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Construction of α,α-disubstituted α-Amino Acid Derivatives *via* aza-Morita-Baylis-Hillman Reactions of 2-Aminoacrylates with Activated Olefins

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A useful and convenient strategy for the synthesis of α,α-disubstituted α-amino acid (α-AA) derivatives via aza-Morita-Baylis-Hillman reaction of 2-aminoacrylates with activated olefins has been developed. A variety of α-AA derivatives containing an α-amino tertiary center were synthesized in good to excellent yields. The kinetic profiles and calculated methyl anion affinity (MAA) values were employed to rationalize the reactivities of different Michael acceptors used in the reaction.

Introduction

α,α-Disubstituted α-amino acids (α-AAs) are versatile building blocks for biologically and pharmacologically important compounds or natural products.[1] Numerous α-AAs such as selected examples in Figure 1 have demonstrated great bioactivities.[2] On the other hand, the introduction of α-AAs to the design of novel non-natural peptides and proteins can extremely enhance their pharmacological and biological capabilities.[3] Due to those unique characteristics of α-AAs and their derivatives, it is necessary to develop more synthetic strategies to construct these architectures that contain the desired core scaffolds. In the past few years, several methodologies have already been developed to access α-AAs and their derivatives, and the main synthetic methods have been summarized in Scheme 1 (previous work).[4] The first method is the further substitution of α-substituted amino acids or their derivatives.[5] Another strategy is the amination of secondary acids.[6] α-AAs and their derivatives can be easily obtained by the ring-opening of disubstituted azlactones and similar heterocyclic substrates.[7] The direct addition to ketoimines containing an ester group is also considered to be an efficient approach to access α-AAs.[8] Some special synthetic methods for the formation of α-AAs and their derivatives by the rearrangement of unique substrates or through a three-component reactions have been put forward as well.[9,10]

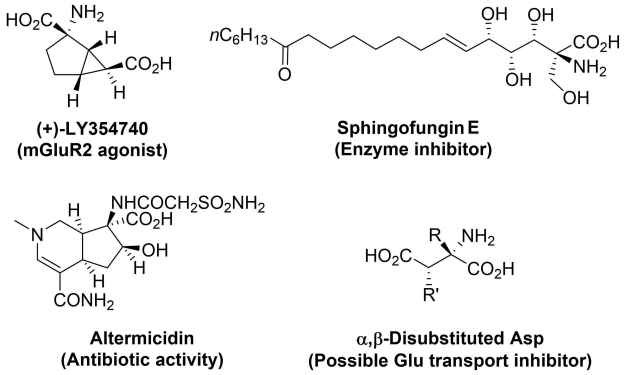

Figure 1. Representative bioactive molecules of α,α-disubstituted α-amino acids and their derivatives.

The aza version of the Morita-Baylis-Hillman (MBH) reaction, which is known as aza-MBH reaction, is a powerful and atom-economic tool for constructing α-aminocarbonyl compounds.[11] Extensive studies have probed the utility of aldimines to form α-amino-substituted products through aza-MBH reactions. However, as far as we know, reports on the synthesis of α-amino-disubstituted compounds through aza-MBH reaction of ketoimines are quite limited, which is probably due to the instability and the steric hindrance of the ketoimine moiety.[12] The ketoimine substrates used in those successful cases are mainly isatin-derived ketoimines or ketoimines containing electron-

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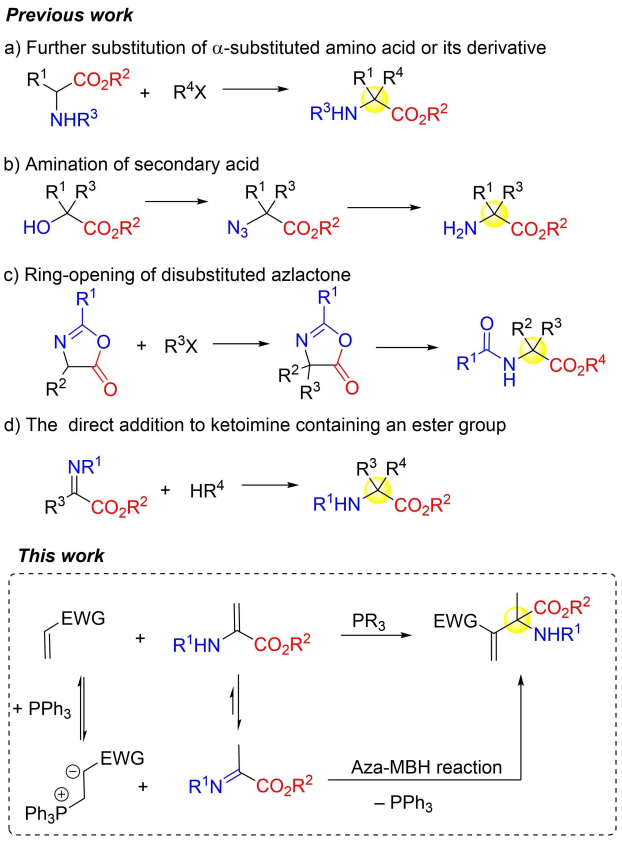


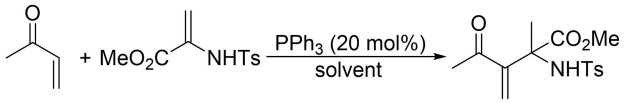
Scheme 1. Previous work and this work.

deficient groups, which will lead to great substrate limitations. To solve these problems, we now propose to employ a new type of ketoimine species. Inspired by the recent reports on 2-aminoacrylates together with the experimental phenomena about the tautomerization between 2-aminoacrylates and their imine forms, we assume that such kind of *in situ* generated ketoimine intermediate can be used as an active intermediate to participate in the aza-MBH reaction to produce the target α-AA derivatives as products.[13] Based on our previously successful studies on aza-MBH reactions,[14] we made a series of attempts of 2-aminoacrylates to react with methyl vinyl ketone (MVK). Herein, we wish to report a tertiary phosphine catalyzed aza-MBH reaction of 2-aminoacrylates with activated olefins, affording a series of α-AA derivatives under mild conditions and the studies on the reactivities of substrates.

Results and Discussion

To investigate the unprecedented aza-MBH reaction of 2-aminoacrylates and MVK, we first surveyed the reaction of 2-aminoacrylate **2a** with MVK **1a** in the presence of PPh_3 in DCM. The desired product **3aa** was obtained in 91% yield (Table 1, entry 1). To establish the optimal conditions for the reaction, several solvents, different proportions of **1a** and **2a**, catalyst loading and different catalysts have been examined as shown

Table 1. Optimization of the reaction conditions.



1a **2a** **3aa**

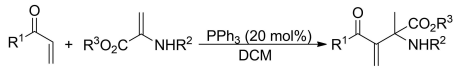
Entry[a]	1a [mmol]	2a [mmol]	Solvent	Yield [%][b]
1	0.2	0.1	DCM	91
2	0.2	0.1	THF	21
3	0.2	0.1	MeCN	18
4	0.2	0.1	PhMe	78
5	0.15	0.1	DCM	91
6	0.1	0.1	DCM	85
7[c]	0.15	0.1	DCM	83
8[d]	0.15	0.1	DCM	N.D

[a] Unless otherwise indicated, all reactions were carried out with **1a**, **2a** in solvent (1.0 mL) at room temperature in a reaction tube for 12 h. [b] Isolated yield. [c] 10 mol% PPh_3 was used. [d] DABCO instead of PPh_3.

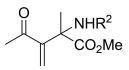
in Table 1. The screening of the solvents revealed that the reaction proceeded more smoothly in DCM, affording **3aa** in 91% yield (Table 1, entries 1–4). Changing the proportion of **1a** and **2a** from 2:1 to 1.5:1 had no obvious influence on the reaction. However, when the proportion was changed to 1:1, a decrease in yield occurred (Table 1, entries 5–6). Reducing the catalyst loading to 10 mol% also decreased the yield from 91% to 83% (Table 1, entry 7). No reaction occurred when DABCO was used instead of PPh_3 (Table 1, entry 8).

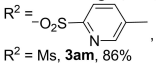
With the optimal conditions in hand, we next surveyed the substrate scope of this aza-MBH reaction by using various 2-aminoacrylates **2** to react with MVK. As shown in Table 2, we first investigated the effect of substituents on the aryl group of

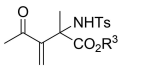
Table 2. Reaction of 2-aminoacrylate **2** with electron-deficient olefin **1**.[a,c]



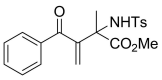
1 **2** **3**



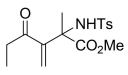
R^2 = Ts, **3aa**, 91%
R^2 = Bs, **3ab**, 68%[b]
R^2 = Ns, **3ac**, 56%[b]
R^2 = SO_2Ph(4-F), **3ad**, 81%[b]
R^2 = SO_2Ph(4-CN), **3ae**, 66%[b]
R^2 = SO_2Ph, **3af**, 85%
R^2 = SO_2Ph(4-*t*Bu), **3ag**, 90%
R^2 = SO_2Ph(4-OMe), **3ah**, 92%
R^2 = SO_2Ph(4-Cl), **3ai**,70%
R^2 = SO_2Ph(2,4,6-Me), **3aj**, 94%
R^2 =  , **3ak**, 61%
R^2 =  , **3al**, 43%
R^2 = Ms, **3am**, 86%
R^2 = Boc, no reaction
R^2 = Ac, no reaction



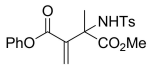
R^3 = Et, **3an**, 88%
R^3 = phenyl, **3ao**, 71%
R^3 = 2-naphthyl, **3ap**, 48%
R^3 = Bn, **3aq**, 92%



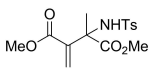
3ba, 45%



3ca, 82%



3da, 26% (85%[d])



3ea, no reaction

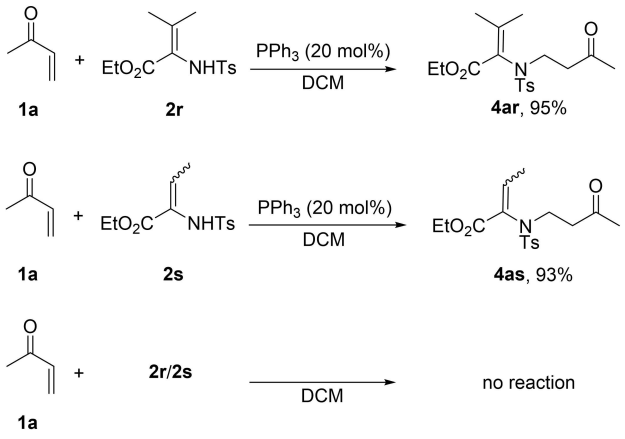
[a] Unless otherwise indicated, all reactions were carried out with **1** (0.2 mmol), **2** (0.3 mmol) and PPh_3 (0.04 mmol) in DCM (2.0 mL) at room temperature in a reaction tube for 12 h. [b] Toluene instead of DCM. [c] Isolated yield. [d] 0.2 mmol PPh_3 was used.

the benzenesulfonyl moiety for this aza-MBH reaction. Electron-donating groups including alkyl groups (substrates **2a**, **2g** and **2j**), alkoxy (substrate **2h**) group as well as H atom (substrate **2f**) were well tolerated in the reaction, giving the desired products in yields ranging from 85% to 92%. However, the introduction of electron-withdrawing groups to the aryl group of benzenesulfonyl group caused a large decrease in yield when the reaction was carried out in DCM. In these cases, the yields could be effectively improved by replacing the solvent with toluene (substrates **2b**, **2c**, **2d**, **2e** and **2i**). Subsequently, sulfonyl groups containing a heteroaromatic ring such as thiophene (substrate **2k**) and 5-methylpyridine (substrate **2l**) were tested; the required products could also be obtained in the yields of 61% and 43%, respectively. The reaction proceeded smoothly when the protecting group was a methylsulfonyl group (substrate **2m**); however, no reaction occurred when the protecting group was replaced with an acyl protecting group. To evaluate the effect of ester groups for this aza-MBH reaction, the methyl ester was replaced by ethyl ester (substrate **2n**), phenyl ester (substrate **2o**), 2-naphthyl ester (substrate **2p**) and benzyl ester (substrate **2q**). The corresponding products **3an**-**3aq** were produced in good to excellent yields ranging from 48% to 92%. The relatively low yield of product **3ap** containing a naphthyl ester moiety was probably due to ambient moisture leading to the hydrolysis of substrate.

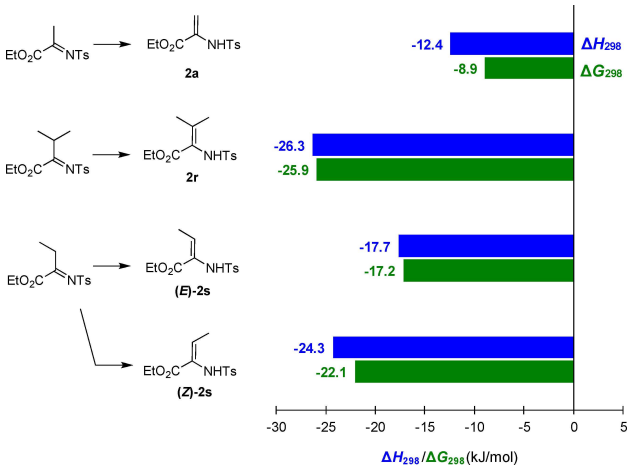
Furthermore, different kinds of electron-deficient olefins **1** were subsequently examined. Ethyl vinyl ketone (substrate **1c**, EVK) exhibited good reactivity, giving the desired product **3ca** in 82% yield. When phenyl vinyl ketone (substrate **1b**, PVK) was tested, the yield of corresponding product was greatly reduced. This was mainly owing to the self-polymerization of PVK. Compared with PVK, phenyl acrylate (substrate **1d**) showed lower reactivity in this case, but the yield was greatly increased when one equivalent of PPh_3 was used. The reaction could not take place when methyl acrylate (substrate **1e**) was used.

Non-terminal olefin substrates **2r** and **2s** showed completely different reactivities. Instead of aza-MBH reactions, a Michael addition type reaction took place, giving the Michael type products **4ar** and **4as** in almost equivalent yield, and no reactions occurred in the absence of phosphine catalyst (Scheme 2).

The relative stabilities of imine and enamine tautomers of **2** may contribute to their reactivity differences. The relative energies of imine and enamine tautomers of substrates **2a**, **2r** and **2s** were thus calculated at the SMD(DCM)/B3LYP/6-311++G(3df,2pd)//B3LYP/6-31G(d) level of theory, and the results are shown in Scheme 3. The free energy difference in DCM between the enamine and the imine tautomer of **2a** amounts to −8.9 kJ/mol, indicating that the enamine tautomer of **2a** is more stable at ambient temperature. However, this stability difference is small enough for the imine tautomer to still form sufficiently under our standard reaction conditions to undergo the aza-MBH reaction. As for non-terminal olefin substrates **2r** and **2s**, the free energy differences in DCM between the enamine and imine tautomers are −25.9 kJ/mol, −17.2 kJ/mol (*E*-isomer) and −22.1 kJ/mol (*Z*-isomer), respectively. These results indicate that the enamine tautomer forms of non-terminal olefin substrates **2r** and **2s** are much more stable, thus they are difficult to tautomerize to the imine form under our standard reaction conditions, which may account for why they could not undergo aza-MBH reactions.



Scheme 2. The reactions using non-terminal olefin substrates.



Scheme 3. Relative energies of imine and enamine tautomers of substrates **2a**, **2r** and **2s** as calculated at the SMD(DCM)/B3LYP/6-311++G(3df,2pd)//B3LYP/6-31G(d) level of theory.

Time-dependent NMR studies were carried out to explain the reactivities of different Michael acceptors used in this reaction, and the results were further correlated with the calculated methyl anion affinity (MAA) values. In a recent report[15] it was shown that calculated MAA values can serve as indicators of the electrophilicities of Michael acceptors. The reactions of 2-aminoacrylate **2a** with Michael acceptors **1a**, **1c** and **1d** were investigated in the presence of 50 mol% PPh_3 in $CDCl_3$, and the kinetic profiles are shown in Figure 2 (the kinetic profiles were also investigated using 20 mol% PPh_3, see SI). The experimental results were basically consistent with the results of quantum-chemical calculations, except for **1d** (Figure 3). The methyl acrylate (substrate **1e**), having the lowest MAA value is only weakly electrophilic; indeed, no aza-MBH reaction was observed experimentally using **1e** as substrate (see Table 2).

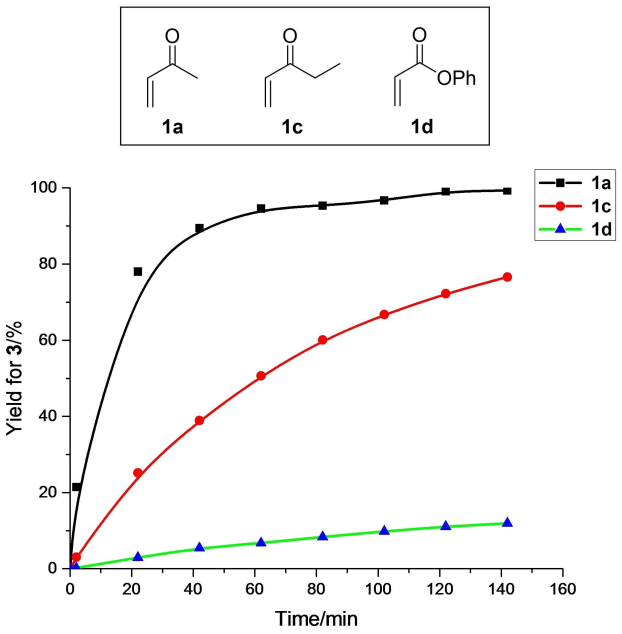


Figure 2. Time-dependent ^{1}H-NMR spectroscopic monitoring of the aza-MBH reaction.

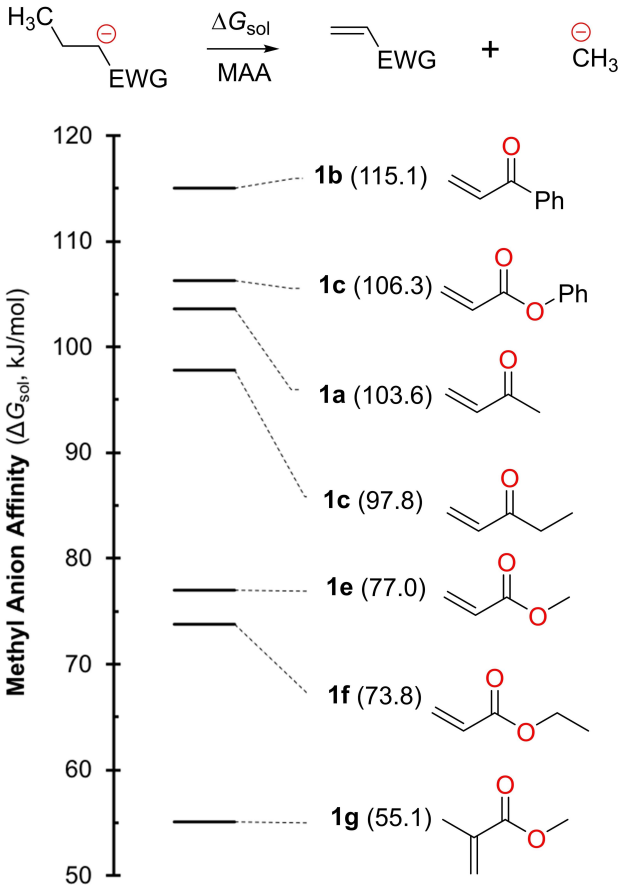


Figure 3. Methyl anion affinity (MAA) values for selected Michael acceptors as calculated at the SMD(DCM)/B3LYP/6-311++G(3df,2pd)//B3LYP/6-31G(d) level of theory.

The kinetic curves of MVK (**1a**) and EVK (**1c**) also fit the calculation results well. MVK (**1a**), having considerably higher MAA and electrophilicity *E* than methyl acrylate (**1e**) now reacts within minutes in the aza-MBH reaction. The slightly lower MAA of ethyl vinyl ketone (**1c**) than that of **1a** is in accord with the observed more sluggish reactions of **1c** in the aza-MBH reaction when compared to **1a** (Figure 2). Several hours of reaction time were needed at ambient temperature to achieve high yields when starting from **1c**. This observation also matches with reported reactivity differences of methyl vinyl ketone (MVK, **1a**) and ethyl vinyl ketone (EVK, **1c**) in Michael additions with methoxide ions (in MeOH)[16] and glutathione (in water),[17] which consistently show that MVK is about twice as electrophilic as EVK in analogous reactions. However, phenyl acrylate (substrate **1d**), the most potent electrophile among the tested Michael acceptors, gave relatively low yields. This may indicate that for **1d** the initial C−C σ-bond formation step is not rate-determining for the overall process and the electrophilicity of Michael acceptors ceases to serve as a useful indicator in this situation.

Conclusions

In summary, we have developed a novel tertiary phosphine-catalyzed aza-MBH reaction of 2-aminoacrylates with MVK, affording the corresponding α-AA derivatives under mild conditions. A new type of *in situ* generated ketoimine is introduced to the aza-MBH reaction for the first time and has been powerfully proven to be the key intermediate of the reaction, which provides a new way of thinking about constructing biologically and pharmacologically important α-AA derivatives. The kinetic profiles and the calculations of methyl anion affinity (MAA) values reveal that the electrophilicities of Michael acceptors effectively influence the overall reaction rate. Further studies on the asymmetric catalytic version of this reaction are currently underway in our laboratory.

Experimental Section

General information: Melting points were determined on a digital melting point apparatus and temperatures were uncorrected. ^{1}H NMR spectra were measured on a Bruker AC 400 (400 MHz) spectrometer. Data were reported as follows: chemical shifts in ppm referenced to the internal solvent signal (peak at 7.26 ppm in the case of $CDCl_3$), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double-doublet, m = multiplet), coupling constants (Hz), and assignment. ^{13}C NMR spectra were measured on a Bruker AC 400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from the internal solvent signal (peak at 77 ppm in the case of $CDCl_3$). Infrared spectra were recorded on a Perkin-Elmer PE-983 spectrometer with absorption in cm^{-1}. Flash column chromatography was performed using 300–400 mesh silica gel. For thin-layer chromatography (TLC), silica gel plates (Huanghai GF254) were used. Mass spectra were recorded by ESI, and HRMS was measured on a HP-5989 instrument. The employed solvents were dried by standard methods when

necessary. Commercially obtained reagents were used without further purification.

General Procedure for the Preparation of 2: To a 100 ml round-bottom flask equipped with a Dean-Stark trap was charged with *p*-$TsNH_2$ (1.71 g, 10 mmol), methyl pyruvate (9.19 g, 9 mmol), *p*-TsOH (2 mg, 0.01 mmol), 4-methoxyphenol (1.2 mg, 0.01 mmol) and toluene (40 ml). The stirred mixture was heated under reflux for 24 hours then the solvent was removed under reduced pressure and the residue was purified by a flash column chromatography (SiO_2) to give the corresponding product **2a**.Substrates **2b**–**2q** were prepared according to the above method.

General Procedure for the Preparation of 3: To a 20 mL flame-dried tube was charged with methyl vinyl ketone **1** (0.3 mmol, 1.5 equiv), 2-aminoacrylates **2** (0.2 mmol, 1.0 equiv) and PPh_3 (0.04 mmol, 0.2 equiv). Then, 2.0 mL DCM was added into the tube. The reaction mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the residue was purified by a flash column chromatography (SiO_2) to give the corresponding product **3**.

General Procedure for the Preparation of 4: To a 20 mL flame-dried tube was charged with methyl vinyl ketone **1a** (0.3 mmol, 1.5 equiv), 2-aminoacrylates **2** (0.2 mmol, 1.0 equiv) and PPh_3 (0.04 mmol, 0.2 equiv). Then, 2.0 mL DCM was added into the tube. The reaction mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the residue was purified by a flash column chromatography (SiO_2) to give the corresponding product **4**.

Acknowledgements

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Keywords: phosphine catalysis · aza-MBH reaction · α,α-disubstituted · α-amino acids · methyl anion affinity values

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