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Organocatalytic Enantioselective Diels−Alder Reaction of Dienes with α-(*N*,*N*-Diacylamino)acroleins

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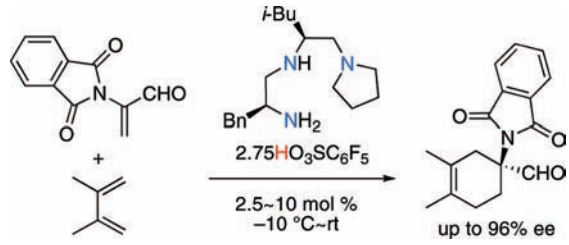
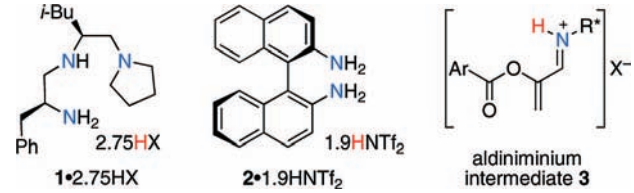
ABSTRACT



Catalytic and highly enantioselective Diels−Alder reaction of cyclic and acyclic dienes with α-phthalimidoacroleins provides cyclic α-quaternary α-amino acid precursors. The conformationally flexible chiral ammonium salt of H-L-Phe-L-Leu-N(CH_2CH_2)$_2$-reduced triamine with pentafluorobenzensulfonic acid is very effective as an asymmetric catalyst for the Diels−Alder reaction.

Optically active α-amino acids as well as α-hydroxy acids are valuable chiral synthons that bear two functional groups. We have recently developed organocatalytic enantioselective Diels−Alder (DA)[1a−c] and [2 + 2][1d] cycloaddition reactions with α-acyloxyacroleins based on acid−base combination chemistry.[2,3] H-L-Phe-L-Leu-N(CH_2CH_2)$_2$-reduced triamine (**1**)•2.75HX and (*R*)-2,2′-diamino-1,1′-binaphthyl (**2**)•1.9HNTf$_2$ activate α-acyloxyacroleins as an aldiminium cation intermediate **3** to react with dienes or monoalkenes to provide cycloaliphatic α-quaternary[4] α-hydroxy acid equivalents with high enantioselectivity (Chart 1).[2] In contrast, to the best of our knowledge, there has been only one example of the enantioselective DA reaction with α-(*N*-acylamino)acrolein derivatives: in 1991, Cativiela et al. reported the Diels−Alder reaction of cyclopentadiene with methyl α-(*N*-acetylamino)acrylate promoted by 50 mol % of chiral titanium(IV) Lewis acid (64% yield, 78% exo, 70%

Chart 1. Chiral Organoammonium Salt Catalysts **1**•2.75HX and **2**•HNTf$_2$ and Their Aldiminium Intermediate **3** for Cycloaddition Reactions with α-(Acyloxy)acroleins



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(2) (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244. (b) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458–2459. For our account, see: (c) Ishihara, K.; Sakakura, A.; Hatano, M. *Synlett* **2007**, 686–703. For a recent review of iminium catalysis, see: (d) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416–5470.

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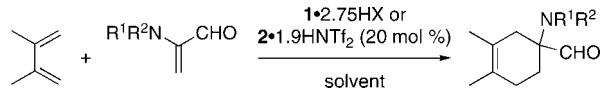
Table 1. DA Reaction of 2,3-Dimethylbutadiene with α-(*N*-Acylamino)- or α-(*N*,*N*-Diacylamino)acroleins Catalyzed by **1**•2.75HX or **2**•1.9HNTf$_2$[a]



entry	Dienophile (R^1, R^2)	catalyst	Conditions solvent, *T* (°C), t (h)	product Yield (%)[b]	product Ee (%)[c]
1[d]	**4** (Bz, H)	**1**•2.75$C_6F_5SO_3H$	$EtNO_2$, 0, 36 to rt, 24	59	81
2	**5a** (phthal)	**1**•2.75$C_6F_5SO_3H$	**$EtNO_2$, rt, 4.5**	**97**	**92**
3	**5a** (phthal)	**1**•2.75$C_6F_5SO_3H$	$MeNO_2$, rt, 4.5	77	89
4	**5a** (phthal)	**1**•2.75$C_6F_5SO_3H$	MeCN, rt, 4.5	86	89
5	**5a** (phthal)	**1**•2.75$C_6F_5SO_3H$	THF, rt, 4.5	71	93
6	**5a** (phthal)	**1**•2.75$C_6F_5SO_3H$	DME, rt, 4.5	74	94
7	**5a** (phthal)	**1**•2.75$C_6F_5SO_3H$	DMF, rt, 4.5	41	74
8	**5a** (phthal)	**1**•2.75CF_3CO_2H	$EtNO_2$, rt, 84	43	42
9	**5a** (phthal)	**1**•2.75$ArSO_3H$[e]	$EtNO_2$, rt, 4.5	91	90
10	**5a** (phthal)	**1**•2.75TfOH	$EtNO_2$, rt, 4.5	90	89
11	**5a** (phthal)	**1**•2.75$HNTf_2$	$EtNO_2$, rt, 3	<5[f]	
12	**5a** (phthal)	**2**•1.9$HNTf_2$	EtCN, −78, 31	<5[f]	
13	**5a** (phthal)	**2**•1.9$C_6F_5SO_3H$	$EtNO_2$, −78, 24	0	

[a] Unless otherwise noted, the reaction of 2,3-dimethylbutadiene (0.6 mmol) with α-(*N*-acyl- or *N*,*N*-diacylamino)acroleins (0.5 mmol) was carried out in a solvent (0.5 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] 2,3-Dimethylbutadiene (1.0 mmol) was used in $EtNO_2$ (156 μL). [e] $ArSO_3H$ = 2,4-$(NO_2)_2C_6H_3SO_3H$. [f] A complex mixture was obtained.

ee (exo)).[5,6] We describe here the catalytic and highly enantioselective DA reaction of dienes with α-(*N*,*N*-diacylamino)- or α-(*N*-acylamino)acroleins to give optically active cyclic α-quaternary[4] α-amino acid precursors. Conformationally constrained α-amino acids are valuable in biochemistry as modified peptides, enzyme inhibitors, and ligands for probing receptor recognition.[5−7]

In an initial investigation, the DA reaction of 2,3-dimethylbutadiene with α-(*N*-benzoylamino)acrolein (**4**)[8] was examined in nitroethane in the presence of 20 mol % of **1**•2.75$C_6F_5SO_3H$. The reaction was slow even at room temperature, and stirring for 24 h led to the desired cycloadduct with 81% ee in 59% yield (Table 1, entry 1). Next, α-phthalimidoacrolein (**5a**) was examined instead of **4** under the same conditions as above. Both the reactivity and the enantioselectivity were increased, and stirring at room temperature for 4.5 h led to the desired cycloadduct (**6a**) with 92% ee in 97% yield (entry 2). Next, the solvent effect was investigated (entries 2−7): most aprotic polar solvents except for DMF were suitable, and the best result was observed with nitroethane. Brønsted acids were also examined as HX of **1**•2.75HX (entries 2, 8−11): most sulfonic acids were effective, but on the other hand, trifluoroacetic acid and superacidic triflylimide were not suitable. Another candidate, **2**•1.9$HNTf_2$, did not catalyze the DA reaction with **5a** because **2** irreversibly reacted with **5a** even at −78 °C in the presence of triflylimide (entry 12). **2**•1.9$C_6F_5SO_3H$ did not catalyze the DA reaction with **5a** at −78 °C (entry 13) and did not induce high enantioselectivity at room temperature.

The absolute configuration of cycloadduct **6a**, which was obtained as a major enantiomer in Table 1, was determined to be (*S*) by X-ray crystallographic analysis, as shown in Figure 1.

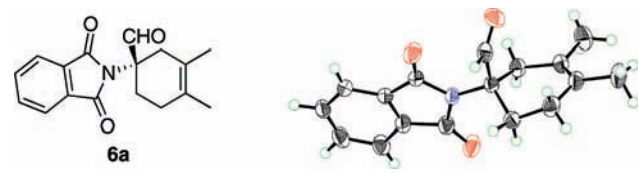


Figure 1. ORTEP illustration of (*S*)-**6a** with thermal ellipsoids drawn at the 50% probability level (Flack parameter = 0.1228).

α-Phthalimidoacrolein **5a**, which was a novel compound, was prepared by a one-pot procedure of dehydrative condensation between 2-amino-1,3-propanediol and phthalic

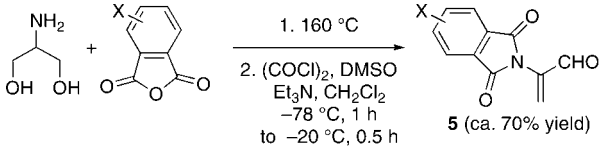
(4) α,α-Dialkyl-substituted α-hydroxy- or α-amino acids are often called "α-quaternary α-hydroxy or α-amino acids". See refs 5–7.

(5) Cativiela, C.; López, P.; Mayoral, J. A. *Tetrahedron: Asymmetry* **1991**, *2*, 1295–1304.

(6) For the diastereoselective DA reaction with chiral α-amino acrylic acid derivatives, see: (a) Cativiela, C.; López, P.; Mayoral, J. A. *Tetrahedron: Asymmetry* 1990, *1*, 61−64; (b) 1990, *1*, 379−388; (c) 1991, *2*, 449−456. (d) Sankhavasi, W.; Kohmoto, S.; Yamamoto, M.; Nishio, T.; Iida, I.; Yamada, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 935–937. (e) Cativiela, C.; Carcía, J. I.; Mayoral, J. A.; Pires, E.; Royo, A. J.; Figueras, F. *Appl. Catal. A-Gen.* **1995**, *131*, 159–166. (f) Cativiela, C.; Carcía, J. I.; Mayoral, J. A.; Pires, E.; Royo, A. J.; Figueras, F. *Tetrahedron* **1997**, *51*, 1295–1300. (g) Chinchilla, R.; Favello, L. R.; Galindo, N.; Nájera, C. *Tetrahedron: Asymmetry* **1999**, *20*, 821–825. (h) Abellán, T.; Nájera, C.; Sansano, J. M. *Tetrahedron: Asymmetry* **2000**, *11*, 1051–1055. (i) Chinchilla, R.; Falvello, L. R.; Galindo, N.; Nájera, C. *J. Org. Chem.* **2000**, *65*, 3034–3041. (j) Urkett, B.; Chai, C. L. L. *Tetrahedron Lett.* **2001**, *42*, 2239–2242. (k) Abellán, T.; Mancheño, B.; Nájera, C.; Sansano, J. M. *Tetrahedron* **2001**, *57*, 6627–6640. (l) Caputo, F.; Clerici, F.; Gelmi, M. L.; Pellegrino, S.; Pocar, D. *Tetrahedron: Asymmetry* **2006**, *17*, 1430–1436. (m) Cernak, T. A.; Gleason, J. L. *J. Org. Chem.* **2008**, *73*, 102–110.

anhydride and subsequent oxidative dehydration under Swern conditions (Scheme 1).[8] Other substituted α-phthalimidoacroleins **5** were synthesized in the same manner as **5a**.

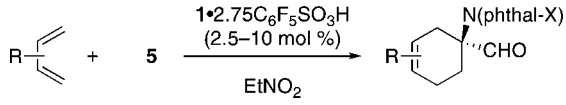
Scheme 1. One-pot Synthesis of **5**

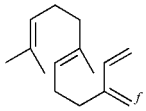
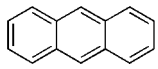


To explore the generality and scope of the **1**•2.75$C_6F_5SO_3H$-induced enantioselective DA reaction with **5a**, representative dienes were examined with 2.5−10 mol % catalyst loading in nitroethane at −10 °C to rt (Table 2). The enantioselectivity in the initial model reaction of 2,3-dimethylbutadiene with **5a** was further increased to 96% ee (entry 1). Isoprene, 2-phenylbutadiene, myrcene, and (*E*)-*β*-farnesene also reacted smoothly with **5a** to give the desired 4-alkyl-substituted cyclohex-3-enecarboxaldehydes **7a**−**10a** with >99% regioselectivity and 88−94% ee (entries 3−6). Although butadiene was less reactive than substituted ones, DA adduct **11a** was obtained in 55% yield with 83% ee (entry 7). The reaction of cyclopentadiene with α-(tetrafluorophthalimido)acrolein (**5b**) gave *endo*-formylbicycloadduct **12b** with 72% ds and 90% ee (entry 9). Anthracene, which was much less reactive, was also usable as a diene, although the chemical yield and enantioselectivity were moderate (entry 10).

Phthalimido groups of DA adducts **6**−**13** were deprotected in high yield by the treatment with hydrazine after conversion to the corresponding methyl esters (Scheme 2). Norbornene derivatives are particularly valuable as important optically active synthetic intermediates of bioactive alkaloids such as norbornene-2-amino-2-methanol derivatives[9] and (−)-altemicidin.[10]

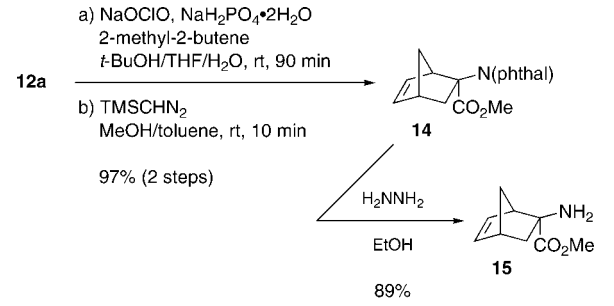
Table 2. Enantioselective DA Reaction of Dienes with **5**[a]



no.	diene	**5**	cat. (mol %)	conditions: concn (*M*), temp (°C), t (h)	product: yield (%)[b]	*endo*:*exo*	*ee* (%)[c]
1		**5a**	10	0.7, 0, 32	**6a**, 82	–	96 (*S*)
2		**5a**	2.5	1, rt, 48	**6a**, 91	–	92 (*S*)
3		**5a**	10	0.7, 0, 48	**7a**, 82	>99:1[d]	94
4[e]		**5a**	10	1, 0, 48	**8a**, 80	>99:1[d]	88
5		**5a**	10	0.7, 0, 48	**9a**, 73	>99:1[d]	94
6		**5a**	10	1, 0, 48	**10a**, 89	>99:1[d]	94
7		**5a**	10	1, rt, 48	**11a**, 55	–	83
8[e]		**5a**	10[g]	1, 0, 36	**12a**, 86	62:38	87[h]
9[e]		**5b**	10	1, –10, 84	**12b**, 73	72:28[i]	90 (2*S*)[h,i]
10		**5a**	10	1, rt, 11[j]	**13a**, 52	–	67

[a] Unless otherwise noted, the reaction of diene (0.6 mmol) with **5** (0.5 mmol) was carried out in $EtNO_2$. [b] Isolated yield. [c] Ee of major diastereomer determined by chiral HPLC analysis. [d] Ratio of 4- and 3-alkyl isomers. The stereochemistry of **8a** was determined by X-ray diffraction analysis. [e] THF was used instead of $EtNO_2$. [f] Diene (2 equiv) was used. [g] H-L-[3-(2-Naph)Ala]-L-Leu-N(CH_2CH_2)$_2$-reduced triamine was used instead of **1**. [h] 54% ee (*exo*-**12a**), 57% ee (*exo*-**12b**). [i] The relative and absolute stereochemistries of major diastereomer of **12b** were determined by X-ray diffraction analysis after its derivation to (*R*)-*N*-phenylethylamide. [j] 11 days.

Scheme 2. Deprotection of the Phthalimido Group of **12a**



Considering that **1**•2$C_6F_5SO_3H$ was much less active than **1**•2.75$C_6F_5SO_3H$ as a catalyst for the DA reaction of dienes with **5** as well as α-(acyloxy)acroleins,[1a,d] we assumed that **1**•3$C_6F_5SO_3H$ might be a real active catalyst, which would activate **5b** as aldiminium salt (**16**) with **1**•3$C_6F_5SO_3H$.[11] The (*Z*)-isomeric preference of **16** was supposed based on theoretical calculations of geometries of its analogous aldiminium salt (**17**) derived from α-maleimidoacrolein and

(7) (a) Clerici, F.; Gelmi, M. L.; Gambini, A. *J. Org. Chem.* **1999**, *64*, 5764–5767. (b) Kotha, S.; Ganesh, T.; Ghosh, A. K. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1755–1757. (c) Clerici, F.; Gelmi, M. L.; Gambini, A.; Nava, D. *Tetrahedron* **2001**, *57*, 6429–6438. (d) Yang, B. V.; Doweyko, L. M. *Tetrahedron Lett.* **2005**, *46*, 2857–2860. For a review of the stereoselective synthesis of cyclic tertiary α-amino acids, see: (e) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645–732.

(8) For preparation of **4**, see: Harada, H.; Morie, T.; Hirokawa, Y.; Kato, S. *Chem. Pharm. Bull.* **1996**, *44*, 2205–2212.

(9) (a) Iwasaki, T.; Yamazaki, H.; Nishitani, T.; Sato, T. *Chem. Pharm. Bull.* **1991**, *39*, 527–529. (b) Yamazaki, H.; Horikawa, H.; Nishitani, T.; Iwasaki, T.; Nosaka, K.; Tamaki, H. *Chem. Pharm. Bull.* **1992**, *40*, 102–108.

(10) Kende; Liu, K.; Jos Brands, K. M. *J. Am. Chem. Soc.* **1995**, *117*, 10597–10598.

(11) In our previous papers,[1a,d] it was assumed that (*Z*)-aldiminium salt derived from **1**•2HX and α-(acyloxy)acrolain would be a key intermediate. However, an aldiminium salt derived from **1**•3HX and α-(acyloxy)acrolain may be more favorable. Further studies are in progress and will be reported in the near future.

H-L-Phe-L-Leu-NMe_2-reduced triamine·3HCl.[12] The geometries of **17** were optimized at DFT calculations with B3LYP,[13] using the 6-31+G(d,p) basis set (Figure 2). After

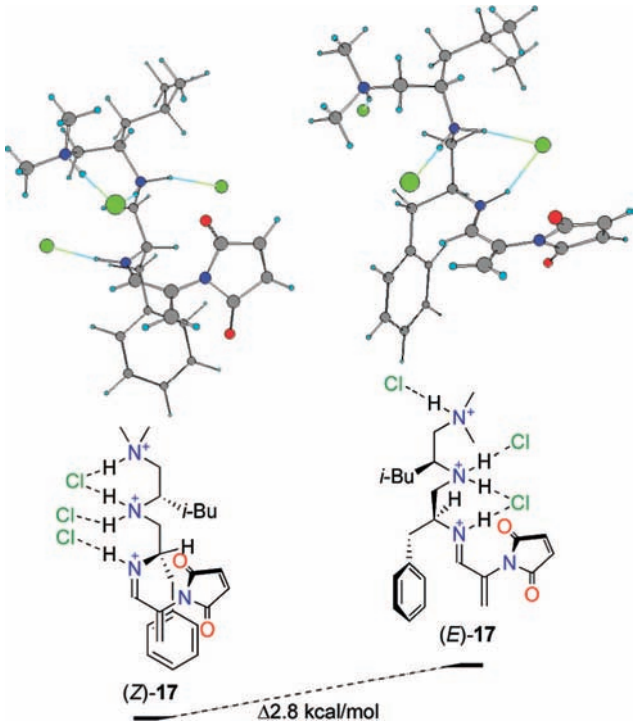


Figure 2. Relative energy defference between (*E*)- and (*Z*)-geometries of aldiminium salt **17** based on theoretical calculations.

satisfactory geometry optimization, the vibrational spectrum of each species was calculated. As shown in Figure 2, the relative energy of (*Z*)-**17** is 2.8 kcal/mol lower than that of (*E*)-**17**, and the *re*-face of the enimide moiety of (*Z*)-**17** is sterically shielded by the benzyl substituent.

Cyclopentadiene should approach enantioselectively the *si* face of the electron-deficient enimide moiety to give *endo*-(2*S*)-**12b** as a major isomeric product. Thus, as well as the (*Z*)-isomeric preference of **17**, it was expected that (*Z*)-transition-state (TS) assembly **18** would be preferred to (*E*)-TS-**18** (Figure 3).

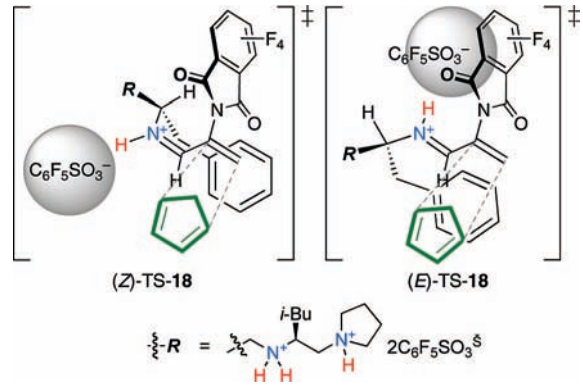


Figure 3. Possible transition-state assemblies (*Z*)-**18** and (*E*)-**18**.

In summary, we have developed a catalytic and highly enantioselective DA reaction of dienes with **5** to provide cyclic α-quaternary[4] α-amino acid precursors for the first time.[5] Chiral triamine **1**, which is conformationally more flexible than **2**, could be used as a catalyst ligand for cycloadditions for not only α-acyloxyacroleins but also **5**. Further mechanistic studies are in progress and will be reported in the near future.

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Supporting Information Available: Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Theoretical calculations were performed using the Gaussian 03 programs. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford CT, 2004.

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