DOI: 10.1002/adsc.201300521

Diastereoselective Methyl Orthoformate Alkylations of Chiral *N*-Acylthiazolidinethiones Catalyzed by Nickel(II) Complexes

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Received: June 14, 2013; Revised: July 25, 2013; Published online: October 9, 2013

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201300521.

Abstract: The completely diastereoselective silyl triflate-mediated methyl orthoformate alkylation of chiral *N*-acyl-4-isopropyl-1,3-thiazolidine-2-thiones catalyzed by commercially available nickel(II) complexes is reported. The simple experimental procedure requires 2.5–5 mol% of bis(phosphine)nickel dichloride [$(R_3P)_2NiCl_2$] complexes, proceeds under very mild conditions, and covers a wide array of acyl groups. Furthermore, it can potentially be expanded to different electrophiles.

Keywords: alkylation; diastereoselectivity; nickel; synthetic methods; thiazolidinethiones

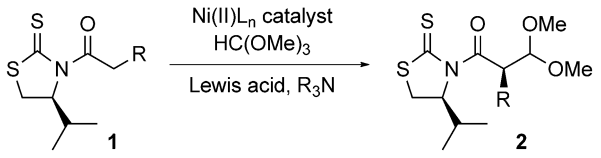
The stereoselective construction of carbon-carbon bonds through an S_N1-like mechanism is a promising approach to the synthesis of compounds with structurally complex molecular architecture.[1] To date, the addition of nucleophiles to chiral oxocarbenium ions has played a key role in the chemistry of carbohydrates and has been much exploited in the development of routes for the synthesis of natural products.[2] More recently, the need for more efficient processes has stimulated the development of new stereoselective additions of carbon nucleophiles to oxocarbenium and carbenium intermediates,[3] but there is still a lack of methods for carrying out such transformations using easily available catalysts in a straightforward manner.[4,5]

Some years ago, Evans reported that the (Tol-BINAP)Ni$(OTf)_2$ complex triggered the reaction of *N*-acyl-1,3-thiazolidine-2-thiones with methyl orthoformate activated by $BF_3{\cdot}OEt_2$ to provide the corresponding 3,3-dimethoxy adducts in high yields and with high enantioselectivities.[6] Unfortunately, that chiral catalyst requires careful preparation and the use of dry-box techniques, which have probably hampered further applications to related transformations.

Inspired by this example and taking advantage of our experience with carbon-carbon bond forming processes based on the Lewis acid-mediated addition of titanium enolates from chiral *N*-acyl-1,3-thiazolidine-2-thiones to acetals[7] and glycals,[8,9] we envisaged that such heterocycles might become an excellent chiral platform to promote diastereoselective additions to oxocarbenium intermediates catalyzed by structurally simple metal complexes. The stereocontrol provided by such chiral auxiliaries might facilitate the installation of both one and two vicinal chiral centers promoted by catalytic amounts of achiral metal complexes.[10,11]

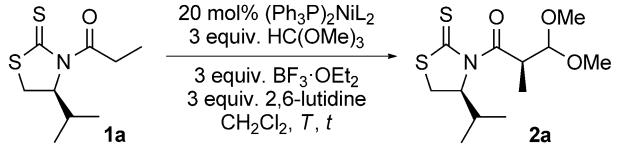
Herein, we report the entirely diastereoselective Lewis acid-mediated addition of (*S*)-*N*-acyl-4-isopropyl-1,3-thiazolidine-2-thiones **1**[12] to methyl orthoformate catalyzed by commercially available nickel(II) complexes (Scheme 1), which could be expanded to more complex reagents.

Preliminary studies using the conditions reported by Evans showed that nickel(II) chloride complexes were unable to promote the addition of (*S*)-*N*-propanoyl-4-isopropyl-1,3-thiazolidine-2-thione **1a** to methyl orthoformate (entry 1 in Table 1). It was necessary to replace the chlorines by sulfonate ligands to obtain the desired adducts. Indeed, freshly prepared



Scheme 1. Lewis acid-mediated additions of **1** to methyl orthoformate catalyzed by nickel(II) complexes.

Table 1. $BF_3{\cdot}OEt_2$-mediated addition of **1a** to $HC(OMe)_3$ catalyzed by nickel(II) complexes.



Entry	Catalyst	T [°C]	t [h]	**2a** [%][a]
1	$(Ph_3P)_2NiCl_2$	20	96	–
2	$(Ph_3P)_2Ni(OMs)_2$	20	16	14
3	$(Ph_3P)_2Ni(OMs)_2$	0	16	24
4	$(Ph_3P)_2Ni(OMs)_2$	−20	16	52
5	$(Ph_3P)_2Ni(OMs)_2$	−20	48	72
6	$(Ph_3P)_2Ni(OTf)_2$	−20	16	36

[a] Isolated yield after column chromatography.

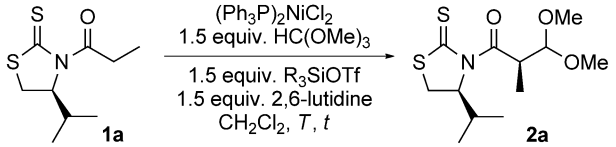
$(Ph_3P)_2Ni(OMs)_2$ produced adduct **2a** as a single diastereomer in yields of up to 72% provided that the reaction was carried out at low temperatures to avoid the formation of decomposition products (compare entries 2–5 in Table 1). These results confirmed our hypotheses about the feasibility of such a process and the absolute control over the configuration of the α-stereocenter imparted by the thiazolidinethione scaffold.[13] Interestingly, the putatively more active $(Ph_3P)_2Ni(OTf)_2$ complex furnished **2a** but in a low yield (entry 6 in Table 1), which suggests that the appropriate preparation of the active species is crucial for the overall process.

Thus, considering that the need to prepare moisture-sensitive catalysts and the use of large amounts of reagents were major hurdles in developing a straightforward and highly efficient method, we paid special attention to Sodeoka's findings regarding the replacement of chlorine *via* the treatment of nickel(II) chloride complexes with silyl triflates.[14] Since those Lewis acids could generate the catalytic species and the oxocarbenium intermediate simultaneously, we next assessed the influence of several silyl triflates on the reaction of **1a** with methyl orthoformate (Table 2). Early experiments with TMSOTf showed that this procedure produced adduct **2a** as a single diastereomer even though the yields were low (entries 1–4 in Table 2). Furthermore, we were pleased to observe that other silyl triflates such as TESOTf or TIPSOTf turned out to be much more suitable and produced **2a** in high yields (entries 5–7 in Table 2) provided that 20 mol% of the nickel(II) complex was used (compare entries 7 and 8 in Table 2).

Parallel studies of more acidic *N*-phenylacetylthiazolidinethione **1b** were much more successful, as high yields of adduct **2b** were obtained at 0 °C irrespective of the silyl triflate (entries 1–3 in Table 3). Remarkably, just 2.5 mol% of $(Ph_3P)_2NiCl_2$ and 1.15 equivalents of TESOTf were enough to deliver adduct **2b** as a single diastereomer with a 94% yield (entries 4–6 in Table 3). Furthermore, smaller amounts of the catalyst also afforded **2b** in yields of up to 91% (entries 7 and 8 in Table 3) but the results proved to be more difficult to reproduce.

Having found a highly efficient and reliable procedure, the influence of other bases and catalysts was next evaluated. We were especially interested in improving the results from **1a**, since the more acidic **1b** already produced a single diastereomer very efficiently under the aforementioned mild conditions. Thus, a large number of tertiary amines and nickel(II) complexes were tested. Surprisingly, none of the bases used in the study produced yields better than or com-

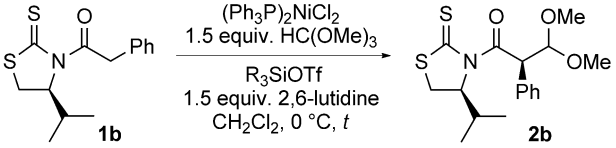
Table 2. Silyl triflate-mediated addition of **1a** to $HC(OMe)_3$ with $(Ph_3P)_2NiCl_2$.



Entry	Catalyst (mol%)	R_3SiOTf	T [°C]	t [h][a]	**2a** [%][b]
1	20	TMSOTf	−20	16	20
2	20	TMSOTf	0	16	33
3	20	TMSOTf	0	72	44
4	20	TMSOTf	20	72	36
5	20	TESOTf	0	16	75
6	20	TESOTf	0	3	77
7	20	TIPSOTf	0	3	77
8	10	TESOTf[c]	0	3	51

[a] The mixture was initially stirred for 20 min at −20 °C.
[b] Isolated yield after column chromatography.
[c] 1.3 equivalents of TESOTf were used

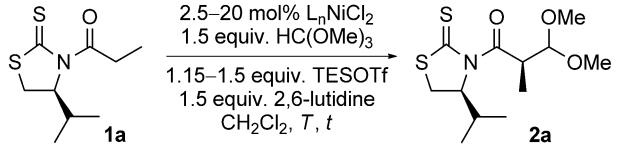
Table 3. Silyl triflate-mediated addition of **1b** to $HC(OMe)_3$ with $(Ph_3P)_2NiCl_2$.



Entry	Catalyst (mol%)	R_3SiOTf	Equiv.	t [h][a]	**2b** [%][b]
1	20	TMSOTf	1.5	3	75
2	20	TESOTf	1.5	3	86
3	20	TIPSOTf	1.5	3	76
4	10	TESOTf	1.3	1	85
5	5	TESOTf	1.2	1	90
6	2.5	TESOTf	1.15	1	94
7	1.5	TESOTf	1.1	1	91
8	1.0	TESOTf	1.1	5	77

[a] The mixture was initially stirred for 20 min at −20 °C.
[b] Isolated yield after column chromatography.

Table 4. Catalytic addition of **1a** to $HC(OMe)_3$.



Entry	L_nNiCl_2	mol%	*T* [°C]	*t* [h][a]	**2a** [%][b]
1[c]	$(Ph_3P)_2NiCl_2$	20	0	3	77
2[c]	(dppe)$NiCl_2$	20	0	3	80
3[e]	(dppp)$NiCl_2$	20	0	3	79
4[c]	$(Cy_3P)_2NiCl_2$	20	0	3	–
5[c]	$(Bu_3P)_2NiCl_2$	20	0	3	79
6[c]	$(Me_3P)_2NiCl_2$	20	0	3	76
7[d]	$(Bu_3P)_2NiCl_2$	5	−20	3	78
8[d]	$(Me_3P)_2NiCl_2$	5	−20	1.5	87
9[e]	$(Me_3P)_2NiCl_2$	2.5	−20	1.5	81
10[c]	(DME)$NiCl_2$	20	0	4	–

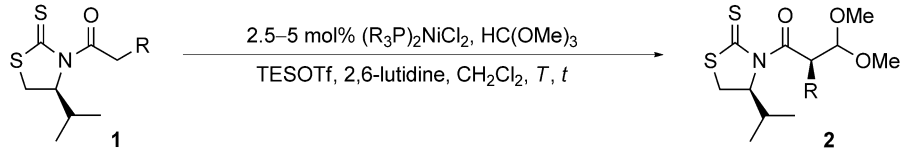
[a] The mixture was initially stirred for 20 min at −20 °C.
[b] Isolated yield after column chromatography.
[c] 1.5 equivalents of TESOTf were used.
[d] 1.2 equivalents of TESOTf were used.
[e] 1.15 equivalents of TESOTf were used.

parable to that of 2,6-lutidine,[15] but some nickel(II) complexes containing trialkylphosphines were fairly active and delivered adduct **2a** in high yields.[16] The results summarized in Table 4 indicated that complexes containing arylphosphines gave almost identical results without observing any beneficial effects of using bidentate ligands (compare entries 1–3 in Table 4). Longer reaction times did not improve these results either. Nevertheless, complexes with alkylphosphines behaved very differently and a promising and significant catalytic activity was observed with complexes possessing basic and unhindered phosphine ligands. Indeed, the sterically hindered complex containing bulky Cy_3P did not yield adduct **2a** at all (entry 4 in Table 4), but Bu_3P and Me_3P counterparts with catalyst loadings of 5–2.5 mol% furnished **2a** in high yields provided that the reaction was carried out at −20 °C (compare entries 5–9 in Table 4). Finally, the more acidic (DME)$NiCl_2$ complex was completely ineffective and no traces of **2a** were observed after long reaction times (entry 10 in Table 4). These results led us to adopt $(Me_3P)_2NiCl_2$ as the complex of choice for the less reactive substrates such as **1a** (Method A), whereas $(Ph_3P)_2NiCl_2$ could be safely used for the more reactive substrates derived from *N*-arylacetyl groups such as **1b** (Method B).

The scope of the process was next examined with several *N*-acylthiazolidinethiones using the conditions optimized for both **1a** and **1b** (Methods A and B, respectively, see the Experimental Section). As shown in Table 5, application of Method A to substrates **1c–e** with alkyl R groups smoothly produced the corresponding adducts **2c–e**, although a certain loss of yield was observed as the steric hindrance of R increased (compare entries 1–4 in Table 5). An acyl chain possessing a methyl ester as well as the introduction of an oxygenated substituent at the α-position were tolerated and the corresponding adducts were obtained as a single diastereomer in high yields (entries 5 and 6 in Table 5). The latter result is particularly significant, since it represents a fruitful example of the uncertain glycolate reaction.[17]

In turn, Method B was successfully applied to substrates **1h–k** irrespective of the electronic character of the aryl group, although yields were slightly lower for

Table 5. TESOTf-mediated catalyzed addition of **1** to $HC(OMe)_3$.



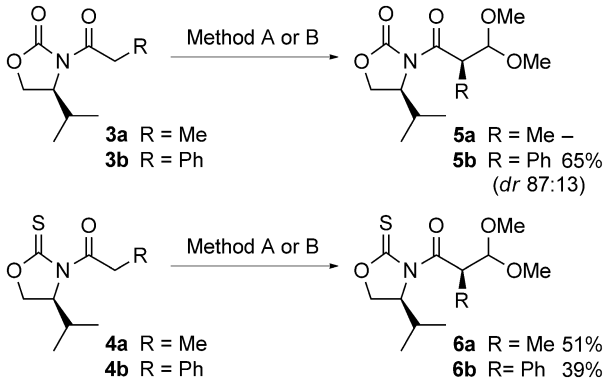
Entry	**1**	R	Catalyst	mol%	TESOTf (equiv.)	*T* [°C]	*t* [h]	**2** [%][a]
1	**a**	Me	$(Me_3P)_2NiCl_2$	5	1.2	−20	1.5	87
2	**c**	Pr	$(Me_3P)_2NiCl_2$	5	1.2	−20	1.5	81
3	**d**	Bn	$(Me_3P)_2NiCl_2$	5	1.2	−20	1.5	73
4	**e**	*i*Pr	$(Me_3P)_2NiCl_2$	5	1.2	−20	1.5	66
5	**f**	$(CH_2)_2CO_2Me$	$(Me_3P)_2NiCl_2$	5	1.2	−20	1.5	67
6	**g**	OPiv	$(Me_3P)_2NiCl_2$	5	1.2	−20	3	82
7	**b**	Ph	$(Ph_3P)_2NiCl_2$	2.5	1.15	0	1[b]	94
8	**h**	4-MeC_6H_4	$(Ph_3P)_2NiCl_2$	2.5	1.15	0	1[b]	88
9	**i**	4-$MeOC_6H_4$	$(Ph_3P)_2NiCl_2$	2.5	1.15	0	1[b]	91
10	**j**	4-$NO_2C_6H_4$	$(Ph_3P)_2NiCl_2$	2.5	1.15	0	1[b]	71
11	**k**	2,4-$F_2C_6H_3$	$(Ph_3P)_2NiCl_2$	2.5	1.15	0	1[b]	74

[a] Isolated yield after column chromatography.
[b] The mixture was initially stirred for 20 min at −20 °C.

those containing electron-withdrawing substituents (compare entries 7–11 in Table 5).[18]

Once the scope of this Lewis acid-mediated addition of *N*-acylthiazolidinethiones to methyl orthoformate had been established, we speculated about the possibility of adapting such a transformation to different chiral auxiliaries.[19] Related oxazolidinones and oxazolidinethiones were promising candidates since their structures are very similar to those of thiazolidinethiones and therefore could result in an extension of the synthetic potential of the reported alkylation.

Following this approach, the optimized experimental conditions were applied to *N*-propanoyl- and *N*-phenylacetyloxazolidinones and -oxazolidinethiones, **3** and **4**, respectively (Scheme 2). The initial results from oxazolidinones **3** were disappointing. Indeed,

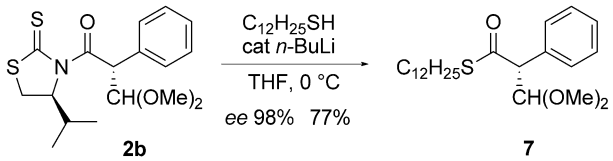


Scheme 2. Influence of different chiral auxiliaries.

the *N*-propanoyloxazolidinone **3a** did not react at all, whereas the more acidic *N*-phenylacetyl counterpart **3b** produced adduct **5b** with a 65% yield but as a mixture of diastereomers (*dr* 87:13). In contrast, oxazolidinethiones **4** were reactive enough and adducts **6** were obtained in a diastereomerically pure form albeit in moderate yields. Careful analyses of the reaction mixtures showed that the yield losses compared to the thiazolidinethione counterparts **1** were due to the partial conversion of the oxazolidinethione scaffold into the corresponding oxazolidinone one. Therefore, these experiments prove that the exocyclic C=S bond is necessary to achieve highly stereocontrolled transformations, whereas the endocyclic sulfur heteroatom is required to avoid undesired decompositions.[20]

The choice of a thiazolidinethione chiral auxiliary was also supported by the mild conditions required for its removal. For instance, enantiomerically pure mandelic-like thioester **7** was obtained with a 77% yield by simple treatment of adduct **2b** with 1-dodecanethiol under basic conditions (Scheme 3).

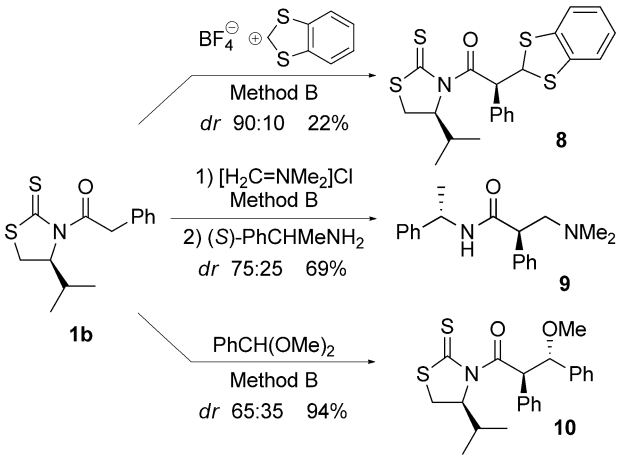
Considering that the conditions optimized for the methyl orthoformate alkylation of *N*-acylthiazolidinethiones **1** could be applied to different cationic inter-



Scheme 3. Removal of the chiral auxiliary.

mediates, we finally explored such alkylation reactions with the different electrophiles represented in Scheme 4. Preliminary studies on the addition of **1b** to 1,3-benzodithiolylium tetrafluoroborate,[21] *N*,*N*-dimethylmethyleneiminium chloride,[22] and benzaldehyde dimethyl acetal gave encouraging results, since the expected adducts **8**–**10** were obtained for all of these reagents.[23] As they encompass intermediates stabilized by sulfur, nitrogen, and oxygen atoms, and they involve the generation of one or two new stereocenters, these results suggest that the method previously developed could be useful for a larger set of transformations that proceed through S_N1-like mechanisms.

In summary, the commercially available and easily to handle nickel(II) complexes $(Me_3P)_2NiCl_2$ and $(Ph_3P)_2NiCl_2$ trigger the completely diastereoselective TESOTf-mediated addition of chiral *N*-acyl-4-isopropyl-1,3-thiazolidine-2-thiones to methyl orthoformate under very mild conditions. This methodology could be expanded to cover other reactions that proceed through oxocarbenium or carbenium intermediates.



Scheme 4. Further transformations.

Experimental Section

General Procedures

Method A: Solid $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol) was added to a solution of **1** (0.5 mmol) and $HC(OMe)_3$ (83 μL, 0.75 mmol) in dry CH_2Cl_2 (1 mL) at room temperature under N_2. The resulting red solution was cooled to −20 °C

and TESOTf (136 μL, 0.6 mmol) and 2,6-lutidine (88 μL, 0.75 mmol) were added dropwise after 3 and 7 min, respectively. The reaction mixture was stirred at −20 °C, quenched with saturated NH_4Cl solution (1.2 mL), and diluted in H_2O. The aqueous layer was extracted with CH_2Cl_2, the combined organic layers were washed with brine, dried and concentrated. The residue was purified by column chromatography on deactivated silica gel to give the desired adduct **2**.

Method B: The reaction was carried out as in Method A using $(Ph_3P)_2NiCl_2$ (8.2 mg, 12.5 μmol) and TESOTf (130 μL, 0.575 mmol). Furthermore, the reaction mixture was stirred at −20 °C for 20 min and in an ice bath for 1 h.

Acknowledgements

Financial support from the Spanish Ministerio de Economía y Competitividad (Grant No. CTQ2012-31034), and the Generalitat de Catalunya (2009SGR825) as well as doctorate studentships to J. M. R. (FPU, Ministerio de Educación) and E. G. (Universitat de Barcelona) are acknowledged.

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[12] For the preparation of **1**, see: E. Gálvez, P. Romea, F. Urpí, *Org. Synth.* **2009**, *86*, 70–80.

[13] The configuration of adduct **2a** was established by conversion into (*R*)-3,3-dimethoxy-2-methylpropanoic acid described by Evans in ref.[6] For further details, see the Supporting Information.

[14] a) T. Suzuki, Y. Hamashima, M. Sodeoka, *Angew. Chem.* **2007**, *119*, 5531–5535; *Angew. Chem. Int. Ed.* **2007**, *46*, 5435–5439; b) Y. Hamashima, T. Nagi, R. Shimizu, T. Tsuchimoto, M. Sodeoka, *Eur. J. Org. Chem.* **2011**, 3675–3678.

[15] Pyridine, 2,6-di-*tert*-butyl-4-methylpyridine, and DBU did not provide adduct **2a** at all, whereas tertiary amines like Et_3N or $(i\text{-}Pr)_2NEt$ afforded **2a** in low yields.

[16] Nickel(II) complexes were purchased from Aldrich and used as received.

[17] For recent examples on the addition of glycolate enolates to oxocarbenium intermediates, see: a) J. Baiget, M. Caba, E. Gálvez, P. Romea, F. Urpí, M. Font-Bardia, *J. Org. Chem.* **2012**, *77*, 8809–8814; b) E. Gálvez, M. Sau, P. Romea, F. Urpí, M. Font-Bardia, *Tetrahedron Lett.* **2013**, *54*, 1467–1470.

[18] The configuration of adduct **2i** was secured through correlation with a compound previously reported by Evans in ref.[6] For further details, see the Supporting Information.

[19] For the influence of chiral auxiliaries on the Lewis acid-mediated addition of titanium enolates to acetals,

see: J. Baiget, A. Cosp, E. Gálvez, L. Gómez-Pinal, P. Romea, F. Urpí, *Tetrahedron* **2008**, *64*, 5637–5644.

[20] Remarkably, Sodeoka reported that the thiazolidinethione and oxazolidinethione heterocycles cannot be used in related asymmetric fluorination reactions because of the high reactivity of the C=S group towards the electrophilic fluorine atom (see ref.[14a]), which proves the crucial role of the auxiliary in this sort of transformations.

[21] For examples of asymmetric reactions with this cation, see: A. Gualandi, E. Emer, M. G. Capdevila, P. G. Cozzi, *Angew. Chem.* **2011**, *123*, 7988–7992; *Angew. Chem. Int. Ed.* **2011**, *50*, 7842–7846.

[22] For overviews on the Mannich reaction, see: a) M. Arend, B. Westermann, N. Risch, *Angew. Chem.* **1998**, *110*, 1096–1122; *Angew. Chem. Int. Ed.* **1998**, *37*, 1044–1070; b) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569.

[23] It was impossible to isolate the adduct derived from *N,N*-dimethylmethyleneiminium chloride, so it was converted into amide **9** by *in situ* treatment of the putative adduct with (*S*)-PhCHMeNH$_2$ (see the Supporting Information).

