Control of Chemical Reactions Using Molecules that Buffer Non-aqueous Solutions

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Abstract: Control of chemical reactions is necessary for obtaining designer chemical transformation products and for preventing decompositions and isomerizations of compounds of interest. For the control of chemical events in aqueous solutions, the use of aqueous buffers is a common practice. However, no molecules that buffer non-aqueous solutions were commonly used. Here we demonstrate that 1,3-cyclohexanedione derivatives have buffering functions in non-aqueous solutions. We also show that these molecules can be utilized to alter and control chemical reactions. 1,3-Cyclohexanedione derivatives inhibited both acid-catalyzed and base-catalyzed isomerizations and decompositions in organic solvents. The reaction products obtained in the presence of the buffering molecule 2-methyl-1,3-cyclohexanedione differed from those obtained in the absence of the buffering molecule. The use of buffering molecules that work in organic solvents provides a strategy to control chemical reactions and expands the range of compounds that can be synthesized.

Introduction

Control of chemical reactions is necessary to obtain desired chemical transformation products and to prevent decompositions and isomerizations of molecules of interest. As organic synthesis is important for drug discovery and related areas,[1] there is a high demand for chemical transformation methods and for strategies to control chemical reactions. To control chemical reactions in aqueous solutions or to maintain conditions suitable for enzyme-catalyzed reactions and for storage of biological samples such as enzymes and antibodies, the use of buffers is a common practice.[2] However, no molecules that have buffering functions in non-aqueous solutions to maintain conditions suitable for chemical reactions were commonly used. For chemical transformations in non-aqueous solutions, the selection of solvents may be the first step to tune the reaction environment.[3] Reagents and/or catalysts are usually developed to meet the requirements of the desired chemical transformations. Scavengers have also been employed to remove certain molecules in non-aqueous solutions to maintain the desired conditions.[4] Common scavenger molecules, however, do not have buffering functions; scavengers that remove acids cannot be used to remove bases and vice versa.[4] We hypothesized that the use of molecules that neutralize both acids and bases in organic solvents and thus have buffering functions in non-aqueous solutions would provide further strategies to control and alter chemical reactions. Here, we report the introduction of the "buffering" concept into the events that occur in non-aqueous solutions. We report that 1,3-cyclohexanedione derivatives have buffering functions in non-aqueous solutions and that the use of these molecules provides a way to control and alter the direction and products of chemical reactions (Figure 1).

In aqueous buffers, buffer molecules neutralize both acids and bases to maintain the pH within certain ranges.[2] Many types of buffer molecules are used in aqueous solutions. The buffer molecules used in aqueous solutions, however, usually cannot be used as buffering molecules in non-aqueous solutions. This may be because the p*K*a values of functional groups of molecules depend on solvent,[5] and thus, molecules that act as buffering molecules in aqueous solutions do not have the p*K*a values required to serve as buffering molecules in non-aqueous solutions.

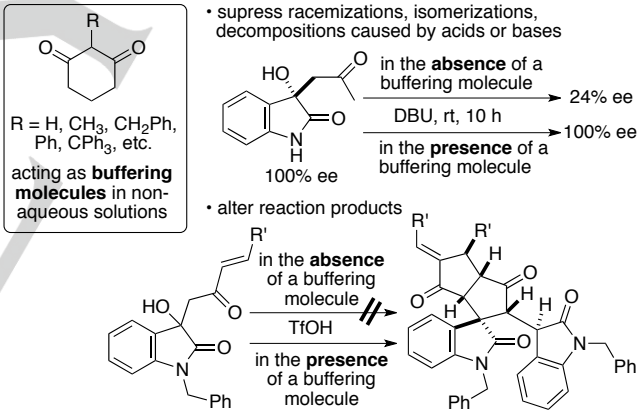

Figure 1. Examples of buffering molecules that function in non-aqueous solutions reported here and the control of reactions using the buffering molecules.

We hypothesized that 1,3-cyclohexanedione derivatives would have buffering functions in organic solvents based on the reactions of 1,3-cyclohexanedione: When 1,3-cyclohexanedione was used as a reactant in organic solvents, an increase in the equivalents of 1,3-cyclohexanedione relative to the reaction partner substrates did not enhance the reaction rates or even slowed the reactions.[6] This was unusual as reaction rates usually increase as the loading (and thus the concentration) of a reactant is increased. In organocatalytic and other catalytic reactions that use simple ketones (such as acetone and cyclohexane) as a reactant, the ketones are often used in excess (5 equivalents or more relative to the partner reactants).[7-9] The excess loadings of the simple ketones in the reactions are often desired and/or required to enhance the reaction rates and/or to obtain the desired products.[7-9] In our survey of the literature on the reactions of 1,3-cyclohexanedione derivatives reported by other research groups, we found that the

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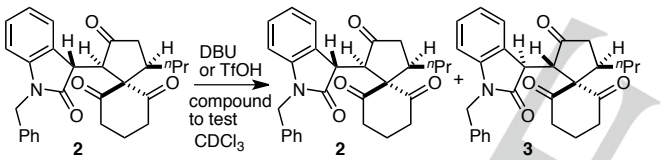
loading amounts of 1,3-cyclohexanedione were not in excess in most cases.[10,11] We reasoned that high loadings of 1,3-cycohexanedione might partially neutralize bases or acids depending on the reaction and that 1,3-cycohexanedione was essentially functioning as a buffering molecule in organic solvents. We hypothesized that the buffering function of 1,3-cyclohexanedione and related compounds could be used for adjusting conditions to control chemical events in non-aqueous solutions (Figure 1). The data reported here support that hypothesis.

Results and Discussion

Evaluation of 1,3-cyclohexanedione to inhibit acid- and base-catalyzed isomerization in organic solvents. To test our hypothesis that 1,3-cyclohexanedione has a buffering function and neutralizes both acids and bases in non-aqueous solutions, we first examined whether 1,3-cyclohexanedione (**1a**) inhibited the isomerization of **2**[12] to **3**[12,13] catalyzed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 25 °C and by trifluoromethanesulfonic acid (TfOH) at 60 °C in $CDCl_3$ (Table 1). Compound **2** is a useful synthetic intermediate in the formation of spirooxindole polycycles and is readily isomerized to **3** under acidic or basic conditions.[12,13] The ratio of **2** to **3** can be easily determined.[12,13]

Table 1. The effect of cyclohexane-1,3-dione (**1a**) in the DBU- and TfOH-catalyzed isomerization of **2** to **3**.[a]



entry	DBU or TfOH (condition)	compound to test	**2**:**3**
1	– (A)	–	>99.5:0.5
2	DBU (A)	–	24:76 (24:76)[b]
3	DBU (A)	**1a**	>99.5:0.5 (>99:1)[b], >99:1[c]
4	DBU (A)	CH_3COOH	>99:1
5	DBU (A)	$PhCH_2NH_2$	24:76
6	– (B)	–	>99.5:0.5
7	TfOH (B)	–	29:71
8	TfOH (B)	**1a**	>99.5:0.5
9	TfOH (B)	CH_3COOH	24:76
10	TfOH (B)	$PhCH_2NH_2$	96:4

[a] A mixture of **2** (**2**:**3** >99.5:0.5, 1.0 equiv) and the test compound (1.0 equiv) in $CDCl_3$ was stirred in the presence of DBU (0.01 equiv) under condition A or TfOH (0.1 equiv) under condition B, and the ratio of **2**:**3** was determined by ^1H NMR analysis at rt. Condition A: rt (25 °C) for 5 min; Condition B: 60 °C for 1 h. [b] Data after 3 days. [c] With DBU (0.1 equiv).

For the isomerization of **2** catalyzed by DBU, the ratio of compound **2** to compound **3** was 24:76 at 5 min after the addition of DBU (Table 1, entry 2). In the presence of compound **1a** (1.0 equivalent relative to **2**), compound **2** was unchanged or was not isomerized by the addition of DBU (Table 1, entry 3); formation of **3** was less than 1% even after 3 days in the presence of **1a**. Similarly, in the presence of **1a**, compound **2** did not isomerize to **3** by the addition of TfOH (Table 1, entry 8). Compound **1a** blocked both the DBU-catalyzed and the TfOH-catalyzed isomerization of **2**, indicating that **1a** neutralized both the base and the acid. Acetic acid suppressed only the base-catalyzed isomerization (Table 1, entries 4 and 9), and benzylamine suppressed only the acid-catalyzed isomerization (Table 1, entries 5 and 10); that is, acetic acid neutralized only the base, and benzylamine neutralized only the acid. Thus, the effect of compound **1a** on both the base and the acid in an organic solvent (Table 1, entries 3 and 8) is novel; the results suggest that compound **1a** has a buffering function in non-aqueous solutions.

Next, the capability of compound **1a** to neutralize various bases and acids in an organic solvent was analyzed by evaluating the effect of **1a** on the isomerization reaction of **2** to **3** catalyzed by various bases and acids (Supporting Information Table S1). Although the degree of isomerization catalyzed by the bases and acids varied depending on the base or acid, compound **1a** completely or almost completely suppressed the isomerization of **2** catalyzed by various bases such as potassium *tert*-butoxide and 1,1,3,3-tetramethylguanidine and by various acids such as methanesulfonic acid and *p*-toluenesulfonic acid. That is, the buffering function of compound **1a** was observed in non-aqueous solutions against various bases and acids.

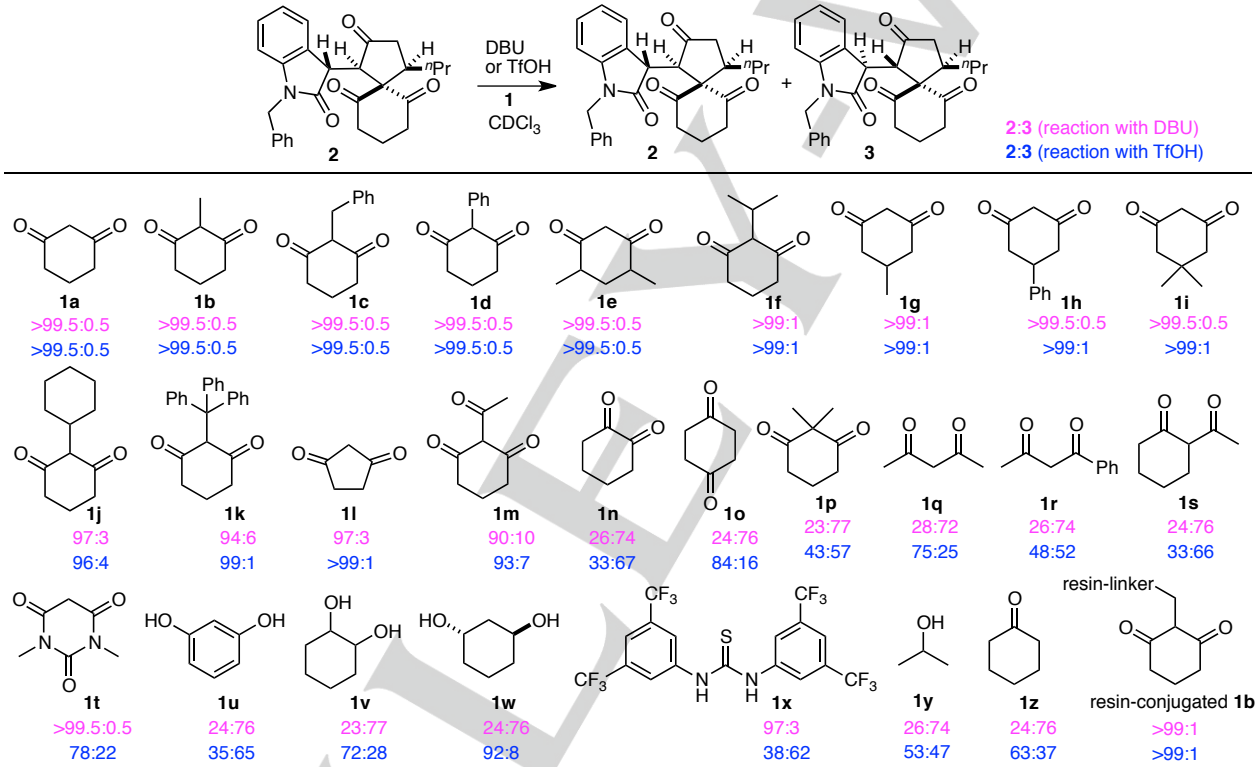
The scope of the inhibition function of **1a** on the isomerization of **2** to **3**, or the buffering function of **1a**, was also investigated in various solvents (Supporting Information Tables S2 and S3). In all solvents tested, the isomerization of **2** to **3** by DBU or by TfOH was observed to some degree in the absence of **1a**. In the presence of **1a**, no isomerization of **2** was detected in chloroform or in toluene. In acetonitrile, acetone, 2-propanol, 1,4-dioxane, and tetrahydrofuran (THF), the isomerization of **2** to **3** was almost completely suppressed (less than 5%) in the presence of **1a**. In dimethylsulfoxide (DMSO), the isomerization was partially inhibited by **1a**. In polar solvents, changes in the p*K*a values of the base, of the acid, and of **1a** from those in non-polar solvents may affect the neutralizing function of **1a**, or the formation of hydrogen bonds between solvent molecules and **1a** may prevent the interaction of **1a** with the base or acid, resulting in a reduction of the buffering function of **1a**. Although the buffering function of **1a** did not work in some polar solvents, compound **1a** buffered various organic solvents, including 2-propanol.

Compound **1a** also inhibited the acid- and base-catalyzed isomerization of **2** to **3** over a wide range of concentrations (Supporting Information Tables S4 and S5). When the DBU-catalyzed and TfOH-catalyzed isomerization reactions of **2** to **3** in $CDCl_3$ were analyzed over various concentrations of **2** in the presence of one equivalent of **1a**, the isomerization was

suppressed to less than 1% in the range from 0.003 M to 0.14 M. Further, even when **1a** was present at less than one equivalent relative to **2**, the buffering function of **1a** was observed (Supporting Information Tables S6 and S7). Further, the buffering function of **1a** was retained in the solution for more than 3 days, even at 60 °C, in the presence of TfOH (Supporting Information Table S8). Compound **1a** has a buffering function over a wide range of conditions in non-aqueous solutions.

Identification of other molecules that show buffering functions in non-aqueous solutions. We then sought to identify other molecules with buffering functions in organic solvents. We evaluated the effects of 1,3-cyclohexanedione derivatives and related molecules on the DBU-catalyzed and TfOH-catalyzed isomerization reactions of **2** to **3** (Table 2; see also SI Table S9). 1,3-Cyclohexanedione derivatives **1b**-**1e** completely inhibited the isomerization of **2**, as did **1a**, indicating that mono substitutions with methyl, benzyl, or phenyl groups at the 2-position of 1,3-cyclohexanedione and methyl substitutions at the 4- and 6-positions of 1,3-cyclohexanedione did not affect the buffering function (Table 2). In the presence of the 1,3-cyclohexanedione derivative bearing an isopropyl group at the 2-position (compound **1f**), the isomerization of **2** was less than 1%. The 1,3-cyclohexanedione derivatives with mono- or di-substitutions at the 5-position (compounds **1g**-**1i**) also inhibited the isomerization to a similar extent to **1f**. 1,3-Cyclohexanediones bearing cyclohexyl or triphenylmethyl groups, which are bulkier substituents than the isopropyl group, at the 2-position (compounds **1j** and **1k**, respectively) had a slightly reduced effect to inhibit the isomerization relative to **1f**. 1,3-Cyclohexanedione conjugated to resin beads (resin-conjugated **1b**) also inhibited the isomerization.

Table 2. Effects of 1,3-cyclohexanedione derivatives and related compounds **1** in the DBU-catalyzed and TfOH-catalyzed isomerization of **2** to **3**.[a]



[a] A solution of **2** (**2**:**3** >99.5:0.5, 1.0 equiv) and **1** (1.0 equiv) in $CDCl_3$ was stirred at room temperature (25 °C) for 5 min in the presence of DBU (0.01 equiv) or at 60 °C for 1 h in the presence of TfOH (0.1 equiv). The **2**:**3** ratio was determined by ^{1}H NMR analysis at room temperature and is shown in magenta for the reaction with DBU and in blue for the reaction with TfOH.

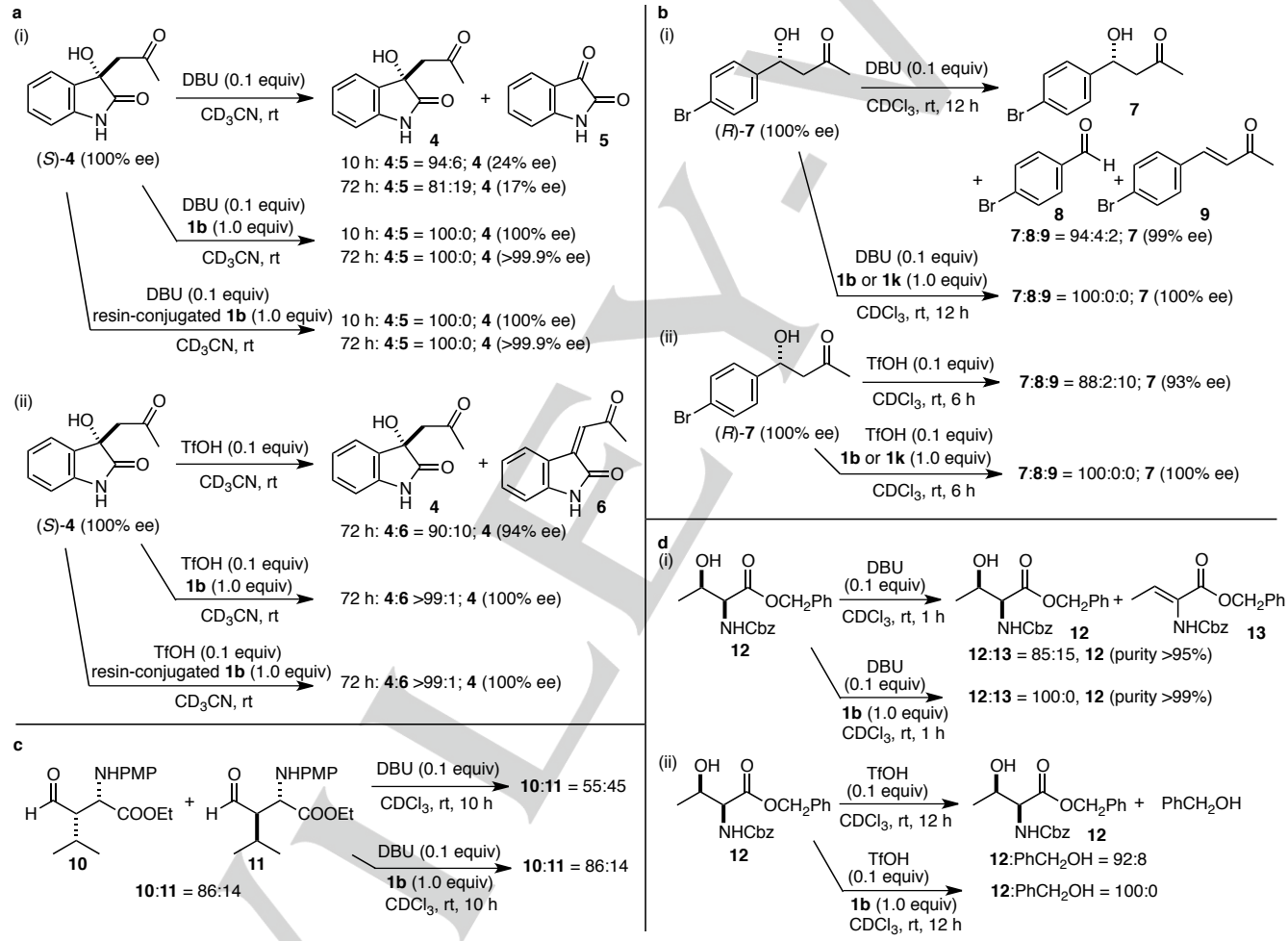
1,3-Cyclopentanedione (**1l**) and 2-acetyl-1,3-cyclohexanedione (**1m**) also had some buffering function in the DBU-catalyzed and TfOH-catalyzed isomerization reactions of **2**. On the other hand, 1,2-cyclohexanedione (**1n**), 1,4-cyclohexanedione (**1o**), and 2,2-dimethyl-1,3-cyclohexanedione (**1p**) did not have a buffering function to suppress the isomerization. Acyclic molecule 2,4-pentanedione (**1q**) also did not inhibit the isomerization. Molecules that are used as buffers in aqueous solutions, such as 2-[bis(2-hydroxy)amino]ethanesulfonic acid (BES), also did not inhibit the isomerization (Supporting Information Table S9).

These results indicate that compounds **1a**-**1e** are the most effective buffering molecules of the compounds tested. Compound **1a** can act as a nucleophile, as compound **2** is synthesized by the reaction with **1a**.[12] The use of compounds **1b**-**1d** may be suitable for providing buffering functions to avoid the use of **1a**, which has a reactive methylene group at the 2-position. Compounds **1f**, **1j**, and **1k** may also be suitable for various applications that require buffering function. Similarly, resin bead-attached 1,3-cyclohexanedione (resin-conjugated **1b**) may also be suitable for various uses to provide buffering functions.

Effects of 1,3-cyclohexanedione derivatives to inhibit acid- and base-catalyzed isomerization and decomposition. Compounds **1** were then evaluated in isomerization and decomposition reactions of aldol products or β-hydroxyketones (Scheme 1a, b). Aldol **4**[7p,14] is readily racemized under basic conditions,[15] and the basic conditions also cause a retro-aldol reaction of **4** to generate **5** (Scheme 1a(i)). The addition of 2-methyl-1,3-cyclohexanedione (**1b**) to the solution of aldol **4** blocked the base-catalyzed racemization and the retro-aldol reaction of **4** (Scheme 1a(i), Supporting Information Tables S10-S13). Resin-supported **1b** also completely inhibited the racemization and the decomposition. The addition of 2-pyridinecarboxylic acid, *N*,*N*-dimethylglycine, or glycine instead of **1a** was unable to prevent the racemization (Supporting Information Table S11). Aldol **4** was also racemized under acidic conditions, and the acidic conditions caused the formation of elimination product **6**[16] (Scheme 1a(ii)). Compound **1b** also prevented the acid-catalyzed racemization and the elimination reactions of **4** (Scheme 1a(ii)).

Similarly, 1,3-cyclohexanedione derivatives **1b** and **1k** also completely inhibited the racemization of β-hydroxyketone **7** and the decomposition of **7**[7d,e] that generated **8** and **9** (Scheme 1b).

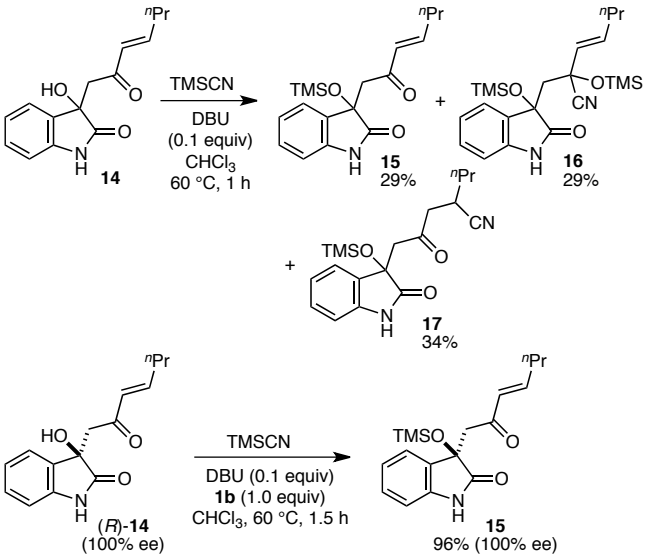
Isomerization of Mannich reaction product or amino aldehyde derivative **10** to **11**[8d] in the presence of DBU was also prevented by the addition of **1b** (Scheme 1c). Decomposition reactions of β-hydroxy-α-amino acid derivative or protected threonine derivative **12** by dehydration that resulted in the formation of **13** and by hydrolysis leading to the generation of benzyl alcohol were also inhibited by **1b** (Scheme 1d).



Scheme 1. Effects of 2-methyl-1,3-cyclohexanedione (**1b**) and related 1,3-cyclohexanedione derivatives on the isomerizations and decompositions of compounds. **a**, Effects on the racemization and decomposition of β-hydroxyketone derivative (aldol) **4**. **b**, Effects on the racemization and decomposition of β-hydroxyketone derivative (aldol) **7**. **c**, Effects on the isomerization of amino aldehyde derivatives (Mannich reaction products) **10** and **11**. **d**, Effects on the isomerization and decomposition of β-hydroxy α-amino acid derivative **12**.

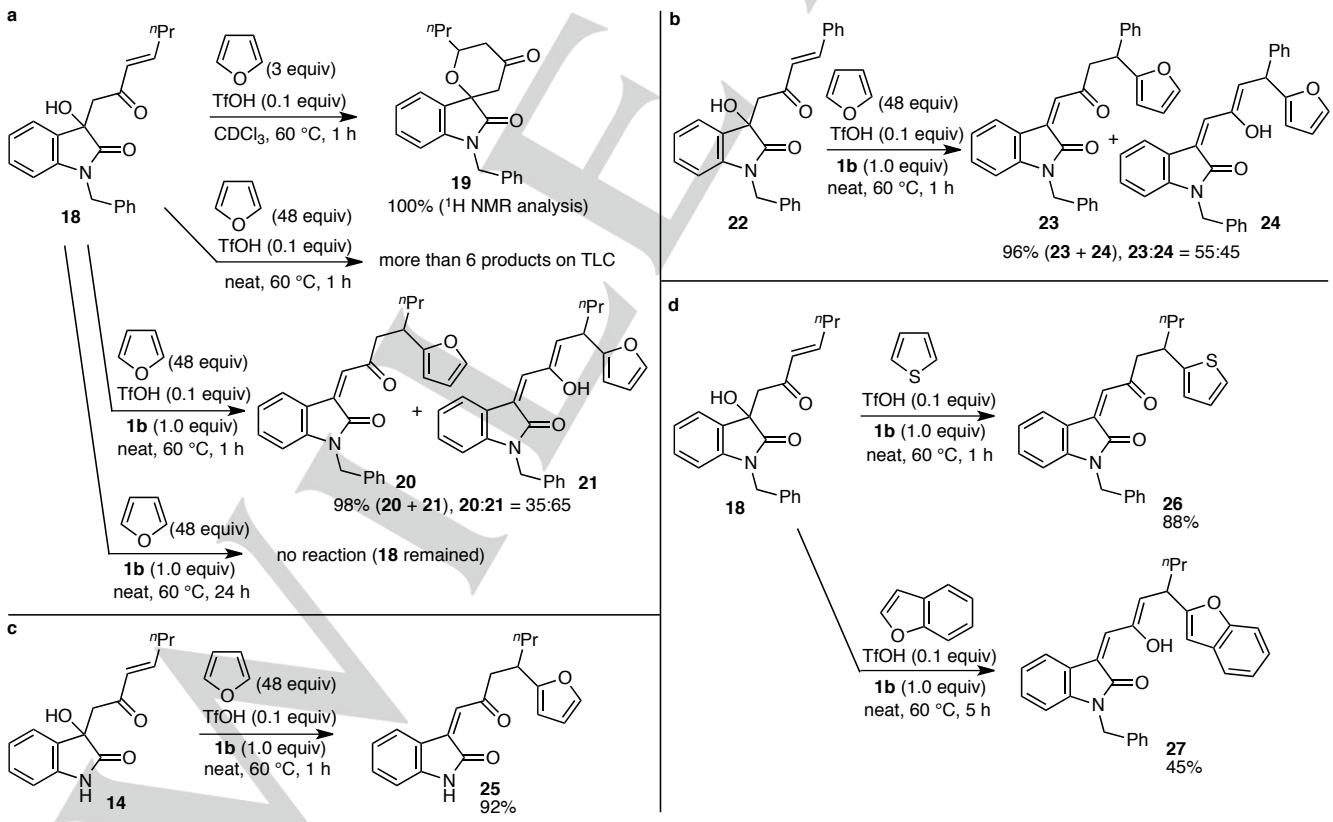
Effects of 1,3-cyclohexanedione derivatives to alter and control chemical transformations. The use of 2-methyl-1,3-cyclohexanedione (**1b**) was not limited to the prevention of isomerization and decomposition of compounds by buffering. The use of **1b** also altered the products of the chemical transformations (Schemes 2-4). For the protection of the hydroxy group of aldol **14**, when **14** was treated with TMSCN[17] in the presence of DBU as a base at 60 °C, products **15**, **16**, and **17** were obtained; selective formation of **15** in a high yield was not achieved (Scheme 2). When the same reaction was

performed but with the addition of **1b**, product **15** was obtained in a high yield, and the enantiopurity of the starting material was retained in the product (Scheme 2). In the absence of **1b**, the cyanide anion generated from TMSCN reacted with **14** to give **16** and **17**. In the presence of **1b**, the cyanide anion may be protonated, preventing it from acting as a nucleophile.

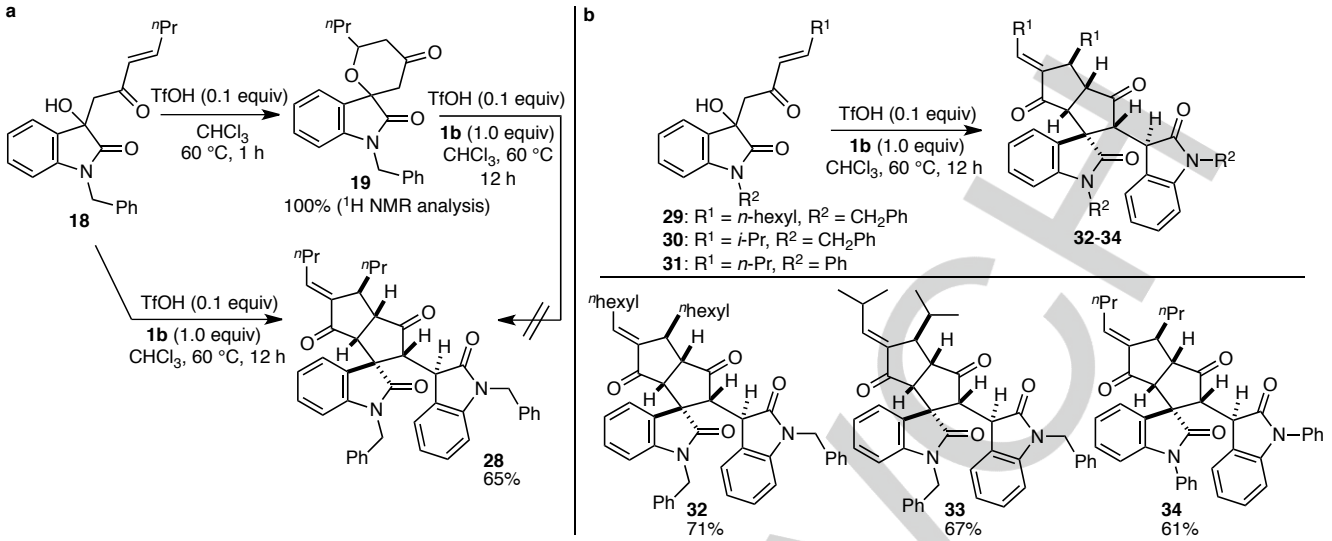


Scheme 2. Effects of 2-methyl-1,3-cyclohexanedione (**1b**) on chemical transformations; protection of hydroxy groups.

The reaction of β-hydroxyenone derivative **18** with furan was also altered by the addition of **1b** (Scheme 3a). Under acidic conditions, compound **18** was readily converted to oxa-Michael cyclization product **19**.[18] Neat conditions for the reaction of **18** with furan using TfOH as catalyst resulted in the formation of a complex mixture containing more than six new spots on TLC analysis; none of them were **20** or **21**. In contrast, the reaction under the same neat conditions but in the presence of **1b** afforded furan-added products **20** (keto form) and **21** (enol form) (Scheme 3a). Similarly, TfOH-catalyzed reactions of β-hydroxyenone derivative **22** with furan in the presence of **1b** afforded corresponding addition products **23** and **24** (Scheme 3b), and the reaction of **14** under these conditions yielded **25** (Scheme 3c). The TfOH-catalyzed reactions of **18** with thiophene or benzofuran in the presence of **1b** afforded corresponding addition products **26** and **27**, respectively (Scheme 3d).



Scheme 3. Effects of 2-methyl-1,3-cyclohexanedione (**1b**) on chemical transformations; addition reactions.



Scheme 4. Effects of 2-methyl-1,3-cyclohexanedione (**1b**) on chemical transformations; dimerization reactions of isatin aldol derivatives to afford spirooxindole octahydropentalenes.

Further, the use of the buffering function of **1b** allowed the synthesis of complex spirooxindole derivatives (Scheme 4). Spirooxindoles bearing fused ring systems are of interest for the development of pharmaceuticals and related molecules.[12,13,19] Concise construction of functionalized fused ring systems is a challenge,[12,13,19,20] however. Under acidic conditions with TfOH, compound **18** was transformed to oxa-cyclization product **19**.[18] The same reaction but with the addition of **1b** led to the dimerization of **18**, resulting in the formation of spirooxindole octahydropentalene derivative **28** (Scheme 4a). The relative stereochemistry of **28** was determined by X-ray crystal structural analysis.[21] Note that treatment of spirooxindole tetrahydropyran **19** under the conditions used for the formation of **28** (i.e., with TfOH and **1b**) did not form **28**. The treatment of **18** with **1b** alone without TfOH did not lead to the formation of **19** or **28**. Milder acids such as acetic acid and trifluoroacetic acid also did not catalyze the formation of **28** from **18**. These results suggest that the use of compound **1b** in the TfOH-catalyzed reaction tunes the reaction conditions for the formation of **28** or that compound **1b** makes the TfOH-catalyzed reaction environment less acidic allowing the formation of the enolate from **18**, which is necessary for the C-C bond formation that leads to the formation of **28**. Similarly, the TfOH-catalyzed reactions of **29**-**31** in the presence of **1b** afforded **32**-**34**, respectively (Scheme 4b). The buffering function of **1b** enabled the synthesis of complex spirooxindole octahydropentalenes.

Mechanisms underlying the buffering functions of 1,3-cyclohexanedione derivatives. The buffering functions of 1,3-cyclohexanedione derivatives may be explained by their p*K*a values, which are associated with the tautomerization equilibrium of these molecules and the fast dynamics of the equilibrium. The p*K*a of **1a** has been experimentally determined to be 10.3 in DMSO[22] and has been theoretically predicted to be 8.0 using MP2 and 5.5 using B3LYP.[23] It has also been reported that 1,3-cyclohexanedione has the proton affinity significantly higher than that of cyclohexanone.[24] Bases easily abstract the proton from 1,3-cyclohexanedione derivatives. The lone pair of the ketone carbonyl oxygen of 1,3-cyclohexanedione derivatives may act as a Lewis base to react with acids. Thus, acids and bases added to the reaction mixtures protonate and deprotonate the 1,3-cyclohexanedione derivatives, respectively. As a result, the acidic/basic environments of the solutions containing acids (such as TfOH) or bases (such as DBU) in the presence of 1,3-cyclohexanedione derivatives with buffering functions may be similar to those that the 1,3-cyclohexanedione derivatives provide, apart from the conditions that the acids (such as TfOH, the p*K*a is 0.3 in DMSO[6]) or bases (such as DBU) originally create.

Conclusion

We have developed strategies to control chemical reactions. The strategies use molecules that have buffering functions in non-aqueous solutions. We have demonstrated that 1,3-cyclohexanedione derivatives have buffering functions in non-aqueous solutions and that the buffering functions of these molecules in non-aqueous solutions can be used for tuning the conditions to control chemical events. Addition of the buffering molecule or its resin-conjugated version in storage solutions of molecules of interest can prevent decompositions and/or isomerizations of the molecules. To suppress decompositions and isomerizations of the molecules by using the buffering molecules that we have disclosed, there is no need to consider whether the decomposition and/or isomerization is caused by a base or an acid or which type of base or acid is causing the decomposition, isomerization, and/or racemization. Additionally, simply adding the buffering molecule to reaction mixtures can completely alter the pathways of the reactions. No such simple operations to control chemical reactions were demonstrated previously, to the best of our knowledge. By introducing the

concept of buffering in non-aqueous solutions, simple ways to control chemical reactions have been realized.

The buffering molecules suppress isomerization and decomposition reactions of various compounds and alter the products of chemical transformations in non-aqueous solutions, allowing access to products that are not generated in the absence of buffering molecules. The use of buffering molecules in non-aqueous solvents provides a strategy to control chemical reactions and expands the range of compounds that can be synthesized.

Acknowledgements

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Keywords: aldol reaction • organocatalysis • Michael addition • reaction control • spiro compounds

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Entry for the Table of Contents

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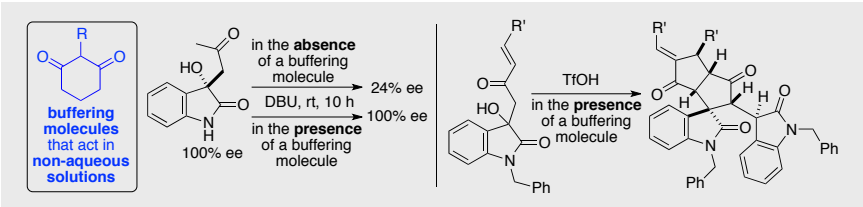

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Control of Chemical Reactions Using Molecules that Buffer Non-aqueous Solutions

A strategy to control chemical reactions was developed with the discovery that 1,3-cyclohexanone derivatives act as buffering molecules in non-aqueous solutions. With the buffering molecules, undesired isomerization and decomposition of molecules of interest were suppressed. The use of the buffering molecules altered the chemical transformation products and expanded the range of molecules that were able to be accessed.