

Ir-Catalyzed Asymmetric Allylic Alkylation of Dialkyl Malonates Enabling the Construction of Enantioenriched All-Carbon Quaternary Centers

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ABSTRACT: An enantioselective iridium-catalyzed allylic alkylation of malonates with trisubstituted allylic electrophiles to form all-carbon quaternary stereocenters is reported. This cross-coupling reaction features unprecedented reactivity at ambient temperature, particularly for challenging fully alkyl-substituted allylic electrophiles, and enables the preparation of a wide range of enantioenriched products in up to 93% yield and 97% ee. The products of this transformation can be readily converted to a number of valuable building blocks including vicinal quaternary stereodiads and β -quaternary acids. This method was also used to prepare an enantioenriched intermediate facilitating the asymmetric formal synthesis of the spirochnol family of natural products.

The enantioselective construction of acyclic all-carbon quaternary centers is an important and challenging problem in synthetic organic chemistry.¹ Ir-catalyzed asymmetric allylic alkylation has emerged as a powerful methodology for the formation of acyclic stereogenic centers, owing to the inherent branched regioselectivity of these intermolecular processes.² While the enantioselective construction of tertiary stereocenters by virtue of this methodology is well-precedented with both carbon and heteroatom nucleophiles,³ the generation of enantioenriched all-carbon quaternary centers by Ir-catalysis remains underexplored and is of interest to our group.

Recently, Carreira and coworkers disclosed an Ir-catalyzed process that forges enantioenriched quaternary products from silyl ketene acetal nucleophiles and tertiary allylic alcohol electrophiles (Figure 1A).⁴ This report hinges on their development of similar processes exploiting branched electrophiles and a novel phosphoramidite ligand, (*S_z*)-L1.⁵ In contrast, our group has taken interest in the formation of all-carbon quaternary centers using linear trisubstituted electrophiles. In previous endeavors, we have reported the use of masked acyl cyanide and substituted malonitrile nucleophiles with these electrophiles to afford the corresponding branched products in high levels of enantioselectivity (Figure 1B). In the case of masked acyl cyanides, these coupling products are precursors to α -quaternary carboxylic acids (Figure 1B, R = OMOM).⁶ When

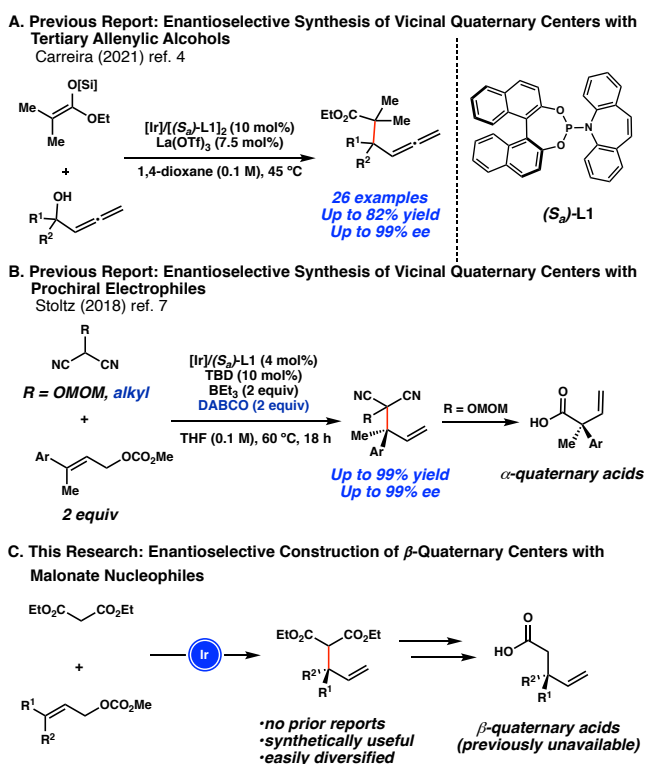


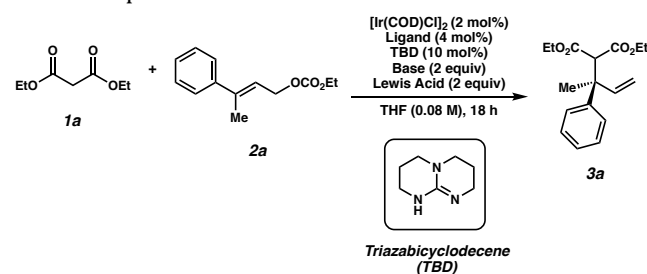
Figure 1. Construction of all-carbon quaternary centers via Ir-catalyzed allylic alkylation.

alkylated malonitrile nucleophiles are employed, the corresponding products are formed in nearly quantitative

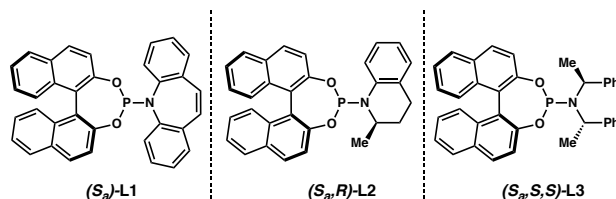
yields and excellent levels of enantioselectivity (Figure 1B, R = alkyl).⁷

Inspired by these efforts, we hoped to expand the scope of this coupling reaction to include malonate nucleophiles, which are ubiquitous in organic synthesis. Such a transformation would allow for the formation of β -quaternary 1,3-dicarbonyl compounds (Figure 1C), which can be converted readily to β -quaternary carboxylic acids, providing a useful functional handle for further diversification. While malonates have historically served as an archetypal nucleophile in allylic substitution reactions,⁸ their application to the efficient, enantioselective construction of β -quaternary centers remains unaddressed in the literature.⁹ Herein, we report the reaction of malonates with 1,1',2-trisubstituted allylic coupling partners to form acyclic quaternary centers in high levels of enantio- and regioselectivity.

Table 1. Optimization Studies^{a,c}



Entry	Ligand	Base	Lewis Acid	Temp.	Yield (%) ^a	ee (%) ^b
1	(<i>S_a</i>)-L1	DABCO	BEt ₃	60 °C	0	–
2	(<i>S_a</i>)-L1	LiOt-Bu	BEt ₃	60 °C	23	–
3	(<i>S_a</i> , <i>R</i>)-L2	LiOt-Bu	BEt ₃	60 °C	0	–
4	(<i>S_a</i> , <i>S,S</i>)-L3	LiOt-Bu	BEt ₃	60 °C	<5	–
5	(<i>S_a</i>)-L1	NaOMe	BEt ₃	60 °C	10	–
6	(<i>S_a</i>)-L1	LiHMDS	BEt ₃	60 °C	46	–
7	(<i>S_a</i>)-L1	LiOt-Bu	LiBr	60 °C	<5	–
8	(<i>S_a</i>)-L1	LiOt-Bu	Yb(OTf) ₃	60 °C	14	–
9	(<i>S_a</i>)-L1	LiOt-Bu	ZnI ₂	60 °C	50	–
10	(<i>S_a</i>)-L1	KHMDS	ZnI ₂	60 °C	28	–
11	(<i>S_a</i>)-L1	LiHMDS	ZnI ₂	60 °C	80	75
12	(<i>S_a</i>)-L1	NaHMDS	ZnI ₂	60 °C	88 ^c	86
13	(<i>S_a</i>)-L1	NaHMDS	ZnI ₂	40 °C	86	93
14	(<i>S_a</i>)-L1	NaHMDS	ZnI ₂	21 °C	83	97
15	(<i>S_a</i>)-L1	NaHMDS	ZnBr ₂	21 °C	14	–
16	(<i>S_a</i>)-L1	NaHMDS	Zn(OTf) ₂	21 °C	0	–
17	(<i>S_a</i>)-L1	NaHMDS	Zn(OAc) ₂	21 °C	83	79



^aYields determined by ¹H NMR relative to a CH₂Br₂ internal standard. Reactions conducted at 0.05 mmol scale, utilizing a 1:1 stoichiometry of **1a**:**2a**. ^bDetermined by chiral SFC. ^cAverage yield from two experiments.

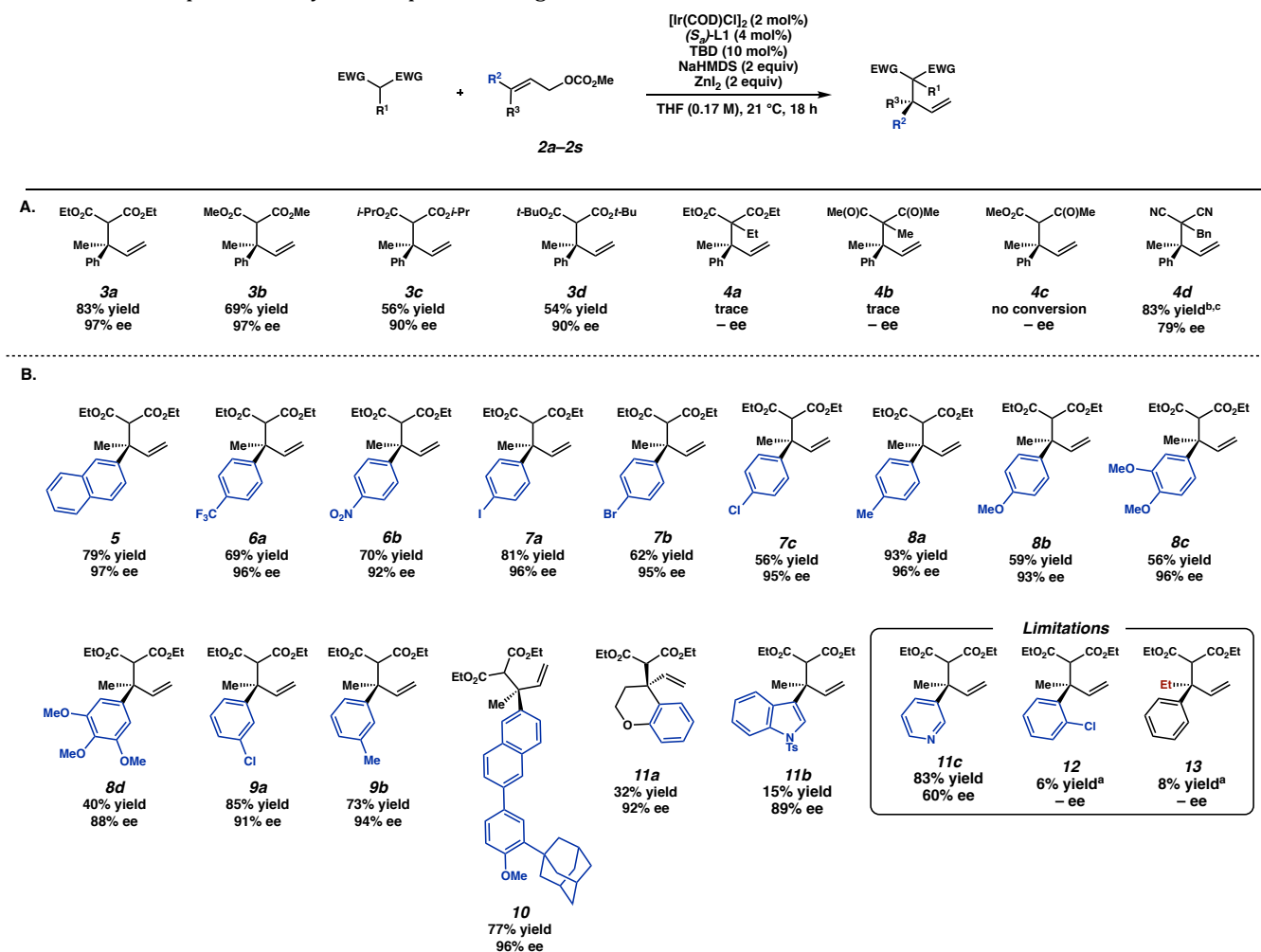
Early attempts to effect this transformation sought to utilize analogous conditions as reported in our previous coupling that featured malonitrile nucleophiles. Unfortunately, the application of BEt₃ as a stoichiometric Lewis acid additive and DABCO as a base led to no conversion (Table 1, entry 1). Using LiOt-Bu instead as the base provided a 23% yield of the desired product (**3a**) when (*S_a*)-L1 was utilized (entry 2), whereas (*S_a*,*R*)-L2¹⁰ and (*S_a*,*S,S*)-L3¹¹ did not lead to significant product formation (entries 3 & 4). While

NaOMe failed to improve conversion, employing LiHMDS as the base increased the yield to 46% (entries 5 & 6). Though lithium salts have been frequently used as Lewis acid additives in Ir-catalyzed allylic alkylations of stabilized carbon nucleophiles,^{12,13} replacement of BEt₃ with LiBr did not lead to appreciable product formation (entry 7). As lanthanide Lewis acids were previously reported by Carreira,⁴ Yb(OTf)₃ was investigated but led to minimal yields (entry 8). However, we were pleased to find that bench-stable ZnI₂, in concert with LiOt-Bu as the base, resulted in an elevated 50% yield and full conversion of starting material (entry 9). Exogenous zinc salt additives have indeed proven beneficial to reactivity and selectivity in a number of related Ir-catalyzed allylic alkylations.¹³ Combination of ZnI₂ with HMDS-derived bases resulted in up to 83% yield and 86% ee (entries 10–12). Finally, decreasing the reaction temperature to ambient 21 °C increased the enantiomeric excess to 97%, delivering the desired product in 83% isolated yield, with no detectable linear alkylation product (entry 14). Interestingly, alternative Zn²⁺ sources performed poorly (entries 15–17). VCD was utilized to determine the absolute stereochemistry of this model product (see Supporting Information).

With optimized reaction conditions in hand, the efficacy of other malonates in conjunction with allylic methyl carbonate electrophile **2a** was explored (Scheme 1A). The reaction utilizing dimethyl malonate afforded the corresponding quaternary product in an identical 97% ee as the diethyl variant (**3b**), albeit with a notable decrease in yield from 83% to 69%. Use of *i*-Pr (**3c**) or *t*-Bu (**3d**) malonates resulted in diminished 54–56% yield and 90% ee. Unfortunately, the use of substituted malonate **4a**, as well as other stabilized carbon nucleophiles (**4b**, **4c**), was unsuccessful under these conditions. Substituted malonitrile nucleophile **4d** generated the desired quaternary product in an improved 83% yield relative to our previous study,⁷ but in a significantly decreased 79% ee. With diethyl malonate as the optimal nucleophile, we aimed to elaborate the electrophile scope.

To our delight, the alkylation protocol accommodated a range of substitution patterns of the arene of the electrophile (Scheme 1B). A relatively sterically encumbered 2-naphthyl substituted electrophile could undergo the alkylation process in a 97% ee (**5**). Electron-withdrawing -CF₃ and -NO₂ substituents at the *para*-position led to the desired coupling products in high yield and ee (**6a**, **6b**). *Para*-substituents with electron-donating character, such as -Me and -OMe groups, also resulted in moderate to high yields and excellent levels of enantioselectivity (**8a**, **8d**). *Meta*-substitution with a -Cl or -Me substituent was well-tolerated (**9a**, **9b**). Heterocyclic scaffolds bearing chromanone and indole-derived fragments proved compatible, (**11a**, **11b**), though a 3-pyridyl substituent leads to deterioration of the enantioselectivity, potentially due to coordination of the substrate to the catalyst (**11c**). Exploring more structurally complex targets, we found that adapalene, a common topical acne medication,¹⁴ could be converted to the corresponding allylic methyl carbonate, which then underwent the Ir-catalyzed allylic alkylation to yield **10** in 77% yield and 96% ee.

Scheme 1. Nucleophile and Aryl Electrophile Investigation^a

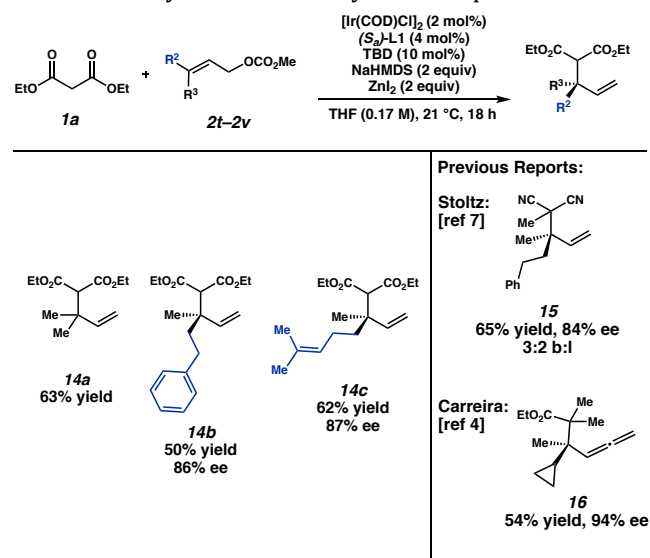


^aReactions conducted at 0.1 mmol scale, with 1 equiv. of both nucleophile and electrophile. ^bYield determined by ¹H NMR relative to a CH₂Br₂ internal standard. ^cReaction conducted at 60 °C and 0.08 M in THF.

Similar to the limitations of our previous research,^{6,7} *ortho*-substitution was not tolerated, possibly indicative of challenges related to the oxidative addition of the catalyst into such hindered systems (**12**). Furthermore, replacement of the methyl substituent of the electrophile with an ethyl group led to a dramatic decrease in yield to 8%. (**13**). Yield was somewhat recovered when this substituent was constrained in the form of a cyclic compound, resulting in the formation of the chromanone-derived product **11a** in 32% yield and 92% ee.

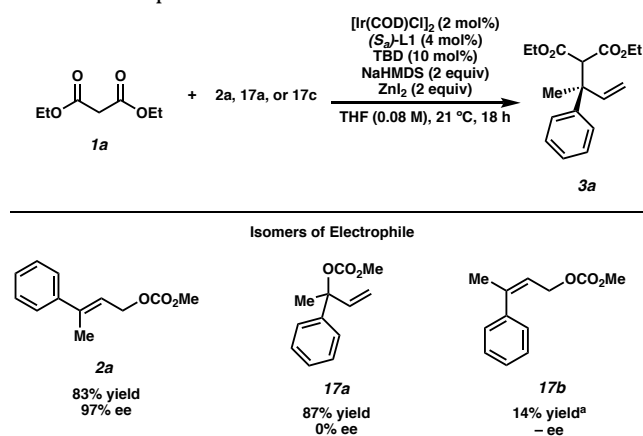
Having established the reactivity and scope of cinamyl-type trisubstituted electrophiles, we turned our attention to the historically challenging fully-alkyl substituted electrophiles. We were pleased to find that under these conditions, this class of substrates could form the corresponding quaternary alkylation products in up to 63% yield (Scheme 2). Phenethyl-substituted compound **14b** and geranyl methyl carbonate-derived product **14c** could be synthesized in 87% and 86% ee, respectively. Notably, the levels of enantiomeric excess and branched-selectivity obtained in this study are among the highest reported for alkyl-substituted electrophiles. The regio- and

Scheme 2. Alkyl-substituted Allylic Electrophiles^a



^aYields determined by CH₂Br₂ ¹H NMR standard. Reactions performed at 0.1 mmol scale.

Scheme 3. Preliminary Mechanistic Studies with Isomers of Model Electrophile^a

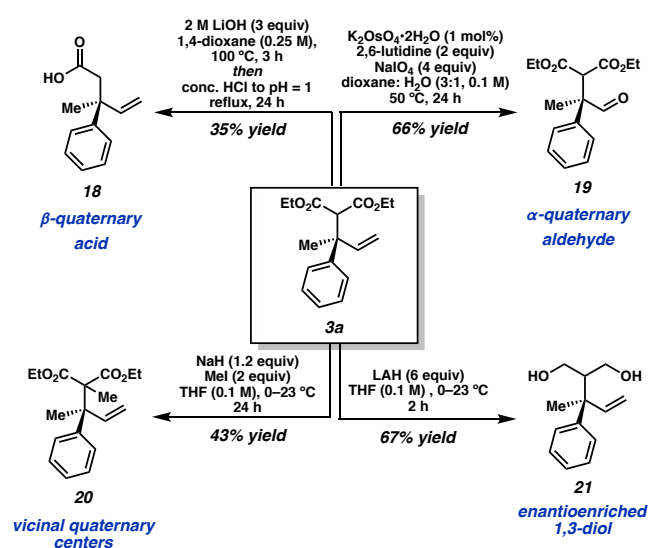


^aYield determined by ¹H NMR relative to a CH_2Br_2 internal standard. %ee was not measured.

stereoselective allylic alkylation of these substrates to form quaternary centers is a problem that has been left unsolved except in a limited number of cases. In our group's previous investigation, 2-methyl malononitrile could be reacted with the phenethyl methyl carbonate to form vicinal quaternary product **15** in a 65% yield and 84% ee, albeit as an inseparable 3:2 mixture of branched and linear isomers.⁷ Similarly, the Carreira group reported the substitution of a silyl ketene acetal with a cyclopropyl-substituted allenylc electrophile to form allene **16** in 94% ee.⁴

As was observed in our previous studies with the Carreira ligand (**L1**),^{6,7} the branched structural isomer of the model electrophile (i.e., **17a**) led to the desired product in a similar yield as the linear analog, but with a 0% ee (Scheme 3). The *Z*-stereoisomer of electrophile (i.e., **17b**) proceeded in a dramatically decreased yield. The lack of enantioinduction for the branched electrophile is consistent with a slow π -allyl equilibration process between diastereomeric Ir-allyl intermediates, which is observed in other reports of Ir-catalyzed allylic alkylation.¹⁵

Scheme 4. Product Diversification

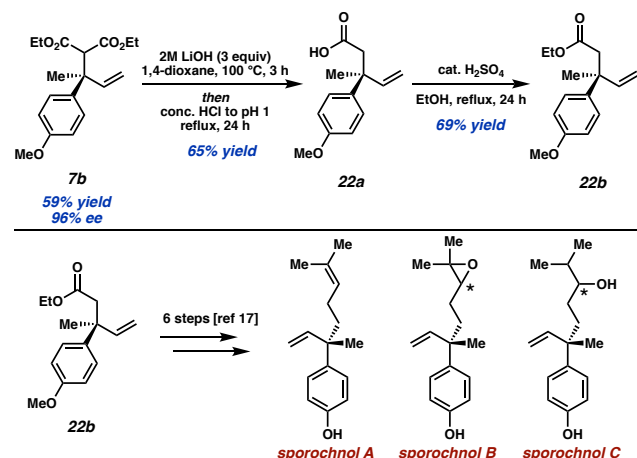


We next examined the synthetic utility of the β -quaternary diester compound **3a**, which was prepared on a 1 mmol scale in 75% yield and 97% ee. A saponification-

decarboxylation sequence furnished the β -quaternary acid **18** in moderate yield (Scheme 4). Standard Lemieux–Johnson oxidation¹⁶ resulted in the formation of the expected α -quaternary aldehyde species **19** in 66% yield. Treatment of **3a** with NaH and MeI generated the methylated diester species **20**, featuring a vicinal quaternary scaffold, in 43% yield. Lastly, exhaustive reduction of the diester functionality with lithium aluminum hydride afforded the corresponding enantioenriched 1,3-diol **21** in 67% yield.

This technology was then applied to generate a key intermediate employed by Prasad and coworkers in their formal synthesis of sporochols A–C,¹⁷ isolated from the marine algae *Sporochnus bolleanus*.¹⁸ Alkylation product **8b**, which was formed in 59% yield and 96% ee at a 1 mmol scale, could undergo saponification and decarboxylation to afford β -quaternary acid **22a** in 65% yield (Scheme 5). Subsequent Fischer esterification generated the desired ethyl ester **22b** in 69% yield. This constitutes an asymmetric formal synthesis of the sporochol natural products.

Scheme 5. Formal Asymmetric Synthesis of Sporochols A–C



In summary, we have developed a novel method for the synthesis of highly enantioenriched β -quaternary carbonyl compounds via an Ir-catalyzed allylic alkylation reaction. This transformation proceeds under mild conditions, and a broad range of allylic electrophiles, including fully alkyl-substituted substrates, are well-tolerated. To date, this report represents a broadly applicable method enabling the formation of enantioenriched β -quaternary centers with acyclic malonate nucleophiles. Further exploration of the mechanism of this reaction is currently underway.

ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures, spectroscopic data (¹H-NMR, ¹³C-NMR, IR, HRMS), and SFC, HPLC data.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally.

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Notes

The authors declare no conflict of interest.

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