UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

Ch5. Monophosphite ligand library

5.3. Screening of a modular sugar-based phosphite ligand library in the asymmetric nickel-catalyzed trialkylaluminium addition to aldehydes

Abstract. We have synthesized a modular sugar-based phosphite ligand library for the Ni-catalyzed trialkylaluminium addition to aldehydes. This library has been designed to rapidly screen the ligands to uncover their important structure features and to determine the scope of the phosphite ligands in this catalytic reactions. After systematic variation of the sugar backbone, the substituents at the phosphite moieties and the flexibility of the ligand backbone, the monophosphite ligand 1,2:5,6-di-*O*-isopropylidene-3-*O*-((3,3';5,5'-tetra-*tert*-butyl-1,1'-biphenyl-2,2'-diyl)phosphite)-α-D-glucofuranose **L7c** was found to be optimal, yielding high activities and enantioselectivities (ee's up to 94 %) for several aryl aldehydes.

5.3.1. Introduction

The catalytic asymmetric carbon-carbon bond formation is one of the most actively pursued areas of research in the field of asymmetric catalysis. In this context, the catalytic addition of dialkylzincs to aldehydes as a route to chiral alcohols has attracted much attention, since many chiral alcohols are highly valuable intermediates for preparing chiral pharmaceutical and agricultural products.[1] For alkylation reagents, trialkylaluminium compounds are more interesting than other organometallic reagents because they are economically obtained in industrial scale from aluminium hydride and olefins.[2] Despite this advantage their use is rare.[3] In this respect, the few most successful catalysts for the enantioselective addition of trialkylaluminium to aldehydes have been titanium complexes bearing chiral diols or *N*-sulfonylated amino alcohols as ligands.[3a-d] However, the high catalyst loadings needed and the slow turnover rate[4] hamper the potential utility of these catalytic systems. Recently, Woodward and coworkers reported the first report of the asymmetric addition of a trialkylaluminium to

aldehydes employing a nickel catalyst, containing a phosphoroamidite ligand. Excellent enantioselectivities with low catalyst loadings were attained.[3e]

To further expand the range of ligands and performance of this asymmetric nickel-catalyzed addition of organoaluminium reagents to aldehydes process, we designed a library of chiral monophosphite ligands **L7-L11a-f** (Figure 1) described in the previous chapter 3. These ligands are derived from natural D-glucose, D-galactose and D-fructose and have the advantage of carbohydrate and phosphite ligands, such as availability at low price from readily available alcohols and facile modular constructions.[5] In addition they are less sensitive to air than typical phosphines, widely used as ligands in asymmetric catalysis. All these favourable features enable series of chiral ligands to be synthesized and screened in the search for high activity and selectivity.[5] Although carbohydrate-based bidentate ligands have been successfully used in some enantioselective reactions (mainly hydrogenation and allylic alkylation),[5] few good monodentate chiral ligands have been reported based on carbohydrates.[6]
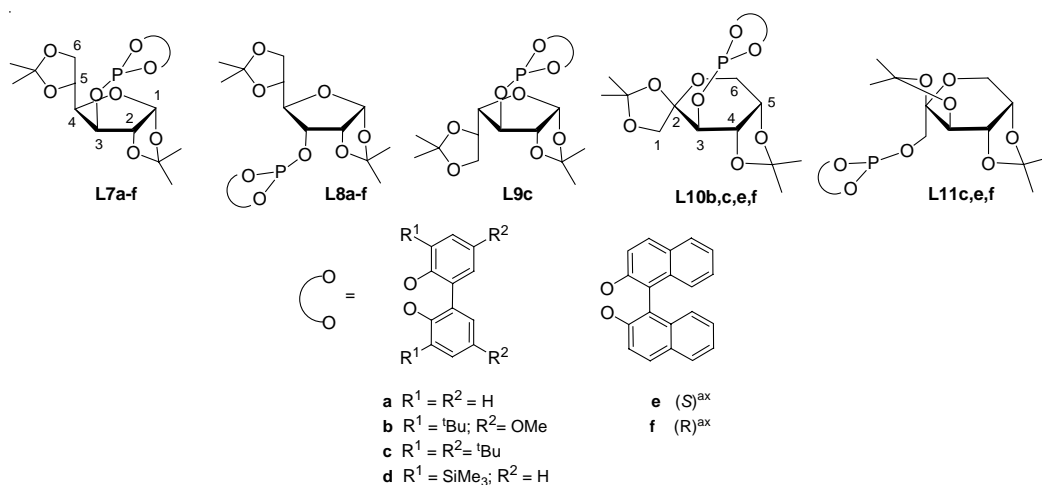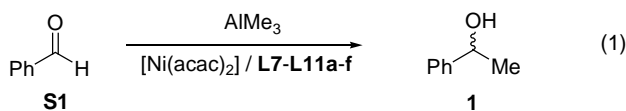

Figure 1. Carbohydrate-based phosphite ligands **L7-11a-f**.

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We report here the design of a library of 30 potential sugar-based chiral phosphite ligands and screen their use in the nickel-catalyzed addition of organoaluminium reagents to aldehydes. The synthesis of this library has been discussed in Chapter 3. With this library we fully investigated the effects of systematically varying the configurations at C-3 and C-4 of the ligand backbone (**L7-L9**), different substituents/configurations in the biaryl phosphite moiety (**a-f**), the carbohydrate ring size (**L7-L10**) and the flexibility of the ligand backbone (**L10-L11**). By carefully selecting these elements, we achieved high enantioselectivities and activities in different substrate types. To the best of our knowledge this is the first example of phosphite ligands applied to this process.

5.3.2. Results and Discussion

5.3.2.1. Asymmetric addition of AlR$_3$ to aldehydes

In a first set of experiments, we evaluated the phosphite ligand library (Figure 1) in the nickel-catalyzed asymmetric addition of trimethylaluminium to benzaldehyde, which is used as a model substrate (eq. 1). The catalytic system was generated *in situ* by adding the corresponding phosphite ligand to a suspension of the catalyst precursor [Ni(acac)$_2$] (acac= acetylacetonate).

$$\text{Ph} \overset{\text{O}}{\underset{\text{S1}}{\diagup\!\!\!\backslash}} \text{H} \quad \xrightarrow[\text{[Ni(acac)}_2] \,/\, \textbf{L7-L11a-f}}{\text{AlMe}_3} \quad \text{Ph} \overset{\text{OH}}{\underset{\textbf{1}}{\diagup\!\!\!\backslash}} \text{Me} \qquad (1)$$

The results, which are summarized in Table 1, indicate that the catalytic performance (activities and enantioselectivities) is highly affected by the configuration of carbon atoms C-3 and C-4, the size of the ring of the sugar backbone and the substituents of the biaryl moieties.

Table 1. Selected results for the nickel-catalyzed asymmetric addition of AlMe$_3$ to benzaldehyde using phosphite library **L7-L11a-f**.[a]

Entry	Ligand	L/Ni	t (h)	% Conv.[b]	% Yield[c]	% ee[d]
1	**L7a**	2	3	16	15	27 (R)
2	**L7b**	2	3	89	80	82 (S)
3	**L7c**	2	3	100	85	89 (S)
4	**L7d**	2	3	100	87	52 (S)
5	**L7e**	2	3	14	11	41 (R)
6	**L7f**	2	3	17	12	10 (R)
7	**L8a**	2	3	15	12	5 (*R*)
8	**L8b**	2	3	98	95	41 (*R*)
9	**L8c**	2	3	100	100	44 (*R*)
10	**L8d**	2	3	100	86	17(*R*)
11	**L8e**	2	3	29	22	6(*R*)
12	**L8f**	2	3	12	3	5(*S*)
13	**L9c**	2	3	100	60	70 (*R*)
14	**L10b**	2	3	99	58	9 (*S*)
15	**L10c**	2	3	100	64	52 (*S*)
16	**l11c**	2	3	83	52	36 (*R*)
17	**L7c**	2.5	3	100	68	88 (*S*)
18	**L7c**	1	3	100	100	89 (*S*)
19	**L7c**	1	1	100	100	90 (*S*)
20	**L7c**	2	1	100	87	91 (*S*)
21	**L8c**	1	1	100	95	45 (*R*)

[a] Reaction conditions: T= -20 ^{o}C, [Ni(acac)$_2$] (1 mol%), AlMe$_3$ (2 equiv.), **S1** (0.25 mmol), THF (2 mL). [b] % Conversion determined by GC. [c] % Yield determined by GC using dodecane as internal standard. [d] Enantiomeric excess measured by GC using Lipodex-A column.

With ligands **L7a-f** we studied how the biaryl phosphite moieties affects the product outcome. We found that the substitutents at the *ortho* positions of the biaryl phosphite moiety affected yield, while enantioselectivities were mainly affected by the substituents at the *para* positions of the biaryl phosphite group.

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Therefore, for high yields bulky substituents in the *ortho* position of the biaryl phosphite moiety are necessary (Table 1, entries 1,5 and 6 vs 2-4). Regarding enantioselectivities, these are better when *tert*-butyl groups are present in the *para* position of the biphenyl phosphite moiety (Table 1, entries 3 vs 2 and 4). The best trade-off between yield and enantioselectivity was therefore obtained using ligand **L7c**.

With ligands **L8**, whose configuration at C-3 is opposite than those of ligands **L7**, we studied the effect of this configuration in the product outcome. The results indicated that there is an influence of this configuration on enantioselectivity (Table 1, entries 7-12). Therefore, the use of ligands **L8** with an *R* configuration at C-3 provided lower enantioselectivities than using ligands **L7**. Concerning the effect of the biaryl substituents, the results using ligands **L8a-d** confirms the previous trends observed with ligands **L7**. Therefore, yields and enantioselectivities were best using the ligand that contains *tert*-butyl groups at both *ortho* and *para* positions of the biphenyl phosphite moiety (ligand **L8c**).

With ligands **L7e**, **L7f**, **L8e** and **L8f**, we studied the possibility of a cooperative effect between the stereocenters of the ligand backbone and the configuration of the biaryl phosphite moieties (Table 1, entries 5, 6, 11 and 12). The results indicated that the matched combination is achieved with ligand **L7e**, which have *S* configuration at both carbon atom C-3 and in the biaryl phosphite moiety.

Ligands **L9**, which configuration at C-4 is opposite to those of ligands **L7**, afforded lower enantioselectivity than the catalytic system Ni/**L7** (Table 1, entry 3 vs 13) but higher than the catalytic system Ni/**L8** (Table 1, entry 9 vs 13). From these results we can conclude that the effect of the configuration of carbon C-3 is more important than the effect of C-4 on the catalytic performance.

Ligands **L10** which has a pyranoside backbone provided lower yields and enantioselectivitities (up to 52% (*S*)) than their related furanoside ligands **L7** (Table 1, entries 2 and 3 vs 14 and 15).

Finally, the most flexible ligand **L11**, which has the phosphite moiety attached to a primary carbon, provided the lowest enantioselectivities (Table 1, entries 16 vs 3, 9, 13 and 15).

We next studied with the ligand that provided the best results (ligand **L7c**) the effect of the ligand-to-nickel ratio in the product outcome. Our results shown that no excess of ligand is needed for high yields and enantioselectivities (Table 1, entries 17 vs 3 and 16).[7] Finally, we optimized the reaction time and we found complete reaction after 1 hour (Table 1, entry 18 vs 3).

To further investigate the catalytic efficiency of these Ni/**L7-L11** systems, we then tested them in the nickel-catalyzed addition of trialkylaluminium (AlR'$_3$; R'= Me or Et) to other benchmark aldehydes with different steric and electronic properties. The results are summarized in Table 2.

We found that enantioselectivity for AlMe$_3$ addition is hardly affected by the presence of electronwithdrawing or electrondonating groups at the *para* position of the phenyl group (Table 2, entries 1, 3, 5, 6, 8 and 10). However, the best yield was achieved using benzaldehyde as substrate, while substrate 4-OMe-Ph gave the poorest (Table 2, entry 1 vs 5). Enantioselectivity of the reaction is also significantly influenced by steric factors. Therefore enantioselectivities are better when *para* substituted aryl aldehydes were used as substrates (Table 2, entries 3, 11 and 12). We have also found that enantioselectivity was more difficulty to control when a more flexible substrate is used (Table 2, entries 13 and 14).

The results of using triethylaluminium as alkylating reagent indicated that the catalytic performance follow the same trend as for the trimethylaluminium addition (Table 2, entries 1, 3, 6 and 8 vs 2, 4, 7 and 9).

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Table 2. Selected results for the nickel-catalyzed asymmetric addition of AlR'_3 (R'= Me or Et) to aldehydes using ligand **L7c**.[a]


Entry	Substrate	R	R'	% Conv.[b]	Yield[c]	% ee[d]
1	**S1**	C_6H_5	Me	100	100	90 (*S*)
2	**S1**	C_6H_5	Et	100	96	88 (S)
3	**S2**	$4\text{-}Cl\text{-}C_6H_4$	Me	100	82	91 (*S*)
4	**S2**	$4\text{-}Cl\text{-}C_6H_4$	Et	100	83	90 (*S*)
5	**S3**	$4\text{-}OMe\text{-}C_6H_4$	Me	93	53	94 (*S*)
6	**S4**	$4\text{-}CF_3\text{-}C_6H_4$	Me	100	95	93 (*S*)
7	**S4**	$4\text{-}CF_3\text{-}C_6H_4$	Et	100	96	94 (*S*)
8	**S5**	$4\text{-}Me\text{-}C_6H_4$	Me	94	84	91 (*S*)
9	**S5**	$4\text{-}Me\text{-}C_6H_4$	Et	98	85	88 (*S*)
10	**S6**	$4\text{-}Br\text{-}C_6H_4$	Me	98	86	92 (*S*)
11	**S7**	$3\text{-}Cl\text{-}C_6H_4$	Me	95	73	74 (*S*)
12	**S8**	$2\text{-}Cl\text{-}C_6H_4$	Me	97	85	41 (*R*)
13[e]	**S9**	$PhCH_2CH_2$	Me	100	89	25 (*S*)
14[f]	**S10**	$PhCH=CH$	Me	97	44	25 (*R*)

[a] Reaction conditions: T= -20 °C, [Ni(acac)$_2$] (1 mol%), **L7c** (1mol%), AlR'_3 (2 equiv.), substrate (0.25 mmol), THF (2 mL). [b] % Conversion determined by GC after 1 hour. [c] % Yield determined by GC using dodecane as internal standard. [d] Enantiomeric excess measured by GC using Cyclodex-B column. [e] **L7c** (2 mol%), reaction time 6 hours. [f] **L7c** (2 mol%), reaction time 5 hours.

5.3.2.2. Asymmetric addition of DABAL-Me₃ to aldehydes

Recently, Woodward and coworkers reported for the first time the advantages of using DABAL-Me$_3$ as air-stable methylating reagent in the nickel-catalyzed additions to aldehydes.[3e] Encouraged by the excellent results obtained using trialkylaluminium reagents to aldehydes, we decided to also tested the

phosphite library **L7-L11a-f** in the nickel-catalyzed addition of DABAL-Me$_3$ to aldehydes (eq. 2).
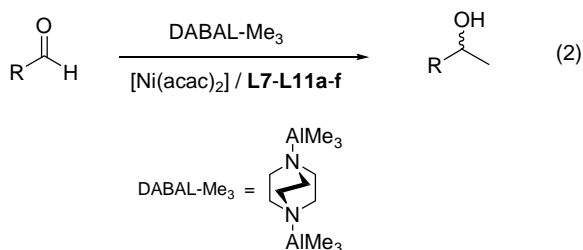
The results, which are summarized in Tables 3 and 4, indicate that the catalytic performance (activities and enantioselectivities) follows the same trend as for the trialkylaluminium addition to aldehydes, which is not unexpected because the reactions have a similar mechanism. However, the yields were lower than in trimethylaluminium addition. Again the catalytic precursor containing the phosphite ligand **L7c** provided the best enantioselectivity (87% ee). It is to note, that in this case the negative effect on yields of the presence of an excess of ligand is more pronounced than when trimethylaluminium was used. Therefore, yields increased almost 100% by reducing the ligand-to-nickel ratio from 2 to 1 (Table 3, entries 3 vs 14).

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Table 3. Selected results for the nickel-catalyzed asymmetric addition of DABAL-Me$_3$ to **S1**.[a]

Entry	Ligand	L*/Ni	Dabal (eq)	t (h)	% Conv.[b]	% Yield[c]	% ee[d]
1	**L7a**	2	1.3	3	75	36	18 (*R*)
2	**L7b**	2	1.3	3	63	35	86 (*S*)
3	**L7c**	2	1.3	3	85	40	87 (*S*)
4	**L7d**	2	1.3	3	73	60	46 (*S*)
5	**L7e**	2	1.3	3	59	37	47 (*R*)
6	**L7f**	2	1.3	3	60	5	0
7	**L8a**	2	1.3	3	74	43	5 (*S*)
8	**L8b**	2	1.3	3	90	51	47 (*S*)
9	**L8c**	2	1.3	3	90	27	58 (*S*)
10	**L8d**	2	1.3	3	70	38	17 (*S*)
11	**L8e**	2	1.3	3	88	38	11 (*S*)
12	**L8f**	2	1.3	3	83	29	4 (*S*)
13	**L7c**	2	0.6	3	61	40	84 (*S*)
14	**L7c**	1	1.3	1.5	97	78	88 (*S*)

[a] Reaction conditions: T= 5 ºC, Ni(acac)$_2$ (1 mol%), **S1** (0.25 mmol), THF (2 mL). [b] % Conversion determined by GC. [c] % Yield determined by GC using dodecane as internal standard. [d] Enantiomeric excess measured by GC using Lipodex-A column.

Table 4. Selected results for the nickel-catalyzed asymmetric addition of DABAL-Me$_3$ to aldehydes using ligand **L7c.**[a]

$$\underset{R}{\overset{O}{\|}}\!\!\!\!\!\!\!\!-\!\!H \quad \xrightarrow[\text{[Ni(acac)}_2\text{] / \textbf{L7c}}]{\text{DABAL-Me}_3} \quad \underset{R}{\overset{OH}{\|}}\!\!\!\!\!\!\!\!-\!\!Me$$

Entry	Substrate	R	% Conv.[b]	Yield[c]	% ee[d]
1	**S1**	C_6H_5	85	78	88 (*S*)
2	**S2**	4-Cl-C_6H_4	99	64	91 (*S*)
3	**S3**	4-OMe-C_6H_4	92	25	78 (*S*)
4	**S4**	4-CF$_3$-C_6H_4	100	53	82 (*S*)
5	**S6**	4-Br-C_6H_4	93	69	90 (*S*)
6	**S5**	4-Me- C_6H_4	96	68	88 (*S*)
7	**S7**	3-Cl-C_6H_4	90	58	67 (*S*)
8	**S8**	2-Cl-C_6H_4	90	62	35 (*R*)
9[e]	**S10**	PhCH=CH	86	22	30 (*R*)

[a] Reaction conditions: T= 5 °C, Ni(acac)$_2$ (1 mol%), **L7c** (1mol%), Dabal-Me$_3$ (1.3 equiv.), substrate (0.25 mmol), THF (2 mL). [b] % Conversion determined by GC after 1.5 hours. [c] % Yield determined by GC using dodecane as internal standard. [d] Enantiomeric excess measured by GC using Lipodex-A column. [e] **L7c** (2mol%).

5.3.3. Conclusions

A library of readily available monophosphite ligands has been synthesized and applied for the first time in the Ni-catalyzed trialkylaluminium addition to several aldehydes. By carefully designing this library we were able to systematically investigate the effect of varying the sugar backbone, the configurations at carbon C-3 and C-4 of the ligand backbone and the type of substituents/configurations in the biaryl phosphite moiety. By judicious choice of the ligand components we obtained high enantioselectivities (ee values up to 94%) and high activities, in several aryl aldehydes, with low catalyst loading (1 mol %) and without excess of ligand.

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To sum up, the combination of high activities and enantioselectivities with low catalyst loading and the low cost of these phosphite ligands open up a new class of ligands for the enantioselective Ni-catalyzed addition of trialkylaluminium reagents to aldehydes that competes favorably with the best ligands designed for this process.[3]

5.3.4. Experimental section

5.3.4.1. General comments

All syntheses were performed by using standard Schlenk techniques under argon atmosphere. Solvents were purified by standard procedures. The synthesis of ligands **L7**-**L11a-f** is described in Chapter 3. DABAL-Me$_3$ was prepared as previously described.[3e] All other reagents were used as commercially available.

5.3.4.2. General procedure for the Ni-catalyzed enantioselective 1,2-addition of trialkylaluminium reagents to aldehydes

[Ni(acac)$_2$] (0.6 mg, 2.33 μmol, 1 mol %) and ligand (2.33 μmol, 1 mol %) were stirred in dry THF (2 mL) under argon atmosphere at -20 ^{o}C for 10 min. Neat aldehyde (0.25 mmol) was then added and trialkylaluminium (0.5 mmol) was added dropwise after a further 10 min. After the desired reaction time, the reaction was quenched with 2M HCl (2 mL). Then dodecane (20 μL) was added and the mixture was extracted with Et$_2$O (10 mL). The organic layer was dried over MgSO$_4$ and analyzed by GC.[3e]

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5.3.4.3. General procedure for the Ni-catalyzed enantioselective 1,2-addition of DABAL-Me₃ to aldehydes

[Ni(acac)₂] (0.6 mg, 2.33 μmol, 1 mol %) and ligand (2.33 μmol, 1 mol %) were stirred in dry THF (2 mL) under argon atmosphere at 5 °C for 10 min. Neat aldehyde (0.25 mmol) was then added and trialkylaluminium (84 mg, 0.325 mmol, 1.3 equiv) was added after a further 10 min. After the desired reaction time, the reaction was quenched with 2M HCl (2 mL). Then dodecane (20 μL) was added and the mixture was extracted with Et₂O (10 mL). The organic layer was dried over MgSO₄ and analyzed by GC.[3e]

5.3.5. Acknowledgements

5.3.6. References

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[4] Addition reactions of AlR_3 to an aldehyde normally require catalyst loadings of 10-20%. See refs. 3a-d.

[5] See for instance: a) Diéguez, M.; Pàmies, O.; Claver, C. *Chem. Rev.* **2004**, *104*, 3189. b) Diéguez, M.; Pàmies, O.; Ruiz, A.; Díaz, Y.; Castillón, S.; Claver, C. *Coord. Chem. Rev.* **2004**, *248*, 2165. c) Diéguez, M.; Ruiz, A.; Claver, C. *Dalton Trans.* **2003**, 2957. d) Pàmies, O.; Diéguez, M.; Ruiz, A.; Claver, C. *Chemistry Today* **2004**, 12. e) Diéguez, M.; Pàmies, O.; Ruiz, A.; Claver, C. in *Methodologies in Asymmetric Catalysis* (Ed. Malhotra, S. V.); American Chemical Society, Washington DC, 2004. f) Diéguez, M.; Pàmies, O.; Claver, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2113.

[6] See for instance: a) Reetz, M. T.; Mehler, G. *Angew. Chem. Int. Ed.* **2000**, *39*, 3889. b) Reet, M. T.; Goossen, L. J.; Meiswinkel, A.; Paetzold, J.; Jense, J. F. *Org. Lett.* **2003**, *5*, 3099. c) Huang, H.; Zheng, Z.; Luo, H.; Bai, C.; Hu, X.; Chen, H. *Org. Lett.* **2003**, *5*, 4137. d) Huang, H.; Liu, X.; Chen, S.; Chen, H.; Zheng, Z. *Tetrahedron: Asymmetry* **2004**, *15*, 2011. e) Huang, H.; Liu, X.; Chen, H.; Zheng, Z. *Tetrahedron: Asymmetry* **2005**, *16*, 693.

[7] At high ligand-to-nickel ratio the diproportionation of benzaldehyde to benzoic acid and benzyl alcohol takes place.