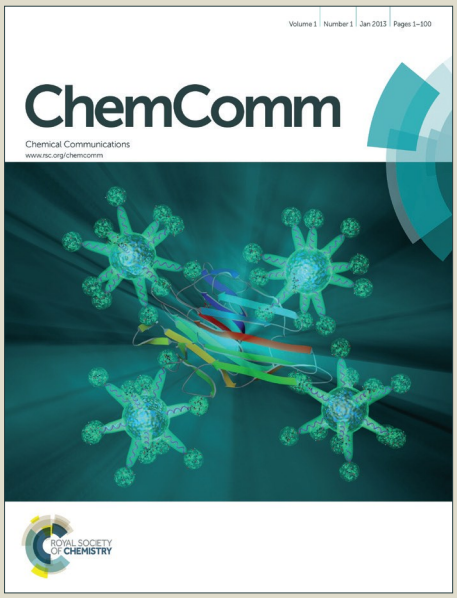
ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: M. Zhang, S. Yu, F. Hu, Y. Liao, L. Liao, X. Xu, W. Yuan and X. Zhang, *Chem. Commun.*, 2016, DOI: 10.1039/C6CC01200K.



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

View Article Online
DOI: 10.1039/C6CC01200K

Journal Name

COMMUNICATION

Highly Enantioselective [3+2] Coupling of Cyclic Enamides with Quinone Monoimines Promoted by a Chiral Phosphoric Acid

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Minmin Zhang,[a,b] Shuowen Yu,[a,b] Fangzhi Hu,[a,b] Yijun Liao,[a,b] Lihua Liao,[a,b] Xiaoying Xu,[a] Weicheng Yuan[a] and Xiaomei Zhang*[a]

Enantioselective [3+2] coupling of cyclic enamides with quinone monoimines was realised using a chiral phosphoric acid as a catalyst. This transformation allowed for the synthesis of highly enantioenriched polycyclic 2,3-dihydrobenzofurans (up to 99.9% ee). The absolute configuration of one product was determined by an X-ray crystal structural analysis. We also found a possible mechanism for this reaction.

2,3-Dihydrobenzofurans are important building blocks found in a wide array of natural products and pharmaceutical substances.[1] Particularly, polycyclic 2,3-dihydrobenzofuran sub-structures exist in many biologically active compounds,[2] such as galanthamine,[2a] aflatoxin B_2 and morphine alkaloids[2b-2d] etc. (Figure 1). Therefore, the construction of polycyclic 2,3-dihydrobenzofurans is of great interest to the researchers.[3]

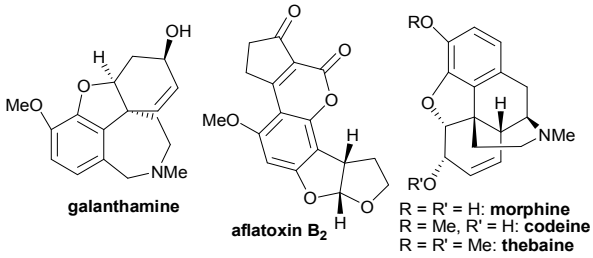


Figure 1. Representative biologically active polycyclic 2,3-dihydrobenzofurans.

Quinone derivatives are highly active electrophiles which have been used in reactions with a large variety of nucleophiles to construct structurally diversed molecules.[4,5] Quinone derivatives are commonly used in asymmetric reactions and for the efficient preparation of numerous valuable enantio-enriched compounds.[3d,5]

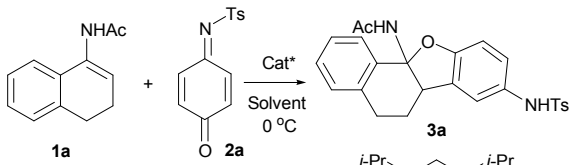
Recently we studied transformations involving quinone derivatives.[5d,5e,6] For example, we used a chiral phosphoric acid[7] to catalyze [3+2] coupling of 3-substituted indoles with a quinone monoimine for the synthesis of highly enantio-enriched benzofuroindolines.[5d] To further our understanding of reactions of quinone derivatives, we conducted this study to show that chiral phosphoric acid promoted highly enantioselective [3+2] coupling of cyclic enamides with quinone monoimines that produced a large variety of polycyclic 2,3-dihydrobenzofurans in moderate to good yields with generally good enantioselectivities.

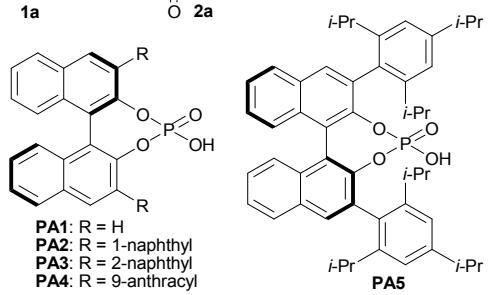
First, several chiral phosphoric acids were evaluated in catalyzing [3+2] coupling of *N*-(3,4-dihydronaphthalen-1-yl) acetamide **1a** with 4-methyl-N-(4-oxocyclohexa-2,5-dienylidene) benzene-sulfonamide **2a** in dichloromethane at 0 °C. As shown in Table 1, chiral phosphoric acids (*S*)-**PA4** and (*R*)-**PA5** which have bulky groups in the 3,3' positions of BINOL, promoted an efficient reaction and produced good yields of polycyclic 2,3-dihydrobenzofuran **3a** with excellent *ee* values (Table 1, entries 4 and 5), but the yield was higher with (*R*)-**PA5**. Therefore **PA5** was determined as the optimal catalyst and was used through out our study. When the catalyst loading was reduced to 5 mol%, the good yield and *ee* value were only maintained by prolonging the reaction time from 7 hours to 12 hours (Table 1, entry 6). As such the catalyst loading was determined as 5 mol%. Next, we tested several solvents. The reaction in 1,2-dichloroethane led to slightly lower yield and enantioselectivity (Table 1, entry 7). No products were produced in toluene and acetonitrile (Table 1, entries 8 and 9). The reaction in THF had good enantioselection but a very poor yield (Table 1, entry 10). Therefore dichloromethane was determined as the optimal solvent for the reaction.

[a] *Key Laboratory for Asymmetric Synthesis and Chiraltechnology of Sichuan Province, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu, China, Fax: (+86)28-85257883; Tel: (+86)28-85257883; E-mail: xmzhang@cioc.ac.cn*
[b] *University of Chinese Academy of Sciences, Beijing,China.*
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C6CC01200K

Table 1 Enantioselective [3+2] coupling of N-(3,4-dihydronaphthalen-1-yl) acetamide **1a** with 4-methyl-N-(4-oxocyclohexa-2,5-dienylidene) benzene-sulfonamide **2a**.[a]





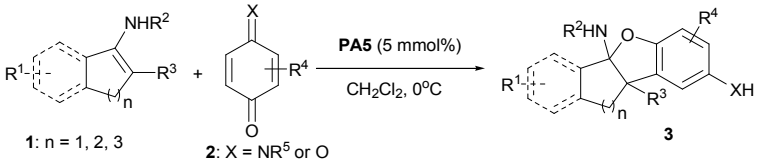
Entry	Cat* (mol%)	Solvent	t (h)	Yield (%)[b]	ee (%)[c]
1	**PA1** (10)	CH_2Cl_2	10	81	23.3
2	**PA2** (10)	CH_2Cl_2	10	45	90.8
3	**PA3** (10)	CH_2Cl_2	10	92	83.0
4	**PA4** (10)	CH_2Cl_2	10	83	98.8
5	**PA5** (10)	CH_2Cl_2	7	89	-99.1
6	**PA5** (5)	CH_2Cl_2	12	88	-99.6
7	**PA5** (5)	$ClCH_2CH_2Cl$	12	85	-99.1
8	**PA5** (5)	Toluene	12	Trace	-
9	**PA5** (5)	CH_3CN	12	Trace	-
10	**PA5** (5)	THF	12	28	-97.1

[a] Unless otherwise specified, the reactions used 0.10 mmol of **1a**, 0.15 mmol of **2a** and the corresponding chiral phosphoric acid in 1 mL of the solvent at 0 ℃. [b] Isolated yield based on **1a**. [c] The *ee* values were determined by using chiral HPLC.

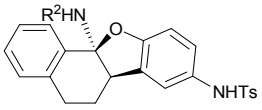
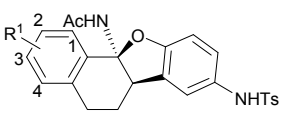
Once we determined the optimized conditions, we next studied its substrate scope. The results are summarized in Table 2. First, when *N*-benzoyl enamide **1b** or *N*-Cbz enamide **1c** was used, only a trace of the desired product was observed after 12 hours (Table 2, entries 2 and 3). We then tested a range of benzo six-membered cyclic enamides bearing various substituents at the benzene ring. In most cases, the products had moderate to good yields with excellent enantioselectivities (up to 99.9 %) (Table 2, entries 4-16). Some substrates resulted in poor yields (Table 2, entries 7, 8 and 15). By increasing the catalyst loading to 10 mol%, the yields increased (Table 2, entries 7 and 8). When 4-methyl quinone monoimine **2b** was used in the reaction with enamide **1a**, no product was detected (Table 2, entry 17). Meanwhile, 2-methyl-enamide **1q** was found to be inactive in the reaction with quinone monoimine **2a** (Table 2, entry 18).

The reactions using the benzo five-membered cyclic enamides in general had lower yields but very high *ee* values (Table 2, entries 19-22). The benzo seven-membered cyclic enamide **1v** exihibited lower acticity and produced a poor yield even when the reaction was prolonged for 110 hours. However the *ee* value was not affected (Table 2, entry 23). Then a non-benzo-fused enamide **1w** was used in the coupling with quinone monoimine **2a**. The yield was fair but had a very poor enantioselectivity (Table 2, entry 24), which may be attributed to a lack of aromatic ring of this enamide. The coupling of acyclic enamide **1x** with quinone monoimine **2a** provided a poor *dr* value of 34.5:65.5 but good enantioselectivities for the diastereomers (Table 2, entry 25). *N*-Benzoyl quinone monoimine **2c** was also used in the coupling with enamide **1a** and good *ee* value was obtained (Table 2, entry 26). Finally, we tried to expand the substrate scope to 1,4-benzoquinone and 1,4-naphthoquinone. However, only traces of the products were detected and most of the enamide **1a** decomposed (Table 2, entries 27 and 28).

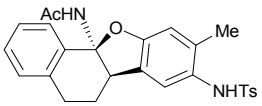
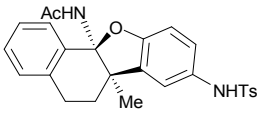
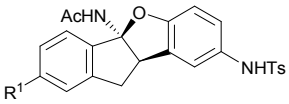
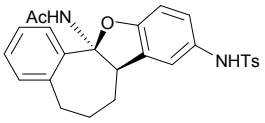
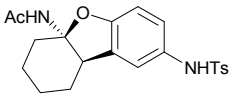
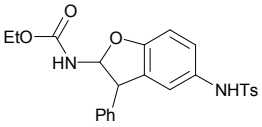
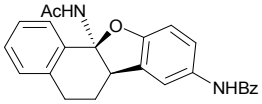
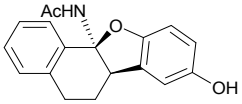
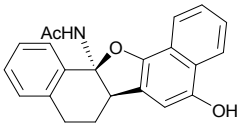
Table 2 Enantioselective [3+2] coupling of cyclic enamides **1** with quinone monoimines or quinones **2**.[a]



1: n = 1, 2, 3 **2**: X = NR^5 or O **3**

Entry	**3**		t (h)	Yield (%)[b]	ee (%)[c,d]
1		**3a**: R^2 = Ac	12	88	99.6
2		**3b**: R^2 = Bz	12	trace	-
3		**3c**: R^2 = Cbz	12	trace	-
4		**3d**: R^1 = 2-OMe	12	70	99.9
5		**3e**: R^1 = 2-Me	36	83	97.2
6		**3f**: R^1 = 2-F	36	74	97.7
7		**3g**: R^1 = 2-Cl	36	20 (51[e])	96.2 (97.5[e])
8		**3h**: R^1 = 2-Br	72	38 (72[e])	97.8 (97.9[e])
9		**3i**: R^1 = 3Me	40	89	99.3
10		**3j**: R^1 = 3-F	48	98	99.5
11		**3k**: R^1 = 4-Me	40	82	99.7
12		**3l**: R^1 = 4-F	48	98	98.6
13		**3m**: R^1 = 4-Cl	36	81	97.0
14		**3n**: R^1 = 4-CF_3	48	81	98.5
15		**3o**: R^1 = 2,3-diMe	48	63	93.7
16		**3p**: R^1 = 2,3-diOMe	12	89	99.2

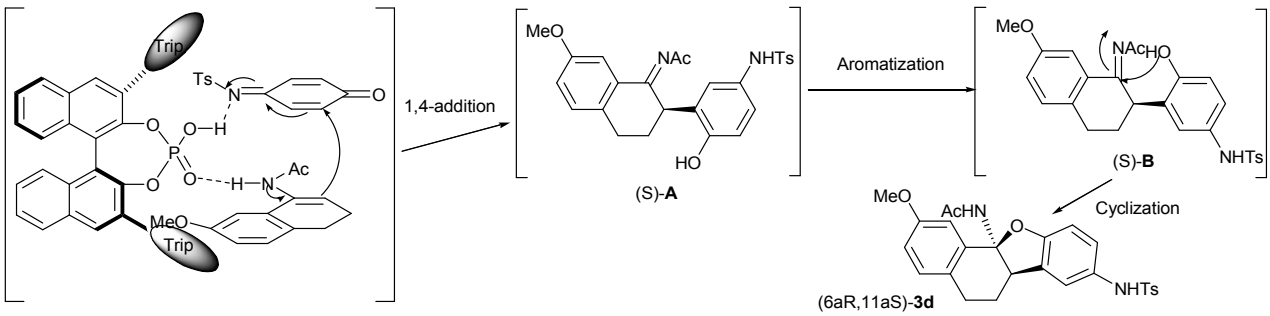
View Article Online
DOI: 10.1039/C6CC01200K

17		**3q**	12	NR	-
18		**3r**	12	NR	-
19		**3s**: R^1 = H	24	52	99.5
20		**3t**: R^1 = F	24	83	99.6
21		**3u**: R^1 = Cl	24	64	99.9
22		**3v**: R^1 = Br	24	40	99.0
23		**3w**	110	30	94.7
24		**3x**	15	70	11
25		**3y**	8	99	97.0 99.8[f]
26		**3z**	4	75	94.3
27		**3A**	12	trace	-
28		**3B**	12	trace	-

[a] Unless otherwise specified, the reactions used 0.10 mmol of **1**, 0.15 mmol of **2** and 0.005 mmol of **PA5** in 1 mL of CH_2Cl_2 at 0 ℃. [b] Isolated yield based on **1**. [c] The *ee* values were determined by using chiral HPLC. [d] The absolute configuration of **3d** was determined by an X-ray crystal structural analysis.[8] The absolute configurations of other products were assigned by analogy. [e] 10 mol% of **PA5** was used. [f] The *dr* value is 34.5:65.5.

Next the absolute configuration of product **3d** (6a*R*,11a*S*) was determined by an X-ray crystal structural analysis[8] (See the supporting information). Consequently, the absolute configurations of other products except **3y** can be assigned by analogy.

Based on the absolute configuration of the product **3d**, we found a possible reaction mechanism (Scheme 1).



Scheme 1 A possible reaction mechanism of enantioselective [3+2] coupling of cyclic enamide **1d** with quinone monoimine **2a**.

View Article Online
DOI: 10.1039/C6CC01200K

Journal Name

COMMUNICATION

As shown in Scheme 1, first, the Brønsted acid moiety of the phophoric acid protonated the quinone monoimine and the Lewis base moiety of the phophoric acid activated the enamide through H-bond. The enamide attacked the quinone monoimine to produce the intermediate (*S*)-**A** which experienced immediate aromatization to produce the phenol intermediate (*S*)-**B**. The phenol attacked the imine from *Si*-face spontaneously to generate polycyclic 2,3-dihydrobenzofuran (6a*R*,11a*S*)-**3d**.

In conclusion, we developed a highly enantioselective [3+2] coupling of cyclic enamides with quinone monoimines promoted by a chiral phosphoric acid. Through this transformation, a wide variety of polycyclic 2,3-dihydrobenzofurans were synthesized in moderate to good yields with generally good enantioselectivities. The absolute configuration of one product was determined as (6a*R*,11a*S*) by an X-ray crystal structural analysis. We also found a possible reaction mechanism for this reaction.

Notes and references

‡ We are grateful for the financial support from National Natural Science Foundation of China (21372218). We thank LetPub for its linguistic assistance during the preparation of this manuscript.

1 For reviews, see: *(a)* R. S. Ward, *Chem. Soc. Rev.* 1982, **11**, 75; (*b*) P. Proksch and E. Rodriguez, *Phytochemistry*, 1983, **22**, 2335.

2 For selected examples, see: (*a*) O. Hoshino in *The Alkaloids*, *Vol. 51* (Ed.: G. A. Cordell), Academic Press, New York, 1998, pp. 323; (*b*) H. L. Holmes in *The Alkaloids*, *Vol. 6* (Ed.: R. H. F. Manske and H. L. Holmes), Academic Press, New York, 1952, Chapter 8; *(c)* G. Stork in *The Alkaloids*, *Vol. 6* (Eds.: R. H. F. Manske), Academic Press, New York, 1952, Chapter 7; *(d)* K. W. Bentley in *The Alkaloids*, *Vol. 13* (Eds.: R. H. F. Manske), Academic Press, New York, 1952, Chapter 1; *(e)* U. V. Mallavadhani, C. V. Prasad, S. Shrivastava and V. G. Naidu, *Eur. J. Med. Chem.* 2014, **83**, 84-91.

3 For some recent examples, see: *(a)* S. Kodama, Y. Hamashima, K. Nishide and M. Node, *Angew. Chem.* 2004, **116**, 2713; *Angew. Chem. Int. Ed.* 2004, **43**, 2659; *(b)* L. Li, Q. Yang, Y. Wang and Y. X. Jia, *Angew. Chem.* 2015, **127**, 6353; *Angew. Chem. Int. Ed.* 2015, **54**, 6255; *(c)* C. M. Cheung, F. W. Goldberg, P. Magnus, C. J. Russell, R. Turnbull and V. Lynch, *J. Am. Chem. Soc*. 2007, **129**, 12320; *(d)* G. Zhou and E. J. Corey, *J. Am. Chem. Soc.* 2005, **127**, 11958; *(e)* J. John, U. Indu and E. Suresh, K. V. Radhakrishnan, *J. Am. Chem. Soc.* 2009, **131**, 5042; *(f)* M. Ueda, Y. Ito, Y. Ichii, M. Kakiuchi, H. Shono and O. Miyata, *Chem. Eur. J.* 2014, **20**, 6763; *(g)* S. J. Gharpure, P. Niranjana and S. K. Porwal, *Org. Lett.* 2012, **14**, 5476; *(h)* G. C. Tsui, J. Tsoung, P. Dougan and M. Lautens, *Org. Lett.* 2012, **14**, 5542; *(i)* N. Takeda, M. Ueda, S. Kagehira, H. Komei, N. Tohnai, M. Miyata, T. Naito and O. Miyata, *Org. Lett.* 2013, **15**, 4382.

4 For reviews, see: *(a)* K. C. Nicolaou, S. A. Snyder, T. Montagnon and G.Vassilikogiannakis, *Angew. Chem.* 2002, **114**, 1742; *Angew. Chem. Int. Ed.* 2002, **41**, 1668; *(b)* D. Magdziak, S. J. Meek and T. R. R. Pettus, *Chem. Rev.* 2004, **104**, 1383; c) S. P. Roche and J. A. Porco, *Angew. Chem.* 2011, **123**, 4154; *Angew. Chem. Int. Ed.* 2011, **50**, 4068; d) C. X. Zhuo, W. Zhang and S. L. You, *Angew. Chem.* 2012, **124**, 12834; *Angew. Chem. Int. Ed.* 2012, **51**, 12662.

5 For selected examples, see: *(a)* Y. H. Chen, D. J. Cheng, J. Zhang, Y. Wang, X. Y. Liu and B. Tan, *J. Am. Chem. Soc.* 2015, **137**, 15062; *(b)* T. Hashimoto, H. Nakatsu and K. Maruoka, *Angew. Chem.* 2015, **127**, 4700; *Angew. Chem. Int. Ed*. 2015, **54**, 4617; *(c)* Y. C. Zhang, J. J. Zhao, F. Jiang, S. B. Sun and F. Shi, *Angew. Chem.* 2014, **126**, 14132; *Angew. Chem. Int. Ed.* 2014, **53**, 13912; *(d)* L. H. Liao, C. Shu, M. M. Zhang, Y. J. Liao, X. Y. Hu, Y. H. Zhang, Z. J. Wu, W. C. Yuan and X. M. Zhang, *Angew. Chem.* 2014, **126**, 10639; *Angew. Chem. Int. Ed.* 2014, **53**, 10471; *(e)* Y. H. Zhang, X. Y. Hu, S. S. Li, Y. J. Liao, W. C. Yuan and X. M. Zhang, *Tetrahedron* 2014, **70**, 2020; *(f)* T. Hashimoto, H. Nakatsu, Y. Takiguchi, K. Maruoka, *J. Am. Chem. Soc.* 2013, **135**, 16010; *(g)* Ł. Albrecht, C. V. Gómez, C. B. Jacobsen and K. A. Jørgensen, *Org. Lett.* 2013, **15**, 3010; *(h)* K. L. Jensen, P. T. Franke, L. T. Nielsen, K. Daasbjerg and K. A. Jørgensen, *Angew. Chem.* 2010, **122**, 133; *Angew. Chem. Int. Ed.* 2010, **49**, 129; *(i)* J. Aleman, C. B. Jacobsen, K. Frisch, J. Overgaard and K. A. Jørgensen, *Chem. Commun.* 2008, 632; *(j)* J. Alemán, S. Cabrera, E. Maerten, J. Overgaard and K. A. Jørgensen, *Angew. Chem.* 2007, **119**, 5616; *Angew. Chem. Int. Ed.* 2007, **46**, 5520; *(k)* J. Alemán, B. Richter and K. A. Jørgensen, *Angew. Chem.* 2007, **119**, 5611; *Angew. Chem. Int. Ed.* 2007, **46**, 5515; *(l)* Z. Y. Han, D. F. Chen, Y. Y. Wang, R. Guo, P. S. Wang, C. Wang and L. Z. Gong, *J. Am. Chem. Soc.* 2012, **134**, 6532; *(m)* C. Wang, X. H. Chen, S. M. Zhou and L. Z. Gong, *Chem. Commun.* 2010, **46**, 1275; *(n)* W. Y. Siau, W. J. Li, F. Xue, Q. Ren, M. H. Wu, S. F. Sun, H. B. Guo, X. F. Jiang and J. Wang, *Chem. Eur. J.* 2012, **18**, 9491.

6 *(a)* C. Shu, L. H. Liao, Y. J. Liao, X. Y. Hu, Y. H. Zhang, W. C. Yuan and X. M. Zhang, *Eur. J. Org. Chem.* 2014, 4467; *(b)* L. H. Liao, M. M. Zhang, Y. J. Liao, W. C. Yuan and X. M. Zhang, *Synlett* 2015, **26**, 1720.

7 For reviews on chiral phosphoric acids catalyzed asymmetric reactions, see, *(a)* J. Yu, F. Shi and L. Z. Gong, *Acc. Chem. Res.* 2011**, 44**, 1156. *(b)* M. Terada, *Synthesis* 2010, 1929; *(c)* M. Terada, *Bull. Chem. Soc. Jpn.* 2010, **83**, 101; *(d)* M. Terada, *Chem. Commun.* 2008, 4097; *(e)* T. Akiyama, *Chem. Rev.* 2007, **107**, 5744; *(f)* A. G. Doyle and E. N. Jacobsen, *Chem. Rev.* 2007, **107**, 5714; *(g)* H. Wu, Y. P. He, F. Shi, *Synthesis* 2015, **47**, 1990.

8 CCDC 1448891 (**3d**) contains 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/data_request/cif.