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Communication

Stereodivergent Carbon–Carbon Bond Formation between Iminium and Enolate Intermediates by Synergistic Organocatalysis

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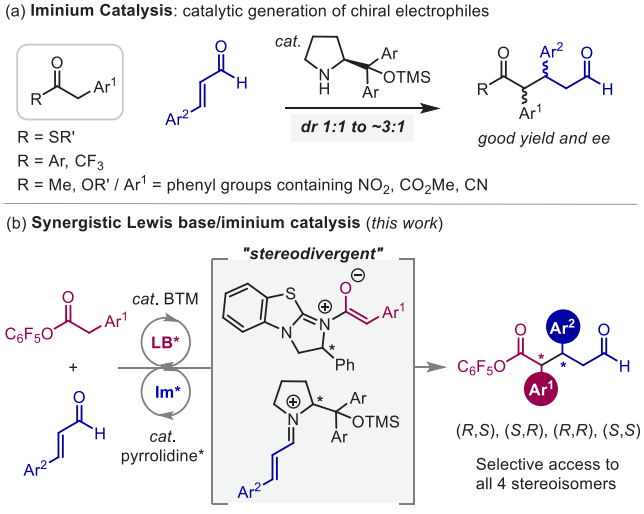
ABSTRACT: We report here a stereodivergent method for the Michael addition of aryl acetic acid esters to α,β-unsaturated aldehydes catalyzed by a combination of a chiral pyrrolidine and a chiral Lewis base. This reaction proceeds through a synergistic catalytic cycle which consists of one cycle leading to a chiral iminium electrophile and a second cycle generating a nucleophilic chiral enolate for the construction of a carbon–carbon bond. By varying the combinations of catalyst enantiomers, all four stereoisomers of the products with two vicinal stereocenters are accessible with high enantio- and diastereoselectivity. The products of the Michael addition, 1,5-aldehyde esters, can be readily transformed into a variety of other valuable enantioenriched structures, including those bearing three contiguous stereocenters in an acyclic system, thus providing an efficient route to an array of structural and stereochemical diversity.

The control of stereoselectivity has been one of the central goals in synthetic organic chemistry due to the wide appearance of chiral molecules in natural products and pharmaceuticals. Over the past decades, numerous asymmetric approaches have provided efficient access to enantioenriched compounds.[1] Despite remarkable advances, the development of catalyst-controlled methods that precisely control relative and absolute configurations of multiple stereocenters is an ongoing challenge.[2] In 2013, Carreira and co-workers disclosed a stereodivergent process for the dual catalytic alkylation of aldehydes with allylic alcohols by the reaction between *in situ* generated chiral (allyl)iridium and chiral enamine intermediates.[3] This process allowed the preparation of all four product stereoisomers containing vicinal stereocenters by altering the combination of catalyst enantiomers from the same set of starting materials. While promising, stereodivergent synergistic catalysis[4] remains scarce,[5] and progress has largely focused on the generation of allylmetal complexes of Ir,[3,6] Pd,[7] and Rh[8] as chiral electrophiles, thus limiting an accessible structural motif. The achievement of stereodivergence with dual chiral catalysts in other transformations such as Michael additions would be an important advance.[9]

Enantioselective Michael addition is one of the most powerful reactions in organic synthesis that forms a carbon–carbon bond, thereby affording synthetically valuable chiral building blocks.[10] One of the most common strategies to enable such reactions includes the organocatalytic activation of electrophiles via iminium catalysis.[11] α,β-Unsaturated aldehydes condense with chiral secondary amine catalysts to create iminium ions as reactive electrophiles that exhibit high facial selectivity. In particular, chiral pyrrolidines[12] have been shown to serve as effective catalysts for the asymmetric Michael additions of aryl acetic acid esters to aldehydes (Scheme 1a).[13] Although highly enantioselective, these reactions have proceeded with poor diastereoselectivity (up to ~3:1), and the scope of aryl acetic acid esters has been restricted to those with high acidities of benzylic protons.

Scheme 1. Strategies for the Stereoselective Michael Additions of Aryl Acetic Acid Esters



In this report, we establish that a synergistic organocatalytic system can address the dual challenges of reactivity and selectivity in stereoselective Michael additions (Scheme 1b). Specifically, a chiral pyrrolidine in conjunction with a chiral Lewis base can achieve enantio- and diastereodivergent

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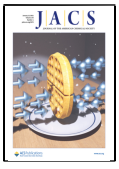

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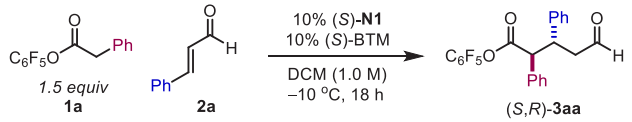
Michael additions of various aryl acetic acid esters to α,β-unsaturated aldehydes, thereby enabling selective synthesis of all four product stereoisomers with two adjacent stereocenters.

To develop a stereodivergent Michael addition of a range of aryl acetic acid esters including those that do not possess highly acidic protons at the benzylic position, we wondered if a chiral iminium electrophile could react with a chiral enolate (an activated nucleophile) generated *in situ* from a reaction with a chiral Lewis base catalyst and form a C−C bond. Among various chiral Lewis bases, we considered benzotetramisole (BTM)[14] that was reported to form C1-ammonium enolates by reacting with acyl precursors such as aryl acetic acid esters and react with high facial selectivity.[15] In particular, BTM has been shown to readily displace the aryloxide of ester substrates bearing electron-deficient aryloxides, and this aryloxide could rebound to the acyl group upon carbon−carbon bond formation, thus regenerating a BTM catalyst; the low nucleophilicity of such aryloxide would prevent the direct reaction with electrophilic reaction partners.[6g,7b,16] This strategy has been successfully combined with transition metal catalysis in synergistic catalytic reactions.[6g,7b,16d−n] However, the chemical and kinetic compatibility of this catalytic cycle with organocatalytic cycles such as a cycle leading to iminium activation has remained unknown. Moreover, it has been uncertain whether the reaction between chiral iminium and enolate intermediates can accomplish stereodivergence, because of the potential matched/mismatched interactions at the transition state.

To assess the synergistic stereoselective Michael additions, we chose phenyl acetic acid pentafluorophenyl ester (**1a**) and cinnamaldehyde (**2a**) as our model substrates. Upon exploring various reaction parameters, we determined that the *anti*-product **3aa** can be obtained as a single diastereomer in 83% yield with 99% ee in the presence of (*S*)-pyrrolidine **N1** and (*S*)-BTM as catalysts (Table 1, entry 1).[17] No Michael addition was observed in the absence of either of the catalysts (entries 2 and 3). The reactions with other (*S*)-amine catalysts or (*S*)-TM proceeded in lower yield or enantioselectivity (entries 4−6). Whereas an acid cocatalyst is commonly used in iminium activation,[11] the acid additive was not necessary (entry 7). The reactions produced low yields of **3aa** when varying the aryloxide leaving group of **2a** (entries 8 and 9), solvents (entries 10 and 11), or temperature (entry 12). The coupling reaction with either of the *racemic* catalysts resulted in inferior yield and enantioselectivity (entries 13 and 14); notably, the product was obtained as a single diastereomer, indicating that either chiral catalyst can control the relative stereochemistry and that *anti*-selectivity is strongly favored.

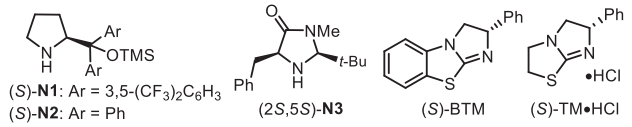
The scope of aryl acetic acid esters that reacted with cinnamaldehyde (**2a**) under our synergistic organocatalytic conditions through the use of (*R*)-**N1** and (*R*)-BTM as catalysts is summarized in Table 2a; in most cases, the product was obtained as a single *anti*-diastereomer with >99% ee. The aryl group of the pentafluorophenyl esters can be *para*-substituted (electron-rich: **3ba**, **3ca**/electron-poor: **3da**, **3ea**, **3fa**), *meta*-substituted (**3ga**), or *ortho*-substituted (**3ha**) phenyl rings, reacting with **2a** to produce a single stereoisomer of 1,5-aldehyde esters in generally high yields. The Michael additions with esters bearing strong electron-withdrawing groups such as 2,4,5-trifluorophenyl or *p*-nitrophenyl moieties proceeded to afford products **3ja** and **3ka** in good yields with high dr (24:1 and 18:1).[18] Pentafluorophenyl esters bearing naphthyl or 2-thienyl groups also underwent the additions in high yields with complete selectivity (**3la** and **3ma**).

Table 1. *Anti*-Selective Synergistic Organocatalytic Michael Additions: Effect of Reaction Parameters

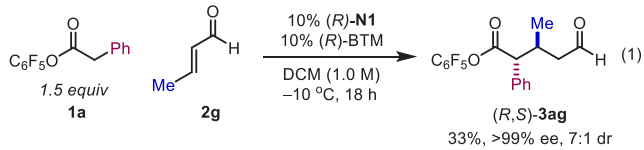


entry	deviation from standard conditions	yield (%)[a]	ee (%)
1	none	**83**	**99**
2	no (*S*)-**N1**	<5	–
3	no (*S*)-BTM	<5	–
4	(*S*)-**N2**, instead of (*S*)-**N1**	83	93
5	(2*S*,5*S*)-**N3**, instead of (*S*)-**N1**	<5	–
6	(*S*)-TM, instead of (*S*)-BTM	48	98
7	with 10% benzoic acid	64	99
8	4-$NO_2C_6H_4$, instead of C_6F_5 of **1a**	27	n.d.
9	2,4,6-$F_3C_6H_2$, instead of C_6F_5 of **1a**	28	n.d.
10	THF, instead of DCM	37	99
11	toluene, instead of DCM	27	99
12	0 °C, instead of −10 °C	68	99
13	*rac*-**N1**, instead of (*S*)-**N1**	41	77
14	*rac*-BTM, instead of (*S*)-BTM	27	87

[a]Determined by ^{1}H NMR analysis with 1,1,2,2-tetrachloroethane as an internal standard. Only *anti*-diastereomer was observed in all cases.



In addition, the C−C bond formation between β-methyl substituted α,β-unsaturated aldehyde **2g** and **1a** occurred to produce (*R*,*S*)-**3ag** with >99% ee and 7:1 dr but in 33% yield (eq 1).[19]



To examine the stereodivergence of our synergistic organocatalytic process, we attempted the synthesis of a *syn*-diastereomer of **3aa** by altering the relative chirality of the catalyst in the reaction of **1a** with **2a** (eq 2). Indeed, the *syn*-product was afforded as a major diastereomer with 99% ee and 8:1 dr, indicating that the catalysts could govern the relative stereochemistry of the process. However, the yield was only

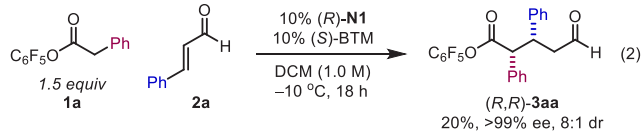


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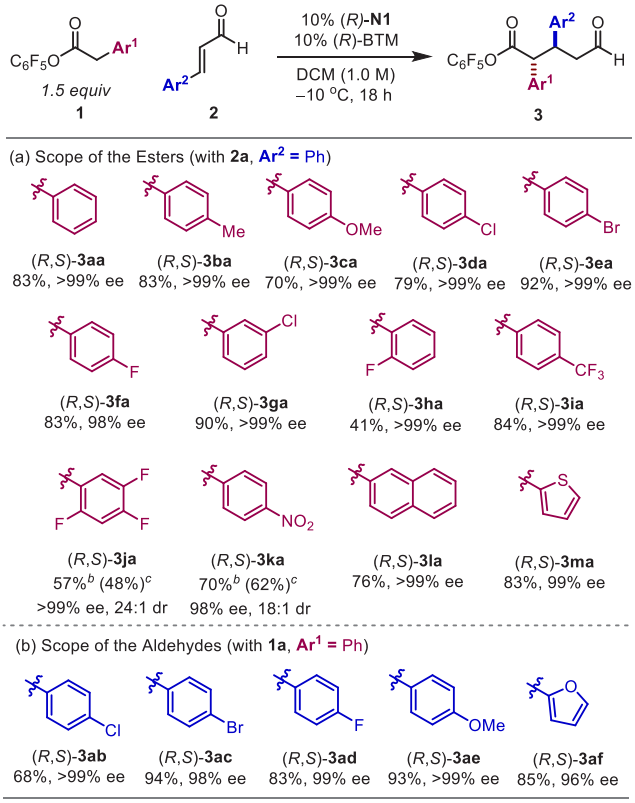
Table 2. Scope of Synergistic Organocatalytic Michael Additions: Synthesis of (*R*,*S*)-Product Stereoisomers[a]

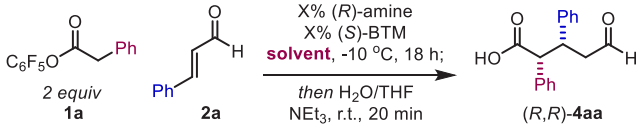


[a]Yield of the purified product. [b]Diastereomeric ratios were determined from the crude mixtures. Combined yield of two diastereomers; determined by ^{1}H NMR analysis with 1,1,2,2-tetrachloroethane as an internal standard. [c]Isolated yield of only *anti*-diastereomer in parentheses.

20% by ^{1}H NMR spectroscopic analysis, perhaps due to the mismatched interaction at the transition state of C−C bond forming event.

Switching the pyrrolidine catalyst to **N2** (that led to a slightly lower enantioselectivity compared to **N1** in the *anti*-selective reaction: Table 1, entry 1 vs 4) enhanced the yield of the *syn*-selective, asymmetric Michael addition of **1a** to **2b** (Table 3, entry 1 vs 2); due to the instability of the *syn*-diastereomer of **3aa**, it was isolated as 1,5-aldehyde acid **4aa** after hydrolysis for 20 min.[20] Addition of water as a cosolvent further improved the yield of **4aa** to 62% with improved dr of 10:1 (Table 3, entry 4).[21] Finally, with 20% catalyst loadings for both catalysts, the *syn*-product was obtained in 85% yield with 99% ee and 12:1 dr (entry 5). These results indicate that either of the product stereoisomers could be obtained in high yields with high stereocontrol through the choice of catalyst combinations from the identical set of starting materials (see Scheme S2 in Supporting Information for the synthesis of all four stereoisomers).

Table 3. *Syn*-Selective Synergistic Organocatalytic Michael Additions: Effect of Reaction Parameters

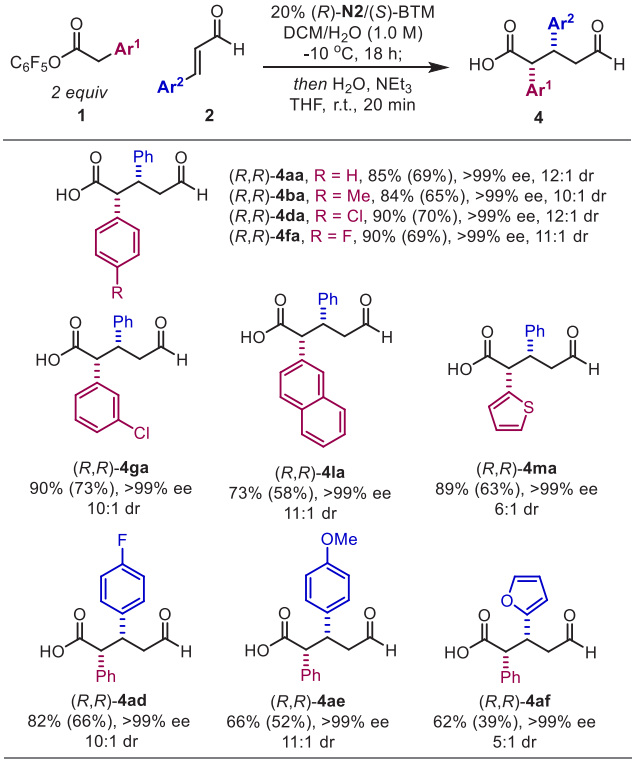


entry	X	amine	solvent	yield (%)[a]	ee (%)	dr (%)[b]
1	10	**N1**	DCM	22	>99	7:1
2	10	**N2**	DCM	40	>99	7:1
3	10	**N1**	DCM/H_2O (1:1)	34	>99	10:1
4	10	**N2**	DCM/H_2O (1:1)	62	>99	10:1
5	20	**N2**	DCM/H_2O (1:1)	85	>99	12:1

[a]Combined yield of two diastereomers; determined by ^{1}H NMR analysis with 1,1,2,2-tetrachloroethane as an internal standard. [b]Diastereomeric ratios were determined from the crude mixtures.

The combination of pyrrolidine (*R*)-**N2** and (*S*)-BTM can synergistically catalyze the coupling reactions between various esters **1** and aldehydes **2** bearing substituted phenyl groups or heteroaryl moieties to produce *syn*-diastereomers of the Michael addition products (mostly >99% ee) in generally good yields with up to 12:1 dr, thus demonstrating the stereodivergence of our organocatalytic method (Table 4).

Table 4. Scope of Synergistic Organocatalytic Michael Additions: Synthesis of (*R*,*R*)-Product Stereoisomers[a]



[a]Combined yield of two diastereomers; determined by ^{1}H NMR analysis with 1,1,2,2-tetrachloroethane as an internal standard; isolated yield of only *syn*-diastereomer in parentheses.

The products generated from this process contain useful functional groups, an aldehyde and a pentafluorophenyl ester, which can be readily transformed in good yields into other enantioenriched compounds with vicinal stereocenters by the reactions with nucleophiles (Scheme 2; **4aa**, **5aa**, and **6aa**).

Catalytic *α*-chlorination of aldehyde **3aa** allowed the introduction of an additional stereocenter via enamine intermediates,[11,22] thus generating structures that are even more stereochemically rich (Scheme 2).[23] For example, treatment of **3aa** with *N*-chlorosuccinimide (NCS) in the presence of L-proline afforded 4-chlorinated product **7aa** in

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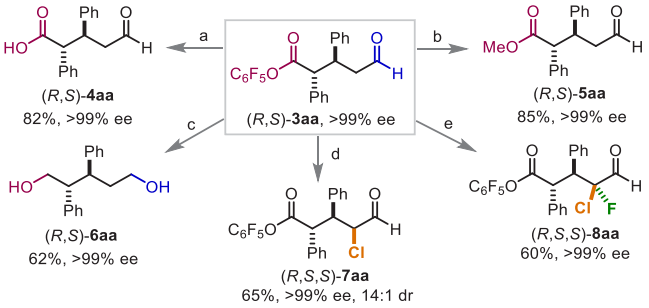
Scheme 2. Derivatizations of the Product[a]

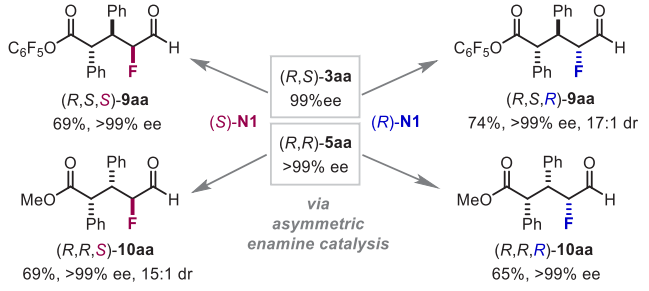


[a]Conditions: (a) NEt_3 (5.0 equiv), H_2O/THF, rt, 2 h; (b) NEt_3 (5.0 equiv), MeOH/THF, rt, 2 h; (c) DIBAL (3.0 equiv), toluene, −78 °C, 1 h; (d) L-proline (10%), NCS (1.1 equiv), DCM, rt, 12 h; (e) (*R*)-**N1** (2.0%), NFSI (1.5 equiv), MTBE, rt, 16 h; then L-proline (20%), NCS (2.0 equiv), DCM, rt, 12 h.

65% yield with 14:1 dr. Furthermore, the one-pot catalytic α-fluorination[23] with *N*-fluorodibenzenesulfonimide (NFSI) followed by chlorination led to the generation of *gem*-chlorofluoro compound **8aa** as a single stereoisomer in 60% yield.[24−26] These products could serve as versatile, chiral synthetic intermediates in organic synthesis. However, the chlorination process proceeded with substrate-controlled rather than catalyst-controlled diastereoselectivity, producing the identical stereoisomer of **7aa** or **8aa** by the halogenations with either catalyst enantiomer.

Catalyst-controlled, asymmetric α-fluorinations of enantioenriched 1,5-aldehyde esters (*anti*-**3aa** or *syn*-**5aa**) were achieved through the use of chiral pyrrolidine **N1** to deliver fluorinated product **9aa** or **10aa** in good yields (Scheme 3).[24]

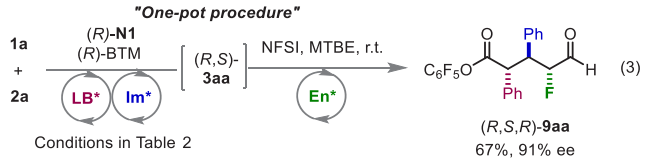
Scheme 3. Enantioselective α-Fluorination of Aldehydes via Enamine Catalysis[a]



[a]Conditions: N1 (2.0−10%), NFSI (1.1−2.0 equiv), MTBE, rt, 16 h.

The fluorination process in combination with our method for the Michael additions could provide rapid access to *all eight stereoisomers* of 4-fluorinated 1,5-aldehyde esters that bear three contiguous stereocenters in an acyclic system, from simple aldehyde and ester substrates; the absolute configurations of all three stereocenters, including the one containing a fluorine atom, can be controlled individually by the choice of catalyst enantiomers.

Finally, a one-pot procedure for the organocatalytic Michael addition/α-fluorination proceeded smoothly to yield the single diastereomer of **9aa** in 67% yield and 91% ee from ester **1a** and aldehyde **2a** (eq 3).[5k] In this process, catalyst **N1** that forms an iminium electrophile in the synergistic Michael addition catalytic cycle generates an enamine nucleophile in the fluorination step.



In conclusion, we have developed a stereodivergent Michael addition of aryl acetic acid esters to α,β-unsaturated aldehydes catalyzed by the combination of two chiral organocatalysts, a pyrrolidine, and a Lewis base. The synergistic catalytic system wherein the C−C bond formation occurs between *in situ* generated activated chiral intermediates, an electrophilic iminium ion and a nucleophilic enolate, allows the coupling between otherwise unreactive ester and aldehyde substrates. Variation of the relative chirality of the catalyst combinations gives access to the full set of stereoisomers of 1,5-aldehyde esters containing two adjacent stereocenters with high enantio- and diastereoselectivity. Moreover, the 1,5-dicarbonyl reaction products are well-suited for further transformations, some of which introduce an additional stereocenter. Combination of the synergistic organocatalytic Michael addition and the subsequent chemo- and stereoselective transformations can serve as a powerful platform for the stereodivergent synthesis of valuable chiral building blocks, enabling rapid construction of structural and stereochemical diversity. Studies to understand the origin of stereoselectivity of this synergistic organocatalysis are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c11077.

Experimental details and procedures, characterization data, determination of configurations, and NMR spectra of isolated compounds (PDF)

X-ray crystal structure for (*S*,*R*)-**3aa** (CIF)

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Notes

The authors declare no competing financial interest.

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(18) The pentafluorophenyl esters (**1j** and **1k**) employed in these reactions contain readily enolizable protons due to the presence of electron-withdrawing groups on the phenyl ring. The diastereomeric ratios remained unchanged (i.e., no racemization of the product was observed) when subjecting these products **3ja** and **3ka** to the reaction conditions.

(19) β-Aliphatic enals show low reactivity towards the reaction with ester **1** under our reaction conditions (ref 13a). The Michael addition of **1a** to 2-hexenal did not occur (see Scheme S5).

(20) Interestingly, the observed absolute configurations of each stereocenter were proven to be opposite to those obtained in the *anti*-selective case with the same catalyst enantiomer. A rationale for the stereochemical outcome is shown in Scheme S4 and Scheme S6.

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