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# Cinchonidinium acetate as a convenient catalyst for the asymmetric synthesis of *cis*-stilbenediamines

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ABSTRACT

Inexpensive and readily available cinchonidinium acetate is an effective catalyst for the *syn*-selective aza-Henry reaction of arylnitromethanes and aryl imines. The resulting masked *cis*-stilbenediamine products are produced in excellent diastereoselectivity and good enantioselectivity, and enantiopure material can be achieved via recrystallization. The features of the *cinchona* catalyst needed for selectivity are discussed, with specific emphasis on formation of a kinetically controlled *syn*-product without epimerization of the highly acidic α-nitro stereocenter.

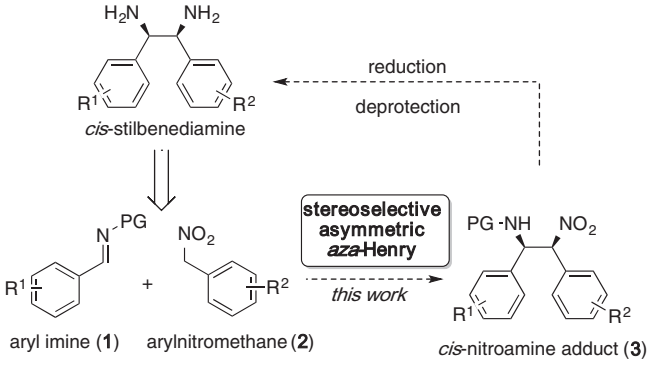


## Introduction

The vicinal diamine moiety is a central structural feature of many biologically significant molecules, ranging from pharmaceuticals to molecular imaging tools.[1] Moreover, this array serves as the critical stereocontrol element in a substantial percentage of both organo- and metal-based asymmetric catalysts.[2] Despite their utility, asymmetric methods for the synthesis of several classes of vicinal diamines remain challenging, often relying on chiral resolutions.[3] In particular, access to *cis*-stilbenediamines, possessing a *syn*-1,2-diaryl unit, has largely remained limited to symmetric compounds via dimerization methods to form the *meso* diamine.[4] Many of these processes suffer from poor diastereoselection, and all require subsequent chiral resolution to afford enantioenriched diamines. Recently, Seidel has elegantly demonstrated the desymmetrization of *meso*-stilbenediamines via thiourea catalysis, providing monobenzoylated diamines in good ee.[5]

An attractive approach for the enantioselective synthesis of both symmetric and unsymmetric *cis*-stilbenediamines exploits the use of the aza-Henry, or nitro-Mannich, reaction for the union of two nitrogen containing fragments. Specifically, addition of an arylnitromethane nucleophile (presumably as the nitronate) into an aryl imine provides the β-nitroamine adduct, which upon reduction and deprotection reveals the free diamine (Scheme 1).

While considerable success has been achieved for the asymmetric aza-Henry reaction using nitromethane and its alkyl congeners,[6] examples using arylnitromethanes are limited, and largely reveal orthogonal reactivity and stereocontrol when utilized with otherwise well-behaved catalyst systems.[7] In addition to identifying suitable conditions for arylnitromethane reactivity, a key challenge lay in constructing and preserving the highly acidic β-nitro stereocenter. Notably, Johnston and coworkers have reported an elegant process for accessing the *syn* β-nitroamine aza-Henry adducts with high diastereo- and enantiocontrol utilizing a bisamidine-quinoline catalyst, highlighted by the synthesis of the p53-MDM2 inhibitor Nutlin-3.[8] The same group recently revealed a




**Scheme 1.** Proposed synthesis of *cis*-stilbenediamines via aza-Henry reaction.

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modified monoamidine-amide catalyst to be effective for this transformation on a variety of substrates, although poorer stereocontrol was observed with electron-deficient arylnitromethanes.[9] Herein, we report a complimentary and convenient method for the asymmetric synthesis of *cis*-stilbenediamines using readily available, inexpensive cinchonidinium acetate as the catalyst. This convergent approach provides exceptional diastereocontrol for unsymmetric products as well as good enantiocontrol, and enantiopure material is readily obtained via recrystallization.

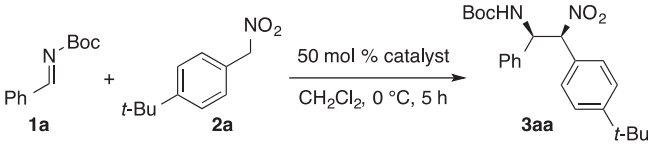
## Results and discussion

Initial investigations of the aza-Henry reaction with arylnitromethanes were conducted using BINOL-salen catalysts previously developed in our laboratories.[10] While these systems proved unselective, a survey of Brønsted acids (Fig. 1) led to the discovery of the *cinchona* alkaloid cinchonidinium acetate as a potential stereocontrol platform. Although proline salts **4** and **5** as well as bisamidinium **7** exhibited moderate diastereocontrol (Table 1), they provided essentially racemic nitroamine adduct. Notably, 3,3′-substituted BINOLphosphoric acid **8**, effective in several asymmetric Brønsted-acid catalyzed transformations,[11] yielded only trace product. In contrast, cinchonidinium acetate, formed via protonation of the quinuclidine nitrogen ($pK_a$ AcOH = 4.76, $pK_a$ cinchonidinium–$H^+$ = 8.40),[12] smoothly provided the desired *syn* product[13] **3aa** with a high 93:7 dr and moderate 61% ee.

Reasoning that the acetate anion plays a role in the asymmetric step, chiral counteranions were examined (Table 2, entries 1 and 2). The similar levels of enantioselection offered by the salts from both enantiomers of **10** pointed away from the counterion being a key controller of the asymmetric environment.[8a] A survey of acids of varying strengths revealed a rather narrow window for optimal selectivity centered on acetic acid. In particular, stronger sulfonic acids, *p*-TsOH and TfOH, inhibited the reaction. Greater success was found by decreasing the reaction temperature, resulting in nearly complete diastereocontrol when performing the reaction at −30 °C. Colder temperatures further increased enantioselectivity, but conversion became problematic, with no product formation at −78 °C after several days. Increasing the acetic acid/catalyst stoichiometry to 3:1 hindered reactivity, whereas a 1:3 ratio resulted in slightly poorer diastereo- and enantiocontrol. Alternative imine protecting groups, including *N*-Ts and *N*-Cbz exhibited diminished reactivity, and afforded the corresponding products in lower selectivity in comparison with *N*-Boc imines **1**.

Effects of catalyst structure were explored using other members of the *cinchona* alkaloid family, as well as synthetically modified

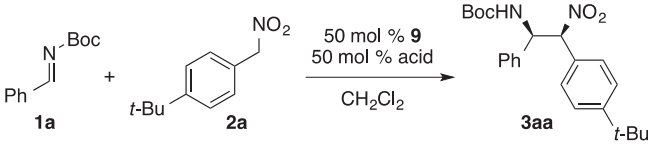
**Table 1**
Survey of chiral amine and Brønsted acid catalysts




| Entry | Catalyst | dr[a] (*syn*:*anti*) | ee[a] (%) |
|---|---|---|---|
| 1 | **4** | 88:12[b] | 0(0) |
| 2 | **5** | 89:11[b] | 1(0) |
| 3 | **6** | 45:55 | 3(1) |
| 4 | **7**[c] | 93:7 | 1(11) |
| 5 | **8**[c] | —[b] | — |
| 6 | **9**·HOAc | 93:7 | **61** |

[a] Determined by HPLC. Numbers in parentheses refer to ee of the *anti* diastereomer.
[b] Trace product formed.
[c] 25 mol % catalyst used.

**Table 2**
Optimization of acid additive and temperature




| Entry | Acid | $pK_a$[a] ($H_2O$) | *T* (°C) | dr[b] (*syn*:*anti*) | ee[b] (%) |
|---|---|---|---|---|---|
| 1 | (*R*)-**10** | 1.29[c] | 0 | 88:12 | 21(44) |
| 2 | (*S*)-**10** | 1.29[c] | 0 | 88:12 | 37(45) |
| 3 | TfOH | −14[d] | −45 | —[e] | — |
| 4 | *p*-TsOH | −2.8[f] | 0 | —[e] | — |
| 5 | TFA | 0.23 | 0 | 86:14 | 33(25) |
| 6 | BzOH | 4.20 | 0 | 93:7 | 31(1) |
| 7 | *p*-Aminobenzoic acid | 4.89 | −45 | 96:4 | 31 |
| 8 | AcOH | 4.76 | 0 | 93:7 | 61 |
| 9 | AcOH | 4.76 | −15 | 95:5 | 68 |
| 10 | AcOH | 4.76 | −30 | 97:3 | 71 |
| 11 | AcOH | 4.76 | −45 | 99:1 | 74 |
| 12 | AcOH | 4.76 | −78 | —[e] | — |
| 13 | AcOH (150 mol %) | 4.76 | −45 | —[e] | — |
| 14 | AcOH (17 mol %) | 4.76 | −45 | 98:2 | 70 |

[a] Ref. 11.
[b] Determined by HPLC. Numbers in parentheses refer to ee of the *anti* diastereomer.
[c] Value for diphenylphosphate.
[d] Ref. 14.
[e] Trace product formed.
[f] Ref. 15.

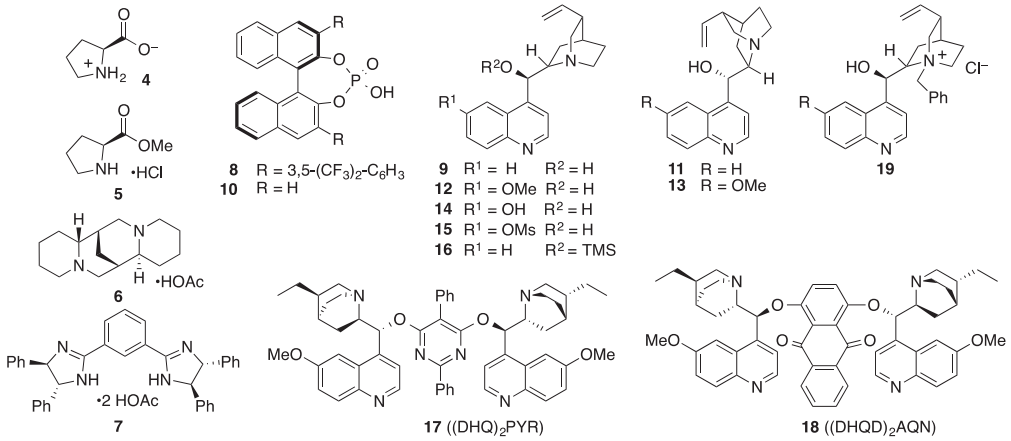
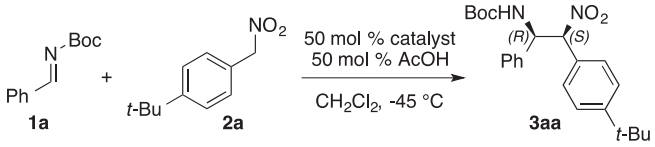



**Figure 1.** Catalyst structures investigated for the aza-Henry reaction of arylnitromethanes.

**Table 3**
Investigation of *cinchona* structure on product selectivity




| Catalyst | dr[a] (*syn*:*anti*) | ee[a] (%) |
|---|---|---|
| **9** (cinchonidine) | 99:1 | 74 (*R*,*S*) |
| **11** (cinchonine) | 99:1 | 71 (*S*,*R*) |
| **12** (quinine) | 98:2 | 44 (*S*,*R*) |
| **13** (quinidine) | 98:2 | 37 (*R*,*S*) |
| **14** | 95:5[b] | 12 (*S*,*R*) |
| **15**[c] | 96:4 | 1 (*R*,*S*) |
| **16** | 99:1 | 15 (*R*,*S*) |
| **17**[d] | 91:9 | 4 (*S*,*R*) |
| **18**[d] | 76:24 | 13 (*R*,*S*) |
| **19**[e] | 88:12 | 13 (*R*,*S*) |

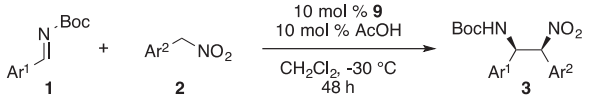
[a] Determined by HPLC.
[b] Trace product formed.
[c] Run with 25 mol % catalyst and AcOH.
[d] Run at 0 °C with 100 mol % AcOH.
[e] Run at 0 °C without AcOH.

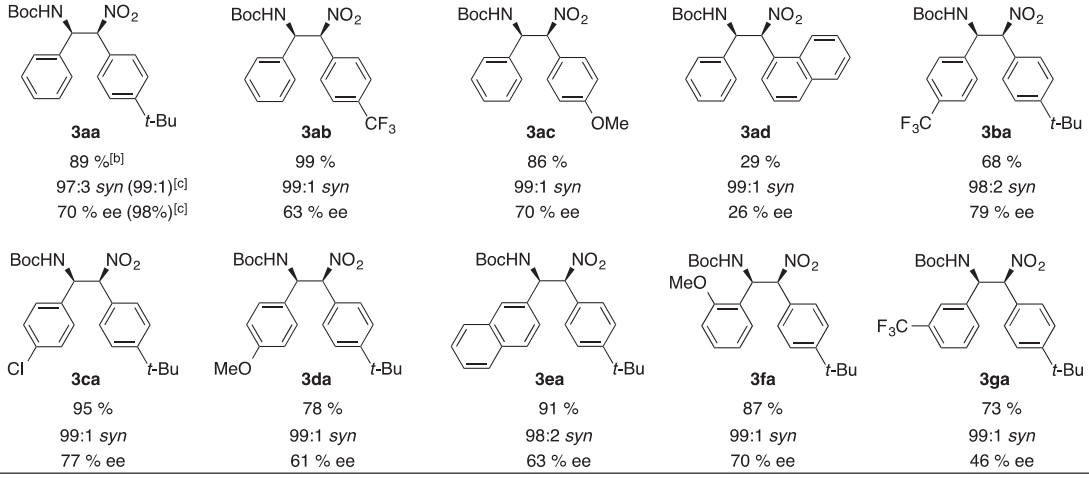
structures, as shown in Table 3. The four canonical *cinchona* structures, **9** and **11**–**13**, exhibited near perfect diastereocontrol. As anticipated, pseudoenantiomer **11** afforded the product with similar enantioselectivity but for the opposite absolute configuration. Catalysts **12** (quinine) and **13** (quinidine) are isostructural to **9** and **11**, respectively, except for the methoxy substitution at the 6-position of the quinoline ring. However, these catalysts provided significantly lower enantioselection compared to their unsubstituted analogs, along with an unanticipated change in product absolute configuration. This effect was further probed via synthetic manipulation to afford **14** and **15**, which contain phenol and methanesulfonyl substitution, respectively. Although replacement of the donating methoxy group with withdrawing sulfonyl group was postulated to enhance ee, catalyst **15** provided negligible enantioinduction. The pseudo-meta position of the 6-substituent only slightly alters the basicity of the quinoline nitrogen (cf. quinolinium p$K_a$ of **9** = 4.17, **12** = 4.32).[12] Consequently, a steric influence of the substituent may play a significant role in the enantiodetermining step of the mechanism, rather than an effect on the basicity of the quinoline nitrogen. Alternative binding modes with the basic atoms of the substituent may also be intervening. For the phenolic catalyst **14**, a separate activation mechanism involving hydrogen-bonding activation of the imine from the phenol may predominate. Based on the results using silyl ether **16** or dimeric catalysts **17** and **18**, the free secondary hydroxyl group is important for high enantioselectivity. The role of the bicyclic amine was explored with N-benzylated catalyst **19**, which was poorly reactive, forming only trace amounts of product in low ee.[16] This result suggests the quinuclidinium N–H acts as an acid or hydrogen bond donor in the active catalyst.

Performing the reaction at −30 °C with lowered catalyst and acetic acid loadings (10 mol %) provided reasonable rates and a minimal decrease in selectivity. The generality of the method was explored under these optimized conditions as illustrated in Table 4.[17]

The arylnitromethane substrate tolerated both electron-withdrawing and electron-donating substitution, providing trifluoromethyl and methoxy products **3ab** and **3ac** in high yield with excellent diastereoselectivity and moderate enantioselectivity. Steric hindrance on the nucleophile led to deleterious results, as exhibited by 1-naphthyl substrate **2d**. Although only the *syn* diastereomer was observed, the product formed with poor conversion and selectivity. The method proved general for a variety of aryl imines, including electron rich, electron poor, and naphthyl substrates. Based on the results observed for trifluoromethyl- and chloro-substituted products **3ba** (79% ee) and **3ca** (77% ee), higher enantioselection is afforded with electron-deficient imines. Accordingly, *para*-methoxy adduct **3da** formed with lower selectivity (61% ee). Notably, *ortho*-substituted imine **1f** performed well in the reaction. In contrast, *meta*-trifluoromethyl product **3ga**

**Table 4**
Substrate scope of the cinchonidinium acetate-catalyzed aza-Henry reaction[a]




[a] Reaction performed on a 0.2 mmol scale using 1.2 equiv imine. Yields refer to isolated yields after purification. Diastereomeric ratio and ee determined by chiral HPLC or SFC analysis.
[b] Performed on a 2.3 mmol scale.
[c] After a single recrystallization from $CH_2Cl_2$.

was obtained in high diastereoselectivity, but with diminished enantioselectivity.

A key feature of the method is the simplicity of both the catalyst system as well as product purification. Eluting the reaction mixture through a small plug of silica with dichloromethane removes the catalyst, and subsequent trituration with hexanes removes unreacted arylnitromethane to afford the pure product as a white solid.[18] The optical purity is easily enhanced via recrystallization of the solid products. As an example, the model reaction was performed on a 2.3 mmol scale, providing adduct **3aa** in 70% ee. One recrystallization from dichloromethane afforded nearly enantiopure product (98% ee), and only *syn* diastereomer detectable by HPLC. In addition, crystallization by slow evaporation yielded crystalline product suitable for X-ray crystallographic analysis,[19] securing both relative and absolute stereochemistry (Fig. 2).

Considering the highly acidic nature of the β-nitro benzylic proton, the exceptional diastereocontrol of the cinchonidine-acetic acid catalyst system is of particular note. Indeed, during the course of these investigations, it was observed that subjecting *syn* product **3aa** to weakly basic conditions produced significant amounts of the *anti* diastereomer. While a retro process (Scheme 2, path a), occurring via deprotonation of the carbamate proton, could account for this transformation, treatment of enantioenriched *syn*-**3aa** with amine bases produced the *anti*-isomer with complete retention of stereochemical information at the β-carbon (Table 5) thus confirming an epimerization mechanism (path b). Favorable deprotonation of the β-nitroalkyl proton is also rationalized based on p$K_a$ values, despite the kinetic barrier associated with nitronate formation.[20]

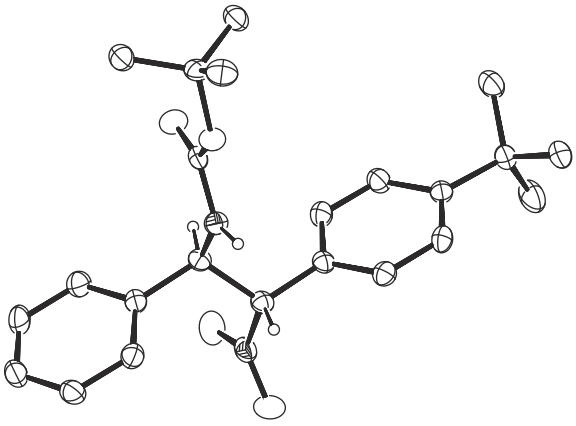
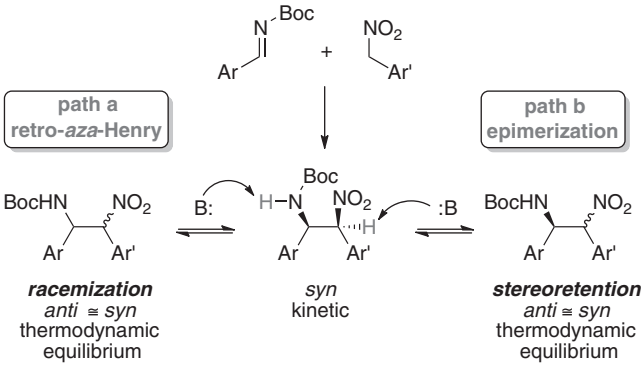


**Figure 2.** X-ray structure of product **3aa**.




**Scheme 2.** Potential base-mediated isomerization pathways of β-nitroamine products.

**Table 5**
Epimerization studies with amine bases


| Base | p$K_a$[a] | dr[b] (*syn:anti*) | ee[b] *syn* (%) | ee[b] *anti* (%) |
|---|---|---|---|---|
| Pyridine | 5.4 | 98:2 | 97 | – |
| DMAP | 9.9 | 44:56 | 97 | **97** |
| DBU | 11.6 | 62:38 | 97 | **97** |

[a] Refers to dissociation constants of the protonated amine in $H_2O$. Ref. 21.
[b] Determined by HPLC.

Ostensibly, the active catalyst is selective for the deprotonation of the primary arylnitromethane nucleophile and formation of the kinetic *syn* product while avoiding epimerization to the thermodynamic mixture of diastereomers. Based on the inactivity of pyridine in the study above (Table 5), the quinoline nitrogen of the *cinchona* catalyst appears unable to effect product epimerization. Similarly, the acetic acid additive may act as an internal buffer to prevent deprotonation by the more basic quinuclidine nitrogen.

## Conclusion

In conclusion, we have demonstrated the utility of catalytic cinchonidinium acetate for the facile synthesis of *cis*-stilbene diamine derivatives with excellent diastereocontrol and good enantioselectivity. The high levels of diastereocontrol across a broad range of substrates are of particular note, highlighting the ability of the catalyst to form one isomer via kinetic control while preventing epimerization to the thermodynamic mixture of *syn* and *anti* products. The only other asymmetric, catalytic method for this transformation achieves higher enantioselectivity, but uses a more costly catalyst.[8,9] In contrast, the report herein defines a simple catalyst useful in situations, such as large-scale applications, where catalyst cost is a primary driver and crystallization can be employed. Additionally, this method achieves excellent diastereoselectivities that do not erode with more acidic products.

## Acknowledgments

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## Supplementary data

Supplementary data (experimental procedures, full characterization, including $^1$H NMR and $^{13}$C NMR spectra, for all new compounds, HPLC and SFC chromatograms, and experimental procedures for epimerization experiments) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.12.105.

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16. *N*-Alkyl cinchonidinium compounds have been successfully applied to the asymmetric aza-Henry reaction with nitromethane and nitroethane: (a) Palomo, C.; Oiarbide, M.; Laso, A.; Lopez, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622; (b) Gomez-Bengoa, E.; Linden, A.; Lopez, R.; Mugica-Mendiola, I.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2008**, *130*, 7955; (c) Wei, Y.; He, W.; Liu, Y.; Liu, P.; Zhang, S. *Org. Lett.* **2012**, *14*, 704. Thorough investigation in our labs has been unsuccessful with arylnitromethanes as nucleophiles under similar conditions.
17. *General procedure for the cinchonidinium acetate catalyzed aza-Henry reaction:* An oven-dried microwave vial was charged with cinchonidine (5.9 mg, 0.020 mmol) and placed under argon. $CH_2Cl_2$ (3 mL) and glacial AcOH (0.020 mmol, 0.2 M in $CH_2Cl_2$) were added, and the solution was cooled to −30 °C. Imine (0.24 mmol, 0.6 M in $CH_2Cl_2$) was added, followed by dropwise addition of arylnitromethane (0.20 mmol, 0.5 M in $CH_2Cl_2$). The mixture was stirred for 48 h at −30 °C, whereupon it was passed through a silica plug with $CH_2Cl_2$ and concentrated. Trituration with hexanes then removed unreacted arylnitromethane and afforded the pure title compound. The diastereomeric ratio and optical purity were determined by chiral HPLC or SFC analysis.
18. No change in product dr or ee was observed through trituration with hexanes.
19. CCDC-1022083 contains the supplementary crystallographic data for compound **3aa**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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