Communication

New Catalytic Asymmetric Formation of Oxygen Heterocycles Bearing Nucleoside Bases at the Anomeric Carbon

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New Catalytic Asymmetric Formation of Oxygen Heterocycles Bearing Nucleoside Bases at the Anomeric Carbon

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Supporting Information Placeholder

ABSTRACT: Pyrimidine nucleosides are an important class of compounds with versatile applications across many fields, including biology and medicinal chemistry. Synthesis of nucleoside analogs in optically pure form via traditional glycosylation has always been a challenge, especially for unnatural carbohydrate motifs which do not have C2 substitution to dictate the stereochemical outcome of the newly formed glyosidic bond. Herein, we report an asymmetric Pd-catalyzed synthesis of nucleoside analogs enabled by the development of a series of chiral ligands. A variety of 5-substituted pyrimidine nucleobases, ranging from 5- to 12-membered ring nucleoside analogs are generated in good yield (68% to 96%), diastereo- (> 20:1), and enantioselectivity (85% ee to 99.5% ee). These nucleoside analogs bearing an iodide functional group handle allow for rapid transformation to a variety of other interesting pyrimidine nucleoside structures.

The ubiquity of biological processes that rely on DNA or RNA for cellular function has made the regulation of interference with pathways related to the replication and translation of DNA and RNA exceptionally useful targets for drug discovery.[1] Almost half of antiviral and anticancer drugs currently on the market are nucleosides.[2] Among them, most contain a tetrahydrofuran ring with a 1' amido-ether linkage to a natural or slightly modified nucleoside base. The most common structural variations are removal or derivatization of either or both of the 2' and/or 3' hydroxyl groups on the tetrahydrofuran ring. While appearing minor, these changes produce compounds with significantly differential biological properties, and more importantly, enhanced selectivity among homologous proteins.[3] Selected examples of nucleoside analogs that represent the broad structural diversity of drugs which are approved by the FDA or currently under various developmental stages are listed in Figure 1. While most nucleoside derivatives contain a tetrahydrofuran core, utilization of alternative tetrahydropyran and oxepane moieties has become increasingly important, as represented by the approved drugs and synthetic nucleoside analogs in Figure 1. Additionally, unnatural nucleosides, such as those containing hexose[9] or oxepane,[10] have been studied as interesting monomer backbones for unnatural oligonucleosides, which are important for gene knockdown and antisense technologies.

Most unnatural nucleosides are synthesized by the derivatization of natural nucleosides or by the coupling of activated bases with anomerically activated sugars using traditional glycosylations.[13] While the former is applicable only if a minor change to the natural nucleoside is required and is limited by the scope of derivatizations, the later reliance on traditional glycosylations often requires the use of additional protecting groups and undesired redox and functional group manipulations to arrive at a suitable glycosylation donor.[14] Common in these methods are poor yields and diastereoselectivities[15] in the glycosylation steps, especially with substrates (Scheme 1) that do not have 2' assisting gr. oups to direct the stereochemistry of the amido-ether bond formation.[16]

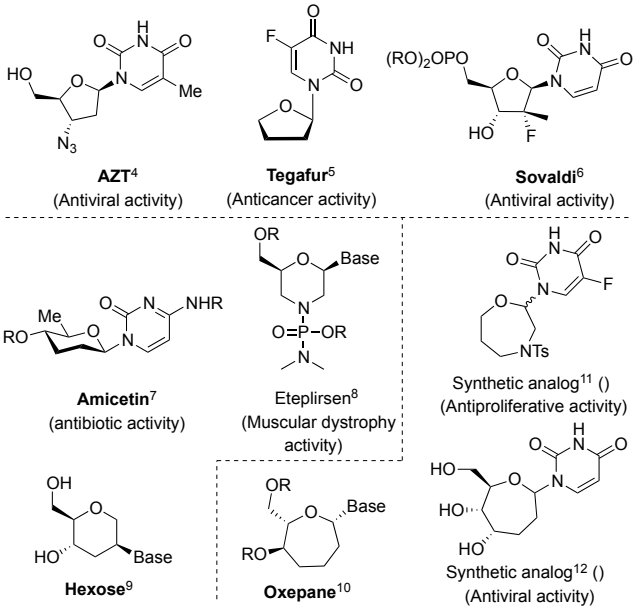


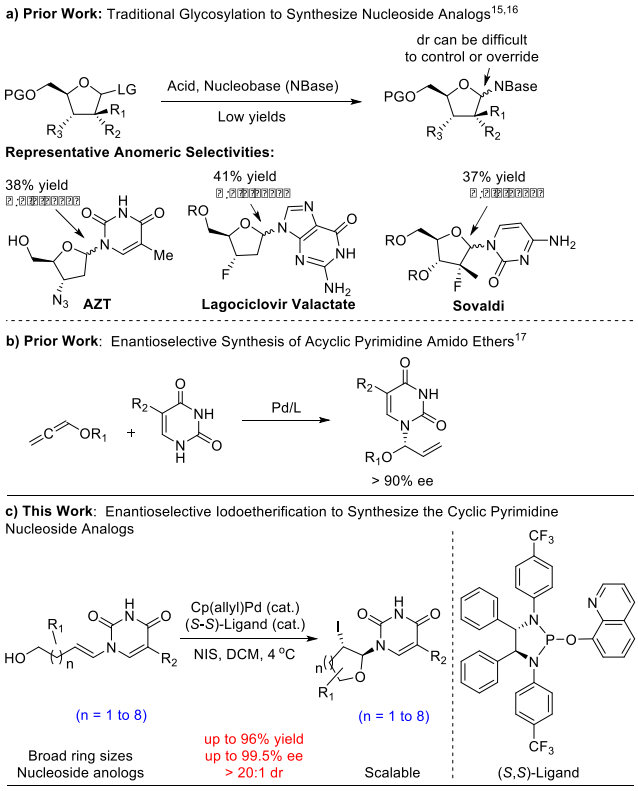
Figure 1. Biologically Important Pyrimidine Nucleoside Derivatives.

Given these limitations, the development of new methods that allow for the high yielding and stereoselective synthesis of nucleoside amido-ether linkages could dramatically improve overall synthetic efficiencies towards such structures. To the best of our knowledge, the first report of an asymmetric synthesis[17] of the N-O amido-ether linkage was reported in 2017 by Rhee et. al (Scheme 1). In this report, acyclic *N*-heterocyclic amide ethers were synthesized by the Pd-catalyzed asymmetric addition of pyrimidines to alkoxyallenes. In spite of this progress, the direct asymmetric synthesis of cyclic pyrimidine nucleosides remains a significant challenge.

As a part of our ongoing investigations on ruthenium chemistry, we have established an efficient synthesis of biologically important and versatile cyclic amido-ether building blocks.[18] While the reported method was a significant development, it lacked en-

antioselectivity and suffered from a lack of generality. Herein, we report the development of a new catalyst system that enables the enantioselective synthesis of pyrimidine nucleoside analogs bearing an iodide functional group handle for further functionalization, with a broad substrate scope via iodoetherification (Scheme 1).

Scheme 1. Summary of Prior and Current Work.



To initiate our studies, we used diene **1a**, which is conveniently prepared in 1 step from commercial materials using a Ru-catalyzed alkene-alkyne coupling,[19] as a standard substrate to evaluate chiral ligands. In the absence of the Pd-catalyst, exclusive iodination of the vinyl silane occurs with the vinyl pyrimidine remaining untouched. While most of the ligands evaluated gave unsatisfactory reactivity and/or enantioselectivity (see SI), the *N*,*P*-bidentate PHOX ligand[20] **L1** and QUIPHOS ligand[21] **L2** (Scheme 2) gave good yields and moderate selectivities, 48% ee and 63% ee respectively. Given these results, we focused on ligands **L3 to L6**, which were synthesized from (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine **3**. Buchwald-Hartwig amination[22] of the diamine with the corresponding aromatic bromide followed by installation of the quinoline or pyridine using PCl_3 gave rapid access to this new class of diamidophosphite ligands. Within these new ligands, changing the chiral backbone of **L2** to **L3** resulted in an inproved ee of 76%. Changing the quinoline ring of **L3** to a pyridine (**L4**) was not productive; however, the more sterically crowded pyridine in **L5** was better tolerated. Having optimized the backbone and the quinoline as the secondary metal coordination site, we turned to optimizing the *N*-aryl group. Pleasingly, placing a *p*-CF_3 group on the *N*-phenyl rings as shown in **L6** further enhances the ee to 80% with a 91% yield.

Scheme 2. Development of Chiral Ligands.

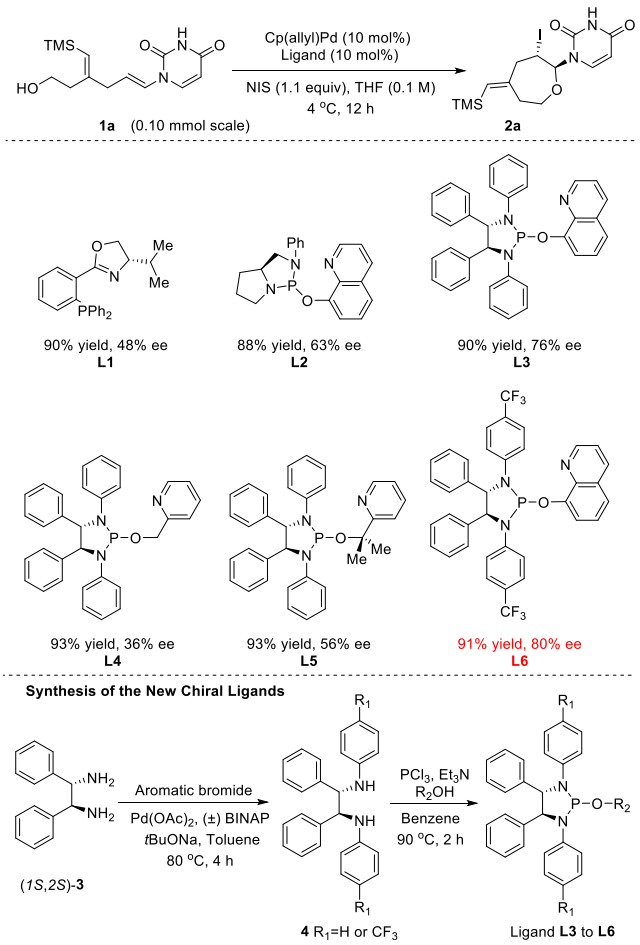
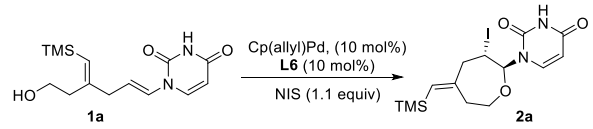


Table 1. Reaction Optimization. [a]



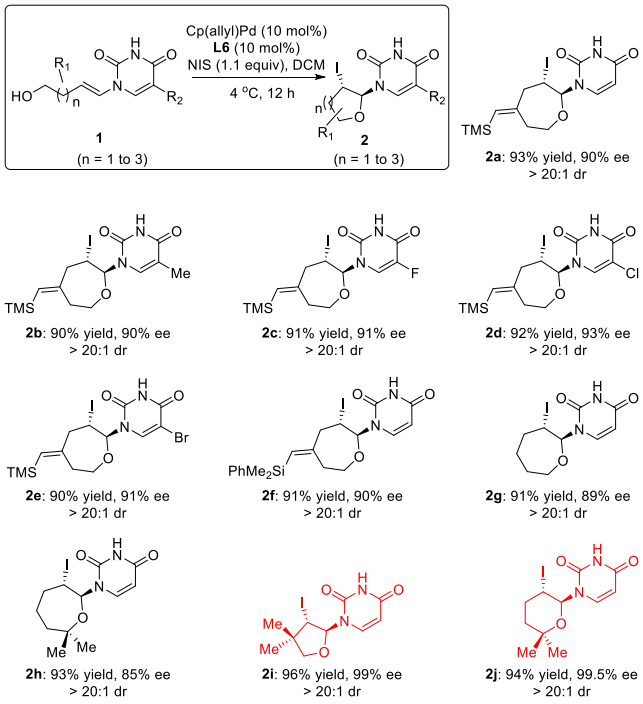
entry	solvent	*T*	yield (%)	dr	ee
1	THF	4 °C	0[b]	–	–
2	THF	4 °C	91	> 20:1	80%
3	DME	4 °C	91	> 20:1	84%
4	Toluene	4 °C	32	> 20:1	54%
5	EtOAc	4 °C	89	> 20:1	74%
6	Et_2O	4 °C	15	> 20:1	22%
7	**DCM**	**4 °C**	**93[c]**	**> 20:1**	**90%**
8	DCM	rt	89	> 20:1	76%
9	DCM	-10 °C	88	> 20:1	89%

[a] All reactions were performed on 0.10 mmol scale at 0.1 M for 12 hours. Yields and dr were determined by crude ^{1}H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as an internal standard; ee determined by chiral HPLC. [b] Without **L6**. [c] Isolated yield.

Adopting **L6** as the standard ligand, variations of the reaction conditions were examined to further enhance the ee (see Table 1). No reactivity was observed without ligand **L6** (entry 1). When the solvent was changed from THF to DME (entry 3), the enantioselectivity increased to 84%. With toluene, EtOAc or Et_2O as solvents, both the yield and enantioselectivity were lower than with THF (entries 4-6). Fortunately, DCM gave significantly better results, and **2a** was obtained in a much-improved 93% isolated yield, > 20:1 dr, and 90% ee (entry 7). Higher or lower temperature had no benefit on yields or selectivities (entries 8, 9).

With optimized conditions (Table 1, entry 7) in hand, we set out to evaluate the scope of pyrimidine nucleobases in this transformation (Scheme 3). Use of thymine did not significantly impact yield or selectivity, giving **2b** in good yield and selectivity. Halogen substituents on the nucleobase were well-tolerated, and excellent results were observed with 5-fluorouracil (**2c**), 5-chlorouracil (**2d**) and 5-bromouracil (**2e**). Varying the substitution on the alcohol tether was also possible. Switching the TMS group in **1a** for a $PhMe_2Si$ group gave **2f**, which bears a vinyl silane that can be directly utilized for cross-coupling reaction.[23] Furthermore, vinyl substitution on the alcohol linker was not required for reactivity, as cyclization of **1g** proceeded cleanly to **2g**. A sterically bulky tertiary alcohol was also tolerated, and **1h** cyclized to **2h** with a slightly reduced enantioselectivity of 85%, but with excellent yield and dr. Interestingly, tetrahydrofuran (**2i**) and tetrahydropyran (**2j**) products with dimethyl substitution on different positions were both obtained remarkably efficiently with 99% ee and 99.5% ee respectively.

Scheme 3. Substrate Scope without Nitrogen on the Ring. [a]

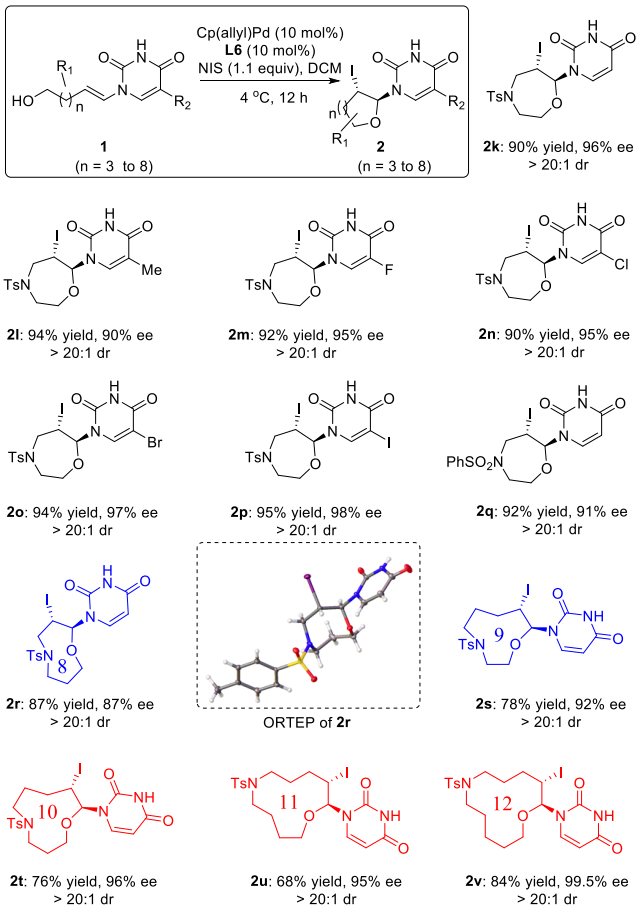


[a] All reactions performed on 0.10 mmol scale. Yields are isolated yields; dr determined by crude ^{1}H NMR, ee determined by chiral HPLC.

Adding a nitrogen linker to the pyrimidine side chain allows access to aza-hetero ring systems, a class of products which show good anticancer activities[11] (Scheme 4). Utilizing uracil with an *N*-tosyl group in the side chain produces aza-oxepane product **2k** in 90% yield, 96% ee and > 20:1 dr. The thymine nucleoside analog (**2l**) was also obtained in high yield and dr with 90% ee. Halogen substituents were well-tolerated; excellent results were observed with 5-fluorouracil (**2m**), 5-chlorouracil (**2n**), 5-bromouracil (**2o**) and 5-iodouracil (**2p**). The nitrogen protecting group could also be changed to $PhSO_2$ (**2q**) while maintaining good yield as well as high ee and dr.

We were pleased to find that our method was not limited to tetrahydrofuran, tetrahydropyran and oxepane ring systems. Notably, this new catalyst system could effectively form medium and large ring systems at concentration as high as 0.1 M, in contrast to many macrocyclization processes. Along these lines, the 8-membered medium ring **2r** was obtained in 87% yield, 87% ee and > 20:1 dr, and its structure was determined by X-ray crystallography.[24] The absolute stereochemistry at C5 and C6 were both determined to have the *S* configuration, placing the uracil and the iodide in a trans configuration. The 9-membered medium ring **2s** was obtained in 92% ee and > 20:1 dr. Excellent enantio- (95% ee to 99.5% ee) and diastereoselectivities (> 20:1 dr) were also observed with the 10-, 11-, and 12-membered large rings **2t**, **2u,** and **2v**.

Scheme 4. Substrate Scope with Nitrogen on the Ring. [a]



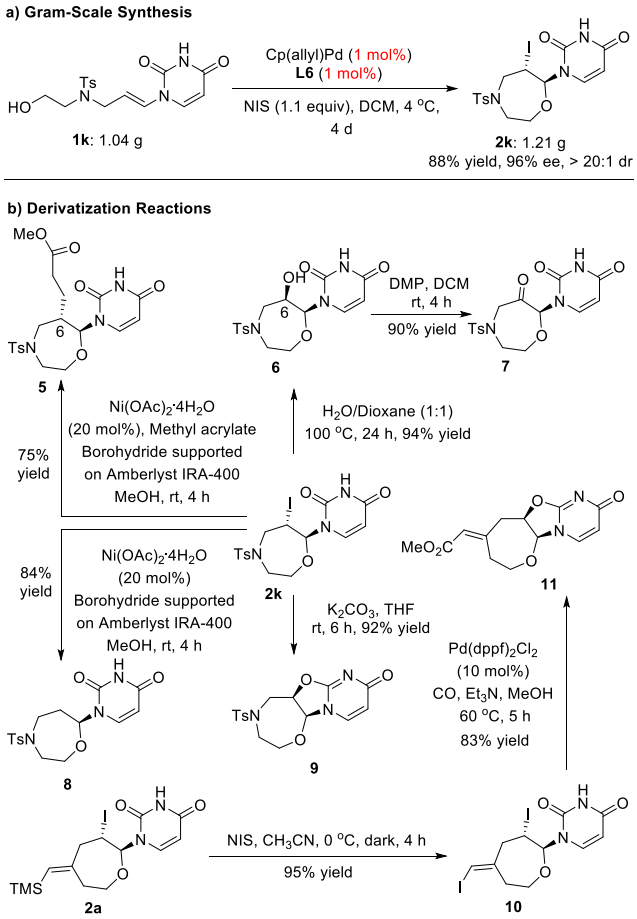
[a] All reactions performed on 0.10 mmol scale. Yields are isolated yields; dr determined by crude ^{1}H NMR, ee determined by chiral HPLC.

To demonstrate the scalability of our method, nucleoside analog **2k** was prepared on gram-scale (Scheme 5). Notably, the reaction could be performed at a reduced catalyst loading of 1 mol% with no deterioration in yield or selectivity (cf. Scheme 4). Product **2k** was obtained in 88% yield, > 20:1 dr, and 96% ee. With this material in hand, we set out to highlight the synthetic utility of the nucleoside analogs bearing an iodide functional group handle that are accessible using this methodology. A Ni-catalyzed radical addition[25] of **2k** to methyl acrylate furnished ester **5** as a single diastereoisomer, presumably due to steric control by the

adjacent nucleobase. Alternatively, nickel in the absence of methyl acrylate reduced the iodide, furnishing compound **8**. Upon treatment with water, nucleoside analog **2k** underwent hydrolysis[26] to afford secondary alcohol **6** with clean inversion of configuration. The absolute stereochemistry at C6 of **5** and **6** were assigned by 2D NOE (see SI). Secondary alcohol **6** could also be oxidized to deliver ketone **7**. Interestingly, intramolecular cyclization of nucleoside analog **2k** occurred upon treatment with K_2CO_3 to afford tricycle **9**.

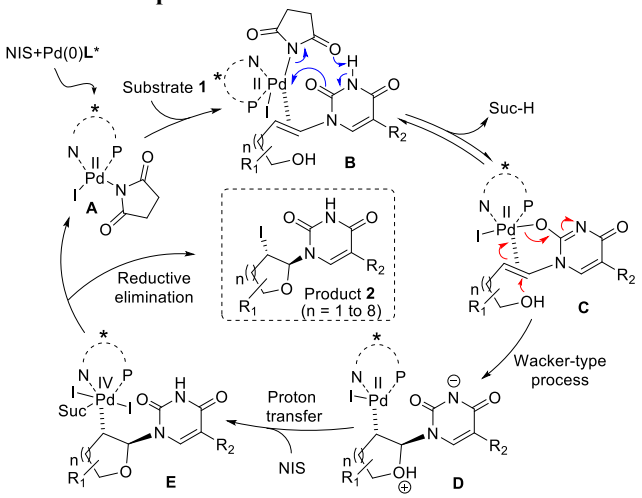
Nucleoside analog **2a** could be converted to vinyl iodide **10** via treatment with NIS in the dark. Palladium catalyzed carboxylation[27] of vinyl iodide **10** occurred with concurrent intramolecular cyclization to give tricyclic vinyl ester **11**.

Scheme 5. Gram-Scale Synthesis and Derivatizations.



A proposed mechanism is depicted in Scheme 6. It should be noted that a N-protected pyrimidine substrate without free N-H did not work. This fact leads to our proposal shown. Presumably this reaction proceeds via a Pd(II)/(IV) catalytic cycle.[28] The catalysis is initiated by oxidative addition of NIS to Pd(0), generating Pd(II) species **A**, which undergoes coordination to the adjacent olefin of nucleobase in substrate **1** providing Pd(II) species **B**. Loss of succinimide and formation of a palladium-oxygen bond generates intermediate **C**, which triggers a Wacker-type process to form **D**. Proton transfer and oxidative addition of NIS to **D** provides Pd(IV) species **E**, which undergoes reductive elimination to release the product **2** and regenerate Pd(II) species **A**. The efficiency of the cyclization going from **C** to **D** accounts for the insensitivity of this reaction to ring size.

Scheme 6. Proposed Reaction Mechanism.



In conclusion, we report the development of a new catalyst system that enables the enantioselective synthesis of pyrimidine nucleoside analogs with a broad substrate scope. The unusual reactivity of this Pd-catalyzed process is highlighted by the reaction of diene **1** in the absence of the Pd-catalyst, wherein exclusive iodination of the vinyl silane occurs and the vinyl pyrimidine is untouched. Thus, the Pd catalyst completely inverts the inherent chemoselectivity. This transformation occurs with good to excellent enantio- and diastereoselectivity and yields are typically high. A variety of 5-substituted pyrimidine nucleobases can be used, and a variety of differently substituted rings are well tolerated. In addition to providing access to the more common 5-, 6-, and 7-membered rings, this process extends to more challenging 8- to 12-membered rings as well, which is rather unusual. The pyrimidine nucleoside analogs bearing an iodide functional group handle that are accessible using this methodology are versatile scaffolds for further functionalization, and can be transformed into a variety of new pyrimidine nucleoside analogs.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and spectral datas (PDF)

Crystallographic data for **2r** (CIF).

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Notes

The authors declare no competing financial interests.

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