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Nickel-Catalyzed Cyanoalkylation of Ketone Derivatives

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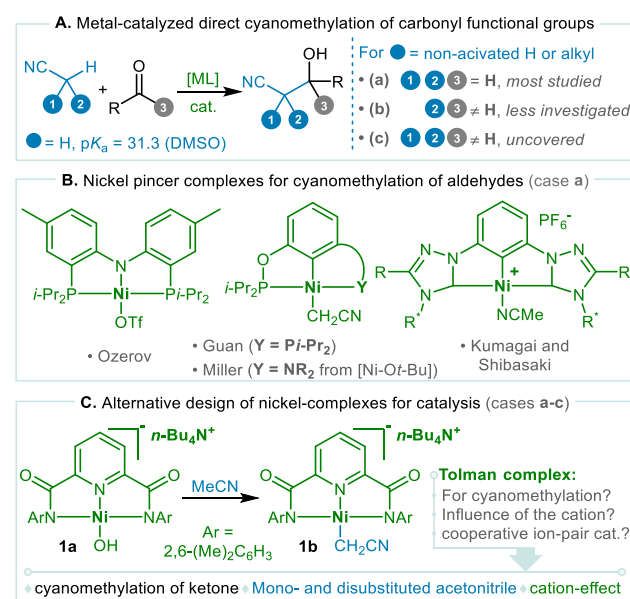
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Abstract. Although the metal-based catalyzed cyanomethylation of aldehydes is well-developed, a similar approach to ketones with acetonitrile derivatives remains a challenge. Thanks to Tolman type complexes, Ni^{II}-complexes with a pyridine(dicarboxamide) pincer ligand, an alternative metal-catalyzed (1-5 mol% catalyst) cyanomethylation of an array of isatins and activated ketones is reported at room temperature. High isolated yields (up to 99%) were obtained not only with the poorly acidic acetonitrile but also with more challenging substituted alkyl cyanide nucleophiles. The *in situ* generated putative ion paired catalysts [NiCR₂CN]⁺Cat⁺ likely benefit from the cation part (Cs⁺ or *n*-Bu₄N⁺) to facilitate their formation and catalytic activity.

Keywords: Cyanoalkylation; Organometallic catalysis; Nickel complexes; Ketone; Pincer ligand

Due to the occurrence of the β-hydroxy nitrile moiety, or motifs derived therefrom, in bioactive molecules, the cyanoalkylation of carbonyl groups has become a key strategy for the development of catalytic methodologies (Scheme 1A).^[1] Beside the classical use of acetonitrile (MeCN) surrogates, which facilitate the generation of the transient α-cyanocarbanion thanks to appropriate electron-withdrawing or leaving groups (R^{1,2}),^[2] the direct formal deprotonation of non-activated acetonitrile derivatives is clearly a more atom-economical approach.^[1b,1e] However, the use of strong bases is required for deprotonation due to the high pK_a value of acetonitrile (31.3 in DMSO).^[1c,3] Alternatively, the development of catalytically competent transition-metal complexes allowed a more facile C(sp³)-H functionalization of MeCN leading to the addition to various aldehydes in moderately basic conditions and a better functional-group tolerance (case a).^[1b,1e] Nonetheless, the catalytic addition of R¹CHCN to ketones (R³ ≠ H) and the use of bulkier non-activated α-functionalized nucleophiles (R¹ ≠ H and R² = H, case b) turned out to be challenging.^[1,4] Kumagai and Shibasaki pioneered CpRu complexes in the presence of DBU to promote the catalytic addition of acetonitrile to trifluoromethylketones and *N*-benzylisatin.^[1e,4a] A Pd^{II}-catalyzed C-H functionalization of MeCN leading to an

addition to isatin at 100 °C was also reported by Yang.^[4b] Cai achieved an enantioselective cyanomethylation of isatins by means of chiral Cu-complexes.^[4c] Singh and, later on, Zhang *et al.* both realized the addition of bulkier but more acidic phenyl acetonitriles to isatins using DBU as the base and water as solvent.^[4d,4e] Worthy of note, the more challenging catalytic addition of disubstituted alkyl cyanide (R^{1,2} ≠ H) is, so far, best performed thanks to the preformation of silyl ketene imine (SKI) derivatives (R^{1,2,3} ≠ H, case c).^{[1a],[5]} In all these studies, the formation of 3-hydroxyoxindole derivatives flanked by a cyanomethylene moiety was tackled due to the versatile nature of these precursors to construct a range of bio-active heterocyclic products.^[2,4,5]



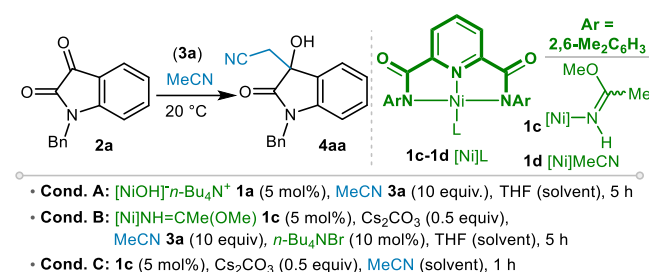
Scheme 1. Catalytic cyanomethylation of carbonyl groups.

In this field, the Ni^{II}-complexes with pincer ligand developed by Ozerov (P^{AN}P pincer ligand), Guan (P^{AC}P), Miller (P^{AC}N) and, recently, by Kumagai and Shibasaki (C^{AC}C) for an enantioselective version, proved to be highly efficient catalysts to promote the addition of acetonitrile to aldehydes (Scheme 1A vs 1B, case a), due usually to a significant *trans*-effect.^[6] Mechanistic investigations

demonstrated two distinct pathways, either through soft metal Lewis acid/Brønsted base cooperative MeCN deprotonation or organometallic sequences.^[7]

We became interested in a unique observation by Tolman and co-workers who highlighted the rapid formation of the $[\text{NiCH}_2\text{CN}]\cdot n\text{-Bu}_4\text{N}^+$ complex **1b** from the corresponding nickel hydroxide precursor **1a** (Scheme 1C).^[8] Several analogous ion-paired hydroxide or alkoxide ($\text{N}^-\text{N}^-\text{N}^-$)-Ni^{II}-pincer complexes, derived from pyridine(dicarboxamide), turned out to be catalytically competent in organic synthesis.^[9] However, to the best of our knowledge, the cyanomethylation reaction has not been reported yet. Next, we questioned the potential influence of the ionic nature of this type of Tolman complex in catalysis, especially taking advantage of the modular cooperativity between the organic and organometallic part.^[10] We are delighted to report herein the performance of complex **1b** and the readily available precursors **1c-1d** in the cyanoalkylation of ketones with an enlarged scope (cases a-c).

Table 1. Proof of concept and optimization with *N*-benzylisatin **2a**.

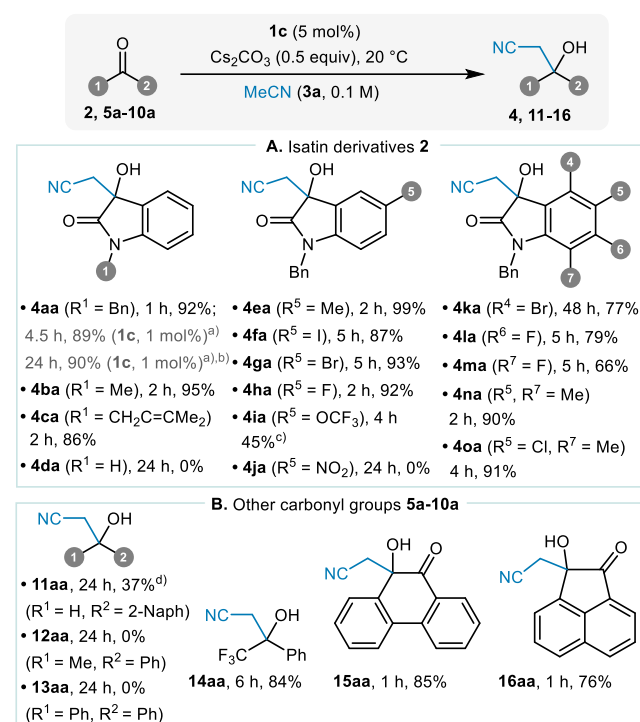


Entry (cond.)	Deviation from standard conditions	Yield (%) ^{a)}
1 (A)	None	80
2 (B)	None (or complex 1d)	90 (93) ^{b)}
3 (B)	no <i>n</i> -Bu ₄ NBr	59
4 (B)	no Cs_2CO_3 or $[\text{Ni}]$ 1c or $\text{Ni}(\text{OTf})_2$	0
5 (B)	Na_2CO_3 or K_2CO_3 as a base	traces
6 (B)	K_3PO_4 as a base	32
7 (B)	Toluene (or CH_2Cl_2) instead of THF in 3 h ^{c)}	26 (20)
8 (C)	None (or with complex 1d)	99 (99) ^{b)}
9 (C)	With or without <i>n</i> -Bu ₄ NBr ^{d)}	93-94
10 (C)	K_3PO_4 as a base with <i>n</i> -Bu ₄ NBr ^{d)}	34
11 (C)	K_3PO_4 without <i>n</i> -Bu ₄ NBr ^{d)}	9
12 (C)	DBU as a base	traces

Reaction performed at 0.1 M (*versus 2a*) on 0.1-0.2 mmol scale with 10 equiv of MeCN for conditions A-B and in MeCN as solvent in condition C. ^{a)} NMR yield determined by an internal standard. ^{b)} Conditions B or C with complex **1d** instead of **1c**. ^{c)} Standard conditions in THF gave 73% yield in 3 hours. ^{d)} In 30 minutes.

First, we were pleased to observe that 5 mol% of the Holm hydroxy $[\text{NiOH}]\cdot n\text{-Bu}_4\text{N}^+$ complex **1a**^[8,9a] smoothly promoted the catalytic addition of acetonitrile **3a** (only 10 equiv. in THF as solvent) to *N*-benzylisatin **2a** to give alcohol **4aa** in a promising 80% NMR yield at 20 °C in 5 hours (Table 1, entry 1, condition A). Most importantly, the transformation took place even more efficiently in 90% yield (**4aa**), by starting from the readily available and rather stable non-charged

complex **1c** $[\text{Ni}]\text{NH}=\text{CMe}(\text{OMe})$,^[11] in the presence of Cs_2CO_3 (50 mol%) as a base (entry 2, condition B). For the sake of comparison (entry 2), we obtained similar results (93% yield) by starting from the known and well-characterized McDonald complex $[\text{Ni}]\text{MeCN}$ **1d** showing that the hypothesized imidate $\text{NH}=\text{CMe}(\text{OMe})$ in **1c**,^[11,12] is possibly a labile ligand (*vide infra*).^[9c] The ammonium salt *n*-Bu₄NBr (10 mol%), likely leading *in situ* to the complex **1b** in Phase-Transfer Catalysis (PTC) conditions, allowed a faster reaction (entries 2 *vs* 3), while Cs_2CO_3 as a base and the Ni-complex **1c** were necessary (entry 4). Carbonate or phosphate bases having a sodium or potassium cation were much less efficient (entries 5-6), and THF was the solvent of choice (entry 7, see also SI). Alternatively, the reaction was straightforward when carried out in acetonitrile as solvent with Cs_2CO_3 (condition C), either with complex **1c** or **1d** (99%, 1 hour, entry 8), even in 30 minutes and without ammonium salt (93-94%, entry 9). However, *n*-Bu₄NBr proved to be beneficial when K_3PO_4 was used instead of Cs_2CO_3 (entries 10-11), albeit in a far less efficient manner. Interestingly, the use of DBU, which proved to be a potent base during the pioneering investigation of Ru- or Ni-complexes proved to be inefficient in our case (entry 12).^[4a,6c,6a]



Scheme 2. Scope and limitation versus ketone derivatives. Reaction performed at 0.1 M (*versus 2a*) on 0.2 mmol scale in MeCN as solvent; isolated yields (%) after purification by column chromatography. ^{a)} Carried out on 1 mmol scale. ^{b)} With 0.1 equivalent of Cs_2CO_3 . ^{c)} 64% of conversion. ^{d)} Around 10% of dehydrated product was obtained.

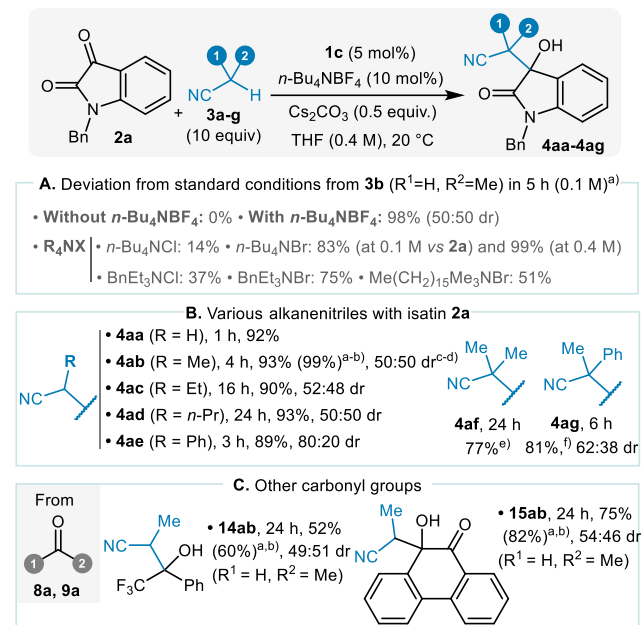
Then, we probed these convenient cyanomethylation conditions to a series of isatins (Scheme 2A). The addition of acetonitrile occurred rapidly on *N*-benzylisatin **2a** to give **4aa** in 92% yield after 1 hour (5 mol% of $[\text{Ni}]\text{NH}=\text{CMe}(\text{OMe})$ **1c**), even with 1 mol% of Ni-catalyst **1c** on a 1 mmol scale (89%,

4.5 h). The rate of the reaction decreased with the amount of Cs_2CO_3 (0.1 equivalent led to **4aa** in 90% yield in 24 hours). *N*-Me (**4ba**, 95%) and *N*-allyl (**4ca**, 96%) oxindoles were formed uneventfully, but these conditions were not compatible with the unprotected isatin precursor **2d**. Various C5- (**4ea-4ha**, 99-87%, $\text{R}^5 = \text{Me, I, Br, F}$), C6- (**4ia**, 79%, $\text{R}^4 = \text{F}$) and C7-substituted (**4ma**, 66%, $\text{R}^7 = \text{F}$) products were synthesized in a few hours of reaction, as were the disubstituted derivatives **4na-4oa** in 90-91% yields. The more hindered C4-substituted precursor **2k** ($\text{R}^4 = \text{Br}$) was successfully transformed into **4ka** in 77% yield but required 48 hours to reach completion. The process proved to be more sluggish with a more electron-withdrawing group at C5 (**2i**, $\text{R}^5 = \text{OCF}_3$), affording 45% yield of compound **4ia**, while a nitro-substituted precursor **2j** did not lead to any product **4ja**. Surprisingly, in the former case, decomposition of product **4ia** was observed with a longer reaction time (> 4.5 h).

Contrariwise to known Ni-complexes,^[6] $[\text{Ni}]\text{NH}=\text{CMe}(\text{OMe})$ complex **1c** turned out to be less competent for the cyanomethylation of aldehydes as testified by the transformation of naphthaldehyde **5a** which yielded **11aa** in 37% after 24 hours (Scheme 2B). Although the poorly reactive and enolizable acetophenone **6** and, also, benzophenone **7a** proved to be resistant to these conditions to provide **12-13aa**, to our delight trifluoroacetophenone **8a** gave the cyanomethylated product **14aa** in 84% yield, and diketones **9-10a** provided the corresponding adducts **15-16aa** in good 85 and 76% yields respectively.

Subsequently, for cost and atom-economy purposes, we revisited the PTC conditions depicted in Table 1 (condition B) in order to decrease the amount of valuable alkanenitrile nucleophiles. Interestingly (Scheme 3A), the addition of ethyl cyanide **3b** (10 equiv.) to *N*-benzylisatin **2a** required the presence of 10 mol% of *n*-Bu₄NBF₄ in THF (no conversion without ammonium salt) to yield product **4ab** in 98% NMR yield after 5 hours in a 50:50 mixture of two diastereoisomers. A preliminary screening of R₄NX showed that BF₄⁻ or Br⁻ anions (BF₄⁻ > Br⁻ > Cl⁻) and *n*-butyl alkyl chains performed the best. Eventually, the reaction carried out at 0.4 M instead of 0.1 M allowed a faster transformation (respectively 83% vs 99% in 5 hours with *n*-Bu₄NBr). With these improved conditions in hand, displaying a marked ammonium effect, the model addition of acetonitrile **3a** led to **4aa** in 92% isolated yield in one hour (Scheme 3B). The more sterically hindered ethyl cyanide **3b** (**4ab**, 93%; 50:50 dr), *n*-propyl cyanide **3c** (**4ac**, 90%; 52:48 dr) and *n*-butyl cyanide **3d** (**4ad**, 93%; 50:50 dr) afforded the corresponding products **4ab-4ad** in times ranging from a few hours to 24 h (with respect to the steric hindrance of the nucleophile), excellent yields but no diastereoselectivity. Benzyl cyanide **3e** gave rise to the formation of **4ae** in 89% yield and improved 80:20 dr. However, further stability investigations of the compounds **4ae** revealed that the reaction was under thermodynamic control,^[4d, 4e] unlike the outcome with less acidic alkylcyanide such as ethyl-derivative **3b** (see SI for details). Accordingly, the two diastereoisomers **4ab** do not equilibrate between each other during the reaction. Worthy of note, the more hindered *i*-propyl cyanide **3f** and α -methyl benzyl cyanide **3g** led to the corresponding adducts **4af** and **4ag**, having two adjacent tetrasubstituted C-centers, in 77% and 81% yields (62:38 dr) respectively, and the use of *n*-Bu₄NBr turned out to be the best additive for the former case. Interestingly the best results were

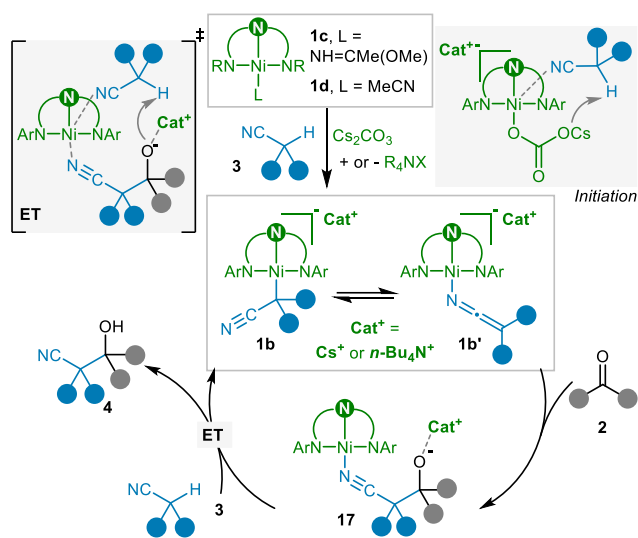
obtained for **4ag** at -20 °C with only 1.2 equivalent of α -methyl benzyl cyanide **3g**. A rapid investigation of other ketones showed that trifluoroacetophenone **8a** and diketones **9a**, underwent the Ni-catalyzed addition of ethyl cyanide **3b** in 52% for **14ab** and 75% for **15ab** respectively. As previously, $[\text{Ni}]\text{MeCN}$ complex **1d** behaved similarly to **1c** for the synthesis of products **4ab**, **14ab** and **15ab** (Scheme 3).



Scheme 3. Scope and limitation: alkyl cyanide nucleophiles. Reaction performed at 0.4 M on 0.2 mmol scale in THF as solvent; isolated yields (%) after column chromatography. ^{a)} NMR yield determined by an internal standard. ^{b)} With complex $[\text{Ni}]\text{MeCN}$ **1d** instead of **1c**, compounds **4ab** (99%), **14ab** (65%) and **15ab** (90%) were obtained in similar NMR yields. ^{c)} 43% NMR yield with 3 equiv of nitrile **3b** for 24 h. ^{d)} The structure of both diastereomers of **4ab** was elucidated by X-Ray analyses (CCDC 2209014, 2209015).^[13] ^{e)} Use of 10 mol% of *n*-Bu₄NBr (*n*-Bu₄NBF₄ gave 30% yield). ^{f)} Reaction performed at -20 °C with catalyst **1d** and 1.2 equiv of **3g** (44% yield, rt).

Preliminary mechanistic investigations showed a kinetic isotope effect (KIE) of 2.7, when carrying out the reaction with an equal amount of acetonitrile-d₃ and acetonitrile,^[4b] while similar results on standard conditions were obtained when starting from either the imidate complex **1c** or the acetonitrile complex **1d** (Scheme 4 and see SI).^[9c] This implies that the imidate ligand is a spectator ligand in this process,^[6c] even though the deprotonation of acetonitrile derivatives might be involved during or prior to the rate determining steps. In order to account for our observations, we propose the catalytic cycle depicted in Scheme 4, inspired by the insightful computational investigation of Ariafard *et al.*^[7] We suggest that the catalytic cycle is initiated by the formation of the $[\text{NiCH}_2\text{CN}]^+\text{Cat}^+$ ate-complex **1b**, with a cesium or ammonium cation depending on the reaction conditions, which might also contribute to the solubilization of the ionic species (*versus* smaller sodium or potassium cations). Pre-complexation of both Cs_2CO_3 and a molecule of R₂CHCN **3** on the square planar d₈ 16-electron

Ni-complexes, followed by a Lewis acid assisted deprotonation event, accounts for the formation of complex **1b** during the initiation step. Then, an equilibrium between the C-bonded complex **1b** and the N-bonded complex **1b'** might occur (shifting toward **1b'** with more sterically hindered nitrile nucleophile), and the latter and more reactive one adds to the carbonyl compound **2** to give the addition product **17**. The cation (**Cat**⁺) may either stabilize the obtained intermediate **17** or the transition state derived therefrom. Eventually, product **4** is released after deprotonation of another alkanenitrile **3**, through the putative transition state **ET**, while reforming the ion-paired reactive species **1b**. The cation with a large ionic radius (**Cs**⁺, **R₄N**⁺) may also exacerbate the basicity of the alcoholate intermediate **17**.



Scheme 4. Proposed catalytic cycle.

In conclusion, we have developed a nickel-catalyzed cyanoalkylation of ketones with a scope extended to various ketones and alkanenitrile derivatives, then more sterically hindered substrates than aldehydes or MeCN are successfully used. Thanks to a Tolman type complex, conveniently *in-situ* generated, the unique use of the putative ion paired catalyst [NiCH₂CN]⁺**Cat**⁺ in cyanoalkylation could benefit from the cation part (**Cs**⁺ or **n-Bu₄N**⁺) to facilitate the formation and/or the catalytic activity. This contrasts with the usual design of Ni^{II}-complexes with pincer ligands having a strong *trans*-effect. The modulation and exploitation of these ion paired Ni-complexes both in racemic and asymmetric catalysis is currently under investigation.

Experimental Section

Representative procedure for the synthesis of **4aa**

To a mixture of [LNi]NH=CMe(OMe) (**1c**, 4.6 mg, 0.05 mmol, 5 mol%) and Cs₂CO₃ (32.4 mg, 0.5 mmol, 50 mol%) in a sealed tube under nitrogen was added anhydrous MeCN (**3a**, 2 mL) and, subsequently, the benzyl isatin **2a** (47.5 mg, 0.2 mmol) in one portion. The reaction was monitored by TLC. Once the reaction was completed (1 hour), the resulting solution was filtered over silica gel with 200 mL of ethyl acetate and the filtrate was concentrated under reduced pressure. The crude product was then purified by silica gel

column chromatography (Petroleum ether/EtOAc: 3/2, *R_f* = 0.39) to give the desired product **4aa** as an off-white solid (51.4 mg, 92%).

Acknowledgements

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- [11] Complex **1c** fulfilled the spectroscopic analyses for L = NH=CMe(OMe), while we were unable to obtain crystals suitable for X-Ray analysis, thus the correct structure of **1c** is hypothesized currently (see SI).
- [12] Complex **1c** could be stored at room temperature under nitrogen for a month and was rapidly weighed without any special precautions.
- [13] CCDC-2209014 and 2209015 (compounds **4ab**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

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