being *O,P*-acetal-type phosphonium salt intermediates. In the course of this study, we found that the PPh_3 and TMSOTf combination, even when used in excess, does not transform ketones to their corresponding phosphonium salts. On the other hand, Kozikowski et al.,[4a] Kim et al.,[4b] and Lee et al.[4c] separately reported β-alkylation reactions of enones using PPh_3 and TBSOTf take place via initial phosphoniosilylation processes. We then expected that the combination of PPh_3 and silyl triflate would react with α,β-unsaturated ketones selectively in the presence of ketones. Although the phosphonium salts were generated as reactive intermediates in the previous

Scheme 1. In Situ Protection Method for Selective Transformation

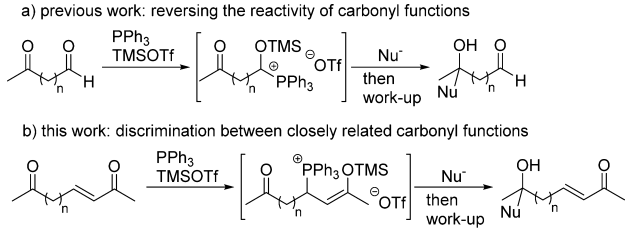


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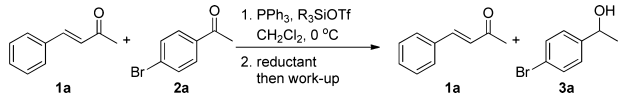
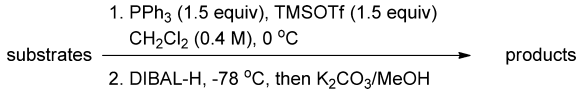
Table 1. Optimization of the Reaction Conditions[a]

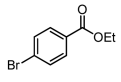
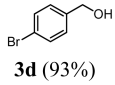
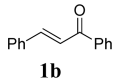
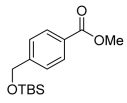
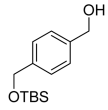
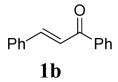
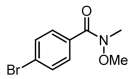
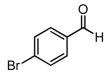
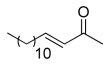
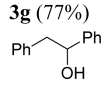
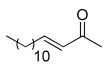
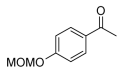
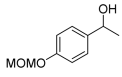


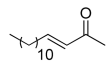
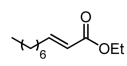
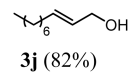
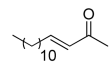
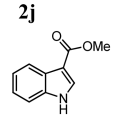
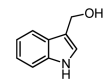
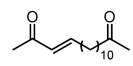
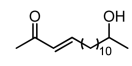
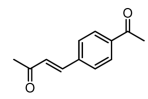
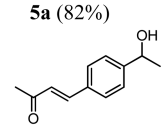
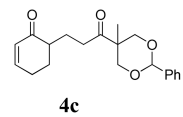
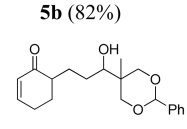
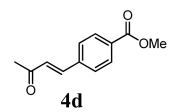
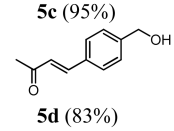
entry	R_3SiOTf (equiv)	PPh_3 (equiv)	reducing conditions	1a[b] (%)	3a[c] (%)
1[d]	TBSOTf (1.2)	1.2	DIBAL-H (2.0 equiv), −78 °C	57	97
2[d]	TBSOTf (1.5)	1.5	DIBAL-H (2.0 equiv), −78 °C	75	94
3[d]	TESOTf (1.5)	1.5	DIBAL-H (2.0 equiv), −78 °C	78	99
4[e]	TMSOTf (1.5)	1.5	DIBAL-H (2.0 equiv), −78 °C	82	82
5[f]			DIBAL-H (1.0 equiv), −78 °C	41	45[i]
6[f,g]			$NaBH_4$ (4.5 equiv), −78 °C	68	47[i]
7[f,h]			$Zn(BH_4)_2$ (1.0 equiv), −20 °C	59	18[i]

[a] **1a** (0.2 mmol) and **2a** (0.2 mmol) were used. [b] Isolated yield. Allylic alcohol was formed as byproduct in all entries. [c] Isolated yield. [d] TBAF (2 equiv) were used at workup. [e] K_2CO_3 suspension in MeOH was used at workup. [f] Reaction was performed in the absence of PPh_3 and silyl triflate. [g] Ward conditions. CH_2Cl_2/MeOH (1:1) was used as a solvent. See ref 2a. [h] Ranu conditions. DME was used as a solvent. See ref 2b. [i] **2a** was recovered.

Table 2. Selective Reduction of Various Carbonyl Functions in the Presence of Enones[a]



entry	substrate		equiv of DIBAL-H	products[b]	
1	 **1a**	 **2b**	2.2	**1a** (77%)	 **3b** (96%)
2	 **1a**	 **2c**	3.0	**1a** (73%)	 **3c** (76%)
3	 **1a**	 **2d**	3.0	**1a** (82%)	 **3d** (93%)
4	 **1b**	 **2e**	2.0	**1b** (84%)	 **3e** (93%)
5	 **1b**	 **2f**	3.0	**1b** (94%)	 **3f** (86%)
6	 **1b**	 **2g**	2.0	**1b** (82%)	 **3g** (77%)
7	 **1c**	 **2h**	2.0	**1c** (89%)	 **3h** (75%)
8	 **1c**	 **2i**	2.0	**1c** (84%)	 **3i** (89%)

entry	substrate		equiv of DIBAL-H	products[b]	
9	 **1c**	 **2j**	3.0	**1c** (70%)	 **3j** (82%)
10	 **1c**	 **2k**	3.0	**1c** (80%)	 **3k** (84%)
11	 **4a**		2.2		 **5a** (82%)
12	 **4b**		2.2		 **5b** (82%)
13	 **4c**		2.0		 **5c** (95%)
14	 **4d**		3.0		 **5d** (83%)
15[c]	**4e**		2.2		**5e** (76%)

[a] **1** (0.2 mmol) and **2** (0.2 mmol) were used. [b] Isolated yields were given in the parentheses. [c] Protection was performed on **4c** (0.6 mmol) with PPh_3 (1.2 equiv) and TMSOTf (1.1 equiv) in CH_2Cl_2 (0.4 M) at −78 °C. [d] TBAF (2.0 equiv) was used instead of sat. K_2CO_3/MeOH. [e] Protection was performed with PPh_3 (1.5 equiv) and TMSOTf (1.7 equiv).

reports,[4] we presumed that if the phosphonium silyl enol ethers could survive during the transformation of remaining ketones, an in situ protection method for discriminating between closely related functional groups would be established (Scheme 1 b).

We began our study on the discrimination between enone **1a** and ketone **2a** (Table 1). In light of previous reports,[4] we first chose TBSOTf and PPh_3 as reagents for enone protection and DIBAL-H as the reducing agent (Table 1, entry 1). Treatment

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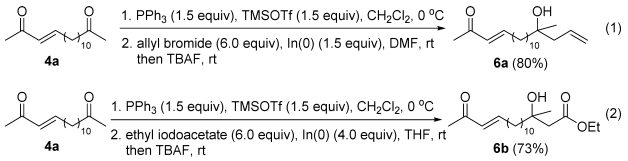
of a mixture of **1a** and **2a** first with TBSOTf and PPh_3 (1.2 equiv each) and then with DIBAL-H followed by TBAF workup led to production of the ketone-reduced alcohol **3a** (97%) along with the recovered enone **1a** (57%). Increasing the amounts of PPh_3 and TBSOTf to 1.5 equiv afforded a higher yield of recovered **1a** (Table 1, entry 2). The use of TESOTf instead of TBSOTf resulted in a slightly higher **1a** recovery (Table 1, entry 3), and when TMSOTf was employed, **1a** was recovered in the highest yield by using weakly basic solvolysis conditions (K_2CO_3/MeOH) (Table 1, entry 4). Nonselective reduction took place in the absence of pretreatment with PPh_3 and silyl triflate (Table 1, entry 5). We also confirmed that the conditions reported previously by the Ward group[2a] and the Ranu group[2b] did not work effectively in these aromatic substrates (Table 1, entries 6 and 7).

The generality of this method was explored (Table 2). The results showed that pretreatment with PPh_3 and TMSOTf can be used to protect not only aromatic enones **1a** and **1b** but also the aliphatic enone **1c** in selective reductions of various ketones **2b**,**e**,**i** and even the easily enolizable ketone **2h**. Moreover, by using this procedure, selective reduction of esters **2d**,**f**, including α,β-unsaturated ester **2j**, and Weinreb amide **2g** proceeded smoothly to produce the corresponding alcohols and aldehyde in high yields (Table 2, entries 1 and 3−9). A pyridyl ketone **2c** and unprotected indolyl ester **2k** could also be reduced selectively (Table 2, entries 2 and 10). Moreover, acid-labile TBS and MOM groups could tolerate the reaction conditions (Table 2, entries 5 and 8). The reaction was then applied to the selective reduction of substrates possessing both enone and other carbonyl moieties in the same molecule (Table 2, entries 11−15). The ketone groups in aliphatic and aromatic keto-enones **4a** and **4b** were reduced selectively to afford the corresponding alcohols **5a** and **5b** in high yields (Table 2, entries 11 and 12). In addition, even the highly hindered ketone moiety in **4c**, which also contains an acid-labile benzylidene acetal group, was reduced in excellent yield leaving the enone and the acetal groups intact (Table 2, entry 13). The ester and Weinreb amide moieties in **4d** and **4e** were also reduced in the presence of enone groups (Table 2, entries 14 and 15).

Scheme 2. Ketone-Selective Allylation (eq 1) and Reformatsky Reaction (eq 2)

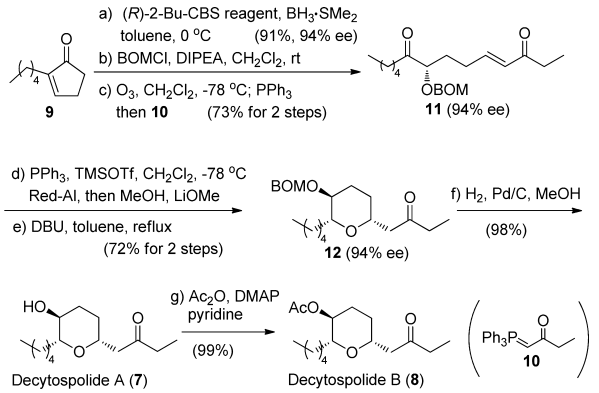


It is noteworthy that the in situ protection method could also be applied to ketone selective alkylation reactions of keto-enone (Scheme 2). In(0)-mediated Barbier-type allylation[5] and Reformatsky reaction[6] of **4a** afforded the ketone-selective alkylated products **6a** and **6b**, respectively, in high yields. These are the first methods of ketone selective alkylation reactions of keto-enones.

To demonstrate the synthetic utility of this method, we carried out the asymmetric total synthesis of decytospolides A (**7**) and B (**8**), which were isolated from *Cytospora* sp., an endophytic fungus from *Ilex canariensis*.[7] Decytospolide B (**8**) shows in vitro cytotoxic activity toward tumor cell lines A549 and QGY. To date, two reports exist describing the total synthesis of these natural products, and those synthetic routes involve multiple processes.[8]

Our synthetic route for the target natural products was summarized in Scheme 3. Corey−Bakshi−Shibata reduction[9] of

Scheme 3. Asymmetric Total Synthesis of Decytospolides A and B



commercially available 2-pentyl-2-cyclopenten-1-one (**9**) afforded a chiral allylic alcohol. Protection of the hydroxyl group with BOM group was followed by a one-pot ozonolysis−Wittig reaction sequence to give the key keto-enone **11**.[10] Following in situ protection of the enone group, diastereo- and chemoselective reduction of ketone moiety in **11** with Red-Al[11,12] proceeded smoothly, and **12**, which has desired stereochemistry, was constructed by DBU-promoted isomerization. It is notable that the chiral center in **11** was not epimerized through this sequence of reactions. Finally, BOM group in **12** was detached by hydrogenolysis to give decytospolide A (**7**), which was acetylated to afford decytospolide B (**8**). These enantioselective syntheses were accomplished in six and seven steps from commercially available cyclopentenone **9**, with overall yields of 47% for decytospolide A and 46% for decytospolide B.

In conclusion, a convenient and versatile in situ protection method for enones has been developed. The process, performed by using a combination of PPh_3 and TMSOTf, generates phosphonium silyl enol ether intermediates. This method can be employed to discriminate between enones and ketones. By using this procedure, the first ketone selective alkylation reactions of a keto-enone were developed. Finally, we demonstrated the asymmetric total synthesis of decytospolides A and B by using the developed method as a key reaction. The route employed for the preparation of these natural products is the most concise and efficient of those developed thus far. Additional investigations of the applicability of other reagents and the protection of α,β-unsaturated carbonyl substrates having other substituent patterns are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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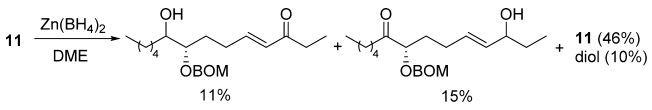

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