Pure Appl. Chem., Vol. 85, No. 6, pp. 1079–1087, 2013.
http://dx.doi.org/10.1351/PAC-CON-12-09-03

Cycloadditions in heterocycle and alkaloid synthesis*

Peter Wipf‡, Zhenglai Fang, Laurent Ferrié, Masafumi Ueda, Maciej A. A. Walczak, Yongzhao Yan, and Michael Yang

Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA

Abstract: Intramolecular cycloadditions of bicyclo[1.1.0]butylalkyl-amines represent a rich source of novel heterocyclic scaffolds. As a function of the side chain attached to the amine, formal ene- or [2 + 2] cycloaddition products can be obtained in moderate to high yields. By suitable further functionalizations, a library of 3-azatricyclo[5.1.1.0^{1,5}]-nonanes was prepared and interrogated in 450 biological assays. This discovery collection was found to generate high hit rates and yet the individual samples demonstrated sufficient selectivity to fulfill robust lead criteria. These applications of bicyclo[1.1.0]butanes demonstrate that new synthetic chemistry and novel architectures are promising starting points for the generation of high-value discovery libraries.

Keywords: alkaloid synthesis; bioactive molecules; cycloadditions; drug discovery; heterocyclic chemistry; organic chemistry.

INTRODUCTION

Many biologically active natural products and pharmaceuticals favor heterocyclic substructures, most likely due to their rigid array of polarizable π-electron clouds, hydrogen donors and acceptors that facilitate strong binding to protein targets, as well as their relatively high stability toward metabolic degradation (Fig. 1). However, the number of unique scaffolds of carbo- and heterocycles in current use is quite limited [1–3]. Pyridines, indoles, imidazoles, thiazoles, thiophenes, quinolines, quinazolines, pyrazoles, pyrimidines, and triazoles rank among the most common heterocycles in pharmaceutical collections, while the breadth of oxygen-, nitrogen-, and sulfur-containing ring systems is far greater in natural products [4–7].

Evolutionary pressure on natural products appears to have favored 3D structures with embedded stereogenic carbons. In contrast, ease of synthetic and commercial access, scope of available literature functionalizations, and precedence for biological activity play important roles in perpetuating the status quo and limit an increase in the diversity of the stable of available pharmaceutical building blocks [8]. Not surprisingly, drug candidates reflect high-throughput screening (HTS) libraries, featuring prominently a few "privileged" heterocycles and their close congeners [9].

Pure Appl. Chem.* **85, 1079–1239 (2013). A collection of invited papers based on presentations at the 19th International Conference on Organic Synthesis (ICOS-19), Melbourne, Australia, 1–6 July 2012.
‡Corresponding author

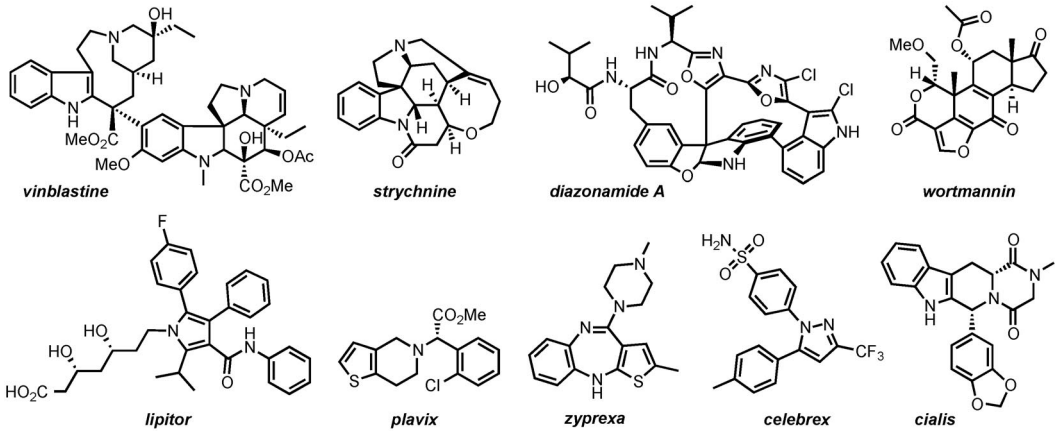


Fig. 1 Representative bioactive natural products and pharmaceuticals.

Several recent studies point out the dearth of diverse scaffolds in the medicinal chemistry toolset, and the challenges to improve the quality of compounds in HTS, lead identification, and lead optimization campaigns [10–12]. While improvements in the methodology to access privileged scaffolds remain a major effort in the synthetic chemistry community, the serendipitous or systematic discovery of fundamentally new reactions to access novel hetero- and carbocyclic scaffolds would be most desirable [2]. New structural diversity will likely increase the number and utility of small molecule modulators of biological functions [13], access new intellectual property (IP) space, and stimulate a more creative deployment of the organic chemistry toolset to solve challenges in biology and medicine (Fig. 2). While initial hits might be more rapidly identified in HTS assays of libraries rich in privileged chemotypes, novel scaffolds showcase the value of an innovative chemistry program, increase the opportunities for the discovery of new biological phenotypes, and bear greater IP value for a platform approach.

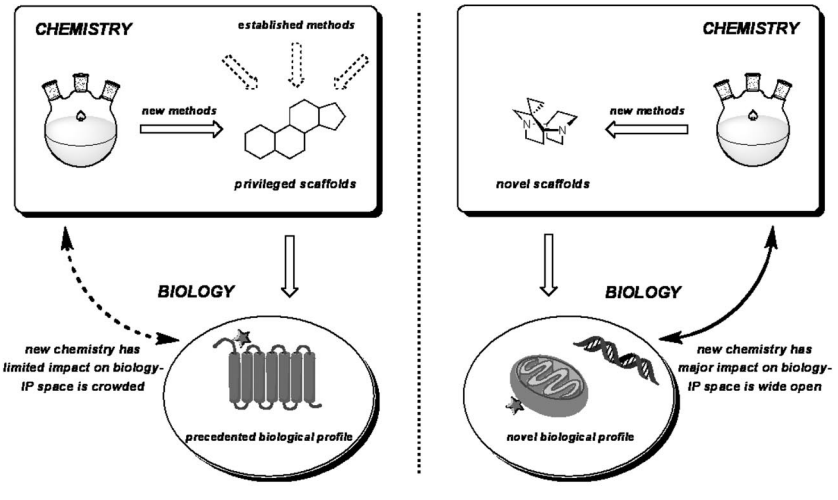


Fig. 2 New methods leading to novel scaffolds have a greater potential impact on biology and are less prone to infringe on established IP.

As part of our program to harvest the potential of strained organic building blocks [14–21], we are investigating the intramolecular cycloaddition chemistry of bicyclo[1.1.0]butanes [22–26]. Among the heterocyclic, fused, bridged, and spirocyclic products available by the ring expansion chemistry of bicyclobutylalkylamines, several completely new scaffolds can be obtained (Fig. 3). Some of these new scaffolds preserve the cyclopropane or the cyclobutane substructures in bicyclobutane; however, in a few cases, all four carbons are integrated into a new five- or six-membered ring system. While the alkylamine substituent was not required for all transformations, it proved crucial for most, both as a handle for the attachment of alkene and alkyne moieties for intramolecular cycloadditions as well as a versatile functional group that allowed for a ready chemical diversification of the product structure.

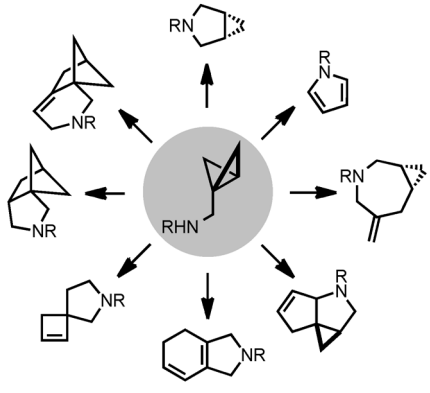


Fig. 3 Scaffold expansions of bicyclo[1.1.0]butylalkylamines.

Among the most attractive chemotypes shown in Fig. 3 are those containing a rigid tricyclic structure, since these carbon/nitrogen scaffolds are considerably more difficult to construct using standard methodologies than monocyclic or fused pyrrolidines and indoles. Tricyclic scaffolds with three- to seven-membered ring systems allow for a precise 3D orientation of substituents and are therefore less likely to result in molecular shapes that are easily molded into diverse enzyme and receptor binding sites. The rigidity of the tricyclic scaffold decreases off-target binding and is also likely to limit metabolic degradation by cytochrome P450 or adverse blockage of hERG potassium channels [27].

This article provides an overview of the synthesis, the structural properties, and the cycloaddition chemistry of bicyclobutanes obtained in our labs, as well as some data on the biological properties of a particular tricyclic scaffold resulting from a formal intramolecular [2 + 2] cycloaddition.

RESULTS AND DISCUSSION

Synthesis of bicyclo[1.1.0]butylalkylamines

At the onset of our studies, we used Simmons–Smith conditions for a double cyclopropanation of propargylic phosphinoylamides (Fig. 4, route a) [26], but the addition of organolithium reagents (route b) [28] has proven to be the most general methodology for the incorporation of bicyclobutyl rings into organic molecules. This practical method is characterized by a broad reaction scope and ease of product purification. Starting with dibromocyclopropanes, two sequential lithium–halogen exchange reactions provide versatile bicyclobutyllithium reagents that add to imines to give a range of functionalized bicyclobutylalkylamines, including enantio- and diastereoenriched derivatives (Fig. 5).

The X-ray structure of a *p*-toluenesulfonyl derivative demonstrates the butterfly-like arrangement of the two cyclopropane rings, whose planes are set at an angle of 122°. The C,C-bond distance of 1.498 Å in the angular bicyclobutane bonds is only slightly shorter than in standard cyclopropane rings,

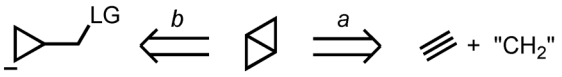


Fig. 4 Two retrosynthetic routes to bicyclo[1.1.0]butanes.

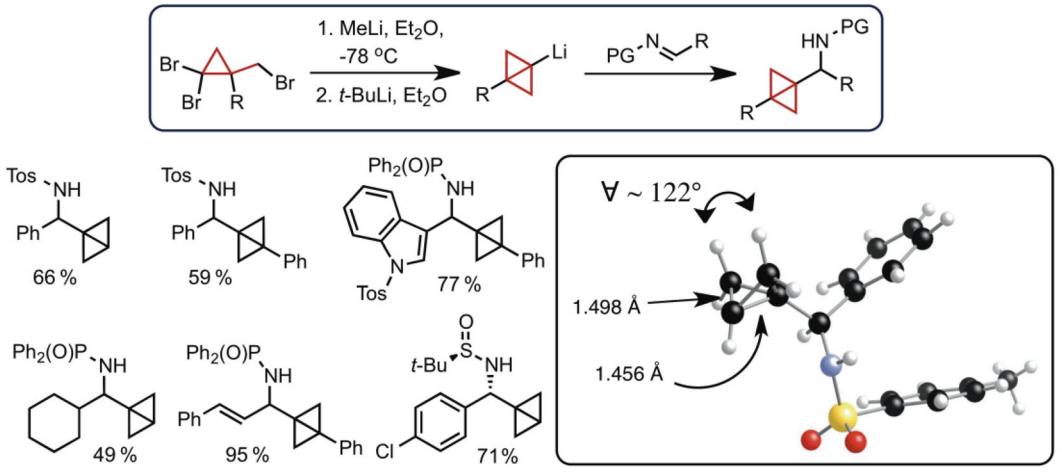


Fig. 5 Preparation of bicyclobutylalkylamines by addition of lithiated bicyclobutanes to imines. Also shown are products illustrating the scope of this methodology, and a typical bicyclobutane X-ray structure.

whereas the central C,C-bond length is ca. 0.05 Å decreased. Much of the chemistry of bicyclobutanes can be explained by the ease of homolytic cleavage of the central C,C-bond by the π-system of alkenes and alkynes, or by a heterolytic opening with nucleophiles in electron-acceptor substituted bicyclobutanes.

New C,C-bond forming pericyclic cascade reactions with bicyclo[1.1.0]butanes

Based on the analysis of highest occupied molecular orbital/lowest unoccupied molecular orbital (HOMO/LUMO) energies, in particular those of arylated bicyclo[1.1.0]butanes (Fig. 6a), we envisioned a cycloaddition of the strained carbocycles with alkenes to be facile. Intermolecular processes, however, proved to be very limited in scope, both in the literature [29] as well as in our hands, most likely due to a relatively large activation barrier and the relative ease of rearrangements of the strained bicycles to 1,3-butadienes [30]. In contrast, we were delighted to see that upon allylation of **1** under phase-transfer conditions, a spontaneous intramolecular ene-reaction provided the spirocycle **2** (Fig. 6b). Furthermore, in the presence of cinnamoyl bromide **3**, a formal [2 + 2] cycloaddition led to the tricycle **4**.

This divergence in the reaction pathways can be explained by the influence of the aryl group (R_1) on the stability of the intermediate biradical **5** (Fig. 6c). With R_1 = H or an alkyl group, the radical at that position is highly reactive and proceeds to form the cyclobutene by a 1,5-hydrogen atom abstraction of the *endo*-hydrogen from the cyclobutane, leading to **2** . With R_1 = Ph, the lifetime of the biradical species is sufficiently long to allow for a ring flip of the cyclobutane, followed by a radical recombination to give the tricyclic product **4**. This mechanistic hypothesis is in good agreement with experimental and simulated electron spin resonance (ESR) data [22].

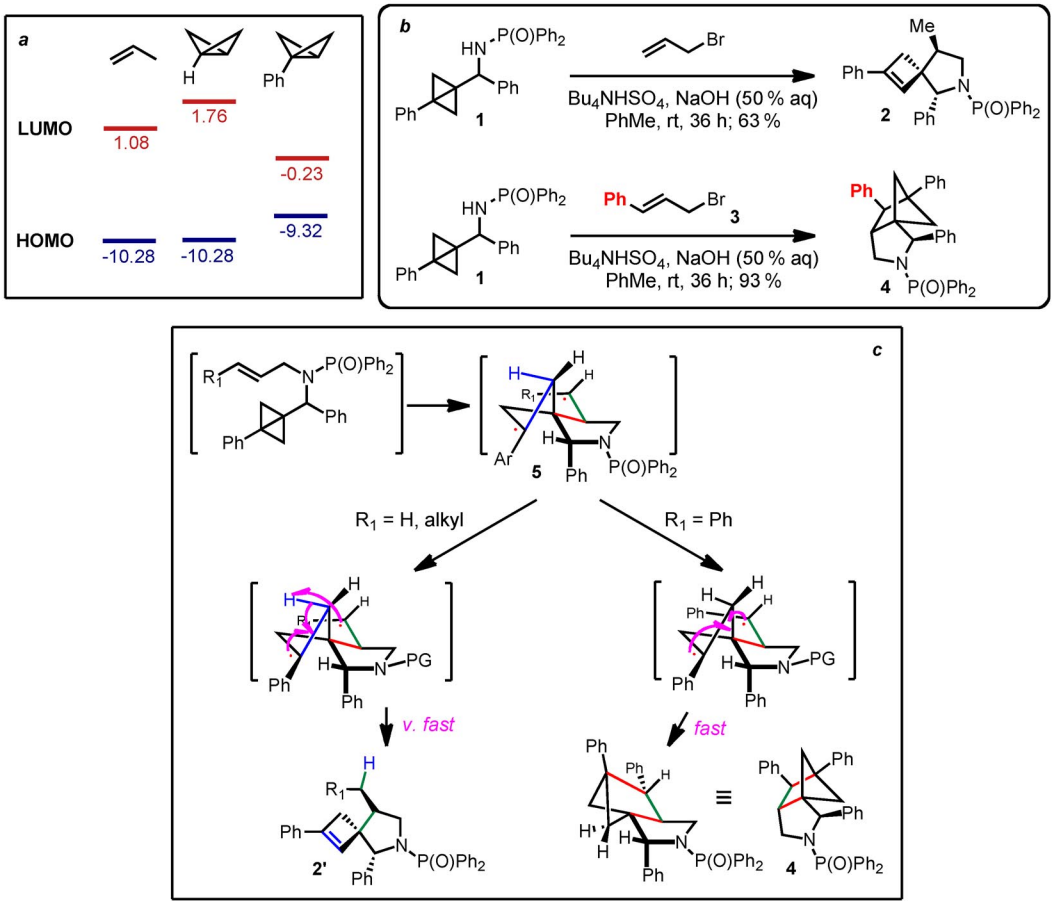


Fig. 6 (a) Frontier orbital scheme, showing HOMO and LUMO of an alkene, a bicyclobutane, and a phenyl substituted bicyclobutane; (b) formal ene- and [2 + 2] cycloaddition products depending on the structure of the allylating agent; (c) mechanism involving biradical intermediates.

The formation of tricyclic pyrrolidinones **4** in the cascade reaction from bicyclobutanes **1** allowed for the first time an investigation of the biological properties of this new heterocyclic scaffold. Prior to our report [25], 3-azatricyclo[5.1.1.0^{1,5}]nonanes such as **4** had never been synthesized, and the parent backbone **6** was not found in the SciFinder and Reaxys chemical databases (Fig. 7). In contrast, the closely related but much more flexible fused bicyclic cyclopenta[*c*]pyrrole scaffold **7** had >10 000 entries in SciFinder. The difference between **6** and **7** is a single, bridging methylene group. Significantly, the four readily modified substituents on **6** extend rather rigidly into a large segment of 3D space around the core of the compact tricycle, as shown in **8**. These trajectories are also nicely illustrated by the X-ray structure **10** of the *p*-bromophenylsulfonyl substituted tricycle **9**.

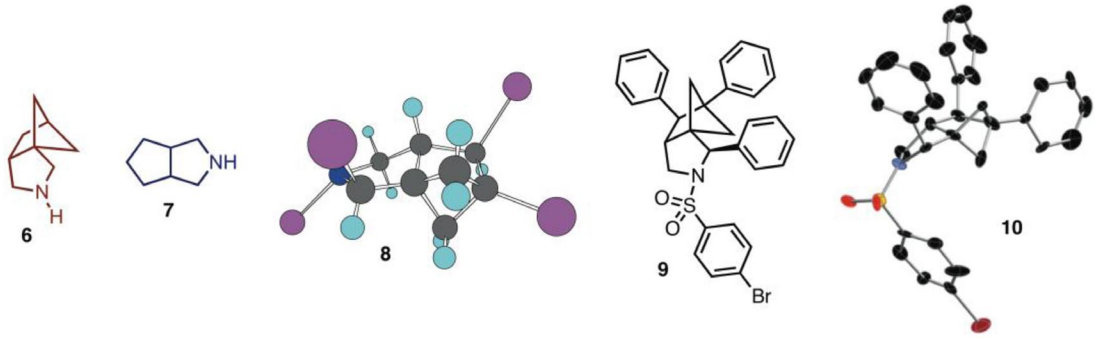


Fig. 7 Scaffolds **6** and **7**, substituent trajectories (in purple) of scaffold **6** shown in computer model **8**, and the X-ray structure **10** of tricyclic pyrrolidine **9**.

Biological assays of bicyclo[1.1.0]butanes

The ease of synthetic access to the novel tricyclic pyrrolidine scaffold **6** inspired us to pursue the synthesis of a small library of analogs, mainly by deprotecting the phosphinoyl group in **4** and subjecting the secondary amine to reductive amination reactions. A discovery library of 75 samples was submitted to the Small Molecule Repository (SMR) of the NIH and screened by the Molecular Libraries Probe Center Network (MLPCN), an NIH Roadmap initiative. The results were deposited into the public domain and are readily retrievable from *PubChem*. Remarkably, after the library of 75 tricycles was screened in >450 assays, hits that met the activity criteria of (generally) IC_{50} <20 μM emerged in ca. 50 of these assays (11 %). In spite of this unusually high hit rate, only 2 individual compounds were active in more than 10 different assays, and, on average, a member of the pyrrolidine series **6** was a positive hit in only 2 (0.4 %) out of the 450 reported assays (Fig. 8).

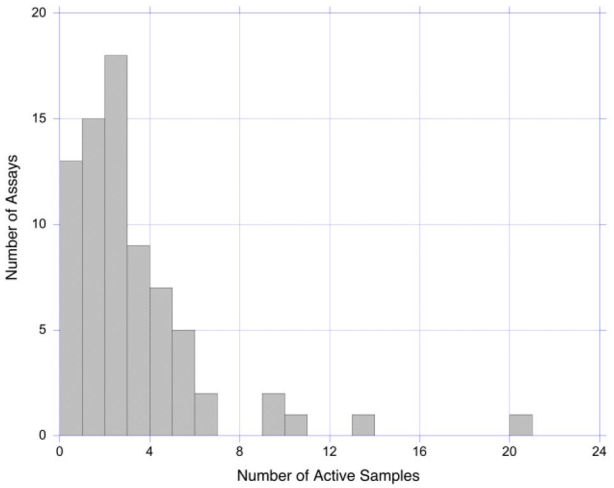
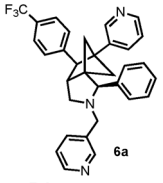
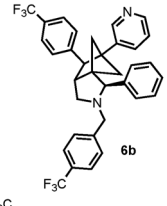
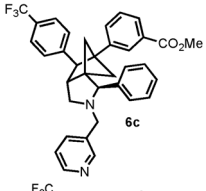
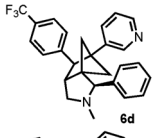
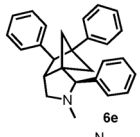
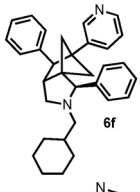
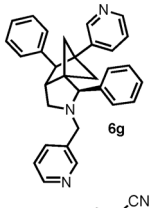
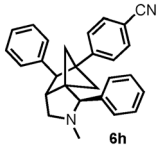


Fig. 8 Number of individual assays as a function of the number of samples of chemotype **6** found as active hits in these assays, from a total of 450 bioassays and a library of 75 derivatives of **6**.

In addition to the targets listed in Table 1, pyrrolidines **6** also showed low μM or better activity as inhibitors of TGF-β, inhibitors of cruzain, inhibitors of the thioesterase domain of fatty acid synthase,

Table 1 Library samples and biological data from six diverse MLPCN bioassays.

Pyrrolidine **6**	CID[a]	Bioassays[b]					
		A	B	C	D	E	F
 **6a**	11949215	5.1 μM	3.1 μM	1.9 μM	–	–	–
 **6b**	11949213	–	–	2.1 μM	–	6.2 μM	–
 **6c**	11949230	–	–	2.3 μM	–	–	–
 **6d**	11949211	–	–	2.3 μM	14.1 μM	–	–
 **6e**	11949162	–	–	–	–	–	18.4 μM
 **6f**	11949193	–	–	4.1 μM	15.0 μM	–	–
 **6g**	11949196	–	–	2.3 μM	–	–	–
 **6h**	11949197	–	–	10 μM	–	–	–

[a]CID: *PubChem* Compound Identifier.

[b]Assay results listed in *PubChem*; A: Inhibition of streptokinase promotor activity (AID: 1902); B: Inhibition of cancer stem cells (AID: 2717; 449748); C: Delayed death inhibitors of the malarial parasite plastid (AID: 504832; 504834); D: Inhibition of mycobacterium tuberculosis H37Rv (AID: 1626); E: Inhibition of beta cell apoptosis (AID: 435005; 449756); F: Potential treatment of ataxia-telangiectasia (AID: 493192).

suppressors for simvastatin-induced mytotoxicity, antagonists of the human cholinergic receptor muscarinic **5**, inhibitors of hepatitis C virus, inhibitors of *C. albicans*, and others. Accordingly, the tricyclic pyrrolidine scaffold **6** can be characterized as a frequent and yet selective modulator of biological targets. It is rare to identify a chemotype that conveys such a high general level of bioactivity without displaying undesirable, promiscuous binding patterns [31].

CONCLUSION

The development of new reactions leading to novel scaffolds with unprecedented chemical and biological properties is a key mission of organic synthesis. Pericyclic reactions are particularly suitable for providing complex scaffolds in a few steps from simple and readily available starting materials. A key feature in our use of bicyclo[1.1.0]butanes is the introduction of the alkyl amine substituent, which allows for a ready functionalization of the strained carbocycles followed by subsequent, thermal or metal-catalyzed intramolecular C,C-bond and concomitant heterocycle formations. Gratifyingly, novel products such as 3-azatricyclo[5.1.1.0^{1,5}]nonanes **6** have already demonstrated an attractive biological profile for these new heterocycles, and we continue to investigate their utility as potentially privileged pharmacophores.

ACKNOWLEDGMENTS

The authors thank Ms. Shelby Anderson for the data analysis in Table 1, and the NSF and NIH (in particular the NIGMS CMLD Program) for their generous support of our research.

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