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Communication

Copper-Catalyzed Enantioselective Difluoromethylation of Amino Acids via Difluorocarbene

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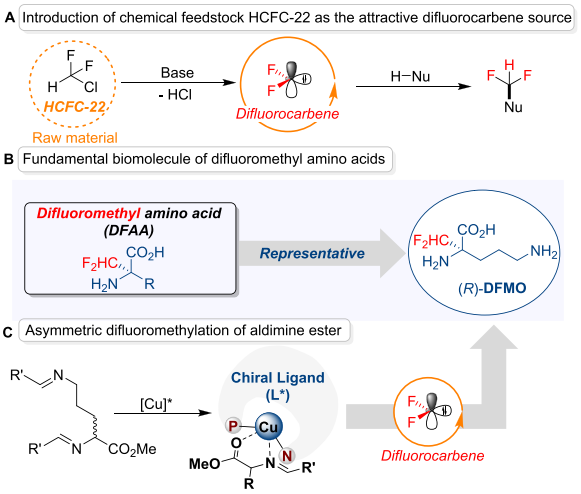
ABSTRACT: Difluoromethyl amino acids (DFAA) exhibit intriguing biological properties, making them highly desirable motifs in agrochemical and pharmaceutical science. However, stereochemical control of direct difluoromethyl transformation via the difluorocarbene species has not been demonstrated. Here we describe an efficient copper-catalyzed asymmetric difluoromethylation reaction that systematically delivers chiral DFAA as rationally designed mechanism-based inhibitors of PLP-dependent amino acid decarboxylases. The reaction employs difluoromonochloromethane, an abundant raw material, as the direct precursor of difluorocarbene species, enabling the unprecedentedly direct conversion of amino esters into corresponding valuable DFAA products in good yields with excellent enantioselectivities. This de novo synthesis creates opportunities to integrate an asymmetric catalytic platform for the preparation of diverse libraries of biologically important DFAA derivatives and will support efforts in both drug discovery and development.

The fluoroalkyl moiety is a key functional group with diverse applications in the fields of pharmaceuticals, agrochemicals, and functional materials.[1−7] Direct difluoromethyl (−CF_2H) transformation[8−17] is a fundamentally important subject of organic synthesis in both the academic and industrial sectors owing to the increasing demand for various difluoromethylated molecules.[18−20] However, the efficient use of low-value, industrial raw materials, such as difluoromonochloromethane (HCFC-22, Freon 22, or R-22), for the manufacturing of the corresponding organofluorine compounds is a critical task in modern chemical research.[21−24] Typically, HCFC-22 upon treatment with an appropriate base is used as a source to yield the difluorocarbene species (:CF_2, in its singlet ground state),[25,26] which is well suited for the synthesis of structurally diverse *gem*-difluorinated compounds[27−29] applicable in drug discovery and development (Scheme 1A).[30,31] Although representing a long-standing problem to access valuable chiral difluoromethylated chemicals[32] and build up molecular complexity, the intrinsic instability and high reactivity of the difluorocarbene species[33−38] make it formidable for the introduction of difluoromethyl moieties in a catalytic and asymmetric fashion.

To date, the difluoromethyl amino acids (DFAA) have been intensively studied for their intriguing chemical structures and promising diverse biological activities (Scheme 1B).[39] As fundamental biomolecules, DFAA, bearing tailored fluorinated functional groups designed to inactivate their target enzymes based upon loss of a fluoride atom by an E2 elimination mechanism, play key roles in diverse cellular processes, and a mechanistic understanding gained from this reaction is the basis of designing many other suicide inhibitors as potential drug candidates.[40] For instance, the enzyme ornithine decarboxylase (ODC) is the key regulator of the biosynthesis of polyamines, and the aberrant expression of ODC is a critical factor contributing to oncogenesis, making it a possible target

Scheme 1. Design Plan for the Asymmetric Synthesis of Quaternary DFAA Using HCFC-22



for therapeutic interventions.[41] Typically, the fluorinated ornithine analogue α-difluoromethylornithine (DFMO), a mechanism-based inhibitor of pyridoxal phosphate (PLP)-dependent ODC, is naturally believed to have potential utility as an anticancer and chemopreventive agent.[42] Furthermore, the development of new stereoisomeric drugs[43] has become a focus in regulatory guidelines for pharmaceutical research,

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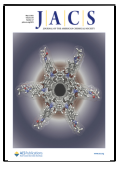

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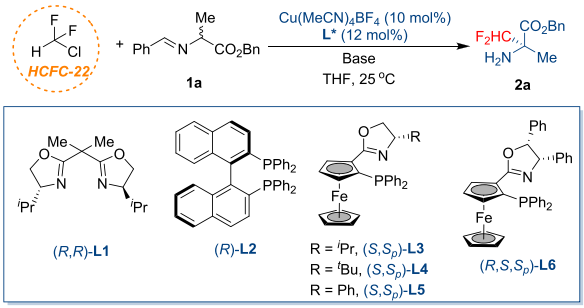
whereas the above-mentioned examples of DFMO and DFAA drugs are still marketed as a mixture of two enantiomers. Consequently, an asymmetric catalytic approach toward the stereoselective difluoromethyl functionalization of amino acids could have a major effect on the discovery and development of new pharmaceuticals.[44]

The conceptual advances of the stereoselective transformation of difluorocarbene species together with the well-established pharmaceutical interest of chiral DFAA prompted us to target a method for enantioselective intermolecular difluoromethylation of amino acids. Over 40 years ago, difluoromethylation of aldimine esters with HCFC-22, pioneered by Bey and co-workers, was reported to generate racemic DFAA.[45−48] Conventionally, existing protocols uniformly require stoichiometric quantities of strong and indiscriminate base involving multistep sequences and/or harsh conditions. We speculated that a mild reaction system with well-established chiral transition metal complexes to generate the *N*-metalated azomethine ylide[49−51] as a binding cavity might meet the aforementioned challenges, and the proposed intermolecular reaction has advantages: readily available feedstock, easily accessible substrate preparation, single-step preparation, increased reaction diversity, and asymmetric transformation of free difluorocarbene species (Scheme 1C). Besides, enantioselective catalytic synthesis offers flexibility in catalyst choice and facile delivery of distinct stereoisomers by inversion of the catalyst configuration. Here, we present a copper-catalyzed asymmetric difluoromethylation of aldimine esters for the direct conversion of HCFC-22 to the structurally diverse DFAA. This de novo synthesis creates opportunities to integrate an asymmetric catalytic platform for the preparation of diverse libraries of biologically important DFAA derivatives and will support efforts in both drug discovery and development.[30,31]

To test our hypothesis, we evaluate the feasibility of the copper-catalyzed reaction between aldimine ester **1a** and HCFC-22 with Cs_2CO_3 as the base in tetrahydrofuran (THF) (Table 1). An initial chiral ligand screen of this reaction showed that the use of BOX ligand (*R*,*R*)-**L1** led to the difluoromethylated adduct **2a** in 9% yield with 8% enantiomeric excess (ee) (entry 1). The assessment of various ligands displayed remarkable effects on the outcome of the reaction. Gratifyingly, the desired **2a** could be obtained in 51% yield with 72% ee when a copper complex modified with the Phosferrox ligand (S,S_p)-**L3** was employed (entry 3). Evaluation of a series of Phosferrox ligands revealed that the use of Cu/(R,S,S_p)-**L6** gave the best results, affording **2a** in 76% yield with 96% ee (entry 6). Control experiments confirmed that the ligand, copper catalyst, and the cofactor base were all required for this transformation. No difluoromethylated adduct **2a** was formed in the absence of any one of the reaction components (ligand, copper, or base) (entries 7−9).

With these optimized reaction conditions for the asymmetric difluoromethylation, we then explored the generality of this reaction with various substituted amino esters (Table 2). As shown in Table 2A, a diverse array of the aldimine esters derived from both natural and non-natural α-amino acids performed well in the presence of the chiral copper catalyst, affording the desired products **2** in high yields and excellent enantioselectivities (up to 98% enantiomeric excess). α-Alkyl-substituted aldimine esters derived from alanine (Ala), leucine (Leu), methionine (Met), aspartic acid (Asp), and glutamic

Table 1. Optimization of the Reaction Conditions[a]



entry	L*	base	yield (%)[b]	ee (%)[c]
1	(*R*,*R*)-**L1**	Cs_2CO_3	9	8
2	(*R*)-**L2**	Cs_2CO_3	52	52
3	(S,S_p)-**L3**	Cs_2CO_3	51	72
4	(S,S_p)-**L4**	Cs_2CO_3	58	92
5	(S,S_p)-**L5**	Cs_2CO_3	66	94
6	(R,S,S_p)-**L6**	**Cs_2CO_3**	**76**	**96**
7	—	Cs_2CO_3	nr	—
8[d]	(R,S,S_p)-**L6**	Cs_2CO_3	nr	—
9	(R,S,S_p)-**L6**	—	nr	—

[a]Reactions were performed by using $Cu(MeCN)_4BF_4$ (10 mol %), **L*** (12 mol %), **1a** (0.1 mmol, 1.0 equiv), HCFC-22 (1 M), and Cs_2CO_3 (1 mmol, 10 equiv) in tetrahydrofuran (THF, 1 mL) at 25 °C; hydrolysis with HCl (1 mol/L, 4 mL). [b]Isolated yields after chromatography are shown. [c]The ee values were determined by chiral high-performance liquid chromatography (HPLC) analysis. [d]In the absence of $Cu(MeCN)_4BF_4$.

acid (Glu) gave the desired quaternary amino esters **2a**−**2e** in 52−76% yield and 90−97% ee. To showcase the scalability and practicability of the present method, the enantioselective difluoromethylation was conducted smoothly on a large scale with a reduced catalyst loading of 5 mol % and reproducibly provided enantioenriched **2a** with equal efficiency (183 mg scale, 80% yield, 96% ee). Moreover, homophenylalanine (HPhe), phenylalanine (Phe), tyrosine (Tyr), tryptophan (Trp), and veratrylglycine-derived aldimine esters could also be tolerated without losses in reaction efficiency or enantiocontrol, thus providing opportunities for further elaboration of the products (**2f**−**2j**). It is worth mentioning that both the *C*-difluoromethylation and *O*-difluoromethylation processes occurred and afforded corresponding bis-difluoromethylated adduct **2k** in 65% yield with 90% ee. Besides, allylglycine and phenylglycine derivatives could also be successfully converted into the corresponding difluoromethylated products (**2l**−**2o**) in excellent enantioselectivities (96−98% ee). Notably, the opposite configuration of **2** can be accessed by using the opposite enantiomer of the ligand (R,S,S_p)-**L6** under otherwise identical conditions (Table 2B).

Furthermore, a variety of ketimine esters also proved to be excellent nucleophiles in the difluoromethylation reaction and afforded the desired DFAA **2** in excellent enantioselectivities, albeit in some instances with slightly diminished yield (Table 3, **2p**−**2t**).

Specifically, DFMO was proved to be beneficial in the treatment of African sleeping sickness,[52] and the configuration of DFMO is crucial for its anesthetic activity.[44] Therefore, concise methods for the asymmetric synthesis of DFMO in high stereochemical purity are particularly valuable in medicinal chemistry and pharmaceutical science. The feasibility of the current methodology was evaluated to generate

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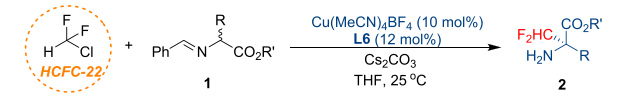
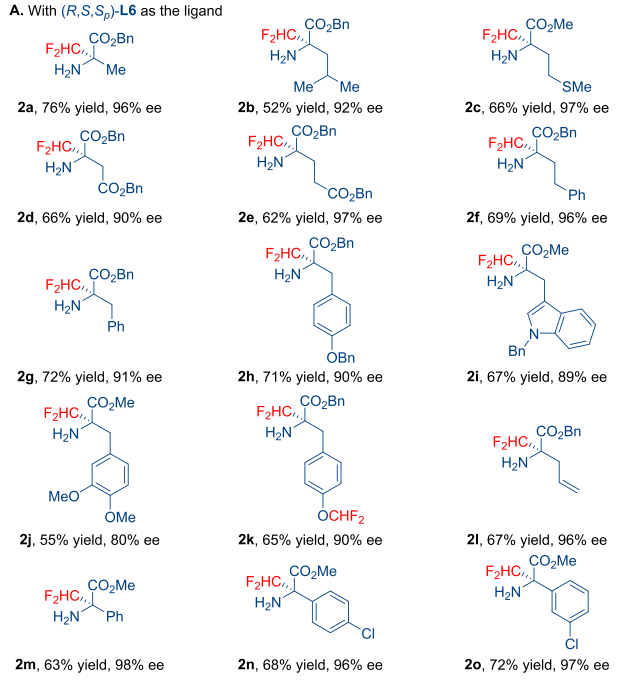
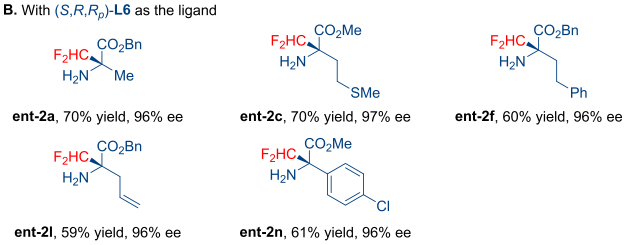
Table 2. Scope of Aldimine Esters 1[a]



A. With (R,S,S_p)-**L6** as the ligand

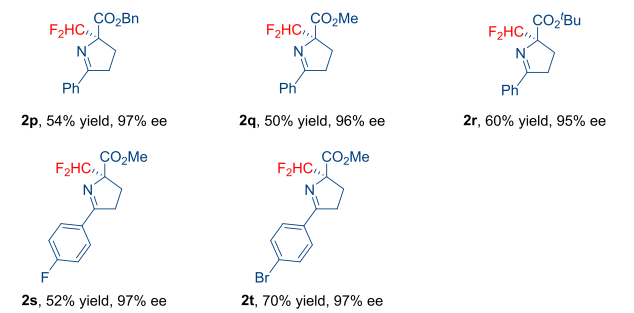


B. With (S,R,R_p)-**L6** as the ligand



[a]Reactions were performed by using $Cu(MeCN)_4BF_4$ (10 mol %), **L6** (12 mol %), **1a** (0.1 mmol, 1.0 equiv), HCFC-22 (1 M), and Cs_2CO_3 (1 mmol, 10 equiv) in tetrahydrofuran (THF, 1 mL) at 25 °C; hydrolysis with HCl (1 mol/L, 4 mL).

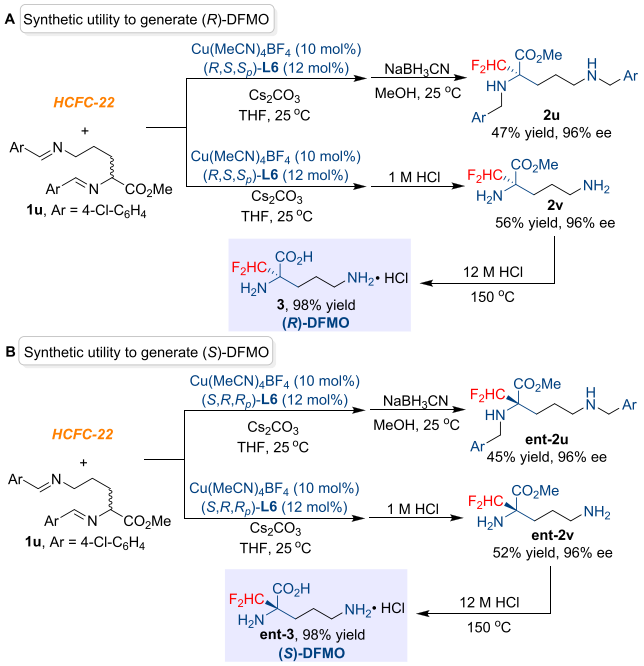
Table 3. Scope of Ketimine Esters 1[a]



[a]Reactions were performed by using $Cu(MeCN)_4BF_4$ (10 mol %), (R,S,S_p)-**L6** (12 mol %), **1a** (0.1 mmol, 1.0 equiv), HCFC-22 (1 M), and Cs_2CO_3 (1 mmol, 10 equiv) in tetrahydrofuran (THF, 1 mL) at 25 °C.

enantioenriched DFMO according to the following sequence. Lysine (Lys)-derived aldimine ester **1u** was subjected to the asymmetric difluoromethylation reaction, and the corresponding DFAA adduct **2u** was obtained under reduction conditions in moderate yield with excellent levels of enantioinduction (Scheme 2A, 96% ee). Similarly, α-difluoromethyl-amino ester

Scheme 2. Synthetic Utility



2v was obtained in 56% yield after hydrolysis with 1 M HCl. Subsequently, hydrolysis of the remaining ester group of **2v** furnished (*R*)-DMFO **3** in 98% yield. In contrast, the reaction with (S,R,R_p)-**L6** under otherwise identical conditions gave DFAA adduct **ent-2u** and (*S*)-DMFO **ent-3** with an opposite absolute configuration, thereby giving comparable results to both DFMO enantiomers (Scheme 2B).

To investigate the catalytic mechanism, the racemate and both enantiomers of aldimine esters **1m** were used in the copper catalytic process (Figure 1A). The chiral ligand (R,S,S_p)-**L6** effectively controls the absolute configuration of the product **2m**, regardless of the stereochemistry of the starting nucleophiles **1m**. The racemization profile of (*R*)-**1m** (97% ee) was subsequently investigated (see Supporting Information for details). We found that Cs_2CO_3 showed a superior ability to promote rapid racemization of chiral imino ester (*R*)-**1m** within 10 min (Figure 1B), which supported the hypothesis that the nucleophilic *N*-metalated azomethine ylide was responsible for the high catalytic activity and the observed enantioinduction of this system.

When the reaction was performed with deuterated water under otherwise standard conditions, the newly formed product **2a′** was detected partially labeled with deuterium (40% D), which is in line with literature reports,[21,53] suggesting the generation of the free difluorocarbene species (Figure 1C). The addition of radical scavengers (TEMPO or BHT) displayed little effect on the outcome of the reaction (see Supporting Information for details), thereby ruling out the possibility of a radical mechanism.[54−57] Moreover, the nonlinear effect study revealed a linear relationship between

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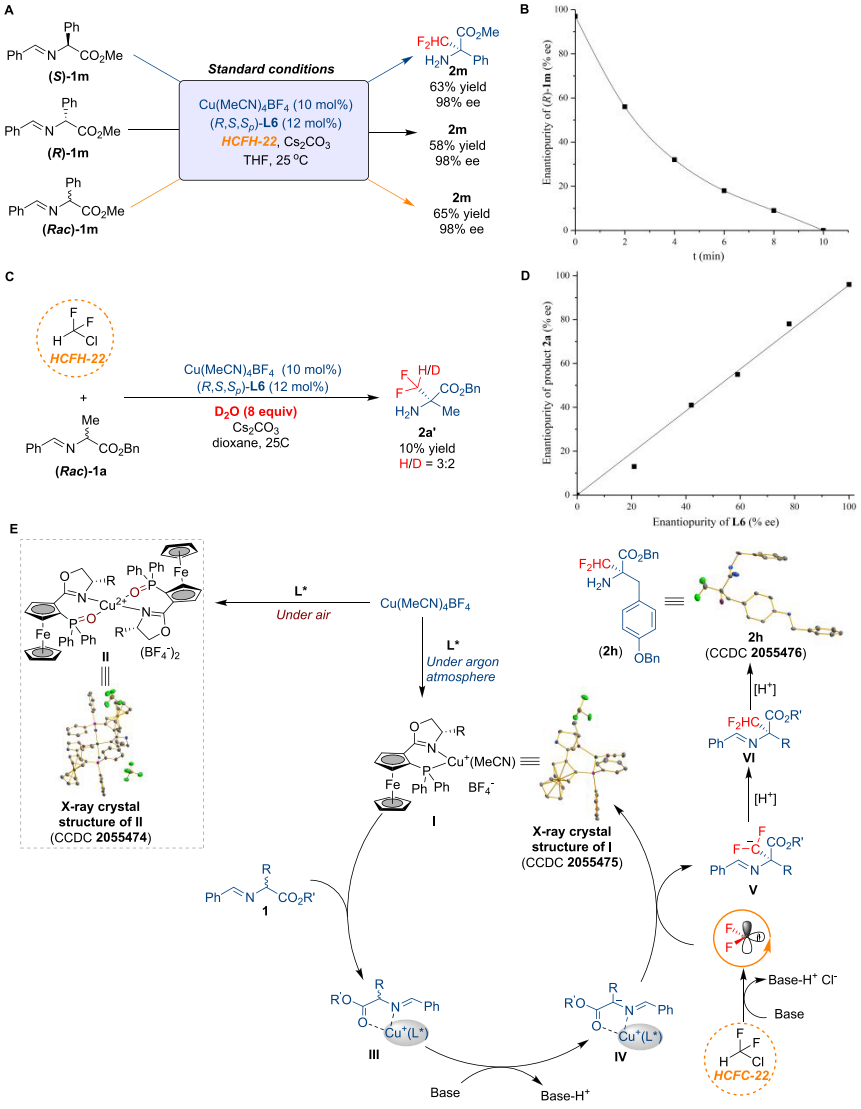

Figure 1. Mechanistic studies. (A) Control experiments with the racemate and both enantiomers of aldimine esters **1m**. (B) Racemization profile of (*R*)-**1m** with Cs_2CO_3 as the base. (C) Deuterium experiments. (D) Nonlinear effect. (E) Proposed catalytic cycles.

the ee of the product **2a** and the enantiopurity of the phosphine ligand **L6**, indicating a single chiral ligand is likely involved in the enantio-determining transition state (Figure 1D).[58] To further identify the active catalyst, Cu(I)/(S,S_p)-**L3** (**I**) was synthesized under argon conditions and characterized by X-ray crystallography (Figure 1E). The copper complex **I** was found to catalyze the asymmetric difluoromethylation of aldimine ester **1** as efficiently and enantioselectively as in the standard reaction conditions. In contrast, the treatment of Phosferrox ligand (S,S_p)-**L3** with $Cu(MeCN)_4BF_4$ under air conditions led to the tetrahedral *N,N,O,O*-coordinated Cu(II) complex **II**, which was unambiguously confirmed by X-ray crystallography. However, no product was formed when the copper complex **II** was used as a catalyst in place of copper complex **I** under otherwise standard reaction conditions, thus confirming the critical role of the chiral ligand.

Taking into account the combined results of our mechanistic studies, the challenging asymmetric difluoromethylation was successfully realized through concomitant in situ generations of two reactive species: a nucleophilic *N*-metalated azomethine ylide and an electrophilic difluorocarbene species. Herein, a plausible mechanistic cycle is outlined in Figure 1E. The transformation is initiated by the coordination of aldimine ester **1** to the copper complex **I**, followed by the formation of an *N*-metalated azomethine ylide (**IV**) upon deprotonation. Meanwhile, the addition of base to the HCFC-22 gives rise to the electrophilic difluorocarbene species. At this point, *N*-metalated azomethine ylide (**IV**), which may serve as a chiral carbon-based nucleophile, can undergo nucleophilic addition to the in situ formed difluorocarbene species to afford the intermediate **V** along with regeneration of the reactive copper complex **I**. Subsequently, protonation and hydrolysis of **V** give rise to the final product **2**, and the absolute configuration of **2h** was assigned by single-crystal X-ray diffraction analysis.

In conclusion, a novel copper-catalyzed enantioconvergent difluoromethylation of amino esters with the abundant chemical feedstock HCFC-22 has been described. The simplicity and generality of this method in achieving stereochemical control of the highly reactive difluorocarbene species provide an unprecedentedly easy entry to valuable enantioenriched quaternary DFAA in high yields with good functional group compatibility. The reaction proceeds smoothly at ambient temperature with high synthetic efficiency and exhibits unprecedented functional group tolerance

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together with the potential to generate difluoromethylated products of broad structural diversity. It is expected that the chemistry reported herein and the direct access to chiral difluoromethylated derivatives will have a major effect on the discovery and development of new pharmaceuticals.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c02697.

Experimental procedures for all reactions and characterization data for all products, including ^{1}H and ^{13}C NMR spectra, HPLC spectra, and crystal data (PDF)

Accession Codes

CCDC 2055474−2055476 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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