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Investigation of Enantioselectivity Using TADDOL Derivatives as Chiral Ligands in Asymmetric Cyanation Reactions

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ABSTRACT: This study investigates the enantioselectivity challenges of asymmetric cyanation reactions using TADDOL derivatives as chiral ligands, specifically focusing on the cyanosilylation of aldehydes and the cyanation of imines. Despite extensive optimization efforts, the highest achieved ee was only modest, peaking at 71% for the cyanosilylation reaction, while the cyanation of imines consistently resulted in racemic mixtures. Our comprehensive analysis, supported by experimental data and computational modeling, reveals significant barriers to enhancing the enantioselectivity. The results highlight a complex interplay between ligand structure and reaction conditions, demonstrating that even promising ligands such as TADDOL derivatives face substantial challenges in these reaction types. This study underscores the importance of understanding the mechanistic details through computational insights to guide future improvements in asymmetric catalysis.
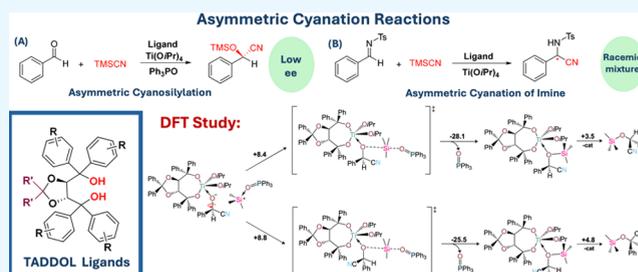
1. INTRODUCTION

Enantioselective transformations are cornerstone processes in modern organic synthesis, playing a crucial role in the production of chiral molecules with a high stereochemical purity. Among various strategies, asymmetric catalysis has proven exceptionally powerful, enabling the synthesis of complex bioactive compounds and pharmaceuticals.[1] The asymmetric cyanosilylation of aldehydes, in particular, has attracted considerable attention due to its utility in constructing versatile chiral building blocks essential for the synthesis of natural products, agrochemicals, and materials with unique properties.[2]

The introduction of a cyano group and a silicon moiety in a single step via asymmetric cyanosilylation offers access to a broad array of valuable synthons. These building blocks serve as versatile intermediates for the synthesis of natural products, pharmaceuticals, agrochemicals, and materials with unique properties.[3] Additionally, the resulting chiral cyanohydrins can serve as versatile precursors for various functional groups, facilitating their further manipulation through subsequent transformations.[4] Additionally, in the realm of cyanation reactions applied to imines, it offers an avenue for the streamlined synthesis of chiral amines, which are crucial components in the preparation of various biologically active compounds and pharmaceuticals.[5] These reactions are marked by their versatility, enabling the creation of diverse molecular scaffolds with high stereochemical control, thus contributing significantly to the toolbox of modern synthetic chemistry.

Historically, numerous chiral ligands such as BINOL,[6] SALEN,[7] β-amino alcohols,[8] and several others[9] have demonstrated their efficacy in promoting high levels of enantioselectivity in these reactions. Despite these advancements, the quest for optimal enantioselectivity remains a significant challenge,[6−9] often restricted by the ligand's structural and electronic properties. In this context, TADDOL (α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol) derivatives have emerged as promising candidates due to their unique structural features that facilitate chiral induction. These ligands are particularly noted for their robustness in various asymmetric catalytic frameworks, offering a balance of steric and electronic effects that are thought to enhance enantioselectivity.[10]

In 2006, Kim et al. explored the potential of a TADDOL derivative, ligand **L1** (Figure 1), reporting up to 50% enantioselectivity in cyanosilylation reactions of benzaldehyde.[11] This initial success underscored both the promise and limitations of TADDOL derivatives in achieving high enantioselectivity in asymmetric cyanation reactions. Despite some instances where enantiomeric excess (ee) values exceeded 90%, demonstrating the significant potential for the
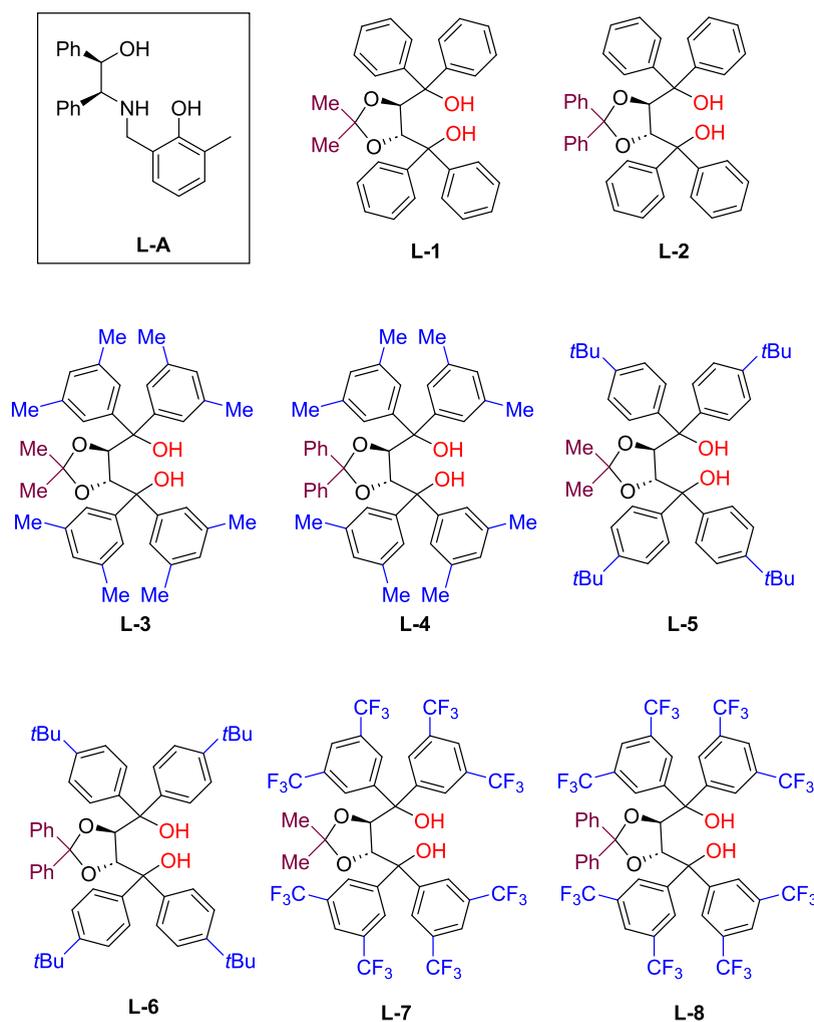
Figure 1. Ligands used for the optimization of the asymmetric cyanosilylation reaction.

synthesis of chiral cyanohydrins with exceptional stereocontrol, consistent achievement of such results across different substrates and reaction conditions has proved challenging.[6−9] These variations in success highlight the need for a deeper understanding of the underlying mechanisms influencing reaction outcomes.

Our study revisits the use of TADDOL derivatives in asymmetric cyanation reactions, particularly the cyanosilylation of aldehydes and cyanation of imines. While previous efforts have shown potential, they often resulted in only moderate ee values. The primary focus of this research is to dissect the mechanistic and theoretical reasons why TADDOL derivatives, despite their promising attributes, frequently fall short of achieving high enantioselectivity in certain environments.[12] We integrate rigorous experimental protocols with detailed density functional theory (DFT) calculations to investigate the interaction dynamics between TADDOL derivatives and substrates, aiming to identify and overcome the observed limitations.

To advance our understanding and potentially enhance the enantioselectivity of these reactions, we synthesized a series of chiral TADDOL ligands (**L1−L8**) (Figure 1), incorporating deliberate structural variations to probe their effects on the reaction dynamics. This comprehensive approach allowed us to explore a wide range of ligand−substrate interactions and steric

effects that could influence the enantioselectivity of the cyanosilylation process. By modifying aryl group arrangements and integrating bulkier groups, we sought to influence ligand orientation and transition state stabilization, enhancing chiral discrimination. These efforts are supported by insights drawn from the existing literature,[12] extending the potential applications of these modifications in asymmetric catalysis.[13]

Our renewed focus on theoretical investigation and experimental validation highlights the intricate relationship between ligand structure, reaction conditions, and enantioselectivity outcomes. By documenting and analyzing both successful and less successful experimental results alongside computational insights, this study contributes to a more nuanced understanding of the challenges in asymmetric synthesis. It underscores the importance of a multidisciplinary approach that melds practical and theoretical perspectives to push the boundaries of enantioselective catalysis.

2. RESULTS AND DISCUSSION

Upon the completion of ligand synthesis, our efforts transitioned to optimizing the reaction conditions using benzaldehyde **4** as the model substrate (Table 1). Initially, employing 12 mol% of **L1** ligand and 10 mol% of Ti(O*i*Pr)$_4$ as the Lewis acid within toluene yielded a 56% yield and 22% ee (entry 2). This outcome initially confirmed the potential for

Table 1. Optimization of the Reaction (Reaction Time, Temperatures, and Ligands)
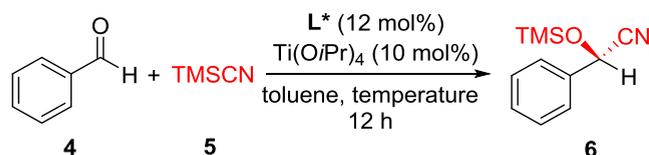
entry	ligand	temp.	yield (%)	ee[a] (%)
1	LA	−20 °C	92	96
2	L1	r.t.[b]	56	22
3[c]	L1	r.t.	58	22
4[d]	L1	0 °C	45	20
5[d]	L1	−20 °C	22	17
6[d]	L1	−40 °C	traces[e]	n.d.[f]
7	**L2**	**r.t.**	**79**	**28**
8	L3	r.t.	45	6
9	L4	r.t.	78	19
10	L5	r.t.	58	13
11	L6	r.t.	82	20
12	L7	r.t.	63	4
13	L8	r.t.	43	0
14	L2	50 °C	45	6
15[g]	L2	r.t.	n.r.[h]	-

[a]ee was determined by chiral HPLC. [b]Room temperature. [c]The reaction time was 72 h. [d]The reaction time was 24 h. [e]4% conversion observed. [f]Not determined. [g]10 mol% of VO(OiPr)₃ was used as Lewis acid. [h]No reaction.

Table 2. Optimization of the Reaction (Solvents and Additives)

entry	solvent	additive	yield (%)	ee[a] (%)
1	toluene		79	28
2	CH₃CN		78	6
3	CH₂Cl₂		52	27
4	THF		n.r.[b]	
5	CHCl₃		65	25
6	Et₂O		n.d.[d]	22
7	toluene	3 Å MS[c]	45	36
8	toluene	iPrOH	74	4
9	toluene	MnO	82	19
10	**toluene**	**Ph₃PO**	**78**	**71**
11	toluene	H₂O	63	43
12	toluene	nBu₃PO	n.d.[d]	43
13	toluene	PhCO₂H	n.d.[d]	R.M.[e]
14	toluene	Et₃N	n.d.[d]	8
15	toluene	DMAP	n.d.[d]	13
16	toluene	HMPA	n.d.[d]	28
16[f]	toluene	Ph₃PO	58	46

[a]ee was determined by chiral HPLC. [b]No reaction. [c]3 Å molecular sieves. [d]Not determined. [e]Racemic mixture. [f]The reaction was carried out with **L1** ligands.

enantioselectivity and the feasibility of success. Extended reaction time up to 72 h exhibited no improvement (entry 3). Examining the temperature effects by varying the reaction conditions to 0, −20, and −40 °C did not elicit enhancements even after an extended 24 h duration (entries 4 to 6). This prompted a shift to alternative ligands to evaluate their efficacy. Notably, ligand **L2** showcased heightened promise with 28% ee, surpassing **L1** and **L3** to **L8** (entries 7 to 13). Curiously, **L8** exhibited nonparticipation in the reaction despite the presence of structurally bulkiest groups (entry 13). Given its superior performance, **L2** was selected for subsequent investigations. Elevating the reaction temperature to 50 °C led to severely diminished enantioselectivity (6% ee) (entry 14). Similarly, employing a vanadium complex as the Lewis acid failed to yield any trace of the desired product (entry 15). These results were compared with those from the previously reported β-amino alcohol ligand[8] **L-A** (entry 1), which provided up to 96% of ee (Supporting Information).

Building upon the improved outcomes from Table 1, entry 7, our exploration expanded to the optimization of solvents, as detailed in Table 2. Extensive scrutiny identified toluene as the most favorable solvent, providing a reliable baseline for further tests. Comparative tests with dichloromethane, chloroform, and diethyl ether (entries 3, 5, and 6, respectively) demonstrated nearly comparable enantioselectivities to toluene. In contrast, acetonitrile (entry 2) yielded a mere 6% enantioselectivity, and tetrahydrofuran (THF) showed no conversion at all (entry 4). These results underscore the significance of solvent choice in influencing the efficiency and outcome of the cyanation reactions.

Subsequent investigations focused on the impact of various additives on the reaction performance. Ph₃PO significantly enhanced enantioselectivity, achieving 71% ee, marking it as the most effective additive tested (entry 10). Other additives

such as 3 Å molecular sieves and water (entries 7 and 11) also improved enantioselectivities, contributing 36 and 43% ee, respectively. However, isopropyl alcohol (entry 8) and manganese oxide (entry 9) were less effective, yielding only 4 and 19% ee, respectively. Further attempts to refine the reaction conditions included using n-butyltriphenylphosphonium oxide and benzoic acid as additives in toluene, which resulted in 43% ee and a racemic mixture, respectively (entries 12 and 13). Additional tests with Et₃N and DMAP in entries 14 and 15, respectively, failed to improve enantioselectivity, yielding 8 and 13% ee. HMPA was also tested as an additive (entry 16), which led to a moderate increase in enantioselectivity at 28% ee. Interestingly, revisiting **L1** in conjunction with Ph₃PO yielded a final 46% ee (entry 17). Ultimately, our optimal conditions converged on using toluene as the solvent and Ph₃PO as the additive, which afforded a commendable 71% ee under room temperature conditions for 12 h.

However, in our ongoing research, we sought to expand the scope of our investigation by optimizing the asymmetric cyanation of N-tosyl imine, employing TMSCN as the cyanating agent. In this extended exploration, all eight ligands (**L1−L8**) were rigorously tested. Additionally, we explored the catalytic potential of various metal complexes, including Ti(OiPr)₄, In(OTf)₃, Sc(OTf)₃, and VO(OiPr)₃. To comprehensively determine the influence of reaction parameters, we employed a range of additives, as listed in Table 2, conducting experiments at different temperatures, including room temperature, 0, −20, and −40 °C (Scheme 1). Even after these extensive efforts, the outcome consistently resulted in a racemic mixture. However, it is noteworthy that the reaction failed to proceed in the absence of a ligand, underscoring the pivotal role played by ligands in the catalytic process.

Scheme 1. Optimization of Asymmetric Cyanation Reaction of Imine
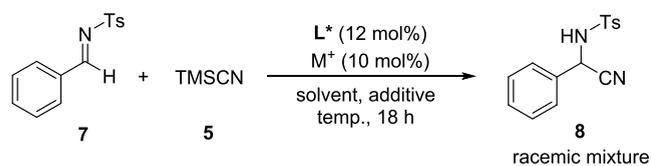
DFT Study. In order to understand the failure of our catalyst for efficient conversion and the effect of the additive on the reaction mechanism, we performed DFT calculations at the (SMD:toluene)ωB97X-D/def2-tzvpp//ωB97X-D/def2-svpp level (Figure 2). Despite our initial assumptions regarding the dissociation of one of the OiPr ligands and other routes (see the Supporting Information for further details), we finally realized that the mechanism goes through an initial coordination of the benzaldehyde (−11.6 kcal/mol) or trimethylsilyl cyanide (−8.6 kcal/mol), both of which are good nucleophiles using ligand **L2** as a model system for our calculations. Since the complexation of benzaldehyde is thermodynamically more favorable, we decided to start from the trigonal bipyramidal **Int1** complex. By only adding the TMSCN, we found that it attacks one of the OiPr oxygens via the trimethylsilyl moiety in transition state **TS1** ($\Delta G_1^{\ddagger} = 34.3$ kcal/mol) to activate the CO double bond where the leaving CN group will bind downhill, generating **Int2** ($\Delta G_{R1} = -5.7$ kcal/mol). After this, a TMS sigmatropic rearrangement in **TS2** ($\Delta G_2^{\ddagger} = 18.4$ kcal/mol) will form the product in **Int3** ($\Delta G_{R2} = -11.6$ kcal/mol) and release it as **6** with a total energy reaction of −13.8 kcal/mol. Therefore, the reason for the modest enantioselectivity lies in the first high-in-energy reaction step and the addition of TMSCN to the less

congested side of benzaldehyde. However, when Ph$_3$PO is used, the reaction proceeds through a different route: the cyano group is the one first transferred, via a nucleophilic attack, to the carbonyl carbon via **TS1$_{PO}$** ($\Delta G_{1PO}^{\ddagger} = 18.9$ kcal/mol), and the TMS coordinates and gets stabilized by the phosphate in **Int2$_{PO}$** ($\Delta G_{R1PO} = +2.4$ kcal/mol). Then, TMS is readily transferred to the carbonyl oxygen via **TS2$_{PO}$** ($\Delta G_{2PO}^{\ddagger} = 8.4$ kcal/mol) to get the final species **Int3** ($\Delta G_{R2PO} = -19.7$ kcal/mol). So, this reaction mechanism presents low energy barriers, increasing the reaction outcome, and the rotation of the C(chiral)-O bond in **Int2$_{PO}$** gives access to a different enantiomer before the migration of the TMS group (see the Supporting Information for the calculated enantioselectivity).

Therefore, by taking the calculated reaction route with Ph$_3$PO, we compared the energy values to get both the R and the S enantiomers of **6** (Table 3). Both routes have similar

Table 3. Comparison of Gibbs Free Energies for R and S Isomers Calculated at the (SMD:toluene)ωB97X-D/def2-tzvpp//ωB97X-D/def2-svpp Level
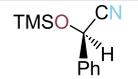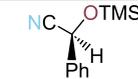
Products	TMSO–CN ... Ph H (R)-6	NC–OTMS ... Ph H (S)-6
TS1$_{PO}$	18.9	20.0
Int2$_{PO}$	2.4	1.9
TS2$_{PO}$	10.8	7.6
Product (6)	-17.3	-16.1
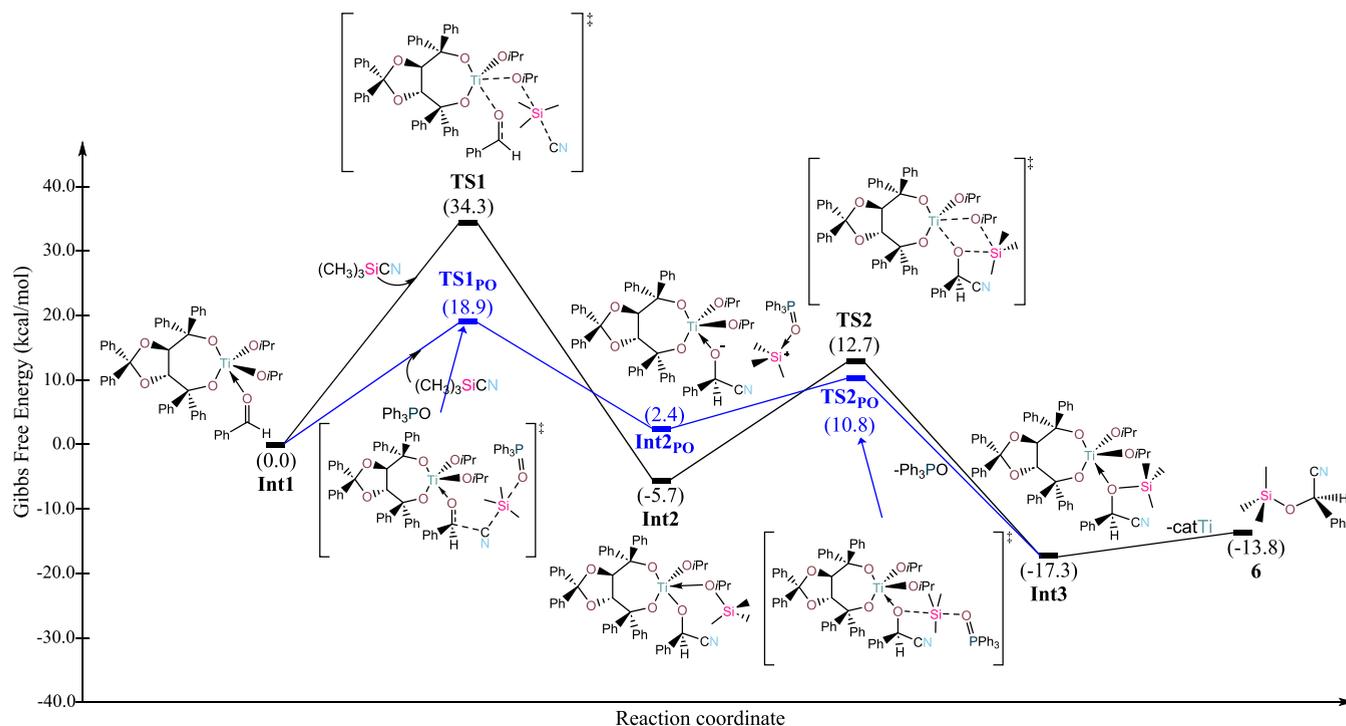
Figure 2. Energy profile of the asymmetric cyanosilylation reaction showing the effect of Ph$_3$PO (blue line) compared to the reaction without the additive (black line) calculated at the (SMD:toluene)ωB97X-D/def2-tzvpp//ωB97X-D/def2-svpp level. Values are expressed as Gibbs free energies in kcal/mol.

energy values, and the enantioselectivity originated from $TS1_{PO}$. The energy difference between R and S is $\Delta\Delta G_{IPO}^{\ddagger}$ = 1.1 kcal/mol, which corresponds to 73% of enantiomeric excess matching with the reported experimental value in Table 2. This low energy difference is due to the indistinct preference of benzaldehyde to coordinate with **L2** to produce R or S enantiomers. It is possible that the OiPr groups attached to TADDOL derivative **L2**, instead of being different, are the cause of the observed low enantioselectivity.

Design Principles of TADDOL Derivative Modifications. To enhance the enantioselectivity in asymmetric cyanation reactions, we strategically modified TADDOL derivatives, focusing on steric and electronic effects. Steric modifications involved increasing the bulk near the ligand's active site to manipulate the spatial environment and promote reaction asymmetry, using larger aryl groups to potentially restrict substrate access to the reactive center. Electronic adjustments included the introduction of electron-donating and -withdrawing groups to alter the electron density at the catalytic site, aiming to influence reactivity and stabilize transition states. We also varied the linkages between the TADDOL scaffold and the metal center to explore the effects of ligand flexibility on catalysis. DFT calculations were employed alongside empirical data to predict how these changes affect the activation energy and transition state stability, enabling a comprehensive evaluation of the ligand designs' effectiveness.

These results significantly contribute to this study by offering valuable insights into the complexity of enantioselective reactions and ligand design. Transparently documenting challenges and least successful outcomes enhances the collective understanding of reaction complexities, guides future research efforts, and promotes methodological refinement. Mechanistic insights can emerge from analyzing reactant behavior even when desired outcomes are not achieved. Sharing negative results fosters data transparency, showcases critical thinking, and advances scientific integrity by providing a comprehensive research narrative. Ultimately, these contributions drive progress by informing future investigations and refining methodologies in the field.

3. CONCLUSIONS

In conclusion, our investigation of the enantioselectivity of asymmetric cyanation reactions employing TADDOL derivatives has unveiled a range of challenges, leading predominantly to modest or even unsuccessful outcomes. While TADDOL derivatives are known for their potential in other catalytic contexts, their performance in the specific reactions studied here was underwhelming. The computational analysis provided valuable insights into the mechanistic aspects of these reactions, explaining the limited success and highlighting the influence of steric and electronic factors imposed by the ligand structure. This detailed understanding points to the necessity of reevaluating the ligand design and reaction parameters to overcome inherent limitations. By transparently reporting these findings, including the less successful outcomes, this work contributes to a more realistic perspective on the development of chiral catalysts and highlights the ongoing need for innovative strategies in the field of enantioselective synthesis.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c04399.

General experimental details; general procedure for the synthesis of chiral TADDOL; NMR spectra; SFC chromatograms; and computational details (PDF)

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